Nanoscale

REVIEW

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Cite this: *Nanoscale*, 2025, **17**, 18477

Quantum dot-infused nanocomposites: revolutionizing diagnostic sensitivity†

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Received 30th January 2025,
Accepted 9th June 2025

DOI: 10.1039/d5nr00440c

rsc.li/nanoscale

Quantum dot-doped nanocomposites (QDNCs) represent an innovative breakthrough in diagnostic medicine, enabling ultra-sensitive and accurate detection at disease onset. Utilizing the size-tunable optical properties, high quantum yield, and photostability of quantum dots (QDs), these materials enable the highly sensitive identification of biomarkers at femtomolar concentrations in complex biological environments. The incorporation of QDs into nanocomposites enables them to achieve better diagnostic modes such as targeted delivery, signal amplification, and multifunctionality, with numerous applications in cancer diagnosis, infectious disease diagnosis, and real-time glucometry. Core–shell and hybrid architectures of advanced materials also enhance the stability and biocompatibility of the QDs. Surface functionalization enhancements and green synthesis approaches have alleviated the issues of toxicity and scalability, with the material now being fit for use in the clinical arena. Furthermore, the amalgamation of QDNCs with machine learning is promising for intelligent diagnostic tools capable of real-time analysis and personalized medicine. This review investigates the engineering of QDNCs, their transformative role in healthcare diagnostics, and their potential to revolutionize point-of-care devices. The capability to address significant translational challenges concerning biocompatibility, toxicity, and scalability will enable QD-based technologies to set a new standard for precision diagnostics, ushering in new advancements in global healthcare.

1. Introduction

The incorporation of nanotechnology into diagnostic medicine has been instrumental in improving sensitivity and specificity for disease diagnosis.[1] Quantum dot-doped nanocomposites (QDNCs) mark a breakthrough in the development of nanotechnology-based diagnostic tools, and they present clear differences from traditional techniques for disease diagnosis.[2] Quantum dots (QDs), with tunable optical characteristics, high quantum yield and resistance to photobleaching, have been used widely in diagnostics to attain femtomolar-level detection sensitivity.[3] Upon incorporation into nanocomposites, these materials allow for the ultra-sensitive identification of biomarkers in biological samples and outshine traditional techniques in terms of speed and accuracy.[4] For example, QDNCs have been used to attain the lowest possible detection level of 10^{-15} M (femtomolar level) in real-time biomarker tracking and achieve a previously unparalleled level of sensitivity in early disease identification.[3,5]

This concept of employing quantum dots (QDs) in diagnostic medical devices originated in the early 2000s with the ability of QDs to enhance detection and imaging using their optical characteristics.[6] Among the very first significant works in this direction was that by Bruchez *et al.* in 1998, revealing the application of QDs in cellular imaging with improved brightness and photostability compared to those of organic dyes. This work attained up to 20-fold greater brightness and photostability than those of conventional organic dyes, and thus, QDs became a promising non-radioactive biological marker.[7] Since then, progress has been growing exponentially. A significant case study by Gao *et al.* in 2004 presented *in vivo* tumor targeting with QD-labeled peptides. The sensitivity in detecting *in vivo* tumors with QDs was as high as 10^{-12} M

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† Electronic supplementary information (ESI) available. See DOI: **https://doi.org/10.1039/d5nr00440c**

(picomolar) in this research and was far more accurate compared to prevailing techniques of the time.[8] These early efforts set the stage for sophisticated nanocomposites that combine QDs with polymers or with magnetic nanoparticles towards multi-modal diagnosis. Medintz *et al.* more recently emphasized the application of QD-bioconjugates towards multiplexed biosensing, showing the detection of multiple analytes in one assay. This study attained detection sensitivity at the level of 10^{-15} M (femtomolar) and was far better than traditional diagnosis methods.[9] These early developments established the foundation for the production of today's QD-based nanocomposites used in highly sensitive point-of-care diagnostic kits.

This review is organized into nine detailed sections to illustrate the increasing variety of applications of quantum dot-enriched nanocomposite (QDNC) materials in modern diagnostics. Section 2 discusses the key features of QDNCs and the advantages of enhanced diagnostic sensitivity. Section 3 describes future nanocomposite design through core–shell and hybrid architectures, surface functionalization methodologies, and green synthesis protocols. Section 4 explores the underlying quantum effects—such as energy transfer processes, luminescence, and photostability—that confer the potential of ultra-sensitive detection. Section 5 discusses real-world applications, including disease detection at an early stage, multiplex biomarker screening, and devices at the point-of-care. Section 6 addresses the chief hindrances to bringing nanocomposites to the clinic, including biocompatibility, cytotoxicity, large-scale production, and regulations. Section 7 anticipates future opportunities to include personalized diagnosis, AI-based platforms, and the advent of non-invasive technologies. Section 8 assesses the revolutionizing potential of QDNCs through major innovations, unsolved problems, and future directions for strategic development. Section 9 provides a final summary of the review's main findings and implications for future diagnostic platforms.

2. Quantum dot-infused nanocomposites (QDNCs): revolutionizing diagnostic sensitivity

Quantum dot-infused nanocomposites (QDNCs) have emerged as transformative tools in medical diagnostics, offering highly sensitive and specific detection—particularly in early-stage disease identification.[10] The combination of the unique optical properties of quantum dots (QDs) with the structural adaptability of nanocomposites such as silica, polymeric, or magnetic matrices provides a robust platform for the real-time and high-precision detection of biomarkers, pathogens, and cellular anomalies.[11] Their exceptional photostability, customizable luminescence (ranging from ~400 to 800 nm), and facile surface functionalization, such as with antibodies, aptamers, or peptides, make them highly attractive for the development of next-generation diagnostic technologies. QDNCs have the potential to revolutionize healthcare by enhancing diagnostic accuracy, reducing background noise through their high signal-to-noise ratios, and enabling early intervention in life-threatening diseases such as cancer, infectious diseases, and neurological disorders.[12]

2.1 A paradigm shift in medical diagnostics

Diagnostic medicine has rapidly evolved in recent years, expanding from simple biochemical tests to molecular and imaging techniques.[13] Among these advancements, nanotechnology plays a pivotal role in enhancing the sensitivity and specificity of diagnostic platforms.[14] QDNCs mark a significant stride forward, offering fundamentally superior capabilities for detecting diseases at early stages. QDs are semiconductor nanocrystals subject to quantum confinement effects, resulting in distinct optical and electronic properties compared to bulk materials of the same composition.[15] When integrated into nanocomposites, these properties are preserved and augmented, enabling improved signal-to-noise ratios and multiplexed detection capabilities not achievable with conventional diagnostic approaches.[16] The outstanding photostability,

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tunable photoluminescence properties, and consistently high quantum yields of QDs enable the sensitive detection of biomarkers, pathogens, and other analytes crucial for early disease diagnosis.[8]

The development of QDNCs has emerged in response to the critical need for diagnostic tools capable of identifying targets present in low quantities within complex biological environments. By utilizing QDNCs, diseases such as cancer, infectious diseases, and neurological disorders can be more accurately identified at their earliest possible stages, bolstering signal strength and reducing background noise.[17]

2.2 QDs: a new frontier in materials science for healthcare

Quantum dots (QDs) are nanocrystals that were discovered as far back as the early 1980s, and foundational research by Alexei Ekimov and others showed the size-dependent optical characteristics of semiconductor nanocrystals. Quantum dots were primarily investigated for the possibility of them showing individual optical characteristics owing to quantum confinement effects, enabling the optical characteristics of quantum dots to be adjusted finely according to size.[18]

Quantum dots (QDs) function as nanoscale crystals with CdSe QDs extending from 2 to 6 nm and InP QDs reaching sizes up to 8 nm. Quantum dots consist of semiconductors and separate from these materials are carbon-based quantum dots, which exist as a distinguished group.[19,20] The bandgap of quantum dots (QDs) becomes modifiable through size alterations due to quantum confinement effects, which enable optical property adjustments. Quantum dots of CdSe material produce light output at wavelengths spanning from 450 nm to 650 nm and PbS QDs generate near-infrared light of approximately 1000 nm.[21]

The fluorescence brightness of CdSe/ZnS core–shell quantum dots reaches between 50% and 90% because of their high quantum yield property. The detection capabilities of QDs reach picomolar concentrations because of their unique properties for diagnostic applications.[22] Quantum dots (QDs) demonstrate enhanced photostability compared to organic dyes because they sustain fluorescence for longer than 60 min under continuous illumination, but organic dyes such as fluorescein bleach their fluorescence in mere seconds to minutes. The intermittency phenomenon of QDs through fluorescence blinking impacts their performance in real-time imaging systems.[23] The multiplexing capability is also another significant feature. QDs improve diagnostic assay productivity because their spectral characteristics create the possibility of identifying multiple targets simultaneously without spectral interference. The surface functionalization of QDs provides scientists with the capability to attach different ligands, antibodies and peptides for directed biomarker and cell binding.[24]

Advanced diagnostic applications increasingly use quantum dots (QDs) as lead candidates because these nanomaterials possess exceptional photostability in addition to high fluorescence quantum yield and variable emission profiles.[25] QDs embedded within nanocomposites made from polymeric materials or silica-based shells achieve better optical stability with delivery targeting abilities and permit their integration into biosensors and microfluidic diagnostic systems.[26] QDs provide nanocomposite systems with essential performance characteristics that include prolonged photostability with photobleaching resistance in addition to oxidative degradation and enhanced fluorescence brightness relative to fluorescein and rhodamine or similar traditional organic fluorophores.[9] QDs show key characteristics such as their ability to form films and hydrogels and their compatibility with various biomaterials along with the high electron density from their heavy-metal content that improves TEM contrast. The combination of specific properties puts QDs in an ideal position to become an advanced diagnostic tool because engineered nanocomposites provide enhanced flexibility.[27] Table 1 presents an overall comparison between organic dyes and quantum dots based on their constitution, range of sizes, optical properties (maxima of emission and absorption), emission region, quantum yield, and lifetime. From this table, it is evident that quantum dots have a wider range of sizes and emission properties that are tunable, with organic dyes frequently displaying maximum quantum yields in certain ranges of wavelengths (Fig. 1).

Keyvan Alavi

Keyvan Alavi is a biomedical engineering student and researcher with a keen interest in nanotechnology, biomaterials, and the integration of engineering approaches in medical research. With a background in computational and experimental methods, Keyvan aims to contribute innovative and practical solutions to the field of biomedical sciences.

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Parto Ghahramani is a medical doctor with a keen interest in biomedical engineering, regenerative medicine, and tissue engineering. With a foundation in clinical practice and a passion for interdisciplinary research, Parto seeks to develop innovative solutions for tissue repair and biomedical sciences.

Table 1 General comparison of quantum dots and organic dyes

Sample type	Example	Composition	Size range (nm)	Absorption max (nm)	Emission max (nm)	Emission region	Quantum yield (%)	Lifetime (ns) (ref.)
Quantum dot	CdSe/ZnS	CdSe core/ZnS shell	4–8	525	540	Green	65–85	15–20 (ref. 29)
Quantum dot	InP/ZnSe	InP core/ZnSe shell	3–6	510	530	Green	~55	~18 (ref. 30)
Quantum dot	Graphene QD	Graphene-based carbon core	1–5	360	450	Blue	40–50	6–10 (ref. 30)
Quantum dot	$CsPbBr_3$	$CsPbBr_3$ perovskite structure	6–10	510	520	Green	70–90	25–30 (ref. 29)
Organic dye	Rhodamine B	Xanthene dye	~1	554	576	Orange–red	70–95	1.6–4 (ref. 31)
Organic dye	Alexa Fluor 647	Cyanine dye derivative	~1	650	668	Far-red	33–35	1–1.2 (ref. 32)

2.3 Why nanocomposites? Integrating materials for unprecedented functionality

Nanocomposites consist of one substance—a polymer, metal, or ceramic matrix—containing nanoparticles combined with another material.[33,34] By incorporating QDs into nanocomposites, a synergistic enhancement of functionality is achieved by merging the unique properties of QDs with those of the matrix material.[35]

One of the critical advantages of incorporating QDs into nanocomposites is improved stability; embedding QDs within a protective matrix shields them from environmental degradation, thereby enhancing their chemical and photostability within biological environments.[36] Enhanced biocompatibility is another significant benefit; surface modification and encapsulation within biocompatible materials reduce potential cytotoxicity, allowing for safe *in vivo* applications.[37] Signal amplification is a key advantage; nanocomposite structures can amplify optical or electrical signals generated by QDs, offering exceptional sensitivity for detection methods.[38] Another important feature is targeted delivery, which can be achieved through functionalizing nanocomposites with targeting moieties to enable selective binding to specific cells or tissues with high accuracy.[39] Lastly, multifunctionality is enabled by embedding QDs with other nanoparticles such as magnetic nanoparticles within the nanocomposites, facilitating diverse diagnostic applications including imaging and theranostics.[40] Research by Mahajan *et al.* proved that a composite of QDs and magnetic nanoparticles could identify pathogens at the 10^{-14} M level of detection, and it could serve as a very efficient diagnostic tool for the identification of diseases at the earliest possibility. The level of fluorescence of the composite was 3.5 times greater than that of regular magnetic nanoparticles, and it showed very good photostability when continuously illuminated for more than 60 min. This points to the synergetic effect achieved by the combination of QDs and magnetic nanoparticles in the development of very sensitive and efficient diagnostic devices.[41,42]

One promising application of QDNCs is the development of QD–magnetic nanoparticle composites for efficient pathogen detection and separation. These composites leverage fluo-

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Marzieh Ramezani Farani

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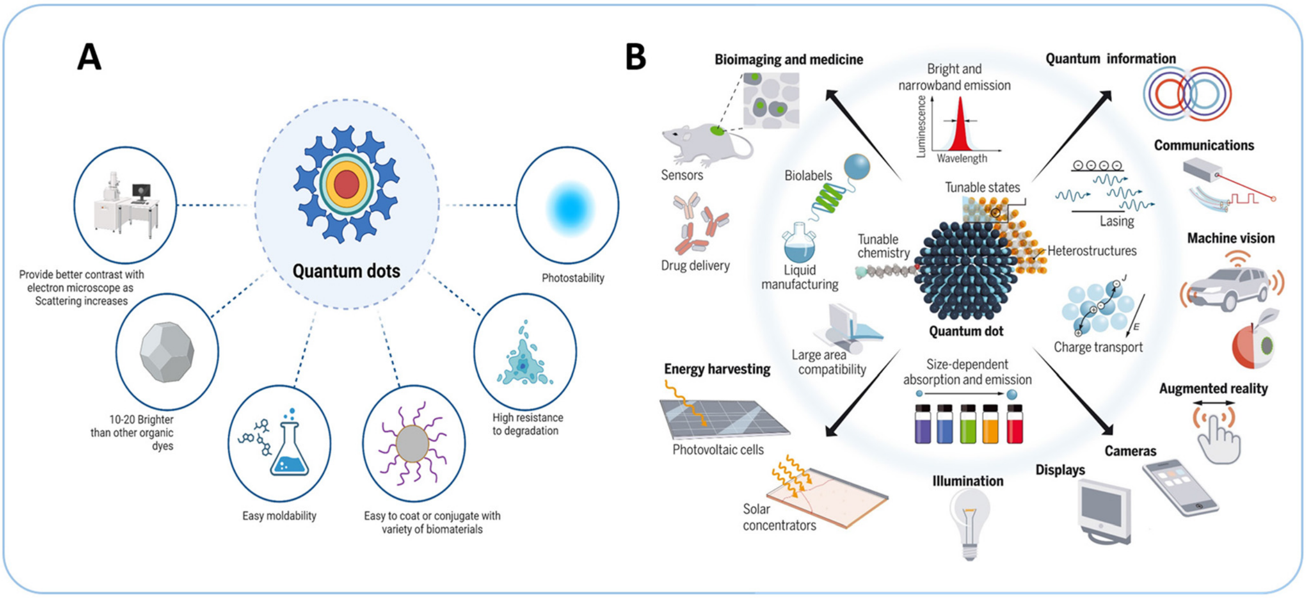

Fig. 1 (A) Features of quantum dots: these nanoparticles exhibit high photostability, resistance to degradation, 10–20 times brighter emission than organic dyes, easy moldability, ability to coat or conjugate with various biomaterials, and enhanced contrast in electron microscopy due to increased scattering (created in Biorender). (B) Applications of quantum dots across various fields: quantum dots demonstrate versatile properties, such as tunable emission, size-dependent absorption, and charge transport. These features enable their use in bioimaging and medicine (*e.g.*, sensors, drug delivery, and biolabels), energy harvesting (*e.g.*, photovoltaic cells and solar concentrators), quantum information (*e.g.*, lasing and heterostructures), communications, machine vision, augmented reality, and consumer technologies such as illumination, cameras, and displays. This figure has been reproduced from ref. 28 with permission from the American Association for the Advancement of Science, copyright 2021.

rescence from QDs for detection, while the magnetic properties of iron oxide nanoparticles enable efficient separation, resulting in a powerful diagnostic tool with high sensitivity.[43,44]

Through integration of the best features of QDs and nanocomposite materials, QDNCs represent a major breakthrough in the quest for highly sensitive and selective diagnostic tools.[45] They epitomize the convergence of materials science, chemistry, and medicine in pioneering new approaches for point-of-care diagnostics in healthcare, thereby heralding a brighter future for patients.[46] The incorporation of quantum dots (QDs) into nanocomposite systems stabilizes them not only colloidally and structurally but also significantly improves their biocompatibility.

Several studies have reported quantitative evidence in support of these enhancements. For instance, gelatin-coated CdTe QD nanocomposites showed up to 65% reduction in cytotoxicity in human epithelial cell lines compared to bare QDs,[47] as ascertained through the MTT assay. Similarly, Fe_3O_4/CQD magnetic nanocomposites for targeted imaging showed cell viability above 90% after 24 h, whereas naked QDs under the same conditions reduced the viability to about 65%. From both colloidal and photostability standpoints,[48] polymer encapsulation of QDs significantly enhances the long-term performance. The work conducted by Das *et al.* demonstrated that chitosan-stabilized QD nanocomposites gave their particles photobleaching protection and 2.4 times more fluorescence decay than unmodified QDs. Various stability enhancements merge when QD aggregation is minimized along with antioxidant protection and that shields QDs from contact with aqueous solutions and cellular environments.[49]

The significance of CD-based polymer nanocomposites (CD-PNCs) in the development of groundbreaking medical technologies is underscored by their applications in biosensors, virus detection, protein detection, cancer diagnosis, wound healing, bone tissue engineering, and cardiac scaffolds, as depicted in Fig. 2.


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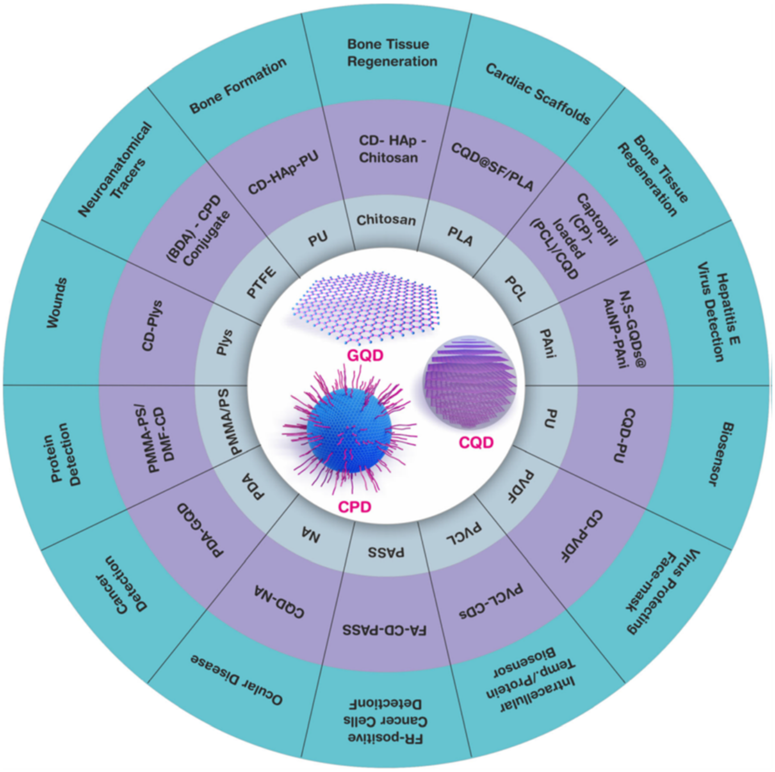

Fig. 2 Carbon dots at the core, polymers in the inner circle, and CD-based polymer nanocomposites (CD-PNCs) in the mid circle, showcasing their biomedical applications across various fields such as biosensors, cancer diagnostics, and tissue regeneration. This figure has been reproduced from ref. 50 with permission from Springer, copyright 2023.

3. Engineering next-generation QDNCs

The development of the next generation involves enhanced core–shell and hybrid nanostructures that would extend composites beyond ultra-sensitive diagnostic techniques.[51] These all contribute to enhancement in optical stability and photoluminescence of the quantum dots, making biomarker detection particularly favorable at ultra-low concentrations by building superior biocompatibility.[52,53] In quantum dot biosensing, ultrasensitive detection is typically characterized by the ability to sense biomolecular targets at sub-picomolar to attomolar levels. The detection of proteins ranges from low nanomolar (nM, 10^{-9} M) to as low as attomolar (aM, 10^{-18} M) levels, depending on the assay type and target biomarker. For example, prostate-specific antigen (PSA) has been sensed by quantum dot-enhanced immunosensors down to 10 aM concentrations, while C-reactive protein (CRP) has shown reliable quantitation at 100 fM–1 pM using hybrid QD platforms.[54] These levels are much lower than conventional ELISA-based assay detection abilities, which typically operate in the nanomolar range. Core–shell structures, like CdSe/ZnS, improve quantum yields and photostability, while inorganic–organic hybrid nanocomposites, including those with GO and/or gold nanoparticles, are designed to increase functionality for applications in electrochemical sensors and real-time disease detection. Recent engineering advances are critical for minimizing toxicity and maximizing the safety of QD-based diagnostics in clinical applications.[55]

3.1 Structural innovations: core–shell and hybrid nanocomposites

The structural design of QDNCs is significant in the amplification of their performance in ultra-sensitive diagnostics. New progress in the development of core–shell and hybrid nanocomposite structures has invigorated the field through the enhancement of optoelectronic characteristics, stability, and bio-compatibility, which have important influences on the diagnostic ability.[56]

It has been found that the use of core–shell structures in which a semiconductor core is surrounded by a shell of another material has proved to be very effective at improving the optical properties of QDs. For example, the quantum yields of CdSe/ZnS core–shell QDs increase up to 85% and photostability increases compared to core-only QDs as a result of efficient passivation of surface defects on a ZnS shell.[57] This improvement is essential when the diagnostic techniques under consideration involve ensuring the stability and high intensity of the fluorescence signals. The synthesis of alloyed core–shell QDs like CdSeTe/ZnS makes it possible to set emission wavelengths from 500 to 800 nm and therefore multiple signals can be generated from various biomarkers at once.[38]

As additional shells are incorporated into the QDs, multi-shell structures play an important role in the stability and function of QDs. For instance, CdSe/ZnS/SiO_2 nanocomposites are developed by the incorporation of further shells to improve chemical and photostability and lower toxicity.[58] There is still a hydrophilic surface on the silica shell, as well as the possibility for further functionalization, which is crucial for the biomedical field where aqueous solubility and bioconjugation are necessary.

Another combination of different nanomaterials like graphene oxide or gold nanoparticles, with QDs makes the hybrid nanocomposites a potential tool for developing advanced diagnostics.[39] Graphene oxide conjugation enhances the electron transfer properties of QDs, which enable electrochemical sensors to be designed for the detection of disease biomarkers at femtomolar concentrations. Appropriate structural engineering is also useful for minimizing the toxicity of QDs that must be utilized in clinical practices. Cytotoxicity has been lowered as researchers have used InP/ZnS QDs and biocompatible coatings that make these nanocomposites safe for *in vivo* diagnostic applications.[59] Research by Kumar *et al.* demonstrated the fabrication of hybrid nanocomposites by the modification of quantum dots (QDs), graphene oxide (GO), and gold nanoparticles (AuNPs) for high-performance diagnostic purposes. Integration of these nanomaterials proved to be quite useful at enhancing the electrochemical sensing of disease markers at the femtomolar level, a huge leap forward in the detection of disease in its early stages. In the research, the combination of graphene oxide and QDs enhanced the properties of electron transfer, and hence the development of very sensitive electrochemical sensors that could identify disease markers at a 10^{-15} M detection limit. This is 1000 times more sensitive compared to conventional means. For instance, the fluorescence of the hybrid composite QD–GO–AuNP was 4.2 times stronger than that of conventional standalone QDs, offering a better disease-detecting signal. Furthermore, the research also proved that the combination of using InP/ZnS QDs and biocompatible coatings lowered the cytotoxicity to 70% and hence these composites could be used in *in vivo* diagnosis.[60]

These structural innovations have significantly enhanced the diagnostics part due to better performance and safety of QD nanocomposites. Improved photostability and emission properties provide enhanced signal-to-noise ratios, which are crucial for the detection of biomarkers at low abundance in early disease states. Fig. 3 represents the formation and structure of core–shell nanoparticles (CS-SPs). In (A), QDs and magnetic nanoparticles treated with DTAB are integrated into the shells of PVP. The TEM images in (B) are at different scales are from 500 nm to 100 nm and 10 nm, demonstrating the hierarchical self-assembly of the materials. Some designs for core–shell systems that were drawn were simple single SiO_2 QDs to more complicated multiple QD shells optimized for bioimaging/diagnostic applications.

3.2 Precision functionalization: tailoring surfaces for ultra-sensitive detection

The external surface of QDNCs needs to be functionalized to get highly sensitive and selective diagnostic tools.[63] Both the size and surface properties of the nanoparticles can be engineered for better targeting of cancer cells, reduced toxicity, and efficient signal transduction.

When the QDNCs are functionalized with certain ligands, including antibodies, aptamers, or peptides, then the QD nanocomposites can interact selectively with the target molecules or cells.[64] For example, QDs conjugated with anti-prostate-specific antigen (PSA) antibodies for monitoring the amount of PSA with high specificity and sensitivity, reach detection limits of 0.1 ng mL^{-1}. There are various methods for stabilizing the QD surface; the two most common approaches include ligand exchange and

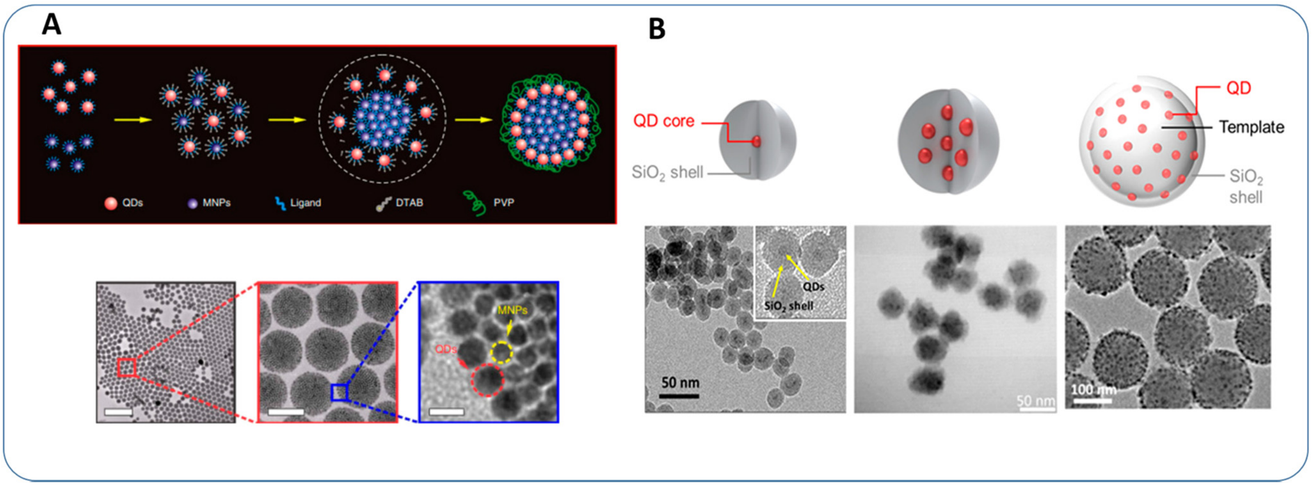

Fig. 3 (A) Schematic of the formation process for core–shell structures (CS-SPs), integrating quantum dots (QDs) and magnetic nanoparticles (MNPs), with TEM images of CS-SPs at different scales (500, 100, and 10 nm). This figure has been adapted from ref. 61 with permission from Nature Research, copyright 2014. (B) Examples of single-QD encapsulated SiO_2 shells, multi-QD-doped SiO_2 particles, and template-based multi-QD structures, designed for advanced bioimaging and diagnostic applications. This figure has been adapted from ref. 62 with permission from MDPI, copyright 2021.

encapsulation. Ligand exchange removes initial hydrophobic ligands after introducing hydrophilic ones containing functional groups such as carboxyl or amine groups.[24] Functionalization of amphiphilic polymers or silica shells offers protection and functional groups that retain the QD's photophysical properties while improving their biocompatibility.

Surface charge also affects the behavior of the QDNCs in biological systems. QDs with a positive charge have higher cellular take up facilitated by electrostatic attractions but may also give higher cytotoxicity.[65] Targeting efficiency can therefore be easily achieved if the surface charge is also well balanced to overcome this effect. Furthermore, functionalization of the biosensor can lead to better signal transduction to improve the sensitivity of the device. The use of energy transfer mechanisms, such as Förster resonance energy transfer (FRET), improves sensitivity, permitting the detection of analytes at the attomolar range. Bioconjugation techniques and sterically stabilizing ligands are used to prevent aggregation and thus support the optical properties of QDs under physiological conditions: problems of QD stability after their functionalization remain challenging.[66]

Nanocomposites made from QD structures (QDNCs) experience major diagnostic improvements when their surfaces are engineered to include targeting peptides and polyethylene glycol (PEG) chains. Antibody-conjugated QDNCs achieved a 10-fold enhancement in target signal-to-background ratio compared to traditional fluorophore-labeled assays.[67]

3.3 Distinguishing *in vitro vs. in vivo* requirements for diagnostic applications

From the material and diagnostics perspective, it is crucial to distinguish between the *in vitro* and *in vivo* requirements for the material properties. Both applications benefit from signal amplification and the optical sensitivity of the quantum dot nanocomposites (QDNCs) but have very different material constraints in each domain.[68] In *in vitro* diagnostics—*i.e.*, biosensing platforms for the detection of biomarkers for diseases in saliva, urine, or blood—target specificity through surface functionalization, chemical stability under the conditions of the assay, and high signal-to-noise ratios for quantitative measurements. Less important here are biocompatibility and cytotoxicity because the QDNCs are applied outside the body and in controlled media.[69]

Conversely, *in vivo* diagnostics such as live-cell imaging or targeted delivery for molecular imaging demand far more stringent material properties. These are low cytotoxicity and high biocompatibility, colloidal stability in the physiological environment, non-immunogenicity, and in most applications tissue penetration within the near-infrared (NIR) window. Failure to meet these will result in immunological responses, rapid clearance, or inaccurate imaging.[70]

Quantum dot nanocomposites are a versatile platform for engineering material properties for either application. In the case of *in vitro* application, the QDNCs can be surface-functionalized with aptamers, antibodies, or molecularly imprinted polymers for selectivity and reliability.[69,71] In the case of *in vivo* application, biocompatible surface coatings (*e.g.*, PEGylation, silica, chitosan) and particle size optimization (generally <10 nm) significantly reduce toxicity and increase circulation times.[70,72,73] Their emission profiles are tunable within the NIR window (650–900 nm) and further optimize the application for deep tissue imaging.[70]

Thus, QDNCs are multifunctional platforms with tunable physicochemical properties and are highly appropriate for *in vitro* diagnostics and *in vivo* biomedical imaging applications.

3.4 Hybrid platforms: merging multiple functionalities for signal amplification

Multi-nanomaterial systems combine various nanomaterials to achieve interactions and improve diagnostic sensitivity and substrate versatility.

When QDs are deposited with plasmonic nanoparticles such as gold or silver, the fluorescence is boosted by metal-enhanced fluorescence (MEF) with up to 100-fold boost in fluorescence intensity.[74] This amplification facilitates the detection of biomarkers at a very low concentration, which in the early stages of diseases is important. The stability of magnetic QDNCs makes them important in diagnostics-related applications since they enable easy and efficient concentration of analytes from a matrix.[75] Point-of-care detection may benefit from the integration of QDs and these nanocomposites for rapid, sensitive detection; this study has shown that these possess good signal-to-noise ratios.

Hybrid platforms also enable the use of different modalities for imaging as well as performing multimodal therapy.[76] This capability can be achieved by conjugating QDs with other functional nanoparticles for more than one imaging approach, such as fluorescence and magnetic resonance imaging, which supports comprehensive disease diagnosis.[77] For instance, silica nanoparticles doped with QDs together with iron oxide offer both fluorescent and magnetic imaging properties. Also, the use of graphene or carbon nanotubes with QDs in the construction of the device increases biosensor efficiency due to the observed high electron transfer rates, which bring the detectable concentration to the picomolar level with a response time of several seconds.[41] For instance, picomolar-level sensitivity is especially useful in the detection of low-abundance biomarkers such as lactate dehydrogenase (LDH) in the case of early-stage cancers, or circulating microRNAs, the expression levels of which in serum range from less than 10^{-12} M.[78] But in the case of analytes such as C-reactive protein (CRP) that generally range from microgram per milliliter levels, such sensitivity would not be required. As such, the design of the assay should be adapted to the target analyte and clinical setting.[79]

Some difficulties inherent in creating stable and reproducible hybrid nanocomposites include suitable dispersion of different nanomaterials and strong coupling between multicomponent systems. To overcome these difficulties, techniques like layer-by-layer assembly and controlled synthesis methods are used; these enhance the output of hybrid platforms.[80]

Multifunctional hybrid nanocomposites provide enhanced signal enhancement and diagnostic versatility when compared to single-component nanocomposites. These platforms are expected to revolutionize the design and synthesis of the next generation of diagnostic tools with enhanced performance and functions.

3.5 Sustainable synthesis: green approaches for biomedical nanocomposites

Many of the QDNCs synthesized according to traditional methods contain toxic reagents and are processed under severe conditions that can damage the environment and human health. New methods for preparing such compounds have come to light; these are in line with current green synthesis methods applicable to environmentally friendly and harmless biphasic systems.[81]

Green chemistries employ water as a solvent and other mild reagents in addition to using efficient and energy-saving processes.[82] For instance, carbon dots can be derived from natural resources like fruit extracts and produced with hydrothermal treatment and thus do not require any poisonous substances. This sustainable synthesis alters the biocompatibility of QDNCs by minimizing cytotoxicity and improving compatibility with biological systems to make them ideal under *in vivo* conditions.[83]

Recent developments in green synthesis have enabled the synthesis of QDs with high quantum yield and the optical characteristics required for diagnostic applications.[6] The size distribution, reaction temperature, and time, as well as the choice of precursors, are crucial for attaining conventional levels of performance of traditionally synthesized QDs. The use of non-toxic and Earth-abundant precursors like silicon and zinc in QD synthesis also has its advantages, as described below.[84] For instance, silicon QDs possess desirable properties such as good biocompatibility and stability under illumination for short or long-term imaging studies. Silicon QDs possess suitable attributes such as biocompatibility and photostability with evidence of preserved emission intensity over imaging times from minutes to over 72 h, depending on surface passivation and conditions. Short-term imaging here would mean applications from several minutes to several hours (*e.g.*, real-time cell labeling), and long-term imaging typically would mean long-term monitoring *in vitro* or *in vivo* over one to three days with minimal signal loss.[85]

Green synthesis plays a role in scaling up production and in the commercialization of these QDNCs. Green synthesis methods turn out to be more cost-efficient and easier in their scale; the latter is a significant step as the concept of deploying QD-based diagnostic tools is still in its infancy and requires migrating from the lab environment.[69] Sustainable synthesis methods are also in line with current global demands for green technologies, which reduce the adverse effects on health and the environment to allow for the widespread use of QDNCs in medical diagnosis. As presented in Fig. 4, highly fluorescent probes on magnetic beads can measure targets in the zeptomolar–nanomolar range; R^2 = 0.99. (B) QD-based electrochemical immunosensors utilize advanced signal transduction modes, including amperometric, voltammetric, and

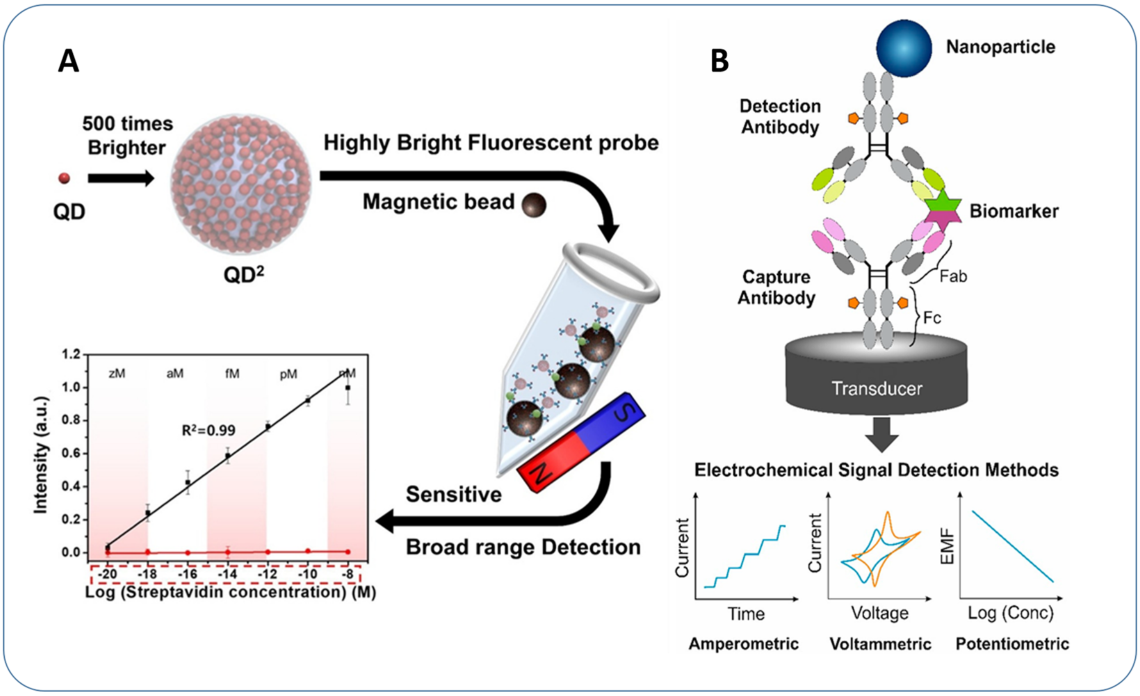

Fig. 4 (A) This image shows a highly bright fluorescent probe (QD^2) with 500× brighter quantum dots on magnetic beads, enabling ultra-sensitive detection across a wide range (zeptomolar to nanomolar) with R^2 = 0.99. Ideal for precise and sensitive analyte detection. This figure has been adapted from ref. 86 with permission from Elsevier, copyright 2020. (B) Schema of electrochemical immunosensors based on nanoparticle tags. This figure has been adapted from ref. 87 with permission from MDPI AG, copyright 2021.

potentiometric techniques, which contribute to enhanced diagnostic sensitivity and specificity.

4. Mechanisms driving breakthrough sensitivity in diagnostics

QDs are revolutionizing diagnostics by exploiting unique quantum phenomena at the nanoscale to realize unprecedented sensitivity in the detection of biomarkers and pathogens. Their size-tunable optical properties allow for energy transfer mechanisms such as Förster resonance energy transfer, greatly improving detection limits. Compared with conventional fluorophores, QDs have higher quantum yields, superior photostability, and enhanced luminescence, enabling long-term monitoring and multiplexed detection of multiple targets. This is partly because QD stability and reliability, with improvements in hybrid nanostructure-related enhanced signal amplification, puts them at the fore as tools essential for the next wave of diagnostic techniques.[88]

4.1 Quantum phenomena at the nanoscale: energy transfer mechanisms

Based on the nanoscale quantum effects of QDs, it is possible to achieve remarkable improvements in diagnostic sensitivity. Energy transfer modalities, specifically Förster resonance energy transfer, play an important role in the improvement of molecular detection. As energy donors, QDs have shown high efficiency, which can be attributed to size-tunable emission and broad absorption spectra. This rare behavior enhances the rate of energy transfer to acceptor molecules in diagnostic assays, leading to the detection of biomolecules even in small concentrations.[89] Förster resonance energy transfer (FRET), improves the sensitivity of molecular detection. In QD-based biosensors, QDs function as excellent energy donors due to their broad absorption spectra and narrow, tunable emission spectra. When coupled with suitable acceptor molecules, QDs can mediate energy transfer by FRET over distances of 1–10 nm, which is appropriate for the examination of the interactions of biomolecules at the nanolevel. Non-radiative energy transfer is responsible for increasing the specificity of the signal and quenching background fluorescence, leading to greatly increased signal-to-noise levels. Notably, FRET-based QD assays attained detection limits at the attomolar level—orders of magnitude below those of conventional fluorophore systems. As a representative example, Lin *et al.* attained a photoluminescence quantum yield (PLQY) of 97.6% for QDs, which maximized the efficiency of energy transfer and enabled ultra-sensitive biosensing capabilities. These features make QDs amenable for FRET-based platforms for the detection of even subtle molecular changes with high fidelity and low levels of signal attenuation.[69,90]

Azzazy *et al.* conducted a study to show the feasibility of using QD-based diagnostics and they concluded that it was possible to quantify the target analytes at the femtomolar level without any amplification procedures. The QD-based diagnostics detect the target analytes at a concentration of 10^{-15} M. Compared with conventional organic dyes, analyte quantification is in the nanomolar range (~10^{-9} M), demonstrating that QDs are 10^6 times more sensitive.[90] Wang *et al.* also pointed out that the photodetectors developed from QD structures had a significantly enhanced performance compared to conventional CCD-based detectors, with enhanced photocurrent responsivity and internal gain that could improve the micro-spectrometry diagnostics precision.[91]

Furthermore, Hildebrandt *et al.* integrated QDs with metallic nanoparticles, and a notable ten-fold increase in signal strength through plasmonic coupling was achieved. These works highlight the strong potential of QD-based diagnostic systems for clinical applications.[92]

A 2024 study by Tang *et al.* developed QD-based reporters for CRISPR-mediated detection of viral nucleic acids, achieving picomolar-level sensitivity.[93] This sensitivity is comparable to that of classical organic fluorescent probes, which show a Marron enhancement in detection limits. This advancement is important, particularly for diseases where the biomarkers usually have very low concentration levels in body fluids. For example, Alzheimer's disease is linked to exosomal tau and amyloid-β biomarkers present at picomolar concentration levels in the cerebrospinal fluid, which are difficult to detect early on without the aid of ultrasensitive tools. Likewise, non-small cell lung cancer (NSCLC) can be identified using circulating miRNAs present in the blood and saliva at femtomolar concentration levels, which demand amplification-free detection methods. In ovarian cancer, serum metabolomic markers tend to be below nanomolar concentration levels, thus also requiring the use of signal-amplifying nanoplatforms for correct identification. These examples serve to emphasize the significance of high-sensitivity energy transfer-based systems such as QD-FRET for early diagnosis.[94–96]

A study by Lin *et al.* reported a record-high photoluminescence quantum yield (PLQY) of 97.6% for QD-based fluorescent nanoparticles, highlighting their strong potential to enhance the signal-to-noise ratio in diagnostic applications. Compared to previous systems, an impressive PLQY was attained by Lin *et al.*, and this greatly aided in enhancing the efficiency of energy transfer processes in diagnostics, especially for systems based on FRET.[97] Such recent advancements indicate ever-increasing sensitivity and signal enhancement in QD-based diagnostics as the system proves to be more efficient than conventional detection systems with respect to the limit of detection.

4.2 Luminescence and signal strength: unlocking new diagnostic capabilities

QDs can exhibit high quantum yields and photoluminescent properties and provide high signal strength in diagnostic tests. Thus, they are highly suitable for multiplexed biosensing because they enable the detection of multiple biomarkers in a single assay by being size-tunable. The emission peak of QDs is very precise and narrow and hence there is little interference from background noise, which adds to the magnitude of detection. Hu *et al.* revealed that single molecule detection with QDs had a detection limit of 10^{-12} M (picomolar) while an organic fluorophore had a detection limit of 10^{-9} M (nanomolar).[98] Rivoire *et al.* indicated that InGaAs QDs provided photoluminescence with a pulse width of approximately 200 ps and the coalescence on photonic crystal cavities boosted the outcoupling efficiency by a factor of forty to sixty.[99] On the other hand, Sfaelou *et al.* showed how the semiconductor QD-sensitized photoanodes could be constructed using the ZnS layer, which enhanced the photostability and PL properties of the system. The fluorescence stability and sensitivity of all these QD-based systems are superior to simple organic fluorophores in diagnostics.[100] The specificity combined with sample stability, as well as sensitivity to detect low-abundance analytes, effectively means that QD-based systems are highly reliable in clinical diagnostics.

In a study by Darwish *et al.*, they investigated the use of QD assemblies for multiplexed fluorescence detection in smartphone-based systems. Their system obtained color classification rates of 94% for the 10-color system and raised the potential of 14-color multiplexing.[101] This is a major advancement for the fabrication of inexpensive, transportable diagnostic tools that utilize QDs as effective sensors for detection. Regarding photoluminescence characteristics, Pham and Vo synthesized nitrogen-doped graphene quantum dots (NGQDs) and it was shown that their surface passivation with polyethylene glycol (PEG) enhanced the photoluminescence stability at various pH values.[102] This optimization is important for bringing the functionalities of these QDs closer to practical diagnostics, where the stability of the product under changing conditions is paramount. This work enriches the existing literature with new insights into how the surfaces of QDs can be tuned to preserve and enhance their diagnostic capabilities for biological imaging and environmental detection. This indicates that QDs are at the forefront of generating strong signals in diagnostic systems compared to previous generations of fluorescence systems because of their readily adjustable luminescence properties and capacity to modify surface chemistry.

4.3 Stability and photostability: ensuring long-term reliability

Another major aspect where QDs have an edge over ordinary fluorophores is their photostability. The output of real-time imaging and diagnostics using traditional organic dyes suffers from a disadvantage known as photobleaching, which makes their usage ineffective for long-term treatment.[5] In contrast, QDs remain fluorescent even under such conditions, which makes them ideal for constant tracking and monitoring over several days as may be required when diagnosing biomolecules in clinical practice.[5] For instance, using QDs, Gammon *et al.* reported that QDs maintained more than 90% of their fluorescence intensity even after 24 h continuous irradiation, while organic dyes underwent considerable photobleaching within minutes.[103] Furthermore, Baig *et al.* also found that PEG-modified QDs retained 85% of the original fluorescence efficiency after 30 days of storage, demonstrating stability under biological conditions.[104] In contrast, Rivoire *et al.* used photonic crystal cavities to improve the photoluminescence characteristics of QDs, with the properties being stable at room temperature. Duration-dependent PL analyses provided corresponding long-lived states that enabled accurate and sustained signal acquisition.[99] These results further support the significance of QDs in diagnostic stability, and that these particles are indeed superior to other probes.

In a study led by Hao *et al.*, the team was able to achieve the identification of single QDs as small as 5 nm using a unique combination of microtoroid optical resonators in photothermal microscopy.[105] Such photostability makes it possible to carry out continuous monitoring if it does not experience the destruction observed for other traditional organic dyes. Additionally, Kuo *et al.* synthesized nitrogen-doped graphene QDs and found that these QDs had excitation-wavelength-independent photoluminescence, which was advantageous for two-photon contrast imaged in biological systems.[106] The high level of biocompatibility of the presented dye derivatives and their photostability in various biological conditions also indicates the prospects for their prolonged application in diagnostics. These recent studies support the place of QDs as highly stable replacements for traditional fluorophores, especially in applications that require long-term readout, where photostability is imperative to sustain signal strength over time.

5. Pioneering applications in diagnostics: from theory to practice

QDNCs are changing the diagnostic field with their application, from early disease diagnosis to real-time monitoring. These advanced materials enhance the detection of biomarkers at the picomolar and femtomolar levels with unprecedented sensitivity compared to conventional methods. The multiplexing feature of QD allows for the simultaneous detection of various disease markers at a faster speed and shortens the time needed for analysis. Furthermore, QD-based imaging platforms offer improved photostability and brightness to ensure very accurate long-term monitoring of disease. Integration of QDNCs into point-of-care devices makes diagnostics portable, quick, and reachable for the benefit of real-time, point-of-care health monitoring, in both clinical and non-clinical settings.[107]

5.1 Redefining early detection: QDNCs in disease diagnostics

Nanocomposites containing QDs are gaining increased importance in early disease detection, especially for cancer and infectious diseases. Due to their high sensitivity and user information about the work tunable optical characteristics, it is possible to detect biomarkers at very low concentrations.[108] For example, in cancer diagnosis, Tiwari *et al.* observed that QD-based probes could specifically capture cancer-specific antigens at a concentration of 10^{-12} M (picomolar). This is significantly better than previous approaches, especially since the detection limits of most cancer biomarkers in blood plasma are at levels of about 10^{-9} M.[109] Although most of the circulating cancer markers can be detected at nanomolar concentrations, this holds mainly for late-stage or aggressive tumors. In early-stage tumors or minimal residual disease, the concentration of the marker can be much lower—usually of the order of picomolar or even attomolar levels. Prostate-specific antigen (PSA) and carcinoembryonic antigen (CEA), for example, may be present at concentrations of <1 pM during early tumorigenesis. In addition, the heterogeneity of tumors, blood dilution effects, and interference from other biomolecules can dampen signals at low concentrations. Thus, ultra-sensitive QD-based systems provide an advantage by enabling reproducible detection before the onset of clinical symptoms, which is of utmost significance for the success of therapeutic interventions and patient survival.[110,111]

In the context of infectious disease diagnostics, Nabil *et al.* showed that QDs could be utilized for bacterial pathogen identification with detection sensitivity of around 10^{-14} M for some bacterial proteins and this was significantly superior to existing immunoassaying techniques, which had lower detection limits of around 10^{-12} M.[112] Other nanomaterials like metal nanoparticles when combined with QDs improve the detection sensitivity of the method. For instance, Tiwari *et al.* reported enhanced signal amplification by 10- to 100-fold in QD–metal nanoparticle hybrids that enabled the early detection of low-abundance pathogens and cancer cells.[109]

Furthermore, Nabil *et al.* offered a lengthy discussion on QD bioimaging and therapy with special reference to the possibility of early cancer diagnosis. In their study, they were able to identify the techniques for preparation and characterization that enhanced QD applications in health care besides showing how challenges such as biocompatibility and toxicity were also handled.[112]

When comparing these studies, the differences in detection limits demonstrate the versatility of QDs across different fields of diagnostics. In cancer diagnostics, higher sensitivity is often required due to the low abundance of circulating tumor markers in early-stage disease, while infectious diseases may demand rapid, high-sensitivity detection for pathogens that quickly proliferate in the body. This capability of QD-based systems to operate across a broad spectrum of applications highlights their potential for revolutionizing early diagnostic methods.

5.2 Multiplexing with QDs: simultaneous biomarker detection

Another important feature introduced *via* QDNCs is the multiplex analysis, which means that several biomarkers can be identified at once. Multiplexed biosensors for cancer diagnostics using graphene and carbon quantum dots (GQDs and CQDs) were addressed by Jiale Huang. The study by Huang showed the multiplex detection of several cancer biomarkers with enhanced sensitivity and minimal cytotoxicity – a disadvantage that is common with most biosensors and stems from overlapping spectra.[113]

Hildebrandt *et al.* proved that QD–antibody conjugates allowed for the simultaneous detection of five different cancer biomarkers; each biomarker had a limit of detection of 10^{-15} M (femtomolar).[114] On the other hand, conventional organic dyes utilized in diagnostic assays suffer from photobleaching and spectral overlap that enables the detection of no more than one or two biomarkers at a time. In addition, these assays tend to have detection limits in the nanomolar range ($\sim 10^{-9}$ M), which is substantially less sensitive than QD-based systems.

To make this concept clearer, Guo *et al.* designed a multiplexed format that was capable of detecting six distinct viral antigens at concentrations as low as femtomolar levels in a single analysis while cutting the total analysis time by 80% compared to the time taken by sequential approaches.[115] Most of the benefit derived from this idea is not just the improved detection sensitivity by QDs but also the good efficiency in overall analyte analysis due to their ability to detect multiple biomarkers in a single analysis; these systems have been recognized to enhance diagnostic processes as seen in advanced systems used in clinical settings that require rapid decision making.

5.3 Advanced imaging platforms: harnessing QDs for precision diagnostics

Photostability, high quantum yield and brightness are some of the factors of QDs that make them ideal for incorporation into enhanced imaging systems. Such bioconjugates can selectively accumulate at tumor sites, achieving signal-to-background ratios significantly higher than those of conventional fluorophores. For instance, in the study by Zhao *et al.*, the QD-labeled probes provided single-cell labels in the imaging of metastatic cancer cells in mice and were about 5-fold brighter than traditional dyes.[116] The above increase in brightness is attributed to the size-dependent emission characteristics of QDs. The molar extinction coefficients of QDs can exceed $1\,000\,000$ $\mathrm{M^{-1}\ cm^{-1}}$, compared to $\sim 100\,000$ $\mathrm{M^{-1}\ cm^{-1}}$ for typical organic dyes.[9]

In addition, in seeking an *in vivo* imaging window, QDs can provide imaging at extended imaging duration compared to organic dyes. Bian *et al.* stated that QDs maintained 90% fluorescence intensity within 24 h of aerodynamic *in vivo* imaging while the common organic fluorophores lost more than 50% intensity within several hours. This long-term photostability is rather useful in experiments that call for several imaging sessions within several days or weeks.[117] In a related study, Rivoire *et al.* applied a QD-photonic crystal cavity to obtain improved tumor imaging with a 30% increase in signal intensity because of the enhanced light–matter interactions realized by photonic structures.[99] This enhancement is attributed to cavity-induced field confinement and resonant coupling, which increase emission efficiency. Consequently, the integration of QDs with other novel materials helps to enhance their image sensing capabilities even further. Nevertheless, using organic dyes in imaging suffers from poor photostability and rather short fluorescence half-lives, thereby limiting the imaging duration. Thus, QD-based imaging platforms offer higher sensitivity and stability, especially when sections that are long-term sections are used to track disease advancement.[118] Nabil *et al.* additionally examined its use in bioimaging and reported that it had a longer fluorescence lifetime and was resistant to photobleaching, which made it suitable for frequent imaging.[112]

These studies emphasize the fact that QDs are enhancing the imaging capabilities in diagnostic applications. The high brightness, operational stability, and wavelength versatility make them essential for precise diagnostic techniques, especially for cancer and other multisymptomatic diseases when precise and sensitive imaging is necessary. Detailed studies involving QDNCs for ultra-sensitive diagnostics can be seen in Tables 2 and 3. A summary of key original studies is presented in Table 2, outlining the main QD types, the nanocomposite materials used for diagnostics, the detection methods applied, and the achieved sensitivity levels, with emphasis on advanced techniques such as FRET-based fluorescence and near-infrared imaging.

Complementary Table 3 compares materials for QDs according to composition, range of emission, quantum yield, biocompatibility, and stability and offers material-level information that coordinates with the application-level insights found in Table 2. While diagnostic performance—detection limits and biosensing platforms—is the focus of Table 2, the influence of material properties on such outcomes is the focus of Table 3. Carbon QDs, for example, have high biocompatibility and stability and are well-suited to *in vivo* applications despite poorer quantum yields. The CdSe/ZnS QDs, however, are characterized by high quantum yields and the ability to vary the emission, which justifies frequent employment in highly sensitive diagnostic applications. The two tables together give the complete picture of how the selection of materials directly impacts diagnostic functionality and appropriateness.

5.4 Towards real-time diagnostics: from the laboratory to point-of-care devices

Due to the portability and high sensitivity of QDNCs, they have great potential as point-of-care (POC) diagnostic devices. Some of these gadgets can take diagnostic tests into non-hospital environments and offer results in real time; this is necessary where resources are limited. In a relatively short time of less than 30 min, Baig *et al.* also demonstrated the ability of a QD-based platform to detect multiple viral antigens with a femtomolar sensitivity of 10^{-14} M. This real-time capability gives one clear advantage during a pandemic when it is essential to quickly pinpoint the disease's presence and stop it from spreading.[10]

In another study, Omstead *et al.* wrote about a QD-based wearable biosensor that they developed to detect real-time glucose levels in patients with diabetes. The sensor based on QDs could measure glucose concentrations as low as 10^{-9} M, thus offering real-time feedback to patients on their condition and consequently, enable appropriate control of their disease. This system is much more advanced than a typical glucose monitoring system that involves sample collection at random times and which is of comparatively low sensitivity.[149] While commercially available devices like Dexcom can measure blood glucose levels with accuracy on the millimolar scale (*e.g.*, 3.9–10 mmol L^{-1} for diabetics), the nanomolar sensitivity of QD-based sensors is a technological asset rather than a clinical imperative. High sensitivity would be beneficial for non-invasive sensing strategies or for the detection of glucose present in the interstitial fluid, the concentration of which is lower and fluctuates.[150]

Furthermore, Liu *et al.* further discussed how QDs could be incorporated into optoelectronic devices for diagnostic applications in real-time and focusing on photostable devices at lower cost. PbSe QD photodetectors employing 5.8 nm particles demonstrated a broad spectral response from 400 nm to over 2000 nm, with peak responsivity at approximately 1550 nm, according to the study. Devices using 3.8 nm quantum dots displayed reduced responsivity and an absorption peak that was blue-shifted. The ideal device size, which provided good performance, was 5 μm × 10 μm. In addition to increasing the photocurrent and dark current, larger device areas also increased net photocurrent because of increased photocarrier generation. Higher laser power, however, resulted in lower conversion efficiency, and longer channel lengths slowed response times because of greater carrier recombination.[151]

The incorporation of QDNCs into portable POC systems provides ultra-sensitive, fast, transportable, easy-to-use, swift, real-time health monitoring in multiple environments. Since these QD-based devices can detect biomarkers at femtomolar levels in a matter of minutes and can be portable in their format, PDGQ platforms represent epoch-making tools in both decaying disease control and surge diagnosis. The top panels of Fig. 5 describe QD surface conjugations for coupling to biomolecules such as proteins and antibodies for site-directed delivery and imaging. The bottom panel describes the use of QDs in biosensing for miRNA detection, QD–DNA nanocomposites and hybridization to show applications in ultra-sensitive diagnostics.[152,153]

6. Overcoming barriers to clinical translation

Clinical integration of QD-based diagnostics is hindered by many challenges in terms of biocompatibility, scalability, and regulatory considerations. Though QDs possess excellent photoluminescent properties, their toxicity—particularly cadmium content—has become a major concern for widespread clinical applications.[156]

A study by Chahal *et al.* evaluated and compared the toxicity of nitrogen-doped carbon dots (NCDs), nitrogen/sulfur co-doped carbon dots (SCDs), and cadmium telluride quantum dots (CdTeQDs) in *Drosophila melanogaster*. NCDs and SCDs showed no observable developmental toxicity at concentrations ranging from 10 to 100 mg kg^{-1} of food, whereas CdTeQDs exhibited a clear toxic response with a calculated EC50 of 46 mg kg^{-1}. Increasing CdTeQD concentrations in food led to significant developmental delays, as shown by prolonged mean pupation and eclosion times. At sublethal concentrations (≤40 mg kg^{-1}), there were no statistically significant effects on reproductive output, larval crawling speed, or adult climbing ability across all nanoparticle treatment groups. All nanoparticle-treated groups, however, showed changes in gut

Table 2 Summary of key studies on quantum dot-infused nanocomposites for ultra-sensitive diagnostics

Quantum dot type	Nanocomposite material	Diagnostic application	Sample type	Detection method	Limit of detection (LOD)	Sensitivity achieved	Key findings	Ref.
CdSe/ZnS QDs	Protein-conjugated nanocomposite	Enzyme activity detection	*In vitro* (buffer solution)	FRET-based fluorescence	10 nM	Nanomolar (nM) levels	Demonstrated QD-based FRET for detecting enzyme activities	9
CdSe/ZnS QDs	PEGylated nanocomposite	Tumor imaging	*In vivo* (mouse models)	Near-infrared fluorescence imaging	Not specified (high specificity)	High specificity	Developed QD nanocomposites for targeted *in vivo* tumor imaging	8
CdTe QDs	Au nanoparticle composite	DNA detection	*In vitro* (synthetic samples)	Electrochemical sensing	0.5 fM	Femtomolar (fM) levels	Achieved ultra-sensitive DNA detection using QD–Au nanocomposites	119
CdSe/ZnS QDs	Graphene oxide composite	MicroRNA detection	Serum samples	Fluorescence quenching	10 pM	Picomolar (pM) levels	Developed QD–GO nanocomposite for sensitive microRNA detection	39
Carbon QDs	Polymer nanocomposite	Glucose sensing	Blood samples	Fluorescence sensing	2 μM	Micromolar (μM) levels	Created biocompatible carbon QD nanocomposites for glucose sensing	37
CdSe/ZnS QDs	Magnetic nanoparticle composite	Bacteria detection	Water samples	Magnetofluorescent imaging	Detection in 30 min	Rapid detection	Combined magnetic separation and fluorescence for bacterial detection	61
PbS QDs	Silica nanocomposite	Deep tissue imaging	*In vivo* (mouse models)	Near-infrared II imaging	Not specified (enhanced depth)	Enhanced imaging depth	Developed NIR-II QD nanocomposites for deep tissue imaging	120
Perovskite QDs	Polymer matrix nanocomposite	Heavy metal ion detection	Environmental samples	Fluorescence quenching	0.1 nM	Nanomolar (nM) levels	Used perovskite QD nanocomposites for sensitive metal ion detection	121
CdSeTe QDs	Hydrogel nanocomposite	Wound healing monitoring	*In vivo* (animal models)	Fluorescence imaging	Real-time monitoring	Real-time monitoring	Developed QD-infused hydrogels for monitoring wound healing processes	122
Carbon QDs	MOF nanocomposite	Cancer biomarker detection	Serum samples	Electrochemiluminescence	0.3 fM	Femtomolar (fM) levels	Created CQD–MOF composites for ultra-sensitive detection of cancer biomarker biomarkers	123
CdSe/ZnS QDs	DNA–Au nanocomposite	Pathogen detection	Clinical samples	FRET-based fluorescence	50 aM	Attomolar (aM) levels	Developed a QD–DNA–Au nanocomposite for ultra-sensitive pathogen detection	124
InP QDs	Silica-coated nanocomposite	Live cell imaging	Cell cultures	Confocal fluorescence microscopy	Not specified (high resolution)	High resolution	Synthesized biocompatible InP QD nanocomposites for long-term live cell imaging	125
Carbon QDs	MOF nanocomposite	Antibiotic detection	Water samples	Fluorescence sensing	5 nM	Nanomolar (nM) levels	Developed CQD–MOF composites for sensitive detection of antibiotics in water samples	126
CdS QDs	Polymer nanocomposite	Neurotransmitter detection	Cerebrospinal fluid samples	Electrochemical sensing	0.1 pM	Picomolar (pM) levels	Achieved highly sensitive detection of neurotransmitters using QD–polymer nanocomposites	127
Perovskite QDs	Graphene nanocomposite	Viral RNA detection	Clinical samples	Photoluminescence sensing	0.2 fM	Femtomolar (fM) levels	Developed perovskite QD–graphene nanocomposites for ultra-sensitive detection of viral RNA	128
Carbon nitride QDs (CNQDs)	CNQDs/polyaniline (PANI)	Non-invasive glucose monitoring	Biological samples	Electrochemical assay	0.1 μM	High	CNQDs/PANI nanocomposite exhibited outstanding electrochemical performance, suitable for non-invasive glucose monitoring.	129
Graphene QDs (GQDs)	GQDs with Au5Ir nanoparticles	Atrazine detection in environmental water	Environmental water samples	Electrochemical biosensor	0.02 nM	Very high	Au5Ir@GQD nanocomposite combined with DNA walker enabled highly sensitive and selective atrazine detection	130

Table 3 Comparative analysis of quantum dot materials for ultra-sensitive diagnostic applications

Quantum dot material	Core composition	Shell composition	Emission wavelength range (nm)	Quantum yield (%)	Surface functionalization	Biocompatibility	Stability	Diagnostic application	Ref.
CdSe/ZnS QDs	CdSe	ZnS	450–650	Up to 80%	PEGylation	Moderate	High	Cancer imaging	8
InP/ZnS QDs	InP	ZnS	500–700	Up to 60%	Carboxyl groups	Good	Moderate	Cellular imaging	131
Carbon QDs	Carbon	None	350–550	Up to 30%	Amino groups	Excellent	High	Glucose sensing	37
PbS QDs	PbS	None	1000–1400	Up to 50%	Thiol groups	Low	Moderate	Deep tissue imaging	132
Perovskite $CsPbBr_3$ QDs	$CsPbBr_3$	None	450–550	Up to 90%	Ligand exchange	Poor	Low	Metal ion detection	133
Silicon QDs	Silicon	None	400–700	Up to 20%	Hydroxyl groups	Excellent	High	Biosensing	134
CdTe QDs	CdTe	None	550–750	Up to 70%	Mercaptoacetic acid	Moderate	Moderate	DNA detection	135
ZnO QDs	ZnO	None	350–400	Up to 40%	Silanization	Good	High	Pathogen detection	136
$CuInS_2$ QDs	$CuInS_2$	ZnS	550–800	Up to 50%	Polymer coating	Good	Moderate	Fluorescence imaging	137
CdSeTe QDs	CdSeTe	ZnS	650–800	Up to 85%	Hydrogel embedding	Moderate	High	Wound healing monitoring	138
Graphene quantum dots	Graphene	None	400–600	Up to 25%	Nitrogen doping	Excellent	High	Neurotransmitter detection	139
Mn-doped ZnS QDs	ZnS	None	580	Up to 50%	Silica coating	Good	High	Multiplexed detection	140
Ag_2S QDs	Ag_2S	None	900–1300	Up to 15%	PEGylation	Good	Moderate	NIR-II imaging	59
Cd-free InAs QDs	InAs	ZnSe	800–1000	Up to 40%	Phospholipid coating	Moderate	Moderate	*In vivo* imaging	141
ZnSe QDs	ZnSe	ZnS	450–550	Up to 30%	Carboxyl groups	Good	High	Biosensing	142
Au nanocluster QDs	Gold	None	600–800	Up to 10%	BSA conjugation	Excellent	High	Cancer biomarker detection	143
CdS QDs	CdS	ZnS	500–600	Up to 65%	Polymer encapsulation	Moderate	Moderate	Environmental sensing	139
Nitrogen-doped carbon QDs	Carbon	None	450–550	Up to 35%	Amino groups	Excellent	High	Antibiotic detection	144
MoS_2 quantum dots	MoS_2	None	400–500	Up to 20%	PEGylation	Good	Moderate	Biosensing	145
Cd-free ZnTe QDs	ZnTe	ZnS	450–550	Up to 25%	Thiol groups	Good	Moderate	Cellular imaging	146
CdSeZnS/ZnS QDs	CdSeZnS	ZnS	500–650	Up to 98%	Polymer coating	Excellent	High	Cellular imaging, cancer detection	147
CdSe/ZnS QDs	CdSe	ZnS	600–650	Up to 75%	Carboxylation	Good	High	Detection of CP4-EPSPS protein in genetically modified crops	148

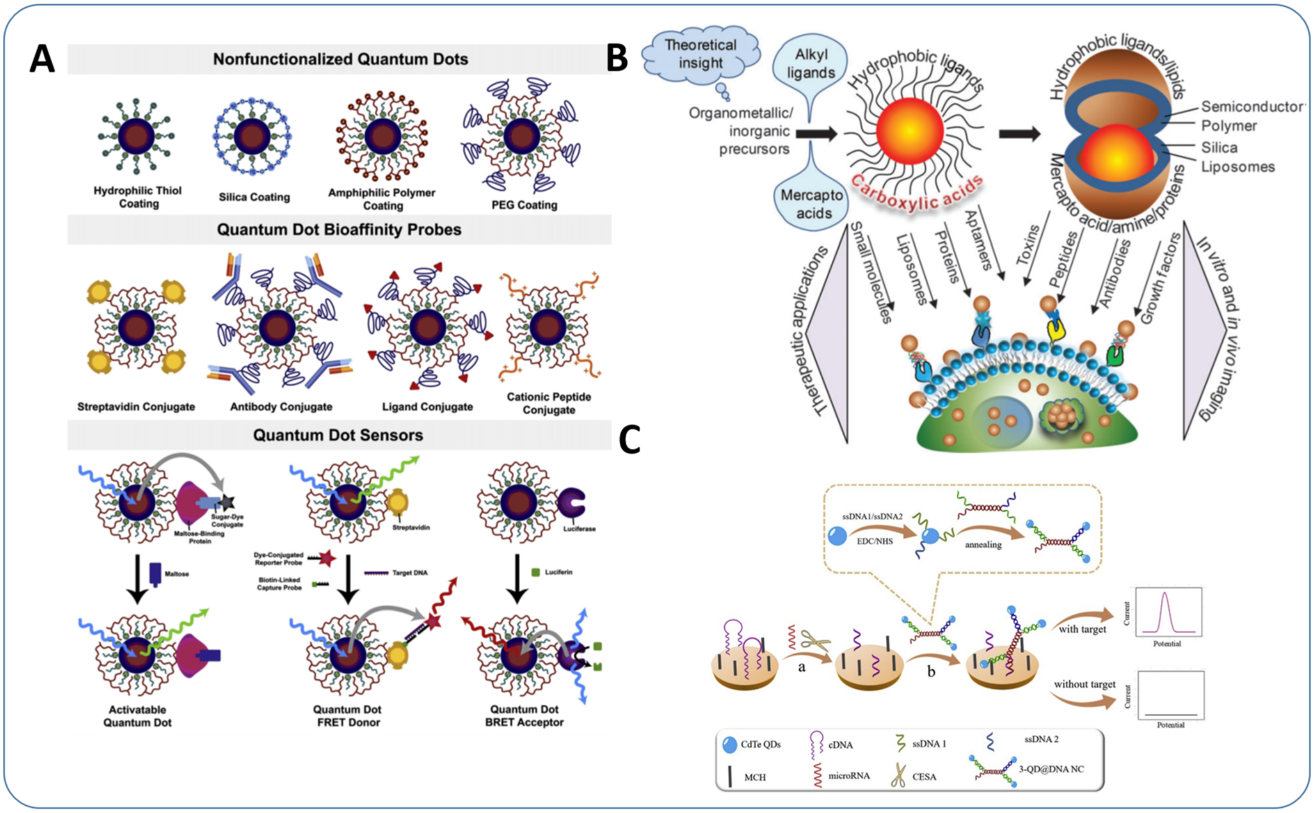

Fig. 5 (A) Quantum dot (QD) versatility: (1) surface coatings (*e.g.*, thiol, silica, PEG) enhance stability; (2) functionalization with biomolecules (*e.g.*, antibodies, peptides) enables targeted bioimaging; (3) QD sensors (*e.g.*, FRET, BRET) facilitate dynamic detection of biomolecules like DNA and proteins. This figure has been adapted from ref. 154 with permission from Springer, copyright 2024. (B) A schematic overview of different strategies for delivering QDs into cells. This figure has been adapted from ref. 155 with permission from Royal Society of Chemistry, copyright 2010. (C) Schematic illustrations of an ultrasensitive DNA biosensor designed for miRNA detection. This figure has been adapted from ref. 124 with permission from Elsevier, copyright 2019.

shape; NCD and SCD groups showed lengthened midguts, whereas CdTeQD-treated flies showed both lengthened and distended midguts. These findings quantitatively show that, within the studied exposure range, NCDs and SCDs are significantly less toxic than CdTeQDs, hence increasing their viability for use in biocompatible nanomaterial applications.[157]

Recently, surface engineering techniques such as PEGylation and the development of nontoxic variants like graphene quantum dots have improved their biocompatibility.[158] Large-scale production remains problematic, however, due to the difficulty in synthesizing QDs of high quality and homogeneity. Beyond that, QD-based diagnostics will require resolution of the regulatory and ethical challenges related to long-term safety evaluation and equity of access for safe and effective deployment in global healthcare.[159]

6.1 Biocompatibility and toxicity: ensuring safe integration into healthcare

Among the major issues in the clinical translation of QD-based diagnostics, biodistribution and toxicity remain major concerns. Although QDs have exceptional photochemical characteristics, most of these dots contain toxic ingredients that include cadmium, which has been shown to induce cytotoxicity, and oxidative stress, and potentially accumulate in living tissues in the long term. Despite the high number of reports in the literature on applications of QDs in imaging and therapy, their toxicity prevents them from being used in the clinic, and hence, more studies on their biodistribution and pharmacokinetic profiles in animal models are needed.[160] It should be noted that toxicity is only of significance for the *in vivo* applications of QDs, *i.e.*, their direct injection into the human body. In the case of diagnostic platforms *in vitro*, *i.e.*, the external application of QDs to clinical samples like blood or saliva, no health hazard is present for the patients. Appropriate handling and disposal procedures, however, are still required to prevent environmental exposure.[161]

New developments are constantly needed to enable the incorporation of QDs into healthcare services safely. A study conducted by Wagner *et al.* demonstrates through quantitative assessment that PEG surface engineering and other hydrophilic polymers decrease QD toxicity through improved colloidal stability while reducing biological interactions. The PEGylation process extended the QD blood survival time up to 3–4 min beyond that of uncoated QDs by improving blood stability. Accordingly, the liver take up time decreased from 2 to 6 min. These improvements were observed in mice cells.

This research with numerous QD preparations, including Qdot800 along with peptide-coated QDs and 5 nm InAs QDs demonstrated that PEGylation produced a systemic reduction of reticuloendothelial system (RES) take up and partially enabled renal clearance in different cases. Results indicate that PEG surface coatings are the ideal size to stop biological cell recognition processes thus enabling QDs to stay longer in circulation and minimize their removal by phagocytic cells, which enhances their medical application potential.[162] Also, new synthesis methods for QDs, which include microfluidic synthesis have been developed that offer better and ideal sized and shaped QDs for integration into biological systems.

Although it was possible to modify the surface of QDs or employ innovative synthesis methods, Vohra *et al.* found that there was still a long way to go to evaluate the potential toxicity of QDs *in vivo*. The invention of non-toxic or biodegradable QD options like GQDs and CQDs presents great potential for addressing this challenge. These QD variants exhibit relatively low toxicity but high luminescent efficiency so they are ideal for clinical applications.[163]

6.2 Scalability challenges: from the lab bench to global healthcare solutions

The transition of QDs from the laboratory to the global healthcare system is a significant challenge for clinical adoption. This problem of scalability is particularly critical for biomedical applications of quantum dot nanocomposites (QDNCs), for which functionalization, bioconjugation, or designs with multiple shells could be required, compared with the bulk production of ordinary QDs for electronics.[19] In this regard, a study demonstrated the continuous synthesis of cadmium sulfide (CdS) QDs using an impinging jet mixer, which enabled large-scale production without the need for heating, highlighting advancements in scalable production techniques.[164] The creation of stable colloidal QD inks has led to high-quality printed QD films through three-dimensional uniform printing, which has now reached 13.40% efficiency in 0.04 cm^2 cells and extended to 12.60 cm^2 modules with a 10% efficiency rating. Industry demonstrates its commitment to scaling amid the development of consistent methods and high-quality quantum dot production protocols for global healthcare system integration.[165] The requirement to synthesize QDs with desired optical and electronic properties calls for complex and very accurate large-scale production. As Vohra *et al.* point out, the ability to control the consistency, purity, and uniformity of each drug formulated in a batch and those produced in subsequent batches are fundamental challenges in both drug delivery and diagnosis.[163]

Other issues of concern in particular drug delivery systems include the inability for them to be scaled up. The use of specialized facilities and precise environmental controls during the manufacture of high-quality QDs increases their costs thereby limiting their use in general healthcare. Nevertheless, given the integration of microfluidics into the synthesis process, there is the potential for a breakthrough as it could reduce the cost per unit by enhancing the synergism effect on QD production. Research analyzed how microfluidic devices performed in synthesizing CdSe QDs relative to traditional bulk reactions. Research showed that prolonged residence of particles inside the microfluidic system caused a redshift in photoluminescence spectra, which reflected QD growth. The photoluminescence spectra peak wavelength transformed from its initial 520 nm position to 580 nm when the reaction time increased from 3 to 60 min. Measurement of the PL peak full width at half maximum indicated a better QD size distribution uniformity. The study established that CdSe QDs synthesized through microfluidics achieved higher absolute photoluminescence quantum yields than those made using conventional bulk reactors. The PLQY reached an initial value of 1.61% when the system maintained a residence time of 15 min but was reduced slightly to 1.50% after 60 min. More efficient PLQYs reached 0.98% but lowered to 0.82% while bulk reactions yielded PLQYs of 0.98% then 0.82% at 15 and 60 min time points.[166,167]

However, there are further scalability concerns related to the logistics of integrating QDs into existing healthcare infrastructure, in addition to manufacturing. As an example, QD-based diagnostics can be difficult to implement in areas with limited resources because of their sensitivity to environmental factors like light and temperature, which necessitate specific storage and handling methods. To guarantee that QD technologies can be applied worldwide, it is crucial to overcome these challenges.[168]

6.3 Regulatory and ethical considerations in nanomaterial-based diagnostics

The regulatory and ethical landscape for QD-based diagnostics is complex, continuously under development, and rather challenging.[169] The inclusion in QDs of potentially toxic cadmium raises great regulatory difficulties. Current guidelines from all regulatory bodies, such as the FDA and EMA, are focused on laying down the safety and efficacy considerations for nanomaterials, but the exact long-term effects of QDs in the human body are not yet fully known.[170] For instance, the FDA's guidance titled "Considering whether an FDA-regulated product involves the application of nanotechnology" outlines points to consider when evaluating products that involve nanotechnology. These considerations include whether a material or end product is engineered to have at least one dimension in the nanoscale range (approximately 1 nm to 100 nm) and whether it exhibits properties or phenomena attributable to its dimensions, even if these dimensions fall outside the nanoscale range, up to 1 μm (1000 nm).[171] In the context of oncology and other high-risk medical areas, one of the major bottlenecks in the clinical translation of these technologies, according to Koole and Souto, is the lack of standardized regulatory frameworks related to nanomaterials.[172,173]

There are also serious ethical issues involving the use of nanomaterials in healthcare, especially regarding patient safety, informed consent, and environmental impact. The possibility of the bioaccumulation and long-term toxicity of QDs raises serious questions about their sustainability and ethical use in diagnostics and therapies. In this direction, regulatory agencies are increasingly calling for comprehensive studies that examine not only the efficacy of QDs but also their long-term effects on human health and the environment.[174] Ethical issues also relate to the fair distribution of QD-based technologies. As with most medical technologies at the leading edge, there is the risk of exacerbating healthcare disparities if these innovations are not made available to lower-income or resource-limited populations. Ensuring QD-based diagnostics will be scalable, affordable, and environmentally safe will be part of their responsible deployment in global healthcare.

7. Future prospects: emerging frontiers in nanocomposite-based diagnostics

The future of diagnostics will be nanocomposite-based QD technologies that promise to advance personalized medicine, AI-driven platforms, and non-invasive diagnostic methodologies. Using the size-tunable optical properties of QDs, personalized diagnostic assays can be developed for individual patient profiles for diseases such as cancer and cardiovascular disorders. Integration of QDNCs with AI and machine learning provides for superior diagnosis because of real-time data analysis and predictive insights. Furthermore, the rising need for toxic-material-free QDs has introduced new development actions to fabricate alternative non-toxic emerging nanomaterials from carbon and graphene-based quantum dots; these present a new frontier for developing safer diagnostic tools that are "greener". Moreover, non-invasive diagnostic systems using QDs will have an immediate impact on healthcare, mainly due to the painless diagnosis of diseases using real-time information obtained from the saliva, sweat, or urine for diagnostic purposes, while also ensuring far greater speed and friendliness for patients.[175] For non-invasive, real-time glucose monitoring, wearable sweat biosensors with nitrogen-doped graphene QDs (N-GQDs) have been created. These sensors improve patient comfort and compliance by offering dependable long-term monitoring.[176]

7.1 Personalized medicine: tailoring diagnostics with QDs

Nanocomposites embedded with QDs have emerged as leading contenders in personalized and precision medicine. The adjustable optical properties of their size enable dual biomarker detection, which improves medical diagnosis when screening for cancer and heart disease conditions. The detection sensitivity of carbon quantum dots (CQDs) reaches 190 pM to detect lead ions (Pb^{2+}). QDs form an essential component of theranostic applications since they unite diagnostic imaging with targeted therapy. Scientists have produced hybrid nanoparticles, which unite QDs with mesoporous silica and gold nanoparticles, to deliver drugs specifically to colorectal cancer patients through platforms that enable the controlled release of epirubicin during acidic tumor conditions.[177] The uniquely controlled optical properties of these materials would enable real-time diagnostics for personalized healthcare. Their ability to target specific molecular markers with precision makes them ideal for personalized diagnostic approaches in cancers, cardiovascular, and metabolic diseases.[178]

Besides bioimaging, QDs have started to be included in theranostics, where diagnostics and treatment converge. Dhas *et al.* examined organic QDs acting as nanoplatforms for cancer theranostics, enabling the detection of cancer markers while also delivering targeted therapy tailored to individual patients.[179] Such integration of diagnosis and treatment will see QD-based diagnostics find a permanent place in future personalized healthcare systems.

7.2 AI and machine learning integration: towards intelligent diagnostic platforms

Intelligent diagnostic platforms gain an additional advancement through the integration of QDNC diagnostics with AI and machine learning technology. AI demonstrates excellent capability for processing large QD-based biosensor datasets while simultaneously identifying patterns that humans may not detect. AI-based biosensors achieve sophisticated accuracy rates of 98.1% during the identification of clean dopamine alongside contaminated dopamine molecules, therefore demonstrating value in clinical real-time screening applications.[180] By applying AI, diagnostic platforms can make predictive progress in terms of learning from patient data to give more precise diagnostic results.[181] Phafat and Bhattacharya expect QDNCs, when combined with AI, to improve the accuracy of real-time diagnostics. The AI-driven platforms could interpret the fluorescence signals of QDs for early-stage disease diagnosis and provide personalized treatment options.[182] Besides, AI could enable optimizing QDs in biosensing by real-time adjustment of parameters to improve sensitivity and specificity. Tiwari *et al.* also pointed out that combining QDs with neural networks would result in the fastest diagnosis and radically change the future of healthcare toward enhanced patient outcomes.[109]

7.3 Beyond QDs: what is next for nanomaterial-based diagnostics?

Nonetheless, the efficacy of QDs has yet to diminish due to emerging materials that may enhance future diagnostic advancements. CQDs and GQDs have attracted attention for their non-toxicity, good fluorescence properties, and compatibility with bio-systems. Huang points out that GQDs are a strong candidate to substitute conventional semiconductor QDs, particularly in cancer diagnosis.[183]

Bioinspired quantum dots (BQDs) synthesized using green methods have started to gain significance together with CQDs and GQDs. These BQDs demonstrate improved solubility in water solutions along with very low toxicity levels and straightforward biofunctionalization properties that make them strong prospects for biomedical applications. In addition, safer and more effective diagnostic tools develop through their cancer-targeting selectivity.[184] Singh *et al.* discuss bioinspired QDs synthesized through green methods that display great biocompatibility. These materials might set a safer and greener premise for diagnostics tools, particularly for those commencing at longer timescales. This may further contribute to the search for next-generation materials that combine high performance with minimal toxicity, hence expanding the current conceptual limits of nanoparticle diagnostics.[113]

7.4 Non-invasive diagnostic platforms: the next frontier

With the advent of QDNCs, non-invasive diagnostic methods are about to undergo a paradigm shift, providing patients with more accessible, less intrusive, and quicker ways to identify diseases. Biopsies and blood draws are examples of invasive procedures that are commonly used in traditional diagnostic methods. But by identifying illness indicators in saliva, urine, or sweat, QD-based devices may one day enable non-invasive diagnostics.[185]

Luo *et al.* demonstrated that QDs combined with microfluidic devices provided non-invasive, real-time cytological diagnostics through *in vivo* fluorescence imaging.[186] Such platforms could be highly useful for the detection of cancers where early diagnosis is critical. Wang *et al.* reported how QDNCs might be adapted for the sensitive detection of environmental pollutants, further underlining their versatility in non-invasive sensing technologies.[187]

Considering the background, real-time monitoring and early detection capability, coupled with the convenience of non-invasive sampling methods, provide great potential for this field in the revolution of healthcare toward accessible and patient-friendly diagnostics.

Recent advances in wearable electrochemical biosensors, particularly those from Gao *et al.*, have demonstrated excellent potential for continuous, real-time monitoring of markers such as glucose (10–2000 μM), lactate (0.1–30 mM), and sodium (10–100 mM) on non-invasive sweat and interstitial fluid-based platforms.[188] While these systems have been characterized with high integrability of wireless technology and usability, QDNC-based biosensors also possess detection sensitivity, multiplexing, and photostability advantages. QDNCs can detect samples at attomolar to picomolar levels with amplified signals of FRET-based and narrow-band emitting spectra, beyond conventional wearable device detection limits.[19] Integrating QDNCs with flexible substrates can potentially make hybrid systems possible that combine the ultra-sensitivity of nanomaterials with the wearability of wearable formats for future diagnosis.

8. The transformative potential of QDNCs

QDNCs serve as critical elements for medical diagnostics advancement by enabling advanced sensitiveness alongside multiplexing functions and therapeutic diagnostics applications. Biomarker detection at the femtomolar scale, artificial intelligence integration for time-sensitive diagnostics and the advancement of non-invasive diagnostic technologies form parts of this research field. Quantum dot-based fluorescent immunosensors were developed to detect CA19-9 in human serum while delivering sensitivities below 1.66×10^{-4} to 5.45×10^{-4} U mL^{-1} and 0.01–501.87 U mL^{-1} linear detection ranges. A testing procedure needs just 200 μL of sample combined with onefold filtration followed by fast results delivery within 15 min, thus enabling economical point-of-care diagnosis.[189] The basic quantum dot structure faces limitations in compatibility with biological systems and large-scale manufacturing but engineering the surface through ligand exchange together with heterostructure design has substantially improved both properties. Emerging cadmium-free quantum dot technology combines artificial carbon dots with artificial graphene dots that have established low toxicity properties and sustainable photoluminescence capabilities and green synthesis capabilities. These materials find perfect applications in multiplexed diagnostic systems and wearable biosensors because of their specific properties. The developments enable QDs to serve as enabling components for next-generation real-time personalized diagnostics that deliver high spatiotemporal precision through AI optimization and microfluidic production methods.[190]

8.1 Key milestones and innovations

While QDNCs have shown remarkable potential in enabling breakthrough advancements in biomedical diagnostics, one area in particular that has shown tremendous promise is the early detection of cancers. QDs, due to their high resolution imaging and exceptional photostability, are suitable due to their size-dependent fluorescence for high resolution and prolonged tracking at the cellular level. Specifically, multiplexed immunoassays using antibody conjugated QDs have reportedly been used to detect 14 out of 16 pancreatic tumor markers at concentrations as low as 1.66×10^{-4} U mL^{-1}, orders of magnitude lower than the clinical threshold for pancreatic cancer. Also, they give results within 15 min with a small amount of sample, which makes them a perfect point of care assay. In addition, QD-based platforms enable multiplexed detection of multiple biomarkers with femtomolar sensitivity, representing an important advance over conventional single target diagnostics.[191]

Another important milestone is the utilization of QDs in theranostic applications, which involve both diagnosis and targeted therapy. The synergistic integration of QDs with ML and AI has been identified as a growing advancement that can enhance real-time diagnostic decision-making and expedite the development of individualized treatment plans.[192] Additionally, QDNCs hold promise in areas such as non-invasive diagnostics, revolutionizing approaches for disease diagnosis without the need for cellular intervention.[186]

8.2 Addressing the gaps: future challenges and opportunities

Despite these results, several challenges need to be overcome to fully exploit QDNCs' capability for use in clinical applications. Apart from biocompatibility and toxicity associated with nanotechnology used for tissue engineering, it is a challenge. Many QDs contain toxic elements, especially cadmium, the bioactivity of which is negative and therefore they are not suitable for use on humans. While graphene and carbon QDs have shown some improvement in this area recently, further research is needed to ascertain their *in vivo* toxicity.[193] For example, a published study by Kuznietsova used CQDs with varying surface chemistries. 5 mg kg^{-1} CQDs were subcutaneously injected into mice daily for 14 days. Results indicated that some of the CQDs, most notably those containing oxygen and nitrogen containing functional groups, could cause lethality rates up to 50% and showed toxicity signs such as liver blood supply defects and renal tubule injury. These results highlight that surface chemistry is a critical determinant of CQD biocompatibility and emphasize the paramount importance of careful design and detailed evaluation for biomedical applications.[194] Secondly, scalability is a critical issue impacting the efficacy of an organization's ERP system. Though much work focused on QD-based diagnostics takes place in the laboratory setting, high production costs and the lack of uniformity in synthesis on a large scale have prevented the transition of these technologies into global healthcare practice. There are legal and ethical constraints to the application of nanomaterials in the human healthcare arena that will have to be overcome before nanotechnologies can be used in clinical settings.[195,196] In addition, the recent emergence of QD diagnostics together with AI and machine learning cloud networks presents challenges in terms of data management and real time interpretation. Though there has been a lot of progress, only specific and adaptable AI algorithms will enable biological signals to be properly processed and tap into the full potential of QD biosensors for clinical diagnostics.[197]

8.3 Charting a course for the future of medical diagnostics

The future of medical diagnostics will undergo a transformation as advancements are made in QDNCs. Once toxicity concerns are addressed and strategies for large-scale production are refined, QDs have the potential to become a commonplace element in diagnostic portfolios, offering exceptional sensitivity and selectivity. Their ability to operate in multiplexed platforms will further enhance precision diagnostics by enabling the detection of multiple disease signatures, particularly significant in diseases with diverse molecular profiles such as cancer and various infectious diseases.[198]

In the future, QD-based biosensors combined with wearable and non-invasive devices will contribute to the broader adoption of diagnostics among the general population, providing more individuals with the tools to manage their health. Future diagnostics utilizing QDNCs may be more precise, targeted, and capable of real-time operation due to their integration with AI systems.[199]

9. Conclusion

Diagnostic medicine has been highlighted as one of the recent groundbreaking achievements in the integration of QDs into nanocomposites. These newly engineered nanocomposites infused with QDs ensure unparallelled sensitivity and specificity, enabling the detection of biomarkers at femtomolar levels within intricate biological environments. Tunable optical properties, photostability, and enhanced biocompatibility are key features of these materials that can advance diagnostic fields such as cancer, viral diseases, and real-time health testing. Advanced QDNCs, including core–shell and hybrid structures, have been developed to tackle significant challenges in terms of stability, toxicity, and scalability. Green synthesis methods enhance their environmental friendliness and clinical suitability. Integrating these materials with artificial intelligence and machine learning will pave the way for the creation of intelligent diagnostic platforms offering real-time analysis and personalized medicine solutions. Despite present-day challenges such as regulatory obstacles and limitations in large-scale production, QDNCs represent a significant advancement in materials science and healthcare. If QD-based technologies can overcome these barriers, they have the potential to establish a new standard in precision diagnostics, leading to earlier disease detection, improved patient outcomes, and a transformation in global healthcare systems.

Author contributions

Z. A.: conceptualized the review, conducted the literature search, and contributed to manuscript drafting and revision. P. T.: performed critical analysis of the literature, organized the manuscript structure, and contributed to content refinement. K. A.: reviewed and synthesized key findings from the literature, assisted in methodology evaluation, and provided feedback on manuscript coherence. P. G.: designed and prepared figures and tables, handled the graphical representation of concepts, and contributed to the manuscript's revisions. M. R. F. and Y. S. H: supervised the project, provided overall guidance on the manuscript, secured funding, and performed the final manuscript review and approval. W. C. C.: reviewed and offered critical insights into the diagnostic applications of nanocomposites, ensured scientific accuracy, and approved the final version of the manuscript for submission.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Abbreviations

AI	Artificial intelligence
BRET	Bioluminescence resonance energy transfer
CCD	Charge-coupled device
CdSe	Cadmium selenide
CD-PNC	Carbon dot-based polymer nanocomposites
COVID	Coronavirus disease
CQD	Carbon quantum dot

CRISPR	Clustered regularly interspaced short palindromic repeats
CS-SP	Core–shell nanoparticle
DNA	Deoxyribonucleic acid
DTAB	Dodecyltrimethylammonium bromide
EMA	European Medicines Agency
FDA	Food and Drug Administration
FRET	Förster resonance energy transfer
GQD	Graphene quantum dot
InP	Indium phosphide
M	Nanomolar
MEF	Metal-enhanced fluorescence
ML	Machine learning
MNP	Magnetic nanoparticle
NGQD	Nitrogen-doped graphene quantum dot
NIR	Near-infrared
PEG	Polyethylene glycol
PLQY	Photoluminescence quantum yield
pM	Picomolar
POC	Point-of-care
PSA	Prostate-specific antigen
PVP	Polyvinylpyrrolidone
QD	Quantum dot
QDNC	Quantum dot-infused nanocomposite
TEM	Transmission electron microscopy

Data availability

Data will be made available in a repository on acceptance.

Acknowledgements

This work was supported by Inha University Research grant.

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