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# Recent Advances in Quantum Dots-Based Sensors for the Detection of Tuberculosis: A Review

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## ABSTRACT

Tuberculosis (TB) remains a major global infectious disease, especially in developing countries where diagnostic limitations contribute to late or incorrect detection and continued transmission. Conventional diagnostic methods, such as sputum smear microscopy and culture-based assays, suffer from low sensitivity, limited specificity, and long processing times, underscoring the need for rapid, accurate, and affordable alternatives. Biosensors have emerged as promising tools for point-of-care (POC) TB detection, employing biorecognition elements to identify *Mycobacterium tuberculosis* (Mtb) biomarkers with high sensitivity. Recent advances incorporate nanoparticles (NPs)—particularly quantum dots (QDs)—to enhance biosensor performance through strong signal amplification and ultrasensitive detection of TB-specific targets. Owing to their high photostability, broad absorption spectra, and size-tunable fluorescence, QDs are well suited for fluorescence-based biosensors, POC devices, and molecular imaging. QD-based platforms also show potential cost-effectiveness in portable electrochemical and colorimetric assays for resource-limited settings. However, commercialization remains limited due to concerns regarding toxicity, biocompatibility, and the complexity and cost of QD synthesis. Current research focuses on developing safer QDs, improving surface modification strategies, and advancing portable detection technologies. Overcoming these challenges through material innovation, reduced fabrication costs, and extensive clinical validation may enable QD-based biosensors to become practical POC diagnostic tools for TB and other infectious diseases.

## 1 | Introduction

Tuberculosis (TB) is a persistent and highly infectious pulmonary disease caused by a bacterium called *Mycobacterium tuberculosis* (Mtb) [1]. Mtb is transmitted primarily through aerosolized droplets generated by infected individuals via coughing, sneezing, or speaking. These droplets can remain suspended for hours, especially in poorly ventilated spaces, allowing the bacteria to be

**Abbreviations:** MPA, 3-mercaptopropionic acid; AFB, acid fast bacilli; Cd, cadmium; CdSe, cadmium selenide; CdTe, cadmium telluride; CNDs, carbon nanodots; CNTs, carbon nanotubes; CQDs, carbon-based QDs; CPDs, carbonized polymeric dots; CVD, chemical vapor deposition; CHA, combined with a catalytic hairpin assembly; CT, computed tomography; ELB, electron beam lithography; ERHS, European Restriction of Hazardous Substances; XDR, extensively drug-resistant; FETs, field-effect transistors; FRET, fluorescence resonance energy transfer; GaP, gallium phosphide; GQDs, graphene QDs; $H_2O_2$, hydrogen peroxide; InAs, indium arsenide; InP, indium phosphide; L-cysteine-InTeSe, indium telluriselenide; IFN-γ, interferon-gamma; IGRAs, interferon-gamma release assays; KNN, *K*-Nearest Neighbors; LTBI, latent TB infection; LFA's, lateral flow assays; Pb, lead; PbSe, lead selenide; PbS, lead sulfide; LARP, ligand-assisted reprecipitation; LODs, limits of detection; LAM, lipoarabinomannan; LAMP, loop-mediated isothermal amplification; MN, methyl nicotinate; MBE, molecular beam epitaxy; MDR, multidrug-resistant; Mtb, *Mycobacterium tuberculosis*; NPs, nanoparticles; NIR, near-infrared; NAATs, nucleic acid amplification tests; PNA, peptide nucleic acid; PQDs, perovskite QDs; PVD, physical vapor deposition; PCR, polymerase chain reaction; PCA, principal component analysis; QDs, quantum dots; RIE, reactive-ion etching; RPA, recombinase polymerase amplification; SQDs, semiconductor QDs; Ag, silver; SWCNT, single-walled carbon nanotube; TPP, target product profiles; TMA, thiomalic acid; SnS, tin sulfide; Sn–Te–Se, tin telluride selenide; TST, tuberculin skin test; TB, tuberculosis; VOCs, volatile organic compounds; WHO, World Health Organization.

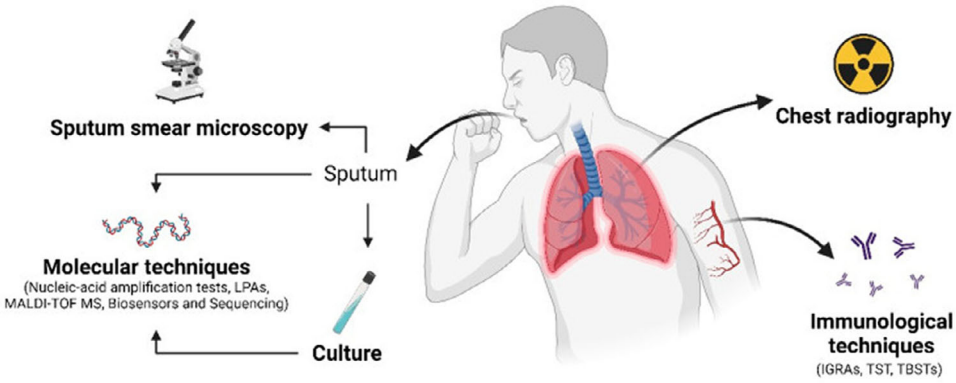


**FIGURE 1** | This figure illustrates the conventional methods for TB diagnosis. The microscopy detects acid-fast bacilli (AFB) in sputum; imaging chest radiography is used for infiltrates, cavities, and effusions; and molecular NAATs, LAMP, biosensors, and sequencing identify Mtb complex genetic material. Culture involves growing mycobacteria for identification and drug susceptibility. Immunological techniques: IGRAs and TST are for immune response. IGRAs, interferon-gamma release assays; TST, tuberculin skin test. *Source:* Original figure by [21], licensed under CC BY, from [https://creativecommons.org/licenses/by/4.0/deed.en].

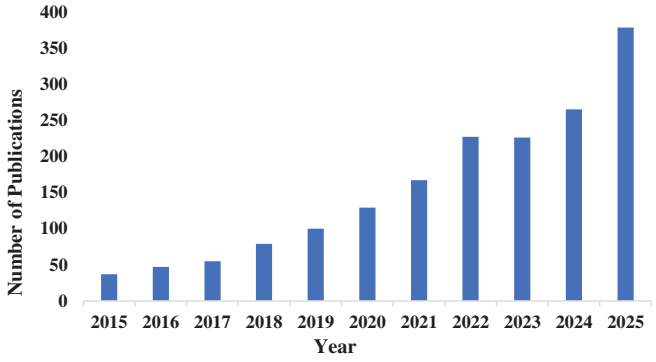


**FIGURE 2** | Number of publications on QD-based biosensors for TB detection from 2015 to 2025. *Source:* Data from the Scopus.

inhaled deep into the lungs, where Mtb can establish infection [2–5]. It is estimated that in 2024, 1.23 million people died from TB; among them, 150,000 were HIV positive. Moreover, TB is the world leading cause of death among the top 10 causes of death globally, and it was also the leading cause of death to people with HIV, and a major cause of deaths related to antimicrobial resistance, according to the World Health Organization (WHO) [6, 7]. Early and accurate TB detection is critical for rapid treatment, which not only improves individual patient outcomes but also prevents further transmission within communities [8].

Current techniques for TB detection include smear microscopy, culture-based methods, and nucleic acid amplification tests (NAATs) such as polymerase chain reaction (PCR) and GeneXpert (Figure 1) [9]. Culture methods remain the gold standard due to their high specificity, and they allow drug susceptibility testing; however, they are time-consuming, often require 2–8 weeks for results, also require sophisticated laboratory infrastructure, and skilled personnel [9, 10]. Molecular diagnostics, such as PCR and loop-mediated isothermal amplification (LAMP), offer improved sensitivity and rapid detection; however, they still depend on expensive instrumentation and skilled personnel, limiting their applicability in resource-constrained settings [11]. Immunological assays, including the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs), are valuable for identifying latent TB, but they cannot reliably differentiate active disease from latent infection [12]. Furthermore, individuals co-infected with HIV often struggle to provide high-quality sputum samples, further complicating TB diagnosis and necessitating more advanced molecular and immunological approaches [13, 14]. These limitations contribute to delayed diagnosis, ongoing transmission, and the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB strains, highlighting the urgent need for innovative, rapid, and cost-effective TB diagnostic solutions [15, 175]. To address these challenges, biosensors have emerged as innovative tools that use biological recognition elements and transducers to rapidly detect TB biomarkers with high accuracy [16]. These devices offer faster, more affordable, and portable solutions compared to conventional techniques and can be designed for on-site use without complicated infrastructure, which is critical for early diagnosis and controlling the disease spread [17–19]. Additionally, biosensors can be integrated with nanomaterials to enhance sensitivity and detect very low concentrations of TB biomarkers, making them highly efficient compared to conventional methods [20].

The integration of nanomaterials into biosensors for TB detection has significantly improved their analytical performance, particularly in terms of sensitivity, specificity, and response time [16]. Nanomaterials are particles engineered at the nanoscale (1–100 nm) and exhibit unique physical and chemical properties, such as high surface-to-volume ratio, excellent electrical conductivity, and catalytic activity, which make them ideal for signal amplification and biomolecule immobilization [22, 23]. These properties allow interactions with biomolecules, making them suitable for biological applications such as drug delivery, imaging, and biosensing, among others [24, 25]. Various nanostructures, including gold nanoparticles (NPs), magnetic NPs, carbon nanotubes (CNTs), and quantum dots (QDs), among others, have been explored for biological applications, including TB detection and diagnostics [24, 26]. Among these nanomaterials, QDs stand out for their exceptional optical properties, including high brightness, tunable emission wavelengths, and photostability [27]. These features make QDs highly promising for TB biosensing, offering sensitive and rapid detection through fluorescence-based assays. Figure 2 shows the exponential growth

of QD-based biosensors searches for TB detection according to Scopus from 2015 to 2025, indicating a rising interest and potential for clinical use of QDs, and how nanotechnology is contributing fight TB in the research field. This review examines recent progress in QD-based sensors for TB detection, emphasizing their diagnostic potential through literature analysis. It addresses current challenges such as toxicity, stability, and cost, while exploring future directions for clinical validation, eco-friendly synthesis, and the development of portable, real-time diagnostic systems.

## 2 | Nanotechnology: QDs

QDs are nanocrystals with dimensions generally below 10 nm and are typically spherical or quasi-spherical in shape [28] and exhibit unique optical and electronic properties due to quantum confinement effects [29, 30]. They are extremely small, with dimensions less than twice their exciton Bohr radius [31]. This size restriction confines electrons and holes within the structure, causing their energy levels to become quantized, meaning they exist as discrete states rather than a continuous spectrum [32]. They also have a size-tunable fluorescence, which allows for precise tuning of their optical properties, and are resistance to photobleaching compared to conventional organic dyes. They also have a broad emission and absorption spectra, meaning that they can be designed to operate across a wide range of the electromagnetic spectrum [33, 34]. QDs can be classified into three main categories in terms of material composition: **semiconductor QDs (SQDs)**, perovskite QDs (PQDs), and **carbon-based QDs (CQDs)**. SQDs are the most traditional type of QDs, made from semiconductor materials composed of elements from Groups III–V, II–VI, or IV–VI of the periodic table [35]. These are crystalline NPs with distinct crystal structures [28]. They can be made from a single semiconductor material (e.g., cadmium selenide [CdSe], CdS, indium phosphide [InP]), and the core materials can be shelled (single or multi-shell) with another semiconductor material to improve stability and optical properties (e.g., CdS/ZnS, InP/ZnSe). Another form is the alloyed, where the QD is composed of mixed elements to enhance optical properties (e.g., CdSeS) [36]. These QDs are widely used in optoelectronics, solar cells, LEDs, and biomedical imaging because of their high brightness, narrow emission spectra, and size-dependent optical properties. However, traditional **SQDs** often contain heavy metals like cadmium (Cd) or lead (Pb), raising environmental and toxicity concerns, which has driven research toward safer alternatives [37].

PQDs are a unique and recent class of QDs made from organic–inorganic hybrid or all-inorganic perovskite materials (e.g., CdPbBr3). They have the general formula $ABX_3$, where A is a monovalent cation (e.g., methylammonium and cesium), B is a divalent metal cation (commonly Pb or tin), and X is a halide anion [38, 39, 40]. They are mostly crystalline in specific lattice structures like cubic, tetragonal, or orthorhombic. These materials can be engineered into core, core–shell, and multi-shell nanostructures as well [41]. PQDs are highly tunable in terms of bandgap and emission wavelength simply by adjusting their composition and size, making them ideal for applications in light-emitting devices, solar cells, and biomedical environments [38, 42]. They have superior optical performance, brightness, and tunability compared to SQDs mainly because of their intrinsic material properties and crystal structure [43]. However, PQDs face challenges, such as instability in moisture and oxygen and potential toxicity due to Pb content, which researchers are addressing through surface passivation and Pb-free alternatives [44]. On the other hand, CQDs are made from carbon-based precursors, such as biomass, polymers, or other organic molecules, such as graphene QDs (GQDs), carbon nanodots (CNDs), and carbonized polymeric dots (CPDs). CQDs exhibit low toxicity, strong photoluminescence due to surface states rather than quantum confinement alone, high biocompatibility, and they are often considered more eco-friendly and less toxic than many SQDs and PQDs [45, 46]. Many CQDs have a core or a core–shell-like structure, where the core is a carbon network and the shell is composed of various functional groups (like hydroxyl, carboxyl, and amine groups) attached to the surface [47]. A comparative analysis of the properties of these QDs is presented in Table 1.

### 2.1 | Synthesis and Characterization Method of QDs

The synthesis of QDs is categorized into top-down and bottom-up approaches as shown in Figure 4. Top-down approaches involve breaking down bulk materials into nanoscale structures, whereas bottom-up synthesis builds nanostructures from atomic or molecular precursors through controlled nucleation and growth [48]. SQDs are primarily synthesized through bottom-up approaches, with colloidal methods such as hot-injection being the most widely used methods, as it creates high-quality, monodisperse NPs by controlling nucleation and growth [49]. This technique involves injecting precursors into heated solvents containing surfactants. However, the use of heavy metals, like Cd and Pb, raises toxicity concerns, requires complex purification steps, and poses environmental risks [37]. To address these issues, researchers increasingly employ nontoxic precursors derived from natural sources and safer solvents such as water and ethanol [50]. Wet chemical techniques, including sol–gel and microemulsion, provide control over QD size, shape, and composition by adjusting reaction parameters [51]. Despite these advantages, they can suffer from drawbacks such as broad size distribution, structural defects, and lower yields [50]. Vapor-phase methods, such as molecular beam epitaxy (MBE), physical vapor deposition (PVD), and chemical vapor deposition (CVD), enable the precise control and modification of QDs growth via vapor-phase deposition [52]. These processes promote self-assembly of QDs on substrates without predefined patterning, with growth modes influenced by factors like surface energy and lattice mismatch [53]. The top-down synthesis involves reducing bulk semiconductor materials, using techniques such as electron beam lithography (EBL), reactive-ion etching (RIE), and wet chemical etching [54]. These methods offer precise control over QD size, shape, and arrangement but may introduce impurities and structural imperfections. Among these, etching processes, like RIE, remain well-established for top-down QD fabrication [48].

Top-down methods for PQD synthesis are extremely rare because perovskite materials are soft and structurally fragile compared to traditional semiconductors [42]. Most PQDs are made via bottom-up chemical routes for better size control and stability [55]. The bottom-up synthesis methods for PQDs also include

**TABLE 1** | Three composition quantum dot (QD) types of classification.

| Property | Semiconductor | Perovskites | Carbon dots |
|---|---|---|---|
| Composition | Inorganic semiconductors | Organic–inorganic hybrid or all-inorganic | Carbon-based materials |
| Shape | Spherical | Spherical, cubic, tetragonal, or orthorhombic-$ABX_3$ | Spherical or diamond like |
| Size (nm) | 2–10 | 5–20 | <10 |
| Fluorescence tuning | Size-dependent | Composition and size tuning | Surface dependent |
| Toxicity | Potentially toxic (heavy metals) | Moderate (Pb content) | Low toxicity |
| Biocompatibility | Moderate to low | Moderate (improving with Pb-free PQDs) | High |
| Synthesis complexity | High | Moderate | Low |
| Cost | High | Moderate | Low |
| Environmental impact | Least eco-friendly | Moderate | Eco-friendly |
| Applications | Electronics, photovoltaics, biomedical imaging, quantum computing | Optoelectronics, sensing, bioimaging, technology display | Biosensing, imaging, drug delivery, photocatalysis |

Abbreviation: PQDs, perovskite quantum dots.

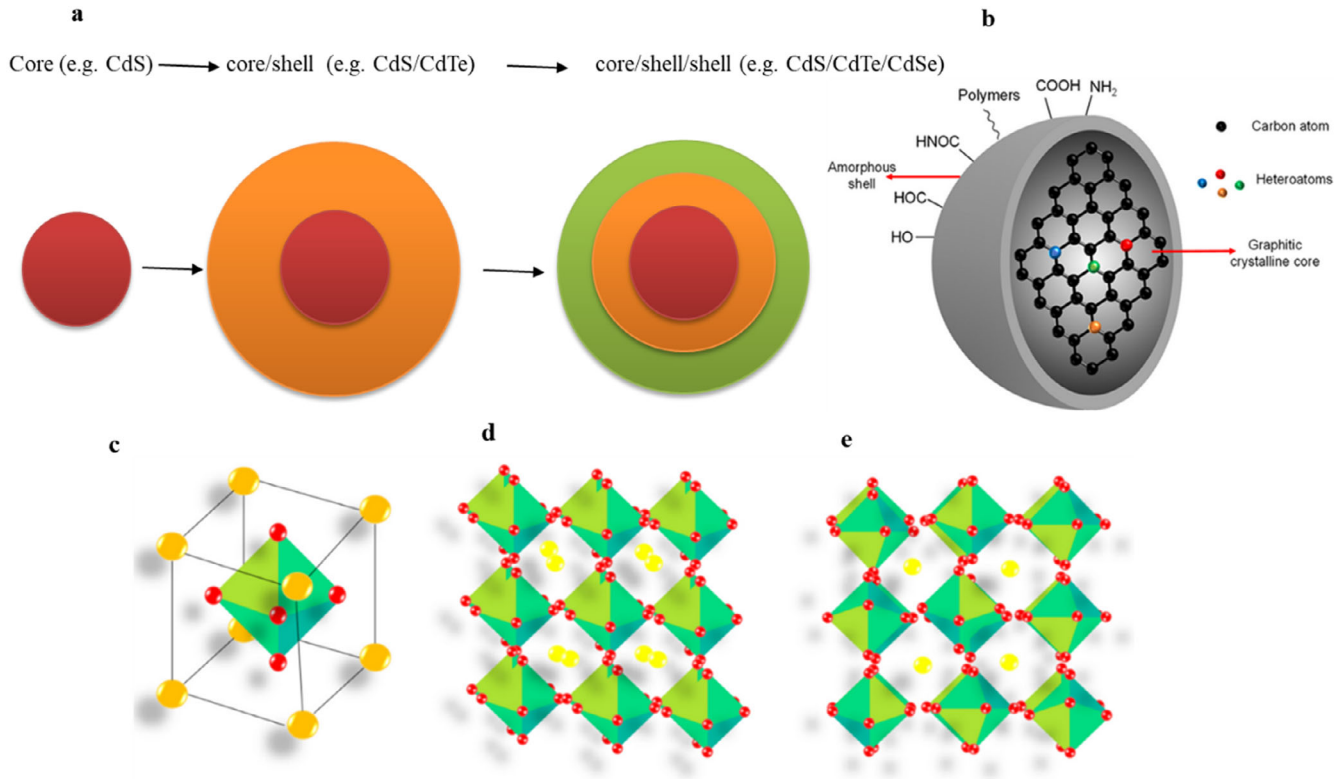


**FIGURE 3** | Schematic showing (a) core, core/shell and core/shell/shell SQDs shape, (b) CQDs shape with surface modification functional groups [60], licensed under CC BY license from https://onlinelibrary.wiley.com/doi/full/10.1002/cnl2.120, and (c) PQDs crystalline form, (d) PQDs cubic form, and (e) PQDs orthorhombic state [61], licensed under CC BY license from https://creativecommons.org/licenses/by/4.0/. CdSe, cadmium selenide; CdTe, cadmium telluride.

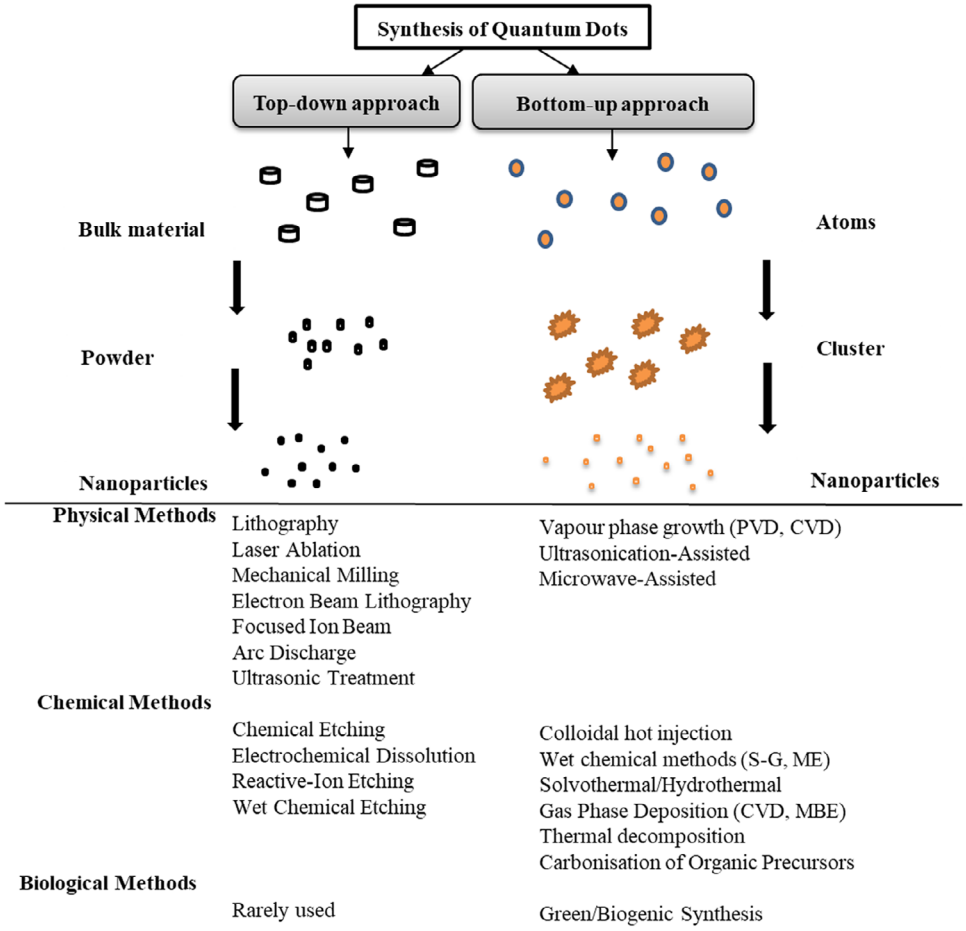


**FIGURE 4** | Synthetic methods of QDs classified by to-down and bottom approaches, and physical, chemical, and biological methods. CVD, chemical vapor deposition; MBE, molecular beam epitaxy; PVD, physical vapor deposition.

hot-injection methods, microwave-assisted, and solvothermal approach. Ligand-assisted reprecipitation (LARP) is also one of the recognized techniques for synthesizing PQDs. This approach involves simply mixing the precursor salts and coordinating diluents and adding them to an antisolvent, which induces the precipitation of the QDs [56]. This method operates under mild conditions and does not necessitate elevated temperatures or harmful diluents, making it an environmentally friendly and cost-effective approach for large-scale production [57]. Furthermore, it provides excellent morphological control over the shape and dimensions of the QDs, resulting in high-standard PQDs with enhanced optical features [42]. Unlike the generally employed hot-injection, LARP methods for synthesizing PQDs, several alternative synthetic strategies have been developed (Figure 3) [57]. The top-down approach for CQDs involves the breaking down of macroscopic carbon materials into smaller nanoscale carbon dots with carbon sources such as graphite, CNTs, and graphene. Common methods include electrochemical oxidation, chemical oxidation, laser ablation, arc discharge, and ball milling. This approach requires a rich source of raw materials and is favorable for the large-scale production of CDs, but the CQDs prepared by these methods tend to have the disadvantages of non-uniformity in morphology and size and often require purification of the initial product several times. Moreover, harsh conditions are often, expensive equipment, and long processing times, as a result, the top-down methods are slowly being replaced by the bottom-up approach methods [58]. The bottom-up approach synthesizes CQDs by assembling them from molecular precursors. These are typically small organic molecules, such as citric acid, or even waste materials like food scraps. Common methods include hydrothermal, solvothermal, and microwave-assisted synthesis. Thermal decomposition method is the commonly used technique as it uses inexpensive carbon-rich precursors, can produce large quantities of CQDs in a single step, making it suitable for bulk synthesis [59]. The precursors usually have organic functional groups such as hydroxyl, carboxyl, and amino groups, which not only facilitate the dehydration and carbonization process at high temperatures but also facilitate the preparation of CQDs that can be used for the specific recognition of chemical substances [46]. The bottom-up methods are mostly favored as they involve simple operations and mild reaction conditions. By selecting appropriate precursors, the structural characteristics of CQDs can be precisely controlled, enabling the fabrication of particles with uniform morphology, tunable size, and stable performance [58].

After synthesis, confirming the successful formation of QDs requires comprehensive characterization using multiple analytical techniques (Figure 5). These methods identify, analyze, and quantify the chemical, physical, and structural properties of the material [46]. Common techniques include spectroscopic analysis, such as like FTIIR, UV–Vis, and XPS, for analyzing chemical composition, and microscopic, such as SEM and TEM,

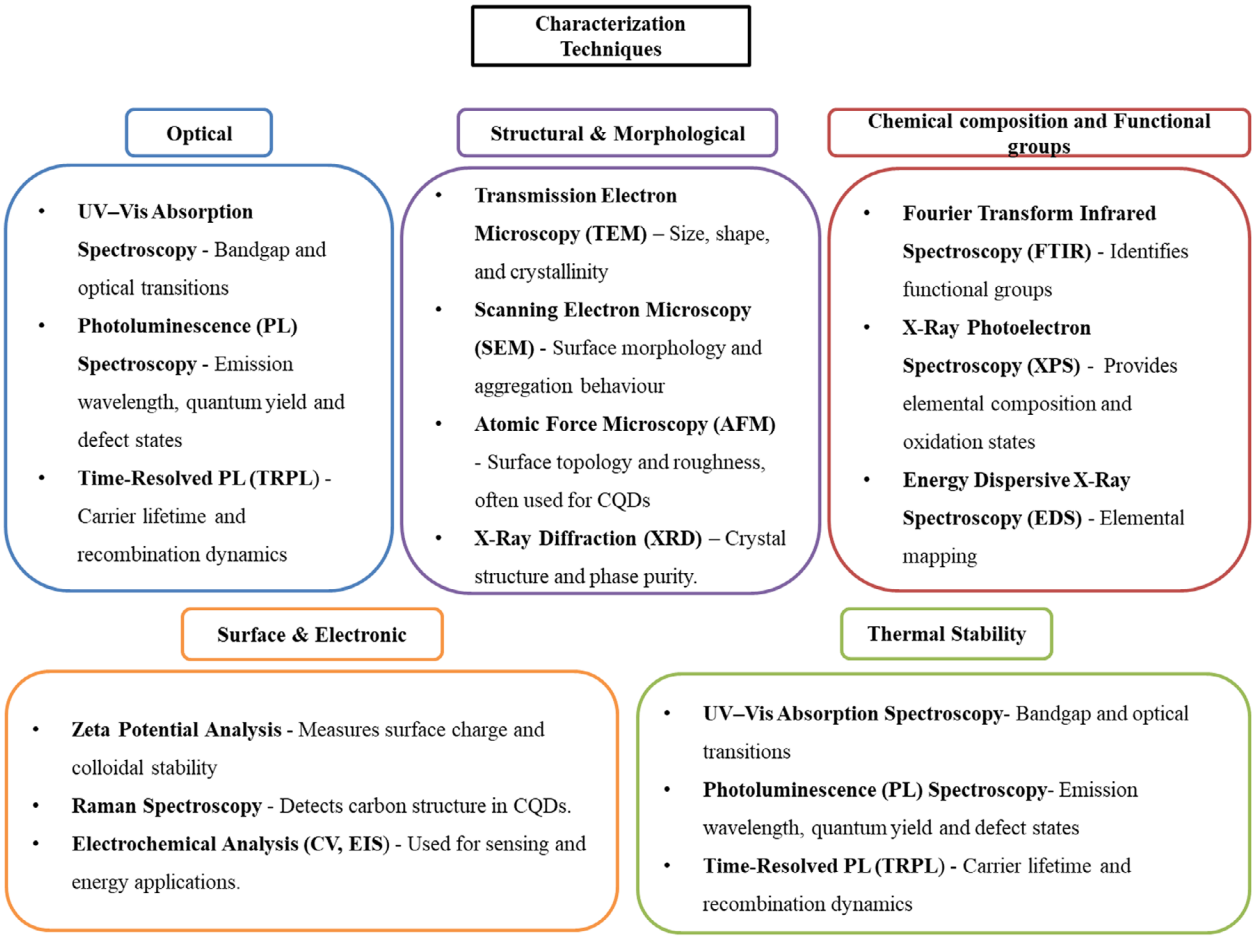


**FIGURE 5** | The characterization techniques for QDs classified into different properties.

for structural analysis. The analysis of QDs using different characterization is important in determining the efficiency of the prepared NPs in a certain application [62]. These techniques provide detailed insights into the physical, chemical, and optical properties of synthesized materials, ensuring that the intended structure and functionality have been achieved [30]. For QDs these techniques confirm parameters, such as crystallinity, particle size, morphology, and surface chemistry, which directly influence their performance in applications like sensing, catalysis, and optoelectronics [32]. Without proper characterization, it would be impossible to validate synthesis success or optimize properties for specific uses.

## 2.2 | Surface Modification of QDs

QDs surface is modified to improve their properties, which in turn improves performance, durability, and functionality [63]. SQDs, such as CdSe, cadmium telluride (CdTe), and ZnS, are widely used in biological applications. However, their surfaces often are hydrophobic right after synthesis and cannot be dispersed in aqueous environment, which is essential for biological applications. Hydrophilic groups, such as hydroxyls (–COOH), alcohols (–OH), and amines ($NH_2$), from polymers or biodegradable compounds are introduced making QDs water-soluble and biocompatible [64–66] (Figure 6). It also enables biorecognition capability by attaching antibodies, aptamers, or oligonucleotides for specific targeting [66]. Hydrophobic SQDs are made hydrophilic by replacing the hydrophobic layer with hydrophilic ligands through ligand exchange, encapsulating amphiphilic polymers, attaching hydrophilic functional groups, or coating QDs with a thin silica layer [66, 67]. Additionally, polymer coatings, like polyethylene glycol (PEG), are employed to enhance water solubility and reduce cytotoxicity [68]. Functionalization with biomolecules, such as streptavidin or antibodies, further enables SQDs to selectively bind to targeted molecules, making them effective [69, 70].

PQDs, such as $CsPbBr_3$, exhibit excellent optoelectronic properties but suffer from poor stability due to moisture and oxygen sensitivity [71, 72]. Surface modification strategies focus on passivating defects and improving environmental resistance. Ligand engineering using long-chain alkyl ammonium halides or zwitterionic molecules helps stabilize PQDs by reducing ion migration and surface trap states [73]. Moreover, encapsulation in polymer matrices or inorganic shells like silicon dioxide or aluminum oxide provides a physical barrier against moisture and oxygen [72, 74, 75]. CQDs, including GQDs and CNDs, are inherently biocompatible and exhibit excellent photostability [76]. Their surface is rich in oxygen-containing groups, which facilitates easy functionalization. Surface modification strategies for CQDs often involve doping with heteroatoms to tune electronic properties and improve fluorescence [77]. CQDs can also be modified with polymers or metallic NPs to create hybrid

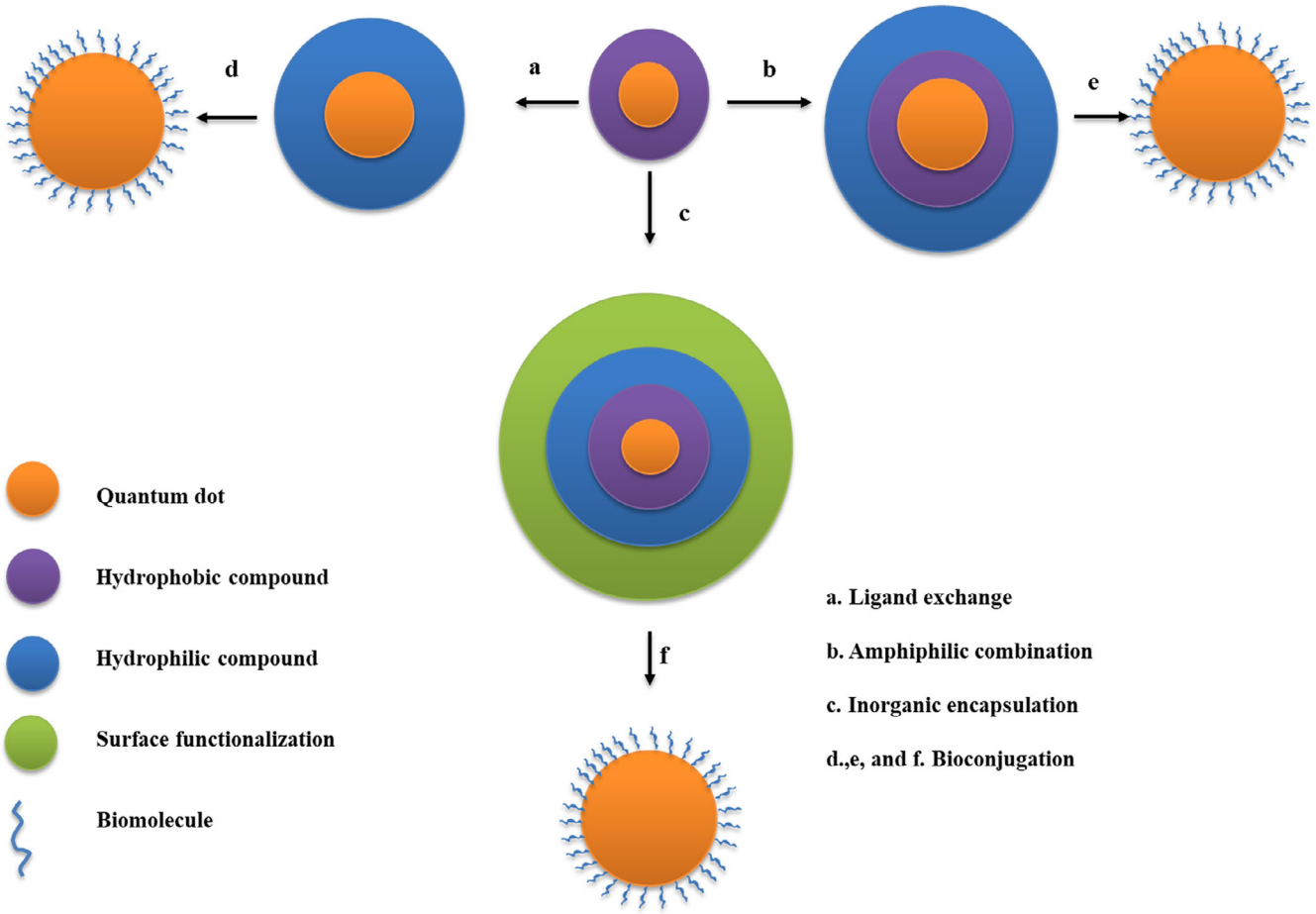


**FIGURE 6** | Schematic diagram showing functionalization of QDs from hydrophobic layer to hydrophilic layer using different methods (a, b, and c). From the hydrophilic layer, biomolecules can then be attached as shown above (d, e, and f). Redrawn with permission from (Karakoti, et al., 2015). Copyrights (2025) Elsevier.

nanostructures, improving properties for targeted application [70, 78].

### 2.3 | QD-Based Biosensors: TB Detection

A biosensor is an analytical device that detects a specific biological substance and converts that recognition event into a measurable signal proportional to the analyte's concentration [79]. QDs properties allow them to serve as fluorescent probes in biosensing applications, such as the detection of food pathogens [58, 75, 80], using electrochemical biosensors, detection of cancer biomarkers using different sensors such as fluorescent immunosensor [81, 82] and electrochemical sensors [83, 84, 85] and other applications, such as pharmaceuticals, forensics, and environmental monitoring. Ever since the discovery of biosensors in the mid-1950's, research in this field has grown exponentially, driven by the need for rapid, sensitive, and cost-effective analytical tools [86, 18]. Today, biosensors represent a cornerstone of modern analytical systems, with ongoing innovations focused on efficiency, portability, and real-time detection [87–89]. In a medical context, biosensors are used to detect biomarkers associated with various diseases, such as glucose for diabetes monitoring or pathogens for infectious diseases [26, 90].

For TB detection, QD-based biosensors offer significant advantages over traditional diagnostic methods, such as sputum smear microscopy or PCR-based assays [89, 91, 92]. QDs can be conjugated with antibodies, aptamers, or nucleic acid probes to specifically recognize TB biomarkers like Mtb-DNA, antigens, or metabolites (Figure 7) [93]. Their strong fluorescence and signal amplification capabilities enable detection of extremely low concentrations of TB biomarkers, which is crucial for early-stage diagnosis and monitoring latent infections [90]. Furthermore, QD-based biosensors can be integrated into portable, point-of-care (POC) devices, providing rapid and accurate TB detection in resource-limited settings where conventional methods are slow, expensive, or require complex infrastructure [93]. This combination of sensitivity, speed, and adaptability positions QD-based biosensors as a transformative technology for TB diagnostics. Despite their promising applications, the **biocompatibility and stability of QDs in biological environments remain critical challenges** [66, 94].

TB biomarkers are measurable indicators used to diagnose TB and monitor its treatment. They can be derived from the bacteria itself, such as bacterial DNA or antigens like lipoarabinomannan (LAM) and ESAT-6, or from the host's immune response, including cytokines, antibodies, and RNA signatures [95, 96]. Volatile organic compounds (VOCs), such as methyl nicotinate (MN),

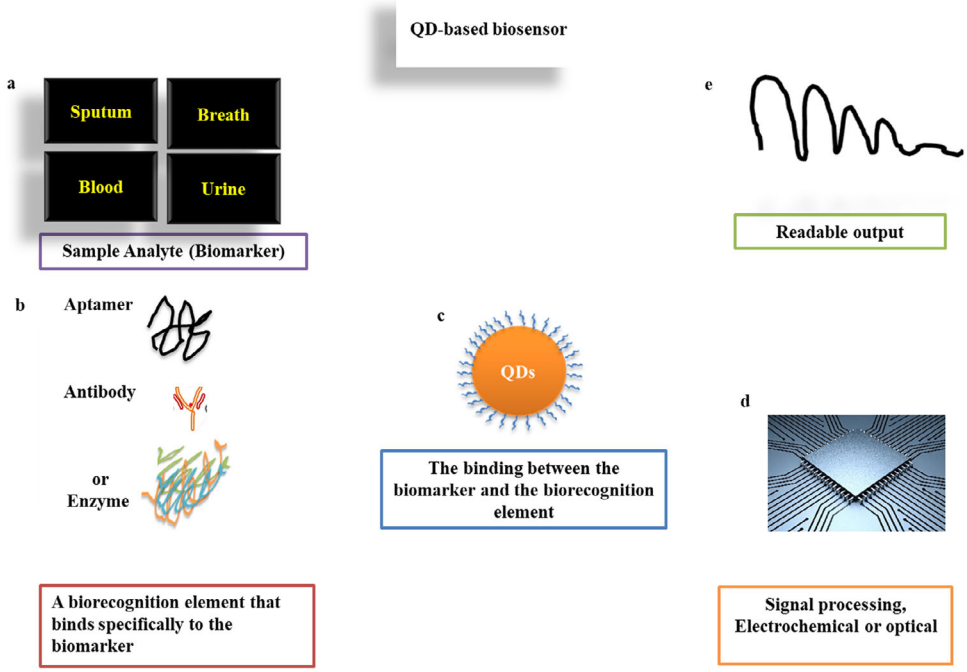


**FIGURE 7** | Schematic diagram of a QD-based biosensor, where a biomarker (sample from blood, urine or sputum) (a) bind to a biorecognition element (aptamer, antibody or enzyme) (b), a biomolecule functionalized QD binds to a targeted biomarker (c) induces a measurable signal (d) that is detectable (e). QDs, quantum dots.

have also been identified as metabolic signatures of TB [97]. These biomarkers serve as critical targets for diagnostic assays because they provide direct or indirect evidence of infection, enabling differentiation between active and latent TB [98]. Current TB detection strategies are designed around these biomarkers. Molecular tests, such as PCR and GeneXpert, target Mtb DNA for rapid and specific identification, whereas immunological assays, like IGRAs, detect host immune biomarkers to diagnose latent TB (162 [91]). Culture-based methods confirm bacterial presence but are slow, and sputum smear microscopy remains widely used despite low sensitivity [91, 99]. Each approach depends on the accurate recognition of these biomarkers, but limitations, such as long turnaround times, high costs, and infrastructure requirements, hinder their effectiveness in resource-limited settings [162].

## 3 | Applications of QD-Based Sensors in TB Detection

### 3.1 | Inorganic SQDs for TB Detection

Inorganic SQDs, such as CdTe, CdSe, and InP, have emerged as powerful tools in biosensing applications due to their unique optical and electronic properties. These nanocrystals exhibit size-dependent fluorescence, high quantum yield, and exceptional photostability, making them superior to conventional organic dyes for diagnostic purposes [93]. Their ability to be functionalized with biomolecules, such as DNA probes, antibodies, and aptamers, enables specific recognition of TB biomarkers, including nucleic acids, proteins, and metabolites. This versatility allows SQDs to serve as fluorescent probes, electro chemiluminescent luminophores, or photoactive materials in biosensing platforms [100].

#### 3.1.1 | II–VI SQDs in TB Detection

Among SQDs, nanocrystals composed of elements from Groups II and VI, such as CdSe, CdS, ZnS, and CdTe, exhibit strong quantum confinement effects, leading to distinct optical and electronic characteristics that enhance biosensor performance [101]. Their high photoluminescence efficiency and tunable emission wavelengths allow for sensitive and specific detection of TB biomarkers. Building on these properties, recent studies have demonstrated their application in TB diagnostics. For instance, CdTe QDs functionalized with a single-stranded DNA probes complementary to the IS6110 gene fragment of Mtb have been integrated into a fluorescence resonance energy transfer (FRET)-based biosensor using a two-dimensional (2D) metal organic framework (MOF) as an energy acceptor. This system achieved a detection limit of approximately 35 pM without PCR amplification, highlighting the potential of QD-based platforms for rapid and highly sensitive TB detection, (Figure 8). The CdTe QDs were synthesized via a one-pot method and made water-soluble using 3-mercaptopropionic acid (MPA), yielding QDs with an average diameter of 3.7 nm. These nanoprobes exhibited bright orange coloration and yellow fluorescence under 365 nm UV light, enabling precise molecular recognition [13].

An electrochemical immunosensor was developed using CdSe/ZnS QDs and silica NPs on a screen-printed carbon electrode for detecting Mtb. The sensor targeted the CFP10–ESAT6 antigen complex to improve diagnostic specificity. QDs enhanced electron transfer and increased the electrode's active surface area, resulting in high sensitivity with a detection limit of $1.5 \times 10^{-10}$ g/mL. This QD-based platform demonstrated strong selectivity and reproducibility, highlighting its potential for rapid TB diagnostics [102]. The study by Zaid et al. introduced

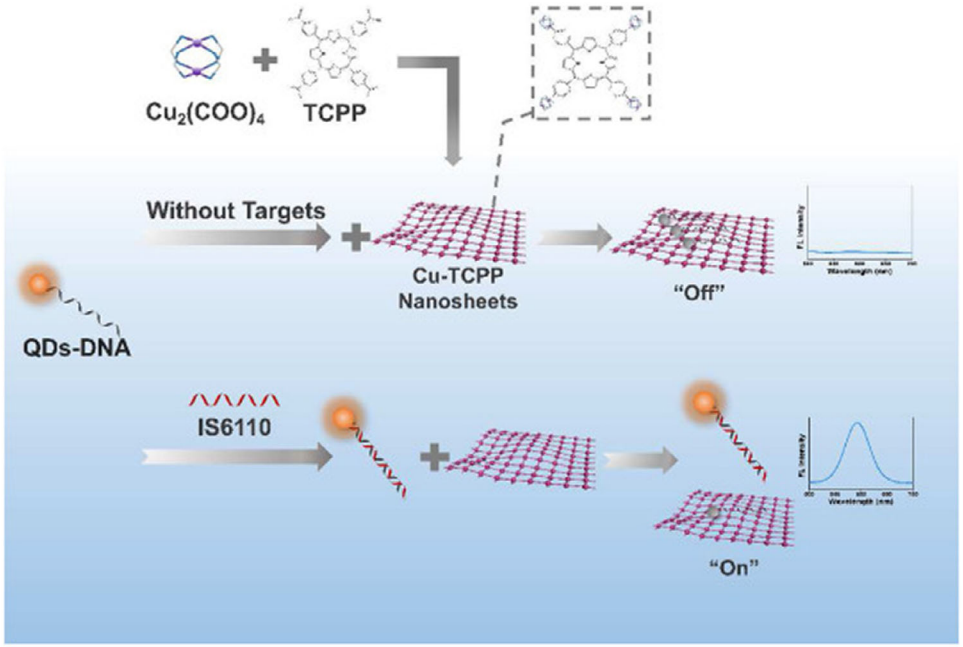


**FIGURE 8** | An illustration demonstrating the detection of the IS6110 gene sequence, which is associated with Mtb. Reprinted with permission from (Liang, et al., 2021), Copyright (2025) Elsevier.

a peptide nucleic acid (PNA)-based biosensor that integrated reduced graphene oxide and water-soluble CdS QDs for detecting Mtb-DNA. The biosensor used PNA probes for high specificity and QDs as fluorescent property to enhance signal intensity. This design achieved sensitive and selective detection of TB genetic material, demonstrating potential for rapid and accurate diagnostics. The reproducibility and stability of the biosensor were evaluated, showing satisfactory reproducibility with a relative standard deviation (RSD) of 1.7 and good storage stability when stored dry at 4°C [103]. The incorporation of QDs in these studies confirms the high sensitivity, strong signal output, and the versatility in different biosensing experiments (electrochemical immunosensor and the other using a PNA biosensor).

Kabwe et al. demonstrated the potential use of Cd-based QDs linked to mycolic acids (MAs) as a fluorescent probe for detecting anti-MA antibodies, which serve as indicators for TB. This research focused on the synthesis, solubility, and lateral flow characteristics of QDs connected to MAs. The water-soluble CdSe/ZnS QDs were synthesized using a one-pot method involving the continuous injection of precursors, capped with L-cysteine, and covalently linked to MAs through amide bonds to create a water-soluble fluorescent probe (MA-CdSe/ZnS QDs). The average size of the MA-CdSe/ZnS QDs was approximately 3.0 nm, with an emission wavelength of 380 nm. The visual paper-based lateral flow test (LFT) of MA-CdSe/ZnS QDs was conducted on nitrocellulose membrane strips using water and membrane-blocking solution eluents (Figure 9). The highly fluorescent MA-CdSe/ZnS QDs exhibited excellent water solubility and lateral flow characteristics, essential for fluorescence sensor applications [104].

The team developed a fluorescent assay using CdTe QDs and cobalt-metalized materials to detect MN in vapor samples, a common VOC associated with Mtb. The ability to precisely identify MN in human breath supports non-invasive, quick, and precise screening for TB infections during epidemics. The red-emitting QDs with a size of 3.67 nm and a fluorescence of 685 nm functioned as a signal switch, where cobalt-metalized nanosheets could significantly diminish their fluorescence but also be restored in the presence of MN. The proposed system demonstrated sensitivity and selectivity for detecting MN in vapor samples. This method was inexpensive, straightforward, and relatively fast, indicating its potential for TB diagnosis in areas lacking resources and trained personnel. This approach highlighted QDs' strong fluorescence and ability to enable sensitive detection of VOCs, expanding TB diagnostics beyond conventional biomarker detection [105]. A sensitive and affordable POC for TB was demonstrated by Hu et al. utilizing a recombinase polymerase amplification (RPA) combined with a catalytic hairpin assembly (CHA) for enhanced dual signal amplification. This POC used CdTe QDs signal reporter, such that when the target DNA (IS1081 gene fragment) was present, RPA amplicons, hindered by short oligonucleotide sequences, could initiate CHA signal amplification. This process resulted in the release of Ag+ from a C–Ag+–C structure and the quenching of fluorescence from CdTe QDs due to the released Ag+. Additionally, a thorough comparison was conducted on the detection performance of CdTe QDs modified with either MPA or thiomalic acid (TMA), referred to as MPA-capped QDs and TMA-capped QDs, respectively. Experimental results indicated that TMA-capped QDs displayed enhanced sensitivity in detection owing to their more robust interaction with Ag+. The limits of detection (LODs) for fluorescence and visual analysis were very low. The proposed method offered advantages such as high sensitivity and specificity, ease of operation, and cost-effectiveness, making it a promising candidate for clinical application. This study introduced a dual-readout platform combining fluorescent and colorimetric signals, where QD nanoprobes provided high signal intensity and stability, enabling POC TB detection with dual

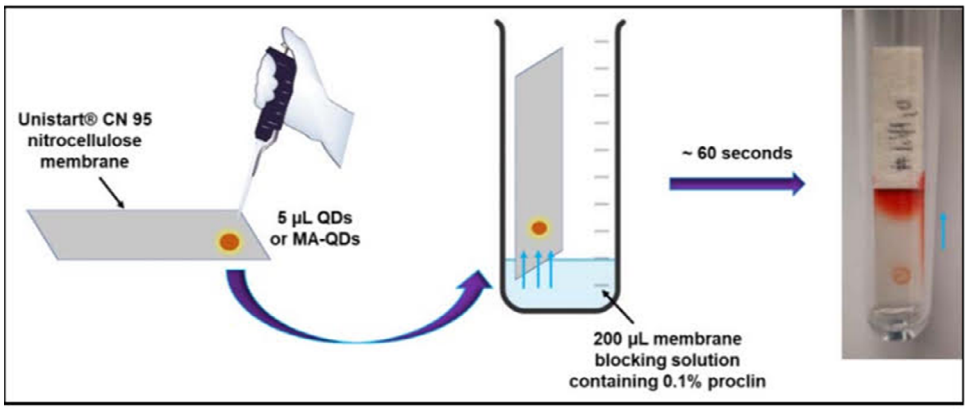


**FIGURE 9** | Procedure for the paper-based lateral flow test for L-cys-CdSe/ZnS QDs. MA, mycolic acid; QDs, quantum dots. *Source:* Reprinted with permission from *Luminescence* [104] with permission from John Wiley and Sons.

amplification for improved accuracy. [106]. Together, these results validate key advantages of QDs high sensitivity, strong and stable luminescence, and adaptability to diverse detection. They also confirm that QDs have significant potential in this field, not only for nucleic acid and protein detection but also for innovative strategies like volatile biomarker sensing and portable diagnostic platforms.

Interferon-$\gamma$-inducible protein 10 (IP-10) showed a significant promise as a new biomarker for TB, especially in tracking the progression of both active and latent TB infection (LTBI). Two distinct research teams developed aptamers for TB diagnosis where in the first study, a tetrad metal ion-mediated molecular switch aptamer sensor was developed for fluorescence-based detection of plasma IP-10, a key TB biomarker. CdTe QDs served as fluorescent reporters, enabling strong and stable signal generation, which allowed precise quantification of IP-10 in clinical samples, were 38 TB-positive, negative, and latent healthcare individuals were evaluated. The findings indicated that the levels of IP-10 measured were notably different between the non-TB group and those with TB or LTBI, and these results correlated with clinical evaluations. Imaging from computed tomography (CT) suggests that this method could be a dependable diagnostic approach for TB (Figure 10) [107]. The other research concentrated on a quick, uniform, sensitive fluorescence quantification method for interferon-gamma (IFN-$\gamma$) and IFN-$\gamma$-induced protein 10 (IP-10). Here, 57 clinical samples confirmed the aptamers' strong affinity for IFN-$\gamma$ and IP-10. The combined detection using dual indicators demonstrated high specificity and sensitivity, indicating an enhancement over the single-indicator method. These results highlight the potential of the process to improve the efficiency and effectiveness of TB clinical diagnostics [108]. These findings reinforce the core advantages of QDs high brightness, excellent photostability, and compatibility with amplification strategies and confirm their potential for clinical TB diagnostics. By enabling multiplexed and highly sensitive detection of both protein and nucleic acid targets, QDs demonstrated versatility and reliability, supporting their role as a cornerstone in next-generation POC TB biosensors.

Groups II–VI QDs have been utilized in various applications for TB detection, such as signal reporters, fluorescent probes, or electroactive species in biosensors, lateral flow assays, and POC testing, as discussed above. It can be observed that among the available II–VI QDs, Cd-based QDs are the most extensively studied, particularly for TB detection. Even though Cd-based QDs have exceptional properties for biological applications, this type of QD is widely recognized for its toxicity due to the release of $Cd^{2+}$ ions in aqueous environments, and it is listed under the European Restriction of Hazardous Substances (ERHS) directives [109]. Despite surface functionalization, research has indicated that these QDs still pose toxicity risks [110]. Nevertheless, no cytotoxicity studies have been performed or documented by the studies above. All the studies have mentioned the use of Cd in the proposed application but failed to assess the stability of the synthesized or purchased QD before and after conjugation, which is a disadvantage in finding viable research for commercialization. Moreover, not disclosing the cytotoxicity studies may lead to repeating the same synthesis procedure instead of modifying it for better or improved results. Consequently, various types of Cd-free QDs have been thoroughly investigated recently, showcasing the potential of QDs for biological uses. In addition to Cd found in Groups II–VI, ZnO QDs have good biocompatibility and antibacterial properties, making them a great candidate for future TB biosensors, especially in hybrid systems or electrochemical sensing [111, 112].

### 3.1.2 | III–V and IV–VI SQDs for TB Detection

Inorganic QDs also include Groups III–V and IV–VI nanocrystals, exhibit emission in the near-infrared (NIR) region. Groups III–V QDs, such as InP, indium arsenide (InAs), and gallium phosphide (GaP), are cadmium-free alternatives that are composed of less toxic elements and are considered a "greener," low-toxicity alternative to II–VI and IV–VI QDs. However, their use in TB detection remains limited due to challenges in synthesis, surface functionalization, and integration into biosensing [113]. Groups IV–VI QDs, including lead sulfide (PbS), lead selenide (PbSe), and tin sulfide (SnS), are less commonly employed in TB diagnostics compared to II–VI QDs like CdSe or CdTe. The primary limitation of Pb-based QDs is their inherent toxicity, necessitating surface modifications or biocompatible coatings to meet regulatory standards for clinical applications [114]. Although these materials offer strong absorption in the NIR region, which is advantageous for deep-tissue imaging, their restricted medical use reduces their

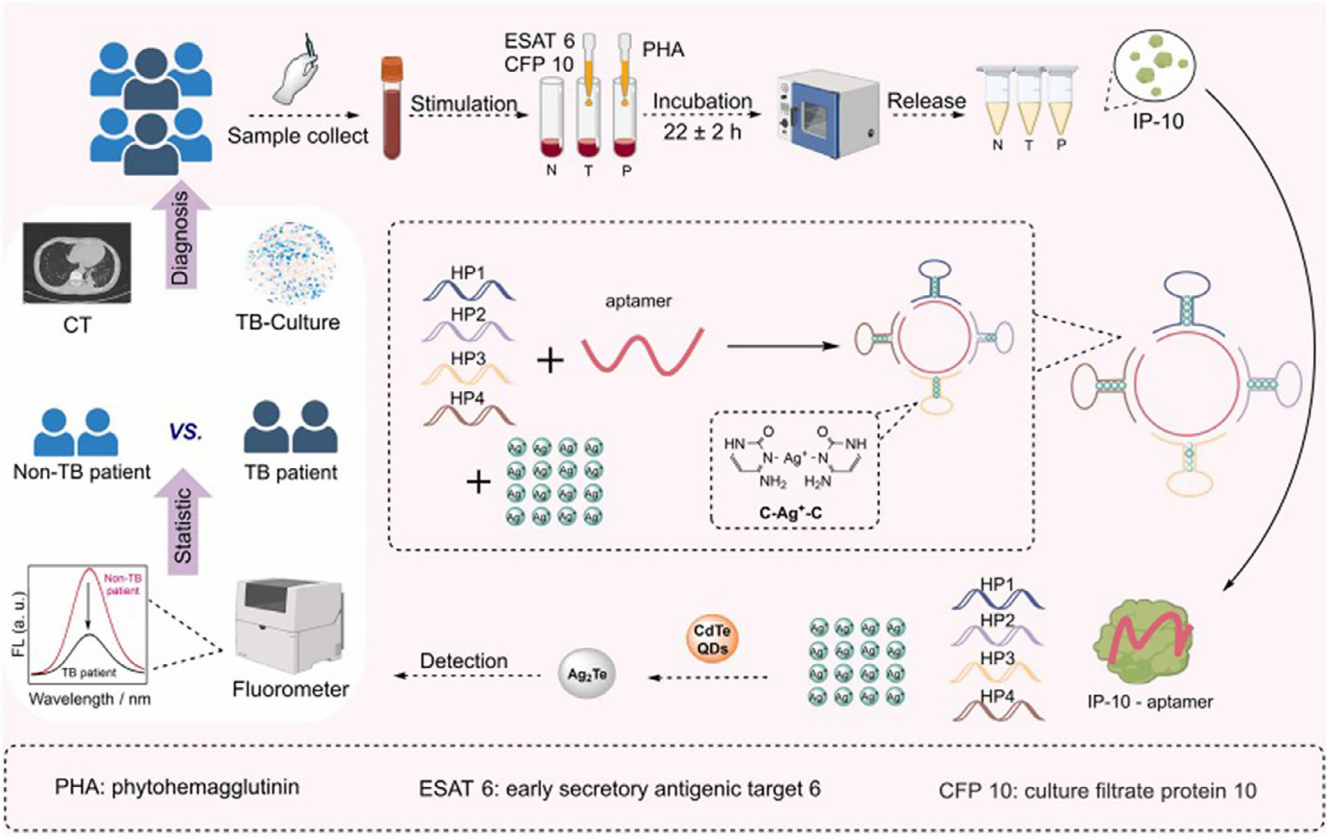


**FIGURE 10** | Schematic diagram of the tetrad metal ion-mediated molecular switch aptasensing for TB diagnosis. TB, tuberculosis; CdTe, cadmium telluride; CT, computed tomography; QDs, quantum dots. *Source:* Reprinted with permission from *ACS Applied Materials & Interfaces* [108] with permission from Elsevier.

impact on TB detection research, hence only a few studies have explored them.

An electrochemical biosensor utilizing tin telluride selenide (Sn–Te–Se) QDs functionalized with L-cysteine to improve stability, solubility, and biocompatibility was studied for detecting the TB biomarker IFN-$\gamma$. These QDs functioned as electroactive elements, enhancing signal amplification due to their excellent electrochemical properties. The aptasensor demonstrated a low detection limit of 0.151 pg/mL; when tested in real samples, the sensor showed recovery rates of 98%–105%, indicating strong potential for clinical TB diagnostics. With a fluorescence emission peak at 500 nm and an average particle size of 3.8 nm, this sensing platform provided a highly sensitive, specific, and stable diagnostic approach without the need for complex processing steps [115]. Another electrochemical aptasensor for detecting IFN-$\gamma$ using L-cysteine-functionalized indium telluriselenide (L-cysteine-InTeSe) QDs was reported. The sensor was constructed by modifying a gold disc electrode with QDs, which were then conjugated to an amine-terminated IFN-$\gamma$ aptamer via carbodiimide-mediated amide bond formation. The QDs provided excellent optical and electrochemical properties, enabling strong signal amplification. Electrochemical analysis using voltammetry revealed a linear response over a concentration range of 10–21 pg/mL and an ultra-LOD of 0.312 pg/mL. The aptasensor demonstrated high selectivity, with no interference from other substances, and achieved recovery rates of 98%–102% in synthetic human serum samples. This work highlighted the role of QDs in enhancing biosensor sensitivity and reliability, offering a promising platform for rapid and accurate TB diagnostics compared to conventional immunoassays [116].

Silicon (Si) QDs, a subset of Group IV, have shown sensing abilities of biomolecules according to a study by Upadhyay et al. [117]. A fluorescent turn-off sensor using Si–QDs for the glucose determination in human blood showed that the proposed method detected glucose as low as 0.54 µM with a good selectivity and allowed the determination of glucose in serum samples. The study further concluded that the method was also simple, rapid, low-toxic and low-cost, thereby holding high application potential for biological assays [118]. Si–QDs present an alternative with low toxicity and high biocompatibility compared to traditional heavy-metal-based QDs. Despite their promising photoluminescence properties, Si QDs have not been extensively explored for TB detection. Their lower quantum yield compared to II–VI and III–V QDs affects their fluorescence sensitivity, which is critical for detecting low-abundance TB biomarkers [119, 120].

### 3.2 | PQDs in TB Detection

PQDs, categorized as inorganic, organic–inorganic hybrids, or fully organic, have gained attention for their tunable fluorescence and high quantum yield. Although their direct application in TB diagnosis is limited, their potential has been demonstrated

in biosensors targeting nucleic acids and proteins [38]. Jiang et al. developed a biosensing platform utilizing FRET between hydrophilic $CsPbBr_3$ QDs-DNA and $MoS_2$ nanosheets for sensitive Mtb-DNA detection. The hydrophilic $CsPbBr_3$ PQDs were functionalized with carboxyl groups to overcome the inherent instability and hydrophobicity of traditional PQDs. This system enabled highly sensitive and selective "turn-on" fluorescence detection of Mtb-DNA, achieving a low detection limit of 51.9 pM and successfully identifying drug-resistant clinical strains. The study demonstrates how PQDs can enhance biosensing performance for TB diagnostics by combining strong optical properties with tailored surface chemistry for biomolecule recognition [121].

Ghinaiya et al. developed a one-step synthesis method for water-soluble methylammonium lead bromide ($MAPbBr_3$) PQDs tailored for TB diagnostics. The PQDs were functionalized to maintain fluorescence stability in aqueous environments and conjugated with specific recognition elements for detecting MN. The sensor employed a fluorescence "turn-on" mechanism, where the presence of MN restored PQD fluorescence quenched by an initial interaction with a quencher material. This approach enabled highly sensitive detection with an LOD and rapid response time, demonstrating strong selectivity against interfering compounds. The study underscores the potential of PQDs in TB biosensing by combining robust optical properties, water stability, and biomarker specificity, offering a promising alternative to conventional diagnostic methods. The as-prepared $MAPbBr_3$ QD-based fluorescent probe has high ability to detect MN, with the detection limit of 71.13 nM. The analytical performance of the developed fluorescent probe was validated by assaying MN in spiked biological samples, showing good recoveries in the range of 97.20%–99.64%, which signifies that $MAPbBr_3$ QDs could be used as a facile portable probe for MN assays in biofluids [122].

Research on PQDs for TB biosensing remain limited, with only a few reports explored these nanocrystals for biological applications other than TB. Cesium lead bromide (CsPbBr3) PQDs have been developed as highly sensitive photosensors for chemiluminescence immunoassays. The photosensor effectively detected biomarkers, such as human hepatitis B surface antigen, HIV antibody, and alpha-fetoprotein, demonstrating its feasibility as a biosensor compared to conventional equipment, thus advancing diagnostic capabilities in disease detection [123]. Cardiac troponin I (cTnI) detection by 2D perovskite-based biosensor integrated with a biopolymer enhanced the thermal stability of the biosensor, allowing it to function effectively at elevated temperatures. This biosensor demonstrated a detection limit of 10 pg/mL, showcasing the potential of perovskite materials in biosensing applications [124]. Toxicity concerns associated with lead-based PQDs create regulatory hurdles for clinical applications, but lead-free PQDs have also been used biosensing, just not for biological studies. The detection of hydrogen peroxide ($H_2O_2$) that falls under environmental monitoring, food and beverage analysis, healthcare, and the pharmaceutical industry using $Cs_3Bi_2Br_9$ PQDs demonstrated an efficient detection range for $H_2O_2$ from 0.002 to 200 μM, with a low detection limit of 0.89 nM [125]. This group of QDs is still ongoing new research with the hopes of new developments on the Pb-free PQDs for TB detection and other vital biomarkers.

### 3.3 | CQDs in TB Detection

CQDs have emerged as promising nanomaterials for biosensing due to their excellent biocompatibility, low toxicity, tunable fluorescence, and ease of functionalization. Unlike traditional SQDs, CQDs are environmentally friendly and can be synthesized from inexpensive precursors using green methods such as hydrothermal or microwave-assisted processes [74]. Recent studies have demonstrated CQD-based biosensors capable of ultrasensitive TB detection where Kabwe et al. developed a water-soluble fluorescent probe by coupling GQDs to MA's, which are unique lipid components of the Mtb cell wall. The study aimed to create a platform suitable for lateral flow assays for TB diagnosis. The GQDs provided strong fluorescence and excellent stability in aqueous environments, whereas conjugation with MA's enabled specific recognition of TB antibodies. This design allowed for a "turn-on" fluorescence mechanism upon antibody binding, offering high sensitivity and selectivity for TB detection. The approach demonstrates how QDs can enhance biosensing performance by combining robust optical properties with pathogen-specific biomolecular interactions, paving the way for rapid, POC TB diagnostics using lateral flow technology [126, 127]. In a related study, CdSe/ZnS QDs conjugated with MA antibodies were evaluated as fluorescent probes for TB diagnosis, but GQDs outperformed Cd-based QDs due to their superior water solubility and nontoxicity [104].

An electrochemical immunosensor for TB detection using a nanotriplex composed of GQDs, $Fe_3O_4$ magnetic NPs, and silver (Ag) NPs was developed by Tufa et al., [128]. The GQDs served as a fluorescent and conductive platform, providing abundant functional groups for antibody immobilization, whereas $Fe_3O_4$ enabled magnetic separation and Ag NPs enhanced electron transfer for signal amplification. This synergistic nanotriplex significantly improved sensitivity and selectivity for detecting TB-specific antigens. The immunosensor demonstrated an LOD of 0.33 ng/mL and rapid response, making it suitable for POC diagnostics. The study highlights how **CQDs**, integrated with other nanomaterials, can overcome limitations of traditional TB assays by offering high sensitivity, portability, and cost-effectiveness for early TB diagnosis [128]. Wang et al., developed a TB diagnostic platform using single-walled CNT (SWCNT)-based field-effect transistors (FETs) functionalized with TB-specific antibodies. The SWCNTs provided exceptional electrical conductivity and high surface area, enabling sensitive detection of TB antigens, antigen 85B (Ag85B) through changes in electrical signals upon antigen–antibody binding. This label-free approach allowed real-time monitoring with a low detection limit and rapid response, outperforming conventional immunoassays in terms of speed and portability. Although not a QD system, the study demonstrates how carbon-based nanomaterials, like carbon QDs, can be integrated into advanced biosensors for TB diagnostics, offering high sensitivity, miniaturization potential, and suitability for POC applications [129].

Research on CQDs for TB detection remains limited as most CQD studies focus on applications, such as bioimaging, cancer therapy, and general biosensing rather than infectious disease diagnostics [130]. Compared to SQDs, CQDs generally exhibit lower quantum yield and brightness, which can restrict their sensitivity in

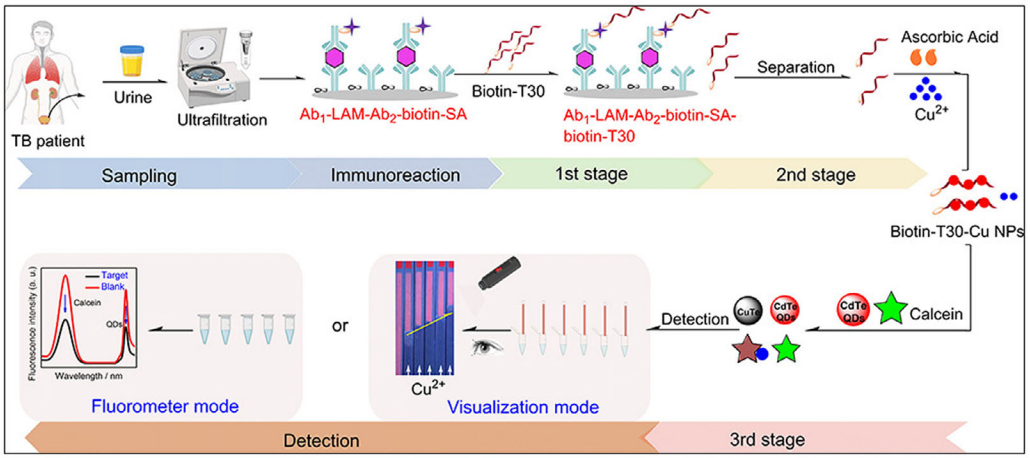


**FIGURE 11** | A schematic diagram illustrating the process of a visualization immunoassay designed to detect LAM in clinical urine samples. This type of test is used to identify the presence of the LAM antigen, a biomarker for TB, in a patient's urine. Reprinted with permission from (Chen, et al., 2023). Copyright (2025) American Chemical Society.

detecting TB biomarkers [131]. Additionally, functionalization strategies for specific TB targets, such as Mtb DNA or proteins, are less developed for CQDs, making them less competitive for highly selective diagnostics [93]. Furthermore, global TB research priorities and funding have historically emphasized molecular techniques like PCR and GeneXpert, leaving nanomaterial-based approaches underexplored (WHO, 2024). These challenges collectively contribute to the limited studies of CQD-based TB detection studies despite their advantages of biocompatibility and eco-friendliness [132].

### 3.4 | QD-Based TB Detection: Unspecified QD Types

Some studies report the use of QDs in TB detection without specifying the exact type. Hu et al. developed a QD-based nano beacon (QD-NB) integrated with a multi-component nucleic acid enzyme (MNAzyme) for rapid colorimetric TB detection. Their assay demonstrated enhanced sensitivity compared to RPA, achieving a low detection limit and high specificity [133]. Chen et al. introduced a highly sensitive immunoassay for detecting LAM in urine samples (Figure 11). Their DNA-linked immunosorbent assay, coupled with QDs and a calcein-$Cu^{2+}$ signal amplification system, achieved 94.1% sensitivity for culture-confirmed TB cases and 85% for unconfirmed cases, with a specificity of 89.2% [134]. These findings highlight the potential of QD-based biosensors for non-invasive TB diagnostics.

SQDs, PQDs, and CQDs have all demonstrated significant potential in TB biosensing, their adoption varies due to distinct material properties and challenges. SQDs, particularly Cd-based II–VI QDs, dominate TB biosensor research because of their superior optical performance, developed synthesis protocols, and well-established surface functionalization strategies, despite toxicity concerns [62, 130]. PQDs offer exceptional photoluminescence and tunable emission, making them attractive for advanced sensing platforms; however, their instability in aqueous environments, lead toxicity, and limited TB-specific studies have restricted widespread application [132]. CQDs stand out for their biocompatibility, low toxicity, and cost-effectiveness, making them ideal for portable and POC TB diagnostics, though their fluorescence intensity and selectivity still require optimization [131]. Collectively, these nanomaterials represent a transformative approach to TB detection, with future research likely focusing on improving stability, functionalization, and integration into multiplexed, real-time biosensing systems [93].

Although QD-based biosensors demonstrate strong technical performance in sensitivity, specificity, and rapid detection, their use in real-world depends on their cost-effectiveness and affordability. Different biosensor types are assembled in distinct ways, which leads to varying design, operational requirements, and costs. Optical, fluorescence biosensors integrated with SQDs normally achieve low detection limit and clear multiplexing of biomarkers due to the high brightness, tunable emission, and photostability of these nanocrystals, which reduces turnaround times from days to minutes or hours and reduces downstream costs from delayed treatment. However, the use of heavy metals in this type of biosensor increases costs as extra safety precautions are needed and regulated disposal procedures, prompting a shift toward CQDs and PQDs to preserve performance while mitigating toxicity and cost [93, 135, 136]. Among different biosensors, fluorescent sensors provide high sensitivity and low detection limits, the cost are dependent on whether the laboratory already owns a fluorescence reader or not. In instances where the fluorescence reader is already available, there are no expensive equipment required, cost come from consumables for each test. This test requires QDs for signal labeling, chemical buffers, and biorecognition probes, but they are relatively low compared to buying a new reader. Additional cost may be needed if the biosensor is deployed in POC, as portable fluorimeters are required. These are additional instruments that cost money upfront, so the economic advantage decreases compared to using existing lab readers [26, 93].

Unlike optical sensors that need expensive readers, electrochemical sensors use potentiostats that are cheaper and easier to use. They can be made into portable devices for use in clinics or field settings making them suitable for resource limited areas. QD-based electrochemical sensor has an increased sensitivity as these nanocrystals improve the electrochemical

response by facilitating electron movement and boosting signal strength. Cost is added when preparing QDs for electrode integration with biomolecules and calibrating the sensors for consistent performance [26, 79, 137]. Colorimetric sensors such as QD-based lateral flow and paper-based devices do not require expensive readers like fluorimeters [138]. They can often be interpreted visually or with a smartphone camera, which reduces equipment costs. As they are simple and cheap, they can be widely produced and distributed for large-scale TB screening in resource-limited settings. However, this type of biosensor is less sensitive compared to fluorescence or electrochemical sensors, making it hard to detect low concentrations of TB biomarkers [90, 139]. FRET-based sensors use QDs as energy donors, and other molecules as acceptors to create a signal. They measure the ratio of two fluorescence signals, which reduces interference and improves accuracy, lowering the risk of incorrect diagnoses. Accurate results mean fewer false positives/negatives, reducing unnecessary treatments and associated costs. The donor and acceptor must have compatible emission and absorption spectra, and the system usually needs sophisticated optical equipment, increasing complexity. Large optical instruments are expensive, but if miniaturized into portable readers, costs can be reduced. These sensors can detect multiple biomarkers in one test, which spreads the cost across several targets, making them more economical for large-scale testing [93, 136].

When compared to conventional TB diagnostics, QD-based biosensors provide economic advantages mainly because they reduce the number of missed cases and prevent costly consequences of delayed or incorrect treatment. Traditional smear microscopy, although cheap upfront, is the least cost-effective because of its poor sensitivity and high rate of missed cases. Molecular tests like GeneXpert improve outcomes but remain expensive and infrastructure heavy. QD-enabled POC platforms strike a balance by offering high analytical performance with lower capital requirements especially in multiplex optical assays and portable electrochemical devices making them a strategic middle ground between low-cost but inaccurate methods and high-cost molecular systems [26, 140, 141]. Overall, literature indicates that when it comes to cost efficiency, the most economically favorable QD-based biosensor type depends on the context of use. For community screening and low-resource settings, colorimetric QD sensors are most cost-efficient, whereas for portable POC with higher sensitivity, electrochemical QD sensors strike the best balance. For high-throughput labs, optical QD sensors become cost-effective due to multiplexing, despite high instrument costs.

## 4 | Summary of Economic Aspects

The QD-based biosensors, including fluorescence and FRET platforms, electrochemical transducers, and colorimetric assays, have emerged as rapid, highly sensitive, and potentially cost-effective alternatives to conventional TB diagnostics, such as culture and PCR, which remain slow, infrastructure-intensive, and expensive. Recent studies demonstrate that QD nanosensors markedly enhance analytical sensitivity for both nucleic-acid and protein targets while enabling compact optical readouts and multiplexed detection of multiple TB biomarkers, including drug-resistance genes, within a single assay (Table 2) [26, 93]. Nanomaterial-based biosensors more broadly offer reduced assay times, low sample-volume requirements, and compatibility with miniaturized, POC systems, addressing key shortcomings of existing nucleic-acid amplification tests such as GeneXpert in resource-limited settings ([90, 127]). Economically, QD biosensors have the potential to lower per-test cost by combining high sensitivity with multiplexing capabilities, decreasing reagent consumption, instrument dependency, and the need for repeat testing. Furthermore, their integration into portable POC platforms minimizes logistical costs associated with centralized laboratory infrastructure ([26, 127]). From a materials perspective, traditional SQDs provide excellent optical properties but present toxicity and regulatory concerns due to their heavy-metal content. This has accelerated interest in CQDs and other metal- or lead-free nanomaterials, which offer improved biocompatibility, aqueous dispersibility, and scalable, low-cost synthesis [142, 143]. PQDs have gained attention for their strong emission and facile, low-temperature synthesis, yet their instability in the presence of moisture, oxygen, and heat remains a barrier to translational use. Current efforts to enhance PQD stability including ligand engineering, core-shell architectures, polymer encapsulation, and crosslinking strategies are showing promise in improving durability and functional robustness [144]. Collectively, these technological, economic, and materials advances highlight the growing significance of QD-based TB diagnostics. By integrating ultrasensitive, multiplexed detection with the development of biocompatible, stable, and manufacturable QD formulations, this emerging platform is well positioned to deliver affordable, clinically validated diagnostic solutions tailored to high-burden, low-resource settings [26, 90, 93].

## 5 | Challenges and Limitations of QDs in TB Biosensing Detection

Since the development of biosensors nearly five decades ago, they have advanced significantly, particularly in the last decade. However, only a few, such as electrochemical glucose sensors and lateral flow pregnancy tests, have achieved widespread commercial success [148–150]. The United Sated of America (USA) first commercialized and approved a test designed for TB diagnosis, specifically for detecting LTBI using IGRA in 2001 [151], marking the first commercial use of IGRA technology for TB diagnosis globally. A USA-based company, Cepheid, commercialized GeneXpert Mtb/RIF biosensor in 2010 for both TB diagnosis and drug resistance detection [152]. This test can identify Mtb-DNA and simultaneously detects rifampicin resistance, which is a key marker for MDR TB. The GeneXpert Mtb/RIF biosensor was able to provide rapid and accurate results in less than 2 h, a significant improvement over traditional culture methods that could take weeks [153]. Whereas India, Molbio Diagnostics commercialized a portable chip-based PCR platform known as Truenat, for TB and drug-resistance detection, ideal for decentralized testing in 2020 [79, 154]. The Truenat platform was endorsed by the WHO in July 2020 as an initial diagnostic test for TB and rifampicin resistance, suitable for use at peripheral health facilities with minimal infrastructure [155].

Currently, commercial TB biosensors are dominated by molecular diagnostic platforms (PCR, IGRA) rather than QD-based or nanomaterial-based sensors. Although QD and advanced nanomaterial biosensors show promise in research, they have not yet

**TABLE 2** | Recent studies of quantum dot (QD)-based nanobiosensor for tuberculosis (TB) detection.

| QDs | Surface modification molecule | Tested sample | Biomarker | Nanosensor | LOD | References |
|---|---|---|---|---|---|---|
| CdTe | Mercaptopropionic acid | Sputum | IS6110 *gene* | Molecular biosensors | 35 pM | [13] |
| CdSe/ZnS | Thioglycolic acid | Pure antigens | CFP10-ESAT6 | Electrochemical immunosensor | 15 pg/mL | [102] |
| CdTe | — | Blood | IP 10 protein | Aptasensor | 3 fg/mL | [108] |
| Sn–Te–Se | L-cysteine | Serum | IFN-$\gamma$ aptamer | Electrochemical biosensor | 0.151 pg/mL | [115] |
| InTeSe | L-cysteine | Serum | IFN-$\gamma$ | Electrochemical aptasensor | 0.312 pg/mL | [116] |
| CdS | Mercaptopropionic acid | Sputum | Mtb-DNA | PNA biosensor | $8.948 \times 10^{-13}$ M | [103] |
| CdSe/ZnS | L-cysteine | — | Anti-MA antibodies | Fluorescent lateral flow assay | — | [104] |
| CdTe | — | Vapor samples | Methyl nicotinate | Fluorescent assay | 0.59 µM | [105] |
| CdTe | Mercaptopropionic acid, thiomalic acid | Sputum | IS1081 gene fragment | POC | 0.13 and 0.33 mol/L | [106] |
| CdTe | — | Clinical sputum | ESAT-6 gene | FRET | 10-fold | [145] |
| CdS | | Blood | IFN-$\gamma$ | Immunosensor | 0.34 pg/mL | [146] |
| CdSe/ZnS | — | Urine | LAM | Fluorescence detector | 50 pg/mL | [147] |
| $MAPbBr_3$ | — | Biological sample | Methyl nicotinate | Fluorescent assay | 71.13 nM | [122] |
| CsPbBr3 | — | Mtb strains | Mtb DNA | Fluorescence detection | 51.9 pM | [121] |
| GQDs | — | Antigen | Antigen CFP-10 | Electrochemical biosensor | 0.33 ng/mL | [128] |
| SWCNT | — | Antigen | Ag85B | FET biosensor | 0.05 fg/mL | [129] |
| GQDs | — | N/A | Anti-MA antibodies | Fluorescent lateral flow assay | N/A | [104] |
| Unspecified QD | — | Sputum | DNA IS1081 | Colorimetric assay | 3.3 mol/L | [133] |

Abbreviations: CdSe, cadmium selenide; CdTe, cadmium telluride; FET, field-effect transistor; FRET, fluorescence resonance energy transfer; GQDs, graphene quantum dots; LAM, lipoarabinomannan; LOD, limit of detection; MA, mycolic acids; Mtb, *Mycobacterium tuberculosis*; PNA, peptide nucleic acid; POC, point-of-care; SWCNT, single-walled carbon nanotube.

reached large-scale commercialization due to challenges in stability, regulatory approval, and cost [87, 156]. Despite the proven success of glucose sensors, the commercialization of new biosensors remains complex. Key difficulties include identifying viable markets, demonstrating advantages over existing analytical techniques, and ensuring long-term stability, biosensors must remain functional for at least 6 months post-manufacture to be commercially viable [86, 87]. Additionally, cost-effective manufacturing and ethical considerations surrounding biosensor deployment are critical factors. Fluorescence-based assays, particularly those using QDs, offer high sensitivity and specificity due to their unique optical properties but require specialized instrumentation and are susceptible to photobleaching. In contrast, electrochemical assays, which leverage carbon-based nanomaterials like graphene, provide rapid response times, high sensitivity, and low production costs but may suffer from electrode fouling [157]. The optimal TB biosensor design must balance sensitivity, specificity, cost, and operational simplicity, aligning with WHO's target product profiles (TPP) for TB diagnostics (WHO, 2024, [158]). Future advancements should integrate multiple detection strategies to enhance diagnostic reliability and real-world applicability [26].

QDs advantageous properties that make them useful in biological application, in particular TB detection, have been discussed in the previous sections. Despite QDs promising optical and electronic properties, among others, QD-based biosensors face several challenges in TB diagnostics [93]. Many QDs consisting of heavy metals, such as Cd, Pb, and Hg, raise concerns about cytotoxicity and environmental issues [93]. Most high performing researched QDs are from Groups II–VI SQDs, and the emerging

PQDs that contain Pb, heavy metals that can leach into biological systems, posing serious health and environmental risks [62]. When used in clinical diagnostics, these NPs interact directly with biological fluids or tissues, which can trigger immune responses, oxidative stress, and cellular damage. Regulatory agencies impose strict safety standards, making approval difficult for materials with potential cytotoxicity [159]. Although strategies, such as surface passivation, polymer encapsulation, and the development of carbon-based or silicon QDs, have been explored to mitigate toxicity, these approaches often increase production complexity and cost [19, 132]. Furthermore, most QD biosensing studies do not run/attach cytotoxicity studies when publishing their results, which leads to a repetition of the same QD-material but with different functionalization molecule or biological application [160].

## 6 | Conclusion and Future Perspective

This review discussed the use of QD-based biosensors for TB detection. QDs were thoroughly introduced highlighting their exceptional properties enable their use in biomedical applications. These nanomaterials enhance TB detection by producing strong, size-tunable fluorescence signals that allow accurate identification of biomarkers at very low concentrations. Additionally, their broad absorption spectra and narrow emission peaks support multiplexed detection of multiple TB targets in a single assay, improving diagnostic efficiency. Three different types of QDs, SQDs, PQDs, and CQDs based biosensors advanced in TB detection were discussed thoroughly. Literature review revealed that majority of researched QDs for TB biosensing studies were SQDs, Cd-based. A few examples of PQDs and CQDs-based biosensors were also discussed highlighting the gap in the research of these types of QDs. The different types QD-based biosensors studied showed a compelling balance between analytical performance and cost-effectiveness, particularly when used in setups that minimize instrumentation operating cost. Although optical biosensors offer high sensitivity and multiplexing for well-equipped laboratories, their reliance on expensive fluorescence readers limits affordability in devolved settings. In contrast, electrochemical and colorimetric QD platforms provide scalable, low-cost alternatives for POC TB screening, reducing logistical expenses and improving early case detection. Affordable, safer QDs, such as CQDs and portable readers, can make QD biosensors cost-effective and scalable, filling the gap between low-cost but poor-performing tests and high-cost molecular platforms.

The integration of QD-based biosensors into TB diagnostics holds transformative potential, not only for improving analytical performance but also for reshaping global health advancements. Future research should focus on scalability and cost optimization, particularly through the development of low-toxicity QDs, carbon and perovskite and simplified fabrication methods that reduce material and safety expenditures. Additionally, the use of optical systems and smartphone-based readouts could bridge the gap between high-sensitivity laboratory assays and affordable POC solutions, enabling widespread usage in resource-limited settings. Another critical aspect is multiplexing capability, which makes QD-based biosensors more cost-effective and clinically valuable by enabling combined testing for TB and related infections (HIV) in a single assay. Beyond technical and economic considerations, regulatory frameworks and standardization protocols will be essential to accelerate clinical translation and ensure reproducibility across diverse environments.

The commercialization of QD-based diagnostics will depend on overcoming regulatory barriers, cost constraints, and global accessibility challenges. Open-source innovation, interdisciplinary collaboration, and public–private partnerships will be essential to drive QD integration into mainstream diagnostics. Future research should focus on scalable manufacturing techniques, ensuring environmental sustainability while optimizing QD longevity and performance in diverse clinical and field settings. With continued breakthroughs in nanotechnology, artificial intelligence, and synthetic biology, the unimaginable possibilities for QD-based TB diagnostics and healthcare applications are just beginning to unfold. By bridging the gap between innovation and practical implementation, QDs could redefine infectious disease detection, personalized medicine, and global health strategies, bringing us closer to a future where rapid, precise, and accessible diagnostics are the norm rather than the exception.

### Conflicts of Interest

The authors declare no conflict of interest.

### Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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