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Probing Nano-systems using Innovative Raman Spectroscopy: A Mini-review on Emerging Frontiers in Human Health, Disease Control and Unexplored Gaps

Adeyinka Aina[1]* and Oluwafemi Michael Adedire[2]

[1]*School of Engineering, University of Lancashire, Preston, PR1 2HE, UK*
[2]*Department of Microbiology, Federal College of Agriculture, Ibadan, Nigeria*

Abstract

Nanotechnology has rapidly emerged as a cornerstone of modern biomedicine, offering innovative solutions for diagnostics, therapeutics and disease monitoring. Among analytical tools, Raman spectroscopy has distinguished itself as a powerful technique for probing nano-systems at unprecedented resolution. This review explores the integration of advanced Raman modalities such as Surface-Enhanced Raman Spectroscopy (SERS), Tip-Enhanced Raman Spectroscopy (TERS) and Coherent Anti-Stokes Raman Scattering (CARS) with engineered nanomaterials. Such materials include metallic nanoparticles, polymeric carriers and grapheme-based systems. These synergistic platforms enable precise characterization of structural integrity, biofunctionalization and real-time interactions at the nano-bio interface. Applications span from probiotic encapsulation and viability assessment to rapid pathogen fingerprinting, antimicrobial nano-formulations, host-microbe characterization and Raman-tracked nano-vaccines. The impact of nano-enabled Raman probes extends beyond infectious diseases, with emerging applications in oncology, as well as cardiovascular and metabolic disorders, while integration with artificial intelligence enhances precision diagnostics. The review also highlights breakthroughs in miniaturized Raman devices, multiplexed probes and hybrid imaging systems, positioning these technologies for point-of-care and personalized medicine. Despite their transformative potential, challenges persist, which are currently unexplored, these include signal reproducibility, depth penetration, safety evaluation, regulatory gaps and workflow integration. Addressing these barriers through standardized protocols, multi-site validation and translational frameworks is key to clinical adoption. Collectively, this review underscores the pivotal role of innovative Raman-guided nano-systems in redefining future healthcare landscapes.

Keywords: Nano-systems • Healthcare • Point-of-care medicine • Raman spectroscopy

Introduction

Nanotechnology has rapidly emerged as one of the most transformative and interdisciplinary fields in the biomedical sciences, offering powerful new platforms for diagnostics, targeted therapy and controlled drug delivery Fard NT, et al. [1]. Nanoscale manipulation offers the opportunity to harness unique physicochemical properties that are not evident at the bulk level, such as enhanced surface-to-volume ratios, tunable optical features and improved biocompatibility [2]. These characteristics have fueled a wave of innovation across medicine and biotechnology, particularly in the context of precision healthcare. As diseases become increasingly understood at the molecular and cellular levels, there is a growing demand for tools that can match this scale of complexity, providing accurate, real-time insights into biological processes [3].

Among the diverse set of characterization techniques available to nanomedicine, Raman spectroscopy has gained significant attention due to its ability to probe molecular structures in a rapid, label-free and non-destructive manner [4]. Unlike traditional biochemical assays that often require invasive sample preparation or destructive chemical labeling, Raman spectroscopy relies on the inelastic scattering of light to reveal molecular fingerprints [3,5]. Recent advances in Raman-based modalities have further expanded their sensitivity and resolution, enabling the investigation of systems at the nanoscale. Such advances include Surface-Enhanced Raman Spectroscopy (SERS), Coherent Anti-Stokes Raman Scattering (CARS) and Tip-Enhanced Raman Spectroscopy (TERS) [6,7].

One of the most promising areas where nanotechnology could intersect with biomedical applications is in the study of host–microbe interactions, probiotics and infectious disease mechanisms [8]. Understanding the complex dynamics of these microbial communities requires tools that can capture biochemical information without disrupting their natural state [4]. Raman spectroscopy integrated with nanoscale platforms offers unique advantages to detect microbial metabolites, monitoring probiotic viability and identification of pathogenic signatures in real time [8]. Conventional diagnostic methods, while effective, are often time-consuming, resource-intensive and limited in their ability to provide rapid actionable data [1]. Nanotechnology-enhanced Raman spectroscopy has the potential to detect specific pathogen directly from clinical samples [9]. This review therefore seeks to explore the evolving landscape at the intersection of nanotechnology and Raman spectroscopy, with a particular highlight on probiotics, infectious disease control and future prospects.

Fundamentals of Raman spectroscopy for nano-systems

Raman spectroscopy is a powerful analytical technique that relies on the inelastic scattering of photons, enabling the detection of vibrational fingerprints unique to different molecules [10]. This property makes it a valuable tool for identifying molecular structures and chemical compositions with high specificity. Over the years, several advanced variants have been developed to enhance the capabilities of conventional Raman spectroscopy, particularly for studying nano-systems (Table 1). Techniques such as Surface-Enhanced Raman Spectroscopy (SERS), Coherent Anti-Stokes Raman Scattering (CARS) and Tip-Enhanced Raman Spectroscopy (TERS) have significantly extended the

***Address for Correspondence:** Adeyinka Aina, School of Engineering, University of Lancashire, Preston, PR1 2HE, UK; E-mail: ATAina@lancashire.ac.uk*

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sensitivity and spatial resolution of the method [6]. For instance, SERS uses metallic nanostructures to amplify weak Raman signals, allowing detection at the single-molecule level. Similarly, CARS provides coherent and background-free signals that are particularly useful in imaging applications, while TERS combines scanning probe microscopy with Raman scattering to achieve nanoscale spatial mapping [6,11].

These innovations make Raman spectroscopy especially well-suited for the characterization of nano-systems and the monitoring of their interactions within biological environments [7]. Compared to more established techniques such as fluorescence microscopy and electron microscopy, Raman offers distinct advantages. It is a label-free approach, meaning that samples do not require external dyes or markers, thus preserving their native state [4]. Moreover, it enables real-time molecular analysis with minimal preparation, making it both efficient and versatile for a wide range of applications [12]. Overall, Raman spectroscopy and its advanced forms represent a crucial set of tools in nanoscience, providing detailed molecular insights that support developments in materials research, biomedical diagnostics, as well as nanotechnology (Table 1).

Engineered nano-systems and Raman-based functional characterization

Engineered nano-systems represent a rapidly evolving class of materials with transformative potential in diagnostics, therapeutics and environmental applications. These systems include metallic nanoparticles such as Gold (Au) and Silver (Ag), polymeric and lipid-based carriers, carbon-derived nanostructures and quantum dots. Each nano-system offers unique physicochemical properties that can be tailored for specific biomedical or environmental functions [21]. For instance, carbon quantum dots have emerged as versatile nanomaterials due to their excellent biocompatibility, tunable fluorescence and capacity to enhance stress tolerance in biological systems. These remarkable features make them attractive for applications that extend beyond medicine to agriculture and soil health improvement [22].

Raman spectroscopy and particularly Surface-Enhanced Raman Spectroscopy (SERS), plays a pivotal role in the functional characterization of these nano-systems. It enables sensitive and label-free monitoring of nanocarrier surface modifications, stability profiles and cargo-loading efficiencies. Importantly, SERS-active nanoparticles serve dual roles as both diagnostic probes and therapeutic carriers, demonstrating strong potential in precision medicine [23]. Their ability to distinguish subtle molecular changes has been leveraged in oncology and pandemic-related diagnostics, where rapid and accurate detection is crucial.

Recent advancements in computational and high-throughput Raman mapping further enhance the translational value of these technologies. Automated spectral profiling allows for systematic evaluation of nanocarrier reproducibility, scalability and long-term stability, thereby addressing one of the key bottlenecks in clinical translation [24]. The integration of ab initio Raman spectral simulations with experimental mapping also provides new opportunities for predictive modeling and rational design of next-generation nanomaterials [25]. Collectively, these developments underscore the convergence of nanotechnology and Raman-based analytics as a promising frontier for clinical diagnostics, therapeutics and sustainable environmental solutions.

Nano-systems and probiotics: Raman-guided investigations

Probiotics are essential for preserving gut microbiota balance and overall systemic health, functioning through mechanisms such as competitive exclusion of pathogens, production of antimicrobial metabolites like short-chain fatty acids, as well as modulation of immune responses [26]. These actions not only bolster intestinal barrier integrity but also mitigate inflammation, improve metabolic functions and confer benefits against conditions like type 2 diabetes and Inflammatory Bowel Disease (IBD) [27]. Probiotics have also been linked to the suppression of neurological disorders by influencing the gut-brain axis [28]. Nano-formulations enhance probiotic efficacy by improving stability against harsh gastrointestinal conditions. This enables efficient encapsulation and facilitates targeted delivery to specific gut sites, which is particularly advantageous for geriatric populations vulnerable to age-related physiological declines and heightened disease risks [29].

Raman spectroscopy emerges as a transformative tool in this domain, offering non-invasive methods to differentiate viable from non-viable cells, through a nano-probiotic interaction assay (Figure 1). The technology evaluates encapsulation efficiency in nano-systems and map metabolic activity within complex biofilms [30]. In this regard, confocal Raman microscopy has demonstrated high precision in identifying bacterial species in oral subgingival biofilm models, achieving 100% accuracy for planktonic cells and 90% for

Table 1. Raman modalities and nano-system applications.

Raman Modality	Principle/Features	Nano-system Applications	References
Conventional Raman Spectroscopy	Inelastic scattering of light providing molecular fingerprints; label-free analysis	- Monitoring structural integrity and functionalization of nanoparticles (Au, Ag, polymers, lipids, quantum dots, CNTs, graphene) - Baseline tool for nano-system screening	Safar W, et al. [13]
Surface-Enhanced Raman Spectroscopy (SERS)	Enhancement *via* plasmonic nanostructures (metal nanoparticles, roughened surfaces); high sensitivity	- Pathogen identification and resistance profiling - Probiotic viability distinction - Detection of cancer biomarkers - Tracking stability of nano-vaccine systems - Biofilm detection and disruption monitoring	Wang Y, et al. [14] and Rojas Martínez V, et al. [15]
Tip-Enhanced Raman Spectroscopy (TERS)	Combines scanning probe microscopy with Raman; nanoscale spatial resolution	- In situ mapping of nano-bio interactions - Investigation of molecular structure - Host-pathogen interaction tracking at nano-bio interface	Safar W, et al. [13] and Britz-Grell AB, et al. [16]
Coherent Anti-Stokes Raman Scattering (CARS)	Nonlinear Raman technique; provides stronger signals and fast imaging	- High-speed, label-free imaging of nano-systems in biological matrices - Highly multiplexed selective imaging - Real-time in vivo detection of oxidative stress and inflammation	Tang Q, et al. [17]
Hybrid Raman Platforms (e.g., Raman–fluorescence, Raman–MRI)	Integrates Raman with other imaging modalities for multimodal analysis	- Multi-scale monitoring of targeted nano-drug delivery - Enhanced cancer and cardiovascular diagnostics - Smart nano-systems with Raman-responsive release	Khadem H, et al. [18]
Portable/Miniaturized Raman Devices	Compact Raman systems for point-of-care	- Rapid nano-system-based infectious disease diagnostics - Potential for bedside monitoring of drug metabolism - Integration with artificial intelligence and machine learning for personalized medicine	Ilchenko O, et al. [19] and Synytsya A, et al. [20]

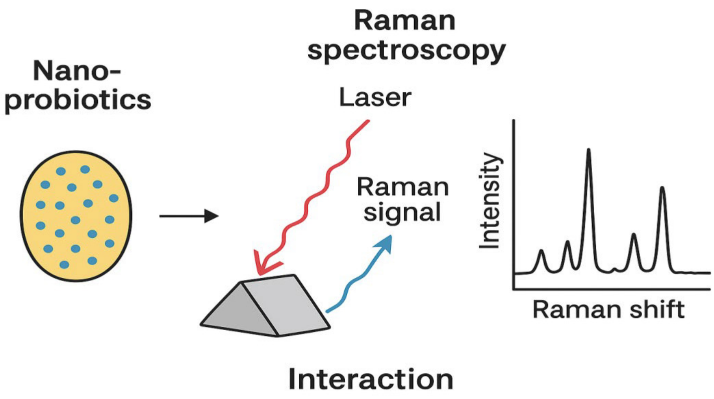

Figure 1. Nano-probiotic interactions monitored by Raman spectroscopy.

mono-species biofilms [31]. Such identification, achieved through orthogonal partial least squares discriminant analysis, highlights spectral differences in nucleotide and amino acid regions. Advancing this, Raman-based metabolic fingerprinting enables real-time, marker-free assessment of probiotic activity in host environments by detecting key metabolites like amino acids and bile acids [32]. The assessment identified dysbiosis biomarkers linked to gastrointestinal disorders such as Inflammatory Bowel Disease (IBD) and colorectal cancer.

Metabolic fingerprinting supports dynamic monitoring of microbiota responses to interventions, fostering novel applications in biomarker discovery and AI-integrated diagnostics. The synergy of nano-enabled probiotic delivery with Raman-guided investigations unlocks pathways for personalized therapies, optimizing geriatric health outcomes by addressing microbial imbalances non-invasively and enhancing therapeutic precision in systemic disease management.

Nano-systems, infectious diseases and Raman-based detection

Nano-systems are increasingly recognized as transformative tools in the fight against infectious diseases, offering advancements in diagnostics, therapeutics and vaccine delivery [33]. Their ability to interact with pathogens at the molecular and cellular level enables highly sensitive and specific interventions that far surpass traditional methods. For instance, Surface-Enhanced Raman Scattering (SERS)-based assays provide ultra-rapid identification of pathogens within minutes by exploiting their unique molecular fingerprints. This approach significantly reduces the diagnostic turnaround time compared to culture-based methods, which often require days to yield results [34]. Such rapid detection not only accelerates patient management but also plays a crucial role in controlling outbreaks through early surveillance.

In addition to diagnostics, nano-antimicrobials are emerging as effective alternatives to conventional antibiotics, particularly in addressing the global challenge of antimicrobial resistance. Silver nanoparticles and polymeric nano-antibiotics exhibit strong antimicrobial properties by disrupting bacterial membranes, preventing biofilm formation and enhancing drug penetration into resistant microbial communities [35]. These properties make them promising candidates for tackling persistent infections caused by opportunistic pathogens. In parallel, nanotechnology is being integrated into vaccine design, where Raman-based imaging allows real-time visualization of nano-vaccine stability, delivery and host–pathogen interactions [33]. Such imaging approaches not only optimize formulation design but also provide insights into immune response modulation, thereby improving vaccine efficacy and control of disease outbreak.

Moreover, Raman spectroscopy and microscopy extend beyond human health into agricultural applications, where they are increasingly used for plant disease diagnosis [36]. This cross-disciplinary utility underscores the versatility of Raman-based detection as a platform technology for both clinical and environmental pathogen monitoring. Collectively, the integration of nanotechnology with Raman-based approaches establishes a powerful paradigm for infectious disease management, as it enables rapid, precise and multi-scale interventions that address both prevention and treatment [37].

Nano-systems for human health monitoring beyond infectious diseases

Beyond infectious diseases, nano-systems are increasingly being applied in diverse medical domains, particularly in cancer diagnostics, cardiovascular disease management and metabolic disorders [38,39]. In oncology, Raman spectroscopy combined with functionalized nanoprobes enables ultrasensitive detection of cancer biomarkers at preclinical stages, thus offering significant improvements in survival outcomes through early intervention [40,41]. Similarly, in cardiovascular medicine, nano-systems facilitate targeted delivery of antioxidants and anti-inflammatory agents to damaged tissues, while real-time Raman monitoring provides dynamic assessment of therapeutic efficacy [39,42].

A major frontier in this field lies in the integration of nano-enabled systems with Artificial Intelligence (AI) and deep learning approaches for spectral interpretation [43]. This synergy not only enhances diagnostic accuracy but also enables high-throughput, personalized disease monitoring with minimal invasiveness. Furthermore, advances in multifunctional and stimuli-responsive nanoparticles could allow simultaneous diagnosis, drug delivery and therapeutic monitoring, thereby ushering in a new era of theranostics [44]. Looking ahead, future perspectives point to the convergence of nanotechnology with wearable biosensors, wireless data transmission and cloud-based analytics. Such integration could establish continuous, remote health monitoring platforms capable of predicting disease onset before clinical symptoms emerge.

Technological innovations and future directions

Recent technological advances in Raman spectroscopy and nanomedicine are opening unprecedented opportunities for precision diagnostics and therapeutics. Miniaturized and portable Raman devices are increasingly being deployed for real-time, point-of-care monitoring, enabling non-invasive and accessible patient assessments outside conventional laboratory settings [45,46]. Furthermore, multiplexed Raman probes have demonstrated the capacity to simultaneously track diverse nano-bio interactions, significantly enhancing the scope of live-cell profiling and biomarker detection [47]. These innovations mark a critical step toward scalable and clinically viable nano-diagnostic platforms.

Hybrid imaging platforms represent another frontier, where the integration of Raman spectroscopy with modalities such as Magnetic Resonance Imaging (MRI) and fluorescence creates powerful multimodal diagnostic systems. These combinations not only enhance sensitivity and specificity but also provide comprehensive molecular and anatomical insights, particularly valuable for drug delivery and disease progression monitoring [48]. In parallel, the emergence of smart nano-systems responsive to Raman excitation and capable of controlled, stimuli-responsive drug release underscores the evolution toward theranostic applications that unite diagnosis and therapy within a single platform [49].

Machine learning is anticipated to play a transformative role by extracting predictive insights from complex Raman datasets. The application of artificial intelligence in spectral analysis promises accelerated development of personalized medicine strategies, where patient-specific nanoscale responses guide therapeutic decisions [50]. Equally critical is the emphasis on sustainability and biocompatibility, with ongoing research directed toward biodegradable, non-toxic nanomaterials that align with global regulatory and environmental imperatives. Future perspectives also highlight the importance of regulatory harmonization and translational research to bridge the gap between laboratory innovation and clinical adoption [51].

Addressing standardization challenges in data acquisition, material characterization and clinical validation will be pivotal for safe and effective deployment. Collectively, these converging advances underscore the potential of Raman-enabled nanotechnologies not only in infectious disease management but also across oncology, regenerative medicine and pharmacological process development, thereby reshaping the landscape of next-generation precision medicine.

Challenges and knowledge gaps

Strengths, such as label-free, multiplexed molecular investigation, specificity, as well as surface-enhanced spectrometry, make Raman approaches attractive for biomarker detection, host-microbe characterization and intraoperative tumor margin screening. Nevertheless, the path from promising laboratory demonstrations to validated clinical tools remains fragmented. Raman signals may be weak and require enhancement strategies, raising reproducibility concerns. The long-term safety of engineered nano-systems in human applications requires extensive toxicological evaluation. Regulatory frameworks for nano-enabled Raman diagnostics and therapeutics are underdeveloped, consequently delaying clinical translation. Ethical considerations regarding personalized nano-therapies also require far-reaching evaluations.

Reproducibility, interference and standardization of nanostructures

Surface-enhanced Raman spectroscopy performance is highly sensitive to nanostructure geometry, composition, interparticle spacing and surface chemistry. Previous studies have shown that broad inter-batch and inter-lab variability in enhancement factors and spectral baselines, complicating meta-analysis and independent verification of reported detection limits [52]. Efforts to produce high-precision substrates have increased (through the adoption of top-down lithography, templated synthesis and flexible substrates), but reproducibility at scale remains unresolved [53].

Reports on Raman spectroscopy demonstrate ultralow limits of detection in simple aqueous buffers or spiked samples, while clinical matrices (whole blood, serum, urine, sputum) introduce proteins, lipids and salts that attenuate signals or cause background interference. Systematic cross-matrix validation is often missing and the clinical relevance of reported Limits of Detection (LODs) is rarely contextualized against physiological concentrations as well as inter-patient variability [52,53].

Safety and toxicology of nanoprobes

Beyond biodistribution, long-term retention in organs such as liver, spleen and brain has raised concerns about chronic exposure risks associated with Raman spectroscopy [54]. Emerging studies point to the potential for oxidative stress, genotoxicity and immune modulation, particularly when nanoparticles are modified with targeting ligands. Harmonized frameworks for toxicological testing, similar to those being shaped for nanomedicines by the FDA and EMA, will be critical to avoid fragmented approaches. Furthermore, advanced *in vitro* human organ-on-chip systems may provide more predictive safety assessments, reducing reliance on animal models while generating regulatory-grade data [55].

Plasmonic nanoparticles (gold, silver) are the core of many *in vivo* SERS probes [56]. Preclinical work indicates variable biodistribution, potential organ accumulation and possible immune recognition, but long-term clearance and chronic toxicity profiles are still incomplete [57]. Regulatory guidance recognizes nanomaterial-specific safety questions, but concrete, standardized toxicology workflows tailored to Raman nanoprobes are only beginning to emerge [58,59].

Depth penetration and *in vivo* sensitivity

The *in vivo* applications of Raman spectroscopy at substantial tissue depths are significantly constrained by the inherent optical properties of biological media [60]. Tissue is a highly scattering and absorptive environment, where photons are subject to multiple scattering events and wavelength-dependent absorption by chromophores such as hemoglobin and water [61]. These phenomena could attenuate both the incident excitation light and the already intrinsically weak Raman-scattered signal, resulting in a pronounced loss of detection sensitivity as depth increases. Near-InfraRed (NIR) excitation has been adopted as a partial solution, since reduced scattering and absorption at longer wavelengths permits somewhat deeper light penetration.

Similarly, the development of NIR-resonant Surface-Enhanced Raman Scattering (SERS) nanoprobes has substantially amplified Raman signals, facilitating detection in more complex tissue environments [62]. Despite these advances, the reliable collection of clinically useful Raman signals from deep tissue remains a formidable challenge. In addition to photon attenuation, tissue autofluorescence, photon diffusion and inter-patient variability in optical properties introduce further noise and inconsistency in signal acquisition [60,63]. Consequently, while Raman spectroscopy and SERS hold considerable promises for applications such as noninvasive cancer diagnostics, intraoperative surgical guidance and metabolic monitoring, depth penetration limits their current clinical implementation.

Data bias and machine-learning overfitting

Addressing data scarcity requires the establishment of large-scale, multi-center Raman spectral repositories, curated with adherence to Findable, Accessible, Interoperable, Reusable (FAIR) data principles [64]. This would mirror successful initiatives in proteomics such as MIAPE, where structured metadata reporting improved reproducibility. Without such shared resources, the risk of inflated performance claims due to overfitting remains significant. Machine learning enhances Raman spectral classification, but many studies rely on small, single-center cohorts and omit external validation, leading to overfitting. The field lacks well-curated spectral repositories and consensus on validation standards [65].

Clinical workflow integration

In addition to acquisition time and ergonomics, integration with hospital IT infrastructure, particularly Electronic Health Records (EHR), constitutes a critical bottleneck impeding the widespread clinical adoption of Raman spectroscopy [66]. Even technically robust Raman platforms frequently fail to integrate seamlessly into established clinical workflows owing to prolonged acquisition times, suboptimal ergonomic design and the absence of clinically actionable outputs [52]. Moreover, heterogeneity in data interpretation, coupled with the lack of standardized clinical guidelines, undermines clinician confidence in the reliability of Raman-derived insights. Financial considerations, including high costs of IT infrastructural acquisition, implementation and maintenance, further exacerbate these challenges, particularly in resource-limited healthcare systems [67]. Unless these systemic and operational limitations are addressed, Raman spectroscopy is likely to remain confined to research and pilot applications rather than achieving widespread integration into routine clinical practice.

Regulatory and manufacturing barriers

One persistent barrier against the adoption of Raman spectroscopy is the lack of clarity in regulatory classification. Raman nanoprobes may be viewed simultaneously as drugs, devices, or combination products, complicating the approval pathway [68]. Good Manufacturing Practice (GMP) at scale remains a technical challenge, particularly in maintaining batch-to-batch reproducibility of SERS substrates, which directly impacts signal consistency [69]. Initiatives from regulatory agencies, including U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) working groups, are beginning to outline harmonized guidance for nanotechnology-enabled diagnostics [57,58]. Regulatory pathways for nanomaterial-enabled devices remain evolving, with ambiguity regarding classification and GMP standards. Manufacturing reproducible SERS substrates at scale has also complicated the classification and standardization of Raman nanoprobes.

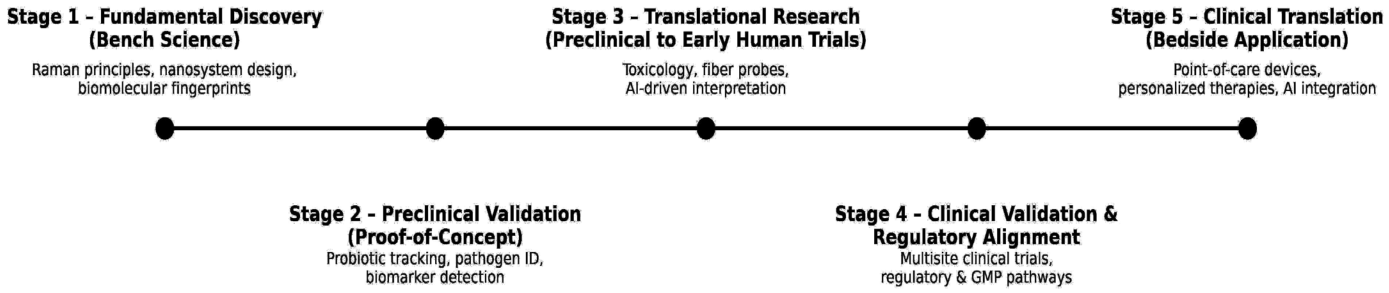

Figure 2. Projected roadmap of technological evolution: From bench to bedside.

Economic and reimbursement gaps

Another major condition limiting the potential of Raman technology in microbial exploitation and human health is the scarcity of prospective cost-effectiveness studies that align with payer decision frameworks [70]. Health economic evaluations in related fields show wide methodological variation, underscoring the need for standardized approaches when evaluating Raman technologies. The targeted seed funding programs of National Institutes of Health (NIH) can accelerate early evidence generation, particularly for point-of-care applications with strong public health relevance.

In parallel, reimbursement models like the Transitional Coverage for Emerging Technologies (TCET) of Centers for Medicare and Medicaid Services (CMS) provide a unique chance for early clinical deployment while evidence collection continues [71]. In addition to direct costs, economic models have failed to effectively incorporate downstream savings associated with early diagnosis and personalized treatments enabled by Raman systems. Health-economic evidence supporting Raman spectroscopy or SERS is sparse. Without demonstrations of cost-effectiveness, payer adoption is limited [71,72]. New reimbursement models like the U.S. TCET provide opportunities if developers generate prospective evidence and such coverage should be provided globally towards the development of Raman diagnostics, therapeutics and gastrointestinal health monitoring.

However, to overcome these limitations associated with the application of Raman spectroscopy in human health and microbial exploration, several methodological, technical and translational strategies can be adopted. Inclusion of universal reference substrates and calibration standards, as well as blind inter-laboratory ring trials, can improve reproducibility. A “Minimum Information for Publication of Raman/SERS Experiments” checklist, modeled on the MIQE/MIAPE initiatives [72,73] which has significantly improved reproducibility in other molecular diagnostics, can be adopted in Raman approaches. Another key requirement is the implementation of systematic multi-matrix validation, supported by standardized preprocessing protocols and the development of matrix-specific correction algorithms. Furthermore, limits of detection should be reported relative to clinically meaningful thresholds to ensure translational relevance [52].

Going forward, technical advances should include hybrid strategies that integrate Near-InfraRed (NIR) excitation with optimized SERS labels, alongside adaptive optical approaches and adherence to evidence-based laser exposure guidelines. While NIR optimization provides partial solutions, deeper integration of Raman spectroscopy with complementary modalities such as photoacoustic imaging and optical coherence tomography could enhance tissue penetration and diagnostic accuracy [74]. Advances in miniaturized fiber-optic probes, particularly those incorporating multi-core designs, open new possibilities for endoscopic and intraoperative applications. Additionally, algorithmic progress in AI-driven noise reduction and adaptive optics may allow useful signals to be extracted even under challenging scattering conditions [75]. Following a clearly defined roadmap to technological evolution, wearable or implantable Raman sensors could, in the future, enable continuous, real-time monitoring of probiotics, pathogens, as well as biochemical changes deep within tissues (Figure 2).

Equally important is the establishment of standardized *in-vivo* pharmacokinetic and toxicological evaluation panels, together with the design of nanoprobes optimized for efficient clearance or biodegradation.

Publicly accessible comparative safety datasets will be vital for transparency and reproducibility, while early engagement with regulatory agencies will help align study protocols with evolving expectations [57,58]. Emphasis should also be placed on translational opportunities in clinically accessible domains, such as dermatology, mucosal surface imaging and intraoperative surgical guidance. In parallel, the establishment of multi-site spectral repositories, requirements for external validation in publications and the development of uncertainty-aware and interpretable analytical algorithms will strengthen reproducibility and reliability. The application of domain-adaptation techniques would further provide a means to mitigate dataset shifts across populations and clinical environments [64]. From an implementation perspective, embedding (engineering) human factors into device design will enhance usability and clinical adoption [68]. Outputs should be designed to support decision-making rather than providing raw spectral data and interoperability with hospital information systems must be ensured. Pragmatic implementation trials, explicitly evaluating workflow integration and clinical impact will provide essential evidence of feasibility.

Translational progress also requires early and sustained interaction with regulatory authorities, supported by the publication of consensus-based roadmaps. Investment in Good Manufacturing Practice (GMP)-compliant nanofabrication technologies is critical, as is the explicit alignment of analytical validation with regulatory endpoints [58]. Finally, the sustainability of Raman spectroscopy within healthcare systems will depend on the incorporation of health-economic analyses into clinical trials Van Lieshout C, et al. [76], early dialogue with payers, pilot implementation studies with economic endpoints and the exploration of outcome-based reimbursement models.

Conclusion

Innovative Raman spectroscopy has become a cornerstone in the functional analysis of nano-systems, with applications spanning exploration of probiotics, as well as infectious and chronic disease management. By providing real-time molecular insights at the nanoscale, Raman-guided nano-systems hold promise for transforming diagnostics and therapeutics. Future integration with AI, smart nanocarriers and portable Raman devices is expected to drive a new era of precision medicine. With these perks, Raman spectroscopy certainly stands at a promising inflection point. However, to transition from experimental demonstrations to clinical utility, the field must pair technical innovation with rigorous standards, large-scale data practices, formal toxicology protocols, workflow integration, regulatory alignment and health-economic evidence. Coordinated, multidisciplinary action will maximize the likelihood that Raman spectroscopy delivers measurable improvements in human health and disease control.

Author Contributions

AA: Abstraction; Writing–review and editing.

OMA: Writing–original draft; Writing–review and editing.

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Conflict of Interest

Authors declare no conflict of interest for this publication.

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