A Review of Lung Cancer Biomarkers Detectable Via Sers: Challenges, Advances, and Future Directions

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Abstract: Lung cancer is one of the most common and deadly forms of cancer in the world, accounting for a significant proportion of all cancer-related deaths each year. Despite advancements in imaging and biopsy techniques, early detection of lung cancer remains a significant challenge due to the limitations of existing diagnostic tools in terms of sensitivity, invasiveness, and cost. This study addresses the growing need for non-invasive, sensitive, and rapid detection platforms by exploring the application of Surface-Enhanced Raman Spectroscopy (SERS) in identifying lung cancer biomarkers.

The methodology that has been utilized for the research is a conceptual review approach that relies on secondary data. A synthesis of information pertaining to the surface-enhanced Raman spectroscopy compatibility of biomarkers for lung cancer was produced using a thematic analysis of papers from the World Health Organization and the International Agency for Research on Cancer, as well as recent research gathered from PubMed and Scopus. The study centered around proteins (EGFR, CYFRA 21-1), DNA methylation markers (SHOX2, RASSF1A), microRNAs (miR-21, miR-126), and volatile organic compounds (VOCs) detectable in body fluids like serum, sputum, plasma, and exhaled breath.

The most important discoveries that were made included a comparison of the performance metrics of a variety of SERS nanostructures (e.g., Au, Ag, Au@Ag core-shell) in the detection of these biomarkers, as well as a comprehensive analysis of the obstacles that are presented by the reproducibility of the signals and biological interference. The necessity of simulation models in the optimization of substrate design was emphasized by the study, which also urged for the establishment of standardized synthesis methods and the use of spectrum interpretation driven by artificial intelligence in order to ensure clinical dependability.

The paper concluded with a proposed theoretical roadmap that emphasized multi-biomarker detection platforms, portable SERS devices, machine learning integration, and policy alignment for future clinical translation. Combining nanotechnology, AI, and biological research, the results provide a thorough approach for building scalable, non-invasive diagnostic tools for early identification of lung cancer.

Keywords: Lung cancer biomarkers, SERS, nanotechnology, early detection, diagnostic spectroscopy

1. INTRODUCTION

With over 2 million new cases diagnosed and about 1.8 million deaths yearly, lung cancer remains one of the leading causes of cancer mortality globally, imposing a tremendous global

cost (Dama et al., 2021; Lu et al., 2025). Tobacco use, pollution, and occupational exposures have all been linked to increased rates of incidence and death in numerous poor and medium income nations, according to recent trend analysis (Jani et al., 2023). Although screening methods, especially low-dose computed tomography (LDCT), have demonstrated reduced lung cancer mortality, many cases are still detected at late stages (Dama et al., 2021; Seijo et al., 2019). Diagnosis is still mostly dependent on biopsies, sputum cytology, and imaging techniques like as CT or PET CT; however, these approaches are costly, intrusive, and frequently fail to detect tiny, early lesions that are present when the tumor burden is minor (Biomarkers in Lung Cancer Screening, 2023; Seijo et al., 2019).

There are a number of limitations to the diagnostic methods that are now in use. For example, low-dose computed tomography (LDCT) and positron emission tomography (PET) are expensive and need a lot of infrastructure, and there are dangers related with the exposure to radiation that occurs during imaging. Biopsies are a method that can be used to confirm a diagnosis; however, they are intrusive, have the possibility of procedural hazards, and are not always feasible to do due to the location of the tumor or the patient's health (Dama et al., 2021). The sensitivity of sputum cytology is limited when it comes to peripheral or tiny cancers. In general, a significant number of lung cancer cases are not discovered until they have advanced to stage III or IV, at which point the options for treatment are more limited and survival rates decrease significantly (Trends in Lung Cancer Incidence and Mortality, 2023; Seijo et al., 2019).

These limitations highlight the fact that there is a compelling need for diagnostic platforms that are not invasive, extremely sensitive, capable of identifying biomarkers in minute quantities, and relevant at an early stage of disease. The ability to identify cancer markers from bodily fluids or non-tissue samples in a reliable, affordable, and reproducible manner is necessary in order to achieve early detection, which has been proven to significantly enhance five-year survival rates (Dama et al., 2021; Biomarkers and Lung Cancer Early Detection, 2021).

Surface-Enhanced Raman Spectroscopy (SERS) is a detection technique that takes use of the phenomenon known as Raman scattering, which is augmented by the presence of metallic nanostructures such as silver or gold. Surface-enhanced Raman scattering (SERS) is a phenomenon that occurs when incoming light interacts with plasmonic materials, resulting in the amplification of weak molecular vibrational signals of analytes in the vicinity of the

metallic surface. This phenomenon enables molecular fingerprinting to be performed even at low analyte concentrations (Recent Progress in SERS Technology Applications in Lung Cancer Detection, 2025). The method has benefits such as label-free analysis, little sample preparation, compatibility with a variety of bodily fluids including serum or plasma, and the possibility of real-time or quick detection.

Nanotechnology plays a central role in amplifying SERS signals: engineered nanoparticles, nanorods, or nanostars act as substrates for enhancement, particularly through localized surface plasmon resonance (LSPR). Specific biomolecules can be captured by means of functionalizing these substrates, which enhances sensitivity and specificity. Recent advances in nanoparticle design have led to enhanced stability, reduced background noise, and improved repeatability (Recent Progress in SERS Technology Applications in Lung) Cancer Detection, 2025).

Biomarkers are defined as biological substances that serve as indicators of either normal or pathogenic biological processes or pharmacological reactions to a treatment intervention. Biomarkers are a helpful tool in lung cancer for identifying individuals who are at high risk, diagnosing the disease early, estimating prognosis, and tracking responses to therapy (Biomarkers and Lung Cancer Early Detection, 2021; Biomarkers in Lung Cancer Screening: Narrative Review, 2021). Categories include protein-based biomarkers like carcinoembryonic antigen (CEA), cytokeratin fragment CYFRA 21-1; nucleic acid markers such as circulating tumor DNA (ctDNA), DNA methylation signatures; noncoding RNAs like microRNAs (miRNAs); and volatile organic compounds (VOCs) detectable in exhaled breath (Biomarkers and Lung Cancer Early Detection, 2021; Serum-based biomarkers associated with lung cancer risk, 2023).

Every category has both advantages and disadvantages. Biomarkers based on nucleic acids and methylation are able to detect molecular changes, but they need sensitive detection methods; proteins, on the other hand, are frequently more stable but may lack specificity. MicroRNAs (miRNAs) are tiny molecules that are occasionally present in extremely low quantities in early illness stages, whereas volatile organic compounds (VOCs) provide noninvasive sampling but are prone to environmental or dietary intervention (Biomarkers and Lung Cancer Early Detection, 2021; A plasma 9-microRNA signature for lung cancer early detection, 2025).

Despite the fact that several research have pinpointed possible biomarkers that are detectable by liquid biopsy procedures, there has been an inadequate consolidation of the biomarkers that

are most compatible with modern detection technologies, such as SERS (Surface-Enhanced Raman Spectroscopy). Typical problems include a lack of consistency in signals, interference from complicated biological matrices, background noise, and the absence of uniformity in sample processing (Biomarkers and Lung Cancer Early Detection, 2021). Furthermore, the majority of biomarker discovery studies emphasize sensitivity and specificity in small cohorts but do not evaluate how well these biomarkers work in actual screening situations or across numerous independent cohorts. Additionally, there is a lack of theoretical frameworks that integrate clinical processes, detection technologies, and biomarker classes in order to provide guidance on the process of selecting biomarkers for SERS-based platforms.

The purpose of this research was to collect, assess, and compare the current literature about biomarkers of lung cancer that are detectable by surface-enhanced Raman spectroscopy (SERS), with a focus on the sensitivity, molecular specificity, and repeatability of these biomarkers. It also presented conceptual principles and a roadmap to increase the scalability of SERS-compatible biomarkers in diagnostics, proposing which biomarker classes and detection technologies have the most potential for clinical translation.

The study was focused on theory and concepts and made use of a design that was centered around a review. Sources utilized included review papers that had been published recently, peer-reviewed publications from journals, studies that had been indexed in PubMed and Scopus, and data from reports by the World Health Organization and the International Agency for studies on Cancer. The strategy involved doing a theme synthesis and comparative study, examining many aspects such as detection limits, biomarker types, technical difficulties, and sample medium. Included were experimental SERS research, assessments of the modeling literature, and biomarker reviews. The only published metrics that were employed originated from previous research. Any studies that included the gathering of original data by the author, freshly conducted patient trials, or newly produced quantitative/statistical modeling were excluded.

2. SERS-COMPATIBLE LUNG CANCER BIOMARKERS: A THEMATIC REVIEW

Overview of Biomarker Types

There are a number of different types of biomarkers that have been investigated for the purpose of detecting lung cancer. CYFRA21 1, carcinoembryonic antigen (CEA), and ProGRP are

examples of protein markers that are typically raised in cases of lung cancer and are employed in traditional diagnostic procedures. Nucleic acid-based biomarkers, including DNA methylation signatures, are now being investigated. Examples of these include RASSF1A and SHOX2. In the past, microRNAs (miRNAs) such as miR 21 and miR 126 have been investigated for the purpose of determining whether or not they are deregulated in lung cancer. Surface-enhanced Raman spectroscopy (SERS) and sensor arrays are being used to assess volatile organic compounds (VOCs) in exhaled breath as non-invasive indicators. VOCs in exhaled breath include hexanal and other aldehydes, hydrocarbons, and nitriles (Li et al., 2025; Bao et al., 2023; Meng et al., 2025).

Below is a summary table of some biomarkers that have been detected (experimentally or in preliminary clinical/sensor settings) using SERS or SERS-combined sensing for lung cancer or related detection

Table 1: Examples of lung cancer biomarkers detectable via or with SERS-based platforms

Biomarker	Biomarker Type	Detection Medium	SERS (or SERS-combined) Substrate or Approach	Detection Limit / Sensitivity
CYFRA21-1	Protein	Serum	Gold nanobipyramids + magnetic beads + catalytic hairpin assembly (CHA) forming “hot spots”	~ 0.7 pg/mL; high reproducibility in serum (Bao et al., 2023)
VOCs (hexanal etc.)	VOCs	Exhaled breath or gaseous samples	Dual-mode SERS & colorimetric sensor; substrate capturing VOCs combined with SERS chip	Trace level - detection of hexanal; low ppb levels (Li et al., 2025)
Multiple cancers via serum fingerprinting	Mixed biomarkers / fingerprint	Serum	SERS + deep learning features; spectral fingerprinting across cancers including lung cancer	Showed discrimination in large case-control cohort; AUC high (Lin et al., 2025)

The biomarkers that are used in surface-enhanced Raman spectroscopy (SERS)-based techniques for the diagnosis of lung cancer are shown in Table 1, along with a description of the detection medium, the SERS platform that was employed, and their sensitivity or detection limit. These examples illustrate the latest breakthroughs in the use of nanotechnology-enabled surface-enhanced Raman spectroscopy (SERS) for detection tactics that are both extremely sensitive and non-invasive.

Comparative Performance

One of the more compelling evidences of SERS detection is the showing of CYFRA21-1. Bao and colleagues (2023) created a platform for the detection of CYFRA21-1 in serum that utilized gold nanobipyramids and magnetic enrichment with CHA amplification. The technology was able to detect CYFRA21-1 at a detection limit of around 0.7 pg/mL and had high repeatability. It has proven possible to identify volatile organic compounds such as hexanal by employing dual mode sensors that combine SERS and colorimetric readouts, and these sensors have potential for the detection of early lung cancer by breath analysis (Li et al., 2025). The large-scale study by Lin et al. (2025) used serum SERS spectral fingerprints and deep learning to distinguish lung cancer cases from healthy controls, indicating high sensitivity and specificity, though not tied to single specific biomarkers.

In comparison to silver or hybrid methods, gold-based nanostructures can have greater detection limits, but they also have the advantage of improved biocompatibility and stability. When using biological media, silver substrates may have a tendency to exhibit stability and reproducibility issues, despite the fact that they frequently produce stronger SERS enhancement. Designs that are hybrid in nature (for example, a gold core with additional improvements) are promising; yet, they are not as often confirmed in large sample sets.

Bodily Fluids and Sample Matrix

The most commonly used matrices for surface-enhanced Raman spectroscopy (SERS) detection of CYFRA21-1 and similar protein markers are serum and plasma. However, the serum matrix can introduce background noise from the abundance of proteins, variation among individuals, and difficulties in sample preparation. In order to address these issues, researchers have used magnetic enrichment and amplification (Bao et al., 2023). Gaseous or vapor phase sampling, which is used for the detection of volatile organic compounds (VOCs) or exhaled

breath, presents the difficulty of collecting volatile chemicals while preventing interference from VOCs in the environment (Meng et al., 2025). Although it is significant, sputum is less commonly employed in published surface-enhanced Raman spectroscopy (SERS) systems for lung cancer biomarkers. This is probably due to the sample's complexity and diverse backdrop. It is still a challenge to ensure that the signals are consistent across different types of samples, such as serum, breath, and sputum.

3. REPRODUCIBILITY CHALLENGES AND SIGNAL OPTIMIZATION IN SERS SYSTEMS

Challenges in Reproducibility

Surface-enhanced Raman spectroscopy (SERS)-based diagnostic tools continue to be hampered by the inability to reproduce results. One factor that contributes to variability is the size, shape, and aggregation of nanoparticles. Varying the form of nanoparticles, such as spheres, rods, stars, and core shells, results in unique plasmonic responses; little changes in the aspect ratio of a rod or tip geometry may result in significant variations in the enhancement factor (EF) (Yuan et al., 2022; Awiaz et al., 2023). Aggregation, especially uncontrolled clustering of particles, leads to “hot-spot” formation in unpredictable locations, which causes inconsistent signal intensities across different measurements (Yuan et al., 2022). Furthermore, changes in surface chemistry, such as variances in stabilizing ligands, capping agents, or residual reactants, might have an impact on the degree to which analytes bind or on the progress of background adsorption. As a result, both sensitivity and reproducibility are impacted (Yuan et al., 2022; Sloan-Dennison et al., 2024).

In addition, substrate manufacturing is another problem that is associated with inconsistencies across batches. Even when a nanoparticle synthesis procedure is standardized, slight variations in the purity of the reagents, the control of temperature, the kinetics of mixing, or the length of the incubation period can lead to significant discrepancies in the morphology of the nanoparticles or in the interactions of the nanoparticles with the substrate (Sloan-Dennison et al., 2024). Such inconsistencies lead to unpredictable signal outputs, which hinder the ability to compare results across labs or over time.

Biological Noise and Interference

Nonspecific adsorption of proteins or other biomolecules that are not the target analytes is introduced by biological fluids. These chemicals could adhere to the surfaces of nanoparticles or inhabit "hot spots," so attenuating or modifying the actual signal emanating from the target biomarker (Yuan et al., 2022). Another important issue is the presence of a fluorescence background. Many biological materials, particularly serum, plasma, or sputum, include fluorescent molecules that glow under the excitation light used for Raman spectroscopy. This can obscure or widen the Raman peaks of interest. It is a complicated matter to remove background fluorescence, especially in the case of low analyte concentrations (Tahir et al., 2021; Yuan et al., 2022).

Theoretical Solutions

One possible method that is being explored in order to solve repeatability difficulties is the shape optimization of nanoparticles. Star-shaped or rod-shaped nanoparticles frequently generate protrusions and sharper tips, which results in the production of hot spots that are more repeatable and higher electromagnetic amplification (Yuan et al., 2022). Another approach involves using core-shell nanostructures such as Au@Ag or Au/Ag alloy systems which combine the stability of gold cores with high enhancement of silver shells. These hybrid systems can improve localized surface plasmon resonance (LSPR) while reducing cytotoxicity or oxidation issues (Awiaz et al., 2023).

It is essential to maintain stability at temperatures and pH levels that are typical of physiological conditions. In biological media, which often contain ionic strength, proteins, and fluctuating pH, substrates must retain their plasmonic characteristics as well as their structural integrity. According to a few research (Tahir et al., 2021; Yuan et al., 2022) There have been reported designs that are able to resist aggregation or preserve hot spots in settings that are buffered and include serum, resulting in the improvement of signal consistency.

Standardization Needs

It is essential to maintain uniformity across all laboratories. It is imperative that common inter-laboratory methods be established for spectrum calibration, substrate preparation, nanoparticle production, and nanoparticle functionalization. The use of simulation methods like as finite difference time domain (FDTD) modeling or software like COMSOL to map out the best

possible nanostructure geometries, substrate layouts, and hot spot distributions can influence repeatable design (Awiaz et al., 2023; Sloan-Dennison et al., 2024).

Stability over time, lifespan in storage or usage, enhancement factor, relative standard deviation (RSD) between various fabrication batches, and signal homogeneity are all examples of the kind of metrics that should be included in the evaluation of a substrate. It is essential to have a full grasp of reproducibility, and accurate characterization techniques (such as SEM/TEM for morphology, UV Vis for plasmon peaks, dynamic light scattering for aggregation, and zeta potential for surface chemistry) are necessary to achieve this (Sloan-Dennison et al., 2024).

4. FUTURE DIRECTIONS AND THEORETICAL ROADMAP FOR CLINICAL TRANSLATION

Toward Multi-Biomarker SERS Platforms

The development of multiplexed detection technologies that are capable of recognizing numerous biomarkers at the same time represents the future of lung cancer diagnosis. By capturing the complicated genetic landscape of lung cancer, this technique increases diagnostic accuracy, decreases the number of false positives, and promotes therapeutic value. Clinicians are able to more thoroughly evaluate the development of a disease by monitoring a number of biomolecules simultaneously through the use of a multi-biomarker method. As an example, the combination of protein markers, such as EGFR and CYFRA 21-1, with microRNAs, such as miRNA-21, might improve the accuracy of a diagnosis. By attaching Raman tags, which are distinct vibrational fingerprints, to nanostructures, it is possible to distinguish signals from numerous biomarkers within the same biological sample, hence allowing for the parallel and real-time study of these biomarkers.

Portable Devices and Real-Time Diagnosis

A significant advancement in point-of-care testing for lung cancer is the incorporation of surface-enhanced Raman spectroscopy (SERS) technology into portable diagnostic instruments. Surface-enhanced Raman spectroscopy (SERS)-active substrates can be embedded into tiny platforms such as breath analyzers or lab-on-a-chip devices, allowing healthcare professionals to do quick, non-invasive testing in outpatient settings, remote clinics, or even at home. It is possible to construct portable Raman spectrometers that are powered by

batteries and shrunk in size to detect volatile organic compounds (VOCs) or protein-based markers in real time, providing rapid clinical insights. These portable devices strive to close the gap between clinical practice and research conducted in laboratories, therefore minimizing delays in diagnosis and boosting accessibility in areas where medical services are lacking.

Machine Learning and AI Integration

There is a strong likelihood that machine learning (ML) and artificial intelligence (AI) will bring about a revolution in the interpretation of surface-enhanced Raman spectroscopy (SERS) spectrum data. There can be significant complexity in raw spectrum outputs, and there may be slight differences between different samples. These spectral fingerprints may be classified and interpreted with a high degree of accuracy using advanced data analysis techniques such as principal component analysis (PCA), linear discriminant analysis (LDA), and neural networks. These models have the ability to learn from hundreds of spectral datasets, which enables them to perform robust pattern identification, anomaly detection, and predictive diagnostics. The integration of artificial intelligence provides a diagnostic procedure that is more uniform and objective, hence reducing human error and increasing sensitivity and specificity.

Interdisciplinary Research and Policy Inclusion

In order to achieve the clinical translation of SERS-based lung cancer diagnostics, it is necessary to coordinate efforts across several disciplines. The design of stable, biocompatible nanostructures must be innovated by material scientists, while biomarker significance and disease pathways must be elucidated by molecular biologists and oncologists. Biological engineers are responsible for making significant contributions to the fields of signal processing, fluidics integration, and device shrinking. Furthermore, governments and public health organizations must be involved in order to incorporate such technology into national screening programs. Policy frameworks must provide support for regulatory approvals, reimbursement systems, and public-private partnerships in order to scale the implementation of these diagnostics across a wide range of healthcare settings.

Visual Roadmap for Clinical Translation

The process of clinical translation starts with biomarker selection, during which researchers determine which molecular targets are of therapeutic significance. This step is followed by *Nano-Substrate Design*, focusing on optimizing shape, surface chemistry, and

functionalization. *Signal Optimization* ensures reproducibility and sensitivity, paving the way for *Device Prototyping*. Once portable devices are built, *Clinical Trials* validate their efficacy across populations. The final step is *Policy Adoption*, where regulatory and health bodies formally approve and integrate the technology into national cancer control strategies.

Flowchart or Roadmap Illustration

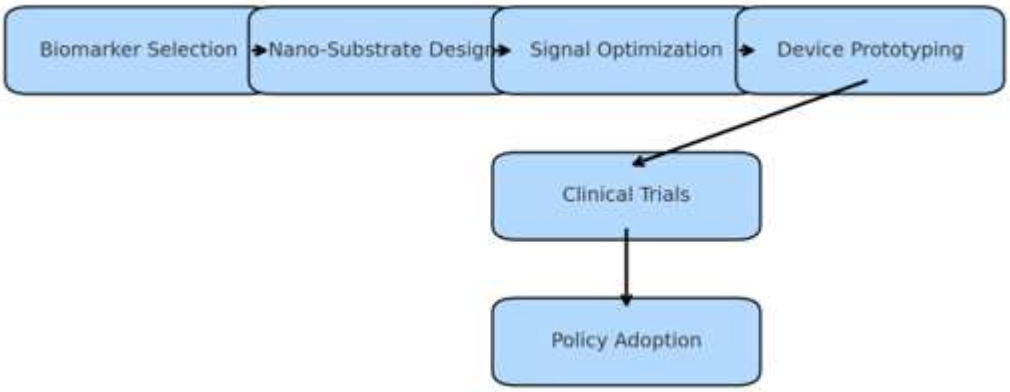

Figure 1: Roadmap for Clinical Translation of SERS-Based Lung Cancer Diagnostics

A timeline that illustrates the sequence of steps required to convert technology known as surface-enhanced Raman spectroscopy into therapeutic applications is depicted in this graphic. It starts with the selection of biomarkers, followed by the design of nanostructured substrates, the optimization of signal detection, and the construction of portable device prototypes. After clinical studies have verified the results, the objective is to get them incorporated into healthcare policies.

5. CONCLUSION AND RECOMMENDATIONS

The purpose of this work was to investigate the growing importance of surface-enhanced Raman spectroscopy (SERS) in the discovery of biomarkers for the noninvasive diagnosis of lung cancer. The need of finding biomarkers that are dependable, repeatable, and physiologically relevant was brought into sharp focus by the research; these biomarkers must also be compatible with SERS-based detection devices. It has been demonstrated that biomarkers such as EGFR, CYFRA 21-1, miRNA-21, and VOCs possess considerable potential for the early identification of disease. This is owing to the fact that these biomarkers

have distinct biochemical signatures and may be detected in biofluids that are minimally invasive, such as serum, sputum, and exhaled breath.

The research highlighted the advantages of surface-enhanced Raman spectroscopy (SERS), such as its ability to detect substances at extremely low concentrations, its label-free method, and its compatibility with a wide variety of biological media. At the same time, it recognized the shortcomings of the present surface-enhanced Raman spectroscopy (SERS) systems—particularly concerns with repeatability, signal variability, and interference produced by non-specific interactions between biomolecules. Obstacles to the translation of laboratory-based research into clinical practice were highlighted by the absence of established techniques for the synthesis of nanoparticles and the lack of uniformity in substrate manufacturing. These limitations do not detract from the fact that the theoretical promise of SERS as a transformational biological diagnostic tool was clearly established. Surface-enhanced Raman spectroscopy (SERS)-based systems have the potential to transform the field of lung cancer diagnostics with the suitable combination of nanotechnology, machine learning, and portable device engineering. Nonetheless, prior to the broad clinical implementation of this technology, numerous real-world problems must be solved. These challenges range from material variability to legislative limits.

Recommendations

1. **Standardized Nanoparticle Synthesis Protocols:** Strong, inter-laboratory methods for the synthesis and fabrication of repeatable SERS-active substrates are urgently required. The consistency of results across investigations and devices depends on these methods, which must take into consideration the fact that nanoparticles might vary in size, shape, surface chemistry, and core-shell structure.

2. **Validation of Core Biomarkers Across Sample Types:** Blood plasma, sputum, and exhaled breath condensates are just a few of the many biofluids that need to be examined and verified in order to verify the identified lung cancer biomarkers. Clinical applicability and diagnostic effectiveness can be better assured by cross-validation in varied demographics and sample matrices.

3. **Development of Multiplexed and Portable SERS Devices:** Compact, easy-to-use devices that can detect several biomarkers at once are the wave of the future for SERS.

It is important that these mobile devices can function in point-of-care environments and be easily integrated into regular diagnostic procedures.

4. **Investment in AI-Driven Spectral Analysis Tools:** Strong artificial intelligence and machine learning systems that can decipher complicated SERS spectra should be the primary focus of long-term funding. When it comes to classifying biomarker signals, methods such as LDA, PCA, and neural networks may significantly enhance precision and uniformity.

5. **Policy and Funding Frameworks for Clinical Translation:** Structured financing methods should be supported by healthcare and government entities to encourage the conduct of pilot clinical trials, the improvement of technology, and multidisciplinary cooperation. Screening and early detection programs for lung cancer should prioritize SERS technology. This could be done through public-private collaborations, university research consortia, and national health programs.

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