

RESEARCH ARTICLE

Transport-Coupled Selection of Surface-Enhanced Raman Breath Sensors for Volatile, Reactive, and Aerosol-Borne Targets

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Abstract

Surface-enhanced Raman spectroscopy (SERS) offers chemically specific optical readout for exhaled volatile compounds, reactive gases, respiratory aerosols, and condensate-associated biomarkers. Breath analysis, however, is controlled not only by the lowest detection threshold but also by transport through humid air, selective retention at the enhancing surface, near-field accessibility, sampling hardware, and spectral decision quality. This paper asks which SERS breath-sensor architectures retain analytical credibility when the complete route from exhaled target to interpretable Raman signal is evaluated as a coupled chemical-transfer problem. A twenty-eight-entry analytical matrix was organized by target phase, recognition or capture layer, enhancement geometry, breath-contact mode, measurement descriptor, and uncertainty status. The resulting method, Transport-Coupled Sensor Stratification (TCSS), evaluates each architecture through seven criteria: threshold strength, selector chemistry, hot-spot/capture architecture, breath-system integration, learning support, breath-target alignment, and uncertainty control. The analysis identifies the T-Si/Al₂O₃/Ag/Au light-trapping substrate, the vapor-generation paper-based thin-film microextraction system containing Au nanorods, quantum dots, and NU-901, and the Ag/Si/Ag micropillar substrate as the strongest sensitivity-mechanism candidates. Deployment-oriented selection gives a different ordering: the Ag nanocube breathalyzer, hollow ZIF-8/gold-superparticle breathing-valve sensor, Au-TiO₂ nanocomposite, and TiO₂-supported Au platforms gain importance because they connect sensing chemistry with breath handling or biomolecular readout. The study concludes that no single SERS substrate is universally optimal for breath testing. Credible selection depends on matching analyte phase, capture chemistry, plasmonic geometry, breath-interface design, and validation status to the intended target class.

Keywords: surface-enhanced Raman spectroscopy; breath analysis; volatile organic compounds; analytical chemistry; chemical sensors; plasmonic nanomaterials; instrumentation; transport-coupled sensor stratification.

1. Analytical Position of the Study

This study is an analytical-method and instrumentation-readiness investigation. It evaluates trace chemical sensing by SERS, compares detection descriptors across plasmonic substrates, interprets preconcentration and breath-sampling interfaces, and establishes a selection route for sensor architectures before clinical validation. The work is not a diagnostic trial. Its purpose is to determine how SERS de-

signs handle breath targets from sampling to spectral decision within analytical chemistry, molecular spectroscopy, and chemical-sensor instrumentation.

2. Introduction

Exhaled breath is a chemically rich but analytically difficult specimen. It carries volatile organic compounds, reactive inorganic gases,

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water vapor, aerosol particles, and condensable molecular material generated by metabolic, inflammatory, infectious, environmental, and microbial processes. Early gas-chromatographic studies showed that many volatile constituents could be detected in breath and related biological vapors, and later clinical work connected breath VOC patterns with lung cancer, asthma, infection, oxidative stress, and systemic physiology [1–7]. The same richness that makes breath attractive also makes it difficult to use as a reliable analytical sample. Target compounds may occur at ppb, sub-ppb, pM, or pattern-level abundance; humidity and ambient contamination can dominate the matrix; and the measured signal depends strongly on sampling route, flow control, storage, background subtraction, and data processing [8–12].

Breath analysis has therefore developed along several instrumental routes. Gas chromatography coupled to mass spectrometry remains powerful for separating and identifying complex VOC mixtures, but it generally requires collection, preconcentration, and laboratory infrastructure. Proton-transfer-reaction and selected-ion-flow-tube mass spectrometry can support direct or near-real-time profiling, yet they depend on expensive instrumentation and careful ion-chemistry interpretation [10, 13]. Optical, electronic-nose, and chemical-sensor approaches offer more compact device concepts, but they must address selectivity, calibration drift, humidity sensitivity, and biological variability. A breath sensor is consequently not just a detector of a molecule; it is a coupled sampling, enrichment, recognition, transduction, and decision system.

Surface-enhanced Raman spectroscopy is attractive in this context because it combines the molecular specificity of vibrational spectroscopy with signal amplification by plasmonic nanostructures. The field began with enhanced Raman signals from molecules adsorbed on roughened silver surfaces and developed through electromagnetic and charge-transfer explanations of signal amplification [14–17]. Subsequent single-molecule and nanoparticle studies established SERS as a highly sensitive optical method, while later studies clarified the roles of localized surface plasmons, hot-spot geometry, adsorbate distance, chemical enhancement, and substrate reproducibility [18–27].

Direct transfer of SERS into breath testing is not automatic. Many VOCs have weak Raman cross sections and poor affinity for bare Au or Ag surfaces. Breath humidity can block adsorption sites, broaden backgrounds, and alter surface chemistry. Structurally similar aldehydes, ketones, nitriles, sulfur compounds, and hydrocarbons can compete for the same hot spots. These limitations explain why modern breath-SERS platforms increasingly use metal–organic porous materials (MOFs), ZIFs, layered double hydroxides, oxides, graphene derivatives, polymeric supports, reporter chemistries, paper extraction formats, breath valves, masks, microfluidics, and classification algorithms. Porous and hybrid materials can increase local analyte concentration, create size or polarity discrimination, orient molecules near plasmonic junctions, and make weakly adsorbing vapors visible to Raman readout [28–32].

The main comparison problem is that SERS breath sensors are heterogeneous. One entry lists a gas-phase aldehyde threshold in ppb, another lists viral-protein detection in pM, and a third gives diagnostic sensitivity and specificity from breath profiles. Direct numerical normalization would imply a false equivalence among physically different measurements. A lowest-limit-of-detection ordering also risks favoring substrates that perform well in simplified laboratory environments but have not been connected to humid breath transfer, practical sampling, or independent model validation. Conversely, a device-level breathalyzer may use a less conventional chemical descriptor while still giving stronger evidence of complete sampling-to-decision operation.

This paper addresses that limitation through a specific research question: which SERS breath-sensor architectures preserve analytical credibility when the full transfer path from exhaled target to interpretable Raman signal is considered? To answer the question, the twenty-eight substrate–performance entries are organized as an interface-annotated

analytical matrix rather than only as a list of materials and detection thresholds. The method is termed Transport-Coupled Sensor Stratification (TCSS). It evaluates the matrix through threshold strength, selector chemistry, hot-spot/capture architecture, breath-system integration, learning support, breath-target alignment, and uncertainty control.

The resulting contribution is a target-specific selection analysis rather than a sensitivity-only sensor ordering. TCSS asks whether a substrate has a plausible route for transporting breath molecules into the near-field zone, whether capture chemistry matches the target class, whether the enhancement structure is physically credible, whether the sampling hardware is deployable, and whether spectral interpretation is transparent enough to guide further validation. The visual inventory in Figure 1 introduces the entry set, while the tables and later figures develop the analytical argument from substrate identity toward breath-interface readiness.



Figure 1: SERS breath-sensor inventory.

The visual inventory clarifies why the comparison cannot be reduced to metal choice. The entries span gas-phase VOCs, reactive sulfur and nitrile species, respiratory-infection profiles, and condensate-associated biomolecules. Each row therefore represents an analytical pathway: breath target, transfer medium, plasmonic surface, capture layer, measurement format, and evidence type. This pathway view is the basis of TCSS.

3. Analytical Dataset and Sensor Stratification Method

3.1. Analytical matrix construction

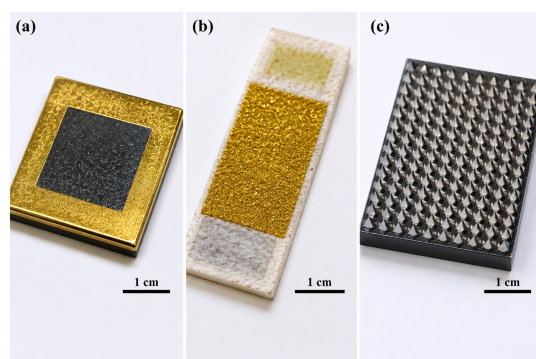
The analytical matrix contains twenty-eight SERS breath-sensor architectures summarized by substrate design, performance descriptor,

target class, modification strategy, and system integration [33]. The entries cover Ag, Ag/Au, Au, non-noble-metal heterostructure, and perovskite/Au platforms. Each entry was annotated for capture chemistry, enrichment strategy, microfluidic or breath-interface component, and machine-learning support. Concentration thresholds, volume-fraction thresholds, diagnostic sensitivity/specificity values, and classification-supported descriptors were retained in their native physical forms so that gas-phase targets, condensate-associated biomolecules, and diagnostic spectral patterns were not forced into a single unit system.

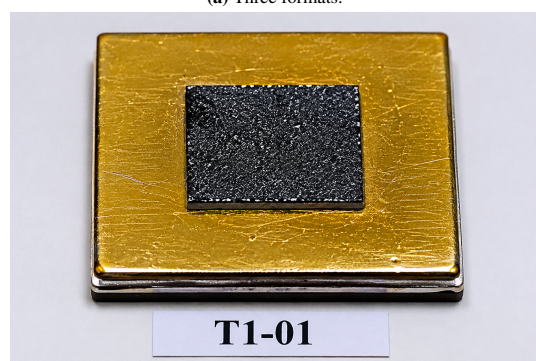
3.2. Substrate-performance matrix

The matrix shows the central difficulty of the study: performance evidence is chemically meaningful but not commensurate. A ppb value for a gas-phase aldehyde, a pM biomolecular detection value, a volume-fraction hydrogen sulfide descriptor, and a sensitivity/specificity result from a breathalyzer should not be collapsed into a single physical unit. The analysis therefore treats the table as a structured evidence set, not as a conventional calibration table.

The annotation fields convert each entry into an analytical pathway in which target chemistry, gas transfer, near-field access, device interface, and validation evidence are judged together. This organization is essential because breath-SERS failure often occurs before spectral acquisition, during sample transfer or surface enrichment.



(a) Three formats.



(b) Nanocube unit.

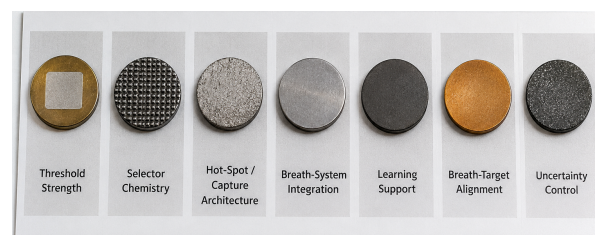
Figure 2: Representative sensing formats.

The representative formats illustrate why TCSS treats the same material family differently across entries. A coated chip, a paper extraction strip, a micropyramid surface, and a nanocube array expose analytes to the plasmonic field through different transport and contact geometries. Interpreting Table 1 therefore requires architecture-level behavior, not just the identity of the enhancing metal.

3.3. Transport-Coupled Sensor Stratification

TCSS was built around seven evidence criteria. Threshold strength records the concentration, volume-fraction, or diagnostic descriptor

without forcing unit conversion. Selector chemistry identifies MOF, ZIF, LDH, oxide, graphene, reporter, or analyte-reactive components. Hot-spot/capture architecture describes the physical route by which molecules are concentrated within the SERS near-field zone. Breath-system integration records sampling hardware, paper extraction, valves, masks, breathalyzer design, or microfluidic connection. Learning support identifies classification or pattern-recognition evidence. Breath-target alignment states whether the target and sampling format directly match breath chemistry. Uncertainty control limits the influence of broad qualitative claims, especially unspecified ppb-level statements or incomplete workflow descriptions. These criteria are visualized in Figure 3.



(a) Evidence lenses.



(b) Lens balance.

Figure 3: TCSS descriptor set.

The descriptor visual emphasizes that sensitivity is only one part of readiness. A low threshold without selective capture or breath-interface control remains vulnerable to matrix effects, whereas a device-oriented entry with classification support can be analytically relevant even when its descriptor is not a conventional limit of detection. The balance view also treats uncertainty as a negative modifier rather than as another positive performance feature.

3.4. Selection logic and stability checks

The selection step used a balanced interpretation of the seven evidence criteria. Threshold strength received the strongest emphasis, followed by selector chemistry and hot-spot/capture architecture. Breath-system integration and learning support were retained as substantial readiness signals, while breath-target alignment and uncertainty control moderated the final interpretation. Three stability checks were then made. The first identified the leading entries under balanced weighting. The second removed one criterion at a time to identify which design dimension controlled the ordering. The third compared threshold-led, deployment-led, and mechanism-led priority settings. The workflow is summarized in Figure 4.

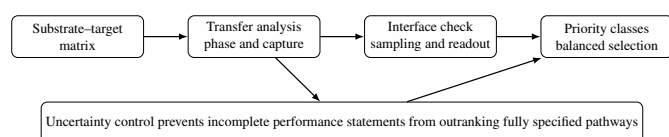
The workflow makes the method explicit. The analysis begins with substrate performance but does not end there. It asks how each target reaches the hot spot, how the surface chemistry supports retention, whether the breath-contact route is specified, and whether the evidence

Table 1: SERS substrate-performance matrix.

ID	Dominant material	SERS architecture	Analytical descriptor	Breath-relevant target or application
T1-01	Ag	Ag nanocubes	10^{-10} M	Breath nitrite
T1-02	Ag	Ag nanocubes	96.2% sensitivity; 99.9% specificity	COVID-19 breathalyzer
T1-03	Ag	Ag nanocubes	60 ppb	Gaseous acetic acid
T1-04	Ag	Dendritic Ag nanocrystals	2.0 ppb–20 ppm	Aldehydes
T1-05	Ag	AgNPs encapsulated with ZIF-67	3 ppb	Aldehydes and ketones
T1-06	Ag	AgNPs@ZIF-67 with graphitic carbon nitride	1.35 nM	Aldehydes
T1-07	Ag	AgNP@ZIF films	10^{-8} M	Aldehydes
T1-08	Ag	Ag nanowires@ZIF-8	10^{-8} M	Aldehydes
T1-09	Ag	Ag nanowires@ZIF-8	10^{-7} M	Methanethiol
T1-10	Ag	PVDF/AgNP/ZnO nanowire/ZIF-8 coating	10^{-10} v/v	Hydrogen sulfide
T1-11	Ag	Ag nanowires with ZIF-67 or Co–Ni LDH	1.9 ppb	Aldehydes
T1-12	Ag	AgNPs coated with FeCoNi-LDH	10 ppb	Aldehydes
T1-13	Ag	AgNPs with graphene and ZnO nanorods	4×10^{-8} M	SARS-CoV-2 spike protein
T1-14	Ag	Ag/Si/Ag micropylramid silicon	0.1 ppb	Aldehydes
T1-15	Ag/Au	T-Si/Al ₂ O ₃ /Ag/Au	0.1 ppb	Hydrogen sulfide
T1-16	Au/Ag	Au@Ag@Au nanocubes and Au@Ag nanocubes	ppb levels	Aldehydes, ketones, and hydrogen sulfide
T1-17	Au	Gold superparticles with ZIF-8 MOF coating	10 ppb	Aldehydes
T1-18	Au	Hollow ZIF-8 on gold superparticles in a breathing-valve sensor	7.7 ppb	Aldehydes
T1-19	Au	Mesoporous Au coated with hollow ZIF-8	0.32 ppb	Aldehydes
T1-20	Au	Au-coated silicon nanopillars	18 ppb	Hydrogen cyanide
T1-21	Au	AuNPs with reduced graphene	>92% specificity; 83% sensitivity	Fourteen VOC biomarkers
T1-22	Au	Vapor-generation paper-based thin-film microextraction with Au nanorods and quantum dots in NU-901	0.1 ppb	Aldehydes
T1-23	Au	Au–TiO ₂ nanocomposite	100 pM	SARS-CoV-2 spike protein
T1-24	Au	TiO ₂ nanomesh–AuNP with ZIF-8 layer	0.19 ppb	Aldehydes
T1-25	Au	AuNPs on TiO ₂ nanowires	2.4 pM plus diagnostic classification	4-ATP and upper respiratory infection
T1-26	Other	Cu-doped NiO _x /Cu–SnO ₂ heterostructure	ppb level	PYR, 2-NT, and aldehydes
T1-27	Other	CuFeSe ₂ /Au nanospheres	1 ppb	Aldehydes
T1-28	Perovskite/Au	Au@CsPbBr ₃ perovskite system	3.29×10^{-9} M	Aldehydes

Table 2: TCSS annotation fields.

Annotation field	Encoding focus	Analytical reason
Target phase	VOC/gas, reactive gas, aerosol or condensate biomarker, or pattern descriptor	Different targets require different sampling and surface-transfer routes.
Capture route	Bare metal, MOF/ZIF, LDH, oxide, graphene, paper extraction, reporter chemistry, or hybrid capture	Breath analytes must be concentrated and retained close to hot spots.
Enhancement geometry	Nanocube, nanowire, micropylramid, porous Au, light-trapping chip, core–shell particle, or heterostructure	Signal strength depends on accessible and reproducible near-field regions.
Interface posture	Open substrate, preconcentration strip, microfluidic route, breath valve, mask or breathalyzer format	A substrate becomes instrument-ready only when sampling is specified.
Evidence mode	Concentration threshold, volume-fraction threshold, sensitivity/specificity, or classification-supported descriptor	Published measurements differ in physical meaning and validation demand.
Validation status	Complete, partial, or limited description of matrix conditions and operational workflow	Broad ppb-level descriptors require caution when architectures are ordered.

**Figure 4:** TCSS workflow.

is sufficiently complete to justify further development.

4. Transport-Coupled Ranking and Breath-Sensor Interpretation

4.1. Balanced priority and transfer classes

The balanced priority list answers the sensitivity-mechanism part of the research question. The three strongest entries all combine sub-ppb thresholds with a clear physical mechanism for improving molecular access to the plasmonic field. The T-Si/Al₂O₃/Ag/Au platform is not favored only because it reports 0.1 ppb hydrogen sulfide detection; it also links a reactive gas target with light trapping and hybrid noble-metal enhancement. The paper-based thin-film microextraction system earns a comparable position because it addresses the transfer bottleneck directly through preconcentration. The Ag/Si/Ag micropylramid entry is strong because ordered topography offers a route to repeated, spatially organized analyte-surface encounters.

The fourth to eighth ranked entries reveal a second result that a

sensitivity-only ranking would obscure. The Ag nanocube breathalyzer, Au–TiO₂ nanocomposite, AuNP/TiO₂ nanowire system, and hollow ZIF-8/gold-superparticle breathing-valve sensor have special value because they move beyond isolated substrate performance. Their evidence includes breath profiling, biomolecular relevance, condensate-compatible detection, classification, or explicit breath-interface hardware. These entries therefore become important when the intended output is an instrument or diagnostic workflow rather than a material-screening experiment.

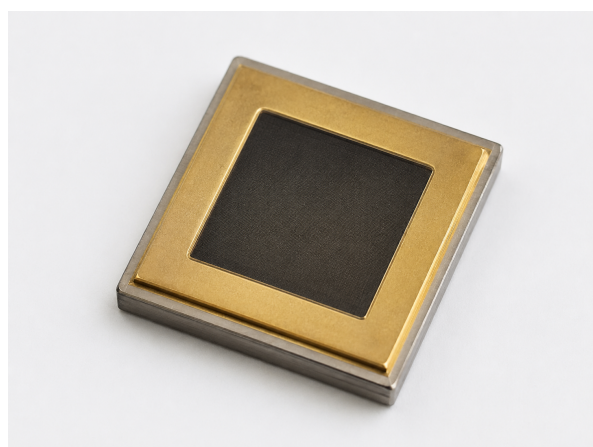
The leading mechanism panels separate three different routes to high analytical priority. Light trapping improves interaction between excitation, plasmonic metal, and gas-exposed surface. Paper-based microextraction reduces the burden on the Raman step by increasing analyte availability before readout. Micropylramid silicon uses ordered topography to organize hot-spot access at a mesoscopic scale. These mechanisms are complementary rather than interchangeable.

4.2. Material family does not determine readiness alone

Silver-dominant entries were numerous and often sensitive, especially when Ag was embedded in porous, layered, or patterned architectures. AgNPs encapsulated with ZIF-67, AgNPs@ZIF-67 with graphitic carbon nitride, Ag nanowires@ZIF-8, Ag nanowires with ZIF-67 or Co–Ni LDH, FeCoNi-LDH-coated AgNPs, and Ag/Si/Ag micropylramids all show that Ag benefits from additional capture and geometry control. The ranking therefore does not support the simple statement that silver is best; it supports the more precise conclusion that Ag becomes useful for breath analysis when its high electromagnetic en-

Table 3: Balanced TCSS priorities.

Rank	Architecture	Target class	Descriptor	Main transfer interpretation
1	T-Si/Al ₂ O ₃ /Ag/Au	Hydrogen sulfide	0.1 ppb	Light-trapping hybrid surface with strong threshold evidence.
2	Vapor-generation paper-based thin-film microextraction with Au nanorods, quantum dots, and NU-901	Aldehydes	0.1 ppb	Preconcentration-led aldehyde capture with porous host support.
3	Ag/Si/Ag micropylramid silicon	Aldehydes	0.1 ppb	Ordered mesoscopic geometry supports repeated gas-surface contact.
4	Ag nanocube breathalyzer	COVID-19 breath profile	96.2% sensitivity; 99.9% specificity	System-level breath profile evidence and learning-supported interpretation.
5	TiO ₂ nanomesh–AuNP with ZIF-8 layer	Aldehydes	0.19 ppb	Oxide/MOF hybrid combines adsorption and plasmonic readout.
6	Au–TiO ₂ nanocomposite	SARS-CoV-2 spike protein	100 pM	Biomolecular sensing with strong interface relevance.
7	AuNPs on TiO ₂ nanowires	URI breath condensate	2.4 pM plus classification	Condensate-oriented sensing and diagnostic classification.
8	Hollow ZIF-8 on gold superparticles in a breathing-valve sensor	Aldehydes	7.7 ppb	Lower threshold strength but high breath-interface maturity.
9	AgNPs encapsulated with ZIF-67	Aldehydes and ketones	3 ppb	Porous confinement improves capture of small carbonyl compounds.
10	Ag nanowires with ZIF-67 or Co–Ni LDH	Aldehydes	1.9 ppb	Layered capture chemistry strengthens aldehyde enrichment.



(a) Light-trapping chip.



(b) Extraction strip.

Figure 5: Leading substrate mechanisms.

hancement is paired with a pathway for concentrating small breath analytes near the metal.

Gold-dominant entries showed a different pattern. Hollow ZIF-8 on gold superparticles in a breathing-valve sensor, mesoporous Au coated with hollow ZIF-8, Au-coated silicon nanopillars, AuNPs with reduced graphene, Au–TiO₂ nanocomposites, and AuNPs on TiO₂ nanowires gained readiness through stability, surface functionalization, oxide

support, porous confinement, biological compatibility, or diagnostic interpretation. The Au platforms were therefore valuable not because gold universally outperformed silver, but because several Au designs were closer to breath-compatible sampling or biomolecular detection.

Mixed-metal and semiconductor-coupled systems were especially informative. The T-Si/Al₂O₃/Ag/Au entry combined light management with hybrid plasmonic behavior, while Au@CsPbBr₃ represented a perovskite-coupled aldehyde sensor. These systems indicate that future breath-SERS design may move toward integrated optical, semiconductor, porous, and plasmonic architectures. Their current evidence remains architecture-specific, however, because the dataset contains too few mixed systems to generalize across an entire material class.

The paired material and architecture panels reinforce a central TCSS finding: substrate identity and surface organization must be interpreted together. Porous shells, layered hydroxides, oxide supports, perovskite coupling, nanowire networks, micropylramids, and light-trapping chips all modify how breath molecules reach hot spots. A material-family label alone is therefore insufficient for analytical selection.

4.3. Criterion-removal analysis

The removal results show that the research question cannot be answered by sensitivity alone. Threshold strength produced the largest single effect, as expected for trace analysis, but the combined influence of capture architecture and selector chemistry exceeded the influence of any operational add-on. This pattern explains why porous and patterned systems repeatedly appear among the strongest candidates. A low limit of detection without molecular retention is fragile in humid mixed breath, whereas a selective capture pathway can make the SERS signal more chemically interpretable.

Operational integration produced a smaller but still important score effect. This does not mean that sampling hardware is secondary in practice. Rather, it indicates that many entries still provide material-level evidence rather than complete instrument-level evidence. As more platforms move into breath bags, valves, masks, or direct-flow formats, the integration criterion is likely to become a stronger differentiator. Learning support showed a similar pattern: classification is valuable for diagnostic profiles, but it should not compensate for poorly controlled chemistry or incomplete external validation. This view is consistent with metabolomics reporting principles that emphasize transparent data analysis, validation scheme definition, and avoidance of false biomarker discovery [34,35].

Table 4: Criterion-removal effects.

Removed or modified criterion	Mean score effect	Analytical interpretation
Threshold strength removed	-25.3 points	Sensitivity remains indispensable for trace breath targets.
Hot-spot/capture architecture removed	-14.5 points	Porous, hollow, layered, light-trapping, and geometric designs strongly shape readiness.
Selector chemistry removed	-13.7 points	MOF selectivity, LDH coatings, oxides, reporter groups, and reactive capture control target access.
Breath-system integration removed	-9.2 points	Breath bags, masks, valves, paper extraction, and microfluidics move substrates toward instruments.
Learning support removed	-6.0 points	Classification evidence matters most when disease profiles rather than single molecules are measured.
Breath-specific relevance removed	-3.7 points	Target alignment improves priority but cannot rescue weak sensing chemistry.
Uncertainty penalty removed	+1.0 point	Broad descriptors create modest but measurable score inflation.

4.4. Priority stability under different analytical aims

The priority-setting test gives the clearest answer to the paper's research question. When the objective is to find the strongest chemical-sensing mechanism, the leading group is stable: paper-based microextraction, T-Si/Al₂O₃/Ag/Au light trapping, and Ag/Si/Ag micropylramids remain dominant. When the objective is deployable breath testing, the Ag nanocube breathalyzer and Au-TiO₂ nanocomposite move upward because they contain system-level or biomolecular interface evidence. A reviewer or device developer should therefore state the analytical objective before naming a best SERS architecture.

The priority-board panels visualize the same shift in decision logic. Stable leading candidates indicate robust chemistry and architecture; changing leaders indicate that the measurement goal has changed. This distinction is useful because breath-SERS studies often treat sensitivity, device readiness, and clinical pattern recognition as one goal. TCSS separates those goals without discarding any of them.

4.5. Target-specific interpretation

Hydrogen sulfide and other reactive sulfur compounds require surfaces that can support efficient interaction without losing reproducibility. The T-Si/Al₂O₃/Ag/Au architecture is strong for this target class because its light-trapping and hybrid plasmonic design plausibly improves signal collection from a small reactive molecule. The PVDF/AgNP/ZnO nanowire/ZIF-8 coating is also relevant because it combines polymeric support, oxide nanowires, Ag enhancement, and porous capture, but it requires careful humidity and reproducibility reporting before it can be placed at the same readiness level as more completely specified entries.

Aldehyde detection is governed by a different bottleneck. Small carbonyl compounds often require enrichment, retention, and selective access to hot spots. This explains why NU-901 paper-based microextraction, TiO₂ nanomesh-AuNP-ZIF-8 layers, hollow ZIF-8/gold systems, AgNPs@ZIF-67, LDH-coated AgNPs, CuFeSe₂/Au nanospheres, and Au@CsPbBr₃ perovskite systems all appear as chemically meaningful candidates. The best aldehyde sensor is therefore not simply the lowest-threshold entry; it is the design that matches aldehyde volatility and polarity with a capture layer and measurement workflow.

Viral proteins and upper-respiratory-infection breath condensate shift the problem from gas-phase VOC transfer to aerosol or condensate handling. Au-TiO₂ nanocomposites and AuNPs on TiO₂ nanowires gained priority because their descriptors include biomolecular detection or diagnostic classification. These platforms require validation criteria different from gas-phase aldehyde sensors: collection of aerosol or condensate material, control of nonspecific protein adsorption, clinically meaningful classification, and external testing.

The sampling-interface panels show why target class must guide hardware choice. VOCs, reactive gases, aerosols, and condensates do not

enter the SERS measurement zone in the same way. A breath bag or valve may be sufficient for some gas-phase targets, while condensate-associated biomolecules may require controlled collection, transfer, and surface blocking. Method development should therefore specify the breath fraction and contact pathway rather than treating sampling as a replaceable accessory.

4.6. Implications for instrumentation and validation

The TCSS results support six validation priorities. First, detection limits should be measured under humidity and matrix conditions that resemble breath, not only under dry gas or solution tests. Second, spatial enhancement uniformity and batch-to-batch substrate reproducibility should be documented because local hot-spot variation can create attractive but unreliable sensitivity claims. Third, capture chemistry should be connected to a target-specific mechanism, particularly for aldehydes, sulfur gases, nitriles, and biomolecules. Fourth, the breath interface should distinguish collection, enrichment, transfer, and direct readout. Fifth, classification models should state training, validation, and external testing procedures. Sixth, broad descriptors such as "ppb levels" should not be treated as equivalent to an exact threshold obtained with a described workflow.

For instrument-facing SERS breath studies, the target phase, ambient-air correction, humidity range, sampling duration, substrate storage, excitation conditions, spectral preprocessing, calibration model, and validation partition should be stated together. Without these details, a SERS response may be chemically interesting but not transferable to instrument design. Such reporting discipline is especially important when machine learning is used, because high apparent accuracy can reflect data leakage, cohort imbalance, or matrix-specific artifacts rather than robust breath chemistry [11, 34, 35].

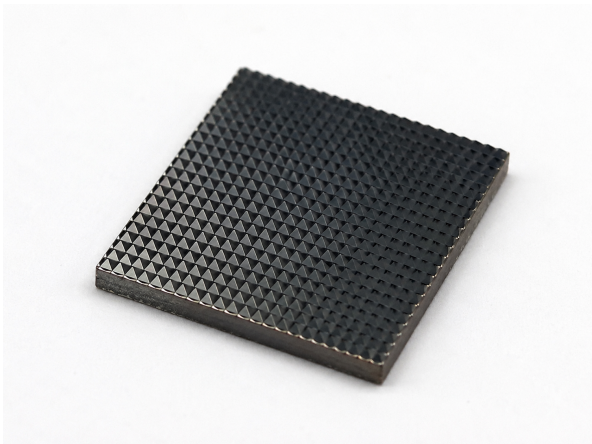
The measurement panels connect material development with instrument validation. A SERS chip that performs under a microscope-stage configuration may still require redesign before use in a flow-through breath instrument. Conversely, bench-top Raman readout paired with a defined sampling accessory can support more realistic method evaluation. The analytical question is therefore not only whether a spectrum can be obtained, but whether the acquisition context matches the intended breath-use case.

5. Boundary Conditions

The study evaluates documented substrate descriptors, matrix entries, and figure-supported architecture evidence rather than raw spectra, calibration files, patient-level records, or laboratory replication. TCSS can identify likely transfer bottlenecks and readiness strengths, but it cannot prove clinical performance or replace humidity-controlled experiments. The ordering depends on ordinal interpretation of heterogeneous evidence, and different clinical or environmental applications

Table 5: Priority-setting robustness.

Priority setting	First candidate	Second candidate	Third candidate
Threshold-led	Vapor-generation paper-based thin-film microextraction with Au nanorods, quantum dots, and NU-901	T-Si/Al ₂ O ₃ /Ag/Au	Ag/Si/Ag micropyramid
Balanced	T-Si/Al ₂ O ₃ /Ag/Au	Vapor-generation paper-based thin-film microextraction with Au nanorods, quantum dots, and NU-901	Ag/Si/Ag micropyramid
Deployment-led	Ag nanocube breathalyzer	Au-TiO ₂ nanocomposite	T-Si/Al ₂ O ₃ /Ag/Au
Mechanism-led	Vapor-generation paper-based thin-film microextraction with Au nanorods, quantum dots, and NU-901	T-Si/Al ₂ O ₃ /Ag/Au	Ag/Si/Ag micropyramid



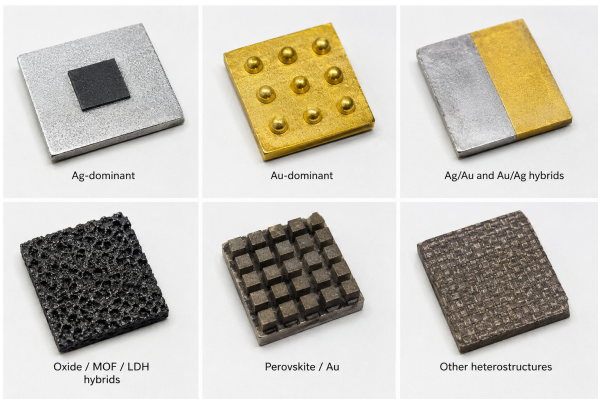
(a) Micropyramid surface.



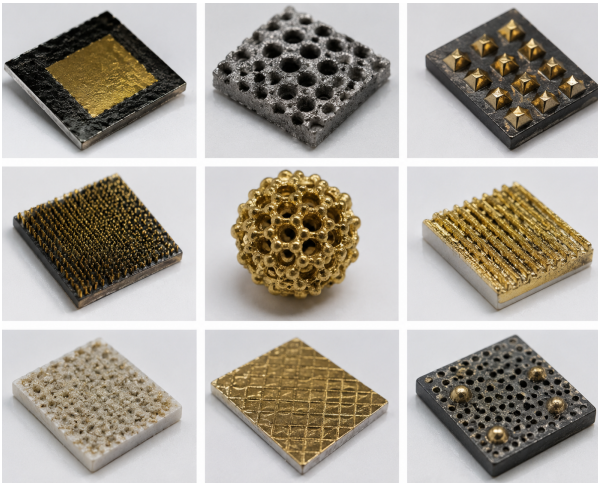
(b) Pyramid detail.

Figure 6: Leading substrate mechanisms.

may require different weighting. Several entries contain broad descriptors, such as unspecified ppb-level performance, that limit confident comparison. The analysis also cannot determine long-term substrate stability, response recovery, fouling, storage sensitivity, or interlabo-



(a) Material families.



(b) Surface geometries.

Figure 7: Materials and architectures.

ratory reproducibility. Future work should pair transport-coupled selection with raw spectral repositories, standardized breath-simulation chambers, controlled humidity studies, independent validation cohorts, and substrate-production quality-control data.

6. Conclusion

This paper asked which SERS breath-sensor architectures remain credible when the complete transfer route from exhaled target to interpretable Raman signal is treated as the main analytical problem. The answer is target- and interface-dependent. For sensitivity-mechanism selection, the strongest candidates are the T-Si/Al₂O₃/Ag/Au light-trapping substrate for hydrogen sulfide at 0.1 ppb, the vapor-generation paper-based thin-film microextraction system with Au nanorods, quantum dots, and NU-901 for aldehydes at 0.1 ppb, and the Ag/Si/Ag micropyramid substrate for aldehydes at 0.1 ppb. These systems combine low thresholds with specific enhancement and transfer mechanisms:

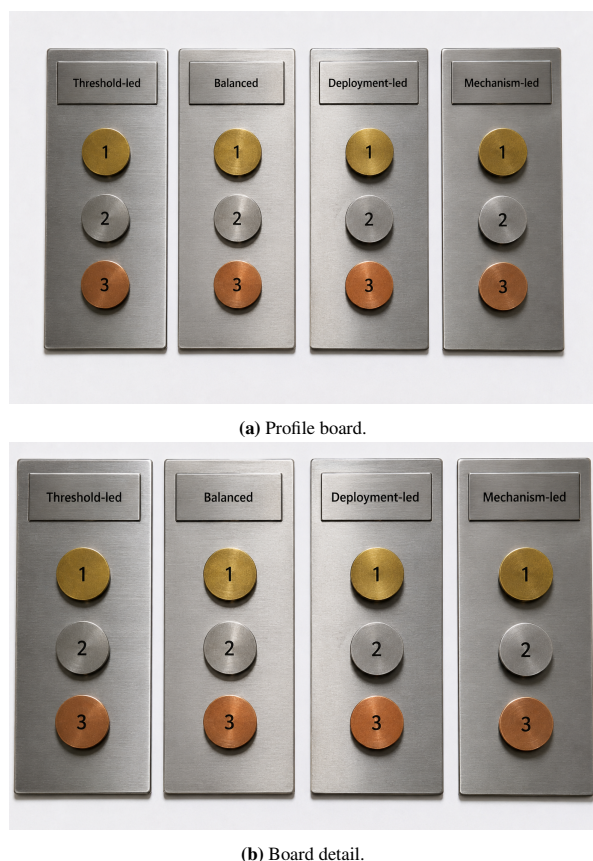


Figure 8: Target-specific priority profiles.



(a) Workflow grid.

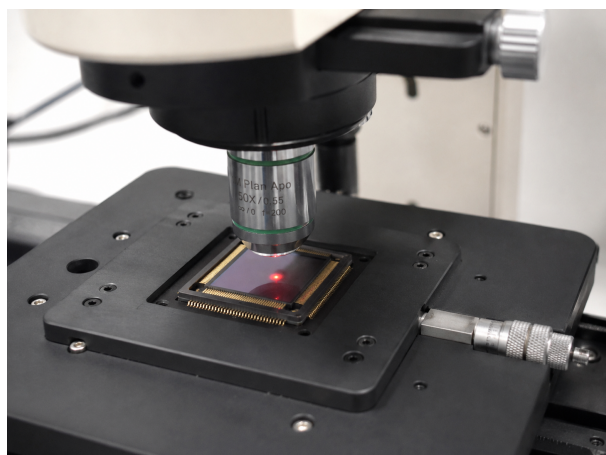
(b) Collection hardware.

Figure 9: Sampling interface.

optical confinement, analyte preconcentration, porous retention, or ordered hot-spot geometry. For deployment-oriented breath testing, the answer changes. The Ag nanocube breathalyzer becomes central because it gives system-level breath-profile discrimination with 96.2% sensitivity and 99.9% specificity, while Au-TiO₂ and AuNP/TiO₂ nanowire systems become important because they connect SERS read-out with biomolecular or condensate-relevant targets. The hollow ZIF-8/gold-superparticle breathing-valve sensor also deserves attention because its breath-contact design addresses the sampling bottleneck even though its threshold is not the lowest in the matrix. The main conclusion is therefore not that one metal, one morphology, or one numerical threshold defines the best breath-SERS sensor. The best architecture is the one whose capture chemistry, hot-spot geometry, breath interface, and validation evidence match the chemical phase and diagnostic purpose of the target. TCSS provides a clear way to make that selection and to identify the next experiment needed for each platform, whether that experiment is humidity testing, external classification validation, substrate-uniformity assessment, or full breath-interface prototyping.

References

- [1] Pauling, L., Robinson, A. B., Teranishi, R., & Cary, P. (1971). Quantitative analysis of urine vapor and breath by gas-liquid partition chromatography. *Proceedings of the National Academy of Sciences*, 68(10), 2374–2376.
- [2] Phillips, M., Gleeson, K., Hughes, J. M. B., Greenberg, J., Cataneo, R. N., Baker, L., & McVay, W. P. (1999). Volatile organic compounds in breath as markers of lung cancer: A cross-sectional study. *The Lancet*, 353(9168), 1930–1933.
- [3] Miekisch, W., Schubert, J. K., & Noeldge-Schomburg, G. F. (2004). Diagnostic potential of breath analysis—Focus on volatile organic compounds. *Clinica Chimica Acta*, 347(1–2), 25–39.
- [4] Risby, T. H., & Solga, S. F. (2006). Current status of clinical breath analysis. *Applied Physics B*, 85(2), 421–426.
- [5] Buszewski, B., Kesy, M., Ligor, T., & Amann, A. (2007). Human exhaled air analytics: Biomarkers of diseases. *Biomedical Chromatography*, 21(6), 553–566.
- [6] Boots, A. W., van Berkel, J. J., Dallinga, J. W., Smolinska, A., Wouters, E. F., & van Schooten, F. J. (2012). The versatile use of exhaled volatile organic compounds in human health and disease. *Journal of Breath Research*, 6(2), 027108.
- [7] Amann, A., Miekisch, W., Schubert, J., Buszewski, B., Ligor, T., Jezewski, T., ... & Risby, T. (2014). Analysis of exhaled breath for disease detection. *Annual Review of Analytical Chemistry*, 7(1), 455–482.
- [8] Amann, A., Costello, B. D. L., Miekisch, W., Schubert, J., Buszewski, B., Pleil, J., ... & Risby, T. (2014). The human volatilome: Volatile organic compounds (VOCs) in exhaled breath, skin emanations, urine, feces and saliva. *Journal of Breath Research*, 8(3), 034001.
- [9] Horváth, I., Barnes, P. J., Loukides, S., Sterk, P. J., Högman, M., Olin, A. C., ... & Vink, T. J. (2017). A European Respiratory Society technical standard: Exhaled biomarkers in lung disease. *European Respiratory Journal*, 49(4).
- [10] Bruderer, T., Gaisl, T., Gaugg, M. T., Nowak, N., Streckenbach, B., Müller, S., ... & Zenobi, R. (2019). On-line analysis of exhaled breath: Focus review. *Chemical Reviews*, 119(19), 10803–10828.
- [11] Hanna, G. B., Boshier, P. R., Markar, S. R., & Romano, A. (2019). Accuracy and methodologic challenges of volatile organic compound-based exhaled breath tests for cancer diagnosis: A systematic review and meta-analysis. *JAMA Oncology*, 5(1), e182815.
- [12] Moura, P. C., Raposo, M., & Vassilenko, V. (2023). Breath volatile organic compounds (VOCs) as biomarkers for the diagnosis of pathological conditions: A review. *Biomedical Journal*, 46(4), 100623.
- [13] Smith, D., & Španěl, P. (2005). Selected ion flow tube mass spectrometry (SIFT-MS) for on-line trace gas analysis. *Mass Spectrometry Reviews*, 24(5), 661–700.
- [14] Fleischmann, M., Hendra, P. J., & McQuillan, A. J. (1974). Raman spectra of pyridine adsorbed at a silver electrode. *Chemical Physics Letters*, 26(2), 163–166.
- [15] Jeanmaire, D. L., & Van Duyne, R. P. (1977). Surface Raman spectro-electrochemistry: Part I. Heterocyclic, aromatic, and aliphatic amines adsorbed on the anodized silver electrode. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry*, 84(1), 1–20.
- [16] Albrecht, M. G., & Creighton, J. A. (1977). Anomalous intense Raman spectra of pyridine at a silver electrode. *Journal of the American Chemical Society*, 99(15), 5215–5217.



(a) Microscope readout.



(b) Bench instrument.

Figure 10: Raman validation context.

- [30] Chen, Q. Q., Hou, R. N., Zhu, Y. Z., Wang, X. T., Zhang, H., Zhang, Y. J., ... & Li, J. F. (2021). Au@ZIF-8 core-shell nanoparticles as a SERS substrate for volatile organic compound gas detection. *Analytical Chemistry*, 93(19), 7188–7195.
- [31] Allegretto, J. A., & Dostalek, J. (2024). Metal-organic frameworks in surface enhanced Raman spectroscopy-based analysis of volatile organic compounds. *Advanced Science*, 11(30), 2401437.
- [32] Liu, Y., Chui, K. K., Fang, Y., Wen, S., Zhuo, X., & Wang, J. (2024). Metal-organic framework-enabled trapping of volatile organic compounds into plasmonic nanogaps for surface-enhanced Raman scattering detection. *ACS Nano*, 18(17), 11234–11244.
- [33] Fernández-Lodeiro, A., Constantinou, M., Panteli, C., Agapiou, A., & Andreou, C. (2025). Breath analysis via surface enhanced Raman spectroscopy. *ACS Sensors*, 10(2), 602–621.
- [34] Broadhurst, D. I., & Kell, D. B. (2006). Statistical strategies for avoiding false discoveries in metabolomics and related experiments. *Metabolomics*, 2(4), 171–196.
- [35] Goodacre, R., Broadhurst, D., Smilde, A. K., Kristal, B. S., Baker, J. D., Beger, R., ... & Wulfert, F. (2007). Proposed minimum reporting standards for data analysis in metabolomics. *Metabolomics*, 3(3), 231–241.
- [17] Moskovits, M. (1985). Surface-enhanced spectroscopy. *Reviews of Modern Physics*, 57(3), 783.
- [18] Kneipp, K., Wang, Y., Kneipp, H., Perelman, L. T., Itzkan, I., Dasari, R. R., & Feld, M. S. (1997). Single molecule detection using surface-enhanced Raman scattering (SERS). *Physical Review Letters*, 78(9), 1667.
- [19] Nie, S., & Emory, S. R. (1997). Probing single molecules and single nanoparticles by surface-enhanced Raman scattering. *Science*, 275(5303), 1102–1106.
- [20] Campion, A., & Kambhampati, P. (1998). Surface-enhanced Raman scattering. *Chemical Society Reviews*, 27(4), 241–250.
- [21] Haynes, C. L., McFarland, A. D., & Van Duyne, R. P. (2005). Surface-enhanced Raman spectroscopy. *Analytical Chemistry*, 77(17), 338A–346A.
- [22] Willets, K. A., & Van Duyne, R. P. (2007). Localized surface plasmon resonance spectroscopy and sensing. *Annual Review of Physical Chemistry*, 58(1), 267–297.
- [23] Stiles, P. L., Dieringer, J. A., Shah, N. C., & Van Duyne, R. P. (2008). Surface-enhanced Raman spectroscopy. *Annual Review of Analytical Chemistry*, 1(1), 601–626.
- [24] Le Ru, E. C., & Etchegoin, P. G. (2009). *Principles of surface-enhanced Raman spectroscopy and related plasmonic effects*. Elsevier.
- [25] Schlücker, S. (2014). Surface-enhanced Raman spectroscopy: Concepts and chemical applications. *Angewandte Chemie International Edition*, 53(19), 4756–4795.
- [26] Pilot, R., Signorini, R., Durante, C., Orian, L., Bhamidipati, M., & Fabris, L. (2019). A review on surface-enhanced Raman scattering. *Biosensors*, 9(2), 57.
- [27] Pérez-Jiménez, A. I., Lyu, D., Lu, Z., Liu, G., & Ren, B. (2020). Surface-enhanced Raman spectroscopy: Benefits, trade-offs and future developments. *Chemical Science*, 11(18), 4563–4577.
- [28] Kreno, L. E., Leong, K., Farha, O. K., Allendorf, M., Van Duyne, R. P., & Hupp, J. T. (2012). Metal-organic framework materials as chemical sensors. *Chemical Reviews*, 112(2), 1105–1125.
- [29] Furukawa, H., Cordova, K. E., O’Keeffe, M., & Yaghi, O. M. (2013). The chemistry and applications of metal-organic frameworks. *Science*, 341(6149), 1230444.