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Towards instant diagnostics: The role of ambient mass spectrometry devices in point-of-care clinical practice

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ABSTRACT

Ambient mass spectrometry (AMS) enables rapid, preparation-free molecular profiling and is increasingly impacting clinical diagnostics and point-of-care (POC) testing. Advances in soft/ambient ionization (DESI, DART, paper spray, MasSpec Pen, REIMS, PESI, and related hybrid sources) broaden analyte coverage, enabling real-time detection of metabolites, lipids, proteins, pathogens, drugs, and other biomarkers directly from tissues, biofluids, and swabs. In parallel, portable and miniaturized mass spectrometers have improved the feasibility of selected bedside, intraoperative, and field workflows, particularly for targeted screening and quantification. Machine-learning integration increasingly automates spectral interpretation for tissue classification, disease diagnosis, and therapeutic drug monitoring. However, routine clinical adoption remains constrained by standardization requirements, multicenter validation, and regulatory pathways. This review summarizes the evolution of AMS and portable MS, surveys emerging clinical applications, and outlines priorities for broader implementation. We also discuss workflow integration, quality assurance, data sharing, and training needs for non-specialist users.

1. Introduction

The increasing demand for personalized medicine and rapid clinical decision-making has driven the development of analytical technologies capable of delivering fast, accurate results with minimal sample preparation. Mass spectrometry (MS) is particularly prominent for its high precision, accuracy, and sensitivity, enabling reliable detection, characterization, and quantification of a wide range of biomolecules, including proteins, pathogens, vitamins, hormones, and tumor markers [1–3].

Although mass spectrometry offers significant analytical advantages, it currently represents only a small fraction of clinical diagnostic testing. The most common clinical MS applications include matrix-assisted laser desorption/ionization (MALDI) BIOTYPER for microbial identification and liquid chromatography–tandem mass spectrometry (LC-MS/MS) for targeted assays, such as therapeutic drug monitoring and the analysis of vitamins, neurotransmitters, and hormones [4–7]. Within this context, ambient mass spectrometry (AMS) has emerged as a transformative approach, enabling direct molecular analysis under atmospheric conditions and overcoming many limitations of conventional MS workflows [1,2,8–12].

AMS techniques such as Desorption Electrospray Ionization Mass Spectrometry (DESI-MS), Direct Analysis in Real Time Mass Spectrometry (DART-MS), Paper Spray Ionization Mass Spectrometry (PSI-MS), Probe Electrospray Ionization Mass Spectrometry (PESI-MS), and new MS–based surgical tools, for instance the MasSpec Pen, allow rapid, *in situ* profiling of biological fluids, tissues, and swabs without extensive preprocessing [13–19]. These capabilities are particularly aligned with the needs of point-of-care (POC) testing, where portability, analytical speed, and simplified user interfaces are essential for deployment outside traditional laboratory environments [20,21]. A conceptual overview of the principles and clinical relevance of ambient mass spectrometry is provided in Fig. 1.

The integration of AMS into POC applications is advancing rapidly,

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driven by the miniaturization of ion sources, vacuum systems, and mass analyzers, as well as by the development of robust ionization strategies that function reliably in ambient conditions. In contrast to laboratory-based MS, POC-oriented AMS platforms prioritize compact design, low operational burden, and immediate clinical interpretability. As a result, these systems are increasingly explored for bedside diagnostics, intraoperative assessment, field analysis, and rapid screening of metabolites, pathogens, drugs, and disease-associated biomarkers [8–10,13–15,22,23].

In this review, we provide an overview of recent advances in mass spectrometry, particularly in ambient ionization techniques and miniaturized platforms, and summarize efforts over the past decade to enable their use in clinical POC settings under ambient conditions. Additionally, we discuss current regulatory frameworks governing these platforms, outline potential directions and future perspectives for their consolidation in clinical practice, and lay the groundwork for technological evolution in the following section.

2. Evolution of mass spectrometry for clinical screening and diagnostics

Mass spectrometry (MS) has evolved from a specialist analytical tool into a strategic platform for selected areas of clinical diagnostics where molecular specificity, selectivity, and multiplexing provide advantages over immunoassays and other routine platforms [24]. Despite this progress, MS remains a minority contributor to overall diagnostic throughput at a global scale [25], with routine impact dominated by MALDI-TOF MS as the first MS technology to enter routine hospital diagnostics, revolutionizing microbial identification due to its affordability, speed, and robustness [26–28] and LC–MS/MS in targeted quantitative assays such as therapeutic drug monitoring (TDM) [29,30], toxicology [31,32], and steroid/endocrine testing [33,34].

This status quo has shaped two complementary development trajectories. The first focuses on consolidation of centralized, high-throughput MS platforms for confirmatory diagnostics and longitudinal monitoring, prioritizing traceable calibration, internal standardization, and routine quality control. The second seeks workflow simplification through reduced sample preparation, direct-analysis strategies, and data-driven interpretation, aiming to shorten turnaround times and move actionable molecular information closer to clinical decision points [35–38].

2.1. Established clinical MS approaches

Routine clinical MS adoption is highest when the clinical question is well defined, and the assay can be locked to a fit-for-purpose analytical specification. In microbiology, MALDI-TOF MS scaled because it couples rapid analysis with standardized vendor ecosystems (instrument-software-database), high throughput, and strong workflow integration aligned with routine laboratory operations [26–28]. In clinical chemistry, targeted LC–MS/MS (and GC–MS) remains the backbone for quantifying small molecules in applications where specificity is essential—most notably TDM, toxicology, steroid/endocrine profiling, and related targeted panels [29,32,34].

Across these mature deployments, common enabling factors include stable pre-analytics, clear measurands, commutable calibration strategies, controllable matrix effects, and reporting that maps to clinically interpretable thresholds. By contrast, approaches that generate large, complex molecular outputs (e.g., untargeted phenotyping) face additional barriers, including harmonization of sample handling and data processing, reproducible identification confidence, and clinically validated interpretive frameworks [35,39].

The integration of machine learning approaches has also improved the diagnostic capabilities of established MS platforms. For instance, Rodríguez-Temporal et al., 2023 demonstrated that MALDI-TOF MS protein spectra combined with machine learning algorithms could differentiate subspecies of *Mycobacterium abscessus*, achieving identification accuracies above 96% using random forest models trained on spectral features. This approach illustrates how data-driven interpretation of MS fingerprints can extend the diagnostic resolution of routine platforms beyond conventional spectral matching strategies [40].

2.2. Instrumentation trends enabling translational diagnostics

A major driver enabling rapid and potentially decentralized molecular phenotyping is workflow simplification at the front end of the analytical pipeline. Innovations in sampling, ionization, and sample introduction have reduced reliance on extensive sample preparation and chromatographic separation in selected screening contexts [41]. From this perspective, AMS has emerged as an important technological direction, enabling direct analysis of complex biological matrices with minimal or no sample preparation. Because AMS platforms differ substantially in workflow fit (biofluids vs intraoperative tissue), decision type (targeted quantification vs classification), and validation maturity, technique-specific clinical applications and readiness comparisons are discussed in detail in Section 4.

Beyond these direct-analysis strategies, MS-based non-invasive phenotyping has expanded through breathomics and volatilomics workflows (see Fig. 2), which are attractive because sampling can be rapid and minimally invasive but is highly sensitive to collection methodology and environmental confounders. Although breathomics workflows have not yet been widely implemented using ambient

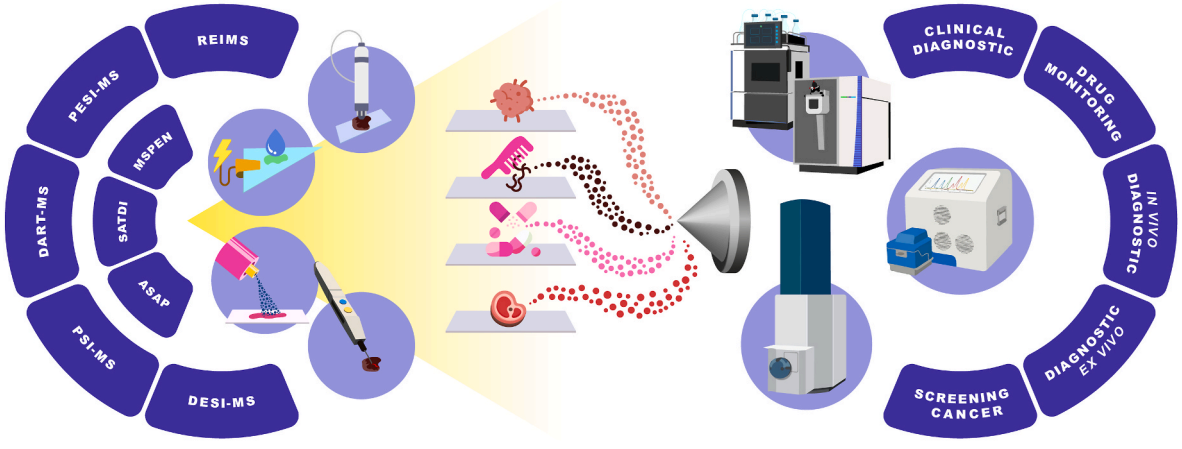

Fig. 1. Conceptual overview of ambient mass spectrometry (AMS) for clinical and point-of-care applications. Some graphical elements were adapted from Freepik (https://www.freepik.com/).

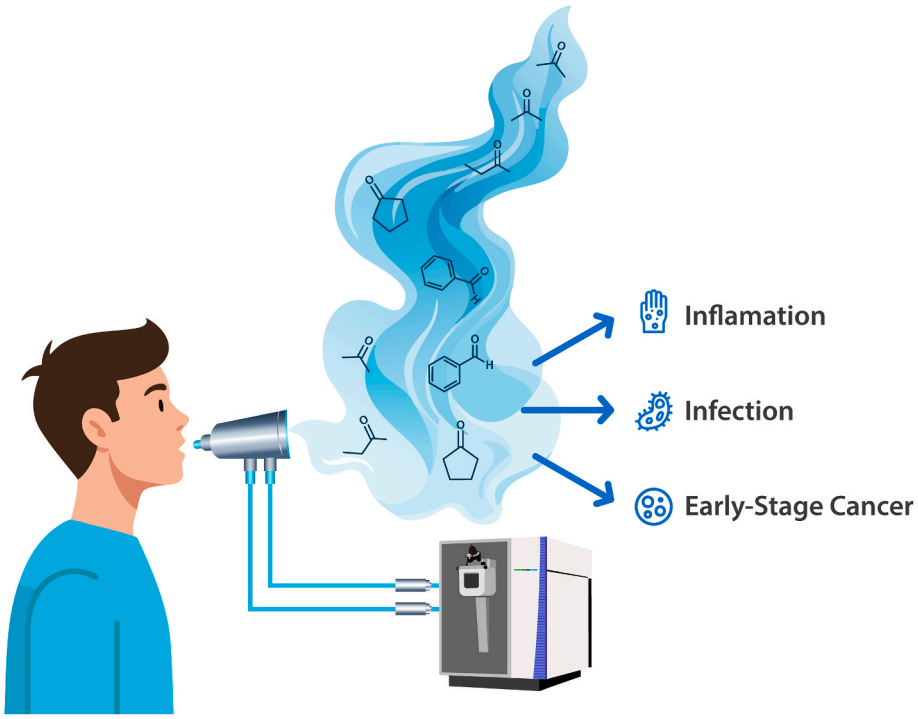

Fig. 2. Illustrative schematic showing the use of mass spectrometry for non-invasive, real-time molecular diagnostics. Exhaled breath is analyzed to detect volatile organic compounds VOCs) biomarkerss associated with infections, inflammation, and early-stage cancer. Some graphical elements were adapted from Freepik (https://www.freepik.com/).

ionization sources, the approach shows considerable potential for future integration with rapid MS platforms. Combining breath analysis with ambient ionization and portable MS could enable real-time clinical screening and point-of-care diagnostics, representing a promising direction for fast and non-invasive analytical strategies [42,43].

Recent breathomics studies illustrate both diagnostic potential and translation challenges. In 2026, Ji et al. developed a targeted GC-MS/MS breathomics assay for colorectal cancer screening based on quantification of exhaled short-chain fatty acids and aldehydes [44]. The method achieved detection limits below 0.25 ng L^{-1} and demonstrated clinically relevant classification performance (AUC = 0.89), outperforming conventional serum markers, highlighting that targeted MS workflows can achieve low-level quantitation and meaningful diagnostic discrimination when sampling conditions and cohort design are rigorously controlled. Conversely, in 2025 Schaar et al. applied an untargeted LC-HRMS/MS workflow to exhaled breath aerosols to identify endogenous biomarkers that could support standardization of breath sampling protocols [45]. Using orthogonal chromatographic separations and high-resolution detection, the authors showed that systematic blank subtraction and feature filtering substantially reduced artifactual signals and enabled reproducible detection of endogenous features, underscoring the importance of strict QC frameworks and harmonized sampling strategies for interpretable untargeted breathomics.

Finally, additional rapid MS concepts—outside routine chromatographic workflows—continue to push toward field/near-patient use cases. For example, portable solvent-assisted thermal desorption ionization MS (SATDI-MS) has been reported for rapid fingerprinting of clinical samples [46]. While these examples illustrate the breadth of rapid MS innovation, routine clinical implementation will depend on prospective validation, standardized protocols, and integration of calibration/QC requirements consistent with clinical quality systems (see Section 6).

3. Portable mass spectrometry

Portable mass spectrometry (PMS) has advanced significantly over the past decade, evolving from basic miniaturized instruments to carefully engineered platforms that balance portability with high analytical performance [47]. The advances detailed in Section 2 enable the miniaturization strategies described here, linking analytical performance with actual point-of-care applicability.

3.1. Advances in instrumentation and hardware

Much of this progress comes from innovations in mass analyzer design. Rectilinear ion traps, as implemented in the Mini-10/11/12 series developed at Purdue University and in the commercial Mini Beta (PURSPEC), remain a central technology because they operate effectively at elevated pressures (~10^{-3} Torr), thereby reducing vacuum requirements while still supporting MS/MS capabilities necessary for the analysis of complex clinical matrices such as whole blood [47–49].

Beyond ion traps, other commercial architectures have matured to provide robust solutions. Although these techniques had not been used or made focusing in POC analysis, they picture the advance of the miniaturization technology in recent years. The Microsaic 3500 MiD utilizes a miniaturized single quadrupole based on microelectromechanical systems (MEMS) technology for routine small-molecule monitoring [50], while the Torion T-9 (PerkinElmer) employs a toroidal ion trap to maintain high ion storage capacity in compact volume and used for drug analysis [51]. For gaseous and volatile clinical samples, portable quadrupole-based systems like the FLIR Griffin G510 have also proven effective for field-based screening [52]. While hyphenated miniaturized GC-MS systems can be found in “all-in-one solutions”, complete portable LC-MS are still one step further. Currently, it is being demonstrated as portable mass spectrometers coupled with regular LC systems as a potential for lower cost metabolomics [53].

Newer systems, such as the Brick-V, incorporate dual linear ion traps

capable of advanced scan modes like pseudo-MRM, which emulate the specificity of high-end triple quadrupoles, an essential feature for quantitative drug monitoring in chemically complex samples [54]. Other architectures, such as the C-CAMMS cycloidal sector mass spectrometer, address traditional performance limitations by replacing conventional slits with spatially coded apertures, thereby achieving more than a 10-fold increase in throughput without sacrificing mass resolution [55]. Even transportable single-quadrupole systems, including the Waters QDa, have gained relevance, particularly when paired with ambient ionization methods such as Matrix-Assisted Ionization (MAI) to support drug and protein analysis in decentralized or mobile environments [56].

In parallel, improvements in vacuum and ion-transfer technologies have further enhanced PMS capabilities. A notable shift from Discontinuous Atmospheric Pressure Interfaces (DAPI) to Continuous Atmospheric Pressure Interfaces (CAPI) has led to more stable operation and improved duty cycles [49,57]. Advances in sensitivity have been driven primarily by hybrid ion funnels with PCB-based rectangular geometries and planar quadrupoles. These designs, as demonstrated by Amsden et al., have increased ion transmission by nearly an order of magnitude, enabling detection limits as low as 1 ng mL^{-1} for compounds such as reserpine [57].

As noted, demand and usage for this category of equipment have increased over the years, and many companies have developed their own solutions. Fig. 3 depicts illustrations of some commercial portable spectrometers.

3.2. Front-end ambient ionization techniques

A major development that has enabled clinically relevant PMS workflows has been the expansion of AMS. Direct analysis of minimally prepared biological samples can reduce front-end complexity and make certain targeted or rapid-screening applications more compatible with portable MS [16,48]. PSI-MS exemplifies this capability by enabling sample-to-result workflows in under 4 min using dried blood spots or urine, and it has already been applied to TDM of HIV and diabetes medications [54,55]. Coated Blade Spray (CBS) further accelerates workflows by integrating extraction and ionization on a sorbent-coated metal strip, offering a rapid alternative to conventional solid-phase extraction for high-throughput screening [16].

Other AMS platforms extend PMS into intraoperative and real-time diagnostic contexts: REIMS (the "iKnife") analyzes aerosolized surgical smoke to distinguish tumor types such as colorectal and ovarian cancers during electrosurgery [16]; the MasSpec Pen [14] uses a gentle aqueous droplet extraction process to collect metabolites from tissue surfaces for nondestructive, intraoperative cancer margin assessment (see Section 4 for more details); and MAI enables ionization of analytes from urine and tissue under vacuum without high voltage, heat, or laser input, improving compatibility with low-power portable systems [16].

3.3. Specific clinical applications

Through this progress, PMS systems have moved beyond theoretical prototypes to selected clinically relevant targeted measurements. Their most defensible current role is in narrow, fit-for-purpose assays where reduced turnaround time may compensate for lower resolving power. Table 1 contextualizes recent PMS results against clinical decision limits. Pandey et al. used the Mini-12 to quantify the HIV therapeutics Cabotegravir and Rilpivirine in whole blood with limits of quantitation of 750 ng mL^{-1} and 20 ng mL^{-1}, respectively, allowing dose adjustments for long-acting injectable therapies [55]. Similar near-patient targeted assays for Metformin and Sitagliptin demonstrated linearity across 20–1000 ng mL^{-1}, supporting medication-adherence or targeted monitoring use cases rather than broad untargeted clinical profiling [54].

In oncology and pathology, portable MS has proven valuable for tissue characterization, particularly through lipidomic profiling. Zou et al. used a Mini-12 with a wire probe to distinguish glioma from normal brain tissue by monitoring the tumor-associated metabolite 2-hydroxyglutarate (2-HG) [56].

PMS also contributes to the diagnosis of infectious diseases. Although portable systems generally lack the resolution of MALDI-TOF, Sasiene et al. developed a multidimensional fingerprinting strategy using combined MS^1 and MS/MS data to classify *E. coli* and *Y. pestis* strains with over 92% accuracy, even from low-resolution analyzers [59].

3.4. Use-case and suitability of portable mass spectrometry for clinical application

Although the miniaturization of mass spectrometers is advancing, some applications are still a challenge. While benchtop systems offer superior mass resolution (for Orbitrap) and mass accuracy (ppm), PMS systems typically operate with unit mass resolution and accuracy in the 100-500 ppm range. These characteristics limit their applicability in settings that require higher selectivity, broader molecular coverage, and more precise analytical discrimination. [53,60]. Consequently, PMS main usage and suitability are for biological and clinical application,

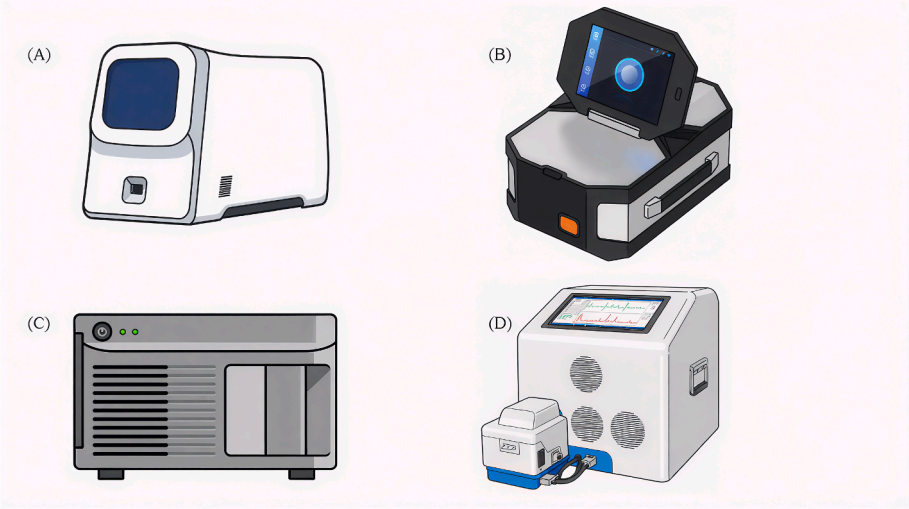

Fig. 3. Illustration of different commercial portable mass spectrometers. (A) Mini-12 Mass Spectrometer. (B) Mini ∏ (PURSPEC, USA). (C) Waters QDa. (D) Continuity Portable MS (BaySpec, USA).

Table 1
PMS Quantitative Performance vs. Clinical Therapeutic Windows.

Analyte	PMS Platform	Reported LOQ	Linear Range	Therapeutic Window/Clinical Limit	Reference
Cabotegravir	Mini-12 (PSI)	750 ng mL^{-1}	750–10,000 ng mL^{-1}	>640 ng mL^{-1}	[55]
Rilpivirine	Mini-12 (PSI)	20 ng mL^{-1}	20–1000 ng mL^{-1}	>50 ng mL^{-1}	[55]
Metformin	Mini-MS (PSI)	20 ng mL^{-1}	20–1000 ng mL^{-1}	500–2500 ng mL^{-1}	[54]
Sitagliptin	Mini-MS (PSI)	20 ng mL^{-1}	20–1000 ng mL^{-1}	100–500 ng mL^{-1}	[54]
Risperidone	LC-Mini MS	1.0 ng mL^{-1}	1–200 ng mL^{-1}	20–60 ng mL^{-1}	[58]

targeted quantification or screening of specific analytes rather than untargeted metabolomic profiling, which requires the high peak capacity and resolution of centralized laboratory equipment [53]. Quantitative performance benchmarks for benchtop and portable equipment are summarized in Table 2.

Although portable mass spectrometry systems offer promising capabilities for targeted quantification and screening assays, they are generally more suited to narrow workflows rather than broad, untargeted metabolomic analysis. While portable MS systems can be extremely valuable for specific applications such as TDM and screening of a small number of analytes, their current capabilities are insufficient for general-purpose use in complex diagnostic workflows that require higher resolution and more precise measurements, as offered by benchtop MS platforms.

4. Mass spectrometry for rapid clinical screening

4.1. Paper spray ionization mass spectrometry (PSI-MS)

The PSI-MS source, introduced in 2010 by Cooks and colleagues, represented a significant advancement in ambient mass spectrometry by enabling rapid, low-cost analyses directly from a paper substrate with minimal sample preparation [64]. Structurally, **PSI-MS** uses a triangular paper substrate—commonly equilateral—to which a high voltage is applied. The potential difference between the paper and the mass spectrometer inlet creates a strong electric field at the tip. This setup drives solvent flow by capillary action toward the apex, where the intense field generates a cone-jet spray like electrospray ionization (ESI), producing charged microdroplets that carry analytes. These droplets are directed into the mass spectrometer inlet, enabling immediate analysis without extensive purification or chromatographic separation. As with other ambient ionization methods, PSI-MS aligns naturally with portable platforms, strengthening its relevance in point-of-care settings [64].

Table 2
Quantitative benchmark comparison between benchtop and portable MS equipment.

Feature	Benchtop Systems (FT-ICR, Orbitrap, Q-ToF)	Portable Systems (Miniature Ion Traps, Quads)	Reference
Mass Resolution	10,000 to >1,000,000; FT-ICR can exceed 10 M at $m/z < 1000$	Unit Resolution (0.5–1.0 Da); typically limited to identifying nominal mass.	[47,61]
Mass Accuracy	Sub-ppm to <5 ppm; enables elemental composition determination	Unit Accuracy; often 0.1–0.5 Da; requires software offsets for field use	[48,62]
Dynamic Range	5+ orders of magnitude; crucial for trace analysis in complex plasma/tissue	Limited (2–3 orders); sensitivity is typically 10–100x lower than benchtop	[47,50, 63]
Turnaround Time (TAT)	Hours to Days; due to sample transport and extensive LC-separation	Rapid (<2 to 4 min); allows for immediate clinical decision-making at the bedside	[16,55]
Duty Cycle	High; ToF systems achieve up to 100% duty cycle for non-scanning modes	Pulsed/Low; Discontinuous interfaces (DAPI) often open for only 15–30 ms per cycle	[47,61]

One of the primary advantages of PSI-MS lies in its simplicity: the use of low-cost cellulose-based substrates, minimal sample manipulation, and compatibility with complex matrices have facilitated its application in bioanalysis and forensic science and have motivated its exploration for POC diagnostics [65].

Recent studies have broadened the scope of PSI-MS, demonstrating improvements in analytical sensitivity, substrate functionalization, and quantitative performance [66,67]. For instance, paper substrates modified with nanomaterials—such as metallic nanoparticles or carbon-based coatings—have been shown to enhance ionization efficiency by improving conductivity and promoting selective enrichment of analytes. In addition, advances in solvent-assisted PSI-MS and internal standardization strategies have significantly strengthened quantitative robustness, enabling reliable measurements of small molecules, pharmaceuticals, and metabolites in biological fluids with minimal sample pretreatment [68–70]. Collectively, PSI-MS continues to evolve as a versatile ambient ionization technique, offering an accessible platform for rapid chemical screening and an attractive alternative to conventional ESI.

The application of PSI-MS for rapid diagnostics and near-patient targeted analyses has become increasingly prominent within analytical chemistry due to its versatility and ability to ionize samples directly under ambient conditions. Since its introduction by Cooks and colleagues, PSI-MS has been explored as a simplified alternative to conventional ionization techniques, particularly because it minimizes sample preparation steps and enables field-deployable analysis [64,71, 72].

Coupling PSI with MS portable systems has further expanded its applicability. The combination of PSI's operational simplicity with the mobility of handheld MS instruments enables rapid diagnostic strategies suitable for resource-limited environments. A notable example is the work of Lee et al., who developed a paper-based microfluidic device capable of remotely collecting biofluids. On this platform, pH-sensitive ionic probes were synthesized and functionalized with monoclonal antibodies specific to the malaria biomarker Plasmodium falciparum histidine-rich protein 2 (PfHRP2) [73]. The conceptual design of this system is illustrated in Fig. 4.

The On-chip Paper Spray Mass Spectrometry (On-chip PS-MS) method proposed by the authors was directly compared to nano-electrospray Ionization (nano-ESI) in terms of elution efficiency. The On-chip PS-MS platform achieved an elution efficiency of 98% with a single addition of elution solvent, whereas nano-ESI yielded approximately 50% under similar conditions. These results underscore the superior analyte recovery and analytical robustness of the On-chip PS-MS approach.

Furthermore, the limit of detection (LOD) was evaluated for both the portable On-chip PS-MS system and a conventional benchtop MS. The On-chip method exhibited an LOD of 0.216 nmol L^{-1}, whereas the benchtop MS achieved an LOD of 0.029 nmol L^{-1}. Although less sensitive than the laboratory-grade instrument, the portable system still demonstrates sufficient analytical performance for rapid diagnostic applications in decentralized settings.

The study also assessed the storage stability of the immunoassay device under ambient conditions. Stability was examined in two stages: (i) preservation of the immobilized antibody's capture activity before

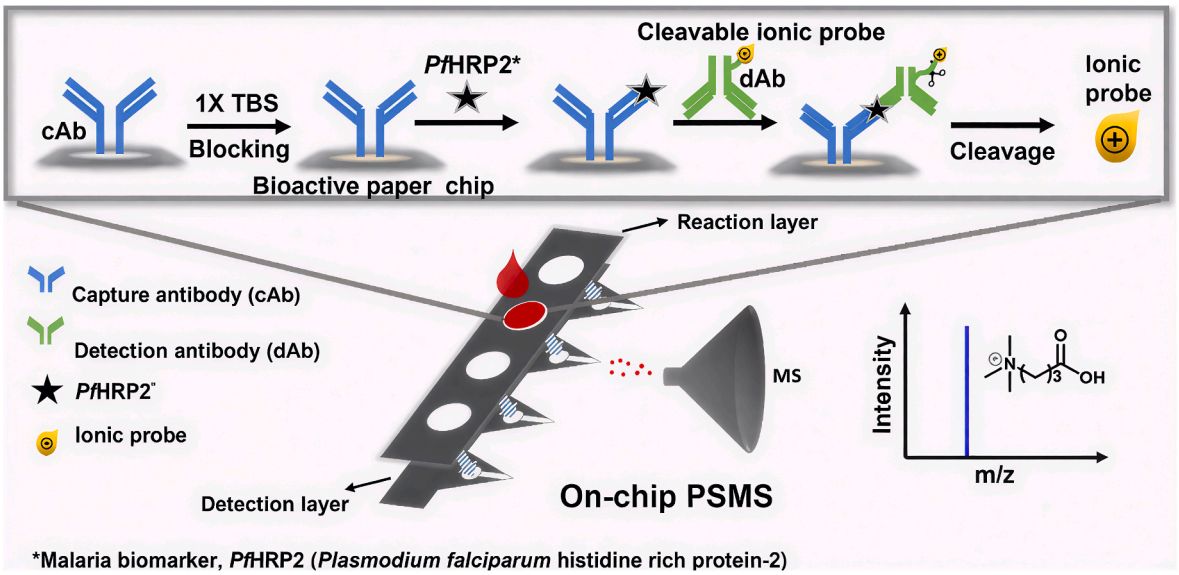

Fig. 4. Schematic illustration of the immobilization of anti-PfHRP2 capture antibodies on the On-chip PS-MS device, where the antibodies are anchored within covalent capture zones, enabling the selective binding of PfHRP2. Copyright 2022 by Analytical Chemistry, License Number 6153050071594 [73].

sample application, and (ii) stability of the fully assembled immunoassay after sample deposition. In both cases, the device maintained adequate stability for up to 25 days, underscoring its suitability for remote or low-infrastructure environments where refrigeration is unavailable.

Taking together, these findings demonstrate the substantial potential of On-chip PS-MS for POC diagnostic immunoassays, especially in resource-limited settings. The robustness of the paper-based immunoassay chip, combined with the operational advantages of portable MS, suggests its feasibility for low-cost and rapid testing, while further validation and technological advances are required to enable large-scale deployment in remote regions.

In this same context of using portable mass spectrometry—not for diagnostic purposes, but for clinical treatment monitoring—Zhou et al. and Chen et al. based their studies on the application of PS-MS for POC testing [46,74]. Zhou and colleagues reported the development of a method employing PSI coupled to a portable linear ion trap (Mini π-pMS), demonstrating its capability for rapid bedside quantification of tirofiban. Tirofiban is a widely used antiplatelet agent for the treatment of acute myocardial infarction (AMI), acting as a highly selective non-peptidic GP IIb/IIIa receptor antagonist with potent antiplatelet effects in patients with acute coronary syndrome.

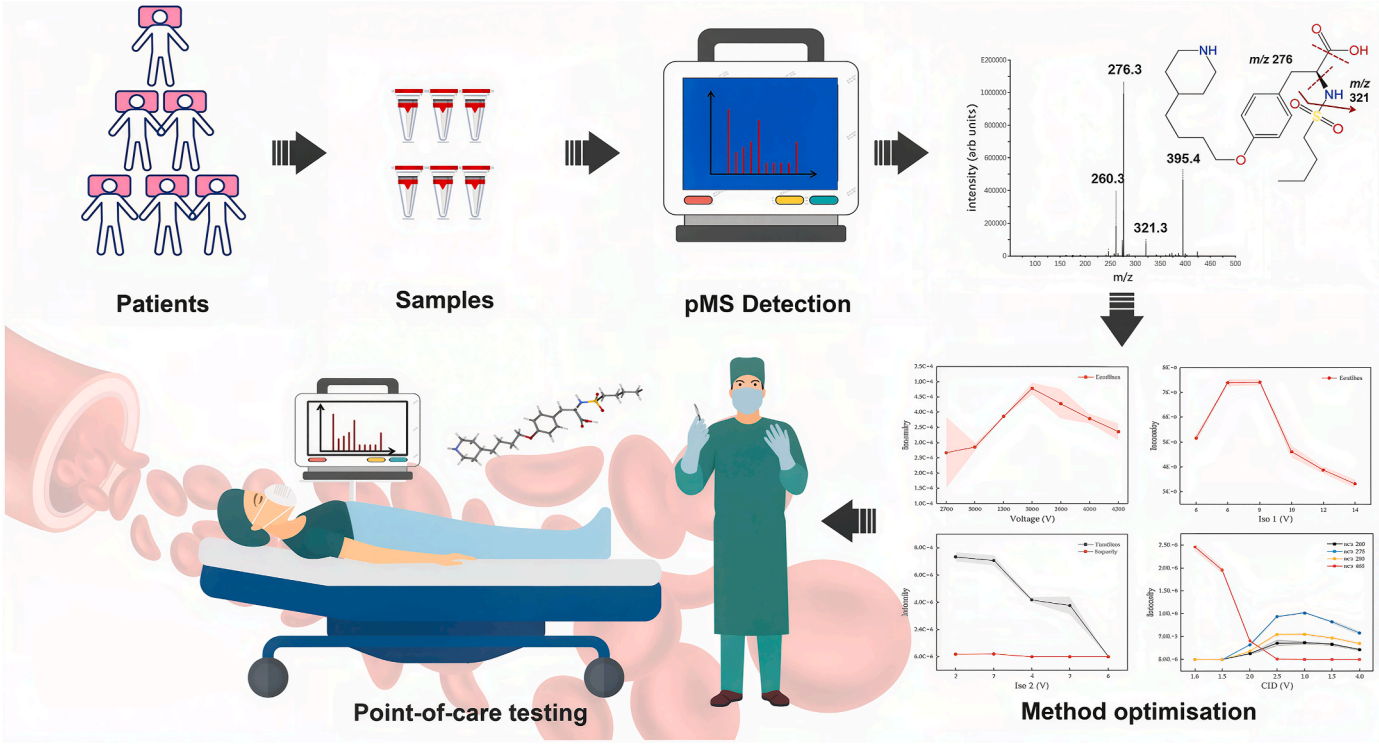

Fig. 5. Schematic illustration of the development of the portable PS-MS method for real-time analysis of tirofiban in blood samples from patients undergoing treatment for acute myocardial infarction (AMI), reproduced from the work of Zhou et al. (2024). Copyright 2024 by ACS Omega [74].

For the analytical workflow, a portable mass spectrometer (PURSPEC Technologies Inc.) was used, along with blood samples collected from AMI patients undergoing treatment. The schematic shown in Fig. 5 illustrates the technical workflow applied in the study.

The Mini π mass spectrometer features a highly compact architecture, low power consumption, and the ability to operate in both MS^1 and MS/MS modes across an *m/z* range of 50–1000. The platform incorporates a discontinuous atmosphere pressure interface coupled to a linear ion trap, enabling rapid analysis without the need for external gases or complex vacuum systems. This configuration provides true portability, allowing deployment in catheterization laboratories, advanced emergency medical units, or intensive care environments—attributes particularly advantageous for POC applications.

The authors demonstrated that tirofiban characterization within the system produced a precursor ion at *m/z* 441.3, along with characteristic product ions at *m/z* 395.4, 321.3, 276.3, and 260.3 upon collision-induced dissociation (CID). Among these, the fragment at *m/z* 276.3 exhibited the highest relative intensity, thereby establishing its suitability as the primary transition for quantitative analysis via multiple reaction monitoring (MRM). Analytical validation of the method revealed sensitivity compatible with clinical requirements, yielding a limit of detection of 10.1 $\mu g\,L^{-1}$ and a limit of quantification of 33.7 $\mu g\,L^{-1}$. Precision metrics were satisfactory, with intraday relative standard deviations ranging from 7.8% to 8.3% and interday relative standard deviations ranging from 4.8% to 6.7%. Recovery assays using human blood as the biological matrix yielded 87.5% - 93.4%, confirming the method's accuracy in a complex biological environment.

Application of the methodology to real clinical samples from patients undergoing percutaneous coronary intervention (PCI) further underscored its translational potential. Of the twelve samples analyzed, ten exhibited tirofiban concentrations within the expected perioperative range (35.4–72.1 $\mu g\,L^{-1}$), whereas two samples fell below the quantification threshold. The integration of PSI with portable MS represents a noteworthy advancement in precision cardiovascular medicine. Significant advantages of this approach include rapid analytical turnaround, minimal sample requirements, operational simplicity, and the feasibility of performing analyses directly at the patient's bedside or in field settings. Although certain limitations persist—such as matrix effects and lower sensitivity than LC–MS/MS—these issues may be mitigated through future developments in rapid pre-treatment strategies, enhanced ionization-interface design, and expanded fragmentation libraries.

Chen and colleagues developed a methodology explicitly tailored for POC therapeutic drug monitoring in chronic conditions, such as type 2 diabetes mellitus (T2DM) [54]. Metformin (MET) and sitagliptin (STG) are widely used in the management of T2DM, and monitoring their plasma concentrations is essential for optimizing individualized therapeutic regimens. The proposed method enables the quantification of both analytes in plasma and urine in under 2 min, with minimal sample preparation, using a portable mass spectrometer (Cell model, PURSPEC Technologies Inc.).

Chen and co-authors demonstrated the high applicability of the technique for rapid quantification, achieving strong linearity for both drugs using isotopically labeled internal standards. The incorporation of such standards is particularly critical in PSI-MS quantification, as ambient ionization sources are inherently susceptible to environmental fluctuations that may compromise analytical reproducibility. The use of internal standards is therefore indispensable for reducing signal variability and enhancing the robustness and reliability of the analytical workflow [54].

In the TDM examples included in the manuscript, the analytical performance of the PSI-MS assays is consistent with clinically relevant exposure ranges. For example, the assay developed for metformin and sitagliptin shows an LOQ of 20 $ng\,mL^{-1}$ and a linear range of 20–1000 $ng\,mL^{-1}$ in blood, which fully encompasses their reported therapeutic concentrations (approximately 100–1000 $ng\,mL^{-1}$ for metformin and 50–380 $ng\,mL^{-1}$ for sitagliptin) [54]. Similarly, for long-acting antiretrovirals such as cabotegravir and rilpivirine, clinically relevant trough thresholds used in TDM interpretation are approximately 664 $ng\,mL^{-1}$ and 50 $ng\,mL^{-1}$, respectively, values that are well above the reported analytical LOQs, indicating that the methods are sufficiently sensitive to detect subtherapeutic concentrations associated with adherence issues or risk of virological failure [55,75].

The authors also note that, although the quantitative performance of PSI-MS has not yet reached the level of precision afforded by established laboratory-based platforms such as LC–MS/MS, the operational advantages—namely rapid analysis, minimal sample handling, and elimination of chromatographic separation—substantially offset these limitations in POC settings, rendering the method up-and-coming for fast screening and decentralized monitoring.

Collectively, these findings illustrate that the miniaturization of mass spectrometry systems has considerably broadened the analytical capabilities beyond traditional laboratory environments. Such instruments facilitate therapeutic drug monitoring, toxicological screening, and the evaluation of bioactive compounds in clinical contexts, and may even support disease diagnosis in home care or remote settings. Moreover, the deployment of these systems promotes analytical decentralization in regions with limited infrastructure, aligning with contemporary public health initiatives to expand diagnostic accessibility [47].

Incorporating paper spray ionization into portable MS systems eliminates labor-intensive extraction, derivatization, and chromatographic steps, thereby allowing healthcare professionals to obtain near-real-time analytical results, as illustrated in Table 3.

4.2. Direct Analysis in Real Time Mass Spectrometry (DART-MS)

DART-MS is a significant analytical technique that has matured considerably since its introduction, emerging as a powerful tool for rapid clinical screening and quantitative diagnostics by addressing the traditional limitations of MS, including lengthy analysis times and complex sample preparation [12,15]. By enabling direct analysis of untreated samples, DART-MS extends the same operational advantages observed in PSI and DESI, further consolidating ambient ionization as a unified diagnostic strategy.

The DART-MS mechanism involves passing a heated stream of inert gas (typically helium) through a chamber where an electrical discharge, also known as glow discharge, creates excited-state (metastable) species. These metastable species interact with atmospheric gases and the sample, inducing ionization [49]. The ionization mechanism is depicted in Fig. 6. Since DART ionization operates in the open environment, it can analyze a wide variety of raw clinical matrices (e.g., urine, whole blood, dried blood spots (DBS)) with minimal or no extraction and zero chromatographic separation [77,78], reducing labor, complexity, and cost.

This type of ionization also significantly reduces the total analysis time (turnaround time) to mere seconds or minutes per sample. For instance, a confirmed methadone finding in urine can be completed in less than 5 min, and anti-arrhythmic drugs can be quantified in as little as 30 s per sample [79]. The fundamental features of DART-MS, speed

Table 3
Comparison between conventional LC–MS/MS and miniaturized PS-MS.

Parameter	Conventional LC–MS/MS	Miniaturized MS and PSI
Total analysis time	15–30 min	<2 min
Sample preparation	Extraction + filtration/ chromatography	3–4 simple steps (mix, dry, elute)
Required volume	100–500 μL	2–50 μL
Sensitivity	Very high	Moderate, suitable for POC
Laboratory requirement	Yes	No
Home-use potential	Low	High

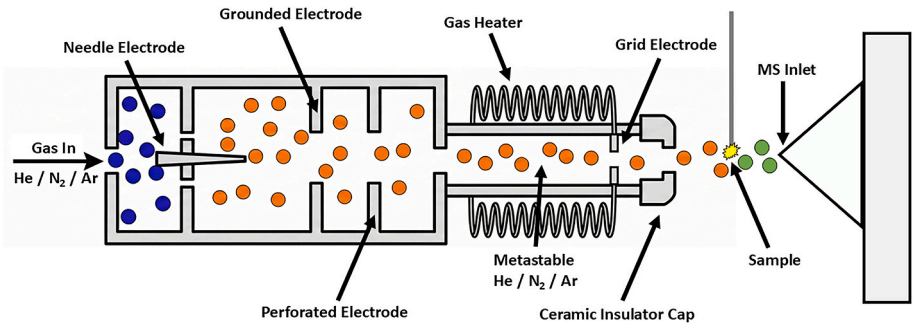

Fig. 6. Schematic of a DART source and the ionization process. The gas passes through section A, where discharge occurs generating metastable molecules, then through section B to remove unwanted ions. In section C, the gas is heated. Outside the heating tube, the metastable gas can interact with nitrogen, oxygen, and water in the air, including the analyte molecule M, thereby generating analyte ions for MS detection. Adapted from Hajslova et al. [76].

and minimized sample handling, are accelerating routine clinical laboratory procedures, toxicological screening, and forensic applications [80,81]. Unlike immunoassays, DART-MS offers high molecular specificity and sensitivity via MS/MS detection, thereby significantly reducing the risk of nonspecific or misleading results [77]. DART-MS is establishing itself as a powerful tool for rapid quantitative screening across several clinical domains. Table 4 summarizes some recent applications.

The evolution of DART-MS for clinical use has focused on addressing challenges related to reproducibility and analysis in complex matrices. For absolute quantitative analysis, the method relies heavily on the co-addition of stable-isotope-labeled internal standards (SIL-IS) [77], which helps normalize signal fluctuations arising from sample variability, matrix effects, or loading inconsistencies.

For ultra-trace analysis, DART-MS has been combined with rapid pre-concentration techniques [16]. Solid-Phase Microextraction (SPME) fibers are used to extract and concentrate analytes from complex matrices before the fiber is introduced into the DART source [82,83]. This combination substantially improves sensitivity and reduces matrix effects.

However, further miniaturization and automation would be required before DART-based workflows could support robust POC clinical use [12]. The combination of DART's ambient capability with portable, low-power mini-MS devices (such as the Mini 12 rectilinear ion trap) creates a system capable of performing molecular-level TDM, toxicological, and disease screening outside of the central laboratory, enabling rapid, robust, and reliable patient care [12,82].

4.3. *Probe Electrospray Ionization Mass Spectrometry (PESI-MS)*

PESI-MS was developed by Hiraoka and his team at the University of Yamanashi in collaboration with Shimadzu Corporation (Kyoto, Japan) in 2007. This is an ambient ionization-based method performed at the tip of a solid needle, initially coupled to a quadrupole mass spectrometer, with high applicability to studies of proteins and peptides that don't require complex sample preparation and provide faster results than conventional MS [85]. Although this combination has produced good results, it is currently preferable to combine PESI with equipment that enables MS/MS and high-resolution analysis [86]. Despite its unique needle-based sampling mechanism, PESI shares the defining characteristics of ambient ionization methods, contributing to rapid, low-preparation clinical analysis.

PESI-MS uses an ultrathin needle that moves along a vertical axis, with a submicrometer tip diameter (approximately 700 nm), functioning as both an ionization source and a samplingunit. The apparatus's principles demonstrate that the metallic needle moves below the axis toward the sample site, whether the sample is solid or liquid. Then, a few picolitres of the sample are attached to the needle surface. After the needle reaches the entrance of the mass spectrometer, a high direct current voltage is applied to the attached solution, inducing electrospray and producing charged droplets. Structurally, PESI-MS offers several advantages: it does not clog, exhibits high ionization efficiency, and enables rapid analysis of various biological samples, including those with high salt concentrations. It also allows researchers to observe real-time changes in biological systems without compromising their integrity by using minimally invasive procedures on live organisms [86–88].

To date, several studies have employed PESI-MS and PESI-MS/MS for real-time, *in vivo* monitoring and metabolomic analysis of rat and rabbit tissues [89–93] and for direct analysis of human biological samples [94–96]. The growing use of this technique is primarily due to its practicality for rapid analysis and the generation of ions in real time, without the need for extensive sample preparation.

Variations of PESI were subsequently developed, including dipping PESI (dPESI) [97], sheet-flow PESI (sfPESI) [98], and adjustable sfPESI (ad-sfPESI) [98], which are most commonly used for biological applications [99]. More recently, rapid-fire probe ESI methods, such as RaDPI-U, have enabled the quantification of multiple drugs and illicit compounds in urine within seconds, underscoring the operational suitability of AMS for emergency and forensic applications [100]. On the other hand, some publications analyze plant metabolomes using picolitre pressure-probe electrospray ionization MS (picoPPESI-MS), while others use tapping-mode scanning probe ESI (t-SPESI) for rat tissue studies [99,101].

Kiritani and collaborators developed a new diagnostic modality by combining dPESI-MS in positive-ion mode with machine learning to discriminate against the intraductal papillary mucinous neoplasm (IPMN) category of pancreatic tumors, using blood samples collected before surgery and pre-treated to recover only serum. Using dPESI-MS, it was possible to acquire around 860 peak intensities from more than 40 samples, with intensities above 500,000 AU. This protocol used rapid sample preparation (<10 min/sample) by combining high-performance machine-learning partial least squares (PLS) regression and support

Table 4
A summary of DART ionization in clinical screening in recent years.

Clinical Application	Analyte/Matrix	Key Findings	References
TDM	Anti-arrhythmic/ Serum	Rapid quantification with high accuracy	[77]
Toxicology/ Drug Screening	Opioids/Urine, Blood	Rapid screening/ confirmation in unprocessed samples	[77,78]
Metabolite Analysis	Cholesterol/Dried Human Serum	Fast quantification from dried spots	[82]
Infectious Disease Diagnostics	VOCs/Microbial Cultures	ML-based classification of bacterial vs fungal VOCs	[83]
Newborn Screening	L-Phenylalanine/ Dried Blood	Feasibility for rapid phenylketonuria (PKU) screening	[82,84]

vector machine (SVM) analysis with PESI-MS [102].

Using the model, it was possible to correctly distinguish between malignant and non-malignant groups, with an accuracy of 71.4% and a sensitivity of 66.7%. However, the authors highlight the most significant difficulty they encountered when developing this methodology: the sample size was insufficient to obtain a truly representative model, even after cross-validation. There were also samples with potential matrix interferents [102].

To facilitate early diagnosis of acute coronary syndrome (ACS), Tran et al. used 5 μL of serum from 32 patients and PESI-MS, in conjunction with chemometric and machine-learning approaches, to establish accurate correlations among potential disease groups. Using this ionization source enabled the replacement of liquid chromatography purification steps, reducing processing time. Initially, the PESI-MS results did not show direct correlations between the control group and the ACS group. Nevertheless, when using PLS, the receiver operating characteristic (ROC) curve and the area under the curve (AUC) indicated an efficiency of 95% by ROC, and sensitivity, precision, and specificity of 93.8% [103].

Other applications of PESI-MS developed between 2016 and 2025 for the early and rapid diagnosis of diseases such as cancer, for screening components, and for performing complete metabolomics of a sample without the need for complex sample preparation, using machine learning, are listed in Table 5.

Most of these studies have limitations in terms of sample size, the need for external and decentralized validation, and the need to combine other techniques for structural identification. Regarding POC, all studies demonstrate direct application in human or animal samples with simple collection procedures and integration with machine learning. However, few have applied PESI-MS to their diagnostic routine or have used it for *in situ* analysis.

4.4. Desorption Electrospray Ionization Mass Spectrometry (DESI-MS)

Among the ambient techniques, DESI-MS, introduced in 2004 by Cooks and coworkers [106], operates by directing a charged solvent spray onto the surface of a sample, enabling desorption and ionization of analytes under atmospheric conditions (Fig. 7) [106]. DESI's ability to directly analyze unmodified tissue surfaces enables real-time chemical imaging and classification, making it particularly suitable for point-of-care and surgical contexts [107,108]. Has been applied in oncology for rapid *ex vivo* molecular diagnostics, including surgical margin evaluation, tumor subtype classification, and lipid Imaging [107]. It enables direct differentiation between healthy and malignant tissues—notably in the brain [109], breast [110,111], and kidney by mapping lipid and metabolite variations from tissue surfaces. In point-of-care workflows, DESI-MS provides fast, label-free chemical fingerprints for tissue identification within minutes, aligning with the goals of real-time intraoperative mass spectrometry for clinical decision-making.

Table 5
Key studies from 2016 to 2025 investigated the application of PESI-MS in clinical diagnosis and drug monitoring.

Clinical Application	Analyte/Matrix	Key finds	References
Detection of Pancreatic Cancer	Serum Carbohydrate Antigen 19-9 (CA19-9)/ Human serum	High sensitivity and specificity (>80%);	[94]
Colorectal Liver Metastasis	Phospholipids/Surgical tissues (tumors)	The accuracy rate of 99.5%, Sample requirement <2.5 mg;	[104]
Forensic Approaches	Drugs Metabolites/ Urine, Blood, Saliva	Direct analysis, POC potential applicability	[105]
Metabolic Profile	Metabolites Distribution/Animal Tissue	Relevance for future analysis	[91]

Recent studies have further expanded the diagnostic potential of DESI-MSI. Kumar et al. presented a comprehensive review describing how DESI-MSI has become an essential tool for disease diagnosis by enabling spatially resolved metabolic and lipidomic profiling under ambient conditions, with direct relevance to intraoperative and rapid-diagnosis settings [107]. Advances discussed in this review highlight improvements in spatial resolution, ionization efficiency, and data analysis workflows that enhance DESI's translational applicability. DESI-MSI is emphasized as one of the most promising modalities for cancer research, particularly for its ability to rapidly classify tumors from metabolomic signatures without requiring label-based methods or elaborate sample preparation.

Beyond lipid and metabolite profiling, Garza et al. demonstrated that DESI-MSI can also map proteins within biological tissues, broadening its molecular coverage and reinforcing its diagnostic versatility [112]. This capability supports its potential use not only for tumor boundary discrimination but also for biomarker discovery and molecular phenotyping at the point-of are. Applications of DESI and related ambient MS techniques for intraoperative evaluation have also been highlighted in broader reviews. Vlocskó et al. described spectrometric approaches—including DESI-MSI—for real-time assessment of tumor resection margins in oral cancer, emphasizing their clinical feasibility and diagnostic accuracy [113]. Earlier work by Pirro et al. provided one of the first demonstrations of mass spectrometry for intraoperative assessment during glioma surgery. Results from 73 biopsies across 10 surgical resections demonstrate that DESI-MS can detect glioma and estimate the tumor cell percentage at surgical margins with 93% sensitivity and 83% specificity. Showing that DESI-like ambient ionization strategies could guide real-time surgical decision-making [114].

Although DESI-MS is most frequently associated with tissue profiling/imaging, quantitative drug monitoring in clinical matrices has been demonstrated, with reported performance that can be mapped to clinically relevant concentration scales. DESI–MS/MS has been used for quantitative analysis of small-molecule drugs in human plasma [115], and quantitative DESI-MS in dried blood spots has shown linearity from 10 to 10,000 ng mL^{-1} [116]. In addition, TLME–DESI-MS enabled rapid clean-up/preconcentration for crude biofluids and reported, for example, a methadone LOD of 4 ng mL^{-1} in urine [117].

These LOQ/linearity ranges are on the same ng mL^{-1}–μg mL^{-1} order as many therapeutic windows/decision limits used in TDM; for instance, methadone literature has reported trough plasma therapeutic threshold values on the order of ~200 ng mL^{-1} (R-methadone [118]), indicating that DESI-based quantitative workflows can reach sensitivities compatible with clinically meaningful thresholds (noting matrix-specific differences between plasma and urine) while still requiring drug-specific decision-limit alignment and standardized calibration/QC for routine deployment.

Despite its diagnostic utility, DESI-MS remains limited in sterile, *in vivo* clinical workflows due to its dependence on pressurized nebulizing gases, organic solvents, and high-voltage operation. These requirements complicate integration into surgical environments that demand strict sterility and compact instrumentation [119,120].

4.5. MasSpec pen: advances in ambient mass spectrometry for point-of-care tissue diagnostics

To overcome DESI-MS challenges, the MasSpec Pen [14] an automated, disposable, and biocompatible handheld device, was developed for direct, real-time, and nondestructive molecular analysis of tissues as a biocompatible alternative optimized for clinical environments. The device (see Fig. 8) employs a gentle liquid extraction mechanism in which a droplet of sterile water is deposited on the tissue surface, extracting small molecules, which are then aspirated and analyzed by mass spectrometry [14]. This technique avoids the need for high voltages, organic solvents, or sample destruction, making it ideally suited for intraoperative diagnostics and real-time clinical decision-making.

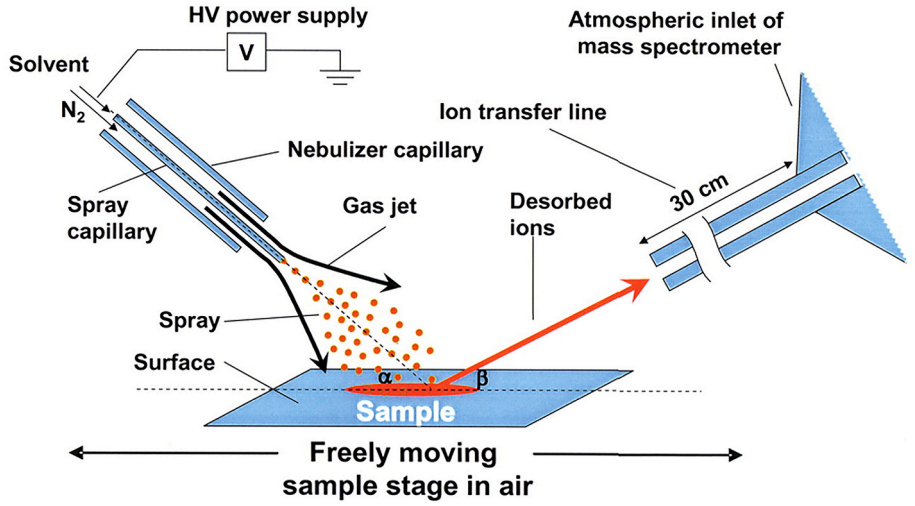

Fig. 7. Schematic of a typical DESI experiment. The sample solution was deposited onto a PTFE surface from solution and dried, and methanol-water (1:1, containing 1% acetic acid or 0.1% aqueous acetic acid) was sprayed at a flow rate of 3 to 15 μl/min under a high (4 kV) voltage. The nominal linear velocity of the nebulizing gas was set to 350 m/s. Reproduced from the work of Takáts et al. (2004). Copyright by AAAS [106].

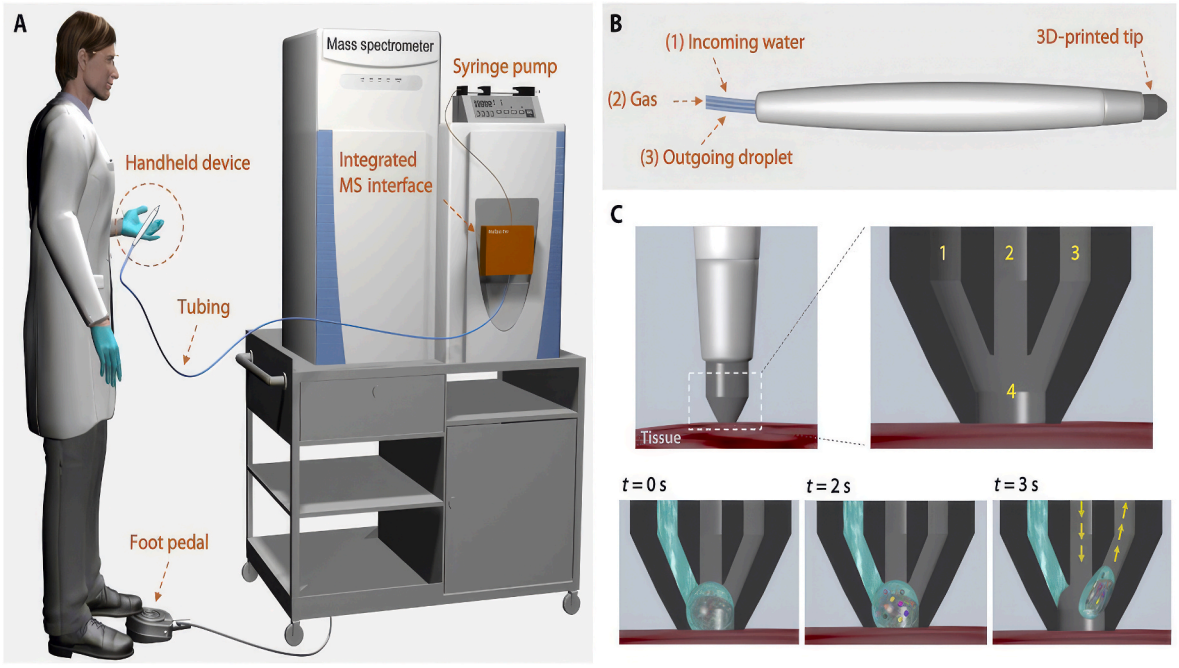

Fig. 8. Schematic representation of the MasSpec Pen system and operational steps. (**A**) The pen-sized handheld device is directly integrated into a laboratory-built MS interface through PTFE tubing. The integrated MS interface houses the pinch valves, microcontroller, and tubing to connect the system to the mass spectrometer inlet. The user triggers the system through a foot pedal. (**B**) The MasSpec Pen (handheld device) is designed with a PDMS tip and three PTFE conduits, which provide incoming water (1) and gas (2) to the tip and an outgoing conduit for the water droplet (3). (**C**) The tip contacts the tissue for analysis. The inset shows the three conduits (1-3) and the solvent reservoir (4) within the tip. When the system is triggered ($t = 0$ s) by using the foot pedal, the syringe pump delivers a controlled volume of water to the reservoir. The discrete water droplet interacts with the tissue to extract the molecules ($t = 2$ s). After 3 s of extraction, the vacuum and gas conduits are simultaneously opened (arrows) to transport the droplet from the MasSpec Pen to the mass spectrometer via the tubing system for molecular analysis, reproduced from the work of Zhang et al. (2017). Copyright by AAAS [14].

The MasSpec Pen methodology has undergone extensive validation in a variety of experimental and clinical settings. The standard setup includes a hand-held pen connected via Tygon tubing to a mass spectrometer, typically an Orbitrap or LTQ system. Each analytical cycle lasts approximately 10 s. The pen deploys a 10 μL droplet of sterile water on the tissue surface for 3 s before aspiration. This extraction enables metabolomic and lipidomic profiling without altering tissue morphology.

In the study by Zhang et al., the MasSpec Pen was tested on 253 human tissue samples from different cancer types, including breast, lung, thyroid, and ovarian tumors. Each sample was analyzed *ex vivo*, and the resulting mass spectra displayed abundant molecular information characteristic of each tissue type. The detected ions included diagnostic metabolites, fatty acids, glycerophospholipids, cardiolipins, and multicharged protein species. Notably, the spectral profiles obtained with the MasSpec Pen showed substantial similarity to those from DESI-MS imaging of serial sections (cosine similarity ~0.9), confirming analytical equivalence while maintaining higher operational simplicity

and biocompatibility [14].

Beyond analytical performance, the MasSpec Pen introduced significant engineering innovations aimed at clinical integration. Its disposable PDMS tip and fully automated solvent control system minimize contamination risks, while using pure water as the solvent ensures safety and sterility. The system's foot-pedal activation allows surgeons to trigger hands-free analysis, aligning the workflow with intraoperative demands. These design elements collectively position the MasSpec Pen as a practical bridge between analytical chemistry and surgical pathology.

Building upon this foundation, Keating et al. [121] expanded the clinical applicability of the MasSpec Pen by integrating it with the da Vinci Xi robotic surgical system, demonstrating the feasibility of *in vivo* molecular analysis during minimally invasive procedures. This work represented a transition from manual, *ex vivo* operation to robot-assisted real-time diagnostics, further solidifying the MasSpec Pen as a bridge between analytical chemistry and robotic surgery. The authors designed a laparoscopic version of the MasSpec Pen compatible with the robotic platform. The validation was performed *in vivo* using porcine models, where 53 analyses of liver and stomach tissues were performed under varying CO_2 pressures, a 26 μL water droplet was applied to the tissue for extraction, and spectra were acquired within 14 s using a Q Exactive Orbitrap. The results showed distinct metabolic and lipid profiles for each tissue type, high spectral reproducibility (cosine similarity $\geq$0.90), and classification accuracy up to 100% using the Lasso statistical method.

The study by Zhang et al. [122] marked the clinical translation of the MasSpec Pen for use in human surgical procedures. This investigation implemented a fully integrated clinical mass spectrometry system, installing an Orbitrap mass spectrometer directly in the operating room to enable real-time molecular analysis in 100 human surgical procedures, including thyroidectomies, parathyroidectomies, and breast and pancreatic surgeries. A sterilizable and disposable clinical version of the MasSpec Pen was employed, delivering a 20 μL droplet of sterile water for nondestructive molecular extraction. Each analytical cycle lasted approximately 15 s, allowing surgeons to obtain molecular information without disrupting the operative workflow.

A total of 715 tissue analyses, performed both *in vivo* and *ex vivo*, generated reproducible mass spectra enriched in metabolites, fatty acids, and lipids, consistent with molecular classes previously linked to potential human disease markers. The study demonstrated high spectral reproducibility, excellent biocompatibility, and the absence of any visible or microscopic tissue damage. No intraoperative complications were associated with the device, and full compliance with surgical sterility standards was maintained. The molecular profiles acquired enabled the differentiation of normal and pathological tissues across multiple organ systems, confirming the diagnostic potential of the technique [122].

In the study by King et al. [123], the MasSpec Pen was tested intraoperatively in 18 pancreatic cancer surgeries (Whipple procedures). A total of 157 *in vivo* and *ex vivo* analyses were performed on pancreatic ductal adenocarcinoma (PDAC), healthy pancreas, lymph nodes, and bile duct tissues. The mass spectra collected was processed using lasso-based machine learning models. The classifier achieved 94.7% sensitivity and 100% specificity for distinguishing PDAC from non-cancerous tissue. Importantly, sampling was performed without delaying the surgical workflow, and histopathological integrity was preserved in all tissues.

Garza et al. [124] conducted a clinical study involving 100 patients undergoing breast surgeries. A total of 715 tissue analyses were performed, covering 10 tissue types, including adipose, fibrous, carcinoma, and lymph node samples. The spectra were used to train classification models using Lasso, SVM, and Random Forest algorithms. The best-performing model demonstrated an overall accuracy of 95.6% in distinguishing normal from malignant tissues. Additionally, the device's ability to assess tumor margins intraoperatively was validated by comparing results with frozen-section and final pathology.

In continuation of previous technological advancements by Zhang et al. [14,122] and Keating et al. [121], Wolfe et al. [120] presented a next-generation evolution of the MasSpec Pen designed to address the technical and operational challenges identified in earlier studies. The upgraded system incorporated a heated external vaporization chamber with dual heated transfer lines, significantly enhancing ion transmission, spectral stability, and signal-to-noise ratios, while reducing contamination and extending cleaning intervals from approximately 10 to over 50 surgeries. The platform demonstrated cross-instrument compatibility with both Orbitrap and Q-TOF systems, preserving analytical consistency across setups. A touchscreen graphical user interface (GUI) enabled real-time control of extraction parameters, improving usability in surgical settings. Furthermore, 3D-printed, sterilizable probes were developed for laparoscopic and bronchoscopic applications, allowing minimally invasive tissue analysis without compromising data quality. Long-term operation confirmed the system's durability and suitability for continuous clinical use.

4.6. Rapid evaporative ionization mass spectrometry (REIMS)

Rapid evaporative ionization mass spectrometry (REIMS) enables near-real-time molecular fingerprinting by analyzing aerosols generated during thermal disruption of biological materials, typically during electrosurgical dissection, minimizing sample preparation and avoiding chromatographic separation [125,126]. In practice, tissue is rapidly heated, producing a smoke/aerosol plume that contains lipids and other small molecules, which is aspirated through a transfer line into the mass spectrometer [125].

Early demonstrations of REIMS showed that species-specific lipid fingerprints can be obtained directly from microorganisms and bacterial cultures without extensive preparation, highlighting the potential of the technique for rapid biological identification [127,128]. Subsequent work further demonstrated that REIMS can accurately identify clinically relevant fungal pathogens such as Candida species with classification accuracies approaching 100%, illustrating its potential for rapid microbial diagnostics [129].

For clinical applications, REIMS is commonly integrated with surgical instruments that generate the aerosol required for ion formation during tissue dissection. Because the method directly probes lipidomic profiles associated with cellular metabolism, REIMS has demonstrated strong capabilities for discriminating between pathological and healthy tissues. For example, lipidomic profiling of glioblastoma tissue demonstrated that REIMS could detect tumor-specific lipid biomarkers and distinguish malignant brain tissue from normal tissue with accuracy exceeding 94%, highlighting its potential for intraoperative tumor identification [130].

A central translational configuration is the “intelligent knife” (iKnife), in which REIMS is coupled with electrosurgery to provide molecular feedback during cutting, enabling discrimination between malignant and healthy tissue without interrupting the workflow. A foundational clinical validation of this concept was reported by Balog and colleagues, who built an *ex vivo* spectral database from tissues of 302 patients and then deployed REIMS intraoperatively during 81 surgical resections, reporting concordance between intraoperative tissue identification and postoperative histology in all intraoperative cases [131].

Subsequent clinical studies have reported strong performance for intraoperative classification tasks in specific indications. For example, REIMS-based profiling has been used to differentiate tissue states in surgical contexts with reported sensitivities/specificities exceeding ~90% when compared with histopathology in gynecological surgery [132]. Similarly, metabolic profiling of surgical aerosols during oral cavity cancer surgery demonstrated discrimination between tumor and normal tissue with reported accuracy approaching ~96.8%, including the ability to detect relatively small proportions of tumor cells [133].

Building on these demonstrations, REIMS–iKnife has also been

evaluated as an intraoperative decision-support tool in non-oncologic surgical contexts. Davies and colleagues (2022) investigated its use in acute aortic dissection surgery and showed that REIMS-derived molecular fingerprints, interpreted using multivariate statistical models, could differentiate aortic wall structural patterns associated with disease-related tissue remodeling, providing rapid intraoperative information to support surgical decision-making [134]. Consistent findings were reported in an earlier study by the same group, in which REIMS differentiated aneurysmal from non-aneurysmal aortic tissue with 88.7% classification accuracy and 85.1% precision [135]. Together, these studies extend the scope of REIMS beyond oncology and highlight the potential of iKnife as a diagnostic support tool in cardiovascular surgery.

Recent developments aim to extend REIMS-like fingerprinting beyond electrosurgical smoke by using alternative energy sources and sampling interfaces. Laser-assisted REIMS (LA-REIMS) has been applied to rapid metabolic fingerprinting of complex clinical matrices, including fecal samples for classification tasks such as type 2 diabetes, with reported analysis times below ~10 s per sample [136].

Collectively, these developments indicate that REIMS is transitioning from a primarily intraoperative analytical technology toward a broader clinical diagnostic platform capable of supporting rapid decision-making in surgery, microbiology, metabolomics and personalized medicine.

4.7. Comparative clinical readiness of ambient mass spectrometry

AMS and PMS technologies show considerable potential for rapid clinical decision support, but their practical relevance depends strongly on the intended workflow and clinical setting. To avoid treating these platforms as a single uniform POC category, they can be more clearly considered in three main groups: (i) near-patient/POC targeted testing, (ii) intraoperative decision support, and (iii) *ex vivo*/near-clinical-laboratory pathology support workflows. In near-patient/POC targeted testing, PSI-MS and related spray-based approaches appear most relevant for narrow applications such as therapeutic drug monitoring and other targeted assays [12,54,55,74]. In intraoperative decision support, technologies such as the MasSpec Pen and REIMS (iKnife) are specifically designed to provide real-time molecular information during surgical procedures, particularly for applications such as tumor margin assessment and intraoperative tissue classification [121,122,131,132]. In *ex vivo*/near-clinical-laboratory pathology support workflows, DESI-MS has been used extensively for tissue characterization in pathology-adjacent or post-surgical settings, and although it has been explored as an intraoperative adjunct, much of its current evidence base remains centered on *ex vivo* tissue analysis [109,114,115]. Overall, these distinctions help align the interpretation of AMS and PMS technologies with the current strength of evidence, showing that some intraoperative and near-patient targeted workflows appear closer to clinical translation in selected contexts, whereas *ex vivo* techniques such as DESI-MS remain more strongly positioned as pathology-support tools than as decentralized POC platforms. Accordingly, Table 6 summarizes these techniques according to their most realistic clinical setting and the strength of the supporting evidence currently available.

To provide a clearer assessment of the technologies presented in Table 6, the levels of validation are categorized according to the type and scope of supporting evidence. Techniques classified as "High" are those supported by multicenter prospective studies or rigorous prospective workflow validations in real clinical environments [121–123]. "Moderate" techniques are supported by prospective in-workflow studies or single-center clinical evaluations, showing promising results but still requiring broader validation [54,55,74]. "Low" classification applies to techniques supported mainly by analytical feasibility studies, retrospective clinical-sample analyses, or *ex vivo* demonstrations [109,114,115]. These categories are intended to reflect the relative maturity of the available evidence rather than regulatory approval status or routine clinical adoption [137].

Based on these criteria, intraoperative platforms engineered around sterility and surgical logistics (MasSpec Pen-type workflows and REIMS/iKnife-type workflows) are generally the closest to clinical integration in their best-fit setting, because they have been deployed in real surgical environments and can deliver actionable information within procedural time constraints, where qualitative or semi-quantitative molecular signatures can directly support intraoperative decisions (e.g., tissue classification and margin assessment) [12,71,122,131].

In contrast, biofluid-focused spray approaches (PSI and related paper-based sprays coupled to portable MS) are closer to routine use for

Table 6
Comparative summary of ambient/near-ambient MS sources, reporting primary sample types, typical analysis time, and representative LOD/LOQ (or linear range), clinical validation context (analytical/*ex vivo* vs clinical specimen's vs prospective in-workflow evidence). Where applicable, values correspond to those explicitly reported in the cited studies. For workflows primarily used for tissue classification/pattern recognition (e.g., intraoperative or *ex vivo* tissue profiling); in such cases, LOD/LOQ is indicated as not applicable (N/A).

Technique	Primary Clinical Domain	Sample type	Typical time scale	LOQ/LOD	Clinical workflow/ application	Translational Readiness	Validation Level	Reference
MasSpec Pen	Intraoperative tissue classification/margin assessment	Tissue; operating room (*in vivo* and *ex vivo*)	~10–15 s per readout (cycle)	N/A	Real-time surgical decision support	High	Prospective in-workflow	[121–123]
REIMS (iKnife)	Intraoperative molecular fingerprinting (oncology + other surgery contexts)	Endometrial biopsy tissue	~1–2 s per spectrum	N/A	Rapid intraoperative	High	Clinical validation	[131,132, 134,135]
PSI-MS	Point-of-care and portable MS diagnostics	Human serum, Human blood, Human urine	~2–4 min	LOD <10 μg.L-1; LOQ <30 μg.L-1	TDM	Moderate	Analytical validation	[54,55,74]
PESI-MS	ML-assisted diagnosis/ classification, animal *in vivo* demonstrations noted	Human serum; other biofluids	Seconds–minutes (setup-dependent)	Often not reported per-analyte (fingerprinting focus)	Rapid screening/ classification	Moderate	Clinical validation	[94,102, 103]
DART-MS	Forensic toxicology, TDM, POC pathogen identification.	Urine/serum/ DBS	Seconds to a few minutes	LOD150-250 ng/ mL; LOQ 10-50 50 ng/mL	Rapid clinical screening	Moderate	Analytical validation	[77,79]
DESI- MS	*Ex vivo tissue* characterization; intraoperative margin assessment; imaging tissue profiling	Tissue; near-clinical pathology/OR-adjunct (mostly *ex vivo*)	Minutes (profiling)	LOD ppt to low ppb; LOQ 0.2–40 ng/mL	Tissue discrimination	Low	Clinical Validation	[109,114, 115]

targeted monitoring and rapid screening, but their scalability depends strongly on controlling matrix effects, reducing operator-dependent variability, and implementing standardized quantitative workflows (internal standardization, calibration, and acceptance criteria) across sites [12,64,71]. DART [77,79] and PESI [102,103] enable rapid, chromatography-free measurements; however, much of the published evidence remains single-center and feasibility-oriented, and multicenter clinical validation for routine diagnostic deployment is still limited. DESI, particularly in tissue applications (including DESI imaging), provides rich molecular information and strong evidence for *ex vivo* tissue classification and intraoperative adjunct use in selected settings, but acquisition time, sterility constraints, and sample-handling requirements often position it closer to near-clinical pathology support than to decentralized "true POC" testing [102,107,108].

5. New methods for ambient ionization for mass spectrometry

Recent years have seen the development of numerous ambient ionization strategies aimed at enabling rapid molecular analysis of biological samples with minimal preparation [13,138,139]. While these technologies expand the analytical capabilities of mass spectrometry, only a limited number currently demonstrate clear potential for clinical or POC applications, largely because translation requires robust workflow integration, standardized QC, and clinical validation beyond feasibility studies [12,71,137]. Consequently, rather than attempting to cover the full diversity of emerging ionization approaches, it is important to highlight those with demonstrated translational relevance while briefly acknowledging other developments that remain largely exploratory.

In this context, PIRL-MS (picosecond infrared laser mass spectrometry) is a laser-based ambient/near-ambient ionization approach for rapid tissue analysis that uses ultrafast mid-infrared pulses to excite endogenous water, enabling efficient desorption with limited thermal damage [140,141]. Proof-of-concept studies have demonstrated rapid tissue classification (e.g., melanoma vs squamous cell carcinoma vs normal skin) on ~10-s time scales, supporting its potential as an intraoperative or near-clinical decision-support tool, although broader clinical validation is still required [142].

Another technology with translational potential is SpiderMass, a water-assisted laser desorption ionization system designed for minimally invasive real-time tissue analysis [143]. In this approach, a tunable infrared laser generates a micro-ablation plume from biological tissues, which is transferred to a mass spectrometer for molecular analysis [144]. For example, the technique has been used to differentiate tumor and non-tumor regions in oral tongue squamous cell carcinoma based on lipidomic signatures obtained directly from tissue samples [145]. More recently, integration of SpiderMass data with machine learning approaches enabled molecular classification of glioblastoma with diagnostic accuracies exceeding 90%, illustrating the potential of this technology for real-time surgical decision support [146].

Atmospheric solids analysis probe mass spectrometry (ASAP-MS) represents another ambient ionization strategy with growing interest for rapid analysis of clinical samples. In ASAP-MS, analytes are desorbed from a probe by a heated nitrogen stream and ionized under atmospheric pressure conditions, enabling rapid molecular fingerprinting of complex biological matrices with minimal sample preparation [147,148].

Recent studies have explored the application of ASAP-MS for metabolite profiling of human plasma and other clinical specimens, demonstrating that the technique can generate reproducible metabolic fingerprints that may support disease classification when combined with multivariate analysis or machine learning models [149]. In addition, efforts have focused on improving experimental protocols and data processing strategies to generate robust clinical datasets and mitigate sources of variability inherent to rapid ambient measurements [150]. Although these studies highlight the potential of ASAP-MS for rapid diagnostic screening and metabolomic fingerprinting, the approach remains largely exploratory and requires further validation in larger clinical cohorts before routine clinical implementation.

Despite rapid innovation, routine clinical MS workflows remain dominated by established platforms, particularly MALDI-based microbial identification and LC-MS-based targeted quantification for drug monitoring and metabolite analysis, as cited in Section 2.1. Nevertheless, technologies designed for direct tissue decision support (e.g., MasSpec Pen, REMS-iknife) illustrate growing interest in integrating MS into real-time clinical workflows. Continued advances in ambient ionization, instrumentation miniaturization, automation, and machine learning may enable emerging platforms to complement conventional MALDI and LC–MS workflows in future clinical and POC diagnostics. Fig. 9 summarizes the key technological, computational, and clinical directions shaping the future of point-of-care mass spectrometry.

6. Regulation

With the growing transition of ambient and miniaturized mass spectrometry from experimental innovation to real-world clinical applications, regulatory oversight becomes essential to bridge technological potential with routine diagnostic practice. The regulatory environment for clinical MS-based assays varies widely across countries, posing challenges for new techniques such as POC tests using AMS [12]. In the United States, the Food and Drug Administration (FDA) oversees in vitro diagnostic devices (IVD). It establishes specific guidelines for laboratory-developed tests (LDTs). At the same time, the Centers for Medicare & Medicaid Services (CMS) enforces standards under the Clinical Laboratory Improvement Amendments (CLIA) program to ensure laboratory quality [137]. While broad requirements for in-house-developed methods exist elsewhere, specific, legally binding rules for the operation, validation, and quantification of MS-based assays are largely absent, unlike in food monitoring or pharmaceutical quality control [137]. These gaps hinder clinical translation and standardization of AMS-based POC technologies.

A systematic review highlights best practices for AMS in POC settings, including the use of matrix-matched calibrators, isotopically labeled internal standards, and robust calibration curves with multiple points or replicates [151]. In the European Union, Regulation (EU) 2017/746 for in vitro diagnostic devices (IVDR) and quality standards such as CLSI 62A and ISO 15189 guide clinical MS procedures [47,152]. Nonetheless, gaps persist for LDTs, limiting standardization and clinical adoption.

The FDA classifies IVD devices into three risk-based categories: Class I devices posing the lowest risk (eg. control materials), Class II devices represent moderate risk and (eg. disease monitoring systems and tests assisting clinical diagnosis) and Class III devices correspond to the highest-risk and most complex systems, such as tests used in critical diagnostic decisions, including cancer detection [153]. Many portable mass spectrometry applications exhibit moderate to high complexity, requiring appropriate laboratory certification, technical supervision, and trained operators [154].

From a regulatory standpoint, the FDA establishes two main pathways for IVDs: Premarket Notification (510(k)), typically associated with Class II devices and based on demonstrating substantial equivalence to a previously authorized device, and Premarket Approval (PMA), required for Class III devices, which involves rigorous evaluation of clinical, analytical, and manufacturing data before commercialization [153–156]. For portable MS intended for therapeutic drug monitoring or direct clinical diagnosis, the applicable pathway will depend on intended use and risk classification; in the absence of suitable predicate device classification or PMA may be required, potentially increasing the evidence burden and extending timelines relative to 510(k) routes.

Despite their strong analytical potential, the broader implementation of AMS-based techniques still faces significant challenges, particularly related to methodological standardization, analytical validation, high

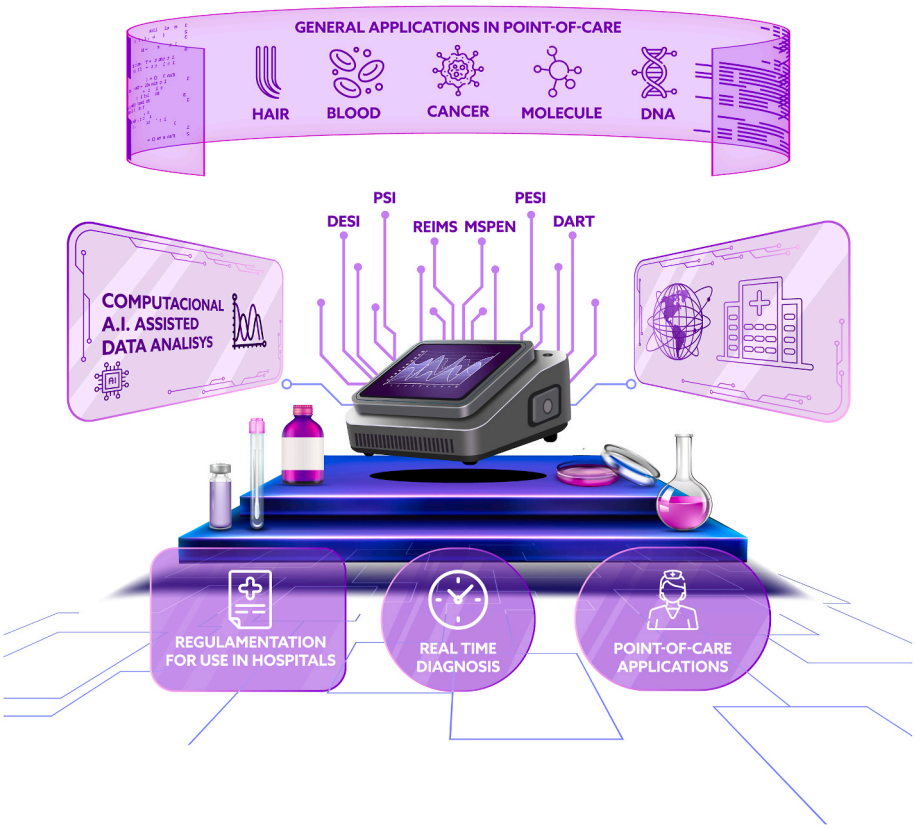

Fig. 9. Future perspectives of point-of-care mass spe**ctrometry.** Conceptual roadmap illustrating the convergence of ambient ionization techniques, portable and miniaturized mass spectrometers, automation, and regulatory harmonization toward fully integrated, decentralized, and clinically deployable point-of-care diagnostic platforms. Some graphical elements were adapted from Freepik (https://www.freepik.com/).

costs, and compliance with regulatory requirements that are not yet fully established [157]. These techniques may exhibit low reproducibility, with significant fluctuations in signal intensities caused by factors such as the nature of the sample, environmental conditions, instrumental parameters, and operator training [157].Therefore, these analyses require highly trained professionals capable of operating advanced instrumentation, interpreting complex mass spectral data, and ensuring appropriate quality control procedures, thereby guaranteeing reliable results and accurate data interpretation [157]. Matrix effects are a limitation for both AMS and LC–MS/MS, often leading to ion suppression and reduced quantitative accuracy. These effects can be minimized using internal standards (IS), which help improve the precision and accuracy of the analyses [158,159].

In the context of tandem LC–MS/MS, which benefits from more established protocols, including validation procedures, quality control measures, and implemented regulatory guidelines, these variations can be better understood and minimized to ensure the quality and reliability of results in clinical diagnostics. In contrast, AMS-based methodologies still lack specific regulatory guidelines for validation in clinical environments [160,161]. Essential analytical parameters, including repeatability, robustness, limits of detection, and matrix effects, may vary considerably depending on the technique employed, the sample type, and the experimental conditions [160,161].

As discussed in the study, research on new POC approaches using AMS remains focused on developing methodologies, instrumentation, and internal validations. Therefore, relying on the regulatory frameworks governing conventional mass spectrometry tests may serve as an initial alternative, though upcoming regulatory changes can be challenging. These regulatory and quality-system expectations directly motivate explicit control of operational failure modes (Section 6.1) and human-factors/training requirements (Section 6.2).

To make these regulatory considerations more practical, two representative translational scenarios can be considered. A lower-risk example is a PSI-based portable assay for a small therapeutic drug monitoring panel in whole blood or dried blood spots. Building on the general analytical and quality requirements outlined above, progression toward clinical use would depend on demonstrating reproducible agreement with an established reference method in the intended near-patient workflow, together with appropriate quality controls and supervised implementation. Because the clinical claim is narrow, quantitative, and closer to established targeted testing, this type of application is more plausibly aligned with existing targeted IVD pathways under CLIA/FDA or analogous IVDR-based frameworks than with broad untargeted diagnostic claims.

A contrasting higher-risk example is an intraoperative tissue-classification workflow based on devices such as the MasSpec Pen or REIMS. In this setting, translation to clinical use depends not only on analytical performance, but also on issues that are more specific to procedural decision support, including sterility, device reproducibility, software locking and classifier versioning, workflow integration in surgery, and prospective evidence that the output can safely support intraoperative decisions. Because these systems may directly influence immediate clinical actions, the evidentiary and regulatory burden is likely to be greater than for narrow targeted assays. Together, these examples show that realistic regulatory pathways for AMS depend strongly on device type, intended use, clinical risk, and whether the output is a targeted quantitative result or a classification-based decision aid.

6.1. Operational failure modes and mitigation strategies in AMS-POC workflows

Across AMS-POC workflows, frequently reported failure modes include (1) matrix effects/ion suppression or enhancement (salts, phospholipids, proteins, and co-extractives), (2) carryover and source/sampling-path contamination (memory effects on substrates, inlets, and ion optics when repeatedly exposed to complex matrices), (3) signal drift (environmental humidity/temperature, gradual source contamination, and calibration shifts), and (4) operator/workflow variability (sample deposition, contact time/geometry for probe/tissue, and swab handling). These issues and their impact on quantitative robustness are widely discussed in ambient/miniature MS clinical translation reviews [65,71] and are exemplified in direct analysis of complex matrices [64].

Practical mitigations include (i) IS strategy using stable-isotope labeled IS (or close structural analogs) added as early as possible and at fixed levels (including pre-loaded substrates) to correct matrix and sampling variance; (ii) standardized "minimalist" sample-prep where required (e.g., dilution, protein precipitation, simple extraction/cleanup) to reduce ion suppression and fouling; and (iii) blank/QC injections and defined cleaning intervals with short-cycle acceptance rules to detect drift and control carryover. When additional selectivity is needed without chromatography, Field Asymmetric Ion Mobility Spectrometry (FAIMS) or ion-mobility (IM) integration can act as an orthogonal gas-phase filter to reduce chemical noise and isobaric interferences, improving robustness for complex matrices [162–164].

6.2. Human factors and training considerations for non-specialist users

For AMS-POC to be reliable outside specialist MS laboratories, workflows must be simplified and engineered for consistent execution by non-specialist operators [12,15,16]. Key human-factor risks include inconsistent sampling (volume, contact time/geometry, swab pressure), cross-contamination/carryover from handling and inadequate cleaning, and misinterpretation of outputs when results are probabilistic (e.g., ML-based classification) or when QC acceptance criteria are unclear. Practical implementation therefore requires standardized consumables (ideally single-use interfaces), step-by-step SOPs with prompts/checklists for critical steps, competency-based training with periodic re-qualification, and clear escalation rules for invalid QC, borderline results, or low-confidence classifications [15,16]. These needs align with best-practice recommendations for AMS in POC settings (e.g., matrix-matched calibration, isotopically labeled internal standards, and robust calibration/QC design) [151] and with quality-system expectations under ISO 15189 and related clinical MS guidance [137,161].

Minimum training/competency **elements** should include: **(i)** sampling consistency and sample identification; **(ii)** IS handling and timing (including pre-loaded substrates when applicable); **(iii)** contamination control and cleaning/blank strategy; **(iv)** QC rules and actions upon QC failure; **(v)** basic instrument readiness checks (drift/calibration verification); and **(vi)** interpretation rules, including decision thresholds and when confirmatory testing (e.g., LC–MS/MS) is required [15,137].

7. Conclusion and perspective

Across all sections, a consistent theme emerges: the convergence of ambient ionization, miniaturized instrumentation, and computational artificial intelligence (AI)-assisted data analysis interpretation is redefining the role of mass spectrometry in modern healthcare. Together, these developments are expanding the potential for MS to be used in real-time diagnostic tools for targeted molecular screening and selected point-of-care applications. Advances in ambient ionization methods—including DESI, DART, PSI, MasSpec Pen and REIMS-iknife—are enabling direct, non-destructive analysis of tissues, biofluids, and swabbed surfaces under atmospheric conditions, reducing sample preparation time and providing chemical information in real-time, which could be compatible with fast clinical decision-making in selected contexts [47].

In parallel, the emergence of miniaturized and portable MS platforms that integrate compact ion optics, efficient vacuum systems, and robust ambient sampling interfaces has improved the practicality of selected decentralized MS workflows while maintaining mobility and reduced operational complexity. Nevertheless, these systems should be viewed as complementary tools, rather than replacements for full-scale benchtop platforms, particularly when high resolution, high mass accuracy, or broad untargeted molecular coverage is required. These systems have shown promising feasibility in selected bedside testing, intraoperative tissue assessment, and decentralized toxicological screening workflows, but most applications still require broader clinical validation, standardization, and regulatory assessment before routine implementation [47].

Equally transformative is the incorporation of AI and machine learning, which enable fast, automated interpretation of complex spectra. Modern algorithms enhance diagnostic accuracy, reduce operator-dependent variability, and allow instantaneous classification of disease biomarkers, tissue types, and chemical contaminants. Studies highlight that AI-enhanced miniature MS systems can achieve rapid, high-accuracy molecular identification, supporting the development of fully automated clinical screening pipelines [152].

These technological advances indicate that MS is undergoing clinical democratization, transitioning from centralized analytical laboratories to decentralized, patient-centered environments. The next phase of progress will require multicenter clinical validation, regulatory harmonization, and integration with electronic health systems to ensure robustness and interoperability. Current evidence supports the view that the combination of robust engineering, ML-based data interpretation, and increased portability will position MS as a cornerstone of rapid, high-accuracy molecular diagnostics in modern medicine [49,123,137,152].

This trajectory suggests that MS is evolving towards increased operational simplicity, real-time capabilities, and potential clinical usability. The maturation of ambient ionization methods and the expansion of portable, automation-ready platforms are expanding the potential scope of molecular diagnostics, enabling applications ranging from intraoperative tissue characterization to therapeutic drug monitoring without chromatographic separation. Their ability to rapidly and reliably analyze complex biological matrices strengthens the connection between analytical chemistry, machine learning, and personalized medicine, though operational challenges remain. Despite ongoing challenges—particularly regarding standardization, regulatory approval, and large-scale validation—the current state of the field indicates that ambient and miniaturized MS systems have the potential to play a significant role supporting decentralized, rapid, and accurate clinical decision-making.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author(s) used OpenAI's ChatGPT-5 for proofreading and grammatical enhancements. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Júlio César de Oliveira Ribeiro: Conceptualization, Data curation, Formal analysis, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jean Carlos Pereira Sousa:** Conceptualization, Data curation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jéssica Gardone Vitório:** Conceptualization, Data curation, Formal

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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