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# Advanced Analytical Chemistry: Emerging Technologies for Biomarker Analysis, Drug Quantification, and Clinical Diagnostics

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## Abstract:

**Background:** Clinical diagnostics and pharmaceutical bioanalysis are undergoing rapid technological transformation, driven by advances in mass spectrometry, molecular and CRISPR-based diagnostic platforms, liquid biopsy analytes, and artificial intelligence (AI)-assisted data interpretation. These emerging technologies promise faster, more sensitive, and more accessible biomarker analysis and drug quantification, but exhibit markedly different degrees of analytical validation and clinical translation. **Objective:** To synthesize recent advances in mass spectrometry-based bioanalysis, CRISPR-based molecular diagnostics, liquid biopsy technologies, and AI-assisted analytical interpretation, with explicit, platform-specific grading of clinical validation and translational status, and to identify priority directions for continued development. **Methods:** A structured, non-systematic literature search of PubMed, Scopus, Web of Science, and Google Scholar (inception–June 2026) was conducted using combinations of technology-, application-, and validation-specific search terms, detailed in Section 2. **Results:** Liquid chromatography-tandem mass spectrometry (LC-MS/MS) remains the most clinically mature and routinely validated platform reviewed, underpinning therapeutic drug monitoring and targeted biomarker quantification with detection limits reaching the low picogram-per-milliliter range. Circulating tumor DNA (ctDNA)-based liquid biopsy has achieved clinical use for selected companion-diagnostic and treatment-monitoring indications in specific cancers, supported by next-generation sequencing and droplet digital PCR. CRISPR-based point-of-care diagnostic platforms (leveraging Cas12/Cas13 effector proteins) show strong analytical performance in a rapidly growing preclinical and early-clinical literature, but a 2024 systematic review of 44 relevant studies identified no CRISPR-based point-of-care diagnostic with documented widespread clinical deployment, though select platforms have progressed into clinical trials. Artificial intelligence is increasingly embedded across all platforms reviewed, from mass spectral interpretation to multimodal liquid biopsy data fusion, but itself requires platform-specific analytical and clinical validation before diagnostic deployment. **Conclusion:** Analytical chemistry continues to deliver transformative tools for biomarker analysis, drug quantification, and clinical diagnostics, with translational maturity varying markedly by platform. Continued progress will depend on rigorous, platform-specific validation; expanded clinical-stage evaluation of CRISPR-based and multimodal liquid biopsy platforms; and careful, appropriately validated integration of AI/ML tools rather than uncritical adoption on the basis of analytical promise alone.

**Keywords:** LC-MS/MS; biomarker discovery; therapeutic drug monitoring; CRISPR diagnostics; liquid biopsy; circulating tumor DNA; point-of-care testing; artificial intelligence

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# 1. Introduction

Clinical diagnostics and pharmaceutical bioanalysis sit at the intersection of analytical chemistry and patient care, translating molecular-level measurement of drugs, metabolites, proteins, nucleic acids, and cells into information that guides diagnosis, treatment selection, and therapeutic monitoring. The scope and sophistication of this measurement capability have expanded substantially over the past decade, driven by parallel advances across several previously distinct analytical domains: mass spectrometry, which has progressed from a primarily research-focused technique to a validated clinical-laboratory tool capable of quantifying drugs and endogenous biomarkers at trace concentrations in complex biological matrices[1]; molecular diagnostics, in which the discovery and adaptation of CRISPR-Cas effector proteins as programmable, highly specific biosensing elements has opened a new category of rapid, potentially point-of-care nucleic acid detection [9,14]; liquid biopsy, in which circulating tumor-derived analytes (DNA, cells, extracellular vesicles) in blood and other body fluids increasingly substitute for, or complement, invasive tissue biopsy in oncology [18,19]; and artificial intelligence and machine learning, now embedded across each of these domains to assist with signal deconvolution, image interpretation, and multimodal data integration [5,10].

These technologies do not exist in isolation: a contemporary clinical diagnostic or pharmaceutical bioanalytical workflow increasingly draws on several of them in combination for example, mass-spectrometry-based proteomic biomarker discovery informing subsequent immunoassay or CRISPR-based biosensor development, or AI-assisted integration of multiple liquid-biopsy analytes (circulating tumor DNA, circulating tumor cells, and exosomal RNA) into a single diagnostic readout [21]. At the same time, these technologies differ markedly in their current stage of clinical validation and regulatory translation: some (LC-MS/MS-based therapeutic drug monitoring, ctDNA-based companion diagnostics for specific approved targeted therapies) are established, routinely used clinical tools, while others (most CRISPR-based point-of-care platforms, many multimodal liquid biopsy panels) remain predominantly in preclinical or early-clinical development despite substantial mechanistic sophistication and a rapidly growing publication base [8,21].

## 1.1 Scope and Rationale of This Review

This review synthesizes recent advances across mass spectrometry-based bioanalysis, CRISPR-based molecular diagnostics, and liquid biopsy technologies, with dedicated attention to the growing role of AI/ML across these domains, structured explicitly to distinguish established clinical practice from promising but still-developing technology. Consistent with the evidence-grading approach applied in our companion reviews of pharmacological and inorganic-chemistry topics, this review applies an explicit, platform-specific grading of clinical validation and translational status (Section 7) to each major technology discussed, intended to give the reader an honest, immediately usable sense of how close a given analytical platform is to routine clinical deployment, rather than treating technological sophistication or publication volume as a proxy for clinical readiness.

## 2. Literature Search Strategy

### 2.1 Databases and Search Terms

PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched from database inception through June 2026, with priority given to reviews, systematic reviews, and primary clinical-validation studies published within the past three years to ensure currency, particularly for the CRISPR-diagnostics and AI-integration discussions in Sections 4 and 6. Search strings combined three term clusters: (i) technology terms "LC-MS/MS", "mass spectrometry", "CRISPR-Cas", "Cas12", "Cas13", "isothermal amplification", "digital PCR", "droplet digital PCR", "next-generation sequencing", "microfluidics", "biosensor"; (ii) application terms "biomarker discovery", "drug quantification", "therapeutic drug monitoring", "liquid biopsy", "circulating tumor DNA", "point-of-care diagnostics", "companion diagnostic"; and (iii) validation terms "clinical validation", "analytical performance", "sensitivity", "specificity", "regulatory approval", "artificial intelligence", "machine learning".

### 2.2 Inclusion and Exclusion Criteria

- Included: peer-reviewed original research and review articles, systematic reviews, and relevant clinical-trial registry records, in English, describing the development, analytical validation, or clinical application of a defined analytical technology relevant to biomarker analysis, drug quantification, or clinical diagnostics.
- Excluded: non-peer-reviewed sources, purely instrumental/engineering literature without a clear biomedical or clinical-diagnostic application, and articles not available in English.

### 2.3 Translational-Validation Grading Approach

Consistent with the grading approach applied in our companion reviews, this review classifies each major technology discussed into one of three translational-validation categories, applied explicitly in Section 7: Established Clinical Use (analytically and clinically validated, in routine clinical or regulated laboratory practice), Clinical-Stage/Emerging Clinical Use (validated for specific, defined clinical applications or under active clinical evaluation, with use more limited or specialized than fully established platforms), and Preclinical/Early Research (supported by analytical proof-of-concept and/or preclinical data without documented widespread clinical deployment for the specific application discussed).

## 3. Mass Spectrometry-Based Bioanalysis and Biomarker Discovery

### 3.1 LC-MS/MS Fundamentals and Clinical Bioanalytical Performance

Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) has become the reference-standard analytical platform for quantifying drugs, drug metabolites, and endogenous biomarkers in complex biological matrices (plasma, serum, urine, tissue), owing to its combination of high specificity (via characteristic mass transitions) and high sensitivity, with contemporary methods routinely achieving limits of quantification in the low nanogram- to sub-nanogram-per-milliliter range, and in select applications extending into the picogram-per-milliliter range, enabled by advances in sample-preparation techniques (solid-phase extraction, hydrophilic interaction liquid chromatography) and optimized mobile-phase composition [3]. Relative to older techniques such as conventional high-performance liquid chromatography (HPLC) with ultraviolet or fluorescence detection, LC-MS/MS offers substantially greater analytical specificity, generally simpler sample preparation, and smaller required sample volumes, factors that collectively underpin its now-dominant role in regulated pharmaceutical bioanalysis and clinical chemistry [3,6].

### 3.2 Proteomic Biomarker Discovery

Beyond targeted small-molecule quantification, high-resolution mass spectrometry frequently in an untargeted or semi-targeted discovery mode has become central to clinical proteomic biomarker discovery, enabling detection of low-abundance proteins and characterization of disease-relevant post-translational modifications (phosphorylation, glycosylation) implicated in conditions spanning cardiology, hematology-oncology, and internal medicine [1]. Proteomic mass spectrometry has achieved particular clinical traction in amyloidosis and multiple myeloma diagnosis, where accurate identification of specific pathological proteoforms is diagnostically essential and is increasingly performed as part of routine hospital laboratory practice rather than exclusively in specialized research settings [2].

### 3.3 Therapeutic Drug Monitoring and Endogenous Biomarker Quantification

LC-MS/MS-based therapeutic drug monitoring (TDM) exemplified by ultra-high-performance LC-MS/MS (UHPLC-MS/MS) methods for antipsychotic drug quantification, the subject of a systematic review of studies published 2013–2024 evaluating precision, recovery, and matrix effects across clinical sample types [4] represents one of the most clinically mature applications of the mass spectrometry platforms discussed in this section, supporting individualized dosing decisions across psychiatry and numerous other therapeutic areas. A related and analytically demanding application involves LC-MS/MS quantification of endogenous biomarkers (e.g., specific metabolites reflecting transporter activity) used as non-invasive probes of drug-drug interaction potential mediated by hepatic and renal drug transporters, an approach of growing regulatory interest as an alternative or complement to traditional probe-drug-based drug-interaction studies [3].

### 3.4 Regulatory and Methodological Consensus

The clinical maturity of mass-spectrometry-based bioanalysis is further reflected in the sustained, structured engagement of industry and regulatory stakeholders on methodological standardization: the 2024 Workshop on Recent Issues in Bioanalysis (WRIB), convening over 1,100 professionals from pharmaceutical/biotechnology companies, contract research organizations, and multiple regulatory agencies, addressed advanced mass spectrometry assay strategies, chromatography and sample-preparation recommendations, and regulatory expectations for regulated bioanalysis [7], underscoring that this platform, while technologically mature, continues to be an active area of methodological refinement and regulatory dialogue rather than a fully static, settled technology.

## 4. CRISPR-Based Molecular Diagnostics

### 4.1 CRISPR-Cas Effector Proteins as Biosensing Elements

CRISPR-based biosensors exploit the programmable, sequence-specific nucleic-acid-targeting activity of Cas effector proteins principally Cas9, Cas12, and Cas13 as highly specific molecular recognition elements, with Cas12 and Cas13 additionally offering a collateral ("trans") cleavage activity upon target recognition that is exploited to generate an amplifiable detection signal [9,14]. These effector proteins can be coupled to a range of readout modalities, including fluorescence, colorimetric, potentiometric, and lateral-flow detection, and are frequently combined with isothermal nucleic-acid amplification methods recombinase polymerase amplification (RPA) and loop-mediated isothermal amplification (LAMP) predominating in the current literature to achieve clinically relevant sensitivity without the thermal-cycling instrumentation required by conventional PCR, a design feature specifically motivated by the goal of enabling decentralized, point-of-care testing [9,15].

### 4.2 Amplification-Free and Microfluidic-Integrated Approaches

A parallel and more recent development trend addresses a recognized limitation of amplification-dependent CRISPR diagnostics the added complexity, time, and potential for cross-contamination introduced by a separate amplification step through amplification-free CRISPR detection strategies capable of direct, sufficiently sensitive target detection (for example, electrochemical CRISPR biosensors achieving picomolar-level direct DNA detection) [13,9]. Complementing this direction, integration of CRISPR-Cas biosensing with microfluidic platforms has emerged as a specific strategy for advancing these assays from benchtop proof-of-concept toward true sample-to-answer point-of-care devices, leveraging microfluidics' inherent advantages in miniaturization, reagent integration, and automation; a 2026 critical review specifically focused on this microfluidics-CRISPR integration trend over the preceding five years, reflecting its status as an active, rapidly developing research direction rather than a mature, settled technology [16].

### 4.3 Clinical Translation Status

Despite the substantial and rapidly growing preclinical and analytical-validation literature on CRISPR-based diagnostics, clinical translation remains at a comparatively early stage: a 2024 systematic review identifying 44 relevant studies published between 2008 and 2024 on point-of-care next-generation CRISPR-based rapid diagnostic technologies explicitly reported that no clinical studies of CRISPR-based point-of-care diagnostics with widespread deployment were identified [8]. Notable exceptions illustrating the leading edge of clinical translation include Sherlock Biosciences' 2024 initiation of a clinical trial (the PROMISE trial, enrolling approximately 2,500 participants) for a rapid, self-collected, over-the-counter CRISPR-based test for chlamydia and gonorrhea benchmarked against conventional PCR, with the company subsequently acquired by OraSure Technologies in 2024 [11], and continued regulatory and technical hurdles including off-target effects, multiplexing-versus-throughput trade-offs, and the general challenge of translating strong analytical performance into validated clinical-grade diagnostic products remain active areas of discussion in the specialized literature [12,15].

### 4.4 Positioning Relative to Established Molecular Diagnostics

CRISPR-based diagnostics are generally positioned in the reviewed literature not as a wholesale replacement for established nucleic-acid amplification testing (NAAT, including quantitative PCR) but as a complementary approach offering potential advantages in speed, instrumentation simplicity, and point-of-care compatibility for specific applications, particularly infectious-disease and, increasingly, oncology-relevant nucleic-acid detection (including CRISPR/Cas13a-based ctDNA mutation detection [17], discussed further in Section 5), while existing high-throughput, well-validated PCR-based platforms retain clear advantages for centralized, high-volume laboratory testing.

## 5. Liquid Biopsy and Circulating Biomarker Analysis

### 5.1 Circulating Tumor DNA

Circulating tumor DNA (ctDNA) tumor-derived cell-free DNA fragments detectable in blood and other body fluids has emerged as the most extensively validated and clinically applied liquid-biopsy analyte, supported by next-generation sequencing (NGS) and droplet digital PCR (ddPCR) detection methodologies capable of identifying tumor-specific mutations at low variant-allele frequencies [18,23]. Clinical trials have evaluated ctDNA monitoring of treatment response across multiple tumor types, including non-small cell lung cancer, breast cancer, and colorectal cancer [18], and 2024 marked a documented peak in the volume of liquid-biopsy scientific publications indexed in PubMed (approximately 1,400 papers on liquid biopsy in solid tumors that year alone) [19], reflecting both the

technology's clinical momentum and the rapidly expanding evidence base supporting its use. A persistent methodological limitation noted across the reviewed literature is that most liquid-biopsy tests introduced into clinical practice to date assess only one or two features of tumor DNA, constraining assay specificity relative to more comprehensive (but less clinically mature) multi-analyte approaches [18].

### 5.2 Circulating Tumor Cells and Extracellular Vesicles

Circulating tumor cells (CTCs) and extracellular vesicles (including exosomes and their cargo, notably microRNA) represent complementary liquid-biopsy analytes offering distinct informational content relative to ctDNA: CTCs enable single-cell-level molecular profiling and functional characterization of tumor heterogeneity and metastatic potential, while extracellular vesicle cargo provides an additional, mechanistically distinct window into tumor biology; technological advances in microfluidics, nanotechnology, and NGS have collectively improved the accuracy and clinical utility of CTC- and extracellular-vesicle-based analysis over the past several years [24].

### 5.3 Multimodal Liquid Biopsy and AI-Assisted Integration

Recognizing the individual limitations of single-analyte liquid biopsy approaches, multimodal platforms integrating two or more analytes for example, a reported system combining CTC, exosome, and cell-free DNA expression profiling via a machine-learning algorithm [21] aim to improve overall diagnostic sensitivity and specificity relative to single-analyte assays, though such multimodal approaches remain considerably earlier in clinical validation than single-analyte ctDNA testing. AI-enhanced analytical approaches are increasingly applied specifically to longitudinal ctDNA mutation-dynamics monitoring during targeted-therapy resistance development, with reported capability to reveal mutation-landscape heterogeneity and temporal evolution correlating with clinical markers of disease progression [20], representing a specific, clinically motivated application of the broader AI/ML integration trend discussed further in Section 6.

### 5.4 Analytical and Pre-Analytical Considerations

Realizing liquid biopsy's clinical potential depends critically on analytical sensitivity for rare variant/cell detection against a high background of normal cell-free DNA or blood cells, and on rigorous standardization of pre-analytical variables (sample collection, processing time, storage conditions) shown to materially affect assay performance; ongoing methodological work including approaches such as high-efficiency error suppression for low-frequency variant detection, and evaluation of alternative sampling approaches including dried blood spot collection [22] continues to address these analytical and pre-analytical challenges as the field matures toward broader clinical implementation.

### 5.5 Summary Table

Table 1 consolidates the technologies discussed in Sections 3–5 with their primary application, analytical strength, translational-status grade (per Section 2.3), and source references.

| Technology / Platform | Primary Application | Analytical Strength | Translational Status | Reference |
|---|---|---|---|---|
| LC-MS/MS | Drug/metabolite quantification; therapeutic drug monitoring; endogenous biomarker | High specificity (mass transitions) and sensitivity (pg/mL–ng/mL LOQ) | Established Clinical Use | Son et al., 2024; Frontiers systematic review, 2024–2025 |

| | | | | |
|---|---|---|---|---|
| | quantification for drug-interaction assessment | | | |
| High-resolution/untargeted MS proteomics | Biomarker discovery; post-translational modification characterization; amyloidosis/myeloma diagnosis | Detection of low-abundance proteins; comprehensive proteoform coverage | Established Clinical Use (selected indications) / Clinical-Stage (discovery applications) | PMC11836596 (2012–2024 review) |
| CRISPR-Cas12/Cas13 biosensors + isothermal amplification | Point-of-care nucleic-acid detection (infectious disease, oncology mutation detection) | High target specificity; instrumentation-light; rapid (often <30 min) turnaround | Preclinical/Early Research (select platforms Clinical-Stage, e.g., Sherlock PROMISE trial) | Springer Clin Exp Med systematic review, 2024; PMC9953454 |
| Microfluidic-integrated CRISPR diagnostics | Sample-to-answer point-of-care biomarker detection | Miniaturization, automation, reduced sample/reagent volume | Preclinical/Early Research | Wang et al., Sens. Diagn., 2026 |
| ctDNA via NGS/ddPCR | Cancer diagnosis, treatment-response monitoring, minimal residual disease detection | Low variant-allele-frequency detection; minimally invasive, repeatable sampling | Clinical-Stage/Emerging Clinical Use (approved for selected companion-diagnostic indications) | Parums, 2025 (Med Sci Monit); ScienceDirect 2024 liquid biopsy review |
| Multimodal liquid biopsy (CTC + cfDNA + exosome) | Improved sensitivity/specificity over single-analyte liquid biopsy | Integrates complementary analytes via machine-learning fusion | Preclinical/Early Research | PMC8335965 |
| AI/ML-assisted diagnostic interpretation | Mass-spectral/image interpretation; multiplex signal deconvolution; longitudinal ctDNA mutation tracking | Improved sensitivity for actionable mutation/pattern detection at scale | Preclinical/Early Research (platform-dependent; requires independent validation) | Kardjadj, 2025 (Diagnostics); PMC12688787 |

*cfDNA, cell-free DNA; CTC, circulating tumor cell; ctDNA, circulating tumor DNA; ddPCR, droplet digital PCR; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LOQ, limit of quantification; MS, mass spectrometry; NGS, next-generation sequencing.*

## 6. Artificial Intelligence and Machine Learning in Analytical Chemistry

### 6.1 Current Scope of AI/ML Integration

Artificial intelligence and machine learning are now embedded across essentially every analytical domain discussed in this review: assisting mass-spectral peak identification and quantification,

automating multiplex signal deconvolution in CRISPR- and immunoassay-based point-of-care platforms, enabling multimodal liquid-biopsy data fusion (Section 5.3), and supporting automated quality control in decentralized point-of-care testing settings. A 2024 special issue of Analytical Chemistry noted that 16 of 22 featured review articles that year addressed applications of machine learning or deep learning across different analytical subfields, reflecting the breadth and pace of this integration trend [5].

## 6.2 AI-Enhanced Point-of-Care Diagnostics

A comprehensive 2025 review of point-of-care infectious-disease diagnostics specifically characterized AI as having transitioned from an experimental tool to an embedded analytical layer within contemporary point-of-care platforms, enhancing image interpretation, multiplex signal deconvolution, and automated quality control, within a global point-of-care diagnostics market valued at approximately USD 53 billion in 2024 and projected to nearly double by 2033; the same review emphasized that rigorous validation encompassing analytical accuracy, clinical performance in the intended-use setting, and usability testing under relevant regulatory frameworks (e.g., CLIA waiver requirements in the United States) remains central to ensuring AI-enhanced diagnostic reliability in decentralized, non-laboratory environments [10].

## 6.3 AI in Liquid Biopsy Mutation Tracking

As introduced in Section 5.3, AI-enabled longitudinal analysis of ctDNA mutation dynamics during targeted-therapy treatment has demonstrated a documented correlation with clinical markers of disease progression [20], illustrating a specific, clinically motivated application in which AI-assisted pattern recognition across serial liquid-biopsy measurements provides information not readily extractable through single-timepoint or manual analysis alone.

## 6.4 Validation Imperative

Across each of these applications, the reviewed literature consistently emphasizes that AI/ML tools require the same rigor of platform-specific analytical and clinical validation applied to any other diagnostic technology, rather than being assumed valid on the basis of algorithmic sophistication or strong performance on a training or internal test dataset; this validation imperative is treated in Section 7 as a specific, cross-cutting consideration applicable to every AI-enhanced platform discussed in this review, consistent with the cautious, benchmark-validated framing applied to deep-learning methods in our companion review of computational drug-discovery methods.

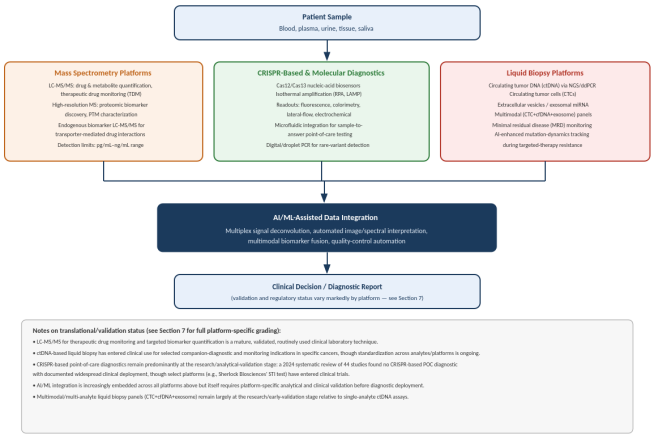


*Figure 1. Integrated overview of emerging analytical technologies mass spectrometry, CRISPR-based molecular diagnostics, and liquid biopsy platforms converging via AI/ML-assisted data integration toward clinical decision-*

*making, with validation and translational status varying markedly by platform. See Section 7 for platform-specific grading.*

## 7. Critical Appraisal: Translational Validation by Platform

### 7.1 Established Clinical Use

LC-MS/MS-based therapeutic drug monitoring and targeted biomarker/drug quantification represent the most clinically mature technologies reviewed, reflecting decades of methodological refinement, regulatory engagement (exemplified by the sustained multi-stakeholder WRIB process described in Section 3.4) [7], and routine incorporation into clinical and regulated bioanalytical laboratory practice [1,3]. Selected proteomic mass spectrometry applications (e.g., amyloidosis/myeloma proteoform identification) [2] and ctDNA-based companion diagnostics for specific, regulatory-approved targeted therapy indications [18] similarly meet this established-use threshold, though the breadth of approved ctDNA companion-diagnostic indications remains considerably narrower than the full scope of research applications described in Section 5.

### 7.2 Clinical-Stage and Emerging Clinical Use

Broader ctDNA-based treatment-response and minimal-residual-disease monitoring applications, beyond specific approved companion-diagnostic indications, are best characterized as clinical-stage/emerging clinical use: supported by an extensive and rapidly growing clinical-trial literature (Section 5.1) [18,19] but not yet uniformly standardized or guideline-embedded across the full range of research applications described. Selected CRISPR-based diagnostic platforms — notably Sherlock Biosciences' PROMISE trial for a self-collected sexually transmitted infection test [11] — represent the leading edge of CRISPR-diagnostic clinical translation, though the 2024 systematic review finding of no CRISPR-based point-of-care diagnostic with documented widespread clinical deployment (Section 4.3) [8] indicates this remains the exception rather than the norm for this technology class as a whole.

### 7.3 Preclinical and Early Research

The majority of CRISPR-based diagnostic platforms, microfluidic-integrated CRISPR systems, and multimodal (multi-analyte) liquid biopsy panels remain, despite substantial and rapidly growing analytical-validation and preclinical literature, in this earliest translational category. This should not be read as a negative assessment of the underlying science — several of the analytical performance metrics reported (e.g., picomolar-level direct DNA detection without amplification) [13] are genuinely impressive relative to established alternatives — but rather as an honest acknowledgment that strong analytical performance in controlled research settings has not yet, for most of these specific platforms, been matched by the clinical validation, regulatory clearance, and real-world deployment evidence that would justify classification as established or even clinical-stage clinical tools.

### 7.4 Cross-Cutting Limitations

- Standardization gaps: liquid biopsy in particular suffers from a lack of standardization across analytes, platforms, and pre-analytical handling protocols, complicating cross-study comparison and, potentially, clinical guideline development [22,19].
- Multiplexing-versus-throughput trade-offs: as noted in the CRISPR-diagnostics literature specifically, most current platforms must trade-off between high sample throughput and high target multiplexing, a practical constraint relevant to real-world clinical deployment scenarios [15].

- AI/ML validation burden: as emphasized in Section 6.4, AI-enhanced analytical tools require dedicated, platform-specific validation and should not be assumed reliable on the basis of strong internal or training-set performance alone.
- Regulatory and reimbursement pathways: several of the technologies reviewed, particularly CRISPR-based point-of-care diagnostics and multimodal liquid biopsy panels, face not only technical/analytical validation requirements but also non-trivial regulatory clearance and clinical reimbursement pathways that further extend realistic timelines to routine clinical availability beyond what analytical performance data alone would suggest.

## 8. Future Perspectives

### 8.1 Advancing CRISPR Diagnostics Toward Clinical Deployment

Building on the leading-edge example of the Sherlock Biosciences PROMISE trial (Section 4.3), continued clinical-stage evaluation of the most analytically mature CRISPR-based diagnostic platforms prioritizing infectious-disease and selected oncology applications where rapid, point-of-care turnaround offers the clearest clinical value proposition represents a key priority for translating this technology class beyond its current predominantly preclinical status.

### 8.2 Standardization of Liquid Biopsy Methodology

Given the standardization gaps identified in Section 7.4, continued development of consensus pre-analytical handling protocols, harmonized variant-calling and reporting standards, and, where appropriate, multi-analyte reference materials would support broader and more consistent clinical adoption of ctDNA and other liquid-biopsy analytes across laboratories and clinical settings.

### 8.3 Rigorous, Independent AI/ML Validation Frameworks

Consistent with the validation imperative discussed in Section 6.4, continued development of standardized, independent validation frameworks analogous to those already established for conventional in vitro diagnostic devices specifically adapted to the particular characteristics of AI/ML-based analytical tools (including requirements for external, held-out validation datasets and prospective clinical performance evaluation) should be prioritized as this technology class continues to expand across the platforms reviewed.

### 8.4 Multimodal Platform Integration

Continued development of multimodal liquid-biopsy and, more broadly, multi-platform diagnostic approaches (combining, for example, mass-spectrometry-based proteomic biomarkers with nucleic-acid-based liquid biopsy analytes) represents a promising direction for improving overall diagnostic sensitivity and specificity beyond what any single analytical modality can achieve, provided such integration is accompanied by the rigorous validation discussed throughout this review rather than presented as inherently superior on the basis of technical complexity alone.

### 8.5 Expanding Access Through Point-of-Care Deployment

Given the substantial global point-of-care diagnostics market growth documented in Section 6.2, continued investment in point-of-care-compatible formats for the most clinically promising technologies reviewed here particularly CRISPR-based and microfluidic-integrated diagnostics offers meaningful potential to expand diagnostic access in resource-limited and decentralized healthcare settings, provided this expansion is matched by appropriate regulatory oversight and post-market surveillance infrastructure.

## 9. Conclusion

Advanced analytical chemistry continues to expand the scope and precision of biomarker analysis, drug quantification, and clinical diagnostics, spanning established, routinely used platforms (LC-MS/MS-based therapeutic drug monitoring, selected ctDNA companion diagnostics) through clinical-stage emerging technologies (broader ctDNA monitoring applications, leading CRISPR-diagnostic clinical trials) to a large and rapidly growing preclinical literature (most CRISPR-based point-of-care platforms, multimodal liquid biopsy panels, and many AI-enhanced analytical tools). As throughout this review, honest, platform-specific translational-validation grading distinguishing established clinical practice from promising but still-developing technology is essential to appropriately calibrate both continued research investment and any clinical or commercial communication regarding the present-day readiness of these analytical technologies, ensuring that genuine, near-term diagnostic opportunity is not conflated with mechanistically elegant but still largely preclinical or early-clinical promise.

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