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Research Progress and Standardization Challenges of NMR Technology in the IVD Field

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Abstract: In Vitro Diagnostics (IVD) is central to precision medicine, enabling disease screening, diagnosis, and therapeutic monitoring. While mass spectrometry (MS) remains the dominant platform for metabolomics, Nuclear Magnetic Resonance (NMR) spectroscopy has emerged as a robust complementary technology due to its high reproducibility, quantitative reliability, and non-destructive nature. This review systematically evaluates the role of NMR-based metabolomics in clinical IVD, focusing on applications in oncology, cardiovascular disease, and neurology. This study critically examines technical strengths and limitations and identifies key barriers to clinical translation, particularly in standardization, data harmonization, and regulatory validation. Finally, we propose a framework to facilitate the integration of NMR into routine clinical workflows.

Keywords: In Vitro diagnostics; NMR spectroscopy; Metabolomics; Clinical standardization; Biomarkers

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1. Introduction

The global healthcare landscape is undergoing a paradigm shift toward precision medicine, which emphasizes individualized diagnosis and treatment based on patient-specific biological characteristics. In this context, in vitro diagnostics (IVD) serves as a cornerstone technology, enabling clinicians to access critical biochemical information from patient-derived samples such as blood, urine, and cerebrospinal fluid. Traditional IVD techniques, including immunoassays and molecular diagnostics, typically focus on a limited number of biomarkers. However, complex diseases such as cancer, cardiovascular disorders, and neurodegenerative conditions involve multifactorial biochemical alterations that cannot be fully captured by single-analyte measurements [1,2].

Metabolomics, defined as the comprehensive analysis of small-molecule metabolites within biological systems, has emerged as a powerful approach for capturing the downstream effects of gene expression and environmental interactions. Among the analytical platforms used in metabolomics, nuclear magnetic resonance (NMR) spectroscopy occupies a unique position due to its inherent reproducibility, minimal sample preparation requirements, and quantitative robustness.

Despite these advantages, NMR has not yet achieved widespread adoption in clinical IVD settings, where mass spectrometry (MS) remains the dominant technology due to its superior sensitivity and broader metabolite coverage. Nevertheless, the strengths of NMR make it particularly suitable for standardized, high-throughput clinical workflows, especially in applications requiring high reproducibility and longitudinal monitoring [1,3].

This review aims to systematically evaluate the current status of NMR-based metabolomics in IVD, analyze its clinical applications, and identify the key challenges that must be addressed to enable its translation into routine clinical practice.

2. Technical characteristics of NMR in clinical settings

2.1. Fundamental principles

NMR spectroscopy is based on the interaction between nuclear spins and an external magnetic field. When placed in a magnetic field, certain atomic nuclei (such as ^{1}H, ^{13}C, and ^{31}P) absorb and re-emit electromagnetic radiation at characteristic frequencies. These frequencies, known as chemical shifts, provide detailed information about molecular structure and environment.

In metabolomics applications, proton (^{1}H) NMR is the most commonly used modality due to its high sensitivity and abundance in biological samples. The resulting spectra consist of peaks corresponding to different metabolites, enabling both qualitative identification and quantitative analysis.

2.2. Analytical advantages

NMR offers several key advantages that make it attractive for clinical applications. The signal intensity in NMR is directly proportional to the molar concentration of the analyte, allowing for absolute or near-absolute quantification without extensive calibration[4]. NMR measurements are highly reproducible across different instruments and laboratories when standardized protocols are followed. Samples remain intact after analysis, enabling repeat measurements or complementary analyses. Compared to MS, NMR requires relatively simple and standardized sample preparation procedures. NMR provides detailed structural insights, facilitating metabolite identification.

2.3. Limitations

Despite its strengths, NMR has several inherent limitations. NMR typically detects metabolites in the micromolar range, which is significantly less sensitive than MS-based techniques. Overlapping peaks in complex biological samples can complicate data interpretation. NMR detects fewer metabolites compared to MS. The acquisition and maintenance of high-field NMR instruments require substantial investment.

3. NMR-based metabolomics workflow in IVD

The application of NMR in IVD involves several key steps, as shown in **Figure 1**.

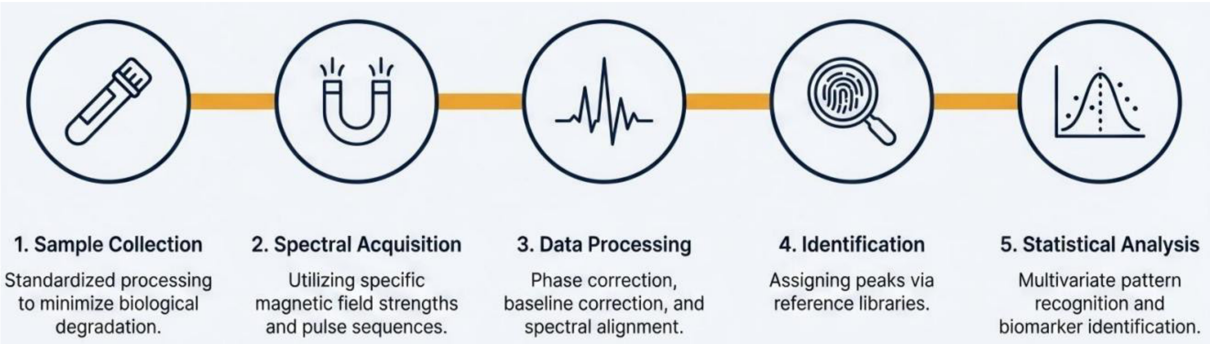

Figure 1. NMR-based metabolomics Workflow in IVD.

(1) Sample collection and preparation
Biological samples are collected and processed under standardized conditions to minimize variability.
(2) Spectral acquisition
NMR spectra are acquired using standardized pulse sequences.
(3) Data processing
Spectral data are processed through phase correction, baseline correction, and alignment.
(4) Metabolite identification and quantification
Peaks are assigned to specific metabolites using reference libraries.
(5) Statistical analysis
Multivariate statistical methods are used to identify patterns and biomarkers.

4. Clinical applications

4.1. Oncology

NMR-based metabolomics has been used to identify metabolic alterations associated with tumorigenesis. Studies have demonstrated its utility in detecting metabolic signatures related to cancer progression, including altered glycolysis and lipid metabolism[5].

Diagnostic models based on NMR-derived metabolite panels have achieved promising performance (AUC > 0.80) in research settings, though large-scale validation remains necessary.

4.2. Cardiovascular disease

NMR enables detailed lipoprotein subclass analysis, providing improved cardiovascular risk stratification beyond conventional lipid measurements. Clinical studies have shown associations between NMR-derived lipoprotein profiles and cardiovascular events[6].

4.3. Neurological disorders

NMR analysis of CSF and plasma has revealed metabolic alterations associated with neurodegenerative diseases. Changes in energy metabolism and neurotransmitter-related metabolites have been reported in conditions such as Alzheimer's disease and multiple sclerosis.

5. Standardization challenges

Despite the analytical strengths of NMR, its translation into routine IVD practice is critically constrained by multi-level standardization challenges that span the entire analytical pipeline.

5.1. Pre-analytical variability

Pre-analytical factors represent one of the largest sources of variability in metabolomics. Variations in patient preparation (fasting vs non-fasting), sample collection tubes (e.g., EDTA vs heparin), processing time, storage temperature, and freeze–thaw cycles can significantly alter metabolite concentrations. Even minor deviations can introduce systematic bias, undermining cross-study comparability. Therefore, strict standard operating procedures (SOPs) and biobanking protocols are essential for clinical-grade reproducibility.

5.2. Analytical and instrumental variability

Although NMR is inherently reproducible, differences in magnetic field strength (e.g., 400 MHz vs 600 MHz), probe design, pulse sequences, and shimming quality can still affect spectral resolution and peak positions. Inter-vendor variability further complicates harmonization. The implementation of standardized acquisition protocols, internal calibration compounds (e.g., TSP), and routine quality control (QC) procedures is necessary to ensure data consistency across laboratories.

5.3. Data processing and quantification

Post-acquisition data processing remains insufficiently standardized. Variations in phase correction, baseline correction, spectral alignment, and binning strategies can lead to inconsistent results. Furthermore, metabolite identification relies on spectral libraries that may differ between platforms. The lack of universally accepted reference databases and validated quantification pipelines limits reproducibility and regulatory acceptance.

5.4. Biological and population variability

Metabolomic profiles are influenced by age, sex, diet, microbiome composition, medication, and circadian rhythms. Without appropriate normalization and large reference cohorts, distinguishing disease-specific signals from physiological variation remains challenging. This highlights the need for population-scale datasets and stratified reference intervals.

5.5. Regulatory and clinical validation barriers

For NMR-based assays to qualify as IVD tests, they must meet stringent regulatory requirements, including analytical validity, clinical validity, and clinical utility. Current evidence is largely derived from small or single-center studies, which limits generalizability. Regulatory frameworks such as ISO 15189, FDA approval pathways, and EU IVDR (2017/746) require robust multi-center validation, traceability, and standardized reporting formats, areas where NMR metabolomics is still evolving [7].

6. Future perspectives

To enable the routine clinical adoption of NMR-based metabolomics in IVD, several strategic advancements are required.

6.1. Development of global standardization frameworks

International collaboration is needed to establish consensus guidelines for sample handling, spectral acquisition, and data processing. Initiatives toward harmonized SOPs and inter-laboratory ring trials will be critical for ensuring reproducibility and comparability across institutions.

6.2. Integration with artificial intelligence and automation

Advances in machine learning and artificial intelligence offer opportunities to automate spectral deconvolution, metabolite identification, and biomarker discovery. AI-driven pipelines can reduce operator-dependent variability and improve scalability, particularly in high-throughput clinical environments.

6.3. Multi-omics and multi-modal integration

Future diagnostic strategies will likely rely on integrating NMR metabolomics with complementary technologies such as LC-MS, genomics, and proteomics. Such multi-omics approaches can provide a more comprehensive understanding of disease mechanisms and improve diagnostic accuracy.

6.4. Expansion of clinical evidence base

Large-scale, multi-center, longitudinal studies are essential to validate NMR-derived biomarkers and establish clinical utility. Prospective trials linking metabolomic profiles to clinical outcomes will be particularly important for regulatory approval and clinical adoption.

6.5. Translation into clinical decision support systems

To be clinically useful, NMR-derived data must be integrated into actionable decision-making frameworks. This includes the development of standardized reporting formats, reference ranges, and risk models that can be readily interpreted by clinicians.

6.6. Cost reduction and technological innovation

Emerging developments in benchtop and low-field NMR systems may reduce costs and improve accessibility. While these systems currently have lower resolution, ongoing improvements may enable their use in targeted clinical applications, particularly in decentralized or resource-limited settings.

7. Conclusion

NMR-based metabolomics offers a reproducible and quantitative platform for clinical diagnostics, with growing applications in multiple disease domains. However, its transition into routine IVD practice is constrained by technical and regulatory challenges. Addressing standardization and validation issues will be essential for broader clinical adoption.

Disclosure statement

The authors declare no conflict of interest.

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