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Review

What's next for metabolomics?

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Metabolomics has become a mainstream approach that examines the metabolic composition of biological systems in relation to their physiological and disease states. Using analytical techniques such as nuclear magnetic resonance spectroscopy and mass spectrometry, metabolomics enables detailed profiling of small molecules in cells, tissues, and biofluids. Recent methodological advances, along with the integration of big data analytics and expanding metabolite databases, have significantly enhanced the accuracy and scope of metabolomics research. However, despite over twenty years of development, metabolomics still encounters challenges in annotation, automation, and standardization, which are crucial for fully leveraging recent advances in machine learning and applying metabolomics in biological and clinical studies. Recently, a group of experts assembled to discuss future strategies for standardization and automation and their potential in clinical research. This review underscores critical and unresolved issues in current metabolomics research and suggests pathways toward solutions.

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Introduction

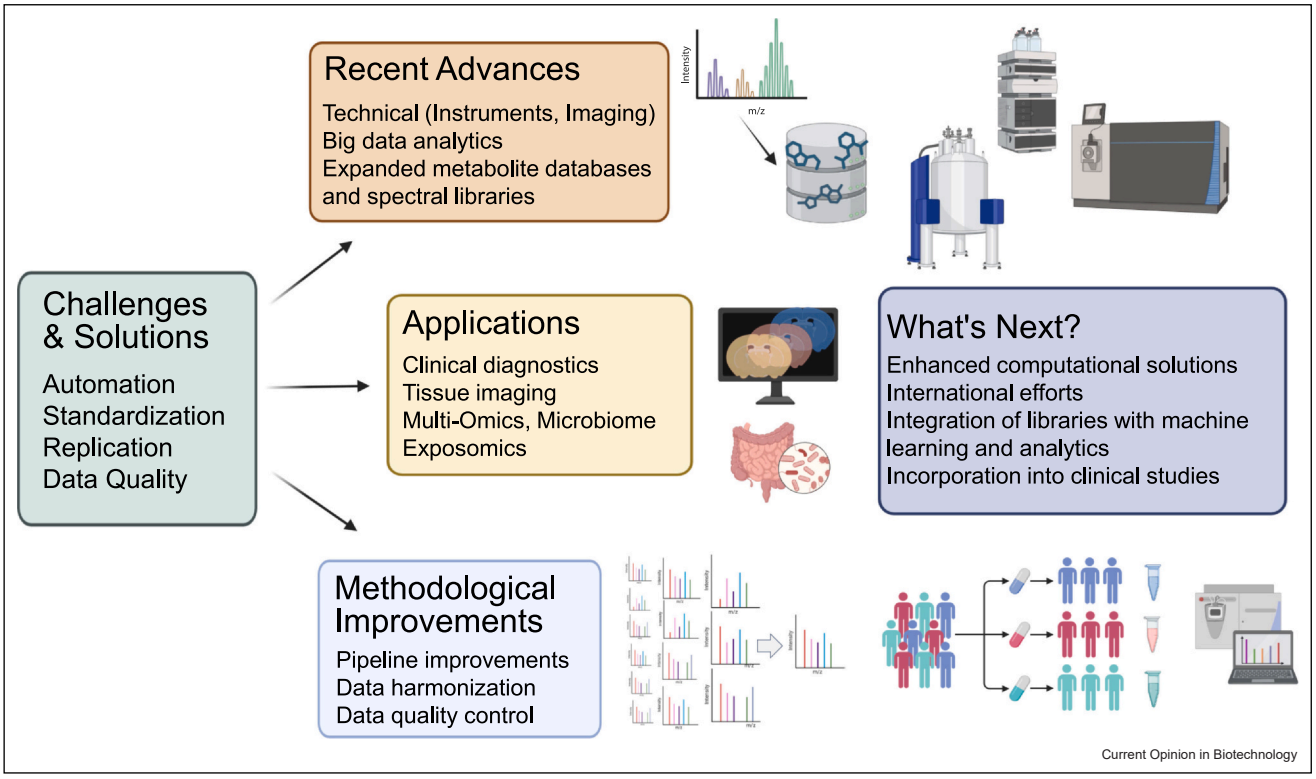
Metabolomics is a key technology in biomedical research, although challenges in standardization, replication, and data quality remain. This review proposes technical, analytical, and computational strategies to improve data quality, enable cross-laboratory reproducibility, and integrate deep learning and multi-omics for emerging biomedical applications (Figure 1).

Improving metabolomics data quality

Overview

The quality and reusability of metabolomics data depend on study design, data acquisition, and data analysis

Figure 1



This perspective article discusses key challenges and solutions, advances, improvements, and applications in metabolomics.

(Figure 2). Technical decisions for these steps affect observed metabolites, their measurements, and the reliability of interpretations. Thus, concise reporting of technical details and stringent quality control practices are imperative for data quality assessment and reusability [1,2].

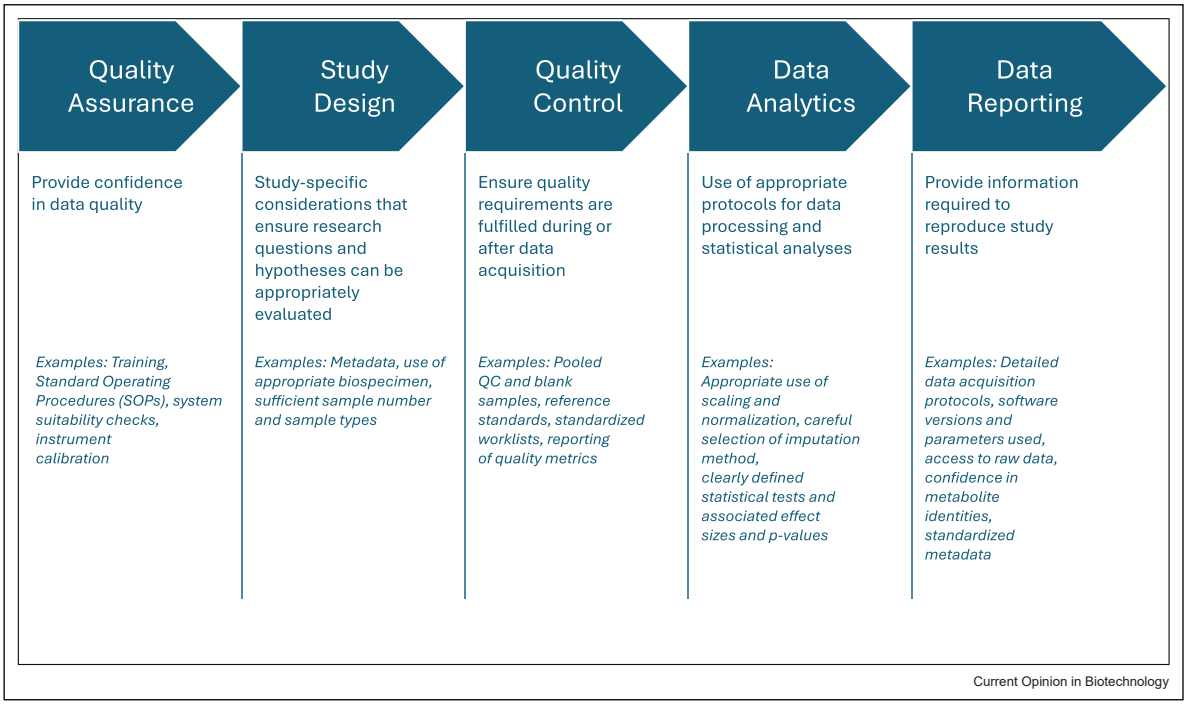
Sample analysis

Quality is established through: 1) quality assurance (QA), which ensures process reliability through training, calibration, and protocols; 2) quality control (QC), which verifies quality via analysis of QC samples, blanks, and reporting metrics [3]. High-quality metabolomics data requires workflows that minimize sample handling variability [4,5], preserve sample integrity, and assess preanalytical issues [6]. Initiatives like Metabolomics Association of North America (MANA) [1] and Metabolomics Quality Assurance & Quality Control Consortium (mQACC) [7] are driving the development of comprehensive community-directed resources of best practices (e.g., use of reference standards or NIST SRM 1950 reference material) to communicate data quality [8], encourage data reuse [9], and enable inter- and intra-laboratory and study comparisons [10]. Reporting standards efforts, including the International Lipidomics Society, mQACC [7], and Best Practices for Non-Targeted Analyses [11], provide guidelines for well-designed and well-disseminated studies.

Data analysis and benchmarking

While standardized data analysis approaches are implemented in commonly used open-source software [12,13], approaches depend on instrumentation and extraction protocols (e.g. there is not a single 'best' approach), and the use of different software may produce different outcomes [14]. Additionally, global assessments across software are limited by the sparse availability of standardized test data sets with known outcomes [15]. Nonetheless, advances in reporting metabolite identity confidence [16], cross-referencing identifiers [17], and common data models [18] are improving consistency in data processing and reporting practices. Benchmarking datasets for LC–MS and/or nuclear magnetic resonance (NMR) are also available, enabling robust performance comparisons across software. These are comprised of synthetic/simulated data, standard chemical mixtures [14], and/or biological data (e.g. NIST plasma [19], human urine [20], *Bovine* saliva, *M. smegmatis* extract [14]).

Figure 2



Aspects of data acquisition, data analysis, and reporting that enhance metabolomics data quality and reuse.

Conclusion

Globally, we encourage continued community efforts and implementation of QA/QC, appropriate study design, data reuse, and standardized workflows to improve reproducibility.

Pipeline advances

Overview

Metabolomics pipelines have undergone significant advancements in recent years; however, challenges in sample preparation, data processing, feature extraction, and quality control persist. Pipeline improvements have centered on enhancing the integration of untargeted metabolomics data, particularly in large human cohort studies, where data consistency and reproducibility are critical.

Sample and analysis quality

Incorporating data quality measures into metabolomics pipelines, especially those that can be automated, will yield numerous benefits. Easily detected metabolites that provide information about sample quality (e.g. hypoxanthine and inosine for blood samples [6]), or data quality metrics that can be provided in supplementary materials in journals [2,21] can enhance data quality and reliability.

Data preprocessing and annotation

To address these challenges, new tools such as Eclipse [22] and MetabCombiner [23] can improve feature alignment and data consistency across datasets. Continuous refinements in these programs enable the detection of compounds that were missed in certain analytical batches. Another innovation, Targeted Feature Extraction (TFE), has emerged as a promising solution for improving peak detection by leveraging both m/z and retention time for enhanced identification [24]. Additionally, artificial intelligence (AI)-based data processing tools can optimize peak detection and integration, key bottlenecks in metabolomics pipelines.

Statistical analysis

Another significant improvement is the introduction of statistical methodologies to address complex study designs involving multiple factors and, increasingly, multiple analytical platforms [1]. Statistical methods to model the homeostasis of metabolites tackle the long-standing issue of significant variations in data collected from different sites [25] and from different instruments [17]. The models significantly reduce these variations by $>90\%$ by modeling each metabolite in relation to others, as well as clinical and demographic variables.

Benchmarking

Benchmarking metabolomics data has also gained attention as researchers strive to evaluate the performance of informatics workflows, particularly those based on R. Many publicly available datasets fail to capture the complexity of real-world samples, often leading to inaccuracies in data processing. To address this problem, standardized sample evaluations have been implemented to assess signal-to-noise, differentiate metabolites from contaminants, and ensure data quality at every stage of the pipeline [7]. The introduction of platforms such as the Metabolomics WorkBench [26] aims to facilitate community-wide comparisons of informatics tools and promote transparency in data processing methodologies.

Conclusion

Peak detection, data quality assessment, and cross-study reproducibility remain central issues in pipeline improvements. The integration of AI-driven tools into data processing workflows offers a promising avenue for improvement, though further optimization is required to maximize their efficacy. Additionally, refining sample handling protocols and standardizing metabolite collection procedures are essential steps toward minimizing degradation and ensuring data consistency. As the field progresses, collaborative efforts will be crucial in establishing robust and reproducible metabolomics methodologies that enhance the accuracy and applicability of metabolomic studies.

Deep learning innovations in metabolomics data analysis/machine learning

Overview

Machine learning (ML) has become central to metabolomics data processing and analysis, and deep learning (DL) is now emerging as a transformative tool in this field. ML is applied to large-cohort studies using algorithms such as random forest, partial least squares discriminant analysis (PLS-DA), regularized regression (e.g. LASSO or elastic net), and Bayesian hierarchical or network models to identify signatures, capture complex study structures, and build classification or prediction models. Conversely, DL uses multi-layered neural networks, enabling predictions on much larger datasets. These more advanced methods hold promise in enhancing spectral resolution, automating spectral profiling, and improving the identification of unknown metabolites. Several recently released tools illustrate the power of DL to streamline workflows and improve analytical performance (Table 1).

Enhancing nuclear magnetic resonance spectral resolution

NMR spectroscopy often struggles with overlapping peaks in complex mixtures, complicating metabolite identification. J-RESGRAN uses a Generative Adversarial Network (GAN) to enhance resolution in J-resolved spectra[27]. Trained on 5000 simulated spectrum pairs, it improved resolution in 80–99% of peak pairs across various biofluids. J-RESGRAN enables faster, cheaper high-resolution spectra without requiring higher magnetic fields or extended acquisition times.

Automating nuclear magnetic resonance spectral profiling

Manual NMR profiling is both time-consuming and prone to errors. DEEP Picker, a DL peak-picking tool trained on synthetic 1D spectra, excels at identifying overlapped peaks [28]. It is integrated into COLMAR (Complex Mixture Analysis by NMR), a suite of automated web tools including COLMAR1d and COLMARq for 1D and 2D profiling [29]. COLMAR1d works across all available NMR field strengths and quantifies up to 40 metabolites. MagMet is another web server that automates preprocessing and quantification for up to 70 metabolites in under 7 minutes [30]. The success of DEEP Picker, COLMAR, and MagMet signifies a new era of automated NMR-based metabolomic analysis.

Deep learning for unknown metabolite identification

A limited number (10–50%) of detectable NMR or MS peaks in biofluid spectra are identifiable due to factors such as limited spectral reference data, peak overlap, contaminants, adducts, and ion suppression. DL tools, such as CFM-ID [31] and FraGNNet [32], predict MS/MS spectra, while RT-Pred forecasts LC retention times with high accuracy [33]. PROSPRE predicts proton NMR shifts with < 0.1 ppm error [34]. DeepMet and BioTransformer use DL methods to generate novel metabolite structures [35,36]. The informatics platform, SIRIUS, incorporates DL-enabled modules such as MSMovelist, to support molecular formula generation and annotation[37]. When these structure predictors are combined with DL-based spectral and chromatographic predictors, they have enabled the discovery of dozens of previously unreported metabolites.

Conclusion

Both ML and DL are reshaping metabolomics, from spectral enhancements to metabolite discovery. In addition, large language models are being used to survey metabolomics literature and software, revealing emerging trends and allowing researchers to address critical challenges, thereby providing powerful frameworks for synthesizing and navigating the metabolomics research landscape [38,39]. These DL-based tools are accelerating analysis, improving reproducibility, and opening new avenues for both NMR- and MS-based untargeted metabolomics.

Metabolomics meets the microbiome: emerging trends and innovations

Overview

Advances in metabolomics pipelines, data quality, and deep learning are transforming microbiome research.

These tools enhance our ability to decode complex metabolic interactions between hosts and their microbial communities.

Computational tools

A major development is the integration of molecular networking and machine learning for improved metabolite annotation and pathway analysis. Platforms like Global Natural Products Social Molecular Networking (GNPS) cluster MS/MS data to identify novel microbial metabolites [40,41]. Predictive tools such as CFM-ID [31] and SIRIUS simulate and/or interpret MS/MS spectra, improving metabolite identification. Machine learning models are increasingly applied to high-dimensional metabolomic datasets, enabling predictions about microbial metabolic functions and their impact on host health.

Flux-based approaches

High-throughput flux-based methods, including metabolic flux analysis (MFA) [42,43] and boundary flux analysis (BFA) [44], provide insights into microbial metabolic networks, particularly in the context of antimicrobial resistance (AMR). Studies on *Pseudomonas aeruginosa* and *Staphylococcus aureus* have revealed species-specific metabolic adaptations that contribute to the development of drug resistance [45,46]. Profiling clinical isolates from large patient cohorts has helped identify metabolic signatures linked to pathogenicity and treatment outcomes [47].

Clinical applications

Clinical and preclinical studies highlight the microbiome's influence on host metabolism [48]. Germ-free and humanized mouse models show microbiome-driven differences in metabolite processing [49]. Tools like AMON [50] integrate metabolomics with genomics to distinguish between microbial and host metabolites. Diet–microbiome interactions, particularly involving bile acids, affect immune signaling and are implicated in various diseases [51]. Despite individual variability, machine learning and molecular networking support robust, multi-dimensional analyses to elucidate the role of the microbiota in human health.

Conclusion

Over the past two decades, high-throughput approaches and bioinformatics have transformed microbial

Table 1

Deep learning and machine learning tools that enable more robust and scalable metabolomics workflows.

Tool or method	Data type	DL category	Primary capability	Citation
J-RESRGAN	NMR	Spectral Resolution	Uses a Generative Adversarial Network to enhance resolution in J-resolved spectra and improve separation of overlapping peaks.	[35]
DEEP Picker	NMR	Spectral Profiling	Detects and characterizes peaks in ^{1}D NMR spectra, including highly overlapped peaks.	[36]
COLMAR	NMR	Informatics Platform	Provides a suite of automated web-based tools for metabolite identification and analysis in complex mixtures.	[37]
COLMAR1d	^{1}D NMR	Web Tool	Performs automated metabolite identification and quantification across NMR field strengths, with reported quantification of up to approximately 40 metabolites.	[37]
COLMARq	NMR	Web Tool	Supports automated quantitative metabolite profiling within the COLMAR suite.	[37]
MagMet	NMR	Web Tool	Automates spectral preprocessing, metabolite identification, and quantification for up to approximately 70 metabolites.	[38]
CFM-ID	MS/MS	Predicts mass spectra to aid identification	Predicts tandem mass spectra and ranks candidate molecular structures to support compound identification.	[39]
FraGNNet	MS/MS	Predicts mass spectra and fragmentation patterns	Uses graph-based deep learning to predict fragmentation patterns or tandem mass spectra.	[40]
RT-Pred	LC–MS	Predicts retention times	Predicts chromatographic retention times based on SMILES.	[41]
PROSPRE	NMR	Predicts chemical shifts	Predicts proton NMR chemical shifts with reported errors below 0.1 ppm.	[42]
Bio Transformer	MS/MS	Predicts transformation products	Predicts biologically plausible metabolites and metabolic transformation products to support unknown identification.	[44]
DeepMet	MS/MS	Predicts metabolite structures	Generates candidate or novel metabolite structures for subsequent spectral and chromatographic evaluation.	[45]
SIRIUS	MS/MS	Predicts metabolite structures and spectra	Generates candidate or novel metabolite structures for subsequent spectral and chromatographic evaluation.	[46]

metabolomics research. MFA and BFA are essential for mapping microbial metabolic networks and identifying functional adaptations, particularly in AMR. Integration of spectral libraries, predictive algorithms, and genomics has deepened insights into host–microbe interactions, with expanding clinical and translational applications.

Technological advances toward clinical applications

Overview

Clinical metabolomics shows great potential in precision medicine, offering novel diagnostic and therapeutic avenues across diverse disease contexts.

Metabolomics in precision medicine strategies

Metabolomics is uniquely positioned to enable precision medicine because it captures the integrated biochemical output of genetic, proteomic, environmental, dietary, microbial, and pharmacological influences, enabling systems-level characterization of metabolic responses to genetic, environmental, and lifestyle factors [52,53]. Compared with genomics and proteomics, metabolomics also offers a more immediate and dynamic readout of current exposures and physiological responses to diet, environment, disease, and treatment. Metabolomics has been used successfully to reveal key molecular nodes and mechanistic insights that inform the development of novel intervention strategies [54]. Metabolomics is informing the development of pharmacological targets [55], providing biomarkers and mechanistic insights for the early detection and diagnosis of disease [56], revealing the etiology of disease [57], monitoring interventions [58], and even informing genetic links [24,49,59,60]

Improved metabolite identification and functional phenotyping

Natural product chemists typically use activity-guided fractionation to isolate metabolites with a desired function. Compounds in NMR metabolomic workflows can be identified more confidently by using high-pressure liquid chromatography to [61–63] create a 'metabolite fraction library' of partially purified molecules from a pooled reference sample [61,62]. An NMR metabolite fraction library can be correlated across fractions to obtain metabolite basis set elements, which represent the collection of NMR observable metabolites in a sample [64]. These basis set elements can then be used to quantitatively fit to unfractionated samples using Bayesian analysis. Collecting NMR and MS spectra on each fraction improves the integration between these complementary technologies. Physical samples can be screened for functional properties such as bioactivity or macromolecular binding.

Multi-omics integration in oncology

Glioblastoma (GBM), a highly aggressive brain cancer, presents significant treatment challenges due to high heterogeneity and metabolic adaptability [65]. Multi-omics offers a comprehensive understanding of tumor metabolism [66]. Mass spectrometry imaging (MSI) can spatially profile metabolic alterations within GBM tissues, providing critical insights into the tumor microenvironment. Integrating MSI and LC–MS has enabled the prediction of GBM patient survival curves [67]. By profiling multiple regions of GBM tumors and margins, including the core and invasive margin, LC–MS can reveal spatially distinct metabolic differences and identify pathways that may represent therapeutic targets [68]. Integration of metabolomic, genomic, and proteomic data, along with immune cell subtyping, can reveal connections between tumor metabolism and immune evasion, thereby highlighting potential therapeutic interventions and improving patient stratification [69]. This type of integrative strategy holds promise for developing personalized treatment based on a patient's unique metabolic phenotype.

Metabolomics in neurological disorders

Metabolomics has provided invaluable insights into the crosstalk between metabolism and neurodegeneration. For example, NMR metabolomics was used to examine the relationship between the gut–brain-metabolism axis of the neurodevelopmental and neurodegenerative disorder, familial dysautonomia (FD) [70,71]. This rare genetic disorder, caused by a point mutation in the *ELP1* gene, results in widespread nervous system dysfunction, gut microbiome dysbiosis, and alterations in central metabolism. Metabolite alterations in serum and fecal samples correlated with alterations in energy-generating pathways and changes in gut microbiota composition, particularly *Clostridium* species, suggesting a potential microbiome-mediated influence on disease pathology.

Mass spectrometry technologies

Developments in mass spectrometry technologies such as multireflecting time-of-flight [72] and Orbitrap Astral [73] mass analyzers are revolutionizing the quality of measurements performed with metabolomics. All-in-one nano-, capillary-, and micro-flow ultrahigh performance liquid chromatography systems are now enabling single-cell lipidomics with much improved annotation numbers [74]. In situ metabolic profiling using the mass spectrometry pen is enabling surgeons to distinguish healthy from cancerous tissue without having to wait for input from the pathologist [75]. Cyclic ion mobility, trapped ion mobility, Structures for Lossless Ion Manipulations (SLIM) ion mobility, and high-resolution demultiplexing (HRdm) drift tube ion mobility are techniques that are now becoming commonplace in LC–MS-based and spatial metabolomics workflows; these techniques

improve peak capacity, decrease spectral congestion and, in some cases, enable tandem ion mobility experiments to separate highly similar isomeric and isobaric species [76].

Nuclear magnetic resonance glycomics

The study of acute-phase protein glycosylation using NMR has yielded significant insights into inflammatory responses and cancer progression [77,78]. NMR spectra of blood show signals from acute-phase protein glycosylations besides those from metabolites [79]. Such signals, previously termed Glyc-A/B, arise from acetyl groups of neuraminic acid and N-acetylglucosamine decorating acute-phase proteins. These signals can be decomposed by line-shape fitting, yielding weighted contributions from different acute-phase proteins [79]. Selective TOCSY experiments can provide valuable insights into glycosylation patterns. Recent work shows the potential of this type of analysis to obtain markers for liver inflammation and fibrosis (PNPLA3 genotype) [78,80]. This new approach enables the rapid assessment of plasma glycosylation markers without requiring any enzymatic sample processing.

Conclusion

Clinical metabolomics faces challenges such as method standardization, multi-omics data integration, and biomarker validation. Future research should focus on mapping metabolic changes in disease states to understand underlying mechanisms, utilizing pluripotent stem cell-derived models and organoids for functional validation. As metabolomics advances, its integration into routine clinical practice could transform disease diagnosis, treatment, and monitoring, ultimately pushing forward the paradigm of precision medicine.

Overall summary

Metabolomics provides valuable insights into various human health states and biological processes. Although challenges persist, standardized approaches are being implemented throughout the metabolomics pipeline. New methods and strategies are enhancing data harmonization, and integrating machine learning provides opportunities to improve results and reproducibility in data analysis. Thought leaders agree that it is crucial for the international metabolomics community to develop vetted and validated protocols covering the entire pipeline, from sample collection and preparation to spectral acquisition and statistical analysis. Importantly, publishers and funding agencies should enforce compliance with these standards. Efforts are ongoing to enhance data quality through advancements in automation and software, as well as recommendations for protocol standards, guidelines for routine QC, the proper application and interpretation of statistical methods, and adherence to the FAIR (Findable, Accessible, Interoperable, and Reusable) principles. Moreover, developing new reference materials will further support quality control initiatives.

Future efforts should focus on refining best practices, increasing the availability of standardized reference materials, and encouraging collaborations to improve data interoperability within the metabolomics research community.

Disclaimer

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Data Availability

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

Declaration of Competing Interest

The authors declare no conflict of interest.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of the annotated references the author(s) used ChatGPT5.0 to suggest summaries for the purpose of consistency in annotating references. After using ChatGPT5.0, the author(s) reviewed and edited the annotated references as needed and take(s) full responsibility for the content of the published annotated references.

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- • of special interest
- •• of outstanding interest

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