Publishable Summary for 25HLT04 Met4Metab
Standardisation of targeted and untargeted metabolomic quantitative methods for their future use in routine clinical diagnosis

Overview

Metabolomics analytical methods have the potential to provide highly multiplexed biomarker quantification, reducing costs whilst expanding the capabilities required for personalised medicine. When operated in a targeted manner, the methods provide metabolite-specific concentrations, while untargeted methods generate large volumes of complex (semi-) quantitative data. The metrological infrastructure required to report such data in clinically interpretable and regulatory-acceptable international system (SI)-traceable units is currently lacking. This project aims to generate the knowledge, analytical methodologies, reference materials (RMs), computational workflows and infrastructure required to enable standardised and SI-traceable reporting of metabolomics measurement results that will be suitable for clinical application.

Need

Healthcare systems are shifting from a ‘one size fits all’ approach towards personalised medicine tailored to individual biological characteristics. Achieving this requires a comprehensive knowledge of biological processes and states which can be guided by omics approaches such as metabolomics. Metabolomics provides a global and objective representation of the phenotype at the level of the metabolome, the entirety of small biochemical molecules in cells, tissues and body fluids, and offers insights into overall health and its dynamics over hours, days and years. Therefore, it offers substantial potential for disease prognosis, therapy optimisation, reduction of adverse drug reactions, and improved healthcare cost and treatment efficiency.

Over the last 20 years mass spectrometry (MS), the prime technique for metabolomics approaches, has become increasingly robust and widely used in clinical laboratories. Targeted MS is routinely employed to quantify steroids, vitamins, and therapeutic drugs. In contrast, untargeted MS approaches enable the simultaneous profiling of hundreds to thousands of small molecules, offering broad coverage of the metabolome in complex human matrices.

Despite the technological advances, translation of metabolomics into regulated clinical practice remains limited due to insufficient measurement comparability, the lack of SI-traceable calibration systems, and limited availability of appropriately characterised RMs. These limitations directly affect compliance with existing regulatory and standardisation frameworks, including the EU In Vitro Diagnostic Regulation (IVDR) and international standards such as ISO 17511, which mandates metrological traceability of calibrators and quality control materials, and ISO 15189, which requires traceable calibration procedures in medical laboratories.

The absence of multiplexed reference measurement systems and matrix RMs currently prevents metabolomics measurements from fully meeting these requirements. Addressing these gaps motivates the project’s objectives as follows: development of SI-traceable reference measurement systems for targeted metabolomics (Objective 1), establishment of calibration and reporting strategies for untargeted metabolomics (Objective 2), provision of community-accepted matrix RMs and quality assurance / quality control (QA/QC) infrastructures (Objective 3), clinical validation and implementation of metabolomics measurements within ISO 15189-compliant laboratory environments (Objective 4).

Objectives

The overall objective is to strengthen the capabilities of European National Measurement Institutes (NMIs) by developing new reference measurement procedures, standard solution calibrators, matrix RMs, and

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computational workflows to transfer highly multiplexed metabolomics methods from research settings into regulated clinical practice.

The specific objectives of the project are:

1. To establish reference measurement systems enabling the comparability and SI traceability of targeted metabolomics data, including the automated preparation of multiplexed calibration standards (> 50 measurands). The standard solutions will be suitable for use as calibrators and/or RMs within the traceability requirements of relevant ISO standards (ISO 17511, ISO 15193, ISO 15194, ISO 17034).
2. To develop standardisation approaches for untargeted metabolomics, including calibration strategies based on >10 “beacon” molecules and chemoinformatics, data mining, machine learning (ML), and artificial intelligence (AI) methods enabling conversion of instrument signals into SI-traceable quantities.
3. To develop and maintain three matrix RMs in collaboration with the Metabolomics Quality Assurance and Quality Control Consortium (mQACC).
4. To improve the acceptance and clinical use of metabolomics measurement results through validation studies. To develop calibration approaches enabling ISO 15189-compliant laboratory practices in collaboration with EU clinical omics facilities and biobanks. To evaluate the suitability of statistical and ML methods for use in metabolomics, including the evaluation of measurement uncertainty, reliability, reproducibility and accuracy in clinical cohorts.
5. To establish a sustainable European infrastructure for the standardisation of metabolomics measurement results, supported by the European Metrology Network for Traceability in Laboratory Medicine (EMN TLM) and metabolomics societies, and to promote the uptake of the project’s technologies and infrastructure by accredited laboratories, instrument manufacturers, regulators and clinical end users.

Progress beyond the state of the art and results

Objective 1: Establish reference measurement systems for targeted metabolomics methods

This project introduces automated gravimetrically controlled robotic liquid-handling systems for the preparation of multiplexed calibration solutions with a target relative expanded uncertainty of < 3 %, which will enable the simultaneous preparation of more than 50 measurands. These systems will be combined with high-accuracy reference measurement procedures based on isotope dilution MS and quantitative nuclear magnetic resonance spectroscopy (qNMR). Calibration materials will be characterised according to ISO 17034 principles. Compared with current single-analyte calibration practice, this approach represents a major advance towards the scalable, automated production of SI-traceable multiplex calibration standards that will be suitable for clinical metabolomics applications.

Objective 2: Develop standardisation approaches for untargeted metabolomics methods

A novel calibration framework based on “beacon molecules” and internal standards will be established. Public metabolomics datasets will be analysed using chemoinformatics and AI/ML methods to identify stable anchor metabolites linking chemically related compound groups. Calibration algorithms will enable the conversion of untargeted instrument responses into SI-traceable quantities across analytical platforms. This approach addresses a key unmet challenge in metabolomics by enabling quantitative interpretation of previously semi-quantitative datasets. Validation will be performed using the calibration materials developed under Objective 1 and the matrix RMs produced under Objective 3, including interlaboratory comparisons and uncertainty evaluation.

Objective 3: Preparation of matrix reference materials and interaction with the Metabolomics Quality Assurance and Quality Control Consortium (mQACC)

Three community-driven matrix RMs will be developed representing clinically relevant biological concentration ranges. Homogeneity and stability studies will be conducted, and reference datasets established through interlaboratory studies. A dedicated web platform will allow qualified users to upload performance data, enabling continuous updating of metabolite information and long-term community engagement. Collaboration with the mQACC will ensure alignment with international metabolomics QA/QC initiatives thus promoting global adoption.

Objective 4: To improve the uptake and use of real patient metabolomics measurement results and establish a European infrastructure for the standardisation of metabolomics measurement results

Pilot clinical studies in plasma, serum and urine, together with large interlaboratory harmonisation studies, will be used to evaluate the accuracy, reproducibility, and measurement uncertainty in real patient cohorts. This project will demonstrate how SI-traceable calibration improves comparability and clinical interpretability of metabolomics data and how it supports implementation within laboratories operating under ISO 15189 accreditation requirements. These studies will provide the evidence required for regulatory acceptance and routine clinical deployment.

Outcomes and impact

Key dissemination and communication activities

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Outcomes for industrial and other user communities

This project will provide automated multiplexed calibration solutions, SI-traceable reporting tools for untargeted metabolomics using MS, and three matrix RMs enabling robust and reliable implementation of metabolomics measurements in common biological matrices. These outputs will support accredited clinical laboratories, instrument manufacturers, metabolomics service providers, and reference standards producers in delivering comparable, SI-traceable and clinically interpretable measurement results across analytical platforms and laboratories. By enabling harmonised calibration strategies and improved measurement uncertainty evaluation, this project will facilitate the transition of metabolomics workflows from research applications towards routine clinical diagnostics and therapeutic decision support.

An openly accessible data and information platform, supported by training and dissemination activities, will provide access to reference datasets, calibration guidance, quality control information, and best-practice protocols developed within the project. Supported by dedicated training materials, workshops, and dissemination activities, this infrastructure will promote consistent implementation across the measurement supply chain. Engagement with clinical laboratories, metabolomics societies, industrial stakeholders, and regulatory actors through the EMN TLM will promote the sustainable uptake of the project's outcomes, strengthen user confidence in metabolomics measurements, and accelerate deployment of standardised metabolomics technologies in personalised and precision medicine.

Outcomes for the metrology and scientific communities

This project will establish new metrological capabilities for highly multiplexed metabolite quantification, including the automated preparation of calibration materials and matrix materials that have been characterised for a large panel of metabolites (> 50), reference measurement procedures, and computational workflows enabling SI-traceable reporting of large-scale metabolomics datasets. The scalable automation approaches will expand the NMIs' capabilities to produce and assess highly multiplexed calibration standards with the homogeneity, stability, and metrological traceability required to support reference measurement services.

These developments will expand the capacity of NMIs to support emerging "omics" technologies and to provide traceability services beyond conventional single-analyte measurements. Harmonised calibration concepts and shared reference datasets will improve interlaboratory comparability, enabling the integration of metabolomics data across studies, analytical platforms, and time scales. This will enable the combination of metabolomics results from different laboratories and time points, which will greatly enhance the value of large-scale data resources. Ultimately, this will enable meta population-based studies, comparable to those in genomics, and support the use of AI/ML techniques for metabolomics for precision medicine approaches.

Outcomes for relevant standards

This project directly supports implementation of international standards including ISO 17511, ISO 15193, ISO 15194, and ISO 17034, whilst facilitating compliance with ISO 15189 requirements for medical laboratories.

At present, the limited availability of appropriately characterised RMs limits fulfilment of the metrological traceability requirements defined in ISO 17511 and represents a barrier to regulatory acceptance under the EU IVDR. By delivering validated calibration systems and matrix RMs (plasma, serum, urine), this project will enable metabolomics measurements to meet these regulatory and standardisation requirements.

The metrological infrastructure needed to support these standards remains under development, and it is currently unclear to what extent metabolomics data comply with existing traceability and quality requirements. This project will therefore provide legislators and standardisation bodies with guidance by identifying the technical and methodological challenges associated with metabolomics measurements. In parallel, the consortium will work closely with clinical omics laboratories to increase awareness of these requirements and to develop implementation approaches that will enable the compliance of metabolomics measurements. Continuous interaction with regulatory and professional organisations, including the Bundesärztekammer (BÄK), will ensure that project results contribute to future standardisation activities and support the integration of metabolomics into regulated clinical practice.

Longer-term economic, social and environmental impacts

Personalised medicine is an emerging approach to prevention, diagnosis, treatment and patient care based on individual patient data (e.g., biochemical signatures, genetic information, personal history). It is expected to play a key role in addressing the challenges associated with Europe's ageing population and the increasing prevalence of chronic diseases. Improved diagnostic reliability, first-time correct treatments and reduced adverse treatment outcomes enabled by comparable metabolomics measurements will contribute to lower healthcare expenditure. In Germany alone, about 8 % of emergency ward admissions are associated with adverse drug effects or inappropriate treatment leading to annual costs of approximately €2.5 billion. At the same time, the project will create new commercial opportunities in RMs, calibration services, and standardised metabolomics-based diagnostic solutions, thereby strengthening European competitiveness in precision medicine and analytical technologies.

By improving the reliability and comparability of metabolomics-based diagnostics, the project will support safer and more individualised therapeutic decisions, contributing to improved patient outcomes and reduced treatment inequalities. Harmonised measurement results across laboratories and countries will facilitate equitable access to advanced diagnostic approaches and enable the integration of large-scale health datasets to support population-level studies and evidence-based healthcare policies. Increased confidence in metabolomics measurements among clinicians and regulators will further promote patient trust in data-driven and AI-supported healthcare systems.

Automated gravimetric preparation workflows will reduce reagent consumption, sample volumes, and material waste compared with conventional preparation approaches. In addition, harmonised and SI-traceable measurements will minimise duplication of experimental studies and interlaboratory reanalysis, thereby reducing analytical resource consumption and associated environmental burden over the long term.

List of publications

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Project start date and duration:		July 2026, 36 months
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Internal Beneficiaries: 1. PTB, Germany 2. BAM, Germany 3. FTMC, Lithuania 4. IAPR, Greece 5. LGC, United Kingdom 6. LNE, France 7. TUBITAK, Türkiye	External Beneficiaries: 8. CEA, France 9. Charité, Germany 10. GTU, Türkiye 11. HZI, Germany 12. ICAN, France 13. TUBS, Germany 14. ULiv, United Kingdom 15. UniL, Switzerland 16. Vetmeduni, Austria	Unfunded Beneficiaries: 17. Merck, Germany