European Partnership on Metrology
Call 2025 – Health, Integrated European Metrology, Regulation and Research Potential

Selected Research Topic number: **SRT-h13**
Version: 1.0

Title: Standardisation of targeted and untargeted metabolomic quantitative methods for their future use in routine clinical diagnosis

Abstract

The monitoring of small molecule biomarkers is essential for clinical diagnosis and prognosis. The simultaneous measurement of all metabolites, “metabolomics”, shows great potential. However, in order to obtain a reliable diagnostic tool relevant data needs to be comparable between laboratories and across large timeframes required to generate data from clinical studies. Proposals are sought to outline approaches required to enable the reporting of metabolomics results in traceable SI units. It includes the identification of calibration approaches, internal standards, matrix certified reference materials and a quality infrastructure that will assure the metrological traceability of non-targeted metabolomics results and vastly improve the comparability of global patient data.

Keywords

Metabolomics, standardisation, metrological traceability for precision medicine, non-targeted quantification

Background to the Metrological Challenges

The comprehensive study of the metabolome, which uses high quantity of small biochemical molecules in cells, tissues, and bodily fluids, at the global or “omics” level for diagnostic purposes has the potential to have a profound impact on medical practice. A person’s metabolic state is an objective measure of phenotype and can provide unrivalled detail on that individual’s overall health status. The metabolome reflects not only what is hard coded by the genome but also the influence of environmental, dietary and microbial factors (e.g. gut microbiome) on cellular and organ health. The last 20 years have seen a vast improvement in the robustness and utilisation of mass spectrometry in the clinical laboratory that enables the study of metabolome. When operating in a targeted manner mass spectrometers are currently used by clinical laboratories for the routine monitoring and quantification of steroids, vitamins, and therapeutic drugs. However, when operated in an untargeted approach, they routinely monitor hundreds to thousands of molecules simultaneously. If properly calibrated, these could provide quantitative patient biochemical information on the global scale, making precision medicine affordable.

National Measurement Institutes (NMIs) and Designated Institutes (DIs) already provide national standards for the most important biomarkers in biomedicine and interact with their national medical societies, reference laboratories and international activities, such as the Joint Committee on Traceability in Laboratory Medicine (JCTLM), to safeguard the reliability and accuracy of such measurements. However, the metrological tools developed by NMIs/DIs have been applied to single or small groups of metabolite measurands and new approaches are required if metabolomics technologies are going to successfully transit from their status, as powerful research tools, to routinely providing data in support of clinical laboratory medicine [1]. Metabolomic measurement need to surpass currently used approaches and develop quantitative measurements for tens to hundreds of metabolite markers in a targeted approach and thousands when used in an untargeted manner. Greater metrological support is needed to move these multiplexed metabolomic methods from the research environment into the clinical laboratory as these currently do not meet reproducibility and repeatability measurement requirements. The metrology for metabolomics methods applied to personalised medicine will

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require completely different approaches to deliver the vast range of “fit for purpose” calibration services to enable omics based in vitro diagnostics (IVDs) to meet the medical needs and legislative requirements.
The metabolomics community has made great efforts to harmonise their data. This has been greatly extended with the help of a USA NIH initiative that enabled the formation of the metabolomics Quality Assurance and Quality Control Consortium. They aim to harmonise and disseminate best practice for untargeted metabolomics methods and to encourage the prioritization and development of reference materials via a dedicated Reference and Test Materials working group led by NIST. The volume of data generated by these platforms benefits from the use of machine learning and artificial intelligence and other computer-based approaches to identify signatures of disease, interpret the impact of therapeutic interventions, and improve prognosis.

Data interpretation is complicated by batch effects in measurements within a study, and calibration, method and instrument effects between studies. Therefore, standardisation of the raw biological quantitative data as well as the algorithms will be required.

To foster personalised medicine, statistically significant biological measurement data on an individual basis must be collected and shared within the health care system in order to enable personalised diagnosis and therapeutic intervention plans. Currently, the data quality of complex biomedical measurements is a key problem in medical diagnostics. The need for more accurate and well-defined data, in biomedicine is essential for a successful diagnosis and treatment of patients. Therefore, the EU IVD regulation (Regulation (EU) 2017/746) [2] requires that all manufacturers of IVD devices provide a summary of device safety and performance, which must include information on the metrological traceability of assigned values.

A review of the unique features that untargeted metabolomics provide in clinical testing concluded that the comparison of results to reference ranges provided by a normal reference cohort would enable the observation of isolated disease cases. However, the convention of reference ranges requires the expression of results in agreed units and the standardisation of results to higher order references to assure the comparability of measurement results over time and between labs. The current practice does not provide results that are traceable to the SI and therefore “absolute” quantification is not possible. The concept of using standardisation has been recently assessed using a combination of certified reference materials and solution reference standards combined with targeted metabolite quantification. The expression of results traceable to the SI system of units by metabolite specific certified reference materials (CRMs), enables both the comparison of measurement results between large metabolomics studies but also provides results that can be compared with reference ranges, an approach which is currently accepted by the clinical community.

Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The proposal shall focus on the development of approaches required to enable the reporting of metabolomics results in SI units.

The specific objectives are:

1. To establish reference measurement systems to support targeted metabolomic data with the aim of improving the comparability of targeted metabolomics methods. Fully automated preparation of calibration standards and reference measurement procedures will be developed to characterise specific multiplexed metabolite standard solutions (>50 measurands) to act as calibrators and/or reference materials that meet the traceability requirements of relevant ISO standards. (ISO17511, ISO15193, ISO15194, ISO17034).
2. To establish standardised untargeted methods for the generation of large-scale quantitative metabolomic measurements, enabling the reporting of these in traceable SI units, where possible. Harmonised sample preparation and calibration strategies will be developed, including “beacon molecules” acting as calibrators for a broader subset of metabolites. Labelled internal standards to convert instrument signals to SI units will be selected and a set of internal standards (naturally incurred and/or exogenous spike molecules) established for untargeted metabolomics measurements traceable to the SI, in serum, plasma, dried blood spot and urine.
3. To ensure the coordination and engagement of a European contribution towards the international community driven mQACC by working with them to establish a set of (>3) community driven matrix reference materials. Community user data will be made available in the initial stages and superseded

with certified values at later stages of the proposal. To establish and promote quality assurance (QA)/QC best practices.

4. To establish a European infrastructure for metabolomic standardisation, ensuring results are fit for purpose for real patient data. Biobank samples, interlaboratory comparisons, and calibration approaches will be used to estimate measurement uncertainty, repeatability, reproducibility and trueness of measurements, helping clinical laboratories meet the quality standard for medical laboratories (ISO15189). Machine learning and artificial intelligence for metabolomic profiling will be assessed and algorithm data processing protocols will be developed for reporting, recording, and archiving of data (meeting all current reporting standards and FAIR principles).
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (NMIs, DIs, metrology networks, European and International metabolomics societies), standards developing organisations (Metabolomics Community, CEN, ISO), and end users (instrument manufacturers, clinicians, core facilities, legislators, clinical laboratories, and personalised and precision medicine providers).

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, medical (academic) hospitals and industry is strongly recommended, both prior to and during methodology development. Where relevant, proposals are encouraged to build on, or seek collaboration with, existing projects and develop synergies with other relevant European, national or regional initiatives and funding programmes. In particular, links are encouraged with (i) the projects funded under earlier relevant topics of the Horizon Europe programme; or (ii) other relevant European Partnerships.

Proposers should establish the current state of the art and explain how their proposed project goes beyond this.

Proposers should note that the programme funds the activity of researchers to develop the capability, not the required infrastructure and capital equipment, which must be provided from other sources.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 2.1 M€ and has defined an upper limit of 2.6 M€ for this proposal.

EURAMET also expects the EU Contribution to the external funded beneficiaries to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

Any industrial beneficiaries that will receive significant benefit from the results of the proposed project are expected to be beneficiaries without receiving funding or associated partners.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the 'end user' community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the "end user" community (e.g. letters of support) is also encouraged.

You should detail how your proposal's results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Facilitate improved industrial capability, or improved quality of life for European citizens in terms of personal health, protection of the environment and the climate, or energy security,
- Transfer knowledge to the healthcare sector.

You should detail other impacts of your proposed JRP as specified in the document "Guide 4: Writing Joint Research Projects (JRPs)"

You should also detail how your approach to realising the objectives will further the aim of the Metrology Partnership to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work.

Timescale

The project should be of up to 3 years duration.

Additional information

The links provided in this section are only correct at the time of publication up until the end of the Call year.

These references have been provided by EURAMET.

[1] EMN-TLM orientation paper for the EPM Health call 2025

https://metpart.eu/component/edocman/call-2025-orientation-emn-tlm-health/download.html?Itemid=0

[2] EU IVD regulation (Regulation (EU) 2017/746)

https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0746