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

Selected Research Topic number: **SRT-h02**
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Title: Metrology for molecular Measurable Residual Disease (MRD) testing in cancer and precision medicine

Abstract

Advances in genomics are transforming cancer care and enabling molecular Measurable Residual Disease (MRD) testing to quantify residual cancer, previously undetectable by conventional methods. This has improved patient outcomes and digital health models by predicting relapse, and enabling personalisation, optimisation, and monitoring of treatment strategies. However, data quality and comparability are reduced or lacking due to the variability of data, metrology frameworks and standards. Therefore, the establishment of a reference measurement system is required to improve accuracy, comparability, and SI-traceability of molecular MRD testing to support standardisation and implementation for patient benefit.

Keywords

molecular Minimal/Measurable Residual Disease (MRD), precision medicine, solid and haematological cancer, liquid biopsy, molecular genomic testing, multi-omics, Next Generation Sequencing (NGS), digital PCR (dPCR), AI-driven digital health models, Reference Measurement Systems (RMS), Reference material (RM).

Background to the Metrological Challenges

Cancer deaths in Europe are set to be the leading cause of death by 2035, with an annual economic impact of over 100 billion of euros. Improved prediction of which patients are likely to relapse and detecting and treating recurrence earlier and more effectively is essential for extending patient survival. Molecular Measurable (or minimal) Residual Disease (MRD) testing detects molecular or cellular biomarkers with low levels of disease remaining after primary treatment (which could prompt relapse). MRD data inclusion into AI-driven digital health models is increasingly used to predict and detect recurrence and support personalised disease management and treatment strategies.

Accurate detection and quantification of MRD at the molecular level is highly challenging due to assay sensitivity and robustness. Analytical method performance currently suffers from a lack of standardisation and Reference Measurement Systems (RMS) to establish SI-traceability and support test development, validation, and implementation. These systems should be used in various labs (potentially varying conditions) in order to test the robustness and comparability of the results. Furthermore, Reference materials (RM) are essential components for accurate and traceable measurements and are lacking. Laboratory developed tests (LDTs) and Research Use Only (RUO) assays currently dominate the testing market, with rapid developments in genomic technologies pushing sensitivity ever lower but lacking standards and metrology, hampering confident and reliable implementation.

Molecular MRD testing is primarily used in haematological cancers, but increasingly also in solid cancers thanks to advances in liquid biopsy technologies. Multiple techniques are currently used to detect molecular MRD (e.g. quantitative PCR (qPCR) and digital PCR (dPCR)) and Next Generation Sequencing (NGS) approaches. Such approaches typically detect levels of mutant/reference gene ratios down to 10^{-3} to 10^{-6}. Sensitivity and predictive accuracy are being increased through use of molecular multi-omics panels of tumour-associated alterations such as DNA, RNA, epigenetic and nucleosomal variants, with AI and machine learning models supporting complex data analysis, integration with other patient data and clinical interpretation. At such low levels, the accuracy and reliability of testing is greatly affected by both biological

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(e.g. cancer type and stage), and technical factors such as platform performance and impact of pre-analytical variables.

Molecular MRD levels are expressed as gene target copies per microlitre of blood, or ratio of gene target to a reference sequence, or percentage of cancer-specific cells, depending on the assay. The World Health Organisation (WHO) has established international standards consisting of a reference panel of materials and an International Scale (IS) to support consistent interpretation. Laboratories use this to calibrate assays and establish conversion factors to convert measurements into the IS but the link with the International System of Units (SI) has not yet been established. Equivalent standards do not exist for other haematological cancers, and for solid cancer liquid biopsy-based multi-gene/omics panels standardisation is even less advanced.

The necessary RMS to establish metrological traceability and underpin accuracy and comparability of testing have not been developed, but the critical mass of metrology expertise and metrological capability to support cancer genomics was initiated in the Metrology Partnership project 22HLT06 GenomeMET. This included new SI-traceable Reference Measurement Procedures (RMPs) for quantification of cancer gene variants and genomic RM value assignment methods to support assay validation, Quality Control and Quality Assurance (QC/QA) and External Quality Assessment (EQA), data analysis and Measurement Uncertainty (MU) determination. Therefore, the establishment of a measurement system is required to improve accuracy, comparability, and SI-traceability of molecular MRD testing to support standardisation and implementation for cancer testing and precision medicine.

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 traceable measurement and characterisation of molecular Measurable Residual Disease testing for cancer and precision medicine.

The specific objectives are

1. To develop Reference Measurement Systems for high accuracy molecular Minimal/Measurable Residual Disease quantification in haematological cancers with sensitivity at or below current thresholds (e.g. 10^{-3} to 10^{-5} ratio of mutant gene to reference gene). This should include i) the implementation of SI-traceable Reference Measurement Procedures (e.g. dPCR) for quantification of key molecular MRD biomarkers, ii) inter-laboratory performance assessment, and iii) the development, characterisation, and SI-traceable value assignment of Reference Materials (RMs).
2. To develop metrological approaches to support emerging molecular multi-omics MRD testing in solid tumours using liquid biopsies. This should include i) the development of higher order methods (e.g. NGS and dPCR) for quantification of tumour-associated analytes (e.g. DNA, RNA, epigenetic, nucleosomal and fragmentomic variants) at tumour fractions of <1 % ii) inter-laboratory performance assessment, iii) the development, characterisation, and performance of value assignment of RMs for multi-omics testing, and iv) the evaluation of statistical and AI models for multi-omics data analysis and MRD monitoring using data from clinical samples and methods/materials developed as part of this objective.
3. To develop methods, quality control materials and statistical models to support validation and quality assurance of molecular MRD test procedures and test kits applicable to haematological cancers and solid tumours. This should include i) analytical performance specifications and critical quality control parameters within MRD workflows, including pre-analytical (e.g. nucleic acid extraction), analytical (e.g. Limit of Detection and Quantification) and post-analytical steps (e.g. data quality assessment, Measurement Uncertainty) determination), and bioinformatics/AI model verification, and ii) the development and SI-traceable value assignment of EQA materials to support existing and/or new EQA schemes.
4. To apply metrological means developed in Objectives 1-3 to support European efforts to standardise molecular MRD testing procedures and analytical thresholds for the determination of diagnostic criteria such as remission and relapse in a haematological and/or solid cancer model. This will be done by implementing RMS to support inter-laboratory evaluations of i) testing procedures and linking SI-traceable values to consensus international values, and ii) standardisation of analytical targets and molecular thresholds via collaboration with European initiatives and consortia.

5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (JCTLM, RM producers, molecular MRD IVD developers, cancer therapeutics developers), standards developing organisations (CEN TC 140, ISO TC 212), other stakeholders (EMN TraceLabMed, EMN Mathmet), and end users (e.g. clinical stakeholders, manufacturers of medical and healthcare products).

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. In particular, proposers should outline the achievements of the Metrology Partnership project 22HLT06 GenomeMET and how the proposal will build on it.

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 and diagnostics sectors.

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 Traceability in Laboratory Medicine (TraceLabMed) Orientation paper 2025 Health
https://metpart.eu/component/edocman/call-2025-orientation-emn-tlm-health/download.html?Itemid=0

[2]. EMN Mathmet Orientation paper 2025 Health
https://metpart.eu/component/edocman/call-2025-orientation-emn-mathmet-all/download.html?Itemid=0

[3]. EMN Mathmet Strategic Research Agenda
https://www.euramet.org/research-innovation/metrology-partnership/strategic-research-and-innovation-agendas

[4]. EMN for Advanced Manufacturing Orientation paper 2025 Health
https://metpart.eu/component/edocman/call-2025-orientation-emn-advanced-manu-health/download.html?Itemid=0