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

Selected Research Topic number: **SRT-h04**
Version: 1.0

Title: Advancing standardised biomarker measurements for diagnosis and treatment of neurodegenerative diseases

Abstract

In Europe, the number of people affected by a neurodegenerative disease (NDD) is expected to rise from 14.1 million cases in 2019 to 25 million cases in 2050, placing a significant burden on health and social care. Recent advances in biomarker research have the potential to revolutionise NDD diagnosis and treatment. As biomarker assays become more precise, they can be clinically used for personalised therapies and earlier interventions in NDD. In order to support NDD diagnosis and treatment monitoring the care pathway (from diagnosis to patient care), biomarker assays need to be standardised, traceability chains for emerging biomarkers established, and characterisation of protein conformational states improved, with a global target of the integration of personalised medicine.

Keywords

Neurodegenerative diseases (NDD), biomarkers, certified reference materials (CRMs), In-vitro Diagnostics (IVD), proteinopathies, phosphorylated tau (P-tau), neurofilament light (NfL), Glial Fibrillary Acidic Protein (GFAP)

Background to the Metrological Challenges

As the global population continues to age due to population growth and increasing life expectancy, the prevalence of NDDs is rising at an unprecedented rate. NDD therapeutic interventions are more likely to be successful when administered in the earlier stages of neurodegeneration and when tailored to individual patient needs. Early detection provides a window of opportunity for timely intervention, potentially slowing or halting disease progression before irreversible damage occurs. Blood-based assays for key biomarkers, such as phosphorylated tau (P-tau), and neurofilament light (NfL), represent a breakthrough for early diagnosis by providing affordable and scalable diagnostic solutions. However, currently there is variability in biomarker assay results which affects the reproducibility and comparability of measurements.

Two previous EMPIR projects, 15HLT04 NeuroMET and 18HLT09 NeuroMET2, established traceability chains for NDD biomarkers. The projects did this for the measurement of total tau and alpha-synuclein in cerebrospinal fluid (CSF) and provided evidence for the clinical utility of key biomarkers P-tau and Glial Fibrillary Acidic Protein (GFAP). However, certified reference materials (CRMs) are still lacking for P-tau217, NfL and GFAP. In addition to this, new NDD biomarkers need to be standardised, and validated methods are needed for multi-protein profiling, to simultaneously measure multiple biomarkers, thus helping to discriminate different dementia aetiologies and disease phenotypes.

Equally important is the integration of precision medicine into biomarker research. Neurodegenerative diseases are highly heterogeneous, and a number of factors, including the patient's gender, ethnicity, and genetic profile, affects NDD progression. Tailoring diagnostic and treatment strategies to individual patient differences is essential for optimising patient outcomes. For example, correlating fluid biomarkers with digital cognitive tests or digital biomarkers could offer a more personalised and precise diagnostic approach.

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European Partnership Co-funded by the European Union
METROLOGY PARTNERSHIP EURAMET

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 biomarkers for the diagnosis and treatment of neurodegenerative diseases.

The specific objectives are

1. To establish SI-traceability for in-vitro diagnostics (IVD) test results for target NDD biomarkers P-tau217, NfL and GFAP, with a target measurement uncertainty of less than 15 %. As part of this CRMs for P-tau and NfL, and a prototype CRM for GFAP will be produced, and clinical decision limits for the biomarkers will be defined.
2. To develop an SI-traceable, metrological framework for improving the reliability of IVD assays for novel NDD biomarkers (e.g. neurogranin, TAR DNA-binding protein 43, YKL-40, synucleins). This will include the development of (i) SI-traceable measurement procedures based on liquid chromatography-mass spectrometry (LC-MS), (ii) calibration and quality control materials, and an uncertainty framework for the measurement procedures, and (iii) validated methods for multi-protein profiling in biological fluids.
3. To develop traceable methods for characterising protein conformational states, using model proteins for proteinopathies (i.e. α-synuclein and tau). Methods should include advanced techniques such as chemical cross-linking coupled with mass spectrometry (CX-MS), native mass spectrometry (nMS), and biophysical methods (e.g., circular dichroism, cryo-electron microscopy, Real-Time Quacking Induced Conversion).
4. Using the results of Objectives 1 and 2, to develop screening approaches to monitor NDD progression based on biomarker measurements and digital tests. This will include (i) the integration of personalised medicine (ii) the validation of novel Point-of-Care Tests (POCT) for NDD patients and (ii) the use of digital cognitive tests and/or digital biomarkers. The results of the latter should be compared with validated immunoassay biomarker data.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain, standards developing organisations (ISO/TC 12, ISO/TC 212, ISO/TC 229, ISO/TC 334, ISO/TC 194, VAMAS, the International Federation of Clinical Chemistry and Laboratory Medicine Working Group on Biomarkers of Neurodegenerative Diseases (IFCC-WG-BND), the Global Biomarker Standardization Consortium (GBSC), the Society of CSF analysis and clinical neurochemistry (CSF Society), The Joint Committee for Traceability in Laboratory Medicine (JCTLM) and BIPM's CCQM Working Group on Protein Analysis (PAWG), stakeholders (EMN TaceLabMed, 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 EMPIR projects 15HLT04 NeuroMET and 18HLT09 NeuroMET2, and Metrology Partnership projects 22HLT07 NEuroBioStand and 23FUN06 ProMET and how their proposal will build on those.

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, biopharma 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) Strategic Research Agenda https://www.euramet.org/research-innovation/metrology-partnership/strategic-research-and-innovation-agendas

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