European Partnership on Metrology
Call 2022 – Digital Transformation, Health, Integrated European Metrology, Normative and Research Potential

Selected Research Topic number: **SRT-h09**
Version: 1.0

Title: Metrology for risk assessment and diagnosis of heart diseases

Abstract

With an aging society and changes in lifestyle in modern societies, heart diseases remain a major cause of mortality in the EU with 1.19 million deaths per year. However, the requirement for accurate risk assessment and diagnosis is reliable test results and thus, lacking reference measurement systems (RMSs) to ensure traceability to the SI and comparability to point of care test (POCTs) delivering quasi-continuous results for several cardiac clinical markers both enable their reliable quantification, when linked to the RMSs, and a real-time evaluation which allows a fast and reliable diagnosis of heart diseases. Therefore, this proposal aims to build on the EMN-TLM need for developing reference measurement systems for major heart diseases and this includes lifestyle factors to ensure the results is comparable over space and time.

Keywords

Clinical marker, heart diseases, quantitative diagnostics, structural heterogeneity, multiplexed analysis, biosensors, reference measurement systems, traceability, personal risk factors, person-centred outcome measures

Background to the Metrological Challenges

Heart diseases is still one of the main causes for morbidity and mortality in Europe affecting all European countries and European health care systems. Clinical markers such as apolipoproteins, cTn, BNP and NT-proBNP as well as lifestyle-based factors are used for risk assessment and diagnosis of patients. The European Society of Cardiology (ESC) has introduced guidelines on the prevention, diagnosis, and treatment of heart disease such as acute and chronic heart failure. The EMN-TLM has identified the need for the development of reference measurement systems (RMSs) for such disease since no RMSs exist for these markers to ensure reliable and comparable measurements in clinical laboratories. Furthermore, recent studies indicated up to 27 % of patience with CVD has no standard modifiable cardiovascular risk factors. Therefore, there is the need for testing methods such as multiplexed measurement of apolipoprotein panels to enable better stratification of patients.

It is challenging to define clinically relevant measurand as the proteins or peptides often exists in different forms including genetic polymorphism, posttranslational modifications (PTM) such as glycosylation or phosphorylation, truncation, and degradation after release into the blood stream and therefore, routine methods based on immunoassays can detect these modifications with differing sensitivity. In case of apolipoproteins, especially apo(a) are showing a huge number of genetic variants and resulting mainly in different sizes of the protein leading to different concentrations of Lp(a) particles, which is an important risk factor for CVD. Therefore, the standardisation of those assays is challenging and the definition of the measurand of the appropriate target analyte for the development of RMSs requires collaboration between clinical laboratories, metrologists and instrument manufactures. In addition, the recent development of new NT-proBNP assays prompts the need for additional efforts to produce traceable and commutable standards to ensure harmonisation and standardisation of results where possible.

A POCT, which can already be used in the ambulance delivering quasi-continuous results for the cTnI concentration, would enable the fast determination of the kinetic of the rise and fall of cTnI in blood and, thus, a faster rule-in/rule-out decision at the time of the presentation at the hospital. Therefore, the development of a multiplexed POCT allowing to quantify a number of cardiac clinical markers can assist in the diagnosis of other heart disease.

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Progress has been made in the development of an RMS for cTn within 18HLT10 CardioMet to ensure reliability and long-term stability. A prototype for a biosensor for cTnI based on an immunochemical flow injection assay has been established and successfully tested on blood plasma. However, further work is needed to address the challenges in clinical samples.

Moreover, besides clinical markers lifestyle risk factors also contribute to heart disease such as smoking, unhealthy diet, physical inactivity, harmful use of alcohol and adiposity. However, to date, lifestyle-related risk factors and lack of traceability to metrological references led to risk of incorrect decision of conformity to be assessed. To conclude, earlier and more accurate diagnoses of heart disease result in decreasing mortality and, thus, result in lower health-care costs in the healthcare system.

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 JRP shall focus on the traceable measurement and characterisation of risk assessment and diagnosis of heart diseases to improve patient outcome in cardiac disease.

The specific objectives are

1. To establish reference measurement systems (RMSs) for clinical markers for cardiac diseases based on the guidelines published by the European Society of Cardiology (ESC) for a panel of apolipoproteins, cardiac troponin (cTn) and the brain natriuretic peptides (BNPs). The standardisation activities around NT-proBNP and apolipoproteins should build on the results from the EMPIR project 18HLT10 CardioMet. In addition, to develop a liquid chromatographic mass spectrometry (LC-MS) method for apolipoproteins, which is linked to the RMSs in CardioMet and should be implemented in clinical laboratories specialised on clinical trials and patient diagnosis.
2. To evaluate the benefits of monitoring different forms of the clinical markers in patient samples and their impact on routine methods compared to the reference methods. This includes modifications such as glycosylation and phosphorylation, for example of cTn and NT-proBNP, as well as the natural heterogeneity regarding polymorphism, fragments and variants of BNPs or apolipoprotein apo(a).
3. To support the evaluation and diagnosis in emergency settings such as POCT and symptom-based evaluation by optimising a biosensor for clinical cardiac markers based on the prototype developed in 18HLT10 and including additional relevant clinical biomarkers to allow their simultaneous detection in a multiplexed sensor array. To employ the RMSs developed in 18HLT10 to ensure the traceability of the biosensor's results and develop a metrological framework for the evaluation of patients' symptoms (e.g., shortness of breath, fatigue, or swelling in the legs).
4. To investigate the clinical markers developed in 18HLT10, measurements and RMSs for potential other risk factors such as lifestyle (e.g., physical activity, diet, smoking and alcohol), or genetic risk factors. For lifestyle risk factors, potential RMSs shall include the definitions of the measurands, a measurement system where the human acts as an "instrument" and shall exploit the unique properties of item response theory (IRT) models to enable measurand restitution and the establishment of metrological references.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (European Metrology Network on Traceability in Laboratory Medicine (EMN-TLM), reference laboratories, proficiency testing (PT) providers), standards developing organisations (International Federation of Clinical Chemistry and Laboratory Medicine working group), IFCC-WG), 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.

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 18HLT10 CardioMet and 18HLT09 NeuroMET2 and how their proposal will build on those.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.9 M€ and has defined an upper limit of 2.6 M€ for this project.

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 JRP 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,
- 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 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.

Time-scale

The project should be of up to 3 years duration.