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

Selected Research Topic number: **SRT-h01**
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Title: Metrology for genomic profiling to support early cancer detection and precision medicine

Abstract

Advances in genomics are transforming cancer care, enabling earlier detection, and driving development of targeted diagnostics and therapies (personalised medicine), improving patient outcomes and effectiveness of health systems. The quality and comparability of tumour genomic profiling currently varies significantly and development of the standards and metrology to support the field is in its infancy. Therefore, there is a need for the application of metrological principles and development of methods and materials to improve quality and reproducibility of critical processes within genomic profiling workflows, and reference measurement systems for high accuracy SI-traceable cancer gene measurement to improve comparability and support assay validation as required by the In Vitro Diagnostic Regulation (IVDR).

Keywords

Genomic profiling, early cancer detection, precision medicine, genomic profiling workflows, SI-traceable, cancer gene measurements, IVDR.

Background to the Metrological Challenges

Genomic profiling is transforming the diagnosis and treatment of cancer, enabling earlier detection and more accurate diagnosis and stratification. It is also crucial to the development of targeted therapies, driving a move from a “one-size-fits-all” approach towards personalised medicine (PM) where more effective treatment is tailored to the unique molecular profile of a patient’s disease. Horizon Europe identifies PM as a key priority to improve healthcare and make health systems more cost-effective and sustainable.

As such, access to high quality genomic profiling is just as vital as access to new precision therapies and is essential for successful implementation of PM. The EU Beating Cancer plan recommends implementing genomic profiling for all cancer patients to enable delivery of PM, with initiatives such as “Cancer Diagnostic and Treatment for All” aiming to establish infrastructures needed to embed genomics into routine practice.

However, development of the standards and reference measurement systems (RMS) needed to support genomic profiling which uses rapidly evolving technologies such as Next Generation Sequencing (NGS) comprising complex multi-step workflows susceptible to significant, often disparate, and poorly understood error, are still in their infancy and lagging far behind where they need to be to support the current rapid roll-out of these advanced testing modalities.

This is leading to significant variability in test quality and performance and a lack of comparability as highlighted by inter-laboratory assessments and external quality assessment (EQA) schemes, impacting test reliability and patient care, and is widely recognised as hindering broader implementation of PM. The lack of metrological approaches to support assay validation and demonstrate traceability is also presenting challenges for IVD developers seeking approval under the IVDR and medical laboratories seeking accreditation under ISO 15189 or ISO 17025.

These challenges can be addressed by initiating development of the RMS needed to improve quality, comparability and traceability of genomic profiling workflows by aligning with the scope of the Health call 2022, the TraceLabMed EMN orientation paper (supporting personalised strategies for healthcare with focus on genomics) and the CCQM strategy (2021-2030) (development of strategies to support advanced sequencing capabilities).

In 2017, the FDA (Food and Drug Administration) approved the first NGS IVD (Next Generation Sequencing) for cancer based on a panel of 468 gene variants for targeted therapies. Since then, several similar assays

have been approved at US and EU level. However, approval rate has been slow with regulators (including EMA) still deciding how best to approach these complex profiling assays and calling for appropriate standards and quality controls to streamline the review process.

As a result, many laboratories are using “Research Use Only“ (RUO) assays or in-house developed tests, employing a variety of profiling strategies e.g. gene panels (10 s to >500 variants) or whole genome sequencing and a variety of platforms e.g. short- and long-read sequencing, for multiple applications e.g. early detection, diagnosis and stratification, and as companion diagnostics for approved targeted therapies.

In common to all is the fact that profiling involves complex multi-step processes typically including: specimen processing, nucleic acid (NA) isolation, nucleic acid library preparation, generation of sequence reads, sequence alignment, variant calling and evaluation, all with the potential to introduce significant error. Confidence in the data generated by these workflows needs to be demonstrated and assured, and data needs to be comparable across different assays/laboratories, but metrologically valid approaches to support this are lacking.

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 development of metrology capability in establishing a metrology framework to improve quality and reproducibility of critical processes within genomic profiling workflows, and reference measurement systems for high accuracy SI-traceable cancer gene measurement to improve comparability and support assay validation as required by the IVDR.

The specific objectives are:

1. To develop higher order methods to measure critical Quality Control (QC) parameters within profiling workflows, such as pre-analytical steps (yield (mass (ng) or genome equivalents (N=1))) as well as analytical steps such as yield and uniformity of NGS library preparations. To improve reproducibility, comparability, and quality assurance (QA) of genomic profiling workflows such as Next Generation multiplex PCR and to sequence and develop reference materials for assessing performance of profiling platforms.
2. To develop Reference measurement procedures (RMPs) for high accuracy (Variation coefficients (VCs) <20 %) and SI traceable (to N=1) measurement of key cancer biomarkers by using higher order methods, such as digital PCR (dPCR). To assess performance of RMPs using contrived reference materials (RMs), such as synthetic/cell line derived and clinical matrix materials, and to demonstrate applicability of RMPs for supporting validation of genomic profiling workflows in objective 1.
3. To develop a guidance for measurement uncertainty (MU) determination for genomic profiles using data (from objectives 1 and 2) for assessment of random and systematic errors influencing measurements such as variant allele frequency (vAF) and models e.g., Bayesian statistics to determine confidence intervals for nominal properties (e.g., NA sequence).
4. To assess i) SI-traceable value assignment (using RMPs from objective 2) and MU (using models from objective 3), for genomic reference materials ,and external quality assessment materials in line with ISO 15194, ISO 17511 and JCTLM, ii) to support comparability and traceability of EQA schemes and profiling workflows identified in objective 1, iii) to develop strategies for assessing commutability using 1) synthetic materials, 2) contrived “patient like” genomic RMs and 3) clinical samples carrying key cancer biomarkers.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (via EMN-TLM), standards developing organisations (e.g., CEN TC 140 and ISO TC 212), and end users (e.g., healthcare and medical laboratories, IVD developers, genomics/cancer/pathology institutes, EQA providers, RM producers, instrument/reagent developers, regulators).

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.

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:

- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the medical and health 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.