Title: Measurements for screening and early diagnosis of lung diseases from exhaled breath

Abstract

Lung diseases such as chronic obstructive pulmonary disease (COPD) and lung cancer are the fourth and fifth leading causes of death in the world. Early detection of lung diseases can reduce mortality by 20 %, however currently there are no reliable screening tests for early diagnosis of such lung diseases. The detection of lung cancer and COPD-related biomarkers in exhaled breath is a simple and non-invasive technique with the potential to become a vital tool for such a diagnostic test. However, the lack of standardisation in breath collection and analysis is a major barrier to adoption into clinical practice. This includes the need to develop validated and accurate breath sampling and measurement methods and suitable reference materials in breath relevant matrices and amount fractions. However, the viability, robustness and accuracy of such methods also needs to be demonstrated in a clinical setting.

Keywords

Exhaled breath analysis, lung cancer, chronic obstructive pulmonary disease, biomarkers, real-time analysis

Background to the Metrological Challenges

COPD has low to no potential cure and has been attributed 3.17 million deaths per year by the World Health Organisation. COPD varies considerably from patient to patient, and therefore a method is needed for the identification of patients with a high risk of exacerbation. So far studies using breath analysis i.e. exhaled volatile organic compounds (VOCs) biomarkers from COPD patients have shown the effectiveness of this method to discriminate between early stage patients (with low exacerbation risk) from advanced stage patients, however further work is needed.

Lung cancer is the most commonly diagnosed cancer in the world and is the cause of more than 1 million deaths globally per year. The majority of patients (> 75 %) have advanced disease at the time of diagnosis and are rarely cured. But, if the cancer is identified early before it has become advanced then surgery offers a favourable prognosis. Currently there is a lack of diagnostic screening tests for lung cancer with sufficient sensitivity for use in clinical practice. However, promising results have been reported for the use of breath analysis for diagnosing lung cancer. To date 77 VOCs have been identified as suitable biomarkers of the disease and analysis of VOCs in exhaled breath could be used for screening for the early diagnosis of lung cancer. Breath analysis is relatively simple, non-invasive and painless and has the potential to become a rapid and cost effective diagnostic tool for lung diseases. But in spite of its potential, the current lack of standardised and traceable breath analysis methods has led to significant variations in the VOC profiles and/or amount fractions observed between different studies.

Presently, more than 1000 VOCs have been found in human breath at concentrations ranging from pmol/mol to µmol/mol, which presents a significant measurement challenge for breath analysis and requires sensitive and selective instrumentation. In addition, whilst some biomarkers are definitive, and their presence is indicative of a disease, many are always present in breath and it is only an elevation in their amount fraction that indicates when a disease is present. Thus the ability to accurately relate amount fractions of biomarkers to disease parameters is needed. Currently the most commonly used method for exhaled VOC detection, is gas chromatography mass spectrometry (GC-MS), however GC-MS-based instruments are limited to a laboratory setting, do not allow online sampling and the analysis time is relatively long (tens of minutes). Therefore further research into novel and emerging breath analysis techniques such as electronic noses ('eNose') is needed. Current eNoses are relatively inexpensive, small in sized and easy-to-use, but they lack sensitivity and selectivity, require frequent calibrations and cannot reliably identify individual biomarker compounds.

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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 focus is to develop a measurement infrastructure to facilitate the wide spread clinical uptake of breath analysis to the early diagnosis and disease evolution of lung cancer and chronic obstructive pulmonary disease (COPD).

The specific objectives are

1. To develop and validate standardised methodologies for breath sampling and real-time analysis. For the key biomarkers of lung cancer and COPD, the proposed research should develop standardised sampling methods in line with the 'Task force for breath sampling' from the International Association of Breath Research. These procedures need to be adapted such that each biomarker in question can be sampled in a uniform way. In addition, emerging techniques (e.g., eNoses) should be tested and validated for real-time breath analysis, e.g. in terms of sensitivity, selectivity and limit of detection.

2. To develop and validate primary static and dynamic reference standards in breath relevant matrices at breath relevant amount fractions of key identified biomarkers of lung cancer and COPD. Gravimetric and dynamic reference materials in the range of 1 – 50 nmol/mol with an expanded uncertainty of less than 5 % need to be developed.

3. To demonstrate and validate standardised breath sampling and real-time analysis methodologies in a clinical setting. Clinical trials of the standardised methodologies are essential to demonstrate their viability, robustness and effectiveness. These clinical trials will be performed in collaboration with the medical sector.

4. To facilitate the uptake of the technology and measurement infrastructures developed by the project by the measurement supply chain (accredited laboratories, instrumentation manufacturers), standards developing organisations (ISO, CEN), medical non-profit organisations (European Respiratory Society, American Thoracic Society) and end users (medical practitioners and hospitals, industry) to improve lung cancer survival rates improving quality of life for EU citizens and reducing the financial burden of lung cancer on European economies.

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, 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 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

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

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 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 EMPIR 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.