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Editorial

# Multimodality Approaches to Screening for Lung Cancer

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Despite modest improvements in 1- and 5-year survival lung cancer remains the most common cause of cancer death in the UK [1]. Unfortunately, around 70% of lung cancers are diagnosed at stage III or IV where the options for treatment with curative intent are greatly reduced [1]. Although targeted therapies and immunomodulators are improving life expectancy in advanced disease they have efficacy in only a small proportion of cases and long-term survival remains low.

The detection and treatment of lung cancer at an early stage (I and II) are strongly associated with improved survival – even small increases in tumour size have been shown to be detrimental to long-term survival, leading to the concept that 'millimetres matter' [2]. Many lung cancer clinicians now believe that lung cancer screening programmes are going to be central to identifying early stage disease thereby increasing the opportunity to offer treatment with curative intent.

## Low-dose Computed Tomography Screening

Low-dose computed tomography is currently regarded as the 'gold standard' for lung cancer screening. The ground-breaking US National Lung Screening Trial enrolled 53 454 patients at high risk for lung cancer and compared annual computed tomography scans with an annual chest radiograph [3]. A dramatic 20% reduction in lung cancer-specific mortality was detected; a success echoed in the more recent NELSON study, where computed tomography screening reduced lung cancer mortality by 26% in men and between 39 and 61% in women [4]. The UK Lung Screening trial found that 85% of screen-detected cancers were potentially curable stage I or II disease [5].

Within the UK 'lung health checks' have been trialled in Manchester where a 2016 pilot study specifically targeted screening at current smokers and those of low socioeconomic status [6]; groups often under-represented in clinical trials [7]. Screening took place in the community where respiratory symptoms, spirometry and cancer risk were assessed. Those considered at high lung cancer risk (>1.51% at 6 years) were offered screening. Overall, the prevalence of lung cancer was 3% and 80.4% of detected tumours were stage I or II, representing a significant stage-shift in disease [6]. Follow-up scans a year later identified a lung cancer incidence of 1.6% and 79% of tumours were stage I [8]. These findings have led to the roll out of NHS England targeted lung health checks at 14 pilot sites in 10 schemes across England. Many hope that this feasibility programme will serve as the forerunner of a more widespread systematic low-dose computed tomography screening programme for lung cancer in England [9].

Low-dose computed tomography is not without challenges. Apart from the cost (the NHS England Lung Health Checks programme has a budget of £70 million) [9], a significant proportion of patients will have false-positive scans, some of whom will require invasive investigations to exclude lung cancer. Therefore, one approach to increase the cost-effectiveness of a screening programme might be to pre-screen the population at risk so as to 'enrich' the population who are scanned. This could potentially increase both the feasibility and acceptability of a nationwide screening programme. How might this be done? Ideally a biomarker or a combination of biomarkers that could be applied in the community could address this issue. Currently there are a variety of strategies being evaluated for the earlier detection of lung cancer, including transcriptomics, proteomics and circulating

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tumour cells. Two approaches that are currently undergoing clinical trials are circulating tumour DNA (ctDNA) and exhaled volatile organic compounds (VOCs).

## Circulating Tumour DNA

Cells throughout the body shed DNA into the bloodstream as short fragments of cell-free DNA [10]. When released by tumour cells this is termed ctDNA and can be sampled from the circulation via a blood test. ctDNA has the potential to provide information regarding tumour origin, genetic profile and disease burden [10].

'Liquid biopsy' tests based on ctDNA are commercially available for molecular profiling of advanced lung cancer. In patients with advanced stage disease there can be hundreds of copies of each mutation per millilitre of plasma and this can constitute >10% of the total cell-free DNA. However, in early stage disease, the detection of ctDNA is far more challenging. Most patients will have less than one copy of tumour genome detected per 5 ml plasma [11].

To improve the sensitivity of ctDNA detection, multiple-gene panels that encompass the most frequently mutated genes seen in a tumour have been developed. However, panels including up to 507 genes have shown a sensitivity of less than 50% for the detection of stage I–IIIa lung cancers [12]. To help determine the number of mutations that would be required to detect early cancers studies have used methods that sequence multiple mutations identified in a patient's tumour. A recent study from the TRACERx cohort, analysed 18–25 clonal and subclonal variants in multiplex but detected ctDNA in <50% of lung cancer cases and, crucially for screening, in only 19% of stage I–II lung adenocarcinomas [13].

The combination of ctDNA with the analysis of protein markers seems to improve the sensitivity of disease detection. The addition of an array of protein markers to a ctDNA-based assay improved overall performance and detected around 60% of stage I–III non-small cell lung cancers [14]. The analysis of DNA methylation patterns within the ctDNA may further improve the detection of early stage disease and assist in identifying the anatomic location of tumours through tissue-specific cell death [15–17].

Two additional studies are examining the role of ctDNA for the early detection of lung cancer in the UK. The SUMMIT study [18], supported by GRAIL Inc., aims to recruit 50 000 individuals, half of whom will be at high risk for lung cancer. All participants will donate blood samples and those at high risk for lung cancer will be screened by low-dose computed tomography. ELUSIVE is a recently funded Cancer Research UK [19] programme aiming to combine ctDNA analysis with methylation and other molecular biomarkers to study plasma from a high-risk population of lung cancer survivors to detect either recurrent lung cancer or second primaries. In parallel, this lung cancer-focused study aims to use panels of 100s–1000s of somatic mutations identified in patient tumour samples to improve sensitivity for detecting early or residual disease, to clarify the sensitivity that may be needed for future screening assays.

## Volatile Organic Compounds

VOCs are metabolites generated through (patho)physiological metabolic reactions and are excreted from the body through the breath, skin, urine and faeces. VOCs can directly reflect metabolic alterations associated with the onset and progression of cancer and can be detected as biomarkers in exhaled breath [20,21]. An example of this is the Warburg effect, where there is aberrant activation of glycolysis, resulting in downstream exhaled volatiles [22]. Compared with ctDNA, which is collected by venepuncture, VOCs are actively expelled from cells and the breath and can be collected to pre-concentrate the biomarkers.

Currently, a few proof of concept studies have examined the potential of VOCs in lung cancer diagnosis. Analysing more compounds resulted in increased sensitivity and specificity [21]. The analysis of four VOCs could allow the identification of 52% of samples from lung cancer patients, increasing to 80% upon inclusion of 21 VOCs [23]. In another study, a panel of 30 VOCs was able to distinguish 193 samples from lung cancer patients from 211 controls (who had a normal computed tomography scan of the chest) with a sensitivity of 84.5% and a specificity of 81% [24].

Despite these encouraging findings, the utility of VOCs for lung cancer detection and screening has been hampered by the lack of large multicentre clinical trials allowing proper external validation. This is linked to a considerable variation in the study design, collection method, VOC analysis technology, patient characteristics and end points, making meta-analysis challenging [21]. A recent European Respiratory Society Taskforce has published guidelines on VOC collection to aid uniformity across studies which will hopefully aid the design of future studies [25].

The LUCID study, funded by the NIHR and Owlstone Medical [26], is an ongoing multicentre study that aims to recruit up to 4000 individuals in the UK with suspected lung cancer to identify a cancer-specific breath signature. This study hopes to address many of the aforementioned challenges.

## Multimodality Approaches

Both VOC analysis and ctDNA have considerable potential and show promise for the earlier diagnosis of lung cancer. However, further well-designed clinical trials are needed to clarify the limitations and performance of these approaches for the detection of lung cancer in different populations, and to support their future use in routine screening and earlier diagnosis.

Although one biomarker approach may turn out to have high accuracy when used alone, another strategy would be to use one or more approaches, combined with education, in series. For instance, mathematical modelling has shown that although the positive predictive value of a computed tomography scan of the chest for lung cancer is 3.77%, when combined with breath testing the positive predictive value increased to 7.91% for cases where both

tests were positive (due to the higher specificity of the combined test and the reduction in false-positive results) [24].

Breath and/or blood testing will probably be acceptable to the general public, can be carried out in a familiar community setting and can limit unnecessary exposure to ionising radiation. This would potentially allow the engagement and risk-stratification of those groups who have either been challenging to recruit to screening studies previously or who do not qualify for screening under current criteria. Of late there has been increasing focus on the 10–25% of lung cancers that occur in never smokers [27]. Using a sequential investigation algorithm, ctDNA analysis (including methylation and/or protein biomarkers) and a positive breath test could identify cases where low-dose computed tomography may be effective (see Figure 1).

Clearly, many questions around sensitivity, specificity, positive and negative predictive value of these approaches have to be answered before we can reach this stage, but these are now being investigated. The prospect of a more refined, risk-stratified, cost-effective approach to lung cancer screening may not be too far away.

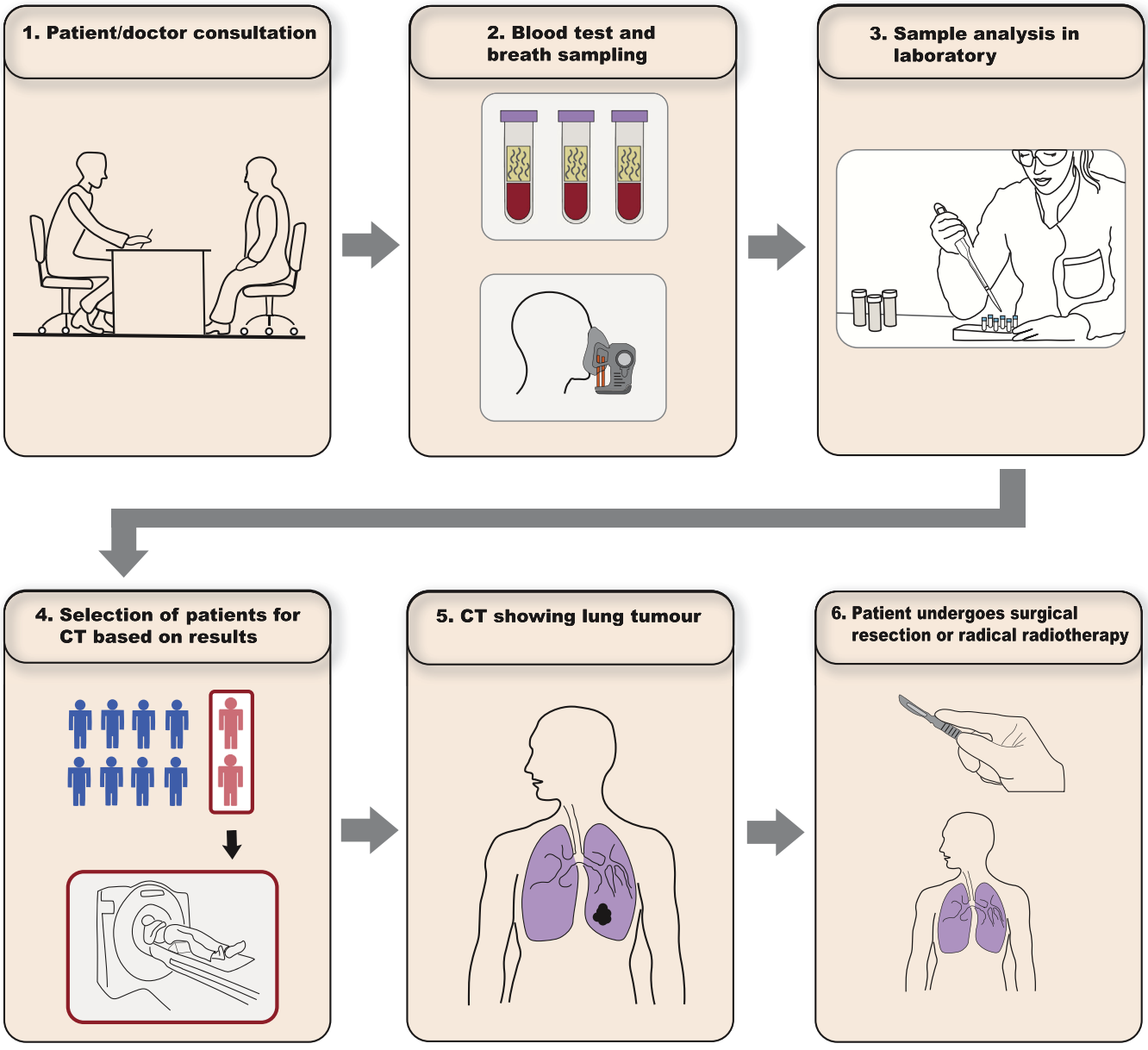


**Fig 1.** Potential pathway for multimodality lung cancer screening. A patient's lung cancer risk factors are assessed and the screening process explained. This leads to blood testing for circulating tumour DNA and other markers, and a non-invasive breath test. Following the analysis of these samples, those at highest risk are selected for a low-dose computed tomography scan. This would enable earlier lung cancer diagnosis and increase the lung cancer resection rate and the potential for radical radiotherapy with cure (illustration by Irena Hudecova).

## Conflict of Interest

N. Rosenfeld is co-founder, shareholder and CSO of Inivata Ltd.


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