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BRIEFING

ctDNA technology in lung cancer: personalised healthcare in action

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Lung cancer is the second most common cancer in the UK after breast cancer. However, while breast cancer survival has improved in recent years, with 80% of patients surviving more than 10 years post diagnosis, for lung cancer the figure is only 5%. New therapies have improved treatment options for some patients, but genetic tests are needed to prescribe these. Circulating tumour (ct) DNA testing (sometimes dubbed 'liquid biopsy') is being offered to improve access to these therapies. What needs to be done to support implementation of ctDNA testing in this group and how can all patients access these services?

Key facts

- In the last few years, more targeted treatments have become available to treat non-small cell lung cancer (NSCLC), such as immunotherapy and therapies known as tyrosine kinase inhibitors (TKIs), which improve progression free survival compared to standard care
- A patient can usually only be prescribed TKIs if a genetic test shows that their tumour has mutations in a gene called *EGFR*
- Up to 40% of patients with advanced or metastatic NSCLC are eligible for tumour genetic testing. However in up to 40% of individuals in this patient sub-group, a genetic test cannot be carried out because there is not enough tumour material or a biopsy is not possible
- By sampling tumour DNA circulating in the blood, ctDNA testing can provide an alternative route to genetic tumour analysis for these patients
- Currently, ctDNA testing cannot be used for primary diagnosis or to determine other information about the lung cancer, such as subtype
- ctDNA testing services that analyse mutations in *EGFR* in NSCLC patients are being offered by a small number of NHS laboratories in England and Wales, with the aim of increasing access to TKIs

How is ctDNA testing used in advanced non-small cell lung cancer?

For advanced NSCLC patients who have tumours with mutations in the *EGFR* gene, a class of drugs called tyrosine kinase inhibitors (TKIs) can improve progression free survival, compared to treatment with standard chemotherapy. Prescribing TKIs to patients without mutations in the *EGFR* gene has been shown not to be beneficial, and so tests to accurately identify patients with and without *EGFR* tumour mutations are an important part of cancer care for this population. In England, the National Institute for Health and Care Excellence (NICE) recommends that TKIs are only prescribed to patients who have a positive genetic test result for *EGFR* mutations in their tumours. However, in up to 40% of advanced or metastatic NSCLC patients this genetic test cannot be performed, either because the biopsy of their tumour yields insufficient tumour material, or because a biopsy cannot be performed due to the inaccessible location of the tumour or the health status of the patient. ctDNA testing provides an alternative route for these patients to have their tumour genetically tested, offering them the opportunity to be considered for TKI treatment if the result is positive.

ctDNA testing for *EGFR* status in NSCLC is currently available in a small number of NHS laboratories in England and Wales. The techniques have been validated and are being used by clinicians to enable previously ineligible patients to receive TKI therapy.

What are the advantages of ctDNA testing in non-small cell lung cancer?

Less invasive

Liquid biopsy (i.e. when ctDNA is extracted from a blood sample and analysed) is a less invasive medical procedure than a solid tumour biopsy, which in lung cancer patients carries some risks, such as lung collapse. Blood tests can also be carried out more frequently throughout treatment, for example to monitor treatment response, or to detect the emergence of resistance to therapy. Patients who require a test to check for the emergence of a resistance mutation to first-line TKIs can have a ctDNA test in the first instance. A solid tumour test is only considered if the liquid biopsy fails.

Increases accessibility

Liquid biopsy improves patient access to genetic testing and optimises the number of patients who could receive therapies that are better suited to treating their tumours.

Quicker results

Liquid biopsy results could, in principle, be obtained faster than solid tumour results, as samples do not need to be sent to a pathology laboratory for processing like solid tumour samples, but could be sent directly to the genetics laboratory. Patients also do not need to wait for a specialist appointment as blood samples can be taken quickly during regular appointments.

Limitations to ctDNA testing in lung cancer

Restricted scope

The ctDNA tests currently in use only detect a defined set of clinically relevant mutations in the *EGFR* gene. They do not for example detect mutations in other genes that could also have an impact on treatment selection or efficiency.

Tumour biology

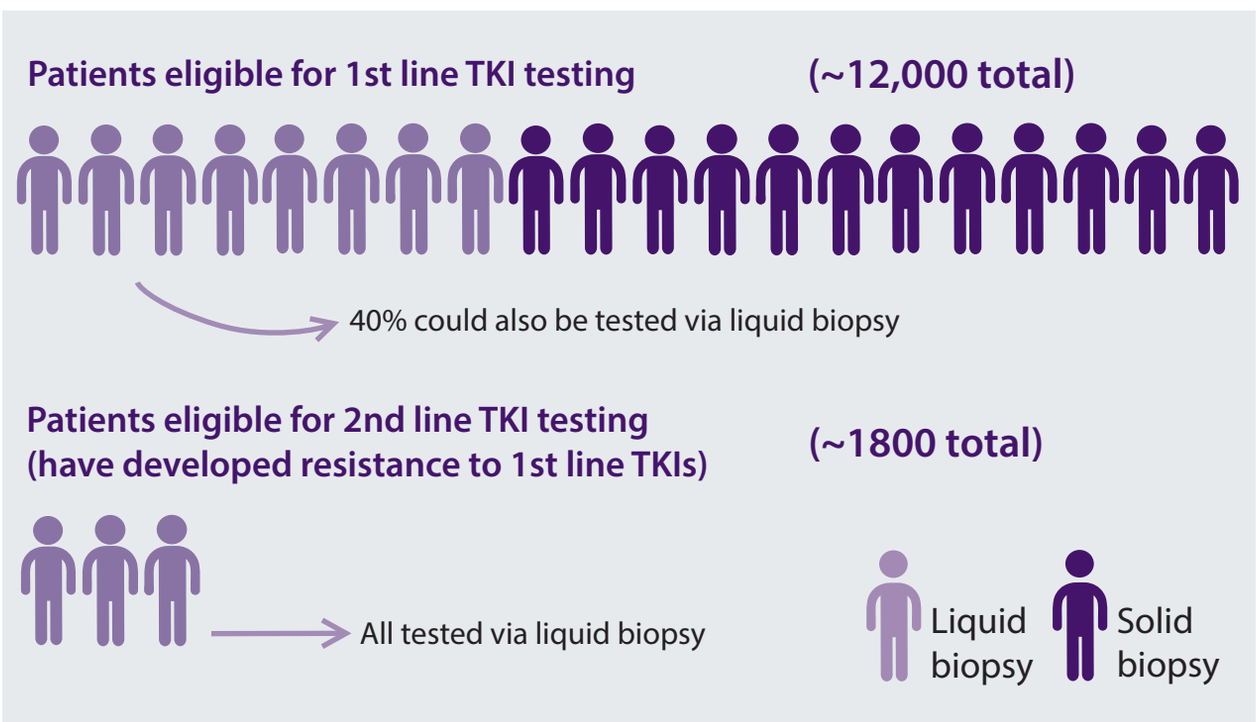
Some patients' tumours may not release enough DNA into the blood to give a reliable result for ctDNA testing. Also, ctDNA testing methods currently in use may not be sensitive enough to give a definitive result in some cases.

Not for primary diagnosis

ctDNA testing is only effective in patients who have already been diagnosed with lung cancer using other methods. It currently cannot be used for diagnosis or to determine other clinical information about the lung cancer, such as subtype. However, a tumour may contain groups of genetically distinct cells: ctDNA can capture this variation (heterogeneity) that could be missed by a solid biopsy from a single site.

How could ctDNA testing improve access to TKIs?

There are around **46,000** cases of lung cancer diagnosed per year in the UK. Of these, around **12,000** have the subtype of advanced NSCLC eligible for testing to determine whether TKIs are a useful treatment.



Supporting implementation of ctDNA testing

What needs to be done to support existing services and expand testing provision such that it is available to all eligible patients regardless of where they live?

Knowledge about genetic testing

Awareness of genetic testing and what it can do varies between different sectors of the health system. Initiatives are needed to engage with clinicians and others in the health system about the benefits of testing for patients, what tests are available and their relative advantages and disadvantages

Communication within the health system

Effective communication between the laboratories, clinicians and healthcare staff who interact with patients is vital, at all levels, to ensure that there is a sufficient awareness about testing and best practice

Sharing knowledge and developing best practice

Sharing knowledge will enable those developing new services to make use of lessons learned, streamlining implementation and facilitating the scale-up of local services to a national level. Further evidence is needed to determine the optimal approach to liquid biopsy testing

Development of test capacity to meet national needs

Capacity needs include support for developing techniques, hiring and / or training staff, equipment and infrastructure

Test payment

Clearer guidance is needed on payment for testing. Currently there is confusion in some laboratories over who should bear the cost of testing - pathology or oncology - and sometimes laboratories carry the cost

ctDNA testing for *EGFR* is clinically useful and addresses an unmet need for patients with advanced NSCLC. While testing currently only benefits a small number of patients, if should be possible to make ctDNA testing routinely available for all eligible NSCLC patients across the NHS. In the future, it is also likely that testing will expand to other cancers and to different parts of the care pathway. Therefore it is important that we learn from the experiences of early adopters of this technology if we are to efficiently and equitably expand services. We held a workshop in Spring 2017 to learn from and share the experiences of the pioneers of this new approach to cancer management.

To find out more, visit:
www.phgfoundation.org/project/ctDNA

PHG Foundation is a health policy think tank with a special focus on how genomics and other emerging health technologies can provide more effective, personalised healthcare

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