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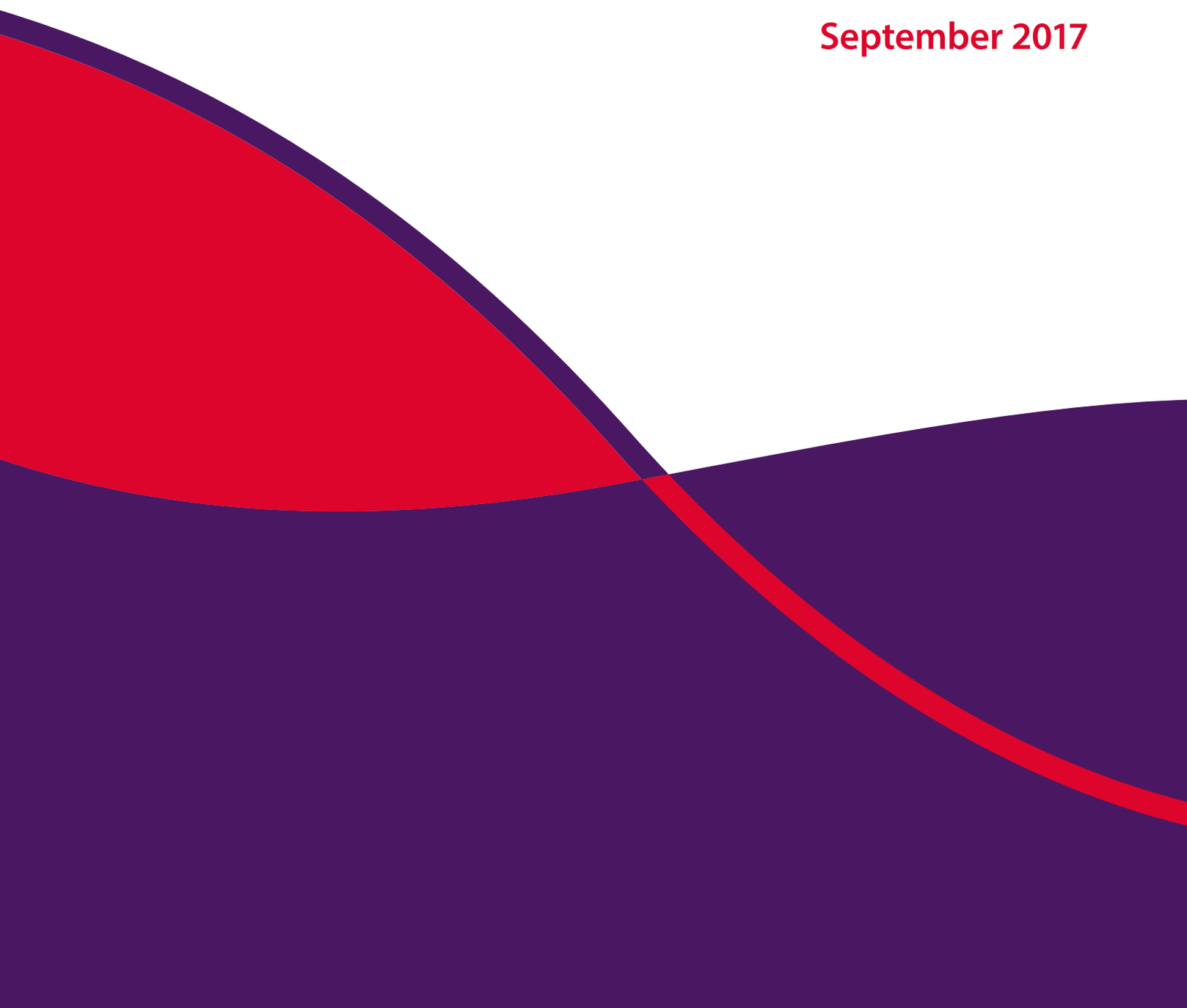
Developing effective ctDNA testing services for lung cancer

September 2017



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Developing effective ctDNA services for lung cancer

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Contents

1. Executive summary

Personalised medicine – a revolution in cancer care?

The era of personalised medicine is upon us, but amid all the promise, and the hype, what does this mean for patients? For patients with cancer, personalised medicine can mean monitoring or clinical intervention based on family history or evidence of inherited susceptibility mutations, or it could mean a therapy that targets tumours with specific genetic mutations. For a sub-set of patients with non-small cell lung cancer (NSCLC) a group of drugs called tyrosine kinase inhibitors (TKIs) treat tumours with mutations in the *EGFR* gene. These patients require a genetic test in order for the clinician to prescribe the therapy. Due to the challenges associated with carrying out a biopsy to collect a solid tumour sample for testing, many patients miss out on genetic testing. In patients for whom biopsies are possible approximately 30% of biopsies fail or do not yield enough material for a genetic test.

Circulating tumour (ct) DNA testing – a pioneering technology to meet clinical need

A new genomic technology, circulating tumour DNA testing, can bridge the gap for these patients. ctDNA testing analyses patient blood samples for mutations in the fragments of tumour DNA found in the circulation. This non-invasive biopsy method has advantages in terms of accessibility and ease of use, allowing patients who would not have received a genetic test from a solid biopsy the chance to have a test carried out using another method.

While there are still technological challenges to overcome in terms of the use of ctDNA technologies, the evidence from clinical trials, combined with the availability of targeted therapies, has been sufficient to see the adoption of ctDNA testing within a small number of NHS laboratories in the UK. Testing is currently used at diagnosis, to determine if a patient's tumour has mutations in *EGFR*, and at progression, to determine if resistance to therapy is caused by an additional mutation in *EGFR* called p.T790M, for which a second line TKI is available.

ctDNA testing is already benefiting some patients with NSCLC; however, this technology is not in widespread use throughout the NHS and not all eligible patients receive testing. The question is how this technology might be delivered in the most effective and equitable way across the health system to ensure that every eligible NSCLC patient receives a ctDNA test as appropriate to their care.

How can the health system maximise the impact of ctDNA testing for NSCLC patients?

A multidisciplinary workshop was held on 7th March 2017 to investigate the current position of NHS ctDNA services for NSCLC patients, with participation from key experts including NHS clinical scientists, clinicians and the commercial sector.

The discussions at the workshop informed the content of this report, which describes the early experiences of some of the laboratories that have pioneered the introduction of this testing into the NHS. It outlines the steps that stakeholders, both internal and external to the health system, will need to take to maximise the impact of this technology for lung cancer patients. Finally, details are provided on emerging possibilities to applying this technology across the care pathways for the management of advanced lung cancer and other cancers.

The workshop also focused on what needs to be done to strengthen and support implementation, improve quality of testing and ensure that more patients receive testing. The key findings are that:

The NHS should consider offering ctDNA testing of *EGFR* in lung cancer to all eligible patients. The evidence of clinical utility demonstrates that ctDNA testing makes a difference to patients, increasing accessibility to targeted therapies. While some improvements are needed to laboratory techniques, these are not a barrier to adoption, since the alternative is that patients miss out on testing, and therefore some will not receive appropriate targeted therapy, which has been assessed as cost-effective treatment for NHS use.

The NHS should use existing ctDNA testing to maximise access to TKIs. To do this, we recommend that the health system support existing services – ctDNA testing at diagnosis and for p.T790M – and establish current services as centres of excellence for ctDNA testing in lung cancer. Clinical guidelines from NICE, or developed by the clinical community, are crucial for raising awareness and providing reassurance to clinicians that these tests have clinical utility and benefit patients. Ongoing NHS service evaluations will provide critical evidence to support wider NHS implementation.

There are lessons that can be learned from existing ctDNA services that will support the wider use of ctDNA tests in future. The laboratory case studies presented demonstrate that there are different paths to take in terms of test development and delivery, which are affected by the resources and infrastructure available in each laboratory. The meeting highlighted the importance of ongoing external quality assurance efforts, which will provide benchmarks on the quality of testing services. Active engagement efforts to inform the health system about ctDNA testing are effective, as demonstrated by the example of the All Wales Medical Genetics Service, but require the laboratories to invest time and resource. Further efforts such as these will be required, however, to improve further engagement within the health system.

Recommendations to support the development of effective ctDNA testing services

Evidence from early adopters of ctDNA technology revealed that whilst testing benefits NSCLC patients in terms of accessing the most appropriate treatment, there are issues that need to be addressed in order to support the implementation of comprehensive, effective and equitable ctDNA testing for NSCLC. Based on the findings, we make seven recommendations to meet these challenges. Establishing a solid foundation now in terms of service development and delivery will be an investment for the future, when more uses of this technology are likely to become available.

- Healthcare commissioners should formally consider the provision of ctDNA services in lung cancer and improve and strengthen current service provision
- Ongoing service evaluation is required to ensure that the health system has the appropriate information for further implementation
- Laboratory websites should include up-to-date and clear electronic referral information and resources, including testing information, costs and logistics
- Engagement about ctDNA testing can take place within the multidisciplinary team (MDT) – ideally via an individual who can act as a point of contact for queries and information. This person could be a clinician, clinical scientist or a pathologist
- Clinical guidelines on the use of ctDNA testing in NSCLC should be developed
- Service establishment and validation should be supported, by and within the health system, by promotion of available funding, promotion of test funding structures, linking of test development into accelerated access of technologies and support of collaborative test development
- NHS England should consider how patients can have improved access to funded targeted therapies and take steps through policy development to ensure that the health system is better prepared to implement targeted therapies when commissioned

2. Personalised medicine in cancer

Cancer care is changing. Over the past 15 years or so there has been an increase in what is termed personalised medicine, whereby interventions are targeted at specific groups of patients based on genetic, physiological or other clinical factors. In cancer care, a personalised therapy does not just refer to a drug that targets a tumour with a particular genetic make-up, but also to targeted screening based on family history or other risk factors, preventive interventions based on genetic risk, or therapeutic approaches that take into account a patient's predicted prognosis.

These targeted approaches can help to bring higher-risk patients into the treatment pathway sooner, sparing them more invasive treatment later on, or aim to benefit patients by prescribing treatments that are more specific to their needs and increase overall- or progression-free survival with fewer side effects.

While targeted approaches to cancer care have contributed to much improved breast cancer survival rates (see Box 1), other cancers, such as those affecting the lung, have not benefited to the same extent.

Box 1. Targeted approaches to breast cancer

The breast cancer drug Herceptin, one of the first-approved targeted cancer drugs, is prescribed to women with *HER2* positive cancer and has improved overall and progression-free survival compared to routine chemotherapy. Also in breast cancer, the OncotypeDx panel test examines the activity of 16 breast cancer associated genes in women with ER+/Her2- breast cancer and those with a low risk score can be spared chemotherapy and its associated side-effects, receiving hormone therapy only. Greater cancer awareness and targeted approaches such as earlier detection, improved surgery, radiotherapy and chemotherapy, have raised the breast cancer survival rate from 4 in 10 in the 1970s to 8 in 10 today.

2.1. Lung cancer – area of unmet clinical need

Lung cancer is the second most common cancer in the UK, after breast cancer, with nearly 47,000 cases diagnosed and around 36,000 deaths per year[1]. Despite progress made in diagnostics, surgical techniques, drug regimens and radiotherapy, only 5% of lung cancer patients survive for 10 years or more post-diagnosis, a figure that has remained relatively constant for the past 40 years.

There are a variety of reasons for this, the main ones being:

- **Late diagnosis**: 75% of patients are diagnosed with stage III or stage IV cancer – that is, cancer that has advanced from its original site into the surrounding tissue, or has metastasised (spread) to other parts of the body
- **Comorbidities:** these present a challenge when treating this patient population. Smoking is implicated in nearly 90% of lung cancer cases, which can cause additional health problems such as chronic obstructive pulmonary disease (COPD) and cardiovascular disease. Taking these comorbidities into consideration when treating lung cancer patients will have an impact on treatment selection

It is clear that a range of clinical approaches will be needed to improve lung cancer survival. Improved strategies for early detection will play a role, but also incremental improvements in and access to the treatments that clinicians already have at their disposal.

Diagnosing and characterising lung cancer

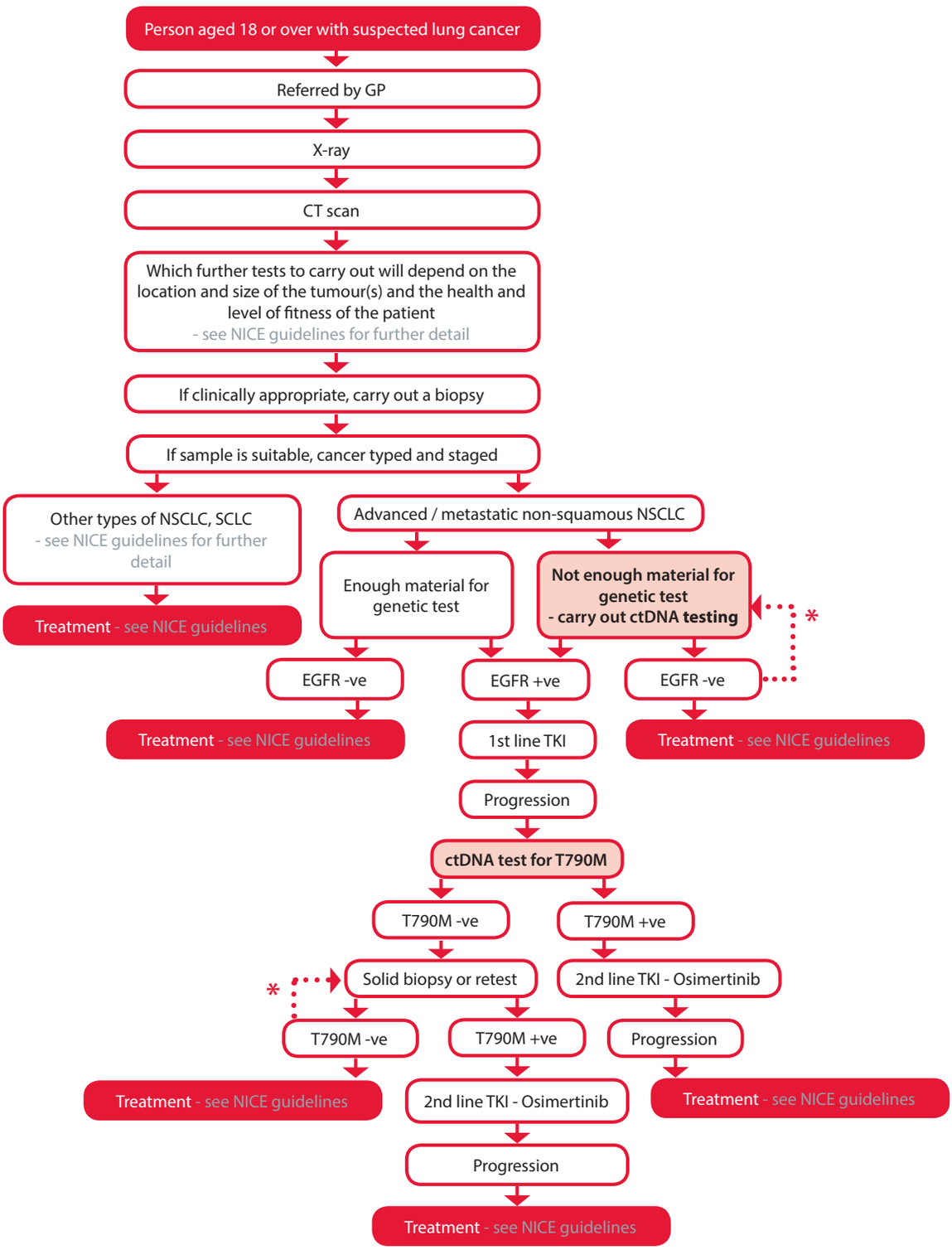
Patients with suspected lung cancer symptoms are referred by their GP for an X-ray (Figure 1). If lung cancer is suspected after the X-ray, the patient is referred to a respiratory physician. The patient will have a CT scan to more accurately determine the location of lesions and the results are used to decide what further tests might be needed to accurately diagnose and stage the cancer. What tests are carried out will depend on:

- Location of tumour(s) in the chest and possibly outside the chest
- Size of the tumour(s)
- Health and level of fitness of the patient

A tumour sample is needed for accurate staging and diagnosis. Easily accessible and small tumours are usually surgically resected – most commonly in patients with stage I or II cancer (see Table 1). Alternatively a sample can be taken using a CT-guided needle biopsy through the chest wall, or a bronchial biopsy if a tumour is more centrally located in the lung. If the tumour site is unsuitable or inaccessible for biopsy or the patient cannot tolerate a biopsy for health reasons, then sputum cytology will be attempted.

If a suitable sample is collected through any of these methods, the pathology laboratory will prepare samples – solid tumour samples will be fixed in formalin and embedded in a paraffin block (FFPE). The type (Figure 2) and stage of the cancer will be determined by examining the characteristics of the cells in the sample. If the tumour is of a type potentially suitable for targeted treatments, then further biochemical or genetic tests will be carried out on the sample. The clinical team will use this information to plan treatment. While FFPE blocks have historically been an effective way of preserving and storing tumour samples, this procedure can affect the quantity and quality of DNA extracted from the tissue sample. This has a major impact on successful whole genome sequencing (WGS) and as such, the 100,000 Genomes Project is implementing pathways to collect fresh frozen tumour samples to preserve DNA for genomic testing, and also working on improved 'genomic friendly' tissue handling protocols to provide high quality DNA samples from FFPE tissue samples.

Figure 1. Example lung cancer patient pathway showing where ctDNA testing could be used



This pathway is based on the comprehensive pathways for lung cancer available from NICE (pathways.nice.org.uk/pathways/lung-cancer) amended to show where ctDNA testing could have an impact on patient care.

*Testing could be repeated at this stage however guidelines are required on the use of repeat ctDNA testing (see page 45).

Challenge in diagnosis - biopsy failure

Biposy failure is one barrier to accurately subtyping lung cancer. In some patients, due to their state of health or due to tumour location, it is not possible to collect a tissue sample. In other patients, a biopsy is carried out but there is only enough tissue for a diagnosis and not enough tissue for further biochemical or genetic tests that could help the clinical team to personalise treatment. These issues mean that approximately 30% of biopsies are classified as 'failed', restricting patient access to the tests needed to determine if targeted therapies are suitable for their cancer.

Figure 2. Subtypes of lung cancer[1, 2]

87%

Non-small cell lung cancer

Adenocarcinoma, which develops from the cells that make mucus in the lining of the airways and is the most common type of primary lung cancer. It often develops in outer parts of the lung and grows more slowly than other types of lung cancer. It is the most common type of lung cancer diagnosed in non-smokers (approximately 40% total lung cancer cases)

Squamous cell cancer, which develops from the epithelial cells that line the airways often in a central position and near a main bronchus (airway), and is often caused by smoking (25-30% total lung cancer cases)

Large cell carcinoma, a quick-growing cancer so-called because the cells look large and rounded under a microscope and which can appear in any part of the lung (10-15% total lung cancer cases)

12%

Small cell lung cancer

Usually caused by smoking and rarely develops in someone who has never smoked

>1%

Rare carcinoid tumours

Start in hormone producing cells

Table 1: Summary of lung cancer disease stage, treatment and prognosis

Disease stage*	Non-small cell lung cancer	Small cell lung cancer
I and II 20.3% cases	Thermal ablation, radiotherapy. Surgery is the gold standard	Radiotherapy, surgery
Prognosis	40–70% survive 5 years (stage I) 25–45% survive 5 years (stage II)	20–40% survive 5 years (stage I and II)
III 18.6% cases	Multimodality treatment. Surgery, chemotherapy, some radiotherapy	No targeted treatment. Chemotherapy and brain radiotherapy
Prognosis	~20% survive 5 years	10–15% survive 5 years
IV 47.3% cases	Chemotherapy, targeted therapy, radiotherapy, supportive care. Palliative care	Chemotherapy: etoposide and platinum. Prophylactic brain radiotherapy
Prognosis	Chemotherapy: 6–12 months Median Overall Survival (MOS) Targeted therapy (TKIs): 2 year MOS; 2–13% survive 5 years	Chemotherapy: 6–12 months MOS; radiotherapy or supportive care can add 2 months. 1% survive 5 years

*13.8% cases are 'stage not known'.
Reference for incidence and survival statistics: www.cancerresearchuk.org/about-cancer/type/lung-cancer/treatment/statistics-and-outlook-for-lung-cancer

Targeted treatments for lung cancer

Non-small cell lung cancer (NSCLC) is a genetically diverse (heterogeneous) disease. Several mutations have been discovered that drive tumour growth. Drugs that target some of these driver mutations have been available on the NHS since 2010 (Table 2). These drugs all demonstrate improved progression-free survival and overall survival compared with standard of care chemotherapy.

Targeted therapies currently available on the NHS target mutations affecting two genes:

- *ALK* – anaplastic lymphoma kinase gene. In 3-5% of NSCLC an *ALK-EML4* fusion drives cancer growth. This fusion is detected using fluorescence *in situ* hybridisation where tumour cells are stained with a specific dye and examined under the microscope
- *EGFR* – epidermal growth factor receptor gene. A number of mutations in *EGFR* are known to drive tumour growth i.e. substitutions, deletions and insertions in exons 18-21. *EGFR* mutations are found in 10-15% of NSCLC patients in European populations. They are more common in females, those of East Asian ethnic origin and in light smokers or those who have never smoked. A genetic test on tumour tissue is required to detect *EGFR* mutations – these are mostly found in non-squamous adenocarcinomas[3] therefore all patients with this type of cancer should be tested

Table 2: Targeted lung cancer drugs currently available on the NHS in England

Drug	Targeted mutation
Crizotinib (Xalkori), ceritinib (Zykadia)	*ALK* fusion – blocks overactive anaplastic lymphoma kinase. Ceritinib is an option for patients whose cancers have stopped responding to crizotinib
Geftitinib (Iressa), erlotinib (Tarceva) First generation tyrosine kinase inhibitors (TKIs)	Target first line mutations in *EGFR*
Afatinib (Giotrif) Second generation TKI	Target first line mutations in *EGFR*
Osimertinib (Tagrisso) Third generation TKI	Targets cancers previously treated with 1st/2nd generation TKIs that have developed resistance due to the p.T790M mutation in *EGFR*

Why prescribe a TKI?

Patients with *EGFR*-positive NSCLC have a better response rate on first line tyrosine kinase inhibitors TKIs, (targeted lung cancer drugs) than on standard of care chemotherapy, while *EGFR*-negative patients have a worse response on TKIs compared to chemotherapy[4]. *EGFR*-positive NSCLC patients taking TKIs have a median overall survival of two years, which is an improvement on 6-12 months overall survival for these patients on chemotherapy. TKI drugs have further advantages over chemotherapy: they are taken as a tablet, once a day, so patients do not need to come into hospital for treatment and they have fewer side effects.

2.2 ctDNA testing - improving access to targeted therapies

As *EGFR* mutation negative patients do worse on TKIs than on chemotherapy it is not possible for a clinician to prescribe TKIs without a genetic test. Therefore it is vital that clinical teams, and patients, have access to accurate and reliable genetic testing.

However, as outlined above, a significant proportion of tumour biopsies fail. A recently developed and validated technology, circulating tumour (ct) DNA testing, often known as liquid biopsy, can be used as an alternative to solid tumour biopsy testing and can increase patient accessibility to *EGFR* genetic testing and TKI treatment.

Clinicians require a genetic test on a tumour sample in order to prescribe TKIs (targeted lung cancer treatment). ctDNA testing gives an alternative to solid tumour biopsy testing and increases patient access to *EGFR* testing and TKI treatment

This form of testing is not currently available to test for *ALK* fusions. While ctDNA analysis has been used to detect *ALK* fusions in patient studies, it is technically more challenging and yet not ready for use in clinical practice[5].

What is cell free (cf) and circulating tumour (ct) DNA?

It has been known since the 1940s that fragments of cell free (cf) nucleic acids can be found in the bloodstream of healthy individuals[6]. This DNA comes from healthy cells in the body, mostly haematopoietic (blood and immune) cells found in circulation or in the bone marrow, that have died due to the body's natural process of programmed cell death (apoptosis)[7]. cfDNA levels in the blood also change in specific clinical circumstances – in pregnant women cfDNA of fetal origin (cffDNA) can be detected in the maternal bloodstream and DNA from tumours can be detected in the bloodstream of cancer patients (Box 2).

The first application of testing to detect and characterise cfDNA in clinical practice occurred in fetal medicine. Cell-free fetal DNA was first identified in maternal plasma in 1997[8] and is detectable from around eight weeks gestation; at around 21 weeks gestation, the percentage of cfDNA in the mother's blood stream that comes from the foetus has risen to around 10%, increasing steadily thereafter as the pregnancy progresses[9]. Non-invasive prenatal testing (NIPT) for aneuploidies (e.g. Down's syndrome) was first shown in 2007[10] and NIPT is now available in many countries, including on the NHS from 2018[11], demonstrating that testing to detect cfDNA is deliverable in a clinical setting.

Researchers first reported the presence of raised cfDNA in the serum of patients with cancer in 1977[12], suggesting that DNA from tumours also makes its way into the circulation. Tumour cells release fragments of DNA, typically 160-180 base pairs in length, into the patient's bloodstream via a variety of mechanisms, such as secretion, apoptosis or necrosis (cell death resulting from injury or damage)[13]. Circulating tumour (ct) DNA differs from cfDNA in that it reflects the genetic makeup of the tumour and as such is an alternative source of tumour genetic material to that extracted from solid tumour samples. Tests to detect ctDNA took longer to develop than those for cffDNA since the total percentage of DNA in the blood that comes from a tumour and contains a detectable mutation can be much lower – down to 0.01%, or fewer than 10 mutant DNA fragments per ml blood[14] – meaning that more sensitive methods needed to be developed to reliably detect it.

Box 2. Types of cell free circulating DNA

Cell free DNA (cfDNA) - DNA from healthy cells in the body, found in the bloodstream

Cell free fetal DNA (cffDNA) - DNA from the foetus (specifically cells in the placenta) found in the bloodstream of pregnant women, in addition to maternal cfDNA. Typically over 10% of the total DNA in circulation during pregnancy

Circulating tumour DNA (ctDNA) - DNA from tumours found in the bloodstream of cancer patients, in addition to cfDNA from the patient's healthy cells. Typically 0.01-10% of the total DNA in circulation

2.3. Uses of ctDNA testing in medicine

Circulating tumour DNA testing (liquid biopsy) is an alternative method to solid tumour testing for monitoring the common mutations of tumours. There are a range of possible uses of ctDNA tests in clinical care, which include:

- **Diagnosis or early detection**

  ctDNA tests could potentially be used in screening programmes to detect early disease in asymptomatic patients or to diagnose those with suspected cancer

- **Treatment selection**

  The availability of therapies that target tumours with particular characteristics means accurate tests are needed to determine which therapies are suitable for which patients. Liquid biopsies can be used in situations when a solid tumour sample is not available

ctDNA testing can also be used in clinical scenarios where solid tumour biopsy testing is impractical or clinically challenging, if not impossible:

- **Monitoring response to treatment**

  Once treatment has started, regular ctDNA testing could be used to monitor treatment response. It has been shown that changes in ctDNA levels in patients who have been monitored during treatment correlate with their tumours' response to treatment[14, 15]. For patients on targeted therapies, ctDNA can be monitored for emergence of resistance mutations

- **Monitoring relapse after treatment with curative intent**

  Once a patient has had surgery or other treatment with curative intent, there is always the question of whether any residual disease remains. ctDNA tests can be used to monitor patients to detect relapse or if all of the tumour was removed by the initial treatment

Extensive progress has been made in the development of ctDNA tests which are now being used in clinical practice to inform treatment decisions. Many technical and biological challenges remain, however, which are discussed in chapter 5.

3. ctDNA testing in lung cancer in the NHS

ctDNA testing services for lung cancer are being delivered by a small number of NHS laboratories in the UK. While the development of these services is a positive advance, they are not being used to their full potential and a proportion of eligible patients are not receiving testing. This report considers three key questions / challenges that must be addressed if the NHS is to capitalise on the work of these early pioneering services to harness the benefits of ctDNA testing technology for patients:

- Should the NHS offer ctDNA testing of *EGFR* in lung cancer to all eligible patients?
- How should the NHS use ctDNA testing to maximise access to TKIs?
- What lessons can be learned from existing ctDNA services to support the wider use of ctDNA tests in the future?

3.1. Drivers for the development of ctDNA testing services in the UK

For patients with NSCLC, ctDNA tests are a viable alternative for determining *EGFR* mutation status. There are several points along the patient pathway where ctDNA testing could be used to inform treatment decisions (see Figure 1) and a number of factors have contributed to the development of ctDNA testing services in NHS laboratories:

1. **The development of targeted therapies that were approved by NICE for use in lung cancer patients** – gefitinib (2010), erlotinib (2012), afatinib (2014), osimertinib (2016, on the Cancer Drugs Fund in England) (see also Table 2). The development of osimertinib coincided with the development of more sensitive and specific ctDNA tests and the drug information states that plasma or solid tumour testing can be used as a companion diagnostic. In addition, the product information for gefitinib was updated in 2014 to include ctDNA testing as a viable companion diagnostic test. The information for osimertinib also states that plasma or tissue are suitable samples for testing. The information for erlotinib and afatanib state that an *EGFR* mutation test should be carried out, using '*well validated and robust methodology*' – test method or sample type are not specified
2. **Area of unmet clinical need** – patients not having access to tests due to solid biopsy failure (not enough material for a genetic test), or because a biopsy cannot be carried out either for clinical reasons or because the tumour is inaccessible
3. **Advances in pre-analytical and analytical performance of ctDNA tests** – these include increased sensitivity, specificity, reduced cost, and ease of use
4. **Laboratories motivated to launch services** – supported by clinician demand and pharma support

Advantages of liquid biopsy over solid biopsy

- **Minimally invasive** – only needs a blood sample, which can be taken during a regular appointment and does not require specialist staff to carry out. The test can also be easily repeated if necessary
- **Improves accessibility to genetic testing and to targeted therapy**
- **Better captures tumour genetic diversity (heterogeneity)** - particularly if a patient has tumours in multiple sites
- **Cheaper than biopsy -** a biopsy is CT guided and performed by a radiologist. For cost comparison, a ctDNA test costs £170 and a biopsy £1,000 without complications/associated care. However this pathway is unlikely to be cost saving in terms of the overall cost of treating the patient, since liquid biopsy is often used after a failed solid biopsy, as outlined above. Health economic analyses are required to resolve this question
- **Fewer side effects** - blood test avoids the side effects of solid biopsy and potential hospital admission to deal with solid biopsy complications.

What is the current guidance on EGFR *mutation testing in NSCLC?*

NICE guidance

The NICE guidance on lung cancer[16] and the technology appraisals (TA) for TKIs both state that TKIs can be prescribed once a successful genetic test on the tumour has taken place (TA310, TA374, TA192, TA258, TA227, TA416[17]). The guidance refers users to the *EGFR*-TKI diagnostics guidance, DG9[18], for information on how to carry out *EGFR* mutation testing. These state that '… DNA extraction and mutation analysis can be carried out on the biopsy tissue..' and that 'if biopsy tissue is not available, DNA extracted from cytology samples can be used for mutation analysis. Other molecular tests may be performed as clinically indicated.'

In January 2017 a four week consultation took place on transferring DG9 to the 'static guidance' list. In their reply to consultation responses, many of which included comments on plasma testing for *EGFR*, the committee stated that it 'is aware' that plasma samples can be used for ctDNA testing and stated that the Qiagen Therascreen kit and Roche cobas® tests are being considered as subjects of future Medtech innovation briefings.

The TAs for first line TKIs do not specifically state the correct medium for a test, only that a test should take place before a prescription decision is made. In the TA for osimertinib (second line TKI), the cost-benefit analysis provided in the background information includes ctDNA testing, meaning that ctDNA testing could be used to test for the p.T790M mutation, however this is not explicitly stated and is likely to be causing confusion among users.

The Scottish Intercollegiate Guidance Network (SIGN)

The SIGN guidelines for lung cancer (2014) currently only include information on tissue testing for *EGFR*[19]. However, the Scottish Medicines Consortium advice on osimertinib states that: 'Molecular pathology experts advise that eligible patients would be identified using a plasma-based circulating tumour DNA (ctDNA) test. This would be followed by a tissue test (biopsy) in patients with a negative result from ctDNA due to the possibility of false negative results'[20].

The All Wales Medicines Strategy Group (AWMSG)

The AWMSG information on osimertinib says 'Product meets AWMSG exclusion criteria due to NICE appraisal'[21]. Osimertinib is available on the Cancer Drugs Fund (CDF) in England but the CDF is not available in Wales, so patients can access osimertinib via Individual Patient Funding Requests, which fund treatments not routinely provided by NHS Wales.

The Royal College of Pathologists

The Royal College of Pathologists has guidance in the form of datasets for histopathology reporting on cancers and the dataset for lung cancer recommends steps that pathologists can take when handling solid tumour specimens to ensure that enough tissue is left over for a genetic test should one be required. While they do not address the issue of plasma testing, they do recommend, in light of different working practices at different hospitals, that local guidelines are put in place to determine who orders genetic tests[22]. There is therefore an opportunity for guideline development on plasma testing at a local level via the MDT.

International guidelines

The latest international guidelines, from College of American Pathologists, International Association for the Study of Lung Cancer, Association for Molecular Pathology (2013)[23] and a European Working Group (2015)[24] do not address the issue of plasma testing for *EGFR*. Australian recommendations for *EGFR* p.T790M testing in advanced NSCLC state that a plasma sample can be used for testing, followed by a solid biopsy if the test is negative or a repeat liquid biopsy after six weeks[25].

3.2. ctDNA test methods

Measuring levels of ctDNA does present challenges, although advances in sample preparation and sequencing technology are making these easier to manage.

ctDNA forms a small proportion of the total DNA in the circulation, the majority being DNA from healthy cells. This proportion can vary greatly, from less than 0.01%, which pushes the limit of detection of the most sensitive methods at our disposal, to up to 40%[14, 15, 26]. This range is due to factors such as tumour size – for many cancers, more advanced and/or bigger tumours are associated with higher levels of ctDNA[27]. The levels of cf- and ctDNA in the blood can also vary due to time of day, exercise, trauma or infection[28, 29]. Each of these characteristics are not yet fully understood but it is clear from measurements made in patients that ctDNA levels can vary greatly from person to person. Even in advanced disease, the amount of ctDNA present varies greatly between individuals and in some ctDNA cannot be detected, for reasons that are not yet fully understood [27]. These factors can have an effect on the usefulness of a ctDNA test for some patients, but are not a barrier to the use of current ctDNA testing in lung cancer. However, if the potential of ctDNA testing is to be fully exploited, more research into the biology of ctDNA and its release into the bloodstream is needed.

ctDNA has a short half-life, estimated to be approximately between 15 minutes to 2.5 hours[28]. One study estimated a ctDNA half-life of 114 mins in a patient who had surgery to remove their tumour[14]. Until relatively recently this meant that blood samples had to be processed almost immediately after collection. However the development of blood collection tubes containing preservative mean that samples can now be stored for several days at room temperature before analysis, if the sample has been collected correctly.

Options for test development

A range of molecular assay methods can be used to analyse ctDNA (Table 3) and there are a variety of factors that help to determine which path laboratories take to deliver a clinical service – either by developing their own method, or by validating a CE-marked or US Food and Drug Administration approved 'out of the box test' such as the Roche cobas® or Qiagen Therascreen. These factors are:

- **Sensitivity and specificity of the method (Table 4)**
- **Time and infrastructure** – does the laboratory have enough time and/or infrastructural capacity to develop its own test? If not, validating an 'out of the box' test might be a more appropriate choice as it is less time-consuming. The manufacturer develops the test protocol and validating laboratories must ensure that the test is performing to the manufacturer's specifications
- **Does the laboratory have equipment and/or experience in using a technique in another context** e.g. in clinical research? If yes, the laboratory can take advantage of expertise already developed by repurposing existing equipment and methods. Developing their own test is more research and time intensive but does mean the laboratory has complete control over every step of the process and can optimise test development for its specific needs

Table 3: Summary of ctDNA analysis methods

Technique	Limit of detection	Optimal application
Sanger sequencing	>10%	Tumour tissue
Pyrosequencing	10%	Tumour tissue
COLD-PCR and pyro	2%	Tumour tissue
NGS	2%	Tumour tissue
Q-PCR	1%	Tumour tissue
ARMS	0.1%	Tumour tissue
Roche cobas®, Qiagen Therascreen (adapted for ctDNA)	0.1%	ctDNA
ddPCR, BEAMing	0.01%	ctDNA

Adapted from *Liquid biopsies: genotyping circulating tumor DNA*[30]. Limit of detection determines the lower limit of the percentage of mutant DNA that can be detected as a fraction of the cfDNA extracted from the sample.

Table 4: Sensitivity and specificity of selected ctDNA methods for *EGFR* mutations, compared to tissue as a reference standard

Test	Mutation tested	Sensitivity	Specificity	Concordance	Reference
Roche cobas®	Panel of *EGFR* mutations	75%	100%	96%	[31]
Roche cobas®	*EGFR* exon 19 deletion p.L858R mutation p.T790M mutation	82% 87% 73%	97% 97% 67%	- - -	[32]
ddPCR	*EGFR* p.L858R mutation	90%	100%	97%	[32]
ddPCR	p.T790M	71%	83%	74%	[32]
ddPCR	*EGFR* p.L858R mutation	80-82%	95-98%	94%	[33]
BEAMing PCR	p.T790M	81%	58%	-	[32]
Therascreen	Panel of *EGFR* mutations	73%	99%	95%	[31]

All laboratories are striving to provide the best test and external quality assurance (EQA) efforts, currently ongoing, will provide quality benchmarks for testing and provide greater clarity as to which is the best testing method to use in a clinical setting (section 5.2). In the meantime, laboratories have taken a pragmatic approach to accelerate patient access to testing by optimising test development according to available resources and infrastructure. While this may mean relying on a less than maximally sensitive but already validated technique, these efforts mean that laboratories are in a position to offer patients testing and to respond to technology improvements and the results of EQA as and when they arise.

Two commonly used methods in UK laboratories are:

- **The cobas® diagnostics platform**, developed by Roche, provides diagnostic tests for a range of medical conditions. The *EGFR* mutation test v2 identifies 42 mutations in exons 18-21 of the *EGFR* gene and can be used on plasma or tissue samples, giving a result in around four hours. Sample preparation kits are available for both tissue and plasma samples as well as the cobas® z 480 system, a device that prepares samples for PCR and carries out the PCR reaction. Finally the cobas® system provides automated result interpretation and test reporting. This type of system is useful for laboratories that do not have the capacity to develop their own test – everything required is provided and the laboratory only needs to validate the technology to confirm that it is working to the manufacturer's specifications. The disadvantages, according to a study comparing different ctDNA detection technologies, are that digital and BEAMing PCR are more sensitive and better able to detect p.T790M than Roche cobas® or Qiagen Therascreen[32]. The technology is also less flexible, for example laboratories cannot analyse mutations not covered by the test, since any interference with the mutation panel invalidates the test's IVD (*in vitro* diagnostic) status.

- **Digital droplet (dd)PCR** is a technological advance on traditional PCR. The sample under investigation is divided into many smaller samples, for example microwell plates or oil emulsion droplets. An individual PCR reaction takes place in each well or droplet. By dividing the sample up in this way, rare molecules in the sample are more likely to be detected. The number of positive droplets can be counted and thus also gives a measurement of the amount of target DNA in a sample. The advantages of using ddPCR is that it is an accurate and sensitive method and a good choice for the detection of low-concentration ctDNA molecules. The development and use of a ddPCR assay requires a certain level of expertise and requires equipment that is not necessarily standard in most molecular pathology laboratories. This is a time-consuming and resource intensive process for a laboratory. However once established ddPCR techniques are accurate and flexible – for example, new mutations can be added for investigation.

3.3. Why should ctDNA testing be used in lung cancer care in the NHS?

Increased interest and research activity in ctDNA technologies have resulted in the development of ever more sensitive methods that can detect a variety of mutations via a liquid biopsy. The approval of ctDNA tests by the US Food and Drug Administration (FDA) and the European Medicines Agency (CE-marked) have contributed to advancing the use of ctDNA testing in clinical practice and in NSCLC the benefits of ctDNA testing include reduced risks to the patient, ease of sample collection and reduced turn-around times[28, 34] (see also laboratory turnaround times in chapter 4).

While there is more work to be done on the biology of ctDNA and on technology improvement, research studies and clinical trials have demonstrated that ctDNA is an accurate proxy of mutations within a tumour[31, 35]. These studies have also examined the effectiveness of TKIs versus standard of care in eligible patients and the difference in lung cancer patient outcomes in those given a solid tumour test against those given a liquid biopsy test[36].

For example, the ASSESS clinical trial evaluated the 'real-world' performance of ctDNA testing compared to tissue based testing. It showed that mutations were less likely to be picked up by plasma tests due to lower sensitivity of ctDNA testing[31]. However, results from the AURA3 trial showed that patients with positive p.T790M tests did equally well in terms of progression free survival when prescribed osimertinib regardless of whether they had had a plasma or a solid tumour test[36].

Continuing technological improvements in ctDNA tests should improve the lower sensitivity of liquid biopsy compared to solid biopsy. However test sensitivity should also be considered in the context of access: the development of liquid biopsy is improving patient access to genetic testing and therefore to targeted therapy if their tumour has a targetable mutation.

In the UK approximately 12,000 lung cancer patients per year have the type of cancer eligible for a genetic test. Assuming a 30-40% biopsy failure rate, ctDNA testing is now an option for up to 4,800 patients who would otherwise not have had their eligibility for TKI therapy assessed. For patients who have already been prescribed TKIs (approximately 1,800) and who progress on treatment, a ctDNA test is now considered the first line test to determine if the p.T790M resistance mutation is present in the patient's tumour and thus whether the patient is eligible for osimertinib therapy. Clinicians will only consider a solid biopsy to test for p.T790M if the ctDNA test is negative. This reduces the number of patients having another invasive and more expensive solid tumour biopsy, since patients who have a positive p.T790M ctDNA result are spared another biopsy.

In the UK approximately 12,000 lung cancer patients per year have the type of cancer eligible for a genetic test. Assuming a 30-40% biopsy failure rate, ctDNA testing is now an option for up to 4,800 patients who would otherwise not have had their eligibility for TKI therapy assessed

There is currently a significant range of evidence from clinical trials to demonstrate that patients benefit from ctDNA testing in lung cancer. As such the laboratories currently offering testing have assessed the potential benefits to patients as being sufficient to make the investment in service development. While some refinement to techniques is necessary, for example to improve test sensitivity compared to solid tumour testing, ctDNA testing works in patients in whom a result from a solid biopsy is not possible. Formal evaluation of these tests is still needed, however, for example to inform the development of guidelines.

Benefits of offering ctDNA testing of *EGFR* to NSCLC patients

- More patients receive clinically appropriate TKIs
- Improved clinical outcomes. Patients who otherwise might not have been prescribed TKIs can receive them and as a result have improved outcomes in terms of progression-free survival

4. Pioneering ctDNA test provision on the NHS

ctDNA testing for patients with NSCLC is available as an NHS service from a small number of laboratories in England and Wales, either as fully accredited services or as services under development. These laboratories have invested time and resource in developing and validating testing services, working with their clinical colleagues to develop tests in the routine clinical care of NSCLC patients. However testing is not currently available routinely to all NSCLC patients and we need to learn from the experiences of early adopters of this technology if we are to efficiently and equitably expand services.

4.1. How is ctDNA testing being used?

There are currently two situations where ctDNA testing is being used in clinical practice in the UK:

- At diagnosis, when insufficient or no tissue is available for a genetic test a plasma ctDNA test is performed to determine *EGFR* mutation status and whether first line TKIs can be prescribed
- At progression, when a patient taking first line TKIs has clinically progressed a ctDNA test is carried out to determine if the p.T790M resistance mutation is present. If the test fails or is negative, a solid biopsy can be attempted

Here we present cases studies from three of these early adopters outlining how services can be established and what drivers and barriers each laboratory encountered.

The laboratories featured below took a variety of approaches to test development, each making use of a distinct combination of technical capabilities, prior research experience and capacity for in-house test development. We outline early results in terms of initial service provision and what key lessons emerge from these laboratories' experiences.

Table 5: Routine NHS ctDNA testing services

Location	Approximate population coverage
Validated testing services	
All Wales Medical Genetics Service	3 million, also offer services to SW England, potentially another 5.3 million
University Hospitals Birmingham – Queen Elizabeth Hospital	1.1 million
Manchester Centre for Genomic Medicine	2.8 million, up to 5 million in NW England
Royal Marsden/Institute of Cancer Research	4 million, but receives referrals from elsewhere, particularly specialist cases
Leeds Genetics Laboratory, The Leeds Teaching Hospitals NHS Trust. p.T790M only at present	Approximately 4 million
Northern Ireland Molecular Pathology Laboratory (NI-MPL)	1.8 million (population of Northern Ireland)
Royal Surrey Hospital / Berkshire and Surrey Pathology Services	2 million (Surrey and Berkshire)
Under development	
Sheffield Children's NHS Foundation Trust/ Sheffield Diagnostics Service. p.T790M test validated to launch soon, in process of validating cfDNA NGS panel assay	Around 1 million
Clatterbridge Cancer Centre in Liverpool/ Royal Liverpool Hospital	Around 2.5 million in Merseyside and Cheshire
Molecular Malignancy Laboratory, Addenbrooke's Hospital, Cambridge	Approximately 4-5 million in East Anglia
Edinburgh and Lothians Laboratory Medicine. Offering ctDNA testing for p.T790M but service is not currently ISO accredited	Approximately 1.5 million in the region (Scottish population 5.4 million)
Newgene, Newcastle. Working up clinical assay for *EGFR* mutation analysis	Approximately 3 million in North East England and North Cumbria

All the laboratories offer testing to patients within their catchment but also from outside – in theory any NHS clinician who chooses to can send samples for testing to one of these centres.

Case study: Manchester Centre for Genomic Medicine

The Manchester Centre for Genomic Medicine is a leading centre for clinical genomics, employing around 250 staff to deliver genetic testing and counselling to patients. It delivers clinical genetics services (adult and paediatric), biochemical and genetic testing for metabolic disorders, cytogenetics, molecular pathology, specialist cell culture services and bioinformatics services. The Centre also undertakes clinical research and takes part in clinical trials in collaboration with the University of Manchester and other stakeholders. The Centre covers a catchment area of up to 5 million people in North West (NW) England but receives referrals from across the UK – requests for ctDNA testing have been received from Scotland, Newcastle, NW England and London.

Drivers of service provision

The ctDNA service evolved from existing research and clinical trials protocols – the laboratory works closely with the Christie Hospital and was involved in clinical trials research using ctDNA. As such, early technique development was supported by these projects. The drivers for service development came from clinical oncologists and the availability of drugs requiring companion diagnostics.

One of the challenges of setting up the service is that it coincided with a period of intense technology development by companies. When new technologies emerged onto the market, the laboratory assessed their effectiveness relative to the techniques that they were already using. The laboratory was therefore able to implement technological improvements as they became available, however this did require a significant time and investment concentrated in a short period of time. The laboratory was able to absorb test development into their available resources, participation in AstraZeneca-funded clinical trials allowed them to develop testing techniques in this context.

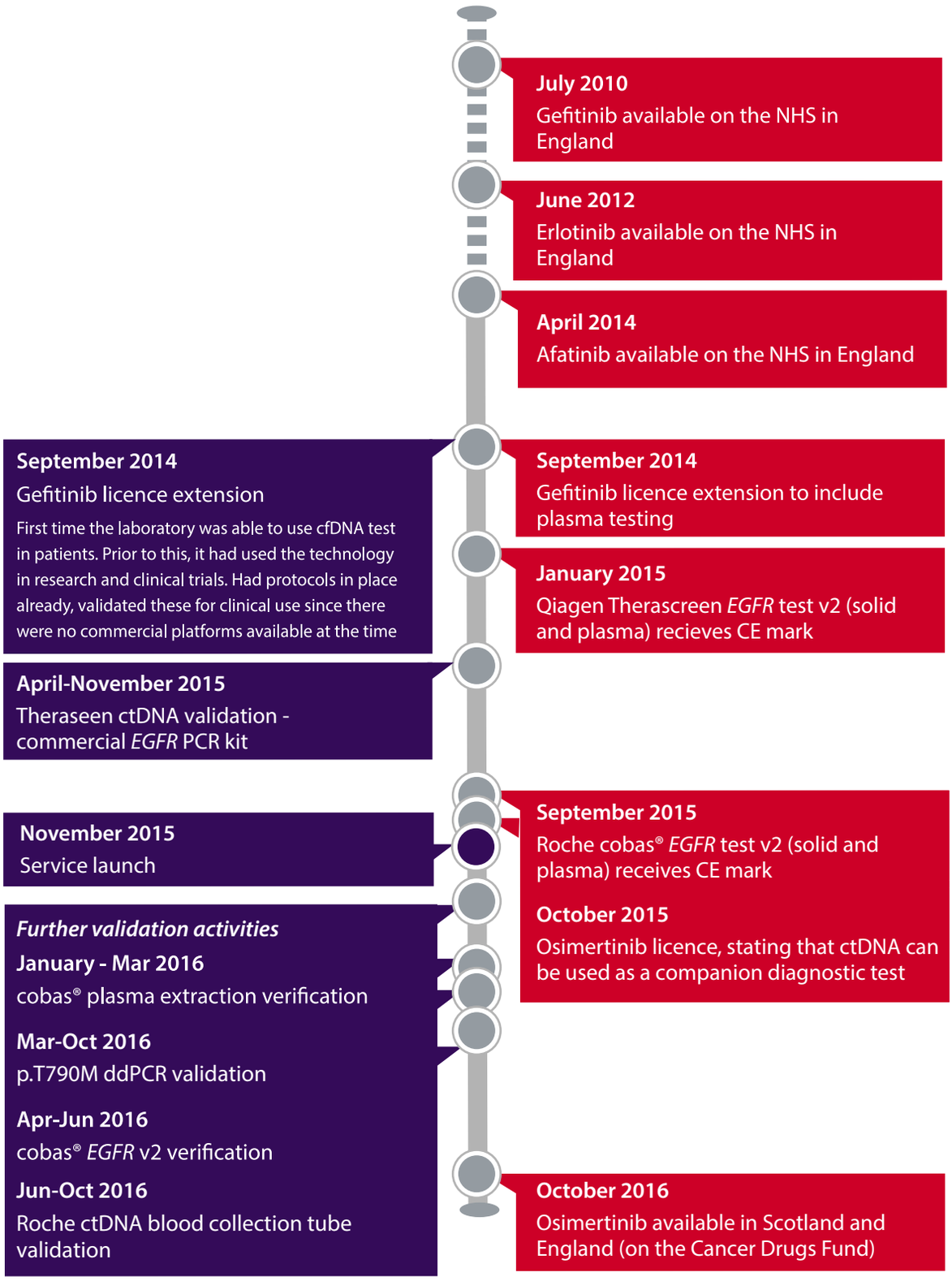
Current service

The current workload for the laboratory is approximately six tests per week for first-line TKI screens and three per week for p.T790M mutations. Plasma tests have a quicker turnaround time from sample collection to test result since blood samples, unlike solid samples, are not sent to the pathology laboratory first before being sent for genetic testing. The turnaround time for plasma is 3.3 working days compared to 5.5 for tissue.

Table 6: Summary of cases analysed and results since service launch (up to March 2017)

	No. samples	Positivity rate
Screens (plasma at primary diagnosis)	101 (16 Therascreen, 85 cobas®)	9.9% (this compares to 11.5% in tissue)
p.T790M	73 (47 samples, 64%, had adequate ctDNA)	34% (in adequate samples). Detection rate depressed by early Therascreen tests and improved following inclusion of ddPCR

Timeline for service development



Case study: University Hospitals Birmingham NHS Foundation Trust – Queen Elizabeth Hospital

The laboratories at Queen Elizabeth Hospital Birmingham (QEHB) offer biochemistry, cellular pathology, haematology, microbiology and transfusion services to University Hospitals Birmingham and external sites, covering a population of approximately 1.1 million people in the greater Birmingham area, extending to 5.7 million in the West Midlands.

The Molecular Pathology Diagnostic Service (MPDS) at QEHB is one of the largest solid tumour genetic-profiling centres in Europe providing a repertoire of tests that are available to both internal and external users. The laboratory has extensive experience in molecular testing of lung cancer and processes more than 300 *EGFR* tissue tests a month, using the validated Roche cobas® platform.

The laboratory first offered early access plasma testing in April 2016 with clinical service launch in October 2016.

Drivers of service provision

Several factors contributed to the laboratory developing a ctDNA testing service:

- The expectation of licencing allowing the testing of ctDNA to allow access to 3rd line TKI (osimertinib)
- Availability of a CE-IVD marked kit, Roche cobas®, for testing
- Complement the current solid tumour testing for *EGFR* performed in the laboratory
- The availability of stabilising tubes improving the logistics around getting blood samples to the laboratory

The Roche cobas® was selected for ctDNA testing as the technology was already available in the laboratory and was already being used for solid tumour EGFR testing. Therefore there were no capital costs involved and the technology was already familiar to laboratory staff. It also allowed the concurrent running of tumour and plasma samples thus offering an efficient testing strategy and removing the need for batching. Both solid and plasma tests cover all of the clinically relevant mutations within *EGFR*. Furthermore, cobas® was the assay used in the trial in which the laboratory had participated so they already had experience of delivering testing in a research context. Test development and service delivery occured using available resources – no additional members of staff were required.

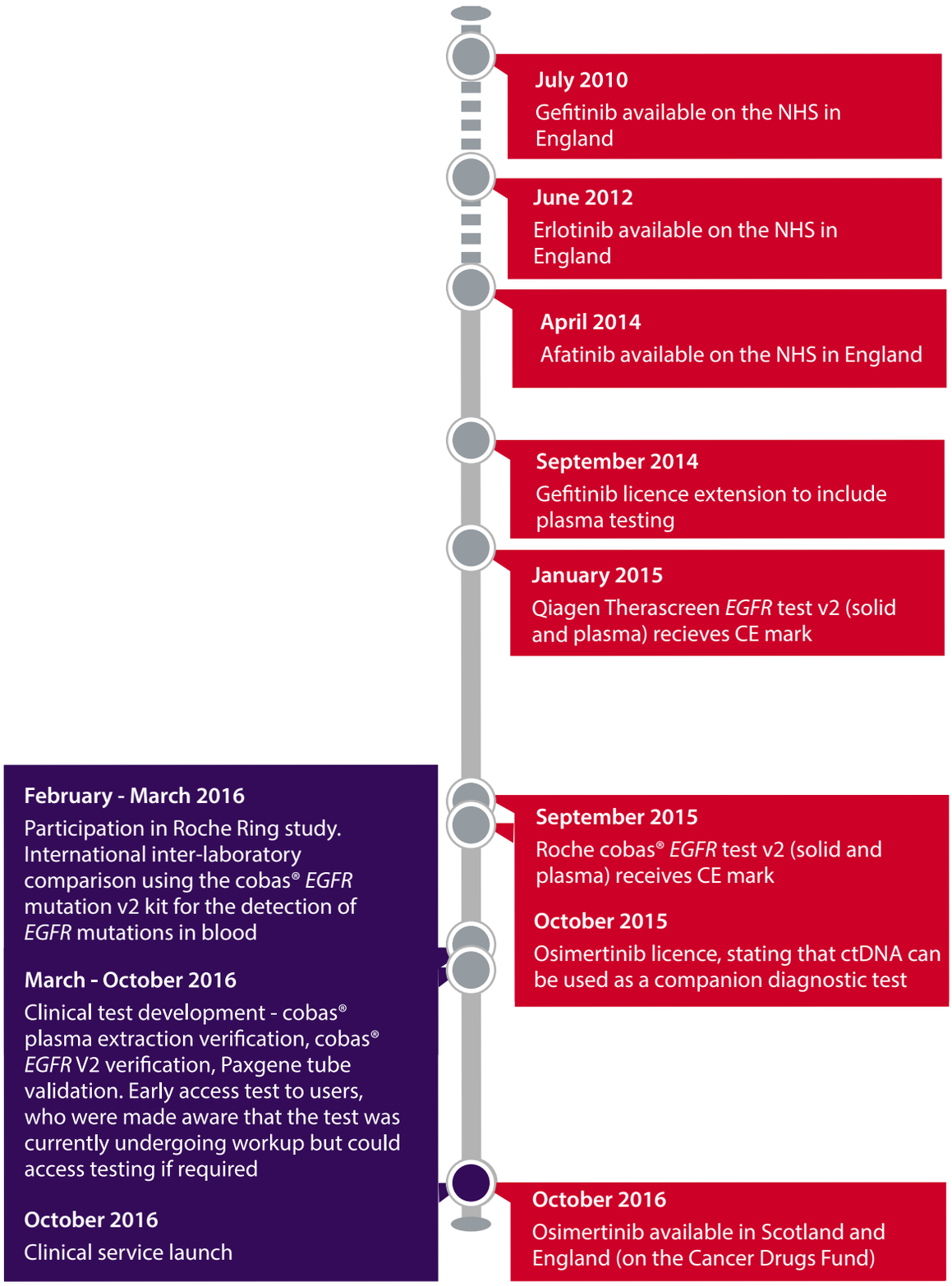
Current service

So far the laboratory has received 308 cases. Inadequate clinical data upon receipt of samples means that classification of some samples was problematic as staging was not available. The data in the table reflects where clinical details were sufficient to categorise the sample. In addition ten patients are undergoing monthly monitoring (range of two to seven repeats received).

Table 7: Summary of cases analysed and results since service launch (up to June 2017)

	No. samples	Positivity rate
Screens (plasma at primary diagnosis)	12	2 (16.5%)
p.T790M	185 (total) of which 104 (original mutation detected)	40 (18.4%) 40 (33.6%), where original mutation detected and hence an indicator that ctDNA level adequate

Timeline for service development



Case study: All Wales Medical Genetics Service

The All Wales Medical Genetics Service (AWMGS) based at the University Hospital of Wales, Cardiff, provides constitutional genetics services, and cancer genetics (solid and haemato-oncology). The service sits within the Directorate of Laboratory Medicine which collectively offers services in cytology, haematology, histopathology, biochemistry and immunology, microbiology and phlebotomy.

The AWMGS provides clinical genetics services for the population of Wales but will also carry out ctDNA testing requests from English hospitals.

Drivers of service provision

The ctDNA testing service was developed over a number of years and relied on a range of individuals – trainees, clinician researchers and clinical scientists – to carry out the work necessary to develop and validate techniques. As outlined below, some of this work was possible due to external funding of staff positions. The laboratory chose ddPCR as its preferred method of analysis due to previous experience of other technologies and the sensitivity of the ddPCR method.

Current service

The patients selected for the clinical validation had been chosen based on a confirmed *EGFR* sensitising mutation result on biopsy within the laboratory. Patients were referred from the Velindre Cancer Centre, Cardiff.

Currently the laboratory sends blood preservative tubes to clinicians when they want to carry out a test. Plasma is stored and batched and there is a ctDNA run twice a week. The number of tests per week fluctuates from roughly two to six samples. Turn around time is less than five working days. The laboratory has received 137 samples from hospitals in Wales and in the south west of England.

Table 8: Summary of number of samples tested and results (as of June 2017)

	Screens (plasma at primary diagnosis)	p.T790M	Total
Within Wales	48	39	87
Outside Wales	13	37	50
Total	61	76	137
Positivity rate	13.11%	22.37%	

Timeline for service development

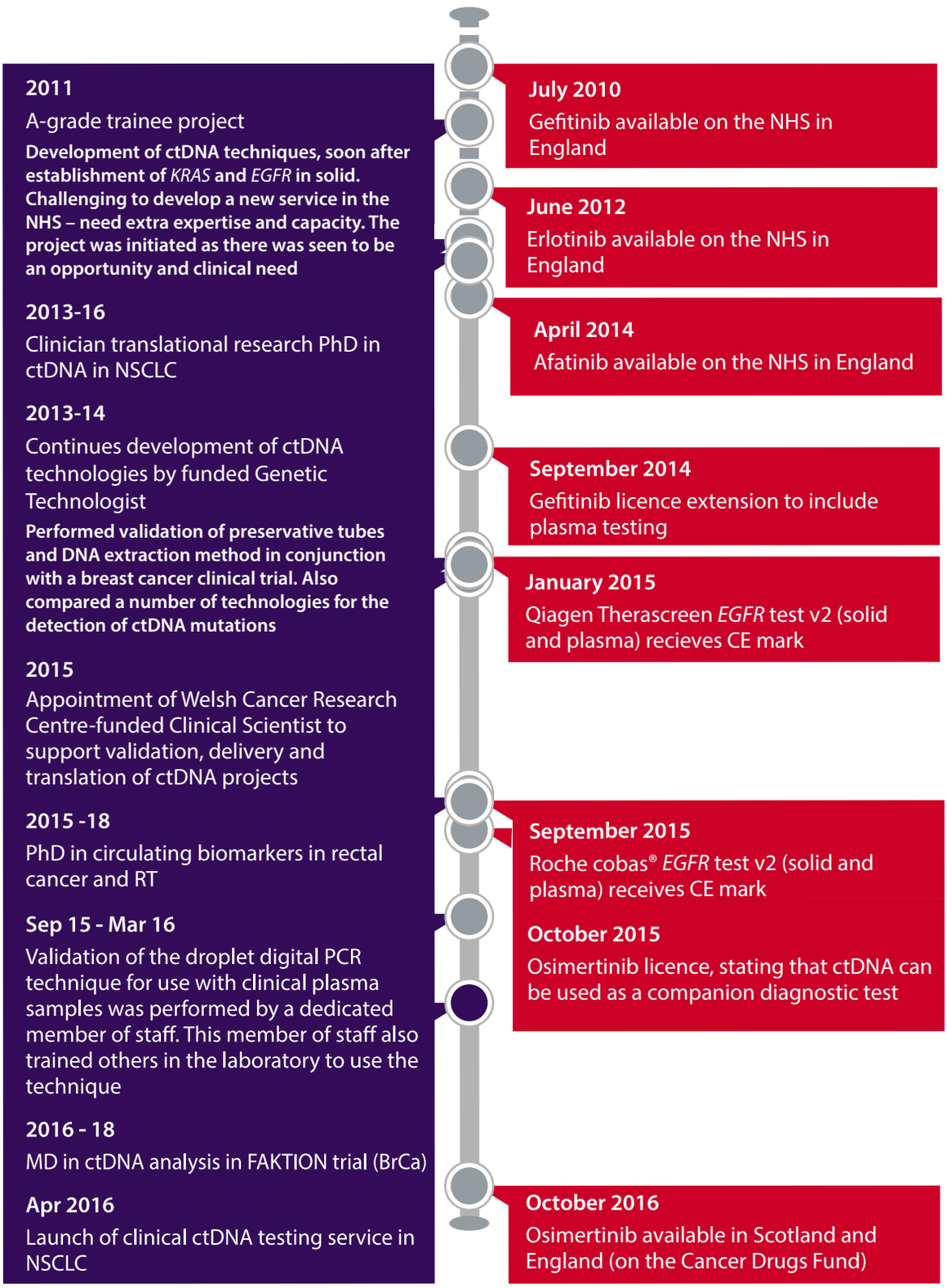


Table 9: Summary of laboratories' ctDNA testing implementation

	Manchester	Birmingham	Cardiff
Collection tubes	Roche cfDNA BCTs	Paxgene	Streck or CellSave
ctDNA extraction method	Roche cfDNA extraction	Roche cfDNA extraction	QIAamp (Qiagen)
Assay method: *EGFR* mutation detection (first line)	cobas® v2 mutation detection (42 *EGFR* mutations)	cobas® v2 mutation detection (42 *EGFR* mutations)	ddPCR
Assay method: p.T790M detection	cobas® v2 mutation detection plus ddPCR	cobas® v2 mutation detection (42 *EGFR* mutations)	ddPCR

4.2. Laboratory accreditation and test validation

All laboratories that deliver medical genetic testing in the UK must be accredited to the ISO15189 standard or be in the process of transitioning to this standard. Accreditation provides assurance to users that a service has been independently evaluated against recognised standards. When implementing new tests, accredited laboratories undergo a process of test validation, an essential and rigorous process to ensure that diagnostic tests meet standards and are fit for purpose, i.e. that when used in the laboratory the test is repeatable, reliable and robust, addresses the clinical question in hand, and has no impact on patient safety. ISO15189 clause 5.5.2 states that: '*The laboratory shall use only validated procedures for confirming that the examination procedures are suitable for intended use*'. While generic guidance is available on validation, laboratories have to develop their own internal guidelines and there is a high degree of professional judgement involved in validating a test. There is a balance to be struck between the accuracy, sensitivity and specificity of methods and ease of use – for example, a laboratory might accept a slightly lower yield for a DNA extraction method if the method is easier to use.

During the process of validating ctDNA tests, laboratories highlighted the importance of excellent communication and collaboration with their clinical colleagues to obtain the patient samples needed. In the case of ctDNA tests, patient blood samples are required before their treatment has started in order to accurately compare the performance of the plasma test with the solid tumour test. Support from clinical teams ensured that samples could be collected from patients at the appropriate point in their clinical journey.

Lessons from current ctDNA service provision

Factors contributing to the successful implementation of ctDNA services:

- **Collaborative working with clinicians to develop services and processes**, driven by clinician demand for services
- **Each laboratory took an approach that worked for them and suited their way of working and expertise** – using the methods that best suited them. This highlights an unanswered question – is there an optimal way of delivering a testing service and is there a best test?

However, laboratories bore the financial and clinical risk. They invested time, money and expertise in developing these services, either absorbing the costs internally or by making use of different external sources of funding. While the laboratories above were able to validate new tests without compromising existing service delivery, financial, infrastructural or logistical constraints can make this a challenge for other laboratories. This could have an impact on future implementation of ctDNA testing services if provision expands when new tests become available.

5. How can the health system maximise the utility of emerging ctDNA services?

Research studies and the development and validation of accredited services by laboratories demonstrate that ctDNA testing can deliver accessible genetic tests to patients with NSCLC in whom solid tumour testing is not possible. The question now is, how can the health system make the most of the pioneering services already established to ensure equitable access to all patients? What are the issues that are having an impact on the ability of laboratories to deliver services and to appropriately expand the reach of services to more patients nationally? What are the outstanding clinical research questions that need to be addressed and what are the areas where the clinical community, the health system and external organisations can work together to optimise the use of current services and build the evidence base, laying stable foundations for future service provision?

5.1. Clinical utility

While clinical trial results and initial results from the laboratories offering testing indicate that ctDNA testing in NSCLC is clinically useful and improves patient access to targeted therapies, there are unresolved questions surrounding the clinical scenarios in which testing can be used and areas for technical improvements.

What are the opportunities for future service improvements?

The ctDNA tests currently used are fit for use in the NHS, however there are a number of opportunities to improve their performance either through technical enhancements or resolution of underlying questions about the biology of ctDNA. Some of these are highlighted below.

Is there a best test for specific clinical circumstances?

Clinical trials have included analyses of different test methods used however this has been in the research context[31]. Ongoing external quality assurance efforts (see section 5.2) will help to address the question of which methods work best in a clinical context, as opposed to in a research context. The question can also be framed in terms of the expertise and resources available in the laboratory, i.e. the best test is that which the clinical laboratory has expertise in using and has validated. However if EQA efforts demonstrate that a test falls below established benchmarks in sensitivity and specificity then laboratories using that test should validate the EQA 'best test'.

Concerns over test sensitivity

Although ctDNA tests are less sensitive than solid tumour tests, this should be considered in the context of how ctDNA testing is providing information for drug treatment – as a second line test, in a situation where a first line test has failed or cannot be attempted. In this situation, lower test sensitivity can be an acceptable compromise compared to not carrying out a test at all. At this stage the key to addressing concerns will be ensuring that clear information is available to clinicians about the limitations of the test, but also how it can benefit patients. These issues are discussed further in section 5.3.

Table 10: What are the implications of reduced ctDNA test sensitivity on test results?

Test result	What does this result mean?	Outcome for the patient
True positive	Patient has *EGFR* mutation, which the test detects	Receives TKI therapy. Improved progression free survival compared to chemotherapy
True negative	Patient does not have *EGFR* mutation, which the test confirms	Receives chemotherapy
False positive	Patient does not have *EGFR* mutation, however test is positive for *EGFR* mutation (specificity issue)	Negative for patient – patients negative for *EGFR* mutation have a worse outcome on TKIs. Want to minimise/avoid this outcome
False negative	Patient does have *EGFR* mutation, however test is negative (sensitivity issue). Could be due to technical test failure or patient not releasing much ctDNA into the blood	Loss of potential benefit to patient as they do not receive TKIs. However will receive chemotherapy. Patient could also be retested if they progress on chemotherapy

In terms of test improvement, the goal with *EGFR* ctDNA testing should be to minimise the false positive rate i.e. optimise specificity even if the trade-off is reduced sensitivity. While false negative results are not ideal for patients, this outcome is not actively harmful.

How to report negative results

ctDNA testing is a new technology and as such there are still some uncertainties over how to distinguish true negative results from false negative results. This presents a challenge for reporting negative results to clinicians. The onus is on laboratories and clinicians familiar with the technology to report back negatives in an understandable way, clearly outlining the implications of a negative result and the options available, if any. Currently, the processes and guidelines are not clear but can be developed over time as service providers and users learn from using testing in a clinical setting. Initially it is appropriate to take a conservative approach to manage negative results – currently, if a patient is being tested for the p.T790M mutation, it is common practice to carry out a solid tumour biopsy if the liquid biopsy is negative and if the patient is a suitable candidate e.g. they are well enough to tolerate the procedure and their tumour(s) is accessible. A strategy employed by the laboratories offering testing is to also re-test patients for their original *EGFR* mutation at the same time as testing for p.T790M, if there is enough DNA: if the original mutation is detected but the p.T790M mutation is not, then this builds confidence in the negative result to p.T790M. An alternative method could be to carry out a repeat test after a set period of time. However, clear guidelines are needed to set out how often and when serial testing can take place. For example, Australian guidelines recommend that p.T790M retesting is an option, after a period of six weeks[25].

Clear guidelines are needed to set out how often and when serial ctDNA testing can take place. For example, Australian guidelines recommend that *T790M* retesting is an option, after a period of six weeks

When to test

Levels of circulating DNA differ according to time of day, exercise levels, obesity or illness, however these need to be better characterised. For patients with cancer, there is still much to learn in terms of how ctDNA levels change during disease progression, for example:

- Is there a better time of day to sample?
- Are there patient or clinical characteristics that correlate with more successful ctDNA tests?
- Is it useful to test before there is clinical or radiological progression, and change treatment accordingly?

It is not yet clear at what point the appearance of ctDNA in the blood indicates a clinically relevant change in a tumour. Clinical trials that use serial testing could help resolve this issue by investigating more deeply the interaction between ctDNA levels, progression of disease and treatment success. For example, the TracerX study used ctDNA testing to profile the evolution of early-stage NSCLC and to monitor 24 patients after surgery. Using ctDNA testing the team identified 90% of the patients who went on to relapse, up to a year before clinical progression of disease was detected by imaging[37]. As clinicians and laboratories grow in experience in delivering and using these tests, they will be able to develop guidelines that help to answer some of the questions raised about when to test.

Is solid tumour testing the gold standard?

When a patient has advanced or metastatic cancer, tumours are located in different sites in the chest and other parts of the body. In addition, only a subset of cancer cells will express first line *EGFR* mutations, and of these cells only a further subset will have p.T790M. Therefore if you want to carry out a solid tumour biopsy, which site do you choose? For p.T790M testing on progression, it is possible that a plasma test better reflects the clinical situation inside the body, reflecting both inter- and intra-tumour heterogeneity[38]. The AURA3 trial showed that there was no difference in response rate or progression free survival in patients treated with osimertinib who had their p.T790M status determined by plasma or solid tumour testing[36]. It can be argued that liquid biopsy is the gold standard for p.T790M testing – all laboratories that offer testing carry out a liquid biopsy first, only proceeding to a solid biopsy if the test is negative. This approach is also recommended by the Scottish Medicines Consortium guidance on osimertinib[19]. Ongoing evaluation of the testing services and clinical outcomes will be necessary for the optimisation of services and to enable wider implementation. An evaluation involving the laboratories at Cardiff, Manchester, Royal Marsden, Birmingham and Belfast is due to report results in early 2018.

5.2. External Quality Assurance

Early approaches to service development have been diverse, varying according to the expertise and resources in each laboratory. The molecular pathology community has recognised, however, the pressing need to undertake comparative benchmarking of the different approaches and to converge towards establishing best practice for ctDNA testing. EQA is the principal process through which this can be achieved. By determining which processes/tests perform the best, EQA provides benchmarks of quality that can stimulate improvements in test provision and motivate laboratories to match the best that is available. It also provides assurances as to the quality and standards of the tests available on the NHS.

The International Quality Network for Pathology, IQNPath, is an organisation that facilitates the exchange of information and expertise and brings together external quality assurance organisations in their efforts to implement new or improved testing methods in clinical practice.

A pilot EQA was set up via IQNPath which aims to:

1. Investigate the feasibility of delivering a technically challenging EQA
2. Assess the ability of laboratories to detect ctDNA in plasma samples
3. Assess the standard of reporting ctDNA testing results
4. Observe any differences between extraction methodologies and testing method strategies
5. Promote high quality ctDNA testing through guidelines

One of the challenges of the pilot project was how to mimic a standard set of blood samples for each laboratory, since it is not possible to send a representative patient sample to each laboratory. Two companies prepared artificial DNA samples which were spiked into pooled plasma samples and distributed to the participating laboratories. Seven European expert laboratories took part in the validation phase of the pilot, using a range of sequencing methods – Therascreen, cobas®, BEAMing, ddPCR, NGS – and extraction methods. The process, completed by March 2017, validated the artificial plasma samples, showing that the reference materials work, and a number of logistical issues such as transport of samples were resolved.

Phase two of this pilot EQA project is underway – validated artificial plasma were distributed to 32 international laboratories in March 2017.

5.3. Education, awareness and outreach

While the initial phase of service development involves a close working relationship between a laboratory and a group of clinicians who are usually located in the same hospital, once testing has been validated it is necessary to increase awareness and engagement of services to ensure that they are being fully utilised and that all clinicians have the opportunity to use testing for the benefit of their patients.

The All Wales Medical Genetics Service (AWMGS) undertook a formal programme of engagement between scientists and clinicians to raise awareness of the ctDNA testing service. When the service was being validated, the laboratory needed a regular supply of samples from suitable patients. Engagement with clinicians involved attending multidisciplinary team meetings, giving seminars and updating the AWMGS website with information on the project. This approach facilitated good communication between the laboratory and lung oncologists which was vital to identify *EGFR*-positive patients who could donate samples for use in service validation.

One of the challenges with any service development is how to improve access and engagement at clinical centres further from the laboratory. The AWMGS did this by working with oncologists based in the central hospitals who also treated patients in clinics at peripheral hospitals.

Expansion of testing to peripheral centres also presented an opportunity to clarify issues of logistics such as:

- Transport of samples to the laboratory
- Ensuring contact information for the laboratory is easily available and accessible
- Where to get a test referral form and blood collection tube
- Instructions on how to collect a sample
- How to send the sample back to the laboratory
- Expected turn around time
- How reports are returned (to the requesting clinician via the NHS secure email network)

Once the service had been established, the challenge was to develop access beyond the initial group of engaged clinical referrers in South Wales and to expand the testing network to other Welsh hospitals and those in South West England. This required engaging with clinicians who were not as knowledgeable about ctDNA testing. The AWMGS took an extremely proactive approach and several members of the laboratory staff and clinical users visited other hospitals to communicate with oncologists in person about the service, or attended multidisciplinary team meetings (MDTs). As a result of these efforts the laboratory has significantly increased the reach of the service, and a number of respiratory physicians have expressed an interest in testing before meeting to discuss the patient at the MDT and are also interested in using testing as a diagnostic test at the initial investigation stage (refer to patient pathway in section 2.1). These efforts slowly increased the number of samples that the laboratory received and allowed it to further develop the service in a controlled manner.

The AWMGS took an extemely proactive approach to engaging clinicans about ctDNA testing. Several members of the laboratory staff and clinical users visited other hospitals to communicate with oncologists in person about the service, or attended multidisciplinary team meetings (MDTs). As a result of these efforts the laboratory has significantly increased the reach of the service

Clinician and patient responses to AWMGS efforts

Initial clinician responses to the establishment of the ctDNA testing service were positive – the test was perceived to be simple and quick and benefited patients through increasing access to a targeted therapy. Ease of testing and consistent turn around times enabled better communication with patients as to when they could expect their results and return to clinic to discuss them.

There were concerns, particularly over how to interpret negative results and when/how often to test. Access to drugs was also a concern as there is no Cancer Drugs Fund in Wales and for a time osimertinib could not be accessed. It was also unclear who pays for the test and drugs in some cases. Differences between England and Wales in terms of which drugs are funded and funding processes caused some confusion.

Patients responded positively to testing, not just because people preferred a blood test to a biopsy, but also recognised the potential to access better tolerated and targeted therapies. However, clinicians need tools to help them manage negative results, in terms of how they help the patient to deal with uncertainty and what the options are should a test be negative.

Lessons learned from AWMGS engagement activities

Patient access to testing could be affected by the level of interest their clinician has in current research - clinicians with a research background are more likely to know what research is ongoing and to understand the possible impact of the latest developments. This highlights the need to give clinicians a very clear message about what testing is for, how it will benefit patients and to develop tools to aid understanding of the relevance of sensitivity and specificity - what can affect test results, clinical utility, when and how often to test.

The success of engagement also relies on open and interactive professional relationships between the laboratories and clinicians. This open relationship facilitates the exchange of information including what the laboratory does and what it can offer, to enabling the clinicians sharing information with the laboratory to understand how the information they provide could improve the service.

5.4. Funding and commissioning

The NHS funding systems differ among the devolved nations of the UK.

The two main areas where stakeholders have reported funding challenges or confusion over funding sources are:

- **Funding for resources and members of staff to validate new tests/technologies** - this is an issue for NHS Trusts providing testing services
- **Funding structures for test payment** - in order to have a systematic roll out of this new NHS service it will be necessary for test providers to establish formal supply arrangements with clinical service providers including service contracts

Pharmaceutical companies provided support in terms of funding testing and other support such as data, expertise, equipment and consumables. The laboratories that have successfully implemented testing made use of a variety of internal and external funding sources to support test development. Clarity is needed as to the sources of potential support for test development and how these can be accessed, particularly in light of available but limited pharma funding.

Many stakeholders also report that funding structures for test payment are unclear. A stakeholder briefing jointly produced by the ABPI, BIVDA and CRUK[39] brings some clarity by outlining the NHS England commissioning and funding arrangements for six molecular genetic tests for cancer and also more established tests such as *HER2/ER* testing in breast cancer and *EGFR* testing in lung cancer. *EGFR* testing in lung cancer is currently reimbursed through the Health Resources Group tariff system and as such both solid and liquid tumour testing should be reimbursed. The processes by which Trusts can claim back the costs of tests is unclear to many and it is possible that this situation is contributing to some patients not having access to the tests that they need. Future engagement efforts will require:

- **Promotion of current funding** and reimbursement arrangements for *EGFR* testing to clinicians and hospital finance teams
- **Improved communication links** between NHS Regional Commissioning managers and hospitals

Procurement challenges

At a more local level, laboratories have encountered procurement challenges with the blood collection tubes needed to collect samples. Oncologists found that their departments did not have a specific budget for ordering tubes and struggled to procure them. The laboratories have therefore developed a system whereby they send the necessary tubes to the oncologists and include the cost of the tube (approximately £5) in the test price. This increases the cost of the test and the laboratory must carefully manage the supply according to the number of patients and clinics, while also considering the shelf-life of the tubes. While this arrangement is more burdensome for the laboratories (they send the tube to the oncologist before sample collection) this approach does ensure that the correct equipment is available.

5.5. Looking to the future – extending the use of testing in lung cancer

Having made the investment and developed a clinical *EGFR* testing service, how can the NHS make the most of the positive impact on patients and extend the clinically appropriate use of the technology within lung cancer care? Are there areas where testing could be expanded?

Laboratories currently only offer ctDNA *EGFR* testing after diagnosis of lung cancer in two situations:

1. When a patient has a diagnosis of lung cancer but there was not enough material in the solid tumour biopsy for a genetic test, or the genetic test failed
2. On progression on TKIs, to test for the p.T790M mutation

Potential for using ctDNA testing in lung cancer

Monitoring patients after surgery, to determine risk of relapse

This technique is currently under investigation in clinical research studies – for example, one of the objectives of the TracerX study is to use ctDNA testing and other methods to explore the relationship between tumour heterogeneity and clinical outcomes after surgery in NSCLC patients.

Use as a 'gateway' technology

As a gateway technology, ctDNA testing could be used to determine if a patient is a good candidate for more expensive invesitigation e.g. CT scan. For example, it has been demonstrated that ctDNA testing can identify patients with diffuse large B-cell lymphoma who are at risk of recurrence before clinical evidence of disease is detected using CT scans, suggesting that ctDNA testing could be used as an adjunct to scanning technology or to identify patients who should be monitored more closely[40].

Monitoring patients on TKIs to detect emergence of resistance

Currently, patients are tested for the p.T790M mutation once tumour progression has been detected on a scan; ctDNA testing could be used to monitor patients and detect the emergence of p.T790M and switch therapy earlier, before the tumour has changed size. However clinical evidence is lacking as to whether this is beneficial to patients in terms of progression-free and overall survival.

Screening and early detection

One of the more controversial uses of ctDNA is its potential use in screening and early detection. Most of the uses outlined above occur in patients in whom a definitive diagnosis has happened by alternative methods. In order to use ctDNA effectively for early detection and screening, the user needs to know which mutations to look for (to distinguish ctDNA from healthy cfDNA) and also which tissue they came from.

Determining tissue of origin using ctDNA is possible but technically challenging and a long way from being ready for clinical use[41]. Should a patient without a cancer diagnosis have a ctDNA screening test that uses a panel test to search for the full spectrum of known cancer mutations, and a positive hit occurs, it is unclear what should happen next. Firstly, it will not be clear what is producing this mutation positive DNA without further extensive testing to determine if a tumour is present. Secondly, what are the clinical implications of finding a mutation in cfDNA in the blood? Is the source harmful or benign? Are these mutations clinically relevant and do clinicians have a clear treatment pathway for managing patients with positive test results? There is therefore a danger of over-investigation and over-treatment with the associated worry for patients should a test be positive. Much more work is needed to determine how ctDNA could be used effectively as a screening tool in a variety of cancers, including lung.

Funding multiple ctDNA tests

More extensive use of testing, for example as a monitoring tool in various scenarios, presents a challenge since this use does not fit into the conventional 'one test, one payment' model. How such testing can be funded will need to be addressed.

Beyond lung cancer

Evidence is developing to support the clinical use of ctDNA testing for *KRAS* mutations in colorectal cancer (anti-EGFR therapies can be effective in *KRAS* wild-type patients) and *BRAF* in melanoma (therapies targeting p.V600E mutation).

How can the NHS maximise the utility of emerging ctDNA services?

- Clinical guidelines are needed on the use of ctDNA testing, and clinician and laboratory expertise should be actively collected to inform their development
- Ongoing external quality assurance efforts will help to answer the question of appropriate levels of test quality and performance
- Engagement with and within the health system about testing will be needed to increase awareness about testing and how it can be used to benefit patients
- Service establishment and validation can be supported by promotion of available funding, promotion of test funding structures, linking of test development into accelerated access of technologies and support of collaborative test development

6. What needs to be done to support service implementation

We have shown that there is growing evidence for the use of ctDNA testing in the treatment of lung cancer. Such testing has increased patient access to tumour genetic testing and therefore to targeted therapies which improve progression-free survival compared to standard chemotherapy. NHS services for ctDNA testing are currently available from a select number of laboratories in the UK, offering ctDNA tests for *EGFR* mutation status in eligible patients with NSCLC.

The main challenges that lie ahead are to:

1. Improve the quality of tests through technical development and further research into the biology of ctDNA
2. Ensure that more eligible patients receive testing

Much progress has already been made and there is now a valuable opportunity for NHS England and other stakeholders to accelerate access to this transformative technology. However, if these opportunities are not seized now, it is likely that patients will be subjected to a postcode lottery in terms of access to testing and therefore to innovative therapy, which will have a knock-on negative effect on patient outcomes in lung cancer.

We outline below measures that can be taken to support further development and awareness of ctDNA testing such that all patients can benefit from the efforts of test pioneers. While there are many areas with potential for improvement, priorities should be to:

1. Improve and strengthen current services
2. Carry out engagement with and within the health system about testing

Improve and strengthen current services

The laboratories currently offering testing have invested considerable resources, time and expertise into developing their services.

Currently much of the expertise in ctDNA testing is concentrated in academic centres and in regional laboratories. Concentrating expertise and continuing technology development in these laboratories will:

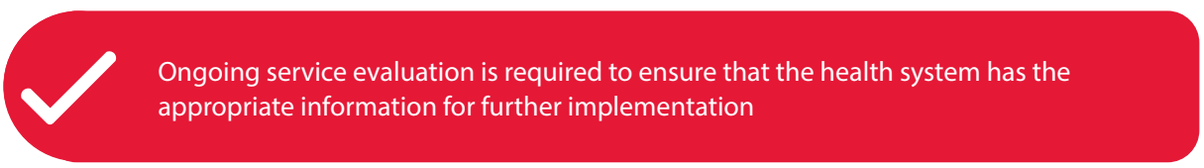
1. Make the most of the opportunities presented to learn from research expertise and technology development, which in turn will contribute to the development of guidelines
2. Enable these laboratories to more easily take part in clinical research studies and closely collaborate with researchers – there is an opportunity to take advantage of initiatives already in place such as the CRUK Experimental Cancer Medicine Centres
3. Provide an opportunity to resolve outstanding issues before the wider roll-out of ctDNA testing beyond lung cancer, which is expected in the next few years

Ongoing NHS service evaluation efforts will also have a role to play by ensuring that the health system has the appropriate information needed for further implementation. Continuing collaboration will be needed between laboratories, clinicians and other stakeholders to resolve outstanding questions that arise as a result of these evaluations.

Advantages of this approach

In broader terms, organisation into services and 'hub and spoke' models of delivery fits with the planned reconfiguration of genomic laboratory services in England. Given that many oncology services operate in this way, with central hospitals providing specialist testing for peripheral hubs, there is an opportunity to develop processes to ensure consistency of delivery. Currently ctDNA testing volumes in NSCLC are relatively low, which supports focusing provision in a defined number of centres.

Any clinical services considering using ctDNA testing services should consider using services already provided by a specialist laboratory centre rather than establishing their own.

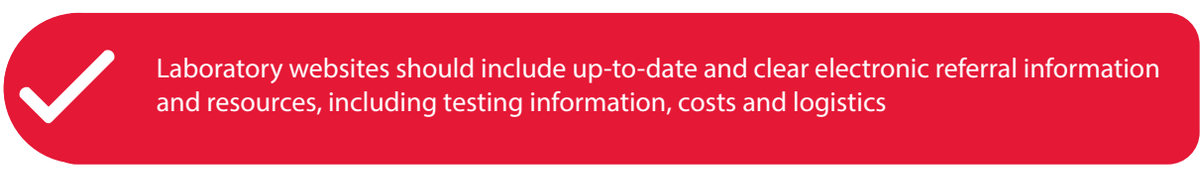


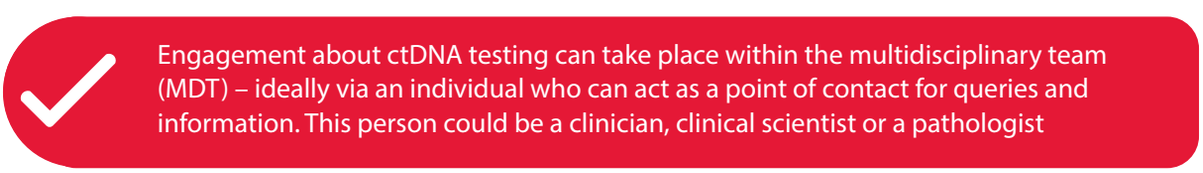
Engagement with and within the health system

The establishment of current services has demonstrated the role of clinician leadership in the development of services. There is an opportunity to capitalise on the expertise that already exists within the clinical community and the laboratories to build a network of clinical champions who can support the development of ctDNA testing in NSCLC.

How might this happen and who would be involved?

- **Engagement of clinical champions** who are knowledgeable about and are already using ctDNA testing
- **Making use of local networks** where clinical champions can promote testing as an option for patients e.g. through MDTs, regional clinical meetings
- **Engaging the professional societies and other organisations to consider and develop clinical guidelines** for ctDNA testing in order to engage those who might have less awareness of testing and what it could be used for e.g. British Thoracic Oncology Group, British Thoracic Society, Royal College of Pathologists, Cancer Research UK (including the ECMC network), NICE (clinical guidelines for lung cancer). As outlined in section 3.1, the Scottish Medicines Consortium is the only UK organisation that has guidelines on the use of ctDNA testing in NSCLC





The experience of the All Wales Medical Genetics Service demonstrates one way that engagement can work in practice. While initial engagement is demanding in terms of time and effort, the strategy has succeeded in terms of increasing knowledge amongst clinicians spread over a wider geographical area, which in turn creates a positive feedback loop for the laboratory by increasing demand.

Development of community-led guidelines

As laboratories and clinicians expand their expertise in using testing they will be gaining knowledge on test performance and use in a clinical setting. This knowledge should be actively collected and inform guideline development and updates.

What questions could be addressed by guidelines?

- **Test sensitivity -** clear explanation and guidance on the limitations of testing compared to solid biopsy (which will change as technological improvements are made)
- **Negative results -** how to report negative results; what negative results mean; clear procedures to follow in the case of negative results e.g. retest, proceed to solid biopsy
- **When to test -** when in the patient journey is best to perform a test; in the case of negative results, when to retest; how often should retesting occur
- **Patient information -** information for patients about testing, what it does and why it is offered, the meaning of positive and negative results and the impact that this will have on their treatment

Clinical guidelines on the use of ctDNA testing in NSCLC should be developed by one or more of the professional societies and organisations, such as: British Thoracic Oncology Group, British Thoracic Society, Royal College of Pathologists, Cancer Research UK (including the ECMC network), NICE (clinical guidelines for lung cancer). Clinician and laboratory expertise in ctDNA testing should be actively collected to inform these guidelines

What can the health system do to support services?

Support for service establishment and validation

Laboratories made use of a range of funding sources to develop current services in some cases to fund equipment and an additional member of staff to develop and validate techniques, in the absence of additional funding being available there could be:

- **Promotion of the sources of funding** already available to support technology development within laboratories
- **For validated testing services, promotion of the test funding structures already in place** – a stakeholder briefing by ABPI, BIVDA and CRUK outlines commissioning and funding arrangements for six molecular genetic tests for cancer and also highlights other tests that are included in the tariff[39]
- **Linking of test development into accelerated access of technologies** and the findings of the accelerated access review
- **Support of collaborative test development** by laboratories to avoid duplication of effort

Service establishment and validation should be supported, by and within the health system, by promotion of available funding, promotion of test funding structures, linking of test development into accelerated access of technologies and support of collaborative test development

Vision for laboratories – to what extent should laboratories drive the implementation of new technologies?

Development of new tests is inherently risky. As experts in this field, laboratories make informed decisions about the risks versus the benefits of implementing new technologies giving them a level level of control over which new technologies they think will have the greatest clinical impact. This presents an opportunity for laboratories to take the lead in this area, taking on some risk but also reaping the rewards for doing so. As the use of ctDNA testing expands beyond *EGFR* and lung cancer, the network of current ctDNA providers have the opportunity to build on the foundations that are already in place and to strengthen and consolidate the services they are offering.

How does ctDNA testing fit into the bigger picture?

One of the goals of the NHS England Cancer Strategy is to find cancer early and cure it early. Future uses of ctDNA might have more of an impact in helping to meet these goals, for example through use in screening or monitoring patients after treatment. ctDNA could also be used as a 'gateway' test to more expensive technology e.g. CT scans. However much research still needs to be done to investigate the use of ctDNA in these areas.

Link science, test development and drug availability

For TKIs, the science in terms of drug and test development was ahead of clinical practice. Targeted drugs and testing had been developed, however there was a delay to drugs being funded. In the case of osimertinib, ctDNA testing was available in Wales, but the drug was not, since Wales is not covered by the Cancer Drugs Fund, however patients could access the drug through Individual Patient Funding Requests.

NHS England should consider how patients can have improved access to funded targeted therapies and take steps through policy development to ensure that the health system is better prepared to implement targeted therapies when commissioned by the NHS

7. Conclusions

Circulating tumour DNA testing in NSCLC increases access to targeted therapies and is meeting an unmet clinical need. In this report we have presented evidence for and made recommendations on three key questions for the NHS:

Should the NHS offer ctDNA testing of EGFR in lung cancer to all eligible patients?

Yes, the evidence of clinical utility demonstrates that ctDNA testing makes a difference to patients, increasing accessibility to targeted therapies. While some improvements are needed to techniques, these are not a barrier to adoption, since the alternative is that patients will not have testing and the opportunity to access targeted therapies.

How should the NHS use ctDNA testing to maximise access to TKIs?

The health system should support existing services – ctDNA testing at diagnosis and for p.T790M – and establish current services as centres of excellence for ctDNA testing in lung cancer. Clinical guidelines from NICE, or developed by the community, are crucial for raising awareness and providing reassurance to clinicians that these tests have clinical utility and benefit patients.

What lessons can be learned from existing ctDNA services to support the wider use of ctDNA tests in future?

Active engagement efforts are effective, as demonstrated by the AWMGS, but require the laboratories to invest time and resource. Further efforts such as these will be required to improve engagement within the health system. Learning from early pioneers and implementing comprehensive and equitable ctDNA testing for NSCLC now will be an investment for the future, when more uses of this technology are likely to become available.

It seems likely that ctDNA testing is here to stay and that its use in cancer care will increase as technological improvements are made and more clinical evidence is gathered to support its use in different stages of the patient pathway. If this potential is to become a reality, the health system should take the opportunity to build the foundations now to support future test implementation.

8. Recommendations

- Healthcare commissioners should formally consider the provision of ctDNA services in lung cancer and improve and strengthen current service provision
- Ongoing service evaluation is required to ensure that the health system has the appropriate information for further implementation
- Laboratory websites should include up-to-date and clear electronic referral information and resources, including testing information, costs and logistics
- Engagement about ctDNA testing can take place within the multidisciplinary team (MDT) – ideally via an individual who can act as a point of contact for queries and information. This person could be a clinician, clinical scientist or a pathologist
- Clinical guidelines on the use of ctDNA testing in NSCLC should be developed
- Service establishment and validation should be supported, by and within the health system, by promotion of available funding, promotion of test funding structures, linking of test development into accelerated access of technologies and support of collaborative test development
- NHS England should consider how patients can have improved access to funded targeted therapies and take steps through policy development to ensure that the health system is better prepared to implement targeted therapies when commissioned

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10. Appendix

Speakers and attendees of the workshop held on 7th March 2017 at the Royal College of General Practitioners, London

Speaker	Title	Organisation
Dr Laura Blackburn	Policy Analyst, Biomedical Science	PHG Foundation
Prof Fiona Blackhall	Thoracic Oncology Chair / Consultant in Medical Oncology	University of Manchester / The Christie NHS Foundation Trust
Dr Rachel Butler	Head of Genetics Laboratory	Cardiff and Vale University Health Board
Dr Qamar Ghafoor	Clinical Oncologist	University Hospital Birmingham
Dr Daniel Nelmes	Oncology SpR	Velindre Cancer Centre, Cardiff
Dr Philippe Tanière	Consultant Histopathologist	Queen Elizabeth Hospital Birmingham
Dr Andrew Wallace	Consultant Clinical Scientist	St Mary's Hospital / Manchester Centre for Genomic Medicine

Delegate	Title	Organisation
Dr Hilary Burton	Director	PHG Foundation
Dr Sandi Deans	Director	UK NEQAS for Molecular Genetics
Dr Tim Forshew	Head of Technology Development	Inivata Ltd.
Dr Louise Gaynor	Policy Intern	PHG Foundation
Dr Susan Harden	Consultant Clinical Oncologist	Cambridge University Hospitals
Dr Rob Hastings	Principal	Precision Medicine Catapult
Dr Crispin Hiley	Academic Clinical Lecturer	King's College London
Dr Said Isse	Consultant Respiratory Physician	Mid Essex Hospitals

Delegate	Title	Organisation
Dr Amy Jones	Principal Scientist	Haemato-oncology diagnostic service, Cambridge University Hospitals
Dr Maria Kapi	Senior Medical Advisor	Roche Diagnostics
Dr Mark Kroese	Deputy Director	PHG Foundation
Dr Angus Lauder	Associate Director, Business Management	Cancer Research Technology Ltd.
Dr Leila Luheshi	Head of Science	PHG Foundation
Stuart McCann	Oncology Healthcare Development Manager	Roche Diagnostics
Prof Clive Morris	Chief Medical Officer	Inivata Ltd.
Mark Richards	Director, Global Product and Portfolio Strategy, Oncology	AstraZeneca
Dr Rowena Sharpe	Head of Precision Medicine	Cancer Research UK
Dr Matthew Smith	Clinical Scientist	Queen Elizabeth Hospital Birmingham
Dr Lisa Thompson	Head of Molecular Diagnostics	The Royal Marsden
Laura Timm	Diagnostic Manager (Lung)	AstraZeneca
Dr Mikel Valganon	Senior Research Associate	University of Cambridge

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