A Health Economics Evaluation of ctDNA testing in NSCLC

A report by Edge Health
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www.edgehealth.co.uk

Edge Health

Terms of reference and scope

This work was commissioned by NHS England in 2023 to help inform consideration of the inclusion of circulating tumour DNA (ctDNA) testing on the NHS Genomic Test Directory. The analysis was completed in 2024 and reflects the evidence, data and stakeholder discussions available during that period. Subsequent developments, including later policy decisions or Test Directory updates, were taken after completion of this work and are outside its scope.

The work focused specifically on lung cancer in England and was undertaken independently by Edge Health. The analysis draws on data and information shared by NHS England and other stakeholders in good faith. While reasonable steps were taken to assure the internal consistency and plausibility of the information used, Edge Health did not independently audit or validate all underlying data sources. The findings and conclusions represent Edge Health's professional judgement at the time and are necessarily time-limited.

Clinical and scientific expertise was drawn from structured discussions with Professor Sanjay Popat, Professor Alastair Greystoke, Dr Matthew Krebs, Professor Michael Hubank, Paul Ryves, Jenny May, and Dr Jane Starczynski. Their advisory input informed both the development and interpretation of the analysis. The resulting findings were subsequently endorsed by Professor Dame Sue Hill.

This published version of the report differs from the original commissioned outputs and has had certain details removed or obscured to protect potentially sensitive information. The report is intended to support understanding and discussion and should not be interpreted as a formal audit, evaluation, or regulatory assessment. No responsibility is accepted for reliance placed on this report by third parties, and any decisions taken on the basis of its contents remain the responsibility of the reader.

Contents

Glossary

BCR	Benefit-cost ratio
CNS	Cancer nurse specialist
ctDNA	Circulating tumour DNA
EGFR	Epidermal growth factor receptor
GMSA	Genomic Medicine Service Alliance
GLH	Genomic Laboratory hub
IHC	Immunohistochemistry
MDT	Multidisciplinary team
NGS	Next-generation sequencing
NSCLC	Non-small cell lung cancer
PS	Performance status
SCLC	Small cell lung cancer
TAT	Turnaround time
TT	Targeted therapy
2WW	Two week-wait

Executive Summary

In 2020, England saw 37,211 new lung cancer diagnoses, with 68% of these cases being advanced stage. Advanced lung cancer places a significant cost on patients, their families, society more generally, and the healthcare system. An advanced diagnosis can be associated with numerous GP consultations, hospital attendances and admissions, and extended hospital stays. The urgency for rapid and precise diagnosis and treatment is vital, not only to improve the quality of life but also to alleviate the impact on healthcare resources.

Advancements in precision medicine, particularly genomic testing, are revolutionising cancer care. Liquid biopsy, a cutting-edge approach that analyses circulating tumour DNA (ctDNA) from blood samples, has emerged as a tool for diagnosing and guiding treatment decisions in patients with advanced non-small cell lung cancer (NSCLC). This technology presents an opportunity to streamline diagnostic pathways, enhance patient outcomes, and potentially deliver cost savings to the NHS.

This report seeks to understand and validate the health economic impact, benefits and costs of integrating ctDNA testing into the NHS's diagnostic lung cancer pathways. It focuses on three distinct scenarios of ctDNA implementation under a range of assumptions relating to existing and planned pathways.

Three different scenarios have been explored:

- **Scenario 1: Early integration during respiratory clinic or hospitalisation.** This scenario looks at the introduction of ctDNA testing at the earliest point in the patient pathway, enabling a broader impact on diagnosis and treatment decisions.
- **Scenario 2: Parallel salvage testing.** Here, ctDNA testing is conducted alongside tissue biopsy and used as a backup when traditional genomic testing on tissue samples is inconclusive.
- **Scenario 3: Serial salvage testing.** ctDNA testing is reserved as a secondary measure, employed after initial genomic testing on the tissue fails, aiming to reduce the need for further invasive procedures.

The implementation of ctDNA testing, particularly if introduced early in the standard diagnostic pathway, shows promising economic benefits. The health economic analysis indicates a positive benefit-cost ratio of 1.3, even without full quantification of all potential benefits like reduced anxiety from reduced uncertainty. The early integration scenario (Scenario 1) has the most significant impact on patient care by reducing diagnostic delays but also offers the potential to decrease hospital-based activities and improve patient longevity.

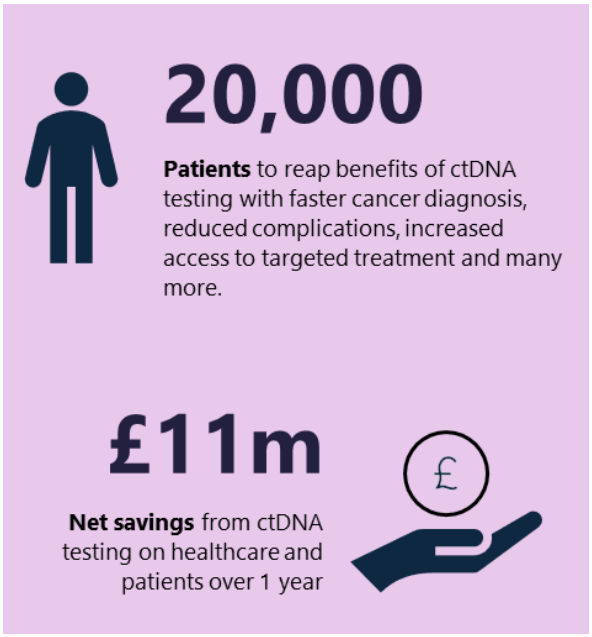
A pilot study involving 2,300 individuals who were given access to ctDNA testing was undertaken in parallel to the work for this report. Data on 1,296 of these participants was received and analysed which has helped understand the operational aspects of implementing ctDNA technology in the NHS and has helped validate key assumptions underpinning the health economic models.

While the results from the pilot differ from the health economic modelling, these differences are minor. Faster turnaround times support the overall findings.

The perspectives of staff from lung cancer support workers to respiratory clinicians and oncologists towards ctDNA were considered through engagement for this project, including a survey that highlighted:

- **Positive impact on treatment timelines.** A significant majority (over 88%) of staff surveyed believe that ctDNA testing can substantially reduce the time to initiate treatment for their patients.
- **Access to targeted therapies.** Staff noted the importance of ctDNA testing in identifying patients eligible for targeted therapies.
- **Workload and patient complications.** While responses varied regarding the impact of ctDNA testing on workload, a majority reported a reduction in patient complications from reduced delays to getting appropriate treatment.

The integration of ctDNA testing within NHS England's lung cancer diagnostic pathways represents a step forward in precision medicine, which aligns with the *Accelerating genomic medicine in the NHS* strategy. Its capacity to speed up diagnosis, reduce healthcare resource use, and improve patient outcomes justifies the cost of the technology. Scenario 1, introducing ctDNA testing at the earliest stage, emerges as the most advantageous approach, offering a comprehensive solution that benefits a wide patient population.



1 Introduction

Over the past few years, the NHS has faced increasing pressure on its services, particularly in meeting targeted cancer waiting times for prompt diagnosis and treatment initiation. Swift diagnosis and treatment not only ensure timely intervention before the cancer progresses or spreads but also alleviate stress and anxiety for patients.

Recent findings from Cancer Research UK[1] regarding cancer waiting times in January 2024 reveal concerning statistics. Only 62% of individuals in England who received their diagnosis and began their initial treatment met the 62-day standard for urgent referral, falling significantly short of the 85% target. Furthermore, 87% of patients in England began their treatment within 31 days of deciding on a treatment plan, below the desired 96% target and 71% received a diagnosis or had cancer ruled out within 28 days of an urgent referral, the target being 75%.

Against this backdrop, genomic testing for cancer patients is increasingly being used to inform cancer diagnosis, prognosis, and treatment. Certain genomic variants can indicate the most effective treatment options for a particular cancer. Currently, the primary method for diagnosing tumours involves taking a tissue sample through biopsy. This sample is then used for both diagnostic purposes and genomic testing. However, obtaining genomic information through tissue biopsy poses numerous challenges, including procedural invasiveness, the risk of complications, difficulties with reproducibility, and occasional issues with sampling representativeness.

The emergence of ctDNA testing has gained considerable momentum as an alternative method to getting genomic information. This less-invasive technology enables the detection of genetic variations usually through a simple blood draw and has been shown to overcome many of the challenges posed by tissue biopsies. Such a shift can redefine standard of care and economic health resource utilisation substantially from a genomic testing perspective.

1.1 Genomic Medicine in the NHS

The UK government's vision, outlined in the policy paper "*Genome UK: The Future of Healthcare*"[2], is to create the most advanced genomic healthcare system in the world, underpinned by the latest scientific advances, to deliver better health outcomes at lower cost. For this to happen, it is important to incorporate the latest genomics advances into routine healthcare to improve the diagnosis, stratification, and treatment of illness. No healthcare system in the world has yet

[1] Lowes, S., & Brown, I. P. (2024, March 14). *Cancer waiting times: Latest updates and analysis*. Cancer Research UK - Cancer News. https://news.cancerresearchuk.org/2024/03/14/cancer-waiting-times-latest-updates-and-analysis/

[2] https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare/genome-uk-the-future-of-healthcare

introduced ctDNA testing at the national level, the UK has hence the opportunity to become a global leader in this field.

The Accelerating Genomic Medicine in the NHS Strategy[3] sets out four priority areas, one of which focuses on "Delivering equitable genomic testing for improved outcomes in cancer, rare, inherited and common diseases and in enabling precision medicine and reducing adverse drug reactions".

A key action within this domain involves *"Enabling the rapid evaluation and adoption of affordable, efficient, and innovative genomic technologies"*. This action aligns directly with the integration of ctDNA testing in diagnostic pathways and its potential to drive innovation and enhance treatment outcomes. Furthermore, NHSE has already implemented NHS treatment regulations that enable oncologists to administer anti-cancer medications based on ctDNA results. This groundwork has been laid, facilitating the swift integration of ctDNA findings into prescription practices.

1.2 Overview of ctDNA Testing

ctDNA stands for circulating tumour DNA and refers to small fragments of DNA that are released into the bloodstream by cancer cells. These fragments contain genetic information specific to the tumour they originated from and are accessible through blood, urine, saliva, or cerebrospinal fluid (CSF) testing. Various methods exist for testing ctDNA, each with different targets, sensitivities, and costs.

Existing literature on ctDNA testing demonstrates the equivalence of ctDNA with tumour tissue testing across various cancers[4]. These tests have also demonstrated strong clinical sensitivity and specificity in numerous clinical scenarios[5]. More specifically, several clinical trials have demonstrated specific benefits of ctDNA for patients diagnosed with suspected advanced lung cancer. Results from the ACCELERATE clinical trial[6] evidenced many benefits of ctDNA including turnaround time for patients receiving genetic test results from ctDNA testing compared to tissue biopsy to be 16 days (median). Furthermore, for patients diagnosed with non-small cell lung cancer (NSCLC), 12% of patients were found to have a genetic variant that could be treated with targeted treatment only from ctDNA testing, and 23% of patients started their targeted treatment

[3] https://www.england.nhs.uk/long-read/accelerating-genomic-medicine-in-the-nhs/

[4] Duffy, M. J., & Crown, J. (2022). Use of Circulating Tumour DNA (ctDNA) for Measurement of Therapy Predictive Biomarkers in Patients with Cancer. Journal of Personalized Medicine, 12(1), 99. https://doi.org/10.3390/jpm12010099

[5] Keller, L., Belloum, Y., Wikman, H., & Pantel, K. (2020). Clinical relevance of blood-based ctDNA analysis: mutation detection and beyond. British Journal of Cancer, 124(2), 345–358. https://doi.org/10.1038/s41416-020-01047-5

[6] García-Pardo, M., Czarnecka-Kujawa, K., Law, J., Salvarrey, A., et al. (2023). Association of circulating tumor DNA testing before tissue diagnosis with time to treatment among patients with suspected advanced lung cancer. JAMA Network Open, 6(7), e2325332. https://doi.org/10.1001/jamanetworkopen.2023.25332

even before they received their tissue genetic test results. On top of that, treatment of NSCLC patients using targeted treatment has shown improvements in treatment outcomes such as reduced side effects, improved quality of life and longer survival rates[7]. There exist many different methods and providers for ctDNA testing for NSCLC, with differing sensitivities and specificities, some of the highest achieved by NGS: custom panels: Safe-SeqS by Illumina with 97% sensitivity and specificity and Guardant360 by Guardant Health with 86% sensitivity and 99% specificity[8].

[7] Chan, B. A., & Hughes, B. G. (2015). Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. Translational lung cancer research, 4(1), 36–54. https://doi.org/10.3978/j.issn.2218-6751.2014.05.01

[8] Singh, A., Cheng, H., Guo, X., Levy, B., & Halmos, B. (2017). Circulating tumor DNA in Non–Small-Cell Lung Cancer: a primer for the clinician. JCO Precision Oncology, 1, 1–13. https://doi.org/10.1200/po.17.00054

2 Aims and Objectives of the Evaluation

To support the development of the proposal to commission ctDNA testing for stage III/IV suspected non-small cell lung cancer patients, NHS England brought together a group of experts as part of a national oversight group to deliver a testing pilot. ctDNA samples have been taken from around 2,300 patients with radiological evidence of stage III/IV thoracic malignancy but without yet a confirmed diagnosis, for direct gene panel analysis for those genes already approved on the National Genomic Test Directory. North Thames and North East & Yorkshire GMSA's are leading the pilot.

Edge Health was commissioned by NHS England in June 2023 to undertake a health economics assessment of ctDNA testing in the diagnosis of advanced lung cancer in England.

This report from Edge Health sets out the conclusion of this work, which is based on extensive engagement with the NTGMSA, a range of stakeholders, and a review of evidence and data on the impact of ctDNA testing. Evidence of the impact of ctDNA testing is still in its early stages and developing rapidly. Where possible this review is based on this evidence, but in several areas, assumptions are drawn from existing literature, discussions with people involved in care delivery and pilot data based on data received from 1,300 samples. Additional benefits that will come from improvements to research and development are not quantified in this report.

The findings of the evaluation aim to inform decision-making for policymakers, potentially helping to develop more patient-centric healthcare with economically sustainable diagnostic technologies.

3 Health Economic Assessment Methodology

In this report, the costs and benefits of introducing ctDNA testing at different points in the NSCLC diagnostic pathway have been analysed and compared with the current standard of care, more details about the considered baseline pathways are outlined in Section 5.

An initial literature review has been carried out to understand fast-moving evidence on ctDNA testing in diagnostic pathways, the unmet need for improved detection of gene variants, and the impact on diagnostic and treatment times. Expert clinical input has been gathered on where ctDNA testing would alter the current standard of care and the broad impacts that this would have across healthcare systems, as well as on individuals themselves. Based on this research, for each inclusion scenario considered (Section 6), a logic model has been developed to outline the key outcomes and impacts of using liquid biopsy as a diagnostic test, for quantification in the economic model.

Based on this impact pathway, an early economic model has been developed to allow users to gain an understanding of the likely cost-benefit of ctDNA testing in NSCLC under different scenarios. To achieve this, an adjustable model has been built in Excel, providing default parameter values based on available evidence or clinical opinion, such as screening population size, ctDNA testing sensitivity and specificity, and cost of the test per person. Key outputs were the net benefit and benefit-cost ratio.

Data from the NSCLC ctDNA testing pilot have then been analysed to check and validate assumptions made in the economic model and to evaluate geographical differences across Genomic Laboratory Hubs (GLH). Findings from this analysis are available in Section 8.

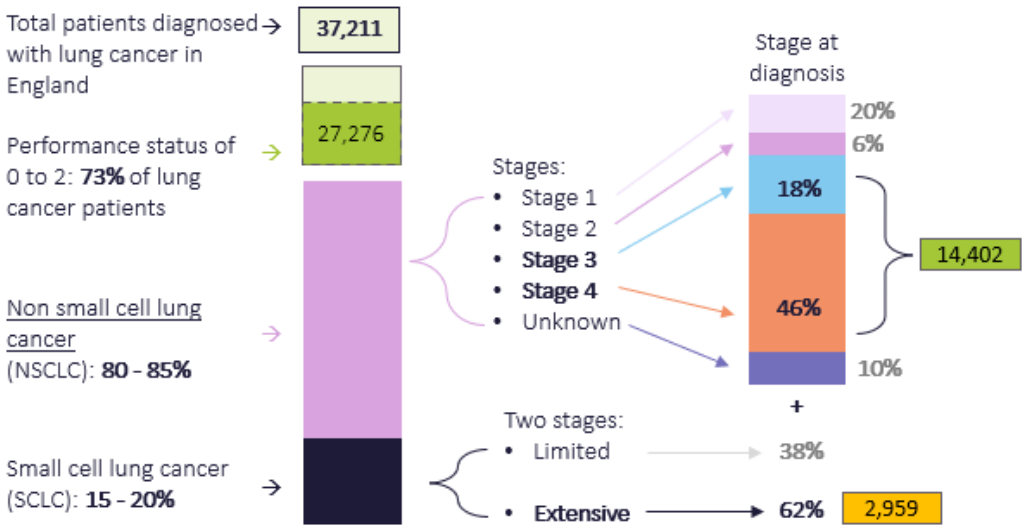
In addition, survey data from oncologists, respiratory clinicians, cancer nurse specialists (CNSs) and other lung cancer workers' experience during the pilot and learnings for the future have been collected and have been reported in Section 9.

4 Understanding the Lung Cancer Population

In 2020[9], 37,211 people were diagnosed with lung cancer in England. 68% of this population are at an advanced stage and have limited life expectancy. People with advanced lung cancer have complex care needs and often experience high levels of GP appointments, hospital admissions and long lengths of stay while waiting for diagnosis and treatment, adding pressure to the healthcare system. This is why timely diagnosis and appropriate and fast treatment are crucial to providing patients with quality care and making the best possible use of healthcare resources.

Figure 1 contains a simplified mapping of the population with advanced stage (III/IV) non-small cell lung cancer (NSCLC) that could benefit from ctDNA testing.[10] After discussions with the experts committee, it has been decided to only include patients with performance status 0 – 2.[11] This is to capture patients with a higher chance of survival.

Figure 1. Breakdown of lung cancer population in England by performance status, type of lung cancer and stage of diagnosis



[9] Latest available data.

[10] https://www.cancerdata.nhs.uk/ , https://www.cancerresearchuk.org/, https://www.macmillan.org.uk/, National Cancer Registration and Analysis Service – Public Health England - https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2021/07/Cancer-Waiting-Times-Annual-Report-202021-Final.pdf

There are two main types of lung cancer:

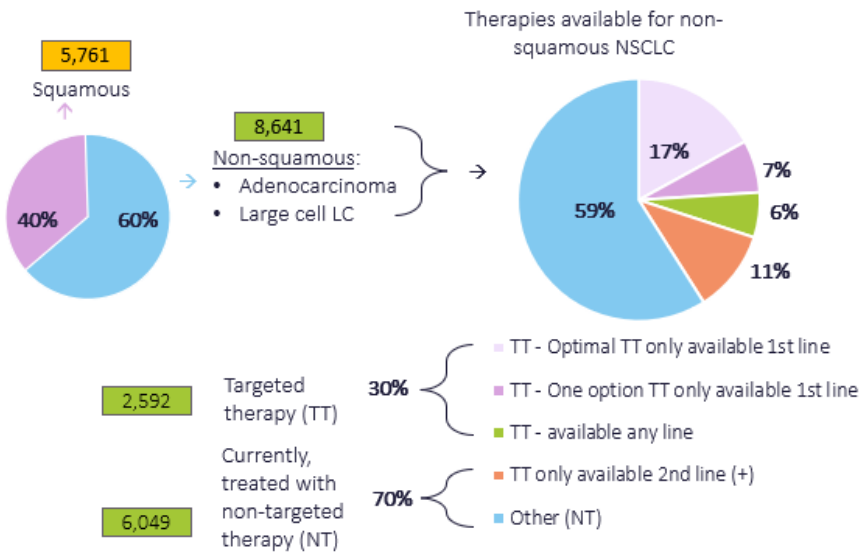
- **Small cell lung cancer** – a less common type of lung cancer which occurs in 15-20% of lung cancer patients, is usually caused by smoking and tends to spread very rapidly. Extensive SCLC population has been included in the cohort of patients receiving ctDNA testing under scenario 1 (more details are available in Section 6.1). This is because the only information available at the respiratory clinic after the first CT scan would be the staging but not the type of cancer.
- **Non-small cell lung cancer** – a more common type of lung cancer which occurs in 80-85% of patients. This type of cancer can also be split into two subtypes, squamous cell cancer and non-squamous cell cancer. Non-squamous cell cancer can be subcategorised into adenocarcinomas or large cell carcinomas. The difference between these two types is the location where the cancer develops. Squamous cell cancers cover the surface of the airways and grow near the centre of the lung whereas, non-squamous most commonly adenocarcinomas develop in the mucus-producing gland cells in the lining of the airways.

60% of lung cancer patients are non-squamous NSCLC. These cancers can occur as a result of genetic variants, in genes such as EGFR, ALK, K-RAS etc. Out of all the genetic variants that have been researched for this cohort, targeted therapies have been developed to target 41% of all the genetic variants, out of which 30% are currently available as first-line treatments[12]. It is important to note as some of these drugs are only funded as 1st line therapies, finding the gene alteration soon is paramount hence for patients getting access to them[13]. The remaining 70% of alterations are currently treated with general cancer treatment usually chemoimmunotherapy, as indicated in Figure 2.

[12] For more details around gene variants and associated targeted therapies please look at Section 11.2.1 in the Appendix.

[13] Key genomic information including known wild type status for EGFR and ALK is required to access this treatment for Non squamous lung cancer in NHSE.

Figure 2. Breakdown of patients diagnosed with Stage III/IV NSCLC by sub-types, including therapies currently available for non-squamous NSCLC[14]



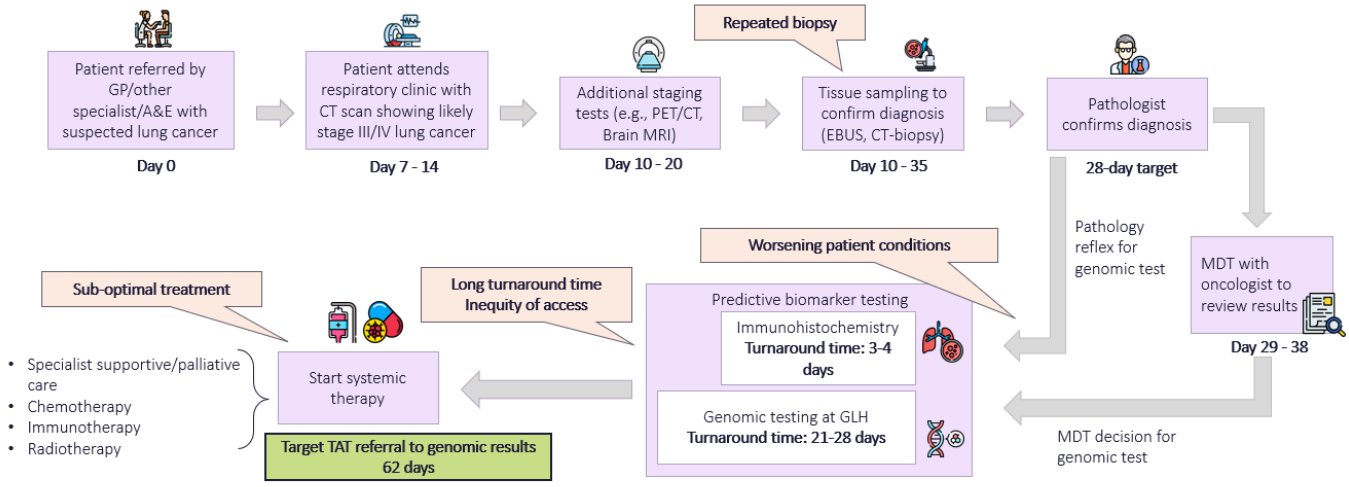
[14] NSCLC pathway, Professor Alastair Greystoke and Rachel Butler, NHS England and NHS Improvement presentation.

5 Suspected Stage III/IV Diagnostic Pathways

5.1 Pathway 1: Standard Pathway for Suspected Stage III/IV Lung Cancer

The current and most widely followed guidance on the diagnosis of Lung cancer adheres to the National Optimal Lung Cancer Pathway (NOLCP)[15]. In line with the NOLCP and after an extensive pathway validation exercise with NHSE clinical and scientific experts, a simplified current standard diagnostic pathway for patients with suspected advanced lung cancer has been developed. The pathway also includes estimates of the turnaround time for each stage of the process, as shown in Figure 3. These estimates have also been discussed in detail with experts from a range of areas across the UK to confirm they are representative and in line with the real-world flow.

Figure 3. Current standard diagnostic pathway with estimated turnaround time at each stage relative to referral day (Day 0)



A standard patient's journey from the point of referral (considered Day 0) to receiving their lung cancer diagnosis and subsequent treatment consists of multiple diagnostic stages:

1. **Referral** – there are multiple referral routes through which a patient can start their diagnostic lung cancer pathway. The main route is through a 2 week-wait (2WW) referral via a GP for suspected lung cancer. Other routes are through emergency referral, lung cancer screening or consultant upgrade.

[15] https://www.cancerresearchuk.org/sites/default/files/national_optimal_lung_pathway_aug_2017.pdf

2. **Respiratory clinic (review)** – patient attends respiratory clinic with CT scan showing likely stage III/IV lung cancer, usually 7 -14 days after referral. The patient might also be directed to undergo additional staging tests e.g. PET scan or Brain MRIs, between day 10 to 20[16].
3. **Tissue biopsy** – a section of the patient's lung tumour biopsied using EBUS or CT biopsy, between day 10 to 35.
4. **Pathologist and MDT review** – pathologist confirms a diagnosis of lung cancer, the target for which is 28 days from referral. The results are also reviewed by an MDT with oncologists, between day 29 - 38 (there are also cases where this stage is bypassed).
5. **Predictive biomarker testing** – biomarker testing is done in two stages that can either take place sequentially or in parallel:
    - Immunohistochemistry (IHC) – such as PDL1 is usually done at path labs where the tissue biopsy block undergoes IHC to determine appropriate treatment options. Typical turnaround time for this process is 3 - 4 days.
    - Genomic testing – these are currently done at Genomic laboratory hubs (GLHs) to determine the genetic variant of the NSCLC from the block of tissue biopsy. Typical turnaround time for this process is 21 - 28 days[17].
6. **Treatment start** – this is the day the patient begins their treatment. A national 62-day target has been set from the date of referral to the date of start of treatment.

During the current process of diagnosis, there are multiple inefficiencies and resource waste at different stages:

- **Repeated tissue biopsy** – around 30% of patients undergo one or many repeated tissue biopsies, usually due to insufficient material in the initial tissue biopsy to obtain a successful full cancer test directory panel result[18].
- **Worsening patient condition** – during the wait for a diagnosis, patient accesses various care through GP attendances, hospital admissions, and undergoing additional scans to manage their condition.

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[16] According to the National Optimal Lung Cancer Pathway, all inpatients should have a CT scan within 24hrs from admission and be seen by respiratory clinician within 48hrs. Irrespective of the referral route, all routes should merge at the triage stage when the outcome of the CT scan is available, following the same pathway subsequently and addressed with the same level of urgency.
(Source: https://www.roycastle.org/app/uploads/2019/07/Lung_Cancer_Implementation_Guide_August_2017.pdf)

[17] Genomic testing turnaround time is only considered for tests via GLH because for other routes like LGL, in-house etc. testing is not likely to be panel-based and or cover all required targets.

[18] This figure is average repeated biopsy rate from reported studies[1,2]. Main reasons for repeated biopsy being insufficient material to obtain a successful "full cancer test directory panel" result. (Sources: 1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7729592/pdf/lmt-09-40.pdf , 2. https://pubmed.ncbi.nlm.nih.gov/25922063/)

- **Long turnaround time** – at the predictive biomarker testing stage, around 20-30% of the tissue biopsy material fails[19] and the patient must undergo repeated tissue biopsy. This leads to the patient falling behind in the diagnostic process lengthening the time to receive a diagnosis and access treatment.
- **Inequalities of access** – there is variability in the current provision of genomic services.
- **Access to treatment** – it takes an average of three weeks to begin chemoimmunotherapy. Often, patients are booked for this treatment even before they receive their genomic test results to reduce the delay between diagnosis and treatment initiation. If a patient receives a positive result for a targetable gene variant, this booking is cancelled.

5.2 Real-life Data Insights on Turnaround Times

Analysis of real-life data on over 200 patients[20] on the current standard diagnostic pathway shows the following mean turnaround times (mean TAT) for patients referred through the GLH route:

- **Standard mean TAT:** eight days from tissue sampling to cellular pathology report and 25 days from tissue genetic testing request to receipt of the genomic report, resulting in a total of 33 days from tissue sampling to tissue genetic testing result on the standard diagnostic pathway.

Additionally, there are examples where turnaround time is quicker. It is important to consider these faster instances, since it is evidence that a faster time is possible.

- **Standard faster TAT:** however, for 30% of patients on the current standard diagnostic pathway, tissue genetic testing results were obtained within 15 days. In these cases, the total time from tissue sampling to tissue genetic result is reduced to 23 days.

Including this faster pathway in our ctDNA benefit modelling is conservative, since the comparator pathway is relatively better than what is often achieved.

The broader implication of obtaining genomic testing results faster is that the total turnaround time from referral to receipt of tissue genetic results report is 51 days, compared to the median TAT of 62 days, resulting in a pathway shortened by around two weeks.

The benefits and costs associated with ctDNA testing introduction (Section 7) have been quantified against both the Standard mean TAT and the Standard faster mean TAT pathways baseline.

[19] Failure rates of tissue obtained from tissue biopsies (avg. failure rates from reported variants) (Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3954776/pdf/nihms561349.pdf)

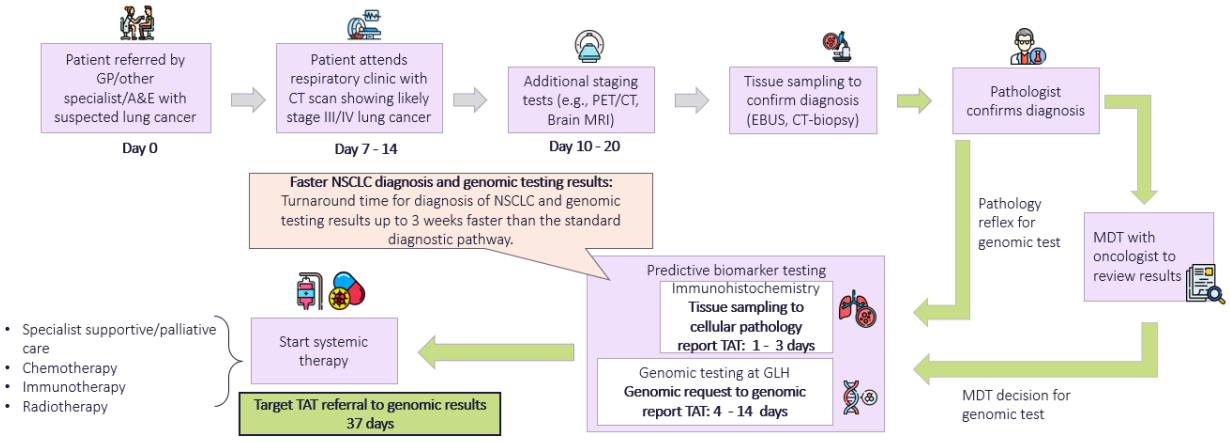
[20] Analysis is based on aggregated mean and standard deviation TAT data on 208 patients shared by Genomics unit at NHSE. Shared data is categorised by TATs for sample transit, cell pathology diagnosis, dispatch report, genomic sample prep and testing and total turnaround time from sampling to genetic report available to clinician.

5.3 Pathway 2: Optimised Diagnostic Pathway for Suspected Stage III/IV Lung Cancer

An Optimised diagnostic pathway has been qualified for projected ideal turnaround times planned to be achieved in the future, aiming for faster diagnosis of late-stage lung cancer by the NHSE which is currently in its planning stages. For this pathway, the target turnaround time is set to be 37 days from referral to obtaining tissue-based genomic results, Figure 4. The main differences between standard and optimised pathways are:

- **Tissue sampling to cellular pathology report** – Currently, the median TAT is 8 days on the standard diagnostic pathway, whereas the target mean TAT on the optimised diagnostic pathway is planned to be between 1 to 3 days from the day of tissue sampling.
- **Cellular pathology report to tissue genomic report** – Currently, obtaining the tissue genomic testing results after receiving the cellular pathology report takes 25 days on the standard diagnostic pathway, while the targeted median TAT is planned to lie within 4 to 14 days on the optimised diagnostic pathway.

Figure 4. Optimised diagnostic pathway for patients with suspected advanced lung cancer to be implemented in the future



The benefits and costs associated with ctDNA testing introduction (Section 7) have also been quantified against this optimal pathway baseline.

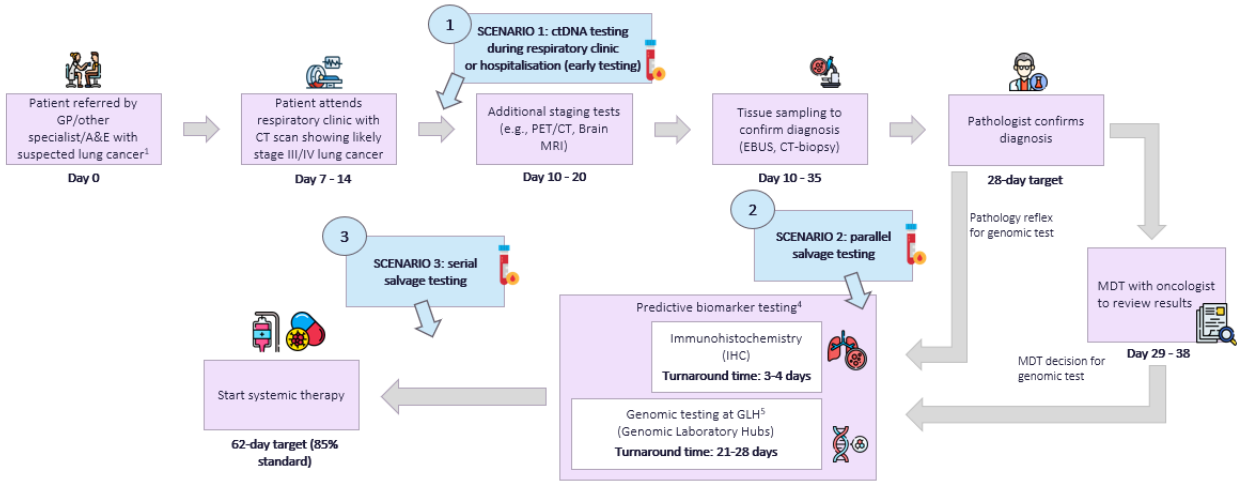
6 Inclusion Scenarios

ctDNA testing can be introduced at different stages of the current diagnostic pathway. For this report, three different scenarios were considered. Each scenario offers an alternative to ctDNA testing inclusion in the advanced lung cancer diagnostic pathway and has been validated by clinicians[21]:

1. **Early testing** - The patient accesses ctDNA testing when presenting to a respiratory clinician with suspected stage III or IV lung cancer or during hospitalisation. Here, the liquid biopsy sample is sent for analysis before the tissue biopsy.
2. **Parallel salvage testing** - The patient accesses ctDNA testing when a non-squamous stage III/IV NSCLC has been confirmed, in parallel to genomic testing on the tissue. This avoids any potential delays due to failure of genomic testing on the tissue biopsy.
3. **Serial salvage testing** - The patient accesses ctDNA testing only if the predictive biomarker testing fails.

The introduction of ctDNA testing at the GP referral stage has been discussed but, in agreement with the clinicians, it has been decided not to include it in the scenarios analysis for this report.

Figure 5. Inclusion scenarios



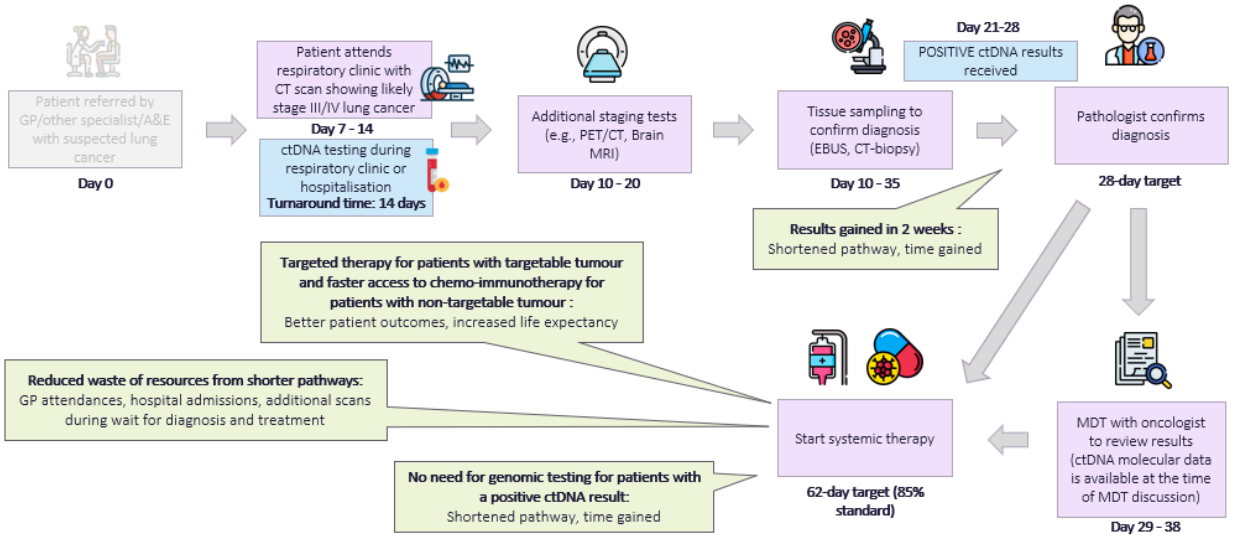
6.1 Scenario 1: ctDNA testing during respiratory clinic or hospitalisation (early testing)

Under scenario 1 (early testing) the patient accesses ctDNA testing when presenting to a respiratory physician with suspected stage III or IV lung cancer or during hospitalisation and the liquid biopsy sample would be sent for analysis before tissue biopsy. Positive lung cancer patients

[21] Names and contacts of contributing clinicians has been included in the appendix.

progress on the pathway outlined while genomic testing on the tissue is still carried out on patients with a negative ctDNA result (regular pathway). In addition, approximately 15% of individuals on the pathway either do not have cancer or have tested positive for a different cancer. Positive individuals with a different cancer will be directed towards the appropriate course of action treatment. It should be noted that patients that receive a negative test result also benefit from ctDNA testing by accessing immunochemotherapy faster.

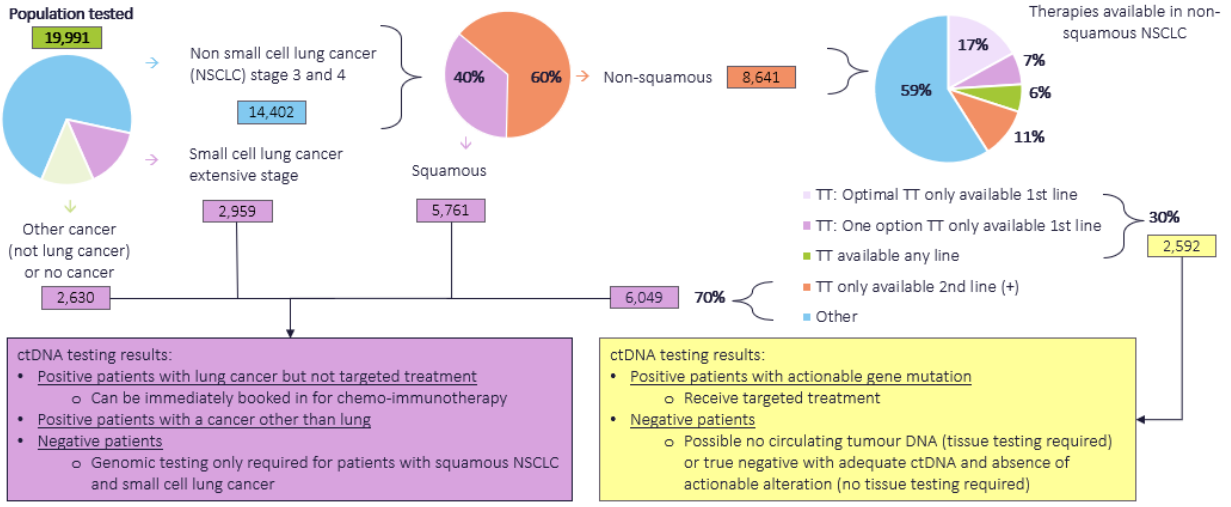
Figure 6. Scenario 1 Diagnostic Pathway



The population tested under scenario 1 is the largest (potentially all patients with stage III or IV lung cancer, and a proportion of patients without cancer or with another type of cancer[22]) and ctDNA testing will lead to three possible results: positive with actionable gene variant, positive with non-actionable gene variant or negative result, no gene variant identified. The course of treatment for the positive patients with an actionable alteration is targeted treatment, patients with a positive result and lung cancer without actionable variant are directed to chemo-immunotherapy while patients with a negative result proceed to genomic testing on the tissue.

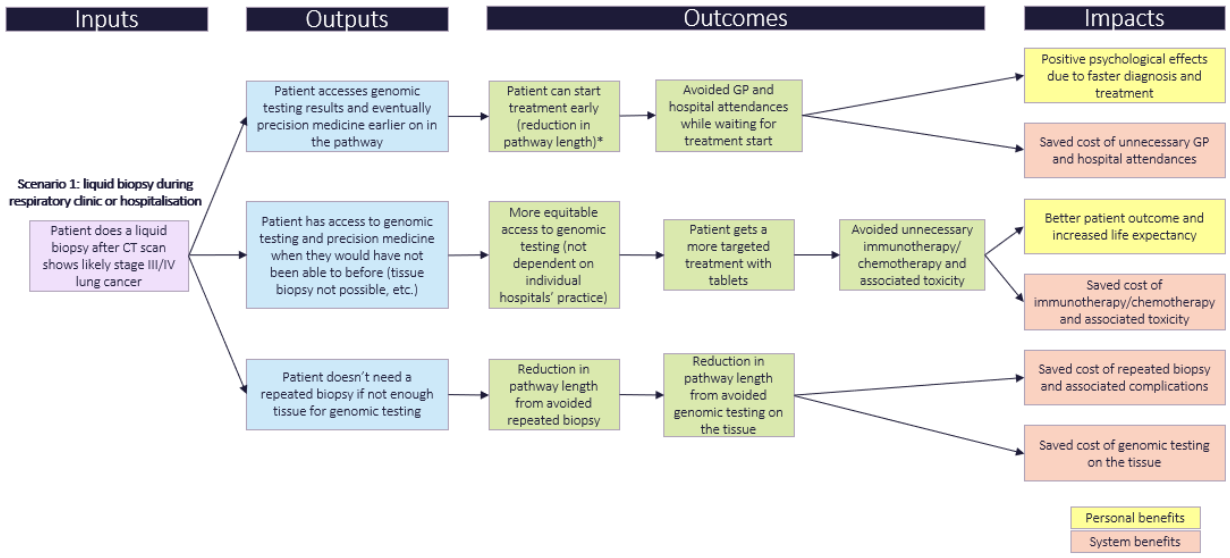
[22] In the case where suspected metastatic lung cancer was discovered to have developed as metastatic cancer from another site such as the breast.

Figure 7. Scenario 1 Population



The logic model below sets out the impacts that ctDNA testing can have on the healthcare system and individual patients across scenario 1.

Figure 8. Scenario 1 Impact Pathway

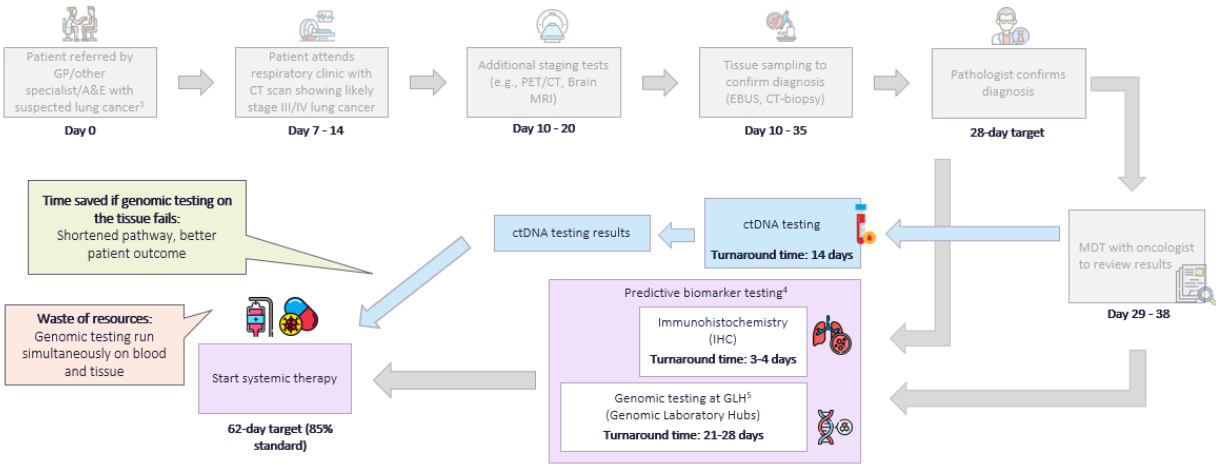


* Note: This is true both for patients with a positive result (with or without actionable gene mutation). Patients with positive, actionable ctDNA results have 3 weeks reduction in pathway length whereas, patients with positive ctDNA results but no actionable mutation have 1 week reduction (can be booked in earlier for chemo-immunotherapy).

6.2 Scenario 2: Parallel salvage testing

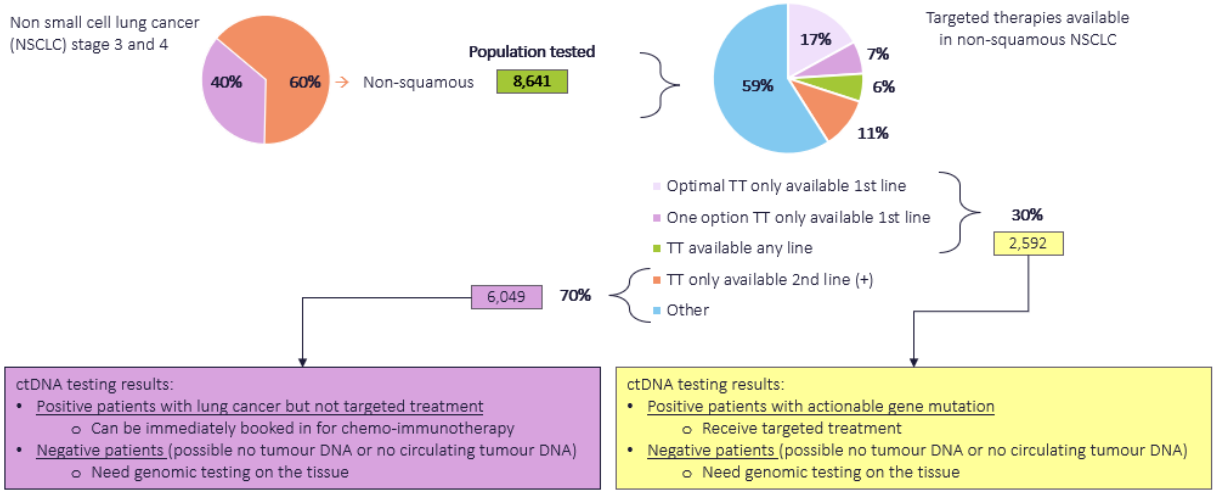
Under scenario 2 the patient accesses ctDNA testing when a non-squamous stage III or IV NSCLC has been confirmed, in parallel to genomic testing on the tissue to avoid potential delays due to genomic testing on the tissue failure.

Figure 9. Scenario 2 Diagnostic Pathway



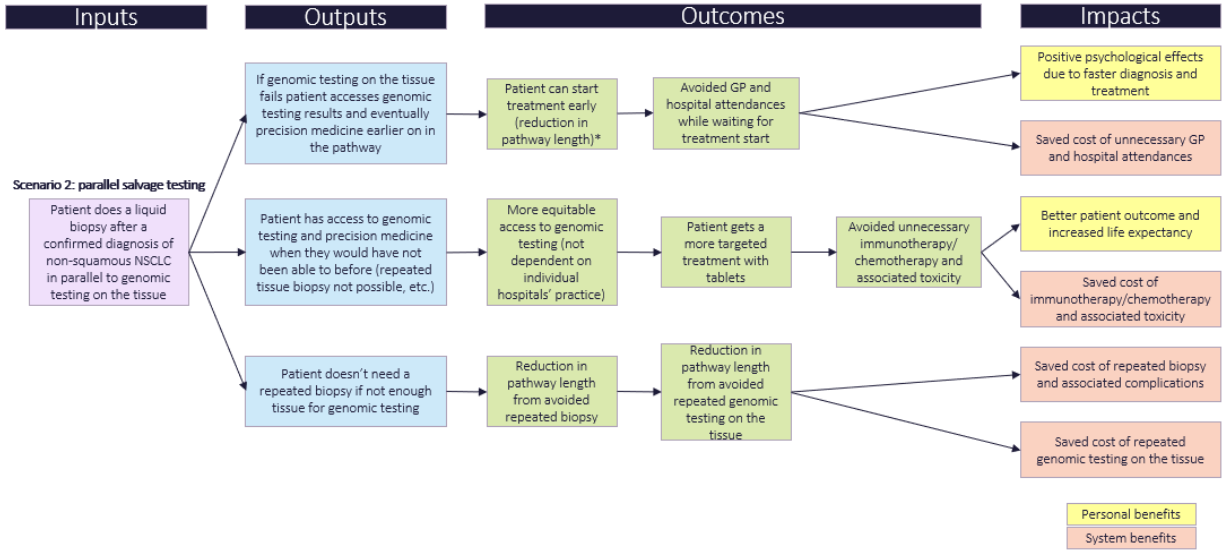
The population tested under scenario 2 (NSCLC patients with stage III or IV) is smaller than the cohort of scenario 1, leading to savings in the cost of ctDNA testing from avoided unnecessary tests. This saving is offset by the duplication of costs due to genomic testing on the tissue still being carried out in parallel for the entire cohort.

Figure 10. Scenario 2 Population



The logic model below sets out the impacts that ctDNA testing can have on the healthcare system and individual patients across scenario 2.

Figure 11. Scenario 2 Impact Pathway

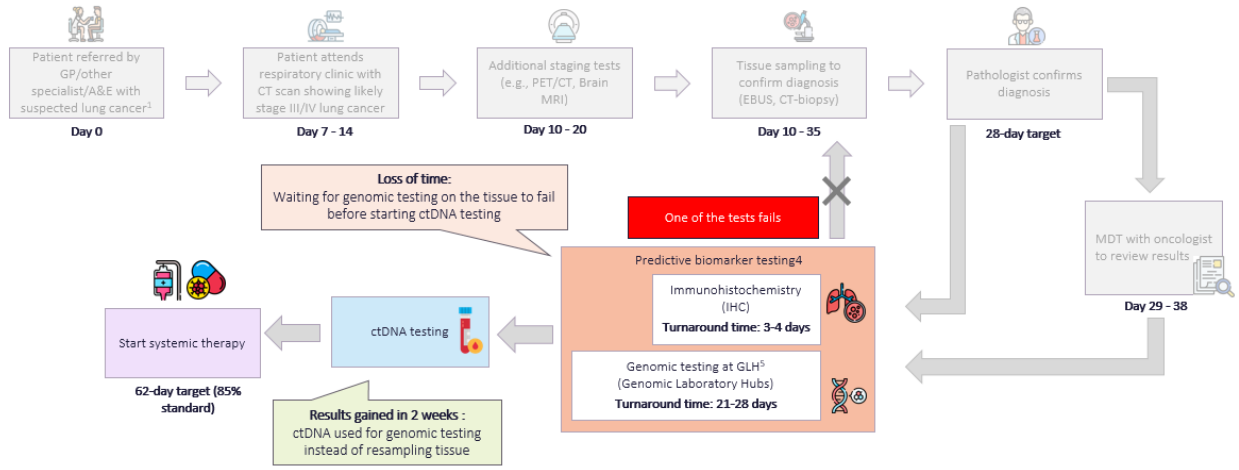


* Note: This is true both for patients with a positive result (with or without actionable gene mutation). Patients with positive, actionable ctDNA results have 3 weeks reduction in pathway length whereas, patients with positive ctDNA results but no actionable mutation have 1 week reduction (can be booked in earlier for chemo-immunotherapy).

6.3 Scenario 3: Serial salvage testing

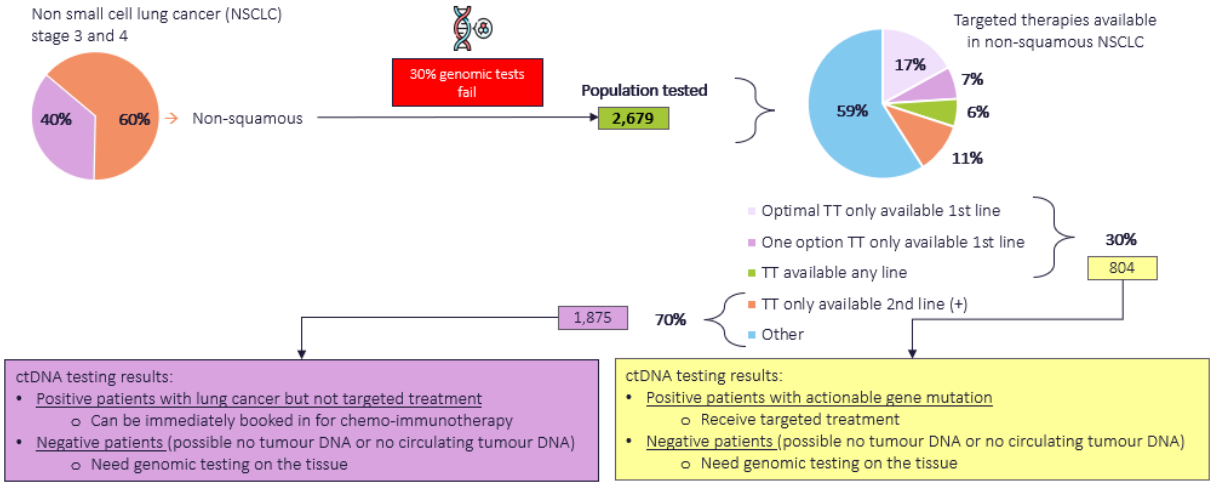
Under scenario 3 the patient accesses ctDNA testing only if the predictive biomarker testing fails. The patient has access to genomic testing when they wouldn't have been able to before.

Figure 12. Scenario 3 Diagnostic Pathway



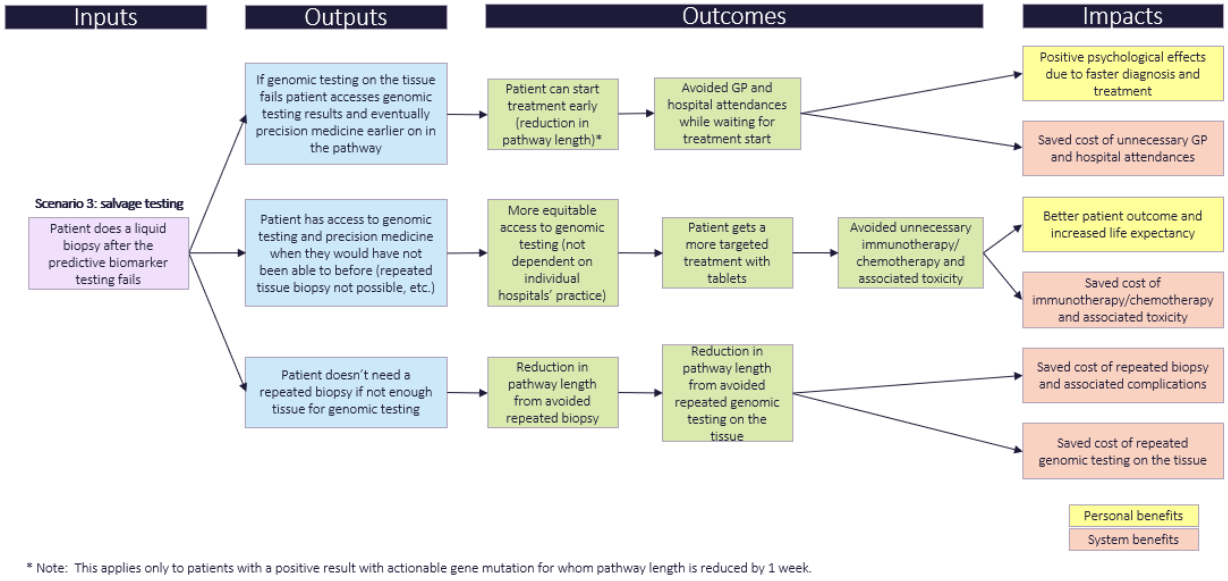
The population tested under scenario 3 is smaller than the cohorts of scenarios 1 and 2. The benefits for this cohort are reduced as ctDNA testing is introduced quite late in the diagnostic pathway.

Figure 13. Scenario 3 Population



The logic model below sets out the impacts that ctDNA testing can have on the healthcare system and individual patients across scenario 3.

Figure 14. Scenario 3 Impact Pathway



* Note: This applies only to patients with a positive result with actionable gene mutation for whom pathway length is reduced by 1 week.

7 Cost Benefit Analysis

While the previous section sets out the impact pathways across the three considered scenarios, here are presented the benefits and costs associated with the introduction of ctDNA testing in the stage III/IV lung cancer diagnostic pathway.

It is important to note that the included benefits and costs are those that can be measured at this point in time with the information currently available. For example, costs for the potential additional workload on respiratory consultants (evidence of which has come out as a result of the pilot survey in Section 9) or benefits from patients' reduced stress and anxiety have not been quantified.

All monetary values presented in this section are rounded and indicative, and are intended to illustrate relative economic performance rather than inform procurement, contracting, or pricing decisions.

Key findings

- Scenario 1 (Early testing) is associated with a positive BCR of 1.3 and a net benefit of almost £11 million. This is driven by a combination of cost savings from diagnostic procedures, avoided mistreatment and associated consequences, cost savings from reduced pathway length and improved patients' quality of life.
- Scenario 2 (Parallel salvage testing) has a BCR of 0.6, meaning that for every £1 invested, there are £0.6 of benefits in return.
- Scenario 3 (Serial salvage testing) has a BCR of 1.4 but a net benefit of only £3 million as it impacts a relatively smaller population and later on in the diagnostic pathway.

7.1 ctDNA Testing Benefits

The estimated impacts of ctDNA testing on the entire population of scenarios 1, 2 and 3 are presented below (calculations can be found in the Appendix) where ctDNA testing is introduced on the Standard mean TAT, Standard faster TAT, and Optimised pathway.

Scenario 1: ctDNA testing during respiratory clinic or hospitalisation (early testing)

Table 1. Scenario 1 benefits

Cohort[23]	Benefit	Standard mean TAT	Standard faster mean TAT	Optimised pathway
+	Cost of genomic testing on the tissue	~£14 million		
+	Cost of repeated biopsy	~£5 million		
+	Cost of repeated tissue biopsy complications	~£1.5 million		
Cost savings from diagnostic procedures		**~£21 million**		
+(t)	Cost of immunotherapy/chemotherapy	~£11 million		
+(t)	Cost immunotherapy/chemotherapy toxicity	~£1 million		
Cost savings from avoided mistreatment and consequences		**~£12 million**		
+(t)	Reduction in pathway length	~£1 million	~£0.5 million	£0
+(nt)	Cost of pathway for patients that drop out	~£0.5 million		
+(nt)	Reduction in pathway length	~£2 million	£0	£0
Cost savings from reduced pathway length		**~£3.5 million**	**~£0.5 million**	**~£0.5 million**
Improved quality of life due to ctDNA testing		**~£16 million**		
Total benefits		**~£53 million**	**~£50 million**	**~£50 million**

The difference in cost-benefit for the different pathways is only seen in the reduction in pathway length:

- 3 weeks Standard mean TAT versus 1 week Standard faster mean TAT for patients with positive ctDNA results with targetable gene.
- 1 week Standard mean TAT versus no reduction Standard faster mean TAT for those with positive ctDNA results with non-targetable gene due to waiting time for IV systemic therapy.
- No reduction in pathway length for any patients on the optimised pathway.

[23] + indicates cohort with positive lung cancer ctDNA result, +(t) indicates cohort with positive ctDNA result for lung cancer with targetable gene, +(nt) indicates cohort with positive ctDNA result for lung cancer with non-targetable gene.

Scenario 2: Parallel salvage testing

Table 2. Scenario 2 benefits

Cohort	Benefit	Standard mean TAT	Standard faster mean TAT	Optimised pathway
+	Cost of genomic testing on the tissue	~£2 million		
+	Cost of repeated biopsy	~£1 million		
+	Cost of repeated tissue biopsy complications	~£0.25 million		
Cost savings from diagnostic procedures for patients with failed genomic test		**~£3 million**		
+(t)	Cost of immunotherapy/chemotherapy	~£4 million		
+(t)	Cost immunotherapy/chemotherapy toxicity	~£0.5 million		
Cost savings from avoided mistreatment and consequences for patients with failed genomic test		**~£4.5 million**		
+(t)	Reduction in pathway length	~£0.5 million	~£0.1 million	£0
+(nt)	Reduction in pathway length	~£0.25 million	£0	£0
Cost savings from reduced pathway length for patients with failed genomic test		**~£0.75 million**	**~£0.1 million**	**£0**
Improved quality of life due to ctDNA testing for patients with failed genomic test		**~£2 million**		
Total benefits		**~£10.5 million**	**~£10 million**	**~£10 million**

The difference in cost-benefit for the different pathways is only seen in the reduction in pathway length:

- 3 weeks Standard mean TAT versus 1 week Standard faster mean TAT for patients with positive ctDNA results with targetable gene.
- 1 week Standard mean TAT versus no reduction Standard faster mean TAT for those with positive ctDNA results with non-targetable gene due to general treatment waiting time.
- No reduction in pathway length for any patients on the optimised pathway.

Scenario 3: Serial salvage testing

Table 3. Scenario 3 benefits

Cohort	Benefit	Standard mean TAT	Standard faster mean TAT	Optimised pathway
+	Cost of genomic testing on the tissue	~£2 million		
+	Cost of repeated biopsy	~£1 million		
+	Cost of repeated tissue biopsy complications	~£0.25 million		
Cost savings from diagnostic procedures for patients with failed genomic test		**~£3 million**		
+(t)	Cost of immunotherapy/chemotherapy	~£4 million		
+(t)	Cost immunotherapy/chemotherapy toxicity	~£0.3 million		
Cost savings from avoided mistreatment and consequences for patients with failed genomic test		**~£4 million**		
+(t)	Reduction in pathway length	~£0.1 million	£0	£0
Cost savings from reduced pathway length for patients with failed genomic test		**~£0.5 million**	**~£0.1 million**	**£0**
Improved quality of life due to ctDNA testing for patients with failed genomic test		**~£2 million**		
Total benefits		**~£10 million**	**~£10 million**	**~£10 million**

The difference in cost-benefit for the different pathways is only seen in the reduction in pathway length with 1 week Standard mean TAT versus no reduction Standard faster mean TAT and Optimised pathway for those with positive ctDNA results with targetable gene due to general treatment waiting time.

7.2 ctDNA Testing Costs

Indicative ctDNA testing costs were developed to inform the economic modelling, based on 2023 delivery assumptions and anticipated activity levels. These estimates reflect typical NHS laboratory delivery models and include staff time, consumables, reagents, quality assurance, overheads, and supporting infrastructure.

Per-test ctDNA costs vary according to laboratory configuration, testing platform, procurement arrangements, and scale of activity. As testing volumes increase over time, economies of scale are expected to apply, with potential reductions in average cost per test and improvements in turnaround times, although variation between providers is likely to persist.

Given the commercially sensitive nature of detailed laboratory cost structures and procurement arrangements, itemised cost breakdowns (previously presented as Table 4) are not presented in this report.

In addition to the cost of ctDNA testing, the analysis also considered the impact of earlier access to targeted therapies for a subset of patients who would otherwise have received immuno-chemotherapy on the standard pathway. These downstream treatment costs were incorporated at a high level to reflect differences in treatment pathways, without seeking to model individual drug prices or prescribing decisions.

7.3 Benefit Cost Ratio (BCR)

The impact of ctDNA testing introduction in the advanced lung cancer diagnostic pathway (Standard mean TAT, Standard faster TAT, and Optimised pathway) has been estimated over three different scenarios and the associated benefit-cost ratios (BCR) are presented below (Table 5, 6 and 7).

An intervention with a BCR higher than one provides a net economic gain (for every pound invested you get back over one pound in benefits) and can be considered economically justified. Overall, the results of this work support the early use of ctDNA testing (Scenario 1).

Table 4. Scenario 1 BCR

Scenario 1: ctDNA testing during respiratory clinic or hospitalisation (early testing)	**Standard mean TAT**	**Standard faster mean TAT**	**Optimised pathway**
Tested population	19,991		
Benefit-cost ratio	**1.3** (0.8 – 1.6)	**1.2**	**1.2**
Net impact	**~£11 million**	**~£8 million**	**~£7.5 million**
Total benefits of ctDNA testing (+)	**~£53 million**	**~£50 million**	**~£50 million**
Total healthcare benefits	~£37 million	~£34 million	~£34 million
Total personal benefit	~£16 million	~£16 million	~£16 million
Total cost of ctDNA testing (-)	**~£42 million**	**~£42 million**	**~£42 million**

Early use of ctDNA testing delivers the highest value of benefits and an overall BCR of 1.3. This is largely driven by improved patient quality of life, avoided cost of genomic testing on tissue and avoided chemo-immunotherapy from detection of targetable gene variants.

Table 5. Scenario 2 BCR

Scenario 2: Parallel salvage testing	**Standard mean TAT**	**Standard faster mean TAT**	**Optimised pathway**
Tested population	8,641		
Benefit-cost ratio	**0.6** (0.4 – 0.7)	**0.6**	**0.6**
Net impact	**~-£7 million**	**-£7.5 million**	**~-£7.5 million**
Total benefits of ctDNA testing (+)	**~£10.5 million**	**~£10 million**	**~£10 million**
Total healthcare benefits	~£8 million	~£8 million	~£7.5 million
Total personal benefit	~£2.5 million	~£2.5 million	~£2.5 million
Total cost of ctDNA testing (-)	**~£17.5 million**	**~£17.5 million**	**~£17.5 million**

Although parallel salvage testing delivers some benefits, it does not outweigh the costs associated with ctDNA testing, since both genomic and ctDNA are carried out in this scenario.

Table 6. Scenario 3 BCR

Scenario 3: Serial salvage testing	Standard mean TAT	Standard faster mean TAT	Optimised pathway
Tested population	2,679		
Benefit-cost ratio	**1.4** (1.1 – 1.5)	**1.4**	**1.4**
Net impact	**~£3 million**	**~£2.5 million**	**~£2.5 million**
Total benefits of ctDNA testing (+)	**~£10 million**	**~£10 million**	**~£10 million**
Total healthcare benefits	~£8 million	~£7.5 million	~£7.5 million
Total personal benefit	~£2.5 million	~£2.5 million	~£2.5 million
Total cost of ctDNA testing (-)	**~£7.5 million**	**~£7.5 million**	**~£7.5 million**

Serial salvage testing delivers a BCR of 1.4 but the lowest quantum of benefit, as liquid biopsy is used by relatively fewer people and at a later stage in the pathway.

7.4 Sensitivity analysis: ctDNA test cost assumptions

Sensitivity analysis was undertaken to explore the relationship between ctDNA test pricing and the estimated benefit–cost ratios across the three implementation scenarios. This analysis assessed how variation in ctDNA test costs could influence the overall economic case under different pathway configurations.

The results of this analysis confirmed that the economic case for early testing and serial salvage testing is robust across a plausible range of ctDNA test prices, while the parallel salvage testing scenario remains more sensitive to test pricing due to duplication of testing activity.

Given the commercially sensitive nature of test pricing and procurement arrangements, detailed price thresholds and scenario-specific cost–benefit curves are not reported in this document (this includes Figure 15). These analyses were used to inform interpretation of the results but are not intended to represent procurement prices or contractual benchmarks.

8 NSCLC ctDNA Testing Pilot Demographics and Outcomes

As part of the evaluation, data from a pilot commissioned by NHSE, involving patients suspected of having stage III/IV non-small cell lung cancer (NSCLC) and who underwent ctDNA testing, have been analysed. A total of 1,296 samples from this pilot have been examined and compared with the assumptions used for economic modelling.

Key findings

- While all pilot patients underwent liquid biopsy, 10% did not have tissue biopsy, mainly due to high risk or mortality before the procedure.
- Histological diagnosis revealed 63% of patients had NSCLC, predominantly adenocarcinomas, with some patients requiring repeated biopsy and experiencing complications.
- Overall comparison of turnaround times showed genomic test results from liquid biopsy were approximately 2 weeks faster than tissue biopsy, with variations across GMSAs.
- The patients prescribed targeted treatment accessed it around two weeks earlier than those prescribed general cancer therapy.
- Pilot data differed from assumptions, with higher patient performance status, lower NSCLC diagnoses, and fewer additional biopsies and complications. Only 18% of NSCLC patients received targeted therapy, contrasting the expected 30%. This underestimation is due to the pilot data only capturing 1st line treatments.
- Genomic testing turnaround times was in agreement with estimated timeframes of 14 days from liquid biopsy sample taken to liquid biopsy genomic report.
- Integrating pilot data into economic models showed Scenario 1 yielding a net savings of £9m with a slightly lower cost-benefit ratio. Both parallel and serial salvage testing scenarios showed lower relative savings. However, overall, economic model results based on pilot data still aligned closely with predictions, demonstrating cost-benefit advantages for implementing ctDNA testing.

8.1 Insights on Pilot Data

To support the development of the proposal to commission ctDNA testing for stage III/IV suspected non-small cell lung cancer patients, NHS England brought together a group of experts as part of a national oversight group to deliver a testing pilot. ctDNA samples were taken from 1,296 prospective patients with radiological evidence of stage III/IV thoracic malignancy but without yet a confirmed diagnosis for direct gene panel analysis for those genes already approved on the Test Directory. The pilot was led by the North Thames and North East & Yorkshire GMSA.

The pilot data was gathered through the seven NHSE Genomic Medicine Service Alliances supporting the NHSE Genomic Medicine Service comprising the following:

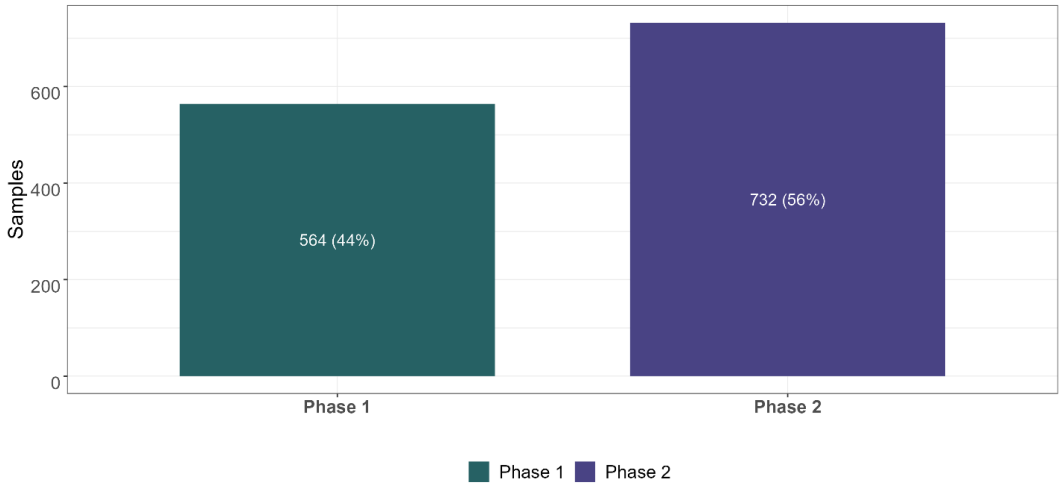
- North West GMSA
- North East and Yorkshire GMSA
- East GMSA
- Central and South GMSA
- North Thames GMSA
- South East GMSA
- South West GMSA.

The pilot comprised two phases:

- Liquid biopsies obtained from 1st January 2023 to 1st August 2023 underwent testing via commercial provider pathways, primarily through Guardant Health and Roche Foundation.
- Samples collected from 1st August 2023 to 20th February 2024 predominantly followed the pathways established by the Royal Marsden NHS Foundation Trust (RMH). However, in instances where RMH could not conduct liquid biopsy analysis, some samples were sent to Guardant for testing.

As shown in Figure 15, more samples were received in Phase 2 (56%) than in Phase 1 (44%).

Figure 15. Samples received from pilot Phase 1 and Phase 2

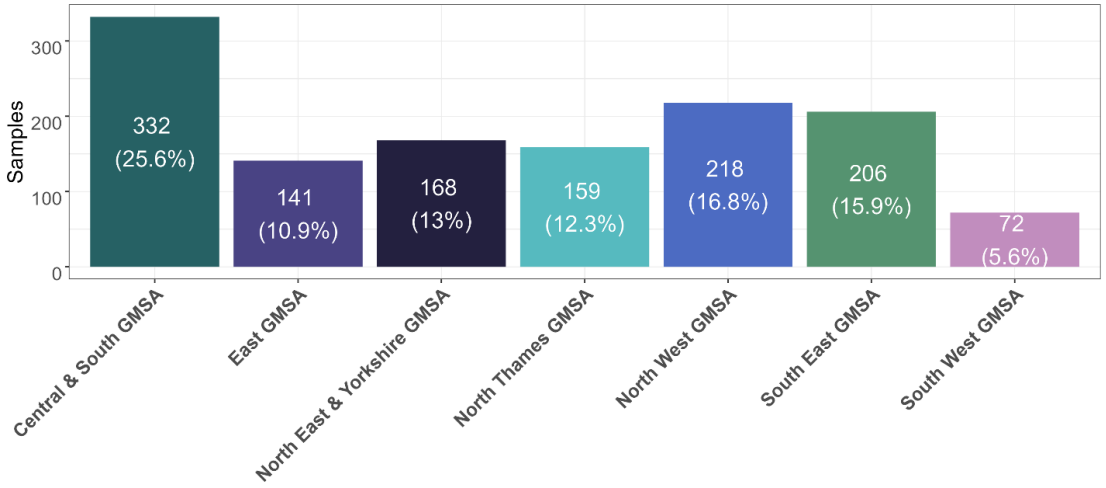


A standardised data template comprising 88 fields was formulated for completion by participating sites, with suggested dropdown options to ensure uniform responses. However, upon discussion with clinicians before circulation, it was found that operational constraints, such as challenges in consolidating patient information from multiple sources and concerns regarding the accuracy of genomic data interpretation by personnel potentially underqualified for such tasks, posed the potential challenge of poor data completeness. Consequently, a decision was reached to identify a subset of 25 fields mandatorily requiring completion by all sites. The remaining fields were designated as optional, with no strict scrutiny in instances where fulfilment was hampered by the mentioned constraints.

8.1.1 Demographics

A variation in the distribution of samples from the GMSAs is observed, with the highest number of samples received from Central and South GMSA, contributing approximately 26%, and the lowest number from South West GMSA, accounting for 6% of the total samples. GMSA specific sample distribution and proportion of total samples are shown in Figure 16. The proportion of samples per GMSA also roughly reflects the size of the GMSA except for East GMSA which has one of the largest catchment areas[24].

Figure 16. Pilot data sample distribution across GMSAs, with percentage of total samples per GMSA



The pilot was conducted in two phases: 564 (44% of the total) liquid biopsy samples were analysed before the 1st of August 2023 and 732 (56%) were analysed in Phase 2, post August 1st, reflecting a fairly even split in samples collected in the two phases. A similar split of 45% and 55% for Phase 1 and 2, respectively is observed for patients with a NSCLC diagnosis.

[24] Population breakdown of the GMSA regions are as follows: Central & South GMSA – 19.3%, East GMSA – 15.1%, North East & Yorkshire – 16%, North Thames GMSA – 13.9%, North West – 12.6%, South East GMSA – 15.4%, South West GMSA – 7%

Demographic data was collected on age, sex, and smoking history[25]. Results are summarised in Table 7.

Table 7. Baseline characteristics of patients participating in the pilot

Baseline characteristics in the pilot data	
Characteristic	**Value (% of total*)**
Age, median (range)	70 (26 – 96)
Sex	
Male	609 (52%)
Female	563 (48%)
Smoking history	
Never smoker	166 (18%)
Ex-smoker	37 (4%)
Smoker	734 (78%)
Performance status	
0	336 (26%)
1	543 (42%)
2	284 (22%)
3	111 (9%)
4	12 (1%)

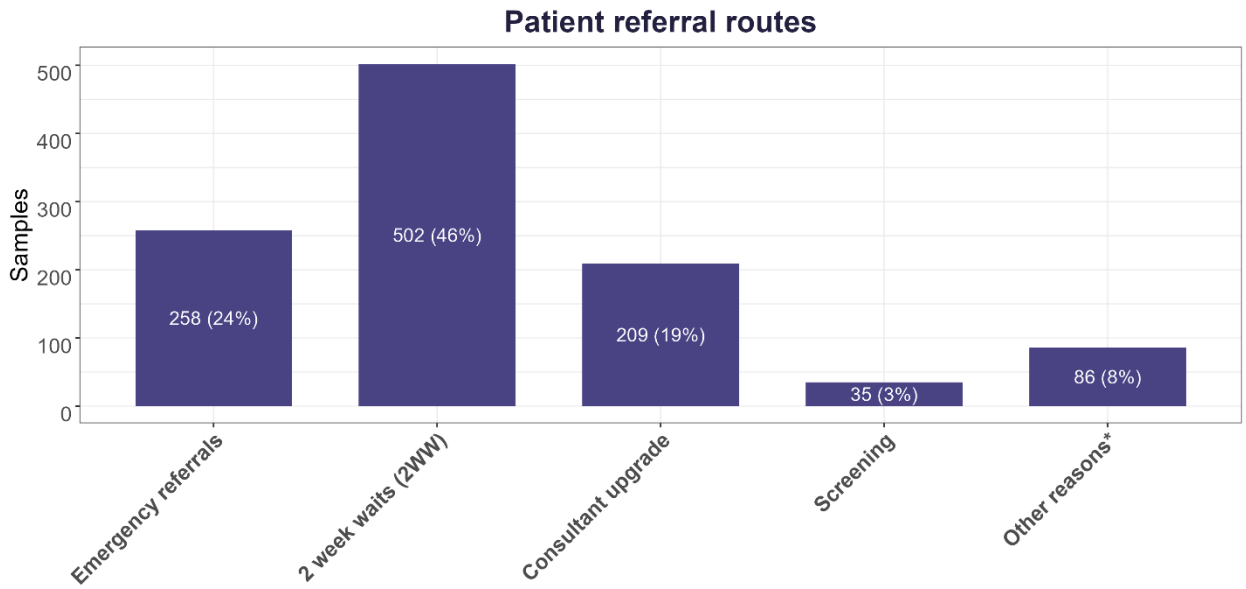
**Total may vary per characteristic due to variation in data completeness*.

[25] This information was not marked as a mandatory field for completion hence, data for each characteristic was not received from all providers.

8.1.2 Referral route

Patients were referred from a variety of routes. As shown in Figure 17, the most likely route of referral was via the 2 week-wait (2WW) with 46% of patients. 24% of patients presented through an emergency referral, followed by 19% through consultant upgrade. Around 3% of patients also presented through screening, and the remaining 8% presented via private appointments, respiratory clinics or internal routes.

Figure 17. Patient referral route distribution



**Other reasons include referrals through private appointment, respiratory clinician, internal, etc.*

8.1.3 Diagnostic Outcomes

About 10% of patients did not undergo a tissue biopsy. This was due to the following reasons (where known):

- Tissue biopsy was deemed high-risk for the patient due to poor performance status or the patient was too unwell
- Other patients died before the tissue biopsy.

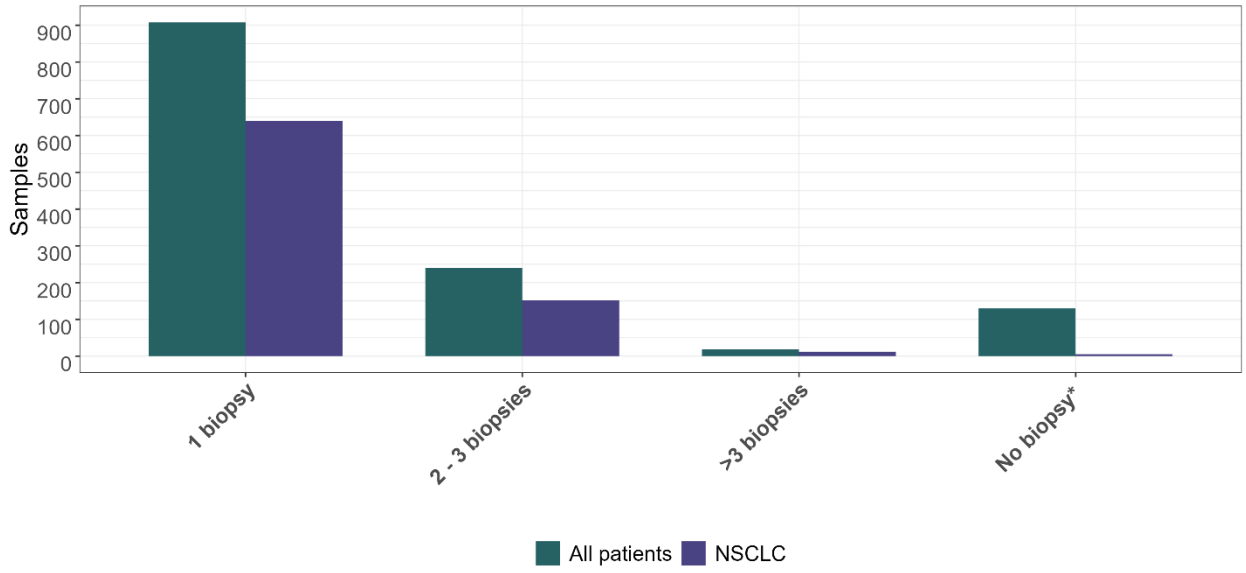
However, all patients underwent ctDNA testing.

Repeated biopsy and associated complications

Out of the overall cohort of patients, as shown in Figure 18, 70% of patients had to only undergo tissue biopsy once to successfully conduct histological testing and genomic testing on the tissue sample. 20% of the patients had to undergo repeated biopsy, where the majority of patients were

successful in the first or second attempt of repeated biopsy and a small proportion of patients that had to undergo more than three biopsies.

Figure 18. Number of tissue biopsy attempts undergone by the entire cohort of patients



**No biopsy - The reasons for patients who did not undergo a biopsy are only known for 29 patients. These reasons include instances where the biopsy was abandoned due to the patient being too unwell to tolerate, or the biopsy was deemed high-risk for the patient by the Multidisciplinary Team (MDT), or the patient deceased before the biopsy could be conducted.*

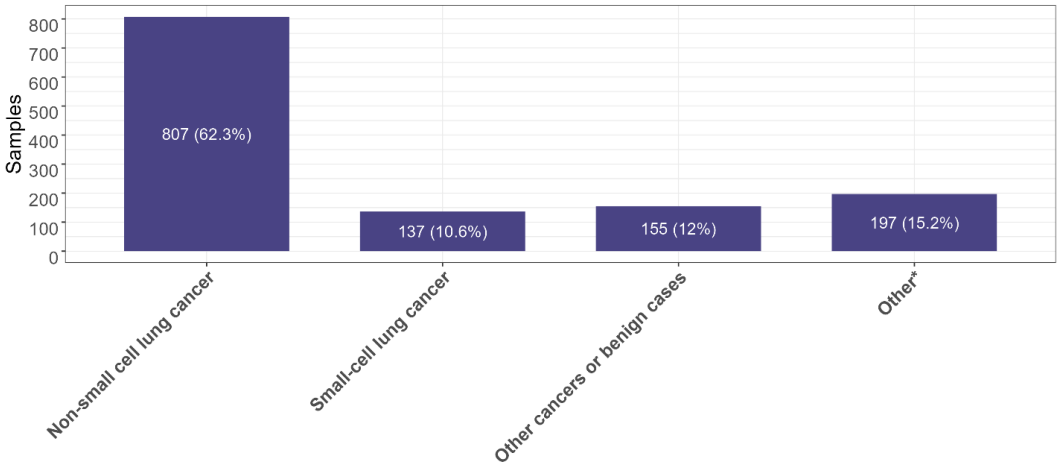
When further sub-setting the entire cohort for only patients that subsequently received a NSCLC histological diagnosis, out of a total of 807 NSCLC patients, it was found that 79% of patients underwent successful tissue biopsy at the first attempt.

Around 6% of all patients also experienced complications, including infections, pneumothorax and other causes that were not reported.

Diagnosis

As shown in Figure 19, 62% of patients received a diagnosis of NSCLC through histological testing of the tissue. 11% of patients received a small-cell lung cancer diagnosis while 12% resulted in other cancers (e.g. mesothelioma, breast, and rectal cancer). The remaining 15% of patients had other outcomes due to a variety of reasons including inconclusive results (64 patients), 22 cases of patients that were too unwell to go through tissue biopsy, died prior to getting a biopsy, one patient refused the biopsy, and remaining patients did not go through a tissue biopsy, however, the reason behind this is unknown. Irrespective of whether patients did or did not undergo tissue biopsy, all patients underwent liquid biopsy.

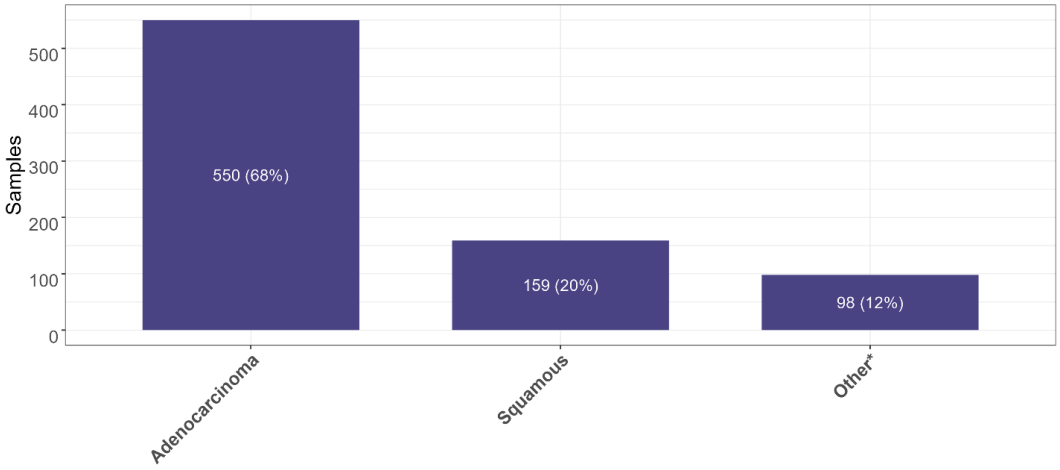
Figure 19. Histological diagnosis from tissue biopsy



Out of all the patients that were diagnosed with NSCLC, 99% were either diagnosed at Stage III or IV, consisting of 76% Stage IVs. The remaining 1% consisted of 3 patients that were either Stage I or II, presented in Figure 20.

Histological diagnosis from tissue biopsy of NSCLC patients revealed 68% of patients had adenocarcinoma NSCLC, 20% were squamous NSCLC and the remaining 8% were diagnosed as 'Not otherwise specified' (NOS), 2 patients with large cell neuroendocrine carcinoma (LCNEC) which is a rare cancer that present features of both NSCLC and SCLC.

Figure 20. Histological subtype of NSCLC patients



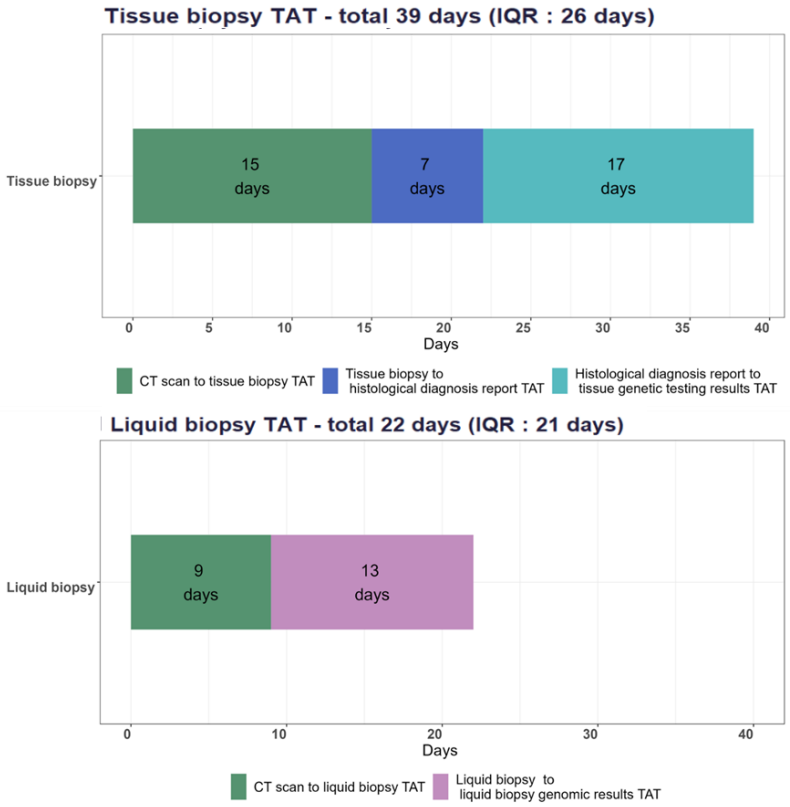
Diagnostic TATs

Tissue biopsy TAT - Overall, the median TAT from CT scan to reporting of tissue genetics[26] is observed to be 38 days. However, there is variation in this TAT achieved across GMSAs with a difference of 17 days between GMSAs with the shortest and longest TAT.

Liquid biopsy TAT - Overall, the median TAT from CT scan to reporting of liquid biopsy results is observed to be 22 days with variation across GMSAs by 13 days.

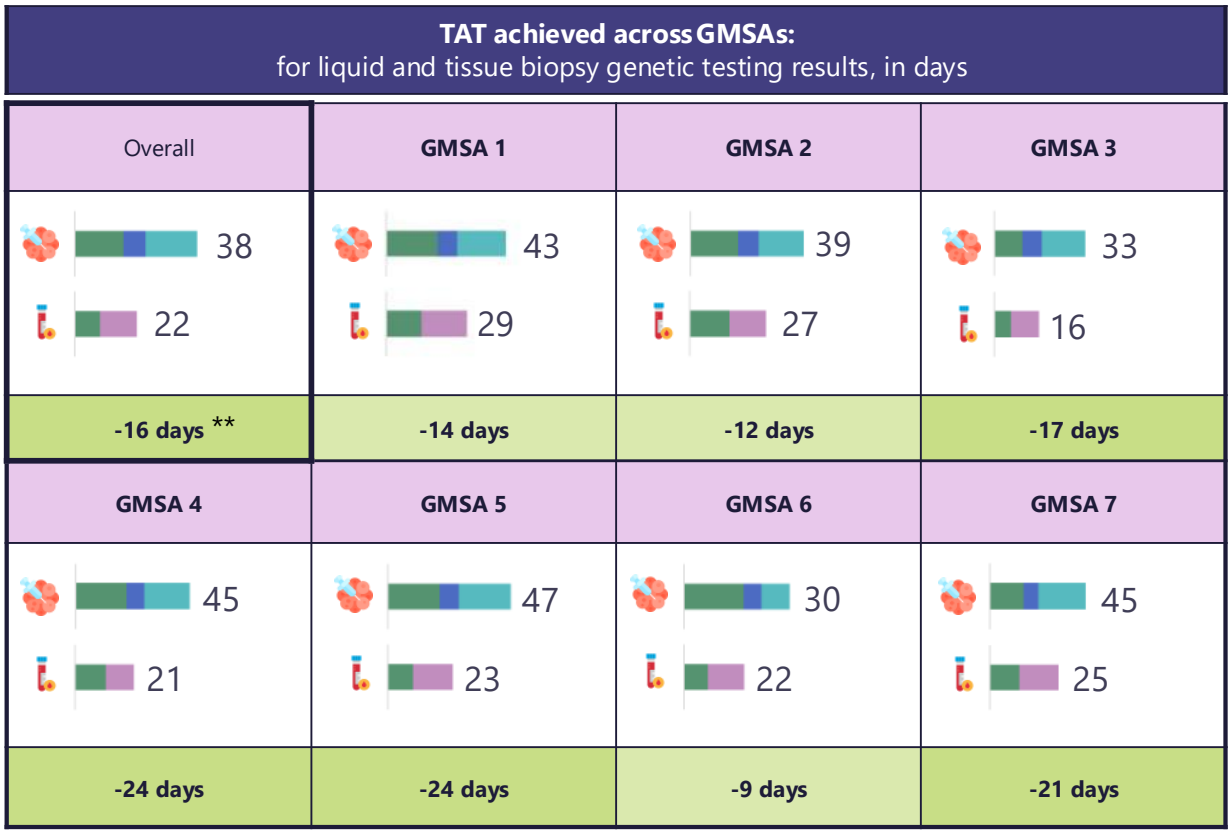
Comparison between the median TAT for tissue biopsy and liquid biopsy resulted in an overall 16 days early reporting of liquid biopsy results compared to tissue biopsy genetic test results, Figure 21. All GMSAs achieved faster median TAT for liquid biopsy results than tissue biopsy, with 4 GMSAs achieving liquid biopsy genetic results up to 3 weeks sooner than tissue biopsy genetic testing results, visualized in Figure 22.

Figure 21. Overall pilot data median TAT for genomic test results from tissue biopsy and liquid biopsy



[26] *Tissue biopsy - date final molecular result authorised* field in submitted dataset was used as tissue genetics date of report.

Figure 22. Median TAT per GMSA for tissue and liquid biopsy for NSCLC patients (in days)



**GMSAs with TAT difference between liquid biopsy and tissue biopsy of 1 – 2 weeks is shaded in light green and GMSAs with TAT difference of over 2 weeks is shaded in darker green.*

***Negative days indicate the number of days by which genetic test results were received earlier from liquid biopsy compared to tissue biopsy.*

Note: Table containing detailed breakdown of TAT per GMSA and hospital is included in the Appendix.

The comparison of turnaround times (TATs) achieved between the two phases shows a significant difference in liquid biopsy genomic results TAT. Phase 1 showed a one-week earlier turnaround in liquid biopsy testing results compared to Phase 2. This difference could be attributed to the change in the pathway for liquid biopsy testing between Phase 1, where testing was via commercial provider pathways; through Guardant and Roche- a faster route than the RMH route adopted in Phase 2. However, it is worth noting that genomic results obtained through liquid biopsy testing maintain faster TAT compared to tissue biopsy in both phases, as shown in Table 8.

Table 8. Comparison of turnaround times (TAT) for tissue and liquid biopsy achieved in the pilot Phase 1 and Phase 2 for patients diagnosed with NSCLC, in days

	Phase 1	Phase 2
NSCLC samples	367	440
Tissue testing TATs - CT scan to tissue genetic test results TAT (median days)	**39**	**38**
ctDNA testing TATs - CT scan to liquid biopsy genomic results TAT (median days)	**19**	**25**
CT scan to liquid biopsy taken TAT	9	11
Liquid biopsy taken to liquid biopsy genomic results TAT	10	14
TAT difference between liquid biopsy results and tissue biopsy results**	**-20**	**-13**

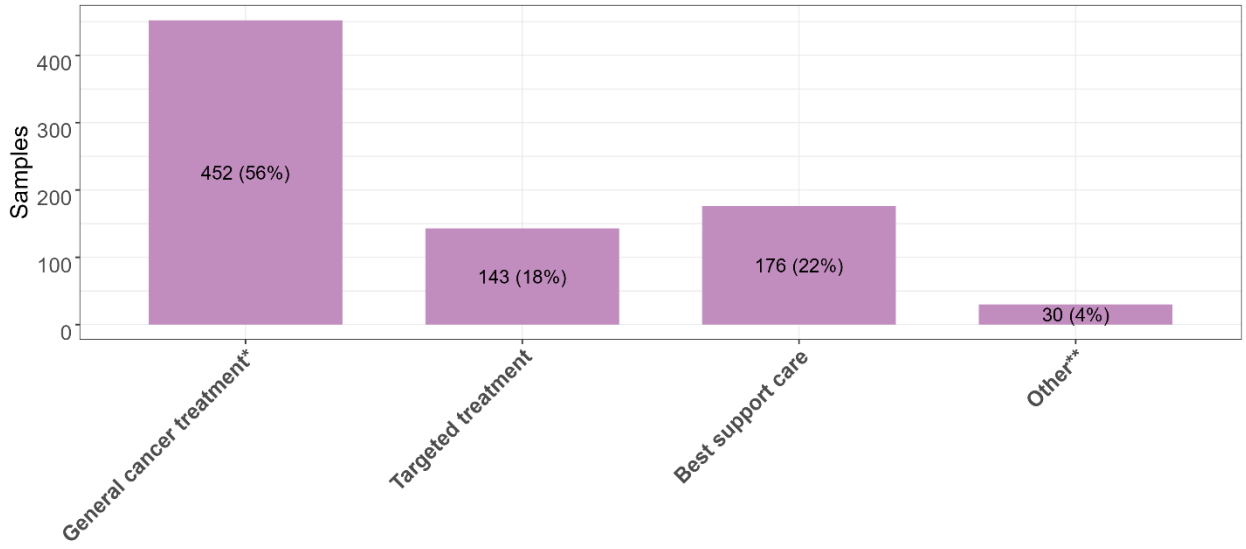
**Only NSCLC samples that underwent 1 biopsy were used for the analysis of turnaround times.*

*** Negative days indicate the number of days by which genetic test results were received earlier from liquid biopsy compared to tissue biopsy*

8.1.4 Treatments

The three main treatments prescribed to patients diagnosed with NSCLC were 54% general cancer treatment which was in most cases a combination of chemo and immunotherapy but could also include radiosurgery, radiotherapy and chemoradiotherapy, 18% received targeted treatment and 22% received 'best supportive care' (Figure 23). A minority of patients (4%) did not commence treatment due to various reasons, such as patient deceased, patient refusal, transfer to another care facility, or not receiving treatment.

Figure 23. Treatments for patients diagnosed with NSCLC



**General treatment is predominantly chemoimmunotherapy but also includes radiosurgery, radiotherapy, surgery, and chemoradiotherapy.*
***'Other' includes patients who were not given any treatment, declined treatment, or died prior to treatment start.*

Concordance between liquid and tissue biopsy results

Comparison of variants reported from ctDNA test and tissue biopsy on patients revealed:

- Concordant results - In 21% of patients with a mutation detected, the same genetic variant was identified in both tests.
- Non-concordant results - Among 79% non-concordant cases, out of which 84% of patients showed a genetic variant through liquid biopsy (including 34% overall where the genetic variant was not specified and was labelled as "Other" in the liquid biopsy result data field), while it wasn't detected via the genomic testing on the tissue. Conversely, 10% exhibited a genetic variant through the tissue but not with liquid biopsy. Additionally, 5% displayed differing genetic variants between the two tests.

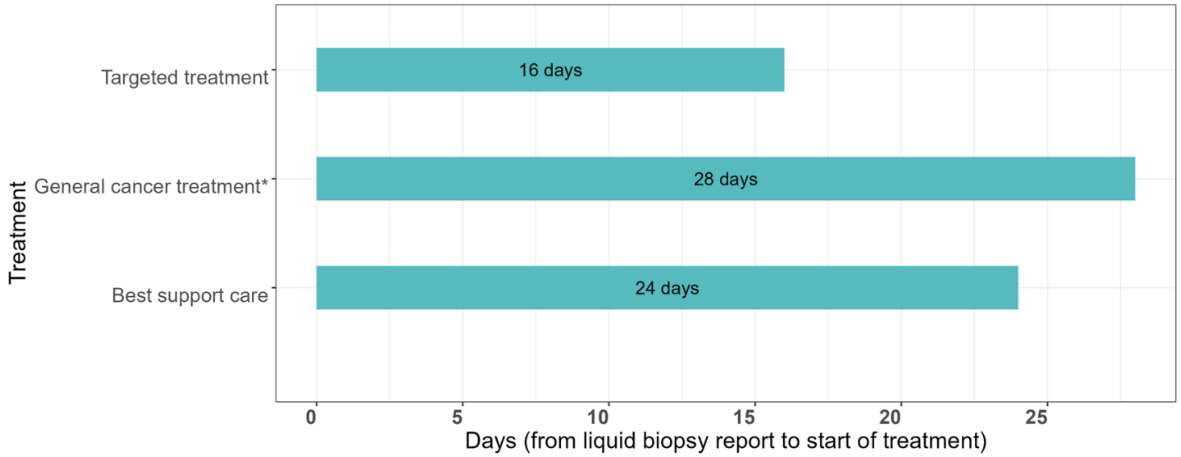
Genetic variant of patients on targeted treatment

Out of the patients who were prescribed targeted treatment, the most common genetic variant found through ctDNA testing was the EGFR variant (68%). The remaining portion of patients include ALK (8%), KRAS (3%), MET (3%), RET (2%), BRAF (1%) or other genetic alterations. 5% of patients genetic variant was detected through tissue biopsy but not liquid biopsy testing.

Treatment TATs

A variation was observed in the start of treatment date from the point of getting the liquid biopsy genomic test results to starting treatment for patients prescribed different treatments (Figure 24). The median TAT was the shortest for patients prescribed with targeted treatment of 16 days, followed by best supportive care at 24 days. The wait is the longest, 28 days for general cancer which concurs with the fact that there is a long waiting list for general cancer treatment as this treatment is also prescribed to patients with other cancers.

Figure 24. Median TAT from liquid biopsy result report to start of treatment date for different treatments for NSCLC patients (in days)



**General treatment is predominantly chemoimmunotherapy but also includes radiosurgery, radiotherapy, surgery, and chemoradiotherapy.*

8.1.5 Clinician Opinion

When clinicians were asked whether they found the test to be clinically helpful, 56% of clinicians answered affirmatively. Specifically, 66% of clinicians found the test helpful for patients diagnosed with NSCLC for reasons such as enabling earlier treatment access for patients through genetic test results from ctDNA testing or access to genetic test results through ctDNA testing for patients who had failed tissue biopsy.

8.2 Comparison with Model Assumptions

Demographics, diagnosis, and treatments

A comparison of the assumptions employed in economic modelling and the outcomes derived from analysing the pilot study revealed differences (figures summarised in Table 9) in the following categories of assumptions:

- **Demographics** – 90% of patients in the pilot had a performance status of 0-2 which is 17% higher than the assumption made for the economic model.
- **Histological diagnosis** – In the pilot study, the number of patients diagnosed with NSCLC was 20% lower than assumed in the economic model. While the proportion of patients with adenocarcinoma exceeded the modelling assumption by only 8% in the pilot, the figure for squamous cell carcinoma remained consistent at 20% for both the pilot and the model assumption. The proportions of patients diagnosed with small cell lung cancer, other cancers, or no cancer showed agreement between the pilot and the modelling assumption. 99% of the patients who received a NSCLC diagnosis had stage III or IV cancer which is much higher than the assumed proportion of 64% of stage III/IV cancer. However, this could be speculated to be a recruitment criterion for the pilot study participants.
- **Diagnostic procedures** – Among the patients who underwent tissue biopsy, 20% required one or more additional biopsies, 10% lower than assumed for the economic model. While it was assumed that 20% of patients would encounter complications from tissue biopsy, the pilot study reported a substantially lower rate of complications, with only 6% of patients experiencing such issues such as infections and pneumothorax. This was because of the methodology used to report complications in the pilot data, discussion with clinicians confirmed that the historic 20% rate is a better representation of reality.
- **Treatments** – Among the various genetic variants observed in NSCLC patients, 30% of these variants are typically eligible for targeted treatment as a first-line therapy. However, the pilot study revealed a lower percentage, with only 18% of diagnosed NSCLC patients undergoing targeted therapy. This difference is primarily driven by the pilot capturing first-line prescribing only, rather than reflecting a change in the underlying prevalence of actionable variants.

Genomic testing turnaround times

The comparison between estimated median TAT based on the standard diagnostic pathway and the actual TAT achieved by pilot data (TAT summarised in Table 10) reveals the following:

- **Genomic results from tissue biopsy TAT** – The estimated median TAT for tissue biopsy genetic test results was 37 days, from the day the patient receives a CT scan to the date they receive their tissue genetic testing results. Upon comparing this to the pilot data outputs, it is observed that they align precisely.
- **Genomic results from liquid biopsy TAT** – In the pilot, there is median 9 days TAT from the CT scan and liquid biopsy taken and 14 days TAT from the date of liquid biopsy taken to the date of liquid biopsy report. The turnaround time from when liquid biopsy is taken to when results are reported is in concordance with our estimation.
- **Faster diagnosis through genetic testing from liquid biopsy** – The pilot data confirms our assumption of a shorter median TAT for genetic testing from liquid biopsy. However, the time saved according to the pilot data is two weeks, whereas our estimation indicated three weeks.

8.3 How does the pilot data affect the economic estimate of introducing ctDNA?

When the economic model was updated using values obtained from the pilot data, it was found that the net impact for the three scenarios was as follows:

- **Scenario 1: ctDNA at respiratory clinic –** Net impact savings of £9m resulting in a cost-benefit ratio of 1.1. This is marginally lower than the results from the previously modelled assumptions of a 1.25 cost-benefit ratio and £10m net impact savings.
- **Scenario 2: Parallel salvage testing -** Net impact loss of around £15m under pilot assumptions, reflecting lower-than-expected uptake of targeted therapy and reduced avoided biopsy activity, compared with losses of around £7–8m under the base-case model.
- **Scenario 3: Serial salvage testing -** Net impact savings of £3m resulting in a cost-benefit ratio of 1.3. This is marginally lower than results from the previously modelled assumptions of 1.4 cost-benefit ratio and £2m net impact savings.

Overall, the results from the economic model of the pilot study align closely with the outcomes predicted by the previous assumptions, although there are some slight discrepancies. Among the scenarios evaluated, Scenario 1 and Scenario 3 continue to demonstrate cost-benefit advantages for the implementation of ctDNA testing.

Table 9. Comparison of assumption values used for economic modelling and results from pilot data

Assumption	Economic model assumption value	Pilot data value
Demographics		
Performance status of 0 - 2	73%	90%
Histological diagnosis		
Non-small cell lung cancer	82%	62%
Stage III/IV	64%	99%
Non-squamous	60%	80% (68% adenocarcinomas)
Squamous cell	40%	20%
Small cell lung cancer	15 - 20%	11%
Other cancers	13%	12%
Non-cancers		15%
Diagnostic procedures		
Repeated biopsies	30%	20%
Complications	20%	6%
Treatment		
NSCLC treated using **targeted treatment** based on ctDNA test results	30%	18%
Genetic variants of NSCLC treated through targeted therapy	ALK, BRAF, EGFR, MET, RET, ROS-1	ALK, BRAF, EGFR, ERBB2, KRAS (and amplification), LRIG-ROS1 fusion, MET, RET

Table 10. Comparison of median TAT estimation for liquid and tissue biopsy genetic test results for the model vs results from the pilot data

	Economic model assumption value	Pilot data value
Tissue testing TATs - CT scan to tissue genetic test results TAT	**37 days**	**38 days**
CT scan to date of tissue biopsy TAT	6 days	15 days
Tissue biopsy to histological diagnosis report TAT	10 days	7 days
Histological diagnosis report to tissue genetic testing results TAT	21 days	16 days
ctDNA testing TATs - CT scan to liquid biopsy genomic results TAT (median days)	**14 days**	**22 days**
CT scan to liquid biopsy taken TAT	0 days	9 days
Liquid biopsy taken to liquid biopsy genomic results TAT	14 days	13 days
TAT difference between liquid biopsy results and tissue biopsy results**	**23 days (~3 weeks)**	**16 days (~2 weeks)**

9 Respiratory MDT Experiences

As part of this evaluation, oncologists, respiratory clinicians, cancer nurse specialists (CNSs) and other lung support workers' opinions on the pilot for the introduction of ctDNA testing in the advanced lung cancer diagnostic pathway have been collected through feedback surveys. Below are summarised the key findings from this data collection.

Key findings

- Respectively 71.2% and 88.5% of respondents believe that introducing ctDNA testing into the advanced lung cancer diagnostic pathway reduces time to diagnosis and treatment.
- 55.7% have experienced ctDNA testing leading to fewer complications and disease deterioration in patients waiting for treatment.
- The majority, 80.8%, agreed that introducing ctDNA testing in the diagnostic pathway increases patients' access to targeted treatment.
- Early testing has been selected as the optimal pathway for the delivery of ctDNA testing by 88.5% of respondents.
- The majority of staff found the ctDNA results clear and easy to interpret (67.8%), 74.2% of respondents didn't need a second opinion in the interpretation and 58% feel confident in only using ctDNA results to inform patient diagnosis.
- There are mixed feelings about the impact the test has on workload.

9.1 Survey Participants

As outlined in Figure 25 and Figure 26, 52 staff surveys have been returned across a range of roles and geographies. Of those that have been returned 23 (44%) are CNSs, 14 (27%) are oncologists, and 13 (25%) are respiratory clinicians.

Figure 25. Survey participants' role

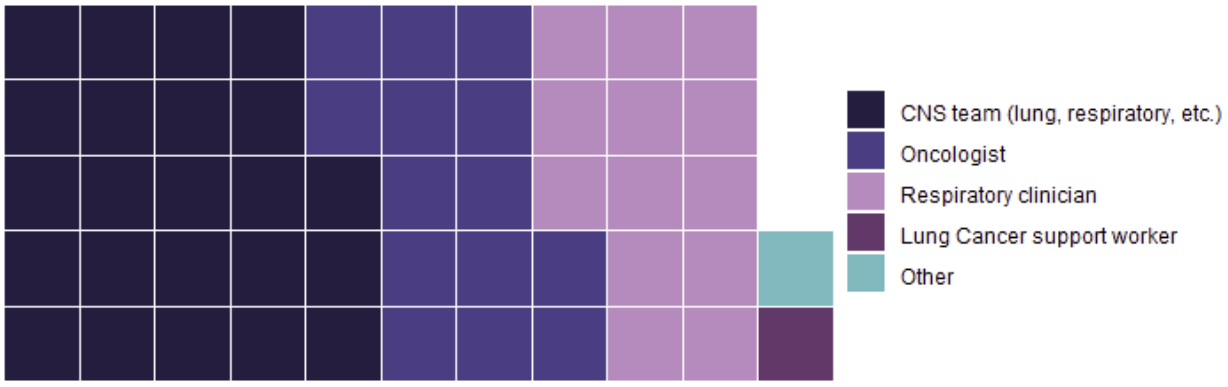


Figure 26. Survey participants' Trust

Hampshire Hospitals NHS Foundation Trust	3
Sheffield Teaching Hospitals NHS Foundation Trust	3
South Tees Hospitals NHS Foundation Trust	3
University Hospital Southhampton NHS Foundation Trust	3
Barts Health NHS Trust	2
Guy's and St Thomas' NHS Foundation Trust	2
Manchester University NHS Foundation Trust	2
Northern Care Alliance NHS Foundation Trust	2
Oxford University Hospitals NHS Foundation Trust	2
Portsmouth Hospitals University NHS Trust	2
Royal Marsden NHS Foundation Trust	2
Salisbury NHS Foundation Trust	2
Somerset NHS Foundation Trust	2
University Hospital Sussex NHS Foundation Trust	2
University Hospitals Bristol and Weston NHS Foundation Trust	2
University Hospitals of Morecambe Bay NHS Foundation Trust	2
Not provided	2

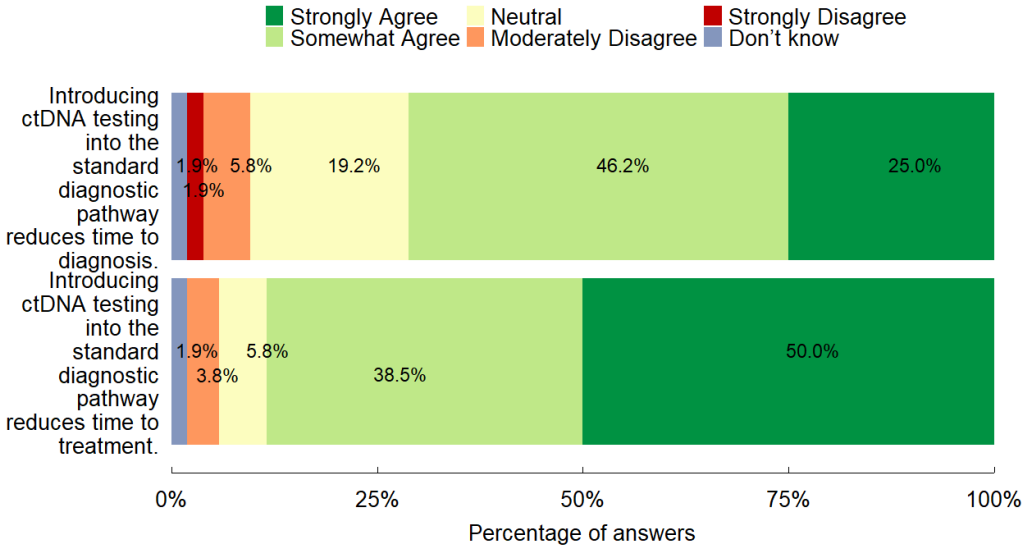
Bradford Teaching Hospitals NHS Foundation Trust	1
Chelsea and Westminster NHS Foundation Trust	1
Dorset County Hospital NHS Foundation Trust	1
Epsom and St Helier University Hospitals NHS Trust	1
Leeds Teaching Hospitals Trust	1
Medway NHS Foundation Trust	1
Newcastle Hospitals NHS Foundation Trust	1
Royal Devon and Exeter NHS Foundation Trust	1
Royal Devon University Healthcare NHS Trust	1
Royal Surrey NHS Foundation Trust	1
South Tyneside and Sunderland NHS Foundation Trust	1
University Hospitals Dorset NHS Foundation Trust	1
Wirral University Teaching Hospital NHS Foundation Trust	1
East and North Hertfordshire / West Hertfordshire Teaching Hospitals NHS Trust	1

9.2 Perceived benefits compared to the standard diagnostic pathway

9.2.1 Timely diagnosis and treatment

Overall, what has emerged from the survey is that the majority of respondents (37 – 71.2%) believe that introducing ctDNA testing into the advanced lung cancer diagnostic pathway reduces time to diagnosis, and (46 - 88.5%) that it reduces time to treatment. Respectively 10 (19.2%) and 3 (5.8%) of participants were neutral, while 4 (7.7%) and 2 (3.8%) don't think that ctDNA testing saves any time (Figure 27).

Figure 27. Distribution of responses to impact of ctDNA testing introduction on timely diagnosis and treatment



Impact on timely diagnosis

Participants that have reported that ctDNA testing reduces time to diagnosis have commented that:

"ctDNA can give valuable clues to diagnosis, such as in the case of small cell lung cancer or when the NSCLC tissue diagnosis is not 100% clear."

"A radiological diagnosis comes before a histological / ctDNA diagnosis but in cases where there is a circulating gene target there can be a definite reduction in time to diagnosis."

"It's a problem that patients are waiting significant lengths after time after tissue diagnosis to have an oncology plan, due to delays in obtaining molecular results from cytology or histology samples. ctDNA has expedited this in several cases."

"The waiting time for molecular results causes so much anxiety and distress for patients. This impacts significantly on the CNS workload, as patients telephone us regularly and it is hard to manage their expectations at times. Some patients do not want a biopsy, however if just a blood test was involved more patients would want to find out their diagnosis."

"The current diagnostic pathway in lung cancer in my trust is not fit for purpose. delays throughout each step in the pathway, especially in pathology & molecular diagnostics. These delays result in progressive symptomatic disease where patients are deconditioned and highly challenging to treat by the time they are seen in oncology ctDNA testing reduces the diagnostic pathway and I believe directly improves patient survival outcomes through faster access to targeted therapies."

"We got the ctDNA and tissue biopsy result back at the same time. This means we no need to wait for another 1-2 weeks for tissue EGFR result back before we can book the patient to see the oncologist for NSCLC patients."

Respondents that were neutral or disagreed with the statement "Introducing ctDNA testing into the standard diagnostic pathway reduces time to diagnosis." have highlighted that:

"We typically get confirmation of lung cancer on the biopsy within a week of the ctDNA result becoming available, so it doesn't appreciably speed diagnosis."

"Does not reduce time to dx as often there are delays in getting a biopsy to confirm which cancer it is."

Impact on timely treatment

One of the two respondents that answered that they disagree with ctDNA testing reducing time to treatment noted that they have seen no significant change so far compared to the standard pathway.

Of those that were neutral, one person said that it is currently taking 3 weeks for them to receive ctDNA results and this is often done in parallel to tissue biopsy.

When asked how much time, in their opinion, ctDNA testing saves compared to the standard pathway, 88.5% of respondents that agreed with the statement gave a variety of responses, ranging from 3 days to 4 weeks.

The staff has also reported that:

"For patients where good quality tissue biopsies are obtained, I think the time saved by ctDNA is very modest (if any). For patients where the tumour content of the initial biopsy is limited, ctDNA is very helpful in avoiding the need for repeat biopsies and can save the patient weeks. Overall, I expect the time saved averages to around 14-21 days."

"For patients with an actionable mutation, ctDNA reduces time to treatment by around 3 weeks. However, only a minority of patients have an actionable mutation."

"As our population has a relatively low incidence of mutation-driven cancers, this is only true for a small number of patients. In these patients, it reduces time to treatment by 5-7 days. During the pilot period, we did not have any patients admitted in extremis with a suspected new diagnosis of mutation driven cancer, but for this group of patients, where time to diagnosis is of the essence, having access to ctDNA testing would be invaluable."

"We have analysed our own data as part of phase 1 of this pilot (n=70 pts). We run a service whereby patients attend day 0 of the pathway for a CT scan which is hot reported, and they have an immediate

consultation. This means we have been doing ctDNA on day 0 for advanced stage patients. The average day of the pathway that ctDNA results are available is Day 10 versus day 33 for tissue results of pathological and molecular diagnosis.
We've also looked at the time to be able to make a treatment decision with a tissue plus ctDNA pathway (pathological diagnosis on tissue and genomic results on ctDNA) versus a tissue alone pathway (pathological diagnosis and molecular results from tissue) and the difference is day 17 versus Day 33. This is even more pronounced for those patients with non-squamous NSCLC (Day 15 versus Day 43)."

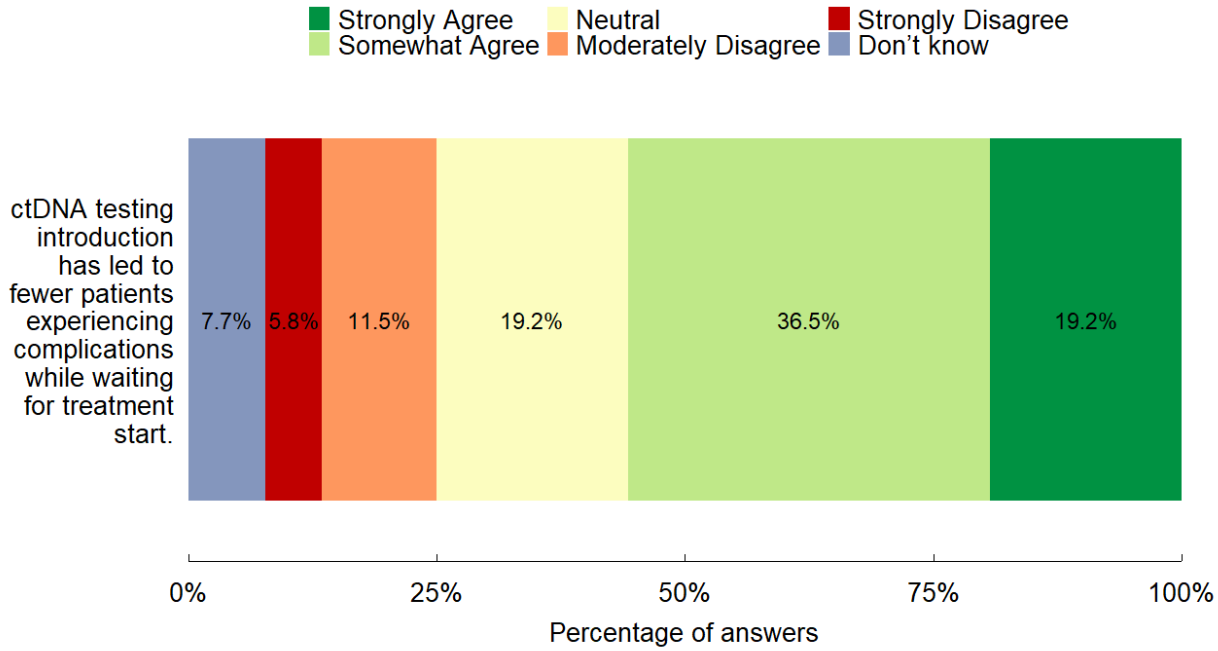
"In my trust current TAT for EGFR tissue testing is up to 6 weeks, ctDNA TAT of <14 days is superior. This enables patient to initiate treatment much faster and can inform optimal management plan also allows patients to be salvaged in event of insufficient tissue for molecular testing - a very frequent occurrence."

"Could be up to 7 days improvement in time saved. However currently our local oncologist has continued to wait for tissue biopsy results including full molecular testing before seeing the patient and initiating treatment. This could be further improved by the reduction in TAT of ctDNA results becoming available."

9.2.2 Avoided patient's complications while waiting for treatment

As shown in Figure 28, the majority of participants (55.7%) have experienced ctDNA testing and associated timely treatment leading to fewer complications and disease deterioration in patients waiting for treatment.

Figure 28. Distribution of responses to impact of ctDNA testing introduction on patients experiencing complications while waiting for treatment start



Staff have reported that:

> *"The time saving a ctDNA + tissue pathway delivers over tissue alone is significant and represents a timeframe when functional status, symptom burden and performance status can deteriorate, affecting the ability to deliver optimal treatment or the risk of treatment related toxicity."*

> *"This patient population have rapidly progressive disease including high incidence of CNS disease diagnostic delays really make a critical difference to outcomes in these patients."*

9.2.3 Increased access to targeted treatment

When asked about whether ctDNA testing increases the chances of patients being diagnosed with an actionable gene alteration and prescribed targeted treatment 3.8% of respondents disagreed, 13.5% were neutral and 80.8% agreed (Figure 29).

The main reason for participants disagreeing or being neutral to the statement was that the same results from ctDNA testing can be obtained from genomic testing on the tissue, hence the percentage of patients accessing targeted treatment doesn't vary.

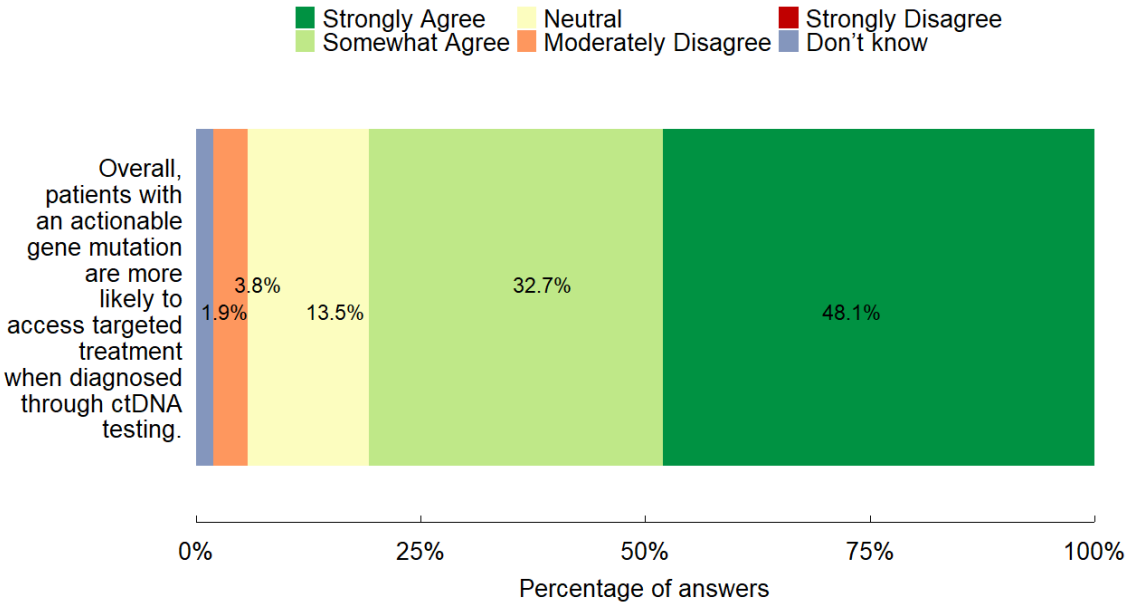
On the other hand, survey respondents who agreed with the statement emphasized that whenever there is a clinical need to start treatment before the tissue results are available, or if genomic testing on the tissue fails, ctDNA testing increases patients' access to targeted therapies. Some others have highlighted how in their region ctDNA testing has been the only routine access many patients had to identifying certain actionable variants.

"Strongly agree. It has been transformative for several patients under my care."

"As tissue NGS testing is so shockingly prolonged, we frequently have to initiate treatment without all relevant molecular results. When a patient is seen in oncology with symptomatic bulky disease, it is very challenging to not initiate conventional chemo/IO rather than having to wait weeks and weeks for tissue NGS results with ctDNA, the optimal treatment can be initiated far sooner."

"ctDNA results are actioned by the oncologist despite results from tissue biopsy, opening up the suitable treatment options and aiming for a positive patient experience/overall survival due to having a targeted treatment option."

Figure 29. Distribution of responses to impact of ctDNA testing introduction on patients accessing targeted treatment



Additional survey results around the perceived benefits of the ctDNA testing pathway compared to the standard diagnostic pathway have been summarised in the Appendix, Section 10.4.

9.3 Changes to clinical practice and workload impact

9.3.1 ctDNA testing stage introduction

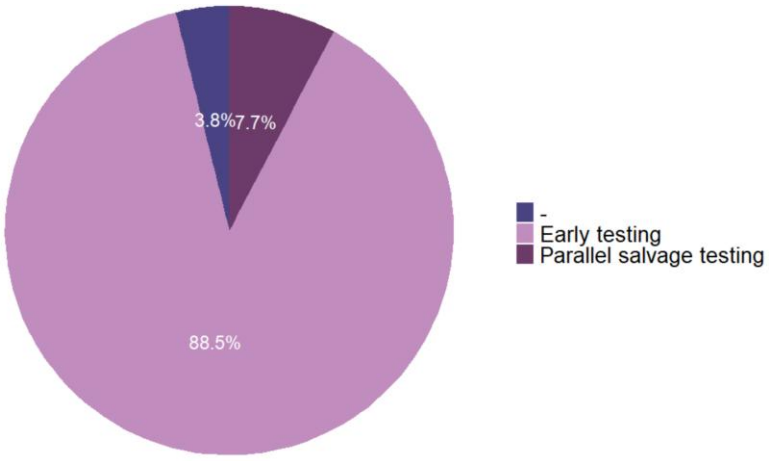
Survey participants were presented with the three scenario options (Section 6) at which to introduce ctDNA testing in the standard diagnostic pathway.

In Figure 30, it is shown how 88.5% of respondents (46 people) selected early testing as the optimal pathway for the delivery of ctDNA testing. Reasons behind this include:

- Having ctDNA report back before tissue means having an idea of treatment options prior to getting the tissue diagnosis
- Getting results quicker allows to make a diagnosis based on genomic and histologic results and use them for optimal therapy decision-making
- Maximisation of impact on treatment.

4 respondents (7.7%) preferred parallel salvage testing highlighting how this pathway can be useful in patients who have relapsed and don't have an easy site to perform a biopsy or have a poor performance status. 2 people (3.8%) didn't answer, and none selected the serial salvage testing as the optimal stage.

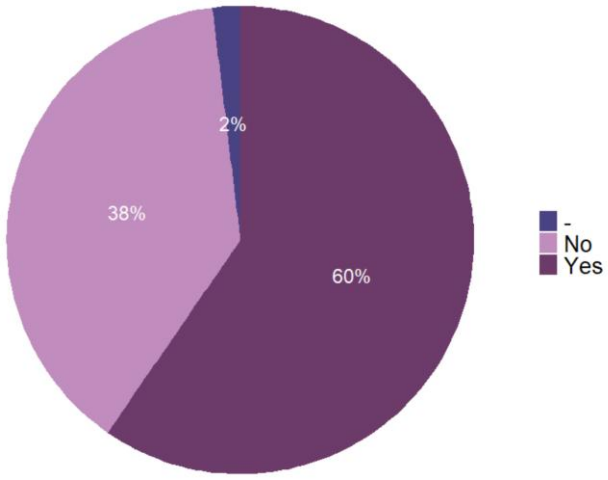
Figure 30. Distribution of answers to "What, in your view, is the optimal stage within the standard pathway to conduct ctDNA testing?"



9.3.2 Results interpretation

A total of 31 (60%) participants (Figure 31) were asked to interpret ctDNA results as part of the pilot. This group includes 8 CNSs, 13 oncologists, 9 respiratory clinicians and 1 "other".

Figure 31. Distribution of answers to "As part of the pilot phase, were you requested to interpret ctDNA results?"



As outlined in Figure 32Figure 31, 74.2% of respondents didn't need a second opinion in the interpretation of ctDNA results. The 16.1% that did, reported that the help of genomic MDT is essential for the interpretation of more complex results and that the involvement of an oncologist or consultant was necessary for double-checking findings.

Again, the majority of staff found the results clear and easy to interpret (67.8%), direct feedback from respiratory clinicians and CNSs is reported below:

> *"Mostly this was straightforward, but I was able to seek help from GLH team members when needed."*

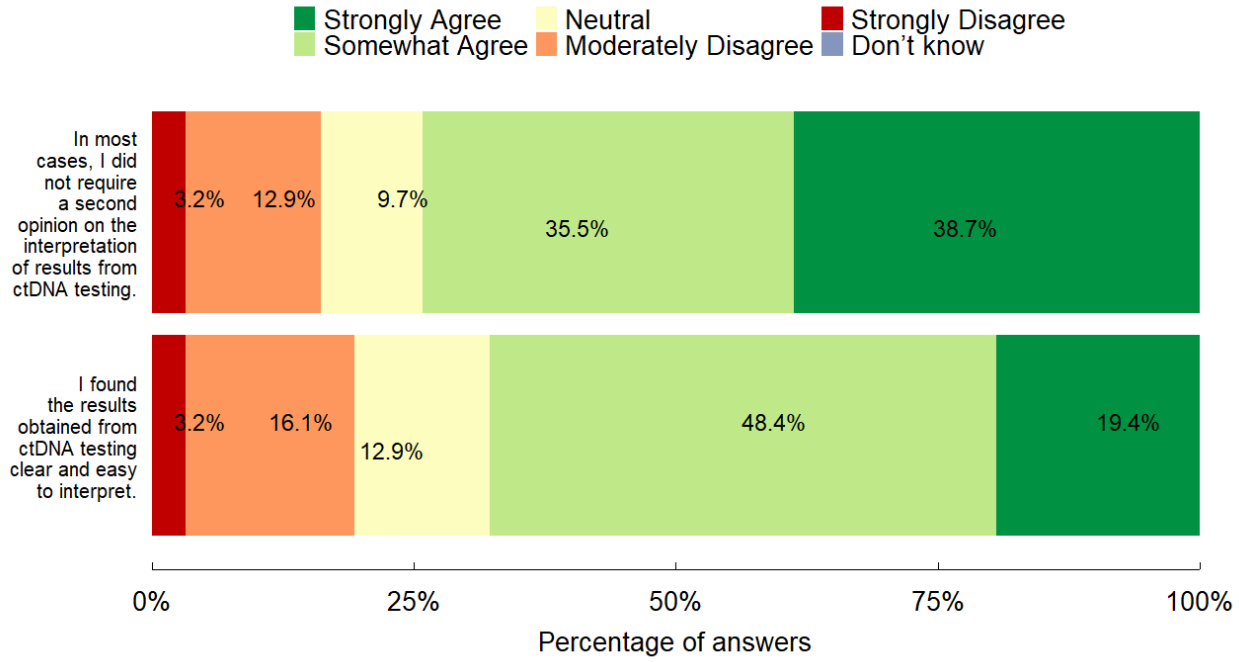
> *"There is a learning curve, but this now needs to be a core competency within lung cancer physicians overseeing diagnostic pathways."*

> *"Lack of education on this topic left the CNS team feeling low in confidence in this area. Reviewing results alongside the oncologists was a valuable learning opportunity that increased confidence in the team overall."*

Respiratory clinicians and CNSs who were neutral or disagreed with the statements (32.2%) included the reasons for their answers:

- The complexity and length of the report
- A lack of education on the topic for the CNS team
- Non-actionable variant results for which is difficult to understand the clinical relevance.

Figure 32. Distribution of responses on interpretation of ctDNA testing results



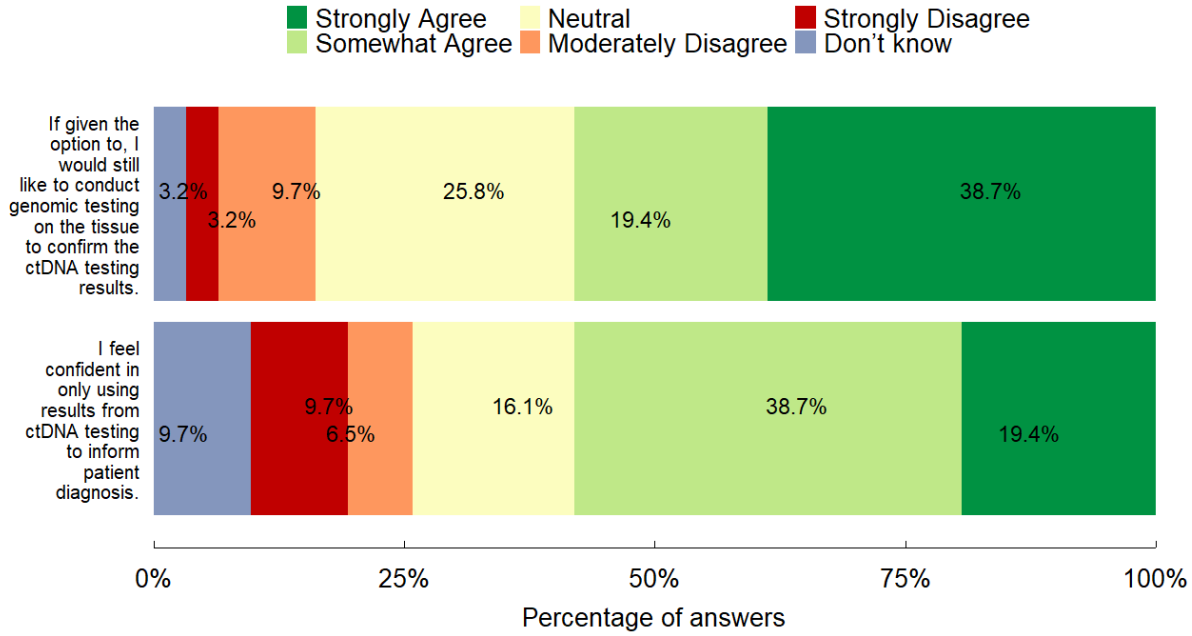
If there is a positive ctDNA result, Figure 33, in most cases over 58% of participants feel confident in only using ctDNA testing results to inform patient diagnosis. Of the people that replied, "Strongly disagree" or "Moderately disagree" (16.2%), one respiratory clinician said they still don't fully understand the results while another one said they are confident only if the patient has an actionable variant.

The 12.9% of survey respondents who wouldn't want to still carry out genomic testing on the tissue if given the option said that this would be the case for positive results.

While the "Neutral", "Somewhat agree" and "Strongly agree" would either still want to check PDL1 expression from a solid biopsy or want more training/data evidence:

> *"Would be good to see data around the need for tissue testing. Genomic testing of tissue can probably be avoided/cancelled in many cases if the ctDNA yields results - but would be good to see data around number of actionable mutations missed by ctDNA and guidelines developed for when tissue testing should still proceed (or not)."*

Figure 33. Distribution of responses on interpretation of ctDNA testing results



9.3.3 Workload impact

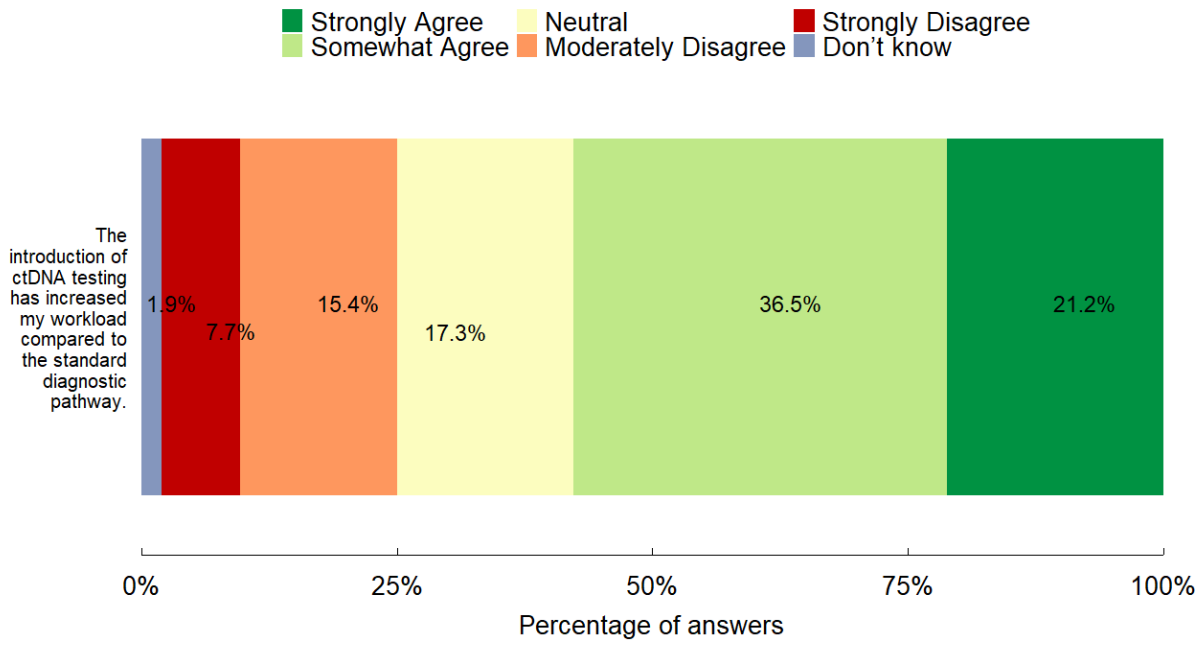
Of the respondents who said that the introduction of ctDNA testing in the advanced lung cancer pathway has a negative impact on their workload (48.4%), the main reasons listed behind this concerns the time spent:

- Identifying eligible patients
- Performing the test
- Interpreting results
- Collecting the data for the pilot.

Part of them recognised that the above will only be true temporarily for the trial phase and eventually decrease if it becomes part of routine care.

The 7.7% that strongly disagreed with the statement and the 15.4% that moderately disagreed, mentioned that either they saw no increase in the overall workload, or the extra work fell somewhere else (for example performing the tests and preparing the samples for dispatch does add to nursing and administrative colleagues' workload), or they saw a decrease because of patients needing less repeated biopsies or appointments.

Figure 34. Distribution of responses on workload impact



9.4 Training, activities, and processes

9.4.1 What worked well during the pilot phase?

Key themes that emerged from the comments provided in the survey can be summarised as follows:

Meetings and training sessions

- Multidisciplinary team (MDT) meetings were informative and effective.
- The slideshow presentation explaining the sampling process was helpful.
- Embedding the process within the CNS team increased access and awareness.
- Training sessions provided by the lung diagnostic CNS and discussions with nurses and healthcare assistants were valuable for understanding procedures and processes.

Communication and support

- Support from the lung diagnostic CNS was crucial for patient interactions and sample collection.
- Open communication within the team facilitated the identification of eligible patients and streamlined the process of requesting blood samples.
- Easy accessibility to the regional lead consultant for queries and collaboration enhanced the efficiency of the pilot phase.

Resources and processes

- Utilization of existing resources such as the lung patient navigator for venepuncture was beneficial.
- Integration of ctDNA testing into the electronic patient record (EPR) system was suggested for streamlined testing procedures.
- Posting arrangements and having all the necessary materials being provided already.
- Having a team email address to receive results that are checked daily.
- An in-house developed prompt to remind everyone of the test availability for relevant patients.

Updates and ongoing education:

- Regular updates from the GLH were appreciated.
- Educational sessions, including lunchtime training sessions, helped in understanding the testing process and ensuring competence in sample collection and handling.
- Catch up training provided by the test provider

9.4.2 What could have been done differently or suggestions for improvements

Respondents have highlighted the need to formally train the wider lung cancer community, including non-medics and non-oncologist personnel, with regard to understanding the purpose of ctDNA and how this can impact treatment times and the treatment itself, in addition to having workshops on how to read and interpret the actual ctDNA report with results. This is particularly true for clinicians who don't see them as frequently.

Access to data has also been described as one of the main challenges and issues to be addressed in the future. Specifically, improve access to "treating Trusts" patient information from the "diagnostic Trusts", and receiving results and uploading them to the patient record to be accessible to the oncology team.

Bringing on board with the process the phlebotomy departments and developing a reference guide for better understanding the ctDNA reports have also been mentioned.

9.5 Future Challenges

Access and timeliness of testing

Concerns for the future revolve around access to testing kits and necessary equipment and ensuring timely delivery to the regional lab via hospital pathology labs. There is also a need for improvement in accessing test results efficiently, as email communication is not always reliable. Another key challenge highlighted is deciding whether tests should be conducted in-house or externally and ensuring that results are uploaded into local systems in a specified and timely manner.

Capacity and TATs

With an increase in processed samples over time, TAT may inevitably increase. Maintaining quick TATs and capacity to meet demand is essential for effective patient care. A need for quicker TAT than current standards to optimize patient management has also been highlighted. This includes improvements to the current logistic processes.

Staffing

Challenges in this area include the time required for central MDT meetings and the involvement of various staff members. It's essential to streamline processes and involve more staff members, such as clinic nurses, phlebotomists, and junior registrars. For example, admin support is crucial for patient bookings and sample handling, which can alleviate the burden on specialized teams.

Training and education

It is key to have enough personnel trained to interpret results and gain the confidence of the wider team in treating based on these results. There are concerns regarding the interpretation of Tier 2 results and the need for adequate support, including the availability of CNSs and locoregional support for result interpretation.

Costs

Cost remains a significant consideration, especially in centres with limited resources.

Acceptance

Clinicians should also be encouraged to play a more active role in offering testing to patients. Encouraging and promoting acceptance and embedding of the practice in and outside the clinical community is vital for widespread adoption.

Patient expectations

Managing patient expectations is important, especially for those hoping for alterations and experiencing disappointment when they are not found. Providing support and clear communication throughout the testing process can help address these concerns and manage them effectively.

9.6 Discussion and Findings

ctDNA testing represents advances in science, technology and medicine that can enable patients to receive targeted treatments much sooner and with less invasive procedures than under the current diagnostic pathway. There are clear benefits for staff, patients, and more generally for hospitals and the UK, but the technology comes at a significant cost and does represent a new way of working, which will mean new processes and additional work, particularly for nurses and respiratory clinicians.

The pilot also revealed some of the challenges around reducing the timeline relative to the current diagnostic pathway, although overall assumptions developed for the modelling were validated by the data collected. If ctDNA is rolled out more generally, included on the Test Directory, and included in the standard diagnostic pathway it will be important to monitor progress and track benefits to ensure that these continue to be delivered, as well as investigate the variation in turnaround times across different hospitals.

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