NICE advice

Plasma EGFR mutation tests for adults with locally advanced or metastatic non-small-cell lung cancer

Medtech innovation briefing
Published: 18 January 2018

www.nice.org.uk/guidance/mib137

Summary

- The 7 **technologies** described in this briefing are plasma epidermal growth factor receptor (EGFR) mutation tests. They are used to inform the decision to offer EGFR tyrosine kinase inhibitors (EGFR-TKIs) for treating locally advanced or metastatic non-small-cell lung cancer (NSCLC) in adults.
- The **innovative aspects** are that the tests measure circulating tumour DNA (ctDNA) in a blood sample rather than the standard histopathological assessment of a tumour biopsy.

- The intended **place in therapy** would be as an alternative to tissue EGFR testing or before tumour testing to inform decisions about prescribing EGFR-TKIs. Plasma testing may be particularly useful for people whose disease has developed resistance to an EGFR-TKI and who could be offered second-line EGFR-TKIs, if appropriate, without having further tissue testing.
- The **main points from the evidence** summarised in this briefing are from 7 non-UK-based prospective studies with 2,106 adults. They show that the diagnostic accuracy of plasma EGFR mutation testing has a similar specificity, but lower sensitivity, compared with tissue EGFR mutation testing in adults with locally advanced or metastatic NSCLC.
- **Key uncertainties** around the evidence or technology are that tests for identifying EGFR-TK mutations are rapidly evolving and there is no established gold-standard test against which to evaluate them.
- The **cost** of plasma EGFR mutation tests range from £138.05 to £230.22 per unit (excluding VAT). The **resource impact** is similar to that of standard care but plasma EGFR mutation testing could be cost saving if it led to fewer tissue biopsies.

The technologies

Epidermal growth factor receptor (EGFR) mutation tests are in vitro diagnostic (IVD) tests used to help identify adults with non-small-cell lung cancer (NSCLC) suitable for treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs). The presence of specific EGFR mutations show how effective treatment with EGFR-TKIs will be. As a result, the test is useful for oncologists for deciding personalised treatment options.

EGFR mutations occur in EGFR exons 18–21 and mutations in exons 18, 19 and 21 and indicate suitability for treatment with EGFR-TKIs. Mutations in exon 20 (with the exception of a few mutations) show the tumours are EGFR-TKI resistant and not suitable for treatment with EGFR-TKIs.

Traditionally, EGFR mutation testing is done on a tumour sample obtained by tissue biopsy. More recently, plasma EGFR mutation tests that use free circulating tumour DNA (ctDNA) have been developed as an alternative. ctDNA is made up of fragments of tumour DNA that have entered the bloodstream. Only a blood sample is needed for plasma testing, so it is sometimes called 'liquid biopsy'.

Plasma testing begins by using centrifugation to separate plasma from the other components of a blood sample. A DNA extraction kit is then applied to isolate ctDNA. Polymerase chain reaction (PCR) amplifies ctDNA in the sample. Depending on which test is done, EGFR mutations are detected by either analogue or digital methods. Analogue detection (known as real-time PCR) uses fluorescent markers that attach to specific mutation sites, making them detectable; fluorescence in the sample is detected as a whole. In digital PCR (dPCR) the sample is separated into many partitions, each tested individually, providing a lower threshold of detection. Fully quantitative plasma EGFR mutation tests can measure the levels of ctDNA in a sample; semi-quantitative tests display the results as above or below thresholds.

Further information on the kits assessed in this report is available in table 1.

Table 1 Summary of technologies

Manufacturer	Technology	Additional information
AmoyDx	EGFR 29 mutations detection kit	• Analogue • Semi-quantitative • Detects 29 mutations
	SuperARMS EGFR mutation detection kit	• Semi-quantitative • Detects 41 mutations
	SuperARMS EGFR T790M mutation detection kit	• Analogue • Semi-quantitative • Only used to detect the T790M mutation

Bio-rad	Droplet digital PCR Dx system	• Digital • Fully quantitative • Detects 13 mutations
Panagene	PANAMutyper R EGFR	• Analogue • Semi-quantitative • Detects 47 mutations
Qiagen	Therascreen EGFR plasma RGQ PCR kit	• Analogue • Semi-quantitative • Detects 21 mutations
Roche	Cobas EGFR mutation test v2	• Analogue • Semi-quantitative • Detects 42 mutations

Innovations

Plasma EGFR mutation tests do not need a biopsy to be taken and are a less invasive alternative to tissue EGFR mutation tests. They can provide testing in people who are unable to, or do not wish to, have a tissue biopsy and whose disease otherwise would remain untested. People may have a lack of available tumour tissue, low-quality tissue sample or poor health making a tissue biopsy infeasible; about 30% of biopsies are classified as 'failed' (PHG Foundation 2017). More than 25% of people with NSCLC in the UK do not have a pathological confirmation of their diagnosis (National Lung Cancer audit report 2016).

Introducing plasma EGFR mutation testing may lead to quicker test results and treatment changes as it removes the need for a tissue biopsy in certain circumstances.

Plasma EGFR mutation testing also avoids problems with tumour evolution and heterogeneity, when the presence of mutations may be missed in a biopsy of a single metastatic site or from using an existing sample. Plasma testing can be repeated easily, allowing for mutation monitoring in people having EGFR-TKI therapy. This method can detect resistance mutations – predominantly T790M – which may need different treatment. Quantitative plasma EGFR mutation tests can measure the levels of ctDNA, which may be a good predictor of treatment response. This is still being researched and not in clinical use.

Current NHS pathway or current care pathway

The NICE clinical guideline on diagnosing and treating lung cancer recommends that people with suspected lung cancer should be referred urgently for a chest X-ray. If the results suggest lung cancer, a contrast-enhanced computed tomography (CT) scan of the chest, upper abdomen and lower neck is done to evaluate the degree of mediastinal and chest wall invasion. Further investigations to confirm a diagnosis and to provide information on the stage of the disease are then done. These investigations generally include a biopsy taken from a central or peripheral lesion for histological confirmation and subtyping, but may also include positron emission tomography/CT (PET/CT), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound-guided fine needle aspiration or non-ultrasound-guided transbronchial needle aspiration. The tumour sample is used for EGFR mutation testing.

NICE recommends 5 tests that use samples of tumour tissue for identifying EGFR-TK mutations in adults with previously untreated locally advanced or metastatic non-small-cell lung cancer to identify people whose disease might benefit from treatment with EGFR-TKIs. The guidance notes that tests and methods are evolving, so new ones are likely to appear in the future.

If an EGFR mutation is confirmed, EGFR-TKIs recommended in NICE technology appraisal guidance such as afatinib, gefitinib or erlotinib can be offered as an alternative to chemotherapy.

If disease progression is seen after first-line EGFR-TKI therapy, a repeat biopsy can be done and tested for EGFR T790M resistance mutation. This can tell whether the tumour has become resistant to the first-line EGFR-TKI, before considering second-line osimertinib, which is recommended as an option in NICE technology appraisal guidance. Testing for EGFR T790M resistance mutation is not routinely done in the NHS.

People who cannot have, or do not want, a tumour biopsy do not routinely have EGFR testing by other means (such as plasma EGFR testing or next-generation sequencing [NGS]) and usually have first-line chemotherapy with a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) and a platinum drug (carboplatin or cisplatin). People who cannot tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug.

Population, setting and intended user

Plasma EGFR testing would be used in adults with locally advanced or metastatic NSCLC in secondary or tertiary care settings. Their disease may either be untreated or relapsing after previous TKI therapy. A blood sample would be taken by a phlebotomist. Sample preparation and test procedures would be completed by pathology laboratory staff. The results are used to aid decision-making by clinicians and the patient.

Costs

Technology costs

The costs of the plasma EGFR mutation tests included in this briefing are listed in table 2.

Table 2 Cost of plasma EGFR mutation tests

Product/device	Cost	Additional information
EGFR 29(AmoyDx)		
Outpatient appointment (for bloods)	£6.00 (PSSRU 2016)	Assumed 1 visit to band-3 phlebotomist lasting 15 minutes
Blood collection tube	£6.16	Based on the list price of PAXgene blood ccfDNA tubes
AmoyDx EGFR 29 mutations detection kit	£106.25 per test	Including training

DNA extraction kit	£13.06 per test	Based on list price of QIAamp circulating nucleic acid kit (Qiagen)
Real-time PCR	£38.83 per test	Uplifted from Sewell et al. 2014
Total cost per test	**£170.30**	
SuperARMS EGFRmutation kit(AmoyDx)		
Outpatient appointment (for bloods)	£6.00 (PSSRU 2016)	Assumed 1 visit to band-3 phlebotomist lasting 15 minutes
Blood collection tube	£6.16	Based on the list price of PAXgene blood ccfDNA tubes
SuperARMS EGFR mutation detection kit	£166.17 per test	Including training
DNA extraction kit	£13.06 per test	Based on list price of QIAamp circulating nucleic acid kit (Qiagen)
Real-time PCR instrument	£38.83 per test	Uplifted from Sewell et al. 2014
Total cost per test	**£230.22**	
SuperARMS EGFRT790Mmutation kit(AmoyDx)		
Outpatient appointment (for bloods)	£6.00 (PSSRU 2016)	Assumed 1 visit to band-3 phlebotomist lasting 15 minutes
Blood collection tube	£6.16	Based on the list price of PAXgene blood ccfDNA tubes
SuperARMS EGFR T790M mutation detection kit	£74.00 per test	Including training

DNA extraction kit	£13.06 per test	Based on list price of QIAamp circulating nucleic acid kit (Qiagen)
Real-time PCR instrument	£38.83 per test	Uplifted from Sewell et al. 2014
Total cost per test	**£138.05**	
Droplet Digital PCR Dx system (Bio-Rad)		
Outpatient appointment (for bloods)	£6.00 (PSSRU 2016)	Assumed 1 visit to band-3 phlebotomist lasting 15 minutes
Blood collection tube	£6.16	Based on the list price of PAXgene Blood ccfDNA tubes
QX200 AutoDG Droplet Digital PCR Dx system (including reader and DNA extraction kit), C1000 thermal cycler and PX1 plate sealer	• If used by 1,000 patients: £131.30 per test • If used by 10,000 patients: £13.13 per test	Including training
Validated mutation assays	£2.63 per reaction	£525 for 200 reactions
Consumables and reagents	£12.40 per sample	Based on a 2-well sample at £6.20 per well
Total cost per test	• **If used by 1,000 patients: £158.49** • **If used by 10,000 patients: £40.32**	
PANAMutyper R EGFR (Panagene)		

Outpatient appointment (for bloods)	£6.00 (PSSRU 2016)	Assumed 1 visit to band-3 phlebotomist lasting 15 minutes
Blood collection tube	£6.16	Based on the list price of PAXgene blood ccfDNA tubes
PANAMutyper R EGFR	£77.59 per test	Reagent price, including training
DNA extraction kit	£13.06 per test	Based on list price of QIAamp circulating nucleic acid kit (Qiagen)
Real-time PCR instrument	£38.83 per test	Uplifted from Sewell et al. 2014
Total cost per test	**£141.64**	
Therascreen EGFR plasma RGQ PCR kit (Qiagen)		
Outpatient appointment (for bloods)	£6.00 (PSSRU 2016)	Assumed 1 visit to band-3 phlebotomist lasting 15 minutes
Blood collection tube	£6.16	Based on the list price of PAXgene blood ccfDNA tubes
Therascreen EGFR Plasma RGQ PCR kit	£112.79 per test	Including training
DNA extraction kit	£13.06 per test	Based on list price of QIAamp circulating nucleic acid kit (Qiagen)
Real-time PCR instrument	£38.83 per test	Uplifted from Sewell et al. 2014
Total cost per test	**£176.84**	
Cobas EGFR mutation test v2 (Roche)		

Outpatient appointment (for bloods)	£6.00 (PSSRU 2016)	Assumed 1 visit to band-3 phlebotomist lasting 15 minutes
Blood collection tube	£6.16	Based on the list price of PAXgene blood ccfDNA tubes
Cobas EGFR mutation test	£125.00 per test	Including training and consumables
DNA extraction kit	£13.06 per test	Based on list price of QIAamp circulating nucleic acid kit (Qiagen)
Real-time PCR instrument	£38.83 per test	Uplifted from Sewell et al. 2014
Total cost per test	**£189.05**	
Abbreviation: ccf, circulating cell free.		

Costs of standard care

Standard clinical practice in England is EGFR mutation testing based on samples of tumour tissue gathered from EBUS-TBNA, CT-guided biopsy or resection.

The cost of standard care ranges from £145.12 to £1,610.26 per test. Costs are outlined in table 3.

A range of diagnostic methods may be used, alongside clinical examination, to identify acquired EGFR-TKI resistance. Clinical progression of disease can be identified by symptoms, radiology, or by further tissue or liquid biopsy mutation analysis. For mutation analysis, the unit cost charged by a sample of NHS laboratories in the costing statement for NICE's diagnostics guidance on EGFR-TK mutation testing ranges from £130 to £155, including reporting results (August 2013).

Table 3 Cost of standard care

Product/ device	Cost	Additional information
Tissue biopsy	• EBUS-TBNA: £1,465.14 (NICE 2011) • CT-guided biopsy £287 (NHS reference cost 2015/16)	The cost of tissue biopsy is only applicable when there is no readily available tissue sample. For biopsy of paratracheal and peribronchial intraparenchymal lung lesions, EBUS-TBNA is used as the standard care. Otherwise, CT-guided biopsy is the standard care. The cost was uplifted to 2015/16 prices using PSSRU 2016.
Standard EGFR mutation testing	£145.12 (NICE 2013)	The cost listed is the average cost of 5 EGFR mutation tests recommended by NICE (NICE 2013): • Therascreen EGFR RGQ PCR kit. • Cobas EGFR mutation test. • Sanger sequencing or Therascreen EGFR PCR kit for samples with insufficient tumour cells. • Sanger sequencing or Cobas EGFR mutation test for samples with insufficient tumour cells. • Sanger sequencing followed by fragment length analysis/real-time PCR. The cost was uplifted to 2015/16 prices using PSSRU 2016.
Total cost per test	• Without tissue biopsy: **£145.12** • With EBUS-TBNA: **£1,610.26** • With CT-guided biopsy: **£432.12**	

Abbreviations: CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; EGFR, epidermal growth factor receptor; PCR, polymerase chain reaction.

Resource consequences

The costs of plasma EGFR mutation tests assessed in this briefing are similar to the costs of tissue EGFR mutation tests. However, tissue EGFR mutation tests are based on samples of tumour tissue gathered during biopsy or resection. If there is no readily available tumour tissue, biopsy will be needed to collect tumour tissue. EGFR mutation tests may be cost effective if they reduce the need for tissue biopsy. There is no published evidence on the resource consequences of adopting plasma EGFR mutation tests for patients with NSCLC.

The resource impact statement for NICE's technology appraisal guidance on osimertinib estimates that about 400 people per year whose cancer has the T790M mutation will see their disease progress after first-line treatment with an EGFR-TKI. If a person's disease progresses after first-line EGFR-TKI therapy, a positive SuperARMS EGFR T790M liquid biopsy test would indicate suitability for osimertinib therapy, in line with NICE's technology appraisal guidance on osimertinib. Training is needed in the use of all plasma EGFR mutation tests assessed in this briefing; this is standard for implementing any new test and is included in the purchase price for each test.

At the time of writing, Cobas EGFR mutation test is used by 7 NHS hospitals. QX200 AutoDG Droplet Digital PCR Dx system is used by 2 NHS hospitals, and AmoyDx EGFR29 mutation detection kit is used by 1 NHS hospital. None of the other EGFR tests are used routinely in the UK.

Regulatory information

The Medicines and Healthcare products Regulatory Agency (MHRA) have issued 1 manufacturer field safety notice for the Cobas epidermal growth factor receptor (EGFR) mutation test v2 (Roche) from April 2016. It reported that several mutation-positive samples generated "no mutation detected" results (false negatives) in internal studies. As a result of these findings, the instructions were revised and no further safety issues have been reported since. No other field safety notices or medical device alerts were identified for the other technologies in this briefing.

The technologies included in this briefing have received regulatory approval under the European Union 98/79/EC in vitro diagnostics (IVD) directive.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

The prevalence of epidermal growth factor receptor (EGFR) mutations in people with non-small-cell lung cancer (NSCLC) is higher in females than in males. Prevalence also varies widely by family origin. In Europe, EGFR mutations are present in 15% of people with NSCLC, whereas in Asia, it is 47% (Midha, Dearden and McCormack, 2015). Sex and ethnicity are protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Seven studies including 2,106 participants are summarised in this briefing. All are prospective studies, 2 are randomised controlled trials (RCTs; n=819). Two studies recruited participants internationally, including within the UK, and 5 studies were done in Asia.

Table 4 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

Although diagnostic test accuracies varied from study to study, concordances between plasma and tissue tests were generally above 80%. Additionally, clinical outcomes and treatment efficacy were similar for people diagnosed with epidermal growth factor receptor (EGFR) mutation-positive disease by either tissue or plasma. The digital droplet polymerase chain reaction (ddPCR) and Cobas v2 had slightly better diagnostic test accuracies relative to the other tests.

One of the studies included (Jenkins et al. 2017) describes the findings from 2 RCTs; it had a robust study design and a relatively large sample population. There was a lack of evidence available on populations with disease who had a negative-mutation status when tested using tissue EGFR, but a positive mutation when tested using plasma EGFR. This is because negative status in tissue samples was an exclusion criteria for many of the studies. In 1 of the included studies, subgroup analysis revealed significant differences in progression-free survival (PFS) based on plasma mutation status for people whose disease has tissue-positive status. They found that people whose disease has plasma-positive and tissue-negative status may have lower PFS than people with disease with a negative status in both plasma and tissue.

Most of the studies did not differentiate between the multiple types of EGFR-sensitising mutations; they instead grouped participants by positive- or negative-mutation status. However, individual mutations might have different sensitivities and specificities and may lead to different clinical outcomes. The reference standard in these studies tended to be a tissue EGFR mutation test; it is generally agreed that this test is not a 'gold-standard' test. Tumour shrinkage or next-generation sequencing (NGS) are also used as reference standards. Five of the 7 studies did not report the time between plasma and tissue testing; it is strongly supported that the time interval should be minimal and that using stored samples is not ideal for diagnostic accuracy studies.

Table 4 Summary of evidence

Jenkins et al. (2017)	
Study size, design and location	551 adults with advanced NSCLC in 2 phase II, single-arm, open-label, multicentre clinical trials (AURA extension and AURA2) recruited in 41 locations across Europe, Asia, Canada and the US.

Intervention and comparator(s)	Index test: Roche Cobas v2 (plasma test). Comparator: Roche Cobas v2 (tissue test) and NGS on an Illumina MiSeq.
Key outcomes	Positive and negative agreements between plasma and tissue tests for detection of T790M mutation were 61% and 79% respectively. Comparing the plasma test with NGS showed positive and negative agreements of higher than 90%. The ORR was 64% in people with T790M mutation-positive assessed by both tissue and plasma tests. People whose disease had positive-tumour and negative-plasma status had higher ORR (70%) than people with both tumour- and plasma-positive statuses.
Strengths and limitations	Inclusion in the sample was based on existing tissue testing results; there are no results for plasma testing alone. NGS was used as the comparator; this is considered to be the gold-standard comparator for EGFR mutation testing in research. Plasma testing was done prospectively, but tissue results were retrospective.
Kim et al. (2017)	
Study size, design and location	102 adults with EGFR-mutated NSCLC in a single-centre, prospective, observational, case-control study, South Korea.
Intervention and comparator(s)	Index test: Panagene PanaMutyper R EGFR (plasma test). Comparator: Panagene PanaMutyper R EGFR (tissue test).
Key outcomes	The agreement between matched tissue and plasma samples for specific mutations was 80.4% for Ex19del, 90.2% for L858R and 56.3% for T790M. At 4 weeks after EGFR-TKI treatment, detection of mutations in plasma predicted lower ORR and PFS. Plasma EGFR testing could detect the presence of T790M (indicating EGFR-TKI resistance) on average 103 days before tumour progression detected by CT imaging.
Strengths and limitations	Results for each mutation were reported separately. Plasma testing conducted prospectively. Case-control study design is not recommended for studies of diagnostic tests.
Li et al. (2017)	

Study size, design and location	109 adults with metastatic NSCLC in a single-centre, prospective, observational study in China.
Intervention and comparator(s)	Index test: AmoyDx SuperARMS EGFR mutation detection kit (plasma test). Comparator: AmoyDx EGFR29 mutation detection kit (tissue test).
Key outcomes	EGFR mutations were detected in 45.9% of the plasma samples and in 56.9% of the matched tumour tissue samples. The overall concordance between matched plasma and tissue tests was 89.9%. Sensitivity, specificity, PPV and NPV for plasma EGFR mutation detection were 82.0%, 100%, 100% and 81.4% respectively. The ORR for people with plasma-positive mutations on first generation EGFR-TKIs was 65.7%, which was comparable to the tissue-positive ORR (64.3%).
Strengths and limitations	PFS and OS are not reported here, however they will be published in a future publication by the authors. The interval of time between tissue and blood testing was relatively small (14 days).
Ma et al. (2016)	
Study size, design and location	219 adults with advanced NSCLC in a single-centre, prospective, observational study in China.
Intervention and comparator(s)	Index test: AmoyDx EGFR29 mutation detection kit (plasma test). Comparator: AmoyDx EGFR29 mutation detection kit (tissue test).
Key outcomes	The overall concordance rate between matched plasma and tissue samples was 82%. The overall sensitivity and specificity were 60% and 97% respectively. No significant difference in median PFS was observed between people with positive mutation status in plasma or tissue testing (10.88 months versus 9.89 months, p=0.411). For people with stage III NSCLC, the sensitivity, specificity and concordance were 50%, 100% and 81.3% respectively. For stage IV, the sensitivity, specificity and concordance were 60%, 96% and 81% respectively.
Strengths and limitations	People with different identified mutations were grouped together as EGFR mutation-positive, however, results by stage of cancer were presented separately.

Thress et al. (2015)	
Study size, design and location	Plasma and tumour samples were obtained from patients with NSCLC enrolled in a multicentre open-label phase 1 trial (NCT01802632). 38 plasma samples were used for an initial assessment of all technologies, an additional 72 plasma and matched tumour samples were used in further investigations of Cobas v2.
Intervention and comparator(s)	Index test: Roche Cobas v2, Qiagen Therascreen, Bio-Rad ddPCR. Comparator: Roche Cobas v2 (tissue test).
Key outcomes	All 3 plasma EGFR mutation tests had high sensitivity (78–90%) and specificity (100%) for EGFR-TKI sensitising mutations. The digital platform (ddPCR) had marginally higher values than the analogue tests (Cobas v2 and Therascreen) when considering all mutations (sensitising and resistance). In further assessments for the T790M mutation, only Cobas v2 was assessed. Sensitivity and specificity were 73% and 67%. Concordance between the Cobas and a digital technology not considered in this briefing was >90%. ORR for people with T790M detected in plasma or tissue was comparable (59% and 61% respectively).
Strengths and limitations	At the time of this study, the Bio-Rad ddPCR test did not detect ex19del mutation, therefore, the overall sensitivity value for this test does not account for ex19del. The sensitivity values for the other tests do account for ex19del. Bio-Rad ddPCR EGFR mutation testing can now detect ex19del mutations.
Wu et al. (2017)	
Study size, design and location	709 people with advanced NSCLC recruited from 2 phase III RCTs (LUX-Lung 3 [LL3] and LUX-Lung 6 [LL6] trials), in China, South Korea and Thailand.
Intervention and comparator(s)	Index test: Qiagen Therascreen (Plasma sample). Comparator: Qiagen Therascreen (tumour tissue sample).

Key outcomes	EGFR mutation detection rates were 28.6% in serum and 60.5% in plasma. People with plasma mutations had shorter PFS and OS than those without. There was no evidence to suggest that the treatment effect (afatinib versus chemotherapy) was different for either group (all subjects were tumour mutation status positive).
Strengths and limitations	The comparator used was tissue testing. Samples were taken from 2 different trials, 1 using serum (LL3) and the other, plasma (LL6). Serum may have a lower overall detection rate accounting for the difference in detection. However, these trials used different DNA extraction kits and methodologies on different populations. Future results from these trials are forthcoming and will update on the results of this study.
Zhou et al. (2017)	
Study size, design and location	306 people with advanced NSCLC having osimertinib in a phase II, open-label, single-arm study (AURA17 trial) recruited in Australia, China and South Korea.
Intervention and comparator(s)	Index test: AmoyDx SuperARMS EGFR T790M mutation detection kit, Roche Cobas v2 and an in-house ddPCR (the Innovation Centre China, AstraZeneca). Comparator: Roche Cobas v2 (tissue test).
Key outcomes	For the 3 tests, PPA for T790M was 42% to 56% and NPA was 73% to 83%. ddPCR had the highest PPA and Roche Cobas had the highest NPA. Using the Cobas plasma test as a reference, OPA was higher than 80% for both SuperARMS and ddPCR. For people with positive T790 statuses in both tumour and plasma tests, the ORR with osimertinib was consistent across the 3 plasma tests (56% to 64%).

Strengths and limitations	Despite being a conference proceeding, the abstract contained detailed methodological information. The PPA found here was lower than previously published values from other AURA trials. The authors suggest this could be associated with the lower prevalence of people with extra-thoracic disease in AURA17. People with extra-thoracic disease are more likely to have a higher disease burden resulting in a higher chance of T790M detection in plasma.
Abbreviations: ddPCR, digital droplet PCR; EGFR, epidermal growth factor receptor; EGFR-TKI, EGFR tyrosine kinase inhibitor; NGS, next-generation sequencing; NPA, negative percentage agreement; NPV, negative predictive value; NSCLC, non-small-cell lung cancer; OPA, overall percentage agreement; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PPA, positive percentage agreement; PPV, positive predictive value; RCT, randomised controlled trial.	

Recent and ongoing studies

- TIGER-3: Open Label, Multicenter Study of Rociletinib (CO-1686) Mono Therapy Versus Single-agent Cytotoxic Chemotherapy in Patients With Mutant EGFR NSCLC Who Have Failed at Least One Previous EGFR-Directed TKI and Platinum-doublet Chemotherapy ClinicalTrials.gov identifier: NCT02322281. Status: This study is ongoing, but not recruiting participants. Indication: NSCLC. Devices: Not specified. Estimated study completion date: August 2017.
- cSMART Liquid Biopsy and Dynamic Monitor of NSCLC Patients in Inner-Mongolia China ClinicalTrials.gov identifier: NCT02980536. Status: This study is currently recruiting participants. Indication: NSCLC. Devices: Not specified. Estimated study completion date: June 2018.
- Detection Cell Free DNA in Lung Cancer Patients ClinicalTrials.gov identifier: NCT02738593. Status: This study is ongoing, but not recruiting participants. Indication: NSCLC. Devices: Not specified. Estimated study completion date: October 2018.
- EGFR Mutation Detection From Advanced NSCLC Patient Tissue and Plasma in EGFR-TKI Treatment ClinicalTrials.gov identifier: NCT02644889. Status: This study is not yet open for participant recruitment. Indication: NSCLC. Devices: Not specified. Estimated study completion date: November 2018.

- Rapid Plasma Genotyping For Early Initiation Of Erlotinib In EGFR Mutant Lung Cancer ClinicalTrials.gov identifier: NCT02770014. Status: This study is currently recruiting participants. Indication: NSCLC. Devices: Not specified. Estimated study completion date: November 2023.

- Analysis of Plasma Tumor DNA in Lung Cancer Patients ClinicalTrials.gov identifier: NCT01930474. Status: This study is currently recruiting participants. Indication: NSCLC. Devices: Not specified. Estimated study completion date: December 2018.

- Phase II Study of AZD9291 in Advanced Stage NSCLC With EGFR and T790M Mutations Detected in Plasma Ct-DNA (PLASMA) ClinicalTrials.gov identifier: NCT02811354. Status: This study is currently recruiting participants. Indication: NSCLC. Devices: Not specified. Estimated study completion date: February 24, 2020.

- Concordance of Key Actionable Genomic Alterations as Assessed in Tumor Tissue and Plasma in Non Small Cell Lung Cancer ClinicalTrials.gov identifier: NCT02762877. Status: This study is currently recruiting participants. Indication: NSCLC. Devices: Not specified. Estimated study completion date: June 2018.

- Liquid Biopsy as a Tool to Evaluate Resistance to First and Third (AZD9291) (EGFR) (TKIs) in (EGFR) Mutant NSCLC ClinicalTrials.gov identifier: NCT02771314. Status: This study is currently recruiting participants. Indication: NSCLC. Devices: Not specified. Estimated study completion date: June 2021.

- Human EGFR Mutations Quantitative Detection Kit (Real-time Fluorescent PCR Method) ClinicalTrials.gov identifier: NCT02661009. Status: This study is not yet open for participant recruitment. Indication: NSCLC. Devices: Not specified. Estimated study completion date: September 2016.

- Resistance & Activating Mutations Diagnosed Among NSCLC Community Dwelling EGFR Mutation Positive Patients (RADIANCE) ClinicalTrials.gov identifier: NCT03137264. Status: This study is not yet open for participant recruitment. Indication: NSCLC. Devices: Not specified. Estimated study completion date: April 23, 2020.

- Novel Detection System for Lung Cancer Curative Effect Monitoring ClinicalTrials.gov identifier: NCT02666755. Status: This study is not yet open for participant recruitment. Indication: NSCLC. Devices: Not specified. Estimated study completion date: April 2018.

- An epidemiOlogy Study to deteRmine the Prevalence of EGFR (Epidermal Growth Factor Receptor) muTations in RUSsian Patients With Advanced NSCLC (Non-Small Cell Lung Cancer) (ORTUS) ClinicalTrials.gov identifier: NCT02321046. Status: This study is currently recruiting participants. Indication: NSCLC. Devices: Not specified. Estimated study completion date: April 30, 2019.
- Study of AZD9291 in NSCLC Patients Harboring T790M Mutation Who Failed EGFR TKI and With Brain and/or LMS ClinicalTrials.gov identifier: NCT03257124. Status: This study is currently recruiting participants. Indication: NSCLC. Devices: PANAMutyper R EGFR. Estimated study completion date: December 31, 2019.
- Osimertinib in First and Second Line Treatment of NSC LC Harboring EGFR Mutations From Circulating Tumor DNA (LiquidLung-O). ClinicalTrials.gov identifier: NCT02769286. Status: This study is currently recruiting participants. Indication: NSCLC. Devices: PANAMutyper R EGFR. Estimated study completion date: December 2019.
- Afatinib in Lung Cancer With EGFR Mutation From Circulating Tumor DNA (LiquidLung-A) ClinicalTrials.gov identifier: NCT02629523. Status: This study is currently recruiting participants. Indication: NSCLC. Devices: PANAMutyper R EGFR. Estimated study completion date: March 2019.
- T790M Plasma Testing Methodology Comparison and Clinical Validation (ADELOS) ClinicalTrials.gov identifier: NCT02997501. Status: This study is ongoing, but not recruiting participants. Indication: NSCLC. Devices: Roche Cobas, AmoyDx Super-ARMS, Bio-Rad Digital PCR and NGS. Estimated study completion date: September 30, 2019.
- TRAcking Non-small Cell Lung Cancer Evolution Through Therapy (Rx) (TRACERx) ClinicalTrials.gov identifier: NCT01888601. Status: This study is currently recruiting patients. Indication: NSCLC. Devices: Not specified. Estimated study completion date: April 2023.
- Real World Treatment Study of AZD9291 for Advanced/Metastatic EGFR T790M Mutation NSCLC (ASTRIS) ClinicalTrials.gov identifier: NCT02474355. Status: This study is currently recruiting patients. Indication: NSCLC. Devices: Roche Cobas EGFR Mutation Test, AmoyDx Super-ARMS, digital PCR and NGS. Estimated study completion date: August 30, 2019.

Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field. The comments received are individual opinions and do not represent NICE's view.

All 5 specialist commentators were familiar with these technologies and 3 are currently using them clinically or experimentally.

Level of innovation

Two specialists thought that plasma epidermal growth factor receptor (EGFR) technology was innovative and represented a paradigm shift in managing lung cancer. One stated that implementing plasma EGFR testing would lead to changes in testing for other cancers. Two specialists believed only digital polymerase chain reaction (dPCR) plasma testing would be a major variation.

Two experts suggested next-generation sequencing (NGS) could supersede this technology in the future and mentioned several tests as current or future competing technologies. One specialist said that they believe mutation testing on 1 gene locus was outdated and NGS on plasma samples would allow for decision-making based on a more appropriate range of somatic variations. However, 1 specialist mentioned that NGS takes significantly longer than plasma EGFR mutation testing and this could have a detrimental effect on patient health. Finally, another specialist described from their experiences of using NGS and dPCR that the more sensitive methods detect mutations which may not drive tumour progression and therefore, are not clinically relevant.

Potential patient impact

Three specialists noted that avoiding rebiopsy was a significant benefit to patients, with 1 specialist adding that biopsies in people with advanced or metastatic non-small-cell lung cancer (NSCLC) have an increased risk of complications such as pneumothorax. Reducing rebiopsy rates would mitigate some of these complications. Two specialists commented that plasma testing does not allow for ALK and PDL1 mutation status to be assessed. Knowing the status is necessary for NSCLC treatment management and therefore, plasma testing cannot negate the need for an initial tissue biopsy. Two stated the potential for longitudinal disease monitoring and patients having diagnoses faster as potential benefits; 1 believed plasma EGFR testing could replace CT imaging for monitoring, whereas another

mentioned that it is more convenient, less invasive and safer for the patient than tissue EGFR testing.

Three specialists noted that plasma EGFR testing would be particularly beneficial for people with disease progression or people whose disease has developed a resistance to their current tyrosine kinase inhibitor (TKI) therapy. Three specialists commented that it could offer more appropriate, personalised treatment options for people unable to have a tissue EGFR test, such as older people or people with poor health.

Potential system impact

Potential system impacts cited by the specialists were reduced need for rebiopsy, fewer hospital visits, more people having the most appropriate treatment and earlier diagnoses. Two specialists thought the reduction in biopsies could result in cost savings and a reduction in biopsy waiting times. Three specialists, however, believed there would be no overall difference in costs compared with the current standard of care. One cited that the decreased diagnostic costs may be offset by increased drug costs from more people being prescribed TKIs.

One specialist explained that as the technology to do these tests is already available in most hospital laboratories, the capital costs would be minimal and they could be used on other cancers. Two specialists commented that implementation of this technology would need more staff in genotyping laboratories, 1 of whom concluded that the costs associated would be minimal, whereas the other stated that staffing costs and implementing a shipping pathway would be balanced by major cost savings from reduced rebiopsy rates. However, another specialist felt this technology would not lead to a cost saving because testing would have to be repeated because of the high rate of false negatives.

Three experts thought no changes to facilities, infrastructure or training would be needed to implement this technology, 2 cited training would be needed and 1 mentioned validation; however, they believe it would lead to minimal extra workload. One specialist commented that plasma EGFR testing could be done in an outpatient setting allowing for convenient monitoring.

General comments

Two specialists believe this technology could replace the current standard of care, 1 believed it could replace the need for repeat biopsy and another 2 thought it would be implemented as an addition to tissue testing, particularly at diagnosis.

One specialist commented that implementing plasma testing for EGFR testing in their laboratory using Roche Cobas had been smooth and relatively easy. They noted that an important practical consideration is preservation of blood samples in blood tubes that prevent cell lysis, which are needed for all plasma EGFR tests. These are more expensive than regular blood collection tubes and not widely used in NHS hospitals. A further 2 specialists cited high costs and reimbursement as issues affecting adoption of this technology across the NHS.

Another specialist noted a major drawback with plasma EGFR testing is the high rate of false negatives for both EGFR-sensitising and acquired resistance mutations.

Two specialists agreed that plasma EGFR mutation testing could not replace a tissue diagnosis of NSCLC. However, they both stated that in late-stage NSCLC when there are no currently available therapies, plasma EGFR testing could prevent rebiopsy, in particular in people with T790M mutations. One noted that this affects a very small number of patients, although 2 experts suggested that plasma testing may be suited for use in people with late-stage disease as sensitivity increases with tumour burden.

One specialist noted that current plasma EGFR mutation tests do not identify C797X mutations, which are likely to be clinically important as mutation-specific drugs are developed.

Specialist commentators suggested further research is needed into:

- the economic impact of this technology
- the difference in time taken to achieve results from plasma and tissue testing in practice
- the clinical utility of plasma EGFR testing in patients with poor performance health status

- similarity of progression-free survival (PFS) and overall survival (OS) for plasma and tissue testing
- how to address high false negatives in practice.

Specialist commentators

The following clinicians contributed to this briefing:

- Dr Pedro Oliveira, consultant histopathologist, The Christie NHS Foundation Trust. No conflicts of interest declared.
- Dr Sanjay Popat, consultant medical oncologist, The Royal Marsden NHS Foundation Trust and reader, Imperial College London, declaration of interests: reimbursed consultant to AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Eli Lilly, Guardant Health, MSD, Novartis, Pfizer, Roche and Takeda.
- Prof Siow Ming Lee, professor of medical oncology, University College London and consultant medical oncologist, University College London Hospitals NHS Foundation Trust. No conflicts of interest declared.
- Dr Philippe Taniere, consultant histopathologist, University Hospitals Birmingham NHS Foundation Trust and honorary senior lecturer, University of Birmingham. Declaration of interests: received fees for giving lectures or being part of advisory board meetings by the following companies: Roche diagnostics, Qiagen, AstraZeneca, Roche, Boehringer, Lilly, Pfizer, Novartis, MSD and BMS. The NHS laboratory he leads has a contract with AstraZeneca; AstraZeneca supports epidermal growth factor receptor (EGFR) plasma testing for any UK patient; contract does not require a specific technology or platform. Has been an advisor of the study by PHG foundation on circulating tumour DNA (ctDNA) testing in lung cancer (recently published).
- Dr Alistair Reid, consultant clinical scientist, Liverpool Clinical Laboratories and honorary senior lecturer, Imperial College London. No conflicts of interest declared.

Additional commentators

- Dr Alastair Greystoke, senior lecturer, Newcastle University/The Newcastle upon Tyne Hospitals NHS Foundation Trust. Declaration of interest: consultancy fees from AstraZeneca for the development of osimertinib.
- Dr Malcolm Lawson, consultant respiratory physician, Mid Essex Hospital Services NHS Trust. No conflicts of interest declared.
- Mr Paul Roberts, consultant scientist, Leeds Genetics Laboratory. No conflicts of interest declared.

Development of this briefing

This briefing was developed for NICE by KiTEC. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

ISBN: 978-1-4731-2784-5