NICE National Institute for Health and Care Excellence

EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer

Diagnostics guidance

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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 The tests and test strategies listed below are recommended as options for detecting epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutations in the tumours of adults with previously untreated, locally advanced or metastatic non-small-cell lung cancer (NSCLC), when used in accredited laboratories participating in an external quality assurance scheme. The laboratory-developed tests should be designed to detect the mutations that can be detected by one of the CE-marked tests as a minimum.

- therascreen EGFR RGQ PCR Kit (CE-marked, Qiagen)

- cobas EGFR Mutation Test (CE-marked, Roche Molecular Systems)

- Sanger sequencing of samples with more than 30% tumour cells and therascreen EGFR RGQ PCR Kit for samples with lower tumour cell contents

- Sanger sequencing of samples with more than 30% tumour cells and cobas EGFR Mutation Test for samples with lower tumour cell contents

- Sanger sequencing followed by fragment length analysis and polymerase chain reaction (PCR) of negative samples.

1.2 There was insufficient evidence for the Committee to make recommendations on the following methods:

- high-resolution melt analysis

- pyrosequencing combined with fragment length analysis

- single-strand conformation polymorphism analysis

- next-generation sequencing

- therascreen EGFR Pyro Kit (CE-marked, Qiagen).

2 The technologies

2.1 Ten epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation methods for identifying adults with previously untreated, locally advanced or metastatic non-small-cell lung cancer (NSCLC) who may benefit from first-line treatment with EGFR-TK inhibitors were evaluated. Three are CE-marked tests; 5 are laboratory-developed tests; and 2 are test strategies combining a CE-marked test and a laboratory-developed test. Additional details of the tests are provided in section 4.

2.2 Other tests and methods for detecting EGFR-TK mutations are available, such as MALDI-TOF. NICE is aware that the tests and methods are evolving, so new ones are likely to appear in the future.

3 Clinical need and practice

The problem addressed

3.1 Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing is indicated in adults with previously untreated, locally advanced or metastatic non-small-cell lung cancer (NSCLC). Clinical trials have shown that patients with EGFR-TK mutation-positive tumours gain more benefit from treatment with EGFR-TK inhibitors than from standard chemotherapy treatment. Conversely, patients with EGFR-TK mutation-negative tumours gain more benefit from standard chemotherapy than from EGFR-TK inhibitors.

3.2 Multiple tests and test strategies for EGFR-TK mutation testing are currently used in NHS laboratories in England. The aim of this evaluation was to identify which tests and test strategies for EGFR-TK mutation testing in adults with previously untreated, locally advanced or metastatic NSCLC are clinically and cost effective for informing first-line treatment decisions as currently recommended by NICE.

The condition

3.3 NSCLC is the most common type of lung cancer in England and Wales, accounting for around 72% of all lung cancer cases. It can be further categorised by histological subtype; the 3 main types being squamous cell carcinoma, adenocarcinoma and large-cell carcinoma.

3.4 The prevalence of EGFR-TK mutations in NSCLC varies widely with population ethnicity, with reported prevalence of EGFR-TK mutations in adenocarcinoma ranging from 10.4% in a study of Italian patients (Marchetti et al. 2005) to 50% in a study of Japanese patients (Kosaka et al. 2004). The estimated proportion of EGFR-TK mutations in NSCLC in England and Wales is 16.6% (Rosell et al. 2009).

The diagnostic and care pathways

3.5   NICE clinical guideline 121 (Lung cancer: the diagnosis and treatment of lung cancer) recommends that patients with suspected lung cancer should be urgently referred for a chest X-ray. If the results suggest lung cancer, a contrast-enhanced CT scan of the chest, upper abdomen and lower neck is performed. Further investigations to confirm a diagnosis and to provide information on the stage of the disease are then carried out. These investigations generally include a biopsy for histological confirmation and subtyping, but may also include positron emission tomography-computed tomography, endobronchial ultrasound-guided transbronchial needle aspiration, endoscopic ultrasound-guided fine needle aspiration or non-ultrasound-guided transbronchial needle aspiration.

3.6   When biopsy is successful, DNA extraction and mutation analysis can be carried out on the biopsy tissue (which is generally stored as formalin-fixed paraffin-embedded tissue) to determine whether the tumour is EGFR-TK mutation-positive or -negative. If biopsy tissue is not available, DNA extracted from cytology samples can be used for mutation analysis. Other molecular tests may be performed as clinically indicated.

3.7   Participants at a European multidisciplinary workshop 'EGFR testing in NSCLC: from biology to clinical practice' (2009) emphasised the importance of standardisation and validation of EGFR-TK mutation tests and recommended that testing should only be undertaken in a quality-assured, accredited setting. However, there was no consensus on which laboratory test should be used for clinical decision-making. Participants agreed that the decision to request EGFR-TK mutation testing should be made by the treating physician and that results should be reported within 7 working days of request. Conversely, guidelines from the Royal College of Pathologists recommend that, to minimise turnaround time, molecular diagnostic tests should be ordered by the pathologist reporting on the histology of the tumour.

3.8   Treatment options for NSCLC include gefitinib and erlotinib, which are EGFR-TK inhibitors indicated for patients with EGFR-TK mutation-positive tumours. NICE's technology appraisal guidance 192 (Gefitinib for the

first-line treatment of locally advanced or metastatic non-small-cell lung cancer) and technology appraisal guidance 258 (Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer) recommend gefitinib and erlotinib respectively as options for the first-line treatment of locally advanced or metastatic NSCLC in people whose tumour tests positive for an EGFR-TK mutation. Other treatment options for NSCLC include chemotherapy regimens. NICE clinical guideline 121 recommends that chemotherapy should be offered to people with stage III or IV NSCLC and a good performance status (WHO 0, 1 or Karnofsky score 80–100) with the aim of improving survival, disease control and quality of life. Treatment with curative intent is not possible for these people. First-line chemotherapy should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) and a platinum drug (carboplatin or cisplatin). People who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug. NICE technology appraisal guidance 181 (Pemetrexed for the first-line treatment of non-small-cell lung cancer) recommends pemetrexed plus cisplatin as a first-line treatment for locally advanced or metastatic NSCLC, if the histology of the tumour has been confirmed as adenocarcinoma or large-cell tumour.

4 The diagnostic tests

The interventions

Therascreen EGFR RGQ PCR Kit

4.1 The therascreen EGFR RGQ PCR Kit (Qiagen) is a CE-marked real-time polymerase chain reaction (PCR) assay for the targeted detection of 29 mutations in exons 18 to 21 of the epidermal growth factor receptor tyrosine kinase (EGFR-TK) gene:

- G719X (G719S/G719A/G719C) in exon 18

- 19 deletions in exon 19

- T790M in exon 20

- S768I in exon 20

- 3 insertions in exon 20

- L858R in exon 21

- L861Q in exon 21.

4.2 To ensure it complies with the CE marking, the DNA is first isolated from a specimen of formalin-fixed paraffin-embedded tissue using the QIAamp DNA FFPE Tissue Kit. The total amount of DNA in the sample is assessed by a control assay. The therascreen EGFR RGQ PCR Kit then uses 2 technologies for detecting mutations: ARMS (amplification-refractory mutation system) for mutation-specific DNA amplification; and Scorpions for detecting amplified regions. Scorpions are bi-functional molecules containing a PCR primer covalently linked to a fluorescently labelled probe. A real-time PCR instrument (Rotor-Gene Q 5-Plex HRM Platform for consistency with CE marking) is used to perform the amplification and to measure fluorescence.

4.3 The limits of detection (the per cent mutant DNA present in a

background of wild-type DNA, at which 95% or more replicates were determined positive) reported by the manufacturer for the different mutations ranged from 0.5% to 7.0%.

4.4 An older version of the test exists (the therascreen EGFR PCR Kit), which was inherited by Qiagen when they acquired DxS Ltd. This older version uses the same methods as the newer therascreen EGFR RGQ PCR Kit, and detects 28 of the same mutations, but is not designed to detect the resistance mutation T790M. The limit of detection claimed by the manufacturer for the therascreen EGFR PCR Kit is 1% mutant DNA in a background of wild-type DNA. This version is no longer being actively marketed by Qiagen, was not used in any of the studies included in this review and has been superseded by the therascreen EGFR RGQ PCR Kit. Further, an earlier version of the therascreen EGFR PCR Kit, which did include an assay for T790M, was used to analyse all samples in the IPASS trial. This version is no longer available, but is considered equivalent to the therascreen EGFR RGQ PCR Kit for the purpose of this assessment.

Cobas EGFR Mutation Test

4.5 The cobas EGFR Mutation Test (Roche Molecular Systems) is a CE-marked real-time PCR test for the targeted detection of 41 mutations in exons 18 to 21 of the EGFR-TK gene:

- G719X (G719S/G719A/G719C) in exon 18

- 29 deletions and complex mutations in exon 19

- T790M in exon 20

- S768I in exon 20

- 5 insertions in exon 20

- L858R in exon 21 (2 variants).

4.6 The tumour tissue is first processed using the cobas DNA Sample Preparation Kit. The second step is PCR amplification and detection of EGFR-TK mutations using complementary primer pairs and fluorescently

labelled probes. The PCR is run using the cobas z 480 Analyzer, which automates amplification and detection. Cobas 4800 software provides automated test result reporting.

4.7   The limits of detection (lowest amount of DNA [nanogram] per reaction well to achieve a 95% or higher 'mutation detected' rate), as reported by the manufacturer for the different mutations, ranged from 0.78 nanograms to 3.13 nanograms of DNA per well.

Sanger sequencing of samples with more than 30% tumour cells and therascreen EGFR RGQ PCR Kit for samples with lower tumour cell contents

4.8   In this test strategy, Sanger sequencing of exons 18 to 21 (described in section 4.19) is used to detect EGFR-TK mutations in test samples with more than 30% tumour cells, and the therascreen EGFR RGQ PCR Kit (described in sections 4.1 to 4.4) is used to detect EGFR-TK mutations in samples with less than 30% tumour cells.

Sanger sequencing of samples with more than 30% tumour cells and cobas EGFR Mutation Test for samples with lower tumour cell content

4.9   In this test strategy, Sanger sequencing of exons 18 to 21 (described in section 4.19) is used to detect EGFR-TK mutations in test samples with more than 30% tumour cells, and the cobas EGFR Mutation Test (described in sections 4.5 to 4.7) is used to detect EGFR-TK mutations in samples with less than 30% tumour cells.

Sanger sequencing followed by fragment length analysis and PCR of negative samples

4.10   Sanger sequencing of exons 18 to 21 is used as an initial test to screen for mutations. Fragment length analysis to detect exon 19 deletions and real-time PCR to detect the exon 21 mutation L858R are then used on samples that produce a negative result using Sanger sequencing.

Pyrosequencing and fragment length analysis

4.11   This test strategy combines in-house methods of pyrosequencing (to detect point mutations) with in-house methods of fragment length analysis (to detect deletions and insertions) for EGFR-TK mutation detection.

4.12   Pyrosequencing involves extracting DNA from the sample and amplifying it using PCR. Nucleotides are added sequentially to the amplified PCR product. A series of enzymes incorporates nucleotides into the complementary DNA strand, generates light proportional to the number of nucleotides added and degrades unincorporated nucleotides. The DNA sequence is determined from the resulting pyrogram trace.

4.13   In fragment length analysis, DNA is extracted from the sample, and then amplified and labelled with fluorescent dye using PCR. Amplified DNA is mixed with size standards and analysed using capillary electrophoresis. The fluorescence intensity is monitored as a function of time, and analysis software can determine the size of the fragments. The presence or absence of deletions and insertions can then be reported.

Therascreen EGFR Pyro Kit

4.14   The therascreen EGFR Pyro Kit (Qiagen) is a CE-marked pyrosequencing kit. It is a targeted method of mutation detection designed to detect and distinguish between:

- G719S, G719A and G719C in exon 18

- the 20 most common deletions in exon 19

- S768I and T790M in exon 20

- L858R and L861Q in exon 21.

4.15   The kit provides all primers, controls, buffers and reagents necessary to perform the assay. Samples are analysed on the PyroMark Q24 System and a plug-in report tool that simplifies analysis of the pyrogram trace is available.

Single-strand conformation polymorphism analysis

4.16   Single-strand conformation polymorphism analysis is a screening method of mutation detection. The DNA is first extracted from the sample and amplified using PCR. The PCR product is then prepared for analysis by heat denature and analysed using capillary electrophoresis under non-denaturing conditions. Sequence variations (single-point mutations and other small changes) are detected through electrophoretic mobility differences.

High-resolution melt analysis

4.17   High-resolution melt analysis is a screening method of mutation detection. The DNA is first extracted from the sample and amplified using PCR. The PCR product is then precisely warmed so that the 2 strands of DNA 'melt' apart. Fluorescent dye, which only binds to double-stranded DNA, is used to monitor the process. A region of DNA with a mutation will 'melt' at a different temperature from the same region of DNA without a mutation. These changes are documented as melt curves and the presence or absence of a mutation can be reported.

Next-generation sequencing

4.18   Next-generation sequencing is a screening method of mutation detection. The concept is similar to Sanger sequencing (described in section 4.19), but the sample DNA is first fragmented into a library of small segments that can be sequenced in parallel reactions.

The comparator

Sanger sequencing

4.19   Sanger sequencing (also called direct sequencing) is a screening method of mutation detection. Sanger sequencing is a commonly used method, but there is a lot of variation in how it is carried out. In general, after DNA is extracted from the sample, it is amplified using PCR. The PCR product is then cleaned up and sequenced in both forward and reverse

directions. The sequencing reaction uses dideoxynucleotides labelled with coloured dyes, which randomly terminate DNA synthesis, creating DNA fragments of various lengths. The sequencing reaction product is then cleaned up and analysed using capillary electrophoresis. The raw data are analysed using software to generate the DNA sequence. All steps are performed at least in duplicate to increase confidence that an identified mutation is real. It should be noted that sequencing only works well when viable tumour cells constitute 25% or more of the sample.

5 Outcomes

The Diagnostics Advisory Committee (section 11) considered evidence from several sources (section 12).

How outcomes were assessed

5.1 The assessment was performed by an External Assessment Group and consisted of a systematic review, a web-based survey and the development of a decision analytic model.

5.2 The systematic review was carried out to identify evidence on the technical performance and clinical effectiveness of the different options available to detect epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutations in previously untreated locally advanced or metastatic non-small-cell lung cancer (NSCLC), and so adults who may benefit from first-line treatment with EGFR-TK inhibitors.

5.3 The web-based survey was conducted to gather data on the technical performance characteristics and costs of EGFR-TK mutation tests in use in NHS laboratories.

5.4 A decision analytic model was developed to assess the cost effectiveness of different methods of EGFR-TK mutation testing in helping to decide between treatment with standard chemotherapy and EGFR-TK inhibitors for patients with locally advanced or metastatic NSCLC. Three different analytic approaches, described below, were used to calculate cost effectiveness, each involving different levels of evidence.

- 'Comparative effectiveness' analysis: This analysis used data on the comparative effectiveness (progression-free survival and overall survival) of EGFR-TK inhibitors and standard chemotherapy in patients with EGFR-TK mutation-positive, EGFR-TK mutation-negative and EGFR-TK mutation-unknown tumours. The tests included in this analysis were the therascreen EGFR PCR Kit and Sanger sequencing of exons 19 to 21.

- 'Linked evidence' analysis: This is the same as the 'comparative effectiveness' analysis, except that it allowed the inclusion of EGFR-TK mutation tests that have data on the accuracy of the test for predicting response to EGFR-TK inhibitors but no data on comparative effectiveness (progression-free survival and overall survival in patients with EGFR-TK mutation-positive, EGFR-TK mutation-negative and EGFR-TK mutation-unknown tumours). Tests included in this analysis were the therascreen EGFR PCR Kit, Sanger sequencing of exons 18 to 21 and Sanger sequencing of exons 19 to 21.

- 'Assumption of equal prognostic value' analysis: For the remaining EGFR-TK mutation tests in the scope, no data were available on either the comparative effectiveness or the accuracy of the test for predicting response to EGFR-TK inhibitors. Therefore, for these tests, it was only possible to make a comparison based on differences in technical performance and test costs retrieved from the web-based survey, while assuming equal prognostic value across tests.

Technical performance

5.5   One study identified from the systematic review evaluated the technical performance of EGFR-TK mutation tests. The study was conducted in the Department of Molecular Diagnostics at the Royal Marsden Hospital and the Institute of Cancer Research. The study reported data for 2 years of EGFR-TK mutation testing from January 2009 to January 2011. During year 1 of the testing, the therascreen EGFR PCR Kit was used. During year 2, a combination of the therascreen EGFR PCR Kit, fragment analysis (for exon 19 deletions and exon 20 insertions) and Sanger sequencing (for the rarer exon 19 or exon 21 mutations) was used. A total of 121 patients were tested during year 1 and 755 during year 2. The mean turnaround time for the therascreen EGFR PCR test alone during year 1 was 4.9 business days (95% confidence interval [CI] 4.5 days to 5.5 days). However, the actual time from the test request to the result was 17.8 days (95% CI 16.4 days to 19.4 days). The total test failure rate for the first year of the study was 19% of all samples assessed, but this improved over time from a failure rate of 33% over the first 3 months to 13% during the last 3 months of year 1 testing. The total failure rate was lower in the second year of the study at only 5% of all samples assessed.

5.6   There were 24 UK laboratories participating in the 2012–2013 UK

National External Quality Assessment Service (NEQAS) pilot scheme for EGFR-TK mutation testing. Of these, 14 provided information to NICE during the scoping phase of the assessment and were invited to participate in the survey. Thirteen of the 14 laboratories completed the web-based survey.

5.7 The therascreen EGFR PCR Kit was the most commonly used EGFR-TK mutation test, with 6 laboratories using it. A combination of fragment length analysis and pyrosequencing was used in 2 laboratories. Sanger sequencing was used in 2 laboratories. However, one of these laboratories also uses the cobas EGFR Mutation Test for verifying mutations or when the sample contains insufficient tumour cells for Sanger sequencing (less than 30%). The second of these laboratories also uses fragment length analysis and real-time PCR to follow up samples found to be negative with Sanger sequencing. Single-strand conformation analysis, high-resolution melt analysis and pyrosequencing were used in single laboratories. One laboratory also provided information on a next-generation sequencing method that is being developed and validated.

5.8 The survey results showed that there were no clear differences between tests. The number of samples screened for EGFR-TK mutations in a typical week varied by laboratory from less than 5 (6 laboratories) to more than 20 (3 laboratories). The frequency at which the laboratories ran the tests ranged from daily to every other week. Batch sizes ranged from less than 3 samples to 10 samples but most laboratories stated that they would match demand rather than waiting for a minimum batch size.

5.9 Most laboratories had a turnaround time from receiving the sample to reporting the result to the clinician of 3–5 days or 6–7 days, with 1 laboratory reporting a turnaround of 24–28 hours (therascreen EGFR PCR Kit) and 1 laboratory reporting a turnaround of 8–10 days (therascreen EGFR PCR Kit). The estimated total number of failed samples ranged from 0% to 10%, with the number of failed samples because of insufficient tumour cells ranging from 0–5%. The most common reasons for failed tests were insufficient tumour cell count and poor-quality DNA or DNA degradation.

5.10   The cost of the EGFR-TK mutation tests ranged from £110 to £190 and the price that the laboratories charged for the tests ranged from £120 to £200. When there was a difference between the test cost and the price charged, this ranged from £10 to £37.50 per test. No single test appeared to be more or less expensive than any of the other tests.

5.11   It was noted by UK NEQAS that error rates seen in the quality assurance scheme for EGFR-TK mutation testing are not always method related, and may be because of processing and reporting problems. In addition, UK NEQAS noted that there had been no correlation between any method used for EGFR-TK mutation testing and errors since the scheme was started in 2010.

Accuracy

5.12   Two randomised controlled trials and 4 cohort studies provided data on the accuracy of EGFR-TK mutation testing for predicting the response to treatment with EGFR-TK inhibitors in patients with advanced or metastatic NSCLC. Three studies included patients treated with gefitinib and 3 included patients treated with erlotinib.

5.13   Patient characteristics varied across studies. One study included mainly white patients and 1 study included mainly East Asian patients (4 studies did not report the ethnicity of patients). All studies reported that a high proportion of patients had metastatic disease. Most patients had a histological diagnosis of adenocarcinoma (45–100%), but 2 studies included some patients with squamous cell carcinoma (9–15%). Four studies mainly, or only, included patients who had never smoked, whereas 2 studies mainly included patients who were current or former smokers.

5.14   Five studies evaluated Sanger sequencing methods for identifying any EGFR-TK mutation; 3 assessed exons 18 to 21, 1 assessed exons 19 to 21, and 1 assessed exons 18 to 24 (Sanger sequencing or WAVE-HS for inadequate samples [less than 50% tumour cells]). One study assessed the therascreen EGFR PCR Kit (the version designed to detect 29 mutations, including T790M).

5.15   The therascreen EGFR PCR Kit appears to have the best overall performance for discriminating between patients who are likely to benefit from EGFR-TK inhibitor treatment and patients who are not. The sensitivity and specificity estimates using objective response as the reference standard were 99% (95% CI 94% to 100%) and 69% (95% CI 60% to 77%) respectively.

5.16   Of the 5 studies that used Sanger sequencing methods to identify EGFR-TK mutations, 4 reported high estimates of specificity (more than 80%) and sensitivities ranged from 60% to 80% when objective response was used as the reference standard. The remaining Sanger sequencing study reported low specificity (61%) with high sensitivity (84%) for objective response as the reference standard.

Clinical effectiveness

5.17   Five randomised controlled trials provided data on the clinical effectiveness of EGFR-TK inhibitors compared with standard chemotherapy in patients with advanced or metastatic NSCLC whose tumours tested positive for EGFR-TK mutations. One additional study reported data for a subgroup of patients from the EURTAC trial whose samples had been re-analysed using a different EGFR-TK mutation testing method. Three of the trials included only patients with EGFR-TK mutation-positive tumours, and the remaining 2 trials (IPASS and First-SIGNAL) included all patients regardless of EGFR-TK mutation status, but also reported a subgroup analysis for patients whose tumours tested positive for EGFR-TK mutations. The trials compared the EGFR-TK inhibitors gefitinib or erlotinib with various single-agent or combination standard chemotherapy regimens.

5.18   Patient characteristics varied across studies. Four studies were conducted in East Asia and 1 was conducted in Western Europe. One study included patients who had never smoked, 1 study included mainly patients who had never smoked (94%) and the rest included between 62% and 71% of patients who had never smoked. One study included only patients with a diagnosis of adenocarcinoma, whereas in the remaining studies approximately 90% had a diagnosis of adenocarcinoma. Most patients (more than 75%) in all studies had

metastatic disease.

5.19   Two studies used Sanger sequencing methods to assess EGFR-TK mutation status, but both limited the definition of positive EGFR-TK mutation status to the presence of an 'activating mutation' (exon 19 deletions or exon 21 mutation L858R). The remaining studies used EGFR-TK mutation tests that targeted a wider range of mutations. One study reported the results of a re-analysis of samples from the EURTAC trial using the cobas EGFR Mutation Test. The other study (IPASS) used the therascreen EGFR PCR Kit (the version designed to detect 29 mutations, including T790M). The North East Japan Study Group (NEJSG) trial used fragment length analysis, targeting exon 19 deletions, exon 21 point mutations (L858R, L861Q), exon 18 point mutations (G719A, G719C, G719S), and exon 20 point mutation (T790M). The First-SIGNAL trial used Sanger sequencing of exons 19 to 21.

5.20   All studies reported improvements in objective response, measured as relative risk. Objective response ranged from a relative risk of 1.51 (95% CI 1.23 to 1.88) to 3.89 (95% CI 2.34 to 6.68) for patients with EGFR-TK mutation-positive tumours who were given EGFR-TK inhibitors compared with patients given standard chemotherapy. All studies also reported statistically significant improvements or trends towards improvement in progression-free survival, with hazard ratios ranging from 0.16 (95% CI 0.10 to 0.26) to 0.54 (95% CI 0.27 to 1.10) for patients with EGFR-TK mutation-positive tumours who were given EGFR-TK inhibitors compared with patients given standard chemotherapy. Four studies reported overall survival but none found a statistically significant difference between patients given EGFR-TK inhibitors and patients given standard chemotherapy, with hazard ratios ranging from 0.89 (95% CI 0.63 to 1.24) to 1.04 (95% CI 0.65 to 1.68).

5.21   The results from the IPASS trial showed that progression-free survival in patients with EGFR-TK mutation-negative tumours was statistically significantly shorter when patients were treated with EGFR-TK inhibitors than with standard chemotherapy (hazard ratio [HR] 2.85, 95% CI 2.05 to 3.98). A similar trend for patients with EGFR-TK mutation-negative tumours, although not statistically significant, was observed in the First-SIGNAL trial (HR 1.42, 95% CI 0.82 to 2.47).

Cost effectiveness

5.22   The External Assessment Group received the health economic model submitted by AstraZeneca for NICE technology appraisal guidance 192 (Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer). The External Assessment Group also took into account amendments and corrections to the model that were accepted by the appraisal committee for NICE technology appraisal guidance 192. This model calculates the expected cost effectiveness of gefitinib compared with standard chemotherapy for the first-line treatment of locally advanced or metastatic NSCLC in patients with a positive EGFR-TK mutation test based on the therascreen EGFR PCR Kit. The External Assessment Group used the AstraZeneca model to develop a de novo model that included patients with a positive, negative or unknown EGFR-TK mutation test result.

5.23   The External Assessment Group developed a decision tree and a Markov model to analyse the long-term consequences of technical performance and accuracy of the different EGFR-TK mutation tests and test combinations followed by treatment with either standard chemotherapy or an EGFR-TK inhibitor in patients with NSCLC. The decision tree was used to model the test result (positive, unknown or negative) and the treatment decision. Patients with a positive test result receive an EGFR-TK inhibitor. Patients with a negative test result or an unknown EGFR-TK mutation status receive standard chemotherapy (pemetrexed and cisplatin). The Markov model was used to estimate the long-term consequences in terms of costs and quality-adjusted life years (QALYs). The model has a cycle time of 21 days (resembling the duration of 1 cycle of chemotherapy), and a time horizon of 6 years. In the model, after a treatment decision is made, patients can either have progression-free disease (subdivided into 'response' and 'stable disease' based on objective response rate), experience disease progression or die.

5.24   The proportions of positive and negative EGFR-TK mutation test results were based on: the estimated proportions of patients with NSCLC and EGFR-TK mutation-positive tumours in England and Wales (16.6%, standard error 0.8%); the test accuracy (sensitivity and specificity with objective response to EGFR-TK inhibitor as reference standard); and the

proportion of patients with an unknown test result, based on data from published studies (IPASS and Jackman et al. 2007). The proportions of positive, negative and unknown EGFR-TK mutation test results for the therascreen EGFR PCR Kit were 32.8%, 44.6% and 22.7% respectively. The proportions of positive, negative and unknown EGFR-TK mutation test results for Sanger sequencing of exons 18 to 21 were 29.0%, 33.4% and 37.7% respectively. In the 'assumption of equal prognostic value' analysis, the proportions of positive, negative and unknown EGFR-TK mutation test results were assumed equal to the therascreen EGFR PCR Kit for all tests and test strategies.

5.25   The objective response rates were based on data from published studies (IPASS, First-SIGNAL and Yang et al. 2008). For EGFR-TK mutation-negative or -unknown tumours (treated with standard chemotherapy), objective response rates were adjusted to correspond to treatment with pemetrexed and cisplatin. Objective response rates for EGFR-TK mutation-positive, -negative and -unknown tumours identified using the therascreen EGFR PCR Kit were 0.712, 0.335 and 0.403 respectively. Objective response rates for EGFR-TK mutation-positive, -negative and -unknown tumours identified using Sanger sequencing of exons 18 to 21 were 0.731, 0.604 and 0.403 respectively. In the 'assumption of equal prognostic value' analysis, the objective response rates for EGFR-TK mutation-positive, -negative and -unknown tumours were assumed equal to the therascreen EGFR PCR Kit for all tests and test strategies.

5.26   Progression-free survival and overall survival after testing with the therascreen EGFR PCR Kit were modelled using Weibull regression models based on the IPASS trial and a hazard ratio favouring treatment with an EGFR-TK inhibitor (HR 0.43, 95% CI 0.34 to 0.53). For testing using Sanger sequencing of exons 19 to 21, progression-free survival and overall survival for patients with EGFR-TK mutation-positive or -negative tumours were modelled using Kaplan-Meier curves extracted from the First-SIGNAL trial. Progression-free survival and overall survival for patients with tumours of unknown EGFR-TK mutation status were based on the IPASS Weibull model for unknown mutations. For testing using Sanger sequencing of exons 18 to 21, progression-free survival and overall survival were assumed equal to testing using Sanger sequencing of exons 19 to 21.

5.27   The test costs were based on the prices charged by the NHS laboratories in England and Wales involved in the web-based survey (see table 1). In the case of an unknown EGFR-TK mutation status, no test costs were taken into account if there was a pre-laboratory clinical failure, but full test costs were taken into account if there was a technical failure in the laboratory.

Table 1 EGFR-TK mutation test costs

Test	Price charged	Standard error
therascreen EGFR PCR Kit	£154.58	£12.01
Sanger sequencing of exons 19 to 21	£147.50	£27.50
Sanger sequencing of exons 18 to 21	£147.50	£27.50
Sanger sequencing or therascreen EGFR PCR Kit for samples with insufficient tumour cells	£137.30	£14.88
Sanger sequencing or cobas EGFR Mutation Test for samples with insufficient tumour cells	£130.00	£19.34
Pyrosequencing combined with fragment length analysis	£187.50	£12.50
Sanger sequencing followed by fragment length analysis/real-time PCR	£140.00	£27.50
High-resolution melt analysis	£150.00	£27.50
cobas EGFR Mutation Test	£140.00	£27.50
Single-strand conformation analysis	£140.00	£27.50
Abbreviations: EGFR, epidermal growth factor receptor; PCR, polymerase chain reaction.		

5.28   Results from the 'comparative effectiveness' analysis showed the therascreen EGFR PCR Kit to be both less effective and less costly compared with Sanger sequencing of exons 19 to 21, with an incremental cost-effectiveness ratio (ICER) of £32,167 saved per QALY lost. Adjustments to costs and the proportions of patients with unknown mutation status in sensitivity analyses had little effect on the results.

When treatment costs and adverse event costs were updated to 2012 costs, the ICER was £32,196 saved per QALY lost for the therascreen EGFR PCR Kit compared with Sanger sequencing. When the proportions of patients with unknown mutation status were based on the results from the web-based survey rather than information from published trials, the ICER was £34,555 saved per QALY lost for the therascreen EGFR PCR Kit compared with Sanger sequencing.

5.29   The External Assessment Group explained that the lower costs and QALYs for the therascreen EGFR PCR Kit were because patients with EGFR-TK mutation-negative tumours had shorter overall survival in the IPASS trial (therascreen EGFR PCR Kit) than in the First-SIGNAL trial (Sanger sequencing of exons 19 to 21), whereas the outcome was comparable for patients whose tumours were EGFR-TK mutation positive. For patients whose tumours were EGFR-TK mutation unknown, overall survival was the same by assumption. Therefore, on average, with the therascreen EGFR PCR Kit patients had shorter overall survival, resulting in fewer QALYs and reduced costs compared with Sanger sequencing of exons 19 to 21.

5.30   The External Assessment Group noted that this analysis is particularly problematic because of the assumption that the differences in relative treatment response, progression-free survival and overall survival between the results of the First-SIGNAL trial (Sanger sequencing of exons 19 to 21) and the results of the IPASS trial (therascreen EGFR PCR Kit) were solely because of the different EGFR-TK mutation tests used to distinguish between patients whose tumours were EGFR-TK mutation positive (and receive EGFR-TK inhibitor treatment) and patients whose tumours were EGFR-TK mutation negative (and receive standard chemotherapy).

5.31   Results from the 'linked evidence' analysis also showed the therascreen EGFR PCR Kit to be both less effective and less costly than Sanger sequencing of exons 18 to 21 at an ICER of £31,849 saved per QALY lost. Sensitivity analyses had little effect on the results. When the treatment costs and adverse event costs were updated to 2012 costs, the ICER was £34,169 saved per QALY lost for the therascreen EGFR PCR Kit compared with Sanger sequencing of exons 18 to 21. When the

proportions of patients with unknown mutation status were based on the results from the web-based survey rather than information from published trials, the ICER was £31,880 saved per QALY lost for the therascreen EGFR PCR Kit compared with Sanger sequencing of exons 18 to 21.

5.32   The reason for the lower costs and QALYs for the therascreen EGFR PCR Kit were the same as for the 'comparative effectiveness' analysis, as described in section 5.28.

5.33   In addition to the assumption described in section 5.30, the 'linked evidence' analysis also assumed that the relative progression-free survival and overall survival for Sanger sequencing of exons 18 to 21 correlated perfectly with the relative progression-free survival and overall survival for Sanger sequencing of exons 19 to 21.

5.34   In the 'assumption of equal prognostic value' analysis, the comparative effectiveness, test accuracy and proportion of patients with unknown mutation status for each test strategy were assumed equal to those of the therascreen EGFR PCR Kit. Therefore, the test strategies only differed with respect to costs. Results showed that the test strategy of Sanger sequencing or the cobas EGFR Mutation Test for samples with insufficient tumour cells was the least expensive (£15 [0.06%] cheaper than Sanger sequencing of exons 18 to 21 alone), and fragment length analysis combined with pyrosequencing was the most expensive strategy (£33 [0.13%] more expensive than Sanger sequencing of exons 18 to 21 alone).

5.35   The External Assessment Group did not include next-generation sequencing and the therascreen EGFR Pyro Kit in any of the cost-effectiveness analyses because of a lack of data. No published studies were identified for either of these methods and neither method is currently in routine clinical use in any NHS laboratories in England and Wales.

6   Considerations

6.1   The Diagnostics Advisory Committee reviewed the evidence available on the clinical and cost effectiveness of epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing to inform first-line treatment decisions in adults with locally advanced or metastatic non-small-cell lung cancer (NSCLC). The Committee considered the report produced by the External Assessment Group and statements from patient experts on the Committee and from clinical specialists who acted as specialist Committee members on this assessment.

6.2   The Committee discussed the External Assessment Group's report on the clinical and cost effectiveness of EGFR-TK mutation tests. It noted that, during scoping, 10 interventions had been identified as suitable for review in this assessment. However, during systematic review of the evidence, the External Assessment Group found limited data for many of the tests and no data on the clinical and cost effectiveness of next-generation sequencing and the therascreen EGFR Pyro Kit.

Technical performance and clinical validity

6.3   The Committee considered the technical performance of the different tests. It heard from clinical specialists on the Committee that, in their experience, the different tests generally have a similar level of accuracy in detecting the mutations that they are designed to detect. The Committee also noted the statement from the UK National External Quality Assessment Service (NEQAS) that errors seen in the EGFR quality assurance scheme are not always method related, and that variations in how tests are processed and implemented can lead to variations in the failure rates (see section 5.11). The Committee also considered the failure rates reported for the different tests in the web-based survey. The Committee considered that, although the survey was limited by its small sample size, it seemed to suggest that failure rates are generally not test-dependent. Furthermore, the Committee heard that it is standard practice for the quality of tissue samples to be initially assessed by a pathologist. Therefore, the decision made by the pathologist about

whether to send a sample for EGFR-TK mutation testing could impact on the number of patients with an unknown EGFR-TK mutation status. The Committee concluded that the technical performance of the tests is not solely influenced by test accuracy, and that processing of samples and testing practices is likely to influence technical performance. It further concluded that, in UK practice, the technical performance of the tests under assessment is likely to be very similar.

6.4   The Committee discussed the lack of a gold standard test for assessing test accuracy, the difficulties relating to the different mutation coverage of the various tests, and the uncertainty about the clinical significance of some mutations. The Committee acknowledged that the approach taken by the External Assessment Group, in which accuracy for predicting response to treatment was calculated using objective response and disease control as reference standards, was a valid approach in this situation. It was advised by clinical specialists on the Committee, however, that deriving accuracy from response to treatment with an EGFR-TK inhibitor is problematic. For instance, the definition of false positives was 'patients identified as having tumours with an EGFR-TK mutation that do not respond to treatment with an EGFR-TK inhibitor'. It noted that there may be other reasons why a tumour does not respond to treatment, such as concomitant medications, patient characteristics and other clinical factors.

6.5   The Committee considered the accuracy of EGFR-TK mutation tests for predicting response to treatment. It noted that the External Assessment Group had only been able to obtain sensitivity and specificity estimates for therascreen EGFR PCR Kit and Sanger sequencing of exons 18 to 21 and exons 19 to 21. The Committee also noted that, when accuracy estimates were available, the accuracy of different tests was calculated from different studies with different patient populations and different ways of classifying resistance mutations. The Committee heard from the External Assessment Group that, ideally, sensitivity and specificity values should be generated for all tests from a single set of samples, therefore limiting the influence of sampling and population differences on the accuracy estimates. The Committee acknowledged that this assessment did not present such a scenario and that it was plausible that differences in patient populations could have impacted on relative accuracy

estimates for individual tests. The Committee therefore concluded that the relative predictive accuracy for the different tests could not be reliably established.

6.6   The Committee considered the effect of tissue quality on the accuracy of EGFR-TK mutation testing. It heard from clinical specialists on the Committee that the quality of tissue samples available for testing often varies, and this may impact on both the test failure rates and test accuracy. The Committee noted that, in addition to obtaining good-quality tumour samples, it is important to use a sensitive test to enable detection of EGFR-TK mutations, especially to ensure correct results in lower-quality tumour samples. It discussed the consequences of assigning the wrong EGFR-TK mutation status to a patient and noted that both the IPASS and the Signal-FIRST trials (see section 5.21) had demonstrated that progression-free survival was shorter for patients receiving an EGFR-TK inhibitor than for patients receiving standard chemotherapy in the EGFR-TK mutation-negative subgroup. For this reason, the Committee concluded that it is important to ensure high accuracy of testing, particularly to minimise the chances of incorrect treatment.

6.7   The Committee then discussed the generalisability of the clinical evidence to UK clinical practice and the UK patient population. It noted that 4 out of the 5 randomised controlled trials identified by the External Assessment Group were conducted in East Asia (see sections 5.18 and 5.19). The Committee acknowledged that the patients included in the trials had characteristics different from patients usually seen in UK practice, most notably that the studies included a high proportion of patients who had never smoked and a high proportion of patients of East Asian origin. The Committee noted that all evidence for the therascreen EGFR RGQ PCR Kit came from the IPASS trial, which looked almost exclusively at patients from East Asia. It also noted that, although most of the evidence came from patients with adenocarcinoma, patients with squamous cell carcinoma would also be tested for EGFR-TK mutations and these patients may have different clinical characteristics. The Committee concluded that, although there were some substantial differences between the trial populations and the population of patients presenting with advanced NSCLC in the UK, the effect on test accuracy

was likely to be minimal and therefore the trial evidence could be used to support the effectiveness of testing in patients with adenocarcinoma and in patients with squamous cell carcinoma in a UK setting.

6.8 The Committee considered the value of tests that identify rare EGFR-TK mutations. It acknowledged that screening tests are designed to detect more mutations than the targeted tests. In addition, the targeted tests (therascreen EGFR PCR Kit and the cobas EGFR Mutation Test) are designed to detect different sets of mutations, which vary in the number of rare forms of mutations included. The Committee heard from clinical specialists on the Committee that the clinical significance of rare mutations is generally unknown, and that treatment decisions for patients with a rare EGFR-TK mutation would be made by the oncologist based on the availability of evidence, such as case studies. The Committee acknowledged that evidence on the clinical effect of rare mutations is being generated. However, it concluded that currently there is little additional value of tests designed to detect rare mutations, except for the purpose of collecting clinical outcome data for research.

6.9 The Committee discussed whether there are any benefits of using CE-marked tests over laboratory-developed tests for detecting EGFR-TK mutations. It heard that the CE-marked EGFR-TK mutation tests (therascreen EGFR RGQ PCR Kit and cobas EGFR Mutation Test) and the simpler laboratory-developed tests such as polymerase chain reaction (PCR) may be easier to implement than tests based on Sanger sequencing for laboratories with little molecular diagnostics experience (for example, pathology laboratories). The Committee therefore concluded that, although there was no distinguishable difference in the technical performance of the tests, the ease of use of the CE-marked tests may be an advantage in some clinical settings, particularly when limited molecular diagnostics technical support is available.

6.10 The Committee considered the turnaround time of EGFR-TK mutation testing. It noted that turnaround time was assumed not to be test-dependent and was therefore not included in the economic modelling. The Committee heard from clinical specialists on the Committee that turnaround time was impacted by factors such as transporting samples between different locations for testing and the set-up of the laboratory.

It also heard from patient experts that waiting for test results causes additional anxiety to patients and that the rapid turnaround of test results is a priority for patients. The Committee acknowledged that, although the survey conducted by the External Assessment Group showed, on average, that similar turnaround times were achieved for all tests in the UK laboratories surveyed, the only test achieving a turnaround time shorter than 3 days was the therascreen EGFR PCR Kit. However, the Committee concluded that, although it is possible that the CE-marked tests could achieve quicker turnaround times, the frequency of batch testing would have a considerable impact on turnaround time in practice, and therefore it is likely that standard turnaround times could be met, irrespective of which test method is used.

6.11   The Committee considered next-generation sequencing and noted that research is currently being done on this method to look at panels of lung cancer genes. It noted that current turnaround time and cost are a hindrance to implementation, but that these practicalities are likely to be resolved in the future. The Committee concluded that next-generation sequencing is likely to be an important method for identifying EGFR-TK mutations in the future.

Cost effectiveness

6.12   The Committee noted that the price a laboratory charged for an EGFR-TK mutation test was used in the cost-effectiveness analyses and that this price is not necessarily a true reflection of the actual cost to a laboratory. The Committee noted that the mean test costs reported in the survey of laboratories in England and Wales ranged from £130 to £188 (see section 5.27). It heard from clinical specialists on the Committee that the true cost to a laboratory may vary depending on their individual set-up, and that costs can change over time as experience and throughput changes. The Committee accepted that the reference case states that costs to the NHS should be used, and therefore that the approach taken by the External Assessment Group in their cost-effectiveness modelling was appropriate. The Committee concluded that the true costs of the tests are likely to be very similar for all the tests included in this assessment and that they are appropriately incorporated in the cost-effectiveness models.

6.13   The Committee noted that the overall survival estimates used in the 'comparative effectiveness' and the 'linked evidence' cost-effectiveness analyses came from the IPASS trial for the therascreen EGFR PCR Kit and from the First-SIGNAL trial for Sanger sequencing. The Committee heard from the External Assessment Group that the reason for this was the need to use the same assumptions as in NICE technology appraisal guidance 192 (Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer). It also heard from the External Assessment Group that, if the IPASS survival estimates were used for both tests, Sanger sequencing was more costly and more effective than the therascreen EGFR PCR Kit. However, if the survival estimates from the First-SIGNAL trial were used for both tests, the therascreen EGFR PCR Kit became more costly and more effective than Sanger sequencing. The Committee noted that that 'comparative effectiveness' and the 'linked evidence' cost-effectiveness models appeared sensitive to the difference in quality-adjusted life year (QALY) gains from the 2 trials, and that these results could be because of relatively small differences in QALYs.

6.14   The Committee considered the assumptions used in the cost-effectiveness analyses. It noted that, in the 'comparative effectiveness' and the 'linked evidence' analyses, a key assumption was that the difference in comparative effectiveness between the studies was solely because of the use of different tests. However, the Committee acknowledged that the differences in comparative effectiveness between the tests may be caused by a variety of factors, such as differences in the patient populations. The Committee therefore concluded that the assumption on comparative effectiveness used in these models is unlikely to hold true.

6.15   The Committee considered the face validity of the 'comparative effectiveness' and the 'linked evidence' analyses. It noted that, although the External Assessment Group had made a good attempt to model the cost effectiveness of EGFR-TK mutation testing, the analyses were severely hampered by lack of evidence and therefore the greater level of assumptions needed. The Committee was especially concerned about the uncertainties in input parameters, such as cost and overall survival (see sections 6.12 and 6.13). The Committee concluded that, given these

problems, the results of the cost-effectiveness analyses were not robust.

6.16   The Committee considered the validity of the results of the 'equal prognostic value' analysis. It acknowledged that the assumption of equal prognostic value across the tests was not an unreasonable approach given the lack of evidence and the similarity in technical performance of the tests. The Committee noted that, in the base case, the difference in total costs between the most expensive and least expensive test strategy was small. It also noted that, in the sensitivity analysis, although the difference in total costs between the different test strategies increased, it still remained relatively small and that the difference in total QALYs was also low. The Committee concluded that, on balance, the cost effectiveness of the different tests and test strategies for EGFR-TK mutation testing are likely to be similar.

6.17   The Committee noted that, for some of the tests (high-resolution melt analysis, pyrosequencing combined with fragment length analysis and single-strand conformation polymorphism analysis), the 'equal prognostic value' analysis was the only economic modelling performed, and that test accuracy and clinical effectiveness were not assessed by the External Assessment Group because data were not available. The Committee acknowledged that this represented a weaker evidence base than that for the therascreen EGFR PCR Kit, the cobas EGFR Mutation Test and Sanger sequencing tests. It noted further that 2 tests (therascreen EGFR Pyro Kit and next-generation sequencing) were not included in the assessment because no information on failure rates in clinical practice in the UK was available. The Committee acknowledged that, although the cost effectiveness of the different tests and test strategies for EGFR-TK mutation testing are likely to be similar, there is insufficient evidence to support this conclusion.

6.18   The Committee noted that the analysis in NICE technology appraisal guidance 192 (Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer) was primarily based on data from the IPASS trial, which used the therascreen EGFR PCR Kit to classify tumours of patients as EGFR-TK mutation positive or negative. The Committee acknowledged that the recommendation of gefitinib for the first-line treatment of locally advanced or metastatic NSCLC in patients

whose tumours test positive for the EGFR-TK mutation (NICE technology appraisal guidance 192) implies that the therascreen EGFR PCR Kit is recommended and cost effective as part of the test-treat strategy. The Committee concluded that, for the cobas EGFR Mutation Test and for Sanger sequencing-based methods, an equivalent evidence base exists, and therefore these tests and the therascreen EGFR PCR Kit can be considered clinically effective and cost effective for informing first-line treatment decisions in patients with previously untreated, locally advanced or metastatic NSCLC in the NHS. The Committee further concluded that, for the non-Sanger sequencing-based tests (high-resolution melt analysis, pyrosequencing combined with fragment length analysis and single-strand conformation polymorphism analysis) and for tests not included in the External Assessment Group's assessment (the therascreen EGFR Pyro Kit and next-generation sequencing), the evidence was insufficient to allow any recommendations to be made on their use.

7 Recommendations for further research

7.1   NICE recommends that studies directly comparing different epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation test methods are performed. These studies should include the re-testing of stored non-small-cell lung cancer (NSCLC) tumour samples using different EGFR-TK mutation test methods and should link to patient outcomes.

7.2   NICE recommends that a multivariate prediction model is developed with the aim of predicting the response of previously untreated, advanced or metastatic non-small-cell lung cancer NSCLC to treatment with an EGFR-TK inhibitor.

8   Implementation

8.1   NICE has developed tools to help organisations put this guidance into practice.

9 Related NICE guidance

Published

- Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer. NICE technology appraisal guidance 258 (2012).

- Lung cancer for adults. NICE quality standard 17 (2012).

- Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer. NICE technology appraisal guidance 227 (2011).

- Lung cancer: the diagnosis and treatment of lung cancer. NICE clinical guideline 121 (2011).

- Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. NICE technology appraisal guidance 192 (2010).

- Pemetrexed for the maintenance treatment of non-small-cell lung cancer. NICE technology appraisal guidance 190 (2010).

- Pemetrexed for the first-line treatment of non-small-cell lung cancer. NICE technology appraisal guidance 181(2009).

- Erlotinib for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 162 (2008).

- Endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal masses. NICE interventional procedure guidance 254 (2008).

- Pemetrexed for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 124 (2007).

Under development

NICE is developing the following guidance:

- Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. NICE technology appraisal. Publication expected September 2013.

- Afatinib for the treatment of EGFR mutation-positive non-small-cell lung cancer. NICE technology appraisal. Publication expected June 2014.

- Erlotinib and gefitinib for the treatment of non-small-cell lung cancer following prior chemotherapy (Review of TA162 and TA175). NICE technology appraisal. Publication expected June 2014.

- Pemetrexed for maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer. NICE technology appraisal. Publication date to be confirmed.

10 Review

NICE will update the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Andrew Dillon
Chief Executive
August 2013

11 Diagnostics Advisory Committee members and NICE project team

Diagnostics Advisory Committee

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. During this assessment the membership of the Diagnostics Advisory Committee changed because some members reached the end of their terms and others were appointed in their place. A full list of the Committee members who participated in this assessment appears below.

Standing Committee members

Professor Ron Akehurst
Professor in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Dr Trevor Cole
Consultant Clinical and Cancer Geneticist, Birmingham Women's Hospital NHS Foundation Trust

Dr Paul Collinson
Consultant Chemical Pathologist, St George's Hospital

Dr Sue Crawford
GP Principal, Chillington Health Centre

Professor Ian A Cree
Senior Clinical Advisor, Warwick Medical School, University Hospitals Coventry and Warwickshire

Professor Erika Denton
National Clinical Director for Diagnostics, NHS England, Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

Dr Steve Edwards

Head of Health Technology Assessment, BMJ Evidence Centre.

Mr David Evans

Lay representative

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Professor Lisa Hall

Professor of Analytical Biotechnology, University of Cambridge

Professor Noor Kalsheker

Professor of Clinical Chemistry, University of Nottingham

Dr Mark Kroese

Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Dr Peter Naylor

GP, Chair Wirral Health Commissioning Consortia

Professor Adrian Newland

Chair, Diagnostics Advisory Committee

Dr Richard Nicholas

Consultant Neurologist; Honorary Senior Lecturer, Heatherwood and Wexham Park Hospitals NHS Foundation Trust

Dr Gail Norbury

Consultant Clinical Scientist, Guy's and St Thomas' NHS Foundation Trust

Ms Margaret Ogden

Lay representative

Dr Diego Ossa

Director of Market Access Europe, Novartis Molecular Diagnostics

Mr Stuart Saw

Head of Financial Strategy London, NHS England

Dr Steve Thomas

Consultant Vascular and Cardiac Radiologist at Sheffield Teaching Hospitals Foundation Trust

Mr Paul Weinberger

CEO, DiaSolve Ltd, London

Mr Christopher Wiltsher

Lay representative

Specialist Committee members

Dr Fiona Blackhall

Consultant Medical Oncologist and Honorary Senior Lecturer, Christie Hospital NHS Foundation Trust

Mrs Mandi Elliott

Chemotherapy Nurse Specialist, Queen's Centre for Oncology and Haematology

Mr Tom Haswell

Lay Representative

Mr Paul Roberts

Consultant Cytogeneticist and Interim Head of Department, St James's Hospital

Dr Mark Slade

Consultant Respiratory Physician and Clinical Director, Papworth Hospital NHS Foundation

Dr Phillipe Taniere

Consultant Histopathologist, Queen Elizabeth Hospital Birmingham

NICE project team

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

Frances Nixon and **Farouk Saeed**

Topic Leads

Pall Jonsson

Technical Adviser

Robert Fernley

Project Manager

Frances Nixon and **Farouk Saeed**

12   Sources of evidence considered by the Committee

The diagnostics assessment report was prepared by Kleijnen Systematic Reviews Ltd in collaboration with Erasmus University Rotterdam and Maastricht University.

- Westwood ME, Joore MA, Whiting P et al. Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer: a systematic review and cost-effectiveness analysis. (January 2013)

Registered stakeholders

The following organisations accepted the invitation to participate in this assessment as registered stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report and the diagnostics consultation document.

Manufacturers/sponsors:

- Roche Molecular Systems, Inc.

- Qiagen Ltd.

Professional/specialist and patient/carer groups:

- All Wales Molecular Genetics Lab

- AstraZeneca

- Boehringer Ingelheim Limited

- Bristol Genetics Laboratory

- British Thoracic Oncology Group (BTOG)

- Cancer Research UK

- Coventry and Warwickshire Pathology Services

- Department of Molecular Haematology, Oxford University Hospitals Trust

- Edinburgh Cancer Centre

- European Molecular Genetics Quality Network

- Guy's and St. Thomas' NHS Foundation Trust

- Leeds Teaching Hospital

- The Lothian University Hospitals

- NCRI Clinical Studies Group/Royal College of Physicians/Royal College of Radiologists/ Joint Collegiate Council on Oncology/Association of Cancer Physicians

- New Gene Ltd

- NHS Grampian

- NHS Greater Glasgow and Clyde

- Royal Devon and Exeter NHS Trust

- Sheffield Diagnostics Genetics Service

- St James's Hospital

- St Mary's Hospital

- UCL Advanced Diagnostics

- UK NEQAS (Edinburgh)

- United Lincolnshire Hospitals NHS Trust

- University College London Hospital and MRC Clinical Trials Unit

- University Hospitals Birmingham NHS

About this guidance

NICE diagnostics technologies guidance is designed to help the NHS adopt efficient and cost-effective medical diagnostic technologies more rapidly and consistently.

The programme concentrates on pathological tests, imaging, endoscopy and physiological measurement, since these represent most of the investigations performed on patients. The types of products that might be included are medical diagnostic technologies that give greater independence to patients, and diagnostic devices or tests used to detect or monitor medical conditions. Diagnostic technologies may be used for various purposes: diagnosis, clinical monitoring, screening, treatment triage, assessing stages of disease progression, and risk stratification.

This guidance was developed using the NICE diagnostic technologies guidance process.

We have produced a summary for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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