Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Protocol

Title of project

Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer

Name of External Assessment Group (EAG) and project lead

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1 Plain English Summary

Lung cancer is the most commonly diagnosed cancer in the world and the most common cause of cancer-related death. It is the second most common cancer in the UK accounting for one in seven new cancer cases. Lung cancer survival rates are generally low because over two thirds of patients present at an advanced stage when treatment to cure the disease is no longer possible. The likelihood of surviving 1 year after diagnosis is around 30%, the likelihood of surviving 5 years after diagnosis is less than 10%.

Lung cancer occurs when uncontrolled cell growth begins in the lungs, rather than growing into normal healthy lung cells the abnormal cells form lumps or masses of tissue called tumours which may interfere with normal lung function. Lung cancer is classified based on the appearance of the cancer cells. Non-small cell lung carcinoma (NSCLC) is the most common type accounting for around 80% of lung cancers. NSCLC is classified further into squamous cell carcinoma, adenocarcinoma, bronchioalveolar carcinoma, and large-cell undifferentiated carcinoma. The best treatment varies depending upon the specific type of lung cancer from which a patient is suffering. The first step in treating lung cancer is therefore to determine the specific type of lung cancer. This is done by taking a biopsy followed by microscopic examination to determine the lung cancer type.

Certain mutations within tumour cells can make them more or less receptive to specific treatments. Some EGFR-TK mutations make certain tumours responsive to treatment with EGFR-TK inhibitors but less responsive to treatment with standard chemotherapy. Before deciding on which treatment to offer patients with NSCLC patients are therefore tested to see if they have a mutation in the EGFR-TK tumour gene. There are a variety of tests available to detect these specific mutations but it is not known which test is the best test to use. The different tests vary in the specific mutations which they attempt to detect, the amount of tumour cells needed for the test to work, the time that it takes to give a result, the error rate of the test, and the cost of the test.

This projects aims to evaluate EGFR-TK mutation tests to determine which should be the recommended test or tests. The review will consider both clinical effectiveness (improvement in patients' symptoms associated with the test) and cost effectiveness (cost of different testing strategies).

2 Decision problem

2.1 Population

The indication for this assessment is the detection of mutations in the EGFR-TK oncogene in previously un-treated adults with locally advanced, or metastatic NSCLC. The presence of EGRF-TK mutations can affect the response of tumours to standard chemotherapy and oral EGFR-TK inhibitors and mutation status is thus used to select the most appropriate course of treatment.[1]

The 2010 age-standardised incidence rate for lung cancer in England was 55.9 per 100,000 in men and 37.9 per 100,000 in women. Since 2001 the incidence rate has declined by 15% for men and increased by 10.8% for women.[2] In 2009 there were 35,406 new cases of lung cancer recorded in England and Wales, and in 2010 there were 29,914 deaths from lung cancer.[3] The National Lung Cancer Audit (NLCA) data for 2010 included 32,347 new cases for England and Wales, of which 19,379 (71.9%) were histologically confirmed NSCLC and 5,932 (18%) were stage IIIB or IV NSCLC.[4] The prevalence of EGFR-TK receptor mutations in NSCLC varies widely with population ethnicity. Estimates from observational studies ranged from 4.5% in a study conducted in Italy[5] to approximately 40% in two studies conducted in Japan and Taiwan.[6, 7] The great majority of EGFR-TK mutations occur in adenocarcinomas; from three studies, with a total of 1,238 participants (189 EGFR-TK mutation positive), only one mutation occurred in a patient with tumour cytology other than adenocarcinoma.[5-7] The prevalence of EGFR-TK mutations in NSCLC (adenocarcinoma) therefore ranged from 10.4% in the Italian study[5] to 50% and 39% in the Japanese and Taiwanese studies, respectively.[6, 7]

Lung cancer incidence and mortality rates are strongly age-related. In the UK between 2007 and 2009 three quarters of new cases were diagnosed in people over the age of 65 and between 2008 and 2010, around 78% of lung cancer deaths were in people aged 65 years and over. In the UK, lung cancer incidence and lung cancer mortality rates in men have been declining since the early 1970s, but both continue to increase in women. Gender-specific time trends in lung cancer reflect patterns in past smoking behavior.[3] Lung cancer incidence and mortality rates are also related to socio-economic factors. Age-standardised incidence rates are twice as high and age standardised mortality rates are around 3 times higher in the most deprived wards of England and Wales compared to the least deprived wards.[3, 8]

Lung cancer survival rates are generally low because over two thirds of patients present at an advanced stage, when curative treatment is no longer possible.[3, 9] The latest cancer survival statistics for England and Wales for patients diagnosed in the period 2005-2009 and followed up to 2010 show one year age-standardised survival rates of 27% in men and 30%

in women; five year age-standardised survival rates were 7% and 9% in men and women respectively.[10]

2.2 Intervention technologies

There are a variety of tests available for EGFR-TK mutation testing (Table 1) in NHS reference laboratories currently providing testing for EGFR-TK mutations. The tests used can be broadly grouped into two subgroups: mutation screening and targeted mutation detection. Mutation screening tests screen samples for all EGFR-TK mutations (known and novel) whilst targeted tests analyse samples for specific known mutations. Successful mutation analysis is dependent on a sufficient quantity of tumour tissue in the sample. The limit of detection varies between different assay methods, with some studies reporting mutation detection when the proportion of tumour cells in a sample is less than 10% (Table 1).[11] There is some evidence that EGFR-TK mutations can be accurately detected in plasma,[12] however, biopsy tissue remains the gold standard. Clinical opinion, provided by specialist advisors during scoping, suggested that plasma testing is currently a 'research only' application which should not be included in this assessment. Further, clinical opinion also stated that cytology samples should be considered equivalent to biopsy.

Targeted mutation detection tests

The different targeted tests look for different numbers of EGFR-TK mutations and may differ in their ability to accurately select patients who are likely to benefit from chemotherapy with tyrosine kinase inhibitors. EGFR-TK receptor mutations are known to be restricted to four exons (18 to 21), with deletions in exon 19 and point mutations in exon 21 accounting for more than 90%.[5, 6, 13] Observational studies have linked deletions in exon 19, point mutations at codons 858 and 861 of exon 21, and point mutations at codon 719 of exon 18 to tumours which are responsive to treatment with gefitinib.[13, 14]

Data from a randomised controlled trial of gefitinib versus standard chemotherapy for first line treatment of patients with advance NSCLC have shown that people who test positive for EGFR-TK mutations using Therascreen®, gain more benefit from treatment with the tyrosine kinase inhibitor gefitinib than from standard chemotherapy. People who test negative for EGFR-TK mutations gain more benefit from standard chemotherapy.[15] Full treatment effectiveness data are available for both Therascreen® positive and Therascreen® negative patients; we are not currently aware of any other EGFR-TK mutation test for which equivalent data are available.

The licensed indication for the tyrosine kinase inhibitors, gefitinib and erlotinib, is treatment of locally advanced or metastatic NSCLC in patients who are previously untreated and who test positive for EGFR-TK mutations. NICE Technology Appraisal 192 recommends gefitinib as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for an EGFR-TK mutation.[1] The mutation test used in the trial that

informed NICE Technology Appraisal 192 was Therascreen®; it should be noted that the Therascreen® kit used in this trial was an earlier version than that which is currently being marketed. NICE Technology Appraisal 258 recommends erlotinib as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for an EGFR-TK mutation.[16] Trials used in this assessment were conducted in EGFR-TK mutation positive patients only and used a direct sequencing approach to select patients with exon 19 deletions or exon 21 L858R point mutations for inclusion.[16, 17]

The Therascreen® EGFR RGQ PCR Kit is a molecular diagnostic kit for detection of the 29 most common EGFR-TK mutations against a background of wild-type genomic DNA. It uses real-time PCR (polymerase chain reaction) on the Rotor-Gene Q 5plex HRM Instrument (a real-time PCR cycler). The Therascreen® EGFR Pyro Kit will also be included in the assessment. The mutations detected by the Therascreen® EGFR RGQ PCR Kit include: 19 deletions in exon 19, T790M, L858R, L861Q, G719X (Therascreen® detects the presence of these mutations but does not distinguish between them), S768I, and 3 insertions in exon 20. The kit includes all reagents needed to perform a PCR-based assay, where specific areas of DNA containing mutations are targeted by ARMS primers and Scorpions technology is used to detect amplifications of those specific areas of DNA. The test uses DNA isolated from Formalin Fixed and Paraffin Embedded (FFPE) tissue obtained from lung biopsy. The Therascreen® EGFR RGQ PCR Kit uses a two-step procedure. The first step is performance of the control assay to assess the total DNA in a sample. The second step is to complete the mutation assay for the presence or absence of mutated DNA.

The cobas EGFR Mutation Testing Kit (Roche Diagnostics) is a CE-marked real-time PCR test for the detection of 41 EGFR-TK mutations (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 point mutation in exon 21). The first step is to process the tumour tissue 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 analyser which automates amplification and detection. Cobas 4800 software provides automated test result reporting.

Mutation screening tests

Direct sequencing is used to screen for all EGFR-TK mutations (known and novel) in exons 18 to 21. This process is known as 'comprehensive testing' and has been considered the routine method for detecting EGFR-TK mutations, however, it requires larger tumour samples than other methods. Randomised controlled trials comparing the effectiveness of erlotinib with standard chemotherapy, in participants who were EGFR-TK mutation positive, selected participants using direct sequencing to identify mutations in exon 19 or 21. A comparison of

Therascreen® with direct sequencing reported that Therascreen® was 'more sensitive', i.e. EGFR-TK mutations were detected in some patients who were not identified by direct sequencing. This was ascribed to low density of tumour cells in the sample.[18]

Table 1: Overview of EGFR-TK mutation tests

Sequencing method	Targeted (Mutations targeted)/ Screening test	Methodology	Limits of detection	Number of laboratories using the method	
				NEQAS report*[19]	Lab contact†
Commerical tests					
Qiagen Therascreen Kit/ARMS	Targeted (29 mutations)	Real-time PCR	0.5-7%	14	6
Roche cobas test	Targeted (41 mutations)	Real-time PCR	0.8-3%	4	1
In house tests					
Sanger sequencing	All mutations	Usually PCR but variation in detail	25%	20	3
Fragment length analysis	Varies	PCR followed by fluorescence to determine fragment size	1-2%†	14	5
Pyrosequencing	Varies	PCR followed by pyrosequencing reaction	~5%†	6	4
TaqMan/Real Time PCR/Entrogen	Targeted (details unclear)	Unclear	Unclear	6	1
High resolution melt analysis	All mutations	PCR followed by HRM	2-5%†	5	1
Single strand conformation analysis	Screening (>98% of all mutations)	PCR followed by electrophotesis	1-10%†	0	1
SnapShot/RFPL/other	Targeted (details unclear)	Unclear	Unclear	2	0
Mass spectrometry	Targeted (details unclear)	Unclear	Unclear	2	0
Next generation sequencing	Screening	DNA first fragements into small segments that can be seuqneced in parallel reactions.	10%†		

* NEQAS pilot scheme 2011-2012.[19] Fifty-one laboratories participated in the scheme, three did not state which method they used.

† NICE contact with laboratories May 2012. Fourteen laboratories provided information on methodologies used.

2.3 Care pathway

Diagnosis and staging of lung cancer

NICE guidance on the diagnosis and treatment of lung cancer was updated in 2011.[20] Patients referred for suspected lung cancer should initially undergo an urgent chest X-ray. If the chest x-ray is suggestive of lung cancer a contrast-enhanced computed tomography (CT) scan of the thorax, upper abdomen and lower neck is performed. Patients can then undergo a variety of diagnostic and staging investigations, which should be selected to provide the most information with the least risk to the patient. Most pathways in the diagnostic algorithm include biopsy for histological confirmation and tissue typing (e.g. to confirm if NSCLC is adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, or large cell carcinoma). The mediastinal lymph nodes are assessed for malignancy using PET-CT, orendobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA), or endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA), or non-ultrasound-guided TBNA. Patients with clinical and/or radiological features of advanced/metastatic disease may undergo further imaging (e.g. PET/CT or MRI) with possible biopsy of the most accessible site.[20]

Where biopsy is undertaken, DNA extraction and mutation analysis may be carried out on the biopsy tissue, after pathological examination, to determine whether the tumour is EGFR-TK mutation positive or negative. NICE clinical guidance recommends that adequate samples are taken without unacceptable risk to the patient to permit tumour sub-typing and measurement of predictive markers.[20] For the 32,347 cases of lung cancer recorded in the 2010 NLCA data, the median (IQR) percentage of patients receiving a histological/cytological diagnosis was 76.0% (70.5 to 83.6%) across NHS trusts in England and Wales. NLCA data for 2010 reported a median of 20.0% (IQR 13.1 to 28.9%) NSCLC patients with un-specified histology, for NHS trusts in England and Wales.[4] This assessment will assume that, in line with current clinical guidance, biopsy is undertaken in all patients for whom it is considered possible and clinically appropriate. However, the proportion of patients in whom the biopsy sample is inadequate is an important consideration for this assessment, as it represents a requirement for additional mutation testing, possible additional invasive procedures (in order to obtain an adequate sample) and associated additional costs.

Treatment of NSCLC

Once NSCLC has been confirmed, NICE clinical guidance 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 patients. 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.[20] Pemetrexed in combination with cisplatin is recommended as a first-line treatment for patients with locally advanced or metastatic NSCLC, if the histology of the tumour has been confirmed as adenocarcinoma or large cell tumour.[21] The most recent data for England and Wales (NLCA 2011) suggest that the median proportion of patients with stage III or IV NSCLC receiving chemotherapy was 51.5% (IQR 48.2 to 64%), however, the case ascertainment rate for this measure was less than 50%.[4]

NICE technology appraisal 192 recommends the tyrosine kinase inhibitor gefitinib as an option for the first-line treatment of people with locally advanced or metastatic NSCLC, who test positive for EGFR-TK mutation.[1] NICE Technology Appraisal 258 recommends erlotinib as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for an EGFR-TK mutation.[16] NICE guidance does not currently include any recommendations on the type of diagnostic tests used to identify EGFR-TK mutations. This assessment will compare the performance and cost-effectiveness of EGFR-TK mutation testing options, currently available in the NHS in England and Wales, to identify previously un-treated adults with locally advanced, or metastatic NSCLC who may benefit from first-line treatment with to EGFR-TK inhibitors (gefitinib or erlotinib).

3 Objectives

The overall objective of this project is to summarise the evidence on the clinical- and cost-effectiveness of EGFR-TK mutation tests (commercial or in-house) to identify those previously un-treated adults with locally advanced, or metastatic NSCLC who may benefit from first-line treatment with EGFR-TK inhibitors (gefitinib or erlotinib). In order to address the clinical-effectiveness we would ideally like data on the analytical validity of the different EGFR-TK mutation tests (sensitivity/specificity for detection mutations known to be linked to be treatment effectiveness). However, there is no gold standard for EGFR-TK mutation testing and the exact mutations, and level of mutation, linked to the effectiveness of EGFR-TK inhibitors is not known. We therefore defined the following research questions to address the review objectives:

- What is the technical performance of the different EGFR-TK mutation tests (e.g. proportion tumour cells needed, failures, costs, turnaround time)?
- What is the accuracy (clinical validity) of EGFR-TK mutation testing, using any test, for predicting response to treatment with tyrosine kinase inhibitors? If individual patient data (IPD) are available, we will investigate the association between individual mutations detected and patient outcome.
- How do clinical outcomes from treatment with EGFR-TK receptor inhibitors vary according to which test is used to select patients for treatment?
- What is the cost-effectiveness of the use of the different EGFR-TK mutation tests to decide between standard chemotherapy or anti-EGFR TKIs

4 Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[22] and NICE Diagnostic Assessment Programme manual.[23] In addition to the effectiveness review additional data will be obtained by contacting the fourteen reference laboratories known to perform EGFR-TK mutation testing.

4.1 Inclusion and exclusion criteria

Separate inclusion criteria were developed for each of the three clinical effectiveness questions. These are summarised in Table 2.

Table 2: Inclusion criteria

Question	What is the technical performance of the different EGFR-TK mutation tests?	What is the accuracy of EGFR-TK mutation testing, using any test, for predicting response to treatment with tyrosine kinase inhibitors?	How do outcomes from treatment with EGFR-TK receptor inhibitors vary according to which test is used to select patients for treatment?
Participants:	Adult patients (≥18 years) with treatment naive, locally and regionally advanced or metastatic (stage IIIb or IV) non-small-cell lung cancer (NSCLC)	Adult patients (≥18 years) with treatment naive, locally and regionally advanced or metastatic (stage IIIb or IV) non-small-cell lung cancer (NSCLC)	Adult patients (≥18 years) with treatment naive, locally and regionally advanced or metastatic (stage IIIb or IV) non-small-cell lung cancer (NSCLC) Patients who test positive on any EGFR-TK mutation test
Setting:		Secondary or tertiary care	
Interventions (index test):	Any commercial or in-house EGFR-TK mutation test	Any commercial or in-house EGFR-TK mutation test.	EGFR-TK receptor inhibitors
Comparators:	Not applicable	Not applicable	Standard care
Reference standard:	Not applicable	Response to treatment with tyrosine kinase inhibitors (e.g. progression free survival)	Not applicable
Outcomes:	Proportion tumour cells needed, failures, turnaround time, costs, expertise/logistics of test	Overall survival or progression free survival in EGFR-TK positive versus EGFR-TK negative patients. Test accuracy – the number of true positive, false negative, false positive and true negative. IPD if available.	Overall survival or progression free survival
Study design:	To be addressed by survey; see below	RCTs (CCTs and cohort studies will be considered if no RCTs are identified)	RCTs (CCTs and cohort studies will be considered if no RCTs are identified)

4.2 Questionnaire

To address the research question on the technical performance of the different EGFR-TK mutation tests, we will need to collect data from sources other than the systematic review. This section provides a brief description of these data and will be expanded as necessary to infrom the economic model. NEQAS and other quality assurance reports will be examined for the following information; an electronic questionnaire will be developed to gather outstanding information from participating laboratories:

1. Assay method used
2. Is the method targeted or sequencing?
3. If targeted method, mutations targeted
4. Limit of detection (% tumour cells/mutation)
5. Definition and proportion of inadequate sample
6. Definition and proportion of failed tests (for reasons other than inadequate sample)
7. What proportion of patients with a mutation get treated with a TKI, by mutation
8. Any data on measures of survival or objective response in treated patients
9. Number of samples processed
10. Batching size – do you wait until you have certain number of samples before running the test
11. Costs of the test (fixed and variable costs, i.e. what is cost of a full batch and what is the cost of e.g. 50% full batch if partial batches are routinely run)
12. What is the proportion of cytology to histology
13. Turnaround time, including definition
14. Any logistic / other issues related to the use of the test?

Information obtained from this survey will be used to provide information on tests that have not been evaluated in studies included in the systematic review.

4.3 Search strategy

Search strategies will be based on target condition and intervention, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[22, 24] Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life will be developed separately.

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase Emtree), existing reviews identified during the rapid appraisal process and initial scoping searches. These scoping searches will be used to generate test sets of target references, which will inform text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity.

The following databases will be searched for relevant studies from 2000 to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (Internet)
- Health Technology Assessment Database (HTA) (Internet)
- Science Citation Index (SCI) (Web of Science)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet) http://regional.bvsalud.org/php/index.php?lang=en
- Biosis
- NIHR Health Technology Assessment Programme (Internet)
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) http://www.crd.york.ac.uk/prospero/

Completed and ongoing trials will be identified by searches of the following resources (2000-present):

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- Current Controlled Trials (http://www.controlled-trials.com/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. References in retrieved articles and relevant systematic reviews will be checked. Search strategies will be developed specifically for each database and the keywords associated with non-small cell lung cancer will be adapted according to the configuration of each database.

No restrictions on language or publication status will be applied. Limits will be applied to remove animal. Searches will take into account generic and other product names for the intervention. Examples of the search strategies to be used are presented in Appendix 1; these will be adapted as necessary following consultation with clinical experts. All searching undertaken at Kleijnen Systematic Reviews Ltd is independently peer reviewed by a second Information Specialist, using the PRESS-EBC checklist.[25]

4.4 Review strategy

Two reviewers will independently screen titles and abstracts of all reports identified by searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess

these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details, participants, EGFR-TK mutation test(s), clinical outcomes, and test performance outcome measures (against treatment response as reference standard), test failure rates, limit of detection. For RCTs that assess the clinical validity of one or more EGFR-TK mutation tests, we will contact the authors directly in order to request IPD linking specific mutation with individual patient outcome. Data will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

4.5 Quality assessment strategy

The methodological quality of included RCTs will be assessed using the Cochrane Risk of Bias Tool.[26] Diagnostic accuracy studies will be assessed using QUADAS-2.[27] The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

4.6 Methods of analysis/synthesis

If sufficient data are available summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions of each mutation test for the prediction of response to treatment will be calculated. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an SROC curve.[28-30] If more than one RCT evaluates treatment effect in patients who were tested with the same EGFR-TK mutation test, then data will be pooled on treatment effect (e.g. hazard ratios, odds ratio, relative risks) within the test positive and, where available test negative arms. The DerSimonian and Laird random effects model will be used to generate summary estimates together with 95% CIs.

If IPD is obtained then we will evaluate which specific mutations, and where possible the level of mutation, associated with a response to treatment. For each mutation reported we will calculate measures of treatment effectiveness (e.g. hazard ratio (HR) together with 95% CI for progression free survival in those treated with tyrosine kinase inhibitors compared to those treated with conventional chemotherapy).

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by EGFR-TK mutation test and by research question addressed. A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

5 Report methods for synthesising evidence of cost-effectiveness

5.1 Identifying and reviewing published cost-effectiveness studies

Exploration of the literature regarding published economic evaluations, utility studies and cost studies will be performed in the literature databases listed above. In addition, specific health economic databases will be searched (e.g. NHSEED (NHS Economic Evaluation Database), and HEED (Health Economic Evaluation Database). Searches will focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses.

The results and the methodological quality of the studies selected will be summarised. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.[23, 31] Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

5.2 Evaluation of costs, quality of life and cost-effectiveness

Decision analytic modelling will be undertaken to determine the cost-effectiveness of different EGFR-TK mutation tests to decide between standard chemotherapy or anti-EGFR TKIs in patients with locally advanced or metastatic non-small-cell lung cancer.

Diagnosis and treatment strategies

The analysis will consider the consequences of technical performance, analytical validity and clinical validity of the different tests followed by treatment with either standard chemotherapy or anti-EGFR TKIs on costs and QALYs. For tests for which technical performance and/or validity is unclear, assumptions will be made to provide some indication of the (range) of cost-effectiveness outcomes.

Model structure

Published studies that report on the value of EGFR-TK mutation testing from initial diagnosis through to final health outcomes have not been identified during the scoping phase, apart from the Therascreen® EGFR PCR kit.[15] Consequently, it is likely that a linked evidence approach will need to be used in the modelling. That is, outcomes of the diagnostic tests to be assessed will need to be related to changes in treatment decisions and final heath outcomes. Necessary choices and definitions regarding the structure of the model will depend on the findings from the literature review and consultation with clinical experts. The models used in the STAs for Gefitinib[1] and Erlotinib[16] will be used as starting points to model treatment pathways. For reasons of simplicity, and because the effectiveness of the two pharmaceuticals is not part of this project, the effectiveness of gefitinib will be used as an approximation of the effectiveness of anti-EGFR TKIs as a class of drugs. In addition, the existence/availability of any other electronic models that reflect the cost-effectiveness of diagnosis and treatment pathways for these patients, and are representative of current care within the NHS, will be determined.

Issues relevant to analyses:

- Longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the models which are based on expert opinion.
- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

A simple draft model structure is presented (Appendix 3); this may be developed/expanded as indicated and as available data allow.

Health outcomes

Utility values, based on literature or other sources, will be incorporated in the economic model. QALYs will be calculated from the economic modelling.

Costs

Resource utilisation will be estimated for the diagnostic tests and treatments. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), discussions with individual hospitals and with the manufacturers of the comparators.

6 Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 23/11/2012. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

7 Competing interests of authors

None

8 Timetable/milestones

Milestones	Completion data
Draft protocol	11/07/2012
Final protocol	31/07/2012
Progress report	23/11/2012
Draft assessment report	09/01/2013
Final assessment report	06/02/2013

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Appendix 1

Clinical effectiveness search

Embase (OvidSP): 2000-2012/wk 28

Searched 18.7.12

1 erlotinib/ or (Erlotinib or Nsc-718781 or nsc718781 or osi-774 or osi774 or r-1415 or r1415 or tarceva or cp-358774 or cp358774 or 183321-74-6 or 183319 69 9).ti,ab,ot,hw,rn. (11968)
2 gefitinib/ or (Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2).ti,ab,ot,hw,rn. (13035)
3 or/1-2 (18405)
4 lung non small cell cancer/ (45170)
5 (nsclc or nsclcs).ti,ab,ot,hw. (22339)
6 (lung$ adj3 (adeno-carcinoma$ or adenocarcinom$)).ti,ab,ot. (9347)
7 ((non-small cell or large cell) adj3 lung$).ti,ab,ot. (35098)
8 (lclc or lclcs).ti,ab,ot,hw. (56)
9 or/4-8 (59672)
10 Receptor, Epidermal Growth Factor/ (34579)
11 (epidermal growth factor receptor$ or epidermis growth factor receptor$ or transforming growth factor alpha receptor$).ti,ab,ot. (24964)
12 ((tgf-alpha or urogastrone) adj2 receptor$).ti,ab,ot. (183)
13 ((erbB1 or erbB-1 or erbB) adj1 (protein$ or receptor$)).ti,ab,ot. (1421)
14 (EGFR or EGFRTK).ti,ab,ot. (30350)
15 EGF receptor$.ti,ab,ot. (8985)
16 (Cobas adj3 EGFR).af. (0)
17 (Cobas adj3 epidermal growth factor).ti,ab,ot. (0)
18 (thera?screen$ or therascreen$).af. (46)
19 or/10-18 (56110)
20 3 and 9 and 19 (4768)
21 lung non small cell cancer/di [Diagnosis] (5261)
22 diagnostic test/ (53292)
23 diagnosis/ (875184)
24 differential diagnosis/ (295658)
25 laboratory diagnosis/ (40591)
26 laboratory test/ (100888)
27 diagnos$.ti,ab,ot. (1925228)
28 (test or tests or testing or tested).ti,ab,ot. (2207310)
29 ((lab or labs or laborator$) adj2 (procedure$ or exam$)).ti,ab,ot. (15288)
30 or/21-29 (4581699)
31 9 and 19 and 30 (2035)
32 animal/ or animal experiment/ (3398728)
33 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (5489895)
34 or/32-33 (5489895)
35 exp human/ or human experiment/ (13717180)
36 34 not (34 and 35) (4418831)
37 20 or 31 (5626)
38 37 not 36 (5547)

39 limit 38 to yr="2000 -Current" (5500)
40 limit 39 to embase (4910)

Appendix 2

Related NICE guidance

Clinical Guidelines:

The diagnosis and treatment of lung cancer: NICE clinical guideline 121 (2011). Available from: http://guidance.nice.org.uk/CG121 Date for review: 2014.

Technology Appraisals: 1st line treatment

Pemetrexed for the first line treatment of non small cell lung cancer. NICE technology appraisal guidance 181 (2009). Available from: http://guidance.nice.org.uk/TA181 Date for review: Jan 2010

Gefitinib for the first line treatment of locally advanced or metastatic non small cell lung cancer. NICE technology appraisal guidance 192 (2010) Available from: http://guidance.nice.org.uk/TA192 Date for review: April 2013

Technology Appraisals: 2nd line treatment

Erlotinib for the second line treatment of non small cell lung cancer. NICE technology appraisal guidance 162 (2008). Available from: http://guidance.nice.org.uk/TA162 Date for review: June 2010

Pemetrexed for the treatment of non small cell lung cancer. NICE technology appraisal guidance 124 (2007). Available from: http://guidance.nice.org.uk/TA124 Date for review: Jan 2010

Erlotinib for the first line treatment of locally advanced or metastatic EGFR-TK-mutation-positive-non-small-cell lung cancer http://guidance.nice.org.uk/TA227

Technology Appraisals: Maintenance treatment

Pemetrexed for maintenance treatment of non small cell lung cancer. NICE technology appraisal guidance 190 (2010). Available from: http://guidance.nice.org.uk/TA190 Date for review: Nov 2012

Erlotinib (monotherapy) for the maintenance treatment of non small cell lung cancer. NICE technology appraisal guidance 227 (2011) Available from http://guidance.nice.org.uk/TA227 Date for review: April 2013

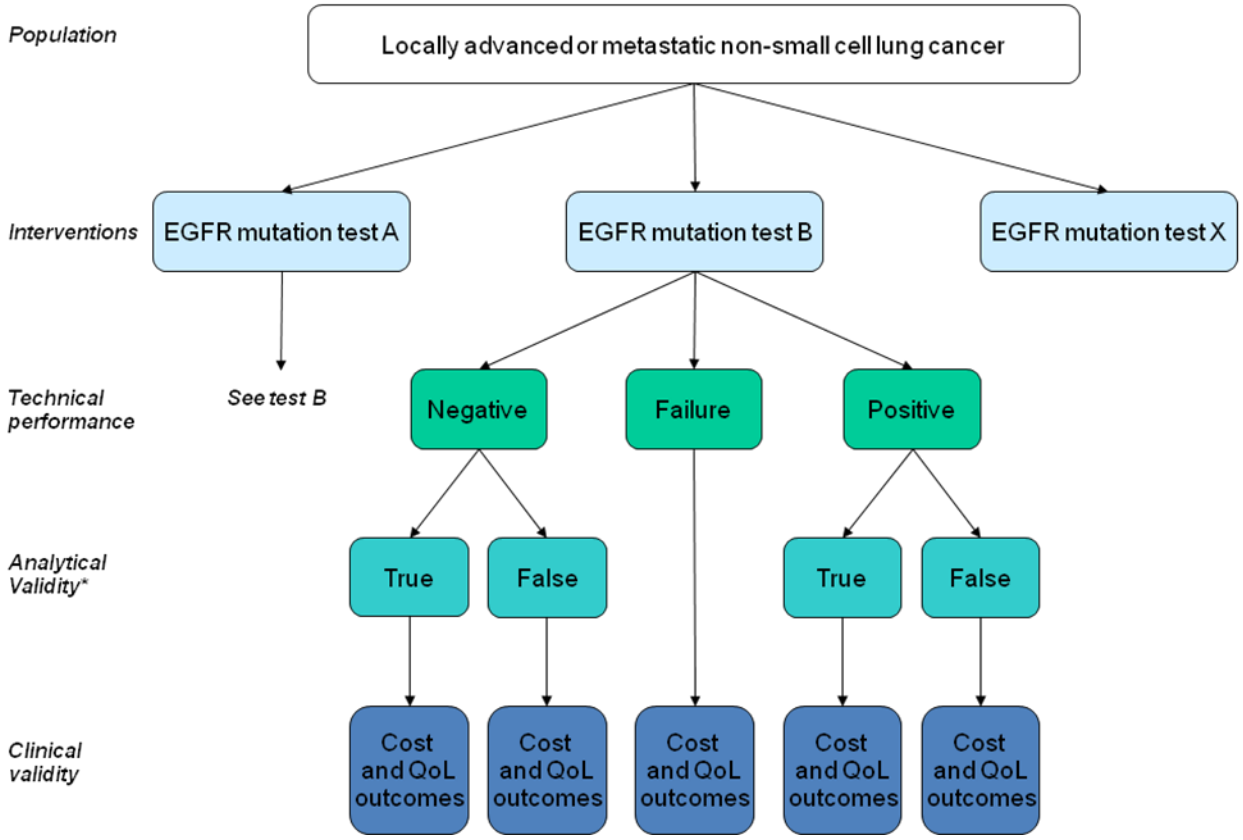
Under development

Cetuximab for the first line treatment of locally advanced or metastatic non-small cell lung cancer. NICE technology appraisal guidance (publication expected July 2013)

Crizotinib for the treatment of previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (publication expected July 2013)

Appendix 3

Draft model structure



**Given the absence of a reference standard to establish analytical validity, an alternative approach will be taken for this step in the model.*