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

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

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

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Date completed 09/01/2013

PROSPERO registration CRD42012002828

Source of funding : This report was commissioned by the NIHR HTA Programme as project number 12/34/01

Declared competing interests of the authors: None declared

All authors have completed the unified competing interest form at www.icmje.org/ coi_disclosure.pdf (available on request from the corresponding author) and declare (1) no financial support for the submitted work from anyone other than their employer; (2) no financial relationships with commercial entities that might have an interest in the submitted work; (3) no spouses, partners, or children with relationships with commercial entities that might have an

interest in the submitted work; and (4) no no-financial interests that may be relevant to the submitted work.

Commercial in confidence data

All commercial in confidence (CIC) data has been highlighted in blue and underlined.

Acknowledgements

The authors acknowledge the clinical advice and expert opinion provided by: Mr Paul Roberts, Consultant Cytogeneticist, Leeds Teaching Hospitals NHS Trust; Dr Phillipe Taniere, Consultant Histopathologist, University Hospitals Birmingham NHS Foundation Trust; Prof Ian Cree, Professor of Pathology, Warwick Medical School, University Hospitals Coventry and Warwickshire; Dr Mark Slade, Consultant Respiratory Physician and Clinical Director, Papworth Hospital NHS Foundation Trust; Dr Fiona Blackhall, Consultant Medical Oncologist, The Christie NHS Foundation Trust; Mrs Mani Elliott, Chemotherapy Nurse specialist, Hull and East Yorkshire Hospitals NHS Trust. The authors would like to thank all NHS laboratories, providing EGFR mutation testing, who kindly completed our on-line survey. The authors would also like to thank AstraZeneca UK Ltd for providing access to the cost-effectiveness model used in NICE Technology Appraisal 192.

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Westwood ME, Joore MA, Whiting P, van Asselt T, Ramaekers B, Armstrong N, Misso K, Severens J, Kleijnen J. 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. A Diagnostic Assessment Report. Kleijnen Systematic Reviews Ltd, 2012.

Contributions of authors

Marie Westwood and Penny Whiting planned and performed the systematic review and interpretation of evidence. Manuela Joore, Thea van Asselt and Bram Ramaekers planned and performed the cost-effectiveness analyses and interpreted results. Nigel Armstrong and Kelly Lee contributed to planning and interpretation of cost-effectiveness analyses and acquisition of input data for modelling. Kate Misso devised and performed the literature searches and provided information support to the project. Jos Kleijnen and Johan Severens provided senior advice and support to the systematic review and cost-effectiveness analyses, respectively. All parties were involved in drafting and/or commenting on the report.

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LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARMS	amplification refractory mutation system
BSA	body surface area
CT	computed tomography
CCT	controlled clinical trial
CI	confidence interval
CR	complete response
DC	disease control
DNA	deoxyribonucleic acid
DTA	diagnostic test accuracy
EBUS	endobronchial ultrasound
EUS	endoscopic ultrasound
ECOG	Eastern Co-operative Oncology Group
EGFR	epidermal growth factor receptor
EGFR-TK	epidermal growth factor receptor tyrosine kinase
FFPE	formalin fixed paraffin embedded
FN	false negative
FNA	fine needle aspiration
FNB	fine-needle biopsy
FP	false positive
G-CSF	granulocyte-colony stimulating factor
HR	hazard ratio
HRQoL	Health-Related Quality of Life
IC	incremental cost
ICER	Incremental Cost-Effectiveness Ratio
IPD	individual patient data
IQR	interquartile range
ITT	intention-to-treat
LY	life year
MRI	magnetic resonance imaging
NA	not applicable
NEQAS	National External Quality Assurance Scheme
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NLCA	National Lung Cancer Audit
NR	not reported
NSCLC	non-small-cell lung cancer
OR	objective response
OS	overall survival
PCR	polymerase chain reaction

PD	progressive disease
PET	positron emission tomography
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival
PR	partial response
PS	performance status
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	risk ratio
ROC	receiver operating characteristic
SD	stable disease
SROC	summary receiver operating characteristic
TBLA	transbronchial lung biopsy
TBNA	transbronchial needle aspiration
TKI	tyrosine kinase inhibitor
TN	true negative
TP	true positive
WBC	white blood cell
WHO	World Health Organisation

GLOSSARY

Cost-effectiveness analysis	An economic analysis that converts effects into health terms and describes the costs for additional health gain.
Decision modelling	A theoretical construct that allows the comparison of the relationship between costs and outcomes of alternative healthcare interventions.
False negative	Incorrect negative test result – number of diseased persons with a negative test result.
False positive	Incorrect positive test result – number of non-diseased persons with a positive test result.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.
Index test	The test whose performance is being evaluated.
Markov model	An analytic method particularly suited to modelling repeated events, or the progression of a chronic disease over time.
Meta-analysis	Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.
Meta-regression	Statistical technique used to explore the relationship between study characteristics and study results.
Metastasis	The spread of a disease from one organ or part to another, non-adjacent organ or part.
Opportunity costs	The cost of forgone outcomes that could have been achieved through alternative investments.
Publication bias	Bias arising from the preferential publication of studies with statistically significant results.
Quality of life	An individual's emotional, social and physical well-being and their ability to perform the ordinary tasks of living.
Quality-adjusted life year (QALY)	A measure of health gain, used in economic evaluations, in which survival duration is weighted or adjusted by the patient's quality of life during the survival period.
Receiver Operating Characteristic (ROC) curve	A graph which illustrates the trade-offs between sensitivity and specificity which result from varying the diagnostic threshold.
Reference standard	The best currently available diagnostic test, against which the index test is compared.
Sensitivity	Proportion of people with the target disorder who have a positive test result.
Specificity	Proportion of people without the target disorder who have a negative test result.
True negative	Correct negative test result – number of non-diseases persons with a negative test result.
True positive	Correct positive test result – number of diseased persons with a positive test result.

EXECUTIVE SUMMARY

Background

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 one year after diagnosis is around 30%, the likelihood of surviving five years after diagnosis is less than 10%.

Certain mutations within tumour cells can make them more or less receptive to specific treatments. Some epidermal growth factor receptor-tyrosine kinase (EGFR-TK) mutations make certain tumours more responsive to treatment with EGFR-TK inhibitors (EGFR TKIs) than to treatment with standard chemotherapy, where as tumours without these mutations are generally more responsive to standard chemotherapy than EGFR-TKIs. Before deciding on which treatment to offer patients with non-small-cell lung cancer (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 there is no consensus on which of the different tests should be used. The different tests vary in the specific mutations which they attempt to detect, the amount of mutation they are able 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.

Objectives

This review compares the performance and cost-effectiveness of EGFR mutation tests used to identify previously untreated adults with locally advanced or metastatic NSCLC who may benefit from first-line treatment with TKIs. It addresses the following research questions:

1. What is the technical performance of the different EGFR mutation tests (e.g. proportion tumour cells needed, failures, costs, turnaround time)?
2. What is the accuracy of EGFR mutation testing for predicting response to treatment with TKIs?
3. How do clinical outcomes from treatment with TKIs vary according to which test is used to select patients for treatment?
4. What is the cost-effectiveness of the use of the different EGFR mutation tests to decide between standard chemotherapy or TKIs?

Methods

Assessment of clinical effectiveness

Twelve databases, including MEDLINE and EMBASE, were searched without language, date or publication status restrictions to August 2012. Supplementary searches were undertaken to identify unpublished and ongoing studies and relevant conference proceedings were searched. To address research question 1 we conducted a web-based survey of laboratories in England and Wales that perform EGFR mutation testing. Research questions 2 and 3 were addressed using a systematic review of the literature. For research question 2 we included studies of adult patients (≥18 years) with treatment naive, locally and regionally advanced or metastatic (stage IIIB or IV) NSCLC, which assessed any EGFR mutation test and that reported data on response to TKIs in both patients with EGFR mutation positive and EGFR mutation negative tumours. For research question 3, we included studies which compared a TKI to standard chemotherapy in adult patients (≥18 years) with treatment naive, locally and regionally advanced or metastatic (stage IIIB or IV) NSCLC who tested positive on any EGFR mutation test, and which reported data on progression-free survival, overall survival, or tumour response.

The results of the searches were screened for relevance independently by two reviewers. Full text inclusion assessment, data extraction, and quality assessment were conducted by one reviewer and checked by a second. RCTs were assessed for methodological quality using the Cochrane Risk of Bias tool. Diagnostic accuracy studies were assessed using the QUADAS-2 tool. There were insufficient data to conduct a formal meta-analysis. For studies that provided data on accuracy, we calculated sensitivity and specificity together with 95% confidence intervals (CIs) and plotted these data in receiver operating characteristic (ROC) space. Survival data were summarised as hazard ratios (HRs) and tumour response data were summarised as relative risks (RRs), with 95% confidence intervals (CIs). The results of individual studies were illustrated in forest plots.

Assessment of cost-effectiveness

In the health economic analysis, the cost-effectiveness of different methods for EGFR-TK mutation testing to decide between standard chemotherapy and EGFR TKIs in patients with locally advanced or metastatic NSCLC was assessed. Direct sequencing of all exon 18-21 mutations was taken as the comparator.

The health economic analysis considered the long-term costs and quality adjusted life years associated with different tests followed by treatment with either standard chemotherapy or a TKI in patients with NSCLC. For this purpose a de novo model was developed. As this assessment does not update NICE Technology Appraisal 192 of gefitinib for the first-line treatment of locally advanced or

metastatic NSCLC, it was ensured that the de novo modelling was consistent with TA192. To facilitate this, the assessment group received the health economic model submitted by Astra Zeneca for TA192. Also, the assessment group took into account the amendments made by the ERG to address technical errors and limitations of this model. The de novo model consisted of a decision tree and a Markov model. The decision tree was used to model the test result (positive, negative or unknown) and the treatment decision. Patients with a positive test result receive an anti-EGFR TKI. It was assumed that patients with a negative test result or unknown EGFR mutation status would receive doublet chemotherapy (Pemetrexed and Cisplatin), as the negative consequences of treatment with TKIs in false positives are greater than the negative consequences of treatment with doublet chemotherapy in false negatives. The long term consequences in terms of costs and QALYs were estimated using a Markov model with a cycle time of 21 days (resembling the duration of one cycle of chemotherapy), and a time horizon of six years. Health states in the Markov model were: progression free (subdivided into 'response' and 'stable disease'), disease progression and death. In the progression-free state patients are on treatment (either TKI or doublet chemotherapy). In each cycle these patients are subdivided over the 'stable disease' and 'response' states, based on the objective response rate, in order to account for a difference in quality of life between those states. In addition, disutilities and costs associated with treatment related characteristics (intra-venous or oral therapy) and adverse events are modelled.

Long term costs and QALYs were discounted using the UK discount rates of 3.5% for both costs and effects. Based on the estimated outcomes (probabilistic), the incremental cost-effectiveness ratio was calculated by dividing the incremental costs by the incremental QALYs. The ICER represents the costs of an additional QALY gained and was used to estimate the cost-effectiveness of a mutation test compared to direct sequencing of all exon 18-21 mutations and compared to the next best alternative strategy. All outcomes are based on probabilistic sensitivity analyses with 5,000 simulations using parameter distributions.

Results

Eleven studies (33 publications) were included in the review.

What is the technical performance of the different EGFR mutation tests?

One study on technical performance of EGFR mutation tests (Therascreen® EGFR PCR Kit, fragment analysis and direct sequencing) was included in the review. The test failure rate was 19% (29/152 samples), but this improved over time from 33% during the first three months to 13% during the last three months of year one testing. The failure rate was lower (5%) in year two, when a combination

of Therascreen® EGFR PCR, fragment analysis (for exon 19 deletions and exon 20 insertions) and direct sequencing (for the rarer econ 19 or exon 21 mutations) were used.

Thirteen laboratories completed the online questionnaire (response rate 93%). The Therascreen® EGFR PCR Kit (version 1 or 2) was the most commonly used EGFR mutation test with six laboratories using this test, fragment length analysis was used in three laboratories and Sanger sequencing in two; other tests were each used in single laboratories. There were no clear differences between tests in terms of batch size, turnaround time, number of failed samples or test cost. Laboratories using the Therascreen® EGFR PCR test reported that between less than 1% and 10% of tumour cells were required, the two laboratories that used fragment length analysis both reported that a minimum of 1 to 5% tumour cells were required, while Sanger sequencing needed >30% tumour cells; other methods required up to 10% tumour cells.

What is the accuracy of EGFR mutation testing, using any test, for predicting response to treatment with tyrosine kinase inhibitors?

Six studies, two RCTs and four cohort studies, provided data on the accuracy of EGFR mutation testing for predicting response to treatment in patients treated with TKIs. Five studies assessed direct sequencing and one assessed the Therascreen ® EGFR PCR Kit. The sensitivity and specificity estimates for the Therascreen ® EGFR PCR Kit were 99% (95% CI: 94, 100) and 69% (95% CI: 60, 77), respectively, using objective response (OR) as the reference standard. Four of the five studies that used direct sequencing methods to identify EGFR mutations reported high estimates of specificity (>80%) and sensitivities ranged from 60 to 80%, using OR as the reference standard. All studies were rated as 'low' risk of bias for the 'index test' and 'reference standard' domains of the QUADAS-2 tool. The two RCTs were rated at 'low' risk of bias for participant selection; none of the other studies reported details of participant selection and so were rated as 'unclear' risk of bias. Three studies had a 'high' risk of bias rating for the 'flow and timing' domain.

How do outcomes from treatment with EGFR receptor inhibitors vary according to which test is used to select patients for treatment?

Five RCTs provided data on the clinical effectiveness of TKIs compared to standard chemotherapy; one additional study reported data for a subgroup of patients from one of the trials whose samples had been re-analysed using a different EGFR mutation testing method. Three of the five RCTs included only patients with EGFR mutation positive tumours; two trials reported a subgroup analysis for patients who had received EGFR mutation testing and provided data on both patients with mutation positive tumours and patients with mutation negative tumours. Three studies used direct sequencing methods, one used fragment length analyses and one used the Therascreen® EGFR PCR Kit; the re-analysis of the existing trial used the cobas® EGFR Mutation Test.

All studies reported improvements in OR and improvements or trends towards improvement in progression-free survival (PFS) for patients with EGFR mutation positive tumours who were treated with TKIs compared to those with EGFR mutation positive tumours who were treated with standard chemotherapy. There were no clear differences in the treatment effects reported by different studies, regardless of which EGFR mutation test was used to select patients.

The two trials that reported data for the subgroup of patients who had received EGFR mutation testing also had data available for those who tested negative. One of the studies reported that PFS was significantly longer for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation positive subgroup (HR 0.48 (95% CI: 0.36, 0.64)) and significantly shorter for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation negative subgroup (HR 2.85 (95% CI: 2.05, 3.98)). The results of the second RCT showed a trend towards longer PFS for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation positive subgroup (HR 0.54 (95% CI: 0.27, 1.10)) and a trend towards shorter PFS for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation negative subgroup (HR 1.42 (95% CI: 0.82, 2.47)).

All studies were rated as 'low' or 'unclear' risk of bias for randomisation, allocation concealment and selective outcome reporting. All studies were rated as 'high' risk of bias for blinding of study participants and personnel as this was not possible in these trials because of the different routes of administration used for the treatment and comparator arms. However, only one study was rated as 'high' risk of bias for blinding of outcome assessors. Three trials were rated as 'low' risk of bias for incomplete reporting of outcome data as they either reported ITT analyses or had very small numbers of withdrawals (<2% of the total study population).

What is the cost-effectiveness of the use of the different EGFR mutation tests to decide between standard chemotherapy or TKIs?

In the health economic analysis, the cost-effectiveness of different methods for EGFR mutation testing to decide between standard chemotherapy or EGFR TKIs for first-line treatment of patients with locally advanced or metastatic NSCLC was assessed. In light of the scarce evidence that was available, three different analyses were calculated: an 'evidence on comparative effectiveness available' analysis, a 'linked evidence' analysis, and an 'assumption of equal prognostic value' analysis.

In the 'evidence on comparative effectiveness available' analysis direct sequencing of all exon 18-21 mutations could not be included due to a lack of information. As a result, testing with the Therascreen® EGFR PCR Kit was compared with direct sequencing of all exon 19-21 mutations (as an

approximation of direct sequencing of all exon 18-21 mutations) in order to estimate lifetime cost and QALYs using the observed response to treatment and the available relative PFS and overall survival (OS) data. The results of this analysis suggested that the Therascreen® EGFR PCR Kit was both less effective and less costly than direct sequencing of all exon 19-21 mutations at an ICER of £32,167 per QALY lost. The sensitivity analyses all resulted in similar outcomes. The key drivers behind this result were the differences in the proportion of patients with EGFR mutation positive, unknown mutation and mutation negative tumours and differences in objective response, PFS and OS. In particular, the predicted OS for mutation negative patients differed substantially between the studies using the Therascreen® EGFR PCR Kit and the study which was used for direct sequencing of all exon 19-21. OS for patients with mutation negative tumours, after testing using the Therascreen® EGFR PCR Kit, was substantially lower than after testing using direct sequencing of all exon 19-21, while PFS was similar. Hence, patients survived longer with progressive disease after testing with direct sequencing of all exon 19-21. As a result, although testing using the Therascreen® EGFR PCR Kit resulted in a high accuracy, it appeared less effective in terms of QALYs, but was also less costly since the gained life years for direct sequencing of all exon 19-21 were mainly spent in the relative expensive disease progression health state.

However, it should be noted that this analysis was based on a number of assumptions, of which the following two are particularly problematic:

- The proportion of patients with a positive or negative test result after the use of these tests in the NHS population, was estimated based on the proportion of EGFR mutation positive patients in England and Wales, the proportion of patients with an unknown test result, and test accuracy for the prediction of treatment response derived from two separate trials.
- The differences in relative treatment response, PFS and OS, between the results of the First-Signal trial that were used to model direct sequencing of all exon 19-21 mutations and the results of the IPASS trial that were used to model testing using the Therascreen® EGFR PCR Kit, were assumed to be solely due to the different tests used to distinguish between patients whose tumours are EGFR mutation positive (and who receive TKI treatment) and patients whose tumours are EGFR mutation negative (and who receive doublet chemotherapy).

The results of the 'evidence on comparative effectiveness available' analysis should therefore be interpreted on the condition that these assumptions hold. Moreover, the uncertainty presented surrounding the results is an underestimation of the true uncertainty, as the uncertainty associated

with the assumptions was not parameterised and is therefore not reflected in the probabilistic sensitivity analyses.

In the 'linked evidence' analysis two other direct sequencing tests (direct sequencing of all exon 18-21 mutations and direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)) for which accuracy data to predict response to treatment with TKIs were available were included in the analysis. The results of this analysis showed that the relevant strategies to be compared were direct sequencing of all exons 18-21 mutations and testing using the Therascreen® EGFR PCR Kit. Therascreen® EGFR PCR Kit was less expensive and less effective as compared to direct sequencing of all exons 18-21 mutations at £32,190 per QALY lost. Sensitivity analyses did not show any substantial changes to these results. However, it should be noted that this analysis is also based on a number of substantive assumptions, including those described for the 'evidence on comparative effectiveness' analysis. The following additional assumption should be noted:

- For direct sequencing of all exon 18-21 mutations and for direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells), the relative PFS and OS for mutation positives and mutation negatives was assumed to correlate perfectly with relative PFS and OS as observed for direct sequencing of all exon 19-21 mutations in the First-SIGNAL trial.

The same caveat for the interpretation of the results and surrounding uncertainty as explained above for the 'evidence on comparative effectiveness available' analysis applies to the interpretation of the results of the 'linked evidence' analysis.

The third analysis, the 'assumption of equal prognostic value' analysis, included all tests for which information on cost and/or technical performance was available from the online survey of NHS laboratories in England and Wales. This included the tests for which neither comparative effectiveness nor response data were available. Therefore, in this analysis, the costs-effectiveness of the tests were assessed given an assumption of equal prognostic value (based on the prognostic value of testing using the Therascreen® EGFR PCR Kit, as this was the only test for which prognostic data were available on patients with positive, negative and unknown tumour EGFR mutation status) and test specific information on costs only. In addition, tests used in NHS laboratories in England and Wales were considered to have technical characteristics (low limit of detection and similar proportion of tumour cells required for analysis) which were more similar to this test than to direct sequencing methods and would therefore be more likely to have similar prognostic value to the Therascreen® EGFR PCR Kit than to direct sequencing. The results of the 'assumption of equal prognostic value' analysis indicated that the effectiveness of the strategies was equal and the costs were almost equal. The lowest total strategy cost was £25,730 (Sanger sequencing or Roche Cobas)

versus £25,777 for the most expensive strategy (Fragment length analysis combined with Pyrosequencing). The sensitivity analysis, where the number of unknowns was based on results from the online survey of NHS laboratories in England and Wales, instead of being assumed equal based on literature, showed a slightly larger range of costs (£24,682 to £25,172) and a small range in QALYs (0.871 to 0.886) for the included mutation tests.

Conclusions

Implications for service provision

There was no strong evidence that any one EGFR mutation test had greater accuracy than any other test, although there was a suggestion that Therascreen® EGFR PCR Kit may be more accurate than direct sequencing for predicting response to treatment with TKIs. The clinical effectiveness of TKIs, in patients whose tumours are positive for EGFR, did not appear to vary according to which test was used to determine EGFR mutation status.

The results of the 'evidence on comparative effectiveness available' analysis and the 'linked evidence' analysis both indicated that the Therascreen® EGFR PCR Kit was less effective and less expensive compared to direct sequencing (all exon 19-21 mutations and all 18-21 mutations respectively) at £31,000 to £35,000 per QALY lost. The lower QALYs for the Therascreen® EGFR PCR Kit seem counterintuitive as the accuracy data show a higher accuracy for Therascreen® EGFR PCR Kit. This contradiction possibly results from the problematic and substantial assumptions made to arrive at the economic results. In particular, the assumption that the differences in treatment response and survival between tests as observed between the different studies are solely due to the different tests used. This ignores all other factors that can explain variations in outcomes between the studies. Therefore, these outcomes of the assessment of cost-effectiveness should be interpreted with extreme caution.

The results of the 'assumption of equal prognostic value' analysis (including all tests for which information on cost and/or technical performance was available from the online survey of NHS laboratories in England and Wales) showed that the costs of the EGFR mutation tests were very similar (range from £25,730 for Sanger sequencing or Roche Cobas for samples with insufficient tumour cells to £25,777 for Fragment length analysis combined with pyrosequencing).

There are no data on the clinical or cost-effectiveness of Therascreen® EGFR Pyro Kit or next generation sequencing. No published studies were identified for either of these two methods and neither method is currently in routine clinical use in any of NHS laboratories in England and Wales

who responded to our survey; one laboratory is currently developing and validating a next generation sequencing method.

Suggested research priorities

Re-testing of stored samples from previous studies, where patient outcomes are already known, could be used to provide information on the relative effectiveness of TKIs and standard chemotherapy in patients with EGFR mutation positive and negative tumours, where mutation status is determined using tests for which adequate data are currently unavailable. Should quantitative testing become part of routine practice, longitudinal follow-up studies relating the level of mutation and/or the presence or rarer mutations to patient outcomes would become possible. Studies of this type could help to assess which features of EGFR mutation tests are likely to be important in determining their clinical effectiveness.

As the uncertainties associated with clinical effectiveness forced the major assumptions in the economic evaluation this type of research would also facilitate economic analyses of EGFR mutation testing.

1. OBJECTIVE

The overall objective of this project is to summarise the evidence on the clinical and cost-effectiveness of commercial or UK in-house EGFR-TK mutation (hereafter to be referred to as EGFR mutation) tests to identify those previously un-treated adults with locally advanced, or metastatic non-small-cell lung cancer (NSCLC) who may benefit from first-line treatment with EGFR-TK inhibitors (gefitinib or erlotinib). In order to address the clinical effectiveness, data on the analytical validity of the different EGFR mutation tests (sensitivity/specificity for detection of mutations known to be linked to be treatment effectiveness) are required. However, there is no gold standard for EGFR mutation testing and the relationship between the effectiveness of EGFR-TK inhibitors and the presence of specific mutations or combinations of mutations, as well as the relationship between the effectiveness of EGFR-TK inhibitors and the level of mutation present, are uncertain. Therefore, the following research questions were formulated to address the review objectives:

1. What is the technical performance of the different EGFR mutation tests (e.g. proportion tumour cells needed, failures, costs, turnaround time)?
2. What is the accuracy (clinical validity) of EGFR 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.
3. How do clinical outcomes from treatment with EGFR-TK receptor inhibitors vary according to which test is used to select patients for treatment?
4. What is the cost-effectiveness of the use of the different EGFR mutation tests to decide between standard chemotherapy or anti-EGFR TKIs?

2. BACKGROUND AND DEFINITION OF THE DECISION PROBLEM(S)

2.1 Population

The indication for this assessment is the detection of mutations in the EGFR-TK oncogene in previously untreated adults with locally advanced or metastatic NSCLC. The presence of EGFR mutations can affect the response of tumours to standard chemotherapy and oral EGFR-TK inhibitors (TKIs) and mutation status is thus used to select the most appropriate course of treatment.[7, 8]

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.[9] 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.[10] 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.[11] The prevalence of EGFR mutations in NSCLC varies widely with population ethnicity. Estimates from observational studies ranged from 4.5% in a study conducted in Italy[12] to approximately 40% in two studies conducted in Japan and Taiwan.[13,14] The great majority of EGFR mutations occur in adenocarcinomas; from three studies, with a total of 1,238 participants (189 with EGFR mutation positive tumours), only one mutation occurred in a patient with tumour cytology other than adenocarcinoma.[12-14] The prevalence of EGFR mutations in NSCLC (adenocarcinoma) therefore ranged from 10.4% in the Italian study[12] to 50% and 39% in the Japanese and Taiwanese studies, respectively.[13, 14]

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 behaviour.[10] 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 three times higher in the most deprived wards of England and Wales compared to the least deprived wards.[10, 15]

Lung cancer survival rates are generally low because a substantial proportion of patients present at an advanced stage, when curative treatment is no longer possible.[10,16] 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.[17]

2.2 Intervention technologies

There are a variety of tests available for EGFR mutation testing; Table 1 summarises the methods currently used in NHS laboratories participating in the UK NEQAS pilot scheme for EGFR mutation testing, who responded to a request to provide information to NICE. The tests used can be broadly classified into two subgroups: mutation screening and targeted mutation detection. Mutation screening tests screen samples for all EGFR 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% and Sanger sequencing requiring up to 25% tumour cells (Table 1).[18,19] There is some evidence that EGFR mutations can be accurately detected in plasma,[20] however, biopsy tissue or cytology samples remain 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. In 2009, a European multidisciplinary workshop "EGFR testing in NSCLC: from biology to clinical practice" was held by the International Association for the Study of Lung Cancer and the European Thoracic Oncology Platform. This workshop included 122 molecular biologists, pathologists, chest physicians, surgeons and medical oncologists and produced consensus recommendations for the implementation of EGFR mutation testing in Europe.[18] Although there was no consensus on which laboratory test should be used, emphasis was placed upon the importance of standardisation and validation and a recommendation was made that EGFR mutation testing should only be undertaken in a quality assured, accredited setting.[18] Participants also agreed that the decision to request EGFR mutation testing should be made by the treating physician and that results should be reported within seven working days of request.[18]

2.2.1 Targeted mutation detection tests

The different targeted tests look for different numbers and combinations of EGFR mutations and are able to detect different levels of mutation; for example a sample may contain a high proportion of tumour cells but only a low proportion of these may harbour mutations and a low proportion of mutation, though detectable by some tests, may not be clinically significant. Thus tests may differ in their ability to accurately select patients who are likely to benefit from chemotherapy with tyrosine

kinase inhibitors. EGFR 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%.[12,13,19] 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.[19, 21]

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 whose tumours test positive for EGFR 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 mutation.[7] The mutation test used in the trial that informed NICE Technology Appraisal 192 was version 1 of the Therascreen® EGFR PCR Kit; it should be noted that this version is no longer being marketed and has been superseded by version 2, the Therascreen® EGFR RGQ PCR Kit. 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 mutation.[8] Trials used in this assessment were conducted only in patients whose tumours were EGFR mutation positive and used a direct sequencing approach to select patients with exon 19 deletions or exon 21 L858R point mutations for inclusion.[8,22]

The Therascreen® EGFR RGQ PCR Kit is a molecular diagnostic kit for detection of the 29 most common EGFR 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). All versions of the Therascreen® EGFR PCR Kit and the Therascreen® EGFR Pyro Kit will be included in the assessment. The mutations detected by the currently available 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 three insertions in exon 20; version 1 of the Therascreen® EGFR PCR Kit, as used in the studies included in this assessment but no longer available detected the same mutations. A version of the Therascreen® EGFR PCR Kit that did not detect the resistance mutation T790M was previously marketed by Qiagen, but this version is no longer available and was not used in any of the studies included in this review. Versions 1 and 2 of the Therascreen® EGFR PCR Kit, referred to in this assessment, may therefore be considered equivalent. The Therascreen® EGFR RGQ PCR 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 mutations (G719X (G719S/G719A/G719C) in exon 18, 29 deletions and complex mutations in exon 19, T790M in exon 20, S768I in exon 20, five 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 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.

Pyrosequencing methods are usually set up to detect specific EGFR-TK mutations and are sometimes used to look for point mutations alongside fragment length analysis to look for deletions and insertions. The process involves first extracting DNA from the sample and amplifying it using PCR. The PCR product is then cleaned up before the pyrosequencing reaction. The reaction involves the sequential addition of nucleotides to the mixture. A series of enzymes incorporate nucleotides into the complementary DNA strand, generate light proportional to the number of nucleotides added and degrade unincorporated nucleotides. The DNA sequence is determined from the resulting pyrogram trace.

Fragment length analysis can be used to detect deletions in exon 19 and insertions in exon 20. DNA is first extracted from the sample then it is amplified and labelled with fluorescent dye using PCR. Amplified DNA is mixed with size standards and is 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 a deletion/insertion can then be reported.

2.2.2 Mutation screening tests

Direct sequencing is used to screen for all EGFR 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 mutations; however, it requires larger tumour samples than other methods. Randomised controlled trials comparing the effectiveness of erlotinib with standard chemotherapy, in participants whose tumours were EGFR mutation positive, selected participants using direct sequencing to identify mutations in exon 19 or 21. A comparison of version 1 of the Therascreen® EGFR PCR Kit with direct sequencing reported that Therascreen® was ‘more sensitive’, i.e. some

EGFR mutations were detected which were not identified by direct sequencing. This was ascribed to low density of tumour cells in the sample.[23] Other mutation screening methods include single strand confirmation polymorphism, high resolution melt analysis and next generation sequencing.

For single strand conformation polymorphism, DNA is first extracted from the sample and amplified using PCR. The PCR product is then prepared for analysis by heat denaturing 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 (HRM) analysis detects all mutations, known and novel. The DNA is first extracted from the sample and amplified using PCR. The HRM reaction is then performed. This involves a precise warming of the DNA during which the two 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 to 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 can also be used to identify all mutations. As with Sanger sequencing, there is much variation in the methodology used. The concept is similar to Sanger sequencing, however the sample DNA is first fragmented into a library of small segments that can be sequenced in parallel reactions.

2.3 Care pathway

2.3.1 Diagnosis and staging of lung cancer

NICE guidance on the diagnosis and treatment of lung cancer was updated in 2011.[24] 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, or endobronchial 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.[24]

Table 1: Overview of available EGFR mutation tests

Sequencing method	Targeted (Mutations targeted)/ Screening test	Methodology
Commercial tests		
Qiagen Therascreen® Kit/ARMS	Targeted (version 1 – 28 mutations, version 2 -29 mutations)	Real-time PCR
Qiagen Therascreen® Pyro kit	Targeted (28 mutations)	Pyrosequencing
Roche cobas® EGFR Mutation Testing Kit	Targeted (41 mutations)	Real-time PCR
In house tests		
Sanger sequencing	All mutations	Usually PCR but variation in detail
Fragment length analysis	Varies	PCR followed by fluorescence to determine fragment size
Pyrosequencing	Varies	PCR followed by pyrosequencing reaction
TaqMan/Real Time PCR/Entrogen	Targeted (details unclear)	Real-time PCR
High resolution melt analysis	All mutations	PCR followed by HRM
Single strand conformation analysis	Screening (>98% of all mutations)	PCR followed by electrophoresis
SnapShot/RFPL/other	Targeted (details unclear)	PCR restriction-fragment-length polymorphism
Mass spectrometry	Targeted (details unclear)	Mass spectrometry
Next generation sequencing	Screening	DNA first fragments into small segments that can be sequenced in parallel reactions.

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 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.[24] 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 unspecified histology, for NHS trusts in England and Wales.[11] 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.

2.3.2 Treatment of NSCLC

Once NSCLC has been confirmed, NICE clinical guidance recommends that chemotherapy should be offered to people with stage III or IV (locally and regionally advanced or metastatic) 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.[24] 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.[25] 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%.[11]

NICE technology appraisal 192 recommends the EGFR 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 mutation.[7] 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 mutation.[8] NICE guidance does not currently include any recommendations on the type of diagnostic tests used to identify EGFR mutations and there is no consensus on which testing method should be preferred for clinical decision making.[18]

2.3.3 Measuring response to treatment

In 1979 the World Health Organisation and the International Union Against Cancer introduced criteria for the classification of the response of solid tumours to treatment.[26] These criteria were an early attempt to standardise reporting of response outcomes and was widely adopted, however, some problems with their use have subsequently developed: there has been variation in the methods used for incorporating into response assessments the change in size of measurable lesions, as defined by WHO; the minimum lesion size and number of lesions to be recorded have also varied; the definitions of progressive disease have sometimes been related to change in a single lesion and sometimes to change in overall tumour load (sum of the measurements of all lesions); there has been confusion around how to use three dimensional measures from new technologies, such as CT

and MRI, in the context of WHO criteria.[27] The Response Evaluation in Solid Tumours (RECIST) Group is a collaborative initiative which was initiated to review the WHO criteria. The RECIST criteria use the same categories (complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)).[27] RECIST guidance states that "CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment" and that imaging-based evaluation is generally preferable to clinical examination. It is suggested that follow-up assessments every 6-8 weeks is a "reasonable norm".[27] Taking into account the longest diameter only for all target lesions, the RECIST criteria, as they are applicable to this assessment, can be summarised as follows[27]:

CR disappearance of all target lesions and no new lesions

PR at least 30% decrease in the sum of the longest diameter of target lesions, taking the sum of the baseline diameters as the reference, and no new lesions

PD at least a 20% increase in the sum of the longest diameter of target lesions, taking the smallest sum of the longest diameters recorded since treatment started as the reference, or appearance of one or more new lesions

SD neither sufficient shrinkage to be classified as PR or sufficient increase to be classified as PD, taking the smallest sum of the longest diameters recorded since treatment started as the reference, and no new lesions.

Best overall response is defined as the best response recorded from the start of treatment to disease progression.[27]

This assessment compares the performance and cost-effectiveness of EGFR mutation testing options, currently available in the NHS in England and Wales, to identify previously untreated adults with locally advanced or metastatic NSCLC who may benefit from first-line treatment with to EGFR inhibitors (gefitinib or erlotinib).

3. ASSESSMENT OF CLINICAL EFFECTIVENESS

A systematic review was conducted to summarise the evidence on the clinical effectiveness of the different EGFR mutation testing options, currently available in the NHS in England and Wales, for the identification of previously untreated adults with locally advanced or metastatic NSCLC who may benefit from first-line treatment with EGFR-TK inhibitors (gefitinib or erlotinib). Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care, the NICE Diagnostic Assessment Programme interim methods statement and the Cochrane Handbook for Diagnostic Test Accuracy Reviews. [28] and NICE Diagnostic Assessment Programme manual.[29, 30]

3.1 Systematic review methods

3.1.1 Search strategy

Search strategies were 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.[28,31]

Candidate search terms were 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 were used to generate test sets of target references, which informed text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development involved an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases and aimed to reach a satisfactory balance of sensitivity and specificity.

The following databases were searched for relevant studies from 2000 to August 2011:

- MEDLINE (OvidSP) (2000-2012/07/wk 1)
- MEDLINE In-Process Citations and Daily Update (OvidSP) (up to 2012/07/17)
- EMBASE (OvidSP) (2000-2012/wk 28)
- Cochrane Database of Systematic Reviews (CDSR) (Internet) (2000-2012/Issue 7)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) (2000-2012/Issue 7)
- Database of Abstracts of Reviews of Effects (DARE) (via Cochrane Library) (2000-2012/Issue 3)
- Health Technology Assessment Database (HTA) (via Cochrane Library) (2000-2012/Issue 3)
- Science Citation Index (SCI) (Web of Science) (2000-2012/07/18)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet) (2000-2012/07/06) http://regional.bvsalud.org/php/index.php?lang=en

- Biosis Previews (Web of Knowledge) (2000-2012/08/24)
- NIHR Health Technology Assessment Programme (Internet) (2000-2012/07/18)
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) (up to 2012/07/19) http://www.crd.york.ac.uk/prospero/

Completed and ongoing trials were identified by searches of the following resources:

- NIH ClinicalTrials.gov (2000-2012/07/19) (Internet) http://www.clinicaltrials.gov/
- Current Controlled Trials (2000-2012/08/30) (Internet) http://www.controlled-trials.com/
- WHO International Clinical Trials Registry Platform (ICTRP) (2000-2012/08/30) (Internet) http://www.who.int/ictrp/en/

Searches were undertaken to identify studies of EGFR-TK mutation testing in non-small cell lung cancer. The main Embase strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the PRESS-EBC checklist.[32] Search strategies were developed specifically for each database and the keywords associated with non-small cell lung cancer were adapted according to the configuration of each database. Searches took into account generic and other product names for the intervention. No restrictions on language or publication status were applied. Limits were applied to remove animal studies. Full search strategies are reported in Appendix 1.

Electronic searches were undertaken for the following conference abstracts:

- ASCO Conference Proceedings (American Society of Clinical Oncology) (2007-2012) (Internet) http://www.asco.org/ASCOv2/Meetings/Abstracts
- ESMO Conference Proceedings (European Society of Medical Oncology) (2007-2012) (Internet) http://www.esmo.org/no_cache/education/abstracts-and-virtual-meetings.html
  2008 33rd ESMO Congress, Stockholm - http://annonc.oxfordjournals.org/content/vol19/suppl_8/
  2009 ECCO 15 and 34th ESMO Multidisciplinary Congress - http://www.ejcancer.info
  2010 35th ESMO Congress, Milan - http://annonc.oxfordjournals.org/content/21/suppl_8
  2011 ECCO 16 and 36th ESMO Multidisciplinary Congress, Brussels - http://www.ejcancer.info/issues
  2012 37th ESMO Congress, Vienna - http://annonc.oxfordjournals.org/content/23/suppl_9
- World Conference on Lung Cancer (International Association for the Study of Lung Cancer) (2007-2012) Internet)

http://iaslc.org/

14th World Conference on Lung Cancer - http://journals.lww.com/jto/toc/2011/06001

13th World Conference on Lung Cancer - http://journals.lww.com/jto/Citation/2009/09001/Abstracts.1.aspx

12th World Conference on Lung Cancer - http://journals.lww.com/jto/toc/2007/08001

Identified references were downloaded in Endnote X4 software for further assessment and handling.

References in retrieved articles were checked for additional studies. The final list of included papers was also checked on PubMed for retractions, errata and related citations.[33-35]

3.1.2 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 mutation tests?	What is the accuracy of EGFR 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 mutation test
Setting:	Secondary or tertiary care		
Interventions (index test):	Any commercial or in-house EGFR mutation test	Any commercial or in-house EGFR 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 patients whose tumours are EGFR positive versus EGFR negative. 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:	Survey of NHS laboratories participating in the UK NEQAS pilot scheme for EGFR mutation testing.	RCTs, CCTs and cohort studies	RCTs (CCTs and cohort studies where no RCTs were identified)

3.1.3 Inclusion screening and data extraction

Two reviewers (MW and PW) independently screened the titles and abstracts of all reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all studies deemed potentially relevant were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of studies excluded at the full paper screening stage are presented in Appendix 5.

Studies provided by the manufacturers of Therascreen®, (Qiagen) and cobas® EGFR Mutation Testing Kit (Roche Diagnostics), were first checked against the project reference database, in Endnote X4; any studies not already identified by our searches were screened for inclusion following the process described above.

Data were extracted on the following: study design/details, participant details (e.g. tumour stage, histological diagnosis, performance status, smoking status, ethnicity), EGFR mutation test(s) and mutations targeted, clinical outcomes, test performance outcome measures (against treatment response as reference standard), details of specific mutations identified by outcome measure (where reported) and test failure rates. Data were extracted by one reviewer, using a piloted, standard data extraction form and checked by a second (MW and PW); any disagreements were resolved by consensus. Full data extraction tables are provided in Appendix 2.

3.1.4 Quality assessment

The risk of bias in included RCTs was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials.[36] Studies used to derive accuracy data, for the ability of EGFR mutation tests to predict treatment response, were assessed using QUADAS-2.[37] Studies which provided both accuracy data and data on the effectiveness of treatment with TKIs following testing were assessed using both tools. Risk of bias assessments undertaken by one reviewer and checked by a second reviewer (MW and PW), and any disagreements were resolved by consensus.

The results of the risk of bias assessments were summarised and presented in tables and graphs in the results of the systematic review and were presented in full, by study, in Appendix 3.

3.1.5 Survey of Laboratories providing EGFR mutation testing

We conducted a web-based survey to gather data on the technical performance characteristics of EGFR mutation tests. We sent an e-mail invitation to NHS laboratories participating in the UK NEQAS pilot scheme for EGFR mutation testing, who had responded to a request to provide information to

NICE at the start of this assessment. We used the Survey Monkey online software to run the survey. We structured the survey into sections on:

- Laboratory details
- EGFR testing methods
- Logistics
- Technical Methods
- Costs

Where possible we used multiple choice options with tick boxes to make the survey quick and easy to complete. A copy of the survey is provided in Appendix 4.

3.1.6 Methods of analysis/synthesis

The results of studies included in this review were summarised by research question (see Section 1), i.e. studies providing technical information on EGFR mutation testing in NHS laboratories in England and Wales (Section 3.2.1), studies providing information on the accuracy of EGFR mutation tests for predicting response to TKI treatment (Section 3.2.2), and studies reporting information on how clinical outcomes may vary according to which test is used to select patients for TKI treatment (Section 3.2.3). We planned to use a bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an SROC curve for test accuracy data,[38-40] and a DerSimonian and Laird random effects model to generate summary estimates of treatment effects. However, because the review identified a relatively small number of studies with between study variation in participant characteristics, methods used to test for EGFR mutations and mutations targeted, we did not consider meta-analyses to be appropriate and have provided a structured narrative synthesis.

For all studies that provided data on accuracy for the prediction of response to treatment with TKIs, the absolute numbers of true positive, false negative, false positive and true negative test results, as well as sensitivity and specificity values, with 95% confidence intervals (CIs) are presented in results tables, for each reference standard response (e.g. objective response (OR), disease control (DC)) reported. Where reported, data on the numbers of failed EGFR mutation tests and reasons for failure were also included in the results tables. The results of individual studies were plotted in the ROC plane to illustrate the trade-off between sensitivity and specificity and for ease of comparison between test methods; separate plots were provided for each reference standard response. For RCTs providing information on how clinical outcomes may vary according to which test is used to select patients for TKI treatment, hazard ratios (HRs), with 95% CIs, are provided survival outcome measures (progression-free survival (PFS) and overall survival (OS)) and relative risk (RR), with 95%

CIs, are reported for tumour response outcomes (OR and DC). The results of individual studies were illustrated in forest plots. Between-study clinical heterogeneity was assessed qualitatively. There were insufficient studies to assess heterogeneity statistically such as the chi-squared test and I^2 statistic.[41]

3.2 Results of the assessment of clinical effectiveness

The literature searches of bibliographic databases identified 6,932 references. After initial screening of titles and abstracts, 152 were considered to be potentially relevant and ordered for full paper screening. No additional papers were ordered based on screening of papers provided by test manufacturers. One conference abstract,[6] which was provided as part of the submission from Roche Molecular Systems, was included in the review; all other studies submitted cited in industry submissions had already been identified by bibliographic database searches. No additional studies were identified from searches of clinical trials registries. One study considered to be potentially relevant and ordered for full paper screening was published in Japanese and no translation could be obtained.[42] Figure 1 shows the flow of studies through the review process, and Appendix 5 provides details, with reasons for exclusions, of all publications excluded at the full paper screening stage.

Based on the searches and inclusion screening described above, 31 publications of 11 studies were included in the review. Hand searching of conference proceedings resulted in the identification of two additional publications[43,44] for two previously identified trials.[2,5] A total of 11 studies in 33 publications were therefore included in the review.

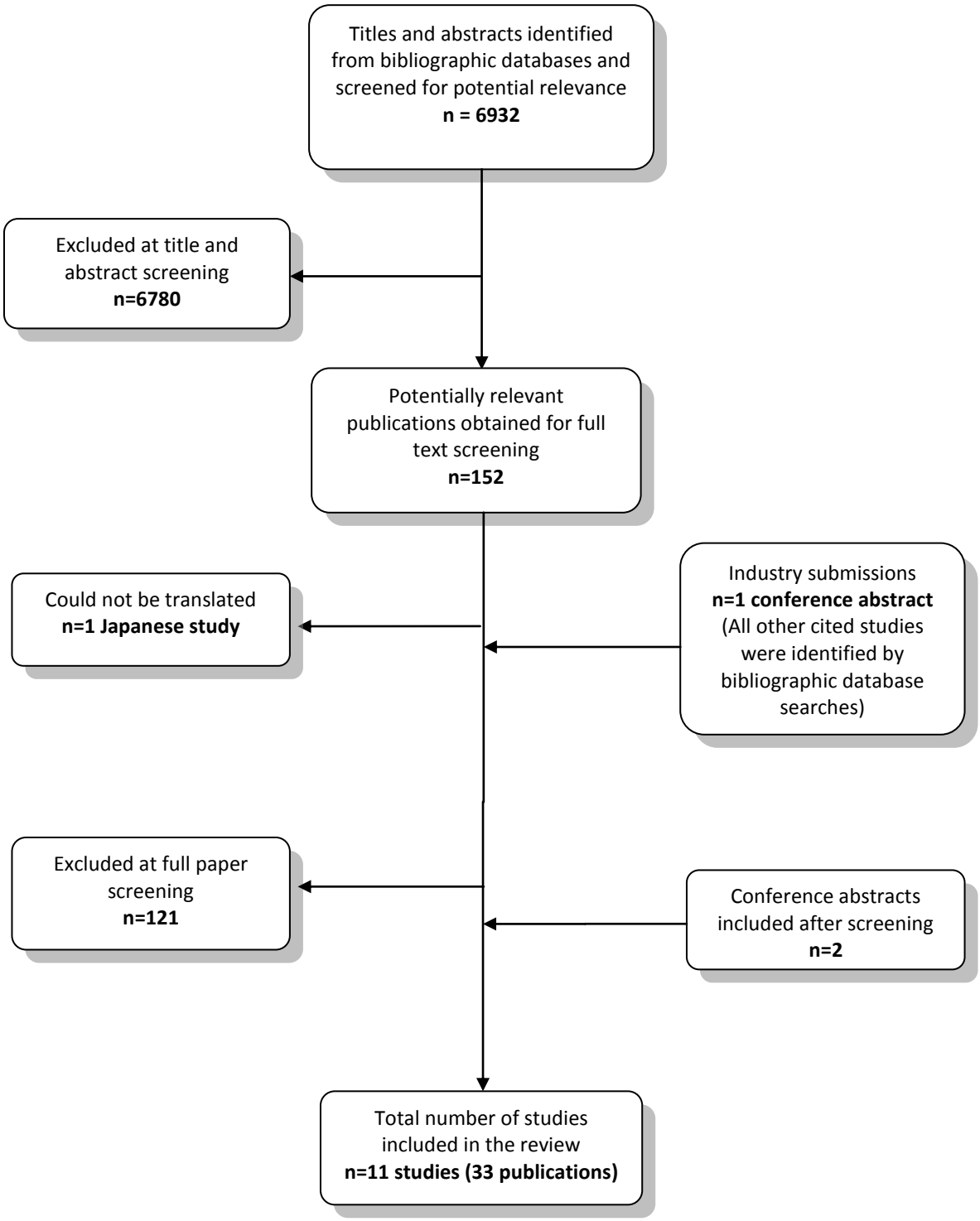
One study was included only for information on the technical performance characteristics of an EGFR mutation test from a UK NHS laboratory.[45] Four studies reported data on tumour response following treatment with TKIs in a group of patients tested for EGFR mutations; all patients in the group were treated, regardless of mutation status.[46-49] These studies provide information on the accuracy of various EGFR mutation tests for the prediction of response to treatment with TKIs. Three RCTs compared the effectiveness of TKIs with that of standard chemotherapy in patients whose tumours were positive for EGFR mutations.[1,2,4] A further study[6] reported a re-analysis of sub-set samples from the EURTAC trial[2] using the Cobas EGFR Mutation Test, Roche Molecular Systems, USA. Because the method used to determine mutation status varied between trials, these RCTs provide information on how clinical outcomes may vary according to which test is used to select patients for TKI treatment. The remaining two studies, the IRESSA Pan-Asia Study (IPASS) and the first-SIGNAL study, could be analysed to provide both accuracy and clinical effectiveness data.[3,5,50] These studies were RCTs which compared TKIs with standard chemotherapy in patients with NSCLC who were not initially tested for EGFR mutations; a sub-group analyses were reported for patients in whom EGFR-

TK mutation status was determined. The IPASS study was reported in two full paper publications. Throughout this report it is cited either as both publications,[3,50] or the specific publication from which the reported data were extracted. Multiple publications of other studies did not provide additional data and are listed in the data extraction tables in Appendix 2. For the remainder of the report, these studies are cited using the primary publication, as given above.

All included studies were published in 2006 or later and all RCTs were published in 2010 or later. Of the studies providing information on test accuracy, two were conducted in Europe,[46,48] one in the USA,[47] and three in East Asia.[5,49,50] With the exception of one European trial, EURTAC,[2] all RCTs were conducted in East Asia. With one exception, the North East Japan Study Group trial,[4] all RCTs were funded by the manufacturers of TKIs (Hoffmann-La Roche Ltd or AstraZeneca); the re-analysis of samples from the EURTAC trial[6] was funded by Roche Molecular Systems, USA.

Full details of the characteristics of study participants, study inclusion and exclusion criteria, EGFR mutation test used and mutations targeted, TKI intervention and (where applicable) standard chemotherapy comparator are reported in the data the extraction tables presented in Appendix 2. For studies providing test accuracy data, full details of the EGFR mutation testing process are reported as part of the QUADAS-2 risk of bias assessment (Appendix 3).

Figure 1: Flow of studies through the review process



3.2.1 What are the technical performance characteristics of the different EGFR mutation tests?

Literature review

One study which evaluated the technical performance of EGFR mutation tests was included in the review. The study was conducted in the Department of Molecular Diagnostics at the Royal Marsden Hospital and the Institute of Cancer Research; this laboratory also contributed to our survey. The study reported data for two years of EGFR testing from January 2009 to January 2011. During year 1 of the testing period version 1 of the Therascreen® EGFR PCR Kit was used, during year 2 a combination of Therascreen® EGFR PCR, fragment analysis (for exon 19 deletions and exon 20 insertions) and direct sequencing (for the rarer econ 19 or exon 21 mutations) were used. A total of 121 patients (152 samples) 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% CI 4.5 to 5.5 days). However, the actual time from the test request to the result was 17.8 days (95% CI 16.4 to 19.4 days). The test failure rate was 19% (29/152 samples) but this improved over time from 33% during the first three months to 13% during the last three months of year 1 testing. The failure rate was lower in year 2 at only 5%.

Laboratory survey results

There were 24 UK laboratories participating in the 2012-2013 NEQAS pilot scheme for EGFR mutation testing; 14 of these had responded to a request to provide information to NICE at the start of this assessment and were invited to participate in the survey. Thirteen of the 14 laboratories invited to participate in the survey completed our online questionnaire (response rate 93%). Three laboratories used more than one EGFR testing method and so completed the questionnaire more than once.

EGFR mutation test methods (Figure 2, Table 3)

The Therascreen® EGFR PCR Kit was the most commonly used EGFR mutation test with six laboratories using this test. A combination of fragment length analysis and pyrosequencing was used in three laboratories and Sanger sequencing in two; other tests were each used in single laboratories. Most laboratories that used the Therascreen® EGFR PCR Kit cited ease of use (n=5) and/or proportion of tumour cells required (n=5) as their reasons for choosing this method, three studies also cited mutation coverage and two cited cost. All studies that used fragment length analysis cited cost as a reason for their choice of this method, one also cited proportion of tumour cells required, mutation coverage, and flexibility of method, one also cited ease of use and the third claimed that accuracy was high. The two laboratories that use Sanger sequencing both cited mutation coverage as a reason for choice and one also cited cost and ease of use and both use a

second testing option for samples with insufficient tumour cells or for verification of mutations. Although only three laboratories completed the questionnaire separately for more than one test, 11 laboratories answered the question on reason for using more than one EGFR testing method. Reasons for this included insufficient tumour cells (n=3), verification of mutations (n=5), validating a new method (n=1), "back up technique in case kits are made unavailable", another that "methods are complementary and detect different mutations", and the last that "coverage of mutations and simplicity, cost". Of the laboratories that completed the questionnaire more than once, one used the Therascreen® EGFR PCR test, but is also developing and validating a new Next Generation Sequencing method which they think may be cheaper and target more mutations. The second use Sanger sequencing and Roche Cobas and cite verification of mutations and insufficient tumour cell as their reason for using multiple tests. The third use Sanger sequencing, TaqMan/Real Time PCR/Entrogen and Fragment Length Analysis and also cite verification of mutations and insufficient tumour cell as their reason for using multiple tests. Two further laboratories indicated that they use a combination of pyrosequencing and fragment length analysis as complementary tests which detect different mutations; laboratories using fragment length analysis always do so as part of a strategy which involves more than one test.

Figure 2: EGFR mutations tests used in NHS Laboratories in England and Wales participating in the UK NEQAS pilot scheme for EGFR mutation testing

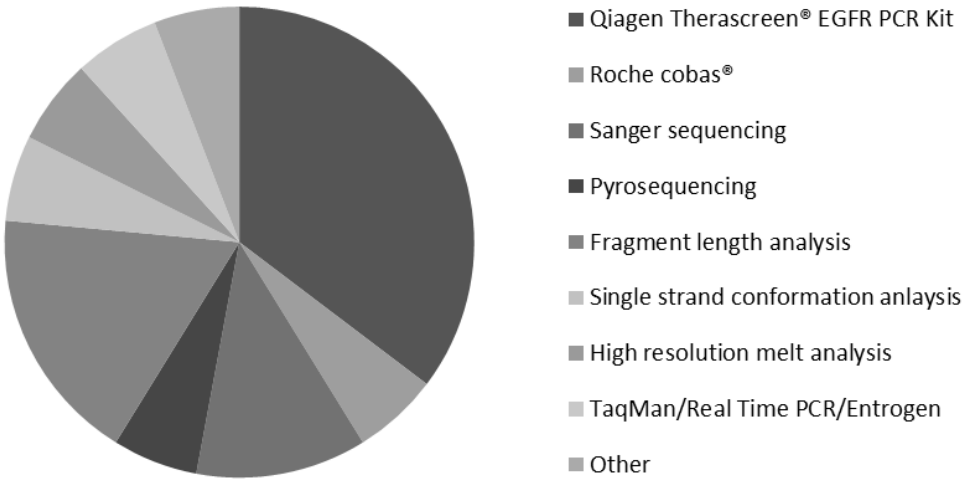


Table 3: Details of EGFR mutation tests used in NHS laboratories in England and Wales participating in the UK NEQAS pilot scheme for EGFR mutation testing

EGFR mutation Test used	Reasons for choosing Test	Mutations Targeted
Qiagen Therascreen® EGFR PCR Kit	Ease of use	28/29 mutations in Therascreen® kit
	Proportion of tumour cells required; Ease of use; "We had a trainee project comparing several different methods. Qiagen picked up more mutations than Sanger (more sensitive), and was very easy to use"	
	Proportion of tumour cells required; Mutation coverage	
	Proportion of tumour cells required; Mutation coverage; Ease of use	
	Cost; Proportion of tumour cells required; Ease of use	
	Cost; Proportion of tumour cells required; Ease of use; Mutation coverage	
Fragment length analysis **and** Pyrosequencing	Cost; Proportion of tumour cells required; Mutation coverage; Not a black box method so easily modified if required	All Exon 18-21 mutations
	Cost; "Sensitivity is greater than Sanger and specificity is good. Equipment for pyrosequencing is in house and is a platform used reliable for many molecular pathology investigations"	Exon 19 deletions Insertions in exon 20 Exon 21 - L858R mutation Targeted Exon 18-21 mutations. 12 mutations in total but other mutations may be detected if they are within the same region.
Sanger sequencing **and/or** Fragment length analysis/ TaqMan/Real Time PCR (used for verification of mutations, or where sample contains insufficient tumour cells for Sanger sequencing (< 30%))[a]	Sanger sequencing: Cost; Ease of use; Mutation coverage; Fits in with laboratory high throughput sequencing pipeline so samples will be processed quickly Fragment length analysis: Cost; Ease of use TaqMan/Real Time PCR: Cost; Ease of use	Sanger sequencing: All Exon 18-21 mutations Fragment length analysis: Exon 19 deletions TaqMan/Real Time PCR: Exon 21 - L858R mutation
Sanger sequencing **and/or** Roche Cobas (used for verification of mutations, or where sample contains insufficient tumour cells for Sanger sequencing (< 30%)[b]	Sanger sequencing: Mutation coverage Roche Cobas: Proportion of tumour cells required	Sanger sequencing: All Exon 18-21 mutations Roche Cobas: 41 mutations in Cobas kit

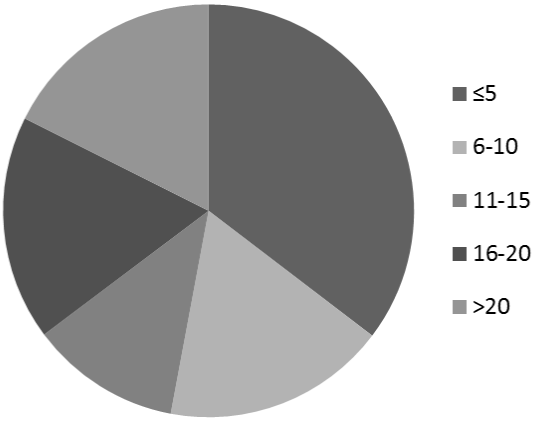
EGFR mutation Test used	Reasons for choosing Test	Mutations Targeted
Next Generation Sequencing, stated "in process of developing and validation"	Cost; Proportion of tumour cells required; Mutation coverage; Capacity to test multiple genes/samples/patients	Potentially all
High resolution melt analysis	Mutation coverage; Ease of use	All Exon 18-21 mutations
Single strand conformation analysis	Cost; Ease of use; The vast majority of cases (90%) are EGFR wild type, therefore an easy method that reliably detects wild type cases with ease of analysis seems cost-effective.	All Exon 18-21 mutations
Pyrosequencing	Cost; Mutation coverage	Exon 19 deletions Insertions in exon 20 Exon 21 - L858R mutation
a: Scoping reported this strategy as 'Sanger sequencing (exons 18-21) followed by fragment length analysis (exon 19 deletions) / PCR (to detect L858R) of negative samples' b: Scoping reported this strategy as 'Sanger sequencing (exons 18-21) of samples with >30% tumour cells and cobas EGFR Mutation Testing Kit for samples with <30% tumour cells'		

EGFR mutation test logistics (Figure 3, Table 4)

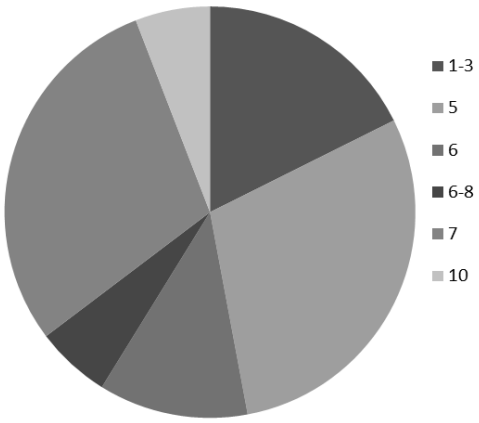
The number of samples screened for EGFR mutations in a typical week varied by laboratory from less than five (six laboratories) to more than 20 (three laboratories). The batch size ranged from less than 3 to 10 samples (Figure 3 and Table 4). Only laboratories with five or less samples screened per week ran batches of three or less. Only one laboratory had a batch size of 10 and this laboratory screened more than 20 samples per week; all other laboratories had batch sizes between 5 and 8. For the Therascreen® EGFR PCR test, all batch sizes were 5 or 7. The frequency at which the laboratories ran the test ranged from daily to every other week, although the laboratory that ran the test every other week stated that they would match demand. Three laboratories stated that they waited for a minimum batch size (5 to 7 samples); although one of these stated that they would match demand.

Figure 3: Summary of logistic information

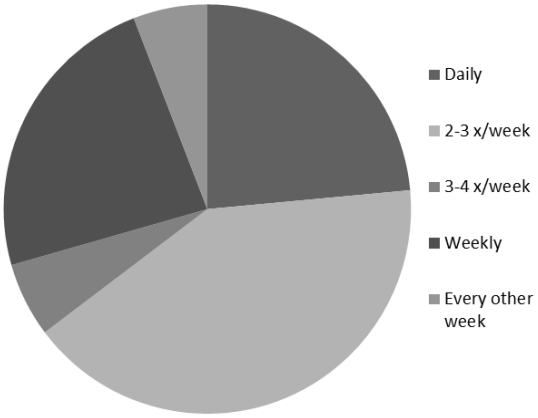
a. In a typical week, how many samples do you screen for EGFR mutations?



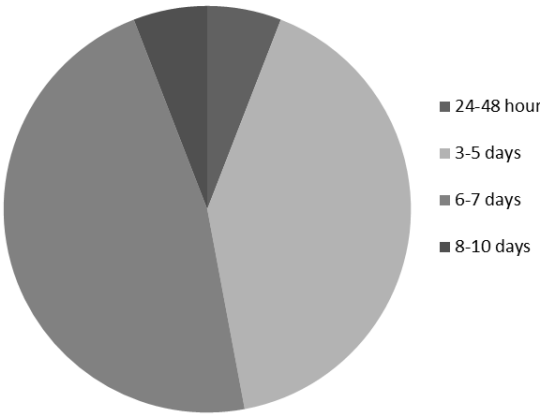
b. What is you average batch size (number of samples)?



c. How often do you run the EGFR mutationtest?



d. On average, how long does it take from receiving a sample at the lab to sending a result back to the clinician?



The majority of laboratories had a turnaround time from receiving the sample to reporting the result to the clinician of 3 to 5 or 6 to 7 days with only one laboratory having a time of 24 to 48 hours and one having a time of 8 to 10 days. The laboratory with the shortest turnaround time was one which used the Therascreen® EGFR PCR test and tested less than five samples per week. The laboratory with the longest turnaround time was also a laboratory that used Therascreen® EGFR PCR, but had a higher throughput of 11 to 15 samples per week. Neither of these two laboratories waited for a minimum batch size before running the test.

Table 4: Laboratory throughput by EGFR mutation test

EGFR mutation test	Samples per week	Batch size	Frequency of test	Wait for batch size?	Time from receiving test to returning result to clinician
Qiagen Therascreen® EGFR PCR Kit	>20	7	Daily	No	3-5 days
	>20	7	3-4 times per week	Yes	3-5 days
	11-15	7	Weekly	No	8-10 days
	6-10	7	weekly + further run when required	No	3-5 days
	≤5	5	Weekly	No	24-48 hours
	≤5	5	every other week	Yes, but will match demand	6-7 days
Fragment length analysis **and** Pyrosequencing	6-10	5	2-3 times per week	No	6-7 days
	6-10	5	2-3 times per week	No	6-7 days
Sanger sequencing **and/or** Fragment length analysis/ TaqMan/Real Time PCR (used for verification of mutations, or where sample contains insufficient tumour cells for Sanger sequencing (< 30%))[a]	≤5	1-3	Daily	No	6-7 days
Sanger sequencing **and/or** Roche Cobas (used for verification of mutations, or where sample contains insufficient tumour cells for Sanger sequencing (< 30%))[b]	16-20	6	2-3 times per week	Yes	6-7 days
	16-20	6	2-3 times per week	No	3-5 days
High resolution melt analysis	11-15	7	2-3 times per week	No	3-5 days
Next generation sequencing	≤5	5	Weekly	No	3-5 days
Pyrosequencing	16-20	6-8	2-3 times per week	No	6-7 days
Single strand conformation analysis	>20	10	2-3 times per week	No	3-5 days

a: Scoping reported this strategy as 'Sanger sequencing (exons 18-21) followed by fragment length analysis (exon 19 deletions) / PCR (to detect L858R) of negative samples'
b: Scoping reported this strategy as 'Sanger sequencing (exons 18-21) of samples with >30% tumour cells and cobas EGFR Mutation Testing Kit for samples with <30% tumour cells'

EGFR mutation test technical performance (Table 5)

The minimum reported percentage of tumour cell required varied between laboratories, even for those using the same EGFR mutation test. For the Therascreen® EGFR PCR test, two laboratories reported that less than 1% of tumour cells were required, three laboratories reported that 1 to 5% of tumour cells were required, while one reported that 6 to 10% tumour cells were required. The two laboratories that used fragment length analysis and pyrosequencing both reported that a minimum of 1 to 5% tumour cells were required. Sanger sequencing needed the greatest percentage tumour cells with a requirement of >30%. High resolution melt analysis and Roche Cobas required 6 to 10%; all other methods were reported to require 1 to 5% tumour cells. One laboratory which used a combination of either fragment length analysis, Sanger sequencing or TaqMan/Real Time PCR/Entrogen indicated on the questionnaire that the minimum percentage of tumour cells required was 30% but stated that they had no failed samples and that "we always get a result out even if using only one of the three methods".

The estimated total number of failed samples ranged from 0 to 10% with the number of failed samples due to insufficient tumour cells ranging from 0 to 5%. The most common reasons for failed tests were insufficient tumour cell count and poor quality DNA/DNA degradation.

Table 5: EGFR mutation test technical performance data

Test	Minimum % tumour cells required	Estimate of total failed samples	Estimate of failures due to insufficient tumour cells	Reasons for failed tests
Qiagen Therascreen® EGFR PCR Kit	≤1%	0	0	All met assay quality control criteria
	≤1%	10%	NR	Large number of original failures related to samples not validated for kit (bone, CSF etc). Most other failures due to inhibition (i.e. require a dilution factor).
	1-5%	5%	NR; not included in 5%	Unknown reason in most cases; decalcification for bone specimens is a classical cause of failure; for others it is assumed to be due to DNA degradation due to delay in formalin fixation
	1-5%	1%	1%	Low levels of amplifiable DNA
	1-5%	2%	0	DNA degradation or scanty material

Test	Minimum % tumour cells required	Estimate of total failed samples	Estimate of failures due to insufficient tumour cells	Reasons for failed tests
	6-10%	5%	5%	NR
Fragment length analysis **and** pyrosequencing	1-5%	5%	NR	Poor quality DNA, we don't test the tumour load but rely on information from the referring pathologist; if they don't supply this information then we add a caveat. We rarely fail samples but may be reporting on non-tumour DNA if incorrect samples are sent.
	1-5%	5%	2%	Insufficient sample mainly.
Sanger sequencing **and/or** Fragment length analysis/ TaqMan/Real Time PCR (used for verification of mutations, or where sample contains insufficient tumour cells for Sanger sequencing (< 30%))[a]	>30%	0	0	We always get a result out even if using only one of the three methods (55 fails on sequencing; 6/77 (7.8%) fluorescent PCR fails; 7/74 (9.55%) L858R real time PCR fails). Reasons for failed tests usually insufficient quantity of tissue and DNA quality
Sanger sequencing **and/or** Roche Cobas (used for verification of mutations, or where sample contains insufficient tumour cells for Sanger sequencing (< 30%))[b]	>30%	4%	3%	Poor DNA quality and low tumour cell count
	6-10%	5%	4%	Insufficient tumour cell count and poor samples which are degraded
Pyrosequencing	1-5%	5%	2%	Poor quality DNA, generally due to inadequate fixation
High resolution melt analysis	6-10%	0.2%	0.2%	Lack of good PCR amplification
Single strand conformation analysis	1-5%	10%	2%	Degraded DNA (70%), low DNA quantity (25%), technical errors (5%)
Next generation sequencing	1-5%	NR	NR	NR – state that in the process of validation

a: Scoping reported this strategy as 'Sanger sequencing (exons 18-21) followed by fragment length analysis (exon 19 deletions) / PCR (to detect L858R) of negative samples'

b: Scoping reported this strategy as 'Sanger sequencing (exons 18-21) of samples with >30% tumour cells and cobas EGFR Mutation Testing Kit for samples with <30% tumour cells'

EGFR mutation test costs (Table 6)

The cost of the EGFR mutation tests ranged from £110 to £190 and the price that the laboratories charged for the test ranged from £120 to £200. Most laboratories reported that the cost of the test was the same as the price charged for the test; where there was a difference this ranged from £10 to £37.50 per test. The variation in the cost of the test was similar within tests as it was between tests with no single test appearing more or less expensive than any of the other tests, despite most laboratories citing cost of test as their reason for selecting a particular EGFR mutation testing method. Costs were similar for laboratories using single tests and those using strategies involving multiple tests. The cost and price charged for the Therascreen® EGFR PCR test ranged from £120 to £190.

Table 6: Summary of EGFR mutation test costs

Test	**What is the cost of the test (including purchase costs, personnel, material and overheads)?**	**What is the price that you charge for the test?**
Qiagen Therascreen® EGFR PCR Kit	£190	£190
	£180.00	£180
	Approx £160.00	£160
	approximately £120	£157.50
	real cost unknown	£120
	£120	£120
Fragment length analysis **and** Pyrosequencing	£175 excluding overheads	£200
	£150	£175
Sanger sequencing **and/or** Fragment length analysis/ TaqMan/Real Time PCR (used for verification of mutations, or where sample contains insufficient tumour cells for Sanger sequencing (< 30%))[a]	NR	£140
Sanger sequencing **and/or** Roche Cobas (used for verification of mutations, or where sample contains insufficient tumour cells for Sanger sequencing (< 30%))[b]	NR	£120
	NR	£140
Pyrosequencing	~£175	£175
High resolution melt analysis	£140	£150
Single strand conformation analysis	£110	£140
Next generation sequencing	NR	NR

a: Scoping reported this strategy as 'Sanger sequencing (exons 18-21) followed by fragment length analysis (exon 19 deletions) / PCR (to detect L858R) of negative samples'. b: Scoping reported this strategy as 'Sanger sequencing (exons 18-21) of samples with >30% tumour cells and cobas EGFR Mutation Testing Kit for samples with <30% tumour cells'

3.2.2 What is the accuracy of EGFR mutation testing, using any test, for predicting response to treatment with tyrosine kinase inhibitors?

Six studies, two RCTs[3,5,50] and four cohort studies,[46-49] provided data on the accuracy of EGFR mutation testing for predicting response to treatment in patients with stage IIIB or IV NSCLC, when they are treated with TKIs. Three studies were conducted in patients treated with gefitinib,[3,5,49] and three were conducted in patients treated with erlotinib.[46-48] These studies are particularly useful as they provide full information on the extent to which EGFR mutation tests are able to discriminate between patients who will have benefit from TKI treatment and those who will not. We defined true positives as those patients with an EGFR mutation who have a positive response to TKI treatment. Where presence or absence of objective response (OR) was the reference standard, a positive response was defined as best observed response = complete response (CR) or partial response (PR). Where presence or absence of disease control (DC) was the reference standard, a positive response was defined as best observed response = CR, PR, or stable disease (SD). False positives were defined as those patients with an EGFR mutation who did not have a positive response to TKI treatment (SD or progressive disease (PD) for the reference standard OR, or disease progression for the reference standard DC), false negatives were defined as those without an EGFR mutation who had a positive response to TKI treatment and true negatives were defined as those without EGFR mutation who did not have a positive response to TKI treatment. Full definitions of CR, PR, SD and PD are provided in section 2.3.3.

<u>Study details</u>

Participant characteristics varied across studies. Four studies did not report any details of the ethnicity of participants,[5,46,48,49] one study included mainly Caucasian participants,[47] and one study included almost entirely (>99%) East Asian participants.[3] All studies reported a high (>75%) proportion of participants with stage IV disease. Most study participants had a histological diagnosis of adenocarcinoma, but the proportion varied (range 45% to 100%). Only two studies specifically reported the inclusion of any patients with squamous cell carcinoma (9%[47] and 15%[46]); neither study reported separate data for these patients. Three studies included mainly (92%),[3] or only participants who had never smoked[5,48] one study included mainly (71%) patients who had never smoked, and the remaining two studies included mainly (70%[46] and 90%[47]) current and former smokers. Full details of study participants are reported in Appendix 2.

Five studies evaluated direct sequencing methods for the identification of any EGFR mutation; three assessed exons 18-21,[46,48,49] one assessed exons 19-21,[5] and one assessed

exons 18-24.[47] In one study two patients, one with the exon 20 resistance mutation T790M and one with a previously undescribed exon 20 mutation V802I, were classified as test negative,[46] and in one study two patients with a non-sensitising mutation G863S were classified as test negative.[48] One study assessed version 1 of the Therascreen® EGFR PCR Kit, which detects 19 exon 19 deletions (does not distinguish between individual deletions), exon 21 point mutations L858R and L861Q, the exon 20 mutations S768I and T790M, exon 18 mutations G719X (does not distinguish between G719S, G719A and G719C), and three exon 20 insertions.[3]

All but one study used the Response Evaluation Criteria In Solid Tumours (RECIST) criteria[27] to evaluate response to TKI treatment and response was defined as the best response to TKI treatment observed during treatment. In the other study criteria used were not clearly defined.[5] Tumour response was assessed every six weeks,[46,47,50] every eight weeks,[48,49] or every nine weeks[5] during treatment. Three studies did not report the duration of TKI treatment, i.e. the response evaluation period, and this could not be assumed to be the same as the follow-up period for the study as all studies allowed further therapies after disease progression.[46,47,49] The remaining three studies reported similar median treatment durations of 5.4 to 5.7 months.[5,48,50] All studies reported data for OR (best observed response was partial or complete response) and all but one[5] also reported data for DC (best observed response was partial or complete response, or stable disease).

<u>EGFR mutation test accuracy</u>

The Therascreen® EGFR PCR Kit appeared to have the best overall performance for discriminating between patients who are likely to benefit from TKI treatment and those who are not. The sensitivity and specificity estimates for OR were 99% (95% CI: 94, 100) and 69% (95% CI: 60, 77) respectively.[50] As might be expected the specificity was higher where a lower threshold (DC) was used to define response to treatment and, conversely, sensitivity was higher where a higher threshold (OR) was used to define response to treatment (see Table 7). Figure 4 illustrates the results for all studies reporting accuracy data with the Therascreen® EGFR PCR Kit study (IPASS) indicated in red. Four of the five studies, which used direct sequencing methods to identify EGFR mutations reported high estimates of specificity (>80%) for OR and specificities ranged from 60 to 80%.[5,46-48] Three of these studies also assessed DC; specificities remained high (>90%), whilst sensitivity estimates were very low (≤35%).[46-48] The remaining direct sequencing study reported low sensitivity (66%) and specificity (50%) for DC and low specificity (61%) with high sensitivity (84%) for OR. All direct

sequencing studies had small sample sizes, reflected in the wide confidence intervals around sensitivity and specificity estimates. There were no clear common participant characteristics, across studies which reported similar sensitivity or specificity estimates for DC or OR. All test accuracy results are summarised in Table 7. It is possible that the lower specificity values observed in two studies[49,50] may, at least in part, be explained by the classification of resistance mutations as a positive result for EGFR mutation testing. The four direct sequencing studies which reported high specificity estimates for DC and/or OR[5,46-48] either stated that patients whose tumours showed resistance or non-sensitising mutations were classified as EGFR mutation negative, or did not identify any patients whose tumours showed these types of mutation (see Table 8). Although the number of resistance mutations identified was generally small, their potential effect on specificity estimates was magnified by the very small sample size in most studies. Data relating best response to individual mutations appeared to indicate that there may be a less favourable response to TKIs in patients with T790M or other exon 20 mutations (see Table 8); [redacted]. The most commonly observed mutations were exon 19 deletions and the exon 21 point mutation L858R and most patients with these mutations achieved a minimum response of stable disease. Two studies did not report sufficient information to derive best response data by mutation type and both of these studies identified only exon 19 deletions and exon 21 point mutation L858R.[5,48] One study reported a complete response (CR) in three patients whose tumours were positive for EGFR mutations and no complete responses in patients whose tumours were negative for EGFR mutations;[50] all other studies did not report any complete responses.

The IPASS trial, which used version 1 of the Therascreen® EGFR PCR Kit, reported the minimum quantity of DNA required to detect 1% for each mutation targeted (1.5ng for all mutations except insertions which required 3.0ng).[3] No direct sequencing study reported information on the limit of detection of the EGFR mutation test method used. Two studies specified a minimum proportion of tumour cells as a sample quality pre-requisite for testing; these were 50% tumour cells[47] and 80% tumour cells,[48] respectively. Details of non-evaluable samples were generally poorly reported; any information reported is presented in Table 7 below.

Table 7: Accuracy of EGFR mutation testing for the prediction of response to treatment with TKIs

Study	EGFR test and mutations targeted	Non-evaluable samples	Disease Control						Objective Response					
			TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fukuoka (IPASS)(2011)[3, 50]	Therascreen® EGFR PCR Kit (version 1)	386/609 unknown mutation status (number with insufficient sample quality NR)	121	10	36	47	77 (70, 83)[a]	83 (70, 91)[a]	94	37	1	82	99 (94, 100)[a]	69 (60, 77)
Giaccone(2006)[46]	Direct sequencing (nested PCR) of all exon 18-21 mutations.	24/53 no sample available, no samples of insufficient quality reported	5	0	12	12	29 (10, 56)[a]	100 (74, 100)[a]	4	1	1	23	80 (28, 100)[a]	96 (79, 100)[a]
Han (first-SIGNAL)(2012)[5]	Direct sequencing (PCR) of all exon 19-21 mutations	53/159 unknown mutation status (number with insufficient sample quality NR)	NR	NR	NR	NR	NR	NR	22	4	7	20	76 (57, 90)[a]	83 (63, 95)[a]
Jackman(2007)[47]	Direct sequencing (34 samples), or WAVE-HS (9 samples) for	4/80 no sample available, 26/80 samples of	9	0	17	11	35 (15, 56)[a]	100 (72, 100)[a]	3	6	2	26	60 (15, 95)[a]	81 (64, 93)[a]

Study	EGFR test and mutations targeted	Non-evaluable samples	Disease Control						Objective Response					
			TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
	inadequate samples (<50% tumour cells) of all exon 18-24 mutations	insufficient quality												
Pallis(2012)[48]	Direct sequencing (PCR) of all exon 18-21 mutations.	13/49 no sample available, no samples of insufficient quality reported	8	1	16	11	33 (16, 55)[a]	92 (62, 100)[a]	6	3	4	23	60 (26, 88)[a]	89 (70, 98)
Yang(2008)[49]	Direct sequencing (PCR) of all exon 18-21 mutations.	16/106 EGFR mutation status not sucessfully determined, no details reported.	47	5	24	5	66 (54, 71)[a]	50 (19, 81)[a]	38	14	7	22	84 (71, 94)[a]	61 (44, 77)[a]

CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive

[a]: calculated values

Figure 4: ROC plane plots comparing EGFR mutation testing methods for the prediction of response to treatment with TKIs

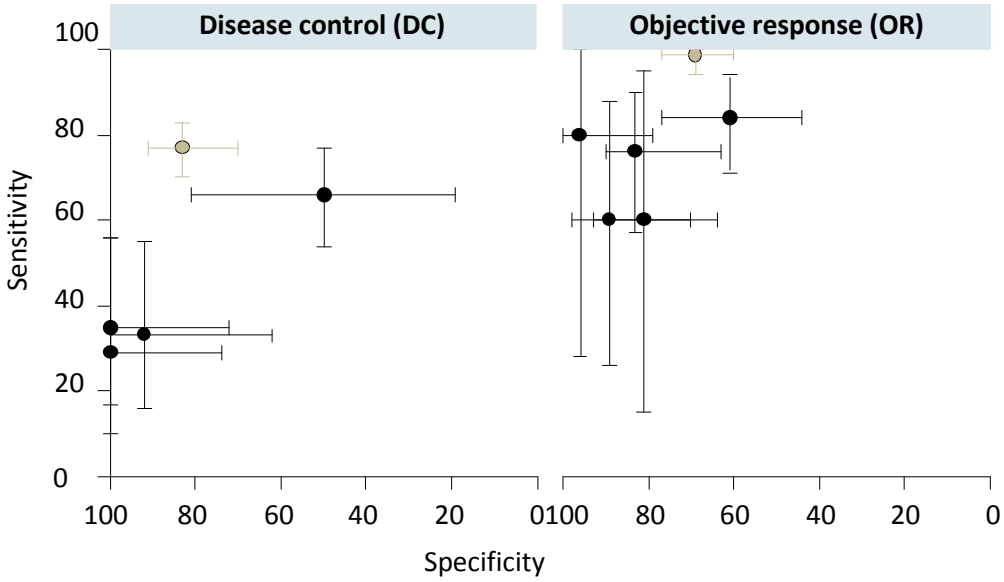


Table 8: Best response to treatment by mutation type in EGFR mutation positive patients treated with TKIs

Study	EGFR mutation	N	Best response			
			Complete response	Partial response	Stable disease	Progressive disease
[redacted]						
Giaccone(2006)[46]	exon 19 deletion only	5	0	4	1	0
Jackman(2007)[47]	exon 19 deletion only	3	0	2	1	0
	exon 21 L858R only	5	0	1	4	0
	exon 19 deletion & exon 21 L861Q	1	0	0	1	0
Yang(2008)[49]	exon 19 deletion only	20	0	19	0	1
	exon 21 L858R only	22	0	17	5	0
	exon 21 L861R	1	0	0	1	0
	exon 21 L858R & H850D	2	0	0	1	1
	exon 21 L861Q & R831H	1	0	0	1	0
	exon 20 SVD 786-770 insertions	3	0	1	0	2
	exon 21 L858R & exon 20 S768I	1	0	1	0	0
	exon 21 L858R & exon 20 T790M	1	0	0	0	1
	exon 21 L861Q & exon 20 R776H	1	0	0	1	0

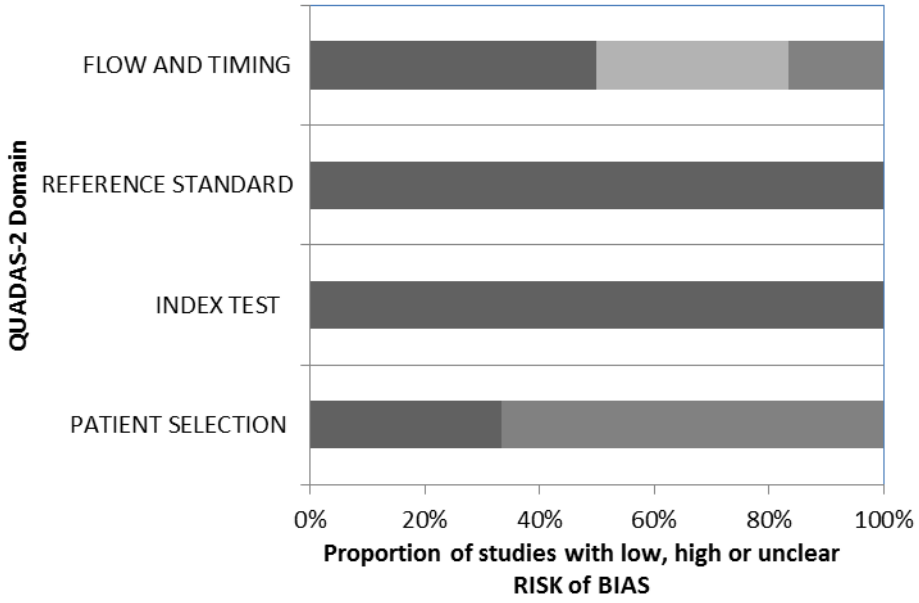
QUADAS-2 Assessments

All studies in this section were rated as 'low' risk of bias for the 'index test' and 'reference standard' domains of the quality assessment tool.[5,46-51] The two RCTs, IPASS[3,50] and first-SIGNAL,[5] were rated at 'low' risk of bias for participant selection; none of the other studies reported details of participant selection and consequently all were rated as 'unclear' risk of bias for this domain. Three studies had a 'high' risk of bias rating for any domain.[5,47,49] All of these were for the 'flow and timing' domain. For two cohorts the 'high' risk of bias rating arose because patients who were not evaluable for response were excluded from the analysis and these patients were judged to represent a significant proportion of the study population.[47,49] One RCT was rated as 'high' risk of bias for the 'flow and timing' domain because only a small proportion of trial participants were assessed for tumour EGFR mutation status, no reasons were reported for why participants were not assessed, and no information was available to assess possible differences between those with and without known mutation status. The results of QUADAS-2 assessments are summarised in Table 9 and Figure 5 below and full QUADAS-2 assessments for each study are provided in Appendix 3.

Table 9: QUADAS-2 results for studies assessing the accuracy of EGFR mutation testing methods for the prediction of response to treatment with TKIs

Study	RISK OF BIAS			
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Fukuoka(IPASS) (2011)[3, 50]	☺	☺	☺	☺
Giaccone(2006)[46]	?	☺	☺	☺
Han (fast-SIGNAL) (2012)[5]	☺	☺	☺	?
Jackman(2007)[47]	?	☺	☺	☹
Pallis(2012)[48]	?	☺	☺	☺
Yang(2008)[49]	?	☺	☺	☹

Figure 5: Summary of QUADAS-2 results



3.2.3 How do outcomes from treatment with EGFR receptor inhibitors vary according to which test is used to select patients for treatment?

Five RCTs provided data on the clinical effectiveness of TKIs compared to standard chemotherapy in patients with stage IIIB or IV NSCLC whose tumours tested positive for EGFR mutations,[1,2,4,5,50] and one additional study[6] reported data for a subgroup of patients from the EURTAC trial[2] whose samples had been re-analysed using a different EGFR mutation testing method (cobas® EGFR Mutation Test). The trials compared the TKIs gefitinib or erlotinib with various single agent or combination standard chemotherapy regimens (see Table 10). Three of the trials included only patients with EGFR mutation positive tumours,[1,2,4] and the remaining two trials (IPASS and first-SIGNAL) included chemotherapy naïve patients with stage IIIB or IV NSCLC and reported a subgroup analysis for patients who had received EGFR mutation testing.[3,5]

Study details

Participant characteristics varied across studies. Four studies were conducted in East Asia, one reported that it included >99% East Asian participants,[3] and three other studies did not report details of participant ethnicity, but were conducted entirely in Japan[4], China[1] and South Korea.[5] The remaining study was conducted in multiple centres across Spain and France and included almost entirely (>99%) Caucasian patients.[2] One study included only participants who had never smoked,[5] one study included mainly (94%) participants who had never smoked,[3] and the remaining studies included similar proportions of participants who had never smoked (range 62% to 71%).[1,2,4] One study included only participants with

adenocarcinoma,[5] and in the remaining studies approximately 90% of participants had a histological diagnosis of adenocarcinoma. Two studies reported the inclusion of very small numbers of participants with squamous cell carcinoma (n=5[4] and n=1[2]. The majority of participants (>75%) in all studies had stage IV disease. Full details of study participants are reported in Appendix 2.

The included trials used various methods to assess EGFR mutation status. Two studies, the EURTAC[2] and OPTIMAL[1] trials, used direct sequencing methods, however, both limited the definition of positive EGFR mutation status to the presence of an 'activating mutation' (exon 19 deletions or exon 21 mutation L858R). One additional study reported the results of a re-analysis of samples from the EURTAC study using the cobas® EGFR Mutation Test, which can detect 41 EGFR 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).[6] The remaining three studies also used EGFR mutation tests which targeted a wider range of mutations. The IPASS trial used version 1 of the Therascreen® EGFR PCR Kit, which detects 19 exon 19 deletions (does not distinguish between individual deletions), exon 21 point mutations L858R and L861Q, the exon 20 resistance mutation T790M, exon 20 mutation S768I, exon 18 mutations G719X (does not distinguish between G719S, G719A and G719C), and three exon 20 deletions.[3] The North East Japan Study Group trial used fragment length analysis, targeting exon 19 deletions, exon 21 point mutations (L858R, L861Q), exon 18 point mutations (G719A, G719C, G719S), exon 20 point mutation (T790M).[4] The first-SIGNAL trial used direct sequencing of exons 19 to 21.[5]

The primary outcome measure, reported by all studies, was progression-free survival (PFS), defined as the time from date of randomisation to when progression was first observed or death. Three studies reported intention-to-treat (ITT) analyses of PFS,[2,6,50] and three studies excluded withdrawals and patients who did not receive study treatments (four patients,[4] four patients[5] and 21 patients[1]); full details of withdrawals are reported as part of the risk of bias assessment (Appendix 3). With the exception of the re-analysis of samples from the EURTAC trial,[6] studies also reported response to treatment outcomes (DC and/or OR). All but one trial used the Response Evaluation Criteria In Solid Tumours (RECIST) criteria[27] to evaluate best observed response to treatment during the study period. The first-SIGNAL trial reported that response was evaluated according to the WHO criteria,[26] but provided no further details. Tumour response was assessed every six weeks,[1,2,50] every nine weeks,[5] or

every two months[4] until progression. Some limited data were also reported for CR and overall survival (OS).

Clinical outcomes in patients with EGFR mutation positive tumours who were treated with TKIs compared to those treated with standard chemotherapy

All studies in this section reported improvements in OR and improvements or trends towards improvement in PFS for patients with EGFR mutation positive tumours who were treated with TKIs compared to those treated with standard chemotherapy. There were no clear differences in treatment effect, regardless of which EGFR mutation test (selective for activating mutations exon 19 deletions and exon 21 L858R, or targeting a wider range of mutations) was used to select patients (see Figures 6 and 7). Based on subgroup analyses conducted within the trials, three trials reported no significant difference in the HR for PFS between patients with exon 19 deletions and those with the exon 21 mutation L858R.[2-4] However, the IPASS study also noted that, whilst the OR rate was higher in patients with exon 19 deletions who were treated with gefitinib (84.8%) than in those who were treated with standard chemotherapy (43.2%), there was no significant difference between the two treatment groups for patients with the exon 21 mutation L858R (OR rates were 60.9% and 53.2% for the gefitinib and standard chemotherapy groups, respectively).[3] One trial also reported that HRs for PFS did not differ significantly between patients with and without previous surgery, radiotherapy or adjuvant/neoadjuvant chemotherapy, by age, gender or performance status; sub-group analyses by smoking status indicated that the treatment effect in favour of gefitinib was significant only in patients who had never smoked (HR 0.24 (95% CI 0.15 to 0.39)).[2] One further trial noted that HRs for PFS appeared similar across all clinical subgroups (age, gender, performance status, disease stage, histology and smoking status).[1] However, the authors noted that the trial was not powered to detect differences between subgroups. Where reported the median PFS for participants with EGFR mutation positive tumours in the TKI group was 9.7 (95% CI 8.4, 12.3) months,[2] 10.8 months,[4] and 13.1 (95% CI: 10.6, 16.5) months.[1] The corresponding PFS values in the standard chemotherapy groups were 5.2 (95% CI: 4.3, 5.8) months,[2] 5.4 months,[4] and 4.6 (95% CI: 4.2, 5.4) months.[1] The OR rates for participants with EGFR mutation positive tumours in the TKI groups were 71% (94/132),[50] 58% (50/86),[2] 74% (84/114),[4] and 83% (68/82).[1] The corresponding OR rates in the standard chemotherapy groups were 47% (61/129),[50] 15% (13/87),[2] 31% (35/114),[4] and 36% (26/72).[1] Where DC was used as the outcome measure the observed benefits of TKI treatment were generally more marginal, but there were no clear differences between studies using different EGFR mutation testing methods (see Figure 8). Three studies reported

OS,[2-4] but none found a significant difference between patients treated with TKIs and those treated with standard chemotherapy (see Table 10). Four studies reported data on the number of patients with CR as the best observed response; the numbers of CR were small in all cases (2,[2] 2,[1] 3,[3] and 5[4] patients in the TKI groups and 1[50] patient in one standard chemotherapy group.

Figure 6: Progression-free survival in patients with EGFR mutation positive tumours who were treated with TKIs compared to those treated with standard chemotherapy

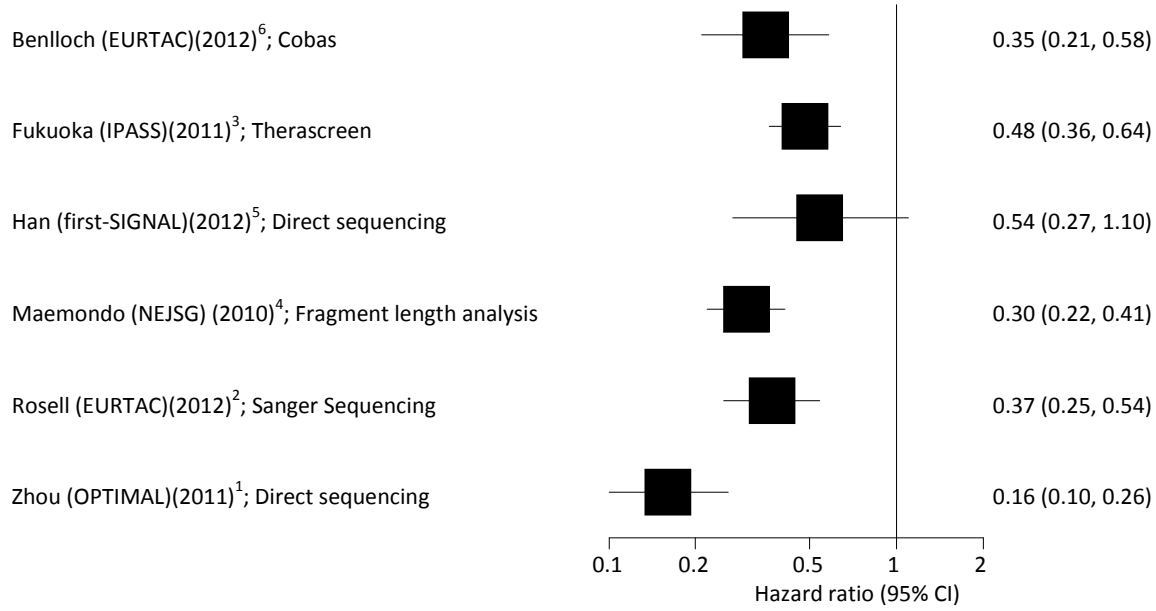


Figure 7: Objective Response in patients with EGFR mutation positive tumours who were treated with TKIs compared to those treated with standard chemotherapy

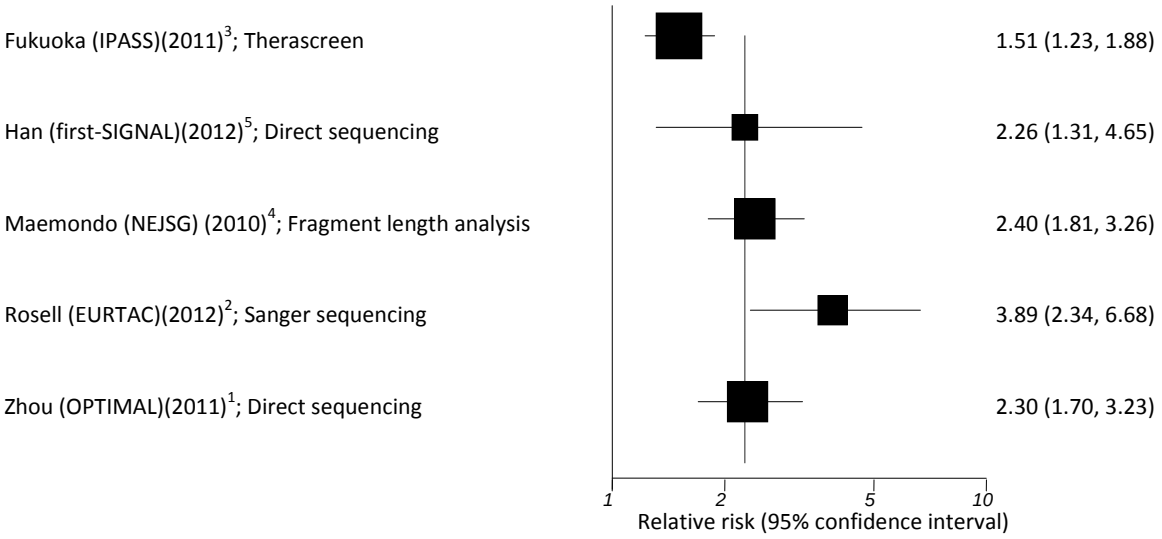
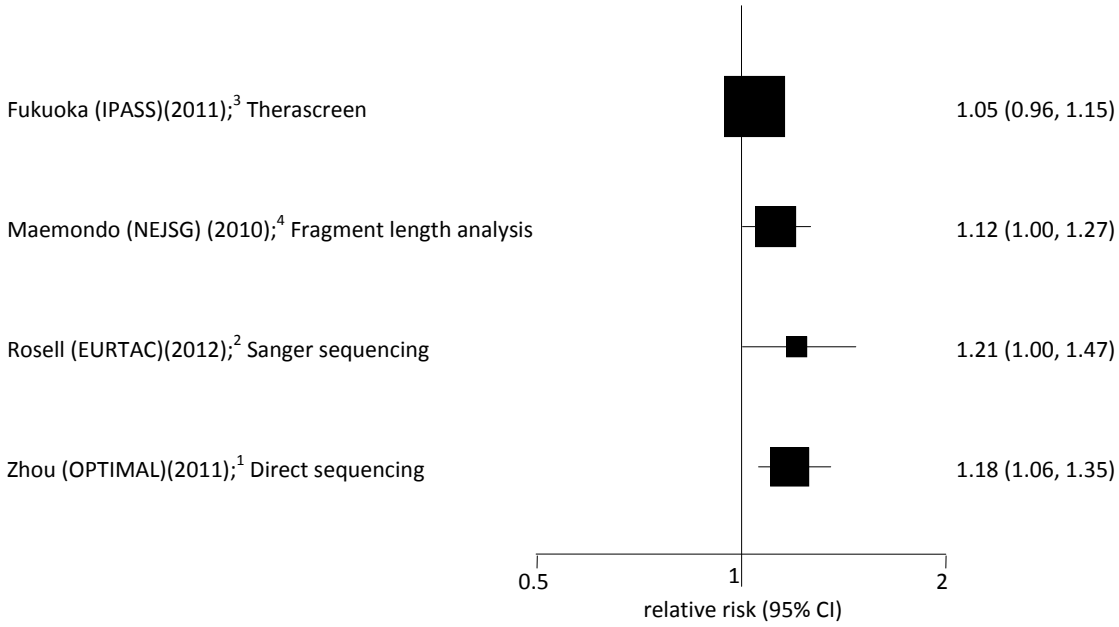


Figure 8: Disease control patients with in EGFR mutation positive tumours who were treated with TKIs compared to those treated with standard chemotherapy



Minimum sample requirements

The IPASS trial, which used version 1 of the Therascreen® EGFR PCR Kit, reported the minimum quantity of DNA required to detect 1% for each mutation targeted was 1.5ng for all mutations except insertions which required 3.0ng.[3] The study[6] that reported data for a subgroup of patients from the EURTAC trial[2] whose samples had been re-analysed using cobas® EGFR Mutation Test reported that the cobas® EGFR Mutation Test had a lower 'invalid rate' (8.8%) than Sanger sequencing (15.5%) and noted that the cobas® EGFR Mutation Test requires a total DNA input of 150ng. No other trial reported information on the limit of detection of the EGFR mutation test method used. Details of non-evaluable samples were generally poorly reported; any information reported is presented in Table 10.

Table 10: Effectiveness of TKIs compared with standard chemotherapy regimens in patients with a positive EGFR mutation test

Study	EGFR test and mutations targeted	Total number of participants (n) Non-evaluable samples	Intervention	Comparator	Outcome	Effect Estimate (95% CI)
Benlloch (EURTAC)(2012)[6]	cobas® EGFR Mutation Test Kit	n = 135 37 no tumour block available and 2 insufficient tumour material	Erlotinib	Cisplatin plus docetaxel or gemcitabine	PFS	HR 0.35 (0.21, 0.58)
Fukuoka (IPASS)(2011)[3, 50]	Therascreen® EGFR PCR Kit (version 1)	n =261 mutation positive subgroup Whole trial (n=1,217): 437 samples evaluable, 534 samples unavailable, 118 cytology samples excluded as the biomarker kit used was not validated for these samples, and 128 histology samples inadequate for testing.	Gefitinib	Carboplatin plus paclitaxel	PFS	HR 0.48 (0.36, 0.64)
					OS	HR 1.00 (.76, 1.33)
					DC	RR 1.05 (0.96, 1.15)
					OR	RR 1.51 (1.23, 1.88)
Han (first-SIGNAL)(2012)[5]	Direct sequencing (PCR) of all exon 19-21 mutations	n = 42 mutation positive subgroup Whole trial (n=313): 217 patients were not assessable for tumour EGFR mutation status (reasons NR)	Gefitinib	Gemcitabine plus cisplatin	PFS	HR 0.54 (0.27, 1.10)
					OS	HR 1.04 (0.50, 2.18)
					OR	RR 2.26 (1.31, 4.65)
Maemondo (NEJSG)(2010)[4]	Fragment length analysis; exon 19 deletions, exon 21 point mutations (L858R, L861Q), exon 18 point mutations (G719A, G719C, G719S), exon 20 point mutation (T790M).	n = 227 None reported	Gefitinib	Carboplatin plus paclitaxel	PFS	HR 0.30 (0.22, 0.41)
					OS	HR 0.89 (0.63, 1.24)
					DC	RR 1.12 (1.00, 1.27)
					OR	RR 2.40 (1.81, 3.26)
Rosell (EURTAC)(2012)[2]	Sanger sequencing; exon 19 deletions and exon mutation 21 L868R	n = 150 None reported	Erlotinib	Cisplatin plus docetaxel or gemcitabine	PFS	HR 0.37 (0.25, 0.54)
					OS	HR 1.04 (0.65, 1.68)
					DC	RR 1.21 (1.00, 1.47)
					OR	RR 3.89 (2.34, 6.68)
Zhou (OPTIMAL)(2011)[1]	Direct sequencing (PCR-based); exon 19 deletions and exon mutation 21 L868R	n =154 None reported	Erlotinib	Carboplatin plus gemcitabine	PFS	HR 0.16 (0.10, 0.26)
					DC	RR 1.18 (1.06, 1.35)
					OR	RR 2.30 (1.70, 3.23)

CI: confidence interval; CR: complete response; DC: disease control; NR: not reported; OR: objective response; OS: overall survival; PFS: progression-free survival; [a]: confidence interval calculated from exact p value

Clinical outcome for studies that provided data for patients according to EGFR mutation test status

The results of the IPASS subgroup analyses indicated that PFS was significantly longer for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation positive subgroup (HR 0.48 (95% CI: 0.36, 0.64)) and significantly shorter for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation negative subgroup (HR 2.85 (95% CI: 2.05, 3.98)),[50] whilst results in the subgroup with unknown mutation status were similar to those observed form the whole study population (HR 0.68 (95% CI: 0.58, 0.81) and HR 0.75 (95% CI: 0.65, 0.85), respectively). The results of the first-SIGNAL subgroup analyses showed a trend towards longer PFS for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation positive subgroup (HR 0.54 (95% CI: 0.27, 1.10)) and a trend towards and significantly shorter PFS for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation negative subgroup (HR 1.42 (95% CI: 0.82, 2.47)); the small size of the EGFR mutation tested subgroup in this study is reflected in the wide confidence intervals around these estimates.[5]

In the IPASS trial, the OR rates for mutation negative participants were 1% (1/91) for the TKI group and 24% (20/85) for the standard chemotherapy group, and for participants whose mutation status was unknown the OR rates were 43% (167/386) for the TKI group and 29% (115/394) for the standard chemotherapy group. The first-SIGNAL trial reported similar data on OR rates for participants whose tumours tested negative for EGFR mutations (26% (7/27) for the TKI group and 52 (14/27) for the standard chemotherapy group).[5]

Risk of Bias

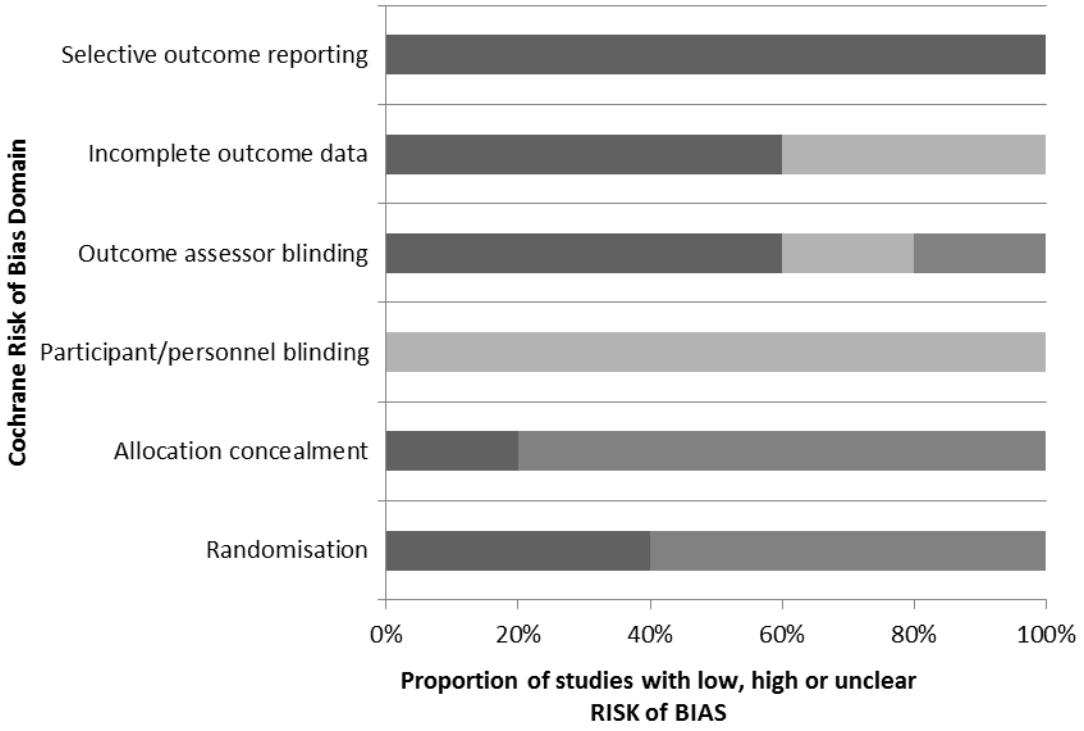
All studies in this section were rated as 'low' or 'unclear' risk of bias for randomisation, allocation concealment and selective outcome reporting. All studies were rated as 'high' risk of bias for blinding of study participants and personnel; blinding of study participants and personnel was not possible in these trials, because of the different routes of administration used for the treatment and comparator arms (oral TKI versus i.v. standard chemotherapy). However, only one study was rated as 'high' risk of bias for blinding of outcome assessors;[1] three studies reported independent outcome assessment,[2,4,5] and the remaining study did not report details of outcome assessor blinding.[3,50] With the exception of the OPTIMAL[1] and first-SIGNAL[5] trials, all studies were rated as 'low' risk of bias for incomplete reporting of outcome data; all other studies either reported ITT analyses,[2,3] or very small numbers of withdrawals (<2% of the total study population).[4] For risk of bias assessment, EURTAC trial[2]

and the re-analysis of the EURTAC trial were treated as one study. The results of risk of bias assessments are summarised in Table 11 and Figure 9 below and full risk of bias assessments for each study are provided in Appendix 3.

Table 11: Risk of bias assessments for RCTs providing data on how the effectiveness of TKIs varies according to which EGFR mutation test is used to select patients for treatment

Study	**RISK OF BIAS**					
	Randomisation	**Allocation concealment**	**Participant and personnel blinding**	**Outcome assessor blinding**	**Incomplete outcome data**	**Selective outcome reporting**
Fukuoka (IPASS)(2011)[4, 50]	?	?	☹	?	☺	☺
Han (fast-SIGNAL) (2012)[3]	?	?	☹	☺	☹	☺
Maemondo (NEJSG)(2010)[5]	?	?	☹	☺	☺	☺
Rosell (EURTAC)(2012)[2]/Benlloch(2012)[6]	☺	?	☹	☺	☺	☺
Zhou (OPTIMAL)(2011)[1]	☺	☺	☹	☹	☹	☺

Figure 9: Summary of risk of bias assessments



4. ASSESSMENT OF COST-EFFECTIVENESS

This chapter explores the cost-effectiveness of the use of different EGFR mutation tests to decide between standard chemotherapy and EGFR TKIs in patients with previously untreated locally advanced or metastatic non-small-cell lung cancer.

4.1 Review of economic analyses of EGFR mutation testing

4.1.1 Search strategy

Searches were undertaken to identify cost-effectiveness studies of EGFR-TK testing in non-small cell lung cancer. As with the clinical effectiveness searching, the main Embase strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the PRESS-EBC checklist.[32] Search strategies were developed specifically for each database and searches took into account generic and other product names for the intervention. All search strategies are reported in Appendix 1.

The following databases were searched for relevant studies from 2000 to present:

- MEDLINE (OvidSP) (2000-2012/09/wk4)
- MEDLINE In-Process Citations and Daily Update (OvidSP) (2000-2012/08/29)
- EMBASE (OvidSP) (2000-2012/wk 34)
- NHS Economic Evaluation Database (NHS EED) (via Cochrane Library) (2000-2012/Issue 3)
- Health Economic Evaluation Database (HEED) (Wiley) (2000-2012/08/30) http://onlinelibrary.wiley.com/book/10.1002/9780470510933
- Science Citation Index (SCI) (Web of Science) (2000-2012/08/29)

Additional searches were undertaken to update the Resource Utilisation searches in the Manufacturer's submission for STA 192.[52] For this work, the following resources were searched:

- MEDLINE (OvidSP) (2000-2012/09/wk4)
- MEDLINE In-Process Citations and Daily Update (OvidSP) (2000-2012/08/29)
- EMBASE (OvidSP) (2000-2012/wk 40)
- NHS Economic Evaluation Database (NHS EED) (Internet) (2009-2012/08/30) http://www.crd.york.ac.uk/crdweb/
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO) (2009-2012/08/24)

Identified references were downloaded in Endnote X4 software for further assessment and handling.

References in retrieved articles were checked for additional studies.

4.1.2 Inclusion criteria

Studies reporting a full economic analysis, which related explicitly to the test-treat combination of EGFR mutation testing and treatment with EGFR TKIs, were eligible for inclusion. Specifically, one of the comparators included EGFR mutation testing and for this comparator the treatment decision was guided by the test result; patients whose tumour was EGFR-mutation negative were also included in the treatment pathway.

4.1.3 Results

The search retrieved 606 references. Studies were independently assessed for inclusion by two health economists (BR and AvA) and any disagreements were resolved by discussion. After initial screening of titles and abstracts four studies remained, all of which were published as conference abstracts only. During the course of the assessment we identified two additional studies, one published as a conference abstract only and one published as a full paper and a conference abstract; the latter did not fully meet our inclusion criteria, as it concerned second-line treatment of advanced NSCLC with erlotinib. In total, six studies were included, of which only one was published as a full paper. A summary of the full paper by Borget et al[53] is provided in Table 12 with a quality checklist based on Drummond et al[54] in Table 13. A condensed summary of the conference abstracts is provided in Table 14.

Borget et al[53] developed a Markov model to compare three hypothetical strategies for second-line treatment with erlotinib in patients with NSCLC in whom at least one platinum-based chemotherapy regimen had failed and who were eligible for erlotinib or chemotherapy.

The three hypothetical strategies were:

1) no patient selection, all patients receive erlotinib
2) clinically guided, patients with favourable clinical features (female never smokers with adenocarcinoma) receive erlotinib, others receive docetaxel
3) biologically guided, patients with known EGFR mutations received erlotinib, others receive docetaxel

Clinical inputs were derived from individual patient data in the ERMETIC study[55] and the GFPC0506 study.[56] Utilities were derived from population-based studies of advanced NSCLC performed in the UK.[57] Total costs included the following categories: chemotherapy drugs, erlotinib, supportive treatments (including treatment for adverse events), transfusion and hospitalisation for any reason, costs after progression and palliative care.

Total QALYs were 0.478, 0.558, and 0.559 for the no selection, clinically guided and biologically guided strategies, respectively. The respective total costs were €21,025, €16,005 and €15,210. The no selection strategy was both the least effective and the most expensive. The biologically and clinically guided strategies had comparable effectiveness, but the biologically guided strategy was slightly less expensive. Results were robust in the sensitivity analyses.

Although this study was of good quality, it does not match our decision problem as it concerns second-line use of EGFR TKIs, whereas this assessment concerns first-line treatment with TKIs. The conference abstracts identified all concern the first-line use of TKIs, but not provide sufficient information to be of use. However, as all were relatively resent, more informative full publications may follow.

Table 12: Summary of included full publications of economic analyses

Study details	Borget et al[53]
Population	Patients with advanced NSCLC in whom at least one platinum-based chemotherapy regimen had failed and who were eligible for erlotinib or chemotherapy
Time horizon	30 months
Objective	To compare the cost-effectiveness ratios of three hypothetical strategies for NSCLC
Source of effectiveness information	1) ERMETIC study: multicentre French cohort of 522 patients treated with 2nd line erlotinib 2) GFPC0506 study: randomised multicentre trial in France with 75 patients in each arm comparing docetaxel and pemetrexed
Comparators	1) no selection: all patients receive erlotinib 2) clinically guided: female never smokers with adenocarcinoma receive erlotinib, all others receive docetaxel 3) biologically guided: patients with known EGFR mutations receive erlotinib, patients with negative/unknown mutation status receive docetaxel
Unit costs	Source unclear, probably French healthcare payer?
Measure of benefit	QALYs
Study type	Cost-utility analysis: Markov model
Model assumptions	Patients who progressed were assumed to receive palliative care until death
Perspective	French healthcare payer
Discount rate	3% for costs only
Uncertainty around cost-effectiveness ratio expressed	Yes, in numbers for one way sensitivity analyses, in iCE planes and CEACs for PSA
Sensitivity analysis	One way sensitivity analyses (selection criteria for 2nd strategy, prevalence of EGFR mutation, biological testing cost, post-progression cost, erlotinib tariff), and PSA
Outcome (cost and Lys/QALYs) per comparator	No selection: 0.478 QALY €21,025 Clinically guided: 0.558 QALY € 16,005 Biologically guided: 0.559 QALY € 15,210
Summary of incremental analysis	The biologically and clinically guided strategies were dominant, but the biological strategy was slightly less expensive than the clinical strategy

Table 13: Checklist of study quality for economic analyses

	Borget et al 2012[53]
Study design	
The research question is stated	√
The economic importance of the research question is stated	√
The viewpoint(s) of the analysis are clearly stated and justified	√
The rationale for choosing alternative programmes or interventions compared is stated	√
The alternatives being compared are clearly described	√
The form of economic evaluation used is stated	√
The choice of form of economic evaluation is justified in relation to the questions addressed	√
Data collection	
The source(s) of effectiveness estimates used are stated	√
Details of the design and results of effectiveness study are given (if based on a single study)	√
Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	NA
The primary outcome measure(s) for the economic evaluation are clearly stated	√
Methods to value benefits are stated	√
Details of the subjects from whom valuations were obtained were given	√
Productivity changes (if included) are reported separately	NA
The relevance of productivity changes to the study question is discussed	X
Quantities of resource use are reported separately from their unit costs	X
Methods for the estimation of quantities and unit costs are described	√
Currency and price data are recorded	X
Details of currency of price adjustments for inflation or currency conversion are given	X
Details of any model used are given	√
The choice of model used and the key parameters on which it is based are justified	√
Analysis and interpretation of results	
Time horizon of costs and benefits is stated	√
The discount rate(s) is stated	√
The choice of discount rate(s) is justified	X
An explanation is given if costs and benefits are not discounted	NA
Details of statistical tests and confidence intervals are given for stochastic data	√
The approach to sensitivity analysis is given	√
The choice of variables for sensitivity analysis is justified	√
The ranges over which the variables are varied are justified	√
Relevant alternatives are compared	√

	Borget et al 2012[53]
Incremental analysis is reported	√
Major outcomes are presented in a disaggregated as well as aggregated form	X
The answer to the study question is given	√
Conclusions follow from the data reported	√
Conclusions are accompanied by the appropriate caveats	√

Table 14: Summary of included abstracts for economic analyses

Study details	Arrieta 2010[58]	Chen 2011[59]	Jacob 2011[60]	Lopes 2011[61]	Shiroiwa 2012[62]
Population	Patients with advanced NSCLC	Patients with advanced NSCLC in Ontario	Patients with NSCLC in Sweden	Patients with advanced NSCLC	Patients with NSCLC in Japan
Objective	Assess cost-effectiveness of EGFR mutation testing	Assess the cost-effectiveness of EGFR mutation testing to guide first-line gefitinib treatment	Evaluate the cost-effectiveness of a treatment strategy with gefitinib based on data from the IPASS trial[50]	Determine the cost-effectiveness of EGFR mutation testing and first-line treatment with Gefitinib for patients with EGFR +ve tumours	Not stated
Comparators	1)Gefitinib for EGFR-positive and carboplatin-paclitaxel for EGFR-negative 2)No test: all patients receive carboplatin-paclitaxel	1)testing strategy, EGFR+ would receive gefitinib, (EGFR- not clear, presumably conventional chemotherapy) 2)no testing strategy, all patients would receive conventional chemotherapy	1)EGFR testing, gefitinib for EGFR+ patients and doublet chemotherapy for EGFR- patients 2)No EGFR testing, doublet chemotherapy for all patients	1)EGFR testing: 1st line Gefitinib for EGFR+ patients, not clear what treatment for EGFR- is, presumably standard care 2)standard care: 1st line chemotherapy, 2nd line gefitinib	1)gefitinib treatment for all patients, without testing 2)carboplatin-paclitaxel for all patients, without testing 3)EGFR testing, gefitinib for EGFR+ patients and carboplatin-paclitaxel for EGFR- patients
Method of analysis	Discrete Event Simulation/Markov model	Decision analytic model	Markov model	Markov model	Not stated
Measure of benefit	Progression free months	Lifeyears, QALYs	QALYs	QALY	Life Years
Outcome (cost and Lys/QALYs)	Progression free months 7.57 in testing strategy, 7.11 in no testing strategy. Costs not stated.	Not specified	Not specified	Not specified	Not specified

Summary of incremental analysis	ICER of testing vs. no testing: $1,379.49 per progression free month gained.	ICER for testing vs. no testing $46,021 per LY and $81,071 per QALY gained.	Test and treat strategy associated with a QALY gain of 0.0116 at an IC of €300. ICER for test and treat strategy was €25,900.	EGFR testing and first-line treatment with gefitinib was found to be dominant compared to standard care	ICER of 1) vs. 3) was $12,000 ICER of 2) vs. 3) was $46,500.*
IC: incremental cost; ICER incremental cost-effectiveness ratio; LY: life year; NSCLC: non-small-cell lung cancer; QALY: quality adjusted life year *: If the cost of EGFR testing is increased these ICERs also increase, so the comparators may be in the wrong order and should probably be 3) vs. 1) and 3) vs. 2) respectively.					

4.2 Model structure and methodology

4.2.1 EGFR-TK mutation tests considered in the model

In the health economic analysis, the cost-effectiveness of different methods for EGFR-TK mutation testing to decide between standard chemotherapy and anti-EGFR TKIs in patients with locally advanced or metastatic NSCLC was assessed. A range of methods for EGFR-TK mutation testing are currently used in NHS laboratories in England and Wales.

Ideally, the performance of these tests would be assessed against an objective measure of the true presence/absence of a clinically relevant EGFR-TK mutation (the 'reference standard'). Comparative effectiveness of treatment (TKI versus chemotherapy) conditional upon the true or false presence/absence of the EGFR-TK mutation could then be determined. However, each different testing method targets a different range of mutations and has different limits of detection (lowest proportion of mutation detectable in tumour cells) and the exact combination of mutation type and level which will provide optimal treatment selection remains unclear. For this reason, assessment of test performance based on comparison with a conventional 'reference standard' is currently not possible. In this situation, an alternative way to determine the relative value of diagnostic methods for EGFR-TK mutation testing is to use studies that report on the comparative treatment effect in patients with different EGFR mutation status (positive, negative, or unknown) as defined using different EGFR mutation tests. As outlined in the previous chapter information on comparative effectiveness (progression free survival (PFS) and overall survival (OS)) of TKI and chemotherapy in patients with mutation positive, mutation negative and mutation unknown tumours, were only available for the Therascreen® EGFR PCR Kit[3, 50] and in patients with mutation positive and mutation negative tumours for one type of direct sequencing (direct sequencing of all exon 19-21 mutations).[5] A major assumption underlying the use of these data in the health economic modelling is, however, that the difference in comparative treatment effect between the two treatments (e.g. TKI versus chemotherapy) is solely due to the use of different mutation tests. Although direct sequencing of all exon 19-21 mutations is not listed in the scope, it was included in the analyses because of lacking effectiveness and/or survival data on other direct sequencing methods.

In absence of evidence on the comparative treatment effect in patients with different EGFR mutation status as defined using different EGFR mutation tests, one could consider the accuracy of different EGFR mutation tests for the prediction of response to treatment with TKIs; in this case, response to treatment with TKIs serves as a clinical reference standard.

This type of accuracy data were available for two other direct sequencing tests (direct sequencing of all exon 18-21 mutations[49] and direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells) of all exon 18-24 mutations[47]). These studies provided no data on the relative PFS and/or OS separately for patients with mutation positive and mutation negative tumours. Therefore, evidence available on the relative PFS and OS for mutation positives and mutation negatives as observed for direct sequencing of all exon 19-21 mutations, was 'linked' to direct sequencing of all exon 18-21 mutations[49] and direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells). Again, although the test strategy direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells) is not listed in the scope, it was included in the analysis because it was the only test for which information on the proportion of patients with unknown mutations status was available.

For the remaining EGFR mutation tests listed in the scope, no accuracy data or information to predict (relative) treatment response, PFS or OS in mutation positive patients (after treatment with TKIs), and mutation negative patients or patients with unknown mutation status (after treatment with doublet chemotherapy) were available. As a result, for the remaining tests, it was only possible to make a comparison based on differences in technical performance and test costs retrieved from the online survey of NHS laboratories in England and Wales (Section 3.2.1), whilst assuming equal prognostic value across tests. The latter assumption was not based on evidence of equality, but rather absence of any reliable evidence to model a difference in prognostic value for these tests.

Based on the information available to us, three analyses were performed:

- 'evidence on comparative effectiveness available' analysis: Therascreen® EGFR PCR Kit compared with direct sequencing of all exon 19-21 mutations in order to estimate cost and QALYs using the observed response to treatment and relative PFS and OS data. Information on relative (Hazard ratio of TKI versus chemotherapy) progression free survival (PFS) and overall survival (OS), in mutation positive and mutation negative is not available for other tests. Therefore, in this analysis direct sequencing of all exon 19-21 mutations was used as the closest approximation available to the comparator listed in the scope (direct sequencing of all exon 18-21 mutations).
- 'linked evidence' analysis: In this analysis, besides Therascreen® EGFR PCR Kit compared with direct sequencing of all exon 19-21 mutations, two other direct sequencing tests (direct sequencing of all exon 18-21 mutations and direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)) for which

accuracy data to predict response to treatment were available were included. This was based on the assumption that for the latter two direct sequencing methods, the relative PFS and OS for mutation positives and mutation negatives correlate perfectly with relative PFS and OS as observed for direct sequencing of all exon 19-21 mutations.

- 'assumption of equal prognostic value' analysis: For all tests for which information on cost and/or technical performance were available from the online survey. This includes the tests for which neither comparative effectiveness nor response data were available. In this analysis we assessed whether the tests were likely to be cost effective given an assumption of equal prognostic value and test specific information on cost and failure rate only. The equal prognostic value assigned was based on data for the Therascreen® EGFR PCR Kit, as this was the only test for which prognostic data were available on patients with positive, negative and unknown mutation status. In addition, other tests used in NHS laboratories in England and Wales were considered to have technical characteristics (low limit of detection and similar proportion of tumour cells required for analysis) which were more similar to this test than to direct sequencing methods and would therefore be more likely to have similar prognostic value to the Therascreen® EGFR PCR Kit than to direct sequencing. The following tests were included in this analysis:
    - Therascreen® EGFR PCR Kit
    - Direct sequencing of exon 19-21
    - Direct sequencing or WAVE-HS for samples with insufficient tumour cells
    - Direct sequencing of exon 18-21
    - Fragment length analysis combined with pyrosequencing
    - Sanger sequencing and Fragment length analysis / PCR of negative samples
    - Roche Cobas test
    - High resolution melt analysis
    - Single strand conformation analysis
    - Sanger sequencing or Roche Cobas for samples with insufficient tumour cells
    - Sanger sequencing or Therascreen® for samples with insufficient tumour cells
    - Next generation sequencing
    - Therascreen® and Pyrosequencing Kit

Direct sequencing of all exon 18-21 mutations was taken as the comparator in the 'linked evidence' and 'assumption of equal prognostic value' analyses.

4.2.2 Consistency with related assessments

This assessment does not update the appraisal of gefitinib for the first line treatment of locally advanced or metastatic NSCLC.[7] In order to ensure consistency between the modelling approach used in Technology Appraisal 192 and the assessment of the cost-effectiveness of different methods for EGFR-TK mutation testing in this report, the assessment group received the health economic model submitted by Astra Zeneca for Technology Appraisal 192. This model calculates the expected cost-effectiveness of gefitinib compared to doublet chemotherapy for the first-line treatment of locally advanced or metastatic NSCLC patients with a positive EGFR mutation test based on Therascreen® EGFR PCR Kit. This model, together with the amendments suggested and made by the ERG, was used to inform the development of a de novo model in which the long term consequences of using different EGFR mutation tests were assessed not only in patients with a positive EGFR mutation test, but also in patients with a negative test result, or an unknown test result. The assessment group tested the consistency between the de novo model, the Astra Zeneca model, and the amendments made by the ERG. We compared the results of patients with a positive EGFR mutation test using Therascreen® EGFR PCR Kit with the initial manufacturer's submission. Subsequently, the ERG amendments were incorporated and ICERs from the de novo model were compared with ICERs as reported in the final appraisal determination of STA 192 (see Appendix 6 for results). Furthermore, the health economic analysis did not assess any differences between different TKIs.

4.2.3 Model structure

In the health economic model the mean expected costs, life years and quality adjusted life years (QALYs) were calculated for each alternative.

The health economic analysis considers the long-term consequences of technical performance and accuracy of the different tests/test combinations followed by treatment with either standard chemotherapy or a TKI in patients with NSCLC. For this purpose a decision tree and a Markov model were developed. The decision tree was used to model the test result (positive, negative or unknown) and the treatment decision. Patients with a positive test result receive an anti-EGFR TKI. It is assumed that patients with a negative test result or unknown EGFR mutation status will receive doublet chemotherapy (Pemetrexed and Cisplatin), as the negative consequences of treatment with TKIs in false positives are

greater than the negative consequences of treatment with doublet chemotherapy in false negatives.[50] The decision tree is shown in Figure 10.

The long-term consequences in terms of costs and QALYs were estimated using a Markov model with a cycle time of 21 days (resembling the duration of one cycle of chemotherapy), and a time horizon of six years. Health states in the Markov model are: progression free (subdivided into 'response' and 'stable disease'), disease progression and death. In the progression-free state, patients are on treatment (either TKI or doublet chemotherapy). In each cycle these patients are subdivided over the 'stable disease' and 'response' states, based on the objective response rate, in order to account for a difference in quality of life between those states. In addition, disutilities and costs associated with treatment related characteristics (intra-venous or oral therapy) are modelled. For adverse events of treatment, disutilities and costs were applied for a single cycle in the model. The Markov model structure is shown in Figure 11. The model is described in more detail in NICE Technology Appraisal 192.[7]

4.2.4 Model parameters

Estimates for model input parameters were retrieved from NICE Technology Appraisal 192,[52] the assessment of the clinical effectiveness of different EGFR mutation tests (Sections 3.2.2 and 3.2.3), an online survey of NHS laboratories in England and Wales (Section 3.2.1), and the Personal Social Services Research Unit.[63]

Figure 10: Decision tree structure

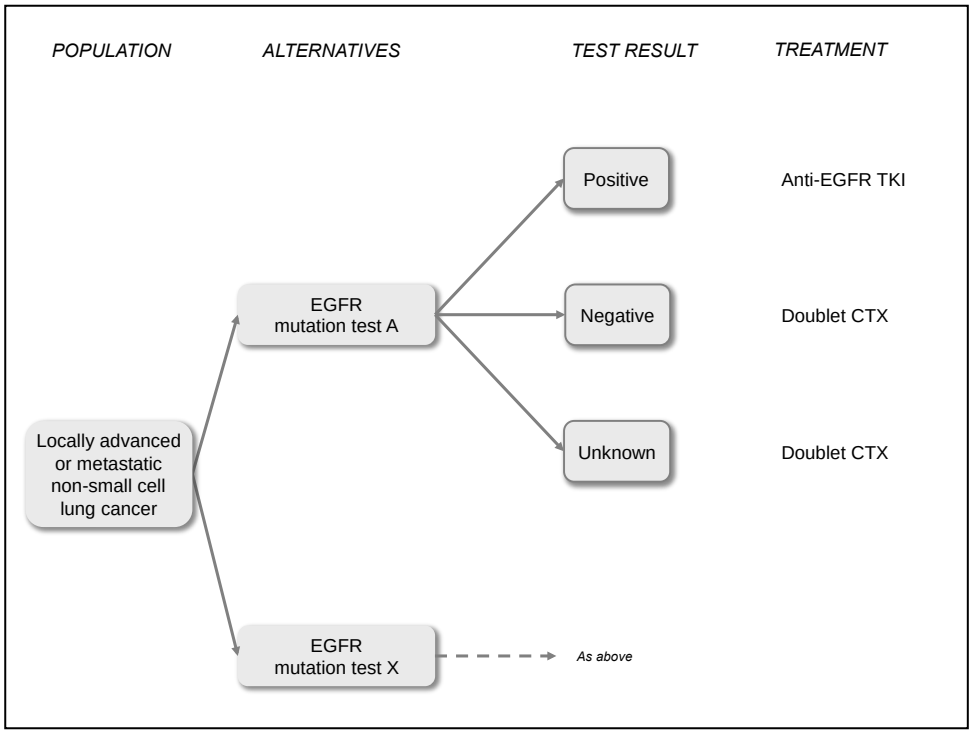
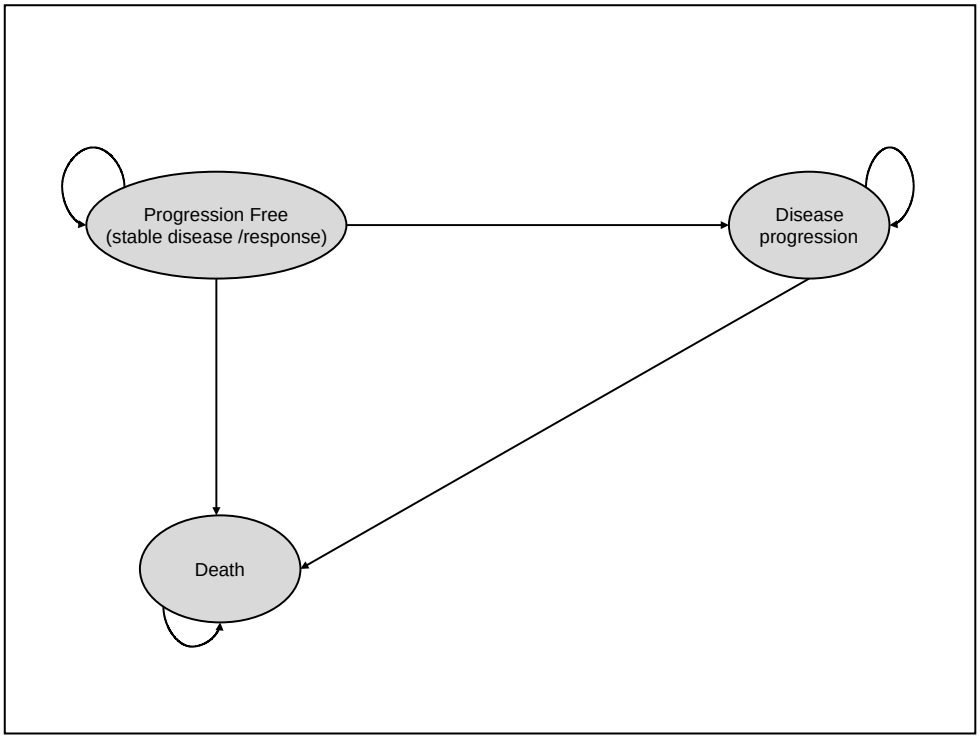


Figure 11: Markov model structure



Test result

The proportions of test failures for the EGFR mutation tests were based on the online survey of NHS laboratories in England and Wales. The proportions of positive and negative test results were based on the estimated proportions of EGFR mutation positive patients in England and Wales (16.6%, standard error: 0.8%),[64] the test accuracy (sensitivity and specificity with objective response to TKI as reference standard, see Table 7 Section 3.2.2) and the proportion of patients with an unknown test result. The proportions of patients with an unknown test result were based on the proportions of patients without mutation status relative to the number of patients for whom a tissue sample was available in the trials. As the trials do not represent clinical practice, this might be an overestimation of the proportion of patients with an unknown test result in clinical practice. One possible reason for this is that in the trials the tissue samples were not generally taken for the purpose of EGFR mutation testing, and may therefore have been inadequate more often than would be the case in current clinical practice. In contrast, the results of the online survey of reference laboratory in England and Wales are likely to provide an underestimation of the total proportion of patients with an unknown test result, as the reference laboratories are not likely to have insight in the total proportion of pre-test failures (samples considered inadequate by the pathologist and therefore not sent to the laboratory). In the base case

analysis the proportion of patients with an unknown test result was based on the literature, while in a sensitivity analysis the results of the online survey were used.

The proportion of true positives (TP), true negatives (TN), false negative (FN) and false positive (FP) test results were calculated by:

TP = proportion of mutation positives × sensitivity × (1 – proportion of unknown tests)

TN = (1 – proportion of mutation positives) × specificity × (1 – proportion of unknown tests)

FN = proportion of mutation positives × (1 – sensitivity) × (1 – proportion of unknown tests)

FP = (1 – proportion of mutation positives) × (1 – specificity) × (1 – proportion of unknown tests)

Subsequently, the proportions of patients with a mutation positive (TP + FP), mutation negative (TN + FN) test result were calculated. The results are listed in Table 15 and Table 16.

Table 15: Input parameters used to calculate the proportion of patients with positive test result, unknown test result and negative test result

Input parameter (Estimated value (se))			**Distribution**	**Source**
Proportion of EGFR mutation positive patients in England and Wales				
Proportion of mutation positives	16.6% (0.8%)		Beta	Rosell 2009[64]
Test accuracy	**Sensitivity**	**Specificity**		
Therascreen	98.9% (1.0%)	68.9% (4.2%)	Beta	Mok 2009[50]
Direct sequencing of all exon 19-21 mutations	75.9% (7.8%)	83.3% (7.5%)	Beta	Han 2012[5]
Direct sequencing of all exon 18-21 mutations	84.4% (5.3%)	61.1% (8.0%)	Beta	Yang 2008[49]
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)	60.0% (20.0%)	81.3% (6.8%)	Beta	Jackman 2007[47]
Probability of unknown test result				
Therascreen	22.7% (1.8%)		Beta	Mok 2009[50]
Direct sequencing of all exon 19-21 mutations	Assumed equal to Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)			
Direct sequencing of all exon 18-21 mutations	Assumed equal to Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)			
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)	37.7% (5.8%)		Beta	Jackman 2007[47]

Table 16: Probability of positive test result, unknown test result and negative test result

Mutation test	**Probability (se) of test result**[a]		
	Positive	**Unknown**	**Negative**
Therascreen	32.8% (2.9%)	22.7% (1.8%)	44.6% (3.0%)
Direct sequencing of all exon 19-21 mutations	16.5% (4.2%)	37.7% (5.2%)	45.8% (5.5%)
Direct sequencing of all exon 18-21 mutations	29.0% (4.6%)	37.7% (4.2%)	33.4% (4.8%)
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)	16.0% (4.4%)	37.7% (5.8%)	46.4% (6.0%)

se: standard error

[a] Standard error is based on probabilistic sensitivity analysis.

In the third analysis ('assumption of equal prognostic value'), the probability of positive, unknown and negative test results were assumed to be equal to the Therascreen® EGFR PCR Kit for all tests. This assumption was relaxed in a sensitivity analysis.

Response to treatment

Patients who are in the progression-free state are subdivided over the 'stable disease' and 'response' states based on the objective tumour response rate. For patients with positive test results, the objective tumour response rate after treatment with TKIs (Table 17) was used and the objective tumour response rate after treatment with doublet chemotherapy was used for the remaining patients (negative or unknown test results).

Table 17: Objective response rate

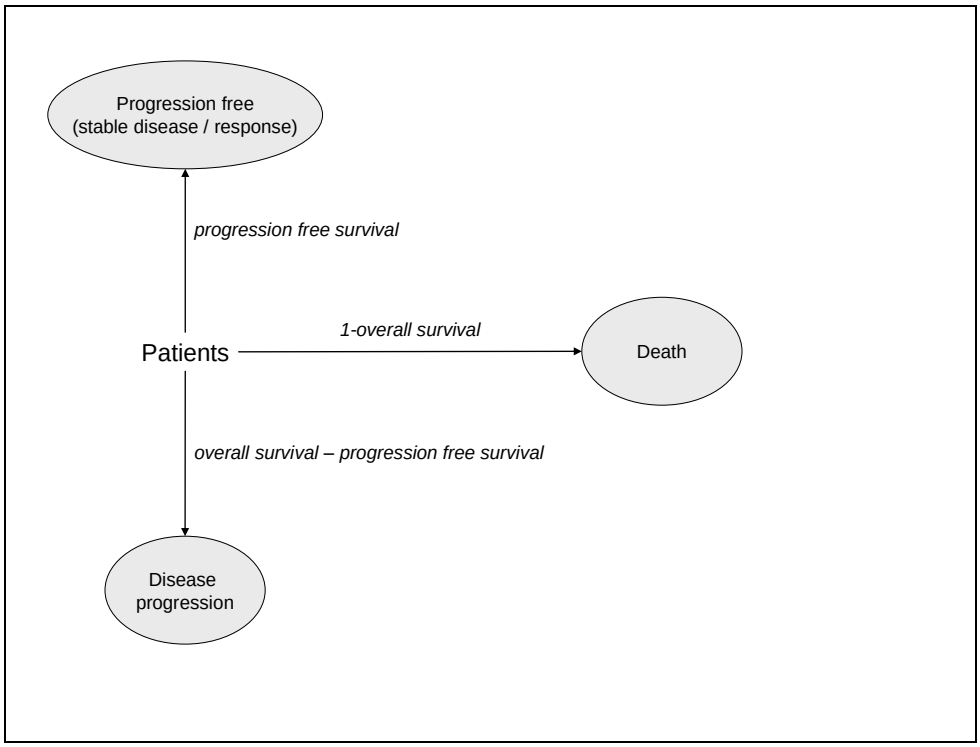
Mutation test	**Objective response rate (se)[a,b]**			**Source**
	Positive	Unknown	Negative	
Therascreen® EGFR PCR Kit	0.712 (0.039)	0.292 (0.023)	0.235 (0.046)	Mok 2009[50]
Direct sequencing of all exon 19-21 mutations	0.846 (0.069)	As for Therascreen® EGFR PCR Kit	0.484 (0.098)[c]	Han 2012[5]
Direct sequencing of all exon 18-21 mutations	0.731 (0.061)	As for Therascreen® EGFR PCR Kit	As direct sequencing of all exon 19 - 21	Yang 2008[49]
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)	0.333 (0.149)	As for Therascreen® EGFR PCR Kit	As direct sequencing of all exon 19 - 21	Jackman 2007[47]

a All objective response rates were modelled using beta distributions.
b In the 'assumption of equal prognostic value' analysis the response rate for Therascreen® EGFR PCR Kit is used for all mutation tests.
c The objective response rate for mutation negative patients as reported in the First-Signal trial[5] (0.519) was based on chemotherapy with Gemcitabine and Cisplatin. This value was adjusted (HR = 0.933) to correspond with Paclitaxel and Carboplatin.[52]

Survival

As was the case in NICE Technology Appraisal 192, two separate Weibull models were used to estimate cycle-dependent transitions for progression-free survival and overall survival while on doublet chemotherapy for positive, negative and unknown mutation status. Figure 12 provides a schematic representation of the modelling approach.

Figure 12: Modelling of overall and progression free survival



For testing using the Therascreen® EGFR PCR Kit, progression-free survival and overall survival were modelled using the Weibull regression models based on the IPASS study[50] and a hazard ratio for TKI (based on a meta-analysis and mixed treatment comparison) used in NICE Technology Appraisal 192.[52] The Weibull regression models have separate Lambda and Alpha parameters for patients with mutation positive, mutation unknown and mutation negative tumours and are based on treatment with doublet chemotherapy (Table 18).

Table 18: Weibull models used to model survival on Paclitaxel and Carboplatin after use of the Therascreen® EGFR PCR Kit [†]

[redacted]

To estimate progression-free survival and overall survival for patients treated with TKIs after a positive test result using the Therascreen® EGFR PCR Kit, a hazard ratio of 0.43 (95% CI: 0.34, 0.53) was applied to the Weibull function for mutation positives. This hazard ratio was modelled using a lognormal distribution.

For Direct sequencing of all exon 19-21 mutations, PFS and OS for mutation positives after EGFR-TKI and negatives after doublet chemotherapy were modelled using Kaplan-Meier curves extracted from the First-Signal trial.[5] The corresponding standard errors were calculated using the Peto method.[65] In the First-Signal trial, mutation negative patients were treated with Gemcitabine and Cisplatin.[5] The PFS and OS estimates obtained for these mutation negative patients were adjusted (HR = 1.087 for PFS and HR = 1.087 for OS) to correspond with treatment with Paclitaxel and Carboplatin.[52] PFS and OS for patients with tumours of unknown mutation status were based on the IPASS Weibull model for unknown mutations, since these were not reported in the First-Signal trial.

Consistent with the use of Pemetrexed and Cisplatin as doublet chemotherapy, the hazard ratios reported in Table 19 were used to recalculate PFS and OS for both comparators.

Accordingly, objective response rate presented in Table 17 was recalculated to correspond with Pemetrexed and Cisplatin. These hazard ratios and odds ratios were retrieved from the updated mixed treatment comparison from NICE Technology Appraisal 192.

Table 19: Hazard ratios and odds ratios for Paclitaxel and Carboplatin compared with Pemetrexed and Cisplatin (updated mixed treatment comparison)[66]

	Estimate	Lower 95% CI	Upper 95%CI	Distribution
Hazard ratios progression free and overall survival				
Progression free survival	0.88	0.74	1.05	Lognormal
Overall survival	0.78	0.65	0.93	Lognormal
Odds ratios				
Objective response rate	1.64	1.15	2.27	Lognormal
Neutropenia	0.46	0.07	1.62	Lognormal
Febrile Neutropenia	0.19	0.01	0.84	Lognormal
Fatigue	2.62	1.30	4.65	Lognormal
Nausea & vomiting	10.92	1.11	41.94	Lognormal
Diarrhoea	1.00	-	-	Fixed
Hair Loss (Grade 2)	1.00	-	-	Fixed
Anaemia	1.62	0.54	3.75	Lognormal

The progression free survival and overall survival curves for patients tested with the Therascreen® EGFR PCR Kit and with direct sequencing of all exon 19-21 mutations for the 'evidence on comparative effectiveness available' analysis are presented in Figure 13 and Figure 14.

In the 'linked evidence' analysis, PFS and OS for patients tested with direct sequencing of all exon 18-21 mutations and direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells) were assumed equal to the PFS and OS as described above for direct sequencing of all exon 19-21 mutations. PFS and OS for patients tested with the Therascreen® EGFR PCR Kit and with direct sequencing of all exon 19-21 mutations in the 'linked evidence' analysis was equal to the estimates used in the 'evidence on comparative effectiveness available' analysis.

Figure 13: Progression free survival for patients tested with the Therascreen® EGFR PCR Kit[50] and with direct sequencing of all exon 19-20 mutations[5]

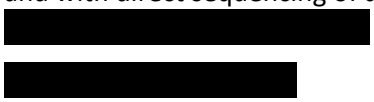


Figure 14: Overall survival for patients tested with the Therascreen® EGFR PCR Kit[50] and with direct sequencing of all exon 19-20 mutations[5]

Adverse events

The occurrence of adverse events was assumed to be dependent on treatment and independent of EGFR mutation status, i.e. adverse events for patients with mutation negative and mutation unknown tumours were assumed to be equal after chemotherapy. The occurrence of adverse events is presented in Table 20.

Table 20: Adverse events associated with TKIs and Paclitaxel and Carboplatin

Adverse event per treatment	Probability	Standard error	Distribution	Source
EGFR tyrosine kinase inhibitor				
Neutropenia	0.0%	-	Fixed	NICE Technology Appraisal 192[52]
Febrile Neutropenia	0.0%	-	Fixed	NICE Technology Appraisal 192[52]
Fatigue	0.0%	-	Fixed	NICE Technology Appraisal 192[52]
Nausea &/or vomiting	0.0%	-	Fixed	NICE Technology Appraisal 192[52]
Diarrhoea	5.3%	-	Fixed	NICE Technology Appraisal 192[52]
Hair Loss (grade 2)	1.2%	-	Fixed	NICE Technology Appraisal 192[52]
Rash	2.3%	-	Fixed	NICE Technology Appraisal 192[52]
Anaemia	1.5%	-	Fixed	NICE Technology Appraisal 192[52]
Paclitaxel and Carboplatin				
Neutropenia	33.3%	-	Fixed	NICE Technology Appraisal 192[52]
Febrile Neutropenia	3.9%	-	Fixed	NICE Technology Appraisal 192[52]
Fatigue	2.3%	-	Fixed	NICE Technology Appraisal 192[52]
Nausea &/or vomiting	4.7%	-	Fixed	NICE Technology Appraisal 192[52]
Diarrhoea	0.8%	-	Fixed	NICE Technology Appraisal 192[52]
Hair Loss (grade 2)	31.6%	-	Fixed	NICE Technology Appraisal 192[52]
Rash	0.0%	-	Fixed	NICE Technology Appraisal 192[52]
Anaemia	9.3%	-	Fixed	NICE Technology Appraisal 192[52]

As for PFS and OS, the occurrence of adverse events after doublet chemotherapy (as presented in Table 20) is adjusted using the odds ratios in Table 19 to correspond to treatment with Pemetrexed and Cisplatin. The odds ratios for diarrhoea and hair loss were assumed to be 1.00 (resulting in an equal occurrence of toxicity as Paclitaxel and Carboplatin), since no data were available to calculate these odds ratios.[52]

Health state utilities

Utility values were in line with those used in NICE Technology Appraisal 192[52] and based on the study by Nafees et al.[57] Utilities for health states and adverse events were calculated using a baseline utility for stable disease with no adverse events of 0.653 (standard error 0.022). This baseline utility was increased in case of treatment response and/or decreased using adverse events and/or treatment related disutilities (Table 21).

Table 21: Utility scores used in all three analyses

	Estimate	Standard error	Distribution	Source
Health state utilities				
Baseline utility (Progression Free, stable disease)	0.653	0.022	Beta	Nafees 2009[57]
Disease progression (disutility)	0.180	0.022	Beta	Nafees 2009[57]
Progression Free - Response (utility increment)	0.019	0.007	Beta	Nafees 2009[57]
Disutilities related to adverse events (grade 3 or 4)[a]				
Neutropenia	0.090	0.015	Beta	Nafees 2009[57]
Febrile Neutropenia	0.090	0.016	Beta	Nafees 2009[57]
Fatigue	0.073	0.018	Beta	Nafees 2009[57]
Nausea &/or vomiting	0.048	0.016	Beta	Nafees 2009[57]
Diarrhoea	0.047	0.016	Beta	Nafees 2009[57]
Hair Loss (Grade 2)	0.045	0.015	Beta	Nafees 2009[57]
Skin and subcutaneous tissue disorders	0.032	0.012	Beta	Nafees 2009[57]
Anaemia	0.073	0.018	Beta	Lilly[67]
Disutilities related to treatment				
IV therapy	0.043	0.020	Beta	Roche 2006[68]
Oral therapy	0.014	0.012	Beta	Roche 2006[68]

[a] Consistent with STA 192, a disutility for adverse events was applied for a single cycle in the model.

If the mutation tests were to differ substantially in turnaround time, there could be a difference in process disutility associated with waiting for a test result, or even health outcome due to delayed start of treatment. To investigate this, an item on turnaround time was included in the online survey. The results (Section 3.2.1) showed that the tests were very similar. In most laboratories, the turnaround times were generally between 3 and 7 days. One laboratory (using the Therascreen® EGFR PCR Kit) had a turnaround time of 1 to 2 days and one laboratory (also using the Therascreen® EGFR PCR Kit) had a turnaround time of between 8 and 10 days. Based on these results, it was assumed in the health economic analysis that the turnaround times were not test driven, and therefore the tests did not differ with respect to process disutility or health outcomes associated as a result of waiting for the test results.

Resource use and costs

Resource use and costs were taken from NICE Technology Appraisal 192,[7] with the exception of the EGFR mutation test costs. These costs were based on the online survey of NHS laboratories in England and Wales (Section 3.2.1).

Test costs

For patients with a positive or negative test result, the full test costs as reported in Table 22 were accounted for. For this purpose, the charged prices from the online survey of NHS

laboratories in England and Wales (Section 3.2.1) were used. These costs were either the same as or did not differ substantially from the actual test costs; the charged prices were reported for more tests than the actual test costs, and the incremental test costs are similar (Table 22). To calculate test costs for patients with an unknown mutation status, it is necessary to differentiate between patients with an unknown mutation because the sample was considered inadequate by the pathologist before sending the specimen to the laboratory (pre-laboratory clinical failure), and patients with a sample considered adequate by the pathologist that results in a failure once inside the laboratory (technical failures within the laboratory). In the case of an unknown mutation status due to a pre-laboratory clinical failure, no test costs were taken into account. In the case of an unknown mutation status due to a technical failure within the laboratory full test costs were taken into account. This proportion was calculated based from the proportion of patients with an unknown mutation status as taken from the literature (see Table 15 and Table 16) and the total proportion of technical failures in the laboratories as reported in the online survey (Table 5, section 3.2.1), using the following formula:

Proportion of patients with an unknown mutation due to a technical failure in the laboratory =

Proportion of technical failures in laboratory * ((1 – Proportion unknown) / (1 - Proportion of technical failures in laboratory))

The results of the calculations of the proportion of patients with unknown test results for which test costs are included are presented in Table 23.

Table 22: EGFR Mutation test costs based results online survey in reference laboratories in England and Wales

Test	Test costs						Charged price						Distribution	Source
	N	Mean (se)[b]		Range			N	Mean (se)[b]		Range				
Therascreen® EGFR PCR Kit	5	154.00	(14.70)	120.00	-	190.00	7	154.58	(12.01)	120.00	-	190.00	Gamma	Online survey
Direct sequencing of exon 19-21[a]	0	175.00	(14.70)	175.00	-	175.00	0	147.50	(27.50)	120.00	-	175.00	Gamma	Online survey
Direct sequencing or WAVE-HS for samples with insufficient tumour cells[a]	0	175.00	(14.70)	175.00	-	175.00	0	147.50	(27.50)	120.00	-	175.00	Gamma	Online survey
Direct sequencing of exon 18-21[a]	0	175.00	(14.70)	175.00	-	175.00	0	147.50	(27.50)	120.00	-	175.00	Gamma	Online survey
Fragment length analysis combined with pyrosequencing	2	162.50	(12.50)	150.00	-	175.00	2	187.50	(12.50)	175.00	-	200.00	Gamma	Online survey
Sanger sequencing and Fragment length analysis / PCR of negative samples[c]	0	NR			-		1	140.00	(27.50)	140.00	-	140.00	Gamma	Online survey
Roche Cobas test	0	NR			-		1	140.00	(27.50)	140.00	-	140.00	Gamma	Online survey
High resolution melt analysis	1	140.00	(14.70)	140.00	-	140.00	1	150.00	(27.50)	150.00	-	150.00	Gamma	Online survey
Single strand conformation analysis	1	110.00	(14.70)	110.00	-	110.00	1	140.00	(27.50)	140.00	-	140.00	Gamma	Online survey
Sanger sequencing or Roche Cobas for samples with insufficient tumour cells[d]	0	NR	-		-		0	130.00	(19.34)[e]	120.00	-	140.00	Gamma	Online survey
Sanger sequencing or Therascreen® for samples with insufficient tumour cells[f]	0	154.00	(14.70)	120.00	-	190.00	0	137.30	(14.88)[e]	120.00	-	190.00	Gamma	Online survey
Next generation sequencing[g]	0	NR	-		-		0	NR	-		-		-	
Therascreen® and Pyrosequencing Kit[f]	0	NR	-		-		0	NR	-		-		-	

NR: not reported; se: standard error

[a] Calculated based on the survey results reported for Sanger sequencing and Pyrosequencing (reported in Table 5).

[b] Where no standard error could be calculated (e.g. in case N=1), the highest standard error was assumed.

[c] This comparators was reported as 'Sanger sequencing and Fragment length analysis / Real time PCR / TaqMan for samples with insufficient tumour cells' in the survey results.

[d] Calculated based on the survey results reported for Sanger sequencing and Roche Cobas (reported in Table 5), assuming a similar proportion of samples going to each test (based on expert opinion).

[e] Based on the probabilistic sensitivity analysis

[f] Calculated based on the survey results for Sanger sequencing and the Therascreen® EGFR PCR Kit(reported in Table 5), assuming a similar proportion of samples going to each test (based on expert opinion).

[g] These are new tests and not in use yet, therefore no data are available and it was not considered informative to model these comparators based on lacking evidence.

Table 23: Explanation of calculation of proportion of patients with unknown mutations status due to a technical failure in the laboratory per test

Test	Total proportion of patients with unknown test result (se)[b]	Distribution	Source	Proportion of technical failures in laboratory (se)[b]	Number of reporting laboratories	Distribution	Proportion of patients with an unknown mutation due to a technical failure (full test costs)
Analysis 1 and 2[a]							
Therascreen® EGFR PCR Kit	22.7% (1.8%)	Beta	Mok 2009[50]	3.8% (1.5%)	6	Beta	3.1%
Direct sequencing of exon 19-21[c]	As for Direct sequencing or WAVE-HS			4.5% (0.5%)	0	Beta	2.9%
Direct sequencing or WAVE-HS for samples with insufficient tumour cells[c]	37.7% (4.2%)	Beta	Jackman 2007[47]	4.5% (0.5%)	0	Beta	2.9%
Direct sequencing of exon 18-21[c]	As for Direct sequencing or WAVE-HS			4.5% (0.5%)	0	Beta	2.9%
Analysis 3 [a]							
Therascreen® EGFR PCR Kit	22.7% (1.8%)	Beta	Mok 2009[50]	3.8% (1.5%)	6	Beta	3.1%
Direct sequencing of exon 19-21[c]	As for Therascreen® EGFR PCR Kit			4.5% (0.5%)	0	Beta	3.6%
Direct sequencing or WAVE-HS for samples with insufficient tumour cells[c]	As for Therascreen® EGFR PCR Kit			4.5% (0.5%)	0	Beta	3.6%
Direct sequencing of exon 18-21[c]	As for Therascreen® EGFR PCR Kit			4.5% (0.5%)	0	Beta	3.6%
Fragment length analysis combined with pyrosequencing	As for Therascreen® EGFR PCR Kit			5.0% (1.5%)	2	Beta	4.1%
Sanger sequencing and Fragment length analysis / PCR of negative samples[d]	As for Therascreen® EGFR PCR Kit			0.1% (1.5%)	1	Beta	0.1%
Roche cobas test	As for Therascreen® EGFR PCR Kit			5.0% (1.5%)	1	Beta	4.1%
High resolution melt analysis	As for Therascreen® EGFR PCR Kit			0.2% (1.5%)	1	Beta	0.2%
Single strand conformation analysis	As for Therascreen® EGFR PCR Kit			10.0% (1.5%)	1	Beta	8.6%
Sanger sequencing or Roche	As for Therascreen® EGFR PCR Kit			4.5% (1.0%)[g]	0	Beta	3.6%

Cobas for samples with insufficient tumour cells[e]					
Sanger sequencing or Therascreen® for samples with insufficient tumour cells[f]	As for Therascreen® EGFR PCR Kit	3.9% (1.1%)[g]	0	Beta	3.2%
Next generation sequencing[h]	As for Therascreen® EGFR PCR Kit	NR	0	-	-
Therascreen® and Pyrosequencing Kit[h]	As for Therascreen® EGFR PCR Kit	NR	0	-	-

NR = not reported, se = standard error.

[a] Analysis 1 is the 'evidence on comparative effectiveness' analysis, analysis 2 the 'linked evidence' analysis, analysis 3 the 'assumption of equal prognostic value' analysis.

[b] In case no standard error could be calculated (e.g. in case N=1), the highest standard error was assumed.

[c] Calculated based on the survey results reported for Sanger sequencing and Pyrosequencing (reported in Table 6).

[d] This comparators was reported as 'Sanger sequencing and Fragment length analysis / Real time PCR / TaqMan for samples with insufficient tumour cells' in the survey results. Additionally, continuity correction was applied for the probabilistic sensitivity analysis for this strategy

[e] Calculated based on the survey results for Sanger sequencing and Roche Cobas (reported in Table 6), assuming a similar proportion of samples going to each test (based on expert opinion).

[f] Calculated based on the survey results for Sanger sequencing and The Therascreen® EGFR PCR Kit(reported in Table 6), assuming a similar proportion of samples going to each test (based on expert opinion).

[g] Standard error is based on the probabilistic sensitivity analysis

[h] These are new tests and not yet in routine use, therefore no data are available and it was not considered informative to model these comparators based on lacking evidence.

Table 24: Other costs used in all three analyses

Type of costs	Costs	Standard error	Distribution	Source
Treatment costs				
TKI[a]	[redacted]	-	Fixed	NICE Technology Appraisal 192[52]
Resource use				
Number of chemotherapy cycles	4.0	-	Fixed	External Review group[66]
Costs per chemotherapy cycle[b]				
Pemetrexed and Cisplatin	£1,536.30	-	Fixed	External Review group[66]
Chemotherapy administration	£307.00	£80.61	Gamma	External Review group[66]
Transport	£28.00	£3.57	Gamma	NICE Technology Appraisal 192[52]
Adverse event costs (grade 3 or 4)[c]				
Neutropenia	£92.80	-	Fixed	NICE Technology Appraisal 192[52]
Febrile Neutropenia	£2.286.00	-	Fixed	NICE Technology Appraisal 192[52]
Fatigue	£38.90	-	Fixed	NICE Technology Appraisal 192[52]
Nausea & vomiting	£700.79	-	Fixed	NICE Technology Appraisal 192[52]
Diarrhoea	£867.12	-	Fixed	NICE Technology Appraisal 192[52]
Hair Loss (Grade 2)	£0.00	-	Fixed	NICE Technology Appraisal 192[52]
Skin and subcutaneous tissue disorders	£116.82	-	Fixed	NICE Technology Appraisal 192[52]
Anaemia	£615.04	-	Fixed	NICE Technology Appraisal 192[52]
Other				
Patient monitoring (per cycle)	[redacted]	[redacted]	Gamma	NICE Technology Appraisal 192[52]
2nd-line therapy following disease progression (per cycle)	£1.022,05	-	Fixed	NICE Technology Appraisal 192[52]
Probability of 2nd-line therapy following disease progression	61.0%	4.3%		NICE Technology Appraisal 192[52]
Best supportive care (per cycle)[d]	£599,69	-	Fixed	NICE Technology Appraisal 192[52]

[a] Single Payment Access Costs
[b] Estimated chemotherapy costs are based on a mean body surface area of 1.762 m^2
[c] Consistent with NICE Technology Appraisal 192,[52] costs for adverse events were applied for a single cycle in the model.
[d] Will be provided if no 2nd-line therapy is administered

4.3 Model analyses

Expected mean costs, life years (LYs) and QALYs were estimated for all EGFR mutation tests. Long-term costs, LYs and QALYs were discounted using the UK discount rates of 3.5% for both costs and effects. Based on the estimated outcomes (probabilistic), the incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs by the incremental QALYs. The ICER represents the costs of an additional QALY gained and was used to estimate the cost-effectiveness of a strategy 1) opposed to direct sequencing of all exon 18-21 mutations and 2) opposed to the next best alternative. All outcomes are based on Probabilistic sensitivity analyses with 5,000 simulations using parameter distributions as presented in this section.

4.3.1 Overview of main model assumptions

The main assumptions in the health economic analyses were:

1. The differences in relative treatment response, PFS and OS reported in the First-Signal trial[5] and those reported for the IPASS trial[50] are solely due to the different tests used (Therascreen® EGFR PCR Kit and direct sequencing of all exon 19-21, respectively) to distinguish between patients whose tumours are EGFR mutation positive (and receive TKI treatment) and patients whose tumours are EGFR mutation negative (and receive doublet chemotherapy) ('evidence of comparative effectiveness available' and 'linked evidence' analyses).
2. To calculate the sensitivity and specificity of the tests, required to calculate the proportion of positive and negative test results (Table 15), positive tested patients were categorised as false positive if no treatment response was observed after TKI while patients were categorised as true positive if treatment response was observed TKI. Similarly, negatively tested patients were categorised as false negative if treatment response was observed after TKI while patients were categorised as true negative if no treatment response was observed after TKI (all analyses).
3. The proportion of patients with unknown mutation status relative to the number of patients for whom a tissue sample was available in the trials[47,50] provides a realistic approximation of the proportion of patients with an unknown test result in clinical practice (all analyses).
4. The objective response rate, PFS and OS in patients with an unknown test result as reported in the IPASS trial[50] is generalisable to direct sequencing methods ('evidence of comparative effectiveness available' and 'linked evidence' analyses).
5. The probability of an unknown test result as reported in the study by Jackman et al[47] (Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)) is generalisable to other direct sequencing methods ('linked evidence' analysis).
6. The objective response rate in patients with a negative test result as reported in the First-Signal trial[5] is generalisable to other direct sequencing methods ('linked evidence' analysis).
7. PFS and OS in patients with positive or negative test result reported in the First-Signal trial[5] (direct sequencing of exon 19-21) is generalisable to other direct sequencing methods (exon 18-21) ('linked evidence' analysis). In other words, no meaning of testing exon 18 mutations.

4.3.2 Sensitivity analyses

For analyses 1 and 2, in a sensitivity analysis the costs reported in Table 24 were updated. For all three analyses, in a sensitivity analysis the proportion of unknown patients was based on the results of the online survey instead of the literature (Table 5, Section 3.2.1).

Sensitivity analysis using up-dated costs

In this sensitivity analysis, the costs reported in Table 23 were updated based on price indices and 2012 reference costs (Table 25), with the exception of EGFR TKI treatment costs.

Table 25: Updated costs

Type of costs	Costs	Standard error	Distribution	Source
Treatment costs				
Costs per chemotherapy cycle				
Chemotherapy administration	£333.67	£83.01		Reference costs 2012[69]
Transport[a]	£30.07			STA 192[52] and PSSRU[63]
Adverse event costs (grade 3 or 4)[a]				
Neutropenia	£99.66	-	Fixed	STA 192[52] and PSSRU[63]
Febrile Neutropenia	£2,455.00	-	Fixed	STA 192[52] and PSSRU[63]
Fatigue	£41.78	-	Fixed	STA 192[52] and PSSRU[63]
Nausea & vomiting	£752.60	-	Fixed	STA 192[52] and PSSRU[63]
Diarrhoea	£931.23	-	Fixed	STA 192[52] and PSSRU[63]
Hair Loss (Grade 2)	£0.00	-	Fixed	STA 192[52] and PSSRU[63]
Skin and subcutaneous tissue disorders	£125.46	-	Fixed	STA 192[52] and PSSRU[63]
Anaemia	£660.51	-	Fixed	STA 192[52] and PSSRU[63]
Other				
Patient monitoring (per cycle)	£113.00	£28.26	Gamma	Reference costs 2012[69]
2nd-line therapy following disease progression (per cycle)[a]	£1,098.00	-	Fixed	STA 192[52] and PSSRU[63]
Best supportive care (per cycle) [a]	£644.32	-	Fixed	STA 192[52] and PSSRU[63]

[a] price indices applied to original source

Sensitivity analysis using the proportion of patients with unknown mutation status based on online survey results

This sensitivity was performed for all three analyses. The proportion of patients with unknown mutation status was based on the survey results, as reported in Table 23, instead of the trials.

4.4 Results of cost-effectiveness analyses

This section reports the results of the 'evidence on comparative effectiveness available' analysis, the 'linked evidence' analysis, and the 'assumption of equal prognostic value' analysis. In the tables the strategies are ranked by costs from least to most expensive. For the 'evidence on comparative effectiveness' analysis, the comparator from the scope (direct

sequencing of all exon 18-21 mutations) could not be included. Therefore, direct sequencing of all exon 19-21 mutations was used as comparator in the 'evidence on comparative effectiveness' analyses. In the 'linked evidence' and 'assumption of equal prognostic value' analyses, direct sequencing of exons 18-21 was included and hence was used as the comparator. For all analyses the results are presented in two ways, first compared to the comparator (direct sequencing of all exon 18-21 mutations or of all exon 19-21 mutations), and second compared to the next cost-effective strategy.

4.4.1 'Evidence on comparative effectiveness available' analysis

The probabilistic results of the 'evidence on comparative effectiveness available' analysis are shown in Table 26. It should be noted that this analysis is based on a number of assumptions outlined in section 4.3, of which the following two are particularly problematic:

- The proportion of patients with a positive or negative test result after the use of these tests in the NHS population, was estimated based on the proportion of EGFR mutation positive patients in England and Wales, the proportion of patients with an unknown test result, and test accuracy for the prediction of treatment response derived from two separate trials.[5, 50].
- The differences in relative treatment response, PFS and OS between the results of First-Signal[5] that were used to model EGFR mutation testing with direct sequencing of all exon 19-21 mutations and the results of the IPASS trial[3, 50] that were used to model EGFR mutation testing with the Therascreen® EGFR PCR Kit, are solely due to the different tests used to distinguish between patients who are EGFR mutation positive (and receive TKI treatment) and patients who are EGFR mutation negative (and receive doublet chemotherapy).

In this analysis, the Therascreen® EGFR PCR Kit was both less effective and less costly compared with direct sequencing of all exon 19-21 at an ICER of £32,167. The lower costs and QALYs for the Therascreen® EGFR PCR Kit can be explained by the fact that patients whose tumours are mutation negative do worse on overall survival in the IPASS trial[3, 50] than in First-Signal,[5] whereas for mutation positive patients the outcome is comparable, and for unknowns it is the same (by assumption), see Figure 13 and Figure 14. Therefore, on average, with the Therascreen® EGFR PCR Kit strategy patients have shorter survival, and therefore less QALYs compared to testing with direct sequencing of all exons 19-21. The apparent shorter survival also reduces costs. The cost-effectiveness acceptability curve

(Figure 15) shows that at a threshold value of £32,500 direct sequencing of all exons 19-21 becomes the preferred strategy.

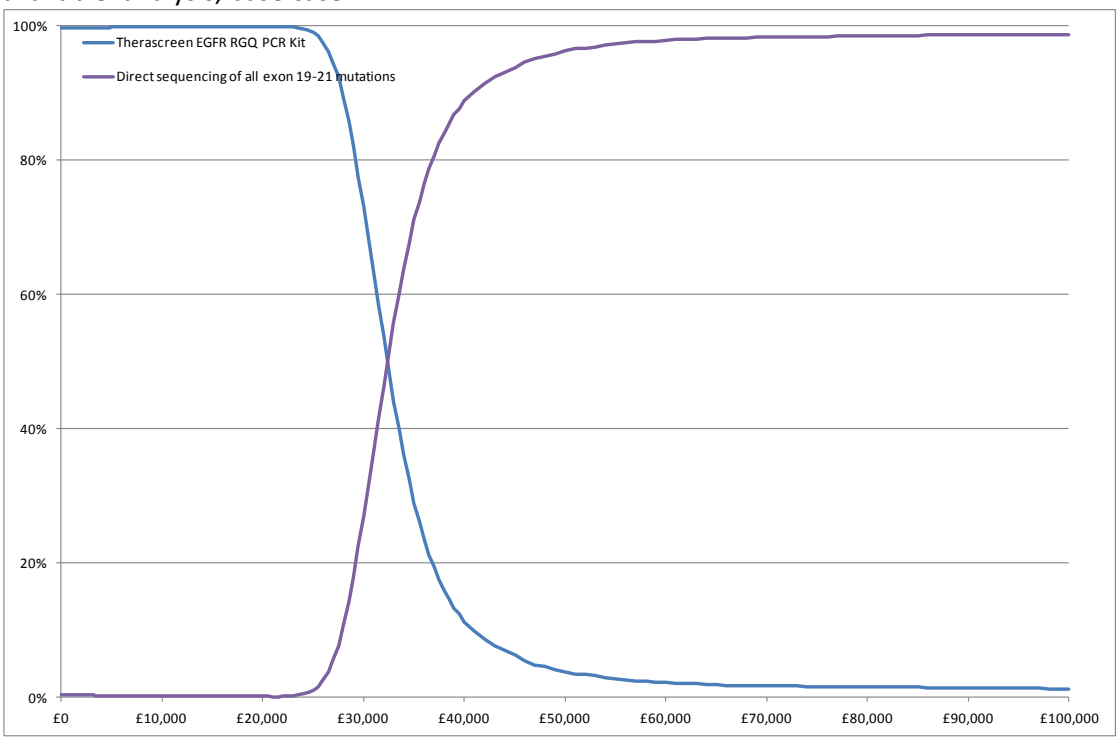
Results were robust for changed assumptions in the sensitivity analyses, in the sense that testing with Therascreen® EGFR PCR Kit was always less effective and less expensive. The ICERs amounted to £34,555 (unknowns from survey) and £32,196 (updated costs). The cost-effectiveness acceptability curves for the sensitivity analyses are presented in Appendix 7.

Table 26: Probabilistic results for 'Evidence on comparative effectiveness available' analysis: base case and sensitivity analyses

Strategy	**Cost**	**QALY**	**Compared to Direct sequencing (exon 19-21**		
			Cost	**QALY**	**Cost/QALY**
Base case					
Therascreen® EGFR PCR Kit	[redacted]	0.902	-£6,660	-0.207	£32,167
Direct sequencing of all exon 19-21 mutations[a]	[redacted]	*1.109*			
Sensitivity analysis: updated costs					
Therascreen® EGFR PCR Kit	[redacted]	0.874	-£9,194	-0.286	£32,196
Direct sequencing of all exon 19-21 mutations[a]	[redacted]	*1.160*			
Sensitivity analysis: unknowns from survey					
Therascreen® EGFR PCR Kit	[redacted]	0.905	-£7,130	-0.206	£34,555
Direct sequencing of all exon 19-21 mutations[a]	[redacted]	*1.111*			

[a] Although this test was not listed in the scope, it was included in the analyses as discussed in section 4.2.1.

Figure 15: Cost-effectiveness acceptability curve for 'evidence on comparable effectiveness available' analysis, base case



4.4.2 'Linked evidence' analysis

The 'linked evidence' analysis includes four tests, i.e. all tests for which either evidence on relative effectiveness or accuracy was available. Table 27 shows the probabilistic results of this analysis.

This analysis was also based on a number of assumptions, including those described in 4.3 and 4.4.1 for the 'evidence on comparative effectiveness available' analysis. The following additional assumption should be particularly noted:

- For direct sequencing of all exon 18-21 mutations and direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells), the relative PFS and OS for mutation positives and mutation negatives correlates perfectly with relative PFS and OS as observed for direct sequencing of all exon 19-21 mutations in the First-SIGNAL trial.[5]

In the base case analysis, compared to direct sequencing of all exon 18-21 mutations, the Therascreen® EGFR PCR Kit was less costly and less effective at an ICER of £31,849 per QALY lost. Direct sequencing of all exon 19-21 mutations and direct sequencing or WAVE-HS for inadequate samples were both more expensive and more effective than the comparator. For thresholds below £33,500, testing with the Therascreen® EGFR PCR Kit is the preferred

strategy, then direct sequencing of all exon 18-21 mutations is preferred up to a threshold of £39,000 where direct sequencing of all exon 19-21 mutations has the highest probability of being cost-effective (Figure 16). The sensitivity analyses (Appendix 7) show that these findings are quite robust in the sense that compared to direct sequencing of all exon 18-21 mutations, the Therascreen® EGFR PCR Kit is always the less expensive and less effective and the remaining two tests are more effective and more expensive.

Table 27: Probabilistic results for 'linked evidence' analysis, base case

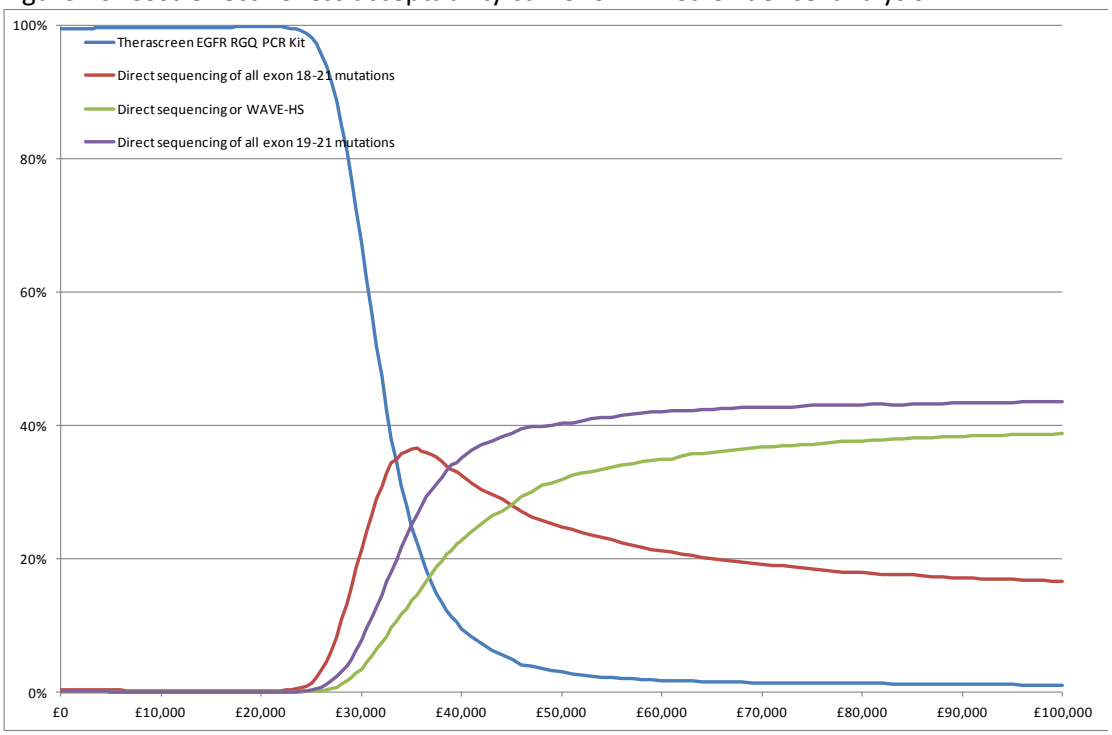
Strategy	**Cost**	**QALY**	**Compared to Direct sequencing (exon 18-21)**		
			Incremental Cost	**Incremental QALY**	**Incremental Cost/QALY**
Therascreen® EGFR PCR Kit	[redacted]	0.902	-£6,040	-0.190	£31,849
Direct sequencing of all exon 18-21 mutations	[redacted]	1.092			
Direct sequencing of all exon 19-21 mutations[a]	[redacted]	*1.109*	*£619*	*0.017*	*£35,634*
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)[a]	[redacted]	*1.109*	*£658*	*0.017*	*£38,251*

[a] Although this test was not listed in the scope, it was included in the analyses as discussed in section 4.2.1.

Strategy	**Cost**	**QALY**	**Comparator**	**Compared to next cost-effective strategy**		
				Incremental Cost	**Incremental QALY**	**Incremental Cost/QALY**
Therascreen® EGFR PCR Kit	[redacted]	0.902				
Direct sequencing of all exon 18-21 mutations	[redacted]	1.092	Therascreen® EGFR PCR Kit	£6,040	0.190	£31,849
Direct sequencing of all exon 19-21 mutation[a]	[redacted]	*1.109*	*Direct sequencing (exon 19-21)*	*£619*	*0.017*	*£35,634*
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)[a]	[redacted]	*1.109*	*Direct sequencing (exon 19-21)*	*£39*	*0.000*	*Dominated*

[a] Although this test was not listed in the scope, it was included in the analyses as discussed in section 4.2.1.

Figure 16: Cost-effectiveness acceptability curve for 'linked evidence' analysis



4.4.3 'Assumption of equal prognostic value' analysis

The 'assumption of equal prognostic value' analysis included all tests for which information on cost and/or technical performance was available from the online survey of NHS laboratories in England and Wales. This includes the tests for which neither comparative effectiveness nor response data were available. Therefore, this analysis assessed whether the tests were likely to be cost-effective given an assumption of equal prognostic value (based on the prognostic value of testing with the Therascreen® EGFR PCR Kit, as this was the only test for which prognostic data were available on patients with positive, negative and unknown tumour EGFR mutation status) and test specific information on cost only. As a result, the strategies only differ with respect to costs. As shown in Table 28, Sanger sequencing or Roche Cobas for samples with insufficient tumour cells is the least expensive and Fragment length analysis combined with pyrosequencing is the most expensive strategy. However, the difference between the costs of these strategies amounts to only £47 (less than 1% of total strategy costs).

In a sensitivity analysis the proportion of patients with tumours of unknown mutation status were taken from the online survey of NHS laboratories in England and Wales instead of based on the literature. As a result, in this sensitivity analysis a difference in health outcomes (QALYs) is modelled. The results in Table 29 show that this assumption has some impact on the relative costs and effects of the strategies, in the sense that single strand

conformation analysis is now the most costly. This is caused by the fact that the percentage of failures as reported in the survey is the highest for single strand conformation analysis (10%, N=1), whereas for Sanger sequencing and Fragment length analysis / PCR it is 0% (N=1). A higher failure rate will in its turn lead to a lower proportion of patients with either a mutation positive or mutation negative tumour, and therefore on average to higher costs. This is because patients with an unknown mutation status are more costly than the average of the patients with a known (positive or negative) mutation status. The cost-effectiveness acceptability curve is presented in Figure 17.

Table 28: Probabilistic results for 'assumption of equal prognostic value' analysis, base case

Strategy	**Costs (95% CI)**	**Incremental costs compared to Direct sequencing (exon 18-21)**
Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	[redacted]	-£15
Sanger sequencing and Fragment length analysis / PCR of negative samples	[redacted]	-£11
Sanger sequencing or Therascreen® EGFR PCR Kit for samples with insufficient tumour cells	[redacted]	-£9
Roche Cobas	[redacted]	-£9
High Resolution Melt analysis	[redacted]	-£3
Direct Sequencing of exon 19-21[a]	[redacted]	*£0*
Direct Sequencing of exon 18-21	[redacted]	
Single strand conformation analysis	[redacted]	£1
Direct Sequencing or WAVE-HS[a]	[redacted]	*£1*
Therascreen® EGFR PCR Kit	[redacted]	£5
Fragment Length analysis combined with Pyrosequencing	[redacted]	£33

[a] Although this test was not listed in the scope, it was included in the analyses as discussed in section 4.2.1.

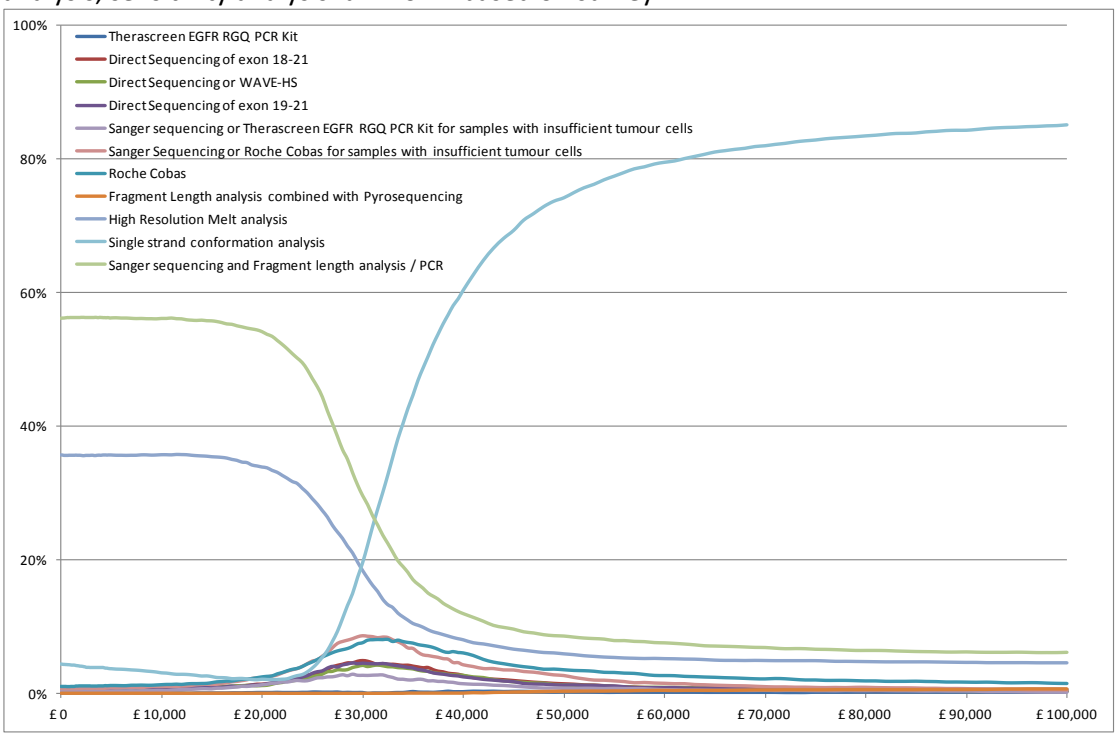
Table 29: Probabilistic results for 'assumption of equal prognostic value' analysis, sensitivity analyses: unknown based on survey

Strategy			**Compared to Direct sequencing of all exon 18-21mutations**			**Compared to next best strategy**			
	Costs	**QALYs**	**Incremental cost**	**Incremental QALYs**	**Incremental cost / QALY**	**Comparator**	**Incremental cost**	**Incremental QALYs**	**Incremental cost / QALY**
Sanger sequencing and Fragment length analysis / PCR of negative samples	[redacted]	0.871	-£226	-0.007	£33,437				
High Resolution Melt analysis	[redacted]	0.871	-£211	-0.007	£31,848	Sanger sequencing and Fragment length analysis / PCR of negative samples	£14	0.000	Extended dominance
Sanger sequencing or Therascreen® EGFR PCR Kit for samples with insufficient tumour cells	[redacted]	0.877	-£40	-0.001	£45,629	Sanger sequencing and Fragment length analysis / PCR of negative samples	£186	0.006	Extended dominance
Therascreen® EGFR PCR Kit	[redacted]	0.877	-£26	-0.001	£24,977	Sanger sequencing and Fragment length analysis / PCR of negative samples	£200	0.006	Extended dominance
Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	[redacted]	0.878	-£18	0.000	Dominated	Sanger sequencing and Fragment length analysis / PCR of negative samples	£207	0.007	£30,602
Direct Sequencing or WAVE-HS[a]	[redacted]	*0.878*	*£0*	*0.000*	*Dominated*	*Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells*	*£18*	*0.000*	*Dominated*

Strategy			Compared to Direct sequencing of all exon 18-21mutations			Compared to next best strategy			
	Costs	QALYs	Incremental cost	Incremental QALYs	Incremental cost / QALY	Comparator	Incremental cost	Incremental QALYs	Incremental cost / QALY
Direct Sequencing of exon 18-21	[redacted]	0.878				Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£18	0.000	Dominated
Direct Sequencing of exon 19-21[a]	[redacted]	*0.878*	*£0*	*0.000*	*£615,549*	*Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells*	*£19*	*0.000*	*Dominated*
Roche Cobas	[redacted]	0.879	£15	0.001	£19,501	Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£33	0.001	Extended dominance
Fragment Length analysis combined with Pyrosequencing	[redacted]	0.879	£62	0.001	£79,807	Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£81	0.001	Extended dominance
Single strand conformation analysis	[redacted]	0.886	£264	0.008	£31,080	Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£283	0.008	£33,338

[a] Although this test was not listed in the scope, it was included in the analyses as discussed in section 4.2.1.

Figure 17: Cost-effectiveness acceptability curve for 'assumption of equal prognostic value' analysis, sensitivity analysis: unknown based on survey



5. DISCUSSION

5.1 Statement of principal findings

5.1.1 Clinical effectiveness

There was no strong evidence that any one EGFR mutation test had greater accuracy than any other test, although there was a suggestion that Therascreen® EGFR PCR Kit may be more accurate than direct sequencing for predicting response to treatment with TKIs. Eleven studies were included in the review, these evaluated the Therascreen® EGFR PCR Kit (version 1), direct sequencing, cobas® EGFR Mutation Test Kit, fragment length analysis, and Sanger sequencing. Six studies (two RCTs and four cohort studies) provided data on the accuracy of EGFR mutation testing for predicting response to treatment with TKIs in patients with stage IIIB or IV NSCLC. Five RCTs, including two which also provided accuracy data, reported data on the clinical effectiveness of TKIs compared to standard chemotherapy in patients with stage IIIB or IV NSCLC with EGFR mutation positive tumours; one additional study reported data for a subgroup of patients from one of these RCTs whose biopsy samples had been re-analysed using a different EGFR mutation testing method. The remaining study was included as a supplement to the survey of laboratories in England and Wales which currently provide EGFR mutation testing and did not report any data on clinical outcomes.

The survey of laboratories providing EGFR mutation testing indicated that the Therascreen® EGFR PCR Kit was the single most commonly used method (6 out of 13 respondents); reasons cited by respondents for their choice of the Therascreen® EGFR PCR Kit were: proportion of tumour cells required; ease of use; cost; mutations covered. There was no clear indication that choice of test method was related to volume of throughput. Most respondents reported turnaround times, from receipt of sample to reporting to the clinician, of between 3 and 7 days. The only laboratory to report a turnaround time of less than three days (24-48 hours) used the Therascreen® EGFR PCR Kit. All respondents reported turnaround times under the 10 working day maximum recommended by the European EGFR Workshop Group.[18] With the exception of those whose testing strategy included direct sequencing methods, all respondents reported a minimum requirement for testing at or below 10% tumour cells, with some of the laboratories that used the Therascreen® EGFR PCR Kit reporting minimum requirements as low as 1%. Although most respondents included costs in their reasons for choosing a particular test, it is worth noting that a relatively narrow range of costs was reported across all tests (£110 to £190), with a similar level of variation apparent within a single test, Therascreen® EGFR PCR Kit, (£120 to £190). When contacted

by NICE UK NEQAS stated that "Error rates are not always method related and it is not always possible to obtain data from all the labs committing critical genotyping errors. Therefore, any data which could be provided would be skewed with processing and reporting issues rather than being method related. There has been no correlation between any method used for EGFR testing and errors since we started providing scheme in 2010."

Studies which provided data on test accuracy assessed the Therascreen® EGFR PCR Kit (version 1) or direct sequencing methods (exons 18 or 19 to exons 21 or 24). No studies were identified which reported accuracy data for any other EGFR mutation testing method. The Therascreen® EGFR PCR Kit appeared to have the best overall performance for discriminating between patients who are likely to benefit from TKI treatment and those who are not. The sensitivity and specificity estimates for OR were 99% (95% CI: 94, 100) and 69% (95% CI: 60, 77), respectively, with specificity increasing and sensitivity decreasing where a lower response threshold (DC) was used.[50] Four of the five direct sequencing studies reported high estimates of specificity (>80%) for OR, with sensitivities ranging from 60 to 80%.[5, 46-48] Three of these studies also assessed DC and reported high specificities (>90%) and very low sensitivities (≤35%). [46-48] The remaining direct sequencing study reported low sensitivity (66%) and specificity (50%) for DC and low specificity (61%) with high sensitivity (84%) for OR.

There were no clear common participant characteristics, across studies which reported similar sensitivity or specificity estimates for DC or OR. Specificity estimates may have been affected by the way in which resistance mutations were classified; the three direct sequencing studies which reported high specificity estimates either stated that patients whose tumours showed resistance or non-sensitising mutations were classified as EGFR mutation negative, or did not identify any patients with tumours showing these types of mutation. Although the number of resistance mutations identified was generally small, their potential effect on specificity estimates was magnified by the very small sample size in most studies. The most commonly observed mutations were exon 19 deletions and the exon 21 point mutation L858R; most patients in the included studies who had these mutations achieved a minimum response of stable disease when treated with TKIs. Large database studies provide some support for the idea that mutations in exon 20, and in particular the mutation T790M, may be associated with a lack of response to TKIs (See section 5.3.1 'Uncertainties' below). A second possible explanation may be that the Therascreen® EGFR PCR Kit has a lower limit of detection, i.e. it is able to detect EGFR mutations at a lower

abundance (fewer cancer cells carrying the mutation) than direct sequencing methods. A lower limit of detection would only be beneficial if it could be shown that patients whose tumours have a lower abundance of EGFR mutation benefit from treatment with TKIs and the apparent improved diagnostic performance of the Therascreen® EGFR PCR Kit, compared to direct sequencing methods, indicates that this may be the case. However, none of the studies identified by this review reported data on the relationship between abundance of EGFR mutation and response to first-line TKI treatment in patients with stage IIIB or IV NSCLC.

The five RCTs included in this review compared the TKIs gefitinib or erlotinib with various single agent or combination standard chemotherapy regimens and reported data on PFS. Three of the trials included only patients with EGFR mutation positive tumours,[2, 4] and the remaining two trials (IPASS and first-SIGNAL) included chemotherapy naïve patients with stage IIIB or IV NSCLC and reported a subgroup analysis for patients who had received EGFR mutation testing using the Therascreen® EGFR PCR Kit (version 1),[3, 50] or direct sequencing.[5] Though derived from a subgroup analysis of tested patients, data from these trials were most the most complete available in that they provided information on the effectiveness of TKIs compared to standard chemotherapy in both test positive and test negative patients. The results of the IPASS subgroup analyses indicated that PFS was significantly longer for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation positive subgroup (HR 0.48 (95% CI: 0.36, 0.64)) and significantly shorter for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation negative subgroup (HR 2.85 (95% CI: 2.05, 3.98)). This trial formed the basis of the technology appraisal which informed NICE guidance TA192 on gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer.[70] The results of the first-SIGNAL trial indicated a trend towards longer PFS for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation positive subgroup (HR 0.54 (95% CI: 0.27, 1.10)) and a trend towards and significantly shorter PFS for patients receiving gefitinib than for those receiving standard chemotherapy in the EGFR mutation negative subgroup (HR 1.42 (95% CI: 0.82, 2.47)).[5] The remaining trials only provided information on the effectiveness of TKIs compared to standard chemotherapy in patients with EGFR mutation positive tumours; HRs for PFS ranged from 0.48 (95% CI: 0.36, 0.64) to 0.16 (95% CI: 0.10, 0.26). The included trials used various methods to assess EGFR mutation status. Two trials used direct sequencing methods, but limited the definition of positive EGFR mutation status to the presence of an 'activating mutation' (exon 19 deletions or exon 21

mutation L858R). These two trials were included in the technology appraisal which informed NICE guidance TA258 on erlotinib for the first-line treatment of locally advance or metastatic EGFR-TK mutation-positive non-small-cell lung cancer.[71] The re-analysis of samples from one of these trials and the two remaining trials used EGFR mutation tests which targeted a wider range of mutations, including resistance mutations. Overall, there were no clear differences in any measure of TKI treatment effect (PFS, OR, or DC), regardless of which EGFR mutation test (selective for activating mutations exon 19 deletions and exon 21 L858R, or targeting a wider range of mutations) was used to select patients. No study reported a significant difference in TKI treatment effect between patients with exon 19 deletions and those with the exon 20 mutation L858R. One additional trial, the Western Japan Oncology Group study, was included in TA258 but did not meet the inclusion criteria for our review as it focussed on the treatment of patients with post-operative recurrence with or without post-operative adjuvant chemotherapy; patients with stage IIIB or IV NSCLC were also included but no separate data were reported for these patients.[72] EGFR mutation testing in this study also targeted exon 19 deletions and the exon 21 mutation L858R and used a combination of fragment analysis and direct sequencing methods; the reported treatment effect of TKI (gefitinib) compared with standard chemotherapy (cisplatin plus docetaxel) was similar to that seen in the trials included in our review (PFS: HR 0.49 (95% CI; 0.34, 0.71).[72]

The estimates of the effectiveness of first-line treatment with TKIs, compared to standard chemotherapy, in patients with advanced NSCLC whose tumours tested positive for an EGFR mutation reported by studies included in this review were consistent with pooled estimates reported in recent systematic reviews. Three systematic reviews had inclusion criteria which matched ours in terms of population intervention and comparator, but which did not specify reporting of EGFR testing methods. All three reviews reported pooled HRs which indicated increased PFS in patients with EGFR mutation positive tumours who were treated with TKIs compared to those treated with standard chemotherapy (HR 0.43 (95% CI: 0.32, 0.58),[73] HR 0.37 (95% CI: 0.27, 0.52),[74] and HR 0.45 (95% CI: 0.36, 0.58)[75]). Two reviews also reported significantly higher OR rates (RR 5.68 (95% CI: 3.17, 10.18),[74] and HR 2.08 (95% CI: 1.75, 2.46)[75] for patients treated with TKIs and no significant difference in OS between the two treatment groups.[74,75]

5.1.2 Cost-effectiveness

The review of economic analyses of different methods for EGFR TK mutation testing to decide between standard chemotherapy or EGFR TKIs for first-line treatment of patients

with locally advanced or metastatic non-small-cell lung cancer found one full paper[53] and five conference abstracts.[58-62] The full paper did not fit the decision problem as it concerned second-line use of anti EGFR TKIs. Although the conference abstracts were all about first-line use of TKIs, they did not provide enough specific information to be of use; future full publications may provide more information.

In the health economic analysis, the cost-effectiveness of different methods for EGFR-TK mutation testing to decide between standard chemotherapy or EGFR TKIs for first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer was assessed. In light of the scarce evidence that was available, three analyses were performed: 'evidence on comparative effectiveness available', 'linked evidence', and 'assumption of equal prognostic value'. Direct sequencing of all exon 18-21 mutations, the comparator, could only be included in the last two analyses.

In the 'evidence on comparative effectiveness available' analysis, testing with the Therascreen® EGFR PCR Kit was compared with direct sequencing of all exon 19-21 mutations in order to estimate lifetime cost and QALYs using the observed response to treatment and the available relative PFS and OS data. The results of this analysis suggested that direct sequencing of all exon 19-21 mutations was both more effective and more costly than testing with the Therascreen® EGFR PCR Kit at an ICER of £32,167 per QALY gained. The sensitivity analyses all resulted in similar outcomes. The key drivers behind this result were the differences in the proportion of patients with EGFR mutation positive, unknown mutation and mutation negative tumours and differences in objective response, PFS and OS. In particular, the predicted OS for mutation negative patients differed substantially between the studies using the Therascreen® EGFR PCR Kit[3,50] and the study which used direct sequencing of all exon 19-21[5] (Figure 13). OS for mutation negatives after testing using the Therascreen® EGFR PCR Kit was substantially lower than for testing using direct sequencing of all exon 19-21, while PFS was similar. As a result, testing using the Therascreen® EGFR PCR Kit appeared less effective in terms of QALYs, but was also less costly since the gained life years for direct sequencing of all exon 19-21 were mainly spent in the relative expensive disease progression health state.

It should be noted that this analysis was based on a number of assumptions, of which the following two are particularly problematic:

- The proportion of patients with a positive or negative test result after the use of these tests in the NHS population, was estimated based on the proportion of EGFR

mutation positive patients in England and Wales, the proportion of patients with an unknown test result, and test accuracy for the prediction of treatment response derived from two separate trials.[5, 50]

- The differences in relative treatment response, PFS and OS between the results of the First-Signal trial[5] that were used to model direct sequencing of all exon 19-21 mutations and the results of the IPASS trial[3, 50] that were used to model testing using the Therascreen® EGFR PCR Kit, are solely due to the different tests used to distinguish between patients whose tumours are EGFR mutation positive (and who receive TKI treatment) and patients whose tumours are EGFR mutation negative (and who receive doublet chemotherapy).

The results of the 'evidence on comparative effectiveness available' analysis should therefore be interpreted on the condition that these assumptions hold. Moreover, the uncertainty presented surrounding the results is an underestimation of the true uncertainty, as the uncertainty associated with the assumptions was not parameterised and is therefore not reflected in the probabilistic sensitivity analyses.

In the 'linked evidence' analysis two other direct sequencing tests (direct sequencing of all exon 18-21 mutations and direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)) for which accuracy data to predict response to treatment with TKIs were available were also included in the analysis. The results of this analysis showed that compared to direct sequencing of all exons 18-21 mutations, the Therascreen® EGFR PCR Kit was less effective and less costly (ICER: £31,849) while the other tests were more effective and more expensive (ICERs: £35,634 and £38,251). Sensitivity analyses did not show any substantial changes to these results. However, it should be noted that this analysis is also based on a number of substantive assumptions, including those described for the 'evidence on comparative effectiveness available' analysis. The following additional assumption should also be noted:

- For direct sequencing of all exon 18-21 mutations and direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells), the relative PFS and OS for mutation positives and mutation negatives correlates perfectly with relative PFS and OS as observed for direct sequencing of all exon 19-21 mutations in the First-SIGNAL trial.[5]

The same caveat for the interpretation of the results and surrounding uncertainty as explained above for the 'evidence on comparative effectiveness available' analysis applies to the interpretation of the results of the 'linked evidence' analysis.

The 'assumption of equal prognostic value' analysis, included all tests for which information on cost and/or technical performance was available from the online survey of NHS laboratories in England and Wales. This included the tests for which neither comparative effectiveness nor response data were available. Therefore, in this analysis, the costs of the tests were assessed given an assumption of equal prognostic value (based on the prognostic value of testing using the Therascreen® EGFR PCR Kit, as this was the only test for which prognostic data were available on patients with positive, negative and unknown tumour EGFR mutation status) and test specific information on costs only. In addition, prognostic value of testing was based on testing using the Therascreen® EGFR PCR Kit because other tests used in NHS laboratories in England and Wales were considered to have technical characteristics (low limit of detection and similar proportion of tumour cells required for analysis) which were more similar to this test than to direct sequencing methods and would therefore be more likely to have similar prognostic value to the Therascreen® EGFR PCR Kit than to direct sequencing. The results of the 'assumption of equal prognostic value' analysis indicated that the strategies were almost equal, i.e. the lowest total strategy cost was £25,730 (Sanger sequencing or Roche Cobas) versus £25,777 for the most expensive strategy (Fragment length analysis combined with Pyrosequencing). The sensitivity analysis, where the number of unknowns was based on results from the online survey of NHS laboratories in England and Wales, instead of being assumed equal based on literature, showed a slightly larger range of costs (£24,682 to £25,172) and a small range in QALYs (0.871 to 0.886) for the included mutation tests.

5.2 Strengths and limitations of assessment

5.2.1 Clinical effectiveness

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,[76] and potential need to include non-randomised controlled trial, search strategies were developed to maximise sensitivity at the expense of reduced

specificity. Thus, large numbers of citations were identified and screened, many of which did not meet the inclusion criteria of the review.

The possibility of publication bias remains a potential problem for all systematic reviews. Considerations may differ for systematic reviews of test accuracy studies. It is relatively simple to define a positive result for studies of treatment, e.g. a significant difference between the treatment and control groups which favours treatment. This is not the case for test accuracy studies, which measure agreement between index test and reference standard. It would seem likely that studies finding greater agreement (high estimates of sensitivity and specificity) will be published more often. This distinction may be less applicable to studies in this review which provided accuracy data, as in all cases these studies aimed to assess the effectiveness of treatment with TKIs in different patient groups rather than being primarily focussed upon test performance. Our review included small numbers of clinically heterogeneous studies, both for the accuracy of EGFR mutation testing to predict response to treatment with TKIs and for the relative effectiveness of TKIs in populations selected using different EGFR mutation test methods. We were therefore unable to undertake any meta-analyses or formal assessment of publication bias. However, our search strategy included a variety of routes to identify unpublished studies and resulted in the inclusion of a number of conference abstracts.

Clear inclusion criteria were specified in the protocol for this review and the one protocol modification that occurred during the assessment has been documented in the methods section of this report. The eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for excluding all of the studies considered potentially relevant at initial citation screening (Appendix 5). The review process followed recommended methods to minimise the potential for error and/or bias;[28] studies were independently screened for inclusion by two reviewers and data extraction and quality assessment were done by one reviewer and checked by a second (MW and PW). Any disagreements were resolved by consensus.

Studies included in this review were assessed for risk of bias using published tools appropriate to study design and/or the type of data extracted. Studies which provided data on the accuracy of EGFR mutation testing to predict response to treatment with TKIs were assessed using a modification of the QUADAS-2 tool.[37] QUADAS-2 is structured into four key domains covering participant selection, index test, reference standard, and the flow of patients through the study (including timing of tests). Each domain is rated for risk of bias

(low, high, or unclear); the participant selection, index test and reference standard domain are also, separately rated for concerns regarding the applicability of the study to the review question (low, high, or unclear). The version of QUADAS-2 used in this report did not include assessment of applicability because both the index test and study population were tightly defined by our inclusion criteria and clinical outcome measures were treated as the reference standard. Studies which provided data on the effectiveness of treatment with TKIs, compared with standard chemotherapy, in patients with EGFR mutation positive tumours were all RCTs or subgroup analyses from RCTs. These studies were therefore assessed using the Collaboration's tool for assessing risk of bias in randomised trials.[31, 36] The results of the risk of bias assessment are reported, in full, for all included studies (Appendix 3) and in summary in the results (sections 3.2.2 and 3.3.3). The main potential sources of bias identified were exclusion of withdrawals from the analyses (for both studies providing data on the accuracy of EGFR mutation tests to predict response to TKIs and RCTs of TKIs in patients with EGFR mutation positive tumours) and blinding of participants and personnel in treatment trials, which was not possible due to the different delivery modes of intervention and comparator drugs.

All of the studies included in this review have some limitations in respect of their ability to address the overall aim of comparing the clinical effectiveness of different EGFR mutation tests to determine which patients are may benefit from treatment with TKIs and which should receive standard chemotherapy. The IPASS[3, 50] and first-SIGNAL[5] trials represent the closest approximation to the ideal study in that they provide full information on the comparative treatment effect (TKI versus standard chemotherapy) for both patients with EGFR mutation positive and EGFR mutation negative tumours, where mutation status was defined using the Therascreen® EGFR PCR Kit (version 1) and direct sequencing, respectively. However, data were derived from subgroup analyses of patients included in the original trial who had received EGFR mutation testing and, in the case of the first-SIGNAL study, this subgroup included a small number of participants and was poorly described.[5] Because methods of testing EGFR mutation status differ both in terms of the mutations targeted and limit of detection (the lowest proportion of tumour cells with a mutation that can be detected), the definition of EGFR mutation positive varies according to which test is used. All testing methods are essentially reference standard methods for classifying mutation status, as defined by the specific test characteristics. The essential clinical question is ‘which testing method is best at classifying patients, such that the maximum treatment effect is achieved both for mutation positive patients who receive TKIs and mutation negative patients who

receive standard chemotherapy?' To fully address this question IPASS type data would be required mutation positive and negative patients as defined by each proposed classification method (i.e. each different EGFR test). Following the IPASS trial and subsequent NICE recommendations,[7, 77] obtaining these data may be problematic, since it could be argued that a trial where patients are randomised to TKI or standard chemotherapy regardless of tumour EGFR mutation status would be unethical. Additionally, once the principle had been established that TKIs are more effective in EGFR mutation positive patients, subsequent trials have tended to focus on assessing the effectiveness of various TKIs in populations with EGFR mutation positive tumours; trials are not primarily concerned with the method used to establish mutation status. An alternative approach to this problem is provided by studies which report sufficient data to calculate the accuracy of different EGFR mutation tests for predicting response to treatment with TKIs. These studies provide information on the extent to which different EGFR mutation tests are able to discriminate between patients who will respond to TKI treatment and those who will not; treatment response data are reported for both patients with EGFR mutation positive and EGFR mutation negative tumours. However, we were only able to identify four studies of this type; all used direct sequencing methods, three pre-dated the IPASS trial and three had very small sample sizes, which were reflected in the wide confidence intervals around sensitivity and specificity estimates. In addition, no study reported data for more than one EGFR mutation test, hence any apparent differences in test performance observed between studies may have arisen as a result of differences in study populations. Trials which compared the effectiveness of TKIs with that of standard chemotherapy in patients with advanced NSCLC, whose tumours tested positive for EGFR mutations, were also included in this review. These trials were included with the aim of providing some indication on how the favourable TKI treatment effect seen in patients with mutation positive tumours in the IPASS trial may vary according to how these patients are selected (which EGFR mutation test is used). However, it should be noted that differences between these studies, other than the way in which positive EGFR mutation status is defined, particularly in relation to the baseline participant characteristics, may contribute to any differences in treatment effects observed. In addition, these trials can provide no information about the relative effectiveness of TKIs and standard chemotherapy in patients whose tumours are classified as EGFR mutation negative by tests other than the Therascreen® EGFR PCR Kit. Some trials reported the results of subgroup analyses to assess possible variation in treatment effect (e.g. smoking history, tumour histology), however,

trials were generally not powered to detect any difference in treatment effect between subgroups.

This assessment assumes equivalent treatment effects for the two TKIs (gefitinib and erlotinib), which are recommended by NICE as first-line treatments for patients with advanced, EGFR mutation positive NSCLC.[7,77] This assumption is supported by the conclusion of the appraisal committee in NICE guidance 258 that "there was insufficient evidence to suggest a difference in clinical effectiveness between erlotinib and gefitinib."[77] No RCTs directly comparing gefitinib and erlotinib have been identified and the results of indirect treatment comparisons vary.[77,78] Our review identified one retrospective Taiwanese study comparing gefitinib and erlotinib, which did not meet our inclusion criteria. This study included 224 patients, with known tumour EGFR mutation status, who had received TKI treatment (124 gefitinib and 100 erlotinib), but was not restricted to first-line treatment; no significant difference between the two treatments was observed for either PFs or OR rate.[79]

5.2.2 Cost-effectiveness

A de novo probabilistic model was developed to assess the cost-effectiveness of different methods for EGFR-TK mutation testing to decide between standard chemotherapy or EGFR TKIs for first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer. In order to be consistent with related assessments/appraisals, it was first ensured that the results for patients with an EGFR positive mutation tumour, using the Therascreen® EGFR PCR Kit, in the de novo model were similar to the results of these patients in the initial manufacturer's model used in NICE Technology Appraisal 192.[7,52] Subsequently, the ERG amendments were incorporated and ICERs from the de novo model were compared with ICERs as reported in the final appraisal determination of STA 192 (see Appendix 6 for results).

Test failures and costs were based on information obtained from the online survey of NHS laboratories in England and Wales. These real-life data provided an important source of information, which is likely to be representative of clinical practice.

In the assessment of economic value of different tests, a link has to be established between test accuracy, clinical value (e.g. treatment response, PFS, OS) and relative cost-effectiveness. Ideally, the performance of EGFR mutation tests would be assessed against an objective measure of the true presence/absence of a clinically relevant EGFR-TK mutation (the 'reference standard'), and comparative effectiveness of treatment (TKI versus

chemotherapy) conditional upon the true or false presence/absence of the EGFR-TK mutation would be determined. However, each different testing method targets a different range of mutations and has different limits of detection (lowest proportion of mutation detectable in tumour cells) and the exact combination of mutation type and level which will provide optimal treatment selection remains unclear. For this reason, assessment of test performance based on comparison with a conventional 'reference standard' is not currently possible. In this situation, an alternative way to determine the relative value of diagnostic methods for EGFR-TK mutation testing is to use studies that report on the comparative treatment effect in patients with different EGFR mutation status (positive, negative, or unknown) as defined using different EGFR mutation tests. Thus, objective response on anti-EGFR TKIs was assumed to correlate perfectly with the 'true' presence/absence of the EGFR-TK mutation. The use of alternative measures of EGFR-TK mutation in the assessment of cost-effectiveness might impact the proportion of mutation positives and negatives (Table 15 and 16) and thus might substantially impact the assessment of cost-effectiveness (in either direction) as this is one of the key drivers of cost-effectiveness. In absence of an objective measure of the 'true' presence/absence of a clinically significant EGFR-TK mutation (i.e. which mutations, present at what levels, as defined by which testing method, will result in differential treatment effects for TKIs versus standard chemotherapy), the current cost-effectiveness assessment is, at best, an approximation of the 'true' cost-effectiveness of test-guided treatments.

For only two tests (the Therascreen® EGFR PCR Kit and direct sequencing of all exon 19-21 mutations) evidence on the comparative treatment effect in patients with different tumour EGFR mutation status (positive, negative, or unknown) as defined using different tests was available. A major assumption underpinning our analyses was that the differences in objective response, PFS and OS observed in the two included studies from which these data were derived[3,5,50] can be solely ascribed to differences in test performance. In practice this assumption would seem unlikely to hold true. These differences could also be caused by differences in participant characteristics, differences in the standard chemotherapy regimen, or differences in treatment strategies following progression which may affect OS, all of which were apparent between these two studies.

It was not part of the scope of this assessment to update the appraisal of gefitinib for the first-line treatment of locally advanced or metastatic NSCLC (NICE Technology Appraisal 192).[7] However, the external review group's report for NICE Technology Appraisal 192[66]

noted that the cost-effectiveness of the 'EGFR mutation test + TKI treatment if positive and doublet chemotherapy if negative' strategy versus the 'doublet chemotherapy without EGFR mutation testing' strategy is conditional upon the accuracy of the mutation test used to distinguish between patients who receive TKI treatment and patients who receive doublet chemotherapy. This is a simplification of the issue since, as described previously, each EGFR mutation testing method identifies a subtly different combination of type and level of EGFR mutation, and the clinical significance of these different combinations is largely unknown. It is particularly problematic if a test defines positive mutation status for a type and/or level of mutation which is not clinically significant (associated with response to treatment with TKIs), since the patients thus 'falsely' identified as having mutation positive tumours will experience a loss of survival time and quality of life due to not receiving the most effective treatment option for them, while still experiencing treatment related adverse events; the costs of treatment are also considerably increased. The effects of this might even outweigh the relative gains of TKI treatment versus doublet chemotherapy for those patients correctly selected for TKI treatment. Therefore, the economic evaluation of TKI treatment should not be seen as an assessment of the relative value of the drug in isolation from the mutation test used to select eligible patients, but as an assessment of a specific 'mutation test'-'treatment' combination which may not be valid if other methods for mutation testing are used. For this assessment, this means that the results described are partial in the sense that the 'doublet chemotherapy without EGFR mutation testing' strategy was not taken into account.

5.3 Uncertainties

5.3.1 Clinical effectiveness

As discussed in section 5.2.1 'Strengths and Limitations', one key consideration when selecting an EGFR mutation testing method is the variation between tests in limit of detection (i.e. the minimum percentage of mutation in tumour cells required to produce a positive result). A lower limit of detection can enhance the ability of laboratories to produce results from poor quality samples. However, it should not be assumed that a lower limit of detection will necessarily result in a more clinically effective test, as it is possible that TKIs may be less effective in patients with a low proportion of tumour cells harbouring mutation. Discussions with clinical experts suggest that there is ongoing uncertainty around this issue as quantitative results of EGFR mutation testing are not routinely reported. None of the studies which met the inclusion criteria for this review reported any data on variation in treatment effect with the proportion of tumour cells having EGFR mutations. A Chinese study, which did not meet our inclusion criteria, assessed tissue bank tumour samples from

NSCLC patients who had been treated with gefitinib at any stage during the course of their disease.[80] This study analysed samples using both direct DNA sequencing and the Therascreen® EGFR PCR Kit; samples which were positive by both methods were classified as having a high abundance of EGFR mutations, samples which were positive using the Therascreen® EGFR PCR Kit and negative on direct sequencing were classified as having a low abundance of EGFR mutations, and samples which were negative on both tests were classified as wild-type. The results of this study were mixed; median PFS was significantly longer in both the high abundance (11.3 months (95% CI: 7.4, 15.2)) and low abundance (6.9 months (95% CI: 5.5, 8.4)) groups compared with wild type (2.1 months (95% CI: 1.0, 3.2)), however, for other outcome measures (OR rate and OS) benefits were limited to the high abundance group.[80] It should also be noted that this study provides no information on the relative effectiveness of standard chemotherapy in these patient groups.

A further area of uncertainty concerns the clinical value of detecting rare mutations and possible resistance mutations. The majority of the evidence on the effectiveness of first-line treatment with TKIs in patients with EGFR mutation positive NSCLC has been derived from patients with exon 19 deletions or the exon 21 mutation L858R. This is unsurprising since these account for >90% of all EGFR mutations.[12,13,19] The additional clinical value of using tests which target a wider range of mutations remains uncertain, since the low frequency of most EGFR mutations makes it very difficult to adequately assess treatment effects in patients with mutations other than exon 19 deletions or L858R. Some of the studies in our review, which provided data on the accuracy of EGFR testing in predicting response to treatment with TKIs, reported response data by individual mutation; these data appeared to indicate that there may be a less favourable response to TKIs in patients with T790M or other exon 20 mutations (see Table 8, section 3.2.2), however, these data were very limited. There are a number of registry studies, which did not meet our inclusion criteria, but which have reported some information of clinical response in patients with different EGFR mutations. Murray et al. compiled a database of 202 articles, which provided data on 2,548 NSCLC patients (disease stage and previous treatment not specified) who had been treated with TKIs. This study reported an OR rate of 86% for patients with a mutation in exon 19, compared with 33% for those with a mutation in exon 20; subgroup analysis indicated that a mutation in exon 20, in the absence of T790M, was associated with an OR rate of 68% (comparable to that for mutations in exon 18 or 21).[81] Of the 115 different mutations for which response data were available, only 13 demonstrated PD as a response, of which eight were located in exon 20.[81] However, as noted by the authors some caution is required in

interpreting these data as the two most common mutations account for >90%, with T790M occurring in only around 2% of patients.[81] An observational study conducted in 15 of 28 French National Cancer Institute laboratories identified 1,048 EGFR mutations from 10,117 NSCLC patients tested.[82] Of these, 108 were rare mutations (48 in exon 18 and 60 in exon 20); 36 of these patients received a TKI and were evaluable for response and the best response was progression in 18 patients, stabilisation in 11 patients and PR in seven patients.[82] REASON, a large registry study of over 4,000 patients at 151 centres in Germany, aims to generate data on EGFR mutation status and clinical response to TKIs in patients with stage IIIB or stage IV data, however, to date, this study has only been published as a conference abstract with no data for specific mutations.[83] A similar program, EGFR FASTnet exists in Italy, though again we have not been able to identify any publication that reports mutation-specific response data.[84, 85] Both programs are supported by AstraZeneca.

The clinical significance of rare mutations and the possible increased risk of 'false-positives' associated with the use of EGFR mutation tests that are able to detect very low levels of mutation were both highlighted as areas requiring further research by the European EGFR Workshop Group in a 2009 multidisciplinary consensus meeting on the implementation of EGFR mutation testing.[18]

As with the issue of rare mutations, there is uncertainty regarding the clinical effectiveness of identifying EGFR mutations in non-adenocarcinoma NSCLC. The majority of the evidence on the effectiveness of first-line treatment with TKIs in patients with EGFR mutation positive NSCLC has been derived from patients with adenocarcinomas. All but one[5] of the studies included in our review included small numbers of patients with other histological diagnoses, but none reported separate data for these patients. We identified one retrospective analysis of patients with advanced NSCLC and known EGFR mutation status (determined by direct sequencing), which did not meet our inclusion criteria, but which reported comparative data on 12 patients with non-adenocarcinoma and 269 with EGFR mutation positive adenocarcinoma who were treated with TKIs.[86] OR and DC rates were lower in patients with non-adenocarcinoma than in those with adenocarcinoma (50% versus 78% and 75% versus 89%, respectively), and PFS was also significantly longer in the adenocarcinoma group (11.27 (95% CI: 9.87, 12.67) months versus 3.67 (95% CI: 1.34, 5.99) months).[86] Similar results were reported for a systematic review which compared data for 33 EGFR mutation positive non-adenocarinoma NSCLC patients, treated with gefitinib, from 15 studies with adenocarcinoma patients from the same studies.[87] Though it appears that patients with non-adenocarcinoma

NSCLC, which is positive for EGFR mutations, may derive less benefit from treatment with TKIs than those with adenocarcinomas, it should be noted that this question was outside the scope of our review and the studies discussed above do not provide any information of the relative effectiveness of TKIs and standard chemotherapy regimens in this group of patients.

A wide variety of EGFR mutation test methods are currently used by accredited NHS laboratories in England and Wales, however, for the majority of these methods, no studies were identified which could provide data linking the results of EGFR testing to the effectiveness treatment. Therefore, the potential clinical effects of using different EGFR tests to make decisions on first line treatment in patients with stage IIIB or IV remains uncertain. The available data were for version 1 of the Therascreen® EGFR PCR Kit and for direct sequencing methods targeting various mutations. Version 1 of the Therascreen® kit is no longer being actively marketed by Qiagen and equivalent data are not available for its replacement, the Therascreen® EGFR RGQ PCR Kit, or for the Therascreen® EGFR Pyro Kit. However, it may be reasonable to assume equivalent diagnostic performance for all three products as both versions of the Therascreen® EGFR PCR Kit target the same mutations and the Therascreen® EGFR Pyro Kit targets a similar set of mutations, with the addition of one further exon 19 deletion and the exon 21 mutation L861R and the loss of three exon 20 insertions.[88, 89] All three methods have a low limit of detection (≤5%).[88, 89] The Therascreen® EGFR Pyro Kit can also produce quantitative results.[89] No data are currently available for next generation sequencing; a next generation sequencing method is currently being developed and validated by one NHS laboratory, but next generation sequencing is not yet in routine clinical use in any of NHS laboratories in England and Wales who responded to our survey.

5.3.2 Cost-effectiveness

Major assumptions were made in order to be able to model the relative cost-effectiveness of different EGFR mutation tests. It was assumed that the differences in relative treatment response, PFS and OS between the results of First-SIGNAL trial[5] and the results of the IPASS trial[3, 50] were solely due to the different mutation tests used (the Therascreen® EGFR PCR Kit and direct sequencing of all exon 19-21, respectively) to distinguish between patients whose tumours are EGFR mutation positive and those whose tumours are EGFR mutation negative ('evidence of comparative effectiveness' and 'linked evidence' analyses). As described in the previous section, it is highly questionable whether this assumption would hold. Furthermore, in order to calculate the proportion of patients with a positive and negative

test result, positive tested patients were categorised as false positive if no treatment response was observed after TKI, while patients were categorised as true positive if treatment response was observed after TKI. Similarly, negatively tested patients were categorised as false negative if treatment response was observed after TKI, while patients were categorised as true negative if no treatment response was observed after TKI. Ideally, the categorisation of true/false positives/negatives should be based on an objective measure of the true presence/absence of a clinically relevant EGFR-TK mutation. However, as previously described, the uncertainty around the exact definition of a clinically relevant mutation is such that this is not currently possible. It was also assumed that the proportion of patients with unknown mutation status relative to the number of patients for whom a tissue sample was available, as reported in the trials included in the systematic review,[47, 50] provides a realistic approximation of the proportion of patients with an unknown test result in clinical practice. Outcomes in patients with unknown tumour mutation status were only reported in the IPASS trial.[3, 50] These results were used to model the outcomes in patients with an unknown test result for the other testing methods considered in this assessment, assuming that the objective response rate, PFS and OS in patients with an unknown test result after use of the Therascreen® EGFR PCR Kit, as reported in the IPASS trial[3, 50] were generalisable to the direct sequencing methods. In the 'linked evidence' analysis, information from Jackman et al[47] (direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)) and the First-Signal trial[5] were used to model the other direct sequencing methods if information was missing. Thus, assuming this information was generalisable to the other direct sequencing methods. The extent to which these results are actually generalisable to testing methods other than the Therascreen® EGFR PCR Kit is unknown.

Moreover, as this model was partially based on the evidence and model structure used in the appraisal of gefitinib for the first line treatment of locally advanced or metastatic NSCLC (NICE Technology Appraisal 192),[7, 52] the assumptions underlying that appraisal also apply to this assessment; for instance, assumptions regarding the applicability of the findings in the trials to the population in England and Wales.

Finally, it should be emphasised that the uncertainty resulting from the above mentioned assumptions was not parameterised in the model and is therefore not reflected in the probabilistic sensitivity analyses and hence cost-effectiveness acceptability curves.

6. CONCLUSIONS

6.1 Implications for service provision

There was no strong evidence that any one EGFR mutation test had greater accuracy than any other test, although there was a suggestion that Therascreen® EGFR PCR Kit may be more accurate than direct sequencing for predicting response to treatment with TKIs. The clinical effectiveness of TKIs, in patients whose tumours are positive for EGFR, did not appear to vary according to which test was used to determine EGFR mutation status.

The results of the 'evidence on comparative effectiveness available' analysis and the 'linked evidence' analysis both indicated that the Therascreen® EGFR PCR Kit was less effective and less expensive compared to direct sequencing (all exon 19-21 mutations and all 18-21 mutations respectively) at £31,000 to £35,000 per QALY lost. The lower QALYs for the Therascreen® EGFR PCR Kit seem counterintuitive as the accuracy data show a higher accuracy for Therascreen® EGFR PCR Kit. This contradiction possibly results from the problematic and substantial assumptions made to arrive at the economic results. In particular, the assumption that the differences in treatment response and survival between tests as observed between the different studies are solely due to the different tests used. This ignores all other factors that can explain variations in outcomes between the studies. Therefore, these outcomes of the assessment of cost-effectiveness should be interpreted with extreme caution.

The results of the 'assumption of equal prognostic value' analysis (including all tests for which information on cost and/or technical performance was available from the online survey of NHS laboratories in England and Wales) showed that the costs of the EGFR mutation tests were very similar (range from £25,730 for Sanger sequencing or Roche Cobas for samples with insufficient tumour cells to £25,777 for Fragment length analysis combined with pyrosequencing).

There are no data on the clinical or cost-effectiveness of Therascreen® EGFR Pyro Kit or next generation sequencing. No published studies were identified for either of these two methods and neither method is currently in routine clinical use in any of NHS laboratories in England and Wales who responded to our survey; one laboratory is currently developing and validating a next generation sequencing method.

6.2 Suggested research priorities

The available data have limitations in respect of their ability to address the overall aim of this assessment, to compare the clinical effectiveness of different EGFR mutation tests to determine which patients may benefit from treatment with TKIs and which should receive standard chemotherapy. Because each different testing method potentially selects a subtly different population, based on the targeting of a different range of mutations and different limits of detection, the most informative studies are those which provide full information on the comparative treatment effect (TKI versus standard chemotherapy) for both patients with EGFR mutation positive and EGFR mutation negative tumours. Studies of this type are only available for two testing methods, direct sequencing and the Therascreen® EGFR PCR Kit (version 1), and further similar trials are unlikely as randomisation of patients to TKIs or standard chemotherapy, regardless of EGFR mutation status, would be against current clinical guidance and would almost certainly be considered unethical. One possible solution to this problem would be to re-test stored samples from previous studies, where patient outcomes are already known, using those EGFR mutation testing methods for which adequate data are currently unavailable. This approach could provide a 'black box' answer, where by the relative effectiveness of TKIs and standard chemotherapy in patients with EGFR mutation positive and negative tumours could be determined for each test. However, it would not provide any information on the underlying reason for any observed differences between tests.

Newer methods of EGFR mutation testing, e.g. the Therascreen® EGFR Pyro Kit, can provide quantitative results. Should quantitative testing become part of routine practice, longitudinal follow-up studies relating the level of mutation and/or the presence or rarer mutations to patient outcomes would become possible. Studies of this type could help to assess which features of EGFR mutation tests are likely to be important in determining their clinical effectiveness.

As the uncertainties associated with clinical effectiveness forced the major assumptions in the economic evaluation this type of research would also facilitate economic analyses of EGFR mutation testing.

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APPENDIX 1: LITERATURE SEARCH STRATEGIES

Clinical effectiveness search strategies

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)
41 remove duplicates from 40 (4897)

Medline (OvidSP): 2000-2012/07/wk 1
Searched 18.7.12

1 Quinazolines/ (11462)
2 (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. (2563)
3 (Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2).ti,ab,ot,hw,rn. (3588)
4 or/1-3 (12590)
5 Carcinoma, Non-Small-Cell Lung/ (26828)
6 (nsclc or nsclcs).ti,ab,ot,hw. (14105)
7 (lung$ adj3 (adeno-carcinoma$ or adenocarcinom$)).ti,ab,ot. (6982)
8 ((non-small cell or large cell) adj3 lung$).ti,ab,ot. (24330)
9 (lclc or lclcs).ti,ab,ot,hw. (42)
10 or/5-9 (37809)
11 Receptor, Epidermal Growth Factor/ (25521)
12 epidermal growth factor receptor$.ti,ab,ot. (20251)
13 epidermis growth factor receptor$.ti,ab,ot. (0)
14 transforming growth factor alpha receptor$.ti,ab,ot. (10)
15 ((tgf-alpha or urogastrone) adj2 receptor$).ti,ab,ot. (243)
16 ((erbB1 or erbB-1 or erbB) adj1 (protein$ or receptor$)).ti,ab,ot. (1223)
17 EGFR.ti,ab,ot. (19756)
18 EGFRTK.ti,ab,ot. (10)
19 EGF receptor$.ti,ab,ot. (8278)
20 (Cobas adj3 EGFR).af. (0)
21 (Cobas adj3 epidermal growth factor).ti,ab,ot. (0)
22 (thera?screen$ or therascreen$).af. (13)
23 or/11-22 (38939)
24 4 and 10 and 23 (2059)
25 Carcinoma, Non-Small-Cell Lung/di [Diagnosis] (1966)
26 "diagnostic techniques and procedures"/ or diagnostic tests, routine/ (7996)
27 clinical laboratory techniques/ or molecular diagnostic techniques/ (19825)
28 Diagnosis/ (16321)
29 Diagnosis, Differential/ (355501)
30 diagnos$.ti,ab,ot. (1397222)
31 (test or tests or testing or tested).ti,ab,ot. (1683480)
32 ((lab or labs or laborator$) adj2 (procedure$ or exam$)).ti,ab,ot. (10488)

33 or/25-32 (3069443)
34 10 and 23 and 33 (887)
35 24 or 34 (2529)
36 animals/ not (animals/ and humans/) (3660877)
37 35 not 36 (2499)
38 limit 37 to yr="2000 -Current" (2463)
39 remove duplicates from 38 (2318)

Medline In-Process Citations (OvidSP): 2000-2012/07/17
Medline Daily Update (OvidSP): 2000-2012/07/17
Searched 18.7.12

1 Quinazolines/ (31)
2 (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. (278)
3 (Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2).ti,ab,ot,hw,rn. (233)
4 or/1-3 (432)
5 Carcinoma, Non-Small-Cell Lung/ (78)
6 (nsclc or nsclcs).ti,ab,ot,hw. (1275)
7 (lung$ adj3 (adeno-carcinoma$ or adenocarcinom$)).ti,ab,ot. (468)
8 ((non-small cell or large cell) adj3 lung$).ti,ab,ot. (1905)
9 (lclc or lclcs).ti,ab,ot,hw. (6)
10 or/5-9 (2407)
11 Receptor, Epidermal Growth Factor/ (57)
12 epidermal growth factor receptor$.ti,ab,ot. (1221)
13 epidermis growth factor receptor$.ti,ab,ot. (0)
14 transforming growth factor alpha receptor$.ti,ab,ot. (0)
15 ((tgf-alpha or urogastrone) adj2 receptor$).ti,ab,ot. (5)
16 ((erbB1 or erbB-1 or erbB) adj1 (protein$ or receptor$)).ti,ab,ot. (48)
17 EGFR.ti,ab,ot. (1697)
18 EGFRTK.ti,ab,ot. (1)
19 EGF receptor$.ti,ab,ot. (195)
20 (Cobas adj3 EGFR).af. (0)
21 (Cobas adj3 epidermal growth factor).ti,ab,ot. (0)
22 (thera?screen$ or therascreen$).af. (2)
23 or/11-22 (2307)
24 4 and 10 and 23 (163)
25 Carcinoma, Non-Small-Cell Lung/di [Diagnosis] (7)
26 "diagnostic techniques and procedures"/ or diagnostic tests, routine/ (23)
27 clinical laboratory techniques/ or molecular diagnostic techniques/ (86)
28 Diagnosis/ (1)
29 Diagnosis, Differential/ (316)
30 diagnos$.ti,ab,ot. (71695)
31 (test or tests or testing or tested).ti,ab,ot. (101066)
32 ((lab or labs or laborator$) adj2 (procedure$ or exam$)).ti,ab,ot. (550)

33 or/25-32 (160664)
34 10 and 23 and 33 (103)
35 24 or 34 (219)
36 animals/ not (animals/ and humans/) (3555)
37 35 not 36 (219)
38 limit 37 to yr="2000 -Current" (219)
39 remove duplicates from 38 (215)

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 7:2012
Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 7:2012
Database of Abstracts of Reviews of Effects (DARE) (Wiley): Issue 3:2012
Health Technology Assessment Database (HTA) (Wiley): Issue 3:2012
Search limited to 2000-2012
Searched 18.7.12

#1 MeSH descriptor Quinazolines, this term only 612
#2 (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,kw 130
#3 (Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2):ti,ab,kw 171
#4 (#1 OR #2 OR #3) 738
#5 MeSH descriptor Carcinoma, Non-Small-Cell Lung, this term only 1952
#6 (nsclc or nsclcs or lclc or lclcs):ti,ab 2101
#7 (lung* NEAR/3 (adeno-carcinoma* or adenocarcinom*)):ti,ab,kw 73
#8 ((non-small NEXT cell) NEAR/3 lung*):ti,ab,kw 3584
#9 ((large NEXT cell) NEAR/3 lung*):ti,ab,kw 4
#10 (#5 OR #6 OR #7 OR #8 OR #9) 3812
#11 MeSH descriptor Receptor, Epidermal Growth Factor, this term only 264
#12 (epidermal NEXT growth NEXT factor NEXT receptor*):ti,ab,kw 405
#13 (epidermis NEXT growth NEXT factor NEXT receptor*):ti,ab,kw 0
#14 (transforming NEXT growth NEXT factor NEXT alpha NEXT receptor*):ti,ab,kw 0
#15 (tgf-alpha NEAR/2 receptor*):ti,ab,kw 1
#16 (urogastrone NEAR/2 receptor*):ti,ab,kw 0
#17 ((erbB1 or erbB-1 or erbB) NEAR/2 (protein* or receptor*)):ti,ab,kw 292
#18 (EGFR or EGFRTK):ti,ab,kw 446
#19 (EGF NEXT receptor*):ti,ab,kw 23
#20 (Cobas NEAR/3 EGFR) 0
#21 (Cobas NEAR/3 (epidermal NEXT growth NEXT factor)) 0
#22 (thera-screen* or therascreen*) 0
#23 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22) 921
#24 (#4 AND #10 AND #23) 103
#25 MeSH descriptor Carcinoma, Non-Small-Cell Lung, this term only with qualifier: DI 72
#26 MeSH descriptor Diagnostic Techniques and Procedures, this term only 95
#27 MeSH descriptor Diagnostic Tests, Routine, this term only 251

#28 MeSH descriptor Clinical Laboratory Techniques, this term only 111
#29 MeSH descriptor Molecular Diagnostic Techniques, this term only 33
#30 MeSH descriptor Diagnosis, this term only 73
#31 MeSH descriptor Diagnosis, Differential, this term only 1330
#32 diagnos*:ti,ab,kw 70823
#33 (test or tests or testing or tested):ti,ab,kw 127012
#34 ((lab or labs or laborator*) NEAR/2 (procedure* or exam*)):ti,ab,kw 605
#35 (#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34) 174193
#36 (#10 AND #23 AND #35) 38
#37 (#24 OR #36), from 2000 to 2012 116

CDSR search retrieved 0 references.
CENTRAL search retrieved 96 references.
DARE search retrieved 7 references.
HTA search retrieved 11 references.

PROSPERO (International Prospective Register of Systematic Reviews) (Internet): up to 2012/7/19
http://www.crd.york.ac.uk/prospero/
Searched 19.7.12

- displayed all records (n=650) and browsed the titles for the following terms:

Terms	**Records**
lung	0/7
Small cell	0/2
Nsclc	0/1
Therascreen	0
Thera-screen	0
Cobas	0
EGF	0
erbb	0
urogastrone	0
tgf	0
Growth factor	0
Erlotinib	0
gefitinib	0
Total	**0**

LILACS (Latin American and Caribbean Health Sciences): 2000-2012/07/06
http://regional.bvsalud.org/php/index.php?lang=en
Searched 19.7.12

Terms (date limits applied in Endnote)	**Records**
("Quinazolinas" or MH:D03.438.786 or Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2 or Erlotinib or Nsc-	13

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) AND (lung$ or Pulmón or Pulmão or Pulmonar or nsclc or nsclcs or lclc or lclcs or MH:C04.588.894.797.520.109.220.249 or MH:C08.381.540.140.500 or MH:C08.785.520.100.220.500)	
(lung$ or Pulmon or Pulmao or Pulmonar or nsclc or nsclcs or lclc or lclcs or MH:C04.588.894.797.520.109.220.249 or MH:C08.381.540.140.500 or MH:C08.785.520.100.220.500) AND ("Receptor, Epidermal Growth Factor" or "Receptor del Factor de Crecimiento Epidermico" or "Receptor do Fator de Crescimento Epidermico" or MH:D08.811.913.696.620.682.725.400.100 or MH:D12.776.543.750.060.249 or MH:D12.776.543.750.750.360.300 or MH:D12.776.543.750.750.400.340 or thera-screen$ or therascreen$ or "EGF receptor" or EGFR or EGFRTK or erbB1 or erbB-1 or erbB or urogastrone or tgf-alpha or "transforming growth factor" or "epidermis growth factor receptor" or "epidermal growth factor receptor")	14/25
Total	**27**

Spanish and portuguese translations of MeSH terms identified using the DECS (Health Sciences Descriptors) thesaurus:
http://decs.bvs.br/I/homepagei.htm

Date limit applied within Endnote Library.

Clinicaltrials.gov (Internet)
http://clinicaltrials.gov/ct2/search/advanced
Limited 01/01/2000-07/19/2012
Searched 19.7.12

Advanced search option – search terms box

Search terms	Condition	Intervention	Records
(Therascreen OR Thera-screen OR Cobas OR EGF OR EGFR OR EGFRTK OR TGF OR (epidermal growth factor*) OR erbb OR ERBB1 OR urogastrone)	(lung* OR NSCLC OR NSCLCS OR LCLC OR LCLCS)	(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 OR Gefitinib OR Geftinat OR Geftib OR iressa OR zd-1839 OR	**180**

		zd1839 OR 184475-35-2)	
(diagnos* OR test OR tests OR testing OR tested OR (lab procedure*) OR (lab exam*) OR (labs procedure*) OR (labs exam*) OR (laborator* procedure*) OR (laborator* exam*))	(lung* OR NSCLC OR NSCLCS OR LCLC OR LCLCS)	(Therascreen OR Thera-screen OR Cobas OR EGF OR EGFR OR EGFRTK OR TGF OR (epidermal growth factor*) OR erbb OR ERBB1 OR urogastrone)	**54**
Total			**234**

mRCT – metaRegister of Controlled Trials (Internet)
http://www.controlled-trials.com/
Up to 30/08/2012
Searched 30.8.12

Search terms	Results
(Therascreen OR Thera-screen OR Cobas OR EGF OR EGFR OR EGFRTK OR TGF OR (epidermal growth factor*) OR erbb OR ERBB1 OR urogastrone) AND (lung* OR NSCLC OR NSCLCS OR LCLC OR LCLCS)	302
(Therascreen OR Thera-screen OR Cobas OR EGF OR EGFR OR EGFRTK OR TGF OR erbb OR ERBB1 OR urogastrone) AND (Erlotinib OR r1415 OR tarceva OR 183321-74-6 OR 183319-69-9 OR Gefitinib OR Geftinat OR Geftib OR iressa OR zd1839 OR 184475-35-2)	195
(epidermal growth factor*) AND (Erlotinib OR r1415 OR tarceva OR 183321-74-6 OR 183319-69-9 OR Gefitinib OR Geftinat OR Geftib OR iressa OR zd1839 OR 184475-35-2)	100
TOTAL	**597**

WHO International Clinical Trials Registry Platform (ICTRP) (Internet)
http://www.who.int/ictrp/en/
Limited to 01/01/2000-30/08/2012
Searched 30.8.12

Advanced search option

Title	Condition	Intervention	Records
(Therascreen OR Thera-screen OR Cobas OR EGF OR EGFR OR EGFRTK OR	(lung* OR NSCLC OR NSCLCS OR LCLC OR LCLCS)	(Erlotinib OR Nsc-718781 OR nsc718781 OR osi-774 OR osi774	**62**

TGF OR (epidermal growth factor*) OR erbb OR ERBB1 OR urogastrone)		OR r-1415 OR r1415 OR tarceva OR cp-358774 OR cp358774 OR 183321-74-6 OR 183319-69-9 OR Gefitinib OR Geftinat OR Geftib OR iressa OR zd-1839 OR zd1839 OR 184475-35-2)	
	(lung* OR NSCLC OR NSCLCS OR LCLC OR LCLCS)	(Therascreen OR Thera-screen OR Cobas OR EGF OR EGFR OR EGFRTK OR TGF OR (epidermal growth factor*) OR erbb OR ERBB1 OR urogastrone)	**82**
Total			**144**

Biosis Previews (Web of Knowledge): 2000-2012/08/24
Searched 30.7.12

Advanced search (Lemmatization off)

 # 30 44 #28 not #29
Databases=BIOSIS Previews Timespan=2000-2012
29 5,773,678 TS=(cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep OR macaque* OR monkey*)
28 1,954 #21 or #27
27 889 #7 and #20 and #26
26 1,933,480 #22 or #23 or #24 or #25
25 45,681 TS=((laborator* NEAR procedure*) or (laborator* NEAR exam*))
24 99 TS=((labs NEAR procedure*) or (labs NEAR exam*))
23 685 TS=((lab NEAR procedure*) or (lab NEAR exam*))
22 1,913,268 TS=(diagnos* OR test or tests or testing or tested)
21 1,411 #3 and #7 and #20
20 34,254 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
19 13 TS=(thera-screen* or therascreen*)
18 0 TS=(Cobas NEAR epidermal NEAR growth NEAR factor)
17 0 TS=(Cobas NEAR EGFR)
16 7,196 TS=(EGF NEAR receptor*)
15 20,895 TS=(EGFR or EGFRTK)
14 3,256 TS=((erbB1 or erbB-1 or erbB) NEAR (protein* or receptor*))

13 0 TS=(urogastrone NEAR receptor*)
12 700 TS=(tgf-alpha NEAR receptor*)
11 1 TS=(transform NEAR growth NEAR factor NEAR alpha NEAR receptor*)
10 1,962 TS=(transforming NEAR growth NEAR factor NEAR alpha NEAR receptor*)
9 62 TS=(epidermis NEAR growth NEAR factor NEAR receptor*)
8 21,660 TS=(epidermal NEAR growth NEAR factor NEAR receptor*)
7 27,387 #4 or #5 or #6
6 19,225 TS=((non-small NEAR cell NEAR lung*) or (large NEAR cell NEAR lung*))
5 10,230 TS=((lung* NEAR adeno-carcinoma*) OR (lung NEAR adenocarcinom*))
4 8,560 TS=(nsclc or nsclcs or lclc or lclcs)
3 4,669 #1 or #2
2 3,230 TS=(Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2)
1 2,401 TS=(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)

ASCO Conference Proceedings (American Society of Clinical Oncology): 2007-2012

http://www.asco.org/ASCOv2/Meetings/Abstracts
Searched 26.10.12

- Searched 2007-2012 Annual Meetings

Keywords	Search for keyword in title	Search for keyword in Abstract	Total
Therascreen	0	13	13
Thera-screen	0	0/13	0
Cobas	2	14/16	16
EGFR-TK	1	18/19	19
Epidermal growth factor mutation	19		19
Epidermal growth factor mutations	38		38
EGFR mutation	78		78
EGFR mutations	109/116		109
Total			**292**

ESMO Conference Proceedings (European Society of Medical Oncology): 2007-2012

http://www.esmo.org/no_cache/education/abstracts-and-virtual-meetings.html
Searched 31.10.12

- 2008 33rd ESMO Congress, Stockholm - http://annonc.oxfordjournals.org/content/vol19/suppl_8/
- 2009 ECCO 15 and 34th ESMO Multidisciplinary Congress - http://www.ejcancer.info

- 2010 35th ESMO Congress, Milan - http://annonc.oxfordjournals.org/content/21/suppl_8
- 2011 ECCO 16 and 36th ESMO Multidisciplinary Congress, Brussels - http://www.ejcancer.info/issues
- 2012 37th ESMO Congress, Vienna - http://annonc.oxfordjournals.org/content/23/suppl_9

Intervention	2008	2009	2010	2011	2012
Therascreen	0	0	0	4	3
Thera-screen	0	0	0	0	0
Cobas	0	0	0	0	4
EGFR-TK	0	0	1	0	1
EGFR TK	24	0	23	0	34
Epidermal growth factor mutation	40	0	38	0	62
Epidermal growth factor mutations	40	0	38	0	62
EGFR mutation	35	0	31	27	50
EGFR mutations	35	0	31	29	50
Total	**174**	2	**162**	**63**	**266**
Total after deduplication	**41**	**2**	**38**	**51**	**65**

World Conference on Lung Cancer (International Association for the Study of Lung Cancer): 2007-2012
http://iaslc.org/
Searched 30.10.12

- 14th World Conference on Lung Cancer - http://journals.lww.com/jto/toc/2011/06001
- 13th World Conference on Lung Cancer - http://journals.lww.com/jto/Citation/2009/09001/Abstracts.1.aspx
- 12th World Conference on Lung Cancer - http://journals.lww.com/jto/toc/2007/08001

Intervention	2007	2009	2011
Therascreen	0	1	1
Thera-screen	0	0	0
Cobas	0	0	0
EGFR-TK	20	44	25
Epidermal growth factor mutation	0	0	1
Epidermal growth factor mutations	0	0	0/1

Total	**20**	**45**	**27**

PubMed Related Citations search undertaken for included studies
Results sorted by Link Ranking
http://www.ncbi.nlm.nih.gov/pubmed/
Searched 24.10.12

Of 30 included studies, 12 references were indexed on PubMed.
For each reference, the first 20 related citations were retrieved by carrying out a Related Citations search using PubMed's similarity matching algorithm. These records were downloaded for screening. All related citations were checked against the Endnote Library to remove duplicate, and only new unique references were imported and screened.

Reference	PMID	Result retrieved
#5011. Chen[90]	22157367	20/151
#1591. Fukuoka [3]	21670455	20/141
#6550. Giaccone [46]	17062680	20/424
#6471. Jackman [47]	17228019	20/220
#5109. Leary [45]	22036089	20/111
#5637. Maemondo [4]	20573926	20/447
#7377. Mok [50]	19692680	20/275
#7220. Oizumi [91]	22581822	20/97
#4980. Pallis [48]	22000696	20/208
#1295. Rosell [2]	22285168	20/999
#6145. Yang [49]	18509184	20/579
#7352. Zhou [1]	21783417	20/787
Total		**240/4438**
Following duplicate removal, number of records screened		**26**

Cost-effectiveness search strategies
Review of cost-effectiveness literature

NHS Economic Evaluation Database (NHS EED) (Wiley): 2000-2012: Issue 3
Searched 30.8.12

#1 MeSH descriptor Quinazolines, this term only 613
#2 (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,kw 131
#3 (Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2):ti,ab,kw 171
#4 (#1 OR #2 OR #3) 739
#5 MeSH descriptor Carcinoma, Non-Small-Cell Lung, this term only 1953
#6 (nsclc or nsclcs or lclc or lclcs):ti,ab 2101
#7 (lung* NEAR/3 (adeno-carcinoma* or adenocarcinom*)):ti,ab,kw 73
#8 ((non-small NEXT cell) NEAR/3 lung*):ti,ab,kw 3585

#9 ((large NEXT cell) NEAR/3 lung*):ti,ab,kw 4
#10 (#5 OR #6 OR #7 OR #8 OR #9) 3813
#11 MeSH descriptor Receptor, Epidermal Growth Factor, this term only 265
#12 (epidermal NEXT growth NEXT factor NEXT receptor*):ti,ab,kw 406
#13 (epidermis NEXT growth NEXT factor NEXT receptor*):ti,ab,kw 0
#14 (transforming NEXT growth NEXT factor NEXT alpha NEXT receptor*):ti,ab,kw 0
#15 (tgf-alpha NEAR/2 receptor*):ti,ab,kw 1
#16 (urogastrone NEAR/2 receptor*):ti,ab,kw 0
#17 ((erbB1 or erbB-1 or erbB) NEAR/2 (protein* or receptor*)):ti,ab,kw 292
#18 (EGFR or EGFRTK):ti,ab,kw 449
#19 (EGF NEXT receptor*):ti,ab,kw 23
#20 (Cobas NEAR/3 EGFR) 0
#21 (Cobas NEAR/3 (epidermal NEXT growth NEXT factor)) 0
#22 (thera-screen* or therascreen*) 0
#23 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22) 924
#24 (#4 OR #23) 1476
#25 (#10 AND #24), from 2000 to 2012 8

Embase (OvidSP): 2000-2012/wk 28
Searched 30.8.12

1 health-economics/ (31839)
2 exp economic-evaluation/ (188273)
3 exp health-care-cost/ (180330)
4 exp pharmacoeconomics/ (156985)
5 or/1-4 (433309)
6 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (521624)
7 (expenditure$ not energy).ti,ab. (20859)
8 (value adj2 money).ti,ab. (1141)
9 budget$.ti,ab. (21476)
10 or/6-9 (543342)
11 5 or 10 (796287)
12 letter.pt. (796544)
13 editorial.pt. (414244)
14 note.pt. (527749)
15 or/12-14 (1738537)
16 11 not 15 (716763)
17 (metabolic adj cost).ti,ab. (768)
18 ((energy or oxygen) adj cost).ti,ab. (2933)
19 ((energy or oxygen) adj expenditure).ti,ab. (17921)
20 or/17-19 (20863)
21 16 not 20 (712137)
22 exp animal/ (1796019)
23 exp animal-experiment/ (1636900)

24 nonhuman/ (3899172)
25 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (4729791)
26 or/22-25 (6695652)
27 exp human/ (13830628)
28 exp human-experiment/ (303941)
29 27 or 28 (13832063)
30 26 not (26 and 29) (5273705)
31 21 not 30 (661610)
32 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. (12196)
33 gefitinib/ or (Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2).ti,ab,ot,hw,rn. (13183)
34 or/32-33 (18694)
35 lung non small cell cancer/ (45891)
36 (nsclc or nsclcs).ti,ab,ot,hw. (22788)
37 (lung$ adj3 (adeno-carcinoma$ or adenocarcinom$)).ti,ab,ot. (9502)
38 ((non-small cell or large cell) adj3 lung$).ti,ab,ot. (35647)
39 (lclc or lclcs).ti,ab,ot,hw. (56)
40 or/35-39 (60634)
41 Receptor, Epidermal Growth Factor/ (35039)
42 (epidermal growth factor receptor$ or epidermis growth factor receptor$ or transforming growth factor alpha receptor$).ti,ab,ot. (25326)
43 ((tgf-alpha or urogastrone) adj2 receptor$).ti,ab,ot. (183)
44 ((erbB1 or erbB-1 or erbB) adj1 (protein$ or receptor$)).ti,ab,ot. (1443)
45 (EGFR or EGFRTK).ti,ab,ot. (31087)
46 EGF receptor$.ti,ab,ot. (9045)
47 (Cobas adj3 EGFR).af. (0)
48 (Cobas adj3 epidermal growth factor).ti,ab,ot. (0)
49 (thera?screen$ or therascreen$).af. (50)
50 or/41-49 (57139)
51 34 or 50 (66682)
52 31 and 40 and 51 (743)
53 limit 52 to yr="2000 -Current" (743)
54 remove duplicates from 53 (736)
55 limit 54 to embase (703)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Embase (Ovid) weekly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 17.3.11]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

Medline (OvidSP): 2000-2012/08/wk 4
Searched 30.8.12

1 economics/ (26369)
2 exp "costs and cost analysis"/ (167172)
3 economics, dental/ (1844)
4 exp "economics, hospital"/ (18137)
5 economics, medical/ (8482)
6 economics, nursing/ (3868)
7 economics, pharmaceutical/ (2362)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (369952)
9 (expenditure$ not energy).ti,ab. (15358)
10 (value adj1 money).ti,ab. (18)
11 budget$.ti,ab. (15574)
12 or/1-11 (487655)
13 ((energy or oxygen) adj cost).ti,ab. (2460)
14 (metabolic adj cost).ti,ab. (652)
15 ((energy or oxygen) adj expenditure).ti,ab. (14385)
16 or/13-15 (16851)
17 12 not 16 (483875)
18 letter.pt. (757777)
19 editorial.pt. (305167)
20 historical article.pt. (285776)
21 or/18-20 (1335091)
22 17 not 21 (457810)
23 animals/ not (animals/ and humans/) (3680958)
24 22 not 23 (430529)
25 Quinazolines/ (11624)
26 (Erlotinib or Nsc-718781 or nsc718781 or osi-774 or osi774 or r-1415 or r1415 or tarceva or cp-358774 or cp358774 or 183321-74-6 or 183319 69 9).ti,ab,ot,hw,rn. (2631)
27 (Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2).ti,ab,ot,hw,rn. (3648)
28 or/25-27 (12777)
29 Carcinoma, Non-Small-Cell Lung/ (27182)
30 (nsclc or nsclcs).ti,ab,ot,hw. (14335)
31 (lung$ adj3 (adeno-carcinoma$ or adenocarcinom$)).ti,ab,ot. (7087)
32 ((non-small cell or large cell) adj3 lung$).ti,ab,ot. (24664)
33 (lclc or lclcs).ti,ab,ot,hw. (42)
34 or/29-33 (38312)
35 Receptor, Epidermal Growth Factor/ (25843)
36 epidermal growth factor receptor$.ti,ab,ot. (20568)
37 epidermis growth factor receptor$.ti,ab,ot. (0)
38 transforming growth factor alpha receptor$.ti,ab,ot. (10)
39 ((tgf-alpha or urogastrone) adj2 receptor$).ti,ab,ot. (243)
40 ((erbB1 or erbB-1 or erbB) adj1 (protein$ or receptor$)).ti,ab,ot. (1239)
41 EGFR.ti,ab,ot. (20234)
42 EGFRTK.ti,ab,ot. (10)
43 EGF receptor$.ti,ab,ot. (8326)

44 (Cobas adj3 EGFR).af. (0)
45 (Cobas adj3 epidermal growth factor).ti,ab,ot. (0)
46 (thera?screen$ or therascreen$).af. (14)
47 or/35-46 (39620)
48 28 or 47 (47729)
49 24 and 34 and 48 (90)
50 limit 49 to yr="2000 -Current" (90)
51 remove duplicates from 50 (87)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

Medline In-Process Citations (OvidSP): 2000-2012/08/29
Medline Daily Update (OvidSP): 2000-2012/08/29
Searched 30.8.12

1 economics/ (1)
2 exp "costs and cost analysis"/ (111)
3 economics, dental/ (0)
4 exp "economics, hospital"/ (5)
5 economics, medical/ (1)
6 economics, nursing/ (0)
7 economics, pharmaceutical/ (0)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (29272)
9 (expenditure$ not energy).ti,ab. (821)
10 (value adj1 money).ti,ab. (2)
11 budget$.ti,ab. (1501)
12 or/1-11 (30841)
13 ((energy or oxygen) adj cost).ti,ab. (155)
14 (metabolic adj cost).ti,ab. (53)
15 ((energy or oxygen) adj expenditure).ti,ab. (652)
16 or/13-15 (838)
17 12 not 16 (30593)
18 letter.pt. (17056)
19 editorial.pt. (10671)
20 historical article.pt. (96)
21 or/18-20 (27818)
22 17 not 21 (30243)
23 animals/ not (animals/ and humans/) (1498)
24 22 not 23 (30207)
25 Quinazolines/ (16)

26 (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. (259)
27 (Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2).ti,ab,ot,hw,rn. (223)
28 or/25-27 (402)
29 Carcinoma, Non-Small-Cell Lung/ (30)
30 (nsclc or nsclcs).ti,ab,ot,hw. (1282)
31 (lung$ adj3 (adeno-carcinoma$ or adenocarcinom$)).ti,ab,ot. (455)
32 ((non-small cell or large cell) adj3 lung$).ti,ab,ot. (1908)
33 (lclc or lclcs).ti,ab,ot,hw. (6)
34 or/29-33 (2376)
35 Receptor, Epidermal Growth Factor/ (23)
36 epidermal growth factor receptor$.ti,ab,ot. (1197)
37 epidermis growth factor receptor$.ti,ab,ot. (0)
38 transforming growth factor alpha receptor$.ti,ab,ot. (0)
39 ((tgf-alpha or urogastrone) adj2 receptor$).ti,ab,ot. (6)
40 ((erbB1 or erbB-1 or erbB) adj1 (protein$ or receptor$)).ti,ab,ot. (44)
41 EGFR.ti,ab,ot. (1666)
42 EGFRTK.ti,ab,ot. (1)
43 EGF receptor$.ti,ab,ot. (189)
44 (Cobas adj3 EGFR).af. (0)
45 (Cobas adj3 epidermal growth factor).ti,ab,ot. (0)
46 (thera?screen$ or therascreen$).af. (2)
47 or/35-46 (2255)
48 28 or 47 (2406)
49 24 and 34 and 48 (12)
50 limit 49 to yr="2000 -Current" (12)
51 remove duplicates from 50 (12)

Costs filter:
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 28.9.10]. Available from: http://www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

Health Economic Evaluation Database (HEED) (Internet): up to 2012/08/30
http://onlinelibrary.wiley.com/book/10.1002/9780470510933
Searched 30.8.12

Compound search, (all data), unable to limit by date

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 OR Gefitinib OR Geftinat OR Geftib OR iressa OR zd-1839 OR zd1839 OR 184475-35-2
AND
lung* OR NSCLC OR NSCLCS OR LCLC OR LCLCS

N=41

(Therascreen OR Thera-screen OR Cobas OR EGF OR EGFR OR EGFRTK OR TGF OR epidermal OR erbb OR ERBB1 OR urogastrone)
AND
(lung* OR NSCLC OR NSCLCS OR LCLC OR LCLCS)
N=8

HEED search retrieved 49 records.

Science Citation Index (SCI) (Web of Knowledge): 2000-2012/08/29
Search limited to 2000-2012
Searched 30.8.12

Advanced search (Lemmatization off)

 # 32 146 #11 and #15 and #31
31 40,025 #30 OR #29 OR #28
30 6,378 TS=(Gefitinib or Geftinat or Geftib or iressa or zd-1839 or zd1839 or 184475-35-2)
29 3,959 TS=(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)
28 36,741 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
27 13 TS=(thera-screen* or therascreen*)
26 0 TS=(Cobas NEAR epidermal NEAR growth NEAR factor)
25 0 TS=(Cobas NEAR EGFR)
24 8,720 TS=(EGF NEAR receptor*)
23 21,367 TS=(EGFR or EGFRTK)
22 3,781 TS=((erbB1 or erbB-1 or erbB) NEAR (protein* or receptor*))
21 13 TS=(urogastrone NEAR receptor*)
20 702 TS=(tgf-alpha NEAR receptor*)
19 0 TS=(transform NEAR growth NEAR factor NEAR alpha NEAR receptor*)
18 819 TS=(transforming NEAR growth NEAR factor NEAR alpha NEAR receptor*)
17 68 TS=(epidermis NEAR growth NEAR factor NEAR receptor*)
16 20,767 TS=(epidermal NEAR growth NEAR factor NEAR receptor*)
15 34,161 #12 or #13 or #14
14 24,966 TS=((non-small NEAR cell NEAR lung*) or (large NEAR cell NEAR lung*))
13 8,029 TS=((lung* NEAR adeno-carcinoma*) OR (lung NEAR adenocarcinom*))
12 15,691 TS=(nsclc or nsclcs or lclc or lclcs)
11 484,626 #9 not #10
10 1,160,972 TS=(cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep OR macaque* OR monkey*)
9 508,156 #4 not #8
8 26,623 #5 or #6 or #7
7 14,802 TS=((energy or oxygen) NEAR expenditure)

6 1,295 TS=(metabolic NEAR cost)
5 11,720 TS=((energy or oxygen) NEAR cost)
4 521,849 #1 or #2 or #3
3 796 TS=(value NEAR money)
2 10,358 TS=(expenditure* not energy)
1 517,471 TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or budget*)

Update of manufacturer's search in Gefitinib STA 192 (Appendix 10.4: Resource Utilisation)[52]

Embase (OvidSP): 2009/01-2012/08/wk 34
Searched 30.8.12

1 Socioeconomics/ (102445)
2 Cost benefit analysis/ (61757)
3 Cost-effectiveness analysis/ (82283)
4 Cost of illness/ (13206)
5 Cost control/ (42633)
6 Economic aspect/ (99388)
7 Financial management/ (96915)
8 Health care cost/ (111972)
9 Health care financing/ (10847)
10 Health economics/ (31839)
11 Hospital cost/ (12121)
12 (fiscal or financial or finance or funding).tw. (88152)
13 Cost minimization analysis/ (2109)
14 (cost adj estimate$).mp. (1709)
15 (cost adj variable$).mp. (135)
16 (unit adj cost$).mp. (1997)
17 or/1-16 (603136)
18 Carboplatin/ or carboplatin.mp. or Paraplatin.mp. (38879)
19 Cisplatin/ or Cisplatin.mp. or Platinol.mp. (115027)
20 Paclitaxel/ or Paclitaxel.mp. or Taxol.mp. (58541)
21 Topotecan/ or Topotecan.mp. or Hycamtin.mp. (7943)
22 (irinotecan or Campto).mp. (21091)
23 (docetax?l or Taxotere).mp. (27947)
24 (vinorelbine or Navelbine).mp. (11861)
25 (gemcitabine or Gemzar).mp. (27119)
26 (zactima or ZD6474).mp. (615)
27 (bevacizumab or Avastin).mp. (23392)
28 (pemetrexed or Alimta).mp. (4688)
29 (erlotinib or Tarceva).mp. (12217)
30 (bortezomib or Velcade).mp. (11513)
31 (vinflunine or Javlor).mp. (456)
32 (cetuximab or Erbitux).mp. (12952)
33 (gefitinib or Iressa).mp. (13204)

34 Vatalanib.mp. (2098)
35 Panitumumab.mp. (3458)
36 platinum compounds/ or platinum.mp. (40273)
37 Taxoids/ or taxoid$.mp. (3083)
38 exp antineoplastic protocols/ (61147)
39 Antineoplastic Agent/ (204229)
40 Angiogenesis Inhibitor/ (12049)
41 Antimetabolite/ (5559)
42 antineoplastic agents, alkylating/ (12712)
43 antineoplastic agents, phytogenic/ (204229)
44 or/18-43 (479713)
45 Lung non Small Cell Cancer/ (45891)
46 (non small cell or non-small-cell or nonsmall cell or nsclc).mp. (53758)
47 (lung$ or pulmon$).mp. (1175884)
48 (cancer or tumor$ or tumour$ or carcino$ or blastom$ or squamous or neoplas$ or sarcom$ or lymphom$ or adenocarcinom$).mp. (3339510)
49 46 and 47 and 48 (53042)
50 45 or 49 (53042)
51 17 and 44 and 50 (861)
52 limit 51 to yr="2006 -Current" (586)
53 (2009$ or 201$).em. (4309768)
54 52 and 53 (419)
55 remove duplicates from 54 (416)
56 limit 55 to embase (405)

Update of search strategy from Appendix 10.4:
AstraZeneca UK Ltd. Single Technology Appraisal (STA) for Gefitinib for the first line treatment of locally advanced or metastatic non-small lung cancer (submission to National Institute for Health and Clinical Excellence) [Word document provided by AstraZeneca]. Luton, UK: AstraZeneca UK Ltd., 2010 [cited 18.7.12]. 233p.

Medline (OvidSP): 2009-2012/08/wk 4
Searched 30.8.12

1 Economics/ (26369)
2 "costs and cost analysis"/ (40051)
3 Cost allocation/ (1921)
4 Cost-benefit analysis/ (54902)
5 Cost control/ (19311)
6 Cost savings/ (7775)
7 Cost of illness/ (15410)
8 Cost sharing/ (1769)
9 "deductibles and coinsurance"/ (1348)
10 Medical savings accounts/ (462)
11 Health care costs/ (23671)
12 Direct service costs/ (974)
13 Drug costs/ (11210)

14 Employer health costs/ (1044)
15 Hospital costs/ (6965)
16 Health expenditures/ (12574)
17 Capital expenditures/ (1914)
18 Value of life/ (5232)
19 exp economics, hospital/ (18137)
20 exp economics, medical/ (13308)
21 Economics, nursing/ (3868)
22 Economics, pharmaceutical/ (2362)
23 exp "fees and charges"/ (26011)
24 exp budgets/ (11515)
25 (low adj cost).mp. (16966)
26 (high adj cost).mp. (6653)
27 (health?care adj cost$).mp. (3110)
28 (fiscal or funding or financial or finance).tw. (66638)
29 (cost adj estimate$).mp. (1193)
30 (cost adj variable).mp. (27)
31 (unit adj cost$).mp. (1276)
32 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (141586)
33 or/1-32 (403794)
34 Carboplatin/ or carboplatin.mp. or Paraplatin.mp. (11002)
35 Cisplatin/ or Cisplatin.mp. or Platinol.mp. (47742)
36 Paclitaxel/ or Paclitaxel.mp. or Taxol.mp. (22534)
37 Topotecan/ or Topotecan.mp. or Hycamtin.mp. (2326)
38 (irinotecan or Campto).mp. (6288)
39 (docetax?l or Taxotere).mp. (7860)
40 (vinorelbine or Navelbine).mp. (2936)
41 (gemcitabine or Gemzar).mp. (8196)
42 (zactima or ZD6474).mp. (170)
43 (bevacizumab or Avastin).mp. (6308)
44 (pemetrexed or Alimta).mp. (1286)
45 (erlotinib or Tarceva).mp. (2611)
46 (bortezomib or Velcade).mp. (3482)
47 (vinflunine or Javlor).mp. (148)
48 (cetuximab or Erbitux).mp. (2956)
49 (gefitinib or Iressa).mp. (3609)
50 Vatalanib.mp. (249)
51 Panitumumab.mp. (586)
52 platinum compounds/ or platinum.mp. (22109)
53 Taxoids/ or taxoid$.mp. (7866)
54 exp antineoplastic protocols/ (95249)
55 Antineoplastic Agents/ (171356)
56 Angiogenesis Inhibitors/ (13184)
57 Antimetabolites/ (7082)
58 antineoplastic agents, alkylating/ (7002)
59 antineoplastic agents, phytogenic/ (22154)
60 or/34-59 (336727)

61 lung neoplasms/ (148687)
62 carcinoma, non-small-cell lung/ (27182)
63 (non small cell or non-small-cell or nonsmall cell or nsclc).mp. (32947)
64 (lung$ or pulmon$).mp. (849108)
65 (cancer or tumor$ or tumour$ or carcino$ or blastom$ or squamous or neoplas$ or sarcom$ or lymphom$ or adenocarcinom$).mp. (2650656)
66 63 and 64 and 65 (32779)
67 61 or 62 or 66 (151633)
68 33 and 60 and 67 (367)
69 limit 68 to yr="2006 -Current" (204)
70 (2009$ or 201$).ed. (2869749)
71 69 and 70 (142)
72 remove duplicates from 71 (129)

Update of search strategy from Appendix 10.4:
AstraZeneca UK Ltd. Single Technology Appraisal (STA) for Gefitinib for the first line treatment of locally advanced or metastatic non-small lung cancer (submission to National Institute for Health and Clinical Excellence) [Word document provided by AstraZeneca]. Luton, UK: AstraZeneca UK Ltd., 2010 [cited 18.7.12]. 233p.

Medline In-Process Citations (OvidSP): 2009-2012/08/29
Medline Daily Update (OvidSP): 2009-2012/08/29
Searched 30.8.12

1 Economics/ (1)
2 "costs and cost analysis"/ (14)
3 Cost allocation/ (0)
4 Cost-benefit analysis/ (32)
5 Cost control/ (3)
6 Cost savings/ (7)
7 Cost of illness/ (11)
8 Cost sharing/ (2)
9 "deductibles and coinsurance"/ (0)
10 Medical savings accounts/ (1)
11 Health care costs/ (38)
12 Direct service costs/ (2)
13 Drug costs/ (17)
14 Employer health costs/ (0)
15 Hospital costs/ (3)
16 Health expenditures/ (11)
17 Capital expenditures/ (2)
18 Value of life/ (0)
19 exp economics, hospital/ (5)
20 exp economics, medical/ (2)
21 Economics, nursing/ (0)
22 Economics, pharmaceutical/ (0)
23 exp "fees and charges"/ (7)

24 exp budgets/ (4)
25 (low adj cost).mp. (2925)
26 (high adj cost).mp. (456)
27 (health?care adj cost$).mp. (296)
28 (fiscal or funding or financial or finance).tw. (4322)
29 (cost adj estimate$).mp. (64)
30 (cost adj variable).mp. (3)
31 (unit adj cost$).mp. (75)
32 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (10972)
33 or/1-32 (18244)
34 Carboplatin/ or carboplatin.mp. or Paraplatin.mp. (451)
35 Cisplatin/ or Cisplatin.mp. or Platinol.mp. (1599)
36 Paclitaxel/ or Paclitaxel.mp. or Taxol.mp. (927)
37 Topotecan/ or Topotecan.mp. or Hycamtin.mp. (71)
38 (irinotecan or Campto).mp. (297)
39 (docetax?l or Taxotere).mp. (501)
40 (vinorelbine or Navelbine).mp. (127)
41 (gemcitabine or Gemzar).mp. (524)
42 (zactima or ZD6474).mp. (10)
43 (bevacizumab or Avastin).mp. (695)
44 (pemetrexed or Alimta).mp. (96)
45 (erlotinib or Tarceva).mp. (257)
46 (bortezomib or Velcade).mp. (313)
47 (vinflunine or Javlor).mp. (12)
48 (cetuximab or Erbitux).mp. (245)
49 (gefitinib or Iressa).mp. (219)
50 Vatalanib.mp. (5)
51 Panitumumab.mp. (57)
52 platinum compounds/ or platinum.mp. (4025)
53 Taxoids/ or taxoid$.mp. (27)
54 exp antineoplastic protocols/ (47)
55 Antineoplastic Agents/ (185)
56 Angiogenesis Inhibitors/ (18)
57 Antimetabolites/ (2)
58 antineoplastic agents, alkylating/ (4)
59 antineoplastic agents, phytogenic/ (15)
60 or/34-59 (8676)
61 lung neoplasms/ (77)
62 carcinoma, non-small-cell lung/ (30)
63 (non small cell or non-small-cell or nonsmall cell or nsclc).mp. (2057)
64 (lung$ or pulmon$).mp. (24317)
65 (cancer or tumor$ or tumour$ or carcino$ or blastom$ or squamous or neoplas$ or sarcom$ or lymphom$ or adenocarcinom$).mp. (86846)
66 63 and 64 and 65 (2012)
67 61 or 62 or 66 (2060)
68 33 and 60 and 67 (13)
69 limit 68 to yr="2006 -Current" (13)

70 (2009$ or 201$).ed. (556714)
71 69 and 70 (4)
72 remove duplicates from 71 (4)

Update of search strategy from Appendix 10.4:
AstraZeneca UK Ltd. Single Technology Appraisal (STA) for Gefitinib for the first line treatment of locally advanced or metastatic non-small lung cancer (submission to National Institute for Health and Clinical Excellence) [Word document provided by AstraZeneca]. Luton, UK: AstraZeneca UK Ltd., 2010 [cited 18.7.12]. 233p.

NHS Economic Evaluation Database (NHS EED) (Internet): 2009/01/01-2012/08/30
http://www.york.ac.uk/inst/crd/index_databases.htm
Searched 23.8.12

1 (carboplatin or Paraplatin) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 10
2 (Cisplatin or Platinol) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 19
3 (Paclitaxel or Taxol) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 32
4 (Topotecan or Hycamtin) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 2
5 ((irinotecan or Campto)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 8
6 ((docetaxal or docetaxel or Taxotere)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 37
7 ((vinorelbine or Navelbine)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 11
8 ((gemcitabine or Gemzar)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 8
9 ((zactima or ZD6474)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 0
10 ((bevacizumab or Avastin)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 18
11 ((pemetrexed or Alimta)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 14
12 ((erlotinib or Tarceva)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 9
13 ((bortezomib or Velcade)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 3
14 ((vinflunine or Javlor)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 0
15 ((cetuximab or Erbitux)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 8
16 ((gefitinib or Iressa)) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 3
17 (Vatalanib) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 0

18 (Panitumumab) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 1
19 (Advanced non-small cell lung cancer) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 10
20 (NSCLC) IN NHSEED WHERE PD FROM 01/01/2009 TO 30/08/2012 9
21 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 104
22 #19 OR #20 16
23 #21 AND #22 14

Update of search strategy from Appendix 10.4:
AstraZeneca UK Ltd. Single Technology Appraisal (STA) for Gefitinib for the first line treatment of locally advanced or metastatic non-small lung cancer (submission to National Institute for Health and Clinical Excellence) [Word document provided by AstraZeneca]. Luton, UK: AstraZeneca UK Ltd., 2010 [cited 18.7.12]. 233p.

Cinahl (EBSCO): 2009/01-2012/08/24
Searched 30.8.12

S1 (MH "Financial Management") OR (MH "Financial Support") OR (MH "Financing, Organized") OR (MH "Business") (17359)
S2 (MH "Economics") (5503)
S3 S2 not S1 (4967)
S4 (MH "Health Resource Allocation") OR (MH "Health Resource Utilization") (12749)
S5 TX cost or costs or economic* or pharmacoeconomic* or price* or pricing* (164114)
S6 S3 or S4 or S5 (172311)
S7 PT (Editorial or Letter or News) OR MH Animal studies OR SO Cochrane library OR AU Anonymous (279784)
S8 S6 not S7 (159174)
S9 MH Carboplatin (607)
S10 MH Cisplatin (1427)
S11 MH Paclitaxel (1551)
S12 MH Antineoplastic Agents (12767)
S13 MH Antimetabolites (106)
S14 MH Antimetabolites, antineoplastic (608)
S15 MH Angiogenesis Inhibitors (1370)
S16 S9 or S10 or S11 or S12 or S13 or S14 or S15 (16663)
S17 TX carboplatin or paraplatin or cisplatin or Platinol or Paclitaxel or Taxol or Topotecan or Hycamtin or irinotecan or Campto or docetax?l or Taxotere or vinorelbine or Navelbine or gemcitabine or Gemzar or zactima or ZD6474 or bevacizumab or Avastin or pemetrexed or Alimta or erlotinib or Tarceva or bortezomib or Velcade or vinflunine or Javlor or cetuximab or Erbitux or gefitinib or Iressa or Vatalanib or Panitumumab or platinum or taxoid* (7964)
S18 TX carboplatin or paraplatin or cisplatin or Platinol or Paclitaxel or Taxol or Topotecan or Hycamtin or irinotecan or Campto or docetax?l or Taxotere or vinorelbine or Navelbine or gemcitabine or Gemzar or zactima or ZD6474 or

bevacizumab or Avastin or pemetrexed or Alimta or erlotinib or Tarceva or bortezomib or Velcade or vinflunine or Javlor or cetuximab or Erbitux or gefitinib or Iressa or Vatalanib or Panitumumab or platinum or taxoid* (7964)
S19 MH lung neoplasms (8574)
S20 MH carcinoma, non-small-cell lung (2144)
S21 TX (non small cell or non-small-cell or nonsmall cell or nsclc) OR TX (lung* or pulmon*) OR TX (cancer or tumor* or tumour* or carcino* or blastom* or squamous or neoplasm* or sarcom* or lymphoma* or adenocarcinom*) (254889)
S22 S18 or S19 or S20 (15916)
S23 S16 or S17 (19714)
S24 S22 and S21 and S8 Limiters - Published Date from: 20060101-20121231 (382)
Entry date limit (2009-2012) applied in Endnote. **Final results = 241**

Update of search strategy from Appendix 10.4:
AstraZeneca UK Ltd. Single Technology Appraisal (STA) for Gefitinib for the first line treatment of locally advanced or metastatic non-small lung cancer (submission to National Institute for Health and Clinical Excellence) [Word document provided by AstraZeneca]. Luton, UK: AstraZeneca UK Ltd., 2010 [cited 18.7.12]. 233p.

APPENDIX 2: DATA EXTRACTION TABLES

Studies that provided information on the accuracy EGFR mutation testing for predicting response to treatment with TKIs

Study details	Selection Criteria	Population	Intervention	EGFR Mutation Test Details
Study Details Fukuoka (IPASS)(2011)[3, 50, 92-96] **Country** China, Hong Kong, Taiwan, Japan, Indonesia **Study Design** RCT **Funding** AstraZeneca **Recruitment** March 2006 - October 2007 **Number treated with gefitinib for whom EGFR mutation test results were available:** 223	**Inclusion criteria** Adults (minimum 18 years) with stage IIIB or IV NSCLC (histologic or cytologic diagnosis) with histologic features of adenocarcinoma. Non-smokers (<100 cigarettes over lifetime) or former light smokers (stopped smoking at least 15 years previously and had a maximum of 10 pack years smoking). No previous chemotherapy, biologic, or immunotherapy. WHO PS 0-2, measurable disease (RECIST) with at least one measurable lesion not previously irradiated, adjuvant chemotherapy permitted if not platinum-based and completed >6 months previously, neutrophil count >2,000/µL, adequate liver function. **Exclusion criteria** None reported.	**Age** <65 years: 170 **Number Male:** 48 **Ethnicity:** >99% East Asian **Smoking Status** Never smoked: 206 Current/former smoker: 17 **Histological Features:** Not reported **Disease Stage at entry** IIIB: 40 IV: 183 Not stated: 0 **Performance status: WHO** 0 or 1: 204 2: 19 **Previous treatments:** None reported	**Intervention** Gefitinib **Dose** Oral 250mg **Frequency** Daily **Duration** 5.6 months (range 0.1 to 22.8)	**EGFR Mutation Test** Therascreen® EGFR PCR Kit (version 1) **Manufacturer** DxS, Manchester, UK **Mutations Targeted** 29 mutations in Therascreen® kit

Study details	Selection Criteria	Population	Intervention	EGFR Mutation Test Details
Study Details Giaccone(2006)[46] **Country** Netherlands, France **Study Design** Cohort **Funding** Hofmann-La Roche Ltd, AstraZeneca, Genentech **Recruitment** January 2004 - July 2004 **Number enrolled:** 54 **Number treated:** 53	**Inclusion criteria** Adults (≥ 18 yrs), NSCLC (histologic or cytologic diagnosis), not amenable to radical surgery or radiotherapy. No prior chemotherapy or other systemic treatment, measurable disease (RECIST), performance status 0-2, life expectancy ≥12 weeks, time since prior surgery or radiotherapy ≥4 weeks, granulocyte count ≥1,500/µL, platelet count ≥100,000/µL, bilirubin and transaminases ≤ 1.5 x upper limit of normal, creatinine clearance ≥ 60 mL/min, negative pregnancy test in females of childbearing age. Patients with brain metastases were included if there was no evidence of progression in the brain and in the absence of corticosteroid treatment. **Exclusion criteria** Unstable systemic disease (active infection, uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction in the previous year, serious cardiac arrhythmia requiring medication), any other malignancy in previous 5 years (except carcinoma in situ of the cervix or squamous cell skin cancer), significant eye disorders (severe dry eye syndrome, Sjogren syndrome, severe exposure keratinitis, any other disorder likely to increase the risk of corneal epithelial lesions).	**Age** Median: 60 Range: 30-80 **Number Male:** 22 **Ethnicity**: Not stated **Smoking Status** Never smoked: 16 Former smoker: 0 Current smoker: 0 Current/former smoker: 37 **Histological Features** Adenocarcinoma: 24 Bronchoalveolar: 6 Squamous: 8 Not stated or other: 15 **Disease Stage at entry** IIIB: 11 IV: 42 **Performance status: Scale not stated** 0: 13 1: 32 2: 8 **Previous treatments:** Surgery 8, radiotherapy 5, surgery and radiotherapy 3, none 37.	**Intervention** Erlotinib **Dose** 150 mg **Frequency** Daily	**EGFR Mutation Test** Direct sequencing (nested PCR) **Manufacturer** Not specified **Analysis Software** Sequencing of PCR products was done with the ABI PRISM 310 Genetic analyzer (Applied Biosystems). **Mutations Targeted** All Exon 18-21 mutations

Study details	Selection Criteria	Population	Intervention	EGFR Mutation Test Details
Study Details Han (First-SIGNAL) (2012)[5, 44] **Country** South Korea **Study Design** RCT **Funding** AstraZeneca **Recruitment** October 2005 – November 2007 **Number treated: treated with gefitinib for whom EGFR test results were available:** 53	**Inclusion criteria** Adults (>18 years), chemotherapy naïve, never smokers, stage IIIB/IV adenocarcinoma NSCLC with measurable or non-measurable disease, PS 0-2, adequate bone marrow, liver and renal function. **Exclusion criteria** Known severe hypersensitivity to gefitinib or any constituents, any evidence of clinically active interstitial lung disease, severe or uncontrolled systemic disease, concomitant use of phenytoin, carbamazepine, riampin, barbiturate, or St John's wort, and unstable brain metastases.	Baseline characteristics not reported for EGFR tested subgroups; see table in following section for whole trial patient characteristics	**Intervention** Gefitinib **Dose** 250mg **Frequency** Daily	**EGFR Mutation Test** Direct sequencing PCR **Manufacturer** Not specified **Analysis Software** Not specified **Mutations Targeted** Exons 19-21

Study details	Selection Criteria	Population	Intervention	EGFR Mutation Test Details
Study Details Jackman(2007)[47] **Country** USA **Study Design** Cohort **Funding** National Institute of Health, National Cancer Institute Specialised program of Research Excellence in Lung Cancer, Doris and William Krupp Research Fund in Thoracic Oncology, Genentech Inc. **Recruitment** March 2003 - May 2005 **Number enrolled:** 82 **Number treated:** 80	**Inclusion criteria** Stage IIIB/IV NSCLC (histologic or cytologic diagnosis), age ≥70 years. ECOG PS 0-2, WBC ≥3,000/µL, haemoglobin ≥9.0g/dL, platelet count ≥100,000/µL, total bilirubin ≤1.5 mg/dL, AST ≤ 2 x upper limit of normal, creatinine ≤1.5 mg/dL, measurable or assessable lesions (RECIST), life expectancy ≥8 weeks. Patients with satble brain metastases after surgical resection and/or cranial radiation were eligible. **Exclusion criteria** Prior chemotherapy or treatment with any ErbB1- or ErbB2-targeted agent, major surgery or radiation therapy in the previous 21 days, any malignancy in the previous 5 years (except non-melanoma skin cancers or definitively treated cervical cancer), any active gastrointestinal disorder that alters motility or absorbtion, severe and unstable co-morbidities.	**Age** Median: 75 Range: 70-91 **Number Male:** 40 **Ethnicity** Caucasian: 76 Black: 3 Asian: 1 **Smoking Status** Never smoked: 8 Former smoker: 67 Current smoker: 5 **Histological Features** Adenocarcinoma: 47 Bronchoalveolar: 4 Squamous: 7 Not stated or other: 22 **Disease Stage at entry** IIIB: 12 IV: 68 **Performance status: ECOG** 0: 13 1: 59 2: 8 **Previous treatments:** Surgery 13, radiotherapy 12, surgery and radiotherapy 9, none 46.	**Intervention** Erlotinib **Dose** 150 mg; Dose reductions allowed for toxicity. **Frequency** Daily	**EGFR Mutation Test** Direct sequencing (34 samples), or WAVE-HS (9 samples) for inadequate samples (<50% tumour cells) **Manufacturer** Transgenomic Inc, USA (for WAVE-HS) **Mutations Targeted** All Exon 18-24 mutations

Study details	Selection Criteria	Population	Intervention	EGFR Mutation Test
Study Details Pallis(2012)[48] **Country** Greece **Study Design** Cohort **Funding** Cretan Association for Biomedical Research **Recruitment** December 2004 - October 2008 **Number enrolled:** 49 **Number treated:** 49	**Inclusion criteria** Adult (≥18 years) chemotherapy naïve non-smokers (<100 cigarettes over lifetime), with inoperable stage IIIB or IV NSCLC (histolocic or cytologic diagnosis), with histologic features of adenocarcinoma. At least one measurable lesion (RECIST), ECOG PS 0-2, life expectancy ≥3 months, adequate organ function (serum bilirubin ≤1.5 x upper limit of normal, AST and ALT ≤2.5 x upper limit of normal in the absence of perceptible liver metastases or ≤5 x upper limit of normal in presence of liver metastases, serum creatinine ≤1.5 x upper limit of normal, neutrophil count ≥1,500/μL, platelet count ≥100,000/μL). Patients with central nervous system metastases were eligible, provided they had been irradiated and were clinically and radiologically stable. **Exclusion criteria** Active infection, history of significant cardiac disease (unstable angina, congestive heart failure, myocardial infarction in the previous 6 months, ventricular arrhythmias).	**Age** Median: 68 Range: 36-81 **Number Male:** 17 **Ethnicity** Not stated **Smoking Status** Never smoked: 49 Former smoker: 0 Current smoker: 0 **Histological Features** Adenocarcinoma: 46 Bronchoalveolar: 3 **Disease Stage at entry** IIIB: 7 IV: 42 **Performance status: ECOG** 0: 11 1: 35 2: 3 **Previous treatments:** None reported	**Intervention** Erlotinib **Dose** 150 mg **Frequency** Daily **Duration** Median 5.67 months	**EGFR Mutation Test** Direct sequencing (PCR) **Manufacturer** Not specified **Mutations Targeted** All Exon 18-21 mutations All specimens contained at least 80% tumour cells.

Study details	Selection Criteria	Population	Intervention	EGFR Mutation Test
Study Details Yang(2008)[49] **Country** Taiwan **Study Design** Cohort **Funding** Taiwan National Science Council and Department of Health, AstraZeneca Taiwan. **Recruitment** May 2005 - April 2006 **Number enrolled:** 106 **Number treated:** 106	**Inclusion criteria** NSCLC (histologic or cytologic diagnosis) stage IIIB or IV, not amenable to curative treatment. Tumout measurable on imaging, ECOG PS 0-2, adequate liver function (bilirubin ≤2.0 mg/dL, transaminases <2.5 x upper limit of normal, ALP <5 x upper limit of normal), adequate renal function (serum creatinine <2 mg/dL), adequate bone marrow function (haemoglobin >10 g/dL, neutrophil count >2,000/µL, platelet count >100,000/µL), no prior systemic anti-cancer treatment, no immediate need for palliative radiotherapy, candidacy for cisplatin-based combination chemotherapy, life expectncy >6 months. Patients with central nervous system metastases were eligible if they were clinically stable 6 weeks after radiotherapy. **Exclusion criteria** Secondary malignancies and major systemic diseases. Central nervous system metastases.	**Age** Median: 67 Range: 32-86 **Number Male:** 38 **Ethnicity** Not stated **Smoking Status** Never smoked: 75 Former smoker: 19 Current smoker: 12 **Histological Features** Adenocarcinoma: 97 Not stated or other: 9 **Disease Stage at entry** IIIB: 10 IV: 96 **Performance status: ECOG** 0: 0 1: 98 2: 8 **Previous treatments:** None reported	**Intervention** Gefitinib **Dose** 250 mg **Frequency** Daily	**EGFR Mutation Test** Direct sequencing (PCR) **Manufacturer** Not specified **Mutations Targeted** All Exon 18-21 mutations

Studies that provided information on how clinical outcomes may vary according to which test is used to select patients for TKI treatment

Study details	Selection Criteria	Participant Details			Intervention Details		EGFR Mutation Test
		Criteria	EGFR-TKI	SC	EGFR- TKI	SC	
Study Details Benlloch(2012)[6] **Country** France, Spain and Italy **Study Design** RCT **Funding** Hoffman-La Roche **Recruitment** February 2007 - January 2011 **Number enrolled:** 173 **Number treated:** 150 **Number with cobas EGFR test:** 135	**Inclusion criteria** Adults (>18 years) with histologically confirmed NSCLC (stage IIIB (with pleural effusion), or stage IV), measurable or evaluable disease, and the presence of activating EGFR mutations (exon 19 deletions or exon 21 mutation L858R). No history of chemotherapy for metastatic disease (neoadjuvant or adjuvant chemotherapy was allowed if it ended at least 6 months before study entry). Patients with asymptomatic, stable brain metastases were eligible for inclusion. **Exclusion criteria** None stated. **Re-analysis of a sub-set of EURTAC using a different test. Of 174 patients in the EURTAC trial 39 were excluded from this study (37 no tumour block available and 2 insufficient tumour material).**	**Age:**			**Intervention (Dose)** Erlotinib (150 mg daily) **Duration** Median 8.2 months (range 0.3 to 32.9) **Number of participants** 77	**Intervention (Dose)** i.v. cisplatin (75mg/m^2) plus docetaxel (75mg/m^2) administered on day 1 of a 3 week cycle or i.v. cisplatin (75mg/m^2) plus gemcitabine 1.25g/m^2) with cisplatin administered on day 1 and gemcitabine on day 1 and 8 of a 3 week cycle. Median 4 cycles (range 1-6, 2-4) Patients who were ineligible for cisplatin received i.v. carboplatin **Duration** median 2.8 months (range 0.7-5.1, 1.0-2.6) **Number of participants** 73	**EGFR Mutation Test** cobas® EGFR mutation test **Manufacturer** Hoffmann-la Roche, Basel, Switzerland **Mutations Targeted** L858R (exon 21) and 29 exon 19 deletions
		Mean(sd)	63(11)	64(9)			
		Age range	NR	NR			
		Number Male	28	19			
		Ethnicity: All but two patients were white.					
		Smoking Status					
		Never smoked	57	63			
		Former smoker	22	12			
		Current smoker	7	12			
		Histological Features					
		Adenocarcinoma	82	78			
		Bronchoalveolar	0	2			
		Squamous	1	0			
		NS/other	3	7			
		Disease Stage at entry					
		IIIB	6	5			
		IV	78	82			
		NS	2	0			
		Performance status: ECOG					
		0	27	30			
		1	47	45			
		2	12	12			
		Previous treatments	NR	NR			

Study details	Selection Criteria	Participant Details			Intervention Details		EGFR Mutation Test
		Criteria	EGFR-TKI	SC	EGFR- TKI	SC	
Study Details Fukuoka (IPASS)(2011)[3, 50, 92-96] **Country** China, Hong Kong, Taiwan, Japan, Indonesia **Study Design** RCT **Funding** AstraZeneca **Recruitment** March 2006 - October 2007 **Number enrolled:** 1217 **Number treated:** 1196 **Number in EGFR mutation positive subgroup:** 261	**Inclusion criteria** Adults (minimum 18 years) with stage IIIB or IV NSCLC (histologic or cytologic diagnosis) with histologic features of adenocarcinoma. Non-smokers (<100 cigarettes over lifetime) or former light smokers (stopped smoking at least 15 years previously and had a maximum of 10 pack years smoking). No previous chemotherapy, biologic, or immunotherapy. WHO PS 0-2, measurable disease (RECIST) with at least one measurable lesion not previously irradiated, adjuvant chemotherapy permitted if not platinum-based and completed >6 months previously, neutrophil count >2,000/µL, adequate liver function. **Exclusion criteria** None reported. **Comments** Data were extracted for the EGFR positive **subgroup** (132 treated	**Age:**			**Intervention (Dose)** Gefitinib (250mg daily) **Duration** 5.6 months (range 0.1 to 22.8) **Number of participants** 607 (132 in EGFR mutation positive subgroup)	**Intervention (Dose)** Caroplatin (variable), paclitaxel (200mg per m^2) Administered on day 1 of 3 week cycle Median 6 cycles 3.4 (range 0.7 to 5.8) **Number of participants** 589 (129 in mutation positive subgroup)	**EGFR Mutation Test** Therascreen® EGFR PCR Kit (version 1) **Manufacturer** Qiagen **Mutations Targeted** 29 mutations in Therascreen® kit
		Median (range)	57 (24-84)	57(25-84)			
		Subgroup (<65 years)	95	90			
		Number Male	125	127			
		Ethnicity					
		Chinese	314	304			
		Japanese	114	119			
		Other East Asian	179	184			
		Other	2	1			
		Smoking Status					
		Never smoked	571	569			
		Former smoker	38	39			
		Subgroup (Never smoked):	124	122			
		Histological Features					
		Adenocarcinoma	581	591			
		Bronchoalveolar	27	15			
		NS/other	1	2			
		Disease Stage at entry					
		IIIB	150	144			
		IV	459	463			
		NS	0	1			
		Subgroup (IIIB):	19	29			
		Performance status:					
		0	157	161			
		1	391	382			

Study details	Selection Criteria	Participant Details			Intervention Details		EGFR Mutation Test
		Criteria	EGFR-TKI	SC	EGFR- TKI	SC	
	with gefitinib and 129 treated with SC). Full separate baseline data were not available for these patients.	2	61	65			
		Subgroup (0 or 1):	119	122			
		Previous treatments	NR	NR			

Study details	Selection Criteria	Participant Details			Intervention Details		EGFR Mutation Test
		Criteria	EGFR-TKI	SC	EGFR- TKI	SC	
Study Details Han (First-SIGNAL) (2012)[5, 44] **Country** South Korea **Study Design** RCT **Funding** AstraZeneca **Recruitment** October 2005 – November 2007 **Number enrolled:** 313 **Number treated:** 309 **Number in EGFR mutation positive subgroup:** 42	**Inclusion criteria** Adults (>18 years), chemotherapy naïve, never smokers, stage IIIB/IV adenocarcinoma NSCLC with measurable or non-measurable disease, PS 0-2, adequate bone marrow, liver and renal function. **Exclusion criteria** Known severe hypersensitivity to gefitinib or any constituents, any evidence of clinically active interstitial lung disease, severe or uncontrolled systemic disease, concomitant use of phenytoin, carbamazepine, riampin, barbiturate, or St John's wort, and unstable brain metastases. **Comments** Data were extracted for the EGFR positive **subgroup** (26 treated with gefitinib and 16 treated with SC). Separate baseline data were not available for these patients.	**Age:**			**Intervention (Dose)** Gefitinib (250mg daily) **Duration** median 163 days (range 11-885) **Number of participants** 159 (26 in EGFR mutation positive subgroup)	**Intervention (Dose)** i.v. gemcitabine(1250 mg/m^2) on day 1 and day 8 and cisplatin (75 mg/m^2) on day 1 of 3 week cycles **Duration** Median number of cycles 6 (range 1 to 9) **Number of participants** 150 (16 in EGFR mutation positive subgroup)	**EGFR Mutation Test** Direct sequencing PCR **Manufacturer** Not specified **Analysis Software** Not specified **Mutations Targeted** Exons 19-21
		Median	52	57			
		Age range	32-74	19-74			
		Number Male	19	16			
		Ethnicity: Not stated					
		Smoking Status					
		Never smoked	159	150			
		Histological Features					
		Adenocarcinoma	159	150			
		Disease Stage at entry					
		IIIB	17	14			
		IV	142	136			
		Performance status: ECOG					
		0	41	31			
		1	104	105			
		2	14	14			
		Previous treatments	NR	NR			

Study details	Selection Criteria	Participant Details			Intervention Details		EGFR Mutation Test Details
		Criteria	EGFR-TKI	SC	EGFR- TKI	SC	
Study Details Maemondo (NEJSG)(2010)[4, 91, 97-99, 100 , 101 , 102] **Country** Japan **Study Design** RCT **Funding** Japan Society for promotion of Science, the Japanese Foundation for the Multidisciplinary Treatment of Cancer, and the Co-operative Oncology Group **Recruitment** March 2006 - May 2009 **Number enrolled:**	**Inclusion criteria** Chemotherapy naïve, aged 20-75 years, histologically or cytologically confirmed stage IIIB or IV NSCLC, or recurrent disease after surgery, no indication for further surgery or curative radioptherapy. Patients who had received palliative radiation therapy for brain or bone metastases >2 weeks previously were eligible. Confirmed presence of sensitive EGFR mutations. Lesions evaluable by RECIST. ECOG PS 0 or 1. Normal bone marrow function (white blood cell count ≥4,000/μL, platelet count ≥100,000/μL, haemoglobin ≥9.0 g/dL), normal liver function (AST and ALT ≤2 x upper limit of normal, total serum bilirubin ≤1.5 mg/dL). Normal renal function (creatinine clearance ≥40). Prognosis >3 months. **Exclusion criteria** Interstitial pneumomnia or pulmonary fibrosis. Positive for	**Age:**			**Intervention (Dose)** Gefitinib (250 mg Daily) **Duration** median 308 days (range 14-1219) **Number of participants** 114	**Intervention (Dose)** i.v. paclitaxel (220 mg/m^2) and carboplatin (variable) Administered on day 1 of 3 week cycle for median of 4 cycles (range 1-7) **Number of participants** 113	**EGFR Mutation Test** Fragment length analysis **Manufacturer** Not specified **Mutations Targeted** exon 19 deletions, exon 21 point mutations (L858R, L861Q), exon 18 point mutations (G719A, G719C, G719S), exon 20 point mutation (T790M)
		Mean(sd)	64(8)	63(9)			
		Age range	43-75	35-75			
		Number Male	42	41			
		Ethnicity: Not stated					
		Smoking Status					
		Never smoked	75	66			
		Current/former	39	48			
		Histological Features					
		Adenocarcinoma	103	110			
		Squamous	3	2			
		NS/other	8	2			
		Disease Stage at entry					
		IIIB	15	21			
		IV	88	84			
		NS/Other	11	9			
		Performance status: ECOG					
		0	54	57			
		1	59	55			
		2	1	2			
		Previous treatments	NR	NR			

Study details	Selection Criteria	Participant Details		Intervention Details		EGFR Mutation Test Details
		Criteria	EGFR-TKI SC	EGFR- TKI	SC	
228 **Number treated:** 227	resistant EGRF mutation T790M. Radiation therapy for primary lesions. Severe complications (uncontrolled heart, lung, liver, or kidney disease, or diabetes mellitus), pregnant or lactating women, severe malabsorbtion syndrome, diseases affecting digestive function, receipt of systemic steroids for ≥4 weeks, pleural effusion, pericardial effusion and/or peritoneal effusion requiring tube drainage, unless stable for at least 2 weeks after drainage, contra-indications for gefitinib, carboplatin, or paclitaxel, active double cancers (intra-mucosal tumours were not considered to be independent cancers), patients judged inappropriate for enrollment by attending physicians.					

Study details	Selection Criteria	Participant Details			Intervention Details		EGFR Mutation Test Details
		Criteria	EGFR-TKI	SC	EGFR- TKI	SC	
Study Details Rosell (EURTAC)(2012)[2, 43, 103] **Country** France, Spain and Italy **Study Design** RCT **Funding** Hoffman-La Roche and Red Tematica de Investigacion Cooperativa en Cancer grant **Recruitment** February 2007 - January 2011 **Number enrolled:** 173 **Number treated:** 150	**Inclusion criteria** Adults (>18 years) with histologically confirmed NSCLC (stage IIIB (with pleural effusion), or stage IV), measurable or evaluable disease, and the presence of activating EGFR mutations (exon 19 deletions or exon 21 mutation L858R). No history of chemotherapy for metastatic disease (neoadjuvant or adjuvant chemotherapy was allowed if it ended at least 6 months before study entry). Patients with asymptomatic, stable brain metastases were eligible for inclusion. **Exclusion criteria** None stated.	**Age:**			**Intervention (Dose)** Erlotinib (150 mg daily) **Duration** Median 8.2 months (range 0.3 to 32.9) **Number of participants** 77	**Intervention (Dose)** i.v. cisplatin (75mg/m^2) plus docetaxel (75mg/m^2) administered on day 1 of a 3 week cycle or i.v. cisplatin (75mg/m^2) plus gemcitabine 1.25g/m^2) with cisplatin administered on day 1 and gemcitabine on day 1 and 8 of a 3 week cycle. Median 4 cycles (range 1-6, 2-4) Patients who were ineligible for cisplatin received i.v. carboplatin **Duration** median 2.8 months (range 0.7-5.1, 1.0-2.6) **Number of participants** 73	**EGFR Mutation Test** Sanger sequencing. All mutations were independently confirmed with PCR fragment length analysis for exon 19 deletions and TaqMan assay (Applied Biosystems) for exon 21 point mutation L858R **Manufacturer** Not specified **Mutations Targeted** Exon 19 and 21 mutations
		Mean(sd)	63(11)	64(9)			
		Age range	NR	NR			
		Number Male	28	19			
		Ethnicity: All but two patients were white.					
		Smoking Status					
		Never smoked	57	63			
		Former smoker	22	12			
		Current smoker	7	12			
		Histological Features					
		Adenocarcinoma	82	78			
		Bronchoalveolar	0	2			
		Squamous	1	0			
		NS/other	3	7			
		Disease Stage at entry					
		IIIB	6	5			
		IV	78	82			
		NS	2	0			
		Performance status: ECOG					
		0	27	30			
		1	47	45			
		2	12	12			
		Previous treatments	NR	NR			

Study details	Selection Criteria	Participant Details			Intervention Details		EGFR Mutation Test Details
		Criteria	EGFR-TKI	SC	EGFR- TKI	SC	
Study Details Zhou (OPTIMAL)(2011)[1, 104-110] **Country** China **Study Design** RCT **Funding** Hoffmann-la Roche and the Science and technology Commission of Shanghai Municipality **Recruitment** August 2008 - July 2009 **Number enrolled:** 165 **Number treated:** 154	**Inclusion criteria** Adults (>18 years) with histologically confirmed advanced or recurrent stage IIIB or stage IV NSCLC and a confirmed activating EGFR mutation (exon 19 deletions or exon 21 mutation L858R). Measurable disease according to RECIST. ECOG performance status 0-2. Adequate haematological, biochemical and organ function. **Exclusion criteria** Patients with uncontrolled brain metastases, or who had received previous systemic anticancer therapy for advanced disease (adjuvant or neoadjuvant therapy allowed for non-metastatic disease in which relapse had occurred ≥ 6 months after final treatment).	**Age:**			**Intervention (Dose)** Erlotinib (150 mg daily) **Duration** Median 55.5 weeks (range 3.1 to 93) **Number of participants** 82	**Intervention (Dose)** i.v. gemcitabine (1g/m^2) administered on days 1 and 8 and and i.v. carboplatin (variable) administered on day 1 of a 3 week cycle. Median 4 (range 1-6) cycles. **Duration** median 10.4 weeks (range 1.0 to 18.9) **Number of participants** 72	**EGFR Mutation Test** Direct sequencing (PCR-based). Test confirmation methods were applied at the same time: Agarose gel electrophoresis for exon 19 deletions Cycleave real-time PCR for exon 21 L858R point mutations. **Manufacturer** Not specified **Mutations Targeted** exon 19 and 21
		Median	57	59			
		Age range	31-74	36-78			
		Number Male	34	29			
		Ethnicity: Not stated					
		Smoking Status					
		Never smoked	59	50			
		Current/former	23	22			
		Histological Features					
		Adenocarcinoma	72	62			
		NS/other	10	10			
		Disease Stage at entry					
		IIIB	11	5			
		IV	71	67			
		Performance status: ECOG					
		0-1	75	69			
		2	7	3			
		Previous treatments	NS	NS			

APPENDIX 3: RISK OF BIAS ASSESSMENTS

QUADAS-2 assessments

Study: Fukuoka(2011)[3, 50]

DOMAIN 1: PATIENT SELECTION	
A. Risk of Bias	
Describe methods of patient selection: RCT, only patients treated with gefitinib included for accuracy evaluation.	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**

DOMAIN 2: INDEX TEST(S)	
A. Risk of Bias	
Describe the index test and how it was conducted and interpreted: Biomarker status was determined by analysing paraffin-embedded archival tumour tissue. Scientists were blinded to clinical outcome and treatment. Samples underwent central histopathologic review ; only those considered suitable for downstream biomarker analysis were progressed (on the basis of qualtiy, sample source, and tumour content). If a patient provided more than one sample, the appropriate section was selected before database lock and analysed on the basis of sample qualtiy and largest area of tumour tissue. EGFR mutations were detected by using an amplification mutation refractory system with an EGFR mutation detection kit (DxS, Manchester, UK). Tumours were considered EGFR mutation positive if at least one of 29 EGFR mutations was detected. Additional valdiation for samples with T790M mutations was performed by using three methods: DNA sequencing, multithreaded elecontric PCR sequncing, and an alternative amplification mutation refractory system assay.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

DOMAIN 3: REFERENCE STANDARD	
A. Risk of Bias	
Describe the reference standard and how it was conducted and interpreted: Best overall response to treatment (as defined by RECIST criteria[27]) acted as reference standard. Tumour response was assessed every six weeks until disease progression.	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

DOMAIN 4: FLOW AND TIMING
A. Risk of Bias
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table:

386 patients had unknown mutation status as they declined consent for biomarker analysis, had no available tumour sample, or had samples of insufficient quality for EGFR mutation analysis. All cytology samples were excluded as biomarker kit used was not valdiated for these samples. A further 9 patients were not evaluated for tumour response. *Describe the time interval and any interventions between index test(s) and reference standard:* Follow-up continued for over 2 years	
Was there an appropriate interval between index test(s) and reference standard?	Yes
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Low**

Study: Giaccone(2006)[46]

DOMAIN 1: PATIENT SELECTION	
A. Risk of Bias	
Describe methods of patient selection: No details on how patients were enrolled other than inclusion criteria	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**

DOMAIN 2: INDEX TEST(S)	
A. Risk of Bias	
Describe the index test and how it was conducted and interpreted: Paraffin embedded tumour material was cut in 4 um thick sections and placed onto glass slides, stained with H&E and the presence of tumour cells was verified by a pathologist. Tumour cells were microdissected and genomic DNA was isolated using the QIAamp DNA Micro Kit (Qiagen, Venlo, The Netherlands). Nested PCRs were carried out using primers to amplify exons 18 to 21 of EGFR. To facilitate sequncing, internal primers incorporated an M13 Tag. Sequencing of PCR products was done with the ABI PRISM 310 Genetic analyser (Applied Biosystems, Foster City, CA). Mutations were confirmed by sequnecing independent PCR products. Because of concerns about the sensitivity of direct sequencing, DNA from 22 independent samples were analysed by other institutions in a blinded fashion.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

DOMAIN 3: REFERENCE STANDARD	
A. Risk of Bias	
Describe the reference standard and how it was conducted and interpreted: Best overall response to treatment (as defined by RECIST criteria[27]) acted as reference standard. Tumour response was assessed at six weeks and subsequent assessment frequency was unclear.	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

DOMAIN 4: FLOW AND TIMING
A. Risk of Bias
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table: Histological material was not available for 24 patients and so EGFR mutation analysis could not be performed. *Describe the time interval and any interventions between index test(s) and reference standard:* The median duration of response was 333 days.

Was there an appropriate interval between index test(s) and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Low**

Study: Han(First-SIGNAL)(2012)[5]

DOMAIN 1: PATIENT SELECTION	
A. Risk of Bias	
Describe methods of patient selection: RCT, only patients treated with gefitinib included for accuracy evaluation.	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**

DOMAIN 2: INDEX TEST(S)	
A. Risk of Bias	
Describe the index test and how it was conducted and interpreted: Genomic DNA was extracted from paraffin embedded tissue blocks or cells blocks of cytology specimens whichever were available by using the QIAamp DNA mini kit (Qiagen, Valencia, CA). To detect somatic mutations of EGFR genes, exons 19, 20, and 21 were amplified by polymerase chain reaction and directly sequenced according to the method previously reported. All PCR direct sequencing reactions were repeated twice to confirm the results.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: LOW**

DOMAIN 3: REFERENCE STANDARD	
A. Risk of Bias	
Describe the reference standard and how it was conducted and interpreted: Best overall response to treatment (as defined by WHO criteria[26]) acted as reference standard. Tumour response was assessed every nine weeks during treatment.	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

DOMAIN 4: FLOW AND TIMING	
A. Risk of Bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table: 217 patients were not assessed for mutation status; reasons were not given and no information on differences between those with and without known mutation status. 43 received standard chemotherapy so did not contribute to accuracy data. Of the 159 patients who received gefitinib, 53 were assessed for tumour EGFR mutation status. *Describe the time interval and any interventions between index test(s) and reference standard:* Follow-up continued for over 4 years	
Was there an appropriate interval between index test(s) and reference standard?	Yes

Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Unclear**

Study: Jackman(2007)[47]

DOMAIN 1: PATIENT SELECTION	
A. Risk of Bias	
Describe methods of patient selection: No details on how patients were enrolled other than inclusion criteria	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**

DOMAIN 2: INDEX TEST(S) **If more than one index test was used, please complete for each test.**	
A. Risk of Bias	
Describe the index test and how it was conducted and interpreted: Tumour specimens (frozen or paraffin embedded) were collected from previous diagnositc or surgical procedrues. No specific requirements were prospectively mandated for the type of tumour specimen. For patients with sufficient tissue for direct DNA sequencing, tumour cells were isolated by microdissection. Exons 18 through 24 of the EGFR were amplified and sequenced according to previosuly described methods. For tumour samples deemed inadequate by a molecular pathologist for direct sequncing based on a high percentage of normal cells (<50% tumour cells) mutation analysis was perfomed with the WAVE-HS (Transgenomic Inc, Omaha, NE) platform using previously published methods. All detected mutations were confirmed by repeat analysis.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

DOMAIN 3: REFERENCE STANDARD	
A. Risk of Bias	
Describe the reference standard and how it was conducted and interpreted: Best overall response to treatment (as defined by RECIST criteria[27]) acted as reference standard. Tumour response was assessed every six weeks during treatment.	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

DOMAIN 4: FLOW AND TIMING
A. Risk of Bias
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table: 4 samples could not be obtained from other hospitals, 7 patients had not consented to EGFR testing, 26 samples judged inadequate for testing. Response was not assessable in 6 patients with EGFR mutation negative tumours.

Describe the time interval and any interventions between index test(s) and reference standard: Median time to progression was 3.5 month (95% CI 2, 5.5 months). Median survival was 10.9 months, follow-up continued for over 2 years.	
Was there an appropriate interval between index test(s) and reference standard?	Yes
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Study: Pallis(2012)[48]

DOMAIN 1: PATIENT SELECTION	
A. Risk of Bias	
Describe methods of patient selection: No details on how patients were enrolled other than inclusion criteria	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**

DOMAIN 2: INDEX TEST(S)	
A. Risk of Bias	
Describe the index test and how it was conducted and interpreted: Tumour samples obtained from formalin fixed paraffin embedded tissue blocks made on initial diagnosis. Microdissection was used to ensure that specimens contained at least 80% tumour cells. DNA sequence of exons 18-21 of EGFR were determined by direct forward and reverse sequencing of the PCR product from nested PCR reactions as desscribed previously.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

DOMAIN 3: REFERENCE STANDARD	
A. Risk of Bias	
Describe the reference standard and how it was conducted and interpreted: Best overall response to treatment (as defined by RECIST criteria[27]) acted as reference standard. Tumour response was assessed every eight weeks during treatment.	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

DOMAIN 4: FLOW AND TIMING	
A. Risk of Bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table: All patients had data on outcome (reference standard). 13 patients did not have data on mutation status, because samples were not available. *Describe the time interval and any interventions between index test(s) and reference standard:* Median duration of response 10.2 months (95% CI 7.4 to 12.9 months), median follow-up time was 18.9 months (range 0.6 to 50.7 months)	
Was there an appropriate interval between index test(s) and reference standard?	Yes
Did all patients receive a reference standard?	Yes

Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Low**

Study: Yang(2008)[49]

DOMAIN 1: PATIENT SELECTION	
A. Risk of Bias	
Describe methods of patient selection: No details on how patients were enrolled other than inclusion criteria	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**

DOMAIN 2: INDEX TEST(S)	
A. Risk of Bias	
Describe the index test and how it was conducted and interpreted: Most tumour samples were obtained from paraffin embedded blocks made on initial diagnosis. Alternatively, DNA extracted from pleural fluid derived cancer cells were aslo used for analysis. DNA sequence of exons 18 to 21 were determined by direct forward and reverse sequencing of the PCR product from nested PCR reactions as described previously.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**

DOMAIN 3: REFERENCE STANDARD	
A. Risk of Bias	
Describe the reference standard and how it was conducted and interpreted: Best overall response to treatment (as defined by RECIST criteria[27]) acted as reference standard. Tumour response was assessed every eight weeks during treatment.	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct, or its interpretation have introduced bias?	**RISK: Low**

DOMAIN 4: FLOW AND TIMING	
A. Risk of Bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table: EGFGR mutation status was not successfully determined in 16 patients and 9 patients did not have data on outcome, reasons were not given. *Describe the time interval and any interventions between index test(s) and reference standard:* Median time to treatment failure was 5.5 months. Duration of follow-up was a minimum of 12 months	
Was there an appropriate interval between index test(s) and reference standard?	Yes

Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Risk of bias assessments

Study Name: Fukuoka (IPASS)(2011)[3] and Mok(2009)[50]

	Support for judgement	Risk of bias
Random sequence generation	No details reported	Unclear
Allocation concealment	No details reported	Unclear
Participant/Personnel blinding	Open label	High
Outcome assessor blinding	No details reported	Unclear
Incomplete Outcome Data	246 withdrawals in gefitinib arm: 223 died, 19 withdrew consent, 5 lost to follow-up 276 withdrawals in carboplatin-paclitaxel arm: 227 died, 46 withdrew consent, 2 lost to follow-up, 1 did not meet eligibility criteria. 386 patients in the gefitinib arm and 394 patients in the carboplatin-paclitaxel arm had unknown mutation status as they declined consent for biomarker analysis, had no available tumour sample, or had samples of insufficient quality for EGFR mutation analysis. All cytology samples were excluded as biomarker kit used was not valdiated for these samples. Baseline data similar to overall population and between intervention groups for subgroup with known mutation status Subgroup analysis was reported with data available for all subgroups.	Low
Selective outcome reporting	Details on main outcomes reported	Low

Study Name: Han(First-SIGNAL)(2012)[5]

	Support for judgement	Risk of bias
Random sequence generation	No details reported	Unclear
Allocation concealment	No details reported	Unclear
Participant/Personnel blinding	Open label	High
Outcome assessor blinding	All measurable and non-measurable lesions were independently assessed by a referee radiologist who was blinded to treatment assignment	Low
Incomplete Outcome Data	4 patients withdrew consent before treatmentin SC group; no other withdrawals. 43 were assessable for EGFR mutation status in SC group, 53 in gefitinib group were assessable for EGFR mutation status. Only 23 mutation positive in gefitinib and 16 in SC. Reasons for not assessing mutation status in other patients not stated.	High
Selective outcome reporting	Details on main outcomes reported	Low

Study Name: Maemondo (NEJSG)(2010)[4]

	Support for judgement	Risk of bias
Random sequence generation	No details reported	Unclear
Allocation concealment	No details reported	Unclear
Participant/Personnel blinding	No details reported, but one treatment is oral and the other i.v.	High
Outcome assessor blinding	Treatment response and progression-free survival were determined by external review of CT films by experts who were not aware of treatment assignments.	Low
Incomplete Outcome Data	Three patients in the standard chemotherapy group were not evaluated in the progression-free-survival population (one had a severe allergic reaction to paclitaxel and two withdrew consent).	Low
Selective outcome reporting	Details on main outcomes reported	Low

Study Name: Rosell (EURTAC)(2012)[2] and Benlloch (EURTAC)()[6]

	Support for judgement	Risk of bias
Random sequence generation	Central randomisation by an independent clinical research organisation using a computer generated system, patients registered via. fax, stratified randomisation (mutation type, and ECOG PS).	Low
Allocation concealment	No details reported	Unclear
Participant/Personnel blinding	States that this was not possible due to different drug administration routes (oral versus i.v.)	High
Outcome assessor blinding	PFS and treatment responses were confirmed by external review of CT scans by a central review board.	Low
Incomplete Outcome Data	9 patients from the erlotinib group and 10 from the standard chemotherapy group could not be assessed for response (non-measurable disease at baseline or time of response assessment).	Low
Selective outcome reporting	Details on main outcomes reported	Low

Study Name: Zhou (OPTIMAL)(2011)[1]

	Support for judgement	Risk of bias
Random sequence generation	Central computerised randomisation by an independent clinical research organisation	Low
Allocation concealment	Allocation communicated via e-mail or telephone	Low
Participant/Personnel blinding	States that participants and clinicians were not masked due to the nature of the treatments	High
Outcome assessor blinding	Independent review was not done	High
Incomplete Outcome Data	One patient did not receive erlotinib (no target lesion), 10 patients did not receive standard chemotherapy (9 withdrew consent and 1 did not start treatment). For treated patients, 1 patient in the erlotinib group withdrew consent and 1 was lost to follow-up. In the standard chemotherapy group there were 4 protocol violations (treated with erlotinib) and 4 patients were lost to follow-up.	High
Selective outcome reporting	Details on main outcomes reported	Low

APPENDIX 4: SURVEY OF NHS LABORATORIES IN ENGLAND AND WALES PARTICIPATING IN THE UK NEQAS PILOT SCHEME FOR EGFR MUTATION TESTING

LABORATORY DETAILS

This questionnaire has been designed to collect information to inform a NICE diagnostic assessment review on EGFR testing.

*****1. At which laboratory are you based?

- Leeds
- Manchester
- Birmingham
- GSTS
- Sheffield
- Institute of Cancer Research/Royal Marsden
- Royal Devon and Exeter
- Oxford
- UCL
- Liverpool
- Bristol
- Bournemouth
- Coventry and Warwickshire University Hospitals
- Cardiff and Vale UHB

EGFR MUTATION TESTING METHODS

If you use more than one method to test for EGFR mutations in your laboratory, please complete this questionnaire separately for each EGFR mutation test used.

*****2. Which EGFR sequencing method do you currently use in your laboratory? NB If you use more than one method, please just select one method and then complete the questionnaire again for any other methods

- Qiagen Therascreen® Kit (version 1)
- Qiagen Therascreen® Kit (version 2)
- Qiagen Therascreen® Pyro Kit
- Roche Cobas
- Sanger sequencing
- Pyrosequencing
- Fragment length analysis
- Single strand conformation analysis
- High resolution melt analysis
- TaqMan/Real Time PCR/Entrogen
- SnapShot/RFPL/other
- Mass spectrometry

- Next generation sequencing
- Other (please specify)

3. Why have you chosen the EGFR mutation testing method(s) that you have (please select all that apply):

- Cost
- Proportion of tumour cells required
- Mutation coverage
- Ease of use
- Other (please specify)

4. If you use more than one EGFR mutation testing method, what is the reason for using more than one method:

- Insufficient tumour cell
- Verification of mutations
- Other (please specify)

5. Which mutations does your EGFR mutation testing method aim to detect?

- 29 mutations in Therascreen® kit
- 41 mutations in Cobas kit
- Exon 19 deletions
- Insertions in exon 20
- Exon 21 - L858R mutation
- All Exon 18-21 mutations
- Other (please specify)

LOGISTICS

6. In a typical week, how many samples do you screen for EGFR mutations?

- ≤5
- 6-10
- 11-15
- 16-20
- >20

7. What is your average EGFR mutation test batch size?

8. How often do you run the EGFR mutation test?

- Daily
- 2-3 times per week
- Weekly
- Other (please specify)

9. Do you wait until you have certain number of samples before running the EGFR mutation test?

No

Yes

If yes, how many?

10. On average, how long (in actual days i.e. including working and non-working days) does it take from receiving a sample at the lab to sending a result back to the clinician?

- <24-hours
- 24-48 hours
- 3-5 days
- 6-7 days
- 8-10 days
- >10 days

TECHNICAL PERFORMANCE

11. What is the limit of detection of the EGFR mutation test in terms of the % tumour cells?

- ≤1%
- 1-5%
- 6-10%
- 11-20%
- 21-30%
- >30%

12. We would like to get an idea of the number of samples which could not be analysed and reasons for this. If possible please provide details on the exact number of samples tested last year with number of failed samples and reasons for failure. If you do not have access to the numbers for your lab please provide your best estimate for a hypothetical set of 1000 samples seen in your lab:

Total number of samples screened (type 1000 if providing an estimate):

13. Total number of failed samples:

14. Number of failures due to insufficient tumour cells in sample

15. What are the reasons for failed tests?

COSTS	
16. What is the cost of the test (including purchase costs, personnel, material and overheads)?	
17. If you do not have this information, please provide any information on cost that you have available	
18. What is the price that you charge for the test?	

19. Do you have any final comments?

Thank you for taking the time to complete the survey. If you use more than one EGFR mutation testing method in your laboratory please could you complete the survey again for the other testing methods.

APPENDIX 5: TABLE OF EXCLUDED STUDIES WITH RATIONALE

Study	Reason for exclusion (once a study had failed on one criterion it was not assessed further)			
	1. Not a primary study	2. Did not include adults with chemotherapy naive, locally/regionally advanced/metastatic (IIIB or IV) NSCLC	3. EGFR mutation test not performed and/or test and mutation not specified or deducible	4. Study did not report on response to treatment, survival or progression free survival
(2008)[111]	✓			
(2010)[112]	×	×	×	✓
(2010)[113]	×	×	×	✓
Ahn(2008)[114]	×	✓		
Aydiner(2011)[115]	✓			
Bria(2011)[75]	✓			
Cappuzzo(2005)[116]	×	✓		
Carlson(2009)[117]	✓			
Chang(2008)[118]	✓			
Chen(2011)[119]	✓			
Chen(2012)[90]	×	×	×	✓
Chou (2005)[120]	×	✓		
Chung(2012)[121]	×	✓		
Cohen(2010)[122]	✓			
Cohen(2006)[123]	×	✓		

Study	Reason for exclusion (once a study had failed on one criterion it was not assessed further)			
	1. Not a primary study	2. Did not include adults with chemotherapy naive, locally/regionally advanced/metastatic (IIIB or IV) NSCLC	3. EGFR mutation test not performed and/or test and mutation not specified or deducible	4. Study did not report on response to treatment, survival or progression free survival
Cohen(2006)[124]	×	✓		
Crosby(2011)[125]	×	✓		
Dahabreh (2010)[126]	✓			
de Braud (2003)[127]	×	✓		
De Greve (2011)[128]	×	✓		
De Pas (2011)[129]	×	✓		
Dickson (2011)[130]	×	✓		
Eaton (2011)[131]	×	✓		
Eberhardt(2011)[132]	×	×	✓	
Edwards(2010)[133]	✓			
Edwards(2010)[134]	✓			
Enting(2012)[135]	×	×	×	✓
Feld(2006)[136]	✓			
Feng(2010)[137]	×	×	✓	
Gao(2012)[74]	✓			
Gao(2011)[138]	✓			
Goss (2009)[139]	×	×	✓	

Study	Reason for exclusion (once a study had failed on one criterion it was not assessed further)			
	1. Not a primary study	2. Did not include adults with chemotherapy naive, locally/regionally advanced/metastatic (IIIB or IV) NSCLC	3. EGFR mutation test not performed and/or test and mutation not specified or deducible	4. Study did not report on response to treatment, survival or progression free survival
Gracia(2011)[140]	×	✓		
Gupta(2009)[141]	✓			
Han (2005)[142]	×	✓		
Han (2005)[143]	×	✓		
Han (2006)[144]	×	✓		
Han (2007)[145]	×	✓		
Hata (2011)[146]	×	✓		
Hou(2012)[147]	×	×	✓	
Hsieh(2006)[148]	×	✓		
Ibrahim(2010)[149]	✓			
Inoue(2008)[150]	×	×	×	✓
Inoue(2010)[151]	×	×	✓	
Jackman(2009)[152]	✓			
Johnson(2004)[153]	×	×	✓	
Kasahara(2006)[154]	×	✓		
Kashii(2006)[155]	×	✓		
Kim(2011)[156]	×	✓		

Study	Reason for exclusion (once a study had failed on one criterion it was not assessed further)			
	1. Not a primary study	2. Did not include adults with chemotherapy naive, locally/regionally advanced/metastatic (IIIB or IV) NSCLC	3. EGFR mutation test not performed and/or test and mutation not specified or deducible	4. Study did not report on response to treatment, survival or progression free survival
Kimura(2006)[157]	×	✓		
Kimura(2007)[158]	×	×	✓	
Kris(2009)[159]	✓			
Ku(2011)[160]	✓			
Kunimasa(2011)[161]	×	×	✓	
Lee(2011)[162]	×	×	✓	
Lee(2008)[163]	×	×	✓	
Lilenbaum(2008)[164]	×	×	✓	
Liu(2011)[165]	✓			
Massuti(2009)[166]	×	✓		
Massuti(2006)[167]	×	×	×	✓
Massuti(2006)[168]	×	✓		
Meert(2002)[169]	✓			
Miller(2005)[170]	×	✓		
Minegishi(2010)[171]	×	×	×	✓
Mitsudomi(2010)[72]	✓			
Morita(2009)[172]	✓			

Study	Reason for exclusion (once a study had failed on one criterion it was not assessed further)			
	1. Not a primary study	2. Did not include adults with chemotherapy naive, locally/regionally advanced/metastatic (IIIB or IV) NSCLC	3. EGFR mutation test not performed and/or test and mutation not specified or deducible	4. Study did not report on response to treatment, survival or progression free survival
Murray(2010)[173]	✓			
Murray(2008)[174]	✓			
Na(2007)[175]	×	✓		
Naoki(2008)[176]	×	✓		
Naoki (2011)[177]	×	✓		
Okamoto(2006)[178]	×	✓		
Pallis(2007)[179]	×	✓		
Park(2009)[180]	×	✓		
Paz-Ares(2009)[181]	✓			
Paz-Ares (2010)[182]	✓			
Paz-Ares(2006)[183]	×	×	×	✓
Pesek(2009)[184]	×	✓		
Petrelli(2012)[185]	✓			
Petruzelka(2012)[186]	✓			
Plant(2012)[187]	×	✓		
Reck (2005)[188]	×	×	✓	
Ricciardi(2008)[189]	×	✓		

Study	Reason for exclusion (once a study had failed on one criterion it was not assessed further)			
	1. Not a primary study	2. Did not include adults with chemotherapy naive, locally/regionally advanced/metastatic (IIIB or IV) NSCLC	3. EGFR mutation test not performed and/or test and mutation not specified or deducible	4. Study did not report on response to treatment, survival or progression free survival
Riely(2006)[190]	×	✓		
Rizvi(2005)[191]	×	✓		
Rosell(2009)[64]	×	✓		
Satouchi (2010)[192]	×	✓		
Schneider(2008)[193]	×	✓		
Shih(2006)[194]	×	✓		
Shukuya(2010)[195]	✓			
Shukuya(2011)[87]	✓			
Sone(2007)[196]	×	✓		
Sun(2011)[197]	×	✓		
Sunaga(2006)[198]	×	✓		
Sutani(2006)[199]	×	✓		
Takano(2006)[200]	×	✓		
Takano(2005)[201]	×	✓		
Takano(2007)[202]	×	✓		
Tokumo(2005)[203]	×	✓		
Tsai(2005)[204]	×	✓		

Study	Reason for exclusion (once a study had failed on one criterion it was not assessed further)			
	1. Not a primary study	2. Did not include adults with chemotherapy naive, locally/regionally advanced/metastatic (IIIB or IV) NSCLC	3. EGFR mutation test not performed and/or test and mutation not specified or deducible	4. Study did not report on response to treatment, survival or progression free survival
Tsurutani(2009)[205]	×	×	✓	
Tyagi(2005)[206]	×	✓		
van Zandwijk(2007)[207]	×	✓		
Villaflor(2005)[208]	×	✓		
Wang(2012)[73]	✓			
Wang(2009)[209]	×	✓		
Webb(2009)[210]	×	✓		
Won(2011)[211]	×	✓		
Wu(2011)[212]	×	✓		
Wu(2011)[213]	×	✓		
Wu (2011)[214]	×	✓		
Wu(2008)[215]	×	×	×	✓
Wu(2007)[216]	×	✓		
Wu(2006)[217]	✓			
Xu(2011)[218]	✓			
Yang(2011)[219]	✓			
Yoshida(2008)[220]	✓			

Study	Reason for exclusion (once a study had failed on one criterion it was not assessed further)			
	1. Not a primary study	2. Did not include adults with chemotherapy naive, locally/regionally advanced/metastatic (IIIB or IV) NSCLC	3. EGFR mutation test not performed and/or test and mutation not specified or deducible	4. Study did not report on response to treatment, survival or progression free survival
Yoshida(2010)[221]	×	✓		
Zhang(2011)[222]	✓			
Zhang(2008)[223]	×	✓		
Zhong(2011)[224]	×	✓		

APPENDIX 6: CONSISTENCY CHECK WITH THE MODEL USED IN STA192

Deterministic outcomes for patients with EGFR mutation positive tumours as tested with Therascreen® EGFR PCR Kit and treated with gefitinib

Model used	Costs[a]	QALYs[b]	Life years[c]
De novo model	[redacted]	[redacted]	[redacted]
Manufacturer model in STA 192	[redacted]	1.111	[redacted]
De novo model with ERG amendments[d]	[redacted]	1.111	[redacted]

[a] The costs differed slightly from the AstraZeneca model due to different estimates for the test costs. Additionally, the AstraZeneca model included the test costs for mutation negatives since these costs are necessary to identify the mutation positives. These costs were not included in the deterministic outcomes for mutation positives in the current analysis. If the test costs in the AstraZeneca would be adjusted to be equal as for the Therascreen® EGFR PCR Kit(£154.58 per patient) in the current analysis, the costs in the AstraZeneca model would be [redacted].

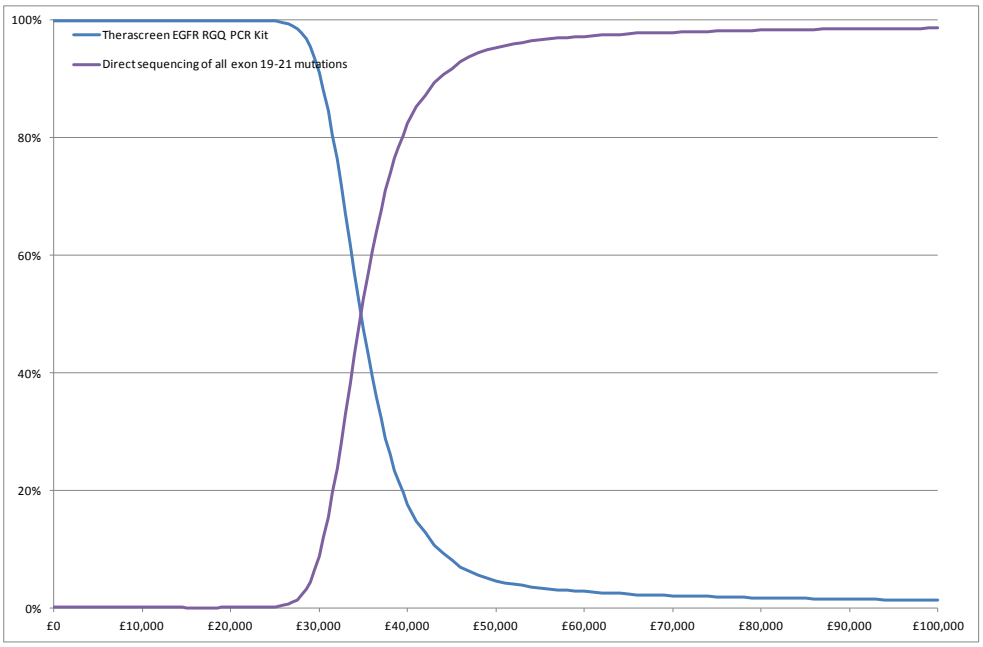
[b] The QALYs differed slightly from the AstraZeneca model since the estimated QALYs for STA 192 (base case analysis) were based on a six year time horizon instead of five year as used for costs due a formula error in the AstraZeneca model. The 5-year QALYs (calculated based on the AstraZeneca model) would be [redacted].

[c] Life Years for STA 192 were calculated based on the AstraZeneca model.

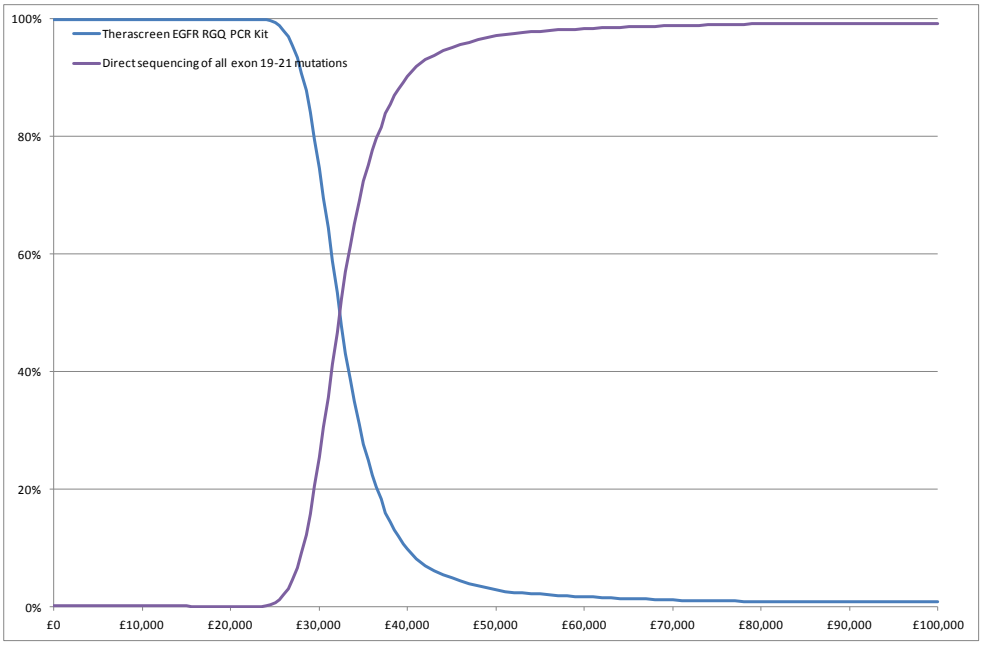
[d] These costs and QALYs correspond to an ICER of £35,393 of gefitinib versus gemcitabine and carboplatin, which is within the range of ICERs as reported in the final appraisal determination of STA 192 (Section 3.39).

APPENDIX 7: COST EFFECTIVENESS ACCEPTABILITY CURVES AND RESULTS FOR SENSITIVITY ANALYSES

Cost-effectiveness acceptability curve for 'evidence on comparative effectiveness' analysis, sensitivity analysis: updated costs



Cost-effectiveness acceptability curve for 'evidence on comparative effectiveness' analysis, sensitivity analysis: unknown based on survey

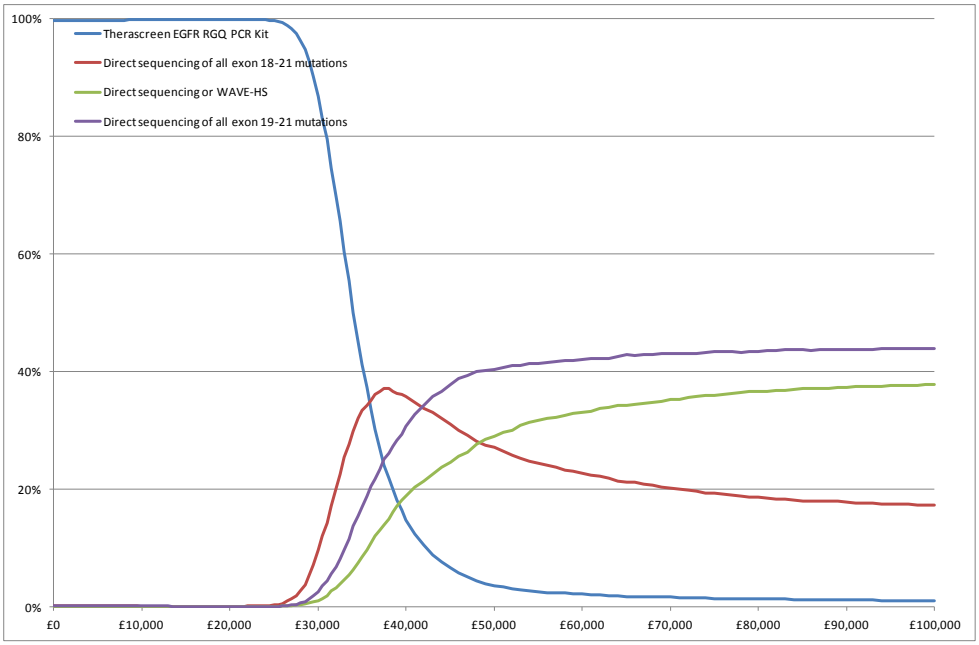


Probabilistic results for 'linked evidence' analysis, sensitivity analysis: updated costs

Strategy	Cost	QALY	Compared to Direct sequencing of all exon 18-21 mutations		
			Incremental Cost	Incremental QALY	Incremental Cost/QALY
Therascreen® EGFR PCR Kit	[redacted]	0.905	-£6,444	-0.189	£34,169
Direct sequencing of all exon 18-21 mutations	[redacted]	1.094			
Direct sequencing of all exon 19-21 mutations	[redacted]	1.111	£685	0.018	£38,659
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)	[redacted]	1.111	£723	0.018	£41,156

Strategy	Cost	QALY	Compared to next cost-effective strategy			
			Comparator	Incremental Cost	Incremental QALY	Incremental Cost/QALY
Therascreen® EGFR PCR Kit	[redacted]	0.905				
Direct sequencing of all exon 18-21 mutations	[redacted]	1.094	Therascreen	£6,444	0.189	£34,169
Direct sequencing of all exon 19-21 mutations	[redacted]	1.111	Therascreen	£7,130	0.206	£34,555
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)	[redacted]	1.111	Therascreen	£7,168	0.206	£34,765

Cost-effectiveness acceptability curve for 'linked evidence' analysis, sensitivity analysis: updated costs

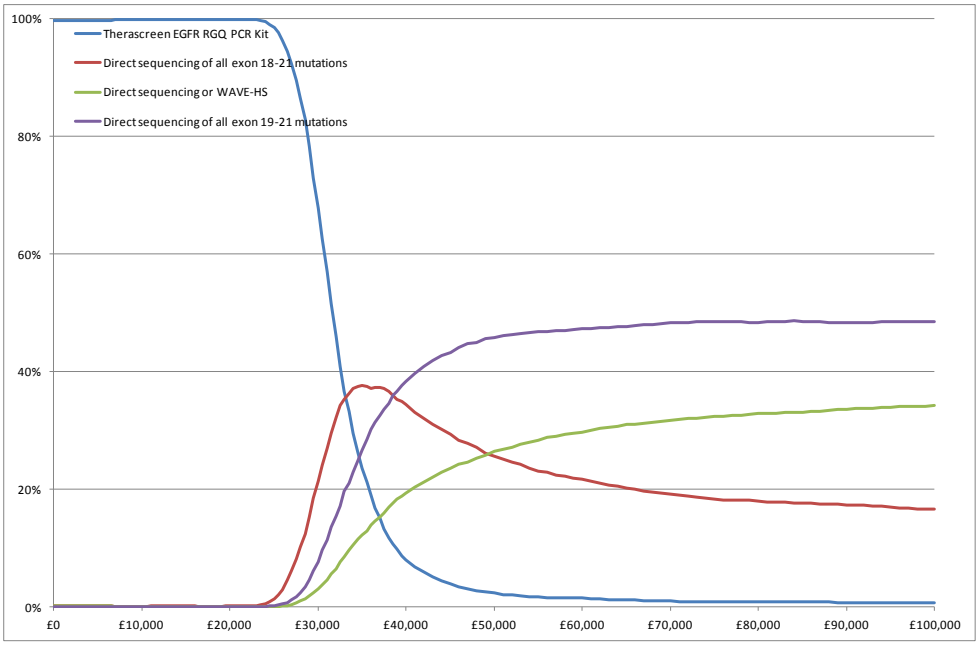


Probabilistic results for 'linked evidence' analysis, sensitivity analysis: unknown based on survey

Strategy	Cost	QALY	Compared to Direct sequencing of all exon 18-21 mutations		
			Incremental Cost	Incremental QALY	Incremental Cost/QALY
Therascreen® EGFR PCR Kit	[redacted]	0.874	-£8,220	-0.258	£31,880
Direct sequencing of all exon 18-21 mutations	[redacted]	1.132			
Direct sequencing of all exon 19-21 mutations	[redacted]	1.160	£973	0.028	£35,138
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)	[redacted]	1.159	£1,014	0.027	£37,452

Strategy	Cost	QALY	Compared to next cost-effective strategy			
			Comparator	Incremental Cost	Incremental QALY	Incremental Cost/QALY
Therascreen	[redacted]	0.874				
Direct sequencing of all exon 18-21 mutations	[redacted]	1.132	Therascreen	£8,220	0.258	£31,880
Direct sequencing of all exon 19-21 mutations	[redacted]	1.160	Therascreen	£9,194	0.286	£32,196
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)	[redacted]	1.159	Therascreen	£9,234	0.285	£32,409

Cost-effectiveness acceptability curve for ‘linked evidence’ analysis, sensitivity analysis: unknown based on survey



APPENDIX 8: NICE GUIDANCE RELEVANT TO EGFR MUTATION TESTING AND THE FIRST-LINE TREATMENT OF LOCALLY ADVANCED OR METASTATIC NON-SMALL-CELL LUNG CANCER

Clinical Guidelines:

National Institute for Health and Clinical Excellence. *Lung cancer: the diagnosis and treatment of lung cancer (CG121) [Internet]*. London: NICE, April 2011 [accessed 20.6.12]. 40p. Available from: http://guidance.nice.org.uk/CG121 Date for review: 2014.

Technology Appraisals: 1st line treatment

National Institute for Health and Clinical Excellence. *Pemetrexed for the first-line treatment of non-small-cell lung cancer. NICE technology appraisal guidance 181 [Internet]*. London: NICE, 2009 [accessed 18.12.12]. 32p. Available from: http://guidance.nice.org.uk/TA181 Date for review: Jan 2010

National Institute for Health and Clinical Excellence. *Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. NICE technology appraisal guidance 192 [Internet]*. London: NICE, 2010 [accessed 20.6.12]. 45p. Available from: http://guidance.nice.org.uk/TA192 Date for review: April 2013

Technology Appraisals: 2nd line treatment

National Institute for Health and Clinical Excellence. *Erlotinib for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 162 [Internet]*. London: NICE, 2008 [accessed 18.12.12]. 29p. Available from: http://guidance.nice.org.uk/TA162 Date for review: June 2010

National Institute for Health and Clinical Excellence. *Pemetrexed for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 124 [Internet]*. London: NICE, 2007 [accessed 18.12.12]. 20p. Available from: http://guidance.nice.org.uk/TA124 Date for review: Jan 2010

National Institute for Health and Clinical Excellence. *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 [Internet]*. London: NICE, 2012 [accessed 18.12.12]. 43p. Available from: http://guidance.nice.org.uk/TA258

Technology Appraisals: Maintenance treatment

National Institute for Health and Clinical Excellence. *Pemetrexed for the maintenance treatment of non-small-cell lung cancer. NICE technology appraisal guidance 190 [Internet]*. London: NICE, 2010 [accessed 18.12.12]. 29p. Available from: http://guidance.nice.org.uk/TA190 Date for review: Nov 2012

National Institute for Health and Clinical Excellence. *Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer. NICE technology appraisal guidance 227 [Internet]*.

London: NICE, 2011 [accessed 10.7.12]. 52p. Available from: http://guidance.nice.org.uk/TA227 Date for review: April 2013

Under development

National Institute for Health and Clinical Excellence. *Lung cancer (non-small-cell, anaplastic lymphoma kinase fusion gene, previously treated) - crizotinib [Internet]*, [accessed 18.12.12] Available from: http://guidance.nice.org.uk/TA/Wave28/3 (publication expected July 2013)

APPENDIX 9: PRISMA CHECK LIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	pg 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Executive summary, pg 11-19 PROSPERO registration, pg 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Section 2.2, pg 22
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Objective, pg 20
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Appendix 10 of this report PROSPERO registration: CRD42012002828
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Table 2, pg 32
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Section 3.1.1, pg 29-31
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Section 3.1.3, pg 33

Section/topic	#	Checklist item	Reported on page #
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Section 3.21.3, pg 33
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Section 3.1.3, pg 33
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Section 3.1.4, pg 33
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Section 3.1.6, pg 34-35
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Section 3.1.6, pg 34-35
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Section 3.2, pg 35-36 Figure 1, pg 37
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 7, pg 50-51 Table 10, pg 60 Appendix 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 9, pg 54 Figure 5, pg 55 Table 11, pg 62 Figure 9, pg 62 Appendix 3

Section/topic	#	Checklist item	Reported on page #
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 7, pg 50-51 Figure 4, pg 52 Table 10, pg 60 Figures 6-8, pg 58-59
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Section 5.1, pg 103-109
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Sections 5.2 and 5.3, pg 109-119
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Section 6, pg 120-121
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	pg 2

APPENDIX 10: PROTOCOL

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 EGFR-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 patients with EGFR-TK mutation positive tumours), 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 whose tumours test positive for EGFR-TK mutations using version 1 of the Therascreen® EGFR PCR Kit, gain more benefit from treatment with the tyrosine kinase inhibitor gefitinib than from standard chemotherapy. People whose tumours 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 whose tumours 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, EGFR mutation positive NSCLC.[1] The mutation test used in the trial that informed NICE Technology Appraisal 192 was version 1 of the Therascreen® EGFR PCR Kit; it should be noted this version is not currently being marketed and has been superseded by version 2, the Therascreen® EGFR RGQ PCR Kit. NICE Technology Appraisal 258 recommends erlotinib as an option for the first-line treatment of people with locally advanced or metastatic, EGFR mutation positive NSCLC.[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 with EGFR-TK mutation positive tumours, 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 tumours which 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 †
Commercial 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 fragments into small segments that can be sequenced in parallel	10%†		

reactions.

* 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, EGFR mutation positive NSCLC.[1] NICE Technology Appraisal 258 recommends erlotinib as an option for the first-line treatment of people with locally advanced or metastatic, EGFR mutation positive NSCLC.[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 patients with EGFR-TK positive versus EGFR-TK negative tumours. 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 inform 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. If any published reports on technical performance, from NHS laboratories in England and Wales, are identified by the systematic review searches, these will be summarised alongside the survey data.

4.3 Search strategy

Search strategies were 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.[28, 31]

Candidate search terms were 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 were used to generate test sets of target references, which informed text mining analysis of high-frequency subject indexing terms using Endnote reference management software. Strategy development involved an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases and aimed to reach a satisfactory balance of sensitivity and specificity.

The following databases were searched for relevant studies from 2000 to August 2011:

- MEDLINE (OvidSP) (2000-2012/07/wk 1)
- MEDLINE In-Process Citations and Daily Update (OvidSP) (up to 2012/07/17)
- EMBASE (OvidSP) (2000-2012/wk 28)
- Cochrane Database of Systematic Reviews (CDSR) (Internet) (2000-2012/Issue 7)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) (2000-2012/Issue 7)
- Database of Abstracts of Reviews of Effects (DARE) (via Cochrane Library) (2000-2012/Issue 3)
- Health Technology Assessment Database (HTA) (via Cochrane Library) (2000-2012/Issue 3)
- Science Citation Index (SCI) (Web of Science) (2000-2012/07/18)
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet) (2000-2012/07/06)
  http://regional.bvsalud.org/php/index.php?lang=en
- Biosis Previews (Web of Knowledge) (2000-2012/08/24)
- NIHR Health Technology Assessment Programme (Internet) (2000-2012/07/18)
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) (up to 2012/07/19)
  http://www.crd.york.ac.uk/prospero/

Completed and ongoing trials were identified by searches of the following resources:

- NIH ClinicalTrials.gov (2000-2012/07/19) (Internet)
  http://www.clinicaltrials.gov/
- Current Controlled Trials (2000-2012/08/30) (Internet)
  http://www.controlled-trials.com/
- WHO International Clinical Trials Registry Platform (ICTRP) (2000-2012/08/30) (Internet)
  http://www.who.int/ictrp/en/

Searches were undertaken to identify studies of Therascreen®/EGFR-TK testing for non-small cell lung cancer. The main Embase strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the PRESS-EBC checklist.[32] Search strategies were developed specifically for each database and the keywords associated with non-small cell lung cancer were adapted according to the configuration of each database. Searches took into account generic and other product names for the intervention. No restrictions on language or publication status were applied. Limits were applied to remove animal studies. Full search strategies are reported in Appendix 1.

Electronic searches were undertaken for the following conference abstracts:

- ASCO Conference Proceedings (American Society of Clinical Oncology) (2007-2012) (Internet)
  http://www.asco.org/ASCOv2/Meetings/Abstracts

- ESMO Conference Proceedings (European Society of Medical Oncology) (2007-2012) (Internet)
  http://www.esmo.org/no_cache/education/abstracts-and-virtual-meetings.html
  2008 33rd ESMO Congress, Stockholm - http://annonc.oxfordjournals.org/content/vol19/suppl_8/
  2009 ECCO 15 and 34th ESMO Multidisciplinary Congress - http://www.ejcancer.info
  2010 35th ESMO Congress, Milan - http://annonc.oxfordjournals.org/content/21/suppl_8
  2011 ECCO 16 and 36th ESMO Multidisciplinary Congress, Brussels - http://www.ejcancer.info/issues
  2012 37th ESMO Congress, Vienna - http://annonc.oxfordjournals.org/content/23/suppl_9

- World Conference on Lung Cancer (International Association for the Study of Lung Cancer) (2007-2012) Internet)
  http://iaslc.org/
  14th World Conference on Lung Cancer - http://journals.lww.com/jto/toc/2011/06001
  13th World Conference on Lung Cancer - http://journals.lww.com/jto/Citation/2009/09001/Abstracts.1.aspx
  12th World Conference on Lung Cancer - http://journals.lww.com/jto/toc/2007/08001

Identified references were downloaded in Endnote X4 software for further assessment and handling.

References in retrieved articles were checked for additional studies. The final list of included papers was also checked on PubMed for retractions, errata and related citations.[33-35]

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

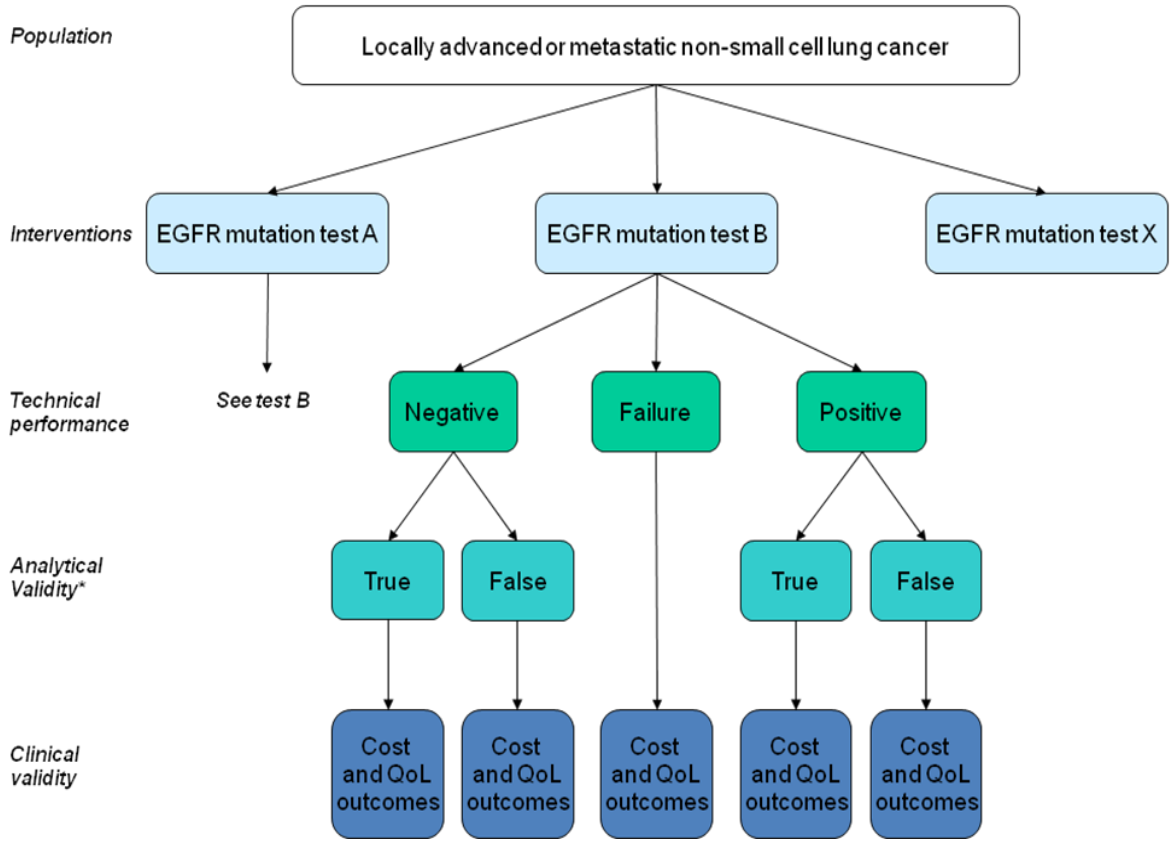
Embase (OvidSP): 2000-2012/wk 28

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

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.*