National Institute for Health and Clinical Excellence

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Diagnostics Assessment Programme

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

Final scope

July 2012

1 Introduction

The Medical Technologies Advisory Committee identified 'epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer' as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note. The final scope was informed by discussions at the scoping workshop held on 6th July and the assessment subgroup meeting held on 16th July. A glossary of terms and a list of abbreviations are provided in appendices A and B.

It should be noted that NICE technology appraisal 192 shows the tyrosine kinase inhibitor, gefitinib, to be cost-effective for the first line treatment of locally advanced or metastatic EGFR-TK positive non-small-cell lung cancer (NSCLC). Similarly, NICE technology appraisal 258 shows the tyrosine kinase inhibitor, erlotinib, to be cost-effective for the first line treatment of locally advanced or metastatic EGFR-TK positive NSCLC. This evaluation will not be re-assessing the cost-effectiveness of gefitinib or erlotinib, but will be looking at the relative cost-effectiveness of the different methods of testing for EGFR-TK mutation status.

2 *Description of the technologies*

This section describes the properties of the diagnostic technologies based on information provided to NICE by manufacturers and expert advisers. NICE has not carried out an independent evaluation of these descriptions.

2.1 Purpose of the medical technologies

EGFR-TK mutation testing is indicated in adults with previously untreated, locally advanced or metastatic NSCLC. Clinical trials have shown that in people who are EGFR-TK mutation positive, treatment with anti-EGFR tyrosine kinase inhibitors (TKIs) leads to improved patient outcomes compared to treatment with standard chemotherapy. Conversely, people who are EGFR-TK mutation negative gain more benefit from standard chemotherapy.

The tyrosine kinase domain of the EGFR gene is made up of exons 18 to 24. EGFR-TK mutations are found in exons 18, 19, 20 and 21, with a lack of reports of mutations in exons 22 to 24. Deletions in exon 19 and the L858R mutation in exon 21 account for approximately 85-90% of all mutations identified (1). People with these mutations exhibit a high response rate and prolonged progression free survival when treated with anti-EGFR TKIs (2). People with less common mutations such as G719X substitutions in exon 18 also respond to anti-EGFR TKIs (3).

Approximately half of all patients treated with anti-EGFR TKIs develop secondary resistance mutations in the EGFR gene, such as T790M (4). However in some people resistance mutations are detected prior to anti-EGFR TKI treatment. These people are likely to have a lower response rate to anti-EGFR TKIs (5-7).

2.2 Product properties

Multiple technologies are available for EGFR-TK mutation testing and they can be divided into two subgroups: mutation screening and targeted mutation detection. The former technologies screen samples for all EGFR-TK mutations, known and novel variants. The latter technologies analyse samples for specific known EGFR-TK mutations only.

Communications with the United Kingdom National External Quality Assessment Service (UK NEQAS) and UK laboratories have helped to identify methodologies for EGFR-TK mutation testing which are currently in use (Table 1). Many laboratories use a combination of methodologies, including:

- Sanger sequencing for samples with tumour content >30% and Roche cobas test for samples with tumour content <30%.
- High resolution melt analysis followed by Sanger sequencing of positive results to confirm the mutation.
- Pyrosequencing and fragment length analysis run concurrently.
- Sanger sequencing followed by fragment length analysis and real-time polymerase chain reaction (PCR) of samples with a negative result from sequencing.

In addition, several laboratories are planning to switch to next generation sequencing for EGFR-TK mutation testing, potentially within the next year.

Table 1: Methodologies for EGFR-TK mutation testing

Method (S = screening; T = targeted)		Number of laboratories using the method	
		NEQAS report (8)*	Lab contact[†]
Sanger sequencing	S	20	3
Qiagen Therascreen Kit/ARMS	T	14	6
Fragment length analysis	S/T	14	5
Pyrosequencing	T	6	4
TaqMan/Real Time PCR/Entrogen	T	6	1
High resolution melt analysis	S	5	1
Roche cobas test	T	4	1
Single strand conformation analysis	S	0	1
SnapShot/RFPL/other	T	2	0
Mass spectrometry	T	2	0

* NEQAS pilot scheme 2011-2012. 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.

2.2.1 Therascreen EGFR RGQ PCR Kit (Qiagen)

The Therascreen EGFR RGQ PCR Kit is a CE-marked real-time PCR assay for the detection of 29 EGFR-TK mutations. The DNA is first isolated from a specimen of formalin fixed and paraffin embedded (FFPE) tissue using the QIAamp DNA FFPE Tissue Kit to adhere to the CE-marking. A control assay is performed to assess the total DNA in a sample. The mutation assay can then be performed. The Therascreen EGFR RGQ PCR Kit uses two technologies for the detection of mutations: ARMS (Amplification Refractory Mutation System) for mutation specific DNA amplification and Scorpions for detection of amplified regions. Scorpions are bi-functional molecules

containing a PCR primer covalently linked to a fluorescently labelled probe. A real-time PCR instrument (Rotor-Gene Q 5-Plex HRM for consistency with CE-marking) is used to perform the amplification and to measure fluorescence (9).

The Therascreen EGFR-RGQ PCR Kit is designed to detect:

- G719X (G719S/G719A/G719C)* in exon 18
- 19 deletions in exon 19*
- T790M in exon 20
- S768I in exon 20
- 3 insertions in exon 20*
- L858R in exon 21
- L861Q in exon 21

* The test detects the presence of these mutations but does not distinguish between them.

The limits of detection (the lowest amount of tumour cells needed in a sample to detect a mutation) for the different mutations detected by the EGFR RGQ PCR Kit are presented in Table 2.

Table 2: Limits of detection for each of the EGFR-TK mutation assays (10)

Mutation	Percentage mutation detectable
T790M	7.02
Deletions	1.64
L858R	1.26
L861Q	0.50
G719X	5.43
S768I	1.37
Insertions	2.03

2.2.2 Cobas EGFR Mutation Testing Kit (Roche Molecular Systems)

The cobas EGFR Mutation Testing Kit is a CE-marked real-time PCR test for the detection of 41 EGFR-TK mutations. 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 (6).

The cobas Kit is designed to detect:

- G719X (G719S/G719A/G719C)* in exon 18
- 29 deletions and complex mutations* in exon 19
- T790M in exon 20
- S768I in exon 20
- 5 insertions in exon 20*
- L858R in exon 21

* The test detects the presence of these mutations but does not distinguish between them.

The limits of detection for the different mutations detected by the cobas Kit are presented in Table 3.

Table 3: Limits of detection for each of the EGFR-TK mutation assays (6)

Mutation	Lowest amount of DNA (ng) per reaction well to achieve ≥95% 'mutation detected' rate
T790M	3.13
Exon 19 deletion	0.78
L858R	0.78
G719A	3.13
S768I	0.78
Exon 20 Insertion	3.13

2.2.3 Sanger sequencing

Sequencing is a screening method which detects all mutations, known and novel. Sequencing is a commonly used method; however, there is much variation in the detail of how the method is carried out. In general, after DNA is extracted from the sample it is amplified using PCR. The PCR product is then cleaned up and sequenced in both forward and reverse directions. The sequencing reaction uses dideoxynucleotides labelled with coloured dyes which randomly terminate DNA synthesis creating DNA fragments of various lengths. The sequencing reaction product is then cleaned up and analysed using capillary electrophoresis. The raw data are analysed using analysis software to generate the DNA sequence. All steps are performed at least in duplicate to increase confidence that an identified mutation is real. It should be noted that sequencing only works well when viable tumour cells constitute at least 25% or more of the sample (11;12).

2.2.4 Pyrosequencing

Pyrosequencing assays are generally set up to detect a specific number of EGFR-TK mutations. Pyrosequencing to look for point mutations is used by several laboratories 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 (13). The limit of detection for pyrosequencing is approximately 5% of tumour cells in the sample (personal communication with laboratory staff).

2.2.5 Therascreen EGFR Pyro Kit (Qiagen)

A CE-marked pyrosequencing kit is available from Qiagen; the Therascreen EGFR Pyro Kit. This kit is designed to detect and distinguish between:

- G719S, G719A and G719C in exon 18
- The 20 most common deletions in exon 19
- S768I and T790M in exon 20
- L858R and L861Q in exon 21.

The kit provides all primers, controls, buffers and reagents necessary to perform the assay. Samples are analysed on the PyroMark Q24 System and a Plug-in report tool is available which simplifies analysis of the pyrogram trace (14).

2.2.6 Fragment length analysis

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 (15). The limit of detection for fragment length analysis is 1-2% of tumour cells in the sample (personal communication with laboratory staff).

2.2.7 Single strand conformation polymorphism analysis

Single strand conformation polymorphism (SSCP) analysis is a screening method which detects >98% of all EGFR-TK mutations detected by sequencing (expert opinion). The DNA is first extracted from the sample and amplified using PCR. The PCR product is then prepared for analysis by heat denature and analysed using capillary electrophoresis under non-denaturing conditions. Sequence variations (single-point mutations and other small changes) are detected through electrophoretic mobility differences (16). The limit of detection for SSCP analysis is 1% for the most common mutations, for example, exon 19 deletions and L858R, and 5-10% for other mutations (personal communication with laboratory staff).

2.2.8 High resolution melt analysis

High resolution melt (HRM) analysis is a screening method which 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 (17). The limit of detection for HRM analysis is 2-5% of tumour cells in the sample (personal communication with laboratory staff).

2.2.9 Next generation sequencing

This is a screening method which can be used to identify all mutations known and novel. As with Sanger sequencing, there is much variation in the methodology used to perform next generation sequencing. 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 (18). The limit of detections is thought to be around 10% of tumour cells in the sample (personal communication with laboratory staff).

3 Target conditions / indications

3.1 Background - Non-small-cell lung cancer

NSCLC is the most common type of lung cancer, accounting for around 72% of all cases in England and Wales (19). There are three main histological subtypes of NSCLC: squamous cell carcinoma (32% of NSCLCs);

adenocarcinoma (26% of NSCLCs); and large cell carcinoma (4% of NSCLCs). Less common sub-types, bronchoalveolar cell and carcinoma-in-situ, account for 2% and 0.4% of NSCLCs respectively. Additionally, a large number of people do not have the histological subtype identified: non-small-cell NOS (not otherwise specified) accounts for 35% of NSCLCs (2006-2008 data) (20). The percentage of mutation positive NSCLC patients is estimated at 10-15% in a Western European population and 30-40% in an Asian population (21).

3.2 Care pathway

3.2.1 Diagnosis

Individuals presenting with signs or symptoms of lung cancer are urgently referred for a chest X-ray and if the results suggest lung cancer, the patient is urgently referred to a lung cancer multi-disciplinary team. These patients are then offered a contrast-enhanced CT scan of the chest, liver and adrenals, and a spirometry test is performed. Further diagnostic investigations, generally including a biopsy, are carried out in order to confirm a diagnosis and to provide information about the stage of the disease (20;22). The choice of tests depends on the location of the lesion and the probability of malignant mediastinal lymph nodes, but may involve:

- PET-CT
- endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration
- endoscopic ultrasound (EUS)-guided fine needle aspiration
- non-ultrasound-guided transbronchial needle aspiration

Tissue from the tumour biopsy is fixed in formalin and embedded in a block of paraffin for storage. The tumour sections are then examined by a pathologist who will sub-type the tumour and confirm the histology. In samples from patients eligible for EGFR mutation analysis, the tumour content of the sample is evaluated, and manual macrodissection may be performed. DNA is then extracted and mutation analysis is carried out to determine whether the tumour is EGFR-TK-mutation positive or negative (23). To minimise turnaround time, pathology guidelines recommend that when the sample is eligible, EGFR-TK mutation testing should be ordered by the pathologist reporting on the sub-type of the tumour (24). However, this is not currently universal practice and often the decision to perform an EGFR-TK mutation test is taken at the multidisciplinary team meeting.

It has been noted by clinical experts that if the first biopsy sample does not contain enough tumour cells to enable EGFR-TK mutation testing then re-biopsy would only occasionally be performed because of the delay which would occur. Instead these patients would be treated as EGFR-TK mutation negative and may be re-biopsied at a later date. Furthermore, cytology samples (bronchial alveolar lavage, bronchial scrapings and fine needle aspirates) may be used for EGFR-TK mutation testing. The use of surrogate samples such as serum or plasma is currently still confined to research (21).

3.2.2 Management

First line treatment

For patients with a confirmed diagnosis of advanced or metastatic NSCLC and a positive EGFR-TK mutation test result, gefitinib and erlotinib are recommended as options for first line treatment in Gefitinib for the first line treatment of locally advanced or metastatic non-small-cell lung cancer (technology appraisal 192) and Erlotinib for the first line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (technology appraisal 258) respectively (25;26).

For patients with a confirmed diagnosis of advanced or metastatic non-squamous (adenocarcinoma or large-cell carcinoma) NSCLC and a negative EGFR-TK mutation test result, pemetrexed in combination with cisplatin is recommended as an option for first line treatment in Pemetrexed for the first line treatment of non-small-cell lung cancer (technology appraisal 181) (27).

The NICE clinical guideline on the diagnosis and treatment of lung cancer (clinical guideline 121) recommends that for patients with locally advanced or metastatic NSCLC of squamous histology, a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (either carboplatin or cisplatin) should be offered as a first line treatment. If patients cannot tolerate a platinum combination, then single-agent chemotherapy with a third-generation drug should be offered (20).

Second line treatment

Platinum-based chemotherapy should be considered for the second line treatment of locally advanced or metastatic NSCLC when cancer relapses after first line treatment with a TKI (local guidelines and clinical opinion). Docetaxel monotherapy or erlotinib monotherapy should be considered for the second line treatment of locally advanced or metastatic NSCLC when cancer relapses after previous chemotherapy (28). Generally, patients with non-squamous histology would be offered erlotinib and patients with squamous

histology would be offered docetaxel. However patients who receive gefitinib first line would not be offered erlotinib as a second line treatment (clinical opinion).

Supportive and palliative care

For patients who cannot be offered disease modifying treatment, palliative radiotherapy is offered either as an immediate treatment or when symptoms arise (20;22).

3.3 Treatment effectiveness

Several randomised controlled trials have shown that gefitinib (29-31) and erlotinib (32;33) given as first line treatments for people with EGFR-TK mutation positive NSCLC improve progression free survival compared with chemotherapy. Conversely, gefitinib as a first line treatment in people with EGFR-TK mutation negative NSCLC is associated with significantly shorter progression free survival compared to first line treatment with chemotherapy (29).

The latest published data from the IPASS study show that in people with EGFR-TK mutation positive NSCLC there is no significant difference in overall survival between first line treatment with gefitinib and first line treatment with chemotherapy (2). However, in this study 64.3% of patients who received chemotherapy first line received subsequent gefitinib or erlotinib treatment following discontinuation of chemotherapy. This suggests that people with EGFR-TK mutation positive NSCLC who are treated with chemotherapy first line may achieve the same overall survival as those treated with a TKI first line, but only if they receive a TKI as a second line treatment following discontinuation of chemotherapy. In practice up to 50% of patients do not receive second line treatment following first line treatment with chemotherapy as they are not fit enough to do so (clinical opinion).

3.4 Technology uses within this indication

EGFR-TK mutation testing is used on patients with a diagnosis of advanced or metastatic NSCLC who have not been previously treated with a chemotherapy regimen. The test will identify which patients are EGFR-TK mutation positive and which are mutation negative and therefore help to define their first line treatment options.

4 Scope of the evaluation

Table 4: Scope of the evaluation

Decision question	Of the scoped interventions, which technologies / methodologies for EGFR-TK mutation testing in adults with chemotherapy naive, locally advanced or metastatic NSCLC are clinically effective and cost-effective for informing first line treatment decisions as currently recommended by NICE, in the NHS in England?
Population	Adults with previously untreated, locally advanced or metastatic (stage III or IV) NSCLC of any histological subtype, with either a biopsy sample or a cytology sample available for EGFR-TK mutation testing.
Interventions	• Therascreen EGFR RGQ PCR Kit • Therascreen EGFR Pyro Kit • Cobas EGFR Mutation Testing Kit • Sanger sequencing (exons 18-21) of samples with >30% tumour cells and Therascreen EGFR RGQ PCR Kit for samples with <30% tumour cells • Sanger sequencing (exons 18-21) of samples with >30% tumour cells and cobas EGFR Mutation Testing Kit for samples with <30% tumour cells • Sanger sequencing (exons 18-21) followed by fragment length analysis (exon 19 deletions) / PCR (to detect L858R) of negative samples • Pyrosequencing (to detect T790M, L858R, L861Q, G719X and S768I) and fragment length analysis (to detect exon 19 deletions and exon 20 insertions) • Single strand conformation polymorphism analysis (exons 18-21) • HRM analysis (exons 18-21) • Next generation sequencing (exons 18-21)
Comparator	A range of methods for EGFR-TK mutation testing are currently used in NHS laboratories. Although not a gold standard, Sanger sequencing (exons 18-21) is the comparator for the purpose of the economic modelling.
Healthcare setting	Secondary and tertiary care
Outcomes	Intermediate measures for consideration may include: • Number of true positives / false positives / true negatives / false negatives for the prediction of treatment benefit • Minimum % tumour cells in biopsy sample needed

	(limit of detection) • Failure rate • Turnaround time
	Clinical outcomes for consideration may include: • Survival (overall and progression free) • Objective tumour response rate • Adverse events • Health related quality of life
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Costs for EGFR-TK mutation testing • Costs associated with administration of a TKI within current NICE recommendations • Costs associated with administration of standard chemotherapy within current NICE recommendations • Costs associated with the downstream events of cancer, including the management of adverse events associated with treatment
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	Patient's lifetime

5 Modelling approach

5.1 Existing models

The manufacturer submissions for the NICE single technology appraisals of Gefitinib for the first line treatment of locally advanced or metastatic non-small-cell lung cancer (technology appraisal 192), Erlotinib for the first line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (technology appraisal 258) and Pemetrexed for the first line treatment of non-small-cell lung cancer (technology appraisal 181) all included de novo economic evaluations. Full descriptions of these models are available in the manufacturer submission documents and models are critiqued in the evidence review group reports.

The de novo economic evaluation included in the manufacturer submission for the gefitinib appraisal estimated the cost-effectiveness of gefitinib compared with doublet chemotherapy in the first line treatment of patients with locally

advanced or metastatic EGFR-TK mutation positive NSCLC. Additional analyses compared gefitinib with pemetrexed / cisplatin.

The de novo economic evaluation included in the manufacturer submission for the erlotinib appraisal estimated the cost-effectiveness of erlotinib compared with gefitinib in the first line treatment of patients with locally advanced or metastatic EGFR-TK mutation positive NSCLC.

The de novo economic evaluation included in the manufacturer submission for the pemetrexed appraisal estimated the cost-effectiveness of a pemetrexed / cisplatin regimen compared to gemcitabine / cisplatin in the first line treatment of patients with locally advanced or metastatic non-squamous NSCLC. Gemcitabine / carboplatin and docetaxel / cisplatin were included as secondary comparators.

An independent health technology assessment report, ‘First line therapy for adult patients with non-small-cell lung cancer’, is currently being compiled by the Liverpool Review and Implementation Group, Liverpool University. This health technology assessment is anticipated to be published in January 2013.

5.2 Modelling possibilities

5.2.1 Availability of evidence

End-to-end data are available for the Therascreen EGFR PCR Kit, which was used in the IPASS study of gefitinib to identify people with EGFR-TK mutations. It should be noted that this is a different version of the test to the Therascreen EGFR RGQ PCR kit described in section 2.2.1. The version of the test used in the IPASS study (Therascreen EGFR PCR Kit) is designed to detect 28 mutations in the EGFR gene, but does not detect T790M, a known resistance mutation (14). The Therascreen EGFR RGQ PCR Kit described in section 2.2.1 detects the same 28 mutations and also detects T790M.

The EURTAC study of erlotinib only included people with a positive EGFR-TK mutation (exon 19 deletion or L858R mutation in exon 21) identified through Sanger sequencing confirmed by either fragment length analysis (exon 19 deletions) or TaqMan-based PCR (L858R). A subset of samples from the EURTAC trial was retrospectively tested using the cobas EGFR Mutation Testing Kit.

The OPTIMAL study of erlotinib also only included people with a positive EGFR-TK mutation (exon 19 deletion or L858R mutation in exon 21) identified through the use of PCR-based direct sequencing.

5.2.2 Use of existing models

The assumptions used in the model submitted by Astra Zeneca for the appraisal of Gefitinib for the first line treatment of locally advanced or metastatic non-small-cell lung cancer (technology appraisal 192) should be used to inform the development of a de novo model. This will ensure consistency between the modelling approaches used in the appraisal of gefitinib (technology appraisal 192) and the assessment of diagnostic methods for EGFR-TK mutation testing. This assessment will not update technology appraisal 192.

5.2.3 Clinical significance of mutations

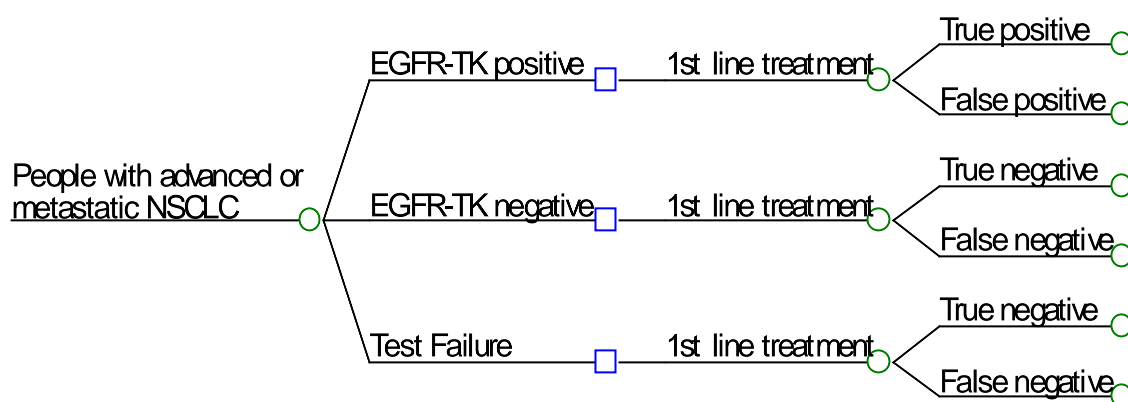
It is often unknown whether uncommon or novel EGFR-TK mutations identified through testing are sensitive to treatment with an anti-EGFR TKI. A test which has the potential to pick up these uncommon and novel mutations may result in additional patient benefit if the mutations identified are sensitising and patients get treated and respond to an anti-EGFR TKI. However if uncommon or novel mutations identified confer resistance to an anti-EGFR TKI then patients may be incorrectly treated with an anti-EGFR TKI which would likely result in worse health outcomes than if they had been treated with standard chemotherapy. For the assessment it will be important to try and understand the clinical significance of individual mutations. If data are not available on the clinical significance of individual mutations, sensitivity analyses using a range of values for the effectiveness of TKIs for people with these mutations should be included in the modelling.

5.2.4 Potential model structure

A potential decision tree for modelling is presented in Figure 1. Patients entering the model have a confirmed diagnosis of advanced or metastatic NSCLC of any histology. Any samples with an inadequate percentage of tumour cells will be captured in the number of test failures.

Following a decision on first line treatment, the model should follow patients through the different health states, for example, treatment response, stable disease, progression and death. Post-progression active treatments should be incorporated into the model where necessary.

Figure 1: Potential decision tree for EGFR-TK mutation testing



6 *Equality issues*

The population in the scope falls within the provisions of the Equality Act 2010 from the point at which a diagnosis of cancer has been made.

The frequency of EGFR-TK mutations is highest in Asian women who have never smoked and have tumours with adenocarcinoma histology. However, NICE technology appraisal 192 (Gefitinib for the first line treatment of locally advanced or metastatic non-small-cell lung cancer) recommends that testing should be carried out on all eligible patients irrespective of gender, ethnicity and smoking status, to ensure that all eligible patients who could benefit from treatment with gefitinib would be identified.

7 *Implementation issues*

Any laboratories testing for EGFR-TK mutation status, either using a CE marked or a non-CE marked technique must show compliance with the an accredited external quality assurance scheme such as those provided by UK NEQAS and the European Molecular Genetics Quality Network (EMQN). Furthermore, laboratories should be accredited in the discipline of molecular diagnostics and any test used should be validated.

Appendix A Glossary of terms

Bronchial alveolar lavage
A way of obtaining a sample of fluid from the airways by inserting a flexible tube through the windpipe

Cytology
The medical and scientific study of cells. Cytologic examinations may be performed on body fluids, on material that is aspirated from the body or on preparations that are scraped or washed from specific areas of the body.

Dideoxynucleotides
A molecule used in DNA sequencing which lacks a hydroxyl group and causes polymerisation to stop when added to the end of a DNA strand

Endobronchial ultrasound
A technique that uses ultrasound to visualise structures within and adjacent to the airway wall

Epidermal growth factor
A protein which promotes growth and differentiation

Epidermal growth factor receptor
A cell membrane spanning protein which binds with epidermal growth factor and sends signals which promote growth and differentiation

Exon
A sequence of DNA that codes information for protein synthesis that is transcribed to messenger RNA

Macrodissection
Manual dissection of a tissue sample to isolate specific portions of the sample

Mediastinal lymph nodes
Lymph nodes located in the central part of the chest in between the two lungs

Nucleotides
The basic building blocks of DNA and RNA

Spirometry
The measurement of the breathing capacity of the lungs

Tyrosine kinase
An enzyme linked to cell signalling. Receptor tyrosine kinases are a class of cell membrane receptors which phosphorylate the amino acid tyrosine.

Tyrosine kinase inhibitor
A drug that interferes with cell signalling and may prevent tumour growth

Appendix B Abbreviations

ARMS	Amplification refractory mutation system
CT	Computed tomography
EGFR-TK	Epidermal growth factor receptor – tyrosine kinase
EMQN	European Molecular Genetics Quality Network
FFPE	Formalin fixed and paraffin embedded
HRM	High resolution melt
NEQAS	National External Quality Assessment Service
NICE	National Institute for Health and Clinical Excellence
NOS	Not otherwise specified
NSCLC	Non-small-cell lung cancer
PCR	Polymerase chain reaction
RFPL	Restriction fragment length polymorphism
SSCP	Single strand conformation polymorphism
TKI	Tyrosine kinase inhibitor

Appendix C Related NICE guidance

Clinical guidelines:

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

Technology appraisals: 1st line treatment

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

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

Erlotinib for the first line treatment of locally advanced or metastatic EGFR-TK mutation positive non-small-cell lung cancer. NICE technology appraisal guidance 258 (2012). Available from: http://guidance.nice.org.uk/TA258 Date for review: TBC

Technology appraisals: 2nd line treatment

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

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

Technology appraisals: Maintenance treatment

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

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

Interventional procedures

Endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal masses. NICE Interventional Procedure Guidance 254 (2008). Available from http://guidance.nice.org.uk/IPG254

Under development

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

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

Appendix D References

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Appendix E Equality impact assessment – scoping

The impact on equality has been assessed during this assessment according to the principles of the NICE Equality scheme.

1. *Have any potential equality issues been identified during the scoping process (scoping workshop discussion, assessment subgroup discussion), and, if so, what are they?*
The frequency of EGFR-TK mutations is highest in Asian women who have never smoked and have tumours with adenocarcinoma histology.

2. *What is the preliminary view as to what extent these potential equality issues need addressing by the Committee?*
This issue does not need to be addressed by the Committee as EGFR-TK mutation testing is carried out on all eligible patients irrespective of gender, ethnicity and smoking status, to ensure that all eligible patients who could benefit from treatment with an anti-EGFR TKI are identified (as recommended in technology appraisal 192).

3. *Has any change to the draft scope been agreed to highlight potential equality issues?*
No

4. *Have any additional stakeholders related to potential equality issues been identified during the scoping process, and, if so, have changes to the stakeholder list been made?*
No

Approved by Associate Director (name): …Nick Crabb…………………..

Date: 23/July/2012

Appendix F Attendees of the assessment subgroup meeting

The following people were in attendance at the assessment subgroup meeting held on 16th July 2012:

	Name	Job Title	Organisation
Standing Committee Member	Mr Paul Weinberger (via teleconference)	Diagnostics Industry Consultant	Diagnostics Industry
Specialist Committee Members	Dr David Gonzalez de Castro	Head, Molecular Diagnostics	The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research
	Dr Fiona Blackhall	Consultant Medical Oncologist and Honorary Senior Lecturer	Christie Hospital NHSFT
	Mrs Mandi Elliott	Chemotherapy Nurse Specialist	Queen's Centre for Oncology & Haematology
	Dr Mark Slade	Consultant Respiratory Physician	Papworth Hospital NHS Foundation Trust
	Dr Paul Cane	Consultant Histopathologist	St Thomas' Hospital
	Mr Tom Haswell	Lay Representative	
External Assessment Group	Manuela Joore (via teleconference)	Health Economist	Kleijnen Systematic Reviews Ltd
	Marie Westwood	Project Lead	Kleijnen Systematic Reviews Ltd
	Thea van Asselt (via teleconference)	Health Economist	Kleijnen Systematic Reviews Ltd
NICE Staff	Professor Adrian Newland	Chair, Diagnostics Advisory Committee	NICE Diagnostics Assessment Programme
	Nick Crabb	Associate Director	NICE Diagnostics Assessment Programme
	Hanan Bell	Technical Adviser	NICE Diagnostics Assessment Programme
	Frances Nixon	Technical Analyst	NICE Diagnostics Assessment Programme
	Jackson Lynn	Project Manager	NICE Diagnostics Assessment Programme