NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 8 May 2013

Comment number	Consultee	Section number	Comment	Response
1	Consultee 1: Healthcare (Other)	1	This is a reasonable recommendation based on the evidence evaluated. However, the analytical performance of the EGFR assays should be evaluated. Analytical performance largely defines CE IVD assays (IVDD 98/79/EC), also the ability of an assay to detect EGFR mutations, which in turn defines its ability to stratify patients for EGFR TKi therapy. If NICE DAP will be able to recommend minimal analytical performance requirements for any EGFR assay adopted into clinical use, this would also allow the introduction new EGFR mutation assays without compromising patient safety, and without requirement for the review of the NICE assessment. The analytical performance assessment and characteristics of the recommended CE IVD tests are (as claimed in their Instructions for Use and/or Technical File) could be a good starting point. Validation data should also be available for all in-house assays used by CPA labs. Consideration should also be given for how consistency of kit or assay performance is ensured from one batch to another. In addition, it is important to note that the types of samples accepted and the DNA extraction method used which affect the performance of any EGFR assay.	Thank you for your comments. As discussed in the Diagnostics Assessment Report, the analytical performance of an EGFR assay (in terms of the mutations targeted and limit of detection) is not a direct indicator of the ability of the assay to appropriately select patients for EGFR TKI therapy. The External Assessment Group informed the Committee that this is because the relationship between specific mutations and levels of mutation and response to treatment remains uncertain and for this reason, the approach adopted in assessing test performance against treatment response, though imperfect, represents the best available option. This approach was defined in the agreed protocol for the assessment. The Committee also considered your comment regarding recommendations for minimal analytical performance requirements for any EGFR assay adopted into clinical use. The Committee felt that such a recommendation would not be within its remit, which is to evaluate the clinical and cost-effectiveness of specific tests and technologies, and produce guidance for the NHS.

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2	Consultee 2: Private Sector Professional	1	In my laboratory Sequenom MALDI-TOF has been used very successfully for EGFR testing for almost 3 years. We probably have the highest referral rate of any lab in the country. I am concerned that the Therascreen and Cobas technologies will be accepted as the 'gold standard' without consideration of other equally valid methods.	Thank you for your comment. The technologies included in NICE diagnostics assessments are selected in the scoping stage which takes place at the start of the assessment. The scoping work includes seeking advice from experts in the clinical area and a workshop where stakeholders participate in work to define the decision problem, which includes defining which technologies are included in the assessment. The use of Sequenom MALDI-TOF for EGFR mutation testing was not raised during this period. The External Assessment Group informed the Committee that 14 UK laboratories participating in the 2012–2013 UK NEQAS pilot scheme for EGFR-TK mutation testing had provided information. Thirteen of the 14 laboratories completed a web-based survey. None of the laboratories participating in the UK NEQAS scheme, who responded to initial contact from the External Assessment Group during the scoping phase, reported using MALDI-TOF and it was therefore, not included in the scope for this assessment. The Committee was also informed by the External Assessment Group that that no studies using MALDI-TOF and meeting the inclusion criteria for the systematic review, were identified. This being the case, had MALDI-TOF been included in the scope, no data would have been available to inform a recommendation. The Committee acknowledged that methodologies for detecting mutations are constantly evolving. Section 2.2 has been amended to include a reference to MALDI-TOF, and other tests being potentially available, in this context.

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3	Consultee 3: NHS Professional	1	1.2 If pyrosequencing is employed as a validated test by and accredited diagnostic genetics laboratory there is no evidence contraindicating use of this test. Can you consider qualifying the statement as it is currently written.	Thank you for your comment. The Committee was not able to make a recommendation on the technologies listed in section 1.2 due to insufficient evidence. This does not contraindicate the use of any of the tests listed in section 1.2.
4	Consultee 4: Manufacturer (Roche)	1	Roche believes that the recommendations should support the promotion of best test practices and access for patients to safe and high quality testing for EGFR-TK mutations with the view of improving current standard of care. Based on the Committee's assessment and our comments in the sections below, we see evidence that in-house developed tests based on Sanger sequencing may not achieve the same performance as CE-marked tests and that wider use of Sanger sequencing may not improve the standard of care. Improvements in standards of care are more likely to be achieved by using CE-marked tests. Recommendations of the use of in-house developed Sanger sequencing testing should therefore acknowledge that laboratory-developed tests should only be carried out in laboratories with extensive molecular diagnostic testing experience and validated to the same standards as CE-marked tests. Roche believes that best practices support the premise that laboratories newly intending to offer EGFR testing for routine clinical use should not develop tests in-house but use CE-marked tests.	Thank you for your comment. The Committee considered the evidence identified and reported in the Diagnostics Assessment Report is not sufficient to reliably draw distinctions between the performance of any of the testing methods assessed.
5	Consultee 2: Private Sector Professional	2	Sequenom MALDI-TOF was not evaluated in this study as a method for EGFR mutation testing. This means that one of the principal technologies as been omitted. In my laboratory, over 1000 tests per year are carried out for EGFR using Sequenom.	Thank you for your comment. Please see response to comment 2.

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6	Consultee 4: Manufacturer (Roche)	2	No comments.	No response required.
7	Consultee 2: Private Sector Professional	3	Prevalence of EGFR mutations and detection rates for specific tests is difficult to assess and define. Our pick up rate is ~10%, below the 16.6% suggested by Rosell et al. We have no reason to be concerned that the sensitivity of our test is low. Comparisons have been made with other technologies, performance in EQA is excellent and pick up rates for mutations in other genes is as expected. The issue with EGFR is that detection rates are highly dependent on ethnicity/sex/smoking habits of the patient. They are also dependent on the tumour type analysed. In the NE of England, there is a preponderance of white, elderly male patients with lung cancer and we are of the opinion that these are factors contributing to the lower than expected detection rate.	Thank you for your comment. The Committee is aware of variation in mutation rates in subgroups of patients and different tumour types. The Committee was informed that most laboratories have an average pick-up rate of around 10%.

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8	Consultee 5: Patient	3	Testing should be done on diagnosis, not further down the line when chemotherapy has failed. I completely agree that erlotinib should be available as first-line treatment for people with the EGFR mutation. Chemo should not automatically be used first, given its effects on white and red blood counts, creating vulnerability to infection which is a particular problem in NSCLC. By contrast, patients who start on erlotinib as first-line often remain asymptomatic for a relatively long period, saving money and resources. The side-effects can usually be managed in the community. The committee may also wish to consider the question of access to testing. I refer to a Merck-Serono survey of cancer specialists, 22 per cent of whom said they were more likely to offer biomarker testing to a private than to an NHS patient. See "Personalised Medicine: A Survey among Cancer Specialists in the UK", March 2012, referenced in Merck Serono briefing for MPs, "Personalised Medicine: A Call for Action", June 2012.	Thank you for your comment. Section 3.8 of the guidance has been amended to emphasise the fact that erlotinib is recommended by NICE (Technology appraisal 258) as an option for first-line treatment of locally advanced or metastatic NSCLC in people whose tumour tests positive for an EGFR-TK mutation. NICE has already published audit tools to help implement the guidance of TA258. With regard to access to testing, NICE intends to publish implementation tools that provide support to health and social care, to maximise uptake and use of NICE's diagnostics guidance.

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9	Consultee 4: Manufacturer (Roche)	3	The importance of standardisation and validation of EGFR-TK mutation testing (3.1) should be mentioned in section 1, together with recent findings published by UK NEQAS and Deans (J Clin Pathol, 2013): although error rates in the external quality control scheme for EGFR testing seem to improve with time, testing is not error free and there is considerable room for improvement in the NHS. False positives resulted in patients being incorrectly treated with an EGFR-TKI, leading to inferior outcomes compared to standard chemotherapy. The report suggests that to avoid false positives, it is crucial that adequate internal quality control measures are employed, including appropriate sample and data transfer checks by competent staff. The cobas® EGFR test offers labs error avoidance with defined pre-analytics, proven sensitivity in real world FFPET, automated result interpretation, IVD instruments and reagents and the shortest workflow, giving labs, clinicians and patients the best chance of accessing life prolonging anti-EGFR TKI therapy in a timely fashion.	Thank you for your comment. Section 1 of the guidance emphasises that tests should be used in accredited laboratories participating in an external quality assurance scheme. Also that laboratory-developed tests should be designed to detect the mutations that can be detected by one of the CE-marked tests as a minimum.

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10	Consultee 1: Healthcare Other	4	Therascreen EGFR RGQ: this is considered equivalent to the old therascreen EGFR PCR. However these two products are quite different including the platform, cycling conditions, reagent volumes and assay components; and analytical performance assessment. They cannot be assumed equivalent without data actually showing that. cobas EGFR Mutation Test: LoD is not just the amount of DNA required, it is also the minimum % mutation detected. For this test, the lowest amount of DNA to reach 5% LoD using plasmid blend DNA was 0.78 to 3.13 ng per well. For real FFPE samples, 50ng is required per well, with LoD from 1.4% to 2.5% for exon 19 deletion, and 4.0-4.3 for L858R. NGS: A targeted NGS assay with high coverage can reach sensitivity <5% for be quantitative. It could be very useful in helping define the relevant % EGFR mutations in tumour relevant for response to EGFR TKis. Sanger: There is a lot of variation in how Sanger sequencing is carried out. How was the minimal tumour percentage requirement defined? Was validation data for labs using Sanger for EGFR testing assessed to check minimum tumour %? Actual LoD (minimum % mutation) for each assay could be a more reliable method.	Thank you for your comment. The Committee was informed by the External Assessment Group that the clinical significance, or otherwise, of a low limit of detection and/or ability to detect rare mutations remains open to question and is an area requiring further research.

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11	Consultee 2: Private Sector Professional	4	In addition to the nucleotide substitution mutations covered in the Therascreen and Cobas assays, the test provided my laboratory using mass spectrometry is more comprehensive and therefore senstitive, in that it specifically identifies mutations in 10 futher codons (689, 700, 709, 761, 765, 783, 826, 839, 846 and 863). Deletions in exon 19 and insertions in exon 20 are tested by fragment size analysis which means that all in/dels will be picked up. The available literature that allows informed decisions with respect to the most appropriate mutations to include in a targetted test is now quite old. If required, modification of the mutation repertoire is relatively straightforward with mass spectrometry, unlike the Therascreen and Cobas kits.	Thank you for your comment. Please see response to comment 2.

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12	Consultee 4: Manufacturer (Roche)	4	EGFR-TK mutation test strategies, based on a 30% tumour cell content threshold for the use of Sanger (4.8 & 4.9), might solve the problem of lower sensitivity of Sanger for samples with low tumour content in principle. Sanger sequencing cannot reliably detect mutations below 25% sensitivity and has the potential of missing patients who would otherwise have been eligible for therapy. However, there are doubts over the practical application of this threshold and the recommendation of its use in Section 1: large variations in tumour cell contents estimates reported by UK NEQAS (Deans) suggest that estimating tumour cell content is not straight-forward and could be over-estimated for some samples with actual low content. Methods which claim sensitivity below 5% have not demonstrated if such patients would benefit from therapy and therefore require extensive experience in respective tumour pathology in combination with extensive experience in molecular analysis. It is only with methods like cobas® EGFR testing that there is clinical study data demonstrating positive patient outcomes as selected by cobas®.	Thank you for your comment. Please see response to comment 4. The Committee was informed that, in practice, issues regarding over-estimation of tumour cell content would be identified in the QA processes.

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13	Consultee 1: Healthcare Other	5	Outcomes: As commented in 5.11, UK NEQAS has not noted correlation between any method used for EGFR-TK testing and errors. This is likely because but also the sample requirements of each lab and the method of DNA extraction used can affect the failure rates. Failure rate for each lab may thus not equal the failure rate of the test alone. Accuracy: EGFR mutation status of the tumour is not the only determinant of response to EGFR-TKi therapy. Not all patients with 'sensitising EGFR mutations' respond. Other patient characteristics may affect drug response. Instead of patient response to therapy, technical accuracy of EGFR mutation tests should be assessed. Cost efficiency: What do the test costs shown actually consist of? Do they include cost of DNA extraction, cost of kit or assay reagents, cost of all labour, cost of reporting, quality control etc? Assurance that the same costs are included by all responding laboratories would be useful information to ensure true comparability of pricing. 5.34: Please note that it is only correct to 'assume equal prognostic value' for those assays which have equal ability to detect the EGFR mutations (ie analytical performance & consistency).	Thank you for your comment. The potential for response to EGFR-TKI therapy to be affected by factors other than EGFR mutation status is noted in the DCD. The costs reported in the survey included in the Diagnostics Assessment Report were not provided with a detailed breakdown. The limitations of the 'equal prognostic value' assumption were also acknowledged in the Diagnostics Assessment Report and by the Committee and are reflected in the guidance.
14	Consultee 2: Private Sector Professional	5	We have compared Sequenom MALDI-TOF with both Cobas and Therascreen and performance measured as detection rates are equally as good. Turn around times are better. Our target is 5 working days, but 2-3 days is achievable. The latter is dependent on staff availability rather than technology.	Thank you for your comment. Please see response to comment 2.

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15	Consultee 5: Patient	5	This section is too long and covers too many different kinds of "outcome" for a sensible comment to be possible. On cost effectiveness, targeted therapies can save money by improving quality of life and reducing the need for hospital admissions, blood transfusions and other complications associated with chemotherapy. Erlotinib is an oral therapy which can be taken at home, making it far easier for a patient to work productively than is possible when being regularly hooked up to an IV in a chemotherapy suite. Erlotinib allows a patient to take control of his or her life, instead of being subject to hospital schedules. In addition, TKIs do not require expenditure on anti-nausea drugs or steroids. The main requirements to manage side-effects are loperamide for diarrhoea and clindomycin or similar topical antibiotics to manage rash.	Thank you for your comment. This assessment is concerned with the diagnostics tests for detecting EGFR mutations, and outcomes included in this section are those that were identified in the scope. The assessment of erlotinib falls outside the remit of diagnostics assessment. Please refer to Technology Appraisal 258 for NICE's assessment of erlotinib.
16	Consultee 3: NHS Professional	5	Technical performance and accuracy. NEQAS 2011/12 indicated 8 labs using pyrosequencing. The UK NEQAS scheme cannot provide any supporting data that the methods listed in section 1.2 are not able to provide high quality results when used in an accredited lab participating in EQA.The essential factor is full test validation. Pyrosequencing has been used as a technical method to validate samples for NEQAS distribution. There is a publication in press A comparison of methods for EGFR mutation testing in non-small cell lung cancer Diagnostic Molecular Pathology Owens et al that provides additional evidence on methods in 1.2 as used in accredited diagnostic laboratories. Tests costs and prices charged are different items and are unlikely to be accurate unless standardised method of calculation used.	Thank you for your comment. Please see response to comment 3. The Committee was informed by the External Assessment Group that the NEQAS data did not provide either technical performance data or any data relating mutation status to clinical outcome (clinical effectiveness data).

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17	Consultee 4: Manufacturer (Roche)	5	Roche strongly believes that the publications by Lopez-Rios should be considered by the Committee. Given the limited UK peer-reviewed published data, patient samples in the study may be representative for the UK and should be included in this assessment, especially since an Asian study (e.g. IPASS) was allowed in this assessment as evidence of clinical effectiveness. In the Lopez-Rios study, the comparison between the cobas® EGFR test and Sanger showed overall agreement of 89.8%. Using the cobas® EGFR test as the reference method, with 100% of discrepant results confirmed in favour of cobas® with MPP, the false positive and negative rates for Sanger were 1.2% and 20.7%, respectively. These results suggest that 1 out of 5 patients negative for a mutation in EGFR (by Sanger) is likely to contain an activating mutation and could benefit from anti-EGFR TKI therapy. Â Sanger sequencing also showed a significantly higher invalid test rate compared to the cobas® EGFR test. These results reflect the established lack of analytical sensitivity for Sanger sequencing and question the assumptions on equal prognostic value of different test made in the economic analysis (5.34).	Thank you for your comment. The External Assessment Group informed the Committee that the additional study cited did not meet the inclusion criteria for the review. Studies of this type only show agreement between two tests which essentially have different definitions of a positive mutation (different target mutations and limits of detection). If tests results are not related to clinical outcome, then it is not possible to determine whether a mutation detected by one test and not the other would in fact have resulted in more appropriate treatment.
18	Consultee 1: Healthcare Other	6	Comment on 6.3: Were the opinions of the clinical specialists on the Committee that the different tests generally have similar level of accuracy based on data shared with the assessors? Comment on 6.9: Please note that the key benefits of CE-marked tests include: The availability of actual performance data relevant to intended use and performance claims; and batch-to-batch consistency of that performance which results from manufacturing QC processes. Such QC processes for batch-to-batch consistency of in-house reagents is often lacking.	Thank you for your comment. The clinical specialists expressed their opinion based on their experience from using the tests in clinical practice. Additionally, it was noted by UK NEQAS that error rates seen in the quality assurance scheme for EGFR-TK mutation testing are not always method-related, and may be because of processing and reporting problems.

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19	Consultee 2: Private Sector Professional	6	Current price of the Sequenom test is £155 which is comparable to the prices for other technologies given in the document.	Thank you for your comment. Please see response to comment 2.
20	Consultee 5: Patient	6	Again, this section is too long and unwieldy for useful comments to be possible. I would welcome any plans to extend testing to people with squamous tumours, in whom EGFR mutations most certainly occur, and who have been ill served by the assumption that such mutations are found only in patients with adenocarcinoma. There is considerable clinical ignorance on this point. I agree with the committee that EGFR is likely to become just one of a panel of tests that will be carried out on lung cancer patients on diagnosis in the near future. The advent of crizotinib, a targeted therapy for patients with the ALK rearrangement, will push this process forward, and I think some reference might be made to this in the committee's recommendations.	Thank you for your comment. The committee noted that evidence relating to the accuracy of testing does support testing in patients with squamous cell carcinoma, as well as adenocarcinoma (see section 6.7 of the guidance). Please also see response to comments 8 and 15.

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21	Consultee 4: Manufacturer (Roche)	6	The Committee's conclusions (6.6) and the UK NEQAS data (Deans) enforce the need to improve current laboratory services and error rates: the cobas® EGFR test significantly reduces the risk of analytical errors by using automated result analysis and reporting. Further internal controls are included in the assay to reduce the risk of false positive. The cobas® EGFR test is highly reproducible (Lopez-Rios), making it easy to standardise across different settings by removing operator error in the interpretation of results. Similar levels of safety and quality should be expected of all in-house developed tests based on Sanger sequencing. In addition, the cobas® EGFR test optimised for batch sizes of only 3 samples and therefore allows fast turnaround times (6.10). The economic analysis seems inconclusive due to the problematic assumptions made (6.13-6.15), including the 'equal prognostic value' analysis (6.16). With the cobas® EGFR test showing better accuracy and less failures than Sanger sequencing (Lopez-Rios) at similar test costs, it is likely to be more cost-effective than Sanger sequencing.	Thank you for your comment. Please see response to comment 17.

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22	Consultee 1: Healthcare Other	7	It is a good idea to perform studies which involve re-testing of stored NSCLC samples using different EGFR TK mutation tests, provided that sample sets that contain sufficient testing material exist. It is essential that further research comparing different EGFR-TK mutation test methods include considerations for their analytical performance and control of batch-to-batch variation, to enable the setting of standards for those parameters for future EGFR mutation tests, including Next Generation Sequencing assays. If NICE will be able to recommend minimal analytical performance requirements for any EGFR assay adopted into clinical use, this would also allow the introduction new EGFR mutation assays without compromising patient safety, and without requirement for the review of the NICE assessment. It would also be very useful to study which type(s) of NSCLC samples should be recommended for EGFR mutation testing, as sample type can affect assay performance.	Thank you for your comment.
23	Consultee 2: Private Sector Professional	7	We would be pleased to participate in any further studies that might result from this prelimiary recommendation	Thank you for your comment.
24	Consultee 5: Patient	7	7.1 I do not see the need for such a study. Clinicians will confirm that the presence of the EGFR mutation (with the exception of exon 20 and some other rare deletions) is usually a reliable predictor of a good response to a TKI inhibitor. Clinical trials have also shown a link between rash and response - see the report on the TOPICAL trial in Lancet Oncology 13(2012, 1161-70. http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(12)70412-6/fulltext. I suggest that this study should be consulted and referenced.	Thank you for your comment.

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25	Consultee 4: Manufacturer (Roche)		Based on consultations with NICE during the pre-scoping meeting, Roche developed a decision tree cost-effectiveness model that utilizes the NICE recommended model structure, epidemiological, test performance and reimbursement data/assumptions to derive a comparison of Sanger sequencing vs. cobas® EGFR test. The results of the 'assumption of equal prognostic value' analysis indicated that the strategies were almost equal, however the cobas® EGFR test offered a substantial increase in QALY's that may benefit the patient's well-being. Roche recommends future studies that further explore the full economic value of tests adapted by the Committee.	Thank you for your comment. The limitations of 'equal prognostic value' have been described in the Diagnostics Assessment Report and in the guidance.
26	Consultee 1: Healthcare Other	8	We would recommend prescriptive standards for detected mutations, min. analytical performance requirements, procedures for assurance of batch to batch quality, with consideration for sample types and DNA extraction methods used.	Thank you for your comment. See response to comment 1. The Committee was informed that practical suggestions from the consultee are currently being considered by the Royal College of Pathology and the European EQAS.
27	Consultee 5: Patient	8	There is still much work to be done in disseminating knowledge about TKIs. Many GPs and hospital doctors outside thoracic oncology are entirely ignorant of what erlotinib, gefitinib and afatinib are, let alone what they can do for patients. Newly diagnosed patients and their families should be encouraged to ask for testing on dx in hospitals where this is not standard practice. In particular, clinicians should be disabused of the widespread but erroneous assumption that the EGFR mutation is only found in adenocarcinomas - and that, therefore, it is "not worth" testing patients with squamous cell lung cancer.	Thank you for your comment. Please see response to comments 8 and 15.

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28	Consultee 4: Manufacturer (Roche)	8	No comments.	No response required.
29	Consultee 5: Patient	9	As I mentioned above, section 6, reference should be made in this document to the use of crizotinib (fast-tracked by the FDA) in the US as a targeted therapy for patients with the ALK rearrangement - and therefore to the NICE technology appraisal of crizotinib.	Thank you for your comment.
30	Consultee 4: Manufacturer (Roche)	9	No comments.	No response required.
31	Consultee 5: (Patient)	10	See my comments on crizotinib, section 9.	Comment noted.
32	Consultee 4: Manufacturer (Roche)	10	No comments.	No response required.