

Comments on the ACD Received from the Public Through the NICE Website

Name	██████████
Role	NHS Professional
Other role	
Location	Scotland
Conflict	no
Notes	I have been paid Consultancy fees and Speakers honoraria by the manufacturers of this technology.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (the technology)	
Section 3 (manufacturer's submission)	<p>Technical test failure is predicated on many factors related to laboratory practice and to what extent testing will be attempted on the very smallest samples.</p> <p>There is no recognised standard our technical test failure rate is about 6%.</p> <p>False negative tests are a risk of testing inadequate samples. False positive tests are much less likely artefacts can be check detected, contamination should be avoided by Good Clinical Laboratory Practice measures.</p>
Section 4 (consideration of the evidence)	<p>Regarding the issue of (likely) prevalence of EGFR mutations in a UK population, the disparity in figures reflects the substantial differences in the denominator in the equation i.e. the population of cases actually tested. Published data vary enormously from less than 5% to around 20% of European or caucasian cohorts. Sample type, testing methodology employed and case selection all influence the chance of finding a mutation.</p> <p>In caucasians, EGFR mutation is extremely unlikely is squamous cell carcinoma (SCC). SCC accounts for perhaps 40-45% of UK NSCLC. By including these cases in a tested population, the prevalence of mutations is diluted. This is one reason for the figures circa 5% quoted by some. Our local experience of some 80 or so cases tested is that EGFR mutation is found in approximately 18% of tested cases. This will reflect an exclusion of squamous cell carcinomas but also some positive selection of patients with a higher chance of mutation. I believe in a non-squamous NSCLC population tested in the UK the prevalence is likely to be somewhere between 10-15% of cases. There may well be differences within the UK.</p>
Section 5 (implementation)	
Section 6 (related NICE guidance)	
Section 7 (proposed date of review of guidance)	
Date	2/19/2010 9:18:00 AM

Name	
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	AstraZeneca has been supporting part (first line, NSCLC patients) of the EGFR testing in our laboratory as a "service to medicine" since December 2009.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	<p>The following is the experience of the Royal Marsden NHS Foundation Trust in routine EGFR genotyping in lung cancer patients (mainly NSCLC but not exclusively, first and second line, adenocarcinomas + squamous) since May 2009 until January 2010. Please note that due to the heterogeneity of the population studied, these data do not reflect the real prevalence of EGFR mutations in "NSCLC Adenocarcinoma subtype":</p> <p>EGFR genotypes £ 228 EGFR mutations £ 27 Failures due to insufficient material, lack of amplifiable DNA or technical issues £ 26 (11%) Total percentage EGFR mutants(not considering failed samples) £ 13% Percentage of female patients tested: 54% Percentage of EGFR mutations in female patients v male patients £ 12% v 8% (this include failed samples, hence percentages 13%)</p> <p>The price per test based on our current workload (10 samples/week) and including consumables, reagents, instrument maintenance, staff costs, etc... ranges from £200 for the DxS technology to £125-£150 for the others. If the number of samples/week was 5, the cost of these tests will increase by approximately 15-25%.</p>
Section 2 (the technology)	
Section 3 (manufacturer's submission)	<p>We have used different methods, ranging from the ARMS-PCR kit (DxS) to ASO-PCR, Fragment analysis and sequencing. In our hands, all methods had a similar sensitivity apart from sequencing, where the sensitivity is significantly lower.</p> <p>In our experience, the risks of identifying EGFR mutations in samples that carry no mutations (i.e. a false positive result) are ver low, specially for the well-characterised mutations (i.e. exon 19del, L858R, exon 20dup). However, the risk of missing EGFR mutations (i.e. false negative cases) is more likely to occur, due to the heterogeneity of the tissue samples and methods used.</p>
Section 4 (consideration of the evidence)	<p>We have studied a wide range of different samples, from core lung biopsie to cytological specimens, such as TBNA, FNA, EBUS, etc... We have found the EGFR genotyping is feasible in most samples, including small biopsies and cytological specimens. This has been published in J Thorac Oncol. 2010</p>

	Jan 8. [Epub ahead of print]
Section 5 (implementation)	
Section 6 (related NICE guidance)	
Section 7 (proposed date of review of guidance)	
Date	2/19/2010 9:17:00 AM

Name	
Role	NHS Professional
Other role	
Location	Wales
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (the technology)	
Section 3 (manufacturer's submission)	
Section 4 (consideration of the evidence)	<p>4.3 EGFR mutation testing is available within South Wales.</p> <p>4.16 For lung cancer patients, the potential quality of life issues related to fewer hospital stays and lengthy visits are perhaps not fully appreciated when measuring specifically health-related quality of life.</p> <p>The expectation of treatment for many lung cancer patients at diagnosis are : good symptom control, an improvement in prognosis, a proactive approach by the team caring for them and minimal disruption to their life allowing them to do as much as possible with the time they have left.</p> <p>The reduced need for hospitalisation impacts positively on the patient and carers, particularly when Oncological treatment and management of side effects thereafter is routinely provided in a Centre many miles away from home.</p> <p>The side effect profile for Gefitinib are more manageable in the outpatient setting than those associated with the platinum based doublet that is the Â current standard of care. Through an improvement in quality of life patients are able to better manage their end of life issues and focus on their personal priorities with greater control.</p>
Section 5 (implementation)	
Section 6 (related NICE guidance)	
Section 7 (proposed date of review of guidance)	
Date	2/19/2010 8:34:00 AM

Name	[REDACTED]
Role	NHS Professional
Other role	
Location	Wales
Conflict	no
Notes	Comments submitted are the data collected from 5 RNHS Regional Genetics Laboratories (Cardiff, Exeter, Sheffield, Aberdeen and Manchester), the contacts for these labs are [REDACTED] respectively.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (the technology)	
Section 3 (manufacturer's submission)	
Section 4 (consideration of the evidence)	<p>Molecular analysis of EGFR mutations has been established as a diagnostic service during the last 6 months in several NHS Regional Genetics Labs (Cardiff, Aberdeen, Exeter, Sheffield and Manchester).</p> <p>249 EGFR tests have now been performed by Regional Genetics labs using DNA sequencing, Pyrosequencing and fragment length analysis. Technologies are designed and validated to detect 98% of published EGFR activating mutations. Mutations are detected with sensitivity of 3-6% (Pyrosequencing) and 10-20% (Sequencing) in an admixture of tumour and normal cell DNA. Results are qualitative, a mutation is either detected or not.</p> <p>33 (18 male / 15 female) EGFR mutations have been detected in 249 (133 male / 166 female) patient samples (13%).</p> <p>Analysing laboratories do not always have access to tumour histology information. Many of the 249 samples analysed were adenocarcinomas, but a significant number of samples were squamous, large cell or not stated.</p> <p>166 (46.6%) of the 249 samples were taken from female patients, the ethnicity of patients is generally unknown.</p> <p>The cost of a single EGFR analysis is generally accepted to be approximately Â£200.</p>
Section 5 (implementation)	
Section 6 (related NICE guidance)	
Section 7 (proposed date of review of guidance)	
Date	2/18/2010 2:56:00 PM

Name	[REDACTED]
Role	NHS Professional
Other role	

Location	England
Conflict	yes
Notes	Research/service provision within my Hospital Department is funded by Astra Zeneca I have no personal financial relationship with the company
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	<p>re: 1.10 evidence of mutation frequencing in the UK population is being generated from a number of clinical laboratories in the UK who have been providing an EGFR testing service over the past few months (Manchester 7/67 Å 10.5%)</p> <p>Selection of patients with NSCLC for EGFR testing is appropriate Å based on histopathology There is no compelling evidence that EGFR mutations are present in squamous NSCLC See Marchetti A, Martella C, Felicioni L, Barassi F, Salvatore S, Chella A, Campese PP, Iarussi T, Mucilli F, Mezzetti A, Cuccurullo F, Sacco R, Buttitta F. J Clin Oncol. 2005 Feb 123(4):857-65. ? series of 454 squamous NSCLC no EGFR mutations detected This study had good histological review to confirm tumour type</p> <p>Selection of patients guided by histological subtype is likely to result in much higher yield of positive EGFR mutation results Screening patients with no likelihood of mutation will have an effect on laboratory work load potentially impacting on turnaround time and would generate costs to the health service with no likelihood of influencing treatment decisions. Testing in all other subtypes of NSCLC would be appropriate.</p>
Section 2 (the technology)	<p>re 2.2</p> <p>Many clinical laboratories are providing EGFR testing within the UK to support oncology practice. External Quality Assessment for EGFR testing will be introduced in these accredited labs in line with other genetic tests. This QA process will ensure the accuracy and sensitivity of the techniques used by the laboratories. Therefore we do not think that a specific type of genetic test for EGFR analysis should be recommended but that different laboratories should employ the test that they can validate and that provides robust coverage of the common EGFR mutations in exons 18-21. Future advances in genetic analysis will mean that different technologies (specifically high throughput DNA sequencing) will be appropriate to provide an EGFR mutation testing service in the next few years</p> <p>Mutation testing is generally successful on tumour tissue samples (1 fail in 68) We have had success in identifying mutations in cytology samples transferred into a paraffin block For this reason we do not believe that microdissection of samples is mandatory. However we do believe that close liaison between histopathologists/cytopathologists and geneticists is vital to provide the optimum service</p>
Section 3 (manufacturer's submission)	RE 3.31: The current costs for EGFR testing ~Å£200 per test are unlikely to reduce in the short term. Increased volume of

	samples will not reduce the unit cost as most costs relate to the analysis and interpretation of the genetic testing and generation of a clinical report
Section 4 (consideration of the evidence)	re 4.3 Many clinical genetics/pathology laboratories are providing EGFR testing within the UK to direct appropriate prescription. Provision is increasingly available and we have disseminated our service profile to relevant physicians throughout the North West
Section 5 (implementation)	
Section 6 (related NICE guidance)	
Section 7 (proposed date of review of guidance)	
Date	2/18/2010 2:33:00 PM

Name	██████████
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	This is a joint submission with ██████████, Consultant Pathologist, University Hospital Birmingham NHS Foundation Trust, who has led the EGFR mutation testing programme in Birmingham
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	<p>Section 1: In Birmingham ██████████ and I have been routinely performing EGFR mutation testing in an NHS facility since May 2009. Â Samples from 185 cases of NSCLC have been submitted. We were able to test successfully 175 without resorting to rebiopsy. Â Activating mutations on exons 19 and 21 were found in 21 (12%). Â The histology of submitted samples was adenocarcinoma/BAC 119, squamous carcinoma 6, adenosquamous carcinomas 2, NSCLC not otherwise specified 46, others 2. Â About 66% of our cases of NSCLC are non-squamous so this approximates to an overall mutation frequency of ~8%. We believe it is unnecessary to routinely test patients with squamous carcinoma because the pickup rate is 1%. In 13 cases we had both histology and cytology specimens and in all these there was concordance, including 2 cases with mutations.</p> <p>Having treated 6 cases of mutation positive disease with either gefitinib or erlotinib since January 2010, I (MHC) am impressed by the response rate (5/6, 83%) which matches published data in SE Asians, and by the excellent tolerance to, and quality of life associated with gefitinib.</p>
Section 2 (the technology)	
Section 3 (manufacturer's submission)	
Section 4 (consideration of the	Since virtually all activating mutation positive cases are adenocarcinoma, gefitinib would replace our current standard

evidence)	therapy for adenocarcinoma which is cisplatin plus pemetrexed. Â Our current second-line therapy for appropriate cases of adenocarcinoma is erlotinib. Â If gefitinib was approved then erlotinib would not be used for any mutation positive cases.
Section 5 (implementation)	
Section 6 (related NICE guidance)	
Section 7 (proposed date of review of guidance)	
Date	2/17/2010 12:13:00 PM

Name	
Role	NHS Professional
Other role	I work within NHS and privately
Location	England
Conflict	no
Notes	I have given advice to the manufacturer with respect to the role of gefitinib in the current pathway of management for NSCLC. I have sought costings information from the manufacturer in order to facilitate local business case development for our PCT commissioners.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This is a very disappointing development for NSCLC patients in the UK. The current option for fit patients is to undergo a course of chemotherapy which carries significant toxicity. I have experience of giving gefitinib within the expanded access programme and this is a much better tolerated drug. We often see audits presented at British Thoracic Oncology Group Annual Meetings showing the first line chemotherapy is associated with a significant rate of admission to an inpatient facility. In my experience about 20% of patients having chemo for NSCLC will end up being admitted either for neutropenic or non neutropenic sepsis. This is a major cost burden on the NHS. Gefitinib causes a minimal degree of myelosuppression. Additionally the oral nature keeps patients away from overburdened chemotherapy units. The impressive quality of life benefits of gefitinib over chemotherapy shown in IPASS need to be given more consideration.
Section 2 (the technology)	The single payment access scheme is interesting. From clinical experience we know that about 10% of patients may remain on this drug for quite long periods of time. While the median OS from IPASS is impressive, extrapolating from BR21 erlotinib data, small numbers of patients could be on this drug for years. There are tens of thousands of British subjects of East Asian origin who reside and pay taxes in the UK. For them I would say denial of gefitinib is potentially discriminatory as many of these patients are predisposed to having an EGFR mutation. While the benefits of gefitinib are driven by mutation, it is fair to say that Western and Asians both benefit however, the mutation is more prevalent per se in Asian patients. The cost/benefit analysis for this subgroup would therefore be totally different.

<p>Section 3 (manufacturer's submission)</p>	<p>The important thing here is the comparator chemotherapy regimen. For a fit patient with adenocarcinoma the standard treatment is cisplatin and pemetrexed. This is in line with NICE guidance. Patients usually receive 4-6 cycles of therapy. In my experience about 80% will stop at 4 cycles but 20% complete 6 cycles.</p> <p>You need to consider all 4 randomised trials of gefitinib in EGFR mutated NSCLC. IPASS and First signal were in clinically selected groups. NEJ002 and WJTOG3405 were in EGFR mutated patients. The latter 2 may be more relevant even though IPASS is the largest study.</p> <p>The holy grail on oncology research has been to find the tests that predict who will benefit from specific treatments. The IPASS trial now defines a new subtype of NSCLC called EGFR mutated NSCLC. You really need to think of this as a new disease with a different treatment paradigm. Continuing to think of this as regular lung cancer is blinkered and unhelpful.</p>
<p>Section 4 (consideration of the evidence)</p>	<p>As an oncologist I would say the main benefit of treatment with metastatic disease is to palliate symptoms and help patients maintain their quality of life. Improvements in PFS and OS are welcome additions.</p> <p>The standard comparator should be cisplatin and pemetrexed.</p> <p>IPASS clearly shows that EGFR mutation is the key driver of benefit. The criteria for trial entry were designed to enrich for EGFR mutation.</p> <p>The prevalence of EGFR mutations in lung cancer have never been properly assessed within the UK population. Based on the unpublished data I have seen it is between 10-20%. There are massive quality control issues with regards to the amounts of tissue obtained during the diagnostic process. Often the test fails due to lack of viable tumour cells.</p> <p>Now that histology is important determining which chemotherapy drugs we use (pemetrexed for adenocarcinoma) I predict that there will be a gradual move to obtain formal tissue. Cytology is increasingly being frowned upon. With more biopsies, there will be more tissue to do molecular testing. It is likely that we will see the incidence of EGFR mutation rise to 15-20%. This is assuming the testing is performed in adenocarcinomas.</p>
<p>Section 5 (implementation)</p>	
<p>Section 6 (related NICE guidance)</p>	
<p>Section 7 (proposed date of review of guidance)</p>	<p>Mature overall survival data for some of the trials may become available shortly after NICE guidance is out. It would be very unfortunate if NICE then took a few years to reassess the data. This would deny thousands of patients a potentially effective drug.</p>

	<p>It took years for erlotinib to get approved in the UK and it would be a real pity if the same happened here.</p> <p>I would be very keen to see an early reassessment if survival data became available shortly after NICE guidance.</p>
Date	2/12/2010 12:03:00 PM

Name	
Role	NHS Professional
Other role	Laboratory Director
Location	England
Conflict	yes
Notes	AstraZeneca are funding provision of an EGFR testing service to NHS patients from my laboratory.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It is not clear whether the economic appraisal includes the impact of testing all NSCLC patients, excluding those with proven squamous cell carcinoma or carcinoid, on the provision of services to lung cancer patients at Cancer Centres. Patients on gefitinib will be treated at home with outpatient/GP appointments, in comparison with the alternative of chemotherapy with more frequent visits and likely requirements for hospitalisation. This will reduce pressure on oncology facilities and their provision. Â Have these potential cost savings been taken into account?
Section 2 (the technology)	
Section 3 (manufacturer's submission)	There seems to be an erroneous view that EGFR-TK mutation testing is not available within the NHS. Â Ten centres within the UK have already signed up to National External Quality Assurance Scheme for testing, and around 10 others are at various stages of start-up. It should be feasible for all NSCLC patients (excluding SCC and carcinoid) in England to have a test within months rather than years of any decision to implement a blanket testing protocol, which is likely to be less expensive and more effective than any alternative. Â A comparison with the introduction of HER2 testing would be apposite.
Section 4 (consideration of the evidence)	The cost of testing using ARMS technology is currently around Â£100 per patient excluding staff costs. It should be feasible to reduce this very substantially using alternative technologies. Â In addition, automation and the use of plasma for testing, particularly in those patients without sufficient biopsy material, are highly likely to be able to reduce the costs of testing further within the next year. UK prevalence data for EGFR-TK mutations will be derived from the manufacturer-funded testing centres in due course.
Section 5 (implementation)	
Section 6 (related NICE guidance)	
Section 7 (proposed date of review of guidance)	This is a rapidly developing field. In my opinion this advice should be reviewed one year after issue.

Date	2/11/2010 1:50:00 PM
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Name	[REDACTED]
Role	NHS Professional
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (the technology)	
Section 3 (manufacturer's submission)	The ICER figures quoted in 3.37 seem implausible. The ERG states that the ICER even in their re-analysis is 38,000 per QALY gained of carboplatin/paclitaxel. I find it unlikely that this figure is more than doubled by changing chemotherapy to pemetrexed/cisplatin, given the very modest advantage of pemetrexed/cisplatin over other standard chemotherapy regimens discussed in TA181. The methodology used by the ERG needs to be examined closely.
Section 4 (consideration of the evidence)	<p>My strong opinion is that it is the ERGs figures which seem implausible, not the manufacturers, and the Committee seems to feel the same. It seems perverse therefore to use this as a basis for not recommending this treatment.</p> <p>It also seems very clear that the committee is underestimating the QoL advantage of oral outpatient therapy with gefitinib compared to combination chemotherapy which is in my experience very significant and is strongly supported by the evidence. Again it seems perverse effectively to ignore this. Would the committee take the same view and ignore the QoL data if it was worse with the technology under evaluation?</p> <p>I would ask the committee to reconsider this opinion which is in my view not supported by the evidence presented</p>
Section 5 (implementation)	
Section 6 (related NICE guidance)	
Section 7 (proposed date of review of guidance)	
Date	2/9/2010 10:51:00 AM