Rapid Review: EGFR gene mutation testing in patients with advanced NSCLC for access to Gefitinib – for sector discussion

June 2012

Key words: NSCLC, EGFR, EGFR-TKIs, New Zealand situation, personalised testing, gefitinib, erlotinib, feasibility, cost-effectiveness, sensitivity, specificity

This document is a summary version of the NHC’s Rapid Review published on the NHC’s website in order to enable sector discussion around the introduction of EGFR gene mutation testing in New Zealand – any of the NHC’s modelling or other commercially sensitive information has been removed.

Summary

Purpose

To provide sufficient information for the National Health Committee to make a recommendation regarding whether Epidermal Growth Factor Receptor (EGFR) mutation testing should be publicly funded in New Zealand, and if so, to provide a basis for engaging with the sector to determine the best option for how this might occur. This analysis has been undertaken in the context of a recent proposal by PHARMAC to fund the tyrosine kinase inhibitor (TKI), gefitinib in the first line and amend the existing funding of erlotinib in the second line\(^1\).

Methods

A non-systematic narrative review of reports published by Health Technology Assessment (HTA) agencies, guidance documents issued by various professional organisations overseas and other papers identified through Google scholar was undertaken. Information from these reports was synthesised under the Committee’s assessment domains to enable the evidence to be evaluated using the Committee’s 11 decision-making criteria.

Results & Discussion

To date there have been five randomised Phase III trials comparing gefitinib or erlotinib monotherapy to first-line chemotherapy, all in predominantly East Asian non-small cell lung cancer (NSCLC) patients. All of these trials provide evidence that EGFR mutation testing followed by treatment with tyrosine kinase inhibitors (TKIs) (proposed) is more clinically safe and clinically effective than no testing and treatment with chemotherapy (status quo). However, \(^1\) http://www.pharmac.govt.nz/2012/05/31/2012-05-31%20PHARMAC%20consultation%20on%20proposal%20for%20TKIs%20for%20Lung%20Cancer.pdf
a number of uncertainties remain around how these safety and efficacy profiles might change outside of trial settings and particularly how different levels of sensitivity and specificity of different tests may affect outcomes in populations with lower incidence of EGFR mutations.

If EGFR gene mutation testing in patients with NSCLC to determine access to TKIs were to be publicly funded in New Zealand, it is estimated that between 597 and 1,214 people per annum would be tested, depending on whether testing is limited to patients with stage IIIB or IV non-squamous NSCLC or to all patients (regardless of stage) with non-squamous and not otherwise specified (NOS) NSCLC. Assuming the costs of testing do not exceed $600 per patient, EGFR testing could cost district health boards (DHBs) between $358,200 and $728,400 per year, depending on what stage in the clinical pathway testing is undertaken and which NSCLC patients are tested. Of those tested, it is estimated that less than 400 will be suitable for TKI treatment and that only 350 people will have a meaningful response to treatment 

The cost-effectiveness of testing and subsequent treatment with TKIs depends on the cost of the TKI, the sensitivity and specificity of the EGFR test, and the incidence of EGFR mutations in NSCLC patients. There is currently insufficient information on many of these parameters to perform an accurate cost-effectiveness analysis. However, assuming an EGFR mutation incidence of 40% in non-squamous NSCLC, and that the test has a sensitivity and specificity comparable to that used in the IPASS trial (Mok et al. 2009), testing followed by treatment with a TKI would be cost-saving compared with the status quo provided that PHARMAC can secure sufficient savings to cover the incremental costs. The precise cost-effectiveness of the proposal is affected by the sensitivity and specificity of the test – decreasing with reduced specificity but increasing with reduced sensitivity. Furthermore, the incidence of the EGFR mutation in patients with non-squamous NSCLC also affects the cost-effectiveness of the proposal – increasing with lower incidence and decreasing with higher incidence.

There is some evidence to suggest that publicly funding EGFR mutation testing in New Zealand would be supported by clinicians and the public. Furthermore, a number of preferences have been identified, including: provision of a centralised testing service, a turn-around time for tests not exceeding 1-2 weeks, appropriate measures to ensure the safety and appropriate disposal of samples, sufficient education of, and communication between patients and clinicians, minimising the waste of samples, and minimising the number of biopsies. It has also been suggested that the patient’s experience of the clinical pathway for lung cancer could be improved in general. There are a number of ethical and equity issues associated with introducing an intervention that while improving PFS overall, does so by increasing the risk of worsening the PFS of some individuals. However, these could be mitigated through informing patients of the risks associated with the different treatment options available to them.

Introducing EGFR testing as part of the clinical pathway for the effective management of advanced NSCLC is likely to be supported by the health sector, but may need to be accompanied by measures to increase the capability and experience of the workforce to ensure the tests are appropriately used, undertaken, and reported. This will be crucial if EGFR testing in New Zealand is to achieve similar improvements in health as were observed in the clinical trials. In the short-term, it may be better to continue sending samples overseas (eg, Australia) where the

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2 It has been estimated that only 70-80% of people treated with a TKI have a meaningful response (Gazdar A. 2011. Tyrosine Kinase Inhibitors and Epidermal Growth Factor Receptor (EGFR) Mutations in Non-Small Cell Lung Cancer: To Test or Not to Test? Medicine 90:168-70)

3 Estimates elsewhere suggest that 10-20% of NSCLC patients are EGFR mutation +ve (MSAC 2012), but NHC estimates derived from New Zealand Cancer Registry data and reported incidence of EGFR mutation +ve by smoking status (D’Angelo et al 2011) found that incidence is most likely between 31% and 41% in patients with non-squamous NSCLC. A figure of 40% was used throughout the NHC modelling
laboratories have had more experience, which will presumably ensure that any test used is validated and has a sensitivity and specificity within a certain range.

**Conclusion:**

Many countries are already testing for EGFR mutations to determine appropriate treatment with TKIs. While there are still a number of uncertainties around whether the health gains observed in the clinical trials are generalizable to the real world, most countries appear to be addressing this through close monitoring and evaluation which will eventually enable a better assessment of the clinical utility and cost-effectiveness of the intervention. Whether or not New Zealand takes a similar approach will depend to what extent decision-makers are comfortable with this. Another consideration is whether funding for EGFR testing and subsequent use of targeted therapies for late stage lung cancer should be prioritised over other interventions in the clinical pathway for lung cancer. If new funding is going to be available for spending in the treatment of lung cancer, it might be better to spend it on addressing barriers to early diagnosis which will increase overall survival, rather than on a test and drug combination for which there is no evidence that overall survival of lung cancer patients is improved.

**Purpose**

On 31 May 2012, PHARMAC went to consultation with a proposal to fund the tyrosine kinase inhibitor (TKI) gefitinib in the first line and amend the existing funding of erlotinib in the second line.

The purpose of this rapid review is to provide information to the National Health Committee (NHC) on the potential use of epidermal growth factor receptor (EGFR) gene testing for eligibility for tyrosine kinase inhibitors (TKIs) in patients with locally advanced or metastatic non-squamous, non-small cell lung cancer (NSCLC) in New Zealand. This information will be used by the Committee to:

1. understand how the use of EGFR testing and associated use of TKIs compares with the current treatment protocol for patients with locally advanced or metastatic NSCLC in terms of safety, clinical effectiveness and cost-effectiveness;
2. recommend whether or not EGFR gene testing should be publicly funded to determine eligibility for TKIs in patients with NSCLC in New Zealand; and if so,
3. use this paper to start engaging with the sector to better understand the various options available for providing the service in New Zealand in the short to medium term.

**Methodology**

Due to restricted timeframes, the information contained in this rapid review is drawn mainly from the work already undertaken by other HTA agencies (including MSAC (MSAC 2011; 2012) and CADTH (CADTH 2010)) in this space and provisional recommendations made by clinical associations overseas such as the American Society of Clinical Oncology (ASCO) (Keedy et al 2011), the Italian Association of Medical Oncology (AIOM) (Marchetti et al 2010), a German Panel for Mutation Testing in NSCLC (Penzel et al 2011), and a consensus statement from a European Workshop on EGFR Mutation Testing in NSCLC (Pirker et al 2010). In addition to

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4 http://www.pharmac.govt.nz/2012/05/31/2012-05-31%20PHARMAC%20consultation%20on%20proposal%20for%20TKIs%20for%20Lung%20Cancer.pdf
these papers, the findings of a recently completed feasibility study (unpublished) on EGFR mutation testing in New Zealand (Batten et al 2012a; Batten et al 2012b; Batten et al 2011) and additional papers identified by the lead investigator for the feasibility study were relied upon for a local perspective. Initial feedback from some parts of the sector has also been included to provide a starting point for further engagement. Various additional review papers were also used and are referenced accordingly. The cost-effectiveness of the proposal was examined using a decision tree built using the TreeAge Pro 2012 software package. The model structure and parameters have are not presented here in order to maintain commercial confidentiality.

**Context & policy issues**

PHARMAC currently fund a TKI, erlotinib, for second line treatment of patients with advanced, non-resectable NSCLC with documented disease progression after first line treatment with platinum based chemotherapy. An activating EGFR gene mutation is currently not required for access to erlotinib for second line treatment and therefore testing is not necessary. Funding applications have been received by PHARMAC for the listing of a TKI as a first line treatment for NSCLC in patients with an activating mutation in the EGFR gene. EGFR gene mutation testing can be used to help guide treatment of NSCLC and to determine whether a patient is likely to benefit from TKI treatment. PHARMAC’s scope is primarily pharmaceuticals, and diagnostic tests currently fall within the scope of the NHC. Therefore, the decision of PHARMAC to fund the drug may be influenced by an NHC decision regarding the public funding of the test which determines eligibility for the drug. Before PHARMAC makes a decision to fund a drug that is dependent on a test, PHARMAC would prefer to know whether the NHC is likely to recommend the public funding of the test. The assessment of co-dependent technologies such as this is an increasing area of focus, and one which many countries, including New Zealand and Australia, are trying to understand. With this in mind, the assessment of EGFR testing was indicated as an appropriate learning project that would develop New Zealand’s understanding in the assessment of co-dependent technologies, in a similar way that it is in Australia.

**Technology Status**

EGFR testing is used to determine the mutation status of the EGFR gene in order to choose the most appropriate therapeutic strategy in selected patients with stage IIIb and IV non-small cell lung cancer (NSCLC) (Marchetti et al 2010). Targeted first-line therapy against EGFR using a TKI such as gefitinib or erlotinib has obtained approval by Health Canada (Lung Cancer Canada 2011), and the Pharmaceutical Benefits Assessment Committee (PBAC) of Australia (MSAC 2012). Many OECD and Asian countries are already undertaking EGFR tests (Batten et al 2012b), however, not all the countries for which the drug has been approved are publicly funding the test. Public funding for the test has only recently been approved in Australia and in Canada it is only available in one province, British Columbia (Lung Cancer Canada 2011). Currently EGFR mutation testing is available privately in New Zealand, with samples being sent overseas either to Australia or the United Kingdom for testing on patient request, or as part of a clinical trial (Batten et al 2011).

Prior to testing for EGFR mutations a number of steps need to occur including sample preparation and pathology. To illustrate the overall process of EGFR mutation analysis, a flowchart previously published in Pirker et al (2010) has been reproduced here (Figure 1).
**Requirements for use**

**Biological sample**

Mutational analysis of the EGFR gene can be carried out on either a surgical specimen or on a biopsy sample of the primary tumour and/or metastases (Marchetti et al 2010). Marchetti et al (2010) recommend that tissue samples, rather than cytological material or serum and plasma be used for mutational analysis, particularly by inexperienced labs. They advise that cytological samples should only be used if the laboratory has adequate experience, and that the use of serum and plasma should be considered experimental at this stage as the sensitivity is not greater than 50-60%.

Tissue samples can be obtained at either diagnosis (bronchial biopsy) or surgical intervention (surgical sample). Formalin-fixed, paraffin-embedded samples are needed for histological diagnosis, and are generally conserved in departmental archives. Unfortunately, tissue samples are not available in a high proportion of patients. In many of these cases, cytological material is available that was obtained by fine-needle biopsy, bronchoalveolar lavage or bronchial scraping. Cytological samples can be archived via cytological smears, cyto-inclusion and cell suspension in alcohol-based fixatives. The use of serum and plasma has also been explored by some investigators.

It is generally agreed that systematic molecular profiling should be integrated early in the diagnostic pathway, with patients being tested at diagnosis of NSCLC (Leary et al 2012; Mileshkin et al 2012; MSAC 2012) given that results may take weeks to obtain. Pirker et al (2010), MSAC (2012), and Mileshkin et al (2012) note the importance of optimizing biopsy methods and conserving tissue from the initial diagnosis for use later on, particularly as tissue collection specifically for EGFR mutation testing is unlikely to occur. There has been some suggestion that re-biopsy may be considered at the time of recurrence or disease progression if diagnostic samples are inadequate. The collection of plasma and blood to be tested if tumour analysis fails has also been suggested, but this is experimental and not recommended for routine clinical practice (Pirker et al 2010).
Accredited laboratories and quality assurance

It is generally recommended that EGFR mutation testing should only be done in a quality-assured setting. Accreditation for EGFR mutation testing has been recommended at a national and even European level in Europe, and has accompanied MSAC’s recommendation that EGFR gene mutation testing in Australia should only be performed in laboratories accredited by the National Association of Testing Authorities (NATA) for genetic testing in humans. The New Zealand equivalent of NATA is the International Accreditation New Zealand (IANZ), which has the same international standard as NATA. MSAC also note that testing should be supported by suitable quality standards and a quality assurance (QA) program specific to EGFR genetic testing developed by the Royal College of Pathologists of Australasia (RCPA). The College of American Pathologists is also currently completing Molecular Testing Guidelines for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors which they anticipate will be published in September 2012 which may inform testing processes in New Zealand.

Turn-around time

The overall process from sampling (or ordering of the test) to availability of the mutation results should not take more than 10 working days (Pirker et al 2010). One study, conducted at the Royal Marsden Hospital in London, England has estimated that the number of working days between the date the sample was received in the Molecular Diagnostics Laboratory and the dates the results were available for the clinicians was 4.9. However, they note that the time from the cancer oncologist requesting the test to receiving the result is actually around 18 days (Leary et al 2012). This includes the time taken to request the sample from the referring hospital, sample identification and retrieval, section cutting, shipping and pathological review.

Types of tests and sensitivity & specificity

A variety of techniques are available for mutational analysis of the EGFR gene and they can be subdivided into screening methods that identify all mutations (including new mutations), and targeted methods that can specifically identify known mutations. A brief comparison of testing methods is provided in Table 1 below. Currently, the most widely used method is direct sequencing of the polymerase chain reaction (PCR) product, and other methods are usually only used by more experienced centres. For more information on recommendations specific to each method see Marchetti et al (2010).

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Notes</th>
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<td>Screenning methods</td>
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<tr>
<td>Direct sequencing of the PCR product using Sanger method/DNA sequencing</td>
<td>-provides information about the type of mutation</td>
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<td></td>
<td>-commonly used &amp; widely available</td>
<td>-lower sensitivity than targeted methods</td>
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<td></td>
<td>-can detect all mutations</td>
<td>-requires experienced operators</td>
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<td>-no need to batch samples</td>
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<td>-better contamination control</td>
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<td>Pyrosequencing</td>
<td>-provides information</td>
<td>-sensitivity and specificity of kits must be determined</td>
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5 Pers Comm: (28/05/2012)
## Rapid Review: EGFR testing in NSCLC

| Screening Method | **Notes:** This table was primarily constructed based on the recommendations of the Italian Association of Medical Oncology (Marchetti et al 2010) and the Consensus established at the European Workshop on EGFR Mutation Testing in NSCLC (Pirker et al 2010). It is not an exhaustive list of all possible methods. Debate is on-going regarding the most appropriate EGFR testing methodology for diagnostic applications (Leary et al 2012; Pirker et al 2010) and there is currently no Therapeutic Goods Administration (TGA) (MSAC, 2012) or Food and Drug Administration (FDA) (Ishibe et al 2011) approved methods available for EGFR gene mutation detection. However, most groups stress the importance of standardization and validation of the available tests (Pirker et al 2010), particularly where they were not used in any of the clinical trials. **Screening Method: PCR followed by direct sequencing**

| **PCR followed by sequencing** is the gold standard for the detection of mutations in tyrosine kinase domain of the EGFR (Ishibe et al 2011; Mundy 2005). The advantages of PCR are that it has high sensitivity, high specificity and good reproducibility (Mundy 2005). It has been inferred that PCR for detecting EGFR mutations in NSCLC has a sensitivity of 77% & specificity of 93% (Wright et al 2012). A study comparing sequencing with a commercially available, mutation-specific PCR test found that 67 of 169 mutations (40%) would have been missed by the commercially available PCR test that were picked up by sequencing (Penzel et al 2011). The authors concluded that the percentage of missed mutations is too high to recommend the use of mutation-specific commercial PCR tests for diagnostic application and that only sequencing-based assays will further enhance our knowledge about EGFR mutations (Penzel et al 2011). **Targeted method: Amplification Refractory Mutation System (ARMS)**

| **The targeted tests focus on the exons shown to most likely harbour an EGFR mutation. Previously only exons 19 and 21 were recommended for inclusion in routine diagnostic testing, however, there is some evidence that exons 18 and 20 should also be included (Penzel et al 2011).** |
|---|---|---|---|
| **High-resolution melting analysis (HRMA) & other methods based on the denaturation of DNA** | - rapid and sensitive | - only provides ‘yes or no’ response to mutation which then needs characterisation | - potentially high rate of false positives |
| **High-resolution melting analysis (HRMA) & other methods based on the denaturation of DNA** | - can be used to select cases for direct sequencing (reducing workload) | - can only detect known, pre-determined mutations | - Requirement for batching of samples |
| **Single-strand conformation polymorphism (SSCP)** | - rapid and sensitive | - can be used to select cases for direct sequencing (reducing workload) | - rapidly and sensitively can be used to select cases for direct sequencing (reducing workload) |
| **Targeted methods** | - Increased sensitivity compared with direct sequencing | - can only detect known, pre-determined mutations | - arms was used in the IPASS clinical trial |
| **Scorpin-ARMS (TheraScreen: EGFR29 mutation Kit)** | - less time consuming than sequencing | - less widely used | Increased sensitivity is associated with an increased risk of false-positive results. |
| **Peptide nucleic acid (PNA)/locked nucleic acid(LNA) clamp** | - requires fewer tumour cells | - costs of reagents usually higher than other screening methods | - Requirement for batching of samples |
| **SNAPshot PCR** | - Mutant-enriched PCR | - can only detect known, pre-determined mutations | - arms was used in the IPASS clinical trial |
| **Notes:** | | | |
TheraScreen EGFR29 ARMS mutation kit (DxSLtd., Manchester, UK) was the test used in the IPASS trial. Leary et al (2012) found that compared with direct sequencing, 10-20% of mutations are missed by ARMs, but that 20% of mutations detected by ARMS at low levels are missed by direct sequencing. They therefore suggest that the best way forward may be a combination of screening technologies and in January 2010 the screening protocol for EGFR at the Royal Marsden Hospital/Institute of Cancer Research was changed to a triple assessment (a combination of ARMS, fragment analysis and direct sequencing of exons 18-21) (Leary et al 2012).

The Australian Pharmaceutical Benefits Advisory Committee (PBAC) has advised MSAC that the method of determination of EGFR gene mutation status does not need to be specified and should not be limited to direct DNA sequencing, but should allow for use of other appropriate methods (MSAC 2012). However, as with many other groups, they state that a minimum performance of eligible tests should be specified in terms of analytical validity, in order to minimise both false positives and false negatives (MSAC 2011).

Failed tests and repeating EGFR tests

There is some evidence that when EGFR mutation testing is introduced, there is an initially high failure rate for tests, but that this improves over time. For example, when testing was first introduced at the Royal Marsden Hospital in London the testing failure rate was initially 33% during the first 3 months but decreased to 13% in the last 3 months of year 1 of testing, and then dropped further to 5% in the second year (Leary et al 2012).

In the case of failed tests, the European Workshop suggest that the following options exist: repeat PCR; fragment analysis for exon 19 (which is very sensitive), TaqMan for exon 20 and 21; DNA extraction from new tissue sections, repeating the test using different samples, if available; and discussing options with the pathology team (Pirker et al 2010).

The European Workshop has also recommended that the EGFR mutation test should be repeated if:

- a new (unreported) mutation is found because of the possibility of a false result.
- poor sequence data is found (with primary PCR and sequencing)
- if the cycle is close to the defined cut-off limit (with ARMS-based tests) or,
- other quality assessment criteria are not met (Pirker et al 2010).

Furthermore, others suggest that as progression and treatment can potentially change the mutation status and create discrepancy between the primary tumour and metastasis, treatment decisions based purely on the histology from the primary tumour may be misleading (Mileshkin et al 2012).

Current Status in New Zealand

EGFR gene mutation testing is not currently publicly funded in New Zealand, however, some samples are sent overseas either to Australia or the United Kingdom for testing on patient request, or as part of a clinical trial (Batten et al 2011). In Australia EGFR gene mutation testing is available in five Australian laboratories (MSAC 2012), namely the Peter MacCallum Cancer Centre (Melbourne), SA Pathology (South Australia), PathWest (Western Australia), Healthscope Ltd (Victoria) and Royal Brisbane Hospital (Queensland).

Until recently EGFR mutation testing has not been available in New Zealand, and even now, it has been suggested that only a few laboratories in New Zealand have the technical competency to perform EGFR testing. According to the genetic testing website, there are no New Zealand
laboratories offering the service. However, the Royal College of Pathologists Australia (RCPA) has advised that PathLab Bay of Plenty has notified IANZ of the EGFR extension of its test range and testing is now in place and funded by the Bay of Plenty DHB as part of a clinical pathway of defining access to erlotinib. The lab’s internal QC and vendor QC are both up to date and the lab is enrolled with RCPA QAP for EGFR, KRAS and BRAFv600E. The extension will be assessed in the routine IANZ review in August 2012. It has also been suggested that LabPlus in Auckland is in the process of setting up EGFR testing. Canterbury Health Laboratories at Christchurch Hospital, while not currently doing EGFR testing, have committed to establishing the method locally, using the Roche kit and reagents in the first instance. They envisage that once this has been established they may move on to other methods. However, they suggest that in the interim it may be sensible to send these samples to the Peter MacCallum Cancer Centre in Melbourne.

Epidemiology and burden of disease

Lung cancer

In New Zealand in 2009 there were 2,006 new cases of lung cancer registered; comprising 10% of all new cancer cases and making it the fourth most commonly registered cancer (Ministry of Health 2011). Lung cancer was also the highest cause of cancer mortality in 2009 with 1,593 deaths reported (55% of deaths were male) (Ministry of Health 2012b). The five-year survival ratio for patients with lung cancer is very low, fluctuating between 0.089 and 0.102 in the years between 1998 and 2009 (Ministry of Health 2012a). There has been no improvement in survival over this period and survival ratios for Māori were significantly lower than those seen for non-Māori.

Audits conducted in 2004 and 2008 have shown that most patients in New Zealand present late with advanced disease to healthcare services. It showed that 60% of patients that presented directly to secondary care had seen a GP within the preceding 6 months for another problem, suggesting that there may be opportunities to detect lung cancer earlier.

In Australia the median survival for patients with stage III or stage IV lung cancer is two years and the number of lung cancer deaths for one year is predictive of the total number of patients with advanced disease two years prior (MSAC 2012). If this were also true for New Zealand, 1,593 deaths in 2009 would indicate that 1,593 patients had locally advanced or metastatic disease in 2007.

Non-small cell lung cancer (NSCLC)

NSCLC is the most common form of lung cancer, accounting for between 80% and 90% of cases, and can be classified as either squamous cell carcinoma (SCC), non-squamous cell carcinoma (NSCC) or not otherwise specified (NOS). Studies have found that approximately 10 to 20% of NSCLC tumours harbour somatic mutations in the EGFR gene. It has been shown that patients with adenocarcinoma histology, female sex, East Asian ethnicity and never smoker status have a higher probability of having an EGFR mutation than other groups (Gazdar 2011). However, the incidence of EGFR mutations among NSCLC in New Zealand is currently unknown.

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8 Pers Comm (30/05/2012)
9 Pers Comm (29/05/2012)
11 Non-squamous includes adenocarcinomas and large cell carcinomas.
The number of people eligible for EGFR gene mutation testing in New Zealand (ie, the ‘target population) depends on the preferred testing scenario. MSAC have proposed two scenarios:

- **Base case scenario:** EGFR gene mutation testing would be performed on the patient population at diagnosis of non-squamous NSCLC or NSCLC not otherwise specified (NOS) irrespective of disease stage.
- **Alternative scenario:** EGFR gene mutation testing would be performed on the patient population that have previously untreated locally advanced (Stage IIIIB) or metastatic (Stage IV) non-squamous NSCLC or NSCLC not otherwise specified (NOS).

In both scenarios the preference is to test the sample collected during the biopsy that was taken to diagnose patients with NSCC rather than a separate biopsy taken at a later stage (see Appendix 1 for MSAC’s current and proposed treatment algorithms). The only distinction is whether the sample is tested immediately (base case scenario) or whether it is stored and only retrieved and tested once patients progress to the stage at which they become eligible for the drug (alternative scenario).

Figures 2 and 3 below use MSAC’s assumptions to show the impact of these two testing scenarios on the potential number of people undergoing EGFR gene mutation testing in New Zealand. It can be seen that while under the base case scenario approximately 1,214 people will undergo testing, in the alternative scenario between 728-850 people will undergo testing.

MSAC note that 89% of all lung cancer is NSCLC (1,785 in NZ) and 68% of all NSCLC is non-squamous or NSCLC NOS (1,214 in NZ). MSAC have therefore assumed that 60.5% of all lung cancer cases are non-squamous NSCLC or NSCLC NOS. Somatic EGFR mutations have been found to occur in 10% to 20% of patients with NSCLC and MSAC have assumed that this is the same for NSCLC non-squamous and NSCLC NOS (121-243 patients in NZ). Approximately 60% to 70% of patients diagnosed with the above are found to be in stage IIIB or IV of the disease (1,071-1,250 in NZ).

However, in the absence of data outlining the percentage of patients staged I, II, or IIIA at diagnosis that progress to having locally advanced or metastatic disease, MSAC used 5-year mortality data for all stages (I-IV) as a proxy for the percentage of all lung cancer cases who either have or progress to have locally advanced or metastatic disease. They therefore assumed that 81% of patients with EGFR mutations are either diagnosed as having, or progress to have, locally advanced or metastatic disease each year (98-197 patients in NZ)\(^{12}\) and that of these an estimated 90% of patients (89-177 in NZ)\(^{13}\) will be suitable for treatment with a TKI (this is based on an assumption by Roche Diagnostics with respect to *erlotinib* but has been included here on the basis it is also likely to be true of treatment of patients with *gefitinib*).

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\(^{12}\) Or this number may be 394 if we assume a 40% EGFR mutation incidence instead of 10-20% in patients with non-squamous NSCLC.

\(^{13}\) Or this number may be 355 if we assume a 40% EGFR mutation incidence instead of 10-20% in patients with non-squamous NSCLC.
Figure 2: Estimated number of patients undergoing EGFR testing and treatment with first-line TKI per year for the proposed base case scenario

Incidence of all lung cancer in New Zealand in 2009 = 2,006 ppl

NSCLC (non-squamous or NOS) who will undergo EGFR gene mutation testing = 1,214 ppl

Number of patients with EGFR gene mutations = 121-243 ppl

Patients who have or progress to locally advanced (IIIB) or metastatic (IV) NSCLC and become eligible for TKI (81% of those diagnosed) = 98-197 ppl

Patients suitable for TKI treatment (an estimated 90% of patients are suitable for treatment) = 89-177 ppl

Source: Adapted from MSAC Application 1173
**Clinical safety & effectiveness**

Information compiled in this section of the paper seeks to address the question of whether or not the use of EGFR mutation testing followed by treatment with a TKI is a more clinically safe and effective first line treatment for patients with stage IIIB and IV non-squamous NSCLC than no testing and treatment with chemotherapy in the first line setting followed by erlotinib in the second line setting (status quo). To date there have been five randomised Phase III trials comparing gefitinib or erlotinib monotherapy to first-line chemotherapy, all in East Asian NSCLC patients (Leary et al 2012). All of these trials provide evidence that EGFR mutation testing followed by treatment with TKIs is more clinically safe and effective than no testing and treatment with chemotherapy. However, a number of uncertainties remain around how the safety and efficacy profiles might change outside of trial settings and particularly how different levels of sensitivity and specificity of different tests may affect outcomes in populations with lower incidence of EGFR mutations.

**Safety**

In the randomised trials comparing first-line gefitinib to platinum-based chemotherapy the most common adverse events in patients receiving gefitinib were cutaneous toxicity (skin rash, dry skin), diarrhoea and liver dysfunction, usually consisting in asymptomatic
hypertensaminasemia (Gridelli et al 2011). In the majority of cases these events were mild or moderate in intensity. Patients receiving gefitinib experienced significantly less haematological toxicity, emesis, fatigue, neurotoxicity, and constipation and hair loss, compared to patients treated with platinum-based chemotherapy (Gridelli et al 2011). Among potentially life-threatening events described with the use of gefitinib, interstitial lung disease resulted in a total of 7 deaths in the 967 patients overall evaluated in 4 trials (Gridelli et al 2011).

**Efficacy**

Two initial trials used clinically selected criteria to enrich for EGFR-M+ NSCLC randomising patients to gefitinib or chemotherapy. Among EGFR-M+ NSCLC both response rate and progression-free survival (PFS) significantly favoured gefitinib, while the converse was true for EGFR-M-patients. Three subsequent trials in proven EGFR-M+ patients confirmed a significant PFS improvement for EGFR TKI compared to chemotherapy, of which the most recent is the randomized phase III clinical trial reported by Mok et al (2009), also known as the Iressa Pan-Asia Study (IPASS) (see Table 2).

<table>
<thead>
<tr>
<th>EGFR mutation status</th>
<th>Response to Gefitinib (median PFS)</th>
<th>Response to Chemotherapy (median PFS)</th>
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<tbody>
<tr>
<td>Mutation positive</td>
<td>9.6 months</td>
<td>6.3 months</td>
</tr>
<tr>
<td>Mutation negative</td>
<td>1.6 months</td>
<td>5.5 months</td>
</tr>
<tr>
<td>All patients</td>
<td>5.7 months</td>
<td>5.8 months</td>
</tr>
</tbody>
</table>

Source: Gridelli et al (2011, p 252)

This trial demonstrated superiority of gefitinib compared with carboplatin paclitaxel (a chemotherapy regimen) for EGFR positive patients (Neal and Sequist 2010). Additionally, EGFR positive patients who received gefitinib had an improved quality of life, reduction in symptoms as measured by the FACT-L questionnaire and a reduction in toxic side effects such as nausea, vomiting, myelosuppresion, and neurotoxicity, despite increased occurrence of grade 1 and 2 rash and diarrhoea. The results from this prospective and randomized trial confirm the value of EGFR mutation testing.

However, selection of patients for TKI therapy based on mutational testing is not a guarantee of response – only about 70-80% of EGFR mutation-positive tumour cases will have meaningful responses to TKI treatment (Gazdar 2011). Certain mutations such as insertions in exon 20, secondary mutations (T790M), or increased copy number (amplification) of the MET oncogene are associated with resistance to TKI therapy. Mutations in the KRAS gene, located downstream of EGFR in its signalling cascade, are mutually exclusive with EGFR mutations and are associated with resistance to TKI therapy (Gazdar 2011).

**Using clinical criteria instead of a test**

As mutation screening at diagnosis is logistically complicated and may delay initial treatment, it has been debated whether clinical criteria would be equally useful for selecting patients for upfront TKIs and whether EGFR mutations are simply prognostic (Neal and Sequist 2010). Gazdar (2011), in citing Wu (2011) has suggested that because mutations and TKI responses largely target identical subsets of NSCLC (specifically adenocarcinoma histology, female sex, East Asian ethnicity, and never smoker status), arbitrary selection of patients for treatment dependent on their pathologic and demographic characteristics may be an acceptable surrogate for testing.
However, others argue strongly against this approach emphasising that using clinical criteria alone may not only miss a percentage of EGFR mutation +ve cases, but may result in EGFR mutation -ve patients being given inferior treatment (EGFR –ve cases respond better to conventional chemotherapy than TKI administration).

**Outstanding issues**

Ishibe et al (2011) and many others recognise that there are a number of gaps in the evidence base that make strong conclusions about the clinical utility of EGFR mutation testing premature. These include: (1) the absence of data from prospective randomized clinical trials comparing EGFR mutation testing to usual care; (2) lack of data regarding whether EGFR-TKI’s provide an overall survival advantage when compared with chemotherapy in patients with EGFR mutations (some have suggested overall survival is similar (Mileshkin et al 2012) ); and (3) lack of adequate assessment of the cost-effectiveness of TKIs as a first line treatment.

Furthermore, not all patients with EGFR activating mutations respond to TKIs (Mileshkin et al 2012) and in some patients the T790M mutation in exon 20 has been associated with acquired resistance to gefitinib (Pirker et al 2010).

**Economic (Cost-effectiveness)**

Information compiled in this section of the paper seeks to address the question of whether or not the use of EGFR mutation testing followed by treatment with gefitinib in the first line and amendment of funding for erlotinib in the second line(proposed) is a more cost-effective first line treatment for patients with stage IIIB and IV non-squamous NSCLC than no testing and treatment with chemotherapy in the first line and erlotinib in the second line (status quo). There are few (if any) studies that have adequately investigated the cost-effectiveness of EGFR mutation testing followed by treatment with gefitinib or erlotinib, compared with chemotherapy in the first line (CADTH 2010; Ishibe et al 2011). As such, this section draws heavily on the work CADTH (2010) and MSAC (2012) have completed in this area and makes a number of assumptions to construct a very basic model.

A rapid review published by CADTH 2010 only found one conference poster that assessed the cost-effectiveness of EGFR mutation analyses for advanced NSCLC. This study showed the incremental cost per additional year of progression-free survival (PFS) was US$17,184 for the EGFR mutation testing (followed by gefitinib) if patients tested positive (Arrieta et al 2010). However, CADTH (2010) note that had the primary outcome been overall survival rather than PFS, the EGFR mutation analysis may have been less cost-effective than it appeared. This is because the analysis ignored the impact on overall survival of the choice of 2nd and 3rd line therapy. The implication being that the differences in costs and outcomes during the subsequent disease progression were assumed to be comparable between strategies, which is unlikely to be the case (CADTH 2010).

MSAC (2012) have constructed a decision tree representing decision options in patients with non-squamous NSCLC or NSCLC NOS which will be used in their assessment (yet to be completed) (Appendix 2) and CADTH (2010) have developed a framework for economic analysis. A simplified version of the MSAC model has been constructed by the NHC Executive with reference to CADTH’s work to test the impact of the uncertainty around the values of different parameters on the cost-effectiveness of EGFR mutation testing followed by treatment with gefitinib compared with the status quo. However, there is a slight difference in that the NHC have used PHARMAC’s proposed treatment algorithm instead of MSAC’s (only testing patients with non-squamous NSCLC once they progress to stage IIIB/IV, compared with testing
non-squamous and NOS NSCLC regardless of stage of disease. The main parameters that have been explored are the sensitivity and specificity of the test, the incidence of EGFR mutations in New Zealand non-squamous NSCLC patients, and the cost of gefitinib.

**Test sensitivity & specificity**

In circumstances where a patient’s improvement in health (e.g., PFS) following treatment with a drug depends on the presence of a specific mutation (as is the case with gefitinib), the ability of a test to accurately determine whether a patient is mutation positive or negative is important. The ability of a test to correctly detect a positive mutation is referred to as the test’s ‘sensitivity’. High sensitivity is important for minimising the number of patients incorrectly identified as mutation negative when they are really mutation positive (false negatives). Conversely, the proportion of truly mutation negative people in the tested population is referred to as ‘specificity’. High specificity is important for minimising the number of false positives. The sensitivity and specificity of testing depends significantly on the quality of tissue sample, the test used and the experience of those involved.

The purpose of the analysis presented in this section of the report is to show the impact of varying levels of test sensitivity and specificity on the cost-effectiveness of a drug treatment dependent on the results of a test. To illustrate this we have assigned the PFS values from the IPASS study to the first line outcomes in the EGFR +ve and –ve patients, and by doing so are assuming that the testing in the IPASS study had 100% sensitivity and specificity. This is unlikely to be the case so the populations assigned to be EGFR +ve and –ve in IPASS would have contained a number of false positive and false negative patients. However, while this may dilute the differences in PFS observed between groups, the analysis still shows the influence of varying levels of sensitivity and specificity and the importance of having a robust, validated and timely testing process.

**Scenario 1: Sensitivity and specificity implicit in IPASS**

It is difficult to assess the cost-effectiveness of a test which determines access to a drug without also assessing the cost-effectiveness of the drug. Prior to investigating the impact of variable test sensitivity and specificity on the cost-effectiveness of the proposed intervention the NHC Executive constructed an initial model which assumes that any test used to determine mutation status is the same as that used in the IPASS trial. Our analysis found that if PHARMAC can save more than $684,900\(^{14}\) from their budget annually then the proposal is likely to be cost-saving to the health sector.

**Scenario 2: Variable levels of sensitivity and specificity**

As noted previously, PCR followed by sequencing is the gold standard for the detection of mutations. Wright et al (2012) inferred that the use of PCR to detect EGFR mutations has a sensitivity of 77% and specificity of 93%. Assuming that 40% of the non-squamous NSCLC population in New Zealand are EGFR mutation +ve\(^{15}\), it was apparent that EGFR testing and subsequent treatment with gefitinib becomes more cost-effective with greater test specificity, but less cost-effective with greater test sensitivity.

\(^{14}\) =167\*$3,805 which includes an estimate of the marginal cost of the EGFR test but not the setup costs for EGFR testing in New Zealand

\(^{15}\) Estimates elsewhere suggest that 10-20% of NSCLC patients are EGFR mutation +ve (MSAC 2012), but NHC estimates derived from New Zealand Cancer Registry data and reported incidence of EGFR mutation +ve by smoking status (D’Angelo et al 2011) found that incidence is most likely between 31% and 41% in patients with non-squamous NSCLC. A figure of 40% was used throughout the NHC modelling.
**Mutation incidence**

In addition to the sensitivity and specificity of the test, the incidence of EGFR mutations in the NSCLC population may also affect the cost-effectiveness of the proposed intervention compared with the status quo. Assuming that the test achieves a sensitivity of 77% and a specificity of 93%, we found that the cost per month of PFS in the first line increases as the incidence of EGFR mutation positive patients in the target population increases.

**Societal & ethical**

**Ethical and equity issues**

*Are the benefits or costs of testing for EGFR mutations versus not testing and using chemotherapy treatment in the first line, experienced disproportionately by different groups?*

As with all funding decisions, there is always an opportunity cost. In this case, the benefits of EGFR mutation testing followed by subsequent treatment with gefitinib in the first line, compared with no testing and treatment with chemotherapy and erlotinib are disproportionately experienced by those with an EGFR mutation. From Table 2, it was clear that those with an EGFR mutation that were tested and provided gefitinib experienced significantly greater progression free survival than those tested and provided gefitinib without an EGFR mutation. Given the association between this mutation and certain demographic and lifestyle factors, it is possible that the benefits of testing will disproportionately be experienced by Asian, women, non-smokers. As patients who continue to smoke do not appear to benefit from treatment with an EGFR TKI due to effects on drug metabolism, it has also been suggested that testing may not be relevant unless the patient is willing to try to stop smoking, meaning the benefits are unlikely to be experienced by smokers (Mileshkin et al 2012).

The costs of EGFR mutation testing followed by subsequent treatment with gefitinib in the first line, compared with treatment with chemotherapy and then erlotinib, are disproportionately experienced by those without an EGFR mutation. As was indicated in the economic domain above, because the sensitivity and specificity of testing is unlikely to be 100%, this means that there will be some EGFR negative patients given gefitinib, resulting in significantly poorer progression free survival than they would have had using chemotherapy in the first line (though it is unknown if their overall survival was any worse). This has important ethical and equity implications as introducing the intervention will decrease the overall PFS of a group (EGFR –ve patients) that already experience lower PFS than the group set to benefit (EGFR +ve patients). Thus, it is possible, that non-Asian, male, smokers may be worse off as a result of this intervention than they are now depending on the specificity of the tests used.

Therefore, introducing EGFR mutation testing and treatment of mutation positive patients with gefitinib in the first line may increase overall PFS in the population compared with the status quo, but will mean that some EGFR negative patients will have shorter PFS following first line treatment than they do now. The question is therefore whether it is ethical to introduce an intervention that has the potential to increase PFS overall for patients with advanced non-squamous NSCLC while reducing the PFS of the EGFR –ve subgroup of this population (ie, improving the health of one sub-group at the expense of another)? One approach to address this ethical concern might be to counsel patients about the risks and benefits of testing (including the possibility of false results) empowering them to make their own informed decisions accordingly.
**Would targeting EGFR mutation testing to certain groups based on clinical criteria be a more ethical and/or cost effective way of maximising the benefits gained while minimising the costs?**

While selecting patients for treatment with TKIs on the basis of clinical criteria alone is not recommended (see clinical safety & effectiveness domain), targeting testing of patients on the basis of such criteria may be a way of reducing the risk of EGFR negative patients receiving inappropriate treatment due to testing methods with low specificity. The European Workshop on EGFR Mutation Testing in NSCLC discussed a number of pre-screening strategies, including whether focus should be on specific patient populations such as never-smokers and/or patients with adenocarcinoma given that the frequencies of mutations are particularly high in these patients (Pirker et al 2010). The Workshop also discussed various molecular pre-screening techniques such as high-resolution melting analysis, immunohistochemistry, circulating tumour cell DNA testing, and KRAS mutation testing. However, there was no consensus agreement on current pre-screening algorithms. Likewise, it has been suggested that 31% of all EGFR mutations would be missed if testing were restricted to women, 40% would be missed if testing were restricted to never smokers, and 57% would be missed if testing were restricted to women who never smoked cigarettes (Mileshkin et al 2012). Leary et al (2012) also found that although targeting testing to non-smoking women with adenocarcinoma would have increased mutation detection rates from 11% to 20%, over 30% of mutant tumours (found in male current or ex-smokers) would have been missed.

**Are there ethical and/or equity issues associated with not publicly funding EGFR mutation testing in New Zealand?**

EGFR mutation testing is already occurring in the private sector in New Zealand. If a decision is made not to publicly fund testing in New Zealand, but PHARMAC funds a TKI subject to a positive test result, only those that are able to afford the test will be eligible for the drug, and thus the potential for increased health gains. This has significant ethical and equity implications, particularly if Maori and Pacific populations exhibit a similar incidence of EGFR mutations to that of Asians as testing followed by TKI treatment may be one way of reducing health disparities related to lung cancer (Batten et al 2012b).

**Acceptability**

*What are the cultural considerations associated with the condition and intervention?*

While unable to necessarily be generalised, the qualitative interview component of a study that investigated the feasibility of testing the tumours of Maori patients with advanced (stage IIIB and IV) NSCLC for somatic EGFR alterations found that there were no universal cultural barriers to genetic testing identified (Batten et al 2012a). However, many of the participants emphasised the importance of not wasting samples, and keeping the samples both physically and spiritually safe, and the importance of cultural practices related to karakia and disposal of samples. If EGFR mutation testing is publicly funded in New Zealand, measures will need to be taken to ensure these considerations are addressed.

*What are the information/advice requirements associated with the intervention?*

The study by Batten et al (2012a) showed that there is often confusion around why certain investigations and treatments take place, and that some of the participants interviewed were not given a choice among treatment options, including the option of no treatment. If EGFR mutation testing and subsequent treatment with gefitinib is introduced, patients will need to be given sufficient information to make an informed decision regarding their treatment.
**What are the patient preferences around the configuration and/or delivery of the intervention?**

The introduction of EGFR mutation testing as part of the pathway of clinical care for lung cancer patients in New Zealand would need to take into account patients preferences around biopsies, diagnostic delays and respite time.

Biopsies are sometimes recalled with differing degrees of anxiety and distress (Batten et al 2012a), so minimising the need to re-biopsy will be important for patients, as well as providing the opportunity for cytological samples to be used when necessary.

A fast turn-around time for test results is essential for EGFR mutation testing to be used in clinical practice and be acceptable to the public. If the time to receive the test results is too long, some patients may deteriorate while waiting, and others may be too nervous to wait, which means they may be started on chemotherapy before test results are received (Hirsh et al 2012), limiting the cost-effectiveness of the intervention. Preference is therefore for mutation testing to occur at the time of diagnosis, rather than waiting for patients to progress to stage IIIB and IV. Difficultly obtaining test results and having to wait for results has already been identified as problem that negatively impacts on the cancer journey of patients in New Zealand, so EGFR mutation testing should not exacerbate this (Batten et al 2012a).

One of the main strengths often associated with the use of TKIs in the first line instead of chemotherapy for EGFR mutation positive patients is the potential for the number of visits to hospital to be reduced. However, Batten et al (2012a) observed that some patients considered the trip to hospital for treatment a respite, providing family members a break and providing patients time to relax. Further investigation of this perspective should be undertaken prior to assuming the use of TKI’s is better than the status quo in this respect. It also suggests that other ways of achieving the non-clinical benefits from a trip to the hospital should be investigated for cancer patients in general, regardless of their course of treatment.

**Feasibility of adoption**

To obtain the benefits from publicly funding EGFR mutation testing in New Zealand a number of things would need to be addressed over time. These include establishing the baseline incidence of EGFR mutation in non-squamous NSCLC tumours of different population groups in New Zealand, educating clinicians and patients about molecular tests, encouraging sufficient biopsies to be collected at diagnosis (where clinically appropriate), and introducing a centralised testing service with a framework to ensure the quality of testing. If EGFR mutation testing is publicly funded in New Zealand within the next year, it may be best for samples to be sent to Australia until the expertise and capability of New Zealand laboratories can be shown to meet similar levels of accreditation.

**Overseas**

In many countries overseas the use of TKI’s has been approved as a first line therapy in patients that test positive for an EGFR mutation. However, in most cases this has happened without considering the implications and issues surrounding testing. As a result, there are still questions about how best to implement these tests in clinical practice and multi-disciplinary groups in various countries are only just beginning to establish frameworks for quality control. The main obstacles to implementation include the availability of good quality tissue specimens, access to the right test (and availability of capable laboratories (Hirsh et al 2012), and consensus about interpretation, funding, and availability (Mileshkin et al 2012).
New Zealand

Introducing EGFR testing as part of the clinical pathway for the effective management of advanced NSCLC is likely to be supported by the health sector, but may need to be accompanied by measures to increase the capability and experience of the workforce to ensure the tests are appropriately consented to, used, undertaken, and reported. This will be crucial if EGFR testing in New Zealand is to achieve similar improvements in health as were observed in the clinical trials and will require consideration of all clinicians in the pathway, not just medical oncologists but respiratory physicians, surgeons, radiologists and pathologists, among others.

Mileshkin et al (2012), with respect to Australia, notes that it is crucial we have enough numbers of appropriate staffed laboratories to provide high-quality services for molecular testing and that the oncology workforce is sufficiently educated about the effective use of co-diagnostics in patient management. The Standards of Service Provision for Lung Cancer Patients in New Zealand (released in August 2011) does not include discussion of molecular tests and their place in the management of lung cancer (Batten et al 2012b) and up until recently the New Zealand health sector has had limited experience using molecular tests such as EGFR to guide the treatment of lung cancer.

A 2010 survey of 137 practicing New Zealand cancer clinicians found that while 92% of them were aware of molecular tests, 47% reported that they had never used molecular tests relevant to their clinical practice (Wright et al 2012). The main factors reported limiting the use of molecular tests were the cost of mutation analysis and, in some instances, the cost of unfunded medications. However, when asked to predict the change in impact of molecular tests on the care of patients with cancer over the next decade, over 85% of participants, whether or not they currently used these tests, predicted that they would have a greater influence and a stronger evidence base within the next 10 years.

In addition to the issues described above around the testing for EGFR gene mutations, there are a number of other issues to consider when implementing this service, including any additional tissue storage and retrieval capacity and costs. Once the tissue specimen has been examined and the appropriate portions of the tissue are selected for further processing via paraffin blocks and glass slides for microscopic examination, the remainder of the specimen is either destroyed or returned to the patient after 6 weeks - 3 months.16

Meanwhile, tissue storage of paraffin blocks and glass slides is usually for at least 20 years. The paraffin blocks and glass slides are stored, either on-site or off-site at hospital-based and community-based laboratories as they take up substantial floor space and are very heavy. Off-site storage and the associated search and retrieval of the material is costly. Retrieving this material is also costly in laboratory man power terms as it takes the laboratory technician / scientist some time to order the material from storage (approximately 48 hours). At present, specific cancer tissue banks are limited in number (Christchurch and Middlemore) and are reliant on donations and tend to store material specifically for research projects only.

Any strategy for implementing EGFR gene mutation testing in New Zealand will need to investigate further the additional resources required (if any) for storage and retrieval of tissue samples. It has been suggested that existing laboratories, such as Canterbury Health Laboratories may be able to provide guidance on this.

16 Pers Comm (30/05/2012)
**Prioritisation**

While access to molecular tests and targeted therapies may be desirable, it is debatable whether funding for EGFR testing and subsequent use of targeted therapies for late stage lung cancer should be prioritised over other interventions in the clinical pathway for lung cancer.

There is no evidence that publicly funding EGFR testing and subsequent treatment with TKIs in New Zealand will improve early diagnosis, overall survival for lung cancer patients or reduce disparities in survival between different ethnic groups.

What evidence does suggest is that significant improvements are required in the pathway of care for lung cancer, and that the only way New Zealand is going to improve overall survival for lung cancer, and decrease disparities between ethnic groups, it to address the barriers to early diagnosis\(^7\).

Therefore, if new funding is going to be available for spending in the treatment of lung cancer, it might be better to spend it on addressing barriers to early diagnosis which will increase overall survival, rather than on a test and drug combination for which there is little evidence that overall survival of lung cancer patients is improved (Ishibe et al 2011; Mileshkin et al 2012).

**Conclusion & Options**

Many countries are already testing for EGFR mutations to determine appropriate treatment with TKIs. While there are still a number of uncertainties around whether the health gains observed in the clinical trials are generalizable to the real world, most countries appear to be addressing this through close monitoring and evaluation which will eventually enable a better assessment of the clinical utility and cost-effectiveness of the intervention. Whether or not New Zealand takes a similar approach will depend on to what extent decision-makers are comfortable with this.

**1. Should EGFR gene testing be publicly funded to determine eligibility for TKIs in patients with NSCLC in New Zealand?**

If decision-makers are comfortable with the approach being taken overseas, including in Australia, then options 1 or 2 may be preferable. If decision-makers wish to minimise the risk of harming EGFR negative patients while still increasing gains for some EGFR positive patients (at the expense of overall gains in PFS and savings), option 3 may be best. If decision-makers do not think that the intervention is cost-saving to the health sector compared with the status quo, option 4 may be best. If decision-makers do not believe they have sufficient information to make a decision, option 5 may be best.

<table>
<thead>
<tr>
<th>Option</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Next step</th>
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</table>
| 1. Yes – for all NSCLC | -Opportunity to re-test before patient’s health deteriorates.  
- In line with base case scenario in Australia.  
- Clinicians are able to provide more certainty to patients around | - More people being tested than option 2.  
- Potential for mutation status to change. | Go to question 2 |

### 2. How could EGFR gene testing services be delivered in New Zealand in the short term to medium term?

If PHARMAC decides to publicly fund gefitinib and amend the criteria for erlotinib as proposed,, prior to the set-up of a centralised testing service in New Zealand that uses New Zealand laboratories, option A may be best. If there is sufficient time between PHARMAC’s decision to make the drug publicly available to ensure the service can be adequately provided in New Zealand, then option B may be best.

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<th>Weaknesses</th>
<th>Next steps</th>
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<tr>
<td>A</td>
<td>Testing undertaken in Australia – no ‘preferred test’</td>
<td>- Australia already has labs capable of the gold standard test, - Potential delay in clinicians receiving test results &amp; expensive (though this would be mitigated by testing at time)</td>
<td>Engage with the health sector and clinicians around their preferred testing options and to inform PHARMAC</td>
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<td>B</td>
<td></td>
<td>- Limiting use of a TKI to second line treatment may mean that a patient may never be able to receive an EGFR TKI in case of rapidly progressive disease and worsening physical conditions at first line failure, - Overall PFS of NSCLC patients will be less than options 1-3.</td>
<td>Inform PHARMAC</td>
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<td>C</td>
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<td>- Fewer people likely to benefit overall if targeting strategy is poor, - Limiting use of a TKI to second line treatment may mean that a patient may never be able to receive an EGFR TKI in case of rapidly progressive disease and worsening physical conditions at first line failure, - Overall PFS of NSCLC patients will be less than options 1-3.</td>
<td>Inform PHARMAC</td>
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<td>E</td>
<td></td>
<td>- Delay decision to publicly fund the drug until incidence of EGFR mutations is determined and/or further issues around implementation have been addressed, - More information may not become available, - If PHARMAC funds the drug on basis of positive test result access to the TKIs will be inequitable due to not funding the test</td>
<td>List what further information is required</td>
</tr>
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identified’ - Already have an accreditation process
- Already have experience of diagnosis rather than only once the disease has progressed)
- Not supporting New Zealand laboratories/profession
- May be more difficult to ensure physical, spiritual and cultural safety of samples
determine feasibility (re: cost, timeliness and cultural issues)
Engage with the National Ethics Advisory Committee (NEAC) and National Screening Advisory Committee (NSAC).

Implementation strategy:
-Determine how the test will be publicly funded
-Speak with HBL regarding laboratories overseas/implementation
-Follow up on RCPA guidelines for testing
-Change current practice-preference for biopsy at diagnosis where appropriate

Evaluation strategy:
– monitoring sensitivity and specificity of different tests
-EGFR mutation Incidence study

B| Testing undertaken in New Zealand – no ‘preferred test identified, but service centralised rather than DHB-based
- Potentially quick turnaround time for test results
- Better able to ensure physical, spiritual and cultural safety of samples
- May be cheaper than sending samples to Australia
| Currently no accreditation process in New Zealand/quality insurance framework
- May be insufficient numbers of tests to ensure adequate experience and thus quality over time
- Small numbers of tests can also be less cost-effective
| Engage with the health sector and clinicians around their preferred testing options and to determine feasibility (re: cost, timeliness and cultural issues)
Engage with the National Ethics Advisory Committee (NEAC) and National Screening Advisory Committee (NSAC).

Implementation strategy:
-Determine how the test will be publicly funded
-Speak with HBL regarding laboratories overseas/implementation
-Follow up on RCPA guidelines for testing
- Change current practice preference for biopsy at diagnosis where appropriate

Evaluation strategy:
- monitoring sensitivity and specificity of different tests
- EGFR mutation
  Incidence study
## Glossary

<table>
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<tr>
<th>Term</th>
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<tr>
<td>Incidence</td>
<td>the number of new mutations identified in a defined population within a specified period of time.</td>
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<tr>
<td>Prevalence</td>
<td>the number of all mutations in a given population at a designated time.</td>
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<tr>
<td>Sensitivity</td>
<td>the proportion of truly EGFR mutation positive people in the tested population who are identified as EGFR mutation positive by the test. Sensitivity is a measure of the probability of correctly diagnosing a case, or the probability that any given case will be identified by the test (synonym: true positive rate). High sensitivity is important for minimising the number of false negatives.</td>
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<tr>
<td>Specificity</td>
<td>the proportion of truly EGFR mutation negative people in the tested population who are so identified by the test. It is a measure of the probability of correctly identifying a non-EGFR positive person with a test (synonym: true negative rate). High specificity is important for minimising the number of false positives.</td>
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<tr>
<td>Survival Ratio</td>
<td>the proportion of persons in a population (or subgroup) at the beginning of a period who are still alive at the end of the period.</td>
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References


Appendix 1: MSAC’s proposed treatment algorithm

Appendix 2: MSAC model structure

Figure A2: Decision tree representing decision options in patients with locally advanced or metastatic large cell NSCLC

Source: MSAC.2012. Application 1173: EGFR testing for erlotinib for advanced or metastatic NSCLC (pg. 3)
National Health Committee (NHC) and Executive

The National Health Committee (NHC) is an independent statutory body which provides advice to the New Zealand Minister of Health. It was reformed in 2011 to establish evaluation systems that would provide the New Zealand people and health sector with greater value for the money invested in health. The NHC Executive are the secretariat that supports the Committee. The NHC Executive’s primary objective is to provide the Committee with sufficient information for them to prioritise interventions and make investment and disinvestment decisions. They do this through a variety of products including Prioritising Summaries, Technology Notes, EpiNotes, CostNotes, Rapid Reviews, and Health Technology Assessments which are chosen according to the nature of the decision required and time-frame within which decisions need to be made.


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This document is available on the National Health Committee’s website:
http://www.nhc.health.govt.nz/

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