



TITLE: Epidermal Growth Factor Receptor Mutation Analysis in Advanced Non-Small Cell Lung Cancer: Review of Economic Evaluations and Framework for Economic Analyses

DATE: 28 July 2010

EXECUTIVE SUMMARY

Context and Policy Issues

Lung cancer is the second most common cancer in Canada and the leading cause of cancer-related death. Non-small cell lung cancer (NSCLC) accounts for over 80% of all lung cancer cases. Some cases of NSCLC are associated with an over-expression of the protein epidermal growth factor receptor (EGFR). Over-expression of EGFR is linked to a more aggressive disease and a poor prognosis. Treatment protocols for NSCLC are evolving to include emerging therapies such as EGFR tyrosine kinase inhibitors (TKIs). Mutations in the EGFR gene have been identified and proposed to be associated with high responsiveness to TKI treatment.

This report focuses on the cost-effectiveness of polymerase chain reaction (PCR)-based methods used to detect the presence of EGFR mutations in patients with advanced NSCLC. The report provides an economic framework to guide future economic evaluations of EGFR mutation analysis, particularly focusing on assessing cost-effectiveness of EGFR mutation analysis for the first-line use of gefitinib for the treatment of advanced NSCLC.

Disclaimer:

This document is prepared by the Health Technology Inquiry Service (HTIS), an information service of the Canadian Agency for Drugs and Technologies in Health. The service is provided to those involved in planning and providing health care in Canada. HTIS responses are based on a comprehensive and systematic search of literature available to CADTH at the time of preparation. The intent is to provide a summary and critical appraisal of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. This response has been peer reviewed by clinical experts. The information in this document is intended to help Canadian health care decision-makers make well-informed decisions and thereby improve the quality of health care services. HTIS responses should be considered along with other types of information and health care considerations. It should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the document to ensure that its contents are accurate, complete and up to date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss or damage arising from or relating to the use (or misuse) of any information, statements or conclusions contained in or implied by the information in this document or in any of the source documentation.

Copyright: Copyright @ CADTH (July 2010) You are permitted to make copies of this document for non-commercial purposes provided it is not modified when reproduced and appropriate credit is given to CADTH.

Links: This document may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third party sites and CADTH is not responsible for any injury, loss or damage suffered as a result of using such third party sites.

Research question

How can the cost-effectiveness of epidermal growth factor receptor mutation analysis for the identification of patients with advanced non-small cell lung cancer who are likely to respond to treatment with tyrosine kinase inhibitors be assessed?

Review of economic evaluations

A literature search was conducted on key health technology assessment resources, including Medline, Embase, Biosis, the Cochrane Library (Issue 2, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and March 16, 2010. Regular alerts are current to June 7, 2010. Filters were applied to limit the retrieval to economic studies. Two independent reviewers screened articles using pre-defined criteria.

A systematic review found one recent conference presentation that assessed the cost-effectiveness of EGFR mutation analyses for advanced NSCLC. The study showed the incremental cost per additional progression-free survival year was US\$17,184 for the EGFR mutation testing (followed by gefinitib treatment if patients tested positive and carboplatin-paclitaxel doublet if patients tested negative) compared with providing carboplatin-paclitaxel doublet to all the patients. However, because the study was available as a poster, limited details were available.

Framework for Economic Analyses

A framework for a decision analytic cost-utility analysis was developed to assess the cost-effectiveness of EGFR mutation analysis compared with the option of no EGFR mutation analysis. The model simulated the EGFR mutation analysis, disease progression, and associated treatment paths from the time of diagnosis of advanced NSCLC to death. The model followed the CADTH economic evaluation guidelines and a recently published CADTH economic guideline on oncology products. Guidance to model building such as study perspective, model structure, time horizon, discounting, clinical outcomes, health state utilities, resource use and costs, and uncertainty analyses were proposed. Potential challenges in conducting future cost-effectiveness analyses included data availability such as the proportion of patients receiving various platinum-doublet therapies and evidence of health state utilities.

Conclusions and Implications for Decision or Policy Making

A systematic review of existing economic studies found a limited evidence on the cost-effectiveness of the EGFR mutation analysis, resulting in one study (a conference presentation) being reviewed. The proposed modeling framework presented in this report was flexible, allowing analysts to adjust the model for jurisdictional needs with respect to EGFR mutation tests and subsequent therapeutic regimen. With the accumulation of clinical evidence on the test validity and clinical utility of EGFR mutation analysis, analysts will be able to conduct formal cost-effectiveness analyses, which help guide future reimbursement decisions on EGFR mutation analysis.

ACRONYMS AND ABBREVIATIONS

CBA	cost benefit analysis
CEA	cost effectiveness analysis
CMA	cost minimization analysis
CUA	cost utility analysis
DNS	genomic deoxyribonucleic acid
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EVPI	expected value of perfect information
EVPII	expected value of perfect partial information
FISH	fluorescent in situ hybridization
HRQL	health-related quality of life
ICER	incremental cost effectiveness ratio
IHC	immunohistochemistry
IPASS	IRESSA Pan-Asia Study
LY	life year
MCS	Monte Carlo simulation
NSCLC	non-small cell lung cancer
PCR	polymerase chain reaction
PFS	progression-free survival
QALY	quality-adjusted life year
QOL	quality of life
SCLC	small cell lung cancer
SF-6D	Short Form 6D
TKI	tyrosine kinase inhibitors
VOI	value of information

GLOSSARY

Cost-effectiveness analysis (CEA)

A type of economic analysis that compares incremental cost and outcomes of alternative interventions, where outcomes are measured as a natural unit (e.g., life year gained, death avoided)

Cost-minimization analysis (CMA)

A type of economic analysis that compares costs among interventions of interest

Cost-utility analysis (CUA)

A type of economic analysis that assesses incremental costs and outcomes, where outcomes incorporate health state preferences (e.g., quality-adjusted life year)

Deterministic sensitivity analysis

An analysis that assesses the degree of impact of changes in one or a set of fixed input parameters on overall cost-effectiveness results

EQ-5D

A generic, multi-attribute, preference-based measure of health-related quality of life. EQ-5D consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels in each dimension, describing 243 unique health states. A score of one represents perfect health defined in the EQ-5D instrument, and a score of zero represents the state of being dead.¹

European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30)

A cancer-specific, multi-attribute measure of health-related quality of life. The 30-item questionnaire consists of five functional scales (physical, role, cognitive, emotional, social), eight symptoms scales often observed in cancer patients (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea), one overall quality of life scale, and one scale measuring financial impact associated with cancer treatment. Scores in each scale range from zero to 100 with a higher score representing greater impairment. Supplementary modules specific to various cancer sites are also available.^{2,3}

Expected value of perfect information (EVPI)

A type of uncertainty analysis in economic modelling that quantifies the level of decision uncertainty by estimating opportunity cost of making an uncertain decision, given currently available information

Expected value of partial perfect information (EVPPPI)

A type of uncertainty analysis in economic modelling that quantifies the level of decision uncertainty attributable to one or a set of stochastic input parameters in economic models over total decision uncertainty

Health-related quality of life (HRQL)

'...value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy.'⁴ (p.22)

Incremental cost effectiveness ratio (ICER)

The ratio of difference in costs (i.e., incremental costs) to difference in effectiveness (i.e., incremental effectiveness).

Probabilistic analysis

A type of uncertainty analysis in economic modelling that assumes a distributional assumption to each stochastic parameter and assesses their parameter uncertainties simultaneously

Quality adjusted life years (QALYs)

Life years weighted by the degrees of decrement in quality of life associated with morbidity. QALY incorporates morbidity and mortality effects of interventions.⁵

Short Form 6D (SF-6D)

A generic, multi-attribute, preference-based measure of health-related quality of life. SF-6D consists of six dimensions (physical functioning, role limitations, social functioning, pain, mental health, and vitality) with four to six levels in each dimension, describing 18,000 unique health states. A score of one represents perfect health defined in the SF-6D instrument, and a score of zero represents the state of being dead.⁶

CONTEXT AND POLICY ISSUES:

In 2010, there will be more than 24,000 estimated new diagnoses of lung cancer, which is the second most common cancer in Canada. Lung cancer is the leading cause of cancer-related death with a five-year survival rate of approximately 15%.⁷ The two most common types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC comprising more than 80% of lung cancer diagnoses.⁷

The treatment options for patients with NSCLC, which depend on the patient's stage of disease and health status, include surgery, radiation, and chemotherapy.⁸ For advanced (stage IIIb/IV), the treatment protocols for conventional chemotherapy typically involve first-line platinum-based doublet therapy, followed by second-line treatment (docetaxel or pemetrexed) for patients who fail on platinum therapy.⁹ The treatment protocols for NSCLC may differ across Canada and are evolving to include combination-based treatment approaches and emerging therapies such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). EGFR is a protein expressed on the surface of normal cells and tumour cells that plays a role in cellular processes such as cell growth, cell differentiation, and cell motility.^{10,11} EGFR is over-expressed on a number of solid tumours including NSCLC and is often associated with a more aggressive disease and a poor prognosis.¹¹

Gefitinib (Iressa™) and erlotinib (Tarceva®) are two TKIs that are approved for use in Canada.¹² Both drugs act by competing for a binding site on the EGFR and prevent activation of the receptor and subsequent downstream events including cell proliferation and cell motility.¹³ Despite the positive expectations about these drugs in the treatment of patients with NSCLC, the clinical response to TKIs has been variable.⁸ Studies report that the responder population is often east Asian and female, with adenocarcinoma and a history of non-smoking.¹⁴ In 2004, activating mutations in the EGFR gene were identified in the TKI responder population and in other patients with NSCLC. These mutations were associated with a high responsiveness to TKIs.¹⁴

There are numerous methods to test the mutational status of the EGFR gene and include direct sequencing of genomic deoxyribonucleic acid (DNA) and polymerase chain reaction (PCR).¹⁵ Adding to the complexity, gene copy number and extent of protein expression have also been evaluated using fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC) respectively, based on an observed positive correlation between high gene copy number or protein over-expression, and the presence of activating mutations.¹⁵

Although these methods may be routine in research and pre-clinical laboratories, clinical laboratories consider additional factors including tissue sample preparation (fresh, frozen, or paraffin-embedded), technical expertise, reliability, costs, turn-around time, and presence of a quality assurance program. Moreover, it is also important that their cost-effectiveness is assessed for those methods to be subject to reimbursement under a publicly-funded health care system.

In this report, we provided an economic framework to guide future economic evaluations of EGFR mutation analysis in advanced NSCLC. There is a growing interest in the use of EGFR-TKIs as a first-line therapy, as was seen in a recent Health Canada approval of gefitinib for the first-line use to locally advanced or metastatic NSCLC with positive EGFR mutations.¹⁶

Therefore, the model developed in this report considered assessing cost-effectiveness of EGFR mutation analysis for the first-line use of gefitinib for the treatment of advanced NSCLC. A formal cost-effectiveness analysis was not performed because these methods are only used in research and pre-clinical laboratories, and clinical evidence on these mutation analyses is still accumulating. A companion CADTH rapid review report¹⁷ summarized the clinical evidence of the EGFR mutation analysis.

RESEARCH QUESTION:

How can the cost-effectiveness of epidermal growth factor receptor mutation analysis for the identification of patients with advanced non-small cell lung cancer who are likely to respond to treatment with tyrosine kinase inhibitors be assessed?

REVIEW OF ECONOMIC EVALUATIONS:

Methods

Literature search

Peer reviewed literature searches were conducted to obtain published literature for this review. The focus was on studies examining the cost effectiveness of EGFR mutation testing. All search strategies were developed by an Information Specialist with input from the project team.

The following bibliographic databases were searched through the Ovid interface: Medline, Medline In-Process & Other Non-Indexed Citations, EMBASE and Biosis Previews. Parallel searches were run in PubMed and the Cochrane Library (Issue 2, 2010). The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. A methodological filter was applied to limit the retrieval to economic studies. Appendix 1 reports the detailed search strategies.

The search was restricted to English language economic articles published between January 1, 2005 and March 16, 2010. Regular alerts were established on Medline, EMBASE and Biosis, and information retrieved via alerts was current to June 7, 2010.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialised databases. Google and other Internet search engines were used to search for additional web-based materials and information. These searches were supplemented by hand searching the bibliographies and abstracts of key papers, and through contacts with appropriate experts and agencies.

Article selection

Two independent reviewers (KA and SC) screened titles and abstracts of the retrieved publications. The same two reviewers independently evaluated the full-text publications for final article selection. Study selection criteria consisted of the following:

- Study design: cost-effectiveness analyses (CEA), cost-utility analyses (CUA), cost-minimization analyses (CMA) and cost-benefit analyses (CBA) were eligible for inclusion. CMA was selected only if justification of the use of CMA was made in the text.
- Population: Adults with advanced NSCLC considered for initial or subsequent therapy
- Intervention: EGFR mutation analysis
- Comparators: No EGFR analysis (for example, best supportive care, palliative care, chemotherapies, use of EGFR-TKI agents in unselected patients [i.e., unknown EGFR expression status])
- Outcomes: Incremental cost-effectiveness (incremental cost and incremental effectiveness). Duplicate publications (for example, a manuscript that summarized a study reported in a longer technical report) were also excluded.

SUMMARY OF FINDINGS

Appendix 2 shows a flowchart that summarizes the article selection process. The initial bibliographic database search identified a total of 40 publications. Periodical alerts (obtained between March 29 and June 7, 2010) found an additional 14 articles. Further hand searching found one study, resulting in a total of 55 citations found. Of these 55 citations, 53 were excluded after screening of titles and abstracts, and the remaining two articles^{18,19} were acquired in full text for further screening. Of these two articles, one study¹⁸ did not meet our inclusion criteria, resulting in one recent conference presentation (Arrieta et al.¹⁹) that assessed the cost-effectiveness of EGFR mutation analysis for advanced NSCLC patients being included. Among excluded studies, two articles^{18,20} may be of further interest to analysts; they are listed in Appendix 3 with brief descriptions.

Arrieta et al.¹⁹ used data from IRESSA Pan-Asia Study (IPASS)²¹ to simulate an evaluation comparing two alternative strategies for treating patients. In the first strategy, all patients receive chemotherapy doublet - carboplatin and paclitaxel. In the second strategy, all patients receive EGFR mutation testing –those who test positive for EGFR mutations will receive gefitinib, and those who test negative will receive doublet therapy. The model does not consider second and third line therapies, and therefore does not allow for potential differences in these based on the first line therapeutic option used.

Information on the probability of adverse events and progression-free survival (PFS) for each therapy were based on IPASS data.²¹ It was assumed that the proportion of patients who were EGFR mutation positive was 13% based on a review of the literature. A sensitivity analysis on test-positive rate was conducted with alternative rates of 7% and 20%. Mexican wholesale drug prices were identified, and costs of adverse events were based on a review of the literature. Costs of EGFR mutation analysis were set as US\$415.

The base-case analysis results showed that the EGFR mutation analysis strategy generated greater average lifetime costs (US\$14,833) with longer average PFS (7.57 PFS months) compared with the no-testing strategy (US\$14,177 and 7.11 PFS months), leading to the incremental cost per additional PFS month of US\$1,432 [or cost per additional PFS year of US\$17,184 (= US\$1,432 * 12 months)] compared with treating all the patients with the standard chemotherapy doublet.

Stratified analyses further assessed the cost-effectiveness of the mutation analysis among those with EGFR mutation positive patients. There seemed to be a greater survival benefit for receiving gefitinib instead of receiving the standard chemotherapy for mutation-positive patients, although this was not statistically significant within the IPASS trial. Had the mutation-positive patients not received the EGFR mutation analysis and instead been treated with carboplatin-paclitaxel doublet as the first-line therapy, the average costs would have been US\$15,978 with 8.10 PFS months. On the other hand, if they had received gefitinib following the EGFR mutation analysis, the average cost would be greater (US\$18,607) with longer PFS (11.51 PFS months), resulting in the incremental cost-effectiveness ratio (ICER) of US\$776 per additional PFS month [or cost per additional PFS year of US\$9,312] compared with no mutation analysis.

Sensitivity analyses showed that the mutation analysis was more cost-effective with higher mutation-positive rates. At the 7% and 20% mutation rates, the corresponding ICERs were US\$1,988 and US\$1,158 per additional PFS months [or cost per additional PFS year of US\$23,856 or US\$13,896], respectively.

In conclusion, the targeted therapy provided the additional 0.46 PFS months compared with providing the carboplatin-paclitaxel doublet to all the patients, resulting in the incremental cost per additional PFS year of US\$17,184. Therefore, the EGFR mutation analysis is cost-effective, if the society's threshold for cost per additional PFS year is at least US\$17,184. Moreover, clinical benefit of the targeted therapy was prominent for mutation-positive patients: the PFS gain was 3.41 months if patients with mutation positive status received gefitinib instead of the carboplatin-paclitaxel doublet as the first-line therapy.

Limitations

A limited literature search was conducted for this rapid review, and it is possible that studies not cited in the databases searched were omitted. In addition, articles published from 2005 to present and of English language were eligible for inclusion. It is acknowledged that potentially relevant evidence that was published before 2005 would have been excluded using this approach.

A number of modeling issues in the work reported by Arrieta et al.¹⁹ are important to note.

First, the primary outcome was PFS, not overall survival. Based on the IPASS study, mutation-positive patients who received gefitinib showed 62% longer PFS compared with the mutation-positive patients who received the carboplatin-paclitaxel therapy (Hazard rate [HR = 0.48, 95% confidence interval [CI] = 0.36-0.64), whereas the overall survival was 22% longer for the former group than the latter (HR=0.78, 95% CI = 0.50-1.20). Therefore, had overall survival been used as an outcome, the EGFR mutation analysis may not have appeared to be as cost-effective as it was shown in the base-case analysis.

Second, PFS data among treatment options were based on the IPASS study, which was based on patients with selected clinical characteristics (i.e., Asian origin and non-smoker [or former smokers]) that were known predictors of greater response to EGFR-TKI, PFS, and overall survival.²¹ However, those clinical characteristics were not considered as an additional screening criterion in the model developed by Arrieta et al. This means that if lower PFS rates were used in the modeling, the ICER could be greater than what was reported. The magnitude

of an increase in ICER depends on the proportion of patients with selected clinical characteristics.

Third, the impact of targeted therapy on costs and outcomes was modeled only in terms of PFS, and ignored the impact on overall survival of the choice of 2nd and 3rd line therapy. The implication is that differences in costs and outcomes during the subsequent disease progression were assumed to be comparable between strategies. This is unlikely to be the case, as the choice of first line strategy directly impacts the choice of later strategies.

Fourth, the author assumed that the expected EGFR positive mutation rate was 13% based on three observational studies²²⁻²⁴ which were conducted in various countries (Spain,²² Italy,²⁴ and multiple countries [Japan, Taiwan, the United States and Australia]²³) and consisted of patients with varying demographic and clinical characteristics. These studies found noticeable heterogeneities in the proportion of mutation-positive patients across various demographic and clinical characteristics. For example, Shigematsu²³ reported that the proportion of EGFR mutation-positive patients over the total sample in each studied country varied between 7% (Australia) and 34% (Taiwan), where all but one patient (East Asian ethnicity) studied in Australia were white and all the patients studied in Taiwan was of East Asian ethnicity. Therefore, it is important to assess whether the demographic mix and clinical characteristics assessed in these observational studies are generalizable to the target population of a particular modeling study.

Fifth, despite potential health-related quality of life (HRQL) burden associated with cancer and its treatment, the authors did not incorporate impact of disease and treatment on HRQL in the modeling.

Finally, the study was only available as a poster and not as a peer reviewed publication. Thus, only limited details of the modeling framework were available, and there exists the possibility that the study results may be revised before publication.

FRAMEWORK FOR ECONOMIC ANALYSES:

Objective, types of economic evaluation and rationale

The objective is to present a proposed economic model to assess the cost-effectiveness of EGFR mutation analysis compared with the option without EGFR mutation analysis. A framework for a decision analytic CUA (cost per quality-adjusted life year [QALY] gained) was developed to simulate the EGFR mutation analysis, disease progression, and associated treatment paths from the time of diagnosis of advanced NSCLC to death.

A CUA was proposed for two reasons. First, the objectives of cancer treatment are not only to prolong overall survival, but also to improve HRQL of patients during the course of care. This is particularly the case for patients with advanced cancer who are often on or headed toward palliative care.^{25,26} Therefore, it is important to assess whether or not alternative interventions will result in differences in mortality and HRQL. Second, cancer treatments are often accompanied by a number of serious but non life-threatening side effects. For example, an economic study comparing EGFR-TKI versus other pharmacotherapies showed that the observed differences in QALYs among interventions were mainly due to differences in

incidence, type and HRQL, of drug-related adverse events.²⁷ In assessing the treatment benefit of an intervention, it is therefore important to consider impacts of treatment on HRQL.

CEA (cost per life-year [LY] gained) may be an alternative in cases when no difference in HRQL among comparators is found (with valid justification), and/or when adequate utility scores cannot be found and adequate assumptions cannot be imposed with respect to utility scores. Justification should be provided if CUA is not used in the analyses.

The following economic framework was developed following the CADTH economic evaluation guidelines²⁸ and a recently published CADTH economic guideline on oncology products.²⁶

Modelling framework:

Population, intervention and comparator

The initial population consists of a group of adult patients diagnosed with advanced (incurable stage IIIb/IV) NSCLC. The intervention considered is EGFR mutation analysis with the use of gefitinib as the first-line therapy for those who are mutation positive, and the use of standard chemotherapy for those who are mutation negative. The comparator is no EGFR mutation analysis, in which a standard chemotherapy regimen was administered to all the patients as the first-line therapy.

Perspective

Consistent with the CADTH guidelines for economic evaluation,^{26,28} the model adopts the perspective of a publicly funded health care system. Therefore, only costs directly associated with this perspective should be considered in the reference-case analysis. A societal perspective that includes non-medical costs (e.g., transportation costs) and indirect costs (e.g., informal caregivers, lost productivity) could be considered. However, the life expectancy of advanced cancer patients is expected to be very short, and differences in non-medical costs and lost productivity between treatment strategies are likely to be small. Thus, the major cost differences between therapies are likely to be identified within the framework of a publicly funded health care system.

Time horizon

Time horizon is set as five years. The median survival for patients with incurable stage IIIb/IV NSCLC was reported to be approximately four to six months following diagnosis.²⁹ Therefore, extrapolating from a 50% survival rate at six months, only a small proportion of patients (approximately 1.5%) are expected to survive at the end of three years. However, EGFR mutation positive patients have a better prognosis, and therefore their survival rates at three years may be a higher.

Discounting

As per CADTH economic guidelines,²⁸ any future costs and outcomes incurred should be discounted at 5% at the base-case analysis; zero and 3% annual rates are used for sensitivity analyses.

Modelling

The framework uses a decision tree and Markov models to describe the EGFR mutation analysis, disease progression, and treatment sequence. The models are presented in two parts, and were constructed with advice from clinical experts. The first part consists of a decision tree describing the diagnostic testing that selects the first-line therapy, and the second part consists of Markov models describing the subsequent treatment regimens. Markov model cycle length of one month is considered in the framework considering most chemotherapies have a three to four week treatment cycle (i.e., one- to three-day chemotherapy, every three to four weeks).³⁰ In addition, it was suggested that the use of gefitinib or erlotinib should be re-evaluated at every month for the first cycle, followed by re-evaluation at least every two months.³¹

Strategy 1 [EGFR mutation analysis]: In Figure 1 under the EGFR mutation analysis strategy, a cohort of patients diagnosed with stage IIIb/IV NSCLC undergoes the EGFR mutation analysis.

For those who are EGFR mutation positive, gefitinib will be administered as the first-line therapy. Upon disease progression, they will receive a platinum-based doublet therapy as a second-line therapy (Figure 2). Upon further progression, they will receive a third-line therapy (docetaxel or pemetrexed). If the third-line therapy fails, all patients are assumed to receive palliative care until death. At any time during the disease process, patients will also face a risk of disease progression and death.

Those who were found to be EGFR mutation negative were assumed to undergo a platinum-based doublet therapy as a standard chemotherapy. Upon disease progression (Figure 3), they will receive either another chemotherapy agent (docetaxel or pemetrexed), or EGFR-TKI (erlotinib) as the second-line therapy. Upon further progression, those who received docetaxel or pemetrexed will receive erlotinib (and vice versa) as the third-line therapy.

Strategy 2 [Standard chemotherapy (no EGFR mutation analysis)]: Under the standard chemotherapy option, the standard chemotherapy will be administered to all the patients (Figure 1). Upon disease progression, all the patients will undergo the same treatment regimen as was described for the mutation-negative patients (Figure 3).

Figure 1: Decision tree

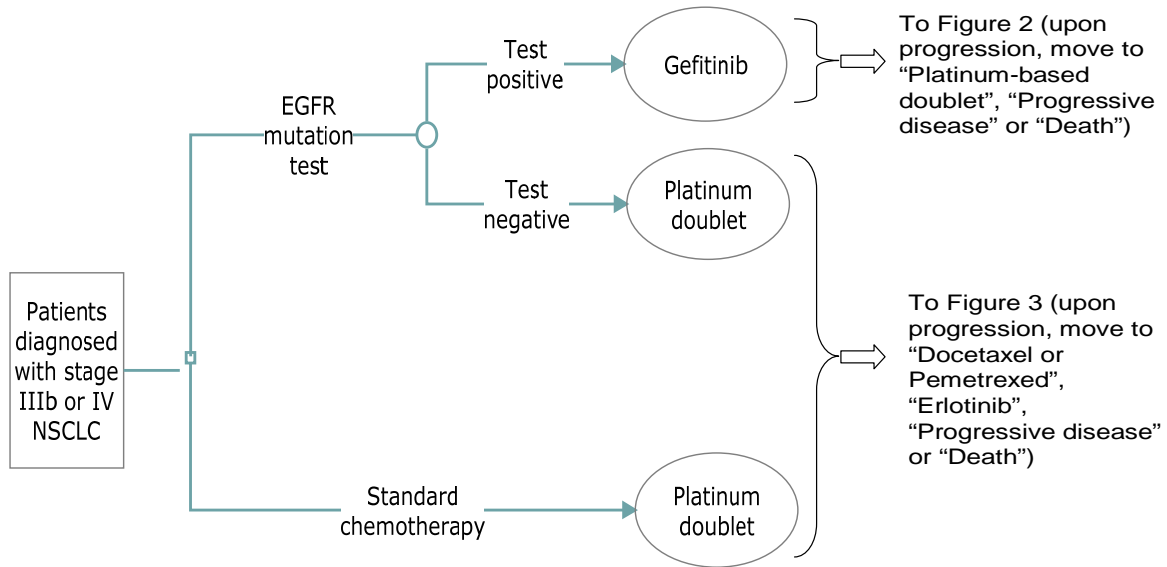


Figure 2: Markov model after gefitinib

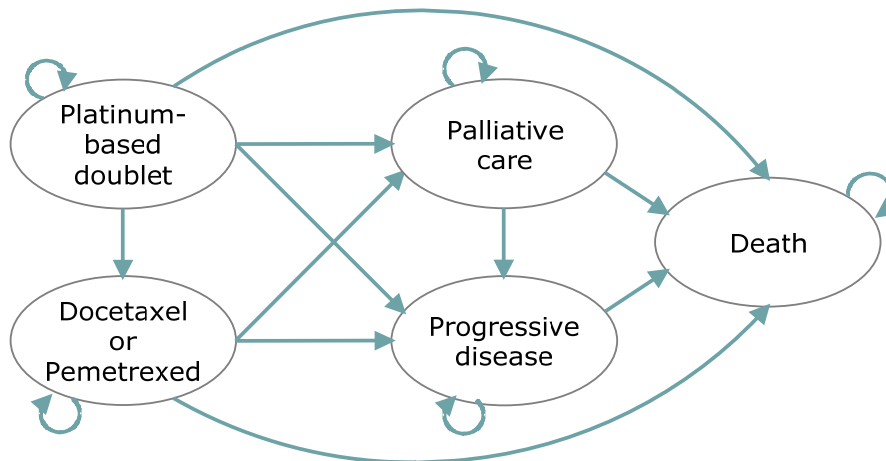
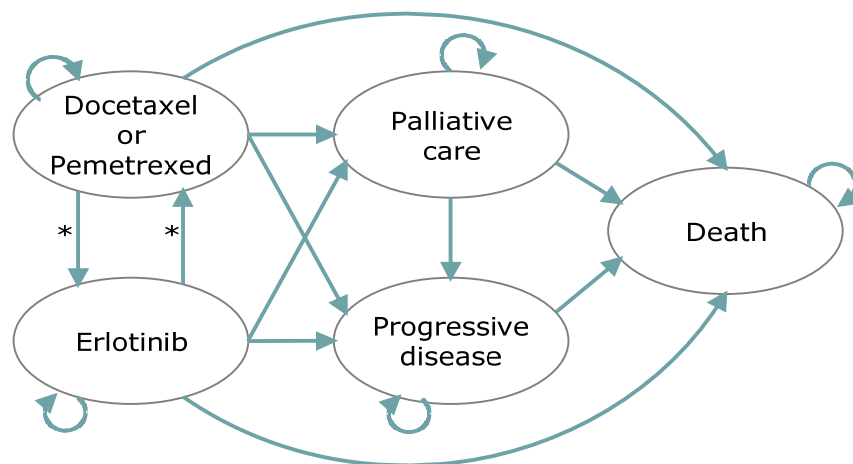


Figure 3: Markov model after platinum doublet



*Transition from “erlotinib” to “docetaxel or pemetrexed” (and vice versa) occurs only once (i.e., a cohort goes through “erlotinib” and “docetaxel or pemetrexed” states only once)

Effectiveness

In the proposed decision tree (Figure 1), information on transition probabilities required is the proportion of EGFR mutation positive patients over the total target population of patients diagnosed with advanced NSCLC. Ideally, the information is obtained from a target population in Canada. If not, non-Canadian studies need to be searched to obtain the estimate, addressing the generalizability issue of the estimates obtained from non-Canadian studies.

Given that a variety of first-line platinum-based doublet therapies is available and the therapeutic choice can vary across jurisdictions, the proportion of patients who receive each type of the doublet therapy can be based on the distribution of the doublet therapies observed in a particular jurisdiction of interest (subsequently, the treatment costs will be calculated as the weighted average costs of each type of doublet therapy). Similarly, upon the failure of the first-line therapy, the proportion of patients receiving second- and third-line therapies (Figures 2 and 3) depends on the current utilization of these therapies in each jurisdiction. If jurisdictional information is not available, a national estimate or data from the literature can be used, provided that uncertainty analyses are conducted and study implications (e.g., generalizability) are discussed.

Efficacy of pharmacotherapies can be measured as overall survival, progression-free survival, time in (partial) remission, and probability of adverse events, which will be based on results from existing clinical trials. Similar to the test performance data, any evidence in a Canadian setting is ideal. However, if clinical data is based on a population that does not correspond to the target population of an economic analysis, implications on generalizability need to be discussed. In terms of using time to event data, mean values from clinical data should be used. If not, reported survival curves should be used to calculate the mean value. If a median value is obtained, it will be transformed to a mean value and methods for the transformation should be

specified and justified.²⁶ If extrapolation is required, the appropriate methods need to be identified following CADTH guidelines²⁶ (page 25). In any instances, uncertainties around the clinical parameter estimates need to be assessed through deterministic sensitivity analyses and/or probabilistic analyses.

In the proposed model, the possibility of treatment non-adherence was not considered. However, given that the estimated non-adherence to oral medication was reported to be between 20% and 80%, it may be important to consider the level of drug adherence on ICERs, although factors associated with compliance can be complex and under-investigated in the field of oncology.³² Data permitting, the probability of non-adherence can be also incorporated at each Markov cycle.

Adverse events

Markov models presented above also incorporate costs and HRQL of potential adverse events associated with treatment. As per the CADTH oncology guidelines, adverse events that have clinical and economic impacts should be considered. Such events are typically categorized as grades III, IV, and V events.²⁶ For example, in recent economic studies,^{18,33} grades III and IV events that have occurrence greater than 5% or those requiring hospitalization were considered in the analyses. Such criteria can be considered. Carlson et al.¹⁸ assumed that adverse events (and impacts of adverse events on HRQL and costs) occurred at the beginning of the therapy and will last no longer than one month. Expected costs and disutilities (i.e., 1-utility) of adverse events should be incorporated into estimates of the costs and utilities associated with each state as the sum of costs or disutilities multiplied by the probability of adverse events.

Valuing outcomes

The outcome considered in the economic model is incremental cost per QALY gained. Therefore, life-years should be weighted by utilities for each state to obtain QALYs. Existing economic models and other published sources can be searched to identify relevant utility weights to be used in the economic analysis.

The following criteria can be considered in identifying appropriate utility scores. First, it is important that the utility weights are representative and derived from an instrument with demonstrated measurement properties, such as validity, reliability, and responsiveness for the population and health states of interest.²⁸ For instance, utility scores based on the SF-6D instrument⁶ may not be appropriate for measuring HRQL in advanced cancer patients because of the instruments' lack of ability to differentiate HRQL among severe health states compared with other HRQL instruments.³⁴⁻³⁶ Second, it is also important that, if possible, the utility weights be derived from a common elicitation method or instrument. For instance, each preference-based measure is based on different conceptual framework and is operationalized in a different way. Therefore, it is not ideal to consider them as interchangeable.³⁷ There are a growing number of studies that explore "mapping" of disease-specific measures to utility measures (also referred to as "cross-walking"; i.e., estimating utility scores from observed scores based on a disease-specific measure).³⁸⁻⁴⁰ These studies may be searched to obtain estimated scoring functions that allow the conversion of disease-specific scores to utility scores. For example, Kind and Macran⁴⁰ developed a set of utility weights that can be applied to the Functional Assessment of Cancer Therapy-Lung (FACT-L) to derive values that can be used in

economic evaluation. A further extensive literature search for available mapping studies is encouraged to identify the most appropriate scoring function.

Efforts should be made to obtain utility weights that meet the above criteria. If these criteria will not be met, justification and potential study implications should be discussed. Sensitivity analyses (at minimum, deterministic sensitivity analyses) are also of particular importance to assess uncertainty around the utility estimates.

For economic evaluations within oncology, cost utility analysis is the preferred form of analysis.²⁶ CADTH oncology guidelines suggest that cost effectiveness analysis should only be used when no differences in utility estimates between therapies are likely and when outcomes are assessed in terms of overall survival. Analysis based on surrogate outcomes or progression free survival is not recommended.

Resource use and cost

Following the proposed study perspective, types of costs under consideration are costs directly incurred by a publicly-funded health care system. Identification and valuation of costs follow CADTH guidelines.^{26,28} Identification of costs should be based on real-world utilization and practice guidelines. It is important that costs and resource use reflect Canadian clinical practice and utilization patterns. Therefore, identification, measurement and valuation of resource use will be based on Canadian sources. Costs associated with the diagnosis of NSCLC will not be included because the initial population in the economic model consists of those who were already diagnosed with stage IIIb/IV NSCLC, and they were equally incurred in each therapeutic option.

Identification of resource use: Resource use is identified and measured based on published literature and publicly available sources. Resource use includes (but is not limited to) EGFR mutation analysis, any additional resource use associated with the subsequent treatment (including follow-up tests [e.g., chest x-rays and CT scans], medication, drug administration and monitoring, outpatient visits, radiotherapy, hospitalization, hospice care-related resource use), and resource use related to treat adverse events and metastasis.¹⁸

Resource use valuation: The resource valuation will be based on publicly available data sources (e.g., claim data, hospital admissions, registry, fee schedule, costing database) and published Canadian studies. Trial-based costing data is used only if data from other sources is not available.²⁶ Costs based on Canadian sources with various reporting years should be adjusted using Canadian consumer price indices.⁴¹ If analysis is being conducted for Canada as a whole, costs obtained from a jurisdiction with the largest population should be used in a base-case analysis with sensitivity analyses using the highest and lowest costs.²⁸ If analysis is being conducted from the perspective of a specific province of jurisdiction clearly, data specific to that context would be preferable. For resource use and cost estimates that are not from Canada, issues regarding comparability of the resource use information to the Canadian clinical practice (e.g., treatment regimen, dosage, unit costs) and potential impact of the use of non-Canadian-based information on study implications should be addressed.

Variability and uncertainty

As per the CADTH economic guidelines, it is important to distinguish variability and uncertainty. Variability refers to "... the known differences in parameter values that are associated with identifiable differences in circumstances", whereas uncertainty refers to model input parameters that "... the true value of a parameter is unknown, thus reflecting the fact that knowledge or measurement is imperfect."²⁸ Therefore, variability cannot be reduced with additional information, whereas uncertainty can be reduced with the accumulation of further evidence. Both variability and uncertainty need to be assessed separately.

Stratified cost-effectiveness analyses may be considered to address potential population heterogeneity. However, such analyses are conditional on the availability of evidence with trials that are powerful enough that results are generalizable to these subpopulations.

To assess uncertainty, probabilistic analyses should be conducted using Monte Carlo Simulations (MCS) for parameters that can be defined probabilistically. Deterministic sensitivity analyses should be also conducted for other input parameters (for example, discount rates and study perspective). Analysis of extremes (for example, highest and lowest treatment costs obtained from jurisdictions, variation in drug prices) may be considered, if applicable.

Following MCS, value-of-information (VOI) analyses can be conducted.⁴² A VOI analysis quantifies the expected cost (or opportunity loss) of a decision made based on currently available but with uncertain information. The objectives of the VOI analyses in this framework are to calculate (1) the expected overall value of information based on current information, and (2) the expected value of information of each (set of) uncertain parameter(s). Expected value of perfect information (EVPI) and expected value of perfect partial information (EVPPI) analyses are conducted to assess each objective, respectively.

The choice of parameters to be investigated for EVPPI can be based on the following strategy:⁴² First, a group of parameters will be selected in a way that will be informative to policy makers. For example, all parameters relating to clinical efficacy will be assessed together so that further information may be obtained simultaneously from an observational and/or an experimental study. Similarly, other sets of parameters (for example, adverse events, costs, utilities) will be categorized as separate parameter groups. Second, if one or more groups of parameters show high EVPPI results relative to others, then EVPPI for individual parameters within a group will be assessed further. To minimize computational burden without compromising the accuracy of our study implications, the calculation of EVPPI can be based on a single-stage MCS method described by Coyle et al.⁴³ and Coyle and Oakley.⁴⁴

Discussion

The modeling framework is able to be adjusted for jurisdictional needs, allowing analysts to be flexible in modeling EGFR mutation analysis and subsequent therapeutic regimen. For example, alternative lines of therapies can be considered by replacing existing therapeutic options with any applicable alternatives, provided data availability. In the proposed framework, it was assumed that the sensitivity and specificity of the EGFR mutation analysis are 100%. Namely, the model did not incorporate false-positive and false-negative rates. If there is systematic evidence on non-negligible testing errors, testing accuracy must be considered

through sensitivity analyses of varying test accuracy rates. The more accurate EGFR mutation analysis is, the more cost-effective it will likely be, given that it will ensure that expensive chemotherapy regimens are targeted only to those who will benefit from them.

A major potential challenge in the proposed modeling study is data availability. For example, the proportion of patients receiving various combinations of platinum-doublet therapies may require an in-depth chart review of jurisdiction-specific patient records. Moreover, evidence on utilities may be lacking, which requires necessary assumptions to be made. In any case, uncertainty analyses are important to assess impacts of parameter uncertainties on study results.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

This report systematically reviewed the existing evidence on the cost-effectiveness of the EGFR mutation analysis. Our review found one preliminary cost-effectiveness study (a conference presentation),¹⁹ showing that the EGFR mutation analysis is cost-effective compared with no-testing strategy, if the society's threshold for cost per additional progression-free survival year was US\$17,184. However, the modeling structure was restrictive because (1) progression-free survival (not the overall survival) was the primary outcome, (2) impacts of therapies on HRQL were not considered, and (3) most importantly, treatment sequence was not modeled (i.e., only the intervention and the subsequent difference in progression-free survival was considered).

Given the relatively early phase of the technological development of the EGFR mutation analysis, an economic framework was developed to provide guidance for analysts in conducting future cost-effectiveness analyses on the EGFR mutation analysis. Our economic modeling framework described comprehensive decision-analytic models to assess cost-effectiveness of EGFR mutation analysis to select first-line therapies for advanced NSCLC patients. The proposed framework reflects closely the CADTH economic guideline²⁸ and the recently published CADTH oncology guidelines.²⁶ With the accumulation of clinical evidence on the test validity and clinical utility of EGFR mutation analysis, analysts will be able to conduct formal cost-effectiveness analyses, which help guide future reimbursement decisions on EGFR mutation analysis.

PREPARED BY:

Keiko Asakawa, MA (Econ), MBA, PhD, Health Economist

Doug Coyle, MSc, PhD, Professor, University of Ottawa

Stella Chen, MD, MSc, Research Officer

Michelle Mujoomdar, BSc, PhD, Research Officer

Carolyn Spry, BSc, MLIS, Information Specialist

Health Technology Inquiry Service

Email: htis@cadth.ca

Tel: 1-866-898-8439

REFERENCES:

1. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997 Nov;35(11):1095-108.
2. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993 Mar 3;85(5):365-76.
3. Erickson P. Assessing health status and quality of life of cancer patients: the use of general instruments. In: Lipscomb J, Gotay CC, Snyder C, editors. *Outcomes assessment in cancer*. Cambridge (UK): Cambridge University; 2005. p. 31-68. Chapter 3.
4. Patrick DL, Erickson P. *Health status and health policy: quality of life in health care evaluation and resource allocation*. New York: Oxford University Press; 1993.
5. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd ed. Oxford (UK): Oxford University; 2005. (Oxford medical publications).
6. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002 Mar;21(2):271-92.
7. Canadian Cancer Society's Steering Committee. *Canadian cancer statistics 2010* [Internet]. Toronto: Canadian Cancer Society; 2010. [cited 2010 Jun 16]. Available from: http://www.cancer.ca/Canada-wide/About%20cancer/Cancer%20statistics/~/_media/CCS/Canada%20wide/Files%20List/English%20files%20heading/PDF%20-%20Policy%20-%20Canadian%20Cancer%20Statistics%20-%20English/Canadian%20Cancer%20Statistics%202010%20-%20English.ashx
8. Carlson JJ, Garrison LP, Ramsey SD, Veenstra DL. Epidermal growth factor receptor genomic variation in NSCLC patients receiving tyrosine kinase inhibitor therapy: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*. 2009 Nov;135(11):1483-93.
9. Tassinari D, Carloni F, Santelmo C, Tamburini E, Agli LL, Tombesi P, et al. Second line treatments in advanced platinum-resistant non small cell lung cancer. A critical review of literature. *Rev Recent Clin Trials*. 2009 Jan;4(1):27-33.
10. Gupta R, Dastane AM, McKenna R Jr, Marchevsky AM. The predictive value of epidermal growth factor receptor tests in patients with pulmonary adenocarcinoma: review of current "best evidence" with meta-analysis. *Hum Pathol*. 2009 Mar;40(3):356-65.
11. Dahabreh IJ, Linardou H, Siannis F, Kosmidis P, Bafaloukos D, Murray S. Somatic EGFR mutation and gene copy gain as predictive biomarkers for response to tyrosine kinase inhibitors in non-small cell lung cancer. *Clin Cancer Res*. 2010 Jan 1;16(1):291-303.

12. Drug Product Database [Internet]. Ottawa: Health Canada. Drug Product Database online query; 2010 [cited 2010 May 3]. Available from: <http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>
13. Garassino MC, Borgonovo K, Rossi A, Mancuso A, Martelli O, Tinazzi A, et al. Biological and clinical features in predicting efficacy of epidermal growth factor receptor tyrosine kinase inhibitors: a systematic review and meta-analysis. *Anticancer Res.* 2009 Jul;29(7):2691-701.
14. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol.* 2010 Feb;11(2):121-8.
15. Gupta R, Dastane AM, Forozan F, Riley-Portuguez A, Chung F, Lopategui J, et al. Evaluation of EGFR abnormalities in patients with pulmonary adenocarcinoma: the need to test neoplasms with more than one method. *Mod Pathol.* 2009 Jan;22(1):128-33.
16. Notice of compliance (NOC) database [Internet]. Ottawa: Health Canada; 2008 -. Iressa; 2008 [cited 2010 May 25]. Available from: <http://205.193.93.51/NocWeb/viewnoce.jsp?noc=cioih>
17. Mujoomdar M, Moulton K, Spry C. Epidermal growth factor receptor mutation analysis in advanced non-small cell lung cancer: a review of the clinical effectiveness. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2010.
18. Carlson JJ, Garrison LP, Ramsey SD, Veenstra DL. The potential clinical and economic outcomes of pharmacogenomic approaches to EGFR-tyrosine kinase inhibitor therapy in non-small-cell lung cancer. *Value Health.* 2009;12(1):20-7.
19. Arrieta O, Anaya P, López J, Polanco AC. Cost-effectiveness analysis of EGFR mutation testing in patients with advanced non small-cell lung cancer (ANSCLC) treated with gefitinib or carboplatin-paclitaxel [Internet]. Poster presented at: 15th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); 2010 May 15-19; Atlanta, GA. [cited 2010 Jun 3]. Available from: http://www.ispor.org/research_pdfs/34/pdf/files/PCN75.pdf
20. Bradbury PA, Tu D, Seymour L, Isogai PK, Zhu L, Ng R, et al. Economic analysis: randomized placebo-controlled clinical trial of erlotinib in advanced non-small cell lung cancer. *J Natl Cancer Inst.* 2010 Mar 3;102(5):298-306.
21. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* [Internet]. 2009 Sep 3 [cited 2010 Jun 3];361(10):947-57. Available from: <http://content.nejm.org/cgi/reprint/361/10/947.pdf>
22. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* [Internet]. 2009

- Sep 3 [cited 2010 May 28];361(10):958-67. Available from:
<http://content.nejm.org/cgi/reprint/361/10/958.pdf>
23. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J Natl Cancer Inst* [Internet]. 2005 Mar 2 [cited 2010 Jun 3];97(5):339-46. Available from:
<http://jnci.oxfordjournals.org/cgi/content/full/97/5/339?view=long&pmid=15741570>
 24. Marchetti A, Martella C, Felicioni L, Barassi F, Salvatore S, Chella A, et al. EGFR mutations in non-small-cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. *J Clin Oncol* [Internet]. 2005 Feb 1 [cited 2010 May 3];23(4):857-65. Available from: <http://jco.ascopubs.org/cgi/reprint/23/4/857>
 25. Carlson JJ. Erlotinib in non-small-cell lung cancer: a review of the clinical and economic evidence. *Expert Rev Pharmacoecon Outcomes Res*. 2009 Oct;9(5):409-16.
 26. Mittmann N, Evans WK, Rocchi A, Longo CJ, AU HJ, Husereau D, et al. Addendum to CADTH's guidelines for the economic evaluation of health technologies: specific guidance for oncology products [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009. [cited 2010 Jun 3]. Available from:
http://www.cadth.ca/media/pdf/H0405_Guidance_for_Oncology_Products_gr_e.pdf
 27. Carlson JJ, Reyes C, Oestreicher N, Lubeck D, Ramsey SD, Veenstra DL. Comparative clinical and economic outcomes of treatments for refractory non-small cell lung cancer (NSCLC). *Lung Cancer*. 2008 Sep;61(3):405-15.
 28. Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada [Internet]. 3rd ed. Ottawa: CADTH; 2006 Mar. [cited 2010 Jun 3]. Available from:
http://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf
 29. Lamont EB. Survival estimates in advanced cancer. 2009 [cited 2010 Jun 3]. In: UpToDate [Internet]. Version 17.3. Waltham (MA): UpToDate; c2005 - . Available from:
www.uptodate.com Subscription required.
 30. Lilenbaum RC. Patient information: non-small cell lung cancer treatment; advanced unresectable, metastatic (stage IV), and recurrent cancer. 2009 [cited 2010 Jun 3]. In: UpToDate [Internet]. Version 17.3. Waltham (MA): UpToDate; c2005 - . Available from:
www.uptodate.com Subscription required.
 31. Feld R, Sridhar SS, Shepherd FA, Mackay JA, Evans WK, Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: a systematic review. *J Thorac Oncol*. 2006 May;1(4):367-76.
 32. Horgan A, Feld R, Leighl NB. Gefitinib: a consideration of cost. *Expert Rev Pharmacoecon Outcomes Res*. 2008;8(3):223-32.

33. Ramsey SD, Clarke L, Kamath TV, Lubeck D. Evaluation of erlotinib in advanced non-small cell lung cancer: impact on the budget of a U.S. health insurance plan. *J Manag Care Pharm* [Internet]. 2006 Jul [cited 2010 Jun 3];12(6):472-8. Available from: http://amcp.org/data/jmcp/form_472-478.pdf
34. Fryback DG, Palta M, Cherepanov D, Bolt D, Kim JS. Comparison of 5 health-related quality-of-life indexes using item response theory analysis. *Med Decis Making*. 2009 Oct 20.
35. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Econ*. 2004 Sep;13(9):873-84.
36. Feeny DH. The roles for preference-based measures in support of cancer research and policy. In: Lipscomb J, Gotay CC, Snyder C, editors. *Outcomes assessment in cancer*. Cambridge (UK): Cambridge University; 2005. p. 69-92. Chapter 4.
37. McDonough CM, Grove MR, Tosteson TD, Lurie JD, Hilibrand AS, Tosteson AN. Comparison of EQ-5D, HUI, and SF-36-derived societal health state values among spine patient outcomes research trial (SPORT) participants. *Qual Life Res* [Internet]. 2005 Jun [cited 2010 Jan 6];14(5):1321-32. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2782497/pdf/nihms141430.pdf>
38. Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the cancer-specific EORTC QLQ-C30 to the preference-based EQ-5D, SF-6D, and 15D instruments. *Value Health*. 2009 Jun 25.
39. McKenzie L, van der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D instrument: the potential to estimate QALYs without generic preference data. *Value Health*. 2009 Jan;12(1):167-71.
40. Kind P, Macran S. Eliciting social preference weights for Functional Assessment of Cancer Therapy-Lung health states. *Pharmacoeconomics*. 2005;23(11):1143-53.
41. Consumer price index, by province (monthly). 2009 [cited 2010 Jun 3]. In: Statistics Canada: summary tables [Internet]. Ottawa: Statistics Canada; c2009 - . Available from: <http://www40.statcan.gc.ca/l01/cst01/cpis01a-eng.htm>.
42. Briggs AH, Claxton K, Sculpher MJ. *Decision modelling for health economic evaluation*. Oxford (UK): Oxford University; 2006. (Handbooks in health economic evaluation series).
43. Coyle D, Coyle K, Vale L, de Verteuil R, Imamura M, Glazener C, et al. Minimally invasive arthroplasty in the management of hip arthritic disease: systematic review and economic evaluation [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2008. [cited 2010 Jun 3]. (Technology report number 102). Available from: http://www.cadth.ca/media/pdf/336_Invasive-Arthroplasty-Man-Hip-Arthritic-Disease_tr_e.pdf
44. Coyle D, Oakley J. Estimating the expected value of partial perfect information: a review of methods. *Eur J Health Econ*. 2008 Aug;9(3):251-9.

APPENDIX 1: Literature search strategy

OVERVIEW	
Interface:	Ovid
Databases:	EMBASE <1996 to 2010 Week 10>
	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <March 16, 2010>
	BIOSIS Previews <1989 to 2010 Week 14>
	Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 16, 2010
Alerts:	Biweekly search updates began March 16, 2010 and ran until June 7, 2010.
Study Types:	Economic studies
Limits:	Publication years 2005 – March 16, 2010 English

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
use	select only Medline results
prmz	
use	select only EMBASE results
emef	
use	select only Biosis results
b10o89	

Multi-database Strategy	
Line #	Search Strategy
1	Carcinoma, Non-Small-Cell Lung/ or NSCLC.ti,ab.
2	(exp Adenocarcinoma/ or Carcinoma, Large Cell/ or exp Carcinoma, Squamous Cell/ or adenocarcinoma*.ti,ab.) and (lung* or pulmonary).ti,ab.
3	((non-small cell lung or nonsmall cell lung) and (neoplasm* or cancer* or carcinoma*

or tumor* or tumour*).ti,ab.
4 ((large cell or squamous or bronchoalveolar or bronchiolo alveolar) and (neoplasm* or
cancer* or carcinoma* or tumor* or tumour*) and (lung* or pulmonary)).ti,ab.
5 or/1-4
6 *Lung non small cell cancer/ or NSCLC.ti,ab.
7 (*Adenocarcinoma/ or *Large cell carcinoma/ or *Squamous cell carcinoma/ or
adenocarcinoma*.ti,ab.) and (lung* or pulmonary).ti,ab.
8 6 or 7 or 3 or 4
9 NSCLC.ti,ab,hw.
10 ((non-small cell lung or nonsmall cell lung) and (neoplasm* or cancer* or carcinoma*
or tumor* or tumour*).ti,ab,hw.
11 (adenocarcinoma* and (lung* or pulmonary)).ti,ab,hw.
12 ((large cell or squamous or bronchoalveolar or bronchiolo-alveolar) and (neoplasm* or
cancer* or carcinoma* or tumor* or tumour*) and (lung* or pulmonary)).ti,ab,hw.
13 or/9-12
14 Receptor, Epidermal Growth Factor/ or exp Genes, erbB/ or EC 2-7-1-112.rn. or
(EGFR or epidermal growth factor receptor* or EGF receptor* or urogastrone
receptor* or transforming growth factor alpha receptor* or TGF alpha receptor* or erbB
or erbB1 or erbB-1 or erbB2 or erb 1 or erb 2 or HER1 or HER 1 or HER 2 or HER2 or
neu).ti,ab.
15 *Epidermal growth factor receptor/ or EC 2-7-1-112.rn. or (EGFR or epidermal growth
factor receptor* or EGF receptor* or urogastrone receptor* or transforming growth
factor alpha receptor* or TGF alpha receptor* or erbB or erbB1 or erbB-1 or erbB2 or
erb 1 or erb 2 or HER1 or HER 1 or HER 2 or HER2 or neu).ti,ab.
16 EC 2-7-1-112.cb. or (EGFR or epidermal growth factor receptor* or EGF receptor* or
urogastrone receptor* or transforming growth factor alpha receptor* or TGF alpha
receptor* or erbB or erbB1 or erbB-1 or erbB2 or erb 1 or erb 2 or HER1 or HER 1 or
HER 2 or HER2 or neu).ti,ab,hw.
17 *Pharmacogenetics/ or (pharmacogenomic* or pharmacogenetic* or personali?e*
medicine or personali?e* treatment* or personali?e* therap* or individuali?e*
treatment* or individuali?e* therap* or target* therap*).ti.
18 *Pharmacogenetics/ or *Pharmacogenomics/ or (pharmacogenomic* or
pharmacogenetic* or personali?e* medicine or personali?e* treatment* or personali?e*
therap* or individuali?e* treatment* or individuali?e* therap* or target* therap*).ti.

- (pharmacogenomic* or pharmacogenetic* or personali?e* medicine or personali?e* treatment* or personali?e* therap* or individuali?e* treatment* or individuali?e* therap* or target* therap*).ti.
- 19
- 20 5 and (14 or 17)
- 21 8 and (15 or 18)
- 22 13 and (16 or 19)
- 23 20 use prmz
- 24 21 use emef
- 25 22 use b10o89
- 26 or/23-25
- 27 limit 26 to english language
- 28 limit 27 to yr="2005 -Current"
- 29 28
- 30 remove duplicates from 28
- 31 *Economics
- 32 Exp "costs and cost analysis"/
- 33 (sensitivity analysis or sensitivity analyses).ti,ab.
- 34 (cost or costs or costing or cost-effective\$).ti,ab.
- 35 or/31-34
- 36 30 and 35

OTHER DATABASES

PubMed	Same MeSH, keywords, limits, and study types used as per Medline search, with appropriate syntax used.
Cochrane Library	Same MeSH, keywords, and date limits used as per Medline search, excluding study types. Syntax adjusted for Cochrane Library databases.

Issue 2, 2010

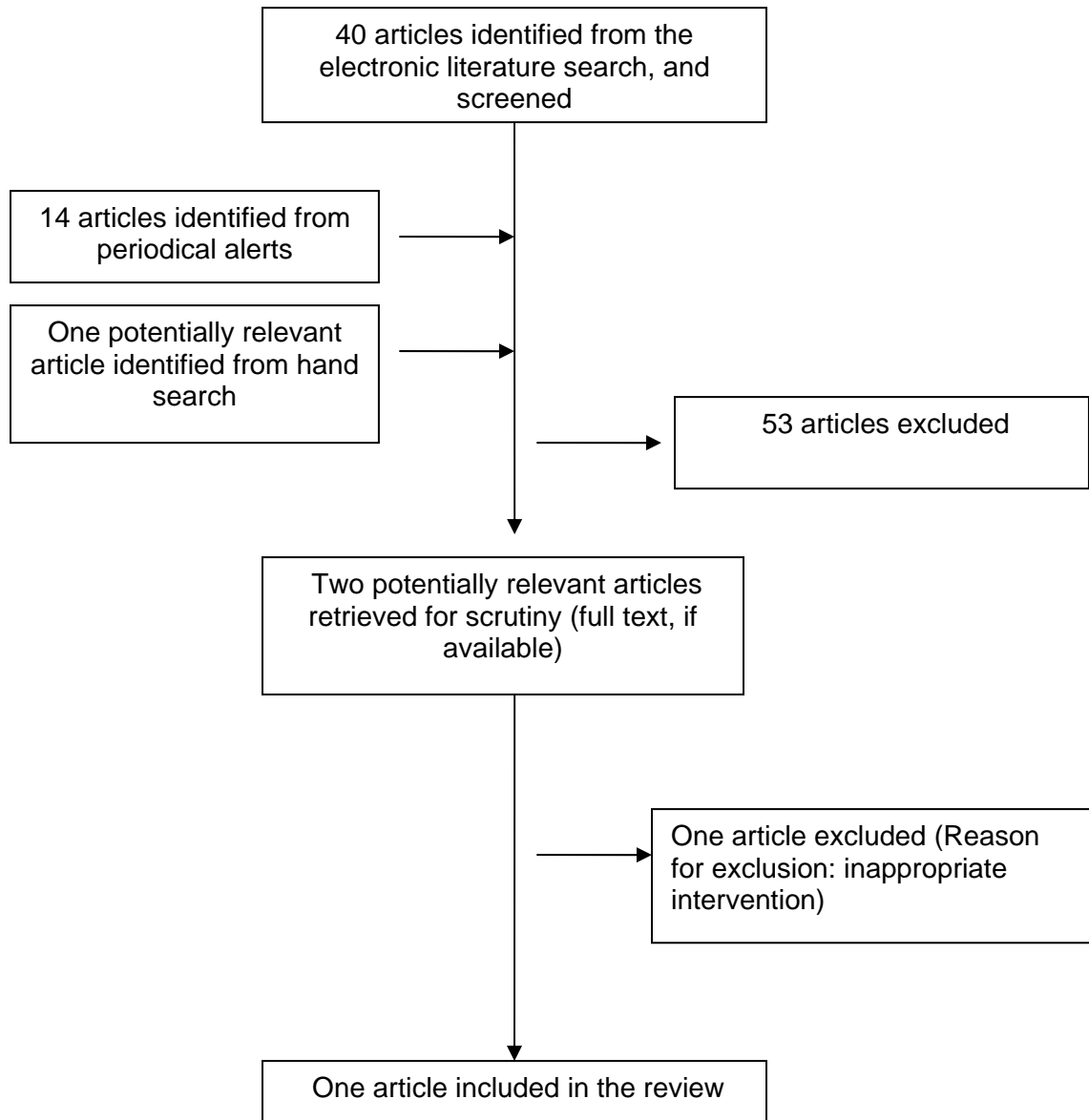
Grey Literature

Dates for Search:	March 15 – 19, 2010
Keywords:	Non small cell lung cancer, epidermal growth factor receptor, polymerase chain reaction.
Limits:	Publication years 2005 – March 19, 2010

The following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based searching” (<http://www.cadth.ca/index.php/en/cadth/products/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Databases (free)
- Internet Search
- Open Access Journals

APPENDIX 2: Selection of Publications



APPENDIX 3: Additional papers of interest

Bradbury PA, Tu D, Seymour L, Isogai PK, Zhu L, Ng R, et al. Economic analysis: randomized placebo-controlled clinical trial of erlotinib in advanced non-small cell lung cancer. *J Natl Cancer Inst.* 2010 Mar 3;102(5):298-306.

- Contains subgroup cost-effectiveness analyses by mutation status

Carlson JJ, Garrison LP, Ramsey SD, Veenstra DL. The potential clinical and economic outcomes of pharmacogenomic approaches to EGFR tyrosine kinase inhibitor therapy in non-small-cell lung cancer. *Value Health* 2009;12(1):20-7.

- CEA (cost per LY gained) and CUA (cost per QALY gained) were conducted to assess cost-effectiveness of EGFR testing (IHC or FISH) for the second-line therapy of refractory NSCLC.
- The comparators were (1) EGFR testing by IHC followed by erlotinib if test positive and docetaxel if test negative, (2) EGFR testing by FISH followed by erlotinib if test positive and docetaxel if test negative and (3) standard care (erlotinib until progression)