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Cost-Effectiveness of Epidermal Growth Factor Receptor Gene Mutation Testing For Patients with Advanced Non-Small Cell Lung Cancer Living in Ontario.

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Table of Contents

Executive Summary

Background: About 20% of patients with non-small cell lung cancer (NSCLC) have an epidermal growth factor receptor (EGFR) gene mutation on exon 19 to 21. Recently, NSCLC patients with an EGFR gene mutation were found to respond to EGFR tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib. EGFR gene mutation testing has been suggested to guide the treatment with TKIs.

Objective: The purpose of this study is to assess the cost-effectiveness of EGFR gene mutation testing for the selection of gefitinib as first-line therapy in patients with advanced NSCLC who are residents in Ontario.

Methods: A decision analytic model was developed to compare the lifetime benefits (life years and quality-adjusted life years (QALY)) and direct medical costs in 2010 Canadian dollars between the strategy of EGFR gene mutation testing and the strategy of no EGFR gene mutation testing in patients with advanced NSCLC (stage 3b or 4). Under the strategy of EGFR gene mutation testing, tumour tissues taken by biopsy were assessed to detect any mutation of EGFR gene from exon 19 to 21. Patients with EGFR gene mutations would receive gefitinib daily as first-line therapy, platinum based chemotherapy (cisplatin plus gemcitabine) as second-line therapy, and docetaxel or pemetrexed as third-line therapy before BSC. Patients without EGFR gene mutation would receive cisplatin plus gemcitabine as first-line therapy, docetaxel or pemetrexed as second-line therapy, and best supportive care (BSC). The other patients whose EGFR gene mutation status remained unknown after the testing (due to inadequate tissue or other technical limitations) would be treated with the combination of cisplatin and gemcitabine as first-line, docetaxel or pemetrexed as second-line, and erlotinib as third-line before BSC. *For the no testing strategy,* all patients would not be assessed for EGFR gene mutations. Patients would receive cisplatin and gemcitabine as first-line, docetaxel or pemetrexed as second-line, and erlotinib as third-line before BSC. The Markov cohort model was constructed to reflect the natural history of advanced NSCLC and the patterns of care for patients with advanced NSCLC in Ontario starting from first-line therapy. The cycle length of the Markov cohort model was 3 weeks. Literature review was conducted to estimate probability variables including distribution of squamous cell carcinoma, prevalence of EGFR gene mutation, failure rate of EGFR gene mutation testing, efficacy of treatments (gefitinib as first-line therapy, cisplatin and gemcitabine as first-line therapy, docetaxel as second-line therapy, pemetrexed as second-line therapy in patients with non-squamous cell carcinoma, erlotinib as third-line therapy, and BSC). A formula derived from a multivariate linear regression analysis was applied to estimate the utility of patients with advanced NSCLC according to the distributions of clinical

responses after treatment and side-effects associated with treatment. Two cost studies estimating direct medical costs for patients with advanced NSCLC in Ontario were the data source for the cost variables. The analytic perspective in this study was the Ontario Ministry of Health and Long-Term Care (MOHLTC). Both benefits and costs (Canadian dollars in 2010) were discounted at 5% per annum. The base case analysis was conducted by using the baseline values of the variables in the model. One-way sensitivity analyses were conducted to identify the main variables affecting the cost-effectiveness of EGFR gene mutation testing. Probabilistic sensitivity analyses were also conducted to assess the relative percentage cost-effectiveness of EGFR gene mutation testing under different willingness to pay (WTP) values. A budget impact analysis was also performed to illustrate the changes of future health care expenditure on patients with advanced NSCLC in Ontario after the adaption of EGFR gene mutation testing.

Results: Under the strategy of no EGFR gene mutation testing, the average lifetime benefit associated with patients with advanced NSCLC was 0.4842 life years or 0.2881 QALY; the average lifetime direct medical cost spent on patients was $14,368. Under the strategy of EGFR gene mutation testing, the average lifetime benefit collected for patients with advanced NSCLC was 0.5383 life years or 0.3188 QALY; the average lifetime direct medical cost consumed by patients was $16,857. Compared to the strategy of no testing, the incremental cost-effectiveness ratio (ICER) for EGFR gene mutation testing was $46,021 per life year or $81,071 per QALY. The one-way sensitivity analyses indicated that cost of care, cost of gefitinib, transition probability per cycle to progressive disease, and transition probability to death per cycle for patients under the treatment with gefitinib could increase the ICER of EGFR gene mutation testing over $10,000 per QALY; Daily cost of erlotinib and the cost of care for patients under the treatment with cisplatin and gemcitabine could decrease the ICER of EGFR gene mutation testing over $10,000 per QALY. Probabilistic sensitivity analysis suggested that the proportions of simulations in which EGFR gene mutation testing was cost-effective under the WTP of $50,000 and $100,000 were 5.2% and 56.1% respectively. Budget impact analysis projected that EGFR gene mutation testing in Ontario would cost MOHLTC $4.6M, $7.0M, $7.9M, $8.1M, and $8.1M more a year from 2011 to 2015, respectively, when compared to the current practices without testing.

Conclusion: Applying EGFR gene mutation testing to guide the use of gefitinib as first-line therapy for patients with advanced NSCLC will be cost-effective if WTP is above $81,000 per QALY. The cost-effectiveness of EGFR gene mutation testing is sensitive to the efficacy and cost of gefitinib.

Overview

Study Question

About 20% of patients with non-small cell lung cancer (NSCLC) have an epidermal growth factor receptor *(*EGFR) gene mutation on exon 19 to 21(1-2). Recently, NSCLC patients with an EGFR gene mutation were found to respond to EGFR tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib (3-4). Therefore, EGFR gene mutation testing has been used to identify EGFR gene mutation status in patients with advanced NSCLC to guide the selection of first-line therapy and avoid the use of expensive EGFR TKIs among those patients without mutation. The study question was whether applying EGFR gene mutation testing to guide the selection of gefitinib as first-line therapy among patients with advanced NSCLC living in Ontario was cost-effective when compared to no testing.

Economic Analysis

A decision analytic model was developed to compare the lifetime benefits (life years and quality-adjusted life years (QALY)) and direct medical costs in 2010 Canadian dollars between the strategy of EGFR gene mutation testing and the strategy of no EGFR gene mutation testing in patients with advanced (stage 3b or 4) NSCLC. Under the strategy of EGFR gene mutation testing, tumour material from patients' biopsies is assessed for mutations on exon 19 to 21 of EGFR gene. The patients having EGFR gene mutations would receive gefitinib as first-line therapy, followed by conventional chemotherapy. The patients having no EGFR mutations or undetermined mutation status were managed by conventional chemotherapy. For the no testing strategy, chemotherapy was offered as per the no EGFR mutation group. The base case analysis was conducted using the baseline values of the variables in the model. Sensitivity analyses were conducted to explore uncertainty associated with the variables in the model. A budget impact analysis was also performed to illustrate the changes of future health care expenditure on patients with advanced NSCLC in Ontario after the adaption of EGFR gene mutation testing.

Background

Economic Literature Review

A comprehensive search of the main medicine related database (MEDLINE and EMBASE) was conducted to identify any economic studies assessing EGFR gene mutation testing for patients with advanced NSCLC up to July 2010. The search was conducted with the following single or combined key words related to the disease (non-small cell lung cancer, lung cancer, NSCLC, non-squamous cell carcinoma, squamous cell carcinoma, adenocarcinoma, bronchoalveolar, and large cell carcinoma), EGFR gene mutation testing *(*epidermal growth factor receptor, EGFR, gene,

mutation), and health economics (Markov, cost, cost-effectiveness, cost-effective, cost-utility, cost-benefit, cost-minimization, utility, quality adjusted life year, and QALY. No economic studies were found related to the application of EGFR gene mutation testing for patients with advanced NSCLC.

For the purpose of developing the framework of this health economic evaluation study, the health economic studies related to advanced NSCLC were searched and reviewed. Through the key words for the disease and the terminology for health economic evaluation, a total of seven health economic studies were identified for patients with NSCLC: 4 studies for cost-utility analysis (CUA)(5-8), 1 study for cost-effectiveness analysis (CEA) (9), 1 economic impact study(10), and 1 cost-minimization study(11). Among these seven studies, four studies assessed drug treatment for advanced NSCLC, one study assessed radiotherapy for stage 1 NSCLC, and two studies assessed image methods for detecting recurrence of cancer after curative treatment and staging the disease before surgical treatment (Table 1). Six studies(5-7, 9-11) reported details regarding the structure of the Markov model in the full publications (Table 2). The six studies have some inconsistencies in the cycle length, time horizon, health states, and discounting rates in the model. The cycle length ranged from one week to one year, the time horizon for the model varied from 1 year to five years, and discounting rate changed from 0% to 4%. Three studies(9-11) disregarded the discounting because only 4–6% of patients have been described to survive for more than 2 years(12-14). Most of studies described health states applied to Markov model. The common health states in the six studies include clinical response status to treatment, progressive status, and vital status.

These seven studies applied different approaches and date sources to estimate variables for probability, utility, and cost in the model (Table 3). Only one study(11) conducted systematic review to collect data for the estimation of probability variables. The other studies made the estimations for probability through the evidence from one trial or single cohort of patients. Among the four studies for cost-utility analysis, two studies(6-7) applied the utility data derived from cross-sectional survey, one study(5) estimated the utility according to a societal valuation study of 100 participants rating health states through standard gamble technique with the consideration of the side effects associated with treatment, and one study(9) estimated the utility for patients with advanced NSCLC through an algorithm that considered both tumour response status and toxicities under the treatment. All seven studies estimated the costs under the perspective of local health care system or health insurance payer. Two studies(5, 10) used bottom-up method to estimate health resource utilization through chart review, three studies(6-7, 11) applied unit cost based on cost research, one study(9) used administrative database to estimate health care expenditure for a population including over 70,000 patients with a possible lung cancer, and one study(8) did

not give any information regarding the cost data source.

All seven studies conducted one-way sensitivity analysis to explore the possible uncertainty associated with variables in the model. However, only three studies(5-7) performed probabilistic sensitivity analysis to report the range of outcomes under the overall uncertainty in the model.

In summary, only one study(9) was considered high quality among these identified seven health economic evaluation studies for patients with NSCLC because the study had the shortest cycle length (one week), included complete health states reflecting the history of the disease, and used reliable methods to estimate the variables for probability, utility, and cost.

Methodology

Target Population

The study population for this cost-effectiveness analysis were Ontario patients having a diagnosis of advanced NSCLC (Stage IIIb or IV) who had not received any first-line therapy with conventional chemotherapy for TKIs.

Perspective

The cost-effectiveness analysis was conducted under the perspective of Ontario Ministry of Health and Long-Term Care (MOHLTC).

Comparators

According to the study framework (Figure 1), the cost-effectiveness analysis compared the following two strategies:

1. *EGFR gene mutation testing*: under this strategy, all patients were assumed to have tumour sample embedded in paraffin after previous biopsy for histological evaluation of NSCLC. The tumour sample was sent to the public laboratory in Ontario to assess the mutation status of exon 19 to 21 on EGFR gene. Patients with any mutation on the exon 19 to 21 were considered positive for EGFR gene mutation. The patients tested positive for EGFR gene mutation would follow Scenario 1 to be treated with gefitinib daily as first-line therapy, platinum based chemotherapy (cisplatin plus gemcitabine) as second-line therapy, and docetaxel (for squamous cell carcinoma) or pemetrexed (non-squamous cell carcinoma) as third-line therapy before BSC. For those patients who were tested negative for EGFR gene mutation, Scenario 2 would be followed by treating patients with platinum based chemotherapy as first-line therapy, docetaxel or pemetrexed as second-line therapy, and BSC as palliative care. The failure rate for current approach used for EGFR gene mutation testing is about 20% due to inadequate tissue or other technical problems. The patients with failed EGFR gene mutation testing would follow Scenario 3 like the patients under the strategy of no testing.

2. *No EGFR gene mutation testing*: all patients would not be assessed for their EGFR gene mutation status. The patients will follow Scenario 3 to receive the combination of cisplatin and gemcitabine as first-line therapy, docetaxel or pemetrexed as second-line therapy, and erlotinib as third-line therapy before BSC.

Time Horizon

The time horizon set up in the Markov cohort model for the cost-effectiveness analysis was life-time in length. In another words, the Markov model would follow up the defined study population until all patients deceased.

Discounting

The cost-effectiveness analysis discounted both benefits and direct medical costs at 5% per annum by following the guideline made by The Canadian Agency for Drugs and Technologies in Health (CADTH) for health economic evaluation studies in Canada.

Model Structure

The decision analytic model was constructed as a decision making tree that included three Markov models reflecting the defined three scenarios under the compared two strategies. The three Markov cohort models were constructed by following the natural history of advanced NSCLC, the patterns of care for advanced NSCLC in Ontario, and the defined three scenarios under the two strategies. In order to be consistent with the duration for the cycle for conventional chemotherapy in patients with advanced NSCLC, the three models set 3 weeks as the cycle length.

The health states in the three Markov cohort models included vital status, treatment status, ongoing treatment status for each included therapy, and clinical response after each included therapy. In addition, the three Markov cohort models set up 4 cycles (three weeks per cycle) as the number of cycles for the conventional chemotherapy (cisplatin and gemcitabine, docetaxel, and pemetrexed) for patients with advanced NSCLC by following the clinical guidelines. The three Markov model assumed that the patients under the oral treatment with gefitinib or erlotinib received the treatment daily until the disease became progressive or patients dropped out due to side effects.

The structures of the three Markov models for the defined three scenarios were illustrated in the Figure 2.

Outcomes

The decision analytic model collected the lifetime benefits (life years and QALY) and lifetime direct medical costs for the hypothetic cohort of patients with advanced NSCLC under the strategy of EGFR gene mutation testing and the strategy of no testing respectively. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in benefits (life years for cost-effectiveness analysis and QALY for cost-utility analysis)

between the two strategies with the difference in lifetime cost between the compared two strategies.

Resource Use and Costs

Since this cost-effectiveness analysis was conducted under the perspective of the MOHLTC, the decision analytic model included health resources utilization for patients with advanced NSCLC under the two strategies during their lifetime follow-up. The cost for EGFR gene mutation testing was estimated at $500 by the public laboratory in Toronto. The unit price for each drug applied in the decision analytic was based on its retail price in the pharmacy store in the Princess Margaret Hospital, which is specialized on oncology in the downtown of Toronto. A systematic search of Medline and EMBASE was conducted to identify any cost studies reporting the health resources utilization for patients with advanced NSCLC in Ontario in order to perform the cost-effectiveness analysis under the perspective of MOHLTC. The systematic search identified two studies which were used as the data source to estimate the health resources utilization in patients with advanced NSCLC living in Ontario. One cost study(15) traced the direct medical costs associated with 204 patients with advanced NSCLC who were included in a randomized clinical trial comparing docetaxel with BSC. This study classified the medical costs by medication for inpatient, medication for outpatient, hospitalization, investigation, outpatient visits, radiotherapy, and community care. Based on the reported mean cost and mean survival time for the patients, the mean cost per week for patients under the treatment with docetaxel and BSC was calculated (Table 4). Because the increased survival time for patients treated with docetaxel was as short as 2 months, the costs of general care excluding the cost for docetaxel and the cost for managing the side effects related to docetaxel were assumed to be the same as the cost of general care for patients under BSC. The difference in the mean medical costs between the two groups of patients was considered as the cost for managing the side effects related to docetaxel. Therefore, the costs for patients under the treatment with docetaxel were classified into the types of cost: cost of docetaxel, cost of managing the side effects related to docetaxel, and the cost of general care. There were no cost studies for patients under the treatment with the combination of cisplatin and gemcitabine, and pemetrexed. This study assumed that patients under chemotherapy had the same cost of general care as the patients under BSC and had the same cost of managing side effects related to chemotherapy as the patients under the treatment with docetaxel. The other one cost study(16) compared the patients under the treatment of erlotinib as third-line therapy with the patients under BSC in terms of health resources utilization (Table 5). Similar with the approach for estimating direct medical costs in patients treated with docetaxel, the cost of general care for patients treated with erlotinib was assumed to be the same as the cost of general care for patients under BSC. The cost of managing the side

effects related to erlotinib was assumed to be the difference in mean cost between the two groups. The cost of general care and the cost of managing side effects related to treatment for patients under the treatment with gefitinib were assumed to be the same as those costs for patients treated with erlotinib in this study due to the lack of data. All estimated costs based on the two cost studies were adjusted to 2010 Canadian dollars using the Statistics Canada Consumer Price Index (CPI) for Ontario (Table 6).

The direct medical costs applied to the decision analytic model were summarized below:

- *EGFR gene mutation testing*: According to the Laboratory Genetics at the University Health Network, it costs $500 per test for the assessment of EGFR gene mutation status.
- *Treatment with gefitinib per cycle*: the drug cost was $1514 at the dose of 250 mg daily. The cost for general care was assumed to be the same as the general care cost for patients taking erlotinib, which was estimated at $540 (15).
- *Treatment with the combination of cisplatin and gemcitabine per cycle*: according to the average doses of cisplatin (80 mg/m^2 at day 2) and gemcitabine (1250 mg/m^2 at days 1 and 8) per cycle and an average body surface area of 1.75 m^2, the total cost of the combination was $492. Treatment and general care costs were assumed to be the same as the costs for treating patients with docetaxel, which were estimated at $453 for treatment-related costs and $582 for general care (16).
- *Treatment with docetaxel per cycle*: according to an average dose of docetaxel (75 mg/m^2) per cycle and average body surface area (as above), the total drug cost was $1499.33. The costs related to treatment and general care were estimated at $453 and $582, respectively.
- *Treatment with pemetrexed per cycle*: according to an average doses of pemetrexed (500 mg/m^2) per cycle and average body surface area (as above), the total drug cost was $4865. The costs related to treatment and general care were assumed to be the same as those for patients treated with docetaxel, which were estimated at $453 for treatment-related costs and $582 for general care.
- *Treatment with erlotinib per cycle*: the cost of the drug was $1698 at a dose of 150 mg daily. The cost for general care for patients under the treatment with erlotinib was estimated at $540.
- *Best supportive care per cycle*: The cost for BSC was estimated at $582.

Parameter Estimates

The decision analytic model for conducting the cost-effectiveness analysis in this study included three types of variables: probability, utility, and cost. The estimations in health resources utilization for patients with advanced NSCLC were described in the section of Resources and Costs. The parameter estimates for the variables of probability and utility in the

decision analytic model were described in this section.

According to the structure of the decision analytic model for cost-effectiveness analysis, this study estimated the following probability variables:

- *Distribution of squamous cell carcinoma in patients with advanced NSCLC*: According to the Canadian Cancer Registry 1992 to 2007, 63,199 cases out of 274,013 patients diagnosed with NSCLC were squamous cell carcinoma (17). The proportion of squamous cell carcinoma in patients with NSCLC in Canada was estimated at 23.1%, with a 95% confidence interval (CI) from 22.9% to 23.2%.

- *Prevalence of EGFR gene mutation in patients with NSCLC*: There were no data reporting the prevalence of EGFR gene mutation in the population of advanced NSCLC in Ontario. Therefore, MEDLINE and EMBASE were searched for any population based study reporting the prevalence of EGFR gene mutation in patients with NSCLC in a country or area having similar ethnicity patterns of residents. One Spanish study was identified. The study screened EGFR gene mutation in 2105 patients with NSCLC in 129 institutions in Spain from April 2005 through November 2008. The prevalence of EGFR gene mutation was reported at 16.6% (95% CI: 15.0% to 18.2%)(1).
- *Failure rate of EGFR gene mutation testing*: Because the EGFR gene mutation testing was conducted in the public laboratory in Ontario, the published Ontario studies involved with EGFR gene mutation testing were searched. One Ontario study assessing the molecular predictors for the clinical response to erlotinib reported 32.3% (95% CI: 27.1% to 37.5%) of cases fail due to inadequate tissue and 1.8% (95% CI: 0% to 3.9%) of cases fail due to other reasons for EGFR gene mutation testing(18).
- *Efficacy of treatments (Table 7, 9, 11, 13, 15, 17)*: The treatments in the decision analytic model included oral taking gefitinib as first-line therapy in patients with EGFR gene mutation, conventional chemotherapy (the combination of cisplatin and gemcitabine as first-line therapy, docetaxel for squamous cell carcinoma and pemetrexed for non-squamous cell carcinoma as second-line therapy), oral taking erlotinib as third-line therapy, and BSC as palliative care for patients with advanced NSCLC. Because of the difficulties in finding randomized clinical trials (RCT) directly comparing the treatments described above in the patients with advanced NSCLC, the efficacy of those treatments were estimated by meta-analysis of single arm of RCTs which assessed the treatments included in the decision analytic model. MEDLINE, EMBASE, and the Cochrane Library were searched up to July 2010 to identify any RCTs assessing gefitinib as first-line therapy in patients with EGFR gene mutation and advanced NSCLC, the combination of cisplatin and gemcitabine as first-line therapy in patients with advanced NSCLC irrespective of EGFR gene mutation

status, docetaxel as second-line therapy for patients with advanced NSCLC, pemetrexed as second-line therapy for patients having advanced non-squamous cell carcinoma type NSCLC, erlotinib as third-line therapy for all types of advanced NSCLC, and BSC as palliative care in patients with advanced NSCLC. Meta-analyses were performed to estimate hazard ratio (HR) for both progressive disease and death using the trial arms from identified RCTs, which had the same treatment in similar patient populations. The estimated HR for being progressive disease for patients under each treatment was converted to transition probability per cycle. The HR for death in patients under each treatment was converted to probability of survival per cycle using survival function formula: $S(t) = exp(- \mathrm{HR}(t))$. The outcomes of meta-analysis were summarized below:

- Gefitinib as first-line therapy in patients with EGFR gene mutation (2 RCTs with 202 patients) (19-20): HR for progressive disease per cycle: 0.0529 (95% CI: 0.0293 to 0.0938); HR for death per cycle: 0.0170 (95% CI: 0.0059 to 0.0478).
- Cisplatin and gemcitabine as first-line therapy in patients with advanced NSCLC (25 RCTs with 4148 patients) (19, 21-44): HR for progressive disease per cycle: 0.0982 (95% CI: 0.0886 to 0.1111); HR for death per cycle: 0.0513 (95% CI: 0.0447 to 0.0588).
- Docetaxel as second-line therapy in patients with advanced NSCLC (15 RCTs with 1853 patients) (45-59): HR for progressive disease per cycle: 0.1888 (95% CI: 0.1625 to 0.2182); HR for death per cycle: 0.0748 (95% CI: 0.0636 to 0.0877).
- Pemetrexed as second-line therapy in patients with non-squamous cell carcinoma type NSCLC (2 RCTs with 578 patients) (50, 60): HR for progressive disease per cycle: 0.1900 (95% CI: 0.1601 to 0.2241); HR for death per cycle: 0.0706 (95% CI: 0.0524 to 0.0947).
- Erlotinib as third-line therapy in patients with advanced NSCLC irrespective of EGFR gene mutation (2 RCTs with 513 patients) (61-62): HR for progressive disease per cycle: 0.2340 (95% CI: 0.2000 to 0.2730); HR for death per cycle: 0.0773 (95% CI: 0.0571 to 0.1038).
- Best supportive care (31, 63-72) (11 RCTs with 1333 patients): HR for death per cycle: 0.1132 (95% CI: 0.0970 to 0.1318).

- Utilities for patients with advanced NSCLC: The disease, the response after treatment, and the side effects of treatment could significantly affect the quality of life in patients with advanced NSCLC.

One study (73) conducted multivariate linear regression analysis by taking the utility of patients with advanced NSCLC as the independent variable and calculating the intercept and coefficients for covariates, including the response after treatment and common side-effects caused by treatments to derive a formula (Utility = 0.6532 – 0.1792*progressive% + 0.0193*response% + 0*stable% - 0.08973*neutropenia% - 0.09002*febrile neutropenia% – 0.07346*fatigue% - 0.04802*nausea & vomiting% - 0.0468*diarrhoea% – 0.04495*hair loss% - 0.03248*rash%) to estimate the utility of patients with advanced NSCLC before, under, and after chemotherapy. The utilities for the health states in the decision analytic model were estimated by the formula combined with the clinical response to each treatment and the main side effects associated with each treatment (Table 8, 10, 12, 14, 16) was based on the formula. The clinical response to each treatment and the main side effects associated with each treatment were estimated through the meta-analyses of the RCTs identified for estimating the efficacy of each treatment. The utilities applied to the decision analytic model were summarized below (Table 18):

- Patients with EGFR gene mutation under the treatment with gefitinib as first-line therapy (2 RCTs with 202 patients): 0.5698.
- Patients under the treatment with cisplatin and gemcitabine as first-line therapy (25 RCTs with 4148 patients): 0.5353.
- Patients after the treatment with cisplatin and gemcitabine as first-line therapy (25 RCTs with 4148 patients): 0.6166.
- Patients under the treatment with docetaxel as second-line therapy (15 RCTs with 1853 patients): 0.4537.
- Patients after the treatment with docetaxel as second-line therapy (15 RCTs with 1853 patients): 0.5704.
- Patients with non-squamous cell carcinoma under the treatment with pemetrexed as second-line therapy (2 RCTs with 578 patients): 0.5362.
- Patients with non-squamous cell carcinoma after the treatment with pemetrexed as second-line therapy (2 RCTs with 578 patients): 0.5865.
- Patients under the treatment with erlotinib as third-line therapy (2 RCTs with 513 patients): 0.4798.
- Patients under best supportive care (11 RCTs with 1333 patients): 0.4734.

Sensitivity Analysis

One-way sensitivity analyses were conducted to explore the impact of each

variable with 95% CI or plausible range on ICER in the cost-utility analysis. Probabilistic sensitivity analyses (PSA), which was able to explore overall uncertainty introduced by variables in the decision analytic model, was performed through Monte Carlo simulation with 20,000 trials and the distributions of variables in the model (beta distribution for probability variables and utility variables; gamma distribution for cost variables). We presented the results of PSA through the relationship between the proportion of cost-effectiveness of EGFR gene mutation testing for patients with advanced NSCLC and willingness-to-pay (WTP) which ranged from $0 to $100,000 per QALY.

Results

The base case analysis was conducted by applying the parameter point estimates (baseline values) in the decision analytic model for the two analyses of interest (both cost-effectiveness analysis (CEA) and cost-utility analysis (CUA)), calculating the incremental cost per life year gained (CEA) (Table 19) and the incremental cost per QALY gained (CUA) (Table 20).

- *Under the strategy of no EGFR gene mutation testing*, the average lifetime benefit associated with patients with advanced NSCLC was 0.4842 life years or 0.2881 QALY; the average lifetime direct medical cost spent on patients was $14,368.
- *Under the strategy of EGFR gene mutation testing*, the average lifetime benefit collected for patients with advanced NSCLC was 0.5383 life years or 0.3188 QALY; the average lifetime direct medical cost consumed by patients was $16,857.

Compared to the strategy of no EGFR gene mutation testing, the ICER for the strategy of EGFR gene mutation testing was $46,021 per life year or $81,071 per QALY.

One-way sensitivity analysis was conducted to explore the impact of varying the range of each variable in the model by its 95% CI, or by increasing/decreasing the baseline value by 50% (Table 21). Note that the latter was done only for variables without a reported 95% CI.

The one-way sensitivity analyses indicated that the ICER of EGFR gene mutation testing could increase over $10,000 per QALY based on the range in values of the following variables:

- *Cost of EGFR gene mutation testing*: ICER increased $12, 387 when the variable ranged from $250 to $750.
- *Cost of medical care for patients taking gefitinib as first-line therapy*: ICER increased $33,016 when the variable ranged from $270 to $810.
- *Probability of disease progression per cycle in patients taking gefitinib as first-line therapy*: ICER increased $35,937 when the variable ranged from 0.0289 to 0.0895.
- *Probability of death per cycle in patients taking gefitinib as first-line therapy*: ICER increased $67,588 when the variable ranged from 0.0059 to 0.0467.
- *Cost of gefitinib per day*: ICER increased $92,586 when the variable ranged from $36.06 to $108.17.

Furthermore, one-way sensitivity analyses indicated that the ICER of EGFR gene mutation testing could decrease over $10,000 per QALY by varying the range of the following variables:

- *Cost of erlotinib per day*: ICER decreased $16,866 when the variable ranged from $40.43 to $121.29.
- *Cost of medical care for patients taking cisplatin and gemcitabine*: ICER decreased $18,052 when the variable ranged from $517.50 to $1552.50.

A PSA was also performed by varying the values of all variables based on certain distributions as a means to explore the impact of overall uncertainty on the ICER of EGFR gene mutation testing. A Monte Carlo simulation with 20,000 trials was run to generate the mean and 95% credible intervals for both benefits and lifetime direct medical costs associated with patients with advanced NSCLC under the two strategies (Table 22).

The PSA projected that the average life years, QALY, and lifetime medical costs were 0.469 years (95% CI 0.387 to 0.562), 0.276 years (95% CI 0.223 to 0.337), and $13,543 (95% CI $6,081 to $23,533) for patients under the strategy of no EGFR gene mutation testing and 0.522 years (95% CI 0.421 to 0.670), 0.305 years (95% CI 0.242 to 0.392), and $16,067 (95% CI $8,741 to $25,866) for patients under the strategy of EGFR gene mutation testing respectively.

In addition, a cost-effectiveness acceptability curve was generated to explore the association between WTP per QALY and the percentage cost-effectiveness of EGFR gene mutation testing. The proportions of simulations in which EGFR gene mutation testing was cost-effective under the WTP of $50,000 and $100,000 were 5.2% and 56.1% respectively (Figure 3).

According to lung cancer clinical experts, erlotinib has been used as third or fourth-line therapy for patients with NSCLC irrespective of their EGFR gene mutation status in Ontario. Therefore, a supplementary analysis was conducted by allowing all patients (EGFR gene mutation positive, negative, undetermined) to receive erlotinib after the failure of docetaxel or pemetrexed under the strategy of EGFR gene mutation testing in the decision analytic model. After the modifications, a base case analysis was conducted by applying the baseline value of the variables in the model. Compared to the strategy of no testing, the ICER for the strategy of EGFR gene mutation testing was $45,338 per life year or $81,807 per QALY.

Budget Impact Analysis

Budget impact analyses were conducted to explore the distribution of lifetime direct medical costs projected by the decision analytic model for patients with advanced NSCLC under the two strategies. The annual cost was projected by aggregating health care expenditures on newly diagnosed patients with advanced NSCLC from 2011 to 2015 in Ontario. Based on the estimated incidence of lung cancer in Canada in 2010

by the Canadian Cancer Society (57 per 100,000) (74), and the proportion of advanced NSCLC (50%) among patients with lung cancer (75-76), the estimated number of newly diagnosed advanced NSCLC cases in Ontario in 2010 was estimated at 3,535; the general population in Ontario reported by the 2006 Canada Census was used in this calculation (77).

By assuming that the yearly incidence of advanced NSCLC in Ontario from 2011 to 2015 would be the same as that in 2010, and EGFR gene mutation testing was performed once for any newly diagnosed patients with advanced NSCLC from 2011 to 2015, the projected annual direct medical costs for advanced NSCLC patients under the strategy of EGFR gene mutation testing would be $4.6M, $7.0M, $7.9M, $8.1M, and $8.1M more than that for patients under the strategy of no testing in the next five years (2011 to 2015) (Table 23).

The distribution of the differences in annual direct medical costs from 2011 to 2015 between the patients with advanced NSCLC under the two strategies were plotted to identify the main contributors for the increased budget associated with EGFR gene mutation testing (Figure 4). The plot demonstrated that the cost of gefitinib contributed to over 90% of the increase of budget in patients under the strategy of EGFR gene mutation testing.

Discussion

This cost-effectiveness analysis applied the latest clinical evidence regarding the efficacy of gefitinib in the patients with EGFR gene mutation and advanced NSCLC to assess potential benefits and health resources utilization associated with EGFR gene mutation testing in Ontario patients with advanced NSCLC under the perspective of MOHLTC. The results of this cost-effectiveness analysis did not look very promising for EGFR gene mutation testing by showing the ICER per QALY over $81,000 and several potential factors which could make EGFR gene mutation testing even less cost-effective. First, the efficacy of gefitinib on advanced NSCLC patients with EGFR gene mutation was based on two Japanese studies with relatively small sample size. The patients under the treatment with gefitinib had 3 to 5 months longer for median progression free survival time than the patients under conventional chemotherapy. The observed small benefits could be easily influenced by the random errors due to small sample size and other bias related to quality of RCTs(78-79). Second, there are no clinical studies assessing the efficacy of gefitinib in advanced NSCLC patients with EGFR gene mutation in a western country which has similar patterns of ethnicity with the population in Ontario. Therefore, caution is needed when conducting the cost-effectiveness analysis using the evidence that might not be applicable to the local study population. The results of this type of cost-effectiveness analysis should be used for identifying future research needs rather than for policy decision making. Third, due to the lack of data, this cost-effectiveness analysis assumed that the efficacy of conventional chemotherapy on patients

with EGFR gene mutation who failed with gefitinib was the same as the efficacy of conventional therapy as first-line therapy. This assumption might overestimate the cost-effectiveness of EGFR gene mutation testing because the clinical evidence has clearly indicated shorter survival time in patients receiving second-line therapy when compared to patients receiving first-line therapy(80). Therefore, this cost-effectiveness analysis should be interpreted carefully and the risk of overestimating the cost-effectiveness of EGFR gene mutation testing is existing.

The one-way sensitivity analyses clearly indicated that the efficacy and cost of gefitinib were the main factors affecting the cost-effectiveness of EGFR gene mutation testing. This finding was not out of our expectation as the main difference for patients under EGFR gene mutation testing was the introduction of gefitinib as first-line therapy. Since gefitinib costs $72 a day for each patient, applying gefitinib as first-line therapy would greatly increase the total budget as the population at the time to receive first-line therapy would be much larger and have longer life expectancy than the population at the time to receive third-line therapy, when gefitinib is normally prescribed in current practices. This was confirmed by the budget impact analysis, which indicated about $8 million increase on the annual budget for patients with advanced NSCLC in the next five years if EGFR gene mutation was introduced in Ontario. The distribution of costs in the budget impact analysis suggested that gefitinib contributed to over 90% of the increased annual budget. This further addressed the needs of future research to clarify the true benefits of gefitinib in advanced NSCLC patients with EGFR gene mutation.

Even though the supplemental analysis did not show any significant change of the cost-effectiveness of EGFR gene mutation testing when patients received erlotinib as third-line therapy irrespective of their EGFR gene mutation status, the current practices might need another cost-effectiveness analysis to evaluate the needs of EGFR gene mutation testing to guide the selection of erlotinib, another TKI, as third-line therapy. EGFR gene mutation testing would be very cost-effective if it could reduce the use of expensive erlotinib in current practices in over 80% of patients who do not EGFR gene mutation(1).

There were several limitations in this study due to the lack of data. First, the current patterns of chemotherapy in Ontario patients with advanced NSCLC have never investigated. The selection of conventional chemotherapy applied to the decision analytic model was based on the expert's opinion. Second, the utility variables in this study were estimated from a formula derived from multivariate regression analysis for patients with NSCLC in order to differentiate the quality of life in patients by clinical response and toxicities associated with drugs. This approach has not been proven to be valid. Third, the health resources utilization for patients with advanced NSCLC was based on two randomized clinical trials for docetaxel and

erlotinib respectively. The cost estimated from RCT might be different from the expenditure in the real world(81). In addition, this study assumed that other chemotherapy in the decision analytic model was the same as docetaxel in terms of managing side effects related to treatment. This assumption could lead to underestimate the cost-effectiveness of EGFR gene mutation as docetaxel causes more side effects when compared to pemetrexed(50) or the combination of cisplatin and gemcitabine(82).

Conclusion

Applying EGFR gene mutation testing to guide the use of gefitinib as first-line therapy for patients with advanced NSCLC is cost-effective if the willingness to pay above $81,000 per QALY.

The cost-effectiveness of EGFR gene mutation testing is sensitive to the efficacy and cost of gefitinib.

The use of erlotinib after the failure of docetaxel or pemetrexed in patients with known EGFR gene mutation status does not affect the cost-effectiveness of EGFR gene mutation testing.

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Exhibits

Tables

Table 1. The characteristics of the identified health economic studies for patients with NSCLC.

Study ID	Country	Type	Study population	Comparison	Cost perspective	Currency
Asukai 2010	Spain	CUA	Advanced or metastatic NSCLC (predominantly non-squamous histology)	Pemetrexed versus docetaxel.	Spanish health care system	Euro
Grutters 2010	Netherlands	CUA	Stage I NSCLC	Stage I NSCLC, carbon-ion and proton therapy versus	Dutch health care system	Euro
van Loon 2010	Netherlands	CUA	NSCLC patients after curative intent therapy	Image methods 3 months after the curative treatment: PET-CT	Dutch health care system	Euro
Klein 2009	USA	CEA	advanced NSCLC regardless of histologic	Pemetrexed Plus Cisplatin versus Cis/Gem, Carb/Pac, and	U.S. payer perspective	U.S. dollar
Kee 2010	UK	CUA	NSCLC referred for surgery	FDG-PET scan versus mediastinoscopy to biopsy	U.K. NHS	U.K. Pound
Chouaid 2007	France	Economic impact analysis	Refractory NSCLC	Gefitinib	French health care payer	Euro
Le Lay 2007	UK	Cost-minimisation analysis	Patients with NSCLC ready for first-line	Oral vinorelbine versus intravenous chemotherapy	U.K. NHS	Pound

Table 2. The structure of Markov model applied to the identified health economic studies for patients with advanced NSCLC.

Study	Cycle length	Time horizon	Health states	Discounting rate for benefits	Discounting rate for costs
Asukai 2010	3 weeks	3 years	Response, progression, adverse events, death	3%	3%
Grutters 2010	1 year	5 years	Alive andwhether they had grade 3 or higher irreversible dyspnoea;Intermediate states were used to represent acute adverse events (pneumonitis or oesophagitis grade 3 or more or treatment-related death) in the first six	1.50%	4.00%
van Loon 2010	6 months	5 years	No evidence of disease, progression without treatment, progression with palliative treatment or progression with curative treatment, death	1.50%	4%
Klein 2009	3 weeks	2 years	Complete response, partial response, stable disease, and progressive disease	None	None
Kee 2010	No information	No information	Berthelot 2000	No information	No information
Chouaid 2007	3 months	2 years	First-line treatment, second- or third-line treatment, remission after respectively first-	None	None
Le Lay 2007	1 week	52 weeks	Induction, Remission with or without dose reduction, Drop-Out, Progression, Death.	None	None

Table 3. Summary of the data sources used by the identified health economic studies for patients with NSCLC.

Study ID	Probability variables	Utility variables	Cost variables
Asukai 2010	Efficacy of intervention: JMEI trial. Median overall survivalto determine the risk of death in the progression state. Adverse events: only include Grade 3/4 from the JMEI study. Mortality associated with febrile neutropenia: a review of 23 studies. Treatment discontinuations: Adverse events and patients' wishes.	A societal valuation study of 100 participants rating health states (Stable, Response and Progression) using the standard gamble technique. A decrement in utility was also obtained for each of the adverse events, which are then applied to the health states.	Chemotherapy Related Costs: Chemotherapy unit costs (1.7 m2), pre-medication, laboratory tests, and administering the chemotherapy (less than 2 hours). Adverse events costs: a weighted average of AE costs in four settings: inpatient including hospitalization costs, outpatient, daycare, and no treatment based on expert's opinion. Best Supportive Care Costs: during active treatment, post treatment and progression, terminal/palliative care costs.
Grutters 2010	Published studies that reported survival data on CRT, SBRT, proton therapy and carbon-ion therapy, the 2- and 5-year overall and disease-specific survival, the occurrence of adverse events.	A cross-sectional survey on NSCLC patients treated with curative intent.	Unit costs based on the Dutch manual for cost research.
van Loon 2010	A prospective study with 100 patients was used to estimate the efficacy of imagine methods The probability of progression after 3 months was from a prospective study. Percentages of patients receiving 2nd and 3rd line chemotherapy were from a retrospective chart review of 417 patients with advanced NSCLC.	Utility was derived from a cross-sectional study.	The Dutch Health Insurance Board.The costs for first line chemotherapy. Costs associated with side effects were from the National Institute forClinical Excellence; The costs associated with dying werea study by Kommer and Polder.
Klein 2009	A clinical trial in patients with advanced NSCLC. Survival and response rate targets for Carb/Pac and Carb/Pac/Bev were calculated by applying relative risks obtained from the indirect comparison.	Utility values were calculated using an algorithm for advanced NSCLC that considered both tumor response status and toxicities.	Premedication, administration of chemotherapy, laboratory monitoring, treating common adverse events, subsequent therapies, direct care for disease-related morbidity, and end-of-life care were based on 74,053 patients with a possible lung cancer diagnosis from January 2002 to September 2007.
Kee 2010	A cohort of patients diagnosed with NSCLC in Scotland in 1995.	75 patients undergoing staging investigation for NSCLC.	No information
Chouaid 2007	Consecutive patients who received gefitinib for at least 1 month as part of a compassionate-use program (thirdlinetreatment) in six public-sector teaching hospitals in France.	No information	Hospitalization costs were assessed on a per diem basis (national unit cost scale for each event) for fixed costs. Nursing, care, ward supplies, pharmacy,diagnostic tests, laboratory tests and professional services were determined retrospectively by chart review.
Le Lay 2007	A literature search from 1990 to 2004 including Medline, Embase, Pascal, Database of Abstracts of Review of Effectiveness, NHS Economic Evaluation Database, and Health Technology Assessment databases.	Not applicable	Acquisition costs for IV agents were from the British National Formulary; hospitalisation and transportation to and from hospital; costs of managing specific grade 3 and 4 toxicities were from publications

Table 4. The summary of the direct medical costs in the cost study reporting health resources utilization for patients with advanced NSCL treated with docetaxel as second-line therapy or BSC.

Classification of direct medical costs	Docetaxel	BSC	Docetaxel (cost/week)	BSC (cost/week)
Medication: inpatient	$296	$200	$8	$5
Medication: outpatient	$695	$506	$19	$14
Investigations	$1,517	$1,315	$42	$36
Hospitalization*	$7,196	$2,527	$198	$69
Outpatient visits	$877	$703	$24	$19
Radiation therapy	$1,028	$1,044	$28	$29
Community care	$968	$752	$27	$21
Total	**$12,577**	**$7,047**	**$346**	**$194**

Table 5. The summary of the direct medical costs in the cost study reporting health resources utilization for patients with advanced NSCL treated with erlotinib as third-line therapy or BSC.

Classfication of direct medical costs	Erlotinib	BSC	Erlotinib (costs/week)	BSC (costs/week)
Diagnostic tests	$1,056	$837	$29	$28
Outpatient visits	$623	$477	$17	$16
Concomitant	$307	$159	$9	$5
Management of	$70	$6	$2	$0
Hospitalizations	$2,525	$2,562	$70	$87
Radiation therapy	$69	$109	$2	$4
Red blood cell	$79	$34	$2	$1
Total	**$4,729**	**$4,184**	**$131**	**$141**

Table 6. Summary of estimated cost variables applied to the decision analytic model.

Type of treatment	Dose of drugs	Unit cost for drugs	Types of costs per cycle (3 weeks)		
			Drugs	Management for treatment	General management
Gefitinib as first-line therapy	250 mg/day	$72.11 per 250mg	$1,514.31	NA	$540.00
Cisplatin and gemcitabine as first-line therapy	gemcitabine 1250mg/m^2 (days 1 and 8) plus cisplatin 80mg/m^2 (day 2) per cycle	$62 per gram for gemcitabine;$78.75 per 50mg for cisplatin	$491.75	$453.00	$582.00
Docetaxel as second-line therapy	75 mg/m^2 per cycle	$913.88 per 80mg	$1499.33	$453.00	$582.00
Pemetrexed as second-line in non-squamous NSCLC	500mg/m^2 per cycle	$2780 per 500mg	$4865.00	$453.00	$582.00
Erlotinib as third-line therapy	150mg/day	$80.86 per 150mg	$1,698.06	NA	$540.00
Best supportive care	NA	NA	NA	NA	$582.00

Table 7. The efficacy of gefitinib as first-line therapy in patients with EGFR gene mutation and advanced NSCLC.

Study	Intervention	Control	Sample size for gefitinib group	Sample size for control group	Progression-free survival (median, months) for gefitinib	HR for progression per three weeks for gefitinib	Overall survival (median, months) for gefitinib	HR for death per three weeks for gefitinib
Mitsudomi 2010	Gefitinib(250 mg/day, orally)	Cisplatin (80mg/m2) and Docetaxel (60mg/m2, 21 days for	88	89	9.2	0.05651	30.9	0.01682
Maemondo 2010	Gefitinib(250 mg/day, orally)	carboplatin–paclitaxel	114	114	10.4	0.04999	30.5	0.01704
Point estimation with 95% CI (Meta-analysis)	NA	NA	NA	NA	NA	0.05292, 0.02928 to 0.09381	NA	0.01695, 0.00587 to 0.04778

Table 8. The clinical response and side effects associated with gefitinib as first-line therapy in patients with EGFR gene mutation and advanced NSCLC.

Study ID		Clinical response (%)			Side effects (%)						
	Sample size	Responsive	Stable	Progressive	Neutropenia	Febrile Neutropenia	Fatigue	Nausea & vomiting	Diarrhoea	Hair loss	Rash
Mitsudomi 2010	88	62.10%	31.00%	6.90%	7.95%	0.00%	38.64%	17.05%	53.41%	9.09%	84.09%
Maemondo 2010	114	73.70%	15.80%	9.60%	6.14%	0.00%	10.53%	14.91%	34.21%	0.00%	71.05%
Point estimation with 95% CI (Meta-analysis)	NA	0.6837, 0.6157 to 0.7447	0.2333, 0.1786 to 0.2987	0.0852, 0.0536 to 0.1328	0.0698, 0.0418 to 0.1145	NA	0.2626, 0.2008 to 0.3354	0.1587, 0.1145 to 0.2158	0.4280, 0.3603 to 0.4986	0.0756, 0.0389 to 0.1418	0.7603, 0.6951 to 0.8153

Table 9. The efficacy of the combination of cisplatin and gemcitabine as first-line therapy in patients with advanced NSCLC.

Study ID	Intervention	Control	Sample size for intervention group	Sample size for control group	Progression-free survival (median, months) for intervention	Hazard rate for progression per 3 weeks for intervention	Overall survival (median, months) for intervention	Hazard rate for death per three weeks for intervention
Alberola 2003	Cisplatin plus gemcitabine	cisplatin and vinorelbine	182	188	Not reported	NA	9.3	0.0559
Brodowicz 2006	Cisplatin plus gemcitabine	CG+ maintenance gemcitabine	68	138	Not reported	NA	11	0.0473
Cardenal 1999	Cisplatin plus gemcitabine	etoposide with cisplatin	69	66	Not reported	NA	8.7	0.0598
Ceribelli 2003	Cisplatin plus gemcitabine	CG (different schedule)	57	55	Not reported	NA	13	0.0400
Chang 2008	Cisplatin plus gemcitabine	vinorelbine	34	39	Not reported	NA	12.9	0.0403
Crinò 1999	Cisplatin plus gemcitabine	mitomycin, ifosfamide, and mesna plus cisplatin	155	152	Not reported	NA	8.6	0.0694
Grigorescu 2007	Cisplatin plus gemcitabine	gemcitabine plus vinorelbine	51	50	Not reported	NA	9.7	0.0536
Hsu 2008	Cisplatin plus gemcitabine	gemcitabine and epirubicin	41	39	Not reported	NA	13.2	0.0394
Kim 2006	Cisplatin plus gemcitabine	etoposide plus cisplatin	40	42	Not reported	NA	18.3	0.0284
Liao 2008	Cisplatin plus gemcitabine	gemcitabine	51	49	4.9	0.1061	12.1	0.0430
Martoni 2005	Cisplatin plus gemcitabine	VNR plus CP	135	137	8	0.0650	11	0.0473
Ohe 2006	Cisplatin plus gemcitabine	cisplatin and vinorelbine	146	145	3.5	0.1485	14	0.0371
Paz-Ares 2006	Cisplatin plus gemcitabine	CG plus aprinocarsen	328	342	5.2	0.1000	10.4	0.0500
Pereira 2007	Cisplatin plus gemcitabine	CG-30min	33	31	5.2	0.1000	7.5	0.0693
Reck 2009	Cisplatin plus gemcitabine	CG plus low-dose bevacizumab	347	345	6.1	0.0852	Not reported	NA
Ricci 2000	Cisplatin plus gemcitabine	CG (cisplatin on Day 15)	42	40	6	0.0866	10	0.0520
Rinaldi 2000	Cisplatin plus gemcitabine	CG (cisplatinon day 2)	45	43	Not reported	NA	15.4	0.0338
Rubio 2009	Cisplatin plus gemcitabine	gemcitabine and docetaxel	55	50	5.4	0.0963	8.9	0.0584
Sandler 2000	Cisplatin plus gemcitabine	cisplatin	260	262	Not reported	NA	9.1	0.0571
Scagliotti 2002	Cisplatin plus gemcitabine	paclitaxel and carboplatin	205	204	Not reported	NA	9.8	0.0510
Scagliotti 2008	Cisplatin plus gemcitabine	cisplatin and pemetrexed	839	830	5.1	0.1019	10.3	0.0505
Syrigos 2010	Cisplatin plus gemcitabine	cisplatin plus pemetrexed	634	618	Not reported	NA	10.12	0.0514
Wachters 2003	Cisplatin plus gemcitabine	epirubicin	119	121	6.5	0.0800	10.75	0.0484
Zatloukal 2003	Cisplatin plus gemcitabine	carboplat	87	89	7.48	0.0695	8.75	0.0594
Zwitter 2009	Cisplatin plus gemcitabine	CG-long infusion	125	124	5.5	0.0945	10.1	0.0515
Point estimation with 95% CI (meta-analysis)	NA	NA	NA	NA	NA	0.0982, 0.08659 to 0.1111	NA	0.0513, 0.04470 to 0.0588

Table 10. The clinical response and side effects associated with the combination of cisplatin and gemcitabine as first-line therapy in patients with advanced NSCLC.

Study ID	Clinical response (%)			Side effects (%)						
	Responsive	Stable	Progressive	Neutropenia	Febrile Neutropenia	Fatigue	Nausea & vomiting	Diarrhoea	Hair loss	Rash
Alberola 2003	42.31%	21.98%	20.88%	32.42%	0.00%	Not reported	21.98%	Not reported	Not reported	Not reported
Brodowicz 2006	39.70%	Not reported	Not reported	18.70%	Not reported	Not reported	6.00%	Not reported	Not reported	Not reported
Cardenal 1999	40.58%	Not reported	Not reported	92.75%	7.00%	Not reported	56.52%	Not reported	Not reported	Not reported
Ceribelli 2003	26.32%	33.33%	40.35%	51.00%	3.51%	25.00%	Not reported	5.00%	Not reported	Not reported
Chang 2008	38.24%	29.41%	32.35%	64.71%	0.00%	28.40%	50.60%	5.70%	Not reported	2.90%
Crinò 1999	38.06%	40.00%	21.94%	40.00%	1.00%	Not reported	18.40%	1.30%	11.80%	Not reported
Grigorescu 2007	25.00%	Not reported	Not reported	9.80%	Not reported	Not reported	13.73%	Not reported	Not reported	Not reported
Hsu 2008	31.71%	Not reported	Not reported	78.05%	Not reported	46.34%	85.37%	9.76%	Not reported	48.78%
Kim 2006	50.00%	30.00%	15.00%	47.50%	Not reported	Not reported	15.00%	Not reported	Not reported	Not reported
Liao 2008	23.53%	29.41%	47.06%	27.45%	1.96%	5.88%	9.80%	Not reported	Not reported	Not reported
Martoni 2005	26.67%	Not reported	Not reported	49.20%	Not reported	Not reported	57.90%	Not reported	Not reported	Not reported
Ohe 2006	30.10%	Not reported	Not reported	57.53%	1.37%	13.70%	39.73%	6.16%	Not reported	Not reported
Paz-Ares 2006	30.79%	31.71%	13.41%	40.50%	2.80%	6.80%	13.10%	Not reported	Not reported	Not reported
Pereira 2007	27.00%	42.00%	31.00%	15.15%	Not reported	18.18%	3.03%	Not reported	Not reported	Not reported
Reck 2009	20.10%	Not reported	Not reported	29.97%	1.15%	2.59%	3.46%	Not reported	Not reported	Not reported
Ricci 2000	40.40%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Rinaldi 2000	42.22%	35.56%	22.22%	73.33%	Not reported	33.33%	71.11%	Not reported	Not reported	Not reported
Rubio 2009	34.55%	30.91%	34.55%	49.09%	1.82%	10.91%	16.36%	Not reported	Not reported	Not reported
Sandler 2000	11.15%	42.69%	33.08%	50.40%	Not reported		50.00%	2.00%	Not reported	Not reported
Scagliotti 2002	30.24%	39.51%	17.56%	38.10%	Not reported	10.10%	6.60%	Not reported	Not reported	Not reported
Scagliotti 2008	28.20%	Not reported		27.00%	4.00%		4.00%	Not reported	Not reported	Not reported
Syrigos 2010	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Wachters 2003	46.22%	33.61%	18.49%	59.66%	1.68%	83.19%	77.31%	10.92%	Not reported	14.29%
Zatloukal 2003	29.89%	44.83%	24.14%	30.30%	Not reported	6.70%	5.60%	Not reported	Not reported	Not reported
Zwitter 2009	32.80%	53.60%	13.60%	45.60%	0.00%	Not reported	23.20%	Not reported	Not reported	Not reported
Point estimation with 95% CI (meta-analysis)	0.3046, 0.2892 to 0.3204	0.3680, 0.3455 to 0.3911	0.2365, 0.2166 to 0.2576	0.3911, 0.3742 to 0.4083	0.0307, 0.0240 to 0.0392	0.1914, 0.1670 to 0.2185	0.2816, 0.2621 to 0.3019	0.0602, 0.0440 to 0.0818	0.118, 0.0759 to 0.1789	0.2382, 0.1752 to 0.3150

Table 11. The efficacy of docetaxel as second-line therapy for patients with advanced NSCLC.

Study	Intervention	Control	Sample size for intervention	Sample size for control	Progression-free survival (median, months) for intervention	Hazard rate of progression per 3 week for intervention	Overall survival (median, months) for intervention	Hazard rate for death per 3 weeks for intervention
Camps 2006	docetaxel	docetaxel low dose	129	125	Not reported	NA	6.6	0.0788
Chen 2006	docetaxel	docetaxel low dose	33	64	Not reported	NA	9.5	0.0547
Cufer 2006	docetaxel	gefitinib	73	68	3.4	0.1529	7.1	0.0732
Gervais 2005	docetaxel	docetaxel low dose weekly	62	63	Not reported	NA	5.8	0.0896
Gridelli 2004	docetaxel	docetaxel low dose weekly	110	110	Not reported	NA	7.25	0.0717
Hanna 2004	docetaxel	pemetrexed	288	283	2.9	0.1793	7.9	0.0658
Jones 2008	docetaxel	topotecan	38	39	Not reported	NA	7.6	0.0684
Krzakowski 2010	docetaxel	vinflunine	277	274	2.3	0.2260	7.2	0.0722
Lai 2005	docetaxel	docetaxel low dose	25	25	Not reported	NA	7.8	0.0666
Lee 2010	docetaxel	gefitinib	79	82	3.4	0.1529	12.2	0.0426
Paz-Ares 2008	docetaxel	paclitaxel poliglumex	422	427	Not reported	NA	6.9	0.0753
Pectasides 2005	docetaxel	docetaxel and irinotecan	65	65	Not reported	NA	6.4	0.0812
Quoix 2004	docetaxel	docetaxel high dose	93	89	Not reported	NA	4.7	0.1106
Schuette 2005	docetaxel	docetaxel low dose	103	105	Not reported	NA	6.3	0.0825
Wachters 2005	docetaxel	docetaxel, irinotecan, and lenogastrim	56	52	4.5	0.1155	8	0.0650
Point estimation with 95% CI (meta-analysis)						0.1888, 0.1625 to 0.2182		0.0748, 0.0636 to 0.0877

Table 12. The clinical response and side effects associated with docetaxel as second-line therapy in patients with advanced NSCLC.

Study	Clinical response (%)			Side effects (%)						
	Responsive	Stable	Progressive	Neutropenia	Febrile	Fatigue	Nausea & vomiting	Diarrhoea	Hair loss	Rash
Camps 2006	9.30%	34.11%	48.06%	14.73%	7.75%	54.26%	29.46%	17.83%	62.02%	9.30%
Chen 2006	6.06%	54.55%	33.33%	78.79%	12.12%	54.55%	12.12%	18.18%	45.45%	Not reported
Cufer 2006	13.70%	45.21%	15.07%	39.73%	2.74%	24.66%	26.03%	39.73%	10.96%	9.59%
Gervais 2005	4.80%	27.40%	67.80%	48.39%	6.45%	4.84%	3.23%	1.61%	Not reported	Not reported
Gridelli 2004	2.70%	Not reported	Not reported	29.00%	5.00%	56.00%	19.00%	21.00%	36.00%	8.00%
Hanna 2004	8.80%	46.40%	44.80%	40.20%	12.70%	35.90%	28.70%	24.30%	37.70%	6.20%
Jones 2008	8.00%	42.00%	50.00%	65.79%	7.89%	78.95%	42.11%	21.05%	28.95%	2.63%
Krzakowski 2010	5.50%	Not reported	Not reported	39.00%	4.70%	33.90%	37.90%	12.40%	35.40%	Not reported
Lai 2005	12.00%	40.00%	48.00%	100.00%	Not reported	Not reported	56.00%	48.00%	Not reported	Not reported
Lee 2010	7.60%	Not reported	Not reported	Not reported	Not reported	35.44%	27.85%	15.19%	41.77%	7.59%
Paz-Ares 2008	12.00%	33.00%	55.00%	43.36%	5.92%	35.07%	50.00%	Not reported	31.75%	Not reported
Pertasides 2005	21.54%	53.85%	24.62%	43.08%	Not reported	13.85%	7.69%	12.31%	84.62%	1.54%
Quoix 2004	7.52%	32.26%	47.31%	43.01%	6.45%	8.60%	5.38%	1.08%	2.15%	Not reported
Schuette 2005	12.62%	37.86%	44.66%	20.39%	1.94%	Not reported	4.85%	Not reported	Not reported	Not reported
Wachters 2005	16.07%	44.64%	35.71%	35.71%	5.36%	62.50%	62.50%	26.57%	55.36%	8.93%
Point estimation with 95% CI (meta-analysis)	0.1027, 0.0892 to 0.1181	0.3913, 0.3656 to 0.4175	0.4717, 0.4448 to 0.4988	0.3948, 0.3714 to 0.4186	0.0745, 0.0624 to 0.0889	0.3801, 0.3561 to 0.4047	0.3542, 0.3307 to 0.3785	0.2102, 0.1873 to 0.2351	0.3849, 0.3602 to 0.4102	0.0746, 0.05813 to 0.0952

Table 13. The efficacy of pemetrexed as second-line therapy in patients with advanced non-squamous cell carcinoma type NSCLC.

Study	Intervention	Control	Sample size for intervention	Sample size for control	Progression-free survival (median, months) for intervention	Hazard rate for progression per three weeks (intervention)	Overall survival (median, months) for intervention	Hazard rate for death per 3 weeks (intervention)
Cullen 2008	pemetrexed 500 mg/m2	pemetrexed 900 mg/m2	295	293	2.6	0.1999	6.7	0.0776
Hanna 2004	pemetrexed 500 mg/m2	docetaxl 75 mg/m2	283	288	2.9	0.1793	8.3	0.0626
Point estimation with 95% CI (meta-analysis)						0.19, 0.1601 to 0.2241		0.0706, 0.0524 to 0.0947

Table 14. The clinical response and side effects associated with pemetrexed as second-line therapy in patients with advanced non-squamous cell carcinoma type NSCLC.

Study	Clinical response (%)			Side effects (%)						
	Responsive	Stable	Progressive	Neutropenia	Febrile Neutropenia	Fatigue	Nausea & vomiting	Diarrhoea	Hair loss	Rash
Cullen 2008	6.10%	43.39%	30.51%	2.10%	1.40%	Not reported	Not reported	Not reported	Not reported	Not reported
Hanna 2004	9.10%	45.80%	45.10%	5.30%	1.90%	34.00%	47.10%	12.80%	6.40%	14.00%
Point estimation with 95% CI (meta-analysis)	0.0771, 0.0578 to 0.1021	0.4457, 0.4056 to 0.4865	0.3794, 0.3402 to 0.4202	0.0403, 0.0265 to 0.061	0.0166, 0.0088 to 0.0311	0.34, 0.287 to 0.397	0.471, 0.413 to 0.529	0.128, 0.094 to 0.172	0.064, 0.041 to 0.099	0.14, 0.104 to 0.185

Table 15. The efficacy of erlotinib as third-line therapy in patients with advanced NSCLC.

Study	Intervention	Control	Sample size for intervention	Sample size for control	Progression-free survival (median, months) for intervention	Hazard rate for progression per three weeks (intervention)	Overall survival (median, months) for intervention	Hazard rate for death per 3 weeks for intervention
Lynch 2009	erlotinib 150 mg/d	erlotinib and bortezomib	25	25	2.7	0.1925	7.3	0.0712
Shepherd 2005	erlotinib 150 mg/d	Placebo	488	243	2.2	0.2363	6.7	0.0776
Point estimation with 95% CI (meta-analysis)	NA	NA	NA	NA	NA	0.234, 0.2 to 0.273	NA	0.0773, 0.0571 to 0.1038

Table 16. The clinical response and side effects associated with erlotinib as third-line therapy in patients with advanced NSCLC.

Study	Clinical response (%)			Side effects (%)						
	Responsive	Stable	Progressive	Neutropenia	Febrile Neutropenia	Fatigue	Nausea & vomiting	Diarrhoea	Hair loss	Rash
Lynch 2009	16.00%	36.00%	44.00%	Not reported	Not reported	60.00%	Not reported	72.00%	Not reported	88.00%
Shepherd 2005	8.90%	36.10%	38.00%	Not reported	Not reported	16.19%	Not reported	11.34%	Not reported	15.67%
Point estimation with 95% CI (meta-analysis)	0.0933, 0.0709 to 0.1219	0.361, 0.3205 to	0.3830, 0.3419 to	NA	NA	0.6, 0.403 to 0.003	NA	0.72, 0.518 to 0.860	NA	0.880, 0.607 to 0.961

Table 17. The efficacy of BSC in patients with advanced NSCLC.

Study	Intervention	Control	Sample size for intervention	Sample size for BSC	Overall survival (median, months) for BSC	Hazard rate for death per 3 weeks for BSC
Anderson 2000	gemcitabine	BSC	150	150	5.9	0.0881
Roszkowski 2000	docetaxel	BSC	137	70	5.7	0.0912
Shepherd 2000	docetaxel	BSC	104	100	4.6	0.1130
Cellerino 1991	cyclophosphamide , epirubicin , and cisplatin	BSC	62	61	5.275	0.0986
Thatcher 2005	gefitinib (250 mg/day)	BSC	1129	563	5.1	0.1019
Ranson 2000	Paclitaxel	BSC	79	78	4.8	0.1083
Rapp 1988	vindesine and cisplatin	BSC	50	50	4.25	0.1223
Thongprasert 1999	IEP regimen	BSC	96	96	4.1	0.1268
Neninger Vinageras 2008	EGFR vaccine	BSC	40	40	3.6	0.1444
Goss 2009	gefitinib (250 mg/d)	BSC	100	101	2.8	0.1857
Kennedy 1995	VP (vindesine and cisplatin), CAP (cyclophosphamide, doxorubicin and cisplatin)	BSC	23	24	Not reported	Not reported
Point estimation with 95% CI (meta-analysis)	NA	NA	NA	NA	NA	0.1132, 0.0970 to 0.1318

Table 18. The summary of estimated utilities applied to the decision analytic model.

Type of treatment	Number of RCTs	Number of patients	Utility	
			During the treatment	Post-treatment
Gefitinib as first-line therapy	2	202	0.5698	NA
Cisplatin and gemcitabine as first-line therapy	25	4148	0.5353	0.6166
Docetaxel as second-line therapy	15	1853	0.4537	0.5704
Pemetrexed as second-line therapy for non-squamous cell carcinoma	2	578	0.5362	0.5865
Erlotinib as third-line therapy	2	513	0.4798	NA
BSC	11	1333	0.4734	NA

Table 19: The result of base case analysis for CEA.

Strategy	Cost	Incr Cost	Life years	Incr life years	ICER
No EGFR mutation testing	$14,368		0.4842		
EGFR mutation testing	$16,857	$2,488	0.5383	0.0541	**$46,021**

Table 20: The result of base case analysis for CUA.

Strategy	Cost	Incr Cost	QALY	Incr QALY	ICER
No EGFR mutation testing	$14,368		0.2881		
EGFR mutation testing	$16,857	$2,488	0.3188	0.0307	**$81,071**

Table 21. The results of one-way sensitivity analysis based on CUA.

Variable	Low value	High value	ICER for low value	ICER for high value	Difference in ICER
Cost of care for patients treated with cisplation and gemcitabine per cycle	$517.50	$1,552.50	$90,097	$72,045	-$18,052
Cost of care for patients treated with gefitinib per cycle	$270	$810	$64,563	$97,579	$33,016
Cost of EGFR gene mutation testing	$250	$750	$74,882	$87,260	$12,378
Cost of erlotinib per day	$40.43	$121.29	$89,504	$72,638	-$16,866
Cost of gefitinib per day	$36.06	$108.17	$34,778	$127,364	$92,586
Cost of pemetrexed per cycle	$2432.5	$7297.5	$85,639	$76,503	-$9,136
Probability of death per cycle for patients treated with gefitinib	0.0059	0.0467	$74,405	$141,993	$67,588
Probability of having progressive disease per cycle for patients treated with gefitinib	0.0289	0.0895	$73,636	$109,572	$35,937

Table 22. The result of PSA.

Strategies	EGFR gene mutation testing	No EGFR gene mutation testing
Costs (mean)	$16,067	$13,543
SD	$4,363	$4,472
95% CI	$8,741 to $25,866	$6,081 to $23,533
Life years (mean)	0.522	0.469
SD	0.063	0.044
95%CI	0.421 to 0.670	0.387 to0.562
QALY (mean)	0.305	0.276
SD	0.038	0.029
95%CI	0.242 to 0.392	0.223 to 0.337

Table 23. The result of budget impact analysis: The projected increase of annual health care expenditure on patients with advanced NSCLC in Ontario from 2011 to 2015 under the strategy of EGFR gene mutation testing.

Type of cost	2011	2012	2013	2014	2015
Testing	$1,343,300	$1,343,300	$1,343,300	$1,343,300	$1,343,300
Gefitinib	$9,162,660	$11,855,280	$12,637,524	$12,778,795	$12,778,795
Cisplatin plus gemcitabine	-$1,339,710	-$1,146,106	-$1,089,861	-$1,079,703	-$1,079,703
Docetaxel	-$169,783	-$160,540	-$151,295	-$149,378	-$149,378
Pemetrexed	-$1,320,419	-$1,248,581	-$1,176,673	-$1,161,757	-$1,161,757
No progression	-$1,431,651	-$1,410,989	-$1,321,666	-$1,302,277	-$1,302,277
Erlotinib	-$1,665,416	-$2,344,001	-$2,408,515	-$2,412,453	-$2,412,453
Best supportive care	$1,543	$68,840	$39,141	$63,700	$65,009
Total	**$4,580,523**	**$6,957,204**	**$7,871,954**	**$8,080,226**	**$8,081,535**

Figures

Figure 1. The study framework.

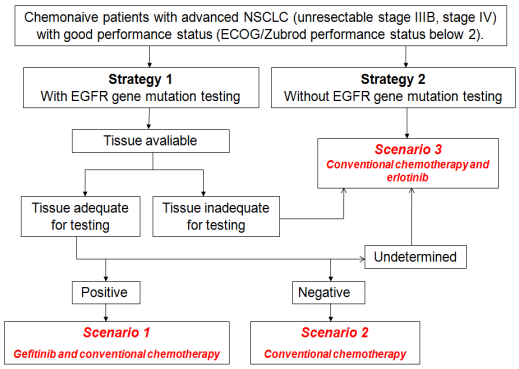
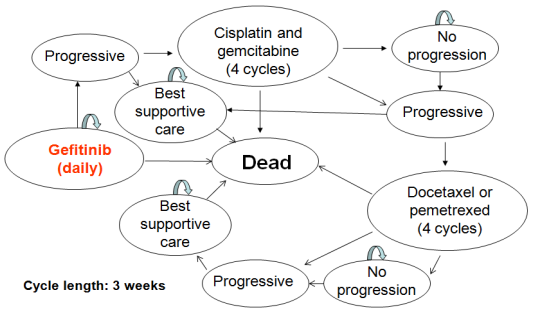
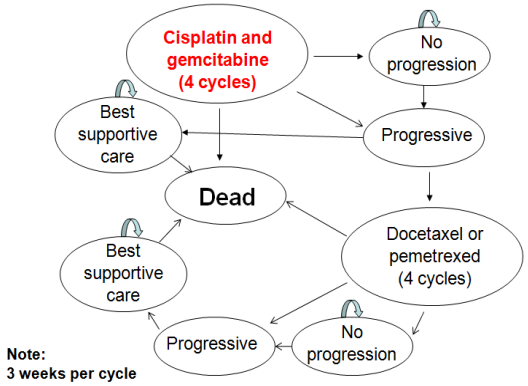


Figure 2. The structure of Markov model for the three scenarios included in the decision analytic model.

Scenario 1:



Scenario 2:



Scenario 3:

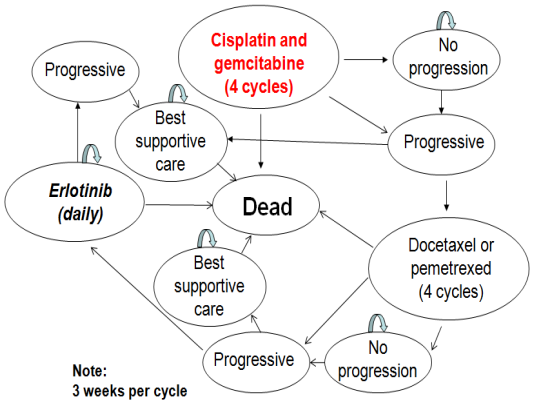
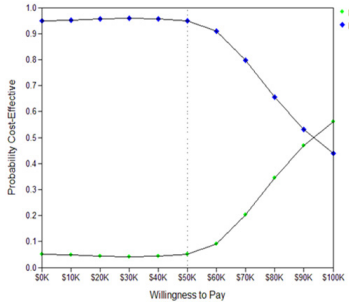


Figure 3. The relationship between the proportion of cost-effectiveness for the strategy of EGFR gene mutation testing and willingness-to-pay per QALY.



•Proportion of cost-effectiveness for EGFR gene mutation testing under $50K: **5.2%.**

•Proportion of cost-effectiveness for EGFR gene mutation testing under $100K: **56.1%.**

Figure 4. Differences in annual medical costs spent on patients with advanced NSCLC in Ontario between the two strategies from 2011 to 2015.