ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Cell-Free Circulating Tumour DNA Blood Testing to Detect *EGFR* T790M Mutation in People With Advanced Non–Small Cell Lung Cancer: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

When people are diagnosed with lung cancer, they undergo a procedure called tissue biopsy to see if they have certain types of genetic mutations that affect the epidermal growth factor receptor (*EGFR*) gene. People with these mutations are given drugs called *EGFR* tyrosine kinase inhibitors. However, about 60% of people with these mutations will develop an *EGFR* resistance mutation called T790M, which makes the drugs they are taking ineffective. Instead of undergoing another tissue biopsy, which can be difficult for many reasons, a blood test (often called liquid biopsy) can be done to see if people have this resistance mutation. If they do, they are currently offered a medication called osimertinib, a type of *EGFR* tyrosine kinase inhibitor specifically for people with an *EGFR* T790M mutation.

This health technology assessment looked at how accurate and useful liquid biopsy is for detecting *EGFR* T790M resistance mutation in people with non–small cell lung cancer, its cost-effectiveness, and the budget impact of publicly funding liquid biopsy in Ontario. It also looked at the experiences, preferences, and values of people with non–small cell lung cancer and their families.

What Did This Health Technology Assessment Find?

Liquid biopsy can identify a high proportion of people with the *EGFR* T790M resistance mutation. However, given its inability to accurately identify people without this mutation, liquid biopsy is used as a triage test; that is, a tissue biopsy is used to confirm a negative liquid biopsy test result.

When treatment is based on mutation status (i.e., the type of treatment a person receives depends on whether they have the *EGFR* T790M resistance mutation), patients' progression-free survival (length of time a person survives without the disease getting worse) is similar. The cost of conducting liquid biopsy (alone or as a triage test) is lower than the cost of conducting tissue biopsy alone. Our analyses indicate that liquid biopsy as a triage test leads to the greatest number of correct treatment decisions. However, given the high cost of targeted treatment for people with the *EGFR* T790M resistance mutation, when incorporating long-term treatment and care costs, liquid biopsy may not be viewed as being cost-effective.

People with lung cancer with whom we spoke said that liquid biopsy would likely be an appropriate test for people with non–small cell lung cancer given their frail condition and because it avoids the pain and anxiety associated with tissue biopsy.

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ABSTRACT

Background

Cell-free circulating tumour DNA blood testing (also called liquid biopsy) can determine if a person with advanced non–small cell lung cancer (NSCLC) whose disease is progressing has developed the epidermal growth factor receptor (*EGFR*) T790M resistance mutation. Identifying this resistance mutation can help physicians choose appropriate treatment (i.e., osimertinib if positive and chemotherapy if negative). Tissue biopsy is typically used to look for the resistance mutation, but this is an invasive test that might not be feasible if the patient is too ill. We conducted a health technology assessment of liquid biopsy for people with advanced NSCLC, which included an evaluation of the diagnostic accuracy, clinical utility, safety, cost-effectiveness, and the budget impact of publicly funding liquid biopsy, as well as an evaluation of patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using Risk of Bias in Systematic Reviews (ROBIS), Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2), Risk of Bias Among Non-randomized Studies (RoBANS), and the Cochrane risk of bias (ROB) tool and assessed quality of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted short-term and long-term cost-effectiveness and cost-utility analyses comparing liquid biopsy as a triage test, liquid biopsy alone, and tissue biopsy alone from a public payer perspective. We also analyzed the budget impact of publicly funding liquid biopsy for people in Ontario with advanced NSCLC. To assess the potential value of liquid biopsy, we spoke with people with lung cancer and people with an understanding of the process of liquid biopsy.

Results

We included 19 studies (within a published systematic review) to examine diagnostic test accuracy and 12 studies to examine clinical utility. In patients with advanced NSCLC, liquid biopsy to detect the *EGFR* T790M resistance mutation demonstrated a positive and negative predictive value of 89% and 61%, respectively, a sensitivity of 68%, and specificity of 86%. No studies examined the clinical utility of liquid biopsy as a triage test. When NSCLC was treated appropriately, progression-free survival was similar in patients with and without the resistance mutation, as ascertained by liquid biopsy.

We estimated that it costs about $700 to conduct a liquid biopsy and $2,500 to conduct a tissue biopsy. Our analyses showed that, when considering costs and effects directly related to testing, liquid biopsy (as a triage test, which means patients who test negative undergo a follow-up tissue biopsy, or alone, which means using only liquid biopsy) was less costly than tissue biopsy alone and led to fewer tissue biopsies. Using liquid biopsy as a triage test produced the most correct treatment decisions and greatest number of people who were given osimertinib.

When considering long-term costs (i.e., treatment and care) and effects (i.e., life-years and quality-adjusted life-years [QALYs]), liquid biopsy as a triage test was the most effective and most costly strategy followed by liquid biopsy alone. Tissue biopsy alone was the least effective and least costly strategy. The incremental cost-effectiveness ratios (ICERs) of liquid biopsy as a triage test compared with liquid biopsy alone and of liquid biopsy alone compared with tissue biopsy alone were greater than $100,000 per QALY. However, this result was largely driven by the cost of osimertinib, which was used more often when liquid biopsy was used as a triage test.

We estimated that the total annual budget impact of publicly funding liquid biopsy as a triage test in Ontario over the next 5 years would range from approximateily $60,000 in year 1 to $3 million in year 5.

People with lung cancer with whom we spoke said that liquid biopsy would likely be an appropriate test for people with NSCLC given their frail condition and because it would avoid the pain and anxiety associated with tissue biopsy.

Conclusions

As a minimally invasive test, liquid biopsy identifies a high proportion of people with the *EGFR* T790M resistance mutation. This identification could better guide treatment for people with advanced NSCLC. However, its relatively low negative predictive value means it is best used as a triage test (i.e., followed by tissue biopsy if the liquid biopsy does not identify a resistance mutation). Liquid biopsy as a triage test is likely more effective than tissue biopsy alone. However, owing to the high cost of treatment, liquid biopsy may not be cost-effective. We estimated that publicly funding liquid biopsy as a triage test in Ontario would result in additional costs (related to more patients being treated) of between $0.06 million and $3 million over the next 5 years.

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OBJECTIVE

This health technology assessment evaluates the diagnostic accuracy, clinical utility, safety, and cost-effectiveness of cell-free circulating tumour DNA [ctDNA] blood testing (referred to in this report as "liquid biopsy") to detect the resistance mutation epidermal growth factor receptor (*EGFR*) T790M in people with advanced non–small cell lung cancer (NSCLC). It also evaluates the budget impact of publicly funding liquid biopsy, as well as the experiences, preferences, and values of people with lung cancer.

BACKGROUND

Health Condition

Lung cancer is characterized by uncontrolled growth of abnormal cells in one or both lungs.[1] In 2017, an estimated 28,600 Canadians were expected to develop lung cancer. The incidence of lung cancer is higher in men (76.5 per 100,000) than in women (65.3 per 100,000).[2] Non–small cell lung cancer includes any type of lung cancer other than small-cell lung cancer and accounts for 75% to 85% of all lung cancers.[3]

Types of Non–Small Cell Lung Cancer

Various subtypes of NSCLC are categorized by the type of cell in the lung that is affected (adenocarcinoma, squamous cell, large cell, or other uncommon subtypes). These subtypes have similar treatments and prognoses[4]:

- Adenocarcinoma: about 60% of NSCLCs are adenocarcinoma. Former or current smoking is often a causal factor in all forms of lung cancer. However, nonsmokers with lung cancer frequently have adenocarcinoma. This type of cancer is usually found on the outer parts of the lung. People with adenocarcinoma tend to have better survival than people with other types of lung cancer
- Squamous cell (epidermoid) carcinoma: 25% to 30% of all NSCLCs are squamous cell carcinomas. Squamous cells are flat cells that line the inside of the airways in the lungs. This type of cancer is often linked to a history of smoking and often found in the outer parts of the lung
- Large cell (undifferentiated) carcinoma: This subtype accounts for 10% to 15% of NSCLC cases. This type of cancer can appear anywhere in the lung and is known to spread quickly, which can make it harder to treat. A subtype of large cell carcinoma, known as large cell neuroendocrine carcinoma, is a very aggressive cancer that is very similar to small cell lung cancer
- Other subtypes: Less common NSCLC subtypes include adenosquamous carcinoma and sarcomatoid carcinoma

The progression of cancer is divided into four stages; a higher number signifies more extensive disease. In stage 1, the cancer is confined to the original site within the lung and there is no sign of spread to lymph nodes (N0) or elsewhere (M0). In stage 2, the cancer has spread to lymph nodes within the lung (N1). In stage 3, the cancer has spread to lymph nodes in the middle of the chest (the mediastinum) (N2 or N3), but not elsewhere (M0). And in stage 4, the cancer has spread to other areas in the body (M1).[5]

About half of patients have stage 3 or 4 NSCLC at time of diagnosis. This could be due to the considerable amount of time it takes for patients with suspected lung cancer to visit a physician, undergo investigations, and commence treatment. In a study examining the delays in diagnosis at a regional cancer centre in Hamilton, Ontario, the median total wait time was roughly 4.5 months.[6] Among those who do not present with advanced stages of NSCLC, most will progress to advanced disease. The 5-year survival rate for NSCLC patients across all stages is only 18%.[7]

Epidermal Growth Factor Receptor

Advances in understanding cell signaling pathways that control cell survival have identified genetic and regulatory abnormalities that suppress cell death, promote cell division, and induce the production of tumours. Some lung cancer tumour cells have a DNA mutation that affects the *EGFR* gene.[3] The importance of the *EGFR* gene has been reported and implicated in the pathogenesis (development) of many human cancers, including NSCLC.[3] These receptors promote growth of tumour cells. Sensitizing mutations in *EGFR* are associated with increased tumour growth, which contributes to the cancer's progression. Knowing the *EGFR* mutation status can assist clinical decision-making about which treatment will work best, as the presence of a sensitizing mutation is predictive of tumour response to tyrosine kinase inhibitors (TKIs) targeting the *EGFR* gene. In advanced NSCLC, there are three main treatment options: chemotherapy, immunotherapy, and targeted therapy.[8] When a patient tests positive for *EGFR* mutation, physicians should choose a targeted therapy, such as an *EGFR*-TKI. When a patient tests negative for *EGFR* mutation, physicians should choose chemotherapy as the initial treatment.[8]

Prevalence of Epidermal Growth Factor Receptor

Adenocarcinoma is the subtype of NSCLC in which *EGFR*-sensitizing mutations are most prevalent.

The prevalence of *EGFR* mutations in adenocarcinomas is 10% in white patients and up to 50% in Asian patients, with higher *EGFR* mutation frequencies in nonsmokers, women, and nonmucinous subtypes of adenocarcinoma.[9] These *EGFR* mutations occur most frequently in *EGFR* exons 18 to 21. Sensitizing mutations in these exons are predictive of response to treatment with TKIs. The most common sensitizing mutations are exon 19 deletion and the exon 21 L858R mutation. These two types of mutations comprise 85% to 90% of *EGFR*-sensitizing mutations in NSCLC.[10-13] Patients with these mutations are treated with targeted therapy, which includes first- (erlotinib, gefitinib) or second-generation (afatinib) *EGFR*-TKIs. When patients are treated with targeted treatment, they have a higher likelihood of tumour response, improved progression-free survival (PFS), fewer adverse effects from treatment, and improved quality of life, as compared with chemotherapy.[14-17]

However, patients treated with *EGFR*-TKIs eventually experience cancer progression. Resistance to *EGFR*-TKI therapy can be associated with secondary acquired *EGFR* resistance mutations, the most common of which is T790M in *EGFR* exon 20. This resistance mutation is the focus of this review. For patients who have *EGFR* sensitizing mutations, progression of NSCLC on initial *EGFR*-TKI therapy develops after a median of 10 to 12 months.[18] Approximately 60% of patients with *EGFR* mutated NSCLC will develop the T790M mutation as a mechanism of resistance to a first- or second-generation *EGFR*-TKI.[18,19]

Testing for Epidermal Growth Factor Receptor Status

Epidermal growth factor receptor mutation tests are in vitro diagnostic tests used to help identify adults with NSCLC suitable for drug treatment with *EGFR*-TKIs.[20] These *EGFR* mutation tests can be used to identify sensitizing mutations for *EGFR*-TKI treatment or to track progression of NSCLC. This review focuses on using mutation tests to detect the *EGFR* T790M resistance mutation in disease progression. As a result, the test is useful for oncologists to identify the *EGFR* T790M mutation for decisions about treating patients with a third-generation *EGFR*-TKI (osimertinib).

Tissue Biopsy

Traditionally at disease progression, *EGFR* mutation testing is done on DNA extracted from a tumour sample obtained by tissue biopsy. It is agreed that tissue biopsy is an imperfect gold standard (also referred to as a reference or criterion standard). Because of tumour heterogeneity, the *EGFR* T790M mutation might not be found in all tumour sites. Also, at disease progression, patients may be at an advanced stage of NSCLC. Therefore, patients have a higher risk of adverse events associated with tissue biopsy than with cell-free circulating tumour DNA (ctDNA) blood testing (also known as liquid biopsy). It is also difficult to obtain usable tissue samples in patients with metastatic cancer that has spread to the brain or bone.

In general, tissue biopsies require the use of interventional radiology to retrieve samples from internal organs with associated risk of pneumothorax, bleeding, pain, and discomfort. Tissue biopsies require access to a hospital biopsy suite that can have long wait times.

Liquid Biopsy

More recently, liquid biopsy via plasma *EGFR* mutation tests that use cell-free ctDNA have been developed as an alternative or complementary test to tissue biopsy. Cell-free ctDNA is made of cell-free fragments of tumour DNA that have been released from tumour cells and have entered the peripheral circulation, which can be extracted from the plasma fraction of a blood sample.[20] Only a blood sample is needed for plasma testing, so it is sometimes called “liquid biopsy.” We refer to this test as liquid biopsy throughout this health technology assessment.

Liquid biopsy is less invasive than tissue biopsy when detecting the *EGFR* T790M mutation. It can be used as a triage test to potentially avoid tissue biopsy or as an alternative for people who are unable to provide a tissue biopsy (e.g., for patients who lack available tumour tissue, who had a low-quality tissue sample, or whose poor health makes a tissue biopsy infeasible) or for people who do not wish to have a tissue biopsy (Figure 1). A recent guideline and multiple experts state that, if a liquid biopsy test for the *EGFR* T790M mutation is negative, then there is still a need for tissue biopsy because of the possibility of a lack of cell-free ctDNA from the tumour in the peripheral circulation. (Up to 30% of negative results from liquid biopsy have positive results from tissue biopsy; alternatively, some patients whose tissue biopsy results are negative have varied distribution of *EGFR* T790M resistance mutation in tumours throughout the body.)[21]

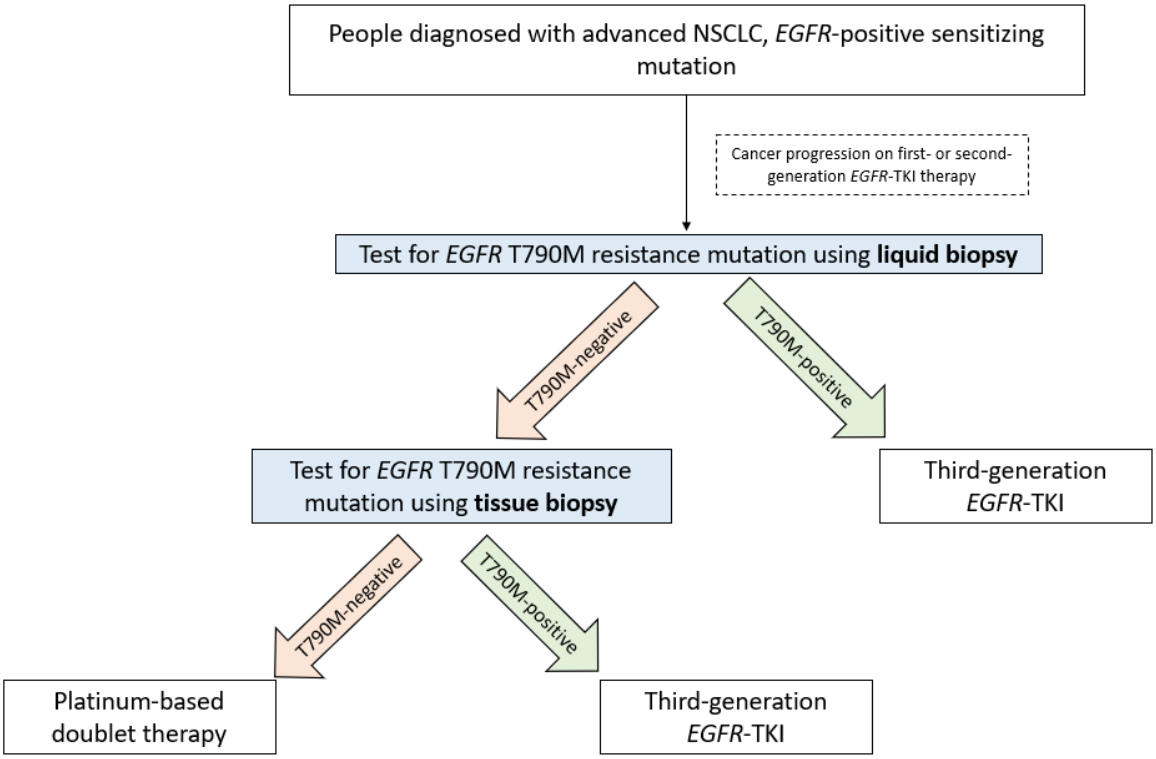

Figure 1: Testing Pathway for People with Advanced NSCLC

Abbreviations: *EGFR*, epidermal growth factor resistance; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

Regulatory Information and Funding Coverage

Liquid biopsy testing can be done using manufacturer-developed validated testing kits or through laboratory-developed validated tests. In Ontario, plasma samples are generally tested by Health Canada–approved manufacturer-developed assays or with laboratory-developed or validated targeted assays such as next-generation sequencing (NGS), quantitative real-time polymerase chain reaction (RT-PCR) or digital PCR (dPCR) (depending on the lab infrastructure). For both approaches, a sensitive lower limit of detection (also known as threshold) of a mutant allele (variant form of a gene) fraction of 0.1% to 0.5% is needed for liquid biopsy, as cell-free ctDNA is not abundant in plasma samples.

Two kits are approved by Health Canada and are used to detect the *EGFR* mutation in blood samples (Table 1).

Table 1: *EGFR* Mutation Kits Approved by Health Canada

Characteristic	Description	
	Therascreen *EGFR* Plasma RGQ PCR Kit	Cobas *EGFR* Mutation Test Version 2
Manufacturer	Qiagen	Roche
Licence number	97247	98447
Type	Test kit	Test kit
Device class	3	3
First issue date	2016-07-08	2017-01-24
Detection method	Analogue Semi-quantitative Detects 21 mutations	Analogue Semi-quantitative Detects 42 mutations

Abbreviations: *EGFR*, epidermal growth factor resistance; PCR, polymerase chain reaction; RGQ, rotor-gene Q.

Ontario and Canadian Context

In Ontario, liquid biopsy is being used to detect the presence of the *EGFR* T790M resistance mutation in patients with NSCLC who are no longer responding (i.e., their cancer has progressed) to first- (gefitinib and erlotinib) or second-generation (afatinib) *EGFR*-TKI therapy. Liquid biopsy is being used for triage, where a negative test result requires confirmation with a tissue biopsy (if feasible).

The use of liquid biopsy testing for detecting the *EGFR* T790M mutation is being funded currently by AstraZeneca in two laboratories in Ontario (University Health Network and London Health Sciences Centre). The Ontario Ministry of Health Out-of-Country program also approves requests for funding the test. Access to and coverage of biomarker testing in patients with NSCLC varies across Canada.[22]

International Context

The National Institute for Health and Care Excellence (NICE) released a Medtech innovation briefing on liquid biopsy (blood) *EGFR* mutation tests in patients with locally advanced or metastatic NSCLC.[20] At the time that briefing was written, 10 National Health Service hospitals were routinely doing *EGFR* T790M mutation testing with liquid biopsy. Given the frequency of *EGFR* mutations among Asians, countries such as China, India, Japan, Philippines, Singapore, South Korea, and Taiwan often test for *EGFR* mutations.[23] However, we do not know if testing is done with liquid biopsy. Australian guidelines recommend using liquid biopsy as a triage test to detect *EGFR* T790M among patients who have progressed despite treatment with first- or second-generation *EGFR*-TKIs.[24] The Medical Services Advisory Committee in Australia recently deferred advice on *EGFR* T790M mutation testing to the government pending advice on funding osimertinib. However, the Medical Services Advisory Committee anticipates that funding for treatment with osimertinib is likely to be funded,[25] and if so, *EGFR* T790M mutation testing could be funded as well.

Expert Consultation

We solicited expert feedback on genetic testing for people with NSCLC in Ontario. The consultation included clinical and methodological experts within organizations such as Cancer Care Ontario as well as geneticists, oncologists, and pathologists. The role of expert advisors was to contextualize the evidence and provide advice on liquid biopsy for the detection of *EGFR* T790M mutation and for genetic test evaluation research and statistical methods, as needed.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42018103688), available at https://www.crd.york.ac.uk/PROSPERO.

CLINICAL EVIDENCE

Research Questions

- What is the diagnostic accuracy of cell-free circulating tumour DNA (ctDNA) blood testing (also called liquid biopsy), using tissue biopsy as the reference standard, in detecting the epidermal growth factor receptor (*EGFR*) T790M mutation in people with advanced non–small cell lung cancer (NSCLC)?

- What is the clinical utility of cell-free ctDNA blood testing as a triage test compared with tissue biopsy in detecting the *EGFR* T790M mutation in patients with advanced NSCLC on process outcomes (e.g., time to test result) and outcomes important to patients (e.g., progression-free survival [PFS])?

Methods

We developed research questions in consultation with health care providers, clinical experts, and other health system stakeholders.

Clinical Literature Search

We performed a clinical literature search on May 25, 2018, to retrieve studies published from January 1, 2000, to the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment, and National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategy using controlled vocabulary (i.e., Medical Subject Headings) and relevant keywords. The final search strategy was peer reviewed using the PRESS Checklist.[26]

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We performed targeted grey literature searching of health technology assessment agency sites as well as clinical trial and systematic review registries. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 2000, and May 25, 2018
- Randomized controlled trials, comparative cohort studies, case-control studies, systematic reviews, and meta-analyses

Exclusion Criteria

- Animal and in vitro studies
- Editorials, case reports, conference abstracts, or commentaries

Participants

Inclusion Criteria

- Patients with NSCLC who have an *EGFR*-sensitizing mutation who have progressed while using first- or second-generation *EGFR*-tyrosine kinase inhibitor (TKI) therapy

Exclusion Criteria

- Patients with other types of cancer

Index Test (Intervention)

Inclusion Criteria

- Liquid biopsy (alone or as a triage test in combination with tissue biopsy) for detection of the *EGFR* T790M mutation via plasma tests that use cell-free ctDNA

Exclusion Criteria

- Studies examining liquid biopsy at any other time in the clinical pathway (i.e., diagnosis of *EGFR*-sensitizing mutations)
- Liquid biopsy used for any other resistance mutations (Kirsten rat sarcoma viral oncogene, anaplastic lymphoma kinase, etc.)

Reference Standard/Comparator

Inclusion Criteria

- Tissue biopsy for detection of the *EGFR* T790M mutation

Outcome Measures

- Diagnostic test accuracy outcomes: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), concordance rate
- Clinical utility outcomes: time to test result, PFS, overall survival, response rate, tissue biopsies avoided, adverse events of liquid biopsy

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using DistillerSR management software, and then obtained the full text of studies that appeared eligible for the review according to the inclusion criteria. The single reviewer then examined the full-text articles and selected studies that were eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information about the following:

- Source (e.g., citation information, country, funding source)
- Methods (e.g., study design, study duration and years, analytical approach, sample size, inclusion and exclusion criteria)
- Baseline characteristics (e.g., age, sex, race, smoking history, NSCLC stage and type, location of tissue biopsy, method of blood and tissue analysis, initial *EGFR*-sensitizing mutations, previous *EGFR*-TKI therapy, time to progression after initial *EGFR*-TKI therapy)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, number of reported liquid and tissue biopsy "failures," unit of measurement, upper and lower limits [for scales], and time points at which the outcome was assessed)

We contacted authors of the studies to provide clarification as needed.

Statistical Analysis

We conducted a meta-analysis on diagnostic accuracy outcomes from included primary studies. We were prepared to report the statistical analysis from a systematic review that was found through our search updates; however, the statistical methods did not adhere to the Cochrane Handbook on diagnostic test accuracy.[27] Therefore, we conducted a meta-analysis on the sensitivity and specificity of liquid biopsy to detect the *EGFR* T790M resistance mutation. Below are the equations to calculate diagnostic test accuracy outcomes of liquid biopsy using 2×2 tables where tissue biopsy is the reference standard:

- Sensitivity: true positives ÷ (true positives + false negatives)
- Specificity: true negatives ÷ (true negatives + false positives)
- PPV: true positives ÷ (true positives + false positives)
- NPV: true negatives ÷ (true negatives + false negatives)
- Concordance rate: (true positives + true negatives) ÷ (true positives + false negatives + false positives + true negatives)

The threshold (limit of detection) to detect *EGFR* T790M in liquid biopsy varied across included primary studies. Only primary studies that reported the threshold used to detect *EGFR* T790M were included in the meta-analysis; otherwise the results for all included studies are presented in tabular format in the Results section below. Both mutant allele concentration (copies/mL) and mutant allele fraction (%) were reported as threshold measures in the included primary studies. Mutant allele concentration (copies/mL) was converted to mutant allele fraction with the equation below:

Mutant allele fraction = (mutant copy number ÷ [mutant + wild type copy number]) × 100

We conducted exploratory analyses using all included primary studies (with reported thresholds), studies with a common threshold and by method of detection (real-time polymerase chain reaction [RT-PCR], digital polymerase chain reaction [dPCR], and next-generation

sequencing [NGS]). We also explored models where tissue biopsy was considered both a perfect and an imperfect reference standard. To assume an imperfect reference standard, we used a Bayesian latent class analysis. Because of the unknown accuracy of tissue biopsy, the variable "true" disease status is included in the model. This variable contains categories "diseased" and "nondiseased," and the real value of this variable is considered unobserved (i.e., latent). When estimating sensitivity and specificity, this binary outcome depends on true disease status, where the chance of the test being positive if a subject is "diseased represents true sensitivity and the chance of the test being negative if a subject is nondiseased is the true specificity. Therefore, this model does not consider any test perfect, but considers the true accuracy of each test for diagnosing the true disease status (diseased or nondiseased).[28]

We used the deviance information criterion to assess model fit where low deviance information criterion shows the best fit to the data. We performed meta-analyses using the hierarchical summary receiver operating characteristics (HSROC) model with random effects to estimate sensitivity and specificity.[28]

We did a subgroup analysis on primary studies that used a common threshold (same limit of detection) of a mutant allele fraction at 0.1%. This limit of detection was chosen because clinical experts stated that this threshold is often used to detect *EGFR* T790M in liquid biopsy in Ontario. All output from the analyses is in Appendix 2.

The final model used to draw conclusions on the sensitivity and specificity of liquid biopsy was the HSROC model using random effects that included studies with a common threshold assuming tissue biopsy as an imperfect reference standard. However, estimates of sensitivity and specificity assuming tissue biopsy as imperfect and perfect reference standard are presented in the results.

We performed meta-analyses in WinBUGS, version 1.4.3, statistical software for Bayesian analysis.

Positive and negative predictive value is based on sensitivity, specificity, and prevalence of the condition (in this review, the prevalence of the *EGFR* T790M resistance mutation). The prevalence of *EGFR* T790M varied across included primary studies. We looked to literature to find the prevalence of the *EGFR* T790M resistance mutation in people with advanced NSCLC. The reported prevalence of the *EGFR* T790M resistance mutation in the North American population is reported as 63%.[29] We used the sensitivity and specificity values derived from the final model to calculate the PPV and NPV. However, estimates of sensitivity and specificity assuming tissue biopsy as a perfect reference standard to calculate PPV and NPV is also presented in the results. The equation to calculate PPV and NPV is below:

PPV = sensitivity × prevalence ÷ (sensitivity × prevalence + [1 – specificity] × [1 − prevalence])

NPV = specificity × (1 − prevalence) ÷ ([1 − sensitivity] × prevalence + specificity × [1 − prevalence])

For clinical utility outcomes, we were prepared to calculate the risk ratio and odds ratio with 95% confidence intervals (CIs) for each outcome as appropriate for studies with minimal clinical heterogeneity, using Review Manager 5.3.[30] However, given the limitations of how data on outcomes of interest were reported in the primary studies, we were able to provide only a narrative summary of the results.

Critical Appraisal of Evidence

We assessed risk of bias of systematic reviews using Risk of Bias in Systematic Reviews (ROBIS),[31] observational studies using Risk of Bias Among Non-randomized Studies (RoBANS),[32] and randomized controlled trials using Cochrane's risk of bias (ROB) tool.[33]

Authors of the systematic review assessed risk of bias of diagnostic test accuracy studies using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2),[34] and we reported this assessment. The risk of bias tables can be found in Appendix 3.

The authors of the systematic review did not undertake a Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment. We evaluated the quality of the body of evidence for each outcome according to the GRADE handbook.[35] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The clinical literature search yielded 4,007 citations published between January 1, 2000, and May 25, 2018, after removing duplicates.

While monitoring our search updates, a systematic review on diagnostic accuracy examining liquid biopsy to detect the *EGFR* T790M mutation in patients whose NSCLC had progressed after initial *EGFR*-TKI therapy was published.[36] This review addressed one of the research questions in this health technology assessment. We assessed the risk of bias and overall quality of this systematic review using ROBIS and A Measurement Tool to Assess Systematic Reviews (AMSTAR).[31,37] Because the systematic review was well aligned with the diagnostic accuracy research question and was of high quality and had low risk of bias, we decided to identify the primary studies within the review and report the authors' risk-of-bias assessment. However, the statistical analysis did not adhere to the Cochrane handbook on diagnostic test accuracy[27]; therefore, we conducted our own meta-analyses. We included the 19 studies within the systematic review. Twelve studies met the inclusion criteria for the clinical utility research question.[18,38-48]

Figure 2 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

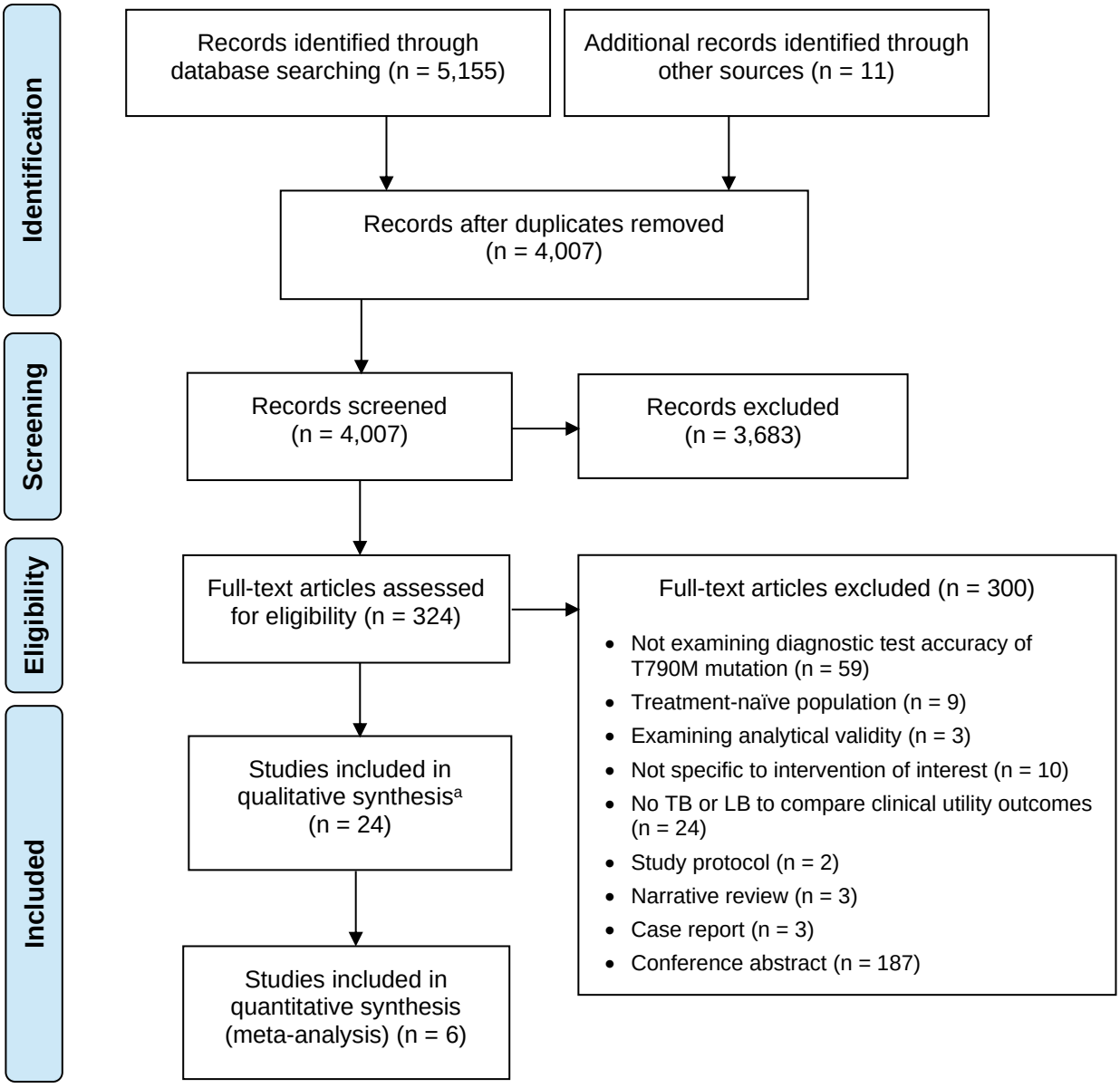

Figure 2: PRISMA Flow Diagram—Clinical Search Strategy

Abbreviations: DTA diagnostic test accuracy; LB, liquid biopsy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; TB, tissue biopsy.
Source: Adapted from Moher et al.[49]
[a]7 studies overlap between DTA and clinical utility results.

Diagnostic Accuracy

We identified a systematic review during our search updates. Nineteen studies were included in the systematic review. This systematic review had low risk of bias assessed by the ROBIS tool and scored 8 of 11 on the AMSTAR tool (Appendix 3). It examined the diagnostic accuracy of liquid biopsy to detect *EGFR* T790M mutation in people with advanced NSCLC. However, the statistical methods did not adhere to the Cochrane handbook on diagnostic test accuracy reviews; therefore, we conducted our own meta-analyses. All diagnostic accuracy outcomes

from the included studies were reported narratively. Only studies that reported the threshold (limit of detection) were included in the meta-analyses.

Studies were conducted in Australia,[39] Austria,[50] Canada,[38] China,[18,38,45,51,52] France,[39] Germany,[39] Japan,[38,46,53-56] Poland,[39] South Korea,[39] the United Kingdom,[38] and the United States.[38,42,44,57-61] Sample sizes in the included studies ranged from 10 to 543 people. All patients included in the review had matched blood and tumour tissue from patients with histologically confirmed diagnosis of advanced NSCLC who progressed after initial *EGFR*-TKI treatment.

Race was not reported in 14 studies[44-46,50-58,60,61]; when race was reported, Asian patients ranged from 16.0% to 63.9%, white patients ranged from 30% to 75%, Black patients ranged from less than 1% to 3%, and Native Hawaiian or other Pacific Islanders made up less than 1%. Age was not reported in three studies[44,57,58]; one study[45] reported age as younger or older than 65. When reported, age ranged from 53 to 68 years of age. Sex was not reported in three studies[44,57,58]; when it was reported, male patients in the samples ranged from 11% to 51% and female patients ranged from 48% to 88%.

Stage of NSCLC was not reported in five studies[18,39,44,53,59] and was reported as "advanced NSCLC" in six studies.[38,46,50,51,57,58] One study included Stage II and IIIA patients (2% and 5%); Stage IIIB ranged from 2.8% to 10%; Stage IV ranged from 85% to 100%, and postoperative recurrence ranged from 6.3% to 21.2%. Stage of NSCLC was not reported in 10 studies[18,44,46,50,51,55-58,60]; when it was reported, adenocarcinoma ranged from 78% to 100%, adenosquamous carcinoma ranged from 1% to 5%, and squamous cell carcinoma ranged from 1% to 6.7%.

Sensitizing mutations were not reported in six studies[39,44,57-59,61]; when they were reported, ex 19 deletion ranged from 38.8% to 73%, L858R ranged from 20% to 55.6%, and other mutations ranged from 1% to 8%. First-line treatments before cancer progression were not reported in eight studies.[39,42,44,51,57-59,61] When reported, erlotinib ranged from 5.6% to 58%, gefitinib ranged from 14.8% to 94.4%, afatinib ranged from 3% to 42%, dacomitinib ranged from 0.5% to 2%, icotinib ranged from 8.9% to 76.9%, and chemotherapy ranged from 10% to 61%.

This review included 19 studies.[36] However, two studies, Karlovich et al[39] and Thress et al,[44] used multiple detection methods (real-time PCR [RT-PCR] and digital PCR [dPCR]) and reported these results separately, so this review is treated as including 21 studies. Method of detection varied across studies; 12 used dPCR[18,39,42,44,45,50,51,53-57]; six used RT-PCR,[38,39,44,46,52,60] and three used NGS.[58,59,61] Detailed study and baseline characteristics can be found in Appendix 4.

We reported the risk of bias from the systematic review using QUADAS-2 and concluded that the studies were of good quality (See Appendix 3).[36]

Sensitivity and Specificity

Sensitivity is the ability of the test to correctly identify patients *with EGFR* T790M resistance mutation. Specificity refers to the ability of the test to correctly identify patients *without EGFR* T790M resistance mutation.[62]

The sensitivity of liquid biopsy ranged from 40% to 93% and the specificity from 18% to 100% across the 19 included studies (Table 2).

The threshold (limit of detection) to detect the *EGFR* T790M resistance mutation in liquid biopsy ranges across included studies. Therefore, our meta-analysis included only studies that had the same threshold (mutant allele fraction of 0.1%). This value is important because this threshold is normally used in Ontario. The sensitivity and specificity were examined by pooling data from six studies in a random-effects HSROC model assuming tissue biopsy as an imperfect reference standard. The pooled sensitivity was 0.68 (95% credible interval [CrI] 0.46–0.88), and the pooled specificity was 0.86 (95% CrI 0.62–0.98). The sensitivity and specificity of tissue biopsy in this model were 0.86 (95% CrI 0.75–0.98) and 0.93 (95% CrI 0.85–0.99), respectively.

Sensitivity and specificity pooling data in a random-effects HSROC model assuming tissue biopsy as a perfect gold standard are similar to the result above. The pooled sensitivity was 0.67 (95% CrI 0.47–0.84) and the pooled specificity was 0.79 (95% CrI 0.55–0.94).

We performed a subgroup analysis by detection methods (RT-PCR, dPCR, NGS) for our economic model (see Appendix 2).

The quality of evidence for sensitivity was moderate (see Appendix 3, Table A7) and was downgraded for indirectness because false-negative results will need to be "confirmed" through tissue biopsy when using liquid biopsy as a triage test. This is an invasive procedure that could have adverse events in this population (people with advanced NSCLC).

The quality of evidence for specificity was moderate (Appendix 3, Table A7) and was downgraded for indirectness because false-positive results will see people treated unnecessarily with osimertinib and could lead to continued disease progression.

Positive and Negative Predictive Value

Positive predictive value of a test is the proportion of patients that have *EGFR* T790M given the positive test result. Negative predictive value is the proportion of patients without *EGFR* T790M given the negative test result. Predictive values and are dependent on the prevalence of the *EGFR* T790M resistance mutation in the population being tested.[62]

The PPV of liquid biopsy ranged from 25% to 100% and the NPV from 25% to 95.2% across the included studies. The prevalence of *EGFR* T790M in the included studies ranged from 8% to 75.6%. Table 2 shows the PPV, NPV, and prevalence across included studies.

When calculating PPV and NPV, we used the pooled sensitivity and specificity reported above and the prevalence of *EGFR* T790M mutation reported in the literature (63%).[29] Therefore, using the estimates of sensitivity and specificity assuming tissue biopsy as an imperfect standard, the PPV and NPV of liquid biopsy is 0.89 and 0.61. We also calculated the PPV and NPV of tissue biopsy using the estimates reported above. The PPV and NPV of tissue biopsy is 0.95 and 0.79.

When using the estimates of sensitivity and specificity assuming tissue biopsy as a perfect reference standard, the PPV is 0.85 and NPV is 0.59.

Positive and negative predictive values are interrelated with sensitivity and specificity, using those estimates along with prevalence to calculate these predictive values. Because of this relationship, the quality of evidence for these outcomes was not assessed (Appendix 3, Table A7).

Concordance Rate

The concordance rate is the rate of agreement between two tests. The concordance rate of matched liquid and tissue biopsy ranged from 50% to 96% across the included studies. Table 2 shows the concordance rate in the included studies.

The quality of evidence for concordance rate was moderate (Appendix 3, Table A7) and was downgraded for indirectness because tissue biopsy is considered an imperfect gold standard.

Table 2: Sensitivity, Specificity, Concordance Rate, Positive and Negative Predictive Value in Included Studies

Author, Year	Sample Size	Threshold for Detection (LOD) for LB, Assay	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Prevalence, %	Concordance Rate (%)
Buder et al,[50] 2018	N = 44	0.01%, dPCR	28/33 (85)	2/11 (18)	28/37 (75.7)	2/7 (29)	75.0	30/44 (68)
Ishii et al,[53] 2015	N = 18	0.03%, dPCR	9/11 (81.8)	6/7 (85.7)	9/10 (90)	6/8 (75)	61.1	15/18 (83)
Jenkins et al,[38] 2017	N = 548	0.1%, RT-PCR	254/414 (61)	99/126 (79)	254/281 (90.4)	99/259 (38.3)	75.5	353/548 (64)
Karlovich et al,[39] 2016	N = 95	0.1%, RT-PCR	21/33 (64)	61/62 (98)	21/22 (95.5)	61/73 (83.6)	34.7	82/95 (86)
	N = 63	0.02%, dPCR	33/45 (73)	9/18 (50)	33/42 (78.6)	9/21 (42.9)	71.4	42/63 (67)
Kasahara et al,[54] 2017	N = 20	0.1%, dPCR	5/7 (71)	7/13 (54)	5/11 (45.5)	7/9 (77.8)	35.0	12/20 (60)
Mellert et al,[57] 2017	N = 55	0.02%, dPCR	13/15 (87)	40/40 (100)	13/13 (100)	40/42 (95.2)	27.2	53/55 (96)
Oxnard et al,[18] 2016	N = 216	0.06%, dPCR	111/158 (70.3)	40/58 (69)	111/129 (86)	40/87 (46)	73.1	151/216 (70)
Paweletz et al,[58] 2016	N = 14	0.4%, NGS	8/10 (80)	2/4 (50)	8/10 (80)	2/4 (50)	71.4	10/14 (71)
Reckamp et al,[59] 2016	N = 105	0.01%, NGS	38/41 (93)	60/64 (94)	38/42 (90.5)	60/63 (95.2)	39.0	98/105 (93)
Sacher et al,[42] 2016	N = 54	0.1%, dPCR	27/35 (77)	12/19 (63)	27/34 (79.4)	12/20 (60)	64.8	39/54 (72)
Seki et al,[55] 2016	N = 10	0.75%, dPCR	5/7 (71)	3/3 (100)	5/5 (100)	3/5 (60)	70.0	8/10 (80)
Sundaresan et al,[60] 2016	N = 25	0.1%, RT-PCR	6/10 (60)	9/15 (60)	6/12 (50)	9/13 (69.2)	40.0	15/25 (60)
Suzawa et al,[51] 2017	N = 59	0.01%, dPCR	9/21 (36)	37/38 (97)	9/10 (90)	37/49 (75.5)	35.6	46/59 (78)
Takahama et al,[56] 2016	N = 41	0.01%, dPCR	20/31 (65)	7/10 (70)	20/23 (87)	7/18 (38.9)	75.6	27/41 (65.9)

Author, Year	Sample Size	Threshold for Detection (LOD) for LB, Assay	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Prevalence, %	Concordance Rate (%)
Thompson et al,[61] 2016	N = 50	0.05%, NGS	2/4 (50)	40/46 (87)	2/8 (25)	40/42 (95.2)	8.0	42/50 (84)
Thress et al,[44] 2015	N = 65	0.1%, RT-PCR	30/41 (73)	16/24 (67)	30/38 (79)	16/27 (59.3)	63.1	46/65 (71)
		NR, dPCR	33/41 (81)	14/24 (58)	33/43 (76.7)	14/22 (63.6)	63.1	47/65 (72)
Wang et al,[45] 2017	N = 16	NR, dPCR	6/9 (66.7)	5/7 (71.4)	6/8 (75)	5/8 (62.5)	56.3	11/16 (69)
Wu et al,[52] 2017	N = 24	NR, RT-PCR	7/17 (41)	5/7 (71)	7/9 (77.8)	5/15 (33.3)	70.8	12/24 (50)
Yoshida et al,[46] 2017	N = 21	NR, RT-PCR	4/10 (40)	11/11 (100)	4/4 (100)	11/17 (64.7)	47.6	15/21 (71)

Abbreviations: dPCR, digital PCR; LB, liquid biopsy; LOD, limit of detection; NGS, next-generation sequencing; NR, not reported; PCR, polymerase chain reaction; RT-PCR, real-time PCR.
Adapted from Passiglia et al[36] (http://creativecommons.org/licenses/by/4.0/).

Clinical Utility

No studies examined the clinical utility of liquid biopsy as a triage test (liquid biopsy + tissue biopsy) compared with tissue biopsy alone. One study reported clinical utility outcomes between patients who tested positive for *EGFR* T790M or negative for *EGFR* T790M via liquid biopsy or tissue biopsy.[18] The rest of the studies compared clinical utility outcomes between patients who tested positive and negative for *EGFR* T790M resistance mutation ascertained by liquid biopsy.

Twelve studies from 14 publications were included (six prospective,[39,40,42,43,47,48] four randomized controlled trials,[14,44,63,64] three retrospective,[18,41,45] one non-randomized controlled trial[46]). Studies were conducted in Australia,[39] Canada,[38] China,[18,45,47,48] France,[39] Germany,[39] Japan,[38,40,41,43,46] Poland,[39] South Korea,[39] the United Kingdom,[38] and the United States.[38,42,44] Sample sizes ranged from 19 to 543 people.

Race was not reported in seven studies[41,43-48]; when race was reported, Asian patients ranged from 16.0% to 71%, white patients ranged from 26% to 75%, Black patients ranged from less than 1% to 3%, and Native Hawaiian or other Pacific Islanders made up less than 1%. Age was not reported in two studies,[40,44] and two studies[45,48] reported age as younger or older than 60 and 65 years. When reported, age ranged from 53 to 68 years. Sex was not reported in two studies.[40,44] When sex was reported, male patients in the sample ranged from 11% to 55% and female patients ranged from 45% to 88%.

The stage of NSCLC was not reported in four studies[18,39,40,44] and was reported as "advanced NSCLC" in two studies.[38,46] One study combined Stage II and III patients (9%); Stage III (no specification of A or B) alone ranged from 2.8% to 15%, Stage IIIA in one study was 16%, Stage IIIB ranged from 4% to 6%, Stage IV ranged from 76% to 100%, and postoperative recurrence ranged from 17% to 29%. The type of NSCLC was not reported in four studies[18,40,44,46]; when it was reported, adenocarcinoma ranged from 78% to 100%, adenosquamous in one study was 1%, nonadenocarcinoma ranged from 5% to 7%, and squamous cell carcinoma ranged from 1% to 6.7%.

Sensitizing mutations were not reported in four studies[39,40,44,48]; when it was, ex 19 deletion ranged from 38.8% to 73%, L858R ranged from 20% to 55.6% and other mutations ranged from 1% to 10%. First-line treatments prior to cancer progression was not reported in 5 studies.[39,40,42,44,48] When treatment was reported, erlotinib ranged from 5.6% to 58%, gefitinib ranged from 14% to 94%, afatinib ranged from 3% to 42%, dacomitinib ranged from 0.3% to 1%, icotinib in one study was 76%, and chemotherapy in one study was 61%. Detailed study and baseline characteristics of the included studies can be found in Appendix 4.

Time to Test Result

One prospective study examined time to test result.[42] They found that the median turnaround time from blood collection to report delivery was 2 business days (range 1–7 days). The median turnaround time for tissue biopsy was longer at 27 business days (range 1–146 days). In the 60 patients with cancer that progressed, 12 patients (20%) needed a repeat tissue biopsy. Turnaround time measurements included the time required to obtain an additional biopsy if one or more biopsy attempts failed. No statistical comparisons were made.

The quality of evidence for time to test result was low (See Appendix 3, Table A7).

Progression-Free Survival

Six studies (three prospective[40,47,48] and three retrospective[18,41,45]) examined the outcome of progression-free survival (PFS) (Table 3). Two studies that stated they were measuring overall survival used definitions similar to PFS and as such are included in our assessment of this outcome.[47,48] One study (Table 4)[45] specified treatment given to patients with and without the *EGFR* T790M mutation, and one study specified treatment given to patients with and without the *EGFR* T790M mutation by disease failure site (Table 5).[47]

One study[18] did not define PFS; three studies[40,41,48] defined PFS as the interval from initiation of first *EGFR*-TKI treatment to first instance of disease progression or death, and two studies[45,47] defined PFS as the interval between treatment resistance (disease progression) to second disease progression or death. All but one study showed no significant difference in PFS between people with or without *EGFR* T790M ascertained by liquid biopsy. Zheng et al[48] reported a significant difference between patients who were *EGFR* T790M positive and who were *EGFR* T790M negative as ascertained by liquid biopsy. This difference could be because patients who were *EGFR* T790M negative received *EGFR*-TKI therapy, which might not be appropriate treatment when a patient does not have the *EGFR* T790M mutation. In Oxnard et al,[18] patients who were *EGFR* T790M positive or *EGFR* T790M negative determined by tissue biopsy had significantly different PFS results, which could also be explained by treatment given to patients who were *EGFR* T790M negative.

The quality of evidence for PFS was low (See Appendix 3, Table A7).

Table 3: Progression-Free Survival in Patients Who Were *EGFR* T790M Positive Versus *EGFR* T790M Negative

Author, Year	Definition of PFS	Study Population	Length of Follow-Up	Results (Median PFS)		*P* Value
				EGFR T790M Negative	*EGFR* T790M Positive	
Nishikawa et al,[41] 2018	Interval between initiation of *EGFR*-TKI therapy and first manifestation of DP or death from any cause	N = 19	NR (up to 60 mo)	10.5 mo	9.1 mo	.58
	Interval between first *EGFR*-TKI treatment failure and death from any cause			24.9 mo	24.5 mo	.46
Wang et al,[45] 2017	Time from date of first DP to second DP or death	N = 91	NR (up to 12 mo)	3.1 mo	4.0 mo	.70
Kimura et al,[40] 2016	Interval between initiation of first *EGFR*-TKI therapy and first manifestation of DP or death from any cause	N = 52	NR (up to 40 mo)[a]	7.7 mo	9.2 mo	.60
Zheng et al,[48] 2016[b]	Initiation of TKI treatment to death for any reason, or last follow-up date (censored)	N = 117	Median follow-up ~16.4 mo (2.7–88.7 mo)	Not reached (most patients are censored alive)	26.9 mo	.04
Zhang et al,[47] 2018[c]	Time of development of TKI resistance to time of death for any reason or last follow-up	N = 278	NR (up to 24 mo)	--	--	--
	PFS by Detection Method					
	Digital polymerase chain reaction	--	--	16.4 mo (95% CI 12.8–20.0 mo)	17.8 mo (95% CI 14.1–21.6 mo)	.55[d]
	Real-time polymerase chain reaction (amplification refractory mutation system)	--	--	17.7 mo (95% CI 14.6–20.8 mo)	16.4 mo (95% CI 12.4–20.3 mo)	--
	PFS by Disease Failure Site					
	Limited to chest	--	--	18.4 mo (95% CI 15.9–20.9 mo)	14.4 mo (95% CI 8.7–20.1 mo)	.24
	Limited to brain	--	--	8.6 mo (95% CI 4.8–12.4 mo)	4.0 mo (95% CI 0.0–10.8 mo)	.19

Author, Year	Definition of PFS	Study Population	Length of Follow-Up	Results (Median PFS)		*P* Value
				***EGFR* T790M Negative**	***EGFR* T790M Positive**	
	Limited to other site	--	--	14.5 mo (95% CI 11.4–17.6 mo)	17.2 mo (95% CI not reached)	.47
Oxnard et al,[18] 2016	Not defined	N = 231	NR (up to 24 mo)	Tissue biopsy 3.4 mo (95% CI 2.1–4.3 mo)	Tissue biopsy 9.7 mo (95% CI 8.3–12.5 mo)	< .001
				Liquid biopsy 8.2 mo (95% CI 5.3–10.9 mo)	Liquid biopsy 9.7 mo (95% CI 8.3–11.1 mo)	.18

Abbreviations: CI, confidence interval; DP, disease progression; *EGFR*, epidermal growth factor receptor; NR, not reported; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

[a]Reported follow-up and PFS in days, converted to months for consistency across studies.

[b]Post-TKI DP treatment was given as follows: half of sample (n = 55) received TKI alone (24 that were *EGFR* T790M positive and 31 that were *EGFR* T790M negative) and half (n = 52) received TKI plus chemotherapy (25 that were *EGFR* T790M positive and 27 that were *EGFR* T790M negative), and 10 received "other" treatment (6 that were *EGFR* T790M positive and 4 that were *EGFR* T790M negative). Progression-free survival of patients with or without *EGFR* T790M was not compared by treatment regimen.

[c]Zhang et al examined PFS by disease failure sites. This was determined by radiography to evaluate DP at the original (primary and metastatic) or new site(s).

[d]*P* value compares detection method across *EGFR* T790M status.

Table 4: Progression-Free Survival by Treatment Regimen for *EGFR* T790M–Positive Versus *EGFR* T790M–Negative Results

Treatment Regimen	Results (Median Progression-Free Survival)		*P* Value
	***EGFR* T790M− (mo)**	***EGFR* T790M+ (mo)**	
Continuous tyrosine kinase inhibitor	2.9	3.1	.83
Chemotherapy	2.8	2.9	.77
Continuous tyrosine kinase inhibitor + chemotherapy	4.3	6.0	.72

Abbreviation: *EGFR*, epidermal growth factor receptor.

Source: Wang et al, 2017.[45]

Table 5: Progression-Free Survival by Treatment Regimen for *EGFR* T790M–Positive Versus *EGFR* T790M–Negative Results

Treatment Regiment	Results (Median PFS) by Disease Failure Site		
	Limited to Chest	Limited to Brain	Limited to Other Site
Osimertinib			
T790M+	Not reached	Not reached	Not reached
T790M−	Not reached	Not reached	14.5 mo (95% CI 1.4–27.6 mo)
Continuation of *EGFR* TKI			
T790M+	9.7 mo (95% CI 2.7–16.8 mo)	0.9 mo (95% CI not reached)	16.4 mo (95% CI 10.9–21.6 mo)
T790M−	14.6 mo (95% CI 9.0–20.2 mo)	2.1 mo (95% CI 0.5–3.6 mo)	11.2 mo (95% CI 0–24.0 mo)
Chemotherapy ± Radiation Therapy			
T790M+	17.8 mo (95% CI not reached)	--	4.0 mo (95% CI 0–17.5 mo)
T790M−	17.8 mo (95% CI 6.4–29.2 mo)	5.1 mo (95% CI not reached)	Not reached
***EGFR* TKI ± Chemotherapy and Radiation Therapy**			
T790M+	11.0 mo (95% CI not reached)	--	9.1 mo (95% CI not reached)
T790M−	Not reached	Not reached	Not reached
Best Supportive Care			
T790M+	6.1 mo (95% CI 3.0–9.1 mo)	4.1 mo (95% CI 0–10.3 mo)	1.3 mo (95% CI 0–3.5 mo)
T790M−	Not reached	8.6 mo (95% CI 3.9–13.4 mo)	2.0 mo (95% CI 0–6.0 mo)
P-Value for *EGFR* T790M Result by Treatment Regimen[a]			
T790M+	.01	.29	.06
T790M−	.02	.03	.02

Abbreviations: CI, confidence interval; *EGFR*, epidermal growth factor receptor; PFS, progression-free survival; TKI, tyrosine kinase inhibitor;
[a]Zhang et al[47] examined PFS by disease failure site across treatments.

Overall Survival

Two studies (one retrospective[45] and one prospective[43]) examined overall survival.

Wang et al[45] defined overall survival as the period from diagnosis with advanced NSCLC to the date of death by any cause or to the date when the patient was last known to be alive. The median overall survival in patients with the *EGFR* T790M mutation was 35.3 months, which was not significantly longer than 30.3 months in patients without the *EGFR* T790M mutation (P = 0.214).

Sueoka-Aragane et al[43] compared overall survival of patients with and without *EGFR* T790M. Patients without *EGFR* T790M had significantly longer overall survival than patients with *EGFR* T790M (median overall survival, 516 days vs. 782 days; hazard ratio for death as *EGFR* T790M

positive by liquid biopsy, 2.15; 95% CI 1.11–4.14; *P* = .020). Combined analysis of *EGFR* T790M and sensitizing mutations with liquid biopsy showed that having neither *EGFR* T790M nor sensitizing mutations was associated with better prognosis than having both *EGFR* T790M and sensitizing mutation or either alone (median overall survival 807 days vs. 509 days; hazard ratio for death with neither *EGFR* T790M nor sensitizing mutation in liquid biopsy 0.240; 95% CI 0.104–0.553; *P* = .010).

The quality of evidence for overall survival was very low (see Appendix 3, Table A7) and was downgraded for inconsistency because of the different direction in estimates.

Response Rate

Eight studies from six publications (four randomized controlled trials,[38,39,44] one prospective,[39] two retrospective,[18,41] one non-randomized controlled trial[46]) measured response rate using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Below are the definitions of the criteria used.[65]

Evaluation of target lesions are assessed by the following categories:

- Complete response: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm
- Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
- Stable disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters on study

Evaluation of non-target lesions are assessed by the following categories:

- Complete response: disappearance of all non-target lesions and return to normal of tumour marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)
- Non-complete response/non-progressive disease: persistence of one or more non-target lesion(s) or maintenance of tumour marker level above normal limits
- Progressive disease: unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression.)

Two studies gave osimertinib to patients whose tissue biopsy results were *EGFR* T790M positive (only two patients whose liquid biopsy results were *EGFR* T790M positive received treatment). Response rate was similar between those who tested *EGFR* T790M positive on liquid versus tissue biopsy; however, no statistical comparisons were made (Table 6).

The quality of evidence for response rate was low (see Appendix 3, Table A7).

Table 6: Response Rate[a] in Patients with *EGFR* T790M–Positive Versus *EGFR* T790M–Negative Results

Author, Year	Sample Size	Treatment Regimen	Results (%)	Notes
Nishikawa et al,[41] 2018	N = 9	Osimerinib	6/9 (66.7%) partial response	Only tissue T790M+ patients were given osimertinib
Yoshida et al,[46,66] 2017	N = 11	Osimertinib	8/11 (72.7%) partial response 3/11 (27.3%) stable disease Objective response rate: • All patients = 73% • Tissue+ = 73% • Liquid+ = 100%	10/11 patients were tissue T790M+ and 1/11 was liquid T790M+
Jenkins et al,[38] 2017	n = 397 (tissue T790M+) n = 235 (tissue and liquid T790M+)	Osimertinib	Tissue+ = 262/397 (66%; 95% CI 61–71) Liquid+ = 150/235 (64%; 95% CI 57–70)	Response rate using RECIST, combining complete and partial response criteria
Karlovich et al,[39] 2016	n = 25 (tissue T790M+) n = 21 (liquid T790M+)	Rociletinib	Tissue+ and liquid+ = 8/15 (53%; 95% CI 28–79) Tissue+ and liquid− = 3/6 (50%; 95% CI 10–90) Tissue− and liquid+ = 1/4 (25%; 95% CI 0–67) Tissue− and liquid− = 0/3 (0%; 95% CI 0–71) Objective response rate: • All patients = 53% • Tissue+ = 52% • Liquid+ = 44%	Response rate using RECIST, combining complete and partial response criteria
Thress et al,[44] 2015	N = 41	Osimertinib	Tissue+ = 25/41 (61%) Tissue−= 7/24 (29%) Liquid+ = 24/41 (59%) Liquid− = 11/31 (35%)	Response rate using RECIST, combining complete and partial response criteria
Oxnard et al,[18] 2016	n = 231 (tissue) n = 271 (liquid)	Osimertinib	Tissue+ = 108/173 (62%; 95% CI 54–70) Tissue− = 15/58 (25%; 95% CI 15–39); *P* < .001 Liquid+ = 103/164 (63%; 95% CI 55–70) Liquid− = 47/102 (46%; 95% CI 36–56) Subset of liquid+ divided by tissue result: • Tissue+ = 69/108 (64%; 95% CI 54–73) • Tissue− = 5/18 (28%; 95% CI 10–53); *P* = .004	Response rate using RECIST, combining complete and partial response criteria

Abbreviations: CI, confidence interval; *EGFR*, epidermal growth factor receptor; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Response rate was determined by RECIST 1.1 criteria.

Tissue Biopsies Avoided and Adverse Events

None of the studies reported on tissue biopsies avoided and adverse events of the actual process of conducting a liquid biopsy. Given that a liquid biopsy is a simple blood draw, as long as proper phlebotomy procedures are followed, it is expected that there would be no adverse outcomes. There is, however, the potential for tissue biopsies avoided; this will be explored in more detail in the economic model in the next chapter.

Ongoing Studies

We are aware of the following ongoing studies comparing liquid with tissue biopsy to detect *EGFR* T790M in patients with advanced NSCLC:

- A multicentre prospective Canadian study out of the University Health Network comparing blood-based profiling to standard of care tissue-based profiling (https://clinicaltrials.gov/ct2/show/NCT03576937)
- Phase II study of osimertinib in patients harbouring *EGFR* T790M who failed to benefit from *EGFR*-TKIs and who have brain or leptomeningeal metastasis. Researchers plan an exploratory analysis of *EGFR* mutation/T790M in tissue, plasma, or cerebrospinal fluid (https://clinicaltrials.gov/ct2/show/NCT03257124?cond=T790M&rank=5)
- A randomized controlled trial comparing osimertinib and bevacizumab with osimertinib alone in patients with *EGFR* T790M mutation. As a tertiary outcome, authors will assess *EGFR* T790M evolution in tissue and plasma (https://clinicaltrials.gov/ct2/show/NCT03133546?cond=T790M&rank=18)
- Phase I study to evaluate the safety and efficacy of BPI-7711 in patients with *EGFR* T790M. A tertiary outcome will assess serial *EGFR* T790M testing via liquid biopsy (https://clinicaltrials.gov/ct2/show/NCT03386955?cond=T790M&rank=32)

Discussion

The pooled sensitivity and specificity of liquid biopsy to detect *EGFR* T790M in patients with NSCLC was 0.68 (95% CrI: 0.46–0.88) and 0.86 (95% CrI: 0.62–0.99), respectively, using an HSROC model that assumed tissue biopsy was an imperfect standard. These results mean that the probability of correctly classifying a patient *who actually has* the *EGFR* T790M mutation is 68% and the probability of correctly classifying a patient *who does not have* the *EGFR* T790M mutation is 86%. The PPV tells us that, given a positive test result and a disease prevalence rate of 63%, 89% of patients will have the *EGFR* T790M mutation while the NPV tells us that, given a negative test result and the same disease prevalence rate, 61% of patients will not have the *EGFR* T790M mutation. Guidelines on *EGFR* T790M testing were released in 2018.[21] These guidelines recommend using liquid biopsy as a triage test, which is current clinical practice in Ontario. If a patient has a negative test result with liquid biopsy, a patient should have a tumour biopsy. The NPV calculated in this review supports that practice.

The sensitivity and specificity of liquid biopsy to detect *EGFR* T790M is influenced by multiple biological factors that make evaluating diagnostic accuracy of the test difficult; therefore, these biological factors introduce some uncertainty into the accuracy of the reported sensitivity and specificity. When examining the diagnostic accuracy of a test, we compare the new test with the reference standard to determine the test's performance. Tissue biopsy is the reference standard used for detecting the *EGFR* T790M mutation in patients with NSCLC. However, tissue biopsy has some limitations. Intertumour heterogeneity exists, where some tumours harbour *EGFR* T790M and others do not. This makes it difficult to detect the *EGFR* T790M mutation when

retrieving a sample from a single tumour. In our statistical methods, to determine the sensitivity and specificity of liquid biopsy, we assumed tissue biopsy was an imperfect reference standard. Our analysis also produced estimates of sensitivity and specificity for tissue biopsy. However, it is difficult to validate these numbers because there are no published estimates of the sensitivity and specificity of tissue biopsy to detect the *EGFR* T790M mutation.

Liquid biopsy can potentially avoid intertumour heterogeneity because it collects cell-free ctDNA from all tumours a patient might have via plasma sample. However, there is further complexity because collection is dependent on how much a tumour sheds its cells and current guidelines have stated that there is no evidence on optimal timing for testing. Clinical experts have stated that there are no clinical attributes of NSCLC to show how a patient's tumours will shed cells (in-person communication, T. Stockley, MD, December 2018). Not knowing whether the sample contains enough cell-free ctDNA to detect the *EGFR* T790M resistance mutation introduces further uncertainty about the accuracy of liquid biopsy. This uncertainty about the appropriate timing of liquid biopsy could be remedied by serial testing using liquid biopsy to detect the *EGFR* T790M mutation. There is evidence that the *EGFR* T790M mutation is biologically present before disease progression is documented.[48] However, no evidence on optimal timing of serial testing is available.

One of the biggest limitations in the diagnostic accuracy literature for this topic is the range of positivity thresholds across the various studies. This factor heavily influences the sensitivity and specificity of a diagnostic test. To ensure results were clinically meaningful and interpretable, we pooled studies that reported the same threshold. We chose the threshold of 0.1% because our clinical experts report this threshold is used in Ontario (telephone communication, T. Stockley, MD; M. Tsao, MD; B. Sadikovic, PhD; April 2018). Future research should standardize and specifically identify the minimum biological threshold that will guide treatment decisions in clinical practice.

Originally for this review, clinical utility outcomes that were of interest were process outcomes (time to test result, tissue biopsies avoided), because outcomes like PFS, overall survival, and response rate are better related to the effectiveness of treatment (e.g., osimertinib, chemotherapy), which is not the focus of this review. Given the predictive nature of the test, we speculated that clinical outcomes such as PFS, overall survival, and response rate would be similar in patients whose results were positive regardless of the method of biopsy (tissue or liquid) because they would be receiving effective treatment based on test result. Only one study included examined time to test result. It showed that the median turnaround time for liquid versus tissue biopsy was 2 versus 27 days, respectively.[42] While these estimates were not statistically compared, the difference in turnaround time is meaningful. Tissue biopsy requires more resources. In order to obtain biopsy samples; oncologists must engage interventional radiologists or surgeons to book a surgical suite. This would include waiting time based on availability. Depending on how advanced the cancer is in the patient, an additional biopsy could be necessary if the biopsy attempt fails (e.g., inadequate sample). Liquid biopsy does not require these resources. However, given how few labs are equipped to process liquid biopsy samples in Ontario, some hospitals will mail the samples to another hospital lab to obtain results, which will add to turnaround time.

Patients tended to have similar PFS times if they tested positive or negative for *EGFR* T790M ascertained by liquid biopsy and were given appropriate treatment. In one study,[18] researchers reported results for patients who tested positive and negative on both tissue and liquid biopsies. Progression-free survival was similar but not statistically compared between those with positive results on either tissue or liquid biopsies (both estimates were 9.7 months). Similar PFS was to

be expected if patients were given appropriate treatment, regardless of the type of biopsy (tissue or liquid).

While there are limitations to studying the diagnostic accuracy of liquid biopsy for *EGFR* T790M and inconsistencies in the literature about timing of liquid biopsy, the evidence supports the guidelines to use liquid biopsy as a triage test to minimize risk to patients and improve efficiency of care delivery. Liquid biopsy identifies a high proportion of people with the *EGFR* T790M mutation and can avoid the need for a tissue biopsy. This is beneficial especially for people who might be unable to have a tissue biopsy.

Conclusions

The pooled sensitivity and specificity of liquid biopsy to detect *EGFR* T790M in patients with NSCLC was 68% (95% CrI, 46%–88%) and 86% (95% CrI, 62%–99%) (GRADE: Moderate). The PPV and NPV was 89% and 61%, respectively. The concordance rate of matched liquid and tissue biopsy ranged from 50% to 96% (GRADE: Moderate).

Evidence for process outcomes (time to test result, tissue biopsies avoided) was limited. One study showed the median time to test result for liquid versus tissue biopsy as 2 versus 27 days (GRADE: Low), but this result was not statistically compared. Progression-free survival was similar in patients with or without *EGFR* T790M ascertained using liquid biopsy (GRADE: Low). One study reported but did not statistically compare the PFS of patients who were *EGFR* T790M positive via tissue and liquid biopsy; it showed similar PFS (9.7 months).

ECONOMIC EVIDENCE

Research Question

What is the cost-effectiveness of cell-free circulating tumour DNA (ctDNA) blood testing (also called liquid biopsy), alone or in combination with tissue biopsy, compared with alternative testing strategies for the detection of the resistance mutation epidermal growth factor receptor (*EGFR*) T790M in people with advanced non–small cell lung cancer (NSCLC)?

Methods

Economic Literature Search

We performed an economic literature search on May 28, 2018, to retrieve studies published from January 1, 2000, until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase, and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Evidence literature search, above, for further details on methods used. See Appendix 1 for the literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 2000, and May 28, 2018
- Studies in people with advanced or metastatic (stage 3 or 4) NSCLC
- Studies in people who have an *EGFR* mutation and who have progressed on first/second generation *EGFR*–tyrosine kinase inhibitor (TKI) therapy
- Studies comparing liquid biopsy (alone or in combination with tissue biopsy) to tissue biopsy alone for the detection of the *EGFR* T790M mutation. Where liquid biopsy was offered in combination with tissue biopsy, liquid biopsy was used as a triage test. People were tested through liquid biopsy first, if that test were negative or inconclusive, they would receive tissue biopsy
- Cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses, cost-consequence analyses, or cost minimization analyses

Exclusion Criteria

- Abstracts, case reports, editorials, commentaries, reviews, letters, unpublished studies
- Costing analyses
- Studies evaluating the cost-effectiveness of osimertinib without consideration of biopsy strategies (i.e., liquid biopsy)
- Studies evaluating non-blood liquid biopsy strategies

Population

- Patients with NSCLC who have an *EGFR*-sensitizing mutation who have progressed while using first- or second-generation *EGFR*-tyrosine kinase inhibitor (TKI) therapy

Interventions

- Liquid biopsy (alone or in combination with tissue biopsy) compared with alternative testing strategies (i.e., tissue biopsy alone) for detection of the *EGFR* T790M mutation

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years [QALYs])
- Incremental costs and incremental effectiveness
- Incremental cost-effectiveness ratio (ICER)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using DistillerSR management software and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. This single reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists for any relevant studies not identified through the search.

Data Extraction

We extracted relevant data on the following:

- Source (e.g., citation information, study type)
- Population (e.g., sample size, age, and percentage of male subjects)
- Intervention(s) and comparator(s)
- Outcomes (e.g., health outcomes, costs, ICERs)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[67] We modified the wording of the questions to

remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be directly applicable.

Results

Economic Literature Search

The economic literature search yielded 189 citations published between January 1, 2000, and May 28, 2018, after removing duplicates. We excluded a total of 129 articles based on information in the title and abstract. We then obtained the full texts of 60 potentially relevant articles for further assessment. One article was included in the final review. See Appendix 5 for a list of studies excluded after full text review. Figure 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

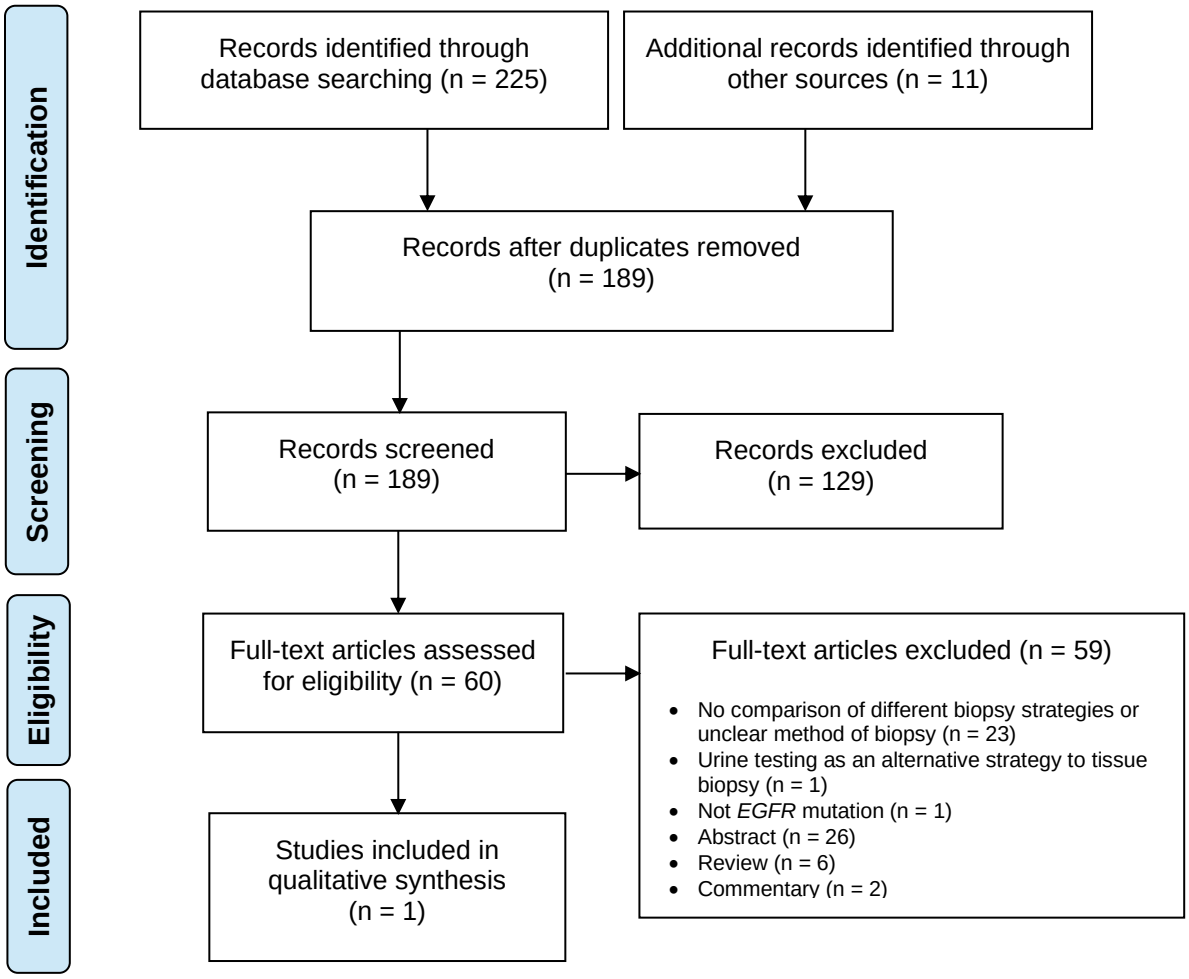

Figure 3: PRISMA Flow Diagram—Economic Search Strategy

Abbreviations: *EGFR*, epidermal growth factor receptor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al, 2009.[49]

Overview of Included Economic Study

We included one study by Wu et al[68] that evaluated the cost-effectiveness of osimertinib versus standard chemotherapy for *EGFR* mutation–positive NSCLC after progression following first-line *EGFR*-TKI therapy. Although the objective of the study is not in line with our research question, the analysis considered multiple scenarios, including liquid biopsy as a triage test (followed by tissue biopsy for people who test negative) and liquid biopsy alone, allowing a comparison of our scenarios of interest. On the basis of the costs and QALYs provided in these scenarios, we were able to obtain the ICER for liquid biopsy as a triage test compared with liquid biopsy alone. The methods and relevant results from the study are summarized in Table 7.

Wu et al[68] used decision trees to model the various methods of biopsy, followed by a Markov model to describe NSCLC progression over 10 years. The Markov cycle length (the time spent in one health state before transitioning to another) was 21 days, which reflected the schedule for chemotherapy treatment. The authors conducted separate analyses from the perspectives of the United States and Chinese health care payers; both are presented in 2017 US dollars.

Clinical inputs were informed by the published literature, including the AURA3 trial evaluating osimertinib versus chemotherapy in people with *EGFR* T790M–positive advanced NSCLC.[69] Key clinical data taken from the AURA3 trial include progression-free survival (PFS) and probabilities of severe adverse events. Systematic reviews were also used to inform real-world treatment patterns and overall survival rates.[70,71] The study took health utility values from a published international study for each health stage of advanced NSCLC (stages III and IV) and complications associated with treatment.[72] The study considered costs related to osimertinib, chemotherapy, biopsy, mutation testing, palliative care, and complications.

Using liquid biopsy as a triage test led to the identification of the *EGFR* T790M mutation in 17.8% more people than using liquid biopsy alone. From both the United States and Chinese health care payer perspectives, the cost of liquid biopsy as a triage test in combination with subsequent treatment was associated with greater costs than the use of liquid biopsy alone.

Since the original analysis did not directly compare the two biopsy methods, we calculated the ICER using the QALYs and costs provided. The ICER for liquid biopsy as a triage test versus liquid biopsy alone was $243,706 USD per QALY using the United States perspective, and $53,913 USD per QALY using the Chinese perspective. The authors did not elaborate in detail on the difference in ICERs between the two perspectives, but the table of base cost estimates showed that all treatments in the United States were 2 to 15 times the cost of the same treatments in China.

Because Wu et al[68] had a different objective and compared all mutation-testing scenarios with chemotherapy, their sensitivity analyses are not applicable to our research question. However, it is noteworthy that the study models were most sensitive to the cost of osimertinib. If the price of osimertinib is discounted by 50% in both the United States and China, it becomes a cost-effective alternative to chemotherapy.

Table 7: Results of Economic Literature Review—Summary

Author, Year, Country of Publication	Analytic Technique, Study Design, Time Horizon, and Perspective	Population	Intervention(s) and Comparator(s)	Results[a]		
				Health Outcomes, QALYs	Costs	ICER
Wu et al, 2018,[68] China	• Cost–utility analysis • Decision tree for mutation testing and Markov model for NSCLC progression • Markov cycle length: 21 d • Time horizon: 10-yr • Health care payer perspective (United States: 3% discount rate; China: 5% discount rate)	People with *EGFR* mutation who have disease progression after treatment with first-line *EGFR*-TKI therapy[b]	**Intervention** Liquid biopsy as triage test: participants undergo liquid biopsy for *EGFR* T790M mutation testing. Those with negative results undergo tissue biopsy for retesting **Comparator** Liquid biopsy alone	**US perspective** • Liquid biopsy as triage test: 0.886 • Liquid biopsy alone: 0.760 • Incremental: 0.126 **China perspective** • Liquid biopsy as triage test: 0.939 • Liquid biopsy alone: 0.824 • Incremental: 0.115	**US perspective** • Liquid biopsy as triage test: $211,180 • Liquid biopsy alone: $180,473 • Incremental: $30,707 **China perspective** • Liquid biopsy as triage test: $42,667 • Liquid biopsy alone: $36,467 • Incremental: $6,200	**US perspective** Liquid biopsy as triage vs. liquid biopsy alone: $243,706.30 per QALY[c] **China perspective** Liquid biopsy as triage vs. liquid biopsy alone: $53,913.04 per QALY[c]

Abbreviations: *EGFR*, epidermal growth factor receptor; ICER, incremental cost-effectiveness ratio; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitors; QALY, quality-adjusted life-year.

[a]All costs in 2017 USD.

[b]The authors did not report sample size, age, or sex.

[c]The authors did not report an ICER. We calculated this ICER using the QALYs and costs provided in the study.

Applicability and Limitations of the Included Study

The results of the applicability and limitations checklist applied to Wu et al[68] are presented in Appendix 6 (Tables A10 and A11). The study was deemed partially applicable to the research question. The study population was directly applicable to our research question, which involved people with *EGFR* T790M mutation who have disease progression after first-line *EGFR*-TKI therapy. The analysis was conducted from the health care payer perspective in the United States and China. The study comparators were partially applicable, as the study considered some but not all possible combinations of biopsy strategy (e.g., they did not consider the cost-effectiveness of liquid biopsy compared with tissue biopsy alone).

In terms of the strengths and limitations of the study, the authors considered the perspectives of multiple health care systems. They used appropriate model structure, cycle length, and time horizon to reflect the disease progression. They attempted to extrapolate long-term survival outcome beyond the duration of the clinical trial by applying additional statistical analysis (e.g., Weibull and log-logistic survival models). Although the authors did not conduct a systematic review to identify clinical inputs, they used published randomized controlled trials and recent systematic reviews for clinical inputs and considered long-term survival and major complication.

Discussion

Our economic evidence review identified one study evaluating the cost-effectiveness of osimertinib versus chemotherapy while considering multiple biopsy strategies.[68] We used the costs and QALYs provided in the study to calculate the ICER from using liquid biopsy as a triage test compared with liquid biopsy alone for detection of the *EGFR* T790M mutation. From the perspective of the US health care payer, using the willingness-to-pay threshold of $100,000 USD per QALY, the calculated ICER of $243,706 per QALY was not cost-effective. From the perspective of the China health care payer, using the threshold of $23,815 USD per QALY (three times the per capita gross domestic product in China in 2016), the calculated ICER of $53,913 per QALY was also not cost-effective.

Several factors limit the applicability of the study to our research question for Ontario. The study by Wu et al[68] considered health care payer perspectives in the US and China. The study did not consider all biopsy combinations of interest, such as liquid biopsy (with or without tissue) versus tissue biopsy alone. We were unable to quantify the uncertainty of our ICER calculations because only the point estimates of the costs and QALYs are available and the original sensitivity analyses were based on different comparisons.

Although they did not meet our inclusion criteria, we identified several abstracts comparing the costs of liquid and tissue biopsy strategies.[73-78] Most reported that, compared with tissue biopsy, liquid biopsy alone or as a triage test reduced costs.

Conclusions

We found one study showing that liquid biopsy as a triage test (followed by tissue biopsy if the test is negative) compared with liquid biopsy alone for the detection of the *EGFR* T790 mutation was not cost-effective from the perspectives of the US and China health care payer systems.[68] The study is not directly applicable to the Canadian perspective. Further, the study did not consider all combinations of biopsy strategies that could be implemented in Ontario.

PRIMARY ECONOMIC EVALUATION

The published economic evaluation identified in the economic literature review addressed the comparison of liquid biopsy as a triage test (followed by tissue biopsy if results are negative) to liquid biopsy alone from the perspectives of the US and China health care payer systems.[68] However, the study did not consider all combinations of biopsy strategies relevant to the Ontario context. Given these limitations, we conducted a primary economic evaluation.

Research Question

What is the cost-effectiveness of cell-free circulating tumour DNA (ctDNA) blood testing (also known as liquid biopsy), as a triage test or alone, compared with tissue biopsy for the detection of the *EGFR* T790M mutation in people with advanced non–small cell lung cancer (NSCLC) from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[79]

Analysis

We conducted a reference case analysis and sensitivity analyses. The reference case analysis adhered to guidelines from the Canadian Agency for Drugs and Technologies in Health (CADTH)[80] when appropriate and represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

We examined the costs and outcomes associated specifically with the diagnostic testing strategies over time from diagnostic testing to treatment decision. The outcomes of interest in our analyses included the following:

- Incremental costs (including only testing and testing-related adverse event costs)
- Incremental number of tissue biopsies avoided
- Incremental number of correct treatment decisions (i.e., when *EGFR* T790M–positive patients are treated with the third-generation *EGFR*-TKI, osimertinib, and *EGFR* T790M–negative patients are treated with chemotherapy)
- Incremental cost per tissue biopsy avoided
- Incremental cost per additional correct treatment decision

We also calculated the time to treatment decision and number of people who received osimertinib to provide additional context to our results.

To capture the effects of testing and treatment on both survival and quality of life, we also conducted long-term cost–utility and cost-effectiveness analyses. The outcomes of interest from these analyses included the following:

- Incremental costs (including testing, treatment, adverse event, and care costs)
- Incremental life-years and QALYs
- Incremental cost per life-year and QALY

Target Population

The target population was adults with advanced NSCLC who have an *EGFR* sensitizing mutation and whose disease has progressed after first-line (first- or second-generation) *EGFR*-TKI therapy. Advanced NSCLC consists of stages IIIB and IV NSCLC.[81]

For our reference case analysis, we modelled a cohort of mostly male (~55%) people aged 64 years or older. This cohort was based on people included in a Canadian multicentre validation study of liquid biopsy for *EGFR* T790M mutation testing.[82] This was slightly different from the age (mean: 60 years) and proportion of males (~45%) in clinical trials.[83] We tested a range of cohort starting ages in our sensitivity analyses.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

In our reference case analysis, we compared:

- Tissue biopsy alone (standard of care)
- Liquid biopsy as a triage test (followed by tissue biopsy if the result is negative)
- Liquid biopsy alone

Tissue biopsy is defined as percutaneous transthoracic lung biopsy, where a sample of the tumour mass is taken using a needle placed through the chest under imaging guidance (usually computed tomography [CT]).[84] In liquid biopsy, a person's blood is drawn and the blood plasma is analyzed to detect cell-free ctDNA with the *EGFR* T790M mutation.[21] If liquid biopsy is used as a triage test, then a negative result would be followed up with a tissue biopsy for further review.

We also conducted sensitivity analyses to examine the cost-effectiveness of different liquid biopsy testing strategies. Cell-free ctDNA from liquid biopsy samples can be analyzed using several detection methods, including real-time polymerase chain reaction (RT-PCR), digital PCR (dPCR), and next-generation sequencing (NGS). Liquid biopsy is currently being conducted in Ontario laboratories using commercially available platforms or laboratory-developed in-house tests. These tests are funded privately. The testing strategies, platforms, and laboratories can differ by diagnostic test accuracy, cost, and other test-, lab-, and operator-related characteristics. We explored how these differences affect the cost-effectiveness and cost–utility of liquid biopsy.

Time Horizon and Discounting

In our short-term analysis, the time horizon was the time from disease progression after first-line (first- or second-generation) *EGFR*-TKI therapy to the treatment decision under various testing strategies. In our long-term analyses, we used a 10-year (life-long) time horizon.

We applied an annual discount rate of 1.5% to both costs and QALYs. We conducted sensitivity analyses to look at a range of discount rates (0% to 5%).

Model Structure

We based our model structure on an economic framework developed by CADTH[85] and previous cost-effectiveness analyses.[68,86,87] The framework from CADTH highlights methods to assess the cost-effectiveness of *EGFR* mutation testing for first-line TKIs. Although we assessed using liquid biopsy to decide on a second-line treatment, the treatment pathways and model structure had many similar features.

We used a decision tree combined with a cohort health state transition (Markov) model. The decision tree was used to model the mutation testing and initial treatment decision. The Markov model was used to capture disease progression, survival, and treatment modifications over time. We used a cycle length of 3 weeks because this corresponded to approximately one round of chemotherapy.[81]

Decision Tree

The clinical pathways of the three testing strategies are summarized in Figures 4, 5, and 6.

Key Assumptions—Testing Strategies

We made the following assumptions in our reference case analysis with respect to the testing strategies:

- All people accept and are able to have liquid biopsy
- Some people might refuse or be unable to receive tissue biopsy
- Some proportion of liquid biopsies fail or have inconclusive results. Because liquid biopsies are a minimally invasive procedure, all people would have a repeat liquid biopsy
- Some proportion of tissue biopsies fail or have inconclusive results. Because tissue biopsies are an invasive procedure, not all people would have a repeat tissue biopsy
- No repeat testing occurs among those with a negative liquid biopsy result. The person would move to the next step in the clinical pathway (i.e., follow-up tissue biopsy or treatment decision). We examined repeat liquid biopsies in our sensitivity analysis
- Tissue biopsy is an imperfect reference standard. However, we also examined a scenario where we treat tissue biopsy as a perfect reference standard
- *EGFR* T790M status directly determines the treatment patients receive (in practice, this is a clinical decision that can involve other factors such as patient history and preference)
- We modelled the sensitivity and specificity independent of previous tests that have been conducted (we were unable to identify evidence on sensitivity or specificity for serial testing strategies, i.e., liquid biopsy followed by tissue biopsy or by a repeat liquid biopsy).

People whom we determined to be *EGFR* T790M–positive received osimertinib as second-line therapy, and people who we determined to be *EGFR* T790M–negative received platinum-based doublet chemotherapy as second-line therapy. The costs of treatment and impact on progression, survival, and quality of life were captured through the long-term Markov model, described below and shown in Figures 7 and 8.

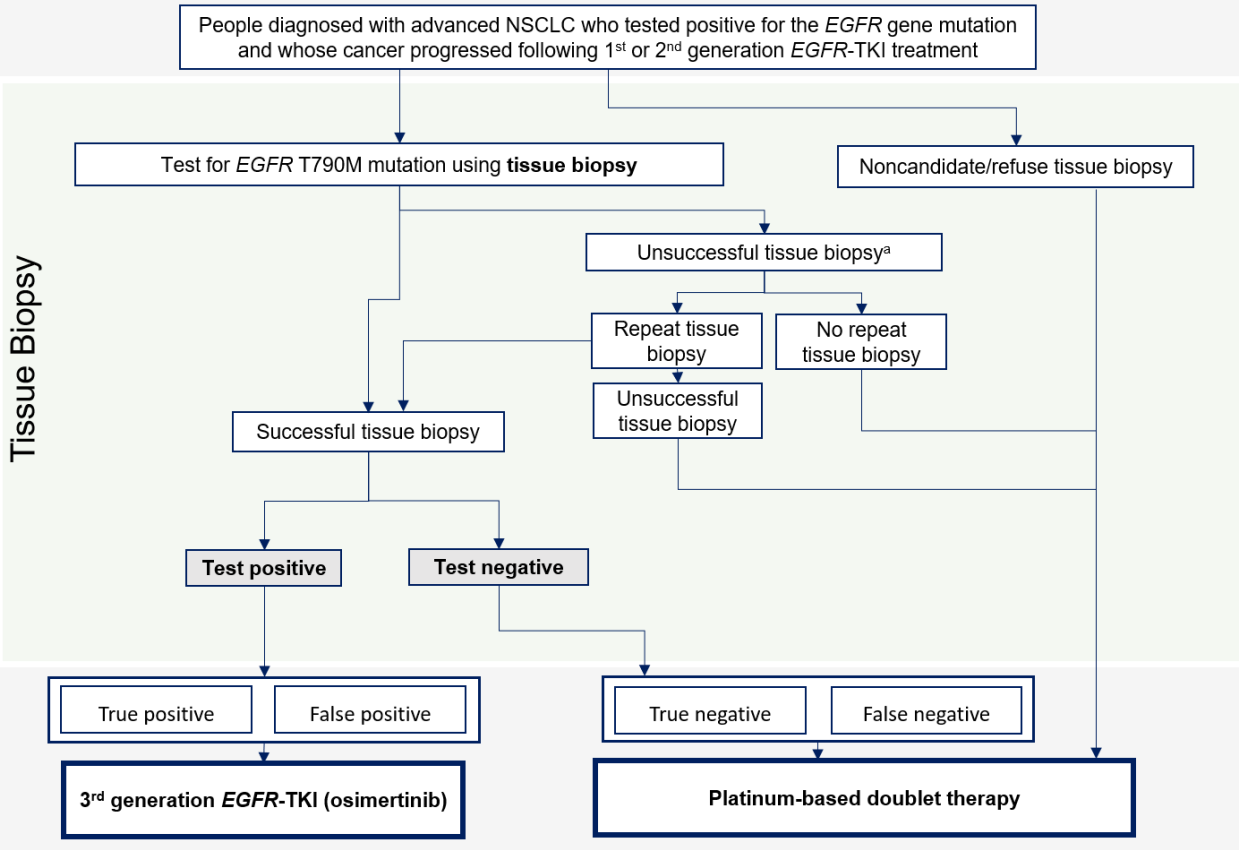

Figure 4: Clinical Pathway Using Tissue Biopsy Alone (Standard of Care) for Detection of *EGFR* T790M Mutation

Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.
[a]Tissue biopsies can be unsuccessful because of insufficient tissue or test failure.

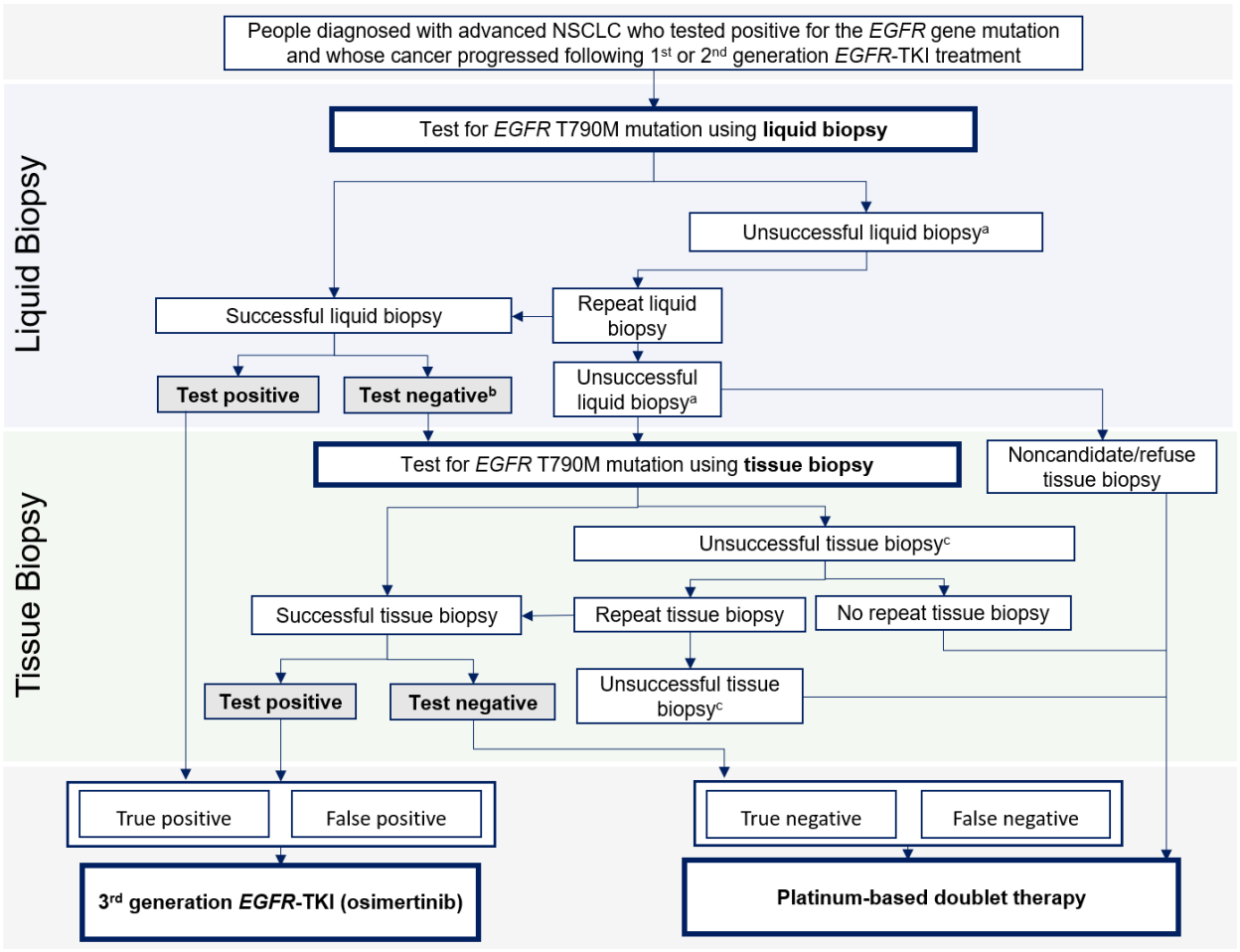

Figure 5: Clinical Pathway of Liquid Biopsy as Triage Test (Followed by Tissue Biopsy if Test Is Negative) for Detection of *EGFR* T790M Mutation

Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.
[a]Liquid biopsies can be unsuccessful because of test failure.
[b]Repeat liquid biopsies after a negative test result were assessed in the sensitivity analysis.
[c]Tissue biopsies can be unsuccessful because of insufficient tissue or test failure.

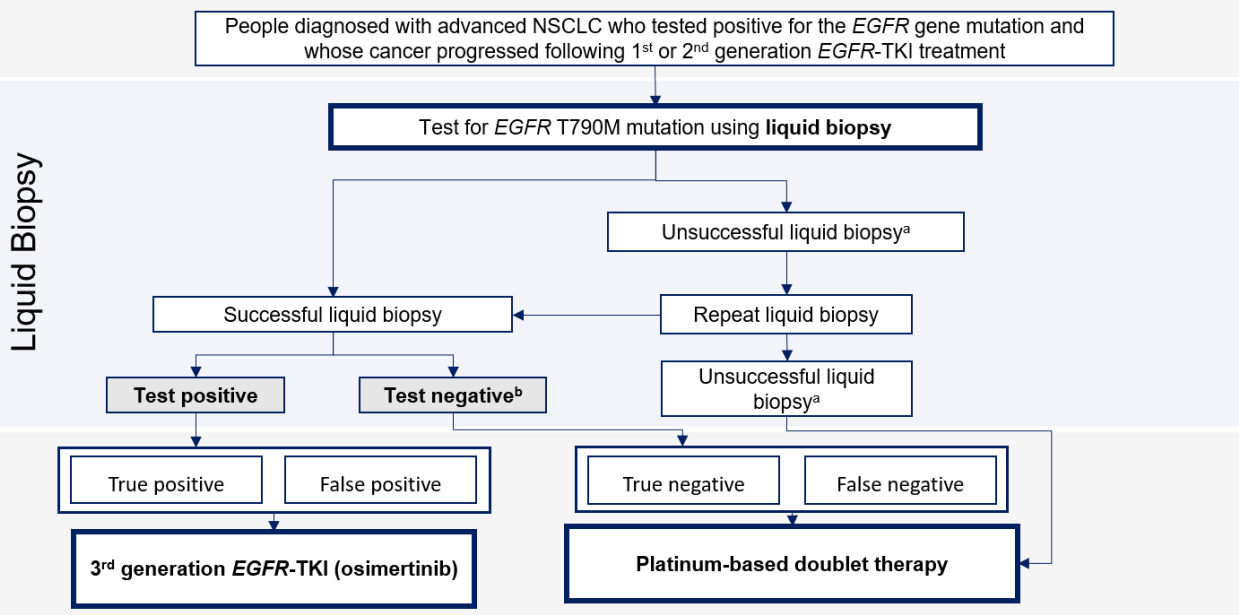

Figure 6: Clinical Pathway of Liquid Biopsy Alone for Detection of *EGFR* T790M Mutation

Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.
[a]Liquid biopsies can be unsuccessful because of test failure.
[b]Repeat liquid biopsies after a negative test result were assessed in the sensitivity analysis.

Markov Model

In the Markov model (Figures 7 and 8), everyone started in a post-progression health state on second line treatment (i.e., third-generation *EGFR*-TKI [osimertinib] or platinum-based doublet chemotherapy), as determined by the decision tree. In this health state, each person's cancer has progressed, and they are receiving additional medical treatment (to which they may or may not respond).

Over time, people could do any of the following:

- Continue to receive treatment
- Finish treatment and receive maintenance therapy, if applicable
- Progress and receive additional active treatment
- Progress and move to best supportive care
- Die

The treatment pathways are described below. They are based on previously published economic models,[68,86] clinical studies,[69,83] guidelines,[81] and clinical expert input.

We modelled up to three additional lines of therapy before people receive best supportive care. Based on a study of people with recurrent NSCLC,[88] after each progression event we assumed 50% of patients would move on to the next line of therapy and 50% would move directly to best supportive care. To simplify, for each line of treatment, we chose only one specific drug or drug combination.

Among those people who tested *EGFR* T790M positive, the active treatment trajectory modelled was as follows:

(1) Receive third-generation EGFR-TKI (osimertinib, 80 mg, once daily) until disease progression
(2) Receive platinum-based doublet chemotherapy for four 3-week cycles (cisplatin plus pemetrexed) followed by pemetrexed maintenance therapy until disease progression
(3) Receive either:
    - Chemotherapy (nivolumab) until disease progression, followed by chemotherapy (docetaxel) until disease progression. On the basis of current guidelines and expert consultation, we assumed nivolumab would be the preferred treatment for people who have a PD-L1 tumour proportion score ≥ 50%.[81] This treatment pathway would be followed for approximately 30% of people (written communication, Peter Ellis, December 17, 2018); or
    - Chemotherapy (docetaxel) until disease progression. This treatment pathway would be followed for approximately 70% of people
(4) Upon further progression, everyone receives best supportive care

Among those people who tested *EGFR* T790M negative, the active treatment trajectory modelled was as follows:

(1) Receive platinum-based doublet chemotherapy (cisplatin plus pemetrexed) followed by pemetrexed maintenance therapy until disease progression
(2) Receive either:
    - Chemotherapy (nivolumab) until disease progression, followed by chemotherapy (docetaxel) until disease progression. Based on current guidelines and expert consultation, we assumed nivolumab would be the preferred treatment for people who have a PD-L1 tumour proportion score ≥ 50%.[81] This treatment pathway would be followed for approximately 30% of people (written communication; Peter Ellis; Dec 17, 2018); or
    - Chemotherapy (docetaxel) until disease progression. This treatment pathway would be followed for approximately 70% of people.
(3) Upon further progression, everyone receives best supportive care

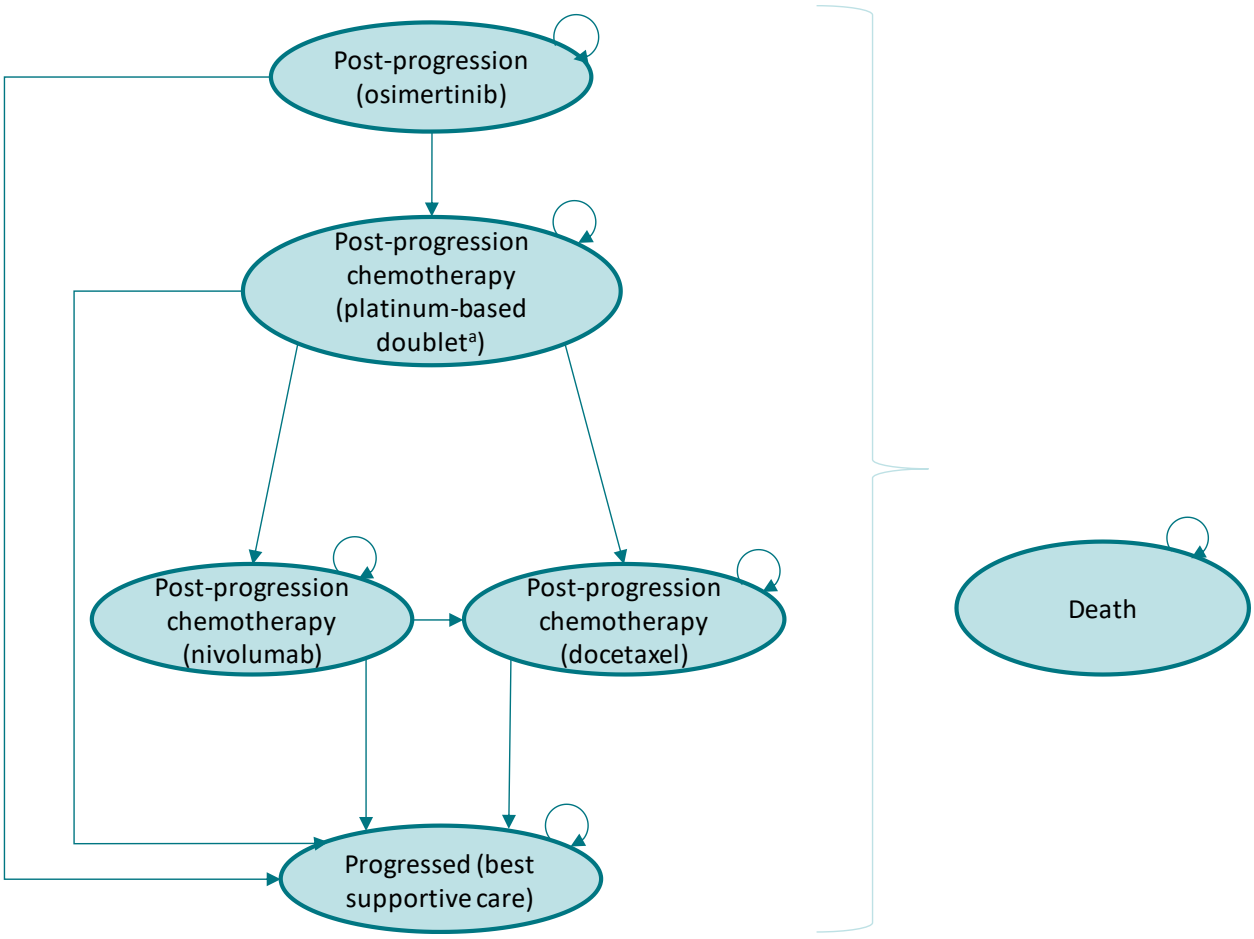

Figure 7: Markov Model Structure Among Those Determined to be *EGFR* T790M Positive

Abbreviation: *EGFR*, epidermal growth factor receptor.
[a]Four 21-day cycles, followed by pemetrexed maintenance therapy.

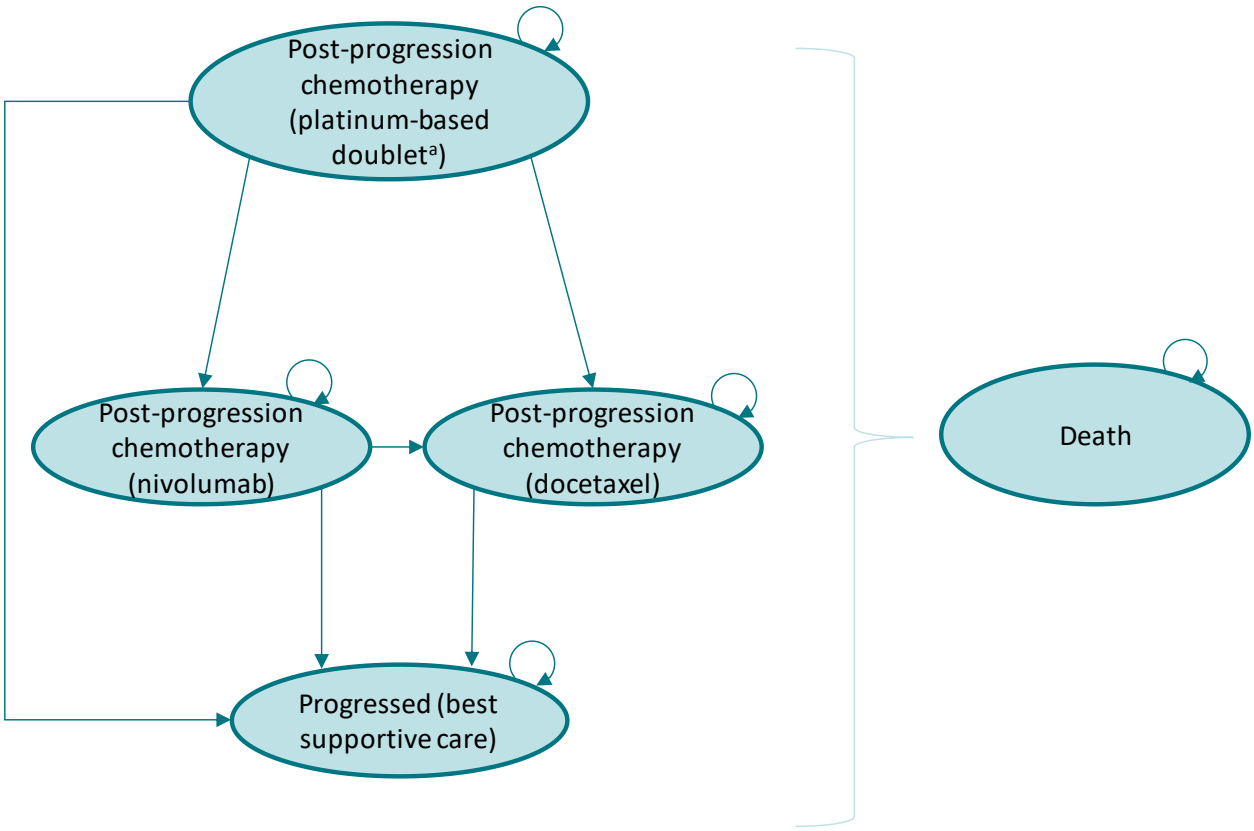

Figure 8: Markov Model Structure Among Those Determined to be *EGFR* T790M Negative

Abbreviation: *EGFR*, epidermal growth factor receptor.
[a]Four 21-day cycles, followed by pemetrexed maintenance therapy.

Key Assumptions in the Markov Model

- After each progression event, 50% of people receive an additional line of treatment and 50% receive best supportive care
- People receive only one treatment at time (i.e., no combination chemotherapy and *EGFR*-TKI)
- Pneumothorax is the only adverse event associated with tissue biopsy that substantially affects resource use and quality of life
- One-time costs associated with treatment-related adverse events are applied during the first cycle of each treatment
- Ongoing disutilities are applied for treatment-related adverse events (for additional details see Utilities, below)

Clinical Effectiveness and Utility Parameters

We used several different input parameters to populate the model. These included the following:

- Variables used to estimate the prevalence of advanced NSCLC in Ontario and the number of people who would be tested for the *EGFR* T790M resistance mutation
- Variables used to model mutation testing and the initial treatment decision
- Variables used to model treatment effects
- Variables used to model adverse events related to biopsy or treatment
- Variables used to capture a person's health-related quality of life

Population Size

Among the people whose disease progresses has progressed after first-line *EGFR*-TKI therapy, 63% have the *EGFR* T790M mutation as the mechanism of resistance (i.e., prevalence of *EGFR* T790M resistance mutation).[29] We expected that 699 people would be tested for the *EGFR* T790M resistance mutation (see Budget Impact Analysis, Target Population).

Genetic Testing Pathway

Several parameters are used to model the mutation testing pathway (Table 8). We used sensitivity and specificity values for liquid and tissue biopsy from the clinical review section of this report. In our reference case analysis, we used the values from the analysis that assumed tissue biopsy is an imperfect reference standard. We chose this for our reference case because it best reflects real-world conditions, where tumour heterogeneity can cause variation in *EGFR* mutations at different tumour sites.[21] In our sensitivity analysis, we examined a scenario where tissue biopsy is a perfect reference standard and would always correctly identify a person's *EGFR* T790M mutation status. In addition, we examined the sensitivity and specificity of liquid biopsy using various detection methods.

As previously highlighted, we assumed that the sensitivity and specificity for sequential tests are independent of one another. However, we incorporated changes in prevalence and in positive and negative predictive values (PPVs and NPVs) in the sequential strategies. These reference case sensitivity and specificity values are summarized in Table 9.

The proportion of people who cannot have tissue biopsy was obtained from a study in France in which 18% of people with advanced NSCLC could not have a repeat tissue biopsy because it was contraindicated or because they declined to be retested.[89] As stated previously, we assumed everyone would be able to have a liquid biopsy (i.e., no one would refuse or be unable to have their blood drawn).

The proportion of people who have a failed tissue or liquid biopsy was informed by Canadian studies.[82,90] The rate of tissue biopsy failure was much higher, as it included both test failure and instances where insufficient tissue was available. We assumed all people with a failed liquid biopsy would have a second liquid biopsy, but that only a small proportion of people with a failed tissue biopsy would have another tissue biopsy. This assumption takes into account the non-invasive nature of liquid biopsy. The rate of repeat tissue biopsy in this circumstance was informed by expert opinion (written communication, Peter Ellis, December 17, 2018). The average time to test result (18 days for liquid biopsy and 42 days for tissue biopsy, obtained from an Ontario abstract and poster presentation,[91] was used to determine the average time to treatment for each of the strategies.

Table 8: Natural History Inputs Used in Economic Model

Model Parameters	Mean	Lower CI	Upper CI	Source
Sensitivity and Specificity, Imperfect Reference Standard (Reference Case, HSROC With Imperfect Reference Standard [Conditional Dependence] Pooled Six Studies With MAF of 0.1%)				
Sensitivity liquid biopsy	0.683	0.460	0.885	Our clinical evidence review (see Appendix 2, Table A1)
Specificity liquid biopsy	0.869	0.626	0.992	
Sensitivity tissue biopsy	0.861	0.759	0.981	
Specificity tissue biopsy	0.934	0.855	0.995	
Sensitivity and Specificity, Perfect Reference Standard (Sensitivity Analyses, HSROC With Perfect Reference Standard, Pooled Six Studies With MAF of 0.1%)				
Sensitivity liquid biopsy	0.673	0.477	0.840	Our clinical evidence review (see Appendix 2, Table A1)
Specificity liquid biopsy	0.799	0.558	0.948	
Sensitivity tissue biopsy	1	–	–	
Specificity tissue biopsy	1	–	–	
Sensitivity and Specificity by Detection Method (Sensitivity Analysis, HSROC With Imperfect Reference Standard, Studies With Various MAFs)				
Sensitivity liquid biopsy (method: RT-PCR)	0.736	0.408	0.968	Our clinical evidence review (see Appendix 2, Table A1)
Specificity liquid biopsy (method: RT-PCR)	0.872	0.536	0.997	
Sensitivity tissue biopsy (method: RT-PCR)	0.922	0.87	0.991	
Specificity tissue biopsy (method: RT-PCR)	0.858	0.736	0.984	
Sensitivity liquid biopsy (method: dPCR)	0.81	0.647	0.954	
Specificity liquid biopsy (method: dPCR)	0.798	0.555	0.977	
Sensitivity tissue biopsy (method: dPCR)	0.815	0.726	0.953	
Specificity tissue biopsy (method: dPCR)	0.754	0.638	0.748	
Sensitivity liquid biopsy (method: NGS)[a]	0.775	0.375	0.985	
Specificity liquid biopsy (method: NGS)[a]	0.847	0.461	0.985	
Sensitivity tissue biopsy (method: NGS)[a]	0.824	0.575	0.983	
Specificity tissue biopsy (method: NGS)[a]	0.94	0.855	0.995	
Additional Testing Parameters				
Proportion who cannot have liquid biopsy (i.e., refuse to have biopsy or noncandidate)	0	0[c]	0.1[c]	Assumption
Proportion who cannot have tissue biopsy (i.e., refuse to have biopsy or noncandidate)	0.18	0.10	0.38	Chouaid et al, 2014[89]
Proportion of liquid biopsies that fail (i.e., test failure)	0.03	0	0.08	Tsao et al, 2017[82]
Proportion of people who will have repeat liquid biopsy after treatment failure	1	0.8[b]	1[b]	Assumption
Proportion of tissue biopsies that fail (i.e., test failure or inadequate tissue)	0.14	0.13	0.15	Shiau et al, 2014[90]
Proportion of people who will have repeat tissue biopsy after treatment failure	0.075	0.05	0.1	Written communication, Peter Ellis, December 17, 2018

Abbreviations: CI, confidence interval; dPCR, digital polymerase chain reaction; HSROC, hierarchical summary receiver operating characteristics; MAF, mutant allele fraction, NGS, next-generation sequencing; RT-PCR, real-time polymerase chain reaction.

[a]Included two studies using in-house assays on Illumina MiSeq platform and one study using the Guardant360 panel.[36]

[b]Used in sensitivity analyses.

Table 9: Mean Sensitivity, Specificity, Prevalence, and Positive and Negative Predictive Values Used in Reference Case Analysis

Test	Sensitivity	Specificity	Prevalence	PPV (%)[a]	NPV (%)[b]
First Test					
Liquid biopsy	0.683	0.689	0.63	89.9	61.7
Tissue biopsy	0.861	0.934	0.63	95.7	79.8
Second Test					
Liquid biopsy (following a successful liquid biopsy with negative results)	0.683	0.689	0.38[c]	76.4	89.0
Tissue biopsy (following a successful liquid biopsy with negative results)	0.861	0.934	0.38[c]	81.5	91.5
Third Test					
Tissue biopsy (following two successful liquid biopsies with negative results	0.861	0.934	0.18[d]	74.7	96.7

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.
[a]Calculated as: (sensitivity × prevalence)/(sensitivity × prevalence + [1 – specificity] × [1 − prevalence]).
[b]Calculated as: (specificity × [1 − prevalence])/([1 – sensitivity] × prevalence + specificity × [1 − prevalence]).
[c]Calculated as proportion of true positives among people who tested negative on first test.
[d]Calculated as proportion of true positives among people who tested negative on second test.

Survival (Mortality) and Progression

We derived survival and progression estimates from the published literature and from our clinical review, where applicable.

We obtained age- and sex-specific rates of all-cause mortality from Statistics Canada Life Tables.[92] In addition, we obtained overall survival after second-line treatment with osimertinib or platinum-based doublet therapy (first lines of treatment modelled in this analysis) from the published literature. In each cycle of the model, we used whichever estimate was higher (i.e., all-cause mortality or mortality derived from overall survival). To avoid double counting, we assumed that people follow this mortality trajectory regardless of additional treatments.

We derived rates of progression for each treatment type. Progression through various treatments affected patients' costs and quality of life.

Second-Line Treatment

We extracted data on progression-free survival (PFS) and overall survival on osimertinib and platinum-based doublet chemotherapy for modelling purposes. The AURA3 clinical trial compared osimertinib and platinum-based doublet chemotherapy among people who had an *EGFR* T790M resistance mutation (i.e., who were *EGFR* T790M positive). So far, only 18-month PFS data have been reported.[69] Data on overall survival have not been published. In absence of overall survival data, we derived PFS and overall survival for *EGFR* T790M–positive patients on osimertinib or platinum-based doublet therapy from a recent study by Mann et al.[83] The study compared pooled data from the AURA extension and AURA2 trials (patients receiving osimertinib with tissue-confirmed *EGFR* T790M mutation) and the control arm of the IMPRESS trial (patients receiving platinum-based doublet therapy). It compared PFS and overall survival using a propensity score–matched dataset and the Cox proportional hazards model. We digitized the Kaplan-Meir curves and extracted data for PFS and overall survival using a free

online platform (WebPlotDigitizer).[93] We then used the methods described by Guyot et al[94] and the R package survHE[95] to fit distributions to the digitized curves. We tested a variety of common distributions (i.e., Weibull, Log-logistic, Exponential, Gompertz, Gamma) and chose the best-fitting distribution on the basis of visual inspection, along with Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC). The distributions are summarized in Table 10.

Table 10: Distributions Used for Progression-Free and Overall Survival

Model Parameters	Shape	Scale/Rate	Distribution[a]
Progres sion-free survival, osimertinib	1.4539	10.9852	Loglogistic
Progression-free survival, platinum-based doublet chemotherapy	1.7809	5.4423	Weibull
Overall survival, osimertinib	0.0330	0.0138	Gompertz
Overall survival, platinum-based doublet chemotherapy	2.2923	16.0870	Loglogistic

[a]Distributions derived from data extracted from Mann et al, 2018,[83] Figure 2A.

We assumed that PFS and overall survival were the same in *EGFR* T790M–negative and *EGFR* T790M–positive people receiving platinum-based doublet chemotherapy. Although several studies identified in our clinical evidence review compared PFS in *EGFR* T790M–positive and *EGFR* T790M–negative people (as determined by liquid biopsy), only one study specified which treatments people received and analyzed outcomes from chemotherapy.[45] This study found that median PFS was not different between people who were *EGFR* T790M positive (2.9 months) and those who were *EGFR* T790M negative (2.8 months).

In our model, some people had a false-positive *EGFR* T790M result after undergoing biopsy and, therefore, some *EGFR* T790M–negative people were incorrectly treated with osimertinib. Studies derived from our clinical review[18,44] show that people receiving osimertinib who are *EGFR* T790M negative have poorer PFS and response rates than those who are *EGFR* T790M positive. We used the ratio of median time to progression reported in Oxnard[18,96] to derive a hazard ratio (2.85) for PFS for people who are *EGFR* T790M negative compared with people who are *EGFR* T790M positive, both treated with osimertinib.

Median time to progression has been shown to have high concordance with the hazard ratio,[96] but a large error estimate (± 50%) was used to reflect uncertainty. Our research did not uncover relevant information on overall survival of *EGFR* T790M–negative people receiving osimertinib, so we assumed the same hazard ratio would apply to overall survival. We examined this assumption in sensitivity analyses.

Additional Treatment

For modelling purposes, we used the published literature to derive transition probabilities of PFS for people on additional lines of treatment. For people who receive third-line platinum-based doublet therapy, estimates were based on the AURA3 trial.[69] For people who receive nivolumab or docetaxel, estimates were based on the 2-year outcome analysis of the CheckMate 017 and CheckMate 057 trials by Horn et al.[97] Using previously described methods,[105] we estimated monthly rate of progression from the median time to progression. Similar methods have been used in a previous economic evaluation by Chen et al.[87,98] These parameters are summarized in Table 11.

Table 11: Clinical Effectiveness Parameters, Additional Treatment

Model Parameters	Median PFS in Months (CI)	Monthly Rate of Progression (CI)[a]	Source
Platinum-based doublet chemotherapy	4.4 (4.2–5.6)	0.157 (0.124–0.165)	Mok et al, 2017[69]
Nivolumab	2.7 (1.9–9.6)	0.259 (0.72–0.365)	Pooled estimate derived from Horn et al, 2017[97]
Docetaxel	3.8 (3.0–8.1)	0.157 (0.085–0.234)	Pooled estimate derived from Horn et al, 2017[97]

Abbreviations: CI, confidence interval; PFS, progression-free survival.
[a]Monthly rate of progression calculated as ln(2)/median PFS.[87]

Adverse Events

We considered adverse events that could alter quality of life and resource use for each of the modelled treatments. We assumed no adverse events related to undergoing a liquid biopsy, in line with the clinical review findings of this report and previous work.[75] We included pneumothorax as a common complication associated with tissue biopsy. According to a Canadian study, pneumothorax occurs in 28% of lung biopsies,[99] but rates from 0% to 61% have been reported in the literature.[84,100] Based on the study by Ayyappan et al,[99] we modelled 30% of pneumothorax cases as severe and requiring chest drainage. We did not consider other complications of tissue biopsy (e.g., bleeding, infection) because they are rare.[84]

We used clinical trials to derive the probability of different adverse events related to treatment (Appendix 7, Table A12).[69,101] Similar to previous economic evaluations,[68,86,102] we considered only adverse events of grade 3 or higher owing to their impact on quality of life and resource use. Further, we included only the adverse events considered by the studies from which we plan to obtain quality of life[72,103] and resource use[104] data. The adverse events included were as follows:

- Anemia
- Asthenia
- Bleeding
- Decreased appetite
- Dehydration
- Diarrhea
- Fatigue
- Febrile neutropenia
- Hair loss
- Hypertension
- Musculoskeletal pain
- Nausea
- Peripheral neuropathy
- Neutropenia
- Pneumonia
- Pneumonitis
- Rash

- Vomiting

Utilities

Utilities for each of the health states were derived using the methods of Nafees et al.[103] This UK study estimated utilities for people receiving second-line treatment for NSCLC. Researchers used the Standard Gamble technique and interviewed members of the general public. Utilities were estimated for several health states using individual preferences for various disease statuses (progressed, stable, responsive) and treatment toxicities (neutropenia, febrile neutropenia, fatigue, nausea and vomiting, diarrhea, hair loss, and rash).

A more recent publication from the same group[72] updated the utility estimates to include internationally applicable values. Utilities for additional health states (for maintenance therapy, hypertension, and bleeding) were also incorporated. However, this study was conducted with people receiving first-line treatment for NSCLC. For this reason, we used the earlier study to estimate our utilities, but used the more recent publication to account for bleeding and hypertension.

We used estimates from the studies and the following equation to derive the utility for each health state (i.e., for a given combination of disease status and treatment toxicity, where "p" stands for "probability"):

$$\begin{aligned}\text{Utility} = {} & 0.6532 + (\text{pProgressed} \times -.1792) + (\text{pResponded} \times 0.0193) + \\ & (\text{pNeutropenia} \times -0.0987) + (\text{pFebrileNeutronpenia} \times -0.0900) + \\ & (\text{pFatigue} \times -0.0735) + (\text{pNausea} \times -0.0480) + (\text{pVomitting} \times -0.0480) + \\ & (\text{pDiarrhea} \times -0.0468) + (\text{pHairLoss} \times -0.0450) + (\text{pRash} \times -0.0325) + \\ & (\text{pBleeding} \times -0.0250) + (\text{pHypertension} \times -0.2460)\end{aligned}$$

A similar equation has been used in a previous economic evaluation.[87] The equation adjusted the health state utility value of someone with stable NSCLC (0.6532) to account for the person's disease status and whether any adverse events occurred during each treatment. As shown in the equation, all factors except disease response were associated with a reduction in quality of life (i.e., a disutility).

We used clinical trials to determine the proportion of people on each treatment who were stable, responsive, or progressive, and the proportion who experienced adverse events (Appendix 7, Tables A12 and A13). For people receiving osimertinib or platinum-based doublet therapy, we derived these proportions from the AURA3 trial.[69] For people receiving nivolumab or docetaxel, we derived these proportions from the CheckMate 017 and CheckMate 057 trials.[101]

We assumed that after each progression event, people would have a utility associated with disease progression for one cycle, after which the disease status for each treatment would be based on treatment response from the corresponding clinical trial (i.e., we used the proportion of people who are stable, who respond, or whose disease progresses after treatment).[69,101] We then adjusted the utilities on the basis of proportion of people who experience adverse events (grade 3 or higher) with each treatment. People receiving best supportive care had a utility associated with progressed disease status.

Finally, we modelled a 1-month impact on quality of life among people having a severe tissue biopsy–related complication (i.e., pneumothorax requiring pleural drainage). This was obtained

from a study estimating the effect on quality of life using a time trade-off technique for people who had experienced spontaneous pneumothorax.[105]

The mean health state utility values are presented in Table 12.

Table 12: Health State Utilities (Annual) Used in Economic Model

Health State	Mean Utility	Reference
Osimertinib	0.652	Equation derived from Nafees, 2008[103]
Platinum-based doublet	0.609	
Nivolumab	0.568	
Docetaxel	0.551	
Best supportive care	0.474	
Disease progression	0.474	
Pneumothorax requiring pleural drainage	0.450	Morimoto et al, 2002[105]

Cost Parameters

We included costs related to:

- *EGFR* T790M testing
- Drug acquisition (purchase), administration, and monitoring
- Adverse events related to tissue biopsy or treatment
- General and end-of-life care

In our analysis, where relevant, costs were updated to 2018 Canadian dollars using the health care product group of the Consumer Price Index.[106]

EGFR T790M Testing Costs

The *EGFR* T790M testing can be done using a commercially developed platform or an in-house laboratory test (if clinically validated with tissue biopsy or with other laboratories). There are several commercially available platforms, including ones that use RT-PCR (Cobas's *EGFR* Mutation Test v2, Qiagen's Therascreen *EGFR* plasma Rotor-Gene Q PCR kit), dPCR (Bio-rad's Droplet Digital PCR Dx system), or NGS (ThermoFisher's Oncomine Lung cfDNA assay). Some assays (e.g., Cobas's *EGFR* Mutation Test v2) can be used for tissue biopsy samples as well. Laboratories use various methods of testing (i.e., in house or laboratory developed; RT-PCR, dPCR, or NGS) according to their volume of testing and infrastructure.

For our analysis, we estimated the cost of a liquid biopsy using commercial tests, in-house tests, and various sequencing methods (RT-PCR, dPCR, and NGS). We used several sources to estimate costs, including published literature, manufacturers, and clinical experts. Costs of testing can vary from one lab to another and one test to another; hence, we looked at a range of costs in our sensitivity analyses.

The cost of liquid and tissue biopsies break down into several components:

- Pre-analytic (i.e., initial consultation, staff wages and fees, blood test and equipment, CT-guided lung biopsy, sample processing, procedure costs, and transport)
- Sequencing (i.e., assays, consumables/reagents, and labour)
- Result interpretation and consultation follow-up
- Capital costs of processing equipment (the instrument on which assays are conducted) and test development
- Overhead, including data management

Table 13 presents the cost breakdown for liquid and tissue biopsy using various testing strategies.

Pre-Analytic Costs

We assumed that each person had two consultations with an oncologist (one pre-biopsy and one after results were available) and that people who had multiple tests (i.e., due to a failed result) received no additional consults. We used the cost of an oncology general consultation in Ontario as the cost of a clinical consultation.[107]

The costs of collection, internal transportation, and processing of biopsy samples are informed by an analysis in a recent poster presentation comparing tissue and liquid biopsy in Ontario. Although the poster is unpublished, an accompanying abstract has been published.[91] We expected most samples (75%) would need to be transported externally, to another facility. The cost of shipping and handling was obtained from an Ontario micro-costing analysis of clinical genomic testing strategies for autism spectrum disorder.[108]

Sequencing Costs

The laboratory costs involved in *EGFR* T790M mutation testing are complex, as the test can be done using either a commercially developed platform or an in-house laboratory test.

For liquid biopsy, we estimated the cost for four commercially developed platforms using either RT-PCR (Roche and Qiagen), dPCR (Bio-Rad Laboratories), or NGS (Thermo Fisher Scientific). In addition, we estimated the cost for in-house laboratory-developed tests using either dPCR or NGS. To our knowledge, there are no RT-PCR tests developed in-house for liquid biopsy in Ontario.

For tissue biopsy, we estimated the cost for one commercially developed platform using RT-PCR (Cobas) and for two in-house laboratory-developed tests (dPCR, NGS—using the Illumina MiSeq platform).

Assays, Consumables, and Reagents

We obtained the cost of Cobas's *EGFR* Mutation Test v2 from the manufacturer, as this assay has already been implemented in Ontario. We obtained the cost of the other commercial assays from a report by the National Institute for Health and Care Excellence (NICE)[109] and from manufacturer and vendor websites.[110,111] The in-house laboratory costs were estimated with guidance from an Ontario clinical expert. For dPCR, we assumed (guided by clinical experts) that there is a negligible cost difference between the in-house methods for liquid biopsy and tissue biopsy. Conducting tissue biopsy with NGS using an in-house–developed platform is less costly than conducting liquid biopsy with NGS using an in-house–developed platform. Based on

expert consultation, we expected tissue biopsy (NGS) to cost approximately 65% of the cost for liquid biopsy (written communication, Tracy Stockley, January 7, 2019).

Labour Costs

We assumed one laboratory technologist was involved. The technologist's average hourly salary was estimated using the Ontario Public Service Employee Union listing,[112] which was then multiplied by the number of hours required to complete a test to calculate the total laboratory labour cost per test. We assumed the time required varied between the sequencing methods (i.e., RT-PCR, dPCR, and NGS), but remained the same whether the test was conducted on a liquid or tissue sample and whether it was conducted using a commercially developed or in-house test.

Results Interpretation and Final Consultation

In addition to the time required to conduct the mutation test, another 15 minutes of technologists' time was added to account for result interpretation and report writing for all tests. A final results interpretation is conducted by the laboratory's medical director.

All patients were assumed to have consulted with an oncologist to discuss their results.

Capital Cost of Processing Equipment and Assay Development

We assumed that many Ontario laboratories have already acquired some processing equipment and so there will be little or no additional capital investment. In addition, we assumed the tests would be conducted using current infrastructure in Ontario and that no further tests would need to be developed in-house. However, we explored incorporating these costs in a scenario analysis.

Overhead, Including Data Management

We assumed that costs associated with overhead and data management would be negligible because it is a single mutation test with a relatively low volume of testing.

Table 13: *EGFR* T790M Testing Costs

Component	Costs of Liquid Biopsy[a]			Costs of Tissue Biopsy[a]
	RT-PCR	dPCR	NGS	
Pre-Analytic				
Initial consultation	$157.00 per consultation × 1 consultation/patient[b] Source: Ontario Schedule of Benefits,[107] code A445 (oncology general consultation)			
Sample collection (staff, equipment, biopsy)	Nurse (meeting, consent, and questionnaire): $10.00 (2017) for staff time of 10 min Lab technician: $4.68 (2017) Equipment and unit cost: $14.94 (2017) Blood collection tube: $9.80 (2018) per tube × 2 tubes **TOTAL: $49.85 (2018) per biopsy** Sources: Barnes et al, 2017[91]; PAXgene blood ccfDA tubes, Qiagen[113]			Nurse (meeting, consent, and questionnaire): $10.00 (2017) for staff time of 10 min Blood test lab technician: $9.37 (2017) Blood test equipment: $4.67 (2017) Blood tube unit cost: $2.60 (2017) Clerk booking for tissue biopsy: $5.00 (2017) CT-guided lung biopsy: $1,576.05 (2017) **TOTAL: $1,641.95 (2018) per biopsy** Source: Barnes et al, 2017[91]
Transport	Internal transport: nurse is paged for sample pick-up and sample is taken to lab for requisition: $10.18 (2017) for staff time of 10 min Source: Barnes et al, 2017[91] External transport: costs for shipping and handling: $52.50 (2015) Source: Tsiplova et al, 2017[108] **TOTAL: $51.47 (2018) per biopsy[c]**			
Processing	Blood processing and DNA extraction: $70.00 (2017) **TOTAL: $71.49 (2018) per biopsy** Source: Barnes et al, 2017[91]			Specimen processing and DNA extraction: $45.00 (2017) Pathologist review: $90.00 (2017) **TOTAL: $137.88 (2018) per biopsy** Source: Barnes et al, 2017[91]

Component	Costs of Liquid Biopsy[a]			Costs of Tissue Biopsy[a]
	RT-PCR	dPCR	NGS	
Sequencing				
Assay, consumables, and reagents	Commercial assays: • Roche, Cobas's *EGFR* Mutation Test v2: $200.00 • Qiagen's Therascreen: $222.55 In-house assay: • N/A **AVERAGE: $211.28** Sources: commercial (manufacturers Cobas[d] and Qiagen), NICE[109] £125,85 (2015)	Commercial assay: • Bio-rad Droplet Digital PCR: $26.57 per sample In-house assay: • $60.00 per sample **AVERAGE: $43.28** Sources: commercial (NICE[109] £15,03 [2018]); in-house (written communication, Tracy Stockley, January 7, 2019)	Commercial assay: • ThermoFisher's Oncomine Lung cfDNA assay[e] $2,530.00 (no batching) or $316.25 (batching 8 samples) In-house assay: • $440.00 **AVERAGE: $1,485.00** Sources: commercial (manufacturer[110]); in-house (written communication, Tracy Stockley, January 7, 2019)	Commercial assay (RT-PCR): • Cobas's *EGFR* Mutation Test v2 (RT-PCR): $182.00 In-house assay (NGS): • $308.00[f] In-house assay (dPCR): • $60.00 Sources: commercial (manufacturer (Cobas[d]); in-house (written communication, Tracy Stockley, January 7, 2019)
Staff time	Lab technologist[g]: $41.78/h × 45 min per sample = $31.33 per biopsy Sources: OPSEU[112]; time provided by manufacturer[114]	Lab technologist[g]: $41.78/h × 29 min per sample = $20.02 per biopsy Sources: OPSEU[112]; time provided by manufacturer[115]; written communication, Tracy Stockley, January 7, 2019	Lab technologist[g]: $41.78/h × 2 h per sample = $83.56 per biopsy Sources: OPSEU[112]; time provided by written communication (Tracy Stockley, January 7, 2019; Harriet Feilotter, December 3, 2018)	Assumed same as liquid biopsy

Component	Costs of Liquid Biopsy[a]			Costs of Tissue Biopsy[a]
	RT-PCR	dPCR	NGS	
Results Interpretation and Consultation				
Interpretation and report writing	Lab technologist[g]: $41.78/h × 10 min per dPCR or RT-PCR sample = $6.96 per biopsy Lab technologist[g]: $41.78/h × 30 min per NGS sample = $20.89 per biopsy Lab director[h]: $92.31/h × 15 min per sample = $23.08 per biopsy Sources: Lab technologist wage, OPSEU[112]; lab director wage,[g] Ontario Public Sector Salary Disclosure[116]			
Result consultation	$157.00 per consultation × 1 consultation per person Source: Ontario Schedule of Benefits,[107] code A445 (oncology general consultation)			
Large Equipment and Test Development Costs (Sensitivity Analyses)				
Initial device (one-time, and amortized[i])	Cobas 4800 PCR system (Roche): $65,000.00 Source: manufacturer[d]	Bio-rad AutoDG QX200 ddPCR system: $232,256.00 Source: NICE[109] £131,300.00 (2016)	ThermoFisher S5 with automated prep library: $375,000.00 Illumina MiSeq: $750,000.00 Sources: ThermoFisher (written communication, Harriet Feilotter, December 3, 2018); Illumina (Tsiplova et al, 2016[108])	Assumed labs already have equipment needed to conduct tissue biopsy (standard of care)
Service contract	10% of initial cost per year (Tsiplova, 2017[108])			
Test development	$10,000.00–$50,000.00 per test (written communication, Harriet Feilotter, December 3, 2018)			
Overhead	Assumed no other overhead costs			
Data management	Assumed no significant data management costs			

Abbreviations: cfDNA, cell-free circulating tumour DNA; CT, computed tomography; ddPCR, droplet digital polymerase chain reaction; dPCR, digital polymerase chain reaction; *EGFR*, epidermal growth factor receptor; NGS, next-generation sequencing; NICE, National Institute for Health and Care Excellence; OPSEU, Ontario Public Service Employee Union; RT-PCR, real-time polymerase chain reaction.

[a]Year in parentheses indicates adjusted Canadian dollars.

[b]One per person, regardless of number of biopsies.

[c]Assuming 75% require cost of internal and external transport, and 25% require internal transport only.

[d]Written communication, Michele D'Elia, Roche; January 13, 2019.

[e]Assuming no batching in reference case.

[f]65% of cost of circulating tumour DNA (here 65%).

[g]Salary based on Ontario Public Service Employee Union listing of Registered Technologist ($31.32–$41.98/h) plus 14% benefit.

[h]Average salary for laboratory director is $180,000.00[116]/(52 wk at 37.5 h = $92.31/h).

[i]Assuming two additional machines for 400 patients in 1 year.

Testing Costs Used in Reference Case and Sensitivity Analyses

Table 14 presents the total cost per biopsy used in our reference case and sensitivity analyses. In our reference case analysis, we used the average cost of the commercial RT-PCR assays and in-house dPCR. These are the two methods currently used to conduct liquid biopsy testing in two Ontario laboratories (University Health Network and London Health Sciences). The reference case cost of tissue biopsy was taken as the average of the commercial assay and dPCR in-house method. We assumed in the reference case that the laboratories would have already acquired the processing equipment; thus, the capital cost would be negligible. In our sensitivity analysis, we looked at the costs for different sequencing methods, along with incorporating capital costs. To incorporate capital costs, we looked at the cost of developing 1 to 14 new tests and purchasing 1 to 14 new machines (there are 14 regional cancer centres in Ontario)[117] and amortizing this over the number of people expected to get liquid biopsy in the next 5 years.

Table 14: Total Cost Per Biopsy

Cost of One Liquid Biopsy[a]		Cost of One Tissue Biopsy[a]	
Testing Method/Scenario	**Cost ($)**	**Variables**	**Cost ($)**
Reference Case			
Average: commercial RT-PCR and in-house dPCR	$677	Average: commercial RT-PCR and in-house dPCR	$2,529
Sensitivity Analysis by Test Type			
RT-PCR (commercial)	$756	RT-PCR (commercial)	$2,593
dPCR (average commercial and in-house)	$580	dPCR (in-house)	$2,464
NGS (average commercial and in-house)	$2,099	NGS (in-house)	$2,767
Sensitivity Analysis by Capital Equipment			
Reference case		--	--
1 machine	$48		
14 machines	$675	--	--
RT-PCR		--	--
1 machine	$24		
14 machines	$340	--	--
dPCR		--	--
1 machine	$72		
14 machines	$1,010	--	--
NGS		--	--
1 machine	$172		
14 machines	$2,405	--	--

Abbreviations: dPCR, digital polymerase chain reaction; NGS, next-generation sequencing; RT-PCR, real-time polymerase chain reaction.
[a]Numbers could appear incorrect because of rounding.

Drug Acquisition, Administration, and Monitoring Costs

We derived drug acquisition costs from several sources. We obtained the cost of osimertinib (Tagrisso) from the exceptional access program[118] and the cost of nivolumab (Opdivo) from a

Pan-Canadian Oncology Drug Review.[119] We obtained the cost of platinum-based doublet therapy and docetaxel from a recent Ontario cost-effectiveness analysis.[86] Finally, we obtained the cost of pemetrexed from Cancer Care Ontario. The corresponding doses, drug cost per day, and drug cost per 21-day cycle are summarized in Table 15.

Table 15: Drug Acquisition Costs

Treatment Type	Dose	Cost/Day ($)	Cost/21-Day Cycle ($)	Source
Osimertinib	80 mg once daily	294.67	6,188.20	CCO, EAP[118]
Platinum-based doublet	Pemetrexed: 500 mg/m^2 per cycle; Cisplatin: 75 mg/m^2	11.86	249.00	Ezeife, 2018[86]
Pemetrexed maintenance	500 mg/m^2 per cycle	8.68	182.33	CCO, PDRP[120]
Nivolumab	3 mg/kg per 2 wk	293.33	6,159.93	pCODR, Opdivo[119]
Docetaxel	75 mg/m^2 per cycle	10.26	72.00	Ezeife, 2018[86]

Abbreviations: CCO, Cancer Care Ontario; EAP, Exceptional Access Program; pCODR, *pan-Canadian Oncology Drug Review*; PDRP, Provincial Drug Reimbursement Program.

Drug administration (dispensing fees, drug preparation and administration, prophylactic medication and administration, and ambulatory day care visit for drug infusions) and monitoring (complete blood count) costs were derived from a Canadian economic evaluation of nivolumab for patients with advanced NSCLC who were previously treated.[104] Drug administration unit costs were assumed to be incurred once per cycle. Drug monitoring costs were adjusted from 4- to 3-week costs to align with our cycle length. These costs are summarized in Table 16.

Table 16: Drug Administration and Monitoring Costs

Treatment Type	Cost per 21-Day Cycle (SE)[a]
Osimertinib	$19.01 (2.42)[b]
Platinum-based doublet	$169.61 (21.63)[c]
Pemetrexed maintenance	$63.05 (8.04)
Nivolumab	$99.56 (12.70)
Docetaxel	$146.67 (18.71)

Abbreviation: SE, standard error.
[a]All costs updated from 2015 to 2018 Canadian dollars.
[b]Drug administration and monitoring based on erlotinib.
[c]Drug administration costs are based on carboplatin and monitoring costs are based on cisplatin.
Source: Goeree et al, 2016.[104]

The injectable cancer drugs (i.e., cisplatin, pemetrexed, nivolumab, and docetaxel) are covered under the New Drug Funding Program for patients with a valid Ontario Health Card[121]; hence, we assumed all costs would be covered by the Ministry of Health. Osimertinib is covered under the exceptional access program for people who are eligible to receive benefits under the Ontario Drug Benefit program (i.e., those who are younger than 25 or older than 65 years of age; who are recipients of long-term care, home care, or social assistance; who have disabilities; or who are covered by the Trillium Drug Program).[118] Thus, we assumed 64% of people (50% of whom are older than 65 years based on median age of 64 years used for our target population[122] and

about 28% of eligible people younger than 65 years of age)[123] would have the costs related to osimertinib covered by the Ministry of Health.

Adverse Event Costs

We assumed that the cost of complications following tissue biopsy includes the cost of interventions for managing pneumothorax, including a follow-up chest x-ray. The cost of a chest x-ray was obtained from Ontario Case Costing Cost Analysis Tool ($431.00 per x-ray)[124] and the Ontario Schedule of Benefits (X091: $32.65).[107] Approximately 30% of pneumothorax cases warrant chest drainage; the cost was obtained from ambulatory cases in the Cost Analysis Tool ($475.00 per chest drain)[124] and the Ontario Schedule of Benefits (Z341: $159.86).[107]

Costs of treatment are applied to adverse events of grade 3 or higher, consistent with previous analyses. The proportion of people experiencing adverse events with each treatment was multiplied by the assigned unit price for each adverse event to arrive at a cost per person. We applied the resulting figure in the first cycle in which people received the drug. The cost of each adverse event was derived from Goeree et al, 2016[104] (Appendix 7, Table A14). Adverse events with costs applied included febrile neutropenia, pneumonia, pneumonitis, anaemia, fatigue, asthenia, diarrhea, nausea, vomiting, dehydration, decreased appetite, peripheral neuropathy, rash, and musculoskeletal pain. In the absence of evidence, we assumed adverse event rates are identical between all people receiving the same treatment (e.g., *EGFR* T790M–positive people receiving osimertinib would have the same adverse event rate as *EGFR* T790M–negative people receiving osimertinib).

General and End-of-Life Care Costs

We derived general care costs from Goeree et al, 2016.[104] Costs were related to routine physician visits, palliative care, radiotherapy, blood transfusion, x-ray, bone scan, and oxygen use. For the first treatment line modelled (osimertinib or platinum-based doublet therapy), we assumed general care costs would be equivalent to the costs for people with progression-free disease. Thereafter, we assumed that general care costs would be equivalent to the costs for people with progressed disease. The costs were adjusted from 4-week costs to 3-week costs and updated to 2018 dollars (Table 17).

Table 17: General Care Costs for Lung Cancer Patients

Disease Status	Cost (4-wk, 2015)	Cost (3-wk, 2018)
Progression-free[a]	$981.35	$771.17
Progressed disease[b]	$1,161.11	$912.43

[a]Progression-free cost was applied to the first treatment line model (osimertinib or platinum-based doublet therapy).
[b]Cost of disease progression was applied to health states after the first treatment line.
Source: Goeree et al, 2016.[104]

Cheung et al[125] used administrative data to estimate the costs associated with the final month of care in adults who died of cancer in Ontario. They reported their results by care type (i.e., aggressive or not aggressive). We used these end-of-life care costs for all cancer patients, weighted by the proportion of lung cancer patients receiving aggressive care, and applied it as a one-time cost in our model when patients die (Table 18).

Table 18: End-of-Life Care Costs for Lung Cancer Patients

Treatment Type	No. of People	Mean Cost (SD)	Source
Aggressive care[a]	5,937	$18,131 ($15,065)	Cheung et al, 2015[125]
Non-aggressive care[a]	19,678	$12,678 ($12,754)	Cheung et al, 2015[125]
Weighted average[a]	25,615	$13,942	Calculation
Weighted average[b]	--	$14,608	Calculation

Abbreviation: SD, standard deviation.
[a]Costs given in 2015 Canadian dollars.
[b]Costs given in 2018 Canadian dollars.

Analysis

Internal Validation

Formal internal validation was conducted by the secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.[80]

Reference Case Analysis

We conducted our analyses in TreeAge Pro.[126] We ran 10,000 simulations (probabilistic analysis) of our model to capture the uncertainty in parameters that we expected to vary. Distributions (e.g., normal, beta, gamma) were assigned (using mean and standard error of the mean) to model variables that we expected to vary (Appendix 7, Table A15).

For our short-term analysis (Table 19), we calculated the mean costs associated with the diagnostic testing pathway (not including treatment costs), number of tissue biopsies, number of correct treatment decisions, and time to treatment for each intervention (liquid biopsy as a triage test, liquid biopsy alone, and tissue biopsy). We also calculated the incremental costs, incremental effects, and incremental cost-effectiveness ratios (ICERs), where appropriate.

For our long-term cost–utility and cost-effectiveness analyses (Table 20), we calculated the mean costs associated with testing and treatment and mean QALYs for each intervention (liquid biopsy as a triage test, liquid biopsy alone, and tissue biopsy). We also calculated the incremental costs, incremental QALYs, incremental life-years, and ICERs for liquid biopsy as a triage test and alone versus tissue biopsy.

Sensitivity Analyses

We assessed variability and uncertainty in the model using probabilistic sensitivity analyses, scenario analyses, and one-way sensitivity analyses. The results of the probabilistic sensitivity analysis for our long-term analysis would be presented as a cost-effectiveness acceptability curve.

We conducted several scenario analyses to test key assumptions in our model. Key scenario analyses included these approaches:

- We looked at tissue biopsy as a perfect reference standard (for tissue biopsy as an imperfect reference standard, see Reference Case Analysis, above)

- Varying the costs (see Table 14), sensitivity, and specificity (see Table 9) on the basis of liquid biopsy testing strategies (i.e., RT-PCR, dPCR, and NGS)
- Including the costs of purchasing and maintaining between 1 and 14 new sequencing machines and the cost associated with developing new in-house tests
- Repeat liquid biopsy testing among those with a negative liquid biopsy result. In absence of evidence on serial testing, we assumed the sensitivity and specificity would be the same as the first round of testing
- To assess the effect drug costs could have on the results, we assumed that osimertinib has the same costs as platinum-based doublet chemotherapy

We conducted one-way sensitivity analyses by varying specific model variables, within plausible ranges, and examined the impact on results. Through our one-way sensitivity analyses, we also examined the impact of several assumptions:

- All people are eligible for tissue biopsy
- Some people are ineligible for liquid biopsy
- All people have subsequent lines of treatment
- There is no impact on mortality from receiving a false-positive result
- All sample transport is done externally
- There is a range of drug costs (to account for other drugs or drug combinations)

We conducted one-way sensitivity analyses for both our short-term (testing only) and long-term (all results) scenarios. We presented the short-term results as cost per additional correct treatment decision and we presented the long-term results as the cost per additional quality-adjusted life-year gained. Due to the large number of parameters considered in the model, we present results only for the parameters that had the biggest impact on outcomes.

Results

Reference Case Analysis

Tables 19 and 20 present the reference case analysis results for our short-term analysis considering the clinical outcomes and costs we obtained from our primary economic evaluation that are associated specifically with the testing strategies. The average total cost of conducting liquid biopsy alone was the lowest ($688), followed by liquid biopsy as a triage test ($1,644). Tissue biopsy alone had the highest cost ($2,149). Tissue biopsy, however, had the fewest false-positive results (2 per 100 tests), followed by liquid biopsy alone (5 per 100) and liquid biopsy as a triage test (6 per 100). Tissue biopsy also had the fewest false-negative results (6 per 100 tests), followed by liquid biopsy as a triage test (8 per 100) and liquid biopsy alone (20 per 100). However, tissue biopsy alone also had the most instances of undetermined mutation status (28 per 100).

In the tissue biopsy alone strategy, 820 tissue biopsies were conducted per every 1,000 persons. In the liquid biopsy as a triage test strategy, 432 tissue biopsies were conducted for every 1,000 persons, meaning nearly 400 tissue biopsies were avoided (0.40 avoided per person). For this strategy, liquid biopsy as a triage test dominated tissue biopsy alone. The liquid biopsy alone strategy dominated both liquid biopsy as a triage test and tissue biopsy alone (least costly and fewest tissue biopsies conducted) because no tissue biopsies were conducted per strategy design.

The number of correct treatment decisions was the highest when liquid biopsy was used as a triage test (858 per 1,000 persons), followed by liquid biopsy alone (750 per 1,000 persons) and tissue biopsy alone (739 per 1,000 persons). Tissue biopsy alone was dominated by liquid biopsy as a triage test, as tissue biopsy alone costs $505 more than liquid biopsy as a triage test, and tissue biopsy alone resulted in about 120 fewer correct treatment decisions per 1,000 persons (or 0.12 per person). When liquid biopsy as a triage test was compared with liquid biopsy alone, the ICER was $8,480 per additional correct treatment decision.

The average time to treatment was the longest for liquid biopsy as a triage test (37 days), followed by tissue biopsy alone (35 days) and liquid biopsy alone (19 days). However, when we assumed that all people can have a tissue biopsy (i.e., no one refuses or cannot have a biopsy, scenarios where the person has 0 days to treatment), the time to treatment result was slightly longer for tissue biopsy alone (42 days) than liquid biopsy as a triage test (40 days).

Finally, the highest number of people would receive osimertinib if liquid biopsy was used as a triage test, followed by liquid biopsy alone, and lowest if tissue biopsy alone was conducted.

Table 19: Clinical Outcomes of Short-Term (Testing Only) Analysis

Strategy	No. of Tissue Biopsies per 1,000 Persons (95% CrI)	No. of Correct Treatment Decisions per 1,000 Persons (95% CrI)	Average Time to Treatment, Days (95% CrI)	No. who Receive Osimertinib per 1,000 Persons (95% CrI)
Liquid biopsy alone	0	750 (600–880)	19 (18–19)	479 (331–622)
Liquid biopsy as a triage test	432 (309–561)	858 (760–929)	37 (31–42)	616 (518–717)
Tissue biopsy alone	829 (746–898)	739 (662–802)	35 (31–38)	403 (324–480)

Abbreviation: CrI, credible interval.

Table 20: Cost, and Cost-Effectiveness Per Person in Short-Term (Testing Only) Analysis

Strategy	Average Total Cost[a] (95% CrI)	Incremental Cost[a,b] (95% CrI)	Incremental No. of Tissue Biopsies (95% CrI)	ICER ($/Tissue Biopsy Avoided)	Incremental No. of Correct Decisions (95% CrI)	ICER ($/Correct Treatment Decision)[a]
Liquid biopsy alone	$688 (644–738)	--	--	--	--	--
Liquid biopsy as a triage test	$1,644 (1,331–2,020)	$956 (646–1,329)	0.43 (0.31–0.56)	Dominated by LB alone (more TB, more costly)	0.11 (0.03–0.20)	8,920
Tissue biopsy alone	$2,149 (1,753–2,626)	$505 (184–873)	0.40 (0.27–0.52)	Dominated by LB alone (more TB, more costly)	−0.12 (−0.21 to −0.01)	Dominated by LB as triage test (fewer correct decisions, more costly)

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; LB, liquid biopsy; TB, tissue biopsy.
[a]Costs in 2018 Canadian dollars.
[b]Numbers could appear incorrect because of rounding.

The results of the long-term (lifetime) cost-effectiveness and cost–utility analyses are presented in Table 21. Liquid biopsy as a triage test was the most expensive strategy and produced the most life-years and QALYs. Tissue biopsy alone was the least expensive test and produced the fewest life-years and fewest QALYs gained.

Liquid biopsy alone cost $2,275 more per person than tissue biopsy alone. The ICERs for liquid biopsy alone compared with tissue biopsy alone were $115,105 per life-year and $122,938 per QALY. Liquid biopsy as a triage test cost $10,539 more per person than liquid biopsy alone. The ICERs for liquid biopsy as a triage test compared with liquid biopsy alone were $117,046 per life-year and $175,502 per QALY.

Table 21: Results Per Person of Long-Term (Testing, Treatment, and Care) Analysis

Strategy	Average Total Cost[a] (95% CrI)	Incremental Cost[a,b] (95% CrI)	Average Effect (95% CrI)		Incremental Effect (95% CrI)[b]		ICER[a,b]	
			LY	QALY	LY	QALY	$/LY	$/QALY
Tissue biopsy alone	$78,952 (70,825–87,079)	--	2.12 (2.06–2.19)	1.10 (0.98–1.21)	--	--	--	--
Liquid biopsy alone	$81,227 (69,583–92,733)	$2,275 (−8,864–12,519)	2.14 (2.02–2.25)	1.12 (0.99–1.25)	0.02 (−0.10–0.13)	0.02 (−0.06–0.09)	$115,105	$122,938
Liquid biopsy as a triage test	$91,767 (83,511–100,065)	$10,539 (4,971–17,561)	2.23 (2.14–2.31)	1.18 (1.06–1.30)	0.09 (0.03–0.16)	0.05 (.02–0.11)	$117,046	$175,502

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; LY, life-years; QALY, quality-adjusted life-years.
[a]Costs in 2018 Canadian dollars.
[b]Numbers could appear incorrect because of rounding.

Sensitivity Analysis

Results from the one-way sensitivity analyses and scenario analyses are presented in Appendix 7 (Figures A1–A4 and Tables A15–A17).

Short-Term (Testing Only) Sensitivity Analyses

For testing-related costs, tissue biopsy remained more costly than liquid biopsy in most scenarios. Liquid biopsy as a triage test was the most expensive alternative in two scenarios: (1) when costs and clinical parameters were associated with NGS, and (2) when the cost of developing 14 new tests and purchasing and maintaining 14 new machines was included.

By design, liquid biopsy alone had no tissue biopsies; it was consistently less costly than tissue biopsy. Liquid biopsy as a triage test avoided up to 540 tissue biopsies when liquid biopsy retesting was used on people who received a negative result, compared with tissue biopsy alone. However, liquid biopsy as a triage test was always more costly than liquid biopsy alone.

Liquid biopsy as a triage test consistently produced the greatest number of correct treatment decisions. In most of our analyses, this strategy dominated (was more effective and less costly) tissue biopsy alone. Compared with liquid biopsy alone, the ICERs ranged from about $6,300 to $33,000 per additional correct decision.

In one-way sensitivity analyses, liquid biopsy as a triage test was consistently less costly and more effective than tissue biopsy alone. Liquid biopsy alone was consistently less costly than tissue biopsy, but effectiveness varied (in favour of either liquid biopsy alone or tissue biopsy alone) depending on our model assumptions (e.g., the sensitivity and specificity of tissue and liquid biopsy; the proportion of people who were not candidates for biopsy, who have a failed tissue biopsy, or who have a repeat tissue biopsy after a failed attempt; and the prevalence of the *EGFR* T790M mutation). A tornado diagram for liquid biopsy as a triage test compared with liquid biopsy alone is presented in Figure A1 (Appendix 7). The incremental cost per additional correct treatment decision was most sensitive to the sensitivity of liquid biopsy, the sensitivity and specificity of tissue biopsy, and the prevalence of the *EGFR* T790M mutation.

Long-Term (Testing, Treatment, and Care) Sensitivity Analyses

Results from the probabilistic sensitivity analyses for the long-term analysis can be found in Figure 9. The figure shows the probability that each intervention is the most cost-effective at various willingness-to-pay values. At willingness-to-pay values less than $125,000 per QALY, tissue biopsy had the highest probability of being cost-effective. At willingness-to-pay values greater than $200,000 per QALY, liquid biopsy as a triage test had the highest probability of being cost-effective. Between these willingness-to-pay values, liquid biopsy alone had the highest probability of being cost-effective.

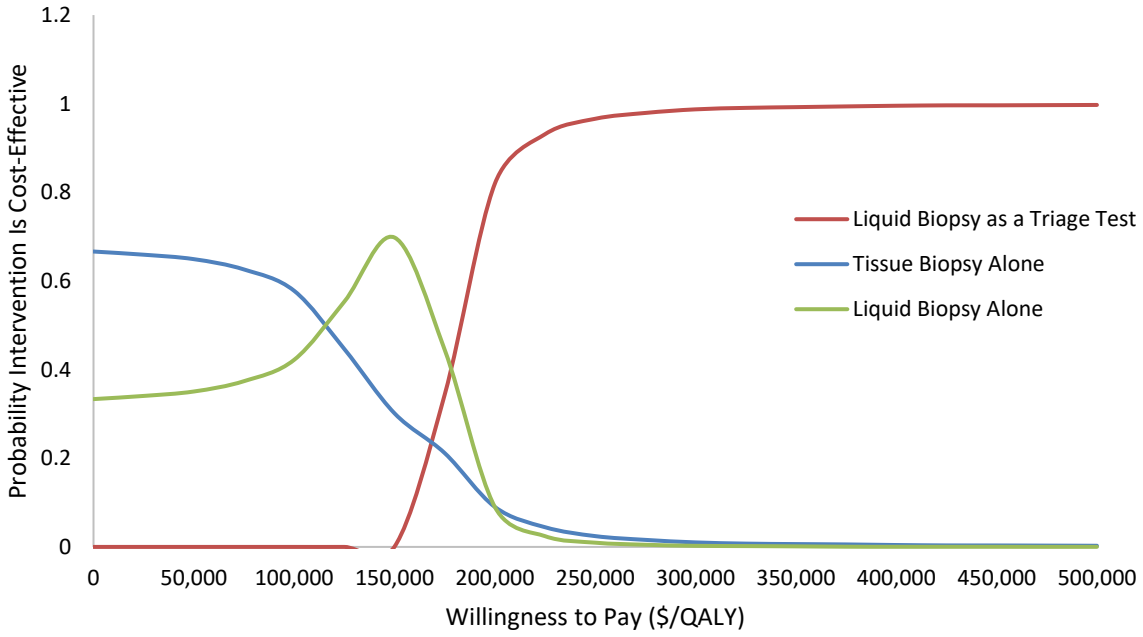

Figure 9: Cost-Effectiveness Acceptability Curve

Abbreviation: QALY, quality-adjusted life-year.

In most scenarios, liquid biopsy as a triage test remained the most costly and most effective strategy, followed by liquid biopsy alone (Appendix 7, Table A18). In these scenarios, tissue biopsy was the least costly and least effective strategy. The ICER for liquid biopsy alone compared with tissue biopsy alone remained high (between approximately $95,000 and $170,000 per QALY). The ICER for liquid biopsy as a triage test compared with liquid biopsy

alone also remained high (between approximately $175,000 and $246,000 per QALY). In line with this, in most scenarios, at willingness-to-pay values less than $100,000 per QALY, tissue biopsy had the highest probability of being cost-effective (Table A19).

Results differed in two scenarios. When we assumed that tissue biopsy is a perfect reference standard, it was more effective and more costly than liquid biopsy alone. The ICER for tissue biopsy alone in this scenario compared with liquid biopsy alone was $42,445 per life-year and $96,258 per QALY. Liquid biopsy as a triage test remained the most effective and most costly intervention, but the ICER compared with tissue biopsy was high (~$190,000 per QALY). At a willingness to pay of $50,000 per QALY, liquid biopsy alone had the highest probability of being cost-effective (64%).

When we assumed that osimertinib costs were equivalent to platinum-based doublet chemotherapy costs, liquid biopsy as a triage test was most likely the optimal choice (99% probability that it was the most cost-effective strategy at a willingness to pay >$50,000 per QALY). In this scenario, liquid biopsy alone dominated tissue biopsy alone (it was more effective and less costly). Liquid biopsy as a triage test had an ICER of about $22,000 per QALY compared with liquid biopsy alone. We found that the treatment costs of osimertinib (which was used most often in the liquid biopsy as a triage test intervention) have a high impact on the cost-effectiveness of liquid biopsy.

In one-way sensitivity analyses, all comparisons were sensitive to changes in the cost and utility of osimertinib (Figures A1–A4). When comparing liquid biopsy as a triage test or tissue biopsy alone to liquid biopsy alone, results were sensitive to changes in sensitivity and specificity. Finally, when comparing liquid biopsy alone and tissue biopsy alone, results were sensitive to changes in the proportion of people who are not candidates for tissue biopsy, who have a failed tissue biopsy, or who have a retest tissue biopsy after a failure.

Discussion

Our results showed that using liquid biopsy as a triage test or alone can reduce the testing cost for *EGFR* T790M mutation compared with using tissue biopsy alone. These results are consistent with previous work.[73,75] The liquid biopsy strategies also led to fewer tissue biopsies, which are more invasive tests with potential complications.[84]

While tissue biopsy had fewer false-positive and false-negative results than either liquid biopsy strategy, some people assigned to tissue biopsy did not receive testing (i.e., they were not a candidate or had insufficient tissue) or had a failed test. Given this limitation of tissue biopsy, both liquid biopsy strategies had a greater number of correct treatment decisions, where people who were *EGFR* T790M positive received the third-generation *EGFR*-TKI (osimertinib) and people who were *EGFR* T790M negative received chemotherapy. Liquid biopsy as a triage test performed better than liquid biopsy alone, and the cost per additional correct decision was approximately $9,000. Our sensitivity analyses demonstrated that, when everyone was eligible for a tissue biopsy or when tissue biopsy was considered a perfect reference standard, tissue biopsy alone produced more correct treatment decisions than liquid biopsy alone but remained inferior to liquid biopsy as a triage test. Similarly, an abstract published in 2018 found that most cases were correctly identified when using liquid biopsy as a triage test to determine second-line treatment (i.e., testing after progression on first-line treatment).[76] However, this study evaluated first- and second-line testing strategies simultaneously and the results cannot be isolated.

In our sensitivity analyses, we found that NGS was the costliest (and most effective) detection method. Under this scenario, liquid biopsy cost more than tissue biopsy. It is important to note that the price used was based on an assay cost that did not incorporate batching of samples. The price was high in part because this analysis focused on testing a single variant (*EGFR* T790M). The cost to test this mutation can be reduced if other mutations related to NSCLC can be analyzed simultaneously or if the absolute costs for this type of sequencing are reduced. While other mutations were out of scope for this analysis, the landscape of genetic tests, including the use of liquid biopsy, is evolving rapidly. In addition, caution is needed in assessing these results, as costs can vary between labs, and the sensitivity and specificity data for each detection method were based on a limited number of studies ($N_{NGS} = 3$, $N_{dPCR} = 10$, $N_{RT\text{-}PCR} = 4$) with varying mutant allele fractions.

When considering lifetime costs and benefits, both liquid biopsy strategies were more costly than tissue biopsy alone but produced the most life-years and QALYs. However, the difference in effectiveness was generally small and hence unlikely to be cost-effective under willingness-to-pay values less than $100,000 per life-year or QALY. Our results were robust to most sensitivity analyses performed. We have elaborated on two scenarios that affected the results below.

In our reference case, we assumed tissue biopsy is an imperfect reference standard. While this assumption is supported by the evidence of tissue heterogeneity,[21] our clinical review used modelling techniques to estimate these parameters due to the absence of published sensitivity and specificity values for tissue biopsy. The scenario that assumed tissue biopsy is a perfect reference standard found that liquid biopsy alone became the least costly and least effective strategy, with a 64% probability of being cost-effective at a willingness to pay of $50,000 per QALY.

We also examined the impact of treatment costs in our analyses. People found to be *EGFR* T790M positive are offered osimertinib, which is more expensive than platinum-based doublet therapy (the alternative treatment). Although there have been mixed results, studies have shown that, due to its high price, osimertinib may not be cost-effective as a second-line treatment.[68,127] When we assumed that the prices of osimertinib and platinum-based doublet therapy are equivalent, liquid biopsy as a triage test became the strategy that was most likely to be cost-effective. The results of our analyses were driven by the cost of treatment and the observation that more people were expected to receive this treatment under the liquid biopsy strategies. The treatment (osimertinib) is currently being publicly funded in Ontario through the exceptional access program.

Strengths and Limitations

Our analyses should be interpreted with consideration of some limitations. The costs of liquid biopsy vary depending on several factors, including the detection method used and number of variants tested. Currently, two laboratories in Ontario offer liquid biopsy testing for the *EGFR* T790M resistance mutation. It is unclear if other testing locations will be added. In addition, it is unclear if additional large sequencing equipment will be needed. We based the estimates on currently available costs and on consultation with clinical experts. We also looked at several cost scenarios (e.g., capital costs and range of testing costs), but these estimates could depend on how testing is implemented, how costs of testing change over time, and any variation in costs across centres.

We were also limited in our ability to identify and model the sensitivity and specificity of tissue biopsy and serial testing strategies. Tissue biopsy is an imperfect reference standard, but our clinical review did not identify published estimates of the sensitivity and specificity. As a result, we used estimates derived through modelling. Further, we assumed that the sensitivity and specificity of sequential tests (i.e., liquid biopsy followed by liquid or tissue biopsy if the result is negative) were the same and independent of one another. To limit the effect this uncertainty would have on our results, we looked at several scenarios, including favouring tissue biopsy (i.e., assuming it is a perfect reference standard). If additional data become available, the impact of sequential testing should be incorporated.

Our assessment also had several strengths. To our knowledge, this is the first analysis that specifically captured the cost-effectiveness of liquid biopsy (as a triage test or alone) compared with tissue biopsy for detection of the *EGFR* T790M mutation. We presented both short-term analyses capturing testing-specific outcomes and long-term analyses capturing the impact of testing on treatment, care, quality, and quantity of life gained. Finally, we conducted an assessment that used Ontario-specific costs for testing, treatment, and care. This is important, as previous analyses have shown wide discrepancies in cost-effectiveness, likely resulting from differences in treatment costs.[68]

Conclusions

Considering testing-related costs and effects only:

- Liquid biopsy, alone or as a triage test, is less costly and more effective (fewer tissue biopsies, more correct decisions) than tissue biopsy
    - Liquid biopsy as a triage test had the greatest number of correct treatment decisions

Considering lifetime costs and effects:

- Liquid biopsy as a triage test was the most effective and most costly, followed by liquid biopsy alone
- Liquid biopsy alone was not cost-effective (incremental cost-effectiveness ratio [ICER] > $100,000 per QALY) compared with tissue biopsy. The higher lifetime cost of liquid biopsy is driven by the high cost of osimertinib. A reduction in the cost of osimertinib would change this result

BUDGET IMPACT ANALYSIS

Research Question

What is the potential budget impact of publicly funding cell-free circulating tumour DNA (ctDNA) blood testing (also known as liquid biopsy), as a triage test or alone, compared with tissue biopsy for the detection of the *EGFR* T790M mutation in people with advanced non–small cell lung cancer (NSCLC), from the perspective of the Ontario Ministry of Health?

Methods

Analytic Framework

The budget impact of liquid biopsy was estimated as the cost difference between two scenarios:

1. The current scenario, which is the current clinical practice without public funding for liquid biopsy: in this scenario we assumed *EGFR* T790M mutation testing is done using liquid biopsy as a triage test for some patients but is funded through private means (i.e., manufacturer funding). For the remaining patients we assumed *EGFR* T790M mutation testing would be done using tissue biopsy
2. The new scenario, which is the anticipated clinical practice with either liquid biopsy as a triage test (followed by tissue biopsy if patients test negative for the *EGFR* T790M resistance mutation) or liquid biopsy alone. The model schematic is shown in Figure 10.

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. In sensitivity analyses we explored how results are affected by varying input parameters and model assumptions.

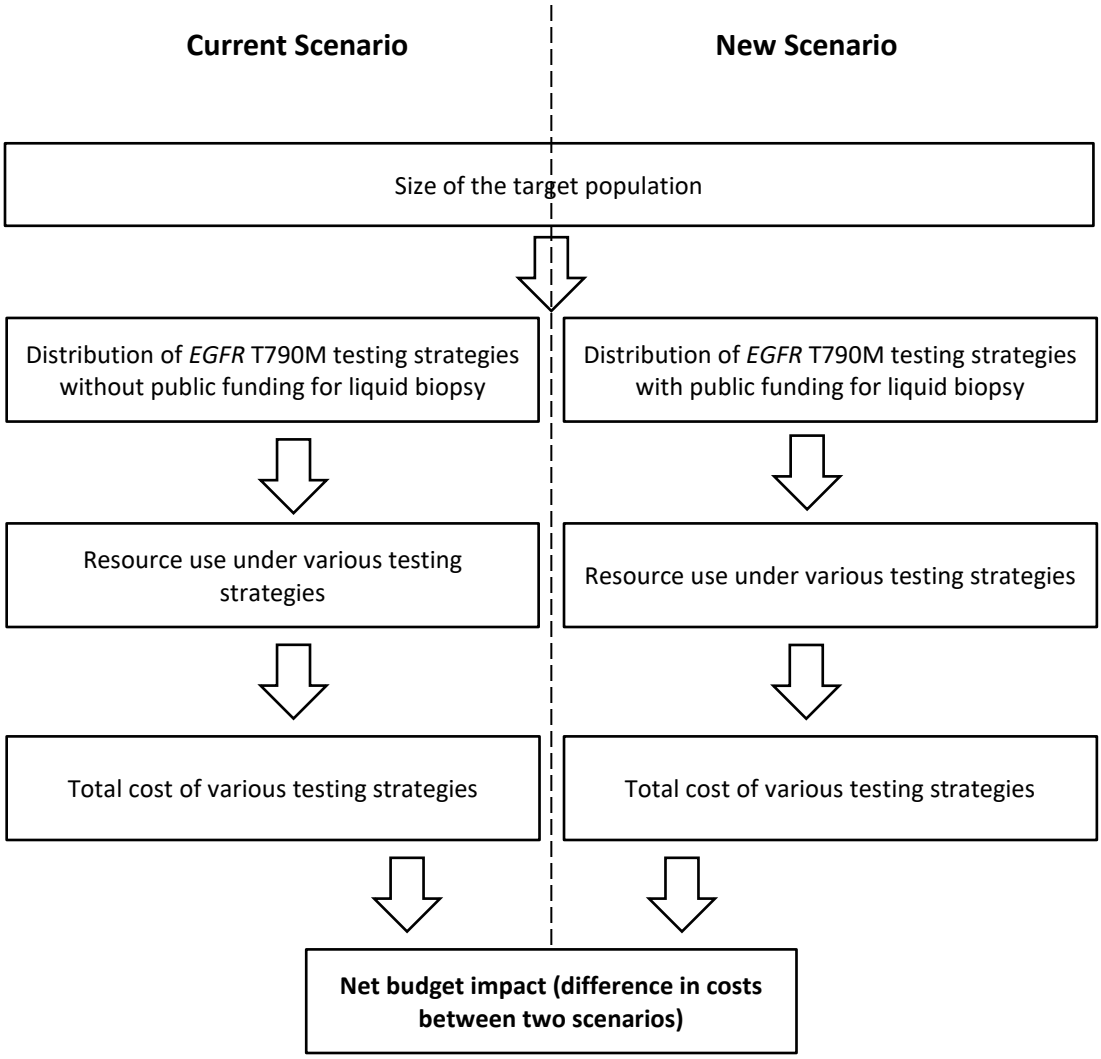

Figure 10: Schematic Model of Budget Impact

Abbreviation: *EGFR*, epidermal growth factor receptor.

Key Assumptions

The assumptions of our primary economic evaluation are relevant to the budget impact analysis.

We made a few additional assumptions:

- Currently, liquid biopsy is not being funded by the public payer
- Large processing equipment is already available in Ontario and would not need to be purchased. We explored this assumption in our sensitivity analysis

Target Population

Our target population is adults with advanced NSCLC who have an *EGFR* sensitizing mutation and whose disease has progressed after first-line (first- or second-generation) *EGFR*-TKI therapy.

Our target population calculation is summarized in Table 22. On the basis of a recent publication, we assumed there would be 11,396 new cases of lung cancer in Ontario in 2018.[128] Data from Statistics Canada indicate that numbers of lung cancer cases could be stable or could decrease over time.[129] To be conservative, we assumed the number of cases would stay stable. Given the short survival times in lung cancer, we considered only incident cases. According to a recent Canadian Cancer Statistics Report, about 88% of lung cancer is NSCLC.[130] Hence, we assumed there would be 10,014 new cases of NSCLC in Ontario per year.

In Ontario, *EGFR* testing (for sensitizing mutations) is conducted for people with NSCLC who are both at risk for *EGFR* mutations and have advanced disease.[81] We assumed that 50% of people with NSCLC would be at risk for *EFGR* mutations (i.e., 40% would have adenocarcinoma,[131,132] and an additional 10% would have other risk factors). In addition, we assumed 87% of people will be diagnosed with or progress to advanced disease. Based on the Canadian Cancer Statistics Report,[130] about 67% of people are diagnosed at a late stage. Given the poor prognosis of people with NSCLC, we assumed that most (60%) of the remaining population would eventually develop advanced NSCLC.

In total, we expected about 4,350 people to be tested for an *EGFR* mutation. We estimated that 21% of people tested would test positive for an *EGFR* mutation and would be treated with a first-line tyrosine kinase inhibitor (TKI). This percentage was based on a recent population-based study on *EGFR* mutation testing in Ontario.[90] We expected that, if these patients were to survive, their disease would progress and they would become eligible for *EGFR* T790M mutation testing. In our reference case, we assumed that about 78% would live, would develop advanced NSCLC, and would be tested. This assumption was based on a recent real-world study conducted in Japan.[133]

In summary, we estimated that annually, 699 people would be tested for *EGFR* T790M mutation with tissue or liquid biopsy. We looked at an upper range of this value in sensitivity analyses.

Table 22: Target Population Calculation

Target Population Estimate	2018	
	Proportion, %[a]	No.[a]
Age-standardized incidence of lung cancer in Ontario	0.0696	11,396
People with NSCLC	88	10,014
People with adenocarcinoma or at risk (eligibility for *EGFR* testing)	50[b]	5,007
Cases of advanced NSCLC or expected to progress to late stage (eligibility for *EGFR* testing)[c]	87[c]	4,350
Prevalence of *EGFR* mutation	20.6	895
People with EGFR mutation who are prescribed *EGFR*-TKI	100	895
People who are alive, whose disease has progressed, and who would be tested for *EGFR* T790 mutation	78	699

Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.
[b]Numbers could appear incorrect because of rounding.
[b]About 40% of people with NSCLC have adenocarcinoma[131,132] and 10% have risk factors making them eligible for *EGFR* mutation testing (assumption).
[c]About 67% of cases are diagnosed at an advanced stage,[130] and 60% of remaining cases will progress to an advanced stage (assumption).

Current Scenario: Uptake and Intervention Mix

Currently, *EGFR* T790M testing using tissue biopsy is publicly funded. Liquid biopsy is being funded, likely for a limited time, by AstraZeneca (manufacturer of osimertinib). With the help of our clinical experts, we estimated that 300 liquid biopsies (100 at London Health Sciences Centre [written communication; Bekhim Sadikovic; Jan 24, 2019], and 200 at University Health Network [written communication; Genome Diagnostics, UHN]) are being done yearly in Ontario. This number is limited by access and funding for testing. Thus, about 57% of people have liquid biopsy as a triage test, followed by tissue biopsy if the result is negative. The remaining 43% of tests would use tissue biopsy (if appropriate).

New Scenario(s): Uptake and Intervention Mix

We assumed that the number of liquid biopsies for *EGFR* T790M mutations would increase rapidly with public funding and that uptake would reach 100% over the next 5 years among eligible patients. We assumed the remaining 5% of tests would be done using tissue biopsy alone (if appropriate).

We looked at two new scenarios, following the comparators included in our economic evaluation:

1. Liquid biopsy as a triage test, followed by tissue biopsy if the test result is negative
2. Liquid biopsy alone

The uptake and intervention mix for each scenario is summarized in Table 23.

Table 23: Uptake of Testing Strategies for Detection of *EGFR* T790M Mutation

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Target Population (n)	699	699	699	699	699	3,496
Current Scenario						
Uptake (liquid biopsy)	0.572	0.572	0.572	0.572	0.572	—
Volume liquid biopsies triage	400	400	400	400	400	2,000
Volume tissue biopsies alone	299	299	299	299	299	1,496
New Scenario 1 (Liquid Biopsy as Triage)						
Uptake (liquid biopsy)	0.572	0.679	0.786	0.893	1.00	—
Volume liquid biopsies triage	400	475	550	624	699	2,748
Volume tissue biopsies alone	299	224	150	75	0	748
New Scenario 2 (Liquid Biopsy Alone)						
Uptake (liquid biopsy)	0.572	0.679	0.786	0.893	1.00	—
Volume liquid biopsies alone	400	475	550	624	699	2,748
Volume tissue biopsies alone	299	224	150	75	0	748

Abbreviation: EGFR, epidermal growth factor receptor.

Resources and Costs

The undiscounted cost per person was derived from our long-term analyses (including testing, treatment, and care costs) from our economic model. We assumed, in our current scenario, that liquid biopsy assay costs are exclusively funded through private means and those costs are not incurred by the Ministry of Health. However, we assumed that all other costs associated with liquid biopsy (e.g., pre-analytic, labour, consultation costs) would be paid for by hospitals and ultimately the Ministry. In our reference case, we excluded the capital cost of processing equipment. The per-person costs for tissue biopsy, liquid biopsy as a triage test, and liquid biopsy alone are presented in Table 24. Costs are broken down into testing-related cost and non–testing-related costs (i.e., treatment-related, general care, and end-of-life care costs).

Table 24: Per-Person Costs Used in Budget Impact Analysis

Scenario	Per-Person Costs Used in Economic Model, $					Total
	Year 1	Year 2	Year 3	Year 4	Year 5	
Current Scenario						
Tissue biopsy						
Testing costs	2,149	—	—	—	—	2,149
Non-testing costs	37,568	20,795	9,777	5,202	2,743	80,682
Liquid biopsy (triage)						
Testing costs	1,506	—	—	—	—	1,470
Non-testing costs	44,776	23,766	11,640	6,297	3,249	91,295
New Scenario						
Tissue biopsy						
Testing costs	2,149	—	—	—	—	2,149
Non-testing costs	37,568	20,795	9,777	5,202	2,743	80,682
Liquid biopsy (triage)						
Testing costs	1,646	—	—	—	—	1,610
Non-testing costs	44,776	23,766	11,640	6,297	3,249	91,295
Liquid biopsy (alone)						
Testing costs	688	—	—	—	—	688
Non-testing costs	39,815	21,547	10,250	5,465	2,851	79,832

Analysis

In the reference case analysis, we calculated the required budget to publicly fund liquid biopsy to detect the *EGFR* T790M mutation in adults with advanced NSCLC whose disease has progressed despite treatment with first-line *EGFR*-TKIs in Ontario. We calculated the budget impact as the cost difference between our new scenario (public funding for liquid biopsy) and the current scenario (no public funding for liquid biopsy). Total costs are presented along with cost breakdowns (i.e., diagnostic testing, treatment and treatment management, general care).

Sensitivity Analyses

We conducted several sensitivity analyses:

- Assessing the impact if tissue biopsy is a perfect reference standard
- Examining a plausible upper estimate of the number of tests that could need to be performed. We did this by adjusting several assumptions in our target population (Table 25)
- Using a repeat liquid biopsy testing, that is, giving a second liquid biopsy test if the first result was negative
- Including capital costs of purchasing processing equipment (1–14 additional machines), maintaining equipment, and developing new in-house tests. These costs were applied as a one-time cost in the first year of the budget impact assessment

Table 25: Budget Impact Scenario Analysis, Adjustment to Target Population

Parameter	Reference Case % (N)[a]	Upper Estimate % (N)[a]
Total cases of lung cancer	0.0696 (11,396)	0.0696 (11,396)
Proportion NSCLC	0.88 (10,014)	0.88 (10,014)
Proportion of NSCLC eligible for *EGFR* testing (e.g., adenocarcinoma)	0.5[b] (5,007)	1[b] (10,014)
Proportion of NSCLC diagnosed or expected to progress to advanced disease	0.87[c] (4,350)	1[c] (10,014)
Prevalence of *EGFR* mutation	0.206[d] (895)	0.206[d] (2,059)
Proportion prescribed *EGFR*-TKI	1[e] (895)	1[e] (2,059)
Proportion who live, whose disease progresses, and who are tested for *EGFR* T790M mutation	0.78[f] (699)	1[f] (2,059)

Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.
[a]Numbers could appear incorrect because of rounding.
[b]Reference case: 40% adenocarcinoma + 10% additional at risk; upper estimate: all.
[c]Reference case: 67% diagnosed with advanced NSCLC+ 60% of remaining will progress to advanced NSCLC; upper estimate: all.
[d]Reference case: Shiau et al, 2014[90]; upper estimate: Shiau et al, 2014.[90]
[e]Assumption.
[f]Reference case: Okamoto et al, 2018[133]; upper estimate: assumption.

Results

Reference Case

The reference case budget impact analysis is presented in Table 26. The total budget in our current scenario ranged from about $30 to $60 million annually over 5 years to test about 3,500 patients. About $1.25 million yearly can be attributed to testing costs, and the remaining $29 million to $61 million yearly can be attributed to non-testing (treatment-related, complication, general, and end-of-life care) costs.

In the new scenario, when liquid biopsy is used as a triage test the total budget impact ranged from $30 million to $63 million yearly, with about $1.15 million to $1.30 million in testing-related costs and $29 to $62 million related to non-testing costs yearly. Compared with our current scenario, this led to a budget impact of between $0.06 million and $3 million yearly. If considering only testing costs, funding liquid biopsy could lead to a small budget impact in the first couple of years and eventually to cost savings of up to $0.09 million yearly.

In the new scenario, when liquid biopsy is used alone, the total budget impact ranged from $28 million to $56 million yearly, with about $0.5 million to $1 million in testing-related costs and $27 million to $55 million related to non-testing costs yearly. Compared with our current scenario, this led to a cost savings of between about $2 million and $4 million yearly.

Table 26: Budget Impact Analysis Results

	Budget Impact, $ Million[a,b]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Total Cost of Current Scenario						
Testing costs	1.25	1.25	1.25	1.25	1.25	6.23
Non-testing costs	29.15	44.88	52.46	56.54	58.66	241.69
Total	30.40	46.13	53.71	57.78	59.90	247.92
Total Cost of New Scenario 1 (Liquid Biopsy Triage)						
Testing costs	1.30	1.26	1.23	1.19	1.15	6.13
Non-testing costs	29.15	45.42	53.76	58.74	61.84	248.92
Total	30.45	46.68	54.99	59.93	62.99	255.05
Budget Impact of New Scenario 1 (Liquid Biopsy Triage)						
Testing costs	0.06	0.02	−0.02	−0.06	−0.09	−0.10
Non-testing costs	0.00	0.54	1.30	2.20	3.18	7.23
Total	0.06	0.56	1.28	2.14	3.09	7.13
Total Cost of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	0.92	0.81	0.70	0.59	0.48	3.50
Non-testing costs	27.17	42.18	49.43	53.43	55.67	227.87
Total	28.09	42.99	50.13	54.02	56.15	231.37
Budget Impact of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	−0.33	−0.44	−0.55	−0.65	−0.76	−2.73
Non-testing costs	−1.98	−2.70	−3.04	−3.11	−2.99	−13.82
Total	−2.31	−3.14	−3.58	−3.76	−3.75	−16.55

[a]In 2018 Canadian dollars.
[b]Numbers could appear incorrect because of rounding.

Sensitivity Analysis

The results from our scenario analyses are presented in the appendix (Tables A11 to A15). When an upper estimate of the number of eligible people was considered, liquid biopsy (as a triage test and alone) led to greater test-related cost savings. However, this scenario also led to higher non-testing costs and, overall, had a higher budget impact. Incorporating repeat liquid biopsies (following an initial negative liquid biopsy result) and capital equipment costs also increased the overall budget impact of funding liquid biopsy.

Discussion

We estimated that 699 people would be eligible for liquid biopsy each year. If funded as a triage test, we estimated liquid biopsy would cost the public payer an additional $60,000 to $3 million yearly. These costs can primarily be attributed to non–testing-related costs, including the costs of treatment, adverse events, and general or end-of-life care. Testing-related costs were estimated to be minimal in the first year and lead to cost savings over time. If liquid biopsy alone is funded (i.e., tissue biopsy eventually is not used to test for *EGFR* T790M), cost savings would range from $2 to $4 million yearly.

Several scenarios led to a higher budget impact including when we used a higher number of eligible patients (N = 2,059), when we incorporated repeat liquid biopsy tests, and when we included capital equipment costs. The budget impact in the higher-volume scenario reached up to $17 million yearly, but again, most of these costs were attributed to non–testing-related costs.

Ultimately, the budget impact is dependent on several factors including implementation, the exact volumes, and need for capital investment. Where the additional costs are incurred, or where the cost savings are realized could vary. Many areas of costs (i.e., long-term costs attributed to treatment and care) would likely be funded through existing mechanisms, including drug programs, the Ontario Health Insurance Plan (OHIP), and hospitals. Although there would be costs to conducting additional liquid biopsies, some of these costs would likely be offset by fewer tissue biopsies conducted in this population.

Strengths and Limitations

We used costs derived from our economic model; hence, limitations from our cost-effectiveness analyses, which have been discussed earlier, could also affect the budget impact. In addition, our budget impact analysis focused on liquid biopsy for detection of the *EGFR* T790M mutation among people whose disease has progressed despite treatment with first-line *EGFR*-TKIs. The scope of the study is narrow, and we acknowledge the budget impact could be affected by other factors. This includes testing for other mutations, or changes to treatment indications. A recent study has been published on using osimertinib as a first-line therapy.[134] An analysis has also looked at the cost-effectiveness of osimertinib in this patient population in Canada.[86] This indication is not currently approved by Health Canada, but if it is approved in the future, fewer people might be eligible for liquid biopsy for detection of the *EGFR* T790M mutation.

Despite limitations, we were able to show the potential budget impact under various biopsy strategies (liquid biopsy alone, liquid biopsy as a triage test, and repeat liquid biopsies) and costing scenarios (including capital costs). If liquid biopsy is publicly funded, some cost savings could be achieved through lower total testing costs. However, these savings could be offset by additional spending on treatment and care, and the amount will depend on how liquid biopsy is used (as a triage test or alone).

Conclusions

- We estimated publicly funding liquid biopsy as a triage test would cost between about $60,000 and $3 million yearly. However, it was cost saving when we considered only testing costs
- We estimated that publicly funding liquid biopsy alone would save between $2 million to $4 million yearly
- A higher budget impact is estimated if liquid biopsy is used with repeat testing or if capital investments are included

QUANTITATIVE PREFERENCES EVIDENCE

Research Questions

- What are the relative preference and values for cell-free circulating tumour DNA (ctDNA) blood testing (also known as liquid biopsy) compared with tissue biopsy?
- What is the relative importance of key attributes of liquid biopsy?
- What trade-offs between attributes of liquid biopsy are people willing to make?

Methods

We developed the research questions in consultation with patients, health care providers, clinical experts, and other health system stakeholders.

The review of quantitative preference evidence (QPE) will be conducted as a literature survey and has methods different from those of the clinical systematic review. Results will be narratively summarized in text or tables.

The objective of this literature survey is to describe and understand patients and providers' values and preferences regarding liquid biopsy in detecting epidermal growth factor receptor *(EGFR*) T790M mutation in patients with advanced non–small cell lung cancer (NSCLC).

Quantitative Preferences Evidence Literature Search

We performed a targeted literature search on May 31, 2018, to retrieve studies published from January 1, 2000, to the search date in MEDLINE.

The search was based on the population and intervention of the clinical search strategy with a methodological filter applied to limit retrieval to quantitative preference evidence by Selva et al.[135] Examples of additional key terms include attitude to health, patient preference, decision-making, and knowledge or user perspective. See the Clinical Literature Search section, above, for further details on methods used.

Medical librarians developed the search strategy using controlled vocabulary (i.e., Medical Subject Headings) and relevant keywords. The final search strategy was peer reviewed using the PRESS Checklist.[26] We created database auto-alerts in MEDLINE and monitored them for the duration of the assessment period. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 2000, and May 31, 2018
- Conference abstracts, case studies, case series
- Studies of patients' or providers' preferences for liquid biopsy using quantitative methods
    - Utility measures: direct techniques (standard gamble, time trade-off, rating scales) or conjoint analysis (discrete choice experiment, contingent valuation and willingness-to-pay, probability trade-off)
    - Non-utility quantitative measures: direct choice techniques, decision aids, surveys, questionnaires

Exclusion Criteria

- Animal and in vitro studies

Participants

Inclusion Criteria

- Patients with NSCLC who have an *EGFR*-sensitizing mutation who have progressed while using first- or second-generation *EGFR*-tyrosine kinase inhibitor (TKI) therapy

Exclusion Criteria

- Patients with other types of cancer

Index Test (Intervention)

Inclusion Criteria

- Liquid biopsy (alone or as a triage test in combination with tissue biopsy) for detection of the EGFR T790M mutation via plasma tests that use cell-free ctDNA

Exclusion Criteria

- Studies examining liquid biopsy at any other time in the clinical pathway (i.e., diagnosis of EGFR-sensitizing mutations)
- Liquid biopsy used for any other resistance mutations (Kirsten rat sarcoma viral oncogene, anaplastic lymphoma kinase, etc.)

Reference Standard/Comparator

Inclusion Criteria

- Tissue biopsy for detection of the *EGFR* T790M mutation

Outcome Measures

- Patient preferences
- Health care provider preferences
- Trade-offs

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using DistillerSR management software, and then obtained the full text of studies that appeared eligible for the review according to the inclusion criteria. The author then examined the full-text articles and selected studies that were eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics using a data form to collect information about the following:

- Source (e.g., citation information, contact details, study type)
- Methods (e.g., study design, study duration)
- Outcomes (e.g., outcomes measured, unit of measurement)

Statistical Analysis

Meta-analysis to provide an overall statistical summary of the effect estimate is inappropriate for our purposes, because we are broadly summarizing the evidence on quantitative preferences. Therefore, we took a descriptive approach using text or tables to summarize the characteristics and findings of the included studies.

Critical Appraisal of Evidence

We did not critically appraise the included studies. There are no standard tools for critical appraisal for this type of literature. The purpose for the QPE literature survey is to gain an overview of QPE in the literature.

Results

Literature Search

The literature search yielded 168 citations published between January 1, 2000, and May 31, 2018, after removing duplicates. Two conference abstracts met the inclusion criteria.

Figure 11 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

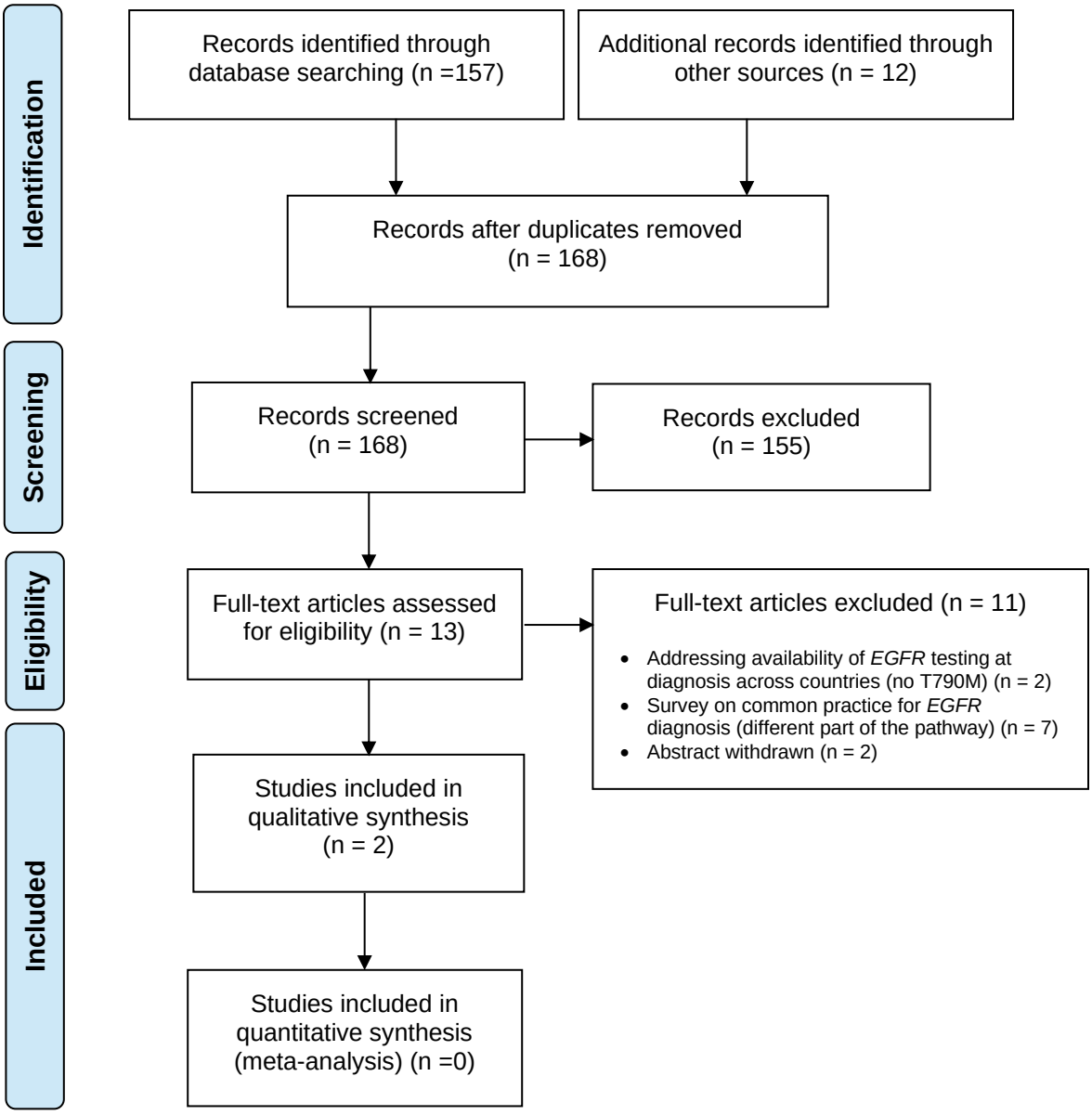

Figure 11: PRISMA Flow Diagram—Quantitative Preferences Evidence Search Strategy
Abbreviations: *EGFR*, epidermal growth factor receptor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[49]

We found no studies that examined patient and practitioner values and preferences of liquid compared with tissue biopsy for people with advanced non–small cell lung cancer (NSCLC) who experience disease progression.

The two conference abstracts[136,137] that were included did not particularly address patient or practitioner preferences or trade-offs but looked at practitioner practices of *EGFR* T790M testing. Also, practitioner practices did not pertain specifically to liquid biopsy, but to *EGFR* T790M testing regardless of the method of biopsy.

Both conference abstracts were written by the same authors. The studies were done in the United States. The objective of the first Hermann et al[136] abstract was to conduct a study using simulation-based technology to assess medical oncologists' current performance in ordering biomarker testing and diagnosing advanced NSCLC. The objective of the second Hermann et al[137] abstract was to determine if simulation-based educational interventions to address clinical practice gaps could improve decisions of oncologists in the management of *EGFR* mutated metastatic NSCLC.

In the first Hermann et al[136] conference abstract, virtual patient simulation was conducted and consisted of two patient cases. This platform allowed oncologists to choose from an extensive database of diagnostic possibilities matching the scope and depth of practice.

In the second Hermann et al[137] conference abstract, a cohort of the oncologists in the first Hermann et al conference abstract pa rticipated in virtual patient simulation-based education, and their performance was evaluated.

Health Care Provider Practices

In the first Hermann et al[136] conference abstract, in the scenario where a patient with *EGFR*-mutated NSCLC who has progressed on first generation *EGFR*-TKI, 40% of oncologists did not order testing for *EGFR* T790M.

In the second Hermann et al[137] conference abstract, clinical decisions were analyzed using a decision engine, and instantaneous clinical guidance employing current evidence-based and expert faculty recommendations was provided after each decision. Oncologists were allowed a second chance at each decision point, and decisions before and after clinical guidance were compared using a 2-tailed paired *t*-test to determine differences before and after receiving clinical guidance.

A total of 197 oncologists made clinical decisions through the virtual patient simulation. As a result of clinical guidance, they made significant improvements in diagnosing patients with *EGFR* T790M among patients who had disease progression (29%, $P < .001$).[137]

Discussion

In our literature search, we did not find any studies on patients' or practitioners' preferences for liquid biopsy compared with tissue biopsy in this specific population (advanced NSCLC with disease progression). Studies might be unavailable because patients in this population have quite advanced cancer, and the only alternative to tissue biopsy might be the less invasive option of liquid biopsy.

We found two conference abstracts that addressed practitioners' current practices with *EGFR* T790M testing. The outcomes reported were not originally of interest; however, they highlight the importance of offering physicians current clinical guidance to make the best informed decisions for and with their patients. Given these are only conference abstracts, we also do not have a fulsome idea of their methods nor the confidence of scientific rigour that comes from research that is peer reviewed and published in an appropriate journal.

To our knowledge, no published literature has explored patients' and health care providers' preferences between liquid and tissue biopsy in patients with advanced NSCLC who have disease progression after receiving first-generation *EGFR*-TKIs.

Conclusions

We found no published literature exploring patients' and health care providers' values and preferences between liquid and tissue biopsy in patients with advanced NSCLC who have disease progression after first- or second-generation *EGFR*-TKIs.

We found two conference abstracts that addressed another outcome (health care providers' practices). These abstracts reported that more than half of oncologists ordered *EGFR* T790M testing. A subset of those oncologists, when given clinical guidance, showed significant improvement in diagnosing patients with *EGFR* T790M among patients with disease progression.

PATIENT PREFERENCES AND VALUES

Objective

The objective of this analysis was to explore the underlying values, needs, impacts, preferences, and perceptions of receiving cell-free circulating tumour DNA (ctDNA) blood testing (also known as liquid biopsy) among people with lived experience of advanced non–small cell lung cancer (NSCLC).

Background

Patient, caregiver, and public engagement provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. This information includes the impact of the condition and its treatment on the patient, the patient's family and other caregivers, and the patient's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared by people with lived experience can also identify gaps or limitations in published research (e.g., sometimes typical outcome measures do not reflect what is important to those with lived experience).[1–3] Lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, priorities, preferences, and values of those with lived experience in Ontario are often inadequately explored in published literature, we contact and speak directly with people who live with a given health condition, including those who have experience with the intervention we are exploring.

Liquid biopsy is used by those with recurrent NSCLC. Usually, oncologists advise patients (who consent) to undergo liquid biopsy rather than other testing for two main reasons: (1) to determine whether the patient has the epidermal growth factor receptor (*EGFR*) T790M (mutation), and (2) to help oncologists identify appropriate treatment. Patients at this stage might be either weak or unable to undergo tissue biopsy. Physicians are more likely to recommend liquid biopsy to patients with advanced NSCLC.

Gaining an understanding of the day-to-day experience of patients and caregivers who have lung cancer or advanced NSCLC helps us assess the potential value of liquid biopsy. We spoke with seven people: this included four people with cancer and three caregivers.

Methods

Engagement Plan

The engagement plan for this health technology assessment focused on examining the experiences of people with lung cancer or advanced NSCLC and of their caregivers. We engaged people via telephone interviews and email and in person.

The qualitative interview was used as our method of engagement. This allowed us to explore the meaning of central themes in the experiences of people with lung cancer or advanced NSCLC, as well as those of their families and caregivers. Our main task in interviewing was

to understand what people told us and to gain an understanding of the story behind their experiences.[4] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that supported our choice of an interview methodology. Given the challenges of recruiting patients who have experience with advanced NSCLC and liquid biopsy, this engagement plan explores only the central themes in the experience of people with lung cancer who have had tissue biopsy.

Participant Outreach

We used an approach called purposive sampling,[5–8] which involved contacting patients, families, and caregivers with direct experience of the health condition and health technology or intervention being reviewed. We sought people who have experience with lung cancer or advanced NSCLC. Various clinical experts, lung cancer health teams in hospitals, organizations, and support groups were contacted by email and telephone. Unfortunately, these outreach methods were unsuccessful in recruiting patients with advanced NSCLC. We heard from our clinical contacts that this failure was either due to their frail condition or because patients felt too physically tired to participate in an interview.

We also conducted in-person recruitment and interviews at a lung cancer clinic in Toronto.

We were unable to recruit patients who have direct experience with advanced NSCLC at the clinic. Patients with this condition who had agreed to participate did not show up to their appointments or canceled on the day of the appointment. We were able to recruit patients with other types of lung cancer who had experience with tissue biopsy.

Interviews were limited in number, because many patients were too fatigued from their appointments to participate. Because of the patients' fatigue, we also limited the time of the interview to 15 minutes. Some patients also would have had to suddenly leave for additional tests that could be done only during the interview time. The in-person recruitment resulted in four interviews, which included interviewing four patients and three caregivers.

Inclusion Criteria

We sought to speak with people and their caregivers who have been actively managing advanced NSCLC by liquid biopsy.

Exclusion Criteria

We did not set specific exclusion criteria.

Participants

Seven adult participants were interviewed in Toronto, Ontario, including four people with lung cancer and three family members. Participants were from different socioeconomic backgrounds and genders. Participants shared their experiences and perceptions in person. Four participants had direct experience with lung cancer but did not have experience with liquid biopsy. However, all interviewees with lung cancer had experienced tissue biopsy.

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of the health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants in a printed letter of information (Appendix 9). We obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews for relevant information.

Interviews lasted 15 to 30 minutes. Interviews were semi-structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[9] Questions focused on how lung cancer affected patients' and families' quality of life, and their perceptions of the benefits or limitations of using various tests to manage their condition (Appendix 10).

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consisted of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[10,11] We used the qualitative data analysis software program Nvivo (QSR International, Doncaster, Victoria, Australia) to identify and interpret patterns in interview data. The patterns we identified then allowed us to highlight the impact of lung cancer and tissue biopsy or liquid biopsy on the patients, family members, and caregivers we interviewed.

Results

During the interviews, patients and caregivers emphasized the substantial effect lung cancer had on their quality of life. While some would be able to function in their day-to-day lives with some assistance from family members, others had limited ability to conduct daily tasks and had to depend on family members or a caregiver to a greater extent. Some patients stated that this dependence affected their mental health; they experience stress and anxiety before and after receiving information about their condition and while undergoing tissue biopsy.

People who had received tissue biopsy were able to compare what their hypothetical experience would be with liquid biopsy. Many patients who had conducted their own research on liquid biopsy or had received information from their oncologist were able to speak about the advantages they perceived of a liquid biopsy. Patients believed that liquid biopsy, would mean they could avoid the painful procedure involved with tissue biopsy, especially important when the patient is already in pain or whose health is fragile. Also, some patients had also perceived the procedure of liquid biopsy to be much faster and more convenient, as they would not have to wait for weeks to get an appointment for a tissue biopsy. Patients and caregivers stated that they could provide a blood sample at the same time they provide samples for other tests.

Patients and caregivers had difficulty speaking hypothetically about the limitations of, challenges of, and barriers to receiving liquid biopsy, other than the fact that they perceived the procedure to be less accurate than tissue biopsy.

Impact of Lung Cancer

Patients and caregivers spoke of serious physical and emotional effects of lung cancer, both before and after receiving a diagnosis, and described changes they had made to their lives once diagnosed. Caregivers also described changes to their personal and professional lives to care for family members who had been diagnosed with lung cancer.

Physical Effects

Half of the patients stated that, before they were diagnosed with lung cancer, they had lived with symptoms such as coughing for a long time. They described receiving various tests, procedures, and medication before being diagnosed with lung cancer. During the path to diagnosis, the patients' physical condition would worsen:

> *At the beginning I didn't feel anything. I [didn't realize I was] sick. I still [went] to work. Only one time I [coughed]. [A] few months [were] not okay. The doctor [said it could be an] allergy. … But [then] I [was coughing] a lot … more and more, and I [took] allergy [pills, but they didn't work]. So, my father told me, "Why don't you take an x-ray?" So, I [took] my father's [advice, and] I went to [get an] x-ray. The x-ray [found] out. I was [in] shock.*

Emotional Effects

Patients and caregivers had both experienced emotional distress and felt panic and anxiety as a result of hearing and accepting the diagnosis of lung cancer. One caregiver stated that it became stressful for him and his family, as they had to make sudden changes to their lives and had to take on additional responsibility for their home and to care for the family member who had been diagnosed with lung cancer:

> *Oh yeah, it was pretty hard on us, too. We always looked up to our mom. She's supposed to be really strong, and … now the roles are kind of reversed; we're like, "If she's gone, then what's going to go on?" So it was a lot of panic for us, too. So [the] role kind of reversed where she used to take care of us and now we have to take care of her.*

Work-Life Impact

Half of the patients and caregivers who were interviewed had retired and did not express stress with regards to any change in their work. One caregiver, however, stated that his career was affected once he was required to take time off work to take care of his mother. The caregiver stated that this can be challenging for someone who does not have support from their work or their colleagues:

> *I took off some time from work. …Luckily, they [my employers] were good with that, a lot of support with that, but I imagine people [who] work in areas that don't have that support [find it] very difficult.*

After being diagnosed with lung cancer, one patient had to give up her job, as she found it challenging to work while managing the emotional consequences of lung cancer:

> *Of course, it's hard for me when I hear that news. … I quit my job right away. … I don't want to work. I feel so sad.*

Currently Available Treatment

In Ontario, the currently available test for diagnosis and determining appropriate treatment for lung cancer, including NSCLC, is tissue biopsy. Four patients who were interviewed had received tissue biopsy.

Process of Receiving Tissue Biopsy

On the basis of prolonged coughing or other conditions such as chronic pneumonia, all patients interviewed were advised to undergo a tissue biopsy to confirm or rule out a diagnosis of lung cancer. None of the patients were able to describe the process of tissue biopsy because they received anesthesia for the procedure. However, most patients were able to describe their understanding of the process from discussions with their physicians:

> *They basically said they're going to take a giant needle and then jab it in her back and pull out some tissue samples, so they can do tests … later on. She did say they shoved something down her throat at first and got tissue that way.*

Benefits to Tissue Biopsy

After undergoing tissue biopsy, all patients reported that the procedure itself did not affect their quality of life in any way. Most patients indicated that they felt no additional pain after the procedure and had no serious adverse effects (only one patient reported substantial adverse effects). These patients had just been diagnosed with lung cancer; they thought that it would be easy for them to recover from the test and feel normal after receiving tissue biopsy and that they could go back to their daily routine. Patients also reported that the test helped them learn about their condition. Before receiving tissue biopsy, they were confused and scared about their physical condition, and after receiving the test, they considered themselves aware and educated about their condition and situation.

Barriers to Receiving Tissue Biopsy

Even though patients said receiving tissue biopsy seemed like a routine procedure with no pain or adverse effects, they identified some barriers to receiving the test at a hospital.

Access to Current Treatment

Patients reported that booking an appointment was a challenge because the clinic's website was not easy to navigate. It was particularly challenging for older patients who were unfamiliar with technology and had trouble navigating websites to book appointments. This affected their appointments, as sometimes they would be booked improperly, and would learn of the error only once they had reached the hospital:

> *Actually, at the start it was a lot of confusion. We didn't know what was going on, but the doctors here are amazing. They explained it very clearly afterwards when we actually did speak to a doctor, but the booking of the appointments was very stressful because we had to login some keys and then we go there and they're like, "Wait. I don't see you on this list," and basically sent us on a wild goose chase.*

Patients also pointed that such services are either unavailable at their nearby hospital or that they would not choose to go to their local hospital. Consequently, patients would have to travel

to downtown Toronto. One caregiver found it to be a challenge, as parking was not accessible for people with wheelchairs and it was a challenge for the patient to walk into the hospital:

> *Luckily we live nearby. It's probably like 20 to 30 minutes away. Parking is a little tough, but it could be worse.*

> *Well my car cannot park in front of the hospital, right? Because the accessible parking, right? Well she [has a] tendency of imbalance or walking very weak. So in the last month or last 2 months she needs to start using a cane and today that's the first day she's using the … walker. Because it's winter, right? So winter the way of walking here is [challenging for the patient to walk].*

Limitations to Tissue Biopsy

Emotional Impact of Tissue Biopsy

Most patients described fear and panic preceding tissue biopsy. Some patients stated that they were not looking forward to having a "large" needle inserted into their body. One caregiver mentioned that, even though needles are used in both tissue and liquid biopsy, the pain and process would be less for liquid biopsy and greater for tissue biopsy, "She would definitely be more scared because it's a bigger needle with blood."

Side Effects of Tissue Biopsy

Overall, most patients were satisfied with the process of being advised and receiving a tissue biopsy and reported no adverse effects. However, one patient did report an unpleasant adverse effect of the procedure. A fragment of tissue remained, which created a foul smell and had to be forced out of her lung by coughing. This situation caused panic and frustration for both the patient and caregiver, as they did not know what had occurred, had no information on how to deal with the situation, and received very little information from the physician at a follow-up appointment:

> *I was very, very disappointed. After the biopsy was completed and I went home, about 3 days later, I started to smell inside. I felt like a foul smell coming from me and I coughed up two lung biopsy clots, not clots but two lung biopsy tissues. They were the size of my fingernail. … They just left it in there. I don't know why they didn't take it out. Anyway, I kept it, I took a picture of it, showed my respirologist, … and he felt bad, but that's the way it was.*

Intervention Under Study—Views on Liquid Biopsy

None of the patients or caregivers interviewed had direct experience with liquid biopsy. However, patients and caregivers did have prior knowledge about liquid biopsy from their own research and from information provided by their oncologists. These patients had been recently diagnosed with lung cancer and were interested in taking part in the review to learn more about liquid biopsy. Some patients and caregivers thought that the process of liquid biopsy seemed to be more convenient and perceived the procedure to be less invasive. They anticipated this procedure would cause less pain and discomfort. One caregiver stated that, if a patient is already undergoing various blood tests, then liquid biopsy could be easily included:

> *Definitely blood sample would be better, but at the end of the day they're both sticking needles into her. It's just which one hurts more. ... She's already getting*

> *bloodwork done. You probably already need to do that, so if you're already doing that, might as well use that for the biopsy as well. ... Might as well pull out as much blood as you can. We just want to stick as [few] needles in her as possible.*

Another patient thought that, even though the test is convenient, there is still some doubt about its accuracy and questioned if such a procedure could eliminate the use of tissue biopsy overall. Patients thought that not every condition would benefit from liquid biopsy and that a tissue biopsy would still be needed:

> *The problem is that, having a tissue biopsy, they were able to look at the different receptors and so if I had a liquid biopsy and if I [were] a candidate for immunotherapy, I'd still end up having a tissue biopsy, right? … So for diagnostic purposes I guess, yeah, liquid but I'm not dissatisfied having tissue.*

Discussion

Patients and caregivers shared their personal experiences about the burden and struggle of being diagnosed with lung cancer. This affected both the patients' and caregivers' day-to-day activities, their well-being, and their work.

We had some difficulty recruiting patients who had direct experience with advanced NSCLC and liquid biopsy. Feedback from four patients told us this difficulty was due to the patients being too ill or physically exhausted to participate. We then took a different recruitment approach in which in-person interviews were conducted at a lung cancer clinic. Patients who participated had direct experience with lung cancer and tissue biopsy. Overall, patients found going through tissue biopsy to be a routine process; most did not experience any sort of pain or serious adverse effects.

There were, however, barriers and limitations to getting a tissue biopsy. Patients reported that they were required to book their own appointments and that some struggled to navigate through the booking website. Patients also thought that traveling to the hospital was a barrier, especially for those who use wheelchairs. Access to the hospital can be difficult when patients find entrances to be inconvenient.

One patient experienced discomfort from the tissue biopsy and, although the physical discomfort was brief, both the patient and the caregiver felt uncertainty and panic when this happened. Most patients interviewed who had received tissue biopsy reported that the pain was minimal and that they had few, if any, adverse effects from the procedure.

In discussions about their understanding and perceptions of liquid biopsy, patients were familiar with the process of liquid biopsy and were keen on learning more. After hearing more information, patients thought that the test would be better for people who had advanced lung cancer and who would not be strong enough to go through tissue biopsy. One caregiver considered liquid biopsy convenient because it can be combined with the bloodwork that is already being done. That way the patient would not need to come for multiple appointments. The caregiver also thought that liquid biopsy would be less painful than tissue biopsy because it does not include the "large" needle commonly used for tissue biopsy. However, one patient wondered whether the results from liquid biopsy would be as accurate as tissue biopsy and questioned whether it would be able to accurately identify different receptors. Patients and caregivers believed that, for people in a frail condition, it would be better to go with a non-invasive procedure than an invasive procedure, to cause as little pain as possible.

Conclusions

We were able to recruit only patients who had been recently diagnosed with lung cancer and have had experience with tissue biopsy and their caregivers. Patients and their caregivers reported that, after lung cancer was diagnosed, the quality of life declined. Further, most of the patients who had received tissue biopsy reported that the pain was minimal and that they had few, if any, adverse effects from the procedure. Patients were then asked hypothetical questions related to liquid biopsy, and their responses were based on information from research of their own, from their oncologist, and from information provided during the interview. All patients perceived liquid biopsy to be more convenient than tissue biopsy, as it can be combined with other blood tests and can limit the number of appointments needed. However, one patient did question the accuracy of liquid biopsy and questioned whether liquid biopsy would be able to detect the various receptors.

CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT

The pooled sensitivity and specificity of cell-free circulating tumour DNA (ctDNA) blood testing (also called liquid biopsy) to detect *EGFR* T790M in patients with NSCLC was 68% (95% CrI, 46%–88%) and 86% (95% CrI, 62%–99%) (GRADE: Moderate). The PPV and NPV was 89% and 61%, respectively, at a mutation prevalance rate of 63%. The concordance rate of matched liquid and tissue biopsy ranged from 50% to 96% (GRADE: Moderate).

Evidence for process outcomes (time to test result, tissue biopsies avoided) was limited. One study showed the median time to test result for liquid versus tissue biopsy was 2 versus 27 days. Progression-free survival (PFS) was similar in patients with or without *EGFR* T790M ascertained using liquid biopsy (GRADE: Low). One study reported but did not statistically compare the PFS of patients who were *EGFR* T790M positive via tissue and liquid biopsy; it showed similar PFS (9.7 months).

When considering only short-term testing-related costs and effects, liquid biopsy was more effective and less costly than tissue biopsy used alone. Using liquid biopsy as a triage test led to the greatest number of correct treatment decisions (i.e., where people who were *EGFR* T790M positive received osimertinib and people who were *EGFR* T790M negative received chemotherapy). When considering all long-term costs and effects, liquid biopsy was not cost-effective because of the high cost of the third-generation *EGFR*-TKI treatment (i.e., osimertinib).

We estimated that publicly funding liquid biopsy as a triage test in Ontario would result in additional costs of between $0.06 and $3 million over the next 5 years.

We found no published literature exploring patient and practitioner values and preferences between liquid and tissue biopsy in patients with advanced NSCLC who have disease progression after first- or second-generation *EGFR*-TKIs. However, people with lung cancer with whom we spoke said that liquid biopsy would likely be an appropriate test for people with NSCLC given their frail condition and because it could avoid the pain and anxiety associated with tissue biopsy.

ABBREVIATIONS

AMSTAR	A Measurement Tool to Assess Systematic Reviews
CI	Confidence interval
CrI	Credible interval
ctDNA	Circulating tumour DNA
dPCR	Digital polymerase chain reaction
EGFR	Epidermal growth factor receptor
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HSROC	Hierarchical summary receiver operating characteristics
ICER	Incremental cost-effectiveness ratio
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
NSCLC	Non–small cell lung cancer
PFS	Progression-free survival
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
QALY	Quality-adjusted life-year
QPE	Quantitative preference evidence
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies
RECIST	Response Evaluation Criteria in Solid Tumors
ROB	Risk of bias
ROBANS	Risk of Bias Among Non-randomized Studies
ROBIS	Risk of bias in systematic reviews
RT-PCR	Real-time polymerase chain reaction
TKI	Tyrosine kinase inhibitor

GLOSSARY

Adverse event	An adverse event is any unexpected problem that happens during treatment, regardless of the cause or severity.
Biopsy	A biopsy is an examination of tissue (or liquid) removed from a living body to discover the presence, cause, or extent of a disease.
Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on a health care budget (i.e., its affordability). It is based on predictions of how changes in the intervention mix impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes also referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Cell-free circulating tumour DNA	Cell-free circulating tumour DNA consists of cell-free fragments of tumour DNA that have been released from tumour cells into the peripheral circulation. This DNA can be extracted from the plasma fraction of a blood sample.
Cost-effective	An intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Cost-effectiveness acceptability curve	A cost-effectiveness acceptability curve is a graphic representation of the results of a probabilistic sensitivity analysis, which illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values for all comparators under evaluation. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values are plotted on the vertical axis.
Cost-effectiveness analysis	Used broadly, “cost-effectiveness analysis” refers to an economic evaluation used to compare the benefits of two or more interventions relative to their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, “cost-effectiveness analysis” refers to a specific type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-years, symptom-free days) gained.
Cost–utility analysis	A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care

	interventions relative to their costs. The benefits are measured using health-related quality-of-life measures, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is typically the incremental cost per quality-adjusted life-year gained.
Credible interval	A credible interval is the interval in which an unobserved parameter has a given probability. It is the Bayesian equivalent of the confidence interval, but, unlike a confidence interval, it is dependent on the prior distribution.
Dominant	A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).
First-, second-, and third-generation *EGFR*-TKIs	First-, second-, and third-generation *EGFR* tyrosine kinase inhibitors (TKIs) are a type of targeted therapy. TKIs come as pills, which are taken orally. A targeted therapy identifies and attacks specific types of cancer cells while causing less damage to normal cells.
Health-related quality of life	Health-related quality of life is a measure of a person's health, including dimensions such as physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.
Incremental cost	An incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio is a summary measure that determines the additional cost per additional unit of benefit. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically measured in cost per life-year gained or cost per quality-adjusted life-year gained.
Markov model	A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using the health care intervention(s) of interest. Markov models are useful for clinical problems that involve events of interest that can recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period before moving to another health state based on transition probabilities. The health states and events modelled can be associated with specific costs and health outcomes.
Mutation	A mutation occurs when the structure of a gene changes, resulting in a variant form of the gene. Mutations are caused by an alteration of single base units in DNA or by the deletion, insertion, or rearrangement of larger sections of genes or chromosomes.
Natural history	The natural history of a disease is the progression of a disease over time in the absence of any health intervention.

Next-generation sequencing	Next-generation sequencing, also known as high-throughput sequencing, is the catch-all term used to describe several modern sequencing technologies. These technologies allow for DNA and RNA to be sequenced much more quickly and less expensively than the previously used Sanger sequencing.
Probabilistic sensitivity analysis	A probabilistic sensitivity analysis is an approach used to simultaneously explore the uncertainty in several parameters in an economic model. It is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g. 10,000 times) to provide the proportion of times (i.e., the probability) that the health care intervention of interest is cost-effective.
Quality-adjusted life-year (QALY)	The quality-adjusted life-year is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for having a particular health status (i.e., being in a particular health state). One year of perfect health is represented by 1 quality-adjusted life-year.
Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.
Scenario analysis	A scenario analysis is an approach used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of various scenarios on the cost-effectiveness of a health care intervention. For instance, scenario analyses include varying structural assumptions from the reference case.
Sensitivity analysis	Every economic evaluation contains some degree of uncertainty, and study results can vary depending on the values taken by key parameters. Sensitivity analysis is a method that allows estimates for each parameter to be varied to show the impact of these variations n study results. There are various types of sensitivity analyses, including deterministic, probabilistic, and scenario.
Specificity	In the context of this health technology assessment, “specificity” refers to the ability of a tissue biopsy or liquid biopsy to correctly identify people without *EGFR* T790M resistance mutation.
T790M resistance mutation	Also known as Thr790Met, the T790 resistance mutation is a gatekeeper mutation of the epidermal growth factor receptor (*EGFR*). The mutation substitutes a threonine (T) with a

	methionine (M) at position 790 of exon 20, which affects the ATP binding pocket of the *EGFR* kinase domain.
Tornado diagram	A Tornado diagram is a type of diagram used to assess the model parameters that have the greatest influence on results. Tornado diagrams present the results of multiple one-way sensitivity analyses in a single graph.
Triage test	In the context of this health technology assessment, a triage test consists of liquid biopsy followed by tissue biopsy. Triage testing is performed when the results of the liquid biopsy are negative.
Utility	Utilities represent health state preference values, which characterize individual preferences for different health states. Typically, utility values are anchored between 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health considered worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measurement of economic evaluations.
Willingness-to-pay	A willingness-to-pay value represents the dollar value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay represents the cost the consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay, the intervention is considered not to be cost-effective.

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: May 25, 2018

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2018>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 23, 2018>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2018 Week 21>, Ovid MEDLINE(R) ALL <1946 to May 24, 2018>

Search Strategy:

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1 Carcinoma, Non-Small-Cell Lung/ (48178)
2 (non small cell lung* or nonsmall cell lung* or NSCLC* or NS CLC* or large cell lung cancer* or large cell lung carcinoma*).ti,ab,kf. (153616)
3 Lung Neoplasms/bl [Blood] (5049)
4 Lung Neoplasms/ge [Genetics] (24788)
5 or/1-4 (178816)
6 Receptor, Epidermal Growth Factor/ (94555)
7 ((epidermal growth factor adj receptor*) or (egf adj receptor*) or EGFR or EGFRTK or EGFR-TK or EGFRTKI or EGFR-TKI).ti,ab,kf. (184007)
8 ((erbb or erbb1 or HER1) adj2 (receptor* or protein*)).ti,ab,kf. (6710)
9 (transforming growth factor alpha* receptor* or tgf alpha* receptor* or urogastron receptor*).ti,ab,kf. (150)
10 (T790M or T790 mutat*).ti,ab,kf. (4456)
11 or/6-10 (207556)
12 5 and 11 (30832)
13 Liquid Biopsy/ (1426)
14 ((liquid or blood or plasma) adj2 biops*).ti,ab,kf. (7654)
15 (LiquidLung-O or LiquidLung-A).ti,ab,kf. (1)
16 Circulating Tumor DNA/ (802)
17 (((circulating or cell free or cellfree) adj2 DNA) or ct-DNA or ctDNA or cf-DNA or cdDNA).ti,ab,kf. (17336)
18 DNA Mutational Analysis/ (57387)
19 (DNA adj2 mutation* analys#s).ti,ab,kf. (861)
20 plasma test*.ti,ab,kf. (8927)
21 (((next generation or next gen or nextgen) adj2 (sequenc* or platform*)) or NGS).ti,ab,kf. (66118)
22 (AmoyDX or super-ARMS or superARMS).ti,ab,kf. (28)
23 ((ARMS or Amplification refractory mutation system*) adj2 (mutant* or mutat* or plasma* or PCR or dPCR or polymerase chain reaction* or blood* or genotyp*)).ti,ab,kf. (4592)
24 roche.ti,ab,kf. (24897)
25 cobas*.ti,ab,kf. (9005)

26 (bio-Rad or biorad).ti,ab,kf. (6148)
27 (((PCR or polymerase chain reaction*) adj2 (digital or droplet*)) or ddPCR or dd PCR or dPCR or d PCR).ti,ab,kf. (5831)
28 (panagene* or PANAMutyper).ti,ab,kf. (35)
29 qiagen.ti,ab,kf. (6819)
30 therascreen*.ti,ab,kf. (367)
31 ((EGFR* or T790M*) adj2 (mutant* or mutat*) adj2 (kit* or test* or assay* or platform* or plasma* or blood* or PCR or dPCR or polymerase chain reaction* or genotyp*)).ti,ab,kf. (2144)
32 or/13-31 (200767)
33 12 and 32 (4516)
34 exp Animals/ not Humans/ (15533460)
35 33 not 34 (2637)
36 (Comment or Editorial).pt. (1605032)
37 35 not 36 (2606)
38 limit 37 to yr="2000 -Current" (2601)
39 limit 38 to english language [Limit not valid in CDSR; records were retained] (2469)
40 39 use medall,cctr,coch,clhta,cleed (1777)
41 exp non small cell lung cancer/ (110908)
42 (non small cell lung* or nonsmall cell lung* or NSCLC* or NS CLC* or large cell lung cancer* or large cell lung carcinoma*).tw,kw. (155406)
43 or/41-42 (190978)
44 epidermal growth factor receptor/ (102063)
45 ((epidermal growth factor adj receptor*) or (egf adj receptor*) or EGFR or EGFRTK or EGFR-TK or EGFRTKI or EGFR-TKI).tw,kw. (186448)
46 ((erbb or erbb1 or HER1) adj2 (receptor* or protein*)).tw,kw. (6909)
47 (transforming growth factor alpha* receptor* or tgf alpha* receptor* or urogastron receptor*).tw,kw. (152)
48 (T790M or T790 mutat*).tw,kw. (4492)
49 or/44-48 (211514)
50 43 and 49 (34083)
51 liquid biopsy/ (1426)
52 ((liquid or blood or plasma) adj2 biops*).tw,kw,dv. (7959)
53 (LiquidLung-O or LiquidLung-A).tw,kw,dv. (1)
54 (((circulating or cell free or cellfree) adj2 DNA) or ct-DNA or ctDNA or cf-DNA or cdDNA).tw,kw,dv. (17502)
55 dna mutational analysis/ (57387)
56 (DNA adj2 mutation* analys#s).tw,kw,dv. (1048)
57 plasma test*.tw,kw,dv. (8950)
58 next generation sequencing/ (27721)
59 (((next generation or next gen or nextgen) adj2 (sequenc* or platform*)) or NGS).tw,kw,dv. (67061)
60 (AmoyDX or super-ARMS or superARMS).tw,kw,dv. (31)
61 ((ARMS or Amplification refractory mutation system*) adj2 (mutant* or mutat* or plasma* or PCR or dPCR or polymerase chain reaction* or blood* or genotyp*)).tw,kw,dv. (4643)
62 roche.tw,kw,dv. (51486)
63 cobas*.tw,kw,dv. (9927)
64 (bio-Rad or biorad).tw,kw,dv. (7612)
65 droplet digital polymerase chain reaction/ (1037)
66 (((PCR or polymerase chain reaction*) adj2 (digital or droplet*)) or ddPCR or dd PCR or dPCR or d PCR).tw,kw,dv. (5890)
67 (panagene* or PANAMutyper).tw,kw,dv. (39)

68 qiagen.tw,kw,dv. (8082)
69 therascreen*.tw,kw,dv. (408)
70 ((EGFR* or T790M*) adj2 (mutant* or mutat*) adj2 (kit* or test* or assay* or platform* or plasma* or blood* or PCR or dPCR or polymerase chain reaction* or genotyp*)).tw,kw,dv. (2172)
71 or/51-70 (236843)
72 50 and 71 (5023)
73 (exp animal/ or nonhuman/) not exp human/ (10423987)
74 72 not 73 (4995)
75 Comment/ or Editorial/ (1612126)
76 74 not 75 (4943)
77 limit 76 to yr="2000 -Current" (4938)
78 limit 77 to english language [Limit not valid in CDSR; records were retained] (4780)
79 78 use emez (3378)
80 40 or 79 (5155)
81 80 use medall (1645)
82 80 use emez (3378)
83 80 use coch (0)
84 80 use cctr (127)
85 80 use clhta (4)
86 80 use cleed (1)
87 remove duplicates from 80 (4089)

Economic Evidence Search

Search date: May 28, 2018

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2018>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 23, 2018>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2018 Week 22>, Ovid MEDLINE(R) ALL <1946 to May 25, 2018>
Search Strategy:
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1 Carcinoma, Non-Small-Cell Lung/ (48190)
2 (non small cell lung* or nonsmall cell lung* or NSCLC* or NS CLC* or large cell lung cancer* or large cell lung carcinoma*).ti,ab,kf. (153754)
3 Lung Neoplasms/bl [Blood] (5051)
4 Lung Neoplasms/ge [Genetics] (24792)
5 or/1-4 (178958)
6 Receptor, Epidermal Growth Factor/ (94618)
7 ((epidermal growth factor adj receptor*) or (egf adj receptor*) or *EGFR* or *EGFR*TK or *EGFR*-TK or *EGFR*TKI or *EGFR*-TKI).ti,ab,kf. (184020)
8 ((erbb or erbb1 or HER1) adj2 (receptor* or protein*)).ti,ab,kf. (6713)
9 (transforming growth factor alpha* receptor* or tgf alpha* receptor* or urogastron receptor*).ti,ab,kf. (150)

10 (T790M or T790 mutat*).ti,ab,kf. (4469)
11 or/6-10 (207587)
12 5 and 11 (30867)
13 Liquid Biopsy/ (1435)
14 ((liquid or blood or plasma) adj2 biops*).ti,ab,kf. (7670)
15 (LiquidLung-O or LiquidLung-A).ti,ab,kf. (1)
16 Circulating Tumor DNA/ (809)
17 (((circulating or cell free or cellfree) adj2 DNA) or ct-DNA or ctDNA or cf-DNA or cdDNA).ti,ab,kf. (17361)
18 DNA Mutational Analysis/ (57400)
19 (DNA adj2 mutation* analys#s).ti,ab,kf. (861)
20 plasma test*.ti,ab,kf. (8928)
21 (((next generation or next gen or nextgen) adj2 (sequenc* or platform*)) or NGS).ti,ab,kf. (66286)
22 (AmoyDX or super-ARMS or superARMS).ti,ab,kf. (28)
23 ((ARMS or Amplification refractory mutation system*) adj2 (mutant* or mutat* or plasma* or PCR or dPCR or polymerase chain reaction* or blood* or genotyp*)).ti,ab,kf. (4595)
24 roche.ti,ab,kf. (24913)
25 cobas*.ti,ab,kf. (9011)
26 (bio-Rad or biorad).ti,ab,kf. (6151)
27 (((PCR or polymerase chain reaction*) adj2 (digital or droplet*)) or ddPCR or dd PCR or dPCR or d PCR).ti,ab,kf. (5846)
28 (panagene* or PANAMutyper).ti,ab,kf. (35)
29 qiagen.ti,ab,kf. (6819)
30 therascreen*.ti,ab,kf. (367)
31 ((*EGFR** or T790M*) adj2 (mutant* or mutat*) adj2 (kit* or test* or assay* or platform* or plasma* or blood* or PCR or dPCR or polymerase chain reaction* or genotyp*)).ti,ab,kf. (2146)
32 or/13-31 (201012)
33 12 and 32 (4523)
34 economics/ (257187)
35 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (809645)
36 economics.fs. (405722)
37 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (803768)
38 exp "costs and cost analysis"/ (557755)
39 (cost or costs or costing or costly).ti. (245283)
40 cost effective*.ti,ab,kf. (289209)
41 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (190176)
42 models, economic/ (11440)
43 markov chains/ or monte carlo method/ (73415)
44 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (37326)
45 (markov or markow or monte carlo).ti,ab,kf. (117001)
46 quality-adjusted life years/ (35573)
47 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (62573)
48 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (102105)
49 or/34-48 (2384526)
50 33 and 49 (216)

51 50 use medall,cctr,coch,clhta (72)
52 33 use cleed (1)
53 or/51-52 (73)
54 limit 53 to yr="2000 -Current" (73)
55 limit 54 to english language [Limit not valid in CDSR; records were retained] (70)
56 exp non small cell lung cancer/ (111071)
57 (non small cell lung* or nonsmall cell lung* or NSCLC* or NS CLC* or large cell lung cancer* or large cell lung carcinoma*).tw,kw. (155544)
58 or/56-57 (191191)
59 epidermal growth factor receptor/ (102126)
60 ((epidermal growth factor adj receptor*) or (egf adj receptor*) or *EGFR* or *EGFR*TK or *EGFR*-TK or *EGFR*TKI or *EGFR*-TKI).tw,kw. (186460)
61 ((erbb or erbb1 or HER1) adj2 (receptor* or protein*)).tw,kw. (6912)
62 (transforming growth factor alpha* receptor* or tgf alpha* receptor* or urogastron receptor*).tw,kw. (152)
63 (T790M or T790 mutat*).tw,kw. (4505)
64 or/59-63 (211545)
65 58 and 64 (34127)
66 liquid biopsy/ (1435)
67 ((liquid or blood or plasma) adj2 biops*).tw,kw,dv. (7974)
68 (LiquidLung-O or LiquidLung-A).tw,kw,dv. (1)
69 (((circulating or cell free or cellfree) adj2 DNA) or ct-DNA or ctDNA or cf-DNA or cdDNA).tw,kw,dv. (17529)
70 dna mutational analysis/ (57400)
71 (DNA adj2 mutation* analys#s).tw,kw,dv. (1048)
72 plasma test*.tw,kw,dv. (8951)
73 next generation sequencing/ (27840)
74 (((next generation or next gen or nextgen) adj2 (sequenc* or platform*)) or NGS).tw,kw,dv. (67240)
75 (AmoyDX or super-ARMS or superARMS).tw,kw,dv. (31)
76 ((ARMS or Amplification refractory mutation system*) adj2 (mutant* or mutat* or plasma* or PCR or dPCR or polymerase chain reaction* or blood* or genotyp*)).tw,kw,dv. (4646)
77 roche.tw,kw,dv. (51509)
78 cobas*.tw,kw,dv. (9937)
79 (bio-Rad or biorad).tw,kw,dv. (7618)
80 droplet digital polymerase chain reaction/ (1038)
81 (((PCR or polymerase chain reaction*) adj2 (digital or droplet*)) or ddPCR or dd PCR or dPCR or d PCR).tw,kw,dv. (5905)
82 (panagene* or PANAMutyper).tw,kw,dv. (39)
83 qiagen.tw,kw,dv. (8085)
84 therascreen*.tw,kw,dv. (408)
85 ((*EGFR** or T790M*) adj2 (mutant* or mutat*) adj2 (kit* or test* or assay* or platform* or plasma* or blood* or PCR or dPCR or polymerase chain reaction* or genotyp*)).tw,kw,dv. (2174)
86 or/66-85 (237153)
87 65 and 86 (5031)
88 Economics/ (257187)
89 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (131637)
90 Economic Aspect/ or exp Economic Evaluation/ (431430)
91 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (828441)

92 exp "Cost"/ (557755)
93 (cost or costs or costing or costly).ti. (245283)
94 cost effective*.tw,kw. (300244)
95 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (197829)
96 Monte Carlo Method/ (58891)
97 (decision adj1 (tree* or analy* or model*)).tw,kw. (41086)
98 (markov or markow or monte carlo).tw,kw. (121968)
99 Quality-Adjusted Life Years/ (35573)
100 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (66362)
101 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (121571)
102 or/88-101 (2023791)
103 87 and 102 (233)
104 103 use emez (156)
105 limit 104 to yr="2000 -Current" (156)
106 limit 105 to english language [Limit not valid in CDSR; records were retained] (155)
107 55 or 106 (225)
108 107 use medall (61)
109 107 use emez (155)
110 107 use coch (0)
111 107 use cctr (6)
112 107 use cleed (1)
113 107 use clhta (2)
114 remove duplicates from 107 (183)

Quantitative Preferences Evidence Search

Search date: May 31, 2018

Database: Ovid MEDLINE(R) ALL <1946 to May 30, 2018>

Search Strategy:

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1 Carcinoma, Non-Small-Cell Lung/ (44573)
2 (non small cell lung* or nonsmall cell lung* or NSCLC* or NS CLC* or large cell lung cancer* or large cell lung carcinoma*).ti,ab,kf. (55561)
3 Lung Neoplasms/bl [Blood] (5055)
4 Lung Neoplasms/ge [Genetics] (24793)
5 or/1-4 (80353)
6 Receptor, Epidermal Growth Factor/ (36161)
7 ((epidermal growth factor adj receptor*) or (egf adj receptor*) or EGFR or EGFRTK or EGFR-TK or EGFRTKI or EGFR-TKI).ti,ab,kf. (68390)
8 ((erbb or erbb1 or HER1) adj2 (receptor* or protein*)).ti,ab,kf. (3031)
9 (transforming growth factor alpha* receptor* or tgf alpha* receptor* or urogastron receptor*).ti,ab,kf. (84)
10 (T790M or T790 mutat*).ti,ab,kf. (1351)
11 or/6-10 (75790)
12 5 and 11 (11668)
13 Liquid Biopsy/ (158)
14 ((liquid or blood or plasma) adj2 biops*).ti,ab,kf. (2817)

15 (LiquidLung-O or LiquidLung-A).ti,ab,kf. (0)
16 Circulating Tumor DNA/ (149)
17 (((circulating or cell free or cellfree) adj2 DNA) or ct-DNA or ctDNA or cf-DNA or cdDNA).ti,ab,kf. (6677)
18 DNA Mutational Analysis/ (56172)
19 (DNA adj2 mutation* analys#s).ti,ab,kf. (365)
20 plasma test*.ti,ab,kf. (4417)
21 (((next generation or next gen or nextgen) adj2 (sequenc* or platform*)) or NGS).ti,ab,kf. (26025)
22 (AmoyDX or super-ARMS or superARMS).ti,ab,kf. (5)
23 ((ARMS or Amplification refractory mutation system*) adj2 (mutant* or mutat* or plasma* or PCR or dPCR or polymerase chain reaction* or blood* or genotyp*)).ti,ab,kf. (1838)
24 roche.ti,ab,kf. (7390)
25 cobas*.ti,ab,kf. (2503)
26 (bio-Rad or biorad).ti,ab,kf. (1581)
27 (((PCR or polymerase chain reaction*) adj2 (digital or droplet*)) or ddPCR or dd PCR or dPCR or d PCR).ti,ab,kf. (2086)
28 (panagene* or PANAMutyper).ti,ab,kf. (7)
29 qiagen.ti,ab,kf. (1233)
30 therascreen*.ti,ab,kf. (85)
31 ((EGFR* or T790M*) adj2 (mutant* or mutat*) adj2 (kit* or test* or assay* or platform* or plasma* or blood* or PCR or dPCR or polymerase chain reaction* or genotyp*)).ti,ab,kf. (561)
32 or/13-31 (107731)
33 12 and 32 (1794)
34 *Attitude to Health/ (40814)
35 *Patient Participation/ (12575)
36 *Patient Preference/ (3871)
37 (choice or choices or value* or valuation*).ti. (181018)
38 (preference* or health state values or expectation* or attitude* or acceptab* or knowledge or point of view).ti,ab. (1031369)
39 ((user or users or patient or patients) adj (participation or perspective* or perception* or perceiv* or view*)).ti,ab. (25632)
40 health perception*.ti,ab. (2390)
41 (decision* and mak*).ti. (24347)
42 (decision mak* or decisions mak*).ti,ab. (114484)
43 or/41-42 (115884)
44 (patient* or user* or men or women).ti,ab. (6649010)
45 43 and 44 (60541)
46 (discrete choice* or decision board* or decision analy* or decision-support or decision tool* or decision aid* or discrete-choice*).ti,ab. (22258)
47 *Decision Making/ (36535)
48 (patient* or user* or men or women).ti. (1935414)
49 47 and 48 (5007)
50 decision support techniques/ (17569)
51 (health and utilit*).ti. (1220)
52 (gamble* or prospect theory or preference score or preference elicitation or health utilit* or utility value* or utility score* or Utility estimate* or health state or feeling thermometer* or best-worst scaling or standard gamble or time trade-off or TTO or probability trade-off or utility score).ti,ab. (11428)
53 (preference based or preference score* or multiattribute or multi attribute).ti,ab. (2188)

54 (EuroQol 5D or EuroQol5D or EQ5D or EQ 5D or SF6D or SF 6D or HUI or 15D).ti,ab. (9672)
55 "Surveys and Questionnaires"/ (400250)
56 Health Care Surveys/ (29644)
57 self report/ (23414)
58 (questionnaire* or survey*).ti,ab,kf. (888802)
59 or/34-40,45-46,49-58 (2164418)
60 33 and 59 (163)
61 limit 60 to yr="2000 -Current" (163)
62 limit 61 to english language (157)

Grey Literature Search

Performed: May 24–30, 2018

Websites searched:
HTA Database Canadian Repository, Alberta Health Technologies Decision Process reviews, Canadian Agency for Drugs and Technologies in Health
(CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, ClinicalTrials.gov, PROSPERO, EUnetHTA, Tuft's Cost-Effectiveness Analysis Registry

Keywords used:
liquid biopsy, plasma biopsy, epidermal growth factor receptor, egfr, t790, t790m, nsclc, cell free dna, circulating dna, cobas, qiagen, therascreen, polymerase chain reaction, pcr, digital droplet

Results (included in PRISMA): 11

Ongoing clinical trials (ClinicalTrials.gov): 14

Ongoing HTAs (PROSPERO/EUnetHTA): 1

Appendix 2: Output from Diagnostic Accuracy Meta-Analysis

Table A1: Sensitivity, Specificity, and Model Fit for Meta-Analysis of Diagnostic Test Accuracy

Model Type	Included Studies, N	Deviance Information Criterion	Sensitivity of LB	Specificity of LB	Sensitivity of TB	Specificity of TB
HSROC with perfect reference standard[a]	17 studies[b]	263.623	Mean 0.737 SD 0.04 Median 0.738 2.5% 0.648 97.5% 0.818	Mean 0.755 SD 0.06 Median 0.760 2.5% 0.618 97.5% 0.869	NA	NA
HSROC with imperfect reference standard[a] (conditional independence)	17 studies[b]	265.464	Mean 0.787 SD 0.05 Median 0.789 2.5% 0.672 97.5% 0.891	Mean 0.886 SD 0.06 Median 0.896 2.5% 0.726 97.5% 0.985	Mean 0.901 SD 0.02 Median 0.898 2.5% 0.857 97.5% 0.965	Mean 0.932 SD 0.03 Median 0.935 2.5% 0.854 97.5% 0.992
HSROC with imperfect reference standard[a] (conditional dependence)	17 studies[b]	259.522	Mean 0.752 SD 0.05 Median 0.753 2.5% 0.652 97.5% 0.856	Mean 0.822 SD 0.07 Median 0.827 2.5% 0.664 97.5% 0.951	Mean 0.844 SD 0.04 Median 0.838 2.5% 0.768 97.5% 0.957	Mean 0.858 SD 0.05 Median 0.859 2.5% 0.743 97.5% 0.966
HSROC with perfect reference standard	6 studies (with MAF of 0.1%)[b]	104.159	Mean 0.673 SD 0.08 Median 0.677 2.5% 0.477 97.5% 0.840	Mean 0.799 SD 0.09 Median 0.814 2.5% 0.558 97.5% 0.948	NA	NA
HSROC with imperfect reference standard[c] (conditional dependence)	6 studies (with MAF of 0.1%)[b]	102.895	Mean 0.683 SD 0.10 Median 0.685 2.5% 0.460 97.5% 0.885	Mean 0.869 SD 0.09 Median 0.890 2.5% 0.626 97.5% 0.992	Mean 0.861 SD 0.06 Median 0.856 2.5% 0.759 97.5% 0.981	Mean 0.934 SD 0.03 Median 0.937 2.5% 0.855 97.5% 0.995

Model Type	Included Studies, N	Deviance Information Criterion	Sensitivity of LB	Specificity of LB	Sensitivity of TB	Specificity of TB
HSROC with perfect reference standard[a]	4 studies (with RT-PCR)[b]	74.049	Mean 0.641 SD 0.13 Median 0.648 2.5% 0.344 97.5% 0.887	Mean 0.788 SD 0.13 Median 0.813 2.5% 0.441 97.5% 0.971	NA	NA
HSROC with imperfect reference standard[a] (conditional independence)	4 studies (with RT-PCR)[b]	74.088	Mean 0.736 SD 0.14 Median 0.751 2.5% 0.408 97.5% 0.968	Mean 0.872 SD 0.12 Median 0.907 2.5% 0.536 97.5% 0.997	Mean 0.922 SD 0.03 Median 0.917 2.5% 0.870 97.5% 0.991	Mean 0.858 SD 0.06 Median 0.856 2.5% 0.736 97.5% 0.984
HSROC with perfect reference standard[a]	10 studies (with dPCR)[b]	152.415	Mean 0.744 SD 0.07 Median 0.748 2.5% 0.590 97.5% 0.869	Mean 0.727 SD 0.11 Median 0.736 2.5% 0.480 97.5% 0.917	NA	NA
HSROC with imperfect reference standard[a] (conditional dependence)	10 studies (with dPCR)[b]	141.617	Mean 0.810 SD 0.07 Median 0.813 2.5% 0.647 97.5% 0.954	Mean 0.798 SD 0.11 Median 0.808 2.5% 0.555 97.5% 0.977	Mean 0.815 SD 0.05 Median 0.809 2.5% 0.726 97.5% 0.953	Mean 0.754 SD 0.06 Median 0.748 2.5% 0.638 97.5% 0.900
HSROC with perfect reference standard[a]	3 studies (with NGS)[b]	44.585	Mean 0.775 SD 0.15 Median 0.812 2.5% 0.368 97.5% 0.974	Mean 0.813 SD 0.14 Median 0.853 2.5% 0.420 97.5% 0.975	NA	NA

Model Type	Included Studies, N	Deviance Information Criterion	Sensitivity of LB	Specificity of LB	Sensitivity of TB	Specificity of TB
HSROC with imperfect reference standard[a] (conditional dependence)	3 studies (with NGS)[b]	41.579	Mean 0.775 SD 0.16 Median 0.808 2.5% 0.375 97.5% 0.985	Mean 0.847 SD 0.13 Median 0.885 2.5% 0.461 97.5% 0.985	Mean 0.824 SD 0.10 Median 0.840 2.5% 0.575 97.5% 0.983	Mean 0.940 SD 0.03 Median 0.945 2.5% 0.855 97.5% 0.995

Abbreviations: dPCR, digital polymerase chain reaction; HSROC, hierarchical summary receiver operating characteristics; LB, liquid biopsy; MAF, mutant allele fraction; NA, not applicable; NGS, next-generation sequencing; RT-PCR, real-time polymerase chain reaction; SD, standard deviation; TB, tissue biopsy.

[a]Models run with between-study variation in thresholds.

[b]Only studies that reported the threshold (limit of detection) were included in the meta-analysis.

[c]This model was used to draw conclusions on the sensitivity and specificity of liquid biopsy to detect epidermal growth factor receptor T790M.

Appendix 3: Critical Appraisal of Clinical Evidence

Table A2: AMSTAR Scores of Included Systematic Reviews

Author, Year	AMSTAR Score[a]	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
Passiglia et al,[36] 2018	8	✓	✓	✓	✗[b]	✗	✗[c]	✓	✓	✓	✓	✓

Abbreviation: AMSTAR, A Measurement Tool to Assess Systematic Reviews.
[a]Maximum possible score is 11. Details of AMSTAR score are described in Shea et al.[37]
[b]Included only published articles but did include conference abstracts.
[c]Only number of patients and method of detection were reported for included studies.

Table A3: Risk of Bias[a] Among Systematic Reviews (ROBIS Tool)

Author, Year	Phase 2				Phase 3
	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Risk of Bias in Review
Passiglia et al, 2018[36]	Low	Low	Low	High[b]	Low

Abbreviation: ROBIS, Risk of Bias in Systematic Reviews.
[a]Possible risk of bias levels: low, high, unclear.
[b]Statistical methods did not adhere to the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.*[27]

Table A4: Risk of Bias[a] Among Randomized Controlled Trials (Cochrane Risk of Bias Tool)

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Incomplete Outcome Data	Selective Reporting	Other Bias
Goss et al,[63] 2016	Unclear[a]	Low	Low	Low	Low	Low
Janne et al,[14,138] 2012	Unclear[a]	Unclear[b]	Low	Low	Low	Low
Yang et al,[64,139-142] 2017	Unclear[a]	Unclear[b]	Low	Low	Low	Low

[a]Possible risk of bias levels: low, high, and unclear.
[a]Authors do not state details on how randomization was done.
[b]No details on whether participants knew what group they were assigned to.

Table A5: Risk of Bias[a] Among Nonrandomized Studies (RoBANS)

Author, Year	Selection of Participants	Confounding Variables	Measurement of Exposure	Blinding of Outcome Assessments	Incomplete Outcome Data	Selective Outcome Reporting
Karlovich et al,[39] 2016	Low	Low	Low	Low	Low	Low
Kimura et al,[40] 2016	High[b]	High[c]	Low	Low	Low	High[d]
Nishikawa et al,[41] 2018	Low	High[c]	Low	Low	Low	High[d]
Oxnard et al,[18] 2016	Low	High[e]	Low	Low	Low	Low
Sacher et al,[42] 2016	Low	High[e]	Low	Low	High[f]	Low
Sueoka-Aragane et al,[43] 2016	Low	High[e]	Low	Low	Low	High[d]
Wang et al,[45,143] 2017	Low	High[c]	Low	Low	High[g]	Low
Yoshida et al,[46,66] 2017	Low	High[c]	Low	Low	Low	Low
Zhang et al,[47,144-147] 2018	Low	Low	Low	Low	Low	Low
Zheng et al,[48,145,148] 2016	Low	High[e]	Low	Low	Low	High[d]

[a]Possible risk of bias levels: low, high, and unclear.
[b]No baseline characteristics reported.
[c]No statistical means to adjust for confounders, and details of timing of samples (tissue and liquid) were not reported.
[d]Authors report all expected outcomes, but do not report the treatment patients who test negative for epidermal growth factor receptor T790M receive, which is crucial in interpreting clinical utility outcomes.
[e]No statistical methods to adjust for confounders.
[f]Authors do not specify how many patient samples were used to examine the outcome of “turn around time.”
[g]17 patients did not access treatment; however, how missing data were dealt with was not explained.

Table A6: Risk of Bias[a] Among Diagnostic Accuracy Studies (QUADAS-2 Tool)

Author, Year	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Buder et al,[50] 2018	Low	Low	Low	Low	Low	Low	Low
Ishii et al,[53] 2015	Low	Low	Low	Unclear	Low	Low	Low
Jenkins et al,[38] 2017	Low	Unclear	Unclear	Unclear	Low	Low	Low
Karlovich et al,[39] 2016	Low	Low	Low	Unclear	Low	Low	Low
Kasahara et al,[54] 2017	Low	High	Unclear	Low	Low	High	Low
Mellert et al,[57] 2017	Low	Unclear	Low	Low	Low	Unclear	Low
Oxnard et al,[18] 2016	Unclear	High	Unclear	Unclear	Low	Low	Low
Paweletz et al,[58] 2016	Unclear	Unclear	Low	Unclear	Low	Low	Low
Reckamp et al,[59] 2016	Low	Unclear	Low	Low	Low	Low	Low
Sacher et al,[42] 2016	Low	Unclear	Unclear	Low	Low	Low	Low
Seki et al,[55] 2016	Low	High	Unclear	Unclear	Low	Low	Low
Sundaresan[60] 2016	Low	Low	Low	Low	Low	Low	Low
Suzawa et al,[51] 2016	Unclear	Unclear	Low	Low	Low	Low	Low
Takahama et al,[56] 2016	Low	Unclear	Low	Low	Low	Low	Low
Thompson et al,[61] 2016	High	Unclear	Low	Low	Low	Low	Low
Thress et al,[44] 2015	Low	High	Unclear	Unclear	Low	Low	Low

Author, Year	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Wang et al,[45,143] 2017	Low	Low	Low	Low	Low	Low	Low
Wu et al,[52] 2017	Low	Low	Low	Low	Low	Low	Low
Yoshida et al,[46] 2017	Unclear	Low	Low	Low	Low	Low	Low

Abbreviation: QUADAS-2; Quality Assessment of Diagnostic Accuracy Studies.[34]
[a]Possible risk of bias levels: low, high, unclear from Passiglia et al.[36]

Table A7: GRADE Evidence Profile for Comparison of Liquid Biopsy With Tissue Biopsy on Diagnostic Test Accuracy Outcomes

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Liquid Biopsy Accuracy							
Sensitivity 6 (test accuracy)	No serious limitations	No serious limitations	Serious limitations (−1)[a]	No serious limitations[b]	Undetected	No other considerations	⊕⊕⊕ Moderate
Specificity 6 (test accuracy)	No serious limitations	No serious limitations	Serious limitations (−1)[c]	No serious limitations[d]	Undetected	No other considerations	⊕⊕⊕ Moderate
Positive predictive value	No serious limitations	No serious limitations	Serious limitations (−1)[e]	No serious limitations	Undetected	No other considerations	⊕⊕⊕ Moderate
Negative predictive value	No serious limitations	No serious limitations	Serious limitations (−1)[f]	No serious limitations	Undetected	No other considerations	⊕⊕⊕ Moderate
Concordance rate	No serious limitations	No serious limitations	Serious limitations (−1)[g]	No serious limitations	Undetected	No other considerations	⊕⊕⊕ Moderate
Liquid Biopsy Clinical Utility							
Time to test result 1 (prospective)	No serious limitations	No serious limitations	No serious limitations	No serious limitations[h]	Undetected	No other considerations	⊕⊕ Low
Progression-free survival 6 (3 retrospective and 3 prospective)	No serious limitations	No serious limitations	No serious limitations[i]	No serious limitations	Undetected	No other considerations	⊕⊕ Low
Overall survival 2 (retrospective and prospective)	No serious limitations	Serious limitations (−1)[j]	No serious limitations	No serious limitations	Undetected	No other considerations	⊕ Very Low

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Response rate 4 (RCTs)[k]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	No other considerations	⊕⊕⊕⊕ High
Response rate 4 (1 prospective, 2 retrospective, 1 nRCT)[k]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	No other considerations	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; nRCT, non-randomized controlled trial; NSCLC, non–small cell lung cancer; RCT, randomized controlled trial.
[a]False-negative results will be "confirmed" through tissue biopsy, an invasive procedure that could have adverse events in this population (patients with advanced NSCLC).
[b]Wide confidence intervals are based on few studies with small sample sizes; however, when liquid biopsy is used as a triage test, the same decision would be made to get confirmation through tissue biopsy. Did not downgrade.
[c]False-positive results mean people will be treated unnecessarily with osimertinib and disease might continue to progress.
[d]Wide confidence intervals are based on few studies with small sample sizes; however, given the lack of adverse effects from osimertinib, we did not downgrade.
[e]High positive predictive value means more people will get appropriate treatment (osimertinib) and avoid unnecessary tissue biopsy. However, some people will still require unnecessary tissue biopsy. Equations are also based on sensitivity and specificity.
[f]Low negative predictive value of liquid biopsy means test should be used as triage test, because test cannot accurately identify people without resistance mutation. Equations are also based on sensitivity and specificity.
[g]Limitations in tissue biopsy make it an imperfect gold standard.
[h]Range of turnaround time for tissue biopsy was from 1 to 146 days because it included time required to obtain additional biopsy after failed biopsy attempts.
[i]Two of the six studies do not report on treatment regimen of *EGFR* T790M–positive and *EGFR* T790M–negative patients. This makes it difficult to interpret this outcome.
[j]One study found no difference, where another found a significant difference in overall survival.
[k]Response rate examines effectiveness of osimertinib. It does not provide additional information on method of biopsy and does not compare results between people who are *EGFR* T790M positive according to either liquid or tissue biopsy.

Appendix 4: Baseline Characteristics of Included Studies

Table A8: Baseline Patient Characteristics for Diagnostic Accuracy Studies

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Buder et al,[50,149] 2018						
Overall Sample Size N = 91 **Matched Sample Size** N = 45 **Age (median)** 67 y (range 38–86) **Sex** 69 female (76.0%) 22 male (24.0%) **Race** NR	**NSCLC Stage** Advanced NSCLC **NSCLC Type** NR	*Ex 19 deletion* n = 55 (60.0%) *L858R* n = 28 (31.0%) *G719X* n = 2 (2.0%) *L861Q* n = 3 (3.0%) L858R/G719X n = 2 (2.0%) *Exon 20 insertion* n = 1 (1.0%)	*Gefitinib* n = 38 (42.0%) *Erlotinib* n = 7 (8.0%) *Afatinib* n = 29 (32.0%) *>1 EGFR-TKI* n = 17 (19.0%)	*Cell-free ctDNA* Mutant allele concentration (1 copy) *Tissue* NR	Droplet dPCR	NR
Ishii et al,[53] 2015						
Overall and Matched Sample Size N = 18 **Age (median)** 63 y (range 50–81) **Sex** 16 female (88.9%) 2 male (11.1%) **Race** Japanese (NR)	**NSCLC Stage** NR **NSCLC Type** *Adenocarcinoma* n = 18 (100%)	*Ex 19 deletion* n = 7 (38.8%) *L858R* n = 10 (55.6%) *S752-I759 deletion* n = 1 (5.6%)	*Gefitinib* n = 17 (94.4%) *Erlotinib* n = 1 (5.6%)	*Cell-free ctDNA* Mutant allele fraction (0.032%) Mutant allele concentration for plasma samples (3 copies) *Tissue* Mutant allele concentration for formalin-fixed paraffin-embedded samples (22 copies) Mutant allele concentration for frozen samples (3 copies)	Droplet dPCR	*Lung* n = 7 (38.8%) *Pleural effusion* n = 8 (44.4%) *Lymph node* n = 2 (11.1%) *Pericardial effusion* n = 1 (5.6%)

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Jenkins et al[38] (Yang et al,[142] 2016)[a]						
Sample Size N = 201 **Age (median)** 62 y (range 37–89) **Sex** 133 female (66.0%) 68 male (34.0%) **Race** *White* n = 76 (38.0%) *Asian* n = 114 (57.0%) *Black/African American* n = 1 (< 1.0%) *NR* n = 4 (2.0%)	**NSCLC Stage** Advanced NSCLC **NSCLC Type** *Adenocarcinoma* n = 197 (97.0%) *Adenosquamous carcinoma* n = 1 (<1%) *Other* n = 5 (2.0%)	*Ex 19 deletion* n = 142 (71.0%) *L858R* n = 51 (25.0%) *G719X* n = 4 (2.0%) *S7681* n = 3 (1.0%) *Exon 20 insertion* n = 2 (1.0%) EGFR *T790M only* n = 5 (2.0%)	*Gefitinib* n = 117 (58.0%) *Erlotinib* n = 116 (58.0%) *Afatinib* n = 36 (18.0%) *Afatinib/cetuximab* n = 4 (2.0%) *Dacomitinib* n = 4 (2.0%) *Other EGFR-TKI* n = 5 (2.0%) *Platinum-containing doublet chemotherapy* n = 122 (61.0%) *Platinum-containing doublet chemotherapy/ bevacizumab* n = 25 (12.0%)	*Cell-free ctDNA* Mutant allele fraction (0.1%) *Tissue* NR	RT-PCR (Cobas)	NR

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Jenkins et al[38] (Goss et al,[63] 2016)[a]						
Sample Size N = 210 **Age (median)** 64 y (range 35–88) **Sex** 145 female (69.0%) 65 male (31.0%) **Race** *White* n = 72 (34.0%) *Asian* n = 132 (63.0%) *Black/African American* n = 3 (1.4%) *Native Hawaiian or other Pacific Islander* n = 1 (< 1.0%) *Other* n = 2 (<1.0%)	**NSCLC Stage** Advanced NSCLC **NSCLC Type** *Adenocarcinoma* n = 200 (95.0%) *Adenosquamous carcinoma* n = 1 (0.5%) *Squamous cell carcinoma* n = 2 (1.0%) *Other* n = 5 (2%)	*Ex 19 deletion* n = 137 (65.0%) *L858R* n = 67 (32.0%) *G719X* n = 4 (2.0%) *S7681* n = 3 (1.0%) *Exon 20 insertion* n = 1 (0.5%)	*Gefitinib* n = 122 (58.0%) *Erlotinib* n = 119 (57.0%) *Afatinib* n = 38 (18.0%) *Dacomitinib* n = 2 (1.0%) *Other EGFR-TKI* n = 2 (1.0%)	*Cell-free ctDNA* Mutant allele fraction (0.1%) *Tissue* NR	RT-PCR (Cobas)	NR

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Karlovich et al,[39] 2016 Includes Baseline Characteristics from CO-1686 Phase I Study						
Matched Sample Size N = 94 **Age (median)** 61 (range 29–83) **Sex** 72 female (76.6%) 21 male (22.3%) **Race** *White* n = 71 (75.5%) *Asian* n = 15 (16.0%) *Black/African American* n = 2 (2.1%) *Other* n = 4 (4.3%) *Missing* n = 2 (2.1%)	**NSCLC Stage** *NR* **NSCLC Type** *Adenocarcinoma* n = 83 (88.3%) *Other* n = 11 (11.7%)	NR	NR	NR	RT-PCR (Cobas) BEAMing dPCR	NR
Kasahara et al,[54] 2017						
Overall Sample Size N = 28[e] **Matched Sample Size** N = 20 **Age (median)** 65 y (range 42–81) **Sex** 15 female (54.0%) 13 male (46.0%) **Race** Japanese (NR)	**NSCLC Stage** *Stage IIIB/IV* n = 23 (82.0%) *Postoperative recurrence* n = 5 (18.0%) **NSCLC Type** *Adenocarcinoma* n = 28 (100%)	*Ex 19 deletion* n = 20 (71.0%) *L858R* n = 8 (29.0%)	NR	*Cell-free ctDNA* Mutant allele fraction (0.1%) *Tissue* NR	Chip-based dPCR	NR

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Mellert et al,[57] 2017						
Matched Sample Size N = 55 **Age (median)** NR **Sex** NR **Race** NR	**NSCLC Stage** Advanced NSCLC **NSCLC Type** NR	NR	NR	*Cell-free ctDNA* Mutant allele fraction (0.02%) *Tissue* NR	Droplet dPCR	NR
Oxnard et al,[18] 2016						
Matched Sample Size N = 216 **Age (median)** 59 y **Sex** 132 female (61.1%) 84 male (38.9%) **Race** *White* n = 66 (30.6%) *Asian* n = 138 (63.9%) *Other* n = 4 (1.9%)	**NSCLC Stage** NR **NSCLC Type** NR	*Ex 19 deletion* n = 138 (63.9%) *L858R* n = 78 (36.1%)	*Gefitinib* n = 43 (19.9%) *Erlotinib* n = 59 (27.3%) *Afatinib* n = 32 (14.8%) *Dacomitinib* n = 1 (0.5%) *Rociletinib* n = 1 (0.5%)	*Cell-free ctDNA* Mutant allele fraction (0.06%) *Tissue* NR	BEAMing dPCR	NR
Paweletz et al,[58] 2016						
Matched Sample Size N = 14 **Age (median)** NR **Sex** NR **Race** NR	**NSCLC Stage** Advanced NSCLC **NSCLC Type** NR	NR	NR	*Cell-free ctDNA* Mutant allele fraction (0.4%) *Tissue* NR	NGS	NR

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Reckamp et al,[59] 2016						
Sample Size N = 63 **Age (median)** 64 y (range 40–85) **Sex** 45 female (71.4%) 18 male (28.6%) **Race** *White* n = 44 (69.8%) *Asian* n = 17 (27.0%) *Black/African American* n = 1 (1.6%) *Other* n = 0 (0%) *Missing* n = 1 (1.6%)	**NSCLC Stage** *NR* **NSCLC Type** *Adenocarcinoma* n = 63 (100%)	NR	NR	*Cell-free ctDNA* Mutant allele fraction (0.01%) *Tissue* NR	NGS	NR

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Sacher et al[42] 2016						
Sample Size N = 60 **Age (median)** 58 y **Sex** 42 female (70.0%) 18 male (30.0%) **Race** *White* n = 72 (34.0%) *Asian* n = 132 (63.0%) *Black/African American* n = 3 (1.4%) *Native Hawaiian or other Pacific Islander* n = 1 (<1.0%)	**NSCLC Stage** *Stage IV* n = 60 (100%) **NSCLC Type** *Adenocarcinoma* n = 57 (95.0%) *Adenosquamous carcinoma* n = 3 (5.0%)	*Ex 19 deletion* n = 37 (62.0%) *L858R* n = 18 (30.0%) *Uncommon* n = 5 (8.0%)	NR	*Cell-free ctDNA* Mutant allele fraction (0.1%) *Tissue* NR	Droplet dPCR	*Lung* n = 29 (33%) *Pleural biopsy, fluid* n = 3 (5%) *Liver* n = 6 (10%) *Lymph node* n = 8 (14%) *Other* n = 10 (18%)
Seki et al,[55] 2016						
Overall Sample Size N = 16 **Matched Sample Size** N = 10 **Age (mean)** 62.5 y (range 47–71) **Sex** 10 female (62.5%) 6 male (37.5%) **Race** Japanese (NR)	**NSCLC Stage** *Stage IV* n = 15 (93.8%) *Postoperative relapse* n = 1 (6.3%) **NSCLC Type** NR	*Ex 19 deletion* n = 11 (68.8%) *L858R* n = 5 (31.3%)	*Gefitinib* n = 7 (43.8%) *Erlotinib* n = 5 (31.3%) *Erlotinib/ gefitinib* n = 3 (18.8%) *Erlotinib/afatinib* n = 1 (6.3%)	*Cell-free ctDNA* Mutant allele fraction (0.75%) *Tissue* NR	Droplet dPCR	**Repeat Biopsy** n= 10 *Pericardium* n = 1 (10%) *Primary lesion* n = 2 (20%) *Liver* n = 3 (30%) *Lymph node* n = 2 (20%) *Pleural effusion* n = 2 (20%)

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Sundaresan et al,[60] 2016						
Sample Size N = 40 **Age (median)** 63 y (range 44–90) **Sex** 26 female (65.0%) 14 male (35.0%) **Race** NR	**NSCLC Stage** *Stage IIIA* n = 2 (5.0%) *Stage IIIB* n = 4 (10.0%) *Stage IV* n = 34 (85.0%) **NSCLC Type** NR	*Ex 19 deletion* n = 29 (73.0%) *L858R* n = 8 (20.0%) *Other* n = 3 (8.0%)	*Erlotinib* n = 18 (45.0%) *Afatinib* n = 3 (8.0%) *Erlotinib/ chemotherapy* n = 11 (28.0%) *Erlotinib/ bevacizumab* n = 3 (8.0%) *Afatinib/ cetuximab* n = 1 (3.0%) *Chemotherapy* n = 4 (10.0%)	NR	RT-PCR (Cobas)	*Lung* n = 15 (38.5%) *Pleural biopsy, fluid* n = 7 (17.9%) *Liver* n = 6 (15.4%) *Other* n = 11 (28.2%)
Suzawa et al,[51] 2017						
Matched Sample Size N = 59 **Age (median)** 67 y (range 39–84) **Sex** 17 female (70.8%) 7 male (29.2%) **Race** Japanese (NR)	**NSCLC Stage** Advanced NSCLC **NSCLC Type** NR	*Ex 19 deletion* n = 16 (66.7%) *L858R* n = 7 (29.2%) *G719A* n = 1 (4.2%)	NR	*Cell-free ctDNA* Mutant allele fraction (0.01%) *Tissue* NR	Droplet dPCR	NR

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Takahama et al,[56] 2016						
Overall Sample Size N = 260 **Matched Sample Size** N = 41 **Age (median)** 68 y (range 36–90) **Sex** 182 female (71.5%) 78 male (27.3%) **Race** Japanese (NR)	**NSCLC Stage** *Stage IIIB/IV/inoperable* n = 205 (78.8%) *Postoperative recurrence* n = 55 (21.2%) **NSCLC Type** NR	*Ex 19 deletion* n = 127 (48.8%) *L858R or L861Q* n = 122 (46.9%) *Other* n = 5 (1.9%)	*Gefitinib* n = 205 (78.8%) *Erlotinib* n = 47 (18.1%) *Afatinib* n = 8 (3.1%)	*Cell-free ctDNA* Mutant allele concentration (0.15 copies/mL) *Tissue* Mutant allele concentration (1.11 copies/mL)	Droplet dPCR	NR
Thompson et al,[61] 2016						
Overall Sample Size N = 102 **Matched Sample Size** N = 50 **Age (median)** 64 y (range 34–85) **Sex** 33 female (66.0%) 17 male (34.0%) **Race** NR	**NSCLC Stage** *Stage I* n = 1 (2.0%) *Stage III* n = 0 (0%) *Stage IV* n = 49 (98.0%) **NSCLC Type** *Adenocarcinoma* n = 39 (78.0%) *Squamous* n = 2 (4.0%) *Poorly differentiated carcinoma* n = 7 (14.0%) *Other* n = 2 (4.0%)	NR	NR	*Cell-free ctDNA* NR *Tissue* Mutant allele fraction (4.0%)	NGS	NR

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Thress et al,[44] 2015[b]						
Sample Size ***Escalation*** **N = 31** ***Expansion*** N = 222 **Age (median)** ***Escalation*** 61 y (range 39–81) ***Expansion*** 60 y (range 28–88) **Sex** ***Escalation*** 20 female (65.0%) 11 male (35.0%) ***Expansion*** 136 female (61.0%) 86 male (39.0%) **Race** ***Escalation*** *White* n = 8 (26.0%) *Asian* n = 22 (71.0%) *Other* n = 1 (3.0%) ***Expansion*** *White* n = 82 (37.0%) *Asian* n = 134 (60.0%) *Other* n = 5 (2.0%) *Missing data* n = 1 (< 0.5%)	**NSCLC Stage** NR **NSCLC Type** NR	NR	NR	Mutant allele fraction (0.1% for RT-PCR and NR for dPCR)	RT-PCR (Cobas) BEAMing dPCR	NR

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Wang et al,[45] 2017						
Overall Sample Size N = 108 **Matched Sample Size** N = 16 **Age** < *65 y* n = 23 (21.3%) ≥ *65 y* n = 85 (78.7%) **Sex** 53 female (49.1%) 55 male (50.9%) **Race** Chinese (NR)	**NSCLC Stage** *Stage IIIB* n = 3 (2.8%) *Stage IV* n = 105 (97.2%) **NSCLC Type** *Adenocarcinoma* n = 102 (94.4%) *Nonadenocarcinoma* n = 6 (5.6%)	*Ex 19 deletion* n = 70 (64.8%) *L858R* n = 33 (30.6%) *Other* n = 5 (4.6%)	*Gefitinib* n = 16 (14.8%) *Erlotinib* n = 9 (8.3%) *Icotinib* n = 83 (76.9%)	NR	Droplet dPCR	NR
Wu et al,[52] 2017						
Overall Sample Size N = 48 **Matched Sample Size** N = 24 **Age (median)** 53.2 y (range 36–75) **Sex** 22 female (48.9%) 23 male (51.1%) **Race** Chinese (NR)	**NSCLC Stage** *Stage IIIB* n = 2 (4.4%) *Stage IV* n = 43 (95.6%) **NSCLC Type** *Adenocarcinoma* n = 42 (93.3%) *Squamous cell carcinoma* n = 3 (6.7%)	*Ex 19 deletion* n = 30 (66.7%) *L858R* n = 15 (33.3%)	*Gefitinib* n = 37 (82.2%) *Erlotinib* n = 4 (8.9%) *Icotinib* n = 4 (8.9%)	NR	RT-PCR	NR

Sample Size, Age, Sex, Race	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutations	Previous *EGFR*-TKI or Other Treatment	Threshold of Liquid and Tissue Positivity	Method of Liquid Biopsy Detection	Location of Tissue Biopsy
Yoshida et al,[46] 2017						
Overall Sample Size N = 31 **Matched Sample Size** N = 21 **Age (median)** 66 y (range 39–82) **Sex** 14 female (45.0%) 17 male (55.0%) **Race** Japanese (NR)	**NSCLC Stage** Advanced NSCLC **NSCLC Type** NR	*Ex 19 deletion* n = 15 (48.0%) *L858R* n = 15 (48.0%) *Uncommon* n = 1 (3.0%)	*Gefitinib* n = 18 (58.0%) *Erlotinib* n = 18 (58.0%) *Afatinib* n = 13 (42.0%)	NR	PNA-LNA PCR	NR

Abbreviations: BEAMing, beads, emulsions, amplification and magnetics; ctDNA, circulating tumour DNA; dPCR, digital polymerase chain reaction; *EGFR*, epidermal growth factor receptor; LNA, locked nucleic acid; NSCLC, non–small cell lung cancer; NGS, next-generation sequencing; NR, not reported; PCR, polymerase chain reaction; PNA, peptide nucleic acid; RT-PCR, real-time polymerase chain reaction; TKI, tyrosine kinase inhibitor.

[a]The publication by Jenkins et al[38] on baseline characteristics from the AURA extension and AURA2 includes data from Yang et al[142] in 2017 and Goss et al[63] in 2016.

[b]Information from Janne et al (AURA escalation and expansion cohorts).[14]

Table A9: Baseline Patient Characteristics for Clinical Utility Studies

Sample Size, Age, Sex, Race	Smoking History	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutation	Previous *EGFR*-TKI or Other Treatment	Location of Tissue Biopsy
Jenkins et al,[38] 2017 Includes Baseline Characteristics From AURA Extension (Yang et al,[64,141] 2017) and AURA2 Studies (Goss et al,[63] 2016)					
Sample size N = 201 **Age (median)** 62 y (range 37–89) **Sex** 133 female (66.0%) 68 male (34.0%) **Race** *White* n = 76 (38.0%) *Asian* n = 114 (57.0%) *Black/African American* n = 1 (< 1.0%) *NR* n = 4 (2.0%)	*Never smoker* n = 134 (67.0%) *Ex-smoker* n = 62 (31.0%) *Current Smoker* n = 5 (2.0%)	**NSCLC Stage** Advanced NSCLC **NSCLC Type** *Adenocarcinoma* n = 19 (100%) *Adenosquamous carcinoma* n = 1 (<1%) *Other* n = 5 (2%)	*Ex 19 deletion* n = 142 (71.0%) *L858R* n = 51 (25.0%) *G719X* n = 4 (2.0%) *S7681* n = 3 (1.0%) *Exon 20 insertion* n = 2 (1.0%) EGFR *T790M only* n = 5 (2.0%)	*Gefitinib* n = 117 (58.0%) *Erlotinib* n = 116 (58.0%) *Afatinib* n = 36 (18.0%) *Afatinib/cetuximab* n = 4 (2.0%) *Dacomitinib* n = 4 (2.0%) *Other EGFR-TKI* n = 5 (2.0%) *Platinum-containing doublet chemotherapy* n = 122 (61.0%) *Platinum-containing doublet chemotherapy/ bevacizumab* n = 25 (12.0%)	NR

Sample Size, Age, Sex, Race	Smoking History	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutation	Previous *EGFR*-TKI or Other Treatment	Location of Tissue Biopsy
Sample Size N = 201 **Age (median)** 62 y (range 37–89) **Sex** 133 female (66.0%) 68 male (34.0%) **Race** *White* n = 76 (38.0%) *Asian* n = 114 (57.0%) *Black/African American* n = 1 (< 1.0%) *NR* n = 4 (2.0%)	*Never smoker* n = 160 (76.0%) *Ex-smoker or current smoker* n = 50 (24.0%)	**NSCLC Stage** Advanced NSCLC **NSCLC Type** *Adenocarcinoma* n = 200 (95.0%) *Adenosquamous carcinoma* n = 1 (1.0%) *Squamous cell carcinoma* n = 2 (1.0%) *Other* n = 5 (2%)	*Ex 19 deletion* n = 137 (65.0%) *L858R* n = 67 (32.0%) *G719X* n = 4 (2.0%) *S7681* n = 3 (1.0%) *Exon 20 insertion* n = 1 (1.0%)	*Gefitinib* n = 122 (58.0%) *Erlotinib* n = 119 (57.0%) *Afatinib* n = 38 (18.0%) *Dacomitinib* n = 2 (1.0%) *Other EGFR-TKI* n = 2 (1.0%)	NR
Karlovich et al,[39] 2016, Includes Baseline Characteristics From 2 Studies (Observational Study and CO-1686 Phase I Study)					
Sample Size N = 80 **Age (median)** 61 y (range 27–83) **Sex** 56 female (70.0%) 24 male (30.0%) **Race** *White* n = 35 (43.7%) *Asian* n = 42 (52.5%) *Black/African American* n = 3 (3.8%)	NR	**NSCLC Stage** *NR* **NSCLC Type** *Adenocarcinoma* n = 83 (88.3%) *Other* n = 11 (11.7%)	NR	NR	NR

Sample Size, Age, Sex, Race	Smoking History	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutation	Previous *EGFR*-TKI or Other Treatment	Location of Tissue Biopsy
Sample Size N = 94 **Age (median)** 61 y (range 29–83) **Sex** 72 female (76.6%) 21 male (22.3%) **Race** *White* n = 71 (75.5%) *Asian* n = 15 (16.0%) *Black/African American* n = 2 (2.1%) *Other* n = 4 (4.3%) *Missing* n = 2 (2.1%)	NR	**NSCLC Stage** *NR* **NSCLC Type** *Adenocarcinoma* n = 83 (88.3%) *Other* n = 11 (11.7%)	NR	NR	NR
Kimura et al,[40] 2016					
NR	NR	NR	NR	NR	NR
Nishikawa et al,[41] 2018					
Sample Size N = 19 **Age (median)** 62 y (range 48–78) **Sex** 12 female (63.2%) 7 male (36.8%) **Race** Japanese (NR)	*Never smoker* n = 9 (47.4%) *Ex-smoker or current smoker* n = 10 (52.6%)	**NSCLC Stage** *Stage III* n = 5 (15.8%) *Stage IV* n = 16 (84.2%) **NSCLC Type** *Adenocarcinoma* n = 19 (100%)	*Ex 19 deletion* n = 14 (73.7%) *L858R* n = 4 (21.1%) *L858R/A859S* n = 1 (5.3%)	*Gefitinib* n = 9 (47.4%) *Erlotinib* n = 9 (47.4%) *Afatinib* n = 1 (5.3%)	NR

Sample Size, Age, Sex, Race	Smoking History	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutation	Previous *EGFR*-TKI or Other Treatment	Location of Tissue Biopsy
Oxnard et al,[18] 2016					
Sample Size N = 308 **Age (median)** 59 y **Sex** 132 female (61.1%) 84 male (38.9%) **Race** *White* n = 66 (30.6%) *Asian* n = 138 (63.9%) *Other* n = 4 (1.9%)	NR	**NSCLC Stage** NR **NSCLC Type** NR	*Ex 19 deletion* n = 200 (64.9%) *L858R* n = 108 (35.1%)	*Gefitinib* n = 53 (17.2%) *Erlotinib* n = 96 (31.2%) *Afatinib* n = 40 (13.0%) *Dacomitinib* n = 1 (0.3%) *Rociletinib* n = 5 (1.6%)	NR
Sacher et al,[42] 2016					
Sample Size N = 60 **Age (median)** 58 y **Sex** 42 female (70.0%) 18 male (30.0%) **Race** *White* n = 72 (34.0%) *Asian* n = 132 (63.0%) *Black/African American* n = 3 (1.4%) *Native Hawaiian or other Pacific Islander* n = 1 (< 1.0%)	NR	**NSCLC Stage** *Stage IV* n = 60 (100%) **NSCLC Type** *Adenocarcinoma* n = 57 (95.0%) *Adenosquamous carcinoma* n = 3 (5.0%)	*Ex 19 deletion* n = 37 (62.0%) *L858R* n = 18 (30.0%) *Uncommon* n = 5 (8.0%)	NR	*Lung* n = 29 (33%) *Pleural biopsy, fluid* n = 3 (5%) *Liver* n = 6 (10%) *Lymph node* n = 8 (14%) *Other* n = 10 (18%)

Sample Size, Age, Sex, Race	Smoking History	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutation	Previous *EGFR*-TKI or Other Treatment	Location of Tissue Biopsy
Sueoka-Aragane et al,[43] 2016					
Sample Size N = 89 **Age (median)** 68 y (range 48–89) **Sex** 54 female (61.0%) 35 male (39.0%) **Race** Japanese (NR)	*Never smoker* n = 61 (69.0%) *Ex-smoker or current smoker* n = 28 (31.0%)	**NSCLC Stage** *Stage II/III* n = 8 (9.0%) *Stage IV* n = 55 (62.0%) *Postoperative recurrence* n = 26 (29.0%) **NSCLC Type** *Adenocarcinoma* n = 82 (92.0%) *Squamous cell carcinoma* n = 0 (0%) *Other* n = 7 (8.0%)	*Ex 19 deletion* n = 44 (49.0%) *L858R* n = 45 (51.0%)	*Gefitinib* n = 66 (74.0%) *Erlotinib* n = 13 (15.0%) *Gefitinib/erlotinib* n = 10 (11.0%)	**Repeat Biopsy** n = 8 *Primary lesion* n = 4 (50%) *Pleural effusion* n = 2 (25%) *Lung metastasis* n = 2 (25%)

Sample Size, Age, Sex, Race	Smoking History	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutation	Previous *EGFR*-TKI or Other Treatment	Location of Tissue Biopsy
Thress et al,[44] 2015[a]					
Sample Size ***Escalation*** N = 31 ***Expansion*** N = 222 **Age (median)** ***Escalation*** 61 y (range 39–81) ***Expansion*** 60 y (range 28–88) **Sex** ***Escalation*** 20 female (65.0%) 11 male (35.0%) ***Expansion*** 136 female (61.0%) 86 male (39.0%) **Race** ***Escalation*** *White* n = 8 (26.0%) *Asian* n = 22 (71.0%) *Other* n = 1 (3.0%) ***Expansion*** *White* n = 82 (37.0%) *Asian* n = 134 (60.0%) *Other* n = 5 (2.0%) *Missing data* n = 1 (<0.5%)	NR	**NSCLC Stage** *NR* **NSCLC Type** ***Escalation*** *Adenocarcinoma* n = 29 (94.0%) *Squamous cell carcinoma* n = 1 (3.0%) *Other* n = 1 (3.0%) *Missing data* n = 0 (0%) ***Expansion*** *Adenocarcinoma* n = 213 (96.0%) *Squamous cell carcinoma* n = 2 (1.0%) *Other* n = 5 (2.0%) *Missing data* n = 2 (1.0%)	***Escalation*** Central testing was not performed for escalation cohort ***Expansion*** *Ex 19 deletion* n = 112 (50.0%) *L858R* n = 65 (29.0%) *Other* n = 10 (5.0%) *Unknown* n = 22 (10.0%) *None* n = 13 (6.0%)	NR	NR

Sample Size, Age, Sex, Race	Smoking History	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutation	Previous *EGFR*-TKI or Other Treatment	Location of Tissue Biopsy
Wang et al,[45] 2017					
Overall Sample Size N = 108 **Age** *< 65 y* n = 23 (21.3%) *≥ 65 y* n = 85 (78.7%) **Sex** 53 female (49.1%) 55 male (50.9%) **Race** Chinese (NR)	*Never smoker* n = 71 (65.7%) *Current smoker* n = 37 (34.3%)	**NSCLC Stage** *Stage IIIB* n = 3 (2.8%) *Stage IV* n = 105 (97.2%) **NSCLC Type** *Adenocarcinoma* n = 102 (94.4%) *Nonadenocarcinoma* n = 6 (5.6%)	*Ex 19 deletion* n = 70 (64.8%) *L858R* n = 33 (30.6%) *Other* n = 5 (4.6%)	*Gefitinib* n = 16 (14.8%) *Erlotinib* n = 9 (8.3%) *Icotinib* n = 83 (76.9%)	NR
Yoshida et al,[46] 2017					
Overall Sample Size N = 31 **Age (median)** 66 y (range 39–82) **Sex** 14 female (45.0%) 17 male (55.0%) **Race** Japanese (NR)	*Never smoker* n = 20 (65.0%) *Ex-smoker or current smoker* n = 11 (35.0%)	**NSCLC Stage** Advanced NSCLC **NSCLC Type** NR	*Ex 19 deletion* n = 15 (48.0%) *L858R* n = 15 (48.0%) *Uncommon* n = 1 (3.0%)	*Gefitinib* n = 18 (58.0%) *Erlotinib* n = 18 (58.0%) *Afatinib* n = 13 (42.0%)	NR

Sample Size, Age, Sex, Race	Smoking History	NSCLC Stage, NSCLC Type	Initial *EGFR* Sensitizing Mutation	Previous *EGFR*-TKI or Other Treatment	Location of Tissue Biopsy
Zhang et al,[47] 2018					
Sample Size N = 307 **Age (median)** 63 y (range 32 to 89) **Sex** 172 female (56.0%); 135 male (44.0%) **Race** Chinese (NR)	*Never Smoker* n = 229 (74.6%) *Ex-smoker or Current Smoker* n = 78 (25.4%)	**NSCLC Stage** *Stage IIIA* n = 52 (16.9%) *Stage IIIB* n = 20 (6.5%) *Stage IV* n = 235 (76.5%) **NSCLC Type** *Adenocarcinoma* n = 289 (97.1%) *Adenosquamous* n = 5 (1.6%) *Squamous* n = 4 (1.3%)	*Ex 19 deletion* n = 163 (53.1%) *L858R* n = 121 (39.4%) *Uncommon* n = 23 (7.5%)	NR	NR
Zheng et al,[48] 2016					
Sample Size N = 117 **Age (<60 y, >60 y)** *<60 y* n = 66 (56.4%) *>60 y* n = 51 (43.6%) **Sex** 71 female (60.7%); 46 male (39.3%) **Race** Chinese (NR)	*Never smoker* n = 88 (75.2%) *Current smoker* n = 29 (24.8%)	**NSCLC Stage** *Recurrent* n = 21 (17.9%) *Stage IIIB* n = 5 (4.3%) *Stage IV* n = 91 (77.8%) **NSCLC Type** *Adenocarcinoma* n = 108 (92.3%) *Nonadenocarcinoma* n = 9 (7.7%)	NR	NR	NR

Abbreviations: *EGFR*, epidermal growth factor receptor; NR, not reported; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.
[a]Information from Janne et al[14] (AURA escalation and expansion cohorts).

Appendix 5: Selected Excluded Studies—Economic Evidence

Citation	Primary Reason for Exclusion
Handorf EA, McElligott S, Vachani A, Langer CJ, Demeter MB, Armstrong K, et al. Cost effectiveness of personalized therapy for first-line treatment of stage IV and recurrent incurable adenocarcinoma of the lung. J Oncol Pract. 2012;8(5):267-74.	No comparison of liquid biopsy to tissue biopsy
Lim EA, Lee H, Bae E, Lim J, Shin YK, Choi SE. Economic evaluation of companion diagnostic testing for *EGFR* mutations and first-line targeted therapy in advanced non–small cell lung cancer patients in South Korea. PLoS ONE. 2016;11(8):e0160155.	No comparison of liquid biopsy to tissue biopsy
National Institute of Health and Care Excellence (NICE). *EGFR*-TK mutation testing in adults with locally advanced or metastatic non–small-cell lung cancer [Internet]. London: National Institute of Health and Care Excellence; 2013 [cited 2019 Jan 8]. Available from: https://www.nice.org.uk/guidance/dg9/resources/*EGFR*tk-mutation-testing-in-adults-with-locally-advanced-or-metastatic-nonsmallcell-lung-cancer-pdf-29280700357	No comparison of liquid biopsy to tissue biopsy
Sands J, Li Q, Hornberger J. Urine circulating-tumor DNA (ctDNA) detection of acquired *EGFR* T790M mutation in non–small-cell lung cancer: an outcomes and total cost-of-care analysis. Lung Cancer. 2017;110:19-25.	Compared urine (not plasma) sample versus tissue biopsy
Westwood M, Joore M, Whiting P, van Asselt T, Ramaekers B, Armstrong N, et al. Epidermal growth factor receptor tyrosine kinase (*EGFR*-TK) mutation testing in adults with locally advanced or metastatic non–small cell lung cancer: a systematic review and cost-effectiveness analysis. Health Technology Assessment. 2014;18(32):1-165.	Excluded liquid biopsy; examined types of tissue biopsy methods only

Appendix 6: Results of Applicability and Limitation Checklists for Studies Included in Economic Literature Review

Table A10: Applicability of Studies Evaluating Cost-Effectiveness of Liquid Biopsy as a Triage Test

Author, Year, Country of Publication	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Wu et al 2017,[68] China	Yes (people with *EGFR* T790M mutation who have disease progression after first-line *EGFR*-TKI therapy)	Partially (considered possible combinations of biopsy methods; did not consider tissue biopsy alone)	No (perspectives of United States and Chinese health system)	Yes (United States and Chinese payer perspective)	Yes (appropriate health effects included)	Partially (3% in US context, 5% in Chinese context. As recommended by CADTH and NICE, costs and effects should be discounted at 1.5%)	Yes	NA	Partially applicable

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; *EGFR*, epidermal growth factor receptor; NA, not applicable; NICE, National Institute for Health and Care Excellence; TKI, tyrosine kinase inhibitor.

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA.”

[a]Overall judgment could be “directly applicable,” “partially applicable,” or “not applicable.”

Table A11: Limitations in Studies Evaluating Cost-Effectiveness of Liquid Biopsy as a Triage Test

Author, Year, Country of Publication	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment[b]
Wu et al, 2018,[68] China	Yes (decision tree for mutation testing, and Markov model for disease progression)	Yes (Markov cycle length reflects chemotherapy, 10-y horizon)	Yes (captured health utilities for each health stage, considered long-term survival and major complications)	Yes (estimates from RCT and systematic reviews)	Partly (authors conducted additional analysis to extrapolate long-term outcome)	Yes (included relevant costs)	Yes (estimates from existing systematic review)	Partly (conducted literature review to identify country-specific estimates)	Yes	NA[c]	No	Minor limitations

Abbreviations: NA, not applicable; RCT, randomized controlled trial.

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA”.

[a]Clinical inputs include relative treatment effects, natural history, and utilities.

[b]Overall judgment could be “minor limitations,” “potentially serious limitations,” or “very serious limitations.”

[c]Study’s sensitivity analysis addressed authors’ research question, which was different from ours.

Appendix 7: Primary Economic Evaluation

Table A12: Probability of Having Adverse Event (Grade ≥ 3) While Receiving Treatment

Treatment	Adverse Event[a]	N	Proportion (SE)	Source
Osimertinib (N = 279)	Anemia	2	0.007 (0.0050)	Mok et al, 2017[69]
	Asthenia	3	0.011 (0.0062)	
	Decreased appetite	3	0.011 (0.0062)	
	Diarrhea	3	0.011 (0.0062)	
	Fatigue	3	0.011 (0.0062)	
	Nausea	2	0.007 (0.0050)	
	Neutropenia	4	0.014 (0.0071)	
	Rash	1	0.004 (0.0036)	
	Vomiting	1	0.004 (0.0036)	
Platinum-based doublet (N = 136)	Anemia	16	0.118 (0.0276)	
	Asthenia	6	0.044 (0.0176)	
	Decreased appetite	4	0.029 (0.0145)	
	Diarrhea	2	0.015 (0.0103)	
	Fatigue	1	0.007 (0.0073)	
	Nausea	5	0.037 (0.0161)	
	Neutropenia	16	0.118 (0.0276)	
	Vomiting	3	0.022 (0.0126)	
Nivolumab (N = 418)	Anemia	5	0.012 (0.0053)	Brahmer et al, 2015[150]; Borghaei et al, 2015[101]
	Asthenia	10	0.024 (0.0075)	
	Decreased appetite	6	0.014 (0.0058)	
	Diarrhea	3	0.007 (0.0041)	
	Fatigue	10	0.024 (0.0075)	
	Musculoskeletal pain	1	0.002 (0.0024)	
	Nausea	5	0.012 (0.0053)	
	Neutropenia	1	0.002 (0.0024)	
	Pneumonia	10	0.024 (0.0075)	
	Pneumonitis	4	0.010 (0.0048)	
	Rash	1	0.002 (0.0024)	
	Vomiting	1	0.002 (0.0024)	
Docetaxel (N = 397)	Anemia	16	0.040 (0.0099)	
	Asthenia	16	0.040 (0.0099)	
	Decreased appetite	5	0.013 (0.0056)	
	Dehydration	5	0.013 (0.0056)	
	Diarrhea	6	0.015 (0.0061)	
	Fatigue	28	0.071 (0.0128)	
	Febrile neutropenia	42	0.106 (0.0154)	
	Hair loss (alopecia)	1	0.003 (0.0025)	
	Musculoskeletal pain	1	0.003 (0.0025)	
	Nausea	4	0.010 (0.0050)	
	Peripheral neuropathy	6	0.015 (0.0061)	

Treatment	Adverse Event[a]	N	Proportion (SE)	Source
	Neutropenia	113	0.285 (0.0226)	
	Pneumonia	15	0.038 (0.0096)	
	Pneumonitis	1	0.003 (0.0025)	
	Rash	2	0.005 (0.0036)	
	Vomiting	1	0.003 (0.0025)	

Abbreviation: SE, standard error.
[a]Listed only if number of adverse events reported was > 0.

Table A13: Probability of Response to Treatment

Treatment	Response to Treatment	N	Proportion (SE)	Reference
Osimertinib (n = 278)	Responsive	197	0.709 (0.0273)	Mok et al, 2017[69]
	Progressive	18	0.065 (0.0148)	
Platinum-based doublet chemotherapy (n = 130)	Responsive	44	0.338 (0.0415)	
	Progressive	26	0.200 (0.0351)	
Nivolumab (n = 381)	Responsive	101	0.265 (0.0226)	Brahmer et al, 2015[150]; Borghaei et al, 2015[101]
	Progressive	185	0.486 (0.0256)	
Docetaxel (n = 350)	Responsive	134	0.383 (0.0259)	
	Progressive	133	0.380 (0.0259)	

Abbreviation: SE, standard error.

Table A14: One-Time Cost Related to Adverse Event (Grade ≥ 3) on Treatment

Adverse Event	Cost, $ in 2018 (SE)	Cost, $ (year)	Reference
Anemia	1,356.11 (172.97)	1,294.28 (2015)	Goeree et al, 2016[104]
Asthenia	1,356.11 (172.97)	1,294.28 (2015)	
Decreased appetite	125.73 (16.04)	120 (2015)	
Dehydration	570.55 (72.77)	544.54 (2015)	
Diarrhea	3,244.95 (413.90)	3,097 (2015)	
Fatigue	1,356.11 (172.97)	1,294.28 (2015)	
Febrile neutropenia	7,532.44 (960.77)	7,189 (2015)	
Musculoskeletal pain	8.38 (1.07)	8 (2015)	
Nausea/vomiting	750.71 (95.75)	716.48 (2015)	
Peripheral neuropathy	18.86 (2.41)	18 (2015)	
Pneumonia	7,532.44 (960.77)	7,189 (2015)	
Pneumonitis	7,532.44 (960.77)	7,189 (2015)	
Pneumothorax (chest x-ray)	431.44 (27.03) 32.65	424 (2017)	OCC[124] SOB[107]
Pneumothorax (pleural drain)	475.19 (71.58) 159.86	467 (2017)	OCC[124] SOB[107]
Rash	77.69 (9.91)	74.19 (2015)	Goeree et al, 2016[104]

Abbreviations: OCC, Ontario Cost Analysis Tool; SE, standard error; SOB, Schedule of Benefits.

Table A15: Distributions Used in Economic Model

Parameter	Mean	SE or (Range)[a]	Distribution	Source
Testing Parameters				
Sensitivity, LB (RC, imperfect)	0.683	0.100	Beta	Clinical review (Table A1, Appendix 2)
Specificity, LB (RC, imperfect)	0.869	0.090	Beta	
Sensitivity, TB (RC, imperfect)	0.861	0.060	Beta	
Specificity, TB (RC, imperfect)	0.934	0.030	Beta	
Proportion who cannot have TB	0.18	0.0384	Beta	Chouaid et al, 2014[89]
Proportion LB fail	0.14	0.0067	Beta	Shiau et al, 2014[90]
Proportion TB fail	0.03	0.0022	Beta	Tsao et al, 2017[82]
Proportion TB repeat	0.075	(0.05–0.1)	Uniform	Expert opinion (written communication; Peter Ellis; Dec 17, 2018)
Proportion with TB-related pneumothorax	0.28	0.0434	Beta	Ayyapan et al, 2008[99]
Proportion with severe pneumothorax	0.30	0.0837	Beta	Ayyapan et al, 2008[99]
RT-PCR, sequencing labour (h)	0.67	0.085	Normal	Manufacturer[151]
dPCR, sequencing labour (h)	0.48	0.106	Normal	Manufacturer, clinical expert (written communication, Tracy Stockley, January 7, 2019)
NGS, sequencing labour (h)	2.00	0.255	Normal	Manufacturer, clinical expert (written communication, Tracy Stockley, January 7, 2019; written communication, Harriet Feilotter, December 3, 2018)
Results interpretation, lab technician, PCR (h)	0.17	0.021	Normal	Clinical expert (written communication, Harriet Feilotter, December 3, 2018)
Results interpretation, lab technician, NGS (h)	0.50	0.064	Normal	Clinical expert (written communication, Harriet Feilotter, December 3, 2018)
Treatment Parameters				
Proportion receiving additional treatment	0.505	0.0542	Beta	Valdes et al, 2016[88]
HR of PFS, T790M− vs. T790M+ osimertinib	0.455	0.121	Normal[b]	Derived from Oxnard et al, 2016[18c]
Monthly rate PFS (PBD 3rd line)	0.16	0.0105	Beta	Mok et al, 2018[69]
Monthly rate PFS (nivolumab)	0.26	0.0749	Beta	Horn et al, 2017[97]
Monthly rate PFS (docetaxel)	0.18	0.0380	Beta	Horn et al, 2017[97]
Probability of having adverse event on treatment	See Table A12 (Appendix 7)	See Table A12 (Appendix 7)	Beta	See Table A12 (Appendix 7)
Probability of response to treatment	See Table A13 (Appendix 7)	See Table A13 (Appendix 7)	Beta	See Table A13 (Appendix 7)

Parameter	Mean	SE or (Range)[a]	Distribution	Source
Utilities/Disutilities				
Stable	0.6532	0.0222	Beta	Nafees et al, 2008[103]
Progressive	−0.1792	0.0217	Normal	Nafees et al, 2008[103]
Response	0.0193	0.0066	Normal	Nafees et al, 2008[103]
Neutropenia	−0.0897	0.0154	Normal	Nafees et al, 2008[103]
Febrile neutropenia	−0.0900	0.0163	Normal	Nafees et al, 2008[103]
Fatigue	−0.0735	0.0185	Normal	Nafees et al, 2008[103]
Nausea	−0.0480	0.0162	Normal	Nafees et al, 2008[103]
Vomiting	−0.0480	0.0155	Normal	Nafees et al, 2008[103]
Diarrhea	−0.0468	0.0155	Normal	Nafees et al, 2008[103]
Hair loss	−0.0450	0.0148	Normal	Nafees et al, 2008[103]
Rash	−0.0325	0.0117	Normal	Nafees et al, 2008[103]
Bleeding	−0.2460	−0.0310	Normal	Nafees et al, 2017[72]
Hypertension	−0.0250	−0.0030	Normal	Nafees et al, 2017[72]
Pneumothorax	0.4500	0.0574	Beta	Morimoto et al, 2002[105]
Costs				
Sample transport	51.47	6.57	Gamma	Tsiplova et al, 2016[108]
LB sample collection	49.85	6.359	Gamma	Barnes et al, 2016[91]
LB sample processing	71.49	9.119	Gamma	Barnes et al, 2016[91]
TB sample collection	1641.95	209.43	Gamma	Barnes et al, 2016[91]
TB sample processing	137.88	17.59	Gamma	Barnes et al, 2016[91]
Hourly wage, lab technician	41.78	(35.70–47.86)	Gamma	OPSEU[112]
LB assay, RT-PCR commercial	211.28	26.95	Gamma	Manufacturer (written communication, Michele D'Elia, Roche; January 13, 2019), NICE[152]
LB assay, dPCR commercial	26.57	3.390	Gamma	NICE[152]
LB assay, dPCR in-house	60	7.653	Gamma	Clinical expert (written communication, Tracy Stockley, January 7, 2019)
LB assay, NGS commercial	2,530	322.70	Gamma	Manufacturer[110]
LB assay, NGS in-house	440	56.12	Gamma	Clinical expert (written communication, Tracy Stockley, January 7, 2019)
Results interpretation, lab manager	23.08	9.81	—	Ontario Public Salary Disclosure[116]
Adverse events	See Table A14 (Appendix 7)	See Table A14 (Appendix 7)	Gamma	See Table A14 (Appendix 7)
Palliative care	14,608	114.95	Gamma	Cheung et al, 2015[125]
Disease management, progression free (/cycle)	771.17	78.69	Gamma	Goeree et al, 2016[104]
Disease management, progressed (/cycle)	870.83	93.10	Gamma	Goeree et al, 2016[104]
Drug administration and monitoring	See Table15	See Table 15	Gamma	See Table 15

Parameter	Mean	SE or (Range)[a]	Distribution	Source
Sensitivity Analysis				
Sensitivity, LB (SA, perfect)	0.673	0.080	Beta	Clinical review (Table A1, Appendix 2)
Specificity, LB (RC, perfect)	0.799	0.090	Beta	
Sensitivity, TB (RC, perfect)	1	—	—	
Specificity, TB (RC, perfect)	1	—	—	
Sensitivity, LB (RC, RT-PCR)	0.736	0.140	Beta	
Specificity, LB (RC, RT-PCR)	0.872	0.120	Beta	
Sensitivity, TB (RC, RT-PCR)	0.922	0.030	Beta	
Specificity, TB (RC, RT-PCR)	0.858	0.060	Beta	
Sensitivity, LB (RC, dPCR)	0.810	0.070	Beta	
Specificity, LB (RC, dPCR)	0.798	0.110	Beta	
Sensitivity, TB (RC, dPCR)	0.815	0.050	Beta	
Specificity, TB (RC, dPCR)	0.754	0.060	Beta	
Sensitivity, LB (RC, NGS)	0.775	0.160	Beta	
Specificity, LB (RC, NGS)	0.847	0.130	Beta	
Sensitivity, TB (RC, NGS)	0.824	0.100	Beta	
Specificity, TB (RC, NGS)	0.940	0.030	Beta	
Cost of test development	30,000	(10,000–50,000)	Uniform	Clinical expert (written communication, Harriet Feilotter, December 3, 2018)
Cost of RT-PCR machine	65,000	8,290	Gamma	Manufacturer[151]
Cost of dPCR machine	232,256	29,624	Gamma	NICE[152]
Cost of NGS machine	580,414	74,032	Gamma	Clinical expert (written communication, Harriet Feilotter, December 3, 2018) and Tsiplova, 2016

Abbreviations: dPCR, digital polymerase chain reaction; HR, hazard ratio; LB, liquid biopsy; NGS, next-generation sequencing; NICE, National Institute for Health and Care Excellence; OPSEU, Ontario Public Service Employee Union; PBD, platinum-based doublet chemotherapy; PCR, polymerase chain reaction; PFS, progression-free survival; RC, reference case; RT-PCR, real-time polymerase chain reaction; SA, sensitivity analysis; SE, standard error; TB, tissue biopsy.

[a]Standard error provided for all distributions except the uniform distribution, where range is presented.

[b]Log values presented.

[c]Derived from median time to progression ratio.

Table A16: Scenario Analysis of Short-Term Results (Probabilistic Results) for Clinical Outcomes

Strategy	No. of Tissue Biopsies/1,000 People (95% CrI)	No. of Correct Treatment Decisions/1,000 People (95% CrI)	Average Time to Treatment Result, Days (95% CrI)	No. of Patients who Receive Osimertinib/1,000 People (95% CrI)
Reference Case				
LB alone	0	750 (600–880)	19 (18–19)	479 (331–622)
LB as triage test	432 (309–561)	858 (760–929)	37 (31–42)	616 (518–717)
TB alone	829 (746–898)	739 (662–802)	35 (31–38)	403 (324–480)
Perfect Reference Standard				
LB alone	0	718 (590–831)	19 (18–20)	498 (375–622)
LB as triage test	416 (307–531)	865 (781–929)	36 (31–41)	645 (557–736)
TB alone	829 (746–898)	819 (768–862)	35 (31–38)	449 (380–515)
Liquid Biopsy Retest, Given Negative Result				
LB alone	0	841 (680–953)	28 (25–31)	648 (502–794)
LB as triage test	292 (168–416)	871 (737–957)	41 (33–49)	704 (590–832)
TB alone	829 (746–898)	739 (662–802)	35 (31–38)	403 (324–480)
Cost, Sensitivity, and Specificity for RT-PCR				
LB alone	0	785 (580–923)	19 (18–20)	509 (302–664)
LB as triage test	407 (274–585)	862 (784–922)	36 (30–43)	652 (558–737)
TB alone	829 (746–898)	747 (698–800)	35 (31–38)	451 (379–522)
Cost, Sensitivity, and Specificity for dPCR				
LB alone	0	789 (683–874)	19 (18–20)	601 (491–700)
LB as triage test	331 (244–429)	810 (733–878)	32 (29–37)	719 (636–797)
TB alone	829 (746–898)	671 (605–732)	35 (31–38)	431 (359–503)
Cost, Sensitivity, and Specificity for NGS				
LB alone	0	801 (545–965)	19 (18–20)	544 (291–740)
TB alone	829 (746–898)	723 (608–806)	35 (31–38)	384 (271–479)
LB as triage test	378 (213–591)	871 (720–966)	34 (27–43)	641 (502–785)
Costs, Capital Costs (1 Machine), Maintenance Fees, and Costs With Developing (1) New Test				
LB alone	0	751 (600–880)	19 (18–20)	479 (331–622)
LB as triage test	432 (309–561)	858 (760–929)	37 (31–42)	616 (518–717)
TB alone	829 (746–898)	739 (662–802)	35 (31–38)	403 (324–480)
Costs, Capital Costs (14 New Machines), Maintenance Fees, and Costs With Developing (14) New Tests				
LB alone	0	751 (600–880)	19(18–20)	479 (331–622)
TB alone	829 (746–898)	739 (662–802)	35 (31–38)	403 (324–480)
LB as triage test	432 (309–561)	858 (760–929)	37 (31–42)	616 (518–717)

Abbreviations: CrI, credible interval; dPCR, digital polymerase chain reaction; LB, liquid biopsy; NGS, next-generation sequencing; RT-PCR, real - ime polymerase chain reaction; TB, tissue biopsy.

Table A17: Scenario Analysis of Short-Term Results (Probabilistic Results) for Cost and Cost-Effectiveness Results Per Person

Strategy	Average Total Costs (95% CrI)	Incremental Cost[a] (95% CrI)	Incremental No. of Tissue Biopsies (95% CrI)	ICER[a] ($/Tissue Biopsy Avoided)	Incremental No. of Correct Decisions (95% CrI)	ICER[a] ($/Correct Treatment Decision)
Reference Case						
LB alone	688 (644–738)	--	--	--	--	--
LB as triage test	1,644 (1,331–2,020)	956 (646–1,329)	0.43 (0.31–0.56)	Dominated by LB alone (more TB, more costly)	0.11 (0.03–0.20)	8,920
TB alone	2,149 (1,753–2,626)	505 (184–873)	0.40 (0.27–0.52)	Dominated by LB alone (more TB, more costly)	−0.12 (−0.21 to −0.01)	Dominated by LB as triage (fewer correct decisions, more costly)
Perfect Reference Standard						
LB alone	688 (644–738)	0	--	--	--	--
LB as triage test	1,609 (1,319–1,961)	921 (639–1,268)	0.42 (0.31–0.53)	Dominated by LB alone (more TB, more costly)	0.15 (0.08 to 0.23)	6,258
TB alone	2,149 (1,753–2,626)	540 (248–885)	0.41 (0.31–0.52)	Dominated by LB alone and LB as triage (more TB, more costly)	−0.05 (−0.12 to 0.05)	Dominated by LB as triage (fewer correct decisions, more costly)
Liquid Biopsy Retest, Given Negative Result						
LB alone	882 (799–978)	0	--	--	--	--
LB as triage test	1,529 (1,192–1,904)	646 (361–974)	0.29 (0.17–0.42)	Dominated by LB alone (more TB, more costly)	0.03 (−0.01 to 0.10)	21,673
TB alone	2,149 (1,753–2,626)	620 (217–1,087)	0.54 (0.41–0.67)	Dominated by LB alone and LB as triage (more TB, more costly)	−0.13 (−0.25 to 0.02)	Dominated by LB as triage and LB alone (fewer correct decisions, most costly)
Cost, Sensitivity, and Specificity of Real-Time Polmerase Chain Reaction						
LB alone	770 (708 to 842)	0	--	--	--	--
LB as triage test	1,697 (1,356–2,172)	927 (592–1,397)	0.41 (0.27–0.58)	Dominated by LB alone (more TB, more costly)	0.07 (−0.02 to 0.22)	12,015
TB alone	2,203 (1,804–2,683)	505 (85–925)	0.42 (0.25–0.56)	Dominated by LB alone and LB as triage (more TB, more costly)	−0.12 (−0.19 to −0.04)	Dominated by LB as triage and LB alone (fewer correct decisions, most costly)
Cost, Sensitivity and Specificity of Digital Polymerase Chain Reaction						
LB alone	589 (554–627)	0	--	--	--	--
LB as triage test	1,300 (1,071–1,592)	711 (485–999)	0.33 (0.24–0.43)	Dominated by LB alone (more TB, more costly)	0.02 (−0.03 to 0.09)	33,203

Strategy	Average Total Costs (95% CrI)	Incremental Cost[a] (95% CrI)	Incremental No. of Tissue Biopsies (95% CrI)	ICER[a] ($/Tissue Biopsy Avoided)	Incremental No. of Correct Decisions (95% CrI)	ICER[a] ($/Correct Treatment Decision)
TB alone	2,095 (1,702–2,571)	796 (503–1,150)	0.50 (0.40–0.59)	Dominated by LB alone and LB as triage (more TB, more costly)	−0.14 (−0.22 to −0.07)	Dominated by LB as triage and LB alone (fewer correct decisions, most costly)
Cost, Sensitivity and Specificity of Next-Generation Sequencing						
LB alone	2,158 (1,832–2,523)	0	---	--	--	--
TB alone	2,346 (1,940–2,833)	189 (−360–783)	0.83 (0.75–0.90)	Dominated by LB alone (most TB, more costly)	−0.08 (−0.29 to 0.19)	Dominated by LB alone (fewer correct decisions, more costly)
LB as triage test	3,084 (2,546–3,758)	737 (110–1,378)	−0.45 (−0.62 to −0.24)	Dominated by LB alone (more TB, more costly)	0.15 (−0.01 to 0.29)	13,278[b]
Costs, Capital Costs (1 New Machine), Maintenance Fees, and Costs of Developing (1) New Test						
LB alone	736 (691–787)	0	--	--	--	--
LB as triage test	1,692 (1,379–2,066)	956 (645–1,329)	0.43 (0.31–0.45)	Dominated by LB alone (more TB, more costly)	0.11 (0.03–0.20)	8,920
TB alone	2,149 (1,753–2,626)	457 (136–826)	0.40 (0.27–0.52)	Dominated by LB alone and LB as triage (more TB, more costly)	−0.12 (−0.21 to −0.01)	Dominated by LB as triage and LB alone (fewer correct decisions, most costly)
Costs, Capital Costs (14 New Machines), Maintenance Fees, and Costs of Developing (14) New Tests						
LB alone	1,363 (1,232–1,503)	0	--	--	--	--
TB alone	2,149 (1,753–2,626)	786 (369 to 1,283)	0.83 (0.75–0.90)	Dominated by LB alone (more TB, more costly)	−0.01 (−0.16 to 0.15)	Dominated by LB alone (fewer correct decisions, more costly)
LB as triage test	2,319 (1,977–2,725)	170 (−218 to 518)	−0.40 (−0.52 to −0.27)	Dominated by LB alone (more TB, more costly)	0.12 (0.01–0.21)	8,920[b]

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; LB, liquid biopsy; NGS, next-generation sequencing; TB, tissue biopsy.

[a]Numbers could appear incorrect because of rounding.

[b]ICER for liquid biopsy as a triage test compared with liquid biopsy alone. Tissue biopsy alone removed as dominated.

Table A18: Scenario Analysis of Long-Term Results

Strategy	Average Cost (95% CrI)	Incremental Cost[a] (95% CrI)	Average Effect (95% CrI)		Incremental Effect[a] (95% CrI)		ICER[a]	
			LY	QALY	LY	QALY	$/LY	$/QALY
Reference Case								
TB alone	78,952 (70,825 to 87,079)	--	2.12 (2.06–2.19)	1.10 (0.98–1.21)	--	--	--	--
LB alone	81,227 (69,583 to 92,733)	2,275 (−8,864 to 12,519)	2.14 (2.02–2.25)	1.12 (0.99–1.25)	0.02 (−0.10 to 0.13)	0.02 (−0.06 to 0.09)	115,105	122,938
LB as triage test	91,767 (83,511–100,065)	10,539 (4,971–17,561)	2.23 (2.14–2.31)	1.18 (1.06 to– 1.30)	0.09 (0.03–0.16)	0.05 (0.02–0.11)	117,046	175,502
Perfect Reference Standard								
LB alone	81,208 (71,344–91,338)	--	2.13 (2.02–2.23)	1.11 (0.99–1.23)	--	--	--	--
TB alone	83,459 (76,128–91,140)	2,251 (−6,165 to 11,052)	2.18 (2.13–2.23)	1.13 (1.02–1.25)	0.05 (−0.04 to 0.16)	0.02 (−0.04 to 0.09)	42,445	96,258
LB as triage test	93,284 (85,614–101,269)	9,825 (6,445–13,910)	2.24 (2.15–2.32)	1.19 (1.06–1.30)	0.06 (−0.01 to 0.12)	0.07 (0.04–0.12)	157,497	191,578
Liquid Biopsy Retest, Given Negative Result								
TB alone	78,952 (70,825–87,079)	--	2.12 (2.06–2.19)	1.10 (0.98–1.21)	--	--	--	--
LB alone	91,852 (81,589–101,491)	12,899 (3,678–21,031)	2.23 (2.09–2.33)	1.18 (1.05–1.30)	0.10 (−0.02 to 0.08)	0.08 (0.01–0.14)	123,921	164,202
LB as triage test	96,008 (87,830–104,248)	4,156 (1,276–9,525)	2.26 (2.14–2.35)	1.20 (1.07–1.32)	0.03 (0.00–0.08)	0.02 (0.00–0.05)	146,790	209,715
Cost, Sensitivity, and Specificity of Real-Time Polymerase Chain Reaction								
TB alone	81,389 (73,986–88,966)	--	2.14 (2.07–2.20)	1.11 (1.00–1.22)	--	--	--	--
LB alone	83,720 (67,634–96,992)	2,331 (−13,075 to 13,855)	2.17 (2.01–2.30)	1.13 (0.99–1.27)	0.02 (−0.08 to 0.10)	0.02 (−0.08 to 0.10)	70,787	95,038
LB as triage test	93,553 (84,732–102,071)	9,833 (2,633–20,356)	2.24 (2.15–2.33)	1.18 (1.06–1.31)	0.05 (0.00–0.12)	0.05 (0.00–0.12)	135,686	193,573
Cost, Sensitivity, and Specificity of Digital Polymerase Chain Reaction								
TB alone	78,021 (70,358–85, 860)	--	2.09 (2.02–2.15)	1.08 (0.97–1.19)	--	--	--	--

Strategy	Average Cost (95% CrI)	Incremental Cost[a] (95% CrI)	Average Effect (95% CrI)		Incremental Effect[a] (95% CrI)		ICER[a]	
			LY	QALY	LY	QALY	$/LY	$/QALY
LB alone	87,834 (77,856–97,514)	9,813 (1,216–17,514)	2.19 (2.08–2.29)	1.15 (1.03–1.28)	0.10 (0.01–0.18)	0.07 (0.01–0.12)	96,828	137,824
LB as triage test	94,556 (86,405–103,014)	6,722 (3,089–11,690)	2.22 (2.11–2.32)	1.18 (1.05–1.30)	0.03 (−0.01 to 0.09)	0.03 (0.00–0.06)	202,026	246,290
Cost, Sensitivity, and Specificity of Next-Generation Sequencing								
TB alone	77,866 (67,830–87,139)	--	2.11 (2.02–2.19)	1.09 (0.97–1.21)	--	--	--	--
LB alone	87,256 (68,550–101,104)	9,390 (−9,528 to 23,577)	2.18 (1.99–2.32)	1.15 (0.99–1.29)	0.06 (−0.07 to 0.15)	0.06 (−0.07 to 0.15)	126,790	169,983
LB as triage test	94,722 (84,327–103,994)	7,466 (1,273–18,822)	2.24 (2.12–2.34)	1.19 (1.06–1.31)	0.04 (0.00–0.11)	0.04 (0.00–0.11)	125,227	186,187
Costs, Capital Costs (1 New Machine), Maintenance Fees, and Costs of Developing (1) New Test								
TB alone	78,952 (70,825–87,079)	—	2.12 (2.06–2.19)	1.10 (0.98–1.21)	—	—	—	—
LB alone	81,285 (69,640–92,791)	2,333 (−8,804 to 12,573)	2.14 (2.02–2.25)	1.12 (0.99–1.25)	0.02 (−0.06 to 0. 9)	0.02 (−0.06 to 0.09)	118,003	126,029
LB as triage test	91,825 (83,571–100,125)	12,872 (8,126–18,508)	2.23 (2.14–2.31)	1.18 (1.06–1.30)	0.06 (0.02–0.11)	0.06 (0.02–0.11)	142,954	214,351
Costs, Capital Costs (14 New Machines), Maintenance Fees, and Costs of Developing (14) New Tests								
TB alone	78,952 (70,825–87,079)	—	2.12 (2.06–2.19)	1.10 (0.98–1.21)	—	—	—	—
LB alone	82,029 (70,364–93,526)	3,076 (−8,104 to 13,358)	2.14 (2.02–2.25)	1.12 (0.99–1.25)	0.02 (−0.10 to 0.13)	0.02 (−0.06 to 0.09)	155,634	166,220
LB as triage test	92,573 (84,327–100,861)	10,545 (4,973–17,567)	2.23 (2.14–2.31)	1.18 (1.06–1.30)	0.09 (0.03–0.16)	0.06 (0.02–0.11)	117,103	175,589
Osimertinib Costs Identical to Platinum-Based Doublet Chemotherapy								
LB alone	50,489 (45,195–56,215)	—	2.14 (2.02–2.25)	1.12 (0.99–1.25)	—	—	—	—
TB alone	52,026 (46,906–57,543)	1,537 (127–3,231)	2.12 (2.06–2.19)	1.10 (0.98–1.21)	−0.02 (−0.13 to 0.10)	−0.02 (−0.09 to 0.06)	Dominated by LB alone (more costly, fewer LY)	Dominated by LB alone (more costly, fewer QALY)

Strategy	Average Cost (95% CrI)	Incremental Cost[a] (95% CrI)	Average Effect (95% CrI)		Incremental Effect[a] (95% CrI)		ICER[a]	
			LY	QALY	LY	QALY	$/LY	$/QALY
LB as triage test	52,185 (46,897–57,884)	159 (−1,388 to 1,170)	2.23 (2.14–2.31)	1.18 (1.06–1.30)	0.11 (0.04–0.18)	0.08 (0.04–0.12)	15,445[b]	21,589[b]

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; LY, life-years; QALY, quality-adjusted life-years; LB, liquid biopsy; TB, tissue biopsy.

[a]Numbers could appear incorrect because of rounding.

[b]ICER for liquid biopsy as a triage test as compared with liquid biopsy alone. Tissue biopsy alone removed as dominated.

Table A19: Scenario Analysis of Long-Term Results on Probability of Cost-Effectiveness at Various Willingness-to-Pay Values

Scenario	Intervention	Probability of Cost-Effectiveness at Willingness-to-Pay Levels		
		$50,000/QALY	$100,000/QALY	$200,000/QALY
Reference case	Tissue biopsy alone	0.65	0.58	0.09
	Liquid biopsy alone	0.35	0.42	0.09
	Liquid biopsy as triage	0.00	0.00	0.82
Perfect reference standard	Liquid biopsy alone	0.64	0.49	0.00
	Tissue biopsy alone	0.36	0.51	0.37
	Liquid biopsy as triage	0.00	0.00	0.63
Liquid biopsy retest, given negative result	Tissue biopsy alone	0.99	0.99	0.17
	Liquid biopsy alone	0.01	0.01	0.55
	Liquid biopsy as triage	0.00	0.00	0.28
Cost, sensitivity, and specificity for RT-PCR	Tissue biopsy alone	0.63	0.51	0.03
	Liquid biopsy alone	0.37	0.49	0.45
	Liquid biopsy as triage	0.00	0.00	0.51
Cost, sensitivity, and specificity for dPCR	Tissue biopsy alone	0.98	0.96	0.00
	Liquid biopsy alone	0.02	0.04	0.86
	Liquid biopsy as triage	0.00	0.00	0.14
Cost, sensitivity, and specificity for NGS	Tissue biopsy alone	0.87	0.89	0.19
	Liquid biopsy alone	0.13	0.11	0.39
	Liquid biopsy as triage	0.00	0.00	0.42
Costs, capital costs (1 new machine), maintenance fees, and costs of developing (1) new test	Tissue biopsy alone	0.66	0.65	0.59
	Liquid biopsy alone	0.34	0.35	0.41
	Liquid biopsy as triage	0.00	0.00	0.00
Costs, capital costs (14 new machines), maintenance fees, and costs of developing (14) new tests	Tissue biopsy alone	0.72	0.72	0.15
	Liquid biopsy alone	0.28	0.28	0.09
	Liquid biopsy as triage	0.01	0.00	0.76
Osimertinib costs identical to platinum-based doublet chemotherapy	Liquid biopsy alone	0.01	0.00	0.00
	Tissue biopsy alone	0.00	0.00	0.00
	Liquid biopsy as triage	0.99	1.00	1.00

Abbreviations: dPCR, digital polymerase chain reaction; NGS, next-generation sequencing; RT-PCR, real time polymerase chain reaction; QALY, quality-adjusted life-years.

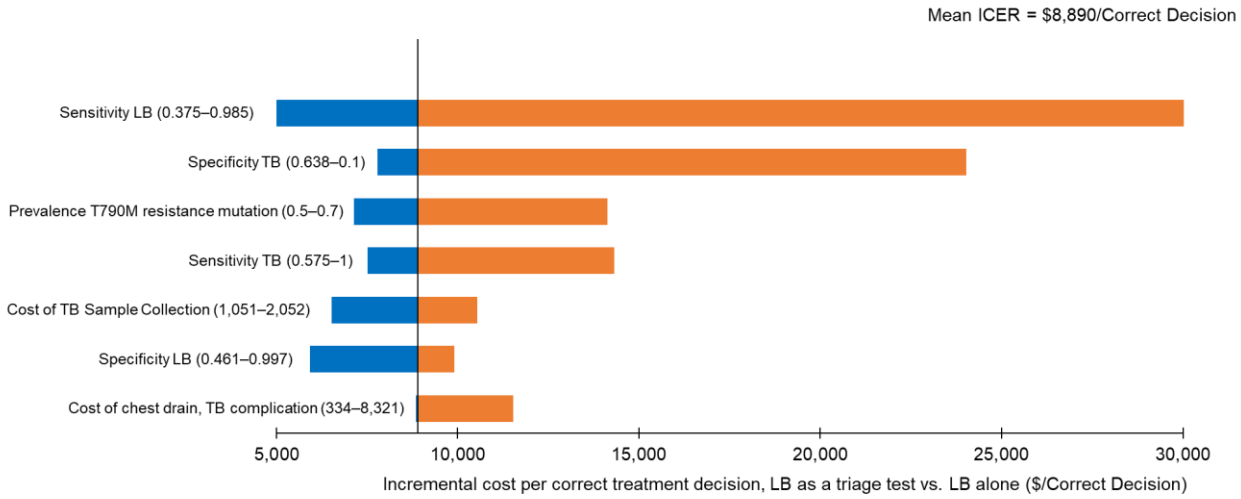

Figure A1: One-Way Sensitivity Analyses (Short Term, Liquid Biopsy as a Triage Test vs. Liquid Biopsy Alone)

Abbreviations: ICER, incremental cost-effectiveness ratio; LB, liquid biopsy; TB, tissue biopsy.
[a]Ranges from positive to negative infinity.

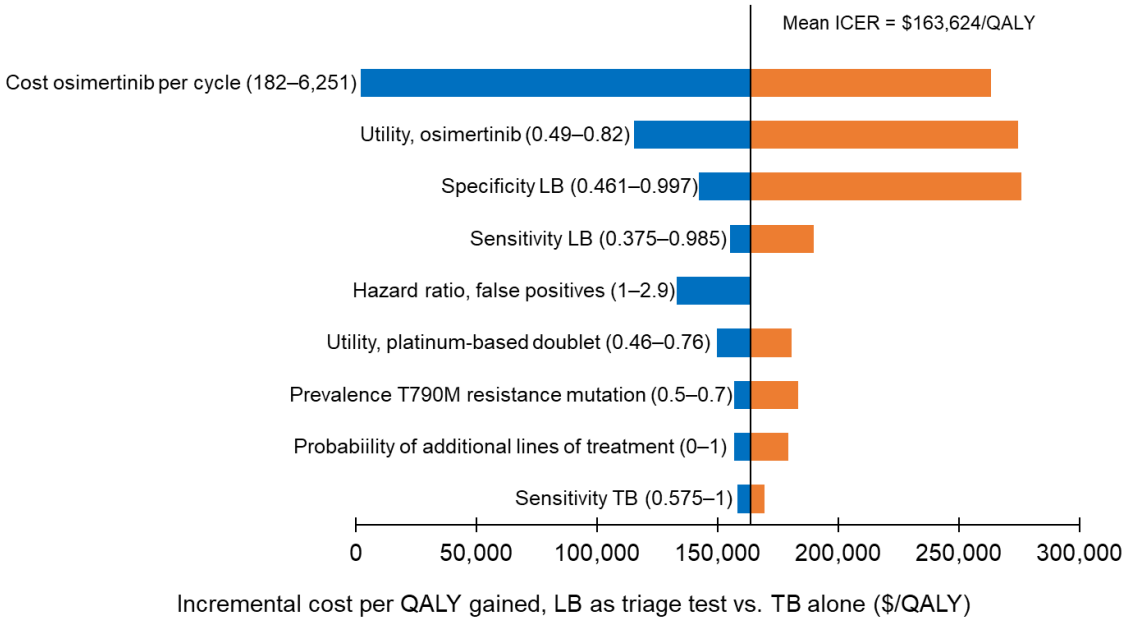

Figure A2: One-Way Sensitivity Analyses (Long Term, Liquid Biopsy as a Triage Test vs. Tissue Biopsy Alone)

Abbreviations: ICER, incremental cost-effectiveness ratio; LB, liquid biopsy; QALY, quality-adjusted life-years; TB, tissue biopsy.

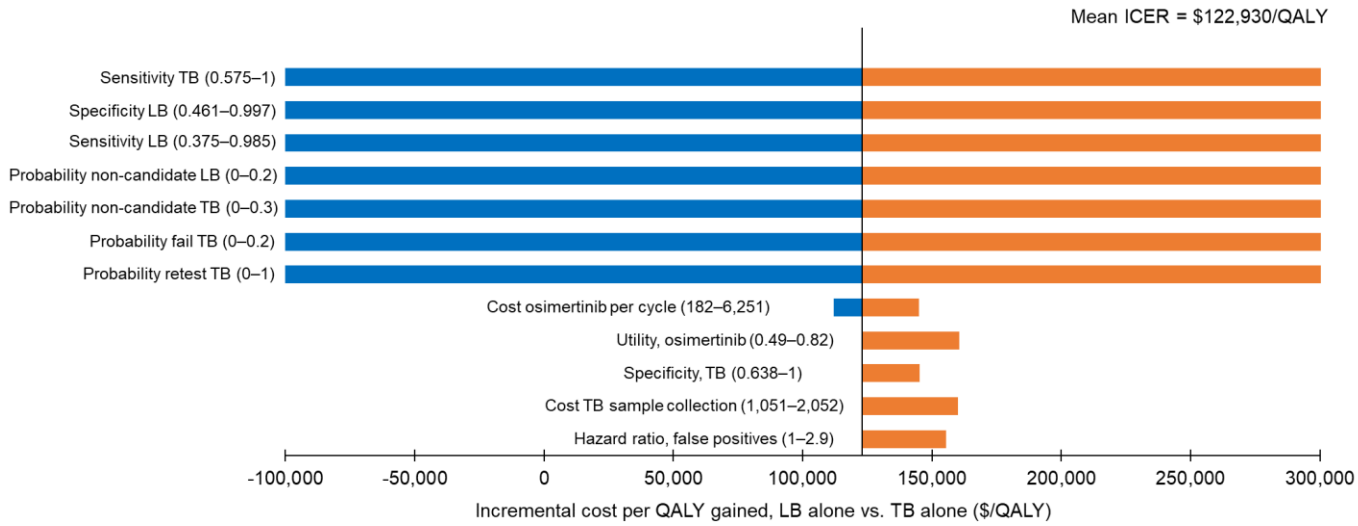

Figure A3: One-Way Sensitivity Analyses (Long Term, Liquid Biopsy Alone vs. Tissue Biopsy Alone)

Abbreviations: ICER, incremental cost-effectiveness ratio; LB, liquid biopsy; QALY, quality-adjusted life-years; TB, tissue biopsy.
[a]Ranges from positive to negative infinity.

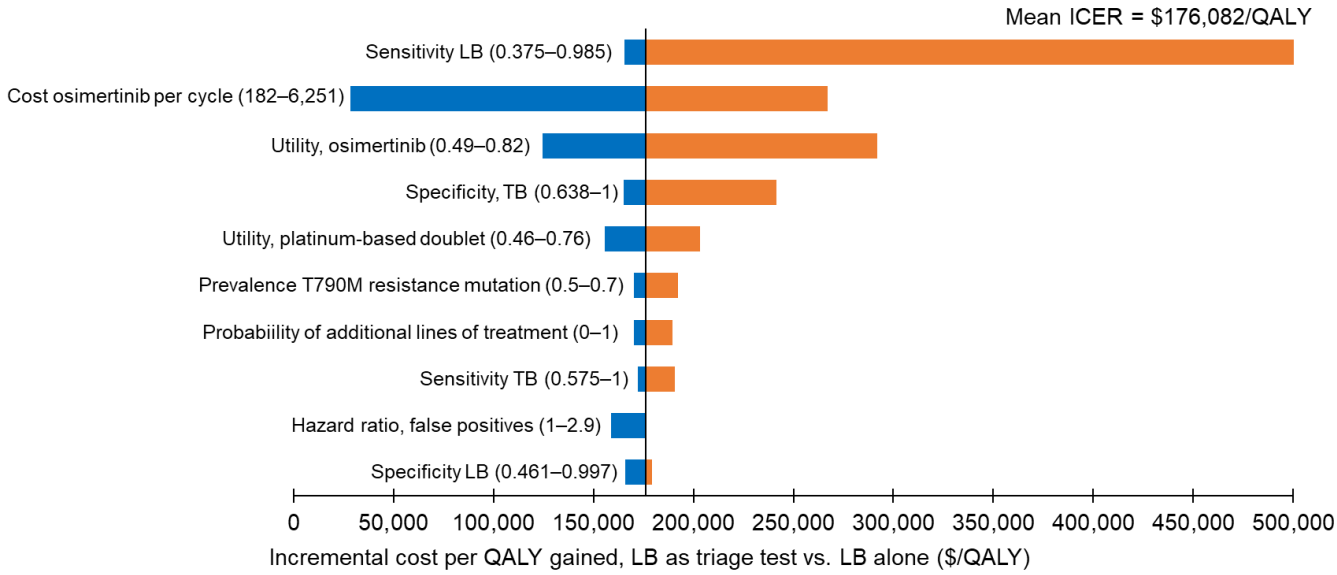

Figure A4: One-Way Sensitivity Analyses (Long Term, Liquid Biopsy as a Triage Test vs. Liquid Biopsy Alone)

Abbreviations: ICER, incremental cost-effectiveness ratio; LB, liquid biopsy; QALY, quality-adjusted life-years; TB, tissue biopsy.

Appendix 8: Budget Impact Analysis

Table A20: Scenario Analysis of Budget Impact Making Assumption of Perfect Reference Standard

Scenario	Budget Impact, $ Million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total Cost of Current Scenario						
Testing costs	1.23	1.23	1.23	1.23	1.23	6.15
Non-testing costs	30.12	46.32	54.20	58.45	60.66	249.74
Total	31.35	47.55	55.43	59.68	61.89	255.90
Total Cost of New Scenario 1 (Liquid Biopsy as Triage Test)						
Testing costs	1.29	1.25	1.21	1.17	1.13	6.03
Non-testing costs	30.12	46.77	55.26	60.23	63.21	255.60
Total	31.40	48.02	56.47	61.40	64.34	261.63
Budget Impact of New Scenario 1 (Liquid Biopsy as Triage Test)						
Testing costs	0.06	0.02	−0.02	−0.06	−0.11	−0.12
Non-testing costs	0.00	0.45	1.07	1.78	2.55	5.85
Total	0.06	0.47	1.04	1.72	2.45	5.73
Total Cost of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	0.92	0.81	0.70	0.59	0.48	3.50
Non-testing costs	27.88	43.05	50.25	54.07	56.03	231.27
Total	28.80	43.86	50.95	54.66	56.51	234.77
Budget Impact of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	−0.31	−0.42	−0.53	−0.64	−0.75	−2.66
Non-testing costs	−2.24	−3.27	−3.95	−4.39	−4.64	−18.48
Total	−2.55	−3.69	−4.48	−5.03	−5.38	−21.13

[a]In 2018 Canadian dollars.
[b]Numbers could appear incorrect because of rounding.

Table A21: Scenario Analysis of Budget Impact Using Upper Estimate for Target Population

Scenario	Budget Impact, $ Million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total Cost of Current Scenario						
Testing costs	4.17	4.17	4.17	4.17	4.17	20.84
Non-testing costs	80.24	124.24	145.12	156.27	162.12	668.00
Total	84.41	128.41	149.29	160.44	166.29	688.83
Total Cost of New Scenario 1 (Liquid Biopsy as Triage Test)						
Testing costs	4.22	4.01	3.81	3.60	3.39	19.03
Non-testing costs	80.24	127.23	152.33	168.48	179.78	708.06
Total	84.46	131.25	156.14	172.07	183.17	727.09
Budget Impact of New Scenario 1 (Liquid Biopsy as Triage Test)						
Testing costs	0.06	−0.15	−0.36	−0.57	−0.78	−1.81
Non-testing costs	0.00	2.99	7.21	12.21	17.66	40.06
Total	0.06	2.84	6.85	11.64	16.88	38.26
Total Cost of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	3.84	3.23	2.63	2.02	1.42	13.15
Non-testing costs	78.25	122.30	143.87	156.13	163.37	663.92
Total	82.09	125.54	146.50	158.15	164.79	677.07
Budget Impact of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	−0.33	−0.93	−1.54	−2.14	−2.75	−7.69
Non-testing costs	−1.98	−1.94	−1.25	−0.14	1.25	−4.07
Total	−2.31	−2.87	−2.79	−2.29	−1.50	−11.77

[a]In 2018 Canadian dollars.
[b]Numbers could appear incorrect because of rounding.

Table A22: Scenario Analysis of Budget Impact for Repeat Liquid Biopsy

	Budget Impact, $ Million[a,b]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Total Cost of Current Scenario						
Testing costs	1.16	1.16	1.16	1.16	1.16	5.82
Non-testing costs	30.26	46.36	54.17	58.37	60.54	249.70
Total	31.43	47.52	55.33	59.53	61.70	255.51
Total Cost of New Scenario 1 (Liquid Biopsy as Triage Test)						
Testing costs	1.25	1.20	1.15	1.11	1.06	5.77
Non-testing costs	30.26	47.10	55.95	61.37	64.87	259.56
Total	31.51	48.30	57.11	62.48	65.93	265.33
Budget Impact of New Scenario 1 (Liquid Biopsy as Triage Test)						
Testing costs	0.09	0.04	−0.01	−0.06	−0.10	−0.05
Non-testing costs	0.00	0.75	1.78	3.00	4.33	9.87
Total	0.09	0.78	1.77	2.95	4.22	9.82
Total Cost ofNew Scenario 2 (Liquid Biopsy Alone)						
Testing costs	1.00	0.90	0.81	0.71	0.62	4.04
Non-testing costs	29.56	45.99	54.48	59.59	62.80	252.42
Total	30.56	46.89	55.29	60.30	63.42	256.46
Budget Impact of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	−0.17	−0.26	−0.36	−0.45	−0.55	−1.78
Non-testing costs	−0.70	−0.36	0.31	1.22	2.26	2.73
Total	−0.87	−0.63	−0.04	0.76	1.71	0.94

[a]In 2018 Canadian dollars.
[b]Numbers could appear incorrect because of rounding.

Table A23: Scenario Analysis of Budget Impact Including Capital Costs (1 New Machine and Test Developed)

	Budget Impact, $ Million[a,b]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Total Cost of Current Scenario						
Testing costs	1.25	1.25	1.25	1.25	1.25	6.23
Non-testing costs	29.15	44.88	52.46	56.54	58.66	241.69
Total	30.40	46.13	53.71	57.78	59.90	247.92
Total Cost of New Scenario 1 (Liquid Biopsy as Triage Test)						
Testing costs	1.47	1.28	1.24	1.20	1.17	6.36
Non-testing costs	29.15	45.42	53.76	58.74	61.84	248.92
Total	30.62	46.70	55.00	59.94	63.01	255.28
Budget Impact of New Scenario 1 (Liquid Biopsy as Triage Test)						
Testing costs	0.22	0.03	0.00	−0.04	−0.08	0.13
Non-testing costs	0.00	0.54	1.30	2.20	3.18	7.23
Total	0.22	0.57	1.30	2.16	3.10	7.36
Total Cost of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	1.09	0.82	0.71	0.61	0.50	3.73
Non-testing costs	27.17	42.18	49.43	53.43	55.67	227.87
Total	28.25	43.00	50.14	54.04	56.17	231.60
Budget Impact of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	−0.16	−0.42	−0.53	−0.64	−0.75	−2.50
Non-testing costs	−1.98	−2.70	−3.04	−3.11	−2.99	−13.82
Total	−2.14	−3.13	−3.57	−3.75	−3.74	−16.32

[a]In 2018 Canadian dollars.
[b]Numbers could appear incorrect because of rounding.

Table A24: Scenario Analysis of Budget Impact Including Capital Costs (14 New Machines and Tests Developed)

	Budget Impact, $ Million[a,b]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Total Cost of Current Scenario						
Testing costs	1.25	1.25	1.25	1.25	1.25	6.23
Non-testing costs	29.15	44.88	52.46	56.54	58.66	241.69
Total	30.40	46.13	53.71	57.78	59.90	247.92
Total Cost of New Scenario 1 (Liquid Biopsy as Triage Test)						
Testing costs	3.66	1.47	1.43	1.40	1.36	9.32
Non-testing costs	29.15	45.42	53.76	58.74	61.84	248.92
Total	32.81	46.89	55.20	60.14	63.20	258.24
Budget Impact of New Scenario 1 (Liquid Biopsy as Triage Test)						
Testing costs	2.42	0.23	0.19	0.15	0.11	3.10
Non-testing costs	—	0.54	1.30	2.20	3.18	7.23
Total	2.42	0.77	1.49	2.35	3.30	10.32
Total Cost of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	3.28	1.02	0.91	0.80	0.69	6.69
Non-testing costs	27.17	42.18	49.43	53.43	55.67	227.87
Total	30.45	43.19	50.34	54.23	56.36	234.56
Budget Impact of New Scenario 2 (Liquid Biopsy Alone)						
Testing costs	2.03	−0.23	−0.34	−0.45	−0.56	0.47
Non-testing costs	−1.98	−2.70	−3.04	−3.11	−2.99	−13.82
Total	0.05	−2.93	−3.37	−3.55	−3.54	−13.35

[a]In 2018 Canadian dollars.
[b]Numbers could appear incorrect because of rounding.

Appendix 9: Letter of Information

LETTER OF INFORMATION

Health Quality Ontario is conducting a review of **Liquid Biopsy** for people who have experience with advanced non-small cell lung cancer or lung cancer. The purpose is to understand whether this test should be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and caregivers with experience with biopsy tests for lung cancer or advanced non-small cell lung cancer. Biopsy can be done either trough tissue and/or liquid biopsy (biopsy by blood). They could have had a biopsy done (tissue and/or liquid), either recently or in the past, and people who could be considering it in the future.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30 minutes of your time for a phone or videoconference
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Health Quality Ontario staff. The interview will last 30 minutes. It will be held over the telephone or videoconference. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about treatment options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project completion, the records will be destroyed.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experience.

IF YOU ARE INTERESTED, PLEASE CONTACT US BEFORE DECEMBER 31, 2018:

Appendix 10: Interview Guide

Introduction
Health Quality Ontario[a] is a provincial advisor to the Ministry of Health. We do a few things for the ministry, but one role we have is to conduct health technology assessments that look at technologies and new health services. We review these technologies and new health services for the consideration for public funding. If any of the questions seem to cause a little emotional distress or make you uncomfortable, please let me know, and you can feel free to either not answer the question or say at little as you like. Having said that, do you have any questions for me?

- History of condition (recurrence of non–small cell lung cancer/lung cancer)
- Experience with non–small cell lung cancer/lung cancer

Lived Experience With Lung Cancer or Advanced Non–Small Cell Lung Cancer With Treatment

- How Is your day-to-day routine?
- What has been the impact and effect on quality of life?
- Did you see any sort of loss of independence?
- Did it have an impact on your family members/caregivers, work, friends? After being diagnosed with lung cancer?

Tissue Biopsy

- How did it meet or not meet your needs? How was it adequate or not adequate?
- What were the adverse effects?
- What were the benefits?
- What were the limitations and barriers?
- Were there issues related to access and knowledge of health care system, etc.?
- Did it meet your needs for treatment?

Liquid Biopsy

- How would it have met your needs? How was it adequate or not adequate?
- How long would you wait to receive it?
- Are you aware of adverse effects?
- Are you aware of the benefits?
- Are you aware of any limitations and barriers?
- Were there issues related to cost, access, knowledge of health care system, etc.?
- Did it meet your needs for treatment?

Treatment After Tissue or Liquid Biopsy

- How did it meet or not meet your needs? How was it adequate or not adequate?
- How long did you have to wait to receive it?
- What were the adverse effects?
- What were the benefits?
- What were the limitations and barriers?
- Were there issues related to cost, access, knowledge of health care system, etc.?

Barriers and Challenges for Both Tissue and Liquid Biopsy

- Did you face any sort of barrier in terms of distance of travel?
- Accessibility of any services?

[a] Health Quality Ontario is now the Quality business unit at Ontario Health.

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This health technology assessment was produced by the Quality business unit at Ontario Health, the government agency that when fully established will be responsible for ensuring all Ontarians receive high-quality health care where and when they need it.

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