ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Plasma-Based Comprehensive Genomic Profiling DNA Assays for Non–Small Cell Lung Cancer

A Health Technology Assessment

MONTH 20XX

Ontario Health

Key Messages

What Is This Health Technology Assessment About?

Non–small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 85% of all cases. Because symptoms are typically mild at first, people are often not diagnosed until an advanced stage. Treatment for NSCLC may involve surgery, systemic therapy (chemotherapy, immunotherapy, or targeted therapy), radiation therapy, or a combination of these approaches.

Some cases of NSCLC are associated with certain genomic alterations (specific genetic or molecular changes) in the DNA of the tumour. Genomic alterations are considered "actionable" when they predict response to treatments known as targeted therapies. For people with actionable genomic alterations, targeted therapies may be more effective than traditional chemotherapy or radiation.

A type of genetic testing called comprehensive genomic profiling can identify actionable genomic alterations in tumour DNA and thus help determine the most effective treatment for a person with NSCLC. In Ontario, this testing is currently done through tissue biopsy (surgically removing a piece of tumour tissue for examination); this is called tissue testing. Plasma-based comprehensive genomic profiling – or liquid biopsy testing – involves taking a blood sample (rather than a tissue sample) to assess for the presence of circulating tumour DNA in the blood. Liquid biopsy testing may offer some advantages over tissue testing.

This health technology assessment looked at the analytical validity, clinical validity, clinical utility, and cost-effectiveness of liquid biopsy testing for people with NSCLC. It also looked at the budget impact of publicly funding this technology and at the experiences, preferences, and values of people with NSCLC.

What Did This Health Technology Assessment Find?

In people with NSCLC, liquid biopsy testing is likely to identify actionable genomic alterations that may be missed by tissue testing or when obtaining a sufficient tissue sample is difficult. Among people testing positive for actionable genomic alterations with liquid biopsy testing, those treated with targeted therapies may have better outcomes than those treated with nontargeted therapies. The sensitivity of liquid biopsy testing varies but generally falls below that of tissue testing.

Using liquid biopsy testing with tissue testing, either in combination or sequentially, would result in increased costs as well as increased life expectancy and health-related quality of life. Of the 4 liquid biopsy testing approaches evaluated, liquid biopsy testing for people with insufficient tissue for tissue testing was associated with the most favourable cost-effectiveness results. We estimate that the 5-year budget impact of publicly funding liquid biopsy testing for people newly diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV) would range from $13.72 million to $134.24 million depending on the testing approach implemented.

People with whom we spoke viewed liquid biopsy testing favourably. Participants appreciated that liquid biopsy testing is noninvasive, and those with experience of both tissue and liquid biopsy testing perceived that the turnaround time for results was quicker for liquid biopsy testing. Barriers to accessing liquid biopsy testing include lack of awareness, cost, and geography. Participants emphasized that implementation should support equitable access.

Acknowledgements

This report was developed by a multidisciplinary team from Ontario Health. The primary clinical epidemiologist was Conrad Kabali, the secondary clinical epidemiologist was Vania Costa, the primary medical librarian was Caroline Higgins, the secondary medical librarian was Corinne Holubowich, the primary health economist was David Rios, the secondary health economist was Yuan Zhang, and the primary patient engagement analyst was Jigna Mistry.

The medical editor was Kara Cowan. Others involved in the development and production of this report were Anisa Shire, Claude Soulodre, Susan Harrison, Sarah McDowell, Chunmei Li, Andrée Mitchell, Charles de Mestral, and Nancy Sikich.

We would like to thank the following people and organizations for lending their expertise to the development of this report:

- Dimitrios Divaris, Grand River Hospital
- Peter Ellis, Hamilton Health Sciences
- Harriet Feilotter, Department of Pathology and Molecular Medicine, Queens University
- Donna Maziak, Division of Thoracic Surgery, Department of Surgery, University of Ottawa
- Aaron Pollett, Ontario Health
- David Stewart, The Ottawa Hospital
- Paul Wheatley-Price, The Ottawa Hospital
- Roche Canada

We also thank our lived experience participants who generously gave their time to share their stories with us for this report.

The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

Citation

TBD

Abstract

Background

Non–small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 85% of all lung cancer cases. Some cases of NSCLC are associated with genomic alterations in the tumour cells that do not respond well to standard therapies but may benefit from targeted therapies. The current standard of care in Ontario involves testing for these actionable genomic alterations via tissue testing alone. However, liquid biopsy testing may complement tissue testing by addressing some of its limitations. We conducted a health technology assessment of liquid biopsy testing for people with NSCLC, which included an evaluation of analytical validity, clinical validity, clinical utility, cost-effectiveness, the budget impact of publicly funding this technology, and 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 the QUADAS-2, QUADAS-C, ROBINS-I, and ROBINS-E tools and the quality of the body 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 a cost–utility analysis of 4 potential liquid biopsy testing strategies in which liquid biopsy testing was added to tissue testing in various ways; our model used a 20-year time horizon and was conducted from a public payer perspective. We also analyzed the budget impact of publicly funding liquid biopsy testing for people with NSCLC in Ontario. To contextualize the potential value of liquid biopsy testing, we spoke with people with NSCLC and family members and care partners of people with NSCLC.

Results

We included 61 studies in the clinical evidence review. Liquid biopsy testing exhibits analytical validity in detecting actionable genomic alterations in certain genes, including *BRAF*, *EGFR*, *ERBB2*, *KRAS* (GRADE: Moderate to High). It improves partial response rates, stable disease rates, and progressive disease rates for people with NSCLC and actionable genomic alterations who are receiving matched targeted therapies (GRADE: Moderate). However, we are uncertain about the clinical validity of liquid biopsy testing in predicting prognosis with standard therapies (GRADE: Very Low). Compared with tissue testing alone, we estimate that all 4 of the potential liquid biopsy testing strategies we evaluated would be more expensive and associated with an increase in quality-adjusted life-years (QALYs). The incremental cost-effectiveness ratio (ICER) of the strategy in which liquid biopsy testing is provided only for people with insufficient tissue for tissue testing ("insufficient tissue") was $96,738 per additional QALY; ICER estimates for the other 3 strategies ("tissue-first," "liquid-first," and "combined") were all higher at $147,636, $157,267, and $173,032, respectively. All 4 potential liquid biopsy testing strategies had a chance of being cost-effective of less than 1% at a willingness-to-pay (WTP) of $50,000 per QALY gained; only the insufficient tissue strategy had a probability of being cost-effective of more than 50% at a WTP of $100,000 per QALY gained. We estimate that the 5-year budget impact of publicly funding the insufficient tissue strategy would be $13.72 million. Publicly funding the other strategies would result in a 5-year budget impact ranging from $110.13 million to $134.24 million. All interview participants viewed liquid biopsy positively. Participants perceived liquid biopsy testing as less invasive than tissue

testing, and those who had undergone both tissue and liquid biopsy testing perceived that the turnaround time for results was quicker for liquid biopsy testing. Barriers to accessing liquid biopsy testing include lack of awareness, cost, and geography.

Conclusions

Liquid biopsy testing has moderate to high sensitivity for detecting actionable genomic alterations in the *BRAF*, *EGFR*, *ERBB2*, and *KRAS* genes (GRADE: Moderate to High) but low sensitivity for the *ALK*, *PIK3CA*, *MET*, *RET*, and *ROS1* genes (GRADE: Low to High). The test has high concordance with tissue testing (87%–99%) but may miss some positive cases. We are uncertain about the clinical validity of liquid biopsy testing in predicting prognosis with standard therapies (GRADE: Very Low). However, we found that targeted therapies improve response rates (GRADE: Moderate) and survival (GRADE: Low) for people with NSCLC and actionable genomic alterations identified through liquid biopsy testing. Compared with tissue testing alone, all 4 potential liquid biopsy testing strategies that we evaluated are more costly but also associated with an increase in QALYs. We estimate that publicly funding liquid biopsy testing for people newly diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV) over 5 years would lead to an additional cost of $134.24 million for the combined strategy, $119.27 million for the liquid-first strategy, $110.13 million for the tissue-first strategy, and $13.72 million for the insufficient tissue strategy. People with NSCLC, family members, and care partners viewed liquid biopsy favourably. Those who had undergone both tissue and liquid biopsy testing perceived that the turnaround time for results was quicker for liquid biopsy testing. Current barriers to accessing liquid biopsy testing include lack of awareness, cost, and geography.

Table of Contents

List of Tables

List of Figures

Objective

This health technology assessment evaluates the analytical validity, clinical validity, clinical utility, and cost-effectiveness of plasma-based comprehensive genomic profiling for non–small cell lung cancer. It also evaluates the budget impact of publicly funding liquid biopsy testing and the experiences, preferences, and values of people with non–small cell lung cancer.

Background

Health Condition

Non–small cell lung cancer (NSCLC) is a type of lung cancer that originates in the epithelial cells (i.e., the cells lining the airways of the lungs). It is the most common form of lung cancer, accounting for about 85% of all cases.[1] NSCLC is generally divided into 3 major subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma is the most prevalent subtype, historically accounting for about 40% of NSCLC cases according to the literature.[2,3] However, clinical experts (Peter Ellis, MD, email communication, April 24, 2023; Paul Wheatley-Price, MD, email communication, May 15, 2023) suggest that the prevalence of adenocarcinoma has increased and that it may now account for up to 65% of cases. This shift is attributed to factors such as reduced tobacco exposure and improved classification of NSCLC subtypes, which has led to a decline in cases classified as "not otherwise specified." Squamous cell carcinoma and large cell carcinoma are less common, comprising about 20% to 30% and 10% to 15% of cases, respectively.[3]

The development of NSCLC is strongly linked to smoking, particularly in cases of squamous cell and large cell carcinoma.[3] However, NSCLC can occur in nonsmokers.[3] While adenocarcinoma is also linked to smoking, the association is not as strong as with squamous cell and large cell carcinoma. Other risk factors for NSCLC include exposure to second-hand smoke and air pollution and occupational exposure to certain chemicals.[3]

NSCLC is often diagnosed through a combination of imaging tests and biopsy procedures (in which cells or tissue are removed for examination). Imaging tests such as computed tomography (CT) scans, combination positron emission tomography (PET)–CT scans, and magnetic resonance imaging (MRI) can be used to detect the presence of a tumour and assess its size and location, as well as to identify whether the cancer has spread to other parts of the body.[3] If imaging tests suggest the presence of lung cancer, a biopsy may be performed to confirm the diagnosis and determine the specific type of cancer.[3] Once a diagnosis of NSCLC has been confirmed, further testing may be done to assess the stage of the cancer and guide treatment decisions.[3] In cases where the cancer has spread beyond the lungs, additional biopsies or imaging tests may be necessary to determine the extent of the disease.

NSCLC is staged based on the extent to which the cancer has spread within the lung or metastasized (i.e., spread to other parts of the body). The most commonly used staging system is the TNM system, which takes into account the size and location of the primary tumour (T), the involvement of nearby lymph nodes (N), and the presence of distant metastases (M).[4] Stage I NSCLC is characterized by a small tumour that has not spread beyond the lung tissue. In stage II, the tumour may be larger, and the cancer has spread to nearby lymph nodes. In stage III, the tumour may again be larger, and the cancer has

spread to lymph nodes in the mediastinum (i.e., the space in the chest that holds the heart, esophagus, thymus, and trachea) or other nearby structures. In stage IV, the most advanced stage, the cancer has spread to distant organs or tissues; a malignant pleural or pericardial effusion (i.e., a build-up of fluid and cancer cells in the lining around the lungs or heart) may be present; and the cancer may have metastasized to the other lung. Clinical stage is initially determined based on biopsy and imaging test results. However, staging can be revised following the examination and analysis of surgically removed tumour tissue and associated lymph nodes by a pathologist (i.e., a clinician specializing in identifying diseases by studying cells and tissues under a microscope).[5]

Treatment for NSCLC may involve surgery, systemic therapy (i.e., chemotherapy, immunotherapy, or targeted therapy), radiation therapy, or a combination of these approaches, depending on the stage of the cancer and the person's overall health.[3]

Genomic Alterations

In addition to the traditional risk factors associated with NSCLC, recent studies have shown that a subset of NSCLC cases harbour specific genomic alterations (i.e., specific genetic or molecular changes) in the DNA of the tumour that contribute to tumour growth and survival.[6,7] These alterations include mutations (i.e., changes in genetic sequencing) in genes such as *ALK*, *BRAF*, *EGFR*, and *ROS1*, among others.[7] The presence of genomic alterations can affect treatment decisions for 2 reasons: (1) treatments known as targeted therapies have been developed to target certain genomic alterations, and these may be more effective than traditional chemotherapy or radiation for people with such alterations, and (2) immunotherapy can be ineffective in people with certain genomic alterations.[7] Genetic testing for people with NSCLC can determine whether these alterations are present and thus help guide treatment decisions.[8]

Clinical Need and Population of Interest

NSCLC represents a substantial health burden both globally and in Canada. Worldwide, lung cancer is the leading cause of cancer-related deaths, accounting for an estimated 1.8 million deaths annually.[9] In Canada, lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths, accounting for about 24% of all cancer deaths in the country.[10] Within Canada, Ontario has one of the highest rates of lung cancer incidence and mortality.[11]

According to Ontario Health (Cancer Care Ontario), an estimated 10,639 new cases of lung cancer were projected to occur in Ontario in 2022,[12] representing about 11% of all new cancer diagnoses in the province. Lung cancer incidence rates are highest among older adults, with most cases developing in people over the age of 50 years.[13] Lung cancer accounts for about 25% of all cancer deaths in Ontario and was responsible for an estimated 6,908 deaths in 2022 alone.[14,15] (At the time of writing, Ontario Health [Cancer Care Ontario] had not yet released official figures for the number of deaths that occurred in 2023.) Between 1991 and 2010, lung cancer rates in Ontario were highest among First Nations communities, with relative risks 1.19 times higher for males and 1.47 times higher for females compared with the general population.[16] About 29% to 60% of NSCLC cases harbour at least 1 actionable genomic alteration.[17-19]

The burden of NSCLC is exacerbated by its high rate of recurrence and relatively low survival rate, particularly in advanced stages of the disease. About 50% of lung cancer cases are diagnosed at stage IV, when the cancer is typically deemed incurable. Despite the progress made in treatment options, the

5-year survival rate for lung cancer following diagnosis remains relatively low and is about 22% in Canada.[20]

Current Testing Options

In Ontario, tissue-based comprehensive genomic profiling – referred to as "tissue testing" throughout this report – is currently the standard of care to identify actionable genomic alterations (i.e., genomic alterations that predict response to targeted therapies).[8] Thus, tissue testing is essential to determining a person's treatment options, whether targeted therapy, immunotherapy, chemotherapy, or a combination of approaches. It involves analyzing samples of tumour tissue obtained through fine-needle aspiration, core biopsy, or surgical tumour resection to identify specific genomic alterations using what is referred to as a next-generation sequencing (NGS) assay.

NGS assays offer several advantages over testing for single or just a few genomic alterations. They allow for the simultaneous analysis of multiple genes and genomic regions, providing a more comprehensive picture of the genetic landscape of a person's cancer,[21] thus identifying a wider range of actionable genomic alterations that can be targeted by specific therapies.[21,22] DNA panels are typically used to identify mutations, whereas RNA panels are employed to detect fusions or transcriptional changes. NGS assays can also detect less common genomic alterations that may not be detected when testing for single or just a few gene alterations.[23] Additionally, relying on limited gene panels can result in overlooking a substantial proportion of actionable genomic alterations.[22] However, tissue testing can sometimes be challenging because of difficulties in obtaining an adequate tissue sample or preserving tissue, and it may not be feasible for people who are not candidates for tissue biopsy procedures (i.e., those with substantial comorbidities, small tumours, or tumours in difficult-to-reach locations).[21] It is estimated that such difficulties affect the ability to obtain an adequate tissue biopsy in up to 30% of NSCLC cases.[24]

Actionable Genomic Alterations Identified in NSCLC

The following represents a compilation of actionable genomic alterations identified in NSCLC.[25] However, it is important to note that this list is continuously evolving, and additional alterations may have been discovered since the time of writing.

ALK Alterations

ALK alterations involve rearrangements, mutations, and amplifications of the *ALK* gene.[26] Rearrangements such as *EML4–ALK* fusion create chimeric fusion proteins with constitutive *ALK* kinase activity: a defect in which a cellular signaling pathway or protein is continuously activated independently of normal regulatory signals. Mutations such as L1196M and G1269A result in constitutive activation of ALK signaling pathways. *ALK* amplifications lead to overexpression of ALK receptor tyrosine kinase, driving tumour growth and metastasis. The prevalence of *ALK* alterations in NSCLC ranges from 2% to 7%.[27]

BRAF Alterations

BRAF alterations encompass a variety of mutations, including the well-known V600 mutations, as well as amplifications of the *BRAF* gene.[28] These mutations and amplifications can lead to dysregulated *BRAF* kinase activity, resulting in abnormal MAPK signaling and tumour growth. *BRAF* mutations, such as the V600 mutations, lead to constitutive activation of the *BRAF* kinase, whereas *BRAF* amplifications cause

overexpression of the BRAF protein, driving aberrant *BRAF* signaling pathways. *BRAF* mutations occur in 1% to 5% of NSCLC cases.[29]

EGFR Alterations

EGFR mutations and amplifications are common oncogenic drivers in NSCLC (i.e., alterations responsible for initiating and maintaining the cancer).[30] Among these genetic alterations, exon 19 deletions and exon 21 L858R mutations are the most common.[31] These 2 alterations lead to the constitutive activation of *EGFR* signaling pathways. *EGFR* amplifications result in overexpression of EGFR receptor tyrosine kinase, thereby promoting aberrant signaling and tumour progression. *EGFR* mutation represents one of the most frequently observed alterations in NSCLC, occurring in about 20% to 25% of cases.[19] In Canada, *EGFR* mutations are identified in about 15% of all lung cancer cases.[31]

ERBB2 Alterations

ERBB2 alterations include amplifications and mutations.[32] *ERBB2* amplifications result in overexpression of the *HER2* protein, thereby promoting aberrant *HER2* signaling and tumour growth. *ERBB2* mutations, particularly exon 20 insertions, activate the *HER2* kinase domain, driving oncogenic signaling pathways (i.e., a process that contributes to cancer growth). The prevalence of *ERBB2* mutations in NSCLC in Europe and the United States ranges from 1% to 3%.[33]

FGFR1 Alterations

FGFR1 alterations involve amplifications and fusion events.[34] *FGFR1* amplifications lead to overexpression of the FGFR1 protein, resulting in aberrant *FGFR1* signaling and tumour progression. Fusion events create chimeric fusion proteins with constitutive *FGFR1* kinase activity, contributing to tumour growth. Squamous cell lung carcinoma exhibits the highest frequency of *FGFR1* amplification, accounting for about 9% of cases, compared with lung adenocarcinoma, in which all types of *FGFR* abnormalities account for about 4% of cases.[35]

KRAS Alterations

KRAS alterations primarily consist of mutations affecting codons 12 and 13.[36] Mutations such as G12C, G12D, G12V, and G13D result in constitutive activation of the *KRAS* protein, promoting tumour growth and metastasis. *KRAS* is the most frequently mutated oncogene (i.e., a gene with the potential to cause cancer if mutated) in NSCLC, with a prevalence of about 30%.[36]

MET Alterations

MET alterations include amplifications, exon 14 skipping mutations, and gene fusions.[37] *MET* amplifications lead to overexpression of MET receptor tyrosine kinase, resulting in tumour progression. Exon 14 skipping mutations and gene fusions result in constitutive activation of *MET* signaling pathways, driving tumour growth. *MET* exon 14 skipping mutations are detected in 2% to 4% of lung adenocarcinoma cases.[38]

NRG1 Alterations

NRG1 alterations involve gene fusions.[39] The most common fusion variant is *CD74–NRG1*, which involves the fusion of the *CD74* and *NRG1* genes. Other less common variants are *TMPRSS2–NRG1* and *SQSTM1–NRG1*.

NTRK1, *NTRK2*, and *NTRK3* Alterations

NTRK alterations involve gene fusions.[40] Rearrangements create chimeric fusion proteins with constitutive *NTRK* kinase activity, driving tumour growth. *NTRK* fusions occur in about 0.1% to 1% of NSCLC cases.[41]

PIK3CA Alterations

PIK3CA alterations include mutations affecting hotspot regions within the *PIK3CA* gene.[42] Hotspot mutations, like H1047R and E545K, activate the *PI3K* signaling pathway, driving tumour growth. The prevalence of PIK3CA mutations in NSCLC is estimated at 3.7%.[43]

RET Alterations

RET alterations consist of rearrangements, mutations, and amplifications.[44] Rearrangements such as *KIF5B–RET* fusion create chimeric proteins with constitutive *RET* kinase activity. Mutations like M918T and C634R activate *RET* signaling pathways. Amplifications lead to overexpression of RET receptor tyrosine kinase, driving tumour growth. RET rearrangements occur in about 1% of NSCLC cases.[45]

ROS1 Alterations

ROS1 alterations primarily consist of rearrangements,[46] resulting in the fusion of the *ROS1* gene with various partners such as the *CD74*, *SLC34A2*, *SDC4*, and *TPM3* genes. These fusions activate *ROS1* signaling pathways, contributing to tumour growth. While less common, point mutations and amplifications of *ROS1* have also been reported.[47,48] *ROS1* rearrangements are found in 0.9% to 2.6% of NSCLC cases.[49]

Figure 1 provides a high-level summary of the current clinical pathway in Ontario for testing for actionable genomic alterations in people newly diagnosed with NSCLC.

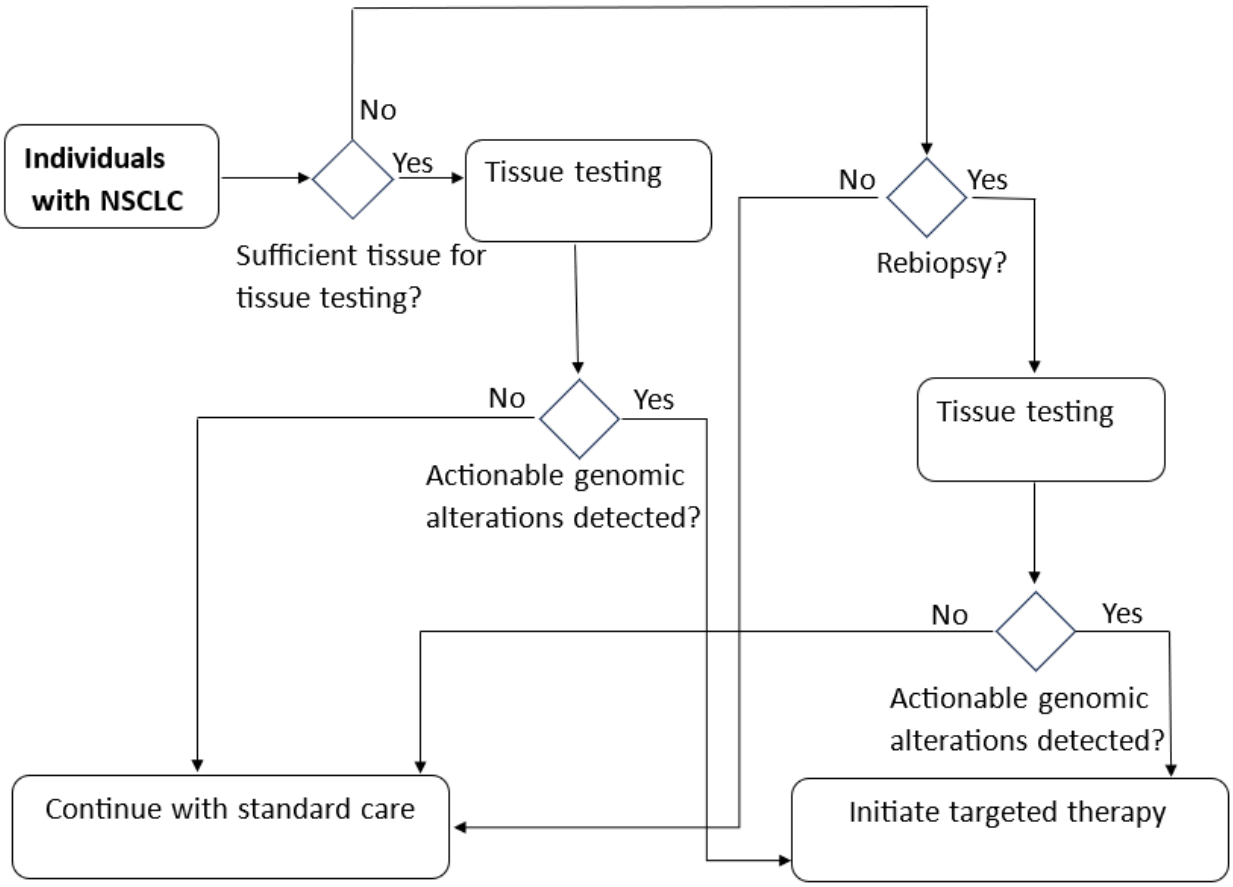

Figure 1: Streamlined Clinical Pathway for Tissue Testing to Identify Actionable Genomic Alterations in People With NSCLC in Ontario

Health Technology Under Review

Tissue testing has traditionally been the standard method of identifying actionable genomic alterations in NSCLC. In Ontario, Ontario Health (Cancer Care Ontario) is currently funding tissue testing on a selection of biomarkers in a testing strategy called reflex testing in which additional diagnostic tests are automatically ordered based on the results of a primary test; this procedure is available at 9 sites across the province (Table 1).[8] However, the tissue testing procedure is time-consuming, involves invasive biopsy extraction, and can sometimes fail to capture the heterogeneity of the tumour.[21,50] Further, not all laboratories have the equipment or expertise to analyze tissue biopsy samples, which leads to further delays when samples must be shipped to laboratories where testing can be done (Donna Maziak, MD, email communication, April 16, 2023). It is worth noting that this limitation is not exclusive to tissue testing.

Table 1: Biomarkers Included in the Reflex Testing Strategy Funded by Ontario Health (Cancer Care Ontario) for People Newly Diagnosed With NSCLC

Test indication[a]	Biomarkers[b]	Testing sites
Reflex testing on newly diagnosed cases of NSCLC (adenocarcinoma or nonsquamous)	*ALK*, *BRAF*, *EGFR*, *FGFR1*, *HER2 (ERBB2)*, *KRAS*, *MET* (*MET* skipping), *NTRK1*, *NTRK2*, *NTRK3*, PD-L1, *PIK3CA*, *RET*, *ROS1* Optional: *KEAP1*, *NRG1*, *STK11*, *TP53*	Hamilton Health Sciences/ St. Joseph's Healthcare Hamilton Health Sciences North Kingston Health Sciences Centre London Health Sciences Centre Sunnybrook Health Sciences Centre The Ottawa Hospital Trillium Health Partners – Credit Valley Hospital University Health Network William Osler Health System

[a]Although this funded reflex testing is intended for people with adenocarcinoma or nonsquamous NSCLC, some of the included genes, such as *KRAS*, *KEAP1*, and *TP53*, are involved in both nonsquamous and squamous NSCLC.[51] Large cell NSCLC is not specifically associated with any of the included genes.

[b]*KEAP1*, PD-L1, *STK11,* and *TP53* are not considered actionable genomic alterations. PD-L1 is a protein encoded by the *CD274* gene. It is often used as a biomarker to predict response to immunotherapy but is not a genomic alteration that can be targeted with specific drugs.[52,53] *KEAP1, STK11*, and *TP53* are tumour-suppressor genes that are frequently mutated in cancer, but they are not yet considered actionable genomic alterations because there are currently no targeted therapies available for these mutations.

In recent years, plasma-based comprehensive genomic profiling – referred to as "liquid biopsy testing" throughout this report – has emerged as a promising alternative to tissue testing or as a complementary method of identifying actionable genomic alterations in NSCLC.[21] This technology involves purifying fragments of circulating tumour DNA (ctDNA) that have been released into the bloodstream by tumour cells that have undergone apoptosis or necrosis (i.e., cell death)[21] and then using that DNA as an input for an NGS assay. It is estimated that about 0.01% to 10% of tumour cells shed their DNA into the bloodstream.[54] However, the exact percentage can vary widely depending on factors such as tumour size, stage, and molecular characteristics.[55] Liquid biopsy testing is minimally invasive and a more accessible approach to identifying actionable genomic alterations than tissue testing.[21] However, liquid biopsy testing may fail to identify tumour DNA in some cases, for example, when there is insufficient ctDNA in the bloodstream or owing to the technical limitations of the test.[56,57] Assessing the ctDNA tumour fraction helps estimate the proportion of ctDNA in a cell-free DNA sample, thereby aiding in evaluating the sensitivity of ctDNA genomic profiling and providing oncologists with confidence in the results of liquid biopsy testing.[58]

Both tissue testing and liquid biopsy testing can detect several types of genomic alterations, including single nucleotide variants (SNVs), small insertions and deletions (indels), copy number alterations (CNAs), and gene rearrangements.[21] These alterations can be used to identify therapeutic targets, predict response to therapy, and monitor disease progression.

Although recurrent actionable fusions can be detected with a well-designed DNA assay,[59] gene rearrangements are commonly detected using RNA.[60] Currently, the availability and accuracy of liquid biopsy assays for circulating tumour RNA are uncertain.[61] This report focuses solely on DNA-based liquid biopsy testing to guide targeted therapies in NSCLC.

Several commercial and laboratory-based assays are available for liquid biopsy testing in NSCLC. These assays use hybrid capture techniques in combination with NGS – referred to as "hybrid capture-based

targeted sequencing" – to detect and interrogate ctDNA.[21] Three commercially available assays are the following:

- FoundationOne Liquid CDx (Foundation Medicine): This assay can detect alterations in 300 genes, including *EGFR*, *ALK*, *ERBB2*, *PIK3CA*, *NTRK1*, *NTRK2*, *NTRK3*, *ROS1*, *BRAF*, *MET*, and *RET*, and can detect SNVs, indels, CNAs, and gene rearrangements. The assay has a limit of detection of 95% for samples with a variant allele frequency (VAF) as low as 0.4% for certain SNVs and 0.37% for certain gene rearrangements. For certain CNAs, the assay can detect a tumour fraction of 21.7%[62]
- Guardant360 (Guardant Health): This assay can identify alterations in 74 genes, including NSCLC-associated genes such as *EGFR*, *ALK*, *ROS1*, *KRAS*, *HER2* (*ERBB2*), *PIK3CA*, *BRAF*, *MET*, *NTRK1*, *NTRK2*, *NTRK3*, and *RET*. It can detect SNVs, indels, CNAs, and gene rearrangements and has a reported limit of detection of ≥ 95% for samples with a VAF as low as 0.2% for certain SNVs, indels, and gene rearrangements and as low as 2.3 copies for certain CNAs[63]
- Tempus xF (Tempus): This assay covers 105 genes, including *EGFR*, *ALK*, *ROS1*, *BRAF*, *KRAS*, *NTRK1*, *MET*, *ERBB2*, *PIK3CA*, and *RET*, and can detect SNVs, indels, CNAs, and gene rearrangements. The reported limit of detection based on a DNA quantity of 30 ng is 100% for samples with a VAF as low as 0.5% for specific SNVs, 96% for samples with a VAF of 0.5% for certain indels, 100% for samples with a VAF of 0.5% for certain CNAs, and 90% for samples with a VAF of 1% for specific gene rearrangements[64]

Although the number of genes detected varies across these assays, all are capable of identifying most or all actionable genomic alterations included in the biomarkers tested for in the reflex testing strategy funded by Ontario Health (Cancer Care Ontario) (see Table 1). In addition to commercial assays, laboratory-based assays developed in house can also be used to test for actionable genomic alterations and can be tailored to the specific needs of each patient.[21]

Of note, Imagia Canexia Health, the Canadian-based company that created the Follow It assay, filed for bankruptcy on August 21, 2023, and was liquidated on August 28, 2023.[65]

As mentioned, liquid biopsy testing may fail to identify actionable genomic alterations in certain cases, for example, when there is an insufficient release of ctDNA into the bloodstream or when metastases are isolated within the brain. To address this issue, some guidelines recommend using liquid biopsy testing in conjunction with tissue testing, which can identify actionable genomic alterations that liquid biopsy testing may miss, as is estimated to occur in 15% to 30% of cases.[21] Performing liquid biopsy testing at the same time as tissue testing may also be useful for people whose tissue testing results are inconclusive. This dual approach may also reduce the turnaround time for results; if a person were to undergo both tests sequentially, the wait would be about 4 weeks for tissue testing results, followed by another 1 to 2 weeks for liquid biopsy testing results (Peter Ellis, MD, telephone communication, February 17, 2023; David Stewart, MD, telephone communication, March 6, 2023). Reducing the time to receive results is critical in this patient population because patients may deteriorate or become untreatable while awaiting results (David Stewart, MD, telephone communication, March 6, 2023). However, tumour biopsy remains necessary to determine histology and PD-L1 expression levels, which are important considerations in determining the most effective treatment (Peter Ellis, MD, email communication, March 25, 2024). Thus, the combined approach is believed to provide a more

comprehensive understanding of the tumour, improve test accuracy, and reduce scheduling and turnaround time.

Besides its complementary role, liquid biopsy testing is also sometimes considered an initial approach ("liquid-first") to biomarker evaluation at diagnosis and to monitor the effectiveness of targeted therapies.[21]

Figures 2 to 5 illustrate 4 clinical pathway scenarios for combined tissue and liquid biopsy testing in a hypothetical setting where liquid biopsy testing is widely accessible.

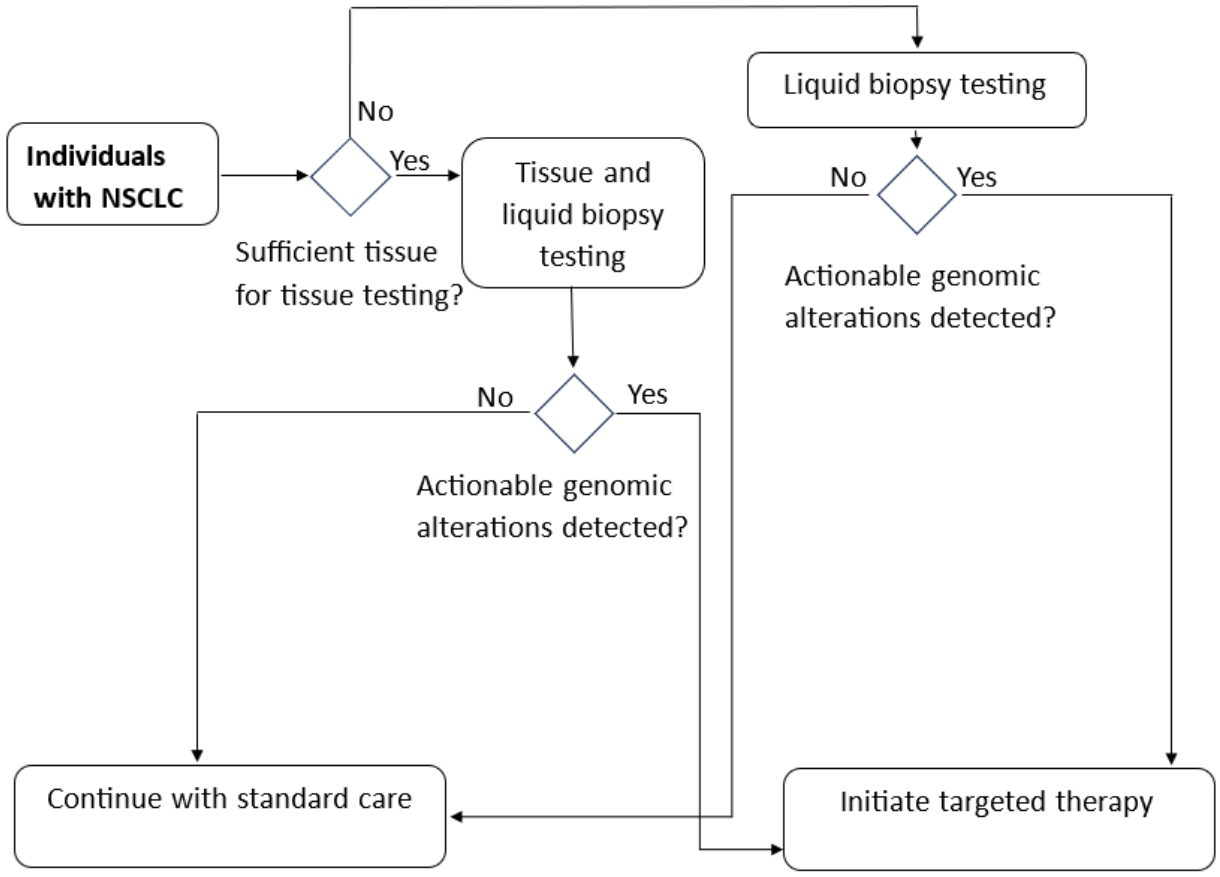

Figure 2: Scenario 1 – Hypothetical Clinical Pathway for a Simultaneous Approach to Combined Tissue and Liquid Biopsy Testing

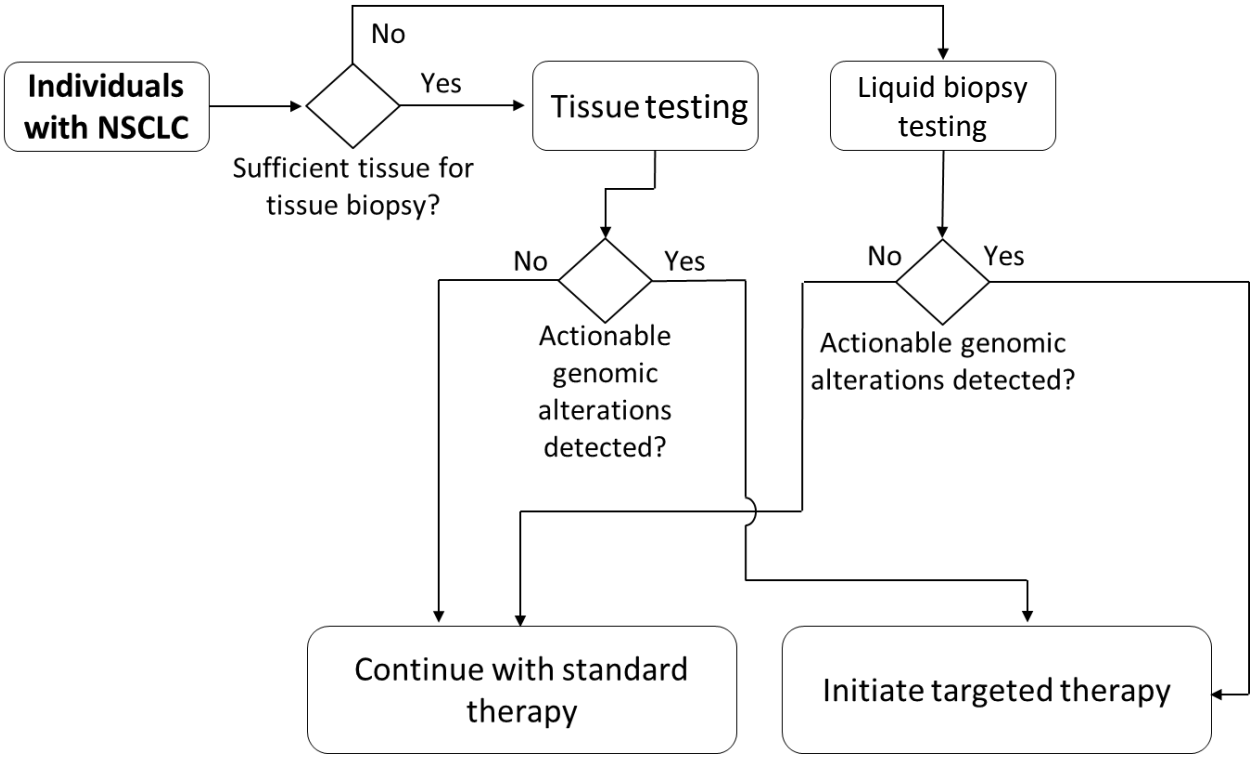

Figure 3: Scenario 2 – Hypothetical Clinical Pathway for a "Tissue-First" Approach to Combined Tissue and Liquid Biopsy Testing

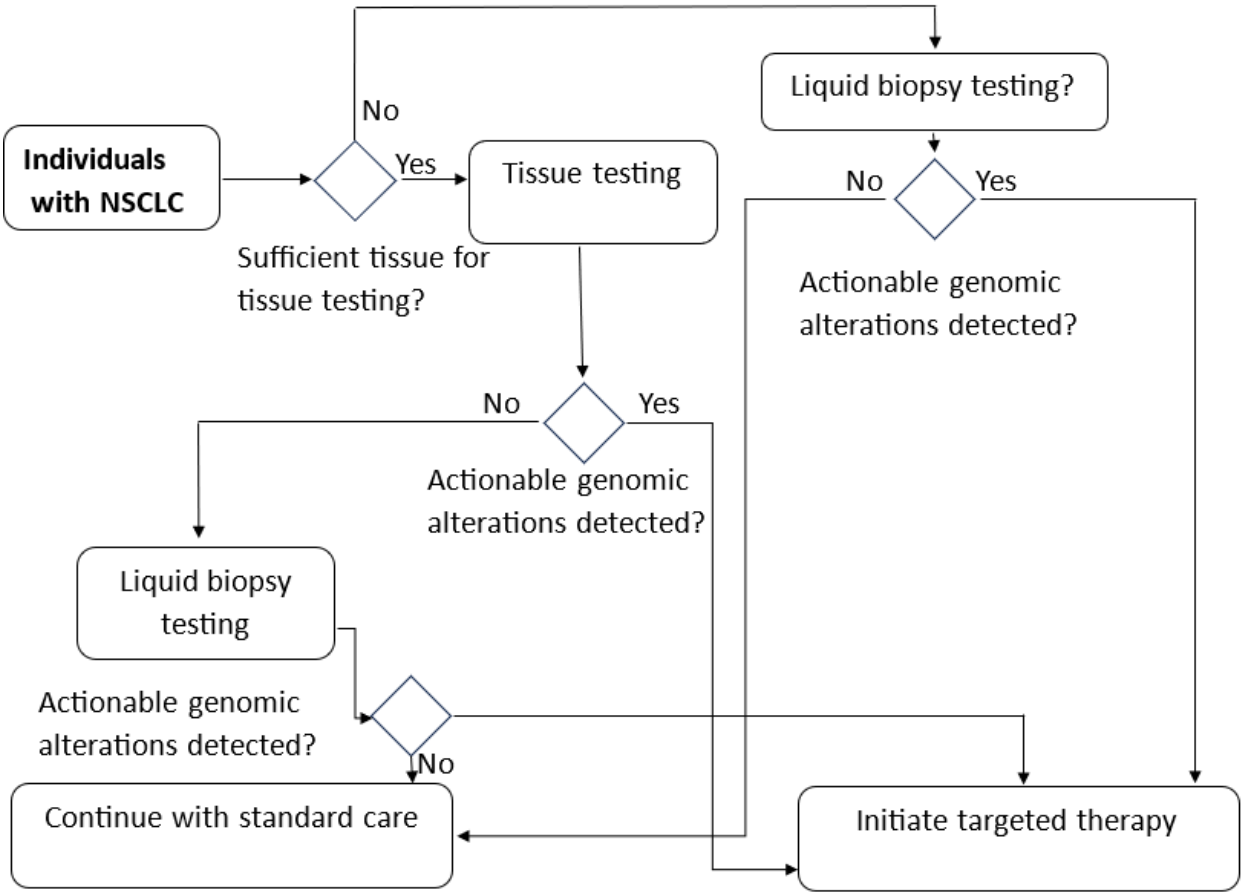

Figure 4: Scenario 3 – Alternative Hypothetical Clinical Pathway for a "Tissue-First" Approach to Combined Tissue and Liquid Biopsy Testing

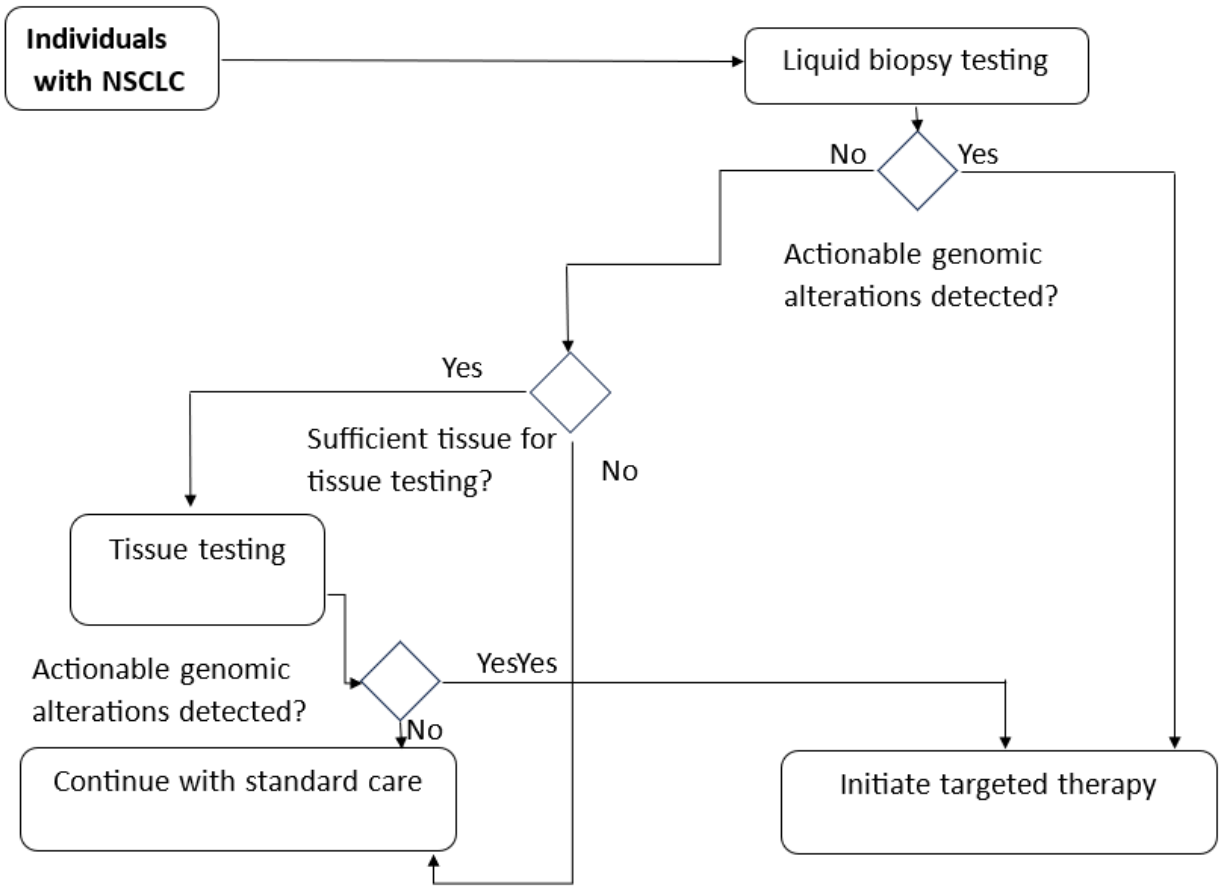

Figure 5: Scenario 4 – Hypothetical Clinical Pathway for a "Liquid-First" Approach to Combined Tissue and Liquid Biopsy Testing

Regulatory Information

To be used in Canada, pharmacogenomic testing (used to examine a person's DNA to predict their response to certain medications) must be licensed for sale in Canada or be authorized by Health Canada for investigational testing.[66] This requirement applies when test results are intended for diagnostic purposes, for patient management, or to support a clinical trial application or drug submission to Health Canada.[66] However, assays to detect actionable genomic alterations are not classified as pharmacogenomic tests (Harriet Feilotter, PhD, email communication, March 28, 2024). Unlike pharmacogenomic tests, which directly examine the enzymes involved in drug metabolism, assays for detecting actionable genomic alterations focus on different aspects of molecular analysis and are therefore not subject to the same regulatory requirements (Harriet Feilotter, PhD, email communication, March 28, 2024). In the case of laboratory-developed tests targeting certain genes for specific indications, provincial licensing approval is necessary. For commercial tests ordered in Canada but conducted in laboratories outside the country, neither federal nor provincial approval is required.

Imagia Canexia Health secured a Health Canada licence for its Follow It assay (MDEL no. 21008), whereas the FoundationOne Liquid CDx assay (developed by the Massachusetts-based Foundation

Medicine and marketed in Canada by Roche Canada) and the Guardant360 assay (developed by the California-based Guardant Health) have been granted licences by the US Food and Drug Administration.

Ontario and Canadian Context

At present, liquid biopsy testing for NSCLC is not publicly funded in Ontario. Thus, people must pay out of pocket or seek alternative insurance coverage. Because the FoundationOne Liquid CDx, Guardant360, and Tempus xF assays were developed in the United States, samples taken via these assays in Canada must be sent to US labs for analysis (Guardant Health, telephone communication, February 6, 2023; Roche Canada, telephone communication, September 8, 2023; Tempus, telephone communication, February 2, 2023).

According to the 2023 US National Comprehensive Cancer Network (NCCN) guidelines, liquid biopsy testing should not replace tissue testing.[67] However, the guidelines suggest considering liquid biopsy testing in certain clinical situations, including when a person is not medically fit for invasive tissue sampling, when there is not enough material for molecular analysis following pathologic confirmation of an NSCLC diagnosis, when tissue testing does not fully evaluate all recommended biomarkers because of limited tissue quantity, or when the timeliness of tissue testing is uncertain in the initial diagnostic setting. In contrast, in 2021, the International Association for the Study of Lung Cancer endorsed the use of liquid biopsy testing, suggesting it not only as a complement to tissue testing but also as a viable initial ("liquid-first") strategy to assess biomarkers at the point of diagnosis and to monitor the effectiveness of targeted therapies.[21] To the best of our knowledge, there are currently no Canadian-specific guidelines available regarding the application of liquid biopsy testing in the management of NSCLC.

Although several targeted therapies exist for cases of NSCLC with the actionable genomic alterations tested for in the reflex testing strategy funded by Ontario Health (Cancer Care Ontario) (see Table 1), only a subset are currently publicly funded in Ontario (Table 2).

In 2020, the Ontario Health Technology Advisory Committee recommended publicly funding liquid biopsy testing as a triage test to detect the *EGFR* T790M mutation in people with NSCLC who have relapsed after previous treatment with a tyrosine kinase inhibitor.[68]

Table 2: Targeted Therapies for the Genomic Alterations Tested for in the Reflex Testing Strategy Funded by Ontario Health (Cancer Care Ontario)

Gene	Drugs[a]	Drugs available for use in Canada[a,b]
ALK	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib (all *ALK* inhibitors)	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
BRAF	Dabrafenib (*BRAF* inhibitor) + trametinib (*MET* inhibitor)	Dabrafenib,[c] trametinib[c]
EGFR	Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib (all *EGFR* tyrosine kinase inhibitors)	Afatinib, dacomitinib,[d] erlotinib, gefitinib, osimertinib
ERBB2	Pertuzumab, trastuzumab, xenocutuzumab (all *HER2* inhibitors) + docetaxel or paclitaxel (microtubule inhibitors), trastuzumab deruxtecan	Docetaxel, paclitaxel,[d] pertuzumab, trastuzumab[d]
FGFR1	Debio 1347, infigratinib, (both *FGFR* inhibitors)	None
KRAS	Adagrasib (*KRAS G12D* inhibitor), sotorasib (*KRAS G12C* inhibitor)	Sotorasib[e,f]
MET (MET skipping*)*	Capmatinib, crizotinib, savolitinib, tepotinib (all *MET* inhibitors)	Capmatinib,[e,g] crizotinib,[h] tepotinib[e,g]
NRG1	Seribantumab (*HER3* inhibitor), zenocutuzumab (*HER2* inhibitor)	None
NTRK1, NTRK2, NTRK3	Entrectinib, larotrectinib, (both *NTRK* inhibitors)	Entrectinib, Larotrectinib
PIK3CA	Alpelisib, copanlisib (both *PIK3* inhibitors)	Alpelisib[d]
RET	Pralsetinib, selpercatinib (both *RET* inhibitors)	Pralsetinib,[g,i] selpercatinib,[g,i]
ROS1	Crizotinib, entrectinib (both *ROS1* inhibitors)	Crizotinib, entrectinib

[a]The list of targeted therapies is constantly evolving as new drugs and clinical trials become available.
[b]These drugs are also listed in the Ontario Health (Cancer Care Ontario) drug formulary.
[c]Publicly funded for melanoma but not NSCLC.
[d]Not publicly funded.
[e]Approved by Health Canada but not publicly funded.
[f]This drug has received Health Canada approval and is currently being reviewed by CADTH.
[g]Yet to be added to the Ontario Health (Cancer Care Ontario) drug formulary.
[h]Not publicly funded for people with *MET* skipping alterations; funded only for *ALK* alterations.
[i]These drugs have received approval from Health Canada and are recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH). They are currently undergoing the Pan-Canadian Pharmaceutical Alliance process to determine public funding.

Equity Context

We use the PROGRESS-Plus framework[69] to help explicitly consider health equity in our health technology assessments. PROGRESS-Plus is a health equity framework used to identify population and individual characteristics across which health inequities may exist. These characteristics include place of residence; race or ethnicity, culture or language; gender or sex; disability; occupation; religion; education; socioeconomic status; social capital; and other key characteristics that stratify health opportunities and outcomes.

Expert Consultation

We engaged with experts in the specialty areas of molecular medicine, laboratory genetics, medical oncology, and thoracic surgery to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42023437968), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the analytical validity, clinical validity, and clinical utility of liquid biopsy testing in identifying actionable genomic alterations in people diagnosed with non–small cell lung cancer?

The definitions we use for *analytical validity*, *clinical validity*, and *clinical utility* are as follows[70]:

- **Analytical validity** refers to a test's ability to accurately and reliably measure the genotype (i.e., specific genetic variant) of interest. That is, it is a measure of how well a laboratory assay can detect the specific genetic change being tested for. This aspect of our research question focuses on the technical performance of the test itself, including factors such as sensitivity, specificity, precision, and reproducibility
- **Clinical validity** refers to a test's ability to detect or predict the clinical disorder or phenotype associated with a specific genotype. It answers the question, does a positive genetic test result correlate with an increased risk of developing a particular disease or condition?
- **Clinical utility** refers to the impact of test results on patient outcomes and clinical decision-making. It considers not only clinical end points but also emotional, social, cognitive, and behavioral aspects that affect a patient's well-being. For example, even if there is no effective clinical treatment, a test may still have clinical utility by providing clarity on the condition and helping patients and families cope with the associated prognosis

Figure 6 provides a schematic presentation of the research question.

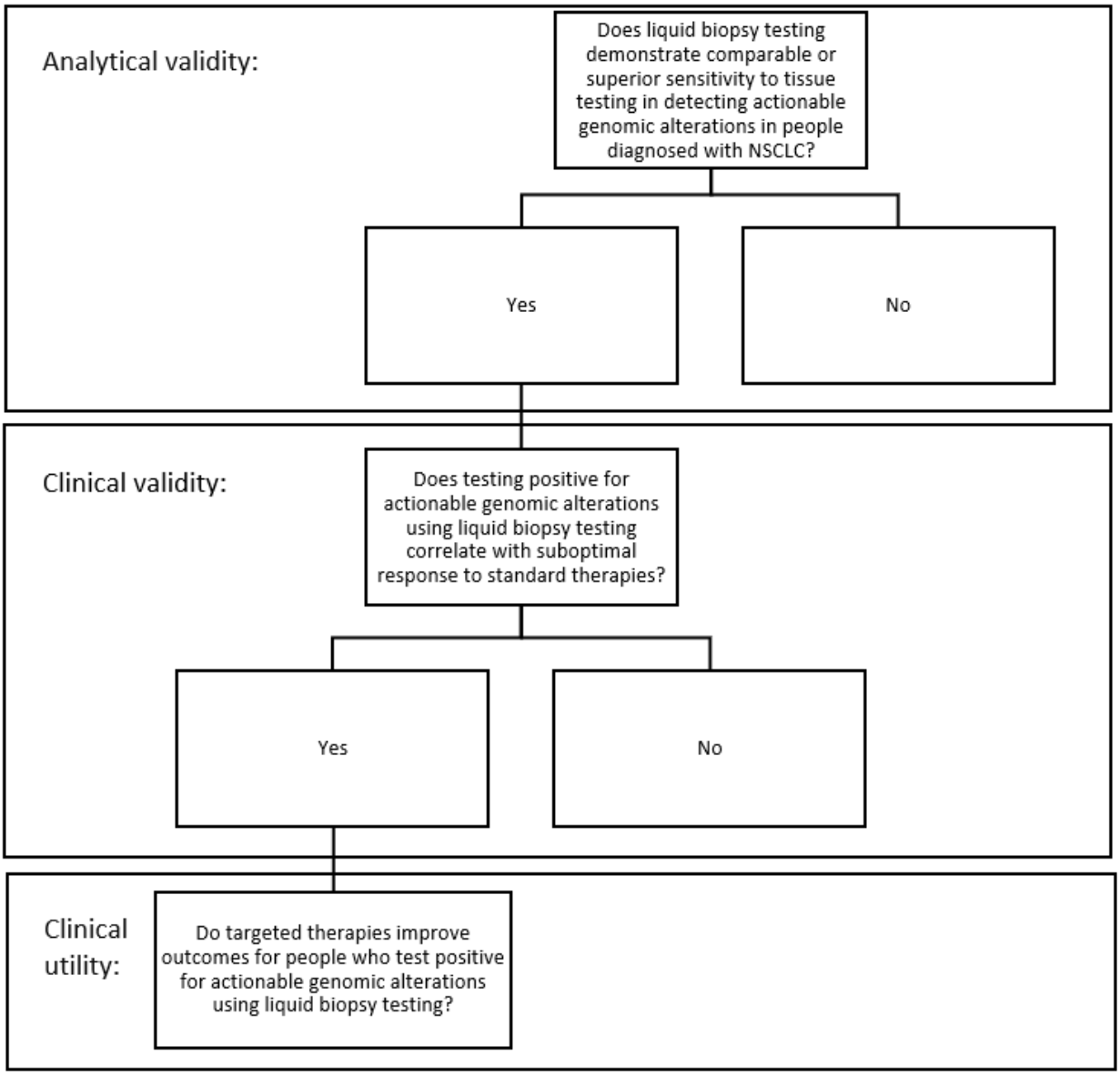

Figure 6: Schematic Presentation of the Clinical Evidence Review Research Question

Methods

Clinical Literature Search

We performed a clinical literature search on May 31, 2023, to retrieve studies published from January 1, 2010, until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[71]

We created database auto-alerts in MEDLINE and Embase and monitored them until May 20, 2024. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Analytical Validity

Studies

Inclusion Criteria

- English-language full-text publications
- Fully paired design, partially paired design with random subset, partially paired design with nonrandom subset, unpaired randomized design, unpaired nonrandomized design
- Systematic reviews and meta-analyses to identify any relevant studies that might not have been captured by our search strategy

Exclusion Criteria

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries

Population

- People diagnosed with non–small cell lung cancer (NSCLC)

Index Test

- Liquid biopsy testing

Comparator Test

- Tissue testing

Reference Standard

- Testing positive with either liquid biopsy or tissue testing (applies only to the evaluation test sensitivity)
    - The use of the refence standard defined here inherently assumes perfect specificity. Although there are situations in which false positives may occur (and hence specificity will be less than 100%),[72] most commercial assays have high analytical specificity[67]

Measure of Accuracy

- Sensitivity
    - While there are no universally established thresholds for determining adequate sensitivity for tissue or liquid biopsy assays, within the scope of this report, we aimed for the test to outperform a random coin toss. As an unbiased coin toss would have a pretest possibility of 50%, we sought a sensitivity value notably exceeding this threshold. Accordingly, we implemented the following cutoff points:
        - High: ≥ 90%
        - Moderate: 80% to 90%
        - Modest: 61 to 79%
        - Low: 50% to 60%
        - Very low: < 50%

Measures of Concordance

- Overall percent agreement
- Percentage of results that are positive with tissue testing but negative with liquid biopsy testing
- Percentage of results that are positive with liquid biopsy testing but negative with tissue testing
- Percentage of results that are positive with both tissue and liquid biopsy testing

Clinical Validity

Studies

Inclusion Criteria

- English-language full-text publications
- Cohort studies
- Systematic reviews and meta-analyses to identify any relevant studies that might not have been captured by our search strategy

Exclusion Criteria

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries

Population

- People diagnosed with NSCLC and tested for actionable genomic alterations with liquid biopsy

Exposure

- With liquid biopsy testing, testing positive for any of the actionable genomic alterations included in the reflex testing strategy funded by Ontario Health (Cancer Care Ontario) (see Table 1)

Nonexposure

- With liquid biopsy testing, testing negative for any of the actionable genomic alterations included in the reflex testing strategy funded by Ontario Health (Cancer Care Ontario) (see Table 1)

Outcomes

- Progression of NSCLC despite undergoing standard therapies (e.g., chemotherapy, immunotherapy) or in treatment-naïve individuals. End points include the following:
    - Objective response (i.e., reduction in tumour size or disappearance of tumour)
    - Complete response
    - Stable disease
    - Progressive disease
    - Survival
    - Progression-free survival

Measures of Effect

- Differences in the following:
    - Objective response rates
    - Complete response rates
    - Partial response rates
    - Stable disease rates
    - Progressive disease rates
    - Progression-free survival between those who tested positive (i.e., exposure) and those who tested negative (i.e., nonexposure) for actionable genomic alterations with liquid biopsy testing
- Hazard ratio

Clinical Utility

Studies

Inclusion Criteria

- English-language full-text publications
- Randomized controlled trials, cohort studies with a before–after design, cohort studies with a concurrent-measures design
- Systematic reviews and meta-analyses to identify any relevant studies that might not have been captured by our search strategy

Exclusion Criteria

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries

Population

- People diagnosed with NSCLC who have tested positive with liquid biopsy testing for any of the actionable genomic alterations included in the reflex testing strategy funded by Ontario Health (Cancer Care Ontario) (see Table 1)

Intervention

- Targeted therapy administered after testing positive with liquid biopsy testing for any of the actionable genomic alterations included in the reflex testing strategy funded by Ontario Health (Cancer Care Ontario) (see Table 1)

Comparators

- Any standard therapy or no therapy before testing for actionable genomic alterations with liquid biopsy testing

Outcomes

- Progression-free survival
- Disease-free survival
- Health-related quality of life
- Objective response rate
- Complete response rate
- Partial response rate
- Stable disease rate

- Progressive disease rate
- Time to treatment
- Initiation of targeted therapy

Measures of Effect

- Hazard ratio
- Risk ratio
- Rate ratio
- Rate difference
- Mean difference

Literature Screening

Two reviewers screened titles and abstracts to assess the eligibility of a sample of 100 citations to validate the inclusion and exclusion criteria. A single reviewer then screened all remaining citations using Covidence[73] and obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

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

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, reporting of missing data, reporting of outcomes, whether the study compared two groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower confidence limits, time points at which the outcomes were assessed)

Equity Considerations

Potential equity issues related to the analytical validity, clinical validity, or clinical utility of liquid biopsy testing were not evident during scoping. However, we report the available participant characteristics in the included studies.

Statistical Analysis

One reviewer assessed for the presence and extent of heterogeneity across studies and considered this when interpreting the results.[74] For the assessment of clinical utility, we undertook a meta-analysis using the meta package in R.[75] We employed a random effects model in our meta-analysis to handle potential heterogeneity among assay types with potentially differing sensitivity levels, accounting for both within-study and between-study variability. We used the I^2 index to estimate the proportion of variance in the forest plots that results from variation in test sensitivity in the target population rather than sampling error, whereas we used the T^2 statistic to estimate the extent of true heterogeneity in test sensitivity across the included studies. We did not conduct a meta-analysis to assess clinical validity because only 1 of the included studies would have been eligible. Similarly, we did not perform a meta-analysis to evaluate clinical utility because of the heterogeneity in follow-up time across studies. Instead, we provide a narrative summary of results.

We were unable to undertake a subgroup analysis by age and socioeconomic status because information on analytical validity, clinical validity, and clinical utility across these subgroups was not available. Similarly, we did not perform a subgroup analysis based on disease stage because most studies included participants at various stages of NSCLC. However, most participants were at stage III or IV.

Critical Appraisal of Evidence

For the analytical validity research question, we used the QUADAS-C[76] tool in combination with QUADAS-2[76] to evaluate risk of bias and applicability concerns (Appendix 2, Table A1). For the clinical validity research question, we used the ROBINS-E tool[77] to evaluate risk of bias (Appendix 2, Table A2). And for the clinical utility research question, we used the ROBINS-I tool[78] to assess risk of bias (Appendix 2, Table A3).

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[79] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness (as derived from the "applicability concerns" component of the QUADAS-C and QUADAS-2 tools), imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The clinical literature search yielded 4,984 citations, including grey literature results and after removing duplicates, published between January 1, 2010, and May 31, 2023. In total, we identified 61 studies that met our inclusion criteria (49 on analytical validity, 1 on clinical validity, and 12 on clinical utility; 1 study was included in the assessment of both analytical validity and clinical utility). See Appendix 4 for a list of selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

Although we identified 22 systematic reviews and meta-analyses on liquid biopsy testing for NSCLC,[80-100] we could not fully use them because of their limited alignment with our research questions. We thus

used these sources to supplement our literature search, seeking out any additional references that might have been overlooked in our initial search strategy.

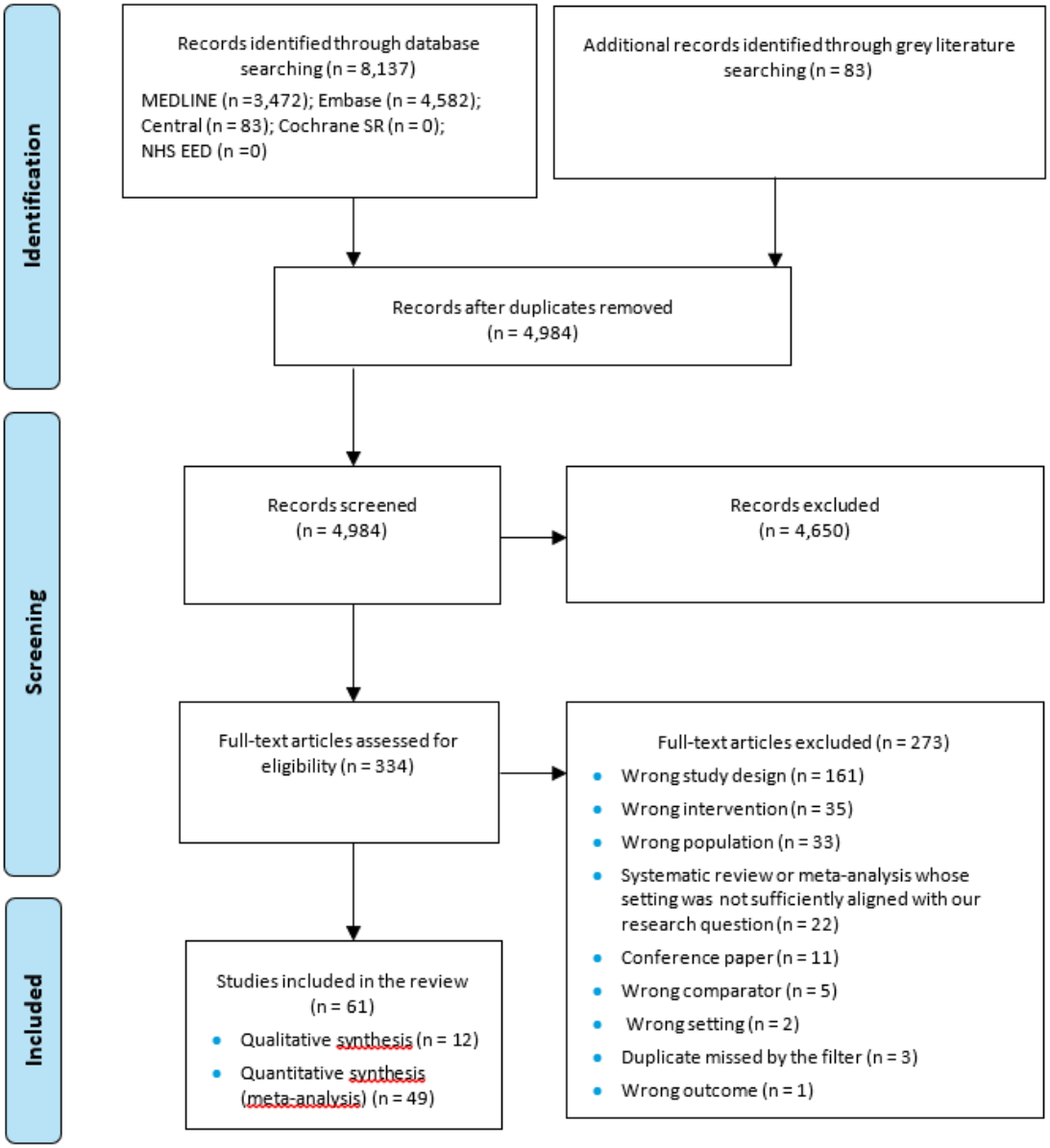

Figure 7: PRISMA Flow Diagram – Clinical Systematic Review

PRISMA flow diagram showing the clinical systematic review. The clinical literature search yielded 4,984 citations, including grey literature results and after removing duplicates, published between January 1, 2010, and May 31, 2023. We screened the abstracts of 4,984 identified studies and excluded 4,650. We assessed the full text of 334 articles and excluded a further 273. In the end, we included 12 articles in the qualitative synthesis and 49 articles in the quantitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[73]

Characteristics of Included Studies

The populations of most studies were predominantly people with late-stage non–squamous cell carcinoma, and the brands of assays used varied across studies. Table 3 summarizes the characteristics of the included studies.

Table 3: Characteristics of Studies Included in the Clinical Literature Review

Author, year, country	Type of assessment	NSCLC stage	Genes covered	Liquid biopsy assay (manufacturer)	Tissue biopsy assay (manufacturer)	No. of participants
Bai et al, 2019, China[101]	Analytical validity	I–IV	*EGFR*	AllNGS (Shanghai Yunying Medical Laboratory)	AllNGS (Shanghai Yunying Medical Laboratory)	79
Buburuzan et al, 2022, Romania[102]	Analytical validity	III/IV	*ALK, BRAF, EGFR, ERBB2, FGFR1, KRAS, MET, PIK3CA*	Ion Torrent Oncomine Pan-Cancer Cell-Free Assay (Thermo Fisher Scientific)	Oncomine Solid Tumor (Thermo Fisher Scientifi)	26
Bustamante Alvarez et al, 2020, United States[103]	Analytical validity Clinical utility	IV	For analytical validity: *KRAS* For clinical utility: *ALK, EGFR, ROS1*	Guardant360 (Guardant Health)	In house	For analytical validity: 94 For clinical utility: 8
Chen et al, 2016, China[104]	Analytical validity	I–IIA	*ALK, EGFR, KRAS, PIK3CA*	Ion AmpliSeq (Thermo Fisher Scientific)	Ion AmpliSeq (Thermo Fisher Scientific)	58
Chen et al, 2019, China[105]	Analytical validity	I–IV	*ALK, EGFR, ERBB2, KRAS, NTRK1, PIK3CA*	Genecast (in house)	Genecast (in house)	50
Couraud et al, 2014, United States[106]	Analytical validity	I–IV	*BRAF, EGFR, ERBB2, KRAS, PI3KCA*	In house	In house	68
Cui et al, 2017, China[107]	Analytical validity	IB–IV	*ALK*	LungPlasma (Burning Rock Biotech)	LungPlasma (Burning Rock Biotech)	39
Dagogo-Jack et al, 2019, United States[108]	Analytical validity	I–IV	*ROS1*	Guardant360 (Guardant Health)	DFCI Oncopanel (in house), FoundationOne (Foundation Medicine), MGH Solid Fusion Assay (Massachusetts General Hospital), MSK-IMPACT (Memorial Sloan Kettering Cancer Center)	7

Author, year, country	Type of assessment	NSCLC stage	Genes covered	Liquid biopsy assay (manufacturer)	Tissue biopsy assay (manufacturer)	No. of participants
Dziadziuszko et al, 2021, Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Costa Rica, France, Germany, Hong Kong, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Panama, Peru, Poland, Russia, Serbia, Singapore, Spain, Taiwan, Thailand, Turkey, United States[109]	Clinical utility	IIIB/IV	*ALK*	FoundationACT CDx (Foundation Medicine)	NA	87
Fernandes et al, 2021, Portugal[110]	Analytical validity	IIIB/IV	*ALK, BRAF, EGFR, ERBB2, KRAS, PIK3CA*	Oncomine Lung (Thermo Fisher Scientific)	Ion AmpliSeq v2 (Ion Torrent)	115
He et al, 2016, China[111]	Analytical validity	IA–IIB	*ALK, BRAF, EGFR, ERBB2, FGFR1, KRAS, MET, PIK3CA*	Ion AmpliSeq (Life Technologies)	Ion AmpliSeq (Life Technologies)	10
Jee et al, 2022, United States[112]	Clinical utility	IV or recurrent NSCLC	*ALK, BRAF, EGFR, ERBB2, FGFR1, KRAS, MET, NTRK1, PIK3CA, RET*	Resolution ctDx Lung (Resolution Bioscience)	MSK-IMPACT (Memorial Sloan Kettering Cancer Center)	722
Jiao et al, 2021, China[113]	Analytical validity	IIIB/IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, NTRK3, PIK3CA*	LungPlasma (Burning Rock Biotech), OncoScreen Plus panel (Burning Rock Biotech)	LungPlasma (Burning Rock Biotech), OncoScreen Plus panel (Burning Rock Biotech)	185
Laufer-Geva et al, 2018, Israel[114]	Clinical utility	IIIB/IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, PIK3CA, RET*	Guardant360 (Guardant Health)	NA	37
Lee et al, 2021, United States[115]	Analytical validity	I–IV	*MET*	Unclear (Foundation Medicine)	FoundationOne (Foundation Medicine), FoundationOne CDx (Foundation Medicine)	14
Lee et al, 2022, United States[116]	Analytical validity	Not reported	*ALK, BRAF, EGFR, ERBB2, FGFR1, MET, RET, ROS1*[b]	FoundationACT (Foundation Medicine), FoundationOne Liquid (Foundation Medicine), FoundationOne CDx (Foundation Medicine)	FoundationOne (Foundation Medicine), FoundationOne CDx (Foundation Medicine)	7[a]

Author, year, country	Type of assessment	NSCLC stage	Genes covered	Liquid biopsy assay (manufacturer)	Tissue biopsy assay (manufacturer)	No. of participants
Li et al, 2019, United States[117]	Analytical validity	III/IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, RET, ROS1*	In house	FoundationOne CDx (Foundation Medicine), Ion Torrent Oncomine (Thermo Fisher Scientific), MSK-IMPACT (Memorial Sloan Kettering Cancer), OncoMap (Sequenom)	72[a]
Li et al, 2021, China[118]	Clinical utility	I–IV	*ALK, EGFR, ERBB2, MET, RET, ROS1*	In house (Burning Rock Biotech)	NA	30
Liang et al, 2023, China[119]	Clinical utility	III/IV	*EGFR*	Geneseeq Prime (Geneseeq Technology)	NA	66
Lin et al, 2021, Taiwan[120]	Analytical validity	III/IV	*ALK*	NA	NA	20
Lin et al, 2021, United States[121]	Analytical validity	II–IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, NTRK1, RET, ROS1*	Guardant 360 (Guardant Health)	Oncomine Focus (Thermo Fisher Scientific)	100
Liu et al, 2018, China[122]	Analytical validity	III/IV	*ALK, BRAF, EGFR, KRAS, RET*	In house	In house	46
Marchetti et al, 2015, Italy[123]	Clinical utility	IIIB/IV	*EGFR*	In house	NA	20
Mehta et al, 2021, India[124]	Analytical validity	IIIB/IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, PIK3CA, RET, ROS1*	Oncomine Lung Cell-Free (Thermo Fisher Scientific), Total Nucleic Acid (Thermo Fisher Scientific)	Oncomine Solid Tumor DNA (Thermo Fisher Scientific), Oncomine Solid Tumor Fusion (Thermo Fisher Scientific)	21
Mondaca et al, 2021, United States[125]	Analytical validity	III/IV	*ALK*	Resolution ctDx Lung (Resolution Bioscience)	MSK-IMPACT (Memorial Sloan Kettering Cancer Center)	389
Ohira et al, 2016, Japan[126]	Analytical validity	I–III	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, PIK3CA*	Ion AmpliSeq v2 (Life Technologies)	Ion AmpliSeq v2 (Life Technologies)	149
Page et al, 2021, United States[127]	Clinical utility	IIIB/IV	*ALK, EGFR, ROS1*	Guardant360 (Guardant Health)	NA	32[a]
Park et al, 2021, Republic of Korea[128]	Analytical validity	III/IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, RET, ROS1*	Guardant360 (Guardant Health)	Oncomine Focus Assay (Thermo Fisher Scientific)	287

Author, year, country	Type of assessment	NSCLC stage	Genes covered	Liquid biopsy assay (manufacturer)	Tissue biopsy assay (manufacturer)	No. of participants
Pasquale et al, 2019, Italy[129]	Analytical utility	I–IV, newly diagnosed	*BRAF, EGFR, KRAS, MET, PIK3CA*	Oncomine Lung cfDNA (Thermo Fisher Scientific)	Oncomine Solid Tumour (Thermo Fisher Scientific)	107
Pavan et al, 2021, Italy[130]	Clinical validity	I–IV	*FGFR1, KRAS* (with *STK11/TP53* co-mutations)	Guardant360 (Guardant Health), NGS-IL 56G (Diatech Pharmacogenetics)	NA	103
Pecuchet et al, 2016, France[131]	Analytical validity	IIIB/IV, newly diagnosed, treatment naïve at baseline	*ALK, BRAF, EGFR, FGFR1, KRAS, PIK3CA*	Ion AmpliSeq Colon and Lung Cancer Research Panel, v2 (Life Technologies–Thermo Fisher Scientific)	Ion AmpliSeq Colon and Lung Cancer Research Panel, v2 (Life Technologies–Thermo Fisher Scientific)	105
Phallen et al, 2019, United States[132]	Clinical utility	IV	*EGFR, ERBB2*	In house	NA	5
Pritchett et al, 2019, United States[133]	Analytical validity	IIIB/IV	*BRAF, EGFR, ERBB2, KRAS, MET*	InVisionFirst (Inivata)	SureSelect X (Agilent)	178
Raez et al, 2022, United States[134]	Analytical validity	IV	*ALK, BRAF, EGFR, MET, NTRK, ROS1*	Guardant360 (Guardant Health)	Unclear	153
Roosan et al, 2021, United States[135]	Analytical validity	I–IV	*ALK, BRAF, EGFR, ERBB2, FGFR1, KRAS, MET, PIK3CA, RET*	Guardant360 (Guardant Health)	Caris (Caris Life Sciences), FoundationOne CDx (Foundation Medicine), Gem Extra (Ashion), HopeSeq Lung Tumors (City of Hope), HopeSeq Oncocomplete (City of Hope), HopeSeq Solid Tumors (City of Hope)	64
Roosan et al, 2021, United States[136]	Analytical validity	I–IV	*BRAF, EGFR, ERBB2, FGFR1, KRAS, MET, PIK3CA*	Guardant360 (Guardant Health)	Caris (Caris Life Sciences), FoundationOne CDx (Foundation Medicine), Gem Extra (Ashion Analytics), HopeSeq Lung Tumors (City of Hope), HopeSeq Oncocomplete (City of Hope), HopeSeq Solid Tumors (City of Hope)	64

Author, year, country	Type of assessment	NSCLC stage	Genes covered	Liquid biopsy assay (manufacturer)	Tissue biopsy assay (manufacturer)	No. of participants
Sabari et al, 2019, United States[137]	Analytical validity	Advanced	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, PIK3CA, RET, ROS1*	Resolution ctDx Lung (Resolution Bioscience)	MSK-IMPACT (Memorial Sloan Kettering Cancer Center)	107
Schouten et al, 2021, Netherlands[138]	Analytical validity	IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, RET, ROS1*	AVENIO ctDNA Targeted Kit (Roche Diagnostics)	Ion AmpliSeq (Life Technologies)	192[a]
Schrock et al, 2018, United States[139]	Analytical validity	III/IV	*ALK, BRAF, EGFR, ERBB2, FGFR1, KRAS, MET, PIK3CA, RET, ROS1*	In house	FoundationOne (Foundation Medicine)	35[a]
Schwaederlé et al, 2017, United States[140]	Analytical validity	Not specified	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, PIK3CA, ROS1*	Guardant360 (Guardant Health)	In house	80[a]
Schwartzberg et al, 2020, France, Ireland, Japan, Spain, United Kingdom, United States[141]	Analytical validity	IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, PIK3CA, RET, ROS1*	In house	In house	140
Sugimoto et al, 2023, Japan[142]	Analytical validity	III/IV or recurrence	*BRAF, EGFR, ERBB2, KRAS*	Guardant 360 (Guardant Health)	Oncomine (Thermo Fisher Scientific)	1,062
Sun et al, 2023, China[143]	Analytical validity	II–IIIB	*MET*	Unclear (Integrated DNA Technologies)	Unclear (Integrated DNA Technologies)	261
Sung et al, 2017, Republic of Korea[144]	Analytical validity	I–IV	*EGFR*	Ion AmpliSeq, v2 (Thermo Fisher Scientific)	Ion AmpliSeq, v2 (Thermo Fisher Scientific)	100
Tetik Vardarli et al, 2020, Turkey[145]	Analytical validity	IV	*ALK, BRAF, EGFR, ERBB2, FGFR1, KRAS, MET, PIK3CA*	Ion AmpliSeq (Thermo Fisher Scientific)	Ion AmpliSeq (Thermo Fisher Scientific)	12
Thompson et al, 2016, United States[146]	Analytical validity	IIIB/IV	*BRAF, EGFR, ERBB2, KRAS*	Guardant360 (Guardant Health)	Penn Precision Panel (Penn Center for Personalized Diagnostics), TruSeq Amplicon (Illumina)	40[a]
Toor et al, 2018, United States[147]	Analytical validity	IIIB/IV	*ALK, BRAF, EGFR, ERBB2, FGFR1, KRAS, PIK3CA*	Guardant360 (Guardant Health)	Caris (Caris Life Sciences), Paradigm (unclear)	9
Tran et al, 2019, Vietnam[148]	Analytical validity	Advanced	*EGFR, KRAS*	In house	In house	39[a]

Author, year, country	Type of assessment	NSCLC stage	Genes covered	Liquid biopsy assay (manufacturer)	Tissue biopsy assay (manufacturer)	No. of participants
Tran et al, 2021, United States[149]	Analytical validity	Advanced	*ALK, BRAF, MET, RET, ROS1*[c]	Guardant360 (Guardant Health)	(OncoMine Comprehensive Assay, v1 (Thermo Fisher Scientific)	217
Uchida et al, 2015, Japan[150]	Analytical validity	I–IV	*EGFR*	In house	In house	288
Villaflor et al, 2016, United States[151]	Analytical validity Clinical utility	I–IV	*ALK, BRAF, EGFR, ERBB2, MET, RET, ROS1*	In house	Guardant360 (Guardant Health)	For analytical validity: 29 For clinical utility: 6
Wang et al, 2018, China[152]	Clinical utility	IV	*EGFR*	LungPlasma (Burning Rock Biotech)	NA	174
Wang et al, 2021, China[153]	Clinical utility	III/IV, newly diagnosed	*EGFR*	cSmart (Burning Rock Biotech)	NA	54
Wu et al, 2019, China[154]	Analytical validity	IIIB/IV	*ALK, EGFR, KRAS, MET, PIK3CA*	HiSeq4000 (Illumina)	HiSeq4000 (Illumina)	50
Xie et al, 2018, China[155]	Analytical validity Clinical utility	III/IV	*ALK, EGFR, ERBB2, KRAS, ROS1*	Unclear (Burning Rock Biotech)	Unclear (Burning Rock Biotech)	35
Xu et al, 2016, China[156]	Analytical validity	III/IV	*BRAF, EGFR, ERBB2, KRAS, PIK3CA*	AmpliSeq (Thermo Fisher Scientific)	AmpliSeq (Thermo Fisher Scientific)	42
Yang et al, 2018, China[157]	Analytical validity	IIIB/IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, NTRK1, PIK3CA, RET, ROS1*	In house	In house	56
Yao et al, 2016, China[158]	Analytical validity	III/IV	*ALK, EGFR, KRAS, PIK3CA, RET*	In house	In house	39
Yin et al, 2021, China[159]	Analytical validity	IB–IV	*EGFR, KRAS*	Ion Proton System (Life Technologies)	Ion Proton System (Life Technologies)	146[a]
Zhang et al, 2022, China[160]	Analytical validity	I–IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, PIK3CA, ROS1,*	Unclear (Nanjing Geneseeq Technology)	Unclear (Nanjing Geneseeq Technology)	125
Zhao et al, 2023, China[161]	Analytical validity	III/IV	*ALK, BRAF, EGFR, ERBB2, KRAS, MET, NTRK, RET, ROS1*	Unclear (Burning Rock Biotech)	Unclear (Burning Rock Biotech)	519

Abbreviation: NA, not applicable.
[a]We excluded people with the *EGFR* T790M mutation.
[b]This study focused only on fusion alterations.
[c]We excluded *EGFR* because we were unable to isolate T790M from other types of *EGFR* mutations at an individual level.

Analytical Validity

We organized the evaluation of the analytical validity of liquid biopsy testing into 5 sections:

- Sensitivity of liquid biopsy testing in detecting actionable genomic alterations compared with tissue testing using a composite reference standard; a positive result from either liquid biopsy or tissue testing was regarded as a true positive
- Overall concordance in results between liquid biopsy and tissue testing
- Proportion of people who tested positive for actionable genomic alterations with liquid biopsy testing among those who tested negative with tissue testing
- Proportion of people who tested positive for actionable genomic alterations with tissue testing among those who tested negative with liquid biopsy testing
- Proportion of people who tested positive for actionable genomic alterations with liquid biopsy testing among those who tested positive with tissue testing

These assessments informed us about which of the clinical pathways presented in Figures 2 to 5 are supported by evidence.

Sensitivity

We assessed the performance of liquid biopsy testing in detecting actionable genomic alterations and compared it with that of tissue testing. The number of studies included in this analysis varied from 1 to 42, depending on which genes were assessed. Figure 8 presents pooled estimates for 11 genes (for further details, see the forest plots provided in Appendix 3, Figures A1 to A22).

The sensitivity of liquid biopsy testing in detecting actionable genomic alterations varied across genes. For example, the sensitivity was modest for *KRAS* (73%; 95% confidence interval [CI]: 68% to 78%; GRADE: High) but low for *ALK* (60%; 95% CI: 53% to 67%; GRADE: High) and *PIK3CA* (56%; 95% CI: 46% to 66%; GRADE: Moderate); we downgraded the certainty of the evidence for *PIK3CA* because of imprecision. Similarly, sensitivity was modest for *BRAF* (66%; 95% CI: 57% to 75%; GRADE: Moderate), *EGFR* (72%; 95% CI: 66% to 78%; GRADE: High), and *ERBB2* (66%; 95% CI: 58% to 74%; GRADE: Moderate); we downgraded the certainty of the evidence for *BRAF* and *ERBB2* because of imprecision. Sensitivity was also low for *MET*, *RET*, and *ROS1*, although our certainty in the evidence for each was low because of imprecision and, for *MET*, also because of inconsistency (GRADE: Low). The sensitivity of liquid biopsy testing for *FGFR1* and *NTRK1* alterations was uncertain because of imprecision (GRADE: Very Low).

Tissue testing consistently exhibited a higher sensitivity than liquid biopsy testing across all studies, albeit far from perfect, ranging from low for *PIK3CA* (69%; 95% CI: 57% to 81%; GRADE: Moderate) to high for *EGFR* (90%; 95% CI: 86% to 94%; GRADE: High). Sensitivity results for liquid biopsy and tissue testing for *NTRK3* were available only in the study by Jiao et al.[113] In that study, the sensitivity was 100% (95% CI: 69% to 100%) for liquid biopsy testing and 90% (95% CI: 56% to 100%) for tissue testing (GRADE: Very Low). Our certainty in the evidence was very low because of imprecision. None of the eligible studies provided exclusive information on sensitivity for *NTRK2*. Although Raez et al[134] and Zhao

et al[161] presented results for *NTRK*, they did not partition by *NTRK* classes. Because of this, we did not include their results in our GRADE assessment. None of the eligible studies evaluated *NRG1* alterations.

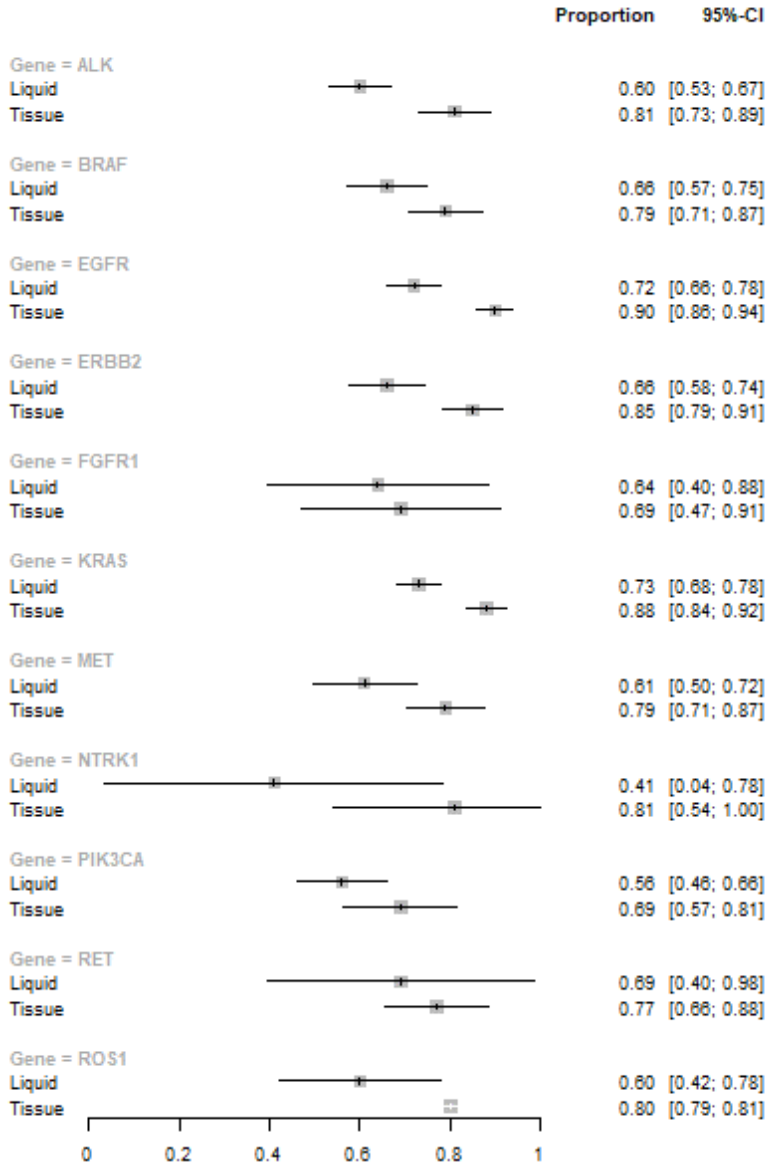

Figure 8: Pooled Estimates of the Sensitivity of Liquid Biopsy and Tissue Testing in Detecting Actionable Genomic Alterations

Overall Concordance

To evaluate the agreement between liquid biopsy and tissue testing results, we calculated overall concordance. This assessment provided insight into the potential value of administering these tests concurrently (see Figure 2). The number of studies included varied from 1 to 42, depending on the genes assessed. Figure 9 displays pooled estimates for 9 genes (for further details, see the forest plots provided in Appendix 3, Figures A23 to A31).

We encountered challenges when attempting to pool the results of studies reporting on *ROS1* and *NTRK1* alterations because of statistical convergence issues. Most studies demonstrated perfect agreement between the 2 tests (Appendix 3, Table A5), leading to zero variance in point estimates. All these studies indicated a high level of concordance between liquid biopsy and tissue testing results.

Only 1 study[113] examined *NTRK3* alterations and reported a concordance of about 100% (95% CI: 97% to 100%; GRADE: High) between liquid biopsy and tissue testing results. Although no study exclusively focused on *NTRK2*, 2 studies provided combined findings for alterations in the *NTRK* gene family and reported an overall concordance of 99% (95% CI: 98% to 100%)[134] and 99% (95% CI: 96% to 100%).[161] However, we did not conduct a GRADE assessment on these aggregated results as our focus was on individual *NTRK* gene classes.

Across all 12 gene alterations assessed, the overall concordance between liquid biopsy and tissue testing results was high (GRADE: High). This high concordance primarily stems from the assays' high specificity and the high prevalence of negative results in both tests. None of the eligible studies evaluated *NRG1* alterations.

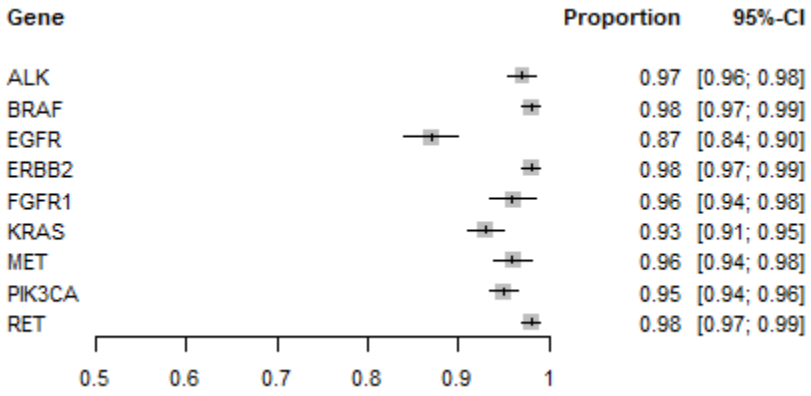

Figure 9: Pooled Estimates of the Overall Concordance of Liquid Biopsy and Tissue Testing in Detecting Actionable Genomic Alterations

Testing Positive With Liquid Biopsy Testing But Negative With Tissue Testing

We evaluated the proportion of people testing positive for actionable genomic alterations with liquid biopsy testing among those testing negative with tissue testing, aiming to shed light on the potential clinical benefit of the "tissue-first" clinical pathway (see Figure 4). The number of included studies varied from 1 to 42, depending on the genes being assessed. Figure 10 presents pooled estimates for 11 genes (for further details, see the forest plots provided in Appendix 3).

Findings on *NTRK3* were provided only by Jiao et al[113] (Appendix 3, Table A5). The proportion of people testing positive with liquid biopsy testing among those testing negative with tissue testing was consistently low, ranging from 1% for alterations in *BRAF*, *ERBB2*, *NTRK1*, *NTRK3*, *RET*, and *ROS1* to 6% for *EGFR* alterations (GRADE: High). While no study exclusively focused on *NTRK2*, 2 studies offered combined insights into alterations in the *NTRK* gene family, where we observed proportions of 0%

(95% CI: 0% to 1%)[134] and 0% (95% CI: 0% to 2%).[161] However, we did not conduct a GRADE assessment on these aggregated results, as our primary focus was on individual NTRK gene classes.

It is important to note that, although the proportions were low, they were not zero, and a nonzero proportion could translate to a large number of cases in settings where many people are diagnosed annually with NSCLC, as is the case in Ontario. None of the eligible studies evaluated *NRG1* alterations.

Testing Positive With Tissue Testing But Negative With Liquid Biopsy Testing

We evaluated the percentage of people testing positive for actionable genomic alterations with tissue testing among those testing negative with liquid biopsy testing, aiming to provide insight into the potential clinical benefit of the "liquid-first" clinical pathway (see Figure 5). The number of included studies varied from 1 to 42, depending on the genes being assessed. Figure 10 presents pooled estimates for 11 genes (for further details, see the forest plots provided in Appendix 3).

Data on *NTRK3* were provided only by Jiao et al[113] (Appendix 3, Table A5). The proportion of people testing positive with tissue testing among those testing negative with liquid biopsy testing was generally low, ranging from 1% (95% CI: 0% to 3%) for *RET* alterations to 6% (95% CI: 5% to 7%) for *KRAS* alterations (GRADE: High); however, the proportion for *EGFR* was higher at 14% (95% CI: 11% to 17%; GRADE: High). While no study exclusively focused on *NTRK2*, 2 studies provided combined insights into alterations in the *NTRK* gene family, where we observed proportions of 1% (95% CI: 0% to 2%)[134] and 1% (95% CI: 0% to 4%).[161] However, we did not conduct a GRADE assessment on these aggregated results, as our primary focus was on individual *NTRK* gene classes.

It is important to note that, although the proportions were generally low, they were not zero, and a nonzero proportion could translate to a large number of cases in settings where many people are diagnosed annually with NSCLC, as is the case in Ontario. None of the eligible studies evaluated *NRG1* alterations.

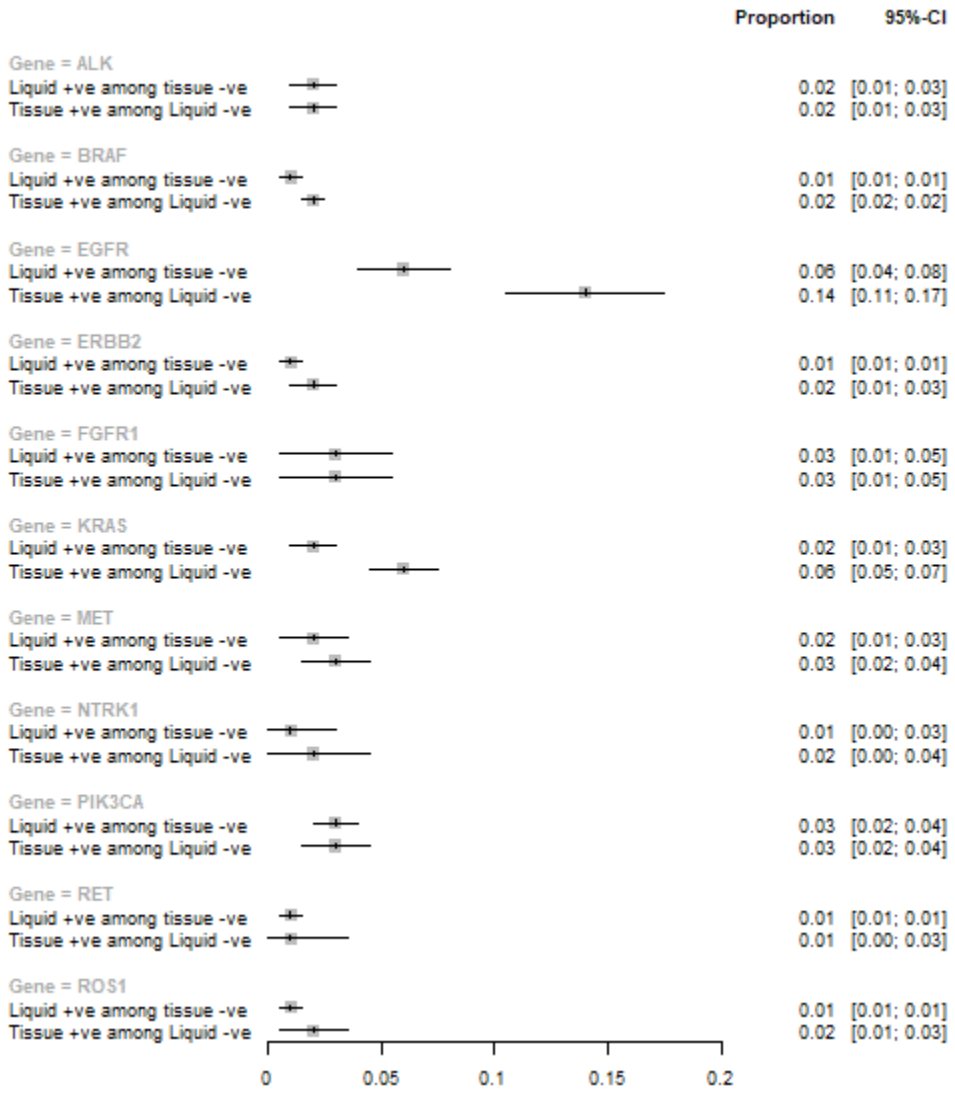

Figure 10: Pooled Estimates of the Proportion of People Testing Positive for Actionable Genomic Alterations With One Type of Assay Among Those Testing Negative With the Other Type

Testing Positive With Liquid Biopsy and Tissue Testing

We evaluated the proportion of people testing positive for actionable genomic alterations with liquid biopsy testing among those also testing positive with tissue testing, aiming to identify the potential clinical benefit of liquid biopsy testing in scenarios where obtaining a sufficient tissue sample for tissue testing is challenging or unfeasible, as depicted in the clinical pathways illustrated in Figures 2, 3, and 4. Specifically, we explored whether ctDNA could serve as a proxy for determining actionable genomic alterations when it is not possible to obtain tissue samples with tumour DNA. The number of included

studies varied from 1 to 42, depending on the genes being assessed. Figure 11 presents pooled estimates for 10 genes (for further details, see the forest plots provided in Appendix 3).

We encountered challenges when attempting to pool 3 studies[105,120,157] reporting on *NTRK1* alterations because of statistical convergence issues. All 3 studies demonstrated a 100% positivity rate for the ability of liquid biopsy testing to identify positive results from tissue testing (Appendix 3, Table A5), resulting in zero variance in point estimates. Data on *NTRK3* were provided only by Jiao et al.[113] None of the studies reported exclusively on *NTRK2* alterations.

Across the pooled studies,[105,120,157] the proportion of people testing positive with liquid biopsy testing among those also testing positive with tissue testing was generally modest, ranging from 45% (95% CI: 35% to 55%) for *PIK3CA* alterations to 70% (95% CI: 65% to 75%) for *EGFR* alterations. For *NTRK1* and *NTRK3*, the proportion was reported as 100% (across all 3 studies) and 99%, respectively.

We rated the certainty of the evidence as high for the assessment of *ALK*, *EGFR*, *KRAS*, *NTRK1*, and NTRK3 alterations. We rated the certainty of the evidence as moderate for *BRAF*, *ERBB2*, and *PIK3CA* alterations; low for *MET* alterations; and very low for *FGFR1*, *RET*, and *ROS1* alterations, downgrading all because of imprecision.

Two studies provided insight into alterations in the *NTRK* gene family, reporting proportions of 100% (95% CI: 98% to 100%)[134] and 100% (95% CI: 99% to 100%).[161] However, we did not conduct a GRADE assessment on these aggregated results, as our primary focus was on individual *NTRK* gene classes. None of the eligible studies evaluated *NRG1* alterations.

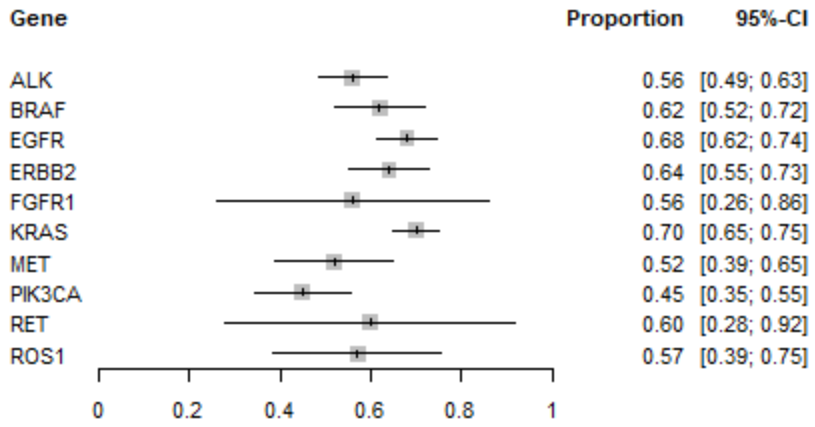

Figure 11: Pooled Estimates of the Proportion of People Testing Positive for Actionable Genomic Alterations With Liquid Biopsy Testing Among Those Testing Positive With Tissue Testing

Clinical Validity

We found only 1 study, conducted by Pavan et al,[130] that examined the prognosis of people with NSCLC based on their genomic alterations as detected with liquid biopsy testing (Table 4). The authors

compared outcomes between people who had tested positive for alterations and those who had tested negative.[130] As part of standard therapy, all received immune checkpoint inhibitors. The authors reported that people with *FGFR1* alterations experienced a shorter progression-free survival (GRADE: Very Low), as did those with *KRAS* co-mutations with other genes not addressed in this report (GRADE: Very Low). We rated the certainty of the evidence for both *FGFR1* and *KRAS* alterations as very low because of imprecision. Risk of bias was also present in the *KRAS* assessment (Appendix 2, Table A2).

Table 4: Clinical Validity of Liquid Biopsy Testing

Gene alteration	No. of participants with an alteration	No. of participants without an alteration	Point estimate (95% CI)[a]
FGFR1	3	100	HR 3.5 (1.0 to 13.0)
KRAS/STK11 co-mutation	3	100	HR 5.1 (0.4 to 62.5)
KRAS/STK11/TP53 co-mutation	2	101	HR 5.6 (1.2 to 25.2)

Note: All participants received an unspecified immune checkpoint inhibitor as part of standard therapy, and the end point assessed for all was progression-free survival.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]The hazard ratio is for the comparison of end points for those with or without an alteration among people treated with immune checkpoint inhibitors.

Source: Pavan et al.[130]

Clinical Utility

We investigated whether receiving targeted therapies after testing positive for actionable genomic alterations with liquid biopsy testing leads to improved clinical outcomes. Most studies assessed response rates using the RESIST criteria[162] (Figure 12). We did not pool these rates because of the heterogeneity in follow-up time, which would have made interpreting pooled results difficult.

Our assessment indicates that targeted therapies generally increased partial response rates (GRADE: Moderate), maintained stable disease rates (GRADE: Moderate), decreased progressive disease rates (GRADE: Moderate), and improved objective response rates (GRADE: Moderate). However, we downgraded our assessment of the certainty of the evidence for all 3 outcomes to moderate because of potential risk bias (Appendix 2, Table A1).

Studies did not report an improvement in complete response rates; however, the point estimates for these rates were imprecise and had a high risk of bias (GRADE: Low). Progression-free survival was reported in the studies by Li et al[118] and Liang et al[119] (Appendix 3, Table A10). Although both studies reported increased progression-free survival, Liang et al[119] did not report the precision of their estimates (GRADE: Low). We rated the certainty of the evidence as low because of concerns over imprecision and risk of bias.

Jee et al[112] assessed overall survival and reported an improvement with targeted therapies (GRADE: Low). We rated the certainty of this evidence as low because of a high risk of bias (Appendix 2, Table A3).

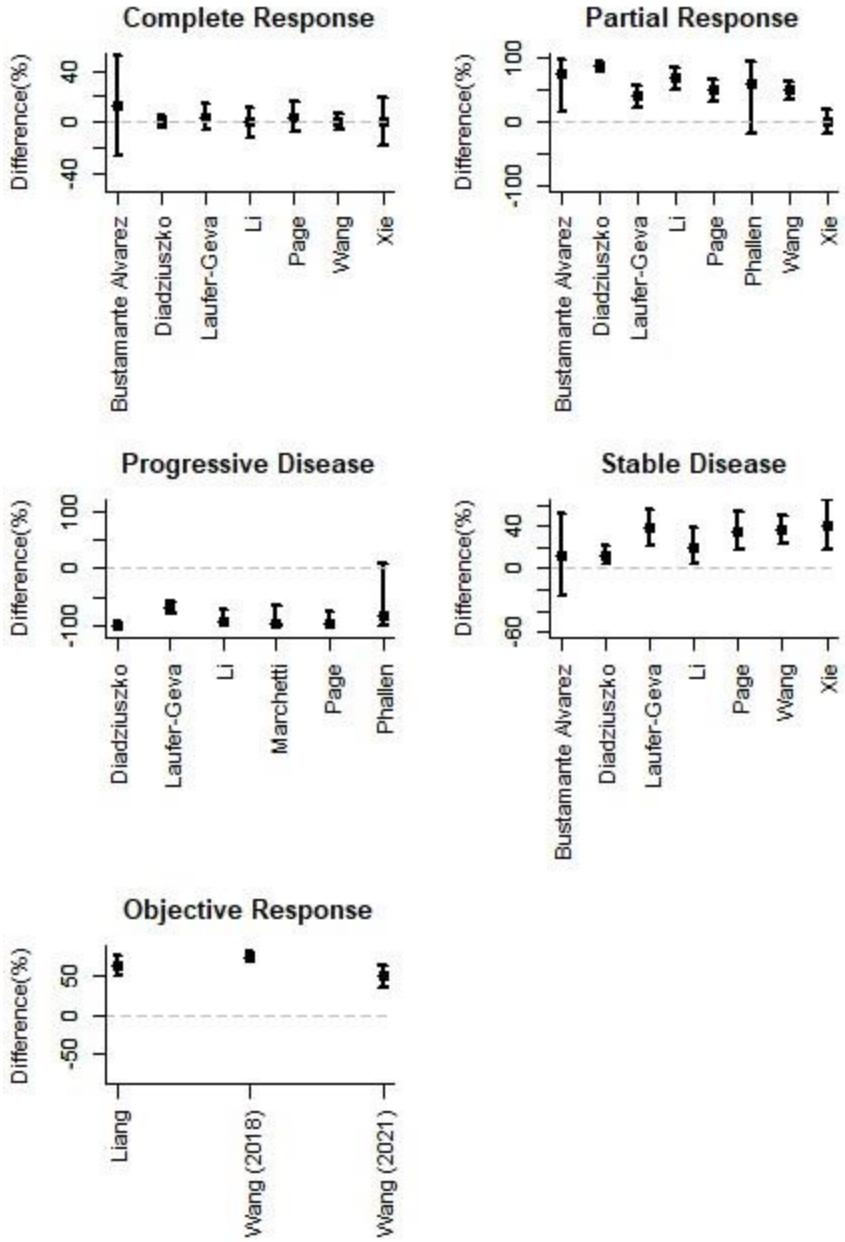

Figure 12: Difference in NSCLC Response Rates After and Before the Administration of Targeted Therapies in People Testing Positive for Actionable Genomic Alterations With Liquid Biopsy Testing

Risk of Bias and Applicability Concerns in the Included Studies

Analytical Validity

In general, we rated the assessment of analytical validity as low for risk of bias and applicability concerns (Appendix 2, Table A1). Among the included studies, 8[103,121,133,138,141,142,145,149] encountered challenges regarding flow and timing of test measurements, raising some concern about risk of bias. Two studies[104] encountered challenges regarding patient selection, raising some concern about the applicability of their findings. Risk of bias was unclear in 5 studies.[115,137,139]

Clinical Validity

In the only study[130] that evaluated clinical validity, we noted a high risk of bias stemming from errors in test and treatment measurements (Appendix 2, Table A2).

Clinical Utility

Overall, the assessment of clinical utility revealed a low risk of bias (Appendix 2, Table A3). However, 2 studies had a serious risks of bias, 1 related to the classification of the intervention[103] and the other related to potential confounding factors.[112] We noted a moderate risk of bias because of the classification of the intervention in 1 study.[155]

Ongoing Studies

We are aware of the following ongoing studies (registered at ClinicalTrials.gov) that may affect this review:

- Longitudinal assessment of genomic alterations and clonal evolution in ALK-positive NSCLC (Galileo Project) (NCT06234579)
- Liquid biopsy based NGS in newly diagnosed NSCLC (NCT05853887)
- Implementing circulating tumor DNA analysis at initial diagnosis to improve management of advanced NSCLC patients (NCT04912687)
- Liquid biopsy to predict responses to first-line immunotherapy in metastatic non–small cell lung cancer (LIBERTY LUNG) (NCT04790682)
- Therapeutic resistance and clonal evolution assessed with liquid biopsy in ICIs treated NSCLC patients (NCT04566432)
- Molecular profiling and dynamic changes of ctDNA in unresectable locally advanced NSCLC (NCT05641870)
- Analysis of circulating tumor DNA dynamics to predict and monitor response to TKI in patients with advanced NSCLC (NCT06167460)
- Clinical utility of liquid biopsy in brigatinib ALK+ patients (CUBIK) (NCT04223596)
- cSMART liquid biopsy and dynamic monitor of NSCLC patients in Inner-Mongolia China (NCT02980536)
- Liquid biopsy for detection of driver mutation in NSCLC (NCT02778854)

- An observational study to evaluate the clinical utility of the Oncomine precision assay within the Exactis network (NCT04564079)
- LIQUIK: Liquid biopsy for detection of actionable genomic biomarkers in patients with advanced non–small cell lung cancer (NCT04703153)
- Liquid biopsy to predict responses to first-line immunotherapy in metastatic non–small cell lung cancer (LIBERTY LUNG) (NCT04790682)
- Molecular profiling and dynamic changes of ctDNA in unresectable locally advanced NSCLC (NCT05641870)
- Analysis of circulating tumor DNA dynamics to predict and monitor response to TKI in patients with advanced NSCLC (NCT06167460)
- Plasma genomic testing in patients with advanced non–small cell lung cancer: the PLAN study (PLAN) (NCT05542485)
- Liquid biopsies in patients presenting non–small cell lung cancer (LIBIL) (NCT02511288)

Discussion

In our review of the clinical evidence, we observed that liquid biopsy testing exhibited varying degrees of sensitivity, ranging from low to modest, and that the sensitivity of liquid biopsy testing generally fell below that of tissue testing across all evaluated genes. However, it is important to note that tissue testing also demonstrated imperfect sensitivity, prompting a consideration of whether liquid biopsy and tissue testing could be used in conjunction to complement each other. We noted that 1% to 3% of cases that tested negative with tissue testing tested positive with liquid biopsy testing, with the notable exception of *EGFR*, for which this figure reached 6%. These findings can be attributed to the high specificity of both types of assays, assumed to be perfect in this review, and the low prevalence of alterations, resulting in a low prevalence of false positives. Similarly, when assessing the percentage of cases testing positive with tissue testing among those testing negative with liquid biopsy testing, we observed estimates of 1% to 6% but rising to 14% for *EGFR*. With about 10,000 annual diagnoses of lung cancer in Ontario,[12] of which 85% are expected to be NSCLC[1] and 29% to 48% of those are predicted to have actionable genomic alterations,[17-19] we anticipate that liquid biopsy testing would detect at least 44 cases with actionable genomic alterations missed by tissue testing annually, and vice versa.

The overall concordance between liquid biopsy and tissue testing was notably high (87%–99%), primarily because of their high specificity and the low prevalence of actionable genomic alterations. This finding suggests that co-administering both tests could result in an overall discordance rate of 1% to 13%, capturing at least 44 additional cases annually in Ontario that might otherwise be missed by employing only 1 test. Additionally, our review found that the percentage of tissue-positive cases detected using liquid biopsy testing ranged from 45% to 70%, depending on the gene. Considering the lower end of this range and acknowledging the potential difficulty in obtaining tissue samples in up to 30% of NSCLC cases,[24] we estimate that liquid biopsy testing could annually uncover a minimum of 333 cases with actionable genomic alterations that would otherwise go undetected in the absence of tissue testing (whether because of issues of access to tissue testing or difficulty obtaining tissue samples).

Further, our review provides evidence suggesting that people who test positive for actionable genomic alterations with liquid biopsy testing, particularly those who are treatment-naïve or have a poor prognosis with standard therapies, are more likely to experience improved response when treated with

targeted therapies. This finding underscores the potential clinical benefit of liquid biopsy testing. Thus, the hypothetical clinical pathways illustrated in Figures 2 to 5 are all supported by the clinical evidence. However, to determine the optimal clinical pathway for people with NSCLC in Ontario, the clinical findings should be considered in conjunction with this report's economic and patient perspective findings.

In the clinical evidence review, we considered all types of NSCLC. However, we found that most studies consisted of populations with late-stage non–squamous cell carcinoma. Further, the NCCN guidelines[67] currently advise against the routine use of liquid biopsy testing except in cases of advanced or metastatic disease, primarily because at earlier stages, tumours may not shed sufficient DNA into the bloodstream to allow for liquid biopsy testing to reliably detect actionable genomic alterations.[163] Consequently, and because most publicly funded targeted therapies in Ontario are for advanced or metastatic NSCLC, we limited the economic analysis in this report to cases of newly diagnosed late-stage non–squamous cell carcinoma. Importantly, however, a definitive diagnosis of tumour type requires histological examination, immunohistochemistry, and molecular testing, which may not be feasible if a tissue sample is inadequate or unattainable. Additionally, certain gene alterations, such as *ALK*, *EGFR*, *MET* (including *MET* exon 14 skipping), and *RET*, can be present in both squamous and non–squamous cell carcinoma, albeit with varying prevalence. Thus, people diagnosed with squamous cell carcinoma may benefit from targeted therapies. One clinical expert also pointed out that in Ontario, laboratory teams typically lack information regarding NSCLC staging. Therefore, implementing a testing strategy involving upfront liquid biopsy testing, especially if not a component of reflex testing and confined to stage III and IV cases, may pose challenges (Peter Ellis, MD, March 25, 2024).

To align with the funding model of Ontario Health (Cancer Care Ontario), our unit of analysis was the gene rather than the person or a specific variant within a gene. One exception in the funding model is the funding for *MET* testing, which is currently restricted to the *MET* exon 14 skipping mutation. However, recent studies have demonstrated that certain *MET* fusion variants, such as *EML4–MET*, can also be targeted by therapies such as crizotinib, prescribed to people testing positive for the *MET* exon 14 skipping mutation.[164] Consequently, our analysis treated *MET* at the gene level, as with the other genes we assessed. Analyzing at the gene level offers advantages, particularly in standardizing comparisons across gene panels of varying sizes. This approach circumvents potential challenges wherein the absence of an alteration in a smaller panel might erroneously be interpreted as a negative result. Conversely, employing a gene variant, such as the *EGFR* L858R mutation or the *EGFR* exon 19 deletion, as the unit of analysis would be time-consuming without added benefit to inform the Ontario Health (Cancer Care Ontario) funding model. Notably, our review of the clinical literature revealed that when an alteration within the same gene was detected by both liquid biopsy and tissue testing, it was almost always the same variant, a finding that reinforces the rationale of analyzing at the gene level.

Although our primary focus was on comprehensive plasma-based genomic profiling using ctDNA assays, other types of NGS cell-free liquid biopsy assays are available that were not within the scope of this health technology assessment. These include circulating tumour RNA (ctRNA) assays, which analyze RNA molecules released by tumour cells into the bloodstream and encompass mRNA, noncoding RNA, and other RNA species.[165] Exosomal RNA (ExoRNA) assays[166] capture RNA molecules encapsulated within exosomes, allowing for the analysis of tumour-specific RNA transcripts. Circulating microRNA (miRNA)[167,168] assays detect and quantify tumour-derived miRNA molecules present in the bloodstream, whereas circulating messenger RNA (mRNA) assays capture and analyze mRNA molecules released by tumour cells into the bloodstream. Extracellular RNA (exRNA) assays encompass various approaches to isolating and analyzing RNA molecules present in extracellular fluids, including blood, urine, and

saliva.[169,170] These alternative assays offer several advantages, such as the ability to capture tumour-specific RNA alterations, including gene expression profiles, fusion transcripts, and splicing variants. However, RNA-based assays are more prone to degradation than ctDNA assays during sample processing and storage, which can affect assay sensitivity and reliability.

The NGS assays covered in the included studies are able to identify more gene variants than those included in the reflex testing strategy funded by Ontario Health (Cancer Care Ontario). This broader scope raises concerns of uncovering incidental or secondary findings unrelated to a person's primary condition. Such discoveries carry ethical and clinical implications, necessitating careful consideration of disclosure, follow-up testing, and subsequent management. Further, some people with NSCLC may lack awareness of the potential risks and implications associated with testing for additional gene variants beyond those directly related to an NSCLC diagnosis. These concerns highlight the importance of transparent communication between clinicians and patients and informed decision-making throughout the testing process.

Equity Considerations

A recent paper by Febbo et al[171] provides recommendations for the equitable and widespread implementation of liquid biopsy testing for people with cancer. The authors highlight racial and income disparities as major barriers likely to hinder access to and the adoption of liquid biopsy testing. To address these challenges, they suggested several measures, including providing clinicians with decision-making support and educational resources to foster trust and confidence in the technology. They also emphasize the importance of complementing clinical trial data with real-world evidence to gain insights into patterns of use and outcomes in a more representative population.

Strengths and Limitations

One of the primary challenges encountered in this review was the identification of a robust reference standard, essential for accurately evaluating the performance of liquid biopsy assays. While some studies relied on tissue testing as a reference standard, its reliability may be compromised, particularly in cases of tumour heterogeneity. To address this challenge, we employed a composite reference standard in which a positive result from either liquid biopsy or tissue testing was considered a true positive. This approach implicitly assumes perfect specificity, as false positives are presumed to be absent. We believe this assumption to be reasonable given the generally high specificity of these assays, as documented in the literature.[67] Conversely, while contamination with clonal hematopoiesis mutations remains a concern in terms of potentially causing false positives, currently approved liquid biopsy assays do not differentiate or report the origin of the mutations detected.[72] Nonetheless, progress has been made in addressing this limitation.[172]

Another limitation encountered was the scarcity of studies assessing the clinical validity of liquid biopsy testing, which limited our ability to gather evidence on the link between the detection of actionable genomic alterations and prognosis with standard therapies. However, gathering this evidence is less important if existing data already support the analytical validity and clinical utility of liquid biopsy testing. Further, many studies failed to report results exclusively by NSCLC subtype, making it difficult to evaluate the utility of liquid biopsy testing across disease stages. But our review benefitted from numerous studies reporting on the analytical validity of liquid biopsy assays, offering valuable insights into their performance in detecting actionable genomic alterations in NSCLC.

Despite encountering a limited number of studies evaluating the clinical utility of liquid biopsy testing compared with tissue testing, it is noteworthy that the response to targeted therapies remains consistent regardless of the type of assay used to accurately identify genomic alterations. This finding implies that we may have leveraged findings from tissue-testing studies as an indirect measure of the clinical utility of liquid biopsy testing, provided that liquid biopsy testing demonstrated adequate sensitivity. However, even with fewer studies available, the evidence supporting the clinical utility of liquid biopsy testing remained robust. Consequently, we did not find it necessary to rely on indirect evidence from tissue testing to assess the clinical utility of liquid biopsy testing.

One further limitation of this review was the lack of empirical studies assessing certain potential benefits of liquid biopsy testing. Although liquid biopsy testing may provide benefits in addition to those provided by tissue testing, such as the avoidance of harm from delayed treatment, invasive biopsy procedures, and unnecessary side effects of nontargeted chemotherapy, empirical studies in these areas are lacking. Exploring the avoidance of harm from delayed treatment, particularly in cases where obtaining a traditional tissue biopsy may be impractical or impossible, could provide valuable insight into the clinical utility of liquid biopsy testing. Additionally, assessing the safety and efficacy of liquid biopsy testing as an alternative to invasive tissue biopsy procedures could offer insights leading to significant advantages, particularly in reducing patient discomfort and the risk of complications. Moreover, investigating the potential reduction in side effects and supportive care requirements associated with targeted chemotherapy based on liquid biopsy testing results could enhance patient outcomes and quality of life. However, further research and empirical studies are needed to comprehensively evaluate these potential benefits and to inform policy decisions.

Conclusions

Analytical Validity

- Liquid biopsy testing has modest sensitivity (66%–73%) in detecting actionable genomic alterations in the *BRAF*, *EGFR*, *ERBB2*, and *KRAS* genes (GRADE: Moderate to High)
- Liquid biopsy testing has low sensitivity (56%–60%) in detecting actionable genomic alterations in the *ALK* and *PIK3CA* genes (GRADE: Moderate to High) and may have low sensitivity (60%–69%) in detecting actionable genomic alterations in the *MET*, *RET*, and *ROS1* genes (GRADE: Low)
- We are uncertain about the sensitivity of liquid biopsy testing in detecting actionable genomic alterations in the *FGFR1*, *NTRK1*, and *NTRK3* genes (GRADE: Very Low)
- The sensitivity of tissue testing in detecting actionable genomic alterations is consistently higher than liquid biopsy testing across all genes assessed, although the point estimates for some of the altetations are imprecise (GRADE: Very Low to High)
- Liquid biopsy testing has an overall high concordance (87 to 99%) with tissue testing in detecting actionable genomic alterations across all genes assessed (GRADE: High)
- The proportion of people testing positive for actionable genomic alterations with liquid biopsy testing among those testing negative with tissue testing is low for the *ALK*, *BRAF*, *EGFR*, *ERBB2*, *FGFR1*, *KRAS*, *MET*, *NTRK1*, *PIK3CA*, *RET*, and *ROS1* genes (GRADE: High). Although this proportion is low, it could translate to a large absolute value in settings where many people are diagnosed with NSCLC annually, as in Ontario

- The proportion of people testing positive for actionable genomic alterations with tissue testing among those testing negative with liquid biopsy testing is low for the *ALK*, *BRAF*, *EGFR*, *ERBB2*, *FGFR1*, *KRAS*, *MET*, *NTRK1*, *PIK3CA*, *RET*, and *ROS1* genes (GRADE: High). Although this proportion is low, it could translate to a large absolute value in settings where many people are diagnosed with NSCLC annually, as in Ontario
- The proportion of people testing positive for actionable genomic alterations with liquid biopsy testing among those testing positive with tissue testing is modest for the *ALK*, *BRAF*, *EGFR*, *ERBB2*, *KRAS*, *NTRK1*, and *PIK3CA* genes (GRADE: Moderate to High) and may be modest for the *MET* gene (GRADE: Low)
- We are uncertain about the extent to which liquid biopsy testing can detect the proportion of people testing positive for actionable genomic alterations with tissue testing among those testing positive with liquid biopsy testing for the *FGFR1*, *RET*, and *ROS1* genes

Clinical Validity

- We are uncertain whether the presence of actionable genomic alterations detected with liquid biopsy testing leads to a poor prognosis with standard therapies (GRADE: Very Low)

Clinical Utility

Among people testing positive for actionable genomic alterations with liquid biopsy testing:

- Targeted therapies can increase partial response rates (GRADE: Moderate), maintain stable disease rates (GRADE: Moderate), decrease progressive disease rates (GRADE: Moderate), and improve objective response rates (GRADE: Moderate)
- Targeted therapies may not improve complete response rates (GRADE: Low) but may improve progression-free and overall survival (GRADE: Low)

Economic Evidence

Research Question

What is the cost-effectiveness of liquid biopsy testing compared with tissue testing for people diagnosed with non–small cell lung cancer?

Methods

Economic Literature Search

We performed an economic literature search on June 1, 2023, to retrieve studies published from January 1, 2010, 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 until March 1, 2024. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Cost–benefit analyses, cost-effectiveness analyses, cost–consequence analyses, cost-minimization analyses, cost–utility analyses, budget impact analyses, or systematic reviews of economic analyses

Exclusion Criteria

- Studies in which the outcomes of interest are not reported or cannot be extracted
- Nonsystematic reviews, editorials, case reports, commentaries, conference abstracts, letters, or unpublished studies
- Noncomparative costing studies or feasibility analyses

Population

Inclusion Criterion

- People diagnosed with non–small cell lung cancer (NSCLC)

Intervention

Inclusion Criterion

- Liquid biopsy testing

Exclusion Criterion

- Liquid biopsy testing to detect the *EGFR* T790M mutation for people receiving *EGFR* tyrosine kinase inhibitors

Comparator

- Tissue testing

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

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

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

We contacted study authors to provide clarification as needed.

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.[173] The NICE checklist has 2 sections: the first is for assessing study applicability, and the second is for assessing study limitations. We modified the wording of the questions of the first section to make it specific to Ontario. Using this checklist, we assessed the applicability of each study to the research question (directly, partially, or not applicable). Next, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be applicable.

Results

Economic Literature Search

The economic literature search yielded 274 citations published between January 1, 2010, and May 31, 2023. We identified 1 additional eligible study from other sources, including database alerts (monitored until March 1, 2024). In total, we identified 6 studies that met our inclusion criteria. See Appendix 5 for a list of selected studies excluded after full-text review. Figure 13 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

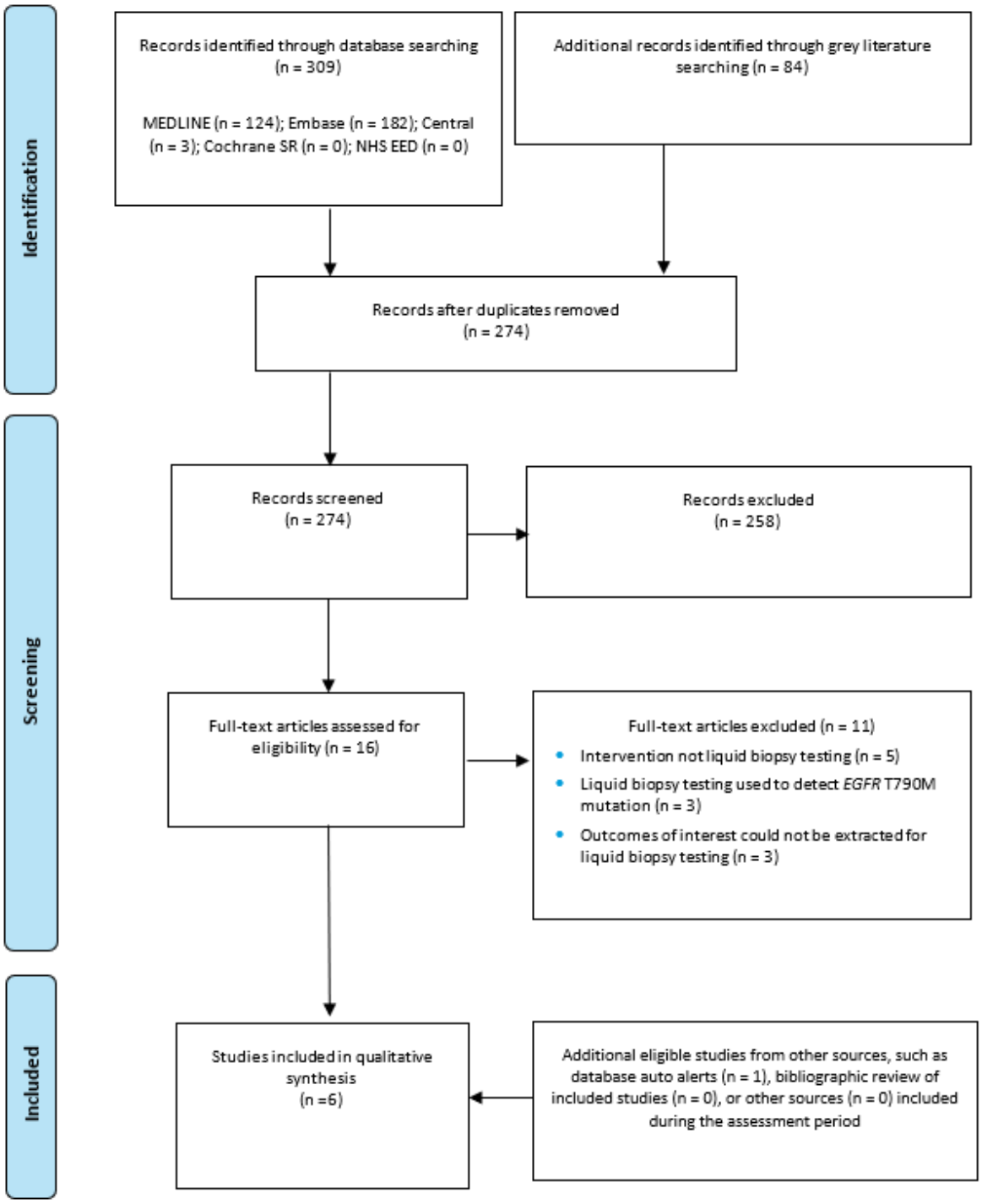

Figure 13: PRISMA Flow Diagram – Economic Systematic Review

PRISMA flow diagram showing the economic systematic review. The economic literature search yielded 274 citations, including grey literature results and after removing duplicates, published between January 1, 2010, and May 31, 2023. We screened the abstracts of the 274 identified studies and excluded 258. We assessed the full text of 16 articles and excluded a further 11. In the end, we included 6 articles in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[73]

Overview of Included Economic Studies

We identified 5 relevant studies published from January 1, 2010, to May 31, 2023,[174-178] and 1 additional study from database auto-alerts.[179] These included 3 Canadian studies[174-176] and 3 international studies.[177-179] All 6 studies were deemed partially applicable to our research question. Table 5 describes the study design, population, interventions, comparators, and results of the included studies.

Canadian Evidence

We identified a Canadian cost–utility analysis conducted by Ezeife et al[174] in which the authors compared the combination of tissue and liquid biopsy testing with tissue testing alone. The authors used a decision tree and a Markov model with a 2-year time horizon and took the perspective of a Canadian public payer. In the model, people with advanced NSCLC (incurable stage IIIB or IV) received either targeted therapy or chemo-immunotherapy. People with an actionable genomic alteration (i.e., an *EGFR* mutation, *ALK* fusion, or *ROS1* fusion) identified by tissue testing alone or by both tissue and liquid biopsy testing received targeted therapy. People with no actionable genomic alterations detected received chemo-immunotherapy. The authors sourced the prevalence of actionable genomic alterations and the sensitivity and specificity of each test from the literature. In the model, the prevalence of actionable genomic alterations varied by testing strategy. After starting treatment, people could continue to receive first-line treatment, experience disease progression, receive best supportive care, or transition to an absorbing death state. The model considered the costs of testing, disease management, drug acquisition, physician fees, outpatient monitoring, and terminal care. The authors sourced estimates of overall survival and progression-free survival from a prospective Canadian study comparing liquid biopsy testing with tissue testing (the VALUE study).[180] The authors discounted costs and health outcomes at a rate of 1.5% and reported costs in 2022 Canadian dollars.[174]

With tissue and liquid biopsy testing combined, 68.5% of people were found to have an actionable genomic alteration compared with 52.7% among those who received tissue testing only.[174] The larger number of people identified with actionable genomic alterations with the combination strategy resulted from the increased sensitivity of the additional liquid biopsy testing and the modelling decision to have the frequency of actionable genomic alterations vary by testing strategy. The authors found that the combination strategy was associated with a cost savings of $3,065 (95% confidence interval [CI]: $2,195; $3,945), despite the increased cost of liquid biopsy testing ($4,447), and an increase of 0.02 quality-adjusted life-years (QALYs) (95% CI: 0.01; 0.02) compared with tissue testing alone. Reductions in costs resulted from targeted therapy being less costly than chemo-immunotherapy. Scenario analyses found that the model was most sensitive to the cost of therapy and the prevalence of actionable genomic alterations.

We identified 2 Canadian budget impact analyses that evaluated the introduction of liquid biopsy testing to standard care for people with NSCLC with insufficient tissue for tissue testing.[175,176] In addition to estimating the budget impact of liquid biopsy testing, both studies calculated changes to life expectancy measured in life-years. Neither study conducted a formal cost-effectiveness analysis using estimated life-years. Patel et al[175] evaluated liquid biopsy testing for people with insufficient tissue for tissue testing over a 3-year time horizon. Insufficient tissue could arise from a tumour being in an unfavourable location or insufficient DNA in a tissue sample. The authors included the costs of molecular testing, drug acquisition and administration, and supportive care. Life-year estimates were sourced from previously published studies that evaluated median overall survival for people receiving targeted and nontargeted

therapies. The authors sourced the size of the target population from epidemiological data and published studies, which they estimated to resemble the Canadian population.

Johnston et al[176] conducted a budget impact analysis on the introduction of comprehensive genetic profiling (including both tissue and liquid biopsy testing) to standard care. As part of this analysis, the authors considered a scenario in which liquid biopsy testing was introduced for people with insufficient tissue for tissue testing. The authors used a 3-year time horizon and took the perspective of a Canadian public payer. The authors calculated increases in life expectancy owing to the increased use of targeted therapy. Survival estimates were sourced from a French registry study.[181] Based on expert opinion, the authors assumed that targeted therapies identified with tissue testing would be 50% less effective than those identified with liquid biopsy testing. The authors assumed that the reduced efficacy of tissue testing resulted from the faster turnaround time for liquid biopsy testing results. The authors reported costs in 2020 Canadian dollars and considered only testing-related costs. They estimated the population size to resemble that of Ontario.

Both Patel et al[175] and Johnston et al[176] found that adding liquid biopsy testing to standard care would increase both costs and life expectancy. Patel et al[175] found that the 3-year budget impact of introducing liquid biopsy testing in Canada would be $14.7 million (for about 2,235 people receiving liquid biopsy testing), while Johnston et al[176] found that the 3-year budget impact of introducing liquid biopsy testing in Ontario would be $4.4 million. Patel et al[175] estimated an increase of 168 life-years for the population of Canada, while Johnston et al[176] estimated an increase of 132 life-years for the population of Ontario. Scenario analyses conducted by Patel et al[175] indicated that budget impact estimates were sensitive to the probability of having sufficient tissue for tissue testing. Both studies estimated that when liquid biopsy testing was available, more people with actionable genomic alterations would be detected than with tissue testing alone (346 more people according to Patel et al[175] and 136 more people according to Johnston et al[176]).

International Evidence

We identified a cost–utility analysis by Englmeier et al[177] comparing liquid biopsy testing (for people with insufficient tissue for tissue testing or with suspected false negative tissue testing results) with the German standard care of tissue testing. The authors used a decision tree and Markov model with a 10-year time horizon that took the perspective of Germany's statutory health insurance. In the model, whether an actionable genomic alteration was detected depended on whether tissue testing was feasible, whether liquid biopsy testing was successful, and the sensitivity of liquid biopsy and tissue testing. After testing, people entered a Markov model in which first-, second-, third-, and fourth-line therapies are considered. Treatment options included targeted therapies, chemotherapy, chemo-immunotherapy, and best supportive care. Costs were reported in 2020 euros and included drug and diagnostic testing costs. The authors sourced utility estimates from previously published studies and varied them by the treatment a person was receiving. The authors sourced the effectiveness of therapies from previously published studies.

Englmeier et al[177] found that, compared with tissue testing, liquid biopsy testing was associated with an increase in both cost (€394) and effectiveness (0.01 QALYs), resulting in an incremental cost-effectiveness ratio (ICER) of €53,909 per additional QALY gained. The benefits of liquid biopsy testing applied only to the subset of people with an actionable genomic alteration detected (0.04 QALYs). Scenario analyses indicated that the model results were most sensitive to the test characteristics of liquid biopsy testing and the probability of a liquid biopsy test failing.

Jansen et al[179] conducted a distributional cost-effectiveness analysis comparing a "liquid-first" strategy (i.e., liquid biopsy testing followed by tissue testing for people with negative liquid biopsy test results) with tissue testing alone for people diagnosed with advanced NSCLC in the United States. The study used estimates of the prevalence of actionable genomic alterations stratified by genetic ancestry (non-Hispanic White, non-Hispanic Black, Asian, and Hispanic).[182] By stratifying the prevalence of actionable genomic alterations, the distributional cost-effectiveness analysis estimated how the costs and benefits (e.g., QALYs) of liquid biopsy testing might be greater for certain genetic ancestry subgroups.[179] The authors used a decision tree and partitioned survival model with a lifetime horizon and took the perspective of a US health system payer. They sourced effectiveness estimates from previously published studies. The model accounted for delays in receiving treatment results and the effectiveness of mismatched treatments resulting from false negative or false positive test results. In the reference case, only test-related costs were considered, whereas scenario analyses included costs related to both treatment and disease management. The authors reported costs in 2022 US dollars, and all outcomes were discounted at a rate of 3%.

Jansen et al[179] found that, compared with tissue testing alone, the liquid-first strategy was associated with an increase of 0.21 QALYs. This benefit was highest for people with an Asian genetic ancestry (0.31 QALYs) and lowest for those with a Hispanic genetic ancestry (0.17 QALYs). The liquid-first strategy was associated with higher testing costs ($3,270) than tissue testing only. When considering the costs of drug acquisition and therapy, the liquid-first strategy had an incremental cost of $57,629 compared with tissue testing only.

Yang et al[178] conducted a cost–consequence analysis from a US societal perspective in which liquid biopsy testing was used for people newly diagnosed with a metastatic lung carcinoma. Three strategies were compared: liquid biopsy testing after receiving negative tissue testing results, combined liquid biopsy and tissue testing, and tissue testing after receiving negative liquid biopsy testing results. The authors found that the combined strategy was associated with the shortest turnaround time for results (12.7 days) compared with the tissue-first (15.3 days) and liquid-first (17.2 days) strategies. The combination strategy was also associated with the highest per-person testing costs ($4,795) compared with the tissue-first ($2,353) and liquid-first ($4,316) strategies. The net monetary benefit analysis found that the tissue-first strategy was associated with the lowest monetary loss. Scenario analyses found that the model was most sensitive to the cost of liquid biopsy testing and the quantity of tissue specimens.

Table 5: Characteristics of Studies Included in the Economic Literature Review

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results: health outcomes	Results: costs	Results: cost-effectiveness
Ezeife et al, 2022, Canada[174]	• Cost–utility • Decision tree and Markov model • Canadian public payer • 2 years	People newly diagnosed with advanced NSCLC	*Intervention* Tissue + liquid biopsy testing *Comparator* Tissue testing alone	*QALYs* Tissue + liquid biopsy testing vs tissue testing alone: 0.02 (95% CI, 0.01; 0.02)	*2022 CAD* Tissue + liquid biopsy testing: $240,998 Tissue testing alone: $244,063	Tissue + liquid biopsy testing was more effective and associated with lower costs compared with tissue testing alone (scenario analyses were conducted on key model parameters)
Patel et al, 2021, Canada[175]	• Cost–consequence • BIA model • Canadian public payer • 3 years	People with advanced NSCLC and insufficient or exhausted tissue who require rebiopsy	*Intervention* Liquid biopsy testing *Comparator* Standard care	*Life-years* The use of liquid biopsy testing resulted in an increase of 168 for the Canadian population	*Budget impact, 2020 CAD* Adding liquid biopsy to standard care: $14.7 million	Budget impact estimates were most sensitive to the probability of sufficient tissue for tissue testing
Johnston et al, 2022, Canada (Ontario)[176]	• Cost–consequence • BIA model • Ontario public payer • 3 years	People with advanced NSCLC	*Intervention* Liquid biopsy testing for people with insufficient tissue for tissue testing *Comparator* Standard care	*Life-years* Increase of 132.1 for the population of Ontario vs standard care	*Incremental budget impact, 2020 CAD* $4.4 million	NA
Englmeier et al, 2022, Germany[177]	• Cost–utility • Markov model • German health care system • 10 years	People with nonsquamous NSCLC, stage IV	*Intervention* Liquid biopsy testing for people with insufficient tissue for tissue testing or suspected false negative tissue testing results *Comparator* Tissue testing	*QALYs* Liquid biopsy: 1.20 (95% CI, 1.18; 1.21) Tissue testing: 1.19 (95% CI, 1.17;1.21)	*2020 EUR* Liquid biopsy: €144,981 (95% CI, €142,545; €147,417) Tissue testing: €144,587 (95% CI, €142,145; €147,029)	ICER, adding liquid biopsy testing to standard care: €53,908 per additional QALY gained Scenario analysis ICER estimates ranged between €64,000 and €75,000
Jansen et al, 2023, United States[179]	• DCEA • Decision tree and partitioned	People with advanced NSCLC, stage IIIB or IV	*Intervention* Liquid biopsy testing followed by tissue testing for people with negative liquid biopsy results	*QALYs* Liquid biopsy + tissue testing: 1.61 (95% CI, 1.26; 2.09) Tissue testing alone: 1.41 (95% CI, 1.13; 1.77)	*2022 USD* Liquid biopsy + tissue testing: $7,342 (95% CI $7,011; $7,699) Tissue testing alone: $4,072 (95% CI; $4,016; $4,127)	Liquid biopsy + tissue testing was cost-effective at a WTP of $150,000 per QALY Scenario analyses that included treatment costs resulted in a

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results: health outcomes	Results: costs	Results: cost-effectiveness
	survival model • US public payer perspective • Lifetime		*Comparator* Tissue testing alone			$57,629 increase in costs; in these scenarios, liquid biopsy + tissue testing was not cost-effective at a WTP of $150,000 per QALY
Yang et al, 2022, United States[178]	• Cost–consequence • Decision tree • US societal perspective • 1 month	People newly diagnosed with a metastatic lung carcinoma	Liquid biopsy testing after receiving negative tissue testing results Combined liquid biopsy and tissue testing Tissue testing after receiving negative liquid biopsy results	*Turnaround time, days* Liquid biopsy after negative tissue testing results: 15.3 Liquid biopsy + tissue testing: 12.7 Tissue testing after negative liquid biopsy results: 17.2	*Per-person testing costs, 2021 USD* Liquid biopsy after negative tissue testing results: $2,354 Liquid biopsy + tissue testing: $4,795 Tissue testing after negative liquid biopsy results: $4,316	Liquid biopsy after tissue testing was associated with the lowest monetary loss Scenario analyses indicated the model was most sensitive to the cost of liquid biopsy testing and the probability of insufficient tissue for tissue testing

Abbreviations: BIA, budget impact analysis; CI, confidence interval; DCEA, distributional cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; NA, not applicable; NSCLC: non–small cell lung cancer; QALY, quality-adjusted life-year; WTP, Willingness-to-pay.

Selected Excluded Studies

We excluded 3 studies that evaluated liquid biopsy testing as a second-line test for *EGFR* T790M alterations, which were out of scope for this analysis.[183-185] We excluded a further 3 studies evaluating liquid biopsy testing in combination with tissue testing because we were unable to extract costs specific to liquid biopsy testing and effectiveness results.[186-188] See Appendix 5 for a more detailed list of selected studies excluded after full-text review along with the primary reason for exclusion.

Applicability and Limitations of the Included Studies

Appendix 6 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. The 3 Canadian studies were deemed partially applicable to our research question because of our uncertainty regarding whether other liquid biopsy testing strategies would have similar cost-effectiveness results to those evaluated.[174-176] The 3 international studies were deemed partially applicable to our research question owing to our uncertainty regarding whether their cost parameters were applicable to the Ontario context.[177-179]

Discussion

We identified 3 Canadian studies that we deemed partially applicable to the Ontario context; the population for all studies was people with advanced NSCLC.[174-176] We did not identify any studies evaluating liquid biopsy testing for people with early-stage NSCLC, which may be due to the uncertain clinical utility of liquid biopsy testing at earlier stages of NSCLC.[189] The cost–utility analysis by Ezeife et al[174] evaluated tissue and liquid biopsy testing combined, whereas the 2 budget impact analyses by Patel et al[175] and Johnston et al[176] evaluated liquid biopsy testing for people with insufficient tissue for tissue testing. All 3 studies found that the use of liquid biopsy testing would increase the number of people with actionable genomic alterations detected and increase the use of targeted therapies. The population sizes and budget impact estimates of the 2 budget impact analyses depended on the rate of insufficient tissue for tissue testing. Johnston et al[176] assumed that 5% of people presenting for testing would have insufficient tissue, whereas Patel et al[175] estimated this figure at 16%. While both studies considered changes in life expectancy, neither included a formal cost-effectiveness analysis, and the cost-effectiveness of liquid biopsy testing for people with insufficient tissue for tissue testing is unknown. Similarly, we were unable to identify Canadian cost-effectiveness evidence for alternative liquid biopsy testing strategies such as the liquid-first or tissue-first strategies evaluated by Yang et al.[178]

The 3 Canadian studies found liquid biopsy testing to be associated with increased testing costs compared with tissue testing despite the fact that liquid biopsy testing has lower sample acquisition costs.[174-176] The greater cost of liquid biopsy testing results primarily from the cost of commercial liquid biopsy tests. Patel et al[175] and Ezeife et al[174] found that the increased use of targeted therapies associated with introducing liquid biopsy testing to standard care resulted in a reduction in drug costs. This was because in both analyses, people without an identified actionable genomic alteration were eligible to receive pembrolizumab (a type of immunotherapy), which has a higher acquisition cost compared with other targeted therapies.

Johnston et al[176] assumed that the effectiveness of targeted therapies was lower when actionable genomic alterations were identified by tissue testing rather than liquid biopsy testing. The rationale for this assumption was that the shorter turnaround time to obtain results for liquid biopsy testing would result in people starting therapy earlier than those who had received tissue testing. It is unclear how

large of an impact this assumption had on the study's life expectancy estimates. Ezeife et al[174] varied the prevalence of actionable genomic alterations by treatment strategy (tissue and liquid biopsy testing combined versus tissue testing only).[174] It is unclear what impact this assumption had on the study's cost-effectiveness results.

Strengths and Limitations

We conducted a review of the economic literature comparing liquid biopsy testing with tissue testing for people with NSCLC. The primary strength of this review is its comprehensiveness in providing a summary of the latest economic evidence for liquid biopsy testing. We were able to identify evidence from a variety of jurisdictions evaluating various liquid biopsy testing strategies from a wide range of perspectives.

This review also has several limitations, including that our results are limited in their applicability. We identified Canadian evidence only for a subset of all potential liquid biopsy testing strategies, and only 1 of the identified Canadian studies included a cost–utility analysis. Further, we were unable to quantify how several modelling decisions affected economic outcomes for several studies.

Conclusions

We identified 6 economic studies, 3 of which were conducted in Canada, comparing various liquid biopsy testing strategies with tissue testing. However, the methods and results of these studies varied, with liquid biopsy testing found to be either cost-saving or cost-effective only at high willingness-to-pay values. None of the studies was deemed directly applicable to our research question. Because we found the cost-effectiveness of liquid biopsy testing to be uncertain based on existing evidence, we conducted a primary economic evaluation.

Primary Economic Evaluation

Research Question

What is the cost-effectiveness of liquid biopsy testing compared with tissue testing for people newly diagnosed with locally advanced or metastatic non–small cell lung cancer (stage IIIB or IV) 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.[190] The content of this report is based on a previously developed economic project plan.

Type of Analysis

In our reference case analysis, we conducted a cost–utility analysis, as recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluation.[191] A cost–utility analysis allowed us to estimate changes in costs and health-related quality of life as a result of an actionable genomic alteration being identified.

Outcomes of Interest

We considered the following outcomes of interest in our cost–utility analysis:

- Costs (including total costs and costs related to testing, treatment, and adverse events)
- Quality-adjusted life-years (QALYs)
- Life-years
- Incremental costs per QALY
- Incremental costs per life-year

In addition to a cost–utility analysis, we conducted a cost-effectiveness analysis related to the short-term testing outcomes in the model. We considered the following outcomes of interest in our cost-effectiveness analysis:

- Testing-related costs
- Number of actionable genomic alterations detected
- Number of rebiopsies conducted
- Number of people receiving targeted therapy (i.e., those whose treatment decision was influenced by actionable genomic alterations detected)
- Incremental costs per rebiopsies avoided
- Incremental costs per person receiving targeted therapy

Population of Interest

Our population of interest was people newly diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV). We used this population in our reference case analysis because published guidelines and consensus statements have highlighted the role of liquid biopsy testing in this population.[21,192]

Comprehensive genomic profiling provides people diagnosed with NSCLC access to targeted therapy. Most (all but 1) of the publicly funded targeted therapies available through the Exceptional Access Program in Ontario are indicated for locally advanced or metastatic NSCLC.[193] People with stage IB to IIIA NSCLC who have undergone complete resection and are confirmed to be positive for an *EGFR* mutation are eligible to receive osimertinib. However, we were unable to identify studies on the effectiveness of liquid biopsy testing to detect *EGFR* mutations in this subpopulation. Further, people who have undergone complete resection are more likely to have sufficient tissue for tissue testing. We excluded people with early-stage NSCLC due to the uncertainty of the clinical utility of liquid biopsy testing in this population.[189]

The Comprehensive Cancer Biomarker Testing Program recommends testing for all people newly diagnosed with nonsquamous NSCLC in the province regardless of stage.[194] Reflex testing reduces the time to treatment initiation.[192] If liquid biopsy testing were to be implemented in Ontario, it is unclear whether it would be provided as a reflex test for all people newly diagnosed with NSCLC or only for those with locally advanced or metastatic NSCLC. Therefore, we conducted scenario analyses in which the population of interest was expanded to include all people newly diagnosed with NSCLC.

We excluded people with squamous NSCLC because the current standard of care for this population in Ontario includes testing only for PD-L1 variants.[194] PD-L1 status is frequently determined using immunohistochemical staining, and most of the commercially available liquid biopsy assays in the province do not provide PD-L1 results.[195-199] For our reference case analysis, the median age at diagnosis in our cohort was 68.8 years, and 48% were female.[200,201]

Perspective

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

Interventions and Comparators

Expert consultation and previously published economic evaluations indicate that a variety of potential implementation strategies for liquid biopsy testing exist. We considered the following 4 strategies:

- Liquid biopsy testing for people with insufficient tissue for tissue testing ("insufficient tissue")
    - All people receive tissue testing, but only those with insufficient tissue receive liquid biopsy testing
- Liquid biopsy testing first ("liquid-first")
    - All people receive liquid biopsy testing, but only those with negative results receive tissue testing
- Tissue testing first ("tissue-first")
    - All people receive tissue testing, but only those with insufficient tissue or negative results receive liquid biopsy testing

- Combined tissue testing and liquid biopsy testing ("combined")
    - All people receive both tissue testing and liquid biopsy testing

We compared these interventions with tissue testing alone, the current standard care in Ontario. In our analysis, all interventions involved the addition of liquid biopsy testing to tissue testing. This was done because clinical experts indicated that a person with negative liquid biopsy testing results may have an actionable genomic alteration detected with tissue testing (H. Feilotter, PhD, email communication, August 22, 2023).

Time Horizon and Discounting

We used a lifetime horizon of 20 years in our reference case analysis. We selected this horizon because liquid biopsy testing is likely to impact health and cost outcomes for the lifetime of a person with NSCLC. In accordance with the CADTH guidelines,[191] we applied an annual discount rate of 1.5% to both costs and QALYs incurred after the first year. We did not discount costs related to short-term testing because we expect these to occur within the first year.

Model Structure

We developed a decision tree and partitioned survival model to estimate health and cost outcomes. The decision tree estimated short-term testing-related costs and outcomes such as the number of people with actionable genomic alterations detected. Figures 14 to 18 depict the decision tree model structure for the 4 interventions and current standard care.

After the decision tree, people enter a long-term partitioned survival model with the following health states: progression-free survival, progressed, and death. Figure 19 shows the structure of the partitioned survival model. In the partitioned survival model, the probability that a person chooses to receive treatment and the choice of treatment depend on whether an actionable genomic alteration was detected. People with no actionable genomic alterations detected could receive either immunotherapy or chemo-immunotherapy depending on PD-L1 test results. People choosing not to receive treatment receive best supportive care. The partitioned survival model used a 21-day cycle length to match the cycle length of several available NSCLC treatments.

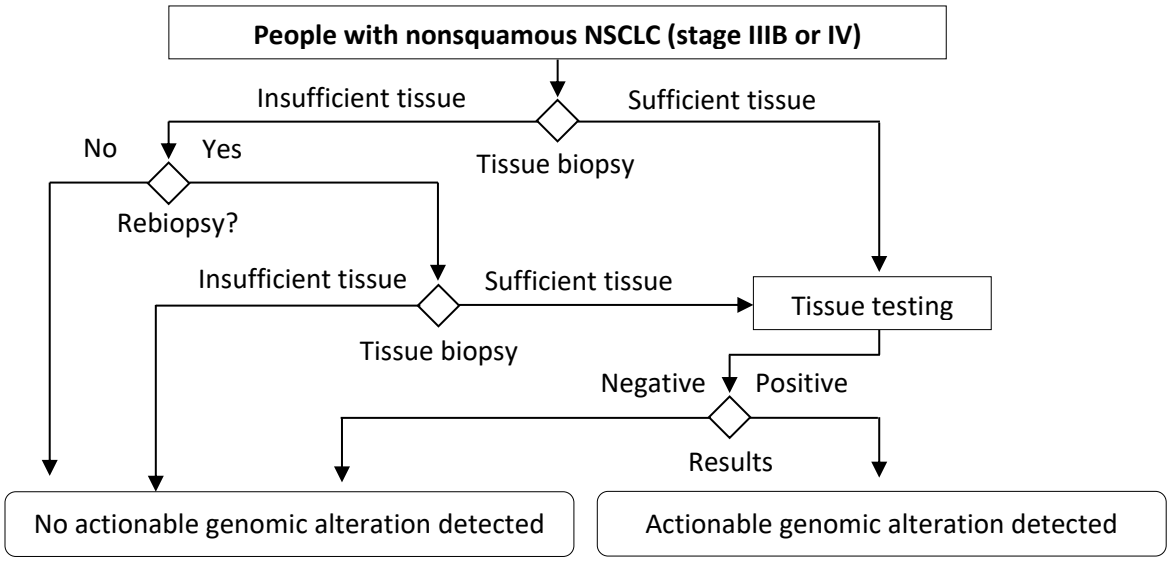

Figure 14: Decision Tree Model – Standard Care

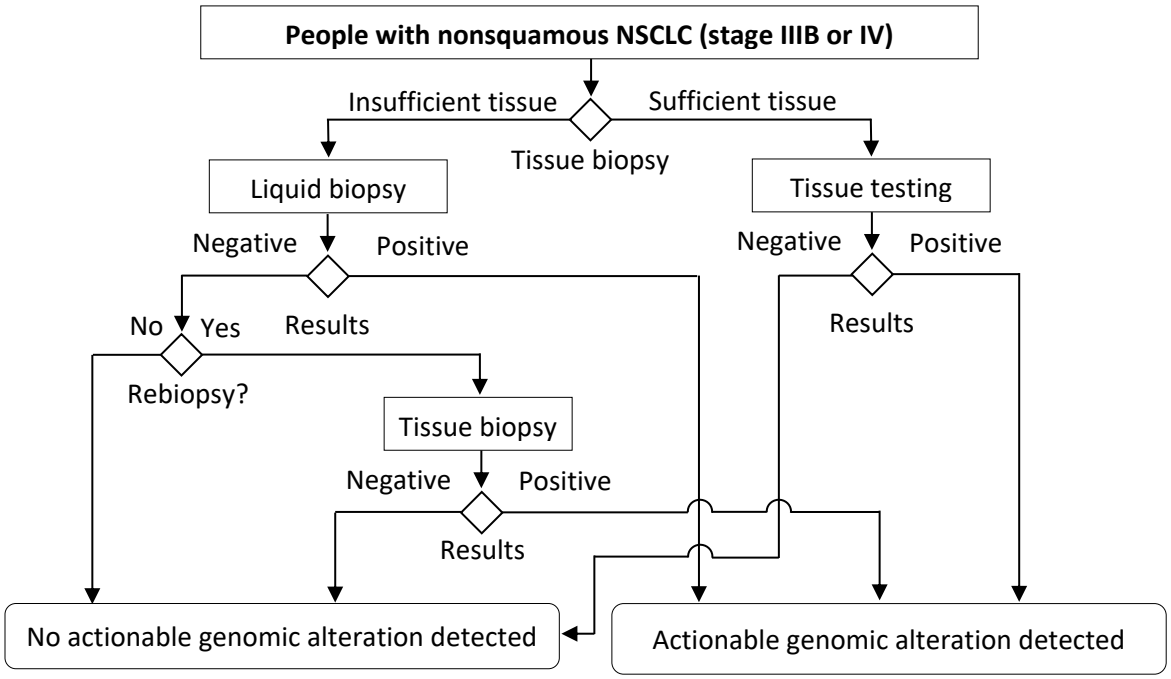

Figure 15: Decision Tree Model – Liquid Biopsy Testing for People With Insufficient Tissue for Tissue Testing

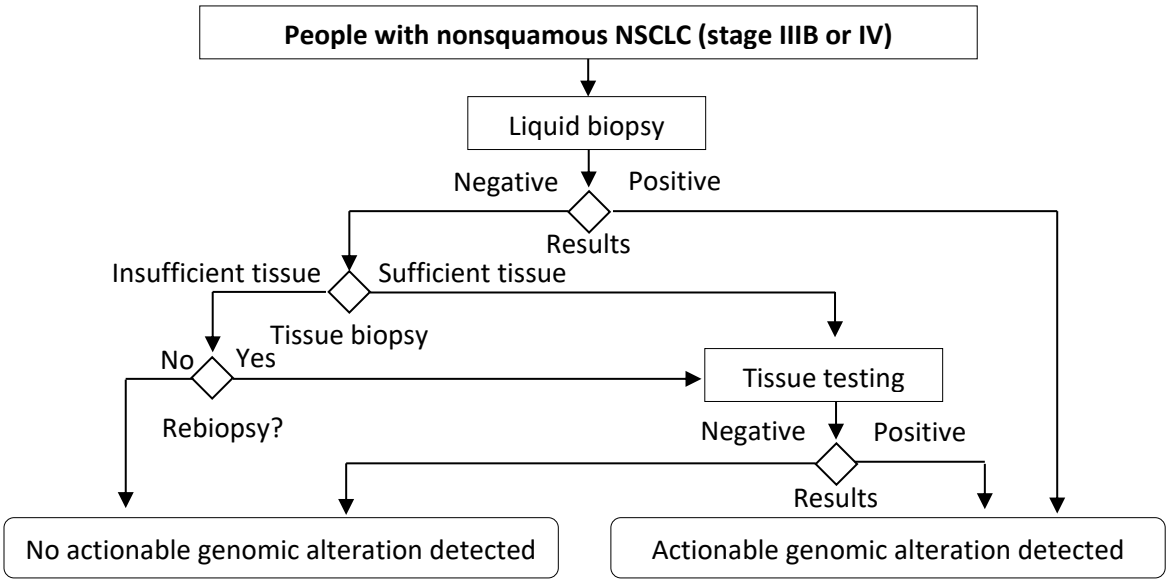

Figure 16: Decision Tree Model – Liquid Biopsy Testing First

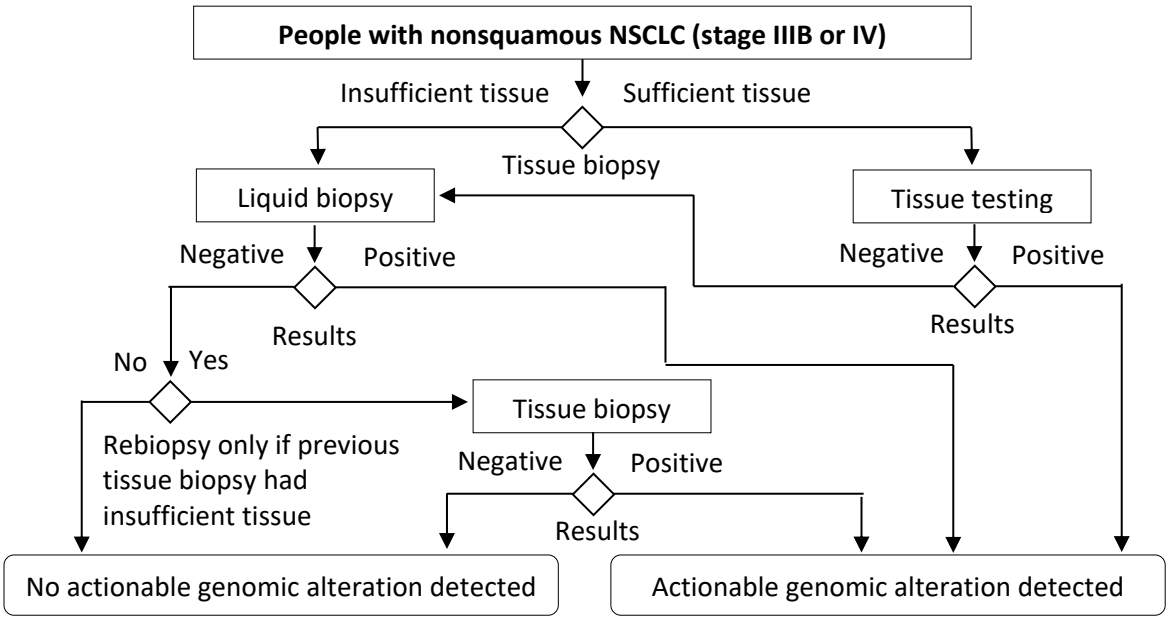

Figure 17: Decision Tree Model – Tissue Testing First

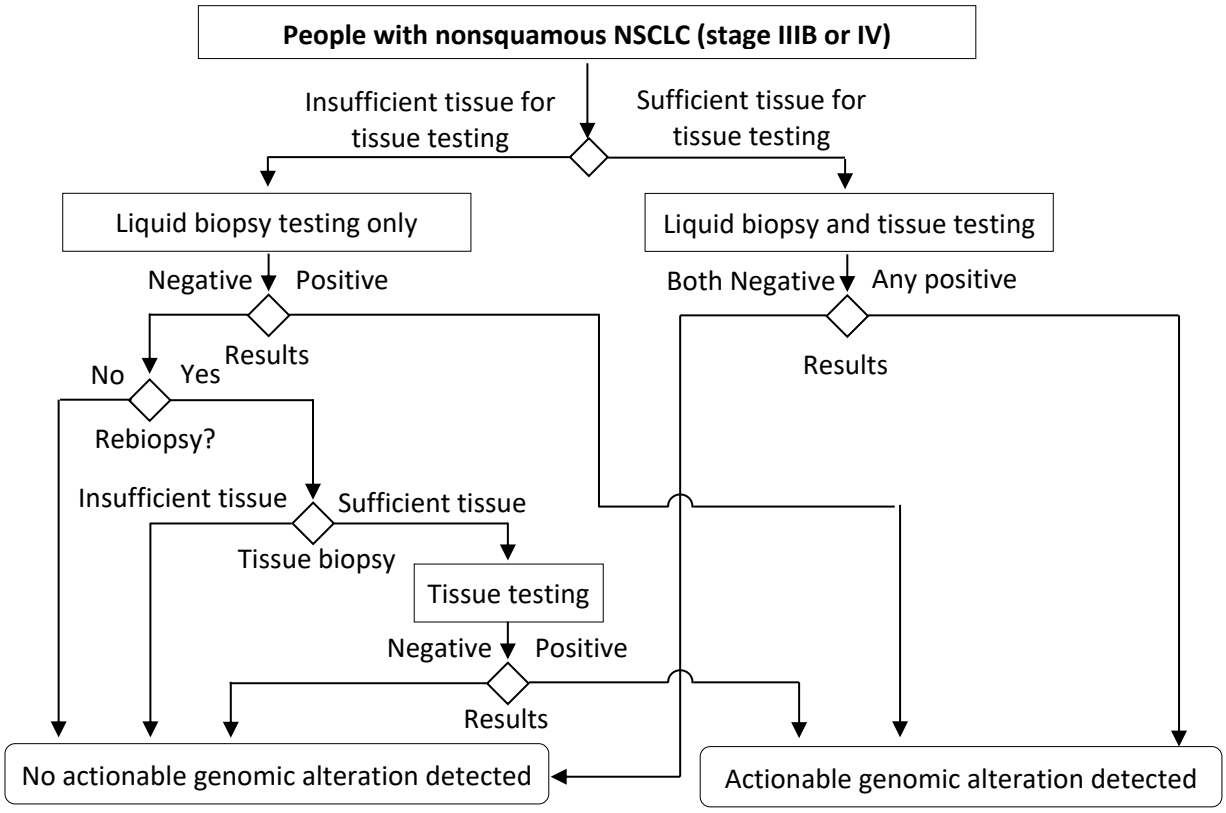

Figure 18: Decision Tree Model – Combined Tissue and Liquid Biopsy Testing

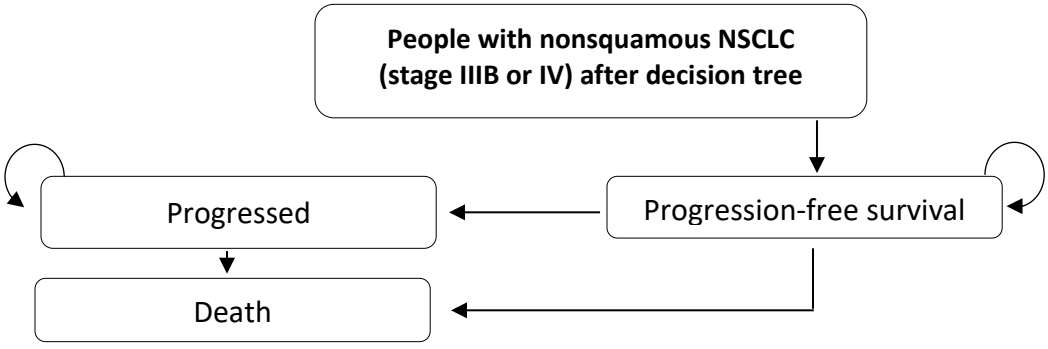

Figure 19: Long-Term Partitioned Survival Model

Main Assumptions

The model's main assumptions were as follows:

- Only people with locally advanced or metastatic NSCLC (stage IIIB or IV) would receive liquid biopsy testing
    - We conducted scenario analyses expanding the population of interest to include all people newly diagnosed with NSCLC
- Liquid biopsy testing would not replace tissue testing
- Because of the structure of the partitioned survival model, we made structural assumptions regarding the relationship between the health states of progression-free survival and progressed, primarily that the probability of dying in the progressed health state would not depend on the time spent in the progression-free survival health state[202]
- Owing to a lack of complete follow-up data for several treatments, we assumed that projections of immature survival data resembled the natural history outcomes of people receiving treatment for NSCLC in Ontario
- The effectiveness of liquid biopsy testing would be independent of the effectiveness of tissue testing (i.e., the probability of having an actionable genomic alteration detected by liquid biopsy testing would not be affected by tissue testing results)
- A person would have only 1 actionable genomic alteration

Clinical and Utility Parameters

Short-Term Decision Tree Parameters

We sourced model parameters from the results of the clinical evidence review, expert opinion, and the published literature. We sourced sensitivity for each actionable genomic alteration from the clinical evidence review. Similar to Englmeier et al,[203] we assumed that both tissue and liquid biopsy testing would have 100% specificity. We sourced the prevalence of actionable genomic alterations, the probability of insufficient tissue after tissue testing, the probability of a liquid biopsy sample not including tumour DNA, and the probability of a second tissue biopsy not being feasible from published studies.[204-212] As in the 2020 Ontario Health health technology assessment of liquid biopsy testing to detect *EGFR* T790M mutations, we assumed that only people who received tissue testing would be at risk of the testing-related adverse event of pneumothorax requiring chest drainage.[184] We sourced the probability of experiencing a pneumothorax requiring chest drainage from Ayyappan et al.[213] We sourced the probability that a person would have a PD-L1 expression level equal to or greater than 50% from Hwang et al.[201] PD-L1 test results depend on the success of tissue testing. We sourced test turnaround time, defined as time between test order date and test report, for both tissue and liquid biopsy testing from Leighl et al.[211] We conducted a scenario analysis in which reduced test turnaround time resulted in improved outcomes for people with actionable genomic alterations detected. Appendix 7 provides a detailed description of how we calculated our model inputs and incorporated uncertainty for each variable.

Long-Term Partitioned Survival Parameters

We sourced the probability that a person would choose to receive systemic therapy after undergoing genomic profiling from Stock-Martineau et al.[214] The probability of receiving treatment was higher for those with actionable genomic alterations detected than for those without an alteration detected. We conducted scenario analyses that varied the probability of choosing to receive treatment. We sourced the effectiveness of targeted therapy, chemo-immunotherapy, and best supportive care from published studies.[214-222] We created pseudo-patient-level data from published Kaplan–Meier curves for both progression-free survival and overall survival using the methods described by Guyot et al.[223,224] We fit parametric survival models using the flexsurv R package.[225] We selected the best-fitting distributions based on the Bayesian information criterion, the Akaike information criterion, and the clinical plausibility of each parametric survival model. We sourced the probability of commonly occurring treatment-related grade 3 or 4 adverse events (e.g., diarrhea, fatigue) from previous studies[215-217,219,220,226,227] and the probability of dying from causes other than cancer from Statistics Canada.[228]

Tables 6a and 6b list the natural history inputs used in the model and provide estimates of the median overall survival and median progression-free survival for the included treatments.

Table 7 lists the first- and second-line treatments that we considered in the model, which were those covered by Ontario's Exceptional Access Program.[193]

Table 6a: Natural History Inputs Used in the Economic Model – Decision Tree Model Parameters

Model parameter	Value	Reference
Sensitivity of liquid biopsy testing (95% CI)		
EGFR mutation	72% (66%; 78%)	Clinical evidence review
ALK mutation	60% (53%; 67%)	Clinical evidence review
ROS1	60% (41%; 77%)	Clinical evidence review
Sensitivity of tissue testing (95% CI)		
EGFR mutation	90% (85%; 93%)	Clinical evidence review
ALK mutation	81% (72%; 88%)	Clinical evidence review
ROS1	80% (66%; 89%)	Clinical evidence review
Specificity of liquid biopsy testing and tissue testing	100%	Assumed
Prevalence of actionable biomarkers (95% CI)		
EGFR mutation	16.6% (14.1%; 19.4%)	Kris et al[204]
ALK mutation	5.3% (4%; 6.6%)	Various studies[205-209]
ROS1	1.3% (1%; 1.6%)	Gainor et al[210]
Probability of a PD-L1 expression ≥ 50% (95% CI)	29.8% (27.6%; 31.9%)	Hwang et al[201]
Insufficient tissue for tissue testing (95% CI)	10.3% (6.9%; 14.2%)	Leighl et al[211]
Tumour not detected by liquid biopsy testing	4.6% (2.5%; 7.1%)	Leighl et al[211]
Probability that a second tissue biopsy is not feasible	18% (11%; 26%)	Chouaid et al[212]
Probability of a pneumothorax after tissue testing	28.0% (19.6%; 36.4%)	Ayyappan et al[213]
Probability that a pneumothorax requires chest drainage	30.0% (13.3%; 46.7%)	Ayyappan et al[213]
Liquid biopsy testing turnaround time	9 days	Leighl et al[211]
Tissue testing turnaround time	15 days	Leighl et al[211]
Tissue testing rebiopsy turnaround time	10.29 days	Yang et al[178]

Table 6b: Natural History Inputs Used in the Economic Model – Partitioned Survival Model Parameters

Model parameter	Value	Reference
Age at diagnosis	68.8 years	Hwang et al[201]
Probability of receiving treatment		
Actionable genomic alteration detected	89.2% (81.5%; 95.4%)	Stock-Martineau et al[214]
No actionable genomic alteration detected	59.2% (54.9%; 63.5%)	Stock-Martineau et al[214]
Median progression-free-survival, months (95% CI)		
EGFR: osimertinib, lognormal	17.9 (15.2;20.1)	Soria et al[215]
EGFR: afatinib, log-logistic	11 (10.4;12.1)	Wu et al[216]
ALK: alectinib, gen-gamma	33.7 (20.1;51.3)	Mok et al[217]
ROS1: crizotinib, log-logistic n	7.37 (5.31; 10.37)	Doebele et al[218]
ROS1: entrectinib, exponential	16.36 (12.83; 21.46)	Doebele et al[218]
PD-L1 < 50%: CRBPPEME+PEMB, log-logistic	3.76 (3.27; 4.33)	Gadgeel et al[219]
PD-L1 ≥ 50%: pembrolizumab, gen-gamma	8.55 (6.67; 11.29)	Reck et al[220]
Median overall survival, months, distribution (95% CI)		
EGFR: osimertinib, gamma	39.2 (34.6;43.3)	Ramalingam et al[221]
EGFR: afatinib, log-logistic	26.2 (24.2;27.7)	Yang et al[222]
ALK: alectinib, lognormal	127.8 (70.9;199.8)	Mok et al[217]
ROS1: crizotinib, log-logistic	20.7 (14.2;29.5)	Doebele et al[218]
ROS1: entrectinib, exponential	56.1 (51.9;60.2)	Doebele et al[218]
PD-L1 < 50%: CRBPPEME+PEMB, log-logistic	19.57 (16.72; 23.09)	Gadgeel et al[219]
PD-L1 ≥ 50%: pembrolizumab, log normal	26.18 (19.73; 34.08)	Reck et al[220]
BSC: log-logistic	3.76 (3.27; 4.33)	Stock-Martineau et al[214]
Other-cause mortality	General Canadian population	Statistics Canada Table 13-10-0837-01[228]
Commonly occurring treatment-related adverse events	Appendix 7	Various studies[215-217,219,220,226,227]

Abbreviations: BSC, best supportive care; CI, confidence interval; CRBPPEME-PEMB: carboplatin + pemetrexed + pembrolizumab.

Table 7: First- and Second-Line Treatments Considered in the Economic Model

Subgroup	First-line therapy, proportion of patients	Second-line therapy, proportion of patients
ALK[a]	Alectinib, 100%	Cisplatin-pemetrexed/carboplatin-pemetrexed, 100%
EGFR	Afatinib, 15%	Osimertinib, 60% Cisplatin-pemetrexed/carboplatin-pemetrexed, 40%
EGFR	Osimertinib, 85%	Cisplatin-pemetrexed/carboplatin-pemetrexed, 100%
ROS1	Crizotinib, 50%	Cisplatin-pemetrexed/carboplatin-pemetrexed, 100%
ROS1	Entrectinib, 50%	Cisplatin-pemetrexed/carboplatin-pemetrexed, 100%
PD-L1 < 50%	CRBPPEME-PEMB, 100%	Docetaxel, 100%
PD-L1 ≥ 50%	Pembrolizumab, 100%	Carboplatin-pemetrexed, 100%
Unknown PD-L1 status	CRBPPEME-PEMB, 100%	Docetaxel, 100%

Abbreviation: CRBPPEME-PEMB, carboplatin + pemetrexed + pembrolizumab.
[a]Loratinib has recently become publicly funded, but it is unclear what proportion of *ALK*-positive people would receive this drug compared to alectinib.

Health State Utilities

A health state utility represents a person's preference for a certain health state or outcome, such as progression-free survival or progressed for people with NSCLC. Utilities are often measured on a scale ranging from 0 (death) to 1 (full health). We sourced health state–related utilities for the progression-free survival and progressed health states from Labbé et al.[229] The authors sourced utility estimates using the EQ-5D-3L health-related quality-of-life instrument from people with metastatic lung cancer treated at a Canadian site. The study reports utility estimates by disease state, actionable genomic alteration, and whether a person received targeted therapy. We describe the calculation we used to generate disease state–specific estimates in Appendix 7. We sourced utility estimates for best supportive care and disutility estimates for commonly occurring adverse events (i.e., neutropenia, fatigue, nausea, diarrhea, and rash) from Nafees et al.[230] The authors elicited utilities using standard gamble methods from a UK population. We used a multiplicative method to combine disutility estimates and conducted a scenario analysis using the additive method as recommended by published guidelines.[191]

Table 8a lists the health state utilities used in the economic model, and Table 8b lists the adverse event disutilities used in the economic model.

Table 8a: Health State Utilities Used in the Economic Model

Health state	Utility (95% CI)	Duration	Reference
Progression-free survival	0.801 (0.778; 0.822)	While in the progression-free survival health state	Labbé et al[229]
Progressed	0.685 (0.651; 0.705)	While in the progressed health state	Labbé et al[229]
Best supportive care	0.473 (0.431; 0.517)	While receiving best supportive care	Nafees et al[230]

Abbreviation: CI, confidence interval.

Table 8b: Adverse Event Disutilities Used in the Economic Model

Adverse event	Disutility (95% CI)	Duration	Reference
Neutropenia	−0.09 (−0.12; −0.059)	1 model cycle	Nafees et al[230]
Fatigue	−0.073 (−0.11; −0.037)	1 model cycle	Nafees et al[230]
Nausea	−0.048 (−0.08; −0.016)	1 model cycle	Nafees et al[230]
Diarrhea	−0.047 (−0.077; −0.016)	1 model cycle	Nafees et al[230]
Rash	−0.032 (−0.056; −0.01)	1 model cycle	Nafees et al[230]

Abbreviation: CI, confidence interval.

Cost Parameters

Appendix 7 provides a detailed description of the testing- and treatment-related cost inputs.

Testing-Related Costs

Testing-related costs for both liquid biopsy and tissue testing included those of sample collection, sample transportation, sequencing, initial consultation, and results consultation. We sourced the cost of sample collection for tissue testing by querying the Ontario Case Costing Initiative (OCCI), accessed using

IntelliHealth Ontario, for costs associated with outpatient lung biopsy for people diagnosed with a lung neoplasm.[231] We sourced physician fees associated with tissue testing from the Ontario Health Insurance Plan (OHIP) Schedule of Benefits.[232] We sourced the cost of sample collection for liquid biopsy testing from Ezeife et al,[174] which used a circulating-tumour DNA peripheral blood test. We sourced the cost of sample transportation from the 2020 Ontario Health health technology assessment of liquid biopsy testing to detect *EGFR* T790M mutations.[184] Transportation costs were applied to both tissue and liquid biopsy testing, and we assumed that most samples would be transported from sites that conducted sample collection to laboratories for sequencing.

We sourced sequencing costs for tissue testing from Perdrizet et al,[233] a Canadian study that sourced the cost of tissue testing from an Ontario hospital. Costs included direct laboratory costs (i.e., reagents, labour) and fixed overhead costs. We conducted scenario analyses with alternative sequencing costs for tissue testing. We sourced liquid biopsy sequencing costs from the manufacturers of commercial tests available in Ontario, arriving at an average cost of $5,393.47 (Guardant, email communication, September 14, 2023; Roche, email communication, November 23, 2023). We considered alternative liquid biopsy sequencing costs in a scenario analysis that included the cost of an in-house liquid biopsy test sourced from Ezeife et al.[174]

As in the 2020 Ontario Health health technology assessment of liquid biopsy testing to detect *EGFR* T790M mutations,[184] we sourced the costs of initial consultation and results consultation from the OHIP Schedule of Benefits.[232] These costs were applied when people received either liquid biopsy or tissue testing. We also used methods similar to those used in the 2020 Ontario Health health technology assessment[184] to estimate the cost of adverse events associated with tissue testing. We sourced the cost of chest x-ray for people with a severe pneumothorax who undergo chest drainage from the OCCI[231] and the OHIP Schedule of Benefits.[232]

Treatment-Related Costs

We sourced drug acquisition costs from drug reimbursement reviews published by CADTH (Appendix 7, Table A15).[234-239] We sourced the dosing for each treatment regimen from Ontario Health (Cancer Care Ontario) treatment regimens[240] and Englmeier et al.[177] We considered all acquisition costs for drugs administered intravenously. We considered drug acquisition costs for take-home oral medications for people whose drug costs are covered by the Ontario Drug Benefit (ODB) program,[241] and we assumed that 100% of people aged 65 years and older would have ODB coverage for these medications. We estimated that 33.7% of people aged 64 years and younger would be eligible for ODB coverage (via enrollment in the Ontario Works program, the Ontario Disability Support Program, or the Trillium Drug Program).[242] Based on the mean age and the standard deviation of the age for the modelled cohort sourced from Hwang et al,[201] we estimated that 35.8% (95% CI, 33.6%; 38.1%) of people would be 64 years of age or younger. We estimated that 76.2% (95% CI, 74.7% ;77.8%) of the modelled cohort would be eligible for ODB coverage.

We sourced pharmacy and nursing workloads for intravenously administered treatments from the Ontario Health (Cancer Care Ontario) drug formulary[240] and matched those with nursing and pharmacy salary estimates.[243,244] We sourced physician costs for intravenously administered treatments from the OHIP Schedule of Benefits.[232] Administration costs for oral medications consisted of a pharmacy dispensing fee incurred once every 21-day cycle. We based the duration of treatment for first-line therapies on treatment protocols and for second-line therapies on published estimates of second-line progression-free survival.[245-247] We sourced adverse event costs for commonly occurring adverse events

from the OCCI.[231] Owing to data limitations, we assumed that an adverse event could occur only once during the first cycle of treatment.

As in the 2020 Ontario Health health technology assessment,[184] we sourced the costs of general care for the progression-free survival and progressed health states from Goeree et al.[248] We sourced the costs of end-of-life care from de Olivera et al[249] and applied these in the last model cycle prior to disease-related mortality.

Tables 9a and 9b list the testing- and treatment-related costs used in the economic model.

Table 9a: Testing-Related Costs Used in the Economic Model

Variable	Unit cost, $ (95% CI)	Reference
Sample collection		
Liquid biopsy testing	115.31 (93.50; 139.30)	Ezeife et al[174]
Tissue testing	2,332.11 (1,888.67; 2,832.14)	OHIP Schedule of Benefits,[232] OCCI[231]
Sequencing		
Proprietary biopsy testing	5,393.47	Personal communication[a]
Tissue testing	1,385.83	Perdrizet et al[233]
Initial consultation	166.50	OHIP Schedule of Benefits[232]
Sample transportation	61.15	Ontario Health[184]
Result consultation	166.50	OHIP Schedule of Benefits[232]
Pneumothorax: chest x-ray	669.51 (606.43; 735.30)	OCCI,[231] OHIP Schedule of Benefits[232]
Severe pneumothorax: chest tube	806.65 (617.47; 1,153.52)	OCCI,[231] OHIP Schedule of Benefits[232]

Abbreviations: CI, confidence interval; OCCI, Ontario Case Costing Initiative; OHIP, Ontario Health Insurance Plan.

Table 9b: Treatment-Related Costs Used in the Economic Model

Variable	Unit cost, $ (95% CI)	Reference
Drug acquisition per cycle		
Osimertinib	6,188.28	CADTH[237]
Afatinib	1,539.30	CADTH[234]
Crizotinib	6,160.14	CADTH[236]
Alectinib	3,451.44	CADTH[239]
Entrectinib	6,003.90	CADTH[235]
Pembrolizumab	8,800.00	CADTH[235]
CRBPPEME-PEMB	10,654.40	CADTH[235]
Cisplatin-pemetrexed	1,394.00	CADTH[235]
Carboplatin-pemetrexed	1,854.40	CADTH[235]
Docetaxel	310.08	CADTH[235]
Drug administration costs		
Oral medications (per cycle)	9.93	Government of Canada[250]
IV medications (per visit)	151.22	Ontario Nurses' Association,[243] Indeed,[244] OHIP Schedule of Benefits[232]
General care costs per cycle		
Progression-free	921.47	Goeree et al[248]
Progressed	1,090.26	Goeree et al[248]
End-of-life costs	3,613.78	de Olivera et al[249]
Adverse event costs	See Appendix 7, Table A16	OCCI[231]

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; CRBPPEME-PEMB: carboplatin + pemetrexed + pembrolizumab; OCCI, Ontario Case Costing Initiative; OHIP, Ontario Health Insurance Plan.
[a]Guardant, email communication, September 14, 2023; Roche, email communication, November 23, 2023.

Internal Validation

The secondary health economist conducted formal internal validation. This process included testing the mathematical logic of the model, checking for errors, and ensuring the accuracy of parameter inputs and equations.

Analysis

Our reference case and sensitivity analyses adhered to the CADTH guidelines when appropriate.[191] The reference case represents the analysis with the most likely set of input parameters and model assumptions. We calculated the reference case by running 1,000 simulations (probabilistic analysis) that simultaneously captured the uncertainty in all parameters expected to vary. We set distributions for variables within the model (Appendix 7 lists the model variables and corresponding distributions). We calculated mean costs with credible intervals and mean QALYs with credible intervals for each intervention assessed. We also calculated mean incremental costs with credible intervals, incremental QALYs with credible intervals, and ICERs for each of the 4 liquid biopsy interventions versus the tissue testing comparator. We used 1,000 simulations to ensure the convergence of ICER model results. The results of the probabilistic analysis are presented in a scatter plot on a cost-effectiveness plane and cost-effectiveness acceptability curve for each of the 4 interventions.

Although not used as definitive willingness-to-pay (WTP) thresholds, including graphical indications of the location of the results relative to guideposts of $50,000 per QALY and $100,000 per QALY facilitated the interpretation of our findings and comparison with historical decisions. We present uncertainty quantitatively as the probability that an intervention is cost-effective at the 2 WTP guideposts. We also present uncertainty qualitatively according to 1 of 5 categories defined by the Ontario Decision Framework[251]: highly likely to be cost-effective (80%–100% probability of being cost-effective), moderately likely to be cost-effective (60%–79% probability), uncertain if cost-effective (40%–59% probability), moderately likely not to be cost-effective (20%–39% probability), or highly likely not to be cost-effective (0%–19% probability).

Scenario Analyses

We conducted several scenario analyses that explored how the results were affected by varying input parameters and model assumptions. Because of our uncertainty regarding whether liquid biopsy testing would be provided as a reflex test for all people newly diagnosed with NSCLC or only for those with locally advanced or metastatic NSCLC, we conducted 2 scenario analyses in which the population of interest was expanded to include all people newly diagnosed with NSCLC. In the first scenario analysis, the population of interest included all people diagnosed with NSCLC, but those with stage IB to IIIA NSCLC who had undergone a complete resection would still require tissue testing to determine their *EGFR* status in order to receive osimertinib. The second scenario analysis allowed people with stage IB to IIIA NSCLC who had undergone a complete resection to have their *EGFR* status detected by liquid biopsy testing. Table 10 lists our scenario analyses.

Table 10: Variables Varied in Scenario Analyses

Scenario	Parameter	Reference case	Scenario analysis
1	Time horizon	20 years	5 years
2	Time horizon	20 years	10 years
3	Time horizon	20 years	15 years
4	Discount rate	1.5%	3%
5	Discount rate	1.5%	0%
6	Population of interest	People with locally advanced or metastatic NSCLC (stage IIIB or IV)	All people newly diagnosed with NSCLC
7	Population of interest	People with locally advanced or metastatic NSCLC (stage IIIB or IV)	All people newly diagnosed with NSCLC; liquid biopsy testing provides actionable results for those diagnosed with stage IB–IIIA NSCLC who have undergone complete resection (NSCLC treatment outcomes sourced from CADTH[238]; see Appendix 7)
8	Drug acquisition cost	No discount	20% discount
9	Drug acquisition cost	No discount	40% discount
10	Drug acquisition cost	No discount	60% discount
11	Drug acquisition cost	No discount	80% discount
12	Drug acquisition cost	No discount	100% discount
13	Liquid biopsy testing	Sequencing costs sourced from manufacturers	Liquid biopsy sequencing cost sourced from Ezeife et al[174]: $1,289.38
14	Liquid biopsy testing	Sequencing costs sourced from manufacturers	Liquid biopsy testing cost increased by 25%: $6,741.84
15	Liquid biopsy testing	Sequencing costs sourced from manufacturers	Liquid biopsy testing cost decreased by 25%: $4,045.10
16	Treatment effectiveness	Effectiveness parameters reported in Table 6	Parameters sourced from the same sources as those used in Englmeier et al[177] (crizotinib from Wu et al,[252] afatanib from Sequist et al,[253] and pembrolizumab from Mok et al[254])
17	Treatment effectiveness	Effectiveness parameters reported in Table 6	Parameters sourced from the same sources as those used in Jansen et al[179] (alectinib from Jahanzeb et al,[255] pembrolizumab from Velcehti et al,[256] and CRBPPEME-PEMB from Velcheti et al[256])
18	Treatment effectiveness	Effectiveness parameters reported in Table 6	Parameters sourced from the same sources as those used in Patel et al[175] (alectinib from Peters et al,[257] crizotinib from Shaw et al,[258] and CRBPPEME-PEMB from Gandhi et al[259])
19	Probability of receiving treatment	With an actionable genomic alteration detected: 89.2% Without an actionable genomic alteration detected: 59.2%	62.7% for people with and without an actionable genomic alteration detected (sourced from Stock-Martineau et al[214])
20	All-cause mortality	Included	Excluded
21	Eligibility for ODB	76.2% of people are eligible	100% of people are eligible
22	Adverse event disutility	Implemented using an additive approach	Implemented using a multiplicative approach
23	Adverse events	Included	Excluded
24	Probability of tumour not being detected in liquid biopsy sample	4.6%	7.1%

Scenario	Parameter	Reference case	Scenario analysis
25	Probability of tumour not being detected in liquid biopsy sample	4.6%	2.5%
26	Probability of insufficient tissue for tissue testing	10.3%	14.2%
27	Probability of insufficient tissue for tissue testing	10.3%	6.9%
28	Probability that a second tissue biopsy is not feasible	18%	26%
29	Probability that a second tissue biopsy is not feasible	18%	11%
30	Duration of end-of-life care	21 days prior to death	3 months prior to death
31	Duration of end-of-life care	21 days prior to death	1 year prior to death
32	Treatment effectiveness	Survival distributions reported in Table 6	Second-best-fitting distributions as judged by AIC
33	Treatment effectiveness	Survival distributions reported in Table 6	Second-best-fitting distributions as judged by BIC
34	Treatment effectiveness	Test turnaround time does not affect health outcomes	Hazard ratio reduction of 0.9 applied to the probability of progressing or dying (sourced from Jansen et al[179]) for people with an actionable genomic alteration detected with a liquid-first strategy
35	Treatment effectiveness	Nontargeted therapy is equally effective for people with and without an actionable genomic alteration detected	Hazard ratio increase of 1.34 applied to the risk of progressing or dying (sourced from Jansen et al[179]) for people with an actionable genomic alteration detected and receiving nontargeted therapy
36	Probability of receiving treatment	With an actionable genomic alteration detected: 89.2% Without an actionable genomic alteration detected: 59.2%	100% for all people
37	Test characteristics	Sourced from clinical evidence review (see Table 6)	Liquid biopsy testing: upper 75th quantile sensitivity estimates Tissue testing: lower 25th quantile sensitivity estimates
38	Test characteristics	Sourced from clinical evidence review (see Table 6)	Liquid biopsy testing: lower 25th quantile sensitivity estimates Tissue testing: upper 75th quantile sensitivity estimates
39	Cost of orally administered drugs	No discount	20% discount
40	Cost of orally administered drugs	No discount	40% discount
41	Perspective	Ministry of Health	Limited societal perspective considering all drug acquisition costs and targeted therapy options available for people with *RET*, *MET*, or *BRAF* actionable genomic alterations (see Appendix 7 for a detailed description of the scenario analysis inputs)
42	Effectiveness of alectinib	Median overall survival: 127.8 months	Median overall survival: 79.56 months

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CADTH, Canadian Agency for Drugs and Technologies in Health; CRBPPEME-PEMB, carboplatin + pemetrexed + pembrolizumab; NSCLC: non–small cell lung cancer; ODB, Ontario Drug Benefit program.

Results

Reference Case Analysis

We estimated that when receiving standard care (i.e., tissue testing alone), 19.3% (95% credible interval [CrI]: 17%; 22.5%) of the modelled cohort would have an actionable genomic alteration detected. All 4 liquid biopsy testing strategies were associated with an increase in the number of people with an actionable genomic alteration detected. When receiving the combined, liquid-first, or tissue-first strategy, 22% (95% CrI: 19.1%; 24.8%) of the modelled cohort had an actionable genomic alteration detected. These 3 strategies detected the same number of people with an actionable genomic alteration since both liquid biopsy and tissue testing were considered to be available to all people in the modeled cohort. For the strategy of liquid biopsy testing only for people with insufficient tissue for tissue testing, 20.3% (95% CrI: 17.5%; 23.1%) of people had an actionable genomic alteration detected. This rate was lower than for the other liquid biopsy testing strategies because liquid biopsy testing was available only for those with insufficient tissue for tissue testing. All 4 liquid biopsy testing strategies were associated with a decreased use of best supportive care and an increased use of targeted therapy.

All 4 liquid biopsy testing strategies were associated with increased testing costs compared with the estimated cost of $4,756 (95% CrI: $4,253; $5,303) for standard care. The combined strategy was associated with the largest estimated cost of $10,602 ($10,112; $11,132), whereas the insufficient tissue strategy was associated with the lowest estimated cost of all the liquid biopsy testing strategies at $5,315 ($4,731; $5,922). All 4 liquid biopsy testing strategies were associated with a decrease in the number of tissue biopsies conducted, with the liquid-first strategy associated with the largest reduction. Test turnaround time for those with an actionable genomic alteration detected was reduced in the combined and liquid-first strategies.

We estimated that standard care alone was associated with 1.79 QALYs (95% CrI: 1.63; 1.96) and a total lifetime cost of $208,974 (95% CrI: $189,607; $230,383). All liquid biopsy testing strategies resulted in an increase in QALYs, with an increase of 0.04 (95% CrI: 0.03;0.06) for people in the combined, liquid-first, and tissue-first strategies. The insufficient tissue strategy was associated with an increase of 0.01 QALYs (95% CrI: 0.01;0.02) compared with standard care. All liquid biopsy testing strategies were associated with increased costs compared with standard care. The combined strategy was associated with the highest increase of $7,310 (95% CrI: $6,438; $8,364), whereas the insufficient tissue strategy was associated with the lowest increase of $970 (95% CrI: $596; $1,481). The increased costs were primarily associated with increased liquid biopsy testing costs, increased first-line therapy costs, and increased costs for general care. We estimated cost savings related to adverse events, drug administration, and tissue testing.

Compared with standard care, the ICER for the combined strategy was $173,032 per additional QALY gained, $157,267 for the liquid-first strategy, $147,636 for the tissue-first strategy, and $96,738 for the insufficient tissue strategy. The probability that any liquid biopsy testing strategy was cost-effective at a WTP of $50,000 per QALY was less than 1%. At a WTP of $100,000 per QALY, the only liquid biopsy testing strategy with a chance of more than 1% of being cost-effective was the insufficient tissue strategy at 55%. At a WTP of $150,000 per additional QALY gained, the probability of being cost-effective was more than 99% for the insufficient tissue strategy, 47% for the tissue-fit strategy, 30% for the liquid-first strategy, and 11.9% for the combined strategy.

Table 11 provides the results of the reference case analysis. Figure 20 presents the cost-effectiveness acceptability curves for each strategy, and Figure 21 presents the cost-effectiveness planes for each strategy.

Appendix 8 provides the short-term testing model outcomes (Table A17), long-term treatment-specific partitioned survival model outcomes (Table A18), and detailed cost outcomes (Table A19).

Table 11: Reference Case Analysis Results

Strategy	Life-years	QALYs	Total cost, $	ICER[a]
Standard care	2.63 (2.38; 2.88)	1.79 (1.63; 1.96)	$208,974 ($189,607; $230,383)	NA
Combined testing	2.69 (2.44; 2.94)	1.83 (1.67; 2.00)	$216,284 ($197,055; $237,814)	NA
vs standard care	0.06 (0.04; 0.08)	0.04 (0.03; 0.06)	$7,310 ($6,438; $8,364)	$173,032
Liquid-first	2.69 (2.44; 2.94)	1.83 (1.67; 2.00)	$215,618 ($196,372; $237,036)	NA
vs standard care	0.06 (0.04; 0.08)	0.04 (0.03; 0.06)	$6,644 ($5,773; $7,703)	$157,267
Tissue-first	2.69 (2.44; 2.94)	1.83 (1.67; 2.00)	$215,211 ($195,950; $236,687)	NA
vs standard care	0.06 (0.04; 0.08)	0.04 (0.03; 0.06)	$6,237 ($5,381; $7,351)	$147,636
Insufficient tissue	2.64 (2.39; 2.90)	1.8 (1.64; 1.97)	$209,944 ($190,498; $231,514)	NA
vs standard care	0.01 (0.01; 0.02)	0.01 (0.01; 0.02)	$970 ($596; $1,481)	$96,738

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life-year.

[a]Results may appear inexact due to rounding.

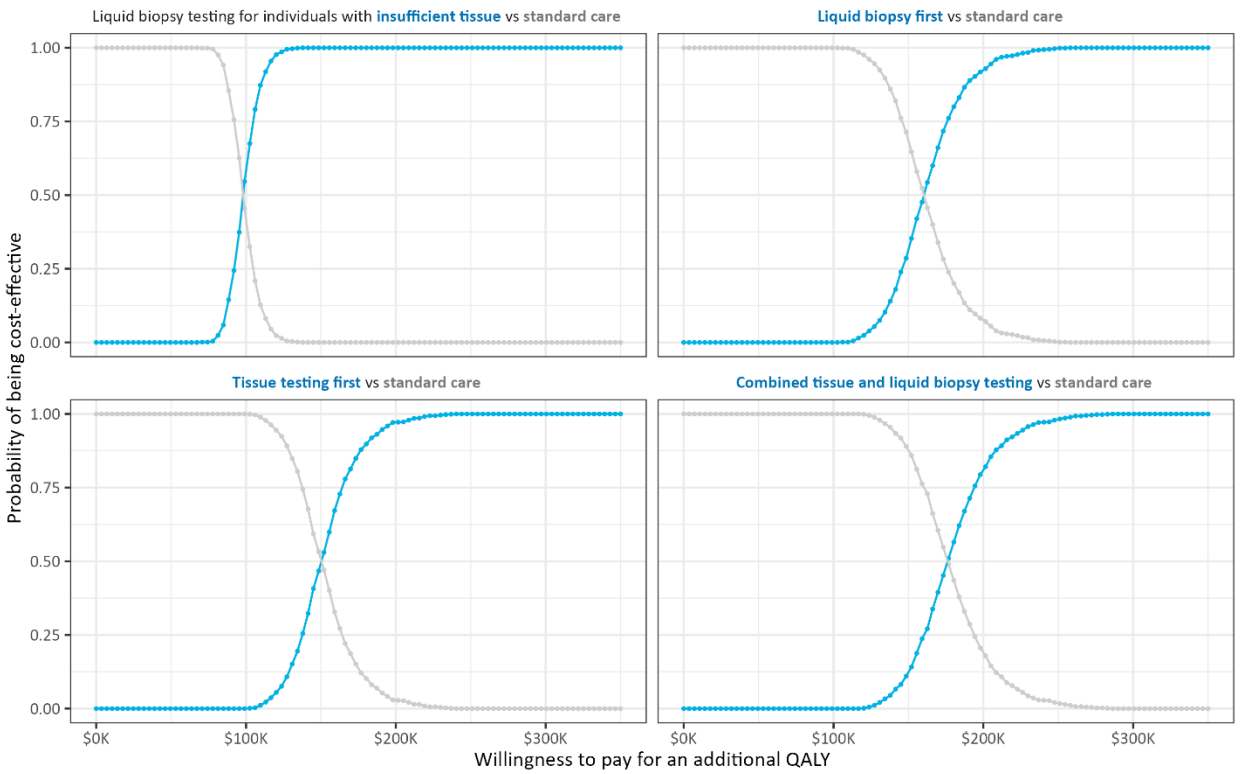

Figure 20: Cost-Effectiveness Acceptability Curves for Each Testing Strategy

Cost-effectiveness acceptability curves for each of the 4 liquid biopsy testing strategies compared with standard care (i.e., tissue testing only). The probability that any liquid biopsy strategy is cost-effective at a WTP of $50,000 per additional QALY is less than 1%. Only the insufficient tissue strategy is likely to be cost-effective at a WTP of $100,000 per additional QALY gained.
Abbreviations: QALY, quality-adjusted life-year; WTP, willingness-to-pay.

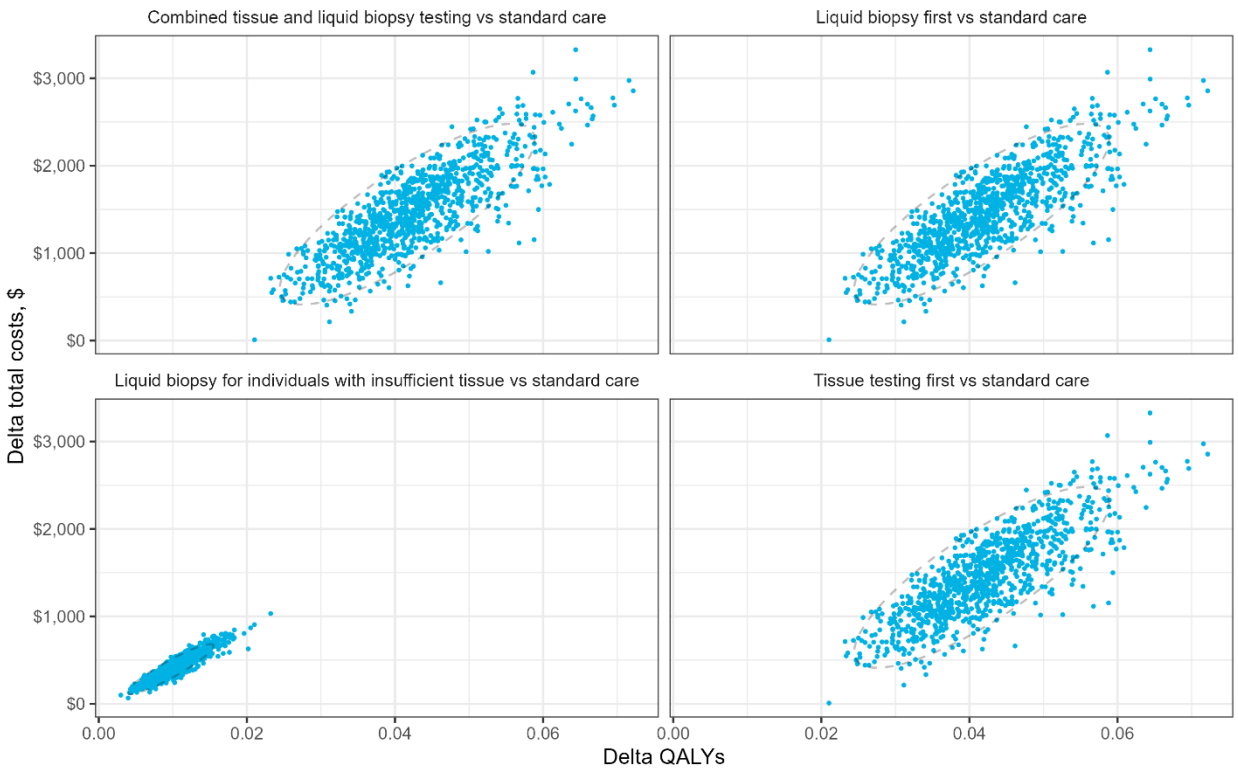

Figure 21: Cost-Effectiveness Planes for Each Testing Strategy

Cost-effectiveness planes for each of the 4 liquid biopsy testing strategies compared with standard care. In all simulations, all strategies were associated with an increase in QALYs and an increase in costs compared with standard care. The insufficient tissue strategy was associated with the smallest increase in QALYs but also the smallest increase in costs. The figures indicate the variation in costs and QALY outcomes owing to uncertain model parameters. Delta costs and QALYs compare each liquid biopsy testing strategy with standard care.
Abbreviation: QALY, quality-adjusted life-year.

Scenario Analysis

Table 12 provides the results of our scenario analysis. The model was most sensitive to the price of liquid biopsy testing. When using the cost of a liquid biopsy assay developed in house, the ICER estimate for each liquid biopsy strategy was less than $100,000 per additional QALY gained. The model was also sensitive to the population receiving the intervention. We estimated substantial ICER increases for scenario analyses in which liquid biopsy testing was provided for all people newly diagnosed with NSCLC. We also observed increases to ICER estimates when the probability of receiving treatment was the same for people with and without an actionable genomic alteration detected. Table A20 (Appendix 8) provides detailed scenario analysis results.

Table 12: Scenario Analysis Results

Scenario	ICER, insufficient tissue strategy, $[a] (% change from reference case)	ICER, liquid-first strategy, $[a] (% change from reference case)	ICER, tissue-first strategy, $[a] (% change from reference case)	ICER, combined strategy, $[a] (% change from reference case)
Reference case	96,738 (0%)	157,267 (0%)	147,636 (0%)	173,032 (0%)
Scenario 1: 5-year time horizon	119,597 (24%)	236,672 (50%)	219,799 (49%)	264,291 (53%)
Scenario 2: 10-year time horizon	102,190 (6%)	181,350 (15%)	169,367 (15%)	200,965 (16%)
Scenario 3: 15-year time horizon	98,282 (2%)	164,847 (5%)	154,453 (5%)	181,861 (5%)
Scenario 4: 3% discount rate	99,454 (3%)	166,205 (6%)	155,746 (5%)	183,326 (6%)
Scenario 5: 0% discount rate	94,078 (−3%)	148,447 (−6%)	139,638 (−5%)	162,868 (−6%)
Scenario 6: Population of interest includes all people newly diagnosed with NSCLC	121,988 (26%)	212,761 (35%)	198,771 (35%)	235,661 (36%)
Scenario 7: Population of interest includes all people newly diagnosed with NSCLC; liquid biopsy testing provides actionable results for those with stage IB–IIIA NSCLC who have undergone complete resection	128,217 (33%)	215,663 (37%)	202,035 (37%)	237,972 (38%)
Scenario 8: 20% discount in drug acquisition cost	91,525 (−5%)	153,354 (−2%)	143,723 (−3%)	169,118 (−2%)
Scenario 9: 40% discount in drug acquisition cost	86,311 (−11%)	149,440 (−5%)	139,809 (−5%)	165,205 (−5%)
Scenario 10: 60% discount in drug acquisition cost	81,098 (−16%)	145,527 (−7%)	135,896 (−8%)	161,291 (−7%)
Scenario 11: 80% discount in drug acquisition cost	75,885 (−22%)	141,613 (−10%)	131,983 (−11%)	157,378 (−9%)
Scenario 12: 100% discount in drug acquisition cost	70,672 (−27%)	137,700 (−12%)	128,069 (−13%)	153,464 (−11%)
Scenario 13: Lliquid biopsy test developed in house (cost sourced from Ezeife et al[174])	53,992 (−44%)	60,123 (−62%)	68,149 (−54%)	75,888 (−56%)
Scenario 14: Liquid biopsy sequencing costs increased by 25%	110,782 (15%)	189,183 (20%)	173,751 (18%)	204,948 (18%)
Scenario 15: Liquid biopsy sequencing costs decreased by 25%	82,694 (−15%)	125,351 (−20%)	121,522 (−18%)	141,116 (−18%)
Scenario 16: Effectiveness parameters sourced from Englmeier et al[177]	99,737 (3%)	163,130 (4%)	153,712 (4%)	178,336 (3%)
Scenario 17: Effectiveness parameters sourced from Jansen et al[179]	137,455 (42%)	375,668 (139%)	342,277 (132%)	430,052 (149%)
Scenario 18: Effectiveness parameters sourced from Patel et al[175]	108,292 (12%)	190,473 (21%)	177,887 (20%)	210,970 (22%)
Scenario 19: Probability of choosing to receive treatment is the same for people with and without an actionable genomic alteration detected	118,859 (23%)	246,692 (57%)	226,505 (53%)	279,549 (62%)
Scenario 20: Excluding all-cause mortality	89,568 (−7%)	141,519 (−10%)	133,140 (−10%)	155,234 (−10%)
Scenario 21: ODB coverage increased to 100%	122,004 (26%)	182,797 (16%)	173,167 (17%)	198,562 (15%)
Scenario 22: Adverse event–related disutility implemented using a multiplicative approach	96,738 (0%)	157,267 (0%)	147,636 (0%)	173,032 (0%)
Scenario 23: Excluding treatment-related adverse events	97,182 (0%)	157,586 (0%)	147,953 (0%)	173,355 (0%)
Scenario 24: Increased probability of tumour not being detected in liquid biopsy sample	98,680 (2%)	161,807 (3%)	151,359 (3%)	177,468 (3%)
Scenario 25: Decreased probability of tumour not being detected in liquid biopsy sample	95,443 (−1%)	154,446 (−2%)	145,330 (−2%)	170,106 (−2%)

Scenario	ICER, insufficient tissue strategy, $[a] (% change from reference case)	ICER, liquid-first strategy, $[a] (% change from reference case)	ICER, tissue-first strategy, $[a] (% change from reference case)	ICER, combined strategy, $[a] (% change from reference case)
Scenario 26: Increased probability of insufficient tissue for tissue testing	93,646 (−3%)	150,366 (−4%)	142,317 (−4%)	165,122 (−5%)
Scenario 27: Decreased probability of insufficient tissue for tissue testing	100,331 (4%)	165,057 (5%)	153,728 (4%)	181,710 (5%)
Scenario 28: Increased probability of choosing to undergo rebiopsy	90,043 (−7%)	153,472 (−2%)	144,160 (−2%)	168,549 (−3%)
Scenario 29: Decreased probability of choosing to undergo rebiopsy	105,048 (9%)	161,406 (3%)	151,386 (3%)	177,630 (3%)
Scenario 30: 3-month duration of end-of-life care	97,890 (1%)	158,275 (1%)	148,644 (1%)	174,039 (1%)
Scenario 31: 12-month duration of end-of-life care	104,025 (8%)	163,659 (4%)	154,029 (4%)	179,424 (4%)
Scenario 32: Second-best-fitting distributions as judged by AIC	94,700 (−2%)	155,640 (−1%)	146,117 (−1%)	171,099 (−1%)
Scenario 33: Second-best-fitting distributions as judged by BIC	97,677 (1%)	158,766 (1%)	148,991 (1%)	174,635 (1%)
Scenario 34: improved treatment effectiveness because of faster test turnaround time	96,738 (0%)	110,633 (−30%)	147,636 (0%)	118,179 (−32%)
Scenario 35: HR increase of 1.34 applied to risk of progressing or dying for people with an actionable genomic alteration detected and receiving nontargeted therapy	96,818 (0%)	157,104 (−0%)	147,523 (−0%)	172,787 (−0%)
Scenario 36: 100% probability of receiving treatment	75,978 (−21%)	149,989 (−5%)	137,447 (−7%)	170,520 (−1%)
Scenario 37: Increased sensitivity for liquid biopsy testing compared with tissue testing	92,281 (−5%)	139,351 (−11%)	131,970 (−11%)	153,234 (−11%)
Scenario 38: Decreased sensitivity for liquid biopsy testing compared with tissue testing	101,978 (5%)	180,309 (15%)	167,607 (14%)	198,123 (15%)
Scenario 39: 20% discount applied to orally administered drugs	79,242 (−18%)	139,780 (−11%)	130,150 (−12%)	155,545 (−10%)
Scenario 40: 40% discount applied to orally administered drugs	61,747 (−36%)	122,293 (−22%)	112,663 (−24%)	138,058 (−20%)
Scenario 41: limited societal perspective	113,150 (17%)	154,991 (−1%)	132,234 (−10%)	194,488 (12%)
Scenario 42: Reduced effectiveness of targeted therapy (i.e., alectinib) for *ALK* alterations	95,735 (−1%)	168,344 (14%)	156,894 (2%)	187,116 (8%)

Abbreviations: ICER, incremental cost-effectiveness ratio; NSCLC, non–small cell lung cancer; ODB, Ontario Drug Benefit program.
[a]ICER when compared to the reference case.

Discussion

We conducted a cost–utility analysis comparing 4 liquid biopsy testing strategies with current standard care (i.e., tissue testing alone) for people newly diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV) from the perspective of the Ontario Ministry of Health. We estimate that all 4 liquid biopsy testing strategies would result in improved health outcomes (i.e., increased QALYs, increased life expectancy, and fewer tissue biopsies), as well as increased costs. Cost increases ranged from $970 ($596; $1,481), for the strategy in which liquid biopsy testing is provided only for people with insufficient tissue for tissue testing, to $7,310 ($6,438; $8,364), for the strategy in which people receive both liquid biopsy and tissue testing. Increased costs were primarily associated with increased testing costs and increased drug acquisition costs. We estimate cost savings related to fewer adverse events,

fewer tissue biopsies, and lower drug administration costs. QALY increases ranged from 0.01 (0.01; 0.02) for the insufficient tissue strategy to 0.04 (0.03; 0.06) for the combined, liquid-first, and tissue-first strategies. We found that liquid biopsy testing had the greatest benefit for those in the modelled cohort with an actionable genomic alteration who would not undergo tissue testing because of insufficient tissue. We estimate that between 0.6% (0.3%; 0.9%) and 2.3% (1.7%; 3%) of the modelled cohort would have an actionable genomic alteration detected with liquid biopsy testing that would not have been detected with tissue testing. We used sensitivity inputs sourced from the clinical evidence review indicating that liquid biopsy testing would have a lower sensitivity than tissue testing. An increase in the number of actionable genomic alterations detected resulted from liquid biopsy testing being added to tissue testing in all strategies.

For the combined, liquid-first, tissue-first, and insufficient tissue strategies, the ICER estimates were $173,032, $157,267, $147,636, and $96,738 per additional QALY gained, respectively. In our scenario analyses, we found a wide range of ICER estimates, with the model being most sensitive to the cost of liquid biopsy testing, the impact of having an actionable genomic alteration detected on the decision to receive best supportive care, and whether liquid biopsy testing was available to all people newly diagnosed with NSCLC or only to those with locally advanced or metastatic NSCLC. The scenario analysis that used the costs of a liquid biopsy test developed in house did not consider the capital expenditures required to establish a liquid biopsy testing program in the province, likely underestimating variable costs. The scenario analysis in which liquid biopsy testing resulted in reduced mortality because treatment could be initiated faster saw large impacts on the ICER estimates for the liquid-first and combined strategies.

Similar to Patel et al[175] and Johnston et al,[176] we estimated that liquid biopsy testing would result in increased life expectancy and increased costs. Our ICER estimates are comparable to those estimated by Engelmeier et al[177] of €53,909 per additional QALY for an insufficient tissue strategy and by Jansen et al[179] of $274,423 USD per additional QALY gained for a liquid-first strategy. Unlike the study by Ezeife et al,[174] we did not find the combined strategy to be cost-saving compared with tissue testing only. This finding likely resulted from our use of an increased model time horizon (20 years vs 2 years) and our assumption that comprehensive genomic profiling would occur before people decide whether to receive systemic therapy or best supportive care. The cost-effectiveness of liquid biopsy testing is directly linked to the cost-effectiveness of the targeted therapies that liquid biopsy testing results recommend. CADTH reimbursement reviews have estimated the ICER for several of these treatments, most of which exceed $150,000 per QALY gained.[234,236,238,239] Scenario analyses that excluded the cost of drug acquisition saw substantial decreases in ICER estimates.

Our study differs from previously published economic evaluations in that our model considered comprehensive genomic profiling to occur before people decide to receive treatment or best supportive care. We made this decision based on the results of the study by Stock-Martineau et al.[214] This modelling decision resulted in an additional benefit for liquid biopsy of fewer people receiving best supportive care and more receiving targeted therapy, but it also allowed people with an actionable genomic alteration detected choosing to receive best supportive care.

We are uncertain how liquid biopsy testing would be implemented in the province if publicly funded. National Comprehensive Cancer Network (NCCN) guidelines recommend that liquid biopsy testing be used when tissue testing is not feasible or when there is insufficient tissue for molecular analysis and follow-up tissue-based profiling will be conducted if an oncogenic driver is not identified.[67] The NCCN guidelines also highlight that liquid biopsy testing alone should not be used to diagnose NSCLC. The

insufficient tissue, tissue-first, and combined strategies examined here all align with the NCCN recommendations. The liquid-first strategy is limited in that certain variants can be detected that are not related to the tumour. Thus, the NCCN guidelines recommend considering whether liquid biopsy test results are indicative of an actionable genomic alteration or an unrelated finding.

NSCLC care is a rapidly changing landscape, and several treatments are not currently publicly funded in Ontario. We considered only targeted therapies currently covered by the Exceptional Access Program. The expansion of coverage for targeted therapies would likely result in a reduced cost per actionable genomic alteration detected. The future drug acquisition costs for people diagnosed with NSCLC are highly uncertain. We conducted a scenario analysis with a limited societal perspective that considered all drug acquisition costs and the targeted therapies available for people with *BRAF*, *MET*, or *RET* actionable genomic alterations. This analysis did not include productivity estimates or costs to care partners (e.g., travel costs, nondrug out-of-pocket costs). This analysis estimated small reductions to ICER estimates for the liquid-first and tissue-first strategies because more actionable genomic alterations were being considered and fewer people tested negative after their first liquid or tissue biopsy test.

We did not consider potential ancillary benefits of liquid biopsy testing such as increased access to clinical trials. In a scenario analysis, we considered a quicker turnaround time for liquid biopsy test results that resulted in improved effectiveness for targeted therapies. In this analysis, the ICERs for the combined and liquid-first strategies were estimated to be less than $150,000 per additional QALY gained. We did not consider the potential benefit of receiving negative liquid biopsy or tissue testing results, but a faster turnaround time for negative results could lead to improved outcomes because treatment with nontargeted therapies could be initiated more quickly. Although turnaround times for both liquid biopsy and tissue testing results are likely to vary by site, one Ontario study has reported an average turnaround time of 32.5 calendar days for tissue testing.[260]

Equity Considerations

Our economic evidence review identified 1 study that included an equity-related distributional cost-effectiveness analysis.[179] The authors estimated changes to health-related quality of life for various genetic ancestry subgroups (i.e., non-Hispanic White, non-Hispanic Black, Asian, and Hispanic). To conduct a similar distributional cost-effectiveness analysis, data on the baseline QALY distribution of different genetic ancestry subgroups in Ontario would be required. Owing to a lack of such data, we were unable to conduct an equity-related subgroup analysis. In Ontario, more research may be required to describe how various populations might access and benefit from liquid biopsy testing. We did not incorporate the impact of liquid biopsy testing improving access to comprehensive genomic profiling for people living far from a surgical center.[179]

Strengths and Limitations

Our study has several strengths. We use pooled sensitivity estimates for liquid biopsy and tissue testing (see the clinical evidence review) as a result of a comprehensive literature search. We were able to source costs and resource use inputs reflective of those incurred in Ontario. We used a long-term 20-year time horizon in our model to capture improved health outcomes during the lifetime of people receiving comprehensive genomic profiling. Our model assessed a wide range of potential liquid biopsy testing implementation strategies, and we conducted extensive scenario analyses on key model parameters.

Our analysis was limited by the available evidence on the effectiveness of targeted therapies. We therefore used extrapolations of immature survival data to estimate the long-term effectiveness of these therapies. We considered a variety of potential model fits and various data sources, but the available evidence is limited. Because of the availability of patient-level survival data, we used a partitioned survival model to estimate long-term effectiveness outcomes. This model type is limited in that it assumes that the probability of dying in the progressed health state does not depend on the time spent in the progression-free survival health state. Because of a lack of data, we were unable to estimate the timing of adverse events and therefore assumed that all adverse events occurred in the first model cycle.

This analysis was also limited by the changing landscape of NSCLC treatments. We considered only targeted therapies that are currently publicly funded in Ontario. It is possible that additions to public drug formularies would result in changes to our cost-effectiveness estimates. We were further limited by our uncertainty regarding which liquid biopsy testing strategy is most likely to be implemented in the province, as well as whether all people newly diagnosed with NSCLC or just those with locally advanced or metastatic NSCLC would be eligible for liquid biopsy testing. To address the latter limitation, we conducted extensive scenario analyses varying the size of the population of interest. Limited information is available on the effectiveness of mismatched targeted therapy for people with an actionable genomic alteration detected, as well as on the potential benefits of a faster turnaround time for comprehensive genomic profiling test results.

Conclusions

We estimate that liquid biopsy testing for people newly diagnosed with advanced or metastatic (stage IIIB or IV) NSCLC is associated with an increase in QALYs (0.04 per person for each of the combined, liquid-first, and tissue-first strategies and 0.01 for the insufficient tissue strategy). We also estimate an increase in costs ($7,310 per person for the combined strategy, $6,644 for the liquid-first strategy, $6,237 for the tissue-first strategy, and $970 for the insufficient tissue strategy) compared with current standard care (i.e., tissue testing alone). The ICER estimates for the 4 liquid biopsy testing strategies we assessed ranged from $96,738 to $173,032 per additional QALY gained.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding liquid biopsy testing for people newly diagnosed with locally advanced or metastatic non–small cell lung cancer (stage IIIB or IV)?

Methods

Analytic Framework

We estimated the budget impact of publicly funding liquid biopsy testing using the cost difference between 2 scenarios: (1) current clinical practice without public funding for liquid biopsy testing (the current scenario), and (2) anticipated clinical practice with public funding for liquid biopsy testing (the new scenario) (Figure 22). Because of the uncertainty regarding which liquid biopsy testing strategy would be implemented, we present budget impact estimates for the 4 liquid biopsy testing strategies described in the primary economic evaluation.

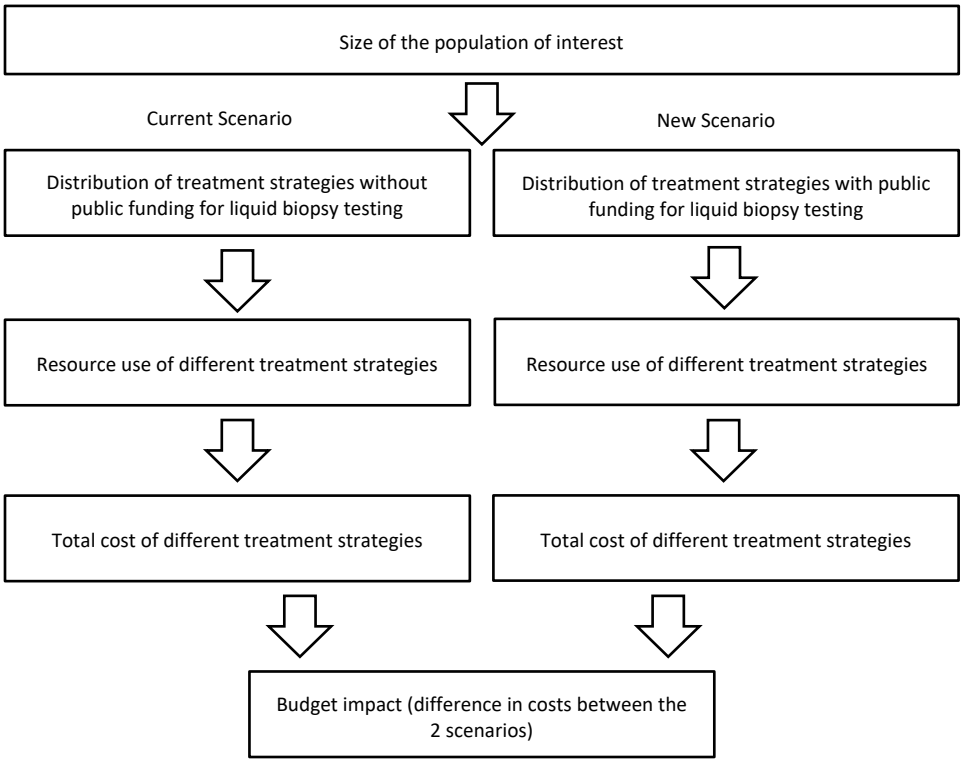

Figure 22: Schematic Model of Budget Impact

Flow chart describing the model for the budget impact analysis. Based on the size of the target population, we created 2 scenarios: the current scenario, which would explore the distribution of treatment strategies, resource use, and total costs without public funding for liquid biopsy testing, and the new scenario, which would explore the distribution of treatment strategies, resource use, and total costs with public funding for liquid biopsy testing. The budget impact would represent the difference in costs between the 2 scenarios.

Key Assumptions

The budget impact analysis used costs inputs sourced from the primary economic evaluation; therefore, all key assumptions of the primary economic evaluation also applied to the budget impact analysis. In addition, we assumed the following:

- Only 1 liquid biopsy testing strategy would be implemented (i.e., people would not have the option to choose among testing strategies)
- In the new scenario, the uptake of liquid biopsy testing would be uniform across the province, resulting in an estimated uptake of 100%
    - We conducted scenario analyses with lower uptake estimates
- Comprehensive genomic profiling (via either or both of tissue and liquid biopsy testing) would occur before a person decides to receive systemic therapy or best supportive care
    - We conducted scenario analyses in which comprehensive genomic profiling would occur only for people choosing to receive systemic therapy
- The population of interest would be people with locally advanced or metastatic non–small cell lung cancer (NSCLC) (stage IIIB or IV)
    - We conducted scenario analyses in which the population of interest was expanded to include all people newly diagnosed with NSCLC
- All cost inputs, including the cost of liquid biopsy sequencing, would remain constant during the model's 5-year time horizon

Population of Interest

Our population of interest was people newly diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV). As in the primary economic evaluation, we excluded people with squamous NSCLC because the current standard of care for this population includes testing only for PD-L1 variants.[194] We conducted scenario analyses in which the population of interest was expanded to include all people newly diagnosed with NSCLC.

We sourced the size of the target population from published studies. We sourced the future incidence of lung cancer and 95% confidence intervals (CIs) from cancer incidence projections for lung cancer from Ontario Health (Cancer Care Ontario).[261] We sourced the probability that a person diagnosed with lung cancer would be diagnosed with NSCLC (87.7%) from *Canadian Cancer Statistics: A 2020 Special Report on Lung Cancer* by the Canadian Cancer Society.[262] We also sourced the probability that a person diagnosed with NSCLC would be diagnosed with nonsquamous NSCLC (83.2%) from that report. We sourced the probability that a person would be diagnosed at stage III (20.3%) or stage IV (48.61%) from Araghi et al.[200] We sourced the probability that a person diagnosed at stage III would diagnosed with stage IIIB from Seung et al (54.7%).[263] These data resulted in an estimate of 54.7% of all cases of nonsquamous NSCLC being diagnosed as stage IIIB or IV.

For the scenario analysis in which comprehensive genomic profiling would occur only for people choosing to receive systemic therapy, we further reduced the population of interest by 62.7%, based on Stock-Martineau et al.[214] For the scenario analysis in which the population of interest included all people

newly diagnosed with NSCLC, we used the estimates of all nonsquamous NSCLC cases provided in Table 13 to determine the size of the population of interest.

Table 13 provides the estimates of our population of interest over the next 5 years.

Table 13: Population of Interest

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)
Lung cancer cases in Ontario, n	11,032	11,142	11,259	11,366	11,467
Upper 95% confidence interval, n	11,241	11,353	11,473	11,582	11,684
Lower 95% confidence interval, n	10,823	10,931	11,407	11,153	11,233
All NSCLC cases (87.7%), n	9,682	9,779	9,881	9,975	10,064
Cases of nonsquamous NSCLC (83.2%), n	8,054	8,134	8,220	8,298	8,372
Cases of stage IIIB and IV NSCLC (54.7%), n	4,406	4,450	4,496	4,539	4,579
Estimate of the population of interest, n	4,406	4,450	4,496	4,539	4,579

Abbreviation: NSCLC: non–small cell lung cancer.
Sources: Araghi et al[200]; Canadian Cancer Society[262]; Ontario Health (Cancer Care Ontario)[261]; Seung et al.[263]

Current Intervention Mix

Currently, all people in Ontario diagnosed with adenocarcinoma or nonsquamous NSCLC are tested for actionable genomic alterations at diagnosis with tissue testing. We therefore assumed that in the current scenario, 100% of our population of interest would receive tissue testing at diagnosis.

Uptake of the New Intervention and New Intervention Mix

In our reference case analysis, we assumed the uptake of liquid biopsy testing would be 100% in year 1. This is because all 4 liquid biopsy testing strategies also included tissue testing, and we expected that liquid biopsy testing would be provided to all of our population of interest, similar to other indications in the Ontario Health (Cancer Care Ontario) Comprehensive Cancer Biomarker Testing Program.[194] We conducted scenario analyses in which the uptake of each liquid biopsy testing strategy was gradual.

Table 14 provides uptake estimates for the current and new scenarios.

Table 14: Uptake of Standard Care and Liquid Biopsy Testing in Ontario

	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)
Current scenario: standard care, %	100	100	100	100	100
New scenario: liquid biopsy testing, %	100	100	100	100	100

Resources and Costs

We sourced costs by running the cost–utility analysis model described in the primary economic evaluation using a 5-year time horizon and a 0% discount rate. We considered all costs described in the primary economic evaluation.

Tables 15a to 15e outline the average per-person cost estimates for standard care and each liquid biopsy testing strategy during the 5-year time horizon of the budget impact analysis.

Table 15a: Average Per-Person Yearly Cost Estimates – Standard Care[a]

Costing variable	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)
Total cost, $	**96,907**	**36,471**	**16,735**	**10,524**	**8,392**
Testing total, $	4,756	0	0	0	0
Tissue testing total, $	4,756	0	0	0	0
Tissue testing, $	4,474	0	0	0	0
Tissue testing AEs, $	282	0	0	0	0
Liquid biopsy testing total, $	0	0	0	0	0
Long-term costs, $	92,151	36,471	16,735	10,524	8,392
First-line drug acquisition, $	67,127	24,699	8,642	4,616	3,888
Second-line drug acquisition, $	2,907	2,898	1,900	1,659	1,254
AEs, $	628	0	0	0	0
Administration costs, $	895	319	96	67	56
General care costs, $	19,937	8,097	5,793	3,994	3,065
End-of-life care, $	658	459	304	188	129

Abbreviation: AE, adverse event.

[a]Standard care is tissue testing only.

Table 15b: Average Per-Person Yearly Cost Estimates – Combined Strategy[a]

Costing variable	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)
Total cost, $	**102,275**	**36,812**	**17,148**	**10,685**	**8,524**
Testing total, $	10,602	0	0	0	0
Tissue testing total, $	4,699	0	0	0	0
Tissue testing, $	4,420	0	0	0	0
Tissue testing AEs, $	279	0	0	0	0
Liquid biopsy testing total, $	5,903	0	0	0	0
Long-term costs, $	91,674	36,812	17,148	10,685	8,524
First-line drug acquisition, $	66,728	24,807	8,946	4,670	3,941
Second-line drug acquisition, $	2,928	3,033	1,891	1,671	1,255
AEs, $	616	0	0	0	0
Administration costs, $	873	312	95	66	55
General care costs, $	19,877	8,200	5,908	4,087	3,141
End-of-life care, $	652	460	308	192	132

Notes for Table 15b

Abbreviation: AE, adverse event.

[a]In the combined strategy, all people receive both tissue and liquid biopsy testing.

Table 15c: Average Per-Person Yearly Cost Estimates – Liquid-First Strategy[a]

Costing variable	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)
Total cost, $	**101,609**	**36,812**	**17,148**	**10,685**	**8,524**
Testing total, $	9,936	0	0	0	0
Tissue testing total, $	4,033	0	0	0	0
Tissue testing, $	3,794	0	0	0	0
Tissue testing AEs, $	239	0	0	0	0
Liquid biopsy testing total, $	5,903	0	0	0	0
Long-term costs, $	91,674	36,812	17,148	10,685	8,524
First-line drug acquisition, $	66,728	24,807	8,946	4,670	3,941
Second-line drug acquisition, $	2,928	3,033	1,891	1,671	1,255
AEs, $	616	0	0	0	0
Administration costs, $	873	312	95	66	55
General care costs, $	19,877	8,200	5,908	4,087	3,141
End-of-life care, $	652	460	308	192	132

Abbreviation: AE, adverse event.

[a]In the liquid-first strategy, all people receive liquid biopsy testing, but only those with negative results receive tissue testing.

Table 15d: Average Per-Person Yearly Cost Estimates – Tissue-First Strategy[a]

Costing variable	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)
Total cost, $	**101,202**	**36,812**	**17,148**	**10,685**	**8,524**
Testing total, $	9,529	0	0	0	0
Tissue testing total, $	4,699	0	0	0	0
Tissue testing, $	4,420	0	0	0	0
Tissue testing AEs, $	279	0	0	0	0
Liquid biopsy testing total, $	4,830	0	0	0	0
Long-term costs, $	91,674	36,812	17,148	10,685	8,524
First-line drug acquisition, $	66,728	24,807	8,946	4,670	3,941
Second-line drug acquisition, $	2,928	3,033	1,891	1,671	1,255
AEs, $	616	0	0	0	0
Administration costs, $	873	312	95	66	55
General care costs, $	19,877	8,200	5,908	4,087	3,141
End-of-life care, $	652	460	308	192	132

Abbreviation: AE, adverse event.

[a]In the tissue-first strategy, all people receive tissue testing, but only those with negative results receive liquid biopsy testing.

Table 15e: Average Per-Person Yearly Cost Estimates – Insufficient Tissue Strategy[a]

Costing variable	Year 1 (2025)	Year 2 (2026)	Year 3 (2027)	Year 4 (2028)	Year 5 (2029)
Total cost, $	**97,343**	**36,567**	**16,855**	**10,573**	**8,432**
Testing total, $	5,315	0	0	0	0
Tissue testing total, $	4,699	0	0	0	0
Tissue testing, $	4,420	0	0	0	0
Tissue testing AEs, $	279	0	0	0	0
Liquid biopsy testing total, $	616	0	0	0	0
Long-term costs, $	92,028	36,567	16,855	10,573	8,432
First-line drug acquisition, $	67,026	24,736	8,738	4,637	3,907
Second-line drug acquisition, $	2,910	2,932	1,894	1,662	1,255
AEs, $	624	0	0	0	0
Administration costs, $	889	317	96	67	56
General care costs, $	19,922	8,123	5,822	4,017	3,084
End-of-life care, $	656	459	305	189	130

Abbreviation: AE, adverse event.

[a]In the insufficient tissue strategy, all people receive tissue testing, but only those with insufficient tissue receive liquid biopsy testing.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

The budget impact analysis model was built in Microsoft Excel.[264] We conducted a reference case analysis and scenario analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our scenario analyses explored how the results are affected by varying input parameters and model assumptions. We conducted scenario analyses using output from the cost-effectiveness model scenario analyses (scenario analyses 8–40 in the primary economic evaluation). In addition, we conducted the following scenario analyses:

1) Increased size of the population of interest
    - Reference case: population of interest described in Table 13
    - Scenario analysis 1: population of interest calculated using the upper 95% CI estimate of lung cancer incidence in Ontario (ranging from 4,489 in year 1 to 4,666 in year 5)
2) Decreased size of the population of interest
    - Reference case: population of interest described in Table 13
    - Scenario analysis 2: population of interest calculated using the lower 95% CI estimate of lung cancer incidence in Ontario (ranging from 4,332 in year 1 to 4,494 in year 5)
3) Population of interest includes all people newly diagnosed with NSCLC
    - Reference case: population of interest is people newly diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV)

   - Scenario analysis 3: population of interest is expanded to include all people newly diagnosed with NSCLC (ranging from 4,406 in year 1 to 4,579 in year 5); same cost inputs as in cost-effectiveness scenario analysis 6 in the primary economic evaluation
4) Population of interest includes all people newly diagnosed with NSCLC, and liquid biopsy testing can provide actionable results
   - Reference case: population of interest is people newly diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV)
   - Scenario analysis 4: population of interest is expanded to include all people newly diagnosed with NSCLC, and liquid biopsy testing provides actionable results for people who have undergone complete resection and been diagnosed with stage IB to IIIA NSCLC; same cost inputs as in cost-effectiveness scenario analysis 7 in the primary economic evaluation
5) Population of interest includes only people who choose to receive systemic therapy
   - Reference case: population of interest is people newly diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV)
   - Scenario analysis 5: population of interest is reduced by 62.7% (sourced from Stock-Martineau et al[214]) to include only people choosing to receive systemic therapy; same cost inputs as in cost–utility scenario analysis 36 (in which all people received treatment)
6) Decreased uptake of liquid biopsy testing, starting at 20% year 1 and increasing to 100% by year 5
   - Reference case: 100% uptake of liquid biopsy testing in year 1
   - Scenario analysis 6: 20% update at year 1; 100% uptake by year 5
7) Decreased uptake of liquid biopsy testing, starting at 16% in year 1 and increasing to 80% by year 5
   - Reference case: 100% uptake of liquid biopsy testing in year 1
   - Scenario analysis 7: 16% uptake at year 1; 80% uptake by year 5
8) Decreased uptake of liquid biopsy testing, starting at 12% in year 1 and increasing to 60% by year 5
   - Reference case: 100% uptake of liquid biopsy testing in year 1
   - Scenario analysis 8: 12% uptake at year 1; 60% uptake by year 5
9) Decreased uptake of liquid biopsy testing, starting at 8% in year 1 and increasing to 40% by year 5
   - Reference case: 100% uptake of liquid biopsy testing in year 1
   - Scenario analysis 9: 8% uptake at year 1; 40% uptake by year 5
10) Decreased uptake of liquid biopsy testing, starting at 4% in year 1 and increasing to 20% by year 5
   - Reference case: 100% uptake of liquid biopsy testing in year 1
   - Scenario analysis 10: 4% uptake at year 1; 20% uptake by year 5

Results

Reference Case

Table 16 provides the results of the reference case analysis (see Appendix 8 for detailed results). We estimate that over 5 years, public funding for the 4 liquid biopsy testing strategies would lead to the following additional costs:

- Combined strategy: $134.24 million
- Liquid-first strategy: $119.27 million
- Tissue-first strategy: $110.13 million
- Insufficient tissue strategy: $13.72 million

We estimate that over 5 years, 22,470 people will be newly diagnosed with locally advanced or metastatic nonsquamous NSCLC (stage IIIB or IV). We estimate that relative to current standard care, the 4 liquid biopsy testing strategies would incur the following additional testing costs:

- Combined strategy: $131.25 million
- Liquid-first strategy: $116.39 million
- Tissue-first strategy: $107.24 million
- Insufficient tissue strategy: $12.57 million

Table 16: Budget Impact Analysis Results

	Budget impact, $ million[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b]**
Current scenario	426.94	591.87	671.73	724.67	768.36	3183.57
Combined strategy						
New scenario	450.59	617.26	699.20	753.12	797.64	3317.81
Budget impact[b]	23.65	25.39	27.47	28.45	29.29	134.24
Liquid-first strategy						
New scenario	447.65	614.29	696.21	750.10	794.59	3302.84
Budget impact[b]	20.71	22.42	24.48	25.42	26.24	119.27
Tissue-first strategy						
New scenario	445.86	612.48	694.38	748.25	792.73	3293.70
Budget impact[b]	18.92	20.61	22.65	23.58	24.37	110.13
Insufficient tissue strategy						
New scenario	428.86	594.23	674.64	727.83	771.72	3197.29
Budget impact[b]	1.92	2.36	2.92	3.16	3.36	13.72

Note: All costs were calculated using the mean cost from the primary economic evaluation's probabilistic results.
[a]In 2023Canadian dollars.
[b]Results may appear inexact due to rounding.

We estimate a reduction in costs for several cost categories for each liquid biopsy testing strategy. These are primarily reductions in costs for tissue testing, first-line drug acquisition, and tissue testing–related adverse events.

Scenario Analysis

Table 17a shows the results of our scenario analyses, and Table 17b shows the results using cost inputs from the cost-effectiveness scenario analyses. The scenario analyses with the largest impact on budget impact estimates were those that increased or decreased the size of the population of interest. The scenario analyses in which the population of interest was expanded to include all people newly diagnosed with NSCLC had the largest increase to the budget impact. Another key model parameter was the cost of liquid biopsy sequencing.

Table 17a: Budget Impact Analysis – Scenario Analysis Results

Scenario	5-year budget impact, insufficient tissue strategy, $ million[a] (% change from reference case)	5-year budget impact, liquid-first strategy, $ million[a] (% change from reference case)	5-year budget impact, tissue-first strategy, $ million[a] (% change from reference case)	5-year budget impact, combined strategy, $ million[a] (% change from reference case)
Reference case	13.72 (0%)	119.27 (0%)	110.13 (0%)	134.24 (0%)
Scenario 1: increased lung cancer incidence projections	13.98 (1.9%)	121.53 (1.9%)	112.22 (1.9%)	136.78 (1.9%)
Scenario 2: decreased lung cancer incidence projections	13.46 (−1.9%)	117.03 (−1.9%)	108.06 (−1.9%)	131.71 (−1.9%)
Scenario 3: population of interest includes all people newly diagnosed with NSCLC	24.42 (78%)	216.4 (81.4%)	199.69 (81.3%)	243.76 (81.6%)
Scenario 4: population of interest includes all people newly diagnosed with NSCLC, and liquid biopsy testing provides actionable results	27.22 (98.4%)	226.11 (89.6%)	209.4 (90.1%)	253.47 (88.8%)
Scenario 5: population of interest includes only people choosing to receive systemic treatment	4.13 (−69.9%)	56.56 (−52.6%)	50.83 (−53.8%)	65.94 (−50.9%)
Scenario 6: decreased uptake of liquid biopsy testing (starting at 20% in year 1)	7.58 (−44.7%)	69.62 (−41.6%)	64.1 (−41.8%)	78.66 (−41.4%)
Scenario 7: decreased uptake of liquid biopsy testing (starting at 16% in year 1)	6.07 (−55.8%)	55.7 (−53.3%)	51.28 (−53.4%)	62.93 (−53.1%)
Scenario 8: decreased uptake of liquid biopsy testing (starting at 12% in year 1)	4.55 (−66.8%)	41.77 (−65%)	38.46 (−65.1%)	47.2 (−64.8%)
Scenario 9: decreased uptake of liquid biopsy testing (starting at 8% in year 1)	3.03 (−77.9%)	27.85 (−76.7%)	25.64 (−76.7%)	31.46 (−76.6%)
Scenario 10: decreased uptake of liquid biopsy testing (starting at 4% in year 1)	1.52 (−88.9%)	13.92 (−88.3%)	12.82 (−88.4%)	15.73 (−88.3%)

Table 17b: Budget Impact Analysis – Scenario Analysis Results Using Cost Inputs from the Cost-Effectiveness Scenario Analyses

Scenario	5-year budget impact, insufficient tissue strategy, $ million[a] (% change from reference case)	5-year budget impact, liquid-first strategy, $ million[a] (% change from reference case)	5-year budget impact, tissue-first strategy, $ million[a] (% change from reference case)	5-year budget impact, combined strategy, $ million[a] (% change from reference case)
20% discount applied to drug acquisition costs	13.6 (−0.8%)	119.15 (−0.1%)	110.01 (−0.1%)	134.12 (−0.1%)
40% discount applied to drug acquisition costs	13.49 (−1.7%)	119.03 (−0.2%)	109.89 (−0.2%)	134 (−0.2%)
60% discount applied to drug acquisition costs	13.38 (−2.5%)	118.92 (−0.3%)	109.77 (−0.3%)	133.88 (−0.3%)
80% discount applied to drug acquisition costs	13.26 (−3.3%)	118.8 (−0.4%)	109.66 (−0.4%)	133.76 (-0.4%)
100% discount applied to drug acquisition costs	13.15 (−4.1%)	118.68 (−0.5%)	109.54 (−0.5%)	133.64 (−0.4%)
Liquid biopsy test developed in house (cost sourced from Ezeife et al[174])	4.09 (−70.2%)	27.05 (−77.3%)	34.67 (−68.5%)	42.02 (−68.7%)
Liquid biopsy sequencing costs increased by 25%	16.88 (23.1%)	149.57 (25.4%)	134.92 (22.5%)	164.53 (22.6%)
Liquid biopsy sequencing costs decreased by 25%	10.55 (−23.1%)	88.97 (−25.4%)	85.34 (−22.5%)	103.94 (−22.6%)
Effectiveness parameters sourced from Englmeier et al[177]	13.88 (1.2%)	122.21 (2.5%)	112.99 (2.6%)	137.09 (2.1%)
Effectiveness parameters sourced from Jansen et al[179]	11.7 (−14.7%)	109.64 (−8.1%)	100.48 (−8.8%)	124.56 (−7.2%)
Effectiveness parameters sourced from Patel et al[175]	13.89 (1.3%)	120.84 (1.3%)	111.68 (1.4%)	135.75 (1.1%)
Probability of choosing to receive treatment is the same for people with and without an actionable genomic alteration detected	8.74 (−36.3%)	100.12 (−16.1%)	90.96 (−17.4%)	115.03 (−14.3%)
Excluding all-cause mortality	13.84 (0.9%)	119.76 (0.4%)	110.62 (0.4%)	134.73 (0.4%)
ODB coverage increased to 100%	17.32 (26.2%)	133.41 (11.9%)	124.27 (12.8%)	148.38 (10.5%)
Adverse event–related disutility implemented using a multiplicative approach	13.72 (0%)	119.27 (0%)	110.13 (0%)	134.24 (0%)
Excluding treatment-related adverse events	13.81 (0.7%)	119.54 (0.2%)	110.4 (0.2%)	134.5 (0.2%)
Increased probability of tumour not being detected in liquid biopsy sample	13.62 (−0.7%)	119.93 (0.6%)	110.32 (0.2%)	134.34 (0.1%)
Decreased probability of tumour not being detected in liquid biopsy sample	13.62 (−0.8%)	119.25 (0%)	110.41 (0.3%)	134.43 (0.1%)
Increased probability of insufficient tissue for tissue testing	18.84 (37.4%)	119.57 (0.3%)	111.45 (1.2%)	134.46 (0.2%)
Decreased probability of insufficient tissue for tissue testing	8.97 (−34.6%)	119.57 (0.3%)	109.47 (−0.6%)	134.43 (0.1%)
Increased probability of choosing to undergo rebiopsy	13.98 (1.9%)	119.91 (0.5%)	110.74 (0.6%)	134.76 (0.4%)
Decreased probability of choosing to undergo rebiopsy	13.28 (−3.2%)	119.2 (−0.1%)	110.03 (−0.1%)	134.06 (−0.1%)

Scenario	5-year budget impact, insufficient tissue strategy, $ million[a] (% change from reference case)	5-year budget impact, liquid-first strategy, $ million[a] (% change from reference case)	5-year budget impact, tissue-first strategy, $ million[a] (% change from reference case)	5-year budget impact, combined strategy, $ million[a] (% change from reference case)
3-month duration of end-of-life care	13.71 (0%)	119.25 (0%)	110.11 (0%)	134.21 (0%)
12-month duration of end-of-life care	13.93 (1.6%)	120.09 (0.7%)	110.94 (0.7%)	135.05 (0.6%)
Second-best-fitting curves as judged by AIC	13.46 (−1.9%)	118.9 (−0.3%)	109.73 (−0.4%)	133.78 (−0.3%)
Second-best-fitting curves as judged by BIC	13.53 (−1.4%)	119.28 (0%)	110.11 (0%)	134.16 (−0.1%)
Improved treatment effectiveness because of faster test turnaround time	13.72 (0%)	141.81 (18.9%)	110.13 (0%)	156.77 (16.8%)
HR increase of 1.34 applied to risk of progressing or dying for people receiving mismatched nontargeted therapies	13.77 (0.4%)	119.51 (0.2%)	110.37 (0.2%)	134.47 (0.2%)
100% probability of receiving treatment	6.59 (−52%)	90.21 (−24.4%)	81.06 (−26.4%)	105.17 (−21.7%)
Increased sensitivity for liquid biopsy compared to tissue biopsy	13.44 (−2%)	119.23 (0%)	111.07 (0.9%)	134.59 (0.3%)
Decreased sensitivity for liquid biopsy testing compared with tissue biopsy	13.43 (−2.1%)	119.74 (0.4%)	109.52 (−0.5%)	134.06 (−0.1%)
20% discount applied to orally administered medications	11.27 (−17.9%)	109.68 (−8%)	100.54 (−8.7%)	124.65 (−7.1%)
40% discount applied to orally administered medications	6.36 (−53.6%)	90.5 (−24.1%)	81.36 (−26.1%)	105.47 (−21.4%)

[a]Budget impact when compared to the reference case.

Discussion

We conducted a budget impact analysis comparing 4 liquid biopsy testing strategies with current standard care (i.e., tissue testing only) for people newly diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV) from the perspective of the Ontario Ministry of Health. We estimate that the strategy of providing liquid biopsy testing only for people with insufficient tissue for tissue testing would lead to additional costs ranging from $1.92 million in year 1 to $3.36 million in year 5, for a total budget impact of $13.72 million over 5 years. We estimate that the liquid-first, tissue-first, and combined strategies would lead to additional costs ranging from $110.13 million to $134.24 million. We attribute the increased budget impact for these 3 strategies to more people receiving liquid biopsy testing compared with the insufficient tissue strategy. Scenario analyses found that the budget impact analysis model was most sensitive to the size of the population of interest and the cost of liquid biopsy testing. We estimate cost savings for first-line drug acquisition and tissue testing for most of the liquid biopsy testing strategies. For all 4 liquid biopsy testing strategies, we estimate a reduction in costs related to fewer tissue biopsies being conducted ranging from $1.21 million to $16.1 million over 5 years.

This analysis assumed that liquid biopsy testing costs would be incurred for all people and that drug acquisition costs would be publicly funded only for people eligible for coverage under the Ontario Drug Benefit program. If liquid biopsy testing were to be publicly funded only for those without private health insurance coverage, the budget impact may be substantially reduced. Further, the difference in the budget impact between the reference case and the scenario using a liquid biopsy assay developed in house was substantial. Of note, the cost of the liquid biopsy assay in this scenario analysis did not include capital expenditures required to purchase equipment and develop an in-house test. However,

the budget impact difference between the reference case and this scenario may justify the capital expenditures required to develop an in-house liquid biopsy assay. But we are uncertain whether the variable costs of a liquid biopsy assay developed in house would resemble the costs reported by Ezeife et al.[174] A clinical expert indicated capacity in the province to develop liquid biopsy assays and an opportunity to standardize reporting (H. Feilotter, PhD, email communication, March 21, 2024). An additional implementation consideration is that the providers of commercial liquid biopsy assays require samples to be sent out of country for sequencing.

Our results are comparable to the 2 Canadian budget impact analyses that evaluated liquid biopsy testing only for people with insufficient tissue for tissue testing. Patel et al[175] estimated a 3-year budget impact of $14.7 million for all of Canada, while Johnston et al[176] estimated a 3-year budget impact of $4.4 million for Ontario. Our estimates are higher than those estimated by Johnston et al,[176] likely owing to our inclusion of drug acquisition costs and our assumption that comprehensive genomic profiling would occur before people decide whether to receive systemic therapy or best supportive care.

Strengths and Limitations

Our budget impact analysis has several strengths. First, by leveraging our cost–utility analysis, cost inputs considered drug acquisition costs and changes in care costs. Second, we conducted extensive scenario analyses on key model parameters. Last, we sourced costs and resource use inputs resembling those incurred in Ontario.

Our budget impact analysis was also limited in several respects. First, it used inputs from the cost–utility analysis developed for our primary economic evaluation, resulting in similar limitations and structural uncertainty. For this reason, we conducted extensive scenario analyses varying key model parameters. We are also uncertain regarding which of the 4 liquid biopsy testing strategies is most likely to be implemented in the province and whether liquid biopsy testing would be provided to all people newly diagnosed with NSCLC or only to those with locally advanced or metastatic disease. To address these uncertainties, we evaluated the budget impact for each liquid biopsy testing strategy compared with standard care and conducted scenario analyses in which the population of interest was expanded to include all people newly diagnosed with NSCLC.

Conclusions

We estimate that publicly funding liquid biopsy testing for people newly diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV) over 5 years would lead to an additional cost of $134.24 million for the combined strategy, $119.27 million for the liquid-first strategy, $110.13 million for the tissue-first strategy, and $13.72 million for the insufficient tissue strategy.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of non–small cell lung cancer (NSCLC), as well as the preferences and perceptions of people with NSCLC and care partners of liquid biopsy testing.

Background

Exploring patient preferences and values 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. It includes the impact of the condition and its treatment on the person with the health condition, their family and other care partners, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[265-267] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of a technology or intervention in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people with NSCLC through direct engagement.

Direct Patient Engagement

Methods

Partnership Plan

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with NSCLC and those of their families and other care partners. We engaged people via phone interviews.

No relevant equity considerations were identified in this health technology assessment; as a result, we did not carry out specific engagement initiatives for distinct populations.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with NSCLC, as well as those of their families and caregivers.[268] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

Participant Outreach

We used an approach called purposive sampling,[269-272] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations, including Lung Cancer Canada, to spread the word about this engagement activity and to contact people with NSCLC, family members, and care partners, including those with experience of liquid biopsy testing.

Inclusion Criteria

We sought to speak with adults with lived experience of NSCLC who had or may have experience with liquid biopsy testing. Participants did not have to have direct experience with liquid biopsy testing to participate.

Exclusion Criteria

We did not set exclusion criteria for participants who otherwise met the inclusion criteria.

Participants

For this project, we spoke with 14 people. Ten had been diagnosed with NSCLC, and of those, 6 had direct experience with liquid biopsy. The remaining 4 participants were family members or care partners of a person with NSCLC.

We also leveraged the 2020 Ontario Health health technology assessment of liquid biopsy testing to detect *EGFR* T790M mutations, which included 7 participants, of whom 3 had been diagnosed with NSCLC and 4 were care partners.[184]

Approach

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

Interviews lasted approximately 20 to 60 minutes. The interview was loosely 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.[273] Questions focused on the impact of NSCLC on the quality of life of people with NSCLC, their experiences of getting diagnosed and, where appropriate, with liquid biopsy testing, and their perceptions of the benefits and limitations of liquid biopsy testing. For family members and care partners, questions focused on their perceptions of the impact of NSCLC and treatments on the quality of life of the person they cared for and on themselves. See Appendix 10 for our interview guide.

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 consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[274,275] We used the qualitative data analysis software program NVivo[276] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of NSCLC, diagnosis, and treatment on the people with NSCLC, family members, and care partners we interviewed.

Results

Diagnosis

Participants reported various initial symptoms they described as fairly mild. These included coughing, difficulty breathing, and chronic regional pain. In a couple cases, people with NSCLC had no symptoms. Because of the mildness of their symptoms, some waited to seek care, believing their symptoms would eventually subside. In most cases, participants described their formal diagnosis journey as streamlined, involving x-ray imaging, which prompted further investigation and additional imaging.

> *I just had pains in my back on my left side, like behind my shoulder, and I had gone to the walk-in clinic, and they just thought it was muscular.*

> *I would speak, and suddenly I would run out of air speaking. So I initially thought that it was probably allergies or [a] spring fever type thing. And so [I] didn't do very much about it until July.*

> *I have had no symptoms which would indicate the diagnosis that I got.*

This experience contrasted with that of a few participants whose diagnostic journey required self-advocacy to access the imaging and tests needed for diagnosis.

> *We did all the hard investigations, which came back negative, and that took about 4 months to go through all the testing.*

> *Pre-diagnosis, he fell between the cracks…The journey was really all kind of backwards…I think the internist would have found it eventually. They were going through a very methodical search.*

Interviewees reflected on the emotional impact of learning about their diagnosis of NSCLC. Most reported being diagnosed with stage IV NSCLC and expressed feelings of shock at both the diagnosis and the fact that the cancer had already progressed to the most advanced stage. Those who were nonsmokers reflected on being confused by the diagnosis as they were unaware that lung cancer could affect them.

> *They came to me [at] about 4 o'clock and said, "You've got lung cancer." And it was a total shock.*

> *I'm not that old...really healthy as far as I'm concerned, and then to find out that you're terminally ill, and they're putting you in palliative care – it's a bit of a shock to the system.*

> *It was pretty shocking for me to hear all this. I've never been a smoker.*

Participants described the fear they experienced upon learning that lung cancer is the leading cause of cancer deaths.

> *Lung cancer is the deadliest cancer. Finding out you have lung cancer at a late stage because there are no symptoms is scary.*

> *Lung cancer is killing 5 times more people than breast cancer, and mostly women actually…The rate is so high for people not surviving. It's caught very late; you don't see symptoms until very late.*

Participants spoke of the stigma of having lung cancer and the negative attitudes toward and perceptions of people with lung cancer in society, where blame is often placed on the person for smoking. Those who were nonsmokers reported feeling the need to tell people they had never smoked when speaking of their diagnosis because of the common misconception of lung cancer being caused solely by smoking.

> *There is quite a [stigma] with lung cancer that people think you did it to yourself because you smoked.*

> *People think it's a smoker's disease, but I've never smoked.*

Tissue Testing

Tissue testing was scheduled for those with sufficient tissue in an accessible location. Participants who underwent tissue testing were given either regional or general anaesthetic. Those who received regional anaesthetic were awake during the procedure and could therefore speak to their experience of it. Those who were fully sedated could not speak to their experience of the procedure but described it as simple and requiring minimal recovery time.

> *So that biopsy with was booked as soon as I met with my thoracic surgeon.*

> *They brought me to a room. I was basically out for it…when I woke up, I just had to [lie] there for 2 hours.*

> *I was awake as far as I remember…I think it did pinch a little bit, but nothing that was totally out of the OR kind of range of hurting.*

One care partner spoke of the procedure causing negative side effects for the person they cared for, who had been fully sedated.

> *It was really awful for him. I think because when they snipped [the tissue] to take a piece of the lung…he was very uncomfortable, and he was spitting up blood like nobody's business…For someone who is palliative or end stage, like, why go through all of that?*

Some participants who underwent tissue testing with regional anaesthesia described the procedure as painful, uncomfortable, and causing feelings of anxiety.

> *I had a lot of residual pain and discomfort from the way [the clinician] did the biopsy…The sample was underneath a piece of my liver that was underneath my rib cage, so [the clinician] made me take a deep breath to push the lever down, and then he'd punctured the site through the skin. He did that several times…I couldn't have as much pain medication because I needed to do the breathing.*

> *He had the CT-guided biopsy, which, to this day, he said is the worst and most painful procedure he's had.*

One care partner stated that the person they cared for required a second, more invasive procedure after the first one failed to retrieve sufficient tissue.

> *They tried to get a biopsy of it, so they went down the trachea, but they couldn't get the sample because it was more on the outer edges of his lung. So, they ended up getting a sample of it from his chest wall. He had to go into a surgical room, and they stuck in a needle in between his ribs, and they pulled out a piece of his lung that way.*

All who underwent tissue testing waited about 2 weeks or more for their results. They commented on the anxiety and stress they experienced while awaiting their results and emphasized the importance of receiving results as quickly as possible given how late most had received their diagnosis. They said that the results were key in guiding their treatment decisions and that faster results meant faster access to the most effective treatments.

> *With biopsies taking so long to come back, it's devastating…because your whole life changes; it's like you're always waiting. You're waiting for something, whether it be an appointment, results appointment, treatment, whatever it is.*

> *That biopsy result was going to be the key for my treatment moving forward. So that was scary – having to wait and just be on edge waiting for that result. That was awful.*

Liquid Biopsy Testing

Participants who underwent liquid biopsy testing described the procedure as a simple and straightforward blood draw. Those who underwent both tissue and liquid biopsy testing were able to compare their experiences and described liquid biopsy testing as less invasive than tissue testing.

> *This is like a usual blood sample. Doesn't hurt at all.*

> *It was very simple compared to the tissue biopsy. It was just a blood draw compared to the surgery involved with the tissue biopsy.*

Those who only underwent liquid biopsy testing were not candidates for tissue testing because of insufficient tissue or the tumour being unreachable.

> *I'm stage IV lung cancer…I don't have enough tissue for tissue biopsy, and I can't wait for [the] cancer to grow.*

> *I didn't have tumours big enough for tissue biopsy. They were all small, and a couple of them were big ones [but] fairly inaccessible.*

Liquid biopsy testing results were available within 7 days. Participants emphasized the value of the speed of this turnaround time compared with tissue testing given the late state at which most had been diagnosed.

> *A week difference was pretty significant when I was that sick, when my lung would not stop filling up, I had trouble breathing, and I was coughing. So even a few days' difference made a difference to me if it meant that I could get treatment faster.*

> *You want to get it [results] as quickly as possible, especially with lung cancer. It's the number one killer of all the cancers.*

> *Those [tissue testing results] took anywhere from 2 to 3 weeks to get back in terms of results. The liquid biopsy took 7 days.*

Treatment

The results of comprehensive genomic profiling, whether from tissue or liquid biopsy testing, are key to guiding decision-making regarding the most effect treatment options. In addition to ensuring the most effective treatment for a particular actionable genomic alteration, participants also mentioned the value of being able to avoid unnecessary side effects from treatments that would not be effective. Some participants with NSCLC reported the plan for their treatment changing because of their tissue or liquid biopsy test results, which highlights the importance of comprehensive genomic profiling in determining the most effective treatment.

> *You know how important it is to have your marker results. For example, if my doctor would have decided to go for immunotherapy as initially discussed, I would be dead by now because people with the* EGFR *mutation…can't have immunotherapy. It doesn't work for them.*

> *This is a difference between life and death because without this [comprehensive genomic profiling test results], it would have been chemo for me, and chemo would have been less effective.*

> *They're on palliative care, and the quality of life in terms of the amount of years that they have left is very important because they don't want to be burdened down by side effects.*

Those prescribed targeted therapy expressed gratitude for being able to avoid high-burden treatments such as chemotherapy. They reflected on the negative experience that others in their lives had had with chemotherapy and reported a positive experience with their own targeted therapy.

> *That's the benefit of avoiding the chemo. I have a friend who [was] going through chemo at the same time as I was taking my pills. She got diagnosed right after me. And just everything, the being exhausted, being in pain, fingers hurting, feet hurting, losing your hair – just, like, the whole process [of] going to the hospital and sitting there every day for hours to get the chemo. I didn't have to go through [that].*

> *I'm scared of the chemotherapy because eventually it's going to happen. I know chemotherapy is not easy to tolerate.*

> *I think people forget that because I always tell people I said, "You know what? All the chemo [is] covered by OHIP, but everything else you need to actually recover from is not.*

Participants with NSCLC spoke about the impact of treatment on their quality of life. The biggest impact mentioned was survival because most had been diagnosed with stage IV NSCLC.

> *I'm still alive and still able to do things with my family. And I kind of pretty much live a normal life.*

> *I want to live; I'm willing to do what it takes. I have grandchildren that I want to see grow.*

> *In 2021, he started a targeted drug therapy….and he's still on it to this day.*

> *I've been on that drug for the last 5 years, and at present everything has been great for the last 5 years.*

> *If you could make the journey easier, and you can live with cancer, then that would be my wish at this point in time.*

Most participants who were candidates for targeted therapy were able to continue their day-to-day activities. Some even noted continuing to be able to work while on targeted therapy.

> *I've had my condition for almost 3 years, and I go to work every day, and nobody knows I'm sick, and that's because of the pill. Because of the [liquid] biopsy, I was offered this pill.*

> *Within days, I started feeling better. And within weeks, they started seeing improvements with my lung fluid. Before treatment, my lung would just fill up faster than it could be drained. They put a tube in me, so I was getting drained, like, 3 times a week.*

Those on targeted treatments that were not publicly funded spoke about the high cost of treatment. Some were able to access treatment because they had private health insurance or through Ontario's Trillium Drug Program, which helps people pay for high prescription-drug costs.

> *The cost is $9,769.49 a month. We use the Trillium Program because we do not have private health [insurance coverage].*

> *It's almost $10,000 a month, and so I have 90% coverage through my employer, and then Trillium covers the [remaining] 10%.*

An important concern raised regarding targeted therapy was the lack of access to treatment in Canada for certain genetic mutations.

> *We don't have any medicine that's approved at this moment. The only thing I can do is search for a clinical trial for this particular mutation.*

> *It all depends on what type of mutation and then hoping that the medication is approved in Canada.*

Barriers to Accessing Liquid Biopsy Testing

Lack of Awareness

One of the main barriers to accessing liquid biopsy testing mentioned by participants with NSCLC was lack of awareness. Most who had undergone liquid biopsy testing were presented with this option by their clinician, while I learned about it through an online support group. Those who had undergone tissue testing were unaware of liquid biopsy testing as another option for comprehensive genomic profiling.

> *I had read about it previously in the support groups that I belong to.*

> *I didn't even know about it until my oncologist told me about this.*

Two participants reported becoming aware of liquid biopsy testing through online support groups but then being denied access to it by their clinicians when they had asked about it. One also reported that their clinician did not know what liquid biopsy testing was.

> *I asked one of the respirologists. I was ready to try it privately. I said, "All I need is a doctor to do this [refer the person for testing], and then they will send me the files." And then he says, "I can't do it. I don't know what this is."*

> *She was very sick, and so I went to her appointment with her and spoke with the doctor about doing a blood biopsy…The doctor wouldn't do it, so they ended up doing a tissue biopsy…It was almost cruel to do a tissue biopsy at that time.*

Cost

As liquid biopsy testing is not currently publicly funded in Ontario, most participants who had undergone liquid biopsy testing had the cost of the test covered by taking part in a clinical trial. They expressed gratitude for this but also concern over the high cost for those not participating in the trial. Those who paid out of pocket reported cost being a barrier.

> *I was lucky because it was [part of] a clinical trial, [so] I didn't have to pay for it.*

> *I paid for it out of pocket. This is a lot of money. I don't work. I'm on disability, [and] I'm stage IV lung cancer…It's a lifesaving decision.*

> *This [cost] is the barrier for patients. They can [only] access it by paying out of the pocket.*

Geography

Geography was also mentioned as a barrier to accessing to liquid biopsy testing since it is currently available only in the Greater Toronto Area. Participants residing within the area expressed gratitude for being able to access liquid biopsy testing easily. Those who lived farther away said they would be willing to travel to Toronto to access to it.

> *It's 3 hours away. Yes, it's a pain to go [to] downtown Toronto, but if we have to, we will. But there [are] people in other areas of Ontario [for whom travelling to Toronto] would be a true hardship.*

> *I come from a position of privilege. I have the education, and I live in the GTA, so…I was able to access this easily.*

Discussion

Direct engagement with people with lived experience of NSCLC allowed us to gather diverse perspectives and thoroughly examine their values and preferences, the factors that influenced their decision-making regarding treatment, and the impact of treatment on people with NSCLC, as well as their family members and care partners. All participants shared their experiences with diagnosis and accessing tissue or liquid biopsy testing. Most participants with NSCLC were diagnosed with stage IV NSCLC, the most advanced stage, which is reflective of the reality of NSCLC diagnosis, as most people with lung cancer are not diagnosed until stage IV.

We found many similarities with the findings of the 2020 Ontario Health health technology assessment of liquid biopsy to detect *EGFR* T790M mutations,[184] particularly in terms of preference for liquid biopsy. However, a notable difference was that all but 1 participant interviewed for the 2020 report who had undergone tissue testing reported having a positive experience with the procedure, whereas several of our interviewees reported discomfort and pain. This discrepancy may result from those interviewed in 2020 not having been diagnosed with advanced NSCLC.

All participants viewed liquid biopsy testing positively, particularly in terms of the faster turnaround time for results compared with tissue testing. Participants' late-stage diagnosis emphasizes the

importance of getting test results quickly so that effective treatment can be initiated as soon as possible. Another perceived advantage for liquid biopsy testing was that it allows access to comprehensive genomic profiling for those with insufficient or difficult-to-access tissue.

Potential limitations of our engagement were the burden of participation for those with advanced NSCLC and that only 6 participants had had experience with liquid biopsy testing. We also had limited rural and northern perspectives. These limitations can be attributed to the fact that liquid biopsy testing is currently available only in Toronto and that the cost is covered only for those participating in a clinical trial at a single Toronto hospital.

Conclusions

Liquid biopsy testing was viewed favourably by all those we interviewed. Participants perceived liquid biopsy testing as less invasive than tissue testing, and those with experience of both tissue and liquid biopsy testing perceived that the turnaround time for results was quicker for liquid biopsy testing. Barriers to accessing liquid biopsy testing included lack of awareness, cost, and geography. Participants emphasized that implementation should require equitable access.

Conclusions of the Health Technology Assessment

Our assessment indicates that the sensitivity of liquid biopsy testing in detecting actionable genomic alterations ranges from low to moderate (GRADE: Moderate to High). This sensitivity falls below that of tissue testing, although neither test reaches an optimal level. The clinical validity of liquid biopsy testing to predict poor response to standard care remains uncertain (GRADE: Very Low). Despite the low clinical validity, liquid biopsy testing has demonstrated clinical utility by improving partial response rates, maintaining stable disease, reducing progressive disease rates, and enhancing objective response rates (GRADE: Moderate). It may also improve progression-free survival and overall survival (GRADE: Low). We estimate that liquid biopsy testing for people newly diagnosed with advanced or metastatic NSCLC (stage IIIB or IV) is associated with an increase in quality-adjusted life-years (QALYs) and an increase in costs compared with current standard care (i.e., tissue testing alone). The incremental cost-effectiveness ratio estimates for the 4 liquid biopsy testing strategies we assessed range from $96,738 to $173,032 per additional QALY gained. We estimate that publicly funding liquid biopsy testing for people with advanced NSCLC and insufficient tissue or difficult-to-reach tissue would lead to an additional cost of $13.72 million over 5 years. The 5-year budget impact of publicly funding the other liquid biopsy testing strategies ranges from $110.13 million to $134.24 million. People with NSCLC, family members, and care partners with whom we spoke viewed liquid biopsy favourably and, valued the fast turnaround time for results that they experienced. Barriers to accessing liquid biopsy testing for patients include lack of awareness, cost, and geography.

Abbreviations

AIC: Akaike information criterion

AE: adverse event

BIC: Bayesian information criterion

BSC: Best supportive care

CADTH: Canadian Agency for Drugs and Technologies in Health

CI: confidence interval

CNA: copy number alteration

CT: computed tomography

ctDNA: circulating tumour DNA

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ICER: incremental cost-effectiveness ratio

indel: insertion and deletion

MDEL: medical device establishment licence

MRI: magnetic resonance imaging

NCCN: National Comprehensive Cancer Network

NGS: next-generation sequencing

NICE: National Institute for Health and Care Excellence

NSCLC: non–small cell lung cancer

ODB: Ontario Drug Benefit (program)

OCCI: Ontario Case Costing Initiative

OHIP: Ontario Health Insurance Plan

OR: odds ratio

PET: positron emission tomography

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: quality-adjusted life-year

RR: relative risk

SD: standard deviation

SNV: single nucleotide variant

VAF: variant allele frequency

WTP: Willingness-to-pay

Glossary

Actionable genomic alteration: A genomic alteration is considered actionable if it predicts therapy response (sensitivity or resistance), affects the function of a cancer-related gene, and can be targeted directly or indirectly with approved or investigational therapies.[277]

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Analytical validity: Analytical validity refers to a test's ability to accurately and reliably measure the genotype (specific genetic variant) of interest. In other words, it assesses how well the laboratory assay can detect the specific genetic change being tested for. This aspect focuses on the technical performance of the test itself, including factors such as sensitivity, specificity, precision, and reproducibility.[70]

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will 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 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).

Clinical validity: Clinical validity pertains to a test's ability to detect or predict the clinical disorder or phenotype associated with a specific genotype. It answers the question, Does a positive genetic test result correlate with an increased risk of developing a particular disease or condition?[70]

Clinical utility: Clinical utility pertains to the impact of test results on patient outcomes and clinical decision-making. It considers not only clinical end points but also emotional, social, cognitive, and behavioral aspects that affect the patient's well-being. For example, even if there is no effective clinical treatment, a test may still have clinical utility by providing clarity and helping patients and their families cope with the associated prognosis.[70]

Cost–consequence analysis: A cost–consequence analysis is a type of economic evaluation that estimates the costs and consequences (i.e., the health outcomes) of 2 or more health care interventions. In this type of analysis, the costs are presented separately from the consequences.

Cost-effective: A health care 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: In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. 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 is plotted on the vertical axis.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost-effectiveness plane: In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

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 with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Disutility: A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[278] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Genomic alteration: a specific genetic or molecular change in a person's DNA.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Incremental cost: The 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 (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the 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 a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may 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 of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Monte Carlo simulation: Monte Carlo simulation is an economic modelling method that derives parameter values from distributions rather than fixed values. The model is run several times, and in each iteration, parameter values are drawn from specified distributions. This method is used in microsimulation models and probabilistic analysis.

Natural history of a disease: The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.

Oncogene: a gene with the potential to cause cancer if mutated.

Oncogenic driver: a genomic alteration responsible for initiating and maintaining a cancer.

Oncogenic signaling pathway: a process that contributes to cancer growth.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and 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 estimate the number 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 (QALY) 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 being in a particular health state. One year of perfect health is represented by one 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 used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses involve varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Societal perspective: The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).

Standard gamble: In economic evaluations, standard gamble is a direct method of measuring people's preferences for various health states. In a standard gamble, respondents are asked about their preference for either (a) remaining in a certain health state for the rest of their life, or (b) a gamble scenario in which there is a chance of having optimal health for the rest of one's life but also a chance of dying immediately. Respondents are surveyed repeatedly, with the risk of immediate death varying each time (e.g., 75% chance of optimal health, 25% chance of immediate death) until they are indifferent about their choice. The standard gamble is considered the gold standard for eliciting preferences as it incorporates individual risk attitudes, unlike other methods of eliciting preferences.

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a

lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a 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 value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: May 31, 2023

Databases searched for 2021 NICE Update: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 23, 2023>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 21>, Ovid MEDLINE(R) ALL <1946 to May 30, 2023>

Search strategy:

---

1 Carcinoma, Non-Small-Cell Lung/ (145580)
2 (non small cell or nonsmall cell or NSCLC* or NS CLC* or aNSCLC* or mNSCLC* or large cell lung*).ti,ab,kf. (267106)
3 (lung* adj3 (cancer* or adenocarcinoma* or squamous*)).ti,ab,kf. (601929)
4 Lung Neoplasms/ge, bl, pa (114451)
5 or/1-4 (671184)
6 Liquid Biopsy/ (13409)
7 ((liquid* or plasma* or blood*) adj5 (biops* or genotyping* or rebiops*)).ti,ab,kf. (49470)
8 (exp High-Throughput Nucleotide Sequencing/ or DNA Mutational Analysis/ or Polymerase Chain Reaction/) and bl.fs. (27149)
9 (exp High-Throughput Nucleotide Sequencing/ or DNA Mutational Analysis/ or Polymerase Chain Reaction/) and (liquid* or plasma* or blood*).ti,ab,kf. (141939)
10 ((liquid* or plasma* or blood*) adj10 (CGP or next* generation* or next gen or nextgen or NGS)).ti,ab,kf. (9240)
11 ((liquid* or plasma* or blood*) adj10 (comprehensive* or genom*) adj3 (profiling* or panel* or biomarker* or assay* or analy* or test*)).ti,ab,kf. (10848)
12 ((genomic* or genetic*) and (comprehensive* or profil*)).ti. (15756)
13 Cell-Free Nucleic Acids/ (5132)
14 (circulating nucleic acid* or cell free nucleic acid* or cell-free deoxyribonucleic acid or cell-free ribonucleic acid or cirdna or cirrna).ti,ab,kf. (2226)
15 Circulating Tumor DNA/ (11582)
16 DNA, Neoplasm/bl (1503)
17 (((circulat* or cell free* or cellfree*) adj3 (DNA* or RNA* or microRNA* or miRNA*)) or ct-DNA* or ctDNA* or cf-DNA* or cfDNA* or ct-RNA* or ctRNA* or cf-RNA* or cfRNA*).ti,ab,kf. (66691)
18 (avenio* or ("follow it*" adj5 (assay* or panel*)) or foundationone* or guardant* or (oncomine* adj5 (assay* or Dx*)) or qiaseq* or tempus* or trusight*).ti,ab,kf. (7126)
19 or/6-18 (285209)
20 5 and 19 (15552)

21 20 use medall (4433)
22 exp Animals/ not Humans/ (16330828)
23 21 not 22 (4410)
24 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6391441)
25 23 not 24 (3937)
26 limit 25 to english language [Limit not valid in CDSR; records were retained] (3807)
27 limit 26 to yr="2010 -Current" (3472)
28 20 use cctr (521)
29 ((Letter not (Letter and Randomized Controlled Trial)) or Conference proceeding or Editorial or Comment or Trial registry record).pt. (4898964)
30 28 not 29 (92)
31 20 use coch,cleed (0)
32 30 or 31 (92)
33 limit 32 to yr="2010 -Current" (83)
34 27 or 33 (3555)
35 exp non small cell lung cancer/ (228760)
36 (non small cell or nonsmall cell or NSCLC* or NS CLC* or aNSCLC* or mNSCLC* or large cell lung*).tw,kw,kf. (267547)
37 (lung* adj3 (cancer* or adenocarcinoma* or squamous*)).tw,kw,kf. (605442)
38 or/35-37 (656780)
39 liquid biopsy/ (13409)
40 ((liquid* or plasma* or blood*) adj5 (biops* or genotyping* or rebiops*)).tw,kw,kf,dv. (50317)
41 (exp high throughput sequencing/ or dna mutational analysis/ or polymerase chain reaction/) and plasma cell/ (1452)
42 (exp high throughput sequencing/ or dna mutational analysis/ or polymerase chain reaction/) and (liquid* or plasma* or blood*).tw,kw,kf,dv. (142370)
43 ((liquid* or plasma* or blood*) adj10 (CGP or next* generation* or next gen or nextgen or NGS)).tw,kw,kf,dv. (9662)
44 ((liquid* or plasma* or blood*) adj10 (comprehensive* or genom*) adj3 (profiling* or panel* or biomarker* or assay* or analy* or test*)).tw,kw,kf,dv. (10932)
45 ((genomic* or genetic*) and (comprehensive* or profil*)).ti. (15756)
46 exp cell free nucleic acid/ (22815)
47 (circulating nucleic acid* or cell free nucleic acid* or cell-free deoxyribonucleic acid or cell-free ribonucleic acid or cirdna or cirrna).tw,kw,kf,dv. (2269)
48 (((circulat* or cell free* or cellfree*) adj3 (DNA* or RNA* or microRNA* or miRNA*)) or ct-DNA* or ctDNA* or cf-DNA* or cfDNA* or ct-RNA* or ctRNA* or cf-RNA* or cfRNA*).tw,kw,kf,dv. (67322)
49 (avenio* or (''follow it*'' adj5 (assay* or panel*)) or foundationone* or guardant* or (oncomine* adj5 (assay* or Dx*)) or qiaseq* or tempus* or trusight*).tw,kw,kf,dv. (7852)
50 or/39-49 (275137)
51 38 and 50 (15692)
52 51 use emez (10956)
53 (exp animal/ or nonhuman/) not exp human/ (11890398)
54 52 not 53 (10827)
55 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11200539)
56 54 not 55 (5053)
57 limit 56 to english language [Limit not valid in CDSR; records were retained] (4836)

58 limit 57 to yr="2010 -Current" (4582)
59 34 or 58 (8137)
60 59 use medall (3472)
61 59 use emez (4582)
62 59 use cctr (83)
63 59 use coch (0)
64 59 use cleed (0)
65 limit 59 to yr="2010 - 2018" (2758)
66 remove duplicates from 65 (1725)
67 limit 59 to yr="2019 - current" (5379)
68 remove duplicates from 67 (3262)

Economic Evidence Search

Search date: June 1, 2023

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 31, 2023>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2023 Week 21>, Ovid MEDLINE(R) ALL <1946 to May 31, 2023>

Search strategy:

---
1 Carcinoma, Non-Small-Cell Lung/ (145562)
2 (non small cell or nonsmall cell or NSCLC* or NS CLC* or aNSCLC* or mNSCLC* or large cell lung*).ti,ab,kf. (267110)
3 (lung* adj3 (cancer* or adenocarcinoma* or squamous*)).ti,ab,kf. (601873)
4 Lung Neoplasms/ge, bl, pa (114399)
5 or/1-4 (671119)
6 Liquid Biopsy/ (13405)
7 ((liquid* or plasma* or blood*) adj5 (biops* or genotyping* or rebiops*)).ti,ab,kf. (49458)
8 (exp High-Throughput Nucleotide Sequencing/ or DNA Mutational Analysis/ or Polymerase Chain Reaction/) and bl.fs. (27149)
9 (exp High-Throughput Nucleotide Sequencing/ or DNA Mutational Analysis/ or Polymerase Chain Reaction/) and (liquid* or plasma* or blood*).ti,ab,kf. (141932)
10 ((liquid* or plasma* or blood*) adj10 (CGP or next* generation* or next gen or nextgen or NGS)).ti,ab,kf. (9242)
11 ((liquid* or plasma* or blood*) adj10 (comprehensive* or genom*) adj3 (profiling* or panel* or biomarker* or assay* or analy* or test*)).ti,ab,kf. (10845)
12 ((genomic* or genetic*) and (comprehensive* or profil*)).ti. (15750)
13 Cell-Free Nucleic Acids/ (5125)
14 (circulating nucleic acid* or cell free nucleic acid* or cell-free deoxyribonucleic acid or cell-free ribonucleic acid or cirdna or cirrna).ti,ab,kf. (2227)
15 Circulating Tumor DNA/ (11577)

16 DNA, Neoplasm/bl (1503)
17 (((circulat* or cell free* or cellfree*) adj3 (DNA* or RNA* or microRNA* or miRNA*)) or ct-DNA* or ctDNA* or cf-DNA* or cfDNA* or ct-RNA* or ctRNA* or cf-RNA* or cfRNA*).ti,ab,kf. (66674)
18 (avenio* or ("follow it*" adj5 (assay* or panel*)) or foundationone* or guardant* or (oncomine* adj5 (assay* or Dx*)) or qiaseq* or tempus* or trusight*).ti,ab,kf. (7126)
19 or/6-18 (285179)
20 5 and 19 (15550)
21 20 use coch,cleed (0)
22 economics/ (264509)
23 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1049873)
24 economics.fs. (470078)
25 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1271148)
26 exp "costs and cost analysis"/ (686017)
27 (cost or costs or costing or costly).ti. (332726)
28 cost effective*.ti,ab,kf. (449714)
29 (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* or increment*)).ab,kf. (310326)
30 models, economic/ (15983)
31 markov chains/ or monte carlo method/ (107547)
32 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (66913)
33 (markov or markow or monte carlo).ti,ab,kf. (179085)
34 quality-adjusted life years/ (55944)
35 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (111837)
36 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (193475)
37 or/22-36 (3366804)
38 20 and 37 (599)
39 38 use medall (130)
40 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6391087)
41 39 not 40 (129)
42 limit 41 to english language [Limit not valid in CDSR; records were retained] (125)
43 38 use cctr (30)
44 ((Letter not (Letter and Randomized Controlled Trial)) or Conference proceeding or Editorial or Comment or Trial registry record).pt. (4898605)
45 43 not 44 (3)
46 21 or 42 or 45 (128)
47 limit 46 to yr="2010 -Current" (127)
48 exp non small cell lung cancer/ (228742)
49 (non small cell or nonsmall cell or NSCLC* or NS CLC* or aNSCLC* or mNSCLC* or large cell lung*).tw,kw,kf. (267551)
50 (lung* adj3 (cancer* or adenocarcinoma* or squamous*)).tw,kw,kf. (605386)
51 or/48-50 (656722)
52 liquid biopsy/ (13405)
53 ((liquid* or plasma* or blood*) adj5 (biops* or genotyping* or rebiops*)).tw,kw,kf,dv. (50305)
54 (exp high throughput sequencing/ or dna mutational analysis/ or polymerase chain reaction/) and plasma cell/ (1452)

55 (exp high throughput sequencing/ or dna mutational analysis/ or polymerase chain reaction/) and (liquid* or plasma* or blood*).tw,kw,kf,dv. (142363)
56 ((liquid* or plasma* or blood*) adj10 (CGP or next* generation* or next gen or nextgen or NGS)).tw,kw,kf,dv. (9664)
57 ((liquid* or plasma* or blood*) adj10 (comprehensive* or genom*) adj3 (profiling* or panel* or biomarker* or assay* or analy* or test*)).tw,kw,kf,dv. (10929)
58 ((genomic* or genetic*) and (comprehensive* or profil*)).ti. (15750)
59 exp cell free nucleic acid/ (22802)
60 (circulating nucleic acid* or cell free nucleic acid* or cell-free deoxyribonucleic acid or cell-free ribonucleic acid or cirdna or cirrna).tw,kw,kf,dv. (2270)
61 (((circulat* or cell free* or cellfree*) adj3 (DNA* or RNA* or microRNA* or miRNA*)) or ct-DNA* or ctDNA* or cf-DNA* or cfDNA* or ct-RNA* or ctRNA* or cf-RNA* or cfRNA*).tw,kw,kf,dv. (67305)
62 (avenio* or ("follow it*" adj5 (assay* or panel*)) or foundationone* or guardant* or (oncomine* adj5 (assay* or Dx*)) or qiaseq* or tempus* or trusight*).tw,kw,kf,dv. (7852)
63 or/52-62 (275106)
64 51 and 63 (15691)
65 Economics/ (264509)
66 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (146600)
67 Economic Aspect/ or exp Economic Evaluation/ (552589)
68 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1291441)
69 exp "Cost"/ (686017)
70 (cost or costs or costing or costly).ti. (332726)
71 cost effective*.tw,kw,kf. (458515)
72 (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* or increment*)).ab,kw,kf. (319909)
73 Monte Carlo Method/ (83548)
74 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (70307)
75 (markov or markow or monte carlo).tw,kw,kf. (182552)
76 Quality-Adjusted Life Years/ (55944)
77 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (115179)
78 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (214160)
79 or/65-78 (2888696)
80 64 and 79 (535)
81 80 use emez (374)
82 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11200180)
83 81 not 82 (188)
84 limit 83 to english language [Limit not valid in CDSR; records were retained] (184)
85 limit 84 to yr="2010 -Current" (182)
86 47 or 85 (309)
87 86 use medall (124)
88 86 use emez (182)
89 86 use cctr (3)
90 86 use coch (0)
91 86 use cleed (0)
92 remove duplicates from 86 (198)

Grey Literature Search

Performed: June 23 to July 4, 2023

Websites searched:

Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, 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), Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, Health Technology Assessment Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services, Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, Cancer Care Ontario, Canadian Task Force on Preventive Health Care, U.S. Preventive Services Task Force, PROSPERO, EUnetHTA, ClinicalTrials.gov

Keywords used: non-small cell, NSCLC, lung cancer, liquid biopsy, plasma biopsy, blood biopsy, cell-free, circulating, cf-dna, comprehensive genomic, comprehensive genetic, next generation, avenio, "follow it", foundationone, guardant, oncomine, qiaseq, tempus, trusight

Clinical results (included in PRISMA): 83

Economic results (included in PRISMA): 84

Ongoing HTAs (PROSPERO/EUnetHTA): 16

Ongoing clinical trials: 121

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Assessment of Bias and Applicability Concerns Using QUADAS-2/QUADAS-C Tool in Evaluating the Analytical Validity of Liquid and Tissue Biopsy Testing

Study	Test	Risk of bias (QUADAS-2)[a]				Applicability concerns (QUADAS-2)[a]			Risk of bias (QUADAS-C)[a]			
		P	I	R	FT	P	I	R	P	I	R	FT
Bai et al., 2019[101]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Buburuzan et al., 2022[102]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bustamante Alvarez et al., 2020[103]	Tissue testing	✓	✓	✓	X[b]	✓	✓	✓	✓	✓	✓	X[b]
	Liquid biopsy testing	✓	✓	✓	X[b]	✓	✓	✓	✓	✓	✓	X[b]
Chen et al., 2016[104]	Tissue testing	✓	✓	✓	✓	X[c]	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	X[c]	✓	✓	✓	✓	✓	✓
Chen et al., 2019[105]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Couraud et al., 2014[106]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cui et al., 2017[107]	Tissue testing	✓	✓	✓	✓	X[d]	✓	✓	X[d]	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	X[d]	✓	✓	X[d]	✓	✓	✓
Dagogo-Jack et al., 2019[108]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fernandes et al., 2021[110]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
He et al., 2016[111]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Jiao et al., 2021[113]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Study	Test	Risk of bias (QUADAS-2)[a]				Applicability concerns (QUADAS-2)[a]			Risk of bias (QUADAS-C)[a]			
		P	I	R	FT	P	I	R	P	I	R	FT
Lee et al., 2021[115]	Tissue testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
	Liquid biopsy testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
Lee et al., 2022[116]	Tissue testing	X[e]	✓	✓	✓	✓	✓	✓	X[e]	✓	✓	✓
	Liquid biopsy testing	X[e]	✓	✓	✓	✓	✓	✓	X[e]	✓	✓	✓
Li et al., 2019[117]	Tissue testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
	Liquid biopsy testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
Lin et al., 2021[120]	Tissue testing	✓	✓	✓	X[f]	✓	✓	✓	✓	✓	✓	X[f]
	Liquid biopsy testing	✓	✓	✓	X[f]	✓	✓	✓	✓	✓	✓	X[f]
Lin et al., 2021[121]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Liu et al., 2018[122]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mehta et al., 2021[124]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mondaca et al., 2021[125]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ohira et al., 2016[126]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Park et al., 2021[128]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pasquale et al., 2019[129]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pe´cuchet et al., 2016[131]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pritchett et al., 2019[133]	Tissue testing	✓	✓	✓	X[b]	✓	✓	✓	✓	✓	✓	X[b]
	Liquid biopsy testing	✓	✓	✓	X[b]	✓	✓	✓	✓	✓	✓	X[b]

Study	Test	Risk of bias (QUADAS-2)[a]				Applicability concerns (QUADAS-2)[a]			Risk of bias (QUADAS-C)[a]			
		P	I	R	FT	P	I	R	P	I	R	FT
Raez et al., 2022[134]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Roosan et al., 2021[135]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Roosan et al., 2021[136]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sabari et al., 2019[137]	Tissue testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
	Liquid biopsy testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
Schouten et al., 2021[138]	Tissue testing	✓	✓	✓	X[g]	✓	✓	✓	✓	✓	✓	X[g]
	Liquid biopsy testing	✓	✓	✓	X[g]	✓	✓	✓	✓	✓	✓	X[g]
Schrock et al., 2018[139]	Tissue testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
	Liquid biopsy testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
Schwaederlé et al., 2017[140]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Schwartzberg et al., 2020[141]	Tissue testing	✓	✓	✓	X[g]	✓	✓	✓	✓	✓	✓	X[g]
	Liquid biopsy testing	✓	✓	✓	X[g]	✓	✓	✓	✓	✓	✓	X[g]
Sugimoto et al., 2023[142]	Tissue testing	✓	✓	✓	X[g]	✓	✓	✓	✓	✓	✓	X[g]
	Liquid biopsy testing	✓	✓	✓	X[g]	✓	✓	✓	✓	✓	✓	X[g]
Sun et al., 2023[143]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sung et al., 2017[144]	Tissue testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
	Liquid biopsy testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
Tetik Vardarli et al., 2020[145]	Tissue testing	✓	✓	✓	X[g]	✓	✓	✓	✓	✓	✓	X[g]
	Liquid biopsy testing	✓	✓	✓	X[g]	✓	✓	✓	✓	✓	✓	X[g]
Thompson et al., 2016[146]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Study	Test	Risk of bias (QUADAS-2)[a]				Applicability concerns (QUADAS-2)[a]			Risk of bias (QUADAS-C)[a]			
		P	I	R	FT	P	I	R	P	I	R	FT
Toor et al., 2018[147]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tran et al., 2019[148]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tran et al., 2021[149]	Tissue testing	✓	✓	✓	X[g]	✓	✓	✓	✓	✓	✓	X[g]
	Liquid biopsy testing	✓	✓	✓	X[g]	✓	✓	✓	✓	✓	✓	X[g]
Uchida et al., 2015[150]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Villaflor et al., 2016[151]	Tissue testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
	Liquid biopsy testing	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	?
Wu et al., 2019[154]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Xie et al., 2018[155]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Xu et al., 2016[156]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Yang et al., 2018[157]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Yao et al., 2016[158]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Yin et al., 2021[159]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Zhang et al., 2022[160]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Zhao et al., 2023[161]	Tissue testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Liquid biopsy testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Notes for Table A1

Abbreviations: FT = Flow and Timing; I = Index Test; P = Patient Selection; R = Reference Standard; ✓ = low risk; X = high risk; ? = unclear risk.

[a]In each study, the evaluation applies to all genes.

[b] The tests could be conducted with a maximum interval of 12 weeks between them.

[c]Restricted to people who underwent tumour resection.

[d]Excluded people with ALK fusion.

[e]Excluded plasma results with no evidence of circulating tumour DNA variants.

[f] The tests could be conducted with a maximum interval of 16 weeks between them.

[g]Plasma and tissue sample may have been collected several weeks apart.

Table A2: ROBINS-E Risk of Bias Tool for Assessing the Clinical Validity of Liquid Biopsy Testing

Author, year	Confounding	Exposure measurement errors	Selection bias	Post exposure interventions	Missing data	Outcome measurement errors	Selective reporting
FGFR1							
Pavan et al., 2021[130]	low	some concerns[b,c]	low	low	low	low	low
KRAS							
Pavan et al., 2021[130]	low	high[b,c,d]	low	low	low	low	low

Abbreviation: ROBINS-E, Risk of Bias in Non-randomized Studies—of Exposure.
[a]Possible risk-of-bias levels: low, some concerns, high, very high.
[b]Sensitivity of liquid biopsy testing to detect alterations in the FGFR1 gene was low.
[c]Different types of immune checkpoint inhibitors with differing levels of effectiveness may have been disproportionately distributed between the two exposure groups.
[d]Evaluation of KRAS mutation was based on its co-existence with mutation on other genes. It is unclear how much the existence of these other mutations influenced the outcomes.

Table A3: ROBINS-I Risk of Bias Tool for Assessing the Clinical Utility of Liquid Biopsy Testing

	Pre-intervention		At intervention		Post-intervention		
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Bustamante Alvarez et al., 2020[103]	low	low	serious[c]	low	low	low	low
Dziadziuszko et al., 2021[109]	low	low	no information	low	low	low	low
Jee et al., 2022[112]	serious[d]	low	no information	low	low	low	low
Laufer-Geva et al., 2018[112]	low	low	no information	low	low	low	low
Li et al., 2021[118]	low	low	no information	low	low	low	low
Marchetti et al., 2015[123]	low	low	no information	low	low	low	low
Page et al., 2021[127]	low	low	no information	low	low	low	low
Phallen et al., 2019[132]	low	low	no information	low	low	low	low
Wang et al., 2018[152]		low	no information	low	low	low	low
Wang et al., 2021[153]	low	low	no information	low	low	low	low
Xie et al., 2018[155]	low	low	moderate[e]	low	low	low	low
Liang et al., 2023[119]	low	low	no information	low	low	low	low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, and no information.

[b]In studies that reported multiple outcomes, the level of risk of bias was consistent across all outcomes.

[c]The sensitivity of liquid biopsy testing to detect KRAS alterations was modest.

[d]The study compared two independent groups without accounting for the differences in characteristics between them, which could potentially confound the results.

[e]Although the sensitivity of liquid biopsy assay to detect EGFR alterations was high, it was notably far from perfect.

Table A4: GRADE Evidence Profile for the Comparison of Analytical Validity of Tissue and Liquid Biopsy Testing

Number of studies (design)	Risk of bias[a]	Inconsistency	Indirectness[a]	Imprecision	Publication bias	Certainty
ALK – Sensitivity						
32 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
ALK – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
34 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
ALK – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
34 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
ALK – Testing positive with liquid biopsy among those testing positive with tissue biopsy						
34 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
ALK – Overall concordance between tissue-based and liquid biopsy						
34 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
BRAF – Sensitivity						
27 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (-1)	Undetected	⊕⊕⊕ Moderate
BRAF – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
31 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
BRAF – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
31 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
BRAF – Testing positive with liquid biopsy among those testing positive with tissue biopsy						
23 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (-1)	Undetected	⊕⊕⊕ Moderate
BRAF – Overall concordance between tissue-based and liquid biopsy testing						
31 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
EGFR– Sensitivity						
42 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
EGFR – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
41 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
EGFR – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
41 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High

Number of studies (design)	Risk of bias[a]	Inconsistency	Indirectness[a]	Imprecision	Publication bias	Certainty
EGFR – Testing positive with liquid biopsy among those testing positive with tissue biopsy						
42 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
EGFR – Overall concordance between tissue-based and liquid biopsys						
42 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
ERBB2– Sensitivity						
23 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (-1)	Undetected	⊕⊕⊕ Moderate
ERBB2 – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
27 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
ERBB2 – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
27 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
ERBB2 – Testing positive with liquid biopsy among those testing positive with tissue biopsy						
22 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (-1)	Undetected	⊕⊕⊕ Moderate
ERBB2 – Overall concordance between tissue-based and liquid biopsy						
27 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
FGFR1– Sensitivity						
7 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (-3)	Undetected	⊕ Very low
FGFR1 – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
8 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
FGFR1 – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
8 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
FGFR1 – Testing positive with liquid biopsy among those testing positive with tissue biopsy						
6 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (-3)	Undetected	⊕ Very low
FGFR1 – Overall concordance between tissue-based and liquid biopsy						
9 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
KRAS– Sensitivity						
34 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
KRAS – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
35 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High

Number of studies (design)	Risk of bias[a]	Inconsistency	Indirectness[a]	Imprecision	Publication bias	Certainty
KRAS – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
35 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
KRAS – Testing positive with liquid biopsy among those testing positive with tissue biopsy						
35 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
KRAS – Overall concordance between tissue-based and liquid biopsy						
35 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
MET– Sensitivity						
24 (fully paired)	No serious limitations	Serious limitations (-1)	No serious limitations	Serious limitations (-1)	Undetected	⊕⊕ Low
MET – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
27 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
MET – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
27 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
MET – Testing positive with liquid biopsy given among those testing positive with tissue biopsy						
22 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (-2)	Undetected	⊕⊕ Low
MET – Overall concordance between tissue-based and liquid biopsy						
27 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
NTRK1– Sensitivity						
3 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (-3)	Undetected	⊕ Very low
NTRK1 – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
3 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
NTRK1 – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
3 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
NTRK1 – Testing positive with liquid biopsy among those testing positive with tissue biopsy						
3 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
NTRK1– Overall concordance between tissue-based and liquid biopsy						
3 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
NTRK3– Sensitivity						
1 (fully paired)	No serious limitations	Not evaluable	No serious limitations	Very serious limitations (-3)	Undetected	⊕ Very low

Number of studies (design)	Risk of bias[a]	Inconsistency	Indirectness[a]	Imprecision	Publication bias	Certainty
NTRK3– Testing positive with liquid biopsy among those testing negative with tissue biopsy						
1 (fully paired)	No serious limitations	Not evaluable	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
NTRK3– Testing positive with liquid biopsy among those testing positive with tissue biopsy						
1 (fully paired)	No serious limitations	Not evaluable	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
NTRK3– Overall concordance between tissue-based and liquid biopsy						
3 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
PIK3CA – Sensitivity						
22 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (-1)	Undetected	⊕⊕⊕ Moderate
PIK3CA – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
23 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
PIK3CA – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
23 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
PIK3CA – Testing positive with liquid biopsy among those testing positive with tissue biopsy						
22 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (-1)	Undetected	⊕⊕⊕ Moderate
PIK3CA – Overall concordance between tissue-based and liquid biopsy						
23 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
RET – Sensitivity						
13 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (-2)	Undetected	⊕⊕ Low
RET – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
16 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
RET – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
16 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
RET – Testing positive with liquid biopsy among those testing positive with tissue biopsy						
13 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (-3)	Undetected	⊕ Very low
RET – Overall concordance between tissue-based and liquid biopsy						
16 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
ROS1 – Sensitivity						
14 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (-2)	Undetected	⊕⊕ Low

Number of studies (design)	Risk of bias[a]	Inconsistency	Indirectness[a]	Imprecision	Publication bias	Certainty
ROS1 – Testing positive with liquid biopsy among those testing negative with tissue biopsy						
17 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
ROS1 – Testing positive with tissue biopsy among those testing negative with liquid biopsy						
17 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High
ROS1 – Testing positive with liquid biopsy among those testing positive with tissue biopsy						
13 (fully paired)	No serious limitations	No serious limitations	No serious limitations	Very serious limitations (-3)	Undetected	⊕ Very low
ROS1 – Overall concordance						
18 (fully paired)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	⊕⊕⊕⊕ High

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]Judgment is based on the assessment outlined in the QUADAS-2/ QUADAS-C table.

Table A5: GRADE Evidence Profile for the Assessment of Clinical Validity of Liquid Biopsy Testing

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
FGFR1 – Progression free survival							
1 (cohort)	Serious limitations (−1)	No serious limitations	No serious limitations	Very serious limitations (-3)	Undetected	None	⊕Very Low
KRAS – Progression free survival							
1 (cohort)	Serious limitations (−2)	No serious limitations	No serious limitations	Very serious limitations (-3)	Undetected	None	⊕Very Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

Table A6: GRADE Evidence Profile for the Assessment of Clinical Utility of Liquid Biopsy Testing

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Complete response							
7 (cohort – before after)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Very serious limitations (-1)	Undetected	None	⊕⊕Low
Partial response							
8 (cohort – before after)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕Moderate
Progressive disease							
6 (cohort – before after)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕Moderate
Progression-free survival							
2 (cohort – before after)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (-1)	Undetected	None	⊕⊕ Low
Overall survival							
1 (cohort)	Very serious limitations (−2)[a,c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Stable disease							
7 (cohort – before after)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕Moderate
Objective response rate							
3 (cohort – before after)	Serious limitations (-1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕Moderate

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

[a]Since we observed that the sensitivity of liquid biopsy testing is generally modest, there is a possibility of bias stemming from the exclusion of false negative cases from the analysis.

[b]We could not assess the degree of imprecision in one of the two studies because the primary study authors did not provide this information.

[c] The study compared two independent groups without accounting for the differences in characteristics between them, which could potentially confound the results.

Appendix 3: Clinical Evidence Tables and Graphs

Table A7: Sensitivity of Liquid Biopsy and Tissue Testing

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
Bai et al., 2019, China	EGFR	9	2	24	94.3 (80.8 to 99.3)	74.3 (56.7 to 87.5)
Buburuzan et al., 2022, Romania	ALK	0	0	0	Undefined	Undefined
	BRAF	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	EGFR	0	2	3	60 (14.7 to 94.7)	100 (47.8 to 100.0)
	ERBB2	0	0	0	Undefined	Undefined
	FGFR1	0	0	0	Undefined	Undefined
	KRAS	0	1	4	80 (28.4 to 99.5)	100 (47.8 to 100.0)
	MET	2	3	0	40 (5.3 to 85.3)	60 (14.7 to 94.7)
	PIK3CA	1	1	0	50 (1.3 to 98.7)	50 (1.3 to 98.7)
Bustamante Alvarez et al., 2020, USA	KRAS	11	7	22	82.5 (67.2 to 92.7)	72.5 (56.1 to 85.4)
Chen et al., 2016, China	ALK	0	1	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
	EGFR	10	6	12	78.6 (59.0 to 91.7)	64.3 (44.1 to 81.4)
	KRAS	2	2	1	60 (14.7 to 94.7)	60 (14.7 to 94.7)
	PIK3CA	1	6	1	25 (31.9 to 65.1)	87.5 (47.3 to 99.7)
Chen et al., 2019, China	ALK	1	3	1	40 (5.3 to 85.3)	80 (28.4 to 99.5)
	EGFR	13	3	4	85 (62.1 to 96.8)	35 (15.4 to 59.2)
	ERBB2	1	0	1	100 (15.8 to 100.0)	50 (1.3 to 98.7)
	KRAS	3	0	1	100 (39.8 to 100.0)	25 (0.6 to 80.6)
	NTRK1	2	0	0	100 (15.8 to 100.0)	0 (0.0 to 84.2)
	PIK3CA	3	1	2	83.3 (35.9 to 99.6)	50 (11.8 to 88.2)
Courad et al., 2014, USA	BRAF	2	0	0	100 (15.8 to 100)	0 (0.0 to 84.2)
	EGFR	13	2	20	94.3 (80.8 to 99.3)	62.9 (44.9 to 78.5)
	ERBB2	2	0	3	100 (47.8 to 100.0)	60 (14.7 to 94.7)

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
	KRAS	1	0	3	100 (39.8 to 100.0)	75 (19.4 to 99.4)
	PIK3CA	1	1	0	50 (1.3 to 98.7)	50 (1.3 to 98.7)
Cui et al., 2017, China	ALK	11	0	13	100 (85.8 to 100.0)	54.2 (32.8 to 74.4)
Dagogo-Jack et al., 2019, USA	ROS1	0	0	7	100 (59.0 to 100.0)	100 (59.0 to 100.0)
Fernandes et al., 2021, Portugal	ALK	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	BRAF	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)
	EGFR	6	2	20	92.9 (76.5 to 99.1)	78.6 (59.0 to 91.7)
	ERBB2	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	KRAS	6	1	17	95.8 (78.9 to 99.9)	75 (53.3 to 90.2)
	PIK3CA	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
He et al., 2016, China[d]	ALK	0	0	1	100 (2.5 to 100)	100 (2.5 to 100)
	BRAF	0	0	0	Undefined	Undefined
	EGFR	2	0	0	100 (15.8 to 100)	0 (0 to 84.2)
	ERBB2	0	0	0	Undefined	Undefined
	FGFR1	0	0	10	100 (69.2 to 100)	10060 (69.2 to 100)
	KRAS	1	0	0	100 (2.5 to 100)	0 (0 to 97.5)
	MET	0	0	2	100 (15.8 to 100)	100 (15.8 to 100)
	PIK3CA	0	0	0	Undefined	Undefined
Jiao et al., 2021, China	ALK	7	0	11	100 (81.5 to 100.0)	61.1 (35.7 to 82.7)
	BRAF	6	1	5	91.7 (61.5 to 99.8)	50 (21.1 to 78.9)
	EGFR	25	9	61	90.5 (82.8 to 95.6)	73.7 (63.6 to 82.2)
	ERBB2	5	2	8	86.7 (59.5 to 98.3)	66.7 (38.4 to 88.2)
	KRAS	9	1	20	96.7 (82.8 to 99.9)	70 (50.6 to 85.3)
	MET	10	1	8	94.7 (74.0 to 99.9)	47.4 (24.4 to 71.1)
	NTRK3	0	1	9	90 (55.5 to 99.7)	100 (69.2 to 100.0)

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
	PIK3CA	13	3	8	87.5 (67.6 to 97.3)	45.8 (25.6 to 67.2)
Lee et al., 2021, USA	MET	1	1	12	92.9 (66.1 to 99.8)	92.9 (66.1 to 99.8)
	ALK	0	4	0	0 (0.0 to 60.2)	100 (39.8 to 100.0)
	BRAF	0	0	0	Undefined	Undefined
	EGFR	0	0	7	100 (59.0 to 100.0)	100 (59.0 to 100.0)
	FGFR1	0	0	0	Undefined	Undefined
	MET	0	0	0	Undefined	Undefined
	RET	0	1	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
	ROS1	0	0	0	Undefined	Undefined
Li et al., 2019, USA	ALK	0	0	5	100 (47.8 to 100.0)	100 (47.8 to 100.0)
	BRAF	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)
	EGFR	0	0	29	100 (88.1 to 100.0)	100 (88.1 to 100.0)
	ERBB2	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)
	KRAS	0	0	19	100 (82.4 to 100.0)	100 (82.4 to 100.0)
	MET	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)
	RET	0	0	0	Undefined	Undefined
	ROS1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
Lin et al., 2021, Taiwan	ALK	5	2	4	81.8 (48.2 to 97.7)	55.4 (23.4 to 83.3)
	ALK	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
	BRAF	2	0	0	100 (15.8 to 100.0)	0 (0.0 to 84.2)
	EGFR	13	2	20	91.4 (76.9 to 98.2)	62.9 (44.9 to 78.5)
	ERBB2	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
	KRAS	10	1	10	95.2 (76.2 to 99.9)	52.4 (29.8 to 74.3)
	MET	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)
	NTRK1	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
	RET	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	ROS1	2	0	1	100 (29.2 to 100.0)	33.3 (0.8 to 90.6)
Liu et al., 2017, China	ALK	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)
	BRAF	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	EGFR	0	0	12	100 (73.5 to 100.0)	100 (73.5 to 100.0)
	KRAS	0	0	6	100 (54.1 to 100.0)	100 (54.1 to 100.0)
	RET	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
Mehta et al., 2021, India	ALK	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	BRAF	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
	EGFR	0	1	7	87.5 (47.3 to 99.7)	100 (63.1 to 100.0)
	ERBB2	0	1	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
	KRAS	1	3	5	66.7 (29.9 to 92.5)	88.9 (51.8 to 99.7
	MET	0	1	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
	PIK3CA	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	RET	0	0	0	Undefined	Undefined
	ROS1	0	0	0	Undefined	Undefined
Mondaca et al., 2021, USA	ALK	11	1	13	96 (79.6 to 99.9)	56 (34.9 to 75.6)
Ohira et al., 2016, Japan	ALK	1	0	0	100 (2.5 to 100.0)	0 (0.0 (97.5)
	BRAF	3	0	0	100 (29.2 to 100.0)	0 (0.0 to 70.8)
	EGFR	53	0	3	100 (93.6 to 100.0)	5.4 (1.1 to 14.9)
	ERBB2	3	0	0	100 (29.2 to 100.0)	0 (0.0 to 70.8)
	KRAS	15	0	0	0 (0.0 to 21.8)	100 (78.2 to 100.0)
	MET	1	0	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
	PIK3CA	2	0	1	66.7 (9.4 to 99.2)	33.3 (0.8 to 90.6)

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
Park et al., 2021, Republic of Korea	ALK	5	0	9	100 (76.8 to 100.0)	64.3 (35.1 to 87.2)
	BRAF	2	1	1	75 (19.4 to 99.4)	75 (19.4 to 99.4)
	EGFR	14	5	52	93 (84.3 to 97.7)	80.3 (69.1 to 88.8)
	ERBB2	3	0	12	100 (78.2 to 100.0)	80 (51.9 to 95.7)
	KRAS	11	3	23	91.9 (78.1 to 98.3)	70.3 (53.0 to 84.1)
	MET	14	11	9	67.6 (49.5 to 82.6)	58.8 (40.7 to 75.4)
	RET	13	2	7	90.9 (70.8 to 98.9)	40.9 (20.7 to 63.6)
	ROS1	13	0	3	100 (79.4 to 100.0)	81.3 (54.4 to 96.0)
Pasquale et al., 2019, Italy	EGFR	7	2	23	93.8 (79.2 to 99.2)	78.1 (60.0 to 90.7)
Pe´cuchet et al., 2016, France	ALK	2	0	1	100 (29.2 to 100.0)	33.3 (0.8 to 90.1)
	BRAF	1	0	2	100 (29.2 to 100.0)	66.7 (9.4 to 99.2)
	EGFR	19	0	28	100 (92.5 to 100.0)	59.6 (44.3 to 73.6)
	FGFR1	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
	KRAS	10	0	19	100 (88.1 to 100.0)	65.5 (45.7 to 82.1)
	PIK3CA	3	2	2	71.4 (29.0 to 96.3)	57.1 (18.4 to 90.1)
Pritchett et al., 2019, USA	BRAF	2	0	5	100 (59.0 to 100.)	71.4 (29.0 to 96.3)
	EGFR	5	0	13	100 (81.5 to 100.0)	72.2 (46.5 to 90.3)
	ERBB2	0	0	2	100 (15.8 to 100.0)	100 (15.8 to 100.0)
	KRAS	12	1	48	98.4 (91.2 to 100.0)	80.3 (68.2 to 89.4)
	MET	3	0	3	100 (54.1 to 100.0)	50 (11.8 to 88.2)
Raez et al., 2022, USA	ALK	1	2	0	33.3 (0.8 to 90.6)	66.7 (9.4 to 99.2)
	BRAF	2	2	0	50 (6.8 to 93.2)	50 (6.8 to 93.2)
	EGFR	7	18	14	53.8 (37.2 to 69.9)	82.1 (66.5 to 92.5)

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
	MET	1	1	1	66.7 (9.4 to 99.2)	66.7 (9.4 to 99.2)
	NTRK	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
	ROS1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
Roosan et al., 2021, USA	ALK	3	2	2	71.4 (29.0 to 96.3)	57.1 (18.4 to 90.1)
	BRAF	3	4	4	63.6 (30.8 to 89.1)	72.7 (39.0 to 94.0)
	EGFR	3	6	25	82.4 (65.5 to 93.2)	91.2 (76.3 to 98.1)
	ERBB2	4	2	1	85.7 (42.1 to 99.6)	42.9 (9.9 to 81.6)
	FGFR1	1	2	1	50 (6.8 to 93.2)	75 (19.4 to 99.4)
	KRAS	5	1	11	94.1 (71.3 to 99.9)	70.6 (44.0 to 89.7)
	MET	5	7	4	56.3 (29.9 to 80.2)	68.8 (41.3 to 89.0)
	PIK3CA	1	5	2	37.5 (8.5 to 75.5)	87.5 (47.3 to 99.7)
	RET	0	1	1	50 (1.3 to 98.7)	100 (15.8 to 100.0)
Roosan et al., 2021, USA	BRAF	0	1	2	66.7 (9.4 to 99.2)	100 (29.2 to 100.0)
	EGFR	4	7	2	46.2 (19.2 to 74.9)	69.2 (38.6 to 90.9)
	ERBB2	2	1	0	66.7 (9.4 to 99.2)	33.3 (0.8 to 90.6)
	FGFR1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	KRAS	1	1	2	75 (19.4 to 99.4)	75 (19.4 to 99.4)
	MET	3	4	3	70 (34.8 to 93.3)	70 (34.8 to 93.3)
	PIK3CA	0	2	1	33.3 (0.8 to 90.6)	100 (29.2 to 100.0)
Sabari et al., 2019, USA	ALK	2	0	4	100 (54.1 to 100.0)	66.7 (22.3 to 95.7)
	BRAF	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)
	EGFR	19	0	23	100 (91.6 to 100.0)	54.8 (38.7 to 70.2)
	ERBB2	1	0	2	100 (29.2 to 100.0)	66.7 (9.4 to 99.2)

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
	KRAS	9	1	8	94.4 (72.7 to 99.9)	50 (26.0 to 74.0)
	MET	1	0	3	100 (39.8 to 100.0)	75 (19.4 to99.4)
	PIK3CA	1	2	0	33.3 (0.8 to 90.6)	66.7 (9.4 to 99.2)
	RET	1	1	1	66.7 (9.4 to 99.2)	66.7 (9.4 to 99.2)
	ROS1	1	1	0	50 (1.3 to 98.7)	50 (1.3 to 98.7)
Schouten et al., 2021, Netherlands	ALK	0	1	3	75 (19.4 to 99.4)	100 (39.8 to 100.0)
	BRAF	1	1	8	90 (55.5 to 99.7)	90 (55.5 to 99.7)
	EGFR	6	0	9	100 (78.2 to 100.0)	60 (32.3 to 83.7)
	ERBB2	1	0	3	100 (39.8 to 100.0)	75 (19.4 to 99.4)
	KRAS	12	13	60	84.7 (75.3 to 91.6)	85.9 (76.6 to 92.5)
	MET	0	2	5	71.4 (29.0 to 96.3)	100 (59.0 to 100.0)
	RET	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	ROS1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
Schrock et al., 2018, USA	ALK	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)
	BRAF	1	0	1	100 (15.8 to 100.0)	50 (12.6 to 98.7)
	EGFR	4	0	8	100 (73.5 to 100.0)	66.7 (34.9 to 90.1)
	ERBB2	2	0	2	100 (39.8 to 100.0)	50 (67.6 to 93.2)
	FGFR1	1	0	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
	KRAS	4	0	5	100 (66.4 to 100.0)	55.6 (21.2 to 86.3)
	MET	0	0	0	Undefined	Undefined
	PIK3CA	4	0	2	100 (54.1 to 100.0)	33.3 (4.3 to 77.7)
	RET	0	0	0	Undefined	Undefined
	ROS1	0	0	0	Undefined	Undefined
Schwaederlé et al., 2017, USA	ALK	0	2	0	0 (0.0 to 84.2)	100 (15.8 to 100.0)
	BRAF	0	2	0	0 (0.0 to 84.2)	100 (15.8 to 100.0)

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
	EGFR	1	8	5	42.9 (17.7 to 71.1)	92.9 (66.1 to 99.8)
	ERBB2	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	KRAS	1	5	4	50 (18.7 to 81.3)	90 (55.5 to 99.7)
	MET	0	3	0	100 (29.2 to 100.0)	0 (0.0 to 70.8)
	PIK3CA	1	1	0	50 (1.3 to 98.7)	50 (1.3 to 98.7)
	ROS1	0	1	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
Schwartzberg et al., 2020, France, Ireland, Japan, Spain, UK, USA	ALK	5	0	5	100 (69.2 to 100.0)	50 (18.7 to 81.3)
	BRAF	1	0	1	100 (15.8 to 100.0)	50 (1.3 to 98.7)
	EGFR	7	0	23	100 (88.4 to 100.0)	76.7 (57.7 to 90.1)
	ERBB2	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)
	KRAS	3	0	15	100 (81.5 to 100.0)	83.3 (58.6 to 96.4)
	MET	2	1	2	80 (28.4 to 99.5)	60 (14.7 to 94.7)
	PIK3CA	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	RET	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	ROS1	2	0	1	100 (29.2 to 100.0)	33.3 (0.8 to 90.6)
Sugimoto et al., 2023, Japan	BRAF	1	1	6	87.5 (47.3 to 99.7)	87.5 (47.3 to 99.7)
	EGFR	60	34	221	89.2 (85.2 to 92.4)	81.0 (76.2 to 85.1)
	ERBB2	3	2	8	84.6 (54.6 to 98.1)	76.9 (46.2 to 95.0)
	KRAS	35	19	110	88.4 (82.5 to 92.9)	78.7 (71.6 to 84.7)
Sun et al., 2023, China	MET	57	7	18	91.5 (83.2 to 96.5)	30.5 (20.8 to 41.6)
Sung et al., 2017, Republic of Korea	EGFR	13	19	19	62.7 (48.1 to 75.9)	74.5 (60.4 to 85.7)
Tetik Vardarli et al., 2020, Turkey	ALK	0	0	0	Undefined	Undefined
	BRAF	0	1	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
	EGFR	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
	ERBB2	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
	FGFR1	0	1	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
	KRAS	0	0	0	Undefined	Undefined
	MET	0	0	0	Undefined	Undefined
	PIK3CA	0	1	1	50 (1.3 to 98.7)	100 (15.8 to 100.0)
Thompson et al., 2016, USA	BRAF	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	EGFR	5	0	10	100 (78.2 to 100.0)	33.3 (11.8 to 61.6)
	ERBB2	1	0	2	100 (29.2 to 100.0)	66.7 (9.4 to 99.2)
	KRAS	1	0	2	100 (29.2 to 100.0)	66.7 (9.4 to 99.2)
Toor et al., 2018, USA	ALK	0	1	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
	BRAF	0	0	0	Undefined	Undefined
	EGFR	3	0	0	100 (29.2 to 100.0)	0 (0.0 to 70.8)
	ERBB2	0	0	0	Undefined	Undefined
	FGFR1	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
	KRAS	2	0	0	100 (15.8 to 100.0)	0 (0.0 to 84.2)
	PIK3CA	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
Tran et al., 2019, Vietnam	EGFR	4	1	11	93.8 (69.8 to 99.8)	75 (47.6 to 92.7)
	KRAS	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)
	ALK	2	1	15	94.4 (72.7 to 99.9)	88.9 (65.3 to 98.6)
	BRAF	0	0	9	100 (66.4 to 100.0)	100 (66.4 to 100.0)
	MET	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)
	RET	0	0	2	100 (15.8 to 100.0)	100 (15.8 to 100.0)
	ROS1	0	0	2	100 (15.8 to 100.0)	100 (15.8 to 100.0)
Uchida et al., 2015, Japan	EGFR	47	22	56	82.4 (74.6 to 88.6)	62.4 (53.3 to 70.9)
Villaflor et al., 2016, USA	ALK	0	0	0	Undefined	Undefined
	BRAF	0	0	0	Undefined	Undefined

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
	EGFR	3	0	3	100 (54.1 to 100.0)	50 (11.8 to 88.2)
	ERBB2	0	0	0	Undefined	Undefined
	MET	1	0	0	100 (2.5 to 100.0)	100 (0.0 to 97.5)
	RET	1	0	0	100 (2.5 to 100.0)	100 (0.0 to 97.5)
	ROS1	0	0	0	Undefined	Undefined
Wu et al., 2019, USA	ALK	3	0	1	100 (39.8 to 100.0)	25 (0.6 to 80.6)
	EGFR	17	5	20	88.1 (74.4 to 96.0)	59.5 (43.3 to 74.4)
	KRAS	1	0	3	100 (39.8 to 100.0)	75 (19.4 to 99.4)
	MET	4	1	3	87.5 (47.3 to 99.7)	50 (15.7 to 84.3)
	PIK3CA	2	0	3	100 (47.8 to 100.0)	60 (14.7 to 94.7)
Xie et al., 2018, China	ALK	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)
	EGFR	4	0	19	100 (82.4 to 100.0)	82.6 (61.2 to 95.0)
	ERBB2	1	0	1	50 (1.3 to 98.7)	100 (15.8 to 100.0)
	KRAS	2	0	1	33.3 (0.8 to 90.6)	66.7 (9.4 to 99.2)
	ROS1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
Xu et al., 2016, China	BRAF	0	1	0	0 (0.0 to 97.5)	100 (2.5 to 100.0)
	EGFR	3	13	4	35 (15.4 to 59.2)	85 (62.1 to 96.8)
	ERBB2	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
	KRAS	0	6	6	50 (21.1 to 78.9)	100 (73.5 to 100.0)
	PIK3CA	0	2	4	66.7 (22.3 to 95.7)	100 (54.1 to 100.0)
Yang et al., 2018, China	ALK	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
	BRAF	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
	EGFR	4	0	24	100 (87.7 to 100.0)	85.7 (67.3 to 96.0)
	ERBB2	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
	KRAS	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
	MET	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)
	NTRK1	0	0	2	100 (15.8 to 100.0)	100 (15.8 to 100.0)
	PIK3CA	1	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)
	RET	0	0	2	100 (15.8 to 100.0)	100 (15.8 to 100.0)
	ROS1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)
Yao et al., 2016, China	ALK	2	0	3	100 (47.8 to 100.0)	60 (14.7 to 94.7)
	EGFR	5	0	12	100 (80.5 to 100.0)	70.6 (44.0 to 89.7)
	KRAS	1	0	3	100 (39.8 to 100.0)	75 (19.4 to 99.4)
	PIK3CA	1	0	1	100 (15.8 to 100.0)	50 (1.3 to 98.7)
	RET	1	0	0	100 (2.5 to 100.0)	0 (0.0 to 97.5)
Yin et al., 2021, China	EGFR	0	5	83	94.3 (87.2 to 98.1)	100 (95.9 to 100.0)
	KRAS	0	1	17	94.4 (72.7 to 99.9)	100 (81.4 to 100.0)
Zhang et al., 2022 China	ALK	1	0	4	100 (47.8 to 100.0)	80 (28.4 to 99.5)
	BRAF	2	0	2	100 (39.8 to 100.0)	50 (6.8 to 93.2)
	EGFR	19	3	39	95.1 (86.3 to 99.0)	68.9 (55.7 to 80.1)
	ERBB2	1	0	4	100 (47.8 to 100.0)	80 (28.4 to 99.5)
	KRAS	4	0	16	100 (83.2 to 100.0)	80 (56.3 to 94.3)
	MET	1	0	4	100 (47.8 to 100.0)	80 (28.4 to 99.5)
	PIK3CA	8	0	4	100 (73.5 to 100.0)	33.3 (99.2 to 65.1)
	ROS1	0	2	3	60 (14.7 to 94.7)	100 (47.8 to 100.0)
Zhao et al., 2022, China	ALK	25	0	18	100 (91.8 to 100.0)	41.9 (27.0 to 57.9)
	BRAF	6	0	12	100 (81.5 to 100.0)	66.7 (41.0 to 86.7)

Study, year, location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Sensitivity of tissue testing, % (95% CI)[b,c]	Sensitivity of liquid biopsy testing, % (95% CI)[b,c]
	EGFR[e]	33	5	278	98.4 (96.3 to 99.5)	89.6 (85.6 to 92.7)
	ERBB2	9	0	15	100 (85.8 to 100.0)	62.5 (40.6 to 81.2)
	KRAS	13	5	37	90.9 (80.0 to	76.4 (63.0 to 86.8)
	MET	20	0	4	100 (85.8 t0 100.0)	16.7 (4.7 to 37.4)
	NTRK	3	0	0	100 (29.2 to 100)	0 (0.0 to 70.8)
	RET	1	3	7	72.7 (39.0 to 94.0)	90.9 (58.7 to 99.8)
	ROS1	6	0	7	100 (75.3 to 100.0)	53.8 (25.1 to 80.8)

Abbreviations: CI = Confidence Interval

[a]Alterations were investigated at the gene level, with no distinction on the specific location or the type of alteration within the gene.

[b]The confidence intervals were computed by the authors of this HTA using the Clopper–Pearson method.

[c]Testing positive with either tissue or liquid biopsy was used as a reference standard.

[d]Only mutations with >0.5% were considered positive by the authors of the primary study.

[e]We excluded *EGFR T790M*.

Table A8: Concordance Between Liquid Biopsy and Tissue Testing

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
Bai et al., 2019, China	EGFR	9	2	24	92.3 (74.9 to 99.1)	72.7 (54.5 to 86.7)	83 (70.2 to 91.9)	95.7 (85.2 to 99.5)	86.1 (76.5 to 92.8)
Buburuzan et al., 2022, Romania	ALK	0	0	0	Undefined	Undefined	100 (86.8 to 100.0)	100 (86.8 to 100.0)	100 (86.8 to 100.0)
	BRAF	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (86.3 to 100.0)	100 (86.3 to 100.0)	100 (86.8 to
	EGFR	0	2	3	60 (14.7 to 94.7)	100 (29.2 to 100.0)	100 (83.9 to 100.0)	91.3 (72.0 to 98.9)	92.3 (74.9 to 99.1)
	ERBB2	0	0	0	Undefined	Undefined	100 (86.8 to 100.0)	100 (86.8 to 100.0)	100 (86.8 to 100.0)
	FGFR1	0	0	0	Undefined	Undefined	100 (86.8 to 100.0)	100 (86.8 to 100.0)	100 (86.8 to 100.0)
	KRAS	0	1	4	80 (28.4 to 99.5)	100 (39.8 to 100.0)	100 (83.9 to 100.0)	95.5 (77.2 to 99.9)	96.2 (80.4 to 99.9)
	MET	2	3	0	0 (0.0 to 70.8)	0 (0.0 to 84.2)	91.3 (72.0 to 98.9)	87.5 (67.6 to 97.3)	80.8 (60.4 to 93.4)
	PIK3CA	1	1	0	0 (0.0 to 97.5)	0 (0.0 to 97.5)	96.0 (79.6 to 99.9)	96.0 (79.6 to 99.9)	92.3 (74.9 to 99.1)
	KRAS	11	7	22	75.9 (56.5 to 89.7)	66.7 (48.2 to 82.0)	83.1 (71.7 to 91.2)	88.5 (77.8 to 95.3)	80.9 (71.4 to 88.2)
Chen et al., 2016, China	ALK	0	1	0	0 (0.0 to 97.5)	Undefined	100 (93.7 to 100.0)	98.3 (90.8 to 100.0)	98.3 (90.8 to 100.0)
	EGFR	10	6	12	66.7 (41.0 to 86.7)	54.5 (32.2 to 75.6)	75 (58.8 to 87.3)	83.3 (67.2 to 93.6)	72.4 (59.1 to 83.3)
	KRAS	2	2	1	33.3 (0.8 to 90.6)	33.3 (0.8 to 90.6)	96.4 (87.5 to 99.6)	96.4 (87.5 to 99.6)	93.1 (83.3 to 98.1)
	PIK3CA	1	6	1	14.3 (0.4 to 57.9)	50 (1.3 to 98.7)	98 (89.6 to 100.0)	89.3 (78.1 to 96.0)	87.9 (76.7 to 95.0)
Chen et al., 2019, China	ALK	1	3	1	25 (0.6 to 80.6)	50 (1.3 to 98.7)	97.8 (88.5 to 99.9)	93.8 (82.8 to 98.7)	92 (80.8 to 97.8)
	ALK	3	3	1	25 (0.6 to 80.6)	25 (0.6 to 80.6)	93.5 (82.1 to 98.6)	93.5 (82.1 to 98.6)	88 (75.7 to 95.5)
	EGFR	13	3	4	57.1 (18.4 to 90.1)	23.5 (6.8 to 49.9)	69.8 (53.9 to 82.8)	90.9 (75.7 to 98.1)	68 (53.3 to 80.5)
	EGFR	13	3	4	57.1 (18.4 to 90.1)	23.5 (6.8 to 49.9)	69.8 (53.9 to 82.8)	90.9 (75.7 to 98.1)	68 (53.3 to 80.5)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	ERBB2	1	0	1	100 (2.5 to 100.0)	50 (1.3 to 98.7)	93.9 (83.1 to 98.7)	100 (92.6 to 100.0)	98 (89.4 to 99.9)
	KRAS	3	0	1	100 (2.5 to 100.0)	25 (0.6 to 80.6)	93.9 (83.1 to 98.7)	100 (92.3 to 100.0)	94 (83.5 to 98.7)
	KRAS	3	0	1	100 (2.5 to 100.0)	25 (0.6 to 80.6)	93.9 (83.1 to 98.7)	100 (92.3 to 100.0)	94 (83.5 to 98.7)
	NTRK1	2	0	0	Undefined	0 (0.0 to 70.8)	96 (86.3 to 99.5)	100 (92.6 to 100.0)	96 (86.3 to 99.5)
	PIK3CA	3	1	2	66.7 (9.4 to 99.2)	40 (5.3 to 85.3)	93.6 (82.5 to 98.7)	97.8 (88.2 to 99.9)	92 (80.8 to 97.8)
	PIK3CA	3	1	2	66.7 (9.4 to 99.2)	40 (5.3 to 85.3)	93.6 (82.5 to 98.7)	97.8 (88.2 to 99.9)	92 (80.8 to 97.8)
Courad et al., 2014, USA	BRAF	2	0	0	Undefined	0 (0.0 to 84.2)	97.1 (89.8 to 99.6)	100 (94.6 to 100)	97.1 (89.8 to 99.6)
	EGFR	13	2	20	90.9 (70.8 to 98.9)	60.6 (42.1 to 77.1)	71.7 (56.5 to 84.0)	94.3 (80.8 to 99.3)	77.9 (66.2 to 87.1)
	ERBB2	2	0	3	100 (29.2 to 100.0)	60 (14.7 to 94.7)	96.2 (89.3 to 99.6)	100 (94.3 to 100.0)	97.1 (89.8 to 99.6)
	KRAS	1	0	3	100 (29.2 to 100.0)	75 (19.4 to 99.4)	98.5 (91.7 to 100.0)	100.0 (94.4 to 100.0)	98.5 (92.1 to 100.0)
	PIK3CA	1	1	0	0 (0.0 to 97.5)	0 (0.0 to 97.5)	98.4 (91.3 to 100.0)	98.4 (91.3 to 100.0)	97.1 (89.8 to 99.6)
Cui et al., 2017, China	ALK	11	0	13	100 (75.3 to 100.0)	54.2 (32.8 to 74.4)	57.7 (36.9 to 76.6)	100 (78.2 to 100.0)	71.8 (55.1 to 85.0)
Dagogo-Jack et al., 2019, USA	ROS1	0	0	7	100 (59.0 to 100.0)	100 (59.0 to 100.0)	Undefined	Undefined	100 (59.0 to 100.0)
Fernandes et al., 2021, Portugal	ALK	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (96.8 to 100.0)	100 (96.8 to 100.0)	100 (96.8 to 100.0)
	BRAF	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)	100 (96.7 to 100.0)	100 (96.7 to 100.0)	100 (96.8 to 100.0)
	EGFR	6	2	20	90.9 (70.8 to 98.9)	76.9 (56.4 to 91.0)	93.5 (86.5 to 97.6)	97.8 (92.1 to 99.7)	93 (86.8 to 96.9)
	ERBB2	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (96.8 to 100.0)	100 (96.8 to 100.0)	100 (96.8 to 100.0)
	KRAS	6	1	17	94.4 (72.7 to 99.6)	73.9 (51.6 to 89.8)	93.8 (87.0 to 97.7)	98.9 (94.1 to 100.0)	93.9 (87.9 to 97.5)
	PIK3CA	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (96.8 to 100.0)	100 (96.8 to 100.0)	100 (96.8 to 100.0)
	ALK	0	0	1	100 (2.5 to 100)	100 (2.5 to 100)	100 (66.4 to 100)	100 (66.4 to 100)	100 (69.2 to 100)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
He et al., 2016, China[b]	BRAF	0	0	0	Undefined	Undefined	100 (69.2 to 100)	100 (69.2 to 100)	100 (69.2 to 100)
	EGFR	2	0	0	Undefined	0 (0 to 84.2)	80 (44.4 to 97.5)	100 (63.1 to 100)	80 (44.4 to 97.5)
	ERBB2	0	0	0	Undefined	Undefined	100 (69.2 to 100)	100 (69.2 to 100)	100 (69.2 to 100)
	FGFR1	0	0	10	100 (69.2 to 100)	10 (69.2 to 100)	Undefined	Undefined	100 (69.2 to 100)
	KRAS	1	0	0	Undefined	0 (0 to 97.5)	90 (55.5 to 99.7)	100 (66.4 to 100)	90 (55.5 to 99.7)
	MET	0	0	2	100 (15.8 to 100)	100 (15.8 to 100)	100 (63.1 to 100)	100 (63.1 to 100)	100 (69.2 to 100)
	PIK3CA	0	0	0	Undefined	Undefined	100 (69.2 to 100)	100 (69.2 to 100)	100 (69.2 to 100)
Jiao et al., 2021, China	ALK	7	0	11	100 (71.5 to 100.0)	61.1 (35.7 to 82.7)	96 (91.9 to 98.4)	100 (97.8 to 100.0)	96.2 (92.4 to 98.5)
	BRAF	6	1	5	83.3 (35.9 to 99.6)	45.5 (16.7 to 76.6)	96.6 (92.8 to 98.8)	96.6 (92.6 to 98.7)	96.2 (92.4 to 98.5)
	EGFR	25	9	61	87.1 (77.0 to 93.9)	70.9 (60.1 to 80.2)	78.3 (69.6 to 85.4)	90.9 (83.4 to 95.8)	81.6 (75.3 to 86.9)
	ERBB2	5	2	8	80 (44.4 to 97.5)	61.5 (31.6 to 86.1)	97.1 (93.5 to 99.1)	98.8 (95.9 to 99.9)	96.2 (92.4 to 98.5)
	KRAS	9	1	20	95.2 (76.2 to 99.9)	69 (49.2 to 84.7)	94.5 (89.8 to 97.5)	99.4 (96.5 to 100.0)	94.6 (90.3 to 97.4)
	MET	10	1	8	88.9 (51.8 to 99.7)	44.4 (21.5 to 69.2)	94.3 (89.8 to 97.2)	99.4 (96.7 to 100.0)	94.1 (89.6 to 97.0)
	NTRK3	0	1	9	90 (55.5 to 99.7)	100 (66.4 to 100.0)	100 (97.9 to 100.0)	99.4 (96.9 to 100.0)	99.5 (97.0 to 100.0)
	PIK3CA	13	3	8	72.7 (39.0 to 94.0)	38.1 (18.1 to 61.6)	92.5 (87.6 to 96.0)	98.2 (94.7 to 99.6)	91.4 (86.3 to 95.0)
Lee et al., 2021, USA	MET	1	1	12	92.3 (64.0 to 99.8)	92.3 (64.0 to 99.8)	0 (0.0 to 97.5)	0 (0.0 to 97.5)	85.7 (57.2 to 100.0)
Lee et al., 2022, USA	ALK	0	4	0	0 (0.0 to 60.2)	Undefined	100 (29.2 to 100.0)	42.9 (9.9 to 81.6)	42.9 (9.9 to 81.6)
	BRAF	0	0	0	Undefined	Undefined	100 (59.0 to 100.0)	100 (59.0 to 100.0)	100 (59.0 to 100.0)
	EGFR	0	0	7	100 (59.0 to 100.0)	100 (59.0 to 100.0)	Undefined	Undefined	100 (59.0 to 100.0)
	FGFR1	0	0	0	Undefined	Undefined	100 (59.0 to 100.0)	100 (59.0 to 100.0)	100 (59.0 to 100.0)
	MET	0	0	0	Undefined	Undefined	100 (59.0 to 100.0)	100 (59.0 to 100.0)	100 (59.0 to 100.0)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	RET	0	1	0	0 (0.0 to 97.5)	Undefined	100 (54.1 to 100.0)	85.7 (42.1 to 99.6)	85.7 (42.1 to 99.6)
	ROS1	0	0	0	Undefined	Undefined	100 (59.0 to 100.0)	100 (59.0 to 100.0)	100 (59.0 to 100.0)
Li et al., 2019, USA	ALK	0	0	5	100 (47.8 to 100.0)	100 (47.8 to 100.0)	100 (94.6 to 100.0)	100 (94.6 to 100.0)	100 (95.0 to 100.0)
	BRAF	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)	100 (94.8 to 100.0)	100 (94.8 to 100.0)	100 (94.8 to 100.0)
	EGFR	0	0	29	100 (88.1 to 100.0)	100 (88.1 to 100.0)	100 (91.8 to 100.0)	100 (91.8 to 100.0)	100 (95.0 to 100.0)
	ERBB2	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)	100 (94.7 to 100.0)	100 (94.7 to 100.0)	100 (95.0 to 100.0)
	KRAS	0	0	19	100 (82.4 to 100.0)	100 (82.4 to 100.0)	100 (93.3 to 100.0)	100 (93.3 to 100.0)	100 (95.0 to 100.0)
	MET	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)	100 (94.8 to 100.0)	100 (94.8 to 100.0)	100 (95.0 to 100.0)
	RET	0	0	0	Undefined	Undefined	100 (94.8 to 100.0)	100 (94.8 to 100.0)	100 (94.8 to 100.0)
	ROS1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (94.9 to 100.0)	100 (94.9 to 100.0)	100 (94.8 to 100.0)
Lin et al., 2021, Taiwan	ALK	5	2	4	66.7 (22.3 to 95.7)	44.4 (13.7 to 78.8)	64.3 (35.1 to 87.2)	81.8 (48.2 to 97.7)	65 (40.8 to 84.6)
Lin et al., 2021, USA	ALK	1	0	0	Undefined	0 (0.0 to 97.5)	99 (94.6 to 100.0)	100 (96.3 to 100.0)	99 (94.6 to 100.0)
	BRAF	2	0	0	Undefined	0 (0.0 to 70.8)	98 (93.0 to 99.8)	100 (96.3 to 100.0)	98 (93.0 to 99.8)
	EGFR	13	2	20	90.9 (70.8 to 98.9)	60.6 (42.1 to 77.1)	83.3 (73.2 to 90.8)	97 (89.6 to 99.6)	85 (76.5 to 91.4)
	ERBB2	1	0	0	Undefined	0 (0.0 to 97.5)	99 (94.6 to 100.0)	100 (96.3 to 100.0)	99 (94.6 to 100.0)
	KRAS	10	1	10	90.9 (58.7 to 99.8)	50 (27.2 to 72.8)	88.8 (80.3 to 94.5)	98.8 (93.2 to 100.0)	89 (81.2 to 94.4)
	MET	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)	100 (96.3 to 100.0)	100 (96.3 to 100.0)	100 (96.4 to 100.0)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	NTRK1	1	0	0	Undefined	0 (0.0 to 97.5)	99 (94.6 to 100.0)	100 (96.3 to 100.0)	99 (94.6 to 100.0)
	RET	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (96.3 to 100.0)	100 (96.3 to 100.0)	100 (96.4 to 100.0)
	ROS1	2	0	1	100 (2.5 to 100.0)	33.3 (0.8 to 90.6)	98 (92.9 to 99.8)	100 (29.2 to 100.0)	98 (93.0 to 99.8)
Liu et al., 2017, China	ALK	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)	100 (91.8 to 100.0)	100 (91.8 to 100.0)	100 (92.3 to 100.0)
	BRAF	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (92.1 to 100.0)	100 (92.1 to 100.0)	100 (92.3 to 100.0)
	EGFR	0	0	12	100 (73.5 to 100.0)	100 (73.5 to 100.0)	100 (89.7 to 100.0)	100 (89.7 to 100.0)	100 (92.3 to 100.0)
	KRAS	0	0	6	100 (54.1 to 100.0)	100 (54.1 to 100.0)	100 (91.2 to 100.0)	100 (91.2 to 100.0)	100 (92.3 to 100.0)
	RET	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (92.1 to 100.0)	100 (92.1 to 100.0)	100 (92.3 to 100.0)
Mehta et al., 2021, India	ALK	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (83.2 to 100.0)	100 (83.2 to 100.0)	100 (83.9 to 100.0)
	BRAF	1	0	0	Undefined	0 (0.0 to 97.5)	95.2 (76.2 to 99.9)	100 (83.2 to 100.0)	95.2 (76.2 to 99.9)
	EGFR	0	1	7	87.5 (47.3 to 99.7)	100 (59.0 to 100.0)	100 (75.3 to 100.0)	92.9 (66.1 to 99.8)	95.2 (76.2 to 99.9)
	ERBB2	0	1	0	0 (0.0 to 97.5)	Undefined	100 (83.2 to 100.0)	95.2 (76.2 to 99.9)	95.2 (76.2 to 99.9)
	KRAS	1	3	5	62.5 (24.5 to 91.5)	83.3 (35.9 to 99.6)	92.3 (64.0 to 99.8)	80 (51.9 to 95.7)	81 (58.1 to 94.6)
	MET	0	1	0	0 (0.0 to 97.5)	Undefined	100 (83.2 to 100.0)	95.2 (76.2 to 99.9)	95.2 (76.2 to 99.9)
	PIK3CA	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (83.2 to 100.0)	100 (83.2 to 100.0)	100 (83.9 to 100.0)
	RET	0	0	0	Undefined	Undefined	100 (83.9 to 100.0)	100 (83.9 to 100.0)	100 (83.9 to 100.0)
	ROS1	0	0	0	Undefined	Undefined	100 (83.9 to 100.0)	100 (83.9 to 100.0)	100 (83.9 to 100.0)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
Mondaca et al., 2021, USA	ALK	11	1	13	92.9 (66.1 to 99.8)	54.2 (32.8 to 74.4)	97.1 (94.8 to 98.5)	99.7 (98.5 to 100.0)	96.9 (94.7 to 98.4)
Ohira et al., 2016, Japan	ALK	1	0	0	Undefined	0 (0.0 to 97.5)	99.3 (96.3 to 100.0)	100 (97.5 to 100.0)	99.3 (96.3 to 100.0)
	BRAF	3	0	0	Undefined	0 (0.0 to 70.8)	98 (94.2 to 99.6)	100 (97.5 to 100.0)	98 (94.2 to 99.6)
	EGFR	53	0	3	100 (29.2 to 100.0)	5.4 (1.1 to 14.9)	63.7 (55.3 to 71.5)	100 (96.1 to 100.0)	64.4 (56.2 to 72.1)
	ERBB2	3	0	0	Undefined	0 (0.0 to 70.8)	98 (94.2 to 99.6)	100 (97.5 to 100.0)	98 (94.2 to 99.6)
	KRAS	15	0	0	Undefined	0 (0.0 to 21.8)	89.9 (83.9 to 94.3)	100 (97.3 to 100.0)	89.9 (83.9 to 94.3)
	MET	1	0	0	Undefined	0 (0.0 to 97.5)	99.3 (96.3 to 100.0)	100 (97.5 to 100.0)	99.3 (96.3 to 100.0)
	PIK3CA	2	0	1	100 (2.5 to 100.0)	33.3 (0.8 to 90.6)	98 (94.2 to 99.6)	100 (97.5 to 100.0)	98.7 (95.2 to 99.8)
Park et al., 2021, Republic of Korea	ALK	5	0	9	100 (66.4 to 100.0)	64.3 (35.1 to 87.2)	98.2 (95.9 to 99.4)	100 (98.7 to 100.0)	98.3 (96.0 to 99.4)
	BRAF	2	1	1	50 (1.3 to 98.7)	33.3 (0.8 to 90.6)	99.3 (97.5 to 99.9)	99.6 (98.1 to 100.0)	99.0 (97.0 to 100.0)
	EGFR	14	5	52	91.2 (80.7 to 97.1)	78.7 (67.0 to 87.9)	93.9 (90.0 to 96.6)	97.7 (94.8 to 99.3)	93.4 (89.9 to 96.0)
	ERBB2	3	0	12	100 (73.5 to 100.0)	80 (51.9 to 95.7)	95.8 (92.6 to 97.9)	100 (98.7 to 100.0)	99.0 (97.0 to 99.8)
	KRAS	11	3	23	88.5 (69.8 to 97.6)	67.6 (49.5 to 82.6)	95.8 (92.6 to 97.9)	98.8 (96.6 to 99.8)	95.1 (92.0 to 97.3)
	MET	14	11	9	45 (23.1 to 68.5)	39.1 (19.7 to 61.5)	94.8 (91.4 to 97.1	95.8 (92.7 to 97.9)	91.3 (87.4 to 94.3)
	RET	13	2	7	77.8 (40.0 to 97.2)	35 (15.4 to 59.2)	95.3 (92.1 to 97.5)	99.3 (97.3 to 99.9)	94.8 (91.5 to 97.0)
	ROS1	13	0	3	100 (29.4 to 100.0)	18.8 (4.0 to 45.6)	95.4 (92.3 to 97.5)	98.9 (96.8 to 99.8)	95.5 (92.4 to 97.6)
Pasquale et al., 2019	EGFR	7	2	23	92 (74 to 99)	76.7 (57.7 to 90.1)	91.6 (83.4 to 96.5)	97.4 (91.0 to 99.7)	91.7 (84.8 to 96.1)
	KRAS	10	Not Reported	16	-	61.5 (40.6 to	-	-	86 (79.4 to 92.6)[c]
Pe´cuchet et al., 2016, France	ALK	2	0	1	100 (2.5 to 100.0)	33.3 (0.8 to 90.6)	98.1 (93.2 to 99.8)	100 (96.4 to 100.0)	98.1 (93.3 to 99.8)
	BRAF	1	0	2	100 (15.8 to 100.0)	66.7 (9.4 to 99.2)	99.0 (94.7 to 100.0)	100 (96.4 to 100.0)	99.0 (94.8 to 100.0)
	EGFR	19	0	28	100 (87.7 to 100.0)	59.6 (44.3 to 73.6)	75.3 (64.1 to 84.4)	100 (93.8 to 100.0)	81.9 (73.2 to 88.7)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	FGFR1	1	0	0	Undefined	0 (0.0 to 97.5)	99.0 (94.8 to 100.0)	100 (96.5 to 100.0)	99.0 (94.8 to 100.0)
	KRAS	10	0	19	100 (82.4 to 100.0)	65.5 (45.7 to 82.1)	88.4 (79.7 to 94.3)	100 (95.3 to 100.0)	90.5 (83.2 to 95.3)
	PIK3CA	3	2	2	50 (67.6 to 93.2)	40 (5.3 to 85.3)	97.0 (91.6 to 99.4)	98.0 (93.0 to 100.0)	95.2 (89.2 to 98.4)
Pritchett et al., 2019, USA	BRAF	2	0	5	100 (47.8 to 100.0)	71.4 (29.0 to 96.3)	98.6 (95.0 to 99.8)	100 (97.4 to 100.0)	98.6 (95.2 to 99.8)
	EGFR	5	0	13	100 (75.3 to 100.0)	72.2 (46.5 to 90.3)	96.6 (92.2 to 98.9)	100 (97.4 to 100.0)	97.0 (93.0 to 99.0)
	ERBB2	0	0	2	100 (15.8 to 100.0)	100 (15.8 to 100.0)	100 (97.3 to 100.0)	100 (97.3 to 100.0)	100 (97.4 to 100.0)
	KRAS	12	1	48	98 (89.1 to 100.0)	80 (67.7 to 89.2)	87.8 (79.6 to 93.5)	98.9 (93.8 to 100.0)	91.2 (85.4 to 95.2)
	MET	3	0	3	100 (29.2 to 100.0)	50 (11.8 to 88.2)	97.8 (93.7 to 99.5)	100 (97.3 to 100.0)	97.8 (93.8 to 99.6)
Raez et al., 2022, USA	ALK	1	2	0	0 (0.0 to 84.2)	0 (0.0 to 97.5)	99.3 (96.4 to 100.0)	98.7 (95.3 to 99.8)	98 (94.4 to 99.6)
	BRAF	2	2	0	0 (0.0 to 84.2)	0 (0.0 to 84.2)	98.7 (95.3 to 99.8)	98.7 (95.3 to 99.8)	97.4 (93.4 to 99.3)
	EGFR	7	18	14	43.8 (26.4 to 62.3)	66.7 (43.0 to 85.4)	94.2 (88.4 to 97.6)	86.4 (79.3 to 91.7)	83.7 (76.8 to 89.1)
	MET	1	1	1	50 (1.3 to 98.7)	50 (1.3 to 98.7)	99.3 (96.4 to 100.0)	99.3 (96.4 to 100.0)	98.7 (95.4 to
	NTRK	1	0	0	Undefined	0 (0.0 to 97.5)	99.3 (96.4 to 100.0)	100 (97.6 to 100.0)	99.3 (96.4 to 100.0)
	ROS1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (97.6 to 100.0)	100 (97.6 to 100.0)	100 (97.6 to 100.0)
Roosan et al., 2021, USA	ALK	3	2	2	50 (67.6 to 93.2)	40 (5.3 to 85.3)	95 (86.1 to 99.0)	96.6 (88.3 to 99.6)	92.2 (82.7 to 97.4)
	BRAF	3	4	4	50 (15.7 to 84.3)	57.1 (18.4 to 90.1)	94.6 (85.1 to 98.9)	93.0 (83.0 to 98.1)	89.1 (78.8 to 95.5)
	EGFR	3	6	25	80.6 (62.5 to 92.5)	89.3 (71.8 to 97.7)	90.9 (75.7 to 98.1)	83.3 (67.2 to 93.6)	85.9 (75.0 to 93.4)
	ERBB2	4	2	1	33.3 (0.8 to 90.6)	20 (0.5 to 71.6)	93.4 (84.1 to 98.2)	96.6 (88.3 to 99.6)	90.6 (80.7 to 96.5)
	FGFR1	1	2	1	33.3 (0.8 to 90.6)	50 (1.3 to 98.7)	98.4 (91.2 to 100.0)	96.8 (88.8 to 99.6)	95.3 (86.9 to 99.0)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	KRAS	5	1	11	91.7 (61.5 to 99.8)	68.8 (41.3 to 89.0)	90.4 (79.0 to 96.8)	97.9 (88.9 to 99.9)	90.6 (80.7 to 96.5)
	MET	5	7	4	36.4 (10.9 to 69.2	44.4 (13.7 to 78.8)	90.6 (79.3 to 96.9)	87.3 (75.5 to 94.7)	81.3 (69.5 to 89.9)
	PIK3CA	1	5	2	28.6 (3.7 to 71.0)	33.3 (0.8 to 90.6)	98.2 (90.6 to 100.0)	91.8 (81.9 to 97.3)	90.6 (80.7 to 96.5)
	RET	0	1	1	50 (1.3 to 98.7)	100 (2.5 to 100.0)	100 (94.2 to 100.0)	96.8 (89.0 to 99.6)	98.4 (91.6 to 100.0)
Roosan et al., 2021, USA	BRAF	0	1	2	66.7 (9.4 to 99.2)	100 (15.8 to 100.0)	100 (94.1 to 100.0)	98.4 (91.3 to 100.0)	98.4 (91.6 to 100.0)
	EGFR	4	7	2	22.2 (2.8 to 60.0)	33.3 (4.3 to 77.7)	92.7 (82.4 to 98.0)	87.9 (76.7 to 95.0)	82.8 (71.3 to 91.1)
	ERBB2	2	1	0	0 (0.0 to 97.5)	0 (0.0 to 84.2)	96.8 (89.0 to 99.6)	98.4 (91.3 to 100.0)	95.3 (86.9 to 99.0)
	FGFR1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (94.1 to 100.0)	100 (94.1 to 100.0)	100 (94.4 to 100.0)
	KRAS	1	1	2	66.7 (9.4 to 99.2)	66.7 (9.4 to 99.2)	98.4 (91.2 to 100.0)	98.4 (91.2 to 100.0)	96.9 (89.2 to 99.6)
	MET	3	4	3	42.9 (9.9 to 81.6)	50 (11.8 to 88.2)	94.7 (85.4 to 98.9)	93.1 (83.3 to 98.1)	89.1 (78.8 to 95.5)
	PIK3CA	0	2	1	33.3 (0.8 to 90.6)	100 (2.5 to 100.0)	100 (94.1 to 100.0)	96.8 (89.0 to 99.6)	96.9 (89.2 to 99.6)
Sabari et al., 2019, USA	ALK	2	0	4	100 (39.8 to 100)	66.7 (22.3 to 95.7)	98.1 (93.2 to 99.8)	100 (96.4 to 100.0)	98.1 (93.4 to 99.8)
	BRAF	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)	100 (96.5 to 100.0)	100 (96.5 to 100.0)	100 (96.6 to 100.0)
	EGFR	19	0	23	100 (85.2 to 100.0)	54.8 (38.7 to 70.2)	77.4 (67.0 to 85.8)	100 (94.5 to 100.0)	82.2 (73.7 to 89.0)
	ERBB2	1	0	2	100 (15.8 to 100.0)	66.7 (9.4 to 99.2)	99 (94.8 to 100.0)	100 (96.5 to 100.0)	99.1 (94.9 to 100.0)
	KRAS	9	1	8	88.9 (51.8 to 99.7)	47.1 (23.0 to 72.2)	99 (94.4 to 100.0)	98.9 (94.0 to 100.0)	90.7 (83.5 to 95.4)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	MET	1	0	3	100 (29.2 to 100.0)	75 (19.4 to 99.4)	99 (94.8 to 100.0)	100 (96.5 to 100.0)	99.1 (94.9 to 100.0)
	PIK3CA	1	2	0	0 (0.0 to 84.2)	0 (0.0 to 97.5)	99 (94.8 to 100.0)	98.1 (93.4 to 99.8)	97.2 (92.0 to 99.4)
	RET	1	1	1	50 (1.3 to 98.7)	50 (1.3 to 98.7)	99 (94.8 to 100.0)	99 (94.8 to 100.0)	98.1 (93.4 to 99.8)
	ROS1	1	1	0	0 (0.0 to 97.5)	0 (0.0 to 97.5)	99.1 (94.9 to 100.0)	99.1 (94.9 to 100.0)	98.1 (93.4 to 99.8)
Schouten et al., 2021, Netherlands	ALK	0	1	3	75 (19.4 to 99.4)	100 (29.2 to 100.0)	100 (98.1 to 100.0)	99.5 (97.1 to 100.0)	99.5 (97.1 to 100.0)
	BRAF	1	1	8	88.9 (51.8 to 99.7)	88.9 (51.8 to 99.7)	99.5 (97.0 to 100.0)	99.5 (97.0 to 100.0)	99 (96.3 to 99.9)
	EGFR	6	0	9	100 (66.4 to 100.0)	60 (32.3 to 83.7)	96.7 (93.0 to 98.8)	100 (97.9 to 100.0)	96.9 (93.3 to 98.8)
	ERBB2	1	0	3	100 (29.2 to 100.0)	75 (19.4 to 99.4)	99.5 (97.1 to 100.0)	100 (98.1 to 100.0)	99.5 (97.1 to 100.0)
	KRAS	12	13	60	82.2 (71.5 to 90.2)	83.3 (72.7 to 91.1)	89.9 (83.0 to 94.7)	89.2 (82.2 to 94.1)	87 (81.4 to 91.4)
	MET	0	2	5	71.4 (29.0 to 96.3)	100 (47.8 to 100.0)	100 (98.0 to 100.0)	98.9 (96.2 to 99.9)	99 (96.3 to 99.9)
	RET	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (98.1 to 100.0)	100 (98.1 to 100.0)	100 (98.1 to 100.0)
	ROS1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (98.1 to 100.0)	100 (98.1 to 100.0)	100 (98.1 to 100.0)
Schrock et al., 2018, USA	ALK	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)	100 (88.8 to 100.0)	100 (88.8 to 100.0)	100 (90.0 to 100.0)
	BRAF	1	0	1	100 (2.5 to 100.0)	50 (1.3 to 98.7)	97.1 (84.7 to 100.0)	100 (89.4 to 100.0)	97.1 (85.1 to 99.9)
	EGFR	4	0	8	100 (63.1 to 100.0)	66.7 (34.9 to 90.1)	85.2 (66.3 to 95.8)	100 (85.2 to 100.0)	88.6 (73.3 to 96.8)
	ERBB2	2	0	2	100 (15.8 to 100.0)	50 (6.7 to 93.2)	87.9 (71.8 to 96.6)	100 (88.8 to 100.0)	94.3 (80.8 to 99.3)
	FGFR1	1	0	0	Undefined	0 (0.0 to 97.5)	97.1 (85.1 to 99.9)	100 (89.7 to 100.0)	97.1 (85.1 to 99.9)
	KRAS	4	0	5	100 (47.8 to 100.0)	55.6 (21.2 to 86.3)	86.7 (69.3 to 96.2)	100 (86.8 to 100.0)	88.6 (73.3 to 96.8)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	MET	0	0	0	Undefined	Undefined	100 (90.0 to 100.0)	100 (90.0 to 100.0)	100 (90.0 to 100.0)
	PIK3CA	4	0	2	100 (15.8 to 100.0)	33.3 (4.3 to 77.7)	87.9 (71.8 to 96.6)	100 (88.1 to 100.0)	88.6 (73.3 to 96.8)
	RET	0	0	0	Undefined	Undefined	100 (90.0 to 100.0)	100 (90.0 to 100.0)	100 (90.0 to 100.0)
	ROS1	0	0	0	Undefined	Undefined	100 (90.0 to 100.0)	100 (90.0 to 100.0)	100 (90.0 to 100.0)
Schwaederlé et al., 2017, USA	ALK	0	2	0	0 (0.0 to 84.2)	Undefined	100 (95.4 to 100.0)	97.5 (91.3 to 99.7)	97.5 (91.3 to 99.7)
	BRAF	0	2	0	0 (0.0 to 84.2)	Undefined	100 (95.4 to 100.0)	97.5 (91.3 to 99.7)	97.5 (91.3 to 99.7)
	EGFR	1	8	5	38.5 (13.9 to 68.4)	83.3 (35.9 to 99.6)	98.7 (93.0 to 100.0)	89.2 (79.8 to 95.2)	88.8 (79.7 to 94.7)
	ERBB2	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (95.4 to 100.0)	100 (95.4 to 100.0)	98.8 (93.2 to 100.0)
	KRAS	1	5	4	44.4 (13.7 to 78.8)	80 (28.4 to 99.5)	98.6 (92.4 to 100.0)	93.3 (85.1 to 97.8)	92.5 (84.4 to 97.2)
	MET	0	3	0	0 (70.8 to 100.0)	Undefined	100 (95.3 to 100.0)	96.3 (89.4 to 99.2)	96.3 (89.4 to 99.2)
	PIK3CA	1	1	0	0 (0.0 to 97.5)	0 (0.0 to 97.5)	98.7 (93.1 to 100.0)	98.7 (93.1 to 100.0)	97.5 (91.3 to 99.7)
	ROS1	0	1	0	0 (0.0 to 97.5)	Undefined	100 (95.4 to 100.0)	98.8 (93.2 to 100.0)	98.8 (93.2 to 100.0)
Schwartzberg et al., 2020, France, Ireland, Japan, Spain, UK, USA	ALK	5	0	5	100 (47.8 to 100.0)	50 (18.7 to 81.3)	95.2 (89.2 to 98.4)	100 (96.4 to 100.0)	95.7 (90.1 to 98.6)
	BRAF	1	0	1	100 (2.5 to 100.0)	50 (1.3 to 98.7)	96.7 (82.8 to 99.9)	100 (88.1 to 100.0)	96.9 (83.8 to 99.9)
	EGFR	7	0	23	100 (85.2 to 100.0)	76.7 (57.7 to 90.1)	92 (84.1 to 96.7)	100 (95.5 to 100.0)	94.0 (88.1 to 97.6)
	ERBB2	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)	100 (89.7 to 100.0)	100 (89.7 to 100.0)	100 (90.7 to 100.0)
	KRAS	3	0	15	100 (78.2 to 100.0)	83.3 (58.6 to 96.4)	91.7 (77.5 to 98.2)	100 (89.4 to 100.0)	94.4 (84.6 to 98.8)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	MET	2	1	2	66.7 (9.4 to 99.2)	50 (6.8 to 93.2)	88.9 (65.3 to 98.6)	94.1 (71.3 to 99.9)	86.4 (65.1 to 97.1)
	PIK3CA	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (83.9 to 100.0)	100 (83.9 to 100.0)	100 (84.6 to 100.0)
	RET	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (83.9 to 100.0)	100 (83.9 to 100.0)	100 (84.6 to 100.0)
	ROS1	2	0	1	100 (2.5 to 100.0)	33.3 (0.8 to 90.6)	97.1 (89.9 to 99.6)	100 (94.6 to 100.0)	97.2 (90.3 to 99.7)
Sugimoto et al., 2023, Japan	BRAF	1	1	6	85.7 (42.1 to 99.6)	85.7 (42.1 to 99.6)	99.9 (99.5 to 100.0)	99.9 (99.5 to 100.0)	99.8 (99.3 to 100.0)
	EGFR	60	34	221	86.7 (81.9 to 90.6)	78.6 (73.4 to 83.3)	92.6 (90.5 to 94.3)	95.6 (94.0 to 97.0)	91.1 (89.3 to 92.8)
	ERBB2	3	2	8	80 (44.4 to 97.5)	72.7 (39.0 to 94.0)	99.7 (99.2 to 99.9)	99.8 (99.3 to 100.0)	99.5 (98.9 to 99.8)
	KRAS	35	19	110	85.3 (78.0 to 90.9)	75.9 (68.1 to 82.6)	96.2 (94.8 to 97.4)	97.9 (96.8 to 98.7)	94.9 (93.4 to 96.2)
Sun et al., 2023, China	MET	57	7	18	72 (50.6 to 87.9)	24 (14.9 to 35.3)	76.7 (70.8 to 81.9)	97.3 (93.8 to 99.1)	76.2 (70.6 to 81.3)
Sung et al., 2017, Republic of Korea	EGFR	13	19	19	50 (33.4 to 66.6)	59.4 (40.6 to 76.3)	79 (66.8 to 88.3)	72.1 (59.9 to 82.3)	68 (57.9 to 77.0)
Thompson et al., 2016, USA	BRAF	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (91.0 to 100.0)	100 (91.0 to 100.0)	100 (91.2 to 100.0)
		5	0	10	100 (69.2 to 100.0)	66.7 (38.4 to 88.2)	83.3 (65.3 to 94.4)	100 (86.3 to 100.0)	87.5 (73.2 to 95.8)
		1	0	2	100 (15.8 to 100.0)	66.7 (9.4 to 99.2)	97.4 (86.2 to 100.0)	100 (90.5 to 100.0)	97.5 (86.8 to 99.9)
		1	0	2	100 (15.8 to 100.0)	66.7 (9.4 to 99.2)	97.4 (86.2 to 100.0)	100 (90.5 to 100.0)	100 (91.0 to 100.0)
Titek Vardarli et al., 2020, Turkey	ALK	0	0	0	Undefined	Undefined	100 (73.5 to 100.0)	100 (73.5 to 100.0)	100 (73.5 to 100.0)
	BRAF	0	1	0	0 (0.0 to 97.5)	Undefined	100 (71.5 to 100.0)	91.7 (61.5 to 99.8)	91.7 (61.5 to 99.8)
	EGFR	1	0	0	Undefined	0 (0.0 to 97.5)	91.7 (61.5 to 99.8)	100 (71.5 to 100.0)	91.7 (61.5 to 99.8)
	ERBB2	1	0	0	Undefined	0 (0.0 to 97.5)	91.7 (61.5 to 99.8)	100 (71.5 to 100.0)	91.7 (61.5 to 99.8)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	FGFR1	0	1	0	0 (0.0 to 97.5)	Undefined	100 (71.5 to 100.0)	91.7 (61.5 to 99.8)	91.7 (61.5 to 99.8)
	KRAS	0	0	0	Undefined	Undefined	100 (73.5 to 100.0)	100 (73.5 to 100.0)	100 (73.5 to 100.0)
	MET	0	0	0	Undefined	Undefined	100 (73.5 to 100.0)	100 (73.5 to 100.0)	100 (73.5 to 100.0)
	PIK3CA	0	1	1	50 (1.3 to 98.7)	100 (2.5 to 100.0)	100 (69.2 to 100.0)	90.9 (58.7 to 99.8)	91.7 (61.5 to 99.8)
Toor et al., 2018, USA	ALK	0	1	0	0 (0.0 to 97.5)	Undefined	100 (63.1 to 100.0)	88.9 (51.8 to 99.7)	88.9 (51.8 to 99.7)
	BRAF	0	0	0	Undefined	Undefined	100 (66.4 to 100.0)	100 (66.4 to 100.0)	100 (66.4 to 100.0)
	EGFR	3	0	0	Undefined	0 (0.0 to 70.8)	66.7 (29.9 to 92.5)	100 (54.1 to 100.0)	66.7 (29.9 to 92.5)
	ERBB2	0	0	0	Undefined	Undefined	100 (66.4 to 100.0)	100 (66.4 to 100.0)	100 (66.4 to 100.0)
	FGFR1	1	0	0	Undefined	0 (0.0 to 97.5)	88.9 (51.8 to 99.7)	100 (63.1 to 100.0)	88.9 (51.8 to 99.7)
	KRAS	2	0	0	Undefined	0 (0.0 to 70.8)	77.8 (40.0 to 97.2)	100 (59.0 to 100.0)	77.8 (40.0 to 97.2)
	PIK3CA	1	0	0	Undefined	0 (0.0 to 97.5)	88.9 (51.8 to 99.7)	100 (63.1 to 100.0)	88.9 (51.8 to 99.7)
Tran et al., 2019, Vietnam	EGFR	4	1	11	91.7 (61.5 to 99.8)	73.3 (44.9 to 92.2)	85.2 (66.3 to 95.8)	95.8 (78.9 to 99.9)	87.2 (72.6 to 95.7)
	KRAS	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)	100 (90.3 to 100.0)	100 (90.3 to 100.0)	100 (91.0 to 100.0)
Tran et al., 2021, USA	ALK	2	1	15	93.8 (69.8 to 99.8)	88.2 (63.6 to 98.5)	99 (96.5 to 99.9)	99.5 (97.2 to 100.0)	98.6 (96.0 to 99.7)
	BRAF	0	0	9	100 (66.4 to 100.0)	100 (66.4 to 100.0)	100 (98.2 to 100.0)	100 (98.2 to 100.0)	100 (98.3 to 100.0)
	MET	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)	100 (98.3 to 100.0)	100 (98.3 to 100.0)	100 (98.3 to 100.0)
	RET	0	0	2	100 (15.8 to 100.0)	100 (15.8 to 100.0)	100 (98.3 to 100.0)	100 (98.3 to 100.0)	100 (98.3 to 100.0)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	ROS1	0	0	2	100 (15.8 to 100.0)	100 (15.8 to 100.0)	100 (98.3 to 100.0)	100 (98.3 to 100.0)	100 (98.3 to 100.0)
Uchida et al., 2015, Japan	EGFR	47	22	56	71.8 (60.5 to 81.4)	54.4 (44.3 to 64.2)	77.6 (71.4 to 83.1)	67.6 (61.3 to 73.5)	76 (70.7 to 80.9)
Villaflor et al., 2016, USA	ALK	0	0	0	Undefined	Undefined	100 (88.1 to 100.0)	100 (88.1 to 100.0)	100 (88.1 to 100.0)
	BRAF	0	0	0	Undefined	Undefined	100 (88.1 to 100.0)	100 (88.1 to 100.0)	100 (88.1 to 100.0)
	EGFR	3	0	3	100 (29.2 to 100.0)	50 (11.8 to 88.2)	88.5 (69.8 to 97.6)	100 (85.2 to 100.0)	89.7 (72.6 to 97.8)
	ERBB2	0	0	0	Undefined	Undefined	100 (88.1 to 100.0)	100 (88.1 to 100.0)	100 (88.1 to 100.0)
	MET	1	0	0	Undefined	0 (0.0 to 97.5)	96.6 (82.2 to 99.9)	100 (87.7 to 100.0)	96.6 (82.2 to 99.9)
	RET	1	0	0	Undefined	0 (0.0 to 97.5)	96.6 (82.2 to 99.9)	100 (87.7 to 100.0)	96.6 (82.2 to 99.9)
	ROS1	0	0	0	Undefined	Undefined	100 (88.1 to 100.0)	100 (88.1 to 100.0)	100 (88.1 to 100.0)
Wu et al., 2019, USA	ALK	3	0	1	100 (2.5 to 100.0)	25 (0.6 to 80.6)	93.9 (83.1 to 98.7)	100 (92.3 to 100.0)	97.5 (86.8 to 99.9)
	EGFR	17	5	20	80 (59.3 to 93.2)	54.1 (36.9 to 70.5)	32 (14.9 to 53.5)	61.5 (31.6 to 86.1)	56 (41.3 to 70.0)
	KRAS	1	0	3	100 (29.2 to 100.0)	75 (19.4 to 99.4)	97.9 (88.7 to 100.0)	100 (92.3 to 100.0)	98 (89.4 to 99.9)
	MET	4	1	3	75 (19.4 to 99.4)	42.9 (9.9 to 81.6)	91.3 (79.2 to 97.6)	97.7 (87.7 to 99.9)	90 (78.2 to 96.7)
	PIK3CA	2	0	3	100 (29.2 to 100.0)	60 (14.7 to 94.7)	95.7 (85.5 to 99.5)	100 (92.1 to 100.0)	96 (86.3 to 99.5)
Xie et al., 2018, China	ALK	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)	100 (88.8 to 100.0)	100 (88.8 to 100.0)	100 (90.0 to 100.0)
	EGFR	4	0	19	100 (82.5 to 100.0)	82.6 (61.2 to 95.0)	75 (47.6 to 92.7)	100 (73.5 to 100.0)	88.6 (73.3 to 96.8)
	ERBB2	1	0	1	100 (2.5 to 100.0)	50 (1.3 to 98.7)	97.1 (84.7 to 99.9)	100 (89.4 to 100.0)	97.1 (85.1 to 100.0)
	KRAS	2	0	1	100 (2.5 to 100.0)	33.3 (0.8 to 90.6)	94.1 (80.3 to 99.3)	100 (89.1 to 100.0)	94.3 (80.8 to 99.3)
	ROS1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (89.7 to 100.0)	100 (89.7 to 100.0)	100 (90.0 to 100.0)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
Xu et al., 2016, China	BRAF	0	1	0	0 (0.0 to 97.5)	Undefined	100 (91.4 to 100.0)	97.6 (87.4 to 99.9)	97.6 (87.4 to 99.9)
	EGFR	3	13	4	23.5 (6.8 to 49.9)	57.1 (18.4 to 90.1)	88 (68.8 to 97.5)	62.9 (44.9 to 78.5)	61.9 (45.6 to 76.4)
	ERBB2	1	0	0	Undefined	0 (0.0 to 97.5)	97.6 (87.4 to 99.9)	100 (91.4 to 100.0)	97.6 (87.4 to 99.9)
	KRAS	0	6	6	50 (21.1 to 78.9)	100 (54.1 to 100.0)	100 (88.4 to 100.0)	83.3 (67.2 to 93.6)	85.7 (71.5 to 94.6)
	PIK3CA	0	2	4	66.7 (22.3 to 95.7)	100 (39.8 to 100.0)	100 (90.3 to 100.0)	94.7 (82.3 to 99.4)	95.2 (83.8 to 99.4)
Yang et al., 2018, China	ALK	1	0	0	Undefined	0 (0.0 to 97.5)	98.2 (90.4 to 100.0)	100 (93.5 to 100.0)	98.2 (90.4 to 100.0)
	BRAF	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (93.5 to 100.0)	100 (93.5 to 100.0)	100 (93.6 to 100.0)
	EGFR	4	0	24	100 (85.8 to 100.0)	85.7 (67.3 to 96.0)	87.5 (71.0 to 96.5)	100 (87.7 to 100.0)	92.9 (82.7 to 98.0)
	ERBB2	0	0	3	100 (29.2 to 100.0)	100 (29.2 to 100.0)	100 (93.3 to 100.0)	100 (93.3 to 100.0)	100 (93.6 to 100.0)
	KRAS	1	0	0	Undefined	0 (0.0 to 97.5)	98.2 (90.4 to 100.0)	100 (93.5 to 100.0)	98.2 (90.4 to 100.0)
	MET	0	0	4	100 (39.8 to 100.0)	100 (39.8 to 100.0)	100 (93.2 to 100.0)	100 (93.2 to 100.0)	100 (93.6 to 100.0)
	NTRK1	0	0	2	100 (15.8 to 100.0)	100 (15.8 to 100.0)	100 (93.4 to 100.0)	100 (93.4 to 100.0)	100 (93.6 to 100.0
	PIK3CA	1	0	3	100 (29.2 to 100.0)	75 (19.4 to 99.4)	98.1 (89.9 to 100.0)	100 (93.2 to 100.0)	98.2 (90.4 to 100.0)
	RET	0	0	2	100 (15.8 to 100.0)	100 (15.8 to 100.0)	100 (93.4 to 100.0)	100 (93.4 to 100.0)	100 (93.6 to 100.0
	ROS1	0	0	1	100 (2.5 to 100.0)	100 (2.5 to 100.0)	100 (93.5 to 100.0)	100 (93.5 to 100.0)	100 (93.6 to 100.0)
Yao et al., 2016, China	ALK	2	0	3	100 (29.2 to 100.0)	60 (14.7 to 94.7)	94.4 (81.3 to 99.3)	100 (89.7 to 100.0)	94.9 (82.7 to 99.4)
	EGFR	5	0	12	100 (73.5 to 100.0)	70.6 (44.0 to 89.7)	81.5 (61.9 to 93.7)	100 (84.6 to 100.0)	87.2 (72.6 to 95.7)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	KRAS	1	0	3	100 (29.2 to 100.0)	75 (19.4 to 99.4)	97.2 (85.5 to 99.9)	100 (90.0 to 100.0)	97.4 (86.5 to 99.9)
	PIK3CA	1	0	1	100 (2.5 to 100.0)	50 (1.3 to 98.7)	97.4 (86.2 to 99.9)	100 (90.5 to 100.0)	97.4 (86.5 to 99.9)
	RET	1	0	0	Undefined	0 (0.0 to 97.5)	97.4 (86.5 to 99.9)	100 (90.7 to 100.0)	97.4 (86.5 to 99.9)
Yin et al., 2021, China	EGFR	0	5	83	94.3 (87.2 to 98.1)	100 (95.7 to 100.0)	100 (91.4 to 100.0)	89.1 (76.4 to 96.4)	95.4 (90.2 to 98.3)
	KRAS	0	1	17	94.4 (72.7 to 99.9)	100 (80.5 to 100.0)	100 (91.4 to 100.0)	97.6 (87.4 to 99.9)	98.4 (90.9 to 100.0)
Zhang et al., 2022 China	ALK	1	0	4	100 (39.8 to 100.0)	80 (28.4 to 99.5)	99.2 (95.5 to 100.0)	100 (97.0 to 100.0)	99.2 (95.6 to 100.0)
	BRAF	2	0	2	100 (15.8 to 100.0)	50 (67.6 to 93.2)	98.4 (94.2 to 99.8)	100 (97.0 to 100.0)	98.4 (94.3 to 99.8)
	EGFR	19	3	39	92.9 (80.5 to 98.5)	67.2 (53.7 to 79.0)	77.1 (66.6 to 85.6)	95.5 (87.5 to 99.1)	82.4 (74.6 to 88.6)
	ERBB2	1	0	4	100 (39.8 to 100.0)	80 (28.4 to 99.5)	99.2 (95.5 to 100.0)	100 (97.0 to 100.0)	99.2 (95.6 to 100.0)
	KRAS	4	0	16	100 (79.4 to 100.0)	80 (56.3 to 94.3)	96.3 (90.9 to 99.0)	100 (96.5 to 100.0)	96.8 (92.0 to 99.1)
	MET	1	0	4	100 (39.8 to 100.0)	80 (28.4 to 99.5)	99.2 (95.5 to 100.0)	100 (97.0 to 100.0)	99.2 (95.6 to 100.0)
	PIK3CA	8	0	4	100 (39.8 to 100.0)	33.3 (9.9 to 65.1)	93.4 (87.4 to 97.1)	100 (96.8 to 100.0)	93.6 (87.8 to 97.2)
	ROS1	0	2	3	60 (14.7 to 94.7)	100 (29.2 to 100.0)	100 (97.0 to 100.0)	94.3 (88.5 to 97.7)	97.6 (93.1 to 99.5)
Zhao et al., 2022, China	ALK	25	0	18	100 (81.5 to 100.0)	41.9 (27.0 to 57.9)	95.0 (92.7 to 96.7)	100 (99.2 to 100.0)	95.2 (93.0 to 96.9)
	BRAF	6	0	12	100 (73.5 to 100.0)	66.7 (41.0 to 86.7)	98.8 (974 to 99.7)	100 (99.3 to 100.0)	98.8 (97.5 to 99.6)
	EGFR	33	5	278	98.2 (95.9 to 99.4)	89.4 (85.2 to 92.6)	86.0 (80.9 to 90.2)	97.6 (94.5 to 99.2)	92.7 (90.1 to 94.8)
	ERBB2	9	0	15	100 (78.2 to 100.0)	62.5 (40.6 to 81.2)	98.2 (96.7 to 99.2)	100 (99.3 to 100.0)	98.3 (96.7 to 99.2)
	KRAS	13	5	37	88.1 (74.4 to 96.0)	74 (59.7 to 85.4)	97.3 (95.4 to 98.5)	98.9 (97.5 to 99.7)	96.5 (94.6 to 97.9)
	MET	20	0	4	100 (39.8 to 100.0)	16.7 (4.7 to 37.4)	96.1 (94.1 to 97.6)	100 (99.3 to 100.0)	96.1 (94.1 to 97.6)
	NTRK	3	0	0	Undefined	0 (0.0 to 70.8)	99.4 (98.3 to 99.9)	100 (99.3 to 100.0)	99.4 (98.3 to 99.9)
	RET	1	3	7	70 (34.8 to 93.3)	87.5 (47.3 to 99.7)	99.8 (98.9 to 100.0)	99.4 (98.3 to 99.9)	99.2 (98.0 to 99.8)

Study, Year, Location	Gene	Samples tested positive with tissue testing only[a]	Samples tested positive with liquid biopsy testing only[a]	Samples tested positive with both tissue and liquid biopsy[a] testing	Concordance with tissue among samples tested positive with liquid biopsy, % (95% CI)[b]	Concordance with liquid Biopsy among samples tested positive with tissue, % (95% CI)[b]	Concordance with tissue among samples tested negative with liquid biopsy, % (95% CI)[b]	Concordance with liquid biopsy among samples tested negative with tissue, % (95% CI)[b]	Overall concordance, % (95% CI)[b]
	ROS1	6	0	7	100 (59.0 to 100.0)	53.8 (25.1 to 80.8)	98.8 (97.5 to 99.6)	100 (99.3 to 100.0)	98.8 (97.5 to 99.6)

Abbreviations: CI = Confidence Interval.

[a]Alterations were investigated at the gene level, with no distinction on the specific location or the type of alteration within the gene.

[b]The confidence intervals were computed by the authors of this HTA using the Clopper–Pearson method.

[c]We present estimates from the authors of the primary study

Table A9: Evaluation of Clinical Utility of Liquid Biopsy Using a Concurrent Control

Study, year, location	Type of targeted therapy	Measure	No. receiving targeted therapy	No. receiving standard therapy	HR % (95% CI)
Jee et al., 2022, USA	Unspecified targeted therapies	Overall survival	255	467	0.63 (0.52 to 0.76)

Abbreviation: CI = Confidence Interval

Table A10: Evaluation of Clinical Utility of Liquid Biopsy Using a Before–After Design

Study, year, location	Study duration	Targeted therapy	Estimate n (%) before receiving a targeted therapy	Estimate n (%) after receiving a targeted therapy	Difference, % (95% CI)[a]
Complete response[b]					
Bustamante Alvarez et al., 2020, USA	3 years	Afatinib, Erlotinib, Osimertinib, Crizotinib	0 (0)[c]	1 (12.5)	12.5 (-25.7 to 52.7)
Dziadziuszko et al., 2021, USA, Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Costa Rica, France, Germany, Hong Kong, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Panama, Peru, Poland, Russia, Serbia, Singapore, Spain, Taiwan, Thailand, Turkey	≥ 1.25 years	Alectinib	0 (0)[d]	0(0)	0 (-4.6 to 4.6)
Laufer-Geva et al., 2018, Israel	≥ 2.5 years	Osimertinib, Afatinib, Vemurafenib, Cabozantinib, Gefitinib	0 (0)[d]	1 (2.7)	2.7 (-6.2 to 14.2)
Li et al., 2021, China	≥ 1.7 years	Afatinib, Cabozantinib, Crizotinib, Gefitinib, Icotinib, Osimertinib	0 (0)[d]	0 (0)	0 (-11.6 to 11.6)
Page et al., 2021, USA	1 year	Afatinib, Alectinib, Crizotinib, Erlotinib, Gefitinib, Osimertinib	0 (0)[d]	1 (3.1)	3.1 (-7.0 to 16.2)
Wang et al., 2021, China	2 years	Unspecified TKIs	0(0)[d]	0 (0)	0 (-6.6 to 6.6)
Xie et al., 2018, China	2 years	Gefitinib, Erlotinib, Icotinib, Crizotinib	0(0)[d]	0 (0)	0 (-18.9 to 18.9)
Partial response[b]					
Bustamante Alvarez et al., 2020, USA	3 years	Afatinib, Erlotinib, Osimertinib, Crizotinib	0 (0)[c]	6 (75)	75 (15.5 to 96.8)
Dziadziuszko et al., 2021, USA, Argentina,	≥ 1.25 years	Alectinib	0 (0)[d]	76 (87.4)	87.4 (78.4 to 93.5)

Study, year, location	Study duration	Targeted therapy	Estimate n (%) before receiving a targeted therapy	Estimate n (%) after receiving a targeted therapy	Difference, % (95% CI)[a]
Australia, Belgium, Brazil, Canada, Chile, China, Costa Rica, France, Germany, Hong Kong, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Panama, Peru, Poland, Russia, Serbia, Singapore, Spain, Taiwan, Thailand, Turkey					
Laufer-Geva et al., 2018, Israel	≥ 2.5 years	Osimertinib, Afatinib, Vemurafenib, Cabozantinib, Gefitinib	0 (0)[d]	15 (40.5)	40.5 (23.4 to 58.2)
Li et al., 2021, China	≥ 1.7 years	Afatinib, Cabozantinib, Crizotinib, Gefitinib, Icotinib, Osimertinib	0 (0)[d]	21 (70.0)	70 (49.4 to 85.3)
Page et al., 2021, USA	1 year	Afatinib, Alectinib, Crizotinib, Erlotinib, Gefitinib, Osimertinib	0 (0)[d]	18 (50.0)	50 (31.6 to 67.4)
Phallen et al., 2019, USA	2.5 years	Erlotinib, afatinib	0 (0)[d]	3 (60)	60 (-17.7 to 94.7)
Wang et al., 2021, China	2 years	Unspecified TKIs	0(0)[d]	27 (50)	50 (35.5 to 62.9)
Xie et al., 2018, China	2 years	Gefitinib, Erlotinib, Icotinib, Crizotinib	0(0)[d]	0 (0)	0.0 (-18.9 to 18.9)
Progressive disease[b]					
Dziadziuszko et al., 2021, USA, Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Costa Rica, France, Germany, Hong Kong, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Panama, Peru, Poland, Russia, Serbia, Singapore, Spain, Taiwan, Thailand, Turkey	≥ 1.25 years	Alectinib	87 (100)[d]	1 (1.1)	-98.9 (-100.0 to -91.3)
Laufer-Geva et al., 2018, Israel	≥ 2.5 years	Osimertinib, Afatinib, Vemurafenib, Cabozantinib, Gefitinib	37 (100)	7 (18.9)	-67.9 (-77.6 to -56.1)
Li et al., 2021, China	≥ 1.7 years	Afatinib, Cabozantinib, Crizotinib, Gefitinib, Icotinib, Osimertinib	30 (100)[d]	3 (10)	-90 (-97.9 to -69.9)

Study, year, location	Study duration	Targeted therapy	Estimate n (%) before receiving a targeted therapy	Estimate n (%) after receiving a targeted therapy	Difference, % (95% CI)[a]
Marchetti et al., 2015, Italy	0.2 year	Erlotinib	20 (100)[d]	1 (5)	-95 (-99.9 to -64.7)
Page et al., 2021, USA	1 year	Afatinib, Alectinib, Crizotinib, Erlotinib, Gefitinib, Osimertinib	32 (100)	2 (6.2)	-93.8 (-99.2 to -74.6)
Phallen et al., 2019, USA	2.5 years	Erlotinib, afatinib	5 (100)	1 (20)	-80 (-99.5 to 8.5)
Progression-free survival[b]					
Li et al., 2021, China	≥ 1.7 years	Afatinib, Cabozantinib, Crizotinib, Gefitinib, Icotinib, Osimertinib	0[d]	9.6	9.6 (6.6 to 12.4)
Liang et al., 2023, China	≥ 2.5 years	Geftinib, erlotinib, afatinib	0[d]	15	15[e]
Stable disease[b]					
Bustamante Alvarez et al., 2020, USA	3 years	Afatinib, Erlotinib, Osimertinib, Crizotinib	0 (0)[c]	1 (12.5)	12.5 (-25.7 to 52.7)
Dziadziuszko et al., 2021, USA, Argentina, Australia, Belgium, Brazil, Canada, Chile, China, Costa Rica, France, Germany, Hong Kong, Israel, Italy, Japan, Republic of Korea, Mexico, Netherlands, New Zealand, Panama, Peru, Poland, Russia, Serbia, Singapore, Spain, Taiwan, Thailand, Turkey	≥ 1.25 years	Alectinib	0 (0)[d]	10 (11.5)	11.5 (4.5 to 20.9)
Laufer-Geva et al., 2018, Israel	≥ 2.5 years	Osimertinib, Afatinib, Vemurafenib, Cabozantinib, Gefitinib	0 (0)[d]	14 (37.8)	37.8 (21.0 to 55.6)
Li et al., 2021, China	≥ 1.7 years	Afatinib, Cabozantinib, Crizotinib, Gefitinib, Icotinib, Osimertinib	0 (0)[d]	6 (20)	20 (5.2 to 38.6)
Page et al., 2021, USA	1 year	Afatinib, Alectinib, Crizotinib, Erlotinib, Gefitinib, Osimertinib	0 (0)[d]	11(34.4)	34.4 (17.5 to 53.2)
Wang et al., 2021, China	2 years	Unspecified TKIs	0(0)[d]	20 (37.4)	37.4 (24.0 to 50.7)
Xie et al., 2018, China	2 years	Gefitinib, Erlotinib, Icotinib, Crizotinib	0(0)[d]	7 (41.2)	41.2 (18.8 to 64.3)
Objective response rate[b]					
Liang et al., 2023, China	≥ 2.5 years	Geftinib, erlotinib, afatinib	0 (0)[d]	42 (63.6)	63.6 (50.8 to 75.3)

Study, year, location	Study duration	Targeted therapy	Estimate n (%) before receiving a targeted therapy	Estimate n (%) after receiving a targeted therapy	Difference, % (95% CI)[a]
Wang et al., 2018, China	1.7 years	Gefitinib	0(0)[d]	129 (74.1)	74.1 (67.0 to 80.5)
Wang et al., 2021, China	2 years	Unspecified TKIs	0(0)[d]	27 (50)	50 (35.5 to 62.9)

Abbreviations: CI = Confidence Interval; TKIs = Tyrosine Kinase Inhibitors

[a]Exact confidence intervals for the difference in proportions were computed using the Shan-Wang method.

[b]The definitions for complete response, partial response, progressive disease, stable disease, and objective response rate are based on RESIST criteria https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf

[c]Treatment-naïve newly diagnosed or at disease progression stage IV NSCLC.

[d] We assumed that, given the advanced stage of NSCLC in these treatment-naïve newly diagnosed patients, the disease must have been progressing prior to commencement of targeted therapy.

[e]The confidence intervals were not provided by authors of the primary study and we did not have access to individual-level data to compute it ourselves.

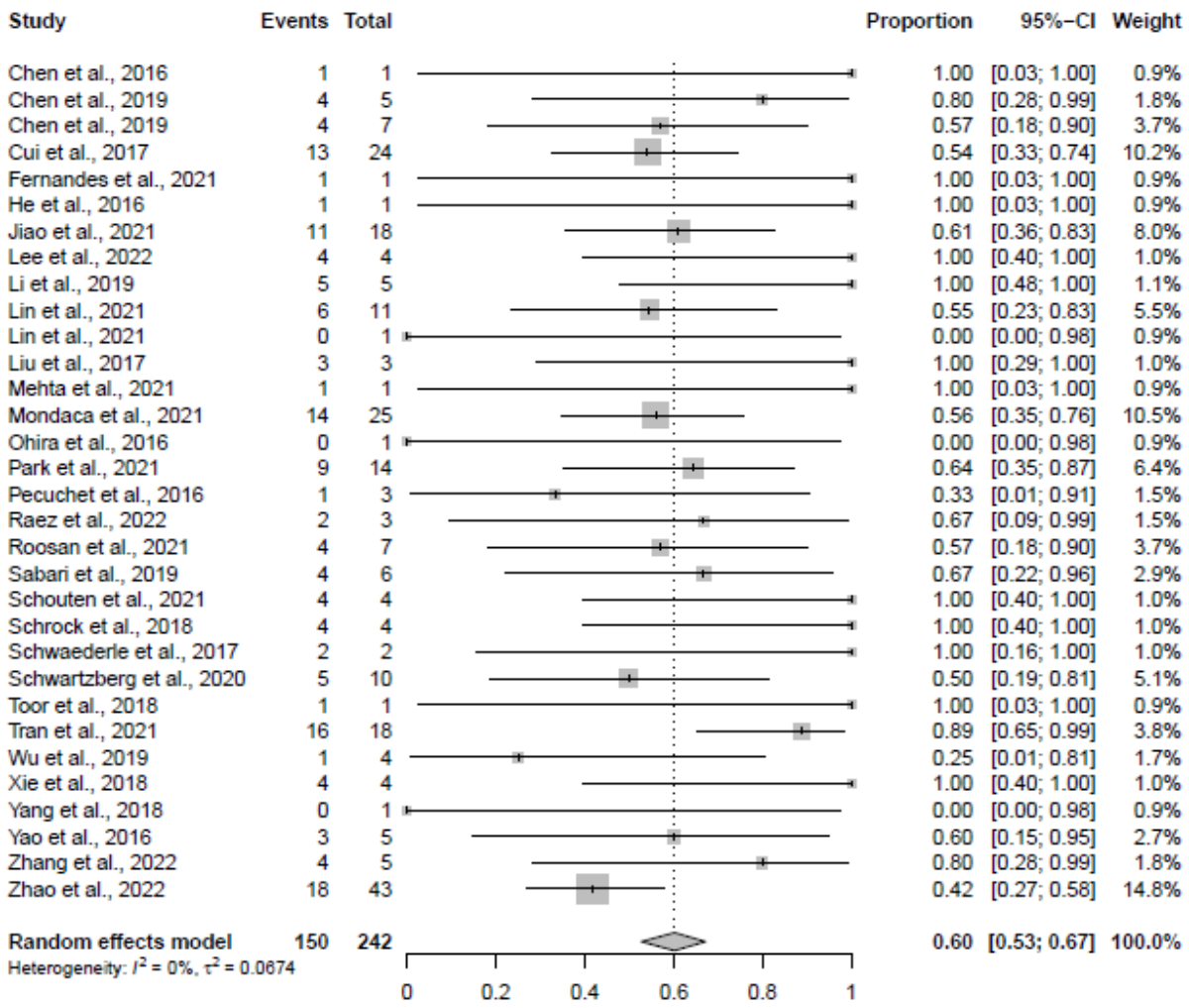

Figure A1: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *ALK* Alterations

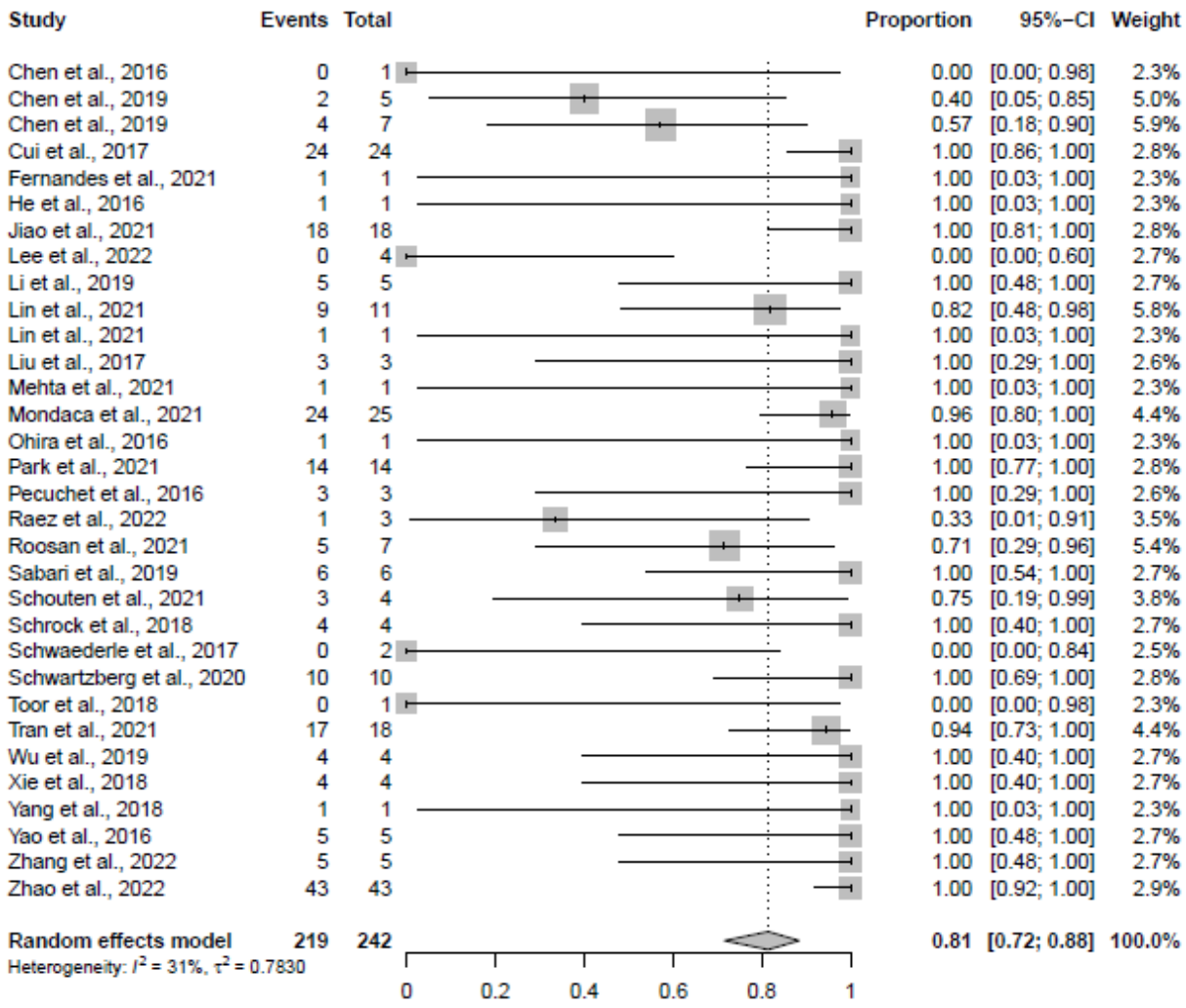

Figure A2: Sensitivity of Tissue Testing in Detecting Actionable *ALK* Alterations

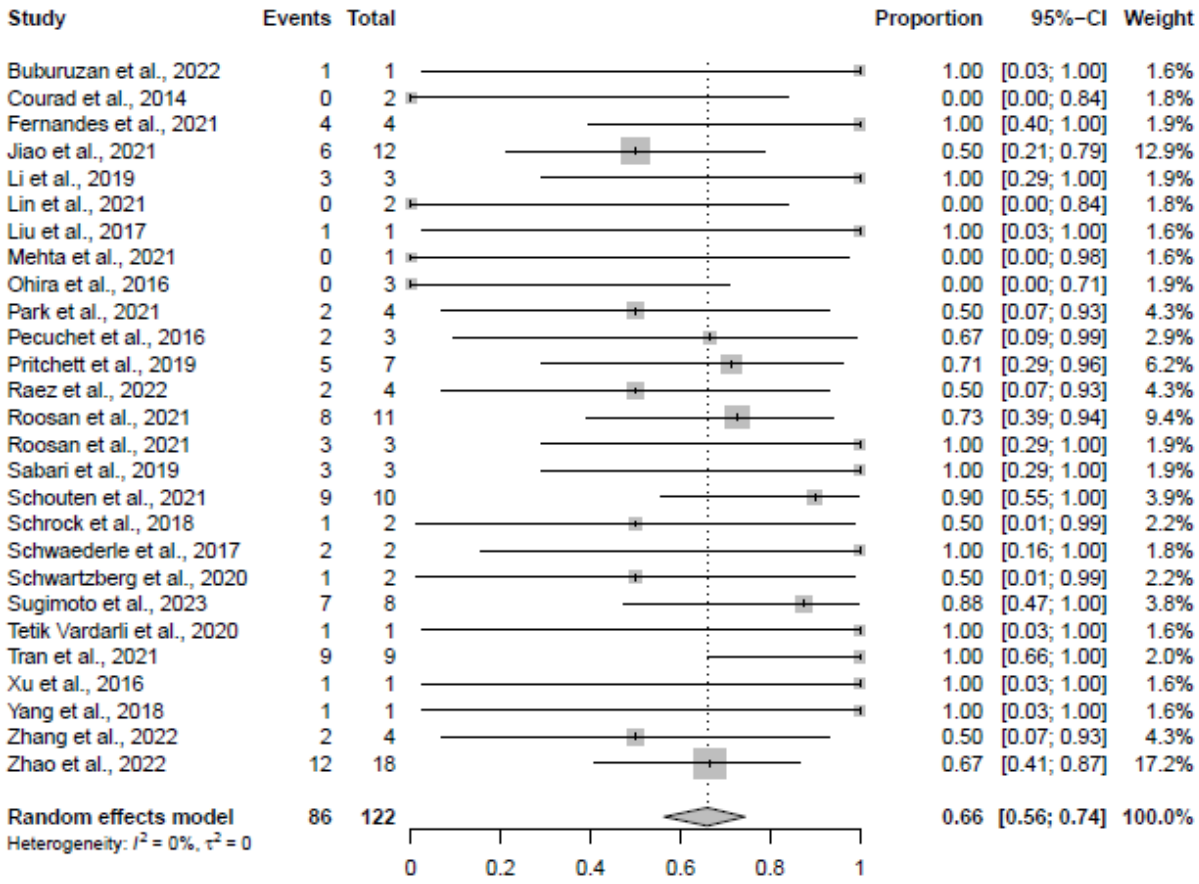

Figure A3: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *BRAF* Alterations

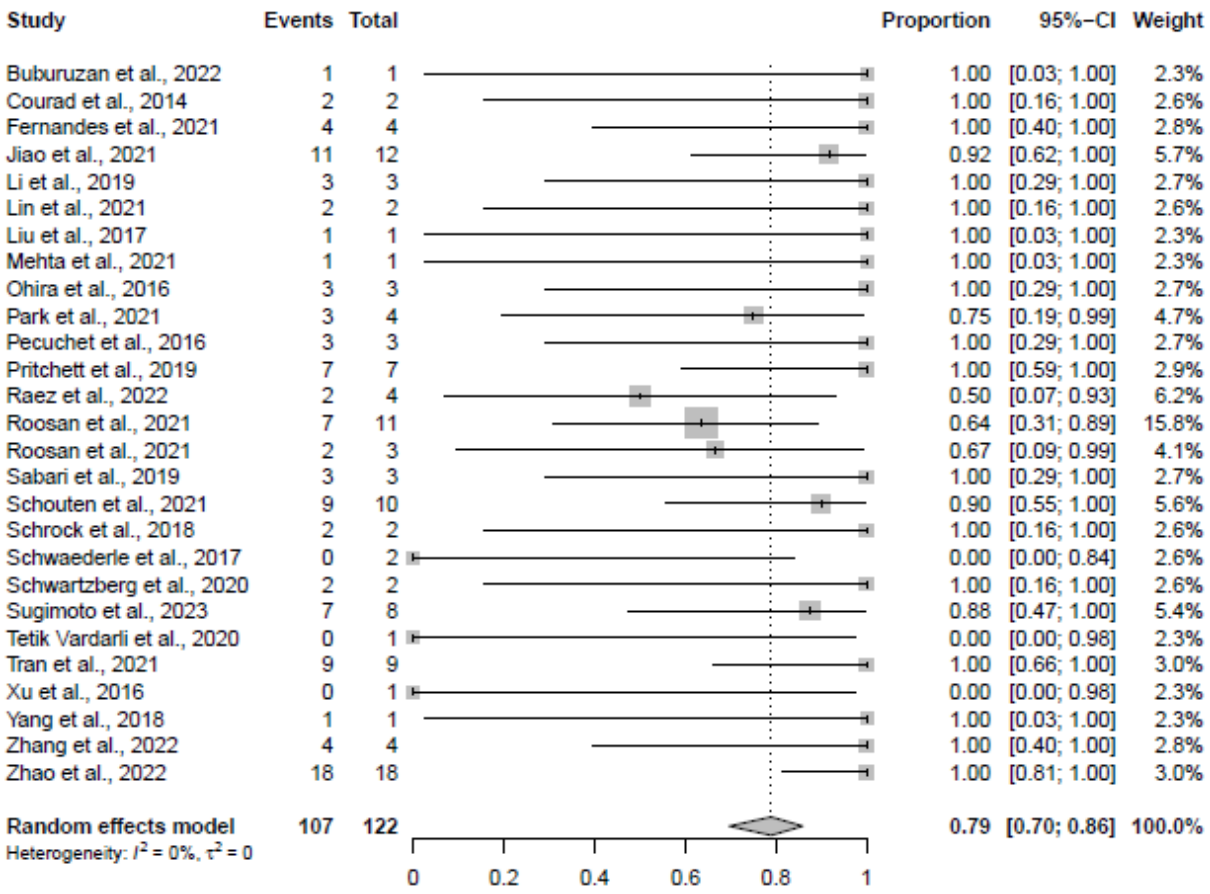

Figure A4: Sensitivity of Tissue Testing in Detecting Actionable *BRAF* Alterations

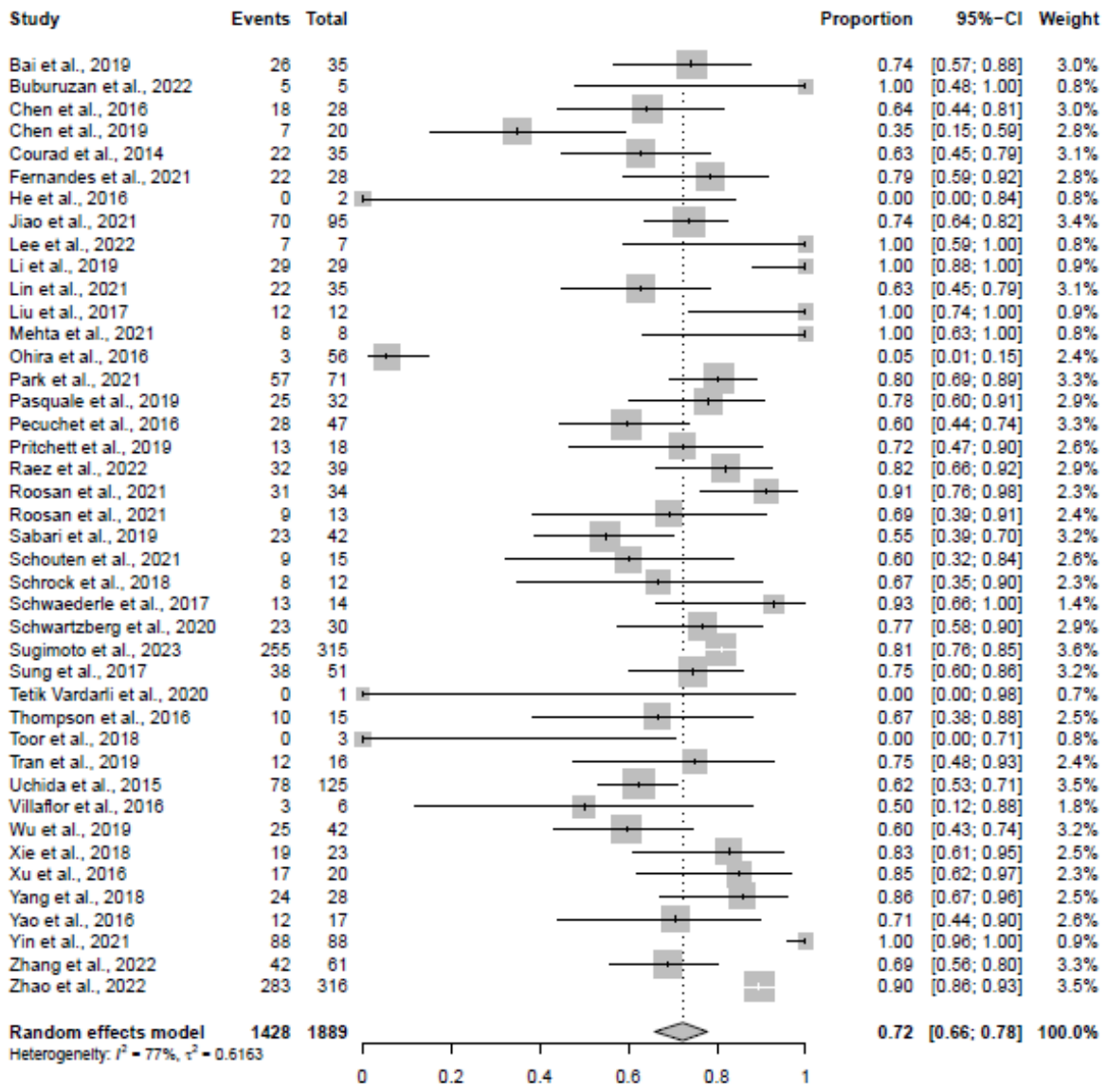

Figure A5: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *EGFR* Alterations

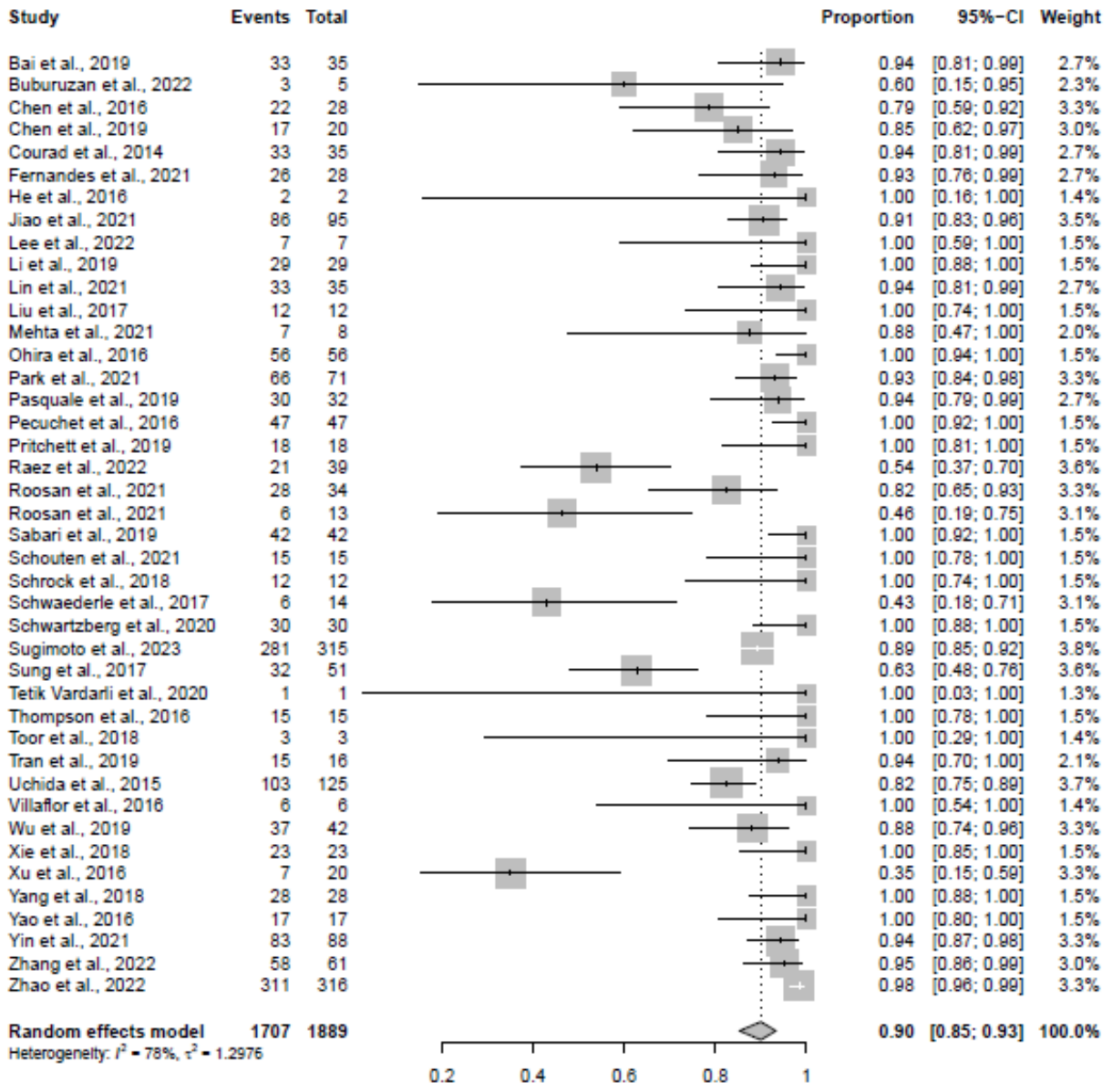

Figure A6: Sensitivity of Tissue Testing in Detecting Actionable *EGFR* Alterations

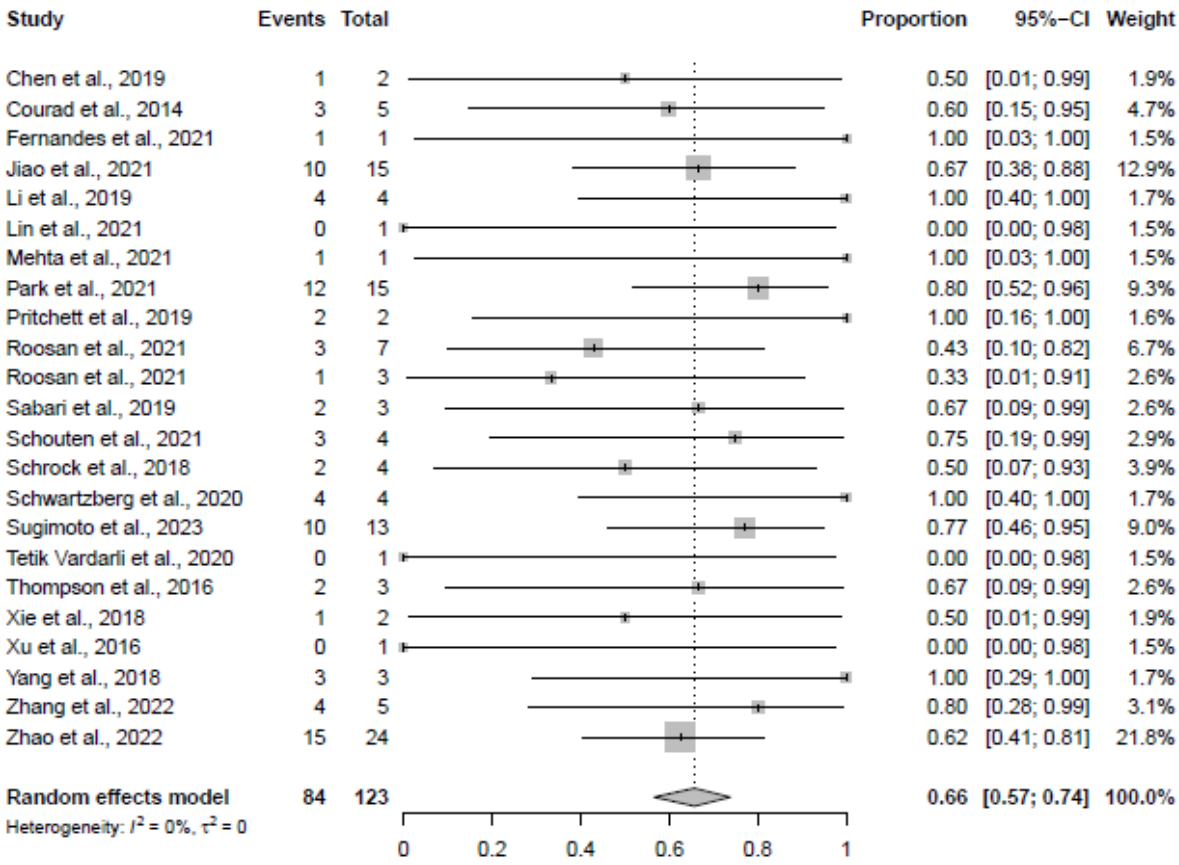

Figure A7: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *ERBB2* Alterations

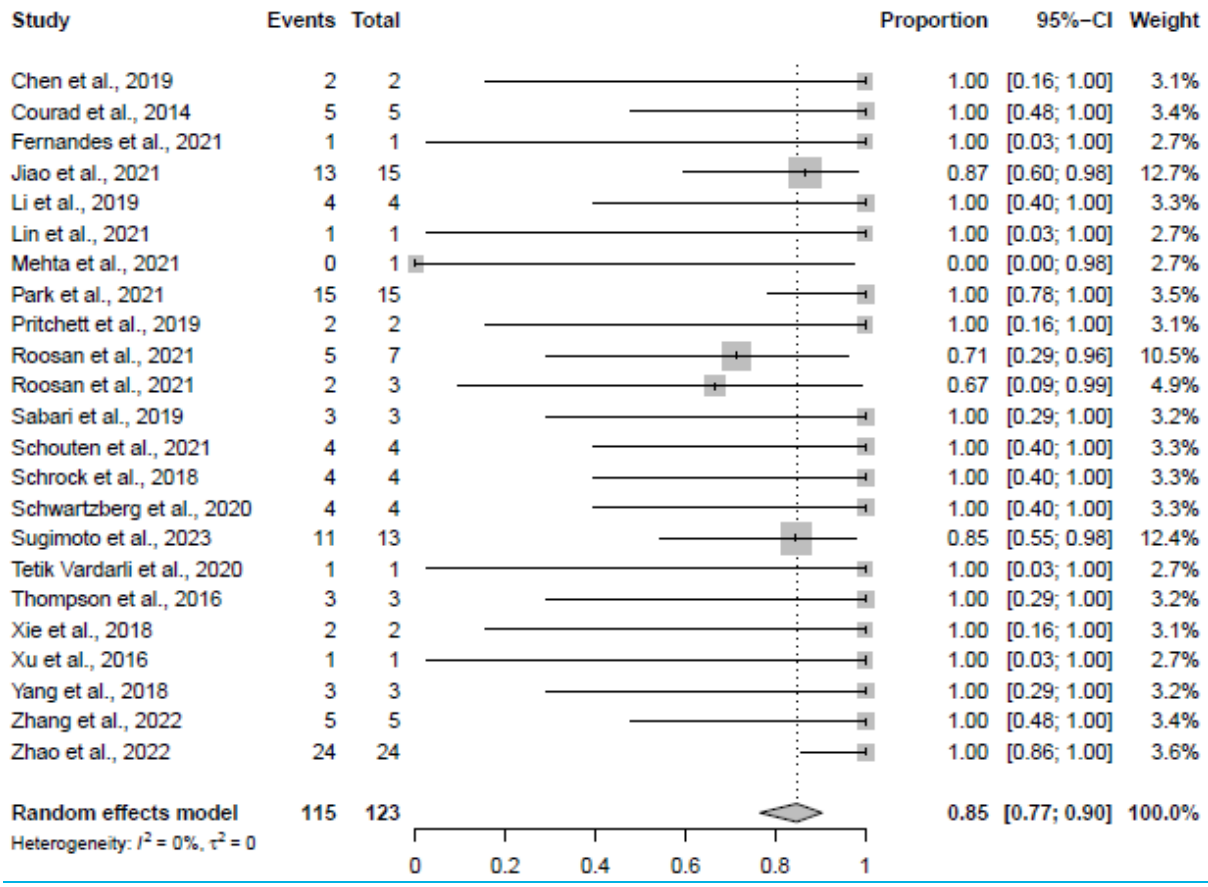

Figure A8: Sensitivity of Tissue Testing in Detecting Actionable *ERBB2* Alterations

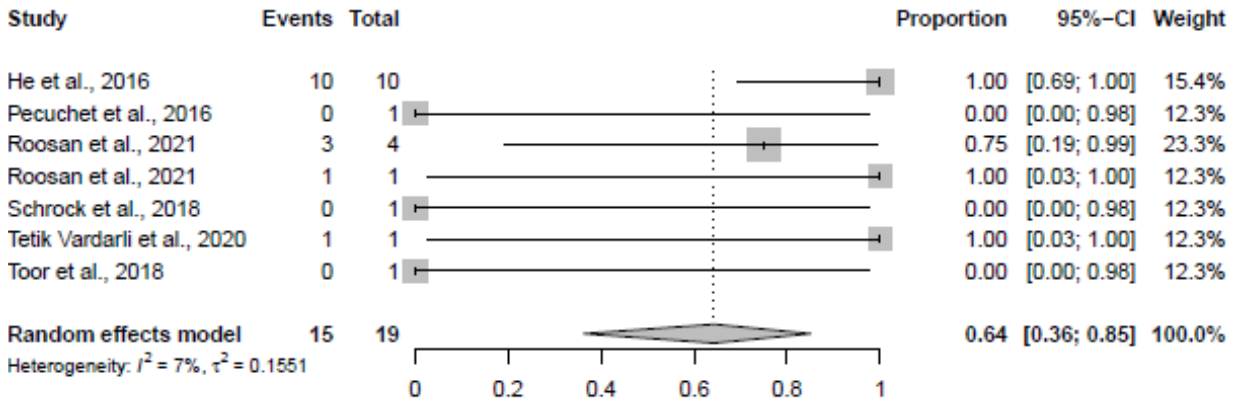

Figure A9: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *FGFR1* Alterations

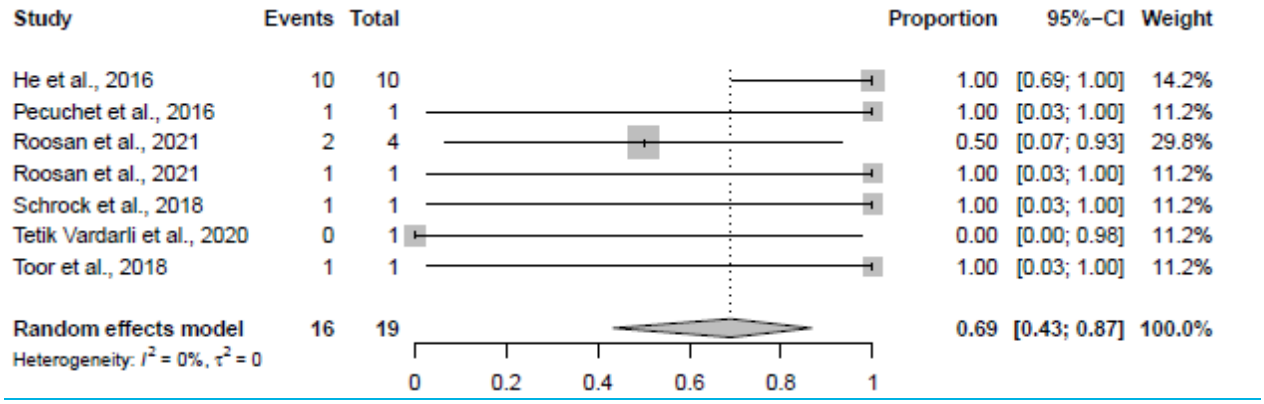

Figure A10: Sensitivity of Tissue Testing in Detecting Actionable *FGFR1* Alterations

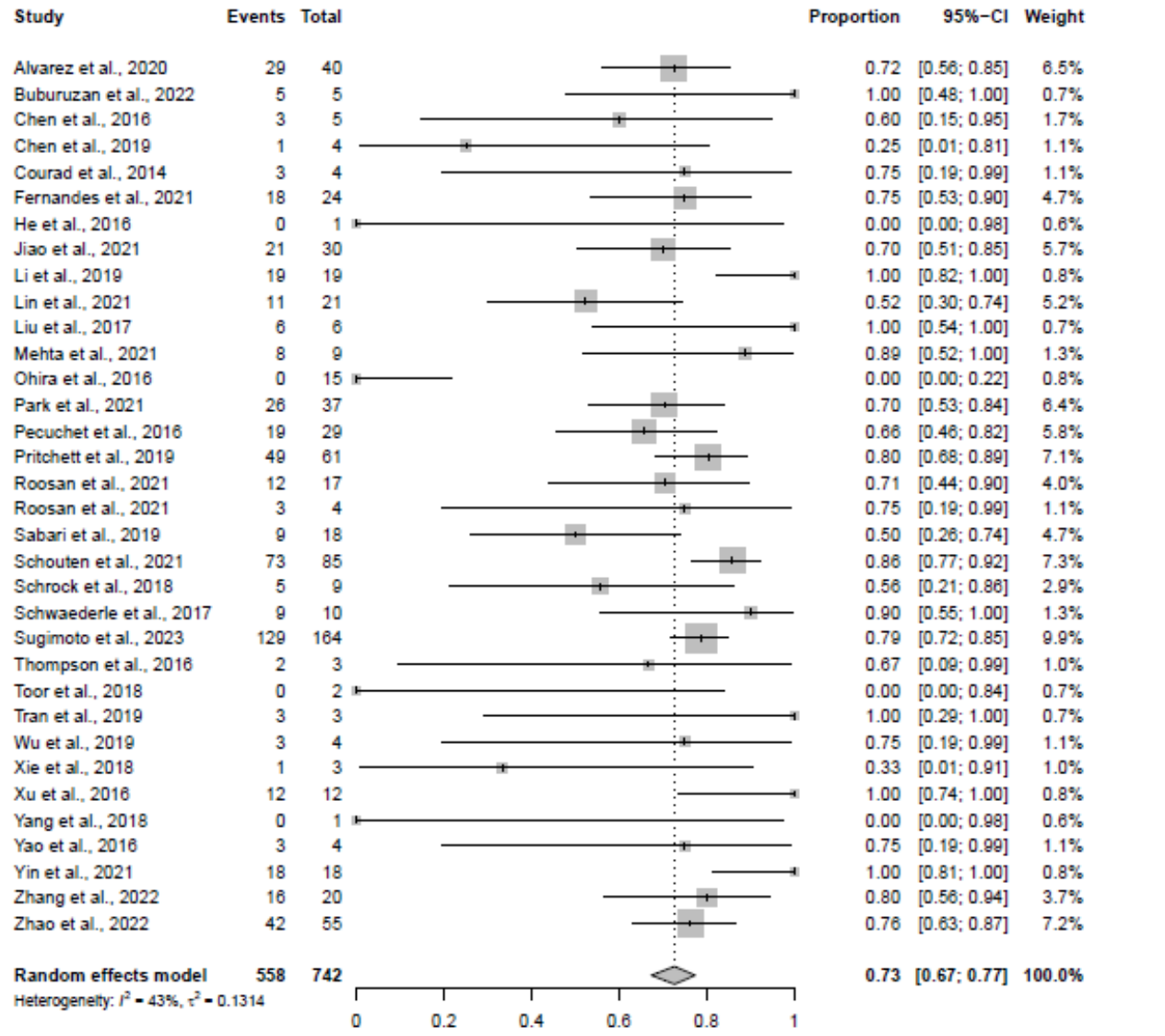

Figure A11: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *KRAS* Alterations

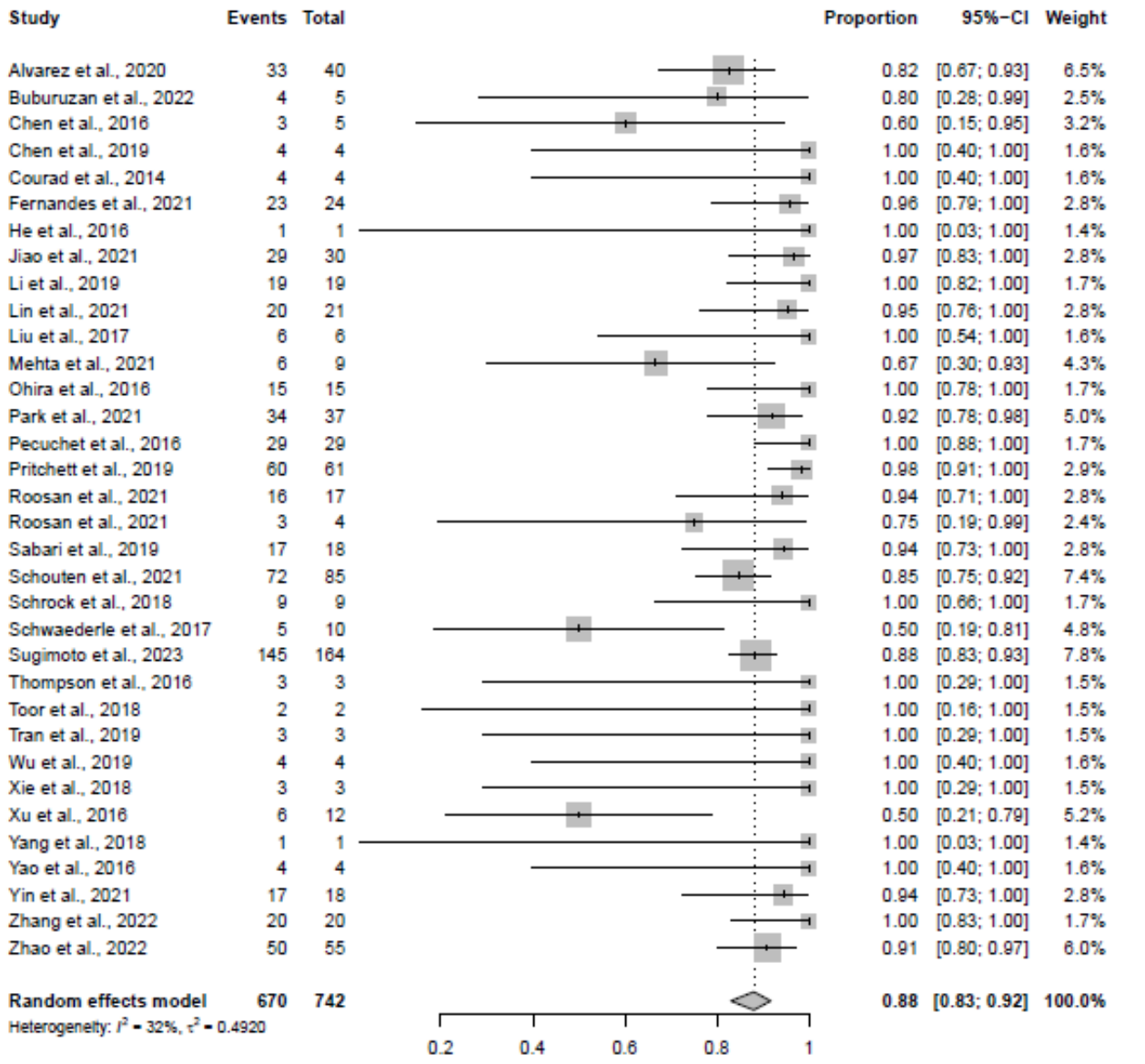

Figure A12: Sensitivity of Tissue Testing in Detecting Actionable *KRAS* Alterations

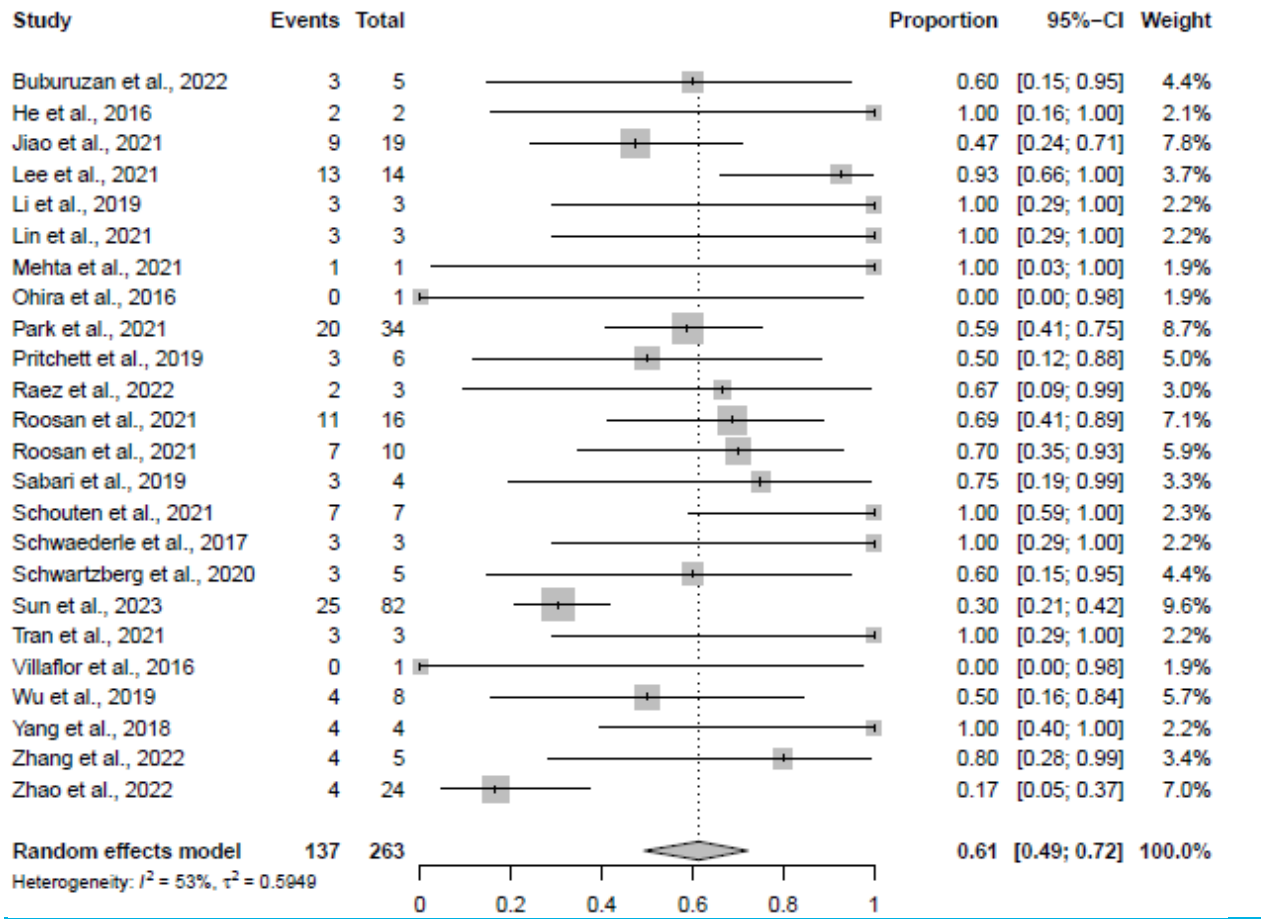

Figure A13: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *MET* Alterations

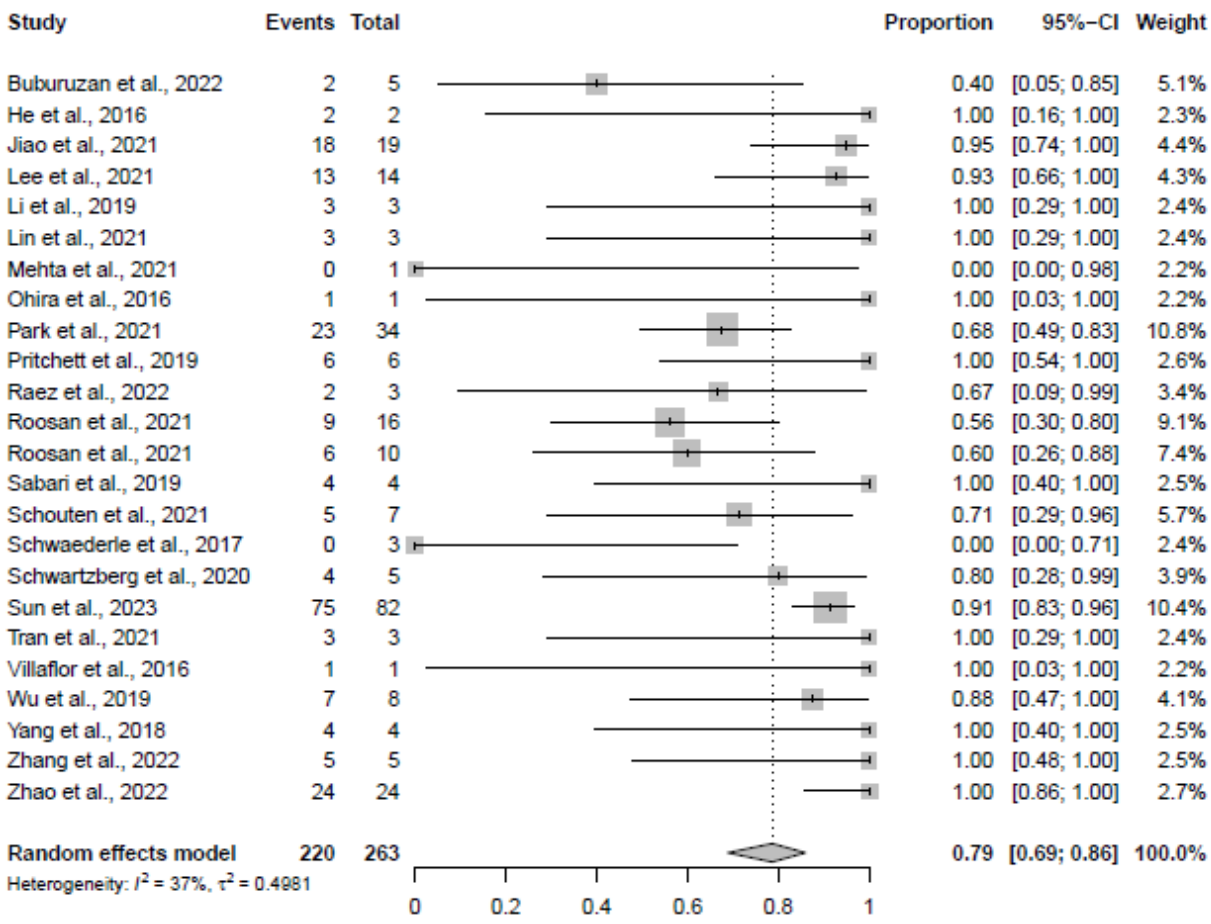

Figure A14: Sensitivity of Tissue Testing in Detecting Actionable *MET* Alterations

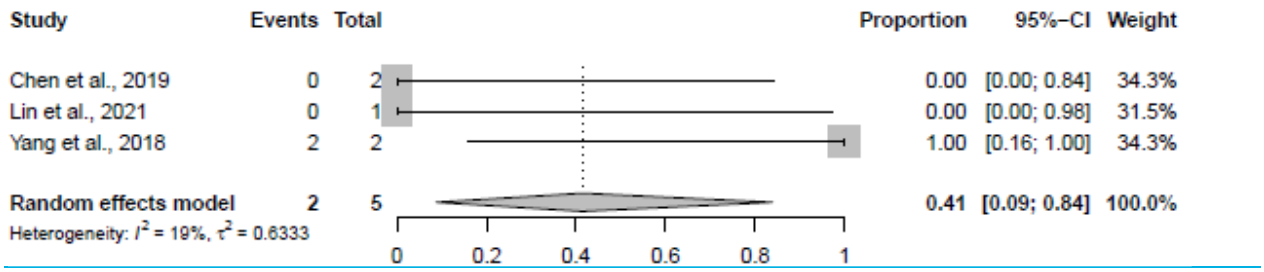

Figure A15: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *NTRK1* Alterations

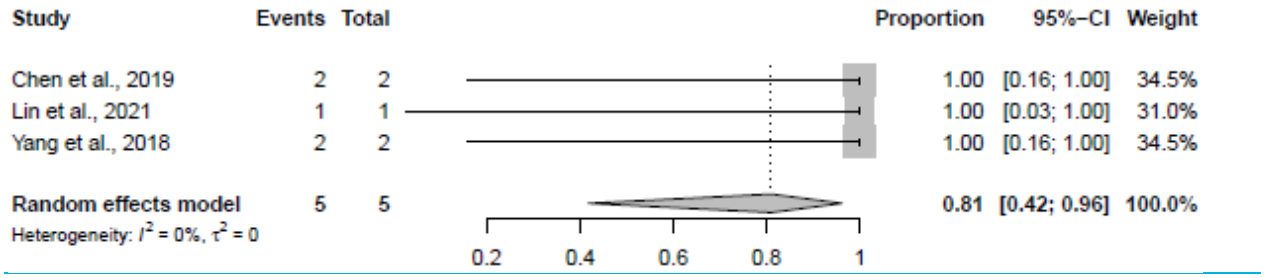

Figure A16: Sensitivity of Tissue Testing in Detecting Actionable *NTRK1* Alterations

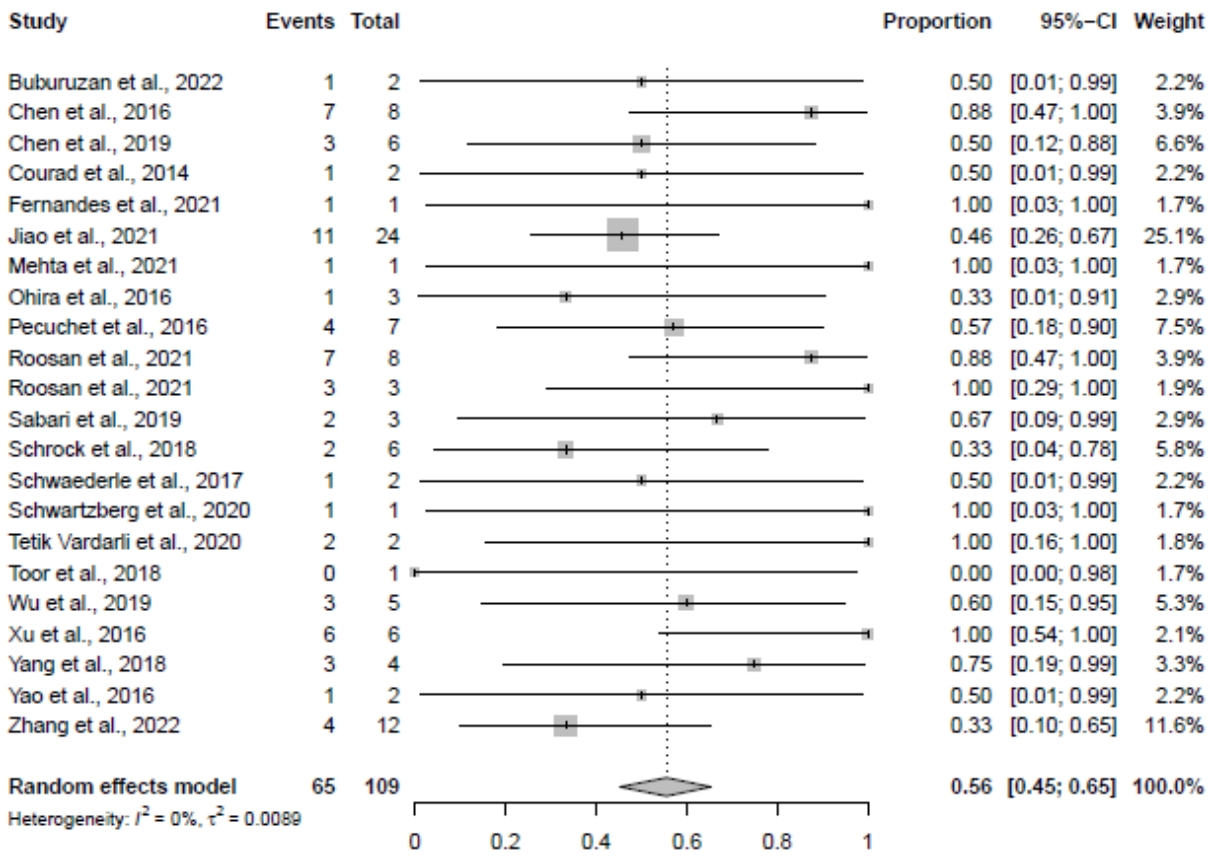

Figure A17: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *PIK3CA* Alterations

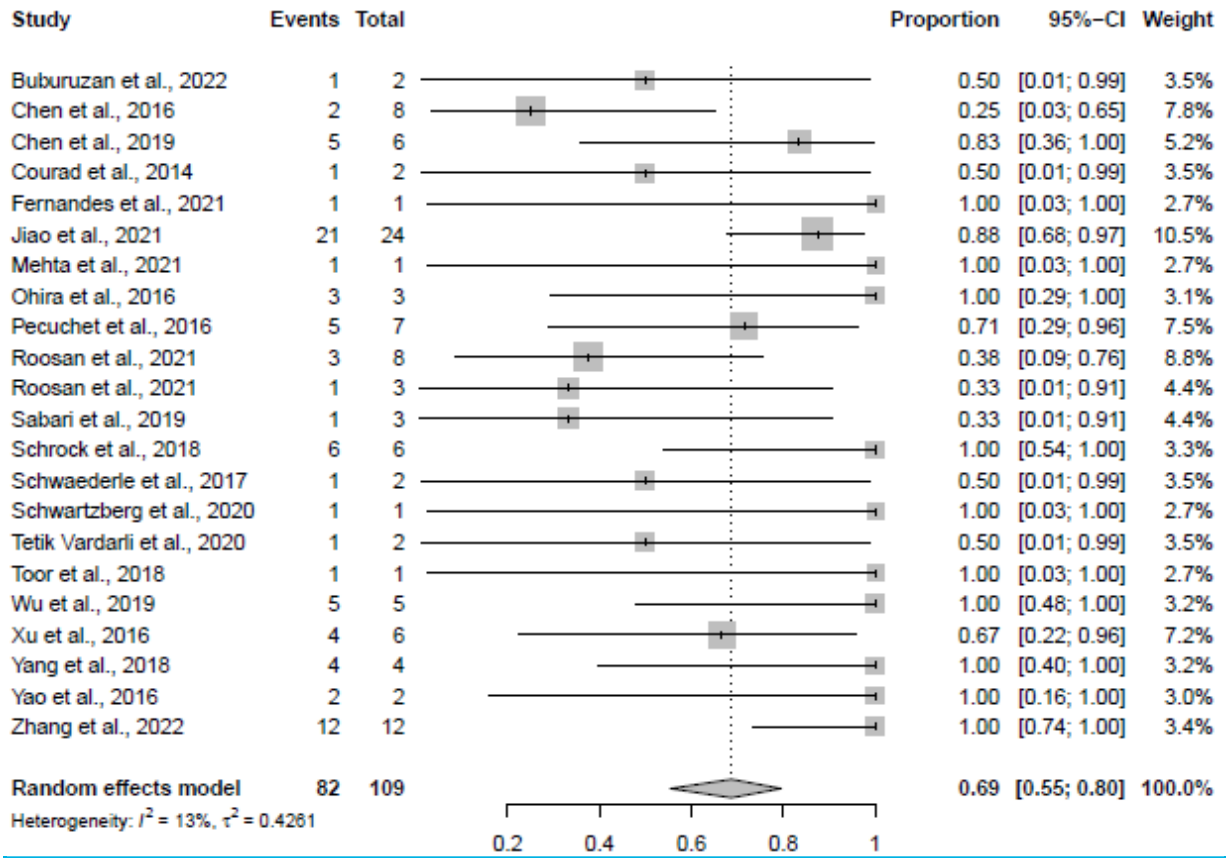

Figure A18: Sensitivity of Tissue Testing in Detecting Actionable *PIK3CA* Alterations

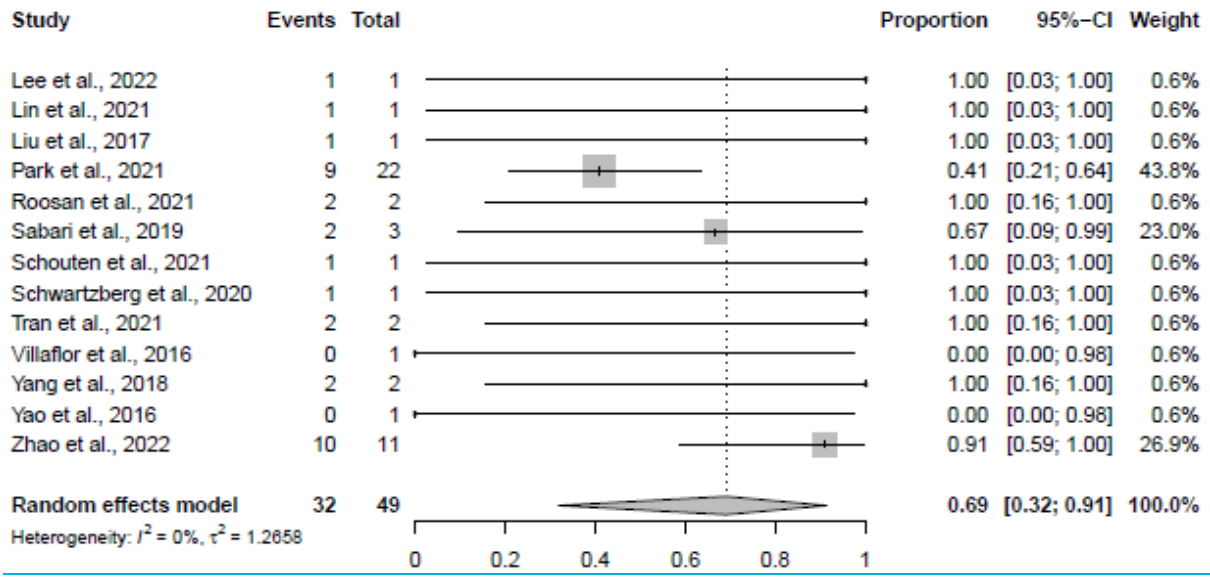

Figure A19: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *RET* Alterations

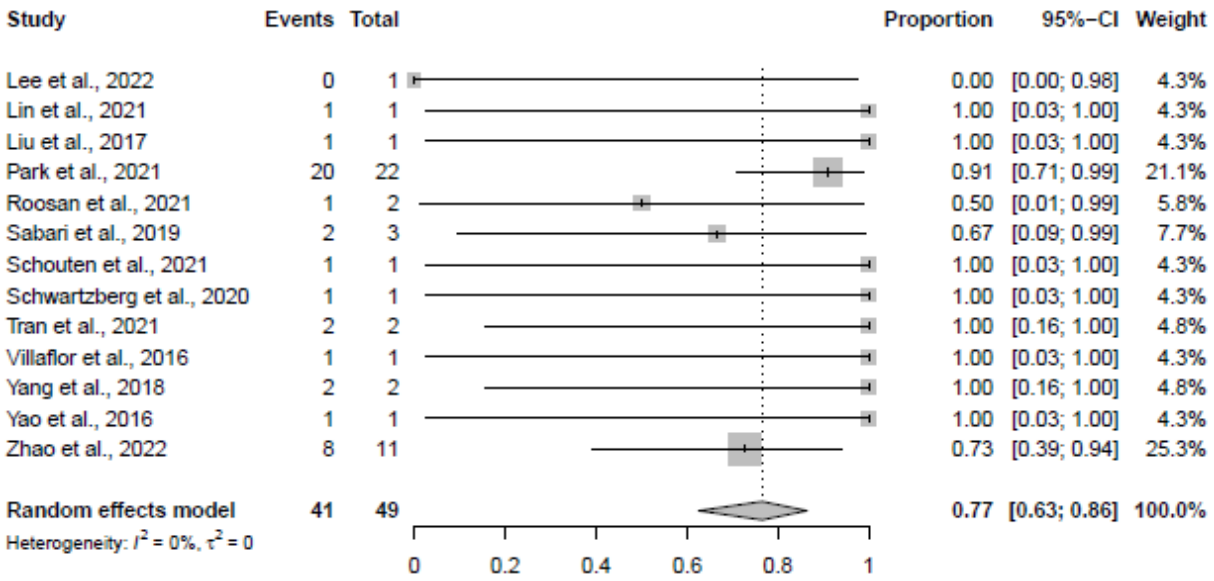

Figure A20: Sensitivity of Tissue Testing in Detecting Actionable *RET* Alterations

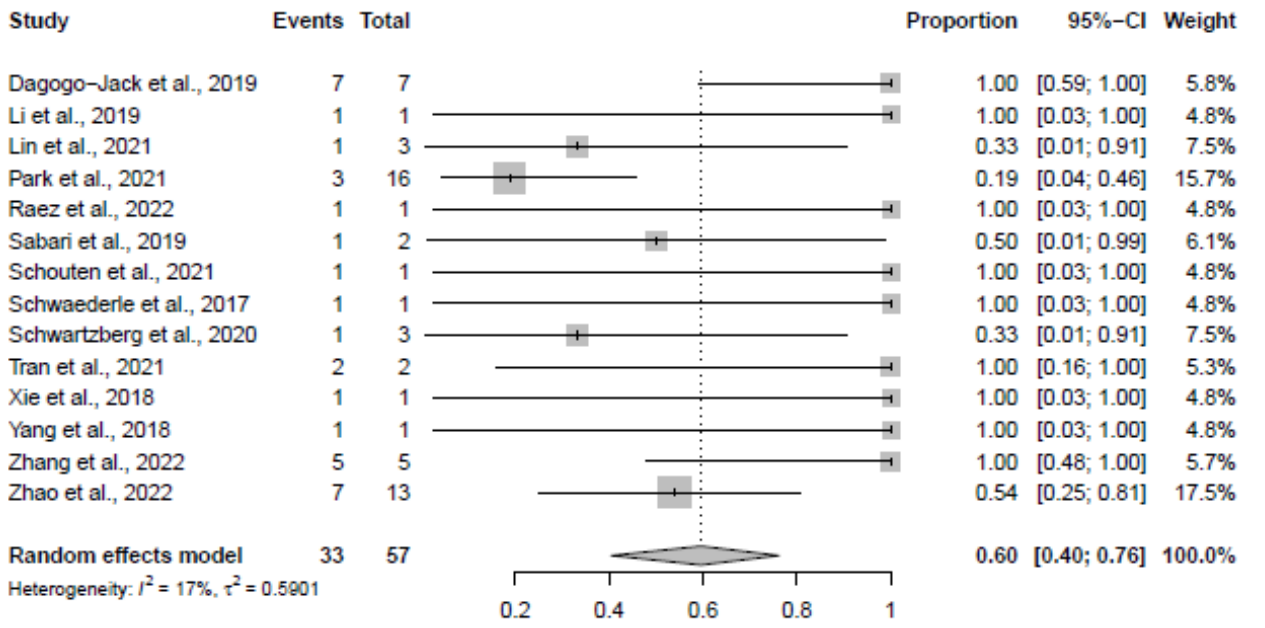

Figure A21: Sensitivity of Liquid Biopsy Testing in Detecting Actionable *ROS1* Alterations

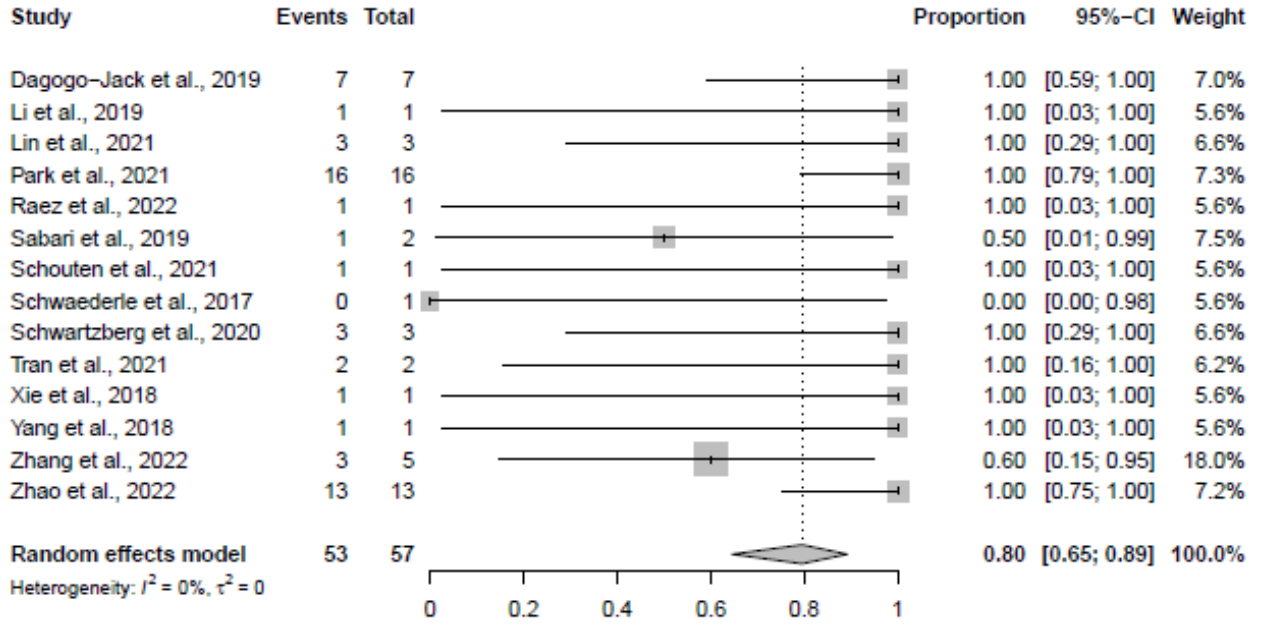

Figure A22: Sensitivity of Tissue Testing in Detecting Actionable *ROS1* Alterations

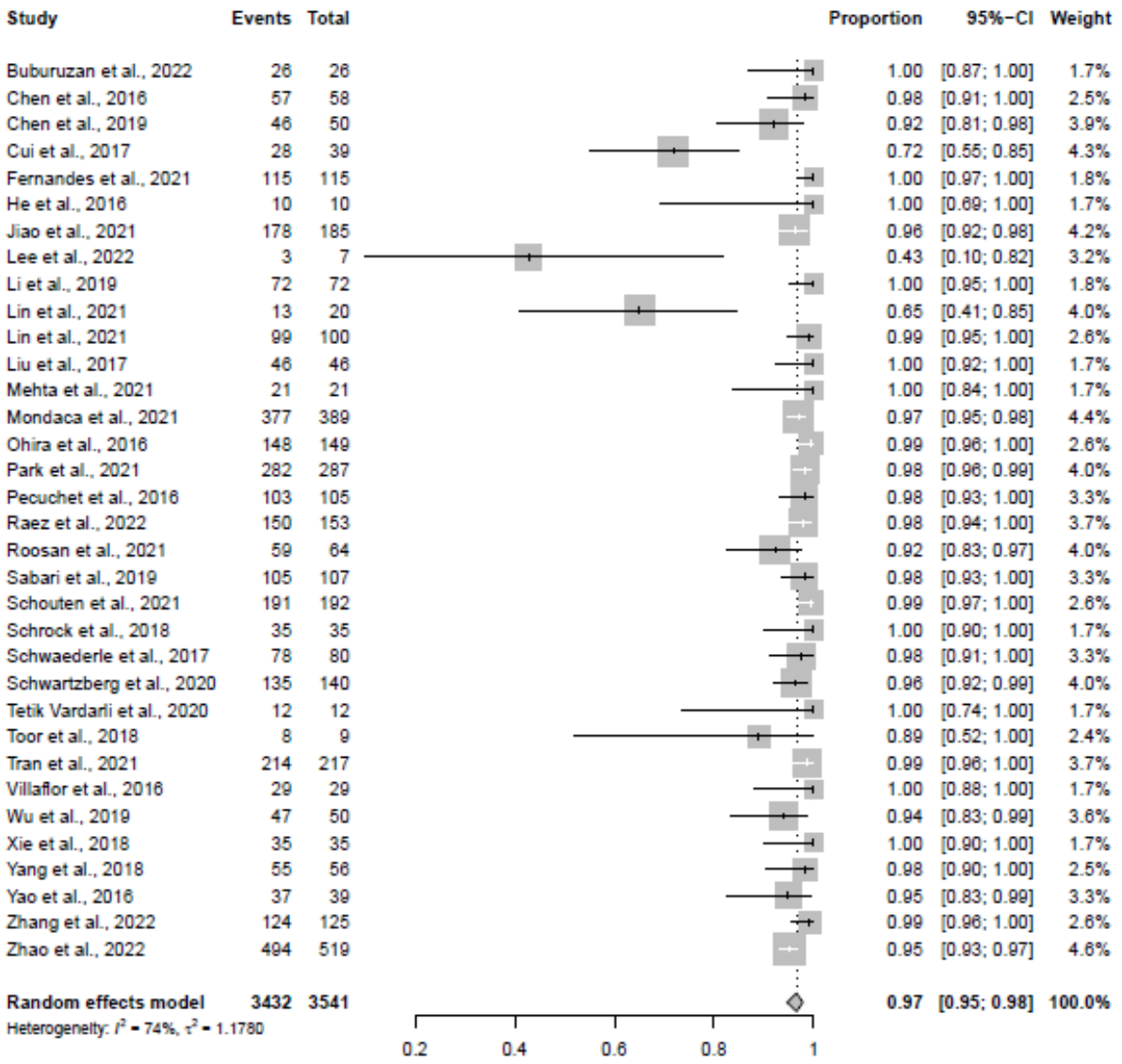

Figure A23: Overall Concordance Between Liquid Biopsy and Tissue Testing in Detecting *ALK* Actionable Alterations

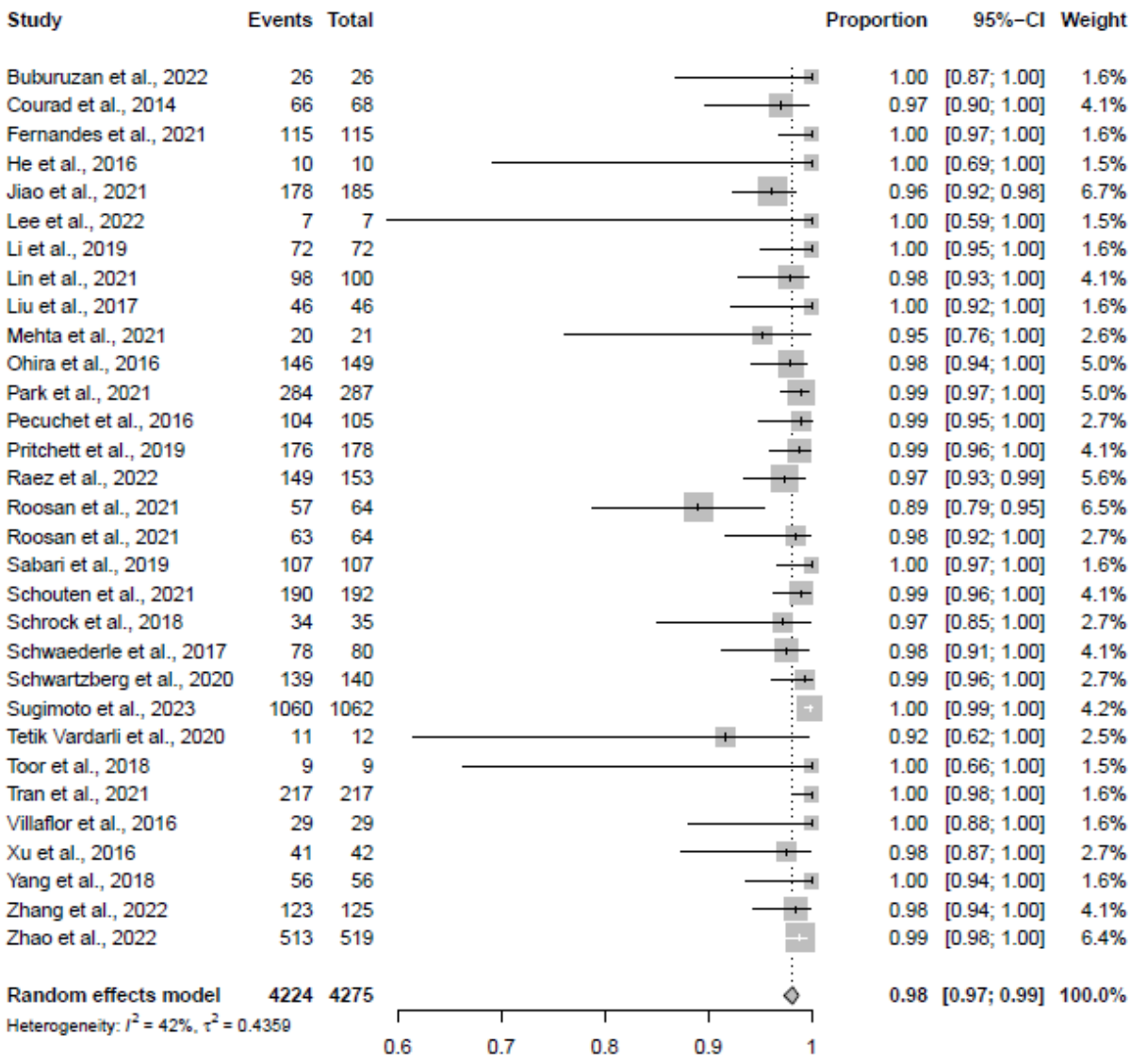

Figure A24: Overall Concordance Between Liquid Biopsy and Tissue Testing in Detecting *BRAF* Actionable Alterations

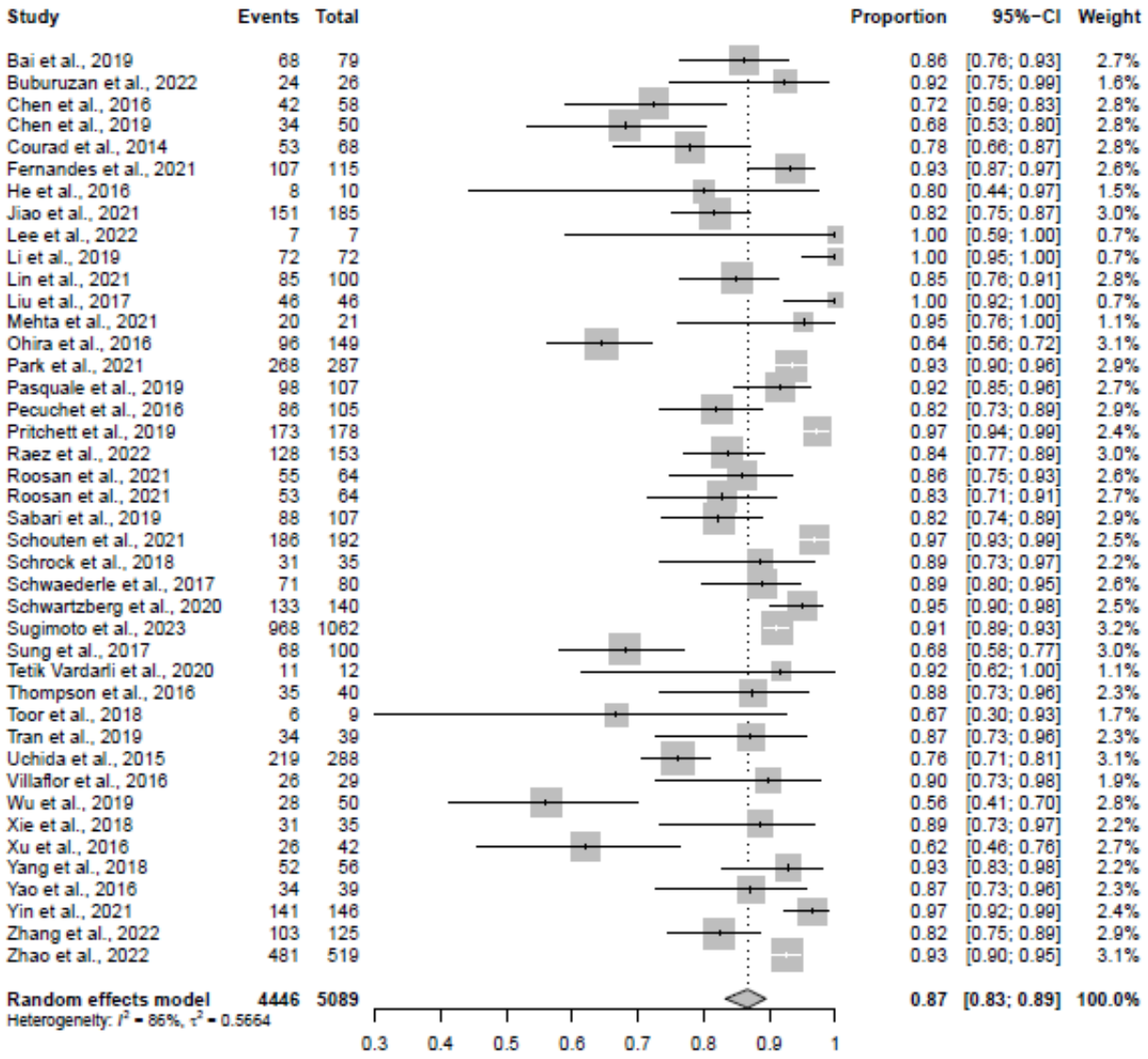

Figure A25: Overall Concordance Between Liquid Biopsy and Tissue Testing in Detecting *EGFR* Actionable Alterations

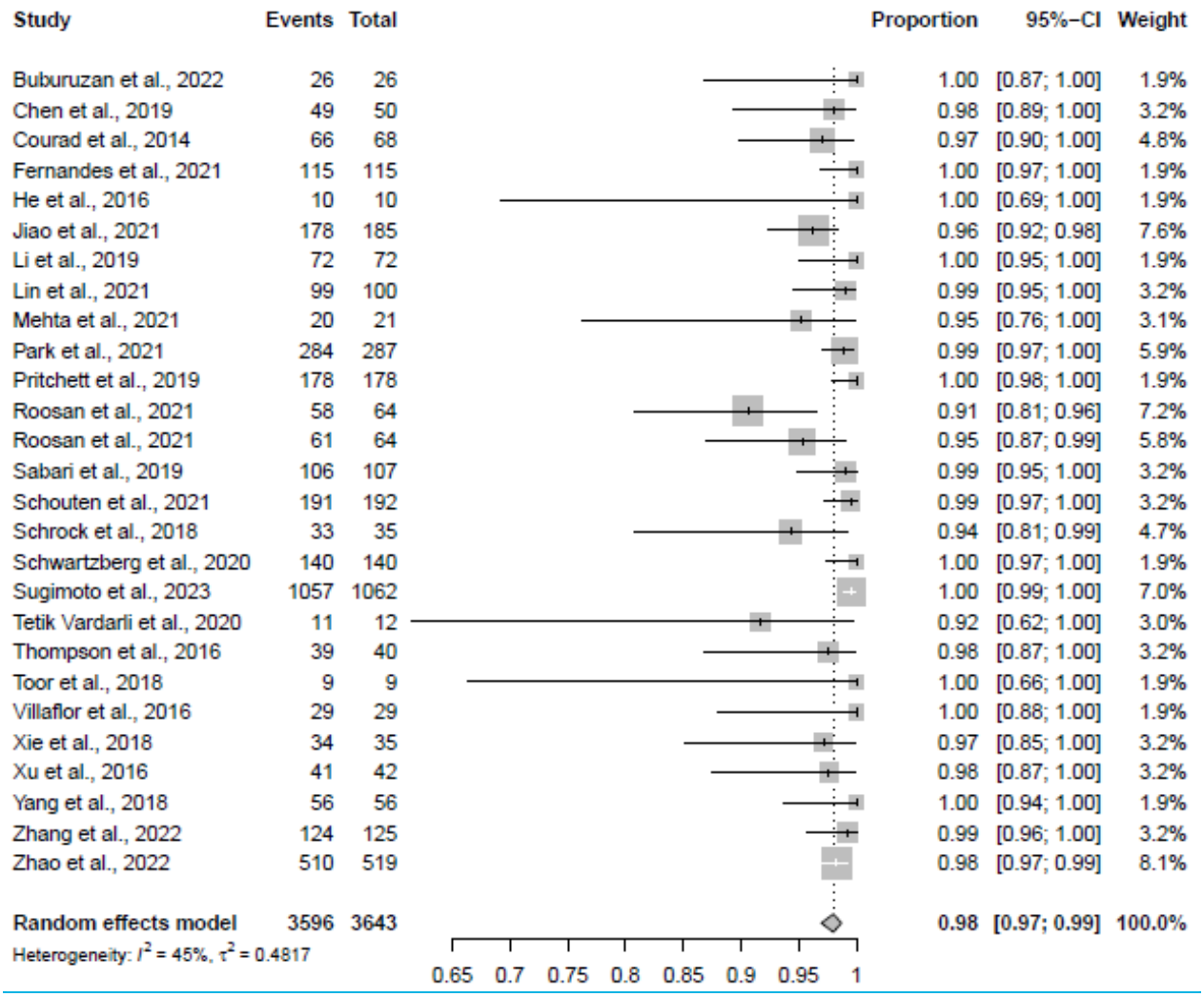

Figure A26: Overall Concordance Between Liquid Biopsy and Tissue Testing in Detecting *ERBB2* Actionable Alterations

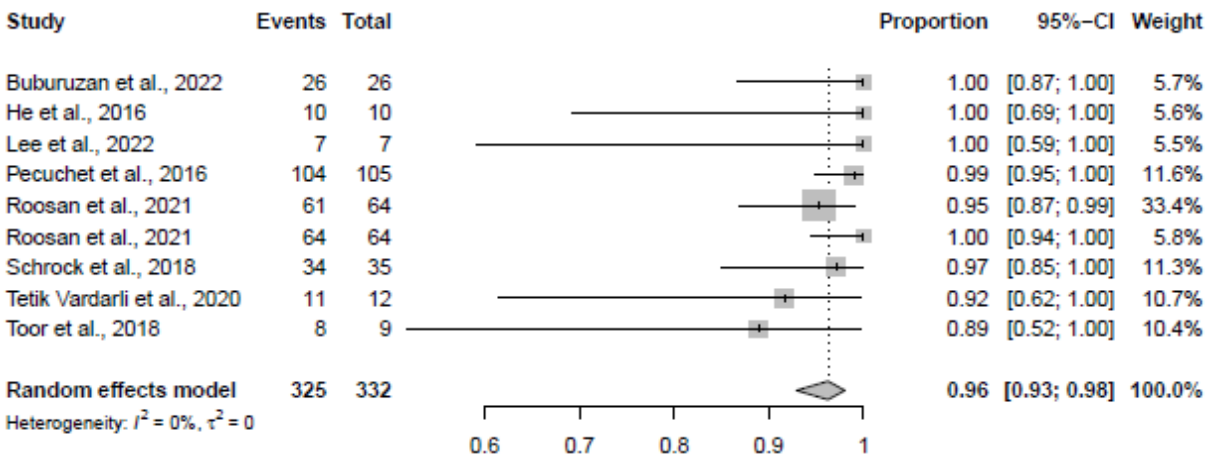

Figure A27: Overall Concordance Between Liquid Biopsy and Tissue Testing in Detecting *FGFR1* Actionable Alterations

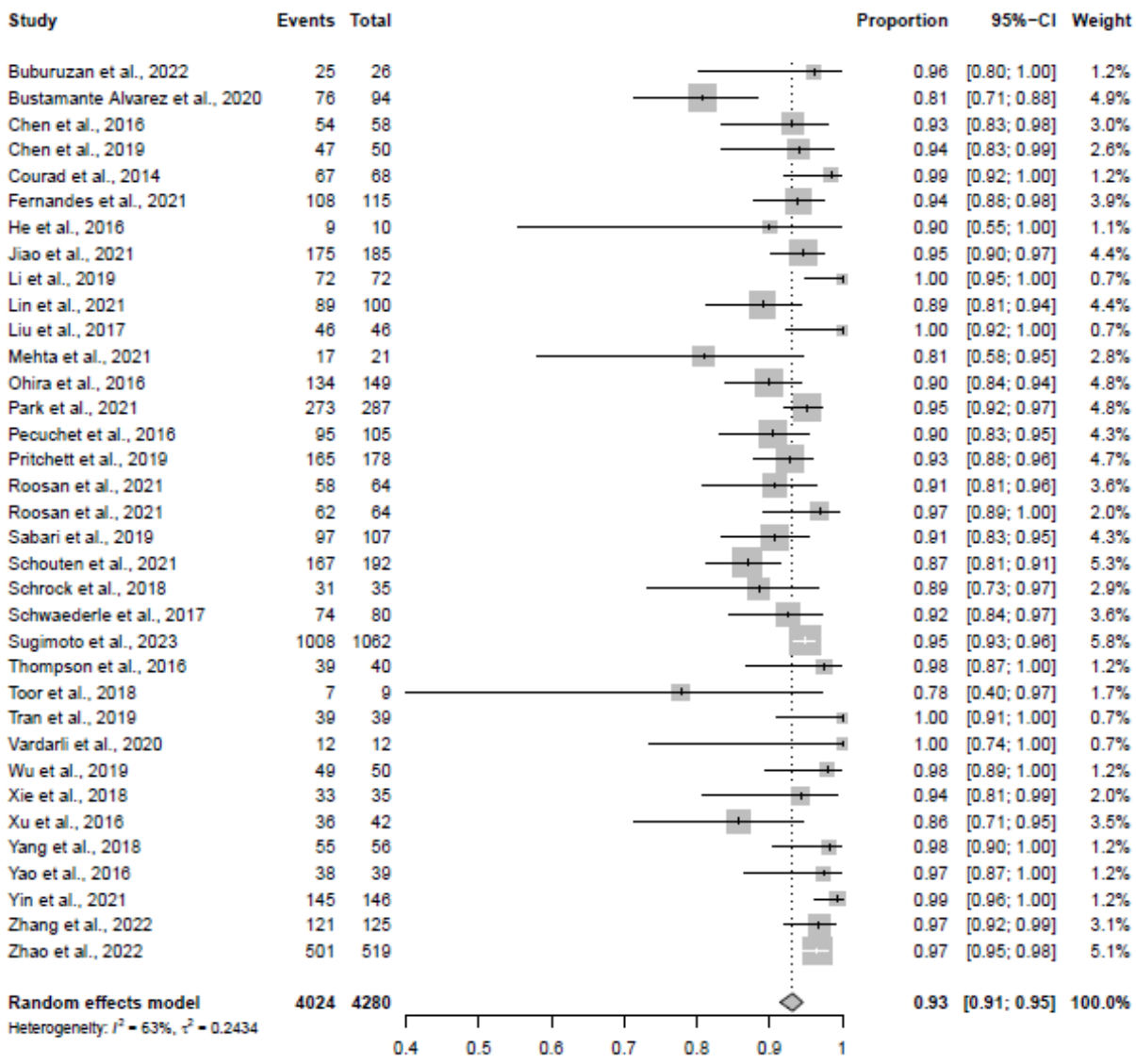

Figure A28: Overall Concordance Between Liquid Biopsy and Tissue Testing in Detecting *KRAS* Actionable Alterations

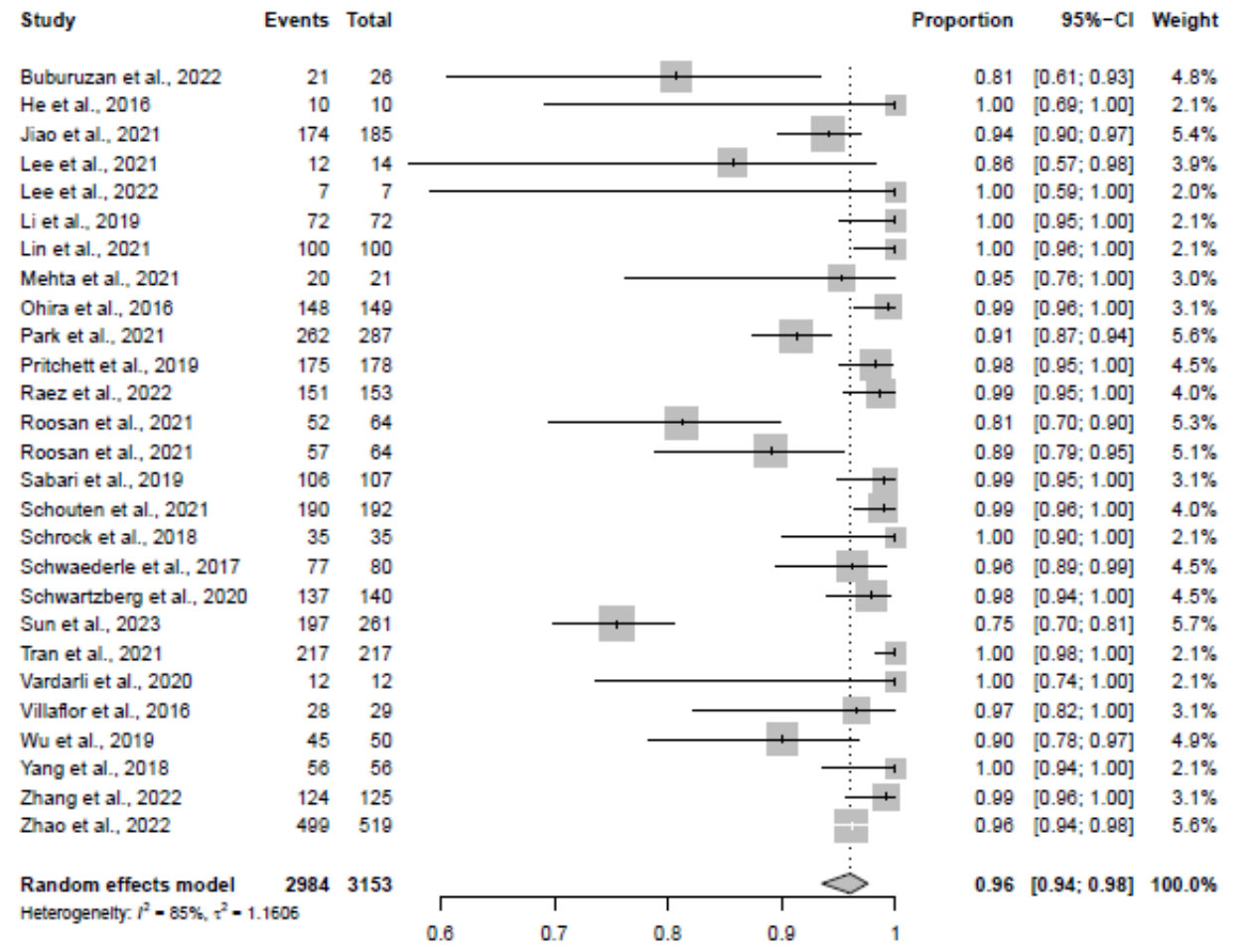

Figure A29: Overall Concordance Between Liquid Biopsy and Tissue Testing in Detecting *MET* Actionable Alterations

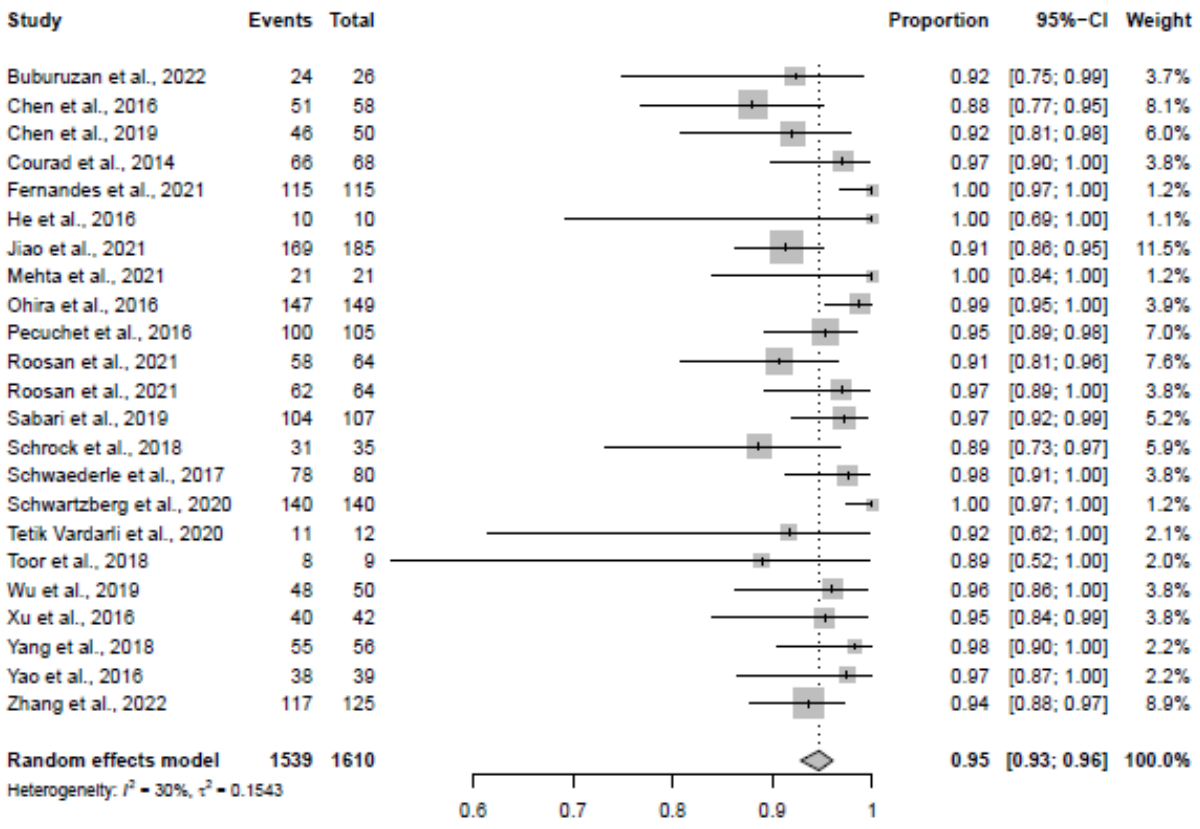

Figure A30: Overall Concordance Between Liquid Biopsy and Tissue Testing in Detecting *PIK3CA* Actionable Alterations

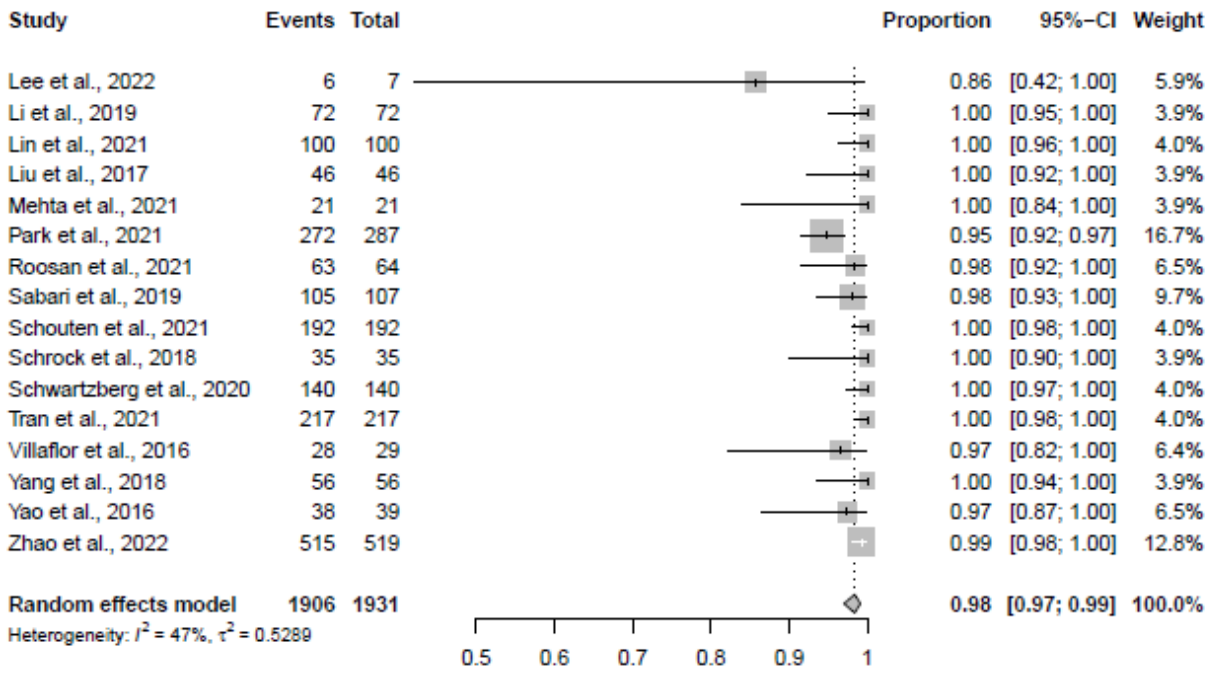

Figure A31: Overall Concordance Between Liquid Biopsy and Tissue Testing in Detecting *RET* Actionable Alterations

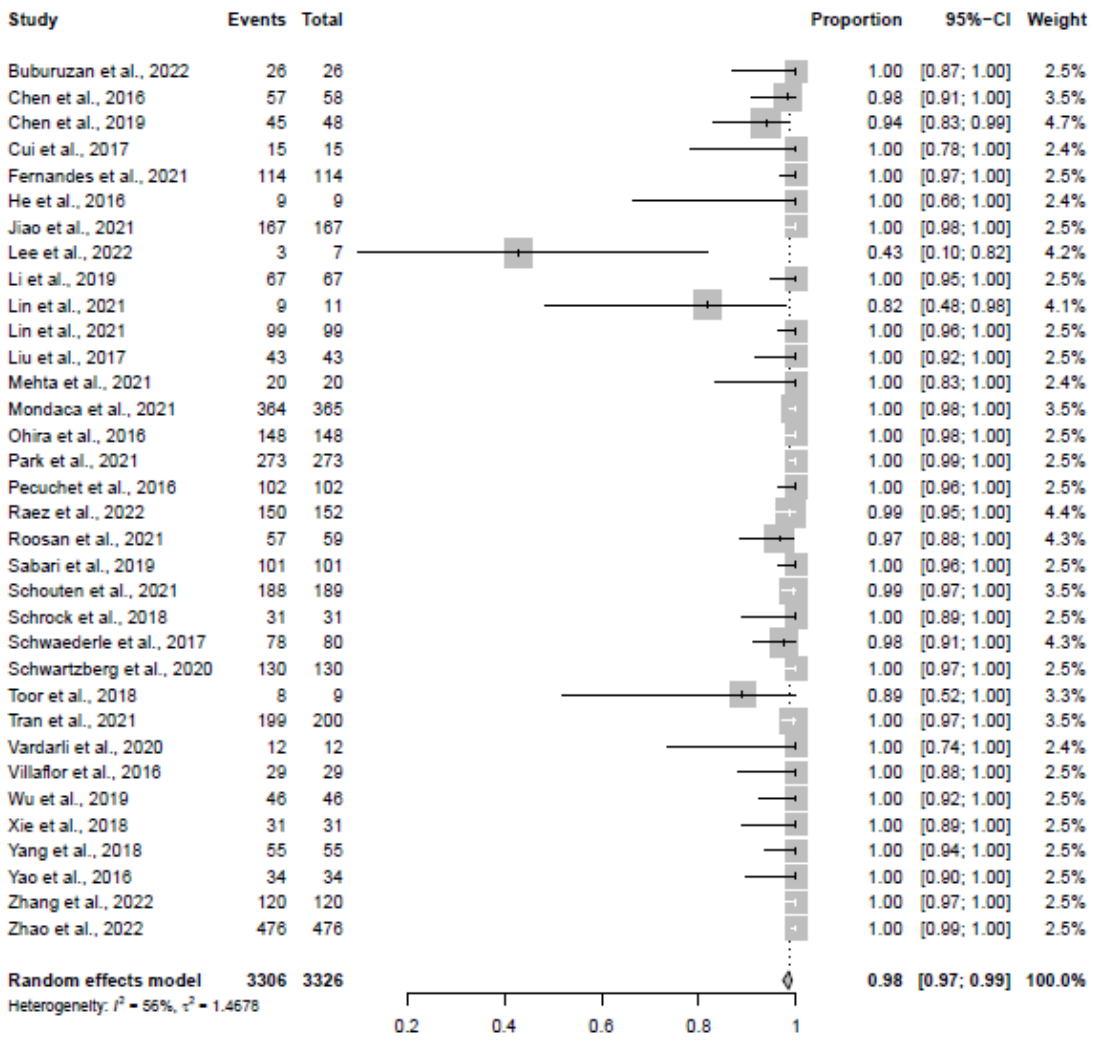

Figure A32: The Proportion of Individuals Testing Negative for Actionable *ALK* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

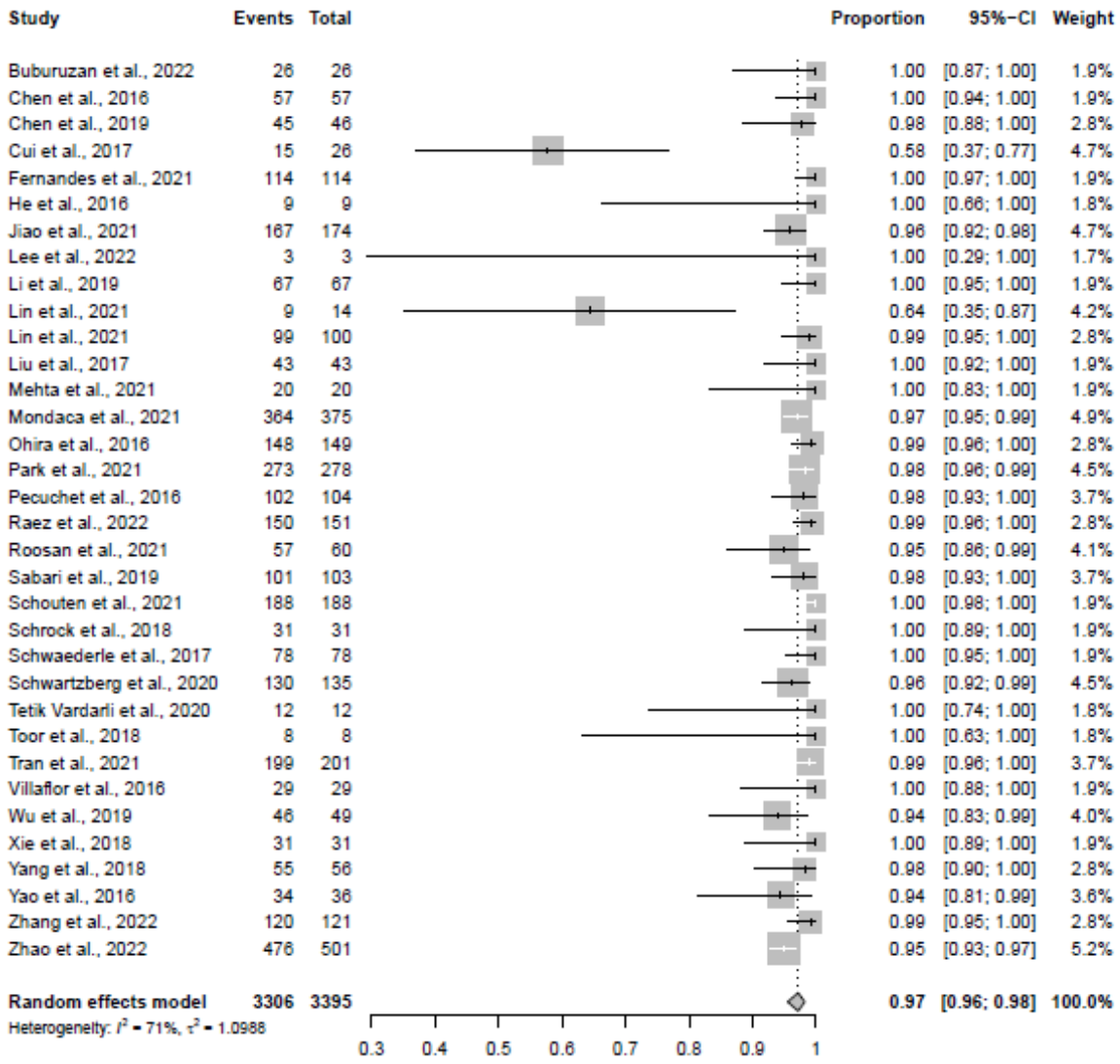

Figure A33: The Proportion of Individuals Testing Negative for Actionable *ALK* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by tissue among liquid negatives

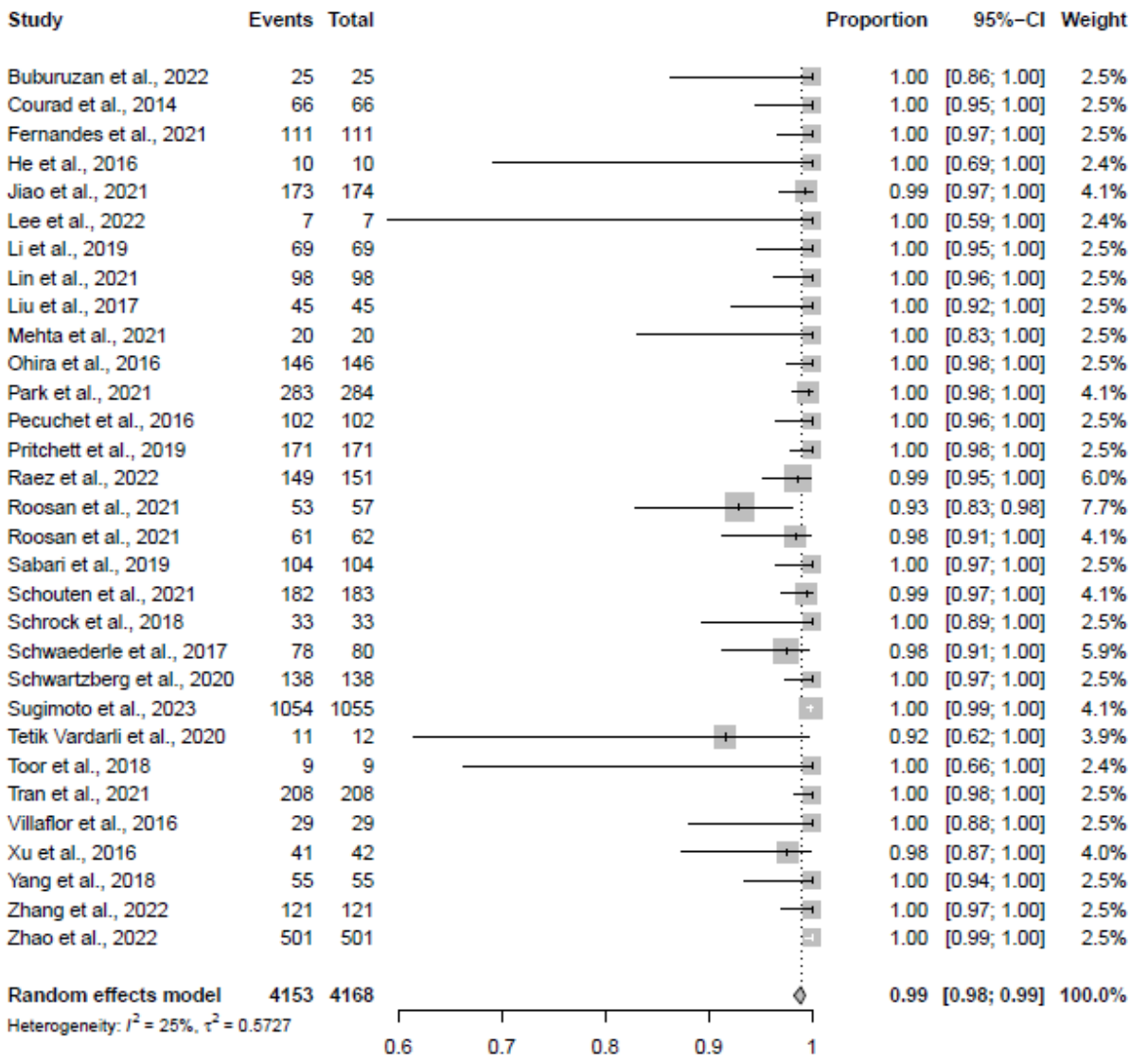

Figure A34: The Proportion of Individuals Testing Negative for Actionable *BRAF* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

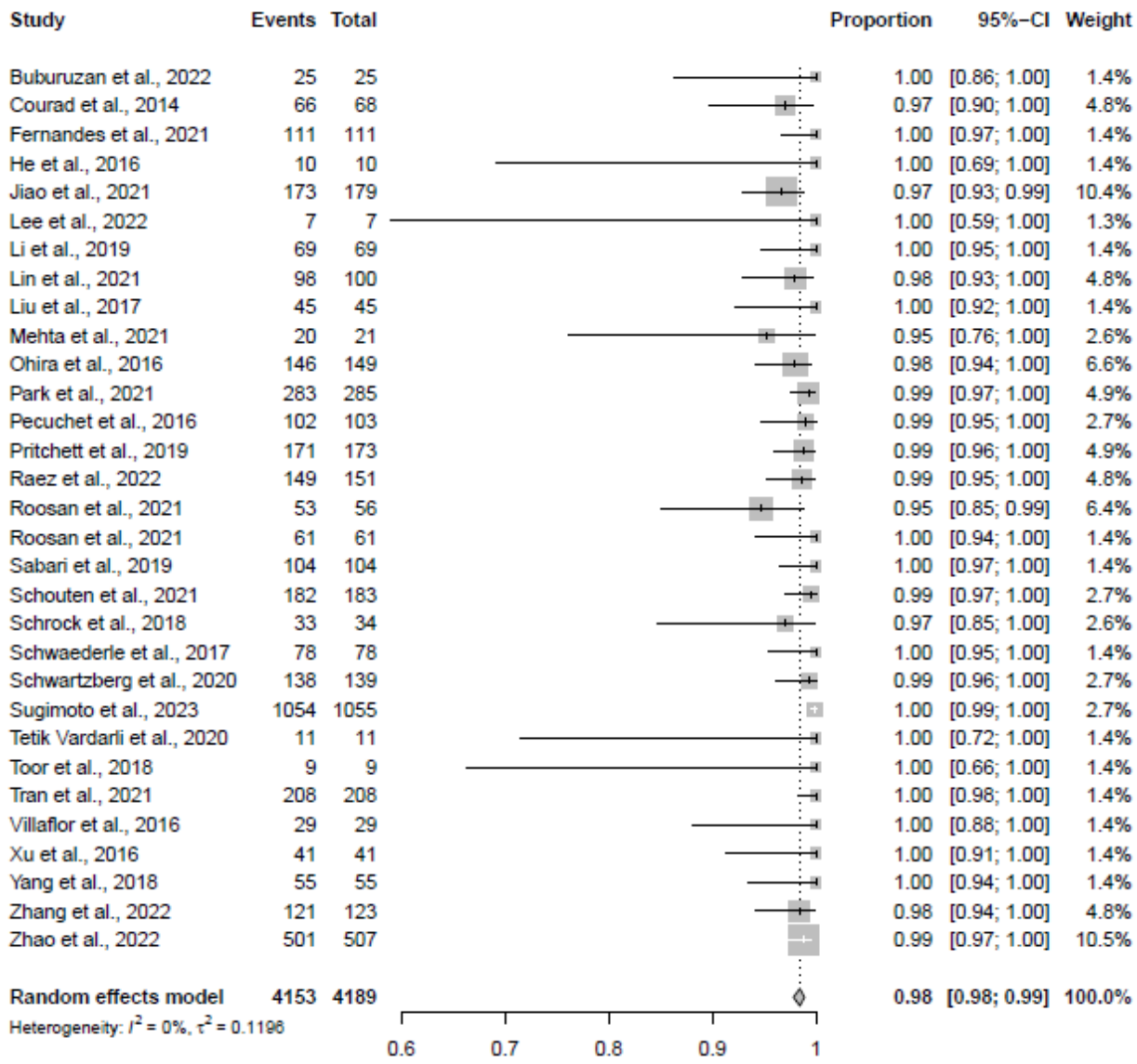

Figure A35: The Proportion of Individuals Testing Negative for Actionable *BRAF* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by tissue among liquid negatives

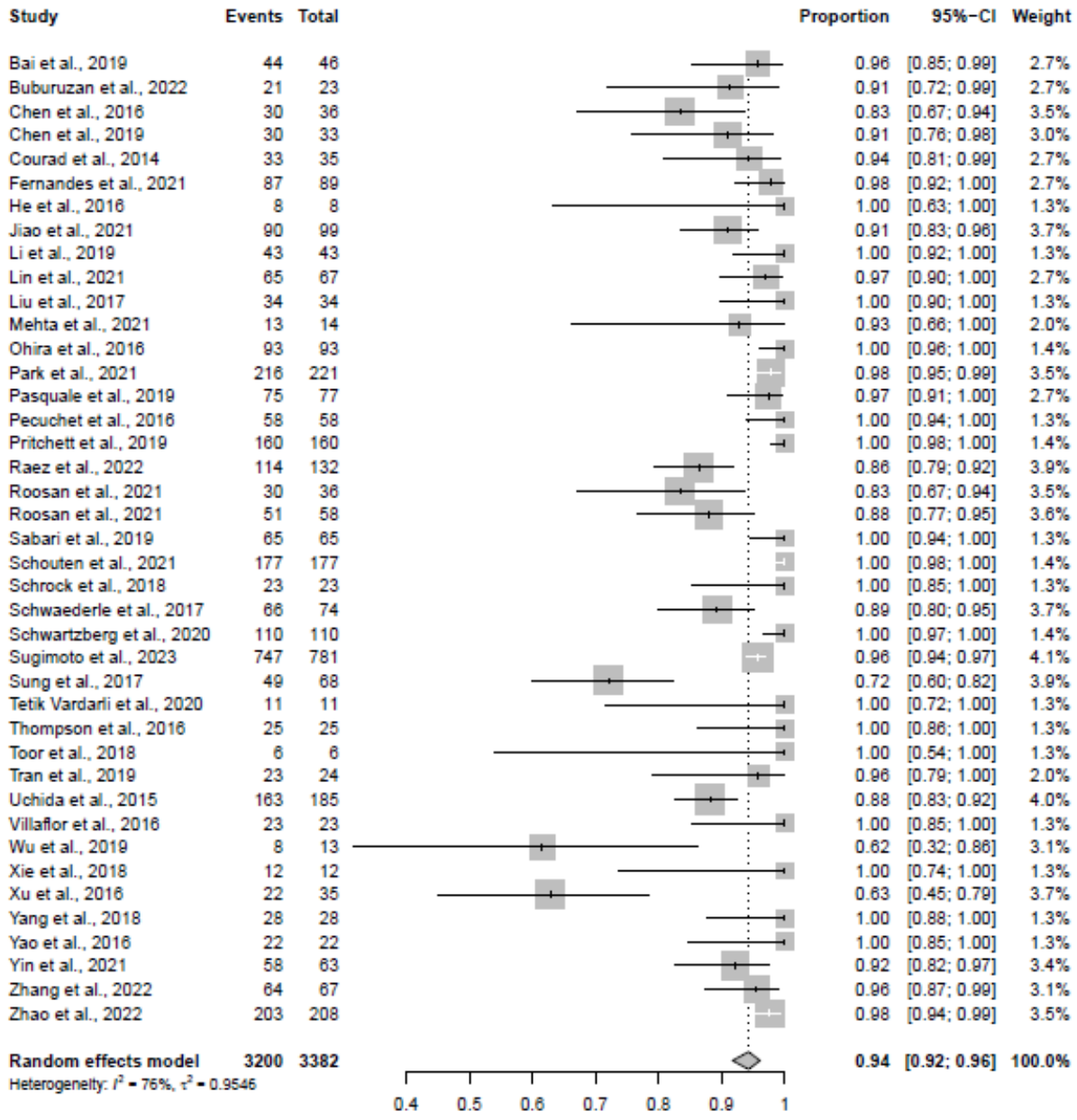

Figure A36: The Proportion of Individuals Testing Negative for Actionable *EGFR* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

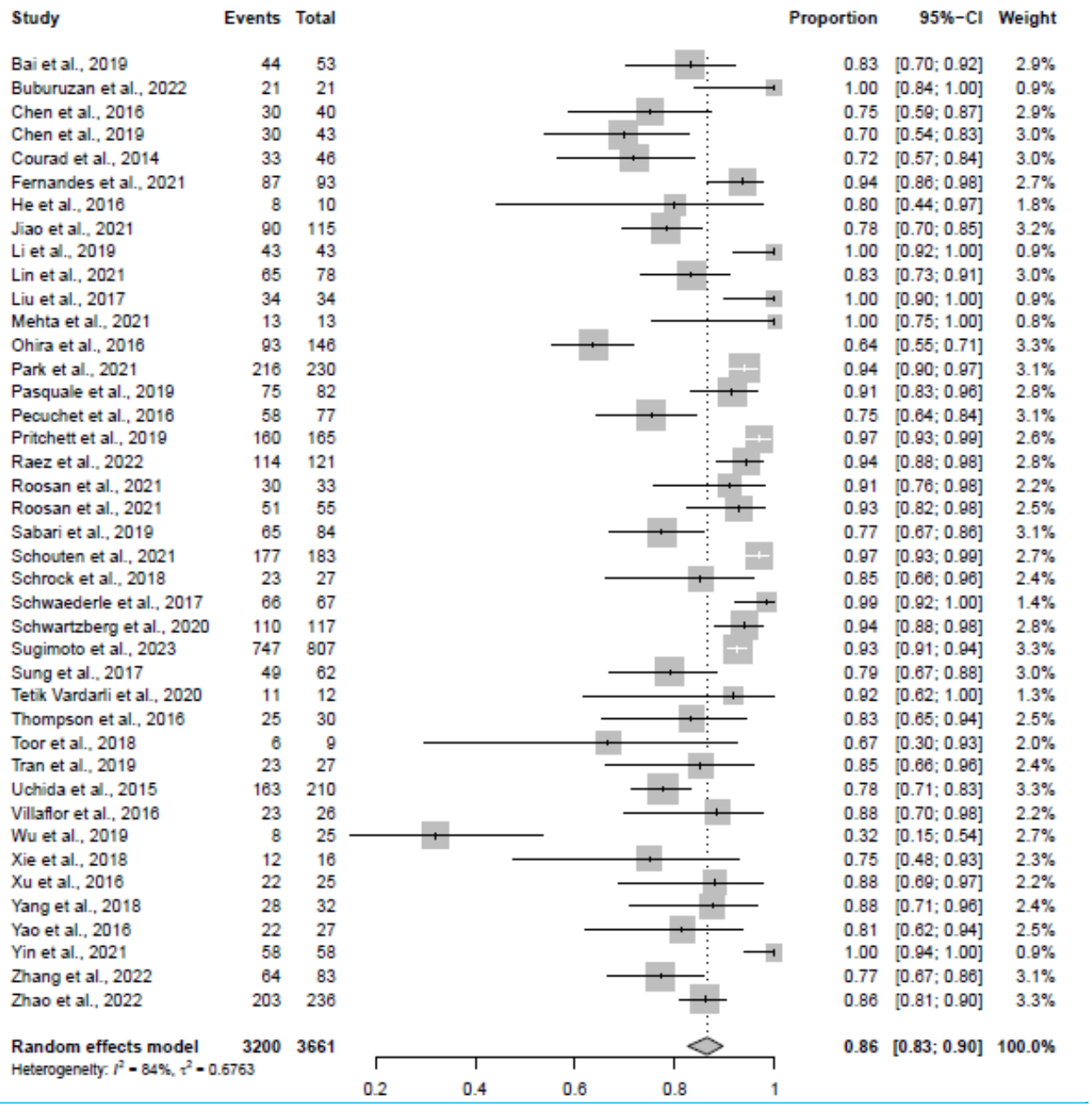

Figure A37: The Proportion of Individuals Testing Negative for Actionable *EGFR* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by tissue among liquid negatives

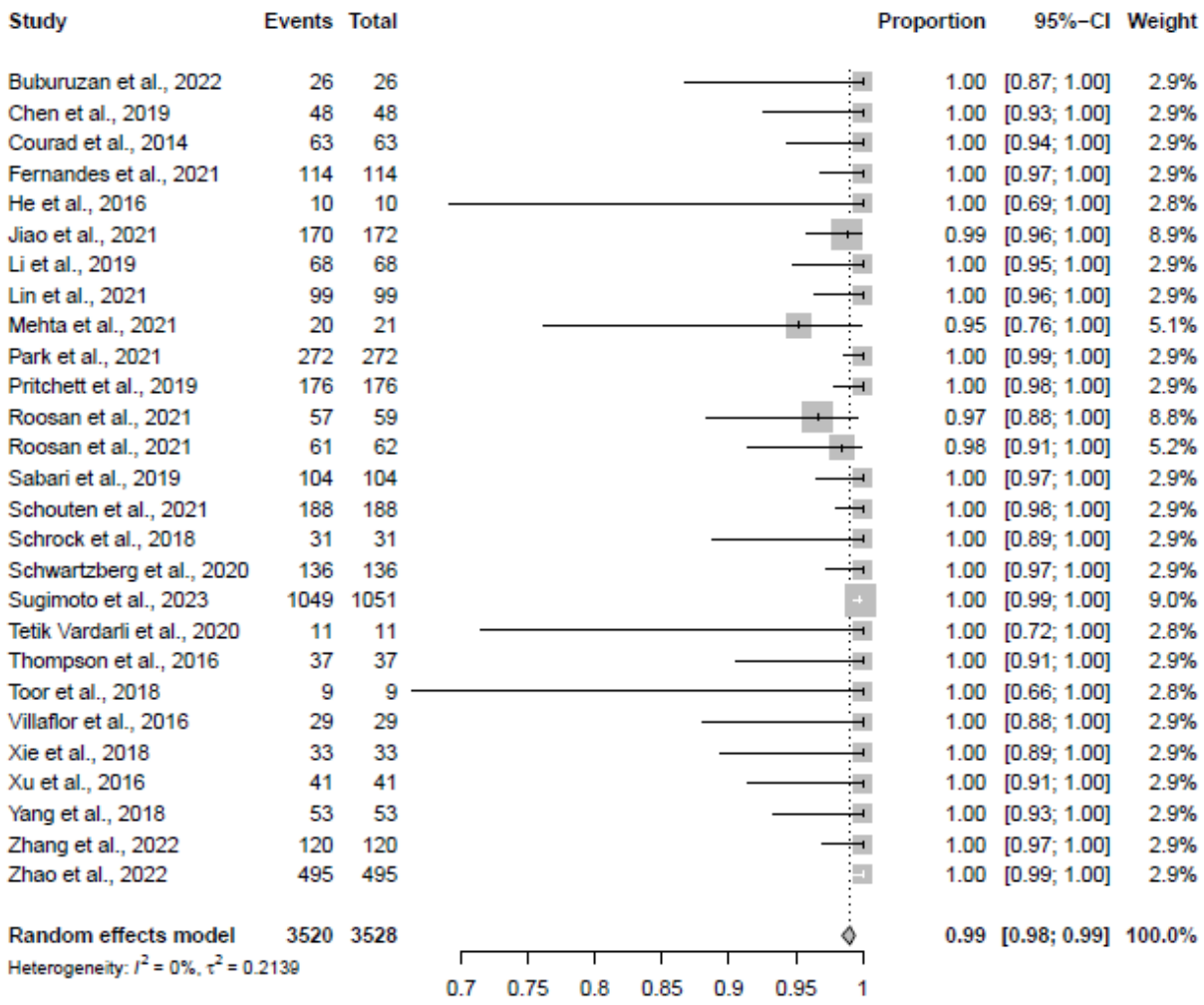

Figure A38: The Proportion of Individuals Testing Negative for Actionable *ERBB2* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

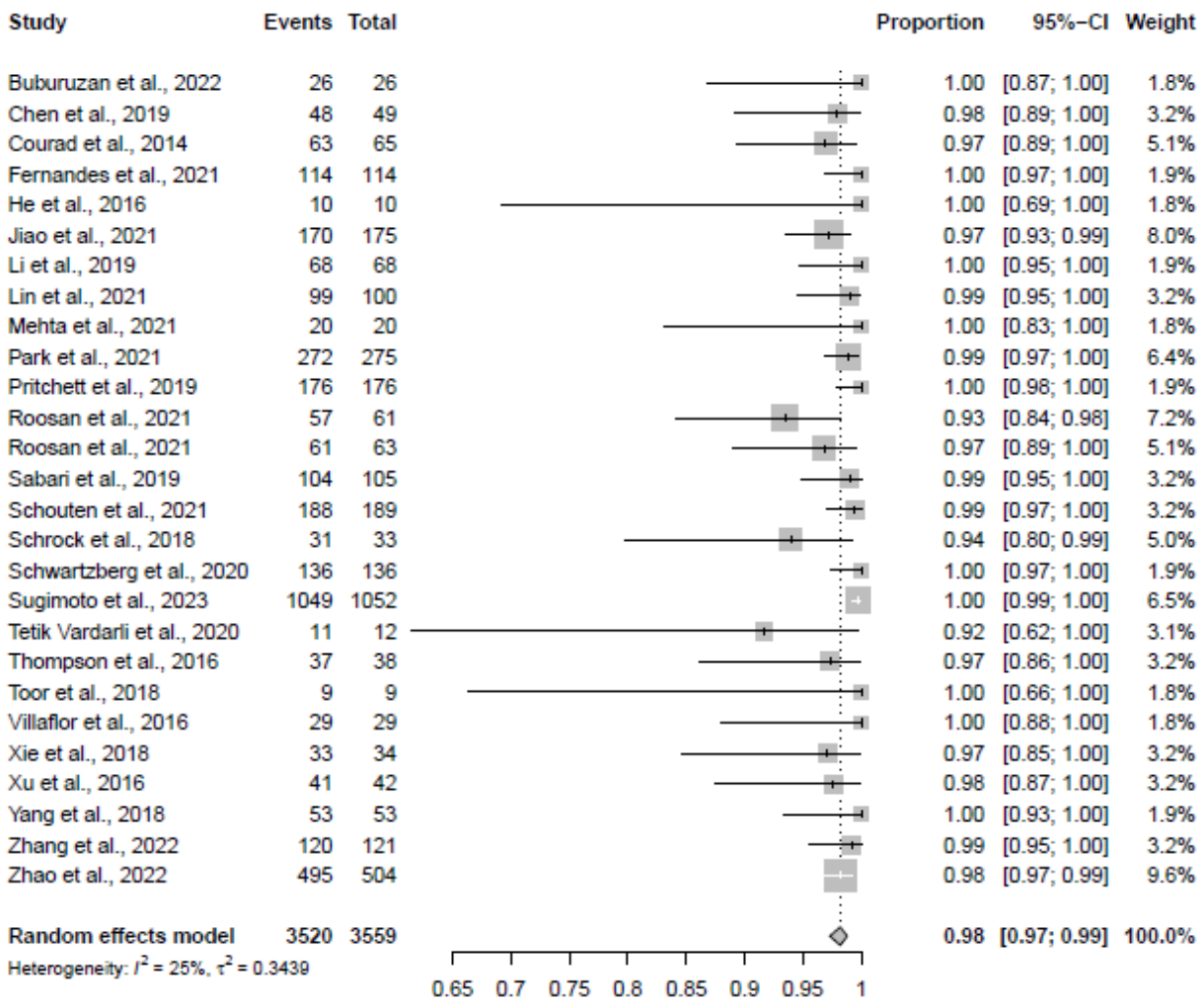

Figure A39: The Proportion of Individuals Testing Negative for Actionable *ERBB2* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

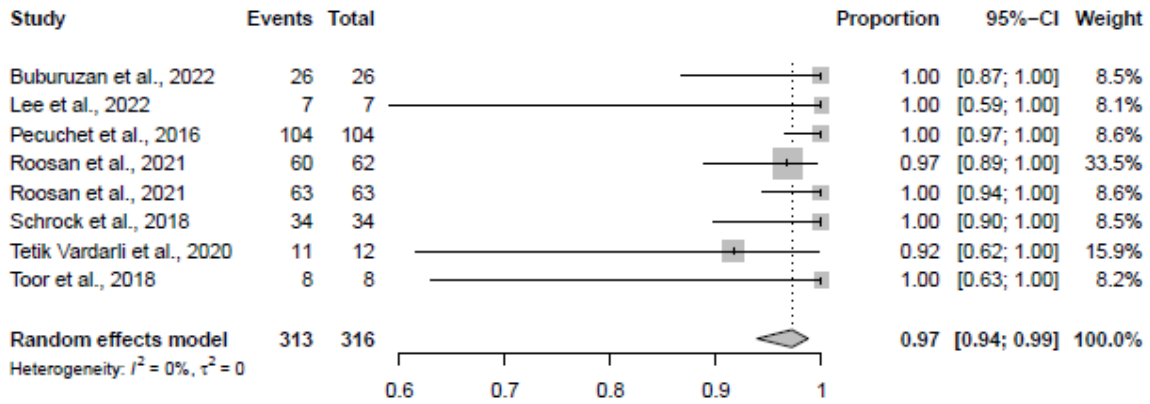

Figure A40: The Proportion of Individuals Testing Negative for Actionable *FGFR1* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

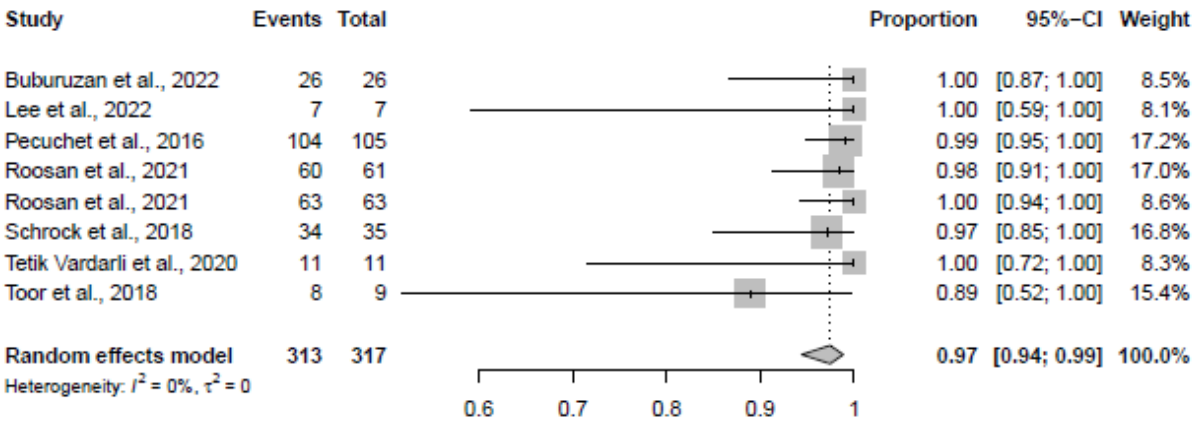

Figure A41: The Proportion of Individuals Testing Negative for Actionable *FGFR1* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by tissue among liquid negatives

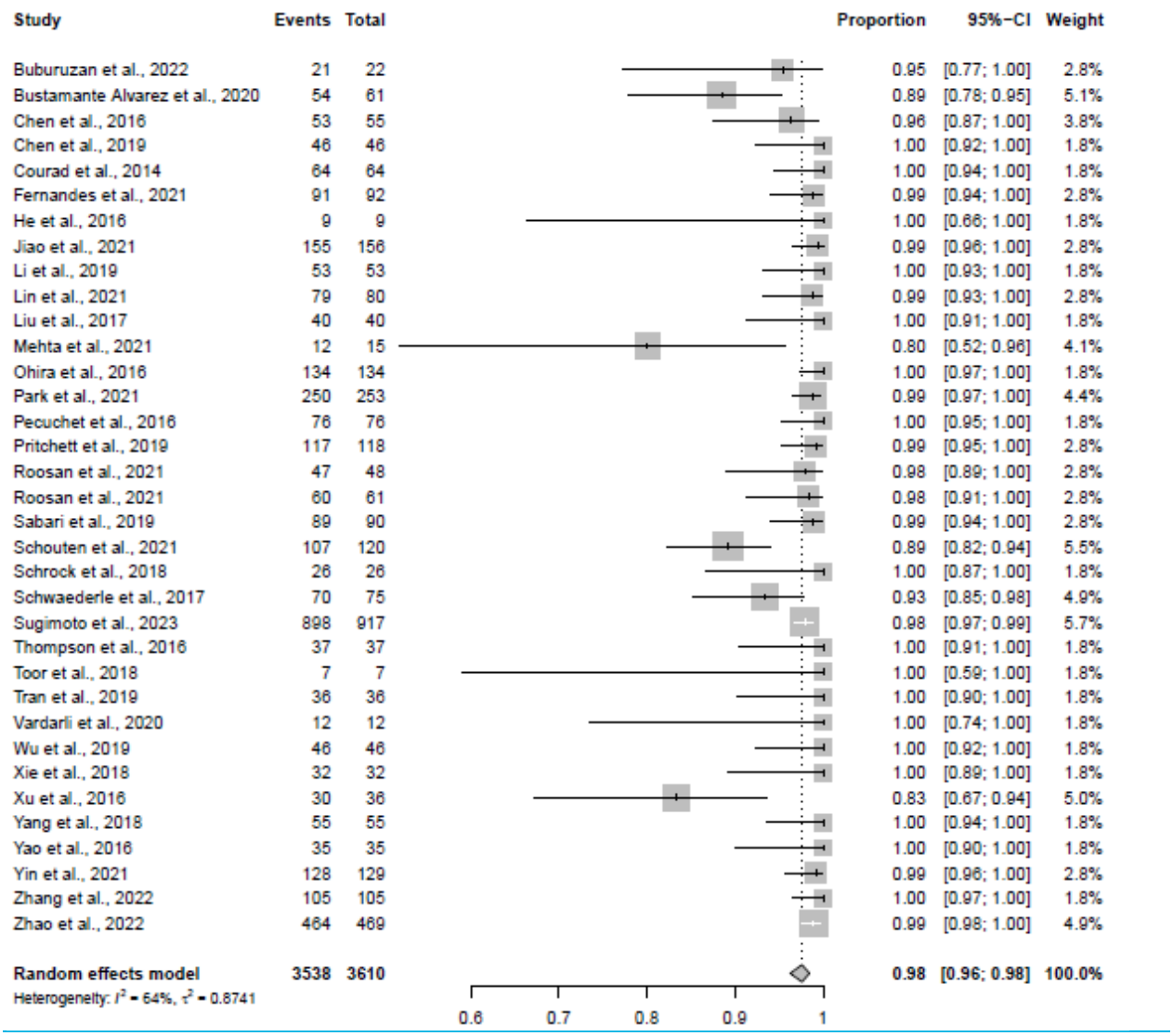

Figure A42: The Proportion of Individuals Testing Negative for Actionable *KRAS* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

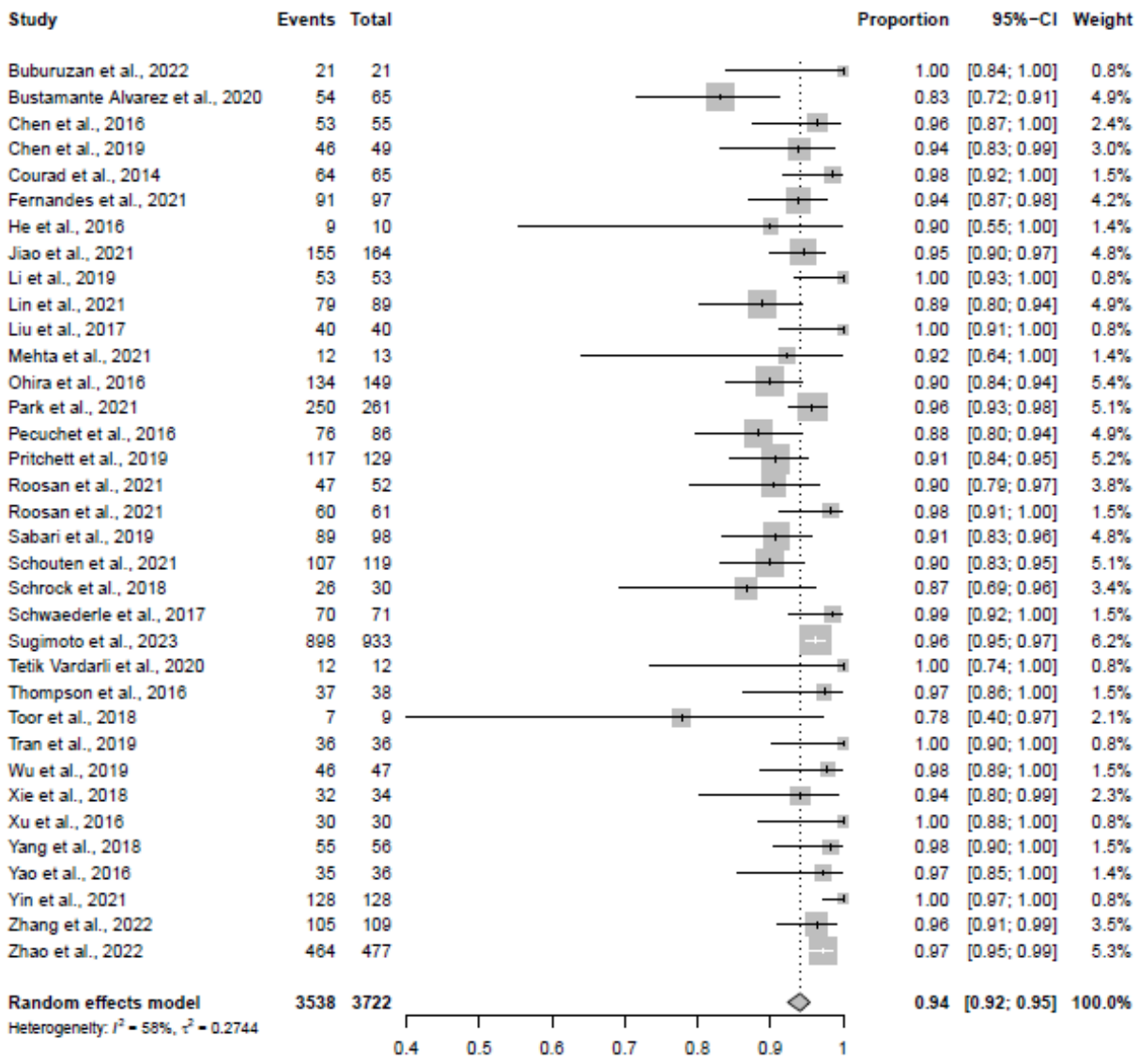

Figure A43: The Proportion of Individuals Testing Negative for Actionable *KRAS* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

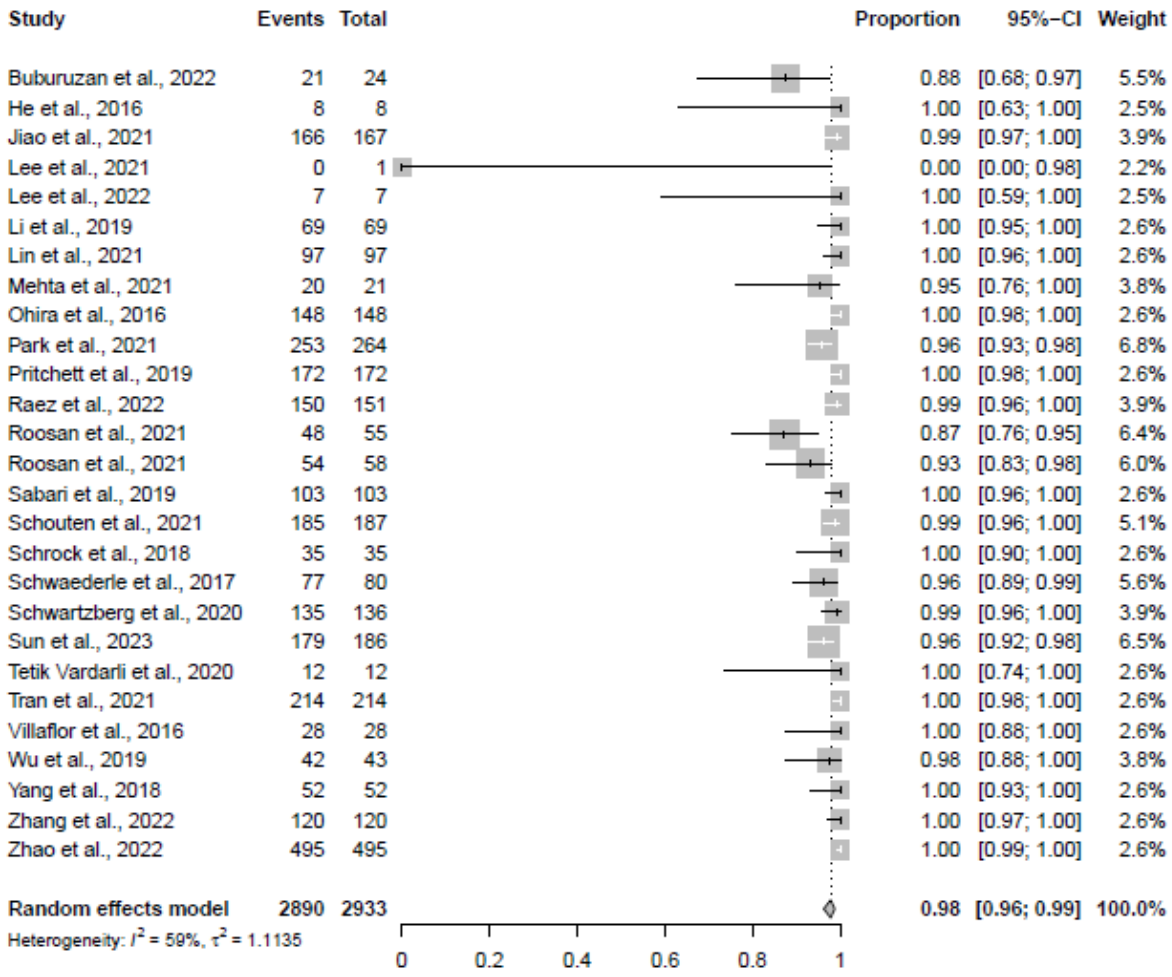

Figure A44: The Proportion of Individuals Testing Negative for Actionable *MET* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

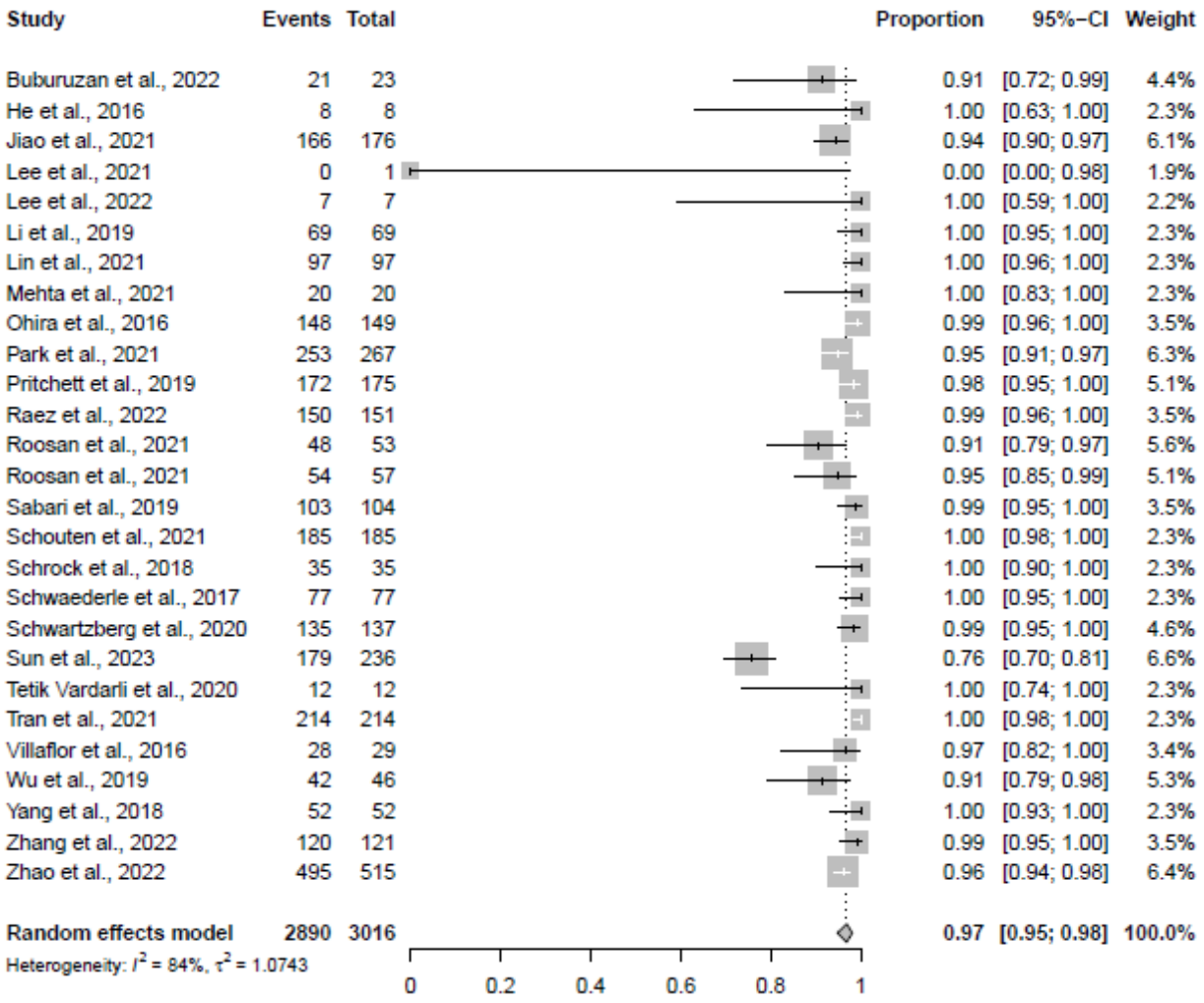

Figure A45: The Proportion of Individuals Testing Negative for Actionable *MET* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by tissue among liquid negatives

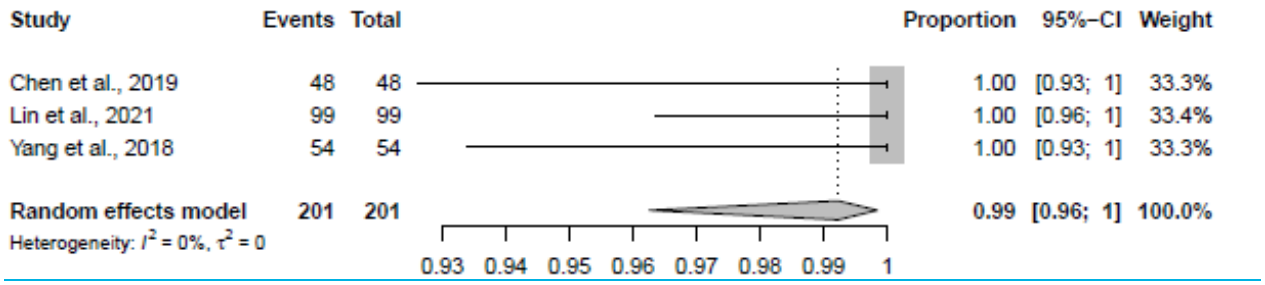

Figure A46: The Proportion of Individuals Testing Negative for Actionable *NTRK1* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

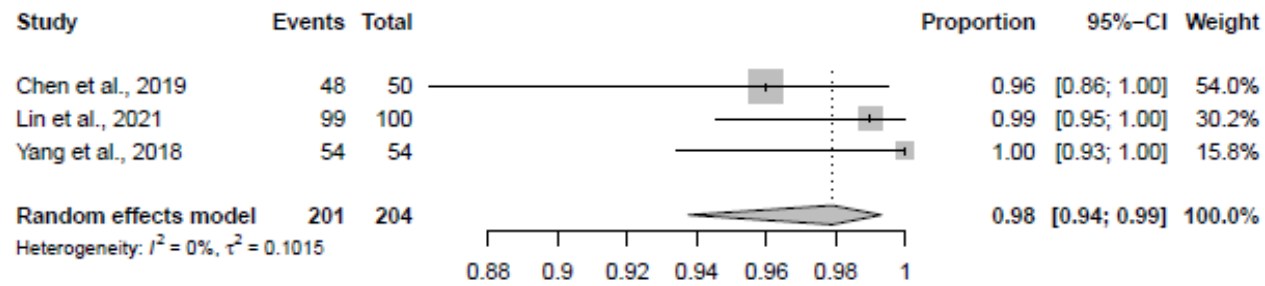

Figure A47: The Proportion of Individuals Testing Negative for Actionable *NTRK1* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by tissue among liquid negatives

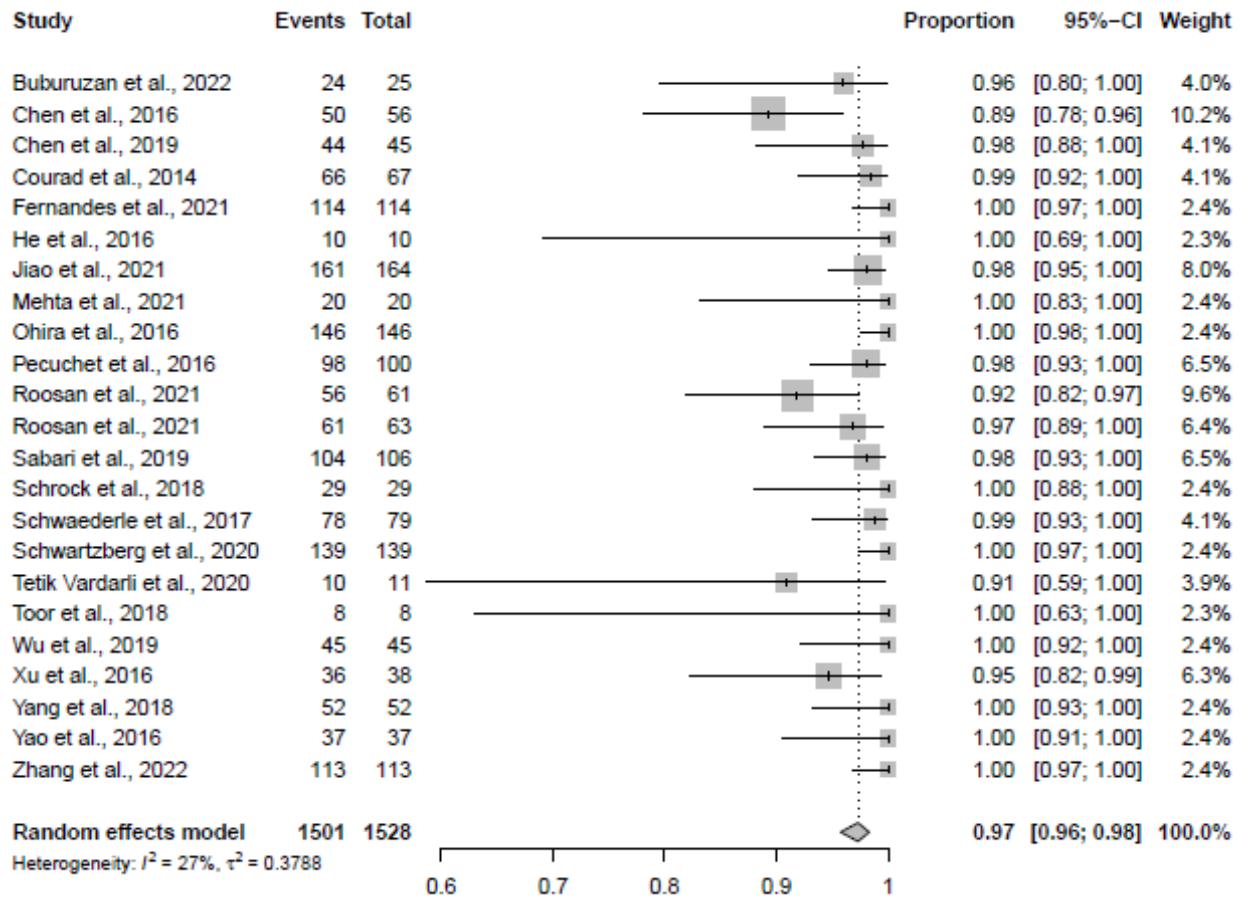

Figure A48: The Proportion of Individuals Testing Negative for Actionable *PIK3CA* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

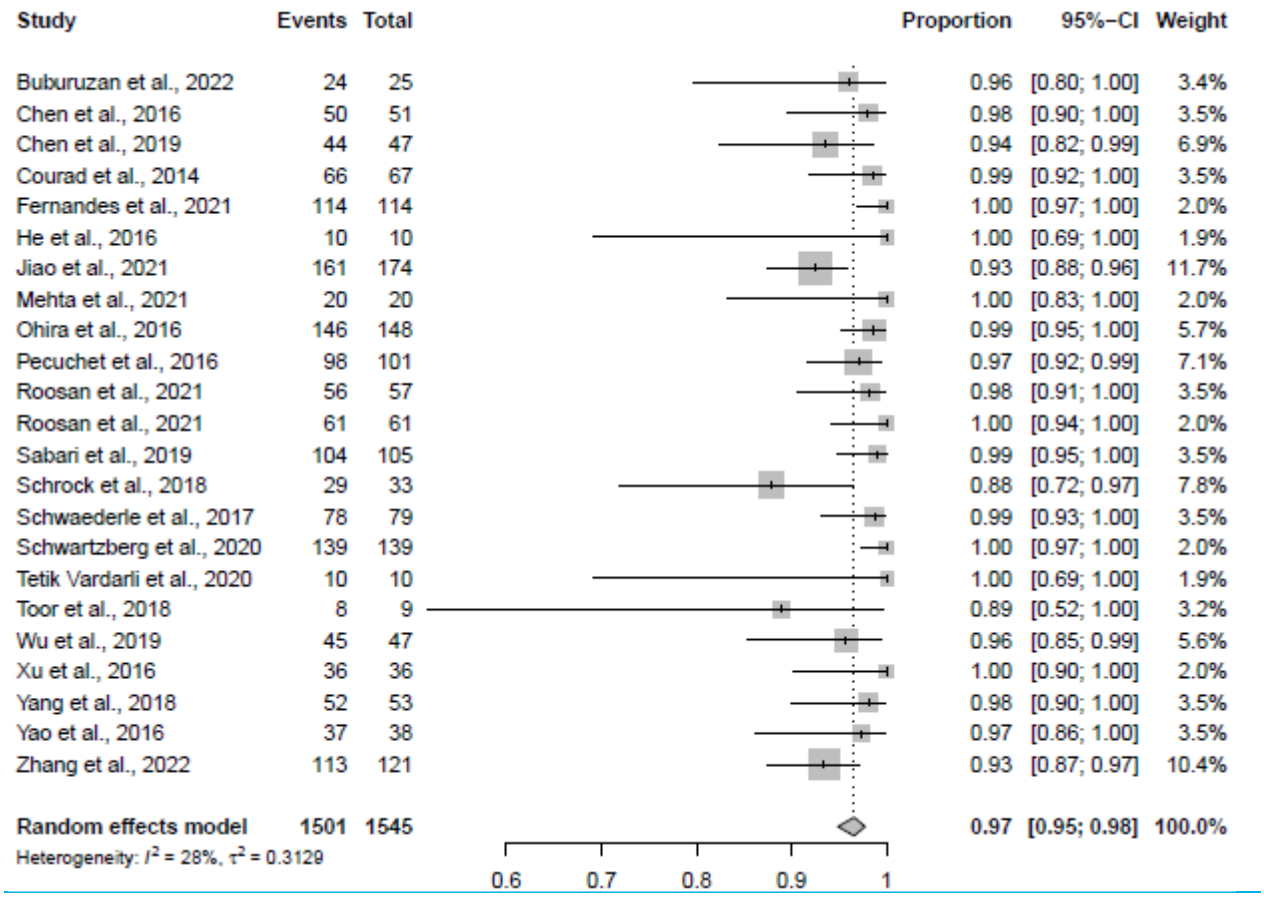

Figure A49: The Proportion of Individuals Testing Negative for Actionable *PIK3CA* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by tissue among liquid negatives

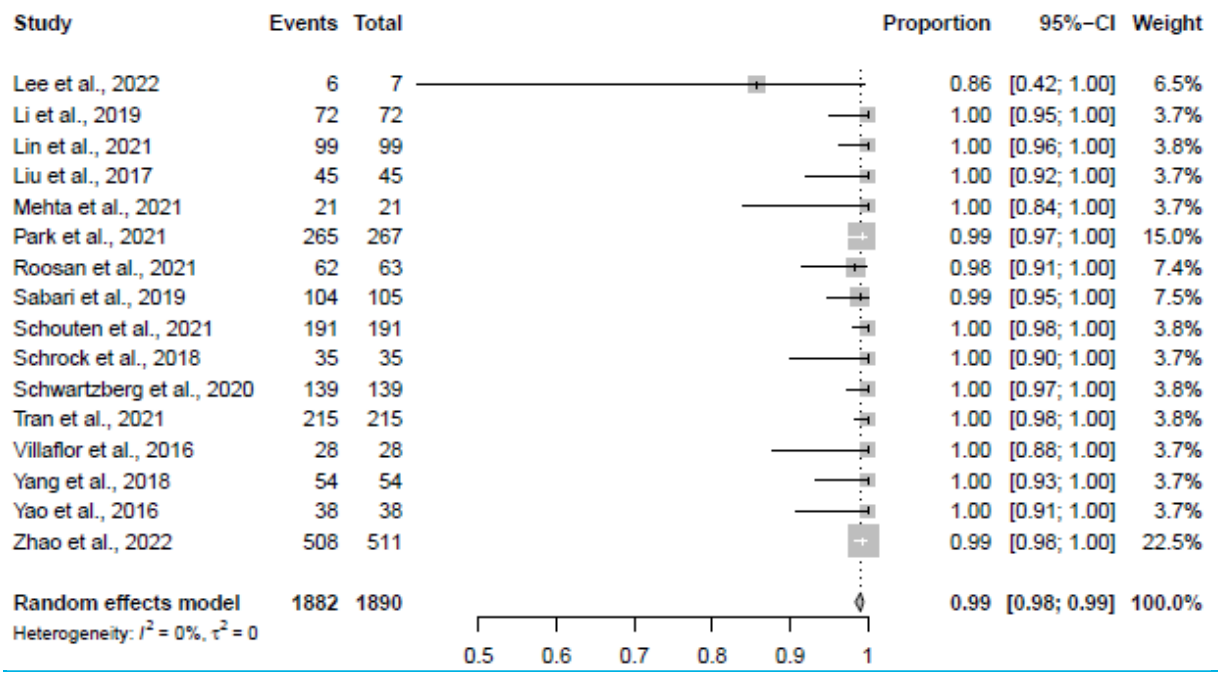

Figure A50: The Proportion of Individuals Testing Negative for Actionable *RET* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

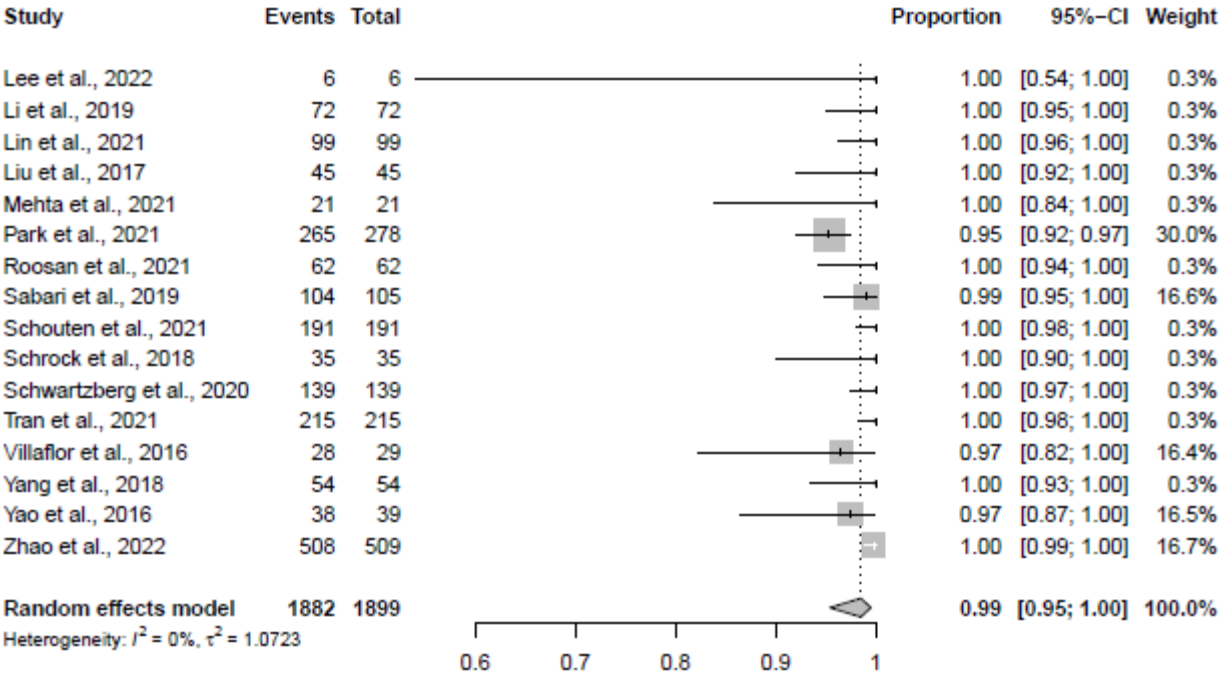

Figure A51: The Proportion of Individuals Testing Negative for Actionable *RET* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

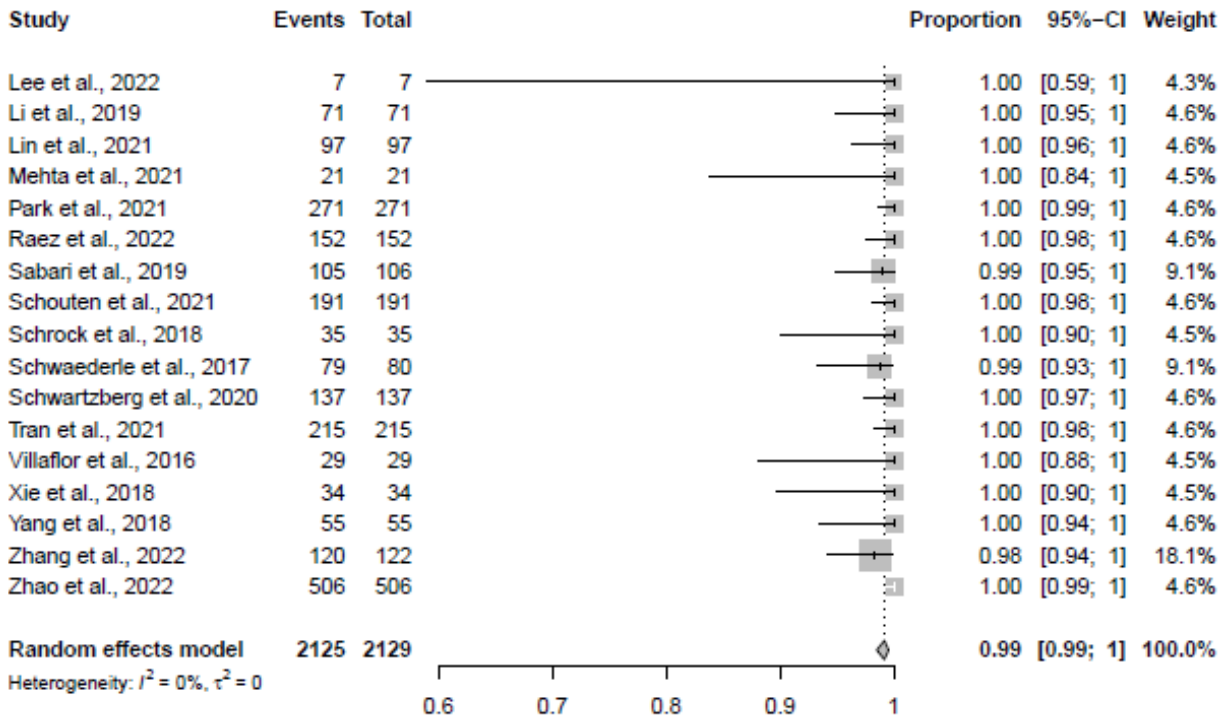

Figure A52: The Proportion of Individuals Testing Negative for Actionable *ROS1* Alterations Using Liquid Biopsy Among Those Testing Negative Using Tissue

Note: subtracting this proportion from 1, one gets the proportion testing positive by liquid among tissue negatives

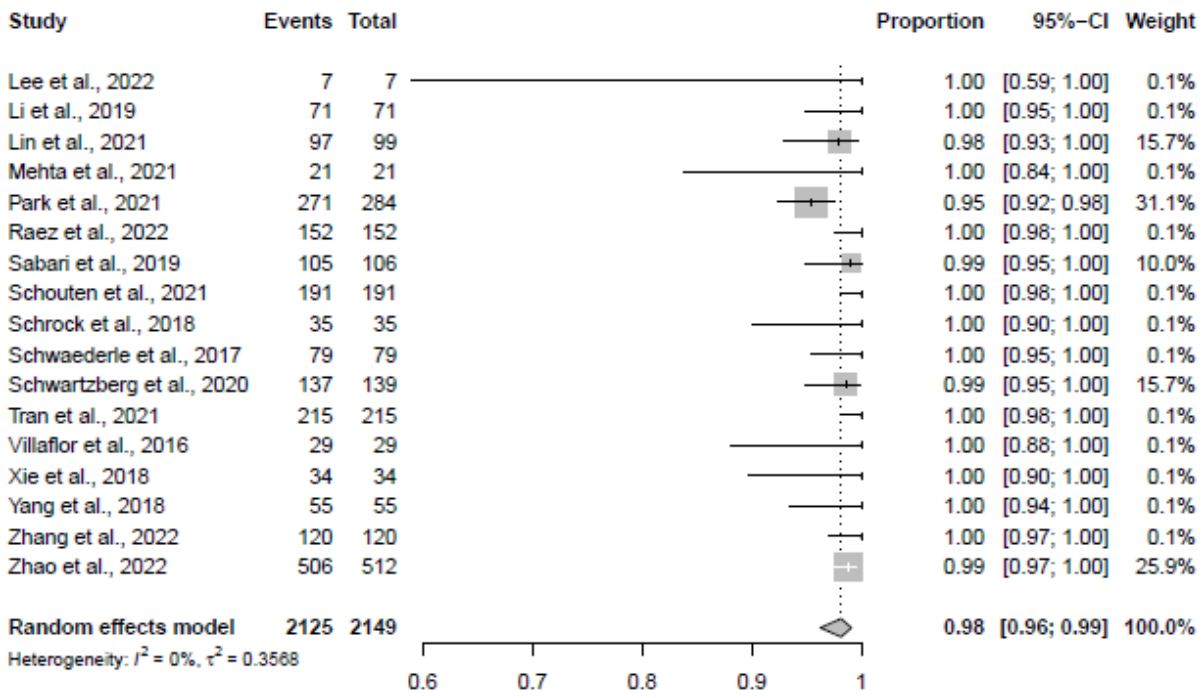

Figure A53: The Proportion of Individuals Testing Negative for Actionable *ROS1* Alterations Using Tissue Biopsy Among Those Testing Negative Using Liquid

Note: subtracting this proportion from 1, one gets the proportion testing positive by tissue among liquid negatives

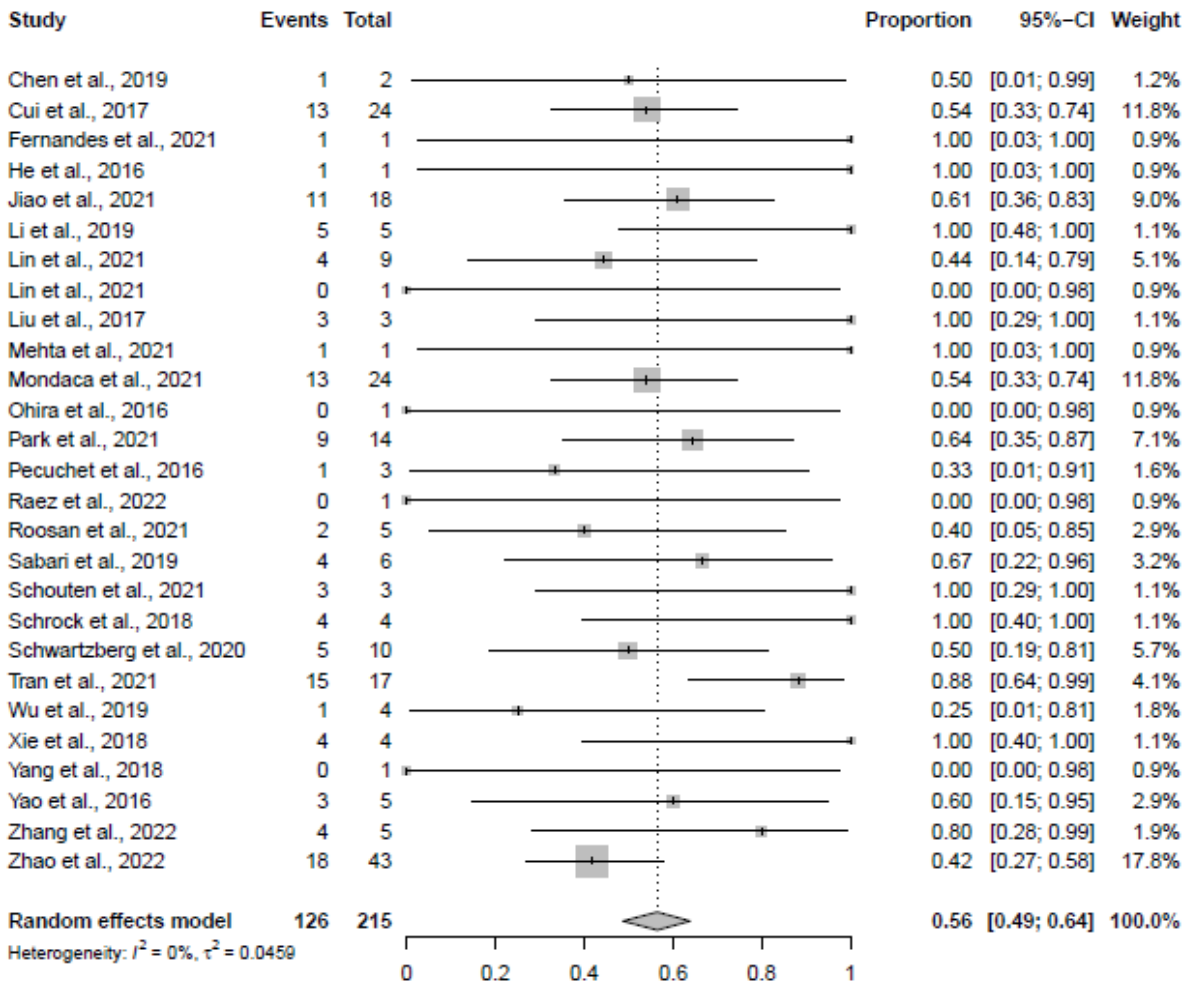

Figure A54: The Proportion of Individuals Testing Positive for Actionable *ALK* Alterations Using Liquid Biopsy Among Those Testing Positive Using Tissue

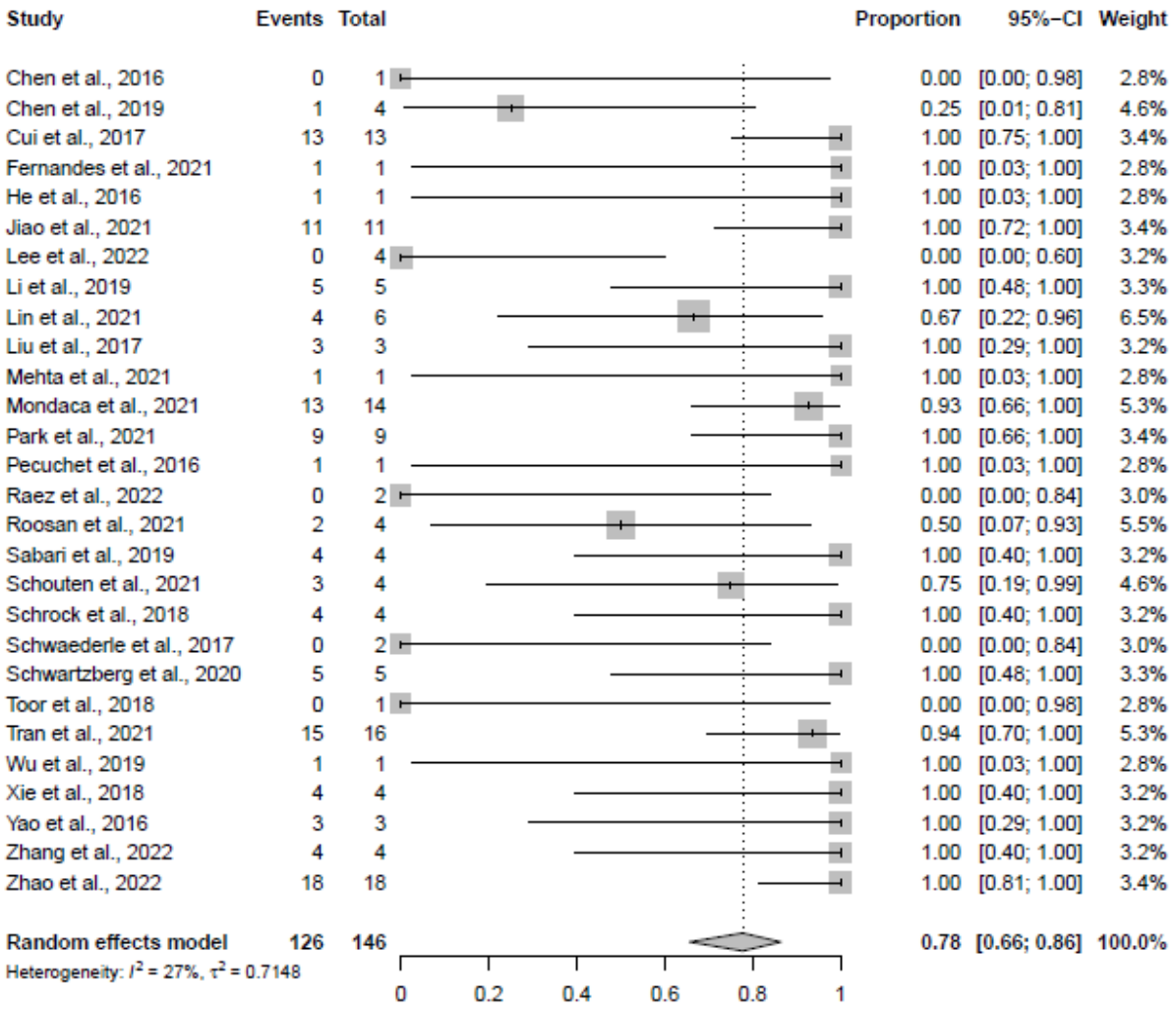

Figure A55: The Proportion of Individuals Testing Positive for Actionable *ALK* Alterations Using Tissue Biopsy Among Those Testing Positive Using Liquid

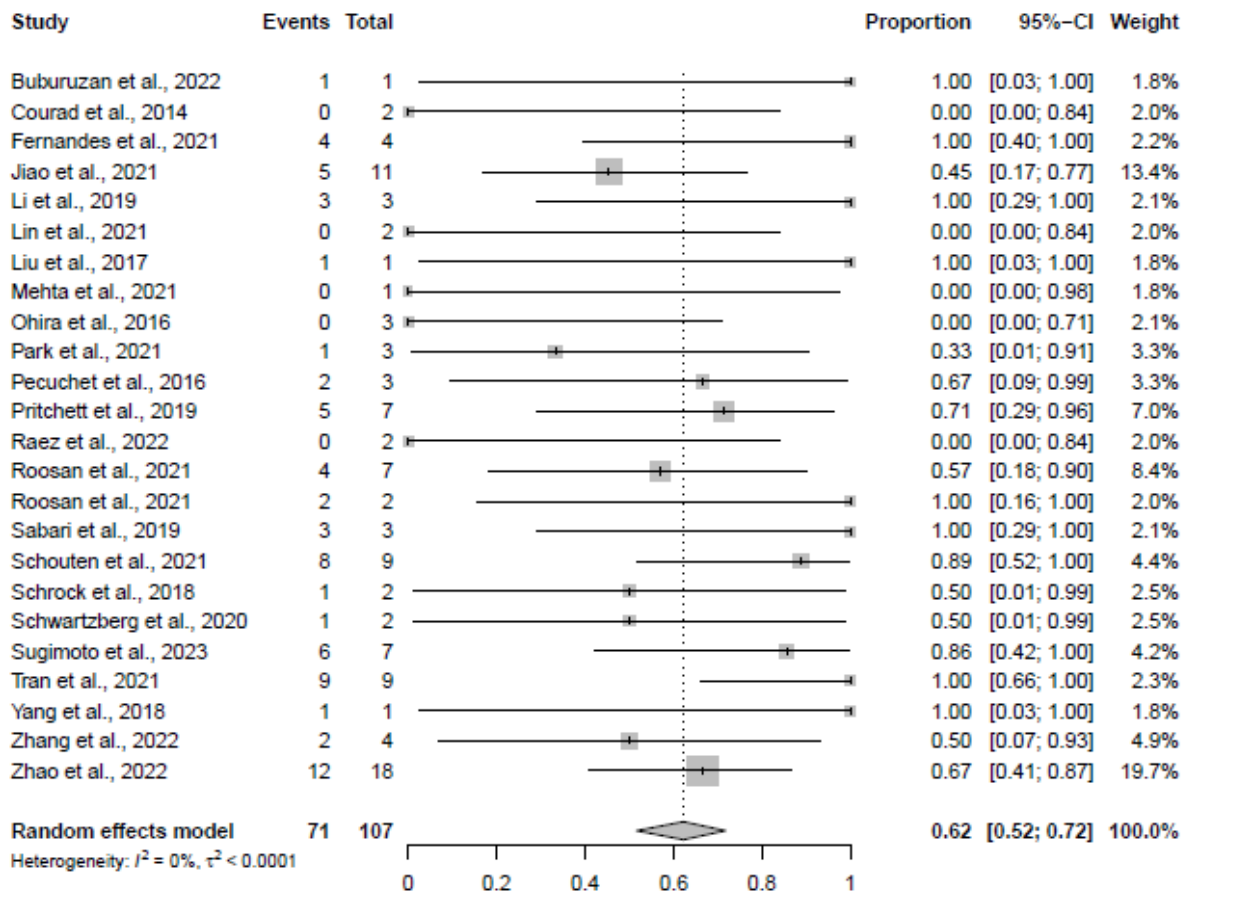

Figure A56: The Proportion of Individuals Testing Positive for Actionable *BRAF* Alterations Using Liquid Biopsy Among Those Testing Positive Using Tissue

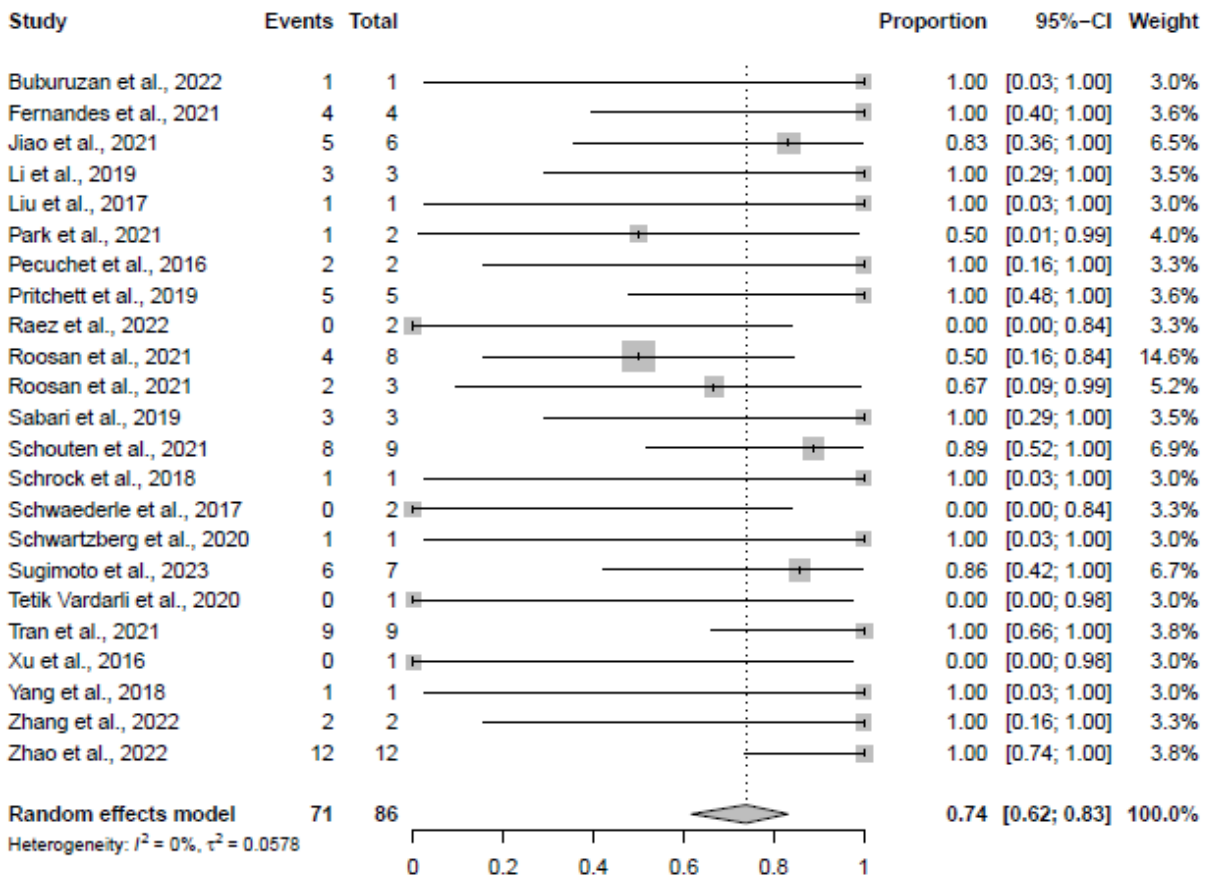

Figure A57: The Proportion of Individuals Testing Positive for Actionable *BRAF* Alterations Using Tissue Biopsy Among Those Testing Positive Using Liquid

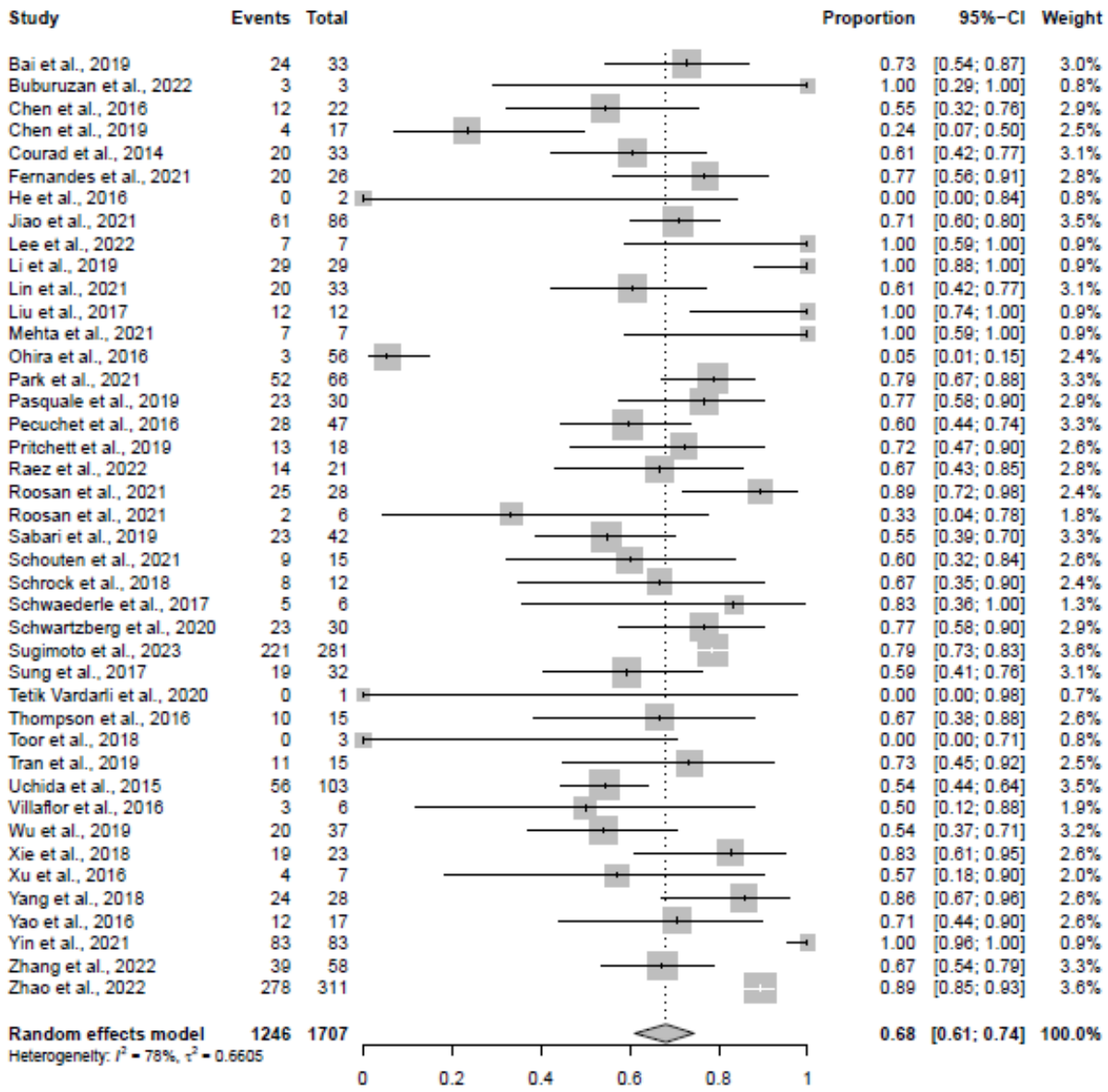

Figure A58: The Proportion of Individuals Testing Positive for Actionable *EGFR* Alterations Using Liquid Biopsy Among Those Testing Positive Using Tissue

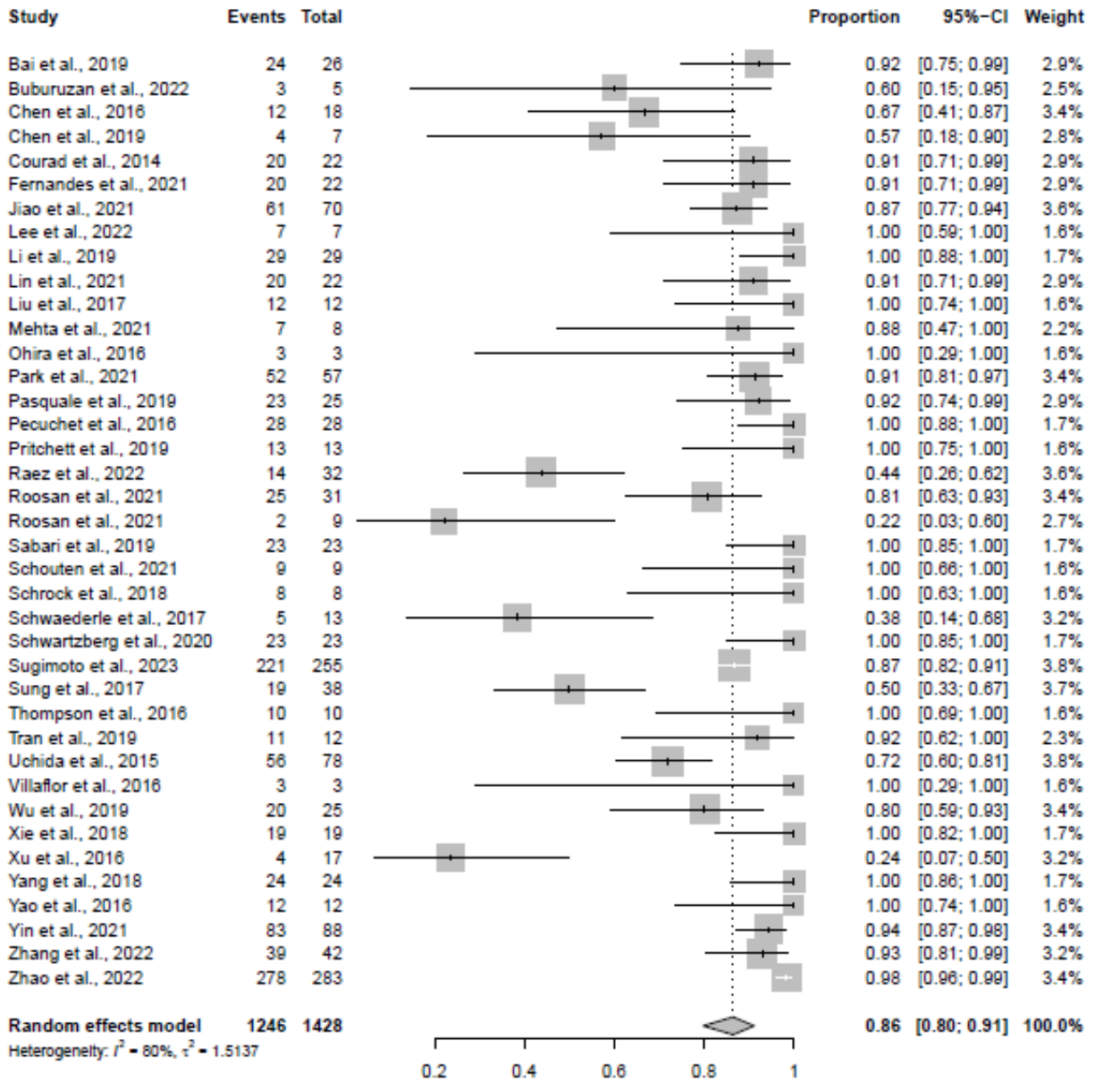

Figure A59: The Proportion of Individuals Testing Positive for Actionable *EGFR* Alterations Using Tissue Biopsy Among Those Testing Positive Using Liquid

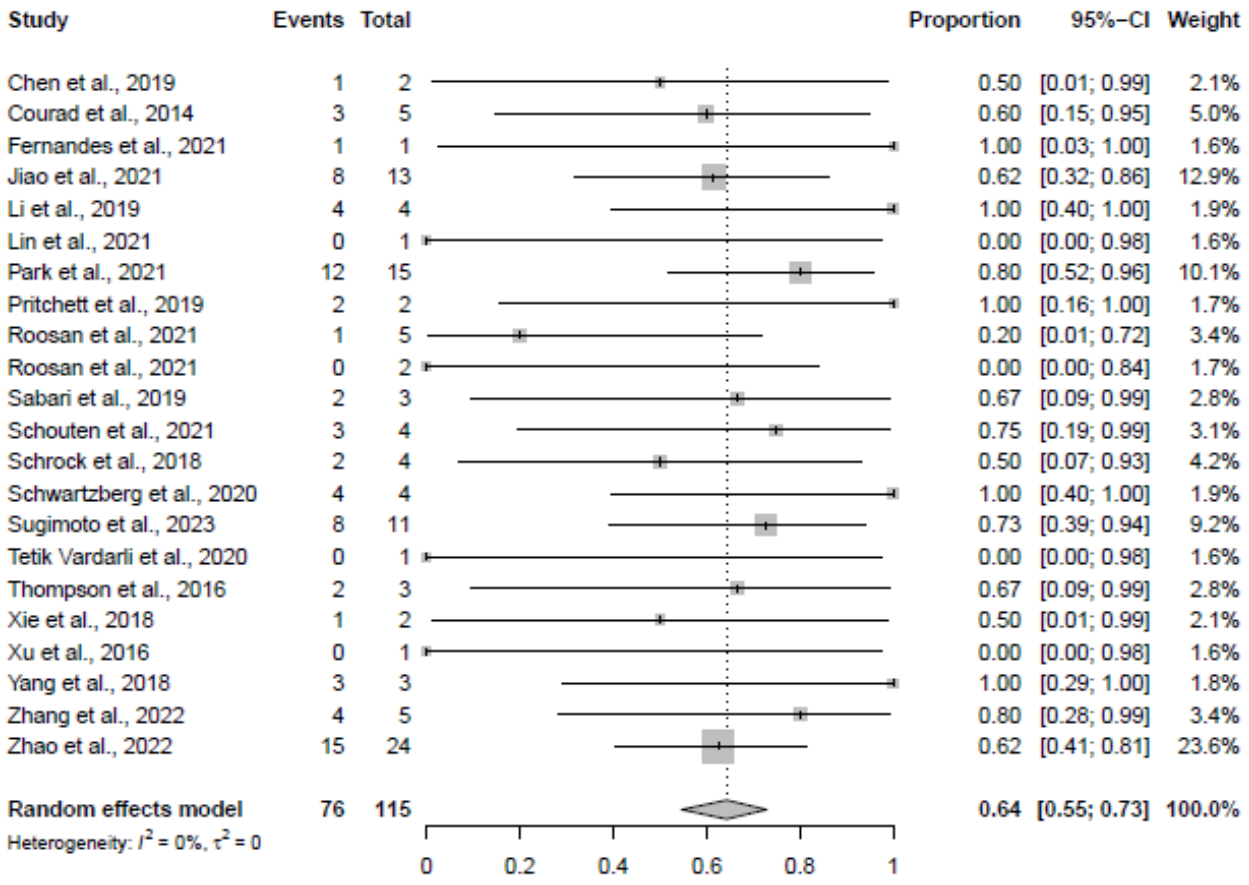

Figure A60: The Proportion of Individuals Testing Positive for Actionable *ERBB2* Alterations Using Liquid Biopsy Among Those Testing Positive Using Tissue

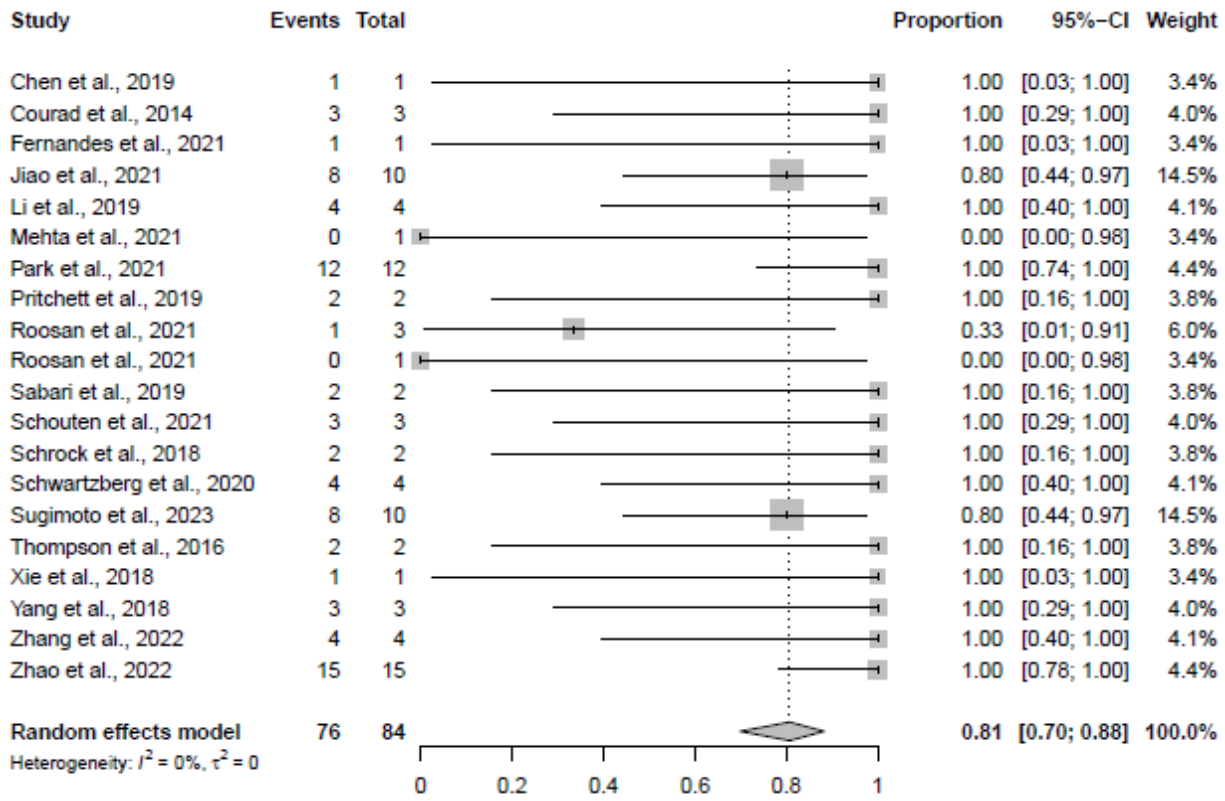

Figure A61: The Proportion of Individuals Testing Positive for Actionable *ERBB2* Alterations Using Tissue Biopsy Among Those Testing Positive Using Liquid

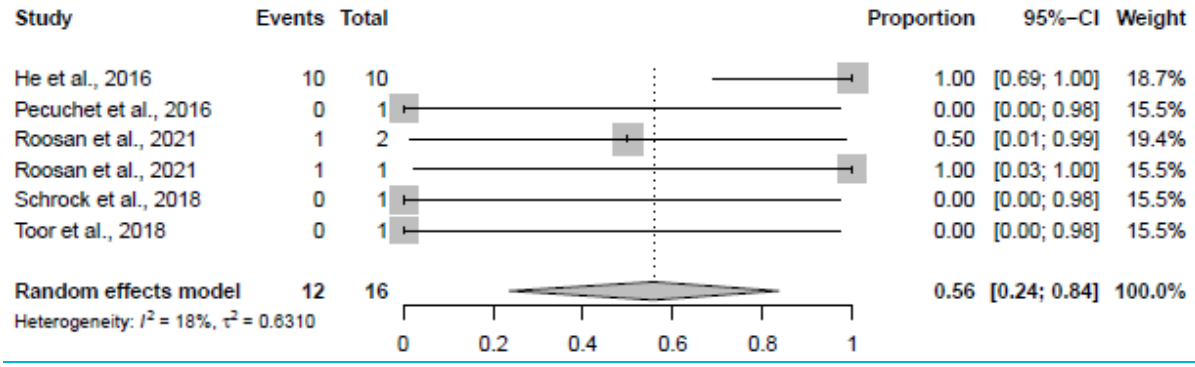

Figure A62: The Proportion of Individuals Testing Positive for Actionable *FGFR1* Alterations Using Liquid Biopsy Among Those Testing Positive Using Tissue

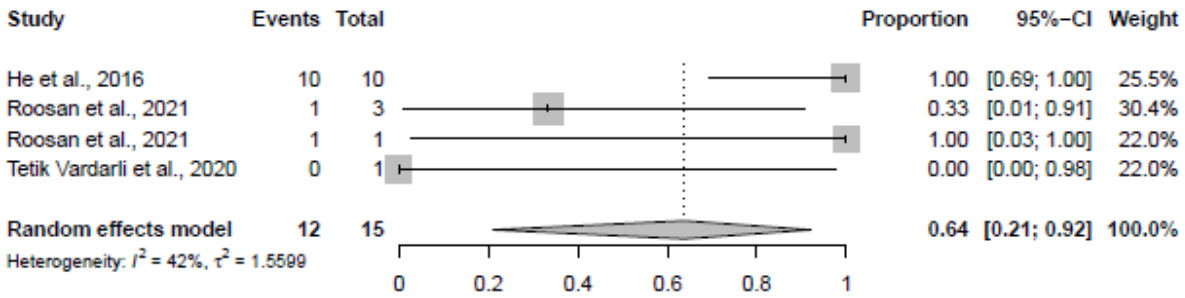

Figure A63: The Proportion of Individuals Testing Positive for Actionable *FGFR1* Alterations Using Tissue Biopsy Among Those Testing Positive Using Liquid

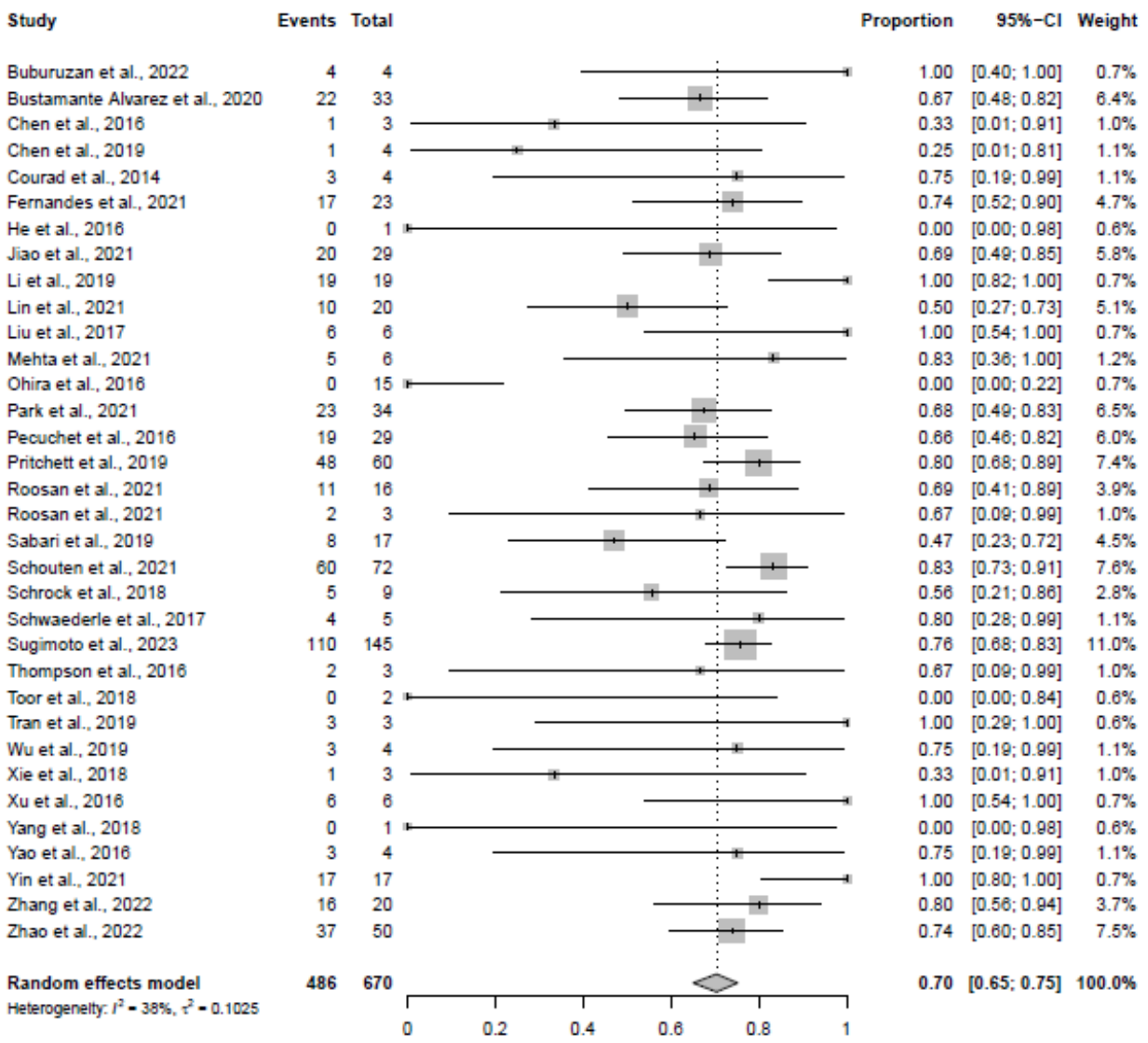

Figure A64: The Proportion of Individuals Testing Positive for Actionable *KRAS* Alterations Using Liquid Biopsy Among Those Testing Positive Using Tissue

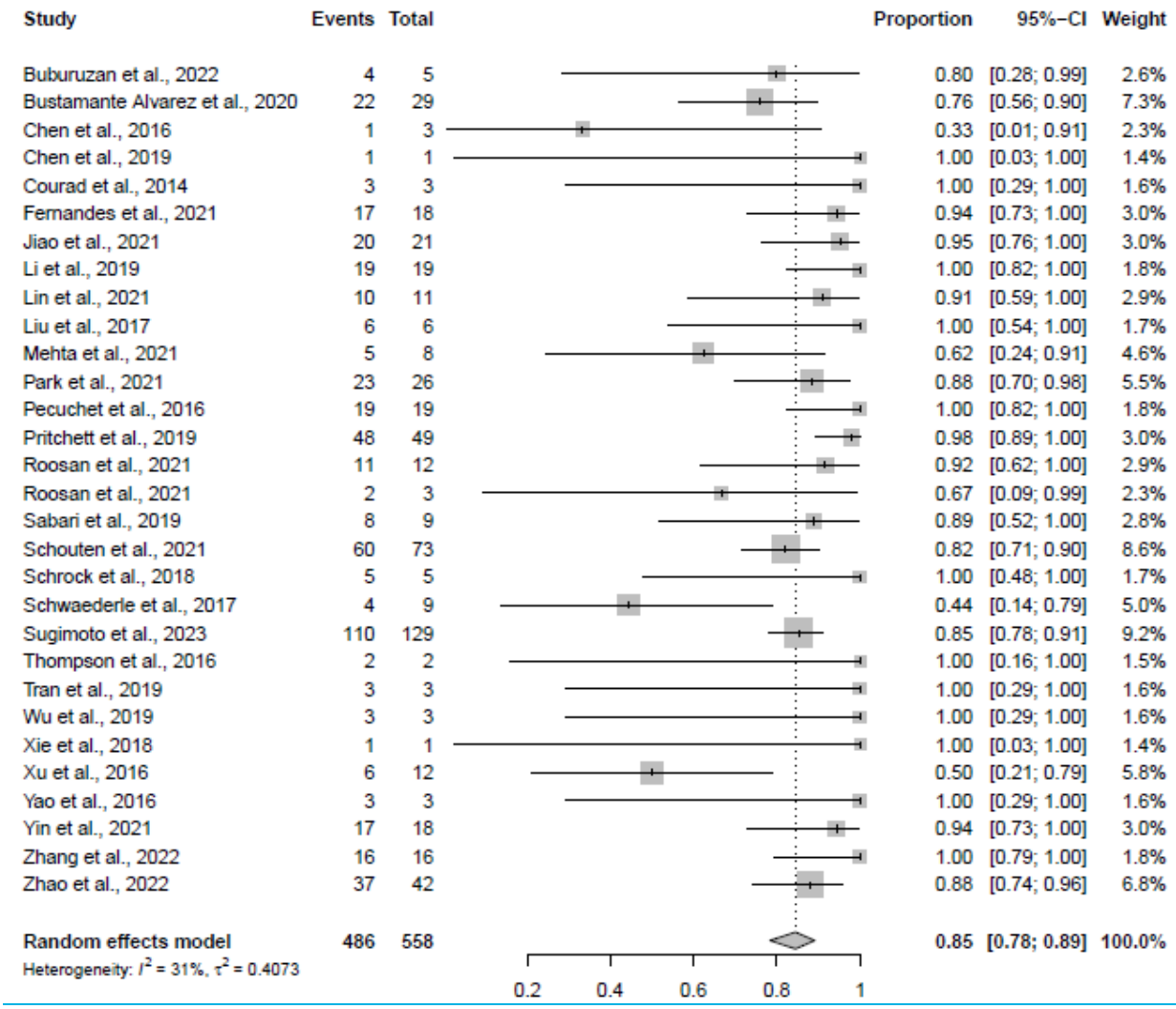

Figure A65: The Proportion of Individuals Testing Positive for Actionable *KRAS* Alterations Using Tissue Biopsy Among Those Testing Positive Using Liquid

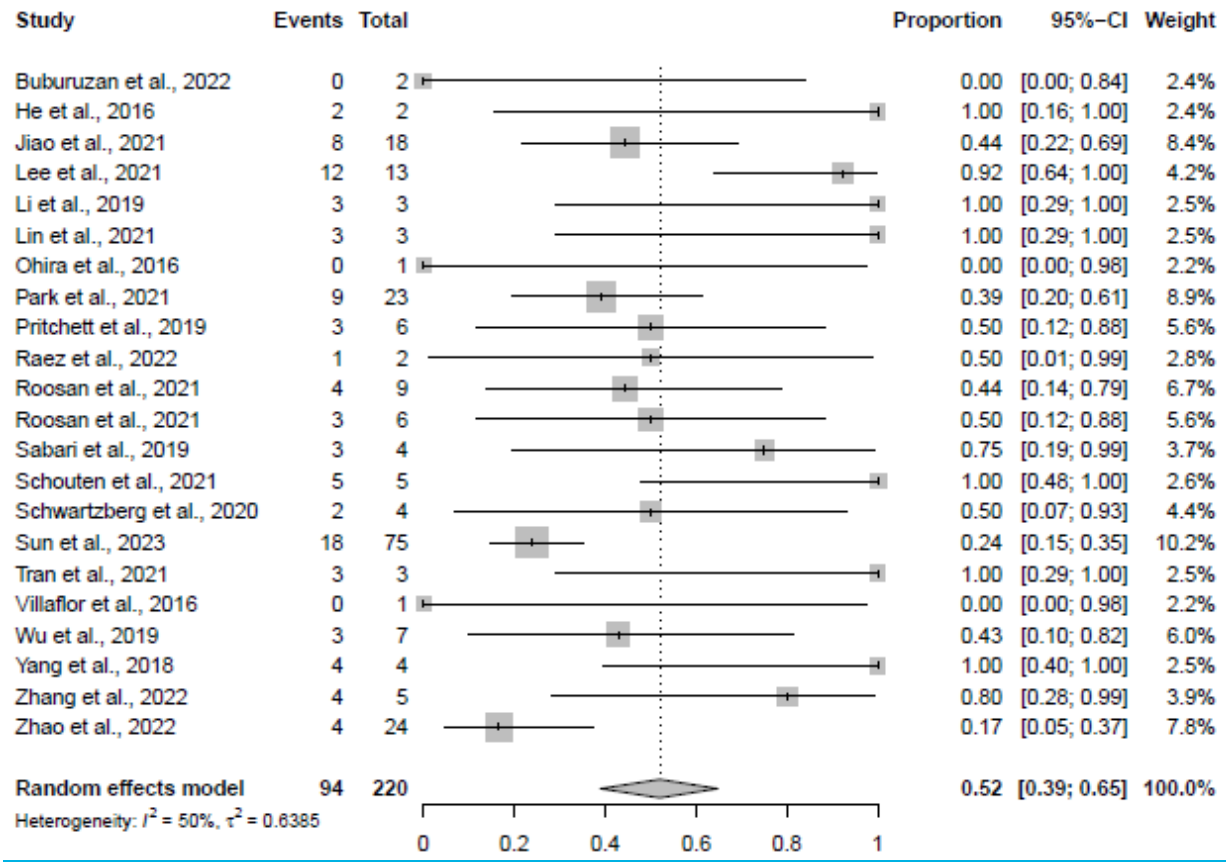

Figure A66: The Proportion of Individuals Testing Positive for Actionable *MET* Alterations Using Liquid Biopsy Among Those Testing Positive Using Tissue

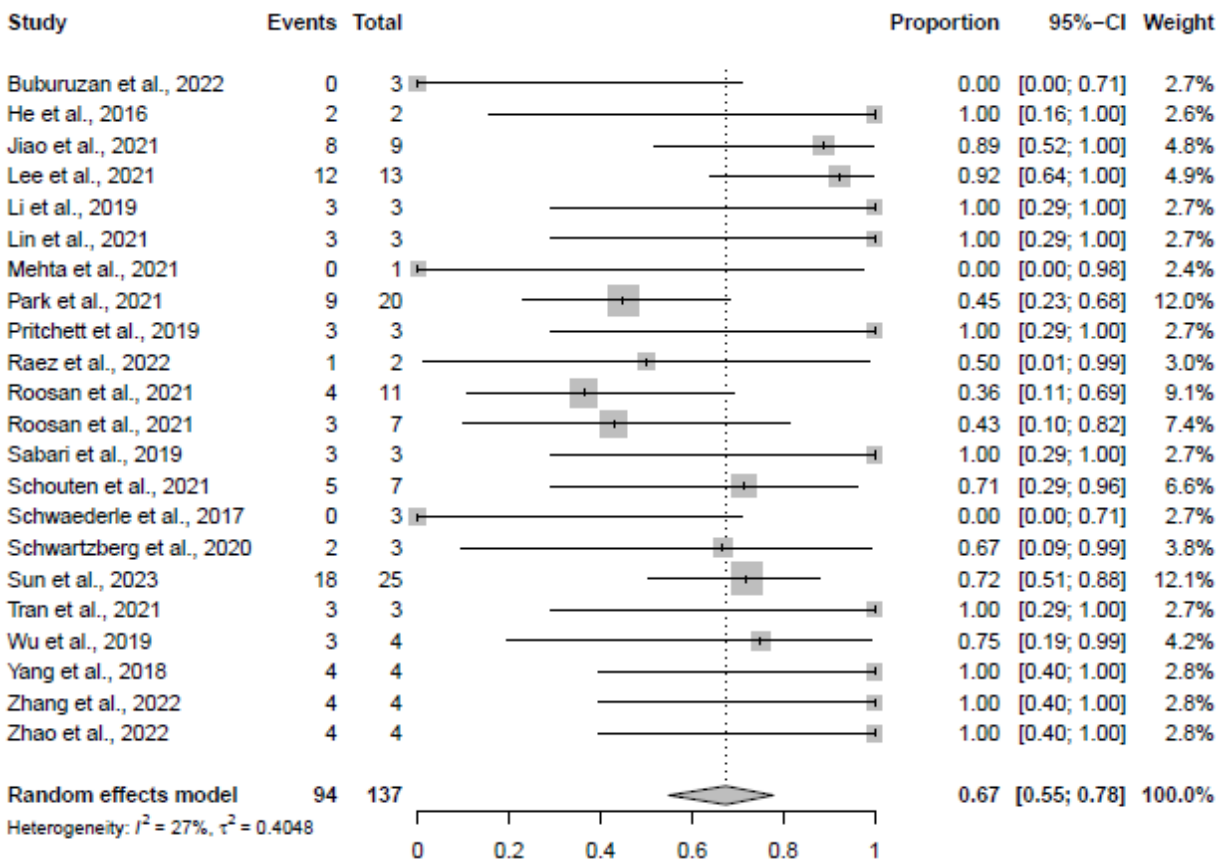

Figure A67: The Proportion of Individuals Testing Positive for Actionable *MET* Alterations Using Tissue Biopsy Among Those Testing Positive Using Liquid

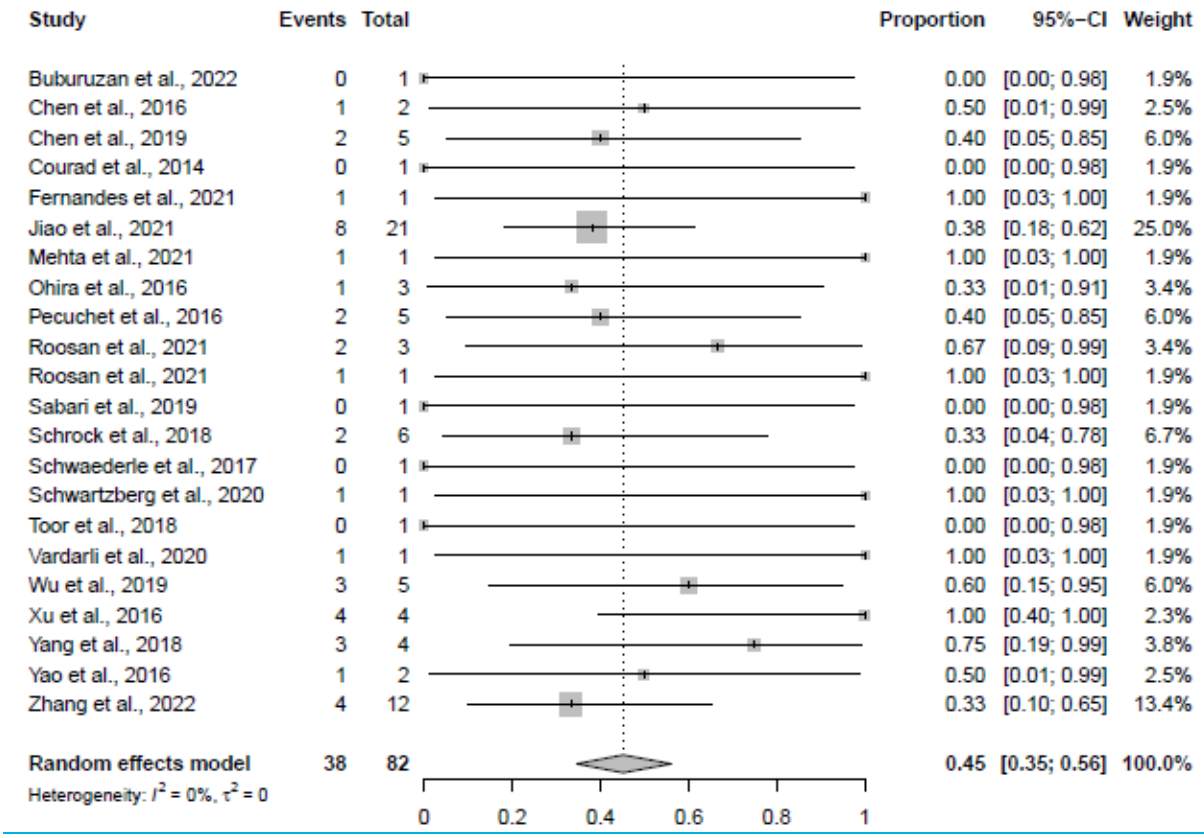

Figure A68: The Proportion of Individuals Testing Positive for Actionable *PIK3CA* Alterations Using Liquid Biopsy Among Those Testing Positive Using Tissue

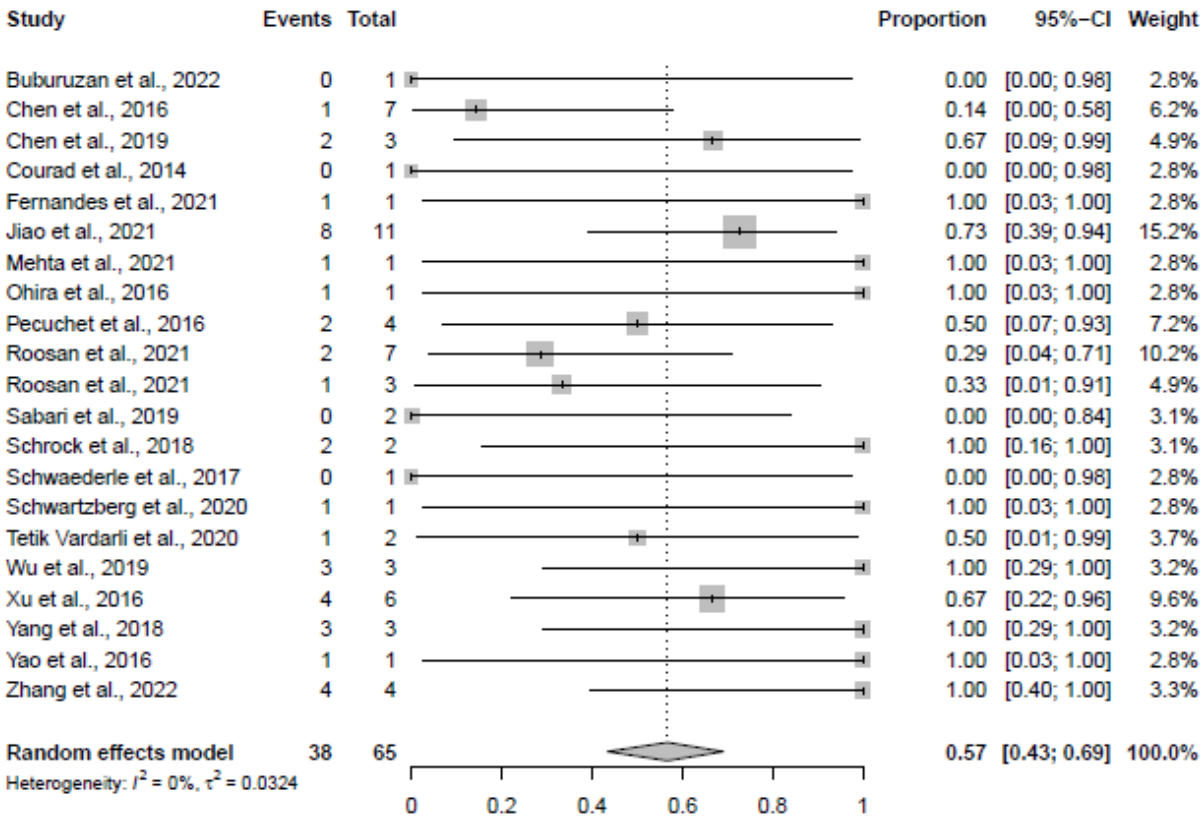

Figure A69: The Proportion of Individuals Testing Positive for Actionable *PIK3CA* Alterations Using Tissue Biopsy Among Those Testing Positive Using Liquid

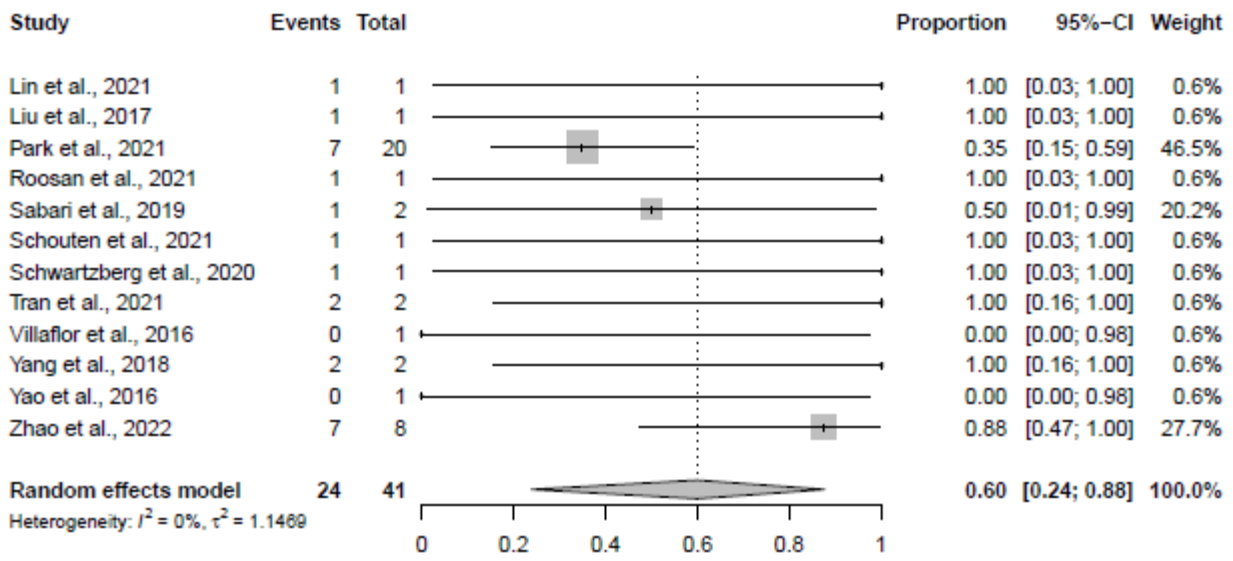

Figure A70: The Proportion of Individuals Testing Positive for Actionable *RET* Alterations Using Liquid Biopsy Among Those Testing Positive Using Tissue

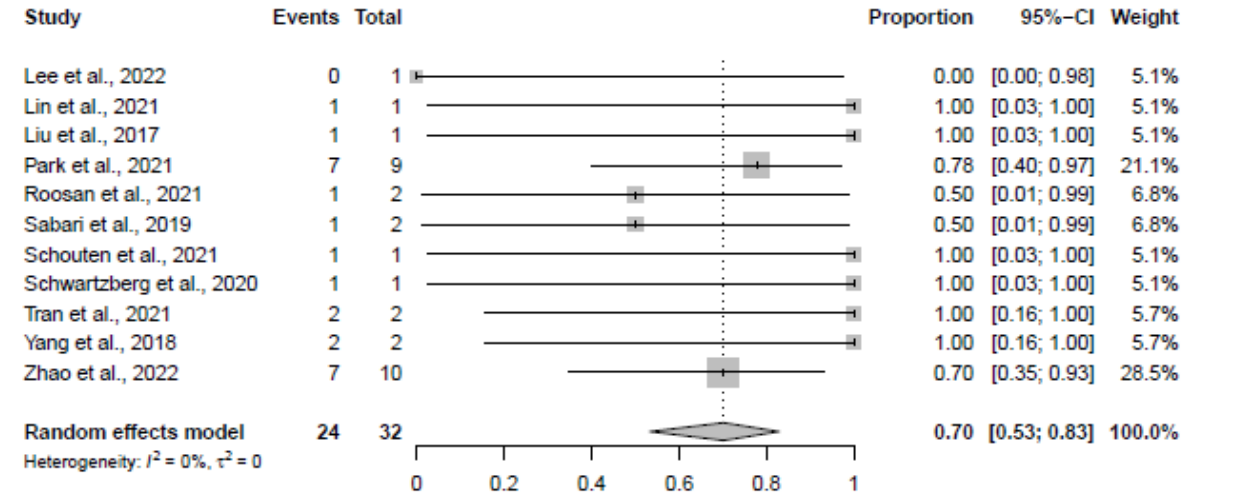

Figure A71: The Proportion of Individuals Testing Positive for Actionable *RET* Alterations Using Tissue Biopsy Among Those Testing Positive Using Liquid

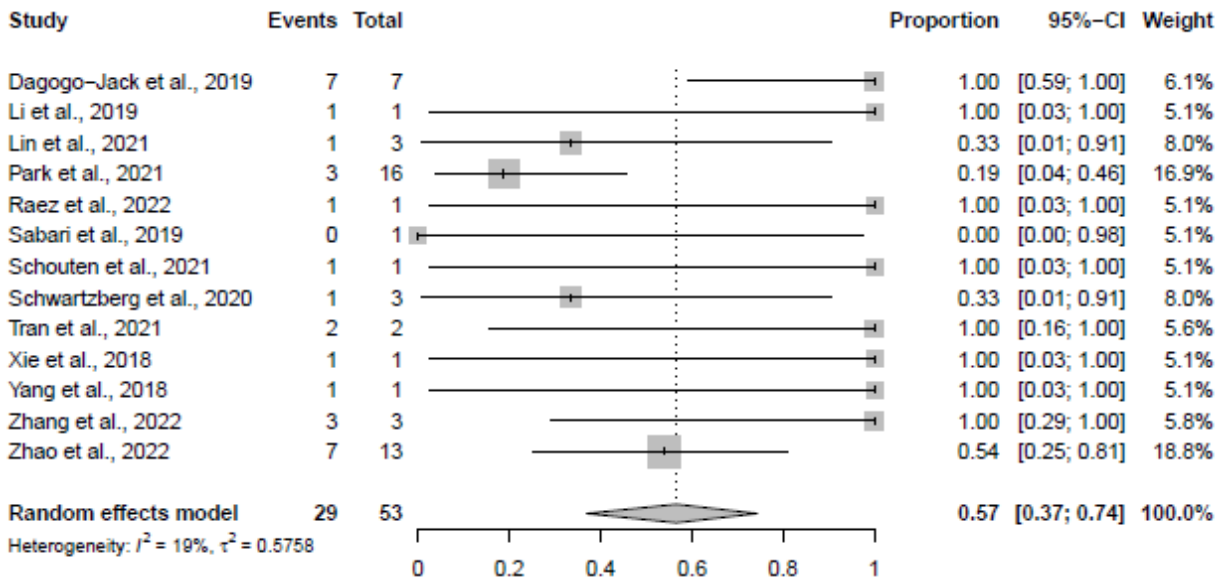

Figure A72: The Proportion of Individuals Testing Positive for Actionable *ROS1* Alterations Using Liquid Biopsy Among Those Testing Positive Using Tissue

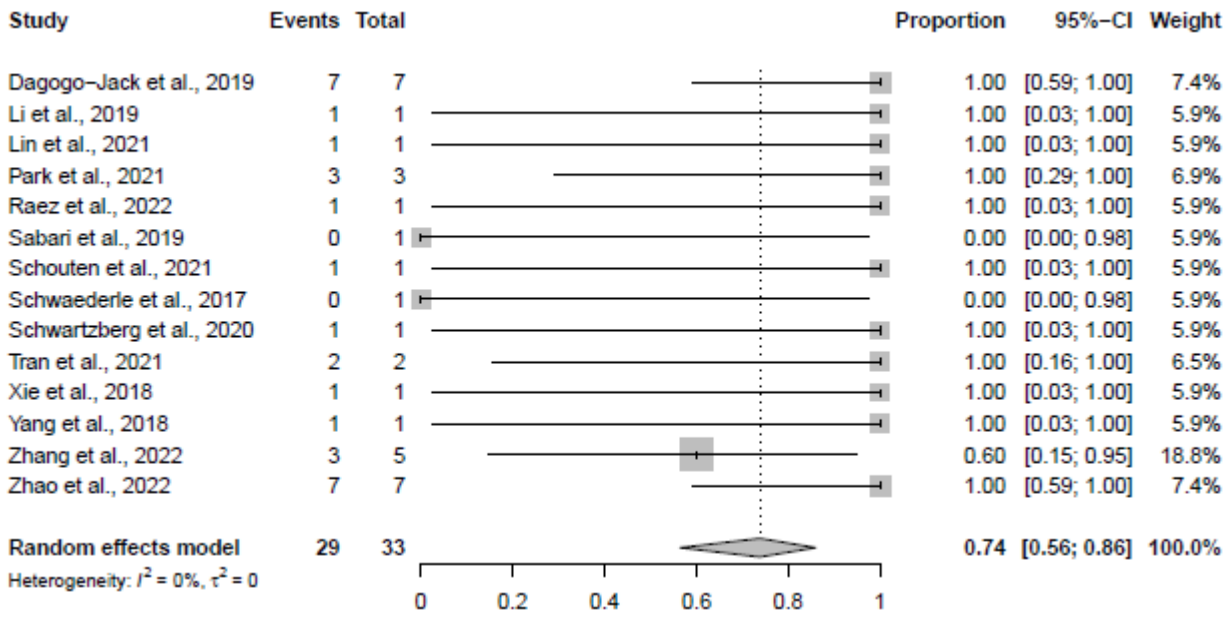

Figure A73: The Proportion of Individuals Testing Positive for Actionable *ROS1* Alterations Using Tissue Biopsy Among Those Testing Positive Using Liquid

Appendix 4: Selected Excluded Studies – Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Dietz S, Schirmer U, Merce C, von Bubnoff N, Dahl E, Meister M, Muley T, Thomas M, Sultmann H. Low input whole-exome sequencing to determine the representation of the tumor exome in circulating DNA of non-small cell lung cancer patients. PLoS ONE. 2016;11(8):e0161012	Wrong study design
Audetat A, Tschida C, Kreston S, Stephen A, D'Alessio B, Bondy M, Jackson L, Mellert H, Givens N, Sathyanarayana UG, Pestano GA. Analytic and clinical validation of a pan-cancer ngs liquid biopsy test for the detection of copy number amplifications fusions and exon skipping variants. Diagnostics (Basel). 2022;12(3):17	Wrong study design
Hua G, Zhang X, Zhang M, Wang Q, Chen X, Yu R, Bao H, Liu J, Wu X, Shao Y, Liang B, Lu K. Real-world circulating tumor DNA analysis depicts resistance mechanism and clonal evolution in ALK inhibitor-treated lung adenocarcinoma patients ESMO open. 2022;7(1):100337	Wrong study design
Jori B, Schatz S, Kaller L, Kah B, Roeper J, Ramdani HO, Diehl L, Hoffknecht P, Grohe C, Griesinger F, Tiemann M, Heukamp LC, Falk M. Comparison of resistance spectra after first and second line osimertinib treatment detected by liquid biopsy. Cancers (Basel.) 2021;13(12):08	Wrong patient population
Drusbosky LM, Dawar R, Rodriguez E, Ikpeazu CV. Therapeutic strategies in METex14 skipping mutated non-small cell lung cancer. J Hematol Oncol 2021;14(1):129	Wrong study design
Sebastiao MM, Ho RS, de Carvalho JPV, Nussbaum M. Diagnostic accuracy of next generation sequencing panel using circulating tumor DNA in patients with advanced non-small cell lung cancer: a Systematic review and meta-analysis	A systematic review/meta-analysis seaarched to identify missed eligible studies
Luo J, Shen L, Zheng D. Diagnostic value of circulating free DNA for the detection of EGFR mutation status in NSCLC: a systematic review and meta-analysis. Sci. 2014;4:6269	A systematic review/meta-analysis seaarched to identify missed eligible studies
Janzic U, Turnsek N, Dediu M, Donev IS, Lupu R, Teodorescu G, Ciuleanu TE, Pluzanski A. Real-world testing practices treatment patterns and clinical outcomes in patients from central eastern Europe with EGFR-mutated advanced non-small cell lung cancer: a retrospective chart review study (REFLECT). Current Oncology. 2022;29(8):5833-5845	Wrong study design
Gimenez-Capitan A, Bracht J, Garcia JJ, Jordana-Ariza N, Garcia B, Garzon M, Mayo-de-Las-Casas C, Viteri-Ramirez S, Martinez-Bueno A, Aguilar A, Sullivan IG, Johnson E, Huang CY, Gerlach JL, Warren S, Beechem JM, Teixido C, Rosell R, Reguart N, Molina-Vila MA. Multiplex detection of clinically relevant mutations in liquid biopsies of cancer patients using a hybridization-based platform. Clin Chem. 2021;67(3):554-563	Wrong intervention
Clement MS, Ebert EBF, Meldgaard P, Sorensen BS. Co-occurring MET amplification predicts inferior clinical response to first-line erlotinib in advanced stage EGFR-mutated NSCLC patients. Clin Lung Cancer. 2021;22(6):e870-e877	Wrong study design
Tran MC, Strohbehn GW, Karrison TG, Rouhani SJ, Segal JP, Shergill A, Hoffman PC, Patel JD, Garassino MC, Vokes EE, Bestvina CM. Brief report: discordance between liquid and tissue biopsy-based next-generation sequencing in lung adenocarcinoma at disease progression. Clinical Lung Cancer. 2023;24(3)():e117-e121	Wrong study design
Metzenmacher M, Hegedus B, Forster J, Schramm A, Horn PA, Klein CA, Bielefeld N, Ploenes T, Aigner C, Theegarten D, Schildhaus HU, Siveke JT, Schuler M, Lueong SS.Combined multimodal ctDNA analysis and radiological imaging for tumor surveillance in Non-small cell lung cancer.Transl Oncol. 2022;15(1):101279	Wrong study design
Kato S, Okamura R, Mareboina M, Lee S, Goodman A, Patel SP, Fanta PT, Schwab RB, Vu P, Raymond VM, Lanman RB, Sicklick JK, Lippman SM, Kurzrock R. Revisiting epidermal growth factor receptor (EGFR) amplification as a target for anti-egfr therapy: analysis of cell-free circulating tumor dna in patients with advanced malignancies. JCO precis. 2019;3	Wrong study design
Li A, Yang JJ, Zhang XC, Zhang Z, Su J, Gou LY, Bai Y, Zhou Q, Yang Z, Han-Zhang H, Zhong WZ, Chuai S, Zhang Q, Xie Z, Gao H, Chen H, Wang Z, Yang XN, Wang BC, Gan B, Chen ZH, Jiang BY, Wu SP, Liu SY, Xu CR, Wu YL. Acquired MET Y1248H and D1246N mutations mediate resistance to MET inhibitors in non-small cell lung cancer. Clin Cancer Res. 2017;23(16):4929-4937	Wrong study design

Citation	Primary reason for exclusion
Lim SM, Kim EY, Kim HR, Ali SM, Greenbowe JR, Shim HS, Chang H, Lim S, Paik S, Cho BC. Genomic profiling of lung adenocarcinoma patients reveals therapeutic targets and confers clinical benefit when standard molecular testing is negative. Oncotarget. 2016;7(17):24172-8	Wrong study design
Passiglia F, Rizzo S, Rolfo C, Galvano A, Bronte E, Incorvaia L, Listi A, Barraco N, Castiglia M, Calo V, Bazan V, Russo A. metastatic site location influences the diagnostic accuracy of ctDNA EGFR-mutation testing in NSCLC patients: a pooled analysis. Curr Cancer Drug Targets. 2018;18(7):697-705	A systematic review/meta-analysis seaarched to identify missed eligible studies
Arrieta O, Hernandez-Martinez JM, Montes-Servin E, Heredia D, Cardona AF, Molina-Romero C, Lara-Mejia L, Diaz-Garcia D, Bahena-Gonzalez A, Mendoza-Oliva DL. Impact of detecting plasma EGFR mutations with ultrasensitive liquid biopsy in outcomes of NSCLC patients treated with first- or second-generation EGFR-TKIs. Cancer Biomark. 2021;32(2):123-135	Wrong study design
Kumar S, Guleria R, Singh V, Bharti AC, Mohan A, Das BC. Efficacy of circulating plasma DNA as a diagnostic tool for advanced non-small cell lung cancer and its predictive utility for survival and response to chemotherapy. Lung Cancer. 2010;70(2):211-7	Wrong study design
Kong SL, Liu X, Tan SJ, Tai JA, Phua LY, Poh HM, Yeo T, Chua YW, Haw YX, Ling WH, Ng RCH, Tan TJ, Loh KWJ, Tan DS, Ng QS, Ang MK, Toh CK, Lee YF, Lim CT, Lim TKH, Hillmer AM, Yap YS, Lim WT. Complementary sequential circulating tumor cell (CTC) and cell-free tumor DNA (ctDNA) profiling reveals metastatic heterogeneity and genomic changes in lung cancer and breast cancer. Front 2021;11:698551	Wrong study design
Caputo V, De Falco V, Ventriglia A, Famiglietti V, Martinelli E, Morgillo F, Martini G, Corte CMD, Ciardiello D, Poliero L, De Vita F, Orditura M, Fasano M, Franco R, Caraglia M, Avitabile A, Scalamogna R, Marchi B, Ciardiello F, Troiani T, Napolitano S. Comprehensive genome profiling by next generation sequencing of circulating tumor DNA in solid tumors: a single academic institution experience. Therapeutic Advances in Medical Oncology. 2022;14	Wrong study design
Tissot C, Toffart AC, Villar S, Souquet PJ, Merle P, Moro-Sibilot D, Perol M, Zavadil J, Brambilla C, Olivier M, Couraud S. Circulating free DNA concentration is an independent prognostic biomarker in lung cancer. Eur Respir J 2015;46(6):1773-80	Wrong study design
Hartmaier RJ, Markovets AA, Ahn MJ, Sequist LV, Han JY, Cho BC, Yu HA, Kim SW, Yang JC, Lee JS, Su WC, Kowalski DM, Orlov S, Ren S, Frewer P, Ou X, Cross DAE, Kurian N, Cantarini M, Janne PA. Osimertinib + savolitinib to overcome acquired met-mediated resistance in epidermal growth factor receptor-mutated MET-amplified non-small cell lung cancer: TATTON. Cancer Discov. 2023;13(1):98-113	Wrong study design
Aldea M, Hendriks L, Mezquita L, Jovelet C, Planchard D, Auclin E, Remon J, Howarth K, Benitez JC, Gazzah A, Lavaud P, Naltet C, Lacroix L, de Kievit F, Morris C, Green E, Ngo-Camus M, Rouleau E, Massard C, Caramella C, Friboulet L, Besse B. Circulating tumor DNA analysis for patients with oncogene-addicted nsclc with isolated central nervous system progression. J Thorac Oncol. 2020;15(3):383-391	Wrong study design
Guo QM, Wang L, Yu WJ, Qiao LH, Zhao MN, Hu XM, Sun YM, Ni S, Xu YH, Lou JT. Detection of plasma EGFR mutations in NSCLC patients with a validated ddPCR lung cfDNA assay. J 2019;10(18):4341-4349	Wrong study design
Choudhury Y, Tan MH, Shi JL, Tee A, Ngeow KC, Poh J, Goh RR, Mong J. Complementing tissue testing with plasma mutation profiling improves therapeutic decision-making for patients with lung cancer. Front Med (Lausanne) 2022;9:758464	Wrong study design
Chua TH, Chuah KL. Concordance of cytological specimens with histological tissue for detection of epidermal growth factor receptor mutation in non-small cell lung cancer: a systematic review. Acta Cytologica. 2022;66(1):61-71	Wrong study design
Remon J, Lacroix L, Jovelet C, Caramella C, Howarth K, Plagnol V, Rosenfeld N, Morris C, Mezquita L, Pannet C, Ngocamus M, Le Pechoux C, Adam J, Grecea AM, Planchard D, Vassal G, Benitez JC, Gazzah A, Green E, Soria JC, Besse B. Real-world utility of an amplicon-based next-generation sequencing liquid biopsy for broad molecular profiling in patients with advanced non-small-cell lung cancer. JCO precis. 2019;3	Wrong study design
Arnold L, Alexiadis V, Watanaskul T, Zarrabi V, Poole J, Singh V. Clinical validation of qPCR target selector TM assays using highly specific switch-blockers for rare mutation detection. J Clin Pathol 2020;73(10):648-655	Wrong study design
Aredo JV, Wakelee HA, Hui AB, Padda SK, Joshi ND, Guo HH, Chaudhuri A, Diehn M, Loo BW Jr, Neal JW. Induction EGFR tyrosine kinase inhibitors prior to definitive chemoradiotherapy in unresectable stage III EGFR-mutated non-small cell lung cancer. Cancer Treat Res Commun. 2022;33:100659	Wrong study design

Citation	Primary reason for exclusion
Gray JE, Okamoto I, Sriuranpong V, Vansteenkiste J, Imamura F, Lee JS, Pang YK, Cobo M, Kasahara K, Cheng Y, Nogami N, Cho EK, Su WC, Zhang G, Huang X, Li-Sucholeiki X, Lentrichia B, Dearden S, Jenkins S, Saggese M, Rukazenkov Y, Ramalingam SS. Tissue and plasma EGFR mutation analysis in the FLAURA trial: Osimertinib versus comparator EGFR tyrosine kinase inhibitor as first-line treatment in patients with EGFR-mutated advanced non-small cell lung cancer. Clin Cancer Res. 2019;25(22):6644-6652	Wrong intervention
Cui W, Milner-Watts C, O'Sullivan H, Lyons H, Minchom A, Bhosle J, Davidson M, Yousaf N, Scott S, Faull I, Kushnir M, Nagy R, O'Brien M, Popat S. Up-front cell-free DNA next generation sequencing improves target identification in UK first line advanced non-small cell lung cancer (NSCLC) patients. Eur J Cancer 2022;171:44-54	Wrong study design
Malapelle U, Mayo C, Rocco D, Garzon M, Pisapia P, Sgariglia R, De Luca C, Ariza NJ, Pepe F, Espinosa DM, Bueno AM, Gonzalez-Cao M, Karachaliou N, Viteri S, Vila MAM, Rosell R, Troncone G. The development of a narrow target gene panel makes next generation sequencing effective for circulating free DNA analysis. Annals of Oncology 2016;27(Supplement 6):vi19	Wrong study design
Song Y, Hu C, Xie Z, Wu L, Zhu Z, Rao C, Liu L, Chen Y, Liang N, Chen J, Yang N, Hu J, Zhao W, Tong G, Dong X, Zheng D, Jin M, Huang M, He Y, Rosell R, Lippi G, Mino-Kenudson M, Han-Zhang H, Mao X, Zhang L, Liu H, Field JK, Chuai S, Ye J, Han Y, Lu S. Circulating tumor DNA clearance predicts prognosis across treatment regimen in a large real-world longitudinally monitored advanced non-small cell lung cancer cohort. Transl 2020;9(2):269-279	Wrong study design
Oxnard GR, Paweletz CP, Kuang Y, Mach SL, O'Connell A, Messineo MM, Luke JJ, Butaney M, Kirschmeier P, Jackman DM, Janne PA. Noninvasive detection of response and resistance in EGFR-mutant lung cancer using quantitative next-generation genotyping of cell-free plasma DNA. Clin Cancer Res 2014;20(6):1698-1705	Wrong intervention
Ma Y, Shi H, Zhao G, Liu X, Cai J, Li G, Chen W, Lei Y, Ye L, Fu C, Zhao L, Zhou Y, Huang Y. Unique profile on the progress free survival and overall survival in patients with advanced non-small cell lung cancer in the Qujing area Southwest China. Frontiers in Immunology. 2023;14	Wrong study design
Kim Y, Shin S, Lee KA. Exosome-based detection of EGFR T790M in plasma and pleural fluid of prospectively enrolled non-small cell lung cancer patients after first-line tyrosine kinase inhibitor therapy. Cancer cell int. 2021;21(1):50	Wrong setting
Ku BM, Kim YJ, Park D, Lee SH, Ahn JS, Park K, Ahn MJ, Sun JM. Role of circulating tumor DNA profiling in patients with non-small cell lung cancer treated with EGFR Inhibitor. Oncology 2022;100(4):228-237	Wrong study design
Majem M, Sullivan I, Viteri S, Lopez-Vivanco G, Cobo M, Sanchez JM, Garcia-Gonzalez J, Garde J, Sampayo M, Martrat G, Malfettone A, Karachaliou N, Molina-Vila MA, Rosell R. First-line osimertinib in patients with epidermal growth factor receptor-mutant non-small-cell lung cancer and with a coexisting low allelic fraction of Thr790Met. European Journal of Cancer. 2021;159:174-181	Wrong patient population
Han X, Tang X, Zhu H, Zhu D, Zhang X, Meng X, Hua Y, Wang Z, Zhang Y, Huang W, Wang L, Yuan S, Zhang P, Gong H, Sun Y, Liu Z, Dong X, Gai F, Huang Z, Zhu C, Guo J. Short-term dynamics of circulating tumor DNA predicting efficacy of sintilimab plus docetaxel in second-line treatment of advanced NSCLC: biomarker analysis from a single-arm phase 2 trial. J Immunother Cancer 2022;10(12):12	Wrong study design
Chen H, Liu M, Dai Z, Li S, Luo Y, Wang Y, Su W, Cai W, Yang D, Huang J, Yang Z. Concomitant genetic alterations are associated with response to EGFR targeted therapy in patients with lung adenocarcinoma. Transl. 2020;9(4):1225-1234	Wrong study design
Cai J, Jiang H, Li S, Yan X, Wang M, Li N, Zhu C, Dong H, Wang D, Xu Y, Xie H, Wu S, Lou J, Zhao J, Li Q. The Landscape of Actionable Genomic Alterations by Next-Generation Sequencing in Tumor Tissue Versus Circulating Tumor DNA in Chinese Patients With Non-Small Cell Lung Cancer. Front. 2021;11:751106	Wrong study design
Tran LS, Nguyen QT, Nguyen CV, Tran VU, Nguyen TT, Le HT, Nguyen MT, Le VT, Pham LS, Vo BT, Dang AH, Nguyen LT, Nguyen TV, Pham HT, Tran TT, Nguyen LH, Nguyen KT, Vu YV, Nguyen NH, Bui VQ, Bui HH, Do TT, Lam NV, Truong Dinh K, Phan MD, Nguyen HN, Giang H. Ultra-deep massive parallel sequencing of plasma cell-free dna enables large-scale profiling of driver mutations in vietnamese patients with advanced non-small cell lung cancer. Front. 2020;10:1351	Wrong study design
So MK, Park JH, Kim JW, Jang JH. Analytical validation of a pan-cancer panel for cell-free assay for the detection of egfr mutations. Diagnostics (Basel) 2021;11(6):02	Wrong study design

Citation	Primary reason for exclusion
Tang Y, Liu X, Ou Z, He Z, Zhu Q, Wang Y, Yang M, Ye J, Han-Zhang H, Qiao G. Maximum allele frequency observed in plasma: A potential indicator of liquid biopsy sensitivity. Oncol 2019;18(2):2118-2124	Wrong patient population
Douillard JY, Ostoros G, Cobo M, Ciuleanu T, Cole R, McWalter G, Walker J, Dearden S, Webster A, Milenkova T, McCormack R. Gefitinib treatment in EGFR mutated caucasian NSCLC: circulating-free tumor DNA as a surrogate for determination of EGFR status. J Thorac Oncol 2014;9(9):1345-53	Wrong intervention
Nakamura T, Sueoka-Aragane N, Iwanaga K, Sato A, Komiya K, Kobayashi N, Hayashi S, Hosomi T, Hirai M, Sueoka E, Kimura S. Application of a highly sensitive detection system for epidermal growth factor receptor mutations in plasma DNA. J Thorac Oncol 2012;7(9):1369-81	Wrong intervention
Cui W, Milner-Watts C, McVeigh TP, Minchom A, Bholse J, Davidson M, Yousaf N, MacMahon S, Mugalaasi H, Gunapala R, Lee R, George A, Popat S, O'Brien M. A pilot of Blood-First diagnostic cell free DNA (cfDNA) next generation sequencing (NGS) in patients with suspected advanced lung cancer. Lung Cancer 2022;165():34-42	Wrong study design
Imamura F, Uchida J, Kukita Y, Kumagai T, Nishino K, Inoue T, Kimura M, Kato K. Early responses of EGFR circulating tumor DNA to EGFR tyrosine kinase inhibitors in lung cancer treatment. Oncotarget. 2016;7(44):71782-71789	Wrong study design
Thompson JC, Aggarwal C, Wong J, Nimgaonkar V, Hwang WT, Andronov M, Dibardino DM, Hutchinson CT, Ma KC, Lanfranco A, Moon E, Haas AR, Singh AP, Ciunci CA, Marmarelis M, D'Avella C, Cohen JV, Bauml JM, Cohen RB, Langer CJ, Vachani A, Carpenter EL. Plasma genotyping at the time of diagnostic tissue biopsy decreases time-to-treatment in patients with advanced nsclc-results from a prospective pilot study. JTO Clin Res Rep 2022;3(4):100301	Wrong study design
Biaoxue R, Shuanying Y. Tissue or blood: which is more suitable for detection of EGFR mutations in non-small cell lung cancer? Int J Biol Markers. 2018;33(1):40-48	A systematic review/meta-analysis searched to identify missed eligible studies
Zhou S, Huang R, Cao Y. Detection of epidermal growth factor receptor mutations in peripheral blood circulating tumor DNA in patients with advanced non-small cell lung cancer: A PRISMA-compliant meta-analysis and systematic review. Medicine (Baltimore). 2020;99(40):e21965	A systematic review/meta-analysis searched to identify missed eligible studies
Dziadziuszko R, Hung T, Wang K, Choeurng V, Drilon A, Doebele RC, Barlesi F, Wu C, Dennis L, Skoletsky J, Woodhouse R, Li M, Chang CW, Simmons B, Riehl T, Wilson TR. Pre- and post-treatment blood-based genomic landscape of patients with ROS1 or NTRK fusion-positive solid tumours treated with entrectinib. Mol Oncol. 2022;16(10):2000-2014	Wrong comparator
Lin YT, Chiang CL, Hung JY, Lee MH, Su WC, Wu SY, Wei YF, Lee KY, Tseng YH, Su J, Chung HP, Lin CB, Ku WH, Chiang TS, Chiu CH, Shih JY. Resistance profiles of anaplastic lymphoma kinase tyrosine kinase inhibitors in advanced non-small-cell lung cancer: a multicenter study using targeted next-generation sequencing. Eur J Cancer. 2021;156:1-11	Wrong comparator
Zhang J, Dong A, Li S, Ren X, Zhang X. Consistency of genotyping data from simultaneously collected plasma circulating tumor DNA and tumor-DNA in lung cancer patients. J 2020;12(12):7290-7297	Wrong patient population
Choudhury NJ, Schoenfeld AJ, Flynn J, Falcon CJ, Rizvi H, Rudin CM, Kris MG, Arcila ME, Heller G, Yu HA, Ladanyi M, Riely GJ. Response to standard therapies and comprehensive genomic analysis for patients with lung adenocarcinoma with EGFR exon 20 insertions. Clin Cancer Res. 2021;27(10):2920-2927	Wrong study design
Phan TT, Tran BT, Nguyen ST, Ho TT, Nguyen HT, Le VT, Le AT. EGFR plasma mutation in prediction models for resistance with EGFR TKI and survival of non-small cell lung cancer. Clin Transl Med 2019;8(1):4	Wrong study design
Pepe F, De Luca C, Smeraglio R, Pisapia P, Sgariglia R, Nacchio M, Russo M, Serra N, Rocco D, Battiloro C, Ambrosio F, Gragnano G, Vigliar E, Bellevicine C, Troncone G, Malapelle U. Performance analysis of SiRe next-generation sequencing panel in diagnostic setting: focus on NSCLC routine samples. J Clin Pathol 2019;72(1):38-45	Wrong intervention
Yang X, Zhuo M, Ye X, Bai H, Wang Z, Sun Y, Zhao J, An T, Duan J, Wu M, Wang J. Quantification of mutant alleles in circulating tumor DNA can predict survival in lung cancer. Oncotarget 2016;7(15):20810-24	Wrong study design
Li F, Wei F, Huang WL, Lin CC, Li L, Shen MM, Yan Q, Liao W, Chia D, Tu M, Tang JH, Feng Z, Kim Y, Su WC, Wong DTW. Ultra-short circulating tumor DNA (usctDNA) in plasma and saliva of non-small cell lung cancer (NSCLC) patients. Cancers (Basel). 2020;12(8):24	Wrong study design

Citation	Primary reason for exclusion
Cho MS, Park CH, Lee S, Park HS. Clinicopathological parameters for circulating tumor DNA shedding in surgically resected non-small cell lung cancer with EGFR or KRAS mutation. PLoS ONE 2020;15(3):e0230622	Wrong intervention
Peng M, Xie Y, Li X, Qian Y, Tu X, Yao X, Cheng F, Xu F, Kong D, He B, Liu C, Cao F, Yang H, Yu F, Xu C, Tian G. Resectable lung lesions malignancy assessment and cancer detection by ultra-deep sequencing of targeted gene mutations in plasma cell-free DNA. J Med Genet 2019;56(10):647-653	Wrong patient population
Zhuang R, Li S, Li Q, Guo X, Shen F, Sun H, Liu T. The prognostic value of KRAS mutation by cell-free DNA in cancer patients: A systematic review and meta-analysis. PLoS ONE. 2017;12(8):e0182562	A systematic review/meta-analysis searched to identify missed eligible studies
Sanz-Garcia E, Genta S, Chen X, Ou Q, Araujo DV, Abdul Razak AR, Hansen AR, Spreafico A, Bao H, Wu X, Siu LL, Bedard PL. Tumor-naive circulating tumor DNA as an early response biomarker for patients treated with immunotherapy in early phase clinical trials. JCO precis. 2023;7:e2200509	Wrong study design
Li Y, Zhang F, Yuan P, Guo L, Jianming Y, He J. High MAF of EGFR mutations and high ratio of T790M sensitizing mutations in ctDNA predict better third-generation TKI outcomes. Thorac Cancer. 2020;11(6):1503-1511	Wrong patient population
Guibert N, Jones G, Beeler JF, Plagnol V, Morris C, Mourlanette J, Delaunay M, Keller L, Rouquette I, Favre G, Pradines A, Mazieres J. Targeted sequencing of plasma cell-free DNA to predict response to PD1 inhibitors in advanced non-small cell lung cancer. Lung Cancer 2019;137:1-6	Wrong study design
Garcia-Pardo M, Czarnecka K, Law JH, Salvarrey A, Fernandes R, Fan J, Corke L, Waddell TK, Yasufuku K, Donahoe LL, Pierre A, Le LW, Ghumman N, Liu G, Shepherd FA, Bradbury P, Sacher A, Stockley T, Pal P, Rogalla P, Tsao MS, Leighl N. B. Plasma-first: accelerating lung cancer diagnosis and molecular profiling through liquid biopsyTher Adv Med Oncol. 2022;14:17588359221126151	Wrong study design
Rich TA, Reckamp KL, Chae YK, Doebele RC, Iams WT, Oh M, Raymond VM, Lanman RB, Riess JW, Stinchcombe TE, Subbiah V, Trevarthen DR, Fairclough S, Yen J, Gautschi O. Analysis of Cell-Free DNA from 32,989 Advanced Cancers Reveals Novel Co-occurring Activating RET Alterations and Oncogenic Signaling Pathway Aberrations. Clin Cancer Res. 2019;25(19):5832-5842	Wrong study design
Rachiglio AM, Esposito Abate R, Sacco A, Pasquale R, Fenizia F, Lambiase M, Morabito A, Montanino A, Rocco G, Romano C, Nappi A, Iaffaioli RV, Tatangelo F, Botti G, Ciardiello F, Maiello MR, De Luca A, Normanno N. Limits and potential of targeted sequencing analysis of liquid biopsy in patients with lung and colon carcinoma. Oncotarget. 2016;7(41):66595-66605	Wrong setting
Niu X, Chuai S, Lu S. Non-invasive detection of response and crizotinib induced resistance in ROS1 fusion advanced stage Chinese lung adenocarcinoma patients using next-generation genotyping from cfDNA. Annals of Oncology 2016;27(Supplement 6):vi438	Wrong study design
Wang J, Bai H, Hong C, Mei TH. Analyzing epidermal growth factor receptor mutation status changes in advanced non-small-cell lung cancer at different sampling time-points of blood within one day. Thorac Cancer. 2017;8(4):312-319	Wrong intervention
Chen Y, Han T, Zhou Y, Mao B, Zhuang W. Efficacy comparison of targeted next-generation sequencing in the identification of somatic mutations in circulating tumor DNA from different stages of lung cancer. Neoplasma 2019;66(4):652-660	Duplicate
Chen K, Zhang J, Guan T, Yang F, Lou F, Chen W, Zhao M, Chen S, Wang J. Comparison of plasma to tissue DNA mutations in surgical patients with non-small cell lung cancer. J Thorac Cardiovasc Surg 2017;154(3):1123-1131.e2	Wrong study design
Palmero R, Taus A, Viteri S, Majem M, Carcereny E, Garde-Noguera J, Felip E, Nadal E, Malfettone A, Sampayo M, Riva F, Nagy RJ, Lanman RB, Faull I, Dix D, Karachaliou N, Rosell R. Biomarker discovery and outcomes for comprehensive cell-free circulating tumor DNA versus standard-of-care tissue testing in advanced non-small-cell lung cancer. JCO precis 2021;5:93-102	Wrong comparator
Shin KH, Lee SM, Park K, Choi H, Kim IS, Yoon SH, Oh SH. Effects of different centrifugation protocols on the detection of egfr mutations in plasma cell-free DNA. Am J Clin. Pathol 2022;158(2):206-211	Wrong study design
Zhou X, Shou J, Sheng J, Xu C, Ren S, Cai X, Chu Q, Wang W, Zhen Q, Zhou Y, Li W, Pan H, Li H, Sun T, Cheng H, Wang H, Lou F, Rao C, Cao S, Fang Y. Molecular and clinical analysis of Chinese patients with anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer. Cancer Sci. 2019;110(10):3382-3390	Wrong study design

Citation	Primary reason for exclusion
Palmieri M, Zulato E, Wahl SGF, Guibert N, Frullanti E. Diagnostic accuracy of circulating free DNA testing for the detection of KRAS mutations in non-small cell lung cancer: A systematic review and meta-analysis. Front. 2022;13:1015161	A systematic review/meta-analysis searched to identify missed eligible studies
Liu X, Li G, Zhang H, Chang Q, Fang M, Lu C, Tian P, Mei F. Molecular characteristics and prognostic factors of leptomeningeal metastasis in non-small cell lung cancer. Clin Neurol Neurosurg. 2023;225:107572	Wrong study design
Madison R, Schrock AB, Castellanos E, Gregg JP, Snider J, Ali SM, Miller VA, Singal G, Alexander BM, Venstrom JM, Chung JH. Retrospective analysis of real-world data to determine clinical outcomes of patients with advanced non-small cell lung cancer following cell-free circulating tumor DNA genomic profiling. Lung Cancer. 2020;148:69-78	Wrong study design
Li J, Chen S, Xue H, Wang H, Huang T, Xie H, He J, Ke C, Yu Z, Ni B. Genomic alteration spectrum of non-small cell lung cancer patients in east-china characterized by tumor tissue DNA and cell-free DNA. Onco Targets Ther. 2022;15:571-584	Wrong study design
Ohara S, Suda K, Sakai K, Nishino M, Chiba M, Shimoji M, Takemoto T, Fujino T, Koga T, Hamada A, Soh J, Nishio K, Mitsudomi T. Prognostic implications of preoperative versus postoperative circulating tumor DNA in surgically resected lung cancer patients: a pilot study. Transl. 2020;9(5):1915-1923	Wrong study design
Angeles AK, Christopoulos P, Yuan Z, Bauer S, Janke F, Ogrodnik SJ, Reck M, Schlesner M, Meister M, Schneider MA, Dietz S, Stenzinger A, Thomas M, Sultmann H. Early identification of disease progression in ALK-rearranged lung cancer using circulating tumor DNA analysis. NPJ Precis Oncol. 2021;5(1):100	Wrong study design
Jiang Y, Shi Y, Liu Y, Wang Z, Ma Y, Shi X, Lu L, Li H, Zhang Y, Liu C, Zhang S, Zhong Z, Lu J, Shi M, Shen B, Zhou G, Yin R, Galetta D, Grenda A, Romero A, Hughes BGM, Chen C, Wang X, Feng J. Efficacy and safety of alectinib in ALK-positive non-small cell lung cancer and blood markers for prognosis and efficacy: a retrospective cohort study. Transl. 2022;11(12):2521-2538	Wrong intervention
Gragnano G, Nacchio M, Sgariglia R, Conticelli F, Iaccarino A, De Luca C, Troncone G, Malapelle U. Performance evaluation of a fully closed real-time PCR platform for the detection of KRAS p.G12C mutations in liquid biopsy of patients with non-small cell lung cancer. J Clin Pathol. 2022;75(5):350-353	Wrong study design
Tran VT, Phan TT, Nguyen ST, Tran BT, Ho TT, Pho SP, Nguyen TB, Pham TTB, Le AT, Le VT, Nguyen HT. Smoking habit and chemo-radiotherapy and/or surgery affect the sensitivity of EGFR plasma test in non-small cell lung cancer. BMC Res Notes. 2020;13(1):367	Wrong study design
Stinchcombe TE, Wang X, Doebele RC, Drusbosky LM, Gerber DE, Horn L, Bertino EM, Liu G, Villaruz LC, Ross Camidge D. Short communication: The activity of brigatinib in patients with disease progression after next generation anaplastic lymphoma tyrosine kinase inhibitors and an exploratory analysis of circulating tumor DNA. Lung Cancer. 2022;165:43-48	Wrong patient population
Jin J, He J, Yan X, Zhao Y, Zhang H, Zhuang K, Wen Y, Gao J. Comparison of EGFR mutations detected by LNA-ARMS PCR in plasma ctDNA samples and matched tissue sample in non-small cell lung cancer patients.Am J Transl Res. 2022;14(8):5605-5613	Wrong study design
Santos ES, Raez L, Castillero LDC, Marana C, Hunis B. 3PD Liquid biopsy in patients with adenocarcinoma of the lung and its correlation with their tumor tissue molecular profile. Journal of Thoracic Oncology. 2016;11(4):S58	Conference paper
Mlika M, Dziri C, Zorgati MM, Ben Khelil M, Mezni F. Liquid biopsy as surrogate to tissue in lung cancer for molecular profiling: a meta-analysis. Curr Respir Med Rev. 2018;14(1):48-60	A systematic review/meta-analysis searched to identify missed eligible studies
Biaoxue R, Shuanying Y. Tissue or blood: which is more suitable for detection of EGFR mutations in non-small cell lung cancer? Int J Biol Markers. 2017:0	A systematic review/meta-analysis searched to identify missed eligible studies
Li M, Yang L, Hughes J, van den Hout A, Burns C, Woodhouse R, Dennis L, Hegde P, Oxnard GR, Vietz C. Driver mutation variant allele frequency in circulating tumor dna and association with clinical outcome in patients with non-small cell lung cancer and EGFR- and KRAS-mutated tumors. J Mol Diagn 2022;24(5):543-553	Wrong study design
Guo ZW, Li JQ, Zhou CL, Zhai XM, Li M, Wu YS, Yang XX. Circulating tumor DNA detection in advanced non-small cell lung cancer patients. Translational Cancer Research. 2017;6(5):878-885	Wrong study design

Citation	Primary reason for exclusion
Ottestad AL, Wahl SGF, Gronberg BH, Skorpen F, Dai HY. The relevance of tumor mutation profiling in interpretation of NGS data from cell-free DNA in non-small cell lung cancer patients. Exp Mol Pathol 2020;112:104347	Wrong study design
Ryan DJ, Toomey S, Smyth R, Madden SF, Workman J, Cummins R, Sheehan K, Fay J, Naidoo J, Breathnach OS, Morris PG, Grogan L, O'Brien ME, Sulaiman I, Hennessy BT, Morgan RK. Exhaled Breath Condensate (EBC) analysis of circulating tumour DNA (ctDNA) using a lung cancer specific UltraSEEK oncogene panel. Lung Cancer 2022;168:67-73	Wrong study design
Yang H, Zhang J, Zhang L, Wen X, Luo Y, Yao D, Cheng T, Cheng H, Wang H, Lou F, Guo J, Liang X, Cao S, Chen J. Comprehensive analysis of genomic alterations detected by next-generation sequencing-based tissue and circulating tumor DNA assays in Chinese patients with non-small cell lung cancer. Oncol .2019;18(5):4762-4770	Conference paper
Wu Y, Chen Q, Zhang Q, Li M, Li H, Jia L, Huang Y, Zhang J. Analysis of whole-exome data of cfDNA and the tumor tissue of non-small cell lung cancer. Ann. 2021;9(18):1453	Wrong study design
Ryu WK, Oh S, Lim JH, Lee SJ, Shin HT, Ryu JS. Monitoring circulating tumor DNA in untreated non-small-cell lung cancer patients. Int. 2022;23(17):23	Wrong study design
Qvick A, Stenmark B, Carlsson J, Isaksson J, Karlsson C, Helenius G. Liquid biopsy as an option for predictive testing and prognosis in patients with lung cancer. Mol Med. 2021;27(1):68	Wrong study design
Hasegawa N, Kohsaka S, Kurokawa K, Shinno Y, Takeda Nakamura I, Ueno T, Kojima S, Kawazu M, Suehara Y, Ishijima M, Goto Y, Kojima Y, Yonemori K, Hayashi T, Saito T, Shukuya T, Takahashi F, Takahashi K, Mano H. Highly sensitive fusion detection using plasma cell-free RNA in non-small-cell lung cancers. Cancer Sci. 2021;112(10):4393-4403	Wrong intervention
Guo N, Lou F, Ma Y, Li J, Yang B, Chen W, Ye H, Zhang JB, Zhao MY, Wu WJ, Shi R, Jones L, Chen KS, Huang XF, Chen SY, Liu Y. Circulating tumor DNA detection in lung cancer patients before and after surgery. Sci 2016;6:33519	Wrong study design
Pisapia P, Pepe F, Smeraglio R, Russo M, Rocco D, Sgariglia R, Nacchio M, De Luca C, Vigliar E, Bellevicine C, Troncone G, Malapelle U. Cell free DNA analysis by SiR_e^R next generation sequencing panel in non small cell lung cancer patients: focus on basal setting. J. 2017;9(Suppl 13):S1383-S1390	Wrong study design
Chow YP, Zainul Abidin N, Kow KS, Tho LM, Wong CL. Analytical and clinical validation of a custom 15-gene next-generation sequencing panel for the evaluation of circulating tumor DNA mutations in patients with advanced non-small-cell lung cancer. PLoS ONE. 2022;17(10):e0276161	Wrong study design
Eide IJZ, Stensgaard S, Helland A, Ekman S, Mellemgaard A, Hansen KH, Cicenas S, Koivunen J, Gronberg BH, Sorensen BS, Brustugun OT. Osimertinib in non-small cell lung cancer with uncommon EGFR-mutations: a post-hoc subgroup analysis with pooled data from two phase II clinical trials. Transl 2022;11(6):953-963	Wrong intervention
Schwartzberg LS, Li G, Tolba K, Bourla AB, Schulze K, Gadgil R, Fine A, Lofgren KT, Graf RP, Oxnard GR, Daniel D. Complementary roles for tissue- and blood-based comprehensive genomic profiling for detection of actionable driver alterations in advanced NSCLC. JTO Clin Res Rep .2022;3(9):100386	Wrong study design
Zulato E, Tosello V, Nardo G, Bonanno L, Del Bianco P, Indraccolo S. Implementation of next generation sequencing-based liquid biopsy for clinical molecular diagnostics in non-small cell lung cancer (NSCLC) patients. Diagnostics (Basel) 2021;11(8):13	Wrong study design
Mack PC, Banks KC, Espenschied CR, Burich RA, Zill OA, Lee CE, Riess JW, Mortimer SA, Talasaz A, Lanman RB, Gandara DR. Spectrum of driver mutations and clinical impact of circulating tumor DNA analysis in non-small cell lung cancer: Analysis of over 8000 cases. Cancer. 2020;126(14):3219-3228	Wrong study design
Zhao S, Zhang Z, Zhan J, Zhao X, Chen X, Xiao L, Wu K, Ma Y, Li M, Yang Y, Fang W, Zhao H, Zhang L. Utility of comprehensive genomic profiling in directing treatment and improving patient outcomes in advanced non-small cell lung cancer. BMC Med. 2021;19(1):223	Wrong intervention
van Delft F, Koffijberg H, Retel V, Heuvel MVD, IJzerman M. The validity and predictive value of blood-based biomarkers in prediction of response in the treatment of metastatic non-small cell lung cancer: a systematic review. Cancers (Basel) 2020;12(5):30	A systematic review/meta-analysis searched to identify missed eligible studies
Ramalingam SS, Yang JC, Lee CK, Kurata T, Kim DW, John T, Nogami N, Ohe Y, Mann H, Rukazenkov Y, Ghiorghiu S, Stetson D, Markovets A, Barrett JC, Thress KS, Janne PA. Osimertinib as first-line treatment of egfr mutation-positive advanced non-small-cell lung cancer. J Clin Oncol. 2018;36(9):841-849	Wrong intervention

Citation	Primary reason for exclusion
Bapat B, Weerasinghe R, Meng R, Dowdell A, Chang SC, Schroeder B, Bifulco C, Piening B. Clinical actionability and therapy selection for advanced NSCLC patients tested using comprehensive genomic profiling. European Journal of Cancer .2022;174(Supplement 1):S97-S98	Conference paper
Chen Z, Miao H, Zeng Q, Xu S, Liu K. Circulating cell-free DNA as a diagnostic and prognostic biomarker for non-small-cell lung cancer: a systematic review and meta-analysis. Biomark. 2020;14(7):587-597	A systematic review/meta-analysis searched to identify missed eligible studies
Bessi S, Pepe F, Russo G, Pisapia P, Ottaviantonio M, Biancalani F, Iaccarino A, Russo M, Biancalani M, Troncone G, Malapelle U. Comparison of two next-generation sequencing-based approaches for liquid biopsy analysis in patients with non-small cell lung cancer: a multicentre study. J Clin Pathol 2023;76(3):206-210	Wrong study design
Giardina T, Robinson C, Grieu-Iacopetta F, Millward M, Iacopetta B, Spagnolo D, Amanuel B. Implementation of next generation sequencing technology for somatic mutation detection in routine laboratory practice. Pathology. 2018;50(4):389-401	Wrong patient population
Dagogo-Jack I, Brannon AR, Ferris LA, Campbell CD, Lin JJ, Schultz KR, Ackil J, Stevens S, Dardaei L, Yoda S, Hubbeling H, Digumarthy SR, Riester M, Hata AN, Sequist LV, Lennes IT, Iafrate AJ, Heist RS, Azzoli CG, Farago AF, Engelman JA, Lennerz JK, Benes CH, Leary RJ, Shaw AT, Gainor JF. Tracking the evolution of resistance to ALK tyrosine kinase inhibitors through longitudinal analysis of circulating tumor DNA. JCO precis. 2018	Wrong study design
Frost N, Christopoulos P, Kauffmann-Guerrero D, Stratmann J, Riedel R, Schaefer M, Alt J, Gutz S, Christoph DC, Laack E, Faehling M, Fischer R, Fenchel K, Haen S, Heukamp L, Schulz C, Griesinger F. Lorlatinib in pretreated ALK- or ROS1-positive lung cancer and impact of TP53 co-mutations: results from the German early access program. Therapeutic Advances in Medical Oncology. 2021;13(no pagination)	Wrong patient population
Torres GF, Bonilla CE, Buitrago G, Arrieta O, Malapelle U, Rolfo C, Cardona AF. How clinically useful is comprehensive genomic profiling for patients with non-small cell lung cancer? A systematic review. Crit Rev Oncol Hematol. 2021;166:103459	A systematic review/meta-analysis searched to identify missed eligible studies
Aggarwal C, Thompson JC, Black TA, Katz SI, Fan R, Yee SS, Chien AL, Evans TL, Bauml JM, Alley EW, Ciunci CA, Berman AT, Cohen RB, Lieberman DB, Majmundar KS, Savitch SL, Morrissette JJD, Hwang WT, Elenitoba-Johnson KSJ, Langer CJ, Carpenter EL. Clinical implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non-small cell lung cancer. JAMA Oncol. 2019;5(2):173-180	Wrong study design
Jiang J, Adams HP, Yao L, Yaung S, Lal P, Balasubramanyam A, Fuhlbruck F, Tikoo N, Lovejoy AF, Froehler S, Fang LT, Achenbach HJ, Floegel R, Krugel R, Palma JF. Concordance of genomic alterations by next-generation sequencing in tumor tissue versus cell-free DNA in stage I-IV non-small cell lung cancer. J Mol Diagn 2020;22(2):228-235	Wrong study design
Iwama E, Sakai K, Azuma K, Harada T, Harada D, Nosaki K, Hotta K, Ohyanagi F, Kurata T, Fukuhara T, Akamatsu H, Goto K, Shimose T, Kishimoto J, Nakanishi Y, Nishio K, Okamoto I. Monitoring of somatic mutations in circulating cell-free DNA by digital PCR and next-generation sequencing during afatinib treatment in patients with lung adenocarcinoma positive for EGFR activating mutations. Ann Oncol 2017;28(1):136-141	Wrong study design
Lam VK, Tran HT, Banks KC, Lanman RB, Rinsurongkawong W, Peled N, Lewis J, Lee JJ, Roth J, Roarty EB, Swisher S, Talasaz A, Futreal PA, Papadimitrakopoulou V, Heymach JV, Zhang J. Targeted tissue and cell-free tumor DNA sequencing of advanced lung squamous-cell carcinoma reveals clinically significant prevalence of actionable alterations. Clin Lung Cancer. 2019;20(1):30-36.e3	Wrong study design
Zhang M, Wu J, Zhong W, Zhao Z, Guo W. Comparative study on the mutation spectrum of tissue DNA and blood ctDNA in patients with non-small cell lung cancer. Transl 2022;11(5):1245-1254	Wrong study design
He Y, Guo W, Xu M, Huang J, Zhang X, Su H, Hong D, Liu Q. Concordance of genomic profiles in matched tissue and plasma samples from chinese patients with lung cancer. Clin Med Insights Oncol. 2022;16:11795549221116834	Wrong patient population
Ottestad AL, Dai HY, Halvorsen TO, Emdal EF, Wahl SGF, Gronberg BH. Associations between tumor mutations in cfDNA and survival in non-small cell lung cancer. Cancer Treat Res Commun. 2021;29:100471	Wrong study design

Citation	Primary reason for exclusion
Verner EL, Jackson JB, Severson E, Valkenburg KC, Greer AE, Riley DR, Sausen M, Maddox C, McGregor PM 3rd; Karandikar A, Hastings SB, Previs RA, Reddy VP, Jensen TJ, Ramkissoon SH. Validation of the labcorp plasma focus test to facilitate precision oncology through cell-free DNA genomic profiling of solid tumors. J Mol Diagn. 2023;15:15	Wrong study design
Lin X, Dong W, Lai X, Feng W, Yu X, Gu Q, Wang C, Xiao W, Zheng X. The clinical value of circulating tumor DNA detection in advanced non-small cell lung cancer. Transl. 2019;8(1):170-179	Wrong study design
Paz-Ares L, Hirsh V, Zhang L, de Marinis F, Yang JC, Wakelee HA, Seto T, Wu YL, Novello S, Juhasz E, Aren O, Sun Y, Schmelter T, Ong TJ, Pena C, Smit EF, Mok TS. Monotherapy administration of sorafenib in patients with non-small cell lung cancer (MISSION) trial: A phase iii multicenter placebo-controlled trial of sorafenib in patients with relapsed or refractory predominantly nonsquamous non-small-cell lung canc. J Thorac Oncol 2015;10(12):1745-53	Wrong patient population
Lee Y, Park S, Kim WS, Lee JC, Jang SJ, Choi J, Choi CM. Correlation between progression-free survival tumor burden and circulating tumor DNA in the initial diagnosis of advanced-stage EGFR-mutated non-small cell lung cancer. Thorac Cancer .2018;9(9):1104-1110	Wrong intervention
Veldore VH, Choughule A, Routhu T, Mandloi N, Noronha V, Joshi A, Dutt A, Gupta R, Vedam R, Prabhash K. Validation of liquid biopsy: plasma cell-free DNA testing in clinical management of advanced non-small cell lung cancer. Lung Cancer (Auckl) 2018;9:1-11	Wrong study design
Li N, Wang BX, Li J, Shao Y, Li MT, Li JJ, Kuang PP, Liu Z, Sun TY, Wu HQ, Ou W, Wang SY. Perioperative circulating tumor DNA as a potential prognostic marker for operable stage I to IIIA non-small cell lung cancer. Cancer. 2022;128(4):708-718	Wrong study design
Sehayek O, Kian W, Onn A, Stoff R, Sorotsky HG, Zemel M, Bar J, Dudnik Y, Nechushtan H, Rottenberg Y, Soussan-Gutman L, Dvir A, Roisman LC, Peled N. Liquid first is "solid" in naive non-small cell lung cancer patients: faster turnaround time with high concordance to solid next-generation sequencing. Front. 2022;12:912801	Wrong outcomes
Dai LJ, Wang C, Ding ZY. A case-control study supporting the use of liquid biopsy in the targeted therapy for lung cancer. Asian Pac J Cancer Prev .2018;19(7):1761-1766	Wrong study design
Falk AT, Ilie M, Long E, Tanga V, Lespinet V, Bordone O, Allegra M, Ribeyre C, Otto J, Poudenx M, Marquette CH, Hofman V, Hofman P. Liquid biopsy testing in routine clinical management of advanced non-small cell lung cancer: clinical validation in a single biopathology laboratory. Annals of Oncology. 2016;27(Supplement 6):vi18	Conference paper
Wang N, Zhang X, Wang F, Zhang M, Sun B, Yin W, Deng S, Wan Y, Lu W. The diagnostic accuracy of liquid biopsy in EGFR-mutated NSCLC: A systematic review and meta-analysis of 40 studies. SLAS Technol. 2021;26(1):42-54	A systematic review/meta-analysis searched to identify missed eligible studies
Liu Y, Meng Z, Wu Y, Wang S, Jin G, Qin Y, Wang F, Wang J, Zhou H, Su X, Fu X, Wang X, Shi X, Wen Z, Jia X, Qin Q, Gao Y, Guo W, Lu S. Plasma EGFR mutation abundance affects clinical response to first-line EGFR-TKIs in patients with advanced non-small cell lung cancer. Annals of Translational Medicine 2021;9(8) (no pagination)	Wrong intervention
Liu L, Qu J, Heng J, Zhou C, Xiong Y, Yang H, Jiang W, Zeng L, Zhu S, Zhang Y, Tan J, Hu C, Deng P, Yang N. A large real-world study on the effectiveness of the combined inhibition of EGFR and MET in EGFR-mutant non-small-cell lung cancer after development of EGFR-TKI resistance. Frontiers in Oncology 2021;11 (no pagination):	Wrong patient population
Ai X, Cui J, Zhang J, Chen R, Lin W, Xie C, Liu A, Yang W, Hu X, Zhao Q, Rao C, Zang YS, Ning R, Li P, Chang L, Yi X, Lu S. Clonal architecture of EGFR mutation predicts the efficacy of EGFR-tyrosine kinase inhibitors in advanced NSCLC: A prospective multicenter study (NCT03059641). Clin Cancer Res. 2021;27(3):704-712	Wrong study design
Esagian SM, Grigoriadou GIota; Nikas IP, Boikou V, Sadow PM, Won JK, Economopoulos KP. Comparison of liquid-based to tissue-based biopsy analysis by targeted next generation sequencing in advanced non-small cell lung cancer: a comprehensive systematic review. J Cancer Res Clin Oncol. 2020;146(8):2051-2066	A systematic review/meta-analysis searched to identify missed eligible studies
Yang X, Zhong J, Yu Z, Zhuo M, Zhang M, Chen R, Xia X, Zhao J. Genetic and treatment profiles of patients with concurrent Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase (ALK) mutations. BMC Cancer 2021;21(1):1107	Wrong study design
Qian X, Liu J, Sun Y, Wang M, Lei H, Luo G, Liu X, Xiong C, Liu D, Tang Y. Circulating cell-free DNA has a high degree of specificity to detect exon 19 deletions and the single-point substitution mutation L858R in non-small cell lung cancer. Oncotarget. 2016;7(20):29154-65	A systematic review/meta-analysis searched to identify missed eligible studies

Citation	Primary reason for exclusion
Shu Y, Wu X, Tong X, Wang X, Chang Z, Mao Y, Chen X, Sun J, Wang Z, Hong Z, Zhu L, Zhu C, Chen J, Liang Y, Shao H, Shao YW. Circulating tumor DNA mutation profiling by targeted next generation sequencing provides guidance for personalized treatments in multiple cancer types. Sci. 2017;7(1):583	Wrong patient population
Madsen AT, Winther-Larsen A, McCulloch T, Meldgaard P, Sorensen BS. Genomic profiling of circulating tumor DNA predicts outcome and demonstrates tumor evolution in ALK-positive non-small cell lung cancer patients. Cancers (Basel) 2020;12(4):11	Wrong study design
Denis MG, Lafourcade MP, Le Garff G, Dayen C, Falchero L, Thomas P, Locher C, Fraboulet G, Oliviero G, Licour M, Normanno N, Reck M, Molinier O. Circulating free tumour-derived DNA (ctDNA) to detect EGFR mutation in patients (pts) with advanced NSCLC (aNSCLC): French subset analysis of the ASSESS study. Annals of Oncology. 2016;27(Supplement 6)():vi17	Conference paper
Qiu M, Wang J, Xu Y, Ding X, Li M, Jiang F, Xu L, Yin R. Circulating tumor DNA is effective for the detection of EGFR mutation in non-small cell lung cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2015;24(1):206-12	A systematic review/meta-analysis searched to identify missed eligible studies
Vanni I, Coco S, Truini A, Rusmini M, Dal Bello MG, Alama A, Banelli B, Mora M, Rijavec E, Barletta G, Genova C, Biello F, Maggioni C, Grossi F. Next-generation sequencing workflow for NSCLC critical samples using a targeted sequencing approach by Ion Torrent PGM TM platform. Int. 2015;16(12):28765-82	Wrong study design
Hanibuchi M, Kanoh A, Kuramoto T, Saito T, Tobiume M, Saijo A, Kozai H, Kondo M, Morizumi S, Yoneda H, Kagawa K, Ogino H, Sato S, Kawano H, Otsuka K, Toyoda Y, Nokihara H, Goto H, Nishioka Y. Development validation and comparison of gene analysis methods for detecting EGFR mutation from non-small cell lung cancer patients-derived circulating free DNA. Oncotarget. 2019;10(38):3654-3666	Wrong patient population
Frank MS, Andersen CSA, Ahlborn LB, Pallisgaard N, Bodtger U, Gehl J. Circulating tumor DNA monitoring reveals molecular progression before radiologic progression in a real-life cohort of patients with advanced non-small cell lung cancer. Cancer Res Commun. 2022;2(10):1174-1187	Wrong study design
Arriola E, Paredes-Lario A, Garcia-Gomez R, Diz-Tain P, Constenla M, Garcia-Giron C, Marquez G, Reck M, Lopez-Vivanco G. Comparison of plasma ctDNA and tissue/cytology-based techniques for the detection of EGFR mutation status in advanced NSCLC: Spanish data subset from ASSESS. Clin Transl Oncol. 2018;20(10):1261-1267	Wrong study design
Zheng J, Wang Y, Hu C, Zhu M, Ii J, Lin C, Lu C, Dou Y, Zhao C, Zhang Y, Wu D, Li L, Tang H, He T, Pan C, Han R, He Y. Predictive value of early kinetics of ctDNA combined with cfDNA and serum CEA for EGFR-TKI treatment in advanced non-small cell lung cancer. Thorac Cancer. 2022;13(22):3162-3173	Wrong study design
Cheung AH, Wong KY, Chiang CH, Liu X, Zhang Y, Hui CH, Chen B, Wang Y, Chow C, Kang W, To KF. Interpretation of lung cancer plasma egfr mutation tests in the clinical setting. Am J Clin Pathol 2023;159(2):181-191	A systematic review/meta-analysis searched to identify missed eligible studies
Kwon M, Ku BM, Olsen S, Park S, Lefterova M, Odegaard J, Jung HA, Sun JM, Lee SH, Ahn JS, Park K, Ahn MJ. Longitudinal monitoring by next-generation sequencing of plasma cell-free DNA in ALK rearranged NSCLC patients treated with ALK tyrosine kinase inhibitors. Cancer Med. 2022;11(15):2944-2956	Wrong intervention
Jia J, Huang B, Zhuang Z, Chen S. Circulating tumor DNA as prognostic markers for late stage NSCLC with bone metastasis. Int J Biol Markers. 2018;33(2):222-230	Wrong study design
Le X, Sakai H, Felip E, Veillon R, Garassino MC, Raskin J, Cortot AB, Viteri S, Mazieres J, Smit EF, Thomas M, Iams WT, Cho BC, Kim HR, Yang JCH, Chen YM, Patel JD, Bestvina CM, Park K, Griesinger F, Johnson M, Gottfried M, Britschgi C, Heymach J, Sikoglu E, Berghoff K, Schumacher KM, Bruns R, Otto G, Paik PK. Tepotinib Efficacy and Safety in Patients with MET Exon 14 Skipping NSCLC: Outcomes in Patient Subgroups from the VISION Study with Relevance for Clinical Practice. Clinical Cancer Research. 2022;28(6):1117-1126	Wrong intervention
Steendam CMJ, Atmodimedjo P, de Jonge E, Paats MS, van der Leest C, Oomen-de Hoop E, Jansen Mphm; Del Re M, von der Thusen JH, Dinjens WNM, van Schaik RHN, Aerts Jgjv; Dubbink HJ. Plasma cell-free DNA testing of patients with EGFR mutant non-small-cell lung cancer: droplet digital pcr versus next-generation sequencing compared with tissue-based results. JCO precis. 2019;3:1-9	Wrong patient population
Paweletz CP, Sacher AG, Raymond CK, Alden RS, O'Connell A, Mach SL, Kuang Y, Gandhi L, Kirschmeier P, English JM, Lim LP, Janne PA, Oxnard GR. Bias-corrected targeted next-generation sequencing for rapid multiplexed detection of actionable alterations in cell-free DNA from advanced lung cancer patients. Clin Cancer Res. 2016;22(4):915-22	Wrong study design

Citation	Primary reason for exclusion
Yasuda H, Ichihara E, Sakakibara-Konishi J, Zenke Y, Takeuchi S, Morise M, Hotta K, Sato M, Matsumoto S, Tanimoto A, Matsuzawa R, Kiura K, Takashima Y, Yano S, Koyama J, Fukushima T, Hamamoto J, Terai H, Ikemura S, Takemura R, Goto K, Soejima K. A phase I/II study of osimertinib in EGFR exon 20 insertion mutation-positive non-small cell lung cancer. Lung Cancer 2021;162:140-146	Wrong intervention
Kim ST, Banks KC, Lee SH, Kim K, Park JO, Park SH, Park YS, Lim HY, Kang WK, Lanman RB, Talasaz A, Park K, Lee J. Prospective feasibility study for using cell-free circulating tumor dna-guided therapy in refractory metastatic solid cancers: an interim analysis. JCO precis. 2017;1	Wrong study design
Deng Q, Fang Q, Sun H, Singh AP, Alexander M, Li S, Cheng H, Zhou S. Detection of plasma EGFR mutations for personalized treatment of lung cancer patients without pathologic diagnosis.Cancer Med. 2020;9(6):2085-2095	Wrong intervention
Zhou YJ, Zheng W, Zeng QH, Ye Y, Wang C, Fang C, Liu CJ, Niu L, Wu LM. Targeted exome sequencing identifies mutational landscape in a cohort of 1500 Chinese patients with non-small cell lung carcinoma (NSCLC). Hum Genomics 2021;15(1):21	Wrong study design
Li J, Gan S, Blair A, Min K, Rehage T, Hoeppner C, Halait H, Brophy VH. A Highly verified assay for KRAS mutation detection in tissue and plasma of lung colorectal and pancreatic cancer. Arch Pathol Lab Med. 2019;143(2):183-189	Wrong study design
Moon SM, Kim JH, Kim SK, Kim S, Kwon HJ, Bae JS, Lee S, Lee HS, Choi MY, Jeon BH, Jeong BH, Lee K, Kim HK, Kim J, Um SW. Clinical utility of combined circulating tumor cell and circulating tumor dna assays for diagnosis of primary lung cancer. Anticancer Res. 2020;40(6):3435-3444	Wrong study design
Phan C, Jespersen F, Weipert C, Li T, Yoneda KY. Interventional pulmonology use of cell-free DNA assay for metastatic non-small cell lung cancer: the UC Davis experience. Therap 2022;16():17534666221135324	Wrong study design
Buyuksimsek M, Togun M, Oguz KI, Bisgin A, Boga I, Tohumcuoglu M, Ogul A, Evren YA, Sahin B, Erdem SH, Mirili C. Results of liquid biopsy studies by next generation sequencing in patients with advanced stage non-small cell lung cancer: single center experience from turkey. BJMG Balk 2019;22(2):17-24	Wrong study design
Jacobs MT, Mohindra NA, Shantzer L, Chen IL, Phull H, Mitchell W, Raymond VM, Banks KC, Nagy RJ, Lanman RB, Christensen J, Patel JD, Clarke J, Patel SP. Use of low-frequency driver mutations detected by cell-free circulating tumor dna to guide targeted therapy in non-small-cell lung cancer: a multicenter case series. JCO precis. 2018;2:1-10	Wrong patient population
Thompson JC, Carpenter EL, Silva BA, Rosenstein J, Chien AL, Quinn K, Espenschied CR, Mak A, Kiedrowski LA, Lefterova M, Nagy RJ, Katz SI, Yee SS, Black TA, Singh AP, Ciunci CA, Bauml JM, Cohen RB, Langer CJ, Aggarwal C. Serial monitoring of circulating tumor DNA by next-generation gene sequencing as a biomarker of response and survival in patients with advanced NSCLC receiving pembrolizumab-based therapy. JCO precis 2021;5	Wrong patient population
Wang S, Han X, Hu X, Wang X, Zhao L, Tang L, Feng Y, Wu D, Sun Y, Shi Y. Clinical significance of pretreatment plasma biomarkers in advanced non-small cell lung cancer patients. Clin Chim Acta. 2014;430():63-70	Wrong patient population
Phallen J, Sausen M, Adleff V, Leal A, Hruban C, White J, Anagnostou V, Fiksel J, Cristiano S, Papp E, Speir S, Reinert T, Orntoft MW, Woodward BD, Murphy D, Parpart-Li S, Riley D, Nesselbush M, Sengamalay N, Georgiadis A, Li QK, Madsen MR, Mortensen FV, Huiskens J, Punt C, van Grieken N, Fijneman R, Meijer G, Husain H, Scharpf RB, Diaz LA Jr, Jones S, Angiuoli S, Orntoft T, Nielsen HJ, Andersen CL, Velculescu VE. Direct detection of early-stage cancers using circulating tumor DNA. Sci Transl Med. 2017;9(403):16	Wrong study design
Noe J, Lovejoy A, Ou SI, Yaung SJ, Bordogna W, Klass DM, Cummings CA, Shaw AT. ALK mutation status before and after alectinib treatment in locally advanced or metastatic ALK-positive NSCLC: Pooled analysis of two prospective trials. J Thorac Oncol. 2020;15(4):601-608	Wrong comparator
Li H, Yan S, Liu Y, Ma L, Liu X, Cheng Y. Analysis of NTRK mutation and clinicopathologic factors in lung cancer patients in northeast China. Int J Biol Markers. 2020;35(3):36-40	Wrong patient population
Papadopoulou E, Tsoulos N, Tsantikidi K, Metaxa-Mariatou V, Stamou PE, Kladi-Skandali A, Kapeni E, Tsaousis G, Pentheroudakis G, Petrakis D, Lampropoulou DI, Aravantinos G, Varthalitis I, Kesisis G, Boukovinas I, Papakotoulas P, Katirtzoglou N, Athanasiadis E, Stavridi F, Christodoulou C, Koumarianou A, Eralp Y, Nasioulas G. Clinical feasibility of NGS liquid biopsy analysis in NSCLC patients. PLoS ONE 2019;14(12):e0226853	Wrong study design

Citation	Primary reason for exclusion
Fan G, Zhang K, Ding J, Li J. Prognostic value of EGFR and KRAS in circulating tumor DNA in patients with advanced non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget 2017;8(20):33922-33932	A systematic review/meta-analysis searched to identify missed eligible studies
Montella M, Ciani G, Granata V, Fusco R, Grassi F, Ronchi A, Cozzolino I, Franco R, Zito Marino F, Urraro F, Monti R, Sirica R, Savarese G, Chianese U, Nebbioso A, Altucci L, Vietri MT, Nardone V, Reginelli A, Grassi R. Preliminary experience of liquid biopsy in lung cancer compared to conventional assessment: light and shadows. J 2022;12(11):12	Wrong study design
He X, Chi Y, Peng J, Hu W, Ding C, Li B. A systematic review and meta-analysis of circulating cell-free DNA as a diagnostic biomarker for non-small cell lung cancer. J. 2022;14(6):2103-2111	A systematic review/meta-analysis searched to identify missed eligible studies
Plagnol V, Woodhouse S, Howarth K, Lensing S, Smith M, Epstein M, Madi M, Smalley S, Leroy C, Hinton J, de Kievit F, Musgrave-Brown E, Herd C, Baker-Neblett K, Brennan W, Dimitrov P, Campbell N, Morris C, Rosenfeld N, Clark J, Gale D, Platt J, Calaway J, Jones G, Forshew T. Analytical validation of a next generation sequencing liquid biopsy assay for high sensitivity broad molecular profiling. PLoS ONE. 2018;13(3):e0193802	Wrong study design
Remon J, Swalduz A, Planchard D, Ortiz-Cuaran S, Mezquita L, Lacroix L, Jovelet C, Rouleau E, Leonce C, De Kievit F, Morris C, Jones G, Mercier K, Howarth K, Green E, Perol M, Saintigny P, Besse B. Outcomes in oncogenic-addicted advanced NSCLC patients with actionable mutations identified by liquid biopsy genomic profiling using a tagged amplicon-based NGS assay. PLoS ONE. 2020;15(6):e0234302	Wrong patient population
Song Z, Li Y, Chen S, Ying S, Xu S, Huang J, Wu D, Lv D, Bei T, Liu S, Huang X, Xie C, Wu X, Fu J, Hua F, Wang W, Xu C, Gao C, Cai S, Lu S, Zhang Y. Efficacy and safety of pyrotinib in advanced lung adenocarcinoma with HER2 mutations: a multicenter single-arm phase II trial. BMC Med 2022;20(1):42	Wrong intervention
Chang LC, Lim CK, Chang LY, Chen KY, Shih JY, Yu CJ. Non-small cell lung cancer harbouring non-resistant uncommon EGFR mutations: Mutation patterns effectiveness of epidermal growth factor receptor-tyrosine kinase inhibitors and prognostic factors. European Journal of Cancer. 2019;119:77-86	Wrong intervention
Wulandari L, Soegiarto G, Febriani A, Fatmawati F, Sahrun. Comparison of Detection of Epidermal Growth Factor Receptor (EFGR) Gene Mutation in Peripheral Blood Plasma (Liquid Biopsy) with Cytological Specimens in Lung Adenocarcinoma Patients. Indian j. 2021;12(Suppl 1):65-71	Wrong study design
Milner-Watts C, Lyons H, Cui W, Yousaf N, Minchom A, Bhosle J, Davidson M, Scott S, Faull I, Nagy R, O'Brien M, Popat S. 70 Detection of tier 1 variants with circulating tumour (ct) DNA next generation sequencing (NGS) in UK non-small cell lung cancer (NSCLC) patients. Lung Cancer. 2021;156(Supplement 1):S28	Conference paper
Xie J, Yao W, Chen L, Zhu W, Liu Q, Geng G, Fang J, Zhao Y, Xiao L, Huang Z, Zhao J. Plasma ctDNA increases tissue NGS-based detection of therapeutically targetable mutations in lung cancers. BMC Cancer. 2023;23(1):294	Wrong patient population
Wu Z, Yang Z, Li CS, Zhao W, Liang ZX, Dai Y, Zeng J, Zhu Q, Miao KL, Cui DH, Chen LA. Non-invasive detection of EGFR and TP53 mutations through the combination of plasma, urine and sputum in advanced non-small cell lung cancer. Oncol. 2019;18(4):3581-3590	Wrong study design
Rodon Font N, No Garbarino Y, Diaz Castello O, Moya Amoros J, Barrios Sanchez P, Coroleu Lletget D, Lequerica Cabello MA, Borras Marcet J, Mecho Meca S, Escape I, Martinez-Agea J, Garcia E, Ferrer M, Puig Torrus X. Concordance analysis between liquid biopsy (ctDNA) and tumor DNA molecular profiles from panel-based next-generation sequencing. Rev. 2022;55(3):156-162	Wrong study design
Sim WC, Loh CH, Toh GL, Lim CW, Chopra A, Chang AYC, Goh LL. Non-invasive detection of actionable mutations in advanced non-small-cell lung cancer using targeted sequencing of circulating tumor DNA. Lung Cancer. 2018;124:154-159	Wrong study design
Wolf J, Garon EB, Groen HJM, Tan DSW, Le Mouhaer S, Riester M, Ji L, Robeva A, Fairchild L, Boran A, Heist RS. Capmatinib response in patients with advanced non-small cell lung cancer (NSCLC) harboring focal MET amplifications: Analysis from the phase 2 multicohort GEOMETRY mono-1 study. European Journal of Cancer. 2022;174(Supplement 1):S21	Conference paper

Citation	Primary reason for exclusion
Visser E, de Kock R, Genet S, Borne BVD, Soud MY, Belderbos H, Stege G, de Saegher M, t Westeinde SV, Broeren M, Eduati F, Deiman B, Scharnhorst V. Up-front mutation detection in circulating tumor DNA by droplet digital PCR has added diagnostic value in lung cancer. Transl Oncol. 2023;27:101589	Wrong study design
Muller JN, Falk M, Talwar J, Neemann N, Mariotti E, Bertrand M, Zacherle T, Lakis S, Menon R, Gloeckner C, Tiemann M, Heukamp LC, Thomas RK, Griesinger F, Heuckmann JM. Concordance between Comprehensive Cancer Genome Profiling in Plasma and Tumor Specimens.J Thorac Oncol 2017;12(10):1503-1511	Wrong study design
Vansteenkiste JF, Canon JL, De Braud F, Grossi F, De Pas T, Gray JE, Su WC, Felip E, Yoshioka H, Gridelli C, Dy GK, Thongprasert S, Reck M, Aimone P, Vidam GA, Roussou P, Wang YA, Di Tomaso E, Soria JC. Safety and Efficacy of Buparlisib (BKM120) in Patients with PI3K Pathway-Activated Non-Small Cell Lung Cancer: Results from the Phase II BASALT-1 Study. J Thorac Oncol. 2015;10(9):1319-1327	Wrong intervention
Shen HB, Li J, Yao YS, Yang ZH, Zhou YJ, Chen W, Hu TJ. Impact of Somatic Mutations in Non-Small-Cell Lung Cancer: A Retrospective Study of a Chinese Cohort. Cancer Manag Res.2020;12:7427-7437	Wrong study design
Maansson CT, Andersen ER, Ulhoi MP, Meldgaard P, Sorensen BS. DNAfusion: an R/Bioconductor package for increased sensitivity of detecting gene fusions in liquid biopsies. BMC Bioinformatics 2023;24(1):131	Wrong study design
Lyu M, Zhou J, Ning K, Ying B. The diagnostic value of circulating tumor cells and ctDNA for gene mutations in lung cancer. Onco Targets Ther. 2019;12:2539-2552	Wrong study design
Mayer S, Schmidtke-Schrezenmeier G, Buske C, Rucker FG, Barth TFE, Moller P, Marienfeld R. Rescue of non-informative circulating tumor DNA to monitor the mutational landscape in NSCLC. Cancers (Basel). 2020;12(7):16	Wrong study design
Dvir K, Galarza-Fortuna GM, Haines JM, Gines P, Ruiz AL, Rodriguez E. Real-world data on liquid biopsy use in non-small cell lung cancer in the community setting. J Immunother Precis Oncol. 2021;4(1):1-5	Wrong study design
Guo AX, Xiao F, Shao WH, Zhan Y, Zhang L, Xiong J, Gao Y, Yin JY. Sequential Whole Exome Sequencing Reveals Somatic Mutations Associated with Platinum Response in NSCLC. Onco Targets Ther. 2020;13:6485-6496	Wrong study design
Zhang S, Su M, Sun Z, Lu H, Zhang Y. Feature article: The signature of pharmaceutical sensitivity based on ctDNA mutation in eleven cancers. Experimental Biology and Medicine 2020;245(8)():720-732	Wrong study design
Kaisaki PJ, Cutts A, Popitsch N, Camps C, Pentony MM, Wilson G, Page S, Kaur K, Vavoulis D, Henderson S, Gupta A, Middleton MR, Karydis I, Talbot DC, Schuh A, Taylor JC. Targeted next-generation sequencing of plasma DNA from cancer patients: factors influencing consistency with tumour DNA and prospective investigation of its utility for diagnosis. PLoS ONE. 2016;11(9):e0162809	Wrong patient population
Shin JY, Kim JO, Lee MR, Kim SR, Beck KS, Kang JH. A Highly sensitive next-generation sequencing-based genotyping platform for EGFR mutations in plasma from non-small cell lung cancer patients. Cancers (Basel). 2020;12(12):30	Wrong study design
Saarenheimo J, Andersen H, Eigeliene N, Jekunen A. Gene-guided treatment decision-making in non-small cell lung cancer - a systematic review. Front. 2021;11:754427	A systematic review/meta-analysis searched to identify missed eligible studies
Barthelemy D, Lescuyer G, Geiguer F, Grolleau E, Gauthier A, Balandier J, Raffin M, Bardel C, Bouyssounouse B, Rodriguez-Lafrasse C, Couraud S, Wozny AS, Payen L. Paired comparison of routine molecular screening of patient samples with advanced non-small cell lung cancer in circulating cell-free DNA using three targeted assays. Cancers (Basel). 2023;15(5):03	Wrong study design
Taylor C, Chacko S, Davey M, Lacroix J, MacPherson A, Finn N, Wajnberg G, Ghosh A, Crapoulet N, Lewis SM, Ouellette RJ. Peptide-affinity precipitation of extracellular vesicles and cell-free dna improves sequencing performance for the detection of pathogenic mutations in lung cancer patient plasma. Int. 2020;21(23):29	Wrong study design
Meng H, Guo X, Sun D, Liang Y, Lang J, Han Y, Lu Q, Zhang Y, An Y, Tian G, Yuan D, Xu S, Geng J. Genomic profiling of driver gene mutations in chinese patients with non-small cell lung cancer. Front. 2019;10:1008	Wrong study design

Citation	Primary reason for exclusion
Yu H, Liu M, Qiu H, Yang K. Urinary and plasma cell-free DNA comparison for lung cancer patients treated with epidermal growth factor receptor-thyroxine kinase inhibitors. Am J Med Sci 2019;357(1):29-36	Wrong intervention
Yang H, Zhou Z, Lin L, Yang M, Li C, Li Z, Yu X, Lizaso A, Han-Zhang H, Li B, Xiang J, Mao X, Xu Q, Zhang Y, Yang N. Characterization of MET exon 14 alteration and association with clinical outcomes of crizotinib in Chinese lung cancers. Lung Cancer. 2020;148:113-121	Wrong intervention
Zaman FY, Subramaniam A, Afroz A, Samoon Z, Gough D, Arulananda S, Alamgeer M. Circulating tumour DNA (ctDNA) as a predictor of clinical outcome in non-small cell lung cancer undergoing targeted therapies: a systematic review and meta-analysis. Cancers (Basel). 2023;15(9):23	A systematic review/meta-analysis searched to identify missed eligible studies
Goto T, Hirotsu Y, Oyama T, Amemiya K, Omata M. Analysis of tumor-derived DNA in plasma and bone marrow fluid in lung cancer patients. Med Oncol 2016;33(3):29	Wrong study design
Shen H, Jin Y, Zhao H, Wu M, Zhang K, Wei Z, Wang X, Wang Z, Li Y, Yang F, Wang J, Chen K. Potential clinical utility of liquid biopsy in early-stage non-small cell lung cancer. BMC Med 2022;20(1):480	A systematic review/meta-analysis searched to identify missed eligible studies
Oxnard GR, Thress KS, Alden RS, Lawrance R, Paweletz CP, Cantarini M, Barrett C, Yang J, Janne P. 135O_PR: Plasma genotyping for predicting benefit from osimertinib in patients (pts) with advanced NSCLC. Journal of Thoracic Oncology. 2016;11(4):S154	Conference paper
Mao X, Zhang Z, Zheng X, Xie F, Duan F, Jiang L, Chuai S, Han-Zhang H, Han B, Sun J. Capture-Based Targeted Ultradeep Sequencing in Paired Tissue and Plasma Samples Demonstrates Differential Subclonal ctDNA-Releasing Capability in Advanced Lung Cancer. J Thorac Oncol. 2017;12(4):663-672	Wrong patient population
Xu J, Liu Z, Bai H, Dong G, Zhong J, Wan R, Zang A, Li X, Li Q, Guo J, Du N, Zhong D, Huang Y, Lv Q, Zhang J, Zhao Y, Gao L, Li L, Zhang C, Zhao J, Li B, Yang Z, Ji D, Wang T, Duan J, Wang Z, Wang J. Evaluation of clinical outcomes of icotinib in patients with clinically diagnosed advanced lung cancer with egfr-sensitizing variants assessed by circulating tumor dna testing: A phase 2 nonrandomized clinical trial. JAMA Oncol. 2022;8(9):1328-1332	Wrong patient population
Satapathy S, Singh V, Nambirajan A, Malik PS, Tanwar P, Mehta A, Suryavanshi M, Thulkar S, Mohan A, Jain D. EGFR mutation testing on plasma and urine samples: A pilot study evaluating the value of liquid biopsy in lung cancer diagnosis and management. Curr Probl Cancer. 2021;45(6):100722	Wrong intervention
Supplee JG, Milan MSD, Lim LP, Potts KT, Sholl LM, Oxnard GR, Paweletz CP. Sensitivity of next-generation sequencing assays detecting oncogenic fusions in plasma cell-free DNA. Lung Cancer 2019;134:96-99	Wrong study design
Dagogo-Jack I, Moonsamy P, Gainor JF, Lennerz JK, Piotrowska Z, Lin JJ, Lennes IT, Sequist LV, Shaw AT, Goodwin K, Stevens SE, Do A, Digumarthy SR, Price K, Muzikansky A, Hata AN, Heist RS. A phase 2 study of capmatinib in patients with MET-altered lung cancer previously treated with a MET inhibitor. J Thorac Oncol .2021;16(5):850-859	Wrong patient population
Bhandari NR, Hess LM, Han Y, Zhu YE, Sireci AN. Efficacy of immune checkpoint inhibitor therapy in patients with RET fusion-positive non-small-cell lung cancer. Immunotherapy .2021;13(11):893-904	Wrong study design
Paik PK, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, Mazieres J, Viteri S, Senellart H, van Meerbeeck J, Raskin J, Reinmuth N, Conte P, Kowalski D, Cho BC, Patel JD, Horn L, Griesinger F, Han JY, Kim YC, Chang GC, Tsai CL, Yang JCH, Chen YM, Smit EF, van der Wekken AJ, Kato T, Juraeva D, Stroh C, Bruns R, Straub J, Johne A, Scheele J, Heymach JV, Le X. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. New England Journal of Medicine. 2020;383(10):931-943	Wrong study design
Jin Y, Shi X, Zhao J, He Q, Chen M, Yan J, Ou Q, Wu X, Shao YW, Yu X. Mechanisms of primary resistance to EGFR targeted therapy in advanced lung adenocarcinomas. Lung Cancer. 2018;124:110-116	Wrong patient population
Heeke S, Hofman V, Ilie M, Allegra M, Lespinet V, Bordone O, Benzaquen J, Boutros J, Poudenx M, Lalvee S, Tanga V, Salacroup C, Bonnetaud C, Marquette CH, Hofman P. Prospective evaluation of NGS-based liquid biopsy in untreated late stage non-squamous lung carcinoma in a single institution. J. 2020;18(1):87	Wrong study design
Agulnik JS, Papadakis AI, Pepe C, Sakr L, Small D, Wang H, Kasymjanova G, Spatz A, Cohen V. Cell-free tumor DNA (ctDNA) utility in detection of original sensitizing and resistant EGFR mutations in non-small cell lung cancer (NSCLC). Curr. 2022;29(2):1107-1116	Wrong study design

Citation	Primary reason for exclusion
Xi Y, Bai Z, Gao S, Guo J, Zhang Z, Zhang H, Qu L, Xu B, Wang W, Shan G, Cui W, Bai W, Ji X. Genomic profiling of NGS-based ctDNA from Chinese non-small cell lung cancer patients. J Cancer Res Clin Oncol. 2023;25:25	Wrong study design
Park CK, Lee SY, Lee JC, Choi CM, Jang TW, Oh IJ, Kim YC. Phase II open-label multicenter study to assess the antitumor activity of afatinib in lung cancer patients with activating epidermal growth factor receptor mutation from circulating tumor DNA: Liquid-Lung-A. Thorac Cancer 2021;12(4):444-452	Wrong intervention
Duan H, Lu J, Lu T, Gao J, Zhang J, Xu Y, Wang M, Wu H, Liang Z, Liu T. Comparison of EGFR mutation status between plasma and tumor tissue in non-small cell lung cancer using the Scorpion ARMS method and the possible prognostic significance of plasma EGFR mutation status. Int J Clin Exp Pathol. 2015;8(10):13136-45	Wrong study design
Li Z, Zhang Y, Bao W, Jiang C. Insufficiency of peripheral blood as a substitute tissue for detecting EGFR mutations in lung cancer: a meta-analysis. Target. 2014;9(4):381-8	A systematic review/meta-analysis searched to identify missed eligible studies
Shaw AT, Solomon BJ, Besse B, Bauer TM, Lin CC, Soo RA, Riely GJ, Ou SI, Clancy JS, Li S, Abbattista A, Thurm H, Satouchi M, Camidge DR, Kao S, Chiari R, Gadgeel SM, Felip E, Martini JF. ALK resistance mutations and efficacy of lorlatinib in advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer. J Clin Oncol. 2019;37(16):1370-1379	Wrong patient population
Sakai H, Morise M, Kato T, Matsumoto S, Sakamoto T, Kumagai T, Tokito T, Atagi S, Kozuki T, Tanaka H, Chikamori K, Shinagawa N, Takeoka H, Bruns R, Straub J, Schumacher KM, Paik PK. Tepotinib in patients with NSCLC harbouring MET exon 14 skipping: Japanese subset analysis from the Phase II VISION study. Jpn J Clin Oncol. 2021;51(8):1261-1268	Wrong intervention
Riess JW, Reckamp KL, Frankel P, Longmate J, Kelly KA, Gandara DR, Weipert CM, Raymond VM, Keer HN, Mack PC, Newman EM, Lara PN Jr. Erlotinib and onalespib lactate focused on EGFR exon 20 insertion non-small cell lung cancer (NSCLC): A California cancer consortium phase I/II trial (NCI 9878). Clin Lung Cancer 2021;22(6):541-548	Wrong patient population
Chae YK, Davis AA, Carneiro BA, Chandra S, Mohindra N, Kalyan A, Kaplan J, Matsangou M, Pai S, Costa R, Jovanovic B, Cristofanilli M, Platanias LC, Giles FJ. Concordance between genomic alterations assessed by next-generation sequencing in tumor tissue or circulating cell-free DNA. Oncotarget. 2016;7(40):65364-65373	Wrong patient population
Song Z, Lv D, Chen SQ, Huang J, Li Y, Ying S, Wu X, Hua F, Wang W, Xu C, Bei T, Gao C, Sun Z, Zhang Y, Lu S. Pyrotinib in patients with her2-amplified advanced non-small cell lung cancer: a prospective multicenter single-arm trial. Clinical Cancer Research. 2022;28(3):461-467	Wrong intervention
Horn L, Wakelee H, Blumenschein G, Reckamp K, Waqar S, Carter CA, Gitlitz BJ, Infante JR, Sanborn RE, Neal J, Gockerman JP, Dukart G, Harrow K, Liang C, Gibbons JJ, Hernandez J, Newman-Eerkes T, Lim L, Lovly C. Phase I/II trial of X-396 in patients (pts) with ALK+ non-small cell lung cancer (NSCLC): Correlation with plasma and tissue genotyping and response to therapy (tx). Annals of Oncology. 2016;27(Supplement 6):vi419	Conference paper
Paik PK, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, Mazieres J, Viteri S, Senellart H, Van Meerbeeck J, Raskin J, Reinmuth N, Conte P, Kowalski D, Cho BC, Patel JD, Horn L, Griesinger F, Han JY, Kim YC, Chang GC, Tsai CL, Yang JC, Chen YM, Smit EF, van der Wekken AJ, Kato T, Juraeva D, Stroh C, Bruns R, Straub J, Johne A, Scheele J, Heymach JV, Le X. Tepotinib in non-small-cell lung cancer with MET Exon 14 skipping mutations. N Engl J Med 2020;383(10):931-943	Wrong intervention
Desmeules P, Dusselier M, Bouffard C, Bafaro J, Fortin M, Labbe C, Joubert P. Retrospective assessment of complementary liquid biopsy on tissue single-gene testing for tumor genotyping in advanced NSCLC. Curr 2023;30(1):575-585	Wrong study design
Ma S, Shi M, Chen X, Wang Y, Yang Z, Lizaso A, Li M, Li H, Zhang L, Mao X, Xu X, Song Y. The prognostic value of longitudinal circulating tumor DNA profiling during osimertinib treatment. Transl. 2021;10(1):326-339	Wrong intervention
Fuchs V, Kian W, Lichtenberg R, Cooper JM, Remilah AA, Levin D, Peled N, Roisman LC. Next-generation sequencing liquid biopsy-guided osimertinib rechallenge in egfr-mutated advanced non-small-cell lung cancer patients. Clin Drug Invest. 2022;42(2):185-192	Wrong comparator
Drilon A, Clark JW, Weiss J, Ou SI, Camidge DR, Solomon BJ, Otterson GA, Villaruz LC, Riely GJ, Heist RS, Awad MM, Shapiro GI, Satouchi M, Hida T, Hayashi H, Murphy DA, Wang SC, Li S, Usari T, Wilner KD, Paik PK. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. Nat Med. 2020;26(1):47-51	Wrong patient population

Citation	Primary reason for exclusion
Ding PN, Becker T, Bray V, Chua W, Ma Y, Xu B, Lynch D, de Souza P, Roberts T. Plasma next generation sequencing and droplet digital PCR-based detection of epidermal growth factor receptor (EGFR) mutations in patients with advanced lung cancer treated with subsequent-line osimertinib. Thorac Cancer. 2019;10(10):1879-1884	Wrong patient population
Batra U, Nathany S, Sharma M, Jain P, Dhanda S, Singh H, Jain A, Mehta A. EGFR detection by liquid biopsy: ripe for clinical usage. Fut Oncol. 2022;18(1):85-92	Wrong study design
Behel V, Chougule A, Noronha V, Patil VM, Menon N, Singh A, Chopade S, Kumar R, Shah S, More S, Banavali SD, Chandrani P, Prabhash K. Clinical utility of liquid biopsy (cell-free DNA) based EGFR mutation detection post treatment initiation as a disease monitoring tool in patients with advanced EGFR-mutant NSCLC. Clin Lung Cancer. 2022;23(5):410-418	Wrong intervention
Wang Y, Tian PW, Wang WY, Wang K, Zhang Z, Chen BJ, He YQ, Li L, Liu H, Chuai S, Li WM. Noninvasive genotyping and monitoring of anaplastic lymphoma kinase (ALK) rearranged non-small cell lung cancer by capture-based next-generation sequencing. Oncotarget. 2016;7(40):65208-65217	Wrong study design
Mezquita L, Swalduz A, Jovelet C, Ortiz-Cuaran S, Howarth K, Planchard D, Avrillon V, Recondo G, Marteau S, Benitez JC, De Kievit F, Plagnol V, Lacroix L, Odier L, Rouleau E, Fournel P, Caramella C, Tissot C, Adam J, Woodhouse S, Nicotra C, Auclin E, Remon J, Morris C, Green E, Massard C, Perol M, Friboulet L, Besse B, Saintigny P. Clinical relevance of an amplicon-based liquid biopsy for detecting ALK and ROS1 fusion and resistance mutations in patients with non-small-cell lung cancer. JCO precis 2020;4	Wrong study design
Mok T, Wu YL, Lee JS, Yu CJ, Sriuranpong V, Sandoval-Tan J, Ladrera G, Thongprasert S, Srimuninnimit V, Liao M, Zhu Y, Zhou C, Fuerte F, Margono B, Wen W, Tsai J, Truman M, Klughammer B, Shames DS, Wu L. Detection and dynamic changes of egfr mutations from circulating tumor dna as a predictor of survival outcomes in NSCLC patients treated with first-line intercalated erlotinib and chemotherapy. Clin Cancer Res 2015;21(14):3196-203	Wrong intervention
Rao C, Nie L, Miao X, Xu Y, Li B, Zhang T. The clinical characteristics and prognostic analysis of Chinese advanced NSCLC patients based on circulating tumor DNA sequencing. Onco Targets Ther. 2018;11:337-344	Wrong study design
Horn L, Whisenant JG, Wakelee H, Reckamp KL, Qiao H, Leal TA, Du L, Hernandez J, Huang V, Blumenschein GR, Waqar SN, Patel SP, Nieva J, Oxnard GR, Sanborn RE, Shaffer T, Garg K, Holzhausen A, Harrow K, Liang C, Lim LP, Li M, Lovly CM. Monitoring therapeutic response and resistance: analysis of circulating tumor dna in patients with alk+ lung cancer. J Thorac Oncol 2019;14(11):1901-1911	Wrong study design
Waldeck S, Mitschke J, Wiesemann S, Rassner M, Andrieux G, Deuter M, Mutter J, Luchtenborg AM, Kottmann D, Titze L, Zeisel C, Jolic M, Philipp U, Lassmann S, Bronsert P, Greil C, Rawluk J, Becker H, Isbell L, Muller A, Doostkam S, Passlick B, Borries M, Duyster J, Wehrle J, Scherer F, von Bubnoff N. Early assessment of circulating tumor DNA after curative-intent resection predicts tumor recurrence in early-stage and locally advanced non-small-cell lung cancer. Mol Oncol. 2022;16(2):527-537	Wrong study design
Prabhash K, Biswas B, Khurana S, Batra U, Biswas G, Advani SH, Mohapatra PN, Rajappa S, Sharma A, Patil S, Dattatreya PS, Roy R, Almel S, Goyal G, Warrier N. CONCORDANCE: A real-world evidence study to evaluate the concordance of detecting epidermal growth factor receptor (EGFR) mutation by circulating tumor DNA versus tissue biopsy in patients with metastatic non-small cell lung cancer. Indian J Cancer 2022;59(Supplement):S11-S18	Wrong study design
Malapelle U, Mayo de-Las-Casas C, Rocco D, Garzon M, Pisapia P, Jordana-Ariza N, Russo M, Sgariglia R, De Luca C, Pepe F, Martinez-Bueno A, Morales-Espinosa D, Gonzalez-Cao M, Karachaliou N, Viteri Ramirez S, Bellevicine C, Molina-Vila MA, Rosell R, Troncone G. Development of a gene panel for next-generation sequencing of clinically relevant mutations in cell-free DNA from cancer patients. Br J Cancer 2017;116(6):802-810	Wrong study design
Leighl NB, Page RD, Raymond VM, Daniel DB, Divers SG, Reckamp KL, Villalona-Calero MA, Dix D, Odegaard JI, Lanman RB, Papadimitrakopoulou VA. Clinical utility of comprehensive cell-free dna analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. Clin Cancer Res 2019;25(15):4691-4700	Wrong study design

Citation	Primary reason for exclusion
Mountzios G, Planchard D, Metro G, Tsiouda D, Prelaj A, Lampaki S, Shalata W, Riudavets M, Christopoulos P, Girard N, Albarran-Artahona V, Garcia Campelo R, Samitas K, Banna GL, Boukovinas I, Agbarya A, Koumarianou A, Perdikouri EI, Kosmidis P, Linardou H, Mauri D, Mavroudis D, Athanasiadis I, Kalofonos H, Xenidis N, Korantzis I, Ardavanis A, Rallis G, Bottiglieri A, Efthymiadis K, Oikonomopoulos G, Kokkalis A, Saloustros E, Tsoukalas N, Bartzi D, Economopoulou P, Psyrri A, Reck M, Lo Russo G. Molecular epidemiology and treatment patterns of patients with egfr exon 20-mutant nsclc in the precision oncology era: The European EXOTIC registry. JTO Clin Res Rep. 2023;4(1):100433	Wrong study design
Yu Q, Huang F, Zhang M, Ji H, Wu S, Zhao Y, Zhang C, Wu J, Wang B, Pan B, Zhang X, Guo W. Multiplex picoliter-droplet digital PCR for quantitative assessment of EGFR mutations in circulating cell-free DNA derived from advanced non-small cell lung cancer patients. Mol Med Report. 2017;16(2):1157-1166	Wrong study design
Horn L, Whisenant JG, Wakelee H, Reckamp KL, Qiao H, Du L, Hernandez J, Huang V, Waqar SN, Patel S, Sanborn RE, Shaffer T, Garg K, Holzhausen A, Harrow K, Liang C, Lim LP, Li M, Lovly CM. Circulating tumor (ct) DNA analysis to monitor response and resistance to ensartinib in patients (pts) with ALK+ non-small cell lung cancer (NSCLC). Annals of Oncology 2019;30(Supplement 2):ii48	Conference paper
Chu T, Zhang W, Zhang B, Zhong R, Zhang X, Gu A, Shi C, Wang H, Xiong L, Lu J, Qian J, Zhang Y, Dong Y, Teng J, Gao Z, Wang W, Shen Y, Nie W, Lim JU, Mehta HJ, Neal JW, Lou Y, Xu J, Zhong H, Han B. Efficacy and safety of first-line anlotinib-based combinations for advanced non-small cell lung cancer: a three-armed prospective study. Translational Lung Cancer Research 2022;11(7):1394-1404	Wrong intervention
Fu R, Huang J, Tian X, Liang C, Xiong Y, Zhang JT, Jiang B, Dong S, Gong Y, Gao W, Li F, Shi Y, Liu Z, Gao X, Chen R, Zhong W, Zhang Y. Postoperative circulating tumor DNA can refine risk stratification in resectable lung cancer: results from a multicenter study. Mol Oncol. 2023;17(5):825-838	Wrong study design
Low SK, Ariyasu R, Uchibori K, Hayashi R, Chan HT, Chin YM, Akita T, Harutani Y, Kiritani A, Tsugitomi R, Manabe R, Ogusu S, Amino Y, Kitazono S, Yanagitani N, Nakamura Y, Nishio M. Rapid genomic profiling of circulating tumor DNA in non-small cell lung cancer using Oncomine Precision Assay with Genexus TM integrated sequencer. Transl. 2022;11(5):711-721	Wrong study design
Jiang J, Adams HP, Lange M, Siemann S, Feldkamp M, McNamara S, Froehler S, Yaung SJ, Yao L, Balasubramanyam A, Tikoo N, Ju C, Achenbach HJ, Krugel R, Palma JF. Plasma-based longitudinal mutation monitoring as a potential predictor of disease progression in subjects with adenocarcinoma in advanced non-small cell lung cancer. BMC Cancer. 2020;20(1):885	Wrong study design
Ho GYF, Wang T, Kwok HH, Rasul R, Peila R, Guzman M, Ip MSM, Lam DCL. Longitudinal multi-gene panel assessment of circulating tumor DNA revealed tumor burden and molecular characteristics along treatment course of non-small cell lung cancer. Transl. 2020;9(5):1873-1884	Wrong study design
Peng H, Lu L, Zhou Z, Liu J, Zhang D, Nan K, Zhao X, Li F, Tian L, Dong H, Yao Y. CNV Detection from circulating tumor DNA in late stage non-small cell lung cancer patients. Genes (Basel). 2019;10(11):14	Wrong study design
Tomlins SA, Hovelson DH, Suga JM, Anderson DM, Koh HA, Dees EC, McNulty B, Burkard ME, Guarino M, Khatri J, Safa MM, Matrana MR, Yang ES, Menter AR, Parsons BM, Slim JN, Thompson MA, Hwang L, Edenfield WJ, Nair S, Onitilo A, Siegel R, Miller A, Wassenaar T, Irvin WJ, Schulz W, Padmanabhan A, Harish V, Gonzalez A, Mansoor AH, Kellum A, Harms P, Drewery S, Falkner J, Fischer A, Hipp J, Kwiatkowski K, Lazo de la Vega L, Mitchell K, Reeder T, Siddiqui J, Vakil H, Johnson DB, Rhodes DR. Real-World Performance of a Comprehensive Genomic Profiling Test Optimized for Small Tumor Samples. JCO precis. 2021;5:08	Wrong patient population
Roepman P, de Bruijn E, van Lieshout S, Schoenmaker L, Boelens MC, Dubbink HJ, Geurts-Giele WRR, Groenendijk FH, Huibers MMH, Kranendonk MEG, Roemer MGM, Samsom KG, Steehouwer M, de Leng WWJ, Hoischen A, Ylstra B, Monkhorst K, van der Hoeven JJM, Cuppen E. Clinical validation of whole genome sequencing for cancer diagnostics.Journal of Molecular Diagnostics 2021;23(7):816-833	Wrong study design
Garcia J, Forestier J, Dusserre E, Wozny AS, Geiguer F, Merle P, Tissot C, Ferraro-Peyret C, Jones FS, Edelstein DL, Cheynet V, Bardel C, Vilchez G, Xu Z, Bringuier PP, Barritault M, Brengle-Pesce K, Guillet M, Chauvenet M, Manship B, Brevet M, Rodriguez-Lafrasse C, Hervieu V, Couraud S, Walter T, Payen L. Cross-platform comparison for the detection of RAS mutations in cfDNA (ddPCR Biorad detection assay, BEAMing assay, and NGS strategy). Oncotarget. 2018;9(30):21122-21131	Wrong study design
Pisapia P, Pepe F, Smeraglio R, Russo M, Rocco D, Sgariglia R, Nacchio M, De Luca C, Vigliar E, Bellevicine C, Troncone G, Malapelle U. Cell free DNA analysis by SiRe next generation sequencing panel in non small cell lung cancer patients: Focus on basal setting. Journal of Thoracic Disease. 2017;9(Supplement13):S1383-S1390	Wrong study design

Citation	Primary reason for exclusion
Lakatos E, Hockings H, Mossner M, Huang W, Lockley M, Graham TA. LiquidCNA: Tracking subclonal evolution from longitudinal liquid biopsies using somatic copy number alterations. iScience. 2021;24(8):102889	Wrong study design
Wolf J, Helland A, Oh IJ, Migliorino MR, Dziadziuszko R, Wrona A, de Castro J, Mazieres J, Griesinger F, Chlistalla M, Cardona A, Ruf T, Trunzer K, Smoljanovic V, Novello S. Final efficacy and safety data and exploratory molecular profiling from the phase III ALUR study of alectinib versus chemotherapy in crizotinib-pretreated ALK-positive non-small-cell lung cancer. ESMO Open 2022;7(1) (no pagination)	Wrong study design
Jahangiri L, Hurst T. Assessing the concordance of genomic alterations between circulating-free DNA and tumour tissue in cancer patients. Cancers 2019;11(12) (no pagination)	Wrong study design
Shen H, Che K, Cong L, Dong W, Zhang T, Liu Q, Du J. Diagnostic and prognostic value of blood samples for KRAS mutation identification in lung cancer: a meta-analysis. Oncotarget. 2017;8(22):36812-36823	A systematic review/meta-analysis searched to identify missed eligible studies
Stitz R, Buder A, Silye R, Baumgartner B, Puhringer F, Filipits M, Oberndorfer E, Heitzer E. Validation of a next-generation sequencing assay for the detection of EGFR mutations in cell-free circulating tumor DNA. Exp Mol Pathol 2021;123:104685	Wrong study design
Guibert N, Hu Y, Feeney N, Kuang Y, Plagnol V, Jones G, Howarth K, Beeler JF, Paweletz CP, Oxnard GR. Amplicon-based next-generation sequencing of plasma cell-free DNA for detection of driver and resistance mutations in advanced non-small cell lung cancer. Ann Oncol. 2018;29(4):1049-1055	Wrong study design
Zugazagoitia J, Ramos I, Trigo JM, Palka M, Gomez-Rueda A, Jantus-Lewintre E, Camps C, Isla D, Iranzo P, Ponce-Aix S, Garcia-Campelo R, Provencio M, Franco F, Bernabe R, Juan-Vidal O, Felip E, de Castro J, Sanchez-Torres JM, Faul I, Lanman RB, Garrido P, Paz-Ares L. Clinical utility of plasma-based digital next-generation sequencing in patients with advance-stage lung adenocarcinomas with insufficient tumor samples for tissue genotyping. Ann Oncol. 2019;30(2):290-296	Wrong patient population
Lee SH, Kim EY, Kim T, Chang YS. Compared to plasma, bronchial washing fluid shows higher diagnostic yields for detecting EGFR-TKI sensitizing mutations by ddPCR in lung cancer. Respir Res 2020;21(1):142	Wrong intervention

Appendix 5: Selected Excluded Studies – Economic Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
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. Ont Health Technol Assess Ser. 2020;20(5):1-176.	Liquid biopsy testing used to detect EGFR T790M mutation
Cheng M, Akalestos A, Scudder S. Budget Impact Analysis of EGFR Mutation Liquid Biopsy for First- and Second-Line Treatment of Metastatic Non-Small Cell Lung Cancer in Greece. Diagnostics (Basel). 2020;10(6).	Liquid biopsy testing used to detect EGFR T790M mutation
Détection de la mutation T790M de l'exon 20 du gène EGFR dans le cancer du poumon résistant aux inhibiteurs de l'EGFR sur ADN tumoral circulant (biopsie liquide). Quebec: Institut national d'excellence en santé et en services sociaux (INESSS); 2022.	Liquid biopsy testing used to detect EGFR T790M mutation
Vanderpoel J, Stevens AL, Emond B, Lafeuille MH, Hilts A, Lefebvre P, et al. Total cost of testing for genomic alterations associated with next-generation sequencing versus polymerase chain reaction testing strategies among patients with metastatic non-small cell lung cancer. J Med Econ. 2022;25(1):457-68.	Outcomes of interest could not be extracted for liquid biopsy testing
Harvey MJ, Cunningham R, Sawchyn B, Montesion M, Reddy P, McBride A, et al. Budget Impact Analysis of Comprehensive Genomic Profiling in Patients With Advanced Non-Small-Cell Lung Cancer. JCO Precis Oncol. 2021;5:1611-24	Outcomes of interest could not be extracted for liquid biopsy testing
Johnston KM, Sheffield BS, Yip S, Lakzadeh P, Qian C, Nam J. Costs of in-house genomic profiling and implications for economic evaluation: a case example of non-small cell lung cancer (NSCLC). J Med Econ. 2020;23(10):1123-9.	Outcomes of interest could not be extracted for liquid biopsy testing
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. Ont Health Technol Assess Ser. 2020;20(5):1-176.	Liquid biopsy testing used to detect EGFR T790M mutation

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

Table A11: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of liquid biopsy testing

Author, year, country	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]
Ezeife et al, 2022,[174] Canada	Yes	Yes	Yes	Yes, public payer	Partially, unclear if alternative testing strategies would have similar results	Yes, 1.5%	Yes	Yes	Partially applicable
Patel et al, 2021,[175] Canada	Yes	Yes	Yes	Yes, public payer	Partially, unclear if alternative testing strategies would have similar results	NA	No, life-years	Yes	Partially applicable
Johnston et al, 2022,[176] Ontario	Yes	Yes	Yes	Yes, public payer	Partially, unclear if alternative testing strategies would have similar results	NA	No, life-years	No, excluding drug cost	Partially applicable
Englmeier et al, 2022,[177] Germany	Yes	Yes	Partially	Yes, public payer	Yes	Yes, 3%	Yes	Yes	Partially applicable
Jansen et al 2023,[179] United States	Yes	Yes	No	Yes, health care payer	Yes	Yes, 3%	Yes	Yes	Partially applicable
Yang et al, 2022,[178] United States	Yes	Yes	No	Yes, societal	Partially	NA	NA	No, excluding targeted therapy costs and benefits	Partially applicable

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Appendix 7: Economic model and budget impact analysis inputs

Sensitivity for liquid and tissue biopsy

We sourced sensitivity for liquid and tissue biopsy from the results of the clinical. We assumed that sensitivity estimates were normally distributed on a logit-transformed scale. The mean and standard error on a logit transformed scale are reported in the table below.

Table A12: Liquid and tissue biopsy sensitivity inputs

Actionable genomic alteration	Intervention	Sensitivity	Logit mean (SE)
EGFR	Liquid	72% (66%;78%)	0.944 (0.154)
ALK	Liquid	60% (53%;67%)	0.405 (0.15)
ROS1	Liquid	60% (41%;77%)	0.405 (0.397)
EGFR	Tissue	90% (85%;93%)	2.197 (0.217)
ALK	Tissue	81% (72%;88%)	1.45 (0.267)
ROS1	Tissue	80% (66%;89%)	1.386 (0.375)

We assumed that both liquid biopsy and tissue biopsy would have a specificity of 100%.

Prevalence of actionable genomic alterations

We sourced the prevalence of EGFR mutations from Kris et al[204] who report 122 of 733 specimens harbouring EGFR mutations (Table 2). We assumed that this value was binomially distributed resulting in an estimated prevalence of 16.6% (95% CI, 14.1%; 19.4%).

We sourced the prevalence of ALK alterations from Koivunen et al Table 1 (8/305), Shaw et al Table 3 (19/141), Wong et al Table 1 (13/266), Takashani et al Table 2 (5/313), and Camidge et al (13/73).[205-209] We assumed this value was binomial distributed resulting in a prevalence estimate of 5.3% (4.0%;6.6%).

The prevalence of ROS1 mutations was sourced from Table 1 in Gainor et al[210] and was assumed to be binomially distributed. This resulted in a prevalence estimate of 1.3% (95% CI, 1%; 1.6%).

Probability of having PD-L1 levels ≥ 50%

The probability of having PD-L1 levels ≥ 50% was sourced from a Canadian prevalence study conducted by Hwang et al Table 1.[201] The authors report that 29.8% (510 out of 1713) of individuals had a PD-L1 expression ≥ 50%. We assumed that probability was binomially distributed for an estimate of 29.8% (27.6%;31.9%).

Probability of insufficient tissue for tissue testing

We sourced the probability of having insufficient tissue after tissue biopsy from Leigh et al.[211] Leighl et al reported rates of insufficient tissue for each of the genomic alterations tested (Table 3 from Leighl et al). We selected the rate of tissue not sufficient for EGFR tested as this was the genomic alteration with the lowest rate of tissue not assessed. The study reported 27 samples not having sufficient tissue out of 261

samples where tissue was assessed. We assumed that this value was binomially distributed resulting in an estimate of 10.3% (95% CI, 6.9%; 14.2%) for the probability of having insufficient tissue.

Probability of tumour not detected in liquid biopsy

The probability that a tumour was not present in a liquid biopsy sample was estimated from Leighl et al.[211] The study reports 281 samples where liquid biopsy was conducted, 13 of which liquid biopsy was unable to detect tumour cells. We assumed that this probability was binomially distributed for an estimated probability of tumour not detected in liquid biopsy of 4.6% (2.5%; 7.1%).

Probability a second tissue biopsy is not feasible

We sourced the probability of not receiving a re-biopsy after a failed tissue biopsy from Chouaid et al Table 3.[212] Chouaid et al conducted a prospective French study evaluating the feasibility of re-biopsy for individuals diagnosed with NSCLC. The study found that 82 out of 100 individuals had a re-biopsy conducted. We assumed that the probably of not receiving a re-biopsy was binomially distributed. This resulted in a probability of not receiving a re-biopsy of 18.0% (95% CI, 11.0%; 26.0%).

Probability of a pneumothorax/severe pneumothorax after tissue testing

Similar to the 2020 OH Health Technology assessment for liquid biopsy to detect EGFR T790M mutations, we sourced the probability of pneumothorax from Ayyappan et al.[213] The study authors conducted a retrospective chart review of 107 fine-needle lung tissue biopsy. The authors report that 30 of the 107 biopsies resulted in pneumothorax. Nine of the 30 pneumothorax cases required a chest tube for drainage. We assumed that these values were binomially distributed for a probability of a tissue biopsy resulting in a pneumothorax of 28.0% (95% CI, 19.6%; 36.4%) and the probability that a pneumothorax required drainage of 30.0% (95% CI, 13.3%; 46.7%).

Test turn around time

We sourced test turn around time from Leighl et al[211]which reported a median turn around time of 9 days for liquid biopsy and 15 days for tissue biopsy. For test-turn around time for tissue re-biopsy we assumed that the turn around time would be 68.6% (10.5 days/15.3 days, sourced from Yang et al[178]) of that of a first time biopsy, for a estimated re-biopsy turn around of 10.29 days. This parameter was not varied in the probabilistic analysis.

Mean Age and Sex of individuals diagnosed with NSCLC

We sourced mean age and the percent female from the study conducted by Hwang et al.[201] The authors report a mean age of 68.8. The study does not report standard deviation for the whole cohort but only for subgroups. We estimate the standard deviation of the sample by pooling the reported standard deviations by sample size. We assumed the mean age of the cohort was normally distributed and estimated to be 68.8 (68.3;69.3).The percentage of the cohort that was female was sourced from Araghi et al.[200] The authors report that 48.1% (28,827/59,969) of individuals diagnosed with NSCLC were female.

Probability of receiving treatment

We sourced the probability that an individual received treatment after an advanced NSCLC diagnosis from Stock-Martineau et al.[214] The study reports rate of treatment received for individuals diagnosed

with NSCLC, at an Ontario hospital, stratified by date of diagnosis and whether an individual was EGFR-positive or ALK-positive.

We used the data from individuals diagnosed between 2015-2018 (Cohorts B + C in Table 2 of Stock-Martineau et al). 555 of these individuals had a known treatment decision (Cohort B = 463 + Cohort C = 92), 348 of which received treatment (Cohort B = 287 + Cohort C = 61).

From Table 3 of Stock-Martineau et al we know that there were 65 individuals who were EGFR-positive (Cohort B = 42 + Cohort C = 9) or ALK-positive (Cohort B = 12 + Cohort C = 2). Of these individuals 58 received 1st line treatment (Cohort B EGFR = 38 + Cohort C EGFR = 7 + Cohort B ALK = 11 + Cohort C ALK = 2). This results in a probability of receiving treatment for those with an actionable genomic alteration to be equal to 58/65, this was assumed to be binomially distributed for an estimate of 89.2% (95% CI; 81.5%; 95.4%). To calculate the probability of receiving treatment for those without an actionable genomic alteration detected we exclude those with an actionable genomic alteration for an estimate of (348-58)/(555-65). We assumed this probability was binomially distributed for an estimate of 59.2% (95% CI, 54.9%; 63.5%).

The study by Stock-Martineau et al observes an increase in the uptake of treatment between individuals diagnosed between 2009-2012 and individuals diagnosed between 2015-2018. We conducted a scenario analysis where 100% of individuals decide to receive treatment.

Parametric survival models

We fit parametric survival models using the flexsurv R package on digitized Kaplan Meier curves for both progression-free survival and overall survival. Table A13, lists the best fitting distributions. We provide estimates of best fitting parametric survival models alongside digitized Kaplan Meier curves in Figure A74.

Table A13: Best fitting survival estimates

Variable	Best fit	Estimated median survival	Study reported median survival	Study
EGFR – osimertinib OS	Gamma	39.2 (34.6;43.3)	38.6 (34.5–41.8)	Ramalingam et al
EGFR – osimertinib PFS	Lognormal	17.9 (15.2;20.1)	18.9 (15.2–21.4)	Soria et al
EGFR – afatinib OS	Loglogistic	26.2 (24.2;27.7)	25.8 (23.1-29.3)	Yang et al
EGFR – afatinib PFS	Loglogistic	11 (10.4;12.1)	11.0 (9.7-13.7	Wu et al
ALK – alectinib OS	Lognormal	127.8 (70.9;199.8)	NE	Mok et al
ALK – alectinib PFS	GenGamma	33.7 (20.1;51.3)	34.8 (17.7-NE)	Mok et al
ROS1 – crizotinib OS	Loglogistic	20.7 (14.2;29.5)	18.5 (15.1-47.2)	Doebele et al
ROS1 – crizotinib PFS	Loglogistic	7.4 (5.5;9.7)	8.2 (6.5-9.9	Doebele et al
ROS1 - entrectinib OS	Exponential	56.1 (51.9;60.2)	NE	Doebele et al
ROS1 - entrectinib PFS	Exponential	16.4 (15.9;17.3)	16.8 (12.0-26.3)	Doebele et al

Variable	Best fit	Estimated median survival	Study reported median survival	Study
PDL1 < 50% -CRBPPEME+PEMB OS	Loglogistic	26.4 (19.7;35.7)	21.8 (17.7 -25.9) 1-49% PDL1, 17.2 (13.8 - 22.8) < 1% PDL1	Gadgeel et al
PDL1 < 50% - CRBPPEME+PEMB PFS	Lognormal	8.5 (6.9;10.4)	9.2 (7.8 - 13.1) 1-49% PDL1, 6.2 (4.9 - 8.1) < 1% PDL1	Gadgeel et al
PDL1 > 50% - pembrolizumab OS	Lognormal	19.5 (16.6;22.2)	26.3 (18.3 - 40.4)	Reck et al
PDL1 > 50% - pembrolizumab PFS	GenGamma	8.1 (7.3;9)	7.7 (6.1 - 10.2)	Reck et al
BSC OS	Loglogistic	3.8 (3.5;4.5)	6.5 (5.7-7.9)	Stock-Martineau et al

Abbreviation: OS :Overal Survival, PFS: Progression-free survival, NE: Not estimable, BSC: Best supportive care, CRBPPEME+PEMB: pembrolizumab & carboplatin & pemetrexed
NE due to not enough events occurring during the trial follow-up period.

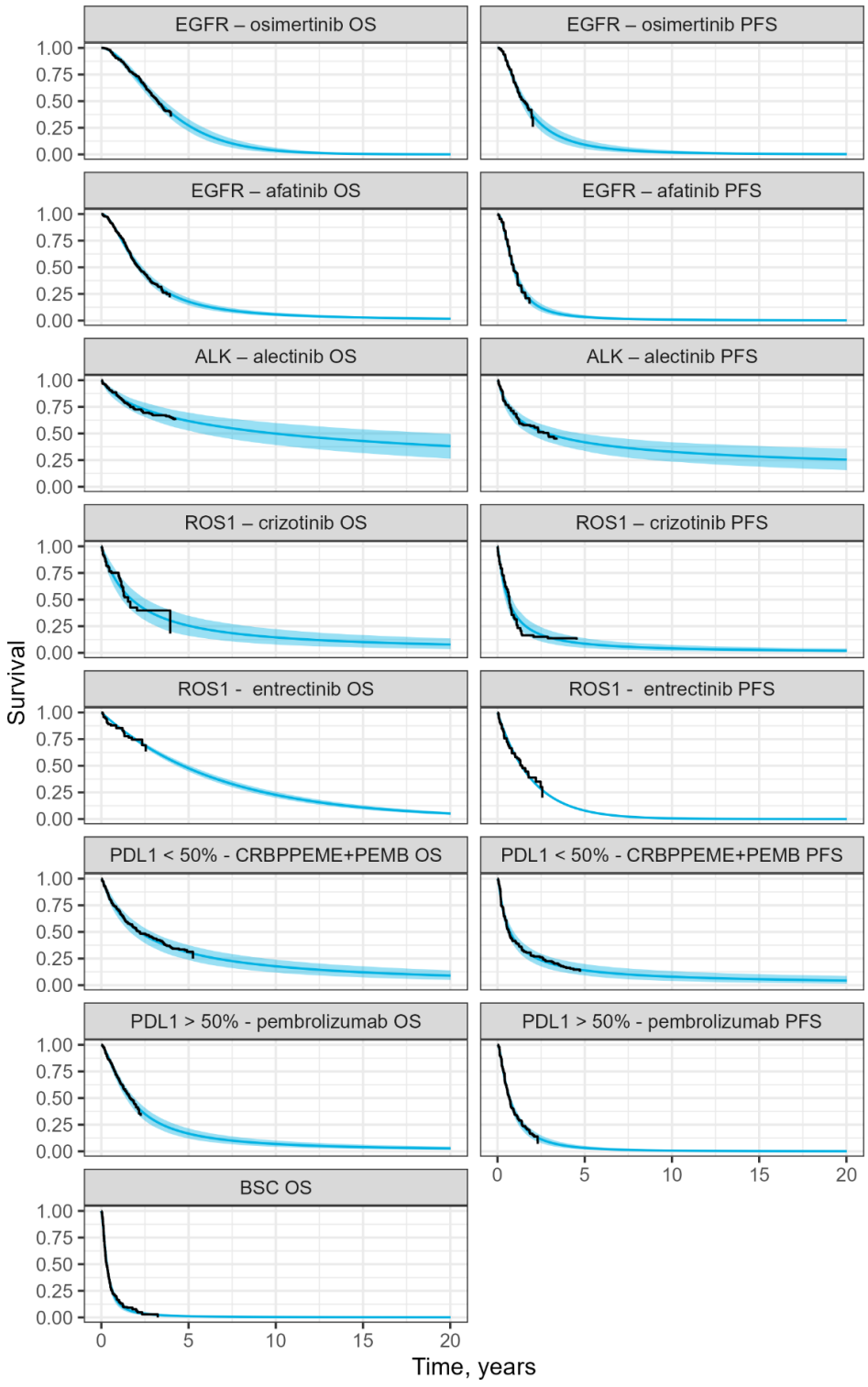

Figure A74: Best-fitting parametric survival model alongside digitized data

Abbreviation: OS: Overall Survival, PFS: Progression-free survival, BSC: Best supportive care, CRBPPEME+PEMB: pembrolizumab & carboplatin & pemetrexed.

Commonly occurring adverse events

We sourced commonly occurring adverse events from the same studies as parametric survival curves were estimated from (Table 3), except for entrectinib and crizotinib which we sourced from Shaw et al and Drilon et al.[215-217,219,220,226,227] We included adverse events that occurred in at least 5% of the study population. The table below lists the frequency of each commonly occurring adverse event (Table A14).

Table A14: Frequency of commonly occurring adverse events

Adverse event	osimertinib	afatinib	alectinib	entrectinib	crizotinib	CRBPPEMEPEMB	PEMB
Alanine aminotransferase elevation	0.4%	0.0%	4.6%	5.7%	0.0%	0.0%	0.0%
Anemia	1.1%	0.0%	4.6%	1.9%	0.0%	18.3%	1.3%
Aspartate aminotransferase increase	0.7%	0.0%	5.3%	3.8%	0.0%	0.0%	0.0%
Asthenia	0.0%	0.0%	0.0%	0.0%	0.0%	6.7%	0.0%
Diarrhea	2.2%	5.4%	2.6%	5.7%	0.0%	5.2%	3.9%
Fatigue	0.7%	0.4%	0.0%	0.0%	0.0%	6.9%	1.9%
hypophosphatemia	0.0%	0.0%	0.0%	0.0%	10.0%	0.0%	0.0%
neutropenia	0.0%	0.0%	2.6%	0.0%	0.0%	3.5%	0.0%
Neutrophil count decrease	0.0%	0.0%	1.3%	9.4%	10.0%	16.0%	0.0%
Rash or acne	0.0%	0.0%	0.0%	5.7%	0.0%	0.0%	0.0%
Stomatitis	1.1%	14.6%	0.0%	3.8%	0.0%	0.0%	0.0%
Thrombocytopenia	0.7%	5.4%	0.0%	0.0%	0.0%	0.0%	0.0%
Weight increase	0.0%	0.0%	0.0%	0.0%	0.0%	8.4%	0.0%
Alanine aminotransferase elevation	0.0%	0.0%	0.0%	18.9%	0.0%	0.0%	0.0%

Due to limitations on the frequency and the timing of adverse events, we assumed that an individual could not have multiple occurrences of the same adverse event and that all adverse events occurred in the first model cycle.

Health State Utilities

We sourced our estimates of utility for progression-free survival and the progressed health state from Labbé et al.[229] The study reports (Table 3 Labbé et al) utility estimates by disease state, actionable genomic alteration, and whether an individual was receiving targeted therapy. For the progression-free survival health state we fit a beta distribution to each of the utility estimates for individuals with NSCLC and in the stable on most appropriate treatment subgroup. We pooled the utility estimates together and fit a beta distribution on the combined estimate. For the progressed health state, we conducted a similar analysis but for individuals in the 'Progressing' health state as defined by Labbé et al.

Similar to Ezeife et al[174] we sourced the utility estimate for best supportive care from Nafees et al (Table 3).[230] We also sourced estimates of disutility associated with commonly occurring adverse events from Nafees et al (Table 3). Disutility estimates were combined using an additive approach, we considered applying disutility estimates using a multiplicative approach in a scenario analysis.

Liquid biopsy sample collection costs

Liquid biopsy sample collection costs were sourced from Ezeife et al.[174] The study reports the cost of a circulating-tumour DNA peripheral blood test to be $110 in 2022 CAD. This value was sourced from Princess Margaret Cancer Center laboratory records. Adjusting for inflation using CPI we get an estimate of $115.31 in 2023 CAD. The study authors assumed a minimum and maximum range that was 20% higher/lower than the mean value. We fit a gamma distribution so that the lower and upper 95% confidence intervals of the distribution would be 20% higher/lower than the mean value. This resulted in an estimate of $115.31 (95% CI, $93.50; $139.30).

Tissue sample collection costs

We sourced facility costs for tissue biopsy sample collection from the OCCI (2021/2022 fiscal year) accessed using IntelliHealth Ontario. We queried for ambulatory costs for individuals who have the following Canadian Classification of Health Interventions (CCI) codes associated with lung biopsy (2GT71BA, 2GT71BP, 2GT71DA, 2GT71HA, 2GT71LA) and whose ICD 10 codes were associated with lung neoplasms (C34). This resulted in a mean cost of $1,969.87 (Standard error = $229.30), adjusting for inflation using CPI (CPI 2023/ CPI 2022= 158.5/151.2=104.8%) for an estimated cost of $2,064.98 (SD = $240.37). We fit a gamma distribution to the mean, standard deviation to facilitate a probabilistic analysis. We assumed that individuals would not receive a tissue biopsy via bronchoscopy, endobronchial ultrasound, or via biopsy at a metastatic site. We also assumed that the cost of lung biopsy for those with lung neoplasms would be representative of the costs incurred for individuals receiving tumour tissue biopsy.

We also included physician costs sourced physician fees from the OHIP Schedule of Benefits and assumed that physicians would bill fee code 'Z340 Biopsy of lung, needle' $158.70 and 7 units of Anaesthesiologist unit fee ($108.43= 7 x $15.49) for a total cost of $267.13. These values are not varied in the probabilistic analysis and are assumed fixed.

We combined physician fees and facility fees for an estimate of $2,332.11 (95% CI, $1,888.67; $2,832.14).

Tissue biopsy sequencing costs

We sourced the cost of tissue biopsy from Perdrizet et al[233] a Canadian prospective single center study that evaluated comprehensive genomic profiling in individuals diagnosed with NSCLC. As part of this study the cost of comprehensive genomic profiling using tissue biopsy was sourced from the University Health Network Hospital. This included direct laboratory costs including reagents and labour costs, as well as fixed overhead costs. The study reports a cost of $1,057 per sample excluding fixed overhead costs and $1,322 per sample including fixed overhead costs. We adjusted the estimate of $1,322 2022 CAD for inflation using CPI for an estimate of $1,385.83 2023 CAD.

Liquid biopsy sequencing costs

We sourced liquid biopsy sequencing costs from the manufacturers of the available liquid biopsy tests in Ontario. The cost of the Guardant Health liquid biopsy was $3,490 USD (Email communication, Guardant, 2023-09-14). We converted to Canadian dollars using a 1.317 spot exchange rate for an estimated cost of $4,596.33 CAD. We sourced the cost of the FoundationOne Liquid CDx at $6,193.60

CAD (Email communication, Roche 2023-11-23). We took the average of both testing costs for an estimated liquid biopsy sequencing cost of $5,393.47 CAD.

We conducted a scenario analysis using the cost of an inhouse developed liquid biopsy test sourced from Ezeife et al.[174] We did not consider test development or capital acquisition costs in this scenario analysis.

Consultation and sample transportation costs

Similar to the previous Ontario Health analysis on liquid biopsy we assumed that for both liquid and tissue biopsy physicians would bill code A445 $166.50 2023 CAD (oncology general consultation) for an initial consultation as well as results consultation.

Additionally both strategies would incur a sample transportation cost of $61.15 2023 CAD ($51.47 2018 CAD adjusting for inflation using the CPI) which was also sourced from the previous Ontario Health analysis and assumed that 75% of samples would need to be transported externally.

This resulted in a consultation and transportation cost of $394.15 ($166.50 x 2 + $61.15).

Tissue biopsy adverse event costs

We assumed that individuals with a pneumothorax would receive a chest x-ray. We queried the OCCI for outpatient visits with a principal procedure code of '3GT10VA x-ray lung without contrast.' This resulted in an average cost of $569, and a standard deviation of $414 in 2021 CAD. We adjusted for inflation using the CPI (CPI 2023/ CPI 2021= 158.5/141.6=111.9%) for an estimated cost of $636.91. We also included physician fees sourced from the OHIP Schedule of Benefits (X091 Chest x-ray two views = $32.6= $21.90 +$10.70). We assumed that OCCI costs would be gamma distributed.

We assumed that individuals who had severe pneumothorax cases would also receive a chest drainage. We sourced the cost of a chest tube by querying the OCCI for ambulatory visits with a principal procedure code of '1SZ52HA: Drainage, soft tissue of the chest and abdomen using percutaneous (needle) approach' or '1SZ52HATS: Drainage, pericardium using percutaneous (needle) approach leaving drainage tube'. This resulted in an estimated cost of $617 2021 CAD. We adjusted for inflation using the CPI for an estimated cost of $690.64. We sourced from the OHIP SoB the associated physician fees (Z341 Tube thoracostomy for closed drainage (chest tube): $169.74 = $76.80 + 6 x $15.49). We assumed that OCCI costs would be gamma distributed.

Drug acquisition costs

We outline the drug acquisition costs below (Table A15).

Table A15: Drug acquisition costs

Medication	Mode of Treatment	Dose	Cost per unit	Cost per 21-day model cycle	Source
osimertinib	PO continuously (365 days)	80mg per day	$294.68 per 80mg	$6,188.28	CADTH review[238]
afatinib	PO continuously (365 days)	40mg per day	$73.30 per 40mg	$1,539.30	CADTH review[237]
crizotinib	PO continuously (365 days)	250 mg per day twice daily	$146.67 per 250 mg	$6,160.14	CADTH review[234]
alectinib	PO continuously (365 days)	1200 mg: 2x 600 mg	$42.16 per 150mg	$3,541.44	CADTH review[236]
entrectinib	PO continuously (365 days)	600 mg	$95.33 per 200mg	$6,003.90	CADTH review[239]
pembrolizumab	IV 200mg every 21 days	200mg every 21 day	$44.00 per mg	$8,800.00	CADTH review[235]
carboplatin	IV AUC 5 every 21 days	605 mg every 21 days	$1.33 per mg	$804.65	CADTH review[235], AUC calculator[a]
pemetrexed	IV 1 time per 21-day cycle (6 cycles)	500mg/m2 on day 1 of a 21-day cycle	$0.83 per mg	$1,049.75	CADTH review[235]
cisplatin	IV 1 time per 21-day cycle (6 cycles)	75 mg /m² on day 1 of a 21 day cycle	$2.70 per mg	$344.25	CADTH review[235]
docetaxel	IV Day 1, 8, 15 every 21-day cycle	40 mg /m²	$1.52 per mg	$310.08	CADTH review[235]

[a]Assuming a BSA of 1.7m^2 and weight of 70kg (Similar to Keytrunda CADTH reimbursement report).

IV medication administration costs per visit

We sourced the salary of a full-time registered nurse (midpoint of 5 years' seniority) of $40.59 2022 CAD from the Ontario Nurses' Association.[243] We sourced an average pharmacist wage for an Ontario pharmacist from a job posting website $48.38.[244] We also assumed physicians would bill OHIP fee code G345 Complex single agent or multi-agent therapy ($75).[232]

We sourced pharmacy workload (average time per visit) of 51.185 minutes and nursing workload (average time per visit) 51.667 minutes from Cancer Care Ontario drug regimes for IV administered medications.

This results in an estimated administration cost of $151.22= (51.667/60)*$40.59 + $48.38*(51.185/60)+ $75 for each visit.

Oral medications administration costs

We sourced a pharmacy dispensing fee of $9.93 which was incurred per cycle.[250]

General care costs

We used the same source of general care costs as those used in the 2019 Ontario Health liquid biopsy HTA, these costs were sourced from Goeree et al.[248] This resulted in a 28 day general care cost for individuals in the progression-free survival health state of $981.35 2015 CAD, and $1,161.11 2015 CAD for individuals in the progressed health state. We multiplied both cost estimates by 75% to account for

our models 21-day cycle length. Adjusting for inflation using the CPI for an estimated cost of $921.47 2023 CAD, and $1,090.26 2023 CAD for the progression-free survival health state, and progressed health state, respectively. For our probabilistic analysis, we used a similar approach as the previous Ontario Health liquid biopsy HTA and assume that the upper and lower 95% confidence intervals would be 20% +/- from the mean.

End of life care costs

We sourced a yearly Canadian end of life care costs for lung cancer from de Olivera et al.[249] The study reports that prior to death males would incur a yearly cost of $39,241 2015 CAD and females $35,664 2015 CAD. Using the percentage female estimate sourced from Araghi et al we estimate that the combined yearly cost would be $37,524.04 or $2,886.46 on a 21-day cycle scale. We adjusted to inflation using the CPI for a 21-day cycle estimate of $3,613.78. We assumed that individuals would incur these costs when in the BSC health state as well as one cycle prior to death.

Commonly occurring adverse events costs

We sourced the cost of commonly occurring adverse events from the OCCI. The table below indicates the inpatient cost of each adverse event, the ICD 10 code used to query the OCCI, as well as the cost estimate adjusted for inflation using the CPI.

Table A16: Adverse event costs

Adverse event	Cost $2023 CAD	ICD 10 code
Alanine aminotransferase elevation	$3,020.93	(R740) ELEVATION OF LEVELS OF TRANSAMINASE AND LACTIC ACID DEHYDROGENASE [LDH]
Anemia	$1,629.28	(D649) ANAEMIA
Aspartate aminotransferase increase	$3,020.93	(R740) ELEVATION OF LEVELS OF TRANSAMINASE AND LACTIC ACID DEHYDROGENASE [LDH]
Asthenia	$1,333.28	(R53) MALAISE AND FATIGUE
Diarrhea	$584.68	(K528) OTHER SPECIFIED NONINFECTIVE GASTROENTERITIS AND COLITIS
Fatigue	$1,333.28	(R53) MALAISE AND FATIGUE
Hypohosphatemia	$2,234.26	(E833) DISORDERS OF PHOSPHORUS METABOLISM AND PHOSPHATASES
Nausea	$1,050.59	(R113) NAUSEA WITH VOMITING
neutropenia	$5,999.28	(D700) NEUTROPENIA
Neutrophil count decrease	$5,999.28	(D700) NEUTROPENIA
Rash or acne	$196.76	(R21) RASH AND OTHER NONSPECIFIC SKIN ERUPTION
Stomatitis	$584.68	(K121) OTHER FORMS OF STOMATITIS
Thrombocytopenia	$2,420.56	(D696) THROMBOCYTOPENIA, UNSPECIFIED
Weight increase	$1,619.35	(R634) ABNORMAL WEIGHT LOSS

Duration of 2nd line treatment

To estimate second line treatment acquisition costs, we sourced time on treatment for various 2nd line interventions. This was estimated to be 2.3 months for individuals receiving Docetaxel[245], 5.4 months for individuals receiving platinum doublet[246], and 10.9 months for individuals receiving osimertinib.[247]

Probability of being diagnoses Stage III and IV NSCLC

The probability of being diagnosed Stage III and IV NSCLC was sourced from Araghi et al.[200] The authors report that 67.7% = 37,743/56,279 of individuals were diagnosed with Stage III or Stage IV NSCLC. We assumed this value was binomially distributed.

Costs and health outcomes for individuals receiving osimertinib after complete resection

For the scenario analysis where liquid biopsy could provide actionable results for individuals with a complete resection and diagnosed with stage IB-IIIA NSCLC, we sourced the proportion of the cohort that would be Stage IB-IIIA with a complete resection (11.7%) from a previously published CADTH review.[238]

For these individuals we allowed liquid biopsy and tissue biopsy testing to detect the two actionable genomic alterations that would allow individuals to access osimertinib (Exon 19 deletion or exon 21 L858R, which make up 90% of EGFR mutations). For individuals with these two actionable genomic alterations detected we assigned the discounted cost ($41,9085 discounted costs for individuals who have undergone a complete resection and did not receive osimertinib, $253,304 discounted costs for individuals who have undergone a complete resection and received osimertinib) and QALY outcomes (7.60 QALYs for individuals who have undergone a complete resection and did not receiving osimertinib, 8.11 QALYs for individuals who have undergone a complete resection and received osimertinib) sourced from a previously published CADTH review.[238]

Limited Societal Analysis Inputs

We conducted a limited societal perspective where we considered all drug acquisition costs (not just for individuals covered by the ODB program. We also considered additional actionable genomic alterations and targeted therapy options for BRAF, MET, and RET actionable genomic alterations.

We sourced the prevalence of RET (0.9%)[45] , BRAF (3%)[279], MET (Met Skipping) (3%)[280], FGFR1 (8.1%)[281], HER2 (ERBB2) (3.7%)[282], KRAS (8.9%)[283], PIK3CA (3.7%)[284], and NTRK1, 2, or 3 (0.2%)[285] from previously published studies. Sensitivity for liquid and tissue biopsy for each of these alterations was sourced from the clinical review.

In this scenario analysis we added the following targeted therapy options selpercatinib for individuals with MET actionable genomic alterations, dabrafenib and trametinib for individuals with BRAF actionable genomic alterations, and tepotinib for individuals with MET actionable genomic alterations. We sourced the effectiveness of each of these targeted therapies by digitizing Kaplan Meier survival curves from previously published studies.[286-288] We than fit survival distributions and selected the best fit according to BIC.

Drug costs were sourced from previously published CADTH reviews: Selpercatinib $133.00 per 80mg[289], dabrafenib $67.32 per 75 mg,[290] trametinib $307.94 per 2mg,[290] tepotinib $153.96 per 225 mg.[291] Dosing information was sourced from Ontario Health (CCO) regime monographs and Health Canada Summary of Basis of Decision.[292-294] We assumed that individuals receiving these targeted therapies would receive treatment until progression.

Appendix 8: Additional Economic Analysis Results

Table A17: Short-term testing outcomes

Variable	Standard care	Combined testing	Combined testing vs standard care	Liquid first	Liquid first vs standard care	Tissue first	Tissue first vs standard care	Insufficient tissue	Insufficient tissue vs standard care
Testing costs	$4,756 ($4,253; $5,303)	$10,602 ($10,112; $11,132)	$5,846 ($5,809; $5,880)	$9,936 ($9,498; $10,414)	$5,180 ($5,038; $5,309)	$9,529 ($9,016; $10,100)	$4,773 ($4,611; $4,929)	$5,315 ($4,731; $5,922)	$559 ($369; $781)
Percent of cohort with an actionable genomic alteration detected	19.7% (17.0%; 22.5%)	22.0% (19.1%; 24.8%)	2.3% (1.7%; 3.0%)	22.0% (19.1%; 24.8%)	2.3% (1.7%; 3.0%)	22.0% (19.1%; 24.8%)	2.3% (1.7%; 3.0%)	20.3% (17.5%; 23.1%)	0.6% (0.3%; 0.9%)
Percent of actionable genomic alterations detected	84.7% (80.6%; 88.3%)	94.5% (92.8%; 95.9%)	9.7% (7.4%; 12.5%)	94.5% (92.8%; 95.9%)	9.7% (7.4%; 12.5%)	94.5% (92.8%; 95.9%)	9.7% (7.4%; 12.5%)	87.2% (83.5%; 90.2%)	2.4% (1.4%; 3.8%)
Percent of cohort receiving targeted therapy	17.6% (14.9% ; 20.5%)	19.6% (16.6% ; 22.6%)	2.0% (1.5% ; 2.7%)	19.6% (16.6% ; 22.6%)	2.0% (1.5% ; 2.7%)	19.6% (16.6% ; 22.6%)	2.0% (1.5% ; 2.7%)	18.1% (15.4% ; 21.0%)	0.5% (0.3% ; 0.8%)
Percent of cohort receiving BSC	35.0% (31.3% ; 38.6%)	34.3% (30.6% ; 37.9%)	-0.7% (-1.0% ; -0.4%)	34.3% (30.6% ; 37.9%)	-0.7% (-1.0% ; -0.4%)	34.3% (30.6% ; 37.9%)	-0.7% (-1.0% ; -0.4%)	34.8% (31.1% ; 38.4%)	-0.2% (-0.3% ; -0.1%)
Average number of tissue biopsies received	1.086 (1.056; 1.119)	1.073 (1.047; 1.101)	-0.013 (-0.019; -0.008)	0.921 (0.884; 0.959)	-0.165 (-0.192; -0.141)	1.073 (1.047; 1.101)	-0.013 (-0.019; -0.008)	1.073 (1.047; 1.101)	-0.013 (-0.019; -0.008)
Average number of liquid biopsies received	0 (0; 0)	1 (1; 1)	1 (1; 1)	1 (1; 1)	1 (1; 1)	0.818 (0.792; 0.844)	0.818 (0.792; 0.844)	0.104 (0.069; 0.146)	0.104 (0.069; 0.146)
Average test-turn around time, all individuals	16.2 (15.9; 16.6)	14.2 (13.8; 14.6)	-2 (-2.3; -1.7)	20.7 (20.2; 21.2)	4.5 (4.1; 4.9)	21.8 (21.4; 22.2)	5.6 (5.4; 5.8)	16.8 (16.3; 17.4)	0.6 (0.4; 0.8)
Average test-turn around time, all individuals testing positive	13.7 (13.1; 14.2)	7.1 (6.9; 7.2)	-6.7 (-7.1; -6.2)	11.3 (10.6; 12)	-2.4 (-3.1; -1.7)	15.9 (15.6; 16.1)	2.1 (1.6; 2.8)	14.3 (13.6; 14.8)	0.5 (0.3; 0.8)
Cost per biopsy avoided	NA	NA	$448,696	NA	$31,378	NA	$366,344	NA	$42,923
Cost per additional individual receiving targeted therapy	NA	NA	$289,303	NA	$256,342	NA	$236,206	NA	$110,159

Abbreviations: BSC: Best-supportive care, NA: Not applicable

Table A18: Treatment related outcomes

Strategy	Life-years	QALYs	Total Cost $
BSC	0.63 (0.52;0.76)	0.29 (0.24;0.35)	$38,590 ($31,912; $46,129)
CRBPPEME-PEMB	2.89 (2.45;3.37)	2 (1.73;2.31)	$245,003 ($227,040; $265,028)
PEMB	4.37 (3.57;5.18)	3.04 (2.54;3.56)	$452,365 ($354,974; $553,528)
afatinib	3.14 (2.83;3.45)	2.21 (2.01;2.41)	$197,242 ($171,398; $219,204)
alectinib	8.8 (7.41;9.93)	6.15 (5.28;6.9)	$433,907 ($372,323; $491,729)
crizotinib	3.8 (2.7;4.96)	2.61 (1.94;3.34)	$240,148 ($192,965; $291,054)
entrectinib	5.7 (5.34;6.05)	3.83 (3.61;4.06)	$274,967 ($259,499; $292,208)
osimertinib	3.7 (3.33;4.09)	2.68 (2.43;2.92)	$216,996 ($201,989; $232,268)

Abbreviations: QALYs: Quality adjusted life-years, CRBPPEME-PEMB: pembrolizumab & carboplatin & pemetrexed.

Table A19: Detailed cost breakdown

		Liquid biopsy Testing strategy			
Variable	**Standard care**	**combined**	**Liquid first**	**Tissue first**	**Insufficient tissue**
Total costs	**$208,974 ($189,607; $230,383)**	**$216,284 ($197,055; $237,814)**	**$215,618 ($196,372; $237,036)**	**$215,211 ($195,950; $236,687)**	**$209,944 ($190,498; $231,514)**
Testing costs	$4,756 ($4,253; $5,303)	$10,602 ($10,112; $11,132)	$9,936 ($9,498; $10,414)	$9,529 ($9,016; $10,100)	$5,315 ($4,731; $5,922)
Tissue testing total	$4,756 ($4,253; $5,303)	$4,699 ($4,209; $5,234)	$4,033 ($3,602; $4,514)	$4,699 ($4,209; $5,234)	$4,699 ($4,209; $5,234)
Tissue testing	$4,474 ($3,986; $5,015)	$4,420 ($3,942; $4,949)	$3,794 ($3,377; $4,273)	$4,420 ($3,942; $4,949)	$4,420 ($3,942; $4,949)
Tissue testing AE	$282 ($192; $406)	$279 ($189; $402)	$239 ($163; $345)	$279 ($189; $402)	$279 ($189; $402)
Liquid testing total	$0 ($0; $0)	$5,903 ($5,881; $5,926)	$5,903 ($5,881; $5,926)	$4,830 ($4,672; $4,981)	$616 ($407; $859)
Long-term costs	**$204,218 ($184,878; $225,521)**	**$205,683 ($186,449; $226,988)**	**$205,683 ($186,449; $226,988)**	**$205,683 ($186,449; $226,988)**	**$204,629 ($185,345; $225,910)**
1st line drug	$132,304 ($115,914; $149,985)	$132,981 ($116,735; $150,534)	$132,981 ($116,735; $150,534)	$132,981 ($116,735; $150,534)	$132,536 ($116,152; $150,113)
2nd line drug	$15,099 ($12,900; $17,479)	$15,248 ($13,077; $17,575)	$15,248 ($13,077; $17,575)	$15,248 ($13,077; $17,575)	$15,128 ($12,929; $17,490)
Adverse events	$628 ($537; $728)	$616 ($528; $714)	$616 ($528; $714)	$616 ($528; $714)	$624 ($534; $723)
Administration	$1,754 ($1,481; $2,061)	$1,720 ($1,452; $2,017)	$1,720 ($1,452; $2,017)	$1,720 ($1,452; $2,017)	$1,748 ($1,474; $2,053)
General care	$52,430 ($45,596; $59,837)	$53,100 ($46,111; $60,546)	$53,100 ($46,111; $60,546)	$53,100 ($46,111; $60,546)	$52,586 ($45,698; $60,021)
End of life care	$2,004 ($1,877; $2,127)	$2,018 ($1,897; $2,138)	$2,018 ($1,897; $2,138)	$2,018 ($1,897; $2,138)	$2,007 ($1,882; $2,129)

Abbreviation: AE, adverse event.

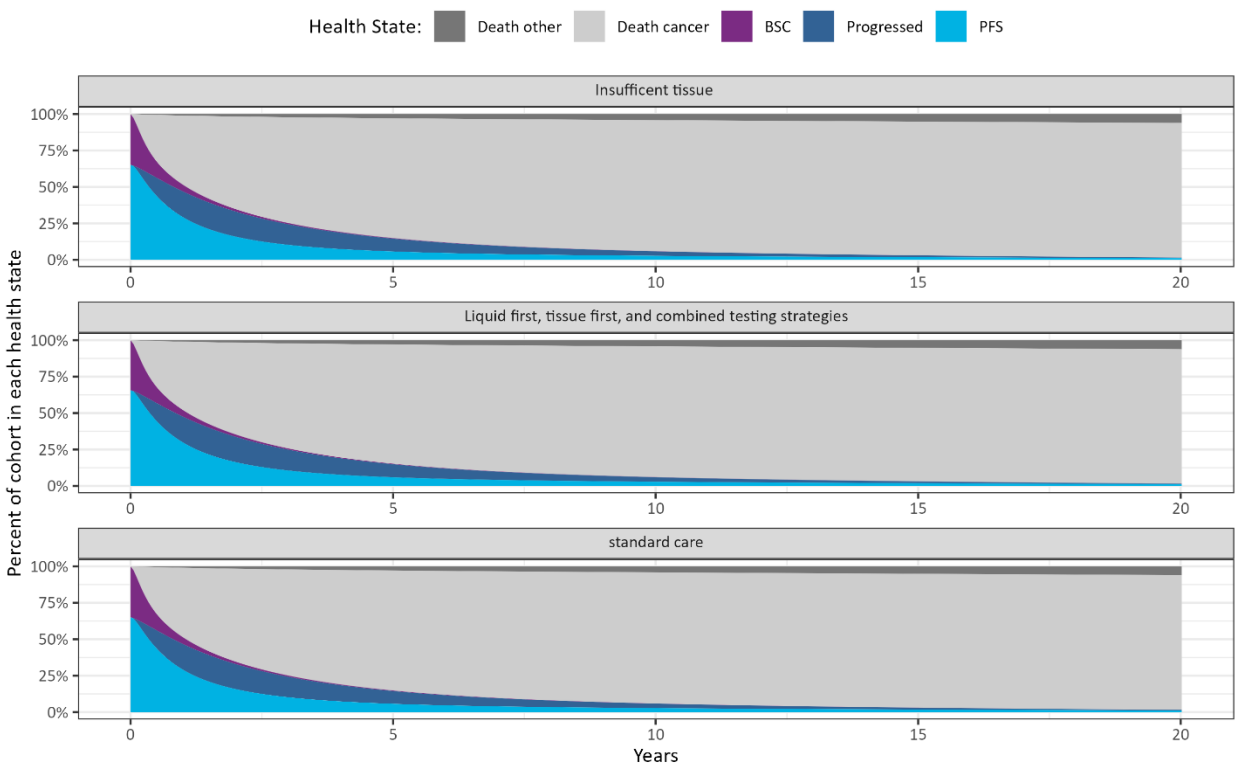

Figure A75: Markov trace

This figure outlines the state occupancy for each of the long-term model health states compared for all liquid biopsy strategies and the standard care.

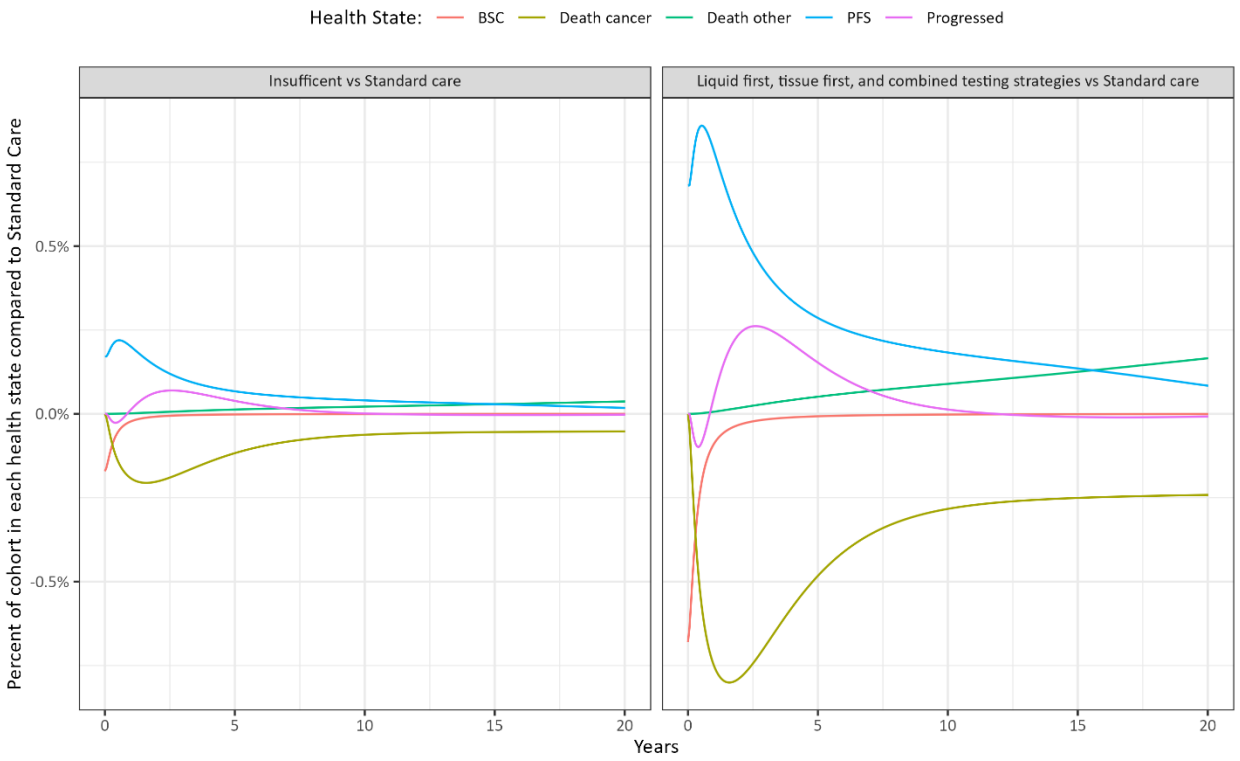

Figure A76: Markov trace for each intervention compared to the standard care

This figure outlines the difference in state occupancy for each of the long-term model health states compared to standard care. For all four liquid biopsy testing strategies individuals spend more time in the progression-free survival health state and the progressed health state. Individuals spend less time in the BSC health state and enter the absorbing death state later. These differences are less pronounced in the liquid biopsy for individuals with insufficient tissue testing strategy compared to the other three liquid biopsy testing strategies.

Table A20: Detailed scenario analysis results

Scenario	Liquid biopsy for individuals with insufficient tissue vs stadnard care		Liquid biopsy first vs standard care		Tissue biopsy first vs standard care		Combined testing vs standard care	
	Delta costs[a]	Delta QALYs[a]	Delta costs[a]	Delta QALYs[a]	Delta costs[a]	Delta QALYs[a]	Delta costs[a]	Delta QALYs[a]
Scenario 01: 5-year time horizon	$728	0.006	$5,707	0.024	$5,300	0.024	$6,373	0.024
Scenario 02: 10-year time horizon	$850	0.008	$6,158	0.034	$5,751	0.034	$6,824	0.034
Scenario 03: 15-year time horizon	$923	0.009	$6,453	0.039	$6,046	0.039	$7,119	0.039
Scenario 04: 3% discount rate	$923	0.009	$6,466	0.039	$6,059	0.039	$7,132	0.039
Scenario 05: 0% discount rate	$1,025	0.011	$6,856	0.046	$6,449	0.046	$7,522	0.046
Scenario 06: Population of interest includes all individuals diagnosed with NSCLC	$842	0.007	$6,188	0.029	$5,781	0.029	$6,854	0.029
Scenario 07: Population of interest includes all individuals diagnosed with NSCLC and liquid biopsy provides actionable results	$913	0.007	$6,439	0.03	$6,032	0.03	$7,105	0.03
Scenario 08: Drug acquisition 20% discount	$917	0.01	$6,479	0.042	$6,072	0.042	$7,145	0.042
Scenario 09: Drug acquisition 40% discount	$865	0.01	$6,313	0.042	$5,907	0.042	$6,979	0.042
Scenario 10: Drug acquisition 60% discount	$813	0.01	$6,148	0.042	$5,741	0.042	$6,814	0.042
scenario11: Drug acquisition 80% discount	$761	0.01	$5,983	0.042	$5,576	0.042	$6,649	0.042
Scenario 12: Drug acquisition 100% discount	$708	0.01	$5,817	0.042	$5,411	0.042	$6,483	0.042
Scenario 13: In house developed liquid biopsy test (cost sourced from Ezeife et al)	$541	0.01	$2,540	0.042	$2,879	0.042	$3,206	0.042
Scenario 14: Liquid biopsy sequencing costs increased by 25%	$1,111	0.01	$7,993	0.042	$7,341	0.042	$8,659	0.042
Scenario 15: Liquid biopsy sequencing costs decreased by 25%	$829	0.01	$5,296	0.042	$5,134	0.042	$5,962	0.042
Scenario 16: Effectiveness parameters sourced from Englmeier et al	$995	0.01	$7,106	0.044	$6,696	0.044	$7,768	0.044
Scenario 17: Effectiveness parameters sourced from Jansen et al	$558	0.004	$4,586	0.012	$4,179	0.012	$5,250	0.012
Scenario 18: Effectiveness parameters sourced from Patel et al	$868	0.008	$6,170	0.032	$5,762	0.032	$6,834	0.032
Scenario 19: Probability of choosing to receive treatment is the same for individuals with or without actionable genomic alterations detected	$574	0.005	$4,981	0.02	$4,574	0.02	$5,645	0.02
Scenario 20: Excluding all cause mortality	$1,019	0.011	$6,872	0.049	$6,465	0.049	$7,538	0.049
Scenario 21: Ontario drug benefit coverage increased to 100%	$1,223	0.01	$7,723	0.042	$7,316	0.042	$8,389	0.042
Scenario 22: Adverse event related disutility implemented using a multiplicative approach	$970	0.01	$6,644	0.042	$6,237	0.042	$7,310	0.042
Scenario 23: Exclude treatment related adverse events	$974	0.01	$6,656	0.042	$6,249	0.042	$7,322	0.042

Scenario	Liquid biopsy for individuals with insufficient tissue vs stadnard care		Liquid biopsy first vs standard care		Tissue biopsy first vs standard care		Combined testing vs standard care	
	Delta costs[a]	Delta QALYs[a]	Delta costs[a]	Delta QALYs[a]	Delta costs[a]	Delta QALYs[a]	Delta costs[a]	Delta QALYs[a]
Scenario 24: Increased probability of tumour not being detected in liquid biopsy sample	$950	0.01	$6,626	0.041	$6,198	0.041	$7,268	0.041
Scenario 25: Decreased probability of tumour not being detected in liquid biopsy sample	$968	0.01	$6,665	0.043	$6,272	0.043	$7,341	0.043
Scenario 26: Increased probability of insufficient tissue for tissue testing	$1,361	0.015	$6,750	0.045	$6,388	0.045	$7,412	0.045
Scenario 27: Decreased probability of insufficient tissue for tissue testing	$617	0.006	$6,551	0.04	$6,102	0.04	$7,212	0.04
Scenario 28: Increased probability of choosing to have a re-biopsy	$1,040	0.012	$6,728	0.044	$6,320	0.044	$7,389	0.044
Scenario 29: Decreased probability of choosing to have a re-biopsy	$887	0.008	$6,576	0.041	$6,168	0.041	$7,237	0.041
Scenario 30: 3-month duration of end-of-life care	$981	0.01	$6,687	0.042	$6,280	0.042	$7,353	0.042
Scenario 31: 12-month duration of end-of-life care	$1,043	0.01	$6,914	0.042	$6,507	0.042	$7,580	0.042
Scenario 32: Second best fitting curves as judged by AIC	$939	0.01	$6,668	0.043	$6,260	0.043	$7,330	0.043
Scenario 33: Second best fitting curves as judged by BIC	$950	0.01	$6,626	0.042	$6,218	0.042	$7,288	0.042
Scenario 34: improved effectiveness because of faster test turn around time	$970	0.01	$9,764	0.088	$6,237	0.042	$10,430	0.088
Scenario 35: Increase HR of 1.34 for mortality and progression for individuals receiving non-targeted therapies which are mismatched.	$976	0.01	$6,672	0.042	$6,265	0.042	$7,338	0.042
Scenario 36: 100% probability of receiving treatment	$594	0.008	$4,866	0.032	$4,459	0.032	$5,532	0.032
Scenario 37: Increased sensitivity for liquid biopsy compared to tissue biopsy	$974	0.011	$6,862	0.049	$6,498	0.049	$7,545	0.049
Scenario 38: Decreased sensitivity for liquid biopsy compared to tissue biopsy	$920	0.009	$6,451	0.036	$5,997	0.036	$7,089	0.036
Scenario 39: 20% Discount to orally administered medications	$794	0.01	$5,905	0.042	$5,498	0.042	$6,571	0.042
Scenario 40: 40% Discount to orally administered medications	$619	0.01	$5,167	0.042	$4,760	0.042	$5,833	0.042
Scenario 41: Limited societal perspective	$1,127	0.01	$5,910	0.04	$5,042	0.04	$7,416	0.04
Scenario 42: Reduced effectiveness of alectinib	$823	0.01	$5,938	0.04	$5,534	0.04	$6,601	0.04

Abbreviations: AIC: Akaike information criterion, BIC: Bayesian information criterion, HR: Hazard ratio, NSCLC: Non-small cell lung cancer

[a] Compared with the standard care strategy

Table A21: Detailed Budget Impact Analysis results

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Cost estimates millions, current standard care						
Total costs	426.94	591.87	671.73	724.67	768.36	3183.57
Testing costs	20.95	21.16	21.38	21.59	21.78	106.87
Tissue testing total	20.95	21.16	21.38	21.59	21.78	106.87
Tissue testing	19.71	19.91	20.12	20.31	20.49	100.53
Tissue testing AE	1.24	1.26	1.27	1.28	1.29	6.34
Liquid testing total	0.00	0.00	0.00	0.00	0.00	0.00
Long-term costs	405.98	570.71	650.34	703.09	746.58	3076.70
1st line drug	295.74	407.50	449.80	474.53	496.03	2123.60
2nd line drug	12.81	25.70	34.34	41.99	47.92	162.75
Adverse events	2.77	2.80	2.82	2.85	2.88	14.12
Administration	3.94	5.38	5.86	6.22	6.52	27.92
General care	87.83	124.38	151.19	170.27	185.37	719.04
End of life care	2.90	4.95	6.34	7.23	7.86	29.27
Budget Impact millions, Combined testing strategy						
Total costs	23.65	25.39	27.47	28.45	29.29	134.24
Testing costs	25.75	26.01	26.28	26.53	26.77	131.35
Tissue testing total	-0.25	-0.25	-0.26	-0.26	-0.26	-1.28
Tissue testing	-0.24	-0.24	-0.24	-0.24	-0.25	-1.21
Tissue testing AE	-0.01	-0.02	-0.02	-0.02	-0.02	-0.08
Liquid testing total	26.01	26.26	26.54	26.79	27.03	132.63
Long-term costs	-2.11	-0.63	1.19	1.91	2.52	2.89
1st line drug	-1.76	-1.30	0.02	0.26	0.50	-2.27
2nd line drug	0.09	0.69	0.65	0.71	0.72	2.87
Adverse events	-0.05	-0.05	-0.05	-0.05	-0.05	-0.27
Administration	-0.09	-0.12	-0.13	-0.14	-0.14	-0.63
General care	-0.26	0.19	0.70	1.11	1.46	3.19
End of life care	-0.03	-0.02	0.00	0.01	0.03	-0.01
Budget Impact millions, Liquid first testing strategy						
Total costs	20.71	22.42	24.48	25.42	26.24	119.27
Testing costs	22.82	23.05	23.29	23.51	23.72	116.39
Tissue testing total	-3.19	-3.22	-3.25	-3.28	-3.31	-16.25
Tissue testing	-3.00	-3.03	-3.06	-3.09	-3.11	-15.28
Tissue testing AE	-0.19	-0.19	-0.19	-0.19	-0.20	-0.96
Liquid testing total	26.01	26.26	26.54	26.79	27.03	132.63
Long-term costs	-2.11	-0.63	1.19	1.91	2.52	2.89
1st line drug	-1.76	-1.30	0.02	0.26	0.50	-2.27
2nd line drug	0.09	0.69	0.65	0.71	0.72	2.87
Adverse events	-0.05	-0.05	-0.05	-0.05	-0.05	-0.27

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Administration	-0.09	-0.12	-0.13	-0.14	-0.14	-0.63
General care	-0.26	0.19	0.70	1.11	1.46	3.19
End of life care	-0.03	-0.02	0.00	0.01	0.03	-0.01
Budget Impact millions, Tissue first testing strategy						
Total costs	18.92	20.61	22.65	23.58	24.37	110.13
Testing costs	21.03	21.24	21.46	21.66	21.86	107.24
Tissue testing total	-0.25	-0.25	-0.26	-0.26	-0.26	-1.28
Tissue testing	-0.24	-0.24	-0.24	-0.24	-0.25	-1.21
Tissue testing AE	-0.01	-0.02	-0.02	-0.02	-0.02	-0.08
Liquid testing total	21.28	21.49	21.72	21.92	22.12	108.53
Long-term costs	-2.11	-0.63	1.19	1.91	2.52	2.89
1st line drug	-1.76	-1.30	0.02	0.26	0.50	-2.27
2nd line drug	0.09	0.69	0.65	0.71	0.72	2.87
Adverse events	-0.05	-0.05	-0.05	-0.05	-0.05	-0.27
Administration	-0.09	-0.12	-0.13	-0.14	-0.14	-0.63
General care	-0.26	0.19	0.70	1.11	1.46	3.19
End of life care	-0.03	-0.02	0.00	0.01	0.03	-0.01
Budget Impact millions, Liquid biopsy for individuals with insufficient tissue testing strategy						
Total costs	1.92	2.36	2.92	3.16	3.36	13.72
Testing costs	2.46	2.49	2.51	2.54	2.56	12.57
Tissue testing total	-0.25	-0.25	-0.26	-0.26	-0.26	-1.28
Tissue testing	-0.24	-0.24	-0.24	-0.24	-0.25	-1.21
Tissue testing AE	-0.01	-0.02	-0.02	-0.02	-0.02	-0.08
Liquid testing total	2.72	2.74	2.77	2.80	2.82	13.85
Long-term costs	-0.55	-0.13	0.40	0.62	0.80	1.15
1st line drug	-0.44	-0.29	0.13	0.23	0.31	-0.06
2nd line drug	0.01	0.16	0.14	0.15	0.16	0.63
Adverse events	-0.02	-0.02	-0.02	-0.02	-0.02	-0.09
Administration	-0.02	-0.03	-0.03	-0.03	-0.03	-0.15
General care	-0.07	0.05	0.18	0.29	0.37	0.83
End of life care	-0.01	-0.01	0.00	0.00	0.01	0.00

Abbreviations: AE: Adverse events
Budget impact compared to the standard care.

Appendix 9: Letter of Information

LETTER OF INFORMATION

Ontario Health

Ontario Health is conducting a review of **Plasma-Based Comprehensive Genomic Profiling Assays for Non–Small Cell Lung Cancer.** The purpose is to better understand how this technique can be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients and caregivers of those who have been diagnosed and/or managed with non-small cell lung cancer and who may or may not have used plasma-based comprehensive genomic profiling.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 30-40 minutes of your time for a phone interview
- ✓ 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 Ontario Health (OH) staff. OH staff will contact interested participants by collecting contact information (i.e., email address and/or phone number) to set up an interview. The interview will last about 30-40 minutes. It will be held over the telephone. 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 your cancer diagnosis and 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 completion of the project, the records will be destroyed. If you are sending us personal information by email, please be aware that electronic communication is not always secure and can be vulnerable to interception.

Ontario Health is designated an "institution" by the *Freedom of Information and Protection of Privacy Act* (FIPPA) and is collecting your personal information pursuant to FIPPA and the *Connecting Care Act, 2019* to support the Health Technology Assessment Program. If you have any questions regarding Ontario Health's collection and use of personal information for the purposes of this program, please contact Team Lead, Jigna Mistry noted below.

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:

DOCUMENTATION OF INFORMED CONSENT

We will give you a copy of this informed consent form after you and the OH staff have signed and dated it.

By signing this form, you confirm that:

- You agree to participate in this interview.
- You understand that your participation is voluntary.
- You understand the purpose, activities, risks and benefits of participating in this interview.
- You authorize the OH staff to use your data as explained in this form.
- OH staff have answered your questions to your satisfaction.

Please check the appropriate boxes:

- You give permission to the OH staff to audio record your interview: YES ☐ NO ☐

Name of Participant (please print):

_____

Signature of Participant (please sign):

_____

Name of OH Staff:

_____

Signature of OH Staff:

_____

Place: _____

Date: _____

Note: For participants who are unable to electronically sign the consent form with their permission to participate in this interview, OH staff will audio-record participants' consent prior to their interview and retain a record of participants' verbal consent through OH's dedicated secure network drive.

Appendix 10: Interview Guide

CGP Interview Guide

Lived Experience
Health care journey involving development of symptoms up to diagnosis of lung cancer

Diagnosis
Diagnosis process
Experience with biopsy (liquid vs tissue)
Information
Access/barriers?

CGP (Liquid Biopsy)
Awareness
CGP Process

- Timing for results

Decision making surrounding treatment
Side effects of treatment, hospitalization due to side effects
Impact of CGP (if applicable)
Impact on quality of life

Any equity/ethical concerns?

References

(1) Parente P, Carbonelli C, Biancofiore G, Sukthi A, Di Micco CM, Vairo M, et al. Handling and standardization of EBUS needle aspiration in NSCLC patients: the value of the cell block, a monoinstitutional experience. Thorac Cancer. 2022;13(17):2480-8.

(2) American Society of Clinical Oncology. Lung cancer - non-small cell: introduction [Internet]. Alexandria (VA): The Society; 2022 [cited 2023 Apr 3]. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/introduction

(3) Yale Medicine. Non-small cell lung cancer [Internet]. New Haven (CT): Yale Medicine; 2023 [cited 2023 Apr 3]. Available from: https://www.yalemedicine.org/conditions/non-small-cell-lung-cancer

(4) Canadian Cancer Society. Staging cancer [Internet]. Toronto (ON): The Society; 2023 [cited 2023 Apr 3]. Available from: https://cancer.ca/en/cancer-information/what-is-cancer/stage-and-grade/staging

(5) National Cancer Institute Dictionary of Cancer Terms [Internet]. Bethesda (MD): The Institute; 2024 [cited 2024 Apr 23]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/pathologist.

(6) Passaro A, Attili I, Rappa A, Vacirca D, Ranghiero A, Fumagalli C, et al. Genomic characterization of concurrent alterations in non-small cell lung cancer (NSCLC) harboring actionable mutations. Cancers (Basel). 2021;13(9):2172.

(7) Jalal SI, Guo A, Ahmed S, Kelley MJ. Analysis of actionable genetic alterations in lung carcinoma from the VA National Precision Oncology Program. Semin Oncol. 2022;49(3-4):265-74.

(8) Ontario Health (Cancer Care Ontario). Comprehensive cancer testing at diagnosis [Internet]. Toronto (ON): Ontario Health; 2023 [cited 2023 Apr 3]. Available from: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/ComprehensiveCancerTestingIndications.pdf

(9) Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.

(10) Brenner DR, Poirier A, Woods RR, Ellison LF, Billette J-M, Demers AA, et al. Projected estimates of cancer in Canada in 2022. Can Med Assoc J. 2022;194(17):E601-E7.

(11) Statista. Estimated cancer incidence rates in Canada by province in 2021 [Internet]. New York: Statista; 2023 [cited 2023 Apr 3]. Available from: https://www.statista.com/statistics/438129/estimated-incidence-rates-of-all-cancers-in-canada-by-province/

(12) Ontario Health (Cancer Care Ontario). Ontario cancer statistics 2022. Ch 1: Estimated current cancer incidence [Internet]. Toronto (ON): Ontario Health; 2022 [cited 2023 Apr 3]. Available from: https://www.cancercareontario.ca/en/data-research/view-data/statistical-reports/ontario-cancer-statistics-2022/ch-1-estimated-current-cancer-incidence-2022

(13) Government of Canada. Lung cancer in Canada [Internet]. Ottawa (ON): Government of Canada; 2021 [cited 2023 Apr 3]. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/lung-cancer.html

(14) Ontario Health (Cancer Care Ontario). Lung cancer [Internet]. Toronto (ON): Ontario Health; n.d. [cited 2023 Apr 3]. Available from: https://www.cancercareontario.ca/en/types-of-cancer/lung

(15) Ontario Health (Cancer Care Ontario). Ontario cancer statistics 2022. Ch 2: Estimated current cancer mortality [Internet]. Toronto (ON): Ontario Health; 2022 [cited 2023 Apr 3]. Available

from: https://www.cancercareontario.ca/en/data-research/view-data/statistical-reports/ontario-cancer-statistics-2022/ch-2-estimated-current-cancer-mortality-2022

(16) Jamal S, Jones C, Walker J, Mazereeuw M, Sheppard AJ, Henry D, et al. Cancer in First Nations people in Ontario, Canada: incidence and mortality, 1991 to 2010. Health Rep. 2021;32(6):14-28.

(17) Shtivelman E. Targetable mutations in NSCLC: more testing needed! [Internet]. Palo Alto (CA): Cancer Commons; 2018 Jan 16 [cited 2024 Mar 11]. Available from: https://cancercommons.org/latest-insights/targetable-mutations-in-nsclc-more-testing-needed/

(18) Cai J, Jiang H, Li S, Yan X, Wang M, Li N, et al. The landscape of actionable genomic alterations by next-generation sequencing in tumor tissue versus circulating tumor DNA in Chinese patients with non-small cell lung cancer. Front Oncol. 2022;11:751106.

(19) Sabari J. An overview of NSCLC and actionable mutations [Internet]. Cranbury (NJ): American Journal of Managed Care; 2022 Jun 22 [cited 2024 Mar 11]. Available from: https://www.ajmc.com/view/an-overview-of-nsclc-and-actionable-mutations

(20) Canadian Cancer Society. Survival statistics for non–small cell lung cancer [Internet]. Toronto (ON): The Society; 2023 Aug [cited 2024 Mar 29]. Available from: https://cancer.ca/en/cancer-information/cancer-types/lung/prognosis-and-survival/non-small-cell-lung-cancer-survival-statistics

(21) Rolfo C, Mack P, Scagliotti CV, Aggarwal C, Arcila ME, Barlesi F, et al. Liquid biopsy for advanced NSCLC: a consensus statement from the International Association for the Study of Lung Cancer. J Thorac Oncol. 2021;16(10):1647-62.

(22) Suh JH, Schrock AB, Johnson A, Lipson D, Gay LM, Ramkissoon S, et al. Hybrid capture-based comprehensive genomic profiling identifies lung cancer patients with well-characterized sensitizing epidermal growth factor receptor point mutations that were not detected by standard of care testing. Oncologist. 2018;23(7):776-81.

(23) Zito Marino F, Pagliuca F, Ronchi A, Cozzolino I, Montella M, Berretta M, et al. NTRK fusions, from the diagnostic algorithm to innovative treatment in the era of precision medicine. Int J Mol Sci. 2020;21(10):3718.

(24) Herbreteau G, Vallée A, Charpentier S, Normanno N, Hofman P, Denis MG. Circulating free tumor DNA in non-small cell lung cancer (NSCLC): clinical application and future perspectives. J Thorac Dis. 2019;11 Suppl 1:S113-26.

(25) Memorial Sloan Kettering Cancer Center. Actionable genes [Internet]. New York: The Center; 2024 [cited 2024 Mar 11]. Available from: https://www.oncokb.org/actionable-genes#cancerType=NSCLC&sections=Tx

(26) Hua G, Zhang X, Zhang M, Wang Q, Chen X, Yu R, et al. Real-world circulating tumor DNA analysis depicts resistance mechanism and clonal evolution in ALK inhibitor-treated lung adenocarcinoma patients. Esmo Open. 2022;7(1):100337.

(27) Blackhall FH, Peters S, Bubendorf L, Dafni U, Kerr KM, Hager H, et al. Prevalence and clinical outcomes for patients with ALK-positive resected stage I to III adenocarcinoma: results from the European Thoracic Oncology Platform Lungscape Project. J Clin Oncol. 2014;32(25):2780-7.

(28) Chae YK, Tamragouri KB, Chung J, Lin X, Miller V, Ali SM, et al. Large-cell neuroendocrine carcinoma of the lung: a focused analysis of BRAF alterations and case report of a BRAF non-V600-mutated tumor responding to targeted therapy. JCO Precis Oncol. 2018;2:1-12.

(29) O'Leary CG, Andelkovic V, Ladwa R, Pavlakis N, Zhou C, Hirsch F, et al. Targeting BRAF mutations in non-small cell lung cancer. Transl Lung Cancer Res. 2019;8(6):1119-24.

(30) Sharma M, Basu D, Shrinidhi N, Amrith BP, Batra U. A narrative review of the role of common *EGFR* mutations in pathogenesis and treatment of non-small-cell lung carcinoma. Cancer Res Stat Treat. 2022;5(3):507-18.

(31) O'Sullivan DE, Jarada TN, Yusuf A, Hu L, Gogna P, Brenner DR, et al. Prevalence, treatment patterns, and outcomes of individuals with EGFR positive metastatic non-small cell lung cancer in a Canadian real-world setting: a comparison of exon 19 deletion, L858R, and exon 20 insertion *EGFR* mutation carriers. Curr Oncol. 2022;29(10):7198–208.
(32) Sharma M, Abhinav D, Himanshi D, Shrinidhi N, Batra U. A narrative review of ERBB2 in non-small cell lung carcinoma. Cancer Res Stat Treat. 2022;5(1):97-104.
(33) Ren S, Wang J, Ying J, Mitsudomi T, Lee DH, Wang Z, et al. Consensus for HER2 alterations testing in non-small-cell lung cancer. ESMO Open. 2022;7(1):100395.
(34) Zhou Z, Liu Z, Ou Q, Wu X, Wang X, Shao Y, et al. Targeting FGFR in non-small cell lung cancer: implications from the landscape of clinically actionable aberrations of FGFR kinases. Cancer Biol Med. 2021;18(2):490-501.
(35) Pacini L, Jenks AD, Lima NC, Huang PH. Targeting the fibroblast growth factor receptor (FGFR) family in lung cancer. Cells. 2021;10(5):1154.
(36) Reita D, Pabst L, Pencreach E, Guerin E, Dano L, Rimelen V, et al. Direct targeting KRAS mutation in non-small cell lung cancer: focus on resistance. Cancers (Basel). 2022;14(5):1321.
(37) Michaels E, Bestvina CM. Meeting an un-MET need: Targeting MET in non-small cell lung cancer. Front Oncol. 2022;12:1004198.
(38) Cheema PK, Banerji SO, Blais N, Chu QSC, Desmeules P, Juergens RA, et al. Canadian consensus recommendations on the management of MET-altered NSCLC. Curr Oncol. 2021;28(6):4552-76.
(39) Rosas D, Raez LE, Russo A, Rolfo C. Neuregulin 1 Gene (NRG1). A potentially new targetable alteration for the treatment of lung cancer. Cancers (Basel). 2021;13(20):5038.
(40) Harada G, Santini FC, Wilhelm C, Drilon A. NTRK fusions in lung cancer: from biology to therapy. Lung Cancer. 2021;161:108-13.
(41) Farago AF, Taylor MS, Doebele RC, Zhu VW, Kummar S, Spira AI, et al. Clinicopathologic features of non–small-cell lung cancer harboring an NTRK gene fusion. JCO Precis Oncol. 2018;2.
(42) Dumbrava EE, Call SG, Huang HJ, Stuckett AL, Madwani K, Adat A, et al. PIK3CA mutations in plasma circulating tumor DNA predict survival and treatment outcomes in patients with advanced cancers. ESMO Open. 2021;6(5):100230.
(43) Daher S, Zer A, Tschernichovsky R, Yacobi R, Barshack I, Tsabari S, et al. Driver mutation characteristics of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) in advanced non-small cell lung cancer. Lung Cancer. 2023;178:229-36.
(44) Li T, Yang WY, Liu TT, Li Y, Liu L, Zheng X, et al. Advances in the diagnosis and treatment of a driving target: RET rearrangements in non-small-cell lung cancer (NSCLC) especially in China. Technol Cancer Res Treat. 2023;22:15330338221148802.
(45) Parimi V, Tolba K, Danziger N, Kuang Z, Sun D, Lin DI, et al. Genomic landscape of 891 RET fusions detected across diverse solid tumor types. NPJ Precis Oncol. 2023;7(1):10.
(46) Isla D, Lozano MD, Paz-Ares L, Salas C, de Castro J, Conde E, et al. New update to the guidelines on testing predictive biomarkers in non-small-cell lung cancer: a national consensus of the Spanish Society of Pathology and the Spanish Society of Medical Oncology. Clin Transl Oncol. 2023;25(5):1252-67.
(47) AACR Project Genie Consortium. AACR Project GENIE: powering precision medicine through an international consortium. Cancer Discov. 2017;7(8):818-31.
(48) Cui M, Han Y, Li P, Zhang J, Ou Q, Tong X, et al. Molecular and clinicopathological characteristics of ROS1-rearranged non-small-cell lung cancers identified by next-generation sequencing. Mol Oncol. 2020;14(11):2787-95.
(49) Gendarme S, Bylicki O, Chouaid C, Guisier F. ROS-1 fusions in non-small-cell lung cancer: evidence to date. Curr Oncol. 2022;29(2):641-58.

(50) Russo A, Lee JK, Pasquina LW, Re MD, Dilks HH, Murugesan K, et al. Liquid biopsy of lung cancer before pathological diagnosis is associated with shorter time to treatment. JCO Precis Oncol. 2024;8:e2300535.
(51) Heist RS, Sequist LV, Engelman JA. Genetic changes in squamous cell lung cancer: a review. J Thorac Oncol. 2012;7(5):924-33.
(52) Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res. 2020;10(3):727-42.
(53) Vareki SM, Garrigós C, Duran I. Biomarkers of response to PD-1/PD-L1 inhibition. Crit Rev Oncol Hematol. 2017;116:116-24.
(54) Arisi MF, Dotan E, Fernandez SV. Circulating tumor DNA in precision oncology and its applications in colorectal cancer. Int J Mol Sci. 2022;23(8):4441.
(55) Dalurzo MN, Avilés-Salas A, Soares FA, Hou Y, Li Y, Stroganova A, et al. Testing for EGFR mutations and ALK rearrangements in advanced non-small-cell lung cancer: considerations for countries in emerging markets. Onco Targets Ther. 2021;14:4671-92.
(56) Abdayem P, Planchard D. Update on molecular pathology and role of liquid biopsy in nonsmall cell lung cancer. Eur Respir Rev. 2021;30(161):200294.
(57) Bertoli E, De Carlo E, Basile D, Zara D, Stanzione B, Schiappacassi M, et al. Liquid biopsy in NSCLC: an investigation with multiple clinical implications. Int J Mol Sci. 2023;24(13):10803.
(58) Rolfo CD, Madison RW, Pasquina LW, Brown DW, Huang Y, Hughes JD, et al. Measurement of ctDNA tumor fraction identifies informative negative liquid biopsy results and informs value of tissue confirmation. Clin Cancer Res. Epub 2024 Mar 25.
(59) Cohen D, Hondelink LM, Solleveld-Westerink N, Uljee SM, Ruano D, Cleton-Jansen A-M, et al. Optimizing mutation and fusion detection in NSCLC by sequential DNA and RNA sequencing. J Thorac Oncol. 2020;15(6):1000-14.
(60) Pecciarini L, Brunetto E, Grassini G, De Pascali V, Ogliari FR, Talarico A, et al. Gene fusion detection in NSCLC routine clinical practice: targeted-NGS or FISH? Cells. 2023;12(8):1135.
(61) Kuang Y, Xu P, Wang J, Zheng Y, Sun X, Li Z, et al. Detecting ALK rearrangement with RT-PCR: a reliable approach compared with next-generation sequencing in patients with NSCLC. Mol Diagn Ther. 2021;25(4):487-94.
(62) Foundation Medicine. FoundationOne Liquid CDx [Internet]. Cambridge (MA): Foundation Medicine; 2023 [cited 2023 May 1]. Available from: https://www.foundationmedicine.com/test/foundationone-liquid-cdx
(63) Odegaard JI, Vincent JJ, Mortimer S, Vowles JV, Ulrich BC, Banks KC, et al. Validation of a plasma-based comprehensive cancer genotyping assay utilizing orthogonal tissue- and plasma-based methodologies. Clin Cancer Res. 2018;24(15):3539-49.
(64) Finkle DJ, Boulos H, Driessen TM, Lo C, Blidner RA, Hafez A, et al. Validation of a liquid biopsy assay with molecular and clinical profiling of circulating tumor DNA. NPJ Precis Oncol. 2021;5(1):63.
(65) Scott J. Cancer-focused Imagia Canexia Health files for bankruptcy 18 months after merger [Internet]. Toronto (ON): BetaKit; 2023 Aug 28 [cited 2024 May 2]. Available from: https://betakit.com/cancer-focused-imagia-canexia-health-files-for-bankruptcy-18-months-after-merger/#:~:text=The%20Aug.,as%20part%20of%20the%20deal.
(66) Health Canada. Notice - revision to guidance document: submission of pharmacogenomic information [Internet]. Ottawa (ON): Health Canada; 2008 Aug 13 [cited 2023 May 15]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/submission-pharmacogenomic-information.html

(67) National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): non-small cell lung cancer, NCCN evidence blocks [Internet]. Plymouth Meeting (PA): The Network; 2023 [cited 2023 Apr 12]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf

(68) Ontario Health (Quality). Cell-free circulating tumour DNA blood testing to detect EGFR T790M mutation in people with advanced non–small cell lung cancer: recommendation [Internet]. Toronto (ON): Queen's Printer for Ontario; 2020 [cited 2024 May]. Available from: https://hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/cell-free-circulating-tumour-dna-blood-testing-to-detect-egfr-t790m-mutation-in-people-with-advanced-nonsmall-cell-lung-cancer

(69) Evidence for equity: PROGRESS-Plus [Internet]. London: Cochrane Collaboration; c2023 [cited 2023 Oct 6]. Available from: https://methods.cochrane.org/equity/projects/evidence-equity/progress-plus

(70) Grosse SD, Kalman L, Khoury MJ. Evaluation of the validity and utility of genetic testing for rare diseases. Adv Exp Med Biol. 2010;686:115-31.

(71) McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol. 2016;75:40-6.

(72) Chan HT, Chin YM, Low SK. Circulating tumor DNA-based genomic profiling assays in adult solid tumors for precision oncology: recent advancements and future challenges. Cancers (Basel). 2022;14(13):3275.

(73) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol [Internet]. 2021 [cited 2021 May 27]; 134: 178-89. Available from: https://www.sciencedirect.com/science/article/pii/S0895435621000731

(74) Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions, version 6.2 (updated 2021 Feb). London: Cochrane Collaboration; 2021. Available from www.training.cochrane.org/handbook.

(75) Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22(4):153-60.

(76) Yang B, Mallett S, Takwoingi Y, Davenport CF, Hyde CJ, Whiting PF, et al. QUADAS-C: a tool for assessing risk of bias in comparative diagnostic accuracy studies. Ann Intern Med [Internet]. 2021 Oct 26 [cited 2023 Apr 13]; 174(11). Available from: https://doi.org/10.7326/M21-2234

(77) Higgins JPT, Morgan RL, Rooney AA, Taylor KW, Thayer KA, Raquel A, et al. A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E), launch version. Environ Int [Internet]. 2023 Jun 20 [cited 2024 May]. Available from: https://www.riskofbias.info/welcome/robins-e-tool

(78) Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355(i4919).

(79) Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook [Internet]. Hamilton (ON): Grade Working Group; 2013 [cited 2017 Dec]. Available from http://gdt.guidelinedevelopment.org/app/handbook/handbook.html.

(80) Biaoxue R, Shuanying Y. Tissue or blood: which is more suitable for detection of EGFR mutations in non-small cell lung cancer? Int J Biol Markers. 2017;33(1):40-8.

(81) Chen Z, Miao H, Zeng Q, Xu S, Liu K. Circulating cell-free DNA as a diagnostic and prognostic biomarker for non-small-cell lung cancer: a systematic review and meta-analysis. Biomark. 2020;14(7):587-97.

(82) Cheung AH, Wong KY, Chiang CH, Liu X, Zhang Y, Hui CH, et al. Interpretation of lung cancer plasma EGFR mutation tests in the clinical setting. Am J Clin Pathol. 2023;159(2):181-91.
(83) Esagian SM, Grigoriadou G, Nikas IP, Boikou V, Sadow PM, Won JK, et al. Comparison of liquid-based to tissue-based biopsy analysis by targeted next generation sequencing in advanced non-small cell lung cancer: a comprehensive systematic review. J Cancer Res Clin Oncol. 2020;146(8):2051-66.
(84) Fan G, Zhang K, Ding J, Li J. Prognostic value of EGFR and KRAS in circulating tumor DNA in patients with advanced non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2017;8(20):33922-32.
(85) He X, Chi Y, Peng J, Hu W, Ding C, Li B. A systematic review and meta-analysis of circulating cell-free DNA as a diagnostic biomarker for non-small cell lung cancer. J Thorac Dis. 2022;14(6):2103-11.
(86) Li Z, Zhang Y, Bao W, Jiang C. Insufficiency of peripheral blood as a substitute tissue for detecting EGFR mutations in lung cancer: a meta-analysis. Target. 2014;9(4):381-8.
(87) Luo J, Shen L, Zheng D. Diagnostic value of circulating free DNA for the detection of EGFR mutation status in NSCLC: a systematic review and meta-analysis. Sci Rep. 2014;4:6269.
(88) Mlika M, Dziri C, Zorgati MM, Ben Khelil M, Mezni F. Liquid biopsy as surrogate to tissue in lung cancer for molecular profiling: a meta-analysis. Curr Respir Med Rev. 2018;14(1):48-60.
(89) Palmieri M, Zulato E, Wahl SGF, Guibert N, Frullanti E. Diagnostic accuracy of circulating free DNA testing for the detection of KRAS mutations in non-small cell lung cancer: a systematic review and meta-analysis. Front Genet. 2022;13:1015161.
(90) Passiglia F, Rizzo S, Rolfo C, Galvano A, Bronte E, Incorvaia L, et al. Metastatic site location influences the diagnostic accuracy of ctDNA EGFR- mutation testing in NSCLC patients: a pooled analysis. Curr Cancer Drug Targets. 2018;18(7):697-705.
(91) Qian X, Liu J, Sun Y, Wang M, Lei H, Luo G, et al. Circulating cell-free DNA has a high degree of specificity to detect exon 19 deletions and the single-point substitution mutation L858R in non-small cell lung cancer. Oncotarget. 2016;7(20):29154-65.
(92) Qiu M, Wang J, Xu Y, Ding X, Li M, Jiang F, et al. Circulating tumor DNA is effective for the detection of EGFR mutation in non-small cell lung cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2015;24(1):206-12.
(93) Saarenheimo J, Andersen H, Eigeliene N, Jekunen A. Gene-guided treatment decision-making in non-small cell lung cancer - a systematic review. Front Oncol. 2021;11:754427.
(94) Sebastiao MM, Ho RS, de Carvalho JPV, Nussbaum M. Diagnostic accuracy of next generation sequencing panel using circulating tumor DNA in patients with advanced non-small cell lung cancer: a systematic review and meta-analysis. J Health Econ Outcomes Res. 2020;7(2):158-63.
(95) Shen H, Che K, Cong L, Dong W, Zhang T, Liu Q, et al. Diagnostic and prognostic value of blood samples for KRAS mutation identification in lung cancer: a meta-analysis. Oncotarget. 2017;8(22):36812-23.
(96) Shen H, Jin Y, Zhao H, Wu M, Zhang K, Wei Z, et al. Potential clinical utility of liquid biopsy in early-stage non-small cell lung cancer. BMC Med. 2022;20(1):480.
(97) Zhou S, Huang R, Cao Y. Detection of epidermal growth factor receptor mutations in peripheral blood circulating tumor DNA in patients with advanced non-small cell lung cancer: A PRISMA-compliant meta-analysis and systematic review. Medicine. 2020;99(40):e21965.
(98) van Delft F, Koffijberg H, Retel V, Heuvel MVD, M IJ. The validity and predictive value of blood-based biomarkers in prediction of response in the treatment of metastatic non-small cell lung cancer: a systematic review. Cancers (Basel). 2020;12(5):30.

(99) Wang N, Zhang X, Wang F, Zhang M, Sun B, Yin W, et al. The diagnostic accuracy of liquid Biopsy in EGFR-mutated NSCLC: a systematic review and meta-analysis of 40 studies. SLAS Technol. 2021;26(1):42-54.
(100) Zaman FY, Subramaniam A, Afroz A, Samoon Z, Gough D, Arulananda S, et al. Circulating tumour DNA (ctDNA) as a predictor of clinical outcome in non-small cell lung cancer undergoing targeted therapies: a systematic review and meta-analysis. Cancers (Basel). 2023;15(9):23.
(101) Bai H, Xia J, Zhao X, Gong Z, Zhang D, Xiong L. Detection of EGFR mutations using target capture sequencing in plasma of patients with non-small-cell lung cancer. J Clin Pathol. 2019;72(5):379-85.
(102) Buburuzan L, Zamfir Irofei MA, Ardeleanu CM, Muresan AH, Vasilescu F, Hudita A, et al. Dual NGS comparative analysis of liquid biopsy (LB) and formalin-fixed paraffin-embedded (FFPE) samples of non-small cell lung carcinoma (NSCLC). Cancers (Basel). 2022;14(24):10.
(103) Bustamante Alvarez JG, Janse S, Owen DH, Kiourtsis S, Bertino EM, He K, et al. Treatment of non-small-cell lung cancer based on circulating cell-free DNA and impact of variation allele frequency. Clin Lung Cancer. 2021;22(4):e519-e27.
(104) Chen KZ, Lou F, Yang F, Zhang JB, Ye H, Chen W, et al. Circulating tumor DNA detection in early-stage non-small cell lung cancer patients by targeted sequencing. Sci Rep. 2016;6:31985.
(105) Chen Y, Han T, Zhou Y, Mao B, Zhuang W. Efficacy comparison of targeted next-generation sequencing in the identification of somatic mutations in circulating tumor DNA from different stages of lung cancer. Neoplasma. 2019;66(4):652-60.
(106) Couraud S, Vaca-Paniagua F, Villar S, Oliver J, Schuster T, Blanche H, et al. Noninvasive diagnosis of actionable mutations by deep sequencing of circulating free DNA in lung cancer from never-smokers: a proof-of-concept study from BioCAST/IFCT-1002. Clin Cancer Res. 2014;20(17):4613-24.
(107) Cui S, Zhang W, Xiong L, Pan F, Niu Y, Chu T, et al. Use of capture-based next-generation sequencing to detect ALK fusion in plasma cell-free DNA of patients with non-small-cell lung cancer. Oncotarget. 2017;8(2):2771-80.
(108) Dagogo-Jack I, Rooney M, Nagy RJ, Lin JJ, Chin E, Ferris LA, et al. Molecular analysis of plasma from patients with ROS1-positive NSCLC. J Thorac Oncol. 2019;14(5):816-24.
(109) Dziadziuszko R, Mok T, Peters S, Han JY, Alatorre-Alexander J, Leighl N, et al. Blood First Assay Screening Trial (BFAST) in treatment-naive advanced or metastatic NSCLC: initial results of the phase 2 ALK-positive cohort. J Thorac Oncol. 2021;16(12):2040-50.
(110) Fernandes MGO, Cruz-Martins N, Machado JC, Costa JL, Hespanhol V. The value of cell-free circulating tumour DNA profiling in advanced non-small cell lung cancer (NSCLC) management. Cancer Cell Int. 2021;21(1):675.
(111) He Y, Zhang X, Wang L, Tian Z, Liu Q, Yao J, et al. Detection of cancer specific mutations in early-stage non-small cell lung cancer using cell-free DNA by targeted sequencing. Int J Oncol. 2016;49(6):2351-8.
(112) Jee J, Lebow ES, Yeh R, Das JP, Namakydoust A, Paik PK, et al. Overall survival with circulating tumor DNA-guided therapy in advanced non-small-cell lung cancer. Nat Med. 2022;28(11):2353-63.
(113) Jiao XD, Ding LR, Zhang CT, Qin BD, Liu K, Jiang LP, et al. Serum tumor markers for the prediction of concordance between genomic profiles from liquid and tissue biopsy in patients with advanced lung adenocarcinoma. Transl Lung Cancer Res. 2021;10(7):3236-50.
(114) Laufer-Geva S, Rozenblum AB, Twito T, Grinberg R, Dvir A, Soussan-Gutman L, et al. The clinical impact of comprehensive genomic testing of circulating cell-free DNA in advanced lung cancer. J Thorac Oncol. 2018;13(11):1705-16.

(115) Lee JK, Madison R, Classon A, Gjoerup O, Rosenzweig M, Frampton G, et al. Characterization of nonsmall-cell lung cancers with MET exon 14 skipping alterations detected in tissue or liquid: clinicogenomics and real-world treatment patterns. JCO Precis Oncol. 2021;5:1354-76.
(116) Lee JK, Hazar-Rethinam M, Decker B, Gjoerup O, Madison RW, Lieber DS, et al. The pan-tumor landscape of targetable kinase fusions in circulating tumor DNA. Clin Cancer Res. 2022;28(4):728-37.
(117) Li BT, Janku F, Jung B, Hou C, Madwani K, Alden R, et al. Ultra-deep next-generation sequencing of plasma cell-free DNA in patients with advanced lung cancers: results from the Actionable Genome Consortium. Ann Oncol. 2019;30(4):597-603.
(118) Li W, Li Y, Guo L, Liu Y, Yang L, Ying J. Metastatic NSCLCs with limited tissues: how to effectively identify driver alterations to guide targeted therapy in Chinese patients. JTO Clin Res Rep. 2021;2(5):100167.
(119) Liang X, Zhang W, Li J, Zhu J, Shao J, Wang J, et al. Clinical implications of ctDNA for EGFR-TKIs as first-line treatment in NSCLC. J Cancer Res Clin Oncol. 2023;149(3):1211-20.
(120) Lin YT, Chiang CL, Hung JY, Lee MH, Su WC, Wu SY, et al. Resistance profiles of anaplastic lymphoma kinase tyrosine kinase inhibitors in advanced non-small-cell lung cancer: a multicenter study using targeted next-generation sequencing. Eur J Cancer. 2021;156:1-11.
(121) Lin LH, Allison DHR, Feng Y, Jour G, Park K, Zhou F, et al. Comparison of solid tissue sequencing and liquid biopsy accuracy in identification of clinically relevant gene mutations and rearrangements in lung adenocarcinomas. Mod Pathol. 2021;34(12):2168-74.
(122) Liu L, Liu H, Shao D, Liu Z, Wang J, Deng Q, et al. Development and clinical validation of a circulating tumor DNA test for the identification of clinically actionable mutations in nonsmall cell lung cancer. Genes Chromosomes Cancer. 2018;57(4):211-20.
(123) Marchetti A, Palma JF, Felicioni L, De Pas TM, Chiari R, Del Grammastro M, et al. Early prediction of response to tyrosine kinase inhibitors by quantification of EGFR mutations in plasma of NSCLC patients. J Thorac Oncol. 2015;10(10):1437-43.
(124) Mehta A, Kumar Sharma S, Kumar D, Vasudevan S. Plasma biopsy by tag-sequencing: an acceptable alternative to tumor tissue profiling in non-small-cell lung cancer. Pol J Pathol. 2021;72(2):117-25.
(125) Mondaca S, Lebow ES, Namakydoust A, Razavi P, Reis-Filho JS, Shen R, et al. Clinical utility of next-generation sequencing-based ctDNA testing for common and novel ALK fusions. Lung Cancer. 2021;159:66-73.
(126) Ohira T, Sakai K, Matsubayashi J, Kajiwara N, Kakihana M, Hagiwara M, et al. Tumor volume determines the feasibility of cell-free DNA sequencing for mutation detection in non-small cell lung cancer. Cancer Sci. 2016;107(11):1660-6.
(127) Page RD, Drusbosky LM, Dada H, Raymond VM, Daniel DB, Divers SG, et al. Clinical outcomes for plasma-based comprehensive genomic profiling versus standard-of-care tissue testing in advanced non-small cell lung cancer. Clin Lung Cancer. 2022;23(1):72-81.
(128) Park S, Olsen S, Ku BM, Lee MS, Jung HA, Sun JM, et al. High concordance of actionable genomic alterations identified between circulating tumor DNA-based and tissue-based next-generation sequencing testing in advanced non-small cell lung cancer: the Korean Lung Liquid Versus Invasive Biopsy Program. Cancer. 2021;127(16):3019-28.
(129) Pasquale R, Forgione L, Roma C, Fenizia F, Bergantino F, Rachiglio AM, et al. Targeted sequencing analysis of cell-free DNA from metastatic non-small-cell lung cancer patients: clinical and biological implications. Transl Lung Cancer Res. 2020;9(1):61-70.
(130) Pavan A, Bragadin AB, Calvetti L, Ferro A, Zulato E, Attili I, et al. Role of next generation sequencing-based liquid biopsy in advanced non-small cell lung cancer patients treated with

immune checkpoint inhibitors: impact of STK11, KRAS and TP53 mutations and co-mutations on outcome. Transl Lung Cancer Res. 2021;10(1):202-20.

(131) Pecuchet N, Zonta E, Didelot A, Combe P, Thibault C, Gibault L, et al. Base-position error rate analysis of next-generation sequencing applied to circulating tumor DNA in non-small cell lung cancer: a prospective study. PLoS Med. 2016;13(12):e1002199.

(132) Phallen J, Leal A, Woodward BD, Forde PM, Naidoo J, Marrone KA, et al. Early noninvasive detection of response to targeted therapy in non-small cell lung cancer. Cancer Res. 2019;79(6):1204-13.

(133) Pritchett MA, Camidge DR, Patel M, Khatri J, Boniol S, Friedman EK, et al. Prospective clinical validation of the InVisionFirst-Lung circulating tumor DNA assay for molecular profiling of patients with advanced nonsquamous non-small-cell lung cancer. JCO Precis Oncol. 2019;3:PO.18.00299.

(134) Raez LE, Brice K, Dumais K, Lopez-Cohen A, Wietecha D, Izquierdo PA, et al. Liquid biopsy versus tissue biopsy to determine front line therapy in metastatic non-small cell lung cancer (NSCLC). Clin Lung Cancer. 2023;24(2):120-9.

(135) Roosan MR, Mambetsariev I, Pharaon R, Fricke J, Husain H, Reckamp KL, et al. Usefulness of circulating tumor DNA in identifying somatic mutations and tracking tumor evolution in patients with non-small cell lung cancer. Chest. 2021;160(3):1095-107.

(136) Roosan MR, Mambetsariev I, Pharaon R, Fricke J, Husain H, Reckamp KL, et al. Utility of circulating tumor DNA in identifying somatic mutations and tracking tumor evolution in patients with non-small cell lung cancer. Chest. 2021;160(3):1095-107.

(137) Sabari JK, Offin M, Stephens D, Ni A, Lee A, Pavlakis N, et al. A prospective study of circulating tumor DNA to guide matched targeted therapy in lung cancers. J Natl Cancer Inst. 2019;111(6):575-83.

(138) Schouten RD, Vessies DCL, Bosch LJW, Barlo NP, van Lindert ASR, Cillessen S, et al. Clinical utility of plasma-based comprehensive molecular profiling in advanced non-small-cell lung cancer. JCO Precis Oncol. 2021;5:PO.20.00450.

(139) Schrock AB, Welsh A, Chung JH, Pavlick D, Bernicker EH, Creelan BC, et al. Hybrid capture-based genomic profiling of circulating tumor DNA from patients with advanced non-small cell lung cancer. J Thorac Oncol. 2019;14(2):255-64.

(140) Schwaederle MC, Patel SP, Husain H, Ikeda M, Lanman RB, Banks KC, et al. Utility of genomic assessment of blood-derived circulating tumor DNA (ctDNA) in patients with advanced lung adenocarcinoma. Clin Cancer Res. 2017;23(17):5101-11.

(141) Schwartzberg LS, Horinouchi H, Chan D, Chernilo S, Tsai ML, Isla D, et al. Liquid biopsy mutation panel for non-small cell lung cancer: analytical validation and clinical concordance. NPJ Precis Oncol. 2020;4:15.

(142) Sugimoto A, Matsumoto S, Udagawa H, Itotani R, Usui Y, Umemura S, et al. A large-scale prospective concordance study of plasma- and tissue-based next-generation targeted sequencing for advanced non-small cell lung cancer (LC-SCRUM-Liquid). Clin Cancer Res. 2023;29(8):1506-14.

(143) Sun B, Qiu T, Zeng X, Duan J, Bai H, Xu J, et al. Detection of MET polysomy by next-generation sequencing and its clinical relevance for MET inhibitors. Cancer Res Commun. 2023;3(4):532-9.

(144) Sung JS, Chong HY, Kwon NJ, Kim HM, Lee JW, Kim B, et al. Detection of somatic variants and EGFR mutations in cell-free DNA from non-small cell lung cancer patients by ultra-deep sequencing using the ion ampliseq cancer hotspot panel and droplet digital polymerase chain reaction. Oncotarget. 2017;8(63):106901-12.

(145) Tetik Vardarli A, Pelit L, Aldag C, Korba K, Celebi C, Dizdas TN, et al. Concordance in molecular genetic analysis of tumour tissue, plasma, and exhaled breath condensate samples from lung cancer patients. J Breath Res. 2020;14(3):036001.
(146) Thompson JC, Yee SS, Troxel AB, Savitch SL, Fan R, Balli D, et al. Detection of therapeutically targetable driver and resistance mutations in lung cancer patients by next-generation sequencing of cell-free circulating tumor DNA. Clin Cancer Res. 2016;22(23):5772-82.
(147) Toor OM, Ahmed Z, Bahaj W, Boda U, Cummings LS, McNally ME, et al. Correlation of somatic genomic alterations between tissue genomics and ctDNA employing next-generation sequencing: analysis of lung and gastrointestinal cancers. Mol Cancer Ther. 2018;17(5):1123-32.
(148) Tran LS, Pham HT, Tran VU, Tran TT, Dang AH, Le DT, et al. Ultra-deep massively parallel sequencing with unique molecular identifier tagging achieves comparable performance to droplet digital PCR for detection and quantification of circulating tumor DNA from lung cancer patients. PLoS One. 2019;14(12):e0226193.
(149) Tran HT, Lam VK, Elamin YY, Hong L, Colen R, Elshafeey NA, et al. Clinical outcomes in non-small-cell lung cancer patients treated with EGFR-tyrosine kinase inhibitors and other targeted therapies based on tumor versus plasma genomic profiling. JCO Precis Oncol. 2021;5:PO.20.00532.
(150) Uchida J, Kato K, Kukita Y, Kumagai T, Nishino K, Daga H, et al. Diagnostic accuracy of noninvasive genotyping of EGFR in lung cancer patients by deep sequencing of plasma cell-free DNA. Clin Chem. 2015;61(9):1191-6.
(151) Villaflor V, Won B, Nagy R, Banks K, Lanman RB, Talasaz A, et al. Biopsy-free circulating tumor DNA assay identifies actionable mutations in lung cancer. Oncotarget. 2016;7(41):66880-91.
(152) Wang Z, Cheng Y, An T, Gao H, Wang K, Zhou Q, et al. Detection of EGFR mutations in plasma circulating tumour DNA as a selection criterion for first-line gefitinib treatment in patients with advanced lung adenocarcinoma (BENEFIT): a phase 2, single-arm, multicentre clinical trial. Lancet Respir Med. 2018;6(9):681-90.
(153) Wang X, Liu Y, Meng Z, Wu Y, Wang S, Jin G, et al. Plasma EGFR mutation abundance affects clinical response to first-line EGFR-TKIs in patients with advanced non-small cell lung cancer. Ann Transl Med. 2021;9(8):635.
(154) Wu Z, Yang Z, Li CS, Zhao W, Liang ZX, Dai Y, et al. Differences in the genomic profiles of cell-free DNA between plasma, sputum, urine, and tumor tissue in advanced NSCLC. Cancer Med. 2019;8(3):910-9.
(155) Xie F, Zhang Y, Mao X, Zheng X, Han-Zhang H, Ye J, et al. Comparison of genetic profiles among primary lung tumor, metastatic lymph nodes and circulating tumor DNA in treatment-naive advanced non-squamous non-small cell lung cancer patients. Lung Cancer. 2018;121:54-60.
(156) Xu S, Lou F, Wu Y, Sun DQ, Zhang JB, Chen W, et al. Circulating tumor DNA identified by targeted sequencing in advanced-stage non-small cell lung cancer patients. Cancer Lett. 2016;370(2):324-31.
(157) Yang N, Li Y, Liu Z, Qin H, Du D, Cao X, et al. The characteristics of ctDNA reveal the high complexity in matching the corresponding tumor tissues. BMC Cancer. 2018;18(1):319.
(158) Yao Y, Liu J, Li L, Yuan Y, Nan K, Wu X, et al. Detection of circulating tumor DNA in patients with advanced non-small cell lung cancer. Oncotarget. 2017;8(2):2130-40.
(159) Yin JX, Hu WW, Gu H, Fang JM. Combined assay of circulating tumor DNA and protein biomarkers for early noninvasive detection and prognosis of non-small cell lung cancer. J Cancer. 2021;12(4):1258-69.
(160) Zhang M, Feng Y, Qu C, Meng M, Li W, Ye M, et al. Comparison of the somatic mutations between circulating tumor DNA and tissue DNA in Chinese patients with non-small cell lung cancer. Int J Biol Markers. 2022;37(4):386-94.

(161) Zhao C, Li J, Zhang Y, Han R, Wang Y, Li L, et al. The rational application of liquid biopsy based on next-generation sequencing in advanced non-small cell lung cancer. Cancer Med. 2023;12(5):5603-14.
(162) Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
(163) Vivancos A, Tabernero J. Circulating tumor DNA as a novel prognostic indicator. Nat Med. 2022;28(11):2255-6.
(164) Sun D, Wu W, Wang L, Qu J, Han Q, Wang H, et al. Identification of MET fusions as novel therapeutic targets sensitive to MET inhibitors in lung cancer. J Transl Med. 2023;21.
(165) Luca CD, Pepe F, Pisapia P, Iaccarino A, Righi L, Listi A, et al. RNA-based next-generation sequencing in non-small-cell lung cancer in a routine setting: an experience from an Italian referral center. Per Med. 2022;19(5):395-401.
(166) Yang Y, Kannisto E, Patnaik SK, Reid ME, Li L, Wu Y. Ultrafast detection of exosomal RNAs via cationic lipoplex nanoparticles in a micromixer biochip for cancer diagnosis. ACS Appl Nano Mater. 2021;4(3):2806-19.
(167) Xu Q, Ye L, Huang L, Zhou L, Chen X, Ye M, et al. Serum exosomal miRNA might be a novel liquid biopsy to identify leptomeningeal metastasis in non-small cell lung cancer. Onco Targets Ther. 2021;14:2327-35.
(168) Chang JW, Shih CL, Wang CL, Luo JD, Wang CW, Hsieh JJ, et al. Transcriptomic analysis in liquid biopsy identifies circulating PCTAIRE-1 mRNA as a biomarker in NSCLC. Cancer Genomics Proteomics. 2020;17(1):91-100.
(169) Li F, Wei F, Huang WL, Lin CC, Li L, Shen MM, et al. Ultra-short circulating tumor DNA (usctDNA) in plasma and saliva of non-small cell lung cancer (NSCLC) patients. Cancers (Basel). 2020;12(8):24.
(170) Ren S, Ren XD, Guo LF, Qu XM, Shang MY, Dai XT, et al. Urine cell-free DNA as a promising biomarker for early detection of non-small cell lung cancer. J Clin Lab Anal. 2020;34(8):e23321.
(171) Febbo PG, Allo M, Alme EB, Carter GC, Dumanois R, Kiernan E, et al. Recommendations for the equitable and widespread implementation of liquid biopsy for cancer care. JCO Precis Oncol. 2024;8:e2300382.
(172) Sun D, Kuang Z, Fine AD, Polisecki E, Gettler H, Al-Rekabi H, et al. Predicting tumor somatic versus clonal hematopoiesis origin for short variants in liquid assay. Poster session presented at: American Association for Cancer Research Annual Meeting; 2023 Apr 14-19; Orlando, FL.
(173) National Institute for Health and Care Excellence. Developing NICE guidelines: the manual (PMG20). London: The Institute; 2014 [updated 2024 Jan 17; cited 2024 Feb 20]. Appendix H: Appraisal checklists, evidence tables, GRADE and economic profiles. Available from: https://www.nice.org.uk/process/pmg20/resources/appendix-h-appraisal-checklists-evidence-tables-grade-and-economic-profiles-pdf-8779777885
(174) Ezeife DA, Spackman E, Juergens RA, Laskin JJ, Agulnik JS, Hao D, et al. The economic value of liquid biopsy for genomic profiling in advanced non-small cell lung cancer. Ther Adv Med Oncol. 2022;14:17588359221112696.
(175) Patel YP, Husereau D, Leighl NB, Melosky B, Nam J. Health and budget impact of liquid-biopsy-based comprehensive genomic profile (CGP) testing in tissue-limited advanced non-small cell lung cancer (aNSCLC) patients. Curr Oncol. 2021;28(6):5278-94.
(176) Johnston KM, Sheffield BS, Yip S, Lakzadeh P, Qian C, Nam J. Comprehensive genomic profiling for non-small-cell lung cancer: health and budget impact. Curr Oncol. 2020;27(6):e569-e77.

(177) Englmeier F, Bleckmann A, Brückl W, Griesinger F, Fleitz A, Nagels K. Clinical benefit and cost-effectiveness analysis of liquid biopsy application in patients with advanced non-small cell lung cancer (NSCLC): a modelling approach. J Cancer Res Clin Oncol. 2022.

(178) Yang SC, Lin CC, Chen YL, Su WC. Economic analysis of tissue-first, plasma-first, and complementary NGS approaches for treatment-naïve metastatic lung adenocarcinoma. Front Oncol. 2022;12:873111.

(179) Jansen JP, Ragavan MV, Chen C, Douglas MP, Phillips KA. The health inequality impact of liquid biopsy to inform first-line treatment of advanced non-small cell lung cancer: a distributional cost-effectiveness analysis. Value Health. 2023;26(12):1697-710.

(180) Hao D, Laskin J, Laurie S, Agulnik J, Juergens R, Ezeife D, et al. P89.03 Demonstrating VALUE of liquid biopsy for lung cancer in a public healthcare system. J Thorac Oncol. 2021;16(3):S689.

(181) Barlesi F, Mazieres J, Merlio JP, Debieuvre D, Mosser J, Lena H, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). Lancet. 2016;387(10026):1415-26.

(182) Adib E, Nassar AH, Abou Alaiwi S, Groha S, Akl EW, Sholl LM, et al. Variation in targetable genomic alterations in non-small cell lung cancer by genetic ancestry, sex, smoking history, and histology. Genome Med. 2022;14(1):39.

(183) Cheng M, Akalestos A, Scudder S. Budget impact analysis of EGFR mutation liquid biopsy for first- and second-line treatment of metastatic non-small cell lung cancer in Greece. Diagnostics (Basel). 2020;10(6).

(184) Ontario Health (Quality). 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. Ont Health Technol Assess Ser. 2020 Mar;20(5):1-176.

(185) Institut national d'excellence en santé et en services sociaux. Détection de la mutation T790M de l'exon 20 du gène EGFR dans le cancer du poumon résistant aux inhibiteurs de l'EGFR sur ADN tumoral circulant (biopsie liquide) [Internet]. Quebec (QC): l'institut; 2022 [cited 2024 Mar]. Available from: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Oncologie/INESSS_Biopsie_liquide_avis.pdf

(186) Vanderpoel J, Stevens AL, Emond B, Lafeuille MH, Hilts A, Lefebvre P, et al. Total cost of testing for genomic alterations associated with next-generation sequencing versus polymerase chain reaction testing strategies among patients with metastatic non-small cell lung cancer. J Med Econ. 2022;25(1):457-68.

(187) Harvey MJ, Cunningham R, Sawchyn B, Montesion M, Reddy P, McBride A, et al. Budget impact analysis of comprehensive genomic profiling in patients with advanced non-small-cell lung cancer. JCO Precis Oncol. 2021;5:1611-24.

(188) Johnston KM, Sheffield BS, Yip S, Lakzadeh P, Qian C, Nam J. Costs of in-house genomic profiling and implications for economic evaluation: a case example of non-small cell lung cancer (NSCLC). J Med Econ. 2020;23(10):1123-9.

(189) Chen Y, Han T, Zhou Y, Mao B, Zhuang W. Comparing the efficacy of targeted next-generation sequencing in the identification of somatic mutations in circulating tumor DNA from different stages of lung cancer. Neoplasma. 2019;66(4):652-60.

(190) Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16(2):231-50.

(191) Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): The Agency; 2017. p. 76.

(192) Ionescu DN, Stockley TL, Banerji S, Couture C, Mather CA, Xu Z, et al. Consensus recommendations to optimize testing for new targetable alterations in non-small cell lung cancer. Curr Oncol. 2022;29(7):4981-97.
(193) Ministry of Health. Exceptional Access Program reimbursement criteria for frequently requested drugs [Internet]. Toronto (ON): King's Printer for Ontario; 2023 [cited 2023 May 12]. Available from: https://www.health.gov.on.ca/en/pro/programs/drugs/docs/frequently_requested_drugs.pdf
(194) Ontario Health (Cancer Care Ontario). Comprehensive Cancer Biomarker Testing Program [Internet]. Toronto (ON): King's Printer for Ontario; 2023 [cited 2024 May]. Available from: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/ComprehensiveCancerTestingIndications.pdf
(195) Akhtar M, Rashid S, Al-Bozom IA. PD-L1 immunostaining: what pathologists need to know. Diagn Pathol. 2021;16(1):94.
(196) Guardant 360 CDx [Internet]. Palo Alto (CA): Guardant Health; c2023 [cited 2023 Jul 19]. Available from: https://www.guardantcomplete.com/guardant-portfolio/cdx
(197) Tempus. Tempus xF gene panel [Internet]. Chicago: Tempus; 2022 [cited 2023 Jul 19]. Available from: https://www.tempus.com/wp-content/uploads/2022/09/Tempus-xF_Gene-Panel.pdf
(198) Foundation Medicine. Foundation One Liquid CDx technical specifications [Internet]. Cambridge (MA): Foundation Medicine; 2021 [cited 2023 Jul 19]. Available from: https://assets.ctfassets.net/w98cd481qyp0/wVEm7VtICYR0sT5C1VbU7/fd055e0476183a6acd4eae6b583e3a00/F1LCDx_Technical_Specs_072021.pdf
(199) Plasma Follow It [Internet]. Montreal (QC): Imagia Canexia Health; c2023 [cited 2023 Jul 19]. Available from: https://imagiacanexia.com/solution/plasma-follow-it/
(200) Araghi M, Fidler-Benaoudia M, Arnold M, Rutherford M, Bardot A, Ferlay J, et al. International differences in lung cancer survival by sex, histological type and stage at diagnosis: an ICBP SURVMARK-2 study. Thorax. 2022;77(4):378-90.
(201) Hwang DM, Albaqer T, Santiago RC, Weiss J, Tanguay J, Cabanero M, et al. Prevalence and heterogeneity of PD-L1 expression by 22C3 assay in routine population-based and reflexive clinical testing in lung cancer. J Thorac Oncol. 2021;16(9):1490-500.
(202) Smare C, Lakhdari K, Doan J, Posnett J, Johal S. Evaluating partitioned survival and Markov decision-analytic modeling approaches for use in cost-effectiveness analysis: estimating and comparing survival outcomes. Pharmacoeconomics. 2020;38(1):97-108.
(203) !!! INVALID CITATION !!! 177.
(204) Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba, II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA. 2014;311(19):1998-2006.
(205) Koivunen JP, Mermel C, Zejnullahu K, Murphy C, Lifshits E, Holmes AJ, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res. 2008;14(13):4275-83.
(206) Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009;27(26):4247-53.
(207) Wong DW, Leung EL, So KK, Tam IY, Sihoe AD, Cheng LC, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer. 2009;115(8):1723-33.
(208) Takahashi T, Sonobe M, Kobayashi M, Yoshizawa A, Menju T, Nakayama E, et al. Clinicopathologic features of non-small-cell lung cancer with EML4-ALK fusion gene. Ann Surg Oncol. 2010;17(3):889-97.

(209) Camidge DR, Kono SA, Flacco A, Tan AC, Doebele RC, Zhou Q, et al. Optimizing the detection of lung cancer patients harboring anaplastic lymphoma kinase (ALK) gene rearrangements potentially suitable for ALK inhibitor treatment. Clin Cancer Res. 2010;16(22):5581-90.
(210) Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. Oncologist. 2013;18(7):865-75.
(211) Leighl NB, Page RD, Raymond VM, Daniel DB, Divers SG, Reckamp KL, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. Clin Cancer Res. 2019;25(15):4691-700.
(212) Chouaid C, Dujon C, Do P, Monnet I, Madroszyk A, Le Caer H, et al. Feasibility and clinical impact of re-biopsy in advanced non small-cell lung cancer: a prospective multicenter study in a real-world setting (GFPC study 12-01). Lung Cancer. 2014;86(2):170-3.
(213) Ayyappan AP, Souza CA, Seely J, Peterson R, Dennie C, Matzinger F. Ultrathin fine-needle aspiration biopsy of the lung with transfissural approach: does it increase the risk of pneumothorax? AJR Am J Roentgenol. 2008;191(6):1725-9.
(214) Stock-Martineau S, Laurie K, McKinnon M, Zhang T, Wheatley-Price P. Evolution of systemic treatment uptake and survival in advanced non-small cell lung cancer. Curr Oncol. 2020;28(1):60-8.
(215) Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378(2):113-25.
(216) Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(2):213-22.
(217) Mok T, Camidge DR, Gadgeel SM, Rosell R, Dziadziuszko R, Kim DW, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol. 2020;31(8):1056-64.
(218) Doebele RC, Perez L, Trinh H, Martinec M, Martina R, Riehl T, et al. Comparative effectiveness analysis between entrectinib clinical trial and crizotinib real-world data in ROS1+ NSCLC. J Comp Eff Res. 2021;10(17):1271-82.
(219) Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. J Clin Oncol. 2020;38(14):1505-17.
(220) Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥ 50. J Clin Oncol. 2021;39(21):2339-49.
(221) Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med. 2020;382(1):41-50.
(222) Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol. 2015;16(2):141-51.
(223) Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.
(224) Baio G. survHE: survival analysis for health economic evaluation and cost-effectiveness modeling. J Stat Softw. 2020;95(14):1-47.

(225) Jackson CH. flexsurv: a platform for parametric survival modeling in R. J Stat Softw. 2016;70:i08.
(226) Drilon A, Siena S, Dziadziuszko R, Barlesi F, Krebs MG, Shaw AT, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21(2):261-70.
(227) Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. 2014;371(21):1963-71.
(228) Statistics Canada. Life expectancy and other elements of the complete life table, single-year estimates, Canada, all provinces except Prince Edward Island: Table 13-10-0837-01 [Internet]. Ottawa (ON): Statistics Canada. c2023 [cited 2023 Jul 20]. Available from: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310083701&pickMembers%5B0%5D=1.6&pickMembers%5B1%5D=3.1&pickMembers%5B2%5D=4.3&cubeTimeFrame.startYear=2016&cubeTimeFrame.endYear=2020&referencePeriods=20160101%2C20200101
(229) Labbé C, Leung Y, Silva Lemes JG, Stewart E, Brown C, Cosio AP, et al. Real-world EQ5D health utility scores for patients with metastatic lung cancer by molecular alteration and response to therapy. Clin Lung Cancer. 2017;18(4):388-95.e4.
(230) Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84.
(231) Ontario Case Costing Initative [Internet]. Toronto (ON): IntelliHealth Ontario. c2023 [cited 2023 Jul 02]. Available from: https://intellihealth.moh.gov.on.ca/
(232) Ministry of Health. Schedule of benefits: physician services under the Health Insurance Act [Internet]. Toronto (ON): King's Printer for Ontario; 2023 [cited 2023 Feb 02]. Available from: https://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master.pdf
(233) Perdrizet K, Stockley TL, Law JH, Smith A, Zhang T, Fernandes R, et al. Integrating comprehensive genomic sequencing of non-small cell lung cancer into a public healthcare system. Cancer Treat Res Commun. 2022;31:100534.
(234) Pan-Canadian Oncology Drug Review. Pan-Canadian Oncology Drug Review final economic guidance report: crizotinib (Xalkori) for advanced non-small cell lung cancer [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2012 Oct 4 [cited 2023 Jun]. Available from: https://www.cadth.ca/sites/default/files/pcodr/pcodr-xalkorinsclc-fn-egr.pdf
(235) Pan-Canadian Oncology Drug Review. Pan-Canadian Oncology Drug Review final economic guidance report: pembrolizumab (Keytruda) non-small cell lung cancer [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Aug 23 [cited 2023 Jun]. Available from: https://www.cadth.ca/sites/default/files/pcodr/pcodr_pembrolizumab_keytruda_nsclc_1stln_fn_egr.pdf
(236) Pan-Canadian Oncology Drug Review. Pan-Canadian Oncology Drug Review final economic guidance report: alectinib (Alecensaro) for non-small cell lung cancer [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Jul 25 [cited 2023 Jun]. Available from: https://www.cadth.ca/sites/default/files/pcodr/pcodr_alectinib_alecensaro_nsclc_1stln_fn_egr.pdf
(237) Pan-Canadian Oncology Drug Review. Pan-Canadian Oncology Drug Review final economic guidance report: dacomitinib (Vizimpro) for non-small cell lung cancer [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 May 31 [cited 2023 Jun]. Available from: https://www.cadth.ca/sites/default/files/pcodr/Reviews2019/10129DacomitinibNSCLC_fnEGR_NOREDACT-ABBREV_Post_31May2019_final.pdf

(238) Canadian Agency for Drugs and Technologies in Health. CADTH reimbursement review: osimertinib (Tagrisso) [Internet]. Ottawa (ON): The Agency; 2022 Mar [cited 2023 Jun]. Available from: https://www.cadth.ca/sites/default/files/DRR/2022/PC0246-Tagrisso.pdf

(239) Canadian Agency for Drugs and Technologies in Health. CADTH reimbursement recommendation: entrectinib (Rozlytrek) [Internet]. Ottawa (ON): The Agency; 2022 Nov [cited 2023 Jun]. Available from: https://canjhealthtechnol.ca/index.php/cjht/article/view/PC0278/1043

(240) Ontario Health (Cancer Care Ontario). Drug formulary [Internet]. Toronto (ON): Ontario Health; 2023 [cited 2023 Oct]. Available from: https://www.cancercareontario.ca/en/drugformulary/regimens?search_api_views_fulltext_regimens=&sort_by=field_universal_date

(241) Get coverage for prescription drugs [Internet]. Toronto (ON): Ministry of Health; c2012-23 [updated 2023 Oct 10; cited 2023 Oct 19]. Available from: https://www.ontario.ca/page/get-coverage-prescription-drugs

(242) Sutherland G, Dinh T. Understanding the gap: a pan-Canadian analysis of prescription drug insurance coverage [Internet]. Ottawa (ON): Conference Board of Canada; 2017 [cited 2023 Jun]. Available from: https://innovativemedicines.ca/wp-content/uploads/2017/12/20170712-understanding-the-gap.pdf

(243) Ontario Nurses' Association. Highlights of collective agreement changes as a result of the Gedalof decision and items in agreement between ONA and participating hospitals [Internet]. Toronto (ON): The Association; 2021 [cited 2022 Jun 6]. Available from: https://www.ona.org/wp-content/uploads/2a-2021_hospitalhighlights.pdf

(244) Pharmacist salary in Ontario [Internet]. Toronto (ON): Indeed; c2023 [cited 2023 Jul 19]. Available from: https://ca.indeed.com/career/pharmacist/salaries/Ontario

(245) Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627-39.

(246) Soria JC, Wu YL, Nakagawa K, Kim SW, Yang JJ, Ahn MJ, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol. 2015;16(8):990-8.

(247) Mann H, Andersohn F, Bodnar C, Mitsudomi T, Mok TSK, Yang JC, et al. Adjusted indirect comparison using propensity score matching of osimertinib to platinum-based doublet chemotherapy in patients with EGFRm T790M NSCLC who have progressed after EGFR-TKI. Clin Drug Investig. 2018;38(4):319-31.

(248) Goeree R, Villeneuve J, Goeree J, Penrod JR, Orsini L, Tahami Monfared AA. Economic evaluation of nivolumab for the treatment of second-line advanced squamous NSCLC in Canada: a comparison of modeling approaches to estimate and extrapolate survival outcomes. J Med Econ. 2016;19(6):630-44.

(249) de Oliveira C, Pataky R, Bremner KE, Rangrej J, Chan KK, Cheung WY, et al. Phase-specific and lifetime costs of cancer care in Ontario, Canada. BMC Cancer. 2016;16(1):809.

(250) Dispensing fee policies in public drug plans, 2020/21 [Internet]. Ottawa (ON): Goverment of Canada; c2023 [cited 2023 Jul 19]. Available from: https://www.canada.ca/en/patented-medicine-prices-review/services/npduis/analytical-studies/supporting-information/dispensing-fee-policies.html

(251) Krahn M, Miller F, Bayoumi A, Brooker AS, Wagner F, Winsor S, et al. Development of the Ontario decision framework: a values based framework for health technology assessment. Int J Technol Assess Health Care. 2018;34(3):290-9.

(252) Wu YL, Lu S, Lu Y, Zhou J, Shi YK, Sriuranpong V, et al. Results of PROFILE 1029, a phase III comparison of first-line crizotinib versus chemotherapy in East Asian patients with ALK-positive advanced non-small cell lung cancer. J Thorac Oncol. 2018;13(10):1539-48.
(253) Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327-34.
(254) Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393(10183):1819-30.
(255) Jahanzeb M, Lin HM, Pan X, Yin Y, Wu Y, Nordstrom B, et al. Real-world treatment patterns and progression-free survival associated with anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor therapies for ALK+ non-small cell lung cancer. Oncologist. 2020;25(10):867-77.
(256) Velcheti V, Hu X, Piperdi B, Burke T. Real-world outcomes of first-line pembrolizumab plus pemetrexed-carboplatin for metastatic nonsquamous NSCLC at US oncology practices. Sci Rep. 2021;11(1):9222.
(257) Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017;377(9):829-38.
(258) Shaw AT, Riely GJ, Bang YJ, Kim DW, Camidge DR, Solomon BJ, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. Ann Oncol. 2019;30(7):1121-6.
(259) Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018;378(22):2078-92.
(260) Fleming KE, Hupel A, Mithoowani H, Lulic-Kuryllo T, Valdes M. Biomarker turnaround times and impact on treatment decisions in patients with advanced non-small cell lung carcinoma at a large Canadian community hospital with an affiliated regional cancer centre. Curr Oncol. 2024;31(3):1515-28.
(261) Ontario cancer profiles [Internet]. Toronto (ON): Ontario Health (Cancer Care Ontario); c2024 [cited 2024 Feb 14]. Available from: https://cancercareontario.ca/ontariocancerprofiles
(262) Canadian Cancer Statistics Advisory Committee. Canadian cancer statistics: a 2020 special report on lung cancer [Internet]. Toronto (ON): Canadian Cancer Society; 2020 [cited 2023 Jun]. Available from: https://cdn.cancer.ca/-/media/files/cancer-information/resources/publications/2020-canadian-cancer-statistics-special-report/2020-canadian-cancer-statistics-special-report-en.pdf
(263) Seung SJ, Hurry M, Walton RN, Evans WK. Retrospective cohort study of unresectable stage III non-small-cell lung cancer in Canada. Curr Oncol. 2020;27(4):e354-e60.
(264) Microsoft Excel [Computer program]. Microsoft Corporation (Redmond, WA). Available at: https://www.microsoft.com/en-ca/microsoft-365/excel.
(265) Barham L. Public and patient involvement at the UK National Institute for Health and Clinical Excellence. Patient. 2011;4(1):1-10.
(266) Messina J, Grainger DL. A pilot study to identify areas for further improvements in patient and public involvement in health technology assessments for medicines. Patient. 2012;5(3):199-211.
(267) Ontario Health Technology Advisory Committee Public Engagement Subcommittee. Public engagement for health technology assessment at Health Quality Ontario—final report from the Ontario Health Technology Advisory Committee Public Engagement Subcommittee [Internet]. Toronto (ON): Queen's Printer for Ontario; 2015 Apr [cited 2018 Apr 30]. Available from:

http://www.hqontario.ca/Portals/0/documents/evidence/special-reports/report-subcommittee-20150407-en.pdf

(268) Kvale S. Interviews: an introduction to qualitative research interviewing. Thousand Oaks (CA): Sage; 1996.

(269) Kuzel AJ. Sampling in qualitative inquiry. In: Miller WL, Crabtree BF, editors. Doing qualitative research. Thousand Oaks (CA): Sage; 1999. p. 33–45.

(270) Morse J. Emerging from the data: cognitive processes of analysis in qualitative research. In: Morse J, editor. Critical issues in qualitative research methods. Thousand Oaks (CA): Sage; 1994. p. 23-41.

(271) Patton MQ. Qualitative research and evaluation methods. 3rd ed. Thousand Oaks (CA): Sage; 2002.

(272) Strauss AL, Corbin JM. Basics of qualitative research: techniques and procedures of developing a grounded theory. 2nd ed. Thousand Oaks (CA): Sage; 1998.

(273) Health Technology Assessment International. Introduction to health technology assessment [Internet]. Edmonton (AB): Health Technology Assessment International; 2015 [cited 2018 Apr 30]. Available from: http://www.htai.org/fileadmin/HTAi_Files/ISG/PatientInvolvement/v2_files/Resource/PCISG-Resource-Intro_to_HTA__KFacey__Jun13.pdf

(274) Strauss AL, Corbin JM. Grounded theory research: procedures, canons, and evaluative criteria. Qual Sociol. 1990;13(1):3-21.

(275) Strauss AL, Corbin JM. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. Thousand Oaks (CA): Sage; 1994. p. 273-85.

(276) NVivo qualitative data analysis software. QSR International (Doncaster, Victoria, Australia). Available at: https://www.qsrinternational.com/nvivo/home.

(277) Meric-Bernstam F, Johnson A, Holla V, Bailey AM, Brusco L, Chen K, et al. A decision support framework for genomically informed investigational cancer therapy. J Natl Cancer Inst. 2015;107(7).

(278) Ontario Health's equity, inclusion, diversity and anti-racism framework [Internet]. Toronto (ON): Ontario Health; 2022 [cited 2023 Mar 22]. Available from: https://www.ontariohealth.ca/sites/ontariohealth/files/2020-12/Equity%20Framework.pdf

(279) Chen D, Zhang LQ, Huang JF, Liu K, Chuai ZR, Yang Z, et al. BRAF mutations in patients with non-small cell lung cancer: a systematic review and meta-analysis. PLoS One. 2014;9(6):e101354.

(280) Awad MM, Oxnard GR, Jackman DM, Savukoski DO, Hall D, Shivdasani P, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and c-Met overexpression. J Clin Oncol. 2016;34(7):721-30.

(281) Bogatyrova O, Mattsson JSM, Ross EM, Sanderson MP, Backman M, Botling J, et al. FGFR1 overexpression in non-small cell lung cancer is mediated by genetic and epigenetic mechanisms and is a determinant of FGFR1 inhibitor response. Eur J Cancer. 2021;151:136-49.

(282) Zhao J, Xia Y. Targeting HER2 alterations in non-small-cell lung cancer: a comprehensive review. JCO Precis Oncol. 2020;4:411-25.

(283) Salem ME, El-Refai SM, Sha W, Puccini A, Grothey A, George TJ, et al. Landscape of KRAS(G12C), associated genomic alterations, and interrelation with immuno-oncology biomarkers in KRAS-mutated cancers. JCO Precis Oncol. 2022;6:e2100245.

(284) Scheffler M, Bos M, Gardizi M, König K, Michels S, Fassunke J, et al. PIK3CA mutations in non-small cell lung cancer (NSCLC): genetic heterogeneity, prognostic impact and incidence of prior malignancies. Oncotarget. 2015;6(2):1315-26.

(285) Solomon JP, Linkov I, Rosado A, Mullaney K, Rosen EY, Frosina D, et al. NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. Mod Pathol. 2020;33(1):38-46.
(286) Paik PK, Pfeiffer BM, Vioix H, Garcia A, Postma MJ. Matching-adjusted indirect comparison (MAIC) of tepotinib with other MET inhibitors for the treatment of advanced NSCLC with MET exon 14 skipping mutations. Adv Ther. 2022;39(7):3159-79.
(287) Johnson BE, Baik CS, Mazieres J, Groen HJM, Melosky B, Wolf J, et al. Clinical outcomes with dabrafenib plus trametinib in a clinical trial versus real-world standard of care in patients with BRAF-mutated advanced NSCLC. JTO Clin Res Rep. 2022;3(5):100324.
(288) Drilon A, Subbiah V, Gautschi O, Tomasini P, de Braud F, Solomon BJ, et al. Selpercatinib in patients with RET fusion-positive non-small-cell lung cancer: updated safety and efficacy from the registrational LIBRETTO-001 phase I/II trial. J Clin Oncol. 2023;41(2):385-94.
(289) Canadian Agency for Drugs and Technologies in Health. CADTH reimbursement review: selpercatinib (Retevmo) [Internet]. Ottawa (ON): The Agency; 2022 Jul [cited 2023 Jun]. Available from: https://www.cadth.ca/sites/default/files/DRR/2022/PC0261-Retevmo_combined.pdf
(290) Canadian Agency for Drugs and Technologies in Health. CADTH drug reimbursement review: dabrafenib (Tafinlar) in combination with trametinib (Mekinist) [Internet]. Ottawa (ON): The Agency; 2021 May 28 [cited 2023 Jun]. Available from: https://www.cadth.ca/sites/default/files/pcodr/Reviews2021/10226Dabrafenib-TrametinibNSCLC_fnEGR_REDACT-ABBREV_Post28May2021_final.pdf
(291) Canadian Agency for Drugs and Technologies in Health. CADTH reimbursement review: tepotinib (Tepmetko) [Internet]. Ottawa (ON): The Agency; 2022 Dec [cited 2023 Jun]. Available from: https://www.cadth.ca/sites/default/files/DRR/2022/PC0255-Tepmetko_combined.pdf
(292) Summary basis of decision - Tepmetko [Internet]. Ottawa (ON): Health Canada; c2021 [cited 2024 Apr 1]. Available from: https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00554
(293) Drug formulary: DABRTRAM [Internet]. Toronto (ON): Ontario Health (Cancer Care Ontario); c2023 [cited 2024 Apr 1]. Available from: https://www.cancercareontario.ca/en/drugformulary/regimens/monograph/47996
(294) Drug formulary: SELP [Internet]. Toronto (ON): Ontario Health (Cancer Care Ontario); c2023 [cited 2024 Apr 1]. Available from: https://www.cancercareontario.ca/en/drugformulary/regimens/monograph/69631

About Us

We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

For more information about Ontario Health, visit OntarioHealth.ca.

Ontario Health
500–525 University Avenue
Toronto, Ontario
M5G 2L3
Toll Free: 1-877-280-8538
TTY: 1-800-855-0511
Email: OH-HQO_HTA@OntarioHealth.ca
hqontario.ca

ISSN 1915-7398 (online)
ISBN TBA (PDF)

Need this information in an accessible format?
1-877-280-8538, TTY 1-800-855-0511, info@OntarioHealth.ca
Document disponible en français en contactant info@OntarioHealth.ca