

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

FINAL RECOMMENDATION

- The Quality business unit at Ontario Health, based on guidance from the Ontario Health Technology Advisory Committee, recommends publicly funding cell-free circulating tumour DNA blood testing (also called liquid biopsy) as a triage test to detect the *EGFR* T790M mutation in people with non–small cell lung cancer whose disease has progressed following initial treatment with an *EGFR* tyrosine kinase inhibitor

RATIONALE FOR THE RECOMMENDATION

The Ontario Health Technology Advisory Committee has reviewed and accepted the findings of the health technology assessment¹ and the recommendation of a subcommittee, the Ontario Genetics Advisory Committee.

The Ontario Genetics Advisory Committee decided that using a minimally invasive test, such as cell-free circulating tumour DNA blood testing (also called liquid biopsy) to guide treatment decisions is helpful for people with advanced lung cancer who are frail or are otherwise unable to undergo tissue biopsy. The committee viewed several findings of the health technology assessment favourably, including the potential cost savings from a reduction in the number of tissue biopsies performed, the potential for targeted treatment to improve survival rates, and the potential for a reduction in the apprehension patients can experience with tissue biopsy.

However, the committee also noted the lower negative predictive value of the test in comparison with tissue biopsy. For this reason, the committee concluded that liquid biopsy should be publicly funded as a triage test for people whose disease has progressed following initial treatment with an *EGFR* tyrosine kinase inhibitor. This means that people whose results from liquid biopsy are negative for the *EGFR* T790M mutation would go on to have a tissue biopsy.

The committee also noted that because of the current high cost of treatment for people with the *EGFR* T790M mutation, using liquid biopsy as a triage test may not appear to be cost-effective compared with tissue biopsy. However, publicly funding liquid biopsy is expected to have a relatively small overall cost.

The committee also considered the lived experience of people with lung cancer who had undergone tissue biopsy, including the time it takes to schedule and attend a tissue biopsy appointment and the apprehension associated with the tissue biopsy procedure. Given these considerations, the committee recommended publicly funding liquid biopsy as a triage test for people with non–small cell lung cancer whose disease has progressed following initial treatment with an *EGFR* tyrosine kinase inhibitor.

Decision Determinants for Cell-Free Circulating Tumour DNA Blood Testing to Detect EGFR T790M Mutation in People With Advanced Non–Small Cell Lung Cancer

Decision Criteria	Subcriteria	Decision Determinants Considerations
Overall clinical benefit How likely is the health technology/intervention to result in high, moderate, or low overall benefit?	Effectiveness How effective is the health technology/intervention likely to be (taking into account any variability)?	With lower sensitivity (68%) and negative predictive value (61%) and high specificity (86%) and positive predictive value (89%) (GRADE: Moderate), liquid biopsy should be used as a triage test. This aligns with Canadian and Australian guidelines. Evidence for process outcomes (e.g., time to test result, tissue biopsies avoided) was limited. One study showed that the median time to test result for liquid biopsy vs. tissue biopsy was 2 vs. 27 d, but this result was not statistically compared (GRADE: Low). Progression-free survival was similar for patients with and without the T790M mutation as ascertained via liquid biopsy (GRADE: Low).
	Safety How safe is the health technology/intervention likely to be?	No evidence on adverse events associated with liquid biopsy was available. Given that this test is a simple blood draw, no adverse outcomes are expected to arise as long as proper phlebotomy procedures are followed.
	Burden of illness What is the likely size of the burden of illness pertaining to this health technology/intervention?	Disease progression in 63% of people with advanced non–small cell lung cancer results from the <i>EGFR</i> T790M mutation.
	Need How large is the need for this health technology/intervention?	Instead of a tissue biopsy, which can be difficult to obtain for many reasons, liquid biopsy can be used as a triage test to determine if a person has this resistance mutation, thus guiding physician decisions about appropriate treatment.
Consistency with expected patient, societal, and ethical values^a How likely is adoption of the health technology/intervention to be congruent with patient, societal, and ethical values?	Patient values How likely is the adoption of the health technology/intervention congruent with expected patient values?	People with lung cancer value having access to a test that is less invasive than tissue biopsy. Further, they value the convenience that liquid biopsy could provide compared with tissue biopsy.
	Societal values How likely is adoption of the health technology/intervention to be congruent with expected societal values?	Interview participants reported a desire for increased access to liquid biopsy in Ontario for people with advanced non–small cell lung cancer. Participants reported that use of this test could avoid pain and anxiety associated with tissue biopsy. Access to this test is consistent with the societal values of independence and fairness.
	Ethical values How likely is adoption of the health technology/intervention to be congruent with expected ethical values?	Publicly funding liquid biopsy is likely consistent with the ethical values of autonomy, fairness, and beneficence. However, the ethical value of balancing benefit and harm is also a consideration.

Decision Criteria	Subcriteria	Decision Determinants Considerations
<p>Cost-effectiveness</p> <p>How efficient is the health technology/intervention likely to be?</p>	<p>Economic evaluation</p> <p>How efficient is the health technology/intervention likely to be?</p>	<p>When considering only testing-related costs and effects, liquid biopsy was found to be more effective and less costly than tissue biopsy alone. When all long-term costs and effects were included, liquid biopsy was unlikely to be cost-effective (ICERs: liquid biopsy as a triage test vs. liquid biopsy alone was greater than \$100,000/QALY; liquid biopsy alone vs. tissue biopsy was greater than \$100,000/QALY). This was driven by the high cost of treatment (i.e., osimertinib).</p>
<p>Feasibility of adoption into health system</p> <p>How feasible is it to adopt the health technology/intervention into the Ontario health care system?</p>	<p>Economic feasibility</p> <p>How economically feasible is the health technology/intervention?</p> <p>Organizational feasibility</p> <p>How organizationally feasible is it to implement the health technology/intervention?</p>	<p>We estimated that it costs about \$700 to conduct a liquid biopsy and about \$2,500 to conduct a tissue biopsy. In addition, costs related to treatment and care are expected to be incurred over time. We estimated that the annual budget impact of publicly funding liquid biopsy as a triage test in Ontario over the next 5 y will range from \$0.06 million in year 1 to \$3 million in year 5.</p> <p>Liquid biopsy is currently offered by two Ontario laboratories. Several commercial platforms are available, and tests can also be developed in-house by laboratories.</p>

Abbreviations: EGFR, epidermal growth factor receptor; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

^aAnticipated or assumed common patient, societal, and ethical values held in regard to the target condition, target population, or treatment options. Unless evidence from scientific sources corroborates the true nature of the patient, societal, and ethical values, expected values are considered.

REFERENCE

- (1) 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 [Internet]. 2020 Mar;20(5): 1–176. Available from: <https://www.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>

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ISBN 978-1-4868-3718-2 (PDF)

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Citation

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 Mar. 4 p. Available from: <https://www.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>