

Circulating tumour DNA (liquid biopsy)-
based EGFR exon 20 T790M mutation
detection in advanced non-small cell
lung cancer after previous EGFR-
directed therapy

English summary

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SUMMARY

	<p>Circulating tumour DNA (liquid biopsy)-based <i>EGFR</i> exon 20 T790M mutation detection in advanced non-small cell lung cancer after previous <i>EGFR</i>-directed therapy</p>
Requester	Institut universitaire de cardiologie et de pneumologie de Québec-Université Laval
Purpose of test	The test is designed to detect the <i>EGFR</i> gene T790M mutation (<i>EGFR</i> -T790M), which is responsible for resistance to tyrosine kinase inhibitors (TKIs), in circulating tumour DNA in non-small cell lung cancer (NSCLC) patients.
Background to the request	Approximately 60% of NSCLC patients treated with a 1 st - or 2 nd -generation TKI will develop the <i>EGFR</i> -T790M resistance mutation and require a change in therapy. Although a test used to detect this mutation from a tissue biopsy is listed in the <i>Répertoire québécois et système de mesure des procédures de biologie médicale</i> (hereinafter the " <i>Répertoire</i> "), the present request concerns the detection of the <i>EGFR</i> -T790M mutation in samples obtained by liquid biopsy, an alternative specimen collection method that enables the patient to avoid a tissue biopsy and the associated risks, and to obtain a change in therapy more quickly.
Expected number of tests	The requester had originally anticipated that between 160 and 250 tests would be required annually to serve the local population and 2000 for all of Québec. However, the listing of osimertinib as a 1 st -line therapy for NSCLC with <i>EGFR</i> -activating mutations is resulting in a significant reduction in the number of patients who will possibly require <i>EGFR</i> -T790M mutation testing by liquid biopsy, based on the use anticipated by the requester. RAMQ data show that a few patients continue to receive 1 st - or 2 nd -generation TKIs and are likely to benefit from this test.
Methodology	The assessment process included a rapid review of the scientific and grey literature, and consultations with experts and other stakeholders. An assessment report on the relevance of using liquid biopsy in the same context as this request was published by Health Quality Ontario (HQO) in March 2020. The report includes an assessment of its diagnostic performance, clinical utility, safety, cost-effectiveness and budget impact, and an assessment of patient preferences and values. The HQO report was deemed to be of good methodological quality and is the main source of data for the present assessment.

	All the scientific, contextual and experiential data were interpreted and assessed using a synthesis grid to guide the Comité scientifique des analyses de biologie médicale (CSABM)'s deliberation process.
Published data	<p>Diagnostic performance</p> <p>According to the Health Quality Ontario assessment report published in 2020, the concordance rate for <i>EGFR</i>-T790M mutation detection results between liquid biopsy and tissue biopsy ranges from 50% to 96%. The sensitivity and specificity, negative predictive value (NPV) and positive predictive value (PPV) are 68% [46%-88%], 86% [62%-99%], 61% and 89%, respectively. The use of droplet digital PCR (ddPCR) appears to increase the rate of positive detection of the <i>EGFR</i>-T790M mutation by liquid biopsy.</p> <p>Clinical utility</p> <p>HQO did not find any data on the use of liquid biopsy as a triage test (liquid biopsy + tissue biopsy) versus tissue biopsy alone. However, the studies examined note that a proportion of <i>EGFR</i>-T790M mutation carriers (17.8%) are identified through the use of liquid biopsy to detect 1st- or 2nd-generation TKI-resistant patients, who thus avoid a tissue biopsy. If the <i>EGFR</i>-T790M mutation is detected, the impact on management would remain the same, regardless of the method used, because when the biopsy is positive, treatment is initiated. A 9.7-month gain in progression-free survival was reported for both methods.</p>
Patient perspective	According to the HQO report, patients perceived liquid biopsy as a faster and more convenient approach because they would not have to wait several weeks to get an appointment for a tissue biopsy, which could require a trip to a specialized centre that might be further away. They also expressed fear and even panic about the tissue sample collection procedure, in which a large-gauge needle is used.
Positions and perspectives of organizations of interest	The National Comprehensive Cancer Network (NCCN) and a number of expert panels have recommended the use of liquid biopsy in patients who are medically unable to tolerate the invasive specimen collection involved in a tissue biopsy. All the learned societies recommend the use of tissue biopsy when the liquid biopsy result is negative. However, they stress that liquid biopsy should not replace tissue biopsy. In any event, a positive liquid biopsy result should be given the same attention as a positive tissue biopsy result.
Economic evaluation	Liquid biopsy as a triage test is less expensive and more effective than tissue biopsy in detecting the <i>EGFR</i> -T790M mutation. However, when the clinical benefits and costs of the subsequent treatments are factored

	<p>in, the incremental cost-utility ratio is high, in part because of osimertinib's non-cost-effectiveness.</p> <p>Since the listing of this drug as a 1st-line therapy in the formularies, the liquid biopsy-eligible population has been steadily decreasing. The current number of people receiving 1st- or 2nd-generation TKIs was estimated to be 32, based on RAMQ data, and 40 if patients with private insurance are included. These analyses estimate the laboratory savings at \$460, but they anticipate that 5 additional patients could receive osimertinib, for a net budget impact of approximately \$537,000 over the next 3 years.</p>
Position of the experts consulted	<p>The experts consulted support the use of liquid biopsy in the context defined by the requester. They did not raise any specific issues, apart from the limited relevance of this test, given the recent listing of osimertinib as a 1st-line therapy. The rapid emergence of a large number of indications for liquid biopsy appears to be imminent and would constitute a technological and oncologic revolution.</p>
Specific issues	<p>In Québec, liquid biopsy is used primarily in research settings. Ethical and clinical issues associated with this test, such as false negatives due to lower sensitivity and the need to assess overall survival in NSCLC patients in whom this technique is used, have also been reported in the literature.</p>
Recommendation	<p>Based on the deliberation, by the CSABM's members, of all the evidence, including the perspective of the experts consulted, INESSS recommends that circulating tumour DNA-based <i>EGFR</i>-T790M mutation detection be included in the <i>Répertoire</i>.</p>

*Institut national
d'excellence en santé
et en services sociaux*

Québec 

Siège social

2535, boulevard Laurier, 5^e étage
Québec (Québec) G1V 4M3
418 643-1339

Bureau de Montréal

2021, avenue Union, 12^e étage, bureau 1200
Montréal (Québec) H3A 2S9
514 873-2563

inesss.qc.ca

