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| <b>Title</b>     | Next generation sequencing gene panel using circulating tumor DNA for medical lung cancer care  |
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| <b>Reference</b> | ISBN number: 978-2-11-179590-7, link to full report: <a href="#">Séquençage haut débit ciblé d'un panel de gènes sur ADN tumoral circulant dans la prise en charge thérapeutique du cancer du poumon</a>  |

### Aim

The objectives were: (1) to evaluate the benefit–risk ratio of circulating tumor DNA (ctDNA)-based next generation sequencing (NGS) gene panel testing for the clinical management of advanced and metastatic non-small cell lung cancer (NSCLC) in routine clinical practice, and (2) to define the conditions for its implementation.

### Conclusions and results

The assessment of the evidence and data demonstrated that ctDNA-based NGS gene panel testing for patients with advanced or metastatic NSCLC (stages IIIB, IIIC, and IV) has a favorable risk/benefit ratio and represented a non-invasive alternative only in the following situations: (1) in cases of therapeutic emergency ; (2) when there is insufficient tumor tissue to perform molecular testing ; and (3) when a tissue biopsy cannot be performed. However, tissue biopsy is considered the gold standard for tumor diagnosis and molecular investigation. CtDNA-based NGS gene panel testing should not replace tissue biopsy but can be considered as a reliable alternative in the above-mentioned indications.

Diagnostic Performance: the meta-analysis (27 studies, 4,774 patients) established that the NGS gene panel (EGFR, BRAF, KRAS, RET, ALK, ROS1) using ctDNA has an acceptable diagnosis performance in the absence of alternative options or urgent diagnostic situations. The combined overall pooled estimates of sensitivity and specificity were 0.71 [95% 0.66 – 0.75] and 0.94 [95% 0.89- 0.96], respectively. The estimated average risk of missed therapeutic opportunity associated with targeted NGS based on ctDNA is 19% (i.e., patients may receive standard treatment instead of targeted treatment due to an undetected molecular alteration). However, a negative ctDNA result does not exclude the presence of a somatic alteration. Therefore, when possible, a (re)biopsy of the progressive lesion should be considered.

Conditions of implementation: The performance of NGS gene panel testing based on ctDNA within the scope of these indications requires compliance with the implementation conditions defined in the report, in agreement with professionals. This includes compliance with pre-analytical, analytical, and post-analytical steps within a laboratory accredited by COFRAC, or within institutions currently undergoing accreditation in somatic genetics (specifically anatomo- cytopathology facilities).

### Recommendations

The French National Authority for Health has recommended funding for the NGS gene panel using ctDNA by the National Health Insurance for patients with advanced and metastatic NSCLC in the above-mentioned indications.

### Methods

An umbrella review was conducted using the following bibliographic databases: MEDLINE/PubMed, Embase, INATHA Database and The Cochrane Library, to identify systematic reviews and meta-analysis reporting on the accuracy (sensitivity and specificity) of NGS using ctDNA in patients with advanced and metastatic NSCLC. Studies were eligible when NGS of ctDNA was compared to a tissue based NGS test detecting at least one of the six molecular alterations (EGFR, BRAF, KRAS, RET, ALK, ROS). Sensitivity and specificity were pooled using a random effects model via Meta-Disc 2.0. In addition, the French National Authority for Health consulted stakeholders (relevant professional bodies, experts and patient and consumer organisations), as well as the National Cancer Institute, to review the report.

## **Further research/reviews required**

The French National Authority for Health emphasizes that the composition of the next-generation sequencing gene panel may be subject to change, depending on favourable assessments of new genetic alterations. These new assessments will be conducted in a dynamically in response to evolving in scientific knowledge (identification of new relevant evidence and/or publication of new advice issued by French National Authority for Health Transparency Committee and/or, compassionate use authorizations issued by the French National Agency for Medicines and Health Products Safety). Furthermore, it seems necessary to implement quality control for fusion alterations detected on ctDNA (particularly for the ALK, ROS1, and RET genes) and further research is needed to investigate resistance mutations that could justify expanding the current composition of the gene panel.

## **Written by**

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