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HC-based NGS impacts treatment decisions in lung cancer patients with adenocarcinoma

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The use of hybrid capture-based (HC-based) next-generation sequencing (NGS) to identify targetable oncogenic drivers in patients with lung adenocarcinoma results in the detection of genomic alterations (GAs) not identified in routine screening, and impacts treatment decisions and clinical outcomes.

Lung cancer is the most common type of cancer with the highest cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for roughly 85% with about 40% being adenocarcinoma. Targeted therapy that targets driver genomic alterations (GAs) significantly prolongs survival in lung adenocarcinoma patients, and tumor genotyping allows for the detection of GAs in approximately 60% of patients. Currently, the technologies (polymerase chain reaction, immunohistochemistry, and fluorescence in situ hybridization) used for the detection of GAs cannon identify all alterations in EGFR exons and introns or all variants of ALK rearrangements. HC-based NGS is a technology that offers broad gene sequencing, extensive genetic information regarding GAs and exon/intron mutations, gene rearrangements and amplifications. However, the utility of HC-based NGS in clinical practice is yet to be extensively reviewed.

A group of Israeli researchers, led by Dr. Nir Peled, conducted a retrospective study on a cohort of 101 patients with advanced lung cancer that were treated at the Davidoff Cancer Center, Rabin Medical Center, Israel between 11/2011 and 10/2015, who underwent HC-based NGS using broad gene panels. Demographic and clinic-pathologic

characteristics, treatments, and outcome data were collected.

The results of the study published in the *Journal of Thoracic Oncology*, the official journal of the International Association for the Study of Lung Cancer (IASLC), show that of the 101 patients with advanced lung cancer included in the study, the median age at diagnosis was 63 years, 94% of the patients were diagnosed at stage III-IV, 53% were women, 45% were never smokers, and 85% had adenocarcinoma. HC-based NGS was performed before standard EGFR/ALK testing (15% of patients due to lack of tissue) or after testing revealed negative or inconclusive (85% of patients) results. HC-based NGS was performed before treatment with 1st-line therapy in 51.5% patients and after treatment failure in 48.5% of patients. HC-NGS identified clinically actionable GAs in 50% of patients (EGFR 18%, RET 9%, ALK 8%, MET 6%, and ERBB2 5%) and identified EGFR/ALK aberrations not detected via standard screening in 15 patients. HC-based NGS results caused deviations to treatment strategy in 43 patients (42.6%). The overall response rate to targeted therapies in these patients was 65% (complete, 14.7%; partial 50%). Median survival was not reached. Immunotherapy was administered in 33 patients, mostly without an actionable driver, presenting disease control rate of 32% and an association to tumor mutation burden.

The authors comment that, "This study draws attention to the rate of high false negative results in clinical routine practice and may not allow patients to have access to therapy targeting driver mutations. It also can expose patients to immunotherapy as 2nd-line treatment that may not work in this population of patients. Our study is restricted by its retrospective nature, its relatively small sample size, and by being a single-center study. In addition, the high percentage of never smokers, female preponderance, and the relatively young median age of our patient group represent a selection bias with a high pre-test probability for the existence of driver mutation. The results of large future

prospective trials such as the National Lung Matrix Trial (NLMT) in the UK, and the Molecular Analysis for Therapy Choice (MATCH) Program, led by the US National Cancer Institute, are thus eagerly anticipated. Nevertheless, the high impact of HC-based NGS on treatment strategy, and the high overall response rate observed in this study, highlight the need for identifying molecular drivers and support the implementation of HC-based NGS in lung cancer."

More information: Anna Belilovski Rozenblum et al. Clinical Impact of Hybrid Capture-Based Next-Generation Sequencing on Changes in Treatment Decisions in Lung Cancer, *Journal of Thoracic Oncology* (2016). DOI: 10.1016/j.jtho.2016.10.021

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