

Study tracks genomics of lung tumor behavior

April 14 2020, by Tom Wilemon



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A study by Vanderbilt researchers has identified genomic alterations in early stage adenocarcinomas of the lung that may indicate whether the lesions develop into aggressive tumors.

The study published in the *American Journal of Respiratory and Critical*

Care Medicine is the largest analysis of in situ and early adenocarcinomas lesions using targeted sequencing. Pierre Massion, MD, Cornelius Vanderbilt Chair in Medicine, led the research team.

The study is part of an initiative by that team to address challenges related to overdiagnosis and overtreatment of indolent [lung](#) adenocarcinomas—an initiative supported by a \$1.2 million grant from the National Cancer Institute.

In the study, the researchers looked at lung adenocarcinoma surgical pathology specimens from 102 patients for whom they had medical histories. The specimens were obtained before treatments, such as chemotherapy and radiation, would have affected the genomic profiles of the adenocarcinomas.

Massion and colleagues studied extracted DNA from 21 adenocarcinomas that had not yet broken through basal membranes (in situ), 27 minimally invasive adenocarcinomas and 54 fully invasive adenocarcinomas then had them submitted for targeted next generation sequencing at Vanderbilt Technologies for Advanced Genomics (VANTAGE). The specimens were tested against a custom 347 cancer gene panel.

A striking result was that even the earliest tumors called "in situ," to describe their lack of invasive properties, are fully equipped with [genomic alterations](#) found in invasive tumors. This suggests a critical role for the [tumor](#) microenvironment to dictate the invasive progression of the tumor.

Mutations in five genes, PIK3CA, ATM, EPPK1, EP300 and KMT2C, together predicted inferior survival in 10 patients even in the absence of EGFR, KRAS and TP53 mutations. The researchers also identified mutations associated with survival. Another 10 patients having ATR,

KDM6A or POLQ mutations without concurrent Gene5 [mutations](#) survived.

"We found in our study that some genetic alterations give us hints as to whether they are more likely to be aggressive," Massion said. "I think equipped with this knowledge we can now test new hypotheses for identifying populations that may benefit from adjuvant therapy."

However, he stressed that the findings should be validated in larger studies before clinical implications can be established.

"We are actually gearing up to get a validation set with the collaborative work we are doing with others with the Pre-Cancer Atlas program," he said.

"There are many roads that lead to lung [adenocarcinoma](#)," Massion said. "It's not one patient, one gene, one alteration. Every tumor is different, but we are trying to find similarities. Why? Because each of these starting points is associated with signaling and alternations of [genes](#) that may be targeted specifically. We now have targets for many of these in the therapeutic world that are being tested aggressively."

Conversely, other genomic profiles may identify indolent lesions that should be observed on a regular basis rather than promptly resected. Screening programs for lung cancer, which have proven instrumental in reducing deaths from the disease in longtime smokers, also set up the scenario for unnecessary surgeries.

More information: Jun Qian et al. Genomic Underpinnings of Tumor Behavior in In Situ and Early Lung Adenocarcinoma, *American Journal of Respiratory and Critical Care Medicine* (2019). [DOI: 10.1164/rccm.201902-0294OC](https://doi.org/10.1164/rccm.201902-0294OC)

Provided by Vanderbilt University

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