

Multimodal genomic analyses predict response to immunotherapy in lung cancer patients

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Lung cancer. Credit: Jennifer Fairman and Valsamo Anagnostou, Johns Hopkins University

Researchers at Johns Hopkins Kimmel Cancer Center, the Bloomberg-Kimmel Institute for Cancer Immunotherapy and the Johns Hopkins University School of Medicine have developed an integrated genomic approach that potentially could help physicians predict which patients with nonsmall cell lung cancer will respond to therapy with immune checkpoint inhibitors.

Immune checkpoint inhibitors are transforming the

field of [cancer](#) therapeutics. However, these successes are limited by the lack of biomarkers that identify patients most likely to respond. Tumor mutational burden (TMB), which is a measure of the number of mutations carried by [tumor cells](#), is considered an emerging biomarker of response, but TMB values are confounded by the [tumor](#) purity—the amount of tumor versus normal cells—of the sample analyzed.

The research team, led by Valsamo Anagnostou, M.D., Ph.D., assistant professor of oncology, developed a novel computational approach that more accurately computes TMB. The researchers also developed an integrated model of response that combined corrected TMB with nuanced genomic features and each patient's antigen presentation ability. A description of the patent pending work is published in the inaugural issue of the journal *Nature Cancer*.

The method also could be used to accurately estimate TMB and optimize prediction of response to immunotherapy among patients with lung cancer, colon cancer, melanoma and other [solid tumors](#), says Anagnostou, the lead study author.

"Immunotherapy is an exciting treatment modality for many tumors, but what we don't truly know is who will respond to immunotherapy and why, and if there are specific molecular features that can help predict response," Anagnostou says.

Current biomarkers used to assess a patient's response to immunotherapy include a test to measure the amount of the protein PD-L1 on cancer cells and TMB. "There are more and more studies coming out that show TMB is actually not as predictive as we thought it would be," says Victor Velculescu, M.D., Ph.D., professor of oncology and the study's senior author. "Some

tumors with a high TMB do not respond to immunotherapy, and some tumors with low TMB benefit from immunotherapy. There is an urgent need to develop integrated biomarkers that explain the nuances of the tumor-immune system crosstalk that can better inform us in terms of the clinical course of the patient."

Anagnostou and colleagues initially evaluated 3,788 tumor samples (from bladder, breast, colon, head and neck, kidney and nonsmall cell lung cancers and melanomas) from the National Cancer Institute's Cancer Genome Atlas database, and 1,661 tumor samples from a previously published cohort of immunotherapy-treated patients. They investigated the complexities of observed TMB estimates derived from whole exome sequencing (a technique that sequences the entire protein-coding region of genes in a genome) and targeted next-generation sequencing (a technique that sequences target regions of interest in a genome). They found a significant correlation between TMB and tumor purity—the higher the tumor purity, the closer it is to the true TMB of the tumor, whereas the lower the tumor purity, the more likely the TMB estimate will be inaccurate. "Observed TMB is strongly affected by low tumor purity, and this simple concept is completely underestimated in the clinical setting," says Noushin Niknafs, Ph.D., postdoctoral fellow and co-first author of the study.

To overcome this limitation, the team developed a computational approach to estimate corrected TMB values for each tumor based on tumor purity. They simulated 20,000 tumors with various levels of TMB and sequencing coverage using information from the Cancer Genome Atlas and generated a correction factor for each simulated tumor based on its purity. "The correction factors can be summarized in a user-friendly look up table," says Anagnostou. "For example, if a tumor sample had a purity of 20% to 30%, a clinician could look at the table and see a coefficient to multiply the sample by to better achieve true TMB." The team also developed an approach to correct TMB derived from targeted [sequence data](#), and in a reanalysis of 1,661 tumor samples treated with immune checkpoint inhibitors, the researchers found that using corrected TMB estimates improved prediction of overall survival.

Next, the team worked to understand additional molecular features that can play a role in patient response to immunotherapy. They performed whole exome sequencing for 104 lung tumors treated with [immune checkpoint inhibitors](#). Through comprehensive analyses of sequence and structural alterations, they discovered more activating mutations in [receptor tyrosine kinase](#) (RTK) genes (receptors that are key regulators of cell processes including cell proliferation, survival and metabolism) among tumors that did not respond to immunotherapy in several cohorts of patients. In addition, they identified a predominance of smoking related mutations in patients that respond to therapy. Together, corrected TMB, RTK mutations, the mutation smoking signature and the number of germline variants of human leukocyte antigen (HLA)—cell-surface proteins responsible for the presentation of foreign antigens—provided the team with a much more accurate prediction of patient response to immunotherapy compared to TMB alone, even the corrected TMB.

The team is continuing studies of this model with more patients who have received immunotherapy and for whom they are generating tumor sequencing data.

"We expect this approach is going to be incorporated into clinical practice, and it can change the way providers make decisions about their patients," Anagnostou says. "For example, if a clinician can know with certainty that the tumor has a high tumor mutation burden, they may choose to give immunotherapy as stand-alone therapy, whereas if the tumor has a low tumor mutation burden, they may choose to give chemotherapy plus [immunotherapy](#)."

More information: Valsamo Anagnostou et al, Multimodal genomic features predict outcome of immune checkpoint blockade in non-small-cell lung cancer, *Nature Cancer* (2020). DOI: [10.1038/s43018-019-0008-8](https://doi.org/10.1038/s43018-019-0008-8)

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