Deadly lung cancers are driven by multiple genetic changes

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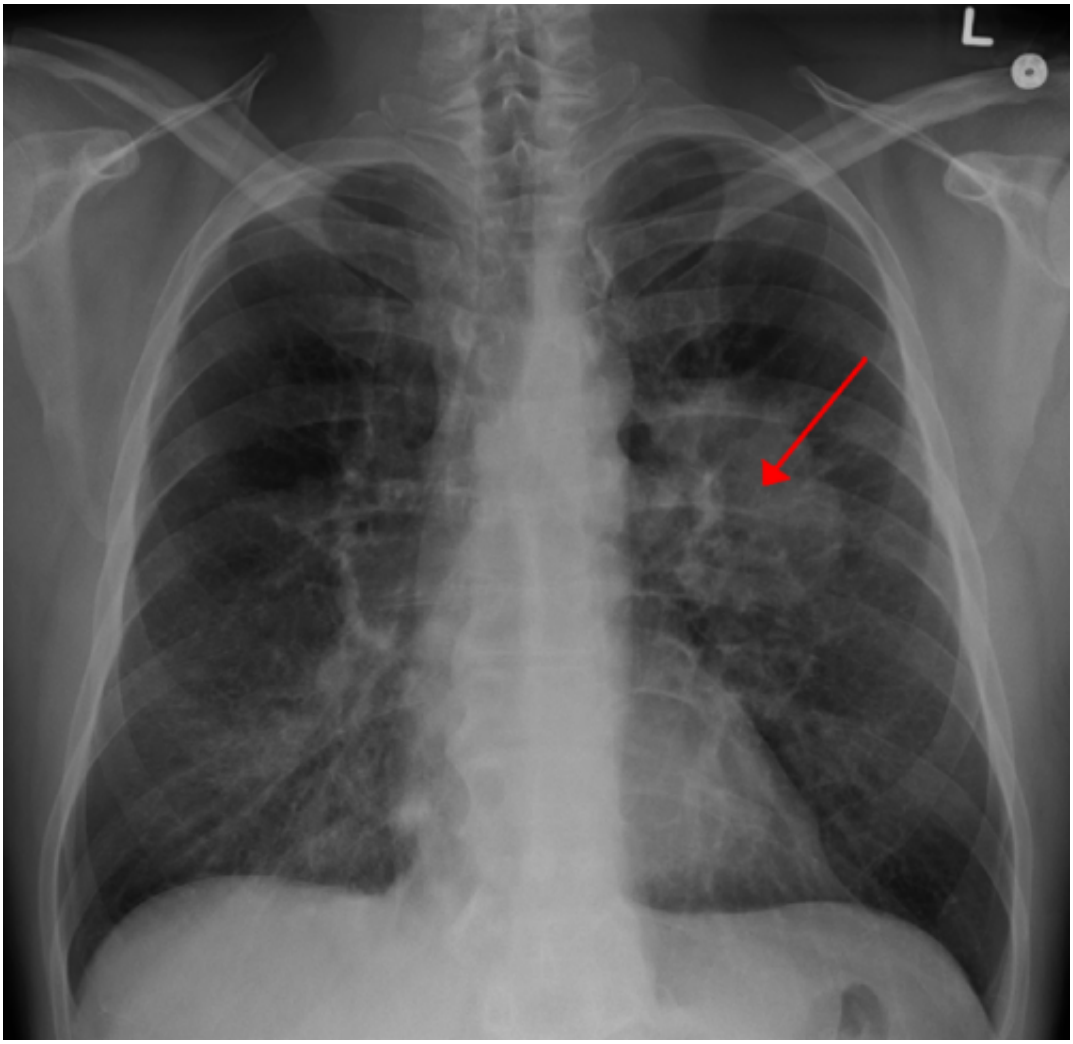

Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

A new UC San Francisco-led study challenges the dogma in oncology that most cancers are caused by one dominant "driver" mutation that can be treated in isolation with a single targeted drug. Instead, the new research finds one of the world's most deadly forms of lung cancer is driven by changes in multiple different genes, which appear to work together to drive cancer progression and to allow tumors to evade targeted therapy.

These findings—published online on November 6, 2017 in *Nature Genetics*—strongly suggest that new first-line combination therapies are needed that can treat the full array of mutations contributing to a patient's cancer and prevent drug resistance from arising.

"Currently we treat patients as if different oncogene mutations are mutually exclusive. If you have an EGFR mutation we treat you with one class of drugs, and if you have a KRAS mutation we pick a different class of drugs. Now we see such mutations regularly coexist, and so we need to adapt our approach to treatment," said Trever Bivona, MD, PhD, a UCSF Medical Center oncologist, associate professor in hematology and oncology, and member of the Helen Diller Family Comprehensive Cancer Center at UCSF.

Lung cancer is by far the leading cause of cancer death worldwide. Efforts to identify the genetic mutations that drive the disease have led to targeted treatments that improve life expectancy for many patients, but these drugs produce temporary remission at best—sooner or later, cancers inevitably develop drug resistance and return, deadlier than ever.

The new UCSF-led study—which analyzed tumor DNA from more than 2,000 patients in collaboration with Redwood City-based Guardant Health—is the first to extensively profile the genetic landscape of advanced-stage non-small cell (NSC) lung cancer, the most common form of the disease.

"The field has been so focused on treating the 'driver' mutation controlling a tumor's growth that many assumed that drug-resistance had to evolve from new mutations in that same oncogene. Now we see that there are many different genetic routes a tumor can take to develop resistance to treatment," said Bivona, who is also co-director of a new UCSF-Stanford Cancer Drug Resistance and Sensitivity Center funded by the National Cancer Institute. "This could also explain why many tumors are already drug-resistant when treatment is first applied."

Distinct mutations predict tumor progression, drug response

The single-driver view of lung cancer has been buttressed by influential genomic studies, such as The Cancer Genome Atlas (TCGA). However, these studies have so far focused on genomic alterations in early, stage 1 tumors, which are usually treatable with surgery and chemotherapy, rather than the more deadly advanced-stage tumors that challenge clinical oncologists.

"Until recently, our field has relied on genomic data from early-stage cancers, but most of the patients we are treating have stage 4 disease," Bivona said. "This study is the first in-depth look at the complex genomics of advanced NSC lung cancer, where it turns out that the genetic landscape is wildly different."

To begin to map out the genetic landscape of stage 4 lung cancer, Bivona's team collaborated with Guardant Health, whose clinically validated Guardant360® cell-free DNA platform finely analyzes patient blood samples to check for any mutations in 73 genes known to contribute to cancer. The researchers analyzed this so-called "liquid biopsy" data from 1,122 patients in Guardant Health's database whose tumors contained a mutated EGFR gene—considered the dominant

genetic driver of about 15 percent of cases of NSC lung cancer—as well as 944 patients whose tumors did not have this mutation.

This analysis revealed that the 92.9 percent of tumors from patients with advanced-stage lung cancer harbored multiple changes in cancer-related genes in addition to the EGFR driver mutation. On average, tumors contained between two and three altered genes in addition to EGFR, but some contained as many as 13.

These included alterations in the cancer gene TP53 in more than 50 percent of tumors, while changes in classic cancer pathways such as receptor tyrosine kinases, RAS-MAP kinase, PI3 kinase, Wnt/beta-catenin, as well as genes involved in cell division, epigenetic modifications, DNA repair, and cellular signaling pathways each occurred in between 10 and 25 percent of tumors.

Using the Guardant Health liquid biopsy data, the researchers identified which of these additional mutations were more common in EGFR-mutant tumors than in non-EGFR-mutant tumors—suggesting that these mutations may work together with EGFR mutations to instigate or drive the progression of this subtype of the disease.

The researchers were also able to identify which mutations cropped up specifically in patients who developed resistance to EGFR-targeted drugs—suggesting that these mutations, rather than alterations in EGFR itself, could be responsible for the onset of resistance. Analysis of a smaller subset of patients for whom tumor DNA had been collected at multiple stages of treatment, and for whom clinical treatment history was known, confirmed these findings, showing how tumors become more genetically complex and accrue more additional mutations as they are exposed to multiple rounds of targeted drugs.

"The implication of this work is that a drug targeted at the EGFR

mutation may be able to wipe out the cells carrying that mutation alone, but they leave behind—and may even enhance—cells with other, additional mutations. In that case, all we've done is reshape the landscape of the tumor, perhaps causing temporary remission, but giving ourselves a harder problem to solve when the cancer returns," Bivona said.

"Many other large-scale genomic studies do not include anything about patient treatment history, but the availability of this information with Guardant Health's liquid biopsy data was a key reason why our analysis is so powerful," added Collin Blakely, MD, PhD, a UCSF Medical Center medical oncologist and assistant professor of medicine at UCSF who collaborated with Bivona's team and was co-first author on the new study.

Liquid Biopsies Could Enable Researchers to Track and Treat Additional Mutations as They Develop

The discovery of multiple genetic alterations in NSC lung cancers suggests an urgent need for oncologists to develop new first-line combination therapies capable of targeting multiple genetic pathways in patients' tumors, rather than waiting for resistance to develop before trying a second drug, the authors say.

"To me, the most interesting single finding was that five to ten percent of patients whose tumors had genetic alterations in both EGFR and cell-cycle genes such as CDK4 and CDK6 did much worse when treated with targeted EGFR inhibitors," Blakely said. "In some cases, patients didn't respond to those drugs at all. Interestingly, there are already FDA-approved drugs for breast cancer that target these cell-cycle genes, so perhaps beginning treatment with a combination of these drugs could improve these patients' chance of responding to therapy and avoiding drug-resistance."

More broadly, Blakely added, the new findings call for doctors to develop a more adaptive strategy to cancer treatment: using regular liquid biopsies to monitor the genetic landscape of a patient's tumor as it responds to treatment or begins to develop resistance, and altering the treatment regimen to target the shifting array of mutations driving the cancer's progression.

In the paper, the authors provide a case study from UCSF that illustrates the kind of real-time information such monitoring could provide. In collaboration with co-author Charles Swanton at the Francis Crick Institute in London, they describe an EGFR-mutant lung cancer patient who received whole-exome gene sequencing of tumor samples and liquid biopsies at seven time points during their treatment, which retrospectively reveal exactly when new genetic mutations arose as the patient's cancer recurred after initial surgery, initially responded to targeted drug treatment, but eventually developed resistance to both a first and second round of EGFR-targeted drugs, then eventually—and fatally—metastasized.

"We need to go beyond the typical call for combination therapy," Blakely said. "These results shed light on how complex and adaptable these cancers are at a genetic level. Even if you come up with one initially effective combination of drugs, there's still likely to be a whole slew of other genetic alterations you ultimately need to overcome to kill the cancer. The only way to do that is to adjust your treatment strategy faster than the cancer can evolve resistance."

More information: Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers, *Nature Genetics* (2017). nature.com/articles/doi:10.1038/ng.3990