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NEWSLETTER

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Biomarker Testing for Non-Small Cell Lung Cancer

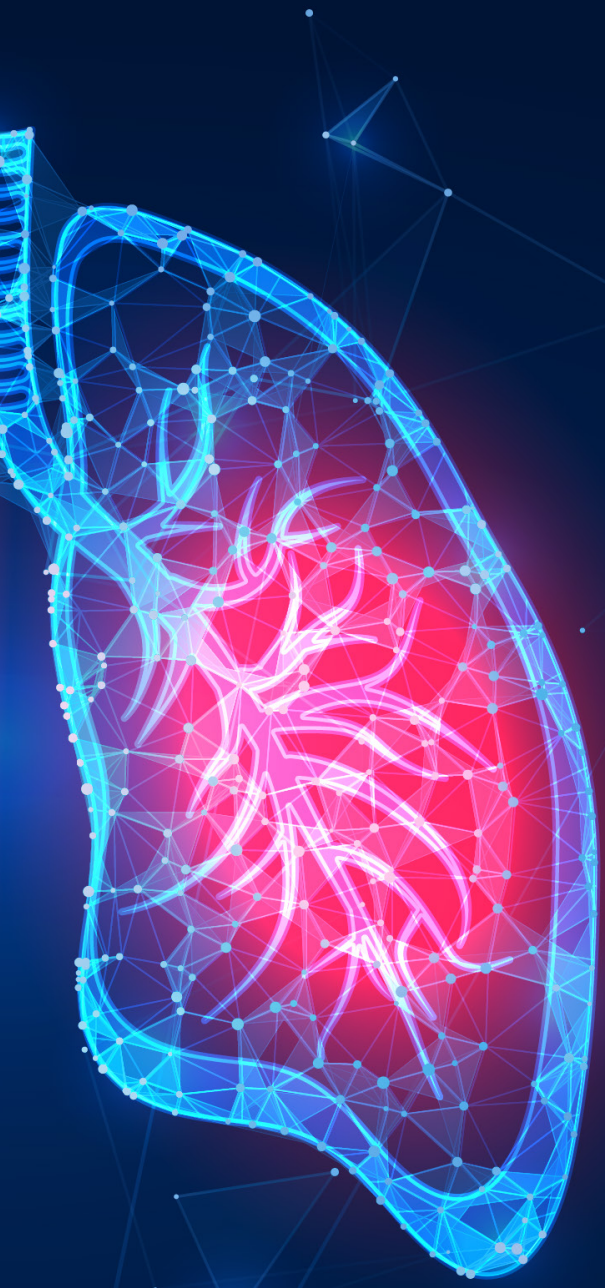
Next-generation sequencing can identify candidates for targeted therapies, yet remains underused.

The arrival of targeted therapies for the treatment of non-small cell lung cancer (NSCLC) heralded a new era in the management of this challenging diagnosis. Multiple clinical studies have confirmed that targeted drugs significantly improve survival over chemotherapy and immunotherapy. Yet, identifying all NSCLC patients who might benefit from targeted therapies requires broad-based genetic testing in the form of next-generation sequencing (NGS). However, surveys indicate that only a minority of NSCLC patients are receiving this advanced form of genomic screening. New research underscores the benefits of expanding the use of NGS in NSCLC—both for patients and for bottom lines.

Missed opportunities

Even though tobacco use has declined in every region of the world over the last generation, lung cancer remains one of the most prevalent and deadly of all cancers. Globally, it's the most common fatal cancer, taking the lives of about 1.8 million people each year. Data from the U.S. National Cancer Institute indicate that 57 percent of people diagnosed with lung cancer in the United States have stage IV disease, which has a five-year survival rate of slightly more than 5 percent. What's more, patients diagnosed with early-stage disease frequently experience recurrence or progression after initial treatment.

However, the emergence of targeted therapies for NSCLC, which accounts for 85 percent of lung cancer cases, has been a game changer. There are now FDA-approved treatments for a fast-growing number of different genetic mutations linked



to non-squamous NSCLC. Data indicate that 29 percent of patients with this cancer have genetic mutations that make them candidates for targeted therapies, and studies confirm that these new-generation medicines prolong survival and improve quality of life in this patient population.

Yet, most people diagnosed with NSCLC still receive chemotherapy and immunotherapy, which offer limited benefits for these patients. The problem is that identifying candidates for the many different targeted therapies now available requires NGS, the powerful scan that analyzes hundreds of genetic mutations and other alterations—but relatively few patients with NSCLC get this test. That's true even though the College of American Pathologists (CAP) and the National Comprehensive Cancer Network recommend NGS as the preferred biomarker-screening tool for patients with advanced or metastatic NSCLC. CAP defines "advanced" as stage IIIB (lymph node involvement on the opposite side of the chest from the affected lung, above the collarbone, or at the top of the lung); or stage IV (distant metastasis) lung cancer.

Unfortunately, many institutions are only equipped to test for mutations in one or two NSCLC-associated genes. Data suggest that just 15 percent of NSCLC patients receive NGS. Another 65 percent undergo single-gene testing (SGT), typically for EGFR and ALK mutations. The remaining 20 percent are not offered any form of genetic testing or do not qualify.

A major barrier to the use of NGS in oncology is the argument that it is too expensive to offer to all or even a majority of oncology patients. But given the growing number of mutations associated with NSCLC, their wide distribution among patients, and the availability of effective treatments to target them, could NGS be a cost-effective tool for making better therapeutic choices for this cancer?

To find out, a team from the Taussig Cancer Institute at the Cleveland Clinic, in Cleveland, Ohio, designed a mathematical model to simulate a population of 89,000 hypothetical patients with newly diagnosed advanced non-squamous NSCLC, which was roughly the annual incidence in the United

States at the time of the study. At that time, seven "actionable driver oncogenes" (ADOs) for NSCLC had been identified—*EGFR, ALK, ROS1, BRAF, RET, MET,* and *NTRK*—and had associated targeted therapies approved for treating the cancer. The scientific literature provided data on the distribution of these ADOs among the population of patients with NSCLC and the relative efficacy of their associated targeted therapies compared to the standard of care (chemotherapy and immunotherapy).

The Cleveland Clinic team first asked the mathematical model to estimate patient outcomes and costs with the current breakdown of 65 percent of patients receiving SGT and 15 percent receiving NGS. For comparison, they then had the model generate the same estimates under a scenario where all patients received NGS. Here's a summary of their findings, which were published last January in *JCO Precision Oncology*:

• Every 10 percent increase in use of NGS among NSCLC patients produced an average addition of 2,627.4 life-years gained (LYG), with an average cost savings per LYG of $75.
• Converting all 80 percent of patients currently tested to NGS would result in an average additional 21,09.6 LYG. The cost per LYG would be reduced by an average of $599.
• Estimated median and 5-year survival of patients with an ADO who receive effective targeted treatment: 39 months and 25 percent.
• Estimated median and 5-year survival of patients with an ADO who go unidentified: 14 months and 5 percent.

In a statement, study coauthor Nathan Pennell, MD, PhD, a hematologist and oncologist at the Cleveland Clinic, noted that it remains debatable whether all oncology patients can benefit from NGS. But in lung cancer, he added, "it is indisputable that every patient—specifically those with non-squamous NSCLC—needs broad testing done."

In addition to allowing clinicians to select candidates for approved targeted therapies, NGS can also play a critical role in identifying patients who could benefit from enrolling in a clinical trial of an investigational oncology treatment (more than 50 percent of trials now involve biomarker data). Contact a Massive Bio representative to learn more about clinical trials of targeted therapies for NSCLC and other forms of cancer.

Source: Lemon, CA, et al. Modeling Costs and Life-Years Gained by Population-Wide Next-Generation Sequencing or Single-Gene Testing in Nonsquamous Non-Small-Cell Lung Cancer in the United States. *JCO Precis Oncol*. 2023 Jan; 7: e2200294.

Research News

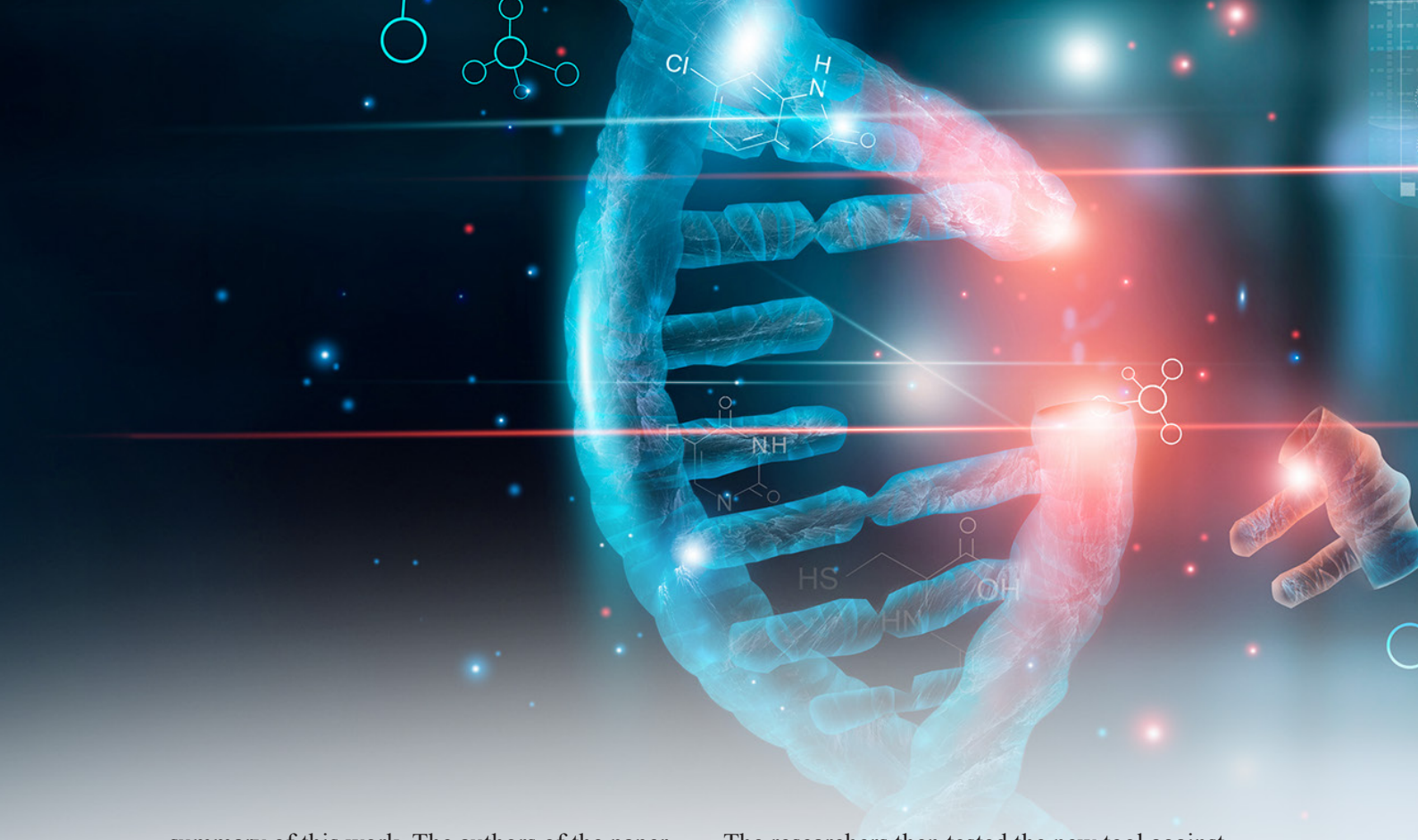
Air Pollution Causes Lung Cancer—But Not By Altering DNA

Breathing polluted air every day has long been known to increase the risk for lung cancer, causing millions of deaths around the world each year. It is also well established that smoking tobacco causes gene mutations that promote lung cancer, but whether inhaling dirty air causes cancer by altering DNA was unknown.

To learn more about the mechanism by which polluted air causes lung cancer, researchers at the University of Cambridge, in the United Kingdom, began by analyzing lung cancer epidemiological data from four countries: the United Kingdom, Canada, South Korea, and Taiwan. To rule out the influence of tobacco smoking on risk, they focused on lung cancers with *EGFR* mutations, which occur more commonly in nonsmokers than in smokers.

By analyzing 32,957 *EGFR*-driven cases, they found a strong association with exposure to air pollution from sources such as motor vehicle engines, coal-fired power plants, and burning wood. Next, they demonstrated that mice bred to have the *EGFR* mutation that were exposed to polluted air were more likely than control mice to develop lung cancer. Chronic exposure to pollutants triggered an influx of macrophages into their lungs and the release of interleukin-1β (IL-1β), resulting in inflammation. (Blocking IL-1β with antibodies prevented lung cancer.)

However, exposure to air pollution did not cause mice that developed lung cancer to acquire new gene mutations. Instead, authors of the study, published in *Nature* in April, speculate that the resulting chronic inflammation caused cells with pre-existing mutations (which likely occurred due to chance) to collect and form tumors. This theory fits with previous work suggesting that many known human carcinogens do not increase DNA mutations in mice, as *Nature* reported in a



summary of this work. The authors of the paper suggest that dietary interventions may be one possible strategy for minimizing the effects of air pollution and other carcinogens.

New Tool May Improve ID of Patients at High Risk for Lung Cancer

Low-dose computed tomography (CT) can spot lung cancer early, when it responds best to treatment, but proper patient selection for this screening procedure is essential to avoid wasting resources. Lung cancer risk-assessment tools to identify candidates for CT screening are available, but recent studies suggest that they are only moderately effective at discriminating patients at high risk from low-risk patients.

With the goal of building a better screening tool, researchers at the University of Nottingham and University of Oxford in the United Kingdom created a risk-prediction model called CanPredict. The model was developed with primary care records for nearly 13,000,000 adult patients, of whom 73,380 were diagnosed with lung cancer. The researchers compared a comprehensive list of predictors in patients who did and did not develop lung cancer, including age, sex, ethnicity, Townsend score (an index of deprivation that includes elements such as employment status and home ownership), body mass index, smoking status, alcohol status, comorbidities, family history of lung cancer, and personal history of other cancers.

The researchers then tested the new tool against a separate database of 2.5 million patient records by having it predict which patients would develop lung cancer, then comparing those predictions with patient outcomes. As reported in *Lancet Respiratory Medicine*, they repeated this process with seven other risk-prediction models and found that it outperformed all of them, more accurately predicting lung cancer risk in people aged 55 to 74 at five-, six-, and 10-year time horizons. The developers of CanPredict hope to make it widely available soon.

New TKI Passes Phase 2 Clinical Trial

Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of NSCLC, and more may be on the way. In a multicenter, open-label, single-arm phase 2 study, researchers gave the experimental TKI taletrectinib (600 mg once daily) to *ROS1*-positive NSCLC patients who were divided into two cohorts, TKI-naïve and previously treated with crizotinib (Xalkori). Patients ranged in age from 26 to 77 (median age, 54). Roughly one in four had previously been treated with chemotherapy and 22 percent had brain metastases.

In the TKI-naïve cohort, overall response rate (ORR) was 90 percent and disease control rate (DCR) was 95 percent. In the crizotinib-pretreated cohort, the ORR was 47.6 percent and the DCR was 76.2 percent. When the data was reported, median duration of response and median progression-free survival had not been reached in either cohort.

Among the six patients with brain metastases and measurable target brain lesions at baseline, the intracranial ORR and intracranial-DCR were 83.3 percent and 100 percent, respectively. Four patients had the *ROS1* G2032R mutation, of whom three had a partial response (PR), while the fourth achieved stable disease (SD). Common side effects includes diarrhea, nausea, vomiting, transaminase elevation, anemia, and decreased neutrophil count, primarily grade 1 or 2. The authors concluded that taletrectinib appears to benefit both TKI-naïve and crizotinib-pretreated *ROS1*-positive NSCLC patients, particularly those with *ROS1* secondary G2032 mutations and patients with brain metastasis. A phase 3 trial awaits.

NCI-Sponsored Trial for NSCLC Drug Eliminates Barriers to Participation

Clinical trials offer some cancer patients access to potentially life-saving therapies, but many others are excluded from enrolling, due to stringent inclusion/exclusion criteria and other factors. In a step toward increasing inclusion in clinical trials, the U.S. National Cancer Institute has launched the Pragmatica-Lung Cancer Treatment Trial, which will evaluate a new therapeutic strategy for NSCLC and, organizers hope, serve as a model for how to remove barriers to participation for patients.

Pragmatica-Lung is a phase 3 clinical trial for people aged 18 and older with stage IV NSCLC, who will be randomized to receive either chemotherapy or a combination of ramucirumab (Cyramza) and pembrolizumab (Keytruda). Ramucirumab targets *EGFR* mutations, while pembrolizumab is a PD-1 inhibitor. The trial objective is to recruit 700 participants.

Importantly, Pragmatica-Lung has been designed to enroll a wider variety of patients than many clinical trials allow. For example, trials often restrict participation to patients with relatively higher scores on scales that measure performance status, such as ECOG. Pragmatica-Lung allows the participation of people with lower performance status, who are more representative of people with advanced lung cancer.

What's more, Pragmatica-Lung will not include many of the extra tests, data collections, and secondary study goals that are often included in clinical trials, which add to the burden for both investigators and patients participating. "This study is designed to eliminate potential barriers to enrollment and provides a model for increasing diversity and enrollment in clinical trials," said Monica M. Bertagnolli, M.D., director of NCI, in a statement. "Pragmatica-Lung, with its critical public and private partnerships, reflects the innovative approaches NCI is taking to achieve the Cancer Moonshot goals, including reducing the cancer death rate by 50 percent within the next 25 years."

Patient Advocacy

American Lung Association®

Patients with lung cancer and their families can find support and other resources from a variety of advocacy groups, but the oldest and largest is the American Lung Association (ALA). Founded in 1904 to fight the leading cause of death in the United States at the time, tuberculosis, the organization has since expanded its mission to help patients with all lung diseases, including lung cancer.

Patients can receive support and information about all forms of lung disease through the ALA's Better Breathers club, which has a network of groups across the United States. For newly diagnosed lung cancer patients, the organization's website features extensive educational materials, including plain-language explanations of how biomarker testing works. The ALA also hosts an online support group for lung cancer survivors.

The ALA's LUNG FORCE initiative raises awareness about lung cancer and holds fundraisers to gain support for research aimed at finding cures for the disease. Many patients can also benefit from the ALA's behavior-based Freedom From Smoking program, which is over four decades old and has helped thousands of people end their addiction to nicotine and live tobacco-free; clinics are held in person and online. To learn more about the ALA, patients can visit www.lung.org.