planning a human trial to investigate the therapeutic potential of antibiotics for patients with primary liver tumors or liver metastases. *–Kristin Harper* ■

Sequencing Detects Lung Cancer in Blood

It may be possible to detect early-stage lung cancer from blood samples using genome sequencing, according to preliminary results from the ongoing Circulating Cell-Free Genome Atlas (CCGA) study presented on June 2 at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, IL (J Clin Oncol 36, 2018 [suppl; abstr LBA8501]). Three different assays showed high sensitivity and specificity in detecting the disease by analyzing cell-free DNA, generating data that could be used to develop a blood-based detection test.

"This is not cancer genotyping, where you're looking in the blood for a gene mutation and targeting that mutation," explained Geoffrey Oxnard, MD, of Dana-Farber Cancer Institute in Boston, MA, who presented the findings. "This is cancer detection, and it requires a different approach—we have to look broadly across the entire genome." Oxnard adds that although low-dose CT lung cancer screening improves survival, it has not been widely adopted, and thus a blood-based test that relies on genome sequencing "could address an unmet medical need."

Oxnard and his team reported results from 127 patients with lung cancer and 580 healthy controls enrolled in the prospective, longitudinal CCGA study. They analyzed blood samples with three tests: targeted sequencing of 507 genes for single-nucleotide variants and small insertions and/or deletions, whole-genome sequencing (WGS) to detect copy-number variation, and whole-genome bisulfite sequencing (WGBS) to detect abnormal methylation patterns.

"Each of these allows you to query for all major somatic and epigenetic features within the cell-free DNA," while also sequencing white blood cells, which contain mutations that can look like cancer, Oxnard explained. "You screen out this interference from white blood cells and other biologic noise, and you're left with the final features: mutations, copy-number variations, and methylation signatures."

Targeted sequencing detected 51% of early-stage (stage I–IIIa) and 89% of late-stage (stage IIIb–IV) cancers, whereas WGS detected 38% of early-stage and 87% of late-stage cancers, and WGBS detected 41% of early-stage and 89% of late-stage cancers. The specificity of all three tests was 98%.

"This first interim analysis of the CCGA study demonstrates that comprehensive sequencing of the plasma cell-free DNA can generate high-quality data across the entire genome, and it permits noninvasive cancer detection," Oxnard said. "Together, these results support the promise of using cell-free DNA-based assays to develop an early cancer detection test with high specificity."

David Graham, MD, of the Levine Cancer Institute in Charlotte, NC, who is not involved in the CCGA study, called the results "an important first step toward an easier way to detect lung cancer at earlier—and hopefully more curable—stages," because CT screening rates are incredibly low. In fact, in the United States only 1.9% of more than 7 million current and former heavy smokers were screened for lung cancer in 2016, according to findings also presented at ASCO (J Clin Oncol 36, 2018 [suppl; abstr 6504]).

"If the promise of this report holds, we could easily see a day when a person could be screened for lung cancer and possibly other cancers simply by going into their regular doctor's office for a blood draw," he said. *–Catherine Caruso* ■

Lynch Syndrome Linked with More Cancers

Findings from a large prospective genomic analysis indicate that Lynch syndrome may be linked with more tumor types than previously thought (J Clin Oncol 36, 2018 [suppl; abstr LBA1509]). The data were presented on June 4 by Zsofia Stadler, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, during the 2018 American Society of Clinical Oncology Annual Meeting in Chicago, IL.

Either sporadic defects in DNA mismatch repair (MMR) proteins—chiefly MLH1, MSH2, MSH6, PMS2, and EPCAM—or Lynch syndrome, which arises from germline mutations

Zsofia Stadler, MD, presented her team's findings.

in these MMR genes, compromises the ability to fix DNA replication errors and results in microsatellite instability (MSI). This phenotype, which may increase neoantigen production and thereby sensitivity to immunotherapy, is classically associated with colorectal cancer, as well as with endometrial and stomach cancers. However, with pembrolizumab (Keytruda; Merck) and nivolumab (Opdivo; Bristol-Myers Squibb) earning tissue-agnostic approvals last year for tumors that exhibit high MSI, clinicians are increasingly assessing patients' MSI status regardless of cancer type, Stadler observed, to determine their likelihood of benefiting from PD-1 blockade.

"Until now, the prevalence of germline MMR gene mutations across all tumors with MSI has been unknown, so we made that the goal of our study," Stadler said. She and her colleagues used MSK-IMPACT, an FDA-authorized next-generation sequencing platform that incorporates MSI detection, to evaluate 15,045 tissue samples representing more than 50 tumor types. Germline analyses to identify MMR gene mutations were then carried out on blood samples from study participants.

Stadler reported that 93.2% of tumor samples were MSI-stable, 4.6% were MSI-indeterminate, and 2.2% were MSI-high. The distribution of germline MMR mutations across these three groups was 0.3%, 1.9%, and 16.3%, respectively. For the MSI-stable patients, Stadler noted, "this prevalence is essentially equivalent to the general population's risk of Lynch syndrome."

Focusing on the MSI-indeterminate and MSI-high cohorts, the investigators used immunohistochemistry to confirm MMR deficiency in these tumors. They also determined that 88% displayed a dominant pattern of tumor mutational signatures