In the near future it may be possible to detect cancer from DNA in a blood sample, a “liquid biopsy.” That is one of the implications of a recent paper by a team of scientists from Yale. Using a technique called “ultra-deep sequencing,” they were able to detect extremely low levels of tumor-derived mutant DNA in the plasma of cancer patients. “I hope that this will provide a clinically useful tool for the future,” said Abhijit A. Patel, MD, PhD, Assistant Professor of Therapeutic Radiology at Yale School of Medicine. “Ultimately we want to use this for purposes such as early detection of cancer.”

The researchers used 117 samples of plasma from 30 patients with non-small cell lung cancer. The samples were taken before, during, and after treatment, then run through a sequencer that analyzed them for DNA containing tumor-specific mutations. To eliminate false positives due to sequencing errors, the researchers designed a strategy that essentially proofread each DNA sequence by checking the forward and reverse strands against each other. This produced an analysis of ultrafine sensitivity – just one variant in 5,000 molecules – that identified mutant DNA released by the tumors.

The method opens tantalizing possibilities for detecting cancer through blood-borne DNA. The advantages are many, noted Patel. For instance, DNA is highly specific, unlike the protein biomarkers now used to spot some cancers. Most protein biomarkers are present in small amounts even in healthy people, and these biomarkers can sometimes be elevated due to conditions other than cancer. “But it would be very unlikely to find a mutation in a cancer-related gene in someone’s blood if they didn’t have cancer,” Dr. Patel explained. “Tumor-specific mutant DNA in the blood would be highly unusual in a healthy person, so we expect the false positive rate to be very low. Specificity is very important when developing a screening test.”

DNA-testing of blood could also deliver a more comprehensive diagnosis of a patient’s mutation profile. A biopsy provides information about an individual tumor sample, a keyhole view. But what if that tumor mutates? What if the patient has multiple tumors in different phases and locations? A blood-based analysis of DNA mutations may be able to detect all of this, revealing the whole landscape and giving doctors a roadmap to direct treatment. “Based on the mutation profile that you find in the blood,” Dr. Patel said, “you might have enough information to tell you that a certain targeted therapy would be most effective.”

In their paper, Dr. Patel and his colleagues offer some evidence that plasma sequencing might also be used diagnostically to assess whether a treatment has failed, is working, or is losing effectiveness – based on changes in tumor DNA levels in the blood. Dr. Patel is especially excited by the possibility of using this technology for early detection. Most cancers are characterized by distinctive mutations. “People at high risk, such as those with a strong family history of cancer or an extremely smoking history could be tested for a broad panel of tumor mutations. If particular sets of mutations suggestive of cancer were found, the patient could be worked up to determine what is going on. You could use the test to find the needle in the haystack – a small tumor in a more curable stage.”

He and his collaborators are now widening their search for mutations found in other cancers, including colorectal, pancreatic, and ovarian cancers. He believes they eventually will be able to test for many others. The sequencing costs have dropped to less than $100 per sample and will keep dropping. Dr. Patel cautions that much remains to be done before the test reaches the clinic, but the potential to help patients is clear. “My hope is that eventually blood-based DNA testing may become a routine part of an annual physical.”