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Liquid Biopsies / A New Way to Diagnose, Understand & Track Cancer

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LIQUID BIOPSIES LOOK FOR DNA FRAGMENTS shed by dying tumors that are circulating in the blood stream. Analysis of this cell-free circulating tumor DNA helps clinicians determine if cancer cells are present, what kind of cancer it is, if the cancer has metastasized or recurred, if it has any of the known genetic mutations that are targets for specific drug therapies, or how it is responding to treatment. That makes liquid biopsies another giant step towards personalized or "precision" medicine. While most liquid biopsies use blood or plasma, researchers also work with saliva, urine, cerebrospinal fluid that bathes the brain and spinal cord, fluids obtained from pancreatic cysts, and Pap and fecal smears.

WHAT CAN LIQUID BIOPSIES DO TODAY?

Liquid biopsies non-invasively detect a cancer-related genetic profile. With this information, oncologists quickly assign patients to an appropriate treatment regimen using therapies targeted to the specific genetics of the tumor. Because liquid biopsies are a non-invasive and low-risk procedure for patients, they can be used to routinely monitor therapeutic responses over time and detect if cancer recurs.

Take a patient with non-small cell lung cancer (NSCLC), the most common type of lung cancer (85 percent of cases). A liquid biopsy of the patient's blood indicates a genetic mutation in the epidermal growth factor receptor (EGFR). EGFR mutations are the most common gene mutation in lung cancer. They can cause uncontrolled growth and spread of cancer cells while blocking signals that normally cause abnormal cells to self-destruct. Fortunately, scientists have developed anti-cancer drugs for tumors with specific EGFR mutations. These anti-cancer drugs selectively attack only those tumor cells with that specific EGFR mutation and inhibit their growth and replication.

Some NSCLC patients have EGFR mutations for which there is no targeted anti-cancer treatment. Accurately determining the mutation profile of the cancer-causing gene is critical to selecting the right course of clinical care. Sometimes, the personalized anti-cancer drug therapy stops killing tumor cells even though the treatment had been effective previously. This can be due to additional gene mutations or other factors.

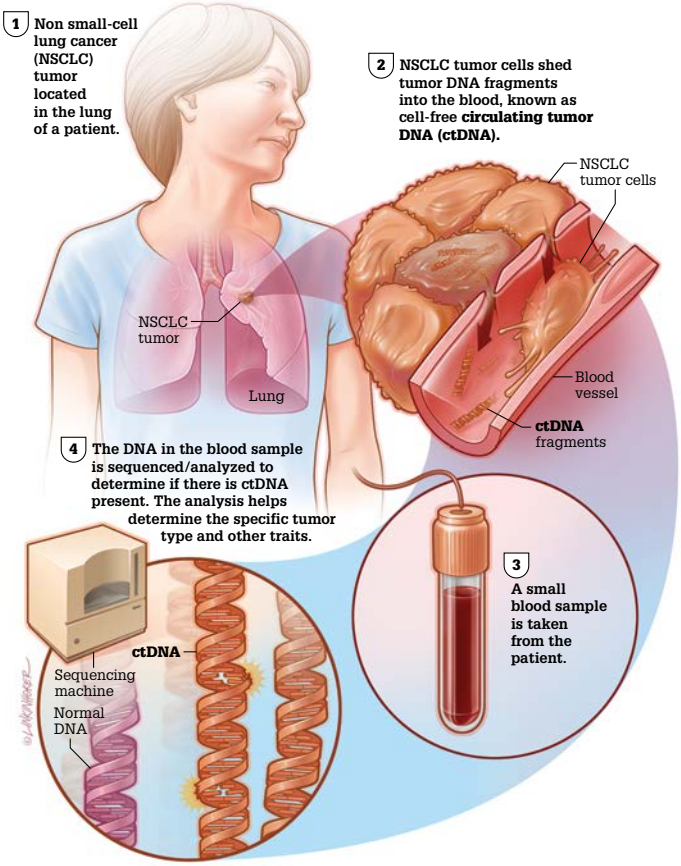

FIGURE 1 / The liquid biopsy in non-small cell lung cancer treatment
Illustration: © Michael Linkinhoker, Link Studio, LLC

A traditional tissue biopsy, where a piece of tumor tissue is surgically removed from the patient and analyzed, may take up to two weeks to determine why the drug no longer works. But a liquid biopsy may be able to provide an answer in as little as two days; simply put, this method can be quicker, easier, and cheaper than traditional tissue biopsies.

Liquid biopsies can be used to confirm a suspected diagnosis of cancer, to screen the tumor for specific genetic mutations that may respond to targeted drug therapy, and to track the efficacy of treatment responses over time. Other clinical applications of liquid biopsies are expected to increase markedly over the next five years. For example, the liquid biopsy may be used to discriminate between patients who are completely cured and those with undetectable traces of residual cancer. Regularly scheduled liquid biopsies during routine patient follow-ups could detect early recurrence, enabling prompt treatment for those patients, while avoiding aggressive chemotherapy for others. Liquid biopsies may also be used to differentiate slow-progressing tumors from aggressive ones and are emerging as a new tool to screen individuals at high risk for certain cancers.

HOW DO LIQUID BIOPSIES WORK?

Cancer develops from a series of genetic alterations in DNA that are acquired by tumor cells. Unlike hereditary mutations that pass from parent to child and are present in every cell in the body, alterations that form in the DNA of cancer cells are present *only* in cancer cells. These alterations can be used as a fingerprint to detect, characterize, and track cancer (Figure 1).

Traditional biopsies are invasive and even dangerous for some very ill patients. Sometimes they are unsuccessful, especially if the tumor is hard to reach or if little tumor tissue is available to remove. But in a liquid biopsy, body fluid, commonly blood, is obtained. Then, a test

identifies and measures the small pieces of tumor DNA that are present in the sample. These tumor DNA fragments, which are released into the bloodstream when a tumor cell dies, are referred to as cell-free **c**irculating **t**umor DNA (ctDNA). Healthy cells also release DNA into the blood stream as a consequence of normal cell death, and this larger fraction of circulating DNA is known as **c**ell-**f**ree DNA (cfDNA).

Identifying ctDNA in a cancer patient is like sifting through a haystack to find a needle; ctDNA from tumor cells typically accounts for about one percent of all cfDNA from healthy cells. However, emerging developments in gene sequencing technology have made it possible to identify the millions of short DNA fragments circulating in the blood and recognize the specific mutations found in ctDNA. These specific ctDNA mutations serve as a signature or genetic fingerprint marking the presence of a specific type of tumor.

better with immunotherapy, but knowing in advance who will respond to treatment has been impossible. Using traditional methods, indications of a successful treatment response can take up to two months to detect. In the NCI report, using liquid biopsies to measure ctDNA provided an answer much more quickly, allowing patients who did not benefit from immunotherapy to be switched to a different therapy.

Additional research is underway to test if liquid biopsies can use different types of fluids to detect cancer in other bodily systems. These include saliva to detect cancers of the mouth and esophagus that are associated with human papillomavirus, cerebral spinal fluid to detect tumor cells in glioblastoma (a common type of brain cancer), fluid from Pap smears to detect ovarian and endometrial cancer, cystic fluids to detect pancreatic cancer, and urine to test for prostate and urological cancer.

WHAT IS THE FUTURE AND HOW DO WE GET THERE?

The holy grail of cancer research has long been pre-emptive diagnosis – cancer detected before symptoms begin. With earlier detection, treatment is more effective, especially for the "silent" cancers that are often in late stages by the time symptoms appear (e.g., ovarian and pancreatic cancer). Despite its appeal, researchers admit that liquid biopsy for general clinical use is still in its infancy and not yet effective as a screening tool. Furthermore, oncologists and researchers have not developed uniform practices to standardize how liquid biopsy tests are performed or how the data is interpreted.

Pancreatic cancer, for example, often progresses markedly before diagnosis. Currently, liquid biopsies can track treatment response in pancreatic cancer, but the tests are not accurate for clinical screens. To address this, scientists at the National Institutes of Health (NIH), the National Institute of Standards and Technology, pharmaceutical companies, and technology companies are building a library of standardized genetic signatures of tumor DNA in cancer. The hope is that this library could be used in liquid biopsies to accurately detect disease in clinical screens, particularly for "silent" cancers.

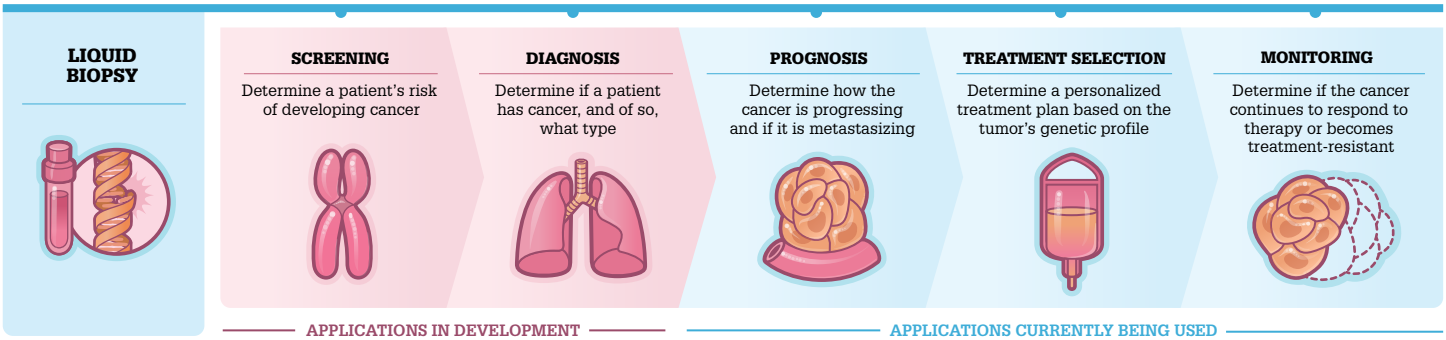

FIGURE 2 / Applications of the liquid biopsy. *Illustration: © Michael Linkinhoker, Link Studio, LLC*

The goal is to find those mutations for which a drug-based treatment plan has been developed. Physicians can use this information to help determine the most appropriate course of therapy for the patient. A liquid biopsy test may also measure the *amount* of ctDNA present in the fluid sample, which is associated with the cancer stage and disease prognosis.

Lung cancer was the first clinical oncology application of the liquid biopsy. Many investigators are now exploring how liquid biopsies can be used to treat other types of cancers, such as breast cancer and gastrointestinal cancers. A recent pilot study at the National Cancer Institute (NCI) suggested that liquid biopsy results can quickly indicate whether immunotherapy, a type of treatment that boosts the body's natural defenses to fight cancer, is working. For example, about 20 percent of patients with metastatic melanoma get

WHAT GIVES LIQUID BIOPSY ADDED VALUE OVER TISSUE BIOPSY?

Tissue biopsy remains the gold standard for determining the presence of cancer and characterizing its features, but this method has limits. Since some tumors have varying genetic aberrations in different regions, a biopsy of tissue from one part may fail to capture genetic changes in another only millimeters away. Furthermore, a one-time tissue biopsy can miss genetic changes taking place as a tumor progresses, metastasizes, or mutates in response to treatment.

Traditional tissue biopsy can be painful, risky, and expensive. For these reasons, oncologists do not routinely use tissue biopsy to follow-up for cancer recurrence, or as part of the watchful waiting of a slow-growing pre-cancer. Non-invasive liquid biopsies are beginning to address these issues.

With support from NIH and other federal agencies, as well as investments by the private sector, basic science researchers are joining forces with physician-scientists to increase the routine use of the liquid biopsy in medical practice (Figure 2). As a new monitoring tool for disease progression and response to therapy, liquid biopsies have advanced cancer management in a remarkable way. This technology should complement existing approaches that utilize surgery, radiation, chemotherapy, and immunotherapy to transform health outcomes and save lives.

Horizons in Bioscience is a product of the Federation of American Societies for Experimental Biology (FASEB) and describes scientific discoveries on the brink of clinical application. These two-page documents are intended to supplement our longer series of illustrated articles, ***Breakthroughs in Bioscience***. Free printed copies may be ordered, and electronic versions of the full series may be found on our website: www.faseb.org/breakthroughs