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Liquid Biopsy: A Minimally Invasive Diagnostic Tool to Identify and Characterize Cancer Cells

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Editorial

A tissue or cell biopsy has been the gold standard for diagnosing and staging neoplastic disease. It involves the extraction of sample cells or tissues that are then microscopically examined by a pathologist. A core biopsy involves surgical removal of abnormal tissue without removal of the entire tumor. If the biopsy is removed without preservation of the tissue histology, it is done *via* needle aspiration. The surgical removal of biopsy tissue has the limitation that some patients may not be good candidates for surgery and the needle aspiration biopsy may be imprecise and painful. Some patients' cancers may be inaccessible to surgical biopsy. Thus, researchers have sought a simpler alternative to surgical biopsy.

The liquid biopsy offers an alternative to the drawbacks of the surgical biopsy. A liquid biopsy is a minimally-invasive alternative and has been advanced with the development of newer molecular techniques. It relies on analyzing tumor cells or bits of tumor materials (cancer biomarkers) that may be found in bodily fluids, primarily blood but may include urine, saliva, cerebrospinal fluid, or seminal fluid [1]. The liquid biopsy samples are analyzed for tumor DNA, RNA, proteins, exosomes, and cells. Liquid biopsy can be tailored to monitor the disease, detect resistance mutation, and tumor recurrence [2]. The accuracy of the test is enhanced by Polymerase Chain Reaction (PCR)-based methods, DNA sequencing, and digital PCR.

The first FDA approved liquid biopsy test in 2016 was a diagnostic test called cobas© EGFR mutation test v.2 for metastatic Non-Small Cell Lung Cancer (NSCLC) [3,4]. The cell-free DNA (cfDNA) from a small (5 ml) blood sample obtained by venipuncture was tested for Epidermal Growth Factor Receptor (EGFR) exon deletion or L858R mutations. These mutations occur in 10% to 35% of patients with NSCLC and identify those patients who may be responsive to erlotinib or gefitinib therapy, both receptor tyrosine kinase inhibitors that interrupt signaling through EGFR in target cells and are only effective in mutated or hyperactive EGFR.

Another minimally-invasive blood test called CancerSEEK can detect cancers of the ovary, liver, stomach, pancreas, esophagus, colorectal, lung or breast [5]. This test overcomes many of the limitations of previous liquid biopsies such as identification of the underlying tissue of origin and early stage detection when patients may harbor less than one mutant template molecule per milliliter of plasma. Because of the latter, the investigators designed a multiplex PCR-based assay that would simultaneously assess multiple regions of driver genes that are commonly mutated in a variety of cancers. Each base flagged in the test must be sequenced thousands of times to detect low prevalence mutations. On the basis of preliminary data and publicly available sequencing data, a 61 amplicon panel was designed with each amplicon querying an average of 33 base pairs within one of 16 genes. The test featured not only the presence of ctDNA mutation but elevations of cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA 19-9), prolactin (PRL), hepatocyte growth factor (HGF), osteopontin (OPN), myeloperoxidase (MPO), and Tissue Inhibitor of Metalloproteinases 1 (TIMP-1) protein levels. Overall CancerSEEK detected cancer with a sensitivity of 69 to 98%, depending upon cancer type, with 99% specificity.

Although not employing molecular techniques, but bearing the name "Liquid," Liquid-Based Cytology (LBC) is a new technology for alternative and complimentary screening of cell alterations in the cervix [6,7]. Cervical cancer is the number two cause of cancer mortality in females. Liquid-based cytology was approved by the FDA in 1996 and today about 80% of cervical cytology tests in the U.S. use the liquid base. Cervical cells, obtained from *Pap* smear brushings are immersed in a conserving liquid from which a monolayer of cells is fixed on a slide, ready for microscopic examination after staining. This avoids desiccation and reduces the quantity of interfering materials. Any Papanicolaou stain can be utilized although several automated proprietary devises and stains are available. The correlation and validation of LBC and histopathological diagnosis remain an area of interest.

In this issue of the journal, Areeuk and Manchana have examined the correlation between squamous cell abnormalities by liquid-based cytology and histopathology in a Thailand population [8]. Despite the validation of LBC tests in many studies, these researchers found only a moderate correlation between LBC and Colposcopic examination and biopsy. The accuracy of LBC for detecting cervical squamous cell abnormalities was 79.8% and the authors recommend that, despite acceptable accuracy of cervical LBC, it should be used only as a screening test and that pathological confirmation should be made before definitive management decisions made. This is a similar conclusion that has been made for molecular liquid biopsies for cancers although the authors conclude that Liquid biopsy tests are likely to become an additional standard for monitoring genomic alterations over tumor evolution during exposure to targeted therapies [9].

Nevertheless, the rapid application of developing molecular techniques to solve shortcomings of the liquid biopsy tests bodes well for the future detection of early-stage cancer, the selection of efficacious treatment protocols, and tracking of disease progression. The proof in the pudding will be whether these tests will extend patient survival. Currently there are about 100 commercial laboratories worldwide working on these problems as well as the application of liquid biopsy tests to monitor transplant patients; to identify bacteria, viruses, fungi, and parasites in hospitalized patients; patients with emerging diabetes who have elevated cfDNA from dying pancreatic cells-an early flag to incipient pancreatic disease; TB; Down's Syndrome; Sickle Cell Anemia; and determine brain damage suffered after a heart attack, to name a few

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[10]. The market for liquid biopsy is projected to reach multi-billion dollar levels by the mid-2020s. University of Washington geneticist, Jay Shendure, has envisioned that the techniques of liquid biopsy will represent a molecular stethoscope for the next 200 years [10].

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