**Editorial**

# Liquid biopsy: An Ideal Cancer Biomarkers

**Cheah Yoke Kqueen[1,2,3]**

*[1]Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.*
*[2]Centre for Diagnostic Nuclear Imaging, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.*
*[3]UPM-MAKNA Cancer Research Laboratory, Institute of Bioscience, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia.*

Liquid biopsy is a term used for liquid specimen other than tissue such as whole blood, serum, plasma, sputum, urine, saliva, pleural fluid, peritoneal fluid, tears, amniotic fluid, breast milk, bronchial lavage, colostrum and cerebrospinal fluid. Liquid biopsies are generally considered non-invasive and useful in molecular diagnostics (1). Cell-free DNA (cfDNA) also known as circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) are the two main types of biomarkers found in liquid biopsies. Circulatory tumor DNA are small DNA fragments that are shed by the tumor into the bloodstream and 100 times more abundant than the CTCs. Liquid biopsies provide valuable information for clinicians using targeted therapies to treat cancer because they consist information of tumors that developed resistant to a particular therapy.

According to the National Cancer Institute, a biomarker is "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition disease (2). Biomarkers are useful for diagnostics, prognostics, therapeutics and theranostics. The ideal biomarker should be non-invasive, inexpensive, highly specific, translatable from model systems to humans, and reliable (1). ctDNA perform better than protein biomarkers because of false positives rarer with ctDNA and has a half-life of less than two hours, so it gives a clearer view of a tumor's present, rather than its past (3).

The cost of a liquid biopsy is cheaper than the invasive procedures and processing of dissected tissue in traditional tissue biopsy. However, liquid biopsy cannot replace a tissue biopsy when it comes to an initial diagnosis of cancer. When a patient's treatment proceeds, then the liquid biopsy will be very useful because ctDNA provides an easier way to keep track of the treatment to check if the tumor had mutated and resistant to the treatment. The Cambridge and Johns Hopkins teams found that ctDNA is more sensitive than protein biomarkers in breast (4) and bowel (5) cancer. Both teams also demonstrated that ctDNA was more sensitive than CTCs. Next Generation Sequencing (NGS), microarray, realtime Polymerase Chain Reaction and digital Polymerase Chain Reaction are among the common reliable tools to identify both sensitizing and resistance gene mutation of druggable targets.

The US Food and Drug Aministration (FDA) has approved the first liquid biopsy (blood-based) for EGFR in Non-small Lung Cancer (NSCLC). It was designed to be used as a companion diagnostic for erlotinib, the cobas EGFR MutationTest v2 detects specific NSCLC mutation, such as the exon 19 deletion or exon 21 (L858R) substitutions (6). Tarceva was approved by FDA in 2004 to treat patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen, and in 2013, the FDA approved it for the first-line treatment of patients with metastatic NSCLC whose having EGFR exon 19 deletins or L858R substitution mutations as detected by an FDA-approved test. Tarceva is not recommended for use in combination with platinum-based chemotherapy and the drug has not been evaluated as first-line treatment in patients with metastatic NSCLC whose tumors indicated EGFR mutation other than exon 19 deletions or L858R substitution mutations. The ctDNA detection of EGFR T790M mutation will be highly useful for the osimertinib (third-generation EGFR tyrosine inhibitor (TKI) drug) treatment for patients with metastatic NSCLC. On the other hand, one of the largest cancer genomics studies conducted analysed blood samples from more than 15,000 patients and 50 different tumor types. Moreover, results presented at the 2016 American Society of Clinical Oncology Annual Meeting, confirmed the concordance of genetic changes in circulating tumor DNA with traditional tumor biopsies (7).

The issues need to be addressed before implementation of ctDNA analysis into the clinical decision includes: (i) time point of sampling. (ii) understanding of clinical relevance data when incorporation NGS techniques. (iii) masking of normal ctNA released by dying normal cells (during treatment e.g. chemotherapy, infections) that might lead to false-negative results. (iv) benign tumors (e.g. skin tumors) that carry cancer-associated mutations which contribute to false-positive findings (2).

*Corresponding Author: Cheah Yoke Kqueen
ykcheah@upm.edu.my

## REFERENCES

1 Weber JA, Baxter DH, Zhang S, et al. The MicroRNA spectrum in 12 body fluids. Clin Chem. 2010; 56(11): 1733-1741.

2 Henry NL and Hayes DF. Cancer biomarkers. Mol Oncol. 2012; 6(2): 140-146.

3 Yong E. Cancer biomarkers: Written in blood. Nature. 2014; 511(7511): 524-526.

4 Bettegowda C, Sausen M, Leary RJ, et al. Detection of circulating tumor DNA in Early- and Late- stage human malignancies. Sci Transl Med. 2014; 6(224): 224ra24.

5 Dawson SJ, Tsui DWY, Murtaza M, et al. Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer. N Engl J Med. 2013; 368: 1199-1209.

6 FDA approves first blood test to detect gene mutation associated with non-small cell lung cancer [news release]. Silver Spring, MD: U.S. Food and Drug Administration; June 1, 2016; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm504488.htm

7 Zill OA, Mortimer S, Banks KC, et al. Slmatic genomic landscape of over 15,000 patients with advanced-stage cancer from clinical next-generation sequencing analysis of circulating tumor DNA. Paper presented at: 2016 Annual Meeting of the American Society of Clinical Oncology; June 2016; Chicago, IL.