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Editorial

Cell-Free Circulating DNA in the Diagnosis of Cancer

Toshiro Ito*

Temasek Life Sciences Laboratory (TLL), 1 Research Link, National University of Singapore, Singapore 117604, Singapore

EDITORIAL NOTE

Circulating cell-free DNA (cfDNA), unconfined from normal and cancerous cells, is an exciting new biomarker. Circulating tumor DNA (ctDNA) usually covers genetic changes that could be useful for detecting cancer. ctDNA has supplementary important applications, including prognosis, monitoring therapy and estimating tumor volume. These applications are less controversial than early cancer discovery, and are used extensively in research settings. The cancers were always diagnosed clinically or through imaging. Previously, we calculated tumor size, expected amount of ctDNA in a 10-ml blood draw, ctDNA fraction (percentage of ctDNA compared to total cfDNA; this is equivalent to mutant allele fraction, MAF), number of saved genomes per 10 ml of blood, and likelihood of tumor detection with ctDNA genomic analysis.

ctDNA technologies are unlikely to detect tumors smaller than 10 mm in diameter because not enough ctDNA is saved for analysis. Cell-free DNA analysis cannot usually specify the pretentious organ/tissue in asymptomatic individuals. A positive result must be followed with costly, invasive, stressful, and potentially ineffective tests to identify the primary lesion. Recently cell-free DNA fragmentation length and position within the genome to diagnose cancer through low-depth genomic sequencing of multiple 5-megabase areas.

Cancer-derived cell-free DNA is generally shorter by about 3-6 bases, and the lengths of tumor derived fragments are more variable than those found in controls. Notably, instead of examining one or a few genetic changes found only in cancer-derived DNA, they employed artificial intelligence to examine the whole spectrum length, variation and position, inferring if the pattern is cancerous. They reported compassions from 236 patients with various cancers ranging from 57 to 99% at 98% specificity. New cancer detection tests have the highest clinical value when they can classify cancer at an early, asymptomatic stage, when the chances of cure are highest.

The sensitivity proof-of-concept assay for detecting early stage, asymptomatic tumors (population screening) is unknown, since they only used clinically detected cancers. As demonstrated by GRAIL, sensitivity differed according to clinical versus screening detection. Sensitivity, specificity, as well as positive and negative predictive values, should be reported in future studies employing this test to account for disease prevalence. Perhaps another way to authenticate these new technologies across the course of cancer diagnoses, which has not yet been widely explored, is to analyse samples collected longitudinally through randomized trials.

Markers such as CA 125, with 80% sensitivity in detecting clinical disease, deteriorate to less than 50% sensitivity in asymptomatic patients. Future studies should use longitudinal samples for more realistic estimations of sensitivity and specificity and lead time calculation for cancer detection between asymptomatic and symptomatic stages. It demonstrates proof of concept, and does not yet comprehensively address the difficulties associated with initial cancer detection. The sensitivity of this new approach and other similar methods should be confirmed in the future with experiments involving tumours of known MAF. Pre-diagnostic samples should be tested to calculate both sensitivity and lead time before clinical diagnosis, to determine if the lead time achieved with early detection using ctDNA effects patient outcomes.

Correspondence to: Toshiro Ito, Temasek Life Sciences Laboratory (TLL), 1 Research Link, National University of Singapore, Singapore. E-mail: itotosh@gmail.com

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