Reviewer’s report

Title: Emerging concepts in liquid biopsies

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Reviewer: Kikuya Kato

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This review introduces a current topic of cancer research, i.e., liquid biopsy. Although the review covers a substantial body of literature, it includes only a limited number of literatures from journals on clinical studies, and thus, it is not an appropriate source of information.

The following two points need specific attention:

1. In the treatment of lung cancer, the clinical application of liquid biopsy is more advanced than is recognized by the author.

Osimertinib, a third-generation epithelial growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), should only be administered to patients with T790M mutation-positive lung cancer. T790M is a mutation that confers resistance to first-generation EGFR-TKIs, namely gefitinib and erlotinib. Detection of the T790M mutation requires re-biopsy, but owing to the invasive nature of lung biopsy, liquid biopsies would be highly beneficial. The cobas EGFR Mutation test version 2 for T790M has been approved in US and Japan for detecting this mutation, despite the lack of evidence.

The geographical location of the researchers may also affect their recognition of the clinical application. EGFR-mutation positive lung cancer accounts for ~40% of lung adenocarcinoma in the Asian population, but only ~10% in the Caucasian population. Thus, EGFR-TKIs are an important treatment option for advanced lung cancer in Japan, but not necessarily in other countries. A next-generation sequence-based detection system (Uchida et al. Clin Chem. 2015 61(9):1191-6) is already commercially available in Japan (although still not approved). On the other hand, AstraZeneca withdrew osimertinib from the German market as a result of cost negotiations.

2. In addition to spontaneous somatic mutations in normal cells, DNA damage during the experimental process should be considered as a cause of background variants, i.e., low frequency variants in normal individuals. This is a serious problem in laboratories, but is rarely described in literature. Some description is found in the second paper of CAPP-seq.

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