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Liquid biopsy: Rapid plasma-based genotyping of cancers

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Although targeted therapies have markedly changed the treatment of cancer over the past 10 years, issues remain for tumor heterogeneity and molecular evolution, costs and potential morbidity of biopsies, and technical limitations of molecular tests. To overcome these issues, methods will be needed for a rapid, cost-effective, and noninvasive identification of biomarkers at various time points during the course of disease. One alternative to overcome the limitation of repeated sampling is the analysis of circulating cell-free DNA (cfDNA). Recent progress in cfDNA analyses now allows the monitoring of tumor genomes by noninvasive means. Multiple studies have shown that it is possible to reconstruct tumor genomes from plasma DNA.

There are many biological and technical aspects as well as challenges for a widespread implication of cfDNA in cancer diagnostics. The length of cfDNA is quite short around 168 bp, and recent studies with high-throughput sequencing presented that that more than 80% of cfDNA fragments in cancer patients' plasma were below 145 bp, reflecting the high degree of fragmentation through apoptotic mechanisms. Furthermore, cfDNA is rapidly cleared in plasma, liver, spleen and kidney with half-life beiong estimated to 16 minutes. Therefore, immediate sample processing or use of specific tubes with preservative solution is strongly recommended. Owing to the high degree of fragmentation and its low concentration in the circulation, detecting tumor-derived cfDNA requires specific techniques and many sensitive assays such as digital droplet PCR (ddPCR), beads, emulsions, amplification, and magnetics (BEAMing) technology, Tagged-amplicon deep sequencing (TAm-Seq), and CAncer Personalized Profiling by deep Sequencing (CAPP-Seq) have been tested for cfDNA. Detecting cfDNA could be utilized in diagnosis of early tumors, detecting mutations as potential therapeutic target, establishing prognosis, and monitoring tumor burden during treatment.

Although the analysis of ctDNA is a promising area, harmonization of preanalytical and analytical procedures is needed to provide clinical standards to validate the liquid biopsy as a clinical biomarker in well-designed and sufficiently powered multicenter studies.

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