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Blood-Based and Urine-Based Liquid Biopsies for Detection and Monitoring of HPV Circulating Tumor DNA in HPV-Associated Head and Neck Cancer Patients

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Abstract

Advances in ctDNA detection using liquid biopsies offer significant potential for early diagnosis and monitoring of HPV-associated head and neck cancers. However, standard plasma ctDNA assays for human papilloma virus (HPV)-associated oropharyngeal squamous cell carcinoma (HPV+ OPSCC) often lack sufficient sensitivity, in part due to highly fragmented cell-free DNA (cfDNA) and the inherent limitations of conventional single-probe assays targeting short genomic regions. To address these, we developed a droplet digital PCR assay called 'CHAMP-16', designed to target nine regions across the HPV16 genome. Compared to single-probe assays, CHAMP-16 assay demonstrated markedly increased analytical sensitivity along with superior performance in clinical validation with HPV-positive OPSCC patient plasma samples. We also developed an expanded version of the assay called 'MyHPVscore', using a pool of single-probe assays to detect other high-risk HPV types (HPV18, HPV31, HPV33, HPV35 and HPV39). This blood test has shown promising results, enabling detection of HPV ctDNA approximately 5.5 months before conventional clinical methods during patient relapse monitoring.

Complementing this innovation in plasma-based testing, we explored urine-based ctDNA detection through analysis of "trans-renal" cell-free tumor DNA (TR-ctDNA), which transits from blood into urine and enables non-invasive monitoring even for non-urologic cancers. Our study using single-stranded urine DNA sequencing revealed that TR-ctDNA fragments are predominantly ultra-short (<50 bp), and likely to be missed by conventional ctDNA assays. To address this limitation, we designed an ultra-short fragment-compatible ddPCR assay (42 bp) for HPV TR-ctDNA detection in HPV+ OPSCC patients, yielding substantially improved sensitivity and concordance with plasma ctDNA in clinical validation, even in early-stage patients using remote, at-home urine sample collection.

Together, these innovations illustrate not only how multiprobe assays can dramatically enhance ctDNA detection, but also how these approaches can broaden access to care, particularly for underserved populations. Our findings pave the way for economically viable screening, and post-treatment monitoring strategies in HPV+ OPSCC and potentially other cancers in the future.