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Effective Clinical Follow-Up for ctDNA Multi-Cancer Early Detection Test: A Peer-Reviewed Study of Post-Test Standard Operating Procedure and Real-Life Results

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Cancer Screening World-wide Background

Current cancer screening methods are predominantly organ-specific, utilizing diagnostic imaging tests with multiple modalities.

Limitation of current screening methods, such as low sensitivity and specificity, not only lead to missed cancers at intervenable stages (false negatives) [1] or unnecessary interventions on cancer-free individuals (false positives) [2] but also contribute to patient anxiety.[1]

Delayed the invasive nature of some screening methods can further deter patients from adhering to their recommended screening schedules.

71% cancer deaths are caused by cancers without recommended screenings. [3]

Multi-Cancer Early Detection Test: Performance & Challenges

The performance of Multi-cancer early detection tests like SPOT-MAS has been proven in **multiple studies and a clinical validation involving 9,024 participants**[4]**.** This test **incorporates next-generation sequencing (NGS) and AI technologies** to analyze the methylation profile and multiple features of ctDNA, enabling early detection for the most common and aggressive cancers[5] from a single tube of blood.

Notable Benefits

- Convenience: one single blood draw during a healthcare visit.
- High accuracy: high specificity limits false positive and unnecessary work-up.
- Early Detection: the potential to identify cancer signals at an early stage, before clear symptoms have manifested.
- Assurance: the capability to test for cancers that do not have recommended screenings, and to act as a navigation tool for diagnostic imaging, thereby improving early detection opportunities.

Key Challenges

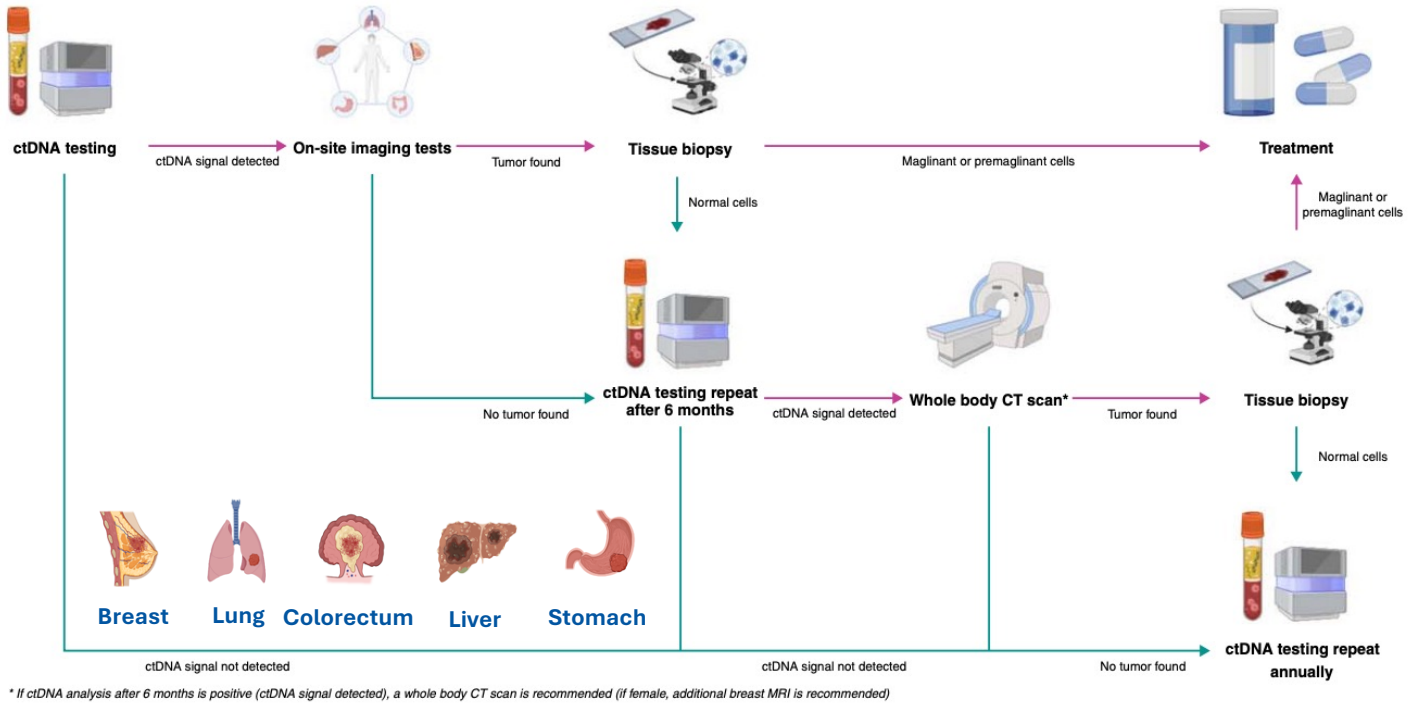
Results follow-up: Positive ctDNA analysis results need confirmation through recommended cancer diagnostic imaging methods. Additionally, post-test counseling and monitoring have revealed emerging situations where there is discordance between the results of ctDNA analysis and diagnostic imaging. These discordances complicate the interpretation of results and raise questions about the application of the test in clinical practice.

A standard diagnostic follow-up protocol to evaluate the performance of an MCED test is needed to improve the clinical utility and widespread adoption of SPOT-MAS test.

Establishing a Standard Operating Procedure (SOP) in K-DETEK study

In this study, we developed a consultation and work-up protocol to achieve definitive diagnostic results for individuals undergoing SPOT-MAS tests. The protocol was created in accordance with **professional guidelines** and the **consensus of an advisory board** to assist general practitioners in accessing, interpreting, and managing SPOT-MAS results.

Figure 1 (A). The process of SPOT-MAS assay Standard operating procedure for positive and negative results of 05 common cancers: **Breast, Lung, Colorectum, Liver, Stomach.**



- The SOP is designed to ensure diagnostic resolution within 12 months after a positive ctDNA signal. It includes consultation pathways, supported by process diagrams, which guide clinicians in interpreting SPOT-MAS results. This involves **imaging diagnostics and biopsies** for suspected cancer cases, following guidelines from the **National Comprehensive Cancer Network**. In the event of a negative result, routine health check-ups and cancer screenings are recommended.
- All research team members at hospitals and institutions participating in the K-DETEK study **are thoroughly trained** for this SOP. This approach ensures that the appropriate steps are taken to achieve diagnostic resolution within the specified timeframe while providing **comprehensive support and consultation** for the patients undergoing ctDNA analysis.
- To demonstrate the utility of this SOP in providing definitive diagnostic results to participants undertaking the SPOT-MAS test, the study also presents **a series of clinical cases** recorded in the K-DETEK study.

Six clinical cases including five true positive cases and one false positive case

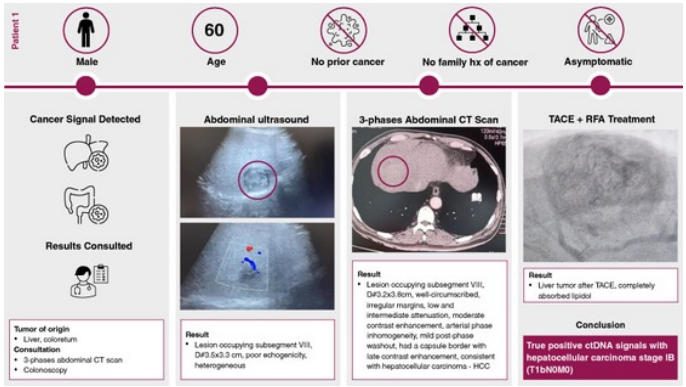


Figure 2. True positive case with stage IB hepatocellular carcinoma.

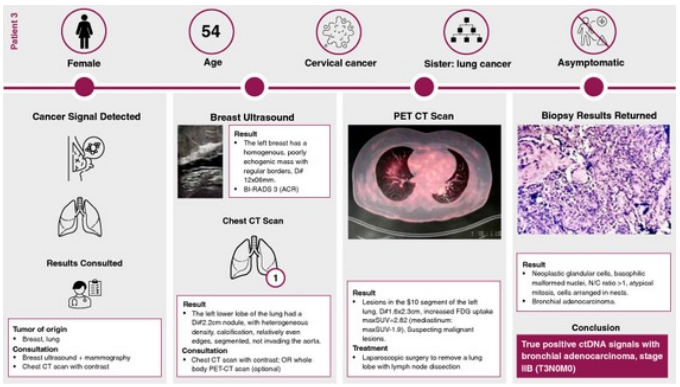


Figure 3. True positive case with stage IIB bronchial adenocarcinoma.

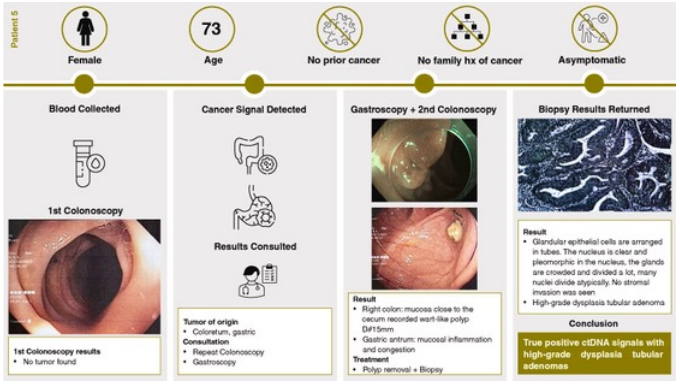


Figure 4. True positive case with high-grade dysplasia tubular adenomas colon polyp.

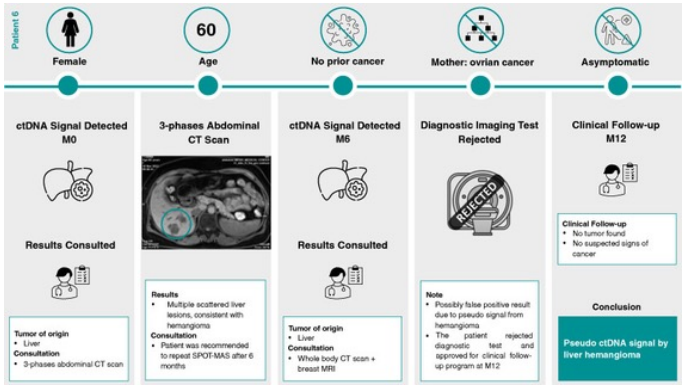


Figure 5. Pseudo ctDNA signal by liver hemangioma.

The results section presents six clinical cases from the K-DETEK study to demonstrate the utility of the SOP in real-world clinical practice. Five cases were confirmed as **true positives**, with tumors found in organs such as **the liver (Figure 2) , lung (Figure 3), breast, colon (Figure 4), and stomach**. One false positive case was also included, highlighting the potential for **benign lesions (Figure 5)** to mimic cancer signals.

True Positives: The five true positive cases demonstrate how the SOP helped identify both **precancerous and malignant lesions using ctDNA analysis**, accurately predicting the tissue of origin and confirming early cancer stages.

False Positives: The false positive case underscores the challenge of **benign conditions**, like liver hemangioma, producing signals similar to cancerous lesions. The SOP's consultation and work-up procedures successfully identified this false positive.

The SOP provides a **structured pathway** for integrating these tests into clinical practice, guiding follow-up diagnostics and **ensuring clarity for both patients and healthcare providers.** It has proven effective in confirming cancer diagnoses and managing precancerous conditions, as demonstrated in several clinical cases.

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