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**Early detection of colorectal cancer using aberrant circulating cell- free mitochondrial DNA fragmentomics**

**Wang S, Peng F, Dang M, et al. Early detection of colorectal cancer using aberrant circulating cell- free mitochondrial DNA fragmentomics. Gut 2025; 74: 961–970. doi:10.1136/gutjnl-2024-333533**

Early diagnosis is key to improving outcomes in colorectal cancer (CRC). Existing tests including faecal occult blood have low sensitivity and specificity in detecting early-stage CRC and advanced adenoma (AA). Emerging biomarkers include cell-free nuclear DNA (cf-nDNA) fragments. As cells die, DNA is cleaved non-randomly; the resulting fragments are released into the bloodstream. Wang et al. had previously established an analytical workflow for circulating cell-free mitochondrial DNA (ccf-mtDNA). This retrospective multicentre study aims to evaluate the ability of their system in detecting CRC and AA.

1147 participants from 5 centres were recruited: 557 with CRC, 112 with AA and 478 healthy controls (HCs). ccf-mtDNA fragment sizes decreased from HC to AA, and from AA to CRC. Significant differences were observed in the nucleotide profiles of fragments between HCs and non-HCs.

Wang et al. developed a model based on these observed differences, discriminating between individuals with CRC and HCs with an AUC (area under the curve) of 0.9863 (p<0.001), sensitivity of 92.7% and specificity of 93.5% in the training cohort; an AUC of 0.9683, sensitivity of 86.0% and specificity of 94.4% in the internal validation cohort; and similar performance in external validation cohorts. This is compared to the sensitivity of 41.5% seen with CEA (Carcinoembryonic antigen) and CA19-9 (Carbohydrate antigen 19-9) in the internal validation cohort. The model also performed well in patients with AA.

This demonstrates the potential of ccf-mtDNA in the early detection of CRC/AA. Limitations include all participants being Chinese, the retrospective study design and questions surrounding the feasibility of widespread analysis of ccf-mtDNA.