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Evaluation of cell-free DNA approaches for multi-cancer early detection

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Background

In the first substudy of the Circulating Cell-free Genome Atlas (CCGA) study (NCT02889978; Sep 2016), cfDNA multi-omics were evaluated in prototype cfDNA-based MCED tests.

Methods

Plasma and matched white blood cells (WBCs) were collected and sequenced from CCGA participants. Where available, tumor biopsies were also sequenced. Six cfDNA-omics were used: whole-genome (WG) methylation data from WG bisulfite sequencing (30×); small somatic variant data from error-corrected targeted sequencing (TS; 60,000×); and somatic copy-number aberration (SCNA), fragment length, fragment endpoint, and allelic imbalance data from WG sequencing (WGS; 30×). Samples were split into independent training (T) and validation (V) sets and 10 classifiers were trained to detect solid cancer (carcinomas, sarcomas, lymphomas): 1 per -omic, 2 corrected for clonal hematopoiesis (CH) using germline DNA from paired WBC sequencing, 1 pan-omics, 1 clinical data only. These were assessed for cancer detection and clinical limit of detection (cLOD), which was estimated as the probability of detecting cancer as a function of circulating tumor fraction (cTF) using matched tumor biopsies. Three additional classifiers (each using WG methylation, TS, or SCNA) were trained to predict cancer signal origin (CSO) and were assessed for accuracy.

Results

Of 2,800 participants, 2,261 (1,414 T; 847 V) had analyzable results. T and V results were similar; all results here are for V. cTF accounted for >72% of the variance in cancer detection scores. The cLOD was >1.5-fold lower for WG methylation than any WGS or TS classifier (even with WBC CH correction for WGS/TS). CSO prediction was >1.8-fold more accurate using WG methylation than TS or SCNA.

Conclusions

The strong correlation between cTF and cancer detection performance suggests that cLOD may be an attractive metric for comparing MCED test performance at equal specificity. Here, a WG methylation assay outperformed WGS or TS without needing additional WBC sequencing for CH. These data informed the design of a significantly improved targeted methylation MCED test for further CCGA substudies to support clinical use.

Clinical trial identification

NCT02889978.

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Legal entity responsible for the study

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Disclosure

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