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Genome-wide cfDNA Fragmentation in Patients with Cancer and Other Diseases

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Introduction

- Genome-wide cell-free DNA (cfDNA) fragmentation patterns have previously been demonstrated to distinguish with high sensitivity and specificity between plasma samples from individuals with and without cancer[1]

Objectives

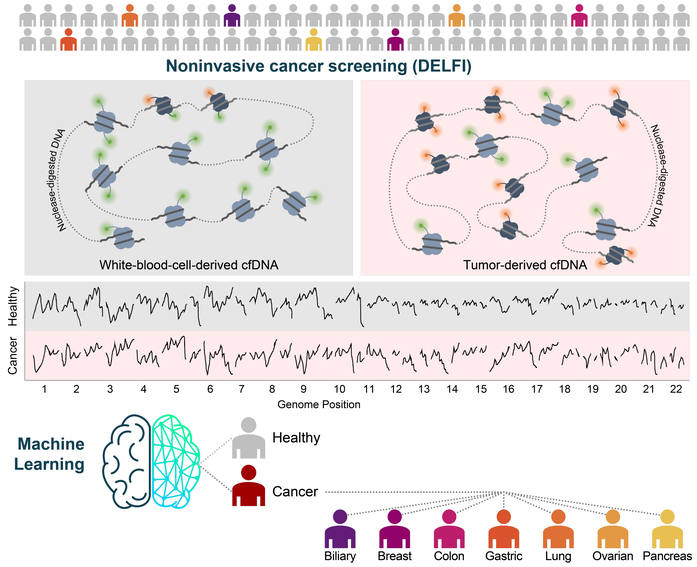
- To evaluate the cfDNA fragmentation assay as a blood-based screening test to detect multiple different solid tumors

Methods

Plasma Samples

- Samples from 281 patients referred to Diagnostic Outpatient Clinic of the Herlev and Gentofte Hospital (Copenhagen University Hospital, Copenhagen, Denmark) due to non-organ specific signs and symptoms of cancer

cfDNA Fragmentation Approach (adapted from Cristiano et al)[1]



- cfDNA fragmentation approach was performed as previously described[1]:
  - cfDNA extracted from plasma, processed into sequencing libraries, examined by low-coverage whole-genome sequencing (WGS), mapped to the genome, and analyzed to determine cfDNA fragmentation profiles across the genome
  - Machine learning used to generate a DELFI score and to classify individuals as healthy or having cancer

Results

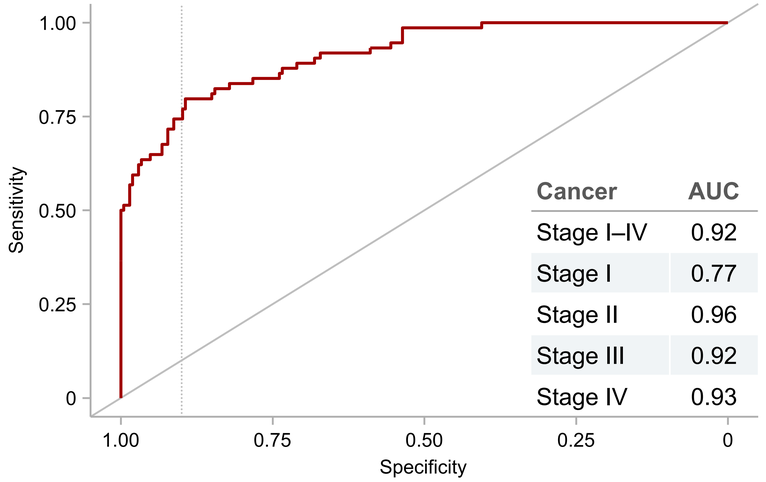
Performance of cfDNA Fragmentation Assay for Noninvasive Detection of Cancer

- Within 3 months of inclusion, 74 patients were diagnosed with 1 of 16 different solid cancers while 207 patients did not have cancer

Cancer	n	AUC	95% CI
All cancers			
Stage I–IV	72	0.92	0.88, 0.96
Stage I–III	24	0.90	0.84, 0.96
Stage IV	48	0.93	0.89, 0.97
Colorectal cancer (Stage I–IV)	12	0.91	0.85, 0.97
Lung cancer (Stage I–IV)	12	0.93	0.86, 1.00
Other cancers	48	0.92	0.87, 0.96

Areas under curves (AUCs) for localized and metastatic cancers and for all stages of colorectal, lung and all other cancers determined using 10-repeat, 10-fold cross validation.

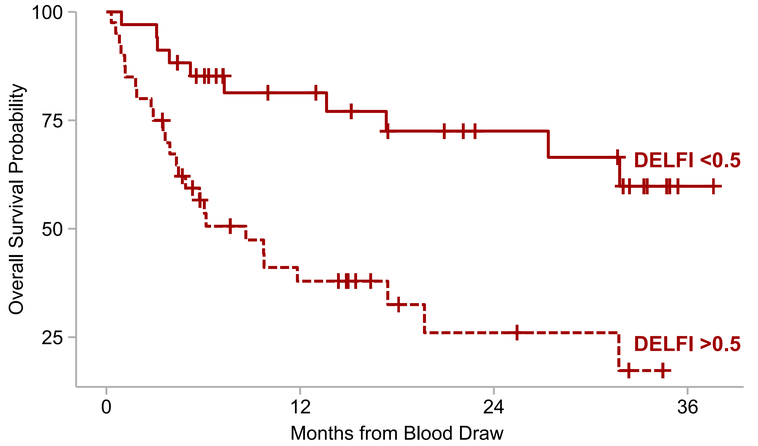
Overall Performance of cfDNA Fragmentation Assay for Cancer Detection



Cancer	AUC
Stage I–IV	0.92
Stage I	0.77
Stage II	0.96
Stage III	0.92
Stage IV	0.93

AUC of receiver operating characteristic (ROC) for analysis of 74 individuals with Stage I–IV cancer and 207 non-cancer controls.

Survival by DELFI Score



- Higher DELFI scores were associated with a decreased overall survival, independent of cancer stage or other clinical characteristics

Conclusions

- This study of prospectively enrolled individuals demonstrated the ability of the cfDNA fragmentation assay to distinguish between individuals with and without cancer
- The assay displayed high performance in a multi-cancer setting using only fragmentation-related information obtained from low-coverage WGS
- Our results suggest that machine learning models can differentiate between cancer and non-cancer despite the presence of common nonmalignant conditions (including cardiovascular, autoimmune, or inflammatory diseases) using cfDNA fragmentation profiles
- Individuals with higher DELFI scores had a worse prognosis, independent of other characteristics
- These data support development of genome-wide cfDNA fragmentation analyses for noninvasive detection of both single and multiple cancers

References: 1. Cristiano S, et al. Nature 2019;570:385-9. **Disclosures:** **J.C., S.J., D.B., M.R., N.C.D.:** Delfi Diagnostics; **A.L.**: founder of Delfi Diagnostics and a consultant for this organization; received honoraria from Amgen, AstraZeneca, Roche; advisor to AstraZeneca, Roche; **J.S.J.:** Nothing to disclose; **R.B.S.**: founder of Delfi Diagnostics and a consultant for this organization; **V.E.V.:** founder of Delfi Diagnostics and Personal Genome Diagnostics, serves on Board of Directors and as consultant for both organizations, and owns Delfi Diagnostics and Personal Genome Diagnostics stock, which are subject to certain restrictions under university policy. Additionally, Johns Hopkins University owns equity in Delfi Diagnostics and Personal Genome Diagnostics. V.E.V. is an advisor to Bristol-Myers Squibb, Genentech, Merck, and Takeda Pharmaceuticals. Within the last five years, V.E.V. has been an advisor to Daiichi Sankyo, Janssen Diagnostics, and Ignyta. These arrangements have been reviewed and approved by the Johns Hopkins University in accordance with its conflict-of-interest policies.

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