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Modeling Cell-free DNA Fragment Size Densities for Non-invasive Detection of Cancer

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Introduction

- Cell-free DNA (cfDNA) is comprised largely of nucleosomal fragments that range in size from 100bp to 220bp
- The relative frequency of short fragments (<150bp) to long fragments (>150bp) across the genome provides a broad characterization of size that has been shown to reflect chromatin organization of blood cells in healthy individuals[1]
- As individuals with cancer often have aberrant fragmentation profiles, DELFI uses the relative frequencies of short and long fragments across the genome as a non-invasive biomarker for cancer detection
- Approaches to characterize the entire distribution of cfDNA fragment length frequencies have not been evaluated as a cancer biomarker

Objective

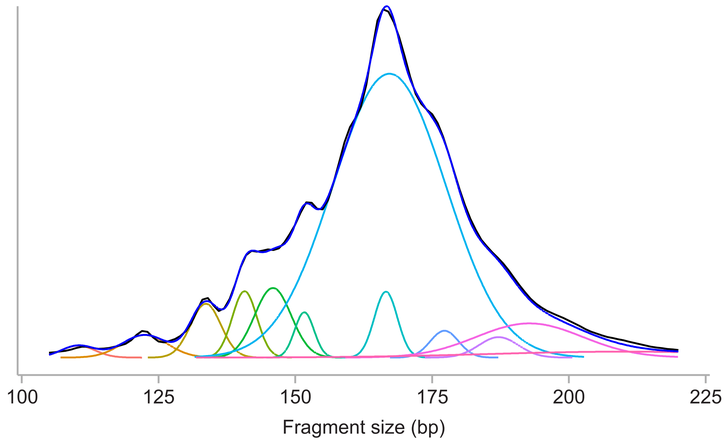
- To evaluate whether modelling the distribution of cfDNA fragment lengths would further improve fragmentation-based approaches for cancer detection

Methods

- We implemented a fully Bayesian finite mixture of truncated normal distributions to approximate the frequency distribution of fragment lengths
- Each mixture component was characterized by a posterior mean, variance, and contribution to the overall mixture
- Posterior means of the mixture model parameters obtained from each participant were used as features in a Gradient Boosted machine learning classifier
- Performance was assessed by ten-fold, ten repeat cross-validation using:
  1) Parameters from mixture model
  2) Genome-wide fragmentation profile approach[1], and
  3) Combination of approaches 1) and 2) as features

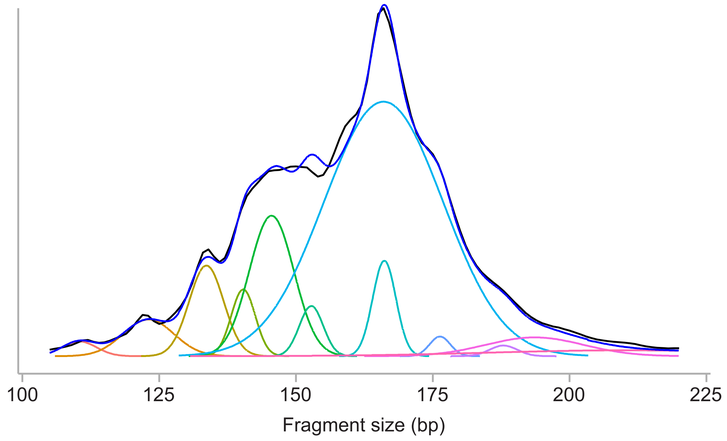
Results

Fragment Length Distribution in a Non-cancer Individual

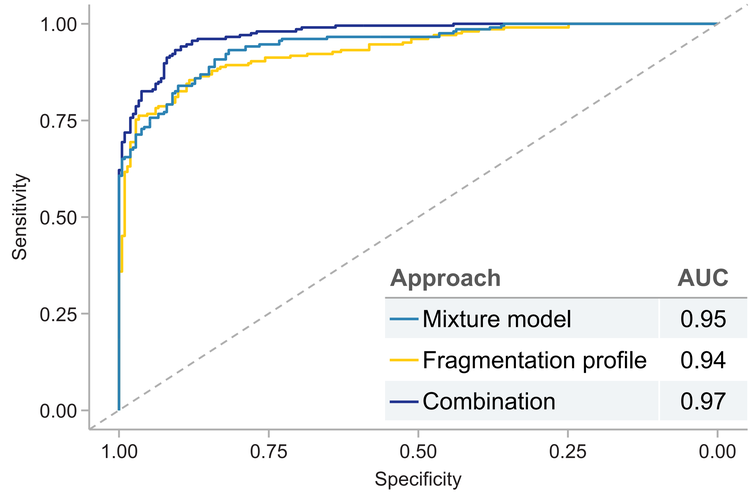


- A 12-component finite mixture model of normal distributions closely approximated the empirical fragment length frequencies for an individual without cancer
- We fit the mixture model independently for 215 individuals with Stage I–IV cancer and 208 non-cancer controls[1]

Fragment Length Distribution in an Individual with Cancer



Cancer Detection with High Sensitivity and Specificity



Area under curve (AUC) of receiver operating characteristic for analysis of 215 individuals with Stage I–IV cancer and 208 non-cancer controls.

Conclusions

- The length and frequency of cfDNA fragments in blood can be closely approximated by a finite mixture model
- Characteristics of the fragment length distributions available from the mixture model can be incorporated directly in a machine learning model to sensitivity detect cancers of all stages at high specificities
- Combining our approach with other fragmentation-based summaries across the genome resulted in improved detection of cancer than either feature alone

References: 1. Cristiano S, et al. Nature 2019;570:385-9.
Disclosures: **J.C., B.C., D.B., M.R., N.C.D.:** Delfi Diagnostics **G.P.:** Co-founder, equity holder in Phaeno Biotechnologies; Scientific Advisory Board of Konica-Minolta Precision Medicine (includes Ambry Genetics and Invicro); consulting for Delfi Diagnostics and Foundation Medicine; **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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