Cell-free DNA for Early Cancer Detection

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Existing approaches to use cfDNA for early cancer detection

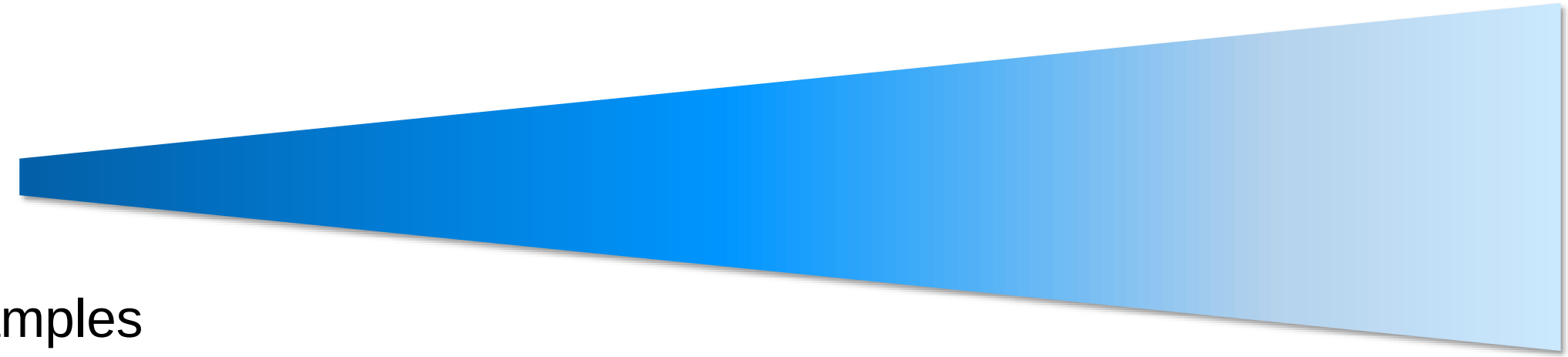
- Methylation
- Fragment length
- Copy number variation
- Microbiome
- SNV

Use cfDNA methylation for cancer detection

- DNA methylation abnormality occurs early in the cancer pathogenesis
- DNA methylation has pervasive feature: enhance the signals
- DNA methylation is tissue-specific: we can predict the cancer site

Landscape of cfDNA methylation test

Targeted Panel | Large Panel | Genome-wide



Examples

Xu et al, Nature Material 2017
Kisiel et al, Hepatology 2018

Liu et al. Annals of Oncology 2020

Chan et al, PNAS 2013
Guo et al. Nat. Gen. 2017
Kang et al. Genome Biol. 2017
Shen et al. Nature 2018

Use cfDNA fragment length for cancer detection

- cfDNA fragment length profiles of healthy individuals reflected nucleosomal patterns of white blood cells, whereas patients with cancer had altered fragmentation profiles

- The Velculescu team (JHU) used the cfDNA fragmentation patterns to detect seven types of cancers, and achieved sensitivities of detection from 57% to >99% among the seven cancer types at 98% specificity, with an overall area under the curve value of 0.94. They also identified the tissue of origin of the cancers to a limited number of sites in 75% of cases.

Cristiano et al. Nature June 2019

Using cfDNA CNV for cancer detection

nature COMMUNICATIONS

ARTICLE

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Scalable whole-exome sequencing of cell-free DNA reveals high concordance with metastatic tumors

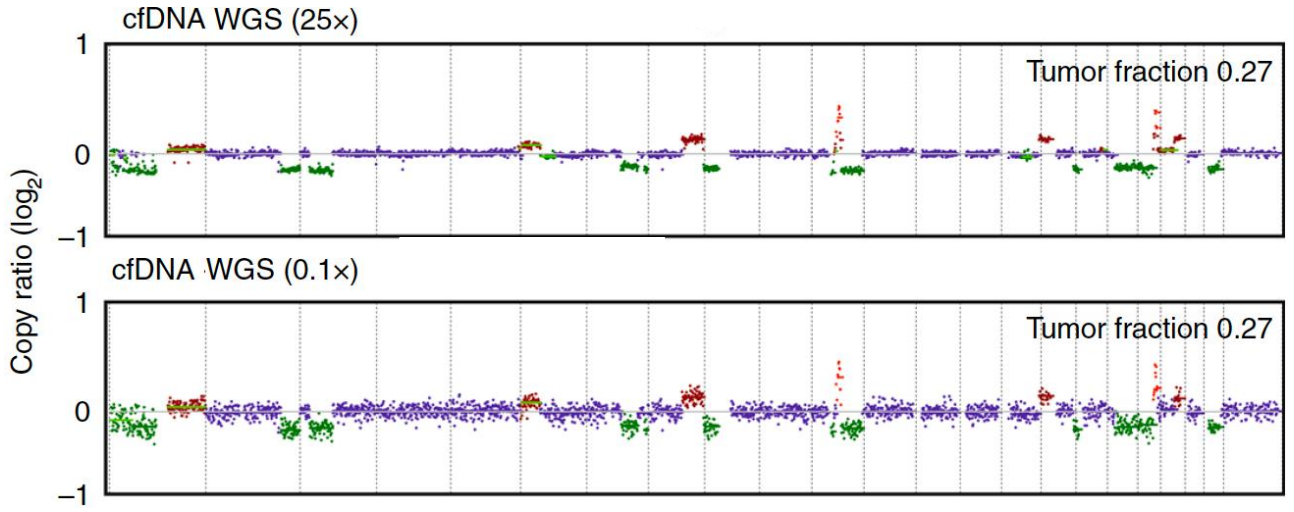
CURRENT PROTOCOLS in Human Genetics

Copy-Number Variants Detection by Low-Pass Whole-Genome Sequencing

Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

Low-pass Whole-genome Sequencing of Circulating Cell-free DNA Demonstrates Dynamic Changes in Genomic Copy Number in a Squamous Lung Cancer Clinical Cohort



Ultra low sequencing coverage (Ultra-low pass) whole-genome sequencing can detect CNV

Using cfDNA microbiome for cancer detection

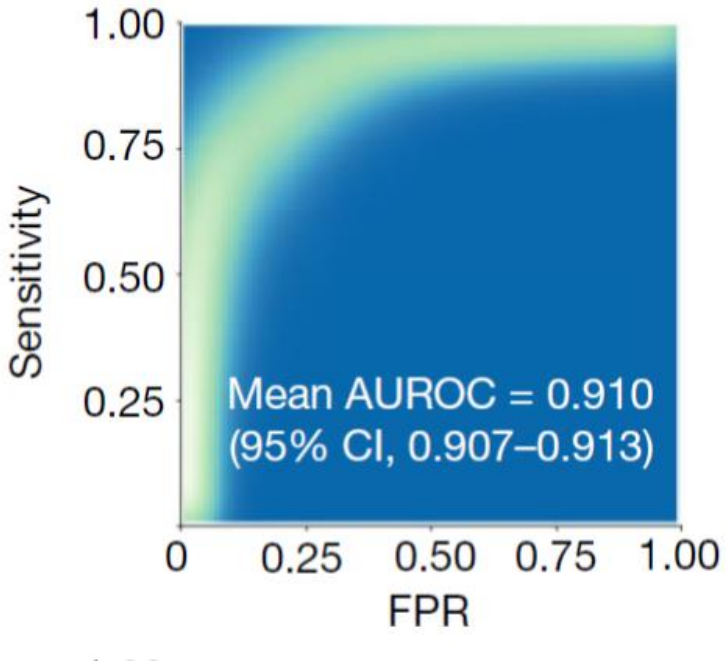
- Patients with cancer carry specific cell-free microbial DNA signatures that could potentially be used for early detection as well as determination of tumor type and stage in the clinic.

- Poore et al. re-examined whole-genome and whole-transcriptome sequencing studies in TCGA of 33 types of cancer (a total of 18,116 samples) for microbial reads, and found unique microbial signatures within and between most cancer types, including when using blood-based mbDNA at low-grade tumor stages and in patients without any detectable genomic alterations on commercial ctDNA assays.

nature

Article | Published: 11 March 2020

Microbiome analyses of blood and tissues suggest cancer diagnostic approach



Challenges of cfDNA-based Cancer Detection

- Very low amount of tumor DNAs in cfDNA
- Heterogeneous pathological landscape (many cancer subtype)
- Diverse co-founding factors (age, gender, ethnicity)

Possible ways to address the challenges

- Big panels or Genome-wide approaches
- Integrate multiple features of ctDNAs

The advantage of the genome-wide approach

- ***Robust capture of a very low amount of tumor cfDNA*** **(major challenge for the early cancer detection)**

1ml plasma -> 5 ng cfDNA -> ~15,000 genome

If the tumor cfDNA fraction is 0.02%, only 3 tumor genomes are present.

Given the efficiency of most capture kits, capturing tumor cfDNA fragments from 3 genomes that exactly cover a small gene panel risks false negatives.

The advantage of the genome-wide approach

- ***Comprehensive* coverage of heterogeneous patient populations:** The large number of biomarkers can encompass the large molecular aberration landscape of diverse cancer etiologies.

- **The diagnostic test can be continually refined and expanded** to accommodate more ethnic populations and cancer subtypes, because the validation cohort data can be repeatedly used to validate new biomarkers.

- **All-in-one test allows multi-purpose diagnosis and prognosis:** the test and training/validation data can be repurposed to develop other applications.

Integrate multiple features of ctDNAs

- Integrating SNV and serum protein markers *(Cohen et al. Science 2018)* to detect multiple types of cancer

- Lung-CliP integrate SNV and CNV to detect lung cancer *(Chabon et al, Nature, 2020)*

- Integrating fragment length and SNV can increase the detection rate for multiple types of cancer (*Cristiano et al. Nature June 2019)*

Thank you!