# Combined genomic and epigenomic assessment of cell-free circulating tumor DNA (ctDNA) improves assay sensitivity in early stage colorectal cancer (CRC)

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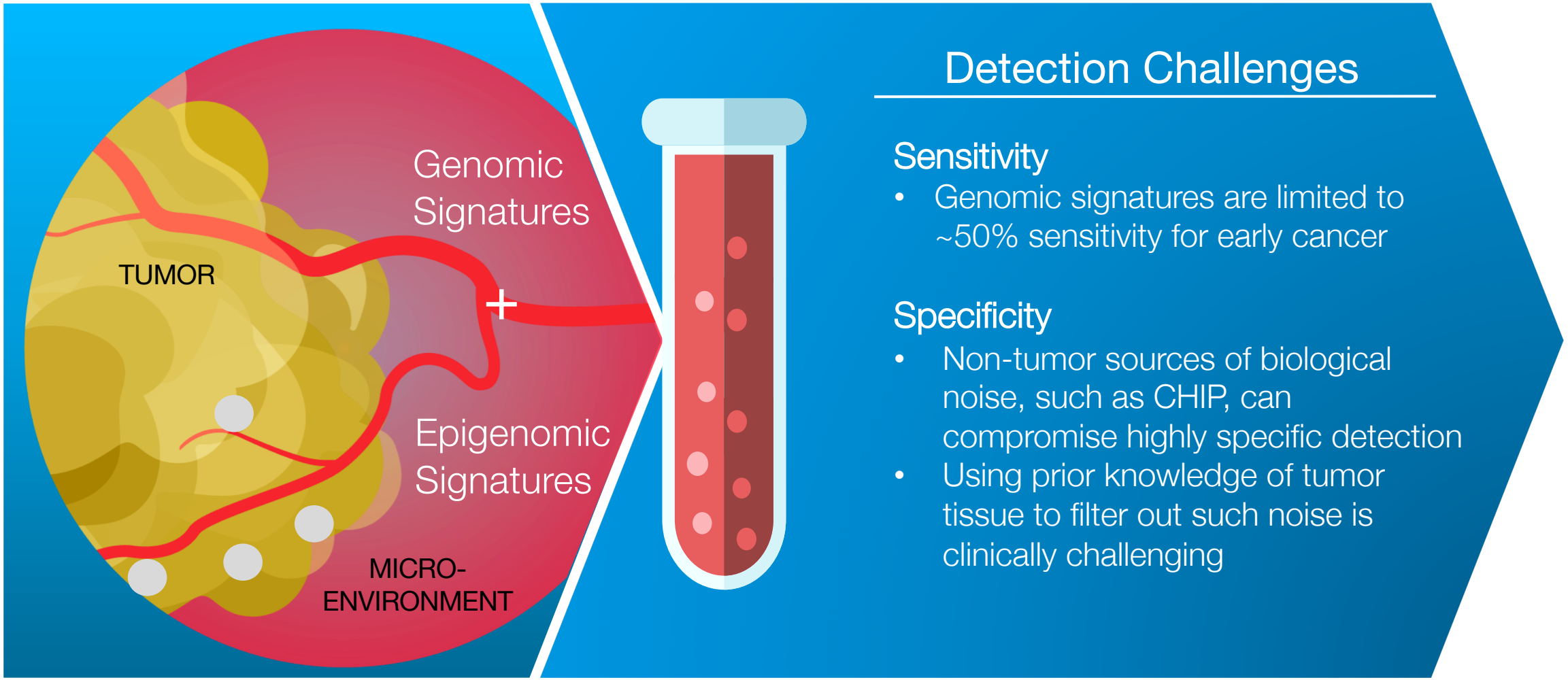
# Disclosures

Employee, Director, and Shareholder of Guardant Health, Inc.

# ctDNA has the potential to identify patients with early stage cancer, but accurate detection is challenging




## Detection Challenges

### Sensitivity

- Genomic signatures are limited to ~50% sensitivity for early cancer

### Specificity

- Non-tumor sources of biological noise, such as CHIP, can compromise highly specific detection
- Using prior knowledge of tumor tissue to filter out such noise is clinically challenging

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# Diverse sources of signal motivate multimodal analysis of ctDNA

## Genomic Alterations

A C T A C G T A C C T G

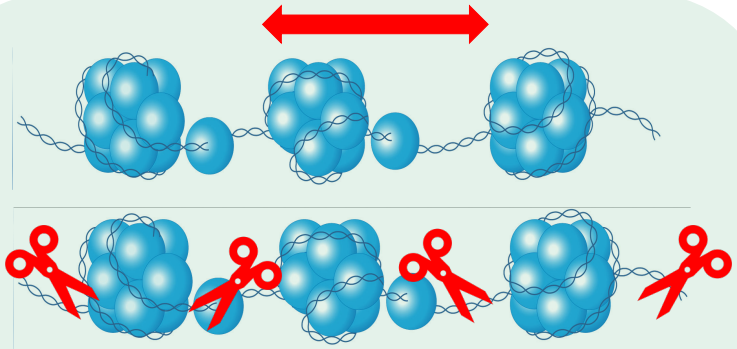
### Genomic Alterations

- SNVs, InDels, Fusions, and CNVs

## Epigenomic Alterations

### Methylation

- Aberrant methylation signals in tumor vs benign tissues



### Nucleosomal Positioning & Fragmentomics

- ctDNA has differential fragment genomic position via nucleosomal positioning or epigenomic alterations at transcription factor binding sites

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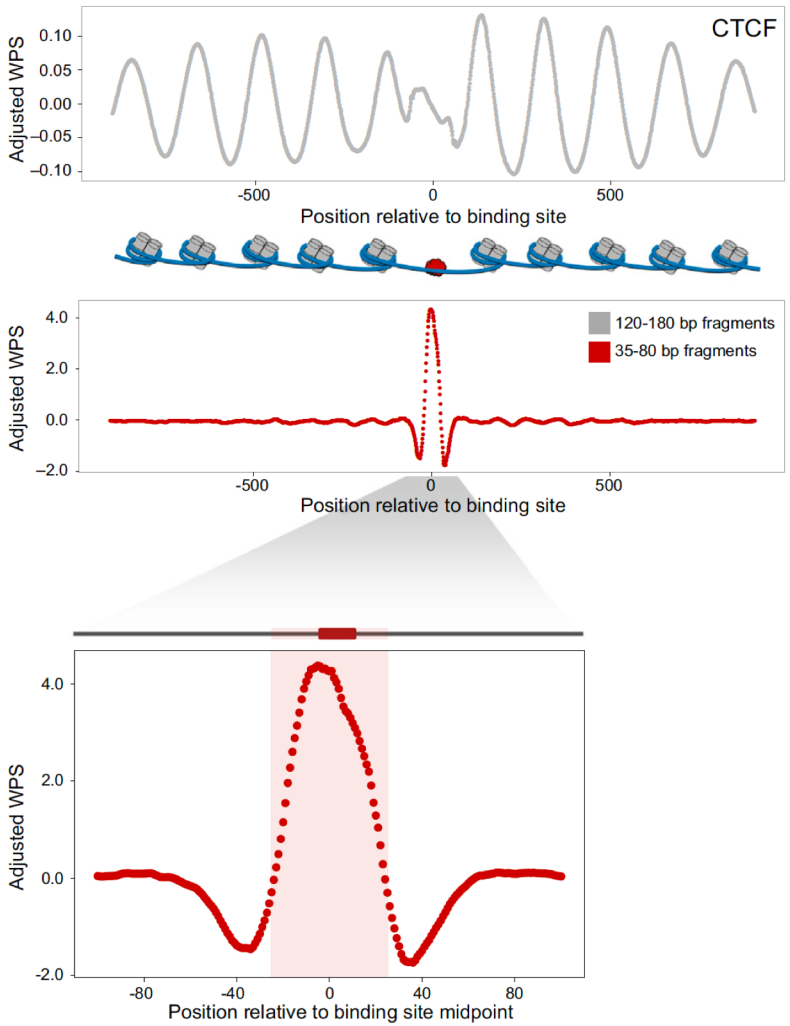
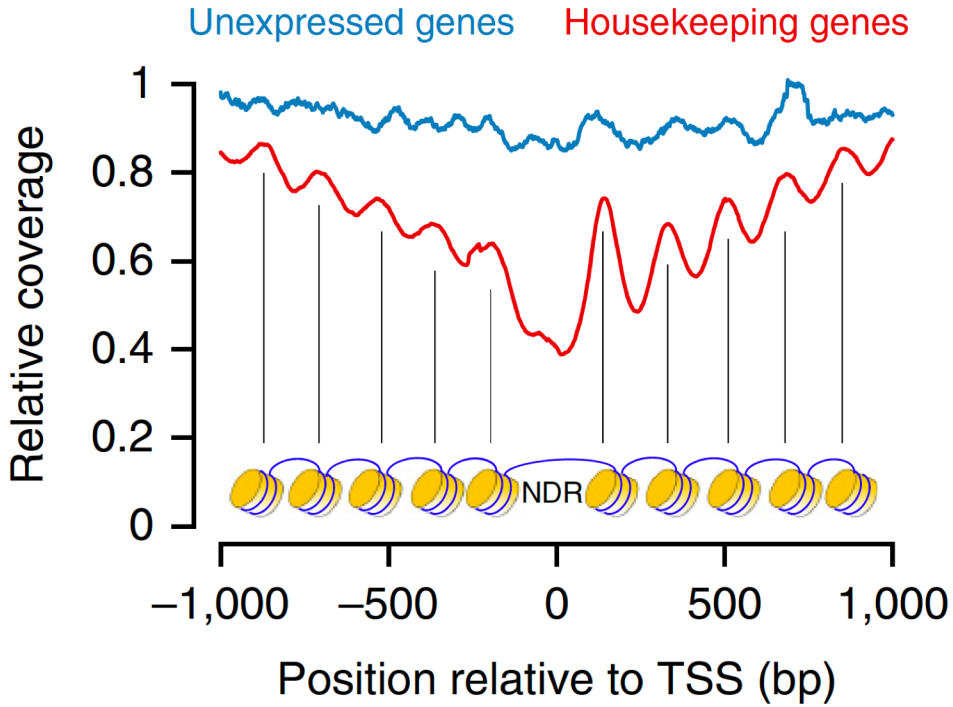
# ctDNA fragment genomic position provides biological information




Nucleosomal (long) fragments

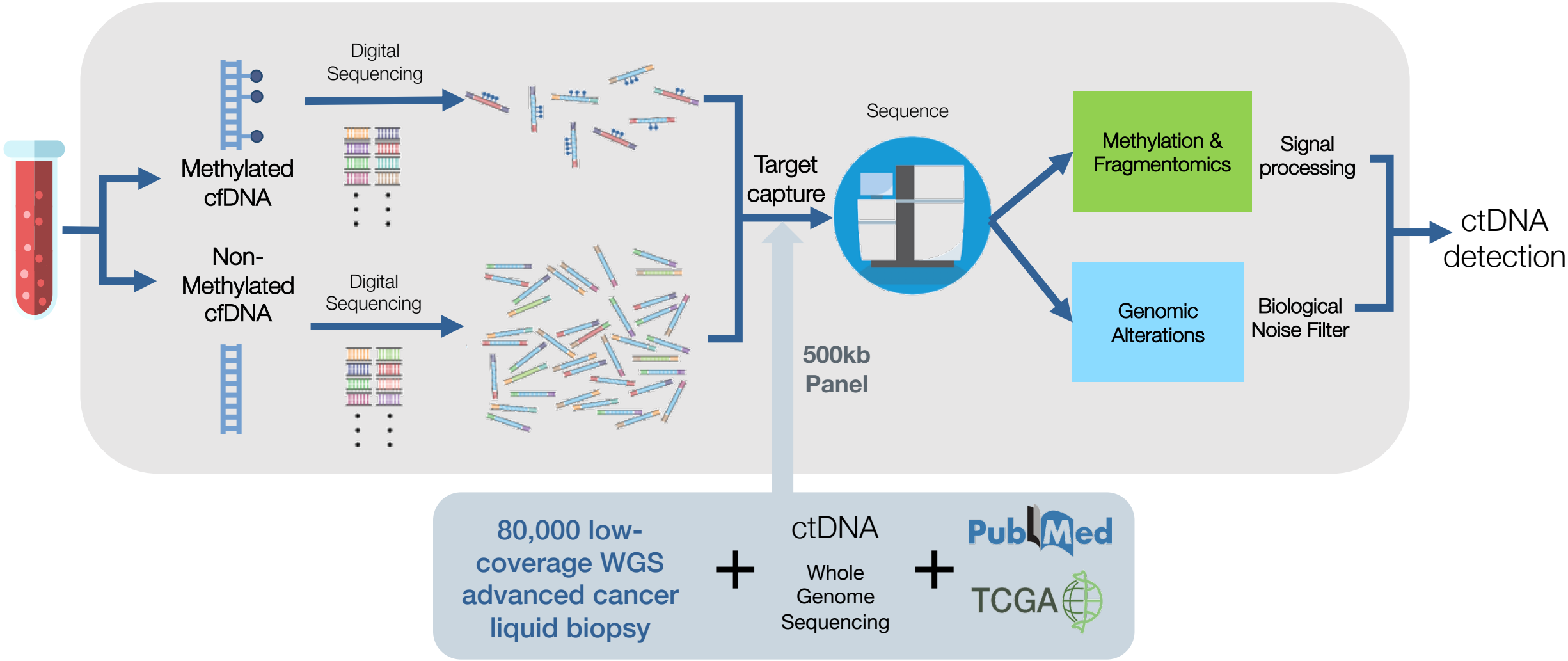
Sub-Nucleosomal (short) fragments




**TSS:** Transcription Start Site
**CTCF:** a DNA binding protein that binds to tens of thousands of genomic sites, some tissue-specific and others ultra-conserved

Snyder, et al. Cell 2016.
Ulz, et al. Nature Genetics. 2016

# Integrated genomic and epigenomic analysis of ctDNA

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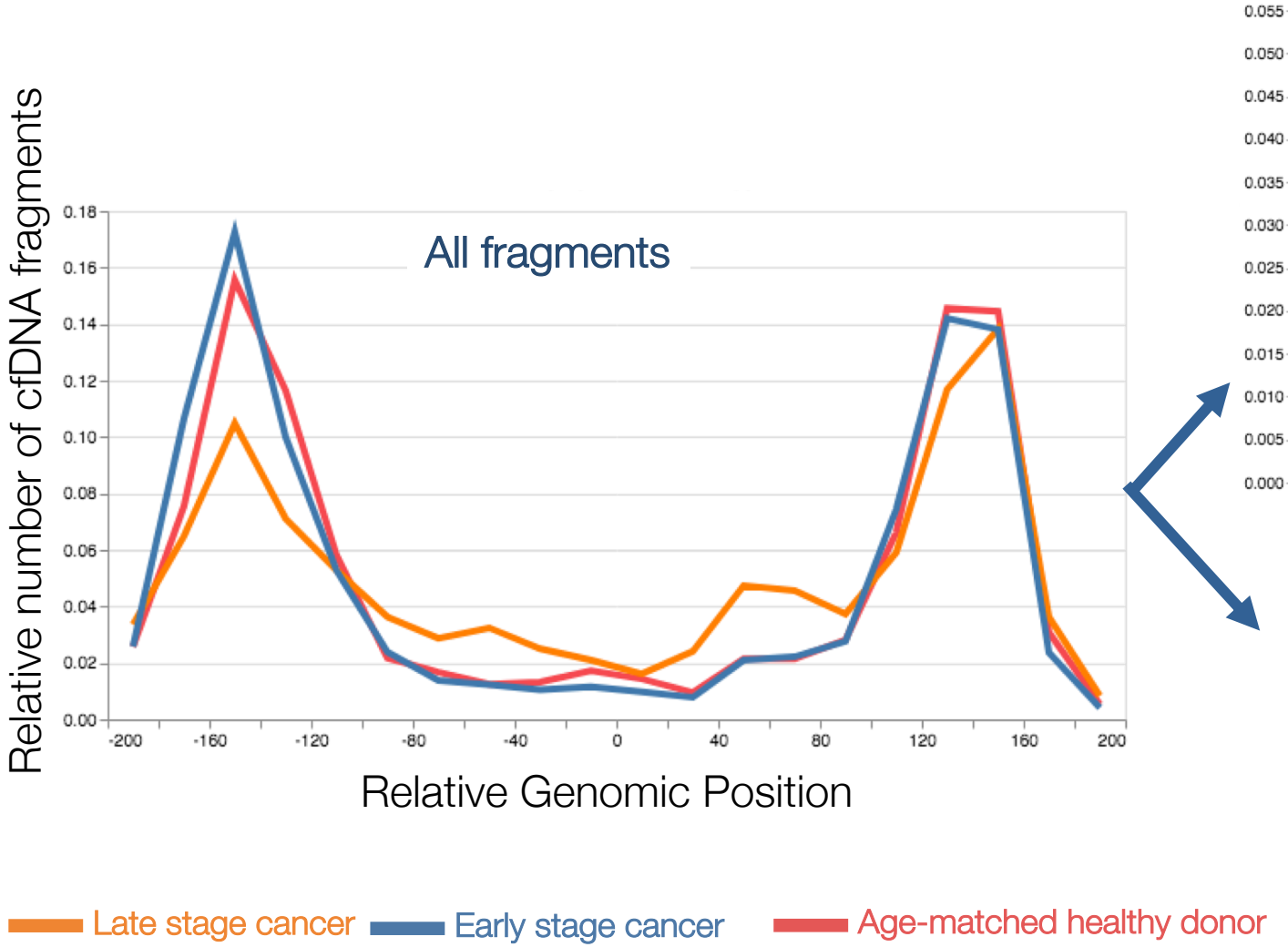
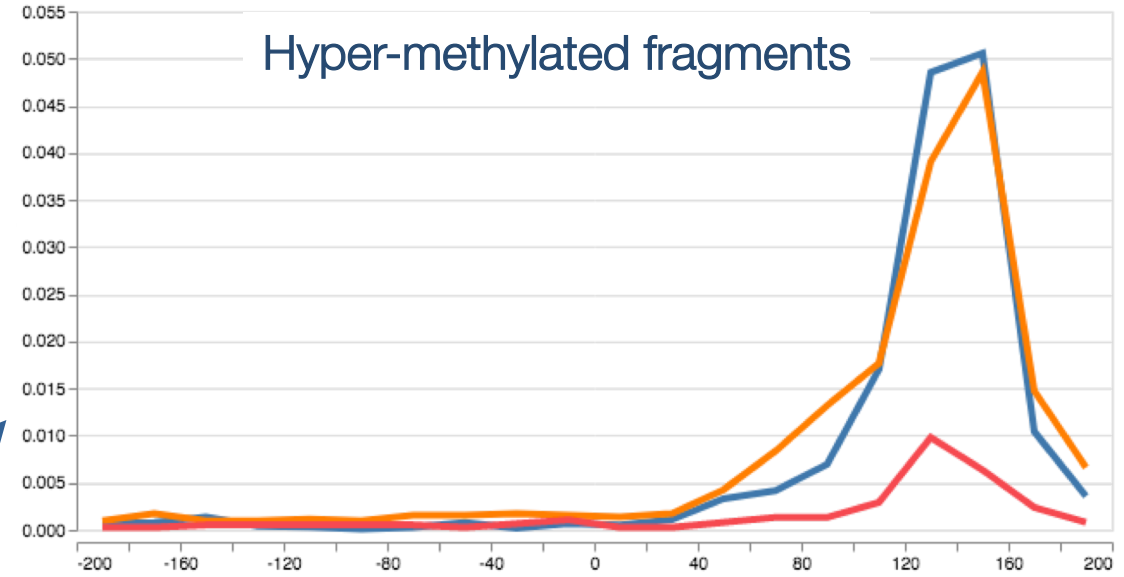
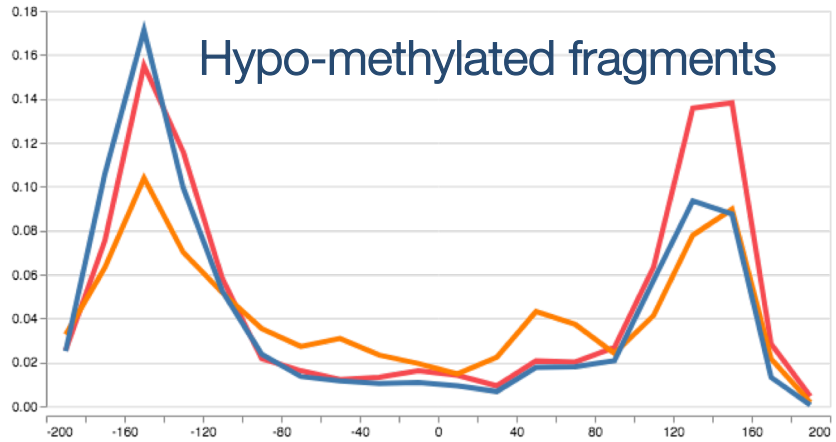
# Multi-modal epigenomics approach integrating methylation and fragmentomics improves signal-to-noise




Late stage cancer  Early stage cancer  Age-matched healthy donor

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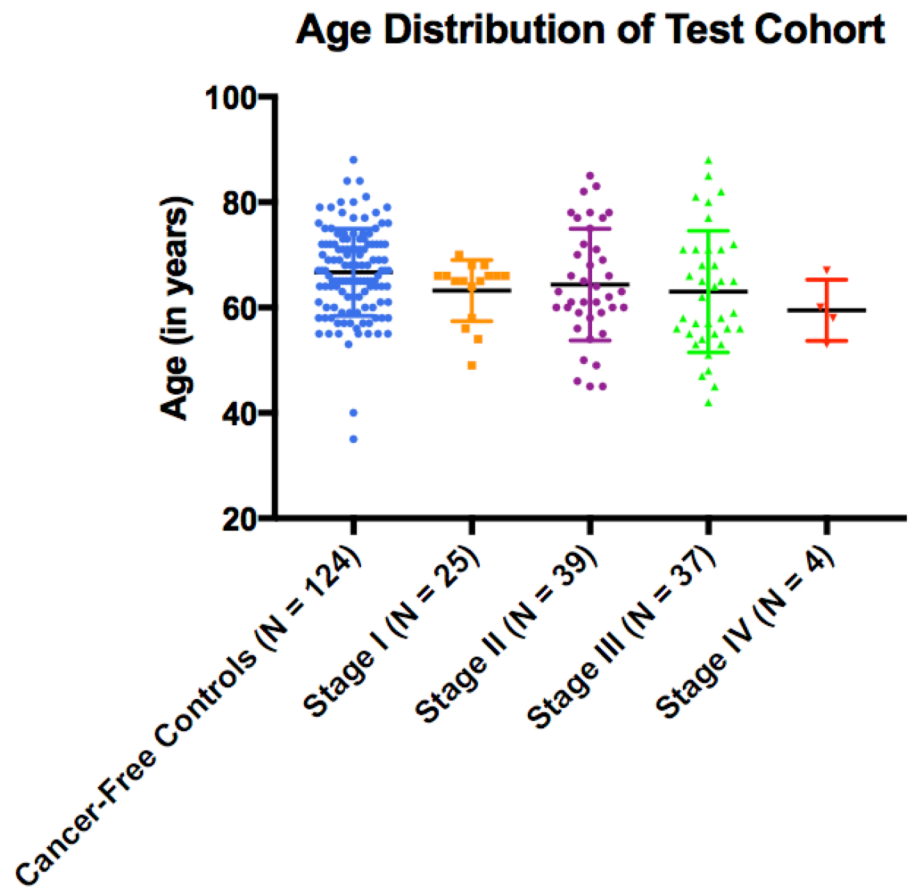
# Accurate testing cohort required age-matched cases and controls

- 105 patients with a diagnosis of colorectal cancer had plasma collected **prior to surgical resection**
  - From three independent cohorts
- Cancer-free controls were age-matched
  - Median age was 67 years, consistent with the median age at colorectal cancer diagnosis per SEER Data
  - 8% had a diagnosis of inflammatory bowel disease

| | Median age (in years) | Range (in years) |
|---|---|---|
| Cancer Free Controls | 67 | 35 - 88 |
| Stage I | 65.5 | 49 - 70 |
| Stage II | 63 | 45 - 85 |
| Stage III | 62 | 42 - 88 |
| Stage IV | 59 | 53 - 67 |

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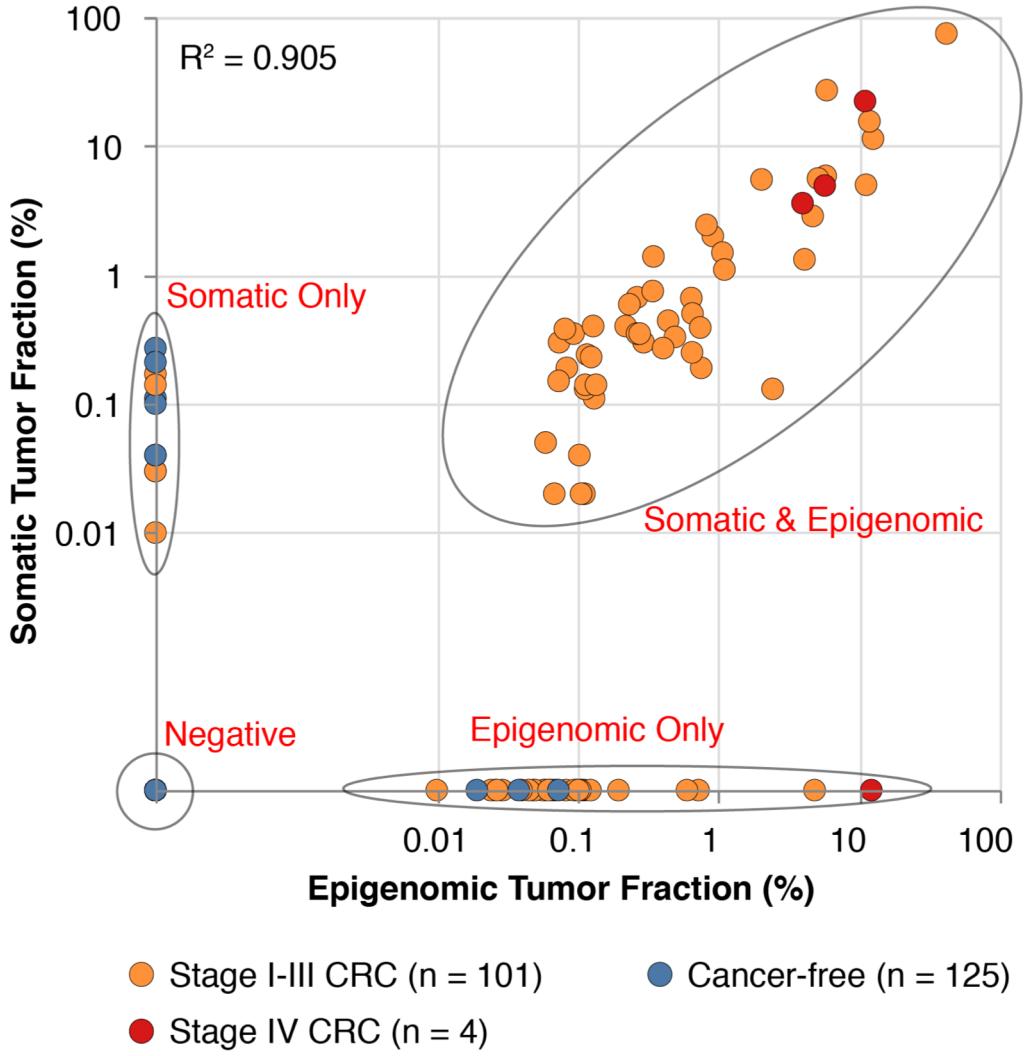
# Inferred tumor level correlates between epigenomic and genomic estimate

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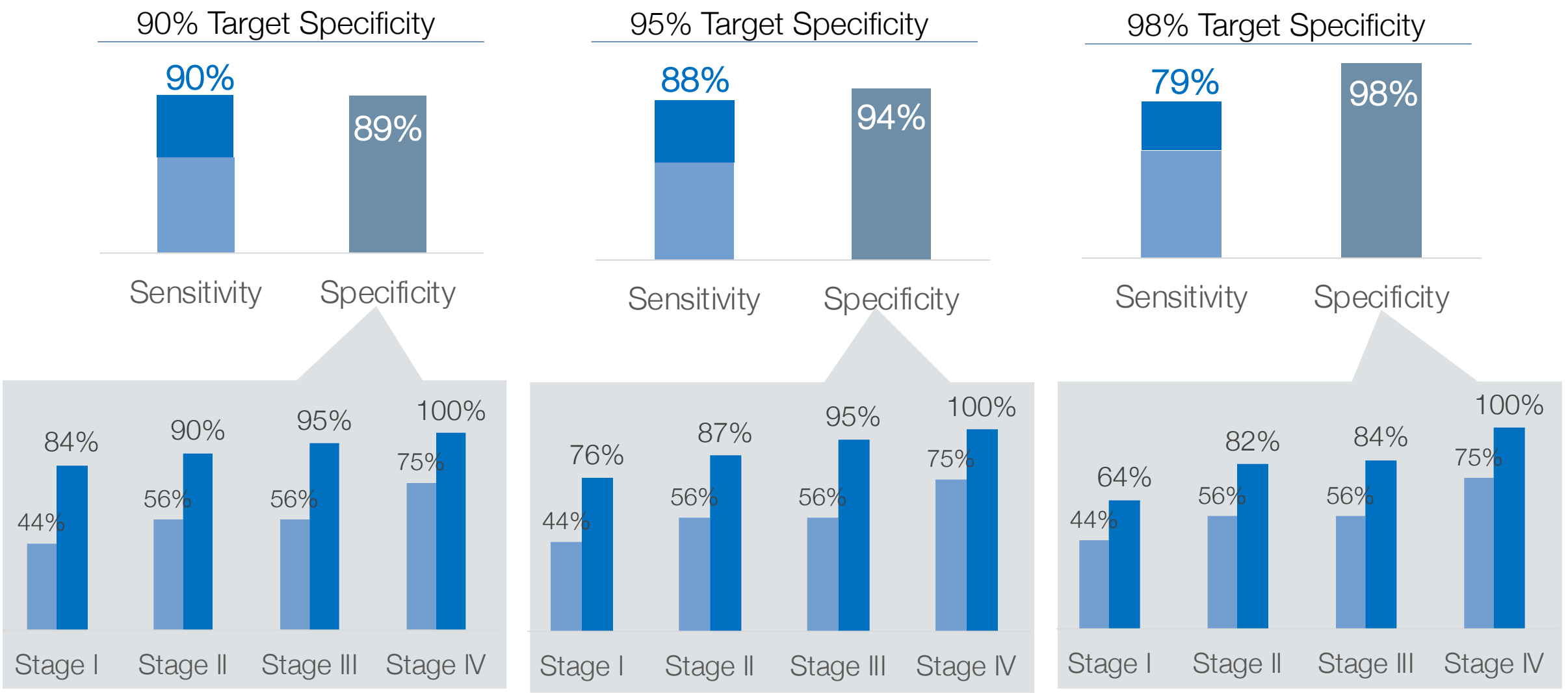
# Promising ctDNA sensitivity and specificity for early stage CRC

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# Summary and Next Steps

- Utilizing a **plasma-only** sequencing assay incorporating **somatic genomic and epigenomic analysis**, and a bioinformatic classifier to filter non-tumor derived variants, ctDNA detection rate in early stage CRC (I-III) can far **outperform** the detection rate of somatic sequence variant detection alone
- The performance of the ctDNA assay needs to be further validated in larger cohorts
- In a subgroup of patients, longitudinal ctDNA samples were collected and clinical follow-up is ongoing to evaluate post-surgery ctDNA detection rate and disease recurrence
- These results have potentially significant implications for the clinical utility of ctDNA in early stage cancer management

# Acknowledgements


- Patients and Providers who collaborated on this research

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