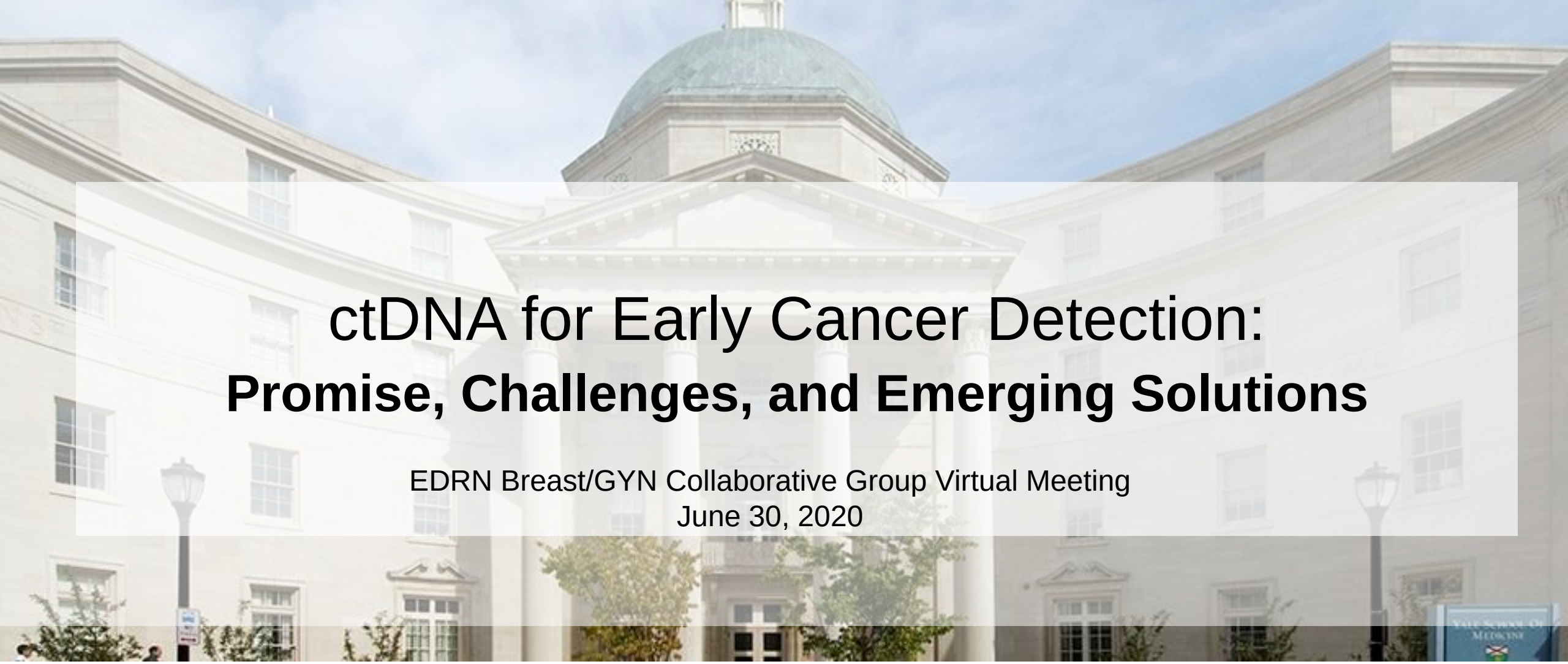

ctDNA for Early Cancer Detection:
Promise, Challenges, and Emerging Solutions

EDRN Breast/GYN Collaborative Group Virtual Meeting
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Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

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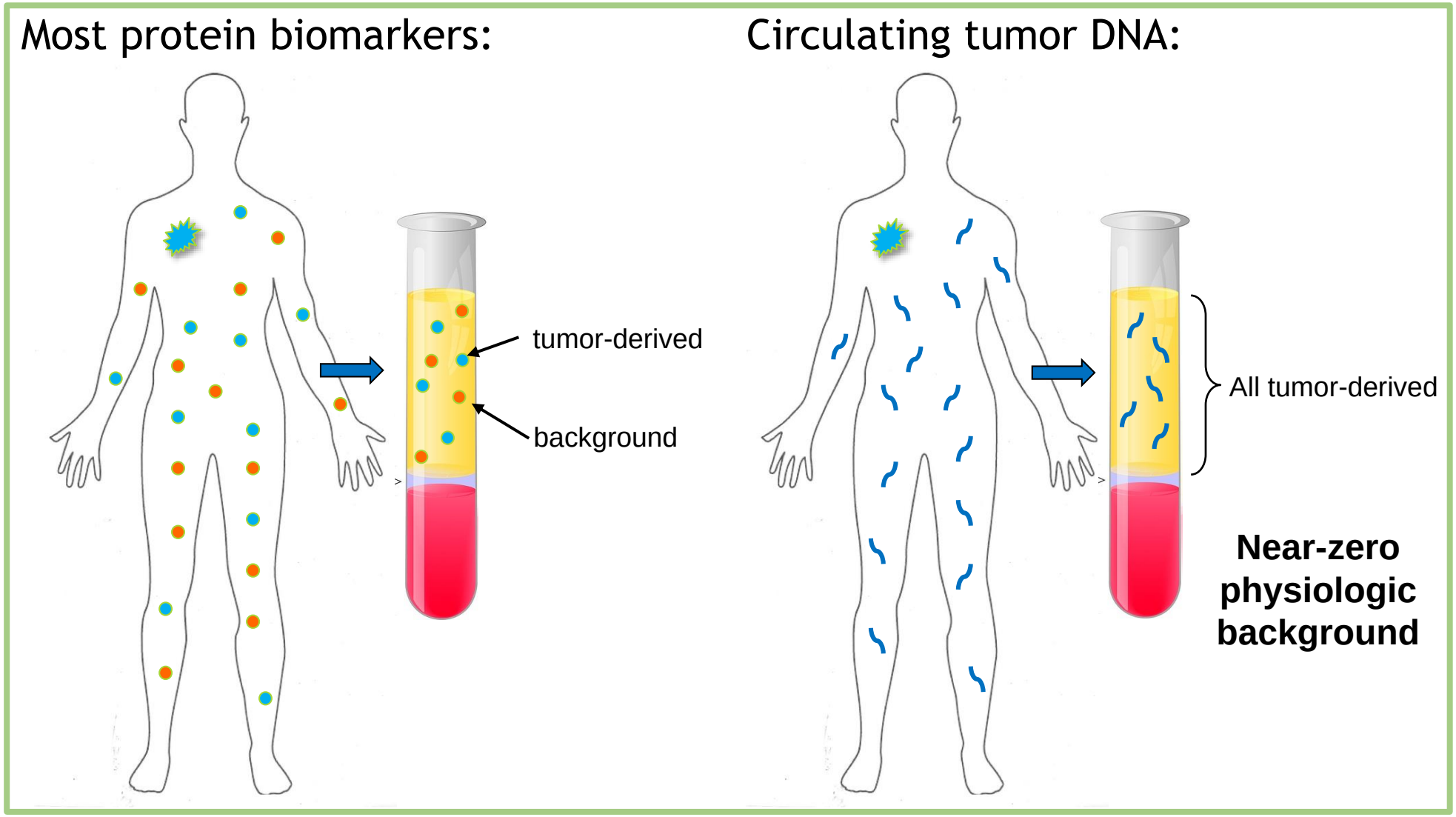
OUTLINE

- Why is ctDNA promising as an early detection biomarker?
- What are the key challenges?
- How can innovative strategies overcome these challenges?

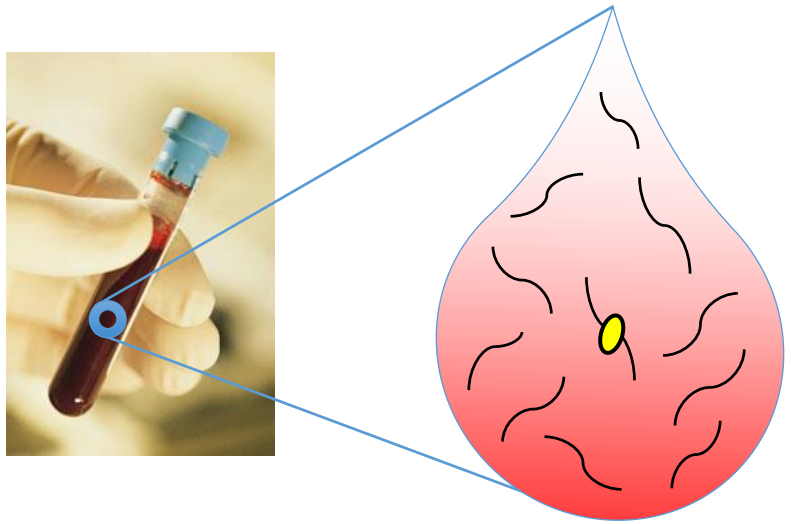
Promise of ctDNA for Early Cancer Detection



CHALLENGES

Biological Challenges:

- Early-stage tumors shed very little DNA.
- Excess of background “healthy” DNA.
- Cancer-like signals in healthy DNA (e.g. clonal hematopoiesis).
- Variable shedding of DNA from different cancer types and subtypes.



CHALLENGES

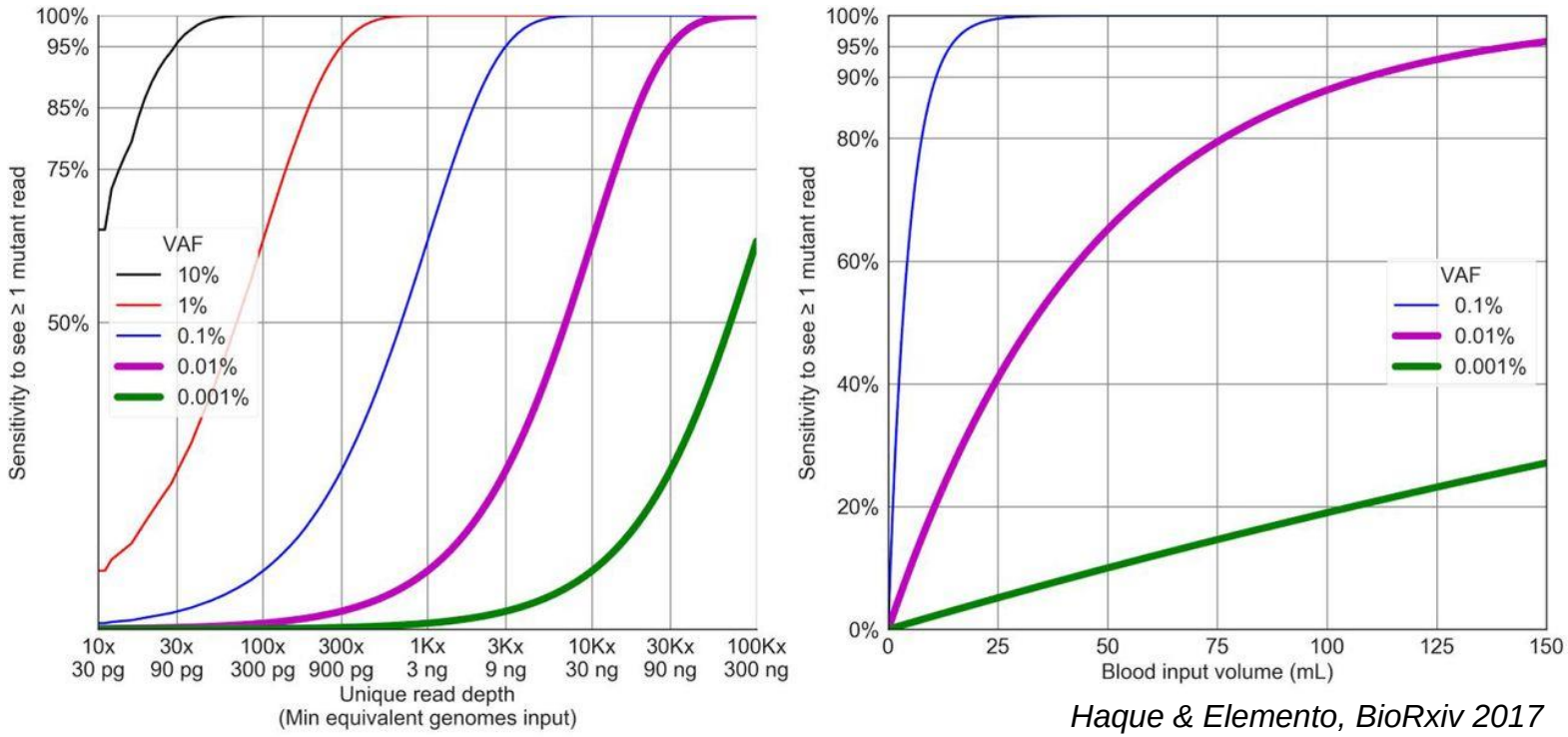
Technical Challenges:

- Artifacts can limit sensitivity (PCR errors, sequencer errors, DNA damage).
- Low conversion yield can limit sensitivity.

Practical Challenges:

- Cost must be reasonable.
- Large-scale validation studies required.

MUTATION-BASED CTDNA DETECTION

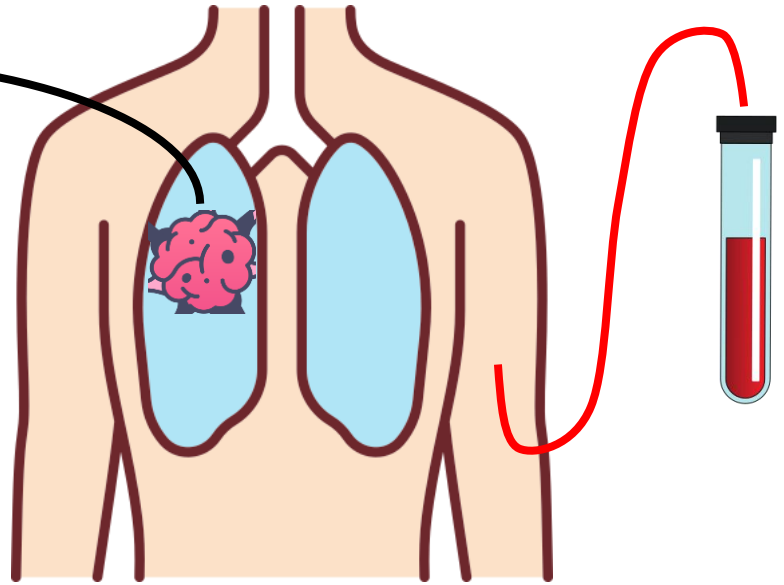


Haque & Elemento, BioRxiv 2017

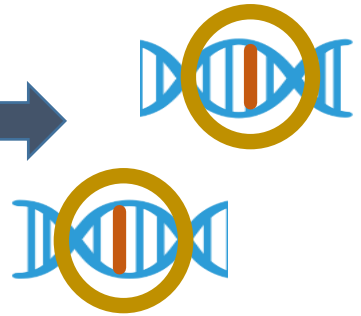
Achieving high sensitivity for early-stage cancers may require unreasonably large volumes of blood.

Tumor-Informed Detection of MRD

Multiple mutations identified in tumor tissue

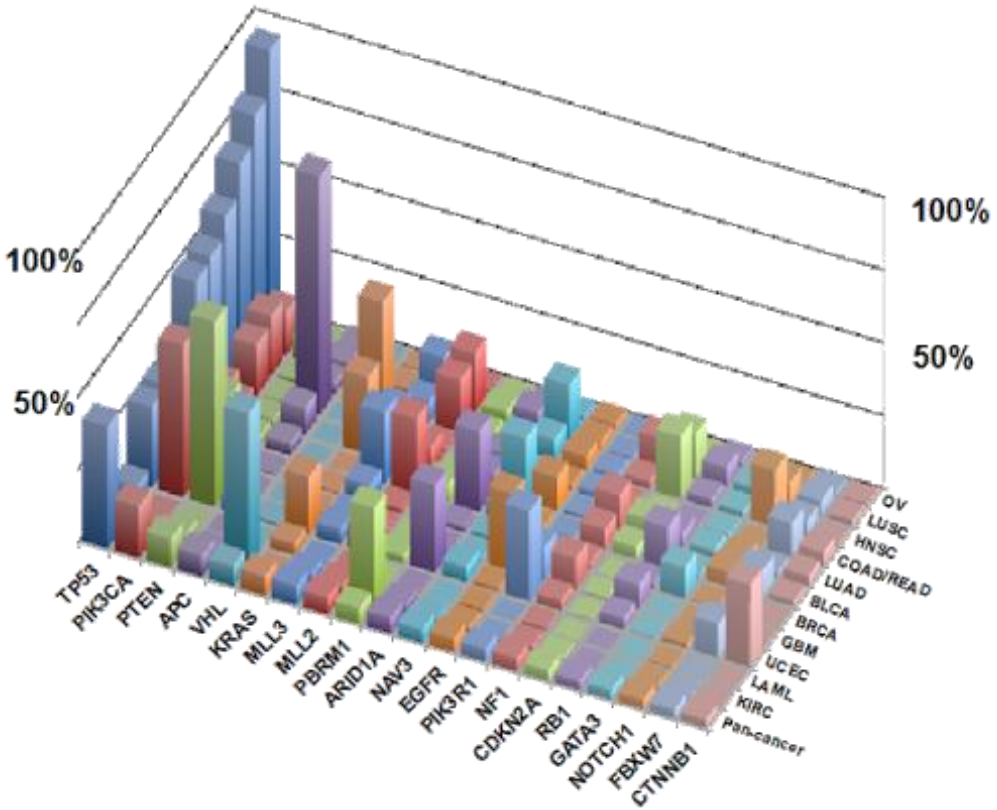


Customized blood test created to probe for specific mutations



... But this approach won't work for cancer screening.

MUTATION PANELS



T. Soussi, Atlas Genet Cytogenet Oncol Haematol. 2016

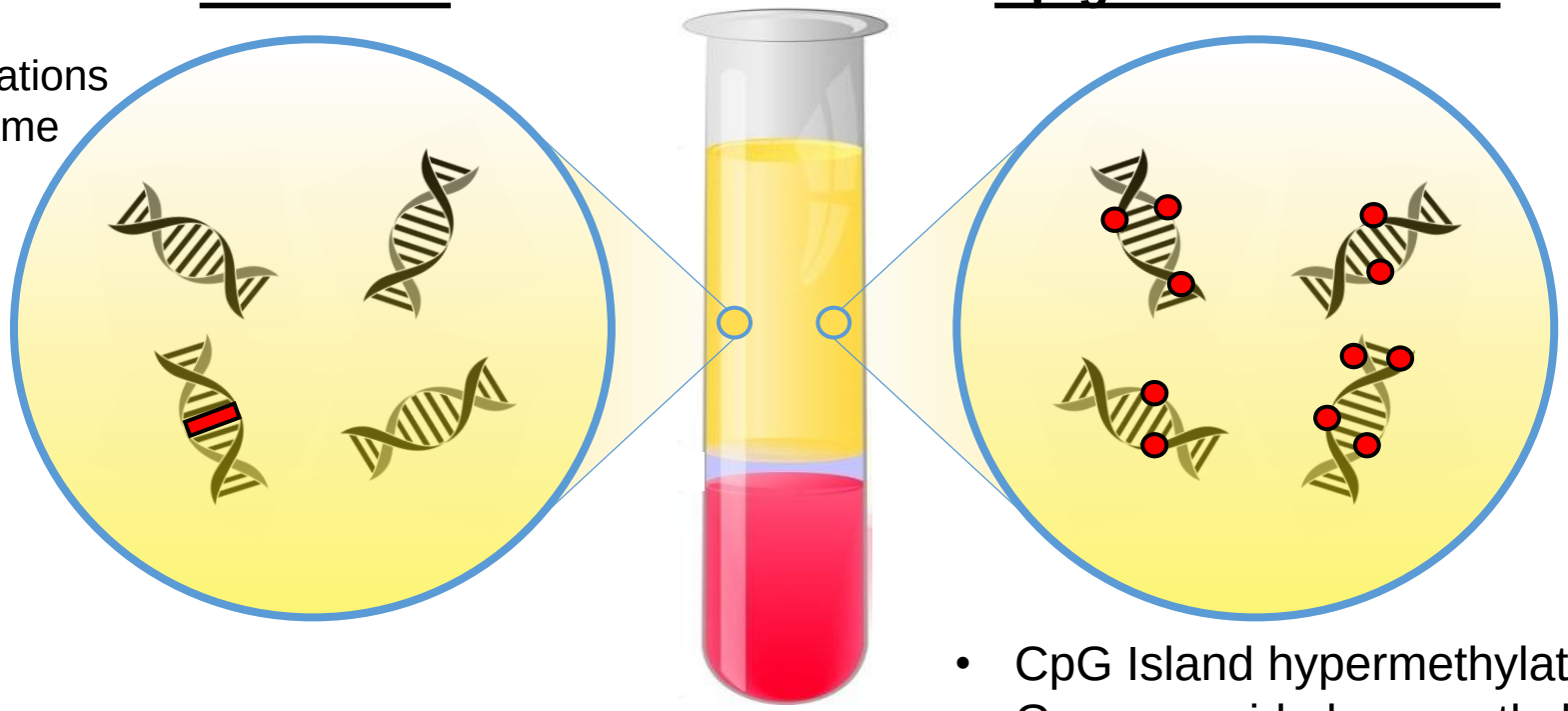
<u>Dilemma</u>:

- Broad mutation coverage is expensive.
- Narrow coverage may not be adequately sensitive.

Probing Epigenetic Features

Mutations

Few mutations per genome



Epigenetic Features

Epigenetic signatures are found throughout the genome.

- CpG Island hypermethylation
- Genome-wide hypomethylation
- Fragment size
- Nucleosome position

Integrating Multiple Signals

Improvements in sensitivity can be achieved by combining signals from multiple analytes or cfDNA features.

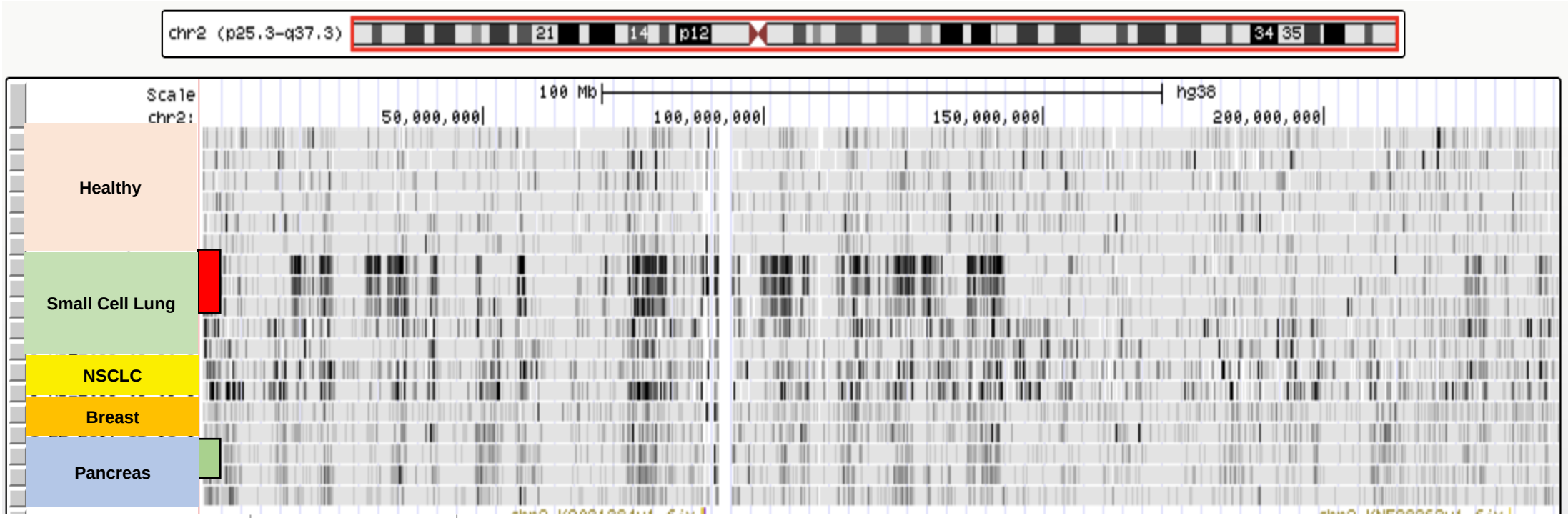
Examples:

- SNVs + Aneuploidy + Protein Markers (Johns Hopkins group)
- SNVs + Methylation + Fragmentomics (Guardant Health)
- SNVs + CNVs (Stanford group)

Methylation Signatures in Plasma

- Aberrant methylation appears in clusters.
- Genome-wide methylation patterns appear to be patient-specific.
- Common features are seen across tumor-types.

Chromosome 2



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