Blood-Based Screening for Cancer Detection

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COI Disclosure

- Freenome – UPMC/Dr. Schoen study site for PREEMPT clinical trial
- Research Collaboration with Johns Hopkins
ctDNA: Circulating Tumor DNA

• As cancer cells turn over, release DNA into adjacent media
• Blood, stool, urine, pancreatic juice, cysts, cervical mucous, CSF, saliva, bronchial, etc.
• ctDNA – searching for somatic mutations within driver genes that are responsible for clonal growth
Targets in Blood Beyond ctDNA

- Epigenetic changes (methylation)
- Proteins
- Fragmentomics
Vast majority of cfDNA is from hematopoietic cells.

Release arises from apoptosis

We don’t understand etiology of level/amount – not necessarily proportional to tumor size/stage (though generally so), varies by tumor site
Challenges for ctDNA as a Biomarker

1. Sensitivity – can be <1 mutant molecule/ml of plasma: requires large volume plasma for testing

2. Specificity – other sources of mutant DNA must be excluded, e.g., CHIP – clonal hematopoiesis of indeterminate potential

3. Tissue of origin: Mutations not specific to one type of cancer: Find a mutation: Where is it coming from?
Digital Genomics

Conceptual Elements of Molecular Barcoding

UID assignment

Amplification

Wild type

True positive (pre-existing mutation)

False positive (artifact)

UID – Unique IDentifier

Cohen J. Can Epi Biomark 2020
Pan-Cancer vs Single Cancer?

It is better to develop a test that seeks to identify multiple cancers?

Or, should we focus on a blood test for a single cancer of interest, e.g., colorectal cancer?
Pan-Cancer Testing

Grail: targeted methylation: detecting >50 cancer types
Challenges/Benefits to Pan-Cancer Testing

1. **Specificity**: Concern for unintended consequences of false positive test

2. **Search** for more cancers means higher population prevalence, leads to higher PPV

3. **Each cancer has its own idiosyncrasies** – is screening efficacious?, work up burden, variable sensitivity – ctDNA is highly sensitive for liver, ovary, not so for breast cancer
Colorectal Cancer

Specificity not an issue: false positive test that leads to CS not much of a concern
Blood Based Screening

Pan Cancer

- Grail (1.1B): targeted methylation
- Thrive/Exact (2.1B): ctDNA, proteins

Colorectal Cancer

- Freenome (260M): multiomics
- Guardant (550M): ctDNA, methylation, fragmentomics

Fits within framework for multiphase approach for evaluating new tests? Yes

No
CRC focused Blood Based “Registration” Trials

1. Freenome - “Preempt” (N=24K)

Blood-based CRC Trials: Prevention?

• How will blood tests be at detecting advanced adenomas?

• In PLCO trial: 2/3’rds mortality benefit estimated to be due to prevention (reduction in incidence) as opposed to early detection of CA

Douroudi M. Cancer 2017:123:4815
Detecting cancers Earlier Through Elective mutation-based blood Collection and Testing

i. Can a multi-cancer blood test detect CA?

ii. Can test intervene/affect CA progression?

iii. Can it not interfere with SOC screening?

iv. Can it performed safely without incurring a lot of futile or dangerous work-up?
A Testing Process

- Scored positive if any DNA or protein analytes were above preset threshold
- Scored positive if CHIP excluded and *the identical analyte* elevated in the baseline test was abnormal in the confirmation test
- Imaging (generally diagnostic PET-CT) was used to provide orthogonal evidence of cancer and localize it if present
- Participants whose PET-CT shows features concerning for cancer were referred to specialists for further evaluation
- All participants asked to complete detailed surveys at 12 months following enrollment
9911 ♀ Baseline Test (16 genes + 9 proteins)

490 positive (4.9%)

134 positive again (1.4%)
127 PET-CT

26 Cancers

TP

101 No Cancer

FP

24 Cancers detected by SOC
46 Cancers detected by neither

26/96 = 27%

Geisinger – Hopkins/Thrive

214 CHIP
142 NOT identical
## Stage of Cancers Detected by Blood Screening

<table>
<thead>
<tr>
<th>Stage</th>
<th>#</th>
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<tr>
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<td>9</td>
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The False Positive Burden in #101 Without Cancer

A Diagnostic outcome following PET-CT in 101 participants without cancer
- 62% (63) no further procedures
- 16% (16) non-invasive
- 19% (19) minimally-invasive
- 3% (3) surgery

B All minimally-invasive and surgical procedures in 22 participants without cancer

Non-invasive: Xray, CT, USG
Min invasive: EGD, hysteroscopy
Surgery: HGD in colon, mucinous cystadenoma ovary, in situ CA appendix
DETECT-A

- Can a multi-cancer blood test detect CA?  YES
- Can test intervene/affect CA progression?  Suggestive – No Control Group
- Can it not interfere with SOC screening?  YES
- Can it be performed safely without incurring a lot of futile or dangerous work-up?  YES
DETECT-A: Observations

- Even with high specificity (>99%), the low prevalence of cancer means that most positive pan-cancer blood tests will be FALSE POSITIVES.
- Sensitivity – 46/96 (48%) cancers not detectable by blood test nor SOC screening.
Conclusions

• Blood based biomarkers could potentially screen unscreened
• Potential for multi-cancer detection
• We are in early stages in determining efficacy