Implementation of Multi Cancer Early Detection at UPMC as a Supplement to Population Based Cancer Screening

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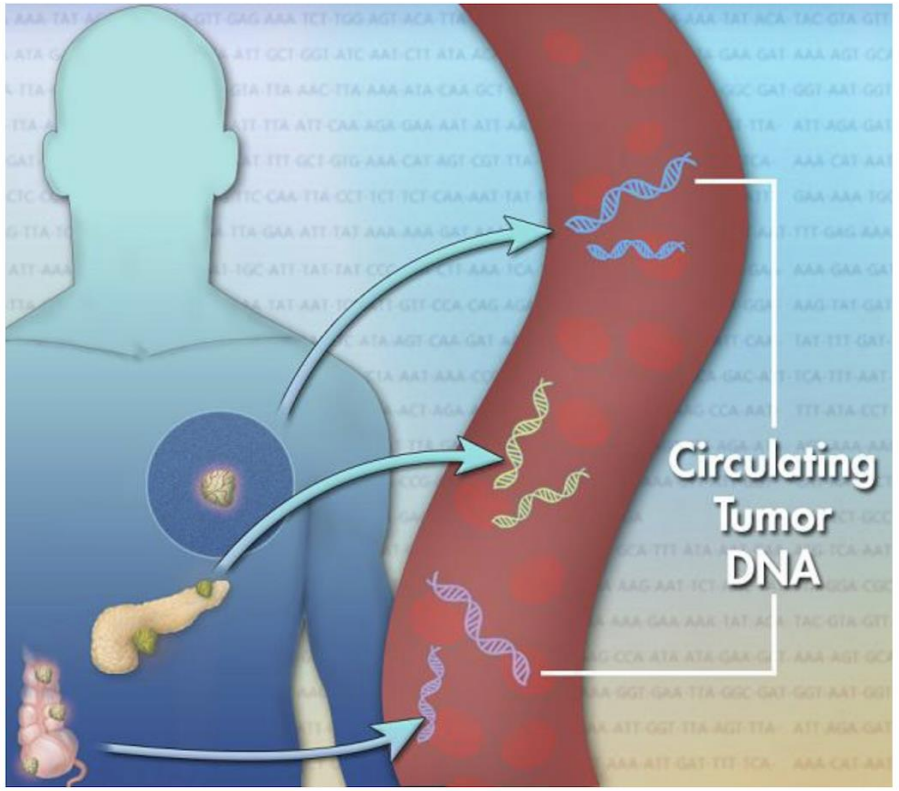
Disclosures:

Speakers' bureau-Grail

Scientists have discovered that dying tumor cells release small pieces of their DNA into the bloodstream. These pieces are called cell-free circulating tumor DNA (ctDNA).



Credit: Jonathan Bailey, NHGRI

Cell Free DNA

- Cell free DNA (cfDNA)
- Circulating tumor DNA-circulating tumor DNA (ctDNA) is found in the bloodstream and refers to DNA that comes from cancerous cells and tumors.
- As a tumor grows, cells die and are replaced by new ones. The dead cells get broken down and their contents, including DNA, are released into the bloodstream.
- The quantity of ctDNA varies among individuals and depends on the type of tumor, its location, and the stage of the cancer.

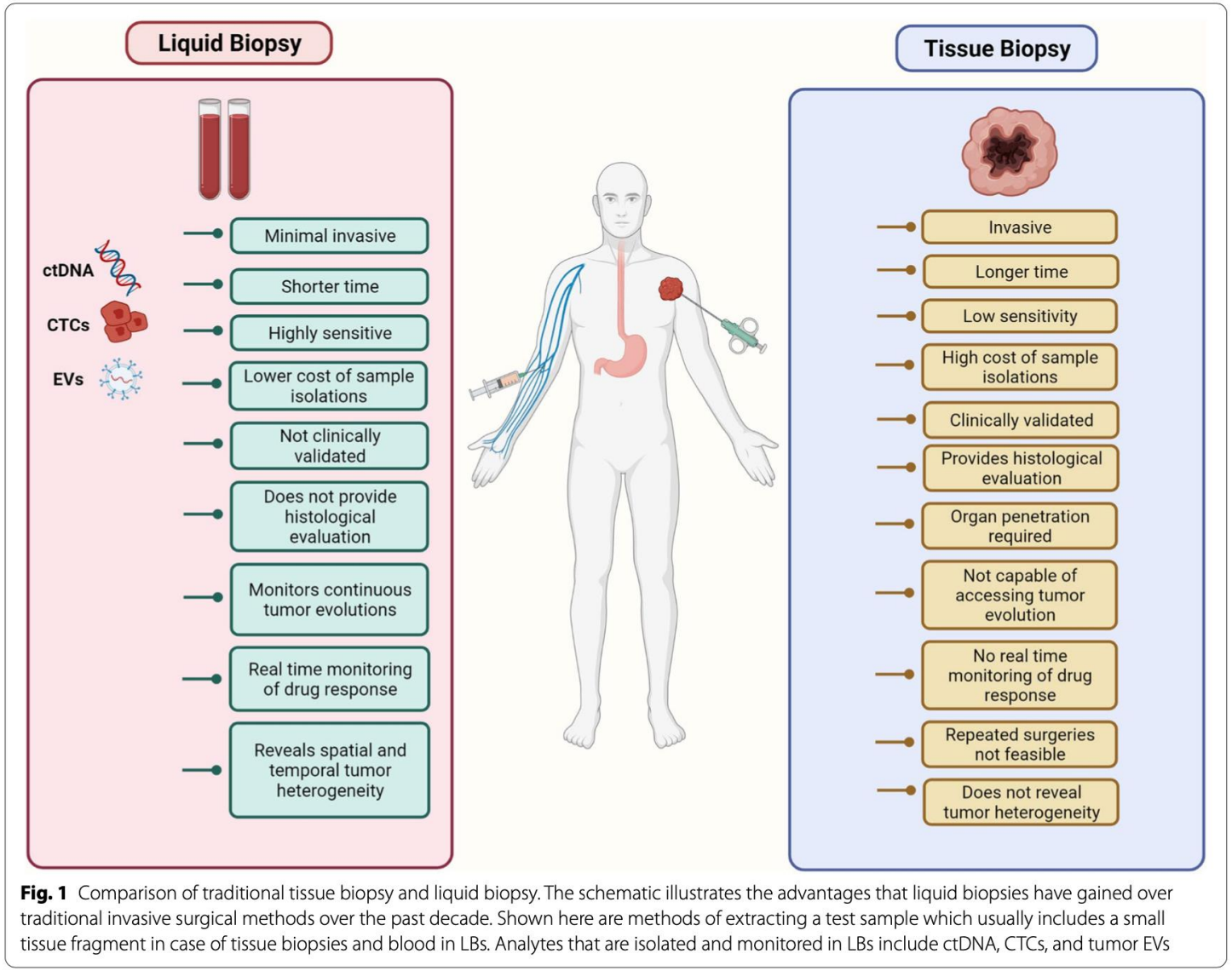


Fig. 1 Comparison of traditional tissue biopsy and liquid biopsy. The schematic illustrates the advantages that liquid biopsies have gained over traditional invasive surgical methods over the past decade. Shown here are methods of extracting a test sample which usually includes a small tissue fragment in case of tissue biopsies and blood in LBs. Analytes that are isolated and monitored in LBs include ctDNA, CTCs, and tumor EVs

Liquid Biopsy

- ctDNA are small pieces of DNA, usually less than 200 nucleotides in length
- Used for screening
- Companion diagnosis
- Minimally invasive
- Low cost

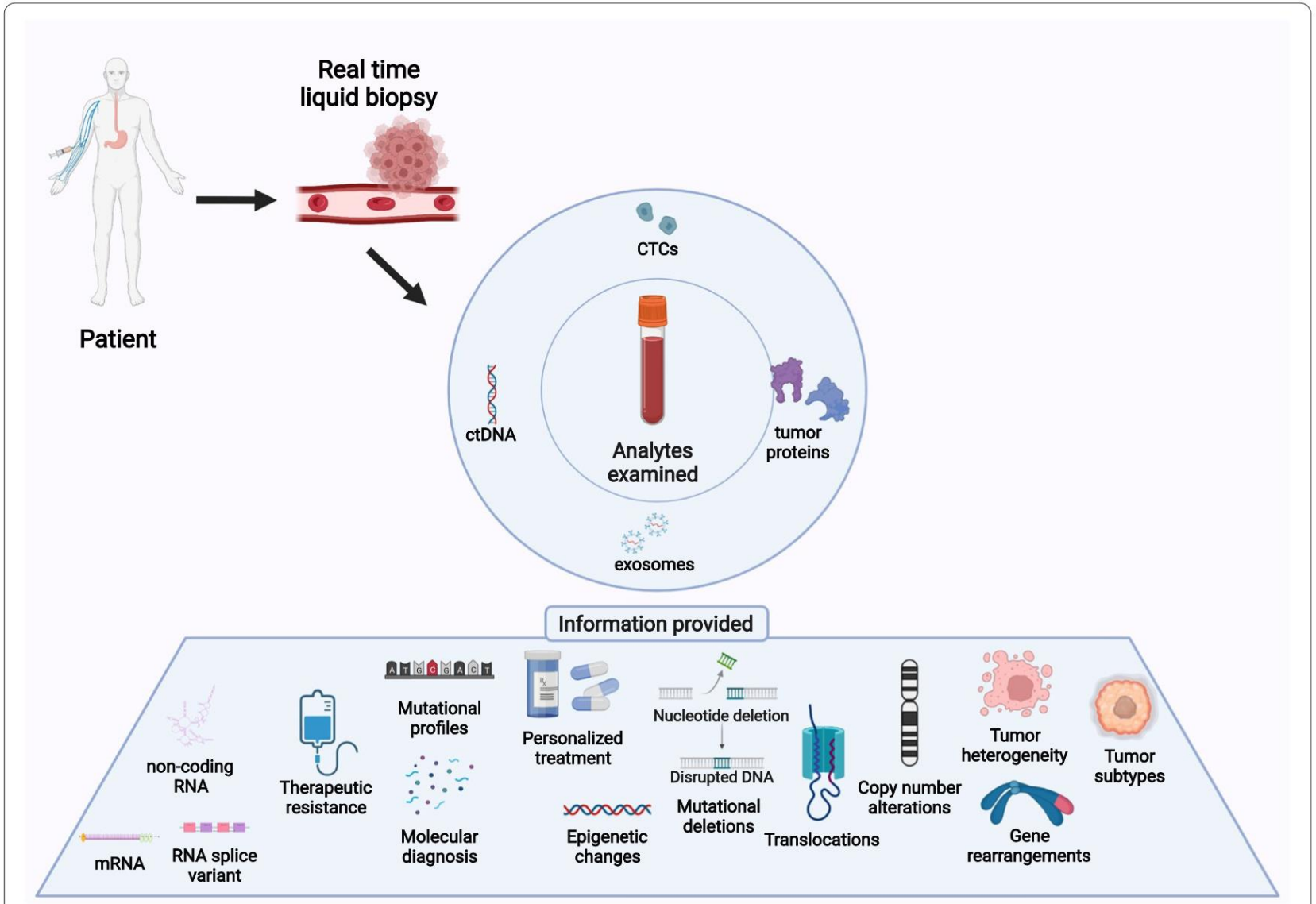
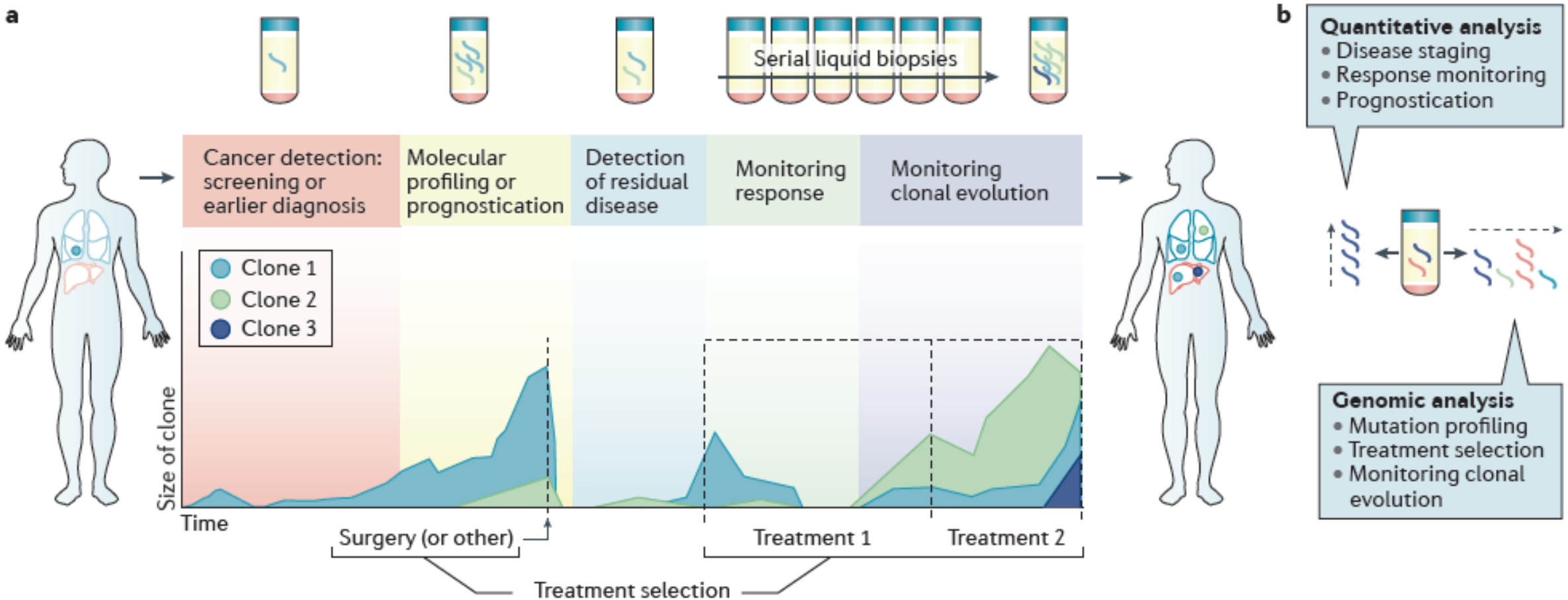


Fig. 2 Entities analyzed in liquid biopsies and their application. The various analytes isolated from blood in LBs provide a wide variety of information regarding tumors. Each analyte has a specific application in tumor diagnosis, monitoring, and treatment as described

Use of Liquid Biopsies in Cancer



Benefit:

Liquid biopsies do not require standard more invasive procedures, can be performed on peripheral blood, allowing for more widespread use.

Could reduce time to detection, reduce time to treatment, improve efficiency of resources and be used to screen more diseases.

Can avoid some of the risk of traditional biopsy, like bleeding, tumor spread, tissue injury.

Capture regional heterogeneity that can be limited in a tissue-based biopsy for full molecular profiling of the tumor to inform molecular targeted therapies.

Could help identify patients for clinical trials, guide mutation driven therapy

Possibly identify disease that can be more safely monitored over time instead of aggressive treatment

Challenges:

Need for the development of standards for adoption and clinical validation

Approval by FDA

Uncertainty around reimbursement

FDA Breakthrough Device Designation and Lab Developed Tests (LDTs)

- The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.
- The goal of the Breakthrough Devices Program is to provide patients and health care providers with timely access to these medical devices by speeding up their development, assessment, and review, while preserving the statutory standards for premarket approval, 510(k) clearance, and De Novo marketing authorization, consistent with the Agency's mission to protect and promote public health.

2020, the FDA approved FoundationOne Liquid CDx which can detect alterations in all solid tumors with specific diagnostics.

- Approved initially:
  - to identify mutations in *BRCA1* and *BRCA2* genes in patients with ovarian cancer eligible for treatment with rucaparib and
  - to identify *ALK* rearrangements in patients with non-small cell lung cancer eligible for treatments with alectinib and
  - to identify mutations in the *PIK3CA* gene in patients with breast cancer eligible for treatment with alpelisib.
- Subsequently approved:
  - To identify mutations in *BRCA1*, *BRCA2* and *ATM* genes in patients with metastatic castration resistance prostrate cancer (mCRPC) eligible for treatment with Olaparib.

2020, the FDA approved Guardant360 CDx which is able to detect EGFR mutations in cfDNA in patients affected by NSCLC who may benefit from osimertinib.

May 2019, the FDA grants breakthrough device designation to Galleri test for multicancer screening test.

May 2019, the FDA grants breakthrough device designation to Natera Signatera test for post-surgical detection and quantification of circulating tumor DNA.

2021 Galleri received approval by New York state regulators which is one of the most rigorous validation standards in the country for a laboratory developed test requiring an additional laboratory permit to ensure accuracy and reliability of clinical tests.

Liquid Biopsy technology and Population Cancer Screening

Colon Cancer

Lung Cancer (high-risk groups)

Challenges of Current Cancer Screening Paradigm:

Breast Cancer

Cervical Cancer

- Current challenges in cancer screening:
  - Second leading cause of death
  - Cancer has a huge cost burden
  - Screening is limited 5 cancers only 4 with USPSTF guidelines A/B
  - Current screening paradigms are invasive, time consuming and present significant barriers to access
  - Adherence to current screening is not at goal
  - Covid-19 has caused a dramatic drop in screening
    - Cancellations
    - De-prioritization by health systems early in pandemic
    - Fear of exposure by patients
    - Increased barriers and disparity gaps

Missing Many Cancers:

USPSTF Screening covers 29% of annual cancer incidence age 50-79

71% incident cancers without current screening modality

Cancer	Prevalence (%)	USPSTF Recommended Screening	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Compliance with Recommended Screening (%)
Breast	0.6	Biennial mammography, women ages 50-74	87	89	4.4	78.3
Cervical	<0.1	Triennial cytology or quinquennial cytology/HPV test women ages 21-65	95	85.5	<1	80
Colorectal	0.65	Decennial colonoscopy Triennial stool-based screening (Cologuard) Annual Stool based screening (FIT) Ages 45-75	75-93% adenomas 6mm or greater 92.3 73.8	86% 86.6 94.9	3.9-100 depending on study and reference (avg. 22.9%) 3.7 8.7	69.7
Lung	1.1 (high risk)	Annual low-dose CT ages 50-80	85	87	6.9	5
Prostrate	15.5	Biennial PSA testing, men 55-69	21	91	30	33

New Cancer Screening Paradigm

Goal:

- Shift cancer detection to earlier stage to hopefully increase treatability
- Provide screening for cancers without previous rigorous screening options

To be successful:

- Low false positives
- Ability to localize the cancer with high accuracy
- Limit over diagnosis (not over detect indolent cancers)
- Need data from prospective studies that show that liquid biopsies deliver benefits to patients beyond being non-invasive such as increasing quality-adjusted life-years.

Could MCED be a Solution?

MCED	Standard Screening
• **Lower the barrier to access** • **Less invasive** • **Fast** • **One blood draw for 50 cancers**	• **travel to imaging centers and colonoscopy centers** • **mammograms uncomfortable, colonoscopies invasive, pap smear invasive** • **require scheduling and prep and up to full day off work** • **5 different screens for 5 different cancers**

Implementation Partnership

MCED screening with Galleri

Executive health patients

PCPM patients

Foundation funding submitted to expand to underserved population within Family Medicine

Appropriate patients

- Anyone who is at an increased risk of cancer:
  - >50 years
  - Personal history of cancer > 1yr out from completion of treatment
  - Hereditary predisposition (BRCA/Lynch)
  - Significant family history of cancer
  - Know high risk exposure (firefighter)

PCP
Recommends
MCED

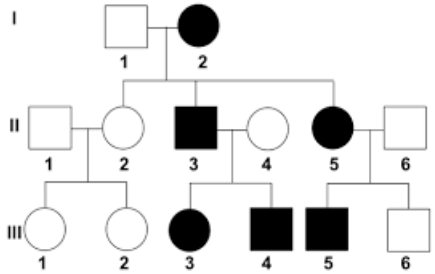
PCP
Notifies
PCPM

PCPM
Holds Virtual
Pre-test Consult

TEST KIT

Patient Agrees
Blood Draw
Completed

Positive Result
Workup and Consult
Oncology



FedEx

Sample
Sent to Lab
TAT-10d

PCPM
Holds Optional Virtual
Post-test Consult

PCPM
Identifies Additional
Risk-Recommendations
GCRA/PGx/CV/Carrier
Back to PCP

Personalized medicine and weighing risk (SCREEN vs TEST):

Pre-test Probability 1/120

Post-test Probability 1/2

Diagnostic work up is Positive

Diagnostic work up is Negative

Negative testing: how frequent to repeat?
Residual risk and False negatives (0.6%): specific cancer has poor sensitivity, type of tumor
Does not secrete cfDNA into blood stream at high enough levels to detect
Cancer is pre-detection level

Plan for positive results and collaboration of care

1-2% of those tested will have a positive results

Each positive results is a post test probability of 1 out of 2 for cancer

How can we best collaborate and prepare to care for patients with a positive screen.

- Support patients and their providers
- Minimize invasive procedures
- Minimize cost
- Maximize identification of cancer in timely manner