Cancer Screening Clinical Trials: A Platform for Research in Cancer Screening

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Past NCI Cancer Screening Clinical Trials

Large randomized screening clinical trials which were initiated as randomized controlled trials with mortality endpoints

- Prostate, Lung, Colorectal, and Ovarian Screening Trial (PLCO)
- National Lung Cancer Screening Trials (NLST)

Converted to observational studies with long-term follow up

- Linkages to National Death Index and Medicare
  - Long-term follow up for cancer cases, treatment, and other analyses
- Biospecimens for additional correlative endpoints
- Digital images (NLST) available for correlative studies as well.

Prostate, Lung, Colorectal, Ovarian (PLCO) Trial

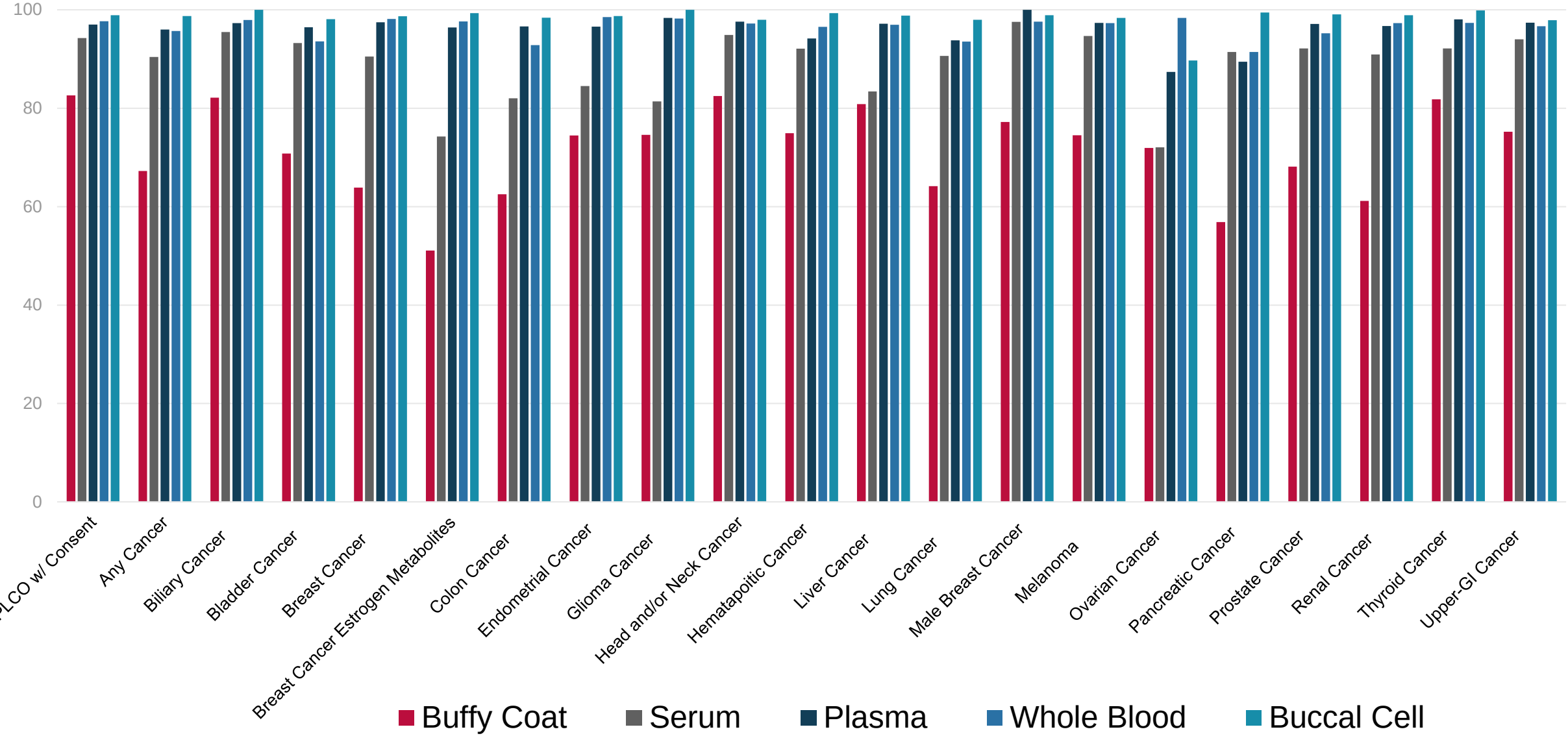
About 155,000 men & women enrolled from 1993-2001

Randomized to either screening intervention or control arm

Screening intervention included:

- Digital rectal exam, PSA annually for 5 years (Prostate Cancer)
- Chest x-ray annually for 4 years (Lung Cancer)
- Flexible sigmoidoscopy baseline, year 3 and 5 (Colorectal Cancer)
- Transvaginal ultrasound (TVU) annually for 4 years (Ovarian Cancer)
- CA-125 annually for 6 years (35 IU/ml cutoff)

PLCO Biospecimens for Multiple Different Cancer Types



Research Opportunities with Screening Trials

Evaluate the relationship of the screening biomarker or imaging modality with benign lesions, pre-cancer lesions, and cancer

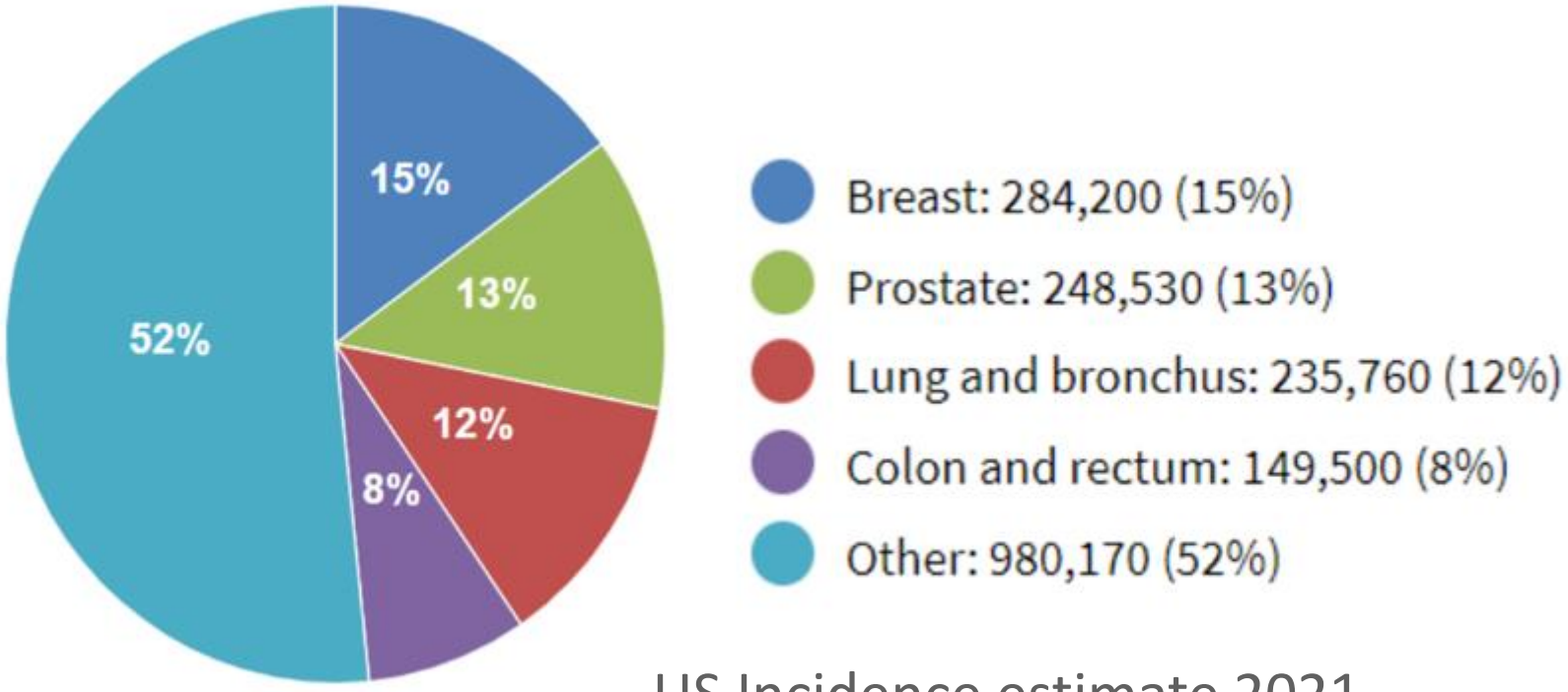
- Longitudinal follow up of participants without cancer.
  - Does screening with the modality improve cancer mortality?
  - What is the relationship of the biomarker analyte or imaging to the different stages or pathologic subtypes of cancer?
- Longitudinal follow up of those with abnormal screening tests, but not cancer.
  - Detection of pre-malignant lesions and abnormalities which may or may not progress to cancer

Current Cancer Screening Issues

Cancer Screening Exists for Common Cancers

Currently, screening tests exist for only a few organ sites, but they are some of the most common cancers in the US:

- Breast, cervix, colon, lung (in high-risk individuals)
- Prostate (on an individual basis)



US Incidence estimate 2021

But more than half of cancer deaths are at sites that have no screening tests, including highly deadly cancers like ovarian cancer and pancreatic cancer.

Personal Genome Diagnostics
Foundation Medicine
Burning Rock
Biological Dynamics
20/20 GeneSystems
Precision Epigenomics
EarlyDiagnostics
Epic Sciences
Singlera Genomics
Biocept
QIAGEN
Exact Sciences
Guardant Health
GRAIL
Natera
Bluestar Genomics
Oncocyte
Delfi Diagnostics
Freenome
StageZero
Cardiff Oncology
LungLife AI
Resolution Bioscience
Elypta
Exosome Diagnostics
Adela
Caris Life Sciences

I think I'd like to have an MCD test, Doc, but which one?

Multi-Cancer Detection Assays

Measure biological signals in body fluids shed by cancer cells.

- Patterns of DNA methylation, fragmentation, genetic mutations
- Changes in RNA sequences, levels of protein biomarkers
- Combinations of above or other

Developed to screen for several cancers from different organ sites.

Have two parts to the test:

- Biologic measurement of the specific signals
- Software algorithms for determining the cut-point for a positive test

Each assay may screen for several different types of cancers

Examples of MCD Assays

Company	Assay	Technology	Targeted Cancers															
			Lung	CRC	Breast	Pancreas	Liver	Esophagus	Stomach	Ovary	Prostate	Bladder	Kidney	Uterus	H&N	Lymphoma	Leukemia	Plasma Cell
Adela Bio	adela	cfMeDIP-seq; cfDNA fragmentomics	■	■	■	■						■	■				■	
Biological Dynamics	Tr(ACE)	EV proteins; AI				■				■		■						
Bluestar Genomics	BluestarMCED	cfDNA 5hmC-seq; fragmentomics	■	■	■	■	■	■	■	■								
Burning Rock	OverC™	ELSA-seq	■	■		■	■	■		■								
Caris Life Sci	MI GPSai	cfDNA/cfRNA NGS; AI	■	■	■				■				■	■				
Delfi Dignostics	DELFI	cfDNA fragmentomics	■	■		■			■	■								
Early Diagnostics	cf Methyl-Seq	cfDNA mC-NGS	■	■			■		■									
Exact Sciences	CancerSEEK	cfDNA NGS; protein markers	■	■	■	■	■	■	■	■								
Freenome	FMBT	Multi-Omics/AI	■	■	■	■	■	■	■	■	■	■	■	■				
Grail	Galleri™	CpG-cfDNA NGS	■	■		■	■	■	■	■		■			■	■		■
LungLifeAI	LungLB	CTC FISH; Imaging AI	■		■		■						■					
Natera	Signatera™	cfDNA NGS; protein markers	■	■	■	■	■					■		■				
Precision Epigenomics	Sentinel-10™	CpG-cfDNA qPCR	■	■	■	■	■											
20/20 Gene Systems	oneTEST	circul. Cancer Ag's; AI	■	■	■	■	■				■							

Many Unknowns in Using MCD Assays to Screening for Cancer

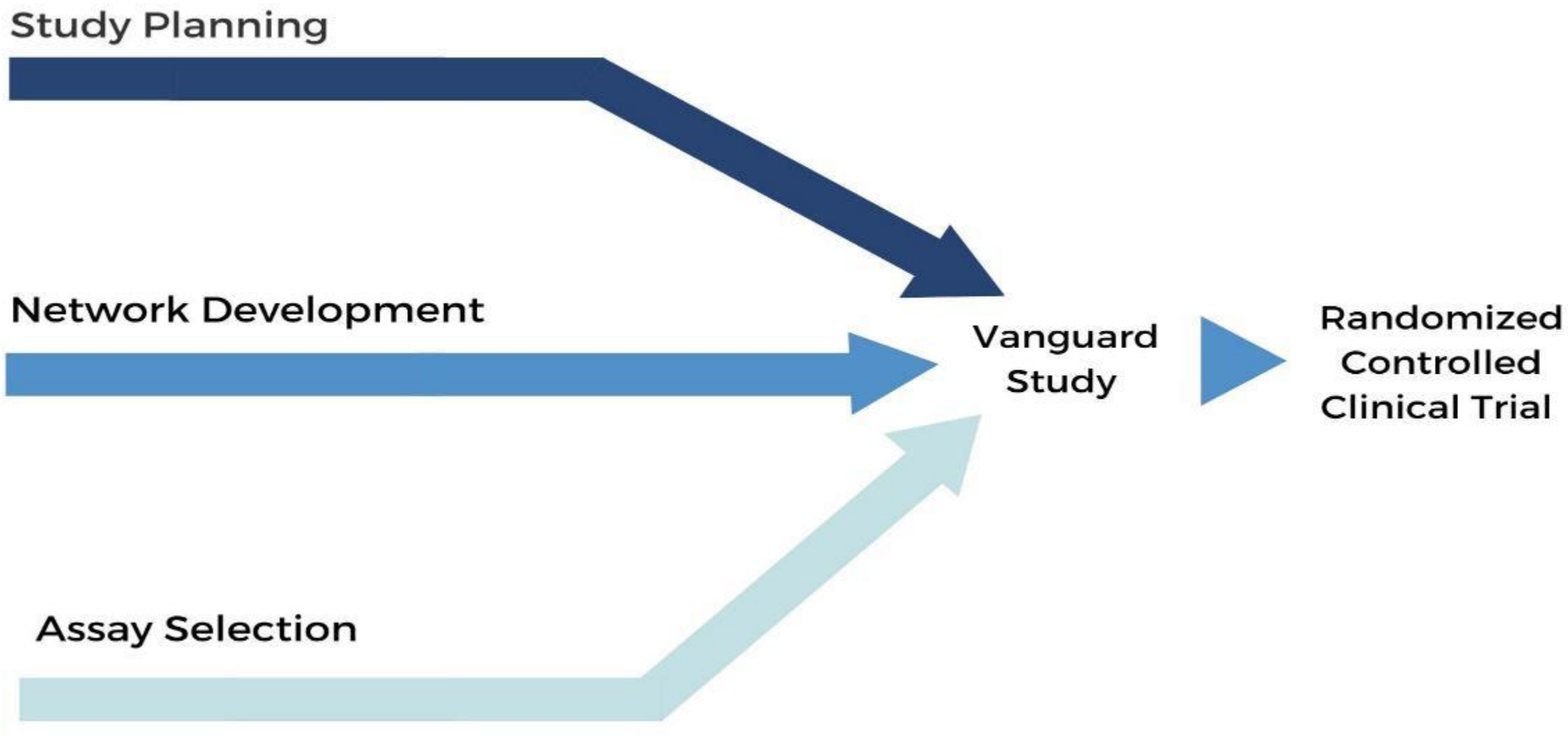
Unknown if screening a population of asymptomatic people for cancer with MCD assays will result in a mortality reduction from cancer.

Harms from using MCD assays to screen for cancer are unknown:

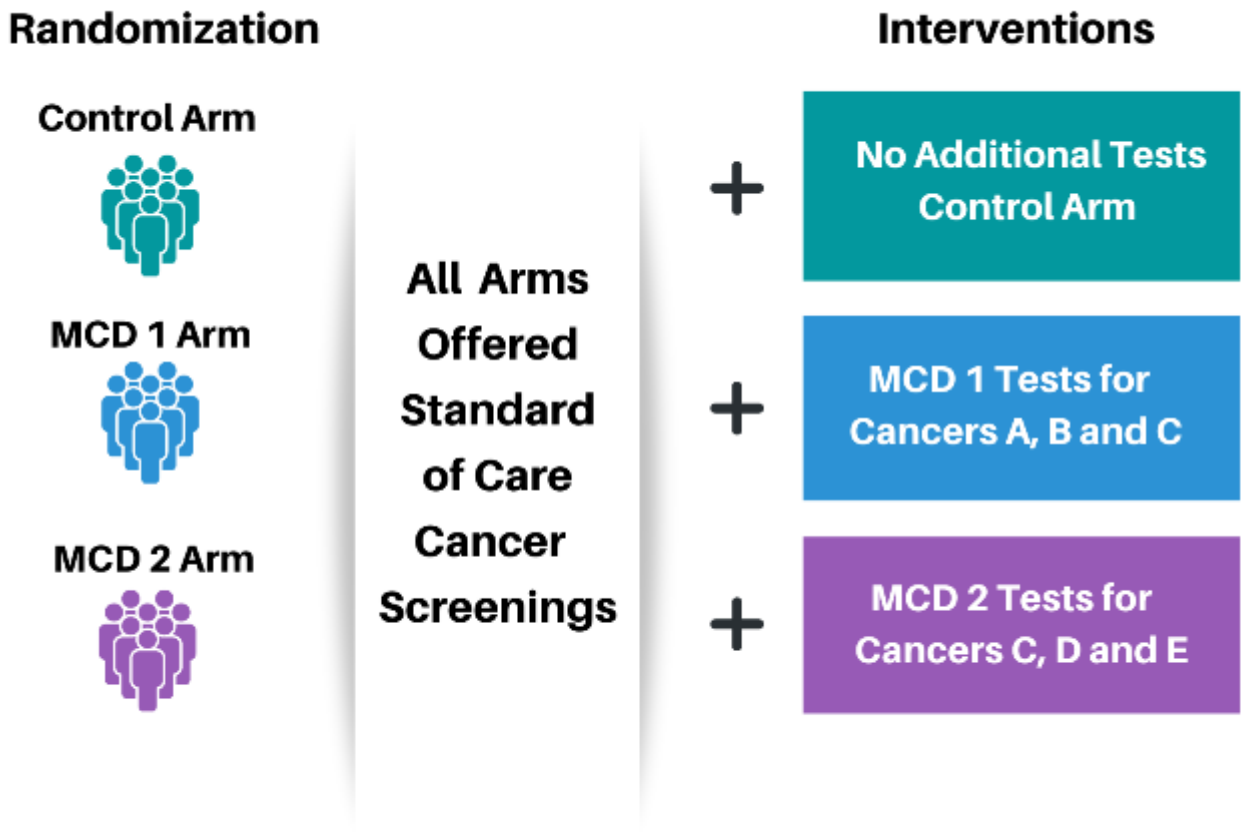
- What kind/how many diagnostic tests are needed to make a cancer diagnosis?
- What happens if following a positive MCD test, you do not find a cancer?
- How many people will be subjected to unnecessary invasive procedures and suffer from various complications of those procedures?
- Will people stop standard of care screening if get a negative MCD test?
- Will a blood test make screening more accessible or exacerbate disparities?
- Will using these assays lead to a mortality reduction from those cancers?

NCI's Approach to Evaluate Multi-Cancer Detection Assays for the Purpose of Cancer Screening

Framework for Developing MCD Clinical Utility Trial



The Vanguard Study: Pilot, Feasibility



Objectives of Vanguard Study

- Assess participant willingness for randomization
- Determine adherence to testing and diagnostic follow-up
- Evaluate feasibility of protocol-defined diagnostic workflows
- Determine reliability and timeliness of blood specimen testing and return by MCD companies
- Identify facilitators and barriers to recruitment/retention/compliance of diverse participant groups

Estimated sample size for the Vanguard is 8,000 persons per arm

November 18, 2022

Cancer Screening Research Network
Funding Opportunity Announcements Published

- ACCrual, Enrollment & Screening Sites (ACCESS) Hub (UG1)
- Coordinating & Communication Center (UG1)
- Statistics & Data Management Center (UG1)

For more information:
https://prevention.cancer.gov/CSRN

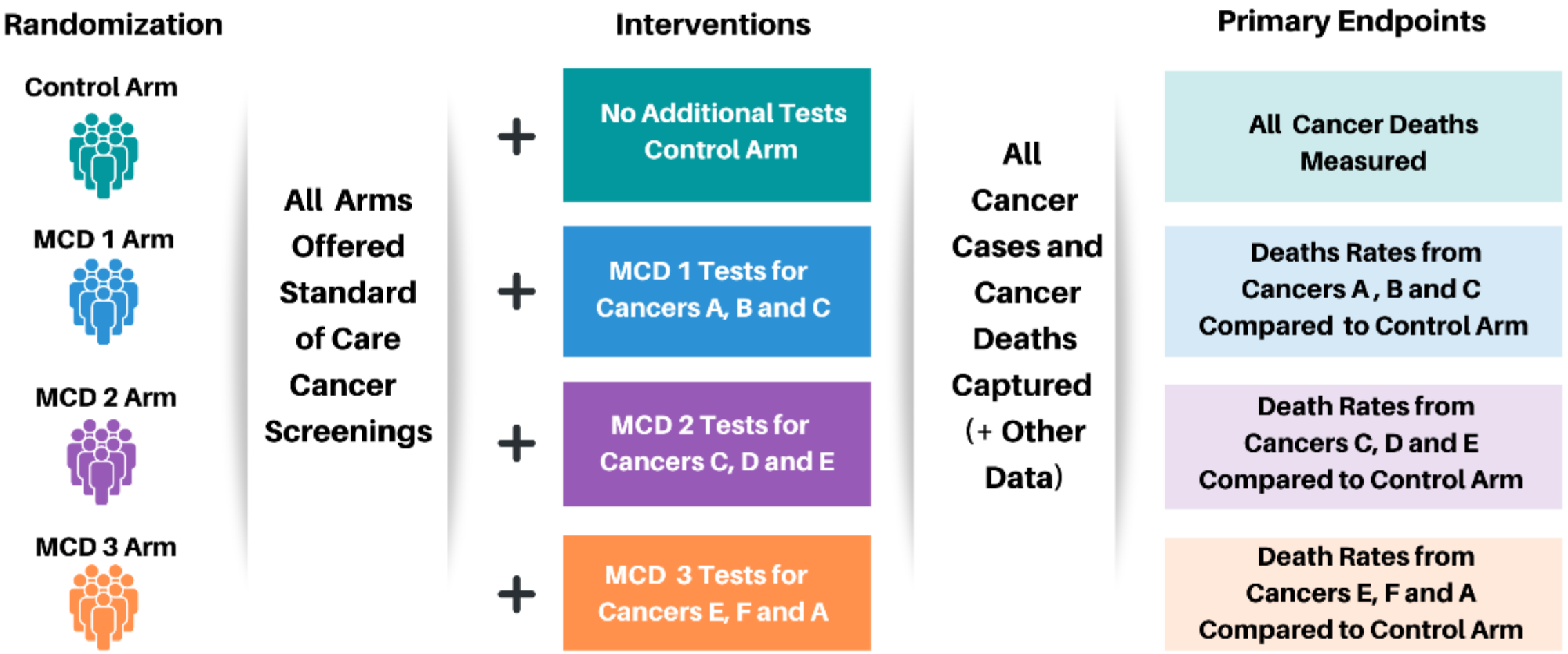
Overall Goals of CSRN

Establish the organizational infrastructure for all necessary components to implement cancer screening clinical studies

- Develop cancer screening trials to evaluate emerging technologies
- Assess the clinical utility of cancer screening programs or biomarkers of detection including downstream interventions and health outcomes
- Apply precision medicine approaches to screening using novel risk assessment tools to individualize screening protocols
- Evaluate the effectiveness, feasibility and scalability of screening strategies
- Identify and address technical, process, cultural challenges to adapt implementation of screening strategies
- Conduct surveillance of cancer screening in diverse populations
- Develop cancer screening studies to evaluate clinical workflow

Anticipated Design for a Large Platform Trial to Evaluate Multi-Cancer Detection Assays

Possible Platform Randomized Control Trial Design



Thank you!

www.cancer.gov

www.cancer.gov/espanol

Opportunities

Evaluate novel technology for the purpose of screening individuals for cancer and assuring that the process improves health outcomes

- Evaluate novel technology to improve screening for cancer
- Evaluate strategies to incorporate risk stratified screening
- Platform design permits some flexibility to add arms for new technology
- Longitudinal follow up for persons with positive screen, but negative cancer workup
- Learn about pre-malignant lesions and natural history
- Ability to validate surrogate endpoints for future trials
- Publicly funded clinical trials where the goal is to improve public health

Challenges

Establish relationships with developers of novel technology and other research partners

- Develop collaboration agreements with developers for formal testing
  - Different perspectives
- Regulatory pathways vary by countries, and not clearly defined for US
- Communication strategies for different stakeholders
  - Availability of technology and trial integrity
- Secure long-term funding

Pilot or Feasibility Study
The Vanguard Study

Sample Size for The Vanguard Study

Large numbers of asymptomatic individuals will be needed to have sufficient numbers of screen positives (positive assay results):

- Assay detects several different cancers, so need sufficient numbers of diagnostic workups in different cancers

Based upon the current published data from existing MCD assays:

- ~1% of assays results will be positive
- ~60% of those will have a diagnostic resolution
- One of the major objectives of the Vanguard is the development of a standard approach to the diagnostic process and collection of the data
- An estimated 8,000 persons per arm for 3 arms for 164 screen + to put some reasonable confidence intervals (CI) around diagnostic resolution (i.e., 60.0%; 95%CI = 52.5-67.5%)