The Cancer Screening Research Network

Elyse LeeVan, MD, MPH

Division of Cancer Prevention, Early Detection Research Group, NCI

NIH NATIONAL CANCER INSTITUTE

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Purpose of the Network

- Conduct multi-center cancer screening trials and studies
- Improve early cancer detection
- Evaluate emerging cancer screening modalities with the ultimate goal of reducing cancer-related morbidity and mortality

Network Components

Accrual, Enrollment, and Screening Sites (ACCESS)

- Participate in the scientific development of CSRN trials and studies, recruit participants, and conduct study protocols

Statistics and Data Management Center (SDMC)

- Provides statistical expertise and centralized data management, quality control, and reporting

Coordinating and Communication Center (CCC)

- Coordinates study operations, and develops and implements communication activities

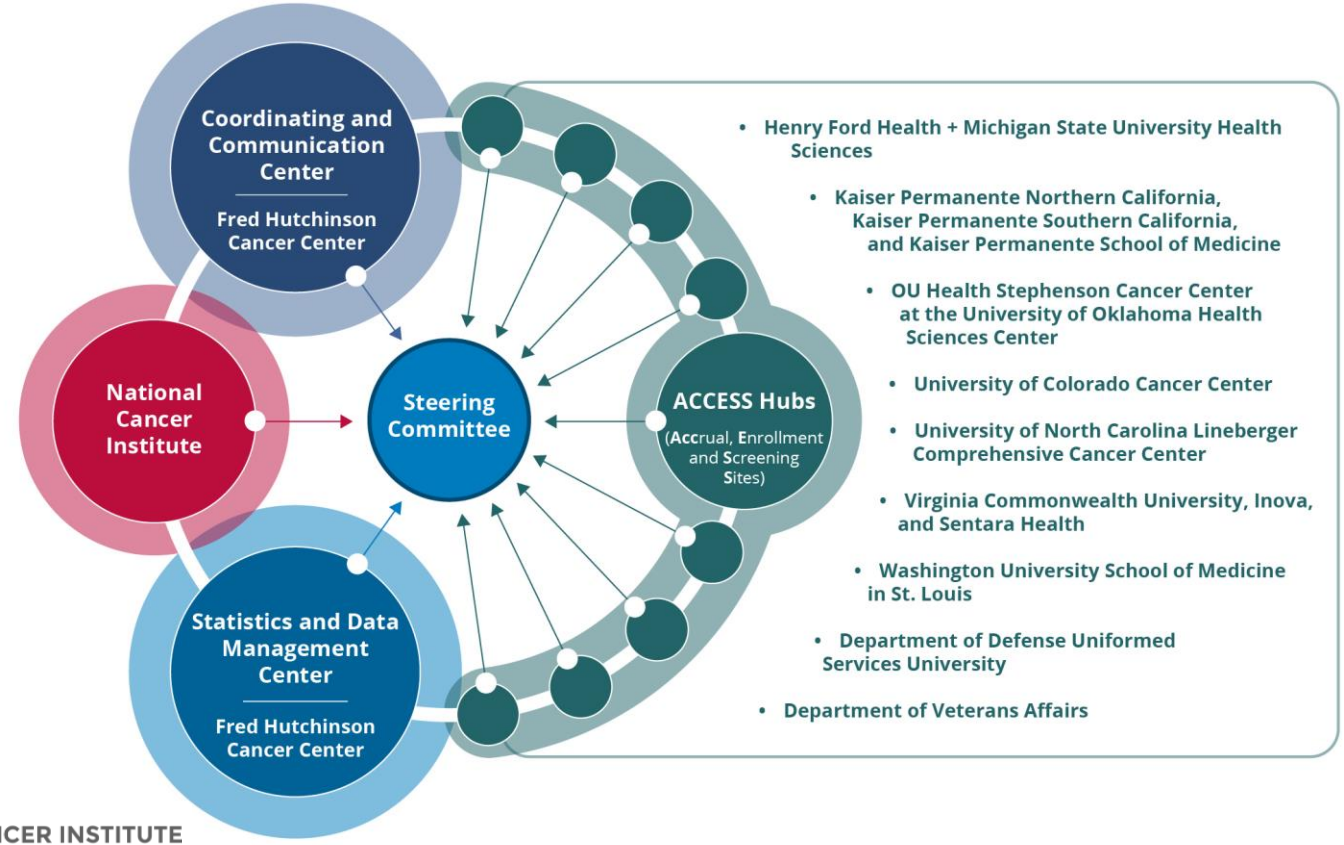
Request for Applications (RFA) Released November 18, 2022

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

CANCER SCREENING RESEARCH NETWORK



Diverse Leadership Teams

PIs:

Biostatistics
Epidemiology
Family Medicine
Gastroenterology
Gynecologic Oncology
Health Economy
Health Policy
Hematology/Oncology
Internal Medicine
Pathology
Preventive Medicine
Pulmonary/Critical Care
Social Psychology

Key Personnel:

Anthropology, Cardiology, Cardiothoracic Surgery, Colorectal Surgery, Dermatology, Ethics, Genetic Counseling, Gerontology, Head and Neck Surgery, Health Services, Informatics, Neuroradiology, Nursing, Nutrition, Psychology, Patient Reported Outcomes Specialty, Psychopharmacology, Public Health, Radiology, Surgical Oncology, Urology

Focus on Participant Diversity

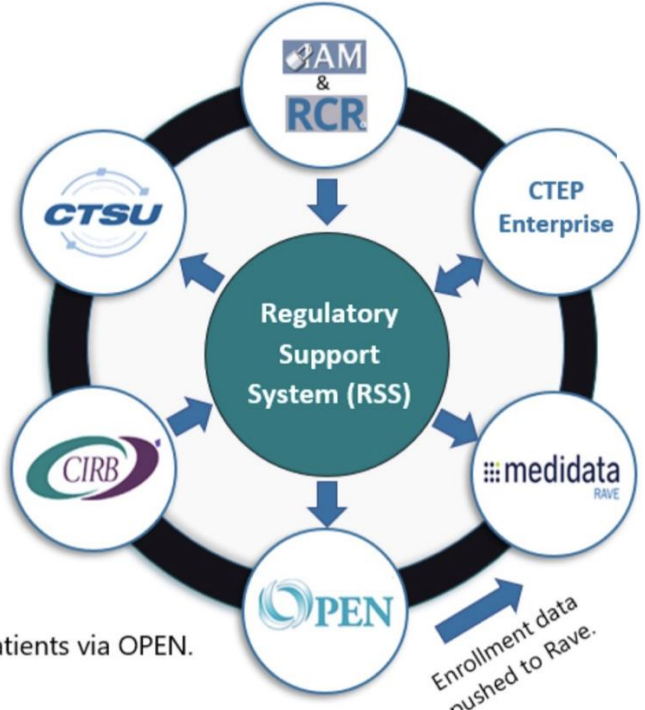
FOA stated: Institutions will be responsible for recruiting, consenting, and registering participants from diverse populations for cancer screening trials and studies.

The Network Contains:

- Federally Qualified Health Centers
- Tribal Populations
- Rural Populations
- Historical Success with recruitment of individuals underrepresented in clinical trials

Network Infrastructure

1 ACCESS Hubs and site staff register with CTEP Identity and Access Management (IAM) and Registration and Credential Repository (RCR).



2 Access to protocol documents, resources, and links to other applications.

3 Obtain Central Institutional Review Board (CIRB) approval; elect CIRB as IRB of record.

4 Enroll patients via OPEN.

5 Enter and manage data in Rave.

6 Systems for protocol development, drug shipment, auditing, and safety reporting.

Vanguard Study

A pilot study to assess feasibility of a Multi-Cancer Detection (MCD) assay platform RCT

Background on MCD Assays

Each MCD assay measures different analytes in blood

- There are many markers in development (e.g., patterns of DNA methylation, DNA fragmentation, RNA sequences, proteins, mutations, etc.)
- Each MCD assay detects a different set of cancer types

Two parts to the assay

- Biologic measurement
- Software algorithm (usually machine learning or artificial intelligence) to determine a cut point for positive versus negative assay results
  - Frequently, assay companies continue to refine and update the algorithms

JOURNAL ARTICLE

Predictive Performance of Cell-Free Nucleic Acid-Based Multi-Cancer Early Detection Tests: A Systematic Review FREE

Elyse LeeVan, Paul Pinsky

Clinical Chemistry, hvad134, https://doi.org/10.1093/clinchem/hvad134

Published: 04 October 2023 **Article history** ▾

Table 2. Sensitivity, specificity, and AUC.

Author/reference	Validation	Model[a]	Sample size[b] (cases |controls)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	AUC (95% CI)
Chen (9) (Phase 2)	Independent	PanSEER	113|207	88 (80–93)	96.1 (92.5–98.3)	97
Chen (9) (Phase 3)	Independent	PanSEER	98|207	95 (89–98)	Same as above	99
Cohen (10)	Cross	CancerSEEK	1005| 812	62 (56–68)	99[c]	91 (90–92)
Constâncio (11)	Cross	PanCancer	223|136	64	69.8	
Cristiano (12)	Cross	DELFI	236|245	73 (67–79)	98[c]	94 (92–96)
Douville (13)	Cross	Aneu + Mut + Proteins [7]	883|812	75 (72–78)	99[c]	94
Gao (14)	Independent	MCEDBT-1 [2]	473 | 473	69 (65–73)	98.9 (97.6–99.7)	—
Haldavnekar (15)	Independent	—	36|6	95 (88–99)	83	—
In' t Veld (16)	Independent	ThromboSeq	1096|146	64 (61–66)	99 (95–100)	91 (89–92)
Jamshidi (17)	Independent	Pan-feature [10]	464|362	36 (31–40)	98	
Kandimalla (18)	Cross	Pan-GI/Git-BS	254|46	—	—	88 (82–94)
Klein (19)	Independent	Galleri	1346|1254	76 (74–79)[d]	99.5 (99–99.8)	—
Lennon (21)	Independent	CancerSEEK Blood test[c]	96| 9815	27 (19–37)	98.9 (98.7–99.1)	—
Liu (22)	Independent	—	68|25	84 (74–91)	100	—
Liu (23)	Independent	—	356|610	76 (73–81)[d]	99.3 (98.3–99.8)	—
Ris (24)	Training	DEEPGEN	260|415	43 (37–49)	99[c]	90 (88–92)
Stackpole (25)	Cross	cfMethyl-Seq	217	81 (69–91)	97.9	97.4 (92.6–99.8)
Sundquist (26)	N/A	n(DNA)	66|136	72 (61–83)	71	78 (70–86)
Zhou (27)	Independent	—	43| 24	—	—	91.2 (83.7–98.7)
Zhou (28) (Phase 2)	Cross	SRFD-Bayes [4]	2000|400	92 (81–97)	99.5[c]	97.6 (97.2–98.0)
Zhou (28) (Phase 3)	Independent	SRFD-Bayes [2]	191| 207	38 (31–44)	95[c]	

[a]Number in brackets indicates total number of models reported on, if >1.
[b]For independent validation, sample size is number in validation set; for cross-validation, sample size is number is total number used is the cross-validation process.
[c]Specificity fixed at the indicated level.
[d]Sensitivity based on 12 pre-specified cancer types, as shown in Table 2.

Published Information about MCDs

Reference	Assay Type	Phase
Chen	DNA Methylation	2
	DNA Methylation	3
Cohen	Multi-modality: Mutation and protein biomarkers	2
Constâncio	DNA Methylation	2
Cristiano	DNA Fragmentation Profiles	2
Douville	DNA Mutation	2
Gao	DNA Methylation	2
Haldavnekar	DNA Mutation	2
In' t Veld	Platelet RNA Mutation	2
Jamshidi	Multiple components [c]	2
Kandimalla	DNA Methylation	2
Klein/Tang	DNA Methylation	2
Lennon	Multimodal: DNA Mutation and protein biomarkers	4
Liu, L	DNA Methylation	2
Liu, M	DNA Methylation	2
Ris	DNA Mutation	2
Stackpole	DNA Methylation- Whole genome	2
Sundquist	Circulating cell free nuclear and mitochondrial DNA levels	2
Zhou M	DNA Methylation: 5-hydroxymethyl-cytosine modification	2
Zhou, X	DNA Methylation: Targeted	2
	DNA Methylation: Targeted	3

Review of Nucleic Acid Based MCDs

- **20 Publications***
- **14 Unique assay developers**
- **86% of studies were on patients newly diagnosed with cancer (phase 2)**
- **Only 1 prospective study on asymptomatic participants (phase 4)**

* Manuscripts only,

Unknowns: Screening for Cancer with MCD Assays

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:

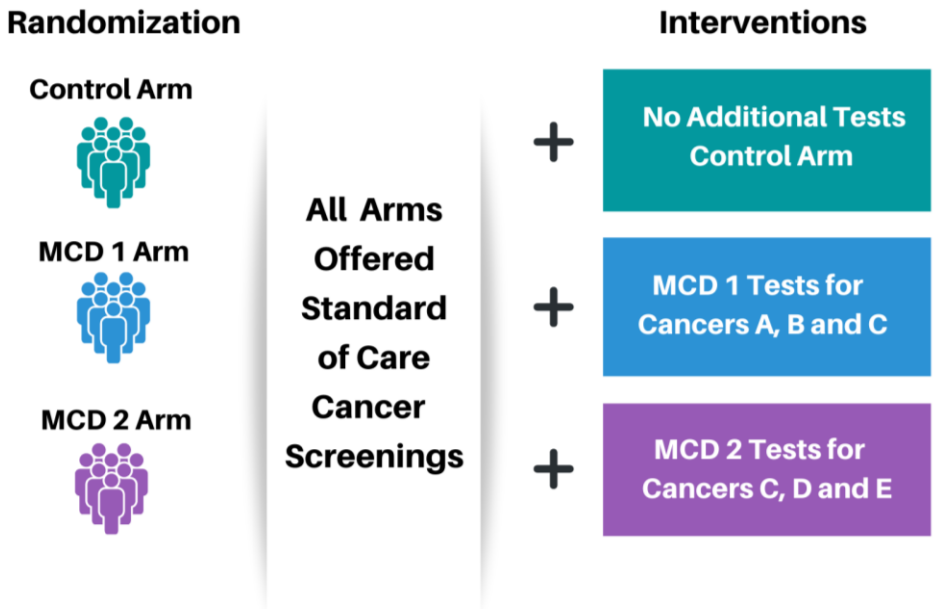
- What kind/how many diagnostic tests are needed to make a cancer diagnosis?
- What happens if following a positive MCD test, you do not find a cancer?
- How many people will be subjected to unnecessary invasive procedures and suffer from various complications of those procedures?
- Will people stop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

Study Design Workshop (October 14 and 29, 2021)

- Participants included 30 external investigators
- Published workshop design (*JNCI*, March 2023)
- Recommendations:
  - NCI needs to evaluate MCD assays for clinical benefit
    - Strong support for a large MCD RCT
  - There is a significant need to evaluate the harms as well as the benefits
  - A pilot study is needed to optimize study design

Initial Project for the Network

The Vanguard Study



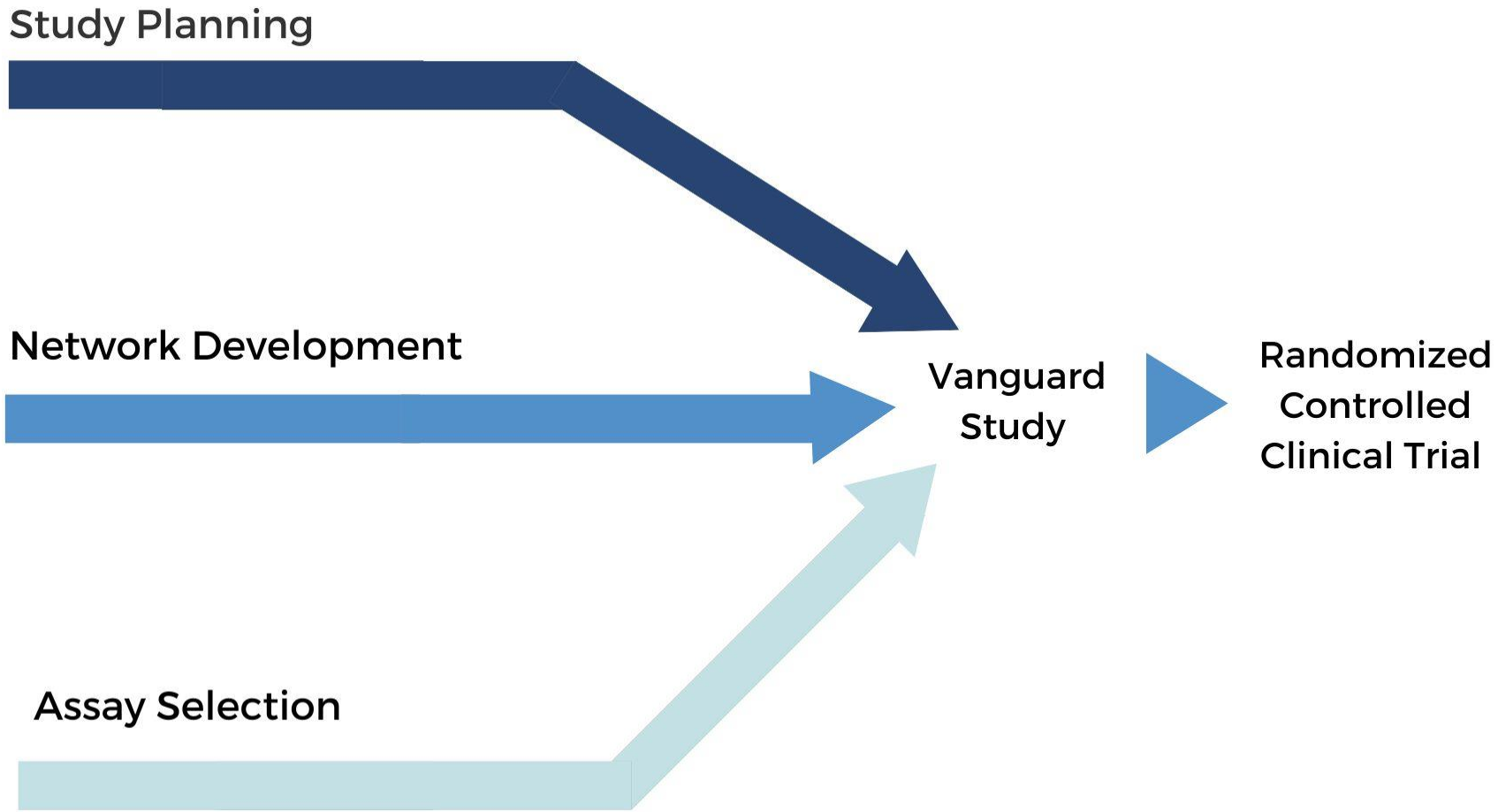
Estimated sample size for the Vanguard is 8,000 persons per arm

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

Diagnostic Workup

- Single cancer screening tests have a clear target for workup, MCDs may not
- How should a suggestion of a Tissue of Origin (TOO) guide diagnostic workup? Should accuracy of TOO matter?
- How will these test be paid for in uninsured and underinsured individuals?
- ACCESS Hub investigators had to propose strategy in Research Plan


Study Planning
Network Development
Assay Selection
Vanguard Study
Randomized Controlled Clinical Trial

Assay Selection Process

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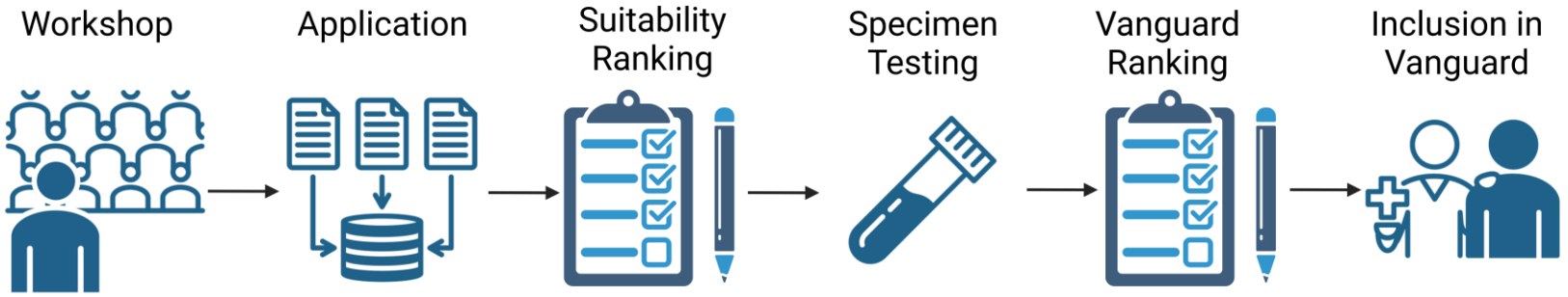
NCI Virtual Workshop to Engage Multi-Cancer Detection (MCD) Assay Developers

May 3, 2023

1:00–5:00 p.m. ET

Bird’s-eye view of the assay selection process



Assay Application Review Criteria

- Types of cancers detected
- Sensitivity
- Specificity
- Tissue of origin accuracy (if applicable)
- Sample type and volume
- Prior studies conducted
- Scalability to meet Vanguard requirements

Alliance Reference Set Collection

For an independent verification of the assay performance characteristics

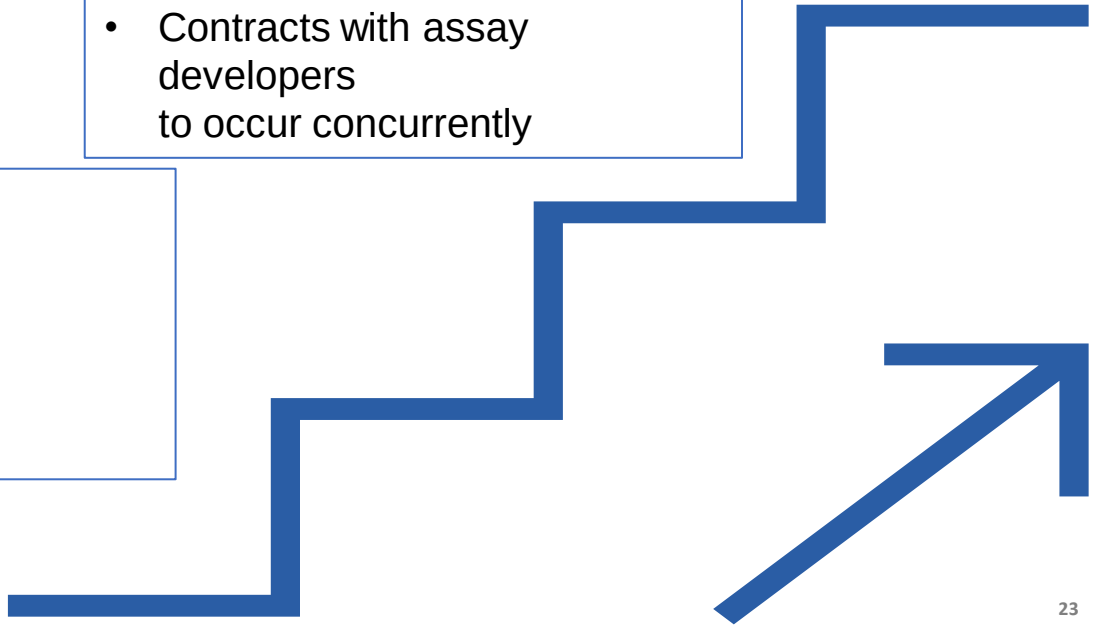
- Alliance recruited participants to provide blood for this assay verification process
  - 1000 newly diagnosed cases and 1000 controls
- Patients with the following cancers include:
  - Bladder, breast, colorectal, endometrium, esophageal/gastric, head and neck, hepatobiliary, kidney, leukemia, lung, lymphoma, melanoma, myeloma, ovary, pancreas, prostate, sarcoma, thyroid
- Plasma and buffy coat collected

Next Steps for CSRN

Late 2024
Vanguard launch

Mid to Late 2024
- Protocol to IRB
- Contracts with assay developers
  to occur concurrently

Early 2024
- Establish/populate workgroups
- Present NCI workgroup findings to investigators
- Begin protocol writing
- Plan for in person meeting at NCI



Summary

- *A variety of technologies are rapidly developing to improve early detection of cancer*
- *Multi-cancer detection assays offer the potential to revolutionize cancer screening, but there is insufficient data to understand how best to use them*
- *The new Cancer Screening Research Network is positioned to carry out studies evaluating new screening modalities in representative populations across the United States*
- *The Vanguard Study will provide data and inform the design of a large-scale trial to evaluate these assays for their potential to reduce death from cancer*

Questions

Do you have any thoughts about ways to improve the Vanguard trial design?

Do you have any recommendations regarding data elements to capture in this pilot trial that would guide the design for a large platform randomized control trial?

What do you foresee as the biggest challenges to the success of this study, and do you have recommendations to mitigate them?

Thank you!

www.cancer.gov

www.cancer.gov/espanol