Cancer Screening Research Network/Multi-Cancer Early Detection Evaluation

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NIH NATIONAL CANCER INSTITUTE

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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 MCED test, Doc, but which one?

NCI Division of Cancer Prevention
https://prevention.cancer.gov/mced

Purpose for a Cancer Screening Research Network

- Develop the network infrastructure to efficiently conduct cancer screening clinical trials and other important screening studies.

- Initial effort is to conduct a feasibility (Vanguard) study in preparation for a large randomized controlled trial (RCT) to evaluate Multi-Cancer Early Detection (M.C.E.D.) assays for the purpose of cancer screening.

Clinical Evaluation of Screening Modalities is Needed

New emerging technologies are coming forward for commercialization without systematic evaluation for their use in the process of cancer screening.

- Pathways for biomarker assays to be used clinically without a rigorous assessment of clinical benefits (e.g., mortality reduction) and potential harms (e.g., morbidity due to treatment of indolent disease)

Studies are needed to address challenges with using M.C.E.D. assays for cancer screening

- How best to screen for multiple cancers with different latencies?
- How to effectively coordinate care after a positive test result?

Clinical Evaluation of Risk-Based Screening Strategies

Trials are needed to evaluate strategies that aim to refine risk stratification of imaging findings and determine when to defer biopsy.

- Lung cancer: indeterminant pulmonary nodules
- Breast cancer: BI-RADS 4a/4b downgrading to BI-RADS 3
- Prostate cancer: Outcomes of active surveillance in patients with low-grade cancer

Trials are needed to evaluate risk stratification for screening

- Use of risk scores (e.g., PRS) to guide who needs screening, how frequently, and how to manage a positive screen
- Modifying the starting age for a screening modality:
  - Colorectal cancer: early screening vs standard screening for colorectal cancer

Approach and Rationale for the Cancer Screening Research Network (CSRN)

DCP developed the proposed CSRN in collaboration with DCCPS to address questions related to the cancer screening continuum of care:

- Efficacy, effectiveness, best practices, adoption, adaption, implementation, etc. for each step in this continuum

Cancer screening trials require health care providers other than oncologists:

- Screening is much more than the test itself. Cancer screening is a process involving multiple steps and non-oncology medical specialists.
- Need sites and clinical investigators (e.g., gynecologists, primary care, gastroenterologists, etc.) who are experienced in cancer screening.

Approach and Rationale (continued)

Site investigators to contribute scientifically to the design of the trial:

- Identifying/implementing workflow and diagnostic work-up for the cancer screening (especially, for a positive M.C.E.D. test result)
- Assessing the potential harms, adverse effects, and other unexpected issues

Need contemporary communication strategy:

- Integrating trial- and local-level communication and recruitment efforts

CSRN Objectives

Establish the infrastructure needed to implement screening RCTs and other studies of screening and management for prevention/interception:

- Start with the Vanguard study

Conduct cancer screening trials to evaluate emerging technologies for cancer screening:

- Conduct clinical utility trials e.g., biomarkers emerging from EDRN

Conduct cancer screening studies to evaluate other aspects of cancer screening, including clinical workflow and coordination of care:

- Adaption and implementation of screening strategies for diverse practice settings
- Risk-informed screening and management
- Pragmatic trials of screening

Organizational Structure of CSRN

Utilizing the NCI Clinical Trials Enterprise System

Coordinating and Communication Center (One UG1 grant)

- Cancer screening leadership
- Operations and coordination for development/conduct of trials and studies
- Communications, recruitment and retention expertise
- Protocol development, monitoring and auditing, and training

Data Management & Statistical Center (One UG1 grant)

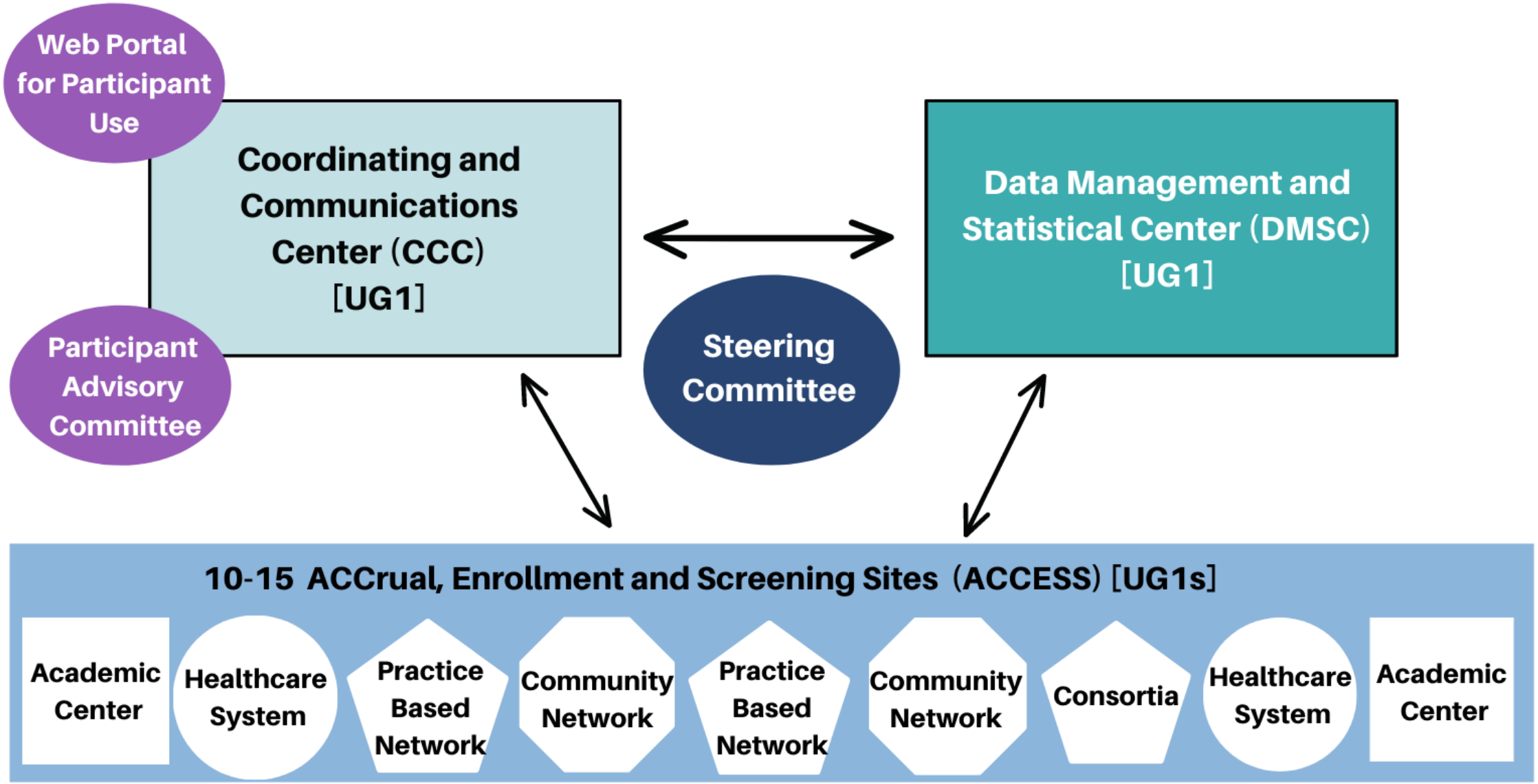
- Statistical expertise for study design & analysis
- Data management
- Coordination with Biorepository

Organizational Structure of CSRN (Continued)

Accrual, Enrollment and Screening Sites (ACCESS) (10-15 UG1 grants)

- Initially 10-15 UG1-funded CSRN sites; additional sites will be needed for the MCED RCT specifically
- Investigators with expertise in cancer screening and history of recruiting participants onto screening and prevention clinical trials and studies
- Institution with demonstrated accrual and retention of participants on disease screening clinical trials, especially cancer screening or prevention
- Variety of healthcare settings (academic, community, healthcare systems, consortia and/or practice-based research networks)
- Demonstrated history of recruiting underserved population

CSRN Structure



Portfolio Analysis

R01 Cancer Prevention and Control Clinical Trials Grant Program (PAR-21-035)

- Clinical trials evaluating the operating characteristics for cancer early detection technologies
- Communications, recruitment and retention expertise
- No current studies of M.C.E.D. technologies

NCI Community Oncology Research Program (NCORP)

- Successful network composed primarily of oncology practices and investigators
- Challenges exist to recruit participants to certain types of screening trials

Justification for the RFA and Cooperative Agreement

Substantial coordination and interaction needed from NCI

- Use of the *existing* clinical trials infrastructure
  - CTSU, CIRB, CTIS, Monitoring/auditing
- Protocol review process
- Coordination of specimen collection and tracking

Substantial NCI input for the statistical methods and modeling of the data from the Vanguard and the large RCT

Substantial resource allocation

- Set-aside funding to assure adequate resources for the Vanguard study

1st CSRN Study:
The Vanguard Study

Background on M.C.E.D. assays

Each M.C.E.D. assay measures different analytes in blood:

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

A positive-test result is a signal for cancer but does not diagnose cancer:

- Some tests suggest a “tissue of origin”.
- Some tests require extensive imaging after a positive M.C.E.D. result.

Some assay companies continue to refine the algorithms for determining a positive versus negative result.

Many Unknowns about Screening for Cancer with M.C.E.D. Assays

Unknown if screening a population of asymptomatic people for cancer with M.C.E.D. assays will result in a mortality reduction from cancer.

Harms from using M.C.E.D. 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 M.C.E.D 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 M.C.E.D. test?
- Will a blood test make screening more accessible or exacerbate disparities?
- Will these assays lead to overdiagnosis of indolent cancers?

Study Design Workshop in October 2021

NCI Staff provided the rationale and schema for large randomized controlled trial and the feedback was:

- Agreement across health care experts that NCI needs to evaluate M.C.E.D. assays for clinical benefit.
- Emphasis on the need to rigorously capture and understand harms from using M.C.E.D. assays for cancer screening.
- Strong support to conduct a study to assess feasibility of randomization, the clinical workflow for the diagnostic pathway, and other issues (“The Vanguard Study.”)

Request for Information (NOT-CA-22-033)

Seeking input from developers of M.C.E.D. assays on their readiness (*and willingness*) to participate in an NCI-sponsored clinical utility screening trial

Released January 21, 2022, Closed March 21, 2022

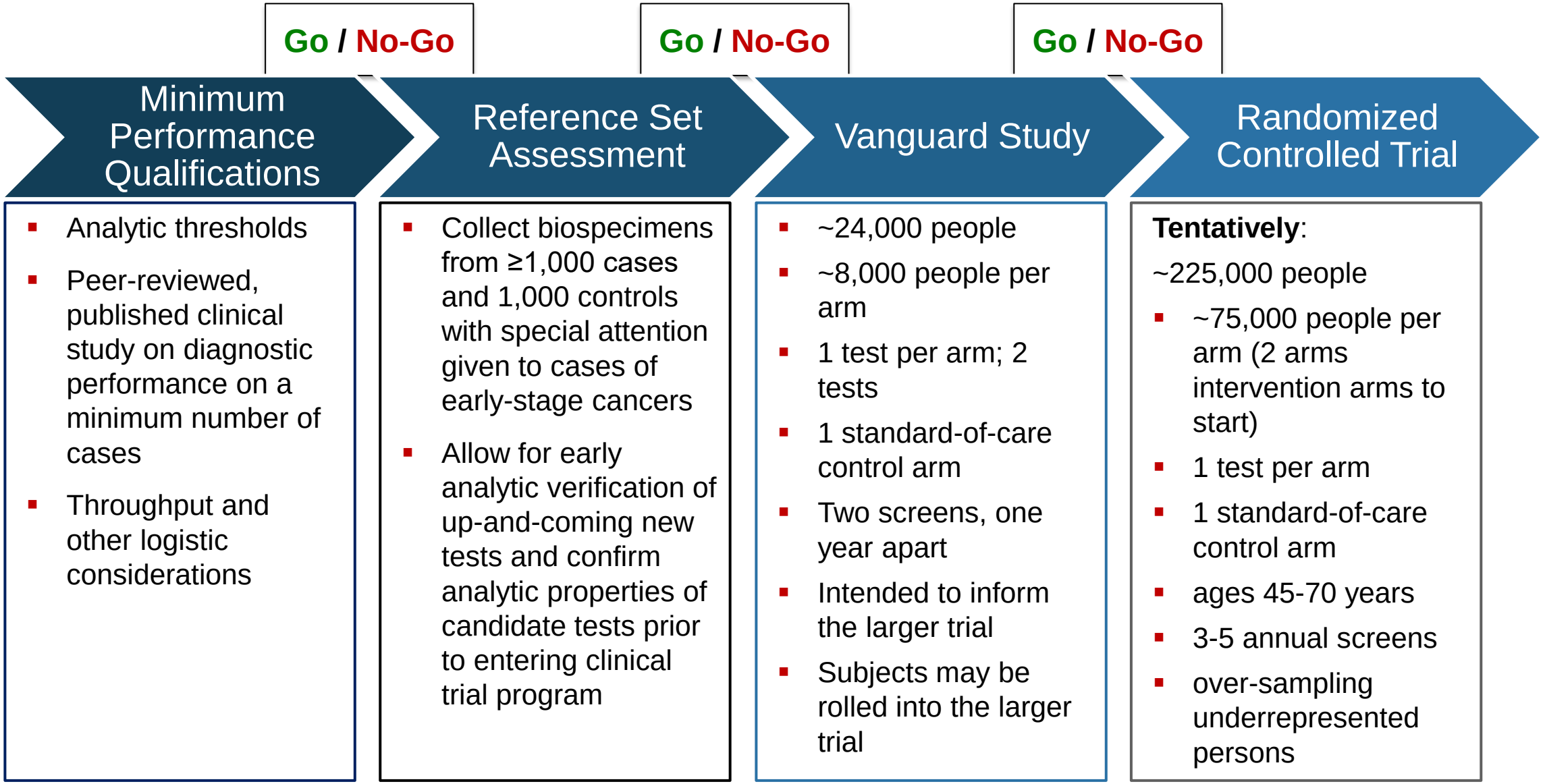
18 Responses:

- 17 developers of assays
  - 14 companies
  - 3 academic centers

  ➢ 9 assays using cell free DNA
  ➢ 3 assays based upon circulating tumor cells
  ➢ 5 assays based upon other analytes
- One request to be a participant!!!!

(*See Supplement Slide #2 for examples of the emerging MCED testing technologies*)

Schema for Step-Wise Validation



The Vanguard Study

Randomization

Control Arm

MCED 1 Arm

MCED 2 Arm

All Arms Offered Standard of Care Cancer Screenings

Interventions

\+ No Additional Tests Control Arm

\+ MCED 1 Tests for Cancers A, B and C

\+ MCED 2 Tests for Cancers C, D and E

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 MCED 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

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 M.C.E.D. 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%)

Possible Platform Randomized Control Trial Design

Randomization

Control Arm

MCED 1 Arm

MCED 2 Arm

MCED 3 Arm

All Arms Offered Standard of Care Cancer Screenings

Interventions

\+ No Additional Tests Control Arm

\+ MCED 1 Tests for Cancers A, B and C

\+ MCED 2 Tests for Cancers C, D and E

\+ MCED 3 Tests for Cancers E, F and A

All Cancer Cases and Cancer Deaths Captured (+ Other Data)

Primary Endpoints

All Cancer Deaths Measured

Deaths Rates from Cancers A , B and C Compared to Control Arm

Death Rates from Cancers C, D and E Compared to Control Arm

Death Rates from Cancers E, F and A Compared to Control Arm

MCED RCT Key Points

- Overarching Goals:
  - Vanguard: Assess Feasibility and Finalize RCT Design and Logistics
  - RCT: Assess Benefits, Harms, and the Generalizability of these Tests
- Assay agnostic
- Multi-Arm Platform Design allows dropping tests that do not perform well, and adding new arms for promising new tests
- Data sharing according to FAIR principles
- Biorepository: Validation of new tests, natural history studies, comprehensive characterization of tumors potentially at molecular stages/states that we have never observed (catalyzing new interception and therapeutic development), supports the NCI MCED program (*See Supplemental Slide 2*)

Ongoing Activities of the NCI M.C.E.D. Trial Team

NCI Staff have started key intramural-extramural working groups:

- Assay Working Group:
  - Meeting with respondents to the RFI and other sponsors of assays to consider readiness and willingness to incorporate assays into NCI studies.
- Diagnostic Pathway Working Group:
  - Evaluating how best to develop diagnostic pathways for study protocols
- Ethics and Equity Working Group:
  - Developing mechanisms for capturing participant understanding of M.C.E.D. technologies and cancer screening in general,
- Trial Design Working Group

Budget for CSRN and The Vanguard Study (Not the RCT)

Anticipate funding one CCC, one DSMC and 10-15 ACCESS sites:

- (VA/DOD is interested and considering participation)
- First year of funding $15.5M; total $73.5M for 4 years of funding

	Year 1	Year 2	Year 3	Year 4	Total
Coordinating Center	$1.5M	$2.0M	$2.0M	$2.0M	$7.5M
Data Management	$1.0M	$2.0M	$2.0M	$2.0M	$7.0M
Sites (10-15)	$8.0M	$9.0M	$9.0M	$9.0M	$35.0M
Contracts:					
CTSU/CIRB/CTIS	$4.0M	$3.5M	$4.0M	$4.0M	$15.5M
Biorepository	$1.0M	$1.5M	$1.0M	$1.0M	$4.5M
Assay Cost Sharing			$4.0M		$4.0M
Total/yr.	$15.5M	$18.0M	$18.0M	$18.0M	**$73.5M**

NCI M.C.E.D. Clinical Trial Team

DCP

- Philip Castle
- Lori Minasian
- Christos Patriotis
- Paul Pinsky
- Phil Prorok
- Sudhir Srivastava
- Carol Weil
- Kara Smigel
- Jack Lee
- Gwen Moulton

DCEG

- Hormuzd Katki

DCTD

- Lyndsay Harris

DCCPS

- Paul Han

NCI/OD

- Tony Dickherber (CSSI)
- Kathleen Carroll (TTC)
- Michael Pollack (TTC)

NIH/ORWH

- Sarah Temkin

FDA

- Wendy Rubenstein
- Dan Edelman

Thank you!

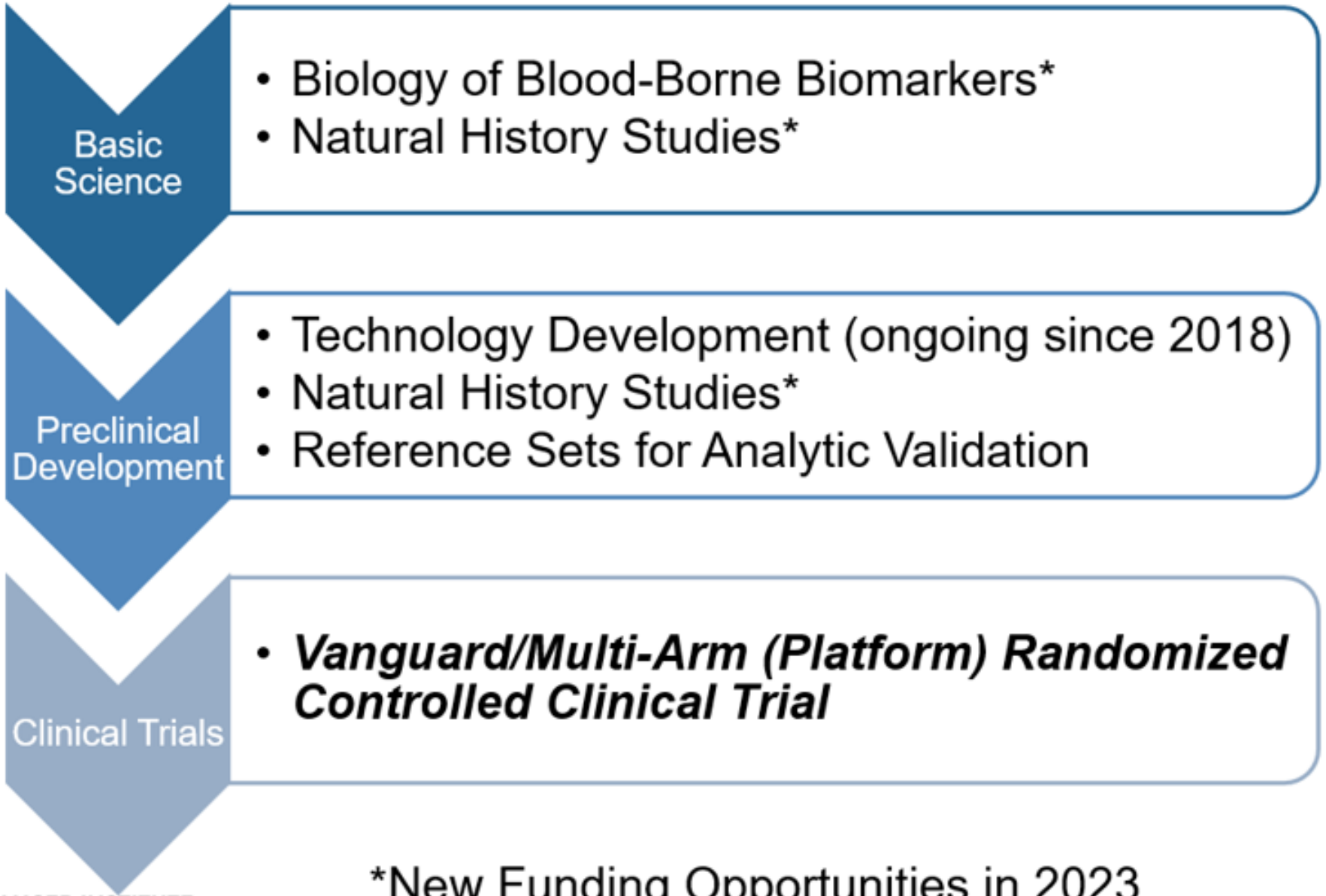
www.cancer.gov

www.cancer.gov/espanol

Supplemental Slide 1: Examples of MCED Assays

			Targeted Cancers															
Company	Assay	Technology	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	■	■	■	■	■				■							

Supplemental Slide 2: NCI's Proposed MCED Research Program



*New Funding Opportunities in 2023

Supplemental Slide 2: NCI's Proposed MCED Research Program

Basic Science

- Biology of Blood-Borne Biomarkers*
- Natural History Studies*

Preclinical Development

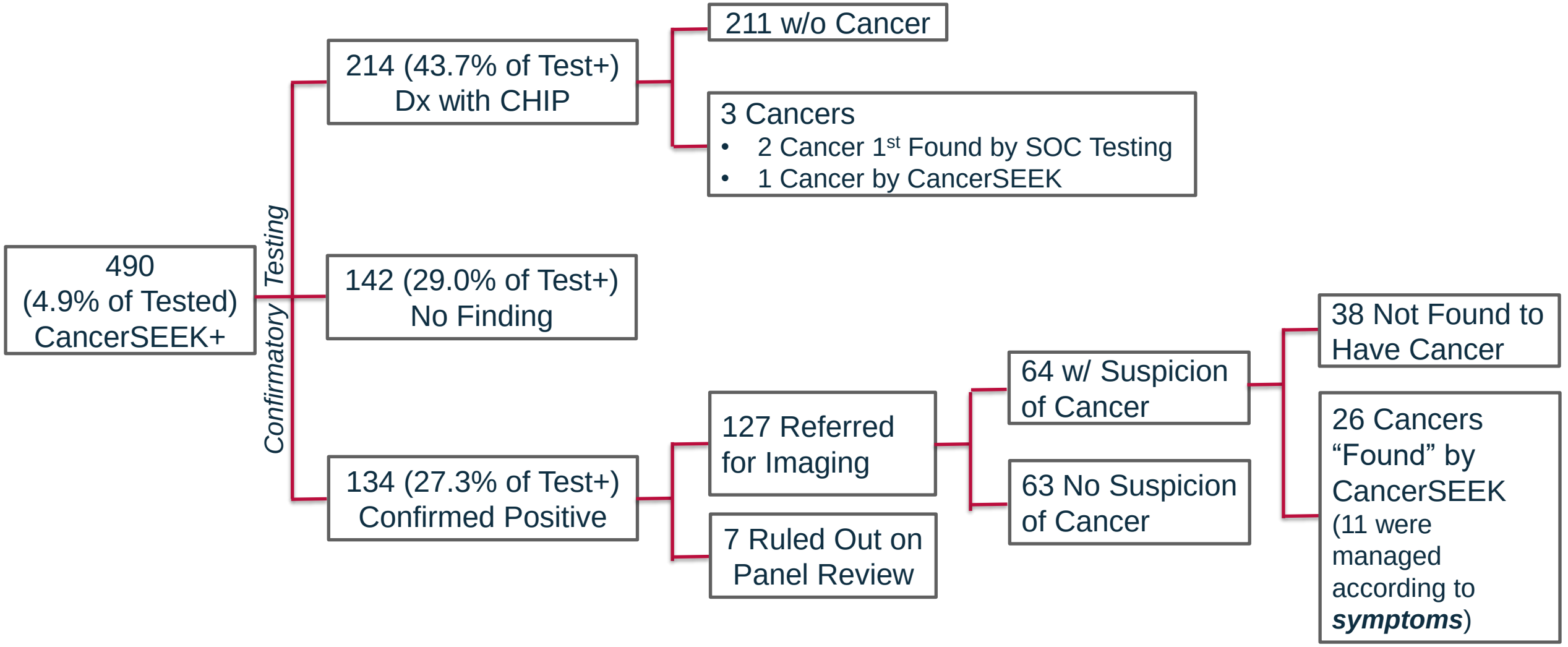
- Technology Development (ongoing since 2018)
- Natural History Studies*
- Reference Sets for Analytic Validation

If any of them work…

- ***Vanguard/Multi-Arm (Platform) Randomized Controlled Clinical Trial***

*New Funding Opportunities in 2023

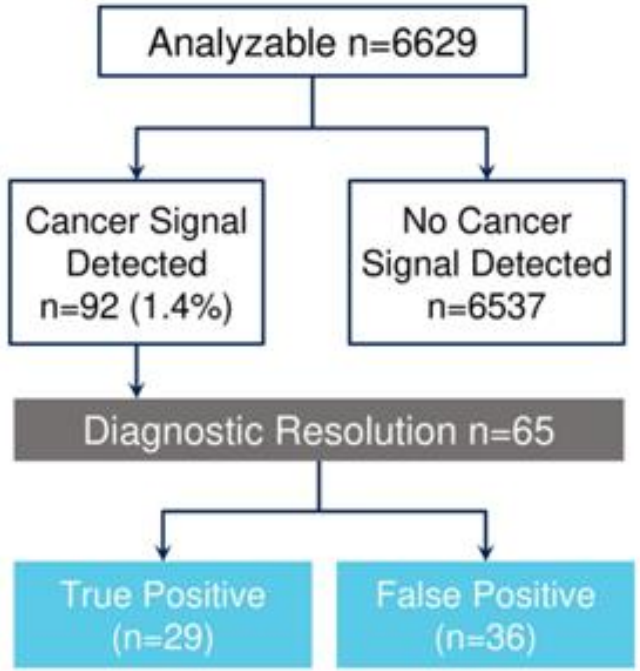
Supplemental Slide 3a: Diagnostic Resolution for CancerSEEK (Detect A Study)



My Conclusion: 16 cancers out of a population of 9,911 (1.6%) screened were uniquely identified by CancerSEEK

A. M. Lennon *et al.*, *Science* 10.1126/science.abb9601 (2020)

Supplemental Slide 3b: Galleria (PATHFINDER Study)



Median (Q1, Q3)	True Positive n=27*	False Positive n=36	Total (n=63*)
All Imaging/Invasive Procedures	2.0 (1.5, 3.0)	1.5 (1.0, 2.2)	2.0 (1.0, 3.0)
All Imaging Tests	1.0 (1.0, 1.5)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Functional	1.0 (0, 1.0)	1.0 (0, 1.0)	1.0 (0, 1.0)
Anatomic	1.0 (0, 1.0)	1.0 (0, 1.0)	1.0 (0, 1.0)
All Invasive Procedures*	1.0 (1.0, 1.0)	0 (0, 0.2)	0 (0, 1.0)
Minimally Invasive	1.0 (0.5, 1.0)	0	0 (0, 1.0)
Surgical	0	0	0
Clinical Lab Tests	3.0 (1.0, 5.5)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)
Days to Resolution	50.0 (27.0, 76.5)	49.0 (30.2, 153.8)	50.0 (28.0, 91.0)

Most participants with diagnostic resolution had at least 1 imaging test (57/63; 90%)
More true positives (21/27; 78%) than false positives (9/36; 25%) had at least 1 invasive procedure
Most invasive procedures were minimally invasive (88%)

*2 participants with 'signal detected' MCED test result (true positives) were excluded from the diagnostic workup analysis because diagnostic testing was initiated before MCED test results were returned. As of March 2021, 30 participants had ≥1 invasive procedure (26 minimally invasive, 2 surgical, 2 both).

Presented By: **Tomasz M. Beer**
OHSU Knight Cancer Institute, Portland, OR

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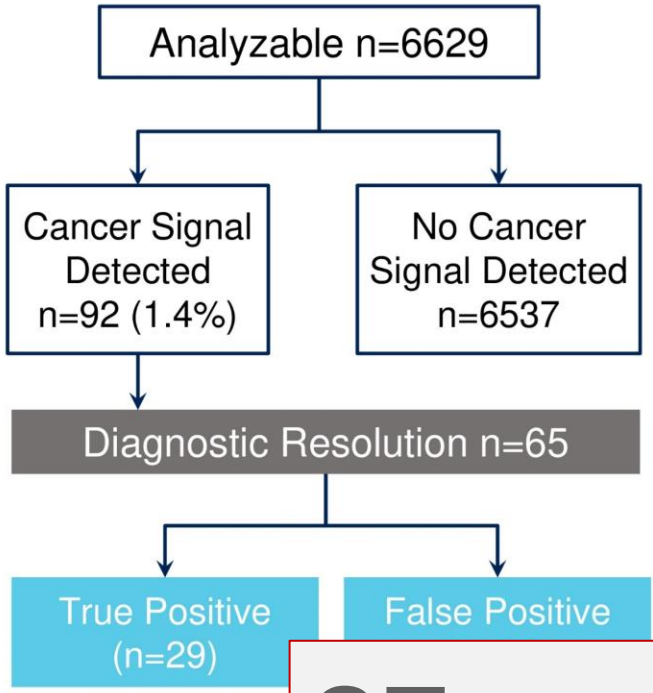
Supplemental Slide 3b: Galleria (PATHFINDER Study)



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Surgical	0	0	0
Clinical Lab Tests	3.0 (1.0, 5.5)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)
Days to Resolution	[illegible]	[illegible]	50.0 (28.0, 91.0)

27 people had a positive test and no diagnostic resolution

More tru [illegible] %) procedure

*2 participants with 'signal det [illegible] test results were returned.
As of March 2021, 30 participa [illegible]

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