



KNIGHT  
CANCER  
*Institute*

# Emerging Multi-Cancer Early Detection Strategies

Presented by Tomasz M. Beer, MD

# Disclosures

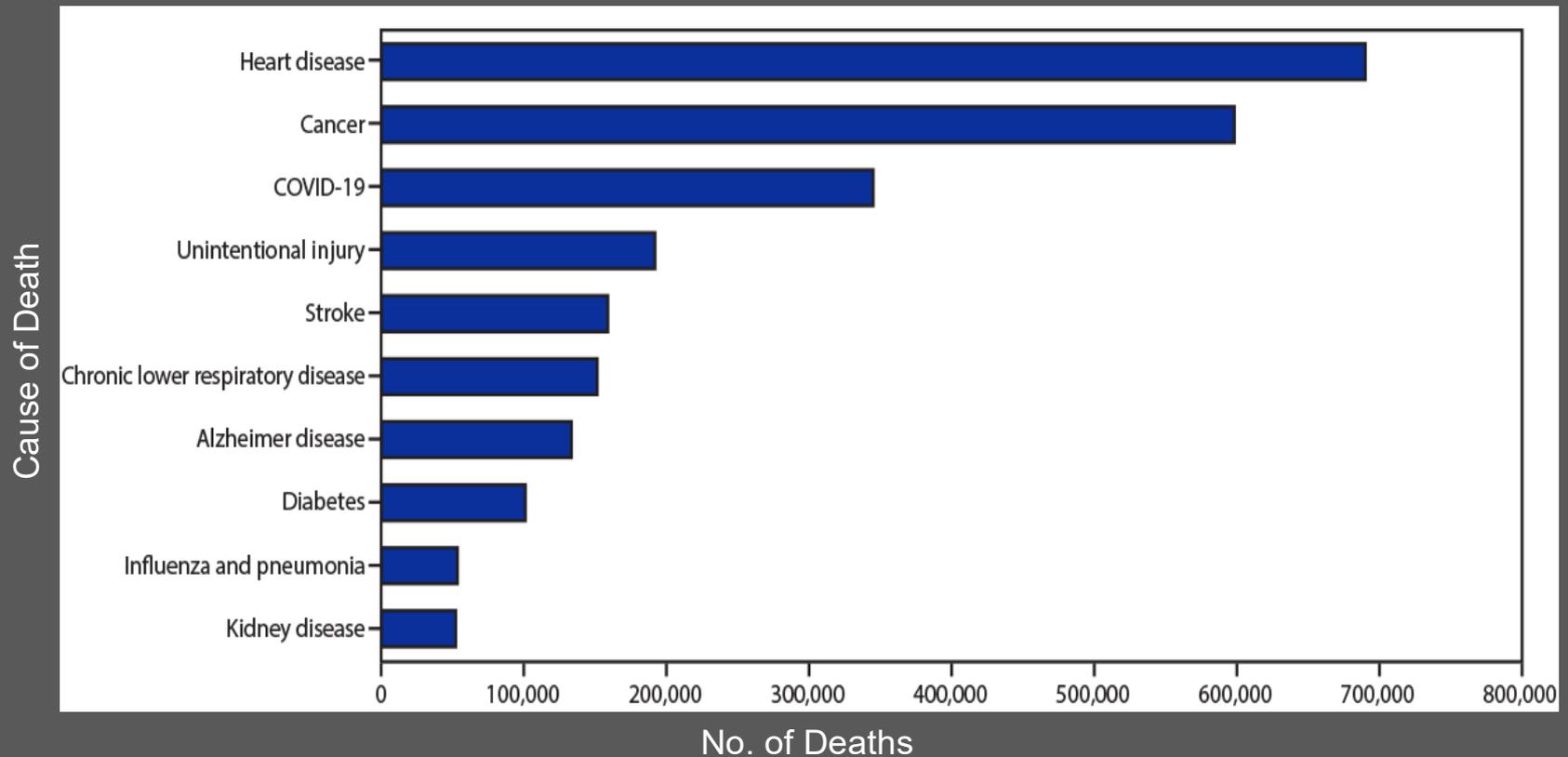
- Consultant for AbbVie, Arvinas, Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Constellation, Grail Inc., Janssen, Myovant Sciences, Pfizer, Sanofi, Sapience Therapeutics
- Stock ownership in Arvinas, and Salarius Pharmaceuticals
- Grant/research support from Alliance Foundation Trials, Astellas Pharma, Bayer, Boehringer Ingelheim, Corcept Therapeutics, Endocyte Inc., Freenome, Grail Inc., Harpoon Therapeutics, Janssen Research & Development, Medivation, Sotio, Theraclone Sciences/OncoResponse, and Zenith Epigenetics

# Learning Objectives

- To review currently available recommended cancer screening strategies
- To compare and contrast single cancer and multiple cancer early detection strategies
- To introduce blood-based multi-cancer early detection technologies
- To review current results from multi-cancer early detection clinical trials

# Overall Burden of Cancer in the US

10 leading causes of death in the US in 2020

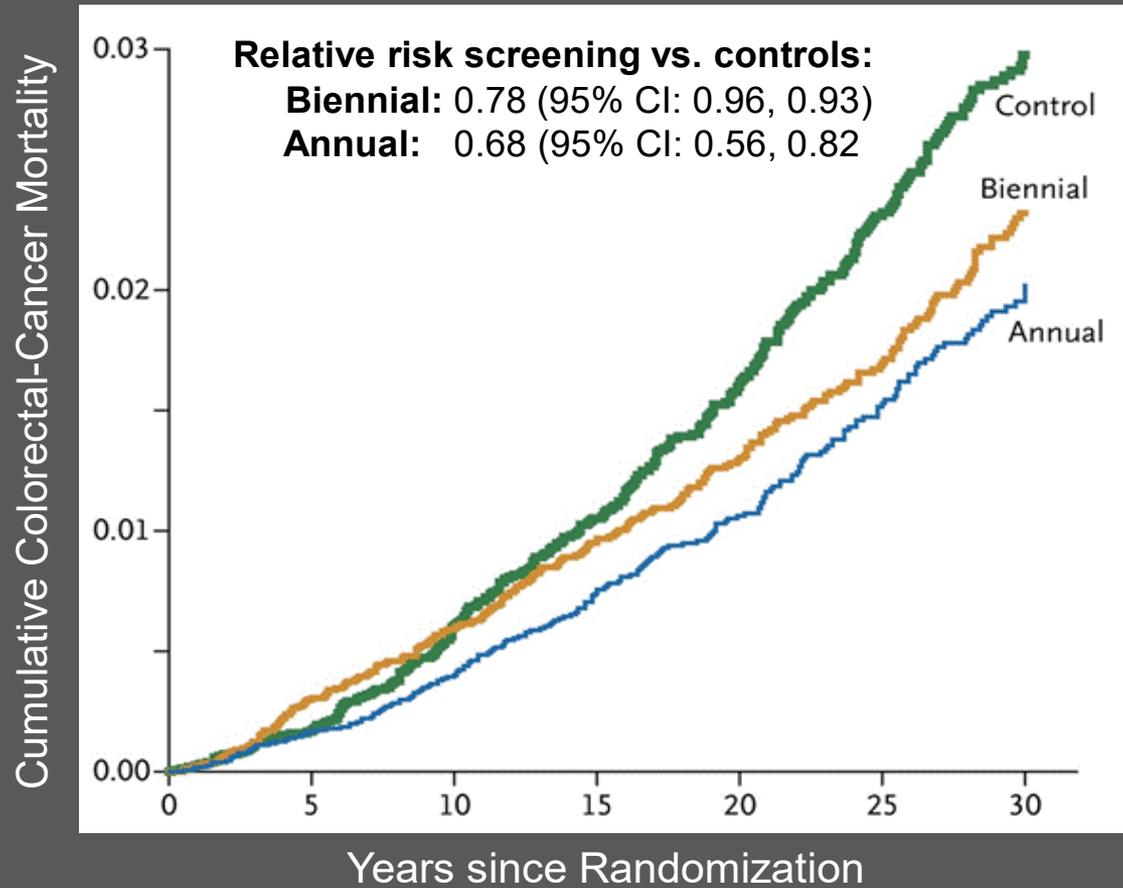


# Current Cancer Screening Guidelines

Cancer	Screening Modality	Age at First Screening	Interval
Lung	Low-dose CT	50 if meets high-risk criteria	Annually
Breast	Mammogram, Ultrasound, MRI	40-50	Every 1-2 years
Colorectal	<u>Stool-based methods</u> -FIT -Stool DNA -High-sensitivity guaiac-based fecal occult blood test  <u>Direct Visualization</u> -CT colonography -Colonoscopy -Flexible sigmoidoscopy	45-50	1-10 years, depending on test
Cervical	Pap test HPV test	21-25	3-5 years
Prostate	PSA Digital rectal exam	50-55	1-4 years

# Colorectal Cancer Mortality

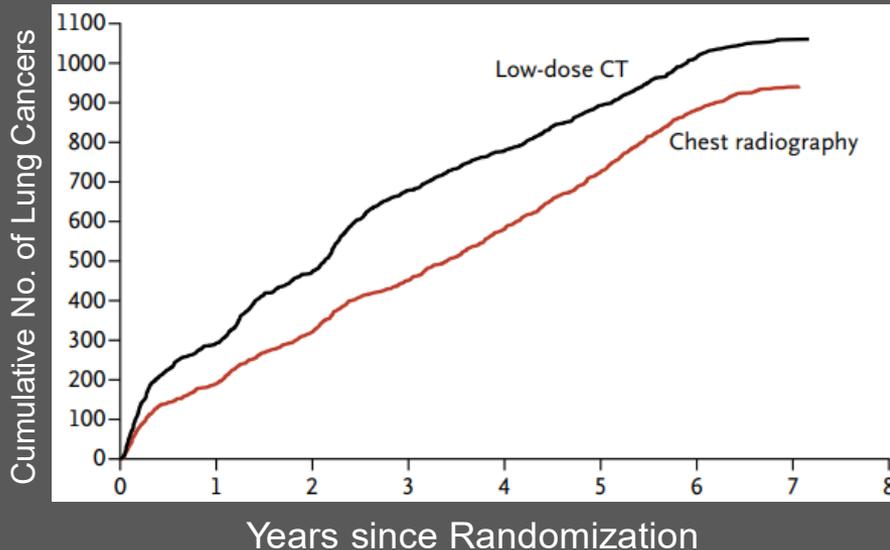
Minnesota Colon Cancer Control Study: FOBT vs usual care



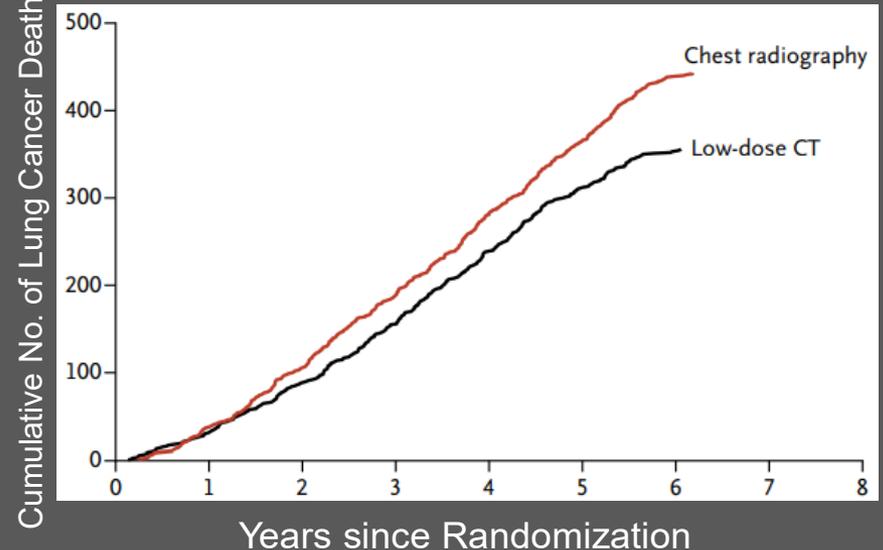
# Lung Cancer Diagnosis and Mortality

Randomized trial of low-dose CT vs chest radiography in 53,454 high-risk individuals

Lung Cancer

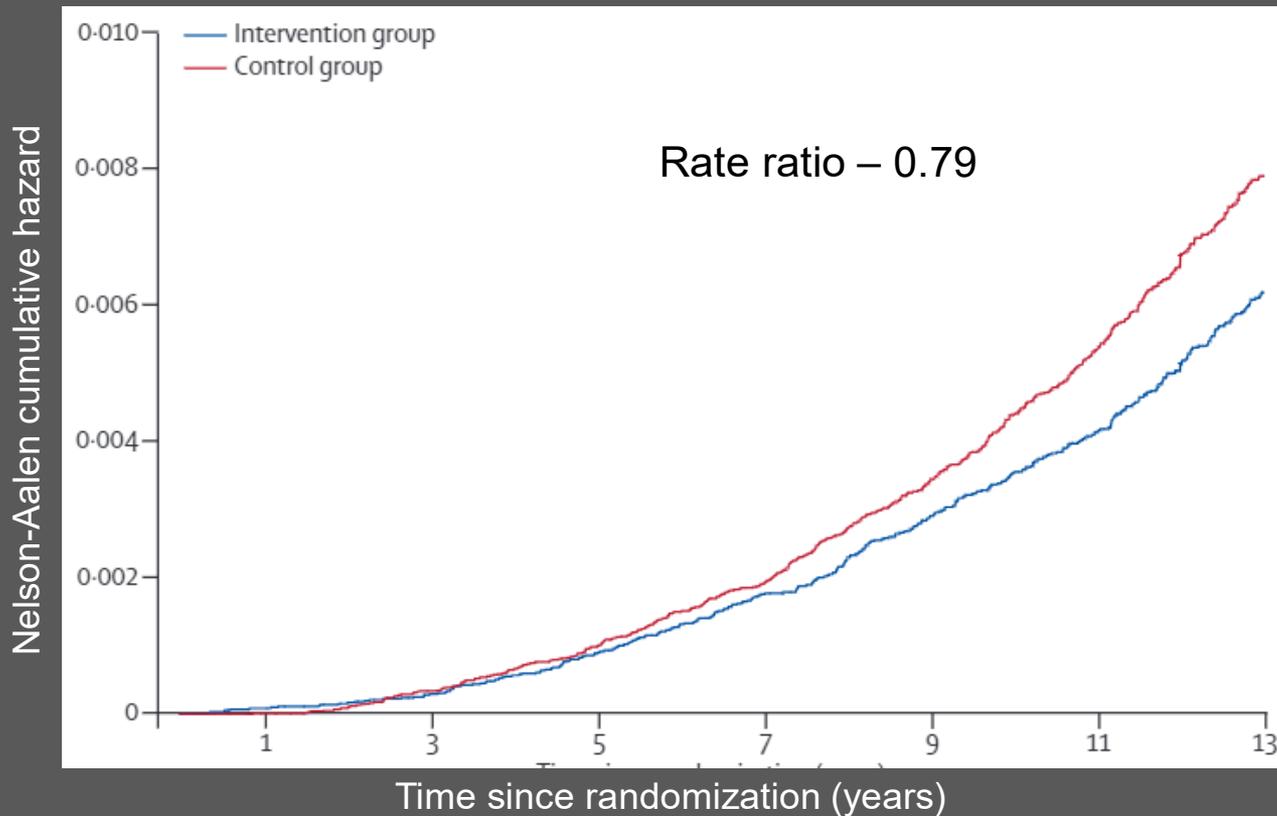


Death from Lung Cancer



# Prostate Cancer Mortality

## ERSPC



1 PCa death averted  
Per 781 men screened  
Per 27 PCa detected

# Single Cancer Screening Test Performance

Cancer	Prevalence (%)	USPSTF Recommended Screening	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Compliance With Recommended Screening (%) <sup>6</sup>
<b>Breast<sup>1</sup></b>	0.6	Biennial mammography, women ages 55–79	87	89	4.4	78.3
<b>Cervical<sup>2</sup></b>	<0.1	Triennial cytology or quinquennial cytology/HPV test, women ages 21–65	95	85.5	<1%	80
<b>Colorectal<sup>3</sup></b>	0.65	Decennial Colonoscopy	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	69.7
		Triennial Stool-based screening (Cologuard) Annual Stool-based screening (FIT)	92.3 73.8	86.6 94.9	3.7 8.7	
<b>Lung<sup>4</sup></b>	1.1 (high risk)	Annual low-dose CT for high-risk persons ages 55–80 <sup>5</sup>	85	87	6.9	14

CT, computed tomography; FIT, fecal immunochemical test; HPV, human papillomavirus; USPSTF, United States Preventive Services Task Force.

<sup>1</sup>USPSTF. 2016. Lehman, et al. *Radiology*. 2017;283(1):49-58. <sup>2</sup>Kim, et al. *JAMA*. 2018;320(7):706-714. <sup>3</sup>USPSTF. 2017. United States Food and Drug Administration Premarket Approval P130017.

Accessed March 26, 2019. Cologuard Test. Available from [www.cologuardtest.com/hcp/crc-screening-redefined](http://www.cologuardtest.com/hcp/crc-screening-redefined). Accessed March 26, 2019. <sup>4</sup>Pinsky et al *Ann Intern Med*. 2015 April 7; 162(7): 485–491.

<sup>5</sup>Pinsky. *J Med Screen*. 2012;19(3):154-156. Recommendation for lung screening limited to high-risk smoking population, which accounts for less than 33% of all lung cancers <sup>6</sup> Compliance from BRFSS

Prevalence & Trends Data. 2015. [accessed Aug 12, 2020]. URL: <https://www.cdc.gov/brfss/brfssprevalence/> except LDCT from Zahnd, et al. *Am J Prev Med* 2019;57(2):250–255.



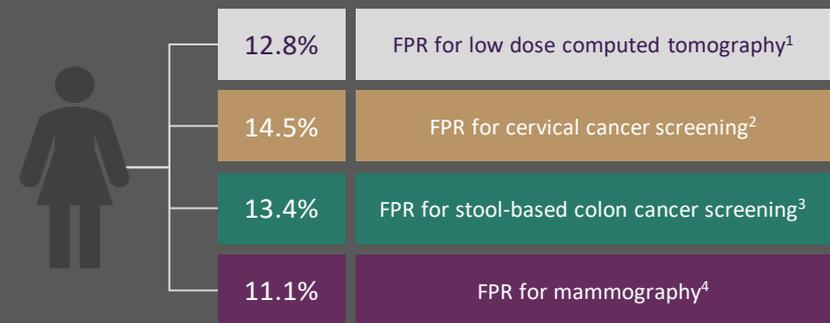
KNIGHT  
CANCER  
Institute

# Cumulative False Positive Rate From Single-Cancer Screening

Existing paradigms are associated with a high cumulative false positive rate

- Each false positive from a screening test would require follow-up tests or interventions with attendant risks
- These risks are not well understood at the population level because current paradigms only evaluate one cancer at a time
- An opportunity for a multi-cancer approach to early cancer detection

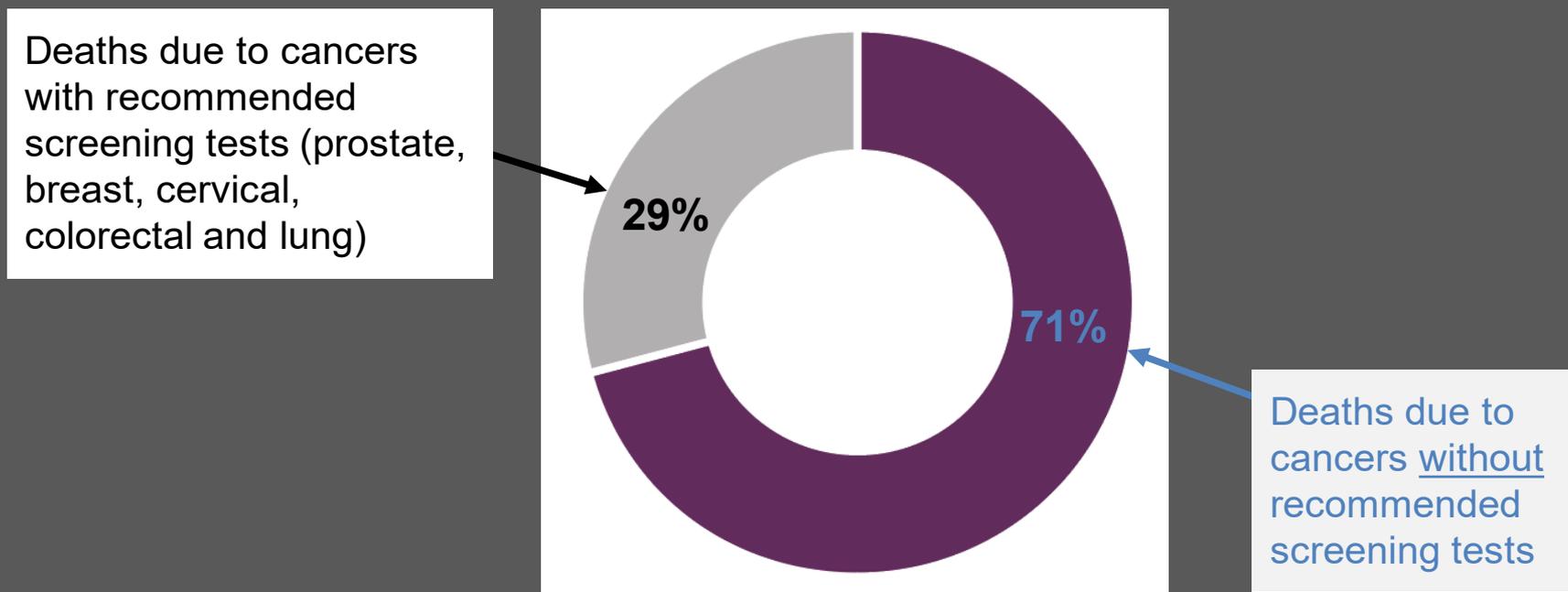
A 60-year-old female with a history of smoking screened for 4 cancers would have a 43% false positive rate (FPR)\*



\*Assumes eligibility for all 4 tests.

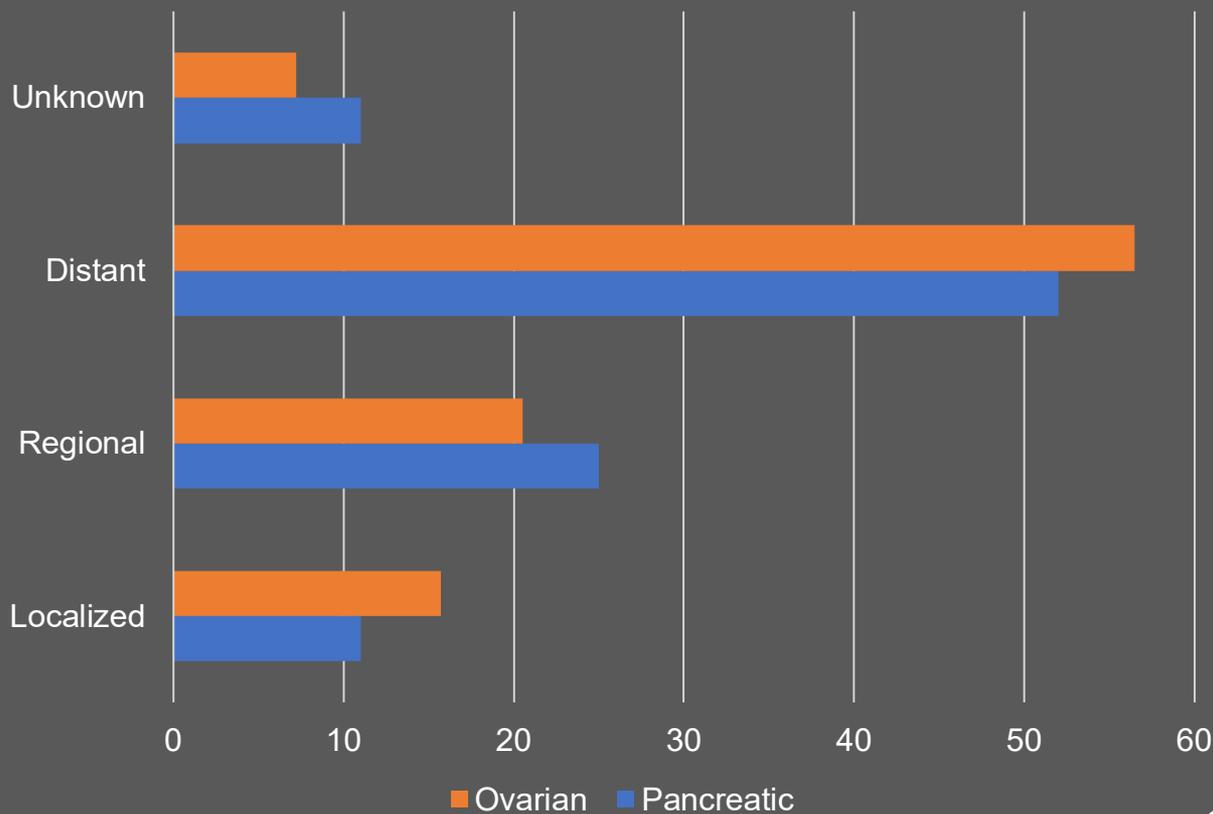
<sup>1</sup>Pinsky PF, et al. *Ann Intern Med.* 2015;162:485-491. <sup>2</sup>Kim, et al. *JAMA.* 2018;320(7):706-714. <sup>3</sup>US Food and Drug Administration PMA P130017: FDA summary of safety and effectiveness data. August 11, 2014. Accessed March 21, 2020. <sup>4</sup>Lehman CD, et al. *Radiology.* 2017;283:49-58.

# Cancers Without Recommended Screening Tests Account for 71% of Cancer Deaths in the United States in 2020<sup>1,2</sup>

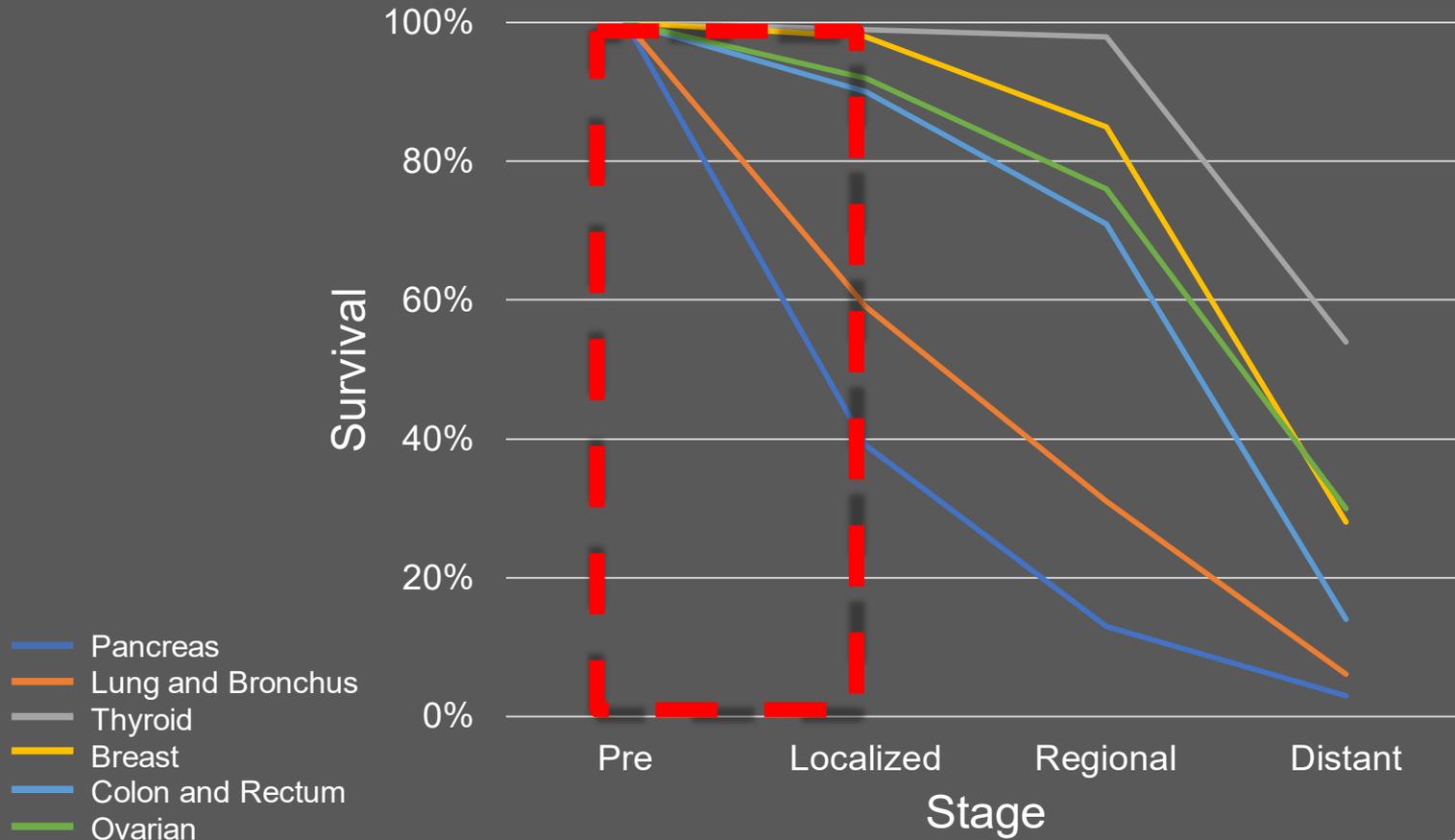


# Lethal Cancers Without Effective Screenings Are Often Diagnosed Late

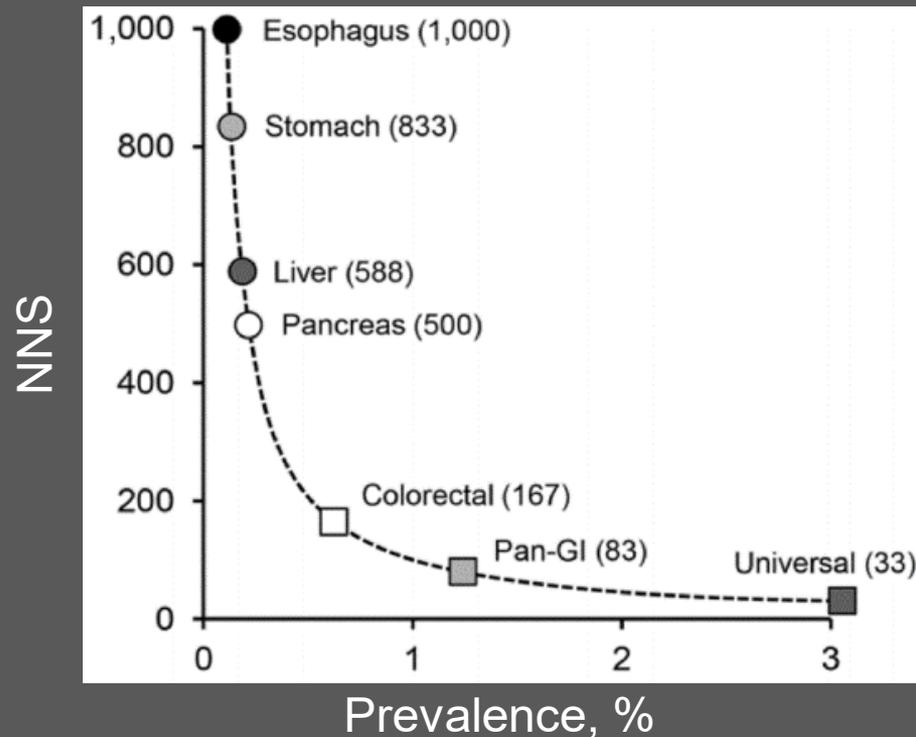
## Stage distribution of SEER Incidence Cases



# 5-year Relative Survival By Stage at Diagnosis



# Low Prevalence of Individual Cancers Presents a Challenge to Early Detection

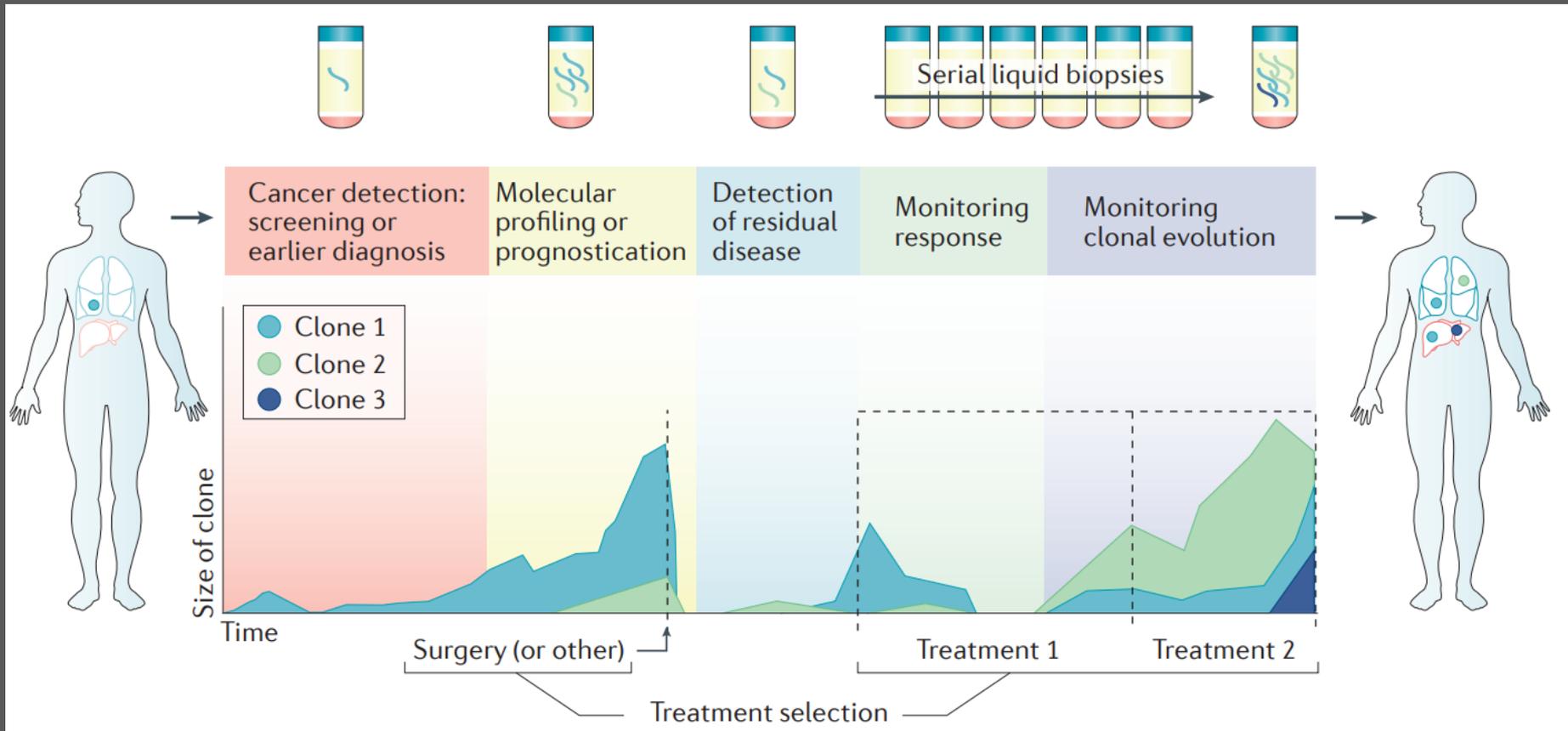


# Integrated Multi-omic Analysis of Circulating Cancer Biomarkers Provides a Potential Avenue for Revolutionizing Early Detection of Cancer

- A range of biomarkers can be comprehensively analyzed
  - DNA (mutations, methylation)
  - Proteins
  - Extracellular Vesicles / Exosomes
  - CTCs and CTC clusters
  - RNA, tumor educated platelets, etc.
- Tissue of origin identification is possible
  - DNA methylation patterns



# Promise and Applications of Circulating Tumor-derived Material



# Development Of Blood-Based Cancer Early Detection Tests

- Assay development
- Test development and initial validation
  - Case control design
- Prospective studies measured against current SOC tests
  - Testing simultaneously with a standard screening procedure
  - Focus on single cancer
  - No return of results
- Prospective studies with return of results
  - Multi-cancer application



# Key Clinical Studies

## CancerSEEK Test:

- Evaluates the levels of 8 cancer proteins and the presence of cancer gene mutations

## Galleri Test:

- Targeted methylation assay

# CANCER-SEEK

# DETECT-A Study

Multicenter prospective trial in 10,006 women ages 65-75 women not known to have cancer to examine the feasibility and safety of **CancerSEEK** coupled with PET-C imaging

Science

RESEARCH ARTICLES

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

## Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention

Anne Marie Lennon<sup>1,4,10\*</sup>, Adam H. Buchanan<sup>11\*</sup>, Isaac Kinde<sup>12\*</sup>, Andrew Warren<sup>12,13\*</sup>, Ashley Honushefsky<sup>11\*</sup>, Ariella T. Cohain<sup>12</sup>, David H. Ledbetter<sup>11</sup>, Fred Sanfilippo<sup>14</sup>, Kathleen Sheridan<sup>11</sup>, Dillenia Rosica<sup>11</sup>, Christian S. Adonizio<sup>11,16</sup>, Hee Jung Hwang<sup>12</sup>, Kamel Lahouel<sup>1,6</sup>, Joshua D. Cohen<sup>1,2,3,4,5</sup>, Christopher Douville<sup>1,3</sup>, Aalpen A. Patel<sup>11</sup>, Leonardo N. Hagmann<sup>12</sup>, David D. Rolston<sup>11</sup>, Nirav Malani<sup>12</sup>, Shibin Zhou<sup>1,3,4</sup>, Chetan Bettegowda<sup>1,3,8</sup>, David L. Diehl<sup>11</sup>, Bobbi Urban<sup>12</sup>, Christopher D. Still<sup>11</sup>, Lisa Kann<sup>12</sup>, Julie I. Woods<sup>11</sup>, Zachary M. Salvati<sup>11</sup>, Joseph Vadamakara<sup>11</sup>, Rosemary Leeming<sup>11</sup>, Prianka Bhattacharya<sup>11</sup>, Carroll Walter<sup>11</sup>, Alex Parker<sup>12</sup>, Christoph Lengauer<sup>12,13</sup>, Allison Klein<sup>1,4,15</sup>, Cristian Tomasetti<sup>1,6,7</sup>, Elliot K. Fishman<sup>1,4,10</sup>, Ralph H. Hruban<sup>1,4,9</sup>, Kenneth W. Kinzler<sup>1,3,4,†</sup>, Bert Vogelstein<sup>1,2,3,4,†</sup>, Nickolas Papadopoulos<sup>1,3,4,9,†</sup>

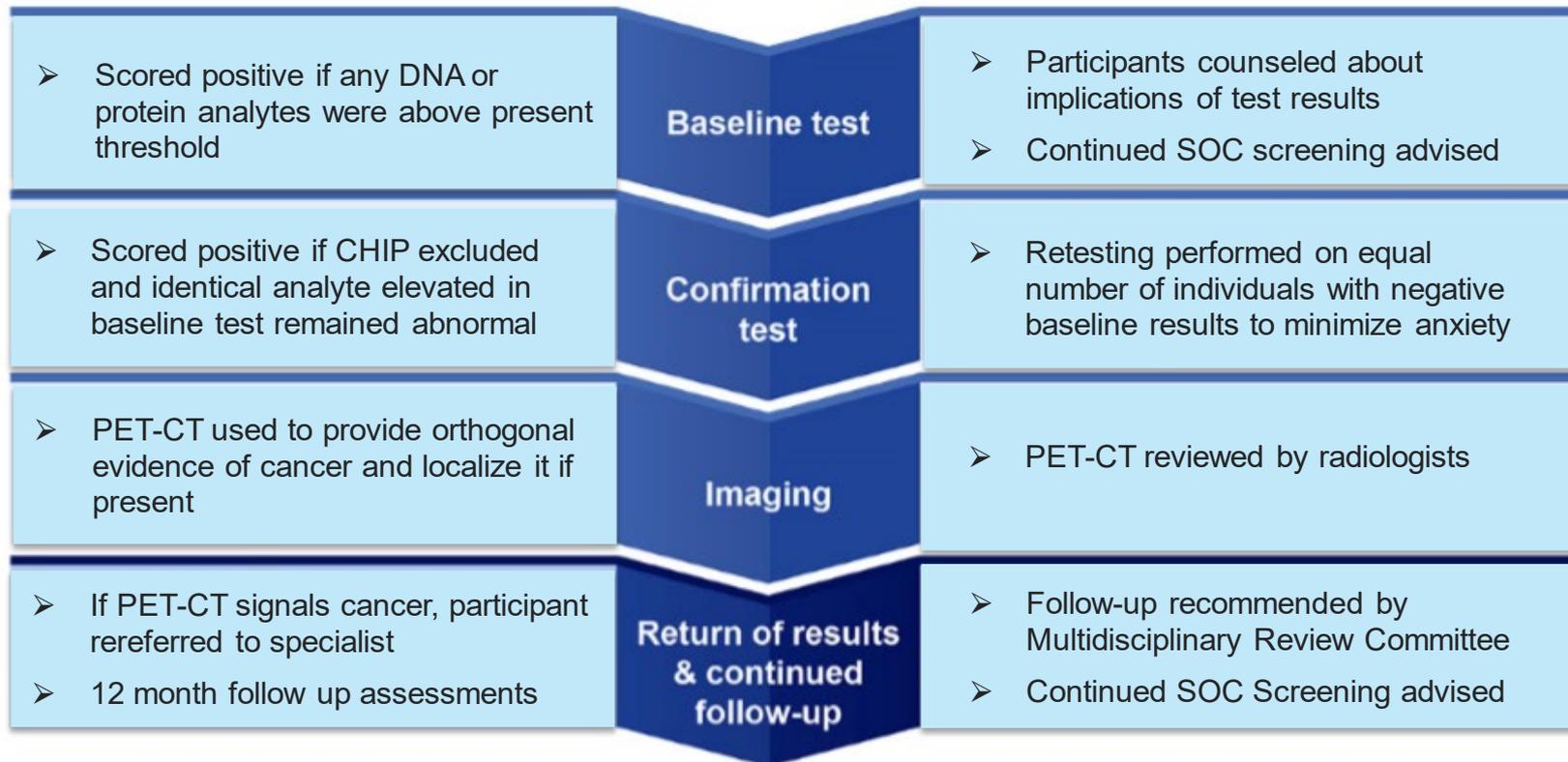


KNIGHT  
CANCER  
Institute

# DETECT-A Testing Process

## Testing Process

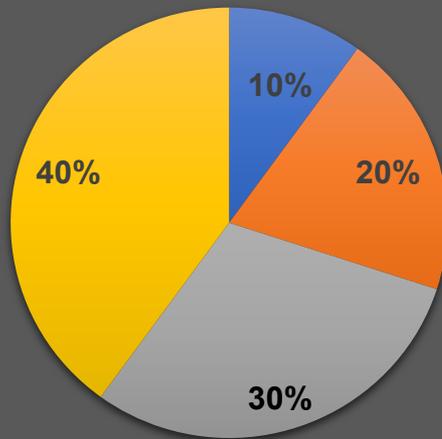
## Safety Features



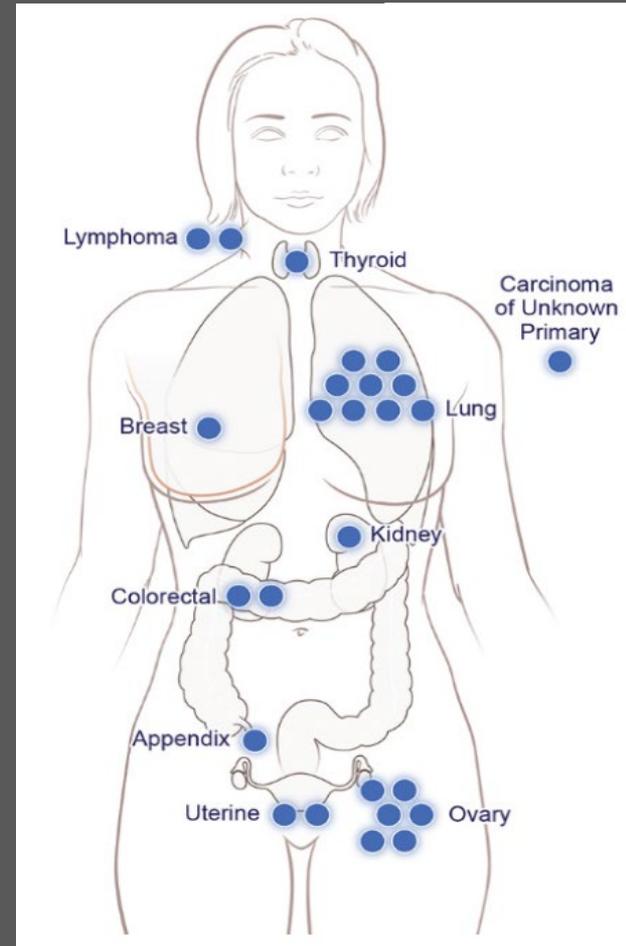
# DETECT-A Results

- 9911 women screened
- 490 positive on baseline test
- 127 positive on both tests
- 26 cancers detected

Stage at Diagnosis



■ 1 ■ 2 ■ 3 ■ 4



# DETECT-A Results (cont.)

- 9911 women screened
- 490 positive on baseline test
- 127 positive on both tests
- 26 cancers detected
  
- 101 participants had imaging based on false-positive test
- 22 invasive diagnostic procedures after false-positive test
  
- 24 cancers detected with routine screening
- 46 cancers detected with neither approach

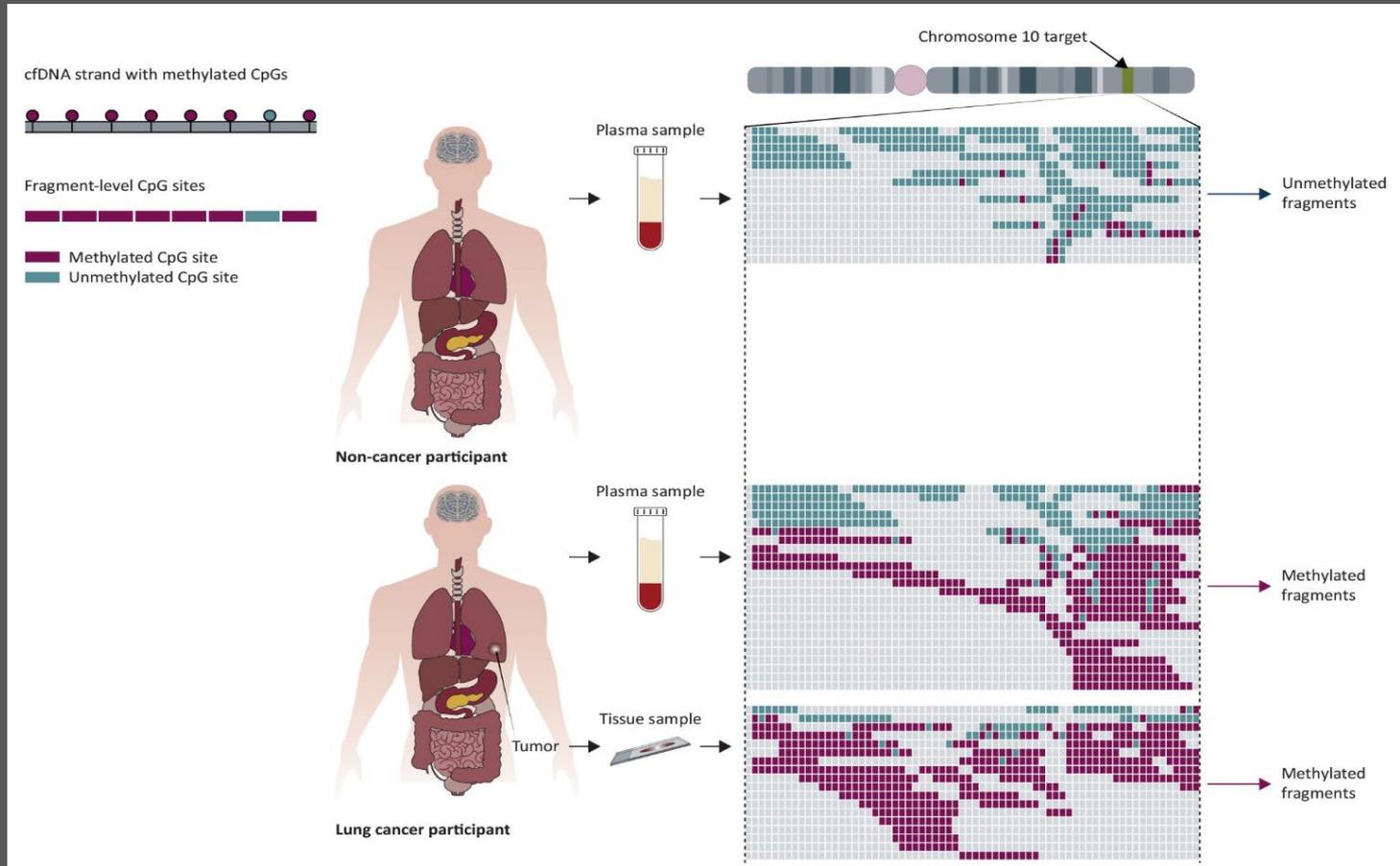
# Test Performance

Performance with and without confirmation test  
and 95% confidence intervals

	Blood Test Without Confirmation	Blood Test With Confirmation
<b>Positive Predictive Value</b>	5.9% (4.0-8.4)	19.4% (13.1-27.1)
<b>Specificity</b>	95.3% (94.9-95.7)	98.9% (98.7-99.1)
<b>Negative Predictive Value</b>	99.3% (99.1-99.4)	99.3% (99.1-99.4)
<b># Needed to Screen to Detect 1 Cancer</b>	342 (238-510)	381 (260-583)
<b>Sensitivity</b>		
All Cancers	30.2 (21.3-40.3)	27.1% (18.5-37.1)
Cancers with SOC Screening	27.5% (15.9-41.7)	23.5% (12.8-37.5)
Cancers with no SOC Screening	33.3% (20.0-49.0)	31.1% (18.2-46.6)

# GALLERI

# Methylation Biology Differentiates Cancer From Non-Cancer



cfDNA, cell-free DNA. Figure from Liu MC, et al. *Ann Oncol.* 2020;31(6):745-759.  
DOI: 10.1016/j.annonc.2020.02.011.

# Characteristics of GRAIL's Targeted Methylation Panel

Approximately 100,000 genomic regions

## Panel Version 1.0

	Size/Count
Targeted regions (Mb)	17.1
Probe regions covering target regions (Mb)	31.3
Probes (n)	1,121,325
Probe size (bp)	120 (60 bp overlap)
CpGs (n)	1,116,720

## Number of CpGs

Probe	CpGs (n)
Hypo	363,033
Hyper	585,181
Binary	218,506
Total	1,116,720

## Type of Genomic Region

	CpGs (n)	%
1-5 kb upstream of start codon	193,818	17
Promoter	278,872	24
Introns	500,996	43
Exons	292,798	25
Intron/Exon Boundaries	247,752	21
5' UTR	134,144	11
Between genes	182,174	16
Not annotated	1,817	<1

UTR, untranslated region.

# Grail MCED Clinical Trials

## CCGA<sup>1</sup>

NCT02889978

15,254 participants



Demonstrate feasibility of detecting cancer and predicting tissue of origin with minimal false positives

## STRIVE

NCT03085888

99,308 participants



Confirm performance in a population with no known active cancer diagnosis

## PATHFINDER

NCT04241796

~6,200 participants



Evaluate implementation of test in clinical practice

## SUMMIT

NCT03934866

~25,000 participants



Additional performance in a population with no known active cancer diagnosis and clinical utility in a high-risk population

<sup>1</sup>Circulating Cell-Free Genome Atlas study.

# Multi-Cancer Early Detection Test

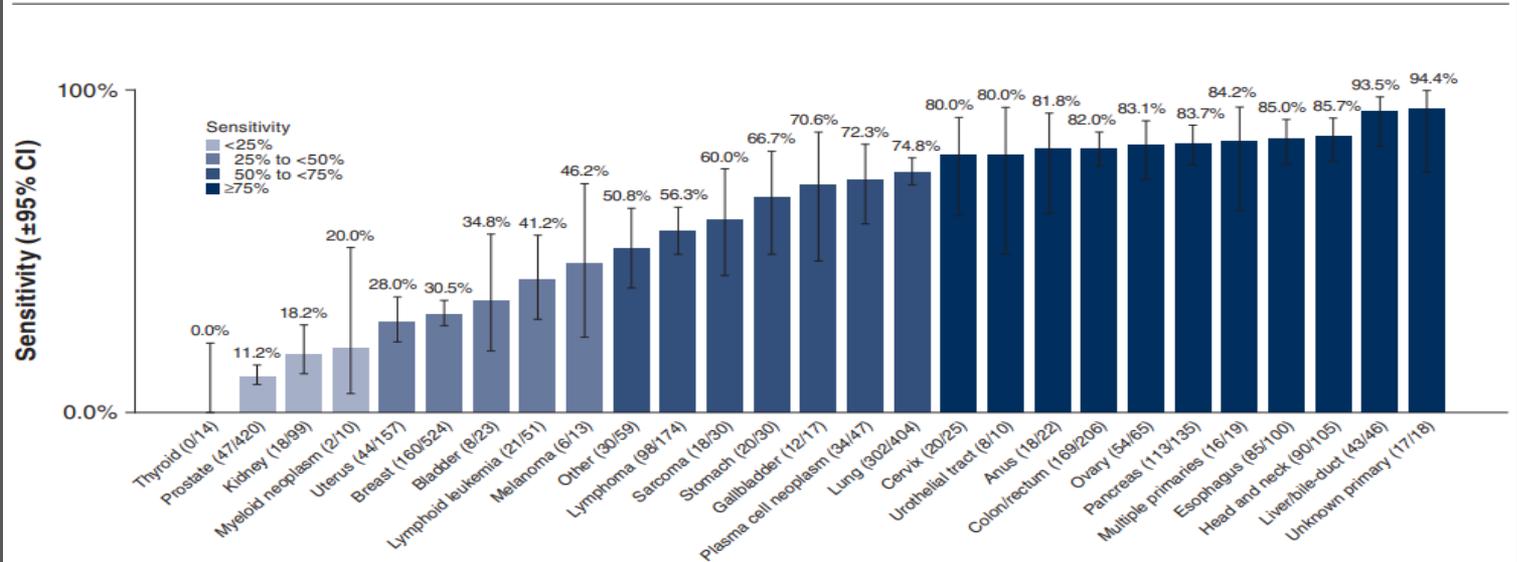
## Sensitivity and Specificity

Overall sensitivity and specificity

	Cancer	Non-cancer	Total
	2823	1254	4077
Test positive	1453	6	1459
Test negative	1370	1248	2618
	Sensitivity = 1453/2823 51.5% (49.6%-53.3%)	Specificity = 1248/1254 99.5% (99.0%-99.8%)	

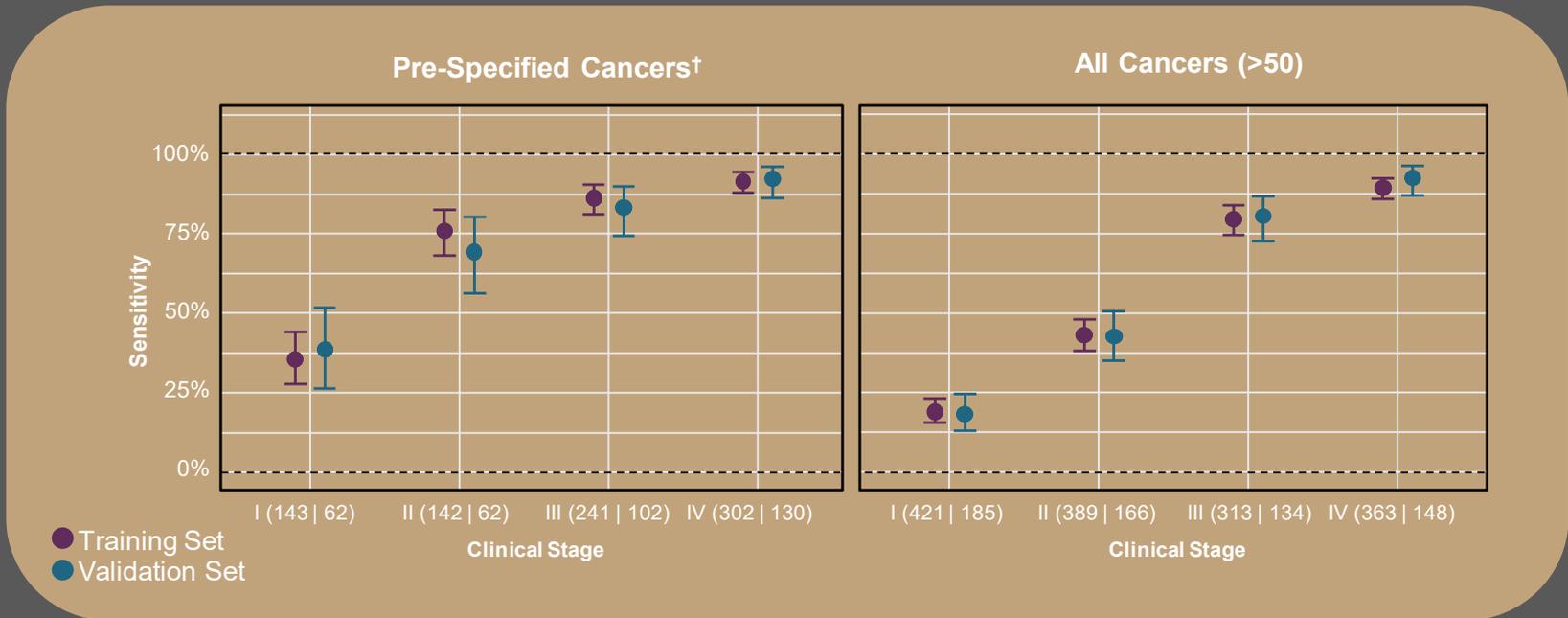
Two-sided 95% Wilson confidence intervals were calculated.

Sensitivity by cancer class



# Circulating Cell-free Genome Atlas (CCGA) Sub-Study 2

- 76.4% (71.6-80.7%) sensitivity in pre-specified<sup>†</sup> cancers (validation set)
- 54.9% (51.0-58.8%) overall sensitivity in >50 cancers (validation set)
- Single fixed false positive rate (0.7%) across all cancers

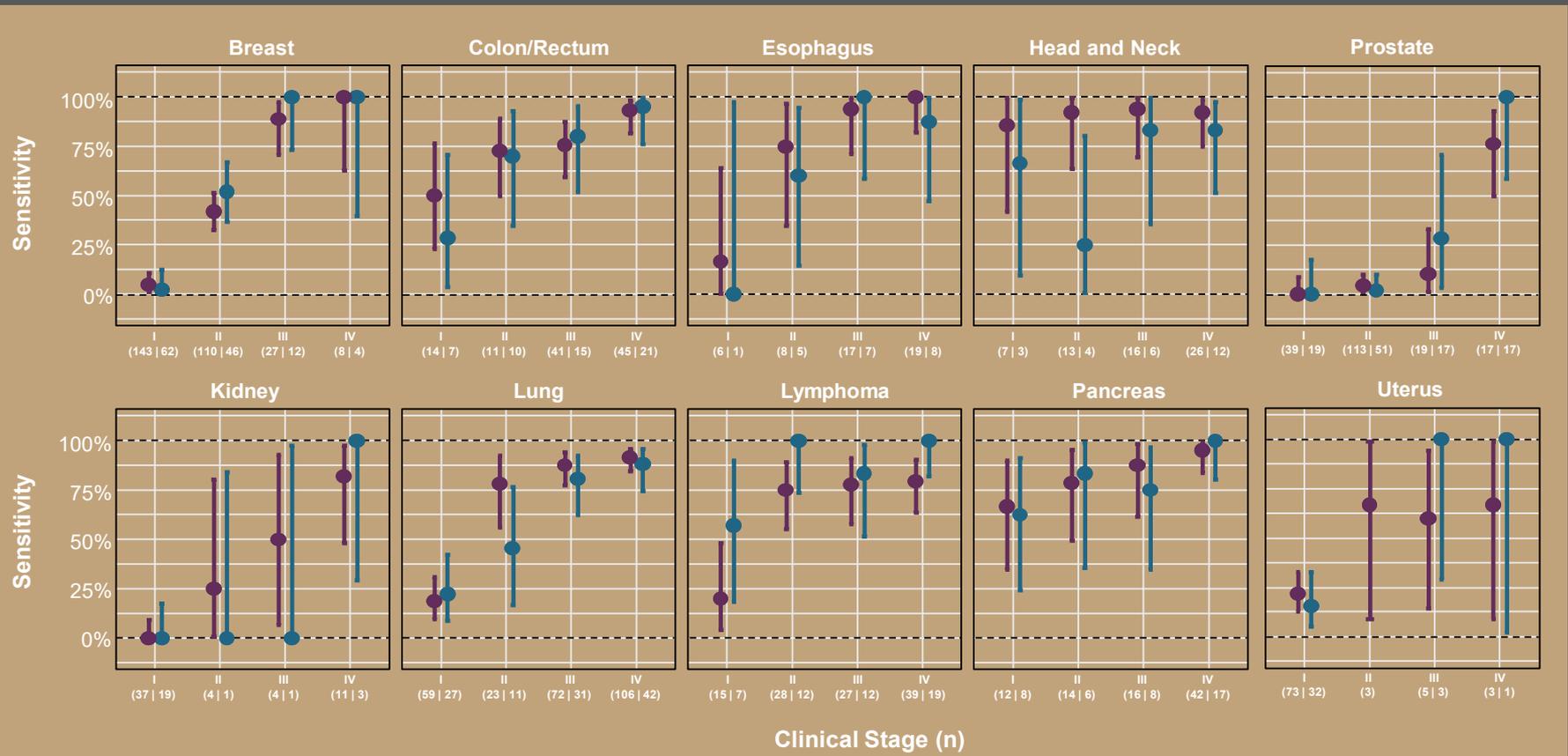


<sup>†</sup>Anus, bladder, colon/rectum, esophagus, head and neck, liver/bile-duct, lung, lymphoma, ovary, pancreas, plasma cell neoplasm, stomach.

Plot excludes unstaged cancers.

Liu MC, et al. *Ann Oncol.* 2020;31(6):745-759. DOI: 10.1016/j.annonc.2020.02.011.

# Circulating Cell-free Genome Atlas (CCGA) Sub-Study 2

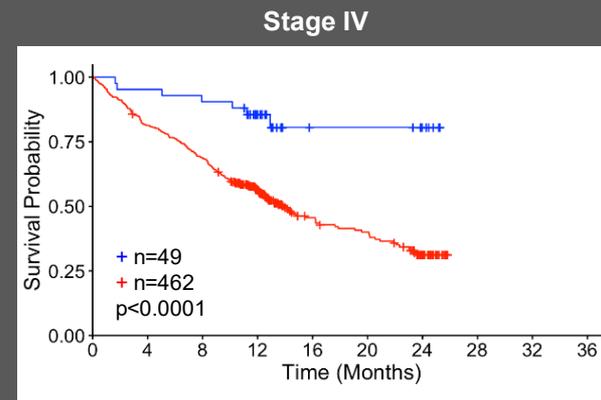
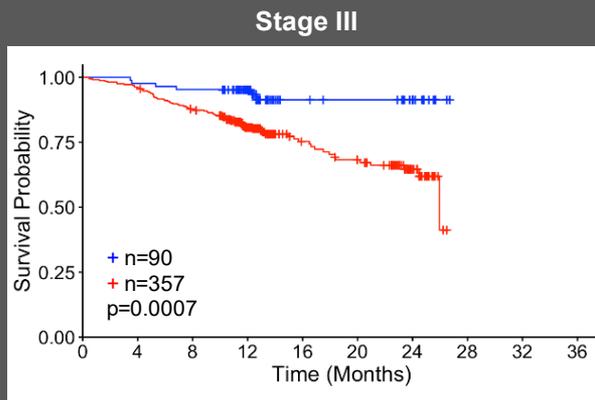
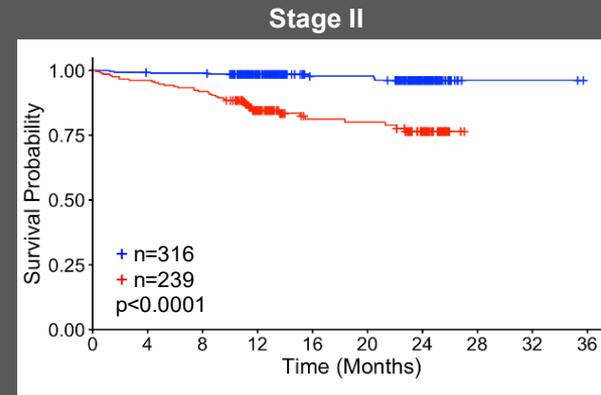
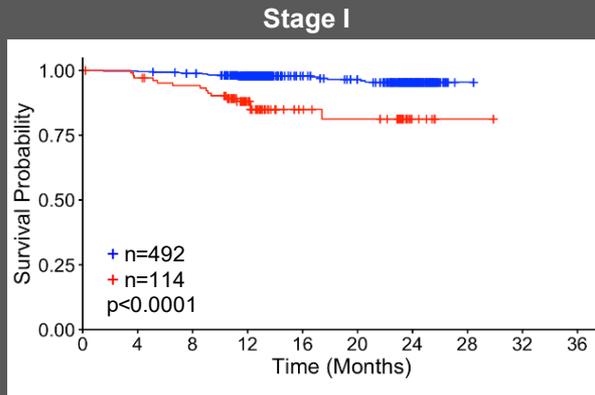


<sup>a</sup>Includes cancers with >50 samples.

Liu MC, et al. Ann Oncol. 2020;31(6):745-759. DOI: 10.1016/j.annonc.2020.02.011.

# Galleri-Detected Cancers Have a Worse Prognosis than not Detected Cancers

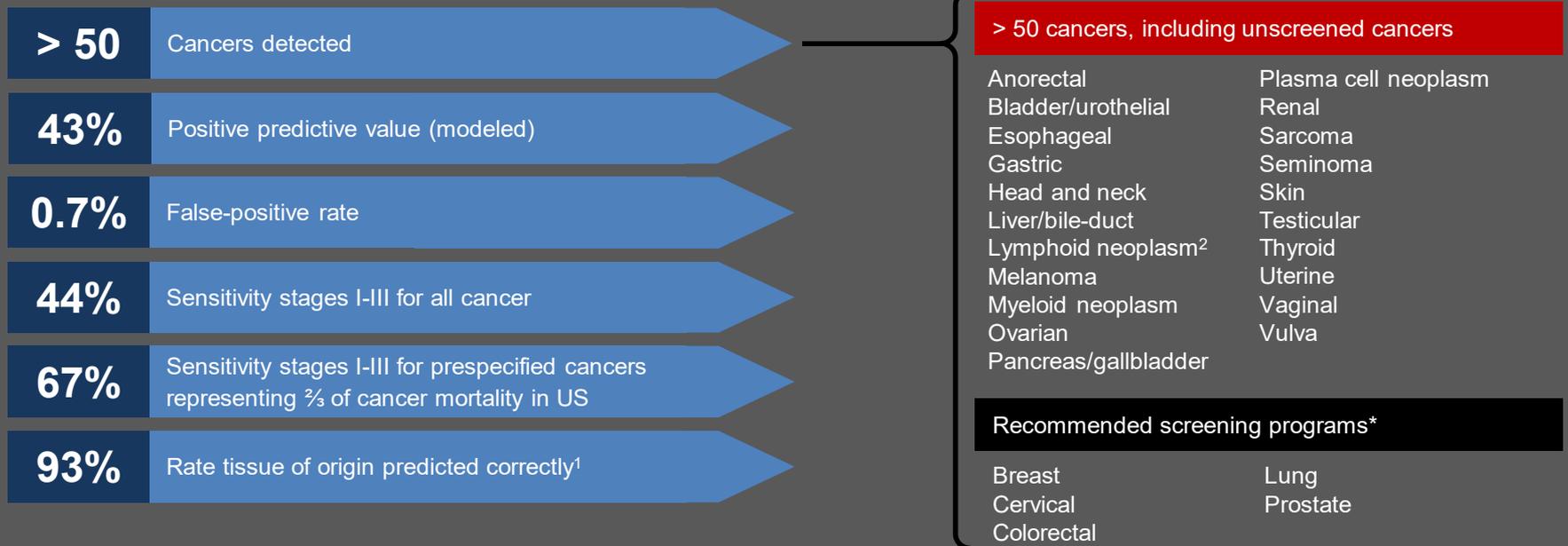
Overall survival  
by stage



Not Detected  
Detected

# Key Performance Features of Galleri Test

Demonstrated in CCGA Case Control Study



CCGA, Circulating Cell-free Genome Atlas.

Liu MC, et al. *Ann Oncol.* 2020;31(6):745-759. DOI: 10.1016/j.annonc.2020.02.011.

<sup>1</sup>Based on tissue of origin class assigned in 96% of cases where cancer was detected.

<sup>2</sup>Lymphoid neoplasm includes lymphoma and leukemia. Leukemia includes chronic lymphocytic leukemia and hairy cell leukemia

\*USPSTF A, B, or C rating.

# The Pathfinder Study: Assessment of A Multi-Cancer Early Detection Test In Clinical Practice

Prospective, multicenter, interventional, return-of-results study (NCT04241796)

## Study Objectives

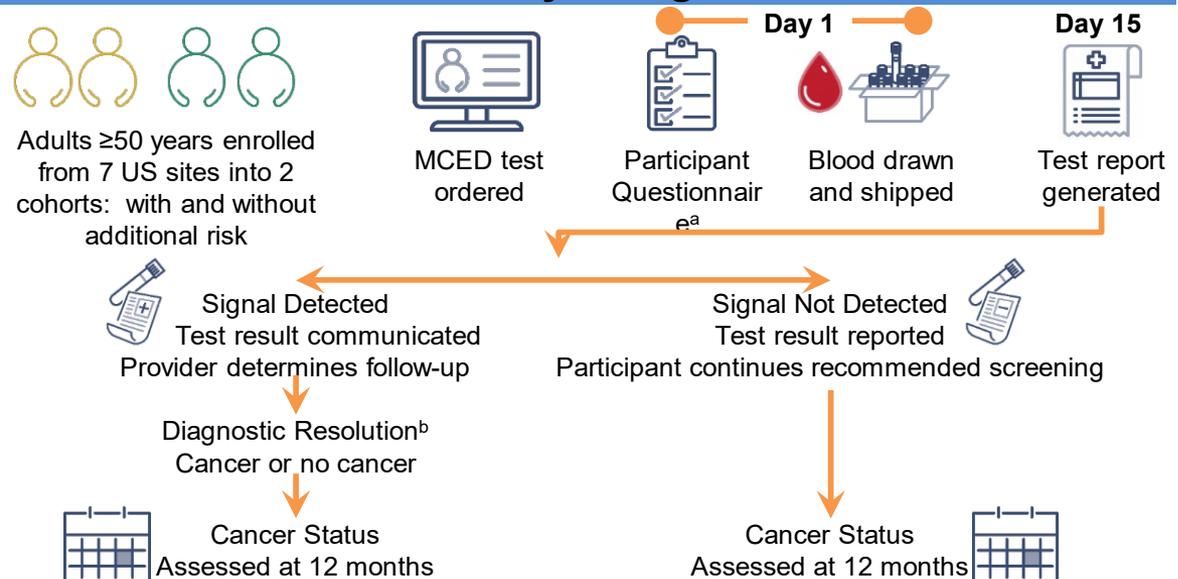
### Primary

- Assess extent of diagnostic testing required to achieve diagnostic resolution following a “signal detected” test result

### Secondary

- Evaluate test performance
- Assess participant-reported outcomes and perceptions of the MCED test

## Study Design



<sup>a</sup>Also collected at other timepoints during the study.

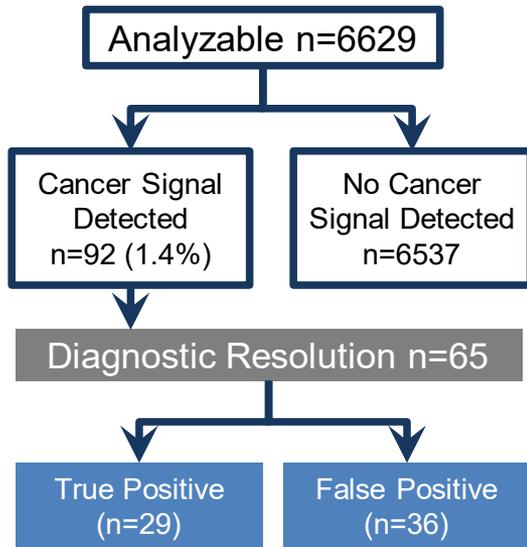
<sup>b</sup>Defined as date when study team determines to end diagnostic evaluation triggered by a “signal detected” test result. MCED, multi-cancer early detection.

# Grail Pathfinder Study: Overall Study Accrual

## PATHFINDER Total Study Enrollment



# Interim Primary Outcome: Extent of Diagnostic Testing



	True Positive n=27*	False Positive n=36	
<b>All Imaging/Invasive Procedures</b>	2.0 (1.5, 3.0)	1.5 (1.0, 2.2)	2.0 (1.0, 3.0)
<b>All Imaging Tests</b>	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)
<b>All Invasive Procedures*</b>	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
<b>Clinical Lab Tests</b>	3.0 (1.0, 5.5)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)
<b>Days to Resolution</b>	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).

# Interim Secondary Outcome: Test Performance

	With Additional Risk	Without Additional Risk	Total
<b>Cancer Signal Detection, No.</b>	n=3695	n=2934	N=6629
Detected, No. (%)	<b>56 (1.5)</b>	<b>36 (1.2)</b>	<b>92 (1.4)</b>
True Positive	20 (0.5)	9 (0.3)	29 (0.4)
False Positive	15 (0.4)	21 (0.7)	36 (0.5)
No Current Diagnostic Resolution	21 (0.6)	6 (0.2)	27 (0.4)
Not Detected	3639 (98.5)	2898 (98.8)	6537 (98.6)
<b>PPV for Cancer Signal Detection, No.</b>	n=35	n=30	n=65
% (95% CI)	<b>57.1 (40.9–72.0)</b>	<b>30.0 (16.7–47.9)</b>	<b>44.6 (33.2–56.7)</b>
<b>CSO Prediction Accuracy</b>	n=19 <sup>a</sup>	n=8 <sup>a</sup>	n=27 <sup>a</sup>
First CSO, % (95% CI)	<b>84.2 (62.4–94.5)</b>	<b>87.5 (52.9–99.4)</b>	<b>85.2 (67.5–94.1)</b>
First/Second CSO	100 (83.2–100.0)	87.5 (52.9–99.4)	96.3 (81.7–99.8)

Cancer signal was detected in 1.4% of all analyzable participants

Nearly half with diagnostic resolution had confirmed cancer, for an estimated 45% PPV

Cancer signal origin was predicted with high accuracy

Data as of March 2021. CSO, cancer signal origin; PPV, positive predictive value. <sup>a</sup>Excludes 1 participant with unknown cancer type and 1 with indeterminate CSO from the true positive set.

# Cancer Characteristics of True Positive Set (n=28)

Cancer Type Diagnosed	Clinical AJCC Stage of New Cancers					Recurrent Cancers		First Predicted Cancer Signal Origin
	I	II	III	IV	Other	Local	Distant	
Colon or rectum				1	1 Unknown			Upper GI Tract (SIV pt); Colon/Rectum (unk pt)
Head and Neck		1		1				Head and Neck
Liver, bile duct	1		1					Liver, bile-duct
Lung			1					Lung
Lymphoid leukemia					2 NA			Lymphoid Neoplasm
Lymphoma	2	3	1	2				Lymphoid Neoplasm
Ovary, peritoneum/FT			1					Uterus (ovary second CSO)
Pancreas		1						Pancreas/Gallbladder
Plasma cell neoplasm					1 NA			Plasma Cell Neoplasm
Prostate				1				Indeterminate
Small intestine	1							Colon/Rectum (upper GI second CSO)
Waldenstrom macroglobulinemia					1 NA			Lymphoid Neoplasm
Breast cancer							4	3 Breast 1 Breast (first CSO), lymphoid (second)
Prostate cancer						1		Lymphoid (first CSO), prostate (second)
<b>Total</b>	<b>4</b>	<b>5</b>	<b>4</b>	<b>5</b>	<b>5</b>	<b>1</b>	<b>4</b>	

AJCC, the American Joint Committee on Cancer version 8; CSO, cancer signal origin; FT, fallopian tube; GI, gastrointestinal; NA, not applicable; pt, participant; SIV, stage IV; unk, unknown.

# CEDAR Clinical Trials

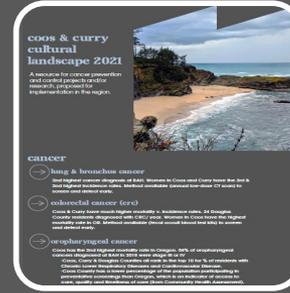
Status at CEDAR	Disease Location	Study	Population	Study Design
● Enrolled 1743	Multi	GRAIL Pathfinder	Age>50, Cohort A: elevated risk (smoking, hx of CA, genetic markers); Cohort B: non-elevated risk	Prospective Interventional with return of results
● Enrolling 500+	Multi	GRAIL Pathfinder II	Age>50, new diversity goals	Prospective Interventional with return of results
● Enrolled 5	UNK	GRAIL Galleri- EAP	CA with unknown tissue of origin For compassionate use in late stage treatment	Pilot Interventional with return of results
● Enrolling 229	Colorectal	Freenome PREEMPT	Age 45-85, colonoscopy as SOC	Prospective observational
● Enrolling 117	Multi	Freenome Danube	Age 45-85, dx of IBD, or untreated CA, or no CA	Case Control
● Pending	Lung	Delfi Lung	Age >50, 20 pk/day history	Prospective observational
● Pending	Multi	Exact	Age>50, untreated cancer or control group	Prospective observational

# The Pathfinder 2 Study

- Multicenter Early Detection Blood Test
- Compared to Pathfinder 1:
  - Refined test
  - Recruitment goal of 20,000 over 18 months
    - 3,600 at OHSU
  - Diverse study population
- Population:
  - Age 50 or older
  - Did not participate in Pathfinder 1
  - No suspicion of cancer, or any cancer since 2018



# Regional Research Assessment System



## Community Preparation

Community stakeholders identified and data collected

## Workgroup Formed

Review the data with a community perspective

## Process Development

Create a cultural landscape summary of the region

Customize the submission process & forms

## Local Advisory Council

Takes over full implementation of the process

Reviews proposals

Approves, suggests changes, or declines projects

OHSU Community Engagement team walks alongside the community

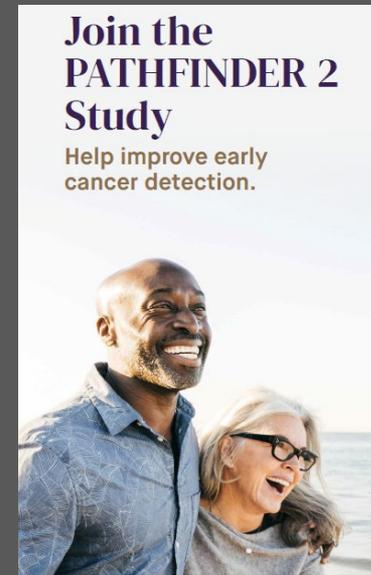
Community owns it!

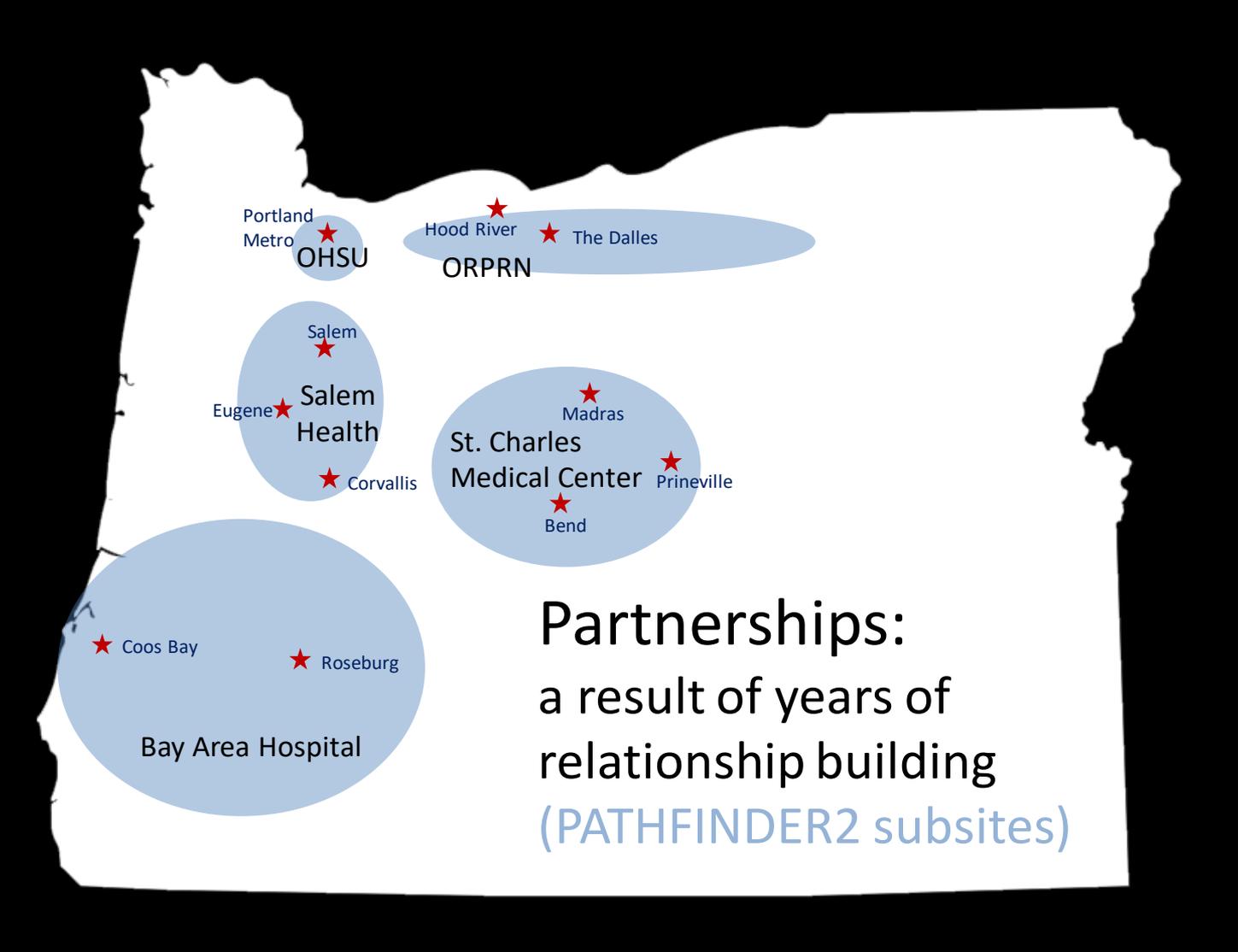


# 2 Specific Stories of Bi-Directional Partnerships

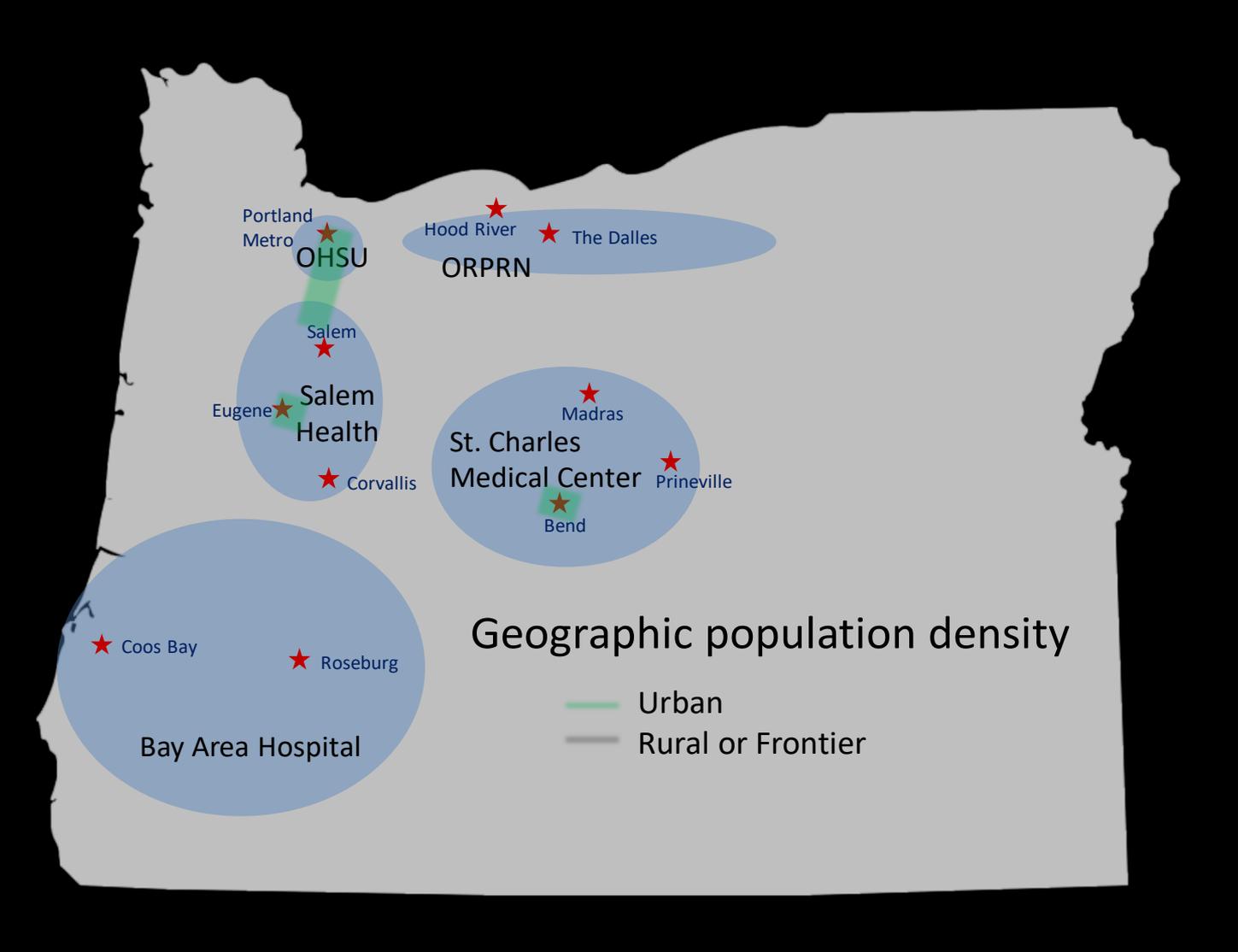
Rural Oregonians in Coos County take part in the Region Research Assessment System and implement the PATHFINDER2 interventional trial as a subsite with OHSU.

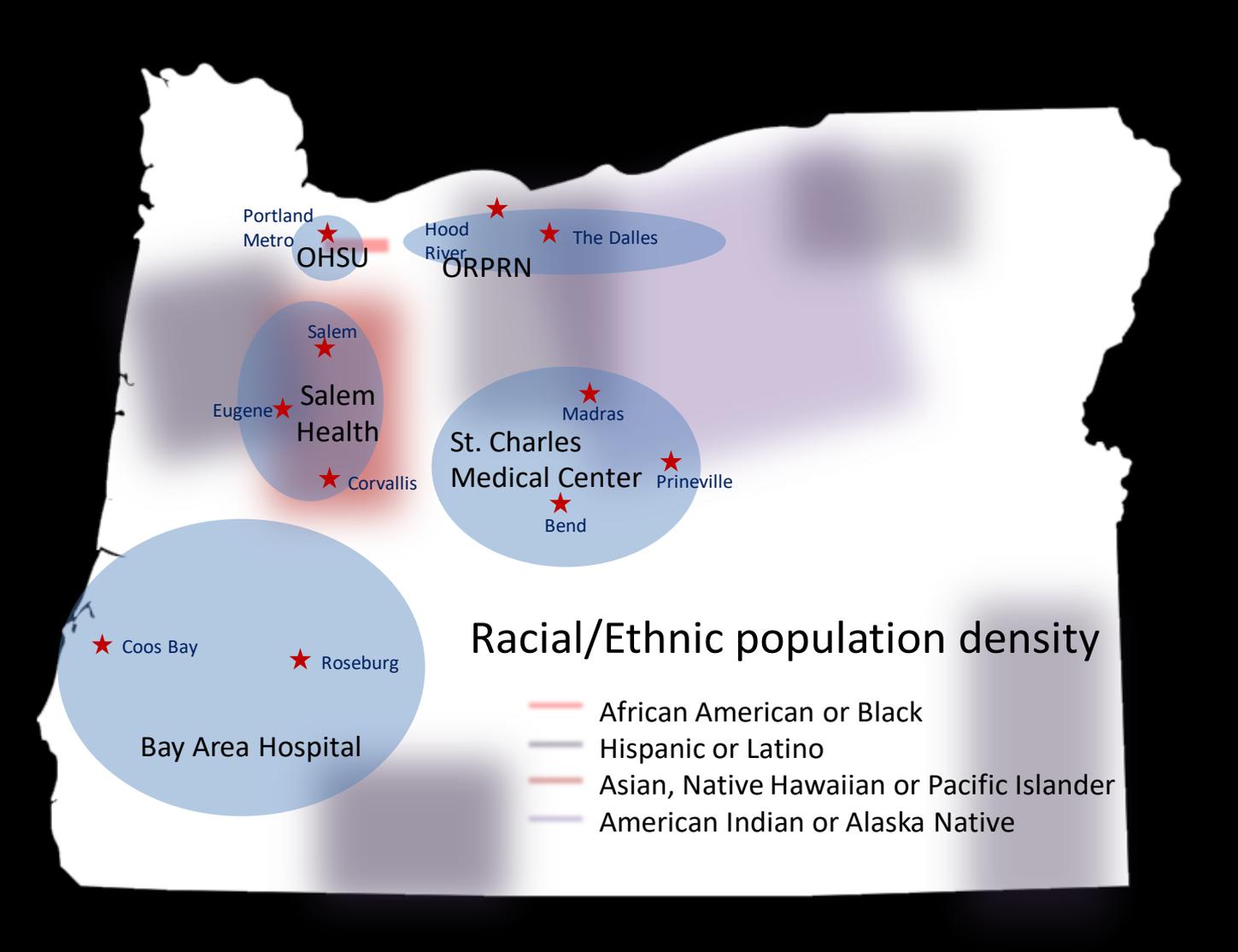
Knight Cancer Advisory Council representatives from the Portland Black community, trusted leaders, help spread the word about the trial which will benefit members of their community





Partnerships:  
a result of years of  
relationship building  
(PATHFINDER2 subsites)





# What Partnership May Look Like

- Subsite Contributes

- Regional relationships and expertise for recruitment
- Local blood draws and diagnostic work-up for signal positives (1%)
- Medical Co-Investigator

**Communities need to retain their patients, but might not have research capacity**

**OHSU has institutional recognition for Early Detection but lacks a diverse patient population**

- OHSU Contributes

- Pharma relationships
- Contracting, IRB oversight, regulatory compliance
- Participant enrollment and follow-up for signal negatives (99%)
- Marketing

# Pathfinder 2 Participation

- More OHSU Employee Early Detection Days to come
- Contact us to participate and for more information!
  - Email: [PATHFINDER@ohsu.edu](mailto:PATHFINDER@ohsu.edu)
  - Phone: (503) 418-8150



*Tom Beer, MD*



*Tiffani Howard, PhD  
Diana Potts, MPA  
Bree Mitchell, PhD*



*John Carter, MD  
Nima Nabavizadeh, MD  
Dan Herzig, MD  
Adel Kardosh, MD*



*Mason McLellan  
Grace Curran  
Mitchell Yep  
Francs De Asis  
Jacob Marquez  
Saron Mekonnen  
Megan Bills*

## The CEDAR Clinical Trials Team

*Thank you.*



KNIGHT  
CANCER  
Institute