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Ahead of the Game: Updates in Multi-Cancer Early Detection Tests

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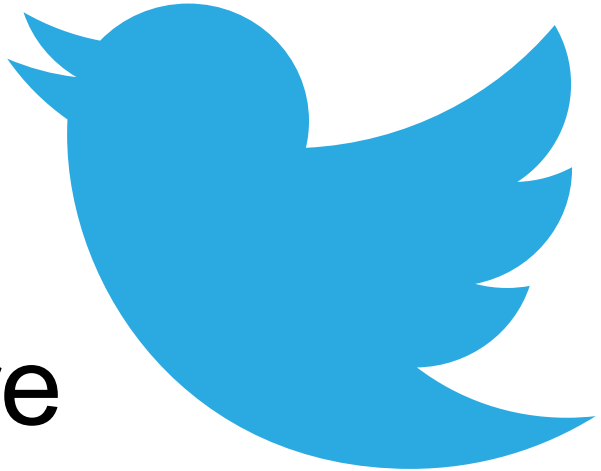

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Learning Objective 1

Explain the benefits and limitations of the current cancer screening approach.

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Learning Objective 2

Assess the emerging MCED tests in development.

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Learning Objective 3

Recognize the clinical considerations regarding emerging blood tests for cancer detection.

Polling Question

What portion of all cancers are covered under existing cancer screening guidelines?

A. 25%
B. 45%
C. 65%
D. 85%
E. I'm not sure

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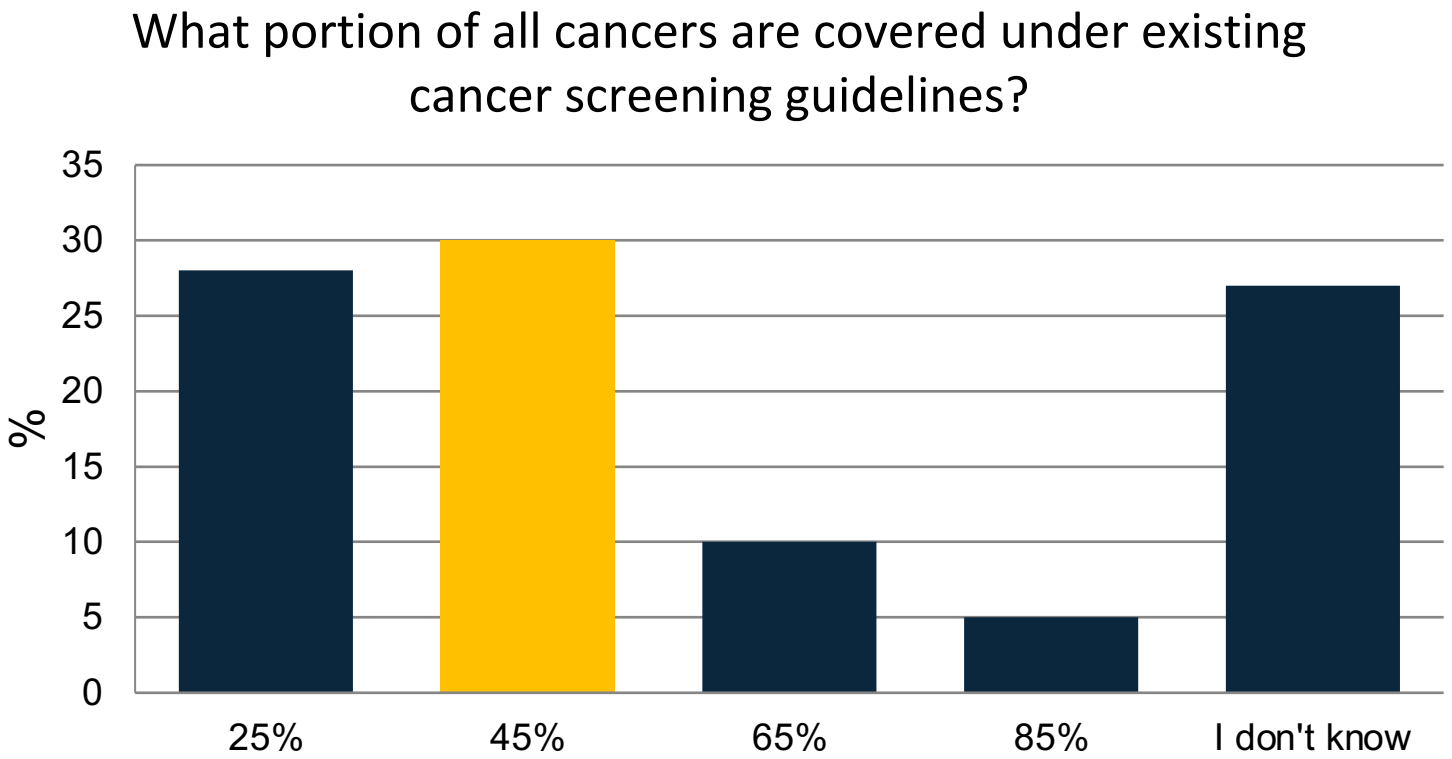
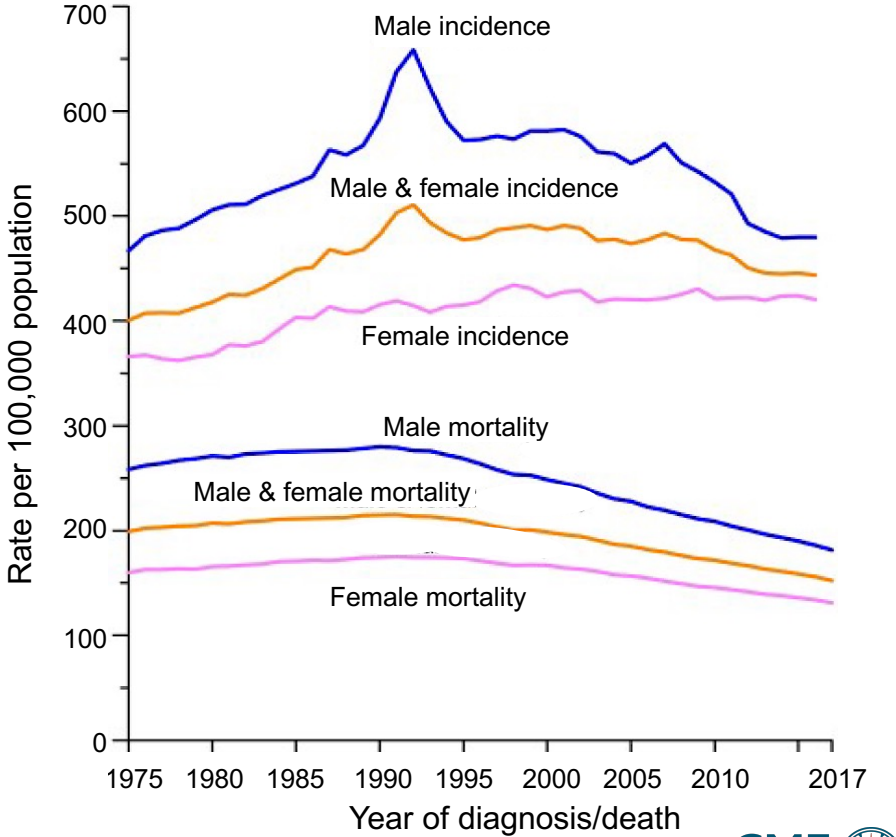
Audience Response



U.S. Cancer Mortality

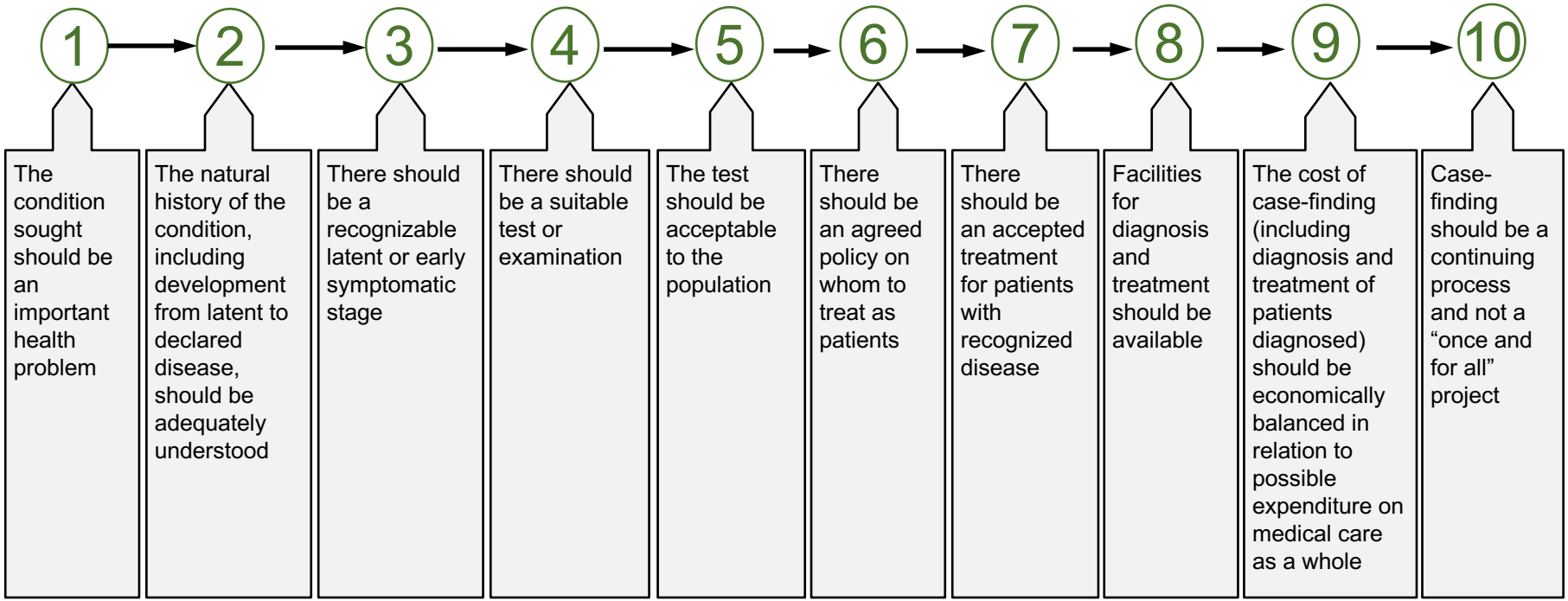
- Cancer is the number two cause of deaths in the U.S.[1]
- Per the American Cancer Society, deaths have decreased since 1990[2]

Cancer screening has played a big part in declining cancer mortality



1. National Center for Health Statistics. Deaths and Mortality. Centers for Disease Control and Prevention Website. 2019. https://www.cdc.gov/nchs/fastats/deaths.htm. Accessed December 20, 2021. 2. Siegel RL, et al. *CA Cancer J Clin*. 2020;70(1):7-30.

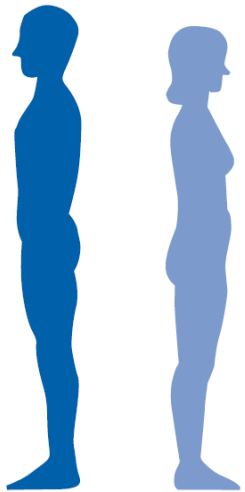
Principles of Screening



Wilson JMG, Jungner G. *Principles and practice of screening for disease.* 1968. WHO_PHP_34.pdf. Accessed January 4, 2022.

Estimated New Cancer Cases in U.S. 2021

Male		
Lung & bronchus	69,410	22%
Prostate	34,130	11%
Colon & rectum	28,520	9%
Pancreas	25,270	8%
Liver & intrahepatic bile duct	20,300	6%
Leukemia	13,900	4%
Esophagus	12,410	4%
Urinary bladder	12,260	4%
Non-Hodgkin lymphoma	12,170	4%
Brain & other nervous system	10,500	3%
All sites	319,420	



Female		
Lung & bronchus	62,470	22%
Breast	43,600	15%
Colon & rectum	24,460	8%
Pancreas	22,950	8%
Ovary	13,770	5%
Uterine corpus	12,940	4%
Liver & intrahepatic bile duct	9,930	3%
leukemia	9,700	3%
Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	8,100	3%
All sites	289,150	

Number of cases exclude basal cell and squamous cell skin cancers and in situ carcinoma, except urinary bladder. Estimates do not include Puerto Rico or other U.S. territories.

Siegel RL, et al. *CA Cancer J Clin*. 2021;71(1):7-33.

USPSTF Lung Cancer Screening Guidelines

- Annual screening for adults aged 50-80 years, who have a 20+ pack-year smoking history and currently smoke or have quit within the past 15 years
- Screening eligibility: 14% per 2013 guidelines, 21% - 24% per 2021 guidelines

2021 guideline changes result in increases in

Eligibility | Lung cancer death prevented | Life years gained

For women and non-Hispanic Black, Hispanic, and American Indian/Alaska Native people

USPSTF = U.S. Preventive Services Task Force.

Meza R, et al. U.S. Preventive Services *Evaluation of the benefits and harms of lung cancer screening with low-dose computed tomography: a collaborative modeling study for the U.S. Preventive Services Task Force*. 2021. Bookshelf_NBK568586.pdf. Accessed January 4, 2022.

Colon Cancer Screening

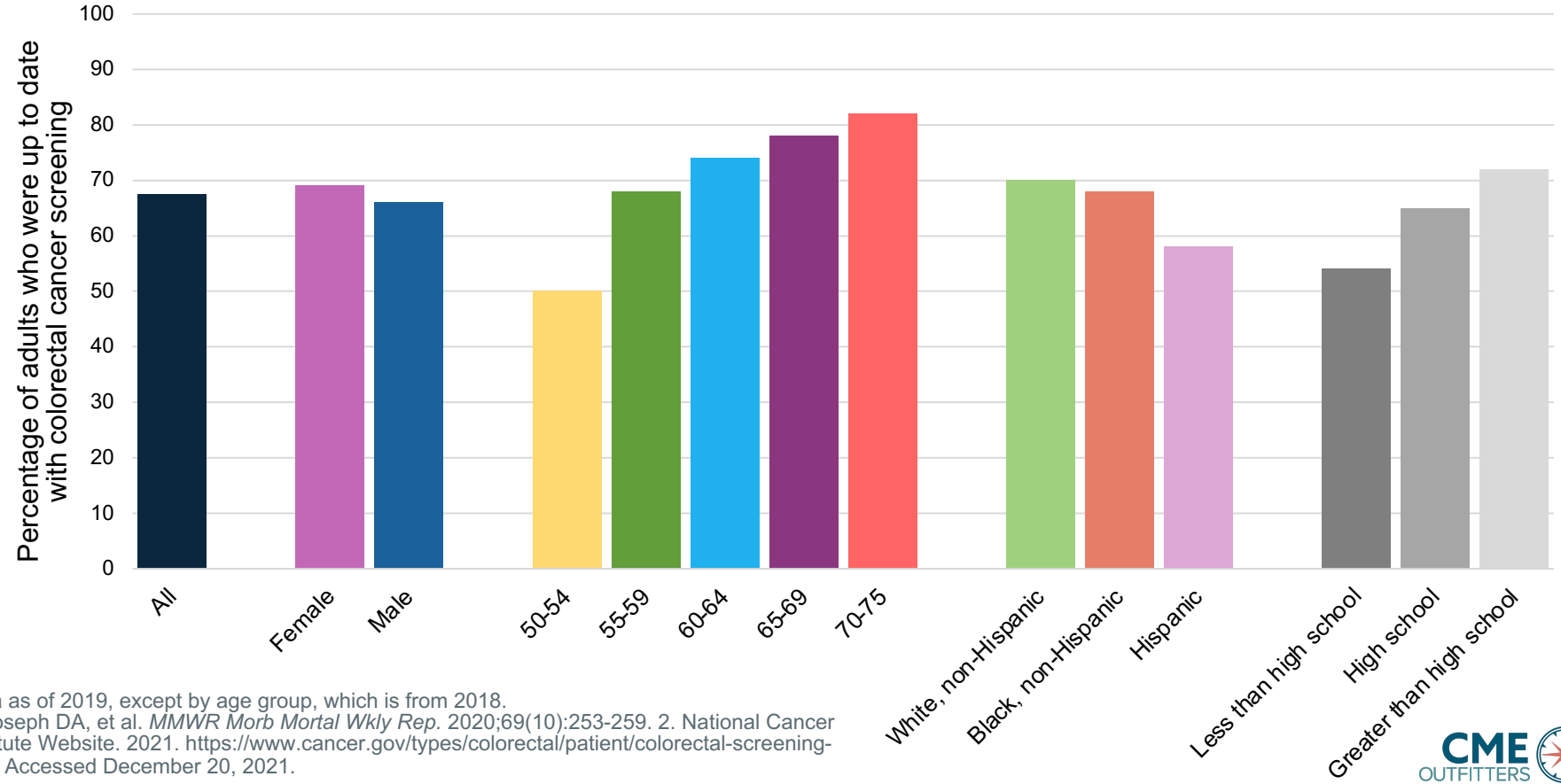
Screen all adults aged 45 to 75 years for colorectal cancer

- High-sensitivity guaiac fecal occult blood test or fecal immunochemical test (FIT) every year
- Stool DNA-FIT every 1 to 3 years
- Computed tomography colonography every 5 years
- Flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 10 years + annual FIT
- Colonoscopy screening every 10 years

Selectively screen adults aged 76 to 85 years for colorectal cancer.

U.S. Preventive Services Task Force Website. 2021. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening. Accessed December 20, 2021.

Adults Up To Date with Colorectal Cancer Screening



Data as of 2019, except by age group, which is from 2018.

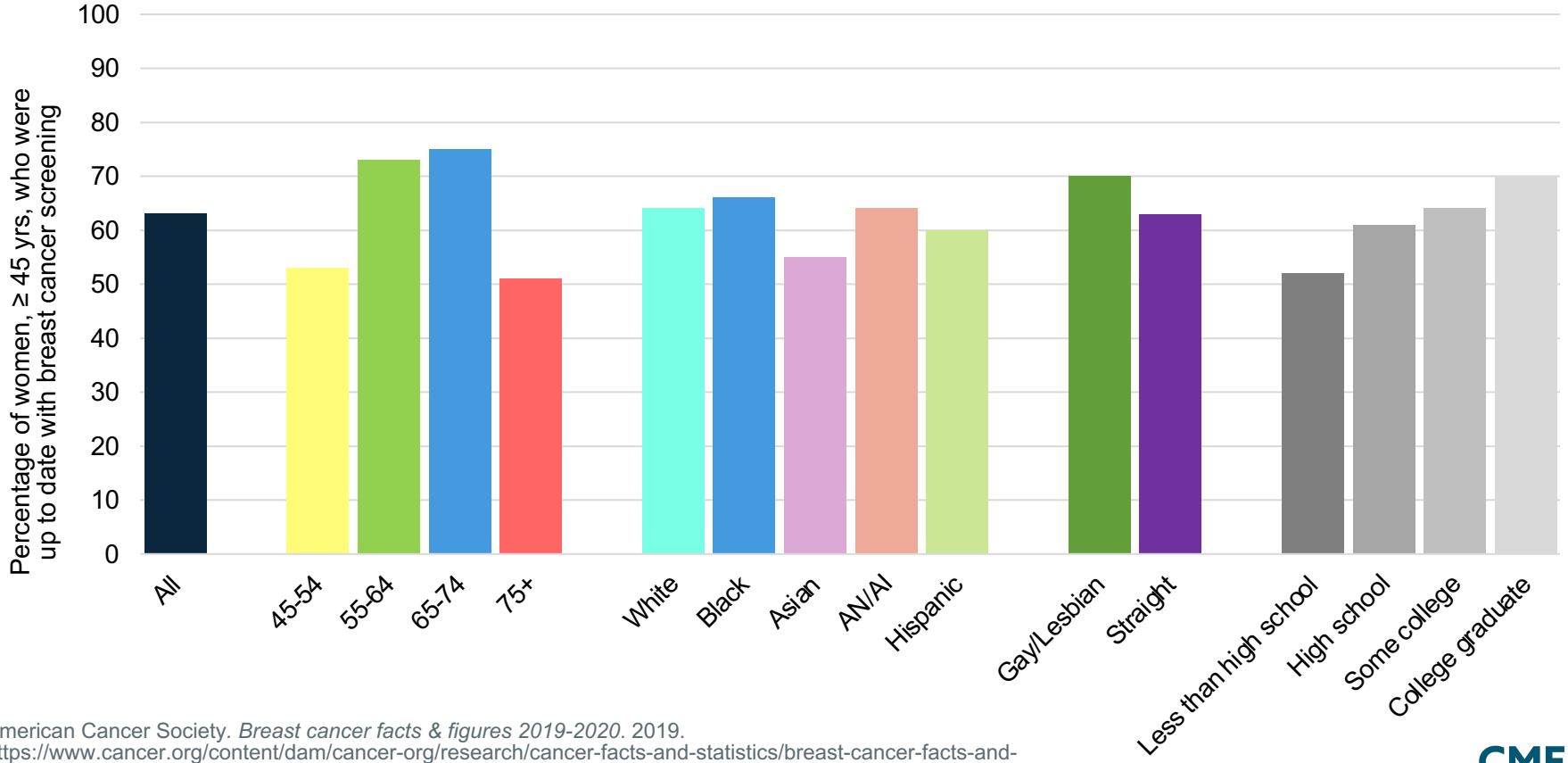
1. Joseph DA, et al. *MMWR Morb Mortal Wkly Rep.* 2020;69(10):253-259. 2. National Cancer Institute Website. 2021. https://www.cancer.gov/types/colorectal/patient/colorectal-screening-pdq. Accessed December 20, 2021.

Breast Cancer Screening Recommendations

	U.S. Preventive Services Task Force[1,2]	American Cancer Society[3]	American College of Obstetricians and Gynecologists[4,5,6]	International Agency for Research on Cancer[7]	American College of Radiology[8,9]	American College of Physicians[10]	American Academy of Family Physicians[11]
Women aged 40 to 49 years with average risk	Biennial in women, placing higher value on the potential benefit than the potential harms	Optional annual for women aged 40 to 44 years; annual for women aged 45 to 49 years	Optional annual or biennial mammography and optional annual clinical breast exams	Screening mammography discouraged	Annual mammography	Screening mammography discouraged	Annual in women, placing higher value on the potential benefit than the potential harms
Women aged 50 to 74 years with average risk	Biennial mammography	Annual mammography for women aged 50 to 54 years; annual or biennial for women aged 55 years and older; clinical breast examination is not recommended	Annual or biennial mammography and annual clinical breast exams	Screening mammography recommended	Annual mammography	Biennial mammography recommended; clinical breast examination not recommended	Biennial mammography

1. Siu AL. *Ann Intern Med*. 2016;164(4):279-296. 2. U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151(10):716-726, W-236. 3. Oeffinger KC, et al. *JAMA*. 2015;314(15):1599-1614. 4. Committee on Gynecologic Practice. *Obstet Gynecol*. 2015;125(3):750-751. 5. Committee on Practice Bulletins-Gynecology. *Obstet Gynecol*. 2017;130(1):e1-e16. 6. Committee on Practice Bulletins-Gynecology, Committee on Genetics, Society of Gynecologic Oncology. *Obstet Gynecol*. 2017;130(3):e110-e126. 7. Jatoi I. *N Engl J Med*. 2015;373(15):1478-1479. 8. Monticciolo DL, et al. *J Am Coll Radiol*. 2017;14(9):1137-1143. 9. Monticciolo DL, et al. *J Am Coll Radiol*. 2018;15(3 Pt A):408-414. 10. Qaseem A, et al. *Ann Intern Med*. 2019;170(8):547-560. 11. American Academy of Family Physicians. *Summary of recommendations for clinical preventive services*. 2017. https://www.aafp.org/dam/AAFP/documents/patient_care/clinical_recommendations/cps-recommendations.pdf. Accessed December 20, 2021.

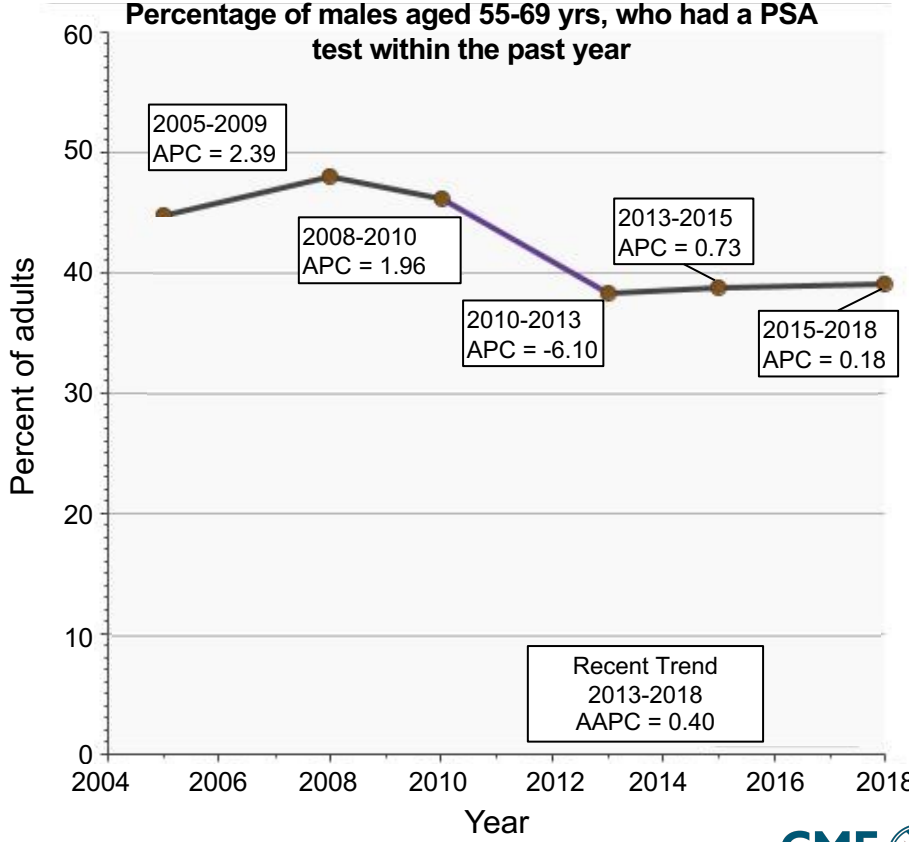
Women Up To Date with Breast Cancer Screening



American Cancer Society. *Breast cancer facts & figures 2019-2020*. 2019. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. Accessed December 20, 2021.

USPSTF Prostate Cancer Screening Guidelines

2018 USPSTF prostate cancer screening guidelines	
Aged 55-69 yrs	Individualize to patient needs and wishes.
Aged < 55 or ≥ 70 yrs	The USPSTF recommends against PSA-based screening.



AAPC = Average annual percent change. PSA = Prostate-specific antigen.
Grossman DC, USPSTF. *JAMA*. 2018;319(18):1901-1913.

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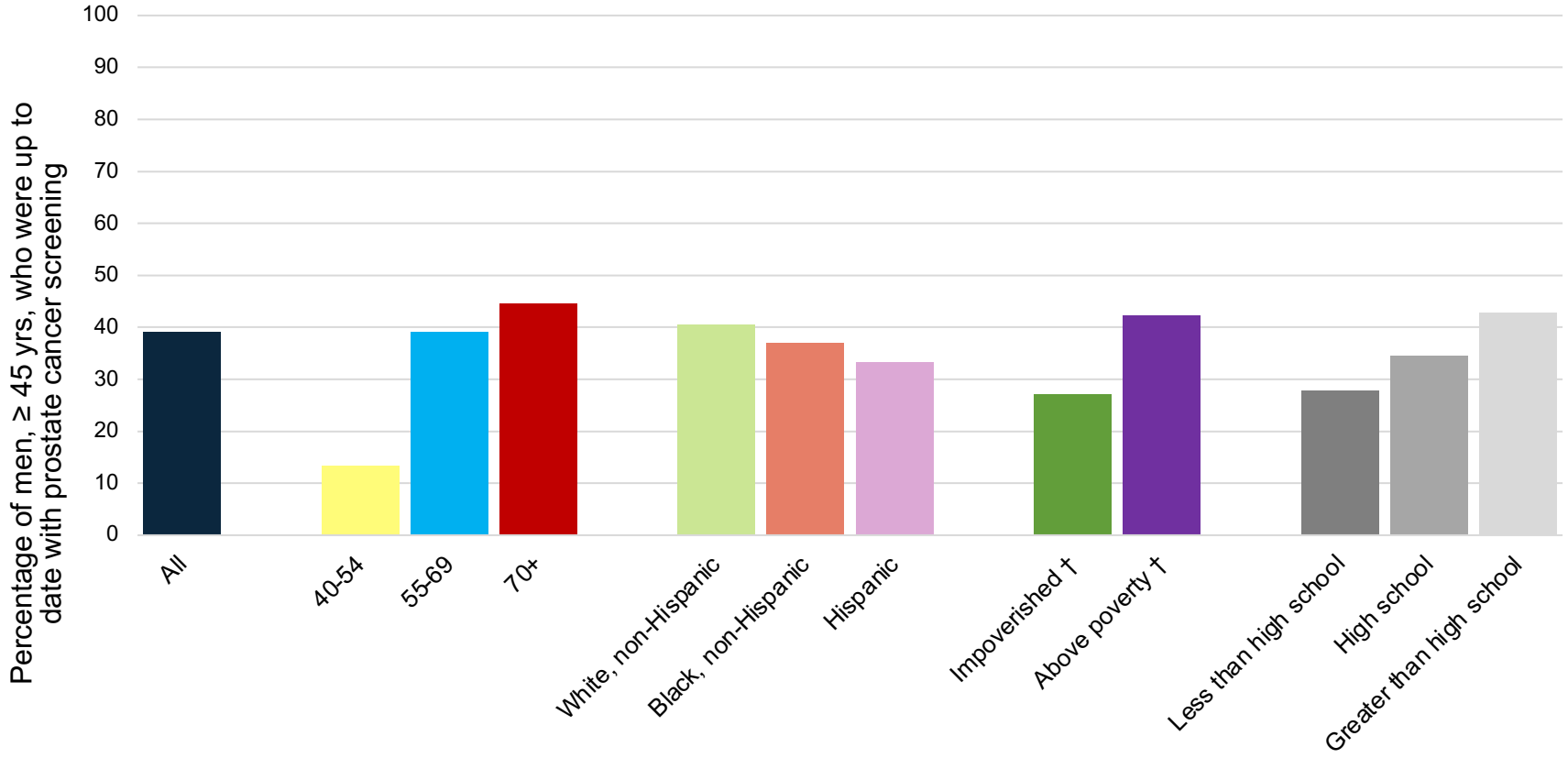
Men Up To Date with Prostate Cancer Screening



† Relative to 200% federal poverty level.

National Cancer Institute Wesbite. 2021. https://progressreport.cancer.gov/detection/prostate_cancer. Accessed December 20, 2021.

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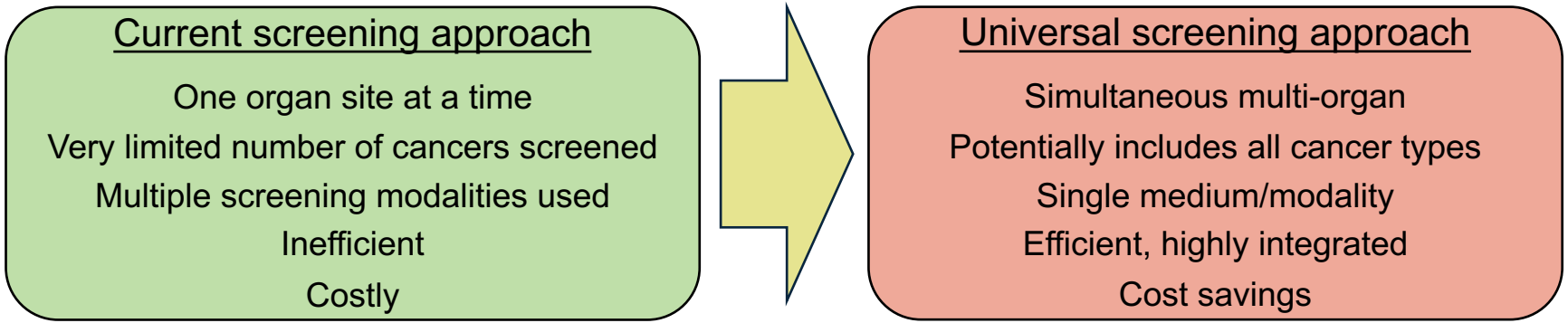
Screening Remains Controversial Across All Cancer Types

- Who to screen?
- What test to use?
- How to interpret results?
- When to start?
- How often?
- When to stop?

The Promise of Multi-Cancer Detection

- Many less common cancers do not have screening tests available
  - E.g., liver, pancreatic, esophageal cancers



A multi-cancer detection test could have a profound impact on cancer detection and public health.

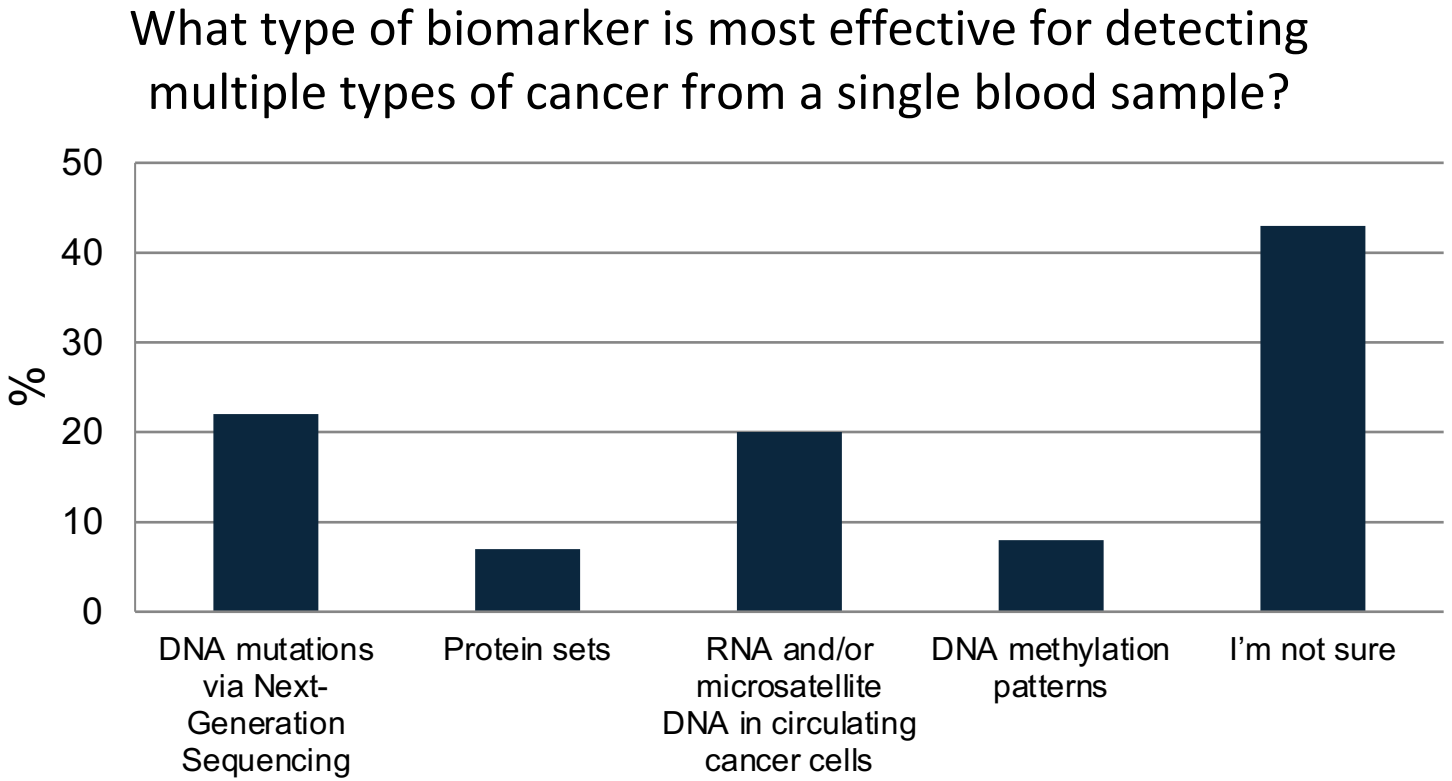
Ahlquist DA. *NPJ Precis Oncol*. 2018;2:23.

Polling Question

What type of biomarker is most effective for detecting multiple types of cancer from a single blood sample?

A. DNA mutation patterns via Next-Generation Sequencing
B. Protein sets
C. Extracellular Vesicles/Exosomes
D. Circulating cancer cells
E. RNA
F. DNA methylation patterns
G. I'm not sure

Audience Response

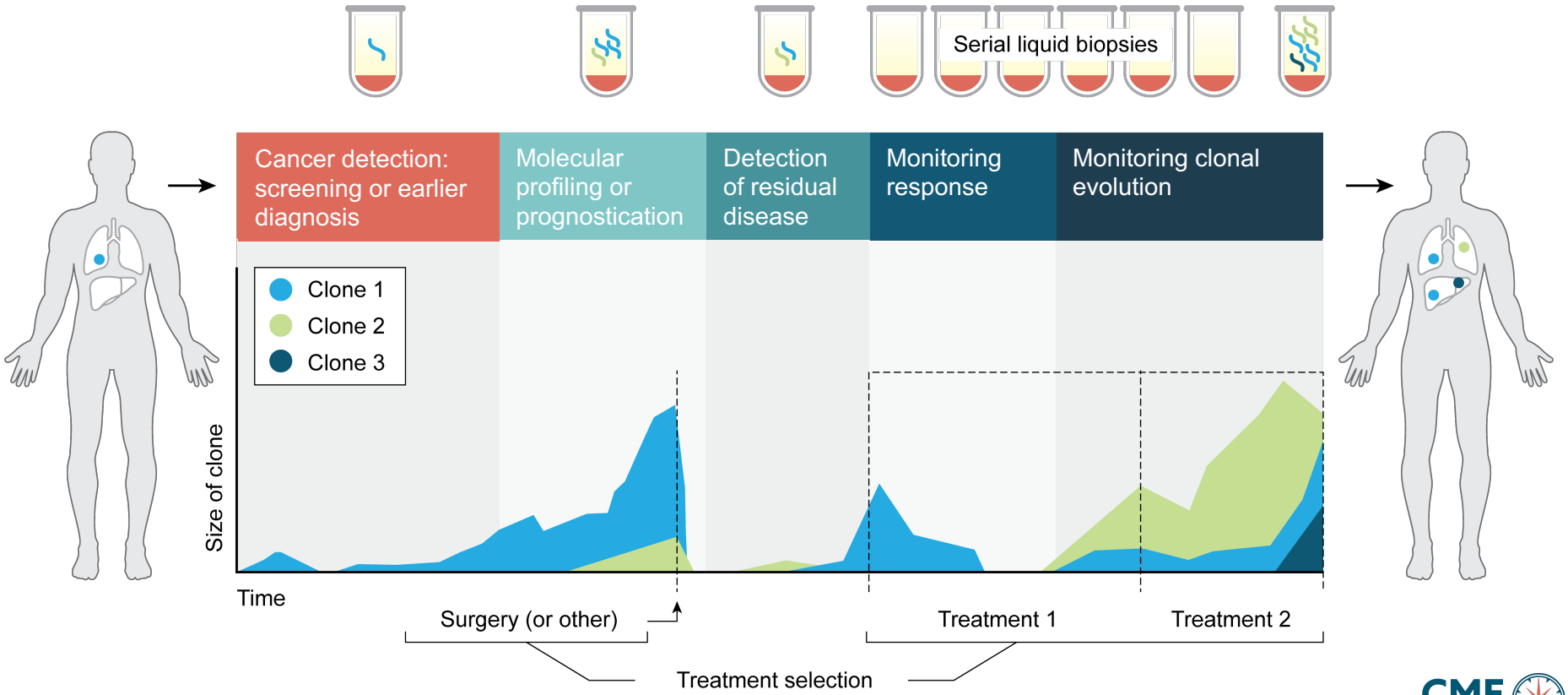


Early Detection of Cancer with Integrated Multi-Omic Analysis of Circulating Cancer Biomarkers

- 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

CTC = Circulating tumor cells.
Ahlquist DA. *NPJ Precis Oncol*. 2018;2:23.

Promise and Applications of Circulating Tumor-Derived Material



Wan JCM, et al. *Nat Rev Cancer*. 2017;17(4):223-238.

DETECT-A Study

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

Science

RESEARCH ARTICLES

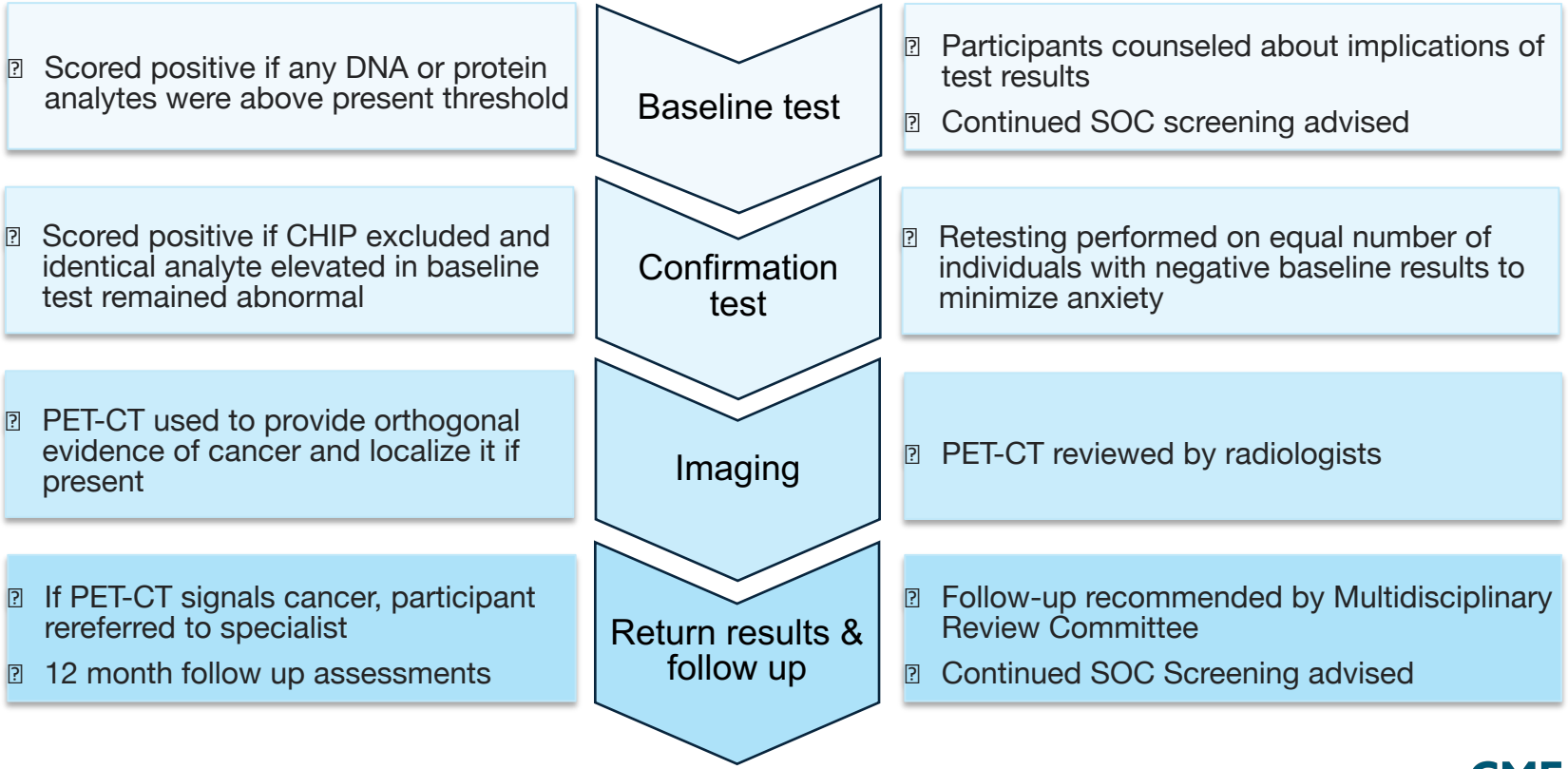
Cite as: A. M. Lennon *et al.*, *Science* 10.1126/science.abb9601 (2020).

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

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

PET-CT = Positron emission tomography-computed tomography.
Lennon AM, et al. *Science*. 2020;369(6499):eabb9601.

DETECT-A Testing Process



CHIP = Clonal hematopoiesis of indeterminate potential. SOC = Standard-of-care.

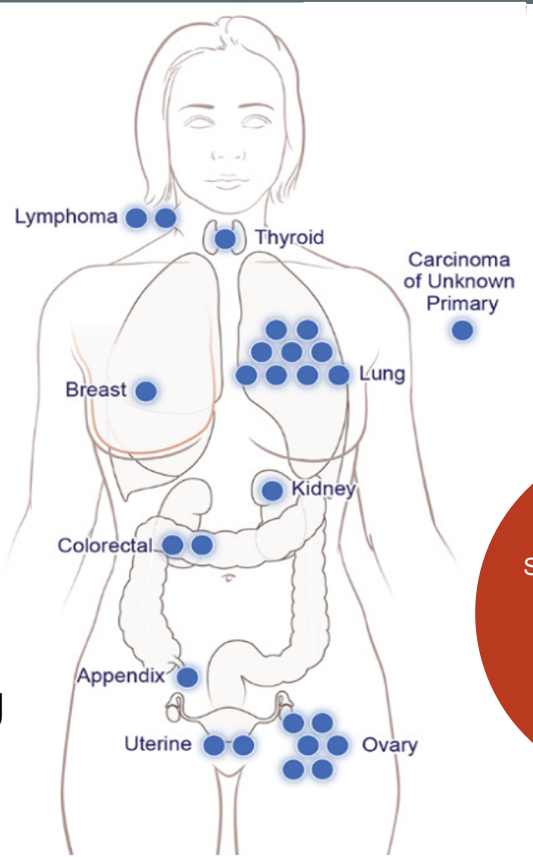
Lennon AM, et al. *Science*. 2020;369(6499):eabb9601.

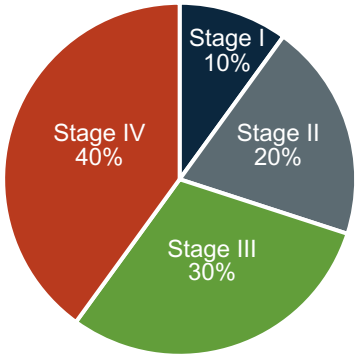
DETECT-A Results

- 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





Lennon AM, et al. *Science*. 2020;369(6499):eabb9601.

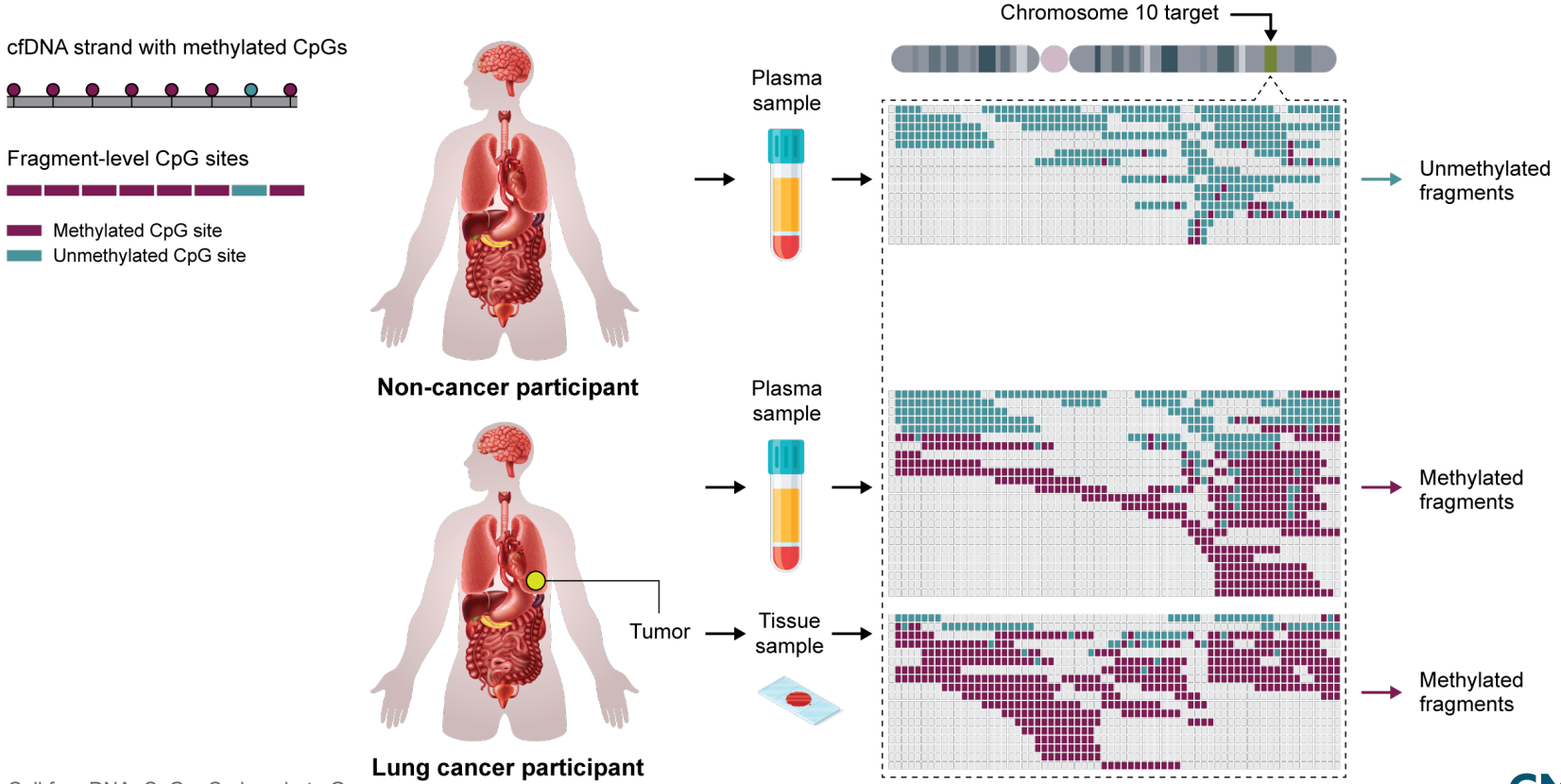
Test Performance

Performance with and without confirmation test and 95% confidence intervals

	Blood Test Without Confirmation	Blood Test With Confirmation
Positive Predictive Value	5.9% (4.0-8.4)	19.4% (13.1-27.1)
Specificity	95.3% (94.9-95.7)	98.9% (98.7-99.1)
Negative Predictive Value	99.3% (99.1-99.4)	99.3% (99.1-99.4)
# Needed to Screen to Detect 1 Cancer	342 (238-510)	381 (260-583)
Sensitivity		
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)

Lennon AM, et al. *Science*. 2020;369(6499):eabb9601.

Cancer and Non-Cancer cfDNA Methylation



cfDNA = Cell-free DNA. CpG = C-phosphate G.

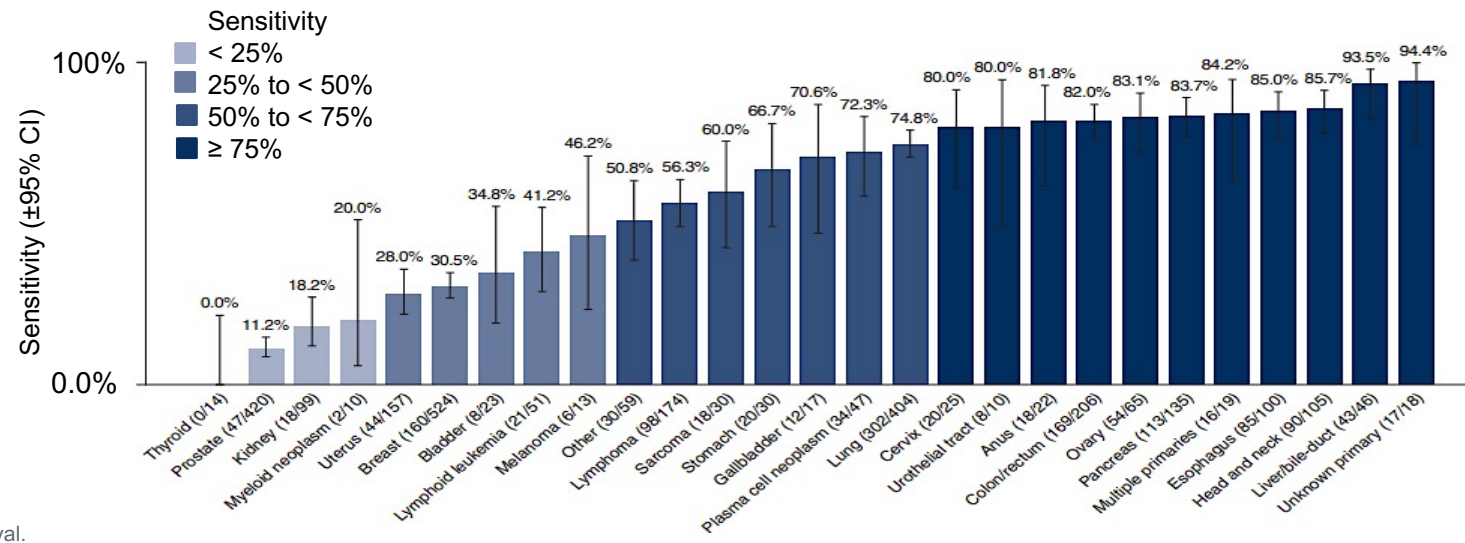
Liu MC, et al. *Ann Oncol*. 2020;31(6):745-759.

Multi-Cancer Early Detection Test

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



CI = Confidence interval.

Klein EA, et al. *Ann Oncol*. 2021;32(9):1167-1177.

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

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

Study Objectives

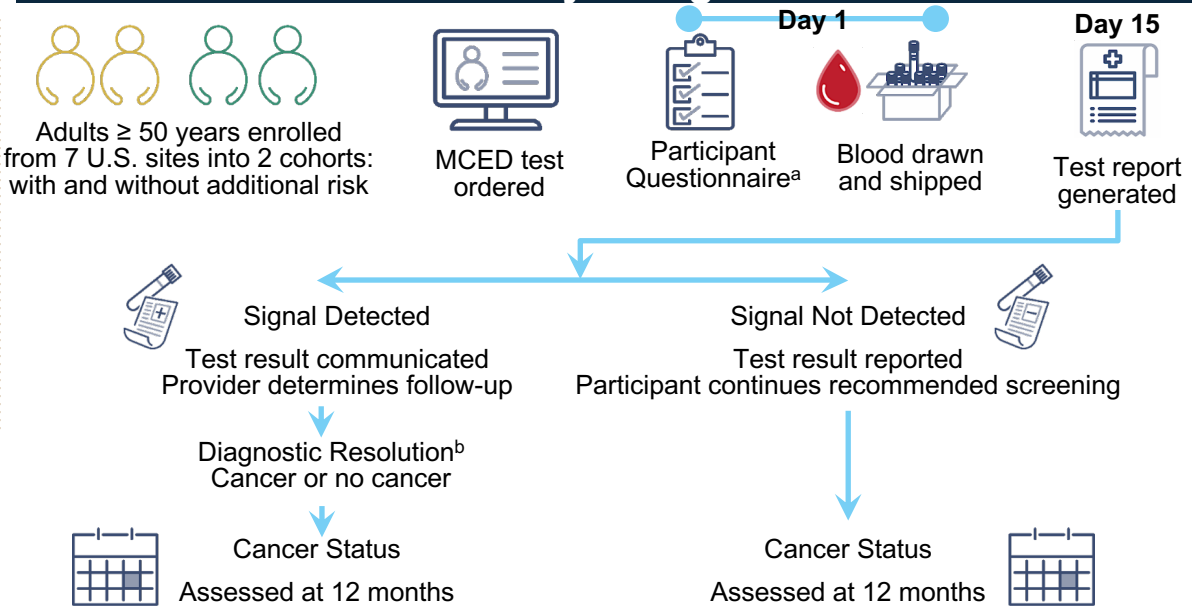
Primary

- 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



[a] Also collected at other timepoints during the study. [b] Defined as date when study team determines to end diagnostic evaluation triggered by a "signal detected" test result. MCED = Multi-cancer early detection.

Klein EA, et al. *Ann Oncol*. 2021;32(9):1167-1177.

Interim Secondary Outcome: Test Performance

	With Additional Risk	Without Additional Risk	Total
Cancer Signal Detection, No.	n = 3695	n = 2934	N = 6629
Detected, No. (%)	**56 (1.5)**	**36 (1.2)**	**92 (1.4)**
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)
PPV for Cancer Signal Detection, No.	n = 35	n = 30	n = 65
% (95% CI)	**57.1 (40.9-72.0)**	**30.0 (16.7-47.9)**	**44.6 (33.2-56.7)**
CSO Prediction Accuracy	n = 19[a]	n = 8[a]	n = 27[a]
First CSO, % (95% CI)	**84.2 (62.4-94.5)**	**87.5 (52.9-99.4)**	**85.2 (67.5-94.1)**
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

CSO = Cancer signal origin. No. = Number. PPV = Positive predictive value. a Excludes 1 participant with unknown cancer type and 1 with indeterminate CSO from the true positive set. Data as of March 2021.
Klein EA, et al. *Ann Oncol*. 2021;32(9):1167-1177.

Cancer Characteristics of True Positive Set

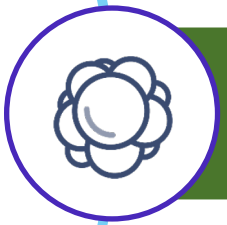
Cancer Type Diagnosed	Clinical AJCC Stage of New Cancers					Recurrent Cancers		First Predicted Cancer Signal Origin
	I	II	III	IV	Other	Local	Distant	
Colon or rectum				1	1 (unknown)			Upper GI Tract (SIV pt); Colon/Rectum (unk pt)
Head and Neck		1		1				Head and Neck
Liver, bile duct	1		1					Liver, 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)
Total	**4**	**5**	**4**	**5**	**5**	**1**	**4**	

AJCC = American Joint Committee on Cancer version 8. FT = Fallopian tube. GI = Gastrointestinal. NA = Not applicable. Pt = Participant. SIV = Stage IV. Unk = Unknown.

Klein EA, et al. *Ann Onc*ol. 2021;32(9):1167-1177.

Pathfinder Interim Analysis Conclusions

In this prespecified interim analysis, the MCED test was safely administered and detected cancer signal in a broad range of cancer types



More than half of new cancers were detected at early stages (clinical stages I-III)

Follow up of PATHFINDER participants continues and will identify the incidence of cancer diagnoses for all participants within 12 months of their initial blood draw, at which time the specificity and negative predictive value of the MCED test will be evaluated

Klein EA, et al. *Ann Oncol*. 2021;32(9):1167-1177.

Summary

- Cancer screening has reduced cancer deaths, but …
  - Screening can be laborious.
  - Screening techniques are specific to cancer type and minimum size.
  - Current screening guidelines are applicable to less than half of all cancers
- Multi-cancer screening would extend cancer screening to all cancer types.
- ctDNA techniques promise to screen for all cancer types.

ctDNA = Circulating tumor DNA.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Clinicians should encourage all patients to be up to date with recommended cancer screening procedures
- Clinicians should explain the benefits and limitations of the current and emerging cancer screening approaches to their patients
- Clinicians should interpret multi-cancer screening results for their patients, keeping in mind the clinical limitations of these tests

CME Outfitters

AFTER THE SHOW

Questions & Answers

CME OUTFITTERS

Visit the

Oncology and Virtual Education Hubs

Free resources and education to educate
health care providers and patients on cancer

https://www.cmeoutfitters.com/oncology-education-hub/

https://www.cmeoutfitters.com/virtual-education-hub/

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.