Multi-cancer Early Detection Technology—Are We There Yet?

Winship Cancer Institute Annual Cancer Conference
July 23, 2022

Ernest Hawk, MD, MPH
Vice President and Head, Division of Cancer Prevention and Population Sciences
The University of Texas MD Anderson Cancer Center
ehawk@mdanderson.org

Disclosure information

Presenter: Ernest Hawk, MD, MPH

I have the following financial relationships to disclose:

Past Consultant: *Cancer Prevention Pharmaceuticals; PLx Pharma, Inc.; Pozen, Inc.*

Speaker's Bureau: *N/A*

Grant/Research support: *NIH/NCI, CPRIT*

Stockholder: *N/A*

Honoraria: *Huntsman Cancer Institute, University of Kansas CCC, Mayo CCC, Roswell Park Cancer Institute, Buffett CC at University of Nebraska, Simmons CCC at UT Southwestern, Fred Hutchinson CCC, Sidney Kimmel CCC at Johns Hopkins, James CCC at Ohio Status U, Hollings CC at MUSC, O'Neal CCC at UAB, Albert Einstein CC, Knight CC at OHSC, ECHO Institute*

Employee: *The University of Texas MD Anderson Cancer Center*

Cancer: a chronic interplay of inherited factors and exposures that progressively alter cellular identity, relationships, and growth control

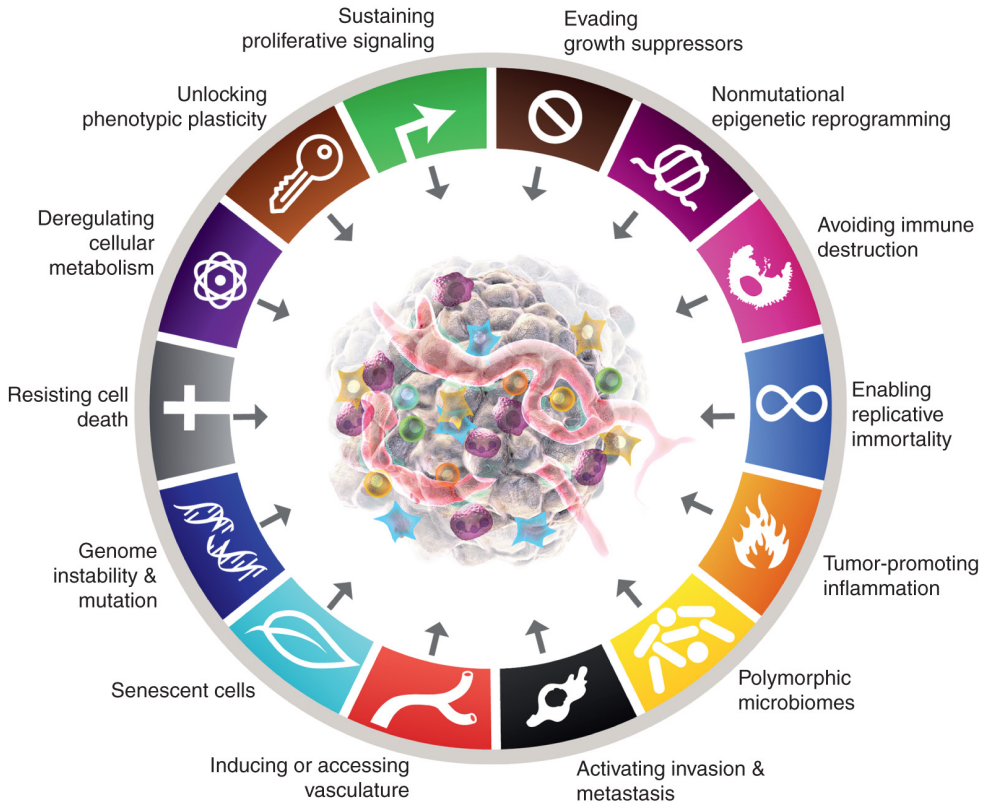
"Non-modifiable" Inherited Susceptibilities

- Major defects in cancer-promoting/ inhibiting genes
- Subtle differences in genetic coding or expression

"Modifiable" Cumulative Exposures

- Tobacco
- Poor diet including excess alcohol
- Physical inactivity
- Excess body weight
- Viruses
- Occupational exposures

14 hallmarks of cancer



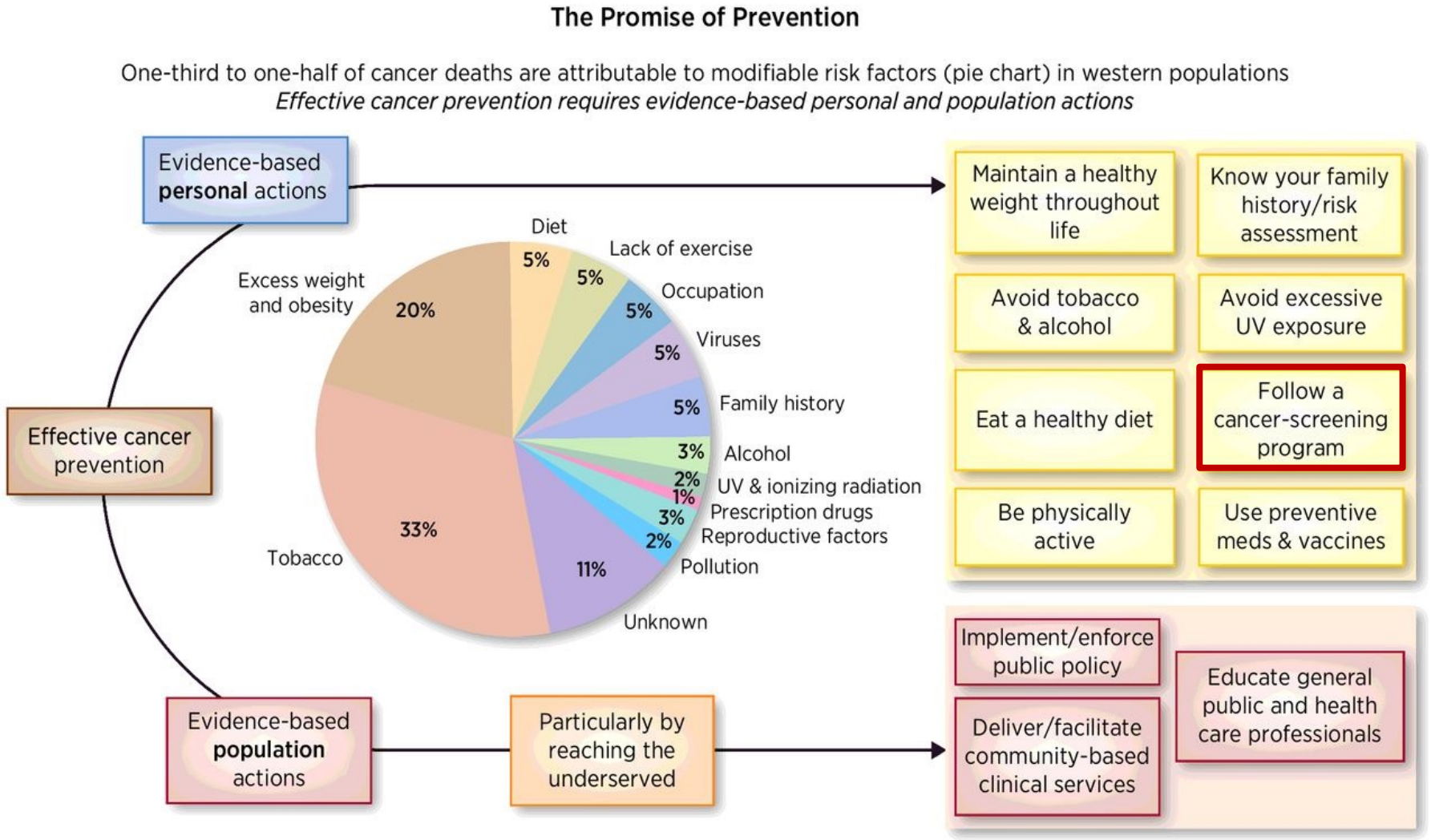
Questions critical to risk assessment & prevention:

- **Mechanisms**: How are pathways damaged? Any of special importance?
- **Sequencing**: When? Does order matter?
- **Frequency**: Which are most likely?
- **Prevalence** in preinvasive neoplasia, especially lesions likely to progress

Hanahan D. Cancer Discovery 12:31-46, 2022

One-third to one-half of cancer deaths are estimated to be preventable in Western populations in 2022

Effective cancer prevention is applied in two domains across the lifespan



- Guideline-recommended tests available
  - Breast (mammography)
  - Cervix (pap smear; HPV)
  - Colon (scope, molecular, or imaging)
  - Lung (low-dose CT scan)
  - Prostate (PSA)
- Current screening rates = 42% by self-report
- Strategies must respond to:
  - Emerging therapies/vaccine prevention
  - Changing population trends (incidence and mortality)
  - Screening benefits/harms

Figure: Lippman S…Hawk E, CaPR 11(12), Dec 2018. Data based on Colditz, et al. Sci Trans Med., 2012 & Wolin, et al., Oncologist, 2010

Current cancer screening guidelines - 2022

Organ	Tools	Sensitivity	Specificity	Age	Frequency
Breast	Mammography	77-95%[1]	94-97%[1]	50-74 years	Every 2 years
Cervix	Cervical cytology; HPV testing	Follow-up protocols for abnormal results varied widely[2]	Varies widely; co-testing has highest FP rates[2]	21-29 years 30-65 years	Every 3 years; cytology Every 3 years, cytology; every 5 years, HPV testing; or every 5 years, both tests
Colorectum	Stool-based Direct visualization	50-97%[3] 86-100%, CT colonography; 18-100%, colonoscopy[3]	83-98%[3] 88-94%, adenomas ≥ 6 mm[3]	45-75 years 76-85 years	Stool based, every year; CT colonography or sigmoidoscopy, every 5 years; colonoscopy, every 10 years; Consult clinician about testing
Blood-based screen for CRC	Epi proColon® 2.0 from Epigenomics	68-72%[8] PPV = 2.4-15.6%	96-99%[8] NPV = 99.7-99.8%	≤ 50 years[9]	Use only when USPSTF CRC screening recommendations are offered/declined[9]
Multi-target stool DNA test for CRC	Cologuard from Exact Sciences	92%[9]	74%[9]	≤ 50 years[10]	Every 3 years for average-risk individuals[10]

20 pack-year history or for previous smokers who have quit in the last 15 years. Kilpeläinen et al. Eur J Cancer 47:2008, 2011. Mettlin et al. Cancer 74:1618, 1994.
[8]Epi procolon. epiprocolon.com/us/patients/test-accuracy/ accessed June 27, 2022. [9]Imperiale et al. NEJM 370(14):1287, 2014. [10]FDA access data. accessdata.fda.gov/cdrh_docs/pdf13/p130017b.pdf; accessed June 27, 2022.

Ahlquist's proposal for *universal cancer screening* - 2018

Current single-organ detection approach

- Five organs w/demonstrated reductions in cancer-associated mortality
- Risk-based
  - Age
  - Exposures
  - Family history
- Serial evaluations
- Excludes most cancer types
- Multiple technologies/modalities
  - Blood proteins
  - Imaging
  - Endoscopy
- Inefficient
- Costly

Universal, multi-organ detection approach

- Theoretically including "all" cancers
- Single medium/modality
- Efficient, highly integrated
- Potentially cost-saving

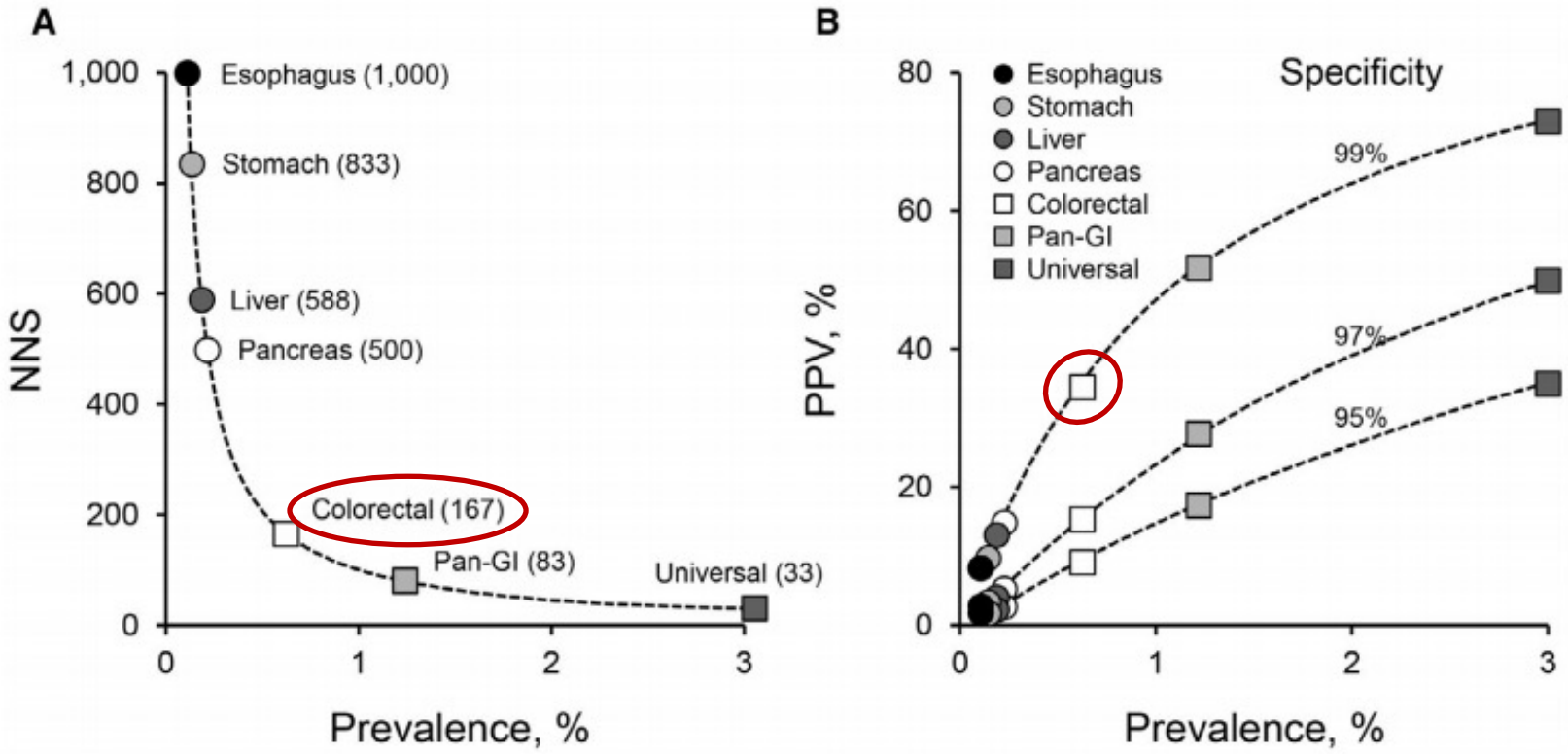
~70% of all US cancer deaths occur in sites without recommended screening options

--JJ Ofman and A Reza
Scientific American, 2020

Modified from Ahlquist DA: npj Precision Oncology 2018;2:23;1-5

High-prevalence cancer screening in average-risk population

Impact of cancer prevalence on screening efficiencies



Multi-organ perspective: aggregate prevalence of less-common cancers overtakes even the most common single-organ cancers; **NNS may be dramatically reduced & PPV significantly improved**

A. Exponential relationship between cancer prevalence and **number of patients needed to be screened (NNS)** to detect 1 cancer (100% sensitivity presumed)

B. Influence of cancer prevalence on **positive predictive value (PPV)** at various specificities

Kisiel, Papadopolous, Liu, Crosby, Srivastava, Hawk: Cancer 128(S4):861-874, 2022

Determining appropriate targets for a test

Cancers

- Most prevalent
  - Provide best chance of high PPV
  - May yield shorter development time (cases are more common)
- Most lethal
  - Societal and ethical imperative
  - Payers more willing to reimburse
  - Patients more willing to undergo testing
- Worst current early-stage detection rate
  - Survival rates are poorest for lung, pancreas, ovary
- Most amenable to existing interventions offering cure

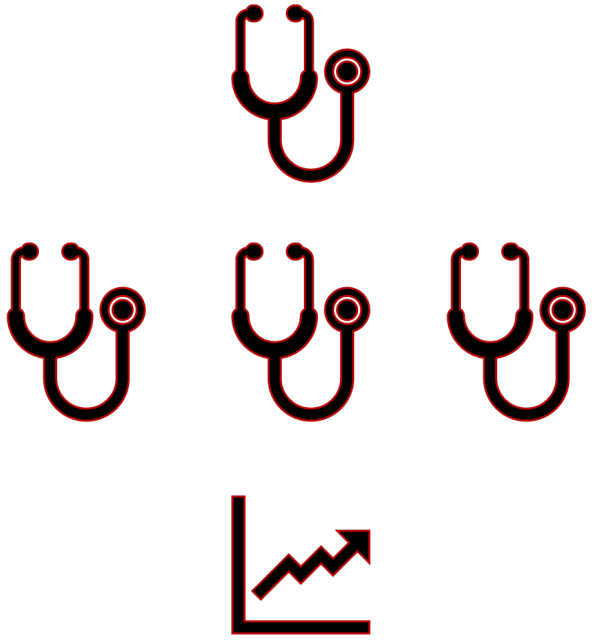
Populations

- Age/comorbidities
  - Minimizes potential harms from false positives
- High-risk groups–germline mutations or consequential exposures
  - Drawbacks
    - Not representative of general population – **smaller market**
  - Advantages
    - Greater clinical need
    - Shorter duration of time to event
    - Smaller sample size required
    - Greater motivation to participate in research and interventions
    - Greater tolerance of side effects
    - Narrower range of biologic/molecular aberrations
- Average risk groups—could vary by geographic region: cultural-, economic-, lifestyle-, other factors
  - Will specific tests be required for specific populations?

Kisiel J,…Hawk E. Cancer 128(S4):861, 2022

What are primary (&/or secondary) goals of MCED test?

- **Early cancer detection** *at a single point* in time?
- **Early cancer detection** *across a span* of time?
- **Risk prediction** (i.e., identify the process)?
  - *In studies and proposals to date, precancers are not typically included in endpoint definitions as 'lesions worthy of identification'*



Kisiel J,…Hawk E. Cancer 128(S4):861, 2022

Idealized multi-cancer early detection (MCED) test characteristics

- Simple, inexpensive, safe sample collection – blood
- Sensitive to multiple cancers and at earlier stages than symptomatic presentations, yielding earlier detection
- High specificity to limit FPs and unnecessary workups
  - Guiding diagnostic evaluations re: 'tissues of origin'
- Acceptable and satisfactory to providers and asymptomatic 'patients'
- Proven 'clinical validity' in intended use populations
- Demonstrated 'clinical utility' in intended use populations
- Complementary benefit when applied alongside established prevention/screening measures

Kisiel J,…Hawk E. Cancer 128(S4):861, 2022

NCI/EDRN's framework for novel cancer-test development

	Discovery	Test performance, refinement, and clinical validation		Clinical decision making and population health outcomes	
	Phase 1	**Phase 2**	**Phase 3**	**Phase 4**	**Phase 5**
Goal	Biomarker identification or target lesion discovery	Analytic validity and refinement of assay	Clinical validity	Clinical utility†	Implementation and ongoing evaluation
Definition	Identify candidates	Ability to detect analyte or lesion; diagnostic accuracy (sensitivity and specificity)	Diagnostic accuracy	Safety and effectiveness (benefits relative to harms using cancer-specific and/or all-cause mortality, morbidity or quality of life)	Reach, acceptability, safety, impact
Design	Exploratory experiments	Experiments and correlative studies	Retrospective cohort with samples or data, prevalence or comparative studies with follow-up	Randomized controlled trials, prospective studies, modeling studies	Variety of designs including mixed methods
Populations	Highly selective	Patients with data and samples plus controls	From purposely selected to gradually selected from population of focus for the test	Diverse population in intended screening setting (may be selected on risk)	More diverse group of people likely to benefit from test
Secondary objectives			Assessing testing interval	Assessing diagnostic strategies in clinic	Post-marketing monitoring, modify screening population and setting

No available tests have completed phase 4 testing to date

[11] *Doubeni et al. Cancer 128(S4):883, 2022*

ctDNA detection: available technologies for MCED tests in 2022

Sponsor	Basis for test	Cancers identified by test
Burning Rock Biotech Limited	Methylation signatures in cell-free DNA using ELSA-seq	Liver (Luo, et al., 2022); esophagus (Qiao et al., 2021); colorectum (Sui, et al., 2021)
Delfi	WGS for genome-wide DNA fragmentation patterns ('fragmentomics')	Breast, colorectum, lung, ovarian, pancreatic, gastric (Cristiano, et al., 2019)
Exact Sciences	Multiplexed PCR for selected DNA mutations & measures of validated protein biomarkers (CancerSEEK)	Twenty-six cancers, including breast, colorectum, lung, ovarian, pancreatic, gastric, uterine, thyroid, renal (Lennon et al., 2020)
Freenome	Multiomics (eg, methylation profiling of cfDNA and CA19-9)	Colorectum, lung, pancreatic (Hsu, et al., 2021)
Grail	WGS for methylation signatures in cell-free DNA (Galleri)	More than 50 cancers (Ofman, et al., 2020)
Guardant	Analyzes >20,000 epigenetic biomarkers (AACR; April 2022) (GuardantLUNAR-2 test)	Any solid cancerous tumor (2022)

Luo et al. BMC Med 20:8, 2022; Qiao et al. BMC Med 19:243:2021; Sui et al Clin Epigenet. 13:26, 2021; Cristiano et al. https://doi.org/10.1038/s41586-019-1272-6; Lennon et al. Science. 369(6499), 2020; Hsu et al. AACR Special Conference on Pancreatic Cancer, Sept 29-30, 2021; Ofman et al. GRAIL white paper, 2020; Guardant press release, (https://investors.guardanthealth.com/press-releases/press-releases/2022/First-Guardant-Health-Liquid-Biopsy-Testing-Service-in-Europe-Now-Operational-at-Vall-dHebron-Institute-of-Oncology/default.aspx) May 25, 2022.

Exact Science/THRIVE's Cancer SEEK

Evaluation of:

- **Mutations in 16 genes: KRAS, NRAS, HRAS, CTNNB1, PIK3CA, FBXW7, APC, EGFR, BRAF, CDKN2A, PTEN, FGFR2, AKT1, TP53, PPP2R1A, GNAS**
  - Minimum number of short amplicons to allow detection of at least one driver gene mutation in each target tumor type
  - 61-amplicon panel in which each amplicon queries an average of 33 bp

- **Elevated concentrations of 8 protein biomarkers: CA-125, CEA, CA19-9, prolactin, HGF, osteopontin, myeloperoxidase, TIMP-1** *(+ CA15-3, in Lennon, et al. 2020)*

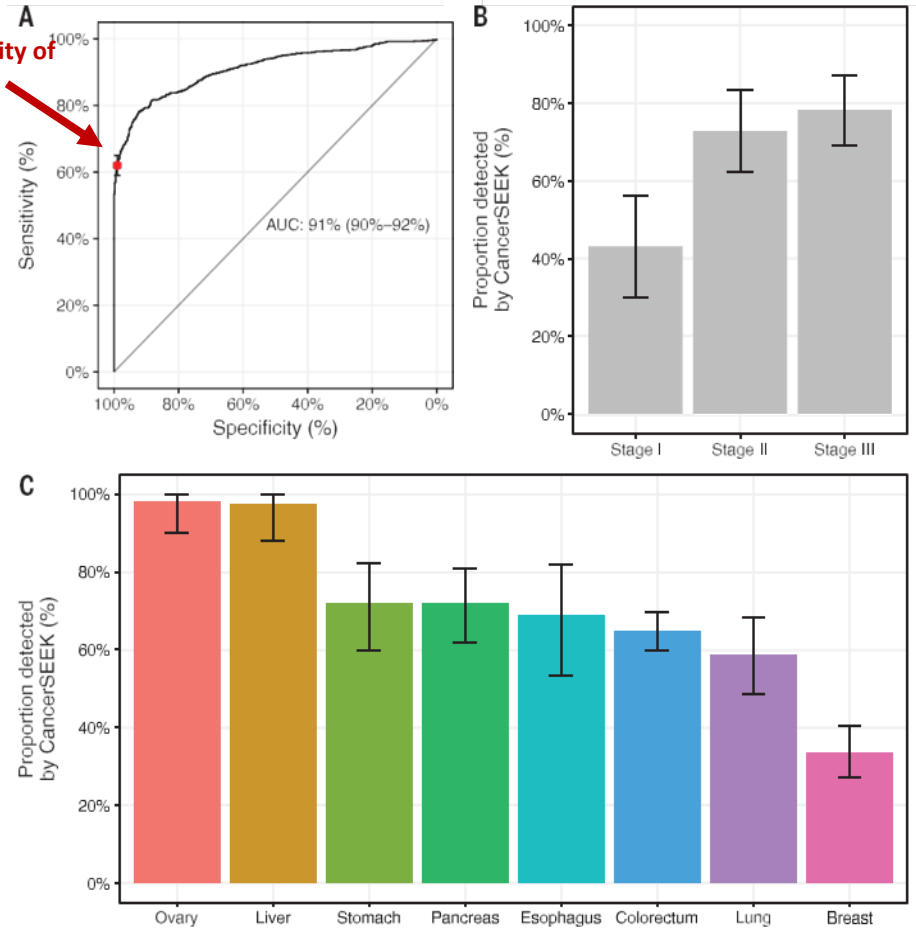
- **Data are evaluated by a logistic regression algorithm that combines data from mutation and protein biomarker concentrations**

Cohen JD, et al. Science 359:926-930, 2018

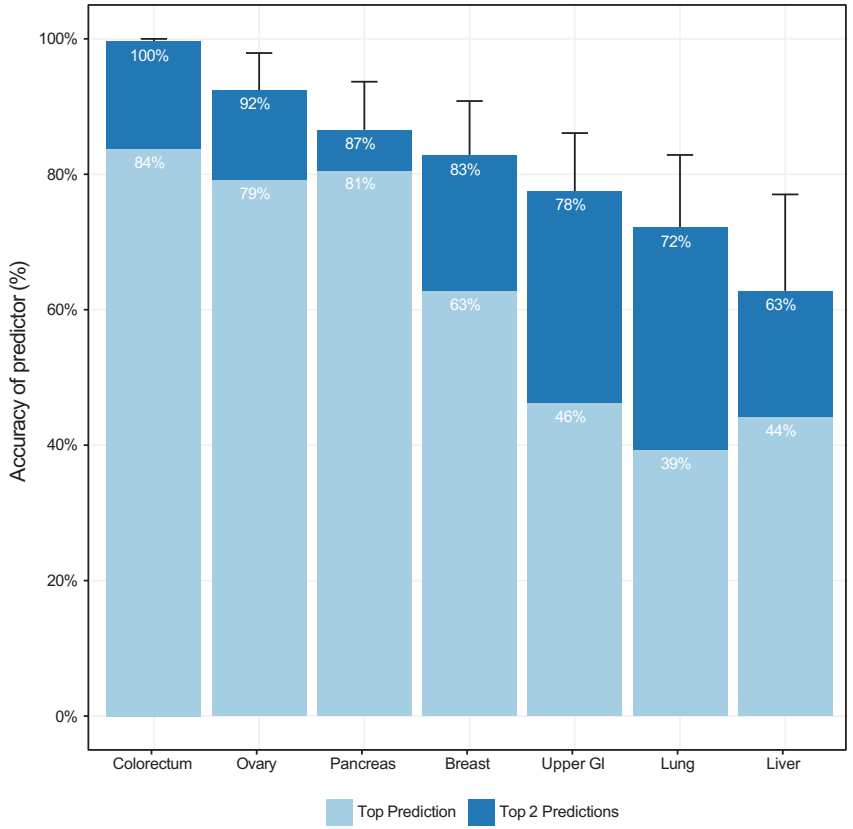
Exact Science/THRIVE's CancerSEEK

Phase 2 re: analytic validity for 8 cancer sites; retrospective study of 1005 cancer patients and 812 healthy controls

Avg. sensitivity of 62% at 99% specificity



Proportion correctly predicted re: tumor of origin for MCED-positive patients



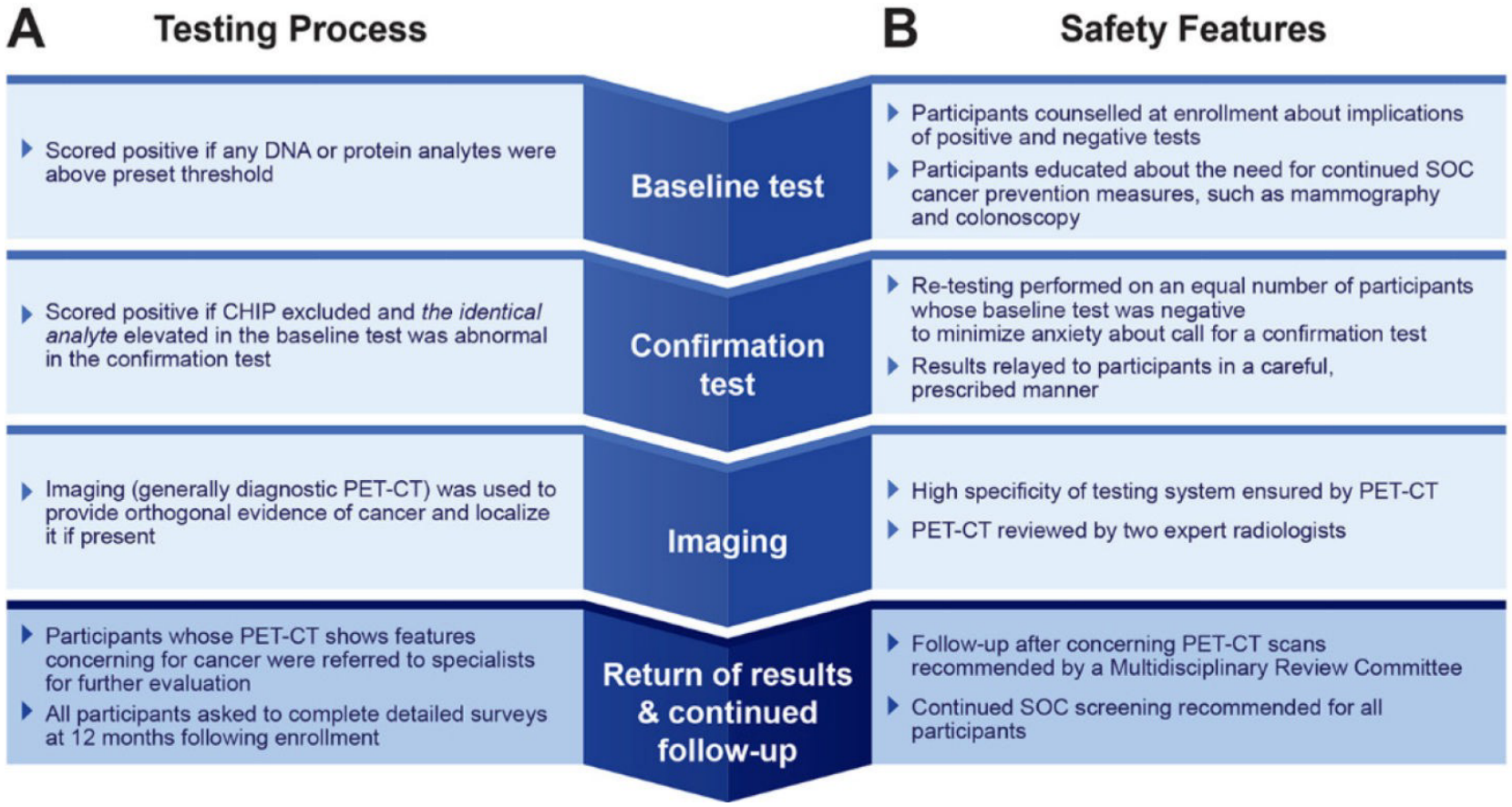
Identification of cancer type by supervised machine learning for patients classified as positive by CancerSEEK. Percentages correspond to the proportion of patients correctly classified by one of the two most likely types (sum of light and dark blue bars) or the most likely type (light blue bar). Error bars represent 95% confidence intervals.

Cohen JD, et al. Science 359:926-930, 2018

Exact Science/THRIVE's CancerSEEK: DETECT-A prospective study

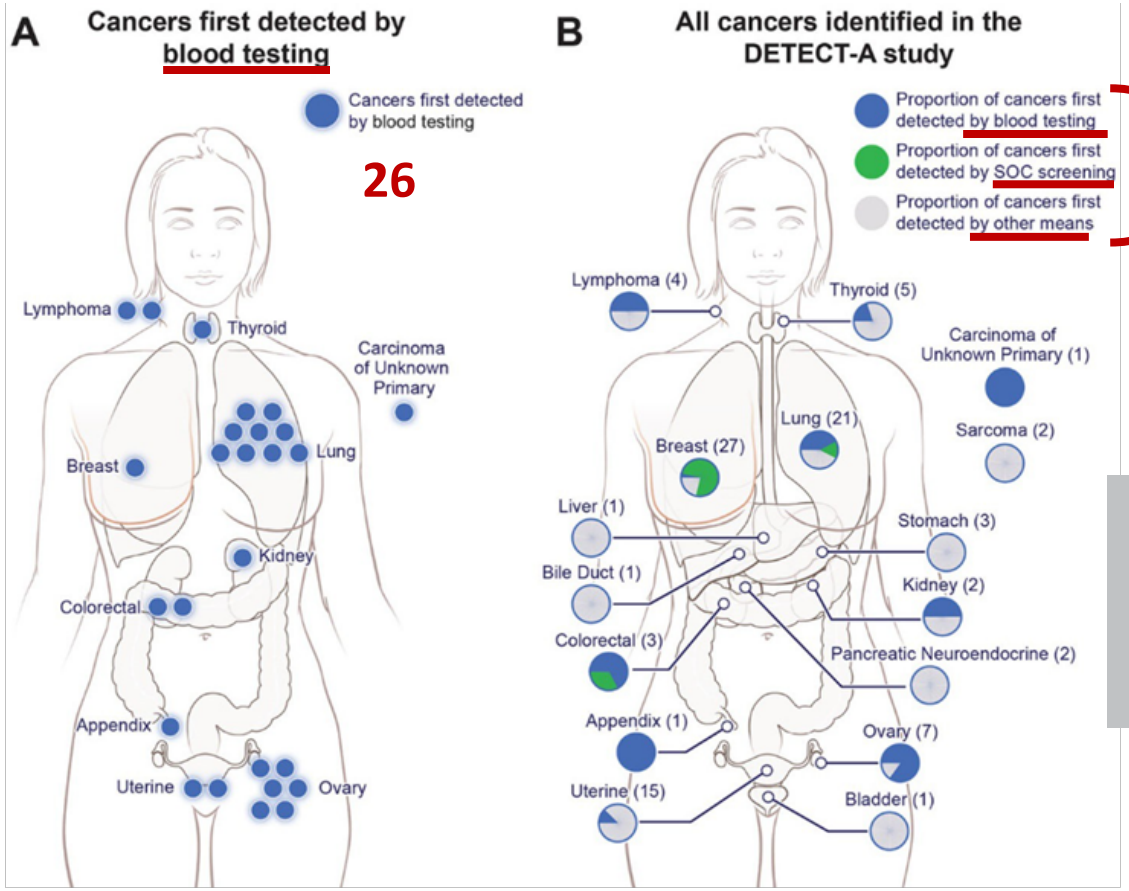
Phase 3, clinical validity study: 10,006 women aged 65-75 years without a personal history of cancer, cared for in 18 Geisinger clinics

DETECT-A process and rationale.
(**A**) Three-step testing process for DETECT-A. (**B**) Safety rationale for study design.



 Lennon AM, et al. Science 369:6499, 2020

Cancer identification & implications in DETECT-A



96 cancers identified
26 by CancerSEEK
24 by SoC screening
46 by other presentation

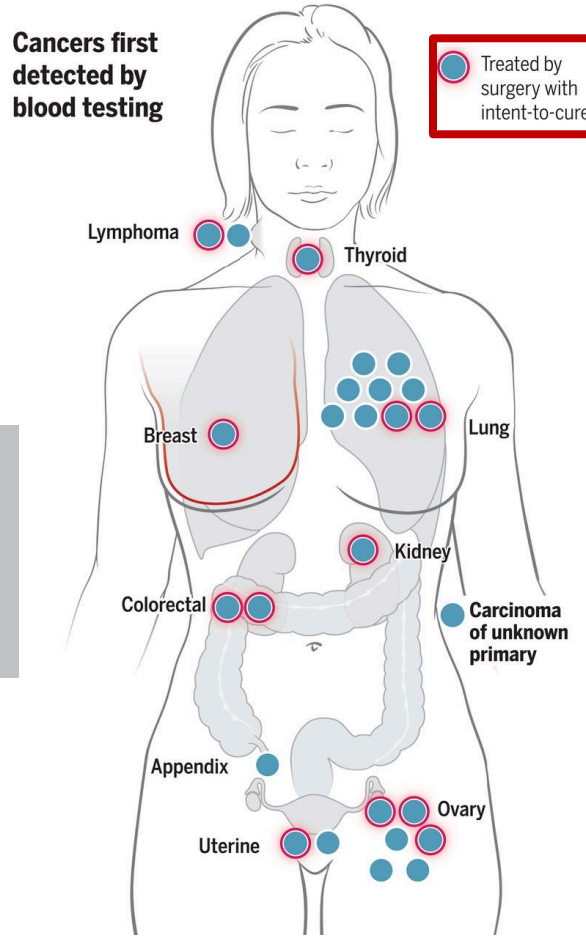
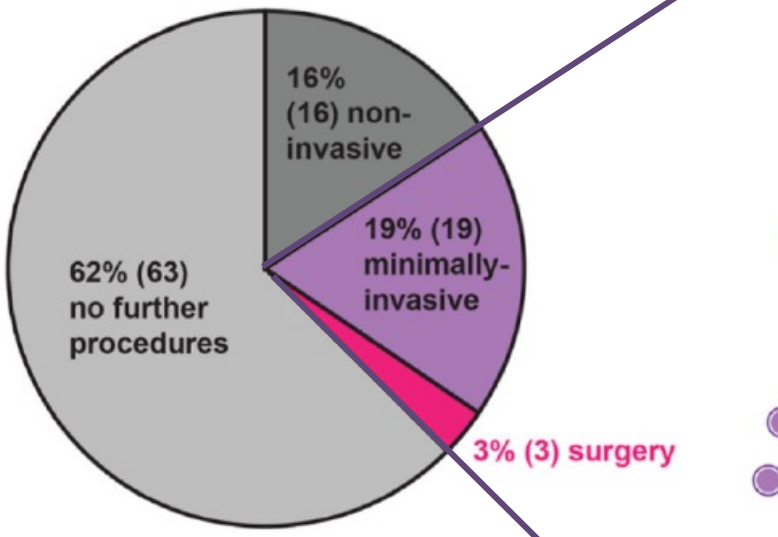


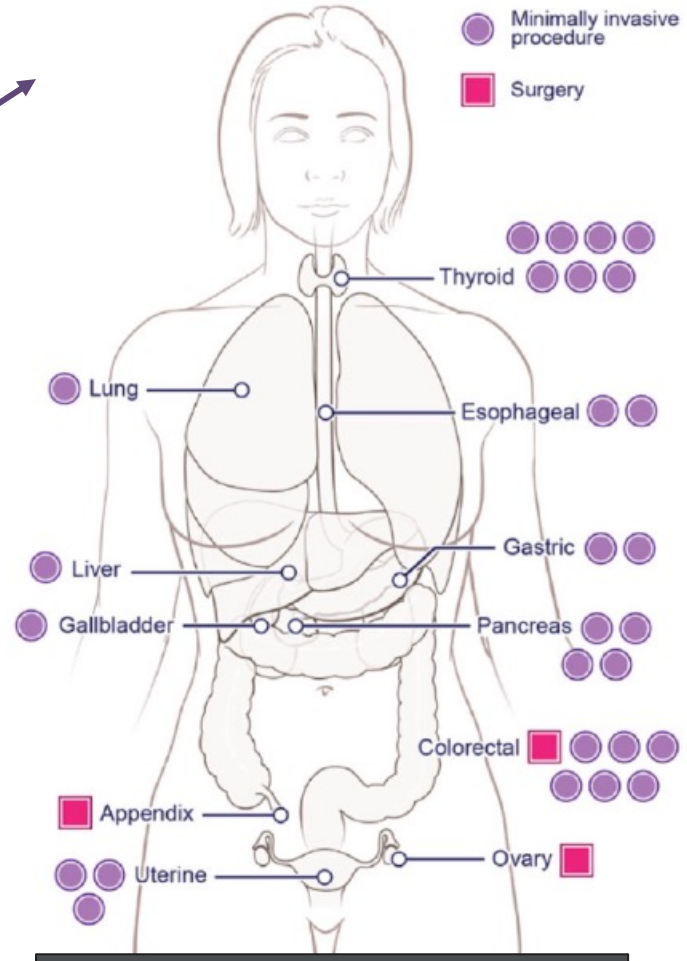
Fig. 3. Overview of cancers incident during the DETECT-A study.
(**A**) Twenty-six cancers (blue) in 10 organs were first detected by blood testing. (**B**) Ninety-six cancers were identified in the study (see Supplementary Materials). The location, and number of those first detected by blood testing (blue), standard-of-care screening (green) or by other means (grey) are shown.

 Lennon AM, et al. Science 369:6499, 2020

DETECT A risks: patients without cancer, but with positive signal on MCED test



Diagnostic outcome after PET-CT: 101 participants



All minimally invasive & surgical procedures: 22 participants

Harms or Benefits?

Risk stratification of procedures performed during diagnostic follow-up

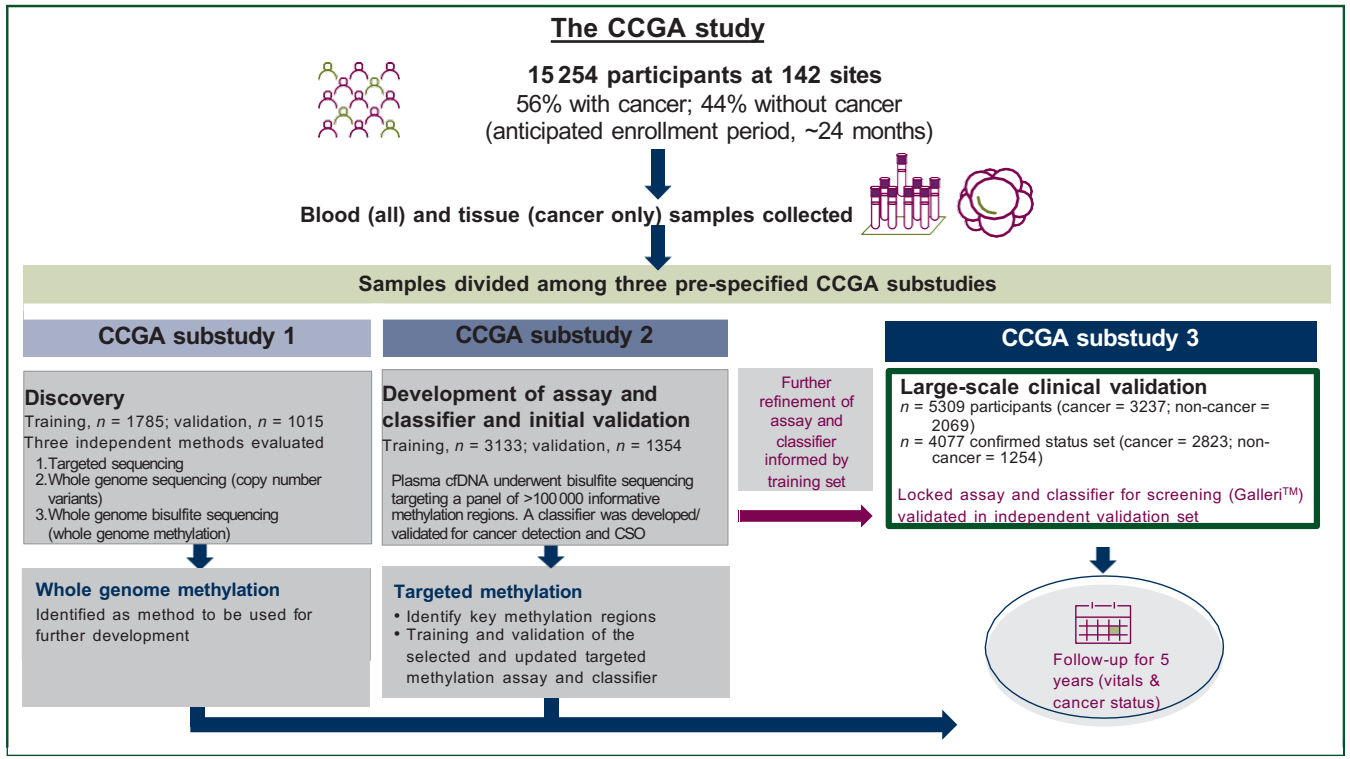
Non-invasive
- Plain X-ray
- CT
- MRI
- Mammogram
- Ultrasound (thyroid, abdomen, pelvis)
- Transvaginal ultrasound
- Nuclear medicine scan

Minimally invasive
- Esophagogastroduodenoscopy
- Colonoscopy
- Endoscopic ultrasound
- ERCP
- Bronchoscopy
- Cystoscopy
- Hysteroscopy
- Fine-needle aspiration: thyroid gland
- Liver biopsy
- Thoracentesis
- Pulmonary arterio-venous malformation embolization

Surgical
- Surgery

Lennon et al, Science 369(6499): 2020. doi:10.1126/science.abb9601

GRAIL Galleri: Circulating Cell-free Genome Atlas (CCGA) study – 3 parts (Phase 2 & 3); Multicenter, prospective case-control w/short-term f/u



Study design.
The study enrolled 15,254 participants with and without cancer to develop and validate a multi-cancer early detection test. The study was divided into three pre-specified substudies; CCGA participants not included in CCGA substudies (*n* = ~2200) were excluded mainly due to incomplete or irregular clinical data at time of selection preventing selection into a substudy, availability of plasma samples, and miscellaneous other reasons. A two-stage classifier further refined for use as a screening tool relative to the one developed and validated in the prior CCGA2 substudy was trained on the data from the training set participants (see also Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2021.05.806). Following the training procedure, all parameters, including thresholds, were fixed and the final two-stage classifier was applied to the independent samples from the validation set to assign cancer/non-cancer and signal-origin labels to each sample.

CCGA, Circulating Cell-free Genome Atlas; cfDNA, cell-free DNA; CSO, cancer signal origin.

Final targeted methylation panel:
- 103,456 distinct regions
- 1,116,720 CpGs

Klein E, et al. Ann Oncol 32:9, 1167-1177, 2021

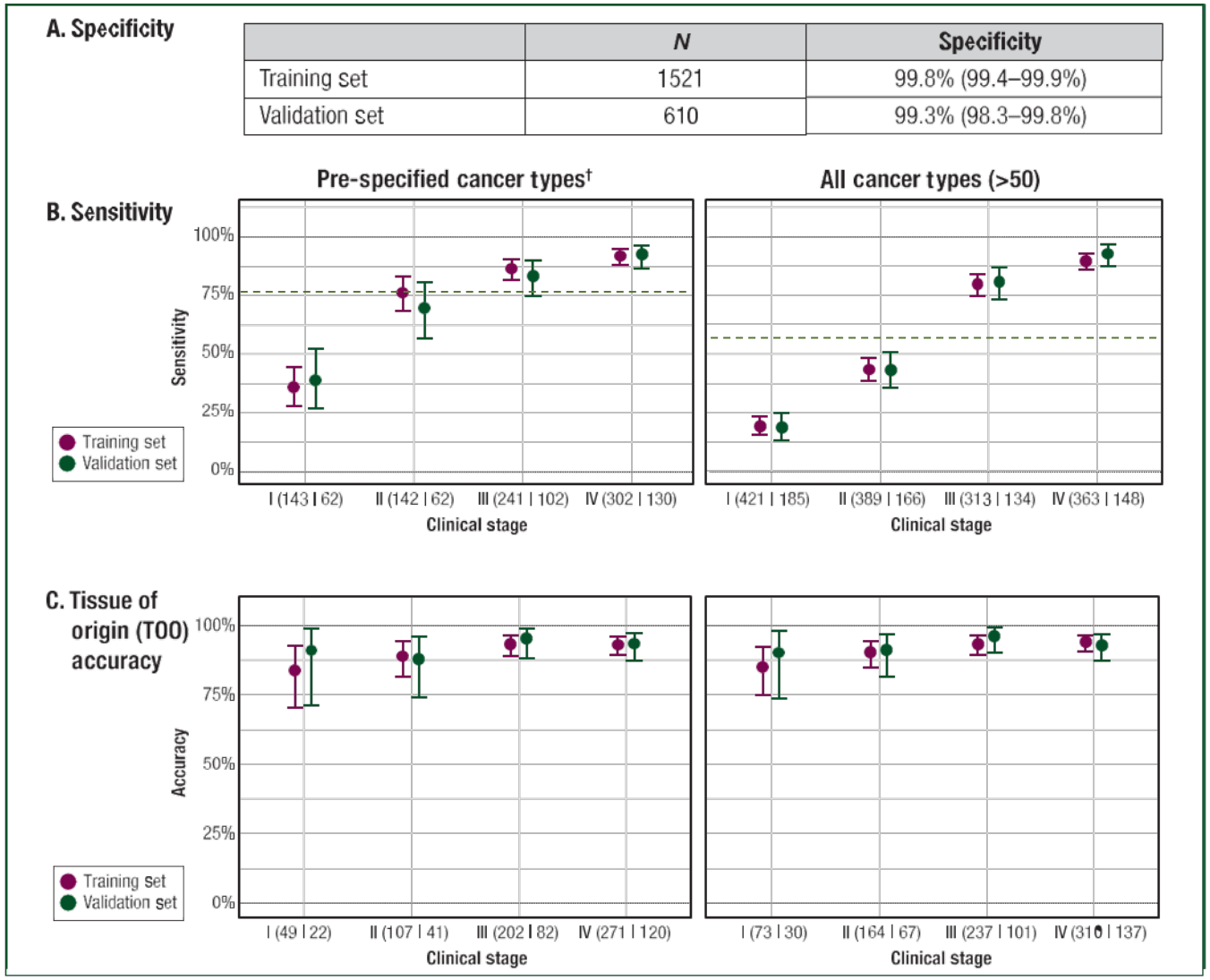


Figure 4. Targeted methylation cfDNA test performance.
(A) Specificity. Specificity was >99% in the training and validation sets. Importantly, this represents a consistent, single false-positive rate (FPR) across the >50 cancer types in this study. (B) Sensitivity. Sensitivity (*y*-axis) is reported by clinical stage (*x*-axis) in the pre-specified cancer types (left panel) and in all cancer types (right panel) for training and validation. Numbers indicate samples in training|validation sets. It excludes 45 samples in training and 21 samples in validation without stage information (e.g. leukemias). (C) Tissue of origin. Tissue of origin (TOO) accuracy (*y*-axis) is reported by clinical stage (*x*-axis) in the pre-specified cancer types (left panel) and in all cancer types (right panel) for training and validation. Numbers indicate samples in training|validation sets.

GRAIL Galleri CCGA2: Targeted methylation cfDNA test performance by pre-specified and all cancer types

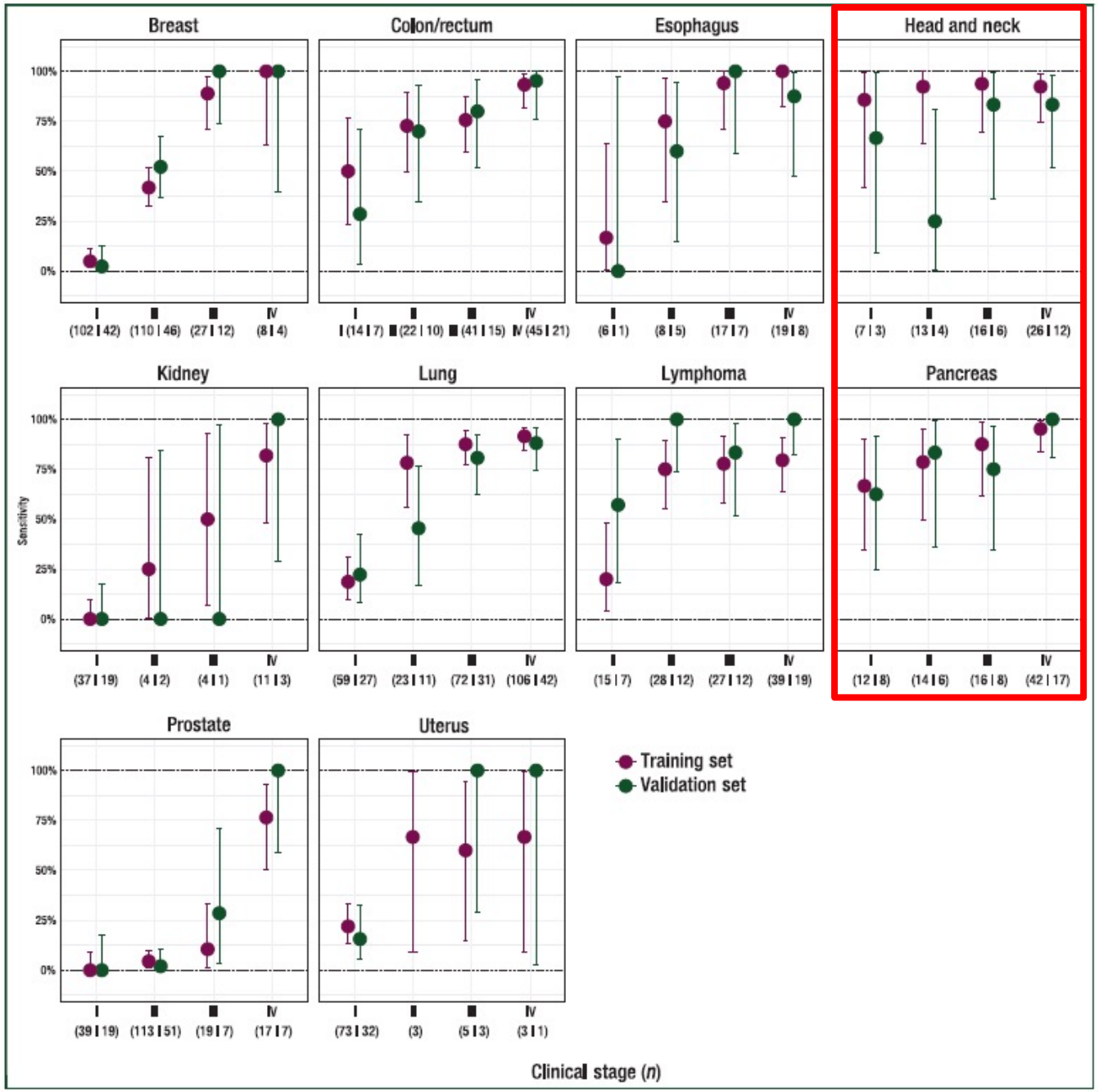
- *Specificity*
- *Sensitivity by clinical stage*
- *Tissue of origin accuracy*

At 99.3% specificity in the validation set
- Sensitivity in pre-specified cancer types was 76% (72-81%)
- Sensitivity overall was 55% (51-59%)

†12 pre-specified cancer types: anus, bladder, colorectum, esophagus, head and neck, liver/bile duct, lung, lymphoma, ovary, pancreas, plasma cell neoplasm, stomach

Liu M, et al. Ann Oncol 31:6, 745-759, 2020

GRAIL Galleri CCGA2: Sensitivity for individual tumors by stage at 99.3% specificity *(for individual cancer types with at least 50 samples)*



Sensitivity in individual tumors by stage. Sensitivity at 99.8% specificity (training) or 99.3% specificity (validation) with 95% confidence intervals is reported for individual cancer types with at least 50 samples.

Clinical stage is indicated below the plots as is the number of samples in training and validation (separated by a vertical line).

Liu M, et al. Ann Oncol 31:6, 745-759, 2020

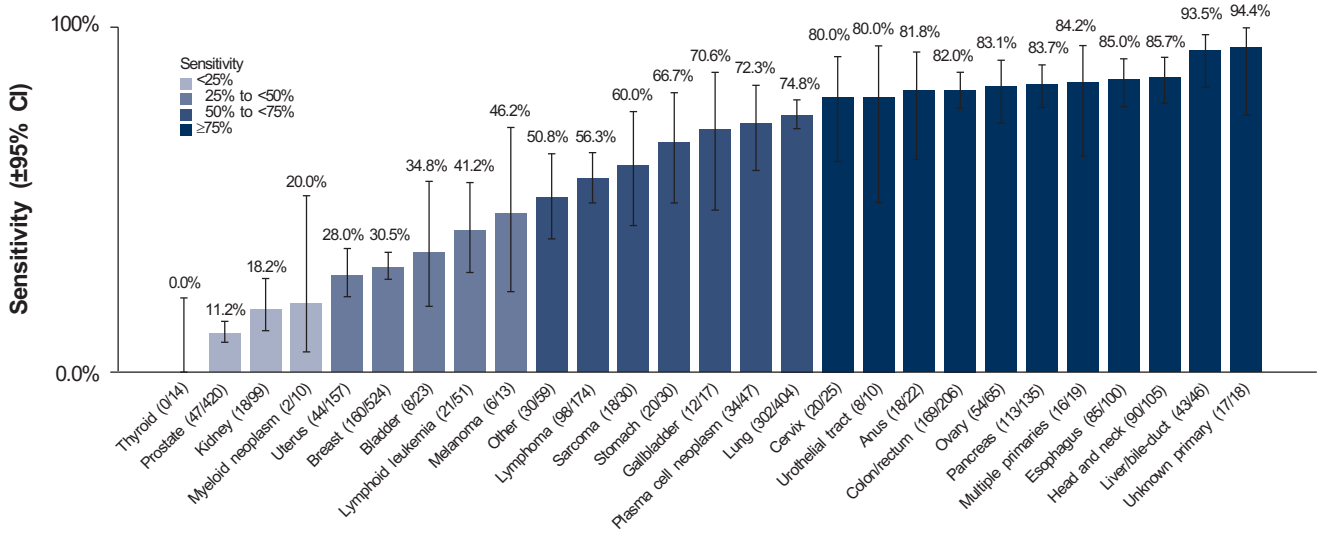
GRAIL Galleri: CCGA 3's overall sensitivity and specificity (A) and sensitivity by organ site (B) w/~1 year f/u

A

	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.

B



MCED test performance for cancer signal detection
(A) overall sensitivity and specificity, (B) sensitivity by cancer class, and (C) sensitivity by stage in 12 pre-specified cancers. **(A)** The 2 x 2 contingency table summarizes overall sensitivity and specificity. **(B)** Sensitivity (y-axis) by cancer class based on individual cancer classes (x-axis), including other, unknown primary, and multiple primaries. Cancer classes are ordered based on increasing sensitivity; bars indicate 95% CI. **(C)** Sensitivity by stage is depicted in each box for each of the 12 pre-specified cancer classes; bars indicate 95% CI.
CI, confidence interval; MCED, multi-cancer early detection.

Klein E, et al. Ann Oncol 32:9, 1167-1177, 2021

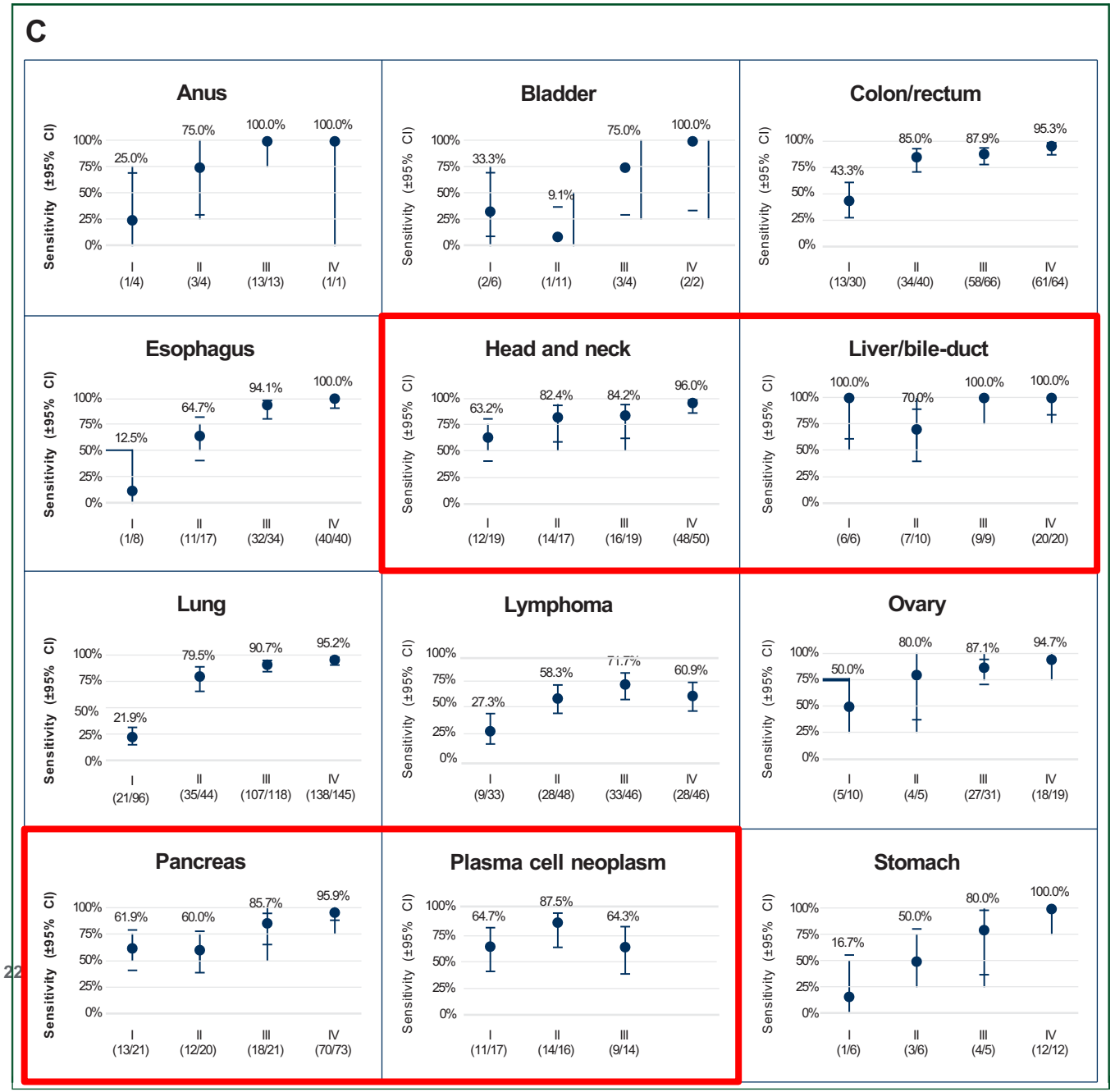


Figure 3. Continued.

GRAIL Galleri CCGA3: sensitivity by stage in 12 pre-specified cancers

Klein E, et al. Ann Oncol 32:9, 1167-1177, 2021

GRAIL Galleri CCGA3: sensitivity of cancer signal detection by clinical stage

Sensitivity of cancer signal detection by clinical stage

Clinical stage	Total *N*	Test positive	Sensitivity % (95% CI)[a]
All	2823	1453	51.5 (49.6% to 53.3%)
I	849	143	16.8 (14.5% to 19.5%)
II	703	284	40.4 (36.8% to 44.1%)
III	566	436	77.0 (73.4% to 80.3%)
IV	618	557	90.1 (87.5% to 92.2%)
I-II	1552	427	27.5 (25.3% to 29.8%)
I-III	2118	863	40.7 (38.7% to 42.9%)
I-IV	2736	1420	51.9 (50.0% to 53.8%)
III-IV	1184	993	83.9 (81.7% to 85.9%)
Not expected to be staged	67	23	34.3 (24.1% to 46.3%)
Missing	20	10	50.0 (29.9% to 70.1%)

CI, confidence interval.
[a] Two-sided 95% Wilson CIs were calculated.

Overall cancer site of origin accuracy = 88.7%

Klein E, et al. Ann Oncol 32:9, 1167-1177, 2021

Published results of MCED tests - cancers

Study	DETECT-A	PATHFINDER (abstract)
Basis for test	DNA & protein biomarkers	Methylation signatures in cell-free DNA (test has false-positive rate of 0.7%)
Population	• 10,006 women; 9911 included in analysis • 65-75 years of age • No personal history of cancer • High adherence to SOC screening	• 4086 consented, 4033 included in analysis (interim results) • 50+ years of age • 2 cohorts (elevated- vs no elevated risk)
Safety features	• 3 steps before diagnostic work-up for cancer: (1) abnormal baseline required confirmatory blood test + clonal hematopoiesis of indeterminate potential (CHIP) negativity; (2) multidisciplinary committee review confirmed result (3) full-body PET-CT to confirm results • To reduce anxiety, consent process noted that might be asked (randomly) to provide second blood sample • Negative test results: patients were counseled several times to continue SOC screening and to practice primary prevention measures	A secondary objective was test satisfaction
Diagnostic work up	With positive PET CT: referred to cancer specialist	With positive cancer signal + predicted cancer-signal origin: referred to provider for diagnostic testing
Cancer diagnosis	Biopsy-proven cancer or other undisputed clinical evidence of disease (excluded benign tumors and noninvasive precancers)	2 outcomes possible: cancer diagnosis or no cancer diagnosis
Results	• 94.9% were non-Hispanic white • 490 (4.9%) positive in baseline test • 134 (1.35%) positive after 2nd blood test (60% of those not confirmed due to CHIP) • 95% (127/134) received imaging • 50% (64/127) had imaging results concerning for cancer • 41% (26/64) had cancer dx (n = 5, 3, 8, 9 with stages I, II, III, IV; 1 unk) • With confirmation of blood test • PPV 19.4% [13.1-27.1] (26/134) • Specificity 98.9% [98.7-99.1] (9707/9815) • NPV 99.3% [99.1-99.4] (9707/9777) • Sensitivity (all cancers) 27.1% [18.5-37.1] 26/96	• 92.1% were white • 1.5% (62/4033) had positive cancer signal • 64.5% (40/62) reached diagnostic resolution • Median time to resolution was 78 [54-151] days • 93% (37/40) had 1 or more imaging test • 72% (13/18) of cancer patients vs 18% (4/22) of patients w/o cancer had 1 or more invasive procedure • With confirmation of blood test • PPV 45% [30.7- 60.2] (18/40) • 89% were satisfied with the test (43.7%, extremely; 30.7%, very; and 14.6% satisfied)—similar in the 2 risk cohorts
Sponsor	Exact Sciences/Thrive Earlier Detection Corp	Grail
Resource	*Lennon et al, Science 369(6499): 2020. doi:10.1126/science.abb9601*	*Beer et al, J Clin Onc DOI: 10.1200/JCO.2021.39.15_suppl.3010, 2021; Nadauld et al, Cancers 13, 3501, 2021*

What do people think after MCED testing?

Participant comments

NY Times
Kolata G. June 10, 2022

- "Considers himself a lucky man" (77-year-old after early-stage pancreatic cancer was found following scans, biopsy, surgery, chemo- and radiation therapy)

- Damocles syndrome: "All of a sudden your life can be changed overnight" (73-year-old former nurse and advocate for preventive medicine after receiving troubling test result for possible liver or ovarian cancer and PET scan/abdominal MRI failed to find tumor)

PATHFINDER interim results

2 cohorts (50+ years, 92% white) with elevated vs not elevated risk; with positive cancer signal + predicted cancer-signal origin, referred to provider for diagnostic testing

Patient Satisfaction at 12 Months

- 43.7% extremely satisfied
- 30.7% very satisfied
- 14.6% satisfied
- 89% 'satisfied' or 'more than satisfied' w/experience
- Satisfaction & signal detection rates were similar in the two risk cohorts

Other considerations

- Short period of follow-up?
- Do feelings change over time?
- What about in medically underserved populations—equitable follow-up care?

Beer et al, J Clin Onc DOI: 10.1200/JCO.2021.39.15_suppl.3010, 2021; Nadauld et al, Cancers 13, 3501, 2021

Early detection – potential harms of MCEDs'

- May not predict progression nor clinical harm, but 'only' indicate a tissue-at-risk and an underlying aberrant process
- Anxiety…for patients, families, and caregivers
- Diagnostic testing can be invasive, morbid, complicated, expensive
  - Subsequent *diagnostic odyssey* may be challenging, unclear, and variable
    - Which tests?
    - How often?
    - How long?
    - Is a positive signal ever completely resolved?
- Unclear value – without an intervention to mitigate risks that is proven, safe, effective, and available
- Relevant context is never fully knowable at the individual level
  - Competing causes of morbidity/mortality – highlighted in population-based analyses often as 'overdiagnosis', 'overtreatment' and 'iatrogenic harm'

 Friends of Cancer Research white paper, March 2022

New technologies can create or exacerbate disparities

Best applications of MCEDs

- Part of screening/early detection process, not simply a test
- Process should be designed to address compelling needs of everyone, especially those who are most vulnerable and least prepared to gain access
  - Low-income
  - Uninsured
  - Medically underserved
  - Geographically/socio-culturally remote
- Validation to confirm intermediate endpoints as surrogates of efficacy, if not effectiveness

75% of world's cancer deaths occur in low- and middle-income countries.

Johnson et al. Cancer 128(S4):375, 2022

Examples of ongoing, phase 3/4, population-based MCED trials

Asymptomatic intended-use screening populations

STRIVE (GRAIL)

- Case-cohort study of ~100,000 women undergoing mammography screening
- Purpose: validate test's ability to detect breast cancer and other invasive cancers

SUMMIT (GRAIL)

- Study of ~25,000 smokers and former smokers at high-risk of lung cancer
- Purpose: investigate how cancer screening can be improved and delivered

PATHFINDER (GRAIL)

- Prospective interventional study of ~6,200 participants with no detected cancer
- Purpose: evaluate clinical implementation of MCED testing in real-world setting
  - Tracks **diagnostic pathways toward resolution** of a *signal-detected* test result
    - Number of tests
    - Types of tests
    - Time to diagnostic resolution
  - Assesses **turn-around time** of test results for clinicians and participants
  - Ascertains **participant-reported outcomes** (eg, health resource use) **and perceptions** of the test

GRAIL/UK NHS Partnership

- Study of ~165,000 patients in the NHS
- Purpose: investigate how cancer screening can be improved and delivered

Liu M. Br J Cancer 124:1475-1477, 2021; Nadauld LD, et al: Cancers 13:3501, 2021.

NCI's Cancer Screening Research Network (CSRN) to evaluate screening tests and strategies, including a clinical utility study of MCEDs

Concept approved – June 14, 2022

$73.5M over four years

Components:

- Coordinating & Communications Center
- Data Management & Stats Center
- Accrual, Enrollment & Screening Sites (15-20)

Objectives:

- Establish the organization and administrative infrastructure to implement screening clinical trials
- Develop cancer screening trials to evaluate clinical utility
- Develop screening studies to evaluate workflow and coordination of care
- Conduct a Vanguard study

Vanguard study objectives

- Assess participant willingness to be randomized to MCED testing vs. control
- Determine participant adherence to MCED testing & diagnostic follow-up
- Evaluate feasibility of diagnostic workflow for detection of various cancer types
- Determine reliability and timeliness of companies in processing blood specimens
- Identify facilitators and barriers to recruitment of diverse participants

Study assumptions

- 1% of assay results will be 'positive'
- 60% of diagnostic workups will be resolved
- Vanguard study will require 8,000 participants in each arm x 2 annual screening rounds to achieve 164 positive assays

The Cancer Letter Vol 48, no. 25; June 24, 2022

Modeled reductions in late-stage cancer with a multi-cancer early detection test

"Results: The MCED test could intercept 485 cancers/year per 100,000 person, reducing late-stage (III + IV) incidence by 78% in those intercepted. Accounting for lead time, this could reduce 5-year cancer mortality by 39% in those intercepted, resulting in an absolute reduction of 104 deaths/100,000, or 26% of all cancer-related deaths. Findings are robust across tumor growth scenarios.

Impact: Modeling performance of a MCED test in a representative population suggests that it could substantially reduce overall cancer mortality if added to usual care."

Hubbell E, Clarke CA, Aravanis AM, Berg CD. Cancer Epidemiol Biomarkers Prev 30:460-468, 2021