City of Hope

ANNUAL

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Decoding Cancer Signals: The High Stakes of AI Genomics and Liquid Biopsies

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Department and Quantitative Medicine

Beckman Research Institute

City of Hope National Medical Center

Disclosures

- CEO of C2T Biosciences

This disclosure has been deemed as irrelevant, as this presentation is limited to basic science research, such as pre-clinical research and drug discovery, or the methodologies of research, and I will not make care recommendations.

- Consultant for PrognomiQ
- Other Financial/material interests (Royalties) in Exact Sciences

The presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research
related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

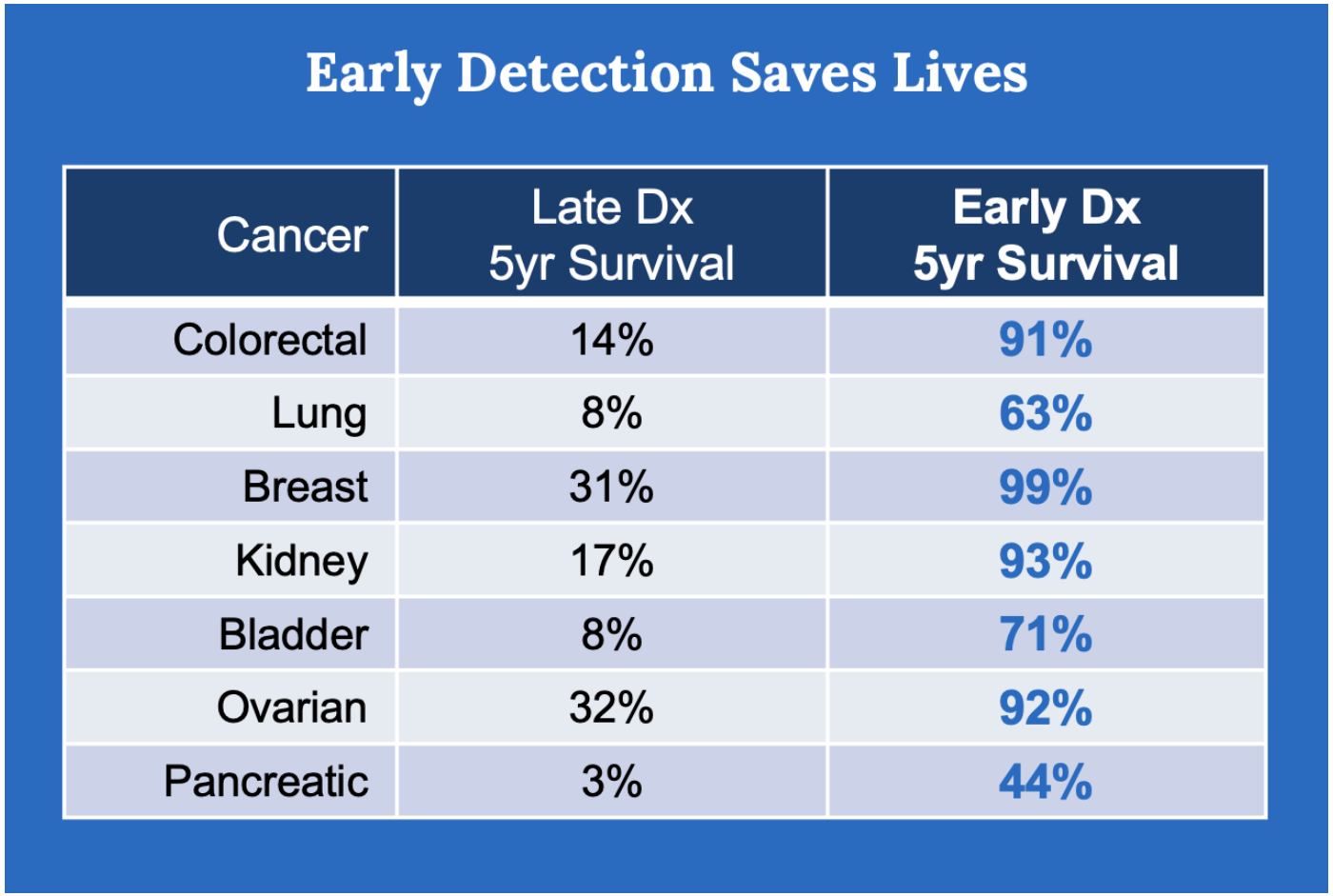
EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

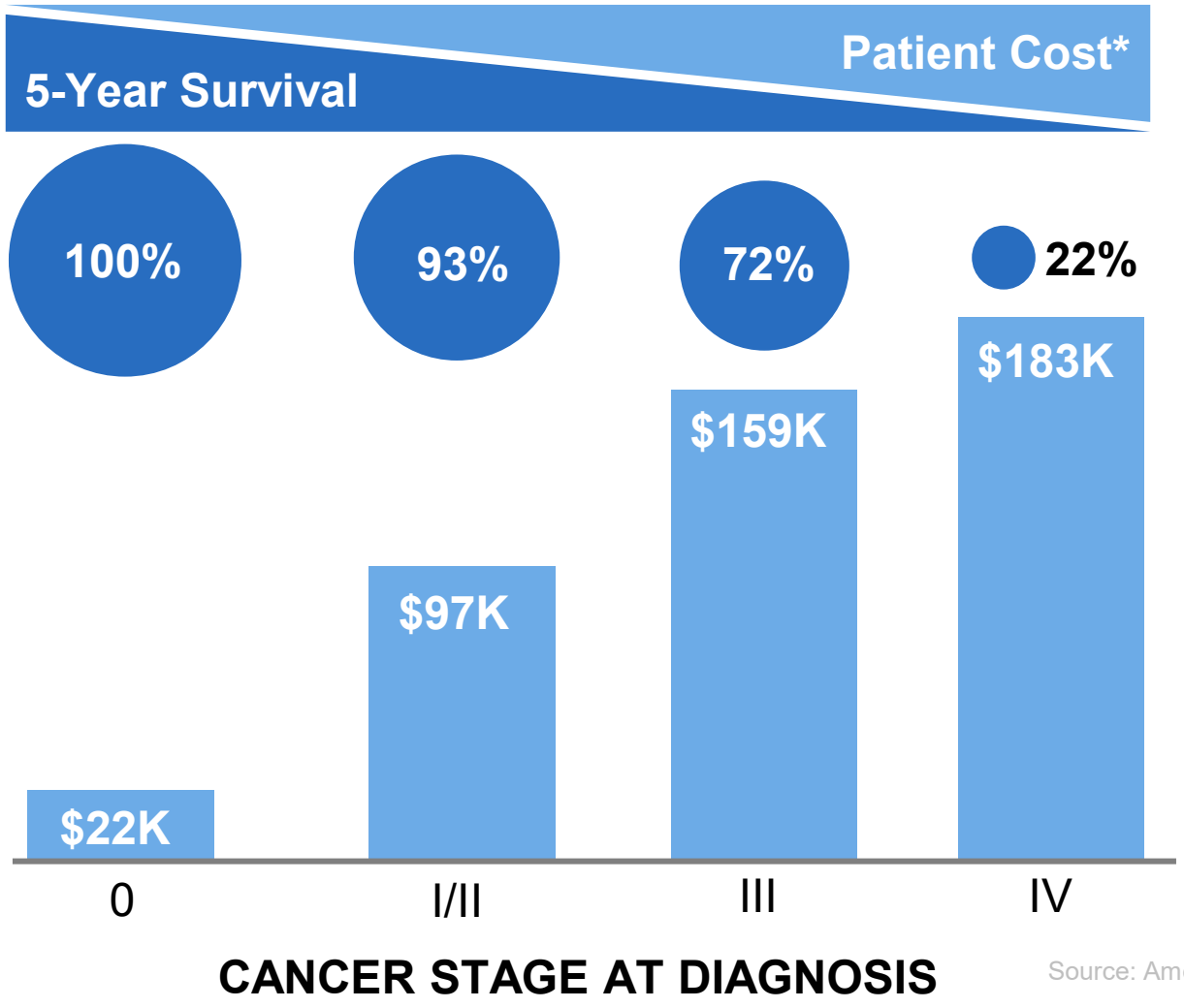
Cancer Earlier Detection

The Way to Win the War: Early Detection



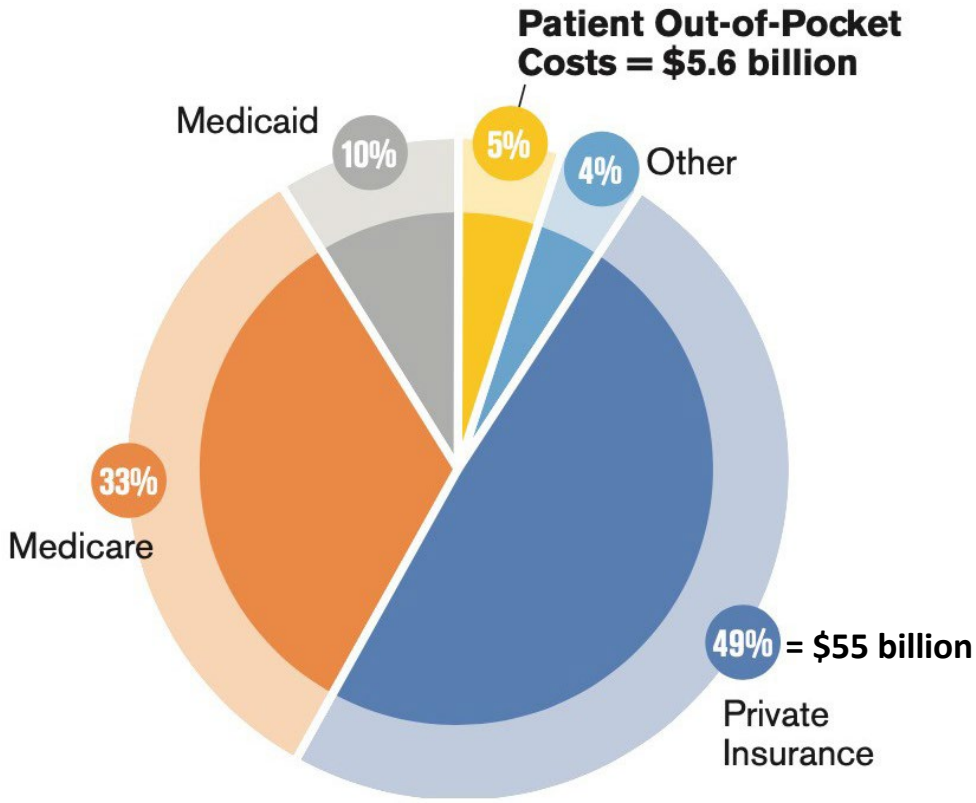
Earlier detection → stage shift

The Human and Financial Cost of Cancer Care



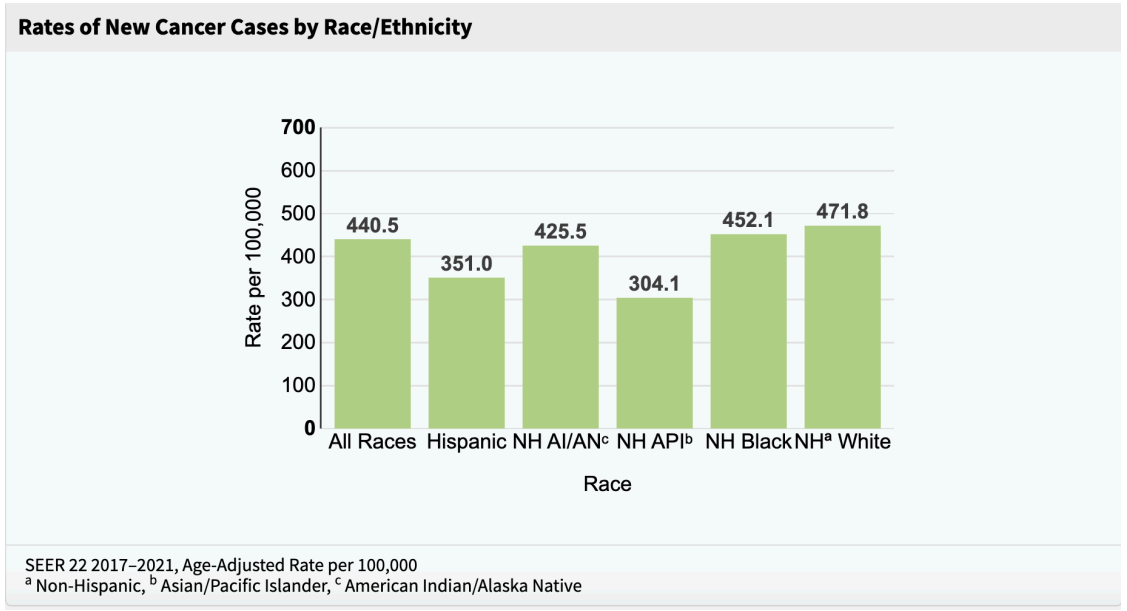
Source: American Cancer Society

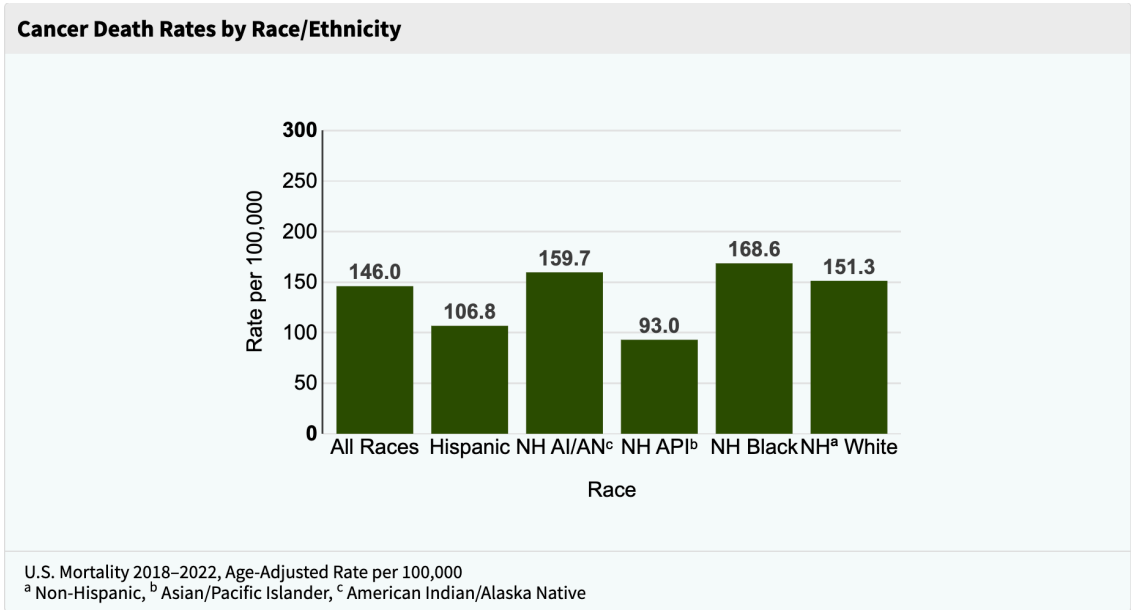
Everyone Pays the Costs of Cancer Treatment



Race/ethnicity Bias in Cancer Screening

- **Persistent racial and ethnic disparities in cancer mortality**. Non-Hispanic Black (NHB) have highest incidence and mortality rates of all major cancer types.

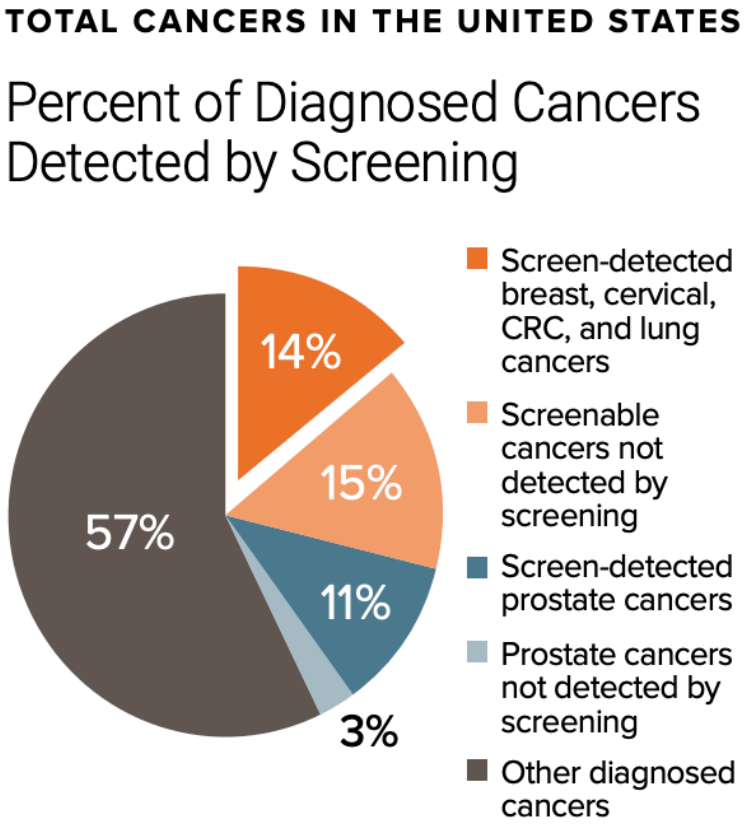




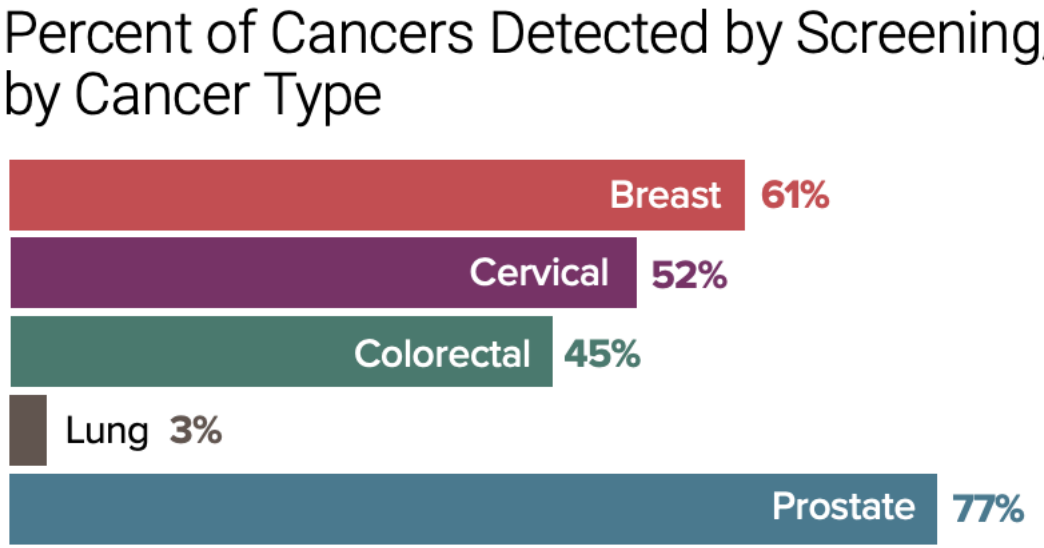
- **Persistent racial and ethnic disparities in cancer screening and stage at diagnosis.** E.g. in LA County: 73.6% of minority females had a Pap test (vs. 82.6% White); 70.0% of minorities had a mammogram (vs. 79.3% White); and 42.0% of Hispanic/Latinx (H/L) and 57.7% of NHB were up-to-date with colonoscopy (vs. 64.4% of White). Minority patients are more likely to be diagnosed in late stage.

The Screening Challenge

No general screening available today for many cancer types (ovarian, liver, pancreatic, esophageal, stomach,…)
Less than half of diagnosed cancers are detected by screening.



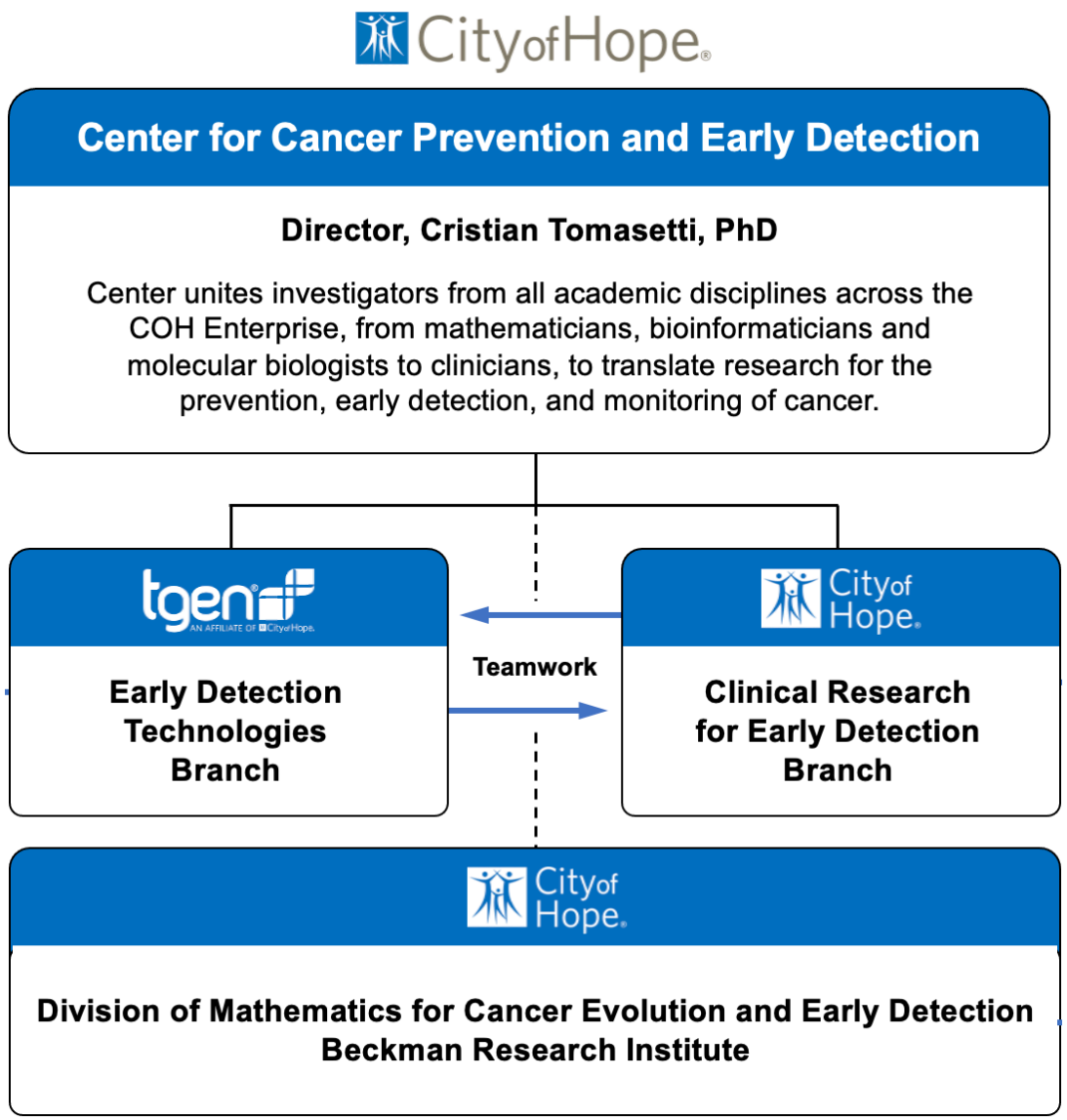
Source: American Cancer Society



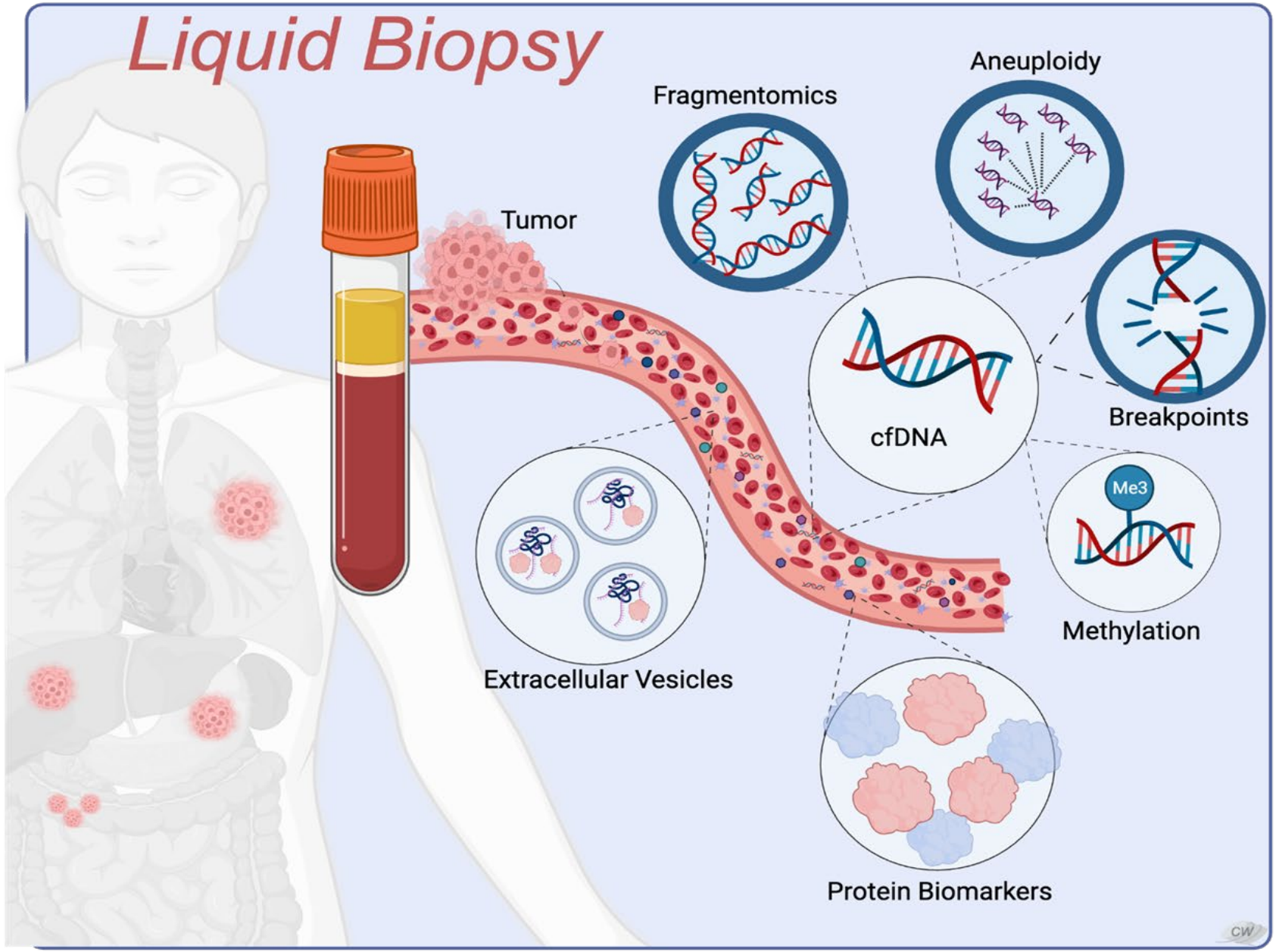
The solution:
Multi-Cancer Early Detection (MCED) Blood Testing

Source: American Cancer Society
NOCR, U Chicago, 2021

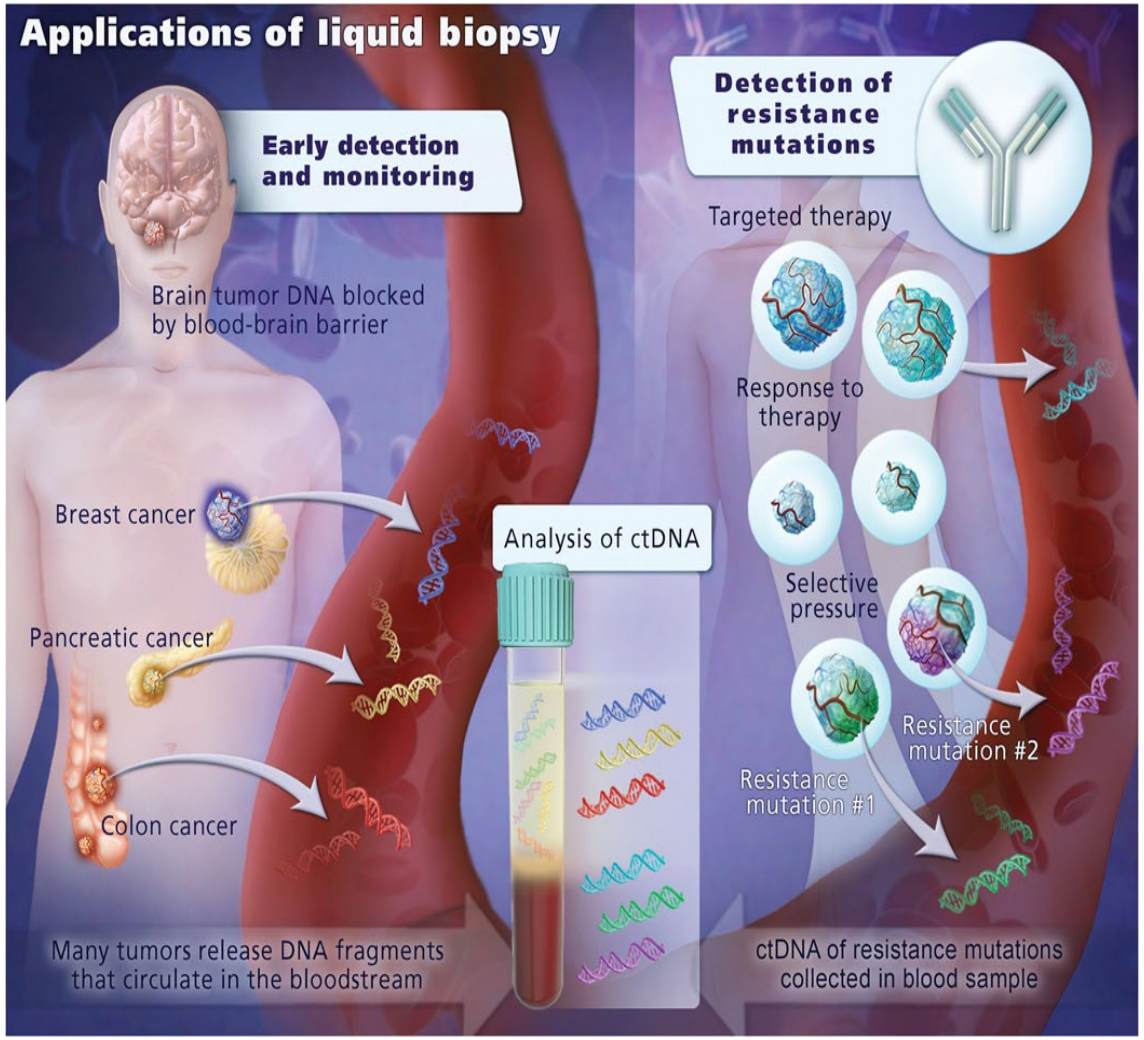
The National Plan



- Novel **risk stratification** for somatic cancer risk
- **Primary prevention** via blood-based detection of pre-cancer lesions (NIH U01)
- Novel **cancer early detection technologies**: A.I. in combination with blood sequencing (BESTSeqS) and imaging (Felix Civitas – Lustgarten Foundation)
- VALETE trial: randomized prospective screening of the general population for **cancer early detection**
- **MRD and monitoring** for recurrence
- **Math/Machine Learning/AI Division** of Mathematical Methods for Cancer Evolution and Early Detection


Liquid Biopsy
Fragmentomics
Aneuploidy
Tumor
cfDNA
Breakpoints
Me3
Methylation
Extracellular Vesicles
Protein Biomarkers

Circulating Tumor DNA (ctDNA) and Cell-free DNA (cfDNA)



Bettegowda et al. STM 2014

ctDNA: Shedding Varies Across Different Organs

SHARE

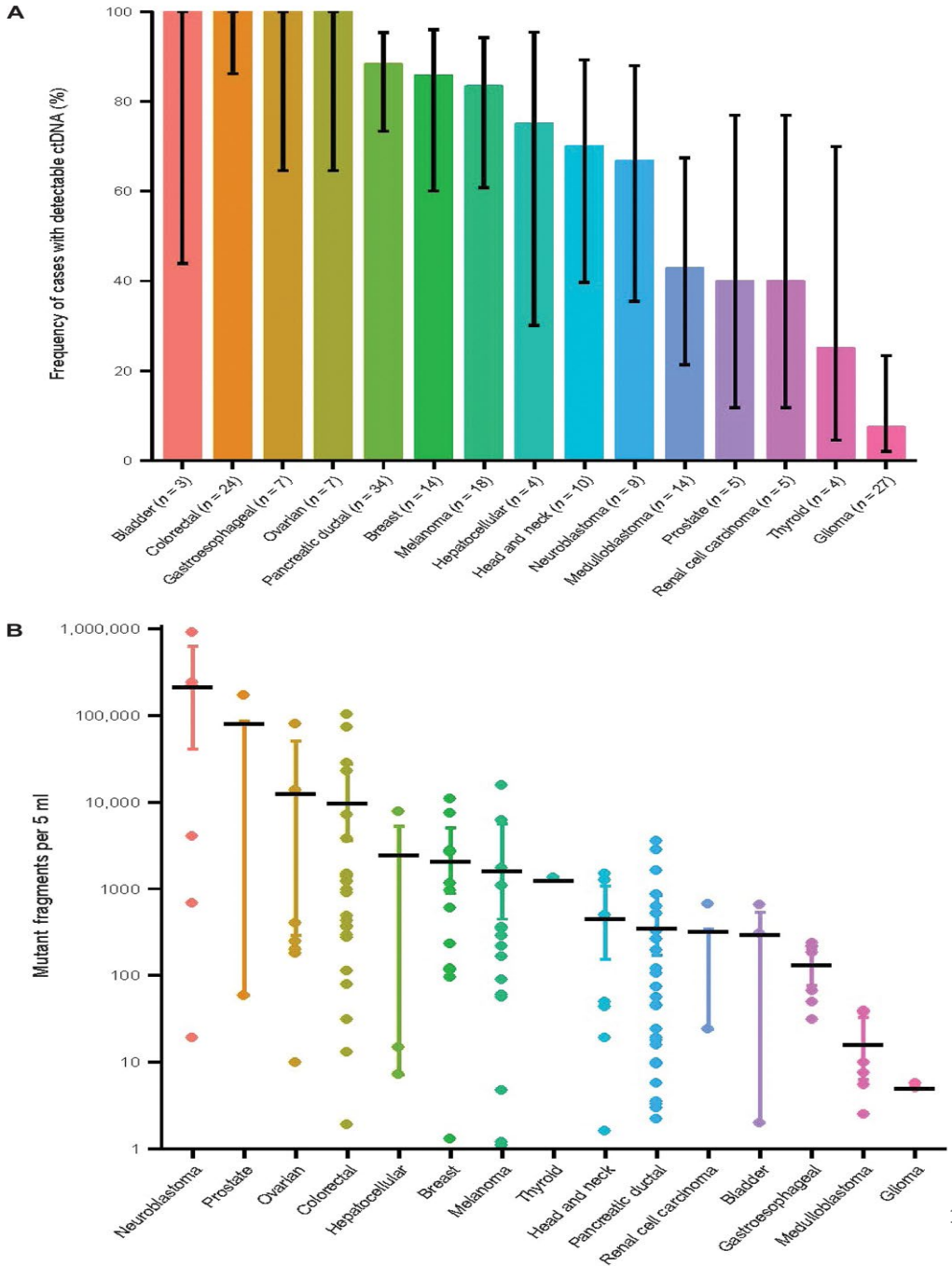
RESEARCH ARTICLE | CANCER

Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies

Chetan Bettegowda[1,2,*], Mark Sausen[1,*,†], Rebecca J. Leary[1,*,‡], Isaac Kinde[1,*], Yuxuan Wang[1], Nishant Agrawal[1,2], Bjarne …

+ See all authors and affiliations

Science Translational Medicine 19 Feb 2014:
Vol. 6, Issue 224, pp. 224ra24
DOI: 10.1126/scitranslmed.3007094



ctDNA: CancerSEEK (Cohen et al. Science 2018)

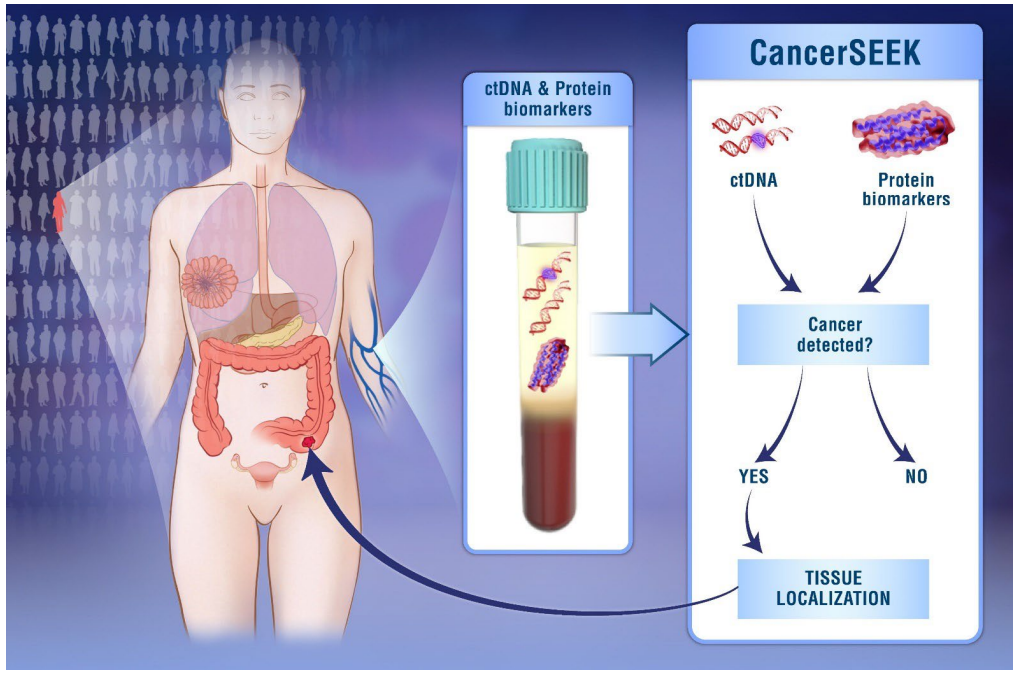
Science

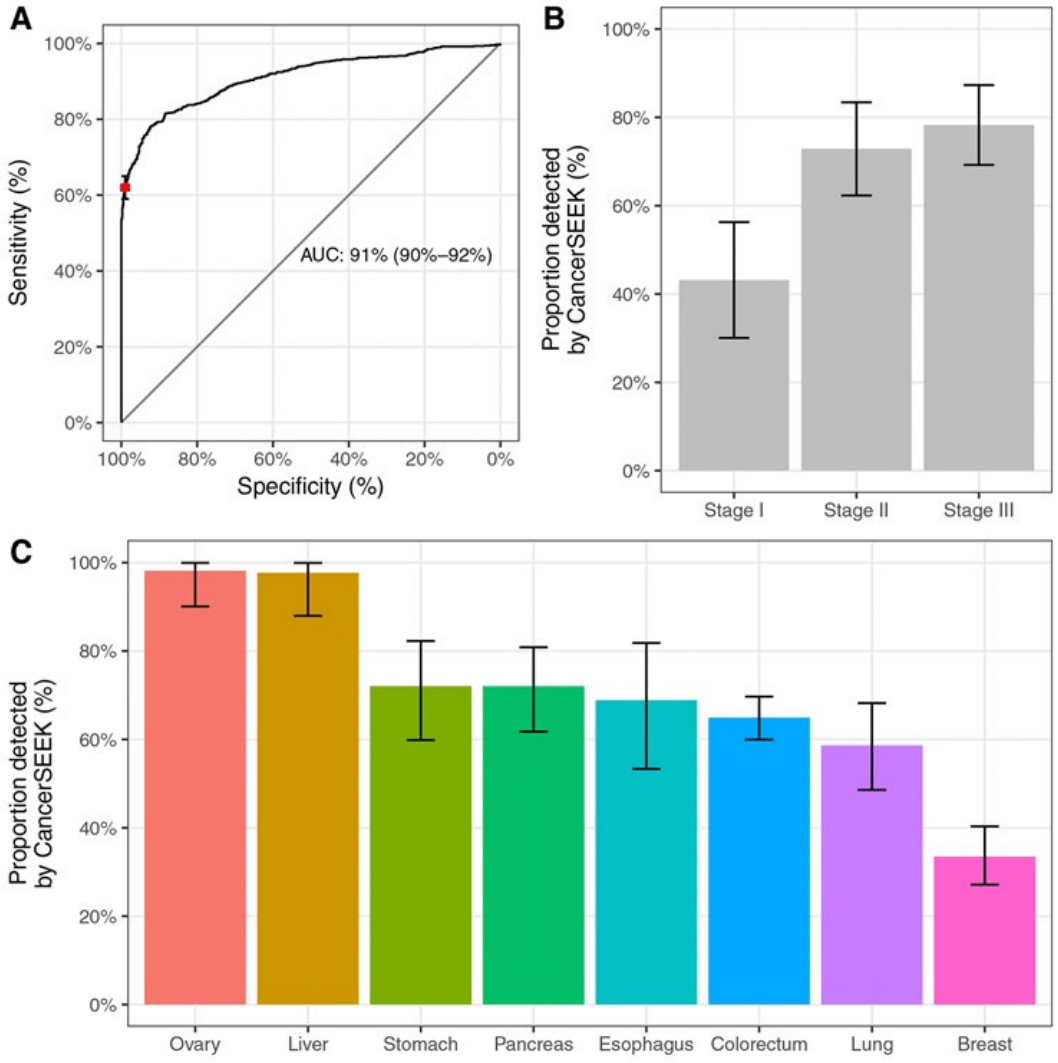
REPORTS

Cite as: J. D. Cohen *et al.*, *Science* 10.1126/science.aar3247 (2018).

Detection and localization of surgically resectable cancers with a multi-analyte blood test

Joshua D. Cohen,[1,2,3,4,5] Lu Li,[6] Yuxuan Wang,[1,2,3,4] Christopher Thoburn,[3] Bahman Afsari,[7] Ludmila Danilova,[7] Christopher Douville,[1,2,3,4] Ammar A. Javed,[8] Fay Wong,[1,2,3,4] Austin Mattox,[1,2,3,4] Ralph. H. Hruban,[3,4,9] Christopher L. Wolfgang,[8] Michael G. Goggins,[3,4,9,10,11] Marco Dal Molin,[4] Tian-Li Wang,[3,9] Richard Roden,[3,9] Alison P. Klein,[3,4,12] Janine Ptak,[1,2,3,4] Lisa Dobbyn,[1,2,3,4] Joy Schaefer,[1,2,3,4] Natalie Silliman,[1,2,3,4] Maria Popoli,[1,2,3,4] Joshua T. Vogelstein,[13] James D. Browne,[14] Robert E. Schoen,[15,16] Randall E. Brand,[15] Jeanne Tie,[17,18,19,20] Peter Gibbs,[17,18,19,20] Hui-Li Wong,[17] Aaron S. Mansfield,[21] Jin Jen,[22] Samir M. Hanash,[23] Massimo Falconi,[24] Peter J. Allen,[25] Shibin Zhou,[1,3,4] Chetan Bettegowda,[1,2,3,4] Luis Diaz,[1,3,4] Cristian Tomasetti,[3,6,7*] Kenneth W. Kinzler,[1,3,4*] Bert Vogelstein,[1,2,3,4*] Anne Marie Lennon,[3,4,8,10,11*] Nickolas Papadopoulos[1,3,4*]





DETECT-A (Lennon, Science 2020)

Science

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HOME > SCIENCE > VOL. 369, NO. 6499 > FEASIBILITY OF BLOOD TESTING COMBINED WITH PET-CT TO SCREEN FOR CANCER AND GUIDE INTERVENTION

RESEARCH ARTICLE

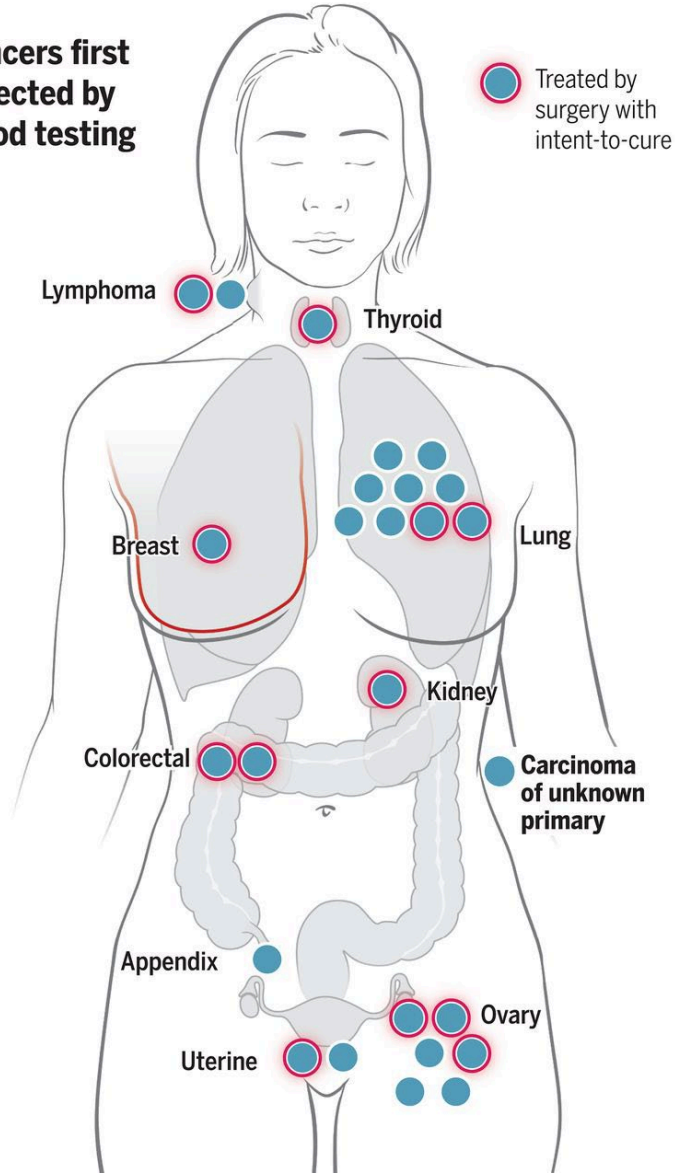
Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention

ANNE MARIE LENNON, ADAM H. BUCHANAN, ISAAC KINDE, ANDREW WARREN, ASHLEY HONUSHEFSKY, ARIELLA T. COHAIN, DAVID H. LEDBETTER, FRED SANFILIPPO, KATHLEEN SHERIDAN, DILLENIA ROSICA, CHRISTIAN S. ADON, PHER DOUVILLE, AALPEN A. PATEL, LEONARDO N. HAGMANN, DAVID D. ROLSTON, BOBBI URBAN, CHRISTOPHER D. STILL, LISA KANN, JULIE I. WOODS, ZACHAR, TACHARYA, CARROLL WALTER, ALEX PARKER, CHRISTOPH LENGAUER, ALISON KI, KENNETH W. KINZLER, BERT VOGELSTEIN, AND NICKOLAS PAPADOPOULOS

SCIENCE • 28 Apr 2020 • Vol 369, Issue 6499 • DOI: 10.1126/science.abb9601

Abstract

Cancer treatments are often more successful when the disease is detected early. We evaluated the feasibility and safety of multicancer blood testing coupled with positron emission tomography–computed tomography (PET-CT) imaging to detect cancer in a prospective, interventional study of 10,006 women not previously known to have cancer. Positive blood tests were independently confirmed by a diagnostic PET-CT, which also localized the cancer. Twenty-six cancers were detected by blood testing. Of these, 15 underwent PET-CT imaging and nine (60%) were surgically excised. Twenty-four additional cancers were detected by standard-of-care screening and 46 by neither approach. One percent of participants underwent PET-CT imaging based on false-positive blood tests, and 0.22% underwent a futile invasive diagnostic procedure. These data demonstrate that multicancer blood testing combined with PET-CT can be safely incorporated into routine clinical care, in some cases leading to surgery with intent to cure.



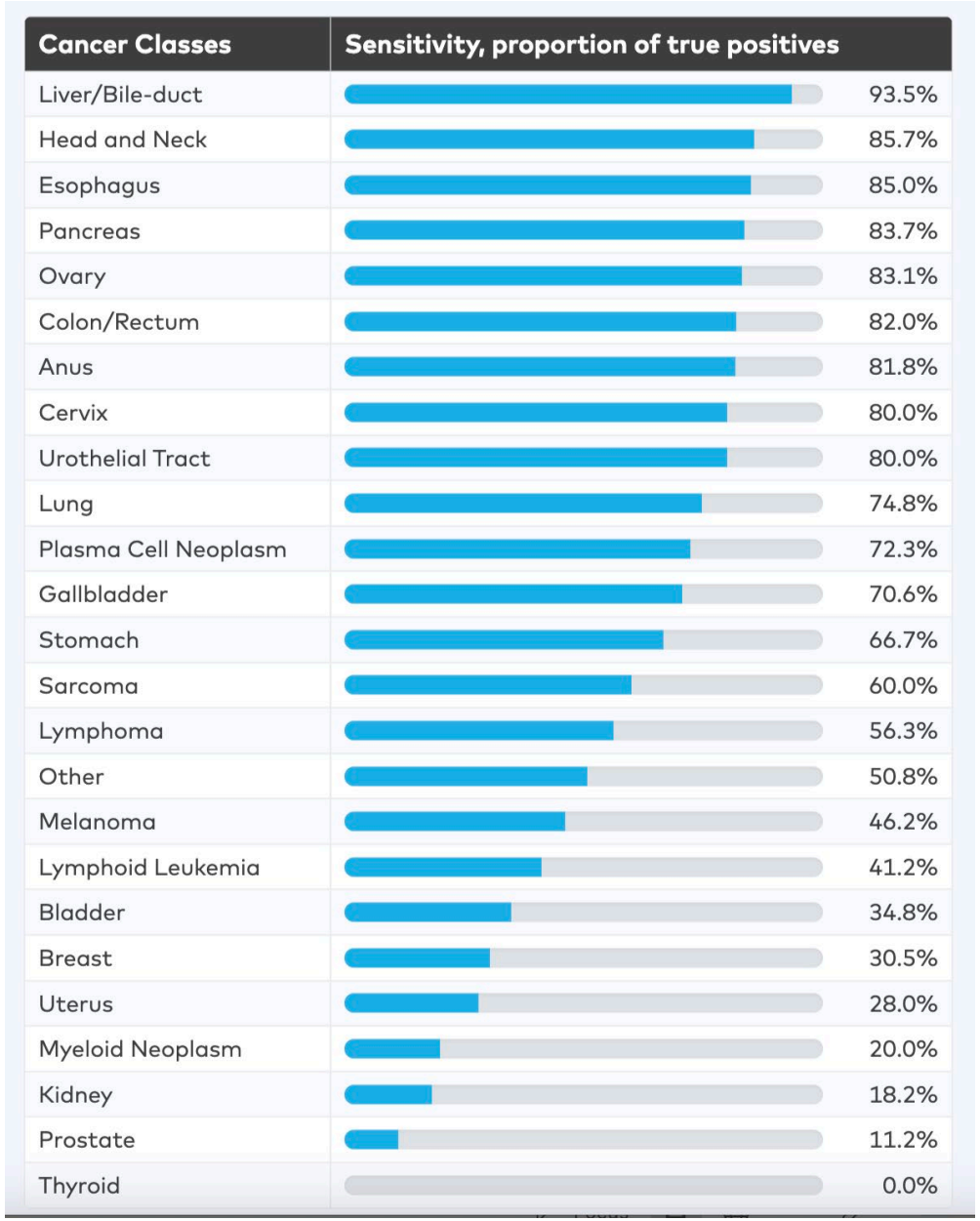
Gallery test (Grail)

Methylation-based test

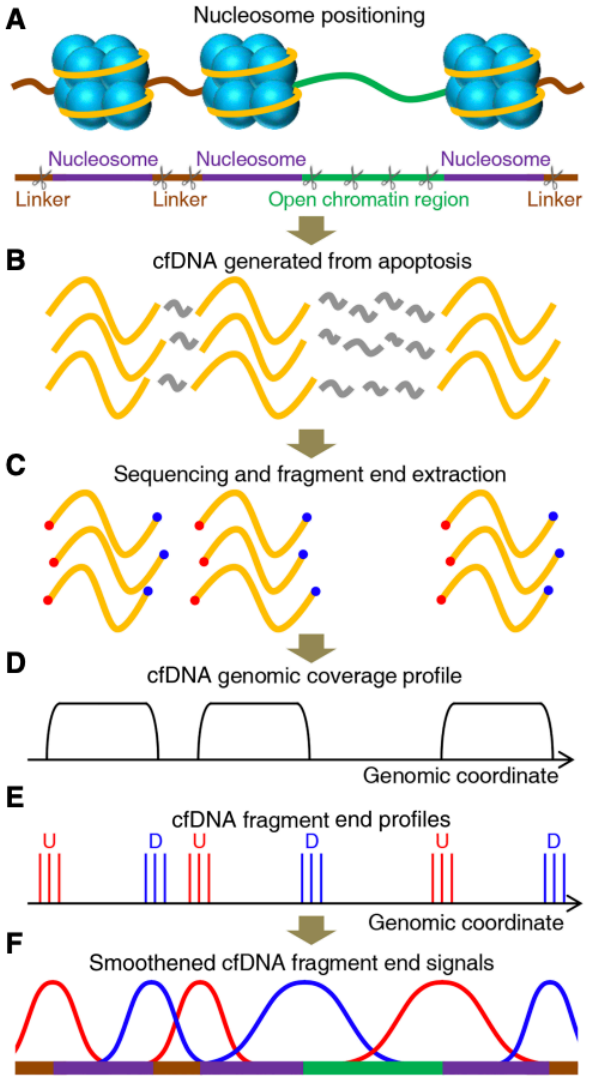
76% Sensitivity
99.5% Specificity
43.1% PPV

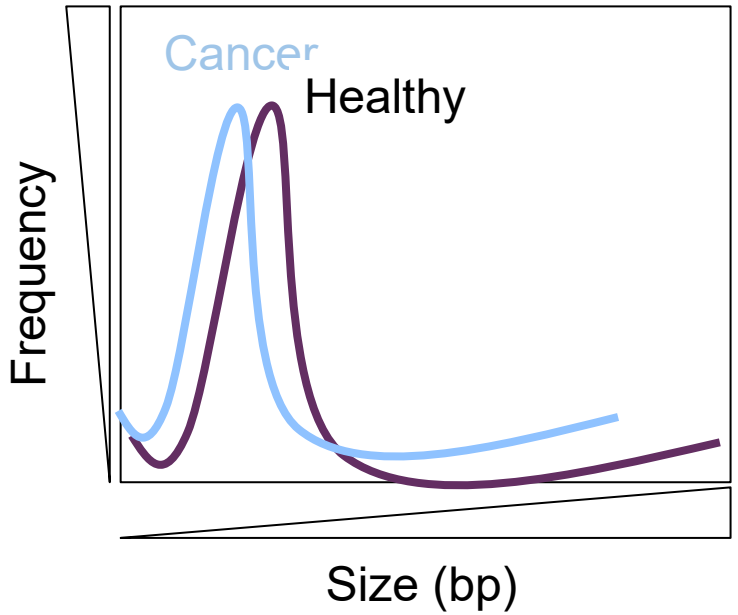
88% Tissue Localization Accuracy

Cost: $949

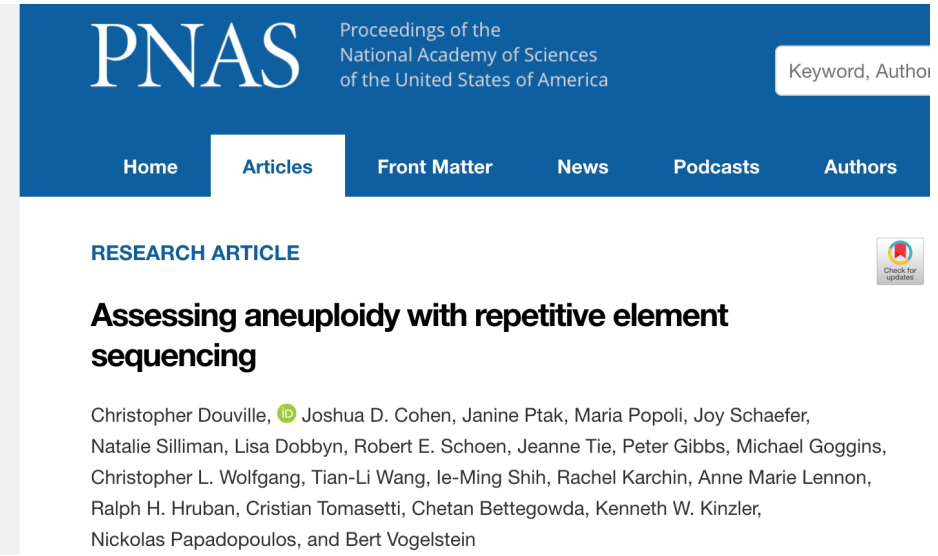


Cell-free DNA (cfDNA) & RealSeqS





- cfDNA can be analyzed for both aneuploidy and fragmentomics
- More pervasive “signal”



RealSeqS

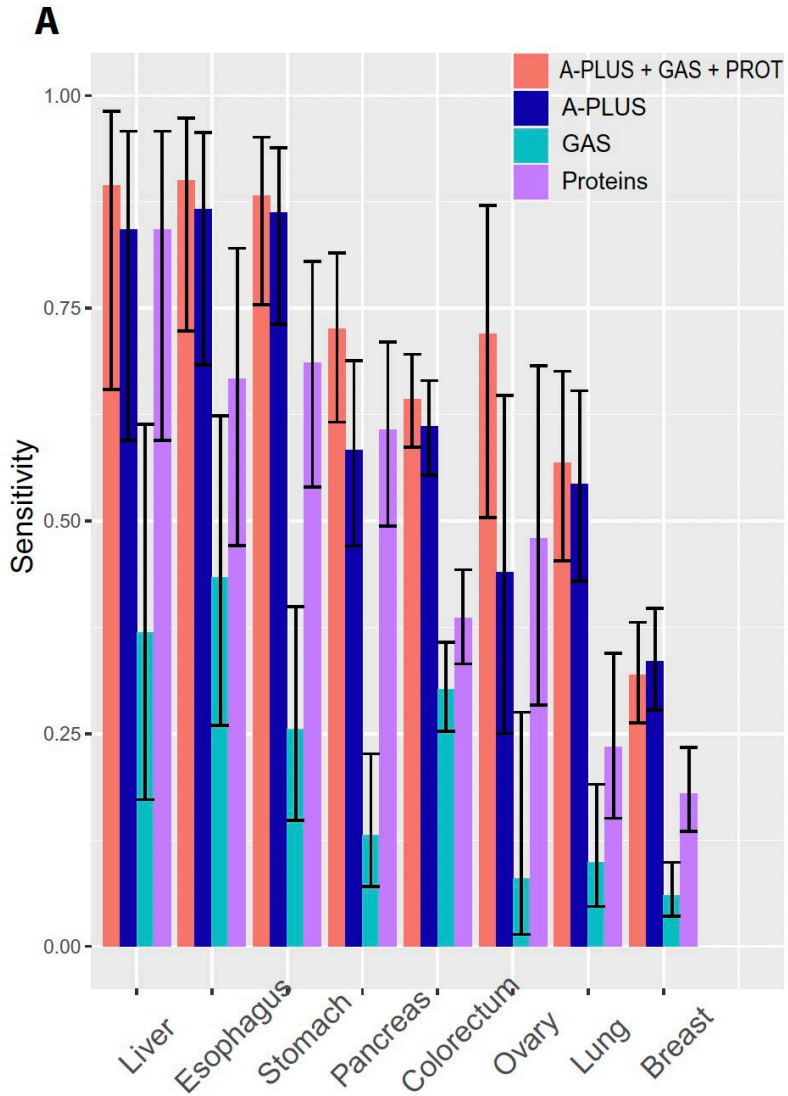
- Single primer pair, 350K amplicons, high coverage of key regions
- 1mL of plasma (3 pg of DNA)

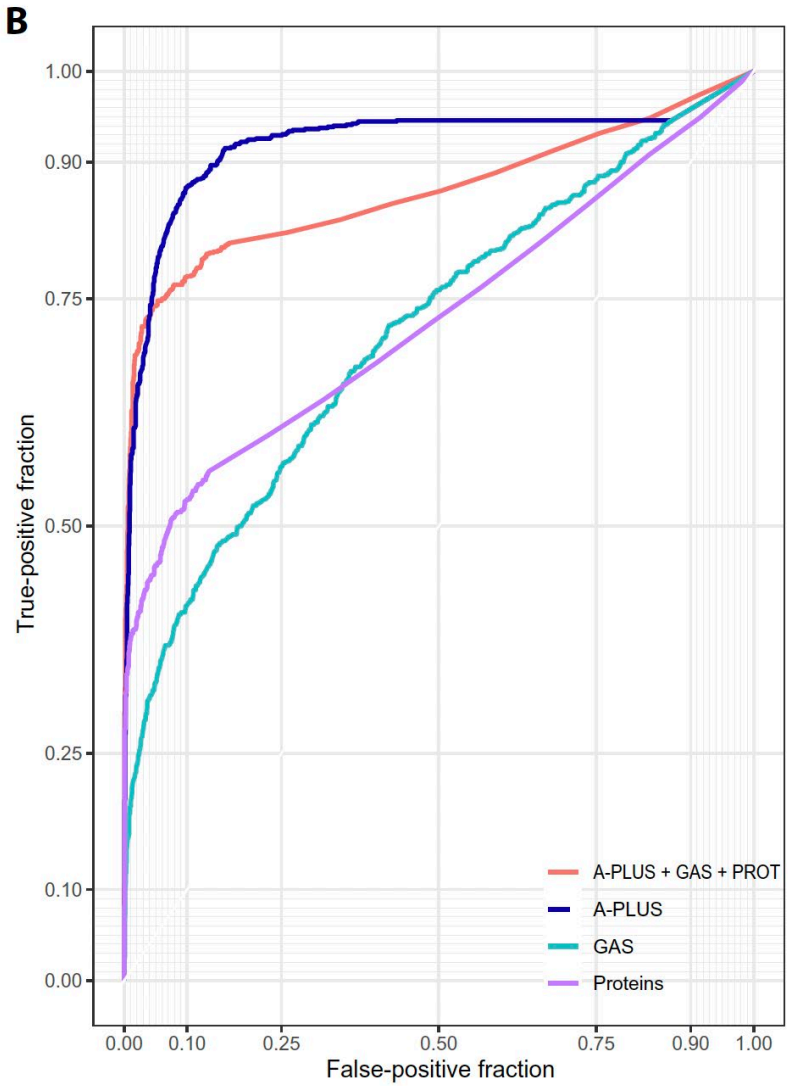
Machine learning to detect the SINEs of cancer

CHRISTOPHER DOUVILLE, KAMEL LAHOUEL, ALBERT KUO, HALEY GRANT, BRACHA ERLANGER AVIGDOR, JOSHUA D. COHEN, YUXUAN WANG, AUSTIN MATTOX, JONATHAN DUDLEY, LISA DOBBYN, MARIA POPO LIMAN, CHERIE BLAIR, KATHARINE ROMANS, CHRISTOPHER THOBURN, JENNIFER GIZZI, ROBERT E. SCHOEI LAN T. HO-PHAM, BICH N. H. TRAN, THACH S. TRAN, TUAN V. NGUYEN, MICHAEL GOGGINS, CHRIS IE-MING SHIH, ANNE MARIE LENNON, RALPH H. HRUBAN, CHETAN BETTEGOWDA, KENNETH W. KINZLER, AND CRISTIAN TOMASETTI fewer Authors Info & Affiliations

Science Translational Medicine

RealSeqS was used in combination with a novel algorithm called Alu Profile Learning Using Sequencing (A-PLUS) to evaluate aneuploidy in plasma cell-free DNA through the amplification of ~350,000 repeated elements with a single primer on 7615 samples provided a sensitivity of 51% at 98.9% specificity.

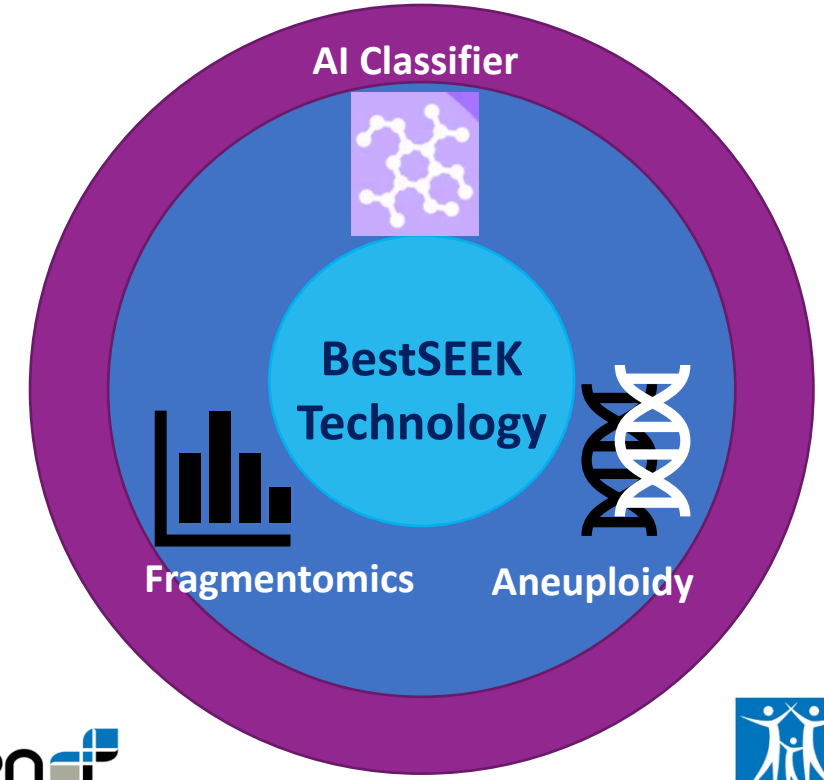


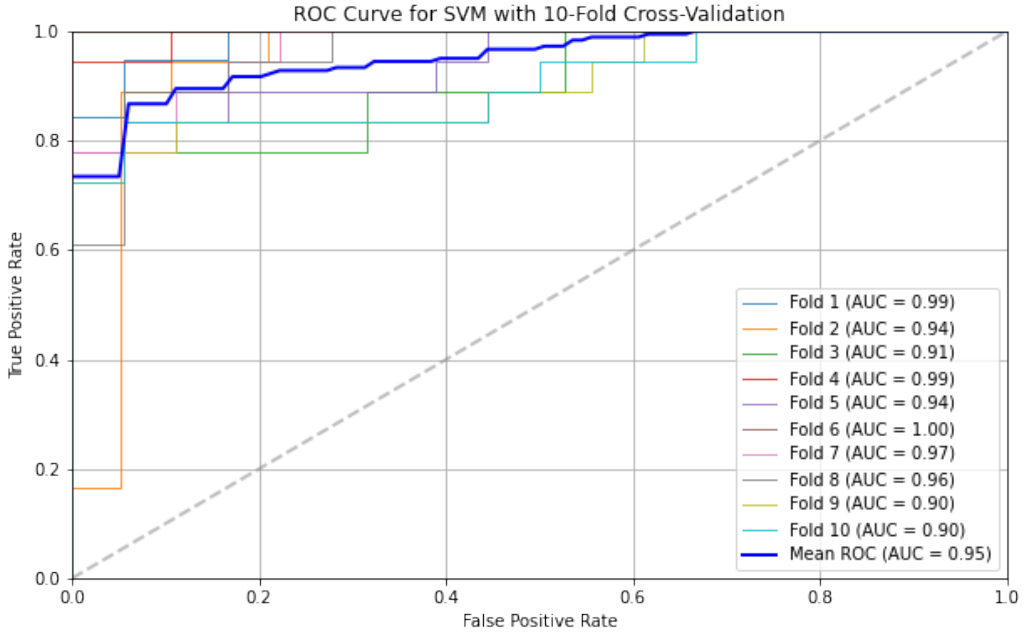


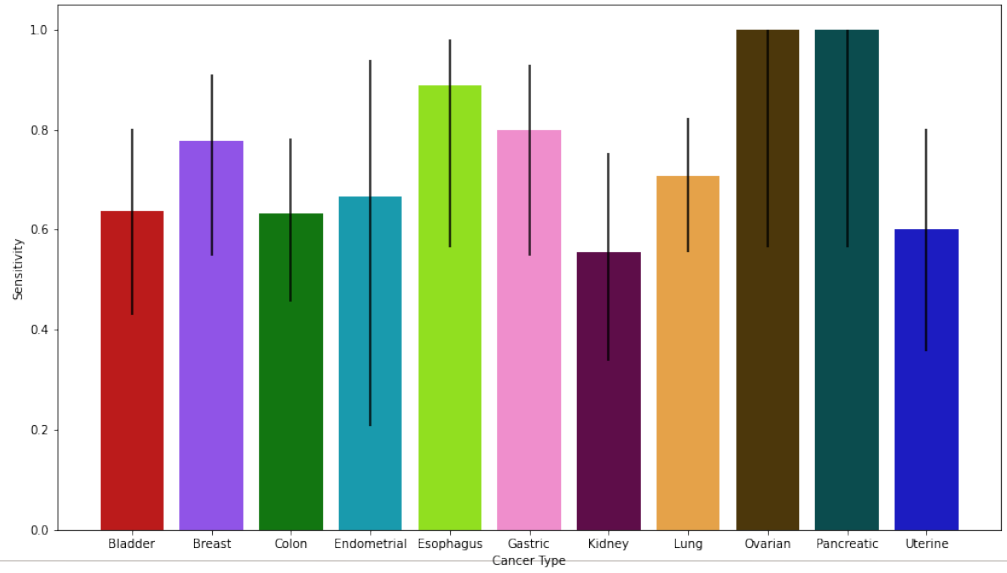
Douville et al. STM 2024

The BestSEEK Technology

- **72% Sensitivity at 99% Specificity, AUC= 0.95**
- **2 primer pairs, high coverage of highly repetitive region**
- **Low Cost**

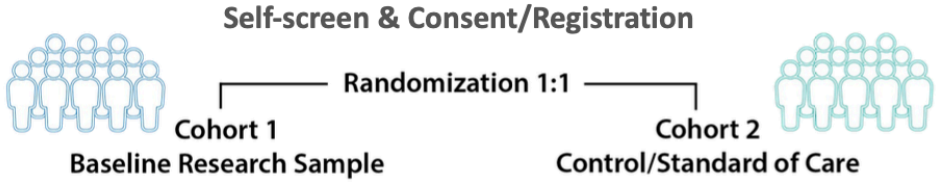




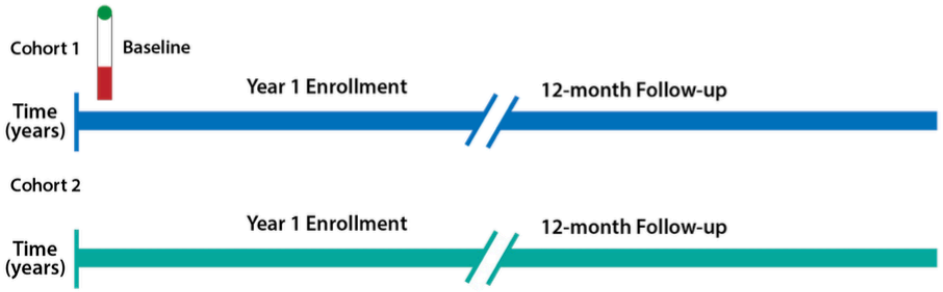


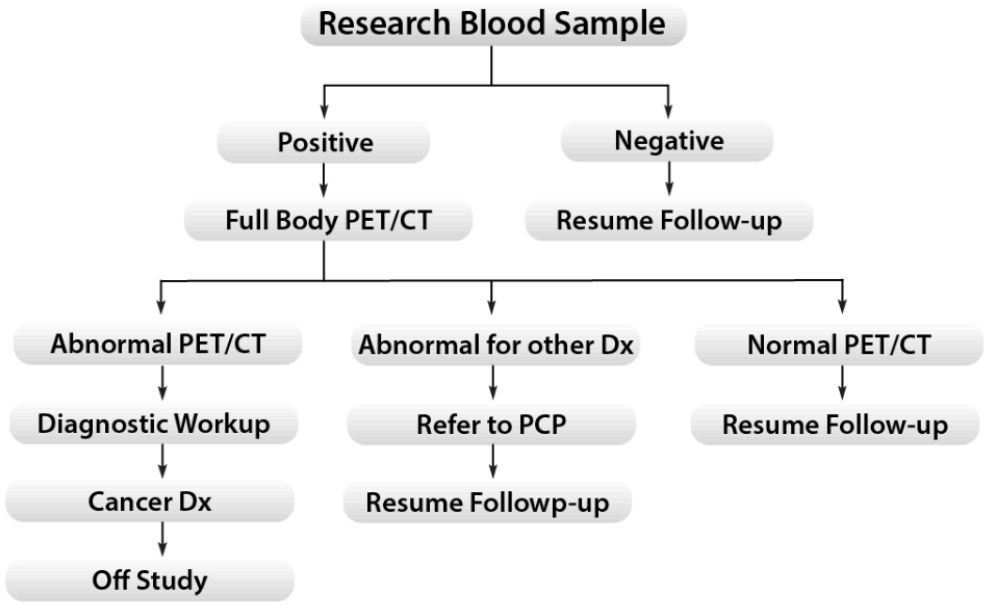
VALETE prospective randomized validation trial (n=30,000)

Validation of Cancer Early Detection via Blood Testing (VALETE):
A randomized study of blood testing for the early detection of cancer



Research blood samples are sent to lab for analysis. Volunteers in Cohort 1 will be contacted by email or telephone if the panel is negative for cancer. Volunteers with a positive cancer panel will be told of the results via telephone by a registered nurse and scheduled for a full-body PET/CT at treating hospital and appropriate diagnostic workup as illustrated in the figure to the right.





Volunteers reporting or diagnosed with any cancer diagnosis at any time during the study will go off study. Medical records of any cancer diagnosis will be reviewed (ordered if necessary) and data recoded in order to analyze sage at diagnosis and estimate life expectancy.

Abbreviations: Dx - Diagnostic, PCP - Primary Care Physician, PET/CT - Positron Emission Tomography/Computed Tomography

Positive tests referred to Early Detection Tumor Board

Early Detection of Advanced Adenomas

Better Detection of Advanced Adenomas (AA) Using cfDNA than ctDNA

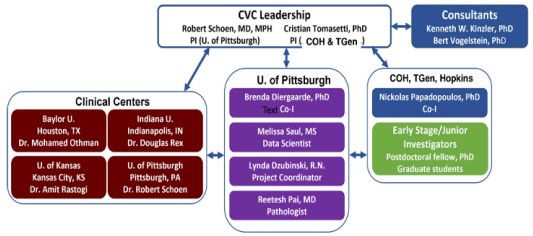
TRANS-DISCIPLINARY COLLABORATION AND COORDINATION

Featured New Grant – U01

Establishment of a Clinical Validation Center (CVC) to advance and validate blood-based detection of colorectal advanced adenoma.

Key Study Features:

- Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer death in the United States.
- Screening for CRC is one of the great public health success stories in cancer prevention and is currently performed with stool-based or endoscopic testing.
- Blood-based screening has the potential to increase population uptake from its current level of compliance in the United States of only 68%.
- We have developed a new blood-based techniques for the detection of advanced adenomas (AA), the next frontier in non-invasive CRC screening
- The main objective of this grant is the creation of a clinical validation center (CVC) to validate new technologies for the early detection of AA.
- Also to predict likelihood of recurrence and potentially guide surveillance of colonoscopy exams



PIs


Cristian Tomasetti, Ph.D.


Robert Schoen, M.D.

Sponsor

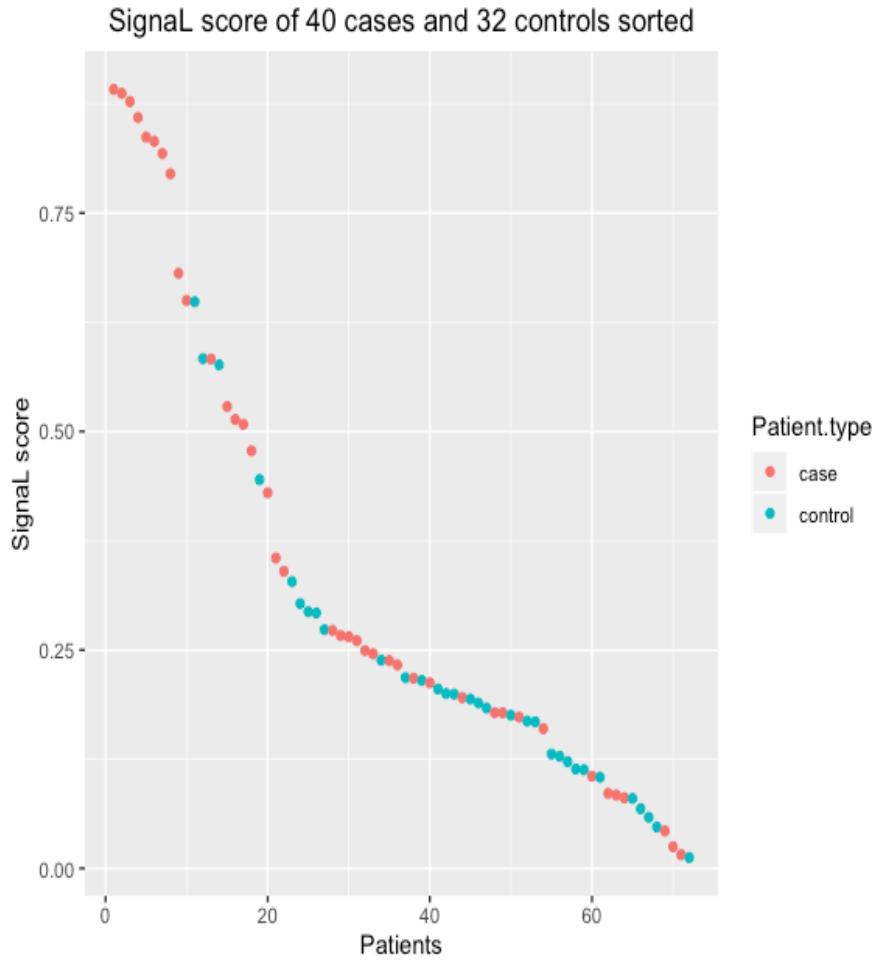
NIH NATIONAL CANCER INSTITUTE Early Detection Research Network

Award # / Title

1 U01 CA271884-01
Blood-Based Testing for Advanced Adenoma

Amount/Year

$855,355/year
(5 years)



- In a pilot study of 20 AA patients the most sensitive tumor-informed mutational approach using ctDNA (digital, with 96 wells per sample) had 8% sensitivity vs 40% sensitivity using RealSeqS on cfDNA

- In a second blinded set of 40 AA patients and 32 controls RealSeqS on cfDNA plus proteins achieved 40% sensitivity with 94% specificity.

To be submitted

Performance Comparison on Adenomas
(sensitivity/specificity)

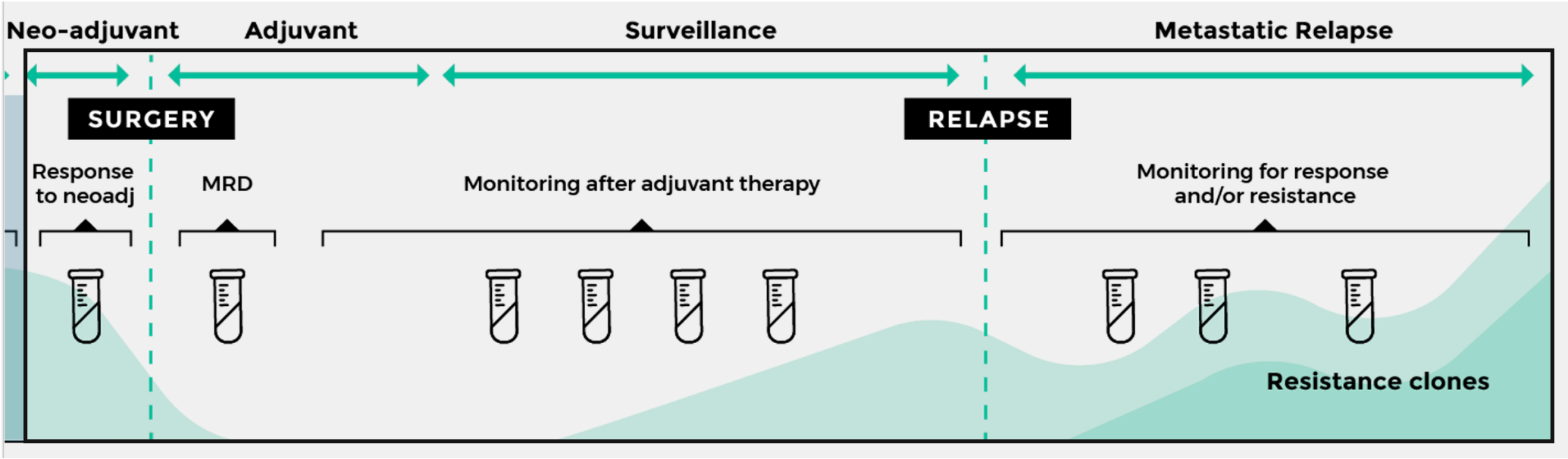
Methodology	All Adenomas	High Grade Dysplasia	≥ 2 cm	≥1 cm but <2 cm
RealSeqS Fragments	22.5, 100	12.5, 100	26.3, 100	23, 100
RealSeqS Aneuploidy	27.5, 93.8	25, 93.8	31.6, 93.8	23, 93.8
17-protein Panel	12.5, 100	37.5, 100	5.3, 100	7.6, 100
RealSeqS + Proteins	**49, 93.8**	**62.5, 93.8**	**42.1, 93.8**	**23, 93.8**
FIT	37.5, 96	50, 96	42.1, 96	23.1, 96
Cologuard (mt-sDNA)	60, 90	75, 90	68.4, 90	38.5, 90
Cologuard Next-Gen	60, 92.7	75, 92.7	68.4, 92.7	38.5, 92.7
Guardant Shield	13.2, 89.9			

11 Imperiale TF, Ransohoff DF, Itzkowitz SH, *et al.* Multitarget Stool DNA Testing for Colorectal-Cancer Screening. *N Engl J Med*. 2014;370:1287–97. doi: 10.1056/NEJMoa1311194

12 Imperiale TF, Porter K, Zella J, *et al.* Next-Generation Multitarget Stool DNA Test for Colorectal Cancer Screening. *N Engl J Med*. 2024;390:984–93. doi: 10.1056/NEJMoa2310336

MRD, Monitoring Recurrence & Guiding Therapy

Monitoring Disease



SaferSeqS technology

nature biotechnology

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Letter | Published: 03 May 2021

Detection of low-frequency DNA variants by targeted sequencing of the Watson and Crick strands

Joshua D. Cohen, Christopher Douville, Jonathan C. Dudley, Brian J. Mog, Maria Popoli, Janine Ptak, Lisa Dobbyn, Natalie Silliman, Joy Schaefer, Jeanne Tie, Peter Gibbs, Cristian Tomasetti, Nickolas Papadopoulos, Kenneth W. Kinzler & Bert Vogelstein

Nature Biotechnology **39**, 1220–1227 (2021) | Cite this article

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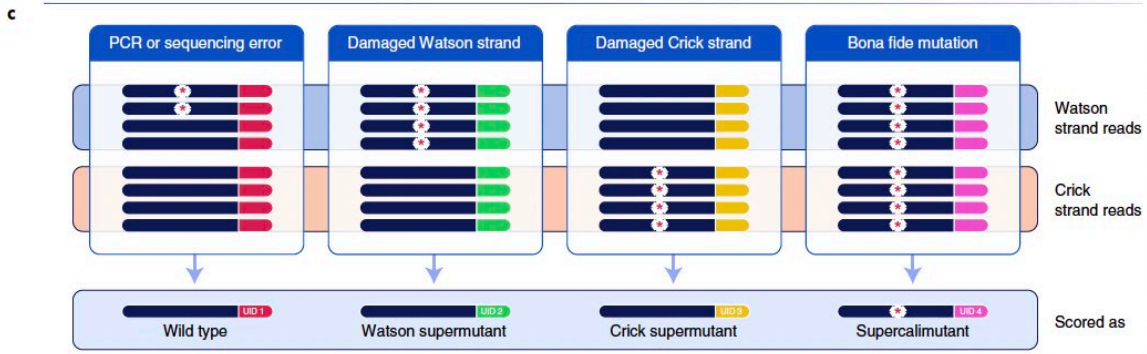


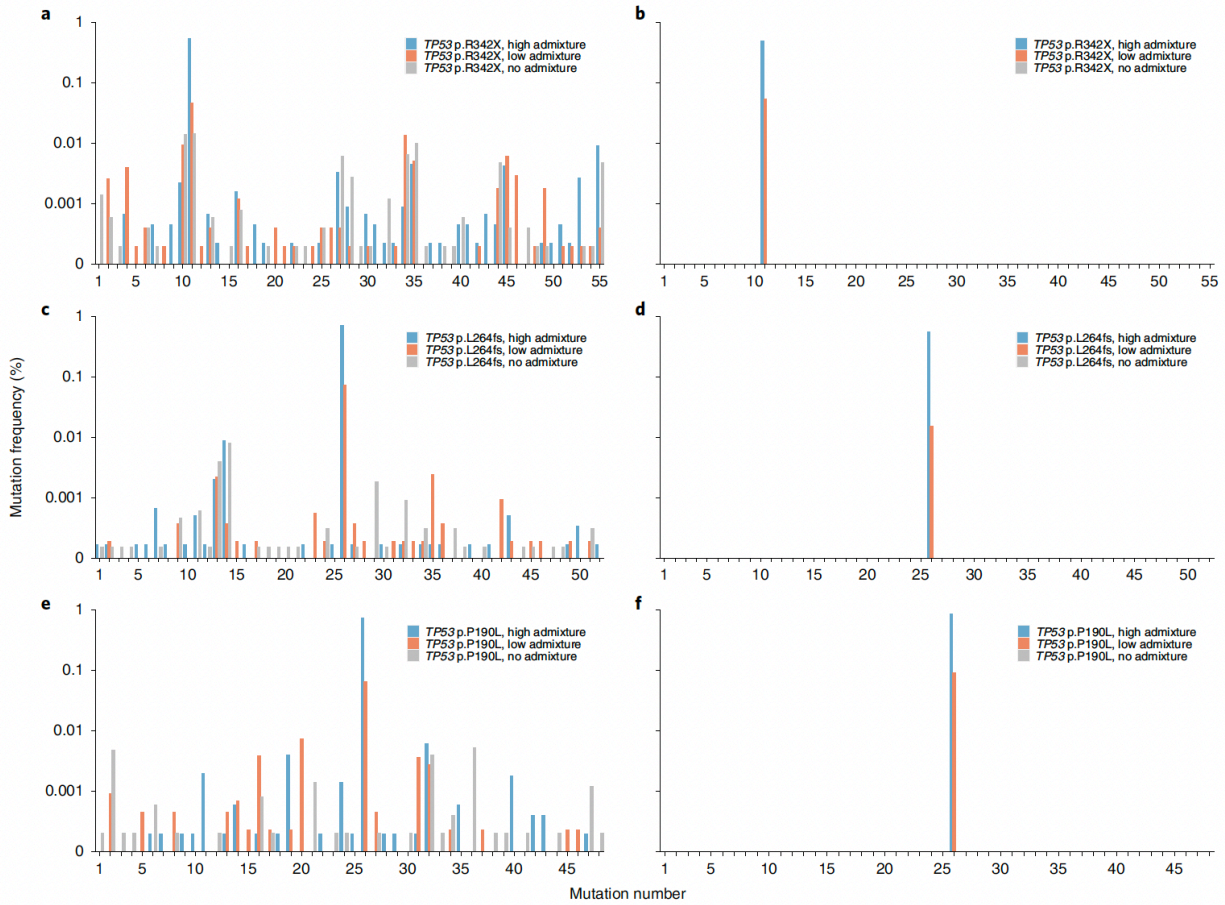


Fig. 2 | Detection of mutations in liquid biopsy samples. Analysis of 33 ng of plasma cell-free DNA from healthy individuals admixed with cell-free plasma DNA from an individual with cancer. Mixtures were created to generate a high frequency (~0.5–1%) of mutation (blue bars), low frequency (~0.01–0.1%) of mutation (orange bars) or no mutation (gray bars). The admixed *TP53* p.R342X sample was assayed with SafeSeqs (**a**) and SaferSeqS (**b**). Similarly, the admixed *TP53* p.L264fs sample was assayed with SafeSeqs (**c**) and SaferSeqS (**d**), and the admixed *TP53* p.P190L sample was assayed with SafeSeqs (**e**) and SaferSeqS (**f**). Mutation numbers represent each of the 153 distinct mutations observed with SafeSeqS defined in Supplementary Table 2.

Cohen *et al.* Nat Biotech 2021

The Dynamics Study

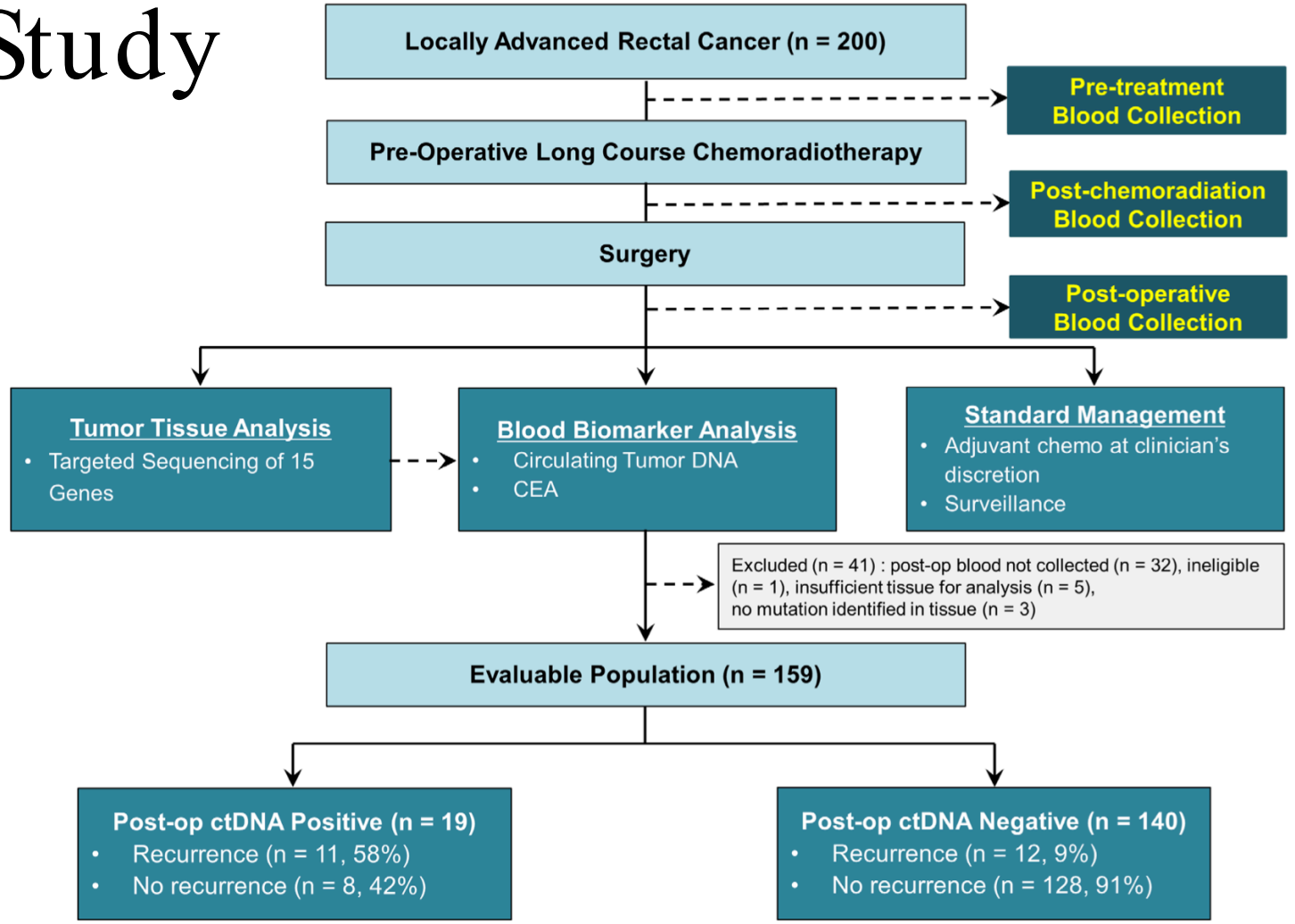
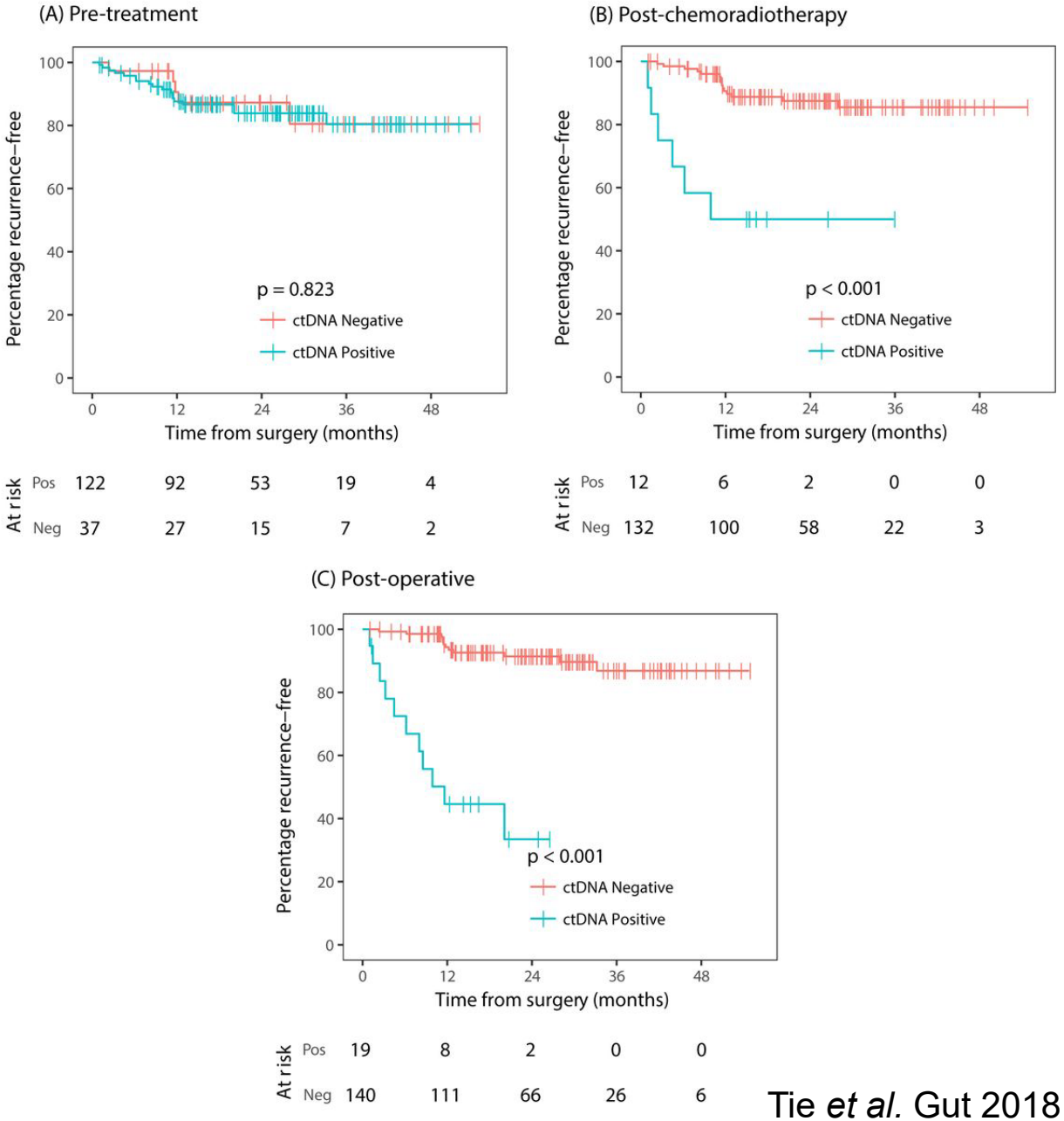


Figure 1 Patient enrolment, sample collections and evaluable population. CEA, carcinoembryonic antigen ; ctDNA, circulating tumour DNA; post-op, postoperative.

Tie *et al.* Gut 2018

The Dynamics Study



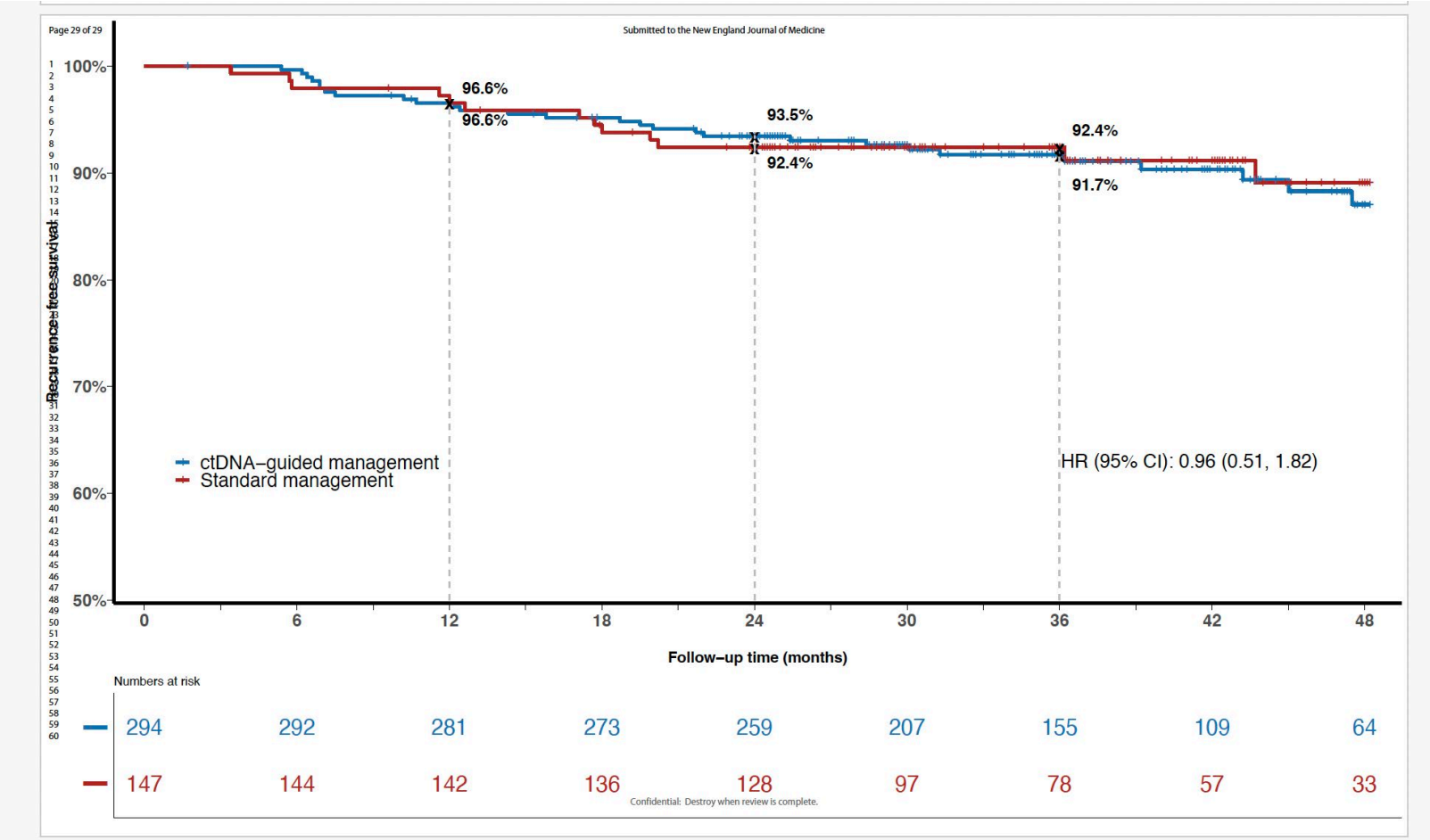
Tie *et al.* Gut 2018

The Dynamics Study (2022)

- Randomized phase II study (N=455) in stage II colon cancer patients where patients were randomized 2:1 to have treatment decisions guided by either ctDNA results or standard clinicopathologic features

- ctDNA-positivity at 4-7 weeks postop prompted chemotherapy initiation whereas ctDNA-negative patients were not treated

- Primary endpoint was RFS at 2 years



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- ctDNA-positivity at 4-7 weeks postop prompted chemotherapy initiation whereas ctDNA-negative patients were not treated
- Primary endpoint was RFS at 2 years
- ctDNA-guided approach resulted in lower chemotherapy use compared to standard management (15% vs. 28%) with a non-inferior 2-yr RFS (93.5% vs. 92.4%)

RESEARCH SUMMARY

Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer

Tie J et al. DOI: 10.1056/NEJMoa2200075

CLINICAL PROBLEM

The benefit of adjuvant chemotherapy for stage II colon cancer is unclear. Circulating tumor DNA (ctDNA) may provide a biomarker to identify which patients would benefit from adjuvant therapy and which patients might forgo it with minimal risk of recurrence.

CLINICAL TRIAL

Design: A phase 2, randomized, controlled noninferiority trial assessed whether ctDNA-guided management, as compared with standard management, could reduce the use of adjuvant therapy without compromising the risk of recurrence after surgery for stage II colon cancer.

Intervention: 455 patients were randomly assigned in a 2:1 ratio to have treatment decisions guided by either ctDNA results or standard clinicopathological criteria. For ctDNA-guided management, patients with positive ctDNA tests at week 4 or 7 after surgery received fluoropyrimidine or oxaliplatin-based chemotherapy, and those with negative tests at both weeks received no chemotherapy. The primary efficacy end point was recurrence-free survival at 2 years. A key secondary end point was adjuvant chemotherapy use.

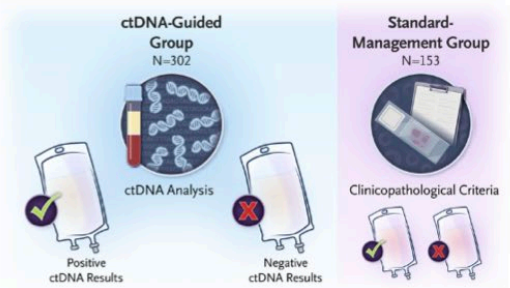
RESULTS

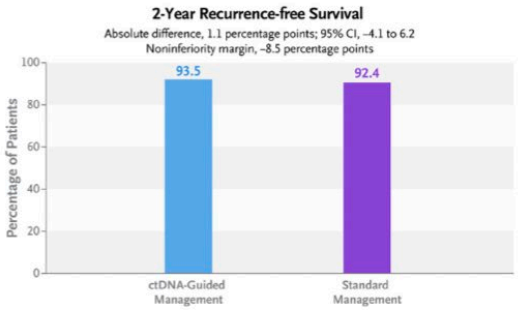
Management guided by ctDNA was noninferior to standard management with respect to 2-year recurrence-free survival and resulted in less use of adjuvant chemotherapy.

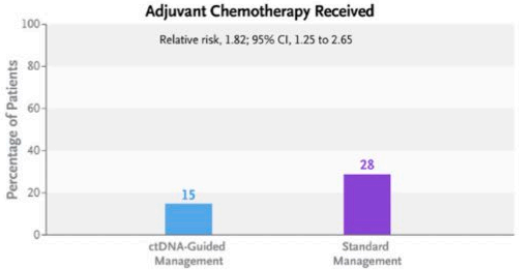
LIMITATIONS AND REMAINING QUESTIONS

- The trial was too small to provide definitive findings for patient subgroups.
- Because management decisions were guided by test results, the patients in the ctDNA-positive and ctDNA-negative subgroups were not randomly assigned to either receive or not receive treatment.
- The effect of a ctDNA-guided strategy was not assessed beyond the initial decision for adjuvant chemotherapy.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

Among patients with stage II colon cancer, ctDNA-guided management was noninferior to standard management with respect to 2-year recurrence-free survival and resulted in reduced use of adjuvant chemotherapy.

The Dynamics Study (2025)

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Article | Published: 07 March 2025

Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer: 5-year outcomes of the randomized DYNAMIC trial

Jeanne Tie ✉, Yuxuan Wang, Serigne N. Lo, Kamel Lahouel, Joshua D. Cohen, Rachel Wong, Jeremy D. Shapiro, Samuel J. Harris, Adnan Khattak, Matthew E. Burge, Margaret Lee, Marion Harris, Sue-Anne McLachlan, Lisa Horvath, Christos Karapetis, Jenny Shannon, Madhu Singh, Desmond Yip, Sumitra Ananda, Craig Underhill, Janine Ptak, Natalie Silliman, Lisa Dobbyn, Maria Popoli, Nickolas Papadopoulos, Cristian Tomasetti, Kenneth W. Kinzler, Bert Vogelstein & Peter Gibbs

A higher than median postoperative tumor-derived mutant molecules per milliliter plasma was associated with worse 5-year RFS (HR 10.62; $P = 0.005$).

Thank you!

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