science.sciencemag.org/cgi/content/full/science.abb9601/DC1

Supplementary Materials for

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. Adonizio, Hee Jung Hwang, Kamel Lahouel, Joshua D. Cohen, Christopher Douville, Aalpen A. Patel, Leonardo N. Hagmann, David D. Rolston, Nirav Malani, Shibin Zhou, Chetan Bettegowda, David L. Diehl, Bobbi Urban, Christopher D. Still, Lisa Kann, Julie I. Woods, Zachary M. Salvati, Joseph Vadakara, Rosemary Leeming, Prianka Bhattacharya, Carroll Walter, Alex Parker, Christoph Lengauer, Alison Klein, Cristian Tomasetti, Elliot K. Fishman, Ralph H. Hruban, Kenneth W. Kinzler†, Bert Vogelstein†, Nickolas Papadopoulos†

*These authors contributed equally to this work.
†Corresponding author. E-mail: npapado1@jhmi.edu (N.P.); vogelbe@jhmi.edu (B.V.); kinzlke@jhmi.edu (K.W.K.)

Published 28 April 2020 on *Science* First Release
DOI: 10.1126/science.abb9601

This PDF file includes:

Other Supplementary Materials for this manuscript include the following:
(available at science.sciencemag.org/cgi/content/full/science.abb9601/DC1)

Materials and Methods

Participants

Participants were prospectively enrolled in the Geisinger Health System between September 2017 and May 2019**.** Females aged between 65 and 75 years of age were eligible for inclusion in the study. The only exclusion criteria were a personal history of cancer of any type, including myeloproliferative disease, other than non-melanoma skin cancer. General demographics and information about recent screening for breast, lung, cervical and colorectal cancers were collected at enrollment.

Overall Study Design and Oversight

The study was approved by the Institutional Review Boards (IRBs) for Human Research at the Geisinger Health System (Geisinger; #2017-0268) and the Johns Hopkins Medical Institutions (#00119844) and complied with The Health Insurance Portability and Accountability Act. Direction of the study was overseen by the IRB and all data were reviewed by a data safety monitoring board.

We estimated that 10,000 participants would provide greater than 99% power to detect 20 or more cancers if the sensitivity of the test in a population highly compliant with standard-of-care (SOC) screening was >10%. The endpoints of this feasibility and safety study were:

Primary Endpoints

- *Recruitment of 10,000 individuals into study cohort.*
- *Marker panel testing in 10,000 subjects.*
- *Histopathology confirming a cancer diagnosis in approximately 20 subjects.*

Secondary Endpoints

- *Obtain survey and medical record data including demographic information and risk factor data.*

Prior to providing a written informed consent, all participants were consulted about the scope and potential outcomes of the study. During this consultation, the participants were informed that the DETECT-A (Detecting cancers Earlier Through Elective mutation-based blood Collection and Testing) blood test was not a substitute for SOC screening and that adherence with SOC screening should continue unabated. They were also informed about other primary and secondary cancer preventive measures. Finally, they were informed that they might be contacted to provide a second blood sample as part of the research study. Negative results from the baseline test component were not returned to the participants unless the participant requested it. In these cases, they were informed that their result was negative, and they were reminded that they should comply with recommended SOC screening tests. They were also advised to promptly bring any symptoms to the attention of their primary care physician. All subsequent communications with participants were also handled in a prescribed manner designed to minimize anxiety and maximize understanding of the nature of this research study (Fig. 1). The participants with a positive baseline test, as well as an approximately equal number of participants with a negative baseline test (study controls), were contacted by phone and asked to provide a second blood sample. As noted in the main text, this was

done in a double-blinded fashion in the hope that it would reduce the anxiety associated with the request for a second blood sample. During this call, participants were again reminded about the importance of SOC screening by the study team member who contacted them.

In the participants in whom the baseline test result was confirmed ("DETECT-A blood test positive"), the recommendation to undergo diagnostic positron emission tomography-computed tomography (PET-CT) was made by a Multidisciplinary Review Committee (MRC). Participants could undergo physician-initiated workup for symptoms, as well as SOC screening, as clinically indicated. It was anticipated that some participants might undergo clinical investigation by their primary physicians as part of their regular care. To account for this, all participants with a positive DETECT-A blood test, irrespective of whether they underwent a diagnostic PET-CT or other types of imaging based on symptoms, were reviewed by the MRC. The MRC represented the following specialties: gastroenterology, gynecology, surgery, internal medicine, genetic counseling, pathology, radiology, scientists, hematology, and oncology. This committee reviewed all available clinical information as well as pre-defined, non-cancerous causes of elevated proteins before recommending an imaging procedure. A health care professional associated with the study disclosed positive DETECT-A blood test results to participants and conveyed the committee's recommendation for imaging. If the patient agreed to diagnostic PET-CT imaging, the results were reviewed by an expert Geisinger radiologist and independently reviewed at the Johns Hopkins Medical Institutions by a single radiologist. Following receipt of the imaging reports, the same MRC evaluated each case to decide if further follow up was warranted. An optional office visit was offered to any participant with negative imaging results. Participants with concerning findings on imaging were referred to an appropriate specialist for further follow up if required. Procedures that were performed as part of the follow up were classified according to their perceived risk as non-invasive, minimally invasive, or surgical (Table S12).

Cancer definition and staging

Cancers defined in this study included all types except those of the skin, central nervous system, or bone marrow (i.e., leukemias). Participants were classified as having cancer on the basis of histopathological examination of their tumors in 94 of the 96 cancer cases. One patient (909448) was defined as having cancer based on a clinical presentation indicating unequivocal metastatic cancer; biopsy confirmation was deemed clinically inappropriate in this patient by her physician. In the second case (907789), the diagnosis of a cancer was not performed within Geisinger, but the diagnosis was confirmed by the patient's primary physician. Histopathological examination was performed both by an expert Geisinger pathologist and centrally reviewed by a single pathologist at the Johns Hopkins Medical Institutions whenever possible. Digestive system tumors were classified using the 2010 World Health Organization classification guidelines (*45*). Carcinomas and sarcomas were staged by recommendations of the AJCC 8th edition and lymphomas were staged using the Lugano system (*46-47*). Premalignant lesions of any type, including in situ carcinomas and highly dysplastic lesions, were not considered cancers. Several such lesions were found in DETECT-A blood test positive

participants but were considered false positives according to the study's definition of cancer. In Figs. 3, 4, and fig. S3, peritoneal and ovarian cancer were grouped together as ovarian.

One-year follow-up and survey

Participants were followed with surveys to evaluate their satisfaction and views on their participation in the DETECT-A study. All participants, including those with positive and negative DETECT-A blood test results, were included in the survey at one year following enrollment (Fig. 1 and main text). In addition to the one-year survey, the Geisinger Healthcare System electronic medical records (EMRs) were used to identify cancers occurring within a year after enrollment. This was achieved via three approaches. First, the EMRs were queried for ICD9 and ICD10 codes related to cancer. Second, the EMRs were reviewed for any participant who was hospitalized. Third, the Tumor Registry was queried for any DETECT-A participants. A formal chart review was performed if any of these three approaches suggested that a patient had cancer. The formal chart reviews were used to identify participants whose cancers were first detected by SOC or other means.

Diagnostic PET-CT

Patients were instructed to avoid vigorous exercise for 48 hours prior to the diagnostic PET-CT examination and fast for 4 to 6 hours prior to it (4 hours for diabetic patients, 6 hours for non-diabetic patients). Patients with diabetes were also instructed about the use of medication prior to the scan per institution protocol. Blood glucose levels were checked prior to the intravenous administration of F18-FDG (7-12 mCi) with a cut off of <= 200 mg/dL. This was followed by a 60-minute uptake period.

After the uptake period, diagnostic CT from the skull base to thighs was performed with intravenous (Optiray 320) and oral (Gastroview) iodinated contrast. CT was acquired with 1.2 mm slice thickness, 130 kV and variable mAs based on weight (quality reference of 170 mAs). This was followed by PET emission data acquisition. PET data was acquired in 3D mode from the skull base to the mid thighs (8 to 10 beds) for 2 to 3 minutes per bed depending on patient weight. A separate deep inspiration breath hold CT of the chest was performed. Multiplanar (axial, coronal and sagittal) reformats and maximum intensity projection of the CT data were generated for review. PET data was reconstructed using either ordered subset expectation maximization method or time of flight and point spread function modeling depending on the scanner used. The CT was used for attenuation correction. Maximum intensity projection and fused PET and diagnostic CT images were generated for review.

Potential contraindications to diagnostic PET-CT with intravenous contrast were at the discretion of the study team and included: a) Creatinine > 1.5 mg/dL, b) Glomerular filtration rate (GFR) < 45 mL/min, c) Glucose >200 mg/dL) Allergy to iodinated contrast, e) Weight restriction (>500 lbs or >27 inch bore size).

Sample collection and DNA purification

Whole-blood was collected in Cell-Free DNA Blood Collection Tubes (Streck cat no. 218961) and plasma and buffy coat were separated within 32 hours. Following separation, plasma and buffy coat components were aliquoted and stored at -80^{0}C until purification. DNA from 10 mL of plasma was purified using a cfPure Cell-Free DNA Extraction Kit (BioChain cat no K5011625MA) as specified by the manufacturer. White Blood Cell (WBC) DNA from buffy coat was purified with a QIAsymphony DP DNA Midi Kit (Qiagen cat no. 937255) as specified by the manufacturer.

Tumor tissues were formalin-fixed and paraffin-embedded (FFPE) according to standard histopathologic procedures. Following macro-dissection to enrich for neoplastic cells, DNA from FFPE tumor tissues was purified with a QIAsymphony DP DNA Midi Kit (Qiagen cat no. 937255).

The DETECT-A blood test

Blood testing was performed in a clinical laboratory certified by the Clinical Laboratory Improvement Amendments (CLIA) program and operated by Thrive Earlier Detection. The DETECT-A blood test comprised a baseline test component followed by a confirmation test component; a positive blood test result required both the baseline and confirmation test to be positive for the same analyte.

Baseline test for mutation detection: DNA purified from plasma was amplified as described previously (*21*). Briefly, 61 primer pairs designed to amplify 66 to 80 bp regions of interest from 16 cancer driver genes, encompassing 1933 bp. The 61 primer pairs were divided into two non-overlapping sets, each containing either 28 or 33 primer pairs (see Table S1 for gene-specific sequences), and included a 16-base degenerate sequence in the forward primer to enable error correction. Each set was used in six independent, 25-µL amplification reactions (i.e.,12 reactions per patient) in a first-round Polymerase Chain Reaction (PCR) using 15 cycles. The first-round PCR amplification products were purified with AMPure XP beads (Beckman Coulter cat no A63882), a fraction of which were amplified in a second-round PCR using 19 cycles with primer pairs complementary to forward and reverse universal priming sites introduced in the first-round amplification and that additionally incorporated sequences facilitating sequencing (5'-3':
AATGATACGGCGACCACCGAGATCTACACCGACGTAAAACGACGGCCAGT
and
CAAGCAGAAGACGGCATACGAGATNNNNNNNNATCGCGCGCACACAGGAAA
CAGCTATGACCATG, respectively, where Ns denote sequences that could distinguish participants).

DNA purified from WBCs was additionally evaluated in patients with positive plasma mutation scores (Omega score ≥1.6, see Mutation Scoring section below). Two hundred ng of WBC DNA template was amplified using two rounds of PCR, as used for plasma DNA but with adjustments made to accommodate the increased input template mass. These adjustments were fewer first-round amplification reactions (two reactions amplifying 100 ng templates per primer set) and fewer second-round amplification cycles (17 cycles).

The PCR products from the two rounds of amplification were purified with AMPure XP beads and sequenced on Illumina HiSeq 4000 or MiSeq instruments. The average coverages of the regions of interest (i.e., unique identifier sequences observed, see Analysis of Sequencing Reads section below) in the plasma and WBC DNA were 66,000 and 270,000, respectively. To be scored as positive in the baseline test, at least one mutation was required to have an Omega-score ≥1.6 and not be the result of Clonal Hematopoiesis of Indeterminate Potential (CHIP) (see Mutation Scoring section below). Sequencing data can be obtained from the European Genome-phenome Archive (EGAS00001004372).

Confirmation test for mutation detection: A confirmation test to exclude CHIP and confirm the original abnormality was performed in each of the 490 participants in which the baseline test was positive (Fig. 2). In 486 (99.0%) of these participants, the confirmation test was performed on a second blood sample obtained after the baseline test. In the other four participants, clinician-initiated care after the baseline test precluded acquisition of a second plasma sample. In these cases, the confirmation test was performed on an independent aliquot of plasma obtained from the first blood sample.

The confirmation test was different than the baseline test in several critical ways. First, instead of amplifying all 61 regions of interest, only the regions containing mutations were evaluated. Up to three regions of interest were assessed simultaneously in multiplex reactions, using the same primer pairs described in Table S1. Second, each primer pair concentration was optimized to detect the particular mutations identified in the baseline test. Third, the second-round PCR amplification was performed with 23 cycles. These modifications provided greater coverage of each mutant base in the plasma than achieved in the baseline test, providing higher confidence in the results (see Statistical section below). As a result, the minimum Mutant Allele Frequency (MAF) acceptable in the confirmation test component was 20% of the MAF detected in the baseline test component of the DETECT-A test. Fourth, the same multiplex reactions covering one to three regions of interest were assessed in the WBC DNA use for the confirmation test. Fifth, the input of WBC DNA for the confirmation test was 150 ng per primer set, 50% higher than used for the baseline test on WBC DNA. These modifications allowed higher coverages of the regions of interest in the confirmation WBC test than in the baseline WBC test, in turn allowing a more stringent exclusion of mutations derived from CHIP. If the MAFs in DNA from the WBCs was >10-fold higher in the plasma, a leukemia or lymphoma was suspected and the participant was referred to a hematologist-oncologist. There was one such case in our cohort (Table S6).

Note that in the 498 study controls, there was no "confirmation test", because no mutations were detected in the baseline test. On the study controls, an independent plasma sample was evaluated by the baseline test to determine the concordance between the two independent baseline tests.

Analysis of sequencing reads: Sequencing of all 9,911 cases produced analyzable data. The template-specific portion of the reads was matched to reference sequences using custom scripts written in Python, SQL, R, and C# (Python version of analysis

pipeline available for download at https://github.com/InSilicoSolutions/SafeSeqS, In Silico Solutions, Falls Church, VA). Reads from a common template molecule were then grouped based on the unique identifier sequences (UIDs) that were incorporated as molecular barcodes (*32*). Artefactual mutations introduced during the amplification or sequencing steps were reduced by requiring a mutation to be present in >90% of reads in each UID family. Redundant reads arising from optical duplication and clustering artifacts were eliminated by requiring reads with the same UID and sample index to be at least 5,000 pixels apart when located on the same tile. UID family counts of 1 or 2 were used to define "UID families" in DNA from WBCs or plasma, respectively (*32*). Mutations that met one of the two following criteria were considered (i) present in the COSMIC database (*48*), or (ii) predicted to be inactivating in tumor suppressor genes (nonsense mutations, out-of-frame insertions or deletions, canonical splice site mutations). Synonymous mutations (except those at exon ends) and intronic mutations (except for those at splice sites) were excluded (48). The MAF within a positive well was defined as the proportion of UIDs in the positive well that were mutant. Thus, the MAFs reflect the mutant fraction within each well and represent an independent sampling of the mutant allele frequency in the sample of interest. Well-level MAFs served as inputs into the mutation scoring algorithm (see Mutation scoring section below). The MAF of a mutation in a sample (rather than the well) was defined as the total number of mutations present in all six independent assays (wells) divided by the total number of UIDs in all six wells. All MAFs reported in this study were calculated at the sample level.

Mutation scoring: For plasma DNA analyses, Omega scores for each mutation were obtained from a statistical test comparing the normalized mutation frequencies of the sample of interest to the distribution of the normalized frequencies of mutations in plasma samples from an independent set of patients with cancer and normal individuals. These statistical tests were performed using the Omega score and data described in (*21*). R code implementing the Omega score algorithm as described in (*21*) is available for download at: https://github.com/cristomasetti/CancerSEEKv1. In the baseline test, an Omega score ≥1.6 was used as a threshold of positivity. In the confirmation test, an Omega score ≥0.63 was used as a threshold of positivity. This threshold for the confirmation test was determined according to the null distribution of the Omega score, conditioned on the event that the mutation was detected by the baseline test at an Omega score ≥1.6. Additionally, in the confirmation test, the wells with the highest and lowest scores were no longer excluded from consideration, allowing a single well to lead to a positive score.

Mutation scoring of CHIP: WBC DNA analyses were performed to determine whether DNA mutations found by the baseline test were derived from clonal hematopoiesis (CHIP). Mutations were excluded when the identical mutation was observed in the WBCs from the same participant and the MAF in plasma exceeded the MAF in WBCs by a certain factor. On the basis of simulations performed on data from the first 257 participants in whom confirmation tests were performed, we eventually chose factors of 3 and 7 for baseline and confirmation testing, respectively. These thresholds employed a Fisher's exact test (odds-ratio statistical test) with a p-value cutoff of 0.02275 to account for sequencing depth. Retrospective analyses of the entire dataset

showed that nine participants could have been spared a confirmation test had these thresholds been applied throughout the study. None of these individuals were found to have cancer.

Baseline test for elevated proteins: Protein biomarkers were evaluated with Luminex bead-based immunoassays obtained from Millipore as described previously (*21*). The HCCBP1MAG-58K panel was used to detect AFP, CA15-3, CA19-9, CEA, CA 125, HGF, Prolactin, and OPN; the HTMP1MAG-54K panel was used to detect TIMP-1. At the outset of the study, we had planned to use Follistatin and G-CSF as biomarkers, but analytical issues with assay specificity or reproducibility for these two markers was recognized to be inadequate after studying 630 participants, and these two markers were dropped after consultation with those responsible for study oversight. Detection assays were quantitated with the Bio-Rad Bio-Plex 200 platform. Protein biomarkers exceeding pre-specified thresholds (Table S2) were scored as positive. Protein biomarker data can be obtained from the European Genome-phenome Archive in the phenotype data section (EGAS00001004372).

Confirmation test for elevated proteins: The confirmation test was performed on a second blood sample obtained after the baseline test, except that only the protein biomarker(s) elevated above the pre-set thresholds (Table S2) were evaluated.

Note that in the 498 study controls, there was no "confirmation test", because no elevated proteins (or DNA mutations) were found in the baseline test in these 498 participants, as noted above.

Evaluation of DNA from FFPE sections of tumors

Amplification and sequencing were performed as described as in Tie et al (*49*) or as above with the exceptions that 2 ng of purified DNA was used as input for each well and two wells rather than 6 wells were employed. Because of the high amounts of DNA damage resulting from the fixation and embedding procedures required to prepare FFPE sections (*50*), only variants with MAF ≥5% were scored as mutations (Table S16).

Adverse events

The study protocol consisted of the blood test and a diagnostic PET-CT in individuals with a positive test. Adverse events related to the study (blood testing and diagnostic PET-CT) were classified based on the SIR classification (*51*).

Statistical analysis

Continuous variables are reported as means and standard deviations or median and interquartile ranges. Categorical variables are reported as proportions with 95% confidence intervals using a binomial distribution. Proportion tests were used to compare survey response rates. To analyze differences in claims data before and after enrollment, a McNemars' test was run to account for the dependent nature of the data. Data for the overall compliance of Geisinger patients with SOC screening was computed based on EMR data used at Geisinger to track adherence. Data were pulled from December 2018 – December 2019 and calculated on a per-month basis. We considered individuals adherent

if they had at least one month in that span of a year where they adhered. Only individuals who were eligible for SOC testing based on USPSTF guidelines were considered for this analysis (Figs. S1 and S8). All statistical analyses were done in R version 3.5.3.

Supplementary Tables

All tables are in Microsoft Excel Format.

Supplementary Figures

All figures are below.

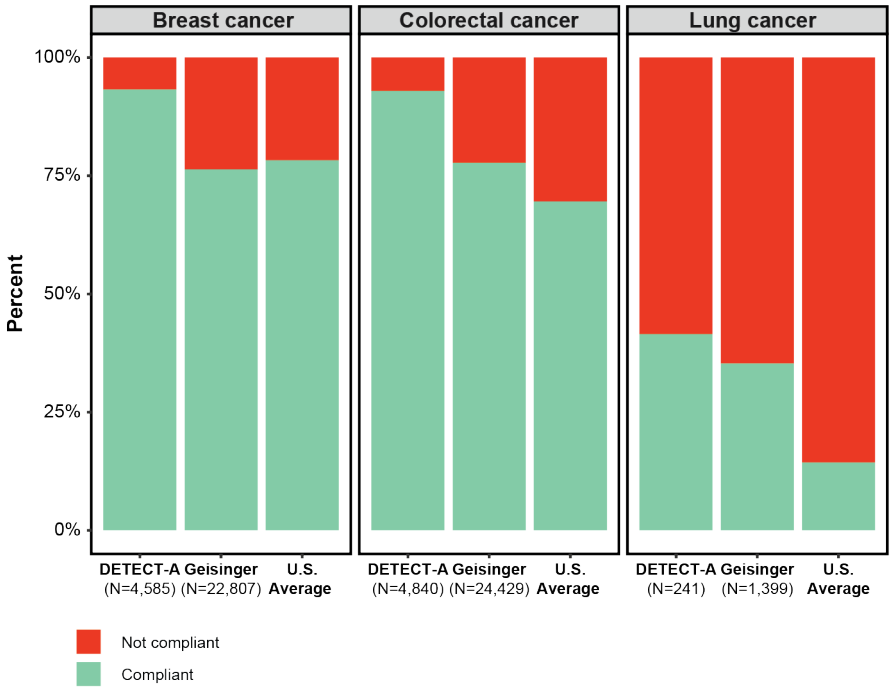

Fig. S1.

Standard-of-care screening adherence. Geisinger's overall adherence and DETECT-A adherence generally exceeded the U.S. average as measured by the CDC 2018 BRFSS survey (breast and colorectal cancers) (*52*) and Zahnd and Eberth (lung cancer) (*53*).

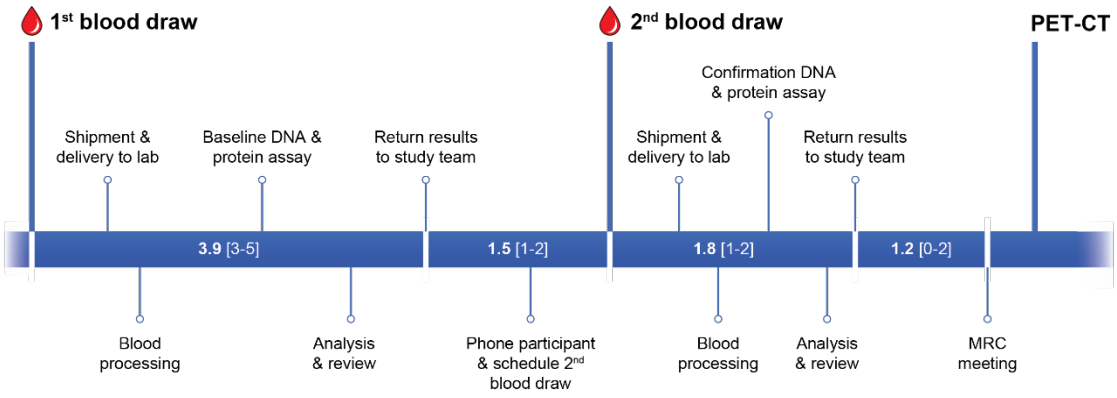

Fig. S2

Study timeline. As a result of the several safety measures incorporated into the protocol, results were not available to the MRC for several months following the first blood draw. The average duration of each workflow component is shown in months; brackets indicate the interquartile range.

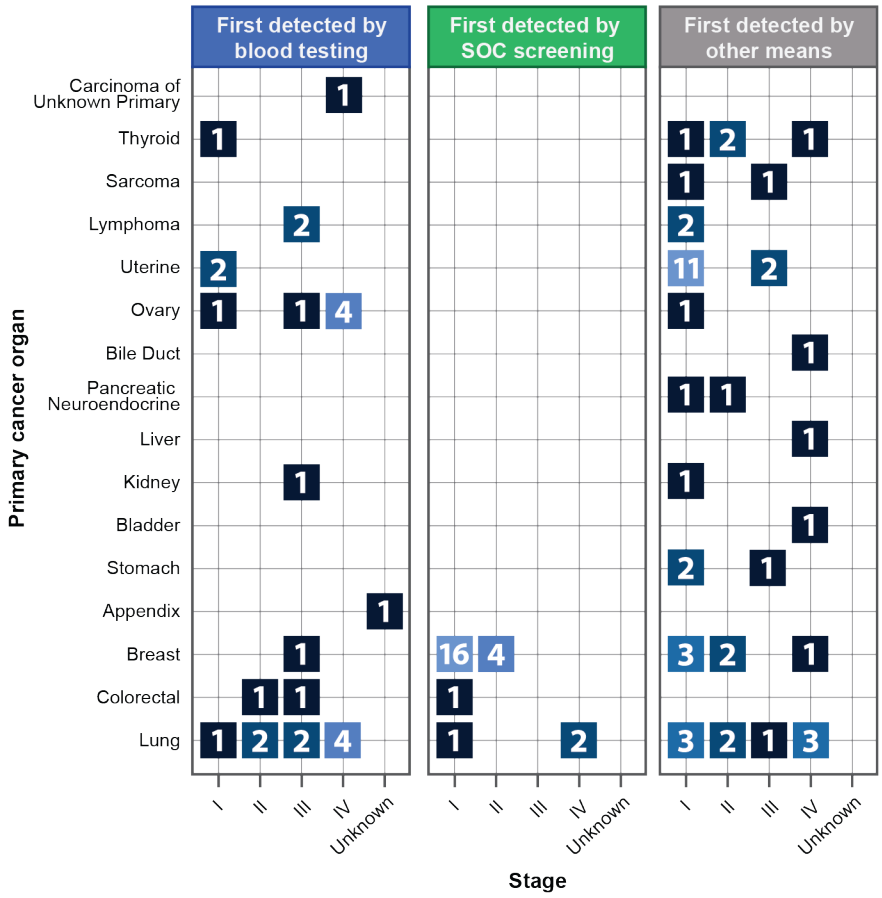

Fig. S3

Type, stage, and detection modality for cancers identified in the DETECT-A study. All cancers identified in the study during the 12-month post-enrollment period were stratified by how they were detected, by site of origin, then by stage. See Table 1 and table S6 for cancers first detected by blood testing and table S9 for all cancers identified in the study.

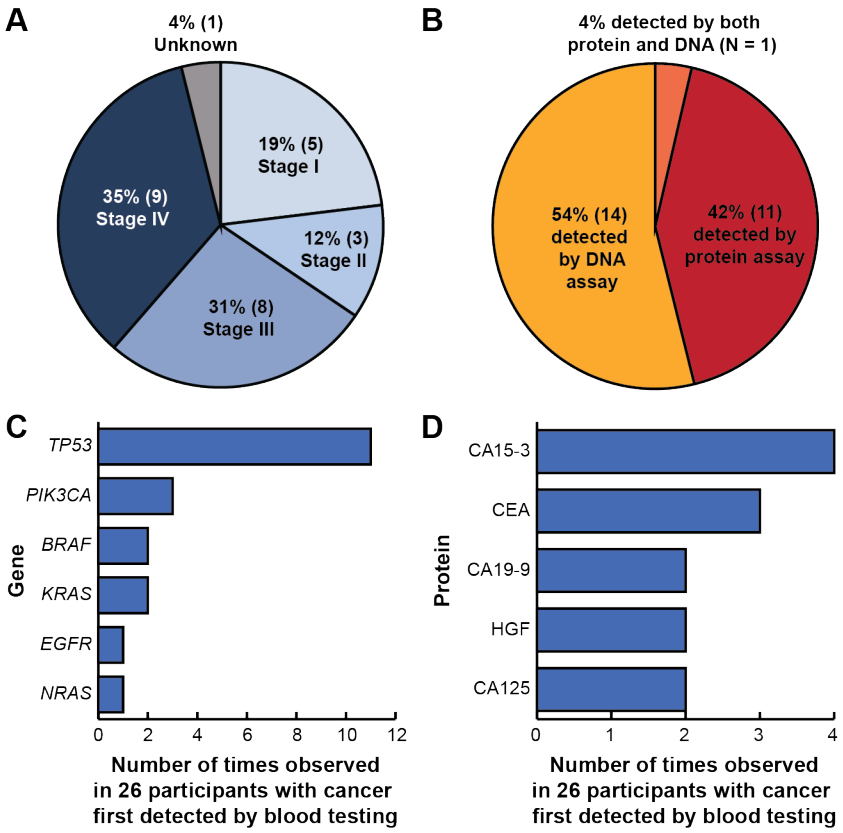

Fig. S4.

Cancer stages and type of analytes in cancers first detected by blood testing. (**A**) The majority of cancers were identified when they were localized (Stage I and II) or regional (Stage III). (**B**) Abnormal analyte detected by blood testing. (**C**, **D**) The most frequently mutated genes (C) and elevated proteins (D) are shown. Some patients had more than one mutation or more than one abnormal protein (detailed in Table 1 and table S6).

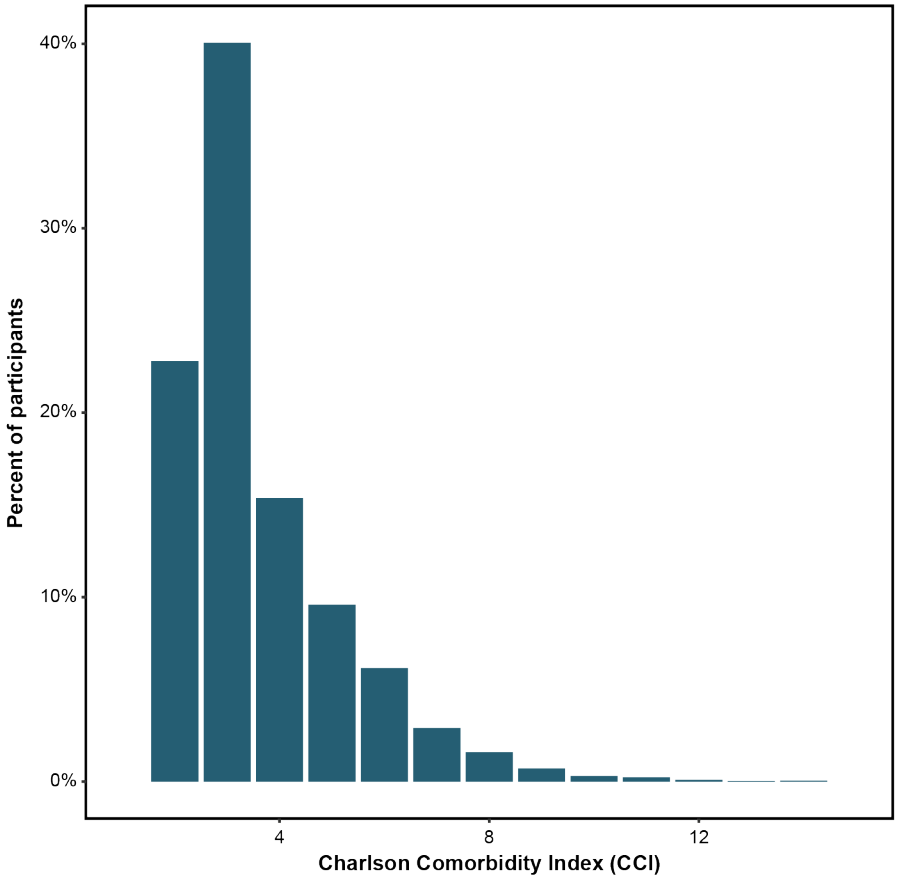

Fig. S5

Charlson Comorbidity Index (CCI) in DETECT-A participants. All participants had a CCI of 2 or higher and 4,336 out of 9,749 (45%) had one or more comorbid conditions as measured using the Charlson Comorbidity Index (*34*).

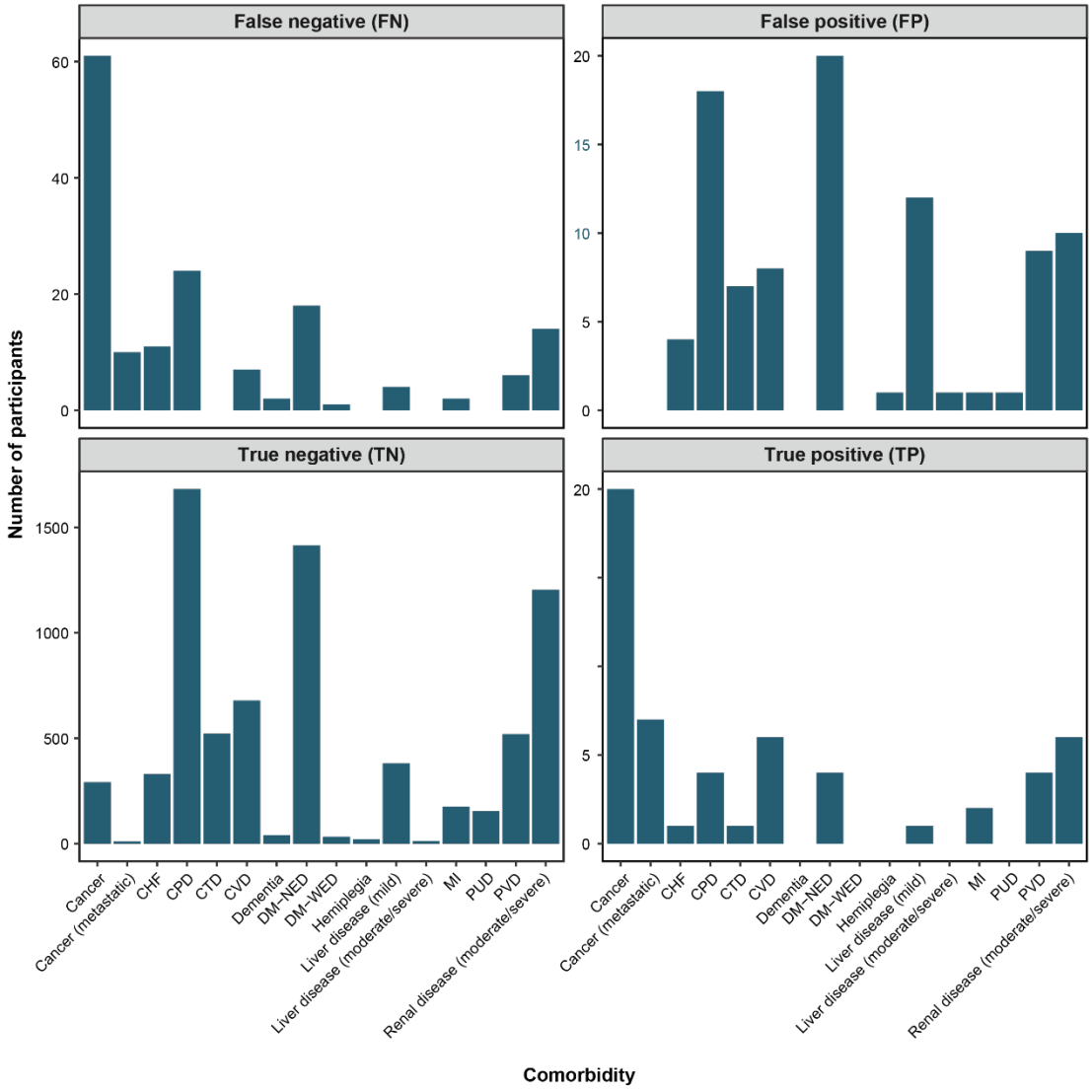

Fig. S6

Detailed breakdown of CCI by component and blood test result type. Comorbid condition include cancer (non-metastatic and metastatic), congestive heart failure (CHF), chronic pulmonary disease (CPD), connective tissue disease (CTD), cerebrovascular vascular disease (CVD), dementia, diabetes mellitus with no end-organ damage (DM-NED), diabetes mellitus with end-organ damage (DM-WED), hemiplegia, liver disease (mild and moderate/severe), myocardial infarct (MI), peptic ulcer disease (PUD), peripheral vascular disease (PVD), and renal disease (moderate/severe). All comorbidities were reported based on ICD9 and 10 codes and have not undergone chart review to confirm them.

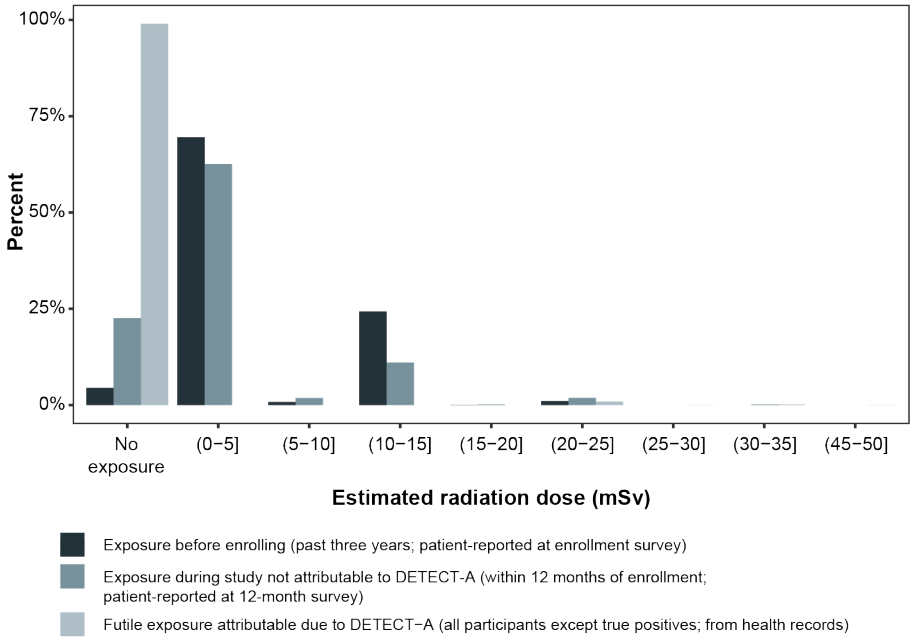

Fig. S7.

Futile radiation exposure attributable to DETECT-A compared to patient-reported exposure not attributable to DETECT-A. Estimated radiation dose (mSv) from futile diagnostic procedures in DETECT-A (largely PET-CT) compared to estimated exposure in participants. These exposures were reported by survey, either during the three years before enrollment (in all participants) or during the 12 months after enrollment (in the true negative participants). No participant received more than 50 mSv as a result of a positive DETECT-A blood test. See Table S14 for estimated radiation dose per diagnostic procedure and table S15 for additional data.

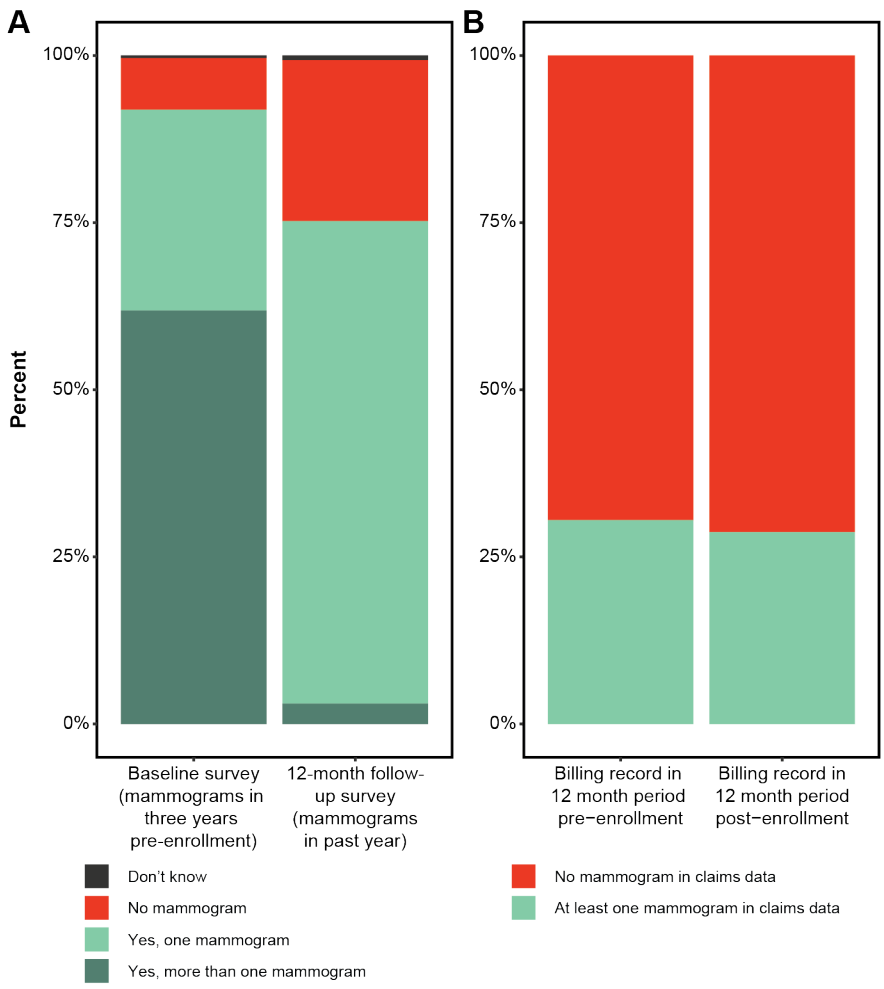

Fig. S8

Impact of blood testing on mammography screening rates. (**A**) Survey data on mammogram usage were available at enrollment (in 9,794 participants) and 12 months after enrollment (in 6,827 participants). The enrollment survey assessed mammogram usage in the three years prior to enrollment. The 12-month follow-up survey assessed mammogram usage in the 12 months between enrollment and the follow-up survey. (**B**) Mammogram screening rates were calculated in 3,295 participants with available claims data. Screening rates were compared between the 12-month period prior to enrollment and the 12-month period after enrollment to understand potential changes in screening rates.

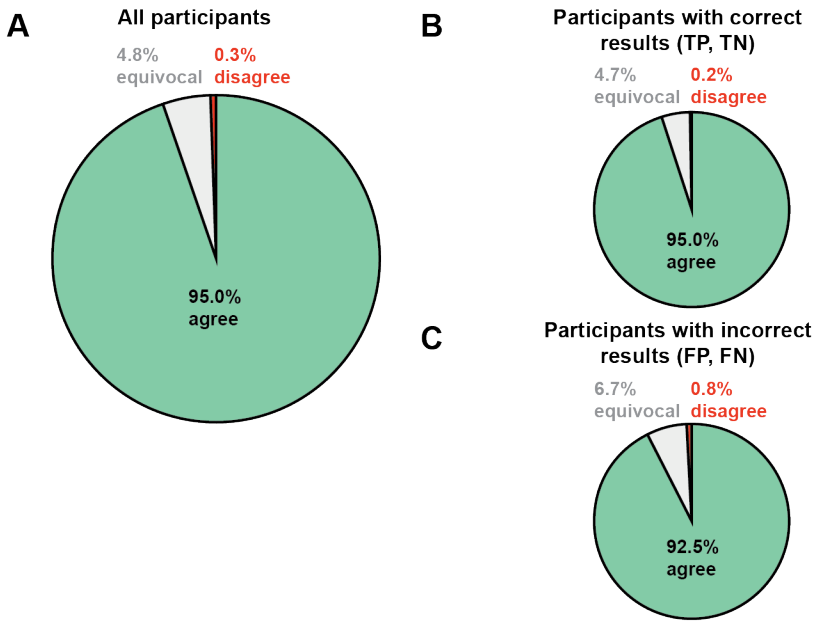

Fig. S9

Participant satisfaction. (**A**) Participants were asked to complete a survey at 12 months after enrollment and were asked if participating in the study was the right decision. Results were available from 6,262 participants. (**B**, **C**) Results were further stratified by whether participants received a correct DETECT-A blood test result (true positive or true negative; N = 6,142; B) or an incorrect DETECT-A blood test result (false positive or false negative; N = 120; C).

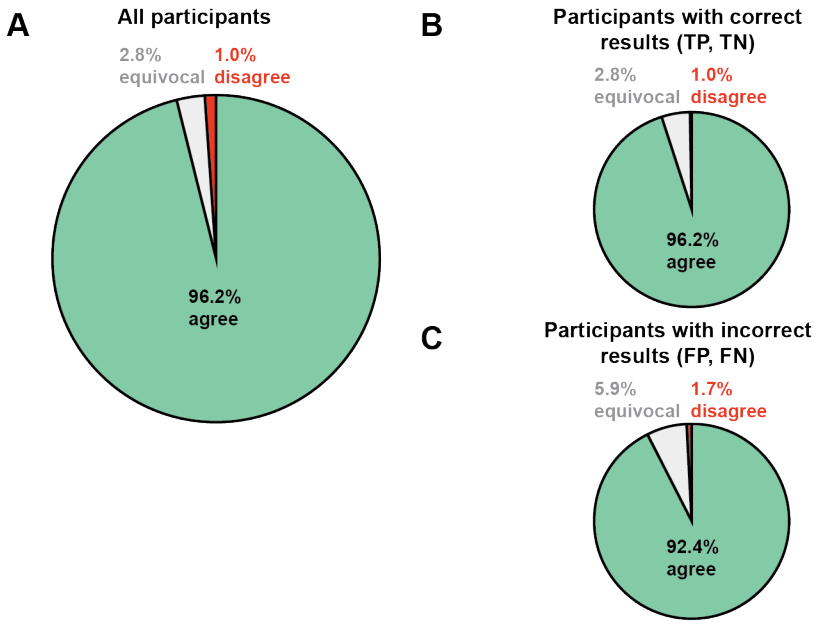

Fig. S10.

Participants who would participate in DETECT-A again. (**A**) Participants were asked to complete a survey 12 months after enrollment and were asked if they would participate in the DETECT-A study again. Results were available from 6,212 participants. (**B**, **C**) Results were further stratified by whether participants received a correct DETECT-A blood test result (true positive or true negative; N = 6,093; B) or an incorrect DETECT-A blood test result (false positive or false negative; N = 119; C).

References and Notes

1. R. L. Siegel, K. D. Miller, A. Jemal, Cancer statistics, 2020. *CA Cancer J. Clin.* **70**, 7–30 (2020). doi:10.3322/caac.21590 Medline

2. N. Howlader *et al*., Eds., SEER Cancer Statistics Review, 1975-2014, National Cancer Institute, Bethesda, MD (2017).

3. D. A. Ahlquist, Universal cancer screening: Revolutionary, rational, and realizable. *NPJ Precis Oncol* **2**, 23 (2018). doi:10.1038/s41698-018-0066-x Medline

4. J. R. Goldblum, L. W. Lamps, J. McKenney, J. L. Myers, *Surgical Pathology*. (Elsevier, 2018).

5. A. D. Singhi, E. J. Koay, S. T. Chari, A. Maitra, Early Detection of Pancreatic Cancer: Opportunities and Challenges. *Gastroenterology* **156**, 2024–2040 (2019). doi:10.1053/j.gastro.2019.01.259 Medline

6. T. André, A. de Gramont, D. Vernerey, B. Chibaudel, F. Bonnetain, A. Tijeras-Raballand, A. Scriva, T. Hickish, J. Tabernero, J. L. Van Laethem, M. Banzi, E. Maartense, E. Shmueli, G. U. Carlsson, W. Scheithauer, D. Papamichael, M. Möehler, S. Landolfi, P. Demetter, S. Colote, C. Tournigand, C. Louvet, A. Duval, J.-F. Fléjou, A. de Gramont, Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study. *J. Clin. Oncol.* **33**, 4176–4187 (2015). doi:10.1200/JCO.2015.63.4238 Medline

7. A. C. Huang, M. A. Postow, R. J. Orlowski, R. Mick, B. Bengsch, S. Manne, W. Xu, S. Harmon, J. R. Giles, B. Wenz, M. Adamow, D. Kuk, K. S. Panageas, C. Carrera, P. Wong, F. Quagliarello, B. Wubbenhorst, K. D'Andrea, K. E. Pauken, R. S. Herati, R. P. Staupe, J. M. Schenkel, S. McGettigan, S. Kothari, S. M. George, R. H. Vonderheide, R. K. Amaravadi, G. C. Karakousis, L. M. Schuchter, X. Xu, K. L. Nathanson, J. D. Wolchok, T. C. Gangadhar, E. J. Wherry, T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. *Nature* **545**, 60–65 (2017). doi:10.1038/nature22079 Medline

8. J. H. Park, I. Rivière, M. Gonen, X. Wang, B. Sénéchal, K. J. Curran, C. Sauter, Y. Wang, B. Santomasso, E. Mead, M. Roshal, P. Maslak, M. Davila, R. J. Brentjens, M. Sadelain, Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. *N. Engl. J. Med.* **378**, 449–459 (2018). doi:10.1056/NEJMoa1709919 Medline

9. H. Brenner, L. Jansen, A. Ulrich, J. Chang-Claude, M. Hoffmeister, Survival of patients with symptom- and screening-detected colorectal cancer. *Oncotarget* **7**, 44695–44704 (2016). doi:10.18632/oncotarget.9412 Medline

10. D. R. Aberle, A. M. Adams, C. D. Berg, W. C. Black, J. D. Clapp, R. M. Fagerstrom, I. F. Gareen, C. Gatsonis, P. M. Marcus, J. D. Sicks; National Lung Screening Trial Research Team, Reduced lung-cancer mortality with low-dose computed tomographic screening. *N. Engl. J. Med.* **365**, 395–409 (2011). doi:10.1056/NEJMoa1102873 Medline

11. L. Tabar, G. Fagerberg, H.-H. Chen, S. W. Duffy, C. R. Smart, A. Gad, R. A. Smith, Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial. *Cancer* **75**, 2507–2517 (1995). doi:10.1002/1097-0142(19950515)75:10<2507:AID-CNCR2820751017>3.0.CO;2-H Medline

12. K. K. Vesco, E. P. Whitlock, M. Eder, B. U. Burda, C. A. Senger, K. Lutz, Risk factors and other epidemiologic considerations for cervical cancer screening: A narrative review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* **155**, 698–705, W216 (2011). doi:10.7326/0003-4819-155-10-201111150-00377 Medline

13. J. S. Lin, M. A. Piper, L. A. Perdue, C. M. Rutter, E. M. Webber, E. O'Connor, N. Smith, E. P. Whitlock, Screening for Colorectal Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* **315**, 2576–2594 (2016). doi:10.1001/jama.2016.3332 Medline

14. P. S. Liang, C. L. Wheat, A. Abhat, A. T. Brenner, A. Fagerlin, R. A. Hayward, J. P. Thomas, S. Vijan, J. M. Inadomi, Adherence to Competing Strategies for Colorectal Cancer Screening Over 3 Years. *Am. J. Gastroenterol.* **111**, 105–114 (2016). doi:10.1038/ajg.2015.367 Medline

15. I. J. Hall, F. K. L. Tangka, S. A. Sabatino, T. D. Thompson, B. I. Graubard, N. Breen, Patterns and Trends in Cancer Screening in the United States. *Prev. Chronic Dis.* **15**, E97 (2018). doi:10.5888/pcd15.170465 Medline

16. S. Srivastava, E. J. Koay, A. D. Borowsky, A. M. De Marzo, S. Ghosh, P. D. Wagner, B. S. Kramer, Cancer overdiagnosis: A biological challenge and clinical dilemma. *Nat. Rev. Cancer* **19**, 349–358 (2019). doi:10.1038/s41568-019-0142-8 Medline

17. D. W. Cescon, S. V. Bratman, S. M. Chan, L. L. Siu, Circulating tumor DNA and liquid biopsy in oncology. *Nature Cancer*. 2020.

18. A. K. Mattox, C. Bettegowda, S. Zhou, N. Papadopoulos, K. W. Kinzler, B. Vogelstein, Applications of liquid biopsies for cancer. *Sci. Transl. Med.* **11**, eaay1984 (2019). doi:10.1126/scitranslmed.aay1984 Medline

19. M. F. Berger, E. R. Mardis, The emerging clinical relevance of genomics in cancer medicine. *Nat. Rev. Clin. Oncol.* **15**, 353–365 (2018). doi:10.1038/s41571-018-0002-6 Medline

20. L. A. Diaz Jr., A. Bardelli, Liquid biopsies: Genotyping circulating tumor DNA. *J. Clin. Oncol.* **32**, 579–586 (2014). doi:10.1200/JCO.2012.45.2011 Medline

21. J. D. Cohen, L. Li, Y. Wang, C. Thoburn, B. Afsari, L. Danilova, C. Douville, A. A. Javed, F. Wong, A. Mattox, R. H. Hruban, C. L. Wolfgang, M. G. Goggins, M. Dal Molin, T.-L. Wang, R. Roden, A. P. Klein, J. Ptak, L. Dobbyn, J. Schaefer, N. Silliman, M. Popoli, J. T. Vogelstein, J. D. Browne, R. E. Schoen, R. E. Brand, J. Tie, P. Gibbs, H.-L. Wong, A. S. Mansfield, J. Jen, S. M. Hanash, M. Falconi, P. J. Allen, S. Zhou, C. Bettegowda, L. A. Diaz Jr., C. Tomasetti, K. W. Kinzler, B. Vogelstein, A. M. Lennon, N. Papadopoulos, Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science* **359**, 926–930 (2018). doi:10.1126/science.aar3247 Medline

22. M. J. Divo, C. H. Martinez, D. M. Mannino, Ageing and the epidemiology of multimorbidity. *Eur. Respir. J.* **44**, 1055–1068 (2014). doi:10.1183/09031936.00059814 Medline

23. C. Bettegowda, M. Sausen, R. J. Leary, I. Kinde, Y. Wang, N. Agrawal, B. R. Bartlett, H. Wang, B. Luber, R. M. Alani, E. S. Antonarakis, N. S. Azad, A. Bardelli, H. Brem, J. L. Cameron, C. C. Lee, L. A. Fecher, G. L. Gallia, P. Gibbs, D. Le, R. L. Giuntoli, M. Goggins, M. D. Hogarty, M. Holdhoff, S.-M. Hong, Y. Jiao, H. H. Juhl, J. J. Kim, G. Siravegna, D. A. Laheru, C. Lauricella, M. Lim, E. J. Lipson, S. K. N. Marie, G. J. Netto, K. S. Oliner, A. Olivi, L. Olsson, G. J. Riggins, A. Sartore-Bianchi, K. Schmidt, M. Shih, S. M. Oba-Shinjo, S. Siena, D. Theodorescu, J. Tie, T. T. Harkins, S. Veronese, T.-L. Wang, J. D. Weingart, C. L. Wolfgang, L. D. Wood, D. Xing, R. H. Hruban, J. Wu, P. J. Allen, C. M. Schmidt, M. A. Choti, V. E. Velculescu, K. W. Kinzler, B. Vogelstein, N. Papadopoulos, L. A. Diaz Jr., Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci. Transl. Med.* **6**, 224ra24 (2014). doi:10.1126/scitranslmed.3007094 Medline

24. G. C. Wood, X. Chu, C. Manney, W. Strodel, A. Petrick, J. Gabrielsen, J. Seiler, D. Carey, G. Argyropoulos, P. Benotti, C. D. Still, G. S. Gerhard, An electronic health record-enabled obesity database. *BMC Med. Inform. Decis. Mak.* **12**, 45 (2012). doi:10.1186/1472-6947-12-45 Medline

25. E. Shumilov, J. Flach, T. Pabst, M. Fiedler, A. Angelillo-Scherrer, L. Trümper, R. Joncourt, A. Kohlmann, U. Bacher, Genetic alterations crossing the borders of distinct hematopoetic lineages and solid tumors: Diagnostic challenges in the era of high-throughput sequencing in hemato-oncology. *Crit. Rev. Oncol. Hematol.* **126**, 64–79 (2018). doi:10.1016/j.critrevonc.2018.03.020 Medline

26. K. C. A. Chan, J. K. S. Woo, A. King, B. C. Y. Zee, W. K. J. Lam, S. L. Chan, S. W. I. Chu, C. Mak, I. O. L. Tse, S. Y. M. Leung, G. Chan, E. P. Hui, B. B. Y. Ma, R. W. K. Chiu, S.-F. Leung, A. C. van Hasselt, A. T. C. Chan, Y. M. D. Lo, Analysis of Plasma Epstein-Barr Virus DNA to Screen for Nasopharyngeal Cancer. *N. Engl. J. Med.* **377**, 513–522 (2017). doi:10.1056/NEJMoa1701717 Medline

27. J. Czernin, M. Allen-Auerbach, D. Nathanson, K. Herrmann, PET/CT in Oncology: Current Status and Perspectives. *Curr. Radiol. Rep.* **1**, 177–190 (2013). doi:10.1007/s40134-013-0016-x Medline

28. L. Schrevens, N. Lorent, C. Dooms, J. Vansteenkiste, The role of PET scan in diagnosis, staging, and management of non-small cell lung cancer. *Oncologist* **9**, 633–643 (2004). doi:10.1634/theoncologist.9-6-633 Medline

29. H. Schöder, M. Gönen, Screening for cancer with PET and PET/CT: Potential and limitations. *J. Nucl. Med.* **48** (Suppl 1), 4S–18S (2007). Medline

30. I. Sachelarie, K. Kerr, M. Ghesani, R. H. Blum, Integrated PET-CT: Evidence-based review of oncology indications. *Oncology* **19**, 481–490, discussion 490–492, 495–496 (2005). Medline

31. C. Douville, J. D. Cohen, J. Ptak, M. Popoli, J. Schaefer, N. Silliman, L. Dobbyn, R. E. Schoen, J. Tie, P. Gibbs, M. Goggins, C. L. Wolfgang, T.-L. Wang, I.-M. Shih,

R. Karchin, A. M. Lennon, R. H. Hruban, C. Tomasetti, C. Bettegowda, K. W. Kinzler, N. Papadopoulos, B. Vogelstein, Assessing aneuploidy with repetitive element sequencing. *Proc. Natl. Acad. Sci. U.S.A.* **117**, 4858–4863 (2020). doi:10.1073/pnas.1910041117 Medline

32. I. Kinde, J. Wu, N. Papadopoulos, K. W. Kinzler, B. Vogelstein, Detection and quantification of rare mutations with massively parallel sequencing. *Proc. Natl. Acad. Sci. U.S.A.* **108**, 9530–9535 (2011). doi:10.1073/pnas.1105422108 Medline

33. K. Tamakoshi, F. Kikkawa, K. Shibata, K. Tomoda, N. H. Obata, F. Wakahara, Y. Tokuhashi, H. Ishikawa, M. Kawai, Y. Tomoda, Clinical value of CA125, CA19-9, CEA, CA72-4, and TPA in borderline ovarian tumor. *Gynecol. Oncol.* **62**, 67–72 (1996). doi:10.1006/gyno.1996.0191 Medline

34. M. E. Charlson, P. Pompei, K. L. Ales, C. R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic Dis.* **40**, 373–383 (1987). doi:10.1016/0021-9681(87)90171-8 Medline

35. J. C. Brehaut, A. M. O'Connor, T. J. Wood, T. F. Hack, L. Siminoff, E. Gordon, D. Feldman-Stewart, Validation of a decision regret scale. *Med. Decis. Making* **23**, 281–292 (2003). doi:10.1177/0272989X03256005 Medline

36. M. C. Liu, G. R. Oxnard, E. A. Klein, C. Swanton, M. V. Seiden, S. R. Cummings, F. Absalan, G. Alexander, B. Allen, H. Amini, A. M. Aravanis, S. Bagaria, L. Bazargan, J. F. Beausang, J. Berman, C. Betts, A. Blocker, J. Bredno, R. Calef, G. Cann, J. Carter, C. Chang, H. Chawla, X. Chen, T. C. Chien, D. Civello, K. Davydov, V. Demas, M. Desai, Z. Dong, S. Fayzullina, A. P. Fields, D. Filippova, P. Freese, E. T. Fung, S. Gnerre, S. Gross, M. Halks-Miller, M. P. Hall, A.-R. Hartman, C. Hou, E. Hubbell, N. Hunkapiller, K. Jagadeesh, A. Jamshidi, R. Jiang, B. Jung, T. H. Kim, R. D. Klausner, K. N. Kurtzman, M. Lee, W. Lin, J. Lipson, H. Liu, Q. Liu, M. Lopatin, T. Maddala, M. C. Maher, C. Melton, A. Mich, S. Nautiyal, J. Newman, J. Newman, V. Nicula, C. Nicolaou, O. Nikolic, W. Pan, S. Patel, S. A. Prins, R. Rava, N. Ronaghi, O. Sakarya, R. V. Satya, J. Schellenberger, E. Scott, A. J. Sehnert, R. Shaknovich, A. Shanmugam, K. C. Shashidhar, L. Shen, A. Shenoy, S. Shojaee, P. Singh, K. K. Steffen, S. Tang, J. M. Toung, A. Valouev, O. Venn, R. T. Williams, T. Wu, H. H. Xu, C. Yakym, X. Yang, J. Yecies, A. S. Yip, J. Youngren, J. Yue, J. Zhang, L. Zhang, L. Q. Zhang, N. Zhang, C. Curtis, D. A. Berry, Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann. Oncol.* (2020). doi:10.1016/j.annonc.2020.02.011

37. M. W. Snyder, M. Kircher, A. J. Hill, R. M. Daza, J. Shendure, Cell-free DNA Comprises an In Vivo Nucleosome Footprint that Informs Its Tissues-Of-Origin. *Cell* **164**, 57–68 (2016). doi:10.1016/j.cell.2015.11.050 Medline

38. S. Cristiano, A. Leal, J. Phallen, J. Fiksel, V. Adleff, D. C. Bruhm, S. Ø. Jensen, J. E. Medina, C. Hruban, J. R. White, D. N. Palsgrove, N. Niknafs, V. Anagnostou, P. Forde, J. Naidoo, K. Marrone, J. Brahmer, B. D. Woodward, H. Husain, K. L. van Rooijen, M. W. Ørntoft, A. H. Madsen, C. J. H. van de Velde, M. Verheij, A.

Cats, C. J. A. Punt, G. R. Vink, N. C. T. van Grieken, M. Koopman, R. J. A. Fijneman, J. S. Johansen, H. J. Nielsen, G. A. Meijer, C. L. Andersen, R. B. Scharpf, V. E. Velculescu, Genome-wide cell-free DNA fragmentation in patients with cancer. *Nature* **570**, 385–389 (2019). doi:10.1038/s41586-019-1272-6 Medline

39. P. Razavi, B. T. Li, D. N. Brown, B. Jung, E. Hubbell, R. Shen, W. Abida, K. Juluru, I. De Bruijn, C. Hou, O. Venn, R. Lim, A. Anand, T. Maddala, S. Gnerre, R. Vijaya Satya, Q. Liu, L. Shen, N. Eattock, J. Yue, A. W. Blocker, M. Lee, A. Sehnert, H. Xu, M. P. Hall, A. Santiago-Zayas, W. F. Novotny, J. M. Isbell, V. W. Rusch, G. Plitas, A. S. Heerdt, M. Ladanyi, D. M. Hyman, D. R. Jones, M. Morrow, G. J. Riely, H. I. Scher, C. M. Rudin, M. E. Robson, L. A. Diaz Jr., D. B. Solit, A. M. Aravanis, J. S. Reis-Filho, High-intensity sequencing reveals the sources of plasma circulating cell-free DNA variants. *Nat. Med.* **25**, 1928–1937 (2019). doi:10.1038/s41591-019-0652-7 Medline

40. R. Lehmann-Werman, D. Neiman, H. Zemmour, J. Moss, J. Magenheim, A. Vaknin-Dembinsky, S. Rubertsson, B. Nellgård, K. Blennow, H. Zetterberg, K. Spalding, M. J. Haller, C. H. Wasserfall, D. A. Schatz, C. J. Greenbaum, C. Dorrell, M. Grompe, A. Zick, A. Hubert, M. Maoz, V. Fendrich, D. K. Bartsch, T. Golan, S. A. Ben Sasson, G. Zamir, A. Razin, H. Cedar, A. M. J. Shapiro, B. Glaser, R. Shemer, Y. Dor, Identification of tissue-specific cell death using methylation patterns of circulating DNA. *Proc. Natl. Acad. Sci. U.S.A.* **113**, E1826–E1834 (2016). doi:10.1073/pnas.1519286113 Medline

41. P. Jiang, K. Sun, W. Peng, S. H. Cheng, M. Ni, P. C. Yeung, M. M. S. Heung, T. Xie, H. Shang, Z. Zhou, R. W. Y. Chan, J. Wong, V. W. S. Wong, L. C. Poon, T. Y. Leung, W. K. J. Lam, J. Y. K. Chan, H. L. Y. Chan, K. C. A. Chan, R. W. K. Chiu, Y. M. D. Lo, Plasma DNA End-Motif Profiling as a Fragmentomic Marker in Cancer, Pregnancy, and Transplantation. *Cancer Discov.* CD-19-0622 (2020). doi:10.1158/2159-8290.CD-19-0622 Medline

42. F. Diehl, M. Li, D. Dressman, Y. He, D. Shen, S. Szabo, L. A. Diaz Jr., S. N. Goodman, K. A. David, H. Juhl, K. W. Kinzler, B. Vogelstein, Detection and quantification of mutations in the plasma of patients with colorectal tumors. *Proc. Natl. Acad. Sci. U.S.A.* **102**, 16368–16373 (2005). doi:10.1073/pnas.0507904102 Medline

43. F. Mouliere, D. Chandrananda, A. M. Piskorz, E. K. Moore, J. Morris, L. B. Ahlborn, R. Mair, T. Goranova, F. Marass, K. Heider, J. C. M. Wan, A. Supernat, I. Hudecova, I. Gounaris, S. Ros, M. Jimenez-Linan, J. Garcia-Corbacho, K. Patel, O. Østrup, S. Murphy, M. D. Eldridge, D. Gale, G. D. Stewart, J. Burge, W. N. Cooper, M. S. van der Heijden, C. E. Massie, C. Watts, P. Corrie, S. Pacey, K. M. Brindle, R. D. Baird, M. Mau-Sørensen, C. A. Parkinson, C. G. Smith, J. D. Brenton, N. Rosenfeld, Enhanced detection of circulating tumor DNA by fragment size analysis. *Sci. Transl. Med.* **10**, eaat4921 (2018). doi:10.1126/scitranslmed.aat4921 Medline

44. X. Hao, H. Luo, M. Krawczyk, W. Wei, W. Wang, J. Wang, K. Flagg, J. Hou, H. Zhang, S. Yi, M. Jafari, D. Lin, C. Chung, B. A. Caughey, G. Li, D. Dhar, W. Shi,

L. Zheng, R. Hou, J. Zhu, L. Zhao, X. Fu, E. Zhang, C. Zhang, J.-K. Zhu, M. Karin, R.-H. Xu, K. Zhang, DNA methylation markers for diagnosis and prognosis of common cancers. *Proc. Natl. Acad. Sci. U.S.A.* **114**, 7414–7419 (2017). doi:10.1073/pnas.1703577114 Medline

45. World Health Organization, International Agency for Research on Cancer, *WHO Classification of Tumours of the Digestive System*, F. T. Bosman *et al*., Eds., World Health Organization Classification of Tumours, vol. 3 (International Agency for Research on Cancer, Lyon, ed. 4, 2010).

46. M. B. Amin, F. L. Greene, S. B. Edge, C. C. Compton, J. E. Gershenwald, R. K. Brookland, L. Meyer, D. M. Gress, D. R. Byrd, D. P. Winchester, The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J. Clin.* **67**, 93–99 (2017). doi:10.3322/caac.21388 Medline

47. A. Rohatiner, F. d'Amore, B. Coiffier, D. Crowther, M. Gospodarowicz, P. Isaacson, T. A. Lister, A. Norton, P. Salem, M. Shipp, R. Somers, Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. *Ann. Oncol.* **5**, 397–400 (1994). doi:10.1093/oxfordjournals.annonc.a058869 Medline

48. S. A. Forbes, D. Beare, H. Boutselakis, S. Bamford, N. Bindal, J. Tate, C. G. Cole, S. Ward, E. Dawson, L. Ponting, R. Stefancsik, B. Harsha, C. Y. Kok, M. Jia, H. Jubb, Z. Sondka, S. Thompson, T. De, P. J. Campbell, COSMIC: Somatic cancer genetics at high-resolution. *Nucleic Acids Res.* **45**, D777–D783 (2017). doi:10.1093/nar/gkw1121 Medline

49. J. Tie, Y. Wang, C. Tomasetti, L. Li, S. Springer, I. Kinde, N. Silliman, M. Tacey, H.-L. Wong, M. Christie, S. Kosmider, I. Skinner, R. Wong, M. Steel, B. Tran, J. Desai, I. Jones, A. Haydon, T. Hayes, T. J. Price, R. L. Strausberg, L. A. Diaz Jr., N. Papadopoulos, K. W. Kinzler, B. Vogelstein, P. Gibbs, Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. *Sci. Transl. Med.* **8**, 346ra92 (2016). doi:10.1126/scitranslmed.aaf6219 Medline

50. H. Do, A. Dobrovic, Sequence artifacts in DNA from formalin-fixed tissues: Causes and strategies for minimization. *Clin. Chem.* **61**, 64–71 (2015). doi:10.1373/clinchem.2014.223040 Medline

51. D. Sacks, T. E. McClenny, J. F. Cardella, C. A. Lewis, Society of Interventional Radiology clinical practice guidelines. *J. Vasc. Interv. Radiol.* **14**, S199–S202 (2003). doi:10.1097/01.RVI.0000094584.83406.3e Medline

52. CDC, *Behavioral Risk Factor Surveillance System Survey Data* (U.S. Department of Health and Human Services, Center for Disease Control and Prevention, Atlanta, GA, 2018).

53. W. E. Zahnd, J. M. Eberth, Lung Cancer Screening Utilization: A Behavioral Risk Factor Surveillance System Analysis. *Am. J. Prev. Med.* **57**, 250–255 (2019). doi:10.1016/j.amepre.2019.03.015 Medline

54. L. L. Humphrey, M. Deffebach, M. Pappas, C. Baumann, K. Artis, J. P. Mitchell, B. Zakher, R. Fu, C. G. Slatore, Screening for lung cancer with low-dose computed tomography: A systematic review to update the US Preventive services task force recommendation. *Ann. Intern. Med.* **159**, 411–420 (2013). doi:10.7326/0003-4819-159-6-201309170-00690 Medline