Evidence-based Practice Center Systematic Review Protocol

Project Title: ***Blood-based Tests for Multiple Cancer Screening: A Systematic Review***

I. Background and Objectives of the Review

Blood-based tests used in asymptomatic people offer a seemingly simple and potentially transformative solution for cancer screening. Further, some have suggested these tests have the potential to reduce racial disparities in cancer diagnosis and outcomes by increasing access to screening and reducing variability in quality and accuracy of existing screening tests received in minoritized communities.[1] Commercial interest in such tests is increasing dramatically and in 2021, the U.S. House of Representatives introduced the Medicare Multi-Cancer Early Detection Screening Coverage Act,[2] which seeks to mandate Centers for Medicare & Medicaid Services (CMS) coverage for multicancer detection tests approved by the U.S. Food and Drug Administration (FDA). However, the simplicity of a single blood draw to screen for many cancers, an attractive feature to both patients and clinicians, belies the extraordinary complexity underlying these tests. Besides the obvious technical intricacies with the assay itself, which may involve next-generation nucleic acid sequencing, methylation analysis, and complex artificial intelligence (AI) algorithms to analyze numerous and varied types of analytes (e.g., cell-free DNA, proteins, metabolites), and the meandering diagnostic pathways that might follow a positive signal on these tests, the enormous policy and downstream cost implications that could occur from widespread adoption of such tests demand a robust synthesis of their clinical benefits, harms, and costs.

Clinicians, patients, and payers need robust evidence about the clinical utility of blood-based tests used in screening for multiple cancers. Unlike treatment, where all who engage have the potential to benefit from quality-of-life improvements, relief of symptoms, prevention of disease progression, or prolongation of life, the evaluation of screening interventions requires precise attention to harms. Many people typically have to be screened for a few to benefit, yet all who engage in screening have the potential to be harmed because of false-positive tests requiring expensive and/or invasive diagnostic evaluations, false-negative tests that offer unwarranted reassurance that could foster risky health behaviors or avoidance of standard of care screening, and overdiagnosis (the identification of indolent cancers that would not otherwise become symptomatic, which can lead to anxiety and unnecessary treatments and all of the side effects, costs, and harms associated with treatment). Clinicians and patients need information about the clinical net benefit of such multiple cancer screening tests (MCSTs) to have conversations about screening with these tests and payers need information about the clinical net benefit to make evidence-informed coverage policies. Should MCSTs have a clinical net benefit, secondary questions include those related to cost-effectiveness, screening intervals, diagnostic pathways after a positive test, and equitable access related to screening, followup testing, and treatment.

Cancer biomarker technology and the analytes evaluated are continually evolving. Tests undergo refinement based on advances in the analysis of tumor- and non-tumor-derived nucleic acids (cell-free or from intact cells), identification of protein biomarkers, and the use of AI in a pan-omics approach.[3] Although many tests in development or currently available have evidence on analytic validity, evidence on clinical validity (i.e., accuracy outcomes such as specificity, sensitivity, positive and negative predictive value) varies, and many tests may never progress to be evaluated in rigorously designed trials to establish a clinical net benefit. Because the technology and analytes used as part of

MCSTs will continue to evolve and it will not be practical to evaluate each new generation of a test in a large trial to assess clinical net benefit, an evidentiary framework for extrapolating clinical validity data for new generations of tests will be needed to regularly reevaluate the impact of these tests on clinical net benefit.

Objectives of the Review

This systematic review will assess the accuracy, effectiveness, and harms of screening for multiple cancers with blood-based biomarkers. The intended audience includes clinicians, professional organizations such as guideline developers, and payers who determine coverage related to laboratory testing.

II. Key Questions

A preliminary analytic framework, key questions (KQs), and scope (**p**opulation, **i**ntervention, **c**omparators, **o**utcomes, **t**iming, **s**tudy design and **s**etting; **PICOTS**) were posted for public comment in February 2024. In addition, between April and May 2024, we interviewed four Key Informants who represented the following perspectives: patient/caregiver advocacy, primary care clinician, Medicaid payers, and cancer research funders. Key changes from the preliminary scope include the addition of non-cell-free DNA-based tests to the scope and the addition of KQs, outcomes, and study designs related to screening test accuracy. Further, blood-based tests developed for single-cancer screening were removed from the scope. Although questions related to equitable implementation and access to MCSTs were identified as important considerations, it is critical to first establish clinical utility for these tests, and we believe questions related to implementation are premature for this topic area. This review will include 5 KQs:

Key Questions
KQ 1: What is the effectiveness of screening with blood-based multicancer screening tests (MCST) on cancer-specific mortality and all-cause mortality? **KQ 2a:** What is the effectiveness of screening with MCSTs on the cumulative detection of cancer overall and by cancer type? **KQ 2b:** What is the effectiveness of screening with MCSTs on the cumulative detection of late-stage cancer (i.e., stage shift) overall and by cancer type? **KQ 3:** What is the accuracy of MCSTs for detection of cancer and does accuracy vary by cancer type or stage? **KQ 4:** What are the harms of screening with MCSTs? **KQ 5:** What are the harms of the evaluation and additional testing following a positive MCST or with surveillance following a negative evaluation after a positive MCST?

For the above KQs, the following PICOTS inclusion/exclusion criteria apply; detailed criteria organized by KQ and PICOTS are in Table 1.

- **Population(s):**
  - With the exception of KQ 3, individuals 18 years of age or older without active cancer or a history of cancer.
- **Intervention:**
  - Blood-based cancer tests designed to detect at least two different types of cancer;

analytes include but are not limited to cell-free nucleic acids (DNA, RNA), proteins, small molecules, and metabolites. Tests designed for single-cancer detection or those based on tissue, urine, or other fluids are excluded.

- **Comparator:**
  - Varies by KQ; no screening or usual cancer screening for KQs 1, 2, and 4; no comparator required for KQ 5; adequate reference standard test for KQ 3 (see Table 1).
- **Outcomes:**
  - Varies by KQ; cancer-specific mortality, overall and late-stage cancer detection, psychosocial distress, overdiagnosis, radiation exposure, adverse events from invasive diagnostic procedures, and patient costs; accuracy (for KQ 3).
- **Timing:**
  - At least 5 years for KQ 1; no restrictions on timing for the other KQs.
- **Setting:**
  - Outpatient settings; countries categorized as high or very high in the 2024 United Nations Human Development Report.
- **Study Designs:**
  - For KQs 1, 2, 4, and 5, randomized controlled trials (RCTs), controlled trials, and non-randomized studies of interventions (with some restrictions for KQs 1 and 2); test accuracy studies (KQ 3); case series, case reports, modeling studies, and reviews are excluded.

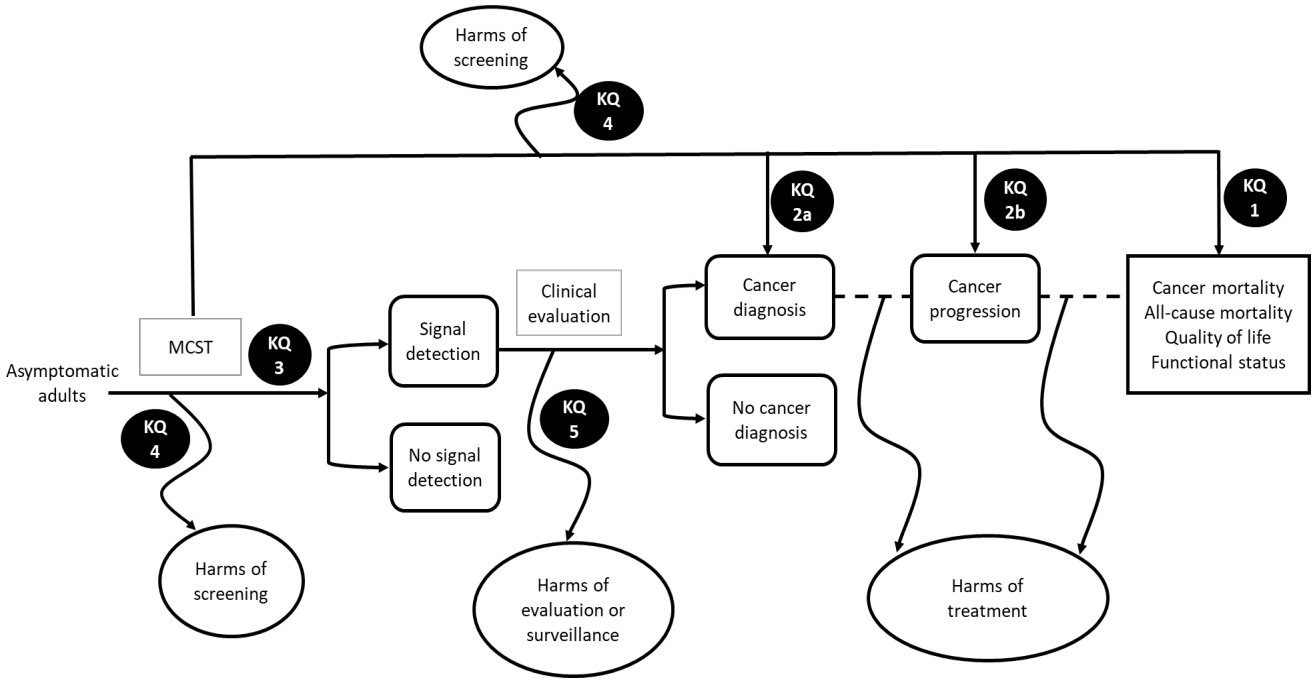
In addition to the KQs that will be systematically reviewed, we have specified several contextual questions (CQs). The purpose of these questions is to provide end users of the review with additional information to put the findings of the KQs into a larger context.

Contextual Questions
CQ 1: What is the relationship between reduction in late-stage cancer detection and reduction in cancer-specific mortality and does this relationship vary by cancer type? **CQ 2:** What is the impact on healthcare resource utilization of screening with MCSTs? **CQ 3:** What is the cost-effectiveness of screening with MCSTs in U.S. settings from societal and payer perspectives? **CQ4:** What are the out-of-pocket costs incurred by individuals who are screened for cancer with MCSTs?

III. Logic Model

An evidence synthesis on this topic within the coming year may not definitively answer the KQs needed to determine the clinical net benefit because the most relevant and rigorous studies will not be completed, but it will establish a current baseline of evidence and can focus on the adaptation of existing methods for evaluating cancer screening, which were developed based on *one test-one cancer* approaches, to an evidentiary framework that can accommodate *one test-many cancers*.[4] The analytic framework guiding this systematic review is depicted in Figure 1.

Figure 1. Analytic framework for blood-based tests for multiple cancer screening.



KQ = key question; MCST = multiple cancer screening test.

IV. Methods

We will follow the guidance from the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews[5] and Methods Guide for Medical Test Reviews.[6] We will supplement this with guidance from the Cochrane Collaboration and the GRADE Working Group, particularly with respect to methods for evaluating test accuracy.[7-9] We will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline and the PRISMA extension for Diagnostic Test Accuracy.[10]

Criteria for Inclusion/Exclusion of Studies in the Review: The criteria for inclusion and exclusion of studies for this systematic review are based on the KQs. These criteria were briefly described in the previous section and are detailed more fully in Table 1. We expect most of the eligible evidence to come from peer-reviewed published literature. We will include unpublished evidence only if enough details are available to make a judgment about eligibility based on our review's eligibility criteria and if enough methods are described to assess the study's risk of bias.

Table 1. Detailed inclusion and exclusion criteria for systematic review on blood-based tests for multiple cancer screening

Inclusion Criteria	Exclusion Criteria
Population	
KQs 1, 2, 4, 5 Asymptomatic people 18 years of age or older. **KQ 3:** People 18 years of age or older with either (1) biopsy-confirmed cancer or (2) who are asymptomatic without suspicion for cancer (i.e., "healthy" individuals).	**All KQ:** People younger than 18 years of age; other than human populations (e.g., animal or in vitro laboratory studies). **KQs 1, 2, 4, 5:** Adults with active cancer; adults undergoing evaluation for suspected cancer or cancer recurrence; adults with a history of invasive or hematologic cancer (other than nonmelanoma skin cancer) within the previous 3 years or a history of untreated cancer. **KQ 3:** Adults undergoing diagnostic evaluation for possible cancer or cancer recurrence.
Intervention	
KQs 1, 2, 3, 4 • Blood tests used for the screening of at least 2 different types of cancer; tests using any analytes with any technology are eligible. • Tests that were designed for cancer prognosis or surveillance in those with cancer or who have completed cancer treatment (i.e., evaluation for minimal residual disease) are eligible as long as they are being evaluated in an eligible population as defined above. • Blood tests used in combination with other tests such as imaging are eligible. • MCSTs used instead of or in addition to usual care screening are eligible. We define usual care screening as follows: mammography (breast), direct visualization such as colonoscopy or stool-based tests (colorectal), low-dose computed tomography (lung), cytology, human papilloma virus testing (cervical), and prostate specific antigen (prostate). **KQ 5:** Tests or procedures (imaging, tissue biopsy, blood, urine, or cerebrospinal fluid) to evaluate positive signal(s) resulting from an MCST or procedures used to surveil patients who have a negative evaluation after a positive MCST signal.	**KQs 1, 2, 3, 4:** Tests that are not blood based (e.g., tissue, saliva, urine, or other bodily fluids). **KQ 5:** Tests or interventions not performed as a result of a positive MCST.
Comparator	
KQs 1, 2, 4 • No screening test. • Usual care cancer screening as defined above. **KQ 3:** Tissue evaluation for confirmation of cancer; healthy asymptomatic status for controls. **KQ 5:** No comparator required.	**KQs 1, 2, 4:** No comparator group. **KQ 3:** No reference standard for comparison. **KQ 5:** Studies without a comparator group will not be excluded.

Inclusion Criteria	Exclusion Criteria
Outcomes	
KQ 1: Cancer mortality overall and by cancer type, all-cause mortality, quality of life, functional status. **KQ 2a:** Cumulative detection of cancer overall and by cancer type. **KQ 2b:** Cumulative detection of late-stage cancer overall and by cancer type (i.e., Stage III or IV or organ-specific definition of late stage); distribution of cancer stage at diagnosis (i.e., stage shift). **KQ 3:** Accuracy (sensitivity, false negatives, specificity, false positives, predictive value) by cancer type and by cancer stage. **KQ 4:** Psychosocial and emotional distress including anxiety and worry, false reassurance resulting in decrease in receipt of usual care screening or change in health behaviors associated with cancer (alcohol, tobacco, drug use, diet, physical activity), overdiagnosis, out-of-pocket patient costs, patient financial toxicity, and impact on insurability. **KQ 5:** Radiation exposure from imaging, harms from invasive procedures, other adverse effects from evaluation that occur after a positive MCST, or out-of-pocket patient costs, patient financial toxicity, and impact on insurability.	Outcomes not specifically indicated as included. Composite measures composed of both included and excluded outcomes will be included but considered only in sensitivity analyses.
Timing	
KQ 1: At least 5 years of followup. **KQs 2, 4, 5:** any timing. **KQ 3:** At least 1 year of followup for prediagnostic performance designs.[a] For diagnostic performance designs, controls must be considered cancer free at the time of the sample.	**KQ 1:** Studies with less than 5 years of followup.
Setting	
• Recruitment from outpatient clinical settings, including primary care or specialty care, community-based or public health settings, electoral rolls, or other population-based registries. • Countries with a United Nations Human Development Index of *high* or *very high*[11] **(Appendix A)**.	• Acute care settings, inpatient care settings. • Countries with a United Nations Human Development Index of less than *high*.
Study Design	
KQs 1, 2, 4, 5: Randomized controlled trials; controlled trials **KQs 1, 2:** Registered NRSIs with 1 or more eligible benefit outcomes listed on study registration.[b] **KQs 4, 5:** Unregistered NRSIs are also eligible. **KQ 3:** Studies that provide data related to test accuracy; both prediagnostic test performance and diagnostic test performance designs are eligible. However, only diagnostic performance designs conducted in external validation cohorts are eligible. Further, if results for multiple variations of the test are reported by authors, only results from the test version selected for future commercial use or for evaluation in future intervention studies will be eligible.	**For all KQ:** Modeling studies, case series, case reports, in vitro lab studies, studies designed to assess analytic validity, narrative reviews, systematic reviews (reviews will not be included but will be manually reviewed to identify primary research studies that the search may have missed). **KQs 1, 2:** Cohort studies that have not been registered or that report eligible outcomes that were not included in the study's registration[b] studies designed

Inclusion Criteria	Exclusion Criteria
	with a sample size that was not based on outcomes related to cancer detection or mortality. **KQ 3:** Accuracy results derived from discovery, development, internal validation, or split sample cohorts are not eligible because multiple analytes, technologies, or AI classifiers are being evaluated to develop the test and these results do not reflect the final state of the test that would be used in routine practice.
Language	
English.	Languages other than English.

[a] KQ 3 prediagnostic accuracy performance studies that use disease-free longitudinal followup as a reference standard should have a minimum of 1 year followup.[12]
[b] Refers to study registration in ClinicalTrials.gov database, or another study registry such as those included in the World Health Organization International Clinical Trials Registry Platform.

KQ = key question; MCST = multiple cancer screening test; NRSI = non-randomized study of interventions.

Literature Search Strategies to Identify Relevant Studies to Answer the Key Questions

Search Dates: 2013 to the present.

Electronic Bibliographic Databases: MEDLINE via PubMed; Cochrane Library.

Search Terms: We will use terms associated with screening, cancer, blood tests, biomarkers, accuracy outcomes, and costs/cost-effectiveness to identify relevant studies. We will use custom and validated PubMed filters to limit the searches to studies in human and adult populations, as well as to limit the search to eligible study designs (KQs only) and geographic location (CQ 2, 3, 4 only). We will divide the search into two strategies: the first search will cover KQs 1–5 and CQ 1, and the second search will cover costs/cost-effectiveness (CQs 2, 3, 4). We will limit the first search to articles published between 2013 and 2024, the period when tests for multicancer screening and detection were first developed. We will limit the second search for costs/cost-effectiveness to studies published from 2019–the present and conducted in the United States using the rationale that recent (last 5 years) healthcare utilization and cost studies from the United States will be most relevant to decision makers in the United States. The proposed search strategies for MEDLINE via PubMed are provided in **Appendix B**.

Gray Literature Searches: For identifying unpublished studies from the gray literature, we will search ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, the Centers for Disease Control and Prevention website, and the CMS website to identify completed and ongoing studies in this topic area. We will also check the websites of test manufacturers with commercially available MCSTs to identify relevant citations.

Quality Control and Supplementary Searching: The search strategy will be peer reviewed by an information specialist from another AHRQ Evidence-based Practice Center (EPC) using the 2015 Peer Review of Electronic Search Strategy Guideline Statement.[13] We will conduct quality checks of the search by evaluating whether known relevant citations are identified by the search and will

revise the search accordingly. We will examine studies cited in recent narrative reviews, editorials, and systematic reviews to identify relevant studies that may have been missed by our search. Additionally, we will employ the Similar articles PubMed feature to identify any missed relevant articles related to key PubMed citations retrieved by the above search approaches.

Update Searches: We will update all electronic searches while the draft report is posted for public comment to capture any new publications. We will use the same search strategies with an updated date.

Supplemental Evidence and Data for Systematic Reviews (SEADS): Supplemental evidence and data will be solicited from the public on the Effective Health Care website for 4 weeks following posting of the final version of this protocol. A notice will be published on the Federal Register to widely disseminate this opportunity to submit SEADS.

Process for Selecting Studies: EndNote (version 21) will be used to manage all retrieved citations. We will use DistillerSR (version 2024.3 release) to screen titles and abstracts and full-text articles identified from our electronic database searches, from supplementary searching, or that were suggested by public comments or peer reviewers.

Two reviewers will independently review titles and abstracts or study registry entries against the criteria specified in Table 1. Titles/abstracts excluded by two reviewers will not be considered further. Title/abstracts without sufficient information to determine exclusion or inclusion will be included for full-text review. Initially, two reviewers will be required to include a citation for full-text review and conflicts within the team will be adjudicated by a third reviewer. Once the team is sufficiently calibrated as evidence by minimal conflicts with respect to include/exclude decisions, citations included by one reviewer will move forward to full-text review without a second reviewer. We will use DistillerSR's AI feature to prioritize citations for screening. Once the highest remaining priority score falls below 0.20, one reviewer will be substituted with DistillerSR's AI function that has been trained based on the abstracts that have already been included and excluded by the team. Any discrepancies between the single reviewer and DistillerSR will be adjudicated by a second human reviewer.

Two reviewers will independently review full-text articles included at title/abstract review against the criteria specified in Table 1. Full-text articles excluded by two reviewers will not be considered further. Reviewers will record one reason for exclusion for documentation in the evidence report. Full-text articles included by two reviewers will be provisionally included. In the event of inclusion/exclusion conflicts between reviewers, we will adjudicate through discussion or by a third reviewer. The principal investigator will review all included studies to ensure they meet eligibility criteria for inclusion prior to data abstraction. During full-text review, we expect to find multiple articles reporting on the same study. We will consider the study our unit of analysis and all relevant companion articles will be identified and linked to an index article for the study for all subsequent steps in the review process.

Ongoing studies that appear to be eligible based on information in the study registration but for which no peer-reviewed publications can be identified will be cataloged in the report as relevant ongoing studies. If the study completion date has passed, we will contact the authors to inquire about approximate dates of publication.

Literature or data identified during the updated search or that is suggested by SEADS submissions, external peer reviewers, or public comment will be assessed using the same methods

as the initially identified records. New eligible studies identified from the update search will be included in the final report.

Data Abstraction and Data Management

We will abstract data from included studies using structured forms that we will design in DistillerSR. We will abstract data from companion articles onto the DistillerSR record of the index article. One reviewer will abstract the data into the forms and a second reviewer will check the data for accuracy. We will contact study authors if key data are missing or unclear in the article. Data abstracted will be compiled into detailed evidence tables for the evidence report and will be used for our synthesis of findings.

One data abstraction form will be tailored to abstract data relevant to KQ 1, 2, 4, and 5 studies. A second data abstraction form will be tailored to abstract data relevant to KQ 3 (test accuracy). The structured forms will include data elements relating to study identifiers and sponsors, study population, screening intervention including details related to the test technology, analytes used, and an indication of whether AI is involved in generating the test result; comparator intervention or test; and reported outcomes. Templates for the data elements we plan to abstract are in **Appendix C**. For trials and non-randomized studies of interventions (NRSIs), we will abstract outcomes for all reported time points for each study. However, our strength of evidence assessments may be limited to a time point that is common across studies.

Assessment of Methodological Risk of Bias of Individual Studies

We will use design-specific instruments for evaluating the risk of bias (ROB) of included studies. The RoB 2 instrument[14] will be used to evaluate RCTs, ROBINS-I[15] will be used to evaluate NRSIs, and QUADAS-2[16] will be used to evaluate test accuracy studies. For test accuracy studies, we will tailor the QUADAS-2 tool for both diagnostic performance and prediagnostic performance study designs.[12] We will report domain-specific ROB ratings and an overall ROB rating for each included study. In some cases, we may report an outcome-specific ROB rating within a study if we assess the outcome as having a different ROB rating than the overall study. Studies will not be excluded from the report based on ROB ratings. Two reviewers will independently assess the ROB for each study; disagreements on domain-level ratings will be adjudicated through discussion or a third reviewer.

Data Synthesis

We will summarize data narratively and in tabular formats organized by KQ and then by test analyte (e.g., cell-free DNA, protein biomarkers). If we have at least two similar studies with minimal clinical and methodologic heterogeneity that report the same outcome at reasonably similar time points, we will assess the feasibility of conducting quantitative synthesis.[17] Quantitative synthesis will be conducted with Stata (version 17.0). A priori subgroups of interest for KQs 1, 2, 4, and 5 include (1) residence in a medically underserved community including rural areas, (2) public, private, or no health insurance coverage, and (3) those defined by race or ethnicity. These subgroups are of interest because of differential access to followup diagnostic evaluation or treatment experienced by such persons, particularly in the United States. Other subgroups of interest include those defined by age (to examine whether the benefits and harms of MCSTs vary across the adult lifespan) and sex (to examine whether the benefits and harms of MCSTs vary in relationship to sex-specific cancers that may be detected). Finally, we will stratify findings for populations defined by average cancer risk versus higher cancer risk as defined by study authors. Populations defined as higher risk may include those with a strong family history of cancer, those with genetic mutations that predispose them to cancer, those with a history of childhood cancer, those with comorbidities associated with a higher cancer risk, and those

with a history of precancerous lesions.

For trials and NRSIs (KQs 1, 2, 4, 5), we will synthesize dichotomous outcomes (e.g., mortality, cancer cumulative detection) using relative (e.g., relative risk, hazard ratios, odds ratios) and absolute (e.g., absolute risk difference) effect measures. If quantitative synthesis is not possible, we will report the range of observed relative and absolute effects across studies. If quantitative synthesis is possible, we will report pooled relative effects and transform pooled relative effects into absolute effects (e.g., number of deaths averted per 1,000 people screened) using established methods.[18] Wherever possible, we will report cumulative cancer detection and mortality outcomes overall and by specific cancer type. For continuous outcomes, we will synthesize outcomes as mean differences or standardized mean differences. If outcomes are quantitatively synthesized, we will conduct a sensitivity analysis excluding studies we rate as high ROB to determine impact on pooled estimates. For outcomes that have studies reporting zero or rare events (<1% incidence), we will use appropriate methods for quantitative synthesis of rare events such as Mantel-Haenszel fixed-effect models or Peto odds ratio. We will assess statistical heterogeneity for any quantitative synthesis with the I^2 statistic and will use Cochrane methods guidance to interpret this statistic.[18, 19] If at least 10 studies are available for quantitative synthesis, we will consider assessing for reporting bias using Egger's test.[20]

For test accuracy studies (KQ 3), we will synthesize data on accuracy for each cancer type (e.g., breast, lung, pancreas) and stage. Further, we will stratify findings based on study design (diagnostic performance vs. prediagnostic performance). For quantitative syntheses, we will conduct sensitivity analyses excluding studies evaluated as high ROB to assess impact on pooled estimates. Because diagnostic performance studies use a case-control study design, any quantitative synthesis of sensitivity and false-negative outcomes will be conducted separately from synthesis of specificity and false-positive outcomes because these outcomes are not correlated as they are derived from different source populations.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes: We will use AHRQ Effective Health Care Program Guidance[5, 6, 21] to assess the SOE, supplemented by selected guidance from the GRADE working group.[22] We will grade outcomes from RCT bodies of evidence separately from outcomes from NRSI bodies of evidence. Based on input from our review's Key Informants and Technical Expert Panel, we will grade SOE for the outcomes detailed in Table 2 as they are critical or important to decision making around the use of MCSTs.

Table 2. Outcomes for strength of evidence assessment

KQ 1 (Direct benefits of screening)	KQ 2 (Direct benefits of screening)	KQ 3 (Accuracy)	KQ 4 (Harms of screening)	KQ 5 (Harms of evaluation/surveillance)
Cancer mortality, cancer mortality by type of cancer, all-cause mortality	Late-stage cancer detection overall and by cancer type, overall cancer detection and by type	None	Psychosocial distress, overdiagnosis; patient financial toxicity, impact on insurability, change in health behaviors associated with cancer, decrease in usual care screening	Adverse effects from invasive tests or procedures, radiation exposure, patient financial toxicity impact on insurability

KQ = key question.

We consider cancer-specific mortality outcomes as the most critical for decision making. This outcome is critical to understanding which cancers may have a mortality benefit from MCSTs and may offer information related to the impact of these tests on cancers with standards of care screening tests. We consider all-cause mortality an important outcome. All-cause mortality is less biased than cancer-specific mortality because it is not subject to misclassification bias based on how deaths are attributed. Further, it is easier to interpret than numerous different cancer mortality outcomes that may not be consistent with each other with respect to magnitude or direction of effect. However, we do not consider all-cause mortality as critical because the proportion of cancer deaths among all deaths is already low and reductions in cancer-specific mortality from screening are typically small resulting in minimal impact on all-cause mortality (estimated at 1% to 3%). Although this impact is minimal, across a population it may still have public health importance.[23, 24]

Cancer-specific mortality from randomized trials that minimize lead- and length-time bias is the most rigorous endpoint to assess benefit, but such trials require exceptionally large sample sizes and long durations. Late-stage detection 3 to 4 years after randomization is the primary endpoint of the NHS-Galleri Trial.[25] Late-stage detection is often touted as a proxy for cancer-specific mortality measured at later followup time points. This might be an acceptable proxy for ovarian cancer, where a 20% reduction in late-stage disease translates to a 13% reduction in mortality, but reduction in late-stage disease does not result in a similar magnitude of reduction in mortality for some cancers.[26] A recent metanalysis of 41 trials found that the detection of late-stage cancer was correlated to cancer-specific mortality for some cancers, but not for others.[27] The reasons why late-stage detection may not be a suitable proxy for cancer-specific mortality for some cancers is not entirely clear.[28] Whether cases shifted from late to early detection through screening have similar prognosis as cases detected early without screening is unknown; evidence from some cancers suggest these are biologically different tumors.[26] Earlier diagnosis of tumors with certain molecular signatures may have worse prognosis than site- and stage-matched tumors without such molecular signals. Thus, detecting such tumors early may not alter the clinical trajectory or reduce mortality. Such tumors might require far more aggressive therapy or new therapies for there to be a benefit from detection. In summary, extrapolation from late-stage detection to cancer-specific mortality may not be valid for some cancers.[27, 28]

Other outcomes that we have identified for SOE assessment within KQs 1, 2, 4, and 5 are important to decision making as they will allow an evaluation of the clinical net benefit of screening with MCSTs. We consider the accuracy outcomes associated with KQ 3 as less important to decision making as they do not directly inform an assessment of clinical net benefit. However, they may be useful for describing the landscape of current tests and determining which tests may be most promising for studying in future screening trials.

If no studies are identified that report an outcome selected for SOE grading, we will grade the outcome as *insufficient because of no evidence available*. Otherwise, we will assign an overall SOE grade for each comparison and outcome as *high*, *moderate*, *low*, or *insufficient* SOE. Suggested definitions of these grades are listed in Table 3.[21] Further, for KQs 1, 2, 4, and 5 we will include the direction of effect (i.e., decreased, increased, no effect) as part of the SOE assessment.

Table 3. Strength of evidence grades and definitions from AHRQ EPC Program.[21]

High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, which precludes us from reaching a conclusion.

AHRQ = Agency for Healthcare Research and Quality; EPC = Evidence-based Practice Center.

For each KQ 1, 2, 4, and 5 outcome and comparison, we will summarize the magnitude and direction of effect across the body of evidence. To grade the SOE, we will consider the domains of consistency, precision, directness, study limitations (i.e., ROB), and reporting bias. For NRSI bodies of evidence, we will also consider the additional domains of plausible confounding, strength of association, and dose-response association, which in this review's context might refer to the frequency of screening, timeliness of evaluation of a positive signal, or timeliness of starting treatment. We consider all of the outcomes we have specified for grading SOE as direct outcomes as they represent patient-centered health outcomes; but depending on how data is ascertained, they may be judged as indirect. For judging consistency in KQs 1, 2, 4, and 5, we will consider both the direction and magnitude of relative effects and evaluate whether confidence intervals around point estimates overlap and whether inconsistencies among estimates can be explained. For pooled estimates, we will also consider the I^2 statistic. For judging precision, we will focus on the confidence interval around the absolute effect using a minimally contextualized approach as described by the GRADE working group.[29] For KQ 1, we will consider the absolute effect in relationship to a minimally important difference (MID). For mortality outcomes, we will consider the MID to be 3 deaths averted per 10,000 patients screened. This absolute difference represents the smallest observed mortality benefit observed among cancer screening tests recommended by the U.S. Preventive Services Task Force.[30-33] We will use this threshold only to evaluate the precision of the mortality effect estimates as part of assessing SOE. Decision makers who use the findings from this review may consider using a different threshold for determining a clinical net benefit from screening, including weighing the mortality benefit observed against the harms of screening. For evaluating the precision of outcomes associated with KQs 2, 4, and 5, we will consider the absolute effect in relationship to a null effect because MIDs for cancer detection and harms from screening are not established. For KQs 1 and 2, we will assess reporting bias by comparing protocols to final reported methods and outcomes.

For KQ 3 (accuracy), for each major class of analyte (e.g., cell-free DNA, specific protein biomarker(s) and cancer type), we will summarize the accuracy outcomes with pooled estimates where possible, and when not possible, we will describe the range of estimates. We will not grade SOE for KQ 3 outcomes because we expect to find numerous studies evaluating various unique tests, with few tests evaluated by more than one study. Further, we expect most of the studies to report accuracy outcomes by cancer type, with data reported for between 2 to 10 different types of cancers. Because SOE must be applied across a body of evidence reporting

the same intervention (i.e., screening test) and outcome, this would require hundreds of different SOE assessments for an outcome that is the least important for decision making. Although this outcome is less important to clinical and policy decision making, it reflects the early stages of research on MCSTs, and a synthesis of accuracy is useful for decisions about future research investments in these tests.

Assessing Applicability: For KQs 1, 2, 4, and 5, we will consider factors such as characteristics of the patient population, for example, how patients were recruited, their underlying cancer risk or concern for cancer including other preventive health behaviors such as smoking, socioeconomic status, insurance status, and other healthcare system factors in determining applicability. For KQ 3, we will consider the pace of evolution and enhancements of the tests evaluated, whether tests are replicable or available outside of the studies where they have been evaluated, secular trends in diagnostic evaluations used for reference standards, and comparability of laboratory processes across in international settings.[34]

Assessing Conflict of Interest: We will use the Tool for Addressing Conflicts of Interest in Trials (TACIT) to systematically evaluate conflicts of interest (COI) in the study sponsors and investigators of included studies.[35] We will report the findings from our COI assessments using this tool in a report appendix. All studies will be included in the review regardless of any notable concerns for COI. However, we may conduct sensitivity analyses based on the presence of notable COI concerns.

Use of Artificial Intelligence and/or Machine Learning: We will use the AI prioritization feature available in the DistillerSR platform to prioritize titles and abstracts and full-text articles for screening. For title and abstract review, we will monitor DistillerSR's priority rankings and when the highest remaining citation rank score is less than 0.20, we will transition to a single human reviewer and use the AI feature as the second reviewer to screen the remaining titles and abstracts. We will use one or more large language models (LLMs) such as ChatGPT or Claude to extract data required for assessing COI with TACIT. We may use one or more LLMs as an editorial assistant to help improve the clarity or succinctness of text written by team members in the draft evidence report. All such uses will be reviewed by a team member to ensure that accuracy and intent is maintained.

V. References

1. Ward A, Van Nuys K, Lakdawalla D. Reducing Racial Disparities In Early Cancer Diagnosis With Blood-Based Tests. University of Southern California, Leonard D. Schaeffer Center for Health Policy and Economics; 2021. https://healthpolicy.usc.edu/wp-content/uploads/2022/07/Reducing_Racial_Disparities_In_Early_Cancer_Diagnosis_With_Blood-Based_Tests.pdf. Accessed on February 9, 2024.
2. 117th Congress (2021-22) Senate Finance Committee. Medicare Multi-Cancer Early Detection Screening Coverage Act of 2021. 2021.
3. Connal S, Cameron JM, Sala A, et al. Liquid biopsies: the future of cancer early detection. J Transl Med. 2023 Feb 11;21(1):118. doi: 10.1186/s12967-023-03960-8. PMID: 36774504.
4. Deverka PA, Douglas MP, Phillips KA. Multicancer screening tests: anticipating and addressing considerations for payer coverage and patient access. Health Aff (Millwood). 2022 Mar;41(3):383-9. doi: 10.1377/hlthaff.2021.01316. PMID: 35254936.
5. Effective Health Care Program. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality, Rockville, MD; 2022. https://effectivehealthcare.ahrq.gov/products/collections/cer-methods-guide. Accessed on May

21, 2024.
6. Effective Health Care Program. Methods guide for medical test reviews. Agency for Healthcare Research and Quality, Rockville, MD; 2012. https://effectivehealthcare.ahrq.gov/products/collections/methods-guidance-tests. Accessed on May 22, 2024.
7. Deeks J, Bossuyt P, Leeflang M, Takwoingi Y, eds. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Version 2.0: Cochrane; 2023. https://training.cochrane.org/handbook-diagnostic-test-accuracy/current. Accessed on July 2023.
8. Schünemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 21 part 1. Study design, risk of bias, and indirectness in rating the certainty across a body of evidence for test accuracy. J Clin Epidemiol. 2020;122:129-41.
9. Schünemann HJ, Mustafa RA, Brozek J, et al. GRADE guidelines: 22. The GRADE approach for tests and strategies—from test accuracy to patient-important outcomes and recommendations. J Clin Epidemiol. 2019;111:69-82.
10. Salameh J-P, Bossuyt PM, McGrath TA, et al. Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): explanation, elaboration, and checklist. BMJ. 2020;370.
11. UNDP (United Nations Development Programme). Human development report 2023-24: breaking the gridlock: reimagining cooperation in a polarized world. New York: 2024. https://hdr.undp.org/content/human-development-report-2023-24
12. Baker SG, Etzioni R. Prediagnostic evaluation of multicancer detection tests: Design and analysis considerations. J Natl Cancer Inst. 2024 Feb 28. doi: 10.1093/jnci/djae050. PMID: 38419575.
13. McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016 2016/07/01/;75:40-6. doi: https://doi.org/10.1016/j.jclinepi.2016.01.021.
14. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898. doi: 10.1136/bmj.l4898. PMID: 31462531.
15. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct 12;355:i4919. doi: 10.1136/bmj.i4919. PMID: 27733354.
16. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009. PMID: 22007046.
17. Morton SC, Murad MH, O'Connor E, et al. AHRQ Methods for Effective Health Care Quantitative Synthesis—An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
18. Deeks J, Higgins J, Altman D. Chapter 10: Analysing data and undertaking meta-analyses. In Cochrane Handbook for Systematic Reviews of Interventions version 6.4. Cochrane. 2023. Available from: https://training.cochrane.org/handbook.
19. Lin L. Comparison of four heterogeneity measures for meta-analysis. J Eval Clin Pract. 2020;26(1):376-84.
20. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629-34. doi: 10.1136/bmj.315.7109.629. PMID: 9310563.

21. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol. 2015 Nov;68(11):1312-24. doi: 10.1016/j.jclinepi.2014.11.023. PMID: 25721570.
22. GRADE Working Group. Welcome to the GRADE working group. 2024. https://www.gradeworkinggroup.org/. Accessed on May 29, 2024.
23. Bretthauer M, Wieszczy P, Løberg M, et al. Estimated Lifetime Gained With Cancer Screening Tests: A Meta-Analysis of Randomized Clinical Trials. JAMA Intern Med. 2023 Nov 1;183(11):1196-203. doi: 10.1001/jamainternmed.2023.3798. PMID: 37639247.
24. Stang A, Jöckel KH. The Impact of Cancer Screening on All-Cause Mortality. Dtsch Arztebl Int. 2018 Jul 23;115(29-30):481-6. doi: 10.3238/arztebl.2018.0481. PMID: 30135006.
25. Neal RD, Johnson P, Clarke CA, et al. Cell-Free DNA-Based Multi-Cancer Early Detection Test in an Asymptomatic Screening Population (NHS-Galleri): Design of a Pragmatic, Prospective Randomised Controlled Trial. Cancers (Basel). 2022 Oct 1;14(19). doi: 10.3390/cancers14194818. PMID: 36230741.
26. Owens L, Gulati R, Etzioni R. Stage shift as an endpoint in cancer screening trials: implications for evaluating multicancer early detection tests. Cancer Epidemiol Biomarkers Prev. 2022 Jul 1;31(7):1298-304. doi: 10.1158/1055-9965.Epi-22-0024. PMID: 35477176.
27. Feng X, Zahed H, Onwuka J, et al. Cancer Stage Compared With Mortality as End Points in Randomized Clinical Trials of Cancer Screening: A Systematic Review and Meta-Analysis. JAMA. 2024 Apr 7. doi: 10.1001/jama.2024.5814. PMID: 38583868.
28. Bach PB. Late-Stage Cancer End Points to Speed Cancer Screening Clinical Trials-Not So Fast. JAMA. 2024 Apr 7. doi: 10.1001/jama.2024.5821. PMID: 38583869.
29. Zeng L, Brignardello-Petersen R, Hultcrantz M, et al. GRADE Guidance 34: update on rating imprecision using a minimally contextualized approach. J Clin Epidemiol. 2022;150:216-24.
30. Kim JJ, Burger EA, Regan C, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Screening for cervical cancer in primary care: a decision analysis for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018.
31. Nelson HD, Cantor A, Humphrey L, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Screening for Breast Cancer: A Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016.
32. Jonas DE, Reuland DS, Reddy SM, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Screening for Lung Cancer With Low-Dose Computed Tomography: An Evidence Review for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2021.
33. US Preventive Services Task Force. Colorectal cancer: screening. 2021. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening#bootstrap-panel--8. Accessed on May 31, 2024.
34. Effective Health Care Program. Methods Guide – Chapter: Chapter 6: Assessing Applicability of Medical Test Studies in Systematic Reviews. Agency for Healthcare Research and Quality, Rockville, MD. 2012. Available from: https://effectivehealthcare.ahrq.gov/products/methods-guidance-tests-applicability/methods.
35. Cochrane Bias Methods Group. TACIT Tool for Adressing Conflicts of Interest in Trials. 2024. https://www.tacit.one/. Accessed on June 5, 2024.

VI. Definition of Terms

None

VII. Summary of Protocol Amendments

If there is a need to amend the protocol, we will provide a numbered list of versions with the date of posting, which will be hyperlinked to previous versions; and a table with the date of each amendment, description of the change, and the rationale. Changes will be incorporated into the protocol.

VIII. Previous Versions of the Protocol

None

IX. Review of Key Questions

AHRQ posted the preliminary Key Questions on the AHRQ Effective Health Care Website for public comment from February 12, 2024, to March 4, 2024. The EPC refined and finalized them after reviewing of the public comments and seeking input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the Key Questions are specific and relevant.

X. Key Informants

Key Informants are the end users of research; they can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of healthcare, and others with experience in making healthcare decisions. Within the EPC program, the Key Informant role is to provide input into the decisional dilemmas and help keep the focus on Key Questions that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for the systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Technical Experts

Technical Experts constitute a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The TEP is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts.

Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the

report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

XIII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

XIV. Role of the Funder

This project was funded under Contract No. 75Q80120D00007 Task Order 75Q80124F32008 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by either the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A.
List of Eligible Countries

Our preliminary scope defines eligibility based on studies conducted in countries with a *high* or *very high* Human Development Index (HDI) designation, based on the 2024 United Nations Human Development Report.[11] Our preliminary evidence scan identified several tests developed and tested in China with FDA breakthrough device designations. Such studies would not be eligible if we limited the scope to very highly developed countries. We expect to identify few to no studies from high HDI countries other than China.

Country	HDI Classification
Albania	High
Algeria	High
Andorra	Very High
Antigua and Barbuda	Very High
Argentina	Very High
Armenia	High
Australia	Very High
Austria	Very High
Azerbaijan	High
Bahamas	Very High
Bahrain	Very High
Barbados	Very High
Belarus	Very High
Belgium	Very High
Belize	High
Bosnia and Herzegovina	High
Botswana	High
Brazil	High
Brunei Darussalam	Very High
Bulgaria	High
Canada	Very High
Chile	Very High
China	High
Colombia	High
Costa Rica	Very High
Croatia	Very High
Cuba	High
Cyprus	Very High
Czechia	Very High
Denmark	Very High
Dominica	High
Dominican Republic	High
Ecuador	High
Egypt	High
Estonia	Very High
Fiji	High
Finland	Very High
France	Very High
Georgia	Very High
Germany	Very High
Greece	Very High
Grenada	High
Guyana	High
Hong Kong, China (SAR)	Very High
Hungary	Very High
Iceland	Very High
Indonesia	High
Iran (Islamic Republic of)	High
Ireland	Very High
Israel	Very High
Italy	Very High
Jamaica	High
Japan	Very High
Jordan	High
Kazakhstan	Very High
Korea (Republic of)	Very High
Kuwait	Very High
Kyrgyzstan	High
Latvia	Very High
Lebanon	High
Libya	High
Liechtenstein	Very High
Lithuania	Very High

(continued)

Country	HDI Classification
Luxembourg	Very High
Malaysia	Very High
Maldives	High
Malta	Very High
Marshall Islands	High
Mauritius	High
Mexico	High
Moldova (Republic of)	High
Mongolia	High
Montenegro	Very High
Netherlands	Very High
New Zealand	Very High
North Macedonia	High
Norway	Very High
Oman	Very High
Palau	High
Palestine, State of	High
Panama	Very High
Paraguay	High
Peru	High
Philippines	High
Poland	Very High
Portugal	Very High
Qatar	Very High
Romania	Very High
Russian Federation	Very High
Saint Kitts and Nevis	Very High
Saint Lucia	High
Saint Vincent and the Grenadines	High
Samoa	High
San Marino	Very High
Saudi Arabia	Very High
Serbia	Very High
Seychelles	Very High
Singapore	Very High
Slovakia	Very High
Slovenia	Very High
South Africa	High
Spain	Very High
Sri Lanka	High
Sweden	Very High
Switzerland	Very High
Thailand	Very High
Tonga	High
Trinidad and Tobago	Very High
Tunisia	High
Türkiye	Very High
Turkmenistan	High
Ukraine	High
United Arab Emirates	Very High
United Kingdom	Very High
United States	Very High
Uruguay	Very High
Uzbekistan	High
Viet Nam	High

Appendix B.
MEDLINE/PubMed Search Strategies

PubMed KQs 1-5 and CQ 1 search, 4/30/2024

Search	Query	Results
#1	"Biomarkers, Tumor"[Mesh] OR "Cell-Free Nucleic Acids"[Mesh] OR "Circulating Tumor DNA"[Mesh] OR (("Liquid Biopsy"[Mesh] OR "liquid biopsy"[tiab:~0]) AND Neoplasms[Mesh]) OR "blood-based biomarker"[tiab:~0] OR "blood-based biomarkers"[tiab:~0] OR "blood-based screening"[tiab:~0] OR "blood-based test"[tiab:~0] OR "blood-based testing"[tiab:~0] OR "blood-based tests"[tiab:~0] OR "blood biomarker"[tiab:~0] OR "blood biomarkers"[tiab:~0] OR ccfDNA[tiab] OR cfDNA[tiab] OR ctDNA[tiab] OR "cell-free DNA"[tiab:~0] OR "cell-free nucleic acid"[tiab:~0] OR "cell-free nucleic acids"[tiab:~0] OR "Cell-Free RNA"[tiab:~0] OR cfRNA[tiab] OR cirRNA[tiab] OR "Cell-Free Ribonucleic Acid"[tiab:~0] OR "Circulating RNA"[tiab:~0] OR "cell-free tumor"[tiab:~0] OR "cell-free tumor"[tiab:~0] OR "circulating cell-free"[tiab:~0] OR "circulating DNA"[tiab:~0] OR "circulating nucleic acid"[tiab:~0] OR "circulating nucleic acids"[tiab:~0] OR "circulating nucleotide"[tiab:~0] OR "circulating nucleotides"[tiab:~0] OR "circulating tumor DNA"[tiab:~0] OR "circulating tumor DNA"[tiab:~0] OR "multicancer early detection"[all fields] OR "multi-cancer early detection"[tiab:~0] OR MCD[tiab] OR MCDs[tiab] OR MCED[tiab] OR MCEDs[tiab] OR "tumor biomarker"[tiab:~0] OR "tumor biomarkers"[tiab:~0] OR "tumor biomarker"[tiab:~0] OR "tumor biomarkers"[tiab:~0] OR tcfDNA[tiab] OR "tumor cell-free DNA"[All Fields] OR "tumor cell-free DNA"[All Fields] OR "tumor DNA methylation"[tiab] OR "tumor DNA methylation"[tiab]	345,654
#2	"Adrenal Gland Neoplasms"[Mesh] OR "Bone Neoplasms"[Mesh] OR "Brain Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh] OR "Carcinoma, Hepatocellular"[Mesh] OR "Carcinoma, Ovarian Epithelial"[Mesh] OR "Carcinoma, Pancreatic Ductal"[Mesh] OR "Esophageal Neoplasms"[Mesh] OR "Fallopian Tube Neoplasms"[Mesh] OR "Gastrointestinal Neoplasms"[Mesh] OR "Head and Neck Neoplasms"[Mesh] OR "Kidney Neoplasms"[Mesh] OR "Liver Neoplasms"[Mesh] OR "Lung Neoplasms"[Mesh] OR "Melanoma"[Mesh] OR "Neoplasms/diagnosis"[Majr] OR "Neoplasms/prevention and control"[Majr] OR "Pancreatic Neoplasms"[Mesh] OR "Prostatic Neoplasms"[Mesh] OR "Sarcoma"[Mesh] OR "Stomach Neoplasms"[Mesh] OR "Urinary Bladder Neoplasms"[Mesh] OR "Uterine Cervical Neoplasms"[Mesh]	2,585,739

Search	Query	Results
#3	"adrenal gland neoplasm"[title] OR "adrenal neoplasm"[title] OR "bladder neoplasm"[title] OR "bone neoplasm"[title] OR "brain neoplasm"[title] OR "breast neoplasm"[title] OR "cervical neoplasm"[title] OR "colon neoplasm"[title] OR "colorectal neoplasm"[title] OR "gastric neoplasm"[title] OR "esophageal neoplasm"[title] OR "oesophageal neoplasm"[title] OR "esophageal carcinoma"[title] OR "oesophageal carcinoma"[title] OR "fallopian tube neoplasm"[title] OR "gastric neoplasm"[title] OR "gastrointestinal neoplasm"[title] OR "gi neoplasm"[title] OR "head and neck neoplasm"[title] OR "hepatocellular carcinoma"[title] OR "intestinal neoplasm"[title] OR "kidney neoplasm"[title] OR "liver neoplasm"[title] OR "lung neoplasm"[title] OR melanoma[title] OR osteosarcoma[title] OR "ovarian epithelial carcinoma"[title] OR "ovarian neoplasm" OR "ovarian carcinoma"[title] OR "pancreatic neoplasm"[title] OR "pancreatic ductal adenocarcinoma"[title] OR "pancreatic ductal carcinoma"[title] OR pdac[title] OR "prostate neoplasm"[title] OR "prostatic neoplasm"[title] OR sarcoma[title] OR "stomach neoplasm"[title] OR ("tubo-ovarian"[tiab] AND (neoplasm[tiab] OR carcinoma[tiab]))	243,790
#4	"adrenal gland neoplasms"[title] OR "adrenal neoplasms"[title] OR "bladder neoplasms"[title] OR "bone neoplasms"[title] OR "brain neoplasms"[title] OR "breast neoplasms"[title] OR "cervical neoplasms"[title] OR "colon neoplasms"[title] OR "colorectal neoplasms"[title] OR "gastric neoplasms"[title] OR "esophageal neoplasms"[title] OR "oesophageal neoplasms"[title] OR "esophageal carcinomas"[title] OR "oesophageal carcinomas"[title] OR "fallopian tube neoplasms"[title] OR "gastric neoplasms"[title] OR "gastrointestinal neoplasms"[title] OR "gi neoplasms"[title] OR "head and neck neoplasms"[title] OR "hepatocellular carcinomas"[title] OR "intestinal neoplasms"[title] OR "kidney neoplasms"[title] OR "liver neoplasms"[title] OR "lung neoplasms"[title] OR melanomas[title] OR osteosarcomas[title] OR "ovarian epithelial carcinomas"[title] OR "ovarian neoplasms" OR "ovarian carcinomas"[title] OR "pancreatic neoplasms"[title] OR "pancreatic ductal adenocarcinomas"[title] OR "pancreatic ductal carcinomas"[title] OR pdacs[title] OR "prostate neoplasms"[title] OR "prostatic neoplasms"[title] OR sarcomas[title] OR "stomach neoplasms"[title] OR ("tubo-ovarian"[tiab] AND (neoplasms[tiab] OR carcinomas[tiab]))	113,853

Search	Query	Results
#5	"adrenal gland cancer"[title] OR "adrenal cancer"[title] OR "bladder cancer"[title] OR "bone cancer"[title] OR "brain cancer"[title] OR "breast cancer"[title] OR "cervical cancer"[title] OR "colon cancer"[title] OR "colorectal cancer"[title] OR "esophageal cancer"[title] OR "oesophageal cancer"[title] OR "fallopian cancer"[title] OR "fallopian tube cancer"[title] OR "gastric cancer"[title] OR "gastrointestinal cancer"[title] OR "gi cancer"[title] OR "head and neck cancer"[title] OR "intestinal cancer"[title] OR "kidney cancer"[title] OR "liver cancer"[title] OR "lung cancer"[title] OR "ovarian cancer" OR "pancreatic cancer"[title] OR "prostate cancer"[title] OR "prostatic cancer"[title] OR "stomach cancer"[title] OR ("tubo-ovarian"[tiab] AND cancer[tiab])	829,331
#6	"adrenal gland cancers"[title] OR "adrenal cancers"[title] OR "bladder cancers"[title] OR "bone cancers"[title] OR "brain cancers"[title] OR "breast cancers"[title] OR "cervical cancers"[title] OR "colon cancers"[title] OR "colorectal cancers"[title] OR "esophageal cancers"[title] OR "oesophageal cancers"[title] OR "fallopian cancers"[title] OR "fallopian tube cancers"[title] OR "gastric cancers"[title] OR "gastrointestinal cancers"[title] OR "gi cancers"[title] OR "head and neck cancers"[title] OR "intestinal cancers"[title] OR "kidney cancers"[title] OR "liver cancers"[title] OR "lung cancers"[title] OR "ovarian cancers" OR "pancreatic cancers"[title] OR "prostate cancers"[title] OR "prostatic cancers"[title] OR "stomach cancers"[title] OR ("tubo-ovarian"[tiab] AND cancers[tiab])	24,609
#7	multicancer[tiab] OR multicancers[tiab] OR multicancerous[tiab] OR "multi-cancer"[tiab] OR "multisite cancer"[tiab] OR "multisite cancers"[tiab] OR "multi-site cancer"[tiab] OR "multi-site cancers"[tiab] OR "multisite neoplasm"[tiab:~3] OR "multi-site neoplasm"[tiab:~3] OR "multisite neoplasms"[tiab:~3] OR "multi-site neoplasms"[tiab:~3]	392
#8	#2 OR #3 OR #4 OR #5 OR #6 OR #7	2,845,262
#9	#1 AND #8	231,677
#10	"Early Detection of Cancer"[Mesh] OR "Mass Screening"[Mesh] OR screen*[tiab] OR detection[title] OR "early detect*"[tiab]	1,456,482
#11	#9 AND #10	31,505

Search	Query	Results
#12	Adela[tiab] OR "Avantect Pancreatic"[tiab:~0] OR "Avantect Ovarian"[tiab:~0] OR Bluestar[tiab] OR "BT-Reveal"[tiab:~0] OR CancerRadar[tiab] OR CancerSEEK[tiab] OR "cfMethyl-Seq"[tiab:~0] OR DEEPGEN*[tiab] OR Delfi[tiab] OR "ECLIPSE Trial"[tiab] OR "Elio Plasma Focus"[tiab:~0] OR EpiSeek[tiab] OR "ExoVerita Pro"[tiab:~0] OR "F1 Liquid CDx"[tiab:~0] OR FMBT[tiab] OR Galleri[tiab] OR Guardant[tiab] OR Guardant360[tiab] OR GutSeer[tiab] OR Harbinger[tiab] OR "OncoCompass Target"[tiab:~0] OR OncoProfiler[tiab] OR OverC*[tiab] OR PanSeer[tiab] OR PATHFINDER[tiab] OR PDACatch[tiab] OR "Personalized MRD"[tiab:~0] OR PredicineCare[tiab] OR "Qx system"[tiab:~0] OR "Sentinel-10"[tiab] OR "Septin 9"[tiab] OR Septin9[tiab] OR Signatera[tiab] OR "SPOT-MAS"[tiab] OR "THUNDER study"[tiab] OR "Tr(ACE)"[tiab] OR "Vanguard Trial"[tiab]	282,815
#13	#9 AND #12	2,560
#14	#11 OR #13	33,600
#15	chemoprevention[tiab] OR chemopreventive[tiab] OR chemopreventative[tiab] OR chemotherapy[title] OR chemotherapies[tiab] OR chemotherapeutic[tiab] OR chemotherapeutics[tiab] OR drug[tiab] OR drugs[tiab] OR laboratory[tiab] OR medication[tiab] OR medications[tiab] OR pharmacogenetic[tiab] OR pharmacogenetics[tiab] OR pharmacogenomic[tiab] OR pharmacogenomics[tiab] OR pharmacotherapy[title] OR pharmacotherapies[tiab] OR pharmacotherapeutic[tiab] OR pharmacotherapeutics[tiab] OR "proof of concept"[tiab] OR "risk stratification"[tiab] OR vitro[tiab]	4,467,333
#16	#14 NOT #15	28,891
#17	#16 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT ("Adult"[Mesh] OR adult[title] OR adults[title] OR Aged[Mesh] OR elder[title] OR elders[title] OR elderly[title] OR "Middle Aged"[Mesh]))	28,694
#18	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt]	3,347,706

Search	Query	Results
#19	#17 NOT #18	27,850
#20	(animals[mesh] NOT humans[mesh]) OR bovine[tiab] OR canine[tiab] OR capra[tiab] OR cat[tiab] OR cats[tiab] OR cattle[tiab] OR cow[tiab] OR cows[tiab] OR dog[tiab] OR dogs[tiab] OR equine[tiab] OR ewe[tiab] OR ewes[tiab] OR feline[tiab] OR goat[tiab] OR goats[tiab] OR hamster*[tiab] OR horse[tiab] OR horses[tiab] OR invertebrate[tiab] OR invertebrates[tiab] OR kangaroo[tiab] OR kangaroos[tiab] OR macaque[tiab] OR macaques[tiab] OR mare[tiab] OR mares[tiab] OR mice[tiab] OR monkey[tiab] OR monkeys[tiab] OR mouse[tiab] OR murine[tiab] OR nonhuman[tiab] OR "non-human"[tiab] OR ovine[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR primate[tiab] OR primates[tiab] OR rabbit[tiab] OR rabbits[tiab] OR rat[tiab] OR rats[tiab] OR rattus[tiab] OR rhesus[tiab] OR rodent[tiab] OR rodents[tiab] OR rodentia[tiab] OR sheep[tiab] OR simian[tiab] OR sow[tiab] OR sows[tiab] OR vertebrate[tiab] OR vertebrates[tiab] OR whale[tiab] OR whales[tiab] OR zebrafish[tiab]	6,661,254
#21	#19 NOT #20	26,908
#22	#19 NOT #20 Filters: English	25,115
#23	#19 NOT #20 Filters: English, from 2013 - 2024	15,217
#24	"Systematic Reviews as Topic"[Mesh] OR "cochrane database syst rev"[ta] OR "systematic literature review"[ti] OR "systematic review"[ti] OR ("systematic review"[tiab] AND review[pt]) OR "this systematic review"[tw] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analyses"[tiab] OR "meta-analysis"[tiab] OR meta synthesis[tiab] OR "Umbrella Review"[tiab]	477,878
#25	#23 AND #24	668
#26	#23 AND (guideline[pt] OR "practice guideline"[pt] OR guideline[tiab] OR guidelines[tiab])	613
#27	#23 AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR randomly [tiab] OR trial [tiab])	1,089

Search	Query	Results
#28	"Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Controlled Before-After Studies"[Mesh] OR "Cross-sectional Studies"[Mesh] OR "Evaluation Study"[Mesh] OR "Evaluation Studies as Topic"[Mesh] OR "Interrupted Time Series Analysis"[Mesh] OR "Prospective Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR "before-after"[tiab:~2] OR "case-control"[tiab] OR cohort[tiab] OR "cross-sectional"[tiab] OR "interrupted time"[tiab:~1] OR longitudinal[tiab] OR prospective[tiab] OR retrospective[tiab]	5,574,981
#29	#23 AND #28	6,048
#30	#23 AND "decision analysis"[tiab]	14
#31	"Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "Reference Standards"[Mesh] OR "False Negative Reactions"[Mesh] OR "False Positive Reactions"[Mesh] OR "predictive value"[tiab] OR sensitivity[tiab] OR specificity[tiab] OR accuracy[tiab] OR "area under curve"[tiab:~1] OR AUC[tiab] OR "false positive*"[tiab] OR "false negative*"[tiab] OR "likelihood ratio"[tw] OR "miss rate*"[tiab] OR "error rate*"[tiab]	2,411,436
#32	#23 AND #31	6,925

PubMed CQs 2, 3, and 4 search for costs and cost-effectiveness, 4/30/2024

Search	Query	Results
#1	"Biomarkers, Tumor"[Mesh] OR "Cell-Free Nucleic Acids"[Mesh] OR "Circulating Tumor DNA"[Mesh] OR (("Liquid Biopsy"[Mesh] OR "liquid biopsy"[tiab:~0]) AND Neoplasms[Mesh]) OR "blood-based biomarker"[tiab:~0] OR "blood-based biomarkers"[tiab:~0] OR "blood-based screening"[tiab:~0] OR "blood-based test"[tiab:~0] OR "blood-based testing"[tiab:~0] OR "blood-based tests"[tiab:~0] OR "blood biomarker"[tiab:~0] OR "blood biomarkers"[tiab:~0] OR ccfDNA[tiab] OR cfDNA[tiab] OR ctDNA[tiab] OR "cell-free DNA"[tiab:~0] OR "cell-free nucleic acid"[tiab:~0] OR "cell-free nucleic acids"[tiab:~0] OR "Cell-Free RNA"[tiab:~0] OR cfRNA[tiab] OR cirRNA[tiab] OR "Cell-Free Ribonucleic Acid"[tiab:~0] OR "Circulating RNA"[tiab:~0] OR "cell-free tumor"[tiab:~0] OR "cell-free tumor"[tiab:~0] OR "circulating cell-free"[tiab:~0] OR "circulating DNA"[tiab:~0] OR "circulating nucleic acid"[tiab:~0] OR "circulating nucleic acids"[tiab:~0] OR "circulating nucleotide"[tiab:~0] OR "circulating nucleotides"[tiab:~0] OR "circulating tumor DNA"[tiab:~0] OR "circulating tumor DNA"[tiab:~0] OR "multicancer early detection"[all fields] OR "multi-cancer early detection"[tiab:~0] OR MCD[tiab] OR MCDs[tiab] OR MCED[tiab] OR MCEDs[tiab] OR "tumor biomarker"[tiab:~0] OR "tumor biomarkers"[tiab:~0] OR "tumor biomarker"[tiab:~0] OR "tumor biomarkers"[tiab:~0] OR tcfDNA[tiab] OR "tumor cell-free DNA"[All Fields] OR "tumor cell-free DNA"[All Fields] OR "tumor DNA methylation"[tiab] OR "tumor DNA methylation"[tiab]	345,654
#2	"Adrenal Gland Neoplasms"[Mesh] OR "Bone Neoplasms"[Mesh] OR "Brain Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh] OR "Carcinoma, Hepatocellular"[Mesh] OR "Carcinoma, Ovarian Epithelial"[Mesh] OR "Carcinoma, Pancreatic Ductal"[Mesh] OR "Esophageal Neoplasms"[Mesh] OR "Fallopian Tube Neoplasms"[Mesh] OR "Gastrointestinal Neoplasms"[Mesh] OR "Head and Neck Neoplasms"[Mesh] OR "Kidney Neoplasms"[Mesh] OR "Liver Neoplasms"[Mesh] OR "Lung Neoplasms"[Mesh] OR "Melanoma"[Mesh] OR "Neoplasms/diagnosis"[Majr] OR "Neoplasms/prevention and control"[Majr] OR "Pancreatic Neoplasms"[Mesh] OR "Prostatic Neoplasms"[Mesh] OR "Sarcoma"[Mesh] OR "Stomach Neoplasms"[Mesh] OR "Urinary Bladder Neoplasms"[Mesh] OR "Uterine Cervical Neoplasms"[Mesh]	2,585,739

Search	Query	Results
#3	"adrenal gland neoplasm"[title] OR "adrenal neoplasm"[title] OR "bladder neoplasm"[title] OR "bone neoplasm"[title] OR "brain neoplasm"[title] OR "breast neoplasm"[title] OR "cervical neoplasm"[title] OR "colon neoplasm"[title] OR "colorectal neoplasm"[title] OR "gastric neoplasm"[title] OR "esophageal neoplasm"[title] OR "oesophageal neoplasm"[title] OR "esophageal carcinoma"[title] OR "oesophageal carcinoma"[title] OR "fallopian tube neoplasm"[title] OR "gastric neoplasm"[title] OR "gastrointestinal neoplasm"[title] OR "gi neoplasm"[title] OR "head and neck neoplasm"[title] OR "hepatocellular carcinoma"[title] OR "intestinal neoplasm"[title] OR "kidney neoplasm"[title] OR "liver neoplasm"[title] OR "lung neoplasm"[title] OR melanoma[title] OR osteosarcoma[title] OR "ovarian epithelial carcinoma"[title] OR "ovarian neoplasm" OR "ovarian carcinoma"[title] OR "pancreatic neoplasm"[title] OR "pancreatic ductal adenocarcinoma"[title] OR "pancreatic ductal carcinoma"[title] OR pdac[title] OR "prostate neoplasm"[title] OR "prostatic neoplasm"[title] OR sarcoma[title] OR "stomach neoplasm"[title] OR ("tubo-ovarian"[tiab] AND (neoplasm[tiab] OR carcinoma[tiab]))	243,790
#4	"adrenal gland neoplasms"[title] OR "adrenal neoplasms"[title] OR "bladder neoplasms"[title] OR "bone neoplasms"[title] OR "brain neoplasms"[title] OR "breast neoplasms"[title] OR "cervical neoplasms"[title] OR "colon neoplasms"[title] OR "colorectal neoplasms"[title] OR "gastric neoplasms"[title] OR "esophageal neoplasms"[title] OR "oesophageal neoplasms"[title] OR "esophageal carcinomas"[title] OR "oesophageal carcinomas"[title] OR "fallopian tube neoplasms"[title] OR "gastric neoplasms"[title] OR "gastrointestinal neoplasms"[title] OR "gi neoplasms"[title] OR "head and neck neoplasms"[title] OR "hepatocellular carcinomas"[title] OR "intestinal neoplasms"[title] OR "kidney neoplasms"[title] OR "liver neoplasms"[title] OR "lung neoplasms"[title] OR melanomas[title] OR osteosarcomas[title] OR "ovarian epithelial carcinomas"[title] OR "ovarian neoplasms" OR "ovarian carcinomas"[title] OR "pancreatic neoplasms"[title] OR "pancreatic ductal adenocarcinomas"[title] OR "pancreatic ductal carcinomas"[title] OR pdacs[title] OR "prostate neoplasms"[title] OR "prostatic neoplasms"[title] OR sarcomas[title] OR "stomach neoplasms"[title] OR ("tubo-ovarian"[tiab] AND (neoplasms[tiab] OR carcinomas[tiab]))	113,853

Search	Query	Results
#5	"adrenal gland cancer"[title] OR "adrenal cancer"[title] OR "bladder cancer"[title] OR "bone cancer"[title] OR "brain cancer"[title] OR "breast cancer"[title] OR "cervical cancer"[title] OR "colon cancer"[title] OR "colorectal cancer"[title] OR "esophageal cancer"[title] OR "oesophageal cancer"[title] OR "fallopian cancer"[title] OR "fallopian tube cancer"[title] OR "gastric cancer"[title] OR "gastrointestinal cancer"[title] OR "gi cancer"[title] OR "head and neck cancer"[title] OR "intestinal cancer"[title] OR "kidney cancer"[title] OR "liver cancer"[title] OR "lung cancer"[title] OR "ovarian cancer" OR "pancreatic cancer"[title] OR "prostate cancer"[title] OR "prostatic cancer"[title] OR "stomach cancer"[title] OR ("tubo-ovarian"[tiab] AND cancer[tiab])	829,331
#6	"adrenal gland cancers"[title] OR "adrenal cancers"[title] OR "bladder cancers"[title] OR "bone cancers"[title] OR "brain cancers"[title] OR "breast cancers"[title] OR "cervical cancers"[title] OR "colon cancers"[title] OR "colorectal cancers"[title] OR "esophageal cancers"[title] OR "oesophageal cancers"[title] OR "fallopian cancers"[title] OR "fallopian tube cancers"[title] OR "gastric cancers"[title] OR "gastrointestinal cancers"[title] OR "gi cancers"[title] OR "head and neck cancers"[title] OR "intestinal cancers"[title] OR "kidney cancers"[title] OR "liver cancers"[title] OR "lung cancers"[title] OR "ovarian cancers" OR "pancreatic cancers"[title] OR "prostate cancers"[title] OR "prostatic cancers"[title] OR "stomach cancers"[title] OR ("tubo-ovarian"[tiab] AND cancers[tiab])	24,609
#7	multicancer[tiab] OR multicancers[tiab] OR multicancerous[tiab] OR "multi-cancer"[tiab] OR "multisite cancer"[tiab] OR "multisite cancers"[tiab] OR "multi-site cancer"[tiab] OR "multi-site cancers"[tiab] OR "multisite neoplasm"[tiab:~3] OR "multi-site neoplasm"[tiab:~3] OR "multisite neoplasms"[tiab:~3] OR "multi-site neoplasms"[tiab:~3]	392
#8	#2 OR #3 OR #4 OR #5 OR #6 OR #7	2,845,262
#9	#1 AND #8	231,677
#10	"Early Detection of Cancer"[Mesh] OR "Mass Screening"[Mesh] OR screen*[tiab] OR detection[title] OR "early detect*"[tiab]	1,456,482
#11	#9 AND #10	31,505

Search	Query	Results
#12	Adela[tiab] OR "Avantect Pancreatic"[tiab:~0] OR "Avantect Ovarian"[tiab:~0] OR Bluestar[tiab] OR "BT-Reveal"[tiab:~0] OR CancerRadar[tiab] OR CancerSEEK[tiab] OR "cfMethyl-Seq"[tiab:~0] OR DEEPGEN*[tiab] OR Delfi[tiab] OR "ECLIPSE Trial"[tiab] OR "Elio Plasma Focus"[tiab:~0] OR EpiSeek[tiab] OR "ExoVerita Pro"[tiab:~0] OR "F1 Liquid CDx"[tiab:~0] OR FMBT[tiab] OR Galleri[tiab] OR Guardant[tiab] OR Guardant360[tiab] OR GutSeer[tiab] OR Harbinger[tiab] OR "OncoCompass Target"[tiab:~0] OR OncoProfiler[tiab] OR OverC*[tiab] OR PanSeer[tiab] OR PATHFINDER[tiab] OR PDACatch[tiab] OR "Personalized MRD"[tiab:~0] OR PredicineCare[tiab] OR "Qx system"[tiab:~0] OR "Sentinel-10"[tiab] OR "Septin 9"[tiab] OR Septin9[tiab] OR Signatera[tiab] OR "SPOT-MAS"[tiab] OR "THUNDER study"[tiab] OR "Tr(ACE)"[tiab] OR "Vanguard Trial"[tiab]	282,815
#13	#9 AND #12	2,560
#14	#11 OR #13	33,600
#15	chemoprevention[tiab] OR chemopreventive[tiab] OR chemopreventative[tiab] OR chemotherapy[title] OR chemotherapies[tiab] OR chemotherapeutic[tiab] OR chemotherapeutics[tiab] OR drug[tiab] OR drugs[tiab] OR laboratory[tiab] OR medication[tiab] OR medications[tiab] OR pharmacogenetic[tiab] OR pharmacogenetics[tiab] OR pharmacogenomic[tiab] OR pharmacogenomics[tiab] OR pharmacotherapy[title] OR pharmacotherapies[tiab] OR pharmacotherapeutic[tiab] OR pharmacotherapeutics[tiab] OR "proof of concept"[tiab] OR "risk stratification"[tiab] OR vitro[tiab]	4,467,333
#16	#14 NOT #15	28,891
#17	#16 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT ("Adult"[Mesh] OR adult[title] OR adults[title] OR Aged[Mesh] OR elder[title] OR elders[title] OR elderly[title] OR "Middle Aged"[Mesh]))	28,694

Search	Query	Results
#18	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt]	3,347,706
#19	#17 NOT #18	27,850
#20	(animals[mesh] NOT humans[mesh]) OR bovine[tiab] OR canine[tiab] OR capra[tiab] OR cat[tiab] OR cats[tiab] OR cattle[tiab] OR cow[tiab] OR cows[tiab] OR dog[tiab] OR dogs[tiab] OR equine[tiab] OR ewe[tiab] OR ewes[tiab] OR feline[tiab] OR goat[tiab] OR goats[tiab] OR hamster*[tiab] OR horse[tiab] OR horses[tiab] OR invertebrate[tiab] OR invertebrates[tiab] OR kangaroo[tiab] OR kangaroos[tiab] OR macaque[tiab] OR macaques[tiab] OR mare[tiab] OR mares[tiab] OR mice[tiab] OR monkey[tiab] OR monkeys[tiab] OR mouse[tiab] OR murine[tiab] OR nonhuman[tiab] OR "non-human"[tiab] OR ovine[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR primate[tiab] OR primates[tiab] OR rabbit[tiab] OR rabbits[tiab] OR rat[tiab] OR rats[tiab] OR rattus[tiab] OR rhesus[tiab] OR rodent[tiab] OR rodents[tiab] OR rodentia[tiab] OR sheep[tiab] OR simian[tiab] OR sow[tiab] OR sows[tiab] OR vertebrate[tiab] OR vertebrates[tiab] OR whale[tiab] OR whales[tiab] OR zebrafish[tiab]	6,661,254
#21	#19 NOT #20	26,908
#22	#19 NOT #20 Filters: English	25,115

Search	Query	Results
#23	"costs and cost analysis"[mesh] OR "cost of illness"[mesh] OR "Health Care Costs"[Mesh] OR "Insurance"[Mesh] OR "Referral and Consultation"[Mesh] OR Budget control*[tiab] OR Budget saving*[tiab] OR Care budget*[tiab] OR care expen*[tiab] OR Care expen*[tiab] OR Care fund*[tiab] OR Care spend*[tiab] OR champus[tiab] OR Claim analysis[tiab] OR Claim review*[tiab] OR Claims Analysis[tiab] OR Claims Review*[tiab] OR Coinsurance*[tiab] OR Competitive Health Plan*[tiab] OR Competitive Medical Plan*[tiab] OR control cost*[tiab] OR Cost allocat*[tiab] OR Cost analy*[tiab] OR Cost apportionment*[tiab] OR Cost benefit*[tiab] OR Cost compar*[tiab] OR Cost contain*[tiab] OR Cost control*[tiab] OR Cost decreas*[tiab] OR Cost effective*[tiab] OR Cost Efficien*[tiab] OR Cost evaluat*[tiab] OR Cost increase*[tiab] OR Cost manag*[tiab] OR Cost minimi*[tiab] OR Cost reduc*[tiab] OR Cost reduction[tiab] OR Cost saving*[tiab] OR Cost sharing[tiab] OR Cost shifting*[tiab] OR Costeffect*[tiab] OR Cost minimisation[tiab] OR Cost minimization[tiab] OR Deductible*[tiab] OR direct cost*[tiab] OR Economic evaluat*[tiab] OR Health Benefit Plan*[tiab] OR Health budget*[tiab] OR health care cost*[tiab] OR Health care saving*[tiab] OR health care spending[tiab] OR health cost*[tiab] OR health expen*[tiab] OR health expenditure*[tiab] OR Health fund*[tiab] OR Health spend*[tiab] OR health spending*[tiab] OR Healthcare budget*[tiab] OR Healthcare cost*[tiab] OR healthcare expen*[tiab] OR Healthcare fund*[tiab] OR Healthcare savings[tiab] OR Healthcare spend*[tiab] OR healthcare spending*[tiab] OR High cost*[tiab] OR High spend*[tiab] OR Increasing cost*[tiab] OR insuran*[tiab] OR Low cost*[tiab] OR managed car*[tiab] OR Medical budget*[tiab] OR Medical Care Cost*[tiab] OR medical cost*[tiab] OR Medical expen*[tiab] OR Medical fund*[tiab] OR medical saving*[tiab] OR Medical saving*[tiab] OR Medical spend*[tiab] OR medicare[tiab] OR Preferred provider*[tiab] OR price[tiab] OR Reducing cost*[tiab] OR Reimburs*[tiab] OR Rising cost*[tiab] OR Saving cost*[tiab] OR societal cost*[tiab] OR Third-Party Pay*[tiab] OR Treatment Cost*[tiab] OR Usage reduction*[tiab] OR Value Based Purchas*[tiab] OR Worker Compensation*[tiab] OR Worker s compensation*[tiab] OR Workers compensation*[tiab] OR Return on investment*[tiab] OR ROI[tiab]	965,883
#24	#22 AND #23	1,331
#25	#22 AND #23 Filters: from 2019 - 2024	465

Search	Query	Results
#26	"united states" OR usa OR "u.s.a." OR "u.s." OR veteran* or alabama OR montgomery OR alaska OR juneau or anchorage OR arizona OR phoenix OR arkansas OR "little rock" OR california OR sacramento OR "los angeles" or colorado OR denver OR connecticut OR hartford or bridgeport OR delaware OR dover OR wilmington or florida OR tallahassee OR jacksonville OR miami or atlanta OR hawaii OR "hawai'i" OR honolulu OR idaho OR boise or illinois OR springfield OR chicago OR indiana or indianapolis OR iowa OR "des moines" OR kansas or topeka OR wichita OR kentucky OR frankfort or louisville OR louisiana OR "baton rouge" OR "new orleans" OR maine OR augusta OR portland or maryland OR annapolis OR baltimore OR massachusetts or boston OR michigan OR lansing OR detroit or minnesota OR "st paul" OR minneapolis OR mississippi or jackson OR missouri OR jefferson city OR montana or billings OR nebraska OR omaha OR nevada OR "carson city" OR "las vegas" OR "new hampshire" OR concord or "new jersey" OR trenton OR newark OR "new mexico" or "santa fe" OR albuquerque OR "new york" OR albany or "north carolina" OR raleigh OR "north dakota" or bismarck OR fargo OR ohio OR columbus OR oklahoma or oregon OR salem OR pennsylvania OR harrisburg or philadelphia OR "rhode island" OR providence or "south carolina" OR columbia OR charleston OR "south dakota" OR "sioux falls" OR tennessee OR nashville or texas OR austin OR houston OR utah OR "salt lake city" or vermont OR montpelier OR burlington OR virginia or richmond OR washington OR olympia OR seattle or wisconsin OR madison OR milwaukee OR wyoming or cheyenne OR "african american*" OR "hispanic american*" OR appalachia* OR "great lake*" OR medicare OR medicaid OR "mid-Atlantic" OR midAtlantic OR mid-west* OR midwest OR "new england" OR "pacific state*"	16,001,608
#27	#25 AND #26	273

PubMed Patch Search 1 for additional MCD+SCD terms, 5/6/2024

Search	Query	Results
#1	Search: "Biomarkers, Tumor"[Mesh] OR "Cell-Free Nucleic Acids"[Mesh] OR "Circulating Tumor DNA"[Mesh] OR (("Liquid Biopsy"[Mesh] OR "liquid biopsy"[tiab:~0]) AND Neoplasms[Mesh]) OR "blood-based biomarker"[tiab:~0] OR "blood-based biomarkers"[tiab:~0] OR "blood-based screening"[tiab:~0] OR "blood-based test"[tiab:~0] OR "blood-based testing"[tiab:~0] OR "blood-based tests"[tiab:~0] OR "blood biomarker"[tiab:~0] OR "blood biomarkers"[tiab:~0] OR ccfDNA[tiab] OR cfDNA[tiab] OR ctDNA[tiab] OR "cell-free DNA"[tiab:~0] OR "cell-free nucleic acid"[tiab:~0] OR "cell-free nucleic acids"[tiab:~0] OR "Cell-Free RNA"[tiab:~0] OR cfRNA[tiab] OR cirRNA[tiab] OR "Cell-Free Ribonucleic Acid"[tiab:~0] OR "Circulating RNA"[tiab:~0] OR "cell-free tumor"[tiab:~0] OR "cell-free tumor"[tiab:~0] OR "circulating cell-free"[tiab:~0] OR "circulating DNA"[tiab:~0] OR "circulating nucleic acid"[tiab:~0] OR "circulating nucleic acids"[tiab:~0] OR "circulating nucleotide"[tiab:~0] OR "circulating nucleotides"[tiab:~0] OR "circulating tumor DNA"[tiab:~0] OR "circulating tumor DNA"[tiab:~0] OR "multicancer early detection"[all fields] OR "multi-cancer early detection"[tiab:~0] OR MCD[tiab] OR MCDs[tiab] OR MCED[tiab] OR MCEDs[tiab] OR "tumor biomarker"[tiab:~0] OR "tumor biomarkers"[tiab:~0] OR "tumor biomarker"[tiab:~0] OR "tumor biomarkers"[tiab:~0] OR tcfDNA[tiab] OR "tumor cell-free DNA"[All Fields] OR "tumor cell-free DNA"[All Fields] OR "tumor DNA methylation"[tiab] OR "tumor DNA methylation"[tiab]	345,946
#2	Search: "multicancer detection"[tiab:~0] OR "multi-cancer detection"[tiab:~0] OR MCD[tiab] OR MCDs[tiab]	5,926
#3	Search: #2 NOT #1	9
#4	Search: "single cancer detection"[tiab:~0] OR SCD[tiab] OR SCDs[tiab]	17,908
#5	Search: #4 NOT #1	17,822
#6	Search: #3 OR #5	17,831

Search	Query	Results
#7	Search: "Adrenal Gland Neoplasms"[Mesh] OR "Bone Neoplasms"[Mesh] OR "Brain Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh] OR "Carcinoma, Hepatocellular"[Mesh] OR "Carcinoma, Ovarian Epithelial"[Mesh] OR "Carcinoma, Pancreatic Ductal"[Mesh] OR "Esophageal Neoplasms"[Mesh] OR "Fallopian Tube Neoplasms"[Mesh] OR "Gastrointestinal Neoplasms"[Mesh] OR "Head and Neck Neoplasms"[Mesh] OR "Kidney Neoplasms"[Mesh] OR "Liver Neoplasms"[Mesh] OR "Lung Neoplasms"[Mesh] OR "Melanoma"[Mesh] OR "Neoplasms/diagnosis"[Majr] OR "Neoplasms/prevention and control"[Majr] OR "Pancreatic Neoplasms"[Mesh] OR "Prostatic Neoplasms"[Mesh] OR "Sarcoma"[Mesh] OR "Stomach Neoplasms"[Mesh] OR "Urinary Bladder Neoplasms"[Mesh] OR "Uterine Cervical Neoplasms"[Mesh]	2,587,219
#8	Search: "adrenal gland neoplasm"[title] OR "adrenal neoplasm"[title] OR "bladder neoplasm"[title] OR "bone neoplasm"[title] OR "brain neoplasm"[title] OR "breast neoplasm"[title] OR "cervical neoplasm"[title] OR "colon neoplasm"[title] OR "colorectal neoplasm"[title] OR "gastric neoplasm"[title] OR "esophageal neoplasm"[title] OR "oesophageal neoplasm"[title] OR "esophageal carcinoma"[title] OR "oesophageal carcinoma"[title] OR "fallopian tube neoplasm"[title] OR "gastric neoplasm"[title] OR "gastrointestinal neoplasm"[title] OR "gi neoplasm"[title] OR "head and neck neoplasm"[title] OR "hepatocellular carcinoma"[title] OR "intestinal neoplasm"[title] OR "kidney neoplasm"[title] OR "liver neoplasm"[title] OR "lung neoplasm"[title] OR melanoma[title] OR osteosarcoma[title] OR "ovarian epithelial carcinoma"[title] OR "ovarian neoplasm" OR "ovarian carcinoma"[title] OR "pancreatic neoplasm"[title] OR "pancreatic ductal adenocarcinoma"[title] OR "pancreatic ductal carcinoma"[title] OR pdac[title] OR "prostate neoplasm"[title] OR "prostatic neoplasm"[title] OR sarcoma[title] OR "stomach neoplasm"[title] OR ("tubo-ovarian"[tiab] AND (neoplasm[tiab] OR carcinoma[tiab]))	243,952

Search	Query	Results
#9	Search: "adrenal gland neoplasms"[title] OR "adrenal neoplasms"[title] OR "bladder neoplasms"[title] OR "bone neoplasms"[title] OR "brain neoplasms"[title] OR "breast neoplasms"[title] OR "cervical neoplasms"[title] OR "colon neoplasms"[title] OR "colorectal neoplasms"[title] OR "gastric neoplasms"[title] OR "esophageal neoplasms"[title] OR "oesophageal neoplasms"[title] OR "esophageal carcinomas"[title] OR "oesophageal carcinomas"[title] OR "fallopian tube neoplasms"[title] OR "gastric neoplasms"[title] OR "gastrointestinal neoplasms"[title] OR "gi neoplasms"[title] OR "head and neck neoplasms"[title] OR "hepatocellular carcinomas"[title] OR "intestinal neoplasms"[title] OR "kidney neoplasms"[title] OR "liver neoplasms"[title] OR "lung neoplasms"[title] OR melanomas[title] OR osteosarcomas[title] OR "ovarian epithelial carcinomas"[title] OR "ovarian neoplasms" OR "ovarian carcinomas"[title] OR "pancreatic neoplasms"[title] OR "pancreatic ductal adenocarcinomas"[title] OR "pancreatic ductal carcinomas"[title] OR pdacs[title] OR "prostate neoplasms"[title] OR "prostatic neoplasms"[title] OR sarcomas[title] OR "stomach neoplasms"[title] OR ("tubo-ovarian"[tiab] AND (neoplasms[tiab] OR carcinomas[tiab]))	113,903
#10	Search: "adrenal gland cancer"[title] OR "adrenal cancer"[title] OR "bladder cancer"[title] OR "bone cancer"[title] OR "brain cancer"[title] OR "breast cancer"[title] OR "cervical cancer"[title] OR "colon cancer"[title] OR "colorectal cancer"[title] OR "esophageal cancer"[title] OR "oesophageal cancer"[title] OR "fallopian cancer"[title] OR "fallopian tube cancer"[title] OR "gastric cancer"[title] OR "gastrointestinal cancer"[title] OR "gi cancer"[title] OR "head and neck cancer"[title] OR "intestinal cancer"[title] OR "kidney cancer"[title] OR "liver cancer"[title] OR "lung cancer"[title] OR "ovarian cancer" OR "pancreatic cancer"[title] OR "prostate cancer"[title] OR "prostatic cancer"[title] OR "stomach cancer"[title] OR ("tubo-ovarian"[tiab] AND cancer[tiab])	830,076

Search	Query	Results
#11	Search: "adrenal gland cancers"[title] OR "adrenal cancers"[title] OR "bladder cancers"[title] OR "bone cancers"[title] OR "brain cancers"[title] OR "breast cancers"[title] OR "cervical cancers"[title] OR "colon cancers"[title] OR "colorectal cancers"[title] OR "esophageal cancers"[title] OR "oesophageal cancers"[title] OR "fallopian cancers"[title] OR "fallopian tube cancers"[title] OR "gastric cancers"[title] OR "gastrointestinal cancers"[title] OR "gi cancers"[title] OR "head and neck cancers"[title] OR "intestinal cancers"[title] OR "kidney cancers"[title] OR "liver cancers"[title] OR "lung cancers"[title] OR "ovarian cancers" OR "pancreatic cancers"[title] OR "prostate cancers"[title] OR "prostatic cancers"[title] OR "stomach cancers"[title] OR ("tubo-ovarian"[tiab] AND cancers[tiab])	24,630
#12	Search: multicancer[tiab] OR multicancers[tiab] OR multicancerous[tiab] OR "multi-cancer"[tiab] OR "multisite cancer"[tiab] OR "multisite cancers"[tiab] OR "multi-site cancer"[tiab] OR "multi-site cancers"[tiab] OR "multisite neoplasm"[tiab:~3] OR "multi-site neoplasm"[tiab:~3] OR "multisite neoplasms"[tiab:~3] OR "multi-site neoplasms"[tiab:~3]	393
#13	Search: #7 OR #8 OR #9 OR #10 OR #11 OR #12	2,847,107
#14	Search: #6 AND #13	263
#15	Search: "Early Detection of Cancer"[Mesh] OR "Mass Screening"[Mesh] OR screen*[tiab] OR detection[title] OR "early detect*"[tiab]	1,457,863
#16	Search: #14 AND #15	44
#17	Search: chemoprevention[tiab] OR chemopreventive[tiab] OR chemopreventative[tiab] OR chemotherapy[title] OR chemotherapies[tiab] OR chemotherapeutic[tiab] OR chemotherapeutics[tiab] OR drug[tiab] OR drugs[tiab] OR laboratory[tiab] OR medication[tiab] OR medications[tiab] OR pharmacogenetic[tiab] OR pharmacogenetics[tiab] OR pharmacogenomic[tiab] OR pharmacogenomics[tiab] OR pharmacotherapy[title] OR pharmacotherapies[tiab] OR pharmacotherapeutic[tiab] OR pharmacotherapeutics[tiab] OR "proof of concept"[tiab] OR "risk stratification"[tiab] OR vitro[tiab]	4,470,495
#18	Search: #16 NOT #17	26

Search	Query	Results
#19	Search: #18 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT ("Adult"[Mesh] OR adult[title] OR adults[title] OR Aged[Mesh] OR elder[title] OR elders[title] OR elderly[title] OR "Middle Aged"[Mesh]))	26
#20	Search: address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt]	3,349,594
#21	Search: #19 NOT #20	24
#22	Search: (animals[mesh] NOT humans[mesh]) OR bovine[tiab] OR canine[tiab] OR capra[tiab] OR cat[tiab] OR cats[tiab] OR cattle[tiab] OR cow[tiab] OR cows[tiab] OR dog[tiab] OR dogs[tiab] OR equine[tiab] OR ewe[tiab] OR ewes[tiab] OR feline[tiab] OR goat[tiab] OR goats[tiab] OR hamster*[tiab] OR horse[tiab] OR horses[tiab] OR invertebrate[tiab] OR invertebrates[tiab] OR kangaroo[tiab] OR kangaroos[tiab] OR macaque[tiab] OR macaques[tiab] OR mare[tiab] OR mares[tiab] OR mice[tiab] OR monkey[tiab] OR monkeys[tiab] OR mouse[tiab] OR murine[tiab] OR nonhuman[tiab] OR "non-human"[tiab] OR ovine[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR primate[tiab] OR primates[tiab] OR rabbit[tiab] OR rabbits[tiab] OR rat[tiab] OR rats[tiab] OR rattus[tiab] OR rhesus[tiab] OR rodent[tiab] OR rodents[tiab] OR rodentia[tiab] OR sheep[tiab] OR simian[tiab] OR sow[tiab] OR sows[tiab] OR vertebrate[tiab] OR vertebrates[tiab] OR whale[tiab] OR whales[tiab] OR zebrafish[tiab]	6,663,603
#23	Search: #21 NOT #22	21
#24	Search: #21 NOT #22 Filters: English	20

PubMed Patch Search 2, additional multicancer screening terms, 5/7/2024

Search	Query	Results
#1	Search: "Biomarkers, Tumor"[Mesh] OR "Cell-Free Nucleic Acids"[Mesh] OR "Circulating Tumor DNA"[Mesh] OR (("Liquid Biopsy"[Mesh] OR "liquid biopsy"[tiab:~0]) AND Neoplasms[Mesh]) OR "blood-based biomarker"[tiab:~0] OR "blood-based biomarkers"[tiab:~0] OR "blood-based screening"[tiab:~0] OR "blood-based test"[tiab:~0] OR "blood-based testing"[tiab:~0] OR "blood-based tests"[tiab:~0] OR "blood biomarker"[tiab:~0] OR "blood biomarkers"[tiab:~0] OR ccfDNA[tiab] OR cfDNA[tiab] OR ctDNA[tiab] OR "cell-free DNA"[tiab:~0] OR "cell-free nucleic acid"[tiab:~0] OR "cell-free nucleic acids"[tiab:~0] OR "Cell-Free RNA"[tiab:~0] OR cfRNA[tiab] OR cirRNA[tiab] OR "Cell-Free Ribonucleic Acid"[tiab:~0] OR "Circulating RNA"[tiab:~0] OR "cell-free tumor"[tiab:~0] OR "cell-free tumor"[tiab:~0] OR "circulating cell-free"[tiab:~0] OR "circulating DNA"[tiab:~0] OR "circulating nucleic acid"[tiab:~0] OR "circulating nucleic acids"[tiab:~0] OR "circulating nucleotide"[tiab:~0] OR "circulating nucleotides"[tiab:~0] OR "circulating tumor DNA"[tiab:~0] OR "circulating tumor DNA"[tiab:~0] OR "multicancer early detection"[all fields] OR "multi-cancer early detection"[tiab:~0] OR MCD[tiab] OR MCDs[tiab] OR MCED[tiab] OR MCEDs[tiab] OR "tumor biomarker"[tiab:~0] OR "tumor biomarkers"[tiab:~0] OR "tumor biomarker"[tiab:~0] OR "tumor biomarkers"[tiab:~0] OR tcfDNA[tiab] OR "tumor cell-free DNA"[All Fields] OR "tumor cell-free DNA"[All Fields] OR "tumor DNA methylation"[tiab] OR "tumor DNA methylation"[tiab]	346,008
#2	Search: "multi-cancer screening"[tiab:~0] OR "multicancer screening"[tiab:~0]	27
#3	Search: #2 NOT #1	14
#4	Search: #2 NOT #1 Filters: English	12
#5	Search: chemoprevention[tiab] OR chemopreventive[tiab] OR chemopreventative[tiab] OR chemotherapy[title] OR chemotherapies[tiab] OR chemotherapeutic[tiab] OR chemotherapeutics[tiab] OR drug[tiab] OR drugs[tiab] OR laboratory[tiab] OR medication[tiab] OR medications[tiab] OR pharmacogenetic[tiab] OR pharmacogenetics[tiab] OR pharmacogenomic[tiab] OR pharmacogenomics[tiab] OR pharmacotherapy[title] OR pharmacotherapies[tiab] OR pharmacotherapeutic[tiab] OR pharmacotherapeutics[tiab] OR "proof of concept"[tiab] OR "risk stratification"[tiab] OR vitro[tiab]	4,471,142

Search	Query	Results
#6	Search: #4 NOT #5	12
#7	Search: #6 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT ("Adult"[Mesh] OR adult[title] OR adults[title] OR Aged[Mesh] OR elder[title] OR elders[title] OR elderly[title] OR "Middle Aged"[Mesh]))	12
#8	Search: address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt]	3,349,895
#9	Search: #7 NOT #8	12
#10	Search: (animals[mesh] NOT humans[mesh]) OR bovine[tiab] OR canine[tiab] OR capra[tiab] OR cat[tiab] OR cats[tiab] OR cattle[tiab] OR cow[tiab] OR cows[tiab] OR dog[tiab] OR dogs[tiab] OR equine[tiab] OR ewe[tiab] OR ewes[tiab] OR feline[tiab] OR goat[tiab] OR goats[tiab] OR hamster*[tiab] OR horse[tiab] OR horses[tiab] OR invertebrate[tiab] OR invertebrates[tiab] OR kangaroo[tiab] OR kangaroos[tiab] OR macaque[tiab] OR macaques[tiab] OR mare[tiab] OR mares[tiab] OR mice[tiab] OR monkey[tiab] OR monkeys[tiab] OR mouse[tiab] OR murine[tiab] OR nonhuman[tiab] OR "non-human"[tiab] OR ovine[tiab] OR pig[tiab] OR pigs[tiab] OR porcine[tiab] OR primate[tiab] OR primates[tiab] OR rabbit[tiab] OR rabbits[tiab] OR rat[tiab] OR rats[tiab] OR rattus[tiab] OR rhesus[tiab] OR rodent[tiab] OR rodents[tiab] OR rodentia[tiab] OR sheep[tiab] OR simian[tiab] OR sow[tiab] OR sows[tiab] OR vertebrate[tiab] OR vertebrates[tiab] OR whale[tiab] OR whales[tiab] OR zebrafish[tiab]	6,664,205
#11	Search: #9 NOT #10	12

Appendix C.
Data Abstraction Elements

KQ 1, 2, 4, and 5 Studies

Question Text	Type	Answer Text
Article Title	Text	
Year Published	Text	
First Author's Last Name	Text	
Study Registration Number (if reported). This will be the NCT number or an alternative trial/study registration number	Text	
Cohort or Trial Name (if applicable)	Text	
Study Design	Radio	RCT
		Non-randomized study of intervention(s)
		Other
Identify the KQs for which this study reports data Link to Draft Protocol	Checkbox	KQ 1: Benefits of Screening (Mortality)
		KQ 2: Benefits of Screening (Detection)
		KQ 4: Harms of Screening
		KQ 5: Harms of Evaluation/Surveillance
Country	Checkbox	U.S. Only
		U.S. + Other Countries
		Multiple Countries other than U.S.

Question Text	Type	Answer Text
		Canada
		Europe
		Asia
		Middle East
		Oceania (Australia, New Zealand)
		Central or South America
Total N randomized/enrolled	Text	
Very brief study population description comprising key age and clinical eligibility criteria, and recruitment setting	Text	
Mean (SD) age of included population. Note: report the mean age for the entire study population, unless authors only report this information by group. If a measure other than mean is reported (e.g., median), indicate that.	Text	
Age range of included population (if reported).	Text	
% of participants ≥65 years (if reported)	Text	
% of participants <50 years (if reported)	Text	
% Female Note: report for study population overall; report by study group if only reported this way by study authors.	Text	

Question Text	Type	Answer Text
Race and ethnicity Note: in this field report the data using the terms and categories that author reports.	Text	
% White/Caucasian/European origin	Text	
Comments	Text	
% Black/African American/African origin	Text	
Comments	Text	
% Native/Indigenous populations (American Indian, Alaska Native, First Nations in Canada, Indigenous Australians, etc.)	Text	
Comments	Text	
% Asian	Text	
Comments	Text	
% Hispanic	Text	
Comments	Text	
% Other	Text	
Comments	Text	
Detailed recruitment setting	Text	
Detailed inclusion criteria Note: include details related to selection based on being at average or higher risk for cancer.	Text	

Question Text	Type	Answer Text
Detailed exclusion criteria Note: focus on criteria related to cancer history or risks, symptom status, or other clinical characteristics.	Text	
Denote whether the population was selected based on their risk for cancer (selected for being average risk, selected for being at higher risk, or no mention of selection based on cancer risk).	Radio	Average Risk
		Higher Risk
		Not reported
Does this study report outcomes based on any subpopulations of interest to this review?	Checkbox	Rural
		Race/ethnicity
		Health insurance coverage
Other comments about study or population characteristics	Text	
Brief Name Screening Intervention Group	Text	
Brief narrative description of screening intervention	Text	
Is test commercially available?	Radio	Yes
		No

Question Text	Type	Answer Text
		Unclear
Commercial name of test (if applicable)	Text	
Narrative description of test Note: succinctly summarize the author's description of test including key steps in the assay and use of AI, machine learning, or software classifiers to process and classify data from specimens.	Text	
Type of analyte	Checkbox	Cell-free nucleic acid (DNA, RNA, microRNA, methylation)
		Protein-based biomarkers (specific proteins, protein modifications)
		Exosome
		Circulating tumor cells
		DNA fragmentation
		Metabolic-based biomarkers
		Others
List protein biomarkers Note: list full names and abbreviations.	Text	
Type of cell-free nucleic acid	Checkbox	DNA
		RNA

Question Text	Type	Answer Text
		microRNA
		Unclear
Type of method/technology	Checkbox	NGS (panel, exome, genome)
		Quantitative PCR (digital droplet, real-time)
		Mass spectrometry
		Immunoassay
		Other
		RNA?
Type of specimen	Radio	Plasma
		Serum
		Other
Sample processing	Radio	Fresh
		Frozen
		Other
Does this test involve a second-stage of testing to determine tissue of origin?	Radio	Yes (describe)
		No
N randomized	Text	
Screening Interval	Radio	One time

Question Text	Type	Answer Text
		Annual
		Other frequency
Duration of Active Screening Intervention Record in months if less than 1 year. Otherwise, record in years. Note: this refers to the time period over which participant were screened. Not the followup time for which outcomes were measured.	Text	
For interventions that involved more than a one-time screening, how many rounds of screening took place?	Text	
Fidelity/Adherence to Screening Intervention Over Duration of Study Report any information about adherence to the screening intervention over the study duration.	Text	
Standard of Care Screening Received Report any information related to the receipt of standard of care screening tests by people in the screening group for breast, colorectal, lung, prostate, or cervical cancer.	Text	
N randomized	Text	
Brief Name Comparator Group	Text	
Brief narrative description of comparator intervention	Text	

Question Text	Type	Answer Text
Standard of Care Screening Received Report any information related to the receipt of standard of care screening tests by people in the comparator group for breast, colorectal, lung, prostate, or cervical cancer.	Text	
Contamination of control group Describe any information related to the receipt of MCSTs in the control group over the period of the study.	Text	
Which outcomes does this study report?	Checkbox	Cancer detection overall
		Cancer detection by stage
		Cancer detection by cancer type
		Cancer-specific mortality
		All-cause mortality
		Quality of life
		Functional status
Screening group author-reported mortality N (%)	Text	
Screening Group N analyzed	Text	
Screening Group N deaths from any cause	Text	

Question Text	Type	Answer Text
Comparator group author-reported mortality N (%)	Text	
Comparator group N analyzed	Text	
Comparator Group N deaths from any cause	Text	
Author-reported relative effect (RR, OR, HR) and 95% CI	Text	
Author-reported absolute effect and 95% CI	Text	
All-cause mortality relevant subgroup results	Text	
Quality of Life Outcomes	Text	
Functional Status Outcomes	Text	
Comments on Benefits Outcomes	Text	
Time frame of followup for harms outcomes. Enter the time frame over which the subsequent harm outcomes reported occur if different than the overall study followup time.	Text	
Adverse events from diagnostic testing after a positive screening test	Text	
Radiation exposure	Text	
Change in health behaviors or receipt of standard of care cancer screening	Text	
Psychosocial harms	Text	

Question Text	Type	Answer Text
Impact on health insurance status (i.e., loss of coverage because of positive screening test)	Text	
Out-of-pocket patient cost/patient financial toxicity	Text	
Overdiagnosis	Text	
Comments on harm outcomes	Text	

AI = artificial intelligence; CI = confidence interval; HR = hazard ratio; KQ = key question; MCST = multiple cancer screening test; N = number; NCT = National Clinical Trial; NGS = next-generation sequencing; OR = odds ratio; PCR = polymerase chain reaction; RR = risk ratio; SD = standard deviation; U.S. = United States.

KQ3 (Accuracy Studies)

Question Text	Type	Answer Text
Year of publication	Text	
First Author last name	Text	
Study Cohort Name (if applicable)	Text	
Study Registration No. (if applicable)	Text	
Relevant companion study reference ids.	Text	
Study Funder	Text	
Country (Country from where patients were recruited)	Radio	U.S. Only
		U.S. + Other Countries
		Multiple Countries other than U.S.
		Canada
		Europe
		Asia
		Middle East
		Oceania (Australia, NZ)
		Central or South America
What is the study aim?	Radio	Multicancer detection test accuracy
		Single-cancer detection test accuracy
		Other
Study design	Radio	Diagnostic performance
		Prediagnostic performance
		Other
Accuracy is reported for which types of cohorts: Note: split sample designs are typically development and internal validation. External validation are cohorts that were not used at all for developing the test.	Radio	Development cohort
		Internal validation cohort
		External validation cohort
		Development and internal validation cohorts
		Development and external validation cohorts

Question Text	Type	Answer Text
		Development, internal, and external validation cohorts
		Other
Brief narrative description of study population.	Text	
Mean (SD) age of included population. Note: report the mean age for the entire study population, unless authors only report this information by group. If a measure other than mean is reported (e.g., median), indicate that.	Text	
Age range of included population (if reported)	Text	
% of participants ≥65 years (if reported)	Text	
% of participants <50 years (if reported)	Text	
% Female Note: report for study population overall; report by study group if only reported this way by study authors.	Text	
Race and ethnicity Note: in this field report the data using the terms and categories that author reports.	Text	
% White/Caucasian/European origin	Text	
Comments	Text	
% Black/African American/African origin	Text	
Comments	Text	
% Native/Indigenous populations (American Indian, Alaska Native, First Nations in Canada, Indigenous Australians, etc.)	Text	
Comments	Text	
% Asian	Text	
Comments	Text	

Question Text	Type	Answer Text
% Hispanic	Text	
% Other	Text	
Comments	Text	
Detailed description of 'control' population (s) Note: source of recruitment, health status, any significant comorbidities.	Text	
Control Population 1 Name	Text	
Control Population 1 N	Text	
Control Population 2 Name	Text	
Control Population 2 N	Text	
Cancer Population Name Note: Diagnosed Cancer for this item	Text	
Cancer Population N	Text	
N enrolled at baseline	Text	
Were all cancer diagnoses confirmed and staged with tissue/specimen biopsy?	Radio	Yes
		No
		Other
Length of followup (in years) used to consider participants cancer free	Text	
Comments on reference standard	Text	
Is test commercially available?	Radio	Yes
		No
		Unclear
Commercial name of test (if applicable)	Text	

Question Text	Type	Answer Text
Narrative description of test Note: succinctly summarize the author's description of test including key steps in the assay and use of AI, machine learning, or software classifiers to process and classify data from specimens.	Text	
Type of analyte	Checkbox	Cell-free nucleic acid (DNA, RNA, microRNA, methylation)
		Protein-based biomarkers (specific proteins, protein modifications)
		Exosome
		Circulating tumor cells
		DNA fragmentation
		Metabolic-based biomarkers
		Others
List protein biomarkers Note: list full names and abbreviations.	Text	
Type of cell-free nucleic acid	Checkbox	DNA
		RNA
		microRNA
		Unclear
Type of method/technology	Checkbox	NGS (panel, exome, genome)
		Quantitative PCR (digital droplet, real-time)
		Mass spectrometry
		Immunoassay
		Other
		RNA?
Type of specimen	Radio	Plasma
		Serum
		Other
Sample processing	Radio	Fresh
		Frozen
		Other
N (%) of participants with cancer identified through clinical presentation (if reported	Text	
N (%) of participants with cancer identified through screening (if reported)	Text	

Question Text	Type	Answer Text
Type of cancers and N for each type	Checkbox	Anus
		Bladder
		Blood or lymph
		Brain
		Breast
		Cervical
		Colorectal
		Esophageal
		Head and neck
		Liver/Gallbladder/Bile duct
		Lung
		Melanoma
		Ovarian
		Pancreas
		Prostate
		Sarcoma
		Stomach
		Uterine
		Other
Stage I N	Text	
Stage I %	Text	
Stage I comments	Text	
Stage II N	Text	
Stage II %	Text	
Stage II comments	Text	
Stage III N	Text	
Stage III %	Text	
Stage III comments	Text	
Stage IV N	Text	
Stage IV %	Text	
Stage IV comments	Text	
Stage missing N	Text	

Question Text	Type	Answer Text
Stage missing %	Text	
Stage missing comments	Text	
Stage not reported N	Text	
Stage not reported %	Text	
Stage not reported comments	Text	
Total Cancer Diagnoses N	Text	
Author-reported Total N cancer diagnoses	Text	
Comments on Total N	Text	

For each test, cancer type, and subpopulation:

N True Positives (participants with cancer and positive test)	
N False Negatives (participants with cancer and negative test)	
N True Negatives(participants without cancer and negative test)	
N False Positives (participants without cancer and positive test)	
Author-reported Sensitivity (95% CI)	
Author-reported Specificity (95% CI)	
Author-reported AUC (95% CI)	
Comments	

AI = artificial intelligence; AUC = analytical ultracentrifugation; CI = confidence interval; N = number; NGS = next-generation sequencing; NZ = New Zealand; PCR = polymerase chain reaction; U.S. = United States.