Topic Brief: Tumor Cell-free DNA for Cancer Screening

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Purpose: This document summarizes information addressing a nomination submitted on June 1, 2023, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: Genomic testing for cancer screening is changing rapidly, with multiple, blood-based screening tests coming to market every year.[1] Sometimes referred to as "liquid biopsies," multicancer early detection (MCED) tests can detect cell-free DNA (cfDNA) or circulating tumor DNA (ctDNA) in the bloodstream for up to 50 different cancers from a single blood sample. However, evidence about the clinical utility of MCEDs remains limited. Clinicians, patients, and payers need robust evidence to determine the potential benefits and harms of these new tests. A review on this topic potentially would be used by the nominator, Medicaid Evidence-based Decisions (MED) project – a collaborative of 22 state Medicaid programs – to inform MCED coverage policies across approximately half of US Medicaid programs.
Link to topic nomination

Findings
The EPC Program will develop a new systematic review based on this nomination. The scope of this topic will be further developed in the refinement phase. When key questions have been drafted, they will be posted on the AHRQ Web site and open for public comment. To sign up for notification when this and other Effective Health Care (EHC) Program topics are posted for public comment, please go to https://effectivehealthcare.ahrq.gov/email-updates.

Background and Nomination Summary
Multicancer early detection (MCED) tests have an intriguing potential for population cancer screening.[1,2] Like many technological advancements, the development of MCEDs was born out of an unexpected discovery.[3] In 2013, researchers discovered a link between discordant findings from a non-invasive prenatal test (NIPT) for fetal chromosomal abnormalities and a subsequent diagnosis of maternal cancer.[4] The previously undiscovered tumor had shed cells into the bloodstream of the expectant mother and were picked up as fetal abnormalities on the NIPT results. The implications for early cancer detection in asymptomatic patients were recognized by test developers and led to a rapid expansion of these technologies.[5]

Malignant tumors can shed DNA fragments into the bloodstream long before becoming symptomatic and therefore provide the possibility of very early cancer detection.[6] For those who are at average or high-risk for certain cancers and who are currently asymptomatic, a simple biomarker test may be able to detect more than 50 different cancers, most of which currently have no recommended screening methods.[7] Genomic testing is used widely in precision medicine to aid in initial targeted treatment selection, identify treatment resistance and to measure minimal residual disease (MRD) at the end of a course of treatment.[8] While payer coverage policies for these uses of cfDNA tests are expanding,[9] coverage for MCEDs is now uncommon, perhaps because payers still consider them to be investigational.[8,10] One measure

of the extraordinary interest in MCEDs is the US Senate's bill titled the Multi-Cancer Early Detection (MCED) Screening Coverage Act which was initially introduced into the 117th Congress and was reintroduced in 2023. If passed into law, this would require CMS to cover an annual MCED test for all Medicare beneficiaries if and when these tests receive FDA approval.[11] Companion legislation in the House of Representatives known as the Nancy Gardner Sewell Medicare Multi-Cancer Early Detection (MCED) Screening Coverage Act (H.R. 2407) is simultaneously attempting to create a legal pathway to coverage. Test developers are undertaking large clinical trials and partnering with health systems and research institutions in the UK, and the large trials in the US are developing evidence of clinical utility that could inform FDA decisions (see under KQ1a/biii in Table 1).

Currently there are only four cancers recommended for screening by the US Preventive Services Task Force (USPSTF) (breast, cervical, colorectal, and lung). An economic model published in August 2023 found that USPSTF-recommended cancer screenings for breast, colorectal, cervical, and lung cancer, have "…saved 12.2–16.2 million life-years since the introduction of USPSTF recommendations, ~ 75% of potential with perfect adherence. These benefits translate into a value of $8.2-$11.3 trillion at full potential and $6.5-$8.6 trillion considering current adherence."[12] The life-year or economic impact of MCED or cfDNA screening technologies on the US population remains unknown. Currently, there are more than a thousand ongoing clinical trials looking at the efficacy of MCEDs for diagnosing, treating, and surveilling cancer. There are, however, significant knowledge gaps for use of this technology for cancer screening.[13]

A report on the available evidence on tumor cell-free DNA for cancer screening in asymptomatic average or high-risk individuals would inform policy and coverage decisions in 22 state Medicaid programs. We worked closely with the nominator to narrow the scope of the initial nomination, including dividing results into three groups: cancers that have no other screening modalities; cancers with screening procedures done in specific populations and circumstances; and cancers with gold standard and routine screening modalities. Importantly, the nominator wanted to focus on the clinical utility of MCED cfDNA tests for population screening of asymptomatic persons. While lab-based validation studies were excluded, the authors of this brief ultimately included studies that evaluated at least two of the following groups in order to validate or evaluate the test of interest: healthy control samples, high risk samples, and samples of those with a known illness. We have reported results on tests for screening for both single and multiple cancer types.

Current Policy Context

While public and private payer coverage policies for circulating tumor DNA tests for cancer diagnostics and treatment are expanding,[8,9] we did not find any evidence of payer coverage for MCEDs in population screening. Currently available literature includes one paper on considerations for payer coverage of screening tests,[7] two overviews of public and private payer policies for cancer diagnostics and treatments,[8,9] and one qualitative study exploring private payer perspectives on screening tests.[10] Two professional societies (AAFP[1] and ACP[14]) have issued statements regarding the use of genomic testing and MCEDs. CMS also released a national coverage determination on blood-based biomarker screening for colorectal cancer in 2023.[15]

Deverka et.al. explored considerations related to payer coverage of MCEDs.[7] Payers require robust evidence to make positive policy coverage decisions. Concerns that will need to be addressed before granting coverage include potential harms of MCEDs such as overdiagnosis and overtreatment based on false positive tests and missed cancers based on false negative tests. Clinical measurements that show true benefit of early detection versus lead time bias will also be important to payer decision-making. Medicare requires specific legislative exceptions or an A or B rating from the USPSTF to cover screening tests. In addition, existing payer

evidentiary frameworks will need to be modified to account for multiple vs. single cancer screening.

Trosman et.al. conducted semi-structured qualitative interviews with senior executives from 19 national and regional payer organizations to explore their perspectives on coverage policies for MCEDs.[10] Respondents were all knowledgeable about or responsible for coverage policy decision making. None of the payers interviewed currently provide population screening with MCEDs as a covered benefit for plan members. Payers expressed interest in the tests as a possible covered benefit, but only as a yet unproven breakthrough. They would be most likely to cover screening for particularly lethal cancers that are without current screening methods such as ovarian, brain or pancreatic cancer if clinical utility can be demonstrated. They also identified significant concerns such as lack of care protocols for MCED identified cancers, high false-negative rates and inclusion of screening for cancers without demonstrated benefit of early detection. In addition, payers did not see MCEDs as an avenue to address health disparities in patient outcomes.

The American Academy of Family Physicians (AAFP) published an editorial describing the use of MCEDs for cancer screening and identified numerous concerns including false positive test results, identification of indolent cancers and lack of clearly defined diagnostic pathways for screening-identified cancers.[1] The editorial warns against promoting the use of these tests unless within "well-designed clinical research studies."[1]

The American College of Physicians (ACP) released a position paper in September 2022 that was written as a complement to the ACP Ethics Manual.[14] Information regarding specific tests for genetic variant testing, whole-genome sequencing and MCEDs are not covered. Rather, the paper offers physicians general information to help them guide shared decision-making in a clinical setting. Suggestions include that genetic testing should be guided by the best interests of the patient while considering the best available evidence of benefits and harms for specific types of testing.[14] Stated concerns include false positive test results, costs of tests not covered by insurance, incidental findings and possible employment or insurance discrimination.[14]

CMS released a National Coverage Determination (NCD) effective January 19, 2021 that covers a "blood-based biomarker test…[for] colorectal cancer screening" once every 3 years for Medicare beneficiaries.[15] The NCD further states that coverage is for people who are asymptomatic, at average risk for developing colorectal cancer and between 45-85 years of age.[15]

These findings illustrate the rapidly evolving clinical and policy context within which MCEDs are developing and coming to market. Overall, public and private payers are waiting for further evidence that demonstrates MCEDs provide an actual benefit for population screening before making coverage determinations.

Scope

KQ1. What is the (a) efficacy and (b) safety of circulating tumor cell-free DNA screening tests compared to alternative screening approaches?

Population: asymptomatic adults at average or high risk for cancer

Intervention: Circulating tumor cell-free DNA blood tests for single or multisite cancer *screening and early detection* across three groups:

i. Cancers that don't have other screening modalities (i.e., pancreatic, liver, ovarian, and fallopian cancers)
ii. Cancers with screening modalities for specific patient groups or circumstances (i.e., lung, prostate)
iii. Cancers with gold standard and routine screening modalities (i.e., breast, cervical, and colon cancers)

Exclude: tests for cancer diagnosis, treatment/management, or tracking disease progression/monitoring.

Comparator: Other cancer screening tests or no comparator.

Outcome: Overall mortality, cancer specific mortality, early cancer detection, harms (e.g., false positives/negatives, additional post-screening testing and treatment, emotional distress, adverse events and safety profile of tests), costs, resource utilization, social harms of test results

Study designs: RCT, controls, observational, other human studies
Exclude: in vitro/lab-based proof of concept

Assessment Methods
See Appendix A.

Summary of Literature Findings
The literature search identified 43 systematic reviews and meta-analyses, of which 13 addressed parts of the intended scope of KQ1. However, because the scope of this nomination covers any cancer type, this set of reviews does not cover all the technology types and cancer types of interest.

We found a total of 25 relevant primary studies from a search total of 327 addressing KQ1. These studies varied in size, with some as small as 100 participants, and one prospective observational study which included 5,461 participants. The overwhelming majority of the studies we identified focus on the utility and validity of specific tests in the early detection of single cancers. We also identified a 2022 review of currently ongoing clinical trials of cell-free DNA analysis.[16] This review identified 1,129 trials in ClinicalTrials.gov and 241 clinical trials from the European Medicines Agency that involve cfDNA/ctDNA analysis in at least 25 types of cancer, covering the cancer types in KQs 1 i, ii, and iii. A narrative review in JAMA Internal Medicine was also published in September 2023, which included a table of 15 ongoing clinical trials.[2] Notably, a National Cancer Institute clinical trial of 24,000 individuals will begin recruiting next year (VANGUARD trial).[17] See Table 1 below. The evidence base on the use of MCEDs will evolve over the next several years, but a systematic review on current published studies would define the state of the evidence at this point in time.

Table 1. Literature identified for KQ 1 a/b

Question	Systematic reviews (8/2020-8/2023)	Primary studies (8/2018-8/2023)
KQ1a/b i. cancers that don't have other screening modalities (i.e., pancreatic, liver, ovarian, and fallopian cancers)	Hepatocellular Carcinoma SR:1[18] Hepatocellular Carcinoma SR & MA:1[19] Pancreatic SR: 4[20-22] Ovarian Cancer MA: 1[23]	**Hepatocellular Carcinoma: 4** • Case-Control: 2[24,25] • Prospective Cohort: 2[26,27] **Pancreatic: 3** • Cohort: 3[28-30] **Ovarian: 1** • RCT: 1[31] **Bladder Cancer: 1** • Prospective Cohort: 1[32]

Question	Systematic reviews (8/2020-8/2023)	Primary studies (8/2018-8/2023)
KQ1a/b ii. cancers with screening modalities for specific patient groups or circumstances (i.e., lung, prostate, gastric, esophageal)	Lung Cancer SR: 1[33] Upper GI Cancers SR: 1[34] Various GI Cancers SR: 1[35]	**Multi-Cancer Screening: 5** • Prospective Observational: 4[36-39] • Longitudinal: 1[40] *Clinical Trials: 1[41]* **Esophageal: 2** • Prospective Cohort: 2[42,43] **Gastric: 1** • Cohort: 1[44]
KQ1a/b iii. cancers with gold standard and routine screening modalities (i.e., breast, cervical, and colon cancers)	Colorectal Cancer SR: 2[45,46] Colorectal Cancer MA: 1[47] Colorectal Cancer SR&MA: 1[48]	**Colorectal Cancer: 6** • Multicenter Cohort: 1[49] • Prospective Cohort: 3[50-52] • Case-Control: 1[53] • Retrospective: 1[54] *Clinical Trials: 3[55-57]* **Breast Cancer: 2** • Case-Control: 1[58] • Prospective: 1[59]

Abbreviations: GI=Gastrointestinal; MA=Meta-Analysis; RCT=Randomized Controlled Trial; SR=Systematic Review

Summary of Selection Criteria Assessment

A systematic review on the use of cell-free DNA for cancer screening in asymptomatic, average- or high-risk individuals would be appropriate, important, and timely. We identified 13 reviews over the past three years and 25 studies and several ongoing clinical trials over the past five years that meet inclusion criteria. A small-medium sized systematic review focusing on this emerging technology and its evidence would help to bring together a diffuse literature base, and potentially identify future research needs.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

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Conflict of Interest
None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance
We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication
We searched for high-quality, completed or in-process evidence reviews published in the last three years August 17, 2020 - August 17, 2023 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
    - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
    - EHC Program https://effectivehealthcare.ahrq.gov/
    - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
    - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
    - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
    - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- University of York Centre for Reviews and Dissemination database https://www.crd.york.ac.uk/CRDWeb/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/
- PCORI https://www.pcori.org/
- Joanna Briggs Institute http://joannabriggs.org/

Impact of a New Evidence Review
The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review
We conducted a limited literature search in PubMed and PsycInfo for the last five years August 17, 2018- August 17, 2023. Because a large number of articles were identified, we reviewed a random sample of 200 titles and abstracts for each question for inclusion. We classified identified studies by question and study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample.

Search strategy

Ovid MEDLINE ALL 1946 to August 17, 2023
Date searched: August 18, 2023

1 Circulating Tumor DNA/ or (exp Neoplasms/ and Liquid Biopsy/) (4262)
2 (ccfDNA or cfDNA or ctDNA or ((cancer* or malignan* or neoplas* or tumo?r*) adj10 ((cell-free adj2 DNA) or "circulating DNA" or "circulating free DNA" or "plasma DNA" or "serum DNA")) or "circulating tumor DNA" or "circulating tumour DNA").ti,ab,kf,nm,rn. (10525)
3 (ALX4 or CA19-9 or "C-X-C motif chemokine ligand" or CXCL8 or EPB41L3 or "exosomal enabled homolog" or ENAH or FAM150A or LOC100128977 or LOC100130148 or "matrix metalloproteinase-9" or MMP-9 or MethyLight or MIR663 or mSEPT9 or Neurog1 or PanSEER or PanCancer or PDAC or PIVKA-II or Sept9 or Septin9 or SIX3 or TRIM73 or Trimeth or Vimentin).ti,ab,kf,kw. (82726)
4 or/1-3 (94160)
5 Mass Screening/ (116440)
6 ((early adj3 detect*) or screen*).ti,kf,kw. (266649)
7 or/5-6 (317282)
8 and/4,7 (1461)
9 limit 8 to english language (1420)
10 9 not ("case report" or dementia or embryo* or faecal or fecal or fetal or foetal or metastat* or nutrition or pregnan* or prenatal* or stool or trimester or trisomy or urine or vitro).ti. (1142)
11 10 not ("case reports" or editorial or letter or news).pt. (1096)
12 limit 11 to yr="2020 - 2024" (582)
13 12 and ((meta-analysis or systematic review).pt. or (meta-anal* or metaanal* or ((evidence or review or scoping or systematic or umbrella) adj3 (review or synthesis))).ti.) (32)
14 limit 11 to yr="2018 - 2024" (774)
15 14 and ((controlled clinical trial or randomized controlled trial).pt. or (random* or trial*).ti,kf.) (13)
16 15 not 13 (13)
17 14 and (Case-Control Studies/ or Cohort Studies/ or Comparative Study/ or Controlled Before-After Studies/ or Cross-Sectional Studies/ or Epidemiologic Studies/ or exp Evaluation Studies as Topic/ or Interrupted Time Series Analysis/ or Prospective Studies/ or ("case-control" or cohort$1 or "before-after" or comparative or epidemiologic or evaluation or cross-sectional or "interrupted time" or longitudinal$2 or prospective$2).ti,kf.) (164)
18 17 not (13 or 16) (151)

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials July 2023
Date searched: August 18, 2023
1 Circulating Tumor DNA/ or (exp Neoplasms/ and Liquid Biopsy/) (82)
2 (ccfDNA or cfDNA or ctDNA or ((cancer* or malignan* or neoplas* or tumo?r*) adj10 ((cell-free adj2 DNA) or "circulating DNA" or "circulating free DNA" or "plasma DNA" or "serum DNA")) or "circulating tumor DNA" or "circulating tumour DNA").ti,ab. (1272)
3 (ALX4 or CA19-9 or "C-X-C motif chemokine ligand" or CXCL8 or EPB41L3 or "exosomal enabled homolog" or ENAH or FAM150A or LOC100128977 or LOC100130148 or "matrix metalloproteinase-9" or MMP-9 or MethyLight or MIR663 or mSEPT9 or Neurog1 or PanSEER or PanCancer or PDAC or PIVKA-II or Sept9 or Septin9 or SIX3 or TRIM73 or Trimeth or Vimentin).ti,ab,kf,kw. (2426)
4 or/1-3 (2506)
5 Mass Screening/ (4521)
6 ((early adj3 detect*) or screen*).ti,kf,kw. (20646)
7 or/5-6 (21942)
8 and/4,7 (92)
9 limit 8 to yr="2018 - 2024" (57)

ClinicalTrials.gov
Date searched: August 18, 2023

screening AND (ccfDNA OR cfDNA OR ctDNA OR "cell-free DNA" OR "circulating DNA" OR "circulating free DNA" OR "plasma DNA" OR "serum DNA" OR "tumor DNA") | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Cancer | First posted from 08/18/2018 to 08/18/2023 (123)

PROSPERO
Date searched: August 18, 2023
(((detect* or screen*) AND (ccfDNA OR cfDNA OR ctDNA OR ((cancer* OR malignan* OR neoplas* OR tumo?r*) AND ((cell-free AND DNA) OR "circulating DNA" OR "circulating free DNA" OR "plasma DNA" OR "serum DNA")) OR "circulating tumor DNA" OR "circulating tumour DNA"))):TI AND (Systematic Review OR Meta-Analysis OR IPD OR Network meta-analysis OR Review of reviews):RT AND (cancer):HA WHERE CD FROM 18/08/2020 TO 18/08/2023 (11)

Gray Literature/Policy Search

The SRC Librarian conducted a search of the gray literature for payer policy coverage in August 2023. Sources searched included webpages for Aetna, the American Cancer Society, Blue Cross Blue Shield, Cigna, CMS, Kaiser Permanente, and UnitedHealth Group webpages. Hand searches were also conducted by SRC staff to identify professional society guidance for the use of MCEDs.

Value
We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change, if a partner organization would use this evidence review to influence practice, and if the topic supports a priority area of AHRQ or the Department of Health and Human Services.

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes. Most of the US population will be screened for cancer at some point in their life.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the United States population or for a vulnerable population	The MED group will use a systematic review on the topic to inform a decision framework for policy and coverage decisions in state Medicaid of 22 states.
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. Coverage of routine cancer screening using noninvasive means could save money by detecting cancer early on, reducing treatment cost burden.
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	Yes. We did not find a systematic review that covers the entire scope of the nomination.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. There are no guidelines.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. There are currently no widely held coverage decisions for these types of routine screening tests.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	Size/scope of review: We identified 13 reviews, 25 primary research studies, and several clinical trials. This systematic review would be medium in size.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change and supports a priority of AHRQ or Department of Health and Human Services	Yes. A review on this topic could be amended as additional literature, evidence, and technology becomes available.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes. The MED group will use a systematic review to inform policy and coverage decisions in their network of 22 state Medicaid programs.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality.