Key Question Tumor Cell-free DNA for Cancer Screening

Background

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.

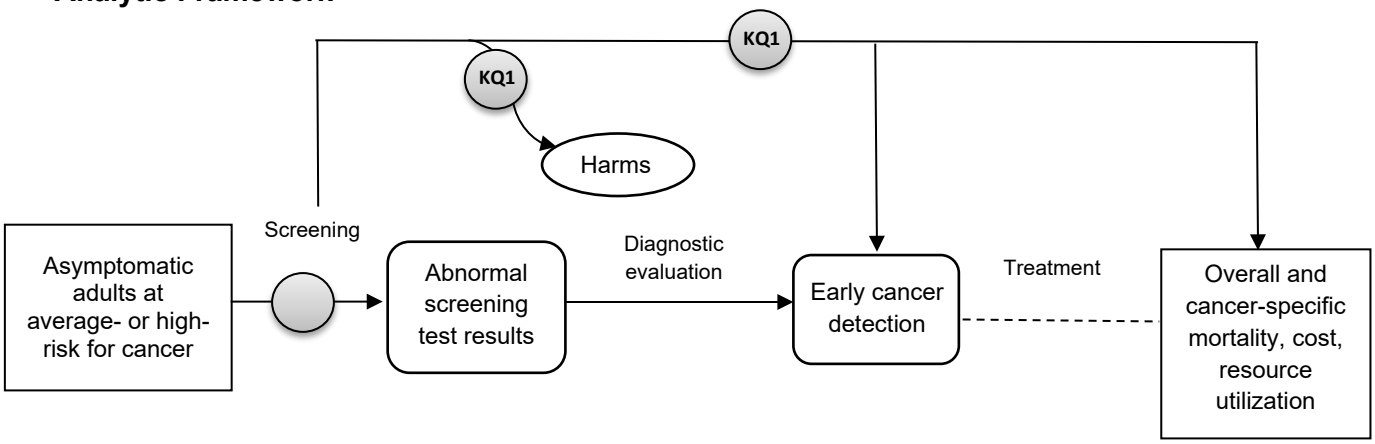
Currently, there are only four cancers recommended for screening by the US Preventive Services Task Force (USPSTF; breast, cervical, colorectal, and lung). An economic model published in August 2023 found that USPSTF-recommended cancer screenings for breast, colorectal, cervical, and lung cancer, have "…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 healthcare policy and coverage decisions. Overall, public and private payers are waiting for further evidence that demonstrates MCEDs provide an actual benefit for population screening before making coverage determinations.

Draft Key Question

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

Analytic Framework



Scope (PICOS Framework)

Population: Asymptomatic adults at average- or high-risk for cancer

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

1. Cancers that don't have other screening modalities (i.e., pancreatic, liver, ovarian, and fallopian cancers)
2. Cancers with screening modalities for specific patient groups or circumstances (i.e., lung, prostate)
3. 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 (accuracy, sensitivity, specificity), harms (e.g., false positives/negatives, additional post-screening testing

and treatment, emotional distress, adverse events, social harms of test results), costs, resource utilization

Study designs: RCT, controls, observational, other human studies

Exclude: in vitro/lab-based proof-of-concept studies

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