MED Scope Statement

Topic

Cell-Free DNA Blood Tests for Cancer Screening

Date: Spring 2023

Background

Small fragments of circulating tumor DNA in the blood (i.e., cell-free DNA) may offer opportunities for prognosis, monitoring, treatment selection, tumor burden, and screening for cancers.[1,2] Distinct from identifying tumor DNA to guide cancer treatment decisions or monitor response, cell-free DNA screening tests could be used to look for cancer in asymptomatic, average, or high-risk individuals.[2,3] Several factors are anticipated to limit the widespread use of cell-free DNA for screening including insufficient amounts of circulating DNA from small tumors or the misidentification of noncancerous DNA changes in white blood cells.[2-4] Taking lessons from the use of fetal cell-free DNA testing (also known as noninvasive perinatal testing [NIPT]), there is a risk of misuse or misinterpretation of these screening tests as diagnostic.[5] Screening tests warrant additional confirmatory diagnostic testing.

A preliminary search of Common Procedural and Testing (CPT) codes reveals relevant items[6,7]:

- 86152: Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood)
- 86153: Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required
- 0091U: Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as positive or negative result
- 0333U: Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in high-risk patients, analysis of methylation patterns on circulating cell-free DNA pls measurement of serum of AFP/AFP-L3 and oncoprotein des-gamma-carboxy-prothrombin, algorithm reported as normal or abnormal result

A 2022 review identified more than a thousand registered clinical trials, most for non-screening indications, on the use of cell-free DNA in cancer, reflecting the growing interest in this technology, with most studies addressing the most common cancer types (e.g., breast, colorectal, lung) or late-stage diagnoses (e.g., pancreas).[8] Other examples of cell-free DNA testing include individuals at high-risk for more rare cancers (e.g., gastric, liver).[9,10] Through the detection of cancer at an earlier stage, proponents of cell-free DNA screening predict it may improve survival.[2]

This report will summarize the available evidence on tumor cell-free DNA for cancer screening in asymptomatic average- or high-risk individuals and identify current coverage policies for these tests. This is distinct from the use of cell-free DNA for diagnosis and treatment planning (e.g.,

liquid biopsy) in individuals with cancer in locations challenging to biopsy or advanced stages (e.g., stage 4 lung cancer).[3]

PICO (for KQ1)

Population: Individuals at average or high risk for cancer

Intervention: Circulating tumor cell-free DNA blood tests for cancer screening

Comparator: Routine cancer screening care, laboratory tests, imaging (e.g., ultrasounds, mammogram) or procedures (e.g., colonoscopy)

Outcome: Overall mortality, cancer specific mortality, harms (e.g, false positives, additional testing, emotional distress), costs

Key Questions

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

KQ2. What are current coverage policies for circulating tumor cell-free DNA testing for cancer screening?

Proposed Approach

We will conduct a rapid review of relevant resources for up to 10 individual screening tests; we will search Center evidence sources (e.g., Ovid MEDLINE, Cochrane Library, other relevant databases) for systematic reviews of randomized controlled trials or individual randomized controlled trials of cell-free DNA compared to alternative methods for cancer screening. We will search databases for registered clinical trials (e.g., clinical trials.gov, ISRCTN). We will also analyze coverage polices from 5 private insurers, 10 state Medicaid agencies, and Medicare. Finally, we will interview 2 to 3 subject matter experts in this field to inform state considerations and future directions in this topic.

Related Center Resources

Godlewski B, King V. *Noninvasive prenatal testing for trisomies 21, 18, and 13 and common sex aneuploidies: Medicaid and commercial payer policies.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2020.https://www.medclearinghouse.org/topicfiles/pregnancy_childbirth_and_family_planning/prenatal_cellfree_dna_screening/

References

1. National Human Genome Research Institute. Cell-free DNA testing. 2022; https://www.genome.gov/genetics-glossary/Cell-Free-DNA-Testing. Accessed August 5, 2022.

2. Fiala C, Diamandis EP. Utility of circulating tumor DNA in cancer diagnostics with emphasis on early detection. *BMC Med.* 2018;16(1):166. doi: 10.1186/s12916-018-1157-9.

3. Krebs MG, Malapelle U, André F, et al. Practical considerations for the use of circulating tumor DNA in the treatment of patients with cancer: A narrative review. *JAMA Oncol.* 2022;8(12):1830-1839. doi: 10.1001/jamaoncol.2022.4457.

4. Fiala C, Diamandis EP. New approaches for detecting cancer with circulating cell-free DNA. *BMC Med.* 2019;17(1):159. doi: 10.1186/s12916-019-1400-z.

5. US Food & Drug Administration. FDA warns of risk associated with non-invasive prenatal screening tests 2022; https://www.fda.gov/news-events/press-announcements/fda-warns-risks-associated-non-invasive-prenatal-screening-tests. Accessed August 8, 2022.

6. Providence Health Plan. Circulating tumor cell and DNA assays for cancer management. 2021; https://s3-us-west-2.amazonaws.com/images.provhealth.org/Providence-Images/PHP_Circulating_Tumor_Cell_Assays_For_Cancer_Management.pdf. Accessed August 11, 2022.

7. Optum. October 2022 code addendum. 2022; https://www.optumcoding.com/upload/docs/CPT_October_2022_Code_Addendum.pdf. Accessed March 2, 2023.

8. Cisneros-Villanueva M, Hidalgo-Pérez L, Rios-Romero M, et al. Cell-free DNA analysis in current cancer clinical trials: a review. *Br J Cancer.* 2022;126(3):391-400. doi: 10.1038/s41416-021-01696-0.

9. Huang ZB, Zhang HT, Yu B, Yu DH. Cell-free DNA as a liquid biopsy for early detection of gastric cancer. *Oncol Lett.* 2021;21(1):3. doi: 10.3892/ol.2020.12264.

10. Xu RH, Wei W, Krawczyk M, et al. Circulating tumour DNA methylation markers for diagnosis and prognosis of hepatocellular carcinoma. *Nat Mater.* 2017;16(11):1155-1161. doi: 10.1038/nmat4997.