Multi-Cancer Early Detection Screening

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Introduction

Multi-cancer early detection screening tests are addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Multi-Cancer Early Detection (MCED) screening tests	81599 81479

Criteria

Introduction

Requests for multi-cancer early detection screening tests are reviewed using the following criteria. This guideline only addresses liquid biopsy screening tests for early cancer detection. Liquid biopsy testing for other purposes, including monitoring disease status and treatment selection in solid tumors and hematologic malignancies, is not addressed by this guideline. For information on liquid biopsy testing for other purposes, please refer to the guideline *Liquid Biopsy Testing*, as this testing is not addressed here.

This test is considered Experimental, Investigational, or Unproven.

- Experimental, Investigational, or Unproven (E/I/U) refers to tests, or uses of tests, that have insufficient data to demonstrate an overall health benefit. This typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity) and significantly improves patient health outcomes (clinical utility). Such tests are also not generally accepted as the standard of care in the evaluation or management of a particular condition.
- In the case of laboratory testing, FDA approval or clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight. In addition, FDA approval or clearance often does not include an assessment of clinical utility.

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What is Multi-Cancer Early Detection Screening?

Multi-cancer early detection (MCED) screening tests analyze biomarkers within blood and urine to predict the presence of cancers. Liquid biopsy to detect circulating free tumor DNA (cfDNA), circulating free tumor proteins, DNA methylation patterns, circulating free immune cell DNA and DNA fragment size is often utilized.[1,2] Multiple biomarkers, including genomic profiles, protein levels, and other analytes, may be combined to provide a comprehensive assessment of individual cancer risk. MCED tests screen for multiple cancer types simultaneously and aim to increase detection rates, particularly at earlier stages when a cancer may be more amenable to treatment.

Incidence

Each year, an estimated 2 million new cancer cases are diagnosed in the United States and over half a million individuals are expected to die from the disease.[3]

Screening and Diagnosis

Population-level screening programs are endorsed for only four cancer types in the United States: breast, cervical, colorectal, and lung cancers.[4] Other cancer types may have individualized screening recommendations, or lack any recognized screening protocols.[4] MCED screening tests are intended to complement existing screening programs and potentially increase rates of cancer detection because patients may be more willing to perform blood-based screening than currently recommended screening methodologies such as mammogram and colonoscopy. Screening for multiple cancer types at once could also allow identification of cancer types that do not have any current screening recommendations, such as pancreatic and stomach cancer.[5]

At this time, the number and type of cancers screened, and the ability to distinguish between cancer types, varies between individual tests. This is partly due to the fact that current MCED screening tests use different biomarkers to identify the presence of cancer.

Positive screening results typically prompt further investigations in an effort to confirm whether cancer is present. Investigations may include gathering of a personal and family medical history, a physical exam, laboratory tests, imaging, and biopsy as needed.[6]

Test information

Introduction

MCED screening tests utilize a variety of techniques for the measuring of biological substances from blood and other body fluids.

Multi-Cancer Early Detection Testing Methodology

MCED test methodology relies on the presence of individual or a combination of biomarkers in circulation, including cfDNA—which may be analyzed using polymerase chain reaction (PCR), methylation analysis, or next-generation sequencing (NGS). These approaches analyze single genes, panels of genes, exomes, or genomes.

Other biomarkers assessed by MCED screening tests may include routine blood and urine analysis, and levels of certain antibodies, proteins, electrolytes, and other analytes.[5,7] Genomic profiles and the combination of multiple biomarkers are used to distinguish between cancer and non-cancer signals.[7,8]

Guidelines and Evidence

Introduction

While there are no specific guidelines relating to multi-cancer early detection screening tests, the following section includes relevant guidelines and evidence that discuss the use of liquid biopsy for cancer screening.

American Society for Clinical Oncology and the College of American Pathologists

The American Society for Clinical Oncology and the College of American Pathologists (ASCO and CAP, 2018) joint review on the use of clinical circulating tumor DNA (ctDNA) assays in patients with cancer stated "[t]here is no evidence of clinical utility and little evidence of clinical validity of ctDNA assays in early-stage cancer, treatment monitoring, or residual disease detection. There is no evidence of clinical validity and clinical utility to suggest that ctDNA assays are useful for cancer screening, outside of a clinical trial."[9]

European Society for Medical Oncology

The European Society of Medical Oncology (ESMO, 2022) provided recommendations on the use of ctDNA assays for cancer.[10] The guidelines stated that insufficient evidence exists for implementing use of ctDNA assays for cancer screening, monitoring of treatment response, or detection of molecular relapse or minimal residual disease.

United States Preventive Services Task Force

The United States Preventive Services Task Force (USPSTF, 2021) stated the following regarding liquid biopsies for cancer screening:[11,12]

- "more research is needed on the accuracy and effectiveness of emerging screening technologies such as serum- and urine-based colorectal cancer screening tests"[11]

- For lung cancer, "potential screening modalities that are not recommended because they have not been found to be beneficial include sputum cytology, chest radiography, and measurement of biomarker levels"[12]

Selected Relevant Publications

Current studies have shown variable sensitivity depending on the test product, cancer type, and cancer stage.[13-16] Clinical validation data has also not yet supported the ability of these tests to detect cancers in earlier stages. The average sensitivity for identifying stage I cancers across nine studies of nucleic-acid based MCED tests was 46.2%.[16]

Consistency in detecting early-stage cancers, identifying tissue of origin, and differentiating cancer-related variants from random and age-related variants has not been demonstrated across MCED screening platforms, leading to practical concerns for usage of these tests in standard clinical practice. More well-designed clinical studies are needed to better define the capabilities of individual tests and document changes to clinical outcomes.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for multi-cancer early detection screening (MCED) will ensure that members will not receive testing for which there is not a body of evidence demonstrating clinical utility and is therefore considered experimental, investigational, or unproven. Use of a test that does not have evidence to support clinical utility can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[17] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

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