Information and Recommendations for Providers Interpreting EPISEEK® MCED Results

EPISEEK Overview

EPISEEK® is a laboratory-developed, blood-based multi-cancer early detection (MCED) test that analyzes patterns of DNA methylation in circulating cell-free DNA (cfDNA). The assay is designed to detect abnormal hypermethylation at genomic regions that are frequently altered in malignant cells and released into the circulation through tumor cell turnover.

The test evaluates a cancer-associated DNA methylation signal and compares these features to reference ranges established in individuals without known cancer. EPISEEK does not identify the tissue of origin, does not provide tumor localization, and does not predict risk of developing cancer in the future.

EPISEEK is intended for use as a screening adjunct and rule-in test. A positive result indicates an increased likelihood of malignancy and warrants further clinical evaluation, while a negative result does not exclude the presence of cancer. Test performance varies by cancer type, tumor biology, and disease stage, reflecting differences in methylation patterns and cfDNA shedding.

EPISEEK results should be interpreted in the context of the patient's clinical presentation, risk factors, and other diagnostic information, and should not be used as the sole basis for clinical decision-making.

False Positive and False Negative Results

False positive EPISEEK results are possible and, given the low incidence of cancer in an average-risk screening population, may occur at a meaningful rate.

One potential source of false positive or false negative results is pre-analytical sample compromise. Extreme heat, freezing, or prolonged transit times may cause DNA degradation that alters assay performance. The laboratory employs sample-level quality control metrics and process controls to mitigate this risk; however, residual effects may remain.

Another potential source of false positive results is true biologic hypermethylation of cancer-associated genomic regions in the absence of detectable malignancy on imaging. These patients may harbor neoplasia below the limit of detection of PET/CT, or they may exhibit persistent methylation patterns driven by biological processes that are not yet fully understood and may or may not become clinically relevant.

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False negative EPISEEK results are also possible. Not all tumors demonstrate hypermethylation at the genomic regions interrogated by EPISEEK. In addition, many early-stage, indolent, or hormonally driven cancers shed minimal amounts of cell-free DNA, limiting detectability.

In the most recent clinical validation study, overall sensitivity was approximately 54%, indicating that roughly half of cancers may be detected by EPISEEK, while the remainder will be diagnosed through other clinical means. Performance was higher in biologically aggressive malignancies.

Interpretation of Results

Negative Result – No Cancer Signal Detected indicates that the amount of hypermethylated cell-free DNA in the sample was not substantially increased relative to the established reference range.

A negative EPISEEK result should not be used to rule out cancer, particularly in patients with symptoms, abnormal imaging, or elevated clinical suspicion. Test sensitivity varies substantially by cancer type and stage. EPISEEK is designed as a rule-in test.

For patients with a negative result, clinicians may continue standard, guideline-recommended cancer screening and consider repeat EPISEEK testing in 1–3 years, depending on individual risk factors.

Positive Result – Abnormal Methylation Signal Detected indicates that the amount and pattern of hypermethylated cancer-associated cell-free DNA differ significantly from reference ranges established in asymptomatic individuals with no known cancer.

A positive result is not diagnostic of cancer. Based on clinical validation data, the estimated positive predictive value is approximately 50–65%.

Clinical Evaluation of a Positive EPISEEK Result

EPISEEK does not localize the tissue of origin. Follow-up evaluation should be individualized based on patient-specific risk factors, including personal and family history, genetic predisposition, and environmental exposures.

For patients without focal symptoms or known elevated cancer risk, ensuring that the patient is up to date on standard of care screening is important. Advanced imaging such as PET/CT or MRI is a reasonable next step. An alternative strategy is the use of serum tumor marker testing to guide targeted imaging.

PET/CT Ordering Guidance

CPT: 78815 (PET/CT, skull base to mid-thigh)
ICD-10: R97.8 (Other abnormal tumor markers)

Proposed Serum Protein Biomarker Panel

AFP
CEA
PSA
CA 19-9
CA 125
CA 15-3
CYFRA 21-1
β-hCG
HE4
β2-microglobulin

Discordant EPISEEK and Imaging Findings

In some cases, EPISEEK may be positive while PET/CT and subsequent workup are negative. This may reflect a false positive EPISEEK result or malignancy below the detection threshold of PET/CT.

In the absence of imaging findings, tissue biopsy is generally not feasible. Such cases are best managed as presumed false positive EPISEEK results, with clinical judgment guiding follow-up.

Certain hematologic malignancies may not be detected by PET/CT. In patients with discordant EPISEEK and imaging results, laboratory evaluation for hematologic disease may be appropriate.

Suggested Hematologic Screening Panel

CBC with differential
Serum protein electrophoresis (SPEP)
Serum free light chains
Lactate dehydrogenase (LDH)