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.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
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<tbody>
<tr>
<td>NETest™</td>
<td>0007M</td>
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</table>

What is NETest

Definition

Neuroendocrine tumors (NETs) are a group of tumors that originate from epithelial cells with neuroendocrine variances; gastroenteropancreatic NETs are a subgroup of NETs that develop from the gastrointestinal tract.¹

• Detection of these lesions is often delayed due to the heterogeneous cellular make-up and inconspicuous symptomology.¹

• The prevalence and incidence of gastroenteropancreatic neuroendocrine tumors (NETs) have been increasing.¹

• Currently, there is a lack of specific blood markers for NET detection. Measurement of the neuroendocrine secretory peptide Chromogranin A (CgA) is often used, but is characterized by flaws since it is a single value, non-specific, and assay data are highly variable.

• As a result, there is greater interest in the discovery of effective biomarkers, such as the NETest, to evaluate disease risk and new therapies targeting gastroenteropancreatic NET.²⁻⁶

Test information

• NETest is a noninvasive blood test designed to assist in identifying activity of neuroendocrine tumor disease.

• This test examines the expression of 52 genes, which can be used to identify active disease and provide information about the biology of the tumor cell.

• As an adjunct to standard clinical assessment, the NETest provides an assessment of treatment responses in patients with NETs.²⁻⁶
The algorithm measures the activity of RNA gene expression and calculates a risk score. Risk scores range from 0-100%. The higher the score, the higher the risk of active disease at the time of testing. The following categories have a sensitivity of 95.7%:2-6

- Very low (≤13.4%) exhibit minimal risk for disease activity.
- Low (13.4% - 43.4%) are classified as low active or stable disease
- High (>43.4%) are classified as highly active disease.

Guidelines and evidence

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines (2018) on Neuroendocrine and Adrenal Tumors indicate that additional research is required before potential prognostic markers and other new molecular assays are routinely used in clinical practice. They state that “a multinational consensus meeting of experts concluded that, to date, no single currently available biomarker is sufficient as a diagnostic, prognostic, or predictive marker in patients with neuroendocrine tumors.”

Literature Review

The overall evidence base of retrospective and prospective clinical studies assessing NETest as a diagnostic, prognostic, and as a tool for treatment monitoring is insufficient. Results of individual studies suggest that NETest performs better than the conventional, single analyte, CgA, when combined with conventional prognostic indicators, and that NETest consistently shows some degree of association with measures of survival, suggesting that it may be useful in estimating the likelihood of recurrence. However, numerous limitations characterize the individual studies, which lowers the confidence in these findings (positive or negative), and hamper any definitive conclusions that can be drawn regarding the value of NETest.

It is still unclear when NETest should be used in a clinical practice setting, particularly in terms of determining the most accurate timing of blood specimen collection, as well as establishing the exact threshold metrics of the NETest to establish diagnosis, predict disease progression, and monitor treatment, such as an adjuvant therapy. There were no available studies of NETest as a companion diagnostic to accurately predict treatment responses. There were also no direct clinical utility studies that evaluated if NETest results improved health outcomes more than conventional testing or evaluated the impact of the NETest on physician treatment decisions.

Well-designed prospective studies, with consecutively enrolled, well-defined patient populations and sufficient follow-up periods are needed to evaluate the value of NETest to establish diagnosis, assess prognosis, and monitor treatment in patients with NET.
Criteria

- This test is considered investigational and/or experimental.
  - Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
  - In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References

2. Understanding the NETest results. NETest website. Available at: http://www.wrenlaboratories.com/patient/understanding-the-netest-results
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