Test Specific Guidelines

NETest

MOL.TS.250.A
v1.0.2023

Introduction

NETest is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedure addressed by this guideline	Procedure code
NETest™	0007M

What Are Neuroendocrine Tumors?

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]

Although some types of neuroendocrine tumors (such as pheochromocytomas, insulinomas and pituitary tumors) secrete specific substances that are useful as biomarkers, good biomarkers are still lacking for many types of neuroendocrine tumors.

The prevalence and incidence of gastroenteropancreatic neuroendocrine tumors (NETs) have been increasing, although it is unclear how much of this increase is due to increased endoscopic sampling versus a true increase in cancer incidence.[1]

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

Currently, there is a lack of specific blood markers for gastroenteropancreatic NET detection and disease monitoring. 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.[2-5]

Test Information

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

This test examines the expression of 51 genes, as determined by RNA measured in peripheral blood, 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 individuals with NETs.[2-5]

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. Per the offering laboratory, the following categories have a sensitivity and specificity of > than 95%:[2-5]

Low (≤40%): associated with longer progression free survival and no or minimal residual disease post surgery

High (≥40%): associated with shorter progression free survival or presence of residual or active recurrent disease

Guidelines and Evidence

European Society of Medical Oncology

The European Society of Medical Oncology (ESMO, 2020 and 2021) stated:[6,7]

"Recently identified prognostic molecular markers may have an impact on therapy strategies in the future if validated in prospective trials. A recent meta-analysis identified a diagnostic accuracy of a NET mRNA genomic biomarker (NETest) of 95%-96%; this marker seems to have a predictive value for PRRT [peptide receptor radionuclide therapy] response and achievement of complete surgery."[6]

"There is no validated tumour marker for recurrence detection; the NETest has potential to predict response to PRRT and detect residual disease after surgery and was superior to CgA in a validation study."[6]

"Insufficient accuracy of CgA (30%-60% at the metastatic stage) makes research on new biomarkers critical. Among these, a multianalyte molecular assay [51 transcripts; neuroendocrine tumor test (NETest)] is currently under development with potentially better sensitivity, but uncertainties remain regarding its positive predictive value and role as a prognostic marker for LC [lung carcinoid]."[7]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2021) guidelines on Neuroendocrine and Adrenal Tumors indicated that additional research is

required before potential prognostic markers and other new molecular assays are routinely used in clinical practice.[1]

"In a validation study, the NETest demonstrated high sensitivity (>95%) in patients with well-differentiated, metastatic NETs. The molecular basis of NETs remains poorly understood, and additional molecular predictors of outcome remain investigational."

“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.”

Selected Relevant Publications

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.[8-41] 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 considered 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. It is unclear if earlier detection of disease relapse by NETest would allow for interventions that change outcome. There are few available studies of NETest as a companion diagnostic to accurately predict treatment responses. There remain 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.

Numerous flaws and limitations characterize the published 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. These include small study populations, lack of blinding, lack of generalizability in clinical practice, and heterogeneity in clinical characteristics across comparator groups. Several studies call into question the manufacturer’s stratification categories (cutoff) for test results. Well-designed prospective studies, with consecutively enrolled, well-defined study populations and sufficient follow-up periods are needed to evaluate the value of NETest to establish diagnosis, assess prognosis, and monitor treatment in individuals 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.

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