The NETest

The Clinical Utility of Multigene Blood Analysis in the Diagnosis and Management of Neuroendocrine Tumors

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KEYWORDS

• NETest • Multigene blood analysis • Neuroendocrine tumors
• Peptide receptor radionuclide therapy • Bronchopulomary carcinoid • Transcript
• Progression • PCR • Blood • Biomarker

KEY POINTS

- The NETest is a blood biomarker test for diagnosis and management of gastroenteropancreatic and bronchopulmonary neuroendocrine neoplasia.
- The test measures 51 individual circulating genes in 1 mL of blood and algorithmic analysis provides a numeric score of disease status.
- The sensitivity and specificity of the test are respectively >95% and >90%.
- In head-to-head comparisons, the test is ~4-fold more precise than CgA and for monitoring disease progress, it is ~10-fold more accurate.
- Clinically, the test can define the completeness of surgical resection, identify residual disease, monitor disease progression and determine efficacy of treatment.
- PRRT efficacy can be accurately (~95%) predicted using a Predictor Quotient gene set and Ki67 (PPQ).
- Neuroendocrine disease status (stable/progressive) can be assessed by regular monitoring of blood NETest levels.

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THE CURRENT CLINICAL STATUS OF NEUROENDOCRINE TUMOR DISEASE

Neuroendocrine neoplasms (NENs), also called neuroendocrine tumors (NETs), and generically referred to as "carcinoids," represent a spectrum of tumors with a diverse range of molecular abnormalities that share a common neuroendocrine cell origin (**Table 1**).[1–9] Anatomically, lesions arise from the diffuse neuroendocrine system of the lungs, gastrointestinal tract, and pancreas as well as discrete organs sites, such as the thymus, pituitary, and adrenal. Functionally, they produce a wide variety of biologically active amines and peptides. As might be predicted, given the diverse cell and tumor types involved, their 5-year survival rates diverge as widely (15%–95%) as their clinical presentations. Overall, this reflects the biological heterogeneity (diverse cell types, disparate molecular regulatory mechanisms, and ill-understood oncogenic drivers) of the tumors and, in reality, suggests that these tumors often bear little relation to each other than their putative common cell of origin.[10,11]

Their management reflects varied approaches often based on local practical experience, eminence-based medicine, or the availability of certain therapies or drug studies. Despite the repetitive development of classification systems and wearisome guidelines (eg, World Health Organization[12] and European Neuroendocrine Tumor Society),[13] there are few evidence-based standardized approaches, particularly for indolent disease or for appropriate sequencing of therapy. Most studies are retrospective, are underpowered, and exhibit significant design flaws. Apart from early identified (usually serendipitous) appendiceal, rectal, or gastric NETs, cure is uncommon and the overwhelming majority of management approaches reflect diverse combinations of strategies in an attempt to delay local or metastatic disease progression and

Table 1
Biological and clinical utility of neuroendocrine tumor biomarkers

Detection Indices	Monoanalyte	Circulating Tumor Cells	MicroRNA	mRNA
Pathobiology				
Mutations	No	No	No	Yes
Proliferation	No	No	No	Yes
Secretion	Yes	No	No	Yes
Metabolism	No	No	No	Yes
Epigenetic remodeling	No	No	No	Yes
Apoptosis	No	No	No	Yes
Signaling pathway activity	No	No	No	Yes
Cell of origin	Yes	No[c]	No	Yes
Clinical utility				
Diagnosis	Yes	No	No	Yes
NET disease identification	Yes	No	No	Yes
Somatostatin receptor expression quantification	No	No	No	Yes
Prediction of therapy efficacy	No	Minimal data	No	Yes
Measurement of treatment response	No[a]	Minimal data	No	Yes
Identification of a residual disease	No[b]	Minimal data	No	Yes

[a] Only symptomatic therapy.
[b] Only in specific cases, for example, gastrinoma/insulinoma.
[c] Detection technique identifies EPCAM (Epithelial Cell Adhesion Molecule).

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