NETest2.0® Accurately Detects Active Disease and Monitors Recurrence in Neuroendocrine Tumors: Results from the RegisterNET Registry

Mark Kidd[1], Daniel M. Halperin[2], Diane Reidy[3], Abdel Halim[1], Kiarash Mashayek[4], Anthony Gulati[5], David K. Imagawa[6]

[1]Wren Laboratories, Branford, CT, [2]Department of Hematology and Medical Oncology, Emory University, [3]Department of Medical Oncology, Duke Cancer Institute, [4]Department of Surgery, University of North Dakota School of Medicine & Health Sciences , [5]Department of Medical Oncology, Stamford Health, [6]Department of Surgery, University of California, Irvine Medical Center

Abstract

Background: Optimal surveillance strategies for neuroendocrine tumors (NETs) remain undefined, and current monitoring relies heavily on serial imaging. NETest2.0® is a blood-based, machine-learning–enhanced multigene transcript assay developed to assess NET disease activity. We evaluated its ability to detect disease and monitor recurrence or progression in a large prospective registry cohort.

Methods: RegisterNET (NCT02270567) is a multicenter observational registry of NET patients. Two analyses were performed. First, NETest2.0® results were compared with contemporaneous imaging findings in 1,290 samples from 886 patients. Second, longitudinal changes in NETest2.0® scores were evaluated in 404 patients with paired samples obtained a median of 7 months apart. Clinical cohorts included post-operative minimal residual disease assessment, recurrence surveillance following curative-intent surgery, watch-and-wait monitoring, and treatment response assessment. Imaging (CT, MRI, or SSTR-PET) served as the clinical comparator.

Results: For disease detection, NETest2.0® demonstrated an AUC of 0.96 with 91.9% sensitivity, 94.9% specificity, 98.4% positive predictive value, and 92.5% overall accuracy. Performance was maintained across tumor grades, primary sites, and imaging modalities.

Among 404 patients undergoing longitudinal surveillance, 286 remained stable or disease-free and 118 experienced recurrence or progression. NETest2.0® scores decreased in stable/responding patients (median −14.6%) but increased in patients with recurrence/progressive disease (median +15.4%; p<0.0001). Changes in NETest2.0® scores yielded an AUC of 0.86 for identifying progression. Using a positive NETest2.0® result with any increase in score, specificity reached 98.3%, positive predictive value 91.1%, and overall accuracy 83.9%.

Conclusions: NETest2.0® accurately identifies active NET disease and provides clinically meaningful longitudinal surveillance information across diverse management settings. Serial molecular assessment distinguished stable from progressive disease and demonstrated high specificity for recurrence/progression. These findings support incorporation of NETest2.0® into risk-adapted surveillance strategies to complement imaging and potentially reduce unnecessary radiologic monitoring.

Background

Despite considerable advances in diagnosis and management of NET patients, challenges remain, particularly in assessing treatment response and monitoring disease progression. While imaging remains standard practice, it has limitations in detecting microscopic or minimal residual disease (MRD), identifying early metastasis or recurrence, or accurately evaluating treatment response. Imaging requires in-clinic procedures, and repeated events (post-operative surveillance can be a decade or longer) may increase patients' cumulative radiation exposure, which is known to be associated with risk for secondary cancers

NETest2.0® is a blood-based, machine-learning-enhanced multigene transcript assay that measures a 51-gene neuroendocrine-specific expression signature in whole blood. The assay is designed as a liquid biopsy, capturing circulating tumor-associated transcripts and generating a standardized 0–100 score with a validated positivity threshold of 50.

The goal of this investigation was to assess whether NETest2.0® could function as a clinically and biologically reliable tool to monitor NET status across diverse patient cohorts.

Objectives

This study evaluated the accuracy of the recently validated (2025) NETest2.0® for two objectives:

(1) to determine its accuracy in detecting the presence of disease, and

(2) to assess whether the NETest2.0® functions as a clinically meaningful and reliable tool for monitoring NET status across diverse patient cohorts

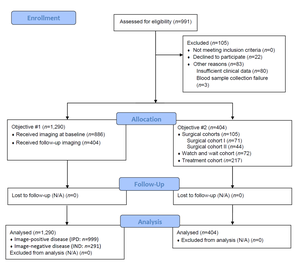
Study Design and Approach

RegisterNET (NCT02270567) patients.

For objective #1,1,290 individual samples were assessed for concordance between NET2.0 and image-detectable disease.

For objective #2, paired blood samples (median time interval 7 months [IQR: 4-13.8]) from 404 U.S. NET patients across multiple NET specialized clinics were analyzed.

Consort Diagram (**Figure 1**).

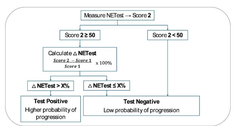


For Objective #1, NETest2.0® scores were evaluated for concordance with imaging-based detection of disease.

The 1,290 included 1,154 GEP, 75 BP and 61 CUP NETs. The 1,154 GEP cohort included pancreas (579), small bowel (465), gastric (28), rectum (34), appendix (14); colon (3), esophagus (6), and duodenum (25).

For Objective #2, relative changes in NETest2.0® scores between two time points for each patient were analyzed alongside clinical follow-up and imaging to assess the NETest2.0®'s ability to monitor disease-free status post-curative surgery, disease stability, progression, or recurrence.

The 404 patients included 386 with GEP-NETs, 18 with BP-NET and with CUP. The GEP cohort included pancreas (183), small bowel (168), appendix (2), duodenum (3), esophagus (1), gastric (4), and rectum (8).



Results

Objective 1

Figure 2. Assessment of NETest2.0® for detecting disease

	NET disease	No disease	
NETest≥50	917	15	932
NETest<50	82	276	358
(No. of events)	999	291	**1,290**

Statistic	Value	95% CI
Sensitivity	91.8%	89.91% to 93.42%
Specificity	94.9%	91.64% to 97.09%
PLR	17.81%	10.87 to 29.16
NLR	0.09	0.07 to 0.11
PPV	98.4%	97.39% to 99.01%
NPV	77.1%	73.20% to 80.58%
Accuracy	92.5%	90.90% to 93.86%

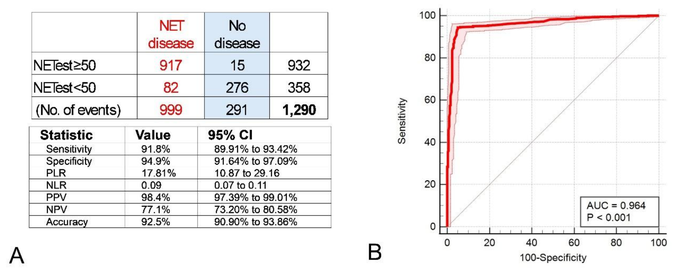
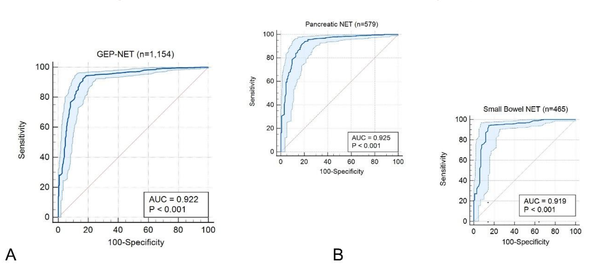


Figure 3. NETest2.0® and different tumor groups



Objective 2

Figure 4. Changes in NETest2.0® score and AUROC analysis (*n*=404)

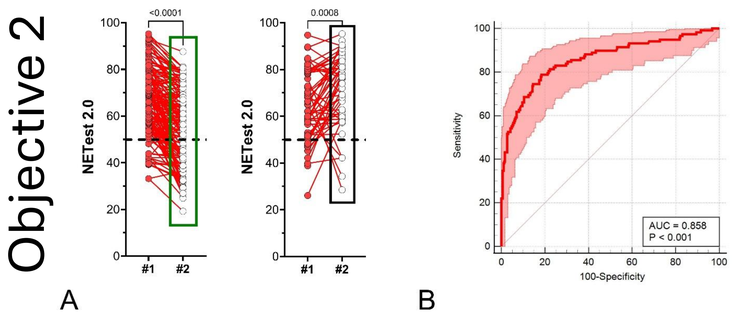


Table 1. NETest2.0® performance characteristics (*n*=404)

Metrics	NETest2.0® score #2 ≥50 with increase in 2nd sample from 1st sample				
Thresholds of increase in the follow-up sample	Any increase (>0%)	> +5%	> +10%	> +15%	> +20%
Sensitivity	78.0% (69-85%)	67.8% (59-76%)	58.5% (49-68%)	51.7% (42-61%)	43.2% (34-53%)
Specificity	83.2% (78-87%)	90.6% (87-94%)	93.7% (90-96%)	97.2% (95-99%)	98.3% (96-99%)
PLR	4.65 (3.53-6.12)	7.18 (4.91-10.50)	9.29 (5.79-14.9)	18.48 (9.13-37.41)	24.72 (10.12-60.39)
NLR	0.26 (0.19-0.37)	0.36 (0.27-0.46)	0.44 (0.36-0.55)	0.50 (0.41-0.60)	0.58 (0.49-0.68)
PPV	65.7% (59-72%)	74.8% (67-81%)	79.3% (71-86%)	88.4% (79-94%)	91.1% (81-96%)
NPV	90.2% (87-93%)	87.2% (84-90%)	84.5% (82-87%)	83.0% (80-86%)	80.8% (78-83%)
Accuracy	81.7% (78-85%)	83.9% (80-87%)	83.4% (79-87%)	83.9% (80-87%)	82.2% (78-86%)

NETest2.0® accurately detects NET disease

- A positive NETest2.0® score (≥50) exhibited an AUC of 0.96 and overall accuracy of >92%.
- Accuracy was independent of tumor grade (G1, G2 or G3), imaging type (anatomical or functional) or site of tumor (GEP, lung, CUP).

Serial NETest2.0® measurements

- Distinguished stable from progressive disease
- demonstrated high specificity for recurrence/progression
- Decreases in were concordant with clinical outcomes such NETest2.0® scores as disease stability and treatment response to multiple different therapies.

CONCLUSION

NETest2.0® accurately identifies active NET disease and provides clinically meaningful longitudinal surveillance information across diverse management settings.

NETest2.0®

WREN LABORATORIES

NANETS
NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

