Neuro
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DOI: 10.1159/000509866
Received: 5/6/2020
Accepted: 7/2/2020
Published(online): 7/2/2020

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ISSN: 0028-3835 (Print), eISSN: 1423-0194 (Online)
https://www.karger.com/NEN
Neuroendocrinology

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Manuscript:	NEN-2020-5-10/R1 RESUBMISSION
Title:	Sensitivity and Specificity of the NETest: A Validation Study
Authors(s):	Taymeyah Al-Toubah (Co-author), Mauro Cives (Co-author), Tiffany Valone (Co-author), Kirsten Blue (Co-author), Jonathan R Strosberg (Corresponding author)
Keywords:	biomarkers, carcinoid tumor, NETest, neuroendocrine tumor, tumor marker
Type:	Research Article

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Title: Sensitivity and Specificity of the NETest: A Validation Study

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Short title: NETest: A Validation Study

ClinicalTrials.gov Identifier: NCT02948946

Keywords: neuroendocrine tumor, carcinoid tumor, NETest, biomarkers, tumor marker

Word Count: 2121

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Abstract

Background: Secretory tumor markers traditionally measured in patients with neuroendocrine tumors (NET) are lacking in sensitivity and specificity, and consequently of limited clinical utility. The NETest, a novel blood multigene RNA transcript assay, has been found to be highly sensitive and specific. We sought to validate the sensitivity of the NETest in a population of metastatic well-differentiated NETs of gastroenteropancreatic and lung origin and evaluate the specificity in a mixed population of metastatic non-NET gastrointestinal (GI) malignancies and healthy individuals.

Design and Methods: 49 patients with metastatic NETs, 21 patients with other metastatic gastrointestinal cancers, and 26 healthy individuals were enrolled. Samples were sent in a blinded fashion to a central laboratory and a NETest value of 0-13% was considered normal.

Results: Using the upper limit of normal (ULN) of 13%, the sensitivity of the NETest was 98% (95% CI, 89% - 100%). The overall specificity was 66% (95% CI, 51% - 79%), with 16 false positive results. Specificity was 81% (95% CI, 62% - 92%) among 26 healthy individuals and 48% (95% CI, 26% - 70%) among patients with other GI malignancies. Using an updated normal range of 0-20%, sensitivity was unchanged, but specificity improved to 100% among healthy participants, and 67% among patients with other cancers.

Conclusions: The sensitivity of the NETest is exceptionally high (>95%) in a population of metastatic, well-differentiated NETs. Specificity within a healthy population of patients is exceptionally high when using a normal range of 0-20% but relatively low when evaluating patients with other GI malignancies.

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Introduction

Neuroendocrine tumors (NETs) are a heterogenous group of neoplasms characterized by a relatively indolent rate of growth and propensity to secrete a variety of hormones and vasoactive peptides. Although they arise in a variety of organs, they predominantly originate within the gastroenteropancreatic (GEP) tract and lungs.[1] Recent epidemiological data suggest a rising incidence of NETs and increased survival durations, however the long-term outcome of patients with advanced-stage disease remains poor.[2] A National Cancer Institute (NCI) summit held in 2007 focused on key research areas to be prioritized in NETs and noted biomarker limitations to be a crucial unmet need in the management of these tumors. In fact, currently available monoanalyte biomarkers (e.g. chromogranin A, urine 5-hydroxyindoleacetic acid [5-HIAA]) have limited sensitivity, specificity, and predictive ability. Some novel biomarkers are in advanced clinical development for NETs, including miRNAs, circulating tumor cells, and a multianalyte whole blood RNA signature (NETest).[3]

The NETest is a novel biomarker encompassing 51 separate gene expressions which define NET biology. It is a PCR-based test, which utilizes a 2-step protocol of RNA isolation and cDNA production. Using a specific algorithm, the NETest provides tumor activity scores ranging from 0-100% in 16 distinct categories (0, 7, 13, 20, 27, 33, 40, 47, 53, 60, 67, 73, 80, 87, 93, 100). Thresholds of 0-13 or 0-20 are generally considered within normal range, >20-40 is considered low range, and high-risk scores have been defined as ≥80%.[4-6] Elevated NETest scores have been reported to correlate with clinical progression in bronchopulmonary NETs, predict disease relapse after curative surgical resection of well-differentiated pancreatic NETs, and predict disease progression in GEP-NETs. [7, 5, 8, 9].

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The NETest is associated with very encouraging sensitivity and specificity (>90%) in patients with grade 1 and 2 GEP-NETs.[10] Based on this information, a validation study was designed to determine the performance metrics (sensitivity and specificity) of NETest in a real-world, heterogenous cohort of NET patients compared to a cohort of controls consisting of healthy subjects (without known diagnosis of cancer) and patients with other gastrointestinal (GI) malignancies.

Patients and Methods

Patient Selection

This study was a prospective, blood collection study comprised of two cohorts: NET and non-NET patients. The study protocol (NCT02948946) was approved by the Advarra Institutional Review Board and conducted in accordance with Good Clinical Practice principles. Written informed consent was obtained from all study participants.

The study was designed to enroll 100 NET and 100 non-NET subjects in two stages. In the first stage, 50 NET and 50 non-NET subjects would be enrolled, and if the false positive or false negative rate was <25%, the study would continue to the second stage of recruitment. A NETest score of ≤13 was initially prospectively defined as normal. We also examined a higher cut-off of 20 since recent publications have reported this to be a better discriminant. [11, 9, 12]

Patients were eligible for the NET cohort if they had histologically confirmed NET of GEP or lung origin (only stage IV, well-differentiated tumors in first stage of the study), had disease documented on a diagnostic scan, were off cytotoxic chemotherapy or PRRT for at least 4 weeks prior to date of blood collection, and had no other active malignancy within 3 years of enrollment, with the exception of adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or any treated stage I or II cancer from which patient was in complete remission.

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Non-NET patients were eligible if they were either healthy subjects or patients with any histologically or cytologically proven diagnosis of other active GI malignancies. Patients with GI malignancies with histological evidence of neuroendocrine differentiation were excluded. The plan called for equal enrollment of healthy subjects, and patients with other GI malignancies.

Blood Collection

After written informed consent was obtained and eligibility of subjects confirmed, a single blood sample was collected per patient. Blood samples were collected in 9mg K_2EDTA tubes (BD Vacutainer Venous Blood Collection Tubes, BD Diagnostics, Franklin NJ). Aliquots of whole blood were stored at -80°C within 2 hours of collection, per standard molecular diagnostic protocols for PCR-based studies. Specimens were stored with individual information, however coded and deidentified prior to shipment for analysis. Samples were sent in batches and analyzed by Wren Laboratories. NETest results were sent to the principal investigator only and no information was communicated to study participants.

Data was collected on Chromogranin A (CgA) for patients who had tumor markers drawn at or around the time of NETest blood sample collection. Samples collected prior to 9/2017 were analysed via the Enzyme Linked Immunosorbent Assay (ELISA) by QuestDiagnostics™. Samples collected from 9/2017 onward were analyzed by ARUP labs using the Cisbio CGA-ELISA-US kit.

Statistical Considerations and Sample Size Calculation

The primary objective of this protocol was to determine the performance metrics (sensitivity and specificity) of the NETest in a real-world, heterogenous cohort of NET patients. Descriptive statistics were used for patient demographics. Receiver operating characteristics (ROC) curve analysis was used to assess the performance metrics of the NETest. Exact 95% confidence intervals

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(CIs) were calculated for each proportion of interest. All tests were one-sided, and statistical significance was declared at a *p* value of .025 or less. Statistical analysis was conducted using IBM® SPSS version 25.

The study was designed to test the null hypotheses that the NETest has a sensitivity and specificity of 70% or less in NET patients. The sample size calculation was based on the assumption that a sensitivity and specificity of greater than 90% would generate further interest in the test for unselected NET patients. Power and type 1 error were 99% and 5%, respectively. Under this model, 80 or more positive tests in a cohort of 100 NET patients would lead to the rejection of the null hypothesis, suggesting that the NETest is sensitive. Likewise, 80 or more negative tests in 100 non-NET patients would suggest that the NETest is specific. An interim analysis was set to be conducted after enrollment of 100 patients, with plans to discontinue enrollment if a false positive or false negative >25% was observed. In other terms, if more than 12 false positives or negatives were observed among the first 100 subjects (50 with NET and 50 without), the study would be suspended.

Results

49 patients with metastatic (stage IV), well-differentiated NETs of GEP or lung origin, 21 patients with other active metastatic gastrointestinal cancers, and 26 healthy individuals were included in this analysis. Table 1 represents the NET patient demographics. A NETest value of 0-13% was prospectively considered within normal range, but an alternate NETest value of 0-20% was also evaluated, given several recent reports using this cutoff.[11, 9, 12] By ROC curve analysis (Figure 1), sensitivity was 98% (95% CI, 89-100%) for both 13% and 20% cutoff ranges, corresponding to a single false-negative result in a patient with widely metastatic, somatostatin receptor positive

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rectal NET, and confirming that the NETest was a sensitive assay. NETest scores for all participants are depicted in Figure 2.

Using the 0-13% cutoff, specificity was 66% (95% CI, 51% – 79%) for all non-NET participants, corresponding to 16 false positive tests among 47 patients with either other GI cancers or no cancer (Table 2). Among healthy participants, the specificity was 81% (95% CI, 62% - 92%), corresponding to 5 mildly elevated NETest results out of 26 patients. Among 21 patients with other GI cancers, the specificity was 48% (95% CI, 26% – 70%), corresponding to 11 false positive tests which included metastatic adenocarcinomas of the colon (n=6), pancreas (n=2), stomach (n=1), esophagus (n=1) and appendix (n=1). Using the cut-off of 13, we could not reject the null hypothesis. The assay specificity therefore was too low using this score and confirms the reports supporting the use of a higher (20) cutoff level.

Using the 20% cutoff (Table 3), however, the specificity was 85% (95% CI, 72% - 94%). It was 100% (95% CI, 87% – 100%) among healthy participants and 67% (95% CI 43% - 85%) among patients with other cancers. In total, 7 patients, all with other GI cancers (including colon [n=5], pancreas [n=1] and esophagus [n=1]), had false positive results, whereas no healthy subjects had false-positive results.

Of the 48 NET patients who had true positive NETest results, there was a dichotomous distribution of results with 15 patients having a score of 27% and 14 having a score of 93% (Figure 2). Tumor burden and disease status of the TP NETest patients are represented in Table 4. Tumor burden was assessed by investigator. High tumor burden corresponded to >20% liver involvement and/or bulky extrahepatic desease, low tumor burden corresponded to <10% liver involvement and minimal extrahepatic disease, and patients who fell into neither category were defined as having moderate tumor burden.

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Among patients with low-risk scores of 27% and 33% (n=17), 11 had stable disease and 6 had progressive disease at time of blood collection. Among patients with high risk scores of 87%, 93% and 100% (n=19), 13 had stable disease and 6 had progressive disease at time of NETest blood collection.

29 of the NET patients (small bowel [n=22], pancreatic [n=5], unknown primary [n=1]) had serum Chromogranin A (CgA) drawn at or around the same time of NETest blood collection. 16 patients had elevated CgA and 13 had normal (false negative) CgA, resulting in a sensitivity of only 55%. There was no statistically significant correlation between NETest score (high vs. low) and CgA results (elevated vs. normal) (p=0.832).

We discontinued the study after the planned interim analysis due to the false positive rate of >25% using the 13% cutoff per original protocol. Using the updated cut-off of 20, the false positive rate (18%) would have allowed us to continue the study.

Discussion

NETs are a heterogeneous group of tumors predominantly originating from the GEP tract and lungs, with a high propensity to secrete various hormones and vasoactive peptides, and recently increasing in incidence and survival durations. Approximately 40% of patients with NETs are diagnosed with stage IV disease. Given the heterogeneity of this disease, the available biomarkers have poor sensitivity, specificity and predictive ability. The NETest has been associated with high levels of sensitivity and specificity, and our study was designed to determine the performance metrics in a real-world, heterogenous cohort of NET patients compared to non-NET patients comprised of both healthy participants and those with other GI malignancies.

We found that the NETest was highly sensitive (98%) for patients with metastatic NETs of varying sites of origin, with no difference using either cutoff range (≤13% or ≤20%). The sensitivity of

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corresponding CgA levels was 55%. Using the 13% cutoff, we found that the NETest was moderately specific, with a specificity of 63% among non-NET patients as a whole, and more specific among healthy participants with a specificity of 81% as opposed to 44% among patients with GI cancers. We found that using the ≤20% cutoff, which has been reported in several recent manuscripts, resulted in a higher specificity among all patients (82%): 100% specificity among healthy participants, and 64% specificity among patients with other GI cancers. The large majority of false-positive results in this study comprised of patients with other GI cancers. This is not surprising given the fact that several of the NETest parameters, such as proliferation and metabolism transcripts, are not unique to NETs. Similar observations regarding elevated NETest scores in non-neuroendocrine tumors of the lung have been noted. [5, 9] However, the relatively low specificity observed in our study with respect to other GI cancers stands in contrast to a prior evaluation of the NETest in patients with carcinomas of the GI tract and pancreas in which only 3/54 patients had positive NETest results (Specificity 94%). [4]

The limitations of this study are its relatively small sample size and single blood sample collection. Measurement of serial blood samples at various timepoints during a patient's treatment (pre- and post-progression) may give a better indication as to whether or not NETest score was indicative of progressive trends in tumor burden as has been demonstrated in other studies.[13, 7] Evaluating the NETest score in patients with non-NET malignancies of various stages and disease status may also lead to a more definitive understanding of the specificity of the test and its clinical utility in these tumors. Finally, CgA assays vary in sensitivty and while use of a higher sensitivity assay may have improved the accuracy of the test, our findings reflect a real-world evaluation of CgA measurements.

Conclusion

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The sensitivity of the NETest is exceptionally high in a population of metastatic well-differentiated NETs. Specificity within a healthy population of participants is exceptionally high when using a normal range of 0-20% and moderately high when using a normal range of 0-13%. Specificity is relatively low when evaluating patients with other GI malignancies.

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Acknowledgments: We thank Mark Kidd, PhD and Irvin Modlin MD, PhD for their scientific contributions to study design, analysis of the blood specimens, and interpretation of the data.

Statement of Ethics:

The protocol was approved by the institutional review board and the study was conducted in accordance with Good Clinical Practice principles. Written informed consent was obtained from all participants.

Disclosure Statement:

Dr. Strosberg has consulted for Novartis and has received honoraria from Ipsen and Lexicon. Tiffany Valone has received honoraria from Abbvie, Genentech, Ipsen, Lexicon and Novartis. None of the other authors declares a personal or financial conflict of interest which could affect the outcome of this study.

Funding: This work was an investigator-initiated trial funded by H. Lee Moffitt Cancer Center & Research Institute

Author contributions: J.S. and M.C. contributed to the conception and design of the protocol. T.V. and K.B. contributed to the acquisition of the data/enrollment of patients. J.S., M.C., and T.A., contributed to data acquisition, analysis, interpretation of data, drafting and revising the manuscript. All authors reviewed and approved the final version of this manuscript, and agree to be accountable for all aspects of the work and its accuracy.

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Figure and Table Legends

Table 1. NET Patient Demographics

Table 2. Specificity using 13% cut-off

Table 3. Specificity using 20% cut-off

Table 4. Disease status and tumor burden of true-positive NET patients.

Figure 1. Performance metrics of the NETest by ROC curve analysis

Figure 2. NETest Scores

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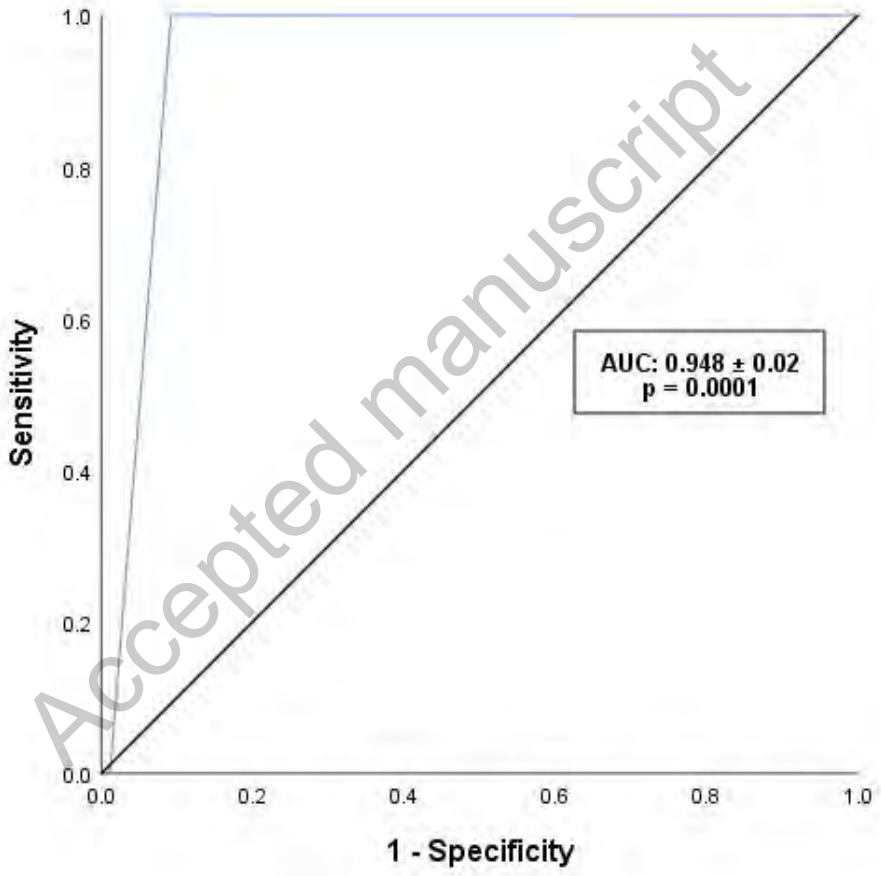

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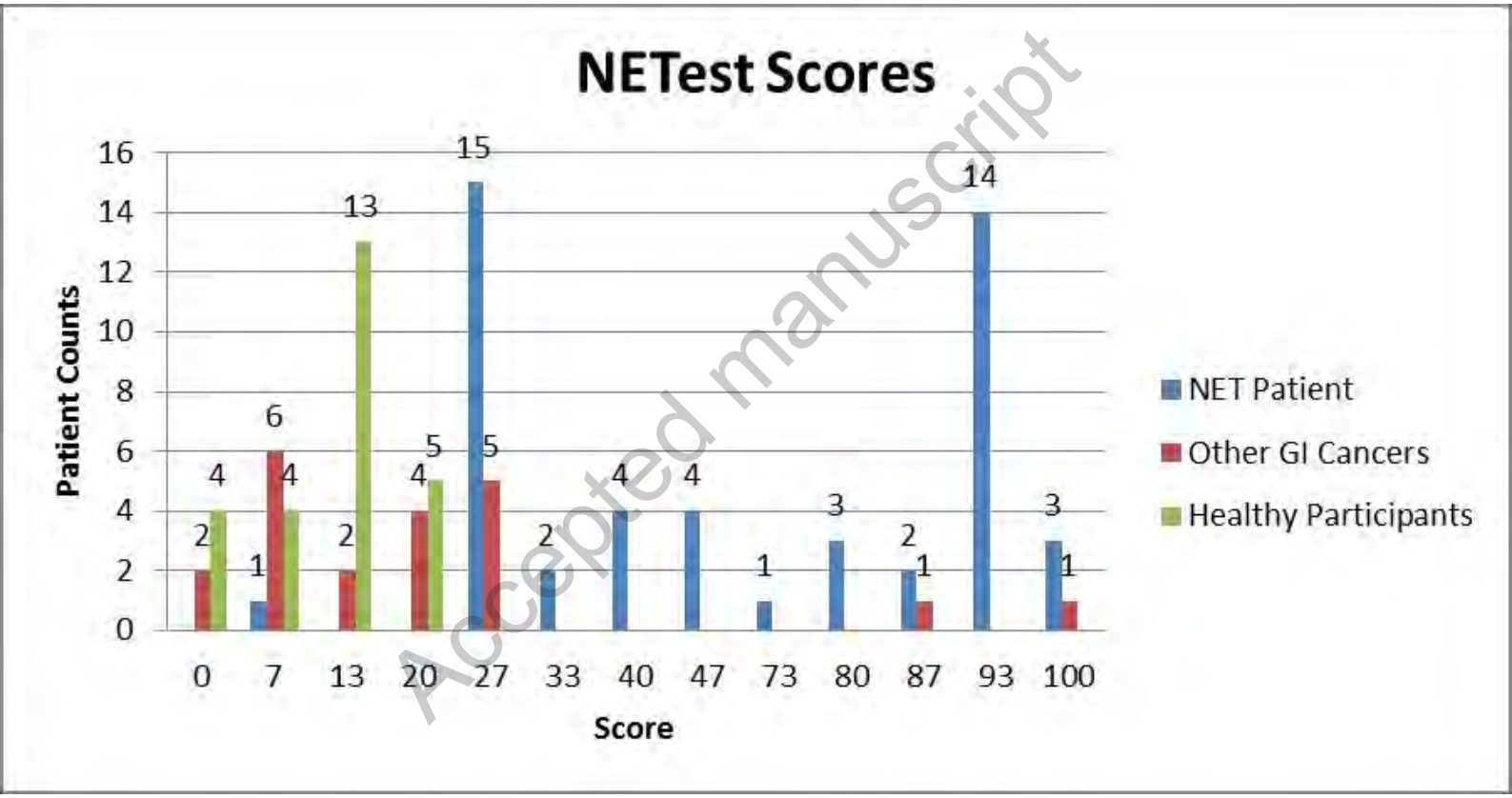

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Table 1. NET patient demographics.

	N (%)
Primary tumor	
Small bowel	24(49%)
Pancreatic	18 (37%)
Rectal	3 (6%)
Gastric	2 (4%)
Lung	1 (2%)
Unknown primary	1 (2%)
Tumor grade	
Grade 1 (Ki-67% <3)	20 (41%)
Grade 2 (Ki-67% 3-20)	23 (47%)
Grade 3 (Ki-67% >20)	1 (2%)
Well-differentiated, unspecified	5 (10%)
Disease Status	
Progression	15 (31%)
Stable disease	34 (69%)
Treatment status	
On active treatment	40 (82%)
Observation only	9 (18%)

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Table 2. Specificity using 13% cut-off.

**Using 13% cut-off*	**Specificity**	**True Negative**	**False Positive**
All Non-NET participants	66% (95% CI 51% - 79%)	31	16
Healthy Participants	81% (95% CI 62% - 92%)	21	5
Other GI Cancers	48% (95% CI 26% - 70%)	10	11

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Table 3. Specificity using 20% cut-off.

**Using 20% cut-off*	Specificity	True Negative	False Positive
All Non-NET participants	85% (95% CI 72% - 94%)	42	9
Healthy Participants	100% (95% CI 87% - 100%)	26	0
Other GI Cancers	67% (95% CI 43% - 85%)	14	7

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Table 4. Disease status and tumor burden of true-positive NET patients.

		Disease Status	
		Stable (n, %)	Progressive (n, %)
Disease Burden	Low	19 (40%)	1 (2%)
	Moderate	10 (20%)	6 (12%)
	High	4 (8%)	8 (17%)

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