LCD - Biomarker Testing for Neuroendocrine Tumors/Neoplasms (L37851)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
National Government Services, Inc.	MAC - Part A	06101 - MAC A	J - 06	Illinois
National Government Services, Inc.	MAC - Part B	06102 - MAC B	J - 06	Illinois
National Government Services, Inc.	MAC - Part A	06201 - MAC A	J - 06	Minnesota
National Government Services, Inc.	MAC - Part B	06202 - MAC B	J - 06	Minnesota
National Government Services, Inc.	MAC - Part A	06301 - MAC A	J - 06	Wisconsin
National Government Services, Inc.	MAC - Part B	06302 - MAC B	J - 06	Wisconsin
National Government Services, Inc.	A and B and HHH MAC	13101 - MAC A	J - K	Connecticut
National Government Services, Inc.	A and B and HHH MAC	13102 - MAC B	J - K	Connecticut
National Government Services, Inc.	A and B and HHH MAC	13201 - MAC A	J - K	New York - Entire State
National Government Services, Inc.	A and B and HHH MAC	13202 - MAC B	J - K	New York - Downstate
National Government Services, Inc.	A and B and HHH MAC	13282 - MAC B	J - K	New York - Upstate
National Government Services, Inc.	A and B and HHH MAC	13292 - MAC B	J - K	New York - Queens
National Government Services, Inc.	A and B and HHH MAC	14111 - MAC A	J - K	Maine
National Government Services, Inc.	A and B and HHH MAC	14112 - MAC B	J - K	Maine
National Government Services, Inc.	A and B and HHH MAC	14211 - MAC A	J - K	Massachusetts
National Government Services,	A and B and HHH	14212 - MAC B	J - K	Massachusetts

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
Inc.	MAC			
National Government Services, Inc.	A and B and HHH MAC	14311 - MAC A	J - K	New Hampshire
National Government Services, Inc.	A and B and HHH MAC	14312 - MAC B	J - K	New Hampshire
National Government Services, Inc.	A and B and HHH MAC	14411 - MAC A	J - K	Rhode Island
National Government Services, Inc.	A and B and HHH MAC	14412 - MAC B	J - K	Rhode Island
National Government Services, Inc.	A and B and HHH MAC	14511 - MAC A	J - K	Vermont
National Government Services, Inc.	A and B and HHH MAC	14512 - MAC B	J - K	Vermont

LCD Information

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CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA):

Section 1862(a)(1)(A) excludes expenses incurred for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Section 1833(e) prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

Code of Federal Regulations:

42 CFR, Section 410.32, indicates that diagnostic tests may only be ordered by the treating physician (or other treating practitioner acting within the scope of his or her license and Medicare requirements) who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem. Tests not ordered by the physician (or other qualified non-physician provider) who is treating the beneficiary are not reasonable and necessary (see Sec. 411.15(k)(1) of this chapter).

CMS Publications:

CMS Publication 100-02, *Medicare Benefit Policy Manual*, Chapter 15, Section 80.1 – Laboratory services must meet applicable requirements of CLIA

CMS Publication 100-02, *Medicare Benefit Policy Manual*, Chapter 15, Section 80.6. 5 which describes the Surgical/Cytopathology Exception.

CMS Publication 100-04, *Medicare Claims Processing Manual*, Chapter 16, Section 40.7 Billing for Noncovered Clinical Laboratory Tests Section and 120.1 Clarification of the Use of the Term “Screening” or “Screen”

CMS Publication 100-04, *Medicare Claims Processing Manual*, Chapter 30, Section 50 Advance Beneficiary Notice of Noncoverage (ABN)

CMS Publication 100-08, *Medicare Program Integrity Manual*, Chapter 13, Local Coverage Determinations

CMS National Correct Coding Initiative (NCCI) Policy Manual for Medicare Services, Chapter 10, Pathology/Laboratory Services, (A) Introduction

CMS National Correct Coding Initiative (NCCI) Policy Manual for Medicare Services, Chapter 10 Pathology/Laboratory Services which addresses reflex testing.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

National Government Services (NGS) will not provide coverage for the oncology (gastrointestinal neuroendocrine tumors) real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index for its use in treating neuroendocrine tumors. It has not been accepted by most neuroendocrine treatment guidelines. Most important, this test has not been shown to result in improved outcomes for Medicare beneficiaries and thus is not medically necessary.

Summary of Evidence

Multianalyte Assays with Algorithmic Analyses (MAAA) codes are Administrative codes. Thus, they do not require adherence to Category I Code Criteria or AMA review for clinical utility. Such codes are unique to a single clinical laboratory or manufacturer. These codes are based on various assays (DNA, RNA, immunoassay, or other biomarkers) and may include other elements such as age and sex. An algorithm (often proprietary) is then used on the assay data to assign a single, patient-specific value that indicates diagnosis, mitigation, treatment, or prevention of disease. Such a code is requested by the laboratory or manufacturer performing the test. Unlike Category I CPT codes, Category II CPT codes, or Category III CPT codes, these are found only in the Appendix O of the *CPT Codebook* (1). It may or may not be FDA approved. Per CPT 2018, these codes "are provided as an administrative coding set to facilitate accurate reporting of MAAA services. The minimum standard for inclusion in this list is that an analysis is generally available for patient care. The AMA has not reviewed procedures in the administrative coding set for clinical utility" (1).

Neuroendocrine tumors are a heterogeneous group of neoplasms (2) that can occur in the gastrointestinal system (including the pancreas), the lungs, and other organs. Previously called carcinoid tumors, these are most commonly referred today as neuroendocrine tumors (NET) or neuroendocrine neoplasms (NEN). Despite new promising effective therapies that have evolved in the past few years for the well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs), advanced metastatic gastroenteropancreatic neuroendocrine tumors continue to be an incurable disease with poor prognosis. There is no standard guideline regarding the optimal selection and sequencing of treatment strategies for patients with advanced GEP-NETs (2).

"Traditionally, neuroendocrine tumors are described as arising from the foregut (bronchopulmonary, thymus, gastric, proximal duodenum, pancreas), midgut (distal duodenum, jejunum, ileum, ascending colon), or hindgut (distal colon, rectum). Primary tumors arising from these different anatomic zones differ in their tumor secretions. For example, tumors originating in the midgut secrete serotonin and are more likely than tumors of other origins to present with carcinoid syndrome. Carcinoid syndrome, when present, may include the following symptoms: flushing (94%), diarrhea (78%), abdominal cramping (50%), valvular heart disease (50%), telangiectasia (25%), wheezing (15%), or edema (19%). Pulmonary tumors are less likely to secrete serotonin (although they may secrete the serotonin precursor, 5-hydroxytryptophan) and more likely to secrete histamine. Although foregut tumors can present with flushing and wheezing, the full carcinoid syndrome with diarrhea is unusual. Hindgut tumors rarely secrete serotonin or cause carcinoid syndrome. In addition, the clinical presentation may vary between tumors of the same originating site, based on the tumor grade and stage. Some biochemical tests have been suggested as markers of tumor grade or differentiation, for example, neuron-specific enolase. Although only about 10% of NET present with features of carcinoid syndrome, this number increases with greater tumor bulk (later stage), especially when liver metastatic disease increases" (3).

In contrast to gastroenteropancreatic neuroendocrine tumors (GEP-NETs), lung carcinoids (LCs) and large cell neuroendocrine lung carcinomas (LCNELC) are less frequent. Lung carcinoids are well-differentiated neuroendocrine tumors and account for 8% of lung neuroendocrine tumors and for 1–2% of all lung tumors (3). They are divided into the low-grade typical carcinoids with minimal mitotic activity (<2 mitoses per 2-mm2 field) without any necrosis,

and the intermediate-grade ACs with more mitoses (2–10 per 2-mm2 field) and presence of focal necrosis. On the other hand, large cell neuroendocrine lung carcinomas are poorly differentiated lung neuroendocrine tumors or neuroendocrine carcinomas with morphological appearance resembling non-small cell lung cancer (NSCLC) but biological similarities with small cell lung cancer (SCLC). Large cell neuroendocrine lung carcinomas account for approximately 12% of lung neuroendocrine tumors and are found in 2.1–3.5% of surgically resected bronchopulmonary neoplasms. Another critical aspect of lung carcinoids that affects treatment decisions is functionality, which means their capability of causing secretory syndromes that are named paraneoplastic when the secretory component is not derived from the expected tissue of origin. However, the majority are non-secretory and usually present similar to other lung cancers (cough, hemoptysis, fever). Paraneoplastic syndromes develop in approximately 10–15% of cases, the most common being carcinoid syndrome or Cushing's syndrome secondary to ectopic serotonin or adrenocorticotropic hormone (ACTH) hypersecretion by tumor cells (4).

The main determinants of treatment planning are the originating site of the tumor, histologic subtype of the tumors and extent of the disease. Historically carcinoid tumors (or neuroendocrine tumors [NET] or neuroendocrine neoplasms [NEN]) have been called rare tumors, but through registries, it is apparent that this is no longer correct. Their annual age-adjusted incidence increased from 1.09 per 100,000 person in 1973 to 6.98 per 100,000 persons by 2012. Neuroendocrine tumors are classified histologically based on tumor differentiation (well or poorly differentiated) and tumor grade (grades 1-3). Most neuroendocrine tumors fall into 3 broad histological categories: well-differentiated, low-grade (G1); well-differentiated, intermediate-grade (G2); and poorly differentiated, high grade (G3)(5). Survival depends on many factors including the site of the tumor, whether the tumor is localized, and the grade of the tumor (6).

Chromogranin A is a secreted protein that may be elevated in patients with neuroendocrine tumors; elevated levels have been associated with poorer prognosis. Currently, Chromogranin A (CgA) is a well-established marker for diagnosis and follow up of patients with gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN). Recently, it has been shown that plasma levels of CgA correlate with tumor load and predict survival of patients with neuroendocrine neoplasms (NEN) of the small bowel but CgA plasma concentration does not appear to mirror tumor burden or prognosis in patients with neuroendocrine tumors of the colon and rectum (7). While chromogranin A testing is recognized by the National Comprehensive Cancer Network (NCCN)(5) Neuroendocrine and Adrenal Tumors, "oncology (gastrointestinal neuroendocrine tumors) real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index" (such as NETest) is not listed by National Comprehensive Cancer Network Guidelines, although "Neuroendocrine Tumor Biomarkers: Current Status and Perspectives" by Dr. Modlin, Oberg, Taylor, Drozdov, Bodei, and Kidd is listed as a reviewed reference (8). NCCN notes, "More research is required, however, before these and other new molecular assays are routinely used in the clinic. 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" (5).

In addition, the guidelines note, "The molecular basis of neuroendocrine tumors remains poorly understood, and additional molecular predictors of outcome remain investigational. A recent study found that overexpression of mammalian target of rapamycin (mTOR) or its downstream targets was associated with shorter overall survival in 195 neuroendocrine tissue samples (15% were located in the pancreas; 85% were GI carcinoids). Small bowel carcinoid tumors have been found to have recurrent mutations in the cyclin-dependent kinase inhibitor, CDKN1B(p27) and loss of CDKN1B expression has been reported to be an adverse prognostic factor in gastroenteropancreatic neuroendocrine tumors. Circulating tumor cells (TCs) have also been studied as possible prognostic markers, based on the idea that tumor cells in the blood would be indicative of more disseminated disease. A recent study found that the presence of greater than or equal to 1 CTC in 7.5 mL of blood was independently associated with worse progression-free survival (PFS) and overall survival in patients with varying pre-treated metastatic neuroendocrine tumors from various primary sites.

Related, Crabtree in her recent review article noted, "Gastrointestinal neuroendocrine tumors are a very

heterogeneous group of tumors. Targeted therapies are available to treat these tumors but despite the many clinical approaches to neuroendocrine tumors, and beyond surgery for localized disease, there is little consensus on first line therapy. Results of ongoing clinical trials will better inform patient management with respect to selection, timing, duration, and combination of available therapies, and immunotherapy holds great promise for NETs and other cancers" (9).

Other prognostic blood-based biomarkers for neuroendocrine tumors have been proposed. MiRNAs are short (approximately 22 nucleotides) RNA sequences that have been shown to broadly regulate gene expression at a post-transcriptional level, by binding to the 3' region of target RNAs, resulting in mRNA degradation and inhibition of translation. A recent small study suggested that elevated circulating levels of two such short RNA sequences and low levels of another are characteristic in patients with metastatic small intestine neuroendocrine tumors, and further suggests that levels of these miRNAs are associated with overall survival (10).

Bodei et al. (11) PRRT Genomic Signature in Blood for Prediction of ^{177}Lu-octreotate Efficacy. This was submitted in a recent reconsideration request and is being reviewed as a new reference. Neuroendocrine tumors (NETs) can be treated with targeted therapies including somatostatin analogues everolimus, sunitinib and targeted radionuclide therapies. Peptide receptor radionuclide therapy (PRRT) utilized octreotide derivatives ^{177}Lu-DOTA-Tyr3, Thr8octreotide, or ^{177}Lu-octreotate. This article discusses the prediction of these therapies using the PRRT Predictive Quotient (PPQ). The results of the PPQ are PRRT-responder or negative: PRRT-non-responder. Originally there were 178 patients enrolled but 20 were excluded. Median progressive free survival (mPFS). Seventy-two were retrospective, 86 were in two different cohorts. The overall accuracy was 94% with 95% being responders and 91% non-responders. There was a difference in the tumor grade between the cohorts. There was an evaluation of retrospective samples from the comparator cohorts. While there was a significant difference in the accuracy of the testing between responders and non-responders, this does not mean that this testing would necessarily influence the treatment of patients, since many patients and physicians would still use a PRRT (peptide receptor radionuclide therapy) despite the negative testing. Most important, while median progressive free survival was different, there was no evidence of true improved outcomes. Thus there is limited support from this document for NETest. Of further note, the second author (Mark Kidd) is an employee of Wren Laboratories and Dr. Modlin is a paid consultant for Wren Laboratories.

Oberg et al. (12) Consensus on Biomarkers for Neuroendocrine Tumour Disease. "The experts were of the opinion that such laboratory tests should be initially undertaken at a single central laboratory." This consensus and this recommendation for a single central laboratory was supported by Clifton Life Sciences, which owns Wren Laboratories. In addition, Irvin M Modlin, Marianne Pavel, David C Metz, Dik Kwekkeboom, Jonathan Strosberg, Timothy Meyer, Eric Liu, and, James Goldenring (eight of the sixteen panelists) are listed as having financial ties to Wren Laboratories. This has previously been submitted and reviewed by this contractor in a prior reconsideration request. Thus there is limited support from this document for NETest.

Kidd et al. (13) This is not a research article, but an explanation of NET treatments. Of note, both authors are associated with Wren Laboratories. This has previously been submitted and reviewed by this contractor in a prior reconsideration request. This is not support for NETest.

Modlin et al. (14) Polymerase chain reaction (PCR) based 51-transcipt signature test was evaluated in two groups of patients (125 prospectively collected with known neuroendocrine tumors) and 29 patients with gastrointestinal disease without known neuroendocrine tumors but taking oral proton pump inhibitors and 50 controls. These were also tested with chromogranin A (CgA). 123 (98.4%) of the known neuroendocrine tumor patients had a positive test score while 50 (40%) had an elevated CgA. The cohort had no positive test score but 24 had a positive CgA. This states that "More pertinently, cancer center groups such as the National Comprehensive Cancer Network (NCCN), have endorsed the use of high performance biomarkers particularly in fields where there are no better alternative." This is a misrepresentation of what was said and attributed to Reinke. Reinke had actually noted "The NCCN

acknowledges the harms of PSA testing; its perspective is that PSA testing is the starting point for diagnosing prostate cancer and that steps should be taken to improve its value. 'The Achilles' heel of PSA testing is overdetection, and the USPSTF [United States Preventive Services Task Force] got that ... 'But the USPSTF did not interpret the data on PSA testing correctly.'" (15) In addition, the use of PSA testing has been shown to give inappropriate information and is no longer recommended as a screening test. This discussion of PSA is not related NETest. Furthermore, the NCCN acknowledges chromogranin A as being the standard biomarker for neuroendocrine tumors. A great concern is that the "Declaration of interest: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported." However, the paper states "This work was supported by Clifton Life Sciences" which owns Wren Laboratories. Also Modlin I, Bodei L, Drozdov I, and Kidd M are listed as being from Wren Laboratories. This has previously been submitted and reviewed by this contractor in a prior reconsideration request. Thus there is limited support from this document for NETest.

Perrier ND. (16) This was submitted in a recent reconsideration request to this contractor and is being reviewed as a new reference. This paper is a review of the history of MEN1 gene and its function and treatment. The NETest is mentioned under "Prediction of response to therapy: Determination of the effect of therapy is importantly needed. The NETest shows the potential value of multidimensional tumor marker studies. Developed by Modlin and his team, NETest is a 2-step multianalyte PCR-based circulating gene test of the mRNA expression levels of 51 target genes. The test involves RNA isolation with cDNA production. Measurement of these gene transcripts in blood can confirm reduction in tumor burden, and quantification of the molecular signature over time may provide information about the efficacy of treatment and amplify the identification of nonresponders. The NETest is now marketed to manage gene transcripts in blood." This review concludes with "Further pursuit of prevention, prediction, pausing progression, with adjunct modalities for diagnosis and roved options for systemic therapy will be beneficial. The time for progress is now." This is not a robust support of the NETest, but is the only paper with any support of NETest that does not appear to be written by Dr. Modlin and/or Wren Laboratories. There is no mention of conflict of interest: this subject is not brought up.

Singh et al. (17) Singh and his colleagues reported on the largest known series examining outcomes of patients with fully resected gastroenteropancreatic neuroendocrine tumors (GEP-NETs). As with other researchers, he notes gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are widely heterogeneous malignant abnormalities. He notes that the natural history of these tumors is poorly described, with little understanding of recurrence patterns. Surveillance for resected GEP-NETs may include clinical review, laboratory tests, and numerous medical and nuclear imaging modalities. These modalities can increase patient anxiety, may be associated with potential harm (eg, exposure to ionizing radiation), and have not been shown to improve outcomes. Current guidelines vary widely in recommendations, reflecting the lack of data. Information on the natural history and recurrence of the disease may improve patient-centered follow-up of this population. He hypothesized that GEP-NETs may recur over a longer time course compared with other gastrointestinal malignant abnormalities. No conflict of interest disclosures were reported. This does not support NETest.

Singh et al. (18) Cancer Treatment Reviews is an over-view of gastrointestinal neuroendocrine tumors in Canada, using evidence based consensus. While three of Dr. Modlin's older papers are cited concerning anatomic sites and secretory syndromes, there is no mention of any markers, including NETest. There are a number of authors who disclosed potential conflict of interests, although not all had any. This paper does not support NETest.

Reichelmann et al. (19) This is a detailed review paper that discusses all phases of the diagnosis, imaging, and treatment of neuroendocrine tumors. It states, "Chromogranin A is acceptable, despite its limitations, as a general marker of NETs. The sensitivity and specificity limitations of chromogranin A may depend on the test used and clinical situations, such as secondary hypergastrinemia, gastrinoma, atrophic gastritis, Helicobacter pylori infection, use of proton pump inhibitors and liver or kidney dysfunction. Elevated levels of chromogranin A may also be caused by other neoplasias, diminishing its specificity."

"Recommendations

- Chromogranin A can be used as a prognostic test [IIIC], and can be used for monitoring purposes [7] [IVC]. It should not be used alone to guide management.
- Repeated chromogranin A measurements can be made to assess tumour response [8], although the results should not be used to determine management [IIIC]."

Conflict of interest is not mentioned. NETest is not mentioned in this article. No articles by either Dr. Kidd or Dr. Modlin are mentioned in the references. This article does not support NETest.

Raphael et al. (20) This review article summarizes the classification, presentation, diagnostic workup and treatment of neuroendocrine tumors. It is interesting in that it is a general overlook of neuroendocrine tumors with the emphasis on "helping generalists to facilitate timely diagnosis and referrals." Thus while it gives an excellent overview and understanding of neuroendocrine tumors, it does not get bogged down in pure research results, and concentrates on understanding the pathology, symptoms, diagnosing and treatments. For patients presenting with symptoms of functioning neuroendocrine tumors (atypical carcinoid, carcinoid, Whipple triad, Zollinger-Ellison, 4D syndrome, somatostatinoma, Vern-Morrison [WDHA syndrome], and Cushing syndrome), biochemical testing should be targeted to the specific syndrome. The usual classical testing is recommended. For those without symptoms of nonfunctioning neuroendocrine tumors, "Chromogranin A is the diagnostic biomarker of choice for neuroendocrine tumors. It has a high sensitivity (53%-91%) but low specificity (<50%). The most common reasons for false elevations include proton-pump inhibitors, renal insufficiency, adenocarcinomas and severe arterial hypertension." The author concludes with an Unanswered Question paragraph. "Several unanswered questions remain. What are the best predictive and prognostic markers for patients with neuroendocrine tumours? What is the optimal follow-up strategy for patients with neuroendocrine tumours? How should the multiple new therapeutic options be sequenced and/or combined? How do the new therapeutic options affect patient quality of life and survivorship?" While one of Dr. Modlin's publications is referenced, there is no mention of NETest. Dr. Raphael does not disclose any "competing interests." Co-authors Law, Singh, and Chan have several industrial ties. This paper does not support NETest.

Kidd et al. (21) In this study, the "goal was to advance from a linear interpretation of disease activity based upon quantification of gene expression (0–8 score) to an amplified algorithm that incorporated gene clusters (GC) representative of NET neoplasia." The researchers had eight samples of normal tissue, two being from small intestines, four being from colon, and two being from rectums. These were the controls. There were 22 tumor samples (one stomach; four pancreas; ten small intestine; one appendix and six rectum. Two of the pancreas tumors, five of the small bowel, and three of the rectum were metastatic tumors; the others were primary tumors. Fifty-one genes as per previous related works were analyzed. Quantification of gene expression in gene clusters was undertaken by summation of individual gene expression. Individual genes clusters that were significantly different between stable disease and progressive disease and were elevated in gastroenteropancreatic neuroendocrine tumor blood compared to control blood, were included in an activity algorithm. Six gene clusters (SSTRome, proliferome, metabolome, secretome (II), epigenome, and plurome) met this criterion and were summated. The authors concluded that using this cluster integrated algorithm, gene clusters differentiate stable disease from progressive disease. They also concluded that gene expression in blood reflect tissue gene expression and that "the NETest captured the biology of NET neoplasia and that integrating these measurements of circulating gene expression could accurately define clinical status." This study is from Wren Laboratories. "Funding: This work was supported by Clifton Life Sciences." "Declaration of interest: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported." This is an interesting study that the later NETesting is based upon. It does suffer from the same potential perception about conflict of interest. It needs external validation. No evidence of improved outcomes are noted. This has previously been submitted and reviewed by this contractor in a prior reconsideration request. There is limited support for NETest.

Zandee et al. (22) Although this article is nine pages, it is a brief overview of classification, presentation, diagnostic

workup and treatment of neuroendocrine tumors, but more in a historical prospective. Biomarkers are not discussed, thus there is no mention of chromogranin A or NETest. There is no mention of conflict of interest. This does not support NETest.

Sato et al. (23) This is another review paper concerning the increasing incidence of gastric and duodenal neuroendocrine tumors, their clinical features, their diagnosis, their histology, their treatment, and their follow-up strategy. The paper specifically recommends chromogranin A levels including in their follow up and using them for monitoring. There is no mention of NETest, although several Modlin/Kidd papers are referenced. The authors declared "no financial or other conflicts of interest." This article does not support NETest.

Oberg et al. (24) This is not a true research paper. It is a consensus statement by thirty-two researchers concerning NETest. This meeting's "financial support was provided by Clifton Life Sciences." "All the authors except Dr. Jensen and Dr. Krenning received reimbursement for accommodation and traveling expenses to and from the NET Consensus Meeting as well as an honorarium. Mark Kidd and Ignat Drozdov receive salary support from Wren Laboratories. Ignat Drozdov did not attend the final meeting and was not involved in the final voting. Mark Kidd did not vote on sections involving biomarkers and the NETest. The impartiality of the research report therefor is not prejudiced." However, Dr. Bodei has on previous papers been listed as being affiliated with Wren Laboratories. Dr. Oberg, Dr. Krenning, Dr. Tesselaar, Dr. Ambrosini, Dr. Baum, Dr. Pavel, Dr. Cwikla, Dr. Drozdov, Dr. Frilling, Dr. Kwekkeboom, Dr. Paganelli, Dr. Severi, Dr. Strosberg, Dr. Prasad, and Dr. Modlin have been frequent co-authors of NETest papers with Wren Laboratory researchers. This in no way is to imply that their opinions are not those of their own, nor to imply any impropriety on their part. This is not robust support for NETest.

Clinical Utility Assay as a Biomarker for Gastroenteropancreatic and Lung Neuroendocrine Tumors (25). This is a clinical trial registered in Clinicaltrials.gov (NCT02948946) with the following Inclusion Criteria:

- NET Cohort- Patients with histologically or cytologically proven diagnosis of any grade, any stage NET of GEP or lung origin; In the first stage of the study (initial 50 patients) only patients with stage IV, well-differentiated tumors (G1/G2) will be enrolled.
- Patients with stable or progressive disease, as documented on a scan (CT, MRI); Progression status will be documented on case report form (CRF).
- Allowed prior therapies include: a.) Surgery (tumor surgery at least four weeks prior to study entry); b.) Locoregional therapy such as: chemoembolization, radio-embolization, radiofrequency ablation, radiotherapy at least six weeks prior to study entry; c.) Any number of previous lines of systemic therapy, providing that cytotoxic therapies (chemotherapy, PRRT) have been discontinued at least 4 weeks prior to study entry.

Non-NET Cohort -

- Healthy participants
- Patients with histologically or cytologically proven diagnosis of any grade, any stage GI malignancies.

Procedure: NETest 5 mL of blood will be drawn from participants for testing.

Estimated Study Completion Date: December 2018

The purpose of this study is to evaluate how well an investigational blood test performs. The study will look at the sensitivity and specificity of a blood-based multitranscriptome assay (NETest). Its purpose is not to evaluate outcomes. This has previously been submitted and reviewed by this contractor in a prior reconsideration request. At present this is not supportive evidence for NETest.

Modlin et al. (26) This is a study of 179 cases with 81 gastrointestinal tumors (41 neuroendocrine tumors of small bowel and 40 being adenocarcinomas [4 esophageal, 3 gastric, 6 small bowel, 11 colon, 13 rectal, and 3 anal] of and 98 pancreatic disease (45 known neuroendocrine tumors and 53 patients with "pancreatic disease") were prospectively collected and assessed using the NETest and chromogranin A (CgA) to determine metrics for detecting small intestinal and pancreatic NETs. The term "pancreatic disease" is confusing since 4 were pancreatic, 31 were pancreatic cysts, 14 were pancreatic adenocarcinoma, and there were four with neuroendocrine tumors but not considered with the previous 45 neuroendocrine tumors. Of note, only 35 of the 45 pancreatic neuroendocrine tumors had pathological data. The NETest did perform significantly better than chromogranin A. However, Dr. Modlin, Dr. Kidd, Dr. Drozdov, listed under Conflict Of Interest their relationships with Wren Laboratories, and that "Financial Support: This work was in part supported by Clifton Life Sciences" which is the parent company of Wren Laboratories. In addition, nothing in the study shows that the results of the testing had any change in the outcomes of the patients. This paper has been previously reviewed by this contractor in a prior reconsideration request. This is not robust support for NETest.

Modlin et al. (27) This is a single case report concerning neuroendocrine tumor testing with NETest and chromogranin A, as well as with imaging. As with all the other Modlin/Kidd papers, this suffers from their association with Wren Laboratories. In addition, this paper does not show any effect on long term survival. This paper has been previously reviewed by this contractor in a prior reconsideration request. This is not robust support for NETest.

Clift et al. (28) Comparison of 3 Systems. This multicenter European study compared calculated percentage estimates for 5- and 10-year disease-specific survival using three different prognostic systems in 70 patients with small bowel neuroendocrine tumors: 1) NET nomogram, 2) the World Health Organization (WHO)/European Neuroendocrine Tumour Society (ENETS) grading system and 3) the American Joint Commission on Cancer (AJCC)/ Union Internationale Contre le Cancer (UICC) TNM staging method. This paper concluded "the NET nomogram may present a viable alternative to these 'classical' systems as it includes multiple different aspects of neuroendocrine disease biology specific to each patient." This is a paper that tries to predict survival. As with all the other Modlin/Kidd papers, this suffers from their association with Wren Laboratories. In addition, this paper does not show any effect on long term survival. This paper has been previously reviewed by this contractor. This is not robust support for NETest.

Modlin et al. (29) A multianalyte PCR blood test outperforms single analyte ELISAs (chromogranin A, pancreastatin, neurokinin A) for neuroendocrine tumor detection. This paper from Wren Laboratories, funded by Clifton Life Sciences, the parent company of Wren Laboratories, compared PCR-based 51 transcript signature (known commercially as NETest) and compared it to chromogranin A (CgA), pancreastatin (PST) and neurokinin A (NKA) testing. Initially there was a validation set of 40 neuroendocrine tumors and controls and then a prospectively collected group of 41 neuroendocrine tumors.

Pancreastatin is a derivative of chromogranin A but typically is not used as a neuroendocrine tumor test. Neurokinin A (NKA, substance K) is a ten amino acid peptide translated from the pre-protachykinin gene but also not typically used as a neuroendocrine tumor test. This paper again suffers from much potential conflict of interest. This paper has been previously reviewed by this contractor in a prior reconsideration request. This is not robust support for NETest.

Aluri et al. (3) This is a detailed review of the current status of biochemical testing in patients with neuroendocrine tumors. The authors note many of the same problems with testing for these tumors including "the neuroendocrine tumors (NET) may be functional (secreting 1 or more products associated with a clinical syndrome) or nonfunctional. Nonfunctional tumors either fail to secrete any known product, or may secrete a product with no known associated clinical outcome." They note that clinical presentation may vary depending on the site of origin of the primary tumor.

They categorize as follows:

Functional	**Local symptoms/incidental**	**CgA, (serotonin), PP**
Neuroendocrine tumor sites of origin, potential associated symptoms, and specific biomarker tests		
Primary Tumor Location	**Symptom**	**Test**
Bronchopulmonary and thymic	**Local symptoms** **Flushing, wheezing** **Cushing syndrome**	**CgA, serotonin,5-HIAA, 5 hydrosytryptophan** **ACTH, cortisol**
Jejunoileal	**Local symptoms** **Carcinoid syndrome**	**Sertonin** **CgA** **Pancreastatin** **NKA**
Colorectal	**Local symptoms** **Incidental findings**	**CgA**
Pancreaticoduodenal		
Nonfunctional	**Local symptoms/incidental**	**CgA, (serotonin), PP**
Functional	**Specific syndrome**	**Varies per syndrome**

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; ACTH, adrenocorticotrophic hormone; CgA, chromogranin A; neurokinin A; PP, pancreatic polypeptide.

They caution that all tumor markers have potential for false-positive and false-negative results.

The authors note, "Because of the difficulties of choosing an optimal biomarker, along with the interpretation issues of each test, professional societies have not provided strong recommendations related to minimal biochemical testing. In general, guidelines from expert committees (European and American NET societies and the National Comprehensive Cancer Network) suggest consideration of CgA for small intestinal, nonfunctional pancreatic, pulmonary, high-grade GEP-NET, and metastases of unknown origin. A 24-hour urine 5-hydroxyindoleacetic acid test could be considered for small intestinal and pulmonary NET and for all tumors with carcinoid syndrome. Pancreatic polypeptide is recommended for nonfunctional pancreatic NET, and neuron-specific enolase can be considered for high-grade tumors. Specific markers to assess functionality in patients with syndromes should be guided by the specific symptoms (eg, urine or plasma 5-hydroxyindoleacetic acid for carcinoid syndrome, insulin for hypoglycemia, etc). Our own practice is to test a broad range of markers initially and then follow markers that are positive."

The authors specifically mention the NETest in detail. "There have been recent developments in nucleic acid–based technologies, like microRNA profiling, and strategies to collect circulating tumor cells, which may become helpful in future for NET diagnosis and management. At this time, however, the only commercially available multianalyte NET test, which may be clinically helpful, is the NETest. The NETest, developed by Wren Laboratories (Branford, CT), is a multianalyte quantitative reverse-transcriptase polymerase chain reaction assay, based on 51 marker genes with an algorithmic analysis, claims a high sensitivity (>95%) and specificity (>95%) in the detection of all GEP-NET tumors. The test offers an assessment of disease status and treatment effectiveness. Early data suggest that the NETest may be more accurate than single biomarker or monoanalyte tests and it is not known to be affected by age, gender, fasting status, or use of proton pump inhibitors. The test requires a single laboratory, Wren Laboratories, to offer the specialized analysis. More information is needed on whether the test is positive in non–GEP-NET or cancers with mixed epithelial and NET phenotype, for example, prostate cancer. Additionally, more prospective verification studies by investigators independent of the manufacturing company are needed. At this time, there is no specific recommendation from any professional organization supporting the NETest." The article notes, "The authors have nothing to disclose." Thus while this article offers positive comments about the NETest, it does not support its use

currently.

Peczkowska et al. (30) This study assessed the proprietary 51-neuroendocrine gene blood analysis (NETest) in 32 well-differentiated paragangliomas and pheochromocytomas compared to chromogranin A (CgA) and catecholamine measurements. A control group (without neuroendocrine tumors) included one person with inflammatory bowel disease, three with IPMN [not defined by the authors, but most likely is intraductal papillary mucinous neoplasm], nine with benign pancreatic cysts and 19 otherwise healthy controls. The results of NETest were 100% positive for those with neuroendocrine tumor and negative for the controls. Again, there is much conflict of interest and no evidence of improved outcomes. This paper has been previously reviewed by this contractor in a prior reconsideration request. This is not robust support for NETest.

Verbeek et al. (31) This is a review of neuroendocrine tumors (NET), including their presentation, location in the body, and associated biomarkers, including Chromogranin A (CgA)) and NETest. The summary is, "NETs are rare tumours, with an annual incidence estimated as 2–5 cases per 100,000 population. They are able to produce non-specific and specific biomarkers. Presently the most frequently used biomarker in GEPNETs [gastrointestinal or pancreatic origin" is CgA, although it is a non-specific biomarker and has its limitations. More specific markers can be used in functioning NET. The use of NEN [neuroendocrine neoplasms] transcripts is promising, but its application of this PCR-based blood test in patients with a NET is still in research." Unlike all the other NETest publications, this one is not affiliated with Wren Laboratories or Clifton Life Sciences. This study also has no evidence of improved outcomes. This paper has been previously reviewed by this contractor in a prior reconsideration request. It is not robust support of NETest.

Bodei et al. (32) Forty-nine patients with neuroendocrine tumors were assessed for the concordance between Ga-somatostatin analog (SSA) positron emission tomography (PET), circulating NET gene transcripts (NETest), chromogranin A (CgA), and the antigen Ki-67. The authors concluded "Ga-SSA PET imaging parameters (SUVmax) [the maximum standardized uptake value] correlated with a circulating NET transcript signature. Disease status could be predicted by an elevated quotient of gene expression (MORF4L2) and SUVmax. These observations provide the basis for further exploration of strategies that combine imaging parameters and disease-specific molecular data for the improvement of NET management. Of note, Dr. Kidd, Dr. Modlin, and Dr. Drozdov are listed as being from Wren laboratories, " but reported "Conflicts of interest: None." This study also has no evidence of improved outcomes. This paper has been previously reviewed by this contractor in a prior reconsideration request. It is not robust support of NETest.

Bodei et al. (33) Seventy-eight patients with neuroendocrine tumors were treated with Peptide Receptor Radionuclide Therapy (PRRT) using ^{177}LuDOTA-Tyr3-Thr8-octreotide (^{177}Lu-octreotate). However, the paper only analyzed fifty-four patients as an interim report. There was definitive data on 60 patients, but three were excluded because of withdrawal of consent, two died, and one was missing data before dropping out due to progression. The study was designed to assess whether a circulating multianalyte 51-gene NET signature (NETest), compared to chromogranin A (CgA), could be used as a surrogate measure of clinical responses to PRRT when assessed at 3- and 6-months follow-up. There was a 72% disease control rate, although this determination is difficult to understand. Changes in NETest accurately (89 %) correlated with treatment response, while chromogranin A (CgA) was only 24 % accurate. However, the paper did conclude, "Confirmation of these observations in larger series will allow identification of likely non-responders and will better define at a molecular level the natural history of individual neuroendocrine tumors." Dr. Kidd listed himself as from Wren Laboratories, although Dr. Modlin did not. "Disclosure of potential conflicts of interest: The authors declare that they have no conflict of interest." This study also has no evidence of improved outcomes. This paper has been previously reviewed by this contractor in a prior reconsideration request. It is not robust support of NETest.

Cwikla et al. (34) This short study (median 10 months) and relatively small study of 35 patients with neuroendocrine tumors reports on patients who were treated with somatostatin analogs (octreotide or pasireotide) and who were

followed by NETest and Chromogranin A (CgA) testing. These patients had known disease status of either stable or progressive. There also was a prospective set of 28 patients who were treated with somatostatin analogs (octreotide or lanreotide). In the test set, the NETest was positive in all patients. Twenty-five (71%) were classified as stable disease by imaging. The NETest activity was significantly lower in stable disease than in progressive disease treated with somatostatin analogs. The twenty-eight patients in the prospective assessment set were evaluated. They were on treatment with somatostatin analogs, although 50% were not on the same ones as the other set. In addition, the description of the differences between the two sets is a bit confusing. The NETest was positive in all patients and the mean levels significantly high in the group that subsequently developed progressive disease. However, fourteen with an elevated NETest of 80-100% during the course of treatment developed progressive disease, but six with these elevated did not develop progressive disease. Chromogranin A (CgA) elevation of greater or equal to 25% may have indicated progressive disease. Dr. Kidd is from Wren Laboratories and the work was supported by Clifton Life Sciences, the parent company of Wren Laboratories. However, the "Disclosure summary" was "The authors have nothing to disclose." There is no evidence that this testing affected outcomes. This paper has been previously reviewed by this contractor in a prior reconsideration request. It is not robust support of NETest.

Pavel et al. (35) This small study (n=34 originally but three were excluded in the follow up) followed patients with gastroenteropancreatic endocrine tumors for a median of 4 years (range 2.2-5.4 years). Seventeen were grade 1, 14 grade 2, and 1 grade 3 (2 had no grade available). Thirty-one were stage IV. They were evaluated using the NETest and chromogranin A (CgA) testing. This was not a prospective study and not a homogenous group. Some of the data were extracted and confirmed retrospectively. At baseline all the NETest were positive and the chromogranin A (CgA) were elevated in 50%. The evaluation is somewhat confusing since three were excluded from the group analysis. The Kaplan-Meier Analysis of T0 to first restaging however, was not significant for the NETest. Overall, the NETest was better than the CgA testing at following patients. The "Disclosure Statement" was, "There is no conflict of interest." However, "The study was supported by Clifton Life Sciences" which is the parent company of Wren Laboratories, Inc. Also, Dr. Drozdov, Dr. Modlin, and Dr. Kidd were listed as being from Wren Laboratories. There is no evidence that this testing affected outcomes. This paper has been previously reviewed by this contractor in a prior reconsideration request. It is not robust support of NETest.

Modlin et al. (36) Thirty five patients with gastroenteropancreatic neuroendocrine tumor were studied. Twenty-seven were operated on: twenty-one to remove the primary tumor and local/regional lymph nodes; two for debulking; three for suspicion of neuroendocrine tumor of the small bowel; and one for appendectomy. It is unknown if the appendix patient had a localized, incidental neuroendocrine tumor. Eight others received non-operative strategies including embolization (three), trans-arterial chemoembolization (two), and radiofrequency ablation (three). Preoperative blood samples were collected (0–24 hours before treatment) and 1 month post-therapy. NETest and chromogranin A (CgA) testing were done. Follow-up including imaging including CT scan, magnetic resonance imaging (MRI), and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-PET (United Kingdom alone) was performed on all patients at three and six months. For the entire operative cohort (n = 27), the pre-surgery NETest scores were increased (79.8 ± 5.1%). Twenty-three (85%) of the 27 subjects exhibited a decreased score post-surgery (4 patients were unchanged). CgA levels were normal in 18 (67%) of the 27 subjects before surgery and in 3 (40%) of 8 subjects before ablation. The postoperative levels of the 2 groups were not significantly different. The post-ablation levels were not reduced. Overall, 6 (22%) of the 27 subjects exhibited a decrease in CgA levels post-surgery. Of the 9 patients with increased preoperative CgA levels, six (67%) exhibited a normalization of values after surgery. The article concluded, "Our results suggest that a PCR-based blood test will be useful in the assessment of the adequacy of operative resection, but a further long-term prospective study is needed to establish the most accurate timing of blood collection (postsurgery) as well as the metrics of the NETest in the prediction of residual/recurrent disease. Under such circumstances, the role of adjuvant therapy may, in the future, become a relevant consideration for NET patients with R0 ["absence of tumor after surgical treatment"] resected disease." There was no conflict of interest disclosure at all. However, Ms. Alaimo, Mr. Callahan, Ms. Teixeira, Dr. Bodei, Dr. Drozdov, and Dr. Kidd were noted to represent Wren Laboratories, the maker of NETest. There is no evidence that this testing affected outcomes. This paper has been previously reviewed by this contractor in a prior reconsideration request. It is not robust support of NETest.

Kidd et al. (37) This was submitted in a recent reconsideration request to this contractor and is being reviewed as a new reference. The authors evaluated whether the NETest identified bronchopulmonary neuroendocrine tumors in 194 samples including 65 controls, 14 benign lung disease, 25 bronchopulmonary neuroendocrine tumors, 25 small bowel neuroendocrine tumors, 36 lung adenocarcinomas and 29 lung squamous cell carcinomas had blood collect immediately prior to surgery or at regular follow-up or controls. Then in seven surgical resected bronchopulmonary neuroendocrine tumors, they compared the tissue NETest with serum testing. They concluded that there was significant correlations between the seven paired tumors and blood samples. Also, there were significant differences in NETest results between lung cancers and benign diseases. In addition gene expression was highly correlated between small bowel and bronchopulmonary neuroendocrine tumors. The paper concluded, "CONFLICTS OF INTEREST None" although Dr. Kidd, Dr. Drozdov, Dr. Matar, and Dr. Chung were from Wren Laboratories. No affiliation for Dr. Modlin was mentioned with Wren Laboratories. Again, there was no evidence that this testing would lead to increased survival. It is not robust support of NETest.

Filosso et al. (38) This was submitted in a recent reconsideration request to this contractor and is being reviewed as a new reference. The authors evaluated their NET multigene blood test (NETest) to diagnose bronchopulmonary neuroendocrine tumours, assess disease status and evaluate surgical resection. This multicenter retrospective diagnostic study of 118 patients who had histological confirmation of bronchopulmonary carcinoids. There were 90 healthy controls, 18 people with chronic obstructive pulmonary disease, 13 "other neuroendocrine neoplasms" (9 large cell neuroendocrine carcinoma and 4 small-cell lung carcinomas), 23 squamous cell lung carcinomas, 26 lung adenocarcinomas. Seventy-four of the carcinoids were stable, 38 had progressive disease and 6 were surgical cures as defined as disease free. Blood testing for NETest and chromogranin A (CgA) were both performed on the samples. The NETest was positive in all the bronchopulmonary carcinoids. The chromogranin A was elevated in 44 of them. There were 28 patients who underwent surgery (19 with lung neuroendocrine neoplasm) and nine described as "lung cancers". The patients with neuroendocrine lung, NETest were significantly reduced following surgery. There was no significant alternation in values noted in the lung cancer cohort. The chromogranin A was not significantly reduced by surgery. While much of the study was retrospective, and the prospective number was small, this does support that NETest is more accurate than chromogranin A. However this work was supported by the Clifton Life Sciences. In addition Dr. Kidd, Dr. Chung, and Dr. Drozdov are listed as being from Wren Laboratories. Despite of this, and the fact that Dr. Modlin has been on other papers been affiliated with Wren Laboratories, "Conflict of interest: none declared" was stated. No evidence was submitted that this led to increased survival. It is not robust support of NETest.

Tsoukalas et al. (4) This is a 2018 "Review Article on Breakthroughs in the Treatment of Advanced Lung Cancer: Progress Through Innovation." It reviews the most recent surgical treatments, medical treatments, molecular-targeted therapies for bronchopulmonary neuroendocrine tumors. There is no mention of NETest. The "Conflicts of Interest: The authors have no conflicts of interest to declare." None of the authors are listed as associated with any proprietary company. It is not support of NETest.

Howe et al. (39) The authors note, "Not surprisingly, there has been much confusion and controversy surrounding the management of patients with SBNETs [small bowel neuroendocrine tumors], and there are no randomized studies that define their optimal surgical treatment. Therefore, in treating these patients, clinicians must rely on their experience and the results of retrospective studies, both of which are subject to bias. Furthermore, there may be significant differences in opinion among the physicians taking care of these patients, depending on whether they are surgical oncologists, medical oncologists, endocrinologists, gastroenterologists, interventional radiologists, or nuclear medicine physicians. Both the European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumor Society (NANETS) have published consensus guidelines for the diagnosis and management of SBNETs, but there remain many clinical scenarios for which the ideal approach is unclear." This consensus guideline from the North American Neuroendocrine Tumor Society does mention chromogranin A and other testing, but not NETest. It does mention several articles by Modlin and Kidd, but none pertained to the NETest. It is not support of NETest.

Hope et al. (40) This paper evaluates the somatostatin receptor positron emission tomography (SSTR-PET) for imaging in patients with neuroendocrine tumors and that it has demonstrated a significant improvement over conventional imaging. They recommend that SSTR-PET should replace In-111 pentetreotide scintigraphy (OctreoScan) in all indications in which SSTR scintigraphy is currently being use. The paper includes one reference from Dr. Modlin, but it is a 2010 one entitled "Pathologic Classification of Neuroendocrine Tumors: a Review of Nomenclature, Grading, and Staging Systems." There is no mention of NETest and thus does not support NETest.

Strosberg et al. (41) This is a review article on midgut neuroendocrine tumors. In particular, monitoring and markers are discussed. A significant majority of the expert panel indicated that they routinely monitor serotonin output in patients with advanced midgut NETs, typically at the time of radiographic staging. There was no consensus regarding the optimal method for measurement of serotonin output including 5-HIAA. Concerning monitoring of nonhormonal tumor markers in patients with advanced midgut NETs, they note, "Chromogranin A is the most commonly measured nonspecific tumor marker in patients with midgut NETs; however, there was consensus that high rates of false-positive and false-negative results as well as unexplained fluctuations limit its utility. Chromogranin A has been validated as a prognostic marker in midgut NET in randomized clinical trials. Pancreastatin, a breakdown product of CgA, may be more specific in certain contexts, such as patients using proton pump inhibitors (which raise CgA levels). A significant majority of the expert panel reported that they measure tumor markers such as CgA and/or pancreastatin in routine practice, but a significant majority also indicated that these tumor markers assist in patient management only occasionally or rarely. As a result, no consensus was achieved on whether tumor markers should be routinely measured in patients with advanced midgut NETs. Studies of the relatively novel 51-gene, polymerase chain reaction–based NETest report higher rates of sensitivity specificity, and accuracy compared with conventional monoanalyte tumor markers. Validation studies are ongoing." Only one person, Dr. Halfdanarson, is listed as having any relationship with Clifton Biosciences, although previously, Dr. Strosberg is noted to have a financial relationship with Wren Laboratories. No evidence was submitted that this led to increased survival. It is not robust support of NETest.

Lipinski et al. (42) This is an overall review of the topic of gastroduodenal neuroendocrine neoplasms. While serum chromogranin A (CgA) is recommended, there is no discussion of NETest. There is no statement of conflict of interest. This does not support NETest.

Bednarczuk et al. (43) This is an overall review of the topic of neuroendocrine neoplasms of the small intestine and appendix. It states that "The most useful laboratory test is the determination of chromogranin A, while concentration of 5-hydroxyindoleacetic acid is helpful in the diagnostics of carcinoid syndrome." There is no discussion of NETest. There is no statement of conflict of interest. This does not support NETest.

Starzynska et al. (44) This is an overall review of the topic of colorectal neuroendocrine tumors/neoplasms. It states that **"**there is a growing body of evidence supporting the thesis that the neuroendocrine neoplasms of the rectum and the neuroendocrine neoplasms of the colon are two different diseases." There is no mention of any biomarkers. There is no discussion of NETest. There is no statement of conflict of interest. This does not support NETest.

Saif MW. (2) In this review article, the author notes, "Targeted therapies such as everolimus and sunitinib resulted in statistically significant improvements in PFS [progression free survival] in randomized studies, and can be used in well to moderately differentiated metastatic pNETs (pancreatic neuroendocrine tumors). However, they are rarely associated with objective radiographic tumor shrinkage by Response Evaluation Criteria in Solid Tumors (RECIST) and the response rates associated with these agents are quite low as well. The choice between everolimus and sunitinib is difficult as they have very similar improvements in PFS [progression free survival] in phase III clinical trials. One major criticism of the results of both phase III studies would be that significant improvement of PFS [progression free survival] is just a surrogate marker, since significant prolongation of OS [overall survival] has not been shown. However, the design of a phase III study with OS [overall survival] as primary endpoint and a study power of 90% would require an estimated sample size of 2800 patients in order to show that a survival benefit of 4

months is significant."

He also notes, "Biomarkers may be used to assist in both the diagnosis and post-treatment follow up in patients with pNETs (pancreatic neuroendocrine tumors). In poorly differentiated tumors, chromogranin-A (CgA), synaptophysin and cytokeratin are often used to establish neuroendocrine differentiation. Ki-67 (MB-1) and the mitotic rate are used as grading criteria for NETs and were shown to correlate with outcome. Blood markers, such as pancreatic polypeptide (PPP) and specific serum hormone levels are also used to diagnose pNETs (pancreatic neuroendocrine tumors) and evaluate response to therapy. Plasma levels of chromogranin-A are thought to correlate with tumor burden and increased levels have been associated with a poor PFS and survival [24]. PPP [pancreatic polypeptide] is a nonspecific biomarker for nonfunctioning pNETs (pancreatic neuroendocrine tumors) with a relatively low sensitivity (63%) and specificity (81%). However, when used in combination with CgA, the sensitivity for nonfunctioning pNETs (pancreatic neuroendocrine tumors) increased from 68% to 93%. For functioning pNETs (pancreatic neuroendocrine tumors), the levels of the secreted hormone represent a more specific tumor marker. As per the National Comprehensive Cancer Network (NCCN) guidelines, serum proinsulin, insulin/glucose ratio and C-peptide levels may be followed in insulinomas; serum gastrin levels may be followed in gastrinomas; serum VIP levels may be followed in VIPomas; serum glucagon, glucose and CBCs may be followed in glucagonomas; serum Somatostatin, calcitonin and parathyroid hormone related peptide levels may be followed in other functioning pNETs (pancreatic neuroendocrine tumors). Novel biomarkers are currently being evaluated, including neuron-specific enolase (NSE), circulating tumor cells (CTCs), and placental growth factor. Currently, no definitively proven predictive biomarkers are available to guide selection of therapies. Therefore, further studies are needed to individualize and optimize their management. Over the past few years, knowledge regarding the molecular pathology of Pancreatic NETs has increased substantially. PNETs (pancreatic neuroendocrine tumors) are characterized by a relatively limited number of mutations in tumor suppressor genes, such as MEN1, ATRX and DAXX. The clinical significance and potential for treatment of these mutations remains uncertain." There is no mention of NETest or Dr. Kidd or Dr. Modlin in this review article. Most important, it specifically noted, "significant improvement of PFS [progression free survival] is just a surrogate marker, since significant prolongation of OS [overall survival] has not been shown." This does not support NETest.

Koenig et al. (7) This paper reviewed 62 individuals treated at the University Hospital of Marburg in Germany. The paper also reviews the neuroendocrine tumors and states "chromogranin A (CgA) is a well-established marker for diagnosis and follow up of patients with gastroenteropancreatic neuroendocrine neoplasms" and "it has been shown that plasma levels of chromogranin A correlate with tumor load and predict survival of patients with neuroendocrine neoplasms of the small bowel." They state that this study "demonstrates that, immunohistochemical CgA (chromogranin A) and synaptophysin are good markers for histological diagnosis in patients with NEN (neuroendocrine neoplasms) of the colon and rectum. However, chromogranin A is a poor marker to follow-up these patients because only a minority exhibited increased levels which did not increase significantly during tumor progression. In contrast to NEN (neuroendocrine neoplasms) of the small bowel, there is no correlation of CgA plasma levels with tumor burden or survival. Patients with NEN (neuroendocrine neoplasms) of the colon and rectum displayed a relatively good prognosis resulting in a median survival of 8.5 years. However, a subset of patients affected by G3 neoplasms, exhibited a poorer prognosis with a median survival of 2.5 years. Taken together, CgA is a valuable marker for immunohistochemical diagnosis, but CgA plasma concentration is not suitable to mirror tumor burden or prognosis in patients with NEN of the colon and rectum." "Usually, NEN are well-differentiated tumors exhibiting a slow growth associated with a good prognosis. However, some of these tumors grow more rapidly, resulting in less favorable survival rates. In fact, there are currently no well-established prognostic markers for patients with these tumors. Histological staining for Ki-67, the degree of differentiation of the tumor, the presence of metastases, or lymph node involvement are currently the most reliable markers to predict tumor growth and survival of patients with neuroendocrine tumors." It notes that "currently, CgA is widely used in the clinical routine for diagnosis and follow-up of patients with gastroenteropancreatic neuroendocrine neoplasms." The paper did note, "NETest was superior in predicting progressive disease and disease alterations compared to CgA. However, patients with colorectal NEN (neuroendocrine neoplasms) were not included in this pilot project and actually the NETest is not routinely available. Whether the use of a recently suggested array-based, multifactor analysis of blood mRNA levels

can overcome this problem in daily patient care must be evaluated in future studies." This is not robust support for NETest.

Bowden et al. (10) As noted above, MiRNAs are short (approximately 22 nucleotides) RNA sequences that have been shown to broadly regulate gene expression at a post-transcriptional level, by binding to the 3' region of target RNAs, resulting in mRNA degradation and inhibition of translation. Using a 742-miRNA panel, the authors identified candidate miRNAs similarly expressed in 19 small intestine neuroendocrine tumors and matched plasma samples. They refined their panel in an independent cohort of plasma samples from 40 patients with metastatic small intestine NET and 40 controls, and then validated this panel in a second, large cohort of 120 patients with metastatic small intestine NET and 120 independent controls. The authors concluded that elevated circulating levels of miR-21-5p and miR-22-3p and low levels of miR-150-5p are characteristic in patients with metastatic small intestine neuroendocrine tumors, and further suggests that levels of these miRNAs are associated with overall survival. These observations provide the basis for further validation studies, as well as studies to assess the biological function of these miRNAs in small intestine neuroendocrine tumors. "CONFLICTS OF INTEREST The authors declared that there are no conflicts of interest in this work." This paper supports the role measuring miRNA in patients with neuroendocrine tumors. However, the results of the testing did not affect survival. In addition, there is nothing to suggest that these are the same testing that is performed by NETest. The authors acknowledge NETest by noting, "Preliminary studies have suggested that a multianalyte approach, using a 51-transcript mRNA panel, may be more sensitive and specific than currently available biomarkers though this assay has yet to be validated in large, prospective studies." This paper has been previously reviewed by this contractor in a prior reconsideration request. This is not robust support for NETest.

Delle Fave et al. (45) This European Neuroendocrine Tumor Society (ENETS) guideline gives a current overview on the histology, classification, and treatments, but does not discuss testing, or follow-up surveillance, outside of endoscopy. There are no disclaimers or conflict of interest mentioned. This is not supportive of NETest.

Niederle et al. (46) This European Neuroendocrine Tumor Society (ENETS) guideline deals only with non-metastatic neuroendocrine neoplasms originating from the small bowel. It does note, "Serum chromogranin A (CgA) remains a relatively sensitive marker for NENs (neuroendocrine neoplasms) of all origins including Si-NENs (small intestine neuroendocrine neoplasms). CgA has also more recently been shown to prognostically predict significantly differing groups, with higher levels of CgA indicating a worse prognosis, probably related to increased tumor cell mass. For longitudinal follow-up purposes, it is important to note that absolute CgA values may differ significantly between different assays and therefore it is recommended to perform repeated measurements in the same laboratory or at least with the same assay whenever possible. Furthermore, the differential diagnosis of elevated CgA values such as in patients on proton pump inhibitors (PPIs), with chronic atrophic gastritis, chronic renal failure, liver cirrhosis or congestive heart failure, as well as other CgA-secreting neoplasms (e.g. hepatocellular carcinoma, medullary thyroid carcinoma) needs to be considered when CgA values are interpreted. CgA may signal NEN (neuroendocrine neoplasms) recurrence after successful curative resection early in patients with a small tumor burden."

"Endocrine tumors of the jejuno-ileum produce serotonin and elevated 24-hour urinary 5-hydroxy indole acetic acid (5-HIAA) levels as a product of the metabolism of serotonin. 5-HIAA has a sensitivity of up to 100% and a specificity of 85–90% for detecting a carcinoid syndrome, and a sensitivity of 70–75% and a specificity of close to 100% for predicting a primary tumor in the jejuno-ileum. Urinary 5-HIAA should be collected with strict dietary restrictions to avoid false positive levels. Serum serotonin determinations are less sensitive and specific and are, therefore, not recommended; serotonin measurements in platelets, where serotonin is stored depending on its availability in the systemic circulation, may be even more sensitive, but is not widely available and therefore currently impractical."

"Minimal Consensus Statement on Laboratory Tests: The minimally required biochemical tests include plasma CgA and urinary 5-HIAA. These tests should be performed at the first visit and then for follow-up or on suspicion of NEN recurrence or progression. Newer markers, either biochemical or based on circulating NEN cells, require further

validation. Neuron- specific enolase has no role for the diagnosis of these almost always well- to moderately differentiated NEN (G1/2 NET).” There are no disclaimers or conflict of interest mentioned. This is not supportive of NETest.

Crabtree JS. (9) This review paper, cited above, referenced three articles by Dr. Modlin, but concluded, “Furthermore, genetics-based approaches may hold the key toward precision therapies and future investigations into novel pathways may help define driver mutations present in the different subtypes of NETs. Future clinical utilization of gene panels, methylation screening tools and other molecular biomarker approaches in addition to classical neuroendocrine markers, will facilitate treatment and improve outcomes of this disease.” This work was supported by the Louisiana State University Health Sciences Center Department of Genetics. No mention of conflict of interest was stated. This does not support NETest.

Childs et al. (47) These authors note, that other biomarkers for evaluating neuroendocrine tumors include overexpressed somatostatin receptors (SSTR) that can be targeted for therapy. Somatostatin receptors 2 and 5 are detectable on CTCs from NET patients and may be a useful biomarker for evaluating SSTR-targeted therapies and this is being prospectively evaluated in the Phase IV CALMNET trial (NCT02075606). “Conflict of Interest: Dr. Meyer received research funding for this work from Ipsen and Dr. Caplin has received grant funding and consultancy fees from Ipsen.” In addition, “The funding was provided by the University College London (UCL) Experimental Cancer Medicine Centre Grant No. C12125/A15576, the UCL Hospitals NIHR Biomedical Research Centre and Ipsen.” This does not support NETest.

Kunz PL. (48) This is a commentary about the Dasari article. It deals with increasing incidents of neuroendocrine tumors and the “need to conduct rigorous basic, translational, clinical, and health services research to move the field forward.” NETest is not discussed, although neither are other markers. It does not support, nor refute NETest.

Berardi et al. (49) This is a detailed review on neuroendocrine tumors (NET) and treatment methods. The authors note, “Therapeutic sequence is still controversial. To date research efforts are focused on translational studies on the available options in order to better select the patients who could benefit from different treatment options. In fact a better understanding of the molecular pathways involved in the NETs carcinogenesis, might predict the efficacy of each therapeutic approach. Furthermore, research on identifying the best strategy involving the available options would be beneficial.” “Conflict of interest: All authors disclose no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.” “Acknowledgement: The authors did not receive specific funding for the manuscript.” This paper does not support NETest.

Kwon et al. (50) This is a review article that brings up a very important point. “The prevalence of gastric NETs is difficult to establish due to a lack of uniform data collection from cancer registries worldwide. A study published in 2015 analyzing national cancer registries in 10 European countries, the US, and Japan determined the prevalence of gastric NETs per 10,000 population to be 0.32 in Europe, 0.17 in the US, and 0.05 in Japan. The authors of this study did note that their values may be underestimations due to a tendency of cancer registries to reflect the aggressive tumors that require treatment as opposed to benign tumors.” While this paper does cite an article by Dr. Kidd and Dr. Modlin, no biomarkers except gastrin are mentioned. “Disclosure: EKB has received research funding (to institution) from Novartis and served as a consultant (unpaid) for Ipsen. The other authors report no conflicts of interest in this work.” This does not support NETest.

Oronsky et al. (51) This is a review article about neuroendocrine tumors including history, workup, and treatment. The article notes, “Commonly measured tumor markers in NENs include serum CgA and 5-HIAA, the final secreted product of serotonin, levels in a 24-hour urine sample. Since serum CgA, which is a more sensitive and broadly applicable marker than urinary 5-HIAA, does not depend on serotonin secretion, it is preferred over 5-HIAA for bronchial and rectal tumors, which do not generally secrete serotonin. In addition to its value in making the

diagnosis, plasma CgA levels correlate with tumor bulk, differentiation and secretory activity, which in turn may predict treatment response and overall survival (OS) (fast rising levels seem to indicate a poor prognosis). Besides CgA and 5-HIAA, NENs are known to produce a plethora of bioactive amines and peptides such as 5-hydroxytryptamine, 5-hydroxytryptophan, serotonin, insulin, gastrin, glucagon, somatostatin, vasoactive intestinal peptide, growth hormone, adrenocorticotropic hormone, melanocyte-stimulating hormone, pancreatic polypeptide, calcitonin, substance P, pancreastatin, etc., resulting in relatively uncommon but unique clinical syndromes." A concern is "Funding: None." and no conflict of interest statement. This is a bit concerning since Dr. Oronsky is from EpicentRx Inc, a pharmaceutical company involved in cancer research. Of note, the paper references Dr. Modlin multiple times, but not for NETest. This is not a supportive paper of NETest.

Falconi et al. (52) This international (European Neuroendocrine Tumor Society) consensus guideline does not mention NETest. This is not a supportive paper of NETest.

Garcia-Carbonero et al. (53) This international (European Neuroendocrine Tumor Society) consensus guideline does not mention NETest although it mentions chromogranin A. There are no disclaimers or conflict of interest mentioned. This is not a supportive paper of NETest.

Kaltsas et al. (54) This international (European Neuroendocrine Tumor Society) consensus guidelines on pre-and perioperative therapy in patients with neuroendocrine tumors does not mention NETest although it mentions chromogranin A. There are no disclaimers or conflict of interest mentioned. This is not a supportive paper of NETest.

Pavel et al. (55) This international (European Neuroendocrine Tumor Society) consensus guidelines for the standards of care in neuroendocrine tumors does not mention NETest. This paper has been previously reviewed by this contractor in a prior reconsideration request. It is the introductory article for the following series of articles. There are no disclaimers or conflict of interest mentioned. This is not a supportive paper of NETest.

Perren et al. (56) This international (European Neuroendocrine Tumor Society) consensus guidelines for standards of care in neuroendocrine tumors and their pathological diagnosis and prognostic stratification does not mention NETest. It does mention and support chromogranin-A. It does conclude, "translational studies are needed to define biomarkers predicting response to other therapies such as targeted therapies or other chemotherapeutic strategies.**"** This is not a supportive paper of NETest.

Sundin et al. (57) This international (European Neuroendocrine Tumor Society) consensus guidelines for standards of care in neuroendocrine tumors and their radiological imaging does not discuss biomarkers. It is included in this review for completeness. It does not support, nor refute NETest.

Oberg et al. (58) This international (European Neuroendocrine Tumor Society) consensus guidelines is completely devoted to biomarkers in neuroendocrine tumors. It goes into great depth on the various biomarkers. In particular, it notes "Overall CgA [chromogranin-A] has been found to be clinically informative and moderately sensitive in the majority of studies devoted to this topic. It does note the false positives associated with chromogranin-A. It notes "A recognized international standard for CgA assay is not available and variations in assay types may influence results. Several assays for measurements of intact CgA and cleavage products have been developed" Commercial CgA kits differ in the types of antibodies used (monoclonal vs. polyclonal) and include enzyme detection (ELISA) and radioimmunoassay. Differences in methods of standardisation have also lead to heterogeneity. In particular it notes:

- CgA is the most practical and useful general serum tumor marker in patients with NETs;
- Elevated CgA can occur in normal individuals and in patients with non-NET tumors although the levels are usually lower than in patients with NETs;
- Sensitivity of elevated CgA varies according to NET tumor type and volume;

- Reference laboratories should be preferred for clinical samples assays;
- Reference intervals and individual patient results differ significantly between different CgA assays and cannot be directly compared;
- Serial measurements should be performed using the same assay;
- If assays are changed, patients should undergo a new baseline measurement;
- False-positive results are possible in patients with hypergastrinemia (especially on antisecretory medications or chronic atrophic gastritis Type A) and in the presence of heterophile antibodies (care in patients with autoimmune diseases or those sensitized to rodent proteins [mouse monoclonal antibodies]);
- Where possible, PPIs should be interrupted, leaving a clearance of at least 3 half-lives, prior to CgA plasma sampling.

It does note, "blood measurements of neuroendocrine gene transcripts have demonstrated significant diagnostic and prognostic potential in recent studies (NET-test). The precise role of these analyses has to be expected in future prospective trials" and does cite three Modlin/Kidd publications. This is not robust support for NETest.

Partelli et al. (59) This international (European Neuroendocrine Tumor Society) consensus guidelines for standards of care for small intestinal and pancreatic neuroendocrine tumors does not discuss biomarkers. It is included in this review for completeness. It does not support, nor refute NETest.

Pavel et al. (60) This is another international (European Neuroendocrine Tumor Society) consensus guideline on the standards of care concerning systemic therapy for neuroendocrine neoplasms. It specifically mentions chromogranin-A and several other biomarkers to be performed before and after treatment, but does not mention NETesting. There are no disclaimers mentioned. This paper does not support NETesting.

Garcia-Carbonero et al. (61) This is another international (European Neuroendocrine Tumor Society) consensus guideline on the standards of care concerning systemic chemotherapy for neuroendocrine neoplasms. Like the preceding reference, it specifically mentions chromogranin-A and several other biomarkers to be performed before and after treatment, but does not mention NETesting. This paper does not support NETesting.

Hicks et al. (62). This is another international (European Neuroendocrine Tumor Society) consensus guideline on the standards of care concerning peptide receptor radionuclide therapy for neuroendocrine neoplasms. It specifically notes, "the availability of serum biomarkers like chromogranin-A (Cg-A) or other specific hormones also provides an important means to assess response." It does mention that chromogranin-A is not always elevated in these metastatic tumors and can be elevated in other situations. It does state, "there is a need for improved biomarkers of response." However, NETesting is not mentioned at all. This paper does not support NETesting.

Modlin et al. (63) This paper is now really a historical paper. It describes the development of the NETest, noting that "PCR-based signature measures multiple transcripts which reflect the diverse biological profile of a proliferating NEN and may, with further examination in appropriate studies, be tested as a measure of tumor responsiveness and, potentially, as a prognostic." It was not associated with any improved clinical outcomes. It was reviewed by this contractor in a prior reconsideration and not felt to adequately support NETest.

Modlin et al. (64) This paper is now also a historical paper. It describes the development of the NETest, noting that "These parameters indicate this may provide an accurate and sensitive multi transcript molecular tool to identify NENs and assess disease progress using peripheral blood sample." It was not associated with any improved clinical outcomes. It was reviewed by this contractor in a prior reconsideration and not felt to adequately support NETest.

Pavel et al. (65) This paper was reviewed by this contractor in a prior reconsideration. It is not from Dr. Modlin or Dr. Kidd. The study does not address NETest and thus does not support the use of NETest.

Caplin et al. (66) This paper was reviewed by this contractor in a prior reconsideration. It is an excellent paper in the *prestigious New England Journal of Medicine* concerning the somatostatin analogue lanreotide in patients with advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor–positive neuroendocrine tumors of grade 1 or 2 (a tumor proliferation index [on staining for the Ki-67 antigen] of <10%) and documented disease-progression status. The tumors originated in the pancreas, midgut, or hindgut or were of unknown origin. This is the CLARINET study. However, NETest is not mentioned by any of the authors in this paper. It is not supportive of NETest.

Strosberg et al. (67) This paper was reviewed by this contractor in a prior reconsideration. It is also an excellent paper in the prestigious *New England Journal of Medicine* concerning use of ^{177}Lu-Dotatate in patients with advanced, progressive, somatostatin-receptor–positive midgut neuroendocrine tumors. However, NETest is not mentioned by any of the authors in this paper. It is not supportive of NETest.

De Wever et al. (68) This paper was reviewed by this contractor in a prior reconsideration. NETest is not mentioned by any of the authors in this paper. It is not supportive of NETest.

Allingham-Hawkins et al. (69) This paper was reviewed by this contractor in a prior reconsideration. NETest is not mentioned by any of the authors in this paper. It is not supportive of NETest.

NCCN Breast Cancer Version 2.2017 (70). This paper was reviewed by this contractor in a prior reconsideration. However, NETest is not mentioned. It is not supportive of NETest.

Smith et al. (71) This paper was reviewed by this contractor in a prior reconsideration. Neither neuroendocrine tumor screening nor the NETest are mentioned by any of the authors in this paper. It is not supportive of NETest.

Knigge et al. (72) This is another international (European Neuroendocrine Tumor Society) consensus guideline on the standards of care. This article discusses the follow-up and documentation of patients with neuroendocrine tumors. It lists a number of tumor markers and specifically starts off with Chromogranin A stating, "At present, the most common and reliable tumor marker is plasma CgA for patients with G1 and G2 NEN [neuroendocrine neoplasms]." It then mentions Chromogranin B, Neuron-Specific Enolase, 5-Hydroxyindoleacetic Acid, Serotonin, Gastrointestinal Hormones (insulinoma, gastrinoma, glucagonoma, VIPoma, somatostatinoma), and NT-pro-Brain Natriuretic Peptide. However, it does not mention NETesting. In addition, it notes "The follow-up should be in accordance with the ENETS consensus guidelines from 2011 and 2016, the present and coming WHO classification and ENETS/UICC recommendations for TNM staging…However, it should be stressed that evidence-based studies for follow-up are largely missing." The article concluded with "Disclosure Statement: The authors have no conflicts of interest." This paper is not supportive of NETest.

Atri et al. (74) This is another paper in the *New England Journal of Medicine*. However, it describes how the consultant revaluated a patient who turned out to have a neuroendocrine tumor. As the publication states, "In this *Journal* feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type).The authors' commentary follows." The author noted, "When a neuro endocrine tumor is suspected as a cause of chronic diarrhea, the serum gastrin, vasoactive intestinal peptide, and chromogranin A and urine 5-hydroxyindoleacetic acid levels should be measured." NETesting is not mentioned, nor are any articles by Dr. Kidd or Dr. Modlin referenced. This paper is not supportive of NETest.

Pallais et al. (75) This is another paper in the *New England Journal of Medicine*. It is a "Case Records of the Massachusetts General Hospital" and describes how an expert clinician evaluated a "45-year-old woman [who] was admitted to this hospital because of dyspnea on exertion, fatigue, and confusion" who turned out to have a

neuroendocrine tumor. Chromogranin A is mentioned as a neuroendocrine marker, but NETesting is not mentioned. The third author, Dr. Lu "reports receiving consulting fees from PQ Bypass and grant support from Nvidia." There were no other reported conflicts by any of the authors. There are no articles by Dr. Kidd or Dr. Modlin referenced. This paper is not supportive of NETest.

The following submissions were received by NGS during the comment period. They have been reviewed and added to the existing list of references. They are numbered as a continuation of the original reference list in this LCD.

Chen et al. (76) This is a very interesting research overview dealing at the molecular level of cancers. The authors, "On the basis of genetic expression data, classified 10,224 cancers, representing 32 determined major types, into 10 molecular based 'classes.'" The authors do not mention NETest by name, but describe it without comment. The authors conclude their review with "there being a clear need for additional and better biomarkers. The more accurate identification of neuroendocrine-associated cancers in particular would have important implications regarding the treatment of this disease." Disclosure of Potential Conflicts of Interest. No potential conflicts of interest were disclosed." This paper does not support, nor refute NETest.

Liu et al. (77) This study is based on NCT022705667 which is a registry on the National Clinical Trials Database. This registry is estimated to be completed March 2020. This paper was critiqued by Rindi and Wiedenmann (#175 above). Neuroendocrine Neoplasia Goes Molecular—Time for a Change. 2018. Clinical Oncology. https://doi.org/10.1038/s441571-018-0118-8. "In this study, 100 patients were monitored for 6-12 months.. Patients received the test at enrolment, were assigned to two groups depending on whether they had stable disease ('watch-and-wait' group) or progressive disease ('intervention' group) according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria, and separately analyzed.

"Seventy-two patients received a single test, and the rest received 2-4 tests. The data provided suggest tumour progression can be predicted earlier using NETest than with established RECIST criteria" However, Rindi and Wiedenmann noted, "The presented data, however, must be considered with caution, given the focus of the study on neuroendocrine cancer. Neuroendocrine neoplasia encompasses distinct tumour entities with growth behaviors that vary from extremely slow to very rapid. The incidence and aggressiveness of neuroendocrine neoplasms is highly dependent on the anatomical site of origin. The most aggressive disease is frequently found in the pulmonary tract (in the form of small-cell lung cancer [SCLC], and is also referred as neuroendocrine carcinoma (NEC) when found at other anatomical sites. The most indolent cases are frequently detected in the digestive system were previously termed carcinoids and are currently referred to as neuroendocrine tumours (NETs).The introduction of standard grading and staging tools for cancer in routine practice in the past decade greatly improved our knowledge of neuroendocrine neoplasia. Necessarily, inclusion criteria (according to anatomical site, and staging and grading parameters) need to be accurately defined before conducting studies in patients with neuroendocrine cancer in order to achieve a clear understanding of the results. Liu and co-workers focused their attention on patients with NET (97 of 100 patients tested). The most aggressive poorly differentiated forms of neuroendocrine cancer were also represent, but only in a very small subgroup (1 patient had SCLC and 2 patients had poorly differentiate NECs). The investigators used NETest to evaluate blood samples of patients who predominantly had advanced-stage neuroendocrine cancer (96 patients had stage IV disease), but with variable disease grades, mostly, low grade (45 of 86 patients) or intermediate grade (37 of 86 patients), and originating from different organs (68% in the digestive tract and pancreas)….The emerging picture in this study of 100 patients is promising, but not all the results aligned with the expectation. Discordance emerged when the NETest did not correlate with either absence or presence of the disease (4%of patients) or with stable or progressive disease status (17%and 23% of patients respectively) determined with stand methods. In 36% to 38% of patients in both groups the use of the test led to changes in patient management, resulting in a reduction of the number of imaging procedures performed.

"Unfortunately, the specificity and sensitivity of the test were not provided nor could they be accurately calculated with the data made available; however, the overall concordance with disease status reported (85) was well below

100%, a value necessary to ensure that not a single patient is misdiagnosed and therefore denied the most appropriate treatment. Understandably, reaching perfection is almost impossible in the real word, and this principle holds true especially in the complex management of patients with neuroendocrine neoplasia. Nevertheless, a clear definition of the sensitivity and specificity of NET is needed before the assay is widely adopted in clinical practice. Furthermore, whether the test performs identically regardless of tumour grade, tumour volume and/or treatment history remains unclear—the presented patient numbers are too small and the selected cohort was to heterogeneous…Thus, the cost-benefit radio needs to be accurately established once NETest has been studied in larger and homogenous populations of patients with neuroendocrine cancer" [note: Medicare does not use cost as a decision for coverage]. Disclosures. Scott Paulson: Ipsen, Taiho, Merrimack Advanced Accelerator Applications, Bristol-Myers Squibb. The other authors indicated no financial relationships. This paper does not support that NETest is proven to have improved overall survival or is proven technology today. It is however a promising paper.

Kulke et al. (78) This old paper deals with the important topic to "identify key unmet needs, develop appropriate study end points, standardize clinical trial inclusion criteria, and formulate priorities for future NET studies to the US cooperative group program. Emphasis was placed on the development of well-designed clinical trials with clearly defined efficacy criteria." The authors do not mention NETest at all. They do propose that progression free survival for both phase II and phase III studies be used rather than overall survival. This view on endpoints is not standard today. Progression-free survival is used to evaluate new drugs for cancers. The NETest is not a drug, but rather a predictive test. This paper does not give any support to NETest. Under Authors Disclosures of Potential Conflicts of Interest, a number of honoraria and research funding related to drug companies were noted.

Singh et al. (79) This paper does not mention NETest. The introduction of the article states, "Overall survival (OS) remains the gold standard end point for randomized controlled clinical trials in patients with cancer." It states that "[Neuroendocrine tumors] represent a tumor type in which [overall survival is particularly difficult to evaluate because disease heterogeneity (resulting in difficult patient recruitment in large Phase II trials), low numbers of eligible patients (ie, those with proper diagnoses), and variable survival times for patients with distal or regional [neuroendocrine tumors] (median OS, 33 or 111 months respectively)." Again, this is not a valid concern here. None of the submitted NETest literature deals with Phase II or Phase III drug trials. This is a paper from a drug company that wants to change the fact that Overall survival (OS) remains the gold standard end point for randomized controlled clinical trials in patients with cancer." The issue of using overall survival (OS) rather than time to disease progression (TDP) or time tumor progression (TTP) for phase II or phase III clinical trials is a different is issue. Disclosure: Dr. Singh received research grants from Novartis and consulting fees and honoraria from Novartis and Pfizer. Dr. Wang is an employee of and a stockholder in Novartis Oncology. Dr. Law has received research grants from Novartis Oncology and consulting fees from Pfizer Oncology and Novartis Oncology and serves on the speaker bureau for Novartis Oncology. This paper does not support NETest.

Ter-Minassian et al. (80) This paper does not mention NETest. It reflects the same issues for changing the current standard of measuring endpoints for drug trials. That is not the issue here. Acknowledgments: This study was funded in part with a grant from Ipsen Pharmaceuticals. This paper does not support NETest.

Imaoka et al. (81) This paper does not mention NETest. This paper's first sentence is "In oncology clinical trials, overall survival (OS) is considered the gold standard outcome measure." It reflects the same issues for want to change the current standard of measuring endpoints for drug trials. That is not the issue here. It does state, "The results of the present analysis indicate the [progression free survival] is significantly correlated with [overall survival], and suggest that progression free survival is an acceptable surrogate for [overall survival] in clinical trials for neuroendocrine tumors." Declaration of interest. "M I has received research funding from Novartis Pharma K.K. and honoraria from Novartis Pharma K.K. and is a member of advisory board for Novartis Pharm K.K., Teijin Pharma and Nobel Pharma. The other authors have no conflicts of interest. This paper does not support NETest.

Imaoka et al. (82) This paper does not mention NETest. It states, "In oncology phase II trials, [overall survival] is

considered the gold stand and is the most commonly used primary endpoint….On the other hand, the primary goal in a phase II trial to determine if there is sufficient evidence of antitumor activity to undertake a phase III trial." The issue of NETesting in any clinical trial of cancer drugs is not the issue. Disclosures: Masafumi Ikeda: Novartis Pharma K.K. (RF, H), Novartis Pharma K.K., Teijin Pharma, Nobel Pharma (SAB. The other authors indicated no financial relationships. This paper does not support NETest.

NCCN Guidelines Version 3.2018—September 11, 2018 (83) The title page for this National Comprehensive Cancer Network (NCCN) Guideline was submitted, although with a page with the list of authors, and the Table of Contents. Nothing else was included. However, NGS went to the NCCN site and looked up the entire publication. There was not support for the NETest. This publication does not support NETest.

Modlin et al. (84) This old article does not mention NETest. It does dwell on improving the management of neuroendocrine tumors. There is no mention of conflict of interest. This paper does not support NETest.

Oberg et al. (85) This paper has been reviewed previously and is #24 in the LCD. This does not give any new support for NETest.

Oberg et al. (86) This paper has been reviewed previously and is #12 in the LCD. This does not give any new support for NETest.

Dattani et al. (87) This paper does not mention neuroendocrine tumors or NETest. It discussed the evaluation of "the oncological and survival outcomes of a Watch and Wait policy in rectal cancer after a clinical complete response (cCR) following neoadjuvant chemoradiotherapy." The tumors do not appear to be neuroendocrine tumors. This paper does not support NETest.

Mazza et al. (88) While neuroendocrine tumors can occur about anywhere in the human body, bladder neuroendocrine tumors must be very rare since no paper submitted has mentioned any. There is no mention of any of these bladder cancers being neuroendocrine tumors. This paper does not support NETest.

Bye et al. (89) This paper does not discuss NETest or neuroendocrine tumors. It does not support NETest.

Moore et al. (90) This paper does not discuss NETest or neuroendocrine tumors. It does not support NETest.

Odogwu et al. (91) This paper does not discuss NETest. It is concerned with the use of Osimertinib. It does not support NETest.

Pavel et al. (92) This paper has been reviewed previously and is #35 in the LCD. This does not give any new support for NETest.

Drukker et al. (93) This paper describes a proprietary gene prognosis method on breast cancer. The proprietary gene prognosis method in this study is not NETest. The breast cancers are not neuroendocrine tumors. It does not support NETest.

Cardoso et al. (94) This paper in the prestigious New England Journal of Medicine further describes the use of a 70-gene signature proprietary test on women with breast cancer. However, the proprietary gene prognosis method in this study is not NETest. The breast cancers are not neuroendocrine tumors. It does not support NETest. Of note, none of the multiple articles submitted in support of NETesting are from the New England Journal of Medicine

although this journal has published neuroendocrine tumor articles, none of which mention NETest.

Burns et al. (95) This paper is from a plastic surgery journal. It does not mention NETest. It does not mention neuroendocrine tumors. We agree with their statement, "Physician are encourage to find the highest level of evidence to answer clinical questions." This supports the obtaining the highest level of evidence and does not support NETest.

Kidd et al. (96) This paper has been reviewed previously and is #37 in the LCD. This does not give any new support for NETest.

Filosso et al. (97) This paper has been reviewed previously and is #38 in the LCD. This does not give any new support for NETest.

Bodei et al. (98) This paper has been reviewed previously and is #33 in the LCD. This does not give any new support for NETest.

Kidd et al. (99) This paper has been reviewed previously and is #21 in the LCD. This does not give any new support for NETest.

Strosberg et al. (100) This paper has been reviewed previously and is #67 in the LCD. This does not give any new support for NETest. Again, this is from the New England Journal of Medicine which does publish neuroendocrine articles but none of them as of yet has mentioned NETest.

Yao et al. (101) This paper in the prestigious New England Journal of Medicine evaluates the new drug everolimus for the treatment of advance pancreatic neuroendocrine tumors. Unfortunately, the article does not mention NETest at all. Thus, it give no support to the use of NETest, especially for pancreatic neuroendocrine tumors.

Kulke et al. (102) This recent paper evaluated everolimus combination with Pasireotide LAR and everolimus by itself in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors. NETest was not used as a biomarker for this study, although chromogranin A was. There is no mention at all of NETest. This article was to evaluate the above cancer drugs. The funding was by Novartis Pharmaceutical Corporation. Under disclosures there were multiple concerning apparent conflicts of interest. This paper does not support NETest.

Yao et al. (103) This paper evaluated everolimus in advanced, nonfunctional neuroendocrine tumors of the lung or gastrointestinal tract. It is a drug study. NETest was not used as a biomarker for this study. There is no mention at all of NETest. The study was sponsored by Novartis Pharmaceutical Corporation. This paper does not support NETest.

Caplin et al. (104) This paper has been reviewed previously and is #66 in the LCD. This does not give any new support for NETest. Again, this is from the New England Journal of Medicine which does publish neuroendocrine articles but none of them as of yet has mentioned NETest. This does not support NETest.

Raymond et al. (105) This paper evaluated sunitinib malate for the treatment of pancreatic neuroendocrine tumors. It is a drug study. There is no mention of NETest. This does not support NETest.

Andersson et al. (106) This is a paper on imaging for appendicitis. This does not pertain to neuroendocrine tumors. It does not mention NETest. This paper does not support NETest

Modlin et al. (107) This paper has been reviewed previously and is #63 in the LCD. This does not give any new support for NETest.

Modlin et al. (108) This paper gives a good overall view of neuroendocrine tumors. However, despite the claim, NETest has not been independently validated. The registry under NCT02270567 is mentioned. However, this voluntary registry is still open and is not expected to be completed until March 2020. There is no Conflict of Interest statement. This gives some support to NETest.

Patel et al. (109) This paper gives a good overview of neuroendocrine tumors including treatments It does specifically state, "Chromogranin A (CgA) is the most established biomarker and is used for diagnosis and monitoring in gastroenteropancreatic neuroendocrine tumors. It does give a brief discussion of Nest citing only two articles. Based solely on two article and the Oberg et al Consensus on Biomarkers for Neuroendocrine Tumour Disease (#12 in the LCD) it concluded "Therefore NETest has a role in the identification of disease progression, defining treatment, efficacy, and completeness of resection." NGS considers the above Consensus opinion as limited support for NETest. The Declaration of interest in the Patel paper shows N. Pavlakis as an advisor for Amgen, Novartis, Pfizer and Roche Pharma; TJ Price on the advisory board for Ipsen.

Capdevila et al. (110) This paper gives a good overall review of neuroendocrine tumors. The authors acknowledge a grant from Novartis. It devotes one paragraph which starts, "One of the main limitations of clinical trials in patients with [neuroendocrine tumors] has been the lack of a potent biomarker program to run alongside drug development." It then discussed NETest citing "Blood and tissue neuroendocrine tumor gene cluster analysis correlate, define hallmarks and predict disease status" in Endocr Relate Cancer. (Kidd M, Drozdov I, Modlin I.)2015;22(4):561-575 which is reference #21 in the LCD. The paragraph concludes with "Several ongoing clinical trials have included the NETest validation and would probably substitute the classical monoanalyte strategies for prognostic and predictive value of blood biomarkers in NETs setting." This statement is not referenced. This paper gives weak support for NETest.

Kyriakopoulos et al. (111) This review is a very baffling paper. It mentions NETest twice. First it merely states, "NETest: The NETest is a multianalyte algorithm analysis PCR-based test recently proposed using 51 'finger-print' genes characterizing a NET. Its clinical value is under investigation and the early reports are promising to predict treatment response as well as early identification of recurrence." The only reference cited about this test is #34 in the policy (Cwikla JB, Bodei L, Kolasinska-Cwikla A, Sankowski A, Modlin IM, Kidd M. Circulating Transcript Analysis (NETest) in GEP-NETs Treated With Somatostatin Analogs Defines Therapy. J Clin Endocrinol Metab. 2015;100(11):E1437-E1445. DOI 10.121/jc.2015-2792) which studied only 35 patients for a median of 10 months. Then under Conclusions, it states, "Test and programs such as the NETest and the MASTER have been already validated from scientific groups and they have been proven effective to select patients who will benefit from specific medications and to predict the response to treatment." This contradictory statement is not supported in the article. This publication does not offer robust support for NETest. It does not actually mention any long term follow-up studies, improved overall survival or independent, external validation of the results. This paper states, "The authors have no conflicts of interest to declare."

Auernhammer et al. (112) This review article states, "We discuss clinical development and controversies in the treatment of neuroendocrine tumours (NETs) that are relevant for clinicians and clinical researchers." It notes, "The serum tumor marker chromogranin A is used extensively as a biomarker for tumour load but has limited sensitivity and accuracy. Improved biomarkers are therefore urgently need. A novel blood-based multi-analyte transcript analysis, encompassing 51mRNA analytes (NETest), had a much higher sensitivity and specificity (90-98%) than chromogranin A. The readouts for NETest correlated with NET tumor load, progressive disease, and response to treatment, including surgery or cytoreduction, somatostatin analogues, or peptide receptor radionuclide therapy (PRRT). Circulating tumour cells and miRNAs are also novel prognostic blood-derived biomarkers for NETS (recently reviewed by Zatelli and colleagues) but the utility of these biomarkers in routine clinical practice has yet to be

evaluated." The paper does not mention NETest in any algorithm or treatment discussion. The "Summary and conclusion" at the end of the article states, "The field of tumor biology and genetics of small intestine and pancreatic NETs has grown substantially. Promising blood-based biomarkers would be further evaluated in the real-world setting." We agree with this need for further evaluations. Declaration of interests: CJA received search contracts from Ipsen, Novartis, and ITM Solucin, lecture honorarium from Ipsen, Novartis, and Falk Foundation, and advisory board honorarium form Novartis. CS has received research grants from Novartis, lecture honoraria from Ipsen and Novartis, and advisory board honoraria from Ipsen, Novartis, and Pfizer. MKA has received research contracts from Novartis. AG has received advisory board and lecture fees from Novartis and Ipsen. SN has received research contracts from Novartis and lecture fees from Ipsen. HI has received a research contract from Novartis, lecture honorarium from Siemens, and advisory board honorarium from Bayer. PB has received a research contract from Roche and advisory board honorarium from Advance Accelerator Applications. SB, TK, JM, and MR declare to competing interests. Also, they do not comment on improved clinical outcome on patients with neuroendocrine tumors. This paper does not give support to NETest.

Ma et al. (113) This is an old historical paper explaining the authors' attempts at developing microarray technologies into cancer research. This paper does not mention NETest at all. No clinical use was described. This paper merely shows their research and their vision for such testing in the future. There were no disclaimers. This paper does not support NETest.

Erlander et al. (114) This is another historical paper explaining the authors' attempts at developing microarray technologies into cancer research, but solely in determining tumor classification. This paper does not mention NETest at all. No clinical use was described. This paper merely shows their research in trying to determine the origin of cancers. Disclaimer. The study was funded by and completed at bioTheranostics, Inc. The authors are employees or former employees and stockholders in bioTheranostics, Inc." This paper does not support NETest.

Greco et al. (115) This paper describes determining the origin of metastatic cancer in 38 out of 501 patients with cancer of unknown primary site (thus 7.6%). This used the technology of #39 above, and not NETest. The purpose was to help identify the primary cancer site. The authors concluded, "This study is too small to make any other meaningful correlations or conclusions regarding the efficacy of therapy." Conflict of interest. This was funded by bioTheranostics and Dr. Greco, Erlander, and Dr. Hainsworth list their financial ties with bioTheranostics, Inc. This paper does not support NETest.

Den et al. (116) This paper describes using the Decipher® genomic classifier by GenomeDx Biosciences which is a whole transcriptome microarray as a predictor for clinical metastases after radical prostatectomy with subsequent radiation therapy. The test was not NETest. Prostate cancer is not a neuroendocrine tumor. They concluded that patients with lower genomic classifier scores may benefit from delayed radiation therapy as opposed to those with higher genomic classifier scores. They cautioned "However, this needs prospective validation." Conflicts of interest: Funding was provided by GenomeDx and M.G., K.Y., and E.D. are employees of GenomeDx." This paper on prostate cancer does not support NETest.

Den et al. (117) This is a follow up paper on #41 above. They concluded that using genomic classifier scores was prognostic for the development of clinical metastasis beyond routine clinical and pathologic features. The authors noted that the data was analyzed retrospective and that the section of adjuvant radiotherapy as oppose to salvage radiotherapy varied among physicians and patients. They also not there were no concrete guidelines for the incorporation of androgen-deprivation therapy with postprostatectomy radiotherapy. Most important, this is not a paper on neuroendocrine tumors, but on prostate cancer. Also, the testing was not NETest. Disclosures: There were conflicts of interest noted and there was funding by Conflicts of interest: Funding was provided by GenomeDx and M.G., K.Y., and E.D. are employees of GenomeDx. This paper on prostate cancer does not support NETest.

Modlin et al. (118) This paper has been reviewed previously and is #64 in the LCD. This does not give any new support for NETest.

NCCN (119) This paper has been reviewed previously and is #5 in the LCD. It was also reviewed before that. This still does not give any support for NETest.

Kulke et al. (120) Only three pages of this old article were sent. NETest was not mentioned. The entire NCCN Neuroendocrine Tumors Vison 1.2015 was subsequently obtained by NGS. A word search failed to reveal NETest. This paper does not give any support for NETest.

Bowden et al. (121) This paper has been reviewed previously and is #10 in the LCD. This does not give any new support for NETest.

Grosse et al. (122) This historical paper is on philosophical issues including societal one and cost-effectiveness of genetic testing. It is not clinical. It does not mention neuroendocrine tumors. Of note, Medicare is not allowed to use cost as a reason for coverage. It does not mention NETest. This does not support NETest.

Buyse et al. (123) This is a historical paper that argues that overall survival on drug trials should be replaced by progression free survival for advanced colorectal cancer. It is not about neuroendocrine tumors. Multiple papers submitted from a later date show that overall survival has been considered the "gold standard." In addition, see the related response by Yothers below in reference 124 who notes, "Time to event can be ascertained with excellent reliability for OS, but the difficulties in ascertaining time to progression lead to less reliability for PFS." The "Authors' Disclosures of Potential conflicts of Interest" note compensation from AstraZeneca to KC and PP as well this paper coming from the "International Drug Development Institute." This does not support NETest.

Yothers (124). This is an editorial about the Buyse study also in the same journal. It does speak positively about Progression Free Survival but notes that the Buyse article is about advanced colorectal cancer. It notes, "Time to event can be ascertained with excellent reliability for OS, but the difficulties in ascertaining time to progression lead to less reliability for PFS." This paper comments on the Buyse being a drug trial, which as noted below is different issue. The author indicated no potential conflicts of interest. This paper does not support NETest.

Tang et al. (125) This is another historical paper that argues that overall survival on drug trials should be replaced by progression free survival for metastatic colorectal cancer. It is not about neuroendocrine tumors. Multiple papers submitted from a later date show that overall survival has been considered the "gold standard." It argues that "A validated shorter term surrogate end point would reduce drug development costs and allow for more rapid completion of randomized controlled trials." No conflicts of interest were reported. Saving pharmaceutical companies money is not something that is appropriate to use for LCD determination criteria. In addition, see the related response by Montagnani et al below in reference 126. Again, this paper does not deal with NETesting or neuroendocrine tumors. It does not support NETest.

Montagnani et al. (126) In the same journal in response to the above Tang article noted, TSurrogate end points of survival have been hypothesized (sic) and validated for patients with metastatic colorectal cancer treated with first-line FU-based cytotoxic chemotherapy. Outside this specific situation, their utility is not clear. In particular, they could be useless when considering newer drugs like BV and other antiangiogenic drugs. In conclusion, the correlation between PFS and OS and between ΔPFS and ΔOS for patients with metastatic colorectal cancer treated with BV-based bio-chemotherapy was not demonstrated. Our opinion is that using BV combined with chemotherapy in first-line treatments for patients with metastatic colorectal cancer survival should remain the primary end point until validity of surrogate end points will be clearly demonstrated." The authors indicated no potential conflicts of interest. This paper does not support that progression free survival can be used rather than overall survival for NETesting.

Heng et al. (127) This paper notes that overall survival has been the traditional gold standard for all endpoints. This study deals with metastatic renal cancers, not neuroendocrine tumors. They concluded that progression-free survival at 3 months and at 6 months predicted overall survival on these renal cancer patients and the current results indicated that profession-free survival may be a meaningful intermediate endpoint for overall survival in patients with metastatic renal cell carcinoma who receive treatment with novel agents. They did conclude, "These results require prospective evaluation." As noted below by Escudier,"There are several weakness this study some of which are highlighted by the authors themselves. First, only 70% of the patients received targeted agents as first-line treatment and therefore were really eligible for the analysis performed. Second, PFS was not independently reviewed and outside of clinical studies, which was the case for the majority of the patients, the treating clinicians are often biased and may overestimate PFS in patients with slow-growing disease. Consequently, such patients may have a longer than expected OS. Finally, only 35% of the patients in the study by Heng et al received additional (i.e., subsequent) therapy, which is different from the current real-life situation, now that so many drugs have been approved." Again, they evaluated metastatic renal cancer, not neuroendocrine tumors. In addition, it seems like almost all the papers submitted which NETest has used were a heterogeneous collection of neuroendocrine tumors with multiple different organs of origin and different degrees of spread. This paper does not support NETest.

Escudier (128) in the same issue of Cancer wrote a response editorial to the above Heng study. "There are several weakness to the study by Heng et al, some of which are highlighted by the authors themselves. First, only 70% of the patients received targeted agents as first-line treatment and therefore were really eligible for the analysis performed. Second, PFS was not independently reviewed and outside of clinical studies, which was the case for the majority of the patients, the treating clinicians are often biased and may overestimate PFS in patients with slow-growing disease. Consequently, such patients may have a longer than expected OS. Finally, only 35% of the patients in the study by Heng et al received additional (i.e., subsequent) therapy, which is different from the current real-life situation, now that so many drugs have been approved. Conflict of interest disclosures: The author made no disclosures." This paper does not support that progression free survival can be used rather than overall survival for NETesting.

Modlin et al. (129) This paper has been reviewed previously and is #26 in the LCD. This does not give any new support for NETest.

Cwikla et al. (130) This paper has been reviewed previously and is #34 in the LCD. This does not give any new support for NETest.

Malczewska et al. (131) This is a single case report of a 52 year old woman with a large ulcerated friable mass obstructing the ileocecal valve which was a 5cm well-differentiated neuroendocrine tumor which was treated by a right hemicolectomy and lymphadenectomy. Post-operatively her NETest was elevated. Following 177Lu peptide receptor radionuclide therapy, the NETest measurements were lower. Then it was elevated and the patient needed a cholecystectomy for symptomatic cholelithiasis. The abdomen was normal but random multiple peritoneal and core needle biopsies from the segment VI were performed. This reveal foci of metastatic tumor but the tumor was too small for accurate Ki-67 assessment. No histological pathology report is mentioned. Somatostatin analogues were increased. The NETest levels remained elevated but lower. The authors concluded "A prospective clinical trial that included image-negative but NETest-positive patients would be of value to demonstrate the clinical utility of the liquid biopsy." We concur with this conclusion about a prospective clinical trial. Disclosure summary. "AM, LB: Nothing to disclose; MK: Laboratory Director of Wren Laboratories; IMM: Medical/Scientific Consultant to Clifton Life Sciences." This single case report gives some support to NETest.

Kaltsas et al. (132) This paper has been reviewed previously and is #54 in the LCD. This does not give any new support for NETest.

Bodei et al. (133) This paper has been reviewed previously and is #11 in the LCD. This does not give any new support for NETest.

Genc et al. (134) This paper listed as "RESEARCH ARTICLE" 35 patients with pancreatic neuroendocrine tumors. Originally there were 124 patients operated on for pancreatic neuroendocrine tumors at Academic Medical Center Amsterdam between 2006 and 2015. 89 were excluded: 21 were deceived; 6 were R2 or unknown resection margins; 6 withdrew consents; and 56 were lost to follow-up. Completely excised tumors were classified as R0 and tumors with microscopic involvement <1 mm were classified as R1. R2 was not defined and there are several classifications of resection margins, but most likely the R2 designation for macroscopic residual tumor. The three groups were R0 (Completely excised tumors) with no recurrence which had n=11; R0 (Completely excised tumors) with recurrence (n=12) and R1 (tumors with microscopic involvement <1 mm) with no recurrence (n=12). The recurrence of the second group (R0 (Completely excised tumors) with recurrence) had 3/12 (25%) being local recurrence, 2/12 (17%) being regional recurrence, and 7/12 (58%) being distant. Of further note, 73% of the first group where Grade I tumors and 27% Grade II, while the second group had 42% Grade I and 58% Grade II, but the third group was 100% grade I. The results are measured in median, not mean. However the median follow up for group 1 was 31 months, for group 2 105 months, and group 3 92.5 months. NETest levels were higher in group 2 than in group 1 or group 3. NETest gave false positive or negative re in 18% using a 40% cutoff. The authors concluded "Larger prospective studies are warranted to more fully explore the utility of the NETest in the identification of postoperative residual pancreatic NET disease or recurrence and to help better stratify patients for post-surgery treatment. This study is interesting. If suffers from several things. Most of the potential enrollees (89 out of 124) were excluded. The study was really retrospective since it included patients as far back as 2016. There does not seem to be any clear evidence that the results of the NETest was used to treat the patients. There is no evidence that the NETest improved overall survival. We agree that this gives some support for NETest and will welcome larger prospective studies to more fully explore the utility of the NETest especially on overall survival. Disclosure and Funding information: "Funding information: Ipsen Fund." IM Modlin is a Medical/Scientific Consultant to Wren Laboratories. M Kidd is the Laboratory Director of Wren Laboratories. I Drozdov is a Bering, Statistical consultant to Wren Laboratories."

Ward et al. (135) This is a review of gene expressions and the treatment of breast cancer. It only discusses six tests, and none of them are NETest. It also considers cost which Medicare cannot use. This paper does not support NETest.

Sparano et al. (136) This paper in the prestigious New England Journal of Medicine does not support NETest. Actually it in a way hurts it since it shows that other gene-expression assays get published in this journal, but NETest results are not. This paper deals only with breast cancer and a different gene-expression assay. It has nothing to do with neuroendocrine tumors, but only breast cancer. Conflicts of interest are not noted. This does not support NETest.

Krop et al. (137) This is another paper giving guidance to physicians treating breast cancer. It is based on the use of genetic tests, but not those of NETest. These are not neuroendocrine tumors. There is no mention of NETest. Authors' Disclosures of Potential Conflicts of Interest. Ian Krop: employment, leadership and stock/other ownership AMAG Pharmaceutical. Consulting or advisory role: Genentech. Research Funding: Genentech; Other Relationship: Novartis. Nofisat Ismaila. No relationship. Fabrice Andre: Research funding AstraZeneca, Novartis, Pfizer, Eli Lilly. Travel, Accommodations, Expenses: Novartis, Roche, GlaxoSmithKline, AstraZeneca. Robert Best: Research funding Arrien; Patents, Royalties, Other Intellectually Property: Fujirebio Diagnostic's royalties for CA0125 ovarian cancer biomarker. Travel, Accommodations, Expenses: Roche. William Barlow: Research Funding: AstraZeneca, Merck. Deborah Collyar: No relations. M. Elizabeth Hammond: No relationship to disclose. Nicole Kuderer: Consulting or Advisory Role: Jannsen, Coherus Biosciences, Halozyme, G1 Therapeutics, Myriad Genetics. Research funding Amgen, Travel, Accommodations, and Expenses: Janssen, coheres BioSciences. Minetta Liu: Research Funding Eisai, Seattle Genetics, Celgene Veridex, Novartis, Genentech, GRAIL Merck. Travel, Accommodations, Expenses: GRAIL, Merck, Celgene. Robert Mennel: Employment: Texas Oncology. Catherine Van Poznak: Research Funding Bayer; Patents, Royalties, other intellectual Property: UpToDate. Antonio Wolff: Consulting or Advisory role Ionis. Research

funding: Myriad Genetics, Pfizer. Patents, royalties, other intellectual property: Named inventor on one or more issued patents or pending patent applications relating to methylation in breast cancer with rights assigned to Johns Hopkins University and participation in a royalty-sharing agreement with Johns Hopkins. Vered Stearns: Research Funding: Abbvie, Merck, Pfizer, MedImmune, Novartis, Celgene, Puma Biotechnology. This paper does not support NETest.

NCCN (138) This is another paper giving guidance to physicians treating breast cancer. It is based on the use of genetic tests, but not those of NETest. Breast cancers are not neuroendocrine tumors. There is no mention of NETest in this guideline. This paper does not support NETest.

Cives et al. (139) This is an overall review of epigenetic modifications (phenotypic trait variations by external or environmental factors that switch genes on and off and affect how cells respond to genes instead of being caused by changes in the DNA sequence) in cancers. The paper does not mention NETest by name but describes it, noting, "A multianalyte whole blood RNA multigene signature has been developed to predict NET activity. Interesting, among the omic clusters capable of differentiating disease activity (sable versus progressive disease), there was the epigenome. Future studies should assess if the epigenomic profiling per se may serve as a predictive biomarker for treatment tailoring in NET patients." Conflicts of interest: The authors declare no affiliation with industries or organization with a financial interest, direct or indict, that may affect the conduct or reporting of the work submitted." This paper does not support that NETest is standard.

Pawa et al. (140) This is a manuscript and there is no published information. Upon checking PubMed Data Base of medical literature, from the US National Library of Medicine, National Institutes of Health, it is noted that this journal has not been included in their index of medical literature since March 2013. Unpublished papers are not adequate peer reviewed literature as indexed in the required PubMed Data Base of medical literature, from the US National Library of Medicine, National Institutes of Health. Thus this does not support NETest.

Oberg et al. (141) This paper has been reviewed previously and is #58 in the LCD. This does not give any new support for NETest. Of note, upon checking PubMed Data Base of medical literature, from the US National Library of Medicine, National Institutes of Health, it is noted that this journal has not been included in their index of medical literature since March 2013.

Svensson J. (142) Targeted Radionuclide Therapy for Patients with Neuroendocrine Tumours. 2016. Department of Oncology, Institute of Clinical Sciences, University of Gothenburg. No other information is available about this. Beside the above noted cover sheet, there one sheet labeled "13" on the bottom with a paragraph stating, "A newer concept to evaluate respons [sic] to treatment is to analyses [sic] changes in disease specific gene transcript in blood. NETest® is a PCR-based analysis of a 51 NET-associated genes, and changes in the transcript profile is reported to have delineated surgical cytoreduction {113] as well as treatment response from 177Lu-DOTATATE [114]. It was also observed that this test could predict response to somatostatin analogue treatment using octreotide [115]." This poorly reference source does not give acceptable support to NETest.

Verbeek et al. (143) This paper has been reviewed previously and is #31 in the LCD. This does not give any new support for NETest.

Freis et al. (144) This paper reported on the various prognostic factor in neuroendocrine carcinomas, using overall survival as the endpoints. While they used a number of laboratory tests, they noted, "Recent studies have also reported the potential of blood transcript analysis as a predictor and prognostic marker of progression in well-differentiated NET, but this was not studied in in NEC (neuroendocrine carcinoma patients. Moreover, molecular analysis such as p53 and retinoblastoma (RB) protein staining are probably promising in NEC, but these analyses are not validated for survival prognosis in NEC." "Competing financial interests: The authors declare no competing

financial interests." This paper does not support NETest although it supports the use of overall survival in determining results in neuroendocrine papers.

van Treijen et al. (145) This paper is a "systematic review [aimed] to evaluate current literature and amplify an up-to-date evidence-based approach to [nonfunctional pancreatic neuroendocrine tumors] diagnosis in [multiple endocrine neoplasia type 1]" the authors state the electronic bibliography databases Medline/PubMed, Embase, and Web of Science were searched December 2017 to review systematically current literature on the diagnostic value of biomarkers and imaging modalities for [nonfunctional pancreatic neuroendocrine tumors] in in [multiple endocrine neoplasia type 1] patients….To gain insight into the penetranc3 and behavior of for [nonfunctional pancreatic neuroendocrine tumors] in in [multiple endocrine neoplasia type 1 and subsequently answer the question on the optimal timing and frequency of follow-up, a third search was operated, also including our study domain in [multiple endocrine neoplasia type 1] patients. The literature searches were reviewed by an experience librarian. Database subject terms such as Mesh terms (Medline) and Emtree terms (Embase), were used as appropriate. Selection of articles was restricted to English, Dutch, German and French, and for original research, there was no restriction for the year of publication of the studies." It is confusing about the second search since there is not much mention of it. Despite the massive effort to locate pertinent papers, the authors did not evaluate NETest, apparently because they could not find supportive literature. They did mention under "Discussion" that, "Future studies should investigate the role of molecular biomarkers, such as the NETest for [multiple endocrine neoplasia type 1-related [nonfunctional pancreatic neuroendocrine tumors] as the current screening tools lack insight in the dynamics of individual tumor behavior." "Disclosure Summary: The authors have nothing to disclose." This paper does not support NETest.

Banck et al. (146) This is a review "summarizing progress in clinical trials and basic science redefining the diagnosis and treatment of well differentiated small intestine neuroendocrine tumors (SI-NET)." Just before the CONCLUSSION, there is a section entitled "NOVEL DIAGNOSTIC TOOLS." It states, "A blood test for tumor-derived RNA was reported by Modlin, et al. The test uses reverse transcriptase polymerase chain reaction (RT-PCR) to quantify 51 NET marker-transcripts and control transcripts in patient whole blood. The sensitivity and specificity of the test to determine whether a patient has a NET was 79-88t and 94%, respectively, suggesting that it is superior to measuring chromogranin A (specificity 85, sensitivity of 68%...How the test score is computed from the 51 transcripts appears not to be fully documented in the report. Furthermore, while blood samples from various clinical centers were employed in the test development, additional studies such as prospective measurements in clinical trial of NET treatment will be required to determine the utility of the test for making clinical decision." This does not support that NETest is standard and/or proven yet and does not support NETesting.

Maxwell et al. (147) This is another review paper on neuroendocrine tumors (NETs). The paper makes a number of points. "The plasma serotonin assay is now considered by reliable for the diagnosis of carcinoids when performed by CLIA-licensed and College of American Pathology (CAP)-approved commercial laboratories in the United States. This test a positive predictive value of 89% and negative predictive value of 93% of patients with midgut carcinoids, but is less accurate in those with foregut and hindgut carcinoids. It may not correlate as well with the tumor burden as other laboratory assays (e.g. chromogranin, pancreastatin) because platelets become saturated at high level of serotonin. It notes in the next paragraph, "Serum CgA (chromogranin A) levels are considered one of the most useful markers for diagnosis and surveillance of patients with gastrointestinal (GI) NETs, including hindgut and foregut tumors, where 5-HIAA and serotonin levels are often with normal limits." It also states, "The National Comprehensive Cancer Network (NCCN) guidelines for GI NETs suggest testing for CgA and collecting a 24 hour urine for 5-HIAA, but do not give specific recommendations for follow-up. It later notes, "The NCNN recommends checking PP, CgA, calcitonin, PTH-rP, and GHRH for generic PNETs. If the patient has a recognizable syndrome they recommend checking specific hormone levels. The "WREN Assay" is discussed under BIOMOLECULAR DIAGNOSITCS IN NETs. They note, "Modlin et al. set out to identify a genetic signature for NETs that could be tested form peripheral blood samples that might be useful for diagnosis, assessment of tumor burden, and response to therapy. The authors concluded that their panel could identify GEP NETs regardless of primary tumor site or metastasis, which could be useful for screening and potentially response to therapy. The group is actively recruiting patients to determine how well it might perform under these circumstances." "Acknowledgments: Dr. Maxwell' work is supported by NIH

5T32#CA148062-05." This does not support that NETest is standard and/or proven yet and does not support NETesting.

Bowden et al. (148) This paper was submitted twice by Wren Laboratories. This paper has also been reviewed previously and is #10 in the LCD. This does not give any new support for NETest.

Barbieri et al. (149) This is another review article about neuroendocrine tumors. It states, "To date, the most widely used biomarker is plasma chromogranin A (CgA), although its sensitivity and specificity in monitoring therapy response is debated. Specific hormone products in functional NETs have also been monitored. More recent, circulating tumor cells (CTCs), a panel of neuroendocrine neoplasm gene signature for PCR-based blood analysis and MiRNA profiling have been proposed as new potential prognostic markers. This is the only reference to using NETesting in the article. There are no conflicts of interested noted. This does not support that NETest is standard and/or proven yet and does not support NETesting.

Chan et al. (150) The authors note, "This review was undertaken to evaluate the literature on tissue-based as well as molecular imaging derived biomarkers for neuroendocrine tumours, in order to identify areas where evince of biomarker is robust and where gaps exist so as to direct further research." In the introduction, it is noted, "Several reviews have focussed [sic] on blood-based biomarkers in NETs. Serum-based assays offer advantages in terms of convenience and safety of collection (compared to repeat tissue biopsies). However, older studies have not demonstrated sufficient power to enable accurate prognostication and have in general looked at individual measures in isolation. Newer studies with multiple analyses show promise, but have not been validated as yet." The paper discusses chromogranin A (CgA). It noted that "Elevated baseline CgA has been shown to predict poorer overall survival in multiple retrospective series...but other series fail to show this correlation." It notes "Alterations in CgA with therapy may also be an indicator of prognosis…this confirmed the prognostic but not predictive power of CgA as a biomarker." It notes, "Unfortunately, there are several practical issues associated with adoption of CgA as the only prognostic biomarker. False elevations of CgA occur with benign conditions, other malignancies as well as medication such as proton pump inhibitors, although the elevations is usually mild… the reference range for CgA may also vary depending on the exact assay utilized, hampering its interpretation and analysis across multiple clinical centres. Elevated chromogranin A may simply reflect increased tumour burden…and its independent contribution as a biomarker may decrease particularly as improvements in imaging (with 68Ga and FDB PET scans) result in improved staging of NETs. Finally CgA being a secretory product is produced less in poorly-differentiated tumours, meaning that it is a poorly sensitive marker for de-differentiated (poor prognosis) disease. Under "3.2.3 Other plasma-based markets in NET" the author note, "A novel multi-transcript molecular signature, the TET3st, is a blood-based assay examining a targeted RNA expression profile. It has been investigated in 130 patients with GEPNETs… with high sensitivity of 85098% and specificity of 93-97%. It showed accuracy of 92-93T for NET when used to evaluate a mixed cohort of NET and non-NET pathology specimens from the GI tract…This NETest score was also higher in patients with clinically progressive disease compared to those with stable disease…and subsets within the NETest score may reflect response to somatostatin analogues…However, a prospective validation of these findings and their prognostic significance at baseline is still ongoing." There are no disclosers from the authors. This gives weak support of NETest.

Strinovic et al. (151) This is a review paper about neuroendocrine tumors with minimal mention of NETest. It notes, "Recent studies investigate multiple bowel NETs which have the potential to act as biomarkers but further studies to define molecular mechanisms and validate these miRNA are needed. Andersson et al. have defined specific gene expression patterns associated with tumor grade and chromosomal alteration transcriptome of small bowel NETs as novel prognostic biomarkers. Darmanis et al. proposed a new potential protein biomarker for classify well-differentiated small intestinal NETs but further investigations of these proteins in larger sample sets are needed. In conclusion, chromogranin A and gastrin should be measured in all patients with d-NETs. Serum NSE should be measured in all patients with d-NEC and G3 d-NETs should. 5-HIAA should be measured only in patients with signs and symptoms of carcinoid syndrome. Patients with serum gastrin>1000 ng/L should undergo ph-metry and the

status of parietal cell antibodies should be obtained. This is important in order to classify the functional status od [sic] d-NETs. Measurement of serum calcium parathyroid hormone, prolactin, IGF-1, ACTH, urinary-free cortisol should be made in all patients as screening for MEN-1 syndrome." There is no mention of any role for NETest. Page 185 of this article has a flowsheet on the workup for D-NET. There is no mention of NETest although other standard biomarkers such as Serum CgA and gastrin are specifically mentioned. There are no disclaimers. This; paper not only does not support NETest, but denies there is any established role for it.

Xavier et al. (152) This is another review paper about neuroendocrine tumors. Under BIOMARKERS AND OTHER LABORATORY TESTS, it states, "Several circulating tumor markers have been evaluated for the diagnosis and follow-up of NETs. Currently chromogranin A (CgA) is the most important of these markers, and current guidelines recommend be measurement of serum CgA at diagnosis." In the same section, it does note, "In an effort to find better NETs biomarkers, Modlin e al recently published a multi-transcript molecular signature for PCR blood analysis which may facilitate future diagnosis of NETs. They analyzed transcripts of 3 microarray datasets (NETs peripheral blood, NETs tissue and adenocarcinoma) and found 51 significantly elevated transcript markers. Based on that, genetic based classifies were created and were able to detect NETs with high sensitivity (85%-98%), specificity (93%-97%), positive predictive value (95%-96%) and negative predictive value (87%-98%). The transcript marker was similarly effect in recognizing pancreatic and gastrointestinal NETs, as well as, metastases. Moreover, the gene-based classifier was significantly more accurate than CgA and, in patients with low CgA, the transcript markers were elevated in 91% of cases. This may reflect the future utility of genetic makers as diagnostic tools of NETs, however further investigation needs to be done to validate this hypothesis." There were no conflict of interest noted. While this supports further investigation of NETest, it does not support that it is currently proven to be of value and standard.

Jimenez et al. (153) This is not a valid article submission and thus does not support NETest. Draft, unpublished literature and not appropriate to review.

Halfdanarson et al. (154) This is a review paper on biomarkers in neuroendocrine tumors. It briefly discusses NETest, although not by name. Under Novel tumor markers, the authors note, "A different approach is to identify a molecular gene signature measurable in peripheral blood to detect NETs. A multi-transcript molecular signature detected with a PCR analysis was compared with CgA measurements in 176 samples of patients with malignancies, including NETs. The gene-based classifier reliably detected patients with NETs and was significantly more accurate than CgA for detecting Nets in patients with low CgA levels. This promising approach to diagnosis of patients with NETs awaits validation in larger studies." Also in Conclusions, the authors note, CgA is currently the only circulating general NET marker in widespread use and is both sensitive and specific for diagnosis of NETs, but nevertheless suffers from significant limitations. …Other markers should be used as indicated based on the clinical presentation of the patients, especially in cases of functional PNETs. Novel markers such as detection of CTCs and molecular gene signatures hold great promise, but await further validation in larger studies." There were no "Financial & competing interests disclosures" listed for the authors. This paper does not support NETest being standard today.

Chabot et al. (155) This is an editorial that states a very important tenet of medicine and Medicare: Because of this variation in tumor biology, the dictum 'first, do not harm' should be a constant whisper in the surgeon's ear when managing PNETs." It states, "The fourth article in this issue of Surgery by Modlin et al describes the utilization of a 51-g3n expression panel from the patient's blood to determine the efficacy of PNET treatment. Perhaps the application of similar technology to blood and/or biopsies of PNETs could more effectively discriminate those tumors that might be observed safely. The article referenced is Modlin IM, Frilling A, Salem RR, et al. Blood measurement of neuroendocrine gene transcripts defines the effectiveness of operative resection and ablation strategies. Surgery. 2016; 159(1):336-347.This article has been reviewed at least twice before. Dr. Chabot does not give any true support for NETest or reflect on whether or not it is standard or effective. This editorial does not support NETest. We agree with the author's premise "first, do not harm."

Manoharan et al. (156) This is another review article. The authors note, "Previously, Modlin and coworkers introduced a new PCT-based blood-based multianalyte neuroendocrine gene transcript assay (NETest) for the diagnosis of gastroenteropancreatic neuroendocrine neoplasia (GEP-NEN)...The NETest comprises 51 multigene transcripts…The results of this test were compared to expression of chromogranin A in sporadic GEP-NEN. The NETest was more sensitive compared to the common tumor marker. The sensitivity/specificity rate was about 92.8%/92.8%...this NETest was than [sic] examined pre-and postoperatively in 27 patients with GEP-NEN to monitor the therapeutic affect…In 23 of 27 patients, the NETest result was significantly reduced (preoperative: 80+/-5%, postoperative: 29+/-, P<0.0001 after curative resection of the GEP-NEN. There are yet no data published regarding the value of the NETest in MEN1 patients. However, if initial results can be confirmed in large prospective MEN1 cohorts, the NETest might be a valuable screening modality for MEN1 patients." The authors declared "There is no conflict of interest that could be perceived as prejudicing the impartially of this review." This paper does not support that NETest is standard today.

Basuroy et al. (157) This review article notes, "Circulating and tissue markers of NET disease can be used to assess for disease prognosis, treatment response, and recurrence. Existing markers may be general, like chromogranin A (CgA) and serotonin, or specific to subtypes of NETs like gastrin and insulin. More novel markers, like mRNA transcript panels and circulating tumor cells, are likely to have a role in the future." There are no disclaimers." This paper does not support that NETest is standard today.

Clift et al. (158) Only a manuscript like, unpublished format was submitted. It is difficult to read because of its format. This is not acceptable as evidence for support of NETest. Draft, unpublished literature and not appropriate to review.

Barriuso et al. (159) This review article mentions NETest. "Promising results have been presented over the last few years using a novel biomarker candidate, the multianalyte algorithm analysis PCR-based test (NETest)." This test is described. It then states, "In conclusion, this qPCR-based blood biomarker test that defines the circulating fingerprint of a NET can be easily repeated at multiple time points during periods between sequential imaging assessments, thus providing additional real-time dynamic evidence regarding tumour behavior as well as treatment efficacy. Confirmation of these observations in larger series and randomized trials will allow the identification of likely non-responders and have clinical utility in treatment decision making." Conflicts of inter: JB has received research funding from Pfizer, Novartis and Ipsen. AC has received fees from Pfizer, Ipsen and Novartis. JC has received fees from Novartis, Ipsen and Pfizer. EG has received fess form Pfizer, Ipsen, Lexicon and ADACAP, and Threshold Pharmaceuticals. MM has received honoraria as speaker from Novartis and Ipsen. The other authors declared no conflicts of interest. This paper shows potential for NETest but does not support that NETest is standard today.

Hofland et al. (160) This review paper discusses many biomarkers, including NETest which it describes and discusses. It noted, "Although these outcomes certainly appear promising, there are concerns about the availability and cost of this biomarker for the diagnosis of NETs in clinical practice. In addition, the specificity of the NETest in population of patients with gastrointestinal disease or other malignancies remains to be determined in more detail. Under "Key Points" it noted, "Circulating transcript represent an emerging opportunity in the diagnosis of gastroenteropancreatic NETs, but whether they can be used to differentiate NETs form other tumours should be subject to further study, while their availability and cost-effectiveness in clinical practice remain to be confirmed. The paper concludes with "With the advent of tests to measure circulating tumour cells, mRNA transcript and superior functional imaging, our clinical repertoire is sure to notably expand and positively affect patient care in the coming years. The authors declared no competing interest. Note that Medicare does not use cost for determining any coverage. This paper shows potential for NETest but does not support that NETest is standard today.

Thorns et al. (161) This review article discusses microRNA testing. It notes "…have been complemented by a first report on the establishment of a gene expression-based classifier generated from peripheral blood samples from patients with gastroenteropancreatic neuroendocrine tumors. While this sentence does not mention NETest by name,

it is describing NETest. It notes that "Evaluation of microRNAs appear to be promising in the assessment of pNEN [pancreatic neuroendocrine neoplasms]. In particular, miR-193b, which is also increased in serum, may be a potential new biomarker of pNEN." miR-193b however is not associated with the NETest description. Conflicts of interest state CT and GB received funding from IPSEN Pharma GmbH, Novartis Pharma GmbH. The other others had nothing to disclose. This paper does not support that NETest is standard today.

Zatelli M. (162) This appears to be a teaching case report in a book concerning a patient with a neuroendocrine tumor. It does note that "…multi-analyte biomarkers have the potential for higher diagnostic sensitivity and specificity as well as prognostic value …Along the line of multi-analyte strategies, multigene signatures have been considered as potential useful on clinical grounds in order to provide real-time information about tumour activity and response to treatment. In these setting, transcript analysis provides copious information that has been employed to implement multi-analyte assays with algorithm analyses (MAAA). The NET MAAA biomarker panel has already been employed displaying high sensitivity and specificity, not depending on age, gender, ethnicity, fasting or medications. However, this method requires a dedicated laboratory and the necessary technical hardware, software and skilled personnel that are not widely available." The case study ends on "Up to Date of the Topic" by noting, "The issue of prognostic markers in the NET field is highly debated and generates more reviews that [sic] original research articles. " It then mentions mTOR pathways profiling might have a prognostic role in lung and pNET. However, validation studies are still lacking, both from the technical and clinical point of view." There are no disclaimers. This short case study does not support that NETest is standard today.

Lewis et al. (163) This brief review paper notes, "A novel 52-gene PCR-based assay performed on peripheral blood may prove to have higher sensitivity and specificity than the CgA biomaker [sic]." It further notes, "Because the assay hinges on the circulating transcript signature of NETs, all 52 included genes were validated as having mRNA that are reliably detectable in the peripheral blood. Both at the time of diagnosis and when measuring responses to therapy, this approach may permit more sensitive and specific test of GI NETs than CgA. The general application of such an approach will require prospective validation." There were no conflicts of interest. This short paper does not support that NETest is standard today.

Ramachandran et al. (164) We fail to see any mention of NETest in this short review paper. This short paper does not support that NETest is standard today.

Basuroy et al. (165) This brief review article devotes three sentences to the summary of "Modlin IM, Drozdov I, Alaimo D, et al. A multianalyte PCR blood test outperforms single analyte ELISAs (chromogranin A, pancreastatin, neurokinin A) for neuroendocrine tumor detection. Endocr Relat Cancer. 2014;21(4):615-628" which is reference #29 in the current LCD. In "Practice Points" IT NOTES, "Circulating gene transcript (mRNA) and tumor cells resent potential NET biomarkers of interest that require further evaluation." It also notes in that section, "Chromogranin A is used in routine clinical practice and is associated with tumor burden, response and survival. Financial & competing interests disclosure: J Ramage and D Sarker and note various payments from Novartis and Pfizer and Dr. Ramage also had fees from Ipsen. This paper does not support that NETest is standard today.

Zatelli et al. (166) This review paper describes the NETest. They note, "The NETest appears to be a very promising tool not only for the diagnosis but also for the follow-up of NET patients, although to date no information is available concerning a predictive role for the NETest as concerns rapalog sensitivity." Funding: M C Zatelli received consultant fees from Novartis and Genzyme. This paper does not support that NETest is standard today.

Patel et al. (167) This review describes NETest and previous published results. It concludes the paragraph with "Therefore, NETest has a role in the identification off disease progression, defining treatment efficacy, and assessment of completeness of resection." However, this statement is attributed to "Oberg K, Modlin IM, De Herder W, et al. Consensus on biomarkers for neuroendocrine tumour disease. Lancet Oncol. 2015;16(9):e435-e446"which

is reference #12 in the LCD. A concern about this endorsement was the fact that this meeting was supported by Clifton Life Sciences, which owns Wren Laboratories, and eight of the sixteen panelists are listed as having financial ties to Wren Laboratories. Declaration of interest. N Pavlakis is an advisor for Amgen, Novartis, Pfizer and Roche Pharma AD and TJ Price is on the advisory board for Ipsen. Again, this gives the same limited endorsement for NETest that reference #12 in the policy gives.

Razzore et al. (168) This short review paper does not mention NETest by name but there is mention about it under "IS THERE A CLINICAL ROLE FOR NOVEL BIOMARKERS? They note, "There is also increasing interest in miRNAs s clinical biomarkers of tumorigenesis, treatment response and outcomes, but to date clinical data are scarce and clinical applications challenging. Similarly, there are several novel monoanalyte assays (i.e. connective tissue growth factor for carcinoid heart disease (CCN2) or paraneoplastic Ma antigen 2 (NMA2) for small intestinal neuroendocrine tumors, but these analyses are not available in clinical practice. Further, panelists of the recent Delphi consensus gave the strongest support to the use of emerging biomarkers in multianalyte based on genomics." Again, this statement is attributed to "Oberg K, Modlin IM, De Herder W, et al. Consensus on biomarkers for neuroendocrine tumour disease. Lancet Oncol. 2015; 16(9):e435-e446"which is reference #12 in the LCD. A concern about this endorsement was the fact that this meeting was supported by Clifton Life Sciences, which owns Wren Laboratories, and eight of the sixteen panelists are listed as having financial ties to Wren Laboratories. There was no financial support or conflicts of interest reported. Again, this gives the same limited endorsement for NETest that reference #12 in the policy gives.

There is a front sheet in a foreign language that we cannot read. (169) It is followed by a page without any header or footer. This is not acceptable medical support for NETest.

Capdevila et al. (170) This short review article notes, "We need pretreatment biomarkers to be used as predictive factors of response, in order to improve patient selection. In this line, the recent development of transcript blood profiles in NETs (NETest) has demonstrated a higher sensibility than classical biomarkers, such as chromogranin A and even tumor grade, and a better predictive value of response to several treatment approaches in this field, such as somatostatin analogs, peptide receptor radionucleotide therapy, surgical resections and locoregional ablation procedures. The blood NET transcript analyses also allow the monitoring of the disease evolution favoring a real-time dynamic assessment and may have an impact in decision-making process. Several ongoing clinical trials have included the NETest validation and would probably substitute the classical monoanalyte strategies for prognostic and predictive value of blood biomarkers in NETs setting. The reference for the statement is from Kidd M, Drozdov I, Modlin I. Blood and tissue neuroendocrine tumor gene cluster analysis correlate, define hallmarks and predict disease status. Endocr Relat Cancer. 2015;22(4):561-575 which is reference #21 in the LCD and previously had been reviewed. We noted that there was no evidence of improved outcomes are noted. This has previously been submitted and reviewed by this contractor in a prior reconsideration request. Conflict of interest: JC fees from Pfizer, Novartis and Ipsen. JPC fees for Novartis and Ipsen. AS fees from Pfizer, Novartis and Ipsen. RS fees from Novartis and Ipsen. Again, this gives the same limited endorsement for NETest that reference #21 in the policy gives.

Koenig et al. (171) The authors analyzed 62 patients with neuroendocrine neoplasms of the colon and rectum. However, it appears that NETesting was not done on any of these patients. This paper does not support NETest.

Marotta et al. (172) The authors reviewed the literature about chromogranin A and studies involving NETest. We believe all these studies have been reviewed for this LCD. The authors concluded, "Hence, the new frontier seems to be represented by multianalyte approaches. Particularly, a blood-based algorithm including simultaneous determination of 51 NEN-specific markers has been developed in recent years(Modlin et al.2013) and all comparative studies were concordant in reporting significantly better metrics as compared with CgA (Modlin et al. 2014a,b, 2015, 2016, Bodei et al. 2016, Pavel et al.2017a)." They also note that current indications from the ENETS and other major societies dealing with NENs, which still recommend broad spectrum use of circulating CgA for the diagnostic definition. In addition, this paper does not show any improved survival for patients using NETest. The declaration of

interest was no conflicts. Since the authors note that specialty societies have not accepted NETesting and that they do not note any increased survival in using NETesting, and they do not show any independent validation, this paper gives minimal support to NETest.

Yur R. (173) This is "in press." Draft, unpublished literature and not appropriate to review. This is not acceptable medical literature and cannot be reviewed. It does not support NETest.

Appetecchia et al. (174) The authors reviewed the literature, and conclude that chromogranin A (CgA) is not a good biomarker for neuroendocrine tumors. They then note, "An mRNA-based, specific multianalyte assay with algorithmic analyses has been shown to have better sensitivity and specificity than CgA in initial clinical studies." The first reference given for this statement is "Modlin IM, Drozdov I, Kidd M. The identification of gut neuroendocrine tumor disease by multiple synchronous transcript analysis in blood. PLoS One. 2013;8(5):e63364" which is reference # 63 in the LCD. This was also reviewed by this contractor in a prior reconsideration and not felt to adequately support NETest. The second of two references is "Modlin IM, Drozdov I, Alaimo D, et al. A multianalyte PCR blood test outperforms single analyte ELISAs (chromogranin A, pancreastatin, neurokinin A) for neuroendocrine tumor detection. Endocr Relat Cancer. 2014;21(4):615-628" which is reference #29 in the policy. In addition, this paper also has been previously reviewed by this contractor in a prior reconsideration request. Upon review both times, neither were felt to give adequate support of NETest. The issue for NETest is whether peer-reviewed medical literature found on the US National Library of Medicine, National Institutes of Health shows that NETest results in improved outcomes. The authors note that the studies cited were initial clinical studies. Further studies including independent clinical verification are need. This paper does not give any new support to NETest.

Auernhammer et al. (175) This paper was submitted twice by Wren Laboratories. Please see #112 above.

Zatelli M. (176) This paper was submitted twice by Wren Laboratories. Please see # 157 above.

Muffatti et al. (177) This appears to be a teaching case report in a book concerning a patient with a neuroendocrine tumor and discussion also on localization. The authors do comment on NETest. "… and novel biomarkers with improved predictive capability are currently in advanced clinical development. Among them, there are circulating tumor cells (CTCs) and multianalyte whole blood RNA signature (NETest). Changes in CC count have been recently associated with treatment response and survival but treatment personalization based on CT7Cs is currently not feasible for PanNENs. On the other hand, the NETest has shown impressive results in terms of sensitivity and specificity and its posttreatment changes seem to accurately predict response to operative resection and PRRT. However, similarly to CTCs, treatment personalization based on NETest baseline value has never been evaluated so far. Both CTCs and NETest might be useful for follow-up in the adjuvant setting, although clinical validation is still needed." There are not conflict of interest disclaimers. This paper does mention some positive features of NETest but does not support that it is established as a proven biomarker or that it improves overall survival. Thus it does not currently support NETest.

Khatami et al. (178) This review paper does mention NETest in paragangliomas and pheochromocytomas. It cites a number of papers that have previously been reviewed for the LCD. These studies also have not shown any improvement in overall survival. This paper does not give robust support for NETest.

La Rosa et al. (179) This review covers many aspects of these tumors. It does note that "The multianalyte-derived NET gene signature encompasses the expression of 51 genes which are assessed by four different prediction algorithms and seem to give information on tumor state and evolution from stability to progression. This approach defines the circulating fingerprint of the tumor showing a higher sensitivity and specificity that traditional secretory markers. The gene expression profile is mathematically analyzed using specific algorithms, which define tumor activity. Interesting, recent data have suggested that Circulating Transcript Analysis (NETest) may identify tumor

categories with a different prognosis and response to somatostatin analogues and peptide receptor radionuclide (PRRT) therapy. However, this new approach shows some problematic issues including technical complexity, which restricts the analysis to specific laboratories." It also cites the Delphic consensus which has been included in the LCD as reference #24 (Oberg K, Krenning E, Sundin A, et al. A Delphic consensus assessment: imaging and biomarkers in gastroenteropancreatic neuroendocrine tumor disease management. Endocr Connect. 2016;5(5):174-187.) The acceptability of this is dampened by the fact that this conference was supported by Clifton Life Sciences, which owns Wren Laboratories, and eight of the sixteen panelists are listed as having financial ties to Wren Laboratories. There are no disclaimers. This publication does not offer robust support for NETest. It does not mention any long term follow-up studies, improved overall survival or independent, external validation of the results.

Holdenrieder et al. (180) This review covers many aspects of these tumors. The author notes, "A consensus paper on the use of biomarkers for NET disease outlined the need for circulating biomarkers for diagnosis, prognosis, monitoring therapy response, identifying minimal residual disease, and detection of recurrent disease. While the limitations of monoanalyte in sensitivity and specific for GEP and lung NETs was recognized, more accurate diagnostic tools were looked for. Current research approaches address circulating DNA, mRNA, microRNA, and metabolomics biomarkers as well as circulating tumor cells; however, their clinical utility still has to be proven." The author declared no conflict of interest. We agree that clinical utility must be proven. That includes prolongation of overall survival, and of course independent, external validation of the results. In addition, the problems with consensus has been noted multiple times in these reviews. Thus at present, this is not robust support for NETest.

Rindi et al. (181) NGS really appreciates this editorial being sent. Since it is an editorial (but with many NETest references) we did not find it on our search for NETest support. These prominent experts give an unbiased evaluation of the paper Liu, E. et al. Assessment of NETest Clinical Utility in a U. S. registry-based Study. Oncologist https://doi.org/10.1634/theoncologist.2017-0623 (2018). "In this study, 100 patients were monitored for 6-12 months. Patients received the test at enrolment, were assigned to two groups depending on whether they had stable disease ('watch-and-wait' group) or progressive disease ('intervention' group) according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria, and separately analyzed. Seventy-two patients received a single test, and the rest received 2-4 tests. The data provided suggest tumour progression can be predicted earlier using NETest than with established RECIST criteria" However, Rindi and Wiedenmann noted, "The presented data, however, must be considered with caution, given the focus of the study on neuroendocrine cancer. Neuroendocrine neoplasia encompasses distinct tumour entities with growth behaviors that vary from extremely slow to very rapid. The incidence and aggressiveness of neuroendocrine neoplasms is highly dependent on the anatomical site of origin. The most aggressive disease is frequently found in the pulmonary tract (in the form of small-cell lung cancer [SCLC], and is also referred as neuroendocrine carcinoma (NEC) when found at other anatomical sites. The most indolent cases are frequently detected in the digestive system were previously termed carcinoids and are currently referred to as neuroendocrine tumours (NETs).The introduction of standard grading and staging tools for cancer in routine practice in the past decade greatly improved our knowledge of neuroendocrine neoplasia. Necessarily, inclusion criteria (according to anatomical site, and staging and grading parameters) need to be accurately defined before conducting studies in patients with neuroendocrine cancer in order to achieve a clear understanding of the results. Liu and co-workers focused their attention on patients with NET (97 of 100 patients tested). The most aggressive poorly differentiated forms of neuroendocrine cancer were also represent, but only in a very small subgroup (1 patient had SCLC and 2 patients had poorly differentiate NECs). The investigators used NETest to evaluate blood samples of patients who predominantly had advanced-stage neuroendocrine cancer (96 patients had stage IV disease), but with variable disease grades, mostly, low grade (45 of 86 patients) or intermediate grade (37 of 86 patients), and originating from different organs (68% in the digestive tract and pancreas)….The emerging picture in this study of 100 patients is promising, but not all the results aligned with the expectation. Discordance emerged when the NETest did not correlate with either absence or presence of the disease (4%of patients) or with stable or progressive disease status (17%and 23% of patients respectively) determined with stand methods. In 36% to 38% of patients in both groups the use of the test led to changes in patient management, resulting in a reduction of the number of imaging procedures performed. "Unfortunately, the specificity and sensitivity of the test were not provided nor could they be accurately calculated with the data made available; however, the overall concordance with disease status reported

(85) was well below 100%, a value necessary to ensure that not a single patient is misdiagnosed and therefore denied the most appropriate treatment. Understandably, reaching perfection is almost impossible in the real word, and this principle holds true especially in the complex management of patients with neuroendocrine neoplasia. Nevertheless, a clear definition of the sensitivity and specificity of NET is needed before the assay is widely adopted in clinical practice. Furthermore, whether the test performs identically regardless of tumour grade, tumour volume and/or treatment history remains unclear—the presented patient numbers are too small and the selected cohort was to heterogeneous…Thus, the cost-benefit radio needs to be accurately established once NETest has been studied in larger and homogenous populations of patients with neuroendocrine cancer" [note: Medicare does not use cost as a decision for coverage]. Competing interests: G.R. has received honoraria from Ipsen and Novartis for is role in their speaker's bureau. B.W. declares no competing interests." This paper refutes the contention that NETest is proven. This paper does not support NETest.

Chen et al. (182) This paper was submitted twice by Wren Laboratories. Please see #76 above.

Liu et al. (183) This paper was submitted twice by Wren Laboratories. Please see #77 above.

Lybaert et al. (184) This paper does not appear to mention NETest. It does not support NETest

Guzman et al. (185) This article is in Spanish. It is not acceptable support for NETest.

Kyriakopoulos et al. (186) This paper was submitted twice by Wren Laboratories. Please see #111 above.

Analysis of Evidence (Rationale for Determination)

- Some of the publications reviewed for NETest are favorable. A few suggest it has potential but needs more independent studies and validation before it can be recommended. Most do not mention NETest at all as an option in diagnosing and/or treating neuroendocrine tumors. All the favorable publications have been authored or co-authored by Modlin & Kidd. Perhaps this is to be expected for a proprietary laboratory developed test, but it nonetheless means there has been no independent validation of the test. Such proprietary laboratory developed tests can be developed with Federal Drug Administration (FDA) review and clearance. Unfortunately, the FDA has no "final guidance on the oversight of laboratory developed tests" (73).
- As noted above, all of the favorable papers have Dr. Irvin Modlin and/or Dr. Mark Kidd as authors. Equally important is the fact that Dr. Kidd is an employee of Wren Laboratories, which has the proprietary rights to NETest. Dr. Modlin is listed on most of the papers as a consultant for Wren Laboratories. On some, he is listed as an employee of Wren Laboratories. Many of the other papers have other co-authors who are listed as employees of Wren Laboratories. Many of the articles are sponsored by Clifton Life Sciences, which is the parent company of Wren Laboratories. There is much perceived conflict of interest that appears to permeate through these publications.
- To make these papers on NETest more credible, an independent, external validation must be performed. In particular, some of the independent review articles also called for "confirmation" of promising results. This has not happened yet.
- Related, independent societies and organizations such as National Comprehensive Cancer Network (NCCN) have not yet recommended the NETest. The only two such endorsements were by Oberg K, Modlin I, et al: *Consensus on Biomarkers for Neuroendocrine Tumour Disease* and by Oberg, Eric Krenning: *Delphic consensus assessment: imaging and biomarkers in gastroenteropancreatic neuroendocrine tumor disease management*. Dr. Modlin was the second author of this first consensus. "The experts were of the opinion that such laboratory tests should be initially undertaken at a single central laboratory." This was supported by Clifton Life Sciences, which owns Wren Laboratories, and eight of the sixteen panelists are listed as having financial ties to Wren Laboratories. The second consensus also had multiple panelists associated with Wren Laboratories. Thus, there is potential concern about how impartial these two recommendations are.

- The favorable papers, all from Wren Laboratories, claim that NETest can detect disease recurrence as long as one year before radiographic evidence of disease. Perhaps this is true. However, are there any clinical ramifications as a result of this finding? Will there be some type of treatment based on detection of this marker of disease which will result in improved outcomes? Unfortunately, there is currently no such evidence.
- Related, this test only offers prognostic information, and its predictive value is neither solid nor associated with improved survival.
- The evidence for clinical utility is limited, the documentation about analytical and clinical validity is also limited.
- Most important, as noted above, none of the articles show any improved overall survival. If beneficiaries do not live longer, the value of the test is questionable.
- One can argue that this kind of "black box" assay that incorporate multiple genetic markers, particularly RNA, into a proprietary calculation that generates some kind of dimensionless risk index, should have a higher burden of proof than individual gene or gene panel tests. With individual gene testing for many cancers, the results of the testing results in a targeted medical treatment (e.g. BRAF testing). With an elevated NETest, one does not know if a specific therapeutic intervention is indicated.

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
02/10/2022	R2	Removed hyperlink in the Summary of Evidence section and in the Bibliography #181.	• Other (Removed hyperlink)
10/17/2019	R1	Consistent with Change Request 10901, all coding information, National coverage provisions, and Associated Information (Documentation Requirements, Utilization Guidelines) have been removed from the LCD and placed in the related Billing and Coding Article, A57059. There has been no change in coverage	• Revisions Due To Code Removal

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
		with this LCD revision.	

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

A57059 - Billing and Coding: Biomarker Testing for Neuroendocrine Tumors/Neoplasms

A56247 - Response to Comments: Biomarker Testing for Neuroendocrine Tumors LCD L37851

Related National Coverage Documents

N/A

Public Versions

UPDATED ON	EFFECTIVE DATES	STATUS
02/04/2022	02/10/2022 - N/A	Currently in Effect (This Version)
10/11/2019	10/17/2019 - 02/09/2022	Superseded
Some older versions have been archived. Please visit the MCD Archive Site to retrieve them.		

Keywords

N/A