

Biomarkers to Inform Prognosis and Treatment for Unresectable or Metastatic GEP-NENs

Jonathan M. Loree, MD, MSc; David Chan, MBBS, PhD; Jennifer Lim, MBBS, MPH; Heather Stuart, MD, MSc; Nicolas Fidelman, MD; Jonathan Koea, MD; Jason Posavad, CPA, CMA, MBA; Meredith Cummins, RN, Grad Cert Oncology, Grad Diploma Business, Grad Cert Clinical Management; Sarah Doucette, MSc; Sten Myrehaug, MD; Boris Naraev, MD, PhD; Dale L. Bailey, PhD; Andrew Bellizzi, MD; David Laidley, MD, MSc; Veronica Boyle, MBChB, PhD; Rachel Goodwin, MSc, MD; Jaydi del Rivero, MD; Michael Michael, MBBS, DM; Janice Pasioka, MD; Simron Singh, MD, PhD

IMPORTANCE Evidence-based treatment decisions for advanced gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) require individualized patient-centered decision-making that accounts for patient and cancer characteristics.

OBJECTIVE To create an accessible guidance document to educate clinicians and patients on biomarkers informing prognosis and treatment in unresectable or metastatic GEP-NENs.

METHODS A multidisciplinary panel in-person workshop was convened to define methods. English language articles published from January 2016 to January 2023 in PubMed (MEDLINE) and relevant conference abstracts were reviewed to investigate prognostic and treatment-informing features in unresectable or metastatic GEP-NENs. Data from included studies were used to form evidence-based recommendations. Quality of evidence and strength of recommendations were determined using the Grading of Recommendations, Assessment, Development and Evaluations framework. Consensus was reached via electronic survey following a modified Delphi method.

FINDINGS A total of 131 publications were identified, including 8 systematic reviews and meta-analyses, 6 randomized clinical trials, 29 prospective studies, and 88 retrospective cohort studies. After 2 rounds of surveys, 24 recommendations and 5 good clinical practice statements were developed, with full consensus among panelists. Recommendations focused on tumor and functional imaging characteristics, blood-based biomarkers, and carcinoid heart disease. A single strong recommendation was made for symptomatic carcinoid syndrome informing treatment in midgut neuroendocrine tumors. Conditional recommendations were made to use grade, morphology, primary site, and urinary 5-hydroxyindoleacetic levels to inform treatment. The guidance document was endorsed by the Commonwealth Neuroendocrine Tumour Collaboration and the North American Neuroendocrine Tumor Society.

CONCLUSIONS AND RELEVANCE The study results suggest that select factors have sufficient evidence to inform care in GEP-NENs, but the evidence for most biomarkers is weak. This article may help guide management and identify gaps for future research to advance personalized medicine and improve outcomes for patients with GEP-NENs.

JAMA Oncol. doi:10.1001/jamaoncol.2024.4330
Published online October 3, 2024.

+ Supplemental content

+ CME at jamacmelookup.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jonathan M. Loree, MD, MSc, Medical Oncology, BC Cancer Agency Vancouver Centre, 600 W 10th Ave, Vancouver, BC V5Z 4E6, Canada (jonathan.loree@bccancer.bc.ca).

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are uncommon, heterogeneous tumors; however, their incidence is substantially increasing.^{1,2} Evidence-based treatment decisions for advanced GEP-NENs are complex owing to disease heterogeneity and the lack of phase 3 studies. This creates a need for patient-centered treatment decisions that account for patient and cancer characteristics. Our aim was to create an accessible guidance document that was supported by a systematic review to educate clinicians and patients on biomarkers informing prognosis and treatment in unresectable or metastatic GEP-NENs. Secondary aims were to establish future research priorities from identified evidence gaps and advocate for access and standardization of care.

Methods

This guidance document was developed as a joint effort of the Commonwealth Neuroendocrine Tumour Collaboration and the North American Neuroendocrine Tumour Society, with patient advocate representation, including the Canadian Neuroendocrine Tumour Society and NeuroEndocrine Cancer Australia. Patient-focused supplementary material was developed to complement the recommendations (eAppendix 1-4 in the [Supplement](#)). A detailed methods description is included in the eMethods and eTables 1 to 4 in the [Supplement](#).

Results

Literature Search Results

The search retrieved 5564 publications, 131 (2.4%) of which were eligible for evidence review, including 8 systematic reviews and meta-analyses, 6 randomized clinical trials, 29 prospective, and 88 retrospective cohort studies (eFigure in the [Supplement](#)). An additional 63 publications were identified that were ineligible but deemed useful to support discussion.

Recommendation Development and Consensus

After data extraction and evidence review, panelists assigned to review individual research questions proposed 27 statements with accompanied gradings of strength. In the first round of the consensus survey, 20 statements were accepted with or without minor rewording, 5 statements were revised based on feedback from at least 1 panelist suggesting a major rework, and 2 statements were revised by expanding each statement into 2 separate statements. Agreement was reached in the second-round consensus survey, including the 7 adjusted statements, totaling 29 recommendations with 100% consensus ([Table 1](#)). Data are summarized for specific statements in the [Supplement](#).

Evidence for the Value of Tumor-Based Biomarkers Grade, Differentiation, and Primary Tumor Location

The World Health Organization has defined 3 grade categories based on mitotic activity and the Ki-67 index that are inversely associated with prognosis ([Table 2](#)).³⁻¹² Mitotic count and Ki-67 index scores should be assessed using manual or digital scoring methods on tissue from core needle biopsy or surgical resection, if feasible.^{13,14} Ki-67

index may be heterogeneous based on the site of sampling and may increase during the disease course.¹⁵⁻²⁰ The highest obtained grade should be used when multiple samples have been assessed. If possible, biopsy and assessment of the fastest growing tumor for grade determination will best reflect prognosis.^{15,16,21,22}

Poorly differentiated GEP-NENs (termed *neuroendocrine carcinomas* [NECs]) are biologically distinct and associated with worse survival than well-differentiated GEP-NENs (termed *neuroendocrine tumors* [NETs]).^{8,23} While poorly differentiated NECs are exclusively grade 3 tumors, the World Health Organization criteria recognize a subset of well-differentiated grade 3 NETs with distinct prognosis ([Table 2](#); eTables 5 and 6 in the [Supplement](#)).²⁴⁻²⁹

Primary tumor site is also associated with prognosis in GEP-NENs. Data from large population-based studies suggest that in the metastatic setting, NENs of the small bowel, appendix, and pancreas have the most favorable survival, while gastric and colonic primaries have worse survival.^{1,30} Tumor grade, differentiation, and primary tumor location are treatment-informing factors; however, in the absence of high-quality data to definitively recommend a particular treatment based on these biomarkers, anticipated prognosis, cross-trial comparisons of efficacy, restrictions in clinical trial inclusion criteria, and drug approvals/access are used to guide treatment ([Table 3](#)^{25,29,31-67}; eTables 7-13 in the [Supplement](#)).

Genomic Profiling and Single-Gene Biomarkers

Next-generation sequencing (NGS) may be a cost-effective and time-efficient alternative to single-gene testing.^{68,69} Most studies assessing NGS in GEP-NENs focused on grade 3 neoplasms, as there is a low frequency of genomic alterations in low-grade, well-differentiated NETs.^{70,71} As specific genomic alterations are enriched in well-differentiated and poorly differentiated GEP-NENs, they may be useful for distinguishing differentiation status when cell morphology is ambiguous ([Table 4](#)^{26,71-84}).

The evidence to support the role of genomic alterations as prognostic or treatment-informing in GEP-NENs is currently minimal and of low quality. Review of individual alterations is presented in the eNarrative in the [Supplement](#). Based on the number of relevant genes to inform prognosis and treatment in GEP-NENs, NGS is not recommended in routine practice except for highly selected cases, such as when screening for a biomarker-selected clinical trial.

Transcriptional and Proteomic Classifiers

Omic multianalyte classifiers have been studied mainly in localized pancreatic NENs; thus, they did not meet the inclusion criteria for the literature review.⁸⁵⁻⁸⁸ Further data are needed.

O6-Methylguanine-DNA Methyltransferase

There is evidence to support O6-methylguanine-DNA methyltransferase (*MGMT*) deficiency being associated with response to temozolomide in glioblastoma multiforme^{89,90}; however, its role in GEP-NENs is unclear (eTables 14 and 15 in the [Supplement](#)). A systematic review and meta-analysis including 12 studies of advanced NETs found that *MGMT*-deficient NETs had higher objective response rates and longer progression-free survival (PFS) after temozolomide-based therapy, but this meta-analysis was limited by the inclusion of low-quality studies and heterogeneity in *MGMT* testing methods.⁹¹ While the phase 2 ECOG-ACRIN E2211 trial randomizing grade 1 and 2 pancreatic NETs to temozolomide or capecitabine-

temozolomide also found that cancers with *MGMT* deficiency had a significantly higher objective response rate compared with *MGMT*-proficient cancers, this did not translate into improved PFS. Without a nontemozolomide arm, validation of *MGMT* as predictive was not possible.^{54,92,93} *MGMT* testing does not currently have a role in standard practice. Further studies (including other mechanisms of *MGMT* dysregulation, such as copy loss) and standardization of *MGMT* testing would be required to make this a treatment-informing biomarker for temozolomide.

Somatostatin Receptor Expression by Immunohistochemistry
Somatostatin receptors (SSTRs) are highly expressed on well-differentiated GEP-NETs and less so in GEP-NECs. Increased SSTR expression assessed by immunohistochemistry (IHC) was prognostic for longer survival in GEP-NENs in most studies.⁹⁴⁻⁹⁶ However, SSTR expression is preferably evaluated by SSTR imaging using radiolabeled somatostatin analogue (SSA) with positron emission tomography/computed tomography (PET/CT), which has the advantage of capturing whole-body SSTR expression, thus identifying

Table 1. Summary of Recommendations and Grading for Using Tumor-Based Prognostic and Treatment-Informing Biomarkers in Advanced Unresectable or Metastatic Gastroenteropancreatic (GEP)-Neuroendocrine Neoplasms (NENs)

Statement description	Quality of evidence	Grading
Tumor-based		
1. Tumor grade and Ki-67 index are prognostic and treatment-informing biomarkers that should be considered when recommending patient care. A higher Ki-67 index predicts a shorter duration of response to somatostatin analogues and PRRT for well-differentiated NETs. A Ki-67 index score of greater than 55% suggests better response to chemotherapy for NEC.	Low	Conditional recommendation
2. Tumor differentiation is a prognostic and treatment-informing biomarker that should be considered when recommending patient care for grade 3 NENs.	Low	Conditional recommendation
3. Repeated tumor biopsy should be considered at time of progression for lesion(s) with an apparent increase in growth rate to assess Ki-67 proliferative index, tumor differentiation, and grade in situations in which these may alter management.	NA	Good clinical practice
4. Clinical features, such as age, performance status, tumor bulk, tumor location, pain, and symptomatology, should be considered when recommending patient care, keeping patient preferences at the core of shared decision-making.	NA	Good clinical practice
5. Primary tumor location is a prognostic and treatment-informing biomarker and should be considered when recommending patient care.	Low	Conditional recommendation
6. Genomic profiling by NGS can identify the mutational status of a select list of genes and/or genomic signatures that may be prognostic based on low levels of evidence. These are generally not treatment informing. Genomic profiling by NGS should only be performed in highly selected cases.	Low	Expert consensus opinion
7. A high tumor mutational burden may suggest an improved prognosis in advanced GEP-NEN; however, there is minimal evidence to support the clinical benefit of immunotherapy in patients with a high mutational burden. Given that this evidence is derived from tumor agnostic studies and is low quality, testing should only be performed in highly selected cases.	Low	Expert consensus opinion
8. The prognostic significance of MSI in neuroendocrine tumors is unclear. There is some evidence to support the clinical benefit of immunotherapy in cancers with MSI; however, given that this evidence is derived from low-quality tumor agnostic studies and the frequency of high MSI in NENs overall is low (1%), testing should only be performed in highly selected cases.	Low	Expert consensus opinion
9. There is some evidence to support the clinical benefit of TRK inhibitors in cancers with NTRK fusions or rearrangements. However, given that the evidence is derived from low-quality tumor agnostic studies and the frequency of these alterations in NENs is low (less than 1%), testing should only be performed in highly selected cases.	Low	Expert consensus opinion
10. Transcriptional and proteomic classifiers are prognostic but not treatment-informing biomarkers. Further research is needed to understand how to incorporate them into clinical practice, and they should not be ordered outside of a research setting.	Very low	Recommendation for use only in research
11. Assessment for <i>MGMT</i> inactivation may suggest response to temozolomide in pancreatic neuroendocrine tumors. Both immunohistochemistry and molecular assays have a lack of standardization. Assays must be standardized before they are clinically used outside of a research setting.	Low	Recommendation for use only in research
12. Although SSTR immunohistochemistry is associated with prognosis following PRRT, it is unable to capture the spatial heterogeneity of SSTR expression. SSTR functional imaging is the preferred treatment-informing biomarker to identify patients who may benefit from PRRT. Further research is needed to validate SSTR protein expression as a surrogate for functional imaging.	Low	Recommendation for use only in research
Imaging-based		
13. High avidity on somatostatin-receptor PET can be treatment informing, and there is an association with improved prognosis. PET is preferred to octreoscan SPECT imaging for ascertaining SSTR expression. It is likely that high avidity on SSTR PET suggests response to PRRT.	Low	Conditional recommendation
14. Dual functional imaging with SSTR PET and FDG PET may provide additive value to inform prognosis and treatment; however, due to the low quality of evidence available, the optimal patient population and approach to incorporate dual functional imaging is currently unclear. Dual imaging should only be performed in selected cases. The following statements outline methods of interpreting dual functional imaging and their recommendation for use based on prognostic and treatment-informing value: (1) the presence of FDG-avid tumor burden in advanced GEP-NEN indicates an inferior prognosis. FDG-avid disease may suggest a worse treatment response to PRRT but is currently not treatment informing; (2) the presence of discordant disease on FDG/somatostatin receptor PET may be a prognostic and treatment informing biomarker. Treatment of FDG-avid and somatostatin receptor occult lesions should be prioritized in treatment decisions.	Low-very low	Expert consensus opinion
15. The NETPET score is a prognostic but not treatment informing biomarker. Further research is needed to understand how to incorporate the NETPET score into clinical practice.	Low	Recommended for use only in research
16. Methods to correlate tumor response on PET imaging with conventional cross-sectional imaging are required to optimize response assessment in clinical practice and for research studies. Further research is needed to understand how to incorporate concurrent functional imaging and cross-sectional imaging into clinical practice. Functional imaging measures, such as SUV, alone are not recommended to assess response to therapy independent of size metrics	NA	Good clinical practice

(continued)

Table 1. Summary of Recommendations and Grading for Using Tumor-Based Prognostic and Treatment-Informing Biomarkers in Advanced Unresectable or Metastatic Gastroenteropancreatic (GEP)–Neuroendocrine Neoplasms (NENs) (continued)

Statement description	Quality of evidence	Grading
Blood-based		
17. Symptomatic carcinoid syndrome is prognostic in patients with metastatic midgut NETs and should be used to inform treatment with SSAs.	Moderate-low	Strong recommendation
18. Subclinically elevated 5-HIAA levels may be prognostic in patients with metastatic midgut NETs and could be used to inform treatment with SSA, but the degree of elevation and perceived tumor burden should be considered. 24-Hour urinary 5-HIAA is the current standard for detecting elevated 5-HIAA levels.	Low	Conditional recommendation
19. Hormone testing for functional syndromes other than carcinoid syndrome should be performed when there is clinical suspicion for functional NEN syndromes based on patient symptoms and clinical signs. Hormone testing does not need to be performed routinely for all patients; however, thorough history taking is essential, as subtle signs can often be overlooked that would inform testing.	NA	Good clinical practice
20. Significantly elevated serum CgA levels at baseline may be prognostic; however, the optimal threshold for prognostication and relevance within specific tumor grades or sites of origin is unclear. Change in CgA levels following treatment may be associated with response, but there is substantial variability within current studies, and high-quality prospective data are lacking. Neither serum CgA levels at baseline or following therapy are treatment informing and should not be ordered/used for the purpose of guiding treatment routinely.	Low	Expert consensus opinion
21. Substantially elevated pancreastatin at baseline may be prognostic; however, there is insufficient evidence to support the value of pancreastatin as a treatment-informing biomarker. It should not be monitored routinely outside the context of a research setting.	Low	Recommendation for use only in research
22. Given the paucity of data that assesses pancreatic polypeptide concentration as a prognostic or treatment informing factor in patients with advanced or metastatic GEP-NEN, no recommendation can be given at this time, and it should not be ordered as part of routine practice.	Very low	No recommendation
23. Significantly elevated NSE at baseline may be prognostic; however, evidence to support the value of NSE as a treatment-informing biomarker is limited. It should not be monitored routinely outside the context of a research setting.	Low	Recommendation for use only in research
24. Given the paucity of data assessing progastrin as a prognostic factor in advanced or unresectable GEP-NEN, further research is needed to determine the value of progastrin as a prognostic marker, and it should not be ordered outside of a research setting.	NA	Recommendation for use only in research
25. The NETest may be prognostic but is not a treatment-informing biomarker. Due to substantial variability between studies, the relevance of the NETest within specific tumor grades or sites of origin and the optimal thresholds for prognostication and detection of progressive disease are unclear. Further research is needed to understand how to incorporate the NETest into clinical practice and if the cost of the test is justified by patient benefit.	Low-moderate	Recommendation for use only in research
26. Liquid biopsy testing, including minimal residual disease testing with blood-based nucleic acid testing or circulating tumor cells, requires further research to understand how to incorporate it into clinical practice and should not be ordered outside of a research setting.	Very low	Recommendation for use only in research
Carcinoid heart disease		
27. Development of carcinoid heart disease is associated with decreased survival in patients with advanced or unresectable midgut NETs. Early identification of carcinoid heart disease through surveillance echocardiography is likely to be associated with improved outcomes, although the optimal frequency of surveillance is unknown. Optimal timing of valvular surgery is unknown, although treatment with SSA is likely to be associated with improved outcomes of carcinoid heart disease.	Very low	Conditional recommendation
28. NT-pro-BNP is associated with carcinoid heart disease, which has a poor prognosis. Monitoring of NT-pro-BNP may be considered in the surveillance of carcinoid heart disease, as carcinoid heart disease is treatment informing. The low quality of evidence to support NT-pro-BNP monitoring is balanced by the relative simplicity and affordability of testing and the potential for a large association with patient quality of life and survival; however, further evidence generation would be beneficial to optimize surveillance.	Low	Expert consensus opinion
29. Refractory carcinoid syndrome despite somatostatin analogues is associated with reduced quality of life and may worsen prognosis. It should inform therapy intensification.	NA	Good clinical practice
Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; FDG, fluorodeoxyglucose; CgA, chromogranin A; GEP, gastroenteropancreatic; MGMT, O6-methylguanine-DNA methyltransferase; MGMT, O6-methylguanine-DNA methyltransferase; MSI, microsatellite instability; NA, not applicable; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; NGS, next-generation sequencing; NSE, neuron-specific enolase; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; NTRK, neurotrophic tyrosine receptor kinase; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SPECT, single-photon emission computed tomography; SSTR, somatostatin receptor; SUV, standardized uptake value; TRK, tropomyosin receptor kinase.		

Table 2. Grade and Morphology Categories Based on the World Health Organization 2019 Diagnostic Criteria for Gastroenteropancreatic Neuroendocrine Neoplasms

Morphology	Grade	Mitotic count (2 mm ² /10 HPF)	Ki-67 index (% Ki-67 positive cells/2000 evaluated cells)
Well differentiated	1	<2	<3%
Well differentiated	2	2-20	3%-20%
Well differentiated	3	>20	>20%
Poorly differentiated neuroendocrine carcinomas; small cell; large cell	3	>20	>20%
MinEN	Mixed neuroendocrine and non-neuroendocrine tumor		

Abbreviation: HPF, high-power field.

Table 3. Use of Tumor Grade, Differentiation Status, and Primary Location to Inform Therapy in Gastroenteropancreatic (GEP)-Neuroendocrine Neoplasms (NENs)

Therapy	Preferred			Other factors to consider ^a	Rationale/evidence
	Grade	Differentiation	Primary location		
Somatostatin analogues (eg, octreotide, lanreotide)	G1/G2	Well (NETs)	Any	<ul style="list-style-type: none"> • Must be SSTR positive • Should be part of therapy for patients with carcinoid syndrome 	<ul style="list-style-type: none"> • SSAs demonstrated antiproliferative activity vs placebo in patients with G1/G2 GEP-NENs (PROMID and CLARINET)³¹⁻³³ • Preferred for G1/G2 tumors with good prognosis due to mild safety profile
PRRT (eg, ¹⁷⁷ Lu-DOTATATE)	Any, stronger evidence for G1/G2	Well (NETs)	Any	<ul style="list-style-type: none"> • Must be SSTR positive • Ongoing COMPETE (¹⁷⁷Lu-edotreotide vs everolimus) and COMPOSE (¹⁷⁷Lu-edotreotide vs best standard of care) trials may better inform optimal sequencing of PRRT 	<ul style="list-style-type: none"> • PRRT (¹⁷⁷Lu-DOTATATE) + standard dose octreotide achieved a significantly prolonged PFS vs high-dose octreotide in G1/G2 midgut NETs (NETTER-1)³⁴ • PRRT (¹⁷⁷Lu-DOTATATE) demonstrated an improved 12-mo PFS vs sunitinib in pancreatic NETs (OCLURANDOM)³⁵ • Retrospective studies suggest PFS following PRRT is shorter with increasing grade/ proliferation index,³⁶⁻⁴² but this does not preclude benefit in higher-grade GEP-NENs • Retrospective studies have demonstrated comparable efficacy for ¹⁷⁷Lu-DOTATATE in patients with pancreatic and midgut NETs^{38,43,44}
Sunitinib	G1/G2	Well (NETs)	Pancreatic	NA	Sunitinib demonstrated improved PFS vs placebo in G1/G2 pancreatic NETs (SUN1111) ⁴⁵
Everolimus	G1/G2	Well (NETs)	Pancreatic, small bowel	Must be nonfunctional ^b	Everolimus achieved prolonged PFS vs placebo in non-functional small bowel and pancreatic NETs (RADIANT-3 and RADIANT-4) ⁴⁶⁻⁴⁸
Streptozotocin + fluorouracil	G2	Well (NETs)	Pancreatic	Prioritize vs everolimus if tumor shrinkage is a priority	<ul style="list-style-type: none"> • Streptozotocin + fluorouracil demonstrated improved PFS in prospective randomized studies in G2 pancreatic NETs⁴⁹⁻⁵² • Streptozotocin + fluorouracil demonstrated similar PFS but improved ORR vs everolimus in pancreatic NETs (SEQTOR)⁵³
CAP-TEM	G1/G2 (pancreatic, less evidence for extra pancreatic) G3 with Ki-67 < 55% (any)	Well (NETs); poor (NECs) with Ki-67 < 55%	Any, strongest evidence for pancreatic	Assessment of MGMT activation may predict response to temozolomide, but evidence is insufficient for use in routine practice	<ul style="list-style-type: none"> • CAP-TEM demonstrated superior PFS vs TEM alone in G1/G2 pancreatic NETs (ECOG-ACRIN E2211)⁵⁴ • Randomized trials of CAP-TEM in G1/G2 extrapancreatic gastrointestinal NETs are lacking • Retrospective studies have reported higher response rates and longer PFS with CAP-TEM for pancreatic vs nonpancreatic NENs; however, evidence quality is low⁵⁵⁻⁶¹
Platinum chemotherapy	G3 with Ki-67 ≥ 55%	Poor (NECs)	Any	NA	<ul style="list-style-type: none"> • Randomized clinical trials of platinum-chemotherapy in G1/G2 extrapancreatic gastrointestinal NETs are lacking • Among G3 GEP-NENs, poorly differentiated disease and Ki-67 ≥ 55% have been associated with higher response rates to platinum chemotherapy^{25,29 62-66}, although quality of evidence is low

Abbreviations: CAP-TEM, capecitabine-temozolomide; G, grade; MGMT, O6-methylguanine-DNA methyltransferase; NA, not applicable; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; ORR, objective response rate; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SSTR, somatostatin receptor.

^a Toxic effect profiles of each therapy, as well as prognosis, age, comorbidities,

performance status, symptoms, tumor burden, tumor distribution, and patient preferences should always be considered when selecting therapy.

^b In RADIANT-2, including functional small bowel NETs, the study did not meet prespecified statistical thresholds for significance.⁶⁷

heterogeneity between lesions.⁹⁷ As such, SSTR IHC should not be used to determine eligibility for PRRT.

Evidence for the Use of Imaging-Based Biomarkers

SSTR PET/CT

SSTR imaging uses radiolabelled SSAs as a functional tracer for SSTRs on the surface of NETs. While ⁹⁸in-pentetreotide (oc-

treoscan) with single-photon emission CT was previously used, higher-affinity radio-labeled SSAs visualized by PET/CT are now preferred given their higher resolution, lower radiation dose, and shorter image acquisition time.⁹⁷⁻⁹⁹ ⁶⁸Ga-DOTATATE, ⁶⁸Ga-DOTATOC, and ⁶⁸Ga-DOTANOC are commonly used tracers, with no major differences in performance reported.¹⁰⁰ ⁶⁴Cu-DOTATATE is also used for SSTR imaging and has the lo-

Table 4. Frequency of Select Genomic Alterations in G3 Gastroenteropancreatic (GEP) Neuroendocrine Neoplasms

Gene name/signature	Frequency range of genomic alterations ^{26,71-84}	
	G3 GEP-NET	GEP-NEC
Associated with differentiation status		
TP53	7%-27%	64%-88%
RB1	<1%-31%	28%-50%
KRAS	<1%-9%	14%-50%
DAXX	Pancreatic: 25%	1%-6%
	Other gastrointestinal: <1%	
ATRX	Pancreatic: 25%	1%-6%
	Any GEP: 12%	
MEN1	Pancreatic: 40%	1%-6%
	Any GEP: 12%	
Associated with tumor-agnostic therapies		
BRAF	<1%-3%	Any: 20%
		Colorectal: 20%-63%
NTRK	<1%	<1%
MSI-H/MMRd	<1%	4%-70%
TMB	All grades: 1.09 mut/MB	5.0-9.9 mut/MB
	G3: 4.6-5.1 mut/MB	

Abbreviations: G, grade; MSI-H/MMRd, high microsatellite instability or mismatch repair deficiency; mut/MB, mutation per megabase; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; NTRK, neurotrophic tyrosine receptor kinase; TMB, tumor mutational burden.

gistical advantage of a long half-life, allowing it to be centrally produced.^{101,102}

Data supporting the prognostic role of SSTR imaging were generally consistent, but the level of evidence was low (eTables 16 and 17 in the Supplement). Maximum standardized uptake value (SUVmax) as a measurement of SSTR expression was reported as an independent positive prognostic marker for PFS in most studies (cut-offs, 14.5-37.8).^{27,103-105} However, some studies reported total SSTR-avid tumor volume to be the only prognostic expression parameter.^{106,107}

Several studies assessing prognosis following SSTR-directed therapy were identified (eTables 18 and 19 in the Supplement). Two retrospective studies found that high SUVmax was associated with improved PFS on SSA therapy.^{108,109} Studies evaluating SSTR imaging as prognostic following PRRT found that SUV measurements, most notably SUVmax, as well as heterogeneity in radiotracer uptake, were associated with response and/or PFS.^{36,110-113} SUVmax measurements are limited by variability in scanner and reproduction parameters, which can affect the accuracy of measurements.¹¹⁴ In addition, studies that focus on SUVmax are not able to account for disease heterogeneity. Currently, uptake on SSTR imaging is treatment informing, as it is required for PRRT eligibility, and it is likely that high avidity on SSTR PET is associated with improved response to PRRT. However, as few studies included a control arm, the true predictive value is unclear. There were no prospective studies evaluating PRRT in poorly differentiated NENs, in which chemotherapy is a preferred treatment option, and the proportion of these tumors with SSTR uptake is lower than well-differentiated NETs. Given this, SSTR imaging is not treatment informing in poorly differentiated NENs, and other societies have sug-

gested that if functional imaging is used in this population to consider fluorodeoxyglucose (FDG) imaging preferably.¹¹⁵⁻¹¹⁹

In addition to its diagnostic and potential prognostic value, SSTR imaging may be useful in assessing treatment response, although this application has not been well studied.¹²⁰ To validate functional imaging in this role, future trials should consider integrating functional imaging into their study design.

FDG PET/CT

Uptake of F-18 FDG visualized by PET/CT is associated with high-grade, poor differentiation, and worse prognosis in GEP-NENs (eTables 20-23 in the Supplement).¹²¹⁻¹²⁵ Dual functional imaging with SSTR PET and FDG PET can identify heterogeneity among lesions, which may inform prognosis; however, due to the low quality of evidence available, the optimal population and approach to incorporate dual functional imaging is unclear.¹²⁶⁻¹²⁹ Discordance between FDG and DOTA-peptide uptake may be treatment informing, as FDG-avid lesions not expressing SSTR should be prioritized in treatment decisions given their more aggressive nature. Several scoring systems that simplify dual functional imaging have been evaluated (eTables 24 and 25 in the Supplement). The NETPET score, which categorizes 3 groups based on the discordance of radiotracer uptake between lesions, was prognostic for survival in retrospective studies.¹³⁰⁻¹³² The role of dual PET imaging as part of standard practice is not determined at this time, acknowledging that it may be helpful in identifying discordant lesions that lack SSTR expression. Prospective studies evaluating dual functional imaging are needed to confirm whether and in which patient population it should be adopted. It is often considered for patients with higher-grade tumors; however, FDG uptake has been noted in approximately 40% of grade 1 and 2 tumors.^{119,133}

Evidence for the Value of Blood-Based Biomarkers

Peptide and Hormone Markers for Functional NENs

Functional syndromes from hormone excess are present in 10% to 40% of pancreatic NENs and are associated with symptoms specific to the overproduced compounds (most commonly insulin, gastrin, glucagon, and vasoactive intestinal polypeptide).^{134,135} Because there is a low probability of detecting elevated hormone levels in the absence of symptoms, testing for these markers is only recommended when symptoms suggest hormone excess.

Carcinoid syndrome is the most common functional syndrome in extrapancreatic NENs, occurring in approximately 20%, with the highest frequency in grade 1 and 2 metastatic midgut NETs (up to 50%).¹³⁶ Serotonin is the most commonly implicated hormone, causing flushing, diarrhea, and dyspnea.⁴⁹ More than 50% of patients with carcinoid syndrome historically developed carcinoid heart disease (CHD), which is associated with poor prognosis.¹³⁷⁻¹³⁹ With increased use of SSAs, this proportion may have decreased; however, CHD remains a significant cause of morbidity and mortality.¹⁴⁰

Circulating serotonin is metabolized and then excreted by the kidney to urinary 5-hydroxyindoleacetic acid (5-HIAA), which can be measured to diagnose carcinoid syndrome. A 24-hour urine collection is the standard for measuring 5-HIAA, with food and drug intake monitored to avoid false positive results.¹⁴¹ Several studies have demonstrated the reproducibility and association of serum or plasma 5-HIAA with 24-hour urinary 5-HIAA, suggesting that plasma testing may be an option.¹⁴²⁻¹⁴⁷

Carcinoid syndrome and elevated urinary 5-HIAA levels are negative prognostic markers in GEP-NENs in some retrospective studies, but results were inconsistent and the evidence as a whole was of low to very low quality (eTables 26 and 27 in the [Supplement](#)).^{136,148-155} Regardless of their prognostic effect, carcinoid syndrome and elevated 5-HIAA levels are associated with symptom burden that affects quality of life^{98,156} and the development of CHD.¹⁵⁷⁻¹⁵⁹ SSAs can improve carcinoid syndrome in approximately 75% of patients¹⁶⁰ in addition to demonstrating antiproliferative effects.^{31,32,161} Thus, SSAs are recommended for the first-line treatment of unresectable midgut NETs presenting with carcinoid syndrome or elevated urinary 5-HIAA levels and should be continued in combination with other therapies on tumor progression.

While there are few data to support the value of serial 5-HIAA determination or the reduction of 5-HIAA in association with CHD development, attempts to lower urinary 5-HIAA levels are warranted given the morbidity associated with CHD. Almost 50% of patients without carcinoid syndrome symptoms in the CLARINET study had elevated baseline urinary 5-HIAA levels, suggesting that 5-HIAA should be evaluated even without overt carcinoid symptoms.¹⁶²

Patients with refractory carcinoid syndrome (or those with persistently high u5-HIAA levels without symptoms) should be considered for therapy intensification. This first includes SSA dose escalation or use of serotonin synthesis inhibitors, such as telotristat ethyl.¹⁶³⁻¹⁶⁵ While the phase 3 TELESTAR study demonstrated reduced bowel movements and decreases in u5-HIAA levels with telotristat, to our knowledge there are no studies evaluating whether telotristat slows development or progression of CHD.^{143,147,165} The addition of systemic therapies, such as interferon, everolimus, or PRRT, as well as liver-directed therapies, can also manage hormone excess.^{163,164} As there are no trials comparing treatment intensification options in refractory carcinoid disease, management decisions should be based on symptom burden, tumor status, biochemical status, and risk/severity of CHD.

Biomarkers for Detecting and Monitoring of CHD

Recent improvements in survival for patients with midgut NETs and CHD may be attributed to increased monitoring and early detection, as well as improved interventions.^{139,166} There is widespread consensus across international guidelines that echocardiography should be used to monitor for CHD; however, the recommended frequency of monitoring is unclear.^{143,147,167,168} The panel recommends considering patient-specific risk for CHD when selecting a monitoring interval while awaiting more data.

The most recent European Neuroendocrine Tumor Society guidelines on carcinoid syndrome also recommends plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) to screen for CHD.¹⁴⁷ Four retrospective studies found a high sensitivity (range, 74%-92%) and specificity (range, 73%-91%) for NT-proBNP to detect CHD at cut-off ranges from approximately 200 to 260 ng/L.¹⁶⁹⁻¹⁷² One of these studies found that NT-proBNP levels less than 260 ng/L had a negative predictive value of 98%, suggesting that concentrations greater than 260 ng/L may prompt investigation of CHD by echocardiography.¹⁷⁰ Although the quality of evidence regarding NT-pro-BNP is low, it is balanced by the relative simplicity and affordability of testing.

Chromogranin A

Chromogranin A (CgA) is secreted in secretory granules of neuroendocrine cells. While serum CgA levels can be elevated in patients with functional and nonfunctional GEP-NENs, its value as a prognostic or treatment-informing biomarker is uncertain. This partly arises from several factors that falsely elevate CgA levels, including non-neoplastic conditions (eg, kidney failure, Parkinson disease) and medications (proton pump inhibitors and glucocorticoids), as well as assay differences.¹⁴¹

Elevated baseline CgA levels are likely prognostic for poorer survival in advanced GEP-NENs; however, this was not consistently reported, and the optimal threshold for prognostication and relevance within specific tumor grades or sites of origin remains unclear (eTables 28 and 29 in the [Supplement](#)).^{6,173-183} A systematic review and meta-analysis investigating serum CgA monitoring found that the pooled sensitivity and specificity of increased CgA levels from baseline in identifying progressive disease in GEP-NENs was 75.4% (range, 46%-100%) and 84.8% (range, 68%-90%), respectively.¹⁸⁴ This analysis was limited by the low to very low quality of studies included, different CgA cut-off values used, and heterogeneous populations studied. CgA levels at baseline or following therapy are not treatment informing and should not be ordered or used for the purpose of guiding treatment routinely.

Other Circulating Peptide Markers

Elevated pancreastatin (a cleavage product of CgA) and neuron-specific enolase have been associated with decreased survival in advanced GEP-NENs (eTables 30-33 in the [Supplement](#)), but varying cut-offs in studies and the low quality of evidence make the utility of these peptides unclear. Neither pancreastatin or neuron-specific enolase are recommended as biomarkers to inform treatment.^{37,173-176,185-188} While pancreatic polypeptide and progastrin have been suggested as diagnostic markers, the lack of current data means neither should be ordered to inform treatment.¹⁸²

NETest

NETest is a blood test analyzing messenger RNA transcripts of 51 genes.¹⁸⁹ Gene expression data are processed through a proprietary algorithm that produces a clinical activity score ranging from 0% to 100%. Five studies found that higher NETest scores were independently prognostic for a higher risk of progression in GEP-NETs; however, the evidence quality was generally very low (eTables 34 and 35 in the [Supplement](#)).¹⁹⁰⁻¹⁹⁴ Moderate- to low-quality evidence suggests that NETest can discriminate between progressive or stable disease at accuracy rates between 73% and 91% in grade 1 and 2 GEP-NETs, although the optimal NETest cut-off score varied between studies (eTables 36 and 37 in the [Supplement](#)).^{190,192-195} Rising NETest scores from baseline have also been reported to identify nonresponders following PRRT with 90% to 98% accuracy.^{194,196} It is unclear whether monitoring for disease progression using NETest improves quality of life or clinical outcomes compared with conventional imaging. Further study in prospective randomized clinical trials is required for NETest to be considered a biomarker to guide management. The NETest may be prognostic, but it is not a treatment-informing biomarker.

Circulating Tumor Cells and DNA

The use of circulating tumor DNA or circulating tumor cells for monitoring minimal residual disease (MRD) and early progression is promising in other cancer types, but the evidence in GEP-NENs is limited.¹⁹⁷⁻²⁰¹ Further evidence is needed, and they are only recommended in a research setting.

Conclusions

There is an unmet need for biomarkers to personalize care for GEP-NENs. Grade, morphology, primary tumor site, and markers of carcinoid syndrome currently have the largest evidence base to guide management. Circulating peptides are not reliable to inform treatment, and although genomic biomarkers are of substantial interest, the poor representation of GEP-NENs in clinical trials of tumor-agnostic therapies and low prevalence of actionable alterations suggests limited value of NGS currently. This topic required the most discussion to reach consensus.

The use of functional imaging provides an opportunity to capture biological heterogeneity between lesions, which can affect treatment decisions. The predictive value of functional imaging requires further evidence to better understand optimal therapy sequencing in relation to tracer uptake. Other factors, such as age, performance status, tumor bulk, tumor location, pain, symptomatology, and patient preference, should be considered, and management should be discussed by a multidisciplinary team specializing in GEP-NENs.

We acknowledge this evidence review and development of recommendations is limited by the lack of high-quality evidence and systematic reviews identified. Additionally, there may be biomarkers (such as DLL3 and immune scores) that were not identified as research questions (eTable 1 in the Supplement) during the in-person meeting and which were subsequently not incorporated into the guidance document. However, we hope this review provides a valuable resource to the NEN community on which to build future efforts to improve the care of patients living with this disease.

ARTICLE INFORMATION

Accepted for Publication: May 20, 2024.

Published Online: October 3, 2024.
doi:10.1001/jamaoncol.2024.4330

Author Affiliations: BC Cancer, Vancouver Centre, Vancouver, British Columbia, Canada (Loree); Northern Clinical School, University of Sydney, Sydney, Australia (Chan); ENETS Centre of Excellence, Department of Medical Oncology, Royal North Shore Hospital, St Leonards, New South Wales, Australia (Chan); St George Hospital, Sydney, New South Wales, Australia (Lim); University of New South Wales, Sydney, New South Wales, Australia (Lim); Garvan Institute of Medical Research, Sydney, New South Wales, Australia (Lim); University of British Columbia and BC Cancer Agency, Vancouver, British Columbia, Canada (Stuart); University of California, San Francisco (Fidelman); Te Whatu Ora Waitemata and the University of Auckland, Auckland, New Zealand (Koea); Canadian Neuroendocrine Tumours Society, Cornwall, Ontario, Canada (Posavad); Neuroendocrine Australia, Australia (Cummins); Impact Medicom Inc, Toronto, Ontario, Canada (Doucette); Odette Cancer Centre, Toronto, Ontario, Canada (Myrehaug); Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada (Myrehaug); Tampa General Hospital Cancer Institute, Tampa, Florida (Naraev); Department of Nuclear Medicine, Royal North Shore Hospital, Sydney, New South Wales, Australia (Bailey); Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia (Bailey); University of Iowa Hospitals and Clinics, Iowa City (Bellizzi); Western University, London, Ontario, Canada (Laidley); Lawson Health Research Institute, London, Ontario, Canada (Laidley); School of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand (Boyle); Department of Oncology, Auckland City Hospital, Te Whatu Ora Tamaki Makaurau, Auckland, New Zealand (Boyle); Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, Ontario, Canada (Goodwin); Developmental Therapeutics Branch, National Cancer Institute, National Institutes of Health,

Bethesda, Maryland (del Rivero); NET Unit and ENETS Centre of Excellence, Peter MacCallum Cancer Centre, Sir Peter MacCallum Department of Medical Oncology, University of Melbourne, Parkville, Victoria, Australia (Michael); Section of General Surgery, Division of Endocrine Surgery and Surgical Oncology, Department of Surgery and Oncology, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada (Pasiela); University of Toronto, Toronto, Ontario, Canada (Singh); Sunnybrook Odette Cancer Center, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada (Singh).

Author Contributions: Drs Loree and Chan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Loree and Chan contributed equally.

Concept and design: Loree, Chan, Lim, Stuart, Fidelman, Cummins, Myrehaug, Naraev, Bellizzi, Goodwin, del Rivero, Singh.

Acquisition, analysis, or interpretation of data: Loree, Chan, Fidelman, Koea, Posavad, Doucette, Myrehaug, Naraev, Bailey, Bellizzi, Laidley, Boyle, Goodwin, Michael, Pasiela, Singh.

Drafting of the manuscript: Loree, Chan, Lim, Fidelman, Posavad, Cummins, Doucette, Myrehaug, Naraev, Boyle, Singh.

Critical review of the manuscript for important intellectual content: Loree, Chan, Stuart, Fidelman, Koea, Cummins, Myrehaug, Naraev, Bailey, Bellizzi, Laidley, Boyle, Goodwin, del Rivero, Michael, Pasiela, Singh.

Statistical analysis: Bailey, del Rivero, Singh.

Obtained funding: Loree, Chan, Singh.

Administrative, technical, or material support: Loree, Chan, Koea, Cummins, Laidley, del Rivero, Michael, Singh.

Supervision: Chan, Naraev, del Rivero, Pasiela, Singh.

Other - expert on the consensus topics: Goodwin.

Other - patient advocate: Posavad.

Conflict of Interest Disclosures: Dr Loree reported grants from Novartis and Ipsen during the conduct of the study as well as personal fees from Ipsen, Novartis, Amgen, Bayer, Merck, Pfizer, and Roche; nonfinancial support from Guardant, Saga Diagnostics, and Foundation Medicine; and grants

from Personalis outside the submitted work.

Dr Chan reported grants from Camurus and personal fees from Ipsen outside the submitted work. Dr Fidelman reported grants from Merck outside the submitted work. Dr Doucette reported grants from the Canadian Neuroendocrine Tumour Society during the conduct of the study.

Dr Myrehaug reported personal fees from Novartis Oncology and Ipsen during the conduct of the study. Dr Naraev reported personal fees from Exelixis, TerSera, and Lexicon and nonfinancial support from Novartis, TerSera, Lexicon, and Ipsen outside the submitted work. Dr Laidley reported personal fees from Novartis, Ipsen, Bayer outside the submitted work. Dr Goodwin reported grants from Ipsen, Pfizer, and Apobiologix and board service for Ipsen, AAA, Novartis, Pfizer, Amgen, Roche, Merck, AstraZeneca, Taiho, Eisai, BMS, Apobiologix, and Astellas outside the submitted work. Dr Singh reported personal fees from Novartis/AAA, Ipsen, and Camurus outside the submitted work. No other disclosures were reported.

Funding/Support: Funding to support medical writing was provided through an educational grant from Advanced Accelerator Applications, a Novartis company, and Ipsen Biopharmaceutical Canada.

Role of the Funder/Sponsor: Funding was used to support a medical writer who helped coordinate and draft this guidance document. The funders had no role in defining the methods, research questions, reviewing the literature, and drafting recommendations and did not provide input in the drafting of this manuscript.

Additional Contributions: We thank Sarah Doucette, MSc, Senior Medical Writer, IMPACT Medicom Inc (which received compensation as part of a contract for study support), for assistance in performing the literature search, drafting of the manuscript, and preparation for submission; the Canadian Neuroendocrine Tumour Society and Neuroendocrine Australia for helping to incorporate the patient voice into this document; and Enrico Mandarino, Executive Manager/Patient Coordinator, Canadian Neuroendocrine Tumour

Society, for assisting in the creation of the patient supplements.

Additional Information: This article represents a joint effort by the Commonwealth Neuroendocrine Tumour Collaboration, North American Neuroendocrine Tumor Society, Canadian Neuroendocrine Tumour Society, and NeuroEndocrine Cancer Australia.

REFERENCES

1. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3(10):1335-1342. doi:10.1001/jamaoncol.2017.0589
2. Hallet J, Law CHL, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer*. 2015;121(4):589-597. doi:10.1002/cncr.29099
3. Pape UF, Jann H, Müller-Nordhorn J, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. *Cancer*. 2008;113(2):256-265. doi:10.1002/cncr.23549
4. Kloepfel G. Pancreatic neuroendocrine neoplasias. In: *WHO Classification of Endocrine Tumors*. eds, Lloyd RV, Osamura RY, Klöppel G, Rosai J. International Agency for Research on Cancer Press;2017.
5. Nagtegaal ID, Odze RD, Klimstra D, et al. *WHO Classification of Tumours of the Digestive System*. 5th ed. International Agency for Research on Cancer Press; 2019.
6. Ahmed A, Turner G, King B, et al. Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study. *Endocr Relat Cancer*. 2009;16(3):885-894. doi:10.1677/ERC-09-0042
7. Khan MS, Luong TV, Watkins J, Toumpanakis C, Caplin ME, Meyer T. A comparison of Ki-67 and mitotic count as prognostic markers for metastatic pancreatic and midgut neuroendocrine neoplasms. *Br J Cancer*. 2013;108(9):1838-1845. doi:10.1038/bjc.2013.156
8. Nuñez-Valdovinos B, Carmona-Bayonas A, Jimenez-Fonseca P, et al. Neuroendocrine tumor heterogeneity adds uncertainty to the World Health Organization 2010 classification: real-world data from the Spanish Tumor Registry (R-GETNE). *Oncologist*. 2018;23(4):422-432. doi:10.1634/theoncologist.2017-0364
9. Rindi G, Falconi M, Klersy C, et al. TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. *J Natl Cancer Inst*. 2012;104(10):764-777. doi:10.1093/jnci/djs208
10. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). *Ann Oncol*. 2010;21(9):1794-1803. doi:10.1093/annonc/mdq022
11. Borbath I, Garcia-Carbonero R, Birkmukhametov D, et al. The European Neuroendocrine Tumour Society registry, a tool to assess the prognosis of neuroendocrine neoplasms. *Eur J Cancer*. 2022;168:80-90. doi:10.1016/j.ejca.2022.03.007
12. Richards-Taylor S, Ewings SM, Jaynes E, et al. The assessment of Ki-67 as a prognostic marker in neuroendocrine tumours: a systematic review and meta-analysis. *J Clin Pathol*. 2016;69(7):612-618. doi:10.1136/jclinpath-2015-203340
13. Tacelli M, Bina N, Crinò SF, et al; Italian Association of Hospital Gastroenterologists and Endoscopists. Reliability of grading preoperative pancreatic neuroendocrine tumors on EUS specimens: a systematic review with meta-analysis of aggregate and individual data. *Gastrointest Endosc*. 2022;96(6):898-908.e23. doi:10.1016/j.gie.2022.07.014
14. Luchini C, Pantanowitz L, Adsay V, et al. Ki-67 assessment of pancreatic neuroendocrine neoplasms: systematic review and meta-analysis of manual vs. digital pathology scoring. *Mod Pathol*. 2022;35(6):712-720. doi:10.1038/s41379-022-01055-1
15. Grillo F, Albertelli M, Brisigotti MP, et al. Grade increases in gastroenteropancreatic neuroendocrine tumor metastases compared to the primary tumor. *Neuroendocrinology*. 2016;103(5):452-459. doi:10.1159/000439434
16. Singh S, Hallet J, Rowsell C, Law CHL. Variability of Ki67 labeling index in multiple neuroendocrine tumors specimens over the course of the disease. *Eur J Surg Oncol*. 2014;40(11):1517-1522. EJSO. doi:10.1016/j.ejso.2014.06.016
17. Holmager P, Langer SW, Federspiel B, et al. Increase of Ki-67 index and influence on mortality in patients with neuroendocrine neoplasms. *J Neuroendocrinol*. 2021;33(9):e13018. doi:10.1111/jne.13018
18. Panzuto F, Cicchese N, Partelli S, et al. Impact of Ki67 re-assessment at time of disease progression in patients with pancreatic neuroendocrine neoplasms. *PLoS One*. 2017;12(6):e0179445. doi:10.1371/journal.pone.0179445
19. Alexandraki KI, Spyroglou A, Kykalos S, et al. Changing biological behaviour of NETs during the evolution of the disease: progress on progression. *Endocr Relat Cancer*. 2021;28(5):R121-R140. doi:10.1530/ERC-20-0473
20. Botling J, Lamarca A, Bajic D, et al. High-grade progression confers poor survival in pancreatic neuroendocrine tumors. *Neuroendocrinology*. 2020;110(11-12):891-898. doi:10.1159/000504392
21. Keck KJ, Choi A, Maxwell JE, et al. Increased grade in neuroendocrine tumor metastases negatively impacts survival. *Ann Surg Oncol*. 2017;24(8):2206-2212. doi:10.1245/s10434-017-5899-y
22. Barnes J, Johnson SJ, French JJ. Correlation of Ki-67 indices from biopsy and resection specimens of neuroendocrine tumours. *Ann R Coll Surg Engl*. 2017;99(3):193-197. doi:10.1308/rcsann.2016.0225
23. Yang M, Zeng L, Hou SZ, et al. Clinical features and long-term survival of metastatic hepatic neuroendocrine neoplasms secondary to gastroenteropancreatic site: an analysis by applying the grading classification. *J Oncol*. 2020;2020:6572398. doi:10.1155/2020/6572398
24. Milione M, Maisonneuve P, Spada F, et al. The clinicopathologic heterogeneity of grade 3 gastroenteropancreatic neuroendocrine neoplasms: morphological differentiation and proliferation identify different prognostic categories. *Neuroendocrinology*. 2017;104(1):85-93. doi:10.1159/000445165
25. Heetfeld M, Chougnat CN, Olsen IH, et al; Knowledge Network members. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer*. 2015;22(4):657-664. doi:10.1530/ERC-15-0119
26. Busico A, Maisonneuve P, Prinzi N, et al. Gastroenteropancreatic high-grade neuroendocrine neoplasms: histology and molecular analysis, two sides of the same coin. *Neuroendocrinology*. 2020;110(7-8):616-629. doi:10.1159/000503722
27. Hayes AR, Furnace M, Shah R, et al. High-grade gastroenteropancreatic neuroendocrine neoplasms and improved prognostic stratification with the new World Health Organization 2019 classification: a validation study from a single-institution retrospective analysis. *Pancreas*. 2021;50(4):516-523. doi:10.1097/MPA.0000000000001808
28. Wang ZJ, An K, Li R, et al. Analysis of 72 patients with colorectal high-grade neuroendocrine neoplasms from three Chinese hospitals. *World J Gastroenterol*. 2019;25(34):5197-5209. doi:10.3748/wjg.v25.i34.5197
29. Hijioka S, Hosoda W, Matsuo K, et al. Rb loss and KRAS mutation are predictors of the response to platinum-based chemotherapy in pancreatic neuroendocrine neoplasm with grade 3: a Japanese multicenter pancreatic NEN-G3 study. *Clin Cancer Res*. 2017;23(16):4625-4632. doi:10.1158/1078-0432.CCR-16-3135
30. Hallet J, Law C, Singh S, et al. Risk of cancer-specific death for patients diagnosed with neuroendocrine tumors: a population-based analysis. *J Natl Compr Canc Netw*. 2021;19(8):935-944. doi:10.6004/jnccn.2020.7666
31. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663. doi:10.1200/JCO.2009.22.8510
32. Caplin ME, Pavel M, Cwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233. doi:10.1056/NEJMoa1316158
33. Caplin ME, Pavel M, Phan AT, et al; CLARINET Investigators. Lanreotide autogel/depot in advanced enteropancreatic neuroendocrine tumours: final results of the CLARINET open-label extension study. *Endocrine*. 2021;71(2):502-513. doi:10.1007/s12020-020-02475-2
34. Strosberg JR, Caplin ME, Kunz PL, et al; NETTER-1 investigators. ¹⁷⁷Lu-dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021;22(12):1752-1763. doi:10.1016/S1470-2045(21)00572-6
35. Baudin E, Walter TA, Beron A, et al. 8870—first multicentric randomized phase II trial investigating the antitumor efficacy of peptide receptor radionuclide therapy with ¹⁷⁷lutetium-octreotate (OCLU) in unresectable progressive neuroendocrine pancreatic tumor: results of the OCLURANDOM trial. *Ann Oncol*. 2022;33:5410-5416. doi:10.1016/j.annonc.2022.07.1013

36. Zhang J, Kulkarni HR, Singh A, Niepsch K, Müller D, Baum RP. Peptide receptor radionuclide therapy in grade 3 neuroendocrine neoplasms: safety and survival analysis in 69 patients. *J Nucl Med*. 2019;60(3):377-385. doi:10.2967/jnumed.118.215848
37. Ezziddin S, Attassi M, Yong-Hing CJ, et al. Predictors of long-term outcome in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors after peptide receptor radionuclide therapy with ¹⁷⁷Lu-octreotate. *J Nucl Med*. 2014;55(2):183-190. doi:10.2967/jnumed.113.125336
38. Carlsen EA, Fazio N, Granberg D, et al. Peptide receptor radionuclide therapy in gastroenteropancreatic NEN G3: a multicenter cohort study. *Endocr Relat Cancer*. 2019;26(2):227-239. doi:10.1530/ERC-18-0424
39. Aalbersberg EA, Huijizing DMV, Walraven I, et al. Parameters to predict progression-free and overall survival after peptide receptor radionuclide therapy: a multivariate analysis in 782 patients. *J Nucl Med*. 2019;60(9):1259-1265. doi:10.2967/jnumed.118.224386
40. Nicolini S, Severi S, Ianniello A, et al. Investigation of receptor radionuclide therapy with ¹⁷⁷Lu-DOTATATE in patients with GEP-NEN and a high Ki-67 proliferation index. *Eur J Nucl Med Mol Imaging*. 2018;45(6):923-930. doi:10.1007/s00259-017-3925-8
41. Thang SP, Lung MS, Kong G, et al. Peptide receptor radionuclide therapy (PRRT) in European Neuroendocrine Tumour Society (ENETS) grade 3 (G3) neuroendocrine neoplasia (NEN)—a single-institution retrospective analysis. *Eur J Nucl Med Mol Imaging*. 2018;45(2):262-277. doi:10.1007/s00259-017-3821-2
42. Pusceddu S, Prinzi N, Tafuto S, et al. Association of upfront peptide receptor radionuclide therapy with progression-free survival among patients with enteropancreatic neuroendocrine tumors. *JAMA Netw Open*. 2022;5(2):e220290. doi:10.1001/jamanetworkopen.2022.0290
43. Katona BW, Roccaro GA, Soulen MC, et al. Efficacy of peptide receptor radionuclide therapy in a United States-based cohort of metastatic neuroendocrine tumor patients: single-institution retrospective analysis. *Pancreas*. 2017;46(9):1121-1126. doi:10.1097/MPA.0000000000000919
44. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine Tumors. *Clin Cancer Res*. 2017;23(16):4617-4624. doi:10.1158/1078-0432.CCR-16-2743
45. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-513. doi:10.1056/NEJMoa1003825
46. Yao JC, Shah MH, Ito T, et al; RAD001 in Advanced Neuroendocrine Tumors, Third Trial Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-523. doi:10.1056/NEJMoa1009290
47. Yao JC, Fazio N, Singh S, et al; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977. doi:10.1016/S0140-6736(15)00817-X
48. Singh S, Carnaghi C, Buzzoni R, et al; RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial Study Group. Everolimus in neuroendocrine tumors of the gastrointestinal tract and unknown primary. *Neuroendocrinology*. 2018;106(3):211-220. doi:10.1159/000477585
49. Pavel M, Öberg K, Falconi M, et al; ESMO Guidelines Committee. Gastroenteropancreatic neuroendocrine neoplasms: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(7):844-860. doi:10.1016/j.annonc.2020.03.304
50. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1980;303(21):1189-1194. doi:10.1056/NEJM198011203032101
51. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992;326(8):519-523. doi:10.1056/NEJM199202203260804
52. Halfdanarson TR, Strosberg JR, Tang L, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical management of pancreatic neuroendocrine tumors. *Pancreas*. 2020;49(7):863-881. doi:10.1097/MPA.0000000000001597
53. Salazar R, Tafuto S, Krogh M, et al. LBA45—randomized open label phase III study comparing the efficacy and safety of everolimus followed by chemotherapy (CT) with streptozotocin (STZ)-5FU upon progression or the reverse sequence, in advanced progressive panNETs: The SEQTOR study (GETNE 1206). *Ann Oncol*. 2022;33(suppl 7):S808-S869. doi:10.1016/j.annonc.2022.08.044
54. Kunz PL, Graham NT, Catalano PJ, et al. Randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors (ECOG-ACRIN E2211). *J Clin Oncol*. 2023;41(7):1359-1369. doi:10.1200/JCO.22.01013
55. Al-Toubah T, Pelle E, Valone T, Haider M, Strosberg JR. Efficacy and toxicity analysis of capecitabine and temozolomide in neuroendocrine neoplasms. *J Natl Compr Canc Netw*. 2021;20(1):29-36. doi:10.6004/jncn.2021.7017
56. Thomas K, Voros BA, Meadows-Taylor M, et al. Outcomes of capecitabine and temozolomide (CAPTEM) in advanced neuroendocrine neoplasms (NENs). *Cancers (Basel)*. 2020;12(1):206. doi:10.3390/cancers12010206
57. Chatzellis E, Angelousi A, Daskalakis K, et al. Activity and safety of standard and prolonged capecitabine/temozolomide administration in patients with advanced neuroendocrine neoplasms. *Neuroendocrinology*. 2019;109(4):333-345. doi:10.1159/000500135
58. Spada F, Maisonneuve P, Fumagalli C, et al. Temozolomide alone or in combination with capecitabine in patients with advanced neuroendocrine neoplasms: an Italian multicenter real-world analysis. *Endocrine*. 2021;72(1):268-278. doi:10.1007/s12020-020-02421-2
59. Peixoto RD, Noonan KL, Pavlovich P, Kennecke HF, Lim HJ. Outcomes of patients treated with capecitabine and temozolomide for advanced pancreatic neuroendocrine tumors (PNETs) and non-PNETs. *J Gastrointest Oncol*. 2014;5(4):247-252. doi:10.1200/jco.2014.32.3_suppl.343
60. Crespo G, Jiménez-Fonseca P, Custodio A, et al. Capecitabine and temozolomide in grade 1/2 neuroendocrine tumors: a Spanish multicenter experience. *Future Oncol*. 2017;13(7):615-624. doi:10.2217/fo-2016-0434
61. Ramirez RA, Beyer DT, Chauhan A, Boudreaux JP, Wang YZ, Woltering EA. The role of capecitabine/temozolomide in metastatic neuroendocrine tumors. *Oncologist*. 2016;21(6):671-675. doi:10.1634/theoncologist.2015-0470
62. Kim HK, Ha SY, Lee J, et al. The impact of pathologic differentiation (well/poorly) and the degree of Ki-67 index in patients with metastatic WHO grade 3 GEP-NECs. *Oncotarget*. 2017;8(43):73974-73980. doi:10.18632/oncotarget.18168
63. Lacombe C, De Rycke O, Couvelard A, et al. Biomarkers of response to etoposide-platinum chemotherapy in patients with grade 3 neuroendocrine neoplasms. *Cancers (Basel)*. 2021;13(4):643. doi:10.3390/cancers13040643
64. Raj N, Valentino E, Capanu M, et al. Treatment response and outcomes of grade 3 pancreatic neuroendocrine neoplasms based on morphology: well differentiated versus poorly differentiated. *Pancreas*. 2017;46(3):296-301. doi:10.1097/MPA.0000000000000735
65. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol*. 2013;24(1):152-160. doi:10.1093/annonc/mds276
66. Elvebakken H, Perren A, Scoazec JY, et al. A consensus-developed morphological re-evaluation of 196 high-grade gastroenteropancreatic neuroendocrine neoplasms and its clinical correlations. *Neuroendocrinology*. 2021;111(9):883-894. doi:10.1159/000511905
67. Pavel ME, Hainsworth JD, Baudin E, et al; RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378(9808):2005-2012. doi:10.1016/S0140-6736(11)61742-X
68. Pennell NA, Mutebi A, Zhou ZY, et al. Economic impact of next-generation sequencing versus single-gene testing to detect genomic alterations in metastatic non-small-cell lung cancer using a decision analytic model. *JCO Precis Oncol*. 2019;3:1-9. doi:10.1200/PO.18.00356
69. Perdrizet K, Stockley TL, Law JH, et al. Integrating comprehensive genomic sequencing of non-small cell lung cancer into a public healthcare system. *Cancer Treat Res Commun*. 2022;31:100534. doi:10.1016/j.ctarc.2022.100534
70. Samsom KG, Levy S, van Veenendaal LM, et al. Driver mutations occur frequently in metastases of well-differentiated small intestine neuroendocrine tumours. *Histopathology*. 2021;78(4):556-566. doi:10.1111/his.14252
71. Puccini A, Poorman K, Salem ME, et al. Comprehensive genomic profiling of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs). *Clin Cancer Res*. 2020;26(22):5943-5951. doi:10.1158/1078-0432.CCR-20-1804

72. Taboada R, Claro L, Felismino T, de Jesus VH, Barros M, Riechelmann RP. Clinicopathological and molecular profile of grade 3 gastroenteropancreatic neuroendocrine neoplasms. *J Neuroendocrinol*. 2022;34(4):e13099. doi:10.1111/jne.13099
73. van Riet J, van de Werken HJG, Cuppen E, et al. The genomic landscape of 85 advanced neuroendocrine neoplasms reveals subtype-heterogeneity and potential therapeutic targets. *Nat Commun*. 2021;12(1):4612. doi:10.1038/s41467-021-24812-3
74. Venizelos A, Elvebakken H, Perren A, et al. The molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer*. 2021;29(1):1-14. doi:10.1530/ERC-21-0152
75. Yachida S, Totoki Y, Noë M, et al. Comprehensive genomic profiling of neuroendocrine carcinomas of the gastrointestinal system. *Cancer Discov*. 2022;12(3):692-711. doi:10.1158/2159-8290.CD-21-0669
76. Chen L, Liu M, Zhang Y, Guo Y, Chen MH, Chen J. Genetic characteristics of colorectal neuroendocrine carcinoma: more similar to colorectal adenocarcinoma. *Clin Colorectal Cancer*. 2021;20(2):177-185.e13. doi:10.1016/j.clcc.2020.09.001
77. Lee SM, Sung CO. Comprehensive analysis of mutational and clinicopathologic characteristics of poorly differentiated colorectal neuroendocrine carcinomas. *Sci Rep*. 2021;11(1):6203. doi:10.1038/s41598-021-85593-9
78. Tanaka H, Hijioka S, Hosoda W, et al. Pancreatic neuroendocrine carcinoma G3 may be heterogeneous and could be classified into two distinct groups. *Pancreatol*. 2020;20(7):1421-1427. doi:10.1016/j.pan.2020.07.400
79. Yachida S, Vakiani E, White CM, et al. Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. *Am J Surg Pathol*. 2012;36(2):173-184. doi:10.1097/PAS.0b013e3182417d36
80. Jiao Y, Shi C, Edil BH, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science*. 2011;331(6021):1199-1203. doi:10.1126/science.1200609
81. Tang LH, Basturk O, Sue JJ, Klimstra DS. A practical approach to the classification of WHO grade 3 (G3) well-differentiated neuroendocrine tumor (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC) of the pancreas. *Am J Surg Pathol*. 2016;40(9):1192-1202. doi:10.1097/PAS.0000000000000662
82. Scarpa A, Chang DK, Nones K, et al; Australian Pancreatic Cancer Genome Initiative. Whole-genome landscape of pancreatic neuroendocrine tumours. *Nature*. 2017;543(7643):65-71. doi:10.1038/nature21063
83. Li K, Liu Y, Han J, Gui J, Zhang X. The genetic alterations of rectal neuroendocrine tumor and indications for therapy and prognosis: a systematic review. *Endocr J*. 2022;70(2):197-205.
84. Elvebakken H, Hjortland GO, Garresori H, et al. Impact of KRAS and BRAF mutations on treatment efficacy and survival in high-grade gastroenteropancreatic neuroendocrine neoplasms. *J Neuroendocrinol*. 2023;35(4):e13256. doi:10.1111/jne.13256
85. Cejas P, Drier Y, Dreijerink KMA, et al. Enhancer signatures stratify and predict outcomes of non-functional pancreatic neuroendocrine tumors. *Nat Med*. 2019;25(8):1260-1265. doi:10.1038/s41591-019-0493-4
86. Di Domenico A, Pipinikas CP, Maire RS, et al. Epigenetic landscape of pancreatic neuroendocrine tumours reveals distinct cells of origin and means of tumour progression. *Commun Biol*. 2020;3(1):740. doi:10.1038/s42003-020-01479-y
87. Missiaglia E, Dalai I, Barbi S, et al. Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. *J Clin Oncol*. 2010;28(2):245-255. doi:10.1200/JCO.2008.21.5988
88. Yang KC, Kalloger SE, Aird JJ, et al. Proteotranscriptomic classification and characterization of pancreatic neuroendocrine neoplasms. *Cell Rep*. 2021;37(2):109817. doi:10.1016/j.celrep.2021.109817
89. Malmström A, Grønberg BH, Marosi C, et al; Nordic Clinical Brain Tumour Study Group (NCBTSG). Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol*. 2012;13(9):916-926. doi:10.1016/S1470-2045(12)70265-6
90. Wick W, Platten M, Meisner C, et al; NOA-08 Study Group of Neuro-oncology Working Group of German Cancer Society. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncol*. 2012;13(7):707-715. doi:10.1016/S1470-2045(12)70164-X
91. Trillo Aliaga P, Spada F, Peveri G, et al. Should temozolomide be used on the basis of O⁶-methylguanine DNA methyltransferase status in patients with advanced neuroendocrine tumors? a systematic review and meta-analysis. *Cancer Treat Rev*. 2021;99:102261. doi:10.1016/j.ctrv.2021.102261
92. Jeong H, Shin J, Jeong JH, et al. Capecitabine plus temozolomide in patients with grade 3 unresectable or metastatic gastroenteropancreatic neuroendocrine neoplasms with Ki-67 index <55%: single-arm phase II study. *ESMO Open*. 2021;6(3):100119. doi:10.1016/j.esmoop.2021.100119
93. Brighi N, Lamberti G, Andriani E, et al. Prospective evaluation of MGMT-promoter methylation status and correlations with outcomes to temozolomide-based chemotherapy in well-differentiated neuroendocrine tumors. *Curr Oncol*. 2023;30(2):1381-1394. doi:10.3390/curroncol30020106
94. Brunner P, Jörg AC, Glatz K, et al. The prognostic and predictive value of sstr₂-immunohistochemistry and sstr₂-targeted imaging in neuroendocrine tumors. *Eur J Nucl Med Mol Imaging*. 2017;44(3):468-475. doi:10.1007/s00259-016-3486-2
95. Nielsen K, Binderup T, Langer SW, et al. P53, somatostatin receptor 2a and chromogranin A immunostaining as prognostic markers in high grade gastroenteropancreatic neuroendocrine neoplasms. *BMC Cancer*. 2020;20(1):27. doi:10.1186/s12885-019-6498-z
96. Qian ZR, Li T, Ter-Minassian M, et al. Association between somatostatin receptor expression and clinical outcomes in neuroendocrine tumors. *Pancreas*. 2016;45(10):1386-1393. doi:10.1097/MPA.0000000000000700
97. Sundin A, Arnold R, Baudin E, et al; Antibes Consensus Conference participants. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine & hybrid imaging. *Neuroendocrinology*. 2017;105(3):212-244. doi:10.1159/000471879
98. Fröjd C, Larsson G, Lampic C, von Essen L. Health related quality of life and psychosocial function among patients with carcinoid tumours: a longitudinal, prospective, and comparative study. *Health Qual Life Outcomes*. 2007;5(1):18. doi:10.1186/1477-7525-5-18
99. Deppen SA, Blume J, Bobbey AJ, et al. 68Ga-DOTATATE compared with 111In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. *J Nucl Med*. 2016;57(6):872-878. doi:10.2967/jnumed.115.165803
100. Johnbeck CB, Knigge U, Kjær A. PET tracers for somatostatin receptor imaging of neuroendocrine tumors: current status and review of the literature. *Future Oncol*. 2014;10(14):2259-2277. doi:10.2217/fo.14.139
101. Carlsen EA, Johnbeck CB, Binderup T, et al. ⁶⁴Cu-DOTATATE PET/CT and prediction of overall and progression-free survival in patients with neuroendocrine neoplasms. *J Nucl Med*. 2020;61(10):1491-1497. doi:10.2967/jnumed.119.240143
102. Johnbeck CB, Knigge U, Loft A, et al. Head-to-head comparison of ⁶⁴Cu-DOTATATE and ⁶⁸Ga-DOTATOC PET/CT: a prospective study of 59 patients with neuroendocrine tumors. *J Nucl Med*. 2017;58(3):451-457. doi:10.2967/jnumed.116.180430
103. Ambrosini V, Campana D, Polverari G, et al. Prognostic value of 68Ga-DOTANOC PET/CT SUV_{max} in patients with neuroendocrine tumors of the pancreas. *J Nucl Med*. 2015;56(12):1843-1848. doi:10.2967/jnumed.115.162719
104. Campana D, Ambrosini V, Pezzilli R, et al. Standardized uptake values of (68)Ga-DOTANOC PET: a promising prognostic tool in neuroendocrine tumors. *J Nucl Med*. 2010;51(3):353-359. doi:10.2967/jnumed.109.066662
105. Sharma P, Naswa N, Kc SS, et al. Comparison of the prognostic values of 68Ga-DOTANOC PET/CT and 18F-FDG PET/CT in patients with well-differentiated neuroendocrine tumor. *Eur J Nucl Med Mol Imaging*. 2014;41(12):2194-2202. doi:10.1007/s00259-014-2850-3
106. Tirosh A, Papadakis GZ, Millo C, et al. Association between neuroendocrine tumors biomarkers and primary tumor site and disease type based on total ⁶⁸Ga-DOTATATE-Avid tumor volume measurements. *Eur J Endocrinol*. 2017;176(5):575-582. doi:10.1530/EJE-16-1079
107. Toriihara A, Baratto L, Nobashi T, et al. Prognostic value of somatostatin receptor expressing tumor volume calculated from ⁶⁸Ga-DOTATATE PET/CT in patients with well-differentiated neuroendocrine tumors. *Eur J Nucl Med Mol Imaging*. 2019;46(11):2244-2251. doi:10.1007/s00259-019-04455-9
108. Koch W, Auernhammer CJ, Geisler J, et al. Treatment with octreotide in patients with well-differentiated neuroendocrine tumors of the ileum: prognostic stratification with Ga-68-DOTA-TATE positron emission tomography. *Molecular Imaging*. 2014;13(4):7290.2014.00009.

109. Lee H, Eads JR, Pryma DA. ⁶⁸Ga-DOTATATE positron emission tomography-computed tomography quantification predicts response to somatostatin analog therapy in gastroenteropancreatic neuroendocrine tumors. *Oncologist*. 2021;26(1):21-29. doi:10.1634/theoncologist.2020-0165
110. Lee ONY, Tan KV, Tripathi V, Yuan H, Chan WW, Chiu KWH. The role of ⁶⁸Ga-DOTA-SSA PET/CT in the management and prediction of peptide receptor radionuclide therapy response for patients with neuroendocrine tumors: a systematic review and meta-analysis. *Clin Nucl Med*. 2022;47(9):781-793. doi:10.1097/RLU.0000000000004235
111. Durmo R, Filice A, Fioroni F, et al. Predictive and prognostic role of pre-therapy and interim ⁶⁸Ga-DOTATOC PET/CT parameters in metastatic advanced neuroendocrine tumor patients treated with PRRT. *Cancers (Basel)*. 2022;14(3):592. doi:10.3390/cancers14030592
112. Ohlendorf F, Henkenberens C, Brunkhorst T, et al. Volumetric ⁶⁸Ga-DOTA-TATE PET/CT for assessment of whole-body tumor burden as a quantitative imaging biomarker in patients with metastatic gastroenteropancreatic neuroendocrine tumors. *Q J Nucl Med Mol Imaging*. 2022;66(4):361-371. doi:10.23736/S1824-4785.20.03238-0
113. Sitani K, Parghane RV, Talole S, Basu S. Long-term outcome of indigenous ¹⁷⁷Lu-DOTATATE PRRT in patients with metastatic advanced neuroendocrine tumours: a single institutional observation in a large tertiary care setting. *Br J Radiol*. 2021;94(1117):20201041. doi:10.1259/bjr.20201041
114. Adams MC, Turkington TG, Wilson JM, Wong TZ. A systematic review of the factors affecting accuracy of SUV measurements. *AJR Am J Roentgenol*. 2010;195(2):310-320. doi:10.2214/AJR.10.4923
115. Reubi JC, Kvols LK, Waser B, et al. Detection of somatostatin receptors in surgical and percutaneous needle biopsy samples of carcinoids and islet cell carcinomas. *Cancer Res*. 1990;50(18):5969-5977.
116. Squires MH III, Volkan Adsay N, Schuster DM, et al. Octreoscan versus FDG-PET for neuroendocrine tumor staging: a biological approach. *Ann Surg Oncol*. 2015;22(7):2295-2301. doi:10.1245/s10434-015-4471-x
117. Hope TA, Bergsland EK, Bozkurt MF, et al. Appropriate use criteria for somatostatin receptor PET imaging in neuroendocrine tumors. *J Nucl Med*. 2018;59(1):66-74. doi:10.2967/jnumed.117.202275
118. Hope TA, Allen-Auerbach M, Bodei L, et al. SNMMI procedure standard/EANM practice guideline for SSTR PET: imaging neuroendocrine tumors. *J Nucl Med*. 2023;64(2):204-210. doi:10.2967/jnumed.122.264860
119. Bahri H, Laurence L, Edeline J, et al. High prognostic value of ¹⁸F-FDG PET for metastatic gastroenteropancreatic neuroendocrine tumors: a long-term evaluation. *J Nucl Med*. 2014;55(11):1786-1790. doi:10.2967/jnumed.114.144386
120. Gabriel M, Oberauer A, Dobrozemsky G, et al. ⁶⁸Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. *J Nucl Med*. 2009;50(9):1427-1434. doi:10.2967/jnumed.108.053421
121. Han S, Lee HS, Woo S, et al. Prognostic value of ¹⁸F-FDG PET in neuroendocrine neoplasm: a systematic review and meta-analysis. *Clin Nucl Med*. 2021;46(9):723-731. doi:10.1097/RLU.0000000000003682
122. Binderup T, Knigge U, Johnbeck CB, et al. ¹⁸F-FDG PET is superior to WHO grading as a prognostic tool in neuroendocrine neoplasms and useful in guiding PRRT: a prospective 10-year follow-up study. *J Nucl Med*. 2021;62(6):808-815. doi:10.2967/jnumed.120.244798
123. Langen Stokmo H, Aly M, Bowitz Lothe IM, et al. Volumetric parameters from [¹⁸F]FDG PET/CT predicts survival in patients with high-grade gastroenteropancreatic neuroendocrine neoplasms. *J Neuroendocrinol*. 2022;34(7):e13170. doi:10.1111/jne.13170
124. Magi L, Prosperi D, Lamberti G, et al. Role of [¹⁸F]FDG PET/CT in the management of G1 gastro-entero-pancreatic neuroendocrine tumors. *Endocrine*. 2022;76(2):484-490. doi:10.1007/s12020-022-03000-3
125. Alevroudis E, Spei ME, Chatziannou SN, et al. Clinical utility of ¹⁸F-FDG PET in neuroendocrine tumors prior to peptide receptor radionuclide therapy: a systematic review and meta-analysis. *Cancers (Basel)*. 2021;13(8):1813. doi:10.3390/cancers13081813
126. Laffi A, Colandrea M, Buonsanti G, et al. A retrospective analysis of the correlation between functional imaging and clinical outcomes in grade 3 neuroendocrine tumors (NETs G3). *Diagnostics (Basel)*. 2021;11(12):2401. doi:10.3390/diagnostics11122401
127. Zhang J, Liu Q, Singh A, Schuchardt C, Kulkarni HR, Baum RP. Prognostic value of ¹⁸F-FDG PET/CT in a large cohort of patients with advanced metastatic neuroendocrine neoplasms treated with peptide receptor radionuclide therapy. *J Nucl Med*. 2020;61(11):1560-1569. doi:10.2967/jnumed.119.241414
128. Nilica B, Waitz D, Stevanovic V, et al. Direct comparison of (⁶⁸Ga)-DOTA-TOC and (¹⁸F)-FDG PET/CT in the follow-up of patients with neuroendocrine tumour treated with the first full peptide receptor radionuclide therapy cycle. *Eur J Nucl Med Mol Imaging*. 2016;43(9):1585-1592. doi:10.1007/s00259-016-3328-2
129. Laffi A, Spada F, Barnardi V, et al. Gastroenteropancreatic grade 3 neuroendocrine tumors: a single entity or a heterogeneous group? a retrospective analysis. *J Endocrinol Invest*. 2022;45(2):317-325. doi:10.1007/s40618-021-01642-0
130. Chan DL, Hayes AR, Karfis I, et al. Dual [(⁶⁸Ga)]DOTATATE and [(¹⁸F)]FDG PET/CT in patients with metastatic gastroenteropancreatic neuroendocrine neoplasms: a multicentre validation of the NETPET score. *Br J Cancer*. 2023;128(4):549-555.
131. Chan DL, Pavlakis N, Schembri GP, et al. Dual somatostatin receptor/FDG PET/CT imaging in metastatic neuroendocrine tumours: proposal for a novel grading scheme with prognostic significance. *Theranostics*. 2017;7(5):1149-1158. doi:10.7150/thno.18068
132. Hayes AR, Furtado O'Mahony L, Quigley AM, et al. The combined interpretation of ⁶⁸Ga-DOTATATE PET/CT and ¹⁸F-FDG PET/CT in metastatic gastroenteropancreatic neuroendocrine tumors: a classification system with prognostic impact. *Clin Nucl Med*. 2022;47(1):26-35. doi:10.1097/RLU.0000000000003937
133. Vasconcelos JPS, Zhou M, Ravi P, et al. Prospective evaluation of the utility of concurrent ¹⁸F-FDG PET/CT and ⁶⁸Ga-DOTA-TOC imaging in gastroenteropancreatic neuroendocrine neoplasms (GEPNENs): The PETNET study. *J Clin Oncol*. 2023;41(16)(suppl):4022-4022. doi:10.1200/JCO.2023.41.16_suppl.4022
134. Daskalakis K. Functioning and nonfunctioning pNENs. *Curr Opin Endocr Metab Res*. 2021;18:284-290. doi:10.1016/j.coemr.2021.04.007
135. Falconi M, Eriksson B, Kaltsas G, et al; Vienna Consensus Conference participants. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology*. 2016;103(2):153-171. doi:10.1159/000443171
136. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *Lancet Oncol*. 2017;18(4):525-534. doi:10.1016/S1473-0245(17)30110-9
137. Lundin L, Norheim I, Landelius J, Oberg K, Theodorsson-Norheim E. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities. *Circulation*. 1988;77(2):264-269. doi:10.1161/01.CIR.77.2.264
138. Møller JE, Connolly HM, Rubin J, Seward JB, Modesto K, Pellikka PA. Factors associated with progression of carcinoid heart disease. *N Engl J Med*. 2003;348(11):1005-1015. doi:10.1056/NEJMoa021451
139. Møller JE, Pellikka PA, Bernheim AM, Schaff HV, Rubin J, Connolly HM. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. *Circulation*. 2005;112(21):3320-3327. doi:10.1161/CIRCULATIONAHA.105.553750
140. Ram P, Penalver JL, Lo KBU, Rangaswami J, Pressman GS. Carcinoid heart disease: review of current knowledge. *Tex Heart Inst J*. 2019;46(1):21-27. doi:10.14503/THIJ-17-6562
141. Oberg K, Couvelard A, Delle Fave G, et al; Antibes Consensus Conference participants. ENETS consensus guidelines for standard of care in neuroendocrine tumours: biochemical markers. *Neuroendocrinology*. 2017;105(3):201-211. doi:10.1159/000472254
142. de Mestier L, Savagner F, Brixi H, et al. Plasmatic and urinary 5-hydroxyindoleacetic acid measurements in patients with midgut neuroendocrine tumors: a GTE study. *J Clin Endocrinol Metab*. 2021;106(4):e1673-e1682. doi:10.1210/clinem/dga924
143. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical management of midgut neuroendocrine tumors. *Pancreas*. 2017;46(6):707-714. doi:10.1097/MPA.0000000000000850
144. Wedin M, Mehta S, Angeräs-Kraftling J, Wallin G, Daskalakis K. The role of serum 5-HIAA as a predictor of progression and an alternative to 24-h Urine 5-HIAA in well-differentiated neuroendocrine neoplasms. *Biology (Basel)*. 2021;10(2):76. doi:10.3390/biology10020076
145. Adaway JE, Dobson R, Walsh J, et al; Annals of Clinical Biochemistry. Serum and plasma 5-hydroxyindoleacetic acid as an alternative to 24-h

- urine 5-hydroxyindoleacetic acid measurement. *Ann Clin Biochem*. 2016;53(Pt 5):554-560. doi:10.1177/0004563215613109
146. Becker A, Schalin-Jäntti C, Itkonen O. Comparison of serum and urinary 5-hydroxyindoleacetic acid as biomarker for neuroendocrine neoplasms. *J Endocr Soc*. 2021;5(8):bvab106. doi:10.1210/jeendo/bvab106
147. Grozinsky-Glasberg S, Davar J, Hofland J, et al. European Neuroendocrine Tumor Society (ENETS) 2022 guidance paper for carcinoid syndrome and carcinoid heart disease. *J Neuroendocrinol*. 2022;34(7):e13146. doi:10.1111/jne.13146
148. Jann H, Roll S, Couvelard A, et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. *Cancer*. 2011;117(15):3332-3341. doi:10.1002/cncr.25855
149. Janson ET, Holmberg L, Stridsberg M, et al. Carcinoid tumors: analysis of prognostic factors and survival in 301 patients from a referral center. *Ann Oncol*. 1997;8(7):685-690. doi:10.1023/A:1008215730767
150. Zandee WT, Kamp K, van Ardicem RC, Feelders RA, de Herder WW. Limited value for urinary 5-HIAA excretion as prognostic marker in gastrointestinal neuroendocrine tumours. *Eur J Endocrinol*. 2016;175(5):361-366. doi:10.1530/EJE-16-0392
151. Turner GB, Johnston BT, McCance DR, et al. Circulating markers of prognosis and response to treatment in patients with midgut carcinoid tumours. *Gut*. 2006;55(11):1586-1591. doi:10.1136/gut.2006.092320
152. van der Horst-Schrivers AN, Post WJ, Kema IP, et al. Persistent low urinary excretion of 5-HIAA is a marker for favourable survival during follow-up in patients with disseminated midgut carcinoid tumours. *Eur J Cancer*. 2007;43(18):2651-2657. doi:10.1016/j.ejca.2007.07.025
153. Laskaratos FM, Diamantopoulos L, Walker M, et al. Prognostic factors for survival among patients with small bowel neuroendocrine tumours associated with mesenteric desmoplasia. *Neuroendocrinology*. 2018;106(4):366-380. doi:10.1159/000486097
154. Formica V, Wotherspoon A, Cunningham D, et al. The prognostic role of WHO classification, urinary 5-hydroxyindoleacetic acid and liver function tests in metastatic neuroendocrine carcinomas of the gastroenteropancreatic tract. *Br J Cancer*. 2007;96(8):1178-1182. doi:10.1038/sj.bjc.6603699
155. Bergestuen DS, Aabakken L, Holm K, Vatn M, Thiis-Evensen E. Small intestinal neuroendocrine tumors: prognostic factors and survival. *Scand J Gastroenterol*. 2009;44(9):1084-1091. doi:10.1080/00365520903082432
156. Pearman TP, Beaumont JL, Cella D, Neary MP, Yao J. Health-related quality of life in patients with neuroendocrine tumors: an investigation of treatment type, disease status, and symptom burden. *Support Care Cancer*. 2016;24(9):3695-3703. doi:10.1007/s00520-016-3189-z
157. Westberg G, Wängberg B, Ahlman H, Bergh CH, Beckman-Suurkula M, Caidahl K. Prediction of prognosis by echocardiography in patients with midgut carcinoid syndrome. *Br J Surg*. 2001;88(6):865-872. doi:10.1046/j.0007-1323.2001.01798.x
158. Bhattacharyya S, Toumpanakis C, Chilkunda D, Caplin ME, Davar J. Risk factors for the development and progression of carcinoid heart disease. *Am J Cardiol*. 2011;107(8):1221-1226. doi:10.1016/j.amjcard.2010.12.025
159. Buchanan-Hughes A, Pashley A, Feuille M, Marteau F, Pritchard DM, Singh S. Carcinoid heart disease: prognostic value of 5-hydroxyindoleacetic acid levels and impact on survival: a systematic literature review. *Neuroendocrinology*. 2021;111(1-2):1-15. doi:10.1159/000506744
160. Modlin IM, Pavel M, Kidd M, Gustafsson BI. Review article: somatostatin analogs in the treatment of gastro-entero-pancreatic neuroendocrine (carcinoid) tumors. *Aliment Pharmacol Ther*. 2010;31(2):169-188. doi:10.1111/j.1365-2036.2009.04174.x
161. Mirakhor B, Pavel ME, Pommier RF, et al. Biochemical responses in symptomatic and asymptomatic patients with neuroendocrine tumors: Pooled analysis of 2 phase 3 trials. *Endocr Pract*. 2018. doi:10.4158/EP-2018-0296
162. Pavel ME, Phan AT, Wolin EM, et al; CLARINET Study Investigators. Effect of lanreotide depot/autogel on urinary 5-hydroxyindoleacetic acid and plasma chromogranin A biomarkers in nonfunctional metastatic enteropancreatic neuroendocrine tumors. *Oncologist*. 2019;24(4):463-474. doi:10.1634/theoncologist.2018-0217
163. Hofland J, Herrera-Martinez AD, Zandee WT, de Herder WW. Management of carcinoid syndrome: a systematic review and meta-analysis. *Endocr Relat Cancer*. 2019;26(3):R145-R156. doi:10.1530/ERC-18-0495
164. Riechelmann RP, Pereira AA, Rego JF, Costa FP. Refractory carcinoid syndrome: a review of treatment options. *Ther Adv Med Oncol*. 2017;9(2):127-137. doi:10.1177/1758834016675803
165. Kulke MH, Hörsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2017;35(1):14-23. doi:10.1200/JCO.2016.69.2780
166. Levy S, Korse CE, de Groot ACA, Meijer RCA, Tesselar MET, Valk GD. Four decades of experience with carcinoid heart disease: an analysis of 84 patients. *J Neuroendocrinol*. 2022;34(10):e13199. doi:10.1111/jne.13199
167. Singh S, Asa SL, Dey C, et al. Diagnosis and management of gastrointestinal neuroendocrine tumors: an evidence-based Canadian consensus. *Cancer Treat Rev*. 2016;47:32-45. doi:10.1016/j.ctrv.2016.05.003
168. National Comprehensive Cancer Network. Neuroendocrine and adrenal tumours clinical practice guidelines in oncology—version 2.2022. Accessed March 1, 2022. <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1448>
169. Dobson R, Burgess MI, Banks M, et al. The association of a panel of biomarkers with the presence and severity of carcinoid heart disease: a cross-sectional study. *PLoS One*. 2013;8(9):e73679. doi:10.1371/journal.pone.0073679
170. Bhattacharyya S, Toumpanakis C, Caplin ME, Davar J. Usefulness of N-terminal pro-brain natriuretic peptide as a biomarker of the presence of carcinoid heart disease. *Am J Cardiol*. 2008;102(7):938-942. doi:10.1016/j.amjcard.2008.05.047
171. Korse CM, Taal BG, de Groot CA, Bakker RH, Bonfrer JMG. Chromogranin-A and N-terminal pro-brain natriuretic peptide: an excellent pair of biomarkers for diagnostics in patients with neuroendocrine tumor. *J Clin Oncol*. 2009;27(26):4293-4299. doi:10.1200/JCO.2008.18.7047
172. Levy S, Kilgallen AB, Korse CM, et al. Elevated serotonin and NT-proBNP levels predict and detect carcinoid heart disease in a large validation study. *Cancers (Basel)*. 2022;14(10):2361. doi:10.3390/cancers14102361
173. Yao JC, Pavel M, Phan AT, et al. Chromogranin A and neuron-specific enolase as prognostic markers in patients with advanced pNET treated with everolimus. *J Clin Endocrinol Metab*. 2011;96(12):3741-3749. doi:10.1210/jc.2011-0666
174. Yao JC, Pavel M, Lombard-Bohas C, et al. Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: overall survival and circulating biomarkers from the randomized, phase III RADIANT-3 study. *J Clin Oncol*. 2016;34(32):3906-3913. doi:10.1200/JCO.2016.68.0702
175. Kečkėš Š, Palaj J, Waczulíková I, et al. Pretreatment levels of chromogranin A and neuron-specific enolase in patients with gastroenteropancreatic neuroendocrine neoplasia. *In Vivo*. 2021;35(5):2863-2868. doi:10.21873/invivo.12574
176. Sharma N, Naraev BG, Engelman EG, et al. Peptide receptor radionuclide therapy outcomes in a North American cohort with metastatic well-differentiated neuroendocrine tumors. *Pancreas*. 2017;46(2):151-156. doi:10.1097/MPA.0000000000000734
177. Arnold R, Wilke A, Rinke A, et al. Plasma chromogranin A as marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors. *Clin Gastroenterol Hepatol*. 2008;6(7):820-827. doi:10.1016/j.cgh.2008.02.052
178. Chou WC, Chen JS, Hung YS, et al. Plasma chromogranin A levels predict survival and tumor response in patients with advanced gastroenteropancreatic neuroendocrine tumors. *Anticancer Res*. 2014;34(10):5661-5669.
179. Fuksiewicz M, Kowalska M, Kolańska-Ćwikła A, et al. Prognostic value of chromogranin A in patients with GET/NEN in the pancreas and the small intestine. *Endocr Connect*. 2018;7(6):803-810. doi:10.1530/EC-18-0059
180. Pulvirenti A, Rao D, McIntyre CA, et al. Limited role of chromogranin A as clinical biomarker for pancreatic neuroendocrine tumors. *HPB (Oxford)*. 2019;21(5):612-618. doi:10.1016/j.hpb.2018.09.016
181. Tian T, Gao J, Li N, et al. Circulating chromogranin A as a marker for monitoring clinical response in advanced gastroenteropancreatic neuroendocrine tumors. *PLoS One*. 2016;11(5):e0154679. doi:10.1371/journal.pone.0154679
182. Walter T, Chardon L, Chopin-laly X, et al. Is the combination of chromogranin A and pancreatic polypeptide serum determinations of interest in the diagnosis and follow-up of gastro-entero-pancreatic neuroendocrine tumours? *Eur J Cancer*. 2012;48(12):1766-1773. doi:10.1016/j.ejca.2011.11.005
183. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res*. 2008;14(23):7798-7803. doi:10.1158/1078-0432.CCR-08-0734
184. Rossi RE, Ciafardini C, Sciola V, Conte D, Massironi S. Chromogranin A in the follow-up of gastroenteropancreatic neuroendocrine

- neoplasms: is it really game over? a systematic review and meta-analysis. *Pancreas*. 2018;47(10):1249-1255. doi:10.1097/MPA.0000000000001184
- 185.** Stronge RL, Turner GB, Johnston BT, et al. A rapid rise in circulating pancreastatin in response to somatostatin analogue therapy is associated with poor survival in patients with neuroendocrine tumours. *Ann Clin Biochem*. 2008;45(Pt 6):560-566. doi:10.1258/acb.2008.008033
- 186.** Strosberg D, Schneider EB, Onesti J, et al. Prognostic impact of serum pancreastatin following chemoembolization for neuroendocrine tumors. *Ann Surg Oncol*. 2018;25(12):3613-3620. doi:10.1245/s10434-018-6741-x
- 187.** Bloomston M, Al-Saif O, Klemanski D, et al. Hepatic artery chemoembolization in 122 patients with metastatic carcinoid tumor: lessons learned. *J Gastrointest Surg*. 2007;11(3):264-271. doi:10.1007/s11605-007-0089-z
- 188.** Ezziddin S, Khalaf F, Vanezi M, et al. Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2014;41(5):925-933. doi:10.1007/s00259-013-2677-3
- 189.** Öberg K, Califano A, Strosberg JR, et al. A meta-analysis of the accuracy of a neuroendocrine tumor mRNA genomic biomarker (NETest) in blood. *Ann Oncol*. 2020;31(2):202-212. doi:10.1016/j.annonc.2019.11.003
- 190.** Liu E, Paulson S, Gulati A, et al. Assessment of NETest clinical utility in a U.S. registry-based study. *Oncologist*. 2019;24(6):783-790. doi:10.1634/theoncologist.2017-0623
- 191.** Pavel M, Jann H, Prasad V, Drozdov I, Modlin IM, Kidd M. NET blood transcript analysis defines the crossing of the clinical rubicon: when stable disease becomes progressive. *Neuroendocrinology*. 2017;104(2):170-182. doi:10.1159/000446025
- 192.** Ćwikła JB, Bodei L, Kolasinska-Ćwikła 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:10.1210/jc.2015-2792
- 193.** van Treijen MJC, van der Zee D, Heeres BC, et al. Blood molecular genomic analysis predicts the disease course of gastroenteropancreatic neuroendocrine tumor patients: a validation study of the predictive value of the NETest. *Neuroendocrinology*. 2021;111(6):586-598. doi:10.1159/000509091
- 194.** Bodei L, Kidd MS, Singh A, et al. PRRT neuroendocrine tumor response monitored using circulating transcript analysis: the NETest. *Eur J Nucl Med Mol Imaging*. 2020;47(4):895-906. doi:10.1007/s00259-019-04601-3
- 195.** Malczewska A, Witkowska M, Makulik K, et al. NETest liquid biopsy is diagnostic of small intestine and pancreatic neuroendocrine tumors and correlates with imaging. *Endocr Connect*. 2019;8(4):442-453. doi:10.1530/EC-19-0030
- 196.** Bodei L, Raj N, Do RK, et al. Interim analysis of a prospective validation of 2 blood-based genomic assessments (PPQ and NETest) to determine clinical efficacy of (177)Lu-DOTATATE in neuroendocrine tumors. *J Nucl Med*. 2023;64(4):567-573.
- 197.** Mandair D, Khan MS, Lopes A, et al. Prognostic threshold for circulating tumor cells in patients with pancreatic and midgut neuroendocrine tumors. *J Clin Endocrinol Metab*. 2021;106(3):872-882. doi:10.1210/clinem/dgaa822
- 198.** Meyer T, Caplin M, Khan MS, et al. Circulating tumour cells and tumour biomarkers in functional midgut neuroendocrine tumours. *J Neuroendocrinol*. 2022;34(4):e13096. doi:10.1111/jne.13096
- 199.** Khan MS, Kirkwood AA, Tsigani T, et al. Early changes in circulating tumor cells are associated with response and survival following treatment of metastatic neuroendocrine neoplasms. *Clin Cancer Res*. 2016;22(1):79-85. doi:10.1158/1078-0432.CCR-15-1008
- 200.** Boons G, Vandamme T, Mariën L, et al. Longitudinal copy-number alteration analysis in plasma cell-free DNA of neuroendocrine neoplasms is a novel specific biomarker for diagnosis, prognosis, and follow-up. *Clin Cancer Res*. 2022;28(2):338-349. doi:10.1158/1078-0432.CCR-21-2291
- 201.** Hsieh JCH, Chen GY, Jhou DDW, et al. The prognostic value of circulating tumor cells in Asian neuroendocrine tumors. *Sci Rep*. 2019;9(1):19917. doi:10.1038/s41598-019-56539-z