Online Supplement

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

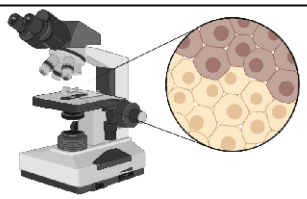
eAppendix 1 Know your NET (neuroendocrine tumor)

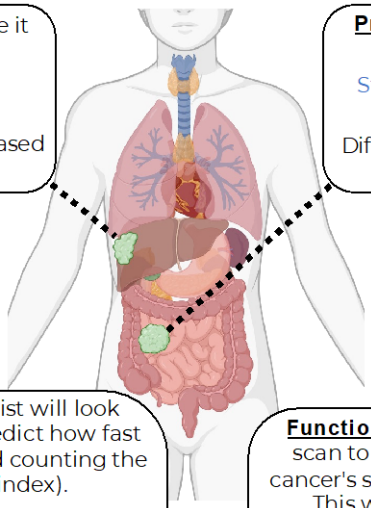
KNOW YOUR NET (NEUROENDOCRINE TUMOR)

Stage: Has the cancer spread from where it started? (circle one) yes / no

If yes: the cancer is metastatic
If no: the cancer is localized

The goals of treatment may be different based on where a cancer has spread.

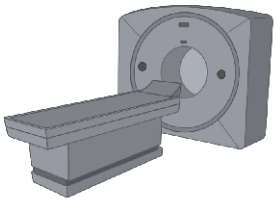




Primary Site: Where did your cancer start? (circle one)

Stomach, small intestine, pancreas, colon, rectum, other: _____

Different surgeries and medications are used depending on where the cancer starts.



Grade and Differentiation: A pathologist will look at your NET under the microscope to predict how fast it is growing using a stain called Ki67 and counting the number of cells dividing (mitotic index).

This assigns the grade based on the table below. They will also look at whether the cancer cells have lost their normal appearance and become poorly differentiated. Poorly differentiated cancers are faster growing. This information is available in a pathology report.

My cancer's Ki67 (%): _____
My cancer's mitotic index: _____
My cancer's differentiation: (circle one)
well differentiated / poorly differentiated

Grade	Mitotic count (2 mm²/10 HPF)	Ki-67 index (%)
Grade 1	<2	<3%
Grade 2	2-20	3-20%
Grade 3	>20	>20%

Functional Imaging: You may have an SSTR-PET scan to look for somatostatin receptors on your cancer's surface if your cancer is well differentiated. This will help determine treatment options.

My tumor: (circle one) did / did not have somatostatin receptors detected.

You may also have a different PET scan to see how fast your cancer is growing, called an FDG scan. If you had one, was the FDG scan positive? (circle one) yes / no

Hormone Secretion: Some NETs make hormones that cause symptoms. You may need a urine or blood test to detect this.

My tumor makes: (circle one) no hormones, serotonin, insulin, gastrin, glucagon, VIP, other: _____

If your NET makes serotonin, it can affect the heart and ultrasounds of the heart may be needed.

My heart ultrasound was: (circle one) normal / abnormal
Date of ultrasound: _____

There are many pieces of information about you and your cancer that will make a treatment plan. Use this sheet to keep track of the key features of your cancer to help discussions with your medical team. Your team will also consider things like your age, other health issues, symptoms from the cancer and past cancer treatments to come up with the best plan for you.

eAppendix 2 Understanding the importance of treating carcinoid heart disease

UNDERSTANDING CARCINOID HEART DISEASE: PREVENTION, MONITORING & TREATMENT

Did you know?

Carcinoid heart disease is a serious condition that can affect individuals with neuroendocrine tumors (NETs). This patient information sheet aims to provide you with valuable information about carcinoid heart disease, its importance, and the treatment options available. Ask your provider if your NET makes these hormones.

What is Carcinoid Heart Disease?

Carcinoid heart disease is a condition that occurs when a NET releases substances into the bloodstream, including serotonin and other bioactive hormones. These substances affect the heart valves, leading to thickening, stiffness, and valve leakage. Untreated carcinoid heart disease can lead to heart failure, which can be life-threatening. Not all NETs make the hormones which cause carcinoid heart disease.

Preventing & Reducing Heart Valve Damage: Treatment with somatostatin analogues (SSAs) can reduce how much hormone is made if your NET produces substances that put you at risk of carcinoid heart disease. This will help prevent carcinoid heart disease. Sometimes you may also need to have your treatment changed to reduce the amount of cancer in your body if SSAs cannot sufficiently reduce hormone levels.

What are the Symptoms of Carcinoid Heart Disease? Initially, there may be no symptoms when the heart valve still works relatively well. Over time, you could develop shortness of breath, tiredness, and swelling in your legs as damage to the heart becomes more serious.

How is Carcinoid Heart Disease Diagnosed: If your NET makes hormones that put you at risk for carcinoid heart disease, you will receive ultrasounds of your heart to monitor for changes. An ultrasound of the heart takes place in a health care facility as an outpatient and takes 30-60 minutes to complete. During the procedure, some gel will be placed on your skin and an ultrasound probe will be moved around your chest to look at the heart from different angles. They may ask you to move around on a hospital bed during the procedure. The frequency of these ultrasounds will depend on how your heart looks on the first ultrasound, the amount of hormone your cancer makes, and other features your healthcare provider will discuss with you. You may also undergo a special blood test called a b-type natriuretic peptide (BNP), which can identify if pressures in the heart are rising, a potential sign of carcinoid heart disease.

Treatment Options After the Heart is Damaged:

1. **Medications:** In addition to SSAs that reduce hormone levels, your healthcare provider may prescribe medications to manage the symptoms of carcinoid heart disease. These medications may include diuretics to reduce fluid retention and heart medications to improve heart function.
2. **Surgery:** In advanced cases, surgical interventions may be necessary to repair or replace damaged heart valves.
3. **Lifestyle Changes**: Adopting a heart-healthy lifestyle is essential for managing carcinoid heart disease. This may include dietary modifications, exercise, and stress reduction to support overall cardiovascular health.

eAppendix 3 Understanding hormones produced by neuroendocrine tumors and diagnostic testing

UNDERSTANDING HORMONES PRODUCED BY NEUROENDOCRINE TUMORS & DIAGNOSTIC TESTING

What is a Neuroendocrine Tumor?

Neuroendocrine tumors (NETs) are cancers that arise in hormone-producing cells and can develop in various parts of your body, including the digestive system, lungs, and other organs. These tumors can produce hormones, which can lead to a range of symptoms. This information sheet will help you understand the hormones that NETs can produce and how they are tested.

Who should be tested for hormone production?

1. All patients with small bowel NETs should undergo testing for 5-HIAA (a metabolite of serotonin) in the urine or blood even without symptoms of diarrhea or flushing due to the risk of carcinoid heart disease with elevated serotonin.
2. Hormone testing for hormones other than serotonin is not recommended unless there are symptoms that suggest another hormone may be elevated as secretion of those other hormones is much less common.

Hormones Produced by Neuroendocrine Tumors:

1. **Serotonin:** NETs in the gastrointestinal tract can produce serotonin, leading to a condition known as carcinoid syndrome. Symptoms may include flushing, diarrhea, wheezing, and heart valve problems. NETs that produce serotonin usually start in the small intestine. Not everyone who makes excess serotonin will have symptoms, but it's important to treat a NET that makes serotonin because it can cause carcinoid heart disease which can be life-threatening & reduce quality of life.
2. **Insulin:** Some NETs in the pancreas can produce excess insulin, leading to low blood sugar (hypoglycemia) & symptoms such as confusion, shakiness, & fainting.
3. **Glucagon:** Production of glucagon by pancreatic NETs can result in symptoms like skin rash, weight loss & diabetes.
4. **Gastrin:** Tumors in the stomach & small intestine may produce excess gastrin, leading to a condition called Zollinger-Ellison syndrome. This can result in stomach ulcers, heartburn, and diarrhea.
5. **Vasoactive Intestinal Peptide (VIP):** Certain NETs overproduce VIP, leading to watery diarrhea & a condition called Verner-Morrison syndrome.
6. **Less common hormones include ACTH, cortisol, even parathyroid hormone, growth hormone and other rarer hormones:** Tumors in the gastrointestinal tract occasionally make hormones that are more commonly produced by NETs that start outside of the digestive system. These are uncommon.

Treatment to Reduce Hormone Secretion:

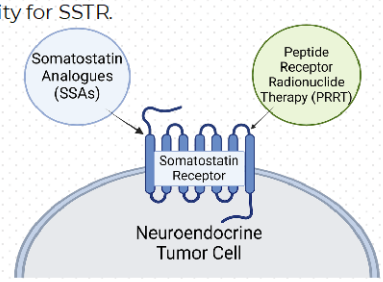
1. **Medications:** A medication called a somatostatin analogue can reduce hormone production from NETs. Depending on the type of hormone made, there may be other medications that can reduce symptoms or production. Sometimes your doctor may suggest other treatments to shrink your cancer if there is too much hormone produced.
2. **Surgery, Radiation, Ablation**: Sometimes it may be important to reduce the amount of tumor in the body so there is less hormone production.

eAppendix 4 Understanding functional imaging in neuroendocrine tumors

FUNCTIONAL IMAGING IN NEUROENDOCRINE TUMORS

Somatostatin Receptor (SSTR) PET Imaging:

SSTR-PET scans use radiotracers that bind to SSTRs present on NET cells. SSTR-PET (e.g. 68Ga-DOTATATE), allows for highly sensitive imaging of neuroendocrine tumors due to their affinity for SSTR.



Use in Neuroendocrine Tumors:

Well-differentiated neuroendocrine tumors, which often express high levels of SSTRs, can be effectively visualized using SSTR-PET. SSTR imaging helps identify where cancer is located in the body and whether it will respond to peptide receptor radioligand therapy (PRRT).

FDG-PET Imaging:

FDG-PET scans involve the injection of a small amount of radioactive glucose/sugar (FDG) that highlights areas of increased sugar consumption. However, in neuroendocrine tumors, especially well-differentiated ones, FDG uptake can vary. Some tumors may exhibit high metabolic activity, suggesting they are growing faster, while other tumors may have less uptake, suggesting they are growing slower. Not all NETs need an FDG scan, particularly if they are very slow growing, but it is sometimes used to determine if there are spots that might not respond to PRRT or if certain areas of the tumor may be more aggressive than what was originally biopsied.

PRACTICAL CONSIDERATIONS

SSTR-PET

- No preparation is required.
- You will not need to fast before the test.
- IV is required for injection.
- Typical 60-minute wait time between injection and scan.
- No side effects after injection are expected.
- Scan takes 10-20 minutes while patient is lying in scanner.
- Once the scan is complete, patient can leave with no public radiation precautions.
- Breastfeeding should not occur for 12 hours after injection.
- No medications need to be held before, however there is controversy around the need to hold octreotide LAR/ lanreotide. Follow recommendations from your local department about what to do with your octreotide LAR/lanreotide.

FDG

- Limit strenuous exercise 2 days prior as it may cause false positives.
- No food for 4 hours before injection, except for water (no candy, gum, coffee or tea).
- Diabetics - try to keep blood sugars below 11 mmol/L (200 mg/dL) the day prior. No short-acting insulin 3 hours before injection.
- IV is required for injection.
- Typical 60-minute wait time between injection and scan.
- No side effects after injection are expected.
- Scan takes 10-20 minutes while patient is lying in scanner.
- Once the scan is complete, patient can leave with no public radiation precautions.
- Breastfeeding should be avoided 24 hours post injection.

During your SSTR or FDG PET, if you have any questions, ask the technologist or physician you are working with.

Positron Emission Tomography (PET) scans

Are imaging techniques that play a crucial role in the diagnosis and management of neuroendocrine tumors (NETs). These scans utilize different tracers, notably Fluorodeoxyglucose (FDG) and Somatostatin Receptor (SSTR) imaging agents, offering unique insights into NETs.

eMethods

Conceptualization, proposed methodology, and development of research questions (eTable 1) were determined over a 2-day in-person meeting (November 30th to December 1st, 2022), including a multidisciplinary panel of Medical Oncologists (7), Surgical Oncologists (3), Nuclear Medicine Physicians (2), Endocrinologists (2), Pathologists (1), Radiologists (1), and Radiation Oncologists (1) who specialize in GEP-NENs. Two patients/patient advocates and a medical writer also participated in development discussions.

A systematic literature search of articles published in English between January 2016 to December 2022 was performed in PubMed (MEDLINE) to investigate factors which inform disease prognosis and treatment choice in advanced GEP-NENs. The search query included the terms: (“neuroendocrine tumor” or “neuroendocrine neoplasm” or “carcinoid”) AND (“gastrointestinal” OR “gastroenteropancreatic” OR “pancreatic” OR "small bowel" OR “colon” OR "small intestine" OR "large bowel" OR "large intestine" OR “rectum” OR “appendix” OR “gastric” OR “stomach” OR “midgut” OR “foregut”) AND (“prognos*” OR “predict*” OR “biomarker*”). Publications were screened to identify articles that answered the research questions proposed by the guideline panel prior to conducting the literature review (eTable 1).

To be included in the evidence review, studies needed to evaluate the predefined outcomes of interest for each research question and include at least 20 patients with advanced/metastatic GEP-NENs. In studies which included NENs from other primary sites and disease stages but that did not report data for the population of interest separately, at least 50% of the population was required to have advanced/metastatic GEP-NENs to be included in the evidence review. Systematic reviews, meta-analyses, randomized controlled studies, and prospective or retrospective cohort studies were eligible for inclusion. Additional publications were acquired through backward and forward referencing of the included studies, as well as searching of conference abstracts from the: American Society of Clinical Oncology (ASCO) annual meeting, ASCO gastrointestinal cancers symposium, European Society for Medical Oncology (ESMO) congress, ESMO congress on gastrointestinal cancers, North American Neuroendocrine Tumor Society (NANETS) Symposium, annual European Neuroendocrine Tumor Society (ENETS) conference, Society of Nuclear Medicine and Molecular Imaging Annual Meeting, and annual congress of the European Association of Nuclear Medicine from 2020-2022. Relevant guidelines published within the last 3 years were also identified by international medical societies and guideline developers (National Comprehensive Cancer Network, National Institute of Health and Care Excellence [United Kingdom], ASCO, ESMO, National Health and Medical Research Council [Australia], NANETS, ENETS, Canadian Neuroendocrine Tumour Society). Identified guidelines were not considered in the evidence review but were referenced in the text to provide a historical overview of management practices and act as a source for citation searching.

Screening of titles, abstracts, and full-text articles from the literature search and extraction of data from included studies into evidence tables was performed by a medical writer. Two expert panelists were assigned to each research question and were responsible for confirming completeness of the literature search and agreement with the proposed protocol. After each group of panelists reviewed, summarized, and assessed the quality of evidence, they proposed a recommendation and grade which reflected their review for each statement. Evidence review, quality assessment, and grading followed the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework with some modifications (eTables 2–4).[1] Consensus of the proposed statements were reached using a modified Delphi process. All drafted recommendations and suggested grading were included in a web-based survey where all panelists responded anonymously. Panelists were asked to rate their agreement with the statements based on the total evidence review given the following options: “accept”, “accept with minor reword”, or “reject/major reword”. An open-ended text field was included to gain feedback where there was disagreement. Statements with minor or major rewords were reviewed by the expert panelists and those with major rewords were included in a second-round survey. Consensus was considered reached if there was agreement among all participants.

eTable 1. Proposed research questions to guide literature search and screening.

Biomarker	Research Questions	Outcomes of interest
Tumor grade[a]	A. Is tumor grade a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Can tumor grade predict response and prognosis following treatment with SSAs, PRRT, or chemotherapy in patients with unresectable advanced or metastatic GEP-NEN (i.e. is it treatment-informing?)	A. OS, PFS B. RECIST response, TTP/PFS
Tumor differentiation[b]	A. Is tumor differentiation a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Can tumor differentiation predict response and prognosis following treatment with PRRT or chemotherapy in patients with unresectable advanced or metastatic GEP-NEN (i.e. is it treatment-informing)?	A. OS, PFS B. RECIST response, TTP/PFS
Primary site[a]	A. Is primary tumor location a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Can primary tumor location predict response and prognosis following treatment with SSA, PRRT or chemotherapy in patients with unresectable advanced or metastatic GEP-NEN (i.e. is it treatment-informing)?	A. OS, PFS B. RECIST response, TTP/PFS
Genomic profiling	A. Does multi or single gene next generation sequencing provide prognostic or treatment informing information? a. Is ATRX/DAXX gene alteration status (alternate lengthening of telomeres [ALT] phenotype) a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? b. Are KRAS, BRAF, RB1, TP53, or MEN1 prognostic factors in patients with unresectable advanced or metastatic GEP-NEN? c. Are KRAS, BRAF, RB1, or TP53 treatment-informing (i.e. can they predict response or prognosis following a specific therapy?	a. OS, PFS b. OS, PFS c. RECIST response, TTP/PFS
TMB	A. Is TMB status a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Can TMB status predict response or prognosis following treatment with immunotherapy in patients with unresectable advanced or metastatic GEP-NEN (is it treatment-informing)?	A. OS, PFS B. RECIST response, TTP/PFS
MSI	A. Is MSI/MMR status a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Can MSI/MMR status predict response or prognosis following treatment with	A. OS, PFS B. RECIST response, TTP/PFS

Biomarker	Research Questions	Outcomes of interest
	immunotherapy in patients with unresectable advanced or metastatic GEP-NEN (is it treatment-informing)?	
NTRK	A. Can NTRK fusion status predict response and prognosis following treatment with TRK inhibitors in patients with unresectable advanced or metastatic GEP-NEN (i.e. is it a treatment informing biomarker for NTRK)?	A. RECIST response, TTP/PFS
Transcriptional/ proteomic classifiers	A. Are transcriptional or proteomic classifiers prognostic in patients with unresectable advanced or metastatic GEP-NEN?	A. OS, PFS
MGMT expression/ methylation	A. Can MGMT expression predict response and prognosis following treatment with alkylating agents for patients with unresectable advanced or metastatic GEP-NEN? (Is MGMT expression a treatment-informing biomarker?)	A. RECIST response, TTP/PFS, OS
SSTR expression by immuno-histochemistry	A. Is SSTR expression (by IHC or PCR) a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Can SSTR expression predict response and prognosis following treatment with PRRT or chemotherapy in patients with unresectable advanced or metastatic GEP-NEN (i.e. is SSTR expression a treatment-informing biomarker)?	A. OS, PFS B. RECIST response, TTP/PFS
SSTR PET imaging	A. Is avidity on SSTR PET imaging a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Does avidity on SSTR PET imaging predict response or prognosis following treatment with PRRT in patients with unresectable advanced or metastatic GEP-NEN (i.e. is it treatment-informing)?	A. OS, PFS B. RECIST response, TTP/PFS
FDG PET imaging	A. Is avidity on FDG PET imaging a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Does avidity on FDG-PET imaging predict prognosis following treatment with PRRT in patients with unresectable advanced or metastatic GEP-NEN (i.e. is it a treatment-informing biomarker for PRRT)?	A. OS, PFS B. RECIST response, TTP/PFS
Dual imaging	A. Is spatial discordance on SSTR-PET/FDG-PET imaging a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Does spatial discordance on SSTR-PET/FDG-PET imaging predict response or prognosis following systemic therapies (SSA, PRRT, chemotherapy) in patients with unresectable advanced or metastatic GEP-NEN? C. Can combined scoring systems based on FDG PET and SSTR PET (e.g. NETPET score) predict prognosis in patients with unresectable advanced or metastatic GEP-NEN?	A. OS, PFS B. RECIST response, TTP/PFS C. OS, PFS

Biomarker	Research Questions	Outcomes of interest
Clinical and subclinical carcinoid syndrome	A. Is symptomatic carcinoid syndrome a prognostic factor in patients with unresectable advanced or metastatic mid-gut NEN? B. Is subclinical carcinoid syndrome (elevated 5-HIAA) a prognostic factor in patients with unresectable advanced or metastatic mid-gut NEN? C. Are SSA therapies effective in decreasing symptoms in patients with symptomatic carcinoid syndrome and unresectable advanced or metastatic mid-gut NEN (is it treatment-informing)? D. Are SSA therapies effective in decreasing 5-HIAA in patients with subclinical carcinoid syndrome (elevated 5-HIAA) and unresectable advanced or metastatic mid-gut NEN (is it treatment-informing)? E. Are SSA therapies effective in prolonging progression-free survival in patients with clinical or subclinical carcinoid syndrome and unresectable advanced or metastatic mid-gut NENs (is it treatment-informing)?	A. OS, PFS B. OS, PFS C. Symptom measures D. Change in 5-HIAA E. PFS
CgA	A. Is baseline CgA concentration a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Does baseline CgA predict response or prognosis following treatment with specific systemic therapies in patients with unresectable advanced or metastatic GEP-NEN? C. Does the change in CgA levels predict response or prognosis following treatment with specific systemic therapies in patients with unresectable advanced or metastatic GEP-NEN?	A. OS, PFS B. RECIST response, TTP/PFS C. RECIST response, TTP/PFS
Pancreastatin	A. Is baseline pancreastatin concentration a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Does the change in pancreastatin levels predict response or prognosis following treatment with specific therapies in patients with unresectable advanced or metastatic GEP-NEN?	A. OS, PFS B. RECIST response, TTP/PFS
Pancreatic polypeptide	A. Is baseline pancreatic polypeptide concentration a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Does the change in pancreatic polypeptide levels following treatment predict disease progression and/or response to therapy in patients with unresectable advanced or metastatic GEP-NEN?	A. OS, PFS B. RECIST response, TTP/PFS

Biomarker	Research Questions	Outcomes of interest
Neuron specific enolase	A. Is baseline NSE concentration a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Does the change in NSE levels following treatment predict disease progression and/or response to therapy in patients with unresectable advanced or metastatic GEP-NEN?	A. OS, PFS B. RECIST response, TTP/PFS
Progastrin	A. Is baseline circulating progastrin a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Does the change in circulating progastrin levels following treatment predict disease progression and/or response to therapy in patients with unresectable advanced or metastatic GEP-NEN?	A. OS, PFS B. RECIST response, TTP/PFS
NETest	A. Can NETest values at baseline or follow-up time points accurately differentiate stable from progressive disease by RECIST criteria in patients with unresectable advanced or metastatic GEP-NEN? B. Can NETest values at baseline or follow-up time points predict prognosis? C. Can change in NETest values from baseline predict response following PRRT?	A. Accuracy measures (e.g. sensitivity/specificity/positive predictive value/negative predictive value) B. OS, PFS C. RECIST response, PFS
ctDNA and CTCs	A. Is minimal residual disease as measured by circulating tumor cells (CTC) or ctDNA a prognostic factor in patients with unresectable advanced or metastatic GEP-NEN? B. Can minimal residual disease as measured by circulating tumor cells (CTC) or ctDNA predict response and prognosis following a specific treatment? (Is it a treatment-informing biomarker?)	A. OS, PFS B. RECIST response, TTP/PFS
Carcinoid heart disease	A. Is carcinoid heart disease associated with poor prognosis in patients with advanced unresectable or metastatic mid-gut NETs? B. Does early identification of carcinoid heart disease through echocardiography monitoring in patients with advanced unresectable or metastatic mid-gut NETs and carcinoid syndrome improve outcomes?	A. OS B. OS
NT-pro-BNP	A. Is NT-proBNP a biomarker that can predict development/presence of carcinoid heart disease?	A. Accuracy measures, correlation

[a] Due to the abundance of studies evaluating this topic, additional inclusion criteria were applied for research question A including: Studies must perform a multivariate analysis; Retrospective studies must include at least 100 patients.

[b] Studies must use WHO 2019 classification for determine grade and differentiation of GEP-NENs.

5-HIAA, 5-hydroxyindoleacetic acid; CgA, chromogranin A; CTC, circulating tumor cells; FDG, fluorodeoxyglucose; GEP-NEN, gastroenteropancreatic neuroendocrine neoplasm; IHC, immunohistochemistry; MSI/MMR, microsatellite instability/mismatch repair; NSE, neuron specific enolase; OS, Overall survival; PCR, polymerase chain reaction; PET, positron emission tomography; PFS,

progression-free survival; PRRT, peptide receptor radionuclide therapy; RECIST, response evaluation criteria in solid tumors; SSAs, somatostatin analogues; SSTR, somatostatin receptor; TMB, tumor mutational burden; TTP, time to progression

eTable 2. Method for grading level [a] and quality [b] of evidence

Evidence level[a]	**Corresponding GRADE[b] quality of evidence level (prior to quality assessment)**	**Factors that may warrant downgrading or upgrading of quality level**
Level 1 RCT or prospective cohort study where marker is the primary objective OR Systematic review of level 2 studies OR Guideline based on systematic review	**High** We are very confident that the true effect lies close to that of the estimate of the effect	Downgrade (1-2 points) if: -Risk of bias -Inconsistency -Indirectness -Imprecision -Publication bias -Other significant study limitations Increase (1-2 points) if: -Large effect -Dose response -All plausible residual confounding would: reduce a demonstrated effect or would suggest a spurious effect if no effect was observed *See Table S3 for checklist when evaluating quality of evidence
Level 2 RCT or prospective cohort study where marker is a secondary objective OR Systematic review of level 3 studies	**Moderate** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	
Level 3 Retrospective cohort study where the marker is evaluated in a multivariate analysis	**Low** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	
Level 4 Retrospective cohort study where the marker is evaluated in a univariate analysis	**Very low** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	
Level 5 Retrospective cohort study looking at correlation with other markers but not outcomes		

[a]Adapted from Hayes DF, Bast RC, Desch CE, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. *J Natl Cancer Inst*. 1996;88(20):1456-1466 and Febbo PG, Ladanyi M, Aldape KD, et al. NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. *J Natl Compr Canc Netw*. 2011;9 Suppl 5:S1-S33.[2,3]

[b] Adapted from Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.[1]

RCT, randomized controlled trial

eTable 3. Checklist for assessing quality of evidence.

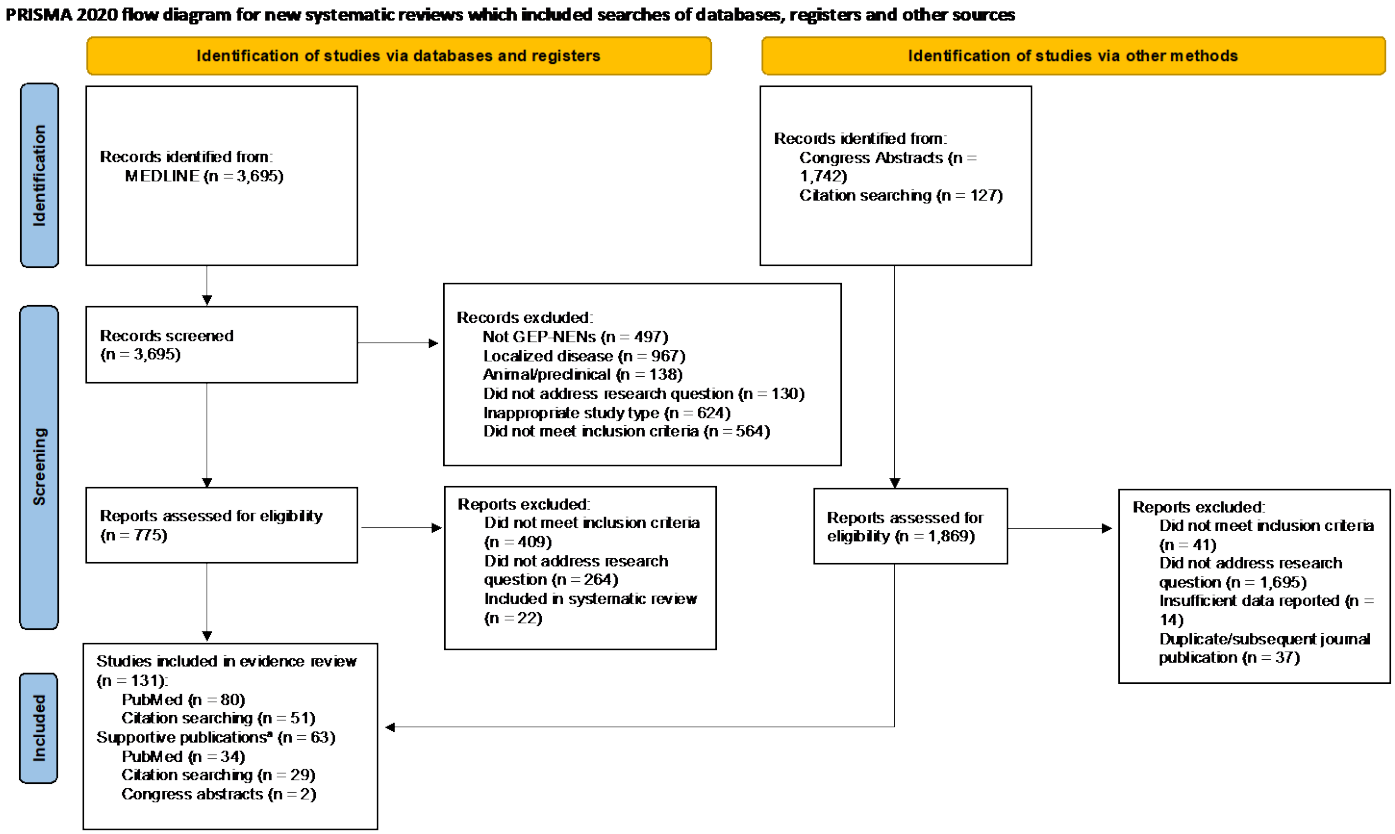
Question	Cohort studies	Randomized controlled trials	Systematic review/meta-analyses	Guidelines
Appropriate/consistent eligibility criteria?	✓			
Limitations to the relevance of the population?	✓	✓		
Reported relevant baseline characteristics?	✓	✓		
Adequately controlled for confounding?	✓	✓		
Adequate follow-up?	✓	✓		
Differences in the intervention of interest?	✓	✓		
Measurement of non-relevant and/or surrogate outcomes?	✓	✓		
Adequate sample size?	✓	✓	✓	
Probability of publication bias?	✓	✓	✓	
Funding source?	✓	✓	✓	✓
Provided details on randomization?		✓		
Provided details on blinding?		✓		
Expected effect size and statistical power calculation stated?		✓		
Reported length of follow-up?		✓		
Appropriate measurement of exposure/outcome?		✓		
Important patient subtypes considered?			✓	✓
Based on systematic review?			✓	✓
Well-described and reproducible methods?			✓	✓
Conflicts of interest examined?			✓	✓
Rated quality of evidence?			✓	✓
Inconsistency/unexplained heterogeneity?			✓	
Multidisciplinary panel?				✓
Patient preferences considered?				✓
Rated strength of evidence?				✓
Includes plan for updating?				✓

eTable 4. Rationale for grading strength of recommendations [a,b]

Designation	Rationale
Strong recommendation	• Panel is confident that the desirable effects of an intervention outweigh its undesirable effects/undesirable effects outweigh its desirable effects • Generally supported by high or moderate quality of evidence • Implies that most or all individuals will be best served by the recommended course of action
Conditional Recommendation	• Desirable effects probably outweigh undesirable effects/undesirable effects probably outweigh desirable effects, but appreciable uncertainty exists • Generally supported by moderate or low quality of evidence • Implies not all individuals will be best served by recommended course of action. • Individual patients' circumstances, preferences, and values need to be carefully considered. • More time needed for shared decision making, with potential benefits/harm clearly explained.
Expert consensus opinion	• Serious limitations in quality of evidence (low or very low), balance of benefits and harms, values, or costs, but panel consensus is that a statement is necessary
Recommendation for use only in research	• Insufficient evidence thus far to support a decision for or against an intervention/practice (low or very low quality of evidence) • Further research has large potential for reducing uncertainty about the effects of the intervention, or further research is thought to be of good value for the anticipated costs
No recommendation	• Confidence in effect estimates is so low that a recommendation is too speculative • Trade-offs are so closely balanced, and values, preferences, and resource implications not known or too variable, that the panel cannot decide a direction for recommendation
Good clinical practice	• A formal literature review was not performed. Recommendations were based on consensus only

[a] Adapted from Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336(7650):924-926.[1] [b] Adapted from Sepulveda AR, Hamilton SR, Allegra CJ, et al. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline From the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. *J Clin Oncol*. 2017;35(13):1453-1486.[4]

eFigure. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram summarizing literature search results.



[a] *did not meet eligibility criteria but were deemed useful to support discussion given the lack of published studies examining select biomarkers. From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

eTable 5. Summary of evidence for studies evaluating the impact of tumor differentiation on prognosis

Reference	Study type	N	Primary sites	Grade/ Differentiation	OS Findings	Significant independent prognostic factor on MVA?
Nuñez-Valdovinos 2018 [5]	P/R	2,813	GEP-NENs Pan 35% SB 18% Appendix 10% Colorectal 11%	WHO 2010 grade (n = 1,799) G1: 25% G2: 26% G3: 13% Missing: 36% Differentiation (n = 2,107): Well: 63% Poor: 12%	UVA (cox-regression) *Poor vs. well differentiation:* • HR 6.63 (95% CI 5.57–7.89); p<0.0001 MVA (cox-regression) *Poor vs. well differentiation:* • HR 2.0159 (95% CI 1.4791-2.7475); p<0.0001 5-year survival *Poor vs. well differentiation:* • 28% vs. 80% *G2 NET vs. G2 NEC:* • 75.5% vs. 58.2% *G3 NET vs. G3 NEC:* • 43.7% vs. 25.4%	Yes
Elvebakken 2021 [6]	R	196	GEP-NENs Pan 27% Colon 22% Unknown 24%	All G3 NET G3: 12% NEC Ki67<55%: 30% NEC Ki67≥55%: 57% Ambiguous: 2%	Median (Kaplan-Meier/log-rank test) *G3 NET vs. G3 NEC (Ki-67 <55%):* • 33 vs. 11 months; p = 0.004 *G3 NET vs. NEC (Ki-67 ≥ 55):* • p = 0.003	Not tested
Milione 2017 [7]	R	136	GEP-NENs Colorectal 34% Pan 24%	All G3 NET G3: 18% NEC Ki67<55%: 22%	UVA (cox-regression) *Poor vs. well differentiation:*	Yes

Reference	Study type	N	Primary sites	Grade/ Differentiation	OS Findings	Significant independent prognostic factor on MVA?
			Stomach 21%	NEC Ki67≥55%: 60%	• HR 4.06 (95% CI 1.47 – 5.47); p<0.0001 <u>MVA (cox-regression)</u> *Poor vs. well differentiated:* • HR 2.83 (95% CI 1.47 – 5.47); p = 0.002 <u>Median (Kaplan-Meier/log-rank test)</u> *G3 NET:* • 43.6 months *G3 NEC (Ki-67 <55%):* • 24.5 months *NEC (Ki-67 ≥ 55):* • 5.3 months p <0.0001	
Heetfeld 2015 [8]	R	204	GEP-NENs Pan 32% Colon 15% Rectum 12% Stomach 8%	All G3 G3 NET: 15% G3 NEC: 79%	<u>UVA (cox-regression)</u> *G3 NEC vs. G3 NET:* • p = <0.001 <u>MVA (cox-regression)</u> *G3 NEC vs. G3 NET:* • HR 8.3 (95% CI: 2.9–23.81); p<0.001	Yes
Yang 2020 [9]	R	150	GEP-NENs Pan 43% Stomach 20%	G1: 7% G2: 17% G3 NET: 22% G3 NEC: 54%	<u>UVA (cox-regression)</u> *G3 NEC vs. G3 NET:* • p = 0.012	Yes

Reference	Study type	N	Primary sites	Grade/ Differentiation	OS Findings	Significant independent prognostic factor on MVA?
			SB 8.0% Colorectal 29%		MVA (cox-regression) *G3 NEC vs. G3 NET:* • HR 4.234 (95% CIs: 1.984–6.763); p = 0.003 Median (Kaplan-Meier/log-rank test) *G3 NET:* • 32.2 months *G3 NEC:* • 21.5 months p <0.0001	
Wang 2019 [10]	R	72	Colorectal NENs	All G3 G3 NET: 15% G3 NEC: 85%	UVA (cox-regression) *G3 NEC vs. G3 NET:* • p <0.0001 MVA (cox-regression) *G3 NEC vs. G3 NET:* • HR 6.647 (95% CI 1.759-25.119); p = 0.005	Yes
Busico 2020 [11]	R	54	GEP-NENs Colon 48% Pan 32% Stomach 20%	All G3 G3 NET: 28% G3 NEC: 72% NEC Ki-67 <55%: 17% NEC Ki-67 ≥55%: 56%	MVA (cox-regression) *G3 NET vs. G3 NEC (Ki-67<55%):* • HR 0.15 (95% CI 0.03-0.89); p = 0.04	Yes
Hijioka 2017 [12]	R	70	PanNENs	All G3 G3 NET: 30% G3 NEC: 70%	UVA (cox-regression) *G3 NEC vs. G3 NET:* • HR 2.75 (95% CI 1.35-5.87); p = 0.008	No

Reference	Study type	N	Primary sites	Grade/ Differentiation	OS Findings	Significant independent prognostic factor on MVA?
					MVA (cox-regression) *G3 NEC vs. G3 NET:* • HR 1.55 (95% CI 0.55-4.36); p = 0.404 Median (Kaplan-Meier/log-rank test) *NET G3:* • 41.8 months *NEC G3 (small cell):* • 11.3 months *NEC G3 (large cell):* • 6.2 months p = 0.0023	
Hayes 2021 [13]	R	142	GEP-NENs Pan 51% GI 36%	All G3 G3 NET: 52% G3 NEC: 48%	MVA (cox-regression) *Poor vs. well differentiated:* • HR 2.07 (95% CI 1.37-3.11); p = 0.0005	Yes

CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; OS, overall survival; Pan, pancreas; P/R, prospective enrollment, retrospective analysis; R, retrospective; SB, small bowel; UVA, univariate analysis; WHO, World Health Organization

eTable 6. Quality assessment for studies included in evidence review which evaluated the impact of tumor differentiation on prognosis.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Nuñez-Valdovinos 2018	Level 2/Moderate	-1	-low proportion of G3 pts -grade or differentiation data missing for 55% of pts	Low
Elvebakken 2021	Level 2/Moderate	No	N/A	Moderate
Milione 2017	Level 3/Low	No	N/A	low
Heetfeld 2015	Level 3/Low	No	N/A	low
Yang 2020	Level 3/Low	No	N/A	low
Wang 2019	Level 3/Low	No	N/A	low
Busico 2020	Level 3/Low	-1	-Small sample size	Very low
Hijoka 2017	Level 3/Low	-1	-Small sample size	Very low
Hayes 2021	Level 3/Low	No	N/A	low

[a] See checklist for evaluating quality of evidence Table S3
N/A, not applicable

eTable 7. Prospective randomized controlled trials of systemic therapy in advanced or metastatic gastroenteropancreatic neuroendocrine tumors

Study name	Phase	Treatment arms	N	Primary site	Grade	PFS Results	OS Results
PROMID Rinke 2009 [14]	III	Arm A: Octreotide LAR 30 Arm B: placebo	A: 42 B: 43	Midgut	G1	Median TTP[a] A vs. B: 14.3 vs. 6.0 months HR 0.34 (95% CI 0.20–0.59); p< 0.001	Median OS: N.E. HR 0.81 (95% CI 0.30-2.18); p = 0.77
CLARINET Caplin 2014 [15]	III	Arm A: Lanreotide LAR Arm B: Placebo	A: 101 B: 103	Pan Other GI	G1/2 (Ki67 < 10%) G1: 69% G2: 20%	Median PFS A vs. B: NR vs. 18 0.0 months[b] HR 0.47 (95% CI 2.1–24.0); p<0.001	Not reported
RADIANT-2 Pavel 2011 and 2017 [16,17]	III	Arm A: Everolimus + Octreotide LAR Arm B: Placebo + Octreotide LAR	A: 216 B: 213	Lung GI with carcinoid syndrome	G1/2	Median PFS[a] A vs. B: 16.4 vs. 11.3 months HR 0.77 (95% CI 0.59–1.00); p = 0.026[c]	Median OS A vs. B[d]: 29.2 vs. 35.2 months HR 1.17 (95% CI, 0.92-1.49)
RADIANT-3 Yao 2011 [18]	III	Arm A: Everolimus Arm B: Placebo	A: 207 B: 203	Pan	G1: 83% G2: 16%	Median PFS[a] A vs. B: 11.0 vs. 4.6 months HR 0.35 (95% CI 0.27–0.45); p<0.0001	Median OS A vs. B: 44.0 vs. 37.7 months HR 1.05 (95% CI 0.71–1.55); p = 0.59
RADIANT-4 Yao 2016 [19]		Arm A: Everolimus Arm B: Placebo	A: 205 B: 97	Lung GI	G1: 83% G2: 16%	Median PFS A vs. B: 11.0 vs. 3.9 months HR 0.48 (95% CI 0.35–0.67); p<0·00001	Median OS A vs. B: 44.02 vs. 37.68 months; HR 0.64 (95% CI 0.40–1.05); one-sided p=0·037[e]
SUN1111 Raymond 2011 [20]	III	Arm A: Sunitinib Arm B: Placebo	A: 86 B: 85	Pan	G1/2 Arm A Ki-67 >5%: 36% Arm B Ki-67 >5%: 45%	Median PFS[a] A vs. B: 11.4 vs. 5.5 months HR 0.42 (95% CI 0.26–0.66); p<0.0001	Median OS A vs. B: NR vs. NR HR 0.41 (95% CI 0.19-0.89; p = 0.02
NETTER-1 Strosberg 2017 and 2021 [21,22]	III	Arm A: ^{177}Lu-Dotatate Arm B: Octreotide LAR 60 mg	A: 116 B: 113	Midgut	G1/2	Median PFS A vs. B: 25.0 vs. 8.5 months HR 0.21 (95% CI 0.13-0.33); p<0.001	Median OS A vs. B: 48 vs. 36.3 months HR 0.84 (95% CI 0.60-1.17); p = 0.30

Study name	Phase	Treatment arms	N	Primary site	Grade	PFS Results	OS Results
OCLURANDOM Baudin 2022 (abstract) [23]	II	Arm A: ^{177}Lu-Dotatate Arm B: Sunitinib	A: 41 B: 43	Pan	G1: 19% G2/3: 81%	12-month PFS[a] A vs. B: 80% vs. 42%	Not reported
ECOG-ACRIN E2211 Kunz 2023 [24]	II	Arm A: Temozolomide Arm B: Capecitabine-temozolomide	A: 72 B: 72	Pan	Arm A, G1/2: 38/62% Arm B. G1/2: 50/49%	Median PFS[a] B vs. A: 22.7 vs. 14.4 months HR 0.58 (95% CI 95% CI, 0.36 to 0.93); p = 0.023	Median OS A vs. B: 53.8 vs. 58.7 months HR 0.8 (95% CI 0.51-1.33); p = 0.42
SEQTOR Salazar 2022 (abstract) [25]	III	Arm A: everolimus ➔ STZ-5FU Arm B: everolimus ➔ STZ-5FU	A: 71 B: 70	Pan	G1: 14% G2: 80%	12-month PFS1[a] A vs. B: 69% vs. 64%	Not reported

[a] Primary endpoint [b] 32.8 vs. 18.0 months in open-label extension; [c] the pre-specified boundary at final analysis was p = 0.0246; [d]open-label extension [e]the boundary for statistical significance was 0.0002

5FU, 5-fluorouracil; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NR, not reached; LAR, long-acting release; OS; overall survival; Pan, pancreas; PFS, progression-free survival; STZ, streptozotocin; TTP, time to progression

eTable 8. Summary of evidence for studies evaluating the impact of WHO 2019 grade on response and prognosis.

Reference	Study type	N	Primary sites	Grade	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
Response/prognosis after SSA therapy							
Ozaslen 2017 [26]	R	165 SSA: 104	NETs Pan 31% GI 30% Lung 16%	G1: 45% G2: 55% WHO 2010 criteria	chi-squared test *G1 vs. G2 (on SSA therapy):* • CR/PR: 18% vs. 11%; p = 0.61 • DCR: 92% vs. 84%; p = 0.26	UVA (cox-regression) *G2 vs. G1:* • HR 1.83 (95% CI 1.04–2.87); p = 0.04 MVA (cox-regression) *G2 vs. G1:* • HR 1.16 (95% CI 0.23–5.70); p = 0.85	No[a]
Laskaratos 2016 [26]	R	254	NETs SB 80% Pan 9% Lung 6%	G1: 58% G2: 23% WHO 2010 criteria	Not reported	UVA (cox-regression) *G2 vs. G1:* • p<0.001 MVA (cox-regression) *G2 vs. G1:* • p = 0.001 (HR not reported)	Yes
Laskaratos 2020 [27]	R	102	GEP-NETs SB 62% Pan 30%	G1: 52% G2: 38% Missing: 10% WHO 2019 criteria	Not reported	MVA (cox-regression) *G2 vs. G1:* • HR 1.64 (95% CI 1.01, 2.67); p = 0.04	Yes
Merola 2021 [28]	R	73	PanNETs	G2: 93% G3: 7% Ki-67: 10%–15%: 71%	Not reported	MVA (cox-regression) *G3 vs. G2:* • HR 4.4 (95% CI 1.2–16.6); p = 0.04	Yes

Reference	Study type	N	Primary sites	Grade	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
				16%–20%: 22% 21%–25%: 4% >25%: 3% WHO 2019 criteria			
Faggiano 2016 [29]	P/R	140	NETs Pan 44% Lung 19% SB 12%	G1: 35% G2: 44% G3: 21% WHO 2010 criteria	chi-squared test *G1 vs. G2 (on SSA therapy):* • CR/PR: 8% vs. 14% p > 0.05 • DCR: 75% vs. 63% p > 0.05	Median (Kaplan-Meier/log-rank test): *G1 vs. G2:* • 89 vs. 43 months; p = 0.15	Not tested, not significant by Kaplan-Meier analysis[a]
Caplin 2014 [15]	RCT	204 LAN: 101 Plb: 103	GEP-NET Pan 45% Midgut 36% Hindgut 13%	G1: 69% G2: 30% WHO 2010 criteria	Not reported	UVA (cox-regression) *LAN vs. Plb:* • G1: HR 0.43 (95% CI 0.25–0.74) • G2: HR 0.45 (95% CI 0.22–0.91)	Not tested
Response/prognosis after PRRT							
Katona 2017 [30]	R	28	NETs Pan 46% SB 29% Lung 14%	G1: 18% G2: 46% G3: 25% Missing: 11% WHO 2010 criteria	Not reported	UVA (cox-regression) *G3 vs. G1/2:* • HR 3.41 (95% CI 1.13–10.30); p = 0.03 MVA (cox-regression) *G3 vs. G1/2:* • HR 3.71 (95% CI 1.01–13.73)	Yes

Reference	Study type	N	Primary sites	Grade	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
Pusceddu 2022 [31]	R	508 CTx or tar-geted: 179 PRRT: 329	GEP-NETs Pan 51% SB 49%	G1: 40% G2: 54% G3: 3% Missing: 4% Ki-67 >10%: 15% WHO 2019 criteria	Not reported	MVA (cox-regression) *G3 vs. G1/2:* • HR 2.64 (95% CI 1.19-6.27); p = 0.01 *PRRT vs. CTx or targeted agents:* • G1: HR 0.21 (95% CI 0.12-0.34) p<0.001 • G2: HR 0.52 (95% CI 0.29-0.73) p<0.001 • G3: HR 0.31 (95% CI 0.12-1.37); p = 0.13	Yes, in adjusted analysis, significant benefit of PRRT was reported in G1 and G2 subgroups, but not G3 subgroup
Response/prognosis after Chemotherapy							
Ozaslen 2017 [26]	R	165 CTx: 61	NETs Pan 31% GI 30% Lung 16%	G1: 45% G2: 55% WHO 2010 criteria	chi-squared test *G1 vs. G2 (on CTx therapy):* • CR/PR: 29% vs. 39%; p = 0.65 • DCR: 86% vs. 74%; p = 0.55	UVA (cox-regression) *G2 vs. G1:* • HR 1.49 (95% CI 0.69–3.21); p = 0.31 MVA (cox-regression) *G2 vs. G1:* • HR 2.27 (95% CI 0.49–10.45); p = 0.29	No
Roquin 2018 [32]	R	74	PanNETs	G2: 69% G3: 31% WHO 2010 criteria	No difference in response was reported by grade (data not shown)[b]	MVA (cox-regression) *G3 vs. G2:* • HR 2.15 (95% CI 1.18–3.92); p = 0.012	Yes

Reference	Study type	N	Primary sites	Grade	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
Childs 2016 [33]	R	173	NENs Pan 46% Midgut 13% Unknown 19% Lung 9%	G1: 10% G2: 46% G3: 43% Well differ-entiated: 51% Poorly differ-entiated: 37% Missing: 12% ENETS criteria	chi-squared test [c] *G1/2 vs. G3 (on CTx therapy):* • CR/PR: 20% vs. 43%; p = 0.002 • DCR: 86% vs. 74%; p = 0.55	Not reported	N/A
Chatzellis 2019 [34]	R	79	NENs Pan 38% GI 19% Lung/thymus 22% Unknown 18%	G1: 14% G2: 34% G3: 30% WHO 2017 criteria Group 1 (<3%) Group 2 (3–20%) Group 3 (21–55%) Group 4 (>56%)	chi-squared test *DCR (on CAPTEM):* • G1: 67% • G2: 75% • G3 Ki-67 ≤55%: 43% • G3 Ki-67 >55%: 33%; p = 0.045	MVA (cox-regression) *G2 vs. G1:* • HR 0.9 (95% CI 0.3–3.6); p = 0.936 *G3 Ki-67 ≤55% vs. G1:* • HR 0.3 (95% CI 0.1–1.1); p = 0.078 *G3 Ki-67 >55% vs. G1:* • HR 0.5 (95% CI 0.2–1.5); p = 0.235	No

Reference	Study type	N	Primary sites	Grade	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
				Ki-67 >56%: 11%			

[a] Ki-67 ≥5% was a statistically significant prognostic factor for patients receiving SSAs. [b] Therapies received: Streptozocin-based, 59%; Platinum-based, 24%; Dacarbazine/temozolomide-based,16%. [c] 72% received streptozocin-fluoropyrimidine-platinum therapy

CAPTEM, capecitabine-temozolomide; CI, confidence interval; CR, complete response; CTx, chemotherapy; DCR, disease control rate; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; LAN, lanreotide; MVA, multivariate analysis; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; OS, overall survival; P, prospective; Pan, pancreas; PFS, progression-free survival; Plb, placebo; PR, partial response; PRRT, peptide receptor radionuclide therapy; R, retrospective; RCT, randomized controlled trial; SB, small bowel; SSA, somatostatin analogue; UVA, univariate analysis; WHO, World Health Organization

eTable 9. Quality assessment for studies included in evidence review which evaluated the impact of WHO 2019 grade on response and prognosis.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Ozaslen 2017	Level 3/Low	No	N/A	Low
Laskaratos 2016	Level 3/Low	No	N/A	Low
Laskaratos 2020	Level 3/Low	No	N/A	Low
Merola 2021	Level 3/Low	No	N/A	Low
Faggiano 2016	Level 3/Low	No	N/A	Low
Caplin 2014	Level 2/Moderate	No	N/A	Moderate
Katona 2017	Level 3/Low	No	N/A	Low
Pusceddu 2022	Level 3/Low	No	N/A	Low
Roquin 2018	Level 3/Low	No	N/A	Low

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Childs 2016	Level 4/Very low	No	N/A	Very low
Chatzellis 2019	Level 3/Low	No	N/A	Low

[a] See checklist for evaluating quality of evidence Table S3
N/A, not applicable

eTable 10. Summary of evidence for studies evaluating the impact of tumor differentiation on response and prognosis following therapy

Reference	Study type	N	Primary sites	Grade/ Differentiation	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
Response/prognosis after Chemotherapy							
Li 2017 [35]	P	40	GEP-NENs Pan 15% Esophagus 20% Stomach 38%	All G3 G3 NET: 13% G3 NEC: Small cell: 50% Large cell: 20% Mixed adeno-carcinoma: 18%	chi-squared test (irinotecan-platinum) *G3 NET vs. G3 NEC:* • CR/PR: 0% vs. 51% p = 0.053 • DCR: 80% vs. 67%	Median (Kaplan-Meier/log-rank test) *G3 NET vs. G3 NEC:* • 8.9 vs. 5.7 months (no p-value reported)	Not tested
Elvebakken 2021 [6]	R	196	GEP-NENs Pan 27% Colon 22% Unknown 24%	All G3 NET G3: 12% NEC Ki67<55%: 30% NEC Ki67≥55%: 57% Ambiguous: 2%	chi-squared test (n = 155) *NEC Ki-67 ≥ 55 vs. NET G3* • CR/PR[a]: 44% vs. 24% p = 0.026 *NEC Ki-67 ≥ 55 vs. NEC Ki-67 <55%:*	Median (Kaplan-Meier/log-rank test) 5 months for all groups	Not tested

Reference	Study type	N	Primary sites	Grade/ Differentiation	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
					• CR/PR: 44% vs. 25%; p = 0.025		
Heetfeld 2015 [8]	R	204	GEP-NENs Pan 32% Colon 15% Rectum 12% Stomach 8%	All G3 G3 NET: 15% G3 NEC: 79%	chi-squared test (platinum etoposide): *G3 NET (n=12) vs. G3 NEC (n=113):* • DCR 33% vs. 68%; p = 0.03	Median (Kaplan-Meier/log-rank test): *G3 NET vs. G3 NEC:* • 2.4 vs. 5.0 months; p = 0.049	Not tested
Hijioka 2017 [12]	R	70	PanNENs	All G3 G3 NET: 30% G3 NEC: 70%	chi-squared test (platinum chemotherapy): *G3 NET vs. G3 NEC* • CR/PR: 0% vs. 61%; p< 0.001	Not reported	N/A
Kim 2017 [36]	R	31	GEP-NENs Unknown 52% Pan 16% Stomach 13% Duodenum 13% Rectum 6%	All G3 G3 NET: 45% G3 NEC: 55%	chi-squared test (etoposide-cisplatin): *G3 NET vs. G3 NEC:* • CR/PR: 36% vs. 41%; p = 0.525 *Ki67 > vs. ≤ 60%:* • CR/PR: 71% vs. 29%; p = 0.043	Median (Kaplan-Meier/log-rank test): *G3 NET vs. G3 NEC:* • 21.2 vs. 6.7 months; p = 0.163 *Ki67 > vs. ≤ 60%:* • 8 vs. 9 months; p = 0.959	Not tested
Lacombe 2021 [37]	R	89	NENs Lung 42% Pan 30% GI 28%	All G3 G3 NET: 11% G3 NEC: 89%	chi-squared test (etoposide-cisplatin): *G3 NET vs. G3 NEC (large cell) vs. G3 NEC (small cell)*: • CR/PR: 20% vs. 32% vs. 75%; p = 0.040 (NEC vs. NET)	MVA (cox-regression) *G3 NEC (small cell) vs. G3 NET/G3 NEC (large cell):* • HR: range 0.54-0.59 on different models; p >0.05	No[b]

Reference	Study type	N	Primary sites	Grade/ Differentiation	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
					• DCR: 60% vs. 71% vs. 94%; p = 0.08 (NEC vs. NET) <u>MVA (logistic regression)</u> *G3 NEC (small cell) vs. G3 NET/G3 NEC (large cell):* • odds ratio: range 7.63-8.89 on different models; p = 0.001		
Vélayoudom-Céphise 2013 [38]	R	28	NEN GEP-NEN 50% Thoracic 14% Unknown 25%	All G3 G3 NET: 43% G3 NEC (large cell): 57%	<u>chi-squared test (cisplatin-chemotherapy):</u> *NET G3 vs. NEC G3 (large cell)* • CR/PR: 0% vs. 31%; p = 0.31	Not reported	N/A
Raj 2017 [39]	R	45	PanNENs	All G3 G3 NET: 36% G3 NEC: 64%	<u>chi-squared test (platinum agents):</u> *NET G3 vs. NEC G3 (large cell):* • CR/PR: 10% vs. 37% <u>chi-squared test (alkylating agents):</u> *NET G3 vs. NEC G3 (large cell):* • CR/PR: 50% vs. 50%	Not reported	N/A

Reference	Study type	N	Primary sites	Grade/ Differentiation	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
Merola 2020 [40]	R	72	GEP-NEN Pan 61% Colorectal 18%	G1: 3% G2: 42% G3 NET: 17% G3 NEC: 39%	Not reported	MVA (cox-regression) *G3 NEC vs. G3 NET (following FOLFOX-4):* • HR 3.86 (95% CI 1.09–13.68); p = 0.03	Yes
Hayes 2021 [13]	R	142	GEP-NENs Pan 51% GI 36%	All G3 G3 NET: 52% G3 NEC: 48%	chi-squared test (platinum chemotherapy, n = 59): *G3 NET vs. G3 NEC* • CR/PR: 42% vs. 54%; p = 0.43 • Progressive disease: 18% vs. 29%; p = 0.36 • Stable disease: 39% vs 17%; p = 0.08	Median (Kaplan-Meier/log-rank test): *G3 NEC vs. G3 NET:* • 5 vs. 7 months; p = 0.07 MVA (cox-regression) *G3 NEC vs. G3 NET:* • not significant (data not reported)	No
Response/prognosis after PRRT							
Carlsen 2019 [41]	R	149	GEP-NEN Pan 60% GI 23% Unknown 17%	All G3 NET G3: 39% NEC G3, Ki-67<55%: 30% NEC G3, Ki-67 ≥55%: 11% Missing: 20%	*G3 NET vs. G3 NEC:* • CR/PR: 42% vs 43%	UVA (cox-regression) *G3 NEC vs. G3 NET:* • HR 1.62 (95% CI 1.11–2.36); p = 0.01 MVA (cox-regression) *G3 NEC vs. G3 NET:* • HR 1.69 (95% CI 0.88–3.23); p = 0.11	No

[a] 164 pts received first-line chemotherapy (88% received platinum-etoposide). [b] Ki67 as a continuous variable was a significant predictor of PFS.

CI, confidence interval; CR, complete response; CTx, chemotherapy; DCR, disease control rate; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; P, prospective; Pan, pancreas; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; R, retrospective; SB, small bowel; UVA, univariate analysis

eTable 11. Quality assessment for studies included in evidence review which evaluated the impact of tumor differentiation on response and prognosis following therapy.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Li 2017	Level 4/Very low	No	N/A	Very low
Elvebakken 2021	Level 2/Moderate	No	N/A	Moderate
Heetfeld 2015	Level 3/Low	-1	-no multivariate analysis	Very low
Hijoka 2017	Level 3/Low	-1	-no multivariate analysis	Very low
Kim 2017	Level 4/Very low	No	N/A	Very low
Lacombe 2021	Level 3/Low	-1	-small G3 NET subgroup, high proportion of lung NENs	Very low
Vélayoudom-Céphise 2013	Level 4/Very low	No	N/A	Very low
Raj 2017	Level 4/Very low	No	N/A	Very low
Merola 2020	Level 3/Low	No	N/A	Low
Hayes 2021	Level 3/Low	No	N/A	Low
Carlsen 2019	Level 3/Low	No	N/A	Low

[a] See checklist for evaluating quality of evidence Table S3
N/A, not applicable; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor

eTable 12. Summary of evidence for studies evaluating the impact of primary tumor site on response and prognosis following therapy

Reference	Study type	N	Primary sites	Grade/ Differentiation	Response data	PFS Findings	Significant independent prognostic factor on MVA?	
							RR	PFS
Response/prognosis after Chemotherapy								
Lamarca 2016 [42]	SR/ M-A	645 in 20 stud-ies	PanNET (n = 381) non-PanNET (n = 264)	All G1/2	Pooled odds ratio for response *non-PanNETs vs. PanNETs (14 studies)[a]:* • 0.35 (95% CI 0.18–0.66); p<0.001 Odds ratio after sensitivity analysis *non-PanNETs vs. PanNETs* • 0.45 (95% CI 0.19–1.07); p = 0.07	5 studies reported on PFS one of which found no difference in median PFS between PanNETs and non-PanNETs (Other studies weren't reported)	N/A	N/A
Elvebakken 2021 [6]	R	196	GEP-NENs Pan 27% Colon 22% Unknown 24%	All G3 NET G3: 12% NEC Ki67<55%: 30% NEC Ki67≥55%: 57% Ambiguous: 2%	chi-squared test (88% platinum-etoposide): *colon vs. other primaries*: • CR/PR: 17% vs. 43%; p = 0.008 MVA (logistic regression) *Colon vs. other primaries:* • NECs: Odds ratio 0.13 (95% CI 0.02–0.82); p = 0.029 • G3 NETs: Odds ratio 0.63 (95% CI 0.06–6.28); p = 0.698	Median (Kaplan-Meier/log-rank test): *colon NEC vs.other NEC:* • 3.1 vs. 6.1 months; (p = 0.170)	Yes	Not tested

Reference	Study type	N	Primary sites	Grade/ Differentiation	Response data	PFS Findings	Significant independent prognostic factor on MVA?	
							RR	PFS
Merola 2020 [40]	R	72	GEP-NEN Pan 61% Colorectal 18%	G1: 3% G2: 42% G3 NET: 17% G3 NEC: 39%	Not reported	UVA (cox-regression) *PanNEN vs. other NEN (following FOLFOX-4):* • HR 0.57 (95% CI 0.34-0.95); p = 0.03 MVA (cox-regression) *PanNEN vs. other NEN (following FOLFOX-4):* • HR 0.96 (95% CI 0.31-2.95); p = 0.94	N/A	No
Heetfeld 2015 [8]	R	204	GEP-NENs Pan 32% Colon 15% Rectum 12% Stomach 8%	All G3 G3 NET: 15% G3 NEC: 79%	chi-squared test (following platinum-etoposide): *PanNEC vs. colon NEC*: • DCR: 63% vs. 64%; p = 0.82	Not reported	Not tested	N/A
Chatzellis 2019 [34]	R	79	NENs Pan 38% GI 19% Lung/ thymus 22% Unknown 18%	G1: 14% G2: 34% G3: 30% WHO 2017 criteria Group 1 (<3%) Group 2 (3–20%) Group 3 (21–55%)	chi-squared test (following CAPTEM): *PanNEC* • DCR: 70% *Lung/thymic* • DCR: 65% *GI* • DCR: 53% *Unknown*	MVA (cox-regression) *GI NEN vs. PanNEN:* • HR: 0.3 (95% CI 0.1–0.8); p = 0.009	Not tested	Yes

Reference	Study type	N	Primary sites	Grade/ Differentiation	Response data	PFS Findings	Significant independent prognostic factor on MVA?	
							RR	PFS
				Group 4 (>56%) Ki-67 >56%: 11%	• DCR: 43% p = 0.374			
Al-Toubah 2022 [43]	R	462	NENs (Pan 71%, SB 9%, Lung 7%)	G1: 15% G2: 41% G3: 20% Missing: 24% Differentiation: Well: 79% Poor: 8% Missing: 13%	chi-squared test (following CAPTEM): *Pan vs. other primaries*: • CR/PR: 51.5% vs. 31.8%; p<0.0001	Median (Kaplan-Meier/log-rank test): *Pan vs. other primaries*: • 23 vs. 10 months; p<0.0001	Not tested	Not tested
Ozaslen 2017 [26]	R	165 CTx[b]: 61	NETs Pan 31% GI 30% Lung 16%	G1: 45% G2: 55% WHO 2010 criteria	chi-squared test (following CTx) *GI vs. Pan*: • CR/PR: 44% vs. 41%; p = 0.72	UVA (cox-regression) *Non-PanNET vs. PanNET:* • HR 2.12 (95% CI 1.08-4.17); p = 0.029 MVA (cox-regression) *Non-PanNET vs. PanNET:* • HR 2.39 (95% CI 0.57–9.92); p = 0.23	Not tested	No
Response/prognosis after SSAs								
Ozaslen 2017 [26]	R	165 SSA: 104	NETs Pan 31% GI 30% Lung 16%	G1: 45% G2: 55% WHO 2010 criteria	chi-squared test (following SSAs) *GI vs. Pan*: • CR/PR: 29% vs. 10%.	UVA (cox-regression) *Non-PanNET vs. PanNET:* • HR 0.77 (95% CI 0.42–1.42);	Not tested	No

Reference	Study type	N	Primary sites	Grade/ Differentiation	Response data	PFS Findings	Significant independent prognostic factor on MVA?	
							RR	PFS
					p = 0.04	p = 0.41 <u>MVA (cox-regression)</u> *Non-PanNET vs. PanNET:* • HR 0.61 (95% CI 0.29–1.27); p = 0.19		
Laskaratos 2016 [44]	R	254	NETs SB 80% Pan 9% Lung 6%	G1: 58% G2: 23% WHO 2010 criteria	Not reported	<u>MVA (cox-regression)</u> HRs not reported, pancreatic primary predictor of shorter time to progression	N/A	Yes
Laskaratos 2020 [27]	R	102	GEP-NETs SB 62% Pan 30%	G1: 52% G2: 38% Missing: 10% WHO 2019 criteria	Not reported	<u>UVA (cox-regression)</u> *PanNET vs. SB:* • HR 0.91 (95% CI 0.54-1.53); p = 0.72 *Colorectal vs. SB:* • HR 1.53 (95% CI 0.72-3.25); p = 0.27 <u>MVA (cox-regression)</u> Not tested	N/A	Not tested
Diamantopoulos 2021 [45]	R	105	GEP-NETs SB 81% Colorectal 11% Pan 8%	G1: 46% G2: 38% G3: 1% Missing: 16%	Not reported	<u>MVA (cox-regression)</u> *Colorectal vs. Pan:* • HR 0.04 (95% CI 0.01-0.34); p<0.01	N/A	Yes

Reference	Study type	N	Primary sites	Grade/ Differentiation	Response data	PFS Findings	Significant independent prognostic factor on MVA?	
							RR	PFS
						SB vs. Pan: • HR 0.48 (95% CI 0.18-0.69); p = 0.01)		
Response/prognosis after PRRT								
Katona 2017 [30]	R	28	NETs Pan 46% SB 29% Lung 14%	G1: 18% G2: 46% G3: 25% Missing: 11% WHO 2010 criteria	Not reported	<u>UVA (cox-regression)</u> *PanNET vs. (reference unclear):* • HR 0.85 (95% CI 0.33–2.17); p = 0.73 *SB vs. (reference unclear):* • HR 1.29 (95% CI 0.45–3.69); p = 0.63	N/A	Not tested
Carlsen 2019 [41]	R	149	GEP-NEN Pan 60% GI 23% unknown 17%	All G3 NET G3: 39% NEC G3, Ki-67<55%: 30% NEC G3, Ki-67 ≥55%: 11% Missing: 20%	Not reported	<u>MVA (cox-regression)</u> *Unknown vs. Pan:* • HR 0.66 (95% CI 0.28-1.57); p = 0.35 *Unknown vs. GI:* • HR 0.80 (95% CI 0.32-2.02); p = 0.64	N/A	No

[a] The most commonly used drugs were 5-FU/ capecitabine (12 studies) and alkylating agents (10 studies). [b] Cisplatin/etoposide (n = 42), CAPTEM (n = 7), streptozocin-based (n = 9), other (n = 3)

CAPTEM, capecitabine-temozolomide; CI, confidence interval; CR, complete response; CTx, chemotherapy; DCR, disease control rate; GI, gastrointestinal; HR, hazard ratio; M-A, meta-analysis; MVA, multivariate analysis; N/A, not applicable; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; OS, overall survival; P, prospective; Pan, pancreas; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; R, retrospective; SB, small bowel; SR, systematic review; SSA, somatostatin analogue; UVA, univariate analysis

eTable 13. Quality assessment for studies included in evidence review which evaluated the impact of primary tumor site on response and prognosis following therapy.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Lamarca 2016	Level 2/Moderate	-1	-High-risk of bias/low quality studies with small populations	Low
Elvebakken 2021	Level 2/Moderate	No	N/A	Low
Merola 2020	Level 3/Low	No	N/A	Low
Heetfeld 2015	Level 3/Low	No	N/A	Low
Chatzellis 2019	Level 3/Low	No	N/A	Low
Al-Toubah 2022	Level 4/Very low	No	N/A	Very low
Ozaslen 2017	Level 3/Low	No	N/A	Low
Laskaratos 2016	Level 3/Low	-1	-Hazard ratios not reported	Very low
Laskaratos 2020	Level 3/Low	No	N/A	Low

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Diamantopoulos 2021	Level 3/Low	No	N/A	Low
Katona 2017	Level 3/Low	-1	-Very small heterogeneous population (n=28)	Very low
Carlsen 2019	Level 3/Low	No	N/A	Low

[a] See checklist for evaluating quality of evidence Table S3

N/A, not applicable

eNarrative

Genomic profiling and single-gene biomarkers

Expression or genomic alterations in *DAXX/ATRX* genes have been studied as prognostic markers in pancreatic NENs. [46-48] The majority of these studies found that *DAXX/ATRX* alterations were not prognostic; however, some studies reporting only on metastatic disease saw a trend for improved OS with altered *ATRX/DAAX*. Loss of *ATRX* and *DAXX* expression is associated with activation of alternative lengthening of telomeres (ALT) pathways, which may serve as a more robust marker than *ATRX* and *DAXX* alone.[49,50]

Similarly, conclusions on the prognostic value of alterations in *RB1*, *KRAS*, and *TP53* from retrospective studies have been mixed.[11,12,51-54] Two retrospective studies identified altered *RB1*expression and/or *KRAS* mutation as significant predictors of sensitivity to platinum-chemotherapy in G3 pancreatic NENs; however, this evidence is currently not sufficient to inform treatment.[12,51]

Mutations in *BRAF* (mostly V600E) occur most frequently in GEP-NECs, particularly in colorectal NECs (Table 3).[54-58] Retrospective studies evaluating the impact of *BRAF* alterations on prognosis and treatment efficacy following conventional therapy in GEP-NENs have reported conflicting results.[11,52,54] *BRAFV600E* remains a promising targetable mutation in GEP-NENs given the approval of dabrafenib and trametinib by the U.S. Food and Drug Administration for metastatic solid tumors with *BRAFV600E* mutations.[59] Several case studies have reported partial responses or stable disease in patients with *BRAF*-mutated colorectal NECs receiving BRAF-targeted therapy.[60-62] Prospective studies are needed to confirm the efficacy of this approach.

Other tumor-agnostic therapies linked to specific genomic alterations have been approved in multiple jurisdictions. These include pembrolizumab for cancers with microsatellite instability/mismatch repair deficiency (MSI-H/MMRd) or high tumor mutational burden (TMB-H), and TRK inhibitors (larotrectinib/entrectinib) for cancers harbouring fusions or rearrangements in *NTRK*. The published studies evaluating the impact of TMB-H or MSI-H on prognosis in G3 GEP-NENs are few and of low quality, with trends reported for correlation with decreased and increased survival, respectively.[7,55] Data supporting the efficacy of immunotherapy in GEP-NENs with TMB-H or MSI-H/MMRd is also limited (3 prospective studies including a total of 11 and 12 patients with TMB-H and MSI-H, respectively); thus, evidence is insufficient to recommend routine testing for these biomarkers.[63-65] Although NTRK alterations are associated with response to TRK inhibitors across histologies, few

studies have reported outcomes specifically in GEP-NENs (13 patients total with reported data).[66-70] Based on this data and the rarity of NTRK alterations in GEP-NENs, routine testing is not recommended. However, patients found to have *NTRK* fusions should be considered for treatment with TRK inhibitors.

eTable 14. Summary of evidence for studies evaluating the impact of MGMT expression/methylation on response and prognosis following initiation of alkylator-based therapy

Reference	Study type	N	Primary sites	Grade/ Differ-enti-ation	MGMT expression testing method	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?	
Trillo Aliaga 2021 [71]	SR/ M-A	858 in 12 stud-ies	Pan-NET and extra-Pan-NET (7 studies) PanNET only (5 studies)	N/A	PSQ MSP IHC	Pooled odds ratio for response *MGMT deficient vs. proficient (11 studies):* • Overall: 2.29 (95% CI 1.34–3.91); p < 0.001; I^2: 55% • MGMT testing by IHC: 2.41 (95% CI 1.11–5.21); p = 0.025; I2: 54% • MGMT testing by promoter methylation: 2.45 (95% CI 1.40–4.30); p = 0.002; I2: 22% • 3 of 11 studies reported statistically significant improve-ment in ORR for pts with MGMT deficiency	Pooled hazard ratio for PFS *MGMT deficient vs. proficient (10 studies):* • Overall: 0.56 (95% CI: 0.43–0.74); p < 0.001 • MGMT testing by IHC: 0.63 (95% CI: 0.47–0.83); p = 0.001 • MGMT testing by promoter methylation: 0.43 (95% CI: 0.28–0.67); p < 0.001 • 2 of 10 studies reported statistically significant improvement in PFS for pts with MGMT deficiency	N/A	N/A
Kunz 2023 [24]	RCT	133	PanNET	G1: 57% G2: 43%	MSP IHC	chi-squared test *TEM vs. CAPTEM*: • CR/PR: 33.8% vs. 39.7%; p = 0.59[a] *MGMT expression[b] by IHC(low vs. high):*	MVA (cox-regression) *TEM vs. CAPTEM*: • Overall: HR 1.36 (95% CI 0.47-3.91) • MGMT deficient: HR 0.51 (95% CI 0.26-1.01)	Not tested	Not tested

Reference	Study type	N	Primary sites	Grade/ Differ-enti-ation	MGMT expression testing method	Response data	PFS Findings	Significant independent prognostic factor on MVA (PFS)?	
						• CR/PR: 52% (33/63) vs. 15% (5 of 34); • Odds ratio 6.38 (95% CI 2.19-18.60); p = 0.0004 *MGMT methylation[b] (yes vs. no):* • CR/PR: 85% (6/7)c vs. 38% (19/50); • Odds ratio 9.79 (95% CI 1.09-87.71); p = 0.04			
Brighi 2023 [72]	P	22	NETs Pan 64% Lung 23%	G1: 14% G2: 54% G3: 32%	PSQ	chi-squared test *MGMT-promoter methylated (n = 5) vs un-methylated (n = 17):* • CR/PR: 60% vs. 24%; p = 0.274 • DCR: 100% vs. 88%; p = 1.00	Median (Kaplan-Meier/log-rank test): *MGMT-promoter methylated (n = 5) vs un-methylated (n = 17):* • Not reached vs. 30.2 months; p = 0.005	Not tested	Not tested
Jeong 2021 [73]	P/R	30	GEP-NEN Pan 43% SB 13% Biliary 13% Rectum 10%	All G3 G3 NET: 77% G3 NEC: 23%	IHC MSP	chi-squared test *MGMT deficient (n = 14) vs. proficient (n = 12) by IHC:* • CR/PR: 21.4% vs. 25.0%; p = 1.000) • DCR 78.6% vs. 75.0%; p = 1.000	Median (Kaplan-Meier/log-rank test): *MGMT deficient (n = 14) vs. proficient (n = 12) by IHC:* • 4.1 vs. 6.3 months; p = 0.712	Not tested	Not tested

[a] study was not powered for a RR end point. [b] Most characteristics have similar patterns of distribution when compared with the overall study population, except sex. In the overall study population, there were more males; in the cohort of patients who underwent MGMT by promoter methylation or by both methods, there was a predominance of females. [c] All patients (n = 7) with positive promoter methylation also had low IHC

CAPTEM, capecitabine-temozolomide; CI, confidence interval; CR, complete response; DCR, disease control rate; GI, gastrointestinal; HR, hazard ratio; IHC, immunohistochemistry;

MGMT, O(6)-methylguanine DNA methyltransferase; MSP, Methylation-specific polymerase chain reaction; MVA, multivariate analysis; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; OS, overall survival; P, prospective; Pan, pancreas; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; PSQ, pyrosequencing; R, retrospective; SB, small bowel; SSA, somatostatin analogue; UVA, univariate analysis

eTable 15. Quality assessment for studies included in evidence review which evaluated the impact of MGMT expression/methylation on response and prognosis following initiation of alkylator-based therapy.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Trillo Aliaga 2021	Level 2/Moderate	-1	-heterogenous/low quality studies included -high variability in MGMT testing methods -possible publication bias	Low
Kunz 2022	Level 2/Moderate	No	N/A	Moderate
Brighi 2023	Level 2/Moderate	-1	-Small population -Statistical power was insufficient to assess factors predictive of the efficacy of CAPTEM -No non-temozolomide control arm	Low
Jeong 2021	Level 2/Moderate	-1	-Small population -Statistical power was insufficient to assess factors predictive of the efficacy of CAPTEM -No non-temozolomide control arm	Low

[a] See checklist for evaluating quality of evidence Table S3
CAPTEM, capecitabine-temozolomide; MGMT, O(6)-methylguanine DNA methyltransferase; N/A, not applicable

eTable 16. Summary of evidence for studies evaluating the impact of SSTR imaging parameters on prognosis.

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
							OS	PFS
Lee 2019 [74]	SR/ M-A	474 8 stud-ies	5 of 8 studies enrolled GEP-NENs exclusively	5 of 8 studies enrolled G1/G2 patients exclusively 1 of 8 studies enrolled G3 patients exclusively	Pooled HR *Low vs. high SUV_{max} :* • HR 2.97 (95% CI: 1.71–5.15); p = 0.0001	Pooled HR *Low vs. high SUV_{max} :* • HR 2.31 (95% CI: 1.34–4.00); p = 0.003	N/A	N/A
Tirosh 2018 [75]	P	184	GEP-NENs Pan 54% SB 31%	G1: 22% G2: 15% G3: 2% Missing: 61%	UVA (cox-regression) for disease specific mortality: *^{68}Ga-DOTATATE TV ≥ vs. < 35.8 mL:* • HR 12.5 (95% CI 2.7-57.7); p = 0.001 *^{68}Ga-DOTATATE SUVmax ≥ vs. < 55.9:* • HR 0.6 (95% CI 0.2-1.9); p = 0.4 MVA (cox-regression) for disease specific mortality: *^{68}Ga-DOTATATE TV ≥ vs. < 10.6 mL:* • HR 12.5 (95% CI 1.6-68.9); p = 0.014	UVA (cox-regression) *^{68}Ga-DOTATATE TV ≥ vs. < 7.0 mL:* • HR 2.4 (95% CI 1.2-4.9); p = 0.02 *^{68}Ga-DOTATATE SUVmax ≥ vs. < 55.9:* • HR 1.0 (95% CI 0.6-1.8); p = 0.9 MVA (cox-regression) *^{68}Ga-DOTATATE TV ≥ vs. < 7.0 mL:* • HR 3.0 (95% CI 1.1-8.7); p = 0.04	TV: yes SUV_{max}: no	TV: yes SUV_{max}: no
Campana 2010 [76]	P	44	NENs Pan 49% GI 38% Lung 13%	WD: 89% PD: 11% Ki-67<5: 61%	Not reported	UVA (cox-regression) *SUV_{max} ≤17.6 vs ≥19.3:* • HR 5.97 (95%: CI 2.22-16.1); p <0.001	N/A	SUV_{max}: yes

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
							OS	PFS
						MVA (cox-regression) *SUV_{max} ≤17.6 vs ≥19.3:* • HR 9.56 (95% CI 2.87-31.8); p <0.001		
Toriihara 2019 [77]	R	92	GEP-NETs SB 44% Pan 25%	G1: 60% G2: 40%	Not reported	UVA (cox-regression) *ΣSRETV ≥ vs. < 11.29 ml:* • p = 0.009 *DOTATATE-avid yes vs. no:* • p = 0.046 *SUV_{max} ≥ vs. < 25.2:* • p = 0.174 *ΣTLSRE ≥ vs. < 146.48 g:* • p = 0.056 MVA (cox-regression) *ΣSRETV ≥ vs. < 11.29 ml:* • HR 3.917 (95% C 1.091-14.07); p = 0.036 *SUV_{max} ≥ vs.< 25.2:* • HR 1.308 (95% CI 0.593–2.885); p = 0.507 *ΣTLSRE ≥ vs. < 146.48 g:*	N/A	ΣSRETV: yes $SUV_{max:}$ no ΣTLSRE: no

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
							OS	PFS
						• HR 0.447 (95% CI 0.112–1.796); p = 0.257		
Hayes 2021 [13]	R	142	GEP-NEN Pan 51% GI 36%	All G3 WD: 52% PD: 48%	<u>UVA (cox-regression)</u> *SSTR + vs. –* • Overall: p<0.0001 • WD NENs HR 0.31 (95% CI, 0.15–0.63); p = 0.001 <u>MVA (cox-regression)</u> *SSTR + vs. –* • overall: HR 1.43 (95% CI 1.05–1.95); p = 0.03	<u>UVA (cox-regression)</u> *SSTR + vs. – (after first-line platinum chemotherapy):* • overall: HR 0.51 (95% CI 0.30-0.88); p = 0.015	SSTR+: yes	Not tested
Ambrosini 2015 [78]	R	43	PanNETs	G1: 32% G2: 68%	Not reported	<u>UVA (cox-regression)</u> *SSTR-PET SUV_{max} ≤37.8 vs ≥38.0:* • HR 3.09 (95% CI 1.46–6.57); p = 0.003 <u>MVA (cox-regression)</u> *SSTR-PET SUV_{max} ≤37.8 vs ≥38.0*: • HR 2.37 (95% CI 1.03–5.47); p = 0.043	N/A	SUV_{max}: yes
Sharma 2014 [79]	R	37	NETs Pan 27% GI 49% Lung 24%	G1: 49% G2: 51%	Not reported	<u>UVA (cox-regression)</u> *SSTR-PET high vs. low (cut-off 14.5) $SUV_{max\ (log\text{-}transformed)}$:*	N/A	SUV_{max}: yes

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
							OS	PFS
						• HR 0.122 (95% CI 0.019 – 0.779); p = 0.026 MVA (cox-regression) *SSTR-PET high vs. low (cut-off 14.5) $SUV_{max\ (log\text{-}transformed)}$:* • HR 0.122 (95% CI 0.019 – 0.779); p = 0.026		
Zhang 2018 [80]	R	83	GEP-NENs Pan 33% GI 52%	G1: 17% G2: 34% G3: 34% WD: 61% PD: 39%	UVA (cox-regression) *SSTR – vs. +* • (unresectable NETs, n = 31): HR 10.4 (95% CI 1.5–78.2); p ≤ 0.001 • (unresectable NECs, n = 26): HR 2.4 (95% CI 0.3–5.4) p = 0.382	Not reported	SSTR -/+ NETs: SSTR -/+ NECs: no	N/A

CI, confidence interval; DOTATATE, DOTA-(Tyr^3)-octreotate; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; N/A, not applicable; NEC, neuroendocrine carcinomas; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; OS, overall survival; P, prospective; Pan, pancreas; PD, poorly differentiated; PET, positron emission tomography; R, retrospective; SB, small bowel; ΣSRETV, sum of somatostatin receptor expressing tumor volume; SR/M-A, systematic review/meta-analysis; SSTR, somatostatin receptor; SUVmax, maximum standardized uptake value; TV, tumor volume; ΣTLSRE, sum of total lesion somatostatin receptor expression; UVA, univariate analysis; WD, well-differentiated

eTable 17. Quality assessment for studies included in evidence review for the impact of SSTR imaging parameters on prognosis.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Lee 2019	Level 2/moderate	No	N/A	Moderate
Tirosh 2018	Level 2/moderate	No	N/A	Moderate
Campana 2010	Level 3/Low	No	N/A	Low
Toriihara 2019	Level 3/Low	No	N/A	Low
Hayes 2021	Level 3/Low	No	N/A	Low
Ambrosini 2015	Level 3/Low	No	N/A	Low
Sharma 2014	Level 3/Low	No	N/A	Low
Zhang 2018	Level 4/Very low	No	N/A	Very low

[a] See checklist for evaluating quality of evidence Table S3

N/A, not applicable; SSTR, somatostatin receptor

eTable 18. Summary of evidence for studies evaluating the impact of SSTR imaging parameters on response and prognosis following the initiation of SSTR-directed therapy.

Reference	Study type	N	Primary sites	Grade	Response Findings	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
Lee 2022 [81]	SR/ M-A	618 15 stud-ies	Majority of patients had GEP-NETs	• 10 studies did not report grade • Only 9 patients with G3	11 studies found SSTR-PET parameters that are significant predictors of response to PRRT: • baseline intratumoral SSTR heterogeneity (4 studies) • baseline SUVmax (6 studies) • baseline SUVmean (2 studies)	A higher baseline SUV was associated with: • longer PFS using SUVmax (3 studies), SUVT/S (1 study) and SUVT/L (1 study) A decreasing ΔSUV from baseline was associated with:	N/A

Reference	Study type	N	Primary sites	Grade	Response Findings	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
					• baseline SUVT/L (3 studies) • baseline SUVT/S (3 studies) • baselines SUVmax-av (SUV max of up to 5 lesions, 1 study) • ΔSUVT/S (1 study) • ΔSUVmax (1 study) • ΔSUVmean (1 study) • ΔSUVmax-av (1 study) • 4 studies found no correlation between PET parameters and response to PRRT (Gabriel, Huizing, Soydal, Weber). These studies evaluated SUVmax or ΔSUVmax • SUVmax thresholds for predicting response varied from >13-17	• longer PFS using ΔSUVmax-av (1 study) • longer TTP using ΔSUVT/S (1 study)	
Durmo 2022 [82]	P/R	46	NET SB 54% Pan 18% Lung 13%	G1: 46% G2: 41% G3: 4% NA: 9%	<u>Mann-Whitney U test</u> *Mean baseline TV in non-responders vs. responders (following PRRT):* • 1073.5 vs. 143.7 p < 0.001	Not reported	Not tested

Reference	Study type	N	Primary sites	Grade	Response Findings	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
					Mean baseline TLA in non-responders vs. responders (following PRRT): • 12,236.4 vs. 3108.13 p = 0.001 *No significant difference in baseline measures between non-responders and responders for:* • SUVmax, SUVmean, SUVT/S, ΔSUVmax, ΔSUVmean, ΔSUVT/S, ΔTV, ΔTLA <u>UVA (logistic regression)</u> *Baseline TV (cut-off value unclear):* • odds ratio: 1.17 (95% CI 1.02–1.32) p = 0.02		
Ohlendorf 2022 [83]	R	32	GEP-NETs	All G1/2	Not reported	<u>UVA (cox-regression)</u> *TLA-SSTR high vs. low following PRRT:* • HR 5.16 (95% CI 1.61-29.67); p = 0.009 <u>MVA (cox-regression)</u> *TLA-SSTR high vs. low following PRRT:* • p = 0.0215	Yes

Reference	Study type	N	Primary sites	Grade	Response Findings	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
						SSTR-TV high vs. low following PRRT: • p = 0.0067	
Sitani 2021 [84]	R	468	NET Pan 30% SB 24% Lung 12%	G1: 49% G2: 44% G3: 6%	Chi-squared test *SUV_{max} ≥20 vs. <20 (following PRRT):* • DCR: 92.8% vs. 83.5%; p = 0.002	UVA (cox-regression) *SUV_{max} <20 vs ≥20:* • HR 2.19 (95% CI 1.35-3.56); p<0.05 MVA (cox-regression) *SUV_{max} <20 vs ≥20:* • HR 1.63 (95% CI 1.0–2.68); p = 0.05	No
Zhang 2019 [85]	R	69	GEP-NEN Pan 67% Midgut 9%	All G3 Ki67 ≤55%: 77% Ki67 >55%: 16%	Not clear	Median (Kaplan-Meier/log-rank test) following PRRT *SUV_{max} >15 vs ≤15:* • 16 vs. 5 months; p<0.05	Not tested
Koch 2014 [86]	R	30	Ileal NETs	G1 and G2	Statistical test used unclear *Stable vs. progressive disease following SSA initiation:* • Baseline SUVmax (in lesions with highest uptake): 39.7 ± 21.2 vs. 30.2 ± 12.9; p = 0.139	UVA (cox-regression) *SUV_{max} > vs. < 29.5:* • HR 0.34 (95% CI 0.13–0.88); p = 0.019 *SUV_{mean} > vs. < 20.3:* • HR 0.34 (95% CI 0.13–0.88); p = 0.02	Yes (data not reported in manuscript)

Reference	Study type	N	Primary sites	Grade	Response Findings	PFS Findings	Significant independent prognostic factor on MVA (PFS)?
					• Baseline SUVmean (in lesions with highest uptake): 26.7 ± 15.5 vs. 20.6 ± 8.5, p = 0.173	MVA (cox-regression) SUV significant predictor (data not reported)	
Lee 2021 [87]	R	108	GEP-NETs (pan 25%, GI, 75%)	G1: 49% G2: 42% Ki67 ≤5%: 56% Ki67 >5%: 24%	Not reported	UVA (cox-regression) following SSA initiation *SUVmax <18.35 vs. ≥18.35:* • HR 4.15 (95% CI 1.88–9.15); p<0.001 MVA (cox-regression) following SSA initiation *SUVmax <18.35 vs. ≥18.35:* • HR 6.85 (96% CI 2.10–22.34); p = 0.001	Yes

CI, confidence interval; CR, complete response; DCR, disease control rate; DOTATATE, DOTA-(Tyr^3)-octreotate; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; N/A, not applicable; NEC, neuroendocrine carcinomas; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; P, prospective; Pan, pancreas; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; P/R, prospective enrollment, retrospective analysis; PR, partial response; PRRT, peptide receptor radionuclide therapy; R, retrospective; SB, small bowel; SD, stable disease; SR/M-A, systematic review/meta-analysis; SSTR, somatostatin receptor; SUVmax, maximum standardized uptake value; SUVmax-av, SUV $_{max}$ of up to 5 lesions; SUVmean, average standardized uptake value; SUVT/L, standardized uptake value tumor-to-liver ratio; SUVT/S, standardized uptake value tumor-to-spleen ratio; TLA, total lesion activity; TTP, time to progression; TV, tumor volume; UVA, univariate analysis; WD, well-differentiated

eTable 19. Quality assessment for studies included in evidence review that evaluate the impact of SSTR imaging parameters on response and prognosis following the initiation of SSTR-directed therapy.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Lee 2022	Level 2/moderate	No	N/A	Moderate
Durmo 2022	Level 3/Low	No	N/A	Low
Ohlendorf 2022	Level 3/Low	-1	small sample size (32 pts), only 18 pts evaluated for volumetric parameters	Very low
Sitani 2021	Level 3/Low	No	N/A	Low
Zhang 2019	Level 4/Very low	No	N/A	Very low
Koch 2014	Level 3/Low	-1	-Small sample size (30 pts) -Did not take into account effect of G1 vs G2 grading or Ki67 index on PFS -did not report details of MVA	Very low
Lee 2021	Level 3/Low	No	N/A	Low

[a] See checklist for evaluating quality of evidence Table S3

MVA, multivariate analysis; N/A, not applicable; PFS, progression-free survival

eTable 20. Summary of evidence for studies evaluating the impact of ^{18}FDG-PET imaging on prognosis

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
							OS	PFS
Han 2021 [88]	SR/ M-A	1799 23 stud-ies	NEN • 3 studies focused exclusively on Lung-NETs	10 studies did not report grade Only 9 patients with G3	Pooled HR *High vs. low FDG uptake:* • HR 3.50 (95% CI 2.75–4.45) I^2 = 12% • No significant difference in pooled HRs found by study	Pooled HR (event-free survival) *High vs. low FDG uptake:* • HR 2.84 (95% CI, 2.21–3.64) I^2 = 54%	N/A	N/A

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
							OS	PFS
			• 9 studies had populations with <50% of pts with distant metastasis or did not report % pts with distant metastasis		design, imaging setting, PET analysis used, or cut-off definition • Metaregression: higher proportion of G3 tumors was associated with increased HRs (adjusted p = 0.0422)			
Binderup 2021 [89]	P	166	GEP-NEN SB 54% Pan 22%	Ki-67 ≤2: 34% Ki-67 3-20%: 50% Ki-67: >20%: 10% Missing: 6%	<u>UVA (cox-regression)</u> *FDG + vs. - :* • Overall: HR 3.8 (95% CI 2.4–5.9); p< 0.001 • All G1/2: HR 3.6 (95% CI 2.2–5.9); p< 0.001 • G1/2 (SB-NETs): HR 3.9 (95% CI 2.1–7.3); p< 0.001 • G1/2 Pan-NETs: HR 9.3 (95% CI 1.2–70); p = 0.009 <u>MVA (cox-regression)</u> *FDG + vs. - :* • HR not reported; p <0.05	<u>UVA (cox-regression)</u> *FDG + vs. - :* • Overall: HR 2.5 (95% CI 1.7–3.5); p<0.001 • All G1/2: HR 2.6 (95% CI 1.8–3.9); p< 0.001 • GI/2 (SB-NETs): HR 2.5 (95% CU 1.5–4.1); p< 0.001 • G1/2 Pan-NETs: HR 6.8 (95% CI 1.5–30); p = 0.004 <u>MVA (cox-regression)</u> *FDG + vs. - :* • HR not reported; p <0.05	Yes, HR not reported	Yes, HR not reported

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
							OS	PFS
Stokmo 2022 [90]	R	66	GEP-NEN Pan 15% Colon 23% rectum 20% esophagus 12% Unknown 17%	All G3 79% poorly differentiated Ki-67 ≥55%: 77%	<u>UVA (cox-regression)</u> *tMTV continuous:* • HR 1.001 (95% CI 1.0006–1.002); p = 0.000003 *tMTV (high vs. low):* • HR 2.53 (95% CI 1.48–4.32); p = 0.0007 *tTLG continuous:* • HR 1.0001 (95% CI 1.00007–1.0002), p = 0.0000001 *tTLG (high vs. low):* • HR 2.42 (95% CI 1.42–4.13); p = 0.001 SUVmax continuous: • HR 1.03 (95% CI 1.01–1.05); p = 0.003 <u>MVA (cox-regression)</u> *tMTV continuous:* • HR 1.001 (95% CI 1.0007–1.0016); p = 0.0000031	Not reported	tMTV: yes tTLG: yes SUV_{max}: Yes/no depending on model	N/A

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
							OS	PFS
					tTLG continuous: • HR 1.00013 (95% CI 1.00008–1.00017); p = 0.000000293 SUVmax (MTV model): • HR 1.03 (95% CI 1.0003–1.05); p = 0.02 SUVmax (TLG model): • HR 1.017 (95% CI 0.99–1.04); p = 0.13			
Magi 2022 [91]	R	55	GEP-NETs GI 56% Pan 44%	All G1	UVA (cox-regression) *FDG + vs. - :* • Not significant, HR not reported	UVA (cox-regression) *FDG + vs. - :* • HR 2.17 (95% CI 1.01–4.69); p = 0.04	Not performed	Not performed

CI, confidence interval; FDG, fluorodeoxyglucose; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; N/A, not applicable; NEC, neuroendocrine carcinomas; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; P, prospective; Pan, pancreas; PET, positron emission tomography; PFS, progression-free survival; R, retrospective; SB, small bowel; SD, stable disease; SR/M-A, systematic review/meta-analysis; SUVmax, maximum standardized uptake value; tMTV, total metabolic tumor volume; tTLG, total total lesion glycolysis; UVA, univariate analysis;

eTable 21. Quality assessment for studies included in evidence review which evaluated the impact of ^{18}FDG-PET imaging on prognosis.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Han 2021	Level 2/moderate	No	N/A	Moderate
Binderup 2021	Level 2/moderate	-1	-did not report details of MVA	Low
Stokmo 2022	Level 3/Low	No	N/A	Low
Magi 2022	Level 4/Very low	No	N/A	Very low

[a] See checklist for evaluating quality of evidence Table S3

MVA, multivariate analysis; N/A, not applicable

eTable 22. Summary of evidence for studies evaluating the impact of ^{18}FDG-PET imaging on response and prognosis following initiation of PRRT

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Response findings	Significant independent prognostic factor on MVA?	
								OS	PFS
Binderup 2021 [89]	P	166	GEP-NEN SB 54% Pan 22%	Ki-67≤2: 34% Ki-67 3-20%: 50% Ki-67: >20%: 10%	<u>UVA (cox-regression)</u> *PRRT vs. no PRRT:* • All: HR 0.6 (95% CI 0.4-0.96); p = 0.033 • FDG-: HR 1.2 (95% CI 0.6-2.6); p = 0.602 • FDG+: HR 0.4 (95% CI 0.3-0.7); p = 0.002 <u>UVA (cox-regression)</u>	Not reported	Not reported	N/A	N/A

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Response findings	Significant independent prognostic factor on MVA?	
								OS	PFS
				Missing: 6%	*FDG+ vs. FDG- in patients receiving PRRT:* • HR 2.4 (95% CI 1.2-4.6); p = 0.007				
Sansovini 2017 [92]	R	60	Pan-NETs	G1: 25% G2: 53%	<u>UVA (cox-regression)</u> *FDG+ vs. - :* • HR not reported p = 0.006 <u>MVA (cox-regression)</u> *FDG+ vs. - :* • HR 4.89 (95% CI 1.35–17.65); p = 0.015 *FDG reduced activity vs. full activity:* • HR 3.17 (95% CI 1.08–9.34); p = 0.0361	<u>UVA (cox-regression)</u> *FDG+ vs. - :* • HR not reported p = 0.0002 <u>MVA (cox-regression)</u> *FDG+ vs. - :* • HR 4.27 (95% CI 1.88–9.69); p = 0.0005 *FDG reduced activity vs. full activity:* • HR 1.18 (95% CI 0.60–2.34); p = 0.627	<u>Descriptive response rates</u> *FDG- vs. FDG+:* • DCR: 95.7% vs. 78.1% • CR/PR: 43% vs. 25%	Yes	Yes
Rodrigues 2021 [93]	R	40	GEP-NET SB 45% Pan 45%	G1: 5% G2: 73% G3: 20%	<u>Median (Kaplan-Meier/log-rank test)</u> *FDG- vs. FDG+:* • 145.5 vs. 95.1 months; p = 0.033	Not reported	Not reported	N/A	N/A
Nilica 2016 [94]	R	66	NENs (Pan 30%, SB	G1: 18%	Not reported	Not reported	<u>Chi-squared test</u> *FDG- vs. FDG+:*	N/A	N/A

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Response findings	Significant independent prognostic factor on MVA?	
								OS	PFS
			37%, Lung 12%)	G2: 71% G3: 11%			• p<0.05		
Severi 2013 [95]	R	52	NETs Pan 56% GI 23% Lung 2%	G1: 37% G2: 63%	Not reported	Median (Kaplan-Meier/log-rank test) *FDG+ vs. FDG- :* • 20 vs. 32 months; p = 0.033	Chi-squared test *FDG+ vs. FDG-:* • CR: 3.1% vs. 10.5% • PR: 18.2% vs. 10.5% • SD: 54.5% vs. 79% • DCR: 76% vs. 100% p = 0.020 • G1 DCR: 91% vs. 100% • G2 DCR: 68% vs. 100%	N/A	N/A
Sitani 2021 [84]	R	468	NETs Pan 30% SB 24% Lung 12%	G1: 49% G2: 44% G3: 6%	Not tested	UVA (cox-regression) *SUVmax ≥ 5 vs. < 5:* • HR 2.18 (95% CI 1.35–3.53); p<0.05 MVA (cox-regression) *SUVmax ≥ 5 vs. < 5:* • HR 1.91 (95% CI 1.16–3.12); p = 0.01	Chi-squared test *SUVmax < vs. ≥ 5:* • DCR: 93% vs. 85%; p = 0.02	N/A	Yes

Reference	Study type	N	Primary sites	Grade	OS Findings	PFS Findings	Response findings	Significant independent prognostic factor on MVA?	
								OS	PFS
Zemczak 2020 [96]	R	75	NET Pan 32% SB 29% Lung 21%	G1: 36% G2: 64%	Median (Kaplan-Meier/log-rank test) *FDG+ vs. FDG- :* • From diagnosis: 71.8 months vs. NR; p = 0.003 • Since PRRT: 55.8 months vs. NR; p = 0.002	Median (Kaplan-Meier/log-rank test) *FDG+ vs. FDG- :* • Overall: 22.2 vs. 59.3 months; p = 0.0027 • G2 only: 22.2 vs. 40.6 months; p = 0.0284 • G1 only: 23.1 vs. 59.3 months; p = 0.049	Descriptive 12-month response *FDG+ vs. FDG-:* • CR: 4.2% vs. 2.1% • PR: 37.5% vs. 14.9% • SD: 41.7% vs. 68.1% • DCR: 83.4% vs. 85.1% • ORR: 41.7% vs. 17%		
Nicolini 2018 [97]	P/R	33	GEP-NENs	Ki-67 ≤35%: 39% Ki-67 >35%: 61%	Not reported	Median (Kaplan-Meier/log-rank test) *FDG- vs. FDG+* • (Ki-67 ≤35%): 65.5 vs. 23.0 months; p = 0.039	Descriptive response rates *FDG- vs. FDG+ (Ki-67 ≤35%):* • DCR: 86% vs. 93%	N/A	N/A
Zhang 2020 [98]	R	495	NENs Pan 40% Midgut 28% Lung 8%	G1: 24% G2: 50% G3: 6%	UVA (cox-regression) *FDG+ vs. - :* • p<0.001 MVA (cox-regression) *FDG+ vs. - :* • HR 0.5 (95% CI 0.3–0.8); p = 0.002	UVA (cox-regression) *FDG+ vs. - :* • p = 0.002 MVA (cox-regression) *FDG+ vs. - :* • HR 0.7 (95% CI 0.5–0.9); p = 0.007	Not reported	Yes	Yes

CI, confidence interval; CR, complete response; DCR, disease control rate; DOTATATE, DOTA-(Tyr^3)-octreotate; FDG, fluorodeoxyglucose; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; N/A, not applicable; NEC, neuroendocrine carcinomas; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; NR, not reached; ORR, overall response rate; P, prospective; Pan, pancreas; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; P/R, prospective enrollment, retrospective analysis; R, retrospective; SB, small bowel; SD, stable disease; SUVmax, maximum standardized uptake value; UVA, univariate analysis

eTable 23. Quality assessment for studies included in evidence review which evaluated the impact of ^{18}FDG-PET imaging on response and prognosis following initiation of PRRT.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Binderup 2021	Level 3/Low	-1	- did not report characteristics of pts with/without PRRT, was not a MVA	Very low
Sansovini 2017	Level 3/Low	No	N/A	Low
Rodrigues 2021	Level 4/Very low	No	N/A	Very low
Nilica 2016	Level 4/Very low	No	N/A	Very low
Severi 2013	Level 4/Very low	No	N/A	Very low
Sitani 2021	Level 3/Low	No	N/A	Low
Zemczak 2020	Level 4/Very low	No	N/A	Very low
Nicolini 2018	Level 4/Very low	No	N/A	Very low
Zhang 2020	Level 3/Low	No	N/A	Low

[a] See checklist for evaluating quality of evidence Table S3

MVA, multivariate analysis; N/A, not applicable, PRRT, peptide receptor radionuclide therapy

eTable 24. Summary of evidence for studies evaluating the impact of SSTR imaging and FDG-PET imaging concordance scores (including NEPET) on prognosis

Reference	Study type	N	Primary sites	Grade	Score definition and distribution	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
								OS	PFS
Chan 2022 [99]	R	319	GEP-NEN Pan 36% Midgut 52%	G1: 29% G2: 51% G3 NET: 8% G3 NEC: 6%	NETPET score categories: P1: SSTRI+/ FDG- P2: FDG uptake <SSTRI uptake P3: FDG uptake = SSTRI uptake P4 FDG uptake >SSTRI P5: SSTRI-/FDG+) P1: 28% P2-4: 61% P5: 12%	<u>UVA (cox-regression)</u> *P1 vs. P5:* • HR 0.375 (95% CI 0.244–0.573); p < 0.001 P2–4 vs. P5 • HR 0.337 (95% CI 0.186–0.609); p < 0.001 P1 vs P2–4 • HR 0.133 (95% CI 0.065–0.274); p < 0.001 <u>MVA (cox-regression)</u> *NETPET score overall:* • HR 2.376 (95% CI 1.682–3.357); p < 0.001	<u>UVA (cox-regression)</u> *P1 vs. P5* • HR 0.375 (95% CI 0.244–0.573); p < 0.001 P2–4 vs. P5 • HR 0.337 (95% CI 0.186–0.609); p < 0.001 P1 vs P2–4 • HR 0.133 (95% CI 0.065–0.274); p < 0.001 <u>MVA (cox-regression)</u> *NETPET score overall:* • HR 2.376 (95% CI 1.682–3.357); p < 0.001	Yes	Yes
Chan 2017 [100]	R	62	NETs Pan 39% Midgut 32%	G1: 23% G2: 53% G3: 19%	NETPET score definitions as above P1: 18%	<u>UVA (cox-regression)</u> *NETPET score overall:* • Overall population: p = 0.0018; HR not reported	Not reported	Yes	N/A

Reference	Study type	N	Primary sites	Grade	Score definition and distribution	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
								OS	PFS
			Other 21%		P2-4: 53% P5: 29%	• GEP-NET: p<0.0001; HR not reported <u>MVA (cox-regression)</u> *NETPET score overall:* • Overall population: not performed, NETPET score was only significant factor on UVA • GEP-NET population: p = 0.0009			
Hayes 2022 [101]	R	87	GEP-NEN Midgut 54%, Pan 33%	G1: 23% G2: 62% G3 NET: 10% G3 NEC: 1%	D1: SSTRI+ and FDG – D2: SSTRI+ and FDG + D3: SSTRI– and FDG PET + or at least one SSTRI– and FDG PET + site D1: 29% D2: 62% D3: 9%	<u>UVA (cox-regression)</u> *D2 vs. D1:* • HR 8.61 (95% CI 1.14-65.3); p = 0.037 *D3 vs. D1:* • HR 15.6 (95% CI 1.73-140); p = 0.014 <u>MVA (cox-regression)</u> *D2 vs. D1:* • HR 4.55 (95% CI 0.72-6.53); p = 0.153 *D3 vs. D1:*	<u>UVA (cox-regression)</u> *D2 vs. D1:* • HR 2.31 (95% CI 1.10-4.82); p = 0.027 *D3 vs. D1:* • HR 3.01 (95% CI 1.11-8.14); p = 0.030 <u>MVA (cox-regression)</u> *D2 vs. D1:* • HR 1.89 (95% CI 0.88-4.03); p = 0.101	D2 vs. D1: no D3 vs. D1: yes	No

Reference	Study type	N	Primary sites	Grade	Score definition and distribution	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
								OS	PFS
						• HR 23.9 (95% CI 1.82–314.0); p = 0.016	*D3 vs. D1:* • HR 2.53 (95% CI 0.77–8.25); p = 0.125		
Karfis 2020 [102]	R	85	GEP-NEN SB 54% Pan 34%	G1: 25% G2: 54% G3: 21%	C1: SSTRI + and FDG– C2: ≥1 FDG+ lesions, all SSTRI+ C3: ≥1 FDG+ lesions, at least one SSTRI– C1: 33% C2: 54% C3: 13%	<u>UVA (cox-regression)</u> *C1 vs. C2:* • HR 0.51 (95% CI 0.25–1.04); p = 0.08 *C2 vs. C3:* • HR 0.39 (95% CI 0.14–1.09); p = 0.013 *C1 vs. C3:* • HR 0.21 (95% CI 0.06–0.70); p<0.001	<u>UVA (cox-regression)</u> *C1 vs. C2:* • HR 0.47 (95% CI 0.27–0.79); p = 0.004 *C2 vs. C3:* • HR 0.49 (95% CI 0.20–1.19); p = 0.036 *C1 vs. C3:* • HR 0.32 (95% CI 0.11–0.90); p = 0.002	Not tested	Not tested
Hou 2022 [103]	R	66	NEN Pan 35% GI 38% Lung 5%	G1: 21% G2: 46% G3: 33%	NETPET score definitions as above P1: 21% P2: 24% P3: 9% P4: 23% P5: 23%	Not reported	<u>UVA (cox-regression)</u> *NETPET score overall:* • HR 1.849 (95% CI 1.144-2.990); p = 0.012 <u>MVA (cox-regression)</u> *NETPET score overall:*	N/A	Yes

Reference	Study type	N	Primary sites	Grade	Score definition and distribution	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
								OS	PFS
							• HR 1.917 (95% CI 1.159-3.170); p = 0.011		
Lee 2022 [104]	R	31 (test co-hort) 21 (val-ida-tion co-hort)	GEP-NENs GI 25% Pan 56%	All G3	FDZ score (continuous variable) = Z-score from SSTRI – Z-score from FDG-PET imaging Z score = (log[SUVmax] - μ) ÷ σ (μ = arithmetic mean of log(SUVmax) and σ = standard deviation of distribution.) In cases where either 18F-FDG or 68GaDOTATATE PET/CT was missing (52%), the respective Z score was taken to be zero	<u>UVA (cox-regression)</u> *FDZ score > vs. <0.05:* • Test cohort: HR 0.20 (95% CI 0.07-0.62); p = 0.005 • Validation cohort: HR 0.20 (95% CI 0.05-0.80); p = 0.023 <u>MVA (cox-regression)</u> *FDZ score > vs. <0.05:* • Test cohort: HR 0.16 (95% CI 0.03-0.73); p = 0.018 • Validation cohort: HR 0.10 (95% CI 0.01-0.75); p = 0.025 <u>Mantel-Cox test</u> • Among patients with SSTRI and FDG-PET scans (n=25), NETPET score was not significantly correlated with OS (p = 0.340)	Not reported	FDZ score: Yes NET-PET: No	N/A

Reference	Study type	N	Primary sites	Grade	Score definition and distribution	OS Findings	PFS Findings	Significant independent prognostic factor on MVA?	
								OS	PFS
					NETPET score definitions as above NETPET distribution (n=25): P1: 8% P2-4: 80% P5: 12%				

CI, confidence interval; FDG, fluorodeoxyglucose; FDZ, FDG-DOTATATE-Z; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; N/A, not applicable; NEC, neuroendocrine carcinomas; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; Pan, pancreas; PET, positron emission tomography; PFS, progression-free survival; R, retrospective; SB, small bowel; SD, stable disease; SSTRI, somatostatin receptor imaging; UVA, univariate analysis;

eTable 25. Quality assessment for studies included in evidence review which evaluated the impact of SSTR imaging and FDG-PET imaging concordance scores (including NEPET) on prognosis.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Chan 2022	Level 3/Low	No	N/A	Low
Chan 2017	Level 3/Low	No	N/A	Low
Hayes 2022	Level 3/Low	No	N/A	Low
Karfis 2020	Level 4/Very low	No	N/A	Very low
Hou 2022	Level 3/Low	No	N/A	Low

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Lee 2022	Level 3/Low	-1	-small populations -More than half of patients were missing PET scan for one of the tracers	Very low

[a] See checklist for evaluating quality of evidence Table S3

N/A, not applicable, PET, positron emission tomography

eTable 26. Summary of evidence for studies evaluating the impact of carcinoid syndrome and urinary 5-HIAA on prognosis.

Reference	Study type	N	Primary sites	Grade	% with CS/ Elevated U5-HIAA	OS Findings	Significant independent prognostic factor on MVA?
Halperin 2017 [105]	R	9,512	NETs SB 23% Colorectal 16% Lung 32% Other 24%	Not reported	46% of metastatic SB-NETs had CS	Median (Kaplan-Meier/log-rank test) *non-CS vs. CS* • Metastatic SB-NETs (n = 436): 7.1 years vs. 4.7 years; p=0.013 MVA (cox-regression) *CS vs. non-CS* • Overall population: HR: 1.102 (95% CI 1.016–1.194); p = 0.019	CS: Yes
Jann 2011 [106]	R	270	GEP-NETs SB 79% Colorectal 9% Appendix 8%	G1: 62% G2: 32% G3:6%	42% with CS	UVA (cox-regression) *CS vs. non-CS* • p = 0.236	Not tested, no significance on UVA
Formica 2007 [107]	R	119	GEP-NETs Pan 22%	Not reported	38% with CS	UVA (cox-regression) *CS vs. non-CS* • not significant	CS: Not tested, no

Reference	Study type	N	Primary sites	Grade	% with CS/ Elevated U5-HIAA	OS Findings	Significant independent prognostic factor on MVA?
			SB 33%		50% with 5-HIAA >2x ULN	*u5-HIAA >/< 2x ULN:* • HR 1.87 (95% CI 1.08–3.24); p = 0.025 <u>MVA (cox-regression)</u> *u5-HIAA >/< 2x ULN:* • HR 2.36 (95% CI 1.28–4.35); p =0.006	significance on UVA u5-HIAA: Yes
Janson 1997 [108]	R	301	GEP-NETs Midgut 85%	Not reported	74% with CS 76% with elevated u5-HIAA	<u>Median (Kaplan-Meier/log-rank test)</u> *u5-HIAA >/< 300 µmol/24 hrs:* • 45 vs. 72 months; p = 0.001 <u>UVA (cox-regression)</u> *u5-HIAA >/< 300 µmol/24 hrs:* • HR 1.8 (95% CI: 1.2-2.5) *CS vs. non-CS* • HR 2.9 (95% CI 1.4-6.0) <u>MVA (cox-regression)</u> *u5-HIAA >/< 300 µmol/24 hrs:* • HR 1.3 (95% CI 0.9-2.0) *CS vs. non-CS* • HR 1.9 (95% CI 0.8-4.3)	CS: No u5-HIAA: No

Reference	Study type	N	Primary sites	Grade	% with CS/ Elevated U5-HIAA	OS Findings	Significant independent prognostic factor on MVA?
Zandee 2016 [109]	R	371	GI-NET SB 53%	G1: 29% G2: 26% G3: 3% Missing: 42%	70% with elevated u5-HIAA (30% with >10x ULN)	UVA (cox-regression) *2-10x ULN vs. normal* • HR 1.09 (95% CI: 0.73–1.63) *>10x ULN vs. normal* • HR 1.62 (95% CI: 1.09–2.39) MVA (cox-regression) *2-10x ULN vs. normal* • HR 0.76 (95% CI: 0.45–1.88) *>10x ULN vs. normal* • HR 0.92 (95% CI: 0.56–1.61)	CS: Not tested u5-HIAA: No
Schrivers 2007 [110]	R	76	Midgut	Not reported	~70% with CS symptoms	MVA (cox-regression) *u5-HIAA > vs. <20mmol/mol creatinine:* • HR 1.003 (95% CI 1.000–1.006); p = 0.033	CS: Not tested u5-HIAA: Yes
Laskaratos 2018 [111]	R	147	SB	G1: 50% G2: 26% G3: 1% Missing: 24%	44% with CS 59% with elevated u5-HIAA (<5x ULN 27%; 5-10x ULN 17%; >10x ULN 15%)	UVA (cox-regression) *u5-HIAA >5x ULN vs. normal:* • HR 2.31 (95% CI 1.13–4.71); p = 0.02 MVA (cox-regression) u5-HIAA >10x ULN vs. normal: • HR 5.82 (95% CI 1.75–19.42); p = 0.004	CS: Not tested u5-HIAA: Yes

Reference	Study type	N	Primary sites	Grade	% with CS/ Elevated U5-HIAA	OS Findings	Significant independent prognostic factor on MVA?
Turner 2006 [112]	R	139	Midgut	Not reported	61% had elevated u5-HIAA	UVA (cox-regression) *u5-HIAA > vs < 42 µmol/24 hrs:* • p = 0.0001 MVA (cox-regression) *u5-HIAA > vs < 42 µmol/24 hrs (n = 35):* • not significant (data not reported)	CS: Not tested u5-HIAA: No
Bergestuen 2009 [113]	R	258	SB	Ki-67 <5%: 101 of 130 pts	54% had CS	Median (Kaplan-Meier/log-rank test) *u5-HIAA > vs. <3.7 mmol/mmol creatinine:* • 5.4 vs. 11.3 years p <0.001 UVA (cox-regression) *CS vs. non-CS:* • not significant *u5-HIAA > vs. <3.7 mmol/mmol creatinine:* • HR 2.35 (95% CI 1.55-3.55) MVA (cox-regression) *u5-HIAA > vs. <3.7 mmol/mmol creatinine:* • HR 1.34 (95% CI 0.79-2.26); p = 0.28	CS: Not tested, UVA not significant u5-HIAA: No

CI, confidence interval; CS, carcinoid syndrome; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; NET, neuroendocrine tumor; OS, overall survival; Pan, pancreas; R, retrospective; SB, small bowel; u5-HIAA, urinary 5-hydroxyindoleacetic acid; ULN, upper limit of normal; UVA, univariate analysis

eTable 27. Quality assessment for studies included in evidence review for carcinoid syndrome and elevated urinary 5-HIAA as a prognostic marker.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Halperin 2017	Level 4/Very low	+1	-large effect size in population of interest and significance confirmed in multivariate analysis of overall population	Low
Jann 2011	Level 4/Very low	No	N/A	Very low
Formica 2007	Level 3/Low	No	N/A	Low
Janson 1997	Level 3/Low	-1	-Grade not considered in multivariate analysis -improvement in management over 15 years may have impacted comparisons	Very low
Zandee 2016	Level 3/Low	No	N/A	low
Schrivers 2007	Level 3/Low	-1	-Grade not considered in multivariate analysis	Very low
Laskaratos 2018	Level 3/Low	No	N/A	Low
Turner 2006	Level 3/Low	-1	- multivariate analysis had very small population included (n=35) and did not include grade	Very low
Bergestuen 2009	Level 3/Low	-1	-Grade not included in multivariate analysis	Very low

[a] See checklist for evaluating quality of evidence Table S3
N/A, not applicable

eTable 28. Summary of evidence for studies evaluating the impact of CgA on prognosis.

Reference	Study type	N	Primary sites	Grade	% with elevated CgA	OS Findings	Significant independent prognostic factor on MVA?
Yao 2016 [19]	RCT	410	Pan	Not reported, only G1/G2 enrolled	CgA > 2× ULN (2 × 36.4 ng/ml):	Median (Kaplan-Meier/log-rank test) *CgA < vs. >2x ULN:*	No

Reference	Study type	N	Primary sites	Grade	% with elevated CgA	OS Findings	Significant independent prognostic factor on MVA?
					41% in everolimus arm 51% in placebo arm	• 57.2 vs. 27.76 months <u>UVA (cox-regression)</u> *CgA < vs. >2x ULN:* • HR 0.54 (95% CI 0.42-0.7); p < 0.00001 <u>MVA (cox-regression)</u> *CgA < vs. >2x ULN:* • HR 0.76 (95% CI: 0.57-1); p=0.05	
Yao 2011 [114]	P	114	Pan	Not reported, only G1/G2 analyzed	CgA > 2× ULN (2 × 36.4 ng/ml): 57%	<u>Median (Kaplan-Meier/log-rank test)</u> *CgA < vs. >2x ULN:* • Not reached vs. 16.95 months <u>UVA (cox-regression)</u> *CgA < vs. >2x ULN:* • HR 0.30 (95% CI 0.15-0.61); p < 0.001 <u>MVA (cox-regression)</u> *CgA < vs. >2x ULN:* • HR 0.36 (95% CI 0.17-0.78); p = 0.01	Yes
Kečkéš 2021 [115]	P/R	65	GEP-NEN SB 34% Pan 30%	G1:55% G2:28% G3:17%	CgA ≥102 ng per mL: 51%	<u>MVA (cox-regression)</u> CgA as continuous variable: • not significant	No

Reference	Study type	N	Primary sites	Grade	% with elevated CgA	OS Findings	Significant independent prognostic factor on MVA?
Sharma 2017 [116]	P/R	135	NEN SB 38% Pan 26% Lung 13%	Not reported	N = 81 Pancreastatin: ≤1.0x ULN: 32% >1.0 to <3.0x ULN: 17% 3.0–10.0x ULN: 21% >10.0x ULN: 30%	MVA (cox-regression) *CgA <3x ULN vs. 3-10x ULN:* • HR 2.81 (95% CI 1.04-7.59); p = 0.042 *CgA <3x ULN vs. >10x ULN:* • HR 4.42 (95% CI 1.72-11.34); p = 0.002	Yes
Arnold 2008 [117]	P/R	344	NET Pan 26% Midgut 57%	Not reported	Plasma CgA ≥ 200 U/L: 51%	UVA (cox-regression) *CgA ≥ vs, < 200 U/L (log10-transformed):* • HR 2.04 (95% CI 1.72-2.41); p<0.001 MVA (cox-regression) *CgA ≥ vs, < 200 U/L (log10-transformed):* • HR 2.14 (95% CI 1.75-2.62); p<0.001	Yes
Chou 2014 [118]	R	60	GEP-NET Pan 53% SB 10%	G1: 35% G2: 32% G3: 33%	CgA levels >2x ULN: 60%	MVA (cox-regression) *CgA <2x ULN vs. >2x ULN:* • HR 0.06 (95% CI 0.01-0.25); p<0.001	Yes
Fuksiewicz 2018 [119]	R	131	GEP-NEN Pan 45% SB 30%	Pan G1:50% G2: 41% G3: 9%	CgA levels ≤84.7 ng/mL Pan: 49%	UVA (cox-regression) *CgA > vs. ≤ 84.7* • Pan: p = 0.04 • SB & Cecum: p = 0.014	Pan: No SB/Cecum: Yes

Reference	Study type	N	Primary sites	Grade	% with elevated CgA	OS Findings	Significant independent prognostic factor on MVA?
				SB & Cecum Pan G1: 63% G2: 35% G3: 2%	SB & Cecum: 52%	MVA (cox-regression) *CgA > vs. ≤ 84.7* • Pan: not significant • SB & Cecum: HR 8.73 (95% CI 6.658–10.810); p = 0.041	
Pulvirenti 2019 [120]	R	99	Pan	G1:19% G2: 35% G3: 6% Missing: 40%	CgA >ULN: 60%	UVA (cox-regression) CgA > ULN vs. <ULN: • HR 5.54 (95% CI 1.74 -17.69) p = 0.004	Not tested
Tian 2016 [121]	R	80	GEP-NET Pan 24% Esophagus-stomach 43%	G1: 6% G2: 28% G3: 66%	Not reported	Median (Kaplan-Meier/log-rank test) *CgA > vs. < 46.2 ng/mL:* • 392 vs. 437 days; p = 0.045	Not tested
Walter 2012 [122]	R	115	GEP-NEN Pan 43% Ileum 33%	G1: 27% G2: 48% G3: 8% Missing: 17%	CgA >ULN: 69%	UVA (cox-regression) CgA > ULN vs. <ULN: • p = 0.86	Not tested, UVA not significant
Ekeblad 2008 [123]	R	324	Pan	G1: 20% G2: 71% G3: 9%	Median CgA: 3.7x ULN	UVA (cox-regression) *CgA > vs. <3x ULN (n=137):* • HR, 2.5 (95% CI 1.5-4.2); p < 0.001	Not tested, missing data
Ahmed 2009 [124]	R	360	Midgut NEN	n = 159 G1: 54% G2: 41% G3: 5%	Not reported	MVA (cox-regression) CgA continuous variable: • HR 1.00 (95% CI 0.998-1.002); p = 0.923	No

CgA, Chromogranin A; CI, confidence interval; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; OS, overall survival; P, prospective; Pan, pancreas; P/R, prospective enrollment, retrospective analysis; R, retrospective; RCT, randomized control trial; SB, small bowel; ULN, upper limit of normal; UVA, univariate analysis

eTable 29. Quality assessment for studies included in evidence review for CgA as a prognostic biomarker.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Yao 2016	Level 2/moderate	No	N/A	Moderate
Yao 2011	Level 2/moderate	No	N/A	Moderate
Kečkéš 2021	Level 3/low	No	N/A	Low
Sharma 2017	Level 3/low	No	N/A	Low
Arnold 2008	Level 3/low	No	N/A	Low
Chou 2014	Level 3/low	No	N/A	Low
Fuksiewicz 2018	Level 3/low	No	N/A	Low
Pulvirenti 2019	Level 4/very low	No	N/A	Very low
Tian 2016	Level 4/very low	No	N/A	Very low
Walter 2012	Level 4/very low	No	N/A	Very low
Ekeblad 2008	Level 4/very low	No	N/A	Very low
Ahmed 2009	Level 3/low	No	N/A	Low

[a] See checklist for evaluating quality of evidence Table S3
N/A, not applicable

eTable 30. Summary of evidence for studies evaluating the impact of pancreastatin on prognosis.

Reference	Study type	N	Primary sites	Grade	% with elevated Pancreastatin	OS Findings	Significant independent prognostic factor on MVA?
Bloomston 2007 [125]	R	122	NEN SB 47% Pan 21% Lung 8%	Not reported	Median pancreastatin level: 2,120 pg/ml (pre-HACE pancreastatin levels only available for 101 pts; 97% of which were elevated [>ULN]	<u>UVA (cox-regression)</u> *< vs. >20% reduction in pancreastatin:* • p = 0.026 <u>MVA (cox-regression)</u> *pancreastatin ≥ vs. < 5,000 pg/mL (before HACE):* • RR 2.6 (95% CI 1.3–5.0); p = 0.005 *< vs. >20% reduction in pancreastatin:* • p = 0.089	Baseline pancreastatin: yes Change in pancreastatin: no
Strosberg 2018* [126]	R	188	NEN SB 36% Pan 23% Unknown 32% Lung 6%	G1: 77% G2: 20% G3:4%	Baseline serum pancreastatin > 5000 pg/mL: 30%	<u>Median (Kaplan-Meier/log-rank test)</u> *pancreastatin reduction > vs. < 50%:* • 53.8 vs. 29.9 months, p = 0.032 <u>MVA (cox-regression)</u> *Pancreastatin > vs. < 5000 pg/mL (before TACE):* • HR 2.39 (95% CI 1.48–3.83); p<0.001	Baseline pancreastatin: yes Change in pancreastatin: not tested
Stronge 2008 [127]	R	59	GEP-NET Ileal 73%	Not reported	Median baseline pancreastatin: 90 pmol/L (range 5– 8640 pmol/L).	<u>MVA (cox-regression)</u> *baseline pancreastatin 25–49 vs. <25 pmol/L:* • HR 2.94 (95% CI 1.00-8.64)	Baseline pancreastatin: yes

Reference	Study type	N	Primary sites	Grade	% with elevated Pancreastatin	OS Findings	Significant independent prognostic factor on MVA?
					Pancreastatin >ULN (25 pmol/l): 73% Rise in pancreastatin after SSA >1.5x to <4.99x: 19% Rise in pancreastatin after SSA >5x increase: 15%	*baseline pancreastatin 50–499 vs. <25 pmol/L:* • HR 1.78 (95% CI 0.58-5.48) *baseline pancreastatin 500+ vs. <25 pmol/L:* • HR 6.48 (95% CI 1.71-24.42) *1.5x increase pancreastatin (after SSA) vs. no increase:* • HR 3.8 (95% CI 1.48-9.75) *>5x increase pancreastatin (after SSA) vs. no increase:* • HR 18.12 (95% CI 6.03-54.42)	Change in pancreastatin: yes
Sharma 2017 [116]	P/R	135	NEN SB 38% Pan 26% Lung 13%	Not reported	N = 80 Pancreastatin: ≤1.0x ULN: 20% >1.0 to <3.0x ULN: 24% 3.0–10.0x ULN: 18% >10.0x ULN: 39%	MVA (cox-regression) *pancreastatin >10x ULN vs. <3x ULN:* • HR: 2.91 (95% CI 1.20-7.08); p = 0.018 *pancreastatin 3-10x ULN vs. <3x ULN:* • HR 0.97 (95% CI 0.26-3.64); p = 0.961	Yes

*From the same institution as Bloomston 2007.

CI, confidence interval; GEP, gastroenteropancreatic; GI, gastrointestinal; HACE, hepatic artery chemoembolization; HR, hazard ratio; MVA, multivariate analysis; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; OS, overall survival; P, prospective; Pan, pancreas; P/R, prospective enrollment, retrospective analysis; R, retrospective; RR, relative risk; SB, small bowel; TACE, transarterial chemoembolization; ULN, upper limit of normal; UVA, univariate analysis

eTable 31. Quality assessment for studies included in evidence review for pancreastatin as a prognostic biomarker.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Bloomston 2007	Level 3/low	No	N/A	Low
Stronsberg 2018	Level 3/low	No	N/A	Low
Stronge 2008	Level 3/low	No for baseline pancreastatin -1 for change in pancreastatin post-TACE	N/A	Low/very-low
Sharma 2017	Level 3/low	No	N/A	Low

[a] See checklist for evaluating quality of evidence Table S3

N/A, not applicable; TACE, transarterial chemoembolization

eTable 32. Summary of evidence for studies evaluating the impact of neuron specific enolase on prognosis.

Reference	Study type	N	Primary sites	Grade	% with elevated NSE	OS Findings	Significant independent prognostic factor on MVA?
Yao 2016 [19]	RCT	410	Pan	Not reported, only G1/G2 enrolled	NSE > ULN (8.6 ng/ml): 24% in everolimus arm	Median (Kaplan-Meier/log-rank test) *NSE < vs. > ULN:* • 52.9 vs. 16.1 months	Yes

Reference	Study type	N	Primary sites	Grade	% with elevated NSE	OS Findings	Significant independent prognostic factor on MVA?
					29% in placebo arm	UVA (cox-regression) *NSE < vs. > ULN:* • HR 0.36 (95% CI 0.27-0.47); p < 0.00001 MVA (cox-regression) *NSE < vs. >ULN:* • HR 0.41 (95% CI 0.30-0.56); p<0.001	
Yao 2011 [114]	P	114	Pan	Not reported, only G1/G2 analyzed	NSE > ULN (8.6 ng/ml): 44%	Median (Kaplan-Meier/log-rank test) *NSE < vs. > ULN:* • 24.90 vs. 13.96 months UVA (cox-regression) *NSE < vs. > ULN:* • HR 0.44 (95% CI 0.24-0.79); p < 0.005 MVA (cox-regression) *NSE < vs. >ULN:* • HR 0.60 (95% CI 0.32-1.11); p = 0.17	No
Kečkéš 2021 [115]	P/R	65	GEP-NEN SB 34% Pan 30%	G1:55% G2:28% G3:17%	N = 44 NSE ≥12.5 ng per mL: 43%	MVA (cox-regression) *NSE as continuous variable:* • HR 1.127 (95% CI 1.038-1.223); p = 0.0044	Yes
Ezziddin 2014a [128]	R	68	Pan	Ki67 ≤2: 28%	NSE >15 ng/mL: 67%	MVA (cox-regression) *NSE > vs. < 15 ng/mL:*	Yes

Reference	Study type	N	Primary sites	Grade	% with elevated NSE	OS Findings	Significant independent prognostic factor on MVA?
				Ki-67 3-20: 72%		• HR 2.2 (95% CI 1.0-4.9); p = 0.039	
Ezziddin 2014b [129]	R	74	GEP-NET Pan 55% Midgut 26%	Ki67 ≤2%: 35% 3-10%: 46% 15-20%: 19%	NSE >15 ng/mL: 47%	MVA (cox-regression) *NSE > vs. < 15 ng/mL:* • HR 2.8 (95% CI 1.3-5.9); p = 0.006	Yes

CI, confidence interval; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; NSE, neuron-specific enolase; OS, overall survival; P, prospective; Pan, pancreas; P/R. prospective enrollment, retrospective analysis; R, retrospective; RCT, randomized control trial; SB, small bowel; ULN, upper limit of normal; UVA, univariate analysis

eTable 33. Quality assessment for studies included in evidence review for neuron specific enolase as a prognostic biomarker.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Yao 2016	Level 2/moderate	No	N/A	Moderate
Yao 2011	Level 2/moderate	No	N/A	Moderate
Kečkéš 2021	Level 3/low	No	N/A	Low
Ezziddin 2014a	Level 3/low	No	N/A	Low
Ezziddin 2014b	Level 3/low	No	N/A	Low

[a] See checklist for evaluating quality of evidence Table S3

N/A, not applicable

eTable 34. Summary of evidence for studies evaluating the impact of NETest on prognosis.

Reference	Study type	N	Primary sites	Grade	Distribution of patients by different NETest score cut-offs	PFS Findings	Significant independent prognostic factor on MVA?
Liu 2019 [130]	P/R	100	NENs GEP 68% Lung 20%	G1:34% G2:13% G3:2% Missing: 51%	Low score ≤40%: 62% Intermediate score >40-<80%: 12% High score ≥80%: 26%	MVA (cox-regression) *NETest score (unclear which categories are being compared):* • Odds ratio 6.1; p<0.0001	Yes
Pavel 2017 [131]	P/R	34	GEP-NEN Gut 74% Pan 26%	G1: 50% G2: 41% G3: 3% Missing: 6%	Median baseline NETest: 40% (range: 6.7–93.4)	MVA (cox-regression) *NETest score ≥80% vs. <80%:* • HR 1.022 (95% CI 1.005– 1.04); p < 0.012	Yes
Cwikla 2015 [132]	P	28	GEP-NEN Pan 32% SB 46%	G1: 43% G2: 57%	High score ≥80%: 71%	UVA (cox-regression) *NETest score ≥80% vs. <80%:* • Odds ratio 5.5 x 108 MVA (cox-regression) *NETest score ≥80% vs. <80%:* • p = 0.0002	Yes
van Treijen 2021 [133]	P	152	GEP-NEN SB 68% Pan 16%	G1: 69% G2: 29% G3: 1% Missing: 0.5%	Low score ≤33%: 61% Intermediate score 34-79%: 17%	MVA (cox-regression) *NETest score ≥80% vs. <80%:* • Odds ratio 12.6 (95% CI 3.7-43.1)	Yes

Reference	Study type	N	Primary sites	Grade	Distribution of patients by different NETest score cut-offs	PFS Findings	Significant independent prognostic factor on MVA?
					High score ≥80%: 22%		
Bodei 2020 [134]	P/R	157	NET GEP 70% Lung 17%	G1: 23% G2: 48% G3: 6% Missing: 8%		UVA (cox-regression) *NETest score < vs. >40%:* • HR 0.04 (95% CI 0.02-0.07); p<0.0001	Not tested

CI, confidence interval; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; MVA, multivariate analysis; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; P, prospective; Pan, pancreas; PFS, progression-free survival; P/R. prospective enrollment, retrospective analysis; R, retrospective; RCT, randomized control trial; SB, small bowel; UVA, univariate analysis

eTable 35. Quality assessment for studies included in evidence review for NETest as a prognostic biomarker.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Liu 2019	Level 2/moderate	-2	Registry set up by Wren laboratories who market NETest, large number of grade data missing, the NETest cut-off categories used in the MVA were unclear	Very low
Pavel 2017	Level 2/moderate	-1	Small population (n =31), industry sponsored/authored	Low
Cwilka 2015	Level 2/moderate	-1	Small population (n =28), short follow-up, industry support from Clifton Life Sciences	Low
Van Treijen 2021	Level 2/moderate	No	N/A	Moderate
Bodei 2020	Level 2/moderate	-1	Industry authorship (Wren laboratories), multivariate analysis not performed	Low

[a] See checklist for evaluating quality of evidence Table S3

N/A, not applicable; MVA, multivariate analysis

eTable 36. Summary of evidence for studies evaluating the impact of NETest (single-test value) on discriminating progressive vs. stable disease[a]

Reference	Study type	N	Primary sites	Grade	Distribution of patients by different NETest score cut-offs	Accuracy findings
Liu 2019 [130]	P/R	100	NENs GEP 68% lung 20%	G1:34% G2:13% G3:2% Missing: 51%	Low score ≤40%: 62% Intermediate score >40-<80%: 12% High score ≥80%: 26%	Accuracy in discriminating progressive/stable disease (cut-off >40/≤40)[b]: • Overall: 81% • Sensitivity: 77% • Specificity: 83% Accuracy in discriminating progressive/stable disease (cut-off ≥80/<80)[b]: • Overall: 81% • Sensitivity: 60% • Specificity: 93%
Malczewska 2019 [135]	P/R	75 (image-positive disease)	GEP-NEN Pan 56% SB 44%	For whole cohort (n = 111) G1: 59% G2: 33% G3 NET: 3% G3 NEC: 3% Missing: 2%	Low score (assumed ≤40%): 87 %	Accuracy in discriminating progressive/stable disease (cut-off >40/≤40)[b]: • Overall: 95% reported in manuscript (91% manually calculated based on data provided) • Sensitivity: 64% • Specificity: 95%
Cwikla 2015 [132]	P	28	GEP-NEN Pan 32% SB 46%	G1: 43% G2: 57%	High score ≥80%: 71%	Accuracy in discriminating progressive/stable disease (cut-off ≥80/<80): • Overall: 79% • Sensitivity: 100% • Specificity: 57%

Reference	Study type	N	Primary sites	Grade	Distribution of patients by different NETest score cut-offs	Accuracy findings
van Treijen 2021 [133]	P	152	GEP-NEN SB 68% Pan 16%	G1: 69% G2: 29% G3: 1% Missing: 0.5%	Low score ≤33%: 61% Intermediate score 34-79%: 17% High score ≥80%: 22%	<u>Accuracy in discriminating progressive/stable disease at 12 months (cut-off >33/≤33):</u> • Overall: 74%[3] • Sensitivity: 77% • Specificity: 72% <u>Accuracy in discriminating progressive/stable disease at 12 months (cut-off >40/≤40):</u> • Overall: 72%[3] • Sensitivity: 68% • Specificity: 74% <u>Accuracy in discriminating progressive/stable disease (cut-off ≥80/<80):</u> • Overall: 73%[c] • Sensitivity: 45% • Specificity: 86%
Bodei 2020 [134]	P/R	157	NET GEP 70% Lung 17%	G1: 23% G2: 48% G3: 6% Missing: 8%		<u>Accuracy of in discriminating progressive/stable disease (unclear whether this is baseline NETest values, or measurement at ~12 months after PRRT, or measurement at time of radiologic progression) (cut-off >40/≤40)[2]:</u> • Overall: 89% • Sensitivity: 80% • Specificity: 93%

[a] One systematic review and meta-analysis was identified in the literature search which addressed the accuracy of NETest in distinguishing progressive versus stable disease; however, it was excluded from evidence review as it included a large proportion of patients with bronchopulmonary NETs. Thus, individual studies from this review that met our inclusion criteria were analysed separately.

[b] Accuracy data was not clearly reported for all parameters of interest. Accuracy data was calculated from presented data using the following equations: overall accuracy = (true positive + true negative) / (true positive + true negative + false positive + false negative); sensitivity = True Positive/True Positive + False Negative; specificity = True Negative/True Negative + False Positive

[c] Overall accuracy was not clearly stated and was thus calculated from the presented specificity and sensitivity data using the following equation: Accuracy = (prevalence of disease progression)(sensitivity) + (1 - prevalence of disease progression)(specificity)

GEP, gastroenteropancreatic; GI, gastrointestinal; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; P, prospective; Pan, pancreas; P/R, prospective enrollment, retrospective analysis; R, retrospective; SB, small bowel

eTable 37. Quality assessment for studies included in evidence review for evaluating the impact of NETest (single-test value) on discriminating progressive vs. stable disease.

Reference	Level of evidence based on study design/ Corresponding quality of evidence	Upgrade/downgrade quality of evidence?	Study limitation causing score change[a]	Final Quality score
Liu 2019	Level 2/moderate	-1	Registry set up by Wren laboratories who market NETest	Low
Malczewska 2019	Level 2/moderate	No	N/A	Moderate
Cwilka 2015	Level 2/moderate	-1	Small population (n =28), short follow-up, industry support from Clifton Life Sciences	Low
Van Treijen 2021	Level 2/moderate	No	N/A	Moderate
Bodei 2020	Level 2/moderate	-1	Lack of clarity in reporting of methodology and outcomes relevant to research question, industry authorship (Wren laboratories)	Low

[a] See checklist for evaluating quality of evidence Table S3

N/A, not applicable

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