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

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

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

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

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

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

Supplemental content

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

Methods

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

Results

Literature Search Results

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

Recommendation Development and Consensus

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

Evidence for the Value of Tumor-Based Biomarkers

Grade, Differentiation, and Primary Tumor Location

The World Health Organization has defined 3 grade categories based on mitotic activity and the Ki-67 index that are inversely associated with prognosis (**Table 2**).[3-12] Mitotic count and Ki-67 index scores should be assessed using manual or digital scoring methods on tissue from core needle biopsy or surgical resection, if feasible.[13,14] Ki-67 index may be heterogeneous based on the site of sampling and may increase during the disease course.[15-20] The highest obtained grade should be used when multiple samples have been assessed. If possible, biopsy and assessment of the fastest growing tumor for grade determination will best reflect prognosis.[15,16,21,22]

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

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

Genomic Profiling and Single-Gene Biomarkers

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

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

Transcriptional and Proteomic Classifiers

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

O6-Methylguanine-DNA Methyltransferase

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

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

Somatostatin Receptor Expression by Immunohistochemistry

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

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

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

(continued)

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

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

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; FDG, fluorodeoxyglucose; CgA, chromogranin A; GEP, gastroenteropancreatic; MGMT, O6-methylguanine-DNA methyltransferase; MGMT, O6-methylguanine-DNA methyltransferase; MSI, microsatellite instability; NA, not applicable; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET; neuroendocrine tumor; NGS, next-generation sequencing; NSE, neuron-specific enolase; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; NTRK, neurotrophic tyrosine receptor kinase; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SPECT, single-photon emission computed tomography; SSTR, somatostatin receptor; SUV, standardized uptake value; TRK, tropomyosin receptor kinase.

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

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

Abbreviation: HPF, high-power field.

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

Therapy	Preferred Grade	Preferred Differentiation	Preferred Primary location	Other factors to consider[a]	Rationale/evidence
Somatostatin analogues (eg, octreotide, lanreotide)	G1/G2	Well (NETs)	Any	• Must be STTR positive • Should be part of therapy for patients with carcinoid syndrome	• SSAs demonstrated antiproliferative activity vs placebo in patients with G1/G2 GEP-NETs (PROMID and CLARINET)[31-33] • Preferred for G1/G2 tumors with good prognosis due to mild safety profile
PRRT (eg, ^{177}Lu-DOTATATE)	Any, stronger evidence for G1/G2	Well (NETs)	Any	• Must be STTR positive • Ongoing COMPETE (^{177}Lu-edotreotide vs everolimus) and COMPOSE (^{177}Lu-edotreotide vs best standard of care) trials may better inform optimal sequencing of PRRT	• PRRT (^{177}Lu-DOTATATE) + standard dose octreotide achieved a significantly prolonged PFS vs high-dose octreotide in G1/G2 midgut NETs (NETTER-1)[34] • PRRT (^{177}Lu-DOTATATE) demonstrated an improved 12-mo PFS vs sunitinib in pancreatic NETs (OCLURANDOM)[35] • Retrospective studies suggest PFS following PRRT is shorter with increasing grade/ proliferation index,[36-42] but this does not preclude benefit in higher-grade GEP-NETs • Retrospective studies have demonstrated comparable efficacy for ^{177}Lu-DOTATATE in patients with pancreatic and midgut NETs[38,43,44]
Sunitinib	G1/G2	Well (NETs)	Pancreatic	NA	Sunitinib demonstrated improved PFS vs placebo in G1/G2 pancreatic NETs (SUN1111)[45]
Everolimus	G1/G2	Well (NETs)	Pancreatic, small bowel	Must be nonfunctional[b]	Everolimus achieved prolonged PFS vs placebo in non-functional small bowel and pancreatic NETs (RADIANT-3 and RADIANT-4)[46-48]
Streptozotocin + fluorouracil	G2	Well (NETs)	Pancreatic	Prioritize vs everolimus if tumor shrinkage is a priority	• Streptozotocin + fluorouracil demonstrated improved PFS in prospective randomized studies in G2 pancreatic NETs[49-52] • Streptozotocin + fluorouracil demonstrated similar PFS but improved ORR vs everolimus in pancreatic NETs (SEQTOR)[53]
CAP-TEM	G1/G2 (pancreatic, less evidence for extra pancreatic) G3 with Ki-67 < 55% (any)	Well (NETs); poor (NECs) with Ki-67 < 55%	Any, strongest evidence for pancreatic	Assessment of MGMT activation may predict response to temozolomide, but evidence is insufficient for use in routine practice	• CAP-TEM demonstrated superior PFS vs TEM alone in G1/G2 pancreatic NETs (ECOG-ACRIN E2211)[54] • Randomized trials of CAP-TEM in G1/G2 extrapancreatic gastrointestinal NETs are lacking • Retrospective studies have reported higher response rates and longer PFS with CAP-TEM for pancreatic vs nonpancreatic NENs; however, evidence quality is low[55-61]
Platinum chemotherapy	G3 with Ki-67 ≥ 55%	Poor (NECs)	Any	NA	• Randomized clinical trials of platinum-chemotherapy in G1/G2 extrapancreatic gastrointestinal NETs are lacking • Among G3 GEP-NENs, poorly differentiated disease and Ki-67 ≥ 55% have been associated with higher response rates to platinum chemotherapy[25,29 62-66], although quality of evidence is low

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

[a] Toxic effect profiles of each therapy, as well as prognosis, age, comorbidities, performance status, symptoms, tumor burden, tumor distribution, and patient preferences should always be considered when selecting therapy.

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

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

Evidence for the Use of Imaging-Based Biomarkers

SSTR PET/CT

SSTR imaging uses radiolabelled SSAs as a functional tracer for SSTRs on the surface of NETs. While ^{98}in-pentetreotide (octreoscan) with single-photon emission CT was previously used, higher-affinity radio-labeled SSAs visualized by PET/CT are now preferred given their higher resolution, lower radiation dose, and shorter image acquisition time.[97-99] ^{68}GA-DOTATATE, ^{68}GA-DOTATOC, and ^{68}GA-DOTANOC are commonly used tracers, with no major differences in performance reported.[100] [64] Cu-DOTATATE is also used for SSTR imaging and has the lo-

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

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

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

gistical advantage of a long half-life, allowing it to be centrally produced.[101,102]

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

Several studies assessing prognosis following SSTR-directed therapy were identified (eTables 18 and 19 in the Supplement). Two retrospective studies found that high SUVmax was associated with improved PFS on SSA therapy.[108,109] Studies evaluating SSTR imaging as prognostic following PRRT found that SUV measurements, most notably SUVmax, as well as heterogeneity in radiotracer uptake, were associated with response and/or PFS.[36,110-113] SUVmax measurements are limited by variability in scanner and reproduction parameters, which can affect the accuracy of measurements.[114] In addition, studies that focus on SUVmax are not able to account for disease heterogeneity. Currently, uptake on SSTR imaging is treatment informing, as it is required for PRRT eligibility, and it is likely that high avidity on SSTR PET is associated with improved response to PRRT. However, as few studies included a control arm, the true predictive value is unclear. There were no prospective studies evaluating PRRT in poorly differentiated NENs, in which chemotherapy is a preferred treatment option, and the proportion of these tumors with SSTR uptake is lower than well-differentiated NETs. Given this, SSTR imaging is not treatment informing in poorly differentiated NENs, and other societies have suggested that if functional imaging is used in this population to consider fluorodeoxyglucose (FDG) imaging preferably.[115-119]

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

FDG PET/CT

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

Evidence for the Value of Blood-Based Biomarkers

Peptide and Hormone Markers for Functional NENs

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

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

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

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Carcinoid syndrome and elevated urinary 5-HIAA levels are negative prognostic markers in GEP-NENs in some retrospective studies, but results were inconsistent and the evidence as a whole was of low to very low quality (eTables 26 and 27 in the Supplement).[136,148-155] Regardless of their prognostic effect, carcinoid syndrome and elevated 5-HIAA levels are associated with symptom burden that affects quality of life[98,156] and the development of CHD.[157-159] SSAs can improve carcinoid syndrome in approximately 75% of patients[160] in addition to demonstrating antiproliferative effects.[31,32,161] Thus, SSAs are recommended for the first-line treatment of unresectable midgut NETs presenting with carcinoid syndrome or elevated urinary 5-HIAA levels and should be continued in combination with other therapies on tumor progression.

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

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

Biomarkers for Detecting and Monitoring of CHD

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

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

Chromogranin A

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

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

Other Circulating Peptide Markers

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

NETest

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

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Circulating Tumor Cells and DNA

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

Conclusions

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

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

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

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