New Frontiers in Neuroendocrine Tumors: Enhancing Diagnosis, Treatment, and Patient Outcomes

PRESENTED BY PAULA S. KENNEDY-NEWTON, MSN, AGNP-C

From Duke Cancer Institute, Durham, North Carolina

Presenter's disclosures of conflicts of interest are found at the end of this article.

https://doi.org/10.6004/jadpro.2026.17.2.11

Abstract

At JADPRO Live 2025, Paula S. Kennedy-Newton, MSN, AGNP-C, discussed the underlying pathophysiology of neuroendocrine tumors (NETs), clinical presentation, diagnostic evaluation, the mechanisms of action and safety/efficacy data for NET therapies, and multidisciplinary care models to address the complex medical and psychosocial needs of patients living with NETs.

In the session "New Frontiers in Neuroendocrine Tumors: Enhancing Diagnosis, Treatment, and Patient Outcomes" presented on October 26, 2025, at JADPRO Live 2025, **Paula S. Kennedy-Newton, MSN, AGNP-C,** a nurse practitioner at Duke Cancer Institute in Durham, North Carolina, presented a comprehensive overview of neuroendocrine tumors (NETs), emphasizing how advances in diagnosis, imaging, systemic therapy, and multidisciplinary care can improve outcomes for patients with this rare and complex malignancy.

PATHOPHYSIOLOGY

Neuroendocrine tumors arise from neuroendocrine cells, which integrate the nervous and endocrine systems. These cells receive nerve impulses and release hormones, helping regulate key physiological processes. Because neuroendocrine cells are distributed widely throughout the body, including the gut, pancreas, lungs, thyroid, liver, prostate, and skin, NETs can develop in multiple organs.

"NETs develop from cells that produce hormones. Thus, the tumors themselves may also produce hormones," explained Ms. Kennedy-Newton during the session.

The distinction between neuroendocrine tumor and neuroendocrine carcinoma is based largely on grade. Lower-grade tumors are typically classified as NETs, while higher-grade, more aggressive disease is categorized as neuroendocrine carcinoma (NEC). Neuroendocrine neoplasm (NEN) is an umbrella term used to encompass both NETs and NECs.

Functional NETs are differentiated from nonfunctional NETs by

J Adv Pract Oncol 2026;17(suppl 1):27–30

whether the tumor secretes hormones, specifically serotonin. Serotonin secretion can result in carcinoid symptoms, which may include flushing, diarrhea, wheezing, abdominal pain, palpitations, or orthostatic hypotension.

Although NETs can arise in many locations, common sites include the lungs, pancreas, rectum, appendix, and small intestine.

"We tend to group the locations into four main anatomical domains," explained Ms. Kennedy-Newton. These are the foregut, midgut, and hindgut locations, and pancreatic NETs. Pancreatic NETs are a separate category due to multiple subtypes, such as insulinomas, glucagonomas, vasoactive intestinal peptide-secreting tumors (VIPomas), and pancreatic polypeptidomas (Table 1).

Rarer neuroendocrine-related tumors include pheochromocytomas, paragangliomas, Merkel cell carcinoma, and NETs of unknown primary.

EVALUATION

There has been an increase in the incidence of NENs over the past 50 years. Outcomes vary based on stage and differentiation, with localized disease associated with better survival than distant metastatic disease.

Risk factors include inherited genetic syndromes (such as multiple endocrine neoplasia (MEN) type 1, neurofibromatosis type 1, and von Hippel–Lindau syndrome), along with acquired risk factors such as chronic pancreatitis, diabetes, tobacco exposure (in certain NET types), and heavy alcohol use.

"It's worthwhile to consider referral to genetic counselling or to order a multigene hereditary cancer screening panel to look for mutations in any of the associated genes," recommended Ms. Kennedy-Newton.

Many patients are diagnosed incidentally because NETs are often slow-growing and discovered during routine screening (such as colonoscopy). Others present with weight loss, abdominal pain, or hormone-driven symptoms.

There are four main categories of diagnostic evaluation for neuroendocrine tumors: (1) Tissue sampling and grading to guide prognosis and treatment selection; (2) cross-sectional imaging with particular attention to liver and chest staging; (3) functional imaging using PET approaches depending on tumor grade; and (4) biochemical testing to identify functional vs. non-functional tumors and can clarify specific types of pNET.

GRADING

Neuroendocrine tumor grade is determined by the Ki-67 index, which measures tumor proliferation. The highest proliferative index across available specimens is used to define grade.

"NETs are heterogeneous and can evolve over time," stated Ms. Kennedy-Newton.

Therefore, clinicians should consider rebiopsy during mixed response or loss of treatment efficacy. Grading for lung neuroendocrine tumors relies more on mitotic rate, necrosis, and morphology rather than Ki-67.

IMAGING AND TESTING

"When thinking about ordering functional imaging via PET scan for your newly diagnosed neuroendocrine patient, it's important to know the grade of the tumor," said Ms. Kennedy-Newton.

DOTATATE PET is preferred for well-differentiated NETs because it detects somatostatin receptor expression. FDG PET is more informative in poorly differentiated, high-grade disease.

This also helps to guide treatment selection. DOTATATE avidity supports the use of somatostatin analogs and PRRT, which depend on somatostatin receptor expression.

Hormonal workups should be guided by symptoms of the excess hormone. Chromogranin A is a commonly used tumor marker but has limitations due to false elevations (including from PPIs, medical conditions, and diet).

Testing for carcinoid syndrome relies on 5-HIAA, which is increasingly available as a plasma test rather than requiring 24-hour urine collection.

TREATMENT

"I cannot stress enough the importance of a multidisciplinary approach when caring for neuroendocrine patients," emphasized Ms. Kennedy-Newton.

Neuroendocrine tumor patients may require input from surgical oncology, medical oncology, radiation oncology, interventional radiology, and nuclear medicine. Surgery is used in the first line whenever feasible, including endoscopic removal of small localized gastric, duodenal, or rectal

Table 1. Neuroendocrine and Adrenal Tumors

Syndrome	Location	Clinical signs or symptoms	Testing
Carcinoid syndrome (NETs of GI tract)	Primary tumors in small bowel and appendix; rarely in rectum	• Primary tumors in the GI tract usually are not associated with symptoms of hormone hypersecretion unless extensive metastasis • Symptoms of hormone secretion may include flushing, diarrhea, cardiac valvular fibrosis, and bronchoconstriction	• 24-hour urine or plasma 5-HIAA • Foods to avoid for 48 hours prior to and during testing: avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts
Carcinoid syndrome (NETs of lung and thymus)	Primary tumors in lung or thymus	• Lung/thymic tumors may be associated with classic carcinoid syndrome as well as hypercortisolemia (+ Cushing syndrome)	• 24-hour urine or plasma 5-HIAA • Foods to avoid for 48 hours prior to and during testing: avocados, bananas, cantaloupe eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts • Test for hypercortisolemia (Cushing syndrome) (NE-E 2 of 4)
Insulinoma	Pancreas	• Hypoglycemia	• Fasting blood glucose • While hypoglycemic: serum insulin; pro-insulin; C-peptide • See Evaluation for insulinoma (PanNET-5)
VIPoma	Most common in pancreas, rarely extra pancreatic	• Severe watery diarrhea, hypokalemia	• Serum VIP
Glucagonoma	Pancreas	• Flushing, diarrhea, hyperglycemia, dermatitis, hypercoagulable state	• Serum glucagon
Gastrinoma	Pancreas or duodenum	• Gastric ulcers, duodenal ulcers, diarrhea	• Serum gastrin
Somatostatinoma	Pancreas or duodenum	• Hyperglycemia, cholelithiasis, diarrhea/ steatorrhea	• Serum somatostatin

Note. Carcinoid syndrome = carcinoid syndrome; NETs = neuroendocrine tumors; GI = gastrointestinal; 5-HIAA = 5-hydroxyindoleacetic acid; NE-E = neuroendocrine tumors—evaluation (endocrine); VIPoma = vasoactive intestinal peptide–secreting tumor; VIP = vasoactive intestinal peptide; PanNET = pancreatic neuroendocrine tumor; C-peptide = connecting peptide. Adapted from NCCN (2025).

NETs and selective resection in metastatic disease for symptom relief or complication prevention.

Not all metastatic NETs require immediate systemic therapy due to indolence and stability in some patients. Observation may be appropriate for low-burden, slow-growing disease.

Key systemic therapies include somatostatin analogs (octreotide LAR, lanreotide) as first-line backbone therapy; mTOR inhibition with everolimus; oral chemotherapy such as capecitabine plus temozolomide; tyrosine kinase inhibitors, including cabozantinib and sunitinib (for pancreatic NETs); platinum-based IV chemotherapy in more aggressive contexts; and peptide receptor radioligand therapy (PRRT) for somatostatin receptor–positive disease.

Somatostatin analogs are used as first-line treatment in many scenarios. "They work by binding to somatostatin receptors on NET cells, mimicking the natural hormone somatostatin, to inhibit the excessive release of other hormones, such as serotonin, and slow tumor growth," explained Ms. Kennedy-Newton.

"Peptide receptor radioligand therapy (lutetium Lu-177 dotatate) has become our gold standard therapy, typically for patients who have been previously treated with a somatostatin analog and who have had progression," said Ms. Kennedy-Newton.

Lutetium Lu-177 dotatate delivers targeted radiation to somatostatin receptor–expressing tumor cells, resulting in DNA damage and tumor cell death.

The NETTER-1 and NETTER-2 trials supported improved progression-free survival and outlined risks such as cytopenias, fatigue, gastrointestinal effects, renal considerations, and a small risk of therapy-related myeloid neoplasms (Strosberg et al., 2017; Singh et al., 2024).

For patients with hepatic-dominant disease, embolization approaches (bland, chemo-, or radioembolization) can be used with or without systemic therapy, with selection influenced by liver function, tumor distribution, and expertise of the interventional radiologist.

Additional strategies are percutaneous ablation and radiation therapy, including stereotactic approaches for oligometastatic sites such as the bone, lung, mediastinum, adrenal, head and neck, and lymph nodes.

MANAGING NET-RELATED COMPLICATIONS

Carcinoid symptoms are most common in metastatic well-differentiated NETs of the distal small intestine and proximal colon, particularly with liver metastases, and less common in pulmonary NETs and pancreatic NETs.

"When we're managing carcinoid symptoms, the key is to treat the underlying disease, and you will hopefully treat the symptoms," said Ms. Kennedy-Newton.

Long-acting somatostatin analogs are described as highly effective for diarrhea and flushing, with short-acting octreotide used for breakthrough symptoms. The presentation emphasizes evaluating other causes of diarrhea, including exocrine pancreatic insufficiency, bile acid excess, and short gut syndrome. Telotristat is an oral inhibitor of serotonin biosynthesis with evidence of reduced bowel movement frequency and decreased 5-HIAA levels in the TELESTAR trial.

Carcinoid crisis is rare but life-threatening, often triggered by tumor manipulation or anesthesia. Procedures should be performed in experienced centers, with octreotide and vasopressors used when necessary.

Carcinoid heart disease is associated with serotonin-induced fibrosis affecting right-sided valves and requires cardiology involvement. Annual echocardiograms are often used for monitoring, although rapid progression can occur.

The presentation closed by addressing how living with a rare cancer such as NETs can be confusing and isolating for patients. "It is important that your patient understands that living with a rare disease does not mean that they are alone in their journey; we are well equipped to provide them with the care that they deserve," concluded Ms. Kennedy-Newton. ●

Disclosure

Ms. Kennedy-Newton has no relevant financial relationships to disclose.

References

National Comprehensive Cancer Network. (2025). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors v3.2025. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

Singh, S., Halperin, D., Myrehaug, S., Herrmann, K., Pavel, M., Kunz, P. L., Chasen, B., Tafuto, S., Lastoria, S., Capdevila, J., García-Burillo, A., Oh, D. Y., Yoo, C., Halfdanarson, T. R., Falk, S., Folitar, I., Zhang, Y., Aimone, P., de Herder, W. W., Ferone, D.,...all the NETTER-2 Trial Investigators (2024). [^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus highdose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): An open-label, randomised, phase 3 study. *Lancet (London, England)*, *403*(10446), 2807–2817. https://doi.org/10.1016/S0140-6736(24)00701-3

Strosberg, J., El-Haddad, G., Wolin, E., Hendifar, A., Yao, J., Chasen, B., Mittra, E., Kunz, P. L., Kulke, M. H., Jacene, H., Bushnell, D., O'Dorisio, T. M., Baum, R. P., Kulkarni, H. R., Caplin, M., Lebtahi, R., Hobday, T., Delpassand, E., Van Cutsem, E., Benson, A.,...NETTER-1 Trial Investigators (2017). Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors. *The New England Journal of Medicine*, *376*(2), 125–135. https://doi.org/10.1056/NEJMoa1607427