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CONSENSUS STATEMENT

Practical considerations for the use of incretin mimetics in patients with neuroendocrine neoplasms: An expert consensus statement

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Abstract

Incretin-based therapies, including glucagon-like peptide-1 receptor agonists (GLP-1RA) and dual incretin agonists, are increasingly used for the management of diabetes, obesity, and cardiometabolic disease. Although their systemic benefits are well established, uncertainty remains regarding their safety in patients with neuroendocrine neoplasms (NENs), a biologically heterogeneous group of tumors with diverse molecular profiles. Preclinical studies suggest that GLP-1 receptor activation may promote tumor growth in select receptor-expressing models, although receptor expression varies widely across NEN subtypes and is often absent in common tumors such as ileal neuroendocrine tumors. Population-level and retrospective clinical data have not demonstrated a consistent increase in oncologic risk but are limited by methodological constraints. In this expert consensus statement, the authors synthesize current evidence and provide a practical framework for the use of incretin mimetics in patients with NENs. The authors emphasize individualized risk assessment, shared decision-making, and multi-disciplinary

collaboration, balancing potential but unquantified oncologic risks against substantial cardiometabolic benefits. Until prospective data are available, careful patient selection, dose optimization, and close clinical and radiologic surveillance remain essential to guide safe and effective use of these agents in this population.

KEYWORDS
GLP-1, incretin mimetics, neuroendocrine neoplasms, neuroendocrine tumors, semaglutide, tirzepatide

Neuroendocrine neoplasms (NENs) are a biologically heterogeneous group of malignancies arising from neuroendocrine cells throughout the body, comprising well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Their incidence has increased substantially over the past several decades, largely because of improvements in diagnostic imaging and pathologic recognition.[1,2] Despite advances in our understanding of NEN biology, the etiologic drivers and risk factors underlying these tumors remain poorly defined and appear distinct from those of other malignancies, even when arising from similar organs of origin.[3] Concurrently, incretin-based therapies are being prescribed at an unprecedented scale for chronic conditions including type 2 diabetes, obesity, and cardiometabolic disease. This therapeutic class includes glucagon-like peptide-1 receptor (GLP-1R) agonists (GLP-1RA), such as semaglutide, as well as dual agonists targeting GLP-1R and glucose-dependent insulinotropic polypeptide receptor (GIPR), such as tirzepatide.[4] Their widespread adoption has been driven by robust evidence from randomized clinical trials and real-world studies demonstrating substantial metabolic, cardiovascular, and renal benefits.[5–9] As indications continue to expand and newer, more potent agents emerge, use of these therapies is expected to increase further.

Although the clinical benefits of incretin mimetics are well established, questions remain regarding their long-term safety profile, including the potential for oncologic effects. To date, population-based studies and meta-analyses have not demonstrated an increased overall risk of cancer. In fact, some studies have suggested a reduced incidence of certain malignancies among treated patients.[10–16] However, whether these reassuring findings extend to NENs remains uncertain. Several factors have contributed to ongoing uncertainty regarding the relationship between incretin therapies and NENs. Preclinical investigations have been limited by important methodological challenges. For example, species-specific differences in GLP-1R expression between rodents and primates are thought to underlie the development of medullary thyroid carcinoma (MTC) observed in rodent models exposed to GLP-1RA.[17] This ultimately led to the FDA boxed warning against use in individuals with a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2). However, there is a serious discordance between these preliminary preclinical data and existing clinical evidence. In the EXSCEL trial, exenatide treatment was not associated with increases in serum calcitonin levels and MTC rates were similar between exenatide and placebo groups. Importantly, all cases occurred in participants with markedly elevated baseline calcitonin levels, and routine calcitonin monitoring did not identify additional cases.[18] Similarly, a widely cited study of pancreata from organ donors with type 2 diabetes exposed to incretin therapies reported approximately 40% greater pancreatic mass, α-cell hyperplasia, and occasional neuroendocrine tumors. However, these findings have subsequently been challenged because of concerns regarding antibody specificity and other methodological limitations and have not been independently replicated.[19–21] Taken together, current evidence supports adherence to the Food and Drug Administration (FDA) contraindication in patients with a personal or family history of MTC or MEN2. However, outside of these high-risk populations, available clinical data do not support routine calcitonin screening before or during incretin-based therapy in otherwise unselected patients. Clinical evaluation should instead remain guided by patient history, symptoms, and standard prescribing recommendations.

Although most population-level studies evaluating cancer risk with incretin mimetics have not specifically included NENs, some signals have emerged that warrant further investigation. In a pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) from 2004–2021, encompassing 8718 incretin mimetic-associated tumor reports, no overall increase in malignancy reporting was identified (proportional reporting ratio [PRR] 0.83). Nevertheless, a significant reporting signal was observed for pancreatic NENs (PRR 2.86), highlighting the need for more nuanced investigation of incretin effects within specific NEN subtypes.[22]

In the context of heterogeneous data, the key concern is less about de novo NEN risk in the general population with incretin mimetics, and more about their effects in patients with established disease. In a preclinical model, semaglutide resulted in increased in vitro tumor cell growth by 19%–22% in GLP-1R–expressing NEN models and a 72% increase in tumor volume in mice with GLP-1R–positive xenografts.[23] Another study demonstrated that GLP-1R–positive duodenal NET models exhibited MAPK pathway activation and tumor growth in response to semaglutide exposure.[24] Within the limitations that NET cell lines may not be definitively representative of NETs in humans, these findings provide preliminary evidence of a plausible proliferative effect of GLP-1 RA in select NEN cell lines. However, this risk (albeit still theoretical) does not appear to be uniform across the NEN spectrum as investigations into GLP-1R expression have highlighted significant heterogeneity. In a large immunohistochemical analysis of 576 NENs across 13 sites of origin, GLP-1R expression was identified in

only 7% of tumors, with enrichment in duodenal, gastric, pancreatic, and pulmonary NETs, and pheochromocytomas. Importantly, GLP-1R expression was absent in ileal NETs and poorly differentiated NENs.[24] Notably, the small bowel is the most common site of origin for NETs in the United States.[1] Similarly, in another analysis of 689 NENs, GLP-1R expression was identified in 34% of pancreatic NETs and 53% of duodenal NETs, with lower prevalence in pulmonary NETs (9%) and small intestinal NETs (13%) and near-complete absence in gastrointestinal and pulmonary neuroendocrine carcinomas. Among pancreatic NETs, GLP-1R positivity was strongly associated with insulin production, observed in 84% of insulinomas and 31% of insulin-immunoreactive pancreatic NETs without clinical signs of insulinoma, compared with 0% in insulin-negative tumors.[25] GLP-1R positron emission imaging (PET) imaging through ^{68}Ga-NODAGA-exendin-4 revealed positive uptake in 94.4% in a series of 64 cases of insulinomas.[26] Additional studies have demonstrated that exendin-based PET imaging has superior sensitivity and diagnostic accuracy compared with conventional imaging modalities for insulinoma localization, supporting its role as a highly specific in vivo marker of GLP-1R expression.[27–29] Although clinical outcome data remain lacking, GLP-1R-targeted imaging may ultimately aid risk stratification by identifying tumors with preserved receptor expression that could theoretically be more susceptible to incretin-mediated signaling. Overall, there is substantial heterogeneity in GLP-1R expression within NENs, and it appears likely that vulnerability to incretin signaling in NENs may be limited to specific NEN subtypes.

Clinical data specific to the effects of incretin mimetics on NENs remain limited and are largely observational. Retrospective analyses comparing outcomes in NET patients exposed to incretin mimetics versus unexposed patients have not demonstrated clear oncologic harm and, in some studies, even suggest improved overall survival.[11,30,31] However, these findings are constrained by confounding, limited capture of recurrence or progression end points, and the inability to reliably distinguish pre-diagnosis exposure from post-diagnosis or post-treatment use. Additionally, these data are leveraged from large *International Classification of Diseases-Tenth Revision* (ICD-10) coding-based databases that are inherently limited in their ability to capture nuanced pathology data, which appear critical given substantial heterogeneity in GLP-1R expression in NENs. Taken together, the available evidence presents a mixed and, at times, conflicting signal leaving clinicians without a clear evidence base to guide clinical recommendations. If there truly is an oncologic risk associated with incretin mimetics, it is likely outweighed by other benefits associated with their use such as reduction in the risk of obesity-related malignancies and cardiovascular disease.[32] As a result, patients are likely to be asked to weigh substantial, well-established metabolic benefits against incompletely defined and currently unquantifiable oncologic risks.

With the level and nature of existing evidence, we do not recommend blanket avoidance of incretin mimetics in patients with NENs, especially in cases where there is a clear indication for use. However, it is also imperative to avoid presenting these agents as risk-neutral and to acknowledge potential for oncologic harm. Therefore, an individualized, shared decision-making approach is advised. Patients should be informed that preclinical data suggest potential tumor-promoting effects in incretin receptor-expressing NENs, whereas clear harm has not been demonstrated thus far in available clinical data.[23] It is also important to highlight that the risk across the NEN spectrum may be heterogenous. For example, ileal NETs that are among the most common sites of origin, seem to uniformly lack GLP-1R expression and may therefore not be at heightened risk of oncologic harm with GLP-1 RAs.[24,25] However, prior studies have demonstrated high GIPR expression in these tumors. In a study of 260 tumors, GIP receptor expression was highly prevalent and specific in pancreatic, ileal, and bronchial NETs, including those lacking SSTR and GLP-1 receptors.[33] Similarly, in a study of 103 primary NETs and 123 metastases, GIPR was significantly overexpressed (approximately 13-fold vs. normal) with absolute expression levels closest to SSTR2 (delta cycle threshold 3.6 vs. 2.7), despite overall lower expression than SSTR2.[34] Additional data suggest that GIPR expression may have biologic relevance, with epigenetic dysregulation of the GIPR locus associated with receptor overexpression and the development of liver metastases in small intestinal NETs.[35] Furthermore, GIPR expression has been shown to vary according to proliferative activity and tumor subtype.[36] Therefore, GLP-1RA may be preferred over other agents targeting both GLP-1R and GIPR. It is important to highlight that although these findings raise a theoretical concern regarding GIPR agonists in certain NET subtypes such as ileal NETs, there are currently no clinical data demonstrating differential tumor outcomes between GLP-1RAs and dual GLP-1/GIP receptor agonists. Treatment decisions should therefore be individualized until prospective data become available. Overall, presenting the risk as uncertain rather than absent, and encouraging patients to weigh this uncertainty against the well-established cardiometabolic benefits of incretin mimetics is crucial. In this regard, it is also vital to collaborate with other specialists involved in the care of specific chronic medical problems serving as the indication for incretin mimetic use.

When incretin mimetic therapy is pursued, we favor careful dose selection, selecting the lowest effective dose, and avoidance of escalation for weight loss alone in patients without strong metabolic indications. Practical considerations regarding currently available GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists, including dosing, expected adverse effects, and NEN-specific considerations, are summarized in Table 1. We are generally more comfortable with continued use in sporadic, well-differentiated tumors than in hereditary syndromes or other biologically high-risk contexts, where greater caution is warranted.[37] With respect to surveillance, closer imaging follow-up may be favored, at least initially, allowing early intervention in case disease progression appears incongruent with grade or biology. We suggest caution while initiating or continuing therapy with incretin mimetics in patients with progressive or a high burden of disease. An additional consideration when prescribing incretin mimetics in patients with NENs is their potential impact on body composition. Although weight loss associated with GLP-1 receptor agonists is predominantly driven by reductions in fat mass, studies suggest that approximately 20%–50% of total weight loss may occur through loss of

TABLE 1 Commonly used incretin-based therapies and practical considerations for patients with NENs.

Agent	Drug class	Approved indications[a]	Starting dose	Maintenance dose[b]	Weight loss	Common adverse effects	NEN-specific considerations
Exenatide	GLP-1RA	T2DM	2 mg weekly	2 mg weekly	Modest	Nausea, vomiting, diarrhea	Use cautiously in stable NENs; monitor GI symptoms; avoid in insulinoma
Liraglutide	GLP-1RA	T2DM, obesity	0.6 mg daily	1.8 mg daily (T2DM); 3.0 mg daily (obesity)	Moderate	Nausea, vomiting, diarrhea, constipation	Use the lowest effective dose; avoid dose escalation solely for weight loss in patients with nutritional compromise
Dulaglutide	GLP-1RA	T2DM	0.75 mg weekly	1.5–4.5 mg weekly	Moderate	GI adverse effects, decreased appetite	Monitor nutritional status and risk of sarcopenia, particularly in advanced disease
Semaglutide	GLP-1RA	T2DM, obesity, cardiovascular risk reduction	0.25 mg weekly	1–2 mg weekly (T2DM); 2.4 mg weekly (obesity)	High	Nausea, vomiting, diarrhea, constipation	Preclinical proliferative signals have been reported in GLP-1R–expressing NEN models; shared decision-making and close clinical monitoring are advised
Tirzepatide	Dual GLP-1/GIP agonist	T2DM, obesity	2.5 mg weekly	5–15 mg weekly	Very high	Nausea, vomiting, diarrhea, constipation	Consider caution in GIPR-expressing NETs (particularly small bowel and pancreatic NETs); monitor for excessive weight loss and nutritional decline
Emerging triple agonists (GLP-1/GIP/glucagon)	Triple agonist	Investigational	Variable	Variable	Very high	GI adverse effects; limited long-term safety data	Insufficient NEN-specific data; individualized use is recommended

Abbreviations: FDA, Food and Drug Administration; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; T2DM, type 2 diabetes mellitus.

[a]Approved indications may vary by regulatory jurisdiction.

[b]Starting doses and maintenance doses reflect current FDA-approved prescribing information for approved indications. Dose escalation should follow product labeling based on tolerability. No evidence-based NEN-specific dose initiation, titration, or discontinuation algorithms currently exist.

lean body mass, including skeletal muscle.[38] This is particularly relevant in patients with NENs, who may already be predisposed to sarcopenia, malnutrition, and impaired quality of life because of chronic disease burden, treatment-related toxicities, and malabsorption.[39–41] Therefore, careful monitoring of nutritional status, muscle mass, and physical function should be considered when initiating incretin-based therapies in this population.

Additionally, incretin mimetics should be prescribed with caution in patients receiving therapies associated with significant gastrointestinal adverse events such as diarrhea, abdominal pain, and malabsorption as these may be exacerbated-particularly in patients with functional syndromes (e.g., carcinoid syndrome, gastrinoma, or VIPoma). Given that symptom burden, nutritional status, and gastrointestinal function are major determinants of quality of life in patients with NENs, worsening of these symptoms may have clinically meaningful consequences beyond treatment tolerability alone.[39] Therefore, careful monitoring of gastrointestinal symptoms and nutritional status should be considered during incretin-based therapy, particularly in patients with preexisting symptom burden or malabsorptive complications. Incretin mimetics should also be avoided in persons with known insulinoma as they may cause severe hyoglycemia.[42] Yet newer agents such as triple GLP-1R, GIPR, and glucagon receptor agonists are now on the horizon, however, their clinical risk or impact in patients with functional NETs such as glucagonoma remains unknown. At present, we do not suggest routine tumor staining for incretin receptor expression to guide clinical decisions, as the clinical implications of receptor positivity remain incompletely defined. However, we believe receptor-level information may become increasingly relevant as standardized assays and outcome-linked data unfold, particularly with emergence of dual- and multi-agonist therapies. In Table 2, we discuss clinical recommendations for the use of incretin-based therapies across common NEN subtypes and clinical scenarios.

Importantly, well-coordinated multi-disciplinary care should be pursued during ongoing incretin mimetic therapy. Ongoing reassessment for tolerability, adverse effects, as well as changes in disease behavior or biology (through clinical and radiologic assessment) is paramount. Until prospective and more nuanced long-term data are available, a transparent, patient-centered shared decision-making model should be adopted in clinical practice. Future investigations

TABLE 2 Clinical considerations for the use of incretin-based therapies across NEN subtypes and clinical scenarios.

Scenario	Suggested approach	Rationale
MTC/MEN2	Avoid	Established labeling warning and biologic risk
Insulinoma	Generally avoid	Incretin receptor activity may exacerbate hypoglycemia
Sporadic, stable, well-differentiated NET with strong metabolic indication	Reasonable to consider	No consistent clinical signal of harm to date
MEN1/hereditary NETs	Use caution	Multifocal disease and limited syndrome-specific data
Progressive or high-burden of disease	Generally avoid; close monitoring of disease advised	Theoretical risk of tumor proliferation with limited prospective evidence
Resected NENs	Consider if strongly indicated; early surveillance advised	Uncertain recurrence risk with no direct safety signal

Abbreviations: MEN1/2, multiple endocrine neoplasia type 1/2; MTC, medullary thyroid carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor.

should attempt to personalize risk stratification and allow patients to weigh quantifiable long-term risk of oncologic harm against cardiometabolic benefits of incretin mimetics.

AUTHOR CONTRIBUTIONS

Udhayvir S. Grewal: Conceptualization; methodology; writing—original draft; writing—review and editing; supervision. **Po H. Ear**: writing—original draft; writing—review editing. **Mohamad B. Sonbol**: Writing—original draft; writing—review and editing. **Andrew M. Bellizzi**: Writing—original draft; writing—review and editing. **Johannes Hofland**: Writing—original draft; writing—review and editing. **Joakim Crona**: Writing—original draft; writing—review and editing. **Joseph S. Dillon**: Writing—original draft; writing—review and editing. **Jennifer A. Chan**: Writing—original draft; writing—review and editing. **James R. Howe**: Writing—original draft; writing—review and editing. **Jonathan Strosberg**: Writing—original draft; writing—review and editing. **Simron Singh**: Writing—original draft; writing—review and editing. **Thorvardur R. Halfdanarson**: Conceptualization; writing—original draft; writing—review and editing; supervision.

CONFLICT OF INTEREST STATEMENT

Jennifer A. Chan reports consulting fees from Boehringer Ingelheim, Lantheus Medical Imaging, Inc, and Sanofi; fees for other professional activities from Curium US LLC and Ipsen; participation on a data and safety monitoring board for Novartis; and stock holdings in Merck. Joakim Crona reports consulting fees from ESTEVE. Udhayvir S. Grewal reports consulting fees from Boehringer Ingelheim; and fees for other professional activities from Exelixis Inc. Thorvardur R. Halfdanarson reports consulting fees from Abdera Therapeutics, Advanced Accelerator Applications, Boehringer Ingelheim GmbH, Camurus, Crinetics, Curium US LLC, Exelixis Inc, Ipsen Biopharmaceuticals, Inc, ITM Isotopen Technologien Muenchen, Perspective Therapeutics, Sanofi, TerSera and Therapeutics LLC; grant and/or contract funding from Abdera Therapeutics, Advanced Accelerator Applications, Camurus, Crinetics, ITM Isotopen Technologien Muenchen, Perspective Therapeutics, and Rezolute. Johannes Hofland reports fees for professional activities from Ipsen Pharma SAS, Novartis, and Serb. Mohamad B. Sonbol reports consulting fees from Bayer and Boehringer Ingelheim, Jazz Pharmaceuticals, Taiho Oncology, Inc, and Novartis; and fees for other professional activities from Eli Lilly and Company. Jonathan Strosberg reports consulting fees from Boehringer Ingelheim, Exelixis, and Merck. The other authors declare no conflicts of interest.

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