Blood-based Biomarkers in NET

or

How I learned to stop worrying and love the CT scan

Daniel M. Halperin, MD
Associate Professor
Vice Chair for Clinical Affairs
Hematology and Medical Oncology
Physician Director for Cancer Service Line Clinic Operations
Winship Cancer Institute of Emory University

Disclosures (24 months)

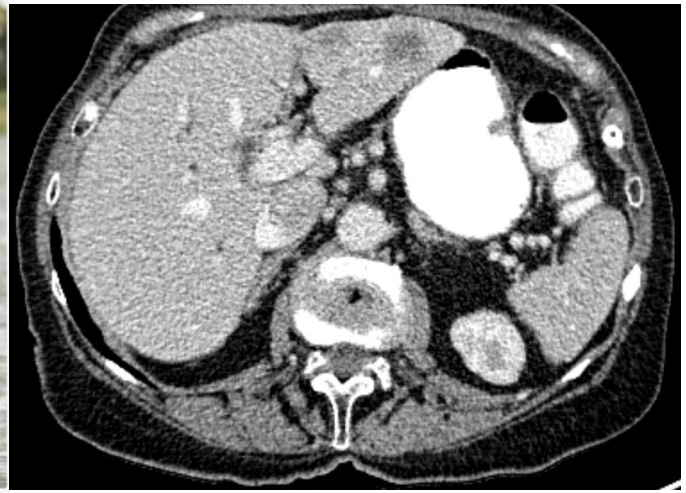
- Consultant for Wren Laboratories, Sanofi, TerSera, Boehringer Ingelheim, Lantheus, Exelixis, AbbVie, Harpoon Therapeutics, ITM, Novartis, Crinetics, Amryt, Camurus, Alphamedix, Chimeric Therapeutics.
- Research funded by Chimeric Therapeutics, Crinetics, Novartis.
- I **will** discuss off-label and/or investigational use.

Salient Disclosures (all time)

- I have (or have had) relationships with companies that market blood-based biomarkers for patients with NETs.
- I hope that blood-based biomarkers will one day be clinically impactful for NET patients.
- I currently do not recommend routine clinical use of blood-based biomarkers for patients with NETs.

A clinical scenario

- AB is a 54M seen in consultation for G1 ileal NET metastatic to liver, discovered incidentally after he fell…
- His disease has been stable on long-acting somatostatin analogue for the past 18 months (last imaging 6 weeks ago).
- He sends a patient portal message that along with his monthly CBC and CMP, his chromogranin A has increased from 84 -> 110 ng/mL, and he would like to fly back to Atlanta for urgent restaging…

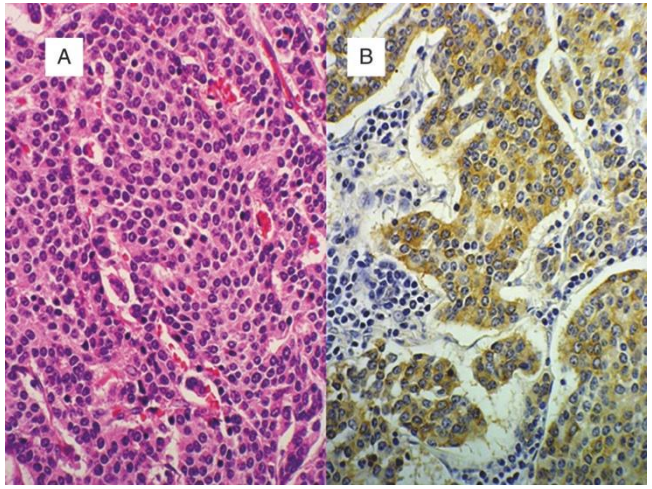


Objectives

- Definitions
- Goals for blood-based biomarkers
- NET biomarker challenges
- NET biomarker evidence

Framework

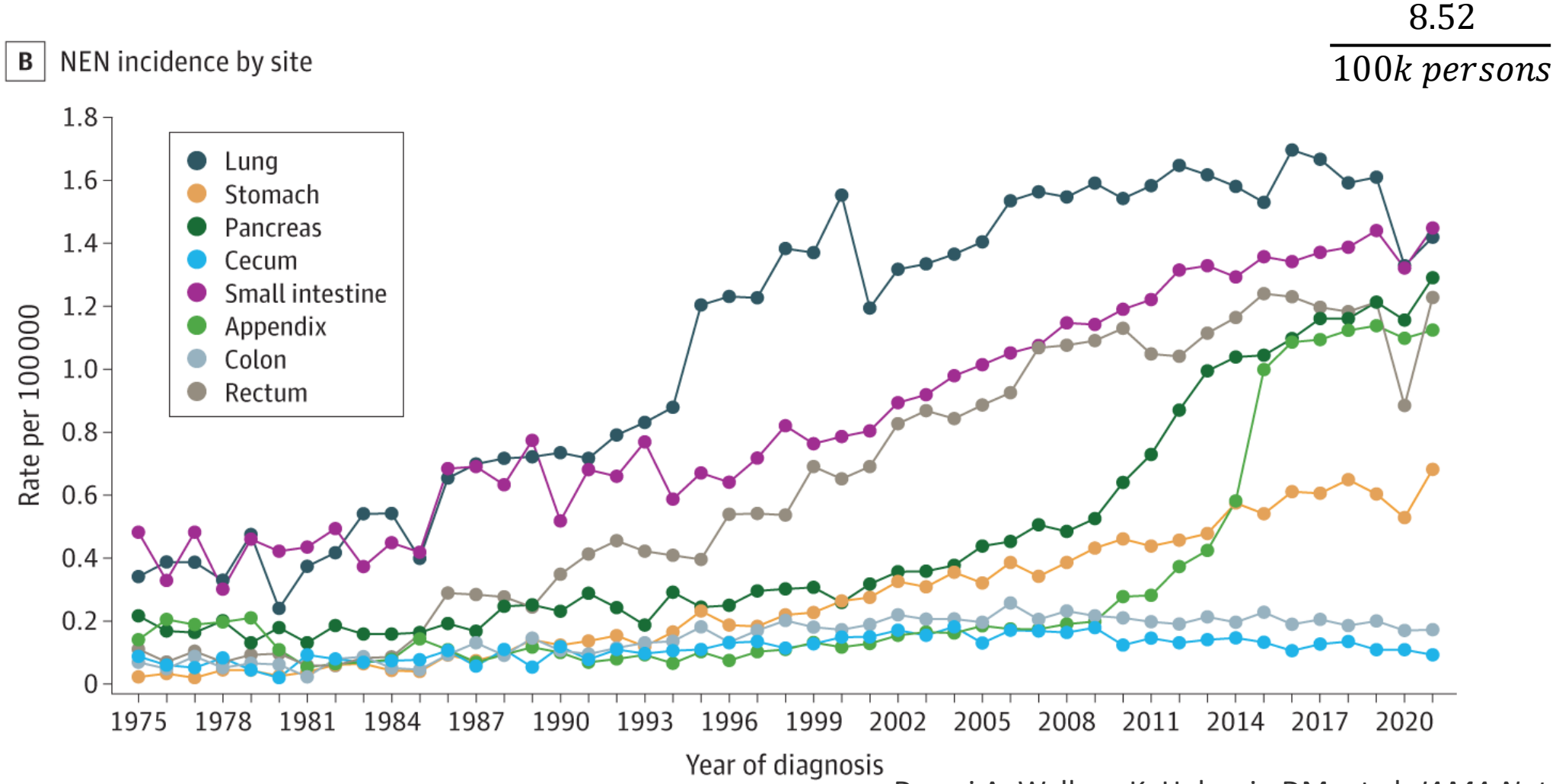
- NETs arise from epithelial endocrine cells distributed throughout the lungs, digestive tract, and pancreas.
- Previously called carcinoid tumors because the are “carcinoma-like.”
- Characterized by secretory granules and metal salt uptake.
- These granules can be secreted and lead to assorted functional syndromes.
- ~80% express somatostatin receptors



Histology of NET. A: H&E; B: CgA

Rising (but still modest) Incidence of NENs

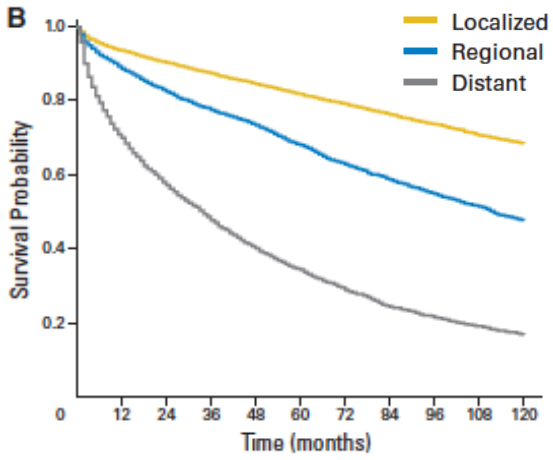
$$\frac{8.52}{100k\ persons}$$



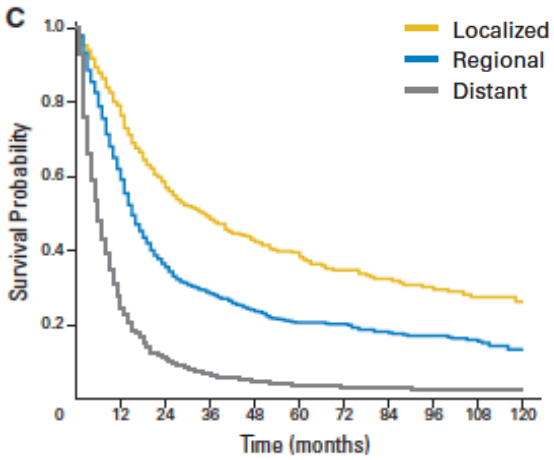
Dasari A, Wallace K, Halperin DM, et al. *JAMA Netw Open.* 2025

Clinical Variables Prognosticate Incompletely

Grade 1-2



Grade 3



Metastatic Grade 1-2 NET

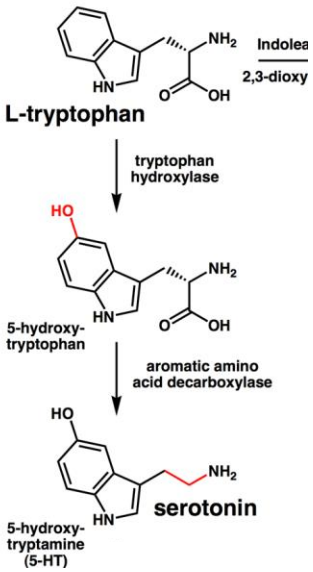
Primary Tumor Site	Median Survival (months)
Appendix	71.2
Cecum	86.1
Colon	26.0
Lung	44.6
Pancreas	57.6
Rectum	39.7
Small Intestine	103.0
Stomach	33.7

Yao et al., J Clin Oncol 2008; 26:3063

Dasari A, Wallace K, Halperin DM, et al. *JAMA Netw Open.* 2025

Carcinoid Syndrome

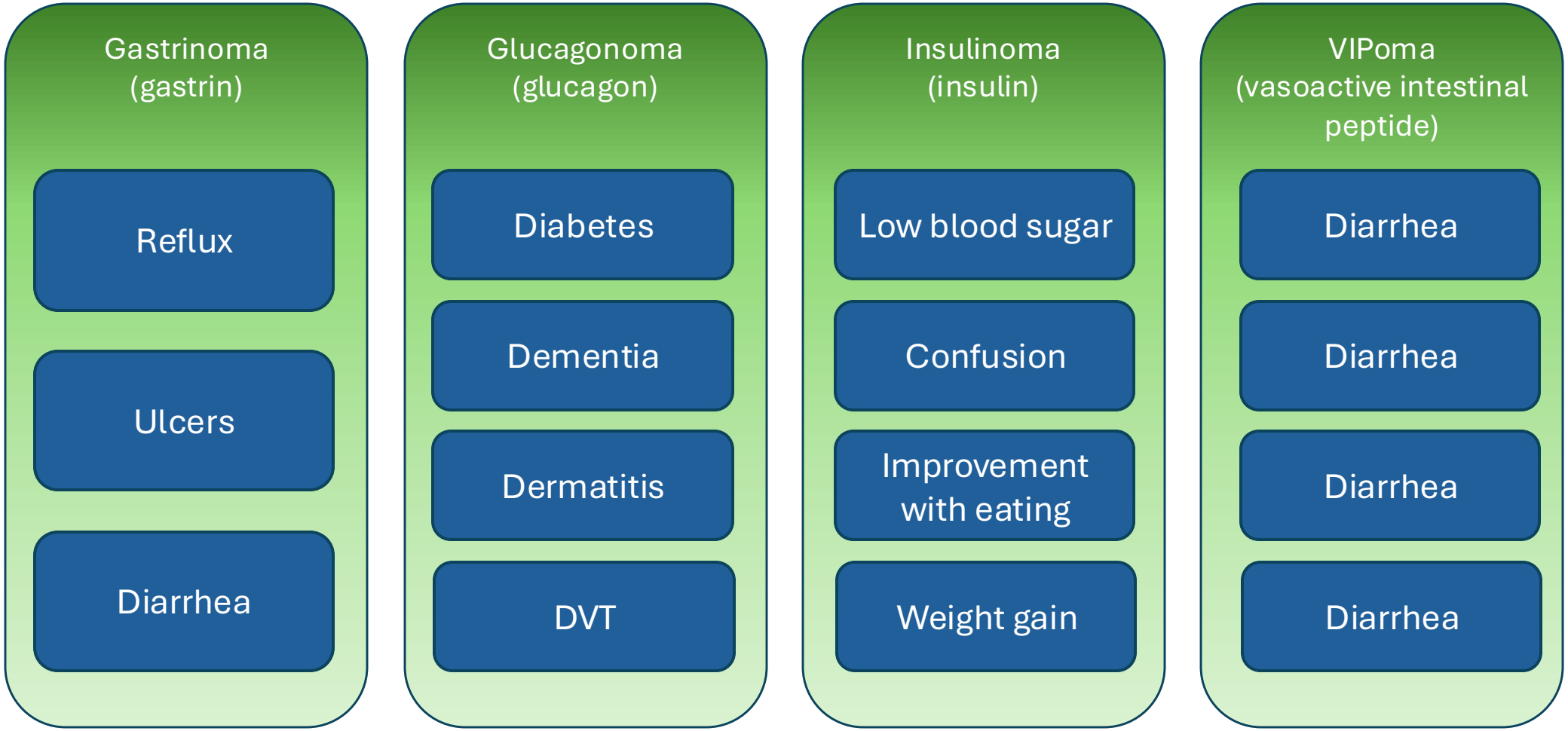
- Carcinoid syndrome: wheezing, flushing, diarrhea, right-sided valvular heart failure.
- The latter appear most linked to serotonin secretion.
- Exacerbated by the “5 E’s”
  - Ethanol
  - Eating specific foods (MAOI foods list)
  - Epinephrine
  - Emotion
  - Exercise
- Carcinoid crisis: acute hypotension, bronchospasm, sometimes in the OR.



	Localized	Regional	Distant
Lung/respiratory organ	83/1044 (8%)	19/239 (8%)	30/196 (15%)
Small Bowel	155/817 (19%)	248/670 (37%)	242/436 (56%)
Caecum	Masked*	38/113 (34%)	28/54 (52%)
Appendix	Masked*	Masked*	Masked*
Colon or rectum	78/945 (8%)	14/54 (26%)	26/75 (35%)
Other	102/604 (17%)	16/62 (26%)	52/100 (52%)

Halperin et al., Lancet Oncol 2017;18:525
http://en.wikipedia.org/wiki/Niacin

Functional Pancreatic NETs



Adapted with permission from James Yao

Definitions

- A functional NEN produces a peptide hormone with a concomitant clinical syndrome.
  - E.g., Measuring 5-HIAA to assess carcinoid syndrome in a patient with diarrhea is standard practice.
- Tumor Markers – used here to describe blood-based assays whose sole purpose is to assess oncologic status

Goals

- Establish a diagnosis of disease
- Assess persistence of disease
- Assess progression of disease

Challenges

- Rarity
  - Use case: screening/diagnostic purposes
  - For most patients, the diagnosis is rarely NET
- Pace of Progression
  - Use case: correlating with radiographic progression
  - For most patients, the tumor rarely grows
- Risk/benefit of earlier intervention
  - Use case: predicting radiographic progression
  - For most patients, treating sooner rarely helps
    - OS curves collapse in RCTs

Chromogranin A

- Prospective multicenter observational protocol
- 153 patients with measurable GEP-NET
- No PPI, H2RA, steroids
- RECIST 1.1 vs. 50% rise > ULN (prospectively defined)
- Hypothesis: Sn > 15.5%, Sp > 87.5%

	Disease status according to RECIST 1.1		
ΔCgA test results	**No progression**	**Progression**	**Row sum**
Negative	339 (TN)	63 (FN)	402
Positive	24 (FP)	33 (TP)	57
Column sum	363	96	459

Diagnostic performance metrics for disease status according to RECIST 1.1	Estimate (95% CI)
Sensitivity, %	34.4 (25.6–44.3)
Specificity, %	93.4 (90.4–95.5)
PPV, %	57.9 (45.0–69.8)
NPV, %	84.3 (80.5–87.6)
LR^+	5.20 (3.23–8.36)
LR^-	0.70 (0.61–0.81)
AUC	0.731 (0.669–0.793)
OR, test-positive vs. test-negative	7.40 (4.12–13.49)
OR, doubling of CgA ratio	3.09 (2.22–4.46)

Meng…Halperin., CCR 2024

NETest (and 2.0)

- Prospective multicenter registry
- 886 patients with NET
- Descriptive statistics, diagnostic accuracy

Objective 1: Disease Detection

All samples	Imaging positive	Imaging negative	Total
NETest positive	917	15	932
NETest negative	82	276	358
Total	999	291	**1,290**

Statistic	Value	95% CI
Sensitivity	91.8%	89.91% to 93.42%
Specificity	94.9%	91.64% to 97.09%
PLR	17.81%	10.87 to 29.16
NLR	0.09	0.07 to 0.11
PPV	98.4%	97.39% to 99.01%
NPV	77.1%	73.20% to 80.58%
Accuracy	92.5%	90.90% to 93.86%

Objective 2: Progression Assessment (RECIST or clinical)

Metrics	NETest2.0® Score #2 ≥ 50 with Increase in Second Sample from First Sample				
Threshold	>0%	>+5%	>+10%	>+15%	>+20%
Sensitivity	78.0% (69–85%)	67.8% (59–76%)	58.5% (49–68%)	51.7% (42–61%)	43.2% (34–53%)
Specificity	83.2% (78–87%)	90.6% (87–94%)	93.7% (90–96%)	97.2% (95–99%)	98.3% (96–99%)
PLR	4.65 (3.53–6.12)	7.18 (4.91–10.50)	9.29 (5.79–14.9)	18.48 (9.13–37.41)	24.72 (10.12–60.39)
NLR	0.26 (0.19–0.37)	0.36 (0.27–0.46)	0.44 (0.36–0.55)	0.50 (0.41–0.60)	0.58 (0.49–0.68)
PPV	65.7% (59–72%)	74.8% (67–81%)	79.3% (71–86%)	88.4% (79–94%)	91.1% (81–96%)
NPV	90.2% (87–93%)	87.2% (84–90%)	84.5% (82–87%)	83.0% (80–86%)	80.8% (78–83%)
Accuracy	81.7% (78–85%)	83.9% (80–87%)	83.4% (79–87%)	83.9% (80–87%)	82.2% (78–86%)

Gulati...Halperin., Cancers 2026

Conclusions

- Peptide hormone levels are of value in establishing specific syndromes in the appropriate clinical context
- Blood-based biomarkers are intriguing
- Current high-level evidence supports at best a narrow use case (exclusion of progression within defined time bounds)
- Studies testing the hypothesis that biomarkers drive action that improves NET patient outcomes outcome are eagerly awaited.

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