

MIRAGE: tumori neuroendocrini, uno sguardo al futuro

Sabato 3 ottobre 2026

**Aula magna Nuovo Arcispedale S. Anna
*Cona, Ferrara***

I nuovi volti dei NET

Massimo Milione

Disclosures of Relevant Financial Relationships

- ✓ **CONSULTING AND ADVISORY SERVICES, PUBLIC PRESENTATIONS** (BOEHRINGER INGELEIM, 3A-NOVARTIS, IPSEN, ROCHE, SAKURA FINTEK, LEICA, DIAPATH, BIOPTICA, MERCK SHARP & DHOME)
- ✓ **FINANCIAL SUPPORT FOR CLINICAL TRIALS** (IGNYTA, ROCHE, ADOPT BBMRI-ERIC, TRANSCAN2, Fondazione IRCCS Istituto Nazionale Tumori Milano, Milan, Italy)

Outline

1. NETs and NECs: From WHO Classification to an Evolving Diagnostic Framework

2. NETs (G3) and NECs: Is There Common Ground?

3. Beyond MiNENs: The Expanding Spectrum of Mixed Neoplasms

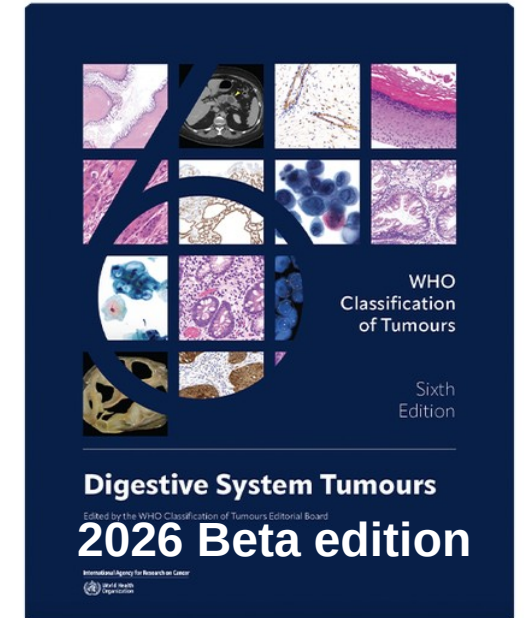
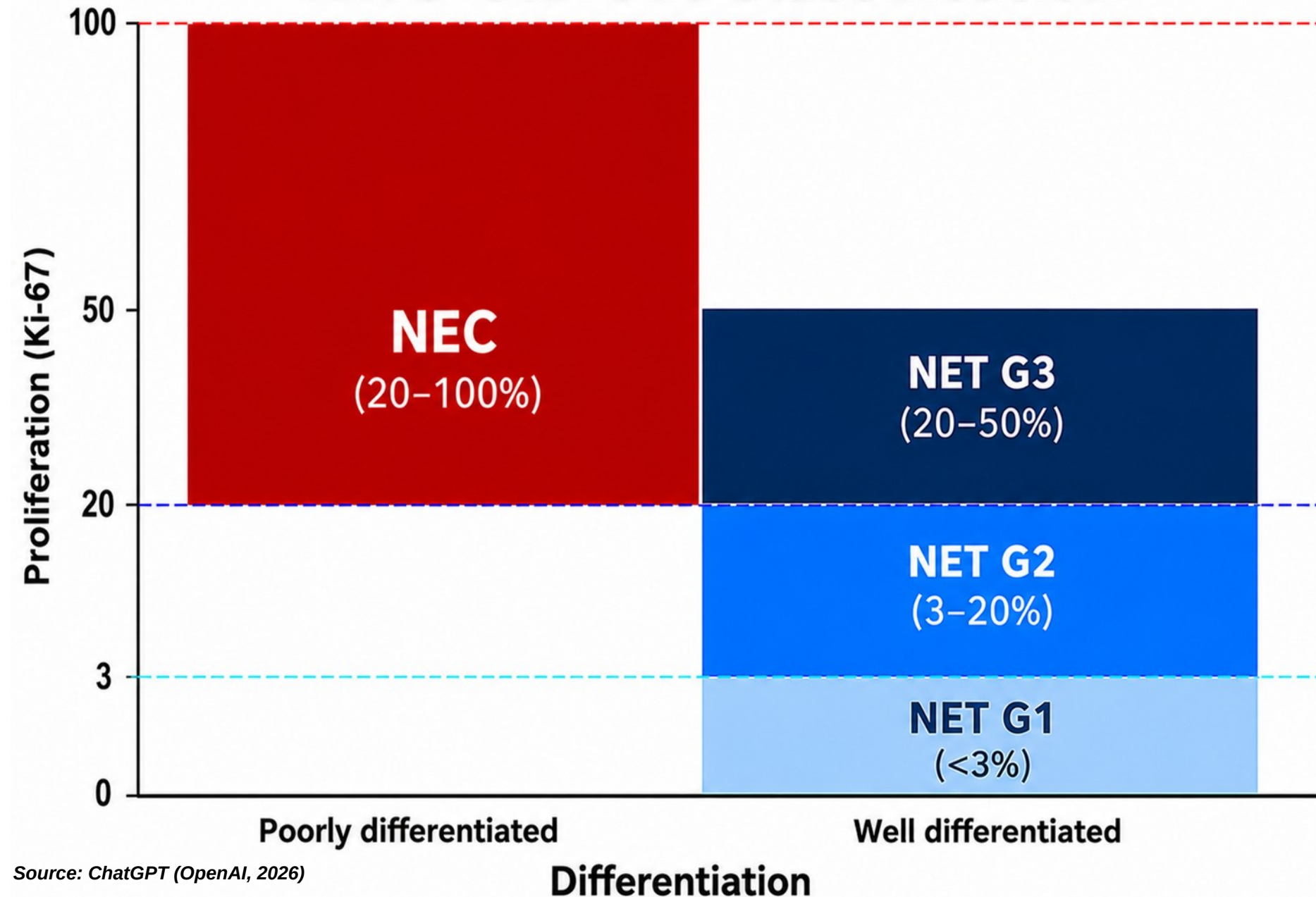
Outline

1. NETs and NECs: From WHO Classification to an Evolving Diagnostic Framework

2. NETs (G3) and NECs: Is There Common Ground?

3. Beyond MiNENs: The Expanding Spectrum of Mixed Neoplasms

WHO Current Classification



Source: ChatGPT (OpenAI, 2026)

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Ferrara 3rd October 2026

Biology and Clinical Behaviour Call for a Rethinking of NET Classification: The Example of NET G2

Ann Surg Oncol (2024) 31:7001–7011
https://doi.org/10.1245/s10434-024-15632-y

Annals of
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ORIGINAL ARTICLE – PANCREATIC TUMORS

Subgrading of G2 Pancreatic Neuroendocrine Tumors as 2A (Ki67 3% to < 10%) Versus 2B (10% to ≤ 20%) Identifies Behaviorally Distinct Subsets in Keeping with the Evolving Management Protocols

Ozgur Can Eren, MD¹, Pelin Bagci, MD², Serdar Balci, MD³, Nobuyuki Ohike, MD⁴, Burcu Saka, MD¹, Cenk Sokmensuer, MD⁵, Can Berk Leblebici, MD⁵, Yue Xue, MD, PhD⁶, Michelle D. Reid, MD, MSc⁷, Alyssa M. Krasinskas, MD⁷, David Kooby, MD⁸, Shishir K. Maithel, MD⁸, Juan Sarmiento, MD⁸, Jeanette D. Cheng, MD⁹, Orhun Cig Taskin, MD¹, Yersu Kapran, MD¹, Zeynep Cagla Tarcan, MD¹⁰, Claudio Luchini, MD, PhD¹¹, Aldo Scarpa, MD¹¹, Olca Basturk, MD¹⁰, and N. Volkan Adsay, MD¹

Journal of Endocrinological Investigation (2025) 48:1483–1493
https://doi.org/10.1007/s40618-025-02552-1

ORIGINAL ARTICLE



Clinical and biological heterogeneity of Grade 2 digestive neuroendocrine neoplasms: prognostic significance of the 10% Ki-67 index cutoff and implications for treatment strategies. A longitudinal study

Sara Massironi^{1,2}, Camilla Gallo³, Lorenzo Coltro⁴, Giuseppe Dell'Anna⁵, Paoletta Preatoni⁵, Silvio Danese^{1,5}

Ann Surg Oncol (2026) 33:3425–3434
https://doi.org/10.1245/s10434-025-18887-1

Annals of
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ORIGINAL ARTICLE – ENDOCRINE TUMORS

The Paradox of Grade 2 Pancreatic Neuroendocrine Tumors: G2a/G2b Subdivision in Patients With and Without Liver Metastases: A Retrospective Single-Center Analysis

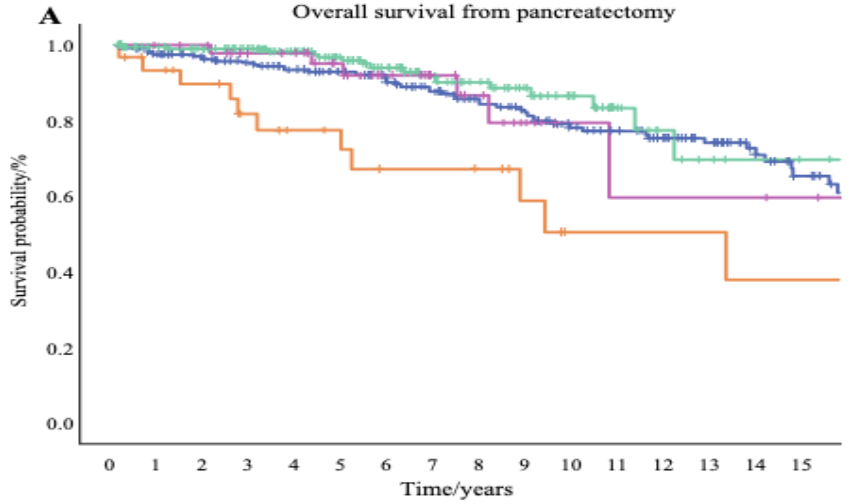
Vanja Podrascanin, MD^{1,2}, Markus Ammann, MD^{1,2}, Hallbera Gudmundsdottir, MD¹, Yawen Dong, MD^{1,3}, Jonas Santol, MD^{1,3}, David Pereyra, MD, PhD^{1,4}, Cornelius A. Thiels, DO¹, Susanne G. Warner, MD¹, Mark J. Truty, MD¹, Michael L. Kendrick, MD¹, Rory L. Smoot, MD¹, Thorvardur R. Halldanarson, MD⁵, David M. Nagorney, MD¹, and Patrick P. Starlinger, MD, PhD, FEBS (Transplant and HPB)¹

¹Department of Surgery, Division of Hepatobiliary and Pancreas Surgery, Mayo Clinic, Rochester, MN; ²Department of Surgery, University Clinic Wiener Neustadt, Wiener Neustadt, Austria; ³Department of Surgery, HPB Center, Vienna Health Network, Clinic Favoriten and Sigmund Freud Private University, Vienna, Austria; ⁴Department of General Surgery, Division of Visceral Surgery, Medical University of Vienna, Vienna, Austria; ⁵Division of Medical Oncology, Department of Oncology, Mayo Clinic, Rochester, MN

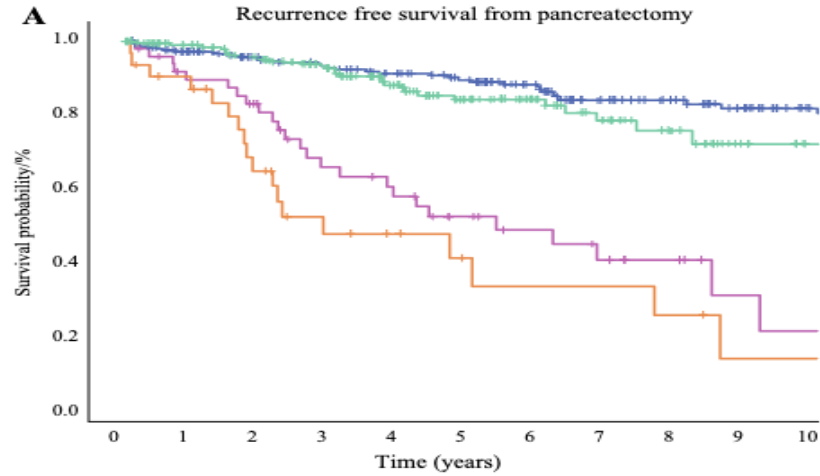
NET G2b

10%

NET G2a

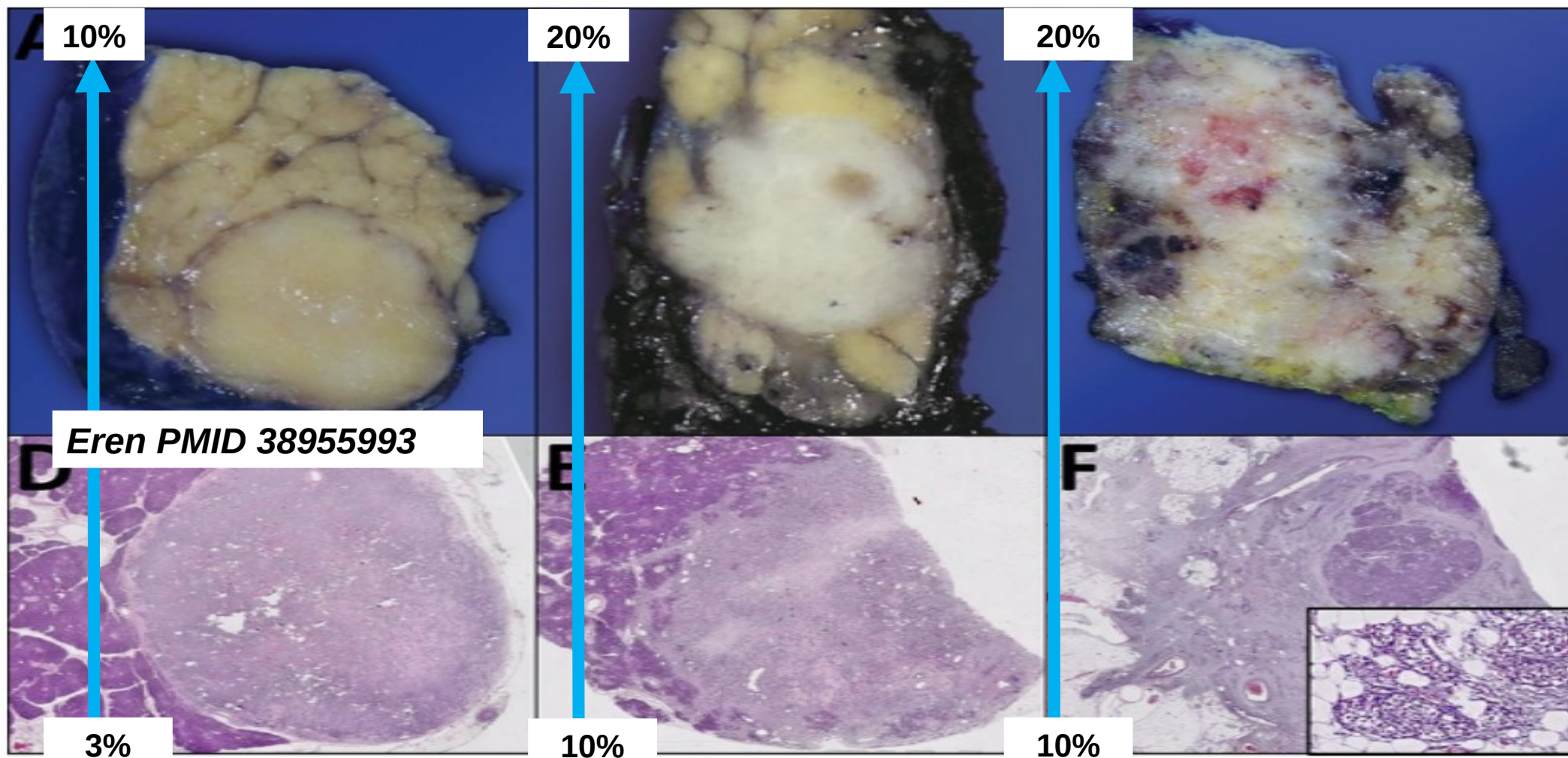


G1	275	230	214	202	190	177	154	137	119	106	90	81	71	60	42	33
G2a	217	191	180	163	134	108	87	65	55	42	28	15	10	5	4	3
G2b	48	47	45	39	37	29	24	17	12	6	3	3	3	3	2	2
G3	30	26	23	18	15	13	13	13	9	7	4	4	4	4	3	2



G1	275	218	197	183	164	153	127	96	83	69	56
G2a	217	180	161	137	104	78	58	38	25	14	8
G2b	48	39	34	25	21	15	11	10	7	2	2
G3	30	24	17	10	7	5	5	5	3	1	1

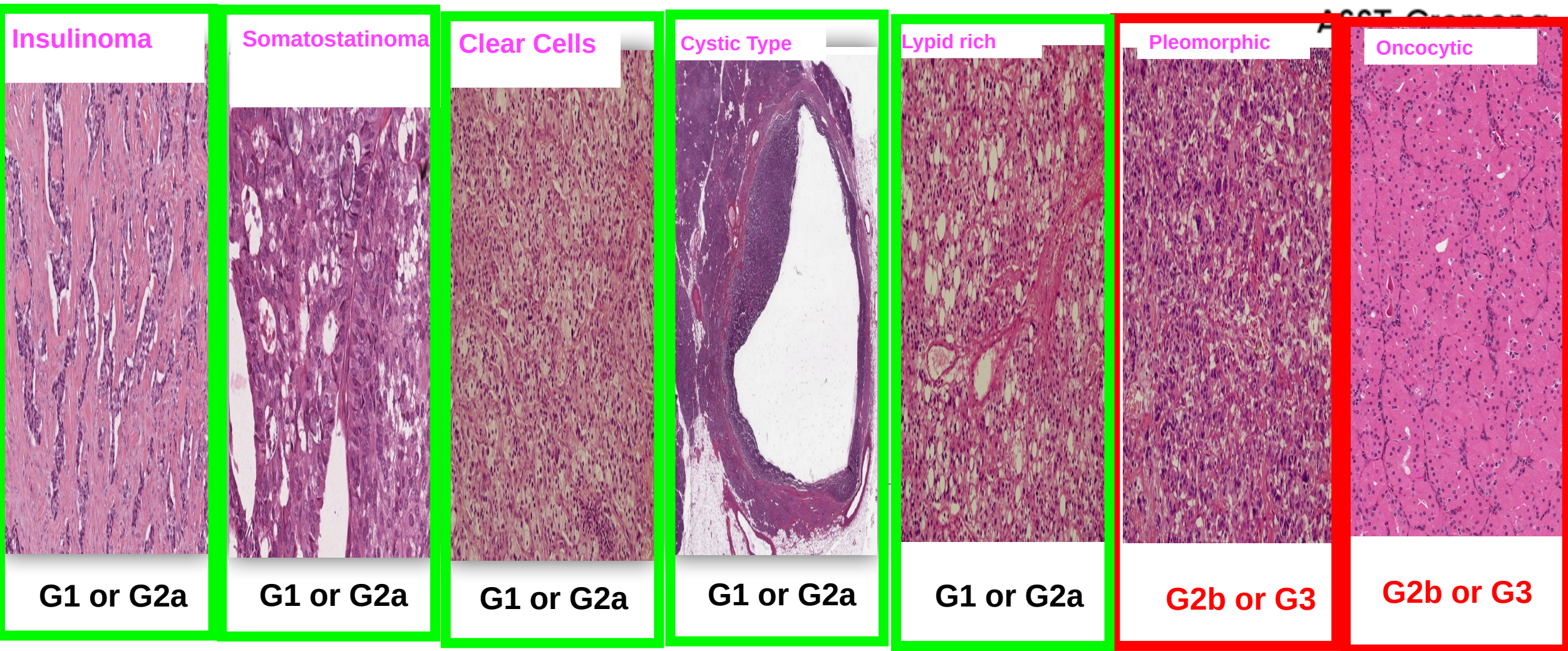
Biology and Clinical Behaviour Call for a Rethinking of NET Classification: The Example of NET G2



G2 may be further subdivided into two biologically distinct subgroups:

G2a (Ki-67 3% to $\leq 10\%$) - G2b (Ki-67 10% to $> 20\%$)

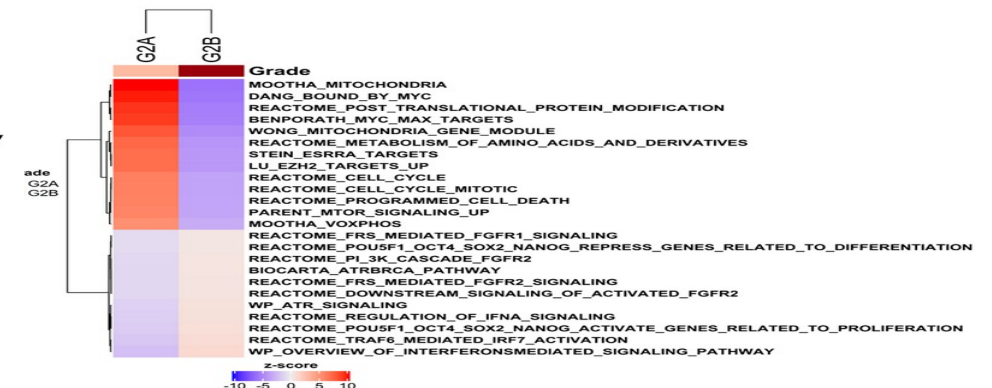
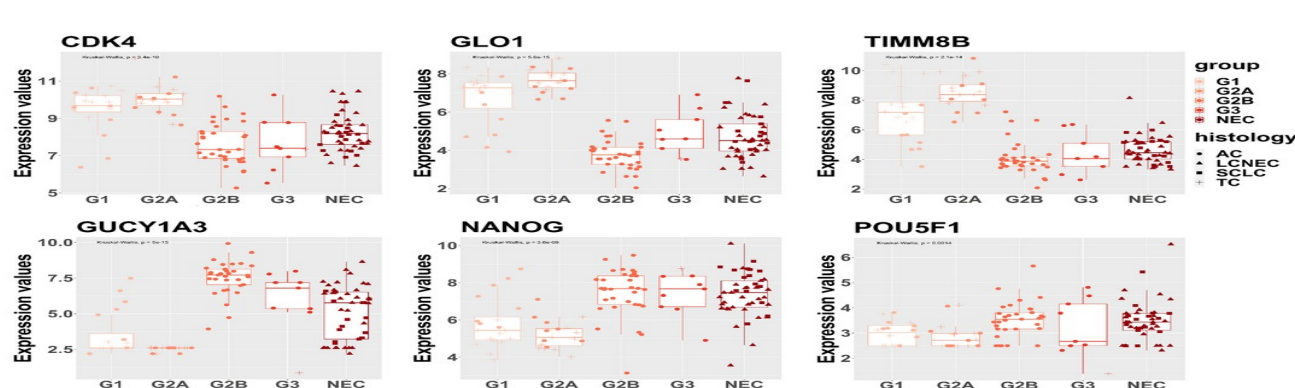
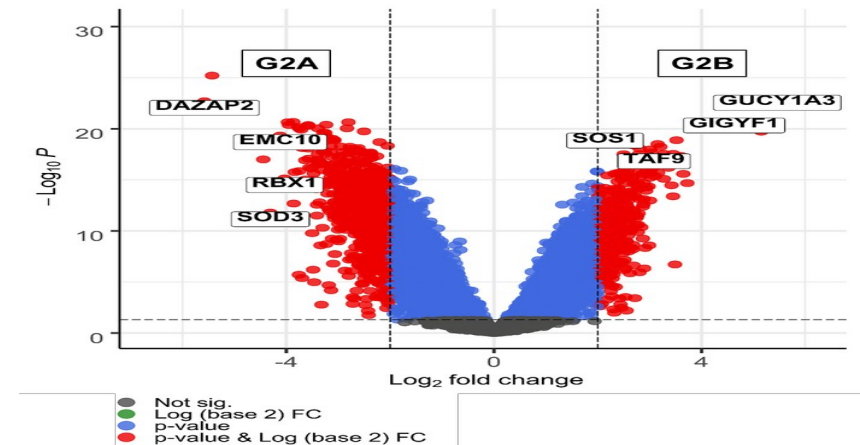
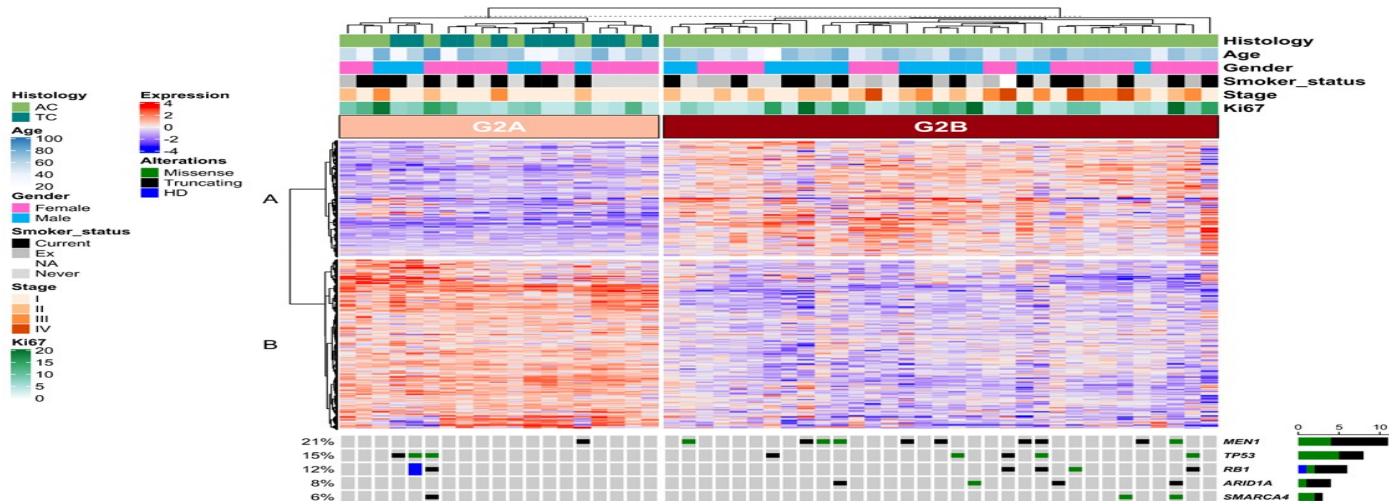
Biology and Clinical Behaviour Call for a Rethinking of NET Classification: The Example of NET G2



Can NET morphology predict NET grade?

Biology and Clinical Behaviour Call for a Rethinking of NET Classification: The Example of NET G2

Transcriptomics further refines G2 NETs into two distinct molecular subgroups:
G2a and G2b.



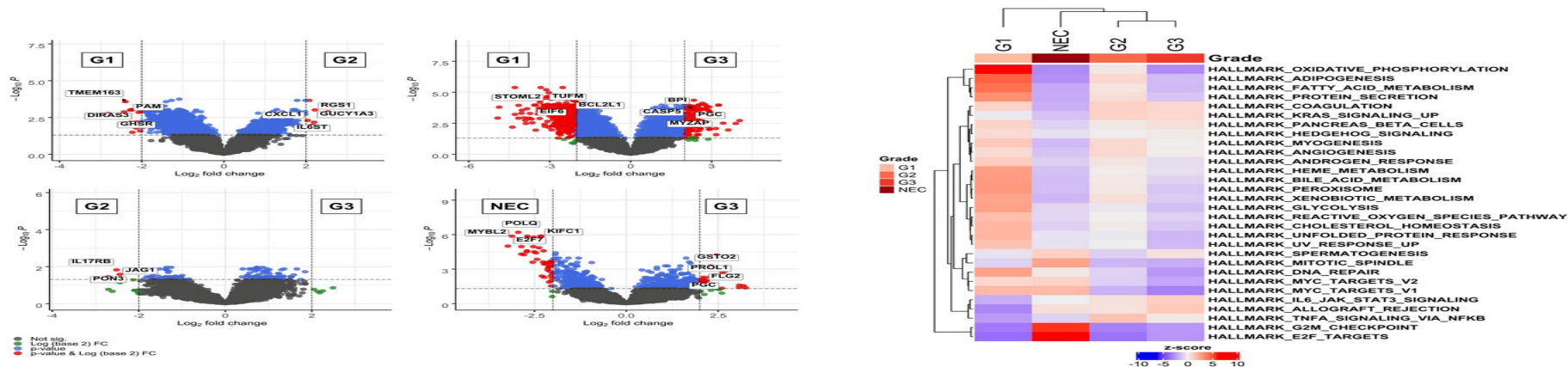
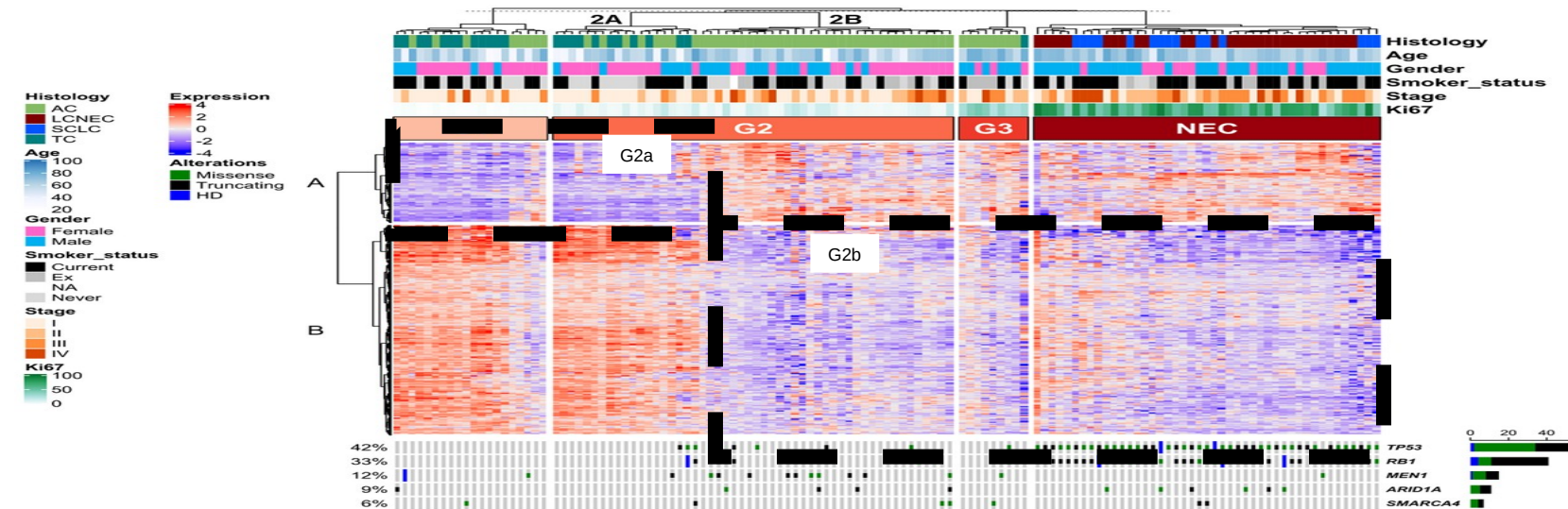
Mangogna et al in preparation

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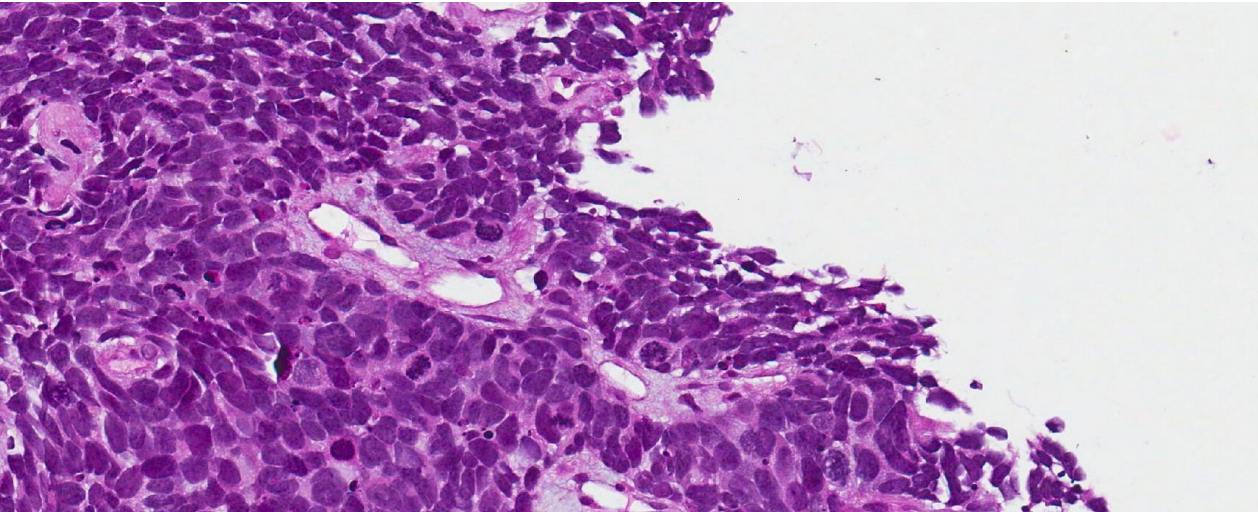
Ferrara 3rd October 2026

Biology and Clinical Behaviour Call for a Rethinking of NET Classification: The Example of NET G2

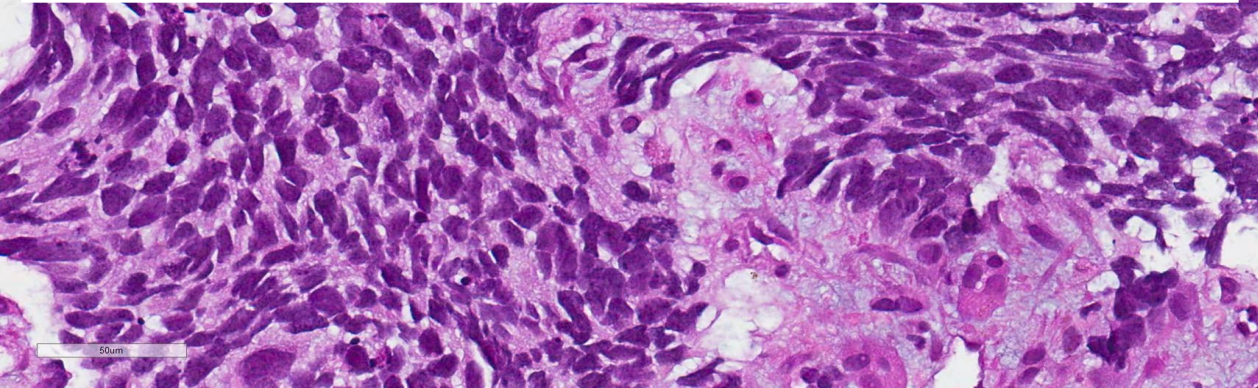
G2a and G2b: Two Distinct Positions Within the NET-NEC Spectrum



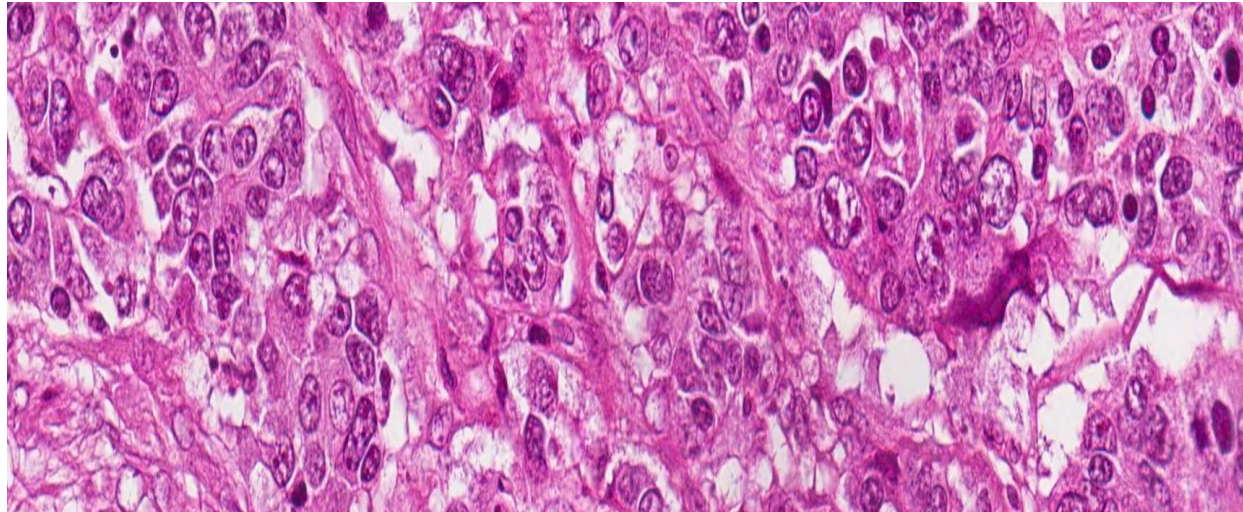
NEC: POORLY Differentiated Neuroendocrine Carcinoma



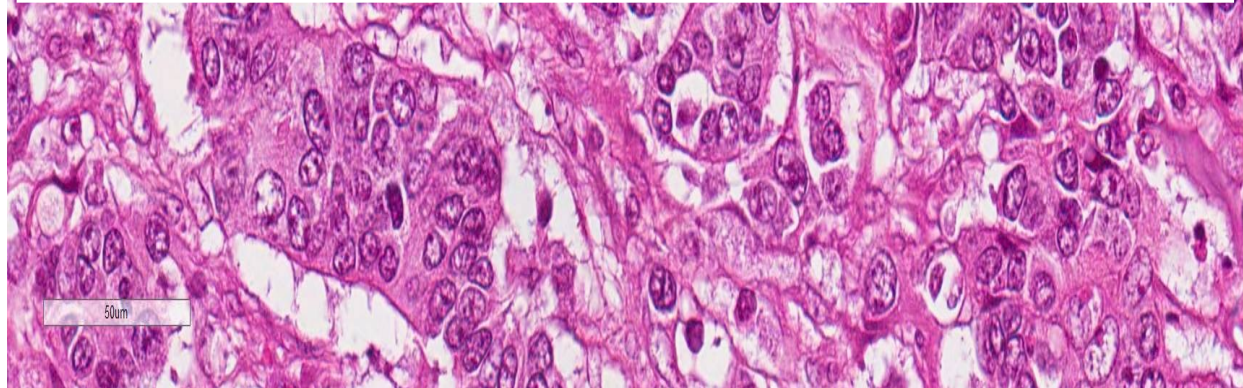
**Small Cells Neuroendocrine
Carcinoma
(SCNEC)**



50um

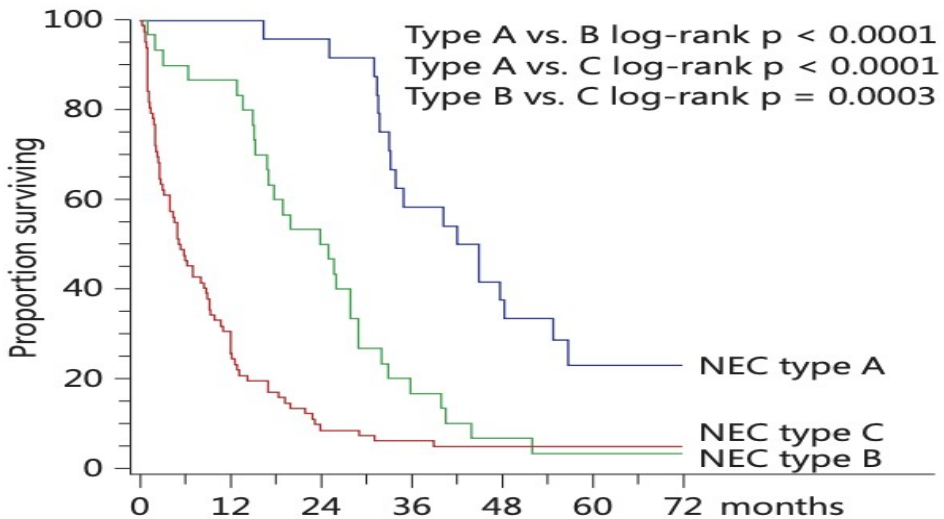
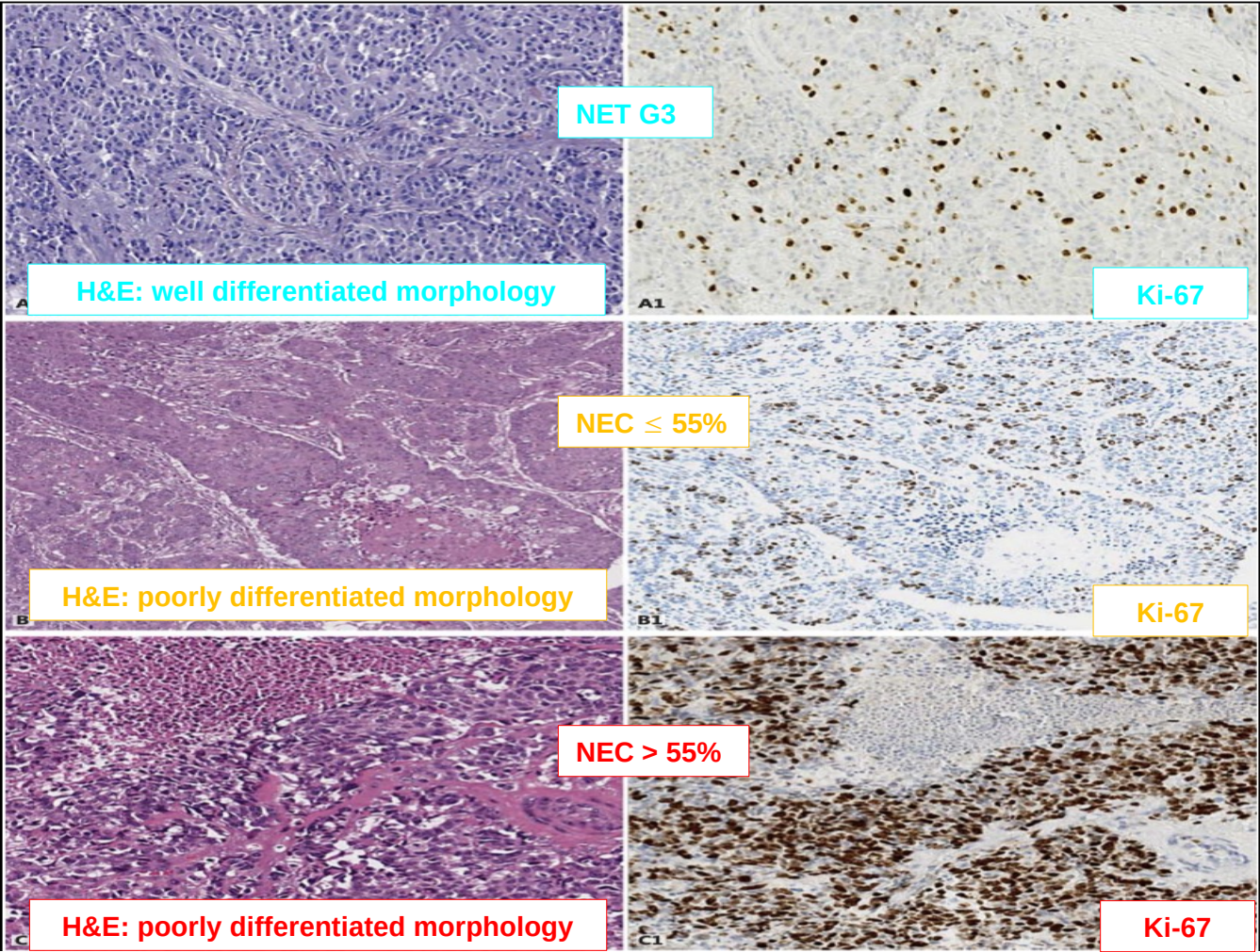


**Large Cells Neuroendocrine
Carcinoma
(LCNEC)**



50um

A 20% Ki-67 cut-off fails to capture the clinical heterogeneity of NECs



Patients at risk (n)

Type A	24	24	23	14	9	4	3
Type B	30	26	16	5	2	1	1
Type C	82	25	7	5	4	4	4
OS (%)							
Type A	100	100	96	58	38	23	23
Type B	100	87	53	17	7	3	3
Type C	100	31	9	6	5	5	5

NET G3 = (Type A) Well Differentiated+Ki-67 21-55% = **MOS: 43,6**

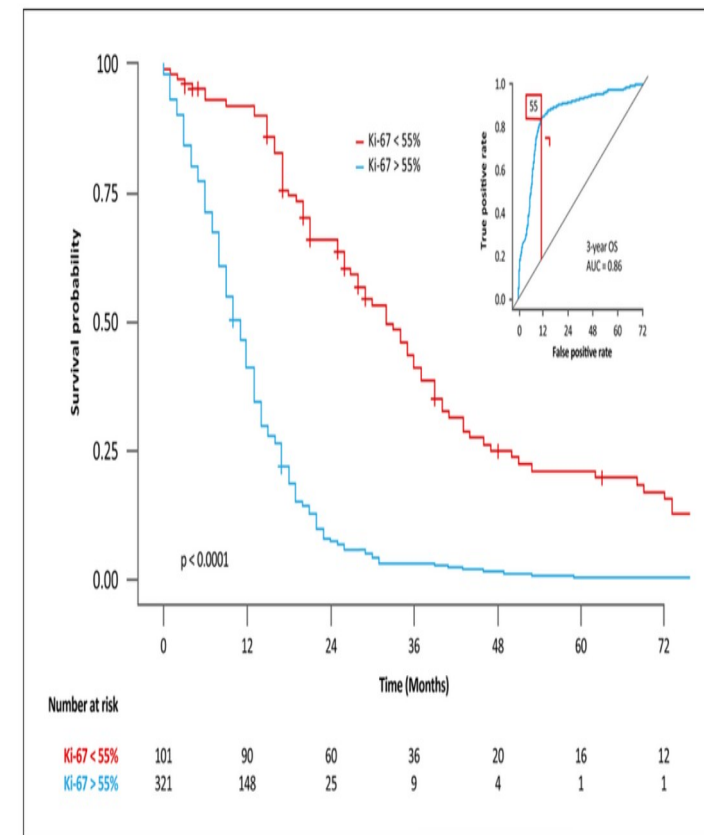
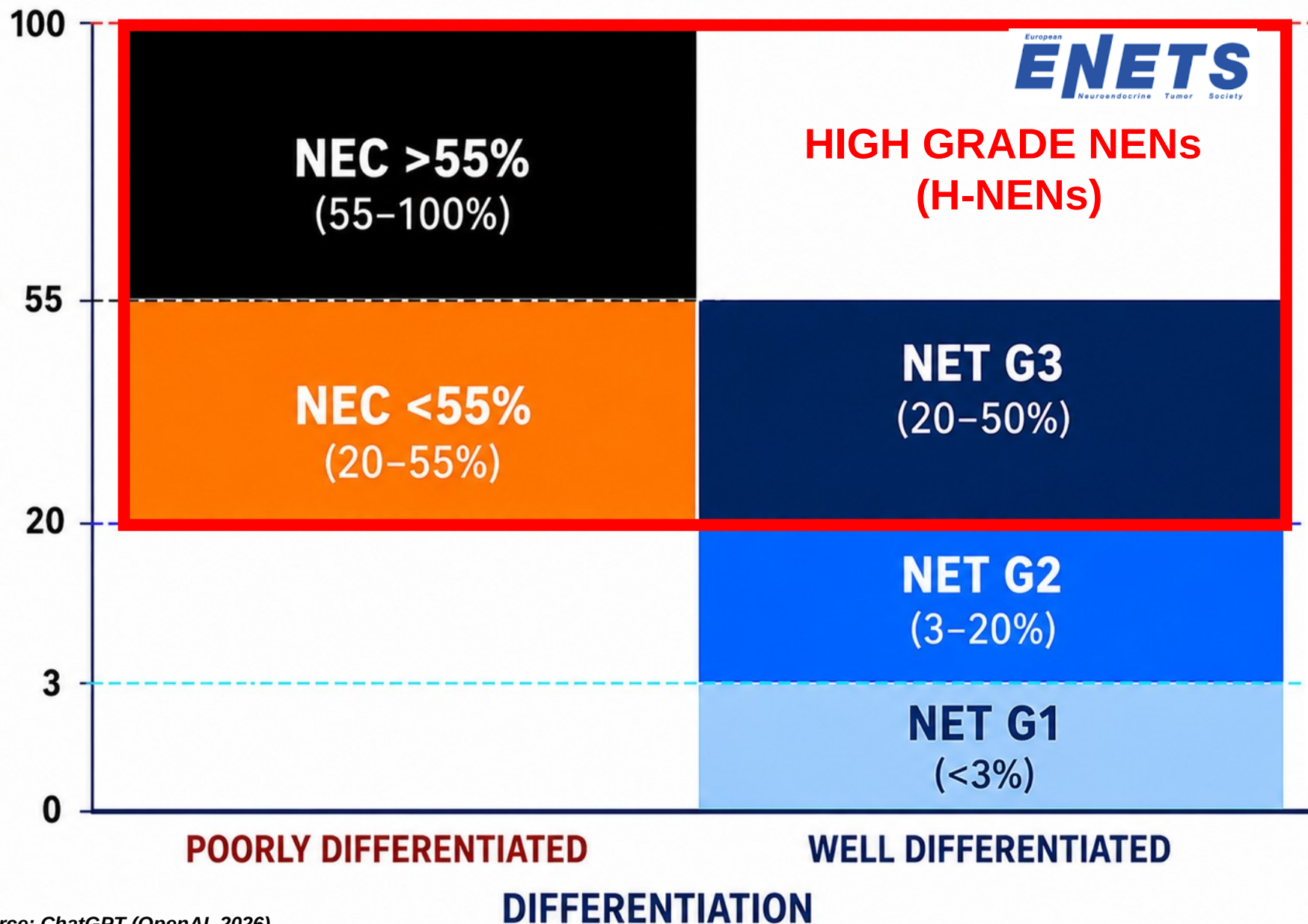
NEC< 55% = (Type B) Poorly Differentiated+Ki-67 21-55% = **MOS: 24,5**

NEC ≥ 55% = (Type C) Poorly Differentiated+Ki-67 >55%) = **MOS: 5,3**

Milione PMID 26943788

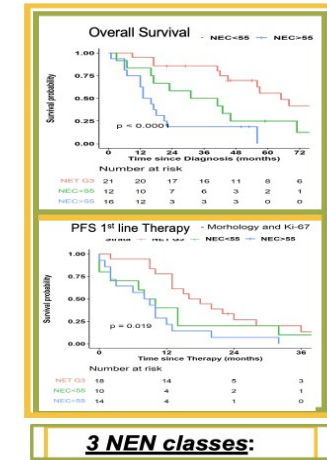
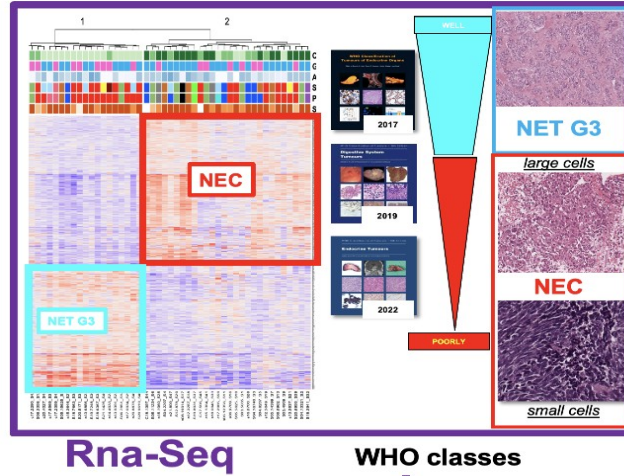
CLASSIFICATION IN CLINICAL PRACTICE

PROLIFERATION INDEX (Ki-67%)



Centonze PMID 36417840

H-NENs: RNA-Seq - Genomic Analysis (TSO) - OS/PFS



- ✓ RNA-Seq results confirmed WHO classes
- ✓ HG-GEP-NENs include only NET G3 and NEC

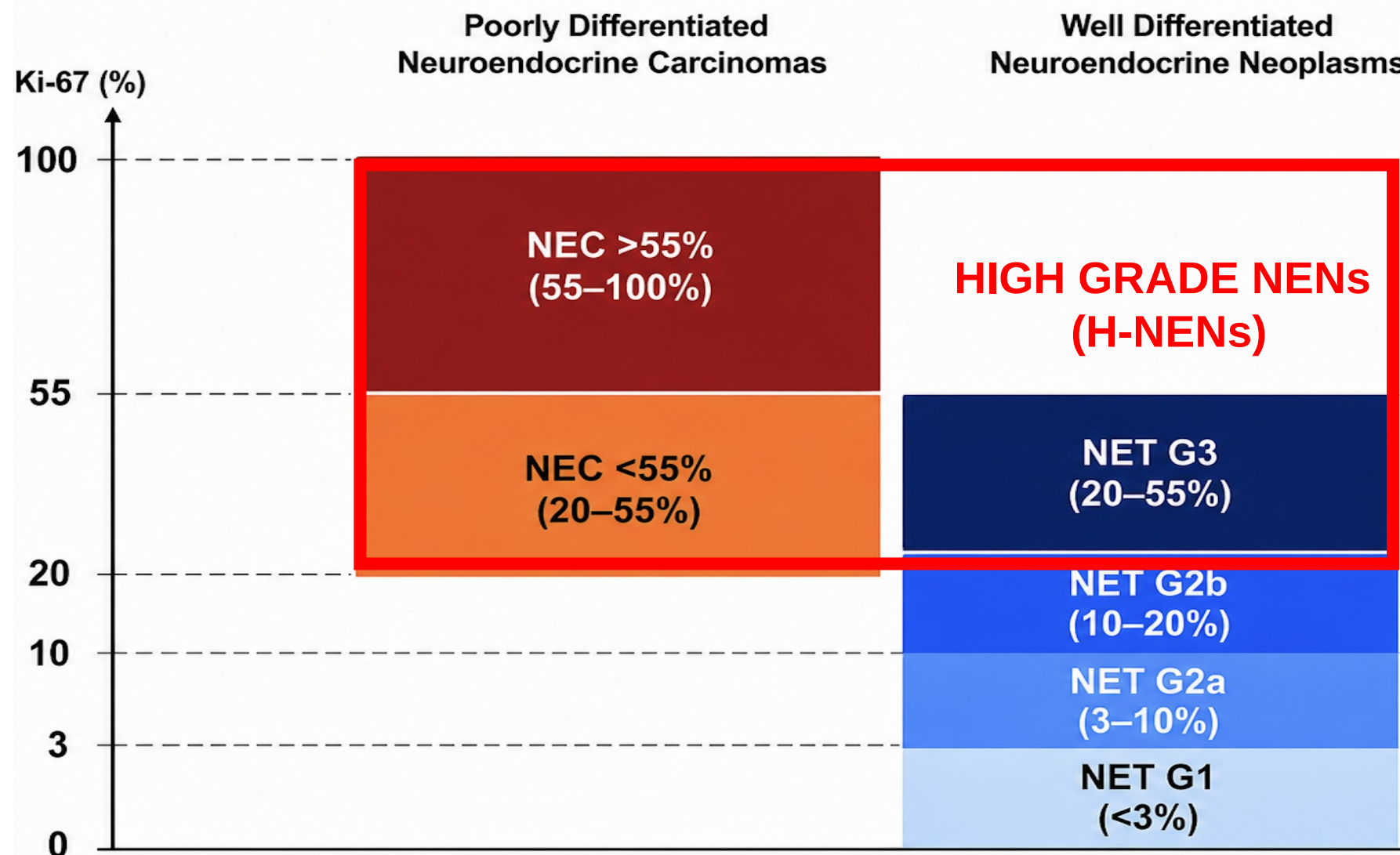
TSO confirmed the 3 new NEN classes:
NET G3, NEC ≤ 55% and NEC > 55%

OS= NET G3, NEC ≤ 55% and NEC > 55%
PFS= WHO classes (NET G3 and NEC)

Both (2 WHO classes & 3 NEN classes) systems for properly describe HG-GEP-NENs heterogeneity deserve!

Angerilli PMID38729995

Towards the Classification of the Future



NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; G, grade.

Source: ChatGPT (OpenAI, 2026)

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2. NETs (G3) and NECs: Is There Common Ground?

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NET & NEC: Two lines are said to be parallel when they lie on the same plane and never intersect, that is, they have no points in common, Can we be sure?



WELL DIFFERENTIATED
Neuroendocrine
Tumors
NET

POORLY
DIFFERENTIATED
Neuroendocrine
Carcinomas
NEC

Not even molecular profiling settles the long-standing

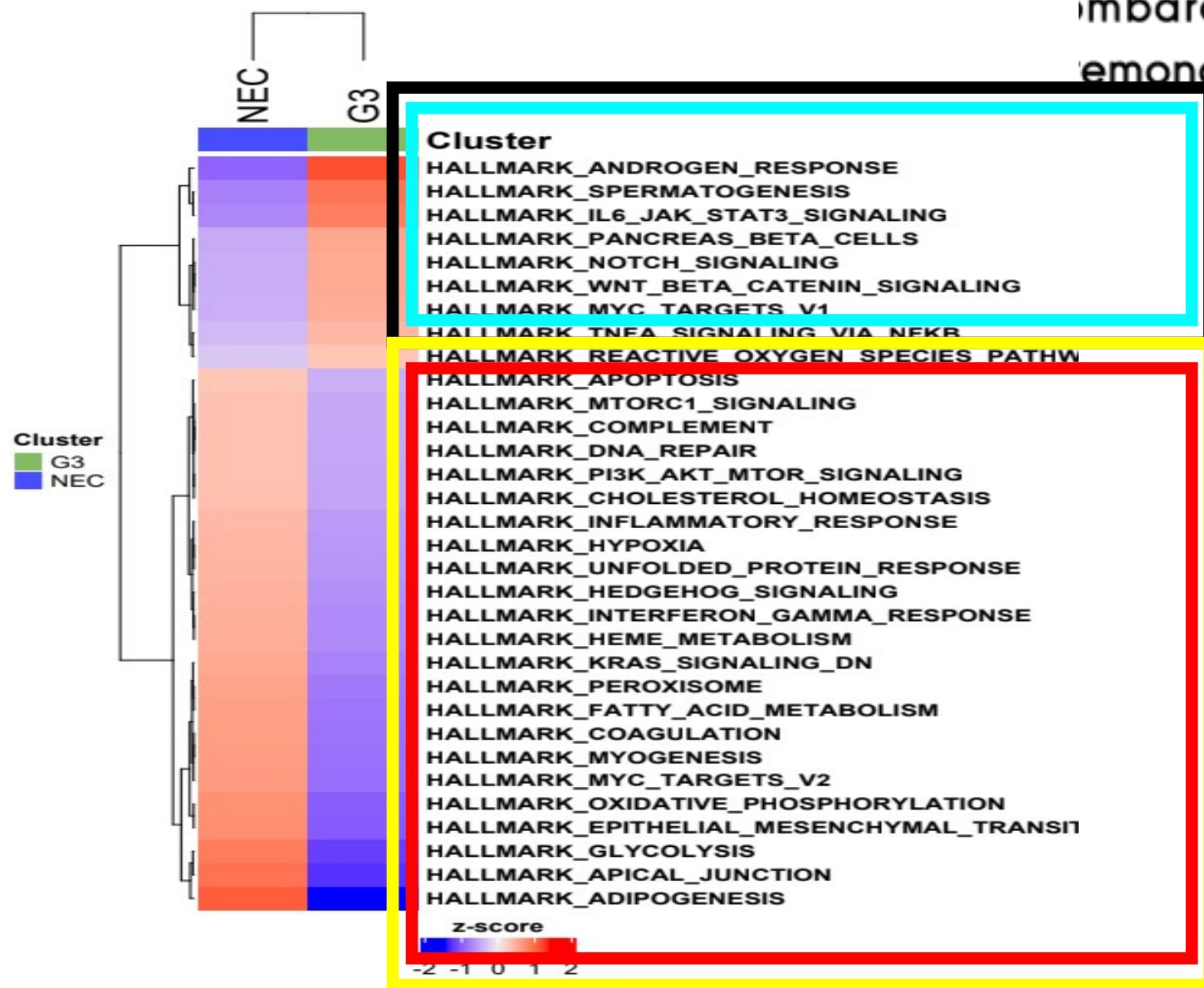
NET G3 vs NEC debate.

NET G3 enriched in:

- ✓ NOTCH
- ✓ WNT Beta Catenin
- ✓ IL-6
- ✓ JAK
- ✓ Stat
- ✓ TNF alpha

NEC enriched in:

- ✓ Apoptosis
- ✓ DNA damage
- ✓ Hypoxia
- ✓ Glycolysis
- ✓ KRAS signalling
- ✓ Mtor pathway



Progression of Low-Grade Neuroendocrine Tumors (NET) to High-Grade Neoplasms harboring the NEC-like co-alteration of *RB1* and *TP53*

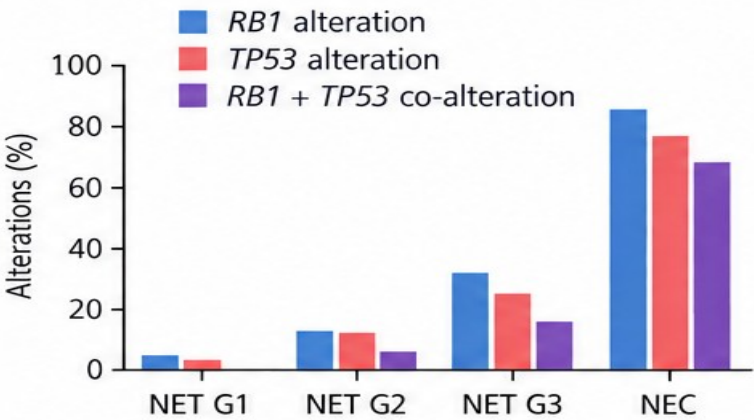
Cohort and methods



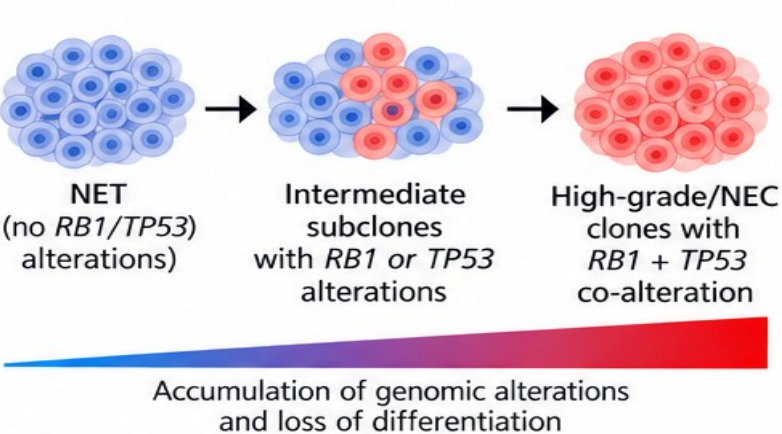
Paired/serial samples of gastroenteropancreatic neuroendocrine neoplasms (NEN) across progression

- Histology and grading (WHO)
- Targeted sequencing / molecular profiling
- Analysis of *RB1* and *TP53* alterations
- Immunohistochemistry for *RB1* and p53

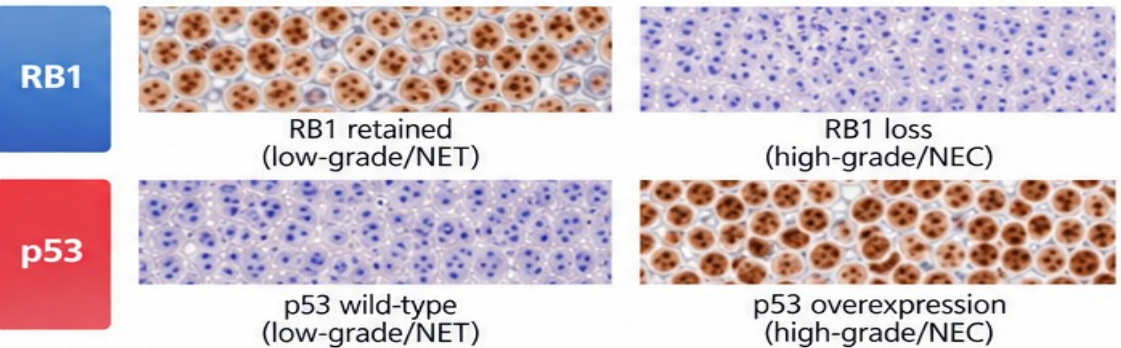
Frequency of *RB1*/*TP53* alterations



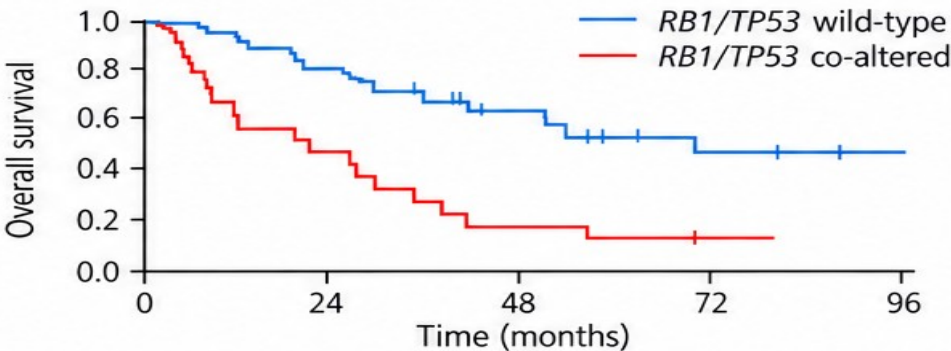
Clonal evolution toward a NEC-like genotype



RB1 and p53 immunohistochemistry



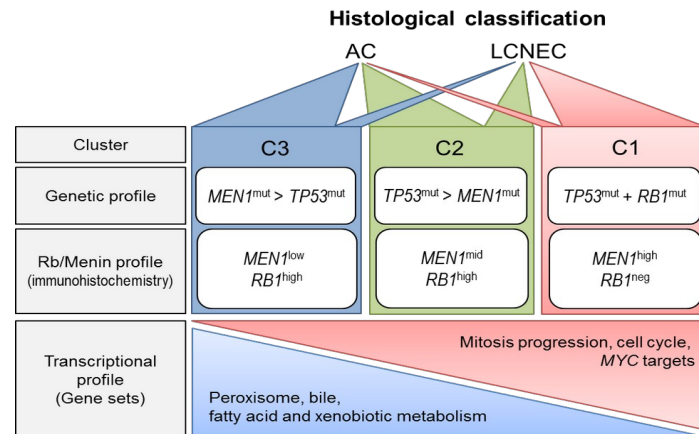
Clinical impact



Key message

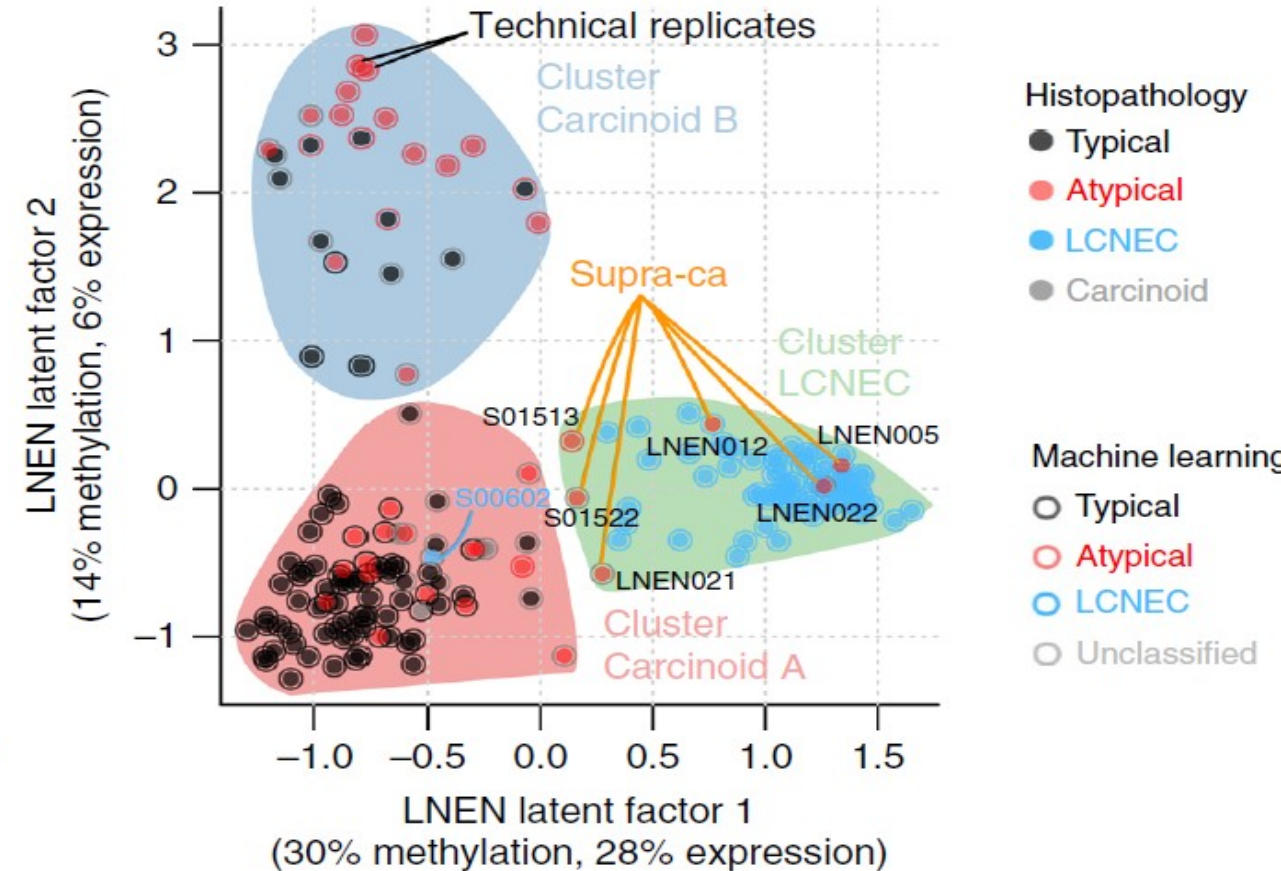
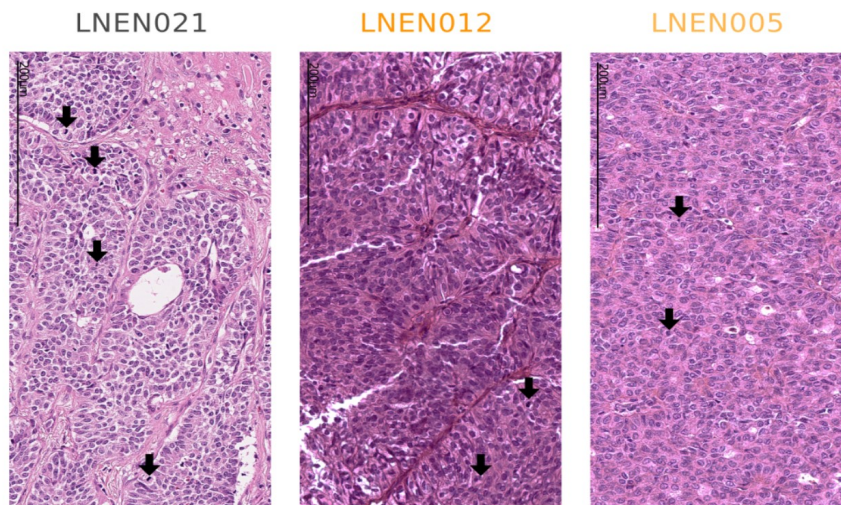
Acquisition of *RB1* and *TP53* co-alterations is a late event in the progression from low-grade NET to high-grade neoplasms, defines a NEC-like genomic profile, parallels loss of differentiation and is associated with aggressive clinical behavior.

LCNECs* + AC** : Molecular Landscape



Simbolo et al. Journal of Thoracic Oncology 2019

* Lung Large Cells Neuroendocrine Carcinomas
** Atypical Carcinoids



Alcala et al. Nature Communications 2019

Supra-carcinoids have carcinoid-like morphology yet molecular and clinical features of LCNEC

Outline

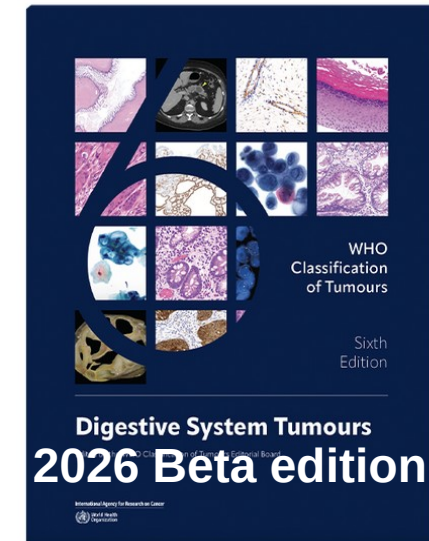
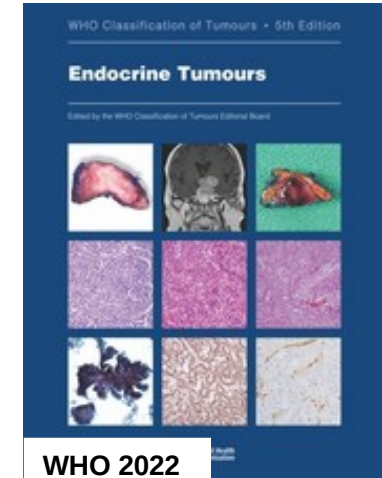
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MiNEN Across the Current WHO Classifications

- ✓ MiNEN has emerged as a unifying concept for mixed neoplasms across organ systems.
- ✓ In non-digestive systems, MiNEN encompasses neoplasms composed of two morphologically distinct components, irrespective of their relative proportions.
- ✓ The 30% cutoff applies exclusively to digestive MiNENs.





MiNEN

>30%

<30% and other categories

Controversies in NEN: An ENETS position statement on the diagnosis and treatment of mixed neuroendocrine / non-neuroendocrine neoplasms (MiNEN) of the digestive system. Spada F [...] Sobye H submitted



MiNEN

>30%

Controversies in NEN: An ENETS position statement on the diagnosis and treatment of mixed neuroendocrine / non-neuroendocrine neoplasms (MiNEN) of the digestive system. Spada F [...] Sobye H submitted

Sistema Socio Sanitario
 Regione Lombardia



WHO
Classification of Tumours

Sixth
Edition

Digestive System Tumours

Edited by WHO Classification of Tumours Editorial Board

2026 Beta edition

LUNG

Ki-67
log-rank $p = 0.0001$

2-year OS
AUC = 0.82

55

Years since surgery

Proportion surviving, %

Years

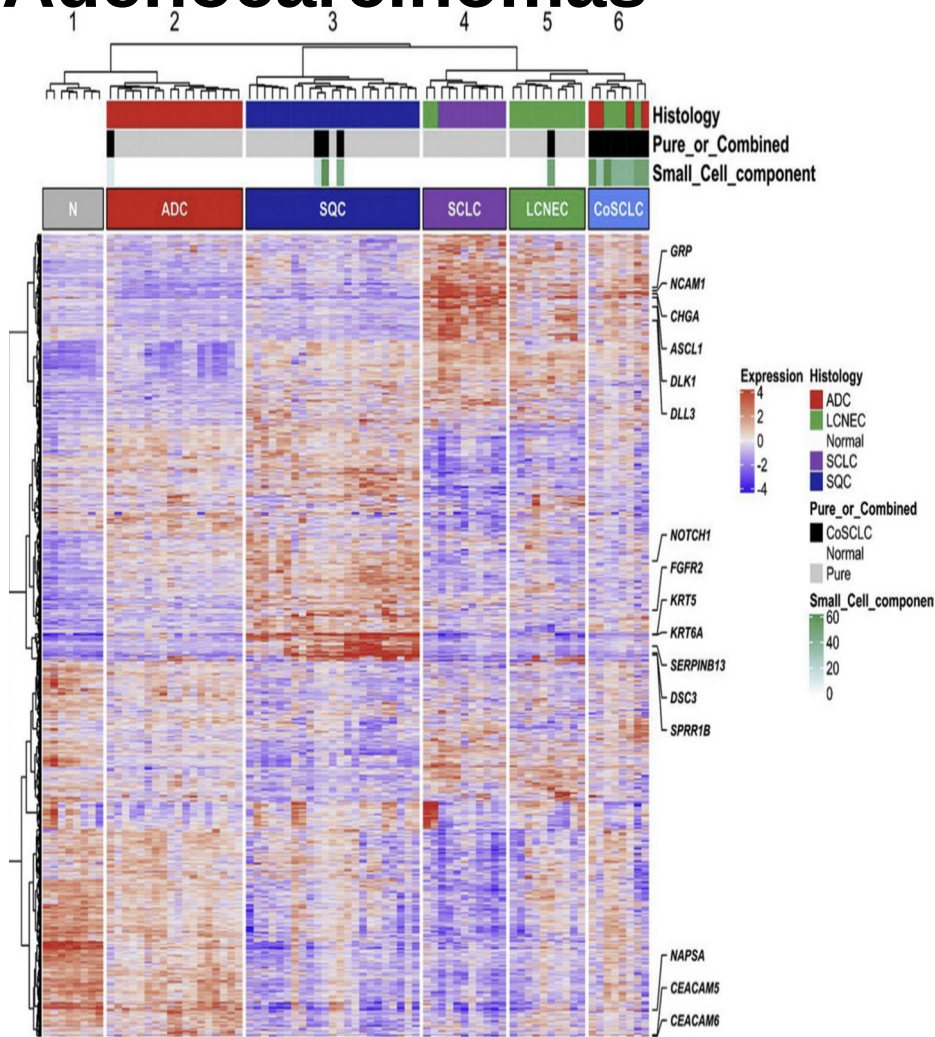
20-54%

≥55%

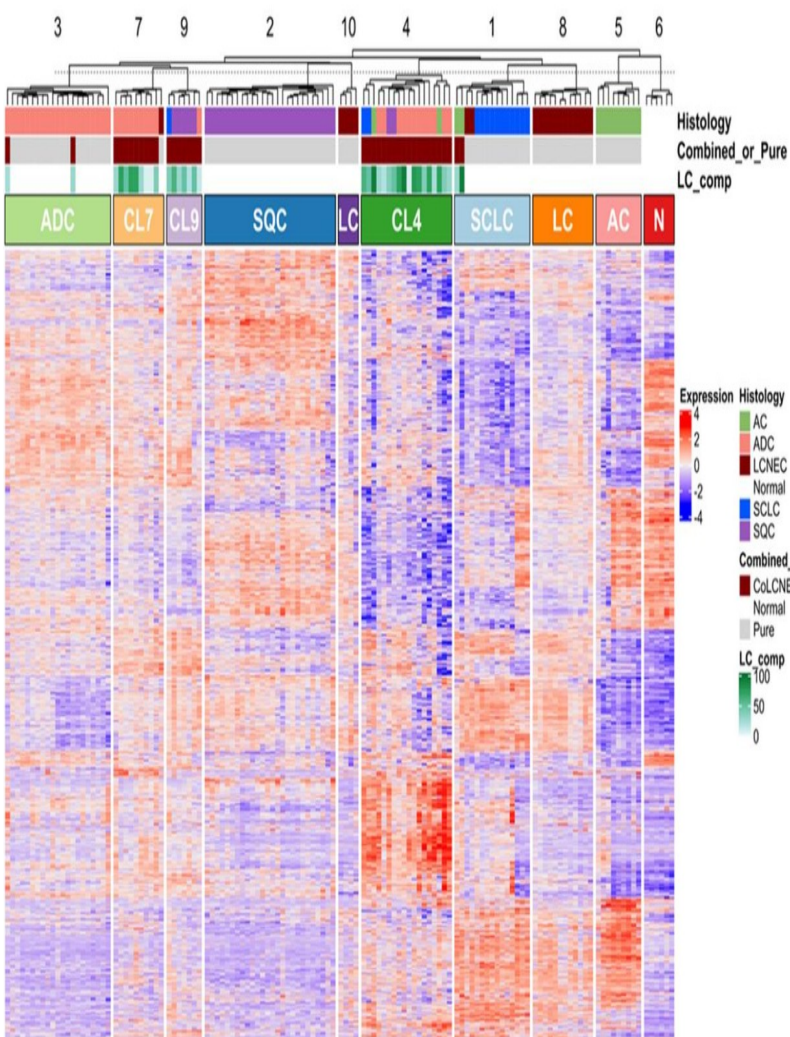
	Patients at risk	Median OS
<55%	34 32 24 18 12 9 8 6 5 4 4	3.3 years
≥55%	77 40 9 3 0 0 0 0 0 0 0	1.0 years

WHO Classification of Tumours

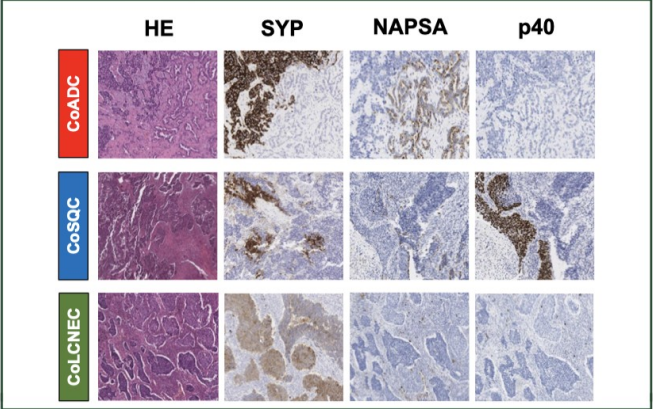
Pulmonary MiNENs cluster with large-cell NECs & Adenocarcinomas



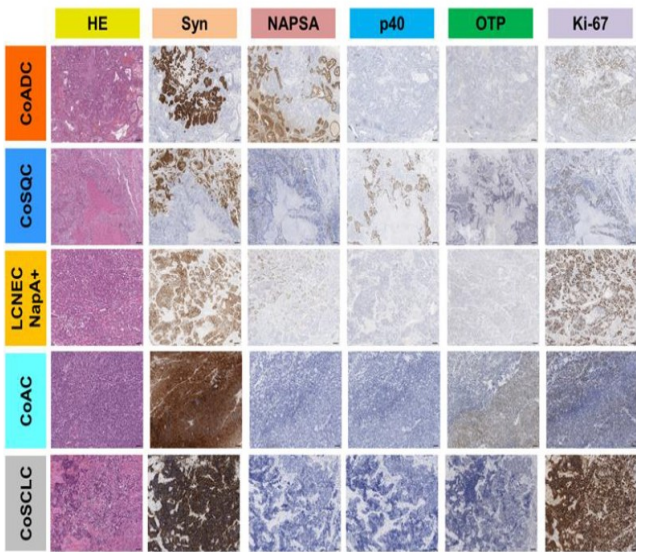
Simbolo PMID34952268



Simbolo PMID 34952268



Simbolo PMID34952268



Simbolo PMID34952268

Shared mutations: MiNENs, adenocarcinomas, large-cell NECs

NEC LARGE CELLS

<55 or >55%

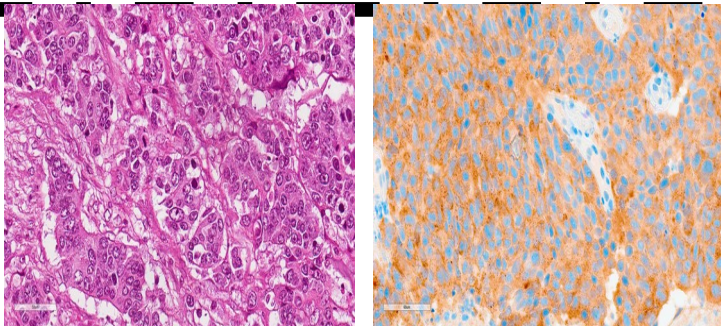
TP53 or RB1

KRAS

APC

BRAF

EGFR



ADENOCARCINOMA

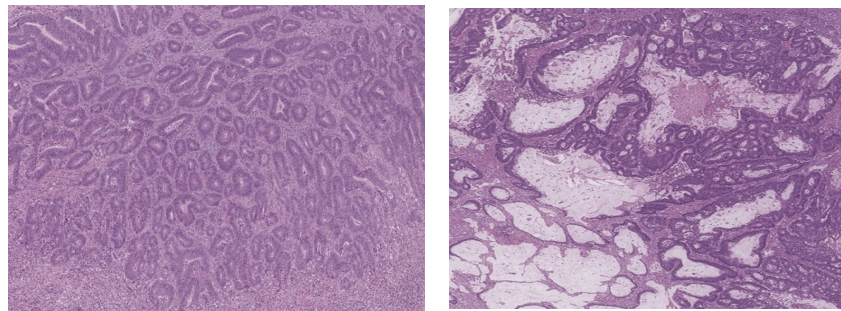
TP53

KRAS

APC

BRAF

EGFR



MiNEN

<55 or >55%

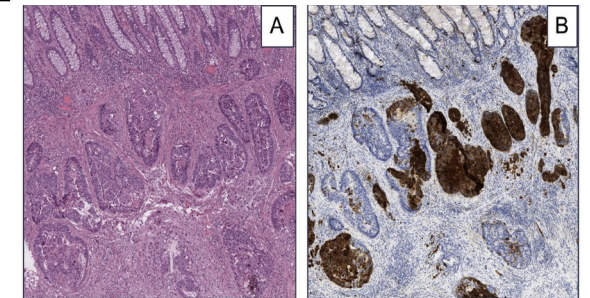
TP53

KRAS

APC

BRAF

EGFR



Non-MiNEN

<30% and other categories

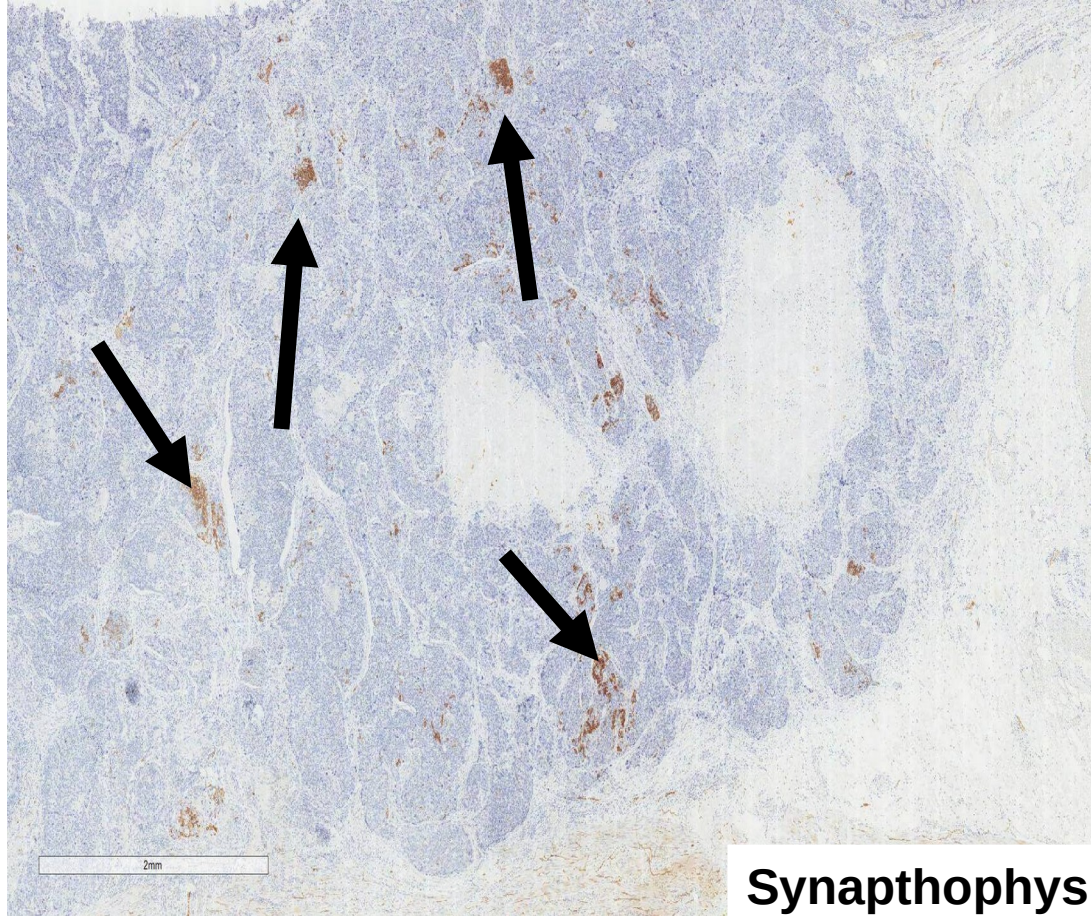
Controversies in NEN: An ENETS position statement on the diagnosis and treatment of mixed neuroendocrine / non-neuroendocrine neoplasms (MiNEN) of the digestive system. Spada F [...] Sorbye H submitted

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Not all non-MiNENs are alike especially when it comes to the “magic” 30% cutoff

Carcinoma with a variable neuroendocrine component



Synapthophysin

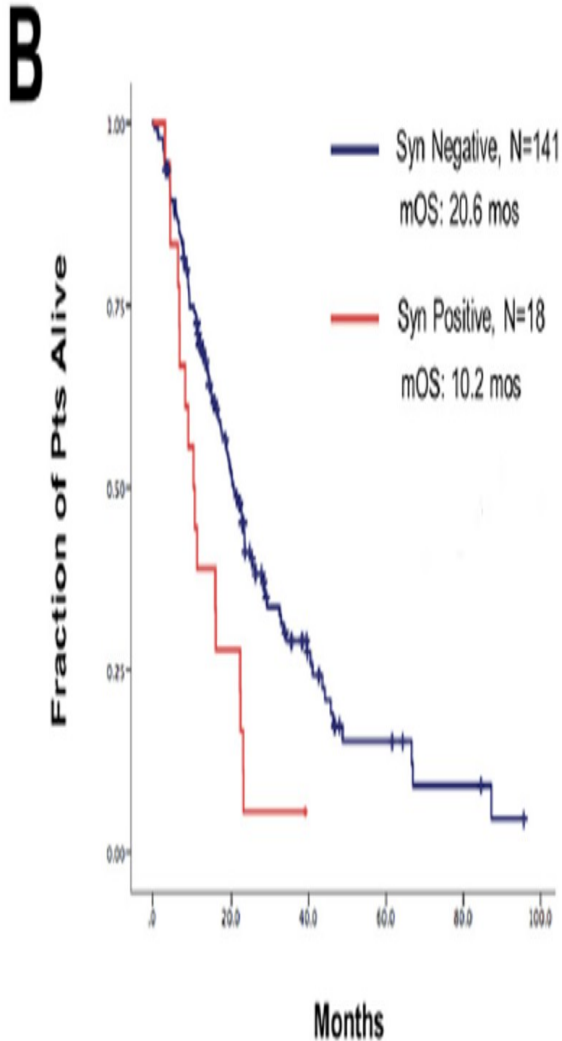
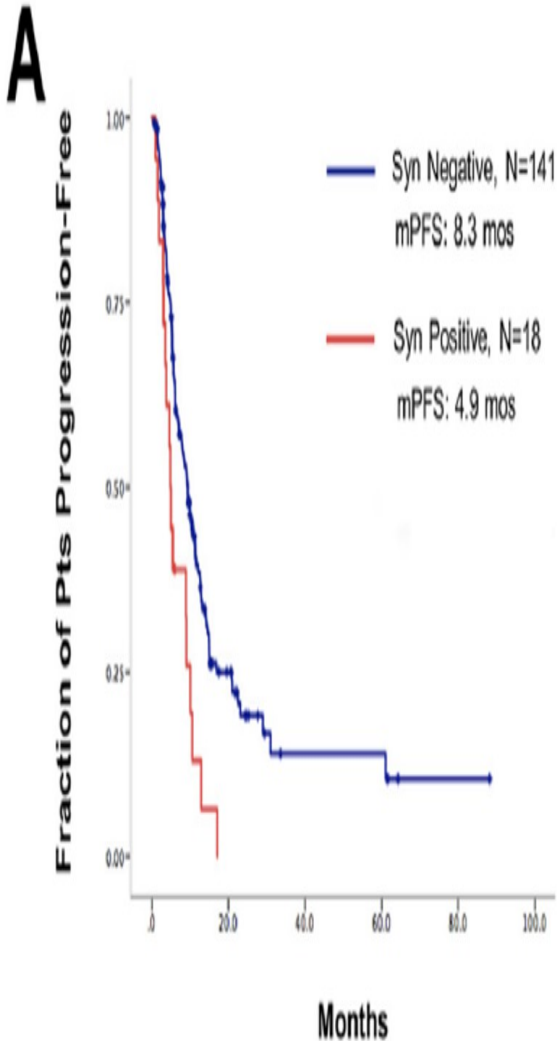
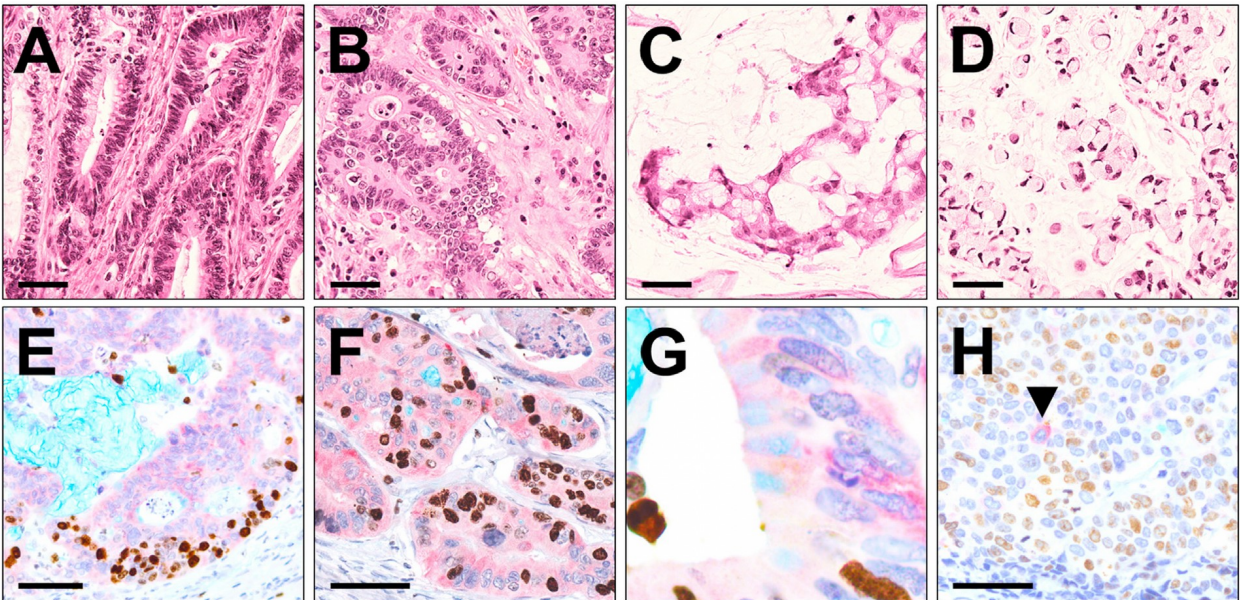
Consistently below the 30% threshold

A true mixed neoplasm by morphology and immunophenotype, but not a MiNEN by the 30% rule. The two components share a monoclonal origin, while NGS may uncover actionable alterations

Histotype (neuroendocrine) matters, not proportion

Characteristic		Synaptophysin				p-Value
		Negative		Positive		
		Count	%	Count	%	
ECOG PS	0	108	76.6%	12	66.7%	0.446
	1	30	21.3%	6	33.3%	
	2	3	2.1%	0	0.0%	
First-line treatment intensity	Anti- <i>BRAF</i>	5	3.5%	0	0.0%	0.013
	Doublet	71	50.4%	17	94.4%	
	immune checkpoint inhibitor (ICI)	10	7.1%	0	0.0%	
	Monotherapy	13	9.2%	0	0.0%	
First-line best response	Triplet	42	29.8%	1	5.6%	0.015
	Not responders	50	36.8%	12	66.7%	
	Responders	86	63.2%	6	33.3%	
	First-line baseline	347.4		111.8		
CEA (Carcinoembryonic antigen) — <i>Mean (min-max)</i>		(0.1—22,260)		(2.9—635.1)		
First-line baseline	CA19.9 — <i>Mean (min-max)</i>	13,371.7		1233.6		0.109 *
		(2.0—563,400)		(2.0—4,482)		
First-line baseline p	latelets — <i>Mean (min-max)</i>	306,410		280,667		0.559 *
		(122,000—865,000)		(191,000—580,000)		
First-line baseline	LDH — <i>Mean (min-max)</i>	368		369		0.994 *
		(130—3,302)		(143—1,075)		
First-line baseline total	WBC — <i>Mean (min-max)</i>	8322		7111		0.281 *
		(1,100—36,000)		(4,190—14,130)		

*p — value expressed for independent samples t test mean comparison.
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; WBC, white blood cell; %, prevalence.

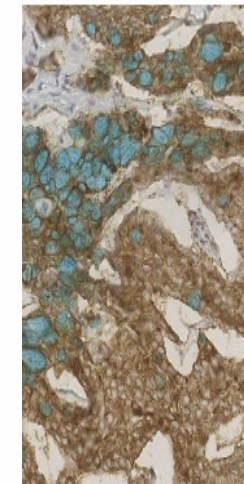
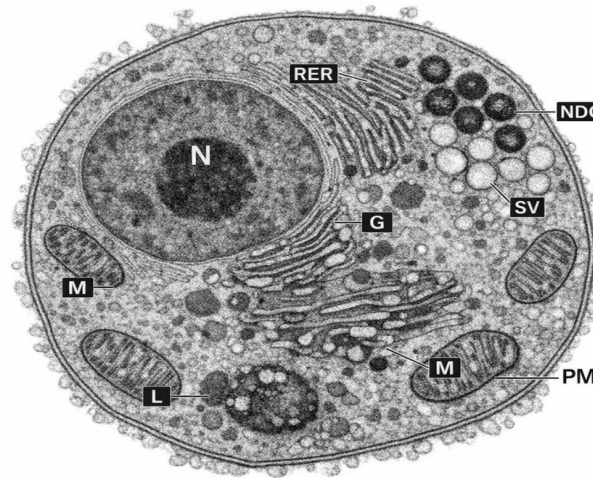
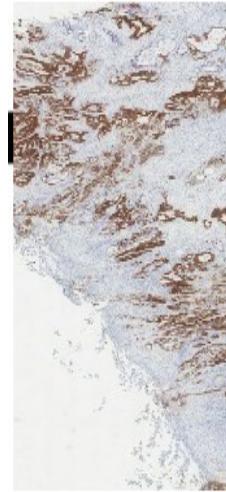


Fassan PMID 33607478

Not all non-MiNENs are alike especially when it comes to the “magic” 30% cutoff (2)

other categories

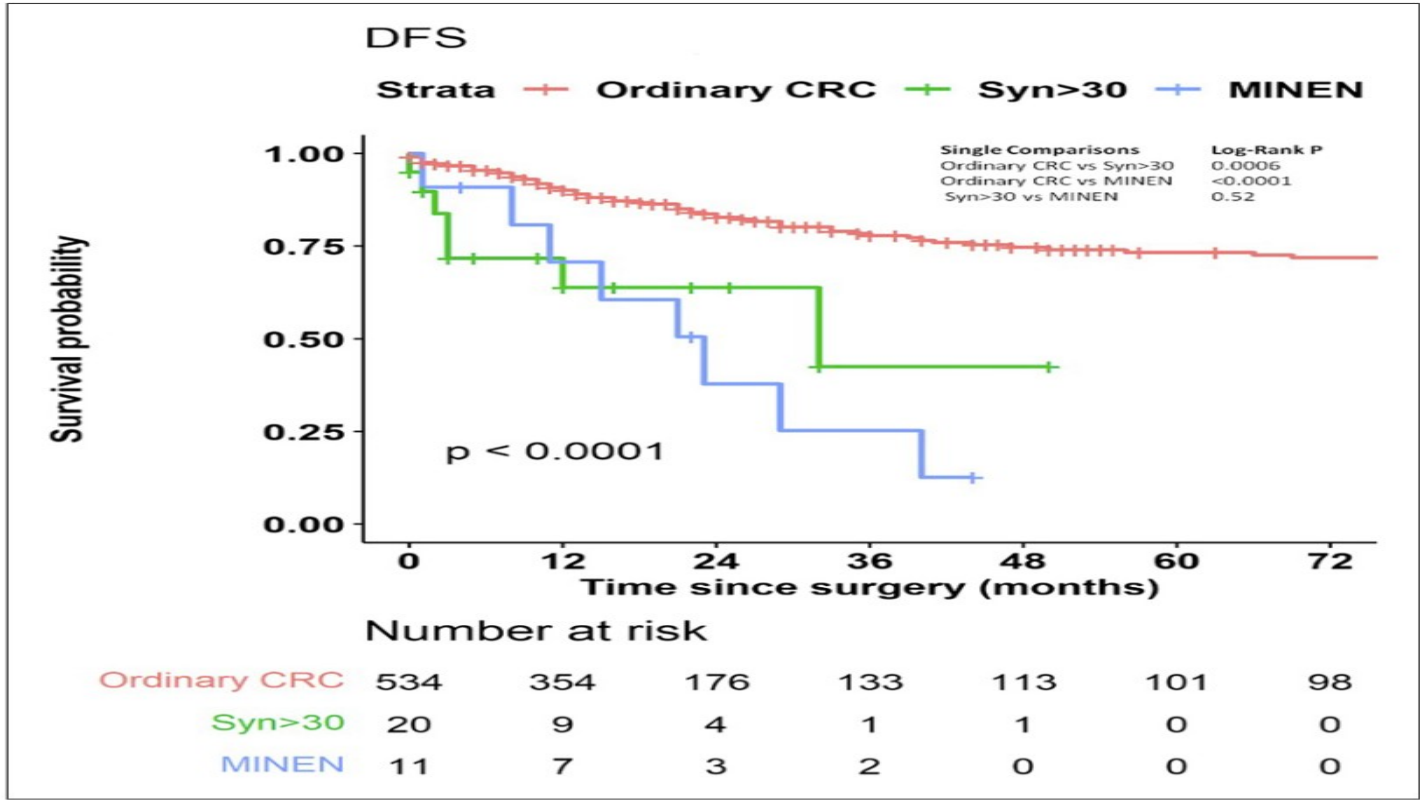
Ordinary Carcinoma Expressing Synaptophysin (OCSE)



Amphicrine Carcinoma

Their mixed nature is not morphological but immunophenotypic: amphicrine tumors co-express neuroendocrine and glandular markers, whereas OCSE retains glandular morphology despite neuroendocrine marker expression. The 30% cutoff is not applicable in the absence of two distinct neoplastic populations

Do Non-MiNEN Mixed Neoplasms Really Matter for Prognosis?

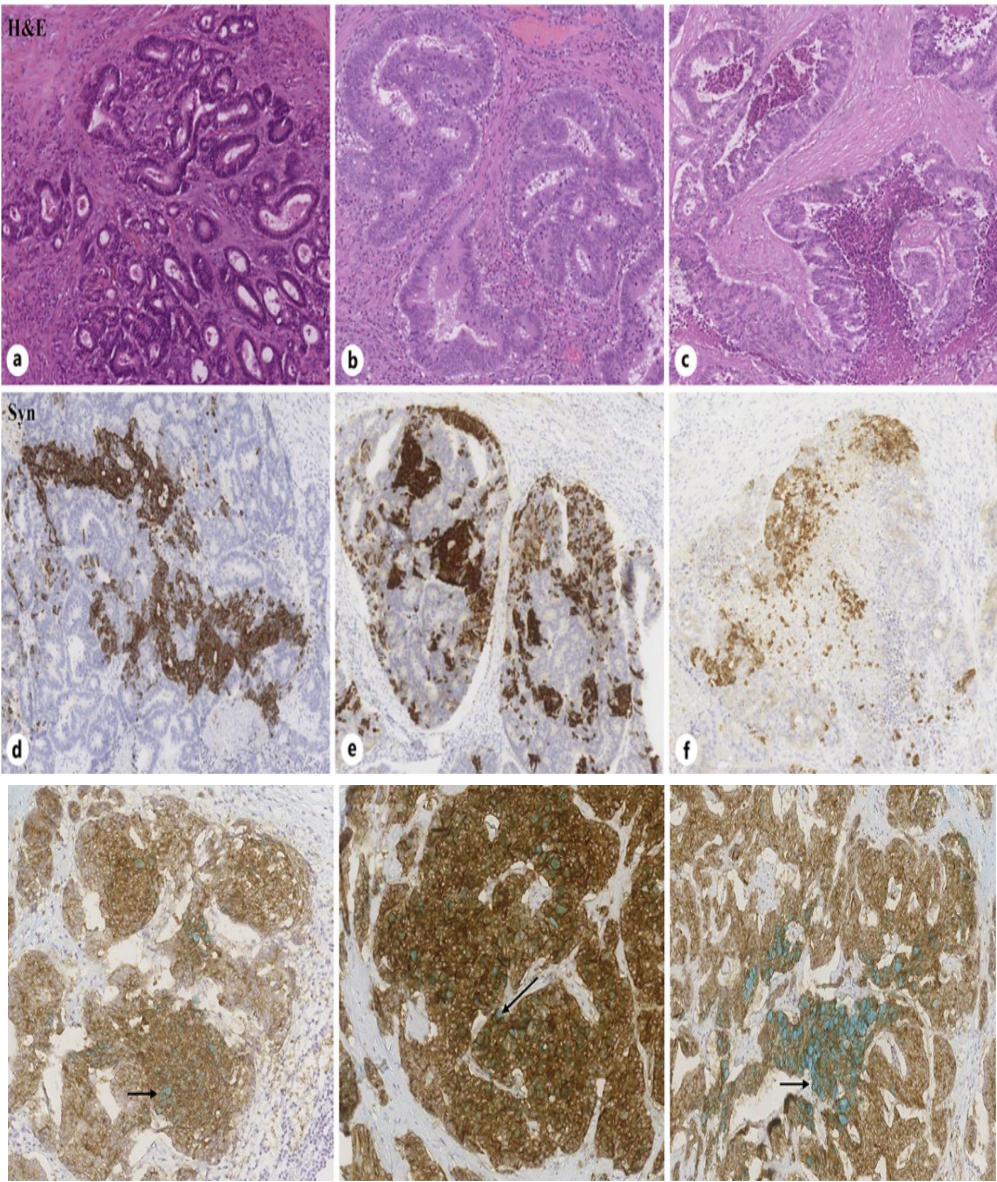


Sabella PMID 40324347

Colorectal **Adenocarcinoma**, **MiNEN**, and the Spectrum of **Non-MiNEN Mixed Neoplasms***: The Prognostic Impact of the Neuroendocrine Component

* Carcinoma with a variable neuroendocrine component + OCSE+ Amphicrine Carcinoma

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Take Home Message

- ✓ **NETs and NECs are biologically distinct entities with different morphology and proliferative activity**
- ✓ **NET G2b, NET G3 and NEC define a biological grey zone: morphologically distinct, molecularly convergent.**
- ✓ **MiNENs: An Evolutionary Bridge Between ADK and LCNECs?**
- ✓ **Even below 30%, a neuroendocrine component may be clinically relevant and should be explicitly reported.**
- ✓ **Non-morphologically mixed neoplasms, Synaptophysin-expressing ordinary carcinomas and Amphicrine carcinomas, show distinct clinical outcomes from both conventional adenocarcinomas and MiNENs**



Thank you