SOM-ALL-003676, SOM-AT-000989 | Date of preparation: February 2024

*NENs: Neuroendocrine neoplasms.

Contents

The importance of distinguishing a ZEBRA from a horse

Neuroendocrine tumors (NETs) commonly arise within the gastrointestinal tract and pancreas. They are thought of as rare 'ZEBRAs' of the cancer world, meaning patients are commonly misdiagnosed and often face long diagnostic delays, with a mean time to a correct diagnosis of ~5 years.[1] However, NETs are not as rare as often thought; they are more prevalent than any other gastrointestinal cancer except colorectal adenocarcinoma.[1–4]

As many patients with NETs are referred to secondary care specialists, such as gastroenterologists, hepatologists and oncologists, following initial investigation by primary care, you have a key opportunity to diagnose NETs earlier, helping to prevent delays in diagnosis.[3]

This booklet has been designed to help you 'Think ZEBRA' in your everyday clinical practice, ultimately helping to end patients' diagnostic odysseys and reduce uncertainty around undiagnosed NETs.

NET=neuroendocrine tumor.

1. Kolarova T, et al. Presented at IASGO 2021, based on INCA SCAN results.
2. CSSC Service Development Prize Submission 2021 – Dr Mohid Khan. 2021 Available from: https://www.bsg.org.uk/service-successstories/cssc-service-development-prize-submission-2021-dr-mohid-khan/ [Last accessed: November 2023].
3. Khan MS, Pritchard DM. Neuroendocrine tumors: what gastroenterologists need to know. Frontline Gastroenterol. 2020;13(1):50-56.
4. Eads JR, et al. Differential Diagnosis of Diarrhea in Patients With Neuroendocrine Tumors. Pancreas. 2020;49(9):1123-1130.

Do you Think ZEBRA?

5 YEARS

Is the mean time to a correct diagnosis of a NET[1]

(N=2,795 NET patients and healthcare professionals; n=2,359 NET patients)

>40%
of GEP-NETs are metastatic at diagnosis[1]
(N=1,670 GEP-NET patients)

45%
of patients did not know or were not told their tumor stage[2]
(N=1,055/2,359)

44%
of patients were initially misdiagnosed[2]
(N=1,043/2,359)

53%
of patients visited a NET specialist in the preceding 12 months[2]
(N=1,255/2,359)

GEP=gastroenteropancreatic; IBS=irritable bowel syndrome; NET=neuroendocrine tumor.

1. Kolarova T, et al. Presented at IASGO 2021, based on INCA Scan survey: Sugandha Dureja et al. J Neuroendocrinol. 2023 Jun;35(6):e13310. doi: 0.1111/jne.13310.
2. Dureja S, et al. J Neuroendocrinol. 2023;35(6):e13310.

IBS or a NET?

NETs often present with non-specific symptoms, like changes in bowel habits and/or abdominal pain. This can lead to a misdiagnosis of IBS.[1]

24%

of NET patients are initially misdiagnosed with IBS[2] in a primary care setting

(n=163)

If your patient has IBS, **Think ZEBRA if...**

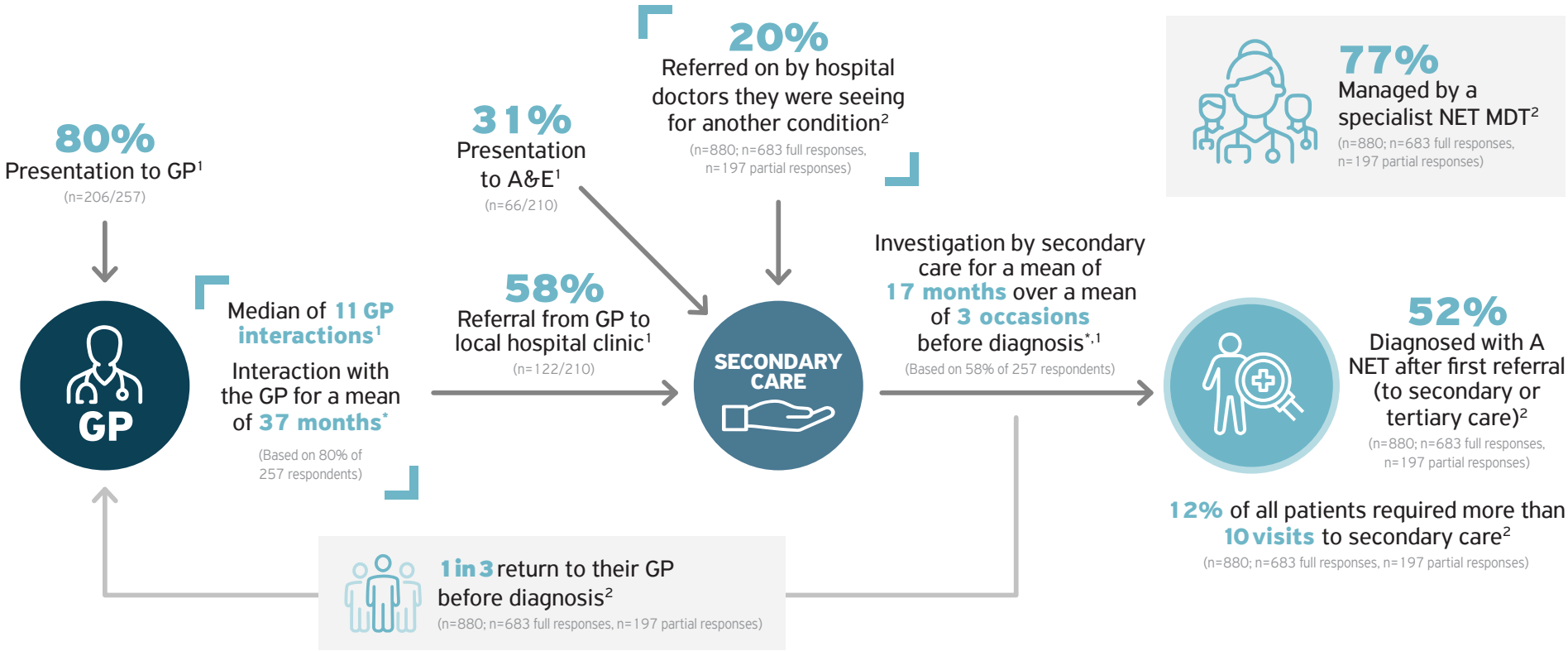
- Persistent symptoms, e.g. diarrhea or abdominal pain[1,2]
- Age >50 at symptom onset[2]
- Features suggestive of bowel obstruction[1]
- Weight loss of >4.5 kg[1,2]
- Facial flushing[1,2]
- Wheeze[1,2]
- Reduced appetite[2]

IBS=irritable bowel syndrome; NET=neuroendocrine tumor.

1. Khan MS, Pritchard DM. Frontline Gastroenterol. 2022;13:50–56.
2. Basuroy R, et al. BMC Cancer. 2018;18(1):1122.

Finding the way to diagnosing a ZEBRA

Patient pathway

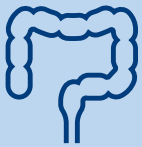


Data from two patient surveys (Basuroy R, et al., 2018[1] [N=303] and Neuroendocrine UK Barriers to Diagnosis report[2] [N=880]) to illustrate the NETs patient pathway and the challenges in diagnosis.

*There is likely to be overlap in primary and secondary care management (37 and 17 months, respectively) given respondents also reported being symptomatic for a similar period of time (mean 53.8 months) and the likelihood of a staggered presentation to first access healthcare.
A&E=accident and emergency; GP=general practitioner; IBS=irritable bowel syndrome; MDT=multidisciplinary team; NET=neuroendocrine tumor.

1. Basuroy R, et al. BMC Cancer. 2018;18(1):1122.
2. Neuroendocrine Cancer UK. Barriers to diagnosis report, 2020. Available from: https://www.neuroendocrinecancer.org.uk/wp-content/uploads/2021/01/Barriers-to-Diagnosis-report-2020.pdf [Last accessed: November 2023].

Neuroendocrine neoplasia (NEN) classification[1]

Site	Category	Family	Type	Grade	Current Terminology
 GUT	Neuroendocrine neoplasm (NEN)	Neuroendocrine tumor (NET)	GUT site[a] NET	G1	GUT site[a] NET G1
				G2	GUT site[a] NET G2
				G3	GUT site[a] NET G3
		Neuroendocrine carcinoma (NEC)	GUT site[a] NEC small cell type		GUT site[a] NEC small cell type
			GUT site[a] NEC large cell type		GUT site[a] NEC large cell type
 PANCREAS	Neuroendocrine neoplasm (NEN)	Neuroendocrine tumor (NET)	Pancreas NET (PanNET)	G1	PanNET G1
				G2	PanNET G2
				G3	PanNET G3
		Neuroendocrine carcinoma (NEC)	Pancreas NEC small cell type		Pancreas NEC small cell type
			Pancreas NEC large cell type		Pancreas NEC large cell type

[a] Site stands for the adjective connoting the different districts of the tubular gut where the NEN develops, that is, esophageal, gastric, duodenal, small intestinal, appendiceal, colonic, rectal and anal canal NET or NEC.
NEC=neuroendocrine carcinoma; NEN=neuroendocrine neoplasm; NET=neuroendocrine tumor; PanNET=pancreas neuroendocrine tumor.

1. Lloyd RV, et al. WHO Classification of Tumors of Endocrine Organs. vol. 10. 4th, Lyon, France: IARC Press. (Based on: Rindi G, Inzani F. Endocr Relat Cancer. 2020;27(6):R211-R218).

WHO 2017 grading system[1]

	WHO 2017 Grading Data	Mitoses/10 HPF	Ki-67 Index
Well-differentiated NENs	**NET grade 1**	< 2	< 3
	NET grade 2	2-20	3-20
	NET grade 3	> 20	> 20
Poorly differentiated NENs	**NEC grade 3** (Small-cell type)	> 20	> 20
	NEC grade 3 (Large-cell type)	> 20	> 20

HPF=high power fields; NEC=neuroendocrine carcinoma; NEN=neuroendocrine neoplasm; NET=neuroendocrine tumor; WHO=World Health Organization.

1. Lloyd RV, et al. WHO Classification of Tumors of Endocrine Organs. vol. 10. 4th, Lyon, France: IARC Press. (Based on: Choe J, et al. Korean J Radiol. 2019;20(1):5-17).

Thinking ZEBRA in practice

These NET case studies are adapted from real patient case studies managed in two ENETS Centers of Excellence (CoE) to help you Think ZEBRA.

Rachel, 51 years old

Outpatient referral

Past medical history:

6 years of intermittent loose stool, labelled as IBS

Journey to gastroenterology Second referral primary care

6 years of intermittent **loose stool**
- Poorly localised mild abdominal pain, exacerbated by stress
- 1 kg weight loss, but recently stable

Previous **normal work-up,** including ultrasound and colonoscopy

Referred 2x through gastroenterology and surgery clinics for diarrhea

IBS management after exclusion of other diagnoses, e.g., celiac

Normal second colonoscopy

Second GP to surgical referral for CT colonoscopy

Adapted from a real patient case study in collaboration with Dr Mohid Khan. This content was created and funded by IPSEN.
CoE=Centers of Excellence; CT=computerised tomography; GP=general practitioner; IBS=irritable bowel syndrome; NET=neuroendocrine tumor.

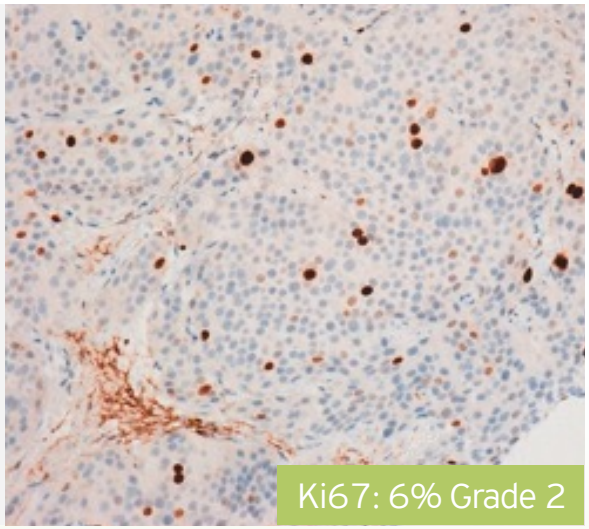
CT colonoscopy

Blood tests and liver biopsy

Blood tests and liver biopsy

Blood tests:
5-hydroxyindoleacetic acid (5-HIAA): normal

Chromogranin A:
75 nmol/L



Diagnosis

Thinking ZEBRA in practice

These NET case studies are adapted from real patient case studies managed in two ENETS Centers of Excellence (CoE) to help you Think ZEBRA.

Martin, 63 years old

Endoscopic identification

Past medical history:
Type 2 diabetes mellitus

Current medication:
Metformin

Journey to gastroenterology Initial visit to primary care

Presentation to a GP with 3-month history of:
- New onset dyspepsia
- No alarm symptoms

Prescription of omeprazole by GP

Referred via **suspected cancer pathway** for **upper gastrointestinal endoscopy within 2 weeks** by GP

Adapted from a real patient case study in collaboration with Professor Mark Pritchard. This content was created and funded by IPSEN.
CoE=Centers of Excellence; CT=computerised tomography; EUS=endoscopic ultrasound; GP=general practitioner; NET=neuroendocrine tumor; PET=positron emission tomography.

First gastroscopy

Oesophagus: normal

Stomach: polyp on greater curve

Duodenum: normal

Histology report: well-differentiated gastric NET, insufficient material to perform a Ki67 index

Blood test results

Full blood count: normal

Biochemical profile, including calcium: normal

Vitamin B12 and folate: normal

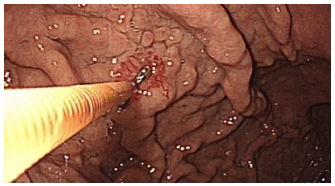
Anti-gastric parietal and anti-intrinsic factor antibodies: negative

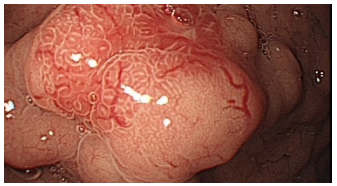
Fasting serum gastrin: 60 picomoles (pM) (normal <40)

Chromogranin A: 35 pM (normal <60)

Repeat gastroscopy[1]

- 9 mm polyp in gastric corpus
- Normal background mucosa: normal antral and corpus biopsies, no atrophy or intestinal metaplasia
- Well-differentiated NET, Ki67 2% (Grade 1)





The World Health Organization categorises NETs according to their Ki67 index as follows[1]:

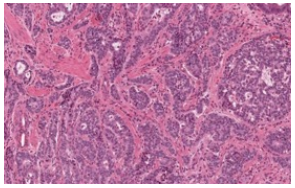
Grade 1 NET <3%

Grade 2 NET 3–20%

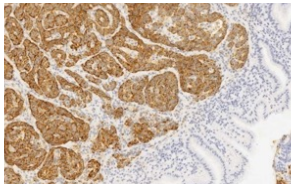
Grade 3 NET >20%

The known unknowns

- Endoscopic features – number, size, location of polyp?
- Type of gastric NET?
- Any associated conditions?
- Tumor grade?
- Tumor stage?



Haematoxylin & eosin



Chromogranin A

Staging

CT chest/abdomen/pelvis (with contrast): normal

^{68}Gallium-DOTATATE PET/CT scan: normal

EUS: 9 mm gastric polyp in submucosal layer, no deep invasion or enlarged perigastric lymph nodes

Diagnosis

Solitary 9 mm Grade 1 sporadic well-differentiated T1NOMO type 3 gastric NET (mild hypergastrinaemia due to proton pump inhibitor and no associated conditions)

Thinking ZEBRA in practice

These NET case studies are adapted from real patient case studies managed in two ENETS Centers of Excellence (CoE) to help you Think ZEBRA.

Silvia, 65 years old

Radiological identification

Past medical history:

Longstanding IBS, hypertension

Journey to gastroenterology Initial visit to primary care

Seen in urology clinic for possible episodes of renal colic (longstanding history of IBS)

Arranged for CT scan

Adapted from a real patient case study in collaboration with Professor Mark Pritchard. This content was created and funded by IPSEN.
CoE=Centers of Excellence; CT=computerised tomography; EUS=endoscopic ultrasound; FNA=fine needle aspiration; IBS=irritable bowel syndrome; NET=neuroendocrine tumor.

CT scan report

- Incidental 2.3 x 1.5 cm rim-enhancing lesion in body/tail of pancreas
- No evidence of metastasis

'Appearances would be compatible with a pancreatic NET, but are not entirely typical.'

The known unknowns

- Is this a NET (or a different type of pancreatic lesion)?
- Is it functional (secretory)?
- Any associated conditions or underlying hereditary syndrome?
- Tumor grade?
- Tumor stage?

EUS

- Hypoechoic single, well-circumscribed lesion 2.1 x 1.6 cm in pancreatic tail
- No enlarged peri-pancreatic lymph nodes

FNA

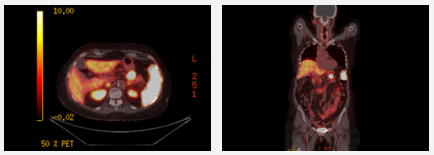
- Well-differentiated NET
- Positive for chromogranin A and synaptophysin by immunohistochemistry
- Ki67 4% (Grade 2)

Blood test results

Vasoactive intestinal peptide: 5 picomoles (pM) (normal <30)
Gastrin: 35 pM (normal <40)
Glucagon: 10 pM (normal <50)
Pancreatic polypeptide: 42 pM (normal <300)
Somatostatin: 43 pM (normal <150)
Chromogranin A: 23 pM (normal <60)
Chromogranin B: 116 pM (normal <150)
Corrected calcium and parathyroid hormone: normal (and no family history of multiple endocrine neoplasia)

Staging

Magnetic resonance imaging of liver:
normal



68Gallium-DOTATATE PET/CT scan

Diagnosis

23 mm Grade 2 sporadic well-differentiated T2NOMO non-functional pancreatic NET

When should you Think ZEBRA?

Do any of these patients highlighted within the case studies reflect those you have seen in clinical practice?

Do they...

- Keep coming back?
- Not fit the typical condition/disease course?
- Not respond to conventional treatments?
- Have a combination of these complaints?

For a checklist on when to Think ZEBRA, see our guide to NET signs and symptoms on the next page.

Symptom[1,2]	Intestinal NET		Pancreatic NET					
			Functioning					Non-functioning
	Functioning (carcinoid syndrome)	Non-functioning	Gastrinoma	Insulinoma	Glucagonoma	VIPoma	Somatostatinoma	
Flushing	✓							
Diarrhea	✓		✓		✓		✓	
Abdominal pain	✓							
Valvular heart disease	✓							
Wheezing	✓							
Pellagra-like skin lesions	✓							
Zollinger-Ellison syndrome Severe peptic ulceration and diarrhea, or diarrhea alone			✓					
Confusion				✓				
Sweating				✓				
Dizziness				✓				
Weakness				✓				
Unconsciousness				✓				
Necrolytic migratory erythema					✓			
Diabetes mellitus					✓		✓	
Weight loss					✓		✓	
Stomatitis					✓			
Watery diarrhea with marked hypokalaemia						✓		
Cholelithiasis							✓	
Steatorrhoea							✓	
Large abdominal masses		✓						
Bleeding from the GI tract		✓						
Intestinal obstruction	✓	✓						
Abdominal discomfort (due to growing tumor)	✓	✓						✓
Pain	✓							✓
Liver enlargement								✓
Jaundice (occasionally)								✓

60–90%
of pancreatic NETs are non-functioning tumors[3]

Functioning NETs
produce symptoms due to the excessive production of hormones[1]

NET=neuroendocrine tumor; VIP=vasoactive intestinal peptide.

1. Ramage JK, et al. Gut. 2012;61(1):6–32;
2. Oberg K. Annals of Oncology. 2004;15(Supplement 4):iv293–iv298;
3. Falconi M, et al. Neuroendocrinology. 2016;103(2):153–171.

About INCA

INCA International Neuroendocrine Cancer Alliance

The International Neuroendocrine Cancer Alliance (INCA) is the global voice in support of patients with neuroendocrine cancers and genetic syndromes (GenNETs). INCA is an umbrella organization representing 33 patient advocacy and research groups from around the world.

A key priority in INCA's work is creating common platforms and working in collaboration with medical communities to fulfill the informational needs of patients, ensure access to the highest standards of care and facilitate patient involvement in research.

INCA is the global voice for patients with neuroendocrine cancer and genetic neuroendocrine tumors (NETs) and their carers with a mission to:

- raise awareness about all types of NETs;
- push for scientific advancements with a focus on identified unmet needs;
- provide a platform for global collaboration to address the many challenges NET patients and the medical community face, in securing a timely diagnosis and accessing optimal treatment, support and care.

To find out more about INCA's incredible work in the NET community, please visit www.incalliance.org

This resource is produced and funded by IPSEN. INCA has carried out a content review.

NOT ALL HOOFBEATS ARE HORSES...

THINK ZEBRA!

IPSEN

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