Phaeochromocytomas
- High blood pressure
- Rapid heart rate
- Forceful heartbeat
- Profound sweating
- Abdominal pain
- Anxiety
- Sudden onset of severe headaches
- Feeling of extreme fright
- Pale skin
- Weight loss

If you don’t suspect it, you can’t detect it
Gastrointestinal NETs

52% of GI NET patients are treated for the wrong disease.¹

Rectal NETs are often asymptomatic until they have metastatised.

31% of patients visited their GP between 4 and 11 times before being referred for further investigation.¹

Carcinoid heart disease will be detected in around 20% of cases presented.³

Around one quarter of Gastrointestinal NETs originate in the appendix.

Possible symptoms

- Diarrhoea that does not clear up
- Bleeding/blood in stools
- Abdominal pain
- Bloating/full feeling
- Wheezing chest
- Hot flushes
- Skin colour changes
- IBS
- Constipation
- Rectal bleeding
- Pain

Refer for investigation

What to expect upon referral?

- Blood tests
- Urine tests
- Endoscopy
- Octreotide scan
- MIBG scan
- Endoscopic ultrasound
- CT scan
- MRI scan
- PET scan
- Bone scan
- Echocardiogram
- Biopsy
- Wireless capsule enteroscopy

Please see algorithm on page 10

“"I was told I had ME, IBS and asthma and told to take up yoga to alleviate the palpitations and diarrhoea.

I have huge confidence in my current team, but none at all in the diagnostic process. My life before diagnosis was miserable & I felt that no-one took my distress seriously.”

If you don’t suspect it, you can’t detect it

Online @ www.netpatientfoundation.org
Gastrointestinal NETs

There are 3 types of gastric NET:

Type I, associated with chronic atrophic gastritis type A

Type II, associated with MEN 1

Type III, sporadic and most malignant

Chromogranin A is raised in all 3 types.

20% of patients with gastric NETs may develop another synchronous cancer affecting the GI tract.

What to expect upon referral?

- Blood tests
- Endoscopy
- CT scan
- MRI scan

Possible symptoms

- Gastric polyps
- Pain
- Dyspepsia
- Anaemia
- Vomiting
- Upper GI bleeding

Refer for investigation

When Steven was diagnosed we were given no literature or information on what this cancer was or how quickly it would devastate our lives.

I think it is important that accurate information is readily available and given to patients, so that people know what they are dealing with and the true reality of what having a NET is.

Any cancer diagnosis is devastating, then you have the added confusion and bewilderment of dealing with a rarer, less well-known cancer; a lack of information and an abundance of unanswered questions.

If you don’t suspect it, you can’t detect it

Online @ www.netpatientfoundation.org
Bronchial NETs

There are 4 types of NET in the lung:

1. Typical Bronchial NET
2. Atypical Bronchial NET
3. Large cell Neuroendocrine Carcinoma
4. Small cell lung cancer

90% of Bronchial NETs are the atypical type.

22% Bronchial NETs present with cough and recurrent pneumonia.³

Possible symptoms

Hormone related symptoms are not common, but a small number of patients may experience 'carcinoid syndrome', symptoms include:

- Flushing
- Diarrhoea
- Palpitations
- Wheezing

Refer for investigation

The operation I had was for a diagnosis of lung cancer. When I came round I was overjoyed to learn it was not the cancer they had suspected but I felt bewildered, alone and frustrated. No-one could explain to me what a 'carcinoid' in the lung was or my future disease course. Worse still was getting to see a specialist in this field: a local consultant in Endocrinology told me to go home and live the rest of my life! I had to fight and produce evidence for funding out of area (as it was at that time) to attend a centre of excellence. Fortunately, my GP was very supportive and we learned about this rare condition together.

What to expect upon referral?

- Blood tests
- Bronchoscopy
- CT scan
- Octreotide scan
- PET scan

If you don’t suspect it, you can’t detect it
Pancreatic NETS (PNETs) are divided into two groups, Functioning and non-functioning:

Functional PNETs produce a recognisable syndrome related to where the tumour is found.

Non-functional PNETs still produce hormones and peptides but with no recognisable syndrome.

PNETs can occur sporadically or as part of an inherited disorder such as Multiple Endocrine Neoplasia (MEN).

5% of insulinomas are related to MEN 1.³

For further information on MEN see page 9.

Possible symptoms

- Low blood sugar
- Heart palpitations
- Sweating
- Confusion
- Relief with eating
- Weight gain

Refer for investigation

“ In May 2011, I experienced a grand mal seizure at home and ended up in hospital. After a series of tests whilst in my local hospital, doctors suspected a benign insulinoma - but instead of picking up the pancreatic primary disease in the scans, they could only find liver lesions. At that point, they weren't sure what was wrong with me and so referred me to The Royal Marsden.

At the end of July, after a series of scans and procedures, I was officially diagnosed with malignant insulinoma with liver metastases. It's been a rollercoaster of a year, but I feel that I am quite lucky to have been diagnosed quickly, I've heard a lot of stories of people who've had insulinomas for 20 years without being able to get a referral.”

What to expect upon referral?

- Fasting blood tests
- Genetic testing for MEN 1
- Octreotide scan
- CT or MRI scan
- Endoscopic ultrasound
- PVS sampling

Please see algorithm on page 10
Functioning Pancreatic NETs - VIPoma

60-80% of VIPomas have metastasised at time of diagnosis and 5% are associated with MEN 1.4

The associated syndrome related to VIPoma is called Verner-Morrison.

The collection of symptoms is known as WDHA - watery diarrhoea hypokalaemia achlorhydria.

VIPomas can affect children and adults.

Possible symptoms
- Severe watery diarrhoea
- Low potassium
- Weakness
- Ongoing fatigue

Refer for investigation

What to expect upon referral?
- Blood tests
- CT scan
- MRI scan
- Octreotide scan

Please see algorithm on page 10

"I have every confidence in the oncology team at my local cancer centre and more recently, the specialist team at the Royal Free.

I have had every possible support i.e. monthly octreotide injections at the local hospital; referral for psychological support from Macmillan; referral to other specialists for related issues such as hypothyroidism; excellent GP support and referral; regular CT scan, nuclear scans, echocardiograms and blood tests to monitor progress of cancer; colonoscopy, ultrasound scans and healthy bacteria breath test to check on other symptoms; ongoing search for reasons for my unusual and severe fatigue, and not least of all, fantastic listening, understanding and positivity in all consultations.

I cannot praise these wonderful people enough from the caring, friendly nurses to the committed doctors."

Online @ www.netpatientfoundation.org
Functioning Pancreatic NETs - Glucagonoma

In **50-80%** of cases, the Glucagonoma starts in malignant form, and in **50%** of these cases, metastasis exists at diagnosis.\(^4\)

10% of Glucagonomas are related to MEN 1.\(^3\) See page 9 for more information.

**Possible symptoms**
- Swelling and irritation of the skin - necrotic migratory erythema
- Sore mouth
- Anaemia
- Weight loss

**Refer for investigation**

**What to expect upon referral?**
- Blood tests
- CT scan
- MRI scan
- Octreotide scan

Please see algorithm on page 10

If you don’t suspect it, you can’t detect it

---

\(^1\) The care of NET cancers can be complex, and for the patient the journey can encompass not only a whole host of emotions, but also a whole range of investigations, treatments and healthcare professionals.

The very fact that there is often not just one treatment option at diagnosis and throughout the patient journey, means that there has to be a collaboration between the key healthcare professionals who are making clinical decisions for individual patients.

Patients will feel more confident in the knowledge that all aspects of their care have been discussed and that the best possible treatment plan will be formulated. A well coordinated and disciplined MDT is a very important aspect for care when striving to achieve the best quality of life and the best outcome for NET cancer patients.

---

Online @ www.netpatientfoundation.org
Functioning Pancreatic NETs - Gastrinoma

Over 50% of Gastrinomas are malignant and can metastasise to regional lymph nodes and the liver. After weeks of tests and being misdiagnosed several times, at just 53, Anne was eventually diagnosed with advanced secondary liver cancer of an unknown primary. She was discharged from hospital in February with this vague analysis and no offer of treatment. As a family, we were determined not to settle for this, so pushed to see another consultant who, on seeing Anne's positivity and surprising good health, decided to give her a chance.

Further investigation found it was an unusually aggressive neuroendocrine tumour and after consultation with NET specialists, a course of chemotherapy was started immediately. It was only then that we realised a neuroendocrine tumour could have been there undetected for sometime, after being told for many years that digestive problems were down to IBS.

Anne's health began to get better each month, blood tests showed significant improvement as the tumours stabilised and we all remained positive but at the same time realistic. Unfortunately, the cancer began to fight back and sadly Anne passed away in August. Whilst the eventual outcome was not what we had all hoped for, we're forever grateful for the extra months that we had together, which we put down to the treatment Anne was eventually offered, and of course, her positive attitude.

Possible symptoms
- Peptic ulcer disease
- Acid reflux
- Abdominal pain
- Diarrhoea
- Weight loss

Refer for investigation

What to expect upon referral?
- Blood tests
- Endoscopic ultrasound
- Endoscopy
- CT scan
- MRI scan
- Octreotide scan

Please see algorithm on page 10
Non-functioning Pancreatic NETs

Non functioning pancreatic NETs have no hormone related clinical features.

60% of all pancreatic NETs are non-functioning.

“A high index of suspicion is needed to identify patients.”

A pancreatic tumour may be large at presentation and around 50% have already metastasised.

Patient symptoms

- Pain
- Jaundice
- Mass
- Obstructive symptoms
- Weight loss

Refer for investigation

What to expect upon referral?

- Blood tests
- Endoscopic ultrasound
- CT scan
- MRI scan
- Octreotide scan
- Biopsy

Please see algorithm on page 10

Sir Peter Stothard
Editor of the Times Literary Supplement.

In my inbox today sits a note about World NET Cancer Awareness Day.

It is there because a decade ago I was given no chance to escape one of these nasty little killer NETs, a neuroendocrine tumour that had settled in and around my pancreas.

I am happy to support the NET Patient Foundation and its campaign for increased awareness and earlier diagnosis of this slothful but determined killer.

Online @ www.netpatientfoundation.org

If you don’t suspect it, you can’t detect it
High Grade NETs

There are several systems for grading NETs, including a new WHO system introduced in 2010, which is shown here.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET Grade 1</td>
<td>Well-differentiated tumour with a low number of cells actively dividing</td>
</tr>
<tr>
<td>NET Grade 2</td>
<td>Well-differentiated tumour, but with a higher number of cells actively dividing</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma (NEC) Grade 3</td>
<td>Poorly differentiated, malignant carcinoma (most aggressive form of NET)</td>
</tr>
</tbody>
</table>

- These NETs are fast growing and aggressive. They are always malignant and metastatic
- A family history of cancer is a significant factor for all types of NET

The European Neuroendocrine Tumour Society (ENETS) have recently proposed a new classification called the TNM staging.

T – primary tumour (this is split into 5 main areas: stomach, small intestine, pancreas, appendix and colon/rectum)

N – disease in the lymph nodes

M – metastatic spread

My husband Andy died just 9 days after we were told he had an advanced, aggressive tumour (only confirmed as a NET after a subsequent biopsy).

He was only 48 and his death left myself, my twin teenage sons and family and friends shocked and devastated. It all started when he complained of tummy and groin ache and not being able to sleep 6 months before his late diagnosis.

He was bounced back and forth from GP to orthopaedic consultants, including an initial CT scan that only focussed on a small area (looking for a slipped disc), when the symptoms had changed to backache and 'sciatica', missing the tumour.

He had 2 months of physio before being referred to urology as he was having problems in that area too. Only after several months in increasing pain did a final scan show the tumour.

Andy's story shows how important it is for GPs and other medical professionals to think 'outside of the box', and wonder if these symptoms could be a NET. Hopefully increased GP awareness of this rare cancer can save future lives, instead of a repeat of Andy's story.
Phaeochromocytomas

20-35% of phaeochromocytomas are related to familial inherited syndromes.²

This type of tumour is rare, occurring in 1 per 100,000 people per year.

The majority (approximately 90%) are benign tumours (i.e. not cancer).

Over 80% arise in the adrenal glands.

The most common age for diagnosis is between the ages of 30-60 years of age, although 10% arise in children.

Possible symptoms

- High blood pressure
- Rapid heart rate
- Forceful heartbeat
- Profound sweating
- Abdominal pain
- Sudden onset of severe headaches
- Anxiety
- Feeling of extreme fright
- Pale skin
- Weight loss

Refer for investigation

Further information for people affected by Multiple Endocrine Neoplasia Disorders and associated endocrine tumours and syndromes is available at:

AMEND
www.amend.org.uk

What to expect upon referral?

- Urine tests
- Blood tests
- CT scan
- MRI scan
- MIBG scan
- PET scan

Please see algorithm on page 10

If you don’t suspect it, you can’t detect it
Algorithm of investigation of GEP Neuroendocrine Tumours

Suspected NET

Biochemical profile:
- CgA
- 24h urine 5 HIAA peptide screen
- Consider Pituitary screen. Calcium. PTH

Consider Familial:
- Men-1: VHL: NF

Cross-sectional imaging:
- Contrast C T (or MRI)
- Thorax / Abdo / Pelvis

Somatostatin Receptor Scintigraphy
- OctreoScan™

Histology
- Differentiation & grade.
- Chromogranin. Synaptophysin. Ki67

Tumour resection or Biopsy

Consider PET Scan:
- FOG
- 68-Gallium DOTAOctreotate
- 5HTP or Dopa

If negative

Additional investigations for specific NETs

Midgut
- Pro-BNP
- Echocardiography
- 1-123 MIBG scan
- Barium F.T. (capsule endoscopy)

Gastrinoma
- Upper G.I. Endo pH studies
- +/- secretin (or calcium) stimulation test

Insulinoma
- Glucose. Insulin.
- Proinsulln, C-peptide
- 72h fast

Pancreatic NET
- Gut hormones

Gastric carcinoid
- Upper G.I. Endo Type 1: gastrin, GPCA
- Type 2: gastrin
- Type 3: exclude above

Rectal carcinoid
- Flexi Sig
- Acid phosphatase

If you don’t suspect it, you can’t detect it

Online @ www.netpatientfoundation.org

GEP = gastroenteropancreatic
Further Reading

Multidisciplinary teams
The care of NET cancers can be complex, and for the patient the journey can encompass not only a whole host of emotions, but also a whole range of investigations, treatments and healthcare professionals.

The very fact that there is often not just one treatment option at diagnosis and throughout the patient journey means that there has to be a collaboration among all key healthcare professional groups, who are making clinical decisions for individual patients.

A patient may see some or all of the following people:
- Oncologist
- Surgeon
- Endocrinologist
- Radiology staff
- Nuclear medicine physician
- Dietitian
- Nurse Specialist
- Palliative Care Team
- Pain Team
- General Practitioner
- Practice Nurse
- Counselling Staff
- Various Technicians
- Clinic Staff
- Hospital Staff
- Hospice Team

Patients can feel more confident in the knowledge that all aspects of their care have been discussed and that the best possible treatment plan will be formulated.

A well coordinated and disciplined MDT is a very important aspect for care when striving to achieve the best quality of life and the best outcome for NET cancer patients.

Further information about NETs is available at:

UKINETS Guidelines
www.ukinets.org

ENETS Guidelines
www.enets.org

World NET Cancer Awareness Day
The World NET Community is a group of patient focused NET groups from around the world who come together annually to speak in one global voice.

Working together to increase awareness and understanding of NET Cancers, improve diagnostic times and be the patient voice shouting for optimal treatment and collaborative care.

www.netcancerday.org
Rarer NETs

Some of the rarer NETs include:

Medullary Thyroid Cancer (MTC)
is a rare neuroendocrine malignancy of the thyroid C cells. Most are sporadic but 25% result within the MEN 2A, 2B setting or as familial MTC.

Merkel Cell Carcinoma (MCC)
arises from the uncontrolled growth of Merkel cells in the skin. It presents with a firm, painless, flesh- coloured to red-violet lump. These lumps predominately arise on sun exposed skin, but can occur anywhere.

Adrenocortical Carcinoma (ACC)
is a cancer of the adrenal cortex. About 50% of all ACCs are non-functional. An ACC is a typically aggressive tumour.

Goblet Cell
These tumours start in the appendix and display features of both a neuroendocrine tumour and an adenocarcinoma.

Paragangliomas
These are phaeochromocytomas that occur elsewhere in the body than the adrenal medulla. They are 'extra adrenal' and develop from the paraganglia, cells that are part of the extra adrenal sympathetic and parasympathetic nervous system.

References:
1. UKINETS guidelines - Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs)
3. The NET Patient Foundation survey
NET Clinics

Hospitals that run multidisciplinary clinics for neuroendocrine patients:

- Basingstoke, Hampshire Hospitals NHS Foundation Trust
- Belfast, Royal Victoria Hospital
- Birmingham, Queen Elizabeth Hospital
- Bristol, Bristol Royal Infirmary
- Calderdale, Calderdale Royal Hospital - Calderdale and Huddersfield NHS Foundation Trust
- Cambridge, Addenbrooke’s Hospital
- Cardiff, University Hospital of Wales
- Colchester, Colchester Hospital University NHS Foundation Trust
- Derriford, Plymouth Hospitals NHS Trust
- Edinburgh, Edinburgh Cancer Centre, Western General Hospital
- Glasgow, The Beatson Oncology Centre, Beatson West of Scotland Cancer Centre
- Gloucester, Gloucestershire Hospitals NHS Trust
- Hull, Castle Hill Hospital - Hull and East Yorkshire Hospitals NHS Trust
- Leeds, Leeds Teaching Hospital NHS Trust
- Leicester, Royal Infirmary - University Hospitals of Leicester NHS Trust
- Lincoln, United Lincolnshire Hospitals NHS Trust
- Liverpool, Aintree University Hospitals NHS Foundation Trust

Scan for more information on clinics in your area

- Liverpool, Royal Liverpool and Broadgreen University Hospitals NHS Trust
- London, St Bartholomew’s Hospital Barts and the London NHS Trust
- London, Guy’s and St Thomas’ Hospital Trust
- London, Hammersmith Imperial College Healthcare NHS Trust
- London, Kings College
- London, Royal Free Hampstead NHS Trust/UCLH
- London, Royal Marsden NHS Foundation Trust
- Maidstone and Tunbridge Wells NHS Trust
- Manchester, The Christie’s NHS Foundation Trust
- Musgrove Park Hospital, Taunton
- Newcastle, Freeman Hospital - Newcastle upon Tyne Hospitals NHS Foundation Trust
- Norfolk and Norwich University Hospital - Norfolk and Norwich University Hospitals NHS Foundation Trust
- Oxford, Oxford Radcliffe Hospitals NHS Trust
- Sheffield, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust
- Southampton, Southampton General Hospital, University Hospital Southampton NHS Foundation Trust

This list is compiled from hospitals that have given us their details

If you don’t suspect it, you can’t detect it

Online @ www.netpatientfoundation.org
Neuroendocrine tumours (NETs) is the umbrella term for a group of unusual and complex cancers that affect neuroendocrine cells. They are most commonly found in the gastrointestinal system but they also originate in many other parts of the body, for example; pancreas, lungs, ovaries, thyroid, pituitary and adrenal glands.

- From onset of symptoms a proper diagnosis can take between 3-7 years
- Over 50% of all NET patients are incorrectly diagnosed and treated for the wrong disease
- Not all NETs are benign or slow-growing; many do spread.

Neuroendocrine tumours are a challenging group of cancers, which present a number of challenges to the international health community. Early data from the UK, Sweden and Switzerland suggested that the incidence of GI NETs was between 2 and 3 per 100,000 persons per year. The largest and most recent analysis of the epidemiology of NETs has examined data from the USA SEER programme and shown a fourfold increase between 1973 and 2004, from 2.1 to 9.3 new cases per 100,000 persons per year. This report concluded that NETs are the most common small bowel tumour.

Whatever the precise incidence of NETs, it appears that the number of patients presenting with these tumours has been steadily increasing. As many NETs are slow-growing, the prevalence is relatively high. However, it is reported that despite the rising number of cases, there is still a delay of up to 7 years between the appearance of first symptoms and a diagnosis of NET cancer.

**NET patients should be under the care of a multidisciplinary team specialising in this tumour type.**

References are inside the back cover

GI = Gastrointestinal

If you don’t suspect it, you can’t detect it