Detecting Neuroendocrine Cancer

PURPOSE OF THIS GUIDE: To shorten the time to diagnosis of neuroendocrine tumors (NETs).

- The average time to diagnosis for symptomatic patients is 6 years. (incalliance.org/scan)
- The only curative intervention is surgery, but only if the diagnosis is made early enough.
- Neuroendocrine neoplasms (NENs)* are highly likely to metastasize.
- Small primary tumors may generate large metastases.
- The incidence of NENs has risen faster than the incidence of malignant neoplasms overall.

THREE PATTERNS OF PRESENTATION

1. ASYMPTOMATIC
   Many NENs are discovered incidentally when imaging is done (e.g., for injury or routine colonoscopy)

2. ACUTE SYMPTOMS CAUSED BY TUMOR GROWTH
   Obstruction, bleeding, or pain may come from both the primary tumor and the metastases (lymph nodes, liver, bone)

3. FUNCTIONAL (HORMONAL) TUMOR SYNDROMES
   About a third of patients experience symptoms from the excess production of hormones caused by the tumors. These patients are likely to repeatedly seek a doctor’s help. Symptoms of NETs are varied and typically occur in other more common diseases, which makes diagnosis a challenge.

## SYSTEM
<table>
<thead>
<tr>
<th>FEATURES OF FUNCTIONAL NENS</th>
<th>FREQUENTLY DIAGNOSED AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GASTROINTESTINAL</td>
<td>Irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), peptic ulcer, hiatal hernia, gallstones</td>
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<tr>
<td>Diarrhea, jaundice, abdominal pain and swelling, recurrent ulcers, intestinal obstruction, GI bleeding, gallstones, heartburn</td>
<td></td>
</tr>
<tr>
<td>DERMATOLOGICAL</td>
<td>Menopause, drug reactions</td>
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<tr>
<td>Flushing, rashes</td>
<td></td>
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<tr>
<td>CARDIOPULMONARY</td>
<td>Anxiety, stress, asthma, primary cardiac disease</td>
</tr>
<tr>
<td>Right-sided heart failure and valvular dysfunction, palpitations, wheezing, blood clots</td>
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<tr>
<td>ENDOCRINE</td>
<td>Diet-related blood sugar problems, diabetes</td>
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<tr>
<td>Hypoglycemia or hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>NEUROPSYCHIATRIC</td>
<td>Anxiety, depression</td>
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<tr>
<td>Mood changes, syncope</td>
<td></td>
</tr>
<tr>
<td>RENAL</td>
<td>Infectious diarrhea</td>
</tr>
<tr>
<td>Electrolyte disturbances, dehydration</td>
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</tbody>
</table>

*A Neuroendocrine neoplasm (NEN) is an umbrella term that encompasses low and high grade well differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs).

A PATIENT JOURNEY
Gayle Morell began having symptoms in 1994, when she was in her early 20s and in pharmacy school. She was unable to get from her dorm to her classes because of digestive issues and related panic attacks. Gayle was misdiagnosed for 18 years before a doctor suspected a functional neuroendocrine tumor. She has been experiencing a much higher quality of life for the past 10 years and is forever grateful to the doctor who found the answer.

A WOLF IN SHEEP’S CLOTHING
Neuroendocrine cells are widely distributed in the body and NENs have a wide range of primary sites with significant variation in presentation. The symptoms in the chart reflect this range of sites.

- 63% originate in the digestive tract (small intestine, rectum, pancreas, stomach, etc.)
- 23% originate in the lungs
- 14% unknown primary and rare sites (uterus, ovary, testis, breast, adrenal glands, etc.)
**NEUROENDOCRINE TUMOR SYNDROMES & DIAGNOSTIC TESTING**

Differentiating NETs from other disease states is helped by the patterns of the hormonal syndromes in the chart below, e.g., if persistent watery stool is accompanied by dry flushing or wheezing, carcinoid syndrome may be present as opposed to the far more common irritable bowel syndrome or inflammatory bowel disease.

**Imaging Studies** support the diagnosis and establish the extent of disease.

CT and/or MRI are typically the first studies pursued if NEN is suspected.
- Arterial phase CTs are important due to robust vascularization of tumors.
- MRIs with contrast have slightly higher yield than triple-phase CT scans in detecting liver metastases.

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### SYNDROME (frequency)

**Scan QR code to view related Case Presentation**

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>SYMPTOMS</th>
<th>DIAGNOSTIC TESTING*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARCINOID SYNDROME (most common)</td>
<td>Flushing, diarrhea, night sweats, wheezing, pellagra, heart valve damage</td>
<td>5-HIAA (preferred) plasma or urine</td>
</tr>
<tr>
<td>ZOLLINGER ELLISON SYNDROME Gastrinoma (frequent)</td>
<td>Diarrhea, peptic ulceration (usually duodenal), heartburn, abdominal pain</td>
<td>Serum gastrin (Proton pump inhibitor use can falsely elevate levels but should only be discontinued in a controlled setting.)</td>
</tr>
<tr>
<td>INSULINOMA (frequent)</td>
<td>Hypoglycemia, (neuroglycopenia or sympathetic overdrive), obesity</td>
<td>Fasting plasma insulin, proinsulin, c-peptide</td>
</tr>
<tr>
<td>PHEOCHROMOCYTOMA adrenal PARAGANGLIOMA extra-adrenal (rare)</td>
<td>Hypertension, headache, sweating, palpitations</td>
<td>Plasma free metanephrines, 24-hr urine catecholamines, metanephrines</td>
</tr>
<tr>
<td>ACTHOMA OR ECTOPIC CUSHINGS (rare)</td>
<td>Bruising, proximal myopathy, central weight gain, striae, glucose intolerance</td>
<td>Plasma cortisol, ACTH</td>
</tr>
<tr>
<td>GLUCAGONOMA (rare)</td>
<td>Diabetes/hyperglycemia, cachexia/weight loss, necrolytic migratory erythema, anemia, venous thrombosis</td>
<td>Plasma glucagon</td>
</tr>
<tr>
<td>VIPOMA (rare)</td>
<td>Watery secretory diarrhea, electrolyte disturbances, hypokalemia, achlorhydria</td>
<td>Plasma VIP</td>
</tr>
</tbody>
</table>

*aFalse negatives and positives can occur with these tests.*

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**DOTATATE-PET CTs**
- The gold standard for detecting well-differentiated NETs, usually performed at specialized centers
- Often negative for poorly differentiated NECs or very small functional tumors

**FDG PET-CTs**
- Often high yield for poorly differentiated NECs (but low for NETs)

**Pathologic Biopsy** confirms the diagnosis of neuroendocrine cancer.

For information about management of neuroendocrine cancer:
- thehealingnet.org/topics-nets
- nanets.org/net-guidelines-library
- nccn.org/guidelines/category_1

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