Inaccurate or delayed diagnosis of neuroendocrine tumors (NET) is common, because many NET are small and asymptomatic.\textsuperscript{1}

When symptoms are present, they are usually nonspecific and related to tumor bulk, making NET difficult to diagnose.\textsuperscript{2-4}

The following biomarkers and imaging tests may help health care professionals detect, diagnose, and stage this rare cancer.

**Typical diagnostic pathway for NET**

1. **Patient presents to primary care physician**\textsuperscript{5,6}
   - Symptoms are vague
     - May be misdiagnosed as a more common condition (eg, IBS)
     - Biochemical tests may be ordered
     - Patients may be referred to specialists, based on symptoms

2. **Referral to multiple specialists**\textsuperscript{2,5,7-9}
   - Initial diagnosis incorrect or diagnosis remains unclear
   - Vague symptoms persist and additional tests or imaging may be ordered

3. **Imaging ordered**\textsuperscript{9-12}
   - Vague symptoms persist
     - Liver metastasis primary lesion is visualized
       - Primary NET may not be found

4. **Biopsy or resection performed**\textsuperscript{2,5,13,14}
   - Histopathology and biochemical confirmation provide diagnosis of NET
     - Patient is referred to a NET specialist
     - Management depends on stage, histology, symptoms

Abbreviation: IBS, irritable bowel syndrome.
## Biochemical tests to assess and diagnose NET

### CIRCULATING AND CELLULAR BIOMARKERS

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<th>Biomarker</th>
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| CgA<sup>15,16</sup> | Elevated in up to 90% of patients with NET  
Can be elevated in patients with functional or nonfunctional NET |
| NSE<sup>16,17</sup>  | Glycolytic enzyme that is secreted into plasma  
Can be elevated in patients with functional or nonfunctional NET |
| Synaptophysin<sup>6</sup> | Widely distributed in neurons and neuroendocrine cells and their neoplasms  
Broad-spectrum neuroendocrine marker |

Some biochemical substances secreted by NET are specific to the type of neoplasm<sup>18</sup>

### SPECIFIC TESTS FOR TYPES OF FUNCTIONAL NET

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| Cardinoid syndrome<sup>14,19,20</sup> | 5-HIAA is the primary metabolite of serotonin  
A 5-HIAA test has diagnostic value in NET associated with carcinoid syndrome that oversecrete serotonin and other substances  
5-HIAA is measured by high-precision liquid chromatography in a 24-hour urine sample |
| Insulinomas<sup>13,18</sup> | A standard 72-hour fasting test should be used to measure blood glucose (<40 mg/dL) and insulin (>36 pmol/L) levels and to exclude all differential diagnoses of insulinoma  
Measurement of proinsulin and C-peptide levels |
| Gastrinomas<sup>18,21,22</sup> | Diagnosis often begins with determination of fasting serum gastrin levels (>1000 pg/mL) and gastric pH (<2.5)  
Over a period of repeated testing, <0.5% of patients with Zollinger-Ellison syndrome (ZES) will have normal values |
| Glucagonomas<sup>13</sup> | Diagnosis can be made when plasma glucagon levels reach 500 to 1000 pg/mL (normal range <50 pg/mL) in the presence of the appropriate symptoms |
| VIPomas<sup>13,21</sup> | Diagnosis is based on elevated levels (>200 pg/mL) of serum plasma vasoactive intestinal peptide (VIP) in patients with large-volume secretory diarrhea (>700 mL/d) |
| Somatostatinomas<sup>13</sup> | Diagnosis can be confirmed by elevated plasma somatostatin levels in the setting of a histologically confirmed PNET with the appropriate symptoms |

Abbreviations: CgA, chromogranin A; 5-HIAA, 5-hydroxyindoleacetic acid; NSE, neuron-specific enolase.
Imaging and endoscopic techniques to diagnose and monitor NET

**CT**

- Appendix
- Colon
- Duodenum
- Liver
- Pancreas
- Lung

**OCTREOSCAN™ (SRS)**

- Duodenum
- Liver
- Pancreas
- Stomach
- Colon
- Rectum
- Jejunum
- Ileum
- Lung
- Thymus
- Appendix

**Ga 68 dotatate PET**

- Jejunum
- Ileum
- Colon
- Duodenum
- Appendix
- Rectum
- Stomach
- Pancreas
- Thymus

**MRI**

- Colon
- Duodenum
- Liver
- Rectum
- Stomach
- Appendix
- Jejunum
- Ileum
- Lung
- Thymus
- Pancreas

Refer to the end of this document for an overview of which tests may be used to assess NET for each organ.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SRS, somatostatin receptor scintigraphy.

Octreoscan is a trademark of Curium.
Baseline multiphasic CT or MRI is recommended to assess for distant metastatic disease. Biochemical testing as clinically indicated. Follow-up imaging is recommended every 3-12 months for advanced disease. Frequency of imaging varies depending on disease grade and site.

Further tests that can be used to assess NET include sodium iodide I 131 metaiodobenzylguanidine scintigraphy, colonoscopy, enteroscopy, and bronchoscopy.

Guidelines cite routine imaging tests as often as every 3 months as the mainstay for monitoring NET progression.

### Monitoring NET progression

**NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY (NCCN Guidelines)**
- Baseline multiphasic CT or MRI is recommended to assess for distant metastatic disease
- Biochemical testing as clinically indicated
- Follow-up imaging is recommended every 3-12 months for advanced disease
  - Frequency of imaging varies depending on disease grade and site

**NANETS RECOMMENDATIONS**
- 3-6 months after curative resection, then every 6-12 months for at least 7 years
- For advanced disease: every 3-6 months
- For patients with stable disease for >12 months: every 6 months

**OVERVIEW OF IMAGING TESTS TO DIAGNOSE AND MONITOR NET**

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Abbreviations: NANETS, North American Neuroendocrine Tumor Society; NCCN, National Comprehensive Cancer Network.
Learn more about how routine monitoring is important to optimize patient outcomes

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