The remaining three chapters guide the clinician through the selection of appropriate assays, profiles, and dynamic challenge protocols for diagnosing and monitoring neuroendocrine symptoms.

- Assays, Including CPT Codes
- Profiles, Including CPT Codes
- Dynamic Challenge Protocols, Including CPT Codes

This book provides you with five informative chapters.

These chapters guide the clinician through:

- Diagnosing and Treating Gastroenteropancreatic Tumors, Including ICD-9 Codes
- Clinical Presentations and Their Syndromes, Including ICD-9 Codes

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The GI Council of Inter Science Institute presents this comprehensive guide to diagnosis and management of neuroendocrine tumors to provide information and inspiration to all levels of clinicians, from novices to those professionally engaged in the field of neuroendocrine research, treatment, and analyses. This guidebook adds the new dimension of patient monitoring, not only through powerfully discriminating assays but through the recognition of clinical presentations and syndromes. This expertise is made possible by more than 150 years of cumulative experience of the advisory council.

Since the publication of the first GI Handbook in 1977 up to the current edition of *Neuroendocrine Tumors*, Inter Science Institute has been at the forefront of bridging the gap between academic medicine and the availability of the most current tests for patient diagnosis. In the intervening three and a half decades, unparalleled progress has been made both in the diagnosis and treatment of gastrointestinal, pancreatic, and neuroendocrine tumors.

This book is meant to be a beacon not only for listing tests but for all aspects of neuroendocrine tumors. Its publication represents a move from static text to the modern era of communication which allows for dynamic, continuously updating links to the ISI website, interscienceinstitute.com, as well as endotext.com as reference sources. Additionally, the book combines several references from the previous edition with an updated bibliography, in recognition of past contributions to the present.

Special thanks to our dedicated reviewers of this publication, Etta J. Vinik and Mia S. Tepper.

Finally, my appreciation and thanks to professors Vinik, Woltering, O’Dorisio, and Go for imparting their knowledge to the synergistic confluence that has given birth to this unique edition. Thank you, Arthur, Gene, O’Do, and Bill.

Gregg Mamikunian  
Inter Science Institute 2006
The great majority of the gastrointestinal and pancreatic peptide hormones and polypeptide assays listed in this handbook would not have been even remotely possible had it not been for the tremendous generosity and cooperation of all the individuals listed below. Without their assistance, the establishment of the GI Hormones Laboratory at Inter Science Institute would not have been a reality.

Inter Science Institute gratefully acknowledges and thanks Professor V. Mutt of GI Hormones Laboratory of Karolinska Institute (Sweden) for his immense assistance and encouragement; Professor N. Yanaihara (Japan); Dr I.M. Samloff (USA); Professor J.C. Brown (Canada); Dr R. Geiger (Germany); Dr R.E. Chance (USA); Professor A.G.E. Pearse (England); Dr J.E. Hall (England); Dr R.I. Harvey (England) and Professor M. Bodanszky (USA).

Our sincerest appreciation to Professor John H. Walsh of the University of California at Los Angeles for his collaboration over the many years and his review and many suggestions regarding this presentation.

Finally, a special acknowledgment to Dr Herbert Gottfried of Inter Science Institute for his long and dedicated years in bringing the GI Hormones Laboratory into fruition.

**Gregg Mamikunian**
Inter Science Institute 1997
The current 1997 edition of the *GI, Pancreatic Hormones, Related Peptides and Compounds*® handbook presents comprehensive information for many rare procedures and tests that have been requested in the course of the past twenty-eight years.

The handbook reflects the tremendous advances that have been made since 1977. The number of tests offered has increased six-fold in addition to increasing specificity, sensitivity of antibodies, and purity of the standards. The protocols dealing with challenges and provocative testing has been expanded with the latest information. The section on the physiology of the GI and Pancreatic Hormones has been updated as an adjunct to the various procedures in the handbook.

Furthermore, the handbook covers a vast area of gastrointestinal, pancreatic, and other related procedures. Many of these procedures are clearly out of the realm of routine testing and request. On the other hand, quite a number of the procedures are indicators in the clinical confirmation of certain syndromes and disease states. Inter Science has witnessed the phenomenon over the years of the transformation of research-oriented procedures becoming useful, routine, and critical determining factors in the diagnosis and management of certain GI-related endocrinopathies.

A special acknowledgment to Alan C. Kacena for his dedication and service of twenty-five years at Inter Science Institute and in bringing the current edition of the GI Hormones handbook into reality.

**Gregg Mamikunian**  
Inter Science Institute 1997  
Reprinted from Inter Science Institute’s *GI, Pancreatic Hormones, Related Peptides and Compounds*® handbook, 1997.
This book is designed for the medical practitioner; it is an educational tool as well as a practical manual for the diagnosis of patients with suspected neuroendocrine tumors and a variety of associated gastrointestinal disorders, guiding the physician to long-term follow-up. Conceptually, this text is more than a list of laboratory tests. It comprises two informational sections on gastroenteropancreatic tumors and clinical syndromes, both of which provide a step-by-step approach to possible diagnoses. Each diagnosis (with its CPT code provided) relates to appropriate tests in one of the three test sections: assays, profiles, and dynamic challenge tests. The assays are alphabetically arranged. Terminology and test names are cross-referenced in the comprehensive index.

**CHAPTER 1**

“Diagnosing and Treating Gastroenteropancreatic Tumors” describes the complexity of the problems involved with suspected neuroendocrine tumors. It then simplifies the problems by breaking them down under headings such as “Distinguishing Signs and Symptoms,” “Diagnosis,” “Biochemical Studies,” and “Hormones and Peptides.” Thus the physician is guided through a decision-making process from diagnosis to follow-up.

**CHAPTER 2**

“Clinical Syndromes” describes the signs, symptoms, and syndromes associated with excessive peptide amine release.

**CHAPTER 3**

“Assays” lists single tests alphabetically. The tests available from ISI are set out with clear and concise requirements. These include patient preparation, specimen collection, important precautions, shipping instructions, and CPT codes for insurance purposes.

**CHAPTER 4**

“Profiles” presents a collection of assays that should provide guidance to the diagnosing physician. Some of these tests are available locally, whereas others are available through ISI. This section also includes the requirements given in Chapter 4: patient preparation, specimen collection, important precautions, shipping instructions, and CPT codes for insurance purposes.

**CHAPTER 5**

“Dynamic Challenge Protocols” describes provocation tests. The drug doses outlined in these tests are recommendations only and should be reviewed and approved by the attending physician on a patient-by-patient basis. Dynamic challenge protocols can be dangerous and should be performed only under the direct and constant supervision of trained medical personnel who are familiar with expected and potentially unexpected responses to provocative testing.

Abbreviations are spelled out in the text the first time each is used. A list of abbreviations appears at the end of the book.
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GASTROENTEROPANCREATIC TUMORS

Endocrine tumors of the gastroenteropancreatic (GEP) axis (involving the gastrointestinal [GI] system, stomach, and pancreas) are comprised of cells capable of amine precursor uptake and decarboxylation, hence the prior name “APUDomas.” The morphologic similarity of the APUD cells suggested a common embryologic origin, indicated by the term “protodifferentiated stem cell,” now believed to derive from the endoderm and capable of giving rise to a variety of tumors (Fig. 1-1).

In some cases, multiple peptides or hormones are responsible for symptoms, and several organs and/or multiple tumors may be involved in the disease state, confounding the clinical diagnosis. To facilitate the diagnostic process, this text classifies GEP syndromes according to their secretory products and the clinical disorder they produce.

In some cases, multiple peptides or hormones are responsible for symptoms, and several organs and/or multiple tumors may be involved in the disease state, confounding the clinical diagnosis. To facilitate the diagnostic process, this text classifies GEP syndromes according to their secretory products and the clinical disorder they produce.

Carcinoid, gastrinoma, insulinoma, somatostatinoma, glucagonoma, and watery diarrhea (WDHHA) syndromes are described as individual syndromes according to their secretory hormones and peptides. Distinguishing signs and symptoms of each syndrome will further aid the diagnosis. These tumors can be subdivided into two main groups:

1. Orthoendocrine tumors secrete the normal product of the cell type (e.g., α-cell glucagon).
2. Paraendocrine tumors secrete a peptide or amine that is foreign to the organ or cell of origin.
Specific tumor syndromes, their clinical manifestations, and the tumor products are indicated in *(Table 1-1)*.

**Table 1-1. The Clinical Presentations, Syndromes, Tumor Types, Sites, and Hormones**

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<td>Carcinoid</td>
<td>Gastric, mid, and foregut, pancreas/foregut, adrenal medulla</td>
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<td>Carcinoid</td>
<td>Carcinoid</td>
<td>As above</td>
<td>As above</td>
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<td></td>
<td>WDHHA</td>
<td>VIPoma</td>
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<td>Carcinoid</td>
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<td>Cushing's</td>
<td>Cushing's</td>
<td>Neuroendocrine tumors</td>
<td>Pancreas</td>
<td>ACTH/CRF</td>
</tr>
<tr>
<td>Anorexia, Nausea, Vomiting</td>
<td>Hypercalcemia</td>
<td>Neuroendocrine tumors</td>
<td>Pancreas</td>
<td>PTHRP</td>
</tr>
<tr>
<td>Constipation, Abdominal Pain</td>
<td>VIPoma</td>
<td>Pancreas</td>
<td>VIP</td>
<td></td>
</tr>
<tr>
<td>Pigmentation</td>
<td>Neuroendocrine tumors</td>
<td>Pancreas</td>
<td>VIP</td>
<td></td>
</tr>
<tr>
<td>Postgastrectomy</td>
<td>Dumping, syncope, tachycardia, hypotension, borborygmus, explosive diarrhea, diaphoresis, mental confusion</td>
<td>None</td>
<td>Stomach/duodenum</td>
<td>Osmolarity, insulin, GLP</td>
</tr>
</tbody>
</table>
These are the common neuroendocrine tumors (NETs):

- Carcinoid
- Insulinoma
- PPoma
- Gastrinoma
- VIPoma
- Glucagonoma
- Somatostatinoma
- Ghrelinoma
- Multiple endocrine neoplasia types I and II (MEN-I and MEN-II)
- Other rare tumors

The great majority of these tumors are carcinoid tumors, accounting for more than half those presenting each year (Fig. 1-2). The incidence of carcinoid has risen in the last 10 years, particularly those found in the stomach and ileum. Insulinomas, gastrinomas, and PPomas account for 17%, 15%, and 9%, respectively, whereas the rest remain around the 1% mark. These tumors are nicknamed “zebras” because of their rarity, but despite their infrequent occurrence, physicians are fascinated by their complexity and the unusual nature of their presentations. For the most part, endocrinologists make their living not by diagnosing and treating one of these tumors, but rather by excluding conditions that masquerade as NETs.

CHARACTERISTICS OF NEUROENDOCRINE TUMORS

- Rare
- Usually small (<1 cm)
- Slow growing (months to years, “cancer in slow motion”)  
- Usually metastasize to liver and bone before becoming symptomatic, often when tumor is larger than 2 cm  
- Episodic expression; may be silent for years  
- Often misdiagnosed; symptoms mimic commonplace conditions  
- Complex diagnosis, rarely made clinically; requires sophisticated laboratory and scanning techniques

To facilitate the proper treatment regimen, diagnostic tests should be selected to
- Determine the peptide(s) or amines responsible for the symptoms
- Locate the site and cause of the abnormality
- Eliminate other possible causes and syndromes

ICD-9 CODE: Carcinoid Syndrome 259.2

ICD-9 CODES for Primary Carcinoid Tumor Sites

<table>
<thead>
<tr>
<th>Foregut</th>
<th>Malignant</th>
<th>Benign</th>
<th>Uncertain Behavior</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>152.0</td>
<td>211.2</td>
<td>235.2</td>
<td>239.0</td>
</tr>
<tr>
<td>Lung</td>
<td>162.9</td>
<td>212.3</td>
<td>235.7</td>
<td>239.1</td>
</tr>
<tr>
<td>Stomach</td>
<td>151.9</td>
<td>211.1</td>
<td>235.2</td>
<td>239.0</td>
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<tr>
<td>Ovary</td>
<td>183.0</td>
<td>220</td>
<td>236.2</td>
<td>239.5</td>
</tr>
<tr>
<td>Thymus</td>
<td>164.0</td>
<td>212.6</td>
<td>235.8</td>
<td>239.8</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Midgut</th>
<th>Malignant</th>
<th>Benign</th>
<th>Uncertain Behavior</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix</td>
<td>153.5</td>
<td>211.3</td>
<td>235.2</td>
<td>239.0</td>
</tr>
<tr>
<td>Colon</td>
<td>154.0</td>
<td>211.4</td>
<td>235.2</td>
<td>239.0</td>
</tr>
<tr>
<td>Ileum</td>
<td>152.0</td>
<td>211.2</td>
<td>235.2</td>
<td>239.0</td>
</tr>
<tr>
<td>Jejunum</td>
<td>152.1</td>
<td>211.2</td>
<td>235.2</td>
<td>239.0</td>
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</table>

<table>
<thead>
<tr>
<th>Hindgut</th>
<th>Malignant</th>
<th>Benign</th>
<th>Uncertain Behavior</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>154.1</td>
<td>211.4</td>
<td>235.2</td>
<td>239.0</td>
</tr>
</tbody>
</table>
ICD-9 CODES for Carcinoid Metastatic Sites

<table>
<thead>
<tr>
<th>Lymph Nodes</th>
<th>Metastatic Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraclavicular</td>
<td>196.0</td>
</tr>
<tr>
<td>Abdominal</td>
<td>196.2</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>196.1</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>196.2</td>
</tr>
</tbody>
</table>

(See Carcinoid Follow-Up Profile [Chapter 4] and Flushing Syndrome Tests [Chapter 4] for specific tests and CPT codes)

ICD-9 CODE: Glucagonoma
Malignant
- Pancreas 157.4
- Specified site—see Neoplasm by site, malignant
- Unspecified site 157.4
Benign
- Pancreas 211.7
- Specified site—see Neoplasm by site, benign
- Unspecified site 211.7
Uncertain behavior, neoplasm of the pancreas 235.5

ICD-9 CODE: Zollinger-Ellison Syndrome 251.5

ICD-9 CODE: Hepatoma
Malignant (M8170/3) 155.0
Benign (M8170/0) 211.5
Congenital (M8970/3) 155.0
Embryonal (M8970/3) 155.0

ICD-9 CODE: Whipple’s Syndrome 040.2
ICD-9 CODE: Sweet’s Syndrome 695.89
ICD-9 CODE: MEN-I and -II 258.0
ICD-9 CODE: Diarrhea 787.91
ICD-9 CODE: Functional Diarrhea 564.5
ICD-9 CODE: Achlorhydric 536.0
ICD-9 CODE: Gastrinoma (M8153/1)
**ICD-9 CODES for Primary Sites**

<table>
<thead>
<tr>
<th>Sites</th>
<th>Malignant</th>
<th>Benign</th>
<th>Uncertain Behavior</th>
<th>Unspecified</th>
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</thead>
<tbody>
<tr>
<td>Ampulla</td>
<td>156.2</td>
<td>211.5</td>
<td>235.3</td>
<td>239.0</td>
</tr>
<tr>
<td>Duodenum</td>
<td>152.0</td>
<td>211.2</td>
<td>235.2</td>
<td>239.0</td>
</tr>
<tr>
<td>Jejunum</td>
<td>152.1</td>
<td>211.2</td>
<td>235.2</td>
<td>239.0</td>
</tr>
<tr>
<td>Pancreas Body</td>
<td>157.9</td>
<td>211.6</td>
<td>235.5</td>
<td>239.0</td>
</tr>
<tr>
<td>Head Islet</td>
<td>157.1</td>
<td>211.6</td>
<td>235.5</td>
<td>239.0</td>
</tr>
<tr>
<td>Neck Tail</td>
<td>157.8</td>
<td>211.6</td>
<td>235.5</td>
<td>239.0</td>
</tr>
</tbody>
</table>

**ICD-9 CODES for Metastatic Sites**

<table>
<thead>
<tr>
<th>Sites</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraclavicular</td>
<td>196.0</td>
</tr>
<tr>
<td>Abdominal</td>
<td>196.2</td>
</tr>
<tr>
<td>Mediastinal</td>
<td>196.1</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>196.2</td>
</tr>
<tr>
<td>Liver</td>
<td>197.7</td>
</tr>
<tr>
<td>Bone</td>
<td>198.5</td>
</tr>
<tr>
<td>Lung</td>
<td>162.0</td>
</tr>
<tr>
<td>Brain</td>
<td>191.9</td>
</tr>
</tbody>
</table>

*(See GI–Neuroendocrine Tests [Chapter 4] for specific tests and CPT codes)*
Carcinoid tumors are the most commonly occurring gut endocrine tumors. The prevalence of carcinoids is about 50,000 cases in any 1 year in the United States. The incidence is estimated to be approximately 1.5 cases per 100,000 of the general population (i.e., approximately 2500 new cases per year in the United States). Nonetheless, they account for 13% to 34% of all tumors of the small bowel and 17% to 46% of all malignant tumors of the small bowel. They derive from primitive stem cells known as Kulchitsky or enterochromaffin (EC) cells, originally described by Feyter as “wasser heller” or “clear water” cells and generally found in the gut wall.

Carcinoids may, however, occur in the bronchus, pancreas, rectum, ovary, lung, and elsewhere. The tumors grow slowly and often are clinically silent for many years before metastasizing. They frequently metastasize to the regional lymph nodes, liver, and, less commonly, to bone. The likelihood of metastases relates to tumor size. The incidence of metastases is less than 15% with a carcinoid tumor smaller than 1 cm but rises to 95% with tumors larger than 2 cm. In individual cases, size alone may not be the only determinant of lymphatic or distant spread. Lymphatic or vascular invasion, or spread into the fat surrounding the primary tumor, may be an indicator of a more aggressive tumor (Table 1-2).

Table 1-2. Tumor Location and Frequency of Metastases (n=5468)

<table>
<thead>
<tr>
<th>Gut</th>
<th>Location</th>
<th>Percentage of Tumors</th>
<th>Incidence of Metastases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foregut</td>
<td>Stomach</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Duodenum</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>32.5</td>
<td>27</td>
</tr>
<tr>
<td>Midgut</td>
<td>Jejunum</td>
<td>2.3</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Ileum</td>
<td>17.6</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Appendix</td>
<td>7.6</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
<td>6.3</td>
<td>71</td>
</tr>
<tr>
<td>Hindgut</td>
<td></td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>


The carcinoid syndrome occurs in less than 10% of patients with carcinoid tumors. It is especially common in tumors of the ileum and jejunum (i.e., midgut tumors) but also occurs with bronchial, ovarian, and other carcinoids. Tumors in the rectum (i.e., hindgut tumors) rarely occur in the carcinoid syndrome, even those that have widely metastasized. Tumors may be symptomatic only episodically, and their existence may go unrecognized for many years (Fig. 1-3). The average time from onset of symptoms attributable to the tumor and diagnosis is just over 9 years, and diagnosis usually is made only after the carcinoid syndrome occurs. The distribution of carcinoids is Gaussian in nature. The peak incidence occurs in the sixth and seventh decades of life, but carcinoid tumors have also been reported in patients as young as 10 years of age and in those in their ninth decade.
During the early stages, vague abdominal pain goes undiagnosed and invariably is ascribed to irritable bowel or spastic colon. At least one-third of patients with small bowel carcinoid tumors experience several years of intermittent abdominal pain before diagnosis. This pain can be due to obstruction (partial or intermittent) or to the development of intestinal angina, which in turn, may be due to bowel ischemia, especially in the postprandial period. Carcinoid tumors can present in a variety of ways. For example, duodenal tumors are known to produce gastrin and may present with the gastrinoma syndrome.

One of the more clinically useful classifications of carcinoid tumors is according to the classification of the primitive gut from which the tumor cells arise. These tumors derive from the stomach, foregut, midgut, and hindgut (Table 1-3).

Table 1-3. Clinical and Biochemical Characteristics of Carcinoid Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>Origin</th>
<th>Clinical Characteristics</th>
<th>Biochemical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>Primary</td>
<td>Same as foregut</td>
<td>Same as foregut</td>
</tr>
<tr>
<td></td>
<td>Secondary to achlorhydria</td>
<td>Pernicious anemia, atrophic gastritis, gastric polyps, gastrin &lt;1000 pg/mL</td>
<td></td>
</tr>
<tr>
<td>Foregut</td>
<td>Atypical carcinoid, ZE, acromegaly, Cushing’s, etc.</td>
<td>5-HTP</td>
<td></td>
</tr>
<tr>
<td>Midgut</td>
<td>Classic carcinoid</td>
<td>Serotonin, substance P, CGRP, kinins, and peptides</td>
<td></td>
</tr>
<tr>
<td>Hindgut</td>
<td>Silent</td>
<td>Nonsecretory</td>
<td></td>
</tr>
</tbody>
</table>
GASTRIC CARCINOID

There are three types of gastric carcinoid tumors:

1. **Type 1 gastric carcinoids** are associated with achlorhydria, high gastrin levels, and multiple, small, relatively nonaggressive tumors. These tumors are more common in patients with achlorhydria accompanied by pernicious anemia and vitamin B₁₂ deficiency, in which there is loss of gastric acid secretion causing impairment of the normal restraint mechanism suppressing gastrin production. Gastrin is trophic to EC cells in the stomach, and when levels rise above 1000 pg/mL, this constitutes a threshold for the induction of gastric carcinoid polyps and tumors.

2. **Type 2 gastric carcinoids** are associated with elevated gastric acid, high gastrin levels, and the Zollinger-Ellison (ZE) syndrome. These tumors are larger and have a higher propensity to metastasize than type 1 carcinoids of the stomach.

3. **Type 3 gastric carcinoids** are much larger than types 1 and 2 and have a high propensity to metastasize. These tumors are sporadic and may be associated with normal gastrin and gastric acid levels. This type of gastric carcinoid is most likely to cause tumor-related deaths.

The clinical picture of type 1 gastric carcinoid, most commonly identified in a patient with evidence of pernicious anemia, is characterized by the following:

- Premature graying of the hair
- Associated autoimmune disorders
- Antibodies to gastric parietal cells and intrinsic factor
- Achlorhydria or hypochlorhydria
- Neutral pH instead of the normal highly acidic pH
- Serum gastrin level greater than 1000 pg/mL

FOREGUT CARCINOID

Sporadic primary foregut tumors include carcinoids of the bronchus, stomach, first portion of the duodenum, pancreas, and ovaries. Midgut carcinoid tumors derive from the second portion of the duodenum, the jejunum, the ileum, and the right colon. Hindgut carcinoid tumors include those of the transverse colon, left colon, and rectum. This distinction assists in distinguishing a number of important biochemical and clinical differences among carcinoid tumors because the presentation, histochemistry, and secretory products are quite different (see Table 1-2). Foregut carcinoids are argentaffin negative. They have a low content of serotonin (5-hydroxytryptamine [5-HT]). They often secrete the serotonin precursor 5-hydroxytryptophan (5-HTP), histamine, and a multitude of polypeptide hormones. Their functional manifestations include carcinoid syndrome, gastrinoma syndrome, acromegaly, Cushing’s disease, and a number of other endocrine disorders. Furthermore, they are unusual in that flushing tends to be of protracted duration, is often purplish or violet instead of the usual pink or red, and frequently results in telangiectasia and hypertrophy of the skin of the face and upper neck. The face may assume a leonine appearance after repeated episodes. It is not unusual for these tumors to metastasize to bone.
Midgut Carcinoid

Midgut carcinoids, in contrast, are argentaffin positive, have high serotonin content, rarely secrete 5-HP, and often produce a number of other vasoactive compounds such as kinins, prostaglandins (PGs), and substance P. The clinical picture that results is the classic carcinoid syndrome of flushing and diarrhea with or without wheezing. These tumors may produce adrenocorticotropic hormone (ACTH) on rare occasions and infrequently metastasize to bone.

Hindgut Carcinoid

Hindgut carcinoids are argentaffin negative, rarely contain serotonin, rarely secrete 5-HTP or other peptides, and usually are silent in their presentation. However, they may metastasize to bone. A further point of interest is that a gender variation is present when a carcinoid tumor coexists with MEN-I; more than two-thirds of the time the tumor is in the thymus in males, whereas in females, more than 75% of the time it is in the lung.

What to Look For

Distinguishing Signs and Symptoms

The major clinical manifestations of carcinoid tumors include the following:

- Cutaneous flushing (84%)
- GI hypermotility with diarrhea (70%)
- Heart disease (37%)
- Bronchial constriction/wheezing (17%)
- Myopathy (7%)
- Abnormal increase in skin pigmentation (5%)

Assessment of the concurrence of the two major symptoms of carcinoid tumors reveals that flushing and diarrhea occur simultaneously in 58% of cases, diarrhea without flushing in 15%, flushing without diarrhea in 5%, and neither flushing nor diarrhea as a symptom complex in 22%. The natural history of these tumors is illustrated in Figure 1-4. Invariably the patient has a long history of vague abdominal symptoms, a series of visits to his or her primary care practitioner, and referral to a gastroenterologist, often with a misdiagnosis of irritable bowel syndrome (IBS). These symptoms persist with a median latency to correct diagnosis of 9.2 years by which time the tumor has metastasized, causing flushing and diarrhea and progressing on its slow but relentless course until the patient dies. Clearly, a greater index of suspicion and a carcinoid tumor profile screen is warranted for all patients presenting with “traditional IBS symptoms.” The diagnosis of metastases to the liver is generally more obvious but often still takes place only after a delay of many years. Even then, an incorrect diagnosis is not uncommon. Unless biopsy material is examined for the secretory peptide chromogranin, synaptophysin, or neuron-specific enolase (NSE), tumors may be labeled erroneously as adenocarcinoma, with a negative impact on physicians’ attitudes regarding management and underestimation of prospects for survival.
Chromogranins belong to a unique family of secretory chromogranin and secretogranin proteins. Chromogranin A (CGA) is an acidic protein co-released with catecholamines during exocytosis from sympathetic nerve terminals and chromaffin cells.

Chromogranin A determination for diagnosis and follow-up in patients with gastroenteropancreatic endocrine tumors (GEP-ET) and MEN-I is considered the standard of care in many institutions. Although the absolute value of a single measurement of CGA is not a determinate of tumor bulk nor the presence or absence of metastasis, the trend in serial CGA levels over time has been proven to be a useful predictor of tumor growth. Changes in CGA levels of more than 25% over baseline are considered significant.

Serial measurements (every 3 to 6 months) of CGA levels in blood can be used to monitor the progression of a variety of gut-derived NETs. Serum CGA level is also an effective tumor marker in patients with pheochromocytoma. Increased levels strongly correlate with tumor mass. The concordance between CGA level and the results of iodine-131 meta-iodobenzylguanidine (131I-MIBG) scintigraphy is high. A CGA level in the reference range is highly predictive of normal scintigraphy findings.

CGA levels may also be elevated in several other endocrine and nonendocrine diseases. It is well known that drugs that suppress gastric acid secretion can increase gastrin levels. Proton-pump inhibitors (PPI) are extensively used to treat patients with ZE syndrome, gastroesophageal reflux disease (GERD) or acid–peptic disease, but their long-term use can cause significant increases in gastrin levels and cause hypertrophy of the EC cells of the stomach. Enterochromaffin-like (ECL) cell hyperplasia secondary
to hypergastrinemia also leads to increased levels of CGA in blood. Treatment with inhibitors of acid secretion, atrophic gastritis, and infection with *Helicobacter pylori* are common conditions leading to hypergastrinemia. These ECL cells are the precursor cells for the development of gastric carcinoids. An increase in CGA levels quickly follows the start of low dosages of PPI. Chronic high-dose PPI use can cause persistent elevations of CGA levels for months after discontinuing PPI therapy.

Renal insufficiency and severe hypertension have been associated with increases in CGA levels. Although antihypertensive drugs do not commonly interfere with the analysis of CGA levels, some false-positive results occur in the presence of renal impairment, hypergastrinemia, corticosteroid therapy, and the use of PPI. CGA has a circadian rhythm unrelated to plasma catecholamines; thus, collection of blood for serial measurement of CGA levels should be done at approximately the same time of day.

**The Next Step**

**Diagnosis**

The diagnosis of carcinoid tumors rests on a strong clinical suspicion in patients who present with flushing, diarrhea, wheezing, myopathy, and right-sided heart disease and includes appropriate biochemical confirmation and tumor localization studies.

**Biochemical Studies**

The rate-limiting step in carcinoid tumors for the synthesis of serotonin is the conversion of tryptophan into 5-HTP, catalyzed by the enzyme tryptophan hydroxylase. In midgut tumors, 5-HTP is rapidly converted to serotonin by the enzyme aromatic amino acid decarboxylase (dopa-decarboxylase). Serotonin is either stored in the neurosecretory granules or may be secreted directly into the vascular compartment. Most of the secreted serotonin is taken up by platelets and stored in their secretory granules. The rest remains free in the plasma, and circulating serotonin is then largely converted into the urinary metabolite 5-hydroxyindoleacetic acid (5-HIAA) by the enzymes monoamine oxidase and aldehyde dehydrogenase. These enzymes are abundant in the kidney, and the urine typically contains large amounts of 5-HIAA.

In patients with foregut tumors, the urine contains relatively little 5-HIAA but large amounts of 5-HTP. It is presumed that these tumors are deficient in dopa-decarboxylase; this deficiency impairs the conversion of 5-HTP into serotonin, leading to 5-HTP secretions into the vascular compartment. Some 5-HTP, however, is converted to serotonin and 5-HIAA, producing modest increases in levels of these metabolites. The normal range for 5-HIAA secretion is 2 to 8 mg per 24 hours, and the quantitation of serotonin and all of its metabolites usually permits the detection of 84% of patients with carcinoid tumors. No single measurement detects all cases of carcinoid syndrome, although the urine 5-HIAA appears to be the best screening procedure. Other peptides involved include substance P, neuropeptide K, pancreatic polypeptide (PP), and CGA.
Neuroendocrine tumors are characterized by their capacity to synthesize, store, and release hormonal products. These substances are stored in neurosecretory vesicles together with CGA. The concentration of CGA in plasma is thought to reflect the neuroendocrine differentiation of the tumor and the total tumor burden as well as to be useful as a means of measuring response to treatment. The “value” of CGA for diagnosis and follow-up of NETs has a sensitivity of 62.9% with specificity of 98.4%; levels are higher in secreting versus nonsecreting tumors (7% vs 45%) and are related to the extent of metastases. In nonsecreting tumors, the positive predictive value for the presence of metastases is 100%, but the negative predictive value is only 50%. In MEN-I, a high value predicts the presence of a pancreatic tumor with 100% specificity, but the sensitivity is only 59%. During follow-up, the concordance of tumor growth and CGA is 80%, better than that with serotonin (81% vs 54%). Thus, owing to its high specificity, CGA determination may help to discriminate the endocrine character of an NET and to establish a pancreatic tumor in MEN-I syndrome. Serial measurements are also useful for evaluating response to treatment.

Figure 1-5 shows the percent positivity of CGA versus 5-HIAA in the different carcinoids. CGA is positive 80% to 100% of the time in fore-, mid-, and hindgut tumors, whereas 5-HIAA detects a little more than 70% of midgut tumors, reveals only 30% of foregut tumors, and fails to recognize the presence of a hindgut carcinoid tumor. Evaluating PP levels in conjunction with CGA levels may further enhance this sensitivity. Both markers were measured in 68 patients (28 functioning and 40 nonfunctioning tumors). CGA sensitivity was 96% in functioning tumors and 75% in nonfunctioning tumors, and 74% in pancreatic and 91% in gastrointestinal tumors. Specificity was 89%.

In contrast to CGA alone, PP sensitivity for NETs was approximately 50%, but combining the two markers increased sensitivity for all tumors to greater than 95%. More specifically, the gain in detection of pancreatic tumors was 93% with CGA and PP versus 68% using CGA alone. It seems reasonable to recommend using both markers under these circumstances. There are, however, always caveats. Gastric parietal cell antibodies neutralize acid secretion thereby unbridling the G cell to produce gastrin that is trophic to the gastric ECL cells. Following a period of progressive hypertrophy, these ECL cells can transform into gastric carcinoid. Measurement of gastrin and CGA, but not NSE and 5-HIAA, is a means of evaluating the ECL mass. This is particularly useful in therapeutic decision-making with regard to doing an antrectomy or simply following conservatively and removing carcinoid polyps as they arise. Of course, this raises the issue of whether reported elevations in CGA in people taking PPI are truly false-positive or reflect ECL hyperplasia. Nonetheless, all evidence points to the combined measurement of the following markers:

- CGA
- PP
- Gastrin
- Gastric pH

These measurements are a very effective means of discovering a NET, identifying its probable site of origin, and monitoring response to intervention. In carcinoid tumors, neurotensin is elevated in 43% of patients, substance P in 32%, motilin in 14%, somatostatin in 5%, and vasoactive intestinal peptide (VIP) rarely.

Common amines and peptides produced by carcinoids that cause symptoms are as follows:

- Serotonin
- Histamine
- Substance P

The following constitute the best clinical practice panel of markers for diagnosis and follow-up of carcinoid tumors:

- CGA
- 5-HIAA
- Gastrin
- Serotonin
- Pancreastatin
- Neurokinin A (NKA; substance K)

In patients who are not responding to octreotide clinically or biochemically or in those who exhibit tumor progression, measurement of the octreotide level will help determine appropriateness of drug dosing. Quantification of plasma hormonal responses to octreotide suppression may help in the prediction of long-term responses to therapy.
ICD-9 CODE: Carcinoid Syndrome 259.2

ICD-9 CODES for Carcinoid Primary Tumor Sites

<table>
<thead>
<tr>
<th>Foregut</th>
<th>Malignant</th>
<th>Benign</th>
<th>Uncertain Behavior</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>152.0</td>
<td>211.2</td>
<td>235.2</td>
<td>239.0</td>
</tr>
<tr>
<td>Lung</td>
<td>162.9</td>
<td>212.3</td>
<td>235.7</td>
<td>239.1</td>
</tr>
<tr>
<td>Stomach</td>
<td>151.9</td>
<td>211.1</td>
<td>235.2</td>
<td>239.0</td>
</tr>
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ICD-9 CODES for Carcinoid Metastatic Sites

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(See Carcinoid Follow-Up Profile [Chapter 4] and Flushing Syndrome Tests [Chapter 4] for specific tests and CPT codes)
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

Insulinomas
The classic description of insulinoma is of Whipple’s triad, which includes symptoms of hypoglycemia with a low blood glucose concentration relieved by the ingestion of glucose. These tumors are most commonly benign (90%) and can be located anywhere within the pancreas. Insulinomas are associated with a memory rule known as “the rule of tens,” which refers to the following characteristics: 10% are malignant; 10% are ectopic; and 10% are related to the MEN-I syndrome. Removal of the tumor, which is invariably in the pancreas, is curative in more than 90% of cases.

Adult-onset nesidioblastosis is a rare condition in which islets become hypertrophied and produce excess insulin. The diagnostic differentiation of an insulinoma from adult-onset nesidioblastosis is possible only by histologic evaluation of sufficient pancreatic tissue; fine needle biopsy does not obtain a specimen of adequate quantity. In the newborn, hypoglycemia and excess insulin production can be caused by nesidioblastosis; insulinomas are rare in this age group.

What to Look For

Distinguishing Signs and Symptoms
The major symptoms of an insulinomas are those of hypoglycemia, which can be adrenergic:

• Nervousness
• Sweating
• Palpitations
• Diaphoresis (profuse sweating)
• Circumoral tingling

Central nervous system symptoms include the following:

• Blurred vision
• Confusion
• Disorientation
• Memory loss leading to coma
• Stupor
• If chronic, dementia

The Next Step
The blood glucose level alone is not diagnostic for insulinoma, nor in general is the absolute insulin level elevated in all cases of organic hyperinsulinism (see Hypoglycemia in Chapter 2). The standard diagnostic test remains a 72-hour fast while the patient is closely observed. More than 95% of cases can be diagnosed based on their response to this test. Serial glucose and insulin levels are obtained every 4 hours over the 72-hour period until the patient becomes symptomatic. When symptoms occur, obtain insulin, glucose, and C-peptide levels. Because the absolute insulin level is not elevated in all patients with insulinomas, a normal level does not rule out the disease; however, a
fasting insulin level of greater than 24 µU/mL is found in approximately 50% of patients with insulinoma. This is strong evidence in favor of the diagnosis. Values of insulin greater than 7 µU/mL after a more prolonged fast in the presence of a blood glucose level less than 40 mg/dL are also highly suggestive. A refinement in the interpretation of glucose and insulin levels has been established by determining the ratio of insulin levels in microunits per milliliter to the concomitant glucose level in milligrams per deciliter. An insulin/glucose ratio greater than 0.3 has been found in virtually all patients proven to have an insulinoma or other islet cell disease causing organic hyperinsulinism. Calculating the amended insulin/glucose ratio as follows can increase the accuracy of the test:

\[
\text{amended ratio} = \frac{\text{insulin (µU/mL)}}{\text{glucose (mg/dL)}} - 30 \text{ normal } <50
\]

If the amended ratio is greater than 50, then organic hyperinsulinism is certain. Measurements of proinsulin and C-peptide have proven to be valuable in patients suspected of having organic hypoglycemia. Normally, the circulating proinsulin concentration accounts for less than 22% of the insulin immunoreactivity but is greater than 24% in more than 90% of individuals with insulinomas. Furthermore, a proinsulin level greater than 40% is highly suspicious for a malignant islet cell tumor. The C-peptide level is useful in ruling out fictitious hypoglycemia from self-administration of insulin. Commercial insulin preparations contain no C-peptide, and combined with high insulin levels, low C-peptide levels confirm the diagnosis of self-administration of insulin. High-performance liquid chromatography to characterize the insulin species found in the blood was useful before the advent of recombinant human insulin, which is not distinguishable from native insulin. Patients who take sulfonylureas surreptitiously may have increased insulin and C-peptide values soon after ingestion, but chronic use will result in hypoglycemia without increased insulin or C-peptide levels. Only an index of suspicion and measurement of urine sulfonylureas will lead to the correct diagnosis. A variety of insulin stimulation and suppression tests were used before precise and accurate insulin measurements were available. Each had its limitations, and all are currently considered obsolete. The insulin response to secretin stimulation (2 U/kg intravenously; peak response in 1–5 minutes) is a valuable measure to differentiate multiple adenomas from nesidioblastosis and single adenomas. The normal maximal increase is 74 µU/mL, whereas in single adenomas it is only 17 µU/mL, in nesidioblastosis it is 10 µU/mL, and in two patients with multiple B-cell adenomas and hyperplasia, the increases were 214 and 497 µU/mL. Patients with single adenomas and nesidioblastosis do not respond to secretin, whereas those with multiple adenomas or hyperplasia have an excessive insulin response to the administration of secretin.

**Hormones and Peptides**

- Insulin
- Proinsulin
- C-peptide
The standard diagnostic test is a 72-hour fast while the patient is closely observed. More than 95% of cases can be diagnosed based on responses to a 72-hour fast (see 72-Hour Supervised Fast for the Diagnosis of Insulinoma, Chapter 5). Symptomatic hypoglycemia must be accompanied by a correspondingly low blood glucose value (<50 mg/dL) with relief of symptoms by the administration of glucose.

ICD-9 CODE: Insulinomas M8151/0
Malignant (M8151/3)
  Pancreas 157.4
  Unspecified site 157.4
  Specified site--see Neoplasm by site, malignant
Benign, unspecified site 211.7
Uncertain behavior, neoplasm of pancreas 235.5

ICD-9 CODES for Primary Islet Cell Sites

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<th>Benign</th>
<th>Uncertain Behavior</th>
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ICD-9 CODES for Metastatic Sites

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<td>Brain</td>
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(See 72-Hour Supervised Fast for the Diagnosis of Insulinoma [Chapter 5], Oral Glucose Tolerance Test for Diabetes, Insulinoma, Impaired Glucose Tolerance, Metabolic Syndrome, PCOS, Reactive Hypoglycemia, and Acromegaly [Chapter 5], Diabetes Type 1 Screen [Chapter 4], and Hypoglycemia/Insulinoma Screening Test [Chapter 4] for specific tests and CPT codes)
Glucagonoma Syndrome

In 1966, McGavran and colleagues called attention to a syndrome that included acquired diabetes and glucagon-producing tumors. Because these tumors usually were accompanied by a very characteristic skin rash, the syndrome is also known as the 4D syndrome, which stands for dermatosis, diarrhea, deep venous thrombosis (DVT), and depression.

What to Look For

Distinguishing Signs and Symptoms

- Characteristic rash (necrolytic migratory erythema [NME]) (82%)
- Painful glossitis
- Angular stomatitis
- Normochromic normocytic anemia (61%)
- Weight loss (90%)
- Mild diabetes mellitus (80%)
- Hypoaminoacidemia
- DVT (50%)
- Depression (50%)

In a study of 1366 consecutive adult autopsies, a tumor frequency of 0.8% was found. All tumors were adenomas, and all contained histochemically defined glucagon cells. None of the tumors had been suspected during life. Although these adenomas contained glucagon, it is not known whether they were overproducing or even secreting glucagon. The incidence in vivo is probably 1% of all NETs.

Features of the Necrolytic Migratory Erythematous Rash

The NME rash of the glucagonoma syndrome has a characteristic distribution. It usually is widespread, but major sites of involvement are the perioral and perigenital regions along with the fingers, legs, and feet. It may also occur in areas of cutaneous trauma. The basic process in the skin seems to be one of superficial epidermal necrosis, fragile blister formation, crusting, and healing with hyperpigmentation. Skin biopsy specimens usually show small bullae containing acantholytic epidermal cells as well as neutrophils and lymphocytes. The adjacent epidermis usually is intact, and the dermis contains a lymphocytic perivascular infiltrate. Different stages of the cutaneous lesions may be present simultaneously. Biopsy examination of a fresh skin lesion may be the most valuable aid in suggesting the diagnosis of glucagonoma syndrome, but repeated biopsy samples may be necessary to confirm the diagnosis. A painful glossitis manifested by an erythematous, mildly atrophic tongue has been associated with the cutaneous lesions.

Two other features of the syndrome are noteworthy:

1. A high rate of thromboembolic complications, particularly pulmonary embolism and the unexplained occurrence of arterial thrombosis. Unexplained thromboembolic disease should alert one to the possibility of glucagonoma. (In some studies, anticoagulation therapy with warfarin has been ineffective). Most
authors recommend heparin-based therapy for patients with this complication of glucagonoma.

2. Depression and other psychiatric disturbances.

Other metabolic disorders associated with cutaneous lesions may closely resemble the NME of the glucagonoma syndrome. These include:

- Acrodermatitis enteropathica
- Zinc deficiency induced by hyperalimentation
- Essential fatty acid deficiency
- Dermatosis of protein calorie malnutrition of kwashiorkor
- Pellagra resulting from niacin deficiency

Cutaneous manifestations associated with malabsorptive states often are nonspecific, affecting approximately 20% of patients with steatorrhea.

**Glucose Intolerance**

Glucose intolerance in the glucagonoma syndrome may relate to tumor size. Fasting plasma glucagon levels tend to be higher in patients with large hepatic metastases than in those without hepatic metastases, and all patients with large hepatic metastases have glucose intolerance. Massive hepatic metastases may decrease the ability of the liver to metabolize splanchnic glucagon, thus increasing peripheral plasma glucagon levels. Glucagon may not directly induce hyperglycemia, however, unless metabolism of glucose by the liver is directly compromised.

**The Next Step**

Measure plasma glucagon concentrations by radioimmunoassay. In patients with glucagonomas, fasting plasma glucagon concentrations may be as high as 2100 ± 334 pg/mL. These levels are markedly higher than those reported in normal, fasting subjects (i.e., <150 pg/mL) or in those with other disorders causing hyperglucagonemia, including diabetes mellitus, burn injury, acute trauma, bacteremia, cirrhosis, renal failure, or Cushing’s syndrome, in which fasting plasma glucagon concentrations often are elevated but remain less than 500 pg/mL.

**Hormones and Peptides**

As with other islet cell neoplasms, glucagonomas may overproduce multiple hormones:

- Glucagon
- Insulin
- CGA
- PP
- Parathyroid hormone (PTH)
- Substances with PTH-like activity
- Gastrin
- Serotonin
- VIP and melanocyte-stimulating hormone (MSH), in that order of frequency

Measure the following:

- Plasma glucagon
- Insulin
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- ACTH, PP
- Gastrin
- Serotonin
- VIP
- PTH
- Parathyroid hormone–related peptide (PTHrP)

ICD-9 CODE: Glucagonoma

Malignant
- Pancreas 157.4
- Specified site–see Neoplasm by site, malignant

Benign
- Pancreas 211.7
- Unclassified behavior, neoplasm of the pancreas 235.5

ICD-9 CODES for Primary Islet Cell Tumor Sites

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ICD-9 CODES for Islet Cell Tumor Metastatic Sites

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(See Glucagon [Chapter 3] and GI–Neuroendocrine Tests (Chapter 4) for specific tests and CPT codes)

Reference

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A Comprehensive Guide to Diagnosis and Management

SOMATOSTATINOMA

Somatostatin (somatotropin release–inhibiting factor [SRIF]) is a tetradecapeptide that inhibits numerous endocrine and exocrine secretory functions. Almost all gut hormones that have been studied are inhibited by SRIF, including insulin, PP, glucagon, gastrin, secretin, gastric inhibitory polypeptide (GIP), and motilin. In addition to inhibition of the endocrine secretions, SRIF has direct effects on a number of target organs. For example, it is a potent inhibitor of basal and PG-stimulated gastric acid secretion. It also has marked effects on GI transit time, intestinal motility, and absorption of nutrients from the small intestine. The major effect in the small intestine appears to be a delay in the absorption of fat and reduced absorption of calcium.

What to Look For

Distinguishing Signs and Symptoms

The salient features of the somatostatinoma syndrome are as follows:

- Diabetes
- Diarrhea/steatorrhea
- Gallbladder disease (cholelithiasis and dysmotility)
- Hypochlorhydria
- Weight loss

Diagnostic Markers

Plasma Somatostatin-Like Immunoreactivity

The mean somatostatin-like immunoreactivity (SLI) concentration in patients with pancreatic somatostatinoma was 50 times higher than normal (range, 1–250 times). Intestinal somatostatinomas, however, present differently and have only slightly elevated or normal SLI concentrations (Table 1-4).

Table 1-4. Comparison of Pancreatic and Intestinal Somatostatinoma

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<th>Intestinal Somatostatinoma</th>
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<tr>
<td>SLI</td>
<td>50x higher than normal (range, 1–250 times)</td>
<td>SLI slightly elevated or normal</td>
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<td>75% of patients have diabetes</td>
<td>11% of patients have diabetes</td>
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</tr>
<tr>
<td>Tumors are large and destroy part of pancreas</td>
<td>Tumors are relatively small</td>
<td></td>
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<tr>
<td>59% of patients have gallbladder disease</td>
<td>27% of patients have gallbladder disease</td>
<td></td>
</tr>
<tr>
<td>Diarrhea and steatorrhea are common</td>
<td>Diarrhea and steatorrhea are rare</td>
<td></td>
</tr>
<tr>
<td>Weight loss in one third of patients</td>
<td>Weight loss in one fifth of patients</td>
<td></td>
</tr>
<tr>
<td>Acid secretion inhibited in 87% of patients</td>
<td>Acid secretion inhibited in 12% of patients</td>
<td></td>
</tr>
<tr>
<td>Café-au-lait spots</td>
<td>Neurofibromatosis</td>
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<td>Paroxysmal hypertension</td>
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</table>
Chapter 1 - Diagnosing and Treating Gastroenteropancreatic Tumors, Including ICD-9 Codes

The Next Step

Diabetes Mellitus
When pancreatic and intestinal tumors result in diabetes, the diabetes is relatively mild and can usually be controlled by diet with or without oral hypoglycemic agents or by small doses of insulin. It is not clear, however, whether the differential inhibition of insulin and diabetogenic hormones can explain the usually mild degree of diabetes and the rarity of ketoacidosis in patients with somatostatinoma. Replacement of functional islet cell tissue by pancreatic tumor may be another reason for the development of diabetes in most patients with pancreatic somatostatinoma, contrasting with the low incidence of diabetes in patients with intestinal tumors. Pancreatic tumors are usually large and therefore destroy substantial portions of the organ.

Gallbladder Disease
The high incidence of gallbladder disease in patients with somatostatinoma and the absence of such an association in any other islet cell tumor suggest a causal relation between gallbladder disease and somatostatinoma. Infusion of somatostatin into normal human subjects has been shown to inhibit gallbladder emptying, suggesting that somatostatin-mediated inhibition of gallbladder emptying (dysmotility) may cause the observed high rate of gallbladder disease in patients with somatostatinoma. This theory is supported by the observation of massively dilated gallbladders without stones or other pathology in patients with somatostatin-secreting tumors.

Diarrhea and Steatorrhea
Diarrhea consisting of 3 to 10 frequently foul-smelling stools per day and/or steatorrhea of 20 to 76 g of fat per 24 hours is common in patients with pancreatic somatostatinoma, even with a controlled amount of fat in the diet. This could result from the effects of high levels of somatostatin within the pancreas serving as a paracrine mediator to inhibit exocrine secretion or, alternatively, from duct obstruction caused by the somatostatinoma. In some cases, the severity of diarrhea and steatorrhea parallels the course of the disease, worsening as the tumor advances and metastatic disease spreads and improving after tumor resection. Somatostatin has been shown to inhibit the pancreatic secretion of proteolytic enzymes, water, bicarbonate, and gallbladder motility. In addition, it inhibits the absorption of lipids. All but 1 patient with diarrhea and steatorrhea have had high plasma somatostatin concentrations. The rarity of diarrhea and/or steatorrhea in patients with intestinal somatostatinomas may result from the lower SLI levels seen in patients with that condition.

Hypochlorhydria
Infusion of somatostatin has been shown to inhibit gastric acid secretion in human subjects. Thus, hypochlorhydria in patients with somatostatinoma, in the absence of gastric mucosal abnormalities, is likely to result from elevated somatostatin concentrations. Basal and stimulated acid secretion was inhibited in 87% of patients with pancreatic tumors tested but in only 12% of patients with intestinal tumors.
**Weight Loss**

Weight loss ranging from 9 to 21 kg over several months occurred in one third of patients with pancreatic tumors and one fifth of patients with intestinal tumors. The weight loss may relate to malabsorption and diarrhea, but in small intestinal tumors, anorexia, abdominal pain, and yet unexplained reasons may be relevant.

**Associated Endocrine Disorders**

Approximately 50% of all patients have other endocrinopathies in addition to their somatostatinoma. Occurrence of MEN-I has been recognized in patients with islet cell tumors, and MEN-II or MEN-III syndromes are present in association with pheochromocytomas and neurofibromatosis, respectively. It seems that an additional dimension of the duct-associated tumors is MEN-II. Secretion of different hormones by the same islet cell tumor, sometimes resulting in two distinct clinical disorders, is now being recognized with increasing frequency. These possibilities should be considered during endocrine workups of patients with islet cell tumors and their relatives.

**Tumor Location**

Of the reported primary tumors, 60% were found in the pancreas and 40% in the duodenum or jejunum. Of the pancreatic tumors, 50% were located in the head, and 25% in the tail, and the remaining tumors either infiltrated the whole pancreas or were found in the body. Regarding extrapancreatic locations, approximately 50% originate in the duodenum, approximately 50% originate in the ampulla, and rarely one is found in the jejunum. Thus, approximately 60% of somatostatinomas originate in the upper intestinal tract, probably a consequence of the relatively large number of delta (somatostatin) cells in this region.

**Tumor Size**

Somatostatinomas tend to be large, similar to glucagonomas but unlike insulinomas and gastrinomas, which, as a rule, are small. Within the intestine, tumors tend to be smaller than somatostatinomas located elsewhere. Symptoms associated with somatostatinomas and glucagonomas are less pronounced and probably do not develop until very high blood levels of the respective hormones have been attained. As a result, somatostatinomas and glucagonomas are likely to be diagnosed late in the course of the disease.

**Incidence of Malignancy**

Eighty percent (80%) of patients with pancreatic somatostatinomas had metastases at diagnosis, and 50% with intestinal tumors had evidence of metastatic disease. Metastasis to the liver is most frequent, and regional lymph node involvement and metastases to bone are less so. Thus, in approximately 70% of cases, metastatic disease is present at diagnosis. This is similar to the high incidence of malignancy in glucagonoma and in gastrinoma, but it is distinctly different from the low incidence of malignant insulinoma. The high prevalence of metastatic disease in somatostatinoma also may be a consequence of late diagnosis but apparently is not dependent on the tissue of origin.
Somatostatin-Containing Tumors Outside the GI Tract

Somatostatin has been found in many tissues outside the GI tract. Prominent among those are the hypothalamic and extrahypothalamic regions of the brain, the peripheral nervous system (including the sympathetic adrenergic ganglia), and the C cells of the thyroid gland. Not surprisingly, therefore, high concentrations of somatostatin have been found in tumors originating from these tissues. Some patients exhibited the clinical somatostatinoma syndrome.

Elevated plasma SLI concentrations also have been reported in patients with small cell lung cancer. In one patient with metastatic bronchial oat cell carcinoma, the tumor caused Cushing’s syndrome, diabetes, diarrhea, steatorrhea, anemia, and weight loss, and the patient had a plasma SLI concentration 20 times greater than normal. A patient with a bronchogenic carcinoma presenting with diabetic ketoacidosis and high levels of SLI (>5000 pg/mL) has been reported. Pheochromocytomas and catecholamine-producing extra-adrenal paragangliomas are other examples of endocrine tumors that produce and secrete somatostatin in addition to other hormonally active substances. One fourth of 37 patients with pheochromocytomas had elevated SLI levels.

Tumors are identified as somatostatinomas by the demonstration of elevated tissue concentrations of SLI and/or prevalence of D cells by immunocytochemistry or demonstration of elevated plasma SLI concentrations. Thus, events leading to the diagnosis of somatostatinoma usually occur in reverse order. In other islet cell tumors, the clinical symptoms and signs usually suggest the diagnosis, which then is established by demonstration of diagnostically elevated blood hormone levels, following which efforts are undertaken to localize the tumors.

The diagnosis of somatostatinoma at a time when blood SLI concentrations are normal or only marginally elevated, however, requires reliable provocative tests. Increased plasma SLI concentrations have been reported after intravenous infusion of tolbutamide and arginine, and decreased SLI concentrations have been observed after intravenous infusion of diazoxide. Arginine is a well-established stimulant for normal D cells and thus is unlikely to differentiate between normal and supranormal somatostatin secretion. The same may be true for diazoxide, which has been shown to decrease SLI secretion from normal dog pancreas as well as in patients with somatostatinoma. Tolbutamide stimulates SLI release from normal dog and rat pancreas, but no change was found in circulating SLI concentrations of three healthy human subjects after intravenous injection of 1 g of tolbutamide. Therefore, at present, tolbutamide appears to be a candidate for a provocative agent in the diagnosis of somatostatinoma, but its reliability must be established in a greater number of patients and controls. Until then, it may be necessary to measure plasma SLI concentrations during routine workups for postprandial dyspepsia and gallbladder disorders, for diabetes in patients without a family history, and for unexplained steatorrhea, because these findings can be early signs of somatostatinoma. Tolbutamide infusions are considered to have significant risks and should only be administered under strict medical observation.
IDC-9 CODE: Somatostatinoma (No Single Code; See Below for Individual Sites)

IDC-9 CODE: Malignant Neoplasm of the Pancreas, Producing Insulin, Somatostatin, and Glucagon
  Islets of Langerhans 157.4

IDC-9 CODE: Malignant Neoplasm of the Intestine
  Intestinal tract, part unspecified 159.0
  Uncertain behavior, neoplasm of the intestine 235.2

IDC-9 CODE: Diabetes
  Type 1 (not specified as uncontrolled) 250.01
  Type 1 (uncontrolled) 250.03
  Type 2 (or unspecified) 250.00
  Type 2 (uncontrolled) 250.02
  Hypoglycemia 250.8

ICD-9: CODE: Hypoglycemia 251.1

ICD-9 CODE: Reactive Hypoglycemia 251.2

IDC-9 CODE: Gallbladder Disease 575.9
  Congenital 751.60

ICD-9 CODE: Diabetes 787.91

ICD-9 CODE: Functional 564.5

ICD-9 CODE: Achlorhydric 536.0

ICD-9 CODE: Hypochlorhydria 536.8
  Neurotic 306.4
  Psychogenic 306.4

ICD-9 CODES for Primary Islet Cell Tumor Sites

<table>
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<tr>
<th>Sites</th>
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ICD-9 CODES for Metastatic Sites

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<td>Brain</td>
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</table>

*(See Somatostatin [Somatotropin Release–Inhibiting Factor (SRIF)] [Chapter 3] for specific tests and CPT codes)*
PPOMA

Pancreatic polypeptide (PP) was discovered in 1972 by Chance and colleagues. These authors discovered and purified a single protein peak from a crude insulin preparation. In mammals, 93% of the cells producing PP are located in the pancreas. Meal ingestion, cerebral stimulation, and hormone administration have dramatic effects on circulating levels of PP. A biologic role for PP has not been established, however.

What to Look For

Distinguishing Signs and Symptoms

The only physiologic effects of PP that are recognized in humans are the inhibition of gallbladder contraction and pancreatic enzyme secretion. Thus, a tumor deriving from PP cells is expected to be clinically silent, although this is not always the case. For example, a tumor that invaded the bile ducts producing biliary obstruction was found to be a PPoma. It has been suggested that WDHHA, which is seen in GEP endocrine tumors, may have its origin in PP overproduction. The picture is complicated by the fact that mixed tumors, PP-cell hyperplasia in association with other functioning islet cell tumors, ductal hyperplasia of PP cells, nesidioblastosis, and multiple islet tumors producing PP also have been described, either alone or as part of the MEN-I syndrome (Table 1-5).

Table 1-5. Coincident Elevations of Pancreatic Polypeptide

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Proportion of Patients With Coincident Elevations</th>
<th>Pancreatic Polypeptide Level in Plasma (pg/mL) or Other Laboratory Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine-secreting tumors</td>
<td>22%&lt;en&gt;77%</td>
<td>&gt;1000</td>
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<tr>
<td>Carcinoid tumors</td>
<td>29%&lt;en&gt;50%</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Adenocarcinomas</td>
<td>53 patients</td>
<td>Not elevated</td>
</tr>
<tr>
<td>Nonfunctional GEP tumors</td>
<td>50%&lt;en&gt;75%</td>
<td>Slightly raised</td>
</tr>
<tr>
<td>Nonfunctional GEP tumors</td>
<td>50%&lt;en&gt;75%</td>
<td>Secretin more elevated</td>
</tr>
</tbody>
</table>

A response of greater than 5000 pg/min/mL (i.e., integrated response) is more than two standard deviations (SD) above that observed in healthy persons. In the absence of factors, such as chronic renal failure, that are known to cause marked elevation of PP levels, a markedly elevated PP level in an older, healthy patient occasionally may indicate a nonfunctioning pancreatic endocrine tumor. Differentiation of a high basal concentration in a healthy person from that appearing in patients with tumor is difficult. It has been suggested that administration of atropine would suppress PP concentrations in healthy subjects and would fail to do so in patients with tumors, but this has not been subjected to extensive examination.
ICD-9 CODE: PPoma (No Single Code; See Below for Individual Sites)

ICD-9 CODES for Primary Islet Cell Tumor Sites

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ICD-9 CODES for Metastatic Sites

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(See Pancreatic Polypeptide [PP] [Chapter 3] and Meal [Sham Feeding] Stimulation for Vagal Integrity [Chapter 5] for specific tests and CPT codes)

Reference

Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

Ghrelinoma

Since its recent discovery, there have been about 650 publications on this peptide, indicating a profound interest in the newest GEP hormone capable of stimulating growth hormone (GH) release by activation of the GH secretogogue type 1a (GHS-R1a) receptor. Ghrelin is the first natural hormone in which a hydroxyl group on one of its serine residues is acylated by n-octanoic acid. This acylation is essential for binding to the GHS-R1a receptor, for the GH-releasing capacity, and also likely for its other actions. Although it has been found to co-segregate with glucagon and insulin by some authors, this is not consistent, and most would agree that its cell of origin in the pancreas constitutes a new cell type.

Ghrelin stimulates the following:
- GH release in animals and humans by acting at both the pituitary and hypothalamic level
- Release of ACTH and prolactin, gastric acid secretion, and intestinal motility
- Gastric motility and gastric acid secretion

Ghrelin regulates the following:
- Energy balance
- Increased appetite and food intake
- Modulation of insulin secretion negatively
- Exertion of a tonic inhibitory role on insulin secretion in animals and humans
- Suppressed by hyperglycemia and insulin, and may, in addition, have a direct role on glycogenolysis

Ghrelin increases the following:
- Blood glucose levels
- Insulin resistance when administered systemically in humans

The expression of ghrelin protein and/or mRNA has recently been identified in almost all gastric and intestinal carcinoids as well as pancreatic NETs. There have been two case reports of ghrelinomas: in one, ghrelin was co-secreted with glucagon in a predominantly glucagon expression syndrome, whereas in the other nonfunctioning tumor, ghrelin levels were greater than 12,000 pM (normal, 300 pM). Despite the 50-fold increase in ghrelin levels, the patient had normal serum GH and insulin-like growth factor type 1 (IGF-1) levels. In this study no attempt was made to distinguish acylated ghrelin from the nonacylated variety, thus all the circulating ghrelin may have indeed been biologically inert.

Based on the physiologic effects of ghrelin, one would expect that the clinical features of a ghrelinoma would include the following:
- Hyperglycemia
- Insulin deficiency
- Insulin resistance
- GH excess
- Increased IGF-1 levels,
- Acromegaly
- Gastric acid hypersecretion
- Intestinal dysmotility
What to Look For

Distinguishing Signs and Symptoms

Ghrelin is a 28–amino acid acylated peptide related to the oxyntomodulin family of intestinal peptides. This peptide was isolated from the X/A-like neuroendocrine cells of the rat and human stomach. It is predominantly produced by the stomach but is also detectable in many other tissues:

- Bowel
- Hypothalamus
- Pituitary
- Pancreas
- Co-segregating with pancreatic alpha cells
- Possibly with pancreatic beta cells

Hormones and Peptides

- Ghrelin
- IGF-1
- CGA

Diagnosis

It seems for now that ghrelin is another hormone produced in almost all GEP NETs; has little, if any, biologic activity; and may be useful as a marker for response to therapy. In terms of screening, ghrelin does not seem to offer a great deal over conventional markers. However, in time it may demonstrate an ability to predict tumors. The initial excitement regarding ghrelin may run a parallel course with the excitement related to the discovery of PP; like PP, ghrelin has since been found to be a nonspecific marker because of its lack of a biologic effect. The difference is that ghrelin has been shown to have many effects when administered in the acylated form, and the increase in the endogenous levels of ghrelin in these tumors may be a variant of the acylated form without biologic activity. This peptide may, however, retain sufficient structural epitopes to be recognized by the antisera to ghrelin. Acylation-specific antisera will help to resolve part of this question.

ICD-9 CODE: Hyperglycemia 790.6
ICD-9 CODE: Diabetes Type I (Insulin Deficiency)
  Not stated as uncontrolled 250.01
  Uncontrolled 250.03
ICD-9 CODE: Dysmetabolic Syndrome X (Insulin Resistance) 277.7
ICD-9 CODE: Acromegaly 253.0
ICD-9 CODE: Gastric Acid Hypersecretion 536.8
ICD-9 CODE: Diarrhea (Intestinal Dysmotility) 787.91
ICD-9 CODE: Carcinoid Syndrome 259.2
ICD-9 CODES for Primary Islet Cell Tumor Sites

<table>
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ICD-9 CODES for Islet Cell Tumor Metastatic Sites

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(See Oral Glucose Tolerance Test for Diabetes, Insulinoma, Impaired Glucose Tolerance, Metabolic Syndrome, PCOS, Reactive Hypoglycemia, and Acromegaly [Chapter 5], MEN Syndrome Screen [Chapter 4], and GI–Neuroendocrine Tests [Chapter 4] for specific tests and CPT codes)
Multiple Endocrine Neoplasia Syndromes

Multiple endocrine neoplasia type I (MEN-I) involves the following:
- Pituitary gland
- Pancreas
- Parathyroid glands

The pituitary tumors are primarily prolactinomas, the pancreatic tumors are PPomas, and the gastrinomas, with rare instances of insulinoma, are more commonly nesidioblastosis or hyperplasia of beta cells and parathyroid hyperplasia rather than adenoma. These tumors are associated with the loss of a tumor suppressor gene on chromosome 11q13. This is the same chromosome on which the insulin gene has been located. It has been suggested, but not proven, that allelic losses in the MEN-I tumor suppressor gene located in the 11q13 region also might be responsible for sporadic parathyroid and pituitary tumors as well as NETs of the stomach, pancreas, and intestine. The few cases of carcinoid tumors studied have not shown losses in the 11q13 region.

Multiple endocrine neoplasia type IIa (MEN-IIa) syndrome is characterized by the occurrence of the following tumors:
- Pheochromocytomas
- Medullary carcinoma of the thyroid (MCT)
- Parathyroid hyperplasia

Multiple endocrine neoplasia type IIb (MEN-IIb), has stigmata of cutaneous and mucosal neuromas and is not associated with parathyroid hyperplasia. MEN-IIa and MEN-IIb and familial MCT are associated with mutations of the RET protooncogene, which is a conventional dominant oncogene located on 10q11.2. Although mutations in this region have been associated with sporadic MCT, the role, if any, of this gene in sporadic GEP tumors is not known. Occasionally there are crossover syndromes in which features of one syndrome occur in the milieu of the other syndrome (e.g., pheochromocytomas appearing in MEN-I).

Diagnosis

Diagnostic tests for the following:
- MCT
- Calcitonin
- Calcium infusion
- RET protooncogene
- Pheochromocytoma
- Vanillyl mandelic acid (VMA), epinephrine, norepinephrine
- Glucagon stimulation
- $^{131}$I-MIBG

ICD-9 CODE: Malignant Neoplasm of the Thyroid Gland 193

ICD-9 CODE: Polyglandular Activity in Multiple Endocrine Adenomatosis 258.0
ICD-9 CODE: Pheochromocytoma (M8700/0)
Malignant (M8700/3)
  Specified site–see Neoplasm by site, malignant
  Unspecified site 194.0
Benign
  Specified site–see Neoplasm by site, benign
  Unspecified site 227.0
Uncertain behavior
  Adrenal neoplasm 239.7
  Neoplasm of bladder 239.4
  Neoplasm of sympathetic nervous system 239.2

ICD-9 CODE: Medullary Carcinoma Thyroid (M8510/3)
With amyloid stroma (M8511/3)
  Specified site, thyroid 193
  Unspecified site 193
With lymphoid stroma (M8512/3)
  Malignant thyroid 193
  Uncertain behavior, neoplasm of thyroid 237.4

ICD-9 CODE: Parathyroid Hyperplasia 252.01

ICD-9 CODES for Primary Islet Cell Tumor Sites

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ICD-9 CODES for Islet Cell Tumor Metastatic Sites

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(See MEN Syndrome Screen [Chapter 4] for specific tests and CPT codes)
NEUROENDOCRINE TUMORS IN CHILDREN

The vast majority of NETs in children are similar to their adult counterparts with the exception of the neuroblastoma, which is unique to infancy and is an aggressive tumor.

CARCINOID

Carcinoid tumors may be the most common NET in childhood. Nearly 15% of carcinoid tumors are found in patients under the age of 25 years. The most common site of carcinoid in children is the appendix, and it often is an incidental finding. Carcinoid may be recognized in adolescents only when it metastasizes. Flushing and diarrhea are common symptoms in healthy children, which makes the diagnosis of carcinoid more difficult.

NEUROBLASTOMA

This tumor may be the second most common NET of childhood, and usually it presents as a mass. It also can present with diarrhea if tumor cells produce VIP. CGA and neuropeptide Y (NPY) levels in blood are helpful for assessing the extent of disease and should be obtained simultaneously with VIP levels. Hypertension also may be seen if catecholamine synthesis is high. Twenty-four–hour urine VMA (and homovanillic acid [HVA]) levels are important screening tests in all neuroblastomas, whether or not hypertension is present. OctreoScan® or 131I-MIBG scan also can be helpful in evaluating extent of disease and may be diagnostic. Biopsy of lymph node, bone marrow, or primary lesion is necessary to confirm the diagnosis.

GASTRINOMA

Diarrhea and peptic ulcer disease are common in children. Gastrinoma is extremely rare in children, but has reported as early as 7 years of age. Normal gastrin levels are similar in children and adults; thus, measuring fasting gastrin levels is an easy and extremely useful test in diagnosing this condition. However, chronic use of PPI can raise gastrin levels, therefore these drugs should be discontinued for at least 72 hours before obtaining blood for measurement of gastrin levels. Note that gastrin levels may remain elevated for several months after discontinuing PPI.

INSULINOMA/NESSIDIOBLASTOSIS

Nesidioblastosis is the result of an overactive pancreas and most often presents at birth with hypoglycemia unresponsive to feeding or intravenous glucose. Neonatal nesidioblastosis, like adult-onset nesidioblastosis, is characterized by islet cell hyperplasia. These hyperplastic islets often vary widely in size. This condition often resolves with close follow-up and octreotide therapy but may resurface when these children reach puberty. Surgical intervention is rarely required. In cases requiring surgery, a subtotal pancreatectomy may be lifesaving. Insulin and C-peptide levels are measured in blood, and normal levels are similar to those in adults. Some of these tumors may be caused by mutations in the sulfonylurea receptor.
Multiple Endocrine Neoplasia

Multiple endocrine neoplasia type I presents in parathyroid, pancreas, and pituitary glands. A family history of MEN-I should prompt genetic screening for all members. MEN-IIa occurs in parathyroid, thyroid, MCT, and adrenal glands (pheochromocytoma), whereas MEN-IIb occurs in MCT, pheochromocytoma, and neural tumors. Family history and blood pressure measurements are the most important screening tools. Children can be tested and a diagnosis made as early as 4 years of age using blood calcitonin levels; the pentagastrin stimulation test, although still available, has now been replaced by genetic screening for the RET protooncogene. Urine catecholamines are also important markers and can be determined using a 24-hour urine test.

Pheochromocytoma

Pheochromocytoma is associated with MEN-IIa and -IIb, von Hippel-Lindau (VHL) syndrome, and neurofibromatosis. The peak incidence occurs between 9 and 12 years of age, nearly 10% of all pheochromocytomas occur in children, and 10% of these are malignant. Headaches, palpitations, diaphoresis, and hypertension are the most common symptoms. Diagnostic testing should include 24-hour urine test for creatinine, VMA, catecholamines, and metanephrine as well as plasma levels of metanephrine and CGA. Since pheochromocytomas can be seen in adolescents and young adults, drug interference with metanephrine testing should be ruled out with a careful history of medication and illicit drug use. False-positive metanephrine tests can be caused by buspirone, benzodiazepines, methyldopa, labetalol, tricyclic antidepressants; levodopa, ethanol, amphetamines, sotalol, and chlorpromazine.

Extra-adrenal pheochromocytomas comprise nearly 25% of pheochromocytomas in children and are characteristic of VHL syndrome. Symptoms are the same as for pheochromocytoma.

Paraganglioma

Extra-adrenal pheochromocytomas comprise nearly 25% of pheochromocytomas in children and are characteristic of VHL syndrome. Symptoms are the same as for pheochromocytoma.
**Munchausen’s by Proxy**

Diarrhea, flushing, sweating, and fatigue are hallmark symptoms of neuroendocrine (carcinoid) tumors; however, each of these symptoms is common in otherwise healthy children and also can be associated with viral infections, topical exposures, and allergies. A parent, relative, or guardian can also easily induce this symptom complex. Diarrhea can be induced with laxatives, and their administration should be ascertained in the screening process. Ricins cause overall irritation of the GI tract, and castor oil induces vomiting as well as some GI upset. These “medicines” can be measured in the stool, and pH and stool electrolytes determined to elucidate their presence.

Flushing is seldom witnessed by medical personnel. It can be caused by allergic reactions, selective serotonin uptake inhibitors such as Zoloft or Prozac, and even by overuse of vitamin A.

Sweating is likewise difficult to provoke in an office setting and thus is seldom witnessed by medical personnel. The sweating associated with Hodgkin’s Disease—described as “drenching”—most often occurs at night. This sweating is easily distinguished from that caused by NETs.

Fatigue is a “soft” symptom that is very difficult to evaluate but is most often the result of too little sleep. Children and adolescents should have 8 to 10 hours of sleep each night—significantly more than most adults require.

Those patients with overly solicitous parents who are extremely knowledgeable about medical terminology and procedures and those patients with a history of multiple professional caregivers should raise the possibility of Munchausen’s by proxy in the differential diagnosis. The availability of medical information on the internet has contributed to this explosion of medical knowledge among lay persons, but in the case of Munchausen’s, important details may be missing from the child’s history that rule against NETs as the true cause of the symptoms.

**ICD-9 CODE: Pheochromocytoma (M8700/0)**
- Malignant (M8700/3)
  - Specified site—see Neoplasm by site, malignant
  - Unspecified site 194.0
- Benign
  - Specified site—see Neoplasm by site, benign
  - Unspecified site 227.0
- Uncertain behavior
  - Adrenal neoplasm 239.7
  - Neoplasm of bladder 239.4
  - Neoplasm of sympathetic nervous system 239.2

**ICD-9 CODE: Insulinoma (M8151/0)**
- Malignant (M8151/3)
  - Pancreas 157.4
Unspecified site 157.4
Specified site—see Neoplasm by site, malignant
Benign, unspecified site 211.7
Uncertain behavior, neoplasm of pancreas 235.5

**ICD-9 CODE: Gastrinoma (M8153/1)**
Malignant (M8153/3)
  Pancreas 157.4
  Specified site—see Neoplasm by site, malignant
  Unspecified site 157.4
  Specified site—see Neoplasm by site, uncertain behavior
Benign, unspecified site 235.5
Uncertain behavior, neoplasm of pancreas 235.5

**ICD-9 CODE: Neuroblastoma (M9500/3)**
Olfactory (M9522/3) 160
  Specified site—see Neoplasm by site, malignant
Unspecified site 194.0
Uncertain behavior, olfactory neoplasm 237.9

**ICD-9 CODE: Carcinoid Syndrome 259.2**

**ICD-9 CODE: MEN-I and -II 258.0**

For additional ICD-9 codes, please see the sections on specific NETs. Codes for children are the same as adults.

*(See MEN Syndrome Screen [Chapter 4], Chromogranin A [CGA] [Chapter 3], and Flushing Syndrome Tests [Chapter 4] for specific tests and CPT codes)*
Chapter 2

Clinical Presentations and Their Syndromes, Including ICD-9 Codes

Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management
The frequency of clinical manifestations related to the GEP neuroendocrine system, is as follows:

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>84%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>79%</td>
</tr>
<tr>
<td>Heart disease</td>
<td>37%</td>
</tr>
<tr>
<td>Bronchoconstriction</td>
<td>17%</td>
</tr>
<tr>
<td>Myopathy</td>
<td>7%</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>5%</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>5%</td>
</tr>
<tr>
<td>Hyper-hypoglycemia</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dermopathy</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Flushing

Flushing, a cardinal symptom of carcinoid tumors, occurs in a variety of other conditions. A good rule of thumb is if the flushing is “wet” (accompanied by sweating), it is due to a cause other than carcinoid. Table 2-1 lists the differential diagnosis and the features that help distinguish flushing caused by carcinoid from flushing associated with other conditions.

Table 2-1. Features Associated With Various Flushing Syndromes

<table>
<thead>
<tr>
<th>Flushing Syndrome</th>
<th>Associated Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>Diarrhea, wheezing</td>
</tr>
<tr>
<td>MCT</td>
<td>Mass in neck, family history</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Paroxysmal hypertension, tachycardia</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Autonomic neuropathy/chlorpropamide</td>
</tr>
<tr>
<td>Menopause</td>
<td>Cessation of menses</td>
</tr>
<tr>
<td>Autonomic epilepsy</td>
<td>Diencephalic seizures</td>
</tr>
<tr>
<td>Panic syndrome</td>
<td>Phobias, anxiety</td>
</tr>
<tr>
<td>Mastocytosis</td>
<td>Dyspepsia, peptic ulcer, dermatographia</td>
</tr>
<tr>
<td>Drugs</td>
<td>Niacin, alcohol, calcium channel blockers</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Diagnosis by exclusion</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Angina in women, mitral valve prolapse</td>
</tr>
</tbody>
</table>

What to Look For

Distinguishing Signs and Symptoms

There are two varieties of flushing in carcinoid syndrome:

1. Midgut carcinoid: The flush usually is faint pink to red in color and involves the face and upper trunk as far as the nipple line. The flush is initially provoked by alcohol and food containing tyramine (e.g., blue cheese, chocolate, aged or cured sausage, red wine). With time, the flush may occur spontaneously and without provocation. It usually lasts only a few minutes and may occur many times per day. It generally does not leave permanent discoloration.

2. Foregut tumors: The flush often is more intense, of longer duration, and purplish in hue. It is frequently followed by telangiectasia and involves not only the upper trunk but may also affect the limbs. The limbs may become acrocyanotic, and the appearance of the nose resembles that of rhinophyma. The skin of the face often thickens, and assumes leonine facies resembling that seen in leprosy and acromegaly.
Because flushing cannot always be attributed to carcinoid syndrome, as mentioned previously, the differential diagnosis of flushing is extremely important and includes the following:

- Postmenopausal state
- Simultaneous ingestion of chlorpropamide and alcohol
- Panic attacks
- MCT
- Autonomic epilepsy
- Autonomic neuropathy
- Mastocytosis
- Ganglioneuromas
- Carotid body tumors
- Pheochromocytomas

### Hormones and Peptides

Measure the levels of the following hormones and peptides ascribed to flushing in carcinoid syndrome:

- Prostaglandins
- Kinins
- Serotonin (5-HT)
- Vasoactive neuropeptides (serotonin, dopamine, histamine)
- 5-HIAA
- Substance P
- Neurtensin
- Somatostatin
- Motilin
- VIP
- Neuropeptide K
- Gastrin-releasing peptide (GRP)

Several tests are used to identify the cause of flushing in carcinoid syndrome (Table 2-2).

### Table 2-2. Tests to Identify Cause of Flushing

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>Urine 5-HIAA, 5-HTP, substance P, CGRP, CGA</td>
</tr>
<tr>
<td>MCT</td>
<td>Calcitonin, calcium infusion, RET protooncogene</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>VMA, epinephrine, norepinephrine, glucagon stimulation, 131I-MIBG</td>
</tr>
<tr>
<td>Diabetic autonomic neuropathy</td>
<td>Heart rate variability, 2-hour PP, glucose</td>
</tr>
<tr>
<td>Menopause</td>
<td>FSH</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>Panic syndrome</td>
<td>Pentagastrin/ACTH</td>
</tr>
<tr>
<td>Mastocytosis</td>
<td>Plasma histamine, urine tryptase</td>
</tr>
<tr>
<td>Hypomastia, mitral prolapse</td>
<td>Cardiac echogram</td>
</tr>
</tbody>
</table>
ICD-9 CODE: Flushing 782.62
ICD-9 CODE: Carcinoid Syndrome 259.2
ICD-9 CODE: Medullary Carcinoma Thyroid (M8510/3)
  With amyloid stroma (M8511/3)
    Specified site, thyroid 193
    Unspecified site 193
  With lymphoid stroma (M8512/3)
    Malignant thyroid 193
ICD-9 CODE: Pheochromocytoma (M8700/0)
  Malignant (M8700/3)
    Specified site–see Neoplasm by site, malignant
    Unspecified site 194.0
  Benign
    Specified site–see Neoplasm by site, benign
    Unspecified site 227.0
ICD-9 CODE: Diabetes, Autonomic Neuropathy 250.6
ICD-9 CODE: Autonomic Epilepsy
  Without mention of intractable epilepsy 345.50
  With intractable epilepsy 345.51
ICD-9 CODE: Panic Attack 300.01
ICD-9 CODE: Mastocytosis 753.33
  Malignant 202.6
  Systemic 202.6
ICD-9 CODE: Hypomastia (Congenital) 757.6
ICD-9 CODE: Mitral Prolapse 424.0

(See Flushing Syndrome Tests [Chapter 4] for specific tests and individual CPT codes)
DIARRHEA

Watery diarrhea syndrome (WDHHA), which is caused by a pancreatic islet cell tumor, was first identified by Verner and Morrison in 1958. As implied by its name, the primary characteristic is watery diarrhea. A critical distinguishing difference from ZE is the absence of hyperacidity and the marked presence of hypokalemia. Diarrhea of ZE improves with inhibition of acid secretion, whereas in WDHHA it does not. The WDHHA usually begins with intermittent diarrhea, but as the tumor grows, the episodic diarrhea becomes continuous and persists despite fasting (i.e., it is secretory, not malabsorptive). Hypercalcemia occurs in WDHHA because of direct effects of VIP on bone. It is important to differentiate this cause of hypercalcemia from the hypercalcemia caused by excess PTH release from parathyroid glands seen in the sporadic (usually caused by adenomas) or familial (usually the result of hyperplastic glands) forms of hyperthyroidism. Factitious diarrhea can be difficult to distinguish and requires the demonstration of an osmolar gap. If 2x [Na⁺ “K⁺”] is less than stool osmolality (i.e., osmotic gap), search for idiogenic osmoles.

The following are characteristics of secretory diarrhea:

- Large-volume stools
- Persists during fasting
- 2 x [Na⁺ “K⁺”] = stool osmolality

The following are characteristics of osmotic diarrhea:

- Small volume (<1 L/d)
- Disappears with fasting

WHAT TO LOOK FOR

Distinguishing Signs and Symptoms

- Profuse diarrhea with the appearance of weak tea
- Presence of marked hypokalemia and hyperchloremic acidosis
- Initial intermittent diarrhea, becoming continuous as tumor grows
- Secretory nature of diarrhea (i.e., does not disappear even after fasting for 48 hours)
- Absence of gastric hyperacidity (a major feature distinguishing WDHHA from ZE)
- Atrophic gastritis or pernicious anemia or gastric carcinoid type 1
- Hypochlorhydria resulting from the gastric inhibitory effect of VIP
- Secretion of HCO₃ and K⁺ causes life-threatening loss of electrolytes into the stool
- Increased intestinal motility as well as secretion adding to the diarrhea
- Hypercalcemia not due to PTH or PTHRBP
- Hyperglycemia or abnormal glucose tolerance
- Dilatation of the gallbladder
- Flushing
- Weight loss
- Colic
**The Next Step**

Patients with watery diarrhea are often severely dehydrated, and their fluid balance and electrolytes should be corrected before specific diagnostic tests are initiated, except for evaluation of stool electrolytes and osmolarity.

Diagnostic tests should be selected to:
- Exclude atrophic gastritis, pernicious anemia, and gastric carcinoid
- Exclude use of proton pump inhibitors
- Exclude ZE
- Determine the probability of a pancreatic-based source of watery diarrhea (VIP, PP, MCT, CT, and OctreoScan®)
- Eliminate other syndromes masquerading as WDHHA and producing similar symptoms

**Hormones and Peptides**

Vasoactive intestinal polypeptide is the primary peptide produced by the majority of pancreatic tumors (VIPomas) causing WDHHA, but substance P, PP, calcitonin gene–related peptide (CGRP) and thyrocalcitonin (TCT) have also been implicated in NET-related diarrhea. Because VIP is also produced by neural cells, elevated levels of other GI and pancreatic hormones and peptides may be markers for establishing the presence of a pancreatic tumor associated with diarrhea. WDHHA in children is most commonly due to a nonpancreatic NET such as neuroblastoma. Occasionally, adults with pheochromocytomas may secrete VIP, which releases prolactin and is a vasodilator in the corpora cavernosa. However, this does not appear to be part of the clinical syndrome (Fig. 2-1).

![Figure 2-1. Pathogenesis of Endocrine Diarrhea](image)

After mechanical causes have been ruled out, use the following ICD-9 codes:
- ICD-9 CODE: Diarrhea 787.91
- ICD-9 CODE: Functional 564.5
- ICD-9 CODE: Achlorhydria 536.0

*(See Table 1-1 for primary tumor sites and common metastatic tumor sites)* *(See Diarrhea Syndrome Tests [Chapter 4] for specific tests and individual CPT codes)*

Reference

Bronchoconstriction (Wheezing)

Wheezing due to bronchospasm occurs in about one third of patients with carcinoid syndrome and in patients with mastocytosis.

What to Look For

Distinguishing Signs and Symptoms

Wheezing can be readily assessed at the bedside by asking the patient to breathe out as quickly as possible and listening to the trachea. Normally the wheezing is almost instantaneous, but with the expiratory bronchospasm in carcinoid and mastocytosis it is often prolonged. A test dose of octreotide acetate (100 µg) administered intravenously will relieve carcinoid bronchospasm. It is not known what effects octreotide has on asthma.

The Next Step

Lung function tests reveal a prolongation of forced expiratory volume in 1 second (FEV₁), which needs to be distinguished from asthma and chronic airways obstructive disease. Refer the patient to a pulmonologist.

Hormones and Peptides

Wheezing is predominantly the result of the bronchoconstrictive effects of substance P, histamine, and possibly 5-HT.

ICD-9 CODE: Wheezing 786.07
ICD-9 CODE: Bronchospasm 519.1
ICD-9 CODE: Carcinoid Syndrome 259.2
ICD-9 CODE: Asthma
  Unspecified 493.90
  With status asthmaticus 493.91
  With (acute) exacerbation 493.92

(See Carcinoid Follow-Up Profile [Chapter 4] for individual tests and CPT codes for substance P, histamine, serotonin; see Bronchospasm Profile [Chapter 4] for specific tests and CPT codes)
DYSPEPSIA, PEPTIC ULCER

GASTRINOMA (ZOLLINGER-ELLISON SYNDROME)

Zollinger-Ellison syndrome is characterized by hyperacidity and gastrin hypersecretion from an islet cell tumor (gastrinoma) of the pancreas or duodenum. Approximately 90% of gastrinomas are found in the “gastrinoma” triangle, an area bordered by the confluence of the cystic and common ducts superiorly, the mesenteric vessels medially, and the lateral sweep of the “C” loop of the duodenum laterally. A primary gastrinoma is rarely found in the liver or ovary, and even more rarely in a lymph node. These tumors may be associated with peptic perforation, obstruction, hemorrhage, and/or hyperacidity. Atrophic gastritis, pernicious anemia, gastric carcinoid, chronic proton pump inhibitor use, and diabetic gastropathy may produce spuriously high gastrin levels. A high gastrin level in the absence of diarrhea suggests atrophic gastritis. Secretory diarrhea in the presence of achlorhydria with normal gastrin levels suggests a VIPoma. Gastric pH measurement remains a valuable tool in distinguishing the causes of hypergastrinemia. Even though this measurement in easily performed, it is often overlooked.

WHAT TO LOOK FOR

Distinguishing Signs and Symptoms

- Highly elevated level of gastrin
- Diarrhea that responds to PPI

THE NEXT STEP

In conjunction with gastric acid measurement, these syndromes may be distinguished, but provocative testing may be necessary.

Hormones and Peptides

Normal values of gastrin are 100 to 120 pg/mL. PPI will raise levels to 400 to 500 pg/mL. Fasting gastrin concentrations greater than 500 pg/mL in the presence of normal or excess gastric acid is suspicious of gastrinoma. Very high levels of greater than 1000 pg/mL may be pathognomonic of gastrinoma. Pernicious anemia and atrophic gastritis can produce gastrin levels greater than 1000 pg/mL, which should alert the clinician to the possibility of gastric carcinoid. Endoscopic pH measurements are essential to distinguish ZE from atrophic gastritis, type 1 gastric carcinoid, and pernicious anemia.

ICD-9 CODE: Dyspepsia/Peptic Ulcer 536.8

ICD-9 CODE: Peptic Ulcer

- Without obstruction 533.90
- With obstruction 533.91
- With hemorrhage 533.4
  - Without obstruction 533.40
  - With obstruction 533.1
- And perforation 533.6
Perforation (chronic) 533.5
With hemorrhage 533.6

ICD-9 CODE: Zollinger-Ellison/Gastrinoma 251.5
Malignant
  Pancreas 157.4
  Specified site—see Neoplasm by site, malignant
  Unspecified site 157.4
Benign
  Unspecified site 235.5
Uncertain behavior, see Neoplasm

(See Table 1-1 for primary tumor sites and common metastatic tumor sites)
(See Gastrin Test [Chapter 3] for specific tests and CPT codes)
Hypoglycemia

Hypoglycemia is a multifactorial disorder. Although the diagnosis of an insulin-secreting lesion of the pancreas is essential to successful management, it is critically important to rule out other causes of hypoglycemia.

What to Look For

Distinguishing Signs and Symptoms

- Organic hyperinsulinemia
  - Islet cell adenoma, carcinoma, hyperplasia, nesidioblastosis
- Fasting hypoglycemia
- Autoimmune with insulin antibodies
- Counter-regulatory hormone deficiency
  - Anterior pituitary insufficiency—GH, ACTH
  - Adrenocortical insufficiency
  - Severe hypothyroidism
  - Large nonislet tumor
  - Impaired hepatic function
  - Hepatocellular insufficiency
  - Ethanol/malnutrition
  - Sepsis
  - Specific enzymatic defects (childhood)
  - Impaired renal function
  - Substrate deficiency
  - Fanconi syndrome (renal loss)
  - Nursing
  - Severe inanition
  - Severe exercise
- Drug induced
  - Reactive hypoglycemia
  - Alimentary
  - “Pre-diabetes”
  - Endocrine
  - Idiopathic
- Factitious
  - Surreptitious insulin administration
  - Surreptitious sulfonylurea administration
  - Leukemoid reaction polycythemia
  - ACTH or GH administration
- Hyperinsulinemia
  - An accurate diagnosis of organic hyperinsulinemia can be established in most cases by a process of exclusion. The diagnosis can usually be made before extensive exploration of neoplastic causes.
• Autoimmunity
  - Syndromes of autoimmunity may lead to hypoglycemia. Antireceptor antibodies usually occur in the presence of other autoimmune disease, mimicking the effect of insulin and reducing insulin clearance. Insulin levels may be normal or high, but C-peptide levels are low because islet cells are suppressed.

• Reactive hypoglycemia
  - Autoimmune hypoglycemic disease syndrome usually occurs in the presence of other autoimmune disorders (e.g., Graves’ disease, rheumatoid arthritis, lupus) and commonly produces reactive hypoglycemia from prolongation of the half-life of circulating insulin. This is also an important mechanism in late dumping syndrome. Insulin levels are generally extremely elevated, which may result from interference by antibodies with the particular insulin assay. C-peptide levels are usually low.

• Neoplasms
  - In the case of large mesenchymal neoplasms, the offending agent may be IGF-2; neither the size of the tumor nor the glucose metabolized by the tumor causes hyperglycemia; however, there is increased disposal of glucose by the liver mimicking the actions of insulin.

• Counter-regulatory hormone deficiency
  - Hypoglycemia resulting from conditions in which there is failure of gluconeogenesis or hormonal counter-regulations for (e.g. Addison’s disease), hypopituitarism usually can be recognized clinically.

• Factitious hypoglycemia
  - Factitious hypoglycemia is extremely difficult to discern. If the patient uses insulin, there may be a low level of C-peptide, but if a sulfonylureas is being used, then insulin and C-peptide may be elevated. In this case look for the presence of insulin antibodies and sulfonylureas.

**Non–Islet Cell Neoplasms Associated With Hypoglycemia**

• Mesenchymal
  - Mesothelioma
  - Fibrosarcoma
  - Rhabdomyosarcoma
  - Leiomyosarcoma
  - Hemangiopericytoma

• Carcinoma
  - Hepatic: hepatoma, biliary carcinoma
  - Adrenocortical carcinoma
  - Genitourinary: hypernephroma, Wilms’ tumor of the prostate
  - Reproductive: cervical or breast carcinoma

• Neurologic/neuroendocrine
  - Pheochromocytoma
  - Carcinoid
  - Neurofibroma
• Hematologic
  - Leukemia
  - Lymphoma
  - Myeloma

The Next Step

Hormones, Peptides, and Enzymes

• Insulin
• IGF-2
• C-peptide
• Glucagon-like peptide type 1 (GLP-1) and GIP
• Sulfonylurea
• ACTH
• GH
• Insulin antibodies
• Liver enzymes

ICD-9 CODE: Hypoglycemia 251
  Diabetic 250.8
  Due to insulin 251.0
  Reactive 251.2

ICD-9 CODE: Hyperinsulinemia 251.2
  NEC 51.1

ICD-9 CODE: Dumping Syndrome
  Nonsurgical 536.8
  Postgastrectomy 654.2

ICD-9 CODE: Complications of Drug Injection or Therapy 999.9
ICD-9 CODE: Complication of Surgical Procedure 998.9

(See Table 1-1 for primary tumor sites and common metastatic tumor sites)
(See Hypoglycemia/Insulinoma Screening Test [Chapter 4] for specific tests and CPT codes)
DERMOPATHY

When dermopathy occurs with glucagonoma syndrome it is also known by the acronym 4D, which stands for dermatosis, diarrhea, DVT, and depression. Pellagra-like eruptions occur in carcinoid as a result of niacin deficiency, and increased pigmentation occurs with MSH overproduction.

WHAT TO LOOK FOR

Distinguishing Signs and Symptoms
- Characteristic NME rash (82%)
- Pellagra rash forming a necklace and forearm pigmentation with the appearance of tiling
- Increased pigmentation in sun-exposed areas with overproduction of MSH
- Painful glossitis, angular stomatitis
- Normochromic normocytic anemia (61%)
- Weight loss (90%)
- Mild diabetes mellitus (80%)
- Hypoaminoacidemia
- DVT (50%)
- Depression (50%)

THE NEXT STEP

Hormones, Peptides, and Amino Acids
- Glucagon
- Plasma amino acids (tryptophan)
- α-MSH
- Serotonin
- 5-HIAA
- Niacin

ICD-9 CODE: Glucagonoma (M8152/0)—For Glucagonoma Rash
Malignant (M8152/3)
- Pancreas 157.4
- Specified site—see Neoplasm by site, malignant
Benign
- Specified site—see Neoplasm by site, benign
- Unspecified site 211.7
- Uncertain behavior, neoplasm of pancreas 235.5

ICD-9 CODE: Pellagra 265.2

(See Table 1-1 for primary tumor sites and common metastatic tumor sites)
(See Glucagon [Chapter 3] and Serotonin [Chapter 3] for specific tests and CPT codes)
Dumping Syndrome

Postgastrectomy dumping syndrome occurs in as many as 25% of patients undergoing ablative or bypass surgery on the pylorus. Approximately 5% of patients have debilitating dumping syndrome following major gastric resections. There may be varying degrees of this pathophysiologic state. Ingestion of cold or carbohydrate-rich foods may precipitate early dumping with cardiovascular (tachycardia and shock-like symptoms) and gastrointestinal components (explosive diarrhea and cramping). Classically, patients with dumping syndrome do not have symptoms with every meal; therefore they commonly use medication to control this syndrome only when they know that they are going to ingest foods that will provoke an attack. Late dumping is characterized by hypoglycemic events. These features can be explained by insulin-induced hypoglycemia. Alterations in gut peptide levels have been implicated in both early and late dumping syndromes. PP, glucagon, insulin, and motilin have been implicated in the pathogenesis of dumping syndrome.

What to Look For

Distinguishing Signs and Symptoms

Early Dumping Syndrome

Early dumping is caused by rapid shifts of water and electrolytes into the duodenum and proximal small bowel lumen in response to the introduction of hyperosmolar chyme into these regions. Fluid shifts into the gut lumen produce intravascular volume reduction, subsequent hemoconcentration, and an adrenergic shock-like response, producing the following symptoms:

- Diaphoresis
- Syncope
- Tachycardia
- Hypotension
- Borborygmus
- Explosive diarrhea

Late Dumping Syndrome

- Tremors
- Diaphoresis
- Syncope
- Mental confusion

The Next Step

Carbohydrate Test

Use a high-carbohydrate test meal to provoke dumping syndrome in a controlled clinical environment. This test meal contains 750 kcal, 21g protein, 30 g fat, and 99 g of carbohydrate (i.e., 2 eggs, 2 strips of bacon, a cup of decaffeinated coffee, 2 pieces of toast, 1 scoop of ice cream, and 1 ounce of chocolate syrup). The meal must be
consumed within 10 minutes. Patients with dumping syndrome usually respond with significant rises in PP, insulin, and glucagon levels within 45 minutes of ingestion of this meal. Increases in motilin levels are usually seen 120 to 180 minutes after ingestion of a provocative meal.

### Hormones and Peptides

- Insulin
- PP
- Glucagon
- GIP
- GLP-1
- Motilin

### Octreotide Suppression Test

Octreotide acetate administration at low doses (100 µg 1 hour before meals) has been effectively used to control the symptoms of early dumping but is less efficacious in the control of late dumping. It can however, be used as a test of hormone and symptom responsiveness. Use of octreotide in patients with late dumping syndrome can be associated with worsening of hypoglycemia and should be done only in a controlled clinical environment.

**ICD-9 CODE: Dumping Syndrome**

- Nonsurgical 536.8
- Postgastrectomy 654.2

*(See Table 1-1 for primary tumor sites and common metastatic tumor sites)*
*(See Provocative Test for Dumping Syndrome [Chapter 5] for further test instructions and CPT codes for specific hormone and peptide measurements)*
Pancreatic Exocrine Diseases

Pancreatic exocrine diseases are not commonly associated with NETs. However, many of the neuroendocrine secretions are affected by neoplastic and non-neoplastic conditions. Additionally, therapeutic interventions used in the treatment of NETs may affect exocrine secretion.

The pancreas is an integrated organ of both endocrine and exocrine functions. The exocrine pancreas is composed of enzyme-secreting acini and the bicarbonate/fluid-secreting ductal system. Inflammatory and neoplastic diseases constitute some of the most prevalent and life-threatening diseases affecting the US population. Acute and chronic pancreatitis affects more than 200,000 individuals; although it often runs a mild course, up to 30% of cases are associated with significant morbidity and mortality. Meanwhile, more than 30,000 individuals are diagnosed with pancreatic cancer each year, with a 5-year survival rate of less than 10%. Recently, diagnostic imaging (CT, ultrasound [regular or endoscopic], and MRI) coupled with laboratory biomarkers have been used routinely for diagnosis of the pancreatic diseases.

What to Look For

Distinguishing Signs and Symptoms

Acute Pancreatitis

- Abdominal pain with elevated pancreatic enzymes (amylase, lipase, and trypsin) in blood and/or urine.
- Clinical manifestation may range from mild and self-limited abdominal discomfort to acute abdomen with shock.

Laboratory Diagnosis of Acute Pancreatitis. Serum amylase and lipase levels are widely and routinely used for the diagnosis of acute pancreatitis clinically. However, the prognostic capability of both of these enzymes to determine the severity of disease has been poor.

The Next Step

The following guidelines (Table 2-3) are suggested based on the recent evidence available for various biochemical markers to distinguish between mild and severe acute pancreatitis in early stages and during the clinical course of the disease.
Neuroendocrine Tumors: A Comprehensive Guide to Diagnosis and Management

Table 2-3. Assessment of Severity of Acute Pancreatitis

- At the time of admission
  - IL-6: ELISA (cutoff value 400 pg/mL)
  - IL-8: ELISA (cutoff value >400 pg/mL)
  - IL-10: ELISA (cutoff value >100 pg/mL)
  - APACHE II: Score greater than 7
- First 24 hours of hospitalization
  - Urine trypsinogen activation peptide: ELISA (cutoff value >35 nmol/L)
  - Urine Trypsinogen-2: dipstick (cutoff value >2000 μg/L)
  - Polymorphonuclear release: ELISA (cutoff value >300 μg/L)
- First 48 hours of hospitalization
  - C-reactive protein: automated (cutoff value > 150 mg/L)
  - APACHE score: >3
- Tools that require further validation
  - Cytokines
    - IL-1
    - TNFα, TNFβ, TNFα receptor
  - Pancreatic markers
    - Carboxypeptidase B activation peptide

What to Look For

Distinguishing Signs and Symptoms

Chronic Pancreatitis
Alcohol abuse is one of the leading causes of chronic pancreatitis. This condition is characterized by a long interval between the onset of alcohol abuse and onset of symptoms, which include the following:

- Recurrent upper abdominal pain
- Weight loss
- Diarrhea
- Steatorrhea with or without endocrine insufficiency (diabetes)
- Pancreatic calcification

Laboratory Diagnosis of Chronic Pancreatitis. Pancreatic serum enzymes such as amylase and lipase are elevated only during the acute attack, but remain normal during symptom-free intervals. Moreover, as the disease progresses, serum pancreatic enzymes are no longer elevated because of pancreatic parenchymal damages accompanied by exocrine pancreatic insufficiency.
The Next Step

To diagnose chronic pancreatitis, imagining procedures (US, CT, or endoscopic ultrasound) and pancreatic function tests should be combined.

Hormones, Peptides, and Enzymes

The measurement of pancreatic-derived enzymes and genetic biomarkers in the setting of inflammation form the basis of the laboratory diagnosis of various pancreatic disorders.

- Lipase
- Trypsin
- Stools for fecal fat
- Fecal elastase
- Ingested particles

ICD-9 CODE: Acute Pancreatitis 577.0
ICD-9 CODE: Chronic Pancreatitis 577.1
ICD-9 CODE: Pancreatic Exocrine Disease 577.8
ICD-9 CODE: Steatorrhea 579.4
ICD-9 CODE: Complications of Surgical Procedures/Treatment 998.9
ICD-9 CODE: Complications of Therapeutic Misadventure NEC 999.9

(See Provocative Pancreatic Exocrine Function Tests (Chapter 5) for specific tests and CPT codes)
ADENOCARCINOMA OF THE PANCREAS

Late presentation of pancreatic cancer and its poor prognosis emphasizes the importance of an effective early detection strategy for patients at risk for developing the disease. The recent discovery of genetic biomarkers expressed at different stages of disease was a major advance (Fig. 2-2). It is hoped that the clinical uses of genetic and epigenetic biomarkers in combination with the development of high-throughput, sensitive techniques such as proteomics will lead to the rapid discovery of a panel of biomarkers for early detection.

What to Look For

Distinguishing Signs and Symptoms

• Unexplained weight loss
• Sudden appearance of jaundice
• Abdominal pain

Clinically useful biomarkers and peptides in pancreatic juice and blood include the following:

• KRAS mutations
• P53 mutations
• BRCA2
• Cancer-associated antigen (CA)19-9
• CA-50
• CA-125
• Carcinoembryonic antigen (CEA)

ICD-9 CODE: Adenocarcinoma of the Pancreas 157.4

(See Adenocarcinoma of the Pancreas [Chapter 4] for specific tests and CPT codes)
**Pituitary and Hypothalamic Disorders**

Diseases of the hypothalamus and pituitary and ectopic production of hypothalamic hormones produce syndromes of hormone excess or deficiency. Nonsecreting pituitary tumors may present with only signs and symptoms of mass effect on adjacent structures (i.e., optic chiasm, cranial nerves 3 and 4 and branches thereof, cranial nerves 5 and 6 as they traverse the cavernous sinus, and the sphenoid sinus) if enough normal pituitary remains to prevent hypopituitarism.

**Diseases of Hormonal Excess**

- Hyperprolactinemia
- Acromegaly and gigantism
- Cushing’s syndrome
- Other pituitary hypersecretion syndromes
  - TSHomas
  - Gonadotropin- or human glycoprotein alpha subunit– (α-GSU) secreting pituitary adenomas
Hyperprolactinemia

The clinical effects of prolactin excess vary according to the time of onset of the disease.

What to Look For

Distinguishing Signs and Symptoms

Children
- Hypogonadism with pubertal delay or arrest
- Absent pubertal growth spurt due to hypogonadism

Women
- Hypogonadism
  - Infertility
  - Oligorrhea/amenorrhea
- Galactorrhea
- Hirsutism due to stimulation of adrenal androgen

ICD-9 CODE: Hyperprolactinemia 253.1
ICD-9 CODE: Hypogonadism
  Ovarian 256.1
  Testicular 257.2
ICD-9 CODE: Amenorrhea 626.0
  Ovarian dysfunction 256.8
  Hyperhormonal 256.8
ICD-9 CODE: Oligomenorrhea 626.1
ICD-9 CODE: Galactorrhea 676.6
ICD-9 CODE: Hirsutism 704.1
ICD-9 CODE: MEN-I Syndrome 258.0

(See MEN Syndrome Screen [Chapter 4] and Pituitary and Hypothalamic Disorders Tests [Chapter 5] for specific tests and CPT codes)
Growth hormone is secreted by the anterior pituitary. Its release is controlled by GHRH and somatostatin. GH is also known as somatotropin and is in the family of compounds known as somatomammotropins, which includes prolactin and human placental lactogen. GH stimulates production of RNA, resulting in increased anabolism. GH levels are elevated in persons with pituitary gigantism and in those with acromegaly that is characterized by growth after the epiphyses have closed resulting in abnormal bone growth of face, hands, and feet. GH levels are decreased in persons with dwarfism. Patients taking GH therapy frequently develop GH antibodies, which act to negate the biologic effect of the medication.

The clinical effects of GH excess vary according to the time of onset of the disease. Relative frequency of symptoms in acromegaly is shown in Table 2-4.

### Table 2-4. The Relative Frequency of Symptoms in Acromegaly

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enlargement of extremities</td>
<td>99</td>
</tr>
<tr>
<td>Facial coarsening</td>
<td>97</td>
</tr>
<tr>
<td>Visceromegaly</td>
<td>92</td>
</tr>
<tr>
<td>Necessity to increase shoe size</td>
<td>88</td>
</tr>
<tr>
<td>Necessity to increase ring size</td>
<td>87</td>
</tr>
<tr>
<td>Sella enlargement</td>
<td>83</td>
</tr>
<tr>
<td>Acroparesthesias</td>
<td>82</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>80</td>
</tr>
<tr>
<td>Hyperhidrosis, seborrhea</td>
<td>78</td>
</tr>
<tr>
<td>Arthrosis</td>
<td>76</td>
</tr>
<tr>
<td>Teeth separation</td>
<td>75</td>
</tr>
<tr>
<td>Frontal bossing</td>
<td>72</td>
</tr>
<tr>
<td>Oily skin</td>
<td>70</td>
</tr>
<tr>
<td>Malocclusion and overbite</td>
<td>65</td>
</tr>
<tr>
<td>Prognathism</td>
<td>65</td>
</tr>
<tr>
<td>Headache</td>
<td>62</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>52</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>42</td>
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<tr>
<td>Impaired glucose tolerance</td>
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<tr>
<td>Skin tags</td>
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<tr>
<td>Goiter</td>
<td>38</td>
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<tr>
<td>Menstrual abnormalities</td>
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<td>Asthenia</td>
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<tr>
<td>Sexual disturbances</td>
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<tr>
<td>Carpal tunnel syndrome</td>
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<td>Overt diabetes</td>
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<tr>
<td>Visual field defects</td>
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<tr>
<td>Galactorrhoe</td>
<td>4</td>
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<tr>
<td>Cranial nerve palsies</td>
<td>3</td>
</tr>
</tbody>
</table>


WHAT TO LOOK FOR

Distinguishing Signs and Symptoms
The somatic changes in children include the following:
- Increase in growth velocity
- Gigantism

The changes in adults and children include the following:
- Enlargement of the extremities (hands, feet, nose, mandible, and supraorbital ridges) compelling patients to seek large gloves, shoes, and rings
- Development of thick skin which is moist, oily, and seborrheic with an increase in sebaceous cysts and skin tags
- Acanthosis nigricans and hypertrichosis
- Widely spaced teeth
- Visceromegaly of the tongue, liver, thyroid, and salivary glands
- Overgrowth of bone and cartilage causing degenerative changes in spine, hips, and knees
- Arthralgia and paresthesias
- Nerve entrapments, particularly of the median nerve but also ulnar and peroneal

Diagnosis of Acromegaly
The basal level of GH and IGF-1 is usually sufficient to make the diagnosis. However, in 15% to 25% of cases, the levels of GH are less than 10 ng/mL and the IGF-1 level may be normal. In these instances it is important to show nonsuppressibility of GH to an oral glucose tolerance test (or a somatostatin inhibition or bromocryptine suppression test). Levels of other pituitary hormones such as prolactin and the α subunit of gonadotropins are also often elevated; measure these as well as thyroid-stimulating hormone (TSH). If ordering a glucose tolerance test, measure GH in addition to glucose, because the criterion for diagnosis of acromegaly is based on suppression of GH and insulin as well as lipids.

The Next Step
Imaging of the sella turcica will show a tumor. In the absence of a tumor and the suggestion of hyperplasia, evaluate for a hypothalamic hamartoma or ectopic production of GHRH. If the GHRH level is greater than 300 pg/mL, CT and MRI of the pancreas, gastroduodenal area, thymus, and lungs should facilitate a diagnosis. Because these NETs express somatostatin receptors, OctreoScan will often reveal their location. In about 20% of patients a pituitary tumor will coexist with MEN-I syndrome; thus it is important to also measure ionized calcium and PTH.

The radiologic study of bones will show thickening of the skull, enlargement of the frontal and maxillary sinuses, prognathism, tufting of the phalanges, and cysts in carpal and tarsal bones. Soft tissue enlargement can be seen, particularly with heel pad thickness. In patients over 50 years old, colonic polyps may become carcinomas, particularly in people with skin tags. For these patients, routine sequential colonoscopy is recommended. The flow diagram presented in Figure 2-3 suggests the diagnostic workup.
Hormones and Peptides

- GH
- IGF-1
- Prolactin
- TSH
- GHRH if no tumor visualized or pituitary hyperplasia on MRI
- PTH

Measure the following:
- GH and IGF-1
- Oral glucose tolerance test; also measure GH, insulin, and lipids
- Somatostatin inhibition test
- Bromocryptine suppression test
- Prolactin
- TSH
- Ionized calcium
- PTH

ICD-9 CODE: Acromegaly 253.0
ICD-9 CODE: Gigantism 253.0
ICD-9 CODE: MEN-I Syndrome 258.0

(See Growth Hormone [HGH, Somatotropin] [Chapter 3] and Thyroid Stimulating Hormone [TSH, Thyrotropin] [Chapter 3] for specific tests and CPT codes)
Cushing’s Syndrome

In Cushing’s disease, oversecretion of pituitary ACTH induces bilateral adrenal hyperplasia. This results in excess production of cortisol, adrenal androgens, and 11-deoxycorticosterone. Cushing’s disease, a subset of Cushing’s syndrome, is due to a pituitary corticotroph adenoma and results in a partial resistance to the suppression of ACTH by cortisol so that secretion is unrestrained. In contrast, causes of Cushing’s syndrome may include the following:

- Adrenal adenoma or carcinoma arise spontaneously. ACTH levels are undetectable.
- Nonpituitary (ectopic) tumors produce ACTH. They most frequently originate in the thorax and are highly aggressive small cell carcinomas of the lung or slow-growing bronchial or thymic carcinoid tumors. Some produce corticotropin-releasing hormone (CRH) instead, which stimulates pituitary ACTH secretion and can therefore mimic a pituitary tumor.
- Other causes include carcinoid tumors of the gastric, pancreatic, and intestinal organs; pheochromocytomas; and MCT.

The hallmark of Cushing’s syndrome is that ACTH levels are partially resistant to suppression with dexamethasone, even at very high doses.

What to Look For

Distinguishing Signs and Symptoms

The clinical features of common varieties of Cushing’s disease include or are related to the following:

- Fat and protein metabolism
- Centripetal weight gain
- Development of the buffalo hump
- Supraclavicular fat pads
- Plethoric moon face
- Thin skin
- Little accumulation of subcutaneous fat over the dorsum of the hand and shin
- Purple striae, often greater than 1 cm wide, usually located over the abdomen but not in traditional stretch areas
- Slow healing of minor wounds
- Muscle wasting in the proximal lower limbs leading to inability to rise from a chair and weakness
- Bone wasting resulting in generalized osteoporosis
- Kyphosis and loss of height
- Elevated blood pressure
- Fluid accumulation leading to congestive heart failure
- Evidence of androgen excess with hirsutism in women
- Clitoromegaly
- Coarsening of the skin
- Hoarse voice due to the androgen excess, particularly true in adrenocortical carcinomas
- Psychic disturbances
• Anxiety
• Emotional lability
• Depression
• Unwarranted euphoria with sleep disturbances

The nonpituitary or ectopic ACTH syndrome is often diagnosed because of its rapid onset and progress. Classically the condition is dominated by the following characteristics:
• Profound muscle wasting
• Electrolyte disturbances
• Severe hypokalemia
• Overproduction of mineralocorticoids
• Impaired insulin secretion resulting in diabetes
• Striking pigmentation due to the structural homology of ACTH and MSH

This pigmentation contrasts with the absence of pigmentation in classic Cushing’s disease and adrenal tumors, in which ACTH is suppressed.

The Next Step

Increased urinary cortisol and plasma cortisol suggest Cushing’s disease. A suppressed ACTH level indicates the presence of an adrenal tumor. Mildly elevated ACTH directs attention to the pituitary. Markedly elevated ACTH suggests a small cell carcinoma of the lung or an ectopic carcinoid type of tumor.

Hormones and Peptides
• ACTH
• Cortisol
• Adrenal
• Androgens
• 11-Deoxycorticosterone
• MSH

First-Line Screening
1. Measure plasma ACTH, cortisol, and 24-hour urinary free cortisol excretion.
2. Repeat at least three 24-hour urinary free cortisol collections if high clinical suspicion exists. One or more collections may be normal due to “cyclic Cushing’s disease,” and in preclinical Cushing’s syndrome, the urinary free cortisol may be normal.
3. Perform low-dose dexamethasone suppression test (DST) either overnight (1 mg between 11:00 PM and 12:00 AM) or 0.5 mg every 6 hours for 48 hours. N–1 suppression is to less than 1.8 µg/dL (50 nmol/L).
4. Measure circadian rhythm of cortisol by obtaining serum cortisols at 8:00 to 9:30 AM, 4:30 to 6:00 PM, and 11:00 PM to 12:00 AM. For the latter measurement, patient should be asleep as an inpatient after 48 hours (only if not acutely ill); if patient is not in the hospital, or is acutely ill, obtain a salivary cortisol level.

(See Pituitary and Hypothalamic Tests [Chapter 5] for more details on ACTH and cortisol testing)
Second-Line Screening

1. Measure circadian rhythm of cortisol, as above.
2. Perform low-dose DST 0.5 mg for 48 hours with measurement of 24-hour urinary free cortisol on the second day. Excretion of less than 10 µg/24 hours (27 nmol/L) is normal.
3. Perform low-dose DST (0.5 mg every 6 hours for 48 hours) followed by CRH stimulation (100 µg or 1 µg/kg of intravenous ovine CRH). A cortisol response greater than 1.4 µg/dL at 15 minutes is consistent with Cushing’s disease.

(See Pituitary and Hypothalamic Tests [Chapter 5] for more details on cortisol testing, low-dose DST, and low-dose DST with CRH stimulation)

What You Need to Know if Cushing’s Syndrome Is Confirmed

1. If ACTH is easily detectable (>20 pg/mL, or 4 pmol/L) focus on the pituitary with MRI of the sella turcica. This test is positive in 50% to 60% of cases of proven pituitary Cushing’s disease.
2. If ACTH level is less than 20 pg/mL, prove that it is suppressed with a CRH test. Administer CRH 1 µg/kg or 100 µg/1 kg (but not dexamethasone) as described previously, and measure ACTH in addition to cortisol at 15, 30, and 45 minutes after CRH. An increase of greater than 50% in ACTH supports a pituitary tumor; ectopic ACTH-secreting tumors generally (but not invariably) do not respond to CRH. Those that do are carcinoids tumors of bronchus, thymus, or pancreas; islet cell tumors; MCTs; or pheochromocytomas rather than the more common small cell carcinomas of the lung.
3. Perform high-dose DST. High doses of glucocorticoids partially suppress ACTH secretion from 80% to 90% of corticotroph adenomas, whereas ectopic tumors usually resist negative feedback inhibition. However, as discussed previously, some benign NETs may be sensitive to feedback inhibition of ACTH, similar to pituitary tumors. In adrenal-based Cushing’s syndrome, plasma cortisol is not suppressed after high-dose DST because cortisol secretion is autonomous and pituitary ACTH secretion is already suppressed. As with the low-dose DST, there are several versions of the high-dose DST, including the standard 2-day oral high dose (2 mg every 6 hours for 48 hours), the 8-mg overnight oral, the intravenous 4 mg, and the ultra-high-dose (8 mg every 6 hours) tests. Plasma and/or urinary cortisol levels are evaluated before, during, and/or after DST. Suppression of plasma cortisol to 50% of baseline provides a specificity of up to 80%.
4. Perform inferior petrosal sinus sampling. If the above tests point to an ACTH-dependent process but no adenoma is evident on MRI, the next step should be bilateral inferior petrosal sinus sampling. An experienced radiologist catheterizes both inferior petrosal sinuses, and samples for ACTH are obtained simultaneously from both the sinuses and a peripheral vein before and at 3, 5, and 10 minutes after intravenous administration of ovine CRH (1 µg/kg or 100 µg/1 kg). An inferior petrosal sinus–to–peripheral ACTH ratio greater than 2.0 at baseline or after CRH administration is consistent with Cushing’s disease. Lower ratios suggest an ectopic ACTH-secreting tumor. A side-to-side ratio of 1.4 or greater may provide direction to neurosurgeons performing transsphenoidal hypophysectomy when no tumor is evident on MRI.
In Search of Occult Ectopic ACTH-Secreting Tumors

If bilateral inferior petrosal sinus sampling confirms the lack of a pituitary ACTH gradient, perform CT and/or MRI of the neck, thorax, and abdomen, because most nonpituitary ACTH-secreting tumors are NETs, as noted previously. Additionally, perform MRI of the chest, because this imaging procedure may uncover (central) bronchial carcinoids missed by CT. Somatostatin analog scintigraphy with $^{111}$In-pentetreotide (OctreoScan) may identify a few occult ACTH-secreting tumors with somatostatin receptors that were not clearly identified by CT or MRI imaging. Positron emission tomography scanning may also prove helpful in the search for occult ACTH-secreting tumors.

Other procedures that have been used to discriminate between pituitary-dependent and ectopic ACTH syndromes include desmopressin with or without CRH; the GH secretatogogues hexarelin and ghrelin, which stimulate ACTH in patients with pituitary adenomas but not in normals; and the opiate agonist loperamide, which suppresses normals but not patients with Cushing’s disease. None of these research procedures can be recommended for standard clinical practice as of yet.

ICD-9 CODE: Cushing’s Syndrome/Cushing’s Disease 255.0

(See Pituitary and Hypothalamic Disorders Tests [Chapter 5] for specific tests and CPT codes)
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

Other Pituitary Hypersecretion Syndromes

TSH-Secreting Pituitary Adenomas (TSHoma)

Thyroid-stimulating hormone is a glycoprotein produced in the pituitary consisting of two subunits: α and β. The α subunit is identical or similar to that of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and chorionic gonadotropin. The β subunit is specific to TSH. The secretion of TSH is controlled by release of thyrotropin-releasing hormone (TRH) from the hypothalamus. TSH stimulates all metabolic and cellular processes involved in synthesis and secretion of thyroid hormones. TSH also stimulates intermediary metabolism and thyroid growth. TSH initiates release of thyroxine and triiodothyronine from thyroglobulin. TSH is increased in almost all cases of primary hypothyroidism and decreased in most cases of hyperthyroidism; TSH thyrotoxicosis is one exception. TSH secretion is increased by estrogens and suppressed by androgens and corticosteroids.

Thyrotropin-releasing hormone is a tripeptide produced primarily by the hypothalamus. TRH is produced from a prohormone that contains multiple copies of the TRH molecule. Several TRH entities can be released from one precursor. TRH has a stimulatory effect on the pituitary, causing it to release TSH. TRH secretion is controlled by hormones via a negative feedback system. Binding of TRH to its receptor causes a rise in calcium, which initiates TSH secretion. It also stimulates adenyl cyclase in the pituitary. Additionally, TRH stimulates secretion of prolactin, GH in acromegaly, and ACTH in Cushing’s and Nelson’s syndromes. Levels of TRH are undetectable or very low in patients with hyperthyroidism and hypothalamic hypothyroidism. Levels are elevated in patients with primary and pituitary hypothyroidism.

What to Look For

Distinguishing Signs and Symptoms

- Approximately 300 cases have been reported in the last 35 years. Previously, TSHomas were not found until they had grown to macroadenoma size (>10 mm); more recently, some of these tumors are discovered at the microadenoma size as a result of the 100-fold increase in sensitivity in TSH assays.
- When pituitary adenomas secrete TSH, they are autonomous and refractory to the negative feedback of thyroid hormones (i.e., inappropriate TSH secretion) and can produce hyperthyroidism. Thus, the key finding is detectable serum TSH levels in the presence of elevated free tri-iodothyronine (T4) and free thyroxine (T3) concentrations. TSH concentrations may be elevated or normal.
- Earlier diagnosis and treatment directed at the pituitary, as opposed to the thyroid, may prevent the loss of visual field caused by impingement on the optic chiasm and hypopituitarism that occur as the tumors enlarge, and furthermore may improve the rate of neurosurgical cure.
TSHomas present with signs and symptoms of hyperthyroidism including goiter, and 25% of these tumors show mixed pituitary hormone secretion, usually GH or prolactin, thus patients should be evaluated for galactorrhea/amenorrhea and acromegaly.

The Next Step

Hormones and Peptides

- TSH
- Free T4 and free T3
- Prolactin
- GH and IGF-1
- α-GSU
- LH, FSH
- Testosterone, sex hormone–binding globulin, or estradiol
- Cortisol and ACTH

Dynamic testing may be required to uncover hypocortisolism. See Pituitary and Hypothalamic Disorders, discussed earlier in this chapter.

Dynamic Testing

- T3 suppression test (75–100 µg/d orally in divided doses for 8–10 days). Inhibition of TSH secretion after T3 suppression test has never been recorded in patients with TSHoma. However, this test is strictly contraindicated in elderly patients or in those with coronary heart disease.
- TRH test. Widely used to investigate the presence of a TSHoma. The TRH collection instructions are available on page 163. After intravenous administration of 200 µg TRH, TSH and α-GSU levels generally do not increase in patients with TSHoma.
- Somatostatin suppression test. Administration of somatostatin or its analogs (octreotide and lanreotide) reduces TSH levels in most cases and may predict the efficacy of long-term treatment, but it is not considered diagnostic for TSHoma.

Imaging Studies and Localization of the Tumor

Nuclear MRI is preferred for imaging other tumors of the sella turcica, such as TSHomas. CT may be used as an alternative to MRI in patients with a contraindication (e.g., pacemaker, claustrophobia).

For more information go to:
http://www.thyroidmanager.org/Chapter13/13A-text.htm

Gonadotropin or α-GSU–Secreting Pituitary Adenomas

Many pituitary adenomas stain positively for either LH or FSH or for their α-glycoprotein subunit (and also that of TSH and human chorionic gonadotropin) few patients have elevated gonadotropin levels. Gonadotropinomas (or α-GSUomas) generally present as macroadenomas with visual field loss, headaches,
or hypopituitarism including infertility, early menopause, or male hypogonadism. In general, elevations of both LH and FSH imply primary hypogonadism rather than gonadotropinoma. Because α-GSU is frequently secreted in mixed or “silent” pituitary adenomas, its concentration should be measured as part of the evaluation of any pituitary adenoma.

ICD-9 CODE: Pituitary Syndrome 253.0
ICD-9 CODE: Other/Unspecified Anterior Pituitary Hyperfunction 253.1
ICD-9 CODE: Thyrotoxicosis of Other Specified Origin Without Mention of Crisis or Storm; Overproduction of TSH 242.80
ICD-9 CODE: Thyrotoxicosis of Other Specified Origin Without Mention of Crisis or Storm; Overproduction of TSH 242.81
ICD-9 CODES for Pituitary Neoplasm

<table>
<thead>
<tr>
<th>Site</th>
<th>Malignant</th>
<th>Benign</th>
<th>Uncertain Behavior</th>
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<td>Pituitary gland</td>
<td>194.3</td>
<td>227.3</td>
<td>237.0</td>
<td>239.74</td>
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</table>

(See Pituitary and Hypothalamic Disorders Tests [Chapter 5] for specific tests and CPT codes)
Pituitary Hormone Insufficiency (Childhood)

Multiple childhood tumors can affect pituitary function, including craniopharyngioma, germinoma, hamartoma, low-grade astrocytoma, Langerhans’ cell histiocytosis, and dermoid and epidermoid tumors. These generally compress the hypothalamus or, in the case of craniopharyngioma and germinoma, the pituitary stalk. Benign pituitary adenomas frequently affect the anterior pituitary. Common posterior pituitary lesions include astrocytoma and Langerhans’ cell histiocytosis.

What to Look For

Distinguishing Signs and Symptoms

• Raised intracranial pressure caused by expansion of tumor with obstruction of the cerebrospinal fluid (CSF), causing headaches, vomiting, and papilledema.
• Cranial nerve palsies, visual field defects, and hypothalamo-hypophyseal dysfunction (one third of cases as the initial presentation).
• Hyposcretion (and occasionally hypersecretion) of pituitary hormones. These are usually easy to recognize.
• Hypothalamo-pituitary syndromes, characterized by variable endocrine disturbances, occur in association with hypothalamic dysfunction. (The hypothalamus is important for the control of many basic cerebral functions, such as appetite, emotion, and temperature homoeostasis).
• Craniopharyngioma and peripituitary lesions with suprasellar extension may cause visual difficulties due to the compression of the optic nerves and/or chiasm.
• Hypopituitarism. Usually, hormone loss is sequential, beginning with loss of GH secretion, followed by gonadotropins, TSH, and ACTH. In children, in contrast to adults, the loss of GH secretion is usually more obvious with growth failure and possibly hypoglycemia.
• Central precocious puberty, defined as signs of puberty (breast development in girls, and increase in testicular volume in boys) occurring under the age of 8 years in a girl and 8.5 years in a boy. These symptoms are gonadotropin dependent and therefore are ameliorated by long-acting gonadotropin-releasing hormone agonists, which downregulate the pituitary gonadotropin-releasing hormone receptors.
• Hypothalamopituitary tumors in the peripubertal age range may present as failure to enter puberty or arrested pubertal development and consequent blunted or even absent growth spurt.

If onset of gonadotropin-releasing hormone insufficiency occurs during fetal development (i.e., congenital), the male genitalia will be abnormal, with micropenis and bilateral small undescended testes due to failure of testosterone secretion in utero. Under these circumstances, perform MRI of the olfactory bulbs/grooves to seek evidence of Kallmann’s syndrome.

ICD-9 CODE: Hypopituitarism 253.2
Hormone therapy 253.7
Hypophysectomy 253.7
Radiotherapy 253.7
Postablative 253.7
Postpartum hemorrhage 253.2

(See Pituitary and Hypothalamic Disorders Tests [Chapter 5] for specific tests (mentioned above) and CPT codes)
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Diabetes Insipidus (Adulthood)
Vasopressin is derived from the supraoptic and periventricular nuclei of the hypothalamus and is released from the nerve endings in the neurohypophysis (i.e., posterior pituitary). Before overt diabetes insipidus occurs, 85% to 90% of vasopressin secretion must be lost. New-onset diabetes insipidus should raise suspicion of a tumor, although 50% of acquired cases have an autoimmune etiology. Tumors may be occult for many years; thus, patients often require serial neuroimaging to reveal the diagnosis.

Causes

Hypothalamic (Central) Diabetes Insipidus (HDI)
- Congenital
  - Genetic: Wolfram syndrome or diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD)
  - Developmental syndromes: septo-optic dysplasia, Lawrence-Moon-Biedel syndrome
- Idiopathic
- Acquired
  - Trauma
  - Neurosurgical injury (transcranial, transsphenoidal)
- Tumor
  - Craniopharyngioma, pinealoma, germinoma, metastases, pituitary macroadenoma (unusual cause as it is a hypothalamic disease)
- Inflammatory
  - Granulomas
  - Sarcoid
  - Tuberculous meningitis
  - Langerhans’ cell histiocytosis
  - Meningitis, encephalitis
- Infundibuloneurohypophysitis
- Autoimmune
  - Anti-vasopressin neuron antibodies
- Vascular
  - Aneurysm
  - Infarction: Sheehan’s syndrome, sickle cell disease
- Pregnancy (associated with vasopressinase)

Nephrogenic Diabetes Insipidus (NDI)
- Genetic
  - X-linked recessive (V2-R defect)
  - Autosomal recessive (AQP2 defect)
  - Autosomal dominant (AQP2 defect)
- Idiopathic
- Chronic renal disease (e.g., polycystic kidneys)
• Metabolic disease
  - Hypercalcemia
  - Hypokalemia
• Drug induced
  - Lithium
  - Demeclocycline
  - Platinum-based antineoplastic drugs
• Osmotic diuretics
  - Glucose
  - Mannitol
  - Urea (post–obstructive uropathy)
• Systemic disorders
  - Amyloidosis
  - Myelomatosis
• Pregnancy

Dipsogenic Diabetes Insipidus (DDI)
• Compulsive water drinking associated with psychologic disorders (i.e., psychogenic polydypsia)
• Drug induced

Structural/Organic Hypothalamic Disease
• Tumors involving hypothalamus
• Head injury

Granulomatous Diseases
• Sarcoid
• Tuberculous meningitis
• Langerhans’ cell histiocytosis

What to Look For

Distinguishing Signs and Symptoms
• Thirst
• Polydipsia
• Polyuria

Exclude the following conditions:
• Hyperglycemia
• Hypokalemia
• Hypercalcemia
• Renal insufficiency

Measure the following values:
• 24-Hour urine volume (abnormal is >40 mL/kg/24 hours)
• Serum sodium (generally maintained in the high-normal range in HDI, but generally maintained in the low-normal range in DDI)
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- Glucose
- Blood urea nitrogen (BUN)
- Serum and urine osmolality
- Plasma vasopressin

The Next Step

Request water deprivation/desmopressin test to determine whether HDI, NDI, or DDI.
- HDI: urine osmolality is less than 300 mOsm/kg accompanied by plasma osmolality greater than 290 mOsm/kg after dehydration; urine osmolality should rise above 750 mOsm/kg after desmopressin acetate (DDAVP)
- NDI: failure to increase urine osmolality above 300 mOsm/kg after dehydration, with no response to DDAVP
- DDI: appropriate urine concentration during dehydration without significant rise in plasma osmolality

If HDI is diagnosed, the next step should be imaging of the hypothalamus/perisellar region with MRI to exclude possible tumors. HDI frequently is associated with loss of the normal posterior pituitary bright spot on T1-weighted MRI, which correlates with posterior pituitary vasopressin content.

For more information go to:
http://www.endotext.com/neuroendo/neuroendo11a/neuroendoframe11a.htm (Children)
http://www.endotext.com/neuroendo/neuroendo2/neuroendoframe2.htm (Diabetes Insipidus and Syndrome of Inappropriate Antidiuretic Hormone [SIADH])

ICD-9 CODE: Diabetes Insipidus 253.5
ICD-9 CODE: Nephrogenic Diabetes Insipidus 588.1
ICD-9 CODE: Pituitary Diabetes Insipidus 253.5
ICD-9 CODE Vasopressin-Resistant Diabetes Insipidus 588.1

(See Water Deprivation/Desmopression Test for Diabetes Insipidus: Hypothalamic [HDI], Nephrogenic [NDI], and Dipsogenic [DDI] [Chapter 5] for specific tests and CPT codes)
Hyponatremia and Syndrome of Inappropriate Antidiuretic Hormone

Hyponatremia (serum sodium level <135 mEq/L) and hypo-osmolality are the most common fluid and electrolyte disorders in hospitalized patients with hyponatremia and syndrome of inappropriate antidiuretic hormone (SIADH). Hyponatremia is important clinically because severe hypo-osmolality (serum sodium level <120 mEq/L) is associated with substantial morbidity and mortality. Excessively rapid correction of hyponatremia can itself cause severe neurologic morbidity and mortality due to osmotic demyelinization (i.e., central pontine demyelinization).

What to Look For

Distinguishing Signs and Symptoms
- Lethargy
- Anorexia
- Headache
- Nausea
- Vomiting
- Muscle cramps
- Disorientation
- Seizure
- Coma
- Death

Criteria for Diagnosis of Hyponatremia Due to SIADH
- Hyponatremia with appropriately low plasma osmolality (<280 mOsm/kg)
- Urine osmolality greater than 100 mOsm/kg (i.e., less than maximally dilute) at a time when the plasma is hypo-osmolar
- Renal (urine) sodium excretion greater than 30 mM/L
- Absence of hypotension, hypovolemia, and edema-forming states
- Normal cardiac, renal, pituitary, thyroid, and adrenal function

Differential Diagnosis
Plasma osmolality can be calculated as \( \text{mOsm/kg } H_2O = 2x [Na^+] (\text{mEq/L}) + \text{glucose (mg/dL)/18 + BUN (mg/dL)/2.8} \) and is accurate under usual conditions but can be misleading under the following conditions:
- Pseudohyponatremia, which is due to gross hyperlipidemia (triglycerides or cholesterol) or serum proteins
- Isotonic or hypertonic hyponatremia, which is due to high concentrations of other solutes (e.g., glucose, mannitol, alcohols/ethylene glycol, radiocontrast dyes, urea)

Hypotonic hyponatremia is best determined by directly measuring plasma osmolality. If direct and calculated measurements agree, then calculated osmolality can be used subsequently.
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Measure the following levels:
• Plasma osmolality
• Serum sodium
• Glucose
• BUN
• Ethanol, methanol, etc. (depending on the situation)
• Urine osmolality
• Urine sodium
• Serum uric acid

Causes of Hypotonic Hyponatremia
• Sodium depletion
  - Renal loss
  - Diuretics
  - Salt-wasting nephropathy
  - Central salt wasting
• Extrarenal loss
  - GI losses (vomiting, diarrhea)
  - Sweating
  - Hemorrhage
• Hypoadrenalism (renal losses if primary, decreased free water excretion in primary or secondary)
• Reduced renal free water clearance
  - Hypovolemia
  - Cardiac failure
  - Nephrotic syndrome
  - Hypothyroidism
  - Renal failure
  - Ascites
  - Hypoalbuminemia
  - Sepsis and vascular leak syndromes
  - Fluid sequestration
• Excess water intake
  - DDI at times when water intake exceeds renal clearance
  - Sodium-free, hyposomolar irrigant solutions
  - Dilute infant feeding formula
  - SIADH

Causes of Drug-Induced Hyponatremia
• Saline depletion: diuretics, spironolactone, thiazides, loop diuretics plus angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers
Causes of Vasopressin-Like Activity

- DDAVP
- Oxytocin
- Potentiation of vasopressin action
- Nonsteroidal anti-inflammatory agents
- Carbamazepine
- Chlorpropamide
- Cyclophosphamide
- Ifosfamide
- Cisplatin
- Carboplatin
- Vincristine
- Vinblastine

Causes of SIADH Other Than Drugs

- Neoplastic disease
- Chest disorders
  - Carcinoma (bronchus, duodenum, pancreas, bladder, ureter, prostate)
  - Thymoma
  - Mesothelioma
  - Lymphoma, leukemia
  - Carcinoid
  - Bronchial adenoma
  - Pneumonia
  - Tuberculosis
  - Empyema
  - Cystic fibrosis
  - Pneumothorax
- Neurological disorders
  - Head injury, neurosurgery
  - Brain abscess or tumor
  - Meningitis, encephalitis
  - Guillain-Barré syndrome
  - Cerebral hemorrhage
  - Cavernous sinus thrombosis
  - Hydrocephalus
  - Cerebellar and cerebral atrophy
  - Shy-Drager syndrome
  - Peripheral neuropathy
  - Seizures
  - Subdural hematoma
  - Alcohol withdrawal
• Miscellaneous
  - Idiopathic
  - Psychosis
  - Porphyria
  - Abdominal surgery
• Drug-induced
  - Dopamine antagonists: phenothiazines, butyrophenones, etc.
  - Antidepressants: tricyclics, monoamineoxidase inhibitors, selective serotonin reuptake inhibitors, venlafaxine
  - Opiates
  - Antiepileptics: carbamazepine, oxcarbazipine, sodium valproate
  - 3,4-Methylenedioxymethamphetamine (MDMA; ecstasy)
  - Clofibrate
  - Cyclophosphamide
  - Chlorpropamide

Table 2-5 provides a diagnostic schema for hyponatremia.

<table>
<thead>
<tr>
<th>Extracellular Na+</th>
<th>Hypovolemia</th>
<th>Euvolemia</th>
<th>Hypervolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph" /></td>
<td>↓↓</td>
<td>→</td>
<td>↑</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total body water</th>
<th>↓</th>
<th>↑</th>
<th>↑↑</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Common causes</th>
<th>Hypovolemia</th>
<th>Euvolemia</th>
<th>Hypervolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineralocorticoid deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt-losing nephritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral salt wasting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra-renal loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIADH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sick cell syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinary Na+ (mmol/L)</th>
<th>&gt;20</th>
<th>&lt;10</th>
<th>&gt;20</th>
<th>&lt;10</th>
<th>&gt;20</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Plasma osmolality (mOsm/kg)</th>
<th>&gt;280</th>
<th>&gt;280</th>
<th>&gt;280</th>
<th>&lt;280</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Urine osmolality (mOsm/kg)</th>
<th>&gt;280</th>
<th>&lt;280</th>
<th>&gt;280</th>
<th>&lt;280</th>
</tr>
</thead>
</table>

ICD-9 CODE: Hyponatremia 271.1
ICD-9 CODE: SIADH 253.6

(See test sections mentioned above and Waterload Test for Impaired Water Clearance [Chapter 5] for specific tests and CPT codes)
Obesity

In the United States, approximately two of three persons over the age of 40 years are overweight. Furthermore, there is increasing concern about the number of children and adolescents with excess adiposity. Obesity is associated with high costs in morbidity, including a significantly increased risk of type 2 diabetes and cardiovascular disease. The comorbidities of diabetes and their prevalences are provided in Table 2-6 and Figure 2-4.

Table 2-6. Comorbidities of Diabetes

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hypertension</td>
<td>- Dyspnea and fatigue</td>
</tr>
<tr>
<td>- Congestive heart failure</td>
<td>- Obstructive sleep apnea</td>
</tr>
<tr>
<td>- Cor pulmonale</td>
<td>- Hypoventilation syndrome</td>
</tr>
<tr>
<td>- Varicose veins</td>
<td>- Pickwickian syndrome</td>
</tr>
<tr>
<td>- Pulmonary embolism</td>
<td>- Coronary artery disease</td>
</tr>
<tr>
<td>- Meralgia paresthetica</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Endocrine</td>
</tr>
<tr>
<td>- Stroke</td>
<td>- Metabolic syndrome</td>
</tr>
<tr>
<td>- Idiopathic intracranial hypertension</td>
<td>- Type 2 diabetes</td>
</tr>
<tr>
<td>- Meralgia paresthetica</td>
<td>- Dyslipidemia</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>- Polycystic ovarian syndrome/</td>
</tr>
<tr>
<td>- Hyperuricemia and gout</td>
<td>hyperandrogenism</td>
</tr>
<tr>
<td>- Immobility</td>
<td>- Amenorrhea/infertility/ menstrual disorders</td>
</tr>
<tr>
<td>- Degenerative arthritis</td>
<td></td>
</tr>
<tr>
<td>- Low back pain</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Integumentary</td>
<td>- Gastroesophageal reflux disease</td>
</tr>
<tr>
<td>- Stasis pigmentation of legs</td>
<td>- Nonalcoholic fatty liver disease</td>
</tr>
<tr>
<td>- Cellulitis</td>
<td>- Cholelithiasis</td>
</tr>
<tr>
<td>- Acanthosis nigricans/skin tags</td>
<td>- Hernias</td>
</tr>
<tr>
<td>- Intertrigo, carbuncles</td>
<td>- Colon cancer</td>
</tr>
<tr>
<td>- Striae distensae (stretch marks)</td>
<td></td>
</tr>
<tr>
<td>- Lymphedema</td>
<td>Genitourinary</td>
</tr>
<tr>
<td>Psychological</td>
<td>- Urinary stress incontinence</td>
</tr>
<tr>
<td>- Depression/low self-esteem</td>
<td>- Hypogonadism (male)</td>
</tr>
<tr>
<td>- Impaired quality of life</td>
<td>- Breast and uterine cancer</td>
</tr>
<tr>
<td>- Social stigmatization</td>
<td>- Pregnancy complications</td>
</tr>
<tr>
<td></td>
<td>- Obesity-related glomerulopathy</td>
</tr>
</tbody>
</table>

How Is Obesity Defined?

Obesity is defined in several different ways. The most common method is calculation of the body mass index (BMI) using the following formula: BMI = ((weight in pounds) / (height in inches) x (height in inches)) x 703. Typically, a table of BMI levels is used. Figure 2-5 allows persons to determine their degree of overweight.

Figure 2-4. Proportion of Disease Prevalence Attributable to Obesity (Adapted from Wolf AM, Colditz GA. Current estimates of the economic cost of obesity in the United States. Obes Res. 6:97-106, 1998.)

Figure 2-5. Body Mass Index Levels
The National Institutes of Health, specifically the National Heart Lung and Blood Institutes and the National Institute for Diabetes and Digestive and Kidney Diseases, together with the North American Association for the Study of Obesity, released guidelines for the treatment of obesity in 2002. These guidelines identify degrees of obesity using BMI as shown in Figure 2-5. This chart provides an easy way to calculate BMI. The area shaded in dark blue represents patients with a BMI >30. These patients are classified as obese and are at high risk for obesity-associated mortality and comorbid diseases. The area shaded in medium blues or dark gray represents patients with BMIs of 25 to 29.9. These patients are classified as overweight with an increased risk of obesity-associated mortality and comorbid diseases. The area shaded in light gray represents patients with normal BMIs (18.5–24.9). A patient with a BMI in the white area is underweight. As an example, a person who is 6 feet tall and weighs 180 lb has a BMI of 24 (see black circle, Fig. 2-5). With increasing abdominal obesity in particular, macrophages infiltrate adipose tissue and secrete a variety of cytokines that cause inflammation, insulin resistance, and predispose to atherosclerotic vascular disease including hypertension, dyslipidemia, type 2 diabetes, and enhanced predisposition to thrombosis. Thus, in obesity it is now possible to evaluate a patient’s risk profile for the development of these comorbidities.

There are key hormones produced by adipose tissue, such as leptin, that signal the brain regarding satiety and food intake (Fig. 2-6).
Adipose tissue also produces cytokines such as resistin and omentin that increase the resistance to insulin (Fig. 2-7), and the gut produces ghrelin (mostly from the duodenum), which is a satiety signal with receptors in the hypothalamus.

**What to Look For**

**Distinguishing Signs and Symptoms**
- BMI >25 (increased risk of morbidity)
- Increased waist circumference (men: >102 cm [>40 in]; women: >88 cm [>36 in])
- Family history of obesity, diabetes, or heart disease
- Evidence of any of the comorbidities listed in Table 2-6
- Risk factor assessment

**The Next Step**
- Recommend the following measures:
  - Reduced-calorie diet (20% below usual intake)
  - Increased physical activity to improve cardiovascular functions (not likely to reduce weight but has potential to reduce comorbidities)
  - Pharmacological treatments
- Consider bariatric surgery (e.g., gastric bypass in severe obesity [BMI >40])
Table 2-7 provides a diagnostic schema for underlying causes of obesity.

Table 2-7. Diagnostic and Laboratory Evaluation of the Obese Patient Based on Presentation of Symptoms and Risk Factors

<table>
<thead>
<tr>
<th>For Diagnosis of</th>
<th>Confirming With</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar hypoventilation (syndrome, hyperventilation, possible right-sided heart failure)</td>
<td>- Complete blood count rule out polycythemia</td>
</tr>
<tr>
<td></td>
<td>- Pulmonary function tests to measure if lung function is reduced</td>
</tr>
<tr>
<td></td>
<td>- Blood gases measure if CO₂ is elevated</td>
</tr>
<tr>
<td></td>
<td>- Electrocardiogram rule out right-heart strain</td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>- 24-Hour urine screen for free cortisol (&gt;150 μg/24 h considered normal)</td>
</tr>
<tr>
<td></td>
<td>- Overnight DST: 1 mg orally at 11:00 pm. At precisely 8:00 am the next morning, draw serum cortisol (&lt;5 μg is normal suppression; axis intact). Failure of suppression indicates dysregulation, possibly Cushing's syndrome</td>
</tr>
<tr>
<td>Gallstones</td>
<td>- Ultrasonography of gallbladder</td>
</tr>
<tr>
<td>Hepatomegaly/nonalcoholic steatohepatitis</td>
<td>- Liver function tests</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>- Serum TSH (normal &lt;5 μU/mL)</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>- Insulin and C-peptide levels will be elevated if insulinoma is present. (Patient should be off insulin and other hyperglycemic drugs for 48 hours prior to test.)</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>- Sleep studies for oxygen desaturation, apneic, and hypopneic events; ear, nose and throat examination for upper airway obstruction</td>
</tr>
<tr>
<td>Polycystic ovary syndrome (PCOS; oligomenorrhea, hirsutism, obesity, and enlarged palpable ovaries)</td>
<td>- Increase in LH/FSH ratio, often &gt;2.5. Increased LH stimulates testosterone and androstenedione, converting it to estrone in adipose tissue, leading in turn to increased LH and a continuous cycle.</td>
</tr>
</tbody>
</table>


ICD-9 CODE: Obesity 278.00

- Adrenal 255.8
- Due to hyperalimentation 278.00
- Endocrine NEC 259.9
- Endogenous 259.9
- Adiposogential dystrophy 253.8
- Glandular NEC 259.9
- Hypothyroid 244.9
- Morbid 278.01
- Of pregnancy 646.1
- Severe 278.01
- Thyroid 244.9

Reference

**Metabolic Syndrome**

The metabolic syndrome is also referred to as dysmetabolic syndrome, syndrome X, insulin resistance syndrome, and multiple metabolic syndrome. It affects 47 million adult Americans, or more than one in five people.

**What to Look For**

**Distinguishing Signs and Symptoms**

Obesity, particularly abdominal obesity, is the hallmark of this condition (Fig. 2-8), and is frequently associated with the following conditions:

- Diabetes and hyperglycemia
- Abnormal lipid profile
- Hyperinsulinemia and/or insulin resistance which may promote vascular endothelial dysfunction and hypertension
- Vascular inflammation
- Accelerated cardiovascular disease
- Derangements of adipocyte cytokines

![Figure 2-8. Visceral Fat Distribution Seen on Abdominal CT and the Use of a Tape Measure](image-url)
There are different criteria (Grundy 2004) for the syndrome based on the World Health Organization (WHO), and the National Cholesterol Education recommends the diagnosis be based on the presence of three of the biochemical values noted in Table 2-8.

**Table 2-8. Diagnostic Criteria for the Dysmetabolic Syndrome: A Comparison of ATPIII and WHO Definitions**

<table>
<thead>
<tr>
<th>Factors for Metabolic Syndrome</th>
<th>ATPIII (3 or More)</th>
<th>Factors for Metabolic Syndrome</th>
<th>WHO (1998) IGT or Insulin Resistance (2 or More)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>&gt;88 cm (&gt;36 in)</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>Triglyceride level</td>
<td>&gt;150 mg/dL</td>
<td>Triglyceride level</td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol level</td>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Blood pressure</td>
<td>&gt;130/85 mm Hg</td>
<td>Blood Pressure</td>
</tr>
<tr>
<td></td>
<td>Fasting blood glucose level</td>
<td>&gt;110 mg/dL</td>
<td>Fasting blood glucose level</td>
</tr>
<tr>
<td></td>
<td>Microalbuminuria</td>
<td>&gt;20 mg/g Cr on at least 2 different occasions</td>
<td></td>
</tr>
</tbody>
</table>


The WHO has a similar definition but requires the sine qua non of an elevated fasting glucose (>110 mg/dL) or a postprandial glucose greater than 200 mg/dL. The American Association of Clinical Endocrinologists proposes a third set of clinical criteria that is a hybrid of the above two but adds age, a family history of vascular disease or diabetes, and inclusion in ethnic groups with a high incidence of diabetes. No defined number of risk factors are specified, rather, identification of the syndrome is left to clinical judgment.

**Insulin Resistance**

Insulin resistance cannot simply be defined by the presence of obesity and hyperglycemia, although in practice this is usually the case. Patients with type 1 diabetes or chronic pancreatitis are hyperglycemic but usually do not have insulin resistance, and there are many syndromes associated with extreme insulin resistance that are not associated with obesity. These include inherited lipodystrophies (complete or partial absence of body fat), insulin receptor mutations (leprechaunism), counter-regulatory hormone excess (e.g., glucocorticoids, GH, catecholamines), pregnancy, starvation, kidney failure, and liver failure (Fig. 2-9).
The gold standard for diagnosing insulin resistance is the euglycemic insulin clamp. Insulin-induced glucose uptake is measured while insulin is infused at a constant rate and the blood glucose concentration is kept constant with a variable glucose infusion to avoid the confounding effect of the counter-regulatory hormones glucagons and epinephrine. This procedure allows determination of the rate of maximal glucose uptake under maximal insulin stimulation. Muscle is the organ most responsible for glucose disposal and is believed to be the major tissue responsible for apparent insulin resistance. Because the insulin clamp is a cumbersome and labor-intensive test, it is only used in research settings. The following metabolic markers have been found to correlate with insulin resistance:

- Triglyceride level greater than 150 mg/dL
- Triglyceride/HDL ratio greater than 3
- Fasting serum insulin level greater than 25 µU/mL

Another laboratory test that generally correlates with the insulin clamp technique is the homeostasis model assessment of insulin resistance (HOMA IR). In this test, the product of fasting glucose (in milligrams per deciliter) and fasting insulin (in microunits per milliliter) of <2.77 correlates loosely with insulin insensitivity.

THE NEXT STEP

Initiate lifestyle changes with nutritional therapy, exercise therapy, and appropriate medications to target associate conditions such as dyslipidemia, hyperglycemia, high blood pressure, and cardiovascular disease. Therapy should be tailored to fit individual needs.

ICD-9 CODE: Dysmetabolic Syndrome X 277.7

(See Diabetes Type 2 Screen [Chapter 4] for lipoprotein profile, peptides and cytokines and Oxidative/Nitrosative Stress Profile [Chapter 4] for specific tests and CPT codes)

Reference

Polycystic Ovary Syndrome

Initially described by Stein and Leventhal (1935) as amenorrhea associated with polycystic ovaries, classic polycystic ovary syndrome (PCOS), which is associated with obesity, acne, and hirsutism in one third of patients, is extremely complex. Two thirds of PCOS patients are not obese, nor are they hirsute. A more functional definition would be chronic, unexplained hyperandrogenism in young women; approximately 95% of these patients are diagnosed with PCOS. This definition is more accurate because 50% of patients with PCOS may not have polycystic ovaries or an elevated LH, which were previously part of the diagnostic constellation.

LH excess is postulated to arise from lack of pituitary suppression because of altered sex steroid feedback (increased androgens counteracting the normally suppressive effects of progesterone on LH release). Paradoxically, the more obese the patient, the more likely LH levels will be normal, perhaps related to hyperinsulinism-induced upregulation of ovarian LH receptors.

Infertility and anovulation are not always seen with PCOS, and some patients with obesity and hyperandrogenism are reproductively normal. Patients with PCOS who seek medical attention because of infertility or hirsutism represent only a small proportion of the population with the syndrome.

What to Look For

Distinguishing Signs and Symptoms

• Hirsutism
• Hyperandrogenism
  - Acne
  - Hair loss
• Hyperhidrosis
• Virilization (rare)
• Menstrual irregularity
  - Oligorrhea or amenorrhea
  - Anovulation with infertility
• Obesity
• Insulin resistance
• Acanthosis nigricans (hyperandrogenism, insulin resistance, and acanthosis nigricans [HAIR-AN] syndrome)

Rule out other causes of androgen excess, which may include the following:

• Cushing’s syndrome
• Congenital adrenal hyperplasia
• Ovarian and adrenal tumors
• Ovarian hyperthecosis
• Hyperprolactinemia
**The Next Step**

**Hormones and Peptides**
- Total and free testosterone
- Sex hormone–binding globulin
- Dehydroepiandrosterone sulphate
- Prolactin
- TSH
- 17-Alphahydroxy progesterone
- Glucose (fasting)
- Insulin
- C-peptide

ICD-9 CODE: PCOS 256.4

ICD-9 CODE: Amenorrhea 626.0
- Ovarian dysfunction 256.8
- Hyperhormonal 256.8

ICD-9 CODE: Oligomenorrhea 626.1

ICD-9 CODE: Hirsutism 704.1

ICD-9 CODE: Hyperhidrosis 705.21

ICD-9 CODE: Obesity 278.00

ICD-9 CODE: Acanthosis Nigricans 701.2

ICD-9 CODE: Virilization 255.2

*(See Polycystic Ovary Syndrome Screen [Chapter 4] for specific tests and CPT codes)*
**DIABETES MELLITUS**

**What to Look For**

**Distinguishing Signs and Symptoms**

Criteria for the diagnosis of diabetes mellitus are presented in Table 2-9.

<table>
<thead>
<tr>
<th>Table 2-9. Criteria for the Diagnosis of Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.</td>
</tr>
<tr>
<td>2. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.</td>
</tr>
<tr>
<td>3. 2-Hour postload glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.</td>
</tr>
</tbody>
</table>


There are two major forms of diabetes mellitus: type 1 and type 2 (Table 2-10).

<table>
<thead>
<tr>
<th>Table 2-10. Characteristics of Type 1 and Type 2 Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Age at diagnosis</td>
</tr>
<tr>
<td>Body weight</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Insulin level</td>
</tr>
<tr>
<td>Ketoacidosis</td>
</tr>
<tr>
<td>Hyperosmolar coma</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
</tr>
<tr>
<td>HLA</td>
</tr>
</tbody>
</table>
Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (previously called juvenile-onset) is characterized by insulin deficiency secondary to the immune destruction of the pancreatic beta cells. The patient cannot survive without exogenous insulin. Other islet cells, including alpha, delta, and PP cells, are normally unaffected. There is a partial genetic link associated with type 1 diabetes, but only about 35% of monozygotic twins share the disorder. Rubella, thyroiditis, and other immunologic disorders tend to coexist with increased incidence of type 1 diabetes. The presence of insulin antibodies and islet cell antibodies are often detected in relatives of patients with type 1 diabetes who subsequently develop the disorder.

Onset can occur soon after birth. However, there is an increase in the onset of type 1 diabetes with the onset of puberty and the development of secondary sexual characteristics. There is a strong association between the histocompatibility (i.e., human leukocyte antigen [HLA]) types and predisposition to and protection from type 1 diabetes (Fig. 2-10).

Figure 2-10. The Natural History of Type 1 Diabetes (From Gennuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care. Nov;11:3160-7, 2003.)

- Risk
  - DR3 with DQB1-0201
  - DR4 with DQB1-0302 (2% of the general population and 40% of those with type 1 diabetes have this haplotype)

- Protection
  - DR2 with DQB1-0602
Type 1 diabetes is an autoimmune condition, and a number of molecular antigens have been characterized:

- Insulin autoantibodies (IAA)
- 64-kd Glutamic acid decarboxylase (GAD)
- Milk albumin–related molecule (ICA 69)
- Neuroendocrine tyrosine phosphatase (ICA 512)
- GM2-1 islet ganglioside with terminal sialic acid
- 37- to 40-kd Tryptic fragment of non–GAD 64-kd molecule
- 38-kd T-cell–identified autoantigen

**WHAT TO LOOK FOR**

### Distinguishing Signs and Symptoms

- Polyuria
- Polydypsia
- Ketonuria
- Rapid weight loss

### The Next Step

#### Hormones and Peptides

Significant hyperglycemia is the primary indicator of type 1 diabetes. It is an autoimmune syndrome superimposed on a genetic susceptibility (HLA DR3 and DR4) and a viral insult resulting in loss of the first phase of insulin secretion in response to intravenous glucose administration culminating in clinical diabetes with greater than 90% destruction of beta cells in the pancreas, loss of insulin secretion, and C-peptide values less than 0.6 ng/mL.

- Measure insulin secretion using the fasting or arginine-stimulated C-peptide level.
- Test for the presence of insulin antibodies that mask insulin production.
- Type for HLA DR3 and DR4 genotype.
- Test for GAD and islet cell, gastric-parietal cell, adrenal, and thyroid antibodies.

Type 1 diabetes is a manageable condition provided detection and treatment are initiated as early as possible. There are many types of insulin delivery systems, including continuous insulin infusion (pumps), daily injections with long- and short-acting insulins mimicking the action of the normal pancreas, as well as inhaled and oral versions of insulin.

**ICD-9 CODE: Diabetes Type 1 (Not Stated as Controlled) 250.01**

**ICD-9 CODE: Diabetes Type 1 (Uncontrolled) 250.03**

*(See Diabetes Type 1 Screen [Chapter 4] for specific tests and CPT codes)*
Type 2 Diabetes Mellitus

Type 2 diabetes is a disorder characterized by diminished liver, muscle, and adipose sensitivity to insulin (insulin resistance) and impaired β-cell function. At the time of diagnosis, most patients with type 2 diabetes present both impaired β-cell function and insulin resistance. It is difficult to determine the primary defect (Burant 2004).

Insulin resistance, which is present, prior to, and early in the development of type 2 diabetes, is frequently found in the relatives of diagnosed type 2 patients, thus providing a means to identify those at risk.

What to Look For

Distinguishing Signs and Symptoms

- Polyuria
- Polydipsia
- Fatigue
- Dizziness
- Fasting blood glucose (FBG) greater than 126 mg/dL; 7.0 mmol/L; fasting is defined as no caloric intake for 8 hours
- Obesity greater than 120% desirable body weight, BMI greater than 27 kg/m²
- Women with previous gestational diabetes mellitus or history of babies heavier than 9 lbs at birth
- Hypertension or dyslipidemia
- Previously identified impaired glucose tolerance (IGT) or impaired fasting glucose

A complete evaluation should be made to determine the following:

- Type of diabetes
- Presence of underlying diseases requiring further evaluation (Table 2-11)
- Presence of complications of diabetes

Table 2-11. Rare Genetic Abnormalities in Diabetes (<0.5% of Type 2 Diabetes Patients)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genetic Defect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODY 1</td>
<td>HNF 4a 20q</td>
<td>2%–4% MODY</td>
</tr>
<tr>
<td>MODY 2</td>
<td>Glucokinase 7p</td>
<td>11%–63%</td>
</tr>
<tr>
<td>MODY 3</td>
<td>HNF1 a Chr 12</td>
<td>21%–73%</td>
</tr>
<tr>
<td>MODY 4</td>
<td>Ipf-1/PDX-1</td>
<td>1%–4%</td>
</tr>
<tr>
<td>MODY 5</td>
<td>HNF-1b</td>
<td>1%–5%</td>
</tr>
<tr>
<td>Maternally-inherited diabetes and deafness</td>
<td>Mitochondrial 3243 tRNA leucine gene</td>
<td>Rare</td>
</tr>
<tr>
<td>Mutant insulins</td>
<td>Insulin gene defects</td>
<td>Rare</td>
</tr>
<tr>
<td>Defective insulin action</td>
<td>Leprechaunism</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Rabson-Mendenhall</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipoatrophic diabetes</td>
<td></td>
</tr>
</tbody>
</table>
The Next Step

Hormones and Peptides
Hyperinsulinemia is insulin release in response to oral or intravenous glucose.

Who to Test for Asymptomatic Diabetes Mellitus?
- All people over 45 years of age; if negative, repeat tests every 3 years
- Test at younger age if the person has any of the following risk factors:
  - Obesity (body weight >120% or BMI >27 kg/m²)
  - First-degree relative with type 2 diabetes
  - High-risk population (e.g., African American, American Indians, Hispanic American, Pacific Islander)
  - Hypertension (blood pressure >130/90 mm Hg)
  - HDL <40 mg/dL in males; <50 mg/dL in females
  - Triglycerides >150 mg/dL
  - IGT on a previous test

Figure 2-11 shows the pathogenesis of diabetic macrovascular complications.

Figure 2-11. Diabetes Disease Initiation/Progression
This schematic suggests the development of microvascular complications early in the course of the disease, well before clinical diabetes is detected. Certain genetic characteristics of polymorphisms (e.g., apolipoprotein E4 (ApoE4), aldose reductase, ACE) may increase an individual’s predisposition for development of microvascular complications of diabetes, whereas other genetic factors, such as the toll receptor, are protective and decrease predisposition. The various inflammatory mediators...
listed under inflammation in Figure 2-11 cause direct cellular injury and initiate the cycle of functional and progressive pathologic changes, which ultimately manifest as microvascular complications. As the disease progresses, lipotoxicity, glucotoxicity, and epigenetic factors further contribute to the functional and pathologic changes. Intervention with insulin or insulin sensitizers, particularly in the early stages of pathogenesis, can counteract inflammatory changes, control glycemia, prevent formation of advanced glycation end products, and ameliorate oxidative stress–induced overactivation of poly adenosine diphosphate ribose polymerase (PARP), with the potential to change the natural history of microvascular complications (Vinik 2004; LeRoith 2004).

ICD-9 CODE: Diabetes Type 2 (Not Stated as Controlled) 250.00
ICD-9 CODE: Diabetes Type 2 (Uncontrolled) 250.02

(See Diabetes Type 2 Screen [Chapter 4] for specific tests and CPT codes)

References

Celiac Disease

Celiac disease is an autoimmune enteropathy, not an allergy. It is the only autoimmune disease in which the initiating antigen is clearly defined. Celiac disease is also known as celiac sprue, nontropical sprue, and gluten-sensitive enteropathy.

What to Look For

Distinguishing Signs and Symptoms

- Symptoms of malabsorption (e.g., weight loss, diarrhea, nutrient deficiencies)
- Occurs mainly in Caucasian children, less often in African-American and Hispanic children
- Osteopenia, bone pain, and pathologic fractures
- Recurrent abdominal pain and/or bloating
- Infertility and/or recurrent miscarriages
- Aphthous stomatitis
- Diarrhea, weight loss, and failure to thrive
- Fatigue and lassitude
- Depression

Serologic Testing

- Anti–tissue transglutaminase (TTG) immunoglobulin A (IgA) and immunoglobulin G (IgG)
- Antiendomysial IgG and IgA
- Antigliadin IgA and IgG
- Antireticulin antibodies

False-negatives can occur in the following patients:
- Children younger than 2 years of age
- Patients on gluten-free diets for 4 to 6 weeks
- Those with IgA fractions with IgA deficiency (up to 2%–3%)

For a gluten challenge, the patient must ingest three to four slices of wheat bread for 2 to 4 weeks.

False-positives are found in patients with the following conditions:
- Cow’s milk protein intolerance
- Parasitic infections (e.g., giardiasis)
- IgA nephropathy
- Crohn’s disease
- Eosinophilic gastroenteritis
- Tropical sprue
- Small bowel bacterial overgrowth

Diagnosis of Celiac Disease

- Enzyme found in many tissues; released after injury
- Human-based versus guinea-pig based—Scimedx
- False-positives
- Concurrent autoimmune or inflammatory diseases
• New TTG dot blot test  
  - Detects anti-TTG antibodies in serum of 1 drop of whole blood  
  - Up to 100% sensitive  
  - 96% Specific  
  - Takes 30 minutes  

Measure the following antibody levels:  
• Endomysial (IgA)  
• Endomysial titer  
• TTG IgG  
• TTG IgA  

ICD-9 CODE: Celiac Disease 579.0
ASSAYS, INCLUDING CPT CODES
Chapter 3 - Assays, Including CPT Codes

Introduction

Patient Preparation and Specimen Handling

For all tests it is critical to follow exactly the specific patient preparation and specimen handling requirements stated for each procedure listed in this catalogue. Factors such as fasting, time of collection, type of specimen, medications used, and method of shipping are vital for obtaining clinically significant information for the appropriate evaluation of a patient. Unless otherwise specified, a morning, fasting specimen is preferred.

Tests that require special preservatives must use these special tubes for the collection of specimens to ensure that there is no loss or degradation of the hormone or peptide measured to enable accurate and meaningful determinations of the requested endocrine analytes. Special GI Preservative tubes and Z-tubes™ are available by request from Inter Science Institute (ISI).

A sample requisition slip is included after the index at the end of this book. Additional requisition slips are available from ISI upon request or directly from the website at interscienceinstitute.com. A requisition slip with the ordering physician’s complete address and phone and fax numbers must accompany each specimen. For more information on specific tests or how to obtain appropriate tubes, please call 1-800-255-2873 or email requests to intersci@earthlink.net.

Collection of Specimens

The majority of hormones are governed by production and clearance rates in blood and urine, which are in dynamic balance in both healthy and disease states. The specific hormone may not be secreted or excreted at a steady rate. Urine tests are requested for various reasons, including eliminating or minimizing the effects of episodic secretion, determining the output of a specific analyte over a full 24-hour period, and obtaining a noninvasive specimen for analysis. The 24-hour urine sampling represents an integrated determination of the individual analytes in question taking into account the production and clearance rates. A random urine specimen is acceptable; however, a 24-hour collection is more readily interpreted within the parameters of the reference range(s).

General Guidelines for Plasma/Serum Specimens

1. Specimens for endocrine procedures preferably should be obtained from patients who have been fasting overnight for 10 to 12 hours.
2. Fasting specimens should be obtained between 6:00 AM and 8:00 AM, unless otherwise stated for a particular procedure.
3. The patient should discontinue medications that may affect hormone levels for at least 48 hours prior to collection under the guidance and consent of their physician (for special instructions see Octreotide [Sandostatin®]).
4. Some tests require the use of the GI preservative collection tube to obtain valid analysis of specimens. Preservative tubes are available from ISI via the internet (intersci@earthlink.net) or via phones: (800) ALL-CURE or (310) 677-3322.
5. Ship specimens frozen via overnight courier service unless otherwise noted under each specific test.
General Guidelines for Collection of a 24-Hour Urine Specimen

1. Begin urine collection after discarding first AM voiding.
2. Collect all other urine voidings during the next 24 hours, including the first AM voiding the next day.
3. Record the 24-hour volume.
4. Mix urine well and remove appropriate aliquot to submit for analysis.
5. Boric acid tablets may be added to urine to reduce bacterial growth.
6. Ensure that urine procedures stating “Do not acidify urine” are not collected with hydrochloric or acetic acid.
7. If possible, urine should be refrigerated during collection and shipped frozen to avoid leakage. Provide total volume per 24 hours.
8. Obtain creatinine values for some urine assays (see individual assays listed later in this chapter).

General Guidelines for Collection of a Saliva Specimen

1. Following an overnight fast, saliva should be collected for 5 to 10 minutes.
2. Instruct patient to rinse mouth with water, and wait 10 minutes to begin collecting saliva. Saliva should be allowed to flow freely into container.
3. Instruct the patient to not brush their teeth the morning of collection, because minor abrasions in mouth and/or gingivitis may introduce plasma constituents that affect the level of the hormone being measured.
4. The patient should refrain from intake of food, coffee, and juices for 8 hours prior to collection.
5. The patient should refrain from smoking or chewing gum 8 hours prior to collection.
6. If specimen is collected at home, ensure it is kept refrigerated after collection before transporting to laboratory or physician’s office.
7. Record name, date, and beginning time of collection.
8. Have physician’s office centrifuge saliva to remove debris before freezing and shipping specimen to ISI.

Fecal Collection

Collect 100 mg (size of dime) of formed stool and store at –20°C. Stool specimens are stable for 7 days when refrigerated. Note on request slip if sample has watery diarrhea consistency, as concentration levels may be decreased due to the dilution factor. See individual tests for additional and specific requirements.

Special Specimens

For tumor/tissue specimens and various fluids (e.g., CSF, peritoneal fluid), see specific test sections or contact ISI for requirements.
Shipping and Instructions
To maintain specimen integrity, ship most specimens frozen in dry ice via an overnight courier such as FedEx® or DHL®. Some specimens are stable at ambient (room) temperature for up to 3 days. See specific tests for stability information and required shipping temperatures.

Contact Information for Inter Science Institute
Phone: (800) 255-2873
Email: intersci@earthlink.net

Some tests listed are in preparation. Contact ISI for availability of tests marked with an asterisk.
ADIPONECTIN*

Reference Range
Reference range is listed on individual patient test reports.

Procedure
Adiponectin is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours, if possible, prior to collection of specimen. Insulin, medications, or other factors that affect insulin or amylin secretion should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL of ethylene amine tetraacetic acid (EDTA) plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
Adiponectin specimens must be collected using the GI Preservative tube. No other methods of collection are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

* In preparation

CPT Code:
Unspecified
Quantitative
Immunooassay 83519
Amylin

Reference Range
Reference range is listed on individual patient test reports.

Procedure
Amylin is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours, if possible, prior to collection of specimen. Insulin, medications, or other factors that affect insulin or amylin secretion should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
Amylin specimens must be collected using the GI Preservative tube. No other methods of collection are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Imunoassay 83519
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

Bombesin/Gastrin-Releasing Peptide (GRP)

Reference Range
50–250 pg/mL

Procedure
Bombesin is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Requirements
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
Bombesin specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Brain Natriuretic Peptide (BNP)*

Reference Range
Reference range is listed on individual patient test reports.

Procedure
BNP is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours, if possible, prior to collection of specimen. Insulin, medications, or other factors that affect insulin or BNP secretion should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
BNP specimens must be collected using the GI Preservative tube. No other methods of collection are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

* In preparation

CPT Code:
Brain Natriuretic Peptide (BNP) 83880
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

C-Peptide

Reference Range
0.9–4.2 ng/mL
Reference range is listed on individual patient test reports.

Procedure
C-peptide is measured by direct radioimmunoassay.

Patient Preparation
The patient should not be on any insulin therapy nor take medications that influence insulin levels, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL of serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Codes:
C-Peptide 80432, 84681
C-Reactive Protein (CRP; Highly Sensitive for Metabolic Syndrome)*

Reference Range
Reference range is listed on individual patient test reports.

Procedure
CRP is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
CRP specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

Reference

* In preparation

CPT Codes:
C-Reactive Protein (Inflammation and CSF) 86140
C-Reactive Protein (Cardiac Risk) 86141
C-Reactive Protein (CRP; Regular for Inflammation)*

Reference Range
Reference range is listed on individual patient test reports.

Procedure
CRP is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
CRP specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

Reference

* In preparation

CPT Codes:

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>86140</td>
<td>C-Reactive Protein (Inflammation and CSF)</td>
</tr>
<tr>
<td>86141</td>
<td>C-Reactive Protein (Cardiac Risk)</td>
</tr>
</tbody>
</table>
Calcitonin (Thyrocalcitonin)

Reference Range
Up to 300 pg/mL
Reference range is listed on individual patient test reports.

Procedure
Calcitonin is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Thyroid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Calcitonin 82308
Carboxy Methyl Lysine (CML)*

**Reference Range**
Up to 80 pg/mL
Reference range is listed on individual patient test reports.

**Procedure**
CML is measured by direct radioimmunoassay.

**Patient Preparation**
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

**Important Precaution**
CML specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

References

* In preparation

| CPT Code: | Unspecified Quantitative Immunoassay 83519 |
CHOLECYSTOKININ (CCK)

**Reference Range**
Up to 80 pg/mL

**Procedure**
CCK is measured by direct radioimmunoassay.

**Patient Preparation**
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

**Important Precaution**
CCK specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**

**CPT Code:**
Unspecified
Quantitative
Immunoassay 83519
Chromogranin A (CGA)

Reference Range
6.0–40.0 ng/mL

Procedure
CGA is measured by direct radioimmunoassay/enzyme immunoassay (EIA)/ELISA.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL whole blood in an EDTA or red-topped tube. Plasma or serum should be separated as soon as possible. CGA is stable at room temperature for 3 days. Specimen can be stored at ambient temperature, refrigerated, or frozen in dry ice.

Important Precaution
Draw sample first thing in the morning because of the diurnal variation. When serial measurements are made, draw samples at the same time each day.

Shipping Instructions
Specimens can be shipped at ambient temperature, refrigerated, or frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Elastase, Pancreatic, Serum

Reference Range
30–125 ng/mL
Reference range is listed on individual patient test reports.

Procedure
Elastase is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Medications that affect pancreatic activity should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum and separate as soon as possible. Freeze serum immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Pancreatic Elastase I
82656
Elastase-1 (EL1), Fecal

Reference Ranges
Normal: 200 to >500 µg/g stool
Moderate to mild pancreatic insufficiency: 100–200 µg/g stool
Severe exocrine pancreatic insufficiency: <100 µg/g stool

Procedure
EL1 is measured by a monoclonal antibody specific only to human pancreatic EL1 employing ELISA.

Patient Preparation
No special patient preparation is required, because substitution therapy has no influence on the specific fecal EL1 levels.

Specimen Collection
Collect 100 mg formed stool and store at –20°C. Stool specimens are stable for 7 days when refrigerated. Minimum specimen size is 20 mg of formed stool. Note if sample has watery diarrhea consistency, as the concentration of EL1 may be decreased due to the dilution factor.

Special Specimens
Stool is the only appropriate specimen for this test (see Elastase, Pancreatic, Serum).

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Fecal Elastase 82656
Exendin*

Reference Range
Reference range is listed on individual patient test reports.

Procedure
Exendin is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Medications that affect pancreatic activity should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

* In preparation

CPT Code:
- Unspecified Quantitative Immunoassay 83519
**Fibrinogen**

**Reference Range**
Reference range is listed on individual patient test reports.

**Procedur**
Fibrinogen is measured by direct radioimmunoassay.

**Patient Preparation**
The patient should fast for 10 to 12 hours prior to collection of specimen. Medications that affect pancreatic activity should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

Reference
1. Please refer to www.endotext.org.

* In preparation

<table>
<thead>
<tr>
<th>CPT Codes:</th>
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<tbody>
<tr>
<td>Fibrinogen</td>
</tr>
<tr>
<td>85384–85385</td>
</tr>
</tbody>
</table>
GALANIN

Reference Range
25–80 pg/mL
Reference range is listed on individual patient test reports.

Procedure
Galanin is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Medications that affect intestinal motility or insulin levels should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
Galanin specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

Gastric Inhibitory Polypeptide (GIP; Glucose-Dependent Insulinotropic Peptide)

Reference Range
75–325 pg/mL
Reference range is listed on individual patient test reports.

Procedure
GIP is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility or insulin secretion should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
GIP specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified Quantitative Immunoassay 83519
GASTRIN

Reference Range
0–100 pg/mL
Reference range is listed on individual patient test reports.

Procedure
Gastrin is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Codes:
Gastrin 82938–82941
Neuroendocrine Tumors
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Gastrin-Releasing Peptide (GRP; Bombesin)

Reference Range
10–80 pg/mL
Reference range is listed on individual patient test reports.

Procedure
GRP is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
GRP specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Glucagon

Reference Ranges

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<tr>
<th>Age (y)</th>
<th>Range (pg/mL)</th>
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<tr>
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<td>50–59</td>
<td>75–170</td>
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<tr>
<td>60–69</td>
<td>50–270</td>
</tr>
</tbody>
</table>

Reference range is listed on individual patient test reports.

Procedure

Glucagon is measured by direct radioimmunoassay.

Patient Preparation

The patient should fast for 10 to 12 hours prior to collection of specimen. The patient should not take any medications that influence insulin secretion or intestinal motility, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection

Collect 10 mL EDTA plasma and separate immediately. Freeze plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens

For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions

Specimens should be shipped frozen in dry ice.

References


CPT Codes:

Glucagon 82943
• Tolerance Panel
  80422–80424
• Tolerance Test 82946
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

GLUCAGON-LIKE PEPTIDE 1 (GLP-1)

Reference Range
Reference range is listed on individual patient test reports.

Procedure
GLP-1 is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility or insulin secretion should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
GLP specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
GROWTH HORMONE (GH, SOMATOTROPIN)

Reference Ranges
Children: up to 20 ng/mL
Adults: up to 10 ng/mL
Reference range is listed on individual patient test reports.

Procedure
GH is measured by direct radioimmunoassay.

Patient Preparation
The patient should not be on any insulin therapy nor take ACTH or gonadotropin medication, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped at room temperature or frozen in dry ice.

References

CPT Code:
<table>
<thead>
<tr>
<th>Growth Hormone</th>
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<td>83003</td>
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</table>
**GROWTH HORMONE–RELEASING HORMONE (GHRH)**

**Reference Range**

5–18 pg/mL
Reference range is listed on individual patient test reports.

**Procedure**

GHRH is measured by direct radioimmunoassay.

**Patient Preparation**

The patient should not take any medications that influence pituitary secretion, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**

Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**

For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**References**


**CPT Code:**

Growth Hormone–Releasing Hormone
83519
Histamine

Reference Range
Up to 60 ng/mL
Reference range is listed on individual patient test reports.

Procedure
Histamine is measured by direct radioimmunoassay.

Patient Preparation
The patient should not take any antihistamine medication, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid), contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Histamine 83088
**Homocysteine**

**Reference Range**
Reference range is listed on individual patient test reports.

**Procedure**
Homocysteine is measured by direct radioimmunoassay.

**Patient Preparation**
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility or insulin secretion should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 10 mL EDTA plasma and separate as soon as possible. Freeze plasma immediately after separation. Minimum specimen size is 2 mL.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**Reference**
1. Please refer to www.endotext.org.

* In preparation

**CPT Code:**
Homocysteine 83090
Chapter 3 - Assays, Including CPT Codes

INSULIN

**Reference Range**

4–24 µU/mL

Reference range is listed on individual patient test reports.

**Procedure**

Insulin is measured by direct radioimmunoassay.

**Patient Preparation**

The patient should fast for 10 to 12 hours prior to collection of specimen. The patient should not take any medications that influence insulin production or secretion, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**

Collect 3 mL serum and separate as soon as possible. Freeze serum immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**

For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**References**


**CPT Codes:**

<table>
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<th>Insulin 80422, 80432–80435</th>
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<td>• Antibody 86337</td>
</tr>
<tr>
<td>• Blood 83525</td>
</tr>
<tr>
<td>• Free 83527</td>
</tr>
</tbody>
</table>
**Reference Range**

4–24 µU/mL

Reference range is listed on individual patient test reports.

**Procedure**

“Free” insulin is measured by radioimmunoassay following removal of insulin bound to insulin antibodies.

**Patient Preparation**

The patient should fast for 10 to 12 hours prior to collection of specimen. The patient should not take any medications that influence insulin production or secretion, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**

Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**References**


**CPT Code:**

“Free” Insulin 83527
Insulin Antibodies

Reference Range
Nondetectable
Reference range is listed on individual patient test reports.

Procedure
Insulin antibody determination is measured by radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Patients on
insulin therapy with signs of insulin resistance are the most likely to test positive for
insulin antibodies.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or
plasma immediately after separation. Minimum specimen size is 1 mL.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References
1. Diaz JL, Wilkins TJ. Effect of iodination site on binding radiolabeled ligand by insulin antibodies and insulin autoantibodies.
2. Patterson R, Mellies CJ, Roberts M. Immunologic reactions against insulin III. IgE anti-insulin, insulin allergy, and combined

CPT Code:

| Insulin Antibody | 86337 |
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

Insulin—Proinsulin

Reference Ranges
Proinsulin in normal fasting plasma is usually 10% to 15% and always less than 22% of total insulin.

Proinsulin component in fasting plasma of patients with islet cell disease is greater than 22% of total insulin.

Reference range is listed on individual patient test reports.

Procedure
Proinsulin is measured by radioimmunoassay following chromatographic purification of specimens.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. The patient should not take any medications that influence insulin production or secretion, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Codes:

Proinsulin 84206
Proinsulin Serum 84206
**LEPTIN**

**Reference Range**
Reference range is listed on individual patient test reports.

**Procedure**
Leptin is measured by direct radioimmunoassay.

**Patient Preparation**
The patient should fast for 10 to 12 hours prior to collection of specimen. The patient should not take any medications that influence insulin production or secretion, if possible.

**Specimen Collection**
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**


* In preparation

**CPT Code:**

Unspecified Quantitative Immunoassay 83519
**Motilin**

**Reference Range**
Up to 446 pg/mL
Reference range is listed on individual patient test reports.

**Procedure**
Motilin is measured by direct radioimmunoassay.

**Patient Preparation**
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped at room temperature or frozen in dry ice.

**References**


**CPT Code:**
Unspecified
Quantitative
Immunoassay 83519
NEUROKININ A (NKA; SUBSTANCE K)

Reference Range
Up to 40 pg/mL
Reference range is listed on individual patient test reports.

Procedure
NKA is measured by direct radioimmunoassay.

Patient Preparation
The patient should not take pain relievers or any medications that affect hypertension or gastrointestinal functions, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in special tube containing the Z-tube™ Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special Z-tube™ Preservative is available from ISI. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Neuropeptide Y (NPY)

**Reference Range**
Up to 5.0 ng/mL
Reference range is listed on individual patient test reports.

**Procedure**
NPY is measured by direct radioimmunoassay.

**Patient Preparation**
The patient should fast for 10 to 12 hours prior to collection of specimen. Medications that affect insulin secretion or gastrointestinal function should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**

**CPT Code:**
Unspecified
Quantitative
Immunoassay 83519
Neurotensin

Reference Range
50–100 pg/mL
Reference range is listed on individual patient test reports.

Procedure
Neurotensin is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect gastrointestinal function should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in special tube containing the Z-tube™ Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special Z-tube™ Preservative is available from ISI. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Nuclear Factor Kappa B (NFkB)*

Reference Range
Reference range is listed on individual patient test reports.

Procedure
NFκB is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. The patient should not take any medications that influence insulin production or secretion, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

Reference

*C in preparation

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Octreotide (Sandostatin®)

Reference Ranges for Therapeutic Octreotide Levels

Long-acting repeatable (LAR) dose-response levels: mean octreotide level ± 2 SD for patients on octreotide LAR for 3 or more months (steady-state). The following represent trough levels measured immediately before an injection of LAR.

- 10 mg/month: 1153 ± 748 pg/mL
- 20 mg/month: 2518 ± 1020 pg/mL
- 30 mg/month: 5241 ± 3004 pg/mL
- 60 mg/month: 10,926 ± 5530 pg/mL

Procedure

Octreotide is measured by direct radioimmunoassay. There is no cross-reactivity with native somatostatin-14 or somatostatin-28. The also is no cross-reactivity with lanreotide, and this test should not be used to measure blood levels of this drug.

Patient Preparation

This test is useful only for those patients being treated with octreotide acetate. No special preparation is needed for this test. For optimal results, blood for this test should be drawn immediately before the patient’s next injection of octreotide LAR (trough levels).

Specimen Collection

Collect 3 mL serum or EDTA plasma and separate as soon as possible. Octreotide is stable at room temperature for 3 days. Specimens can be stored at room temperature, refrigerated, or frozen in dry ice. Minimum specimen size is 1 mL.

Special Specimens

For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions

Specimens can be shipped at ambient temperature, refrigerated, or frozen in dry ice.

Reference


CPT Code:

Therapeutic Drug Assay: Quantitation of Drug, Not Elsewhere Specified 80299
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

Pancreastatin

Reference Range

10–135 pg/mL
Reference range is listed on individual patient test reports.

Procedure

Pancreastatin is measured by direct radioimmunoassay/EIA/ELISA.

Patient Preparation

The patient should fast for 10 to 12 hours prior to collection of specimen. The patient should not take any medications that influence insulin levels, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection

Collect 10 mL EDTA plasma in special tube containing the Z-tube™ Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special Z-tube™ Preservative is available from ISI. Minimum specimen size is 1 mL.

Special Specimens

For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions

Specimens should be shipped frozen in dry ice.

References


CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Pancreatic Polypeptide (PP)

Reference Ranges

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<th>Age (y)</th>
<th>Range (pg/mL)</th>
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<tr>
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<tr>
<td>60–69</td>
<td>40–600</td>
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</table>

Reference range is listed on individual patient test reports.

Procedure

PP is measured by direct radioimmunoassay.

Patient Preparation

The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect insulin levels should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection

Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens

For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions

Specimens should be shipped frozen in dry ice.

References


CPT Code:

Unspecified Quantitative Immunoassay 83519
**Pepsinogen I (PG-I)**

**Reference Range**

28–100 ng/mL

Reference range is listed on individual patient test reports.

**Procedure**

PG-I is measured by direct radioimmunoassay.

**Patient Preparation**

The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications or medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**

Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**

For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**References**


**CPT Code:**

Unspecified Quantitative Immunoassay 83519
PEPSINOGEN II (PG-II)

Reference Range
Up to 22 ng/mL
Reference range is listed on individual patient test reports.

Procedure
PG-II is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications or medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified Quantitative Immunoassay 83519
Peptide Histidine Isoleucine (PHIM)*

Reference Range
10–40 pg/mL
Reference range is listed on individual patient test reports.

Procedure
PHIM is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
PHIM specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

* In preparation

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Peptide YY (PYY)

Reference Range
30–120 pg/mL
Reference range is listed on individual patient test reports.

Procedure
PYY is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
PYY specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified Quantitative Immunoassay 83519
Plasminogen Activator Inhibitor 1 (PAI-1)*

Reference Range
Up to 1.0 IU/mL
Reference range is listed on individual patient test reports.

Procedure
PAI-1 is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
PAI-1 specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

* In preparation

CPT Codes:
PAI-1 85420–85421
Prostaglandin D₂ (PGD₂)

Reference Range
35–115 pg/mL
Reference range is listed on individual patient test reports.

Procedure
PGD₂ is measured by radioimmunoassay/EIA/ELISA following extraction of specimens.

Patient Preparation
The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References
Prostaglandin D₂ (PGD₂), Urine

Reference Range
100–280 ng/24 hours
Reference range is listed on individual patient test reports.

Procedure
PGD₂ is measured by direct radioimmunoassay/EIA/ELISA.

Patient Preparation
The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Submit 5 mL of a 24-hour urine collection. No special preservatives are required. Minimum specimen size is 1 mL. Provide the total volume per 24 hours, if possible; random collections are also acceptable.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Prostaglandin D₂
84150
**PROSTAGLANDIN E\(_1\) (PGE\(_1\))**

**Reference Range**

250–500 pg/mL  
Reference range is listed on individual patient test reports.

**Procedure**

PGE\(_1\) is measured by radioimmunoassay/EIA/ELISA following extraction of specimens.

**Patient Preparation**

The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**

Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**

For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**References**


**CPT Code:**

| Prostaglandin E\(_1\) | 84150 |
Prostaglandin E$_2$ (PGE$_2$)

Reference Range
250–400 pg/mL
Reference range is listed on individual patient test reports.

Procedure
PGE$_2$ is measured by radioimmunoassay/EIA/ELISA following extraction of specimens.

Patient Preparation
The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References
**Prostaglandin E<sub>2</sub> Dihydroketo (DHK-PGE<sub>2</sub>)**

**Reference Range**
Up to 40 pg/mL  
Reference range is listed on individual patient test reports.

**Procedure**
DHK-PGE<sub>2</sub> is measured by radioimmunoassay/EIA/ELISA following extraction of specimens.

**Patient Preparation**
The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**
PROSTAGLANDIN F$_1$α (PGF$_1$α)

**Reference Range**
30–100 pg/mL
Reference range is listed on individual patient test reports.

**Procedure**
PGF$_1$α is measured by radioimmunoassay/EIA/ELISA following extraction of specimens.

**Patient Preparation**
The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**

**CPT Code:**
Prostaglandin F$_1$α
84150
PROSTAGLANDIN F₁α (PGF₁α), URINE

Reference Range
50–400 ng/24 hours
Reference range is listed on individual patient test reports.

Procedure
PGF₁α is measured by direct radioimmunoassay/EIA/ELISA.

Patient Preparation
The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Submit 5 mL of a 24-hour urine collection. No special preservatives are required. Minimum specimen size is 1 mL. Provide the total volume of urine per 24 hours, if possible; random collections are also acceptable.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References
Prostaglandin F\(_1\alpha\), 6-Keto (6-Keto PGF\(_1\alpha\)), Prostaglandin I\(_2\) (PGI\(_2\)) Metabolite

Reference Range
Up to 15 pg/mL
Reference range is listed on individual patient test reports.

Procedure
6-Keto PGF\(_1\alpha\) is measured by radioimmunoassay/EIA/ELISA following extraction of specimens.

Patient Preparation
The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Prostaglandin F\(_1\alpha\)
84150
**Prostaglandin F₁α, 6-Keto (6-Keto PGF₁α), PGI₂ Metabolite, Urine**

**Reference Ranges**
Male: 200–450 ng/24 hours  
Female: 85–300 ng/24 hours  
Reference range is listed on individual patient test reports.

**Procedure**
6-Keto PGF₁α is measured by direct radioimmunoassay/EIA/ELISA.

**Patient Preparation**
The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Submit 5 mL of a 24-hour urine collection. No special preservatives are required.  
Minimum specimen size is 1 mL. Provide total volume per 24 hours, if possible; random collections are also acceptable.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**

**CPT Code:**
Prostaglandin F₁α  
84150
PROSTAGLANDIN $F_2\alpha$ (PGF$F_2\alpha$)

Reference Range
80–240 pg/mL
Reference range is listed on individual patient test reports.

Procedure
PGF$F_2\alpha$ is measured by radioimmunoassay/EIA/ELISA following extraction of specimens.

Patient Preparation
The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Prostaglandin $F_2\alpha$
84150
Prostaglandin F$_2$α Dihydroketo (DHK-PGF$_2$α)

**Reference Range**
10–50 pg/mL
Reference range is listed on individual patient test reports.

**Procedure**
DHK-PGF$_2$α is measured by direct radioimmunoassay/EIA/ELISA.

**Patient Preparation**
The patient should not take aspirin, indomethacin, or anti-inflammatory medications, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**
SECRETIN

Reference Range
12–75 pg/mL
Reference range is listed on individual patient test reports.

Procedure
Secretin is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
Secretin specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Serotonin (5-HT), Serum

Reference Range
12–44 pg/mL
Reference range is listed on individual patient test reports.

Procedure
Serotonin is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Because of the diurnal variation of serotonin secretion, morning specimens are preferred.

Specimen Collection
Collect 5 mL serum. Separate and freeze serum immediately after separation. Minimum specimen size is 1 mL.

Important Precaution
For serotonin measurements, avoid hemolysis. Do not use a tourniquet. Handle specimens gently. Hemolysis results in spuriously high results.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Serum specimens should be shipped frozen in dry ice.

References

CPT Code:
Serotonin 84260
Somatostatin (Somatotropin Release–Inhibiting Factor [SRIF])

**Reference Range**
Up to 25 pg/mL
Reference range is listed on individual patient test reports.

**Procedure**
SRIF is measured by direct radioimmunoassay.

**Patient Preparation**
The patient should fast for 10 to 12 hours prior to collection of specimen. The patient should not take any medications that affect insulin secretion or intestinal motility, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 10 mL EDTA plasma in special tube containing the Z-tube™ Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special Z-tube™ Preservative is available from ISI. Minimum specimen size is 1 mL.

**Important Precaution**
SRIF specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

References
SUBSTANCE P

Reference Range
40–270 pg/mL
Reference range is listed on individual patient test reports.

Procedure
Substance P is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Substance P is stable at room temperature for 3 days. Specimens can be stored at ambient temperature, refrigerated, or frozen in dry ice. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimen can be shipped at ambient temperature, refrigerated, or frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
THYROID-STIMULATING HORMONE (TSH; THYROTROPIN)

**Reference Range**
0.3–5.0 µU/mL
Reference range is listed on individual patient test reports.

**Procedure**
TSH is measured by direct radioimmunoassay.

**Patient Preparation**
The patient should not take any thyroid, steroid, ACTH, estrogen, or corticosteroid medications, if possible, for at least 48 hours prior to collection of specimen.

**Specimen Collection**
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**

**CPT Code:**
Thyroid Stimulating Hormone 84443
Thyrotropin-Releasing Hormone (TRH)

Reference Range
Up to 40 pg/mL
Reference range is listed on individual patient test reports.

Procedure
TRH is measured by direct radioimmunoassay.

Patient Preparation
The patient should not take any thyroid medication, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 5 mL EDTA plasma in a special TRH Preservative tube and separate as soon as possible. Freeze plasma immediately after separation. Special TRH Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
TRH must be collected with the TRH Preservative tube. No other specimen is acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

THROMBOXANE A₂

Reference Range
180–420 pg/mL
Reference range is listed on individual patient test reports.

Procedure
Thromboxane A₂ is measured by radioimmunoassay of its stable metabolite Thromboxane B₂ following extraction of specimens.

Patient Preparation
The patient should not take aspirin, indomethacin, or anti-inflammatory medications for at least 48 hours prior to collection of specimen. Fasting patients may have elevated levels of thromboxane A₂ metabolite.

Specimen Collection
Collect 3 mL EDTA plasma and separate as soon as possible. Freeze plasma immediately after separation. Minimum specimen size is 1 mL.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
**Thromboxane B\(_2\)**

**Reference Range**

180–420 pg/mL

Reference range is listed on individual patient test reports.

**Procedure**

Thromboxane B\(_2\) is measured by radioimmunoassay following extraction of specimens.

**Patient Preparation**

The patient should not take aspirin, indomethacin, or anti-inflammatory medications for at least 48 hours prior to collection of specimen. Fasting patients may have elevated levels of thromboxane B\(_2\).

**Specimen Collection**

Collect 3 mL EDTA plasma and separate as soon as possible. Freeze plasma immediately after separation. Minimum specimen size is 1 mL.

**Special Specimens**

For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**References**


**CPT Code:**

Unspecified
Quantitative
Immunoassay 83519
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

Thromboxane B₂, Urine

Reference Range
50–160 ng/24 hours
Reference range is listed on individual patient test reports.

Procedure
Thromboxane B₂ is measured by radioimmunoassay following extraction of specimens.

Patient Preparation
The patient should not take aspirin, indomethacin, or anti-inflammatory medications for at least 48 hours prior to collection of specimen. Fasting patients may have elevated levels of Thromboxane B₂.

Specimen Collection
Submit 5 mL of a 24-hour urine collection. No special preservatives are required. Minimum specimen size is 1 mL. Provide total volume per 24 hours, if possible; random urine samples are acceptable.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

CPT Code:
Unspecified
Quantitative
Immunoassay 83519
Vasoactive Intestinal Polypeptide (VIP)

Reference Range
Up to 36 pg/mL
Reference range is listed on individual patient test reports.

Procedure
VIP is measured by direct radioimmunoassay.

Patient Preparation
The patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications that affect intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

Important Precaution
VIP specimens must be collected using the GI Preservative tube. No other specimens are acceptable.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References
Profiles, Including CPT Codes
Adenocarcinoma of the Pancreas

Ductal adenocarcinoma of the pancreas accounts for 90% of pancreatic cancers. Imaging investigation using CT, with or without fine needle aspiration and assays for tumor and genetic markers, is the primary approach in evaluating patients with symptoms suggestive of pancreatic cancer. Most tumor markers have limited sensitivity and specificity.

**BLOOD**
- CA 19-9
- CEA

**OTHER RELATED TESTS**
- Islet amyloid polypeptide (IAPP)
- Glucose
- Glucose tolerance test
- KRAS mutation in pancreatic juice

**Patient Preparation**
None for blood test.

**Specimen Collection**

**BLOOD**
Collect 10 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 2 mL.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**


**CPT Codes: Blood**
- CA 19-9 86301
- CEA 82378

**CPT Codes: Other Related Tests**
- Glucose 82947
- Glucose Tolerance 82951
- IAPP
**Bronchospasm Profile**

This profile is useful for ruling out a neuroendocrine tumor cause of bronchospasm.

**BLOOD**
- Prostaglandin D₂
- Histamine
- Serotonin
- Substance P
- VIP
- CGA
- Pancreastatin
- Serum protein immunoelectrophoresis, IgE

**URINE**
- 5-HIAA
- 5-HTP
- VMA
- Tryptase

**Patient Preparation**

The patient should fast for 10 to 12 hours prior to collection of specimen. Alkali antacid medications should be discontinued, if possible, for at least 24 hours prior to collection. PPIs and H₂ blockers should be discontinued for 72 hours or more prior to collection and patients monitored closely. For 48 hours prior to sample collection, patients should not be treated with the following medications, if possible:
- Insulin or oral medications that influence insulin production or secretion
- Aspirin, indomethacin, or anti-inflammatory medications
- Antacids or medications affecting intestinal motility

Patients should not partake of the following foods for 48 hours prior to collection of urine for measurement of 5-HIAA and 5-HTP:
- Red wine
- Cheese
- Hot dogs
- Chocolates
- Vanilla-containing foods (e.g., ice cream)
- Custard
- Pineapple, kiwi, bananas, or cassava

**Specimen Requirements**

**BLOOD**
Collect 10 mL EDTA plasma in special tube containing the Z-tube™ Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special Z-tube™ Preservative is available from ISI. Minimum specimen size is 5 mL.

**URINE**
See complete urine collection instructions in the introduction to Chapter 3.
**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**Further Diagnosis**

Refer patient for allergy testing.

**Reference**


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### CPT Codes: Blood

<table>
<thead>
<tr>
<th>Test</th>
<th>Code</th>
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<td>Serotonin</td>
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<td>Substance P</td>
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<td>VIP</td>
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<td>Chromogranin A</td>
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<td>Pancreastatin</td>
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<td>Serum Protein</td>
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<td>Immunoelectrophoresis</td>
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### CPT Codes: Urine

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<tr>
<td>5-HIAA 24-Hour Urine</td>
<td>83497</td>
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<tr>
<td>5-HTP</td>
<td>86701</td>
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<tr>
<td>Vanillyl mandelic acid (VMA)</td>
<td>84585</td>
</tr>
<tr>
<td>Tryptase</td>
<td>83520</td>
</tr>
</tbody>
</table>
**Carcinoid Follow-Up Profile**

**BLOOD**
Measure every 3 months or immediately following a therapeutic intervention.
- CGA
- Serotonin
- Pancreastatin

If on Sandostatin LAR® for at least three months, consider (measure immediately prior to the LAR® injection):
- Octreotide

For increase in tumor growth or rise in biomarkers, consider other amines, peptides, and markers found to be elevated in the screening evaluation profile, including the following:
- Substance P
- NKA

**URINE**
Measure every 3 months or immediately following a therapeutic intervention.
- 5-HIAA (or 5-HTP if 5-HIAA is negative and 5-HTP is positive at initial screening)

**Patient Preparation**
Patient should fast overnight prior to collection of blood specimens. Because of the diurnal variation of serotonin secretion, morning specimens are preferred. For the pancreastatin assay, patients should be advised to discontinue medications that affect insulin levels, if possible, for 48 hours prior to collection. Patients should not partake of the following foods for 48 hours prior to collection of urine for measurement of 5-HIAA and 5-HTP:
- Red wine
- Cheese
- Hot dogs
- Chocolates
- Vanilla-containing foods (e.g., ice cream)
- Custard
- Pineapple, kiwi, bananas, cassava

**Specimen Requirements**

**BLOOD**
Collect 10 mL EDTA plasma in special tube containing the Z-tube™ Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special Z-tube™ Preservative is available from ISI. Minimum specimen size is 5 mL. For serotonin analysis, use a yellow-topped tube containing 75 mg ascorbic acid (vitamin C). Separate and freeze plasma immediately.
URINE
See complete urine collection instructions in the introduction to Chapter 3.

Important Precaution
For serotonin measurements, avoid hemolysis. Do not use a tourniquet. Handle specimens gently. Use 20-gauge needle. Hemolysis results in spuriously high results.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

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<table>
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<td>5-HTP 86701</td>
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Diabetes Type 1 Screen

General Screen
General screen tests may be ordered from the local laboratory in each physician’s area.

BLOOD
- Glucose
  - Fasting
  - Postprandial
  - Glucose tolerance test

Specific Screening
Specific screening tests are available from ISI.

BLOOD
- Insulin
- C-peptide
- Anti-insulin antibody
- Islet cell antibody
- GAD antibodies (GAD 65, GAD 67)

Patient Preparation
Patient should fast for 10 to 12 hours prior to collection of specimen. Patient should not be on any insulin therapy or taking medications that influence insulin levels, if possible, for at least 48 hours prior to collection of specimen.

Specimen Collection
Collect 10 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 2 mL.

Shipping Instructions
Specimens should be shipped frozen in dry ice.
Chapter 4 - Profiles, Including CPT Codes

References


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<td><strong>Glucose 82947</strong></td>
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<td><strong>Anti-insulin Antibodies 86337</strong></td>
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<td><strong>GAD Antibodies 83519</strong></td>
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**Diabetes Type 2 Screen**

Predictors of the Development of Type 2 Diabetes

**BLOOD**

- Lipoprotein profile (either VAP™ or nuclear magnetic resonance [NMR] method)
  - Triglycerides
  - Total cholesterol
  - HDL-C
  - Low-density lipoprotein (LDL)-C
  - LDL-C particle size
- Peptides and cytokines
  - Insulin
  - IL-6
  - C-peptide
  - C-reactive protein (highly sensitive for macrovascular disease)

**Patient Preparation**

Patient should fast for 10 to 12 hours prior to collection of specimen. Patient should not be on aspirin, pain killers, corticosteroids, indomethacin, or anti-inflammatory medications for at least 48 hours prior to collection of specimen.

**Specimen Collection**

Collect 10 mL serum or EDTA plasma and separate as soon as possible. Freeze plasma immediately after separation. Specimens should not be thawed. Minimum specimen size is 6 mL.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.
Assessment for Risk Factors for Atherosclerotic Vascular Disease

**BLOOD**
- Lipoprotein profile (either VAP™ or NMR method)
  - Triglycerides
  - Total cholesterol
  - HDL-C
  - LDL-C
  - LDL-C particle size
- Arachidonic acid/EPA ratio
- Glucose
- HBA1c
- Fibrinogen
- PAI-1
- Thromboglobulin
  - Homocysteine
- C-reactive protein
- IL-6
- Thromboxane B₂

**Patient Preparation**
Patient should not be on aspirin, pain killers, corticosteroids, indomethacin, or anti-inflammatory medications for at least 48 hours prior to collection of specimens. Fasting patients may have elevated levels of thromboxane B₂.

**Specimen Collection**
**BLOOD**
Collect 10 mL serum or EDTA plasma and separate as soon as possible. Freeze plasma immediately after separation. Specimens should not be thawed. Minimum specimen size is 6 mL.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**CPT Codes:**

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<td>Thromboglobulin</td>
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<td>84999</td>
<td>Arachidonic Acid</td>
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</table>

References

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Gastroparesis or Brittle Diabetes

**BLOOD**
- Gastrin
- B12
- Gastric parietal cell antibody
- Pancreatic polypeptide (consider meal-stimulated PP measurements or insulin-stimulated PP measurements; see Chapter 5, Meal (Sham Feeding) Stimulation for Vagal Integrity)
- TSH (thyrotoxicosis)
- GH (anorexia nervosa)
- Cortisol (anorexia nervosa, Addison’s disease)
- IGF-1 (anorexia nervosa)
- Catecholamines, VMA, and metanephrines (i.e., pheochromocytoma panel)

**Patient Preparation**
Patient should fast for 10 to 12 hours prior to collection of specimen.

**Specimen Collection**
Collect 10 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**
Chapter 4 - Profiles, Including CPT Codes

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<td>TSH 84443</td>
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<td>GH 83003</td>
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<td>Cortisol 82533</td>
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<tr>
<td>IGF-1 84305</td>
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<tr>
<td>Catecholamines 82384</td>
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<tr>
<td>Vanillyl mandelic acid (VMA) 84585</td>
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<tr>
<td>Metanephrines 82570, 83835</td>
</tr>
<tr>
<td>Pheochromocytoma Panel 82382, 82570, 83835</td>
</tr>
</tbody>
</table>
Pseudogastrinoma Syndrome (Atrophic Gastritis With Loss of Acid Inhibition of Gastrin)

**BLOOD**
- Gastrin (elevated)
- Secretin stimulation test of gastrin

If fasting gastrin level is above 100 pg/mL, order a secretin stimulation test. An increase in gastrin level greater than 100 pg/mL above the normal range denotes a gastrinoma.
- Chromogranin A (not due to a neuroendocrine tumor)
  - May be suspected with mean corpuscular volume greater than 100 μm³
- **B₁₂**
- Pepsinogen I and II

**Important Precaution**

Patients submitted to dynamic challenge should be under the direct and constant supervision of their physician at all times. The doses listed are intended as a guideline only. The actual dose and collection schedule must be approved by the patient's physician.

**Specimen Collection**

Collect 10 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 2 mL.

**GASTRIC PH**

**Patient Preparation**

Patient should fast 10 to 12 hours prior to collection of specimen. Alkali antacid medications should be discontinued, if possible, for at least 24 hours prior to collection. PPIs and H₂ blockers should be discontinued for 72 hours or more prior to collection and patients monitored closely.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**References**


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**Chapter 4 - Profiles, Including CPT Codes**

## Diarrhea Syndrome Tests

**BLOOD**
- VIP
- Gastrin
- Gastrin-releasing peptide (bombesin)
- Calcitonin (MCT)
- PGD$_2$
- Histamine
- CGA
- Pancreastatin
- Pancreatic polypeptide
- PTH and PTHRp if hypercalcemic
- CGRP and substance P if flushing

**URINE**
- 5-HIAA
- 5-HTP
- VMA and catecholamines if hypertensive

**STOOL**
Measurement of stool electrolytes and osmolarity should be done early in the diagnostic evaluation. The presence of an osmolar gap suggests factitious diarrhea. A 72-hour supervised fast with intravenous fluid administration may also help determine if the diarrhea is secretory or infectious.

**Patient Preparation**
Patient should fast for 10 to 12 hours prior to collection of blood specimen. Antacid medications, antihistamine medications, aspirin, indomethacin, anti-inflammatory medications, and medications affecting motility or pancreatic function should be discontinued, if possible, for at least 48 hours prior to collection. Patients should not partake of the following foods for 48 hours prior to collection of urine for measurement of 5-HIAA and 5-HT:
- Red wine
- Cheese
- Hot dogs
- Chocolates
- Vanilla-containing foods (e.g., ice cream)
- Custard
- Pineapple, kiwi, bananas, cassava

**Specimen Requirements**

**BLOOD**
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL. For other assays that do not require the GI Preservative, 10 mL serum or EDTA plasma may be submitted.
Neuroendocrine Tumors  
A Comprehensive Guide to Diagnosis and Management

Urine
See complete urine collection instructions in the introduction to (Chapter 3).

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

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Dumping Syndrome

BASAL/FASTING TESTS
Following an overnight fast, patients should have blood drawn for the following tests:
- Pancreatic polypeptide
- Glucagon
- GLP-1
- Insulin
- Motilin
- GIP

Fecal Measurements
- Fecal fat measurement
- Fecal chymotrypsin measurement
- Fecal EL1 measurement

Patient Preparation
Patients should fast for 10 to 12 hours prior to collection of specimens. Patients should discontinue medications that affect insulin production or secretion, antacid medications, or medications affecting intestinal motility, if possible, for 48 hours prior to collection.

Specimen Collection
BLOOD
For the glucagon and GIP analyses, collect 3 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

STOOL
Collect 100 mg of formed stool and store at –20°C. Stool specimens are stable for 7 days at refrigerated temperatures. Minimum specimen size is 20 mg of formed stool. Note on request slip if sample has watery diarrhea consistency, as concentration levels of EL1 may be decreased due to dilution factor.
Shipping Instructions

Specimen should be shipped frozen in dry ice.

References


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Flushing Syndrome Tests

Tests to Identify Causes of Flushing in Different Clinical Syndromes

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Tests</th>
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<tbody>
<tr>
<td>Carcinoid</td>
<td>Urine 5-HIAA, 5-HTP, substance P, CGRP, CGA</td>
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<tr>
<td>MCT</td>
<td>Calcitonin, calcium infusion, RET protooncogene</td>
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<tr>
<td>Pheochromocytoma</td>
<td>VMA, epinephrine, norepinephrine, dopamine, glucagon stimulation test, T2-weighted MRI, OctreoScan*, MIBG</td>
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<tr>
<td>Diabetic autonomic neuropathy</td>
<td>Heart rate variability, 2-hour postprandial glucose</td>
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<td>Menopause</td>
<td>FSH</td>
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<tr>
<td>Epilepsy</td>
<td>Electroencephalogram</td>
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<td>Panic syndrome</td>
<td>Pentagastrin-stimulated ACTH</td>
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<td>Mastocytosis</td>
<td>Histamine (plasma), VIP, tryptase (urine)</td>
</tr>
<tr>
<td>Hypomastia, mitral prolapse</td>
<td>Echocardiography</td>
</tr>
</tbody>
</table>

BLOOD
- CGA
- Pancreastatin
- Substance P
- VIP
- Gastrin
- Neurotensin
- Serotonin
- CGRP
- Calcitonin
- FSH
- Histamine

URINE
For all 24-hour urine collections, measure creatinine.
- 5-HIAA
- 5-HTP
- VMA if hypertensive
- Tryptase

CONSIDER
- Plasma catecholamines if hypertensive
- Dopamine
- Epinephrine
- Norepinephrine
- PTH and PTHRP if hypercalcemic
- MEN screen (gastrin, prolactin, pancreatic polypeptide, and ionized Ca++)
- MEN-I gene and RET protooncogene
- Calcitonin, gastrin, and ACTH for degree of tumor aggression
- CA 19-1
- BNP, otherwise known as atrial natriuretic factor, if echocardiogram abnormal
ADDITIONAL TESTING IN PATIENTS WITH UNUSUAL CLINICAL SYNDROMES

- GHRH
- Bombesin
- Ghrelin
- IGF-1, IGF-2
- Corticotropin-releasing factor (CRF)

TISSUE STAINS

- K167
- CGA
- Synaptophysin
- NSE
- Somatostatin receptor type 2

CONSIDER

- Factor VIII, CD 31, AE1/AE3
- Somatostatin receptor subtypes other than type 2

Patient Preparation

Patient should fast overnight prior to collection of blood specimens. Antacid medications and medications affecting motility should be discontinued, if possible for at least 48 hours prior to collection of specimens. Patients should not partake of the following foods for 48 hours prior to collection of urine for measurement of 5-HIAA and 5-HTP measurements:

- Red wine
- Cheese
- Hot dogs
- Chocolates
- Vanilla-containing foods (e.g., ice cream)
- Custard
- Pineapple, kiwi, bananas, cassava

Specimen Requirements

BLOOD

Collect 20 mL of blood in a green-topped EDTA tube. For serotonin analysis, use a yellow-topped tube containing 75 mg ascorbic acid (vitamin C). Separate and freeze plasma immediately. For bombesin and VIP analyses, collect 5 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

TISSUE

Consult specialist for tissue staining requirements.

URINE

See complete urine collection instructions in the introduction to Chapter 3.
Shipping Instructions

Specimens should be shipped frozen in dry ice.

References


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</table>
**Gastrinoma (Zollinger-Ellison) Screen**

**Basal/Fasting Tests**
- Fasting gastrin concentration
- Gastric pH

**Consider**
- Pancreatic polypeptide for pancreatic location and suspected MEN-I
- MEN-I screen
- ACTH if rapid tumor growth, history of hypertension, diabetes, bruising, etc.
- OctreoScan and CT or MRI

**Patient Preparation**

Patient should fast for 10 to 12 hours prior to collection of specimen. Alkali antacid medications should be discontinued, if possible, for at least 24 hours prior to collection. PPIs and \( H_2 \) blockers should be discontinued for 72 hours prior to collection and patients monitored closely.

**Specimen Collection**

Collect 10 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 1 mL.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**References**


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Generic Follow-Up Profiles
Pancreas and MEN Tests

BLOOD
• Ca++ corrected for albumin concentrations
• Every 3 months, measure specific peptides found to be elevated on screening profile
• Check other components of MEN syndrome screen for MEN measurements (see previous page)

CONSIDER
• Octreotide suppression test, a predictive test for responsiveness to somatostatin analog therapy
• Octreotide levels for patients on drug, if patient symptoms, tumor, and biochemical markers are not responding
• RET protooncogene and MEN-I gene (MENIN) if not tested previously

Patient Preparation
Patient should fast for 10 to 12 hours prior to collection of specimen. Alkali antacid medications should be discontinued, if possible, for at least 24 hours prior to collection. PPIs and H2 blockers should be discontinued for 72 hours prior to collection and patients monitored closely.

Specimen Requirements:
For plasma peptides, collect 10 mL whole blood in an EDTA plasma tube. Separate and freeze plasma immediately. For the isolation of DNA for genetic testing, send 10 mL of whole blood in green-topped tube. Do not separate, do not freeze.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

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CPT Codes:

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<td>• Pancreatic Polypeptide 83519</td>
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<tr>
<td>• Ionized Calcium 82330</td>
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</tbody>
</table>
Genetic Studies

Neuroendocrine Tumors

BLOOD
- MEN-I (MENIN gene)
- RET protooncogene (MEN-II)

Type 1 Diabetes

BLOOD
- HLA
- DR3
- DR4
- A2

Risk Factors for Diabetic Complications
- Superoxide dismutase gene polymorphism
- Toll receptor polymorphism
- ApoE gene polymorphism
- Angiotensin receptor gene polymorphism
- Glut 4 abnormalities
- Hepatic nuclear transcription factor 1 and 4 (MODY)
- Aldose reductase gene polymorphism (Z2 allele)
- Cytochrome P450 polymorphism
- TNFα gene polymorphism
- 5’ Lipoxygenase gene polymorphism
- Mitochondrial DNA mutations
- Glucokinase gene abnormalities
- Mitochondrial DNA

Patient Preparation
Consult specialist for patient preparation.

Specimen Requirements
Consult specialist for specimen requirements.

Shipping Instructions
Consult specialist for shipping instructions.

Reference
1. Please refer to www.endotext.org.

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GI–NEUROENDOCRINE TESTS

BLOOD
- Neurotensin
- Ghrelin
- PTH
- PTHRP
- Prolactin
- Glucagon
- Insulin (if history of hypoglycemia) IGF I and IGF II
- C-Peptide (if history of hypoglycemia)
- Somatostatin
- Calcitonin
- VIP
- Gastrin
- Catecholamines (dopamine, epinephrine and norepinephrine if hypertensive)

Patient Preparation
Patient should be fasting 10 to 12 hours prior to collection of specimen. Antacid medication, Corticosteroid, ACTH, Thyroid, Estrogen or Gonadotropin medications and medications affecting motility, gastrointestinal or pancreatic function should be discontinued, if possible, for at least 48 hours prior to collection.

URINE
- VMA if hypertensive
- Catecholamines [dopamine, epinephrine, (metaepinephrine) norepinephrine (normetanephrine) if hypertensive]

Specimen Requirements
BLOOD
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Minimum specimen size is 2 mL. Special GI Preservative tubes are available from ISI for these assays: glucagon, somatostatin, and VIP. Submit 10 mL serum or EDTA plasma for other assays not requiring the GI Preservative.

URINE (FOR CATECHOLAMINES ONLY)
Measure 10 mL of 24-hour urine collection. Minimum specimen size is 2 mL. Random urine samples are acceptable if 24-hour total volume is not available.

Important Precaution
Specimens for assays specified must be collected using the GI Preservative tube. No other specimens are acceptable for these assays.

Shipping Instructions
Specimens should be shipped frozen in dry ice.
References

1. Please refer to www.endotext.org.

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Chapter 4 - Profiles, Including CPT Codes

Hypoglycemia/Insulinoma Screening Test

Patient Preparation
Patients should be advised to discontinue medications that affect insulin levels, if possible, for 48 hours prior to collection. After an overnight fast, basal blood samples are collected to measure the following:

- Insulin
- Proinsulin
- C-peptide
- IGF-1 and IGF-2

Specimen Requirements
Collect 6 mL of serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 4 mL.

Shipping Instructions
Specimen should be shipped frozen in dry ice.

Reference

©2006 Inter Science Institute. This profile of assays for the hypoglycemia insulinoma screening has been copyrighted.

CPT Codes:

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<tr>
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<tr>
<td>Insulin 83525</td>
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<tr>
<td>Proinsulin 84206</td>
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<td>Proinsulin Serum 84206</td>
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<tr>
<td>C-Peptide 80432, 84681</td>
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<tr>
<td>IGF-1 84305</td>
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<tr>
<td>IGF-2 83520</td>
</tr>
</tbody>
</table>
INTERLEUKINS INDIVIDUALLY AND AS A PROFILE (IL-1 THROUGH IL-18)

Reference Range
See individual assays in Chapter 3.

Procedure
Interleukins are measured by enzyme immunoassay.

Patient Preparation
Patient should not be on any corticosteroids, anti-inflammatory medications, or pain killers, if possible, for at least 48 hours prior to collection.

Specimen Collection
Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze specimen immediately after separation. Minimum specimen size is 1 mL.

Important Precaution
The interleukins are unstable in freeze-thaw cycles. Do not thaw prior to shipping; specimens must remain frozen from immediately after collection until assayed.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

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CPT Codes:
IL-1α, IL-1β or Any Interleukin Through IL-18 83519
Lipoprotein profile (either VAP™ or NMR method)
  • Triglycerides
  • Total cholesterol
  • HDL-C
  • LDL-C
  • LDL-C particle size

Patient Preparation
Consult local laboratory for patient preparation.

Specimen Requirements
Consult local laboratory for specimen requirements.

Shipping Instructions
Consult local laboratory for shipping instructions.

Reference
1. Please refer to www.endotext.org.

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<table>
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<td>HDL-C 83718</td>
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<tr>
<td>Total Cholesterol 82465</td>
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<tr>
<td>Triglycerides 84478</td>
</tr>
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</table>
MEN Syndrome Screen

BLOOD
- Pituitary (MEN-I)
  - Prolactin
  - Growth hormone if features of acromegaly
- Parathyroid (MEN-I and -II)
  - PTH
  - PTHRP
  - Ionized Ca\(^++\) or Ca\(^++\) corrected for serum albumin
  - 24-Hour urine collection for Ca\(^++\) and PO\(_4\)
- Pancreas (MEN-I)
  - Pancreatic polypeptide
  - Gastrin
  - Insulin/C-peptide if patient hypoglycemic
  - CGA
- Thyroid C cells (MEN-II)
  - Calcitonin
  - CEA
- Adrenal (MEN-II)
  - Catecholamines (plasma and urine determinations)

URINE
- VMA
- Catecholamines if hypertensive or VMA is positive
- 5-HIAA
- 5-HTP

TISSUE IMMUNOHISTOCHEMISTRY (FORMALIN-FIXED 2-mm\(^3\) SPECIMENS)
- CGA
- NSE
- Synaptophysin
- Ki-67, AE1, and AE3
- Glucagon
- Gastrin
- Insulin
- Somatostatin
- PP
- Consider factor VIII, CD31, and somatostatin receptors

GENETIC SCREENING
- RET protooncogene
- MEN-I gene

Patient Preparation
Patient should fast overnight prior to collection of blood specimens. Antacid medications and medications affecting intestinal motility should be discontinued, if possible, for at least 48 hours prior to collection of specimens. Patients should not partake of the following foods for 48 hours prior to collection of urine for measurement of 5-HIAA and 5-HTP measurements:
• Red wine
• Cheese
• Hot dogs
• Chocolates
• Vanilla-containing foods (e.g., ice cream)
• Custard
• Pineapple, kiwi, bananas, cassava

**Specimen Requirements**

**BLOOD**
Collect 20 mL of blood in a green-topped EDTA tube. For serotonin analysis, use a yellow-topped tube containing 75 mg ascorbic acid (vitamin C) for the blood collection. Separate and freeze plasma immediately. For bombesin and VIP analyses, collect 5 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Special GI Preservative tubes are available from ISI. Minimum specimen size is 1 mL.

**TISSUE**
Consult specialist for tissue staining requirements.

**URINE**
See complete urine collection instructions in the introduction to Chapter 3.

**Shipping Instructions**
Specimens should be shipped frozen in dry ice.

**References**
1. Please refer to www.endotext.org.

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# Neuroendocrine Tumors
## A Comprehensive Guide to Diagnosis and Management

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<thead>
<tr>
<th>CPT Codes: Blood</th>
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<tr>
<td><strong>Pituitary (MEN-I)</strong></td>
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<tr>
<td>• Prolactin 84146</td>
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<tr>
<td>• Growth Hormone 83003</td>
</tr>
<tr>
<td><strong>Parathyroid (MEN-I and -II)</strong></td>
</tr>
<tr>
<td>• Parathyroid Hormone (PTH) 83519</td>
</tr>
<tr>
<td>• PTHRP 83519</td>
</tr>
<tr>
<td>• Ionized Ca++ or Ca++ Corrected for Serum Albumin 82330</td>
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<tr>
<td><strong>Pancreas (MEN-I)</strong></td>
</tr>
<tr>
<td>• Pancreatic Polypeptide 83519</td>
</tr>
<tr>
<td>• Gastrin 82938–82941</td>
</tr>
<tr>
<td>• Insulin 83525</td>
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<tr>
<td>• C-peptide 84681</td>
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<td>• Chromogranin A 86316</td>
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<td><strong>Thyroid C Cells (MEN-II)</strong></td>
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<tr>
<td>• Calcitonin 82308</td>
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<tr>
<td>• Carcinoembryonic Antigen (CEA) 82378</td>
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<tr>
<td><strong>Adrenal (MEN-II)</strong></td>
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<td>• Catecholamines 82384</td>
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<th>CPT Codes: Urine</th>
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<td>Catecholamines 82384</td>
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<td>5-HIAA 83497, 82570</td>
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<td>5-HTP 86701</td>
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<th>CPT Codes: Tissue Immunohistochemistry (Formalin-Fixed 2-mm³ Specimens)</th>
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<tr>
<td>Chromogranin A 86316</td>
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<tr>
<td>Neuron-Specific Enolase 86316</td>
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<td>Synaptophysin NO CODE AVAILABLE FOR IHC SYNAPTOPHYSIN</td>
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<td>Ki-67 NO CODE AVAILABLE FOR IHC Ki-67; Ki-67, Breast Cancer 88360</td>
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<tr>
<td>AE 1 and AE 3 84999 Unlisted Chemistry Procedure</td>
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<td>Glucagon NO CODE AVAILABLE FOR IHC GLUCAGON</td>
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<td>Glucagon 82943</td>
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<tr>
<td>• Tolerance Panel 80422–80424</td>
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<tr>
<td>• Tolerance Test 82946</td>
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<td>Gastrin NO CODE AVAILABLE FOR IHC GASTRIN</td>
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<tr>
<td>Gastrin 82938–82941</td>
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<tr>
<td>Insulin NO CODE AVAILABLE FOR IHC INSULIN BLOCK</td>
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<tr>
<td>Insulin 83525</td>
</tr>
<tr>
<td>Somatostatin 84307</td>
</tr>
<tr>
<td>Pancreatic Polypeptide 83519</td>
</tr>
</tbody>
</table>
Metabolic Syndrome Profile

- Insulin (1 test)
- Fasting glucose (1 test)
- HOMA index

$$\text{HOMA IR} = \frac{\text{Fasting Insulin (μU/mL)} \times \text{Fasting Glucose (mmol/L)}}{22.5}$$
$$\text{HOMA B} = \frac{\text{Fasting Insulin (μU/mL)}}{\text{Fasting Glucose (mmol/L)} - 3.5}$$

- Insulin secretory index

$$\text{Insulin Secretory Index} = \frac{\text{Insulin 30 min (pmol/L)} - \text{Insulin 0 min (pmol/L)}}{\text{Glucose 30 min (mmol/L)} - \text{Glucose 0 min (mmol/L)}}$$

- HBA1c (1 test)
- C-peptide (2 tests)
- Free fatty acids (FFAs; 2 tests)
- Highly sensitive C-reactive protein (HS CRP; 1 test)
- PAI-1 (1 test)
- Fibrinogen (1 test)
- Adiponectin (1 test)
- IL-6 (1 test)
- Free and total testosterone (free index; 2 tests)
- Sex steroid–binding globulin (2 tests)
- Uric acid (2 tests)
- Lipoprotein profile (VAP™; 1 test)
- Apolipoproteins (2 test)
- Microalbumin (spot/g creatinine; 1 test)
- Angiotensin I and II
- Endothelin I

Patient Preparation

Patient should fast for 10 to 12 hours prior to collection of specimen. Patient should be on a normal-sodium diet (110 mEq sodium) and recumbent for at least 30 minutes prior to draw. Patient should not be on ACTH, corticosteroid, diuretics, mineralocorticoids, glucocorticoids, estrogens, oral contraceptives, or hypertension medications, if possible, for 48 hours prior to collection.

Specimen Collection

Collect 20 mL EDTA plasma and separate as soon as possible. Freeze plasma immediately after separation. Minimum specimen size is 10 mL.
Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

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<tr>
<td>• Free 83527</td>
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<tr>
<td>Fasting Glucose 82947</td>
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<tr>
<td>HBA1c 83036</td>
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<tr>
<td>C-Peptide 80432, 84681</td>
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<tr>
<td>Free Fatty Acids (FFAs) 82725</td>
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<tr>
<td>Highly Sensitive C-Reactive Protein (HS CRP) 86140–86141</td>
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<tr>
<td>PAI-1 85420–85421</td>
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<tr>
<td>Fibrinogen 85384–85385</td>
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<td>Adiponectin 83520, Unspecified Immunoassay</td>
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<td>IL-6 83519</td>
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<td>Free and Total Testosterone 84402, 84403</td>
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<td>Sex Hormone–Binding Globulin 84270</td>
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<td>Uric Acid</td>
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<td>• Uric Acid 84550</td>
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<td>• Uric Acid Random/24-Hour 84560</td>
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<td>Lipoprotein Profile (VAP™)</td>
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<td>Apolipoproteins 84478</td>
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<td>Microalbumin (spot/g Creatinine) 82043, 82570</td>
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<td>Angiotensin I and II</td>
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<td>• Angiotensin II 82163</td>
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<td>Endothelin I 83519</td>
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</table>
OXIDATIVE/NITROSATIVE STRESS PROFILE

NFκB
- CML
- ROS
- NOX nitrotyrosine
- TBARS
- 8-Keto PGF₂α
- 8-OH, guanosine

TEST PROTOCOL
- Vitamin E
- Vitamin C
- Plasma antioxidant capacity
- Superoxide anion

Patient Preparation
Patient should fast for 10 to 12 hours prior to collection of specimen. Patient should not be on any medications that influence insulin production or secretion, if possible.

Specimen Collection
After a 12-hour fast, collect blood by venipuncture into 10-mL sampling vials containing NH₄ and 2.7-mL vials containing EDTA (final concentration 0.1%). Obtain plasma by centrifugation at 1500g at room temperature for 10 minutes. Immediately store samples of plasma from EDTA vials at -85°C for subsequent analysis (vitamins and antioxidant capacity). For F₂ isoprostane analysis, aliquots (1 μL) of plasma from vials containing NH₄ are combined with 10 μL of chain-breaking antioxidant butylated hydroxytoluene at a final concentration of 25 μmol/L and stored at -85°C until analysis.

Special Specimens
For tumor/tissue and various fluids (e.g., CSF, peritoneal fluid, synovial fluid) contact ISI for requirements and special handling instructions.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

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CPT Codes:

| Lipid Peroxide (for TBARS, Thiobarbituric Acid Reactive Substances) 82491 |
| Unspecified Immunoassay 83519 |
Pancreatic Function Screen

BLOOD
- Trypsin
- Amylase
- Lipase
- Elastase

SERUM
- Amylase
- Lipase
- Trypsin

STOOL
- Fat
- Chymotrypsin
- Elastase-1

Patient Preparation
Patient should fast for 10 to 12 hours prior to collection of specimen. Antacid medications and medications affecting intestinal motility or pancreatic function should be discontinued, if possible, for at least 48 hours prior to collection.

Specimen Requirements

BLOOD
Collect 10 mL serum or EDTA plasma and separate as soon as possible. Freeze plasma immediately after separation. Minimum specimen size is 3 mL.

STOOL
See complete fecal collection instructions in the introduction to Chapter 3.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

References

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**Polycystic Ovary Syndrome (PCOS) Screen**

The following measurements are required for the diagnosis of polycystic ovary disease:

**BLOOD**
- Total and free testosterone
- SHBG
- Dehydroepiandrosterone sulfate (DHEA-S)
- Prolactin
- LH/FSH (frequent but not required)
- TSH
- 17α-Hydroxy progesterone
- Glucose (fasting)
- Insulin
- C-peptide

**Patient Preparation**

Patient should fast for 10 to 12 hours prior to collection of specimen. Patient should not be on any medications that influence insulin production or secretion or any corticosteroi d, ACTH, thyroid, estrogen, or gonadotropin medications, if possible, for at least 48 hours prior to collection.

**Specimen Requirements**

Collect 10 mL serum or EDTA plasma and separate as soon as possible. Freeze serum or plasma immediately after separation. Minimum specimen size is 4 mL.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**References**


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**CPT Codes:**

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<td>Dehydroepiandrosterone Sulfate (DHEA-S)</td>
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<tr>
<td>Prolactin</td>
<td>84146</td>
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<tr>
<td>LH/FSH (Frequent but Not Required)</td>
<td>83002/83001</td>
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<tr>
<td>TSH</td>
<td>84443</td>
</tr>
<tr>
<td>17α-Hydroxy Progesterone</td>
<td>83498</td>
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<tr>
<td>Glucose (Fasting)</td>
<td>82947</td>
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<td>Insulin</td>
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Dynamic Challenge Protocols, Including CPT Codes

Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management
RATIONALE FOR DYNAMIC CHALLENGE PROTOCOLS

Careful evaluation of GI and pancreatic disorders involves a multiplicity of interrelated factors governed by a number of hormonal axes with varying degrees of interdependence. From this composite view of interdependency, these challenge protocols are designed to help elucidate specific GI, pancreatic, and neuroendocrine abnormalities. Emphasis is placed on stimulation and/or suppression tests designed to exploit the failure of normal homeostatic regulation through metabolic pathways.

These challenge protocols represent guidelines in evaluating a variety of GI-related syndromes. The listings are selected to provide maximal information, usefulness, and significance for interpretation in the endocrine workup of the patient or research subject.

Important Notes

No patient should undergo a dynamic challenge protocol without the direct and constant supervision of trained medical personnel. The doses listed for the following protocols are intended as guidelines only. The actual dose and collection schedule must be approved by the patient’s physician.
Calcium Stimulation for Gastrinoma

Test, Times of Collection
Gastrin: fasting; 1, 2, and 3 hours

Stimulus/Challenge
Following an overnight fast (after 10:00 pm), the patient should be given 15 mg elemental calcium per kilogram body weight in 500 mL saline. This should be infused over a 4-hour period with continuous cardiac monitoring.

Important Precautions
If secretin is available, avoid performing the calcium infusion test. The calcium infusion test is potentially dangerous and can induce cardiac arrhythmias and standstill if infused too quickly.

Patients undergoing dynamic challenge should be under the direct and constant supervision of medical staff at all times. Continuous cardiac monitoring is mandatory.

Specimen Requirements
In adults, collect 10 mL whole blood in a green-topped EDTA tube. Separate plasma and freeze immediately. Carefully label tubes with time of collection and patient data.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

Expected Response
Gastrin response should increase by more than 100 pg/mL or by more than 50% over baseline when this level is abnormal.

References

CPT Codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>Gastrin 82941</td>
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<tr>
<td>Calcium-Pentagastrin Stimulation 80410</td>
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</table>
INSULIN HYPOGLYCEMIA PROVOCATION OF PANCREATIC POLYPEPTIDE AS A TEST FOR VAGAL INTEGRITY

Test, Times of Collection
Pancreatic polypeptide: fasting; 15, 30, 45, 60, 90, and 120 minutes after injection of insulin

Stimulus/Challenge
Following an overnight absolute fast, patient should be given 0.2 U insulin per kilogram body weight.

Important Precautions
Patients undergoing dynamic challenge should be under the direct and constant supervision of medical staff at all times. The dosages listed are intended as a guideline only. The actual dosage and collection schedule must be approved by the patient’s physician.

Specimen Requirements
Collect 3 mL serum or EDTA plasma at indicated times and separate as soon as possible. Freeze specimens immediately after separation. Minimum specimen size is 1 mL per specimen collected. Specimens should be clearly identified by time of collection.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

Expected Response
Pancreatic polypeptide response should increase at least 2 times over baseline level.

Interpretation
Patients with impaired pancreatic function show little or no increase in pancreatic polypeptide levels. Patients with pancreatitis or diabetes mellitus often have exaggerated responses.

Contraindications, Interferences, Drug Effects
Patients with seizure disorders on dexamethasone or more than 30 mg/day of hydrocortisone or an equivalent other short-acting glucocorticoid (7.5 mg/day prednisone or 6 mg/day methylprednisolone) may have subnormal responses without any permanent hypothalamic-pituitary-adrenal disorder.

Patients with elevated baseline levels of pancreatic polypeptide (seen in some cases of Verner-Morrison syndrome) often have decreased responses.

References

CPT Code:
Pancreatic Polypeptide
83519
INSULIN HYPOGLYCEMIA PROVOCATION OF GROWTH HORMONE, ACTH AND CORTISOL (INSULIN TOLERANCE TEST)

Test, Times of Collection
Glucose, growth hormone, and/or ACTH and/or cortisol: fasting; 15, 30, 45, 60, 90, and 120 minutes

Stimulus/Challenge
Following an overnight fast (calorie-free liquids allowed) with the last dose of prednisone or hydrocortisone at 6:00 pm the prior evening or of dexamethasone 24 or more hours earlier, administer 0.1 to 0.15 U per kilogram body weight, depending on suspicion of adrenal insufficiency (use 0.1 U/kg) and adiposity (BMI >30 use 0.15 U/kg) intravenous push of regular, lispro, aspart, or glulysine insulin. Fingerstick blood glucose levels can be used to assist in determining adequacy of hypoglycemia (blood glucose <45 mg/dL or <50 mg/dL if the patient is symptomatic [e.g., diaphoretic, tremulous, light headed, anxious; experiencing facial paresthesias, altered vision]. An additional dose of insulin should be given after 30 minutes if the target glucose level is not achieved. If the nadir glucose level occurs after 30 minutes, additional blood samples are indicated to encompass the added time. Glucose, both for oral consumption and as dextrose 50%, should be available and can be given immediately upon achieving a satisfactory endpoint (i.e., hypoglycemic symptoms or hypoglycemia). Intravenous dextrose should be reserved for the rare patient who is not able to safely swallow.

Important Precautions
Patients undergoing dynamic challenge should be under the direct and constant supervision of medical staff at all times. The dosages listed are intended as a guideline only. The actual dosage and collection schedule must be approved by the patient’s physician.

Specimen Requirements
Collect 10 mL serum and 10 mL EDTA plasma at indicated times and separate as soon as possible. Freeze specimens immediately after separation. Minimum specimen size is 1 mL per specimen collected. Specimens should be clearly identified by time of collection.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

Expected Response
Normal GH response: increase to 4 ng/mL or higher
Normal cortisol response: increase to 18 µg/mL or higher
Normal ACTH response: >35 pg/mL
Interpretation
Patients with impaired pituitary or adrenal function fail to achieve cortisol levels above 18 µg/mL, whereas primary adrenal failure patients have elevated baseline ACTH levels. Patients with both GH and ACTH/cortisol inadequacy probably will be panhypopituitary with additional TSH/free thyroxine and gonadotropin/sex steroid inadequacy.

Contraindications, Interferences, Drug Effects
Patients with seizure disorders on dexamethasone or more than 30 mg/day hydrocortisone or equivalent other short-acting glucocorticoid (7.5 mg/day prednisone or 6 mg/day methylprednisolone) may have subnormal responses without any permanent hypothalamic-pituitary-adrenal disorder.

Reference

CPT Codes:
- ACTH 82024
- Cortisol 82533
- Glucose Tolerance Test 82951
- Glucose Tolerance Test (each additional beyond three specimens) 82952
- Growth Hormone 83003
Meal (Sham Feeding) Stimulation for Vagal Integrity

Test, Times of Collection
Pancreatic polypeptide: fasting; 30, 45, 60, 90, and 120 minutes after meal

Stimulus/Challenge
Following an overnight absolute fast, give patient 100 g of roast beef or other protein-rich meal or undergo sham feeding (i.e., chew food and spit out without swallowing).

Important Precautions
Patients undergoing dynamic challenge should be under the direct and constant supervision of medical staff at all times. The dosages listed are intended as a guideline only. The actual dosage and collection schedule must be approved by the patient’s physician.

Specimen Requirements
Collect 3 mL serum or EDTA plasma at indicated times and separate as soon as possible. Freeze specimens immediately after separation. Minimum specimen size is 1 mL per specimen collected. Specimens should be clearly identified by time of collection.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

Expected Response
Pancreatic polypeptide response should increase 2 to 5 times over baseline level.

Interpretation
Patients with impaired pancreatic function show little or no increase in pancreatic polypeptide levels. Patients with pancreatitis or diabetes mellitus often have exaggerated responses. Patients with duodenal ulcers frequently have elevated baseline levels of pancreatic polypeptide and exhibit a reduced response.

Contraindications, Interferences, Drug Effects
Patients with elevated baseline levels of pancreatic polypeptide (seen in some cases of Verner-Morrison syndrome) often have decreased responses.

References

CPT Code:
Pancreatic Polypeptide
83519
Octreotide Suppression Test for Carcinoid and Islet Cell Tumors

Octreotide acetate and a variety of other somatostatin type 2–receptor binding analogs such as lanreotide and vapreotide have been effectively used to control symptoms, improve biochemical abnormalities caused by excessive peptide/amine release from NETs, and arrest tumor growth. Octreotide acetate is currently the only commercially available somatostatin analog approved in the United States for the treatment of NETs. Octreotide acetate is available in aqueous and sustained-release formulations (LAR).

Biochemical response:
- The aqueous form of octreotide achieves peak blood levels within 60 to 120 minutes after injection.
- Injection of the sustained-release product achieves peak blood levels in 2 weeks and may require up to three injections at monthly intervals to achieve steady-state blood levels.

Symptom responsiveness can often be predicted by an OctreoScan® in which octreotide is taken up by tumors expressing somatostatin type 2 receptors or by obtaining tissue showing the presence of somatostatin type 2 receptors in the tumor.

A surrogate measure of the potential durability of the response of the clinical syndrome to octreotide therapy is the suppression of the target hormone by octreotide in the acute test.

Patient Preparation

Acute Suppression Test

In islet cell tumor patients, following an overnight absolute fast 10 to 12 hours prior to the test, determine a baseline level by measuring the dominant peptide: in gastrinoma patients measure gastrin; in glucagonoma patients measure glucagon; in VIPoma patients measure VIP; in patients with a nonfunctional tumor measure pancreatic polypeptide levels; in aldosterone-producing adrenal tumor patients measure aldosterone. Patients should fast 1 hour prior to the test (administered in a supine position) to measure aldosterone levels.

Following the determination of the fasting baseline value, an injection of octreotide or other somatostatin analog is given in the physician’s office. In the United States, 100 μg of octreotide acetate is given subcutaneously and the marker value re-measured at 1 and 2 hours after the injection.

Interpretation

A decrease of 50% in the marker value at 1 to 2 hours predicts a durable response in symptoms to long-term therapy with octreotide.
Chronic Suppression Test (of Production of Serotonin and Its Metabolites)

In carcinoid patients, following a nonfasting but diet-controlled regimen, determine a baseline level marker by measuring CGA and 24-hour urinary 5-HIAA as the biomarkers.

Subsequent to determining the 24-hour urine measurement, initiate a 3-day course of octreotide (100 μg subcutaneously three times daily). The 24-hour urinary collection is repeated on the third day. A decrease of 50% in the baseline marker value predicts a good biochemical response to long-term therapy with octreotide acetate or other somatostatin type 2–preferring analogs.

Specimen Requirements

**BLOOD**
Collect 10 mL EDTA plasma in a special tube containing the GI Preservative and separate as soon as possible. Freeze plasma immediately after separation. Minimum specimen size is 2 mL. Special GI Preservative tubes are available from ISI for the VIP and glucagon assays. Three-milliliter serum or EDTA plasma specimens obtained at 60 and 120 minutes following the injection may be submitted for other assays not requiring the GI Preservative.

**URINE**
Patients should not partake of the following foods for 48 hours prior to collection of urine for measurement of 5-HIAA and 5-HTP:

- Red wine
- Cheese
- Hot dogs
- Chocolates
- Vanilla-containing foods (e.g., ice cream)
- Custard
- Pineapple, kiwi, bananas, cassava

Shipping Instructions

Specimens should be shipped frozen in dry ice.

References

**Oral Glucose Tolerance Test for Diabetes, Insulinoma, Impaired Glucose Tolerance, Metabolic Syndrome, PCOS, Reactive Hypoglycemia, and Acromegaly**

**Test, Times of Collection**

Diabetes: measure glucose and insulin at 0, 30, 60, 90, and 120 minutes
Reactive hypoglycemia: measure glucose and insulin at 0, 30, 60, 90, 120, 180, 240, and 300 minutes.

Acromegaly: measure growth hormone and glucose at 0, 30, 60, 90, 120, 180, 240, and 300 minutes

**Stimulus/Challenge**

Glucose: 75 g orally
Pregnant patients: 100 g orally.

**Expected Responses**

- Normal fasting glucose: <100 mg/dL
- Normal peak glucose: <200 mg/dL
- Normal 2h glucose: <140 mg/dL
- Impaired fasting glucose: ≥100 mg/dL
- Impaired glucose tolerance (IGT or prediabetes): fasting glucose >100 mg/dL, peak >200 mg/dL and 2 hours postchallenge 141–198 mg/dL
- Diabetes: fasting glucose >125 mg/dL on 2 occasions or 2-hour glucose >200 mg/dL after oral glucose in nonpregnant patients
- Reactive hypoglycemia: <40 mg/dL between 2 and 5 hours postchallenge
- Normal growth hormone: <1.4 ng/mL after oral glucose
- Reactive hypoglycemia: <40 mg/dL between 2 and 5 hours postchallenge

**Expected Response**

- Fasting insulin: 5–19 µU/mL
- Insulin should increase to at least double the baseline level and at least 10 µU/mL above baseline level
- Peak levels at 30 minutes: 50–150 µU/mL
- Return to fasting at 2 hours

A lack of a rise in serum insulin after glucose is indicative of pancreatic beta cell dysfunction. Glucose levels should be monitored to ensure validation of glucose loading. Glucose levels between 140 and 200 mg/dL indicate impaired pancreatic function. Glucose levels greater than 200 mg/dL may be indicative of diabetes. A fasting insulin/glucose ratio greater than 0.25 is presumptive for insulinoma. Proinsulin/insulin ratio greater than 0.30 is also indicative of insulinoma. Growth hormone suppresses to less than 2 ng/mL in healthy people and in patients with well-controlled acromegaly.
Insulin Resistance and Beta Cell Function

Beta cell function and insulin resistance is assessed by the HOMA model developed by Mathews using the following equations:

\[
\text{HOMA IR} = \frac{\text{Fasting Insulin (µU/mL)} \times \text{Fasting Glucose (mmol/L)}}{22.5}
\]

\[
\text{HOMA B} = \frac{\text{Fasting Insulin (µU/mL)}}{\text{Fasting Glucose (mmol/L)} - 3.5}
\]

Insulin secretory index is assessed by the following equation:

\[
\text{Insulin secretory index} = \frac{[\text{Insulin 30 min (pmol/L)} - \text{Insulin 0 min (pmol/L)}]}{[\text{Glucose 30 min (mmol/L)} - \text{Glucose 0 min (mmol/L)}]}
\]

Insulin secretory index/HOMA IR ratio is used to assess insulin efficacy index. Growth hormone levels should become undetectable within 1 to 2 hours of glucose challenge.

Important Precautions

Patients undergoing dynamic challenge should be under the direct and constant supervision of medical staff at all times. The dosages listed are intended as a guideline only. The actual dosage and collection schedule must be approved by the patient’s physician.

Specimen Requirements

Collect 3 mL serum or EDTA plasma at indicated times and separate as soon as possible. Freeze specimens immediately after separation. Minimum specimen size is 1 mL per specimen collected. Specimens should be clearly identified by time of collection.

Shipping Instructions

Specimens should be shipped frozen in dry ice.

Contraindications, Interferences, Drug Effects

Glucose levels are higher in the evening hours than in the morning hours. Glucose levels also increase with age and obesity. Pregnancy, low-carbohydrate diet, stress, contraceptives, glucocorticoids, clofibrate, thiazides, diphenylhydantoin, caffeine, ranitidine, and propanololl may increase response. Smoking, guanethidine, and salicylates may decrease response. The test should be discontinued if patient experiences vasovagal symptoms. The test should not be given to patients with glucose intolerance (i.e., those with elevated baseline glucose levels). There is also some risk of hyperosmolality.

References


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Pentagastrin Stimulation Test for Calcitonin (Medullary Carcinoma of the Thyroid)

The pentagastrin stimulation test is used to identify patients with MCT who have normal baseline levels of calcitonin. It is also useful to identify members of a family with a known familial form of MEN-II and MCT. Pentagastrin normally stimulates the secretion of calcitonin from the C cell. Women may not respond due to the presence of estrogens. The response in persons with MCT is an exaggeration of the normal response to pentagastrin.

**Stimulus/Challenge**

Pentagastrin: 0.5 µg/kg body weight by intravenous bolus injection.

**Times of Collection**

Calcitonin: 0, 1, 2, 5, and 10 minutes

**Important Precautions**

Patients undergoing dynamic challenge should be under the direct and constant supervision of medical staff at all times.

**Specimen Collection**

Collect 3 mL serum or EDTA plasma and separate as soon as possible. Freeze specimen immediately after separation. Minimum specimen size is 1 mL.

**Expected Response in Patients With Medullary Carcinoma of the Thyroid**

Normal basal or fasting calcitonin levels are less than 50 pg/mL. Healthy people do not experience an increase in calcitonin above 200 pg/mL with the administration of pentagastrin.

**Interpretation**

An exaggerated response is seen in patients with MCT and in C cell hyperplasia. Patients with elevated basal or pentagastrin-stimulated calcitonin levels should receive screening for the RET protooncogene. Carcinoembryonic antigen measurements may be helpful in determining tumor mass.

**Contraindications, Interferences, Drug Effects**

Patients should be warned that they will experience transient (<1–2 minutes) flushing, nausea, chest pain, and sweating with feelings of impending doom after the administration of pentagastrin, but these resolve within minutes.

**References**


**CPT Codes:**

| Calcium-Pentagastrin Stimulation 80410 |
| Calcitonin 82308 |
PITUITARY AND HYPOTHALAMIC DISORDERS TESTS

First-Line Screening

1. Urinary free cortisol (three 24-hour collections if suspicion exists and one or more collections are normal due to “cyclic Cushing’s disease.” In preclinical Cushing’s syndrome, urinary free cortisol may be normal.
2. Low-dose dexamethasone suppression test, either overnight (1 mg between 11:00 PM and 12:00 AM) or 0.5 mg every 6 hours for 48 hours. N1 suppression is to less than 1.8 µg/dL (50 nmol/L).
3. Circadian rhythm of cortisol: obtain serum cortisols at 8:00 AM to 09:30 AM, 4:30 PM to 6:00 PM, and 11:00 PM to 12:00 AM. The latter samples can be obtained with the patient asleep as an inpatient after 48 hours, but only if not acutely ill. Alternatively, the patient can test at home with collections of salivary cortisol.

Second-Line Testing

1. Circadian rhythm of cortisol: see above.
2. Low-dose dexamethasone suppression: 0.5 mg every 6 hours for 48 hours with measurement of 24-hour urine free cortisol on the second day. Excretion of <10 µg/24 hours (27 nmol/L) is normal.
3. Dexamethasone suppression test with CRH stimulation: low-dose DST (0.5 mg every 6 hours for 48 hours followed by 100 µg or 1 µg/kg of ovine CRH intravenously. Cortisol response >1.4 µg/dL at 15 minutes is consistent with Cushing’s disease.

References


CPT Codes:

11-Deoxycortisol, Urine 82634
Cortisol, Serum 82533
Cortisol Level, Urine 83519
Dexamethasone, Serum 83516
Proxovacative Pancreatic Exocrine Function Tests

The secretin-cholecystokinin stimulation test measures the concentration and output of bicarbonate, lipase, and trypsin in the duodenal juice. This test is the gold standard for determining the degree of pancreatic exocrine insufficiency, but it is seldom done in the clinical settings. Most institutions depend on the indirect assessment of pancreatic exocrine insufficiency by determining the presence and severity of fecal steatorrhea and/or by direct pancreatic enzyme measurement.

References for Acute Pancreatitis


References for Chronic Pancreatitis


CPT Code:

Gastrin After Secretin Stimulation 82938
Neuroendocrine Tumors
A Comprehensive Guide to Diagnosis and Management

Provocative Tests for Dumping Syndrome

Dumping occurs following surgical procedures that extirpate or inactivate the pylorus. Two forms of dumping occur: early dumping is characterized by shock-like symptoms, and late dumping is characterized by symptoms of hypoglycemia.

Stimulus/Challenge

Following baseline blood draw, the patient is given a carbohydrate-rich, high-calorie breakfast consisting of two eggs, two strips of bacon, two pieces of whole wheat toast, and a serving of ice cream topped with flavored syrup. This test meal contains 750 kcal, 21 g protein, 30 g fat, and 99 g of carbohydrate. The meal should be ingested within 10 minutes to evoke the maximum response.

Timing of Blood Draws

Collect 5 mL of whole blood in green-topped EDTA tubes at 10, 15, 30, 45, 60, 120, and 180 minutes following completion of the meal. Glucose levels and the hormones listed below should be measured. In patients with late dumping, additional blood samples should be collected at after the test meal.

Hormones Assayed

Insulin, C-peptide, motilin, pancreatic polypeptide, GLP-1

Specimen Requirements

Whole blood should immediately be separated and the plasma frozen.

Shipping Instructions

Specimens should be shipped frozen in dry ice.

References


CPT Codes:

| GLP-1 Unspecified, Immunoassay 83519 |
| C-Peptide 84681 |
| Pancreatic Polypeptide 83519 |
| Insulin 83525 |
| Motilin 83519 |
SECRETIN STIMULATION TEST FOR GASTRINOMA

Test, Times of Collection
Gastrin: fasting; 2, 5, 10, 15, and 30 minutes

Stimulus/Challenge
Following an overnight fast from 10:00 PM, patient should be given secretin 2 U/kg by intravenous bolus injection.

Important Precautions
Patients undergoing dynamic challenge should be under the direct and constant supervision of medical staff at all times. The doses listed are intended as a guideline only. The actual dose and collection schedule must be approved by the patient’s physician.

Specimen Requirements
In adults, collect 10 mL whole blood in a green-topped EDTA tube. Separate plasma and freeze immediately. Carefully label tubes with time of collection and patient data.

Shipping Instructions
Specimens should be shipped frozen in dry ice.

Expected Response
Gastrin response should increase no more than 50% over baseline level in healthy people. In gastrinoma, the rise increase is greater than 100 pg/mL above basal levels.

Interpretation
Patients with gastrinoma exhibit elevated baseline gastrin levels and a paradoxical rise in the gastrin response to secretin greater than 100 pg/mL above their baseline level. Healthy people have a fall or no rise in gastrin levels. Patients with hypochlorhydria or achlorhydria from PPI use, type 1 gastric carcinoid, atrophic gastritis, or pernicious anemia have elevated gastrin levels (>150 pg/mL) but exhibit no response to administration of secretin. Patients with active peptic ulcers may show a 30% to 50% increase over baseline levels. Healthy patients frequently exhibit suppression in gastrin levels following secretin administration.

References

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72-HOUR SUPERVISED FAST FOR THE DIAGNOSIS OF INSULINOMA

A 72-hour fast is the preferred diagnostic procedure for the diagnosis of an insulinoma.

**Patient Preparation**

Patient should fast for 72 hours. Water and diet soft drinks without caffeine are permitted. Patients submitted to a 72-hour fast should be under the direct and constant supervision of medical staff at all times.

**Test, Times of Collection**

Insulin, glucose, and C-peptide samples are drawn at 0, 12, 24, 36, 48, and 72 hours after beginning fast. If the patient becomes symptomatic (i.e., documented fingerstick hypoglycemia) at any time during the test, blood should be drawn immediately for glucose, insulin, and C-peptide levels. Administer glucose and terminate the procedure.

**Specimen Requirements**

Collect 10 mL of whole blood in a green-topped EDTA tube. Separate plasma and freeze immediately. Carefully label 3-mL EDTA tubes with time of collection and patient data.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

**Interpretation**

Expected response in healthy people:
- Insulin levels should decrease to less than 4 µU/mL.
- Insulin/glucose ratio should be less than 0.3.

Expected response in insulinoma:
- A fasting insulin/glucose ratio greater than 0.3 is presumptive of insulinoma.
- An elevated C-peptide level greater than 4 ng/mL in the absence of obesity and insulin resistance suggests insulinoma.

**Caveats**

Ketones should be present in the urine to confirm fasting. 18-Hydroxybutyrate concentrations should also be obtained with each blood draw to support or deny suppression of insulin and release of lipolysis. Suppressed C-peptide levels (<0.5 ng/mL) during fasting suggests factitious hypoglycemia. Elevated C-peptide levels may suggest suspected sulfonylurea-induced factitious hypoglycemia.

**References**


**CPT Codes:**

- C-Peptide 84681
- Glucose 82947
- Insulin 83525
Chapter 5 - Dynamic Challenge Protocols, Including CPT Codes

**Water Deprivation/Desmopressin Test for Diabetes Insipidus: Hypothalamic (HDI), Nephrogenic (NDI), and Dipsogenic (DDI)**

If that patient has moderate polyuria (3–7 L/day), the dehydration test may be started in the evening, with the last fluid being consumed before bed. If polyuria is severe (>7 L/day), begin the test in the morning to avoid dangerous dehydration.

**Patient Preparation**

Patient may have free access to fluid overnight prior to test but should be cautioned to avoid caffeine and smoking. At 7:50 AM the patient voids urine, and starting weight is accurately determined on a scale that can be used throughout the procedure.

**Dehydration Phase**

- At 8:00 AM, measure plasma and urine osmolality and urine volume.
- Patient should fast for the duration of the test.
- Weigh patient at 2-hour intervals or after each liter of urine is excreted.
- Measure plasma and urine osmolality and urine volume every 2 hours and after each urine voided. When two consecutive measures of urine osmolality differ by no more than 10% and the patient has lost 2% of body weight, plasma is drawn for Na⁺, osmolality, and vasopressin determinations.
- Stop the test if weight loss exceeds 3% of starting weight, thirst is intolerable, or serum sodium exceeds normal at anytime during the test. Plasma vasopressin is obtained at the time the test is terminated.
- Supervise patient closely to avoid undisclosed drinking.

**Desmopressin (DDAVP) Phase**

Inject 2 µg DDVAP intravenously/intramuscularly.

Allow patient to eat and drink up to 1.5 to 2.0 times the volume of urine voided during water deprivation.

Measure plasma and urine osmolality and urine volume hourly to 8:00 PM.

**Interpretation**

**HDI:** urine osmolality is less than 300 mOsm/kg accompanied by plasma osmolality greater than 290 mOsm/kg after dehydration; urine osmolality should rise above 750 mOsm/kg after DDAVP.

**NDI:** failure to increase urine osmolality above 300 mOsm/kg after dehydration with no response to DDAVP.

**DDI:** appropriate urine concentration during dehydration without significant rise in plasma osmolality.
If HDI is diagnosed, the next step should be imaging of the hypothalamus/perisellar region with MRI to exclude possible tumors. HDI frequently is associated with loss of the normal posterior pituitary bright spot on T1-weighted MRI, which correlates with posterior pituitary vasopressin content.

**Specimen Requirements**

Collect 5 mL of whole blood in green-topped EDTA tubes and separate as soon as possible. Freeze plasma immediately after separation. Urine osmolality should be determined immediately or the specimens placed in sealed containers to avoid evaporation. Freezing is appropriate if the specimen is to be stored long term.

**Shipping Instructions**

Specimens should be shipped frozen in dry ice.

Reference

1. Please refer to www.endotext.org.

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Caveat
This test is safe only in a patient who has returned to a normal or near normal osmolality. In this case, the test is used chiefly to determine whether the initial problem with hyponatremia has resolved.

Patient Preparation
Patient preparation includes omitting NSAIDs, diuretics, and all other nonessential medications for 24 hours or more in patients on chlorthalidone, spironolactone, or other drugs with long half-lives. The patient should have nothing orally and not smoke for 4 hours before or during the test. After emptying the bladder, 20 mL/kg tepid water should be consumed over 30 minutes. Urine is collected hourly or whenever voided and osmolality and volume recorded. The test is completed at 4 hours. Normal response in a non–saline-depleted subject is 85% to greater than 100% excretion of the water load within 4 hours and drop in urine osmolality to near maximally dilute (i.e., <100 mOsm/kg in healthy young to middle-aged adults without renal disease).

Specimen Requirements
No blood collection is necessary. Determine urine osmolality immediately or place the specimens in sealed containers to avoid evaporation. Freezing is appropriate if specimens are to be stored long term.

Interpretation
For a full discussion on causes of impaired water clearance, see Hyponatremia and Syndrome of Inappropriate Antidiuretic Hormone in Chapter 1.
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Reference

1. Please refer to www.endotext.org.
NEUROENDOCRINE TUMORS
A COMPREHENSIVE GUIDE TO DIAGNOSIS AND MANAGEMENT

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## A Comprehensive Guide to Diagnosis and Management

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ABBREVIATIONS

ACE = angiotensin-converting enzyme
ACTH = adrenocorticotropic hormone (corticotropin)
ApoE4 = apolipoprotein E4
APUD = amine precursor uptake and decarboxylation
BMI = body mass index
BNP = brain natriuretic peptide
BUN = blood urea nitrogen
CA = cancer-associated antigen
CCK = cholecystokinin
CEA = carcinoembryonic antigen
CGA = chromogranin A
CGRP = calcitonin gene–related peptide
CML = carboxy methyl lysine
CRH = corticotropin-releasing hormone
CRF = corticotropin-releasing factor
CRP = C-reactive protein
CSF = cerebrospinal fluid
CT = computed tomography
DDAVP = desmopressin acetate
DDI = dipsogenic diabetes insipidus
DHEA-S = dehydroepiandrosterone sulfate
DHK-PGE₂ = dihydroketo prostaglandin E₂
DHK-PGF₂α = dihydroketo prostaglandin F₂α
DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, and deafness
DST = dexamethasone suppression test
DVT = deep venous thrombosis
EC = enterochromaffin
ECL = enterochromaffin-like
EDTA = ethylene amine tetraacetic acid
EIA = enzyme immunoassay
EL = elastase
ELISA = enzyme-linked immunosorbent assay
FBG = fasting blood glucose
FEV₁ = forced expiratory volume in 1 second
FFA = free fatty acid
FSH = follicle-stimulating hormone
GAD = glutamic acid decarboxylase
GEP = gastroenteropancreatic
GEP-ET = gastroenteropancreatic endocrine tumors
GERD = gastroesophageal reflux disease
GH = growth hormone (somatotropin)
GHRH = growth hormone–releasing hormone
GHS-R1a = growth hormone secretagogue type 1a
GI = gastrointestinal
GIP = gastric inhibitory polypeptide
GLP = glucagon-like peptide
GRP = gastrin-releasing peptide
α-GSU = human glycoprotein hormone alpha subunit
5-HIAA = 5-hydroxyindoleacetic acid
5-HT = 5-hydroxytryptamine (serotonin)
5-HTP = 5-hydroxytryptophan
HDI = hypothalamic (central) diabetes insipidus
HDL = high-density lipoprotein
HLA = human leukocyte antigen
HOMA IR, B = homeostasis model assessment of insulin resistance, of beta cell function
HS CRP = highly sensitive C-reactive protein
HVA = homovanillic acid
$^{131}$I-MIBG = iodine-131 meta-iodobenzylguanidine
IAA = insulin autoantibodies
IAPP = islet amyloid polypeptide
IBS = irritable bowel syndrome
ICA = islet cell antigen
IgA, G = immunoglobulin A, G
IGF-1, -2 = insulin-like growth factor type 1, type 2
IGT = impaired glucose tolerance
IL-1 through IL-18 = interleukin-1 through IL-18
6-Keto-PGF$_1$α = 6-keto prostaglandin F$_1$α
LAR = long-acting repeatable
LDL = low-density lipoprotein
LH = luteinizing hormone
MCT = medullary carcinoma of the thyroid
MDMA = 3,4-methylenedioxymethamphetamine
MEN-I, -II, -III = multiple endocrine neoplasia type I, type II, type III
MODY = mature-onset diabetes of youth
MRI = magnetic resonance imaging
MSH = melanocyte-stimulating hormone
NDI = nephrogenic diabetes insipidus
NET = neuroendocrine tumors
NFκB = nuclear factor kappa B
NKA = neurokinin A
NME = necrolytic migratory erythema
NMR = nuclear magnetic resonance
NPY = neuropeptide Y
NSE = neuron-specific enolase
PAI-1 = plasminogen activator inhibitor 1
PARP = poly(adenosine diphosphate ribose) polymerase
PCOS = polycystic ovary syndrome
PG = prostaglandin
PG-I, -II = pepsinogen I, II
PGD$_2$ = prostaglandin D$_2$
PGE$_1$ = prostaglandin E$_1$
PGE₂ = prostaglandin E₂
PGF₁α = prostaglandin F₁α
PGF₂α = prostaglandin F₂α
PHIM = peptide histidine isoleucine
PP = pancreatic polypeptide
PPI = proton pump inhibitors
PTH = parathyroid hormone
PTHRP = parathyroid hormone–related peptide
PYY = peptide YY
SD = standard deviation
SHBG = sex hormone–binding globulin
SIADH = syndrome of inappropriate antidiuretic hormone secretion
SLI = somatostatin-like immunoreactivity
SRIF = somatostatin release–inhibiting factor
T₃ = triiodothyronine
T₄ = thyroxine
TCT = thyrocalcitonin
TNFα, β = tumor necrosis factor alpha, beta
TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone
TTG = tissue transglutaminase
VIP = vasoactive intestinal polypeptide
VHL = von Hippel-Lindau
VMA = vanillyl mandelic acid
WDHHA = watery diarrhea syndrome (watery diarrhea, hypokalemia, hypochlorhydria, and acidosis)
ZE = Zollinger-Ellison syndrome
Physician, Lab, Hospital: ________________________________

Address: ________________________________

Department: ________________________________

City: __________________ State: ________ Zip: ________

Patient Name: ________________________________

Age: ______ Client Acct. No.: __________________

Sex: ______ Specimen Type: __________________

Collection Date: ________________________________

Collection Time: ______ AM _______ PM

Date Specimen Time Rec’d at ISI: ______ AM _______ PM | ISI Acct. No.: __________________

ALL OF THE FOLLOWING ASSAYS SHOULD BE COLLECTED USING THE GI PRESERVATIVE TUBE AVAILABLE FROM INTER SCIENCE INSTITUTE (ISI).

- AMYLIN
- BOMBESIN
- C-PEPTIDE
- CALCITONIN
- CHOLECYSTOKININ (CCK)
- CHROMOGRAVAN A (CGA)
- ELASTASE: _____ Serum _____ Fecal
- FREE INSULIN
- GALANIN
- GASTRIC INHIBITORY POLYPEPTIDE (GIP)
- GASTRIN
- GASTRIN RELEASING PEPTIDE (GRP)
- GHERLIN
- GLUCAGON
- GROWTH HORMONE RELEASING HORMONE
- HISTAMINE
- INSULIN
- INTERLEUKINS: ______
- MOTILIN
- NEUROKININ A
- NEUROKININ B
- NEUROPEPTIDE K
- NEUROPEPTIDE Y
- NEUROTENSIN
- OCTREOTIDE (Sandostatin®)
- PANCREASTATIN
- PANCREATIC POLYPEPTIDE (PP)
- PEPSINOGEN I
- PEPSINOGEN II
- PEPTIDE YY
- PHIM
- PROSTAGLANDINS (PG): ______
- SANDOSTATIN® (Octreotide)
- SECRETIN
- SEROTONIN (5-HT, Serum only)
- SOMATOSTATIN
- SUBSTANCE P
- THROMBOXANE B2
- VASOACTIVE INTESTINAL POLYPEPTIDE

PROFILES:

- CARCINOID FOLLOW-UP SCREEN
- DIARRHEA SYNDROME
- DUMPING SYNDROME
- FLUSHING SYNDROME
- GASTRINOMA SCREEN
- POLYCYSTIC OVARY SCREEN
- PSEUDOGLASTRINOMA SYNDROME

OTHER ASSAY OR PROFILE: ________________________________

DYNAMIC CHALLENGE PROTOCOLS: ________________________________

COLLECTION TIME(S): ________________________________

TOTAL VOLUME IS REQUIRED FOR URINE ASSAYS: ________/24 hours