TABLE 113-1 GENERAL CHARACTERISTICS OF GASTROINTESTINAL NEUROENDOCRINE TUMORS (GI-NETs [CARCINOIDS], PANCREATIC NEUROENDOCRINE TUMORS [pNETs])

A. Share general neuroendocrine cell markers (identification used for diagnosis)
   1. Chromogranins (A, B, C) are acidic monomeric soluble proteins found in the large secretory granules. Chromogranin A is the most widely used.
   2. Neuron-specific enolase (NSE) is the γ-γ dimer of the enzyme enolase and is a cytosolic marker of neuroendocrine differentiation.
   3. Synaptophysin is an integral membrane glycoprotein of 38,000 molecular weight found in small vesicles of neurons and neuroendocrine tumors.

B. Pathologic similarities
   1. All are APUDomas showing *a*mine *p*recursor *u*ptake and *d*ecarboxylation.
   2. Ultrastructurally, they have dense-core secretory granules (>80 nm).
   3. Histologically, they generally appear similar with few mitoses and uniform nuclei.
   4. Frequently synthesize multiple peptides/amines, which can be detected immunocytochemically but may not be secreted.
   5. Presence or absence of clinical syndrome or type cannot be predicted by immunocytochemical studies.
   6. Histologic classifications (grading, TNM classification) have prognostic significance. Only invasion or metastases establish malignancy.

C. Similarities of biologic behavior
   1. Generally slow growing, but some are aggressive.
   2. Most are well-differentiated tumors having low proliferative indices.
   3. Secrete biologically active peptides/amines, which can cause clinical symptoms.
   4. Generally have high densities of somatostatin receptors, which are used for both localization and treatment.
   5. Most (>70%) secrete chromogranin A, which is frequently used as a tumor marker.

D. Similarities/differences in molecular abnormalities
   1. Similarities
      a. Uncommon—mutations in common oncogenes (*ras, jun, fos,* etc).
      b. Uncommon—mutations in common tumor-suppressor genes (*p53*, retinoblastoma).
      c. Alterations at MEN 1 locus (11q13) (frequently foregut, less commonly mid/hindgut NETs) and $p16^{INK4a}$ (9p21) occur in a proportion (10–45%).
      d. Methylation of various genes occurs in 40–87% (*ras*-associated domain family I, p14, p16, O^6-methylguanine methyltransferases, retinoic acid receptor β).
   2. Differences
      a. pNETs—loss of 1p (21%), 3p (8–47%), 3q (8–41%), 11q (21–62%), 6q (18–68%), Y (45%). Gains at 17q (10–55%), 7q (16–68%), 4q (33%), 18 (up to 45%).
      b. GI-NETs (carcinoids)—loss of 18q (38–88%), >18p (33–43%), >9p, 16q21 (21–23%). Gains at 17q, 19p (57%), 4q (33%), 14q (20%), 5 (up to 36%).
      c. pNETs: *ATRX/DAXX* mutations in 43%, MEN 1 mutations in 44%, mTor mutations (14%); uncommon in midgut GI-NETs (0–2%).

Abbreviations: *ATRX,* alpha-thalassemia X-lined mental retardation protein; *DAXX*, death domain associated protein; *MEN 1*, multiple endocrine neoplasia type 1; TNM, tumor, node, metastasis.

tumors were classified as showing an argentaffin reaction if they took up and reduced silver or as being argyrophilic if they did not reduce it. Currently, immunocytochemical localization of chromogranins (A, B, C), neuron-specific enolase, and synaptophysin, which are all neuroendocrine cell markers, is used (Table 113-1). Chromogranin A is the most widely used.

Ultrastructurally, these tumors possess electron-dense neurosecretory granules and frequently contain small clear vesicles that correspond to synaptic vesicles of neurons. NETs synthesize numerous peptides, growth factors, and bioactive amines that may be ectopically secreted, giving rise to a specific clinical syndrome **(Table 113-2)**. The diagnosis of the specific syndrome requires the clinical features of the disease (Table 113-2) and cannot be made from the immunocytochemistry results alone. The presence or absence of a specific clinical syndrome also cannot be predicted from the immunocytochemistry alone (Table 113-1). Furthermore, pathologists cannot distinguish between benign and malignant NETs unless metastasis or invasion is present.

GI-NETs (carcinoids) frequently are classified according to their anatomic area of origin (i.e., foregut, midgut, hindgut) because tumors with similar areas of origin share functional manifestations, histochemistry, and secretory products **(Table 113-3)**. Foregut tumors generally have a low serotonin (5-HT) content; are argentaffin-negative but argyrophilic; occasionally secrete adrenocorticotropic hormone (ACTH) or 5-hydroxytryptophan (5-HTP), causing an atypical carcinoid syndrome **(Fig. 113-1)**; are often multihormonal; and may metastasize to bone. They uncommonly produce a clinical syndrome due to the secreted products. Midgut carcinoids are argentaffin-positive, have a high serotonin content, most frequently cause the typical carcinoid syndrome when they metastasize (Table 113-3, Fig. 113-1), release serotonin and tachykinins (substance P, neuropeptide K, substance K), rarely secrete 5-HTP or ACTH, and less commonly metastasize to bone. Hindgut carcinoids (rectum, transverse and descending colon) are argentaffin-negative, are often argyrophilic, rarely contain serotonin or cause the carcinoid syndrome (Fig. 113-1, Table 113-3), rarely secrete 5-HTP or ACTH, contain numerous peptides, and may metastasize to bone.

pNETs can be classified into nine well-established specific functional syndromes (Table 113-2), six additional very rare specific functional syndromes (less than five cases described), five possible specific functional syndromes (pNETs secreting calcitonin, neurotensin, pancreatic polypeptide, ghrelin) (Table 113-2), and nonfunctional pNETs. Other functional hormonal syndromes due to nonpancreatic tumors (usually intraabdominal in location) have been described only rarely and are not included in (Table 113-2). These include secretion by intestinal and ovarian tumors of peptide tyrosine tyrosine (PYY), which results in altered motility and constipation, and ovarian tumors secreting renin or aldosterone causing alterations in blood pressure or somatostatin causing diabetes or reactive hypoglycemia. Each of the functional syndromes listed in Table 113-2 is associated with symptoms due to the specific hormone released. In contrast, nonfunctional pNETs release no products that cause a specific clinical syndrome. "Nonfunctional" is a misnomer in the strict sense because those tumors frequently ectopically secrete a number of peptides (pancreatic polypeptide [PP], chromogranin A, ghrelin, neurotensin, α subunits of human chorionic gonadotropin, and neuron-specific enolase); however, they cause no specific clinical syndrome. The symptoms caused by nonfunctional pNETs are entirely due to the tumor per se. pNETs frequently ectopically secrete PP (60–85%), neurotensin (30–67%), calcitonin (30–42%), and to a lesser degree, ghrelin (5–65%). Whereas a few studies have proposed their secretion can cause a specific functional syndrome, most studies support the conclusion that their ectopic secretion is not associated with a specific clinical syndrome, and thus they are listed in Table 113-2 as possible clinical syndromes.