Oncology Clinical Pathways
Gastrointestinal Neuroendocrine Tumors

January 2025 – V1.2025

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Gastrointestinal Neuroendocrine Tumors – Presumptive Conditions

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Atomic Veterans – Exposure to Ionizing Radiation

- Cancer of the small intestine, pancreas, and bile ducts

Gulf War and Post 9/11 Veterans

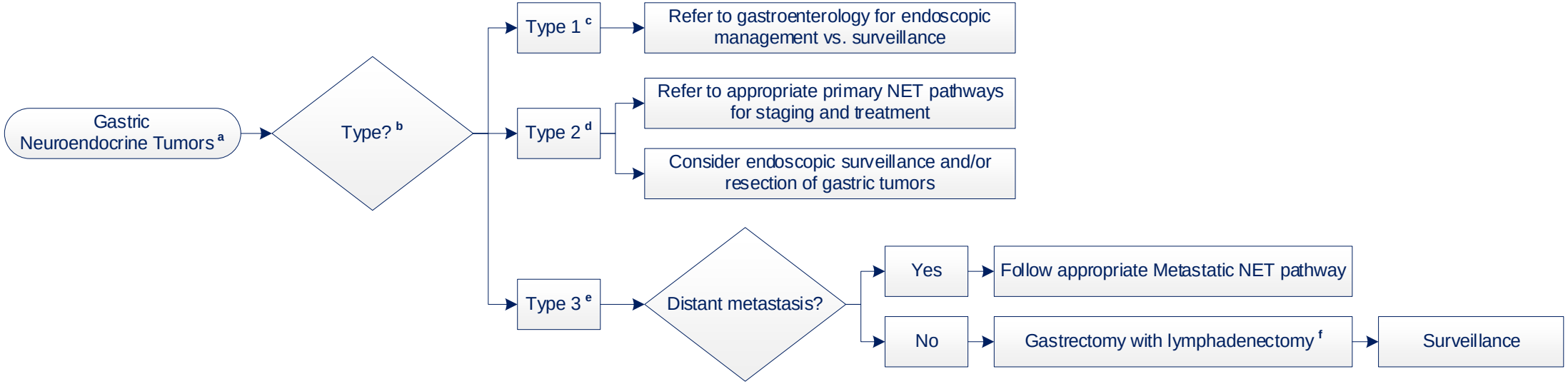
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if you served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Gastrointestinal cancer of any type
- Pancreatic cancer

* The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov)

Gastrointestinal Neuroendocrine Tumors – Gastric



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Gastric Neuroendocrine Tumors** refers to well-differentiated grade 1/2 neuroendocrine tumors

[b] **Type** gastric neuroendocrine tumors are broadly divided into gastrin-dependent (Type 1 and 2) and non-gastrin-dependent (Type 3); gastrin-dependent gastric neuroendocrine tumors are further divided into those due to physiologic hypergastrinemia related to low gastric acid/high gastric pH as in atrophic gastritis (Type 1) and those due to a gastrin-producing tumor typically resulting in a low gastric pH (Type 2)

[c] **Type 1** work up could include EGD, with gastric biopsies and/or gastric pH, serum gastrin level and serum vitamin B12 levels

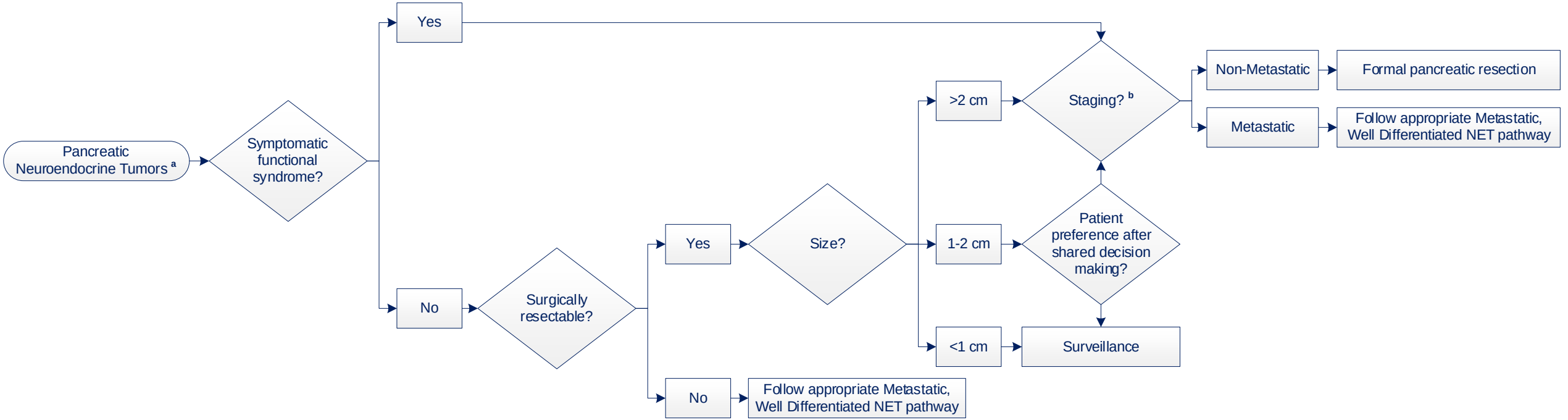
[d] **Type 2** treatment with octreotide long-acting release (LAR) or lanreotide; high dose PPI to manage gastric hypersecretion

[e] **Type 3** recommended staging studies include EUS, multiphasic chest and abdominopelvic CT or MRI, SSTR-PET (if available)

[f] **Gastrectomy with Lymphadenectomy** endoscopic or surgical wedge resection for <1 cm tumors with low-risk features (low-grade, well-differentiated, superficial, no vascular invasion) and no evidence of nodal disease may be appropriate

EGD Esophagogastroduodenoscopy
EUS Endoscopic Ultrasound
NET Neuroendocrine Tumor
PPI Proton Pump Inhibitor
SSTR-PET Somatostatin Receptor Targeted PET (SSTR ligand may include DOTATATE or DOTATOC)

Gastrointestinal Neuroendocrine Tumors – Pancreatic



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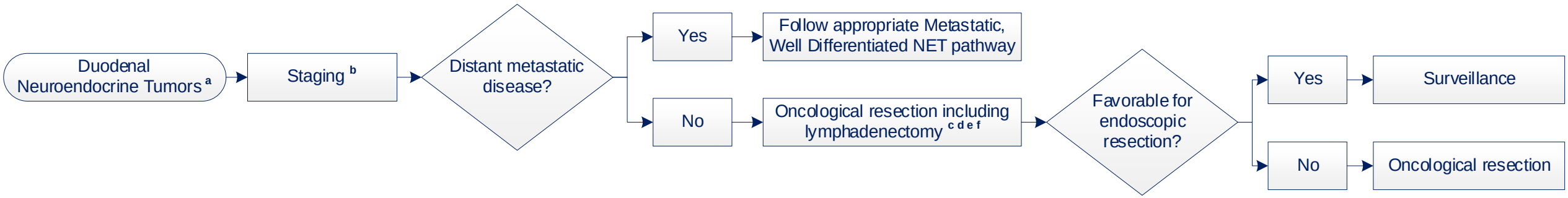
[a] **Pancreatic Neuroendocrine Tumors** refers to well-differentiated grade 1/2 neuroendocrine tumors

[b] **Staging** recommended staging studies include EUS, multiphasic chest and abdominopelvic CT or MRI, SSTR-PET (preferred)

EUS Endoscopic Ultrasound
NET Neuroendocrine Tumor
SSTR-PET Somatostatin Receptor Targeted PET (SSTR ligand may include DOTATATE or DOTATOC)

Gastrointestinal Neuroendocrine Tumors – Duodenal



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[a] **Duodenal Neuroendocrine Tumors** refers to well-differentiated grade 1/2 neuroendocrine tumors

[b] **Staging** recommended studies include multiphasic chest and abdominopelvic CT or MRI, SSTR-PET (preferred), biochemical testing and endoscopy as clinically indicated

[c] **Bowel Resection with Lymphadenectomy** surgery should include manual palpitation of the entire bowel to rule out synchronous tumors

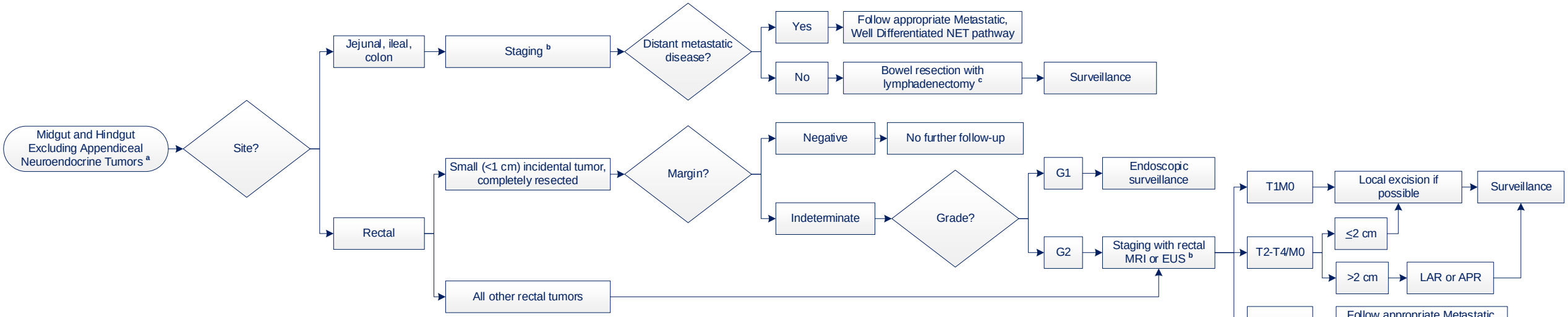
[d] **Endoscopic Excision** preferred if size and histological features favorable for non-ampullary and non-functional duodenal tumors

[e] **Local Excision and Lymphadenectomy or Pancreaticoduodenectomy** recommended for duodenal gastrinoma

[f] **Pancreaticoduodenectomy** recommended for ampullary tumors not amenable to endoscopic or local excision

APR Abdominoperineal Resection
EUS Endoscopic Ultrasound
LAR Low Anterior Resection
NET Neuroendocrine Tumor
SSTR-PET Somatostatin Receptor Targeted PET (SSTR ligand may include DOTATATE or DOTATOC)

Gastrointestinal Neuroendocrine Tumors – Midgut and Hindgut Excluding Appendiceal



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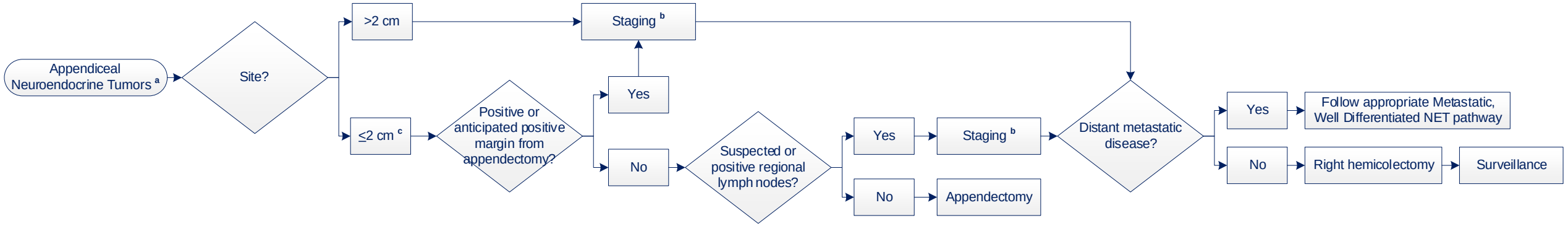
[a] **Midgut and Hindgut** refers to jejunal, ileal, colonic and rectal primaries

[b] **Staging** recommended studies include multiphasic chest and abdominopelvic CT or MRI, SSTR-PET (preferred), biochemical testing and endoscopy as clinically indicated

[c] **Bowel Resection with Lymphadenectomy** surgery should include manual palpitation of the entire bowel to rule out synchronous tumors

APR Abdominoperineal Resection
EUS Endoscopic Ultrasound
LAR Low Anterior Resection
NET Neuroendocrine Tumor
SSTR-PET Somatostatin Receptor Targeted PET (SSTR ligand may include DOTATATE or DOTATOC)

Gastrointestinal Neuroendocrine Tumors – Appendiceal



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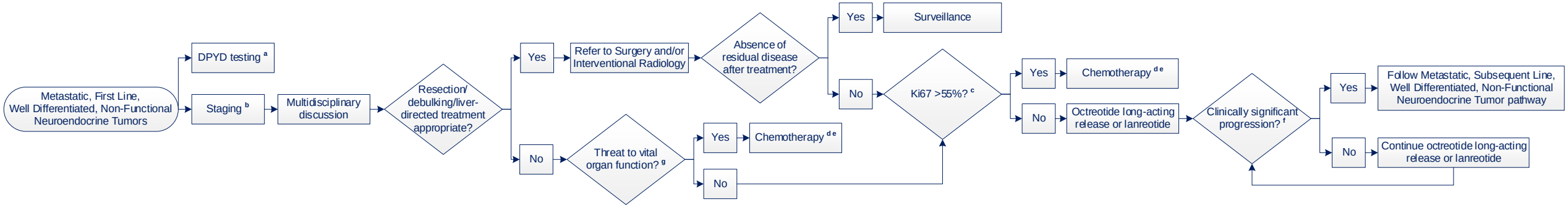
[a] **Appendiceal Neuroendocrine Tumors** refers to well-differentiated grade 1/2 neuroendocrine tumors

[b] **Staging** recommended staging studies include multiphasic chest and abdominopelvic CT or MRI, SSTR-PET (preferred)

[c] **≤2 cm** right hemicolectomy may be considered for 1 to 2 cm tumors with poor prognostic features (e.g. lymphovascular or mesoappendiceal invasion, atypical histologic features)

NET Neuroendocrine Tumor
SSTR-PET Somatostatin Receptor Targeted PET (SSTR ligand may include DOTATATE or DOTATOC)

Gastrointestinal Neuroendocrine Tumors – Metastatic, First Line, Well Differentiated, Non-Functional



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Perform DPYD Testing If Not Already Performed** if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

[b] **Staging** complete staging with multiphasic chest and abdominopelvic CT or MRI, SSTR-PET (preferred)

[c] **Ki67** proliferation index should be performed by counting at least 500 cells in "hotspot" regions identified at scanning magnification (i.e. regions of highest labeling)

[d] **Chemotherapy** CAPTEM strongly preferred; however, for CAPTEM ineligible patients, carboplatin and etoposide could be considered; if the tumor behaves clinically aggressively, consider chemotherapy with carboplatin and etoposide

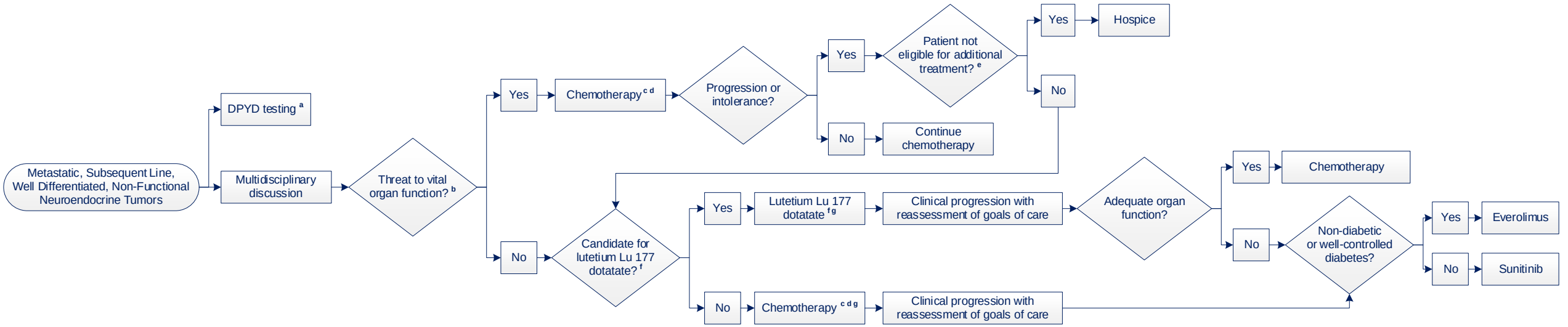
[e] **Capecitabine** avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl < 30ml/min)

[f] **Clinically Significant Progression** recommend using RECIST 1.1 and multidisciplinary discussion to determine clinically significant progression requiring a change in therapy; not all progression based on traditional RECIST criteria requires a change in treatment

[g] **Threat to Vital Organ Function** presence of significant tumor burden in vital organs, for example, liver, lung, lymph nodes and others which in clinician's judgement is likely to lead to deterioration of health if relatively urgent control is not achieved

DPYD Dihydropyrimidine Dehydrogenase
NET Neuroendocrine Tumor

Gastrointestinal Neuroendocrine Tumors – Metastatic, Subsequent Line, Well Differentiated, Non-Functional



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[a] **Perform DPYD Testing If Not Already Performed** if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

[b] **Threat to Vital Organ Function** presence of significant tumor burden in vital organs, for example, liver, lung, lymph nodes and others which in clinician's judgement is likely to lead to deterioration of health if relatively urgent control is not achieved

[c] **Chemotherapy** CAPTEM strongly preferred; however, for CAPTEM ineligible patients or those previously progressed on CAPTEM, mFOLFOX should be considered

[d] **Capecitabine** avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl < 30ml/min)

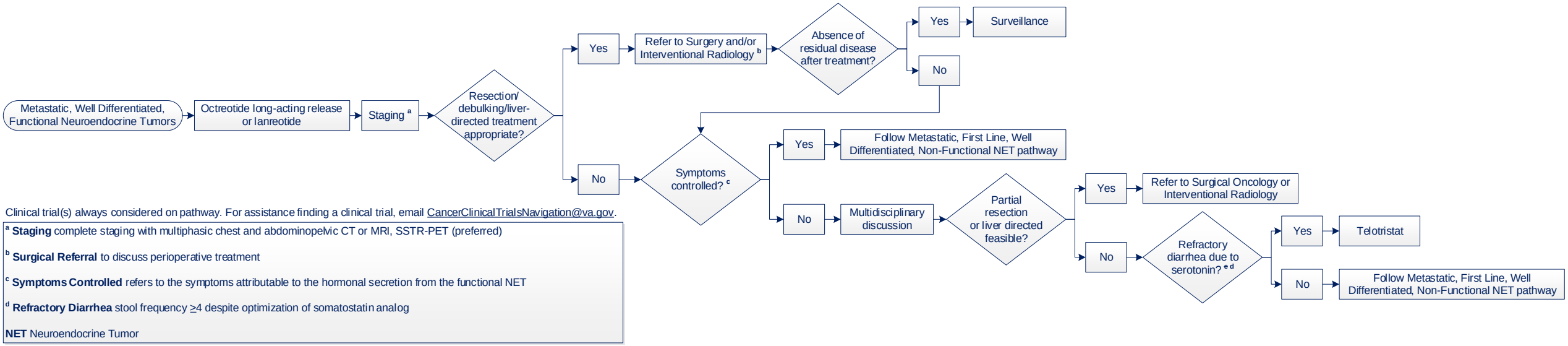
[e] **Patient not eligible for additional treatment** based on poor performance status or inadequate liver function

[f] **Lutetium Lu 177 Dotatate** eligibility includes eGFR > 30 ml/min, adequate liver function L, prothrombin time < 1.5x ULN; hemoglobin > 8g/dL, WBC > 2000 cells/µL, platelet count > 75,000 cells/µL; laboratory values outside of these threshold values are not an absolute contraindication but should include discussion and shared decision making in multidisciplinary manner to weigh risk vs benefit and plans for modification, if necessary; pregnancy and breastfeeding are contraindications to treatment

[g] **Long Acting Octreotide** should be given or continued to control carcinoid symptoms which could evolve over the course of therapy

DPYD Dihydropyrimidine Dehydrogenase

Gastrointestinal Neuroendocrine Tumors – Metastatic, Well Differentiated, Functional



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[a] **Staging** complete staging with multiphasic chest and abdominopelvic CT or MRI, SSTR-PET (preferred)

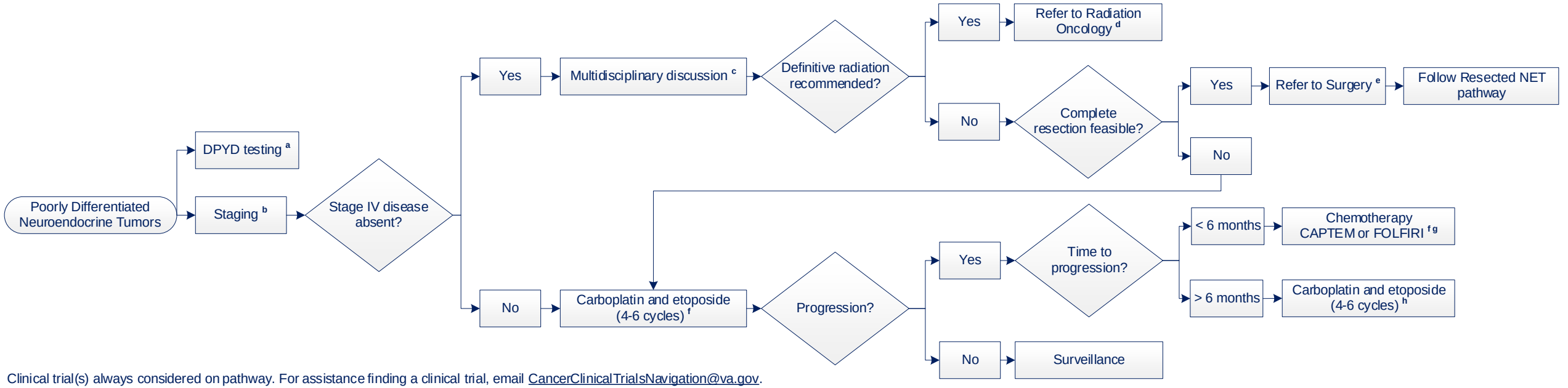
[b] **Surgical Referral** to discuss perioperative treatment

[c] **Symptoms Controlled** refers to the symptoms attributable to the hormonal secretion from the functional NET

[d] **Refractory Diarrhea** stool frequency ≥4 despite optimization of somatostatin analog

NET Neuroendocrine Tumor

Gastrointestinal Neuroendocrine Tumors – Poorly Differentiated



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[a] **Perform DPYD Testing If Not Already Performed** if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

[b] **Staging** complete staging with multiphasic chest and abdominopelvic CT or MRI, FDG-PET

[c] **Multidisciplinary Discussion** consider site of the primary tumor and stage in recommending between definitive chemoradiation and surgery

[d] **Refer to Radiation Oncology** if radiation is chosen, the preferred regimen is Radiation concurrently with carboplatin and etoposide

[e] **Refer to Surgery** strongly recommend involving a GI specialty surgeon, which can include surgical oncologists, general surgeons, and colorectal surgeons

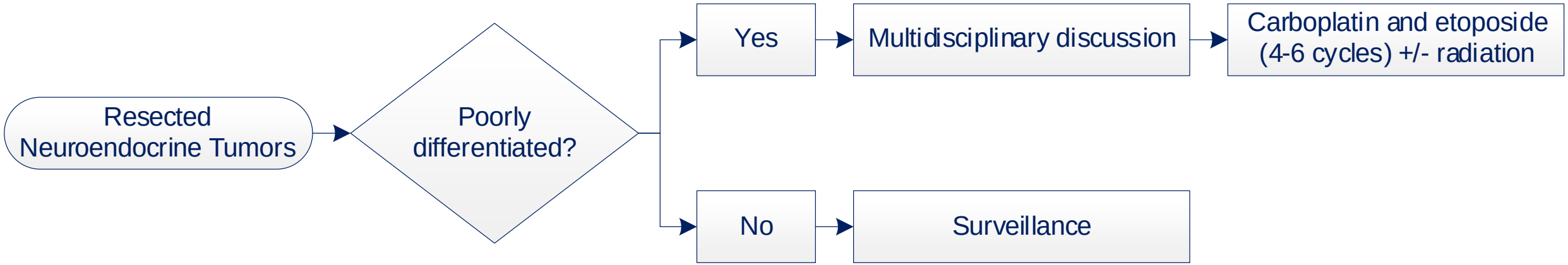
[f] **Capecitabine** avoid capecitabine if adherence issues, unable to self-report toxicity, or severe renal impairment (CrCl < 30ml/min)

[g] **Chemotherapy** CAPTEM strongly preferred; however, for CAPTEM ineligible patients, carboplatin and etoposide could be considered; if the tumor behaves clinically aggressively, consider chemotherapy with carboplatin and etoposide

[h] **Carboplatin and Etoposide** if a patient has developed neuropathy may consider alternative chemotherapy options

CAPTEM capecitabine and temozolomide
DPYD Dihydropyrimidine Dehydrogenase
NET Neuroendocrine Tumor

Gastrointestinal Neuroendocrine Tumors – Resected



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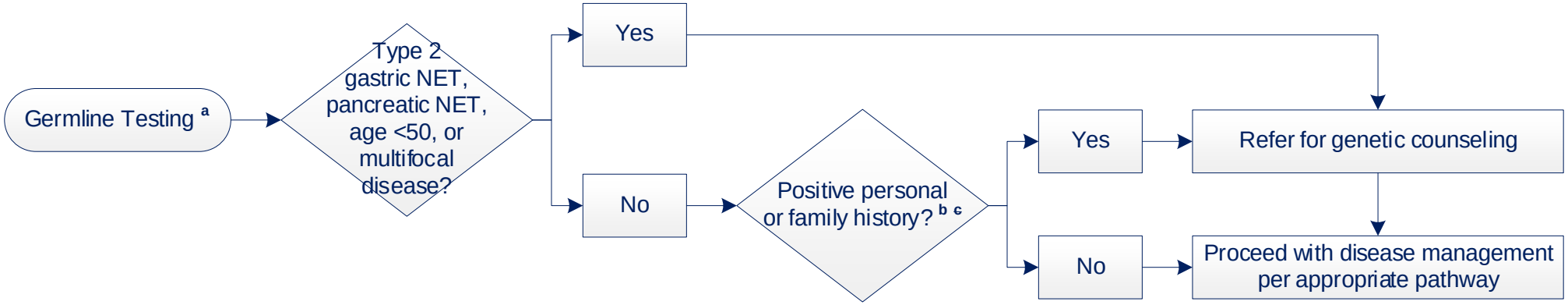
Gastrointestinal Neuroendocrine Tumors – Molecular Testing



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Germline Testing** an appropriate germline testing panel should include at minimum the following genes: MEN1, CDKN1B, NF1, TSC1, TSC2, BRCA2, CHEK2, MUTYH, VHL

[b] **Personal and Family History** consider germline testing if there is:

- a known likely pathogenic or pathogenic cancer gene variant in the family
- a personal history of ovarian, breast, or colorectal cancer
- a personal history of features of:
  - multiple endocrine neoplasia type 1 (e.g., hyperparathyroidism, pituitary adenoma),
  - tuberous sclerosis (e.g., CNS tumors, renal angiolipoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, hamartoma, hypomelanotic macules, facial angiofibroma, ungual fibroma)
  - neurofibromatosis type 1 (e.g., cutaneous or plexiform neurofibromas, pancreatic NET, pheochromocytoma, café-au-lait macules, axillary or inguinal freckling, Lisch nodules, GIST)
  - von Hippel Lindau syndrome (e.g., renal cell cancer, pheochromocytoma, paraganglioma, hemangioblastoma, endolymphatic sac tumor, pancreatic cysts, epididymal and broad ligament cystadenoma)
- one or more first- or second-degree relatives with a neuroendocrine tumor (e.g., pancreatic, paraganglioma, pheochromocytoma, broncho-pulmonary, adrenal cortex)
- one or more first- or second-degree relatives with ovarian cancer, or male breast cancer;
- two or more relatives with female breast or colorectal cancer;
- one or more first- or second-degree relatives with features of multiple endocrine neoplasia type 1, tuberous sclerosis, neurofibromatosis type 1 or von Hippel Lindau syndrome

CNS Central Nervous System
GIST Gastrointestinal Stromal Tumors
NET Neuroendocrine Tumor

Gastrointestinal Neuroendocrine Tumors – Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Age <50 or Pancreatic NET or Type 2 Gastric NET or Multifocal disease	Germline NGS	Germline NGS Panel*	Fulgent	Yes	Blood, Saliva
Personal cancer history: Breast cancer or Ovarian cancer or Colorectal cancer					
Family cancer history: Neuroendocrine tumor (≥1 relative) or Ovarian cancer (≥1 relative) or Male breast cancer (≥1 relative) or Female breast cancer (≥2 relatives) or Colorectal cancer (≥2 relatives)					
Personal or family history (≥1 relative): Multiple endocrine neoplasia type 1 (MEN1) or Tuberous Sclerosis (TS) or Neurofibromatosis type 1 (NF1) or von Hippel Lindau syndrome (VHL)					
Known pathogenic or likely pathogenic cancer gene variant in the family					

* VA Common Hereditary POC panel or Equivalent Germline Test; at minimum the Germline NGS Panel should include MEN1, CDKN1B, NF1, TSC1, TSC2, BRCA2, CHEK2, MUTYH, VHL; For genetic online ordering, refer to CCGS page for further details