

Other Rare Pancreatic Endocrine Neoplasms

Clinicopathologic patterns, tumor biology, and differential diagnosis

Pancreatic neuroendocrine neoplasms • Hormone-associated clinicopathologic patterns

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning outcomes

- Recognize the hormone–syndrome associations of five rare pancreatic endocrine neoplasms.
- Differentiate hypersecretory syndromes from hormonally silent mass lesions.
- Relate rare subtypes to the broader biology and grading of pancreatic neuroendocrine neoplasms.
- Use symptom clusters to choose focused biochemical tests and appropriate differentials.

The pancreatic neuroendocrine family

Pancreatic endocrine neoplasm

Neoplastic endocrine cells
in or near the pancreas



Hormone secretion

Clinically functioning or
clinically silent



Behavior assessment

Proliferation and
differentiation matter
independently of
syndrome

Functionality is not the same as malignancy

Functional neoplasm

- A hormone causes a recognizable clinical syndrome.
- Clinical effects can reveal a small lesion.
- Biochemical evidence must match the syndrome.

Nonfunctional or clinically silent neoplasm

- Secreted hormone may not cause symptoms.
- A mass may be the presenting finding.
- Tumor behavior still requires assessment.

PanNENs in the pancreatic tumor spectrum

- PanNENs are uncommon relative to exocrine pancreatic tumors.
- The source estimates about 2% of pancreatic neoplasms are PanNENs.
- The rare hormone-defined subtypes are only part of this already uncommon group.

Clinical implication

Do not equate a pancreatic mass with a functional endocrine neoplasm.

Possible anatomic distribution

Within pancreas

Tumors may arise throughout pancreatic tissue



Peripancreatic tissues

PanNENs may involve adjacent tissues



Hormone syndrome

Symptoms alone cannot precisely localize the source

Microscopic uniformity can be deceptive

Typical well-differentiated pattern

- Neoplastic cells may appear relatively monotonous.
- Marked pleomorphism may be absent.
- Appearance alone is not a reliable behavior predictor.

What the pathologist still evaluates

- Mitotic activity and Ki-67 index.
- Tumor differentiation and subtype.
- Invasion or metastasis when documented.

Proliferation contributes to PanNET grading

Mitotic activity

Quantifies tumor-cell
divisions



Ki-67 index

Estimates the proliferating
fraction



Histologic grade

Higher proliferation
suggests more aggressive
potential

Grade and differentiation answer different questions

Well-differentiated PanNET

- Preserves neuroendocrine-type morphology.
- Proliferative activity supports grading.
- Bland appearance does not guarantee indolence.

Poorly differentiated PanNEC

- Small-cell or large-cell morphology.
- Usually highly proliferative.
- Separate category from a well-differentiated NET.

Three recurring molecular themes

Molecular theme	Examples in Robbins	Conceptual consequence
MEN1 tumor suppressor	MEN1 alterations	Neuroendocrine tumor predisposition
mTOR signaling	PTEN, TSC2 loss of function	Growth-promoting pathway activation
Telomere maintenance	ATRX, DAXX inactivation	Alternative telomere lengthening

MEN1: Hereditary syndrome and sporadic tumor

Inherited MEN1 setting

Multiple endocrine glands
may be involved



Sporadic PanNEN

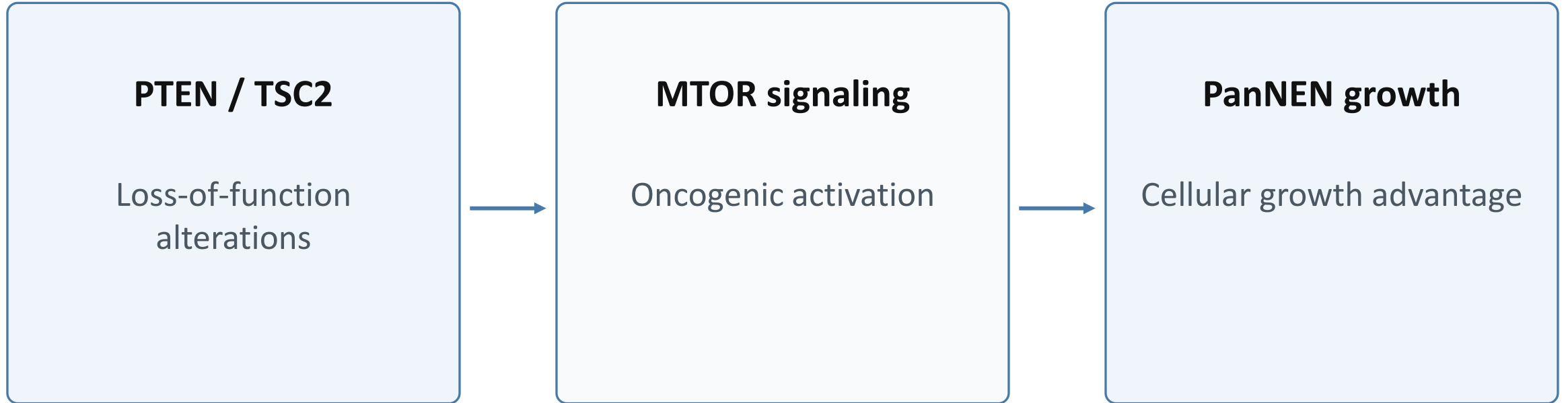
Somatic MEN1 alteration
may occur



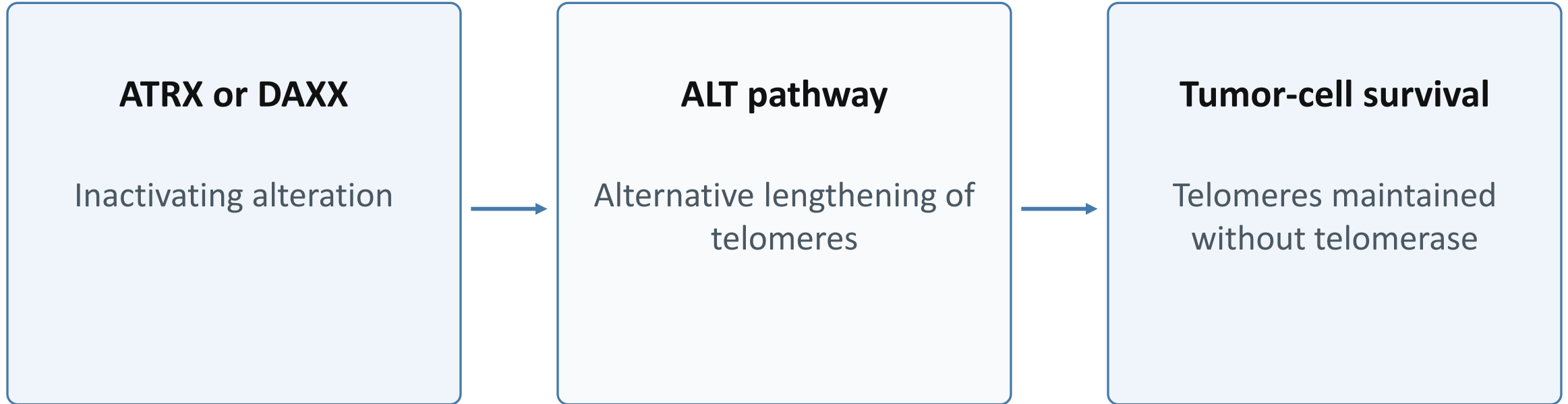
Interpretation

Do not infer inherited
MEN1 from one tumor
alone

MTOR activation is one oncogenic route



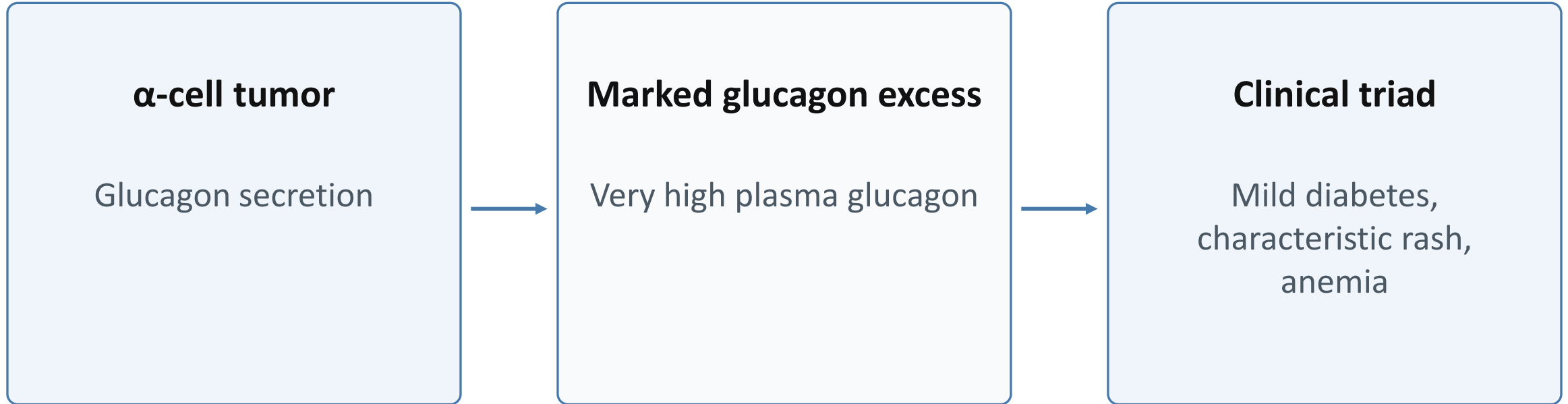
ATRX / DAXX and telomere maintenance



How these rare tumors become recognizable

Subtype	Reported secretion	Characteristic clue
Glucagonoma	Glucagon	Erythema + mild diabetes + anemia
Somatostatinoma	Somatostatin	Diabetes + gallstones + steatorrhea + hypochlorhydria
VIPoma	VIP	Watery diarrhea + hypokalemia + achlorhydria
Pancreatic serotonin-producing tumor	Serotonin	Rare atypical carcinoid syndrome
Pancreatic polypeptide tumor	Pancreatic polypeptide	Mass lesion without hormone syndrome

Glucagonoma: The source-defined phenotype



Necrolytic migratory erythema is the skin clue

- The characteristic skin eruption is termed necrolytic migratory erythema.
- Its value is greatest when recognized with diabetes and anemia.
- A compatible cutaneous finding should prompt consideration of glucagon excess.

Diagnostic reasoning

A dermatologic manifestation can be the clue to an endocrine pancreatic neoplasm.

Glucagonoma-associated diabetes is described as mild

Observed finding

- Mild diabetes mellitus belongs to the glucagonoma syndrome.
- The pancreatic hormone glucagon is elevated.
- The source does not provide glucose cutoffs.

Interpretive limit

- Diabetes alone is common and nonspecific.
- A triad carries more diagnostic weight than one feature.
- Confirmation requires an endocrine evaluation.

Anemia completes the classic glucagonoma cluster

- Anemia accompanies the skin eruption and diabetes in the Robbins description.
- Anemia by itself is not distinctive for glucagonoma.
- Together, the three findings form a clinically useful pattern.

Pattern recognition

Skin + glucose
disturbance +
anemia → consider
glucagonoma.

Age and sex: Supporting, not defining, clues

- Glucagonomas most often in perimenopausal or postmenopausal females.
- This is a demographic tendency, not a diagnostic criterion.
- Laboratory and clinical syndrome recognition remain more informative.

Glucagonoma: From clinical suspicion to evidence

Syndrome recognition

Skin eruption +
dysglycemia + anemia



Biochemical assessment

Extremely high plasma
glucagon



Tumor assessment

Identify and evaluate the
lesion

Clinical application: Glucagonoma

Teaching vignette

A woman develops mild diabetes, anemia, and a distinctive recurrent skin eruption. Endocrine testing demonstrates markedly increased circulating glucagon.

Diagnostic question

Which rare pancreatic endocrine neoplasm best explains this constellation?

Answer: Glucagonoma

The skin finding, dysglycemia, and anemia form the source-described syndrome. • Marked glucagon elevation links the clinical cluster to α -cell hormone secretion.

Glucagonoma vs insulinoma

Glucagonoma

- Glucagon overproduction.
- Typically mild diabetes.
- Necrolytic migratory erythema and anemia.

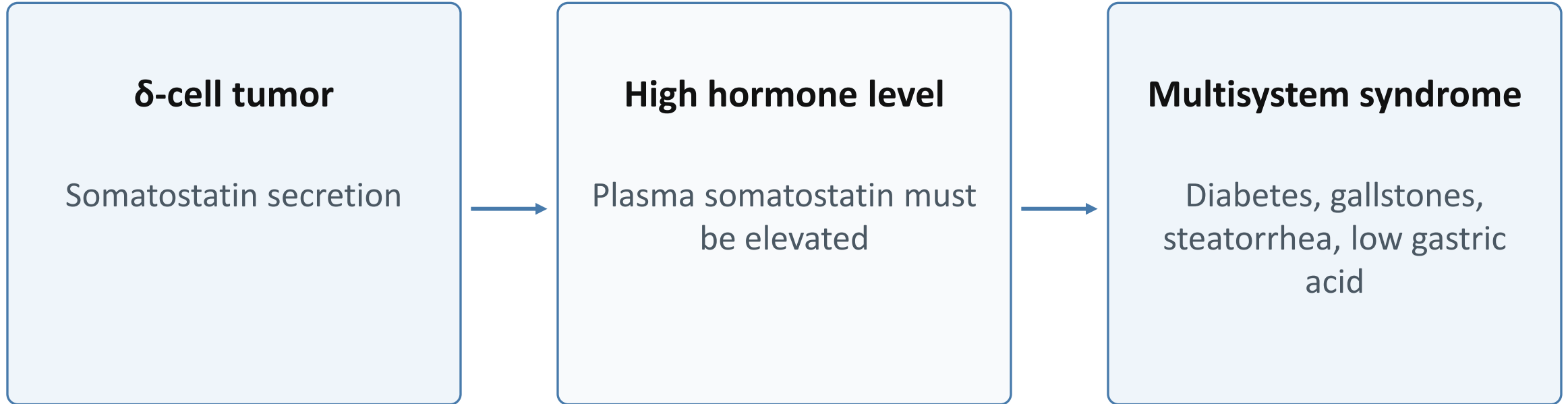
Insulinoma (adjacent topic)

- Excess insulin secretion.
- Hypoglycemic episodes.
- Confusion or loss of consciousness during attacks.

What the glucagonoma pattern does not establish

Question	What the syndrome supports	What it does not prove
Tumor identity	Suggests glucagonoma	Does not locate a lesion by itself
Biochemistry	Plasma glucagon is relevant	No validated cutoff supplied here
Oncologic status	Functional tumor phenotype	Does not establish grade or metastasis

Somatostatinoma: δ -cell secretory phenotype



Four reported components of somatostatinoma

Diabetes mellitus

Metabolic disturbance

Cholelithiasis

Gallstones

Steatorrhea

Fatty stools

Hypochlorhydria

Reduced gastric acidity

Diabetes is shared by two rare subtypes

Glucagonoma

- Dysglycemia is characterized as mild diabetes.
- Skin eruption and anemia supply discrimination.
- Extremely high plasma glucagon supports diagnosis.

Somatostatinoma

- Diabetes may also occur.
- Cholelithiasis, steatorrhea and hypochlorhydria distinguish the syndrome.
- High somatostatin is required for diagnosis.

Gastric acid direction differentiates syndromes

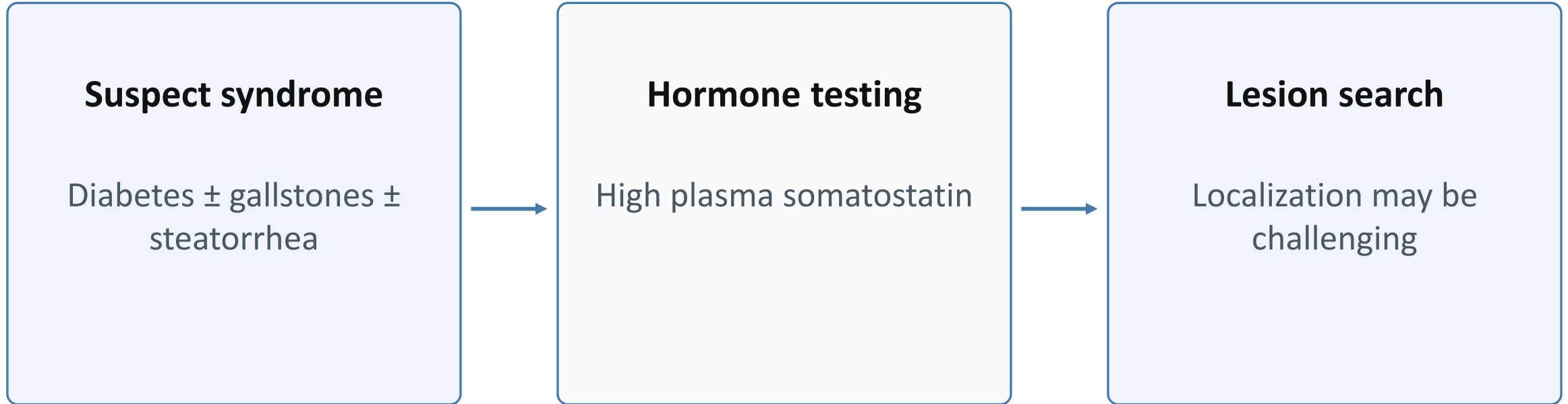
Somatostatinoma

- Hypochlorhydria is associated with the syndrome.
- Gastric acid is reduced.
- Other clues: Diabetes, gallstones and steatorrhea.

Gastrinoma (adjacent topic)

- Hypergastrinemia increases gastric acid secretion.
- Refractory or unusual peptic ulceration is prominent.
- This contrast can orient the differential.

Somatostatinoma: Biochemical confirmation



Localization can be challenging

- Somatostatinomas may be very difficult to localize before surgery.
- A convincing clinical syndrome does not automatically reveal anatomic position.
- Keep biochemical classification distinct from imaging and operative localization.

Source limitation

The supplied passage does not specify preferred imaging sequences.

Clinical application: Somatostatinoma

Teaching vignette

A patient with diabetes also has gallstones, fatty stools, and reduced gastric acidity. Biochemical evaluation detects elevated circulating somatostatin.

Diagnostic question

Which rare functional pancreatic endocrine tumor is most compatible?

Answer: Somatostatinoma

The four manifestations match the described somatostatinoma constellation. • Hormone elevation provides subtype-specific support.

Glucagonoma and somatostatinoma: Fast comparison

Finding	Glucagonoma	Somatostatinoma
Diabetes	Mild diabetes described	Diabetes described
Cutaneous lesion	Necrolytic migratory erythema	Not a defining clue in excerpt
Anemia	Syndromic feature	Not listed here
Gallstones, steatorrhea	Not defining in excerpt	Syndromic features
Hormone	Very high glucagon	High somatostatin

VIPoma: A hormone-driven secretory syndrome

VIP-producing tumor

Vasoactive intestinal
peptide release



Fluid secretion

Severe watery diarrhea



WDHA syndrome

Watery diarrhea,
hypokalemia, achlorhydria

Decode WDHA syndrome

WD: Watery diarrhea

Secretory intestinal fluid loss

H: Hypokalemia

Potassium depletion accompanies
diarrhea

A: Achlorhydria

Absent gastric acid

Clinical pattern

VIP-associated secretory syndrome

Watery secretory diarrhea drives the evaluation

- VIPoma is a recognized cause of severe secretory diarrhea.
- Diarrhea may dominate the clinical presentation before a tumor is localized.
- A source-directed biochemical test is a VIP assay.

VIP excess links the tumor to WDHA



VIPoma and somatostatinoma: Overlapping GI clues

VIPoma

- Watery diarrhea is the dominant clue.
- Hypokalemia is part of the defining syndrome.
- Achlorhydria is described.

Somatostatinoma

- Steatorrhea is part of the syndrome.
- Gallstones and diabetes aid recognition.
- Hypochlorhydria is described.

Achlorhydria vs hypochlorhydria

VIPoma

- Achlorhydria appears in WDHA.
- The acid output descriptor is absent gastric acidity.
- The leading presentation is watery diarrhea.

Somatostatinoma

- Hypochlorhydria is described.
- The acid output descriptor is reduced acidity.
- Gallstones, steatorrhea, diabetes aid recognition.

When to order a VIP assay

- Robbins recommends a VIP assay for all patients with severe secretory diarrhea.
- A biochemical result must be interpreted with the syndrome and lesion evaluation.
- Do not restrict suspicion to pancreatic masses alone.

VIP syndrome can arise outside the pancreas

Origin mentioned in Robbins	Relevant point
Pancreatic VIPoma	Produces VIP and characteristic WDHA syndrome
Neuroblastoma	Neural-crest neoplasm may be linked to VIP syndrome
Ganglioneuroblastoma	Also cited as a possible association
Ganglioneuroma	Also cited as a possible association
Pheochromocytoma	Also associated with VIPoma syndrome

Anatomic diagnosis requires two distinct questions

**Does VIP excess explain
the syndrome?**

Biochemical / clinical
classification



**Where is the source of
VIP?**

Pancreatic or alternative
neoplasm

Does the lesion spread?

Invasion and metastatic
status

VIPomas may invade or metastasize

- Some VIP-producing tumors are locally invasive.
- Some develop metastatic disease.
- Functional symptoms do not establish whether the lesion is localized.

Separate assessments

Secretory
phenotype ≠
histologic grade ≠
anatomic stage.

Clinical application: VIPoma syndrome

Teaching vignette

A patient has persistent severe watery secretory diarrhea and hypokalemia. Gastric acid secretion is absent. A pancreatic or extra-pancreatic neuroendocrine source is under investigation.

Diagnostic question

Which hormone assay is prioritized by the described syndrome?

Answer: Plasma VIP assay

WDHA identifies the source-described VIP-associated syndrome. • The excerpt specifically recommends VIP measurement in severe secretory diarrhea.

VIPoma vs gastrinoma: Opposite gastric acid phenotypes

VIPoma

- Achlorhydria is included in WDHA.
- Diarrhea is a central clue.
- VIP assay addresses hormone excess.

Gastrinoma

- Acid hypersecretion drives peptic ulceration.
- Ulcers can be multiple, refractory or unusually situated.
- Elevated gastrin defines the hormone syndrome.

Serotonin-producing pancreatic tumors are extremely rare

- Pancreatic serotonin-producing carcinoid tumors are exceedingly rare.
- They may cause an atypical carcinoid syndrome.
- This represents a minority phenotype within pancreatic endocrine neoplasia.

“Pancreatic carcinoid” is a phenotype-based term

What the textbook reports

- A pancreatic tumor may produce serotonin.
- An atypical carcinoid syndrome can result.
- The entity is exceedingly rare.

What not to infer

- Not every PanNEN secretes serotonin.
- Not every pancreatic endocrine mass causes carcinoid symptoms.
- “Atypical” is not itself a grade designation here.

Clinical application: Serotonin-associated phenotype

Teaching vignette

A pancreatic endocrine neoplasm is documented to secrete serotonin and is associated with an atypical carcinoid syndrome.

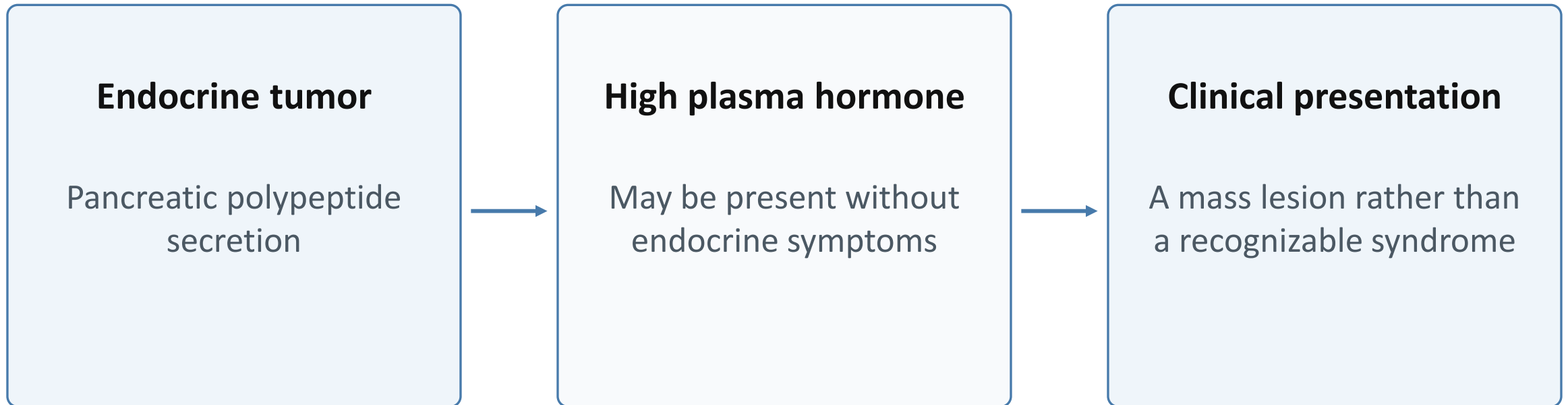
Diagnostic question

How should this endocrine phenotype be classified from the supplied source?

Answer: Exceedingly rare serotonin-producing pancreatic endocrine tumor

The syndrome and hormone are the defining clues in this excerpt. • The source does not provide grading, diagnostic thresholds or detailed symptoms.

Pancreatic polypeptide tumors: Secretion without syndrome



A hormone concentration is not always a functional syndrome

Pancreatic polypeptide-secreting tumor

- Plasma pancreatic polypeptide may be high.
- Even high levels fail to cause a syndrome.
- Mass effect or mass detection drives presentation.

Clinically functional rare tumor

- Glucagonoma: Recognizable skin/metabolic pattern.
- Somatostatinoma: Metabolic/GI constellation.
- VIPoma: Severe secretory diarrhea syndrome.

Why a mass lesion can be the first clue

- Pancreatic polypeptide-secreting neoplasms may be clinically silent hormonally.
- Without a characteristic endocrine syndrome, a lesion can present as a mass.
- Hormone production and hormone-mediated symptoms must be recorded separately.

Clinical application: Hormonally silent presentation

Teaching vignette

A pancreatic endocrine mass is identified. The tumor secretes pancreatic polypeptide, but the patient has no characteristic hormone-excess syndrome.

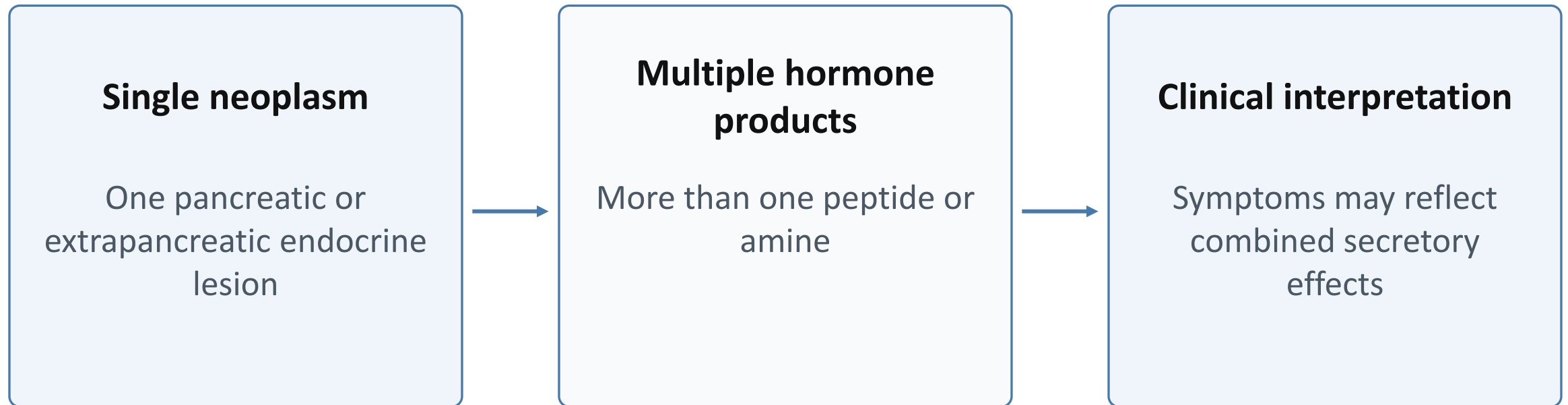
Diagnostic question

What presentation does Robbins specifically emphasize?

Answer: Presentation as a mass lesion

Even high circulating levels of pancreatic polypeptide need not cause symptoms. • Biochemical secretion should not be mistaken for a clinically functional syndrome.

One tumor may produce more than one hormone



Multihormonal tumor is not the same as MEN1

Multihormonal tumor

- One tumor may secrete two or more hormones.
- Endocrine products originate from the same neoplasm.
- A syndrome may combine multiple hormone effects.

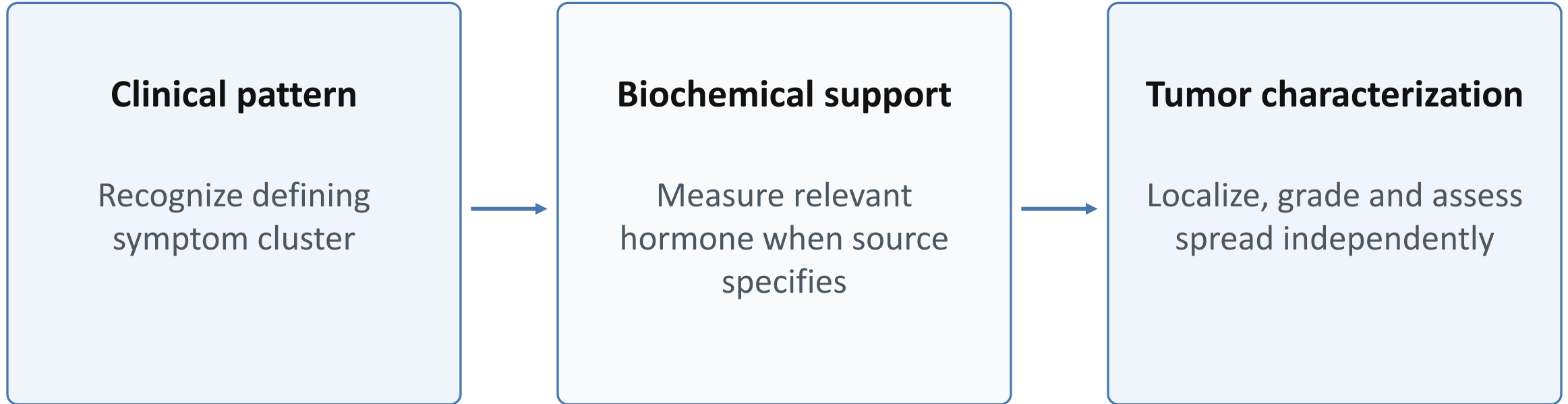
Multiple endocrine neoplasia

- More than one endocrine gland may harbor neoplasia.
- Different tumors may secrete different hormones.
- The anatomic multiplicity is the discriminating concept.

Syndrome-based differential: First-pass assessment

Presenting pattern	Best source-linked subtype	Useful focused laboratory clue
Rash + mild diabetes + anemia	Glucagonoma	Marked plasma glucagon elevation
Diabetes + gallstones + steatorrhea	Somatostatinoma	Elevated plasma somatostatin
Severe watery diarrhea + hypokalemia	VIPoma / VIP syndrome	VIP assay
Serotonin + atypical carcinoid syndrome	Rare serotonin-producing tumor	No cutoff provided in excerpt
Pancreatic mass, no hormonal syndrome	Pancreatic polypeptide tumor possible	No symptomatic polypeptide syndrome

Reason in two stages: Syndrome, then lesion



Hormonal phenotype does not determine oncologic status

Phenotype question	Tumor behavior question
Which hormone(s) are secreted?	Is differentiation well or poor?
Are there clinical hormone effects?	What is mitotic / Ki-67 proliferation?
What syndrome identifies the tumor?	Is there local invasion or metastasis?
Which hormone assay is indicated?	Can appearance alone predict outcome? No.

Applied differential: Three contrasting presentations

Teaching vignette

Three hypothetical patients: A) skin eruption, anemia and mild diabetes; B) watery diarrhea and hypokalemia; C) asymptomatic hormone-secreting pancreatic mass.

Diagnostic question

Match each presentation to the most likely source-described phenotype.

Answer: A: Glucagonoma • B: VIPoma • C: Pancreatic polypeptide-secreting tumor

The strongest clue is the syndrome–hormone pairing. • A mass with hormone secretion but no syndrome is not equivalent to a functional tumor.

Comparative reference: Five rare phenotypes

Tumor	Core clue	Hormone	Nuance
Glucagonoma	NME + diabetes + anemia	Glucagon	Described especially in peri/postmenopausal females
Somatostatinoma	Diabetes + gallstones + steatorrhea	Somatostatin	Difficult preoperative localization
VIPoma	WDHA	VIP	Other nonpancreatic tumors may secrete VIP
Serotonin-producing	Atypical carcinoid syndrome	Serotonin	Exceedingly rare
Pancreatic polypeptide	Mass lesion	Pancreatic polypeptide	No syndrome despite high hormone level

Five distinctions to retain

- Glucagonoma: Necrolytic migratory erythema links dermatology to an endocrine neoplasm.
- Somatostatinoma: Diabetes + cholelithiasis + steatorrhea + hypochlorhydria.
- VIPoma: Watery diarrhea, hypokalemia and achlorhydria warrant VIP testing.
- Serotonin-producing tumors are exceedingly rare; Polypeptide-secreting tumors may be clinically silent.

Critical distinction

Secretory syndrome and tumor aggressiveness are different diagnostic dimensions.

Reference and scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition, 2026.
- Core section: “Other Rare Pancreatic Endocrine Neoplasms.”
- PanNEN biology and insulinoma/gastrinoma comparisons draw on the adjacent textbook sections.
- Detailed clinical testing thresholds and current management algorithms require dedicated specialist references.