

Adrenal Medulla

Normal neuroendocrine tissue, pheochromocytoma and clinicopathologic correlations

Pathology lecture

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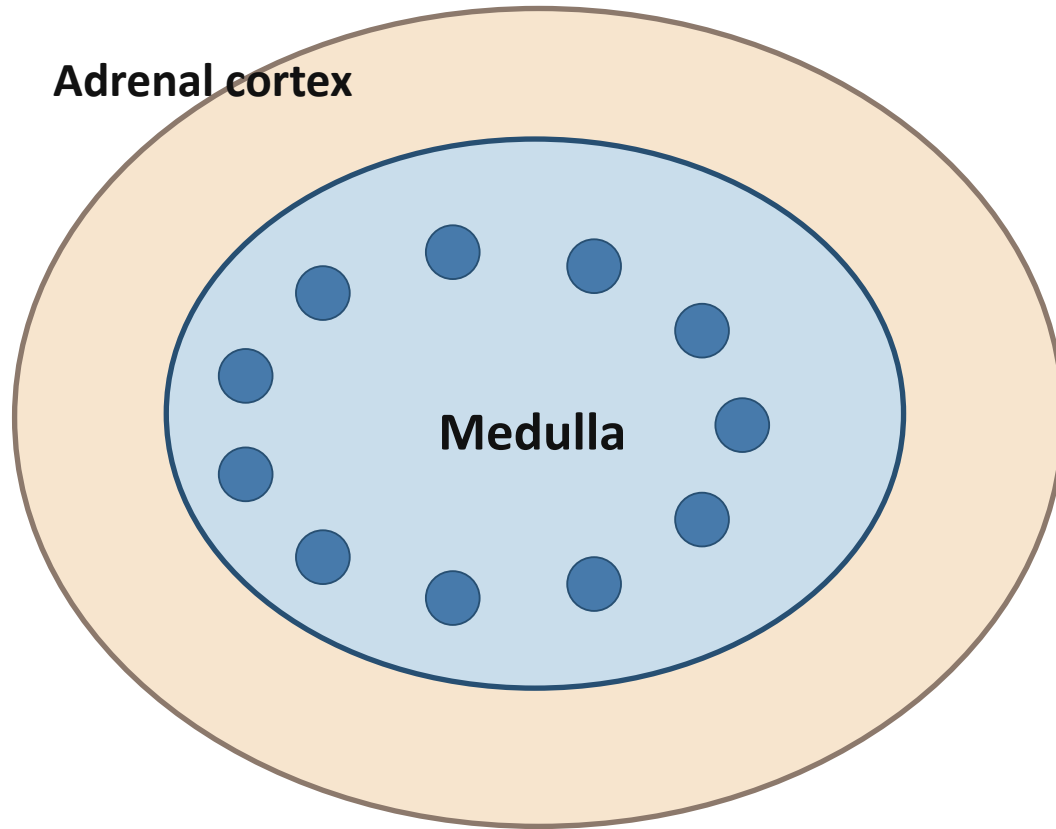
Learning objectives

- Distinguish chromaffin tissue from the adrenal cortex and extra-adrenal paraganglia.
- Explain the inherited molecular pathways associated with pheochromocytoma and paraganglioma.
- Interpret characteristic gross, microscopic and immunophenotypic findings.
- Link catecholamine release to cardiovascular manifestations and diagnostic investigation.
- Explain why metastatic behavior cannot be determined reliably by histology alone.

Medulla and cortex: Two distinct compartments

Adrenal medulla	Adrenal cortex
Specialized neural-crest neuroendocrine cells	Developmentally distinct adrenal compartment
Chromaffin and sustentacular cells	Cortical cells (different cellular lineage)
Source of epinephrine and norepinephrine	Not the major catecholamine-producing compartment
Characteristic neoplasm: Pheochromocytoma	Distinct group of cortical neoplasms

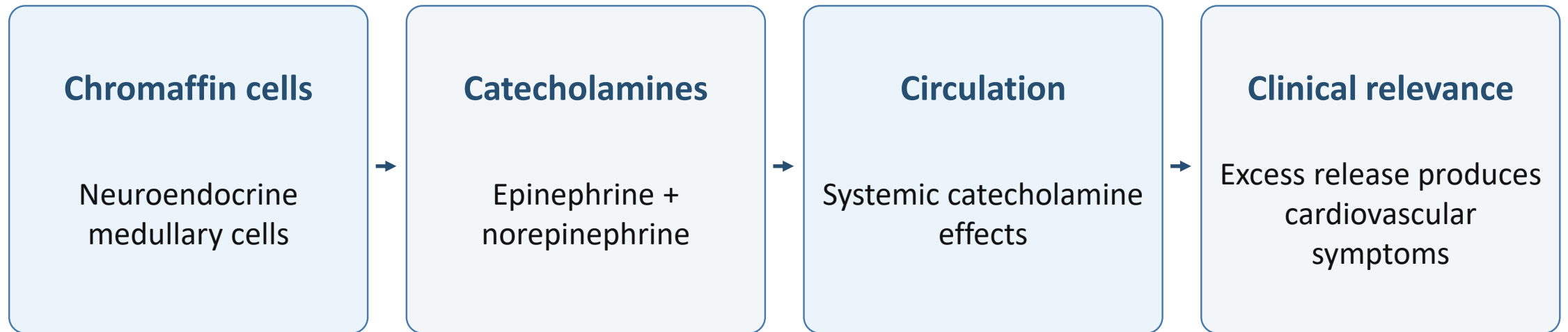
Chromaffin cells and supporting cells



- Chromaffin cells are the catecholamine-producing population.
- Sustentacular cells form a supporting network.
- The two cell populations reappear in the histology of pheochromocytoma.

Schematic – not a histologic specimen

Catecholamine output of the adrenal medulla



Norepinephrine has two physiological contexts

Adrenal endocrine source

Medullary chromaffin cells release catecholamines into circulation.

Part of systemic catecholamine physiology.

Tumor hypersecretion creates an endocrine syndrome.

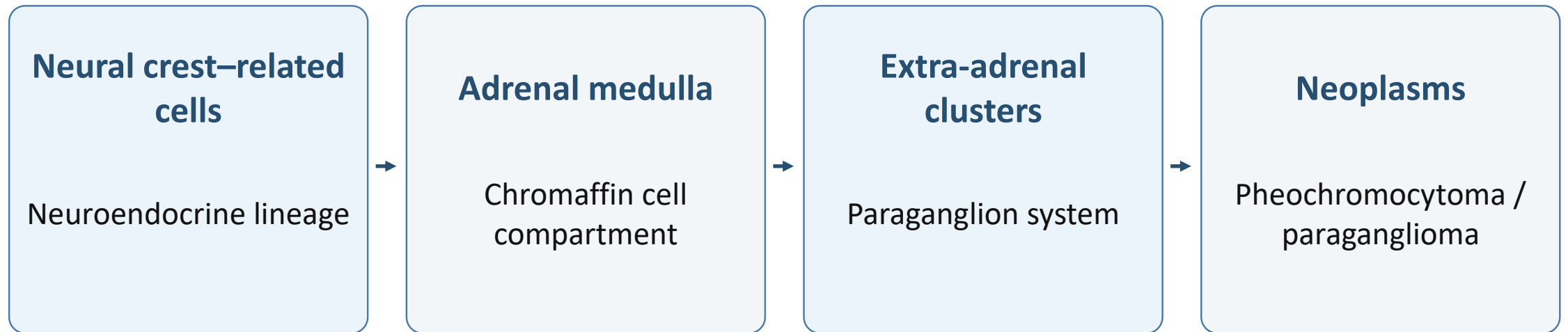
Sympathetic nervous system

Norepinephrine also acts as a neurotransmitter.

Particularly important in sympathetic nerves.

Neural function must not be confused with tumor secretion.

Adrenal and extra-adrenal paraganglia



Neoplastic spectrum of adrenal medullary tissue

Adrenal medulla / related neuroendocrine cells

Chromaffin-cell tumors

Extra-adrenal related tumors

Neuronal neoplasms

Pheochromocytoma

Paraganglioma

Neuroblastic tumors (Chapter 10)

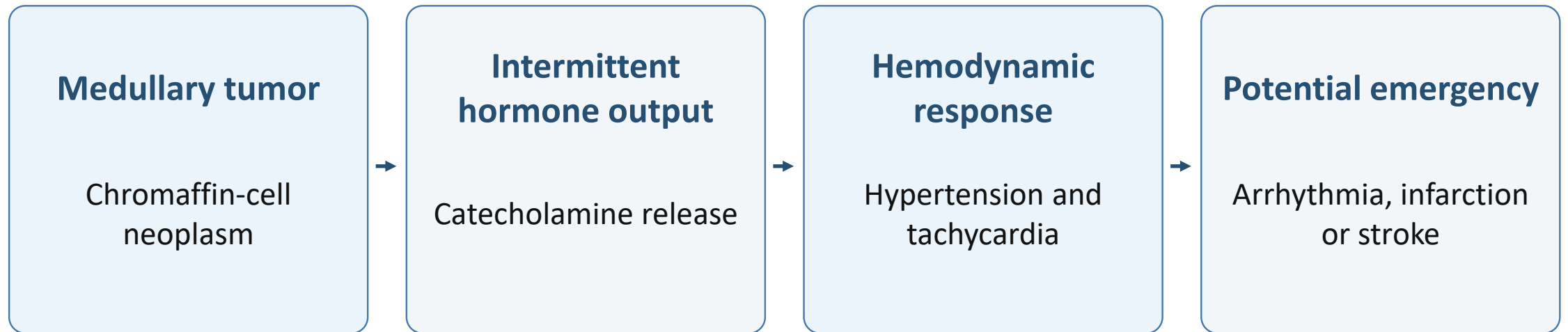
What defines pheochromocytoma?

- A neoplasm composed of chromaffin cells.
- Neoplastic cells synthesize and release catecholamines.
- Some tumors also secrete peptide hormones.
- Recognition matters because it can cause surgically correctable hypertension.

Anatomic terminology has diagnostic consequences

Pheochromocytoma	Paraganglioma
Chromaffin-cell tumor in adrenal medulla.	Related neoplasm in extra-adrenal paraganglia.
May be unilateral or bilateral.	May arise in sites such as carotid body or organ of Zuckerkandl.
Can cause catecholamine excess.	Some extra-adrenal tumors also secrete catecholamines.
Potential for metastatic disease.	Metastatic behavior is particularly important in selected sites and genotypes.

Why pheochromocytoma is clinically important



A substantial fraction has a germline predisposition

30%–40%

Individuals with pheochromocytoma or paraganglioma may harbor an oncogenic germline mutation.

Mutations in at least a dozen genes; Inherited disease cannot be dismissed as exceptional.

Inherited tumors have recognizable patterns

- Individuals with germline mutations typically present at younger ages than sporadic cases.
- Bilateral adrenal tumors occur more often in inherited settings.
- Bilateral pheochromocytomas may occur in up to 50% of patients with a familial tumor syndrome.
- A tumor phenotype should trigger attention to accompanying syndromic lesions.

Two broad molecular classes

Growth signaling

Genes exemplified by RET and NF1.

Increased growth factor receptor pathway signaling.

Altered proliferative signaling is central.

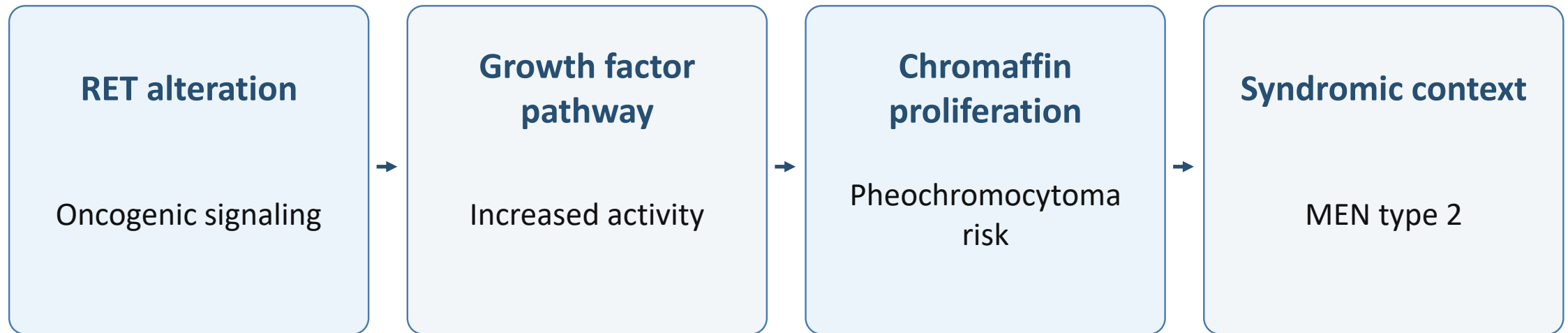
Pseudohypoxia

Genes include VHL, EPAS1 and SDH subunits.

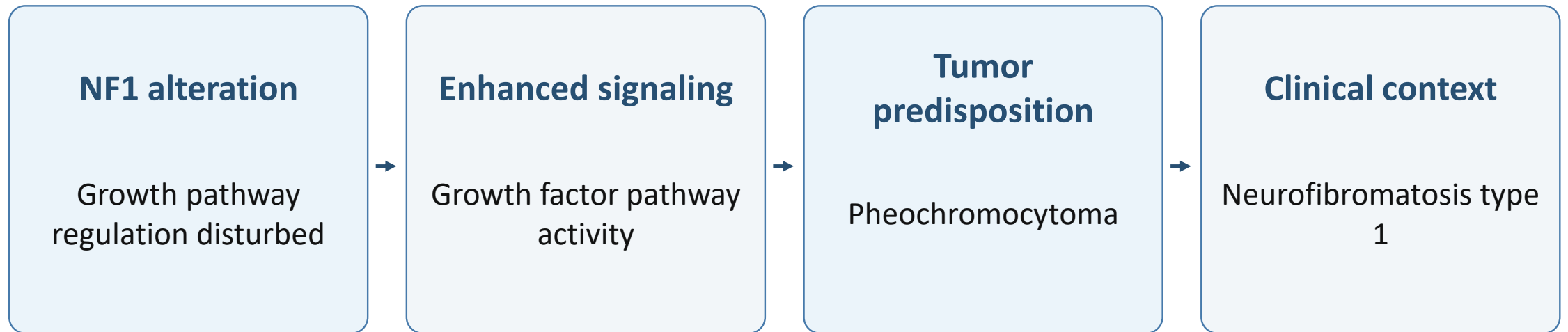
Increased activity or stability of HIF transcription factors.

Altered oxygen-sensing machinery creates a pseudohypoxic state.

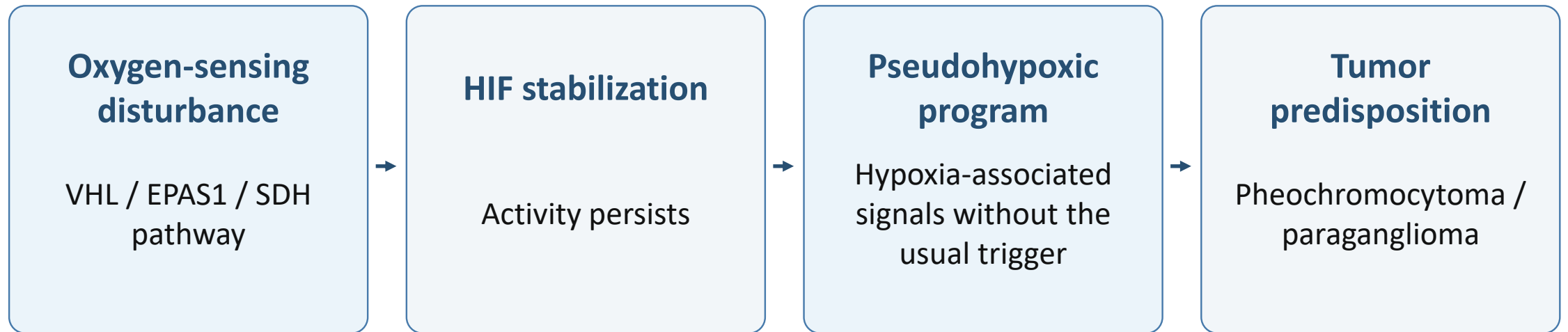
RET-associated tumor susceptibility



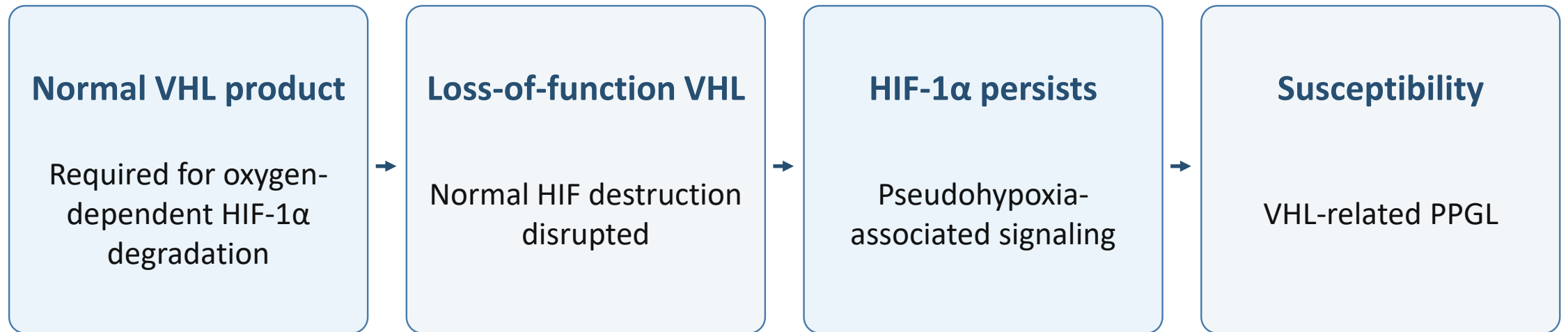
NF1-associated tumor susceptibility



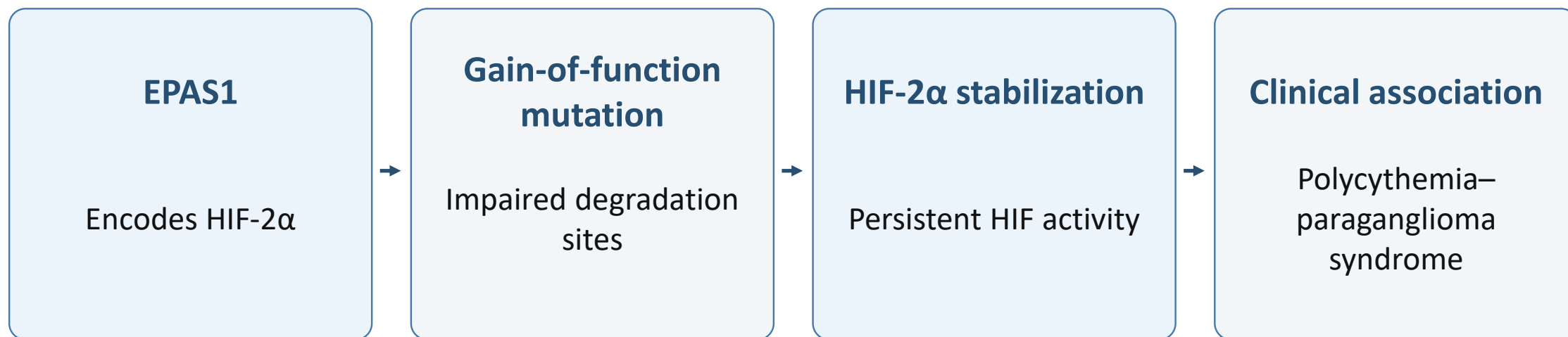
Pseudohypoxia: The central idea



VHL loss alters HIF turnover



EPAS1 mutation stabilizes HIF-2 α



Succinate dehydrogenase genes

- Inherited predisposition may involve components of the succinate dehydrogenase complex.
- The Robbins table identifies SDHB, SDHC and SDHD.
- This mitochondrial complex participates in electron transport and oxygen sensing.
- Impaired function is believed to up-regulate HIF proteins and promote pseudohypoxia.

Contrasting the inherited molecular routes

RET / NF1



Growth-factor signaling



Enhanced proliferative input

VHL / EPAS1 / SDHx



HIF persistence



Pseudohypoxia phenotype

Germline and sporadic disease share oncogenic genes

- Genes implicated in inherited susceptibility can also be altered somatically.
- NF1, VHL, EPAS1 and RET among such genes.
- A sporadic presentation does not imply a completely distinct molecular pathway.
- Distinguish a tumor's somatic driver from an inherited pathogenic variant.

Syndromic associations: Clinical map

Pheochromocytoma / paraganglioma

RET

NF1

VHL

SDHB / SDHC / SDHD

EPAS1

MEN-2A / MEN-2B

Neurofibromatosis type 1

Von Hippel–Lindau

Hereditary paraganglioma

Polycythemia–paraganglioma

MEN-2A: The combination to recognize

- RET is the implicated gene.
- Pheochromocytoma or paraganglioma may coexist with medullary thyroid carcinoma.
- Parathyroid hyperplasia is another associated feature.
- This constellation places a medullary adrenal tumor in a multisystem hereditary syndrome.

MEN-2B: Distinguishing accompanying lesions

- RET-associated endocrine tumor syndrome.
- Pheochromocytoma or paraganglioma and medullary thyroid carcinoma are associated lesions.
- Marfanoid habitus and mucocutaneous ganglioneuromas are distinctive accompanying features.
- Recognizing the nonadrenal phenotype can guide syndromic interpretation.

NF1-related pheochromocytoma

- The NF1 gene is part of the growth-signaling molecular group.
- Pheochromocytoma can occur with characteristic neurofibromatosis.
- The Robbins syndrome table identifies café-au-lait spots and optic nerve glioma.
- A chromaffin tumor is one possible component of a wider hereditary phenotype.

VHL syndrome: Endocrine and nonendocrine tumors

- The VHL gene encodes a tumor suppressor required for regulated HIF-1 α degradation.
- Pheochromocytoma or paraganglioma may arise in VHL syndrome.
- Associated lesions include renal cell carcinoma and hemangioblastoma.
- Pancreatic neuroendocrine neoplasms also appear in the Robbins table.

Hereditary paraganglioma: SDH associations

Hereditary syndrome	Gene	Adrenal / extra-adrenal association
Paraganglioma 1	SDHD	Pheochromocytoma, paraganglioma
Paraganglioma 3	SDHC	Paraganglioma
Paraganglioma 4	SDHB	Pheochromocytoma, paraganglioma

Robbins also lists gastrointestinal stromal tumors as associated lesions.

EPAS1 and polycythemia–paraganglioma

- EPAS1 encodes hypoxia-inducible factor HIF-2 α .
- Gain-of-function changes can stabilize HIF-2 α .
- Associated phenotype includes pheochromocytoma and paraganglioma.
- Polycythemia is the systemic clue captured in the syndrome name.

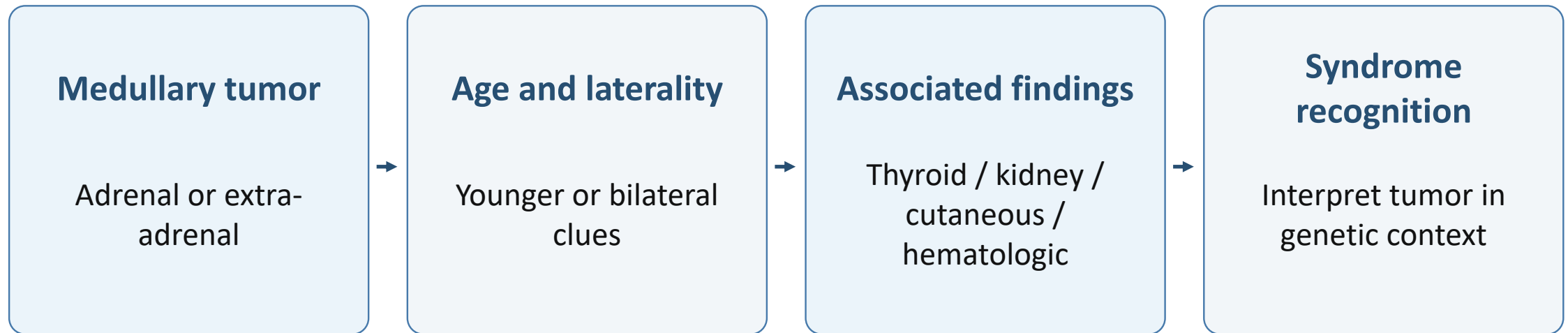
Hereditary syndromes: A comparison

Gene	Tumor syndrome	A distinguishing nonadrenal clue
RET	MEN-2A	Medullary thyroid carcinoma; Parathyroid hyperplasia
RET	MEN-2B	Medullary thyroid carcinoma; Mucocutaneous ganglioneuromas
NF1	NF1	Café-au-lait spots; Optic nerve glioma
VHL	VHL	Renal cell carcinoma; Hemangioblastoma

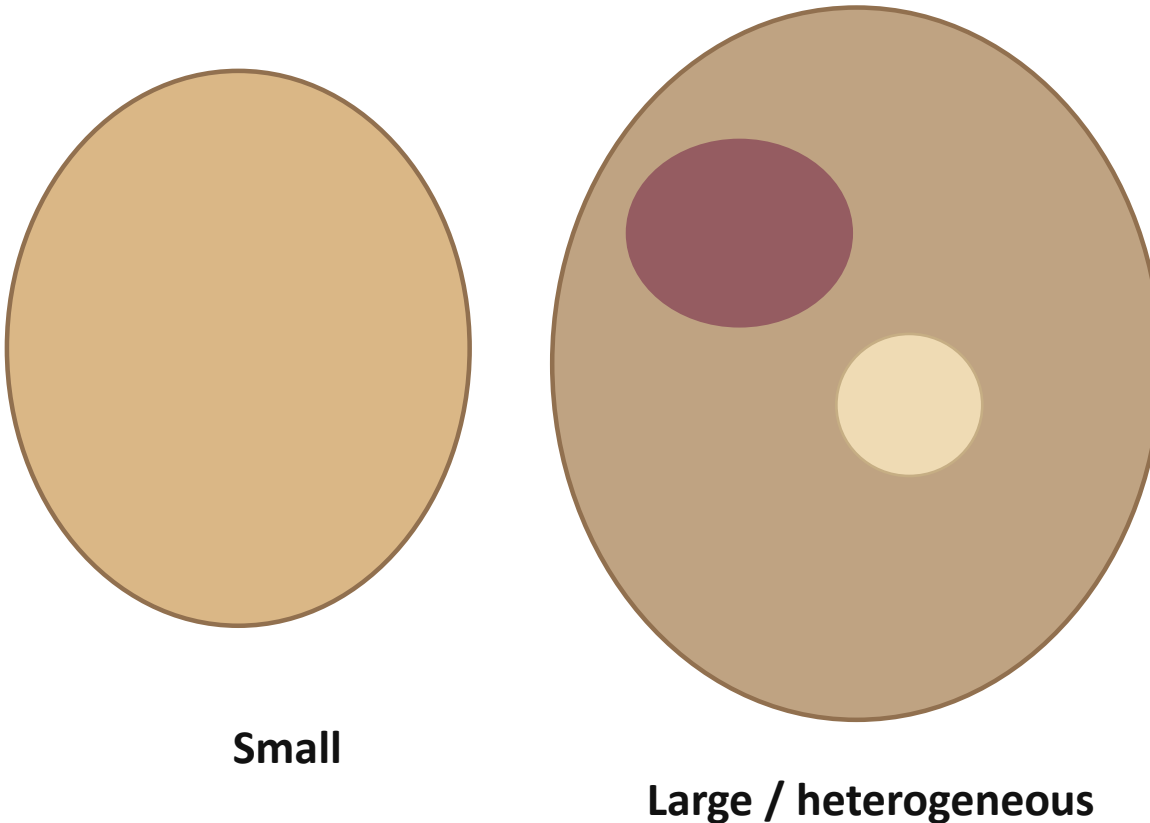
Pseudohypoxia syndromes: A comparison

Gene	Tumor predisposition	Associated feature
SDHD	Hereditary paraganglioma 1	Gastrointestinal stromal tumor
SDHC	Hereditary paraganglioma 3	Gastrointestinal stromal tumor
SDHB	Hereditary paraganglioma 4	Gastrointestinal stromal tumor
EPAS1	Polycythemia–paraganglioma	Polycythemia

Clinical reasoning from an inherited phenotype



Gross appearance spans a wide spectrum



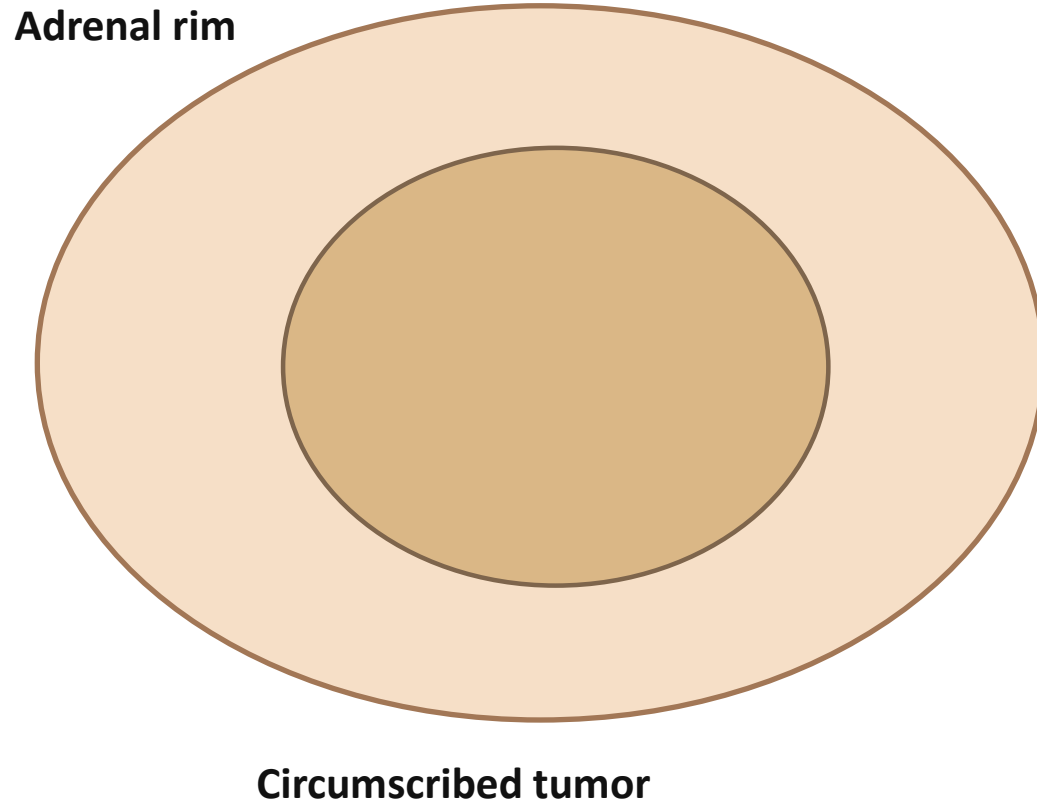
- Small, circumscribed lesions may remain confined to the adrenal.
- Large masses may become hemorrhagic, necrotic or cystic.
- Size and appearance alone do not definitively establish metastatic behavior.

Gross-appearance schematic – not a clinical specimen

Tumor mass can vary dramatically

- A mean weight of approximately 100 g.
- Published examples extend from slightly more than 1 g to almost 4000 g.
- Larger tumors may compress surrounding adrenal tissue.
- Lesion dimensions are descriptive—not a stand-alone classification of malignancy.

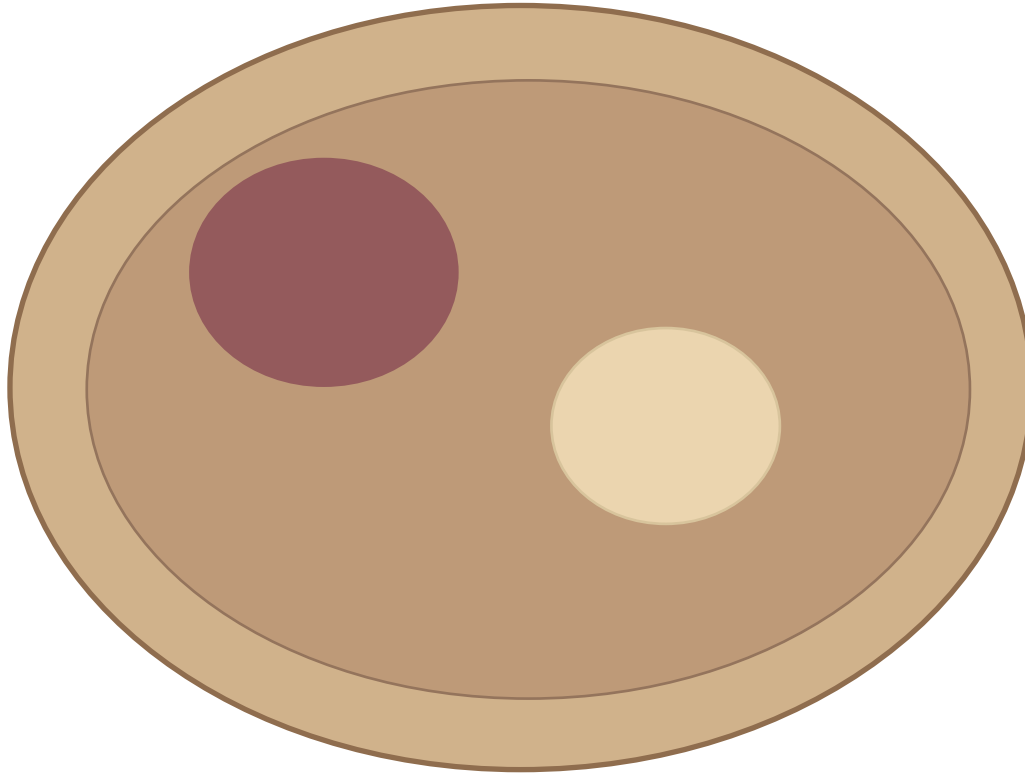
Smaller pheochromocytomas on cut section



- Well-circumscribed lesion within the adrenal gland.
- Cut surfaces of smaller tumors are typically yellow-tan.
- A residual rim of adrenal tissue may remain visible.

Gross-appearance schematic – not a clinical specimen

Larger lesions remodel the adrenal gland



Hemorrhage / cystic change

Gross-appearance schematic – not a clinical specimen

- Often well-demarcated by fibrous tissue or compressed adrenal elements.
- Hemorrhage, necrosis and cystic degeneration are common in larger tumors.
- The normal gland may be effaced or stretched over one pole.

Fibrovascular trabeculae shape gross architecture

Rich vascularity

Prominent intratumoral
vessels



Fibrous trabeculae

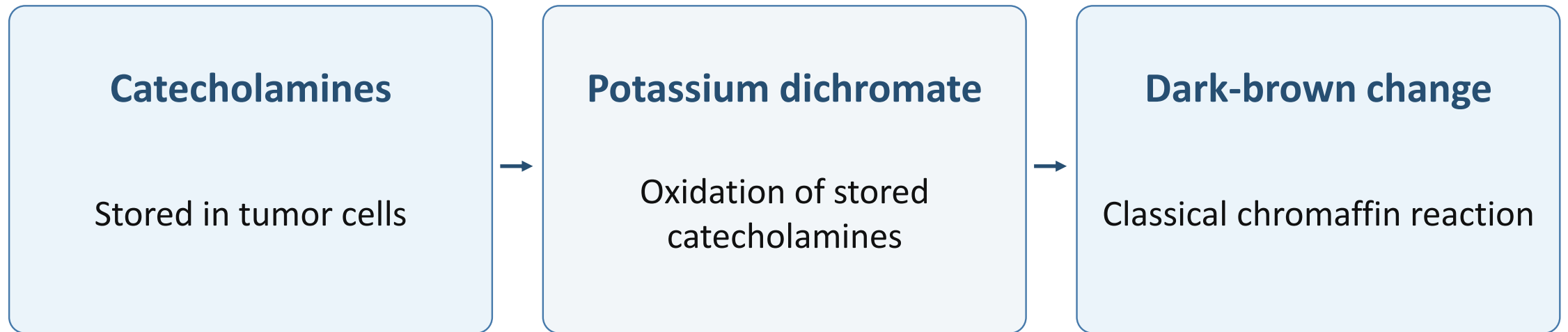
Partition tumor parenchyma



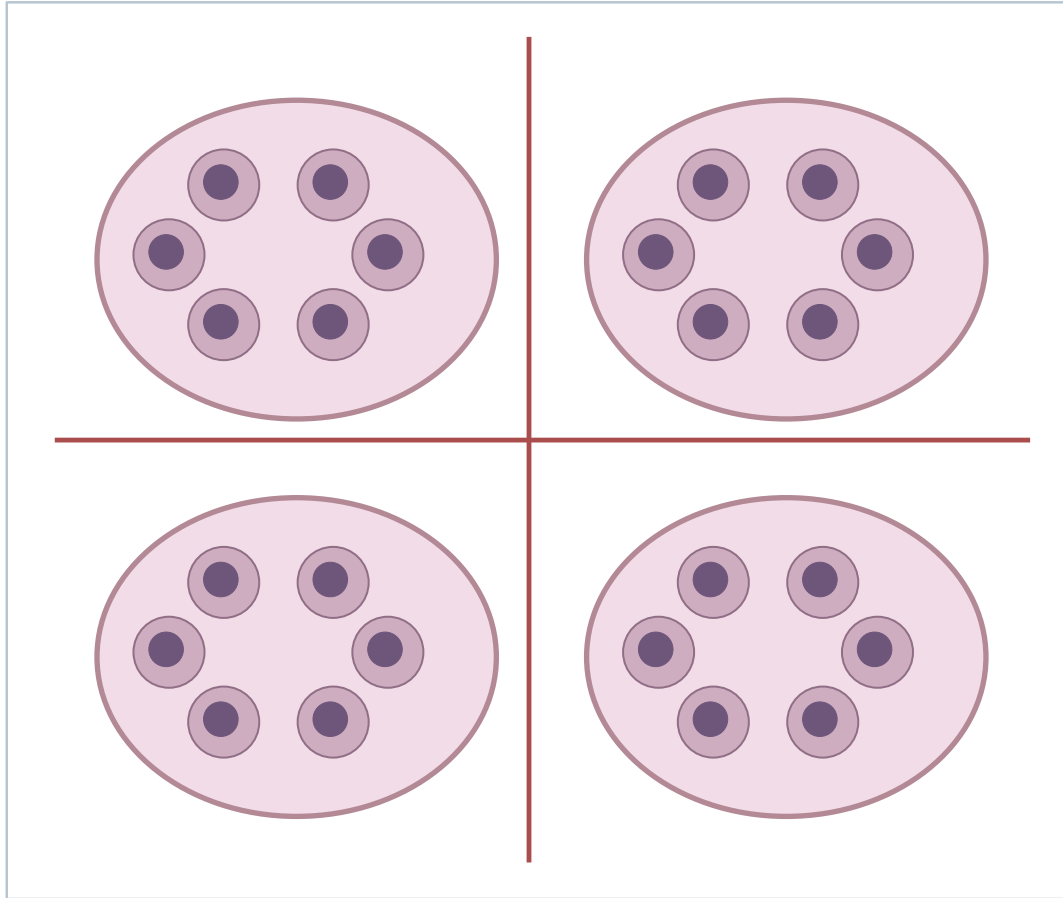
Lobular pattern

Recognizable gross
organization

Chromaffin: Origin of the name



Zellballen architecture of pheochromocytoma



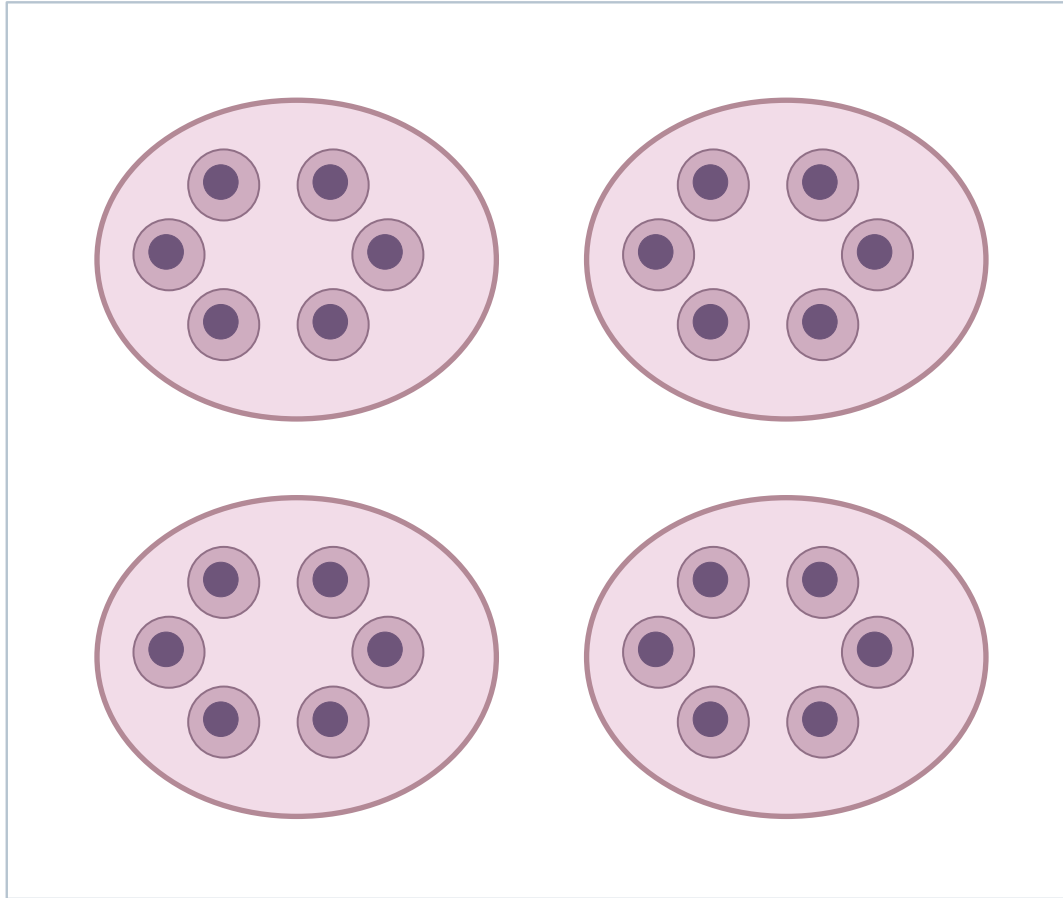
Cell-nest schematic – not a histologic specimen

- Nests of chief cells are separated by a rich vascular network.
- Sustentacular cells lie around the nests.
- Architecture is characteristic but tumor patterns are variable.

Chief-cell cytology

- Chief (chromaffin) tumor cells range from polygonal to spindle-shaped.
- Their cytoplasm is often finely granular because of catecholamine-containing granules.
- Small nests or alveoli are typically richly vascularized.
- A single tumor may contain more than one growth pattern.

Neuroendocrine nuclear chromatin



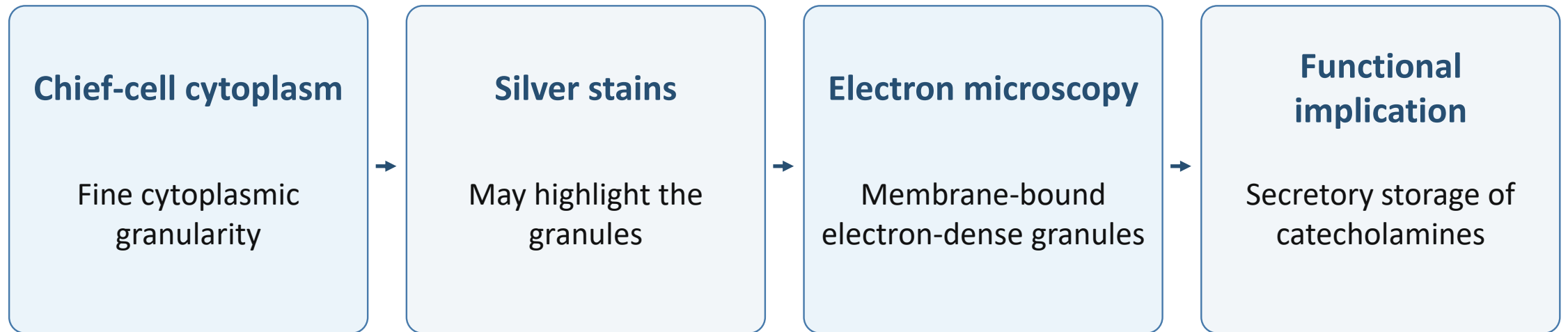
Cell-nest schematic – not a histologic specimen

- Nuclei are usually round to oval.
- Fine stippling creates a “salt-and-pepper” chromatin pattern.
- This is a neuroendocrine cytologic clue, not a prediction of metastasis.

Morphologic variation within one tumor

- Typical nesting is not the only possible architecture.
- Spindle-cell or small-cell patterns can predominate occasionally.
- A variety of patterns may coexist in a single lesion.
- Interpret atypical patterns in conjunction with site, clinical history and neuroendocrine differentiation.

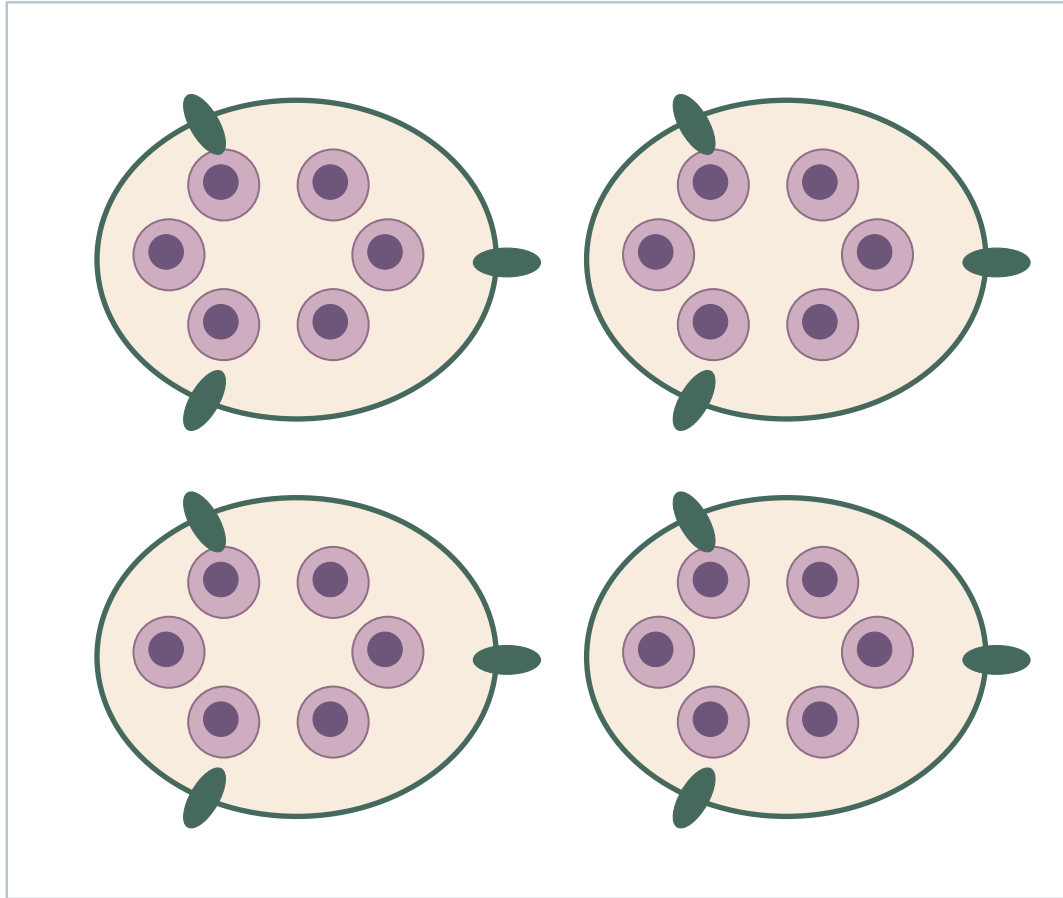
Catecholamine secretory granules



Chromogranin and synaptophysin

- Chief cells are immunoreactive for neuroendocrine markers.
- Chromogranin and synaptophysin highlight neoplastic chief-cell differentiation.
- The staining distribution must be interpreted in the correct cellular compartment.
- These markers confirm neuroendocrine character; They do not determine metastatic potential.

S-100 highlights sustentacular cells



Cell-nest schematic – not a histologic specimen

- Sustentacular cells occupy the periphery of chief-cell nests.
- They express S-100 in the Robbins description.
- The peripheral network differs from chromogranin/synaptophysin-positive chief cells.

Tumor cells versus sustentacular cells

Chief / chromaffin cells	Sustentacular cells
Form the bulk of tumor nests.	Peripheral supporting cells around nests.
Catecholamine secretory granules.	Supporting structural network.
Chromogranin and synaptophysin.	S-100 immunoreactivity.
Neuroendocrine nucleus and granular cytoplasm.	Best recognized by their position and IHC.

Morphology cannot certify a benign course

- Pheochromocytomas and paragangliomas are regarded as potentially metastatic.
- Histologic scoring for malignancy has proven unreliable as a definitive test.
- Tumors with bland morphology may metastasize.
- Highly pleomorphic tumors may remain confined to the adrenal gland.

Features associated with aggressive behavior

- A larger number of mitotic figures has been linked to increased risk.
- Confluent tumor necrosis has been associated with aggressive behavior.
- Spindle-cell morphology may also correlate with risk.
- None of these findings establishes metastasis by itself.

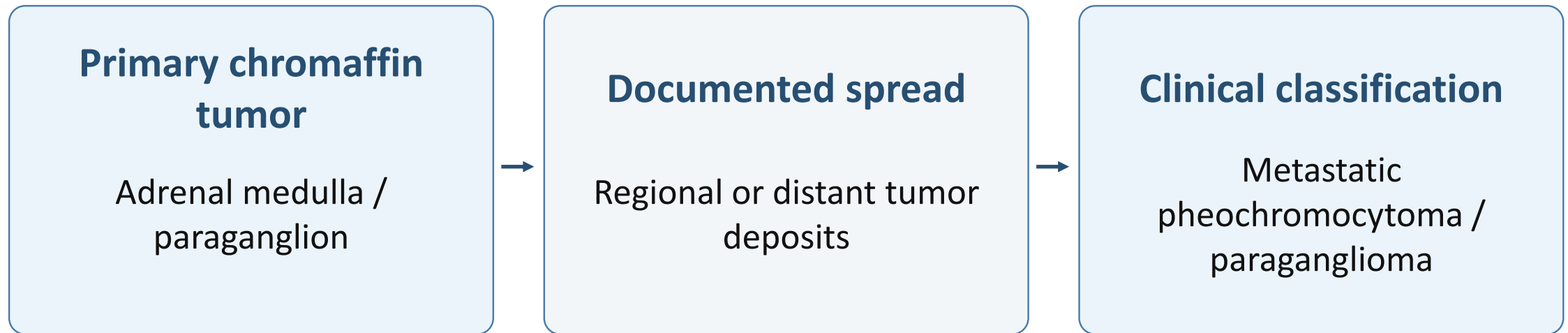
Why pleomorphism is a diagnostic trap

An alarming appearance	What it does not establish
Marked nuclear size variation	Metastatic disease by itself
Bizarre or giant tumor cells	An inevitable aggressive clinical course
Mitotic figures	A sufficiently reliable binary benign/malignant distinction
Bland cytology	A guarantee against future metastasis

Capsular and vascular invasion have limits

- Capsular invasion may be seen in these tumors.
- Vascular invasion also may be encountered.
- Even these findings do not independently provide a definitive metastatic classification.
- Documented metastases for definitive malignant behavior.

Defining metastatic pheochromocytoma



Metastatic distribution: Where to look

Documented metastatic deposits

Regional

Distant solid organ

Distant solid organ

Skeletal

Lymph nodes

Liver

Lung

Bone

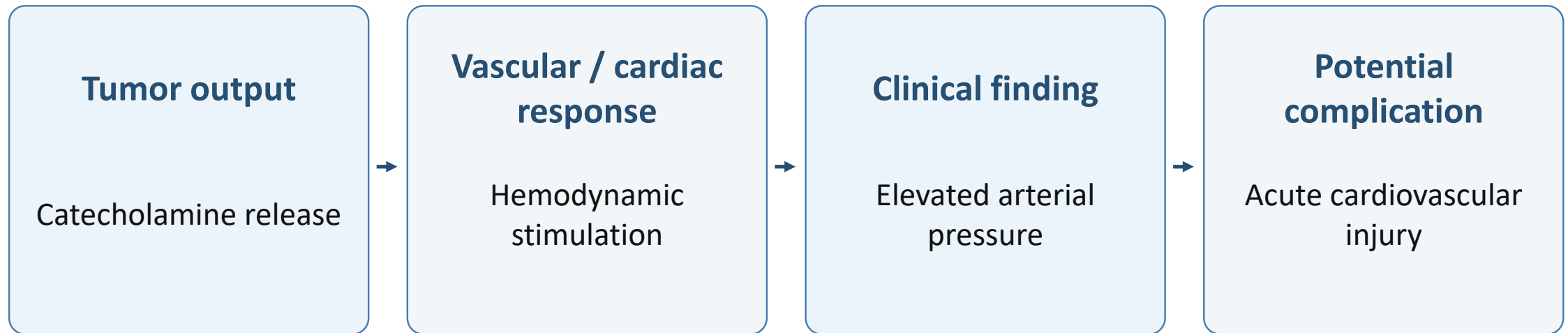
Extra-adrenal tumors may have higher metastatic risk

20%–40%

Metastatic behavior in this range for extra-adrenal paragangliomas.

The text also emphasizes greater risk with certain germline mutations; Do not extrapolate this range to every adrenal tumor.

Catecholamine secretion produces hypertension



Hypertension is the dominant clinical feature

90%

Proportion of pheochromocytoma patients reported to present with hypertension.

The remaining approximately 10% may not show hypertension—absence of the finding does not exclude a tumor.

The paroxysmal catecholamine syndrome

- Abrupt blood-pressure elevation is accompanied by tachycardia or palpitations.
- Headache, sweating, tremor and apprehension are characteristic associated symptoms.
- Chest or abdominal pain, nausea and vomiting may occur.
- Among hypertensive patients, approximately two-thirds have paroxysmal episodes.

Sustained hypertension often coexists with paroxysms

Isolated episodic attacks

Occurs in fewer than half of patients.

Sudden hypertension may dominate the history.

A normal reading between episodes can obscure detection.

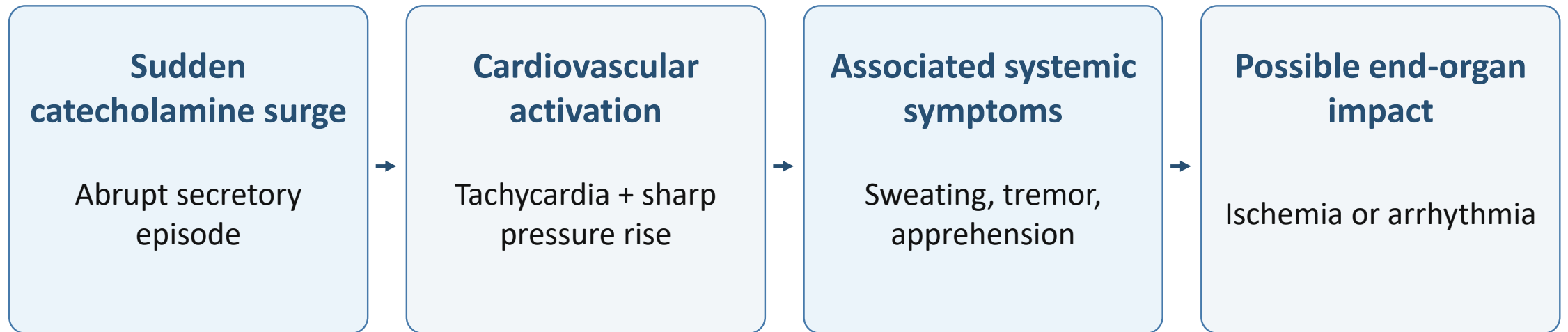
Sustained elevation plus attacks

More common pattern.

Baseline hypertension is punctuated by surges.

Both chronic hypertension and attacks require explanation.

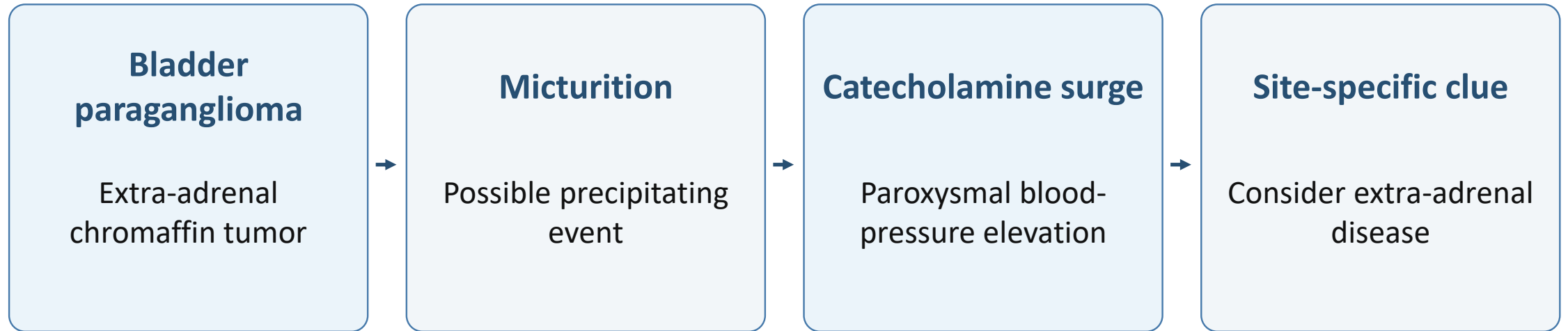
Patterns of symptoms are mechanistically linked



What can precipitate a paroxysm?

- Emotional stress and physical exercise.
- Changes in posture.
- Palpation in the region of the tumor.
- In urinary-bladder paraganglioma, micturition may precipitate an episode.

Micturition-associated hypertension as a clue



Potential cardiovascular and neurologic emergencies

Severe catecholamine surge

Cardiac failure

Pulmonary

Ischemic

Electrical

Neurologic

Congestive heart failure

Pulmonary edema

Myocardial infarction

Ventricular fibrillation

Cerebrovascular accident

Catecholamine cardiomyopathy

- Excess catecholamines can create myocardial instability and ventricular arrhythmias.
- Myocardial injury may reflect catecholamine-related vasospasm and ischemia.
- Direct catecholamine toxicity is an additional proposed mechanism.
- The cardiac presentation can be more consequential than the adrenal mass itself.

Myocardial tissue correlates of injury

- Focal myocardial necrosis.
- Mononuclear inflammatory infiltrates may be present.
- Interstitial fibrosis may develop.
- These changes are nonspecific and require clinical correlation with catecholamine excess.

Peptide hormone secretion can broaden presentation

- Some pheochromocytomas secrete hormones other than catecholamines.
- Corticotropin and somatostatin are examples.
- Associated clinical effects may reflect the secreted peptide rather than catecholamine excess alone.
- Variable secretory behavior explains some atypical clinical presentations.

Biochemical evidence is central to diagnosis

Urinary measurements

Increased excretion of free catecholamines.

Increased urinary metanephrine metabolites.

Interpreted in the appropriate clinical context.

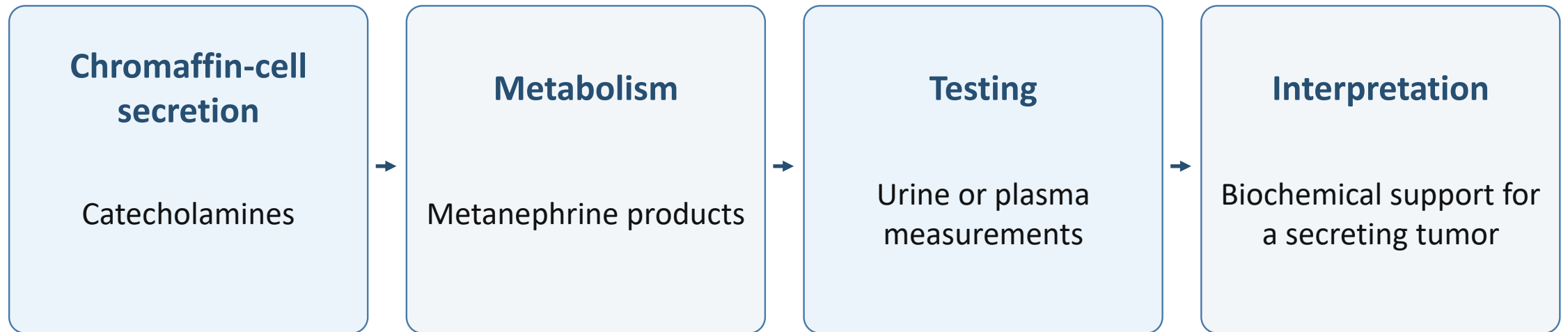
Plasma measurements

Elevated plasma metanephrines.

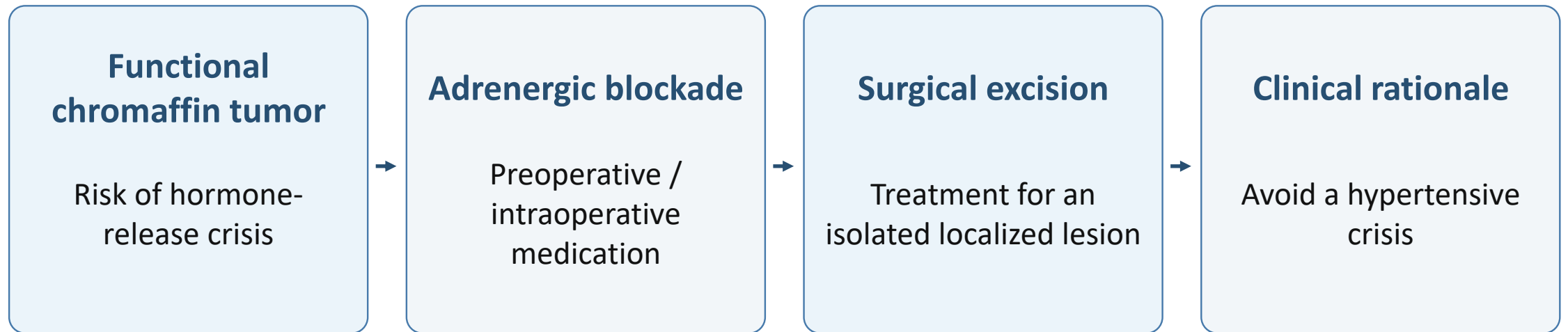
Provides biochemical evidence of catecholamine metabolism.

A biochemical approach complements tumor morphology.

Why metanephrines matter



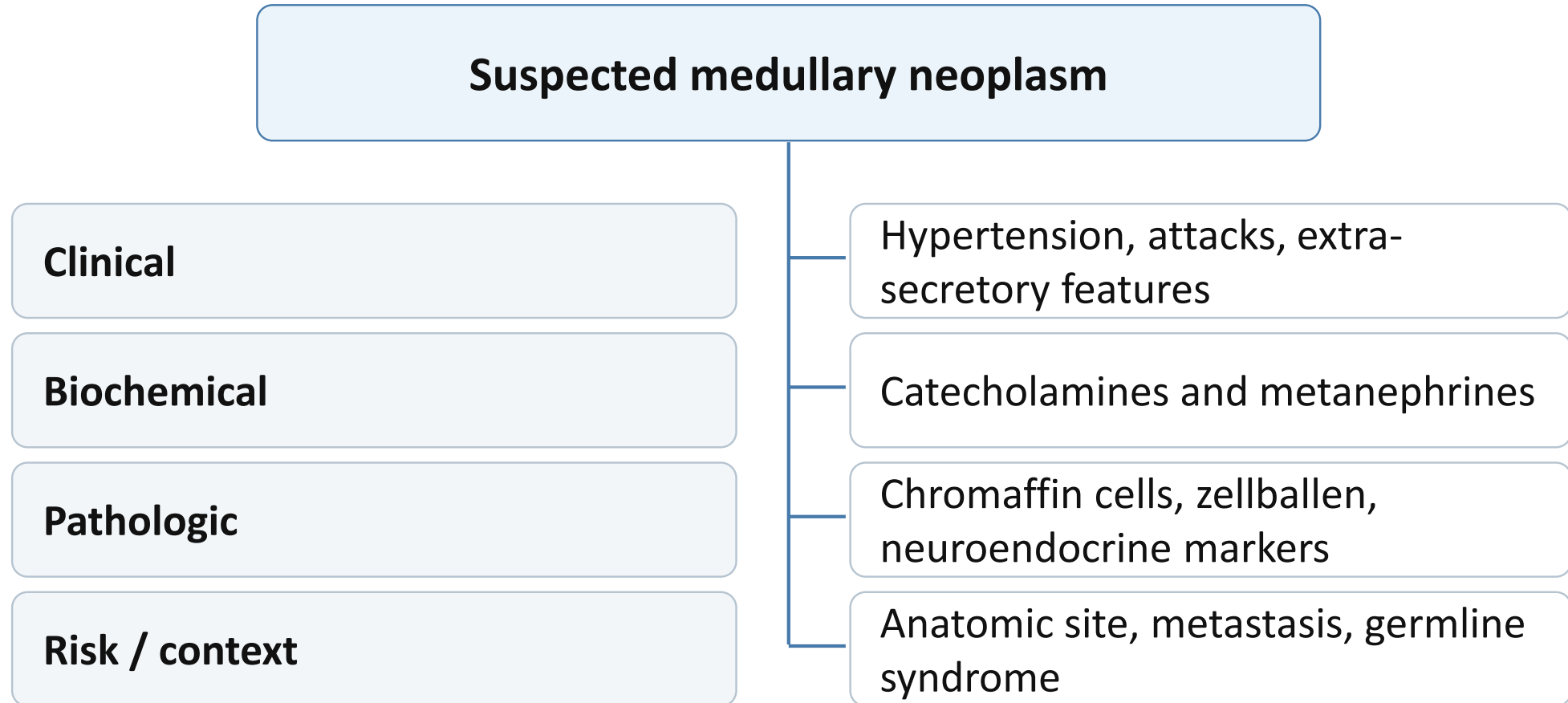
Resection requires adrenergic preparation



Multifocal disease may require continuing management

- Treatment approach differs from excision of an isolated tumor.
- Multifocal lesions may require long-term medical control of hypertension.
- Clinical management must account for tumor distribution and catecholamine output.
- Inherited predisposition can influence the interpretation of multifocal disease.

Diagnostic synthesis: Four connected domains



Case: Episodic hypertension and an adrenal mass

A patient has sudden episodes of headache, sweating, palpitations and marked hypertension. Imaging detects an adrenal mass.

Questions for interpretation

- Which adrenal compartment is most relevant?
- What biochemical measurements are supported by Robbins?
- Why is preparation before surgery important?

Case interpretation: A functional chromaffin tumor

- A medullary chromaffin-cell neoplasm is a major consideration.
- Catecholamine and metanephrine testing provides biochemical support.
- Abrupt catecholamine secretion explains paroxysmal tachycardia and hypertension.
- Adrenergic blockade is used around surgery to reduce hypertensive-crisis risk.

Case: Bilateral tumors with syndromic findings

A younger patient presents with bilateral adrenal medullary masses. Family history and clinical examination reveal other endocrine or systemic lesions.

Questions for interpretation

- Why is inherited susceptibility particularly relevant?
- Which gene groups are implicated?
- What concurrent findings might distinguish RET, NF1 or VHL?

Case interpretation: Inherited molecular context

- Younger presentation and bilateral involvement increase suspicion for germline predisposition.
- RET and NF1 represent growth-signaling susceptibility.
- VHL, EPAS1 and SDH subunits participate in pseudohypoxia-related susceptibility.
- Associated thyroid, parathyroid, renal, neural or hematologic features refine syndromic interpretation.

Five diagnostic principles to retain

- The adrenal medulla is neural-crest-derived chromaffin tissue with supporting sustentacular cells.
- Pheochromocytoma is a catecholamine-secreting chromaffin neoplasm; Some paragangliomas are related extra-adrenal tumors.
- Hereditary predisposition often maps to growth-signaling or pseudohypoxia pathways.
- Zellballen nests, chromogranin/synaptophysin and sustentacular S-100 define a recognizable pathologic pattern.
- Clinical danger arises from catecholamine crises; Documented metastasis—not bizarre cytology—defines metastatic behavior.

References and image provenance

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026). Chapter 24, The Endocrine System.
- Lecture content is based on the supplied Chapter 24 text under “Adrenal Medulla” and “Pheochromocytoma.”
- All medullary, tumor, molecular and histoarchitectural drawings in this deck are original editable schematics—not histologic specimens.
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