

Multiple Endocrine Neoplasia, Type 2

Pathology • RET signaling • clinicopathologic phenotypes

Thyroid C cells

Adrenal medulla

Parathyroid (2A)

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Learning objectives

Explain why activating germline RET variants create an inherited endocrine-tumor syndrome.

Differentiate MEN2A, MEN2B, and familial medullary thyroid carcinoma.

Recognize medullary carcinoma, pheochromocytoma, and parathyroid manifestations.

Apply genetic testing, presurgical safety, and prevention principles.

MEN2: An inherited, multi-organ tumor predisposition

MEN syndromes predispose to proliferative lesions in multiple endocrine organs.

MEN2 is an autosomal dominant RET-associated syndrome.

Medullary thyroid carcinoma is the major shared malignancy.

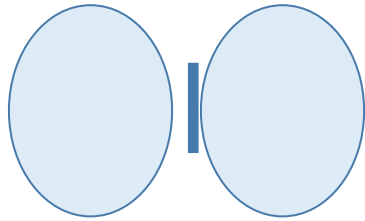
Pheochromocytoma and parathyroid disease vary by phenotype.

Inherited MEN tumors differ from sporadic tumors

Feature	Inherited MEN phenotype	Typical sporadic counterpart
Presentation	Often younger age	Often later onset
Distribution	Multiple organs or bilateral sites	Commonly one primary site
Within one organ	Multifocal lesions frequent	Often solitary
Precursor change	Cell-type hyperplasia may precede tumor	Syndromic precursor less typical

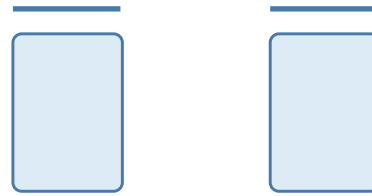
Three clinical tissues explain most MEN2 morbidity

THYROID



Thyroid C cells → medullary carcinoma

ADRENAL



Adrenal medulla → pheochromocytoma

PARATHYROID



Parathyroid → primary hyperparathyroidism (MEN2A)

MEN2 clinical phenotypes

Feature	MEN2A	MEN2B	Familial MTC
Medullary carcinoma	Characteristic	Characteristic; earlier, aggressive	Main manifestation
Pheochromocytoma	Risk present	Risk present	Typically absent in the restricted family phenotype
Parathyroid disease	May occur	Not characteristic	Not typical
Other	—	Mucosal neuromas; marfanoid habitus	MTC-only kindred

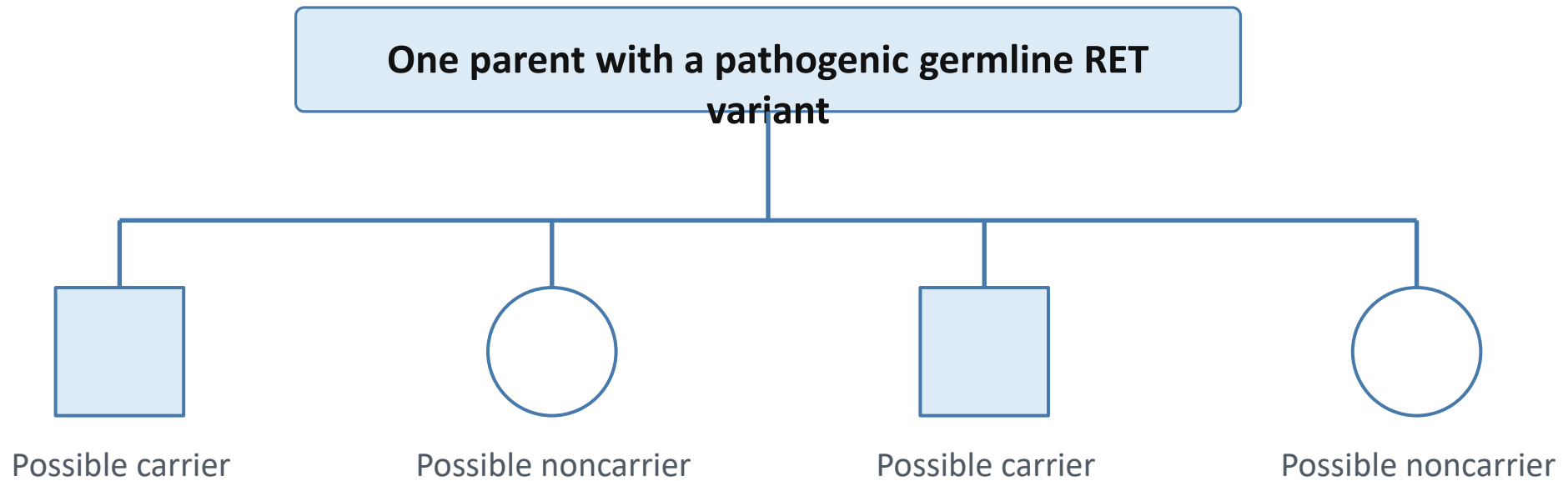
MEN2 is genetically distinct from MEN1

Feature	MEN1	MEN2
Principal gene	MEN1 (menin)	RET (receptor tyrosine kinase)
Genetic mechanism	Tumor-suppressor pathway	Constitutive signaling, gain of function
Signature sites	Parathyroid, pancreatic / duodenal NETs, pituitary	Thyroid C cells; adrenal medulla; parathyroid in 2A
Thyroid malignancy	Not the defining lesion	Medullary thyroid carcinoma

MEN4 is not a subtype of RET-associated MEN2

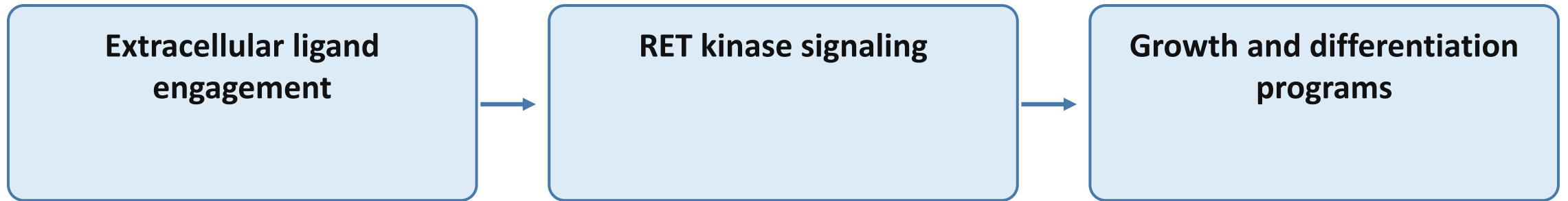
Feature	MEN2	MEN4
Germline gene	RET	CDKN1B
Protein affected	RET receptor tyrosine kinase	p27 cell-cycle checkpoint protein
Typical phenotype	Medullary thyroid carcinoma ± pheochromocytoma	MEN1-like; parathyroid / pituitary lesions
Practical distinction	RET-family cascade testing	Separate molecular diagnosis

Autosomal dominant inheritance: A family-level diagnosis



Each child has a 50% genetic risk; These illustrative offspring do not represent observed family outcomes.

RET: A membrane receptor tyrosine kinase



Constitutively active RET removes ligand dependence

A

**Physiology: Ligand-dependent
receptor signaling**

B

**MEN2: Activating RET variant
sustains signaling without ligand**

The direction of RET dysfunction matters

RET alteration	Functional consequence	Clinical association
Germline gain of function	Constitutive receptor activation	MEN2A / MEN2B
Germline loss of function	Impaired enteric ganglion development	Hirschsprung disease

Genotype influences clinical phenotype

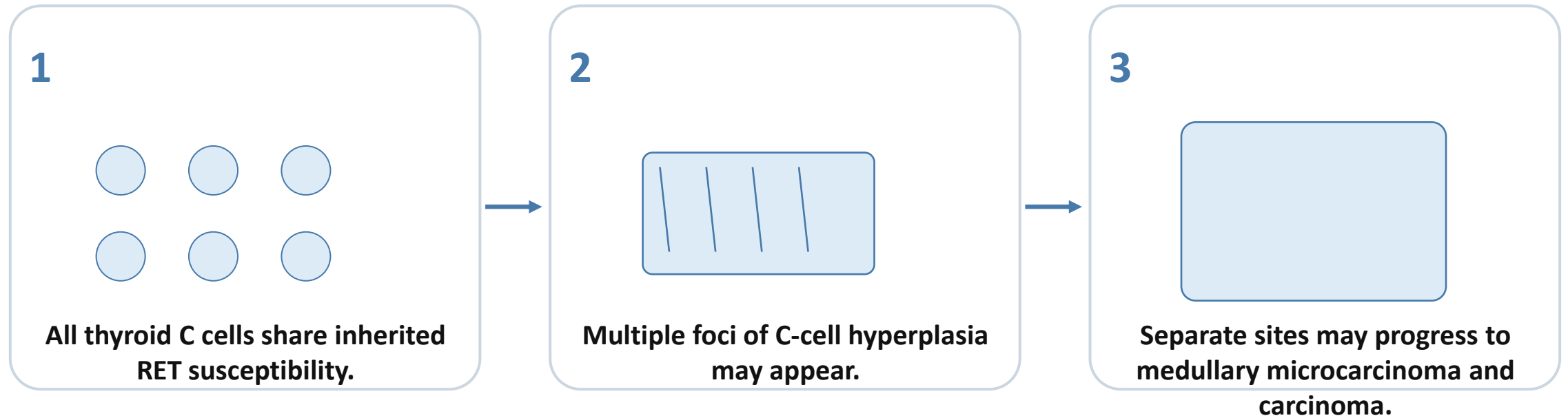
MEN2A and MEN2B are associated with different activating RET variants.

MEN2B classically involves an alteration in the tyrosine kinase domain.

Variant identity is relevant to clinical risk stratification and timing of thyroid surgery.

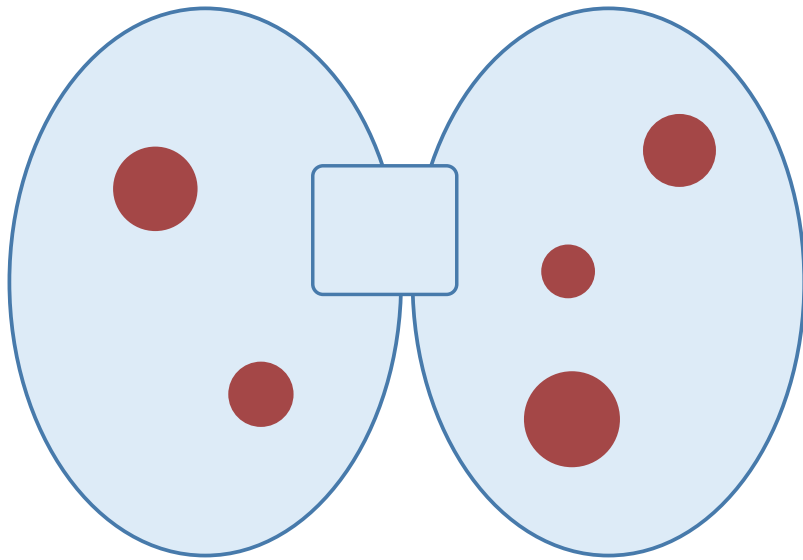
Pathogenic / likely pathogenic status must be distinguished from uncertain variants.

A germline variant creates a multifocal tissue field



C-cell hyperplasia is a key precursor clue

Thyroid topography (schematic)



Separate foci

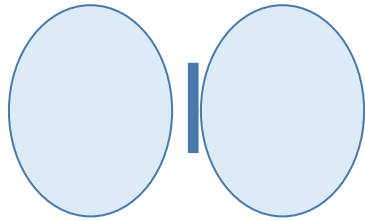
Multiple clusters of parafollicular C cells may be distributed in the thyroid.

Adjacent C-cell hyperplasia strongly supports syndromic medullary carcinoma.

Carefully assess the contralateral lobe;
A dominant nodule need not be solitary disease.

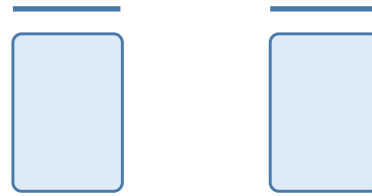
MEN2A: The classical endocrine triad

THYROID



Medullary thyroid carcinoma

ADRENAL



Pheochromocytoma

PARATHYROID



Parathyroid hyperplasia /
hyperparathyroidism

MEN2A: Medullary carcinoma is the dominant threat

Medullary carcinoma in almost all MEN2A patients.

Tumors are commonly multifocal and associated with adjacent C-cell hyperplasia.

Clinical aggressiveness makes prevention through early detection important.

Secretion of calcitonin provides a biologic and clinical biomarker.

MEN2A: Pheochromocytoma is often bilateral

Pheochromocytoma in approximately 40%–50% of MEN2A patients.

Tumors may be bilateral; Extra-adrenal chromaffin tumors are also discussed.

Catecholamine excess can produce dangerous cardiovascular episodes.

Excluding an active pheochromocytoma precedes elective thyroid surgery.

MEN2A: Parathyroid disease is less frequent

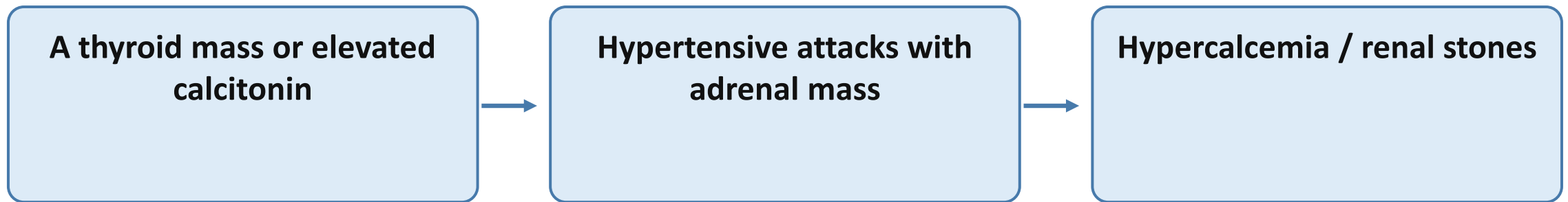
Parathyroid hyperplasia / hypercalcemic manifestations in approximately 10%–20% of MEN2A patients.

Excess parathyroid hormone raises serum calcium.

Nephrolithiasis may be a presenting manifestation.

Absence of hypercalcemia does not exclude RET-associated MEN2.

MEN2A may appear as separate organ presentations



MEN2B has a distinctive non-endocrine phenotype

Medullary thyroid carcinoma and pheochromocytoma overlap with MEN2A.

Mucosal neuromas / ganglioneuromas are characteristic clues.

Marfanoid skeletal habitus may be present.

Primary hyperparathyroidism is not typical of MEN2B.

MEN2B-associated MTC is especially aggressive

MEN2B medullary carcinomas are more aggressive than those in MEN2A.

Onset is often in early childhood in authoritative clinical summaries.

A visible thyroid nodule may be a late manifestation of an inherited process.

Recognizing an extracervical phenotype can permit earlier RET testing.

Mucosal neuromas: A high-value phenotypic clue

Site	Possible manifestation
Lips / oral mucosa	Thickened lips; mucosal neuromas
Tongue	Mucosal neuromas
Eyes	Medullated corneal nerves / neuromatous findings
GI tract	Ganglioneuromatosis; motility symptoms

Marfanoid habitus is a clue, not a diagnosis

An elongated / asthenic body habitus may accompany MEN2B.

Long skeletal proportions and hyperextensible joints are.

The associated mucosal and endocrine findings create the diagnostic pattern.

Avoid diagnosing a RET syndrome from body proportions alone.

MEN2B: Parathyroid hyperfunction is not typical

A

**MEN2A: Parathyroid hyperplasia is
part of the classical triad**

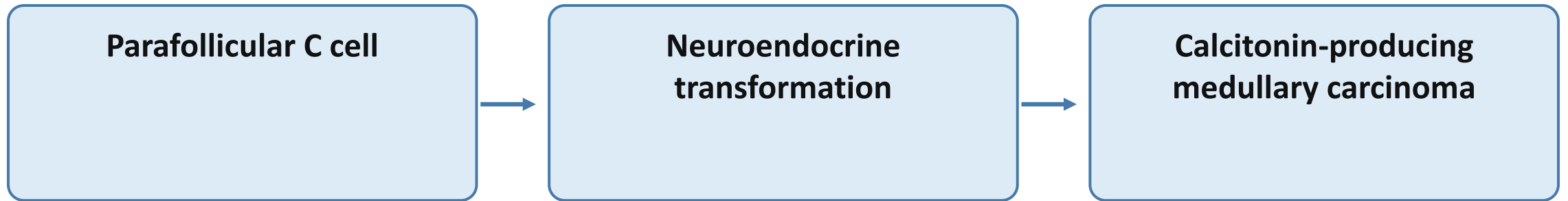
B

**MEN2B: Primary
hyperparathyroidism is generally
absent**

MEN2A and MEN2B: Discriminating findings

Feature	MEN2A	MEN2B
RET mechanism	Activating kinase signaling	Activating kinase signaling
Medullary carcinoma	High risk; often multifocal	Early, often more aggressive
Pheochromocytoma	Present in subset	Present in subset
Hyperparathyroidism	Subset affected	Not characteristic
Neuromas / marfanoid	Not typical	Characteristic

MTC begins in thyroid parafollicular C cells

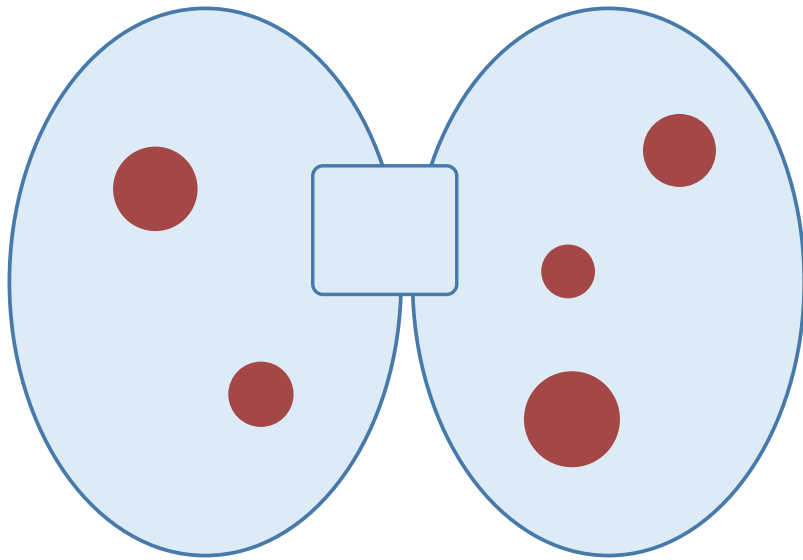


MTC is not a follicular-cell thyroid cancer

Feature	Medullary carcinoma	Papillary / follicular carcinoma
Cell of origin	Parafollicular C cell	Follicular epithelial cell
Functional marker	Calcitonin	Follicular differentiation / thyroglobulin
MEN2 association	Strong with germline RET	Not defining MEN2 lesions

Gross MTC may be multifocal and bilateral

Thyroid topography (schematic)



Separate foci

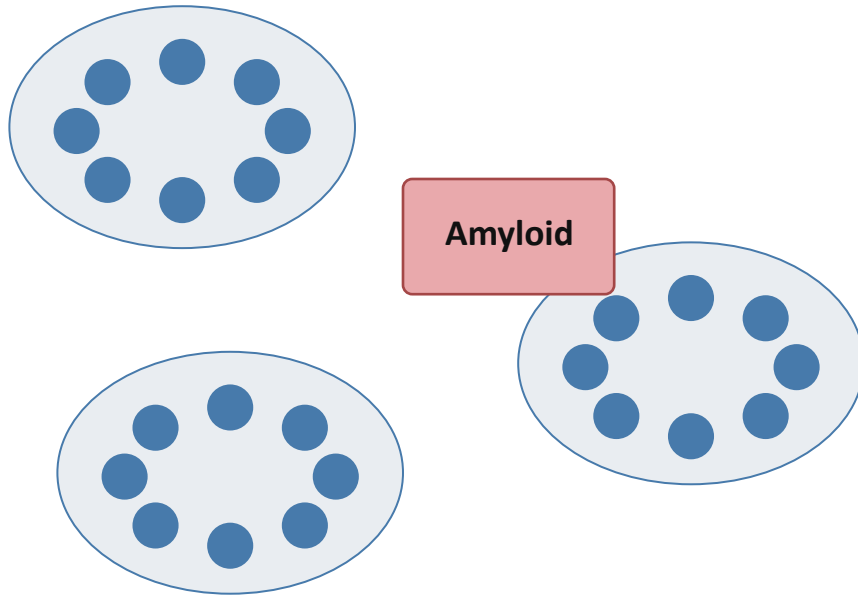
Familial lesions are frequently multicentric and bilateral.

Firm, gray-tan, infiltrative nodules characterize larger tumors.

Larger tumors may show hemorrhage or necrosis.

Microscopic MTC: Neuroendocrine architecture

Tumor nests



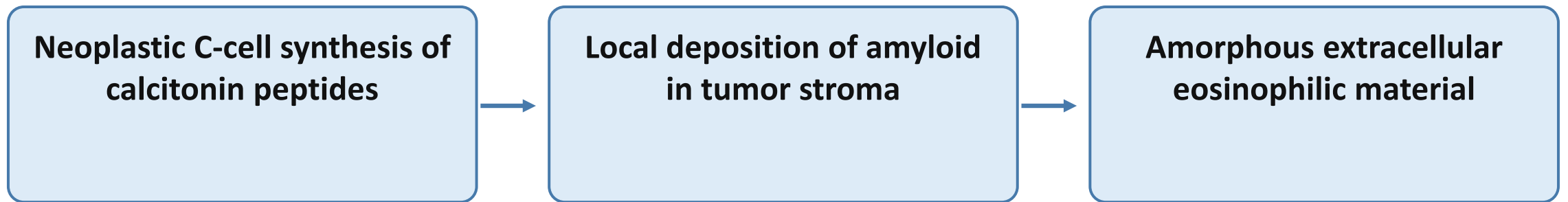
Schematic — not a histologic specimen

Polygonal or spindle-shaped tumor cells form nests or trabeculae.

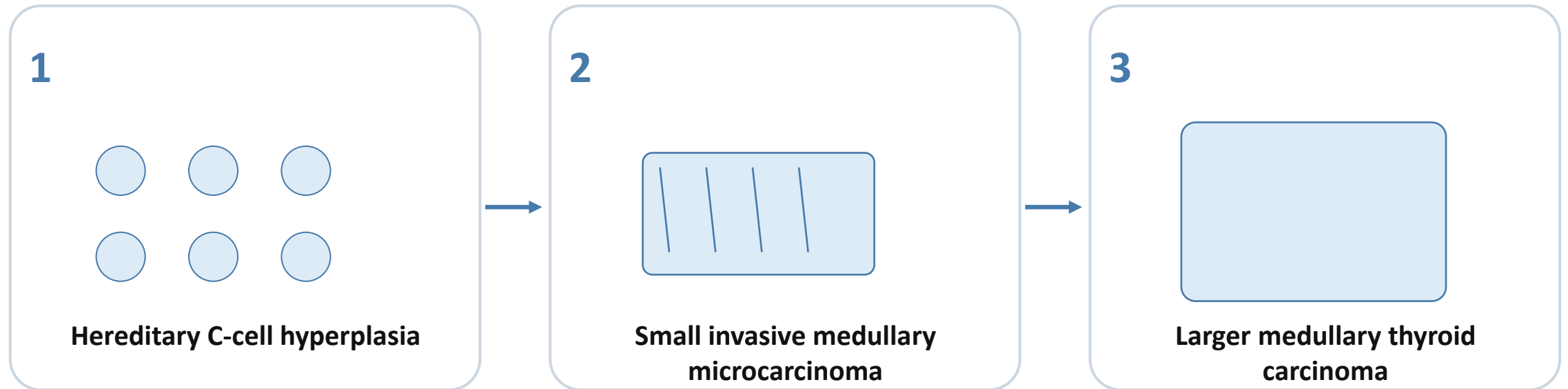
Nuclei often show fine stippled neuroendocrine chromatin.

Stromal amyloid is common but not obligatory.

The amyloid of MTC derives from calcitonin



A C-cell hyperplasia–microcarcinoma continuum



MTC morphology: What the pathologist should report

Unifocal versus multifocal growth; Unilateral versus bilateral distribution.

Relationship to background C-cell hyperplasia.

Tumor extent and evidence of invasion.

Regional nodal involvement and other findings requiring staging.

Sporadic versus hereditary MTC: Pathology clues

Clue	Hereditary / MEN2	Sporadic
Patient age	Often younger	Typically adult
Distribution	Frequently bilateral / multifocal	Commonly solitary
C-cell hyperplasia	Characteristic precursor	Usually absent
RET germline status	Pathogenic variant	Most cases negative

Calcitonin: A tumor-produced biochemical marker

MTC retains the C-cell ability to produce calcitonin.

Serum calcitonin assists diagnosis and follow-up.

Tumor production does not usually cause clinically prominent hypocalcemia.

Interpret results in their clinical context; There is no invented universal cutoff on this slide.

CEA provides a complementary MTC marker

Carcinoembryonic antigen can be secreted by medullary carcinoma.

It contributes to assessment of tumor burden and follow-up.

Calcitonin and CEA are markers of MTC biology, not markers of germline inheritance.

RET testing—not either serum marker—establishes molecular inherited risk.

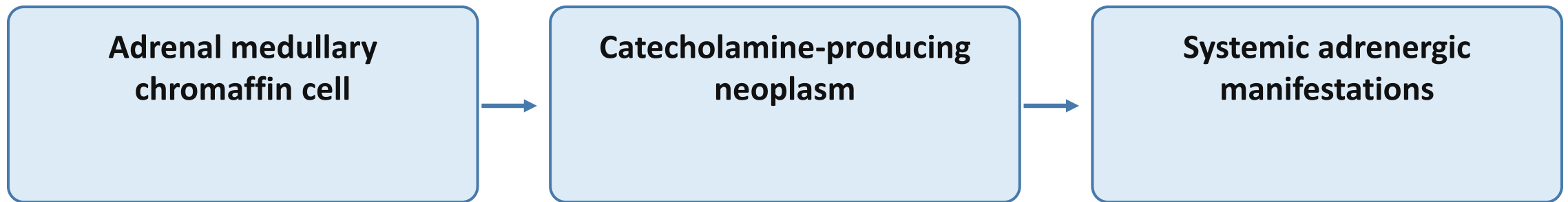
Other MTC peptides may cause paraneoplastic effects

Secretory product	Illustrative consequence
Calcitonin	Useful diagnostic / follow-up biomarker
VIP	Secretory diarrhea in some tumors
ACTH	Ectopic Cushing syndrome in some tumors
Other peptides	Variable syndromic presentations

Biomarker roles must not be conflated

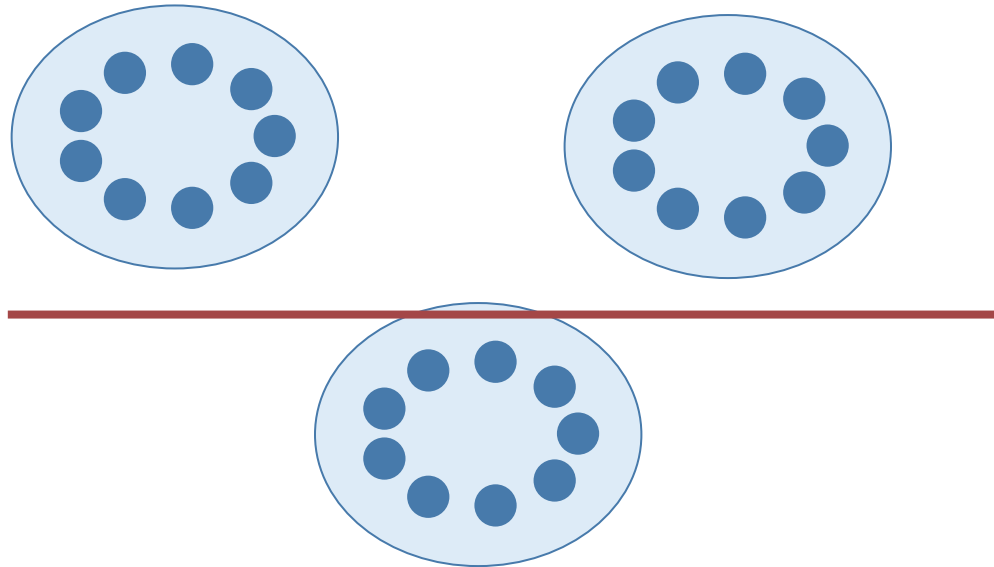
Test	Primary role	Does it establish inherited MEN2?
Germline RET	Molecular predisposition	Yes, if pathogenic / likely pathogenic
Calcitonin	MTC-associated disease marker	No
CEA	MTC-associated disease marker	No
Metanephrines	Pheochromocytoma biochemical testing	No

Pheochromocytoma arises from chromaffin cells



Pheochromocytoma: Classic zellballen nests

Chromaffin cell nests



Capillary-rich intervening stroma

Schematic — not a histologic specimen

Neoplastic chromaffin cells form nests separated by capillaries.

Chief cells have granular cytoplasm; Supporting sustentacular cells lie at the periphery.

Neuroendocrine-type chromatin may be visible; Architecture is variable.

Useful stains in pheochromocytoma

Target / component	Supportive immunophenotypic finding
Chief cells	Chromogranin and synaptophysin expression
Sustentacular cells	S-100 highlights supporting cells
Interpretation	Morphology + context; immunostaining alone does not define hereditary status

Histologic atypia cannot alone prove metastasis

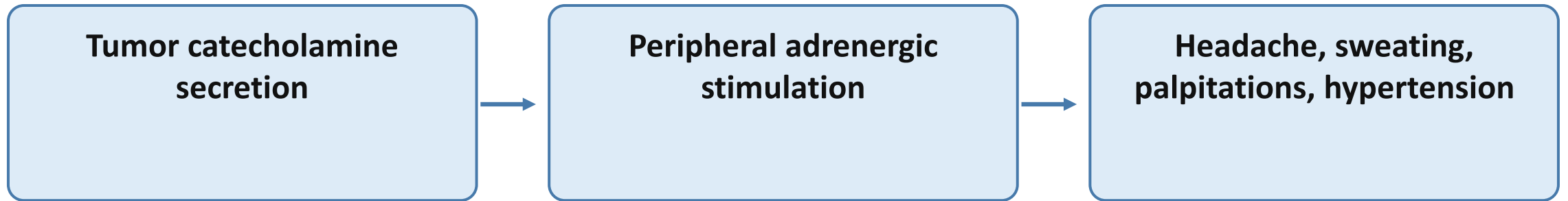
Pheochromocytoma may show pleomorphism without metastatic behavior.

Necrosis, mitoses, invasion, and spindle morphology do not individually settle biologic behavior.

That metastasis is the definitive evidence of malignant behavior.

Modern risk stratification adds contextual factors, not a single reliable histologic switch.

Catecholamine release explains episodic symptoms



A pheochromocytoma crisis can be life-threatening

Hypertension may be sustained, episodic, or both.

Palpitations, sweating, tremor, and apprehension may accompany attacks.

Acute catecholamine surges can precipitate cardiac arrhythmia or pulmonary edema.

Unrecognized disease creates major perioperative risk.

Pheochromocytoma: First establish biochemistry

Plasma free metanephrines or 24-hour urinary fractionated metanephrines are recommended tests.

Cross-sectional localization follows a supported biochemical suspicion.

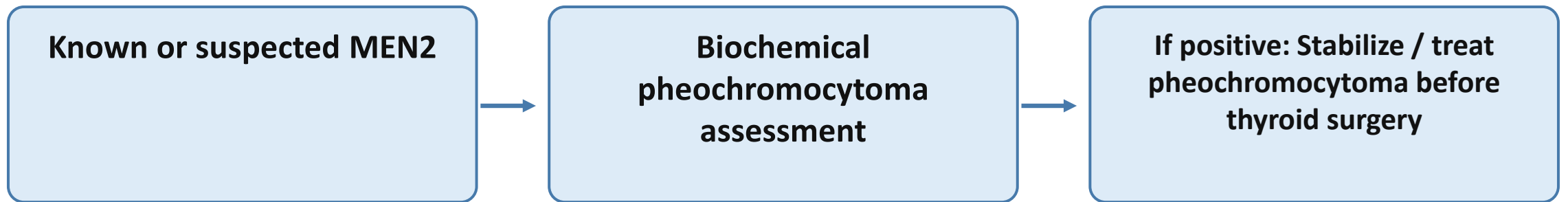
Biochemical investigation is appropriate even without classic episodic hypertension.

Screen for functioning pheochromocytoma before any planned operation in an MEN2 patient.

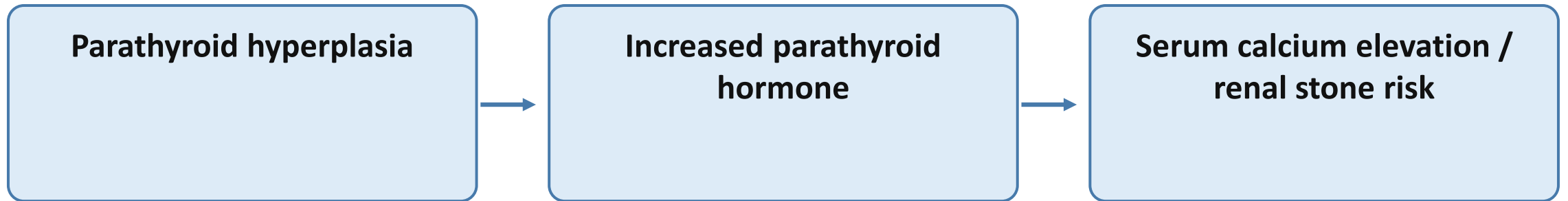
Other inherited pheochromocytoma syndromes

Syndrome	Typical gene	Distinguishing association
MEN2	RET	Medullary thyroid carcinoma
VHL	VHL	Renal cell carcinoma; hemangioblastoma
NF1	NF1	Neurofibromatosis phenotype
Hereditary PGL/PCC	SDHx	Paraganglioma predisposition

The operative sequence prevents a catecholamine crisis



PTH overproduction explains MEN2A hypercalcemia



MEN2A parathyroid disease is not universal

Only a subset develops parathyroid proliferative lesions.

Hypercalcemia or nephrolithiasis may signal functional hyperparathyroidism.

Serum calcium is the key accessible biochemical screen.

The clinical pattern differs from MEN1, in which parathyroid disease dominates.

When to suspect hereditary MEN2

Medullary thyroid carcinoma at any age warrants consideration of inherited RET risk.

Multifocal or bilateral medullary lesions strengthen clinical suspicion.

Pheochromocytoma combined with medullary carcinoma is strongly suggestive.

Mucosal neuromas or a positive family history may identify MEN2B risk.

Germline RET testing is central to diagnosis

A pathogenic / likely pathogenic germline RET variant establishes molecular MEN2.

The result clarifies phenotype and cascade-testing eligibility.

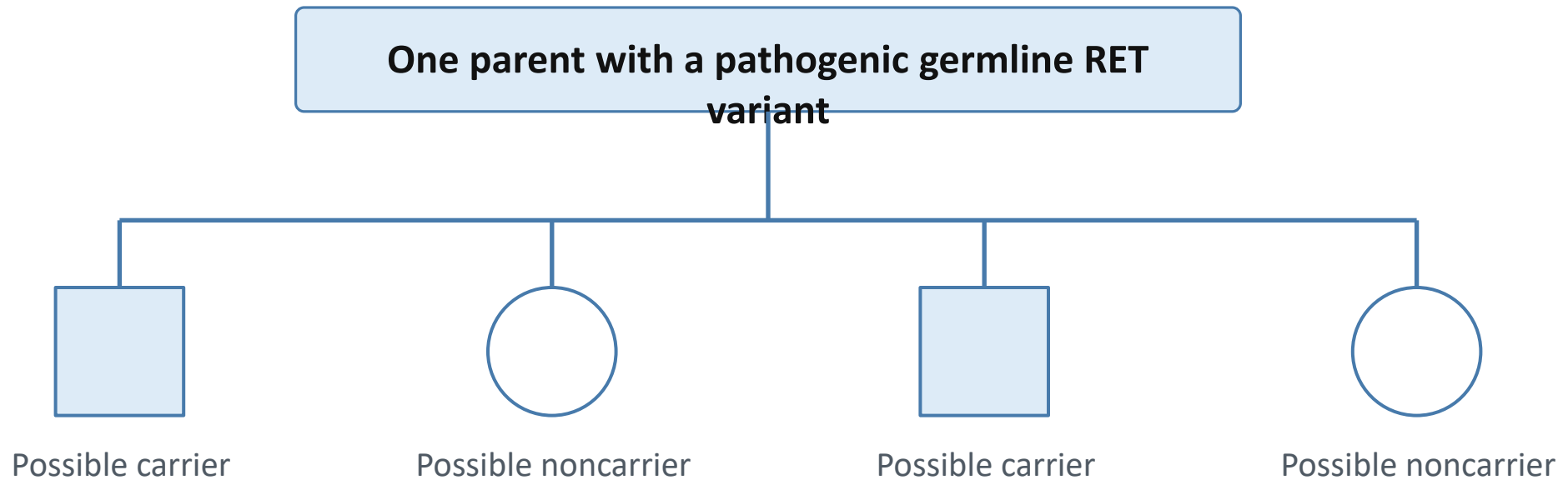
Apparently sporadic medullary carcinoma may still carry a germline variant.

Somatic-only RET tumor changes should not be equated with inherited disease.

An uncertain RET variant is not a diagnosis

Molecular result	Interpretive principle
Pathogenic / likely pathogenic germline RET	Clinically actionable hereditary predisposition
Variant of uncertain significance	Does not establish or exclude MEN2
Tumor-only somatic RET	Does not prove heritable susceptibility
Negative germline study	Interpret in clinical and family context

Cascade testing changes the family risk map



Each child has a 50% genetic risk; These illustrative offspring do not represent observed family outcomes.

Early thyroidectomy is preventive, not reactive

The rationale is intervention before C-cell neoplasia becomes invasive and advanced.

Germline RET genotype and clinical evaluation inform the recommended timing.

Children with high-risk variants may require very early specialist assessment.

Surgical planning also requires evaluation for coexisting pheochromocytoma.

Surveillance targets three separate organ risks

Target	Typical biochemical assessment	Purpose
MTC	Calcitonin; CEA after thyroidectomy	Detect persistent or recurrent disease
Pheochromocytoma	Plasma or urinary metanephrines	Identify potentially dangerous catecholamine-producing tumors
MEN2A parathyroid	Corrected / ionized calcium	Detect primary hyperparathyroidism

Long-term follow-up persists after thyroidectomy

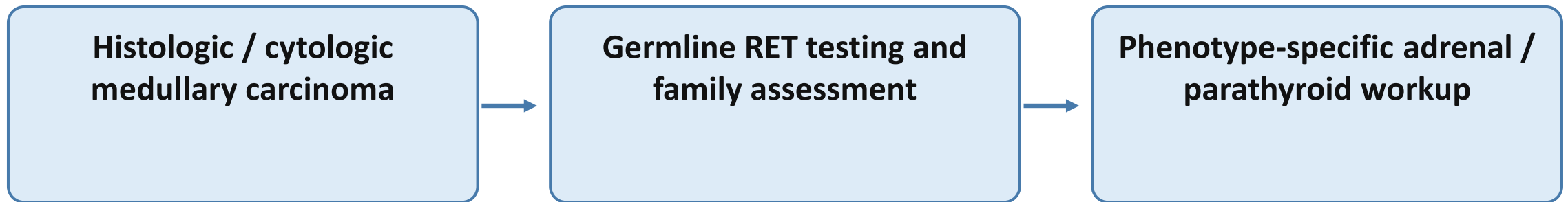
Thyroid removal reduces the risk of future primary medullary carcinoma when appropriately timed.

Calcitonin and CEA are monitored to evaluate persistent / recurrent disease as relevant.

RET carriers still require phenotype-appropriate adrenal screening.

Family cascade testing remains a separate prevention task.

Diagnostic sequence for a newly identified MTC



Clinical case: Oral neuromas and a thyroid lesion

CASE STEM

A child has thickened lips, tongue mucosal nodules, and a thyroid lesion.

The body habitus is elongated; A family history is unavailable.

What inherited syndrome and molecular mechanism should be prioritized?

Apply phenotype → mechanism → immediate clinical priority

Case interpretation: A MEN2B clinical pattern

The combined neuroma and body-habitus phenotype is more specific than either alone.

Early medullary carcinoma makes urgent specialist evaluation appropriate.

Confirm with germline RET testing; Phenotype alone does not specify the sequence variant.

Evaluate the adrenal catecholamine risk before invasive procedures.

Clinical case: Thyroid carcinoma plus adrenal tumors

CASE STEM

A young adult has medullary thyroid carcinoma and bilateral adrenal masses.

Episodes of palpitations, sweating, and labile blood pressure are reported.

What immediate presurgical investigation has priority, and why?

Apply phenotype → mechanism → immediate clinical priority

Case interpretation: Sequence governs safety

The endocrine tumor combination strongly suggests RET-associated MEN2.

Adrenal masses plus adrenergic symptoms raise concern for pheochromocytoma.

Catecholamine excess can provoke perioperative cardiovascular crisis.

Secure adrenal assessment and appropriate management before thyroid intervention.

Clinical case: Multiple medullary foci in one thyroid

CASE STEM

Thyroid histology shows several separate medullary carcinoma nodules.

Adjacent nonneoplastic thyroid contains clusters of proliferating C cells.

How does this change the etiologic assessment and family discussion?

Apply phenotype → mechanism → immediate clinical priority

Case interpretation: Precursor morphology matters

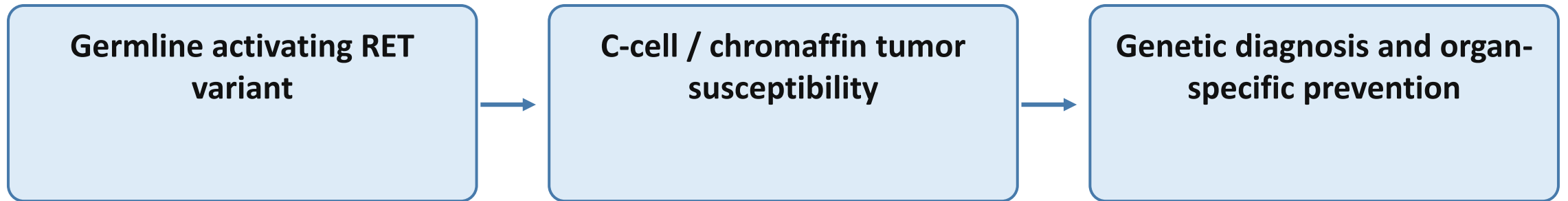
Multifocal medullary growth and C-cell hyperplasia are characteristic of syndromic tumors.

A negative family history does not rule out MEN2.

Germline RET testing may have major implications for asymptomatic relatives.

Calcitonin is a disease biomarker, not the inheritance test.

Integrating MEN2: From gene to prevention



MEN2: The five essential distinctions

MEN2 is an activating RET syndrome; MEN1 and MEN4 involve other genes.

MEN2A may include parathyroid disease; MEN2B has neuromas and marfanoid features.

Medullary carcinoma is the defining cancer; C-cell hyperplasia is a hereditary clue.

Assess pheochromocytoma before surgery to avoid catecholamine crisis.

Genotype-informed thyroid prevention and family testing improve risk detection.

Selected references

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026; Ch 24, pp. 992–993 and 1023–1026.

Eng C, Plitt G. Multiple Endocrine Neoplasia Type 2. GeneReviews. Updated August 10, 2023. NCBI Bookshelf NBK1257.

Brock P, Kirschner L. Multiple Endocrine Neoplasia Type 4. GeneReviews. September 21, 2023. NCBI Bookshelf NBK594826.

Note: current molecular-taxonomy distinctions on MEN4 and clinical surveillance are externally verified supplements, not unmarked quotations from Robbins.