

MEDULLARY THYROID CARCINOMA

C-cell neuroendocrine malignancy | Morphology, RET genetics, MEN2 and clinical correlation

Pathology teaching lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

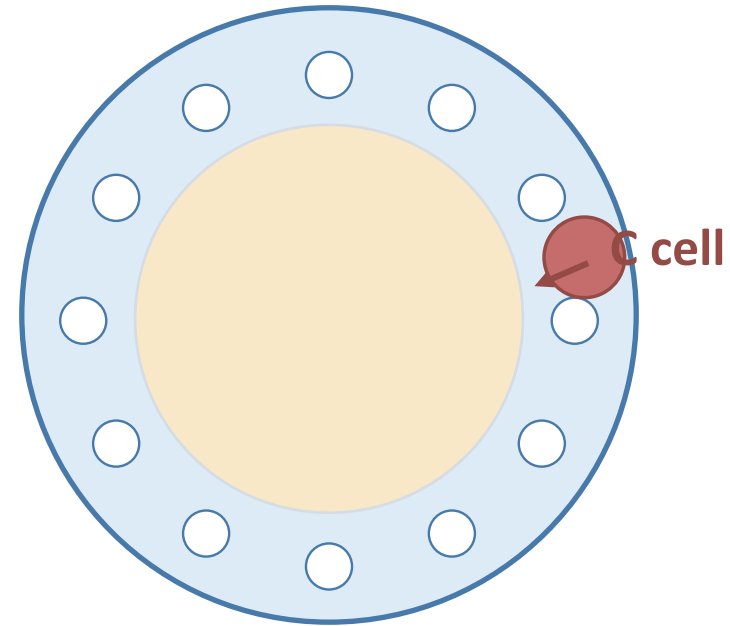
www.abusuraihsakhri.com

Learning outcomes

- Locate medullary carcinoma within the thyroid tumor spectrum.
- Relate RET activation and C-cell biology to hereditary and sporadic disease.
- Recognize the characteristic gross and microscopic morphology.
- Interpret calcitonin, CEA, MEN2 phenotypes, and inherited-risk clues.

A tumor of parafollicular C cells

- Medullary carcinoma arises from the thyroid parafollicular C-cell lineage.
- The neoplastic cells retain neuroendocrine differentiation.
- This lineage differs from the follicular cells forming most other thyroid carcinomas.



Colloid-filled follicle
Schematic

Two thyroid cell lineages, distinct tumor phenotypes

Follicular epithelial lineage	Parafollicular C-cell lineage
Follicular architecture and thyroid-hormone synthesis	Calcitonin secretion and neuroendocrine differentiation
Papillary and follicular carcinomas	Medullary carcinoma
Histologic and genetic classification differs	RET alterations are central to MTC biology

Recognizing the medullary phenotype

C-cell origin

Calcitonin production

Neuroendocrine cytology

Often stromal amyloid

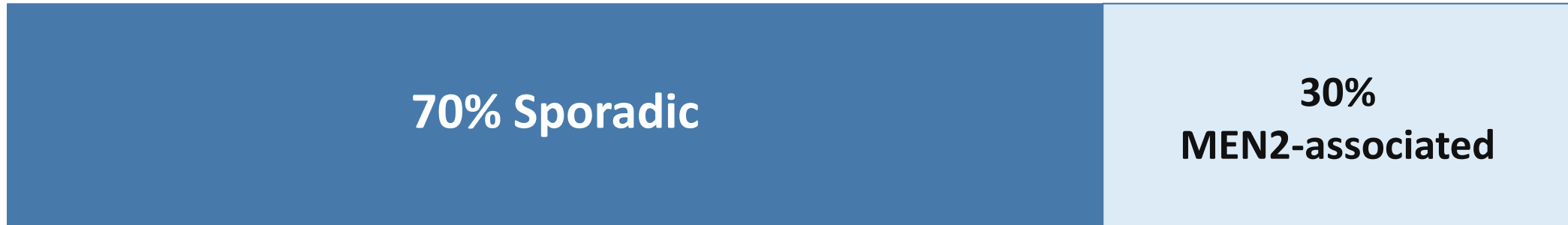
Where medullary carcinoma fits in thyroid cancer

~5%

Of thyroid carcinomas in the Robbins
overview

- The majority of other thyroid carcinomas derive from follicular epithelial cells.
- Despite its relative rarity, medullary carcinoma is clinically significant because of hereditary predisposition and endocrine secretion.

Most cases are sporadic; A substantial minority are inherited

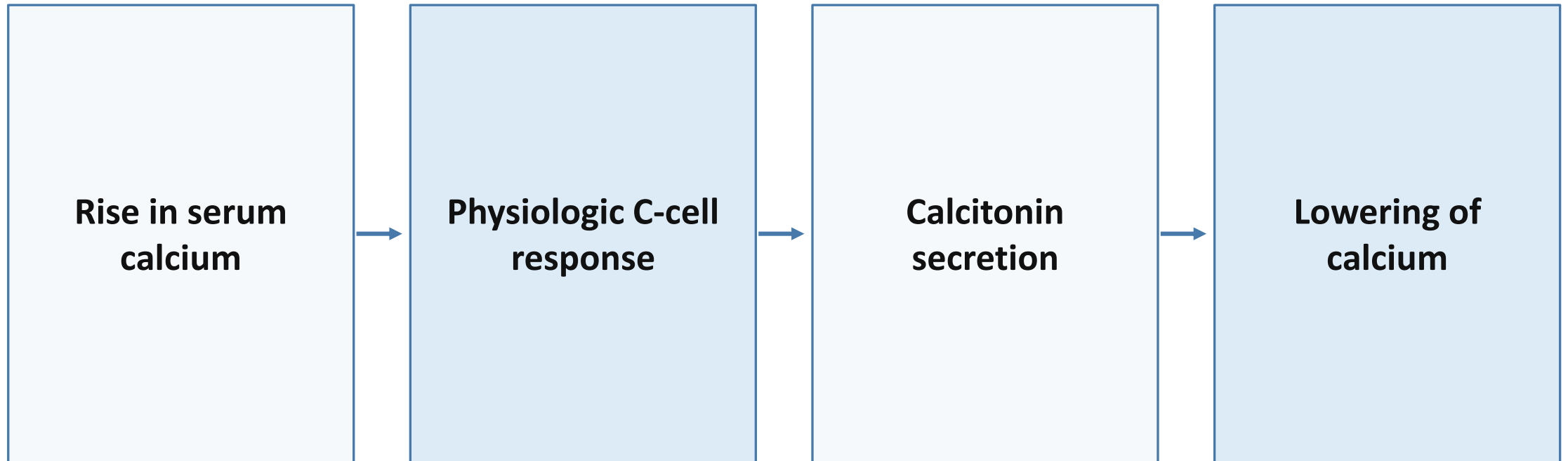


- Approximately 70% as sporadic.
- The remaining approximately 30% arise in a hereditary MEN2 setting.

Age at presentation reflects genetic context

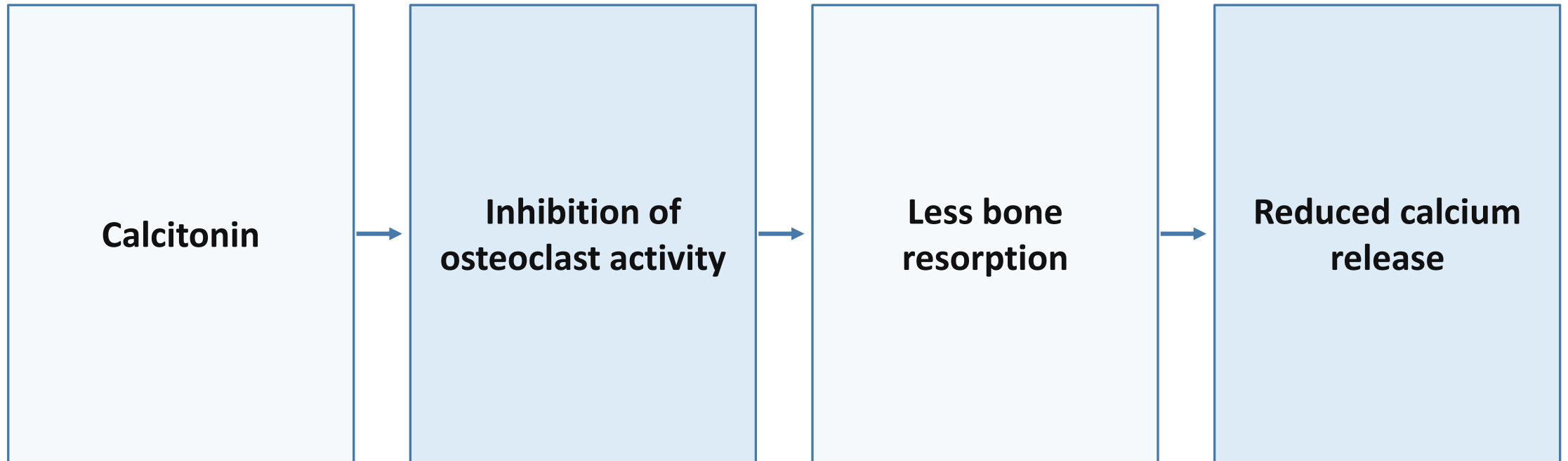
Sporadic MTC	MEN2-associated MTC
Usually a tumor of adulthood	Frequently occurs at a younger age
Peak incidence in the 40s–50s	May appear during the first decade
Often a solitary lesion	Often multifocal or bilateral

Calcitonin: The normal C-cell secretory product



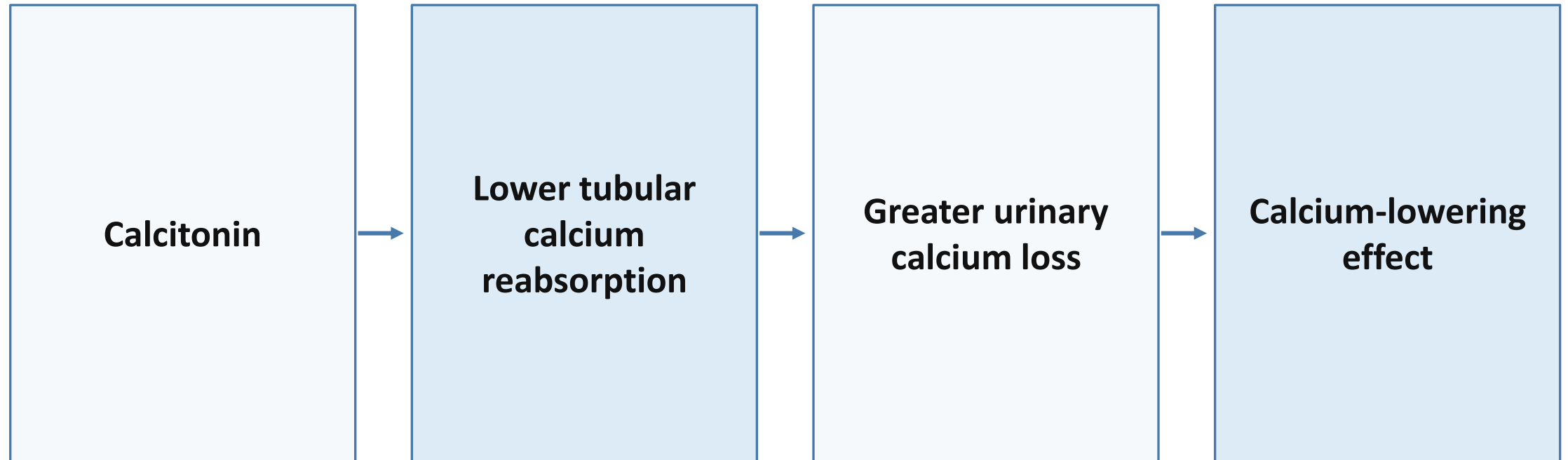
- Calcitonin is secreted in response to hypercalcemia.
- Its effects oppose calcium elevation through bone and renal pathways.

Calcitonin reduces osteoclast activity



- Osteoclast inhibition is a component of normal calcitonin action.
- The endocrine product remains a tissue-lineage marker in MTC.

Calcitonin affects renal calcium handling



- Renal tubular calcium transport as a normal calcitonin target.

Marked calcitonin does not imply prominent hypocalcemia

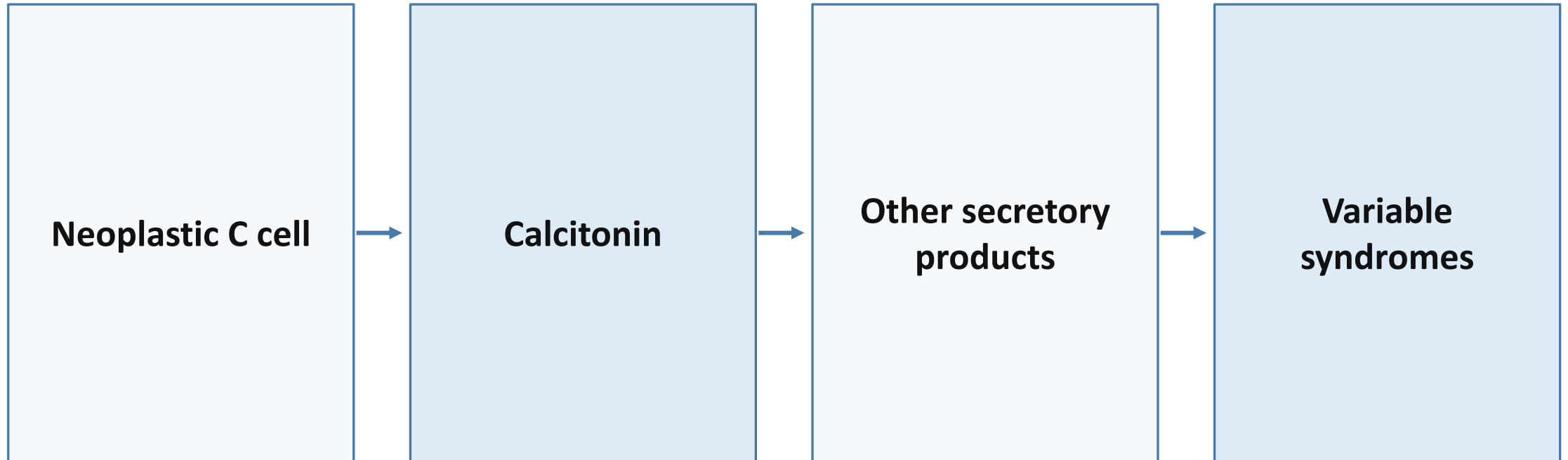
Tumor may secrete abundant calcitonin



Hypocalcemia is generally not a prominent clinical feature

- Biochemical marker abundance is not equivalent to a clinically overt hormone-effect syndrome.
- Do not infer symptomatic hypocalcemia solely from an elevated tumor marker.

MTC can produce additional endocrine products

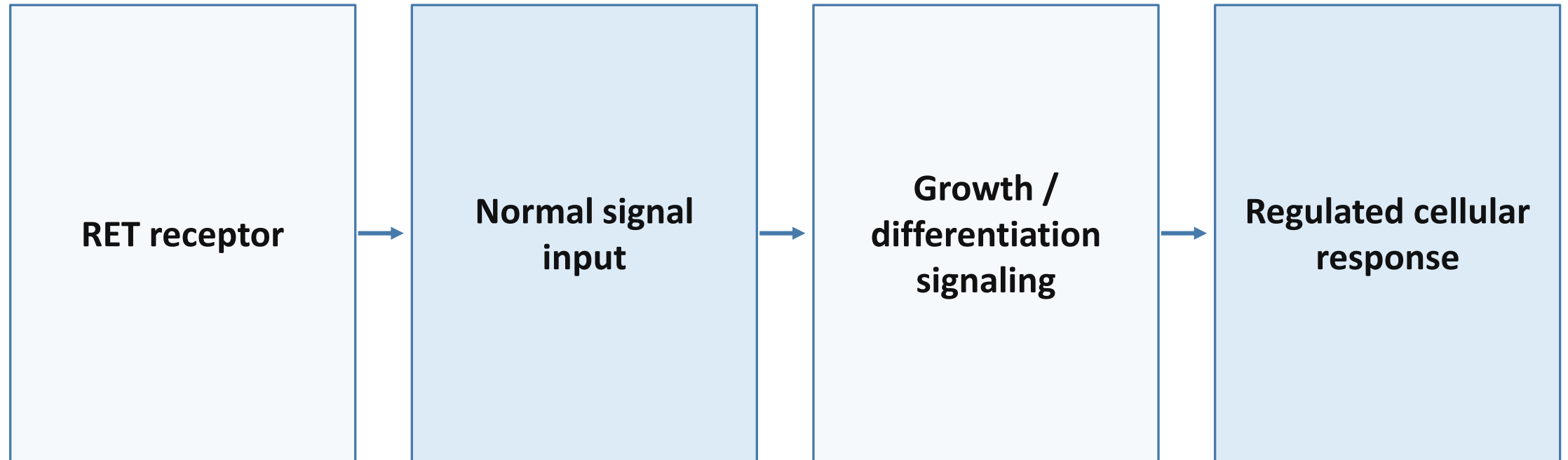


- Reported products include serotonin, corticotropin and vasoactive intestinal peptide (VIP).
- Different secreted products can explain distinct paraneoplastic presentations.

Secretory phenotype and local tumor growth are separate

Local tumor behavior	Endocrine secretion
Neck mass, dysphagia, hoarseness	Raised circulating calcitonin
Infiltration of surrounding tissue	Occasional diarrhea from VIP
Structural symptoms may dominate	Occasional Cushing syndrome from corticotropin

RET is a receptor tyrosine kinase proto-oncogene



- RET as a receptor tyrosine kinase.
- RET signaling participates in normal growth and differentiation.

Oncogenic RET mutations bypass normal regulation

Normal RET: Activation is ligand-dependent



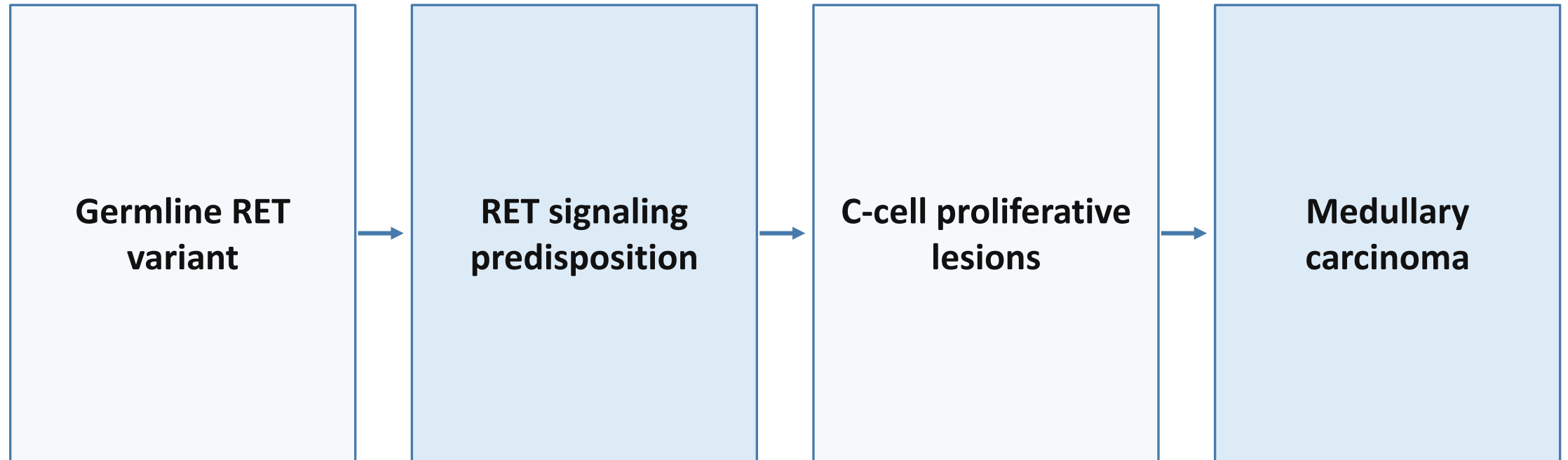
Mutant RET: Signaling can become constitutive

- Gain-of-function mutations activate oncogenic signaling.
- This is central to MEN2-associated tumorigenesis.

RET activation in sporadic medullary carcinoma

- Activating RET point mutations participate in sporadic tumorigenesis.
- The altered gene is present in the neoplastic cells rather than necessarily inherited.
- A sporadic clinical presentation does not reliably exclude a germline RET variant.

Germline RET mutations confer inherited susceptibility



- MEN2-associated MTC develops in a hereditary RET mutation context.
- Early recognition permits preventive management of mutation carriers.

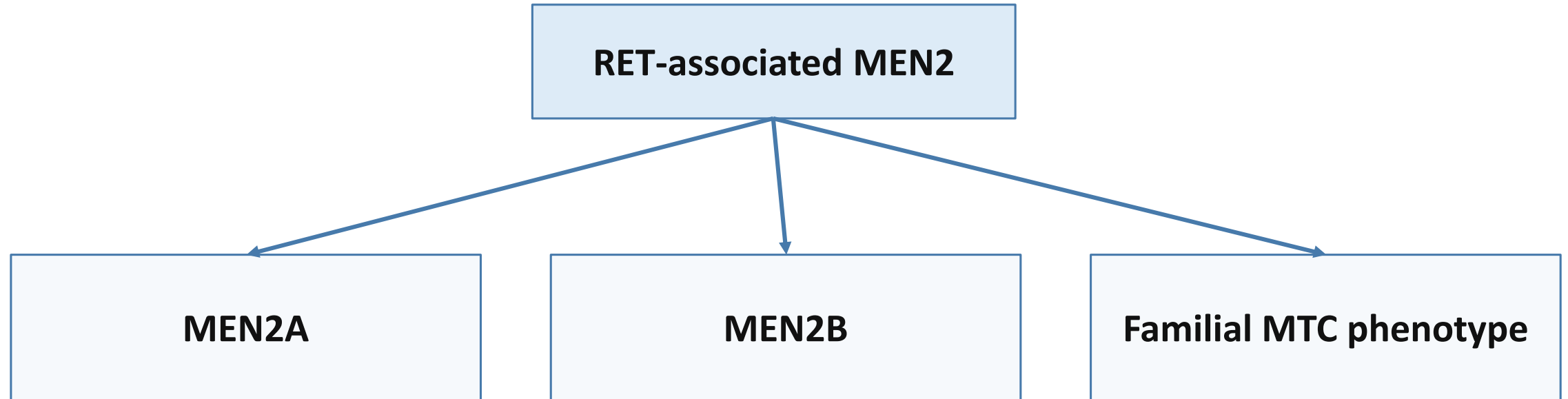
Somatic and germline RET alterations are not interchangeable

Somatic RET alteration	Germline RET alteration
Acquired by tumor-cell lineage	Present from conception across tissues
Typically informs tumor biology	Defines inherited predisposition
Does not itself establish family risk	Has implications for relatives and screening

Molecular results must be interpreted with clinical context

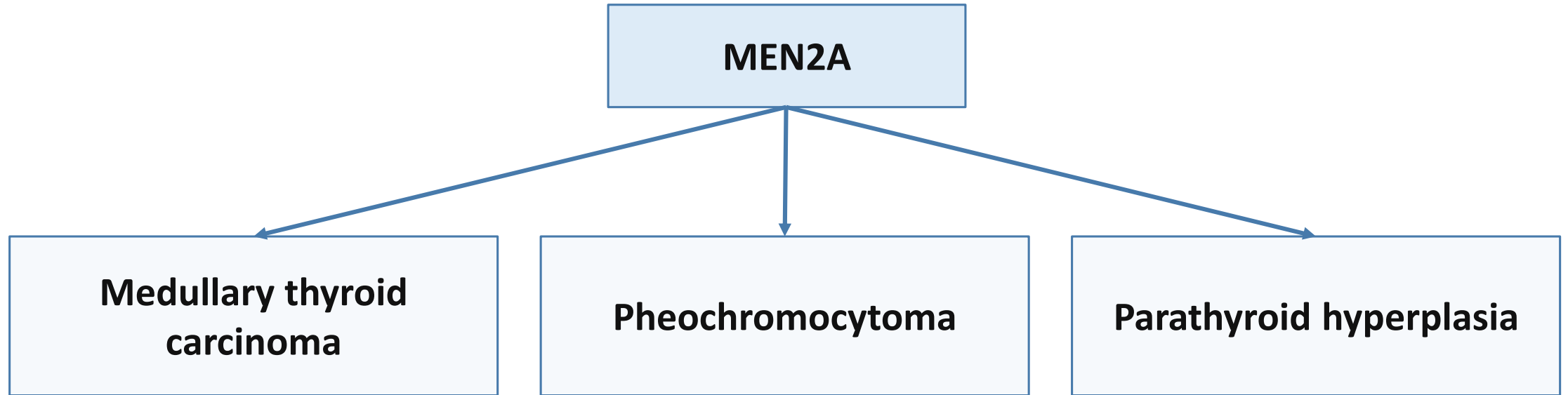
- A thyroid tumor with RET activation may be sporadic or hereditary.
- An apparently negative family history does not exclude inherited risk.
- Germline assessment addresses a different question from tumor-only mutation testing.

MEN2: A hereditary endocrine neoplasia spectrum



- The clinical constellation determines the syndrome designation.
- Medullary thyroid carcinoma is the unifying thyroid manifestation.

MEN2A links three endocrine compartments



- Classical MEN2A is also called Sipple syndrome.
- The thyroid tumor is typically multicentric.

MTC in MEN2A is frequently multicentric

- Medullary carcinomas arise in almost all affected individuals, as.
- Multiple foci and C-cell hyperplasia commonly coexist in the thyroid.
- The multiplicity provides a morphologic clue to hereditary predisposition.

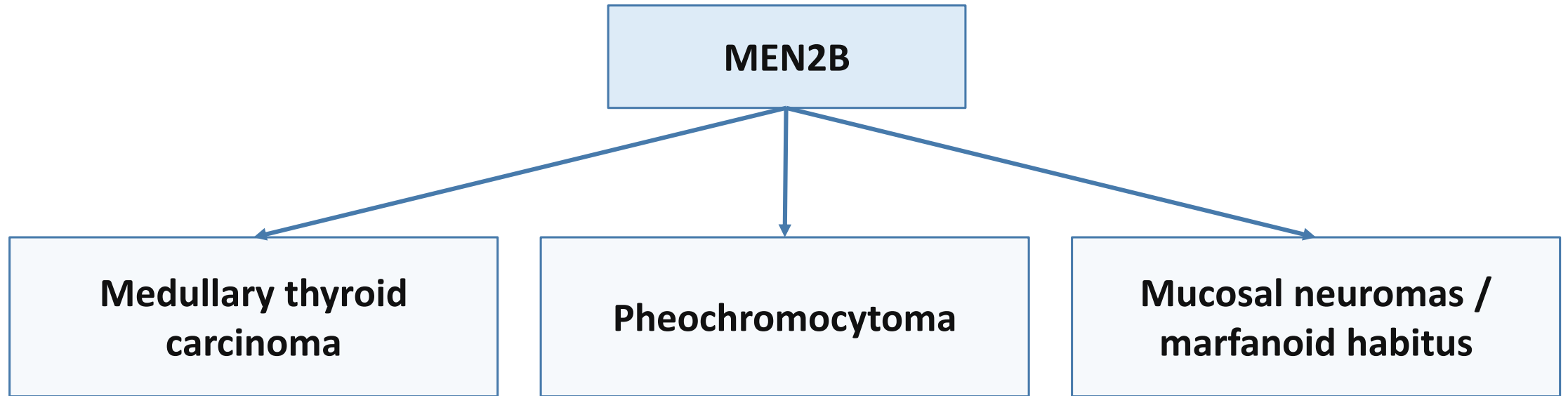
Pheochromocytoma is part of the MEN2A phenotype

- Pheochromocytoma in about 40%–50% of MEN2A patients.
- Pheochromocytomas can be bilateral and sometimes extra-adrenal.
- A thyroid MTC diagnosis warrants attention to the broader MEN2 phenotype.

Parathyroid disease distinguishes MEN2A from MEN2B

- MEN2A may feature parathyroid hyperplasia and hypercalcemia.
- Parathyroid manifestations in approximately 10%–20%.
- MEN2B does not characteristically include primary hyperparathyroidism.

MEN2B combines MTC with extra-thyroid stigmata



- MEN2B-associated MTC may be particularly aggressive.
- Neuromas or ganglioneuromas occur across several sites.

MEN2B phenotype: Neuromas and marfanoid features

- Neuromas or ganglioneuromas may involve oral mucosa, skin, eyes, respiratory tract, and gut.
- Marfanoid body habitus includes elongated skeletal proportions.
- The nonthyroid phenotype can suggest the diagnosis before an obvious neck mass.

MEN2A versus MEN2B

MEN2A	MEN2B
MTC and pheochromocytoma	MTC and pheochromocytoma
Parathyroid hyperplasia may occur	Primary hyperparathyroidism usually absent
C-cell hyperplasia common	MTC often more aggressive
RET gain-of-function mutations	Distinct RET activating mutation spectrum

MEN1 and MEN2 should not be conflated

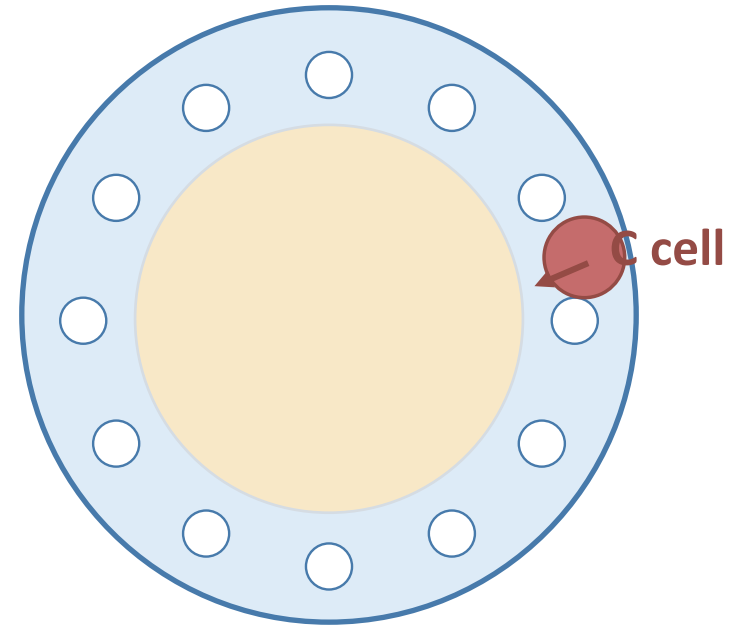
MEN1 syndrome	MEN2 syndrome
MEN1 tumor-suppressor gene	RET proto-oncogene activation
Parathyroid, pancreatic, pituitary tumors	Medullary thyroid carcinoma is central
Different genetic and endocrine spectrum	Pheochromocytoma / neuroma phenotypes

Familial MTC may lack overt extra-thyroid manifestations

- Some families have inherited RET variants with apparently isolated medullary carcinoma.
- The absence of obvious pheochromocytoma or parathyroid disease does not remove hereditary risk.
- Robbins recommends examining the wider MEN2 phenotype carefully.

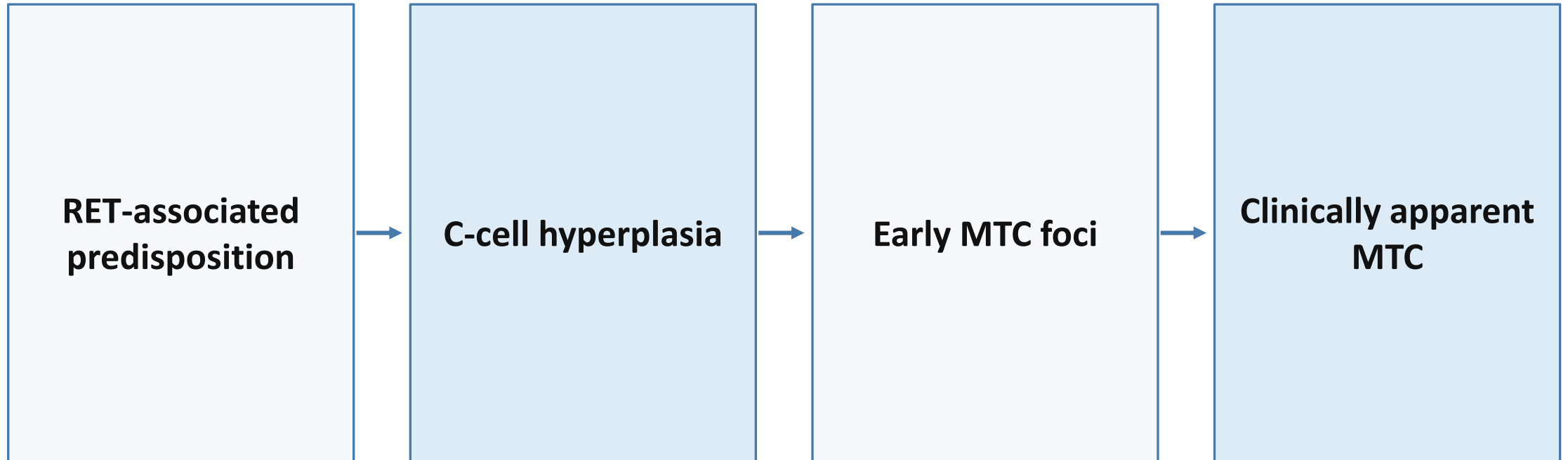
C-cell hyperplasia is an inherited-risk clue

- C-cell hyperplasia often accompanies syndromic medullary carcinoma.
- It is considered a precursor lesion in the familial setting.
- It is usually absent in purely sporadic lesions.



Colloid-filled follicle
Schematic

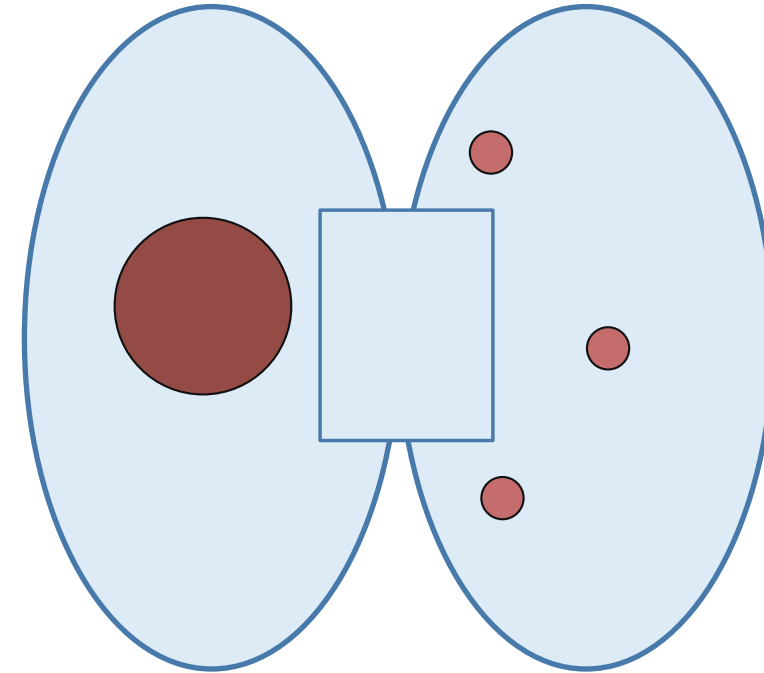
A stepwise C-cell lesion model



- The schematic illustrates the hereditary setting.
- This does not define universal temporal thresholds for every tumor.

The contralateral lobe can contain a diagnostic clue

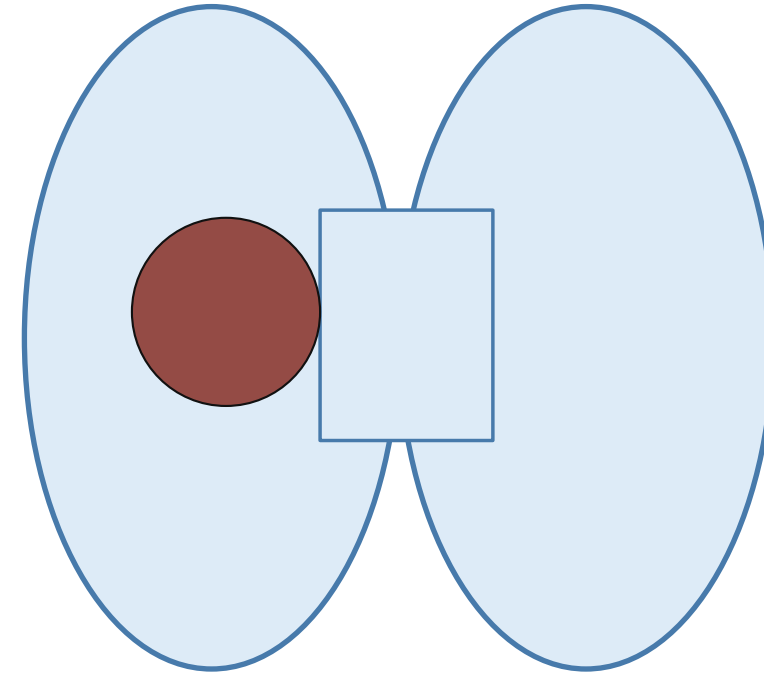
- Clusters of conspicuous C cells away from the dominant tumor suggest a field predisposition.
- Check the opposite thyroid lobe, not only the dominant lesion.



Simplified thyroid schematic

Sporadic MTC often forms a solitary nodule

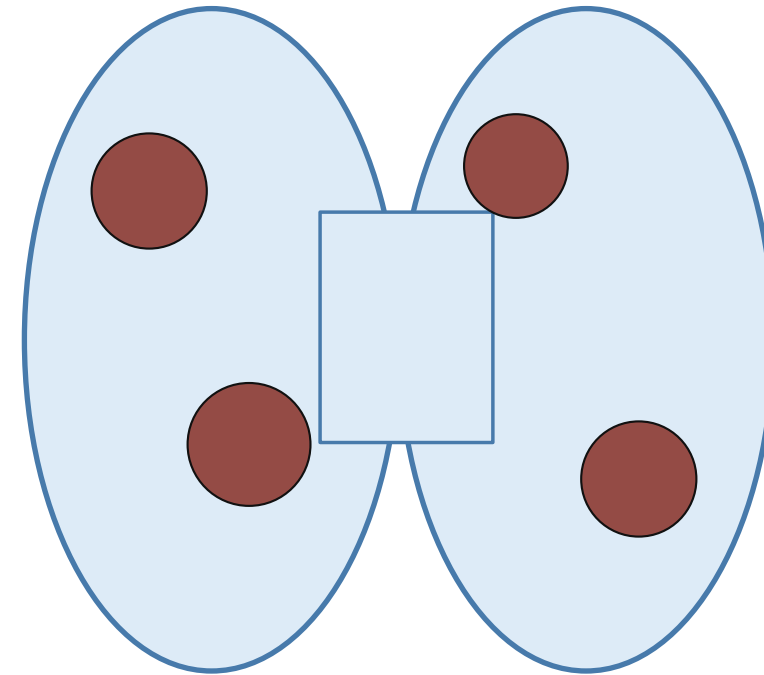
- A single dominant thyroid nodule is characteristic of sporadic disease.
- Clinical and genetic evaluation is still necessary because morphology is not absolute.



Simplified thyroid schematic

Hereditary MTC is often bilateral or multifocal

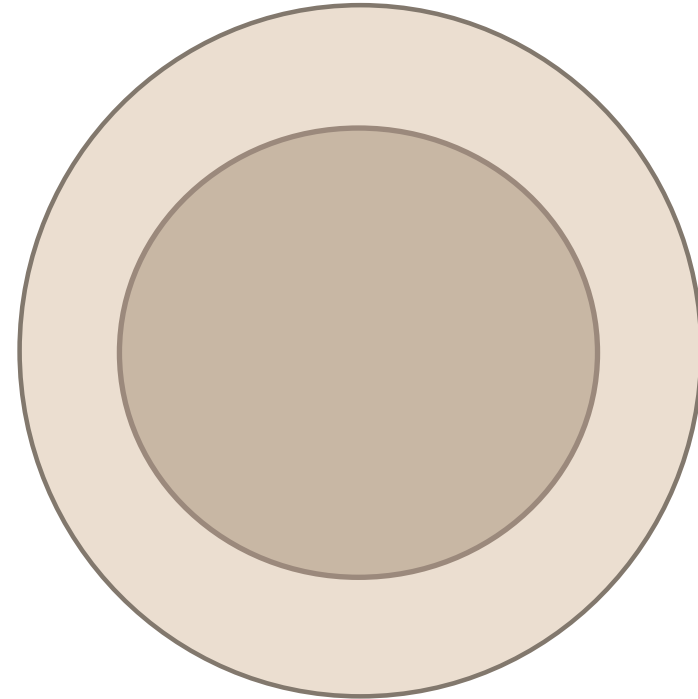
- Multicentricity and bilaterality support a hereditary context.
- Search the intervening and contralateral parenchyma for C-cell hyperplasia.



Simplified thyroid schematic

Gross appearance: Firm, pale gray-to-tan tumor

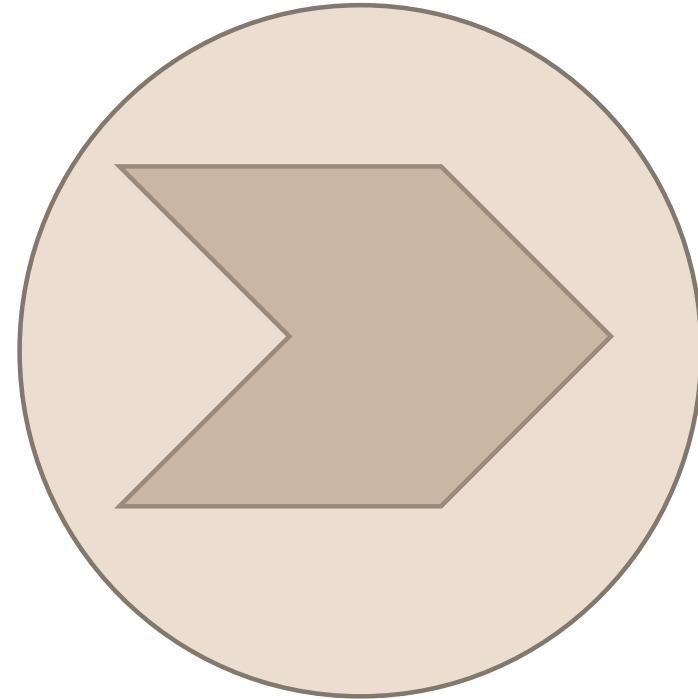
- The cut surface is typically pale gray to tan.
- Infiltrative borders may be apparent; Tumors often lack a distinct connective-tissue capsule.



Gross appearance — schematic

Infiltrative architecture matters more than encapsulation

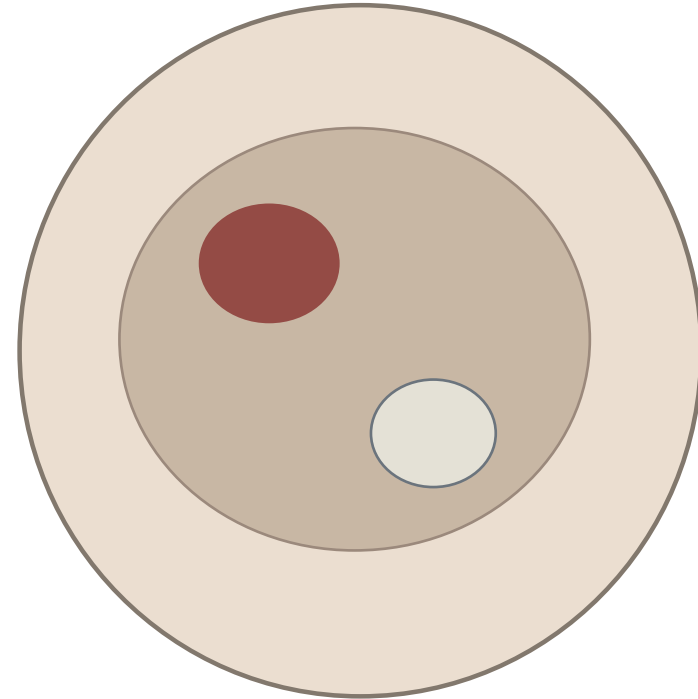
- MTC is usually infiltrative rather than cleanly encapsulated.
- Larger tumors may extend through the thyroid capsule.



Gross appearance — schematic

Large lesions may show hemorrhage and necrosis

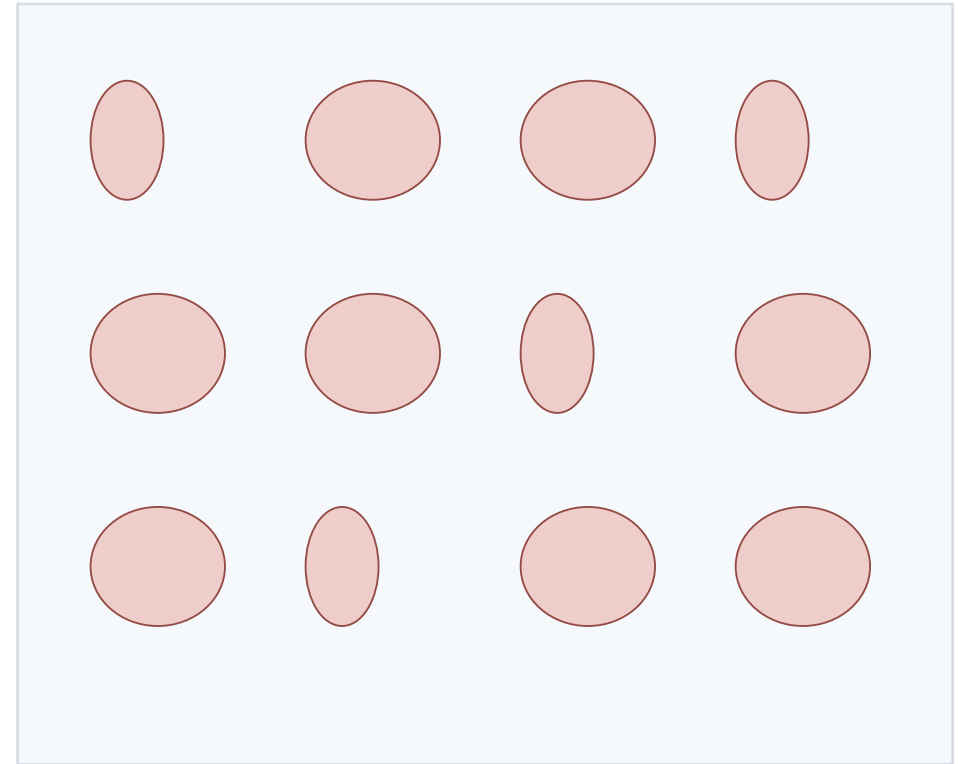
- Hemorrhage and necrosis can occur in larger neoplasms.
- These are gross changes, not required diagnostic criteria.



Gross appearance — schematic

Microscopy: A neuroendocrine-appearing population

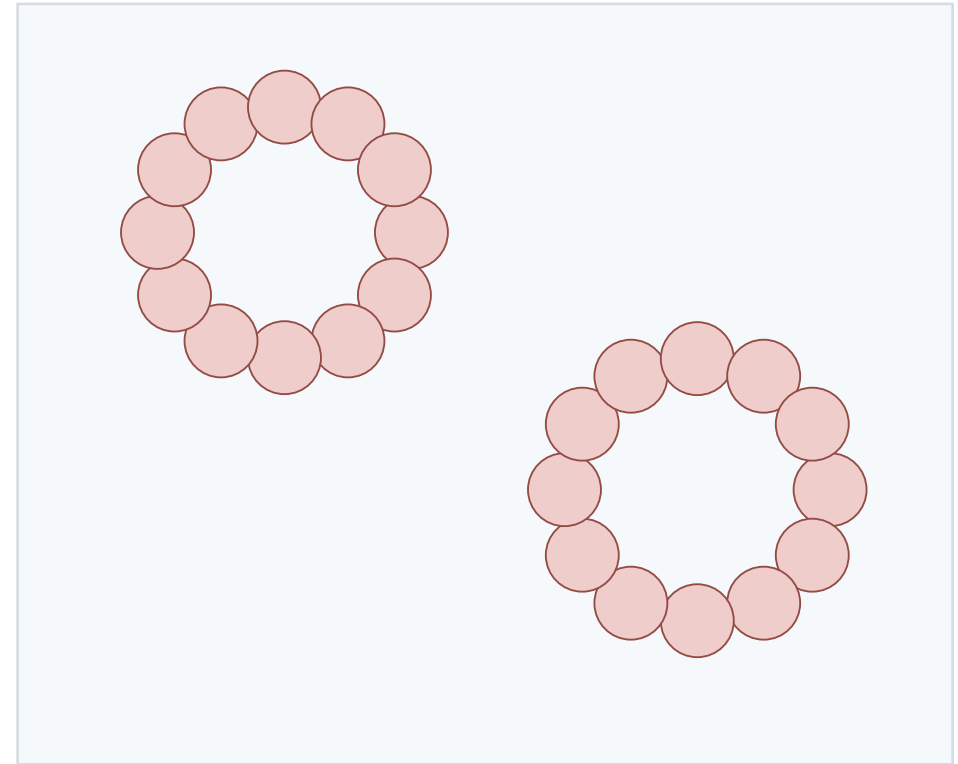
- Cells range from polygonal to spindle-shaped.
- Cytologic variation does not eliminate a shared C-cell lineage.



Schematic; Not a histologic specimen

Nested arrangement is a typical growth pattern

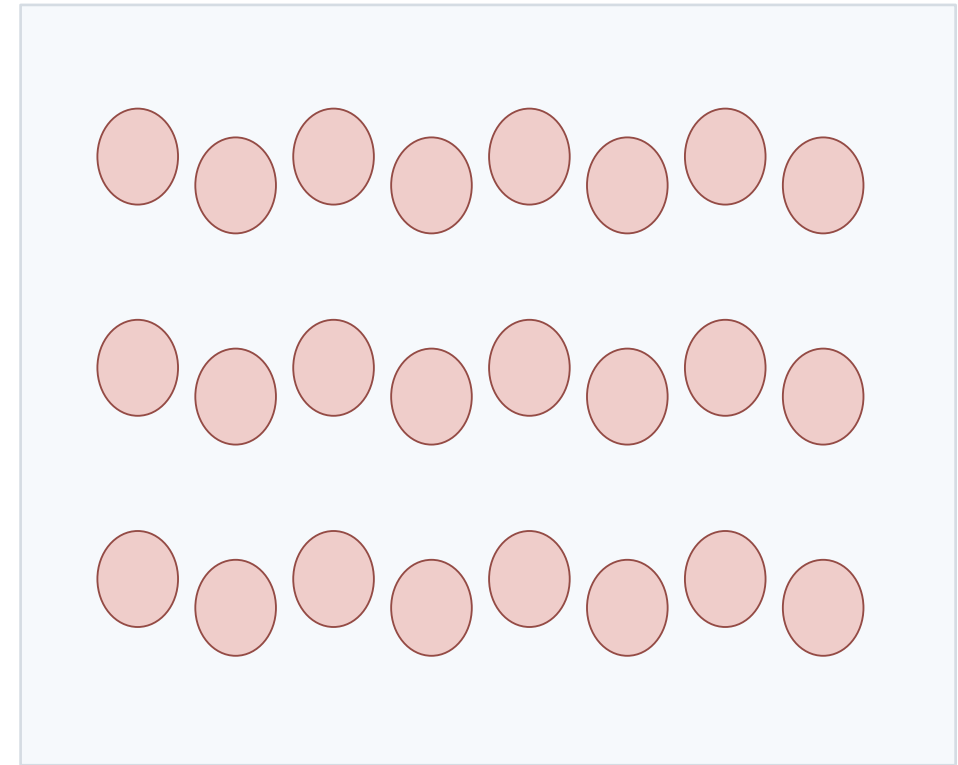
- Tumor cells are often arranged in compact nests.
- Intervening stroma may contain characteristic amyloid.



Schematic; Not a histologic specimen

Trabecular growth is also encountered

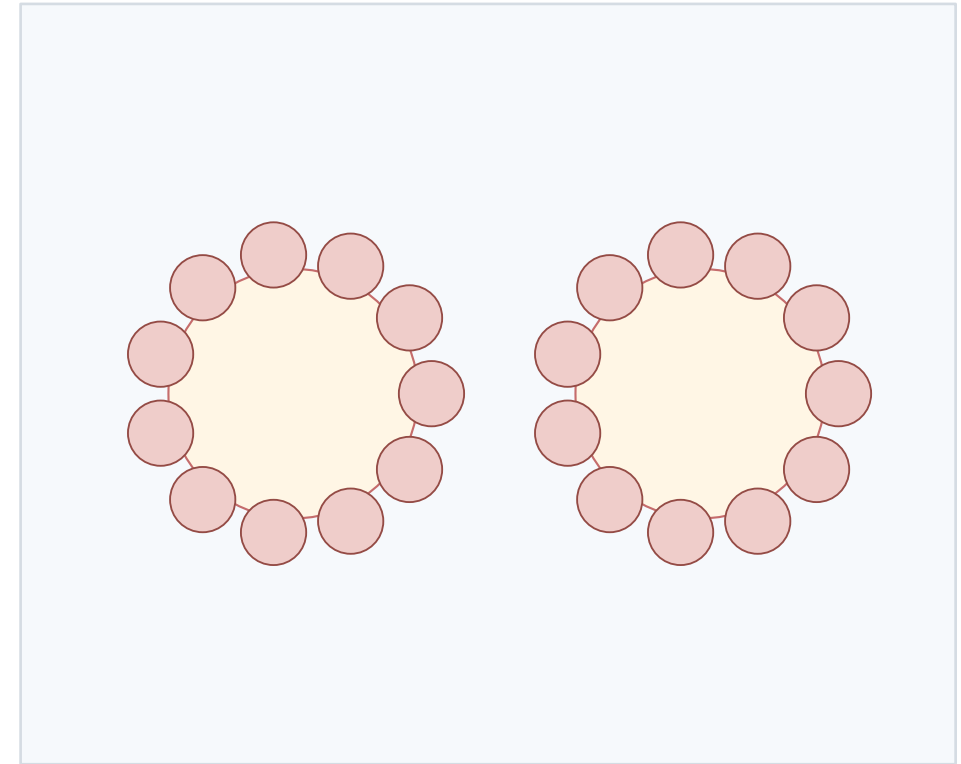
- Elongated ribbons or trabeculae may be present.
- The architectural spectrum requires integration with cytology and secretory phenotype.



Schematic; Not a histologic specimen

Follicle-like structures can occur in medullary carcinoma

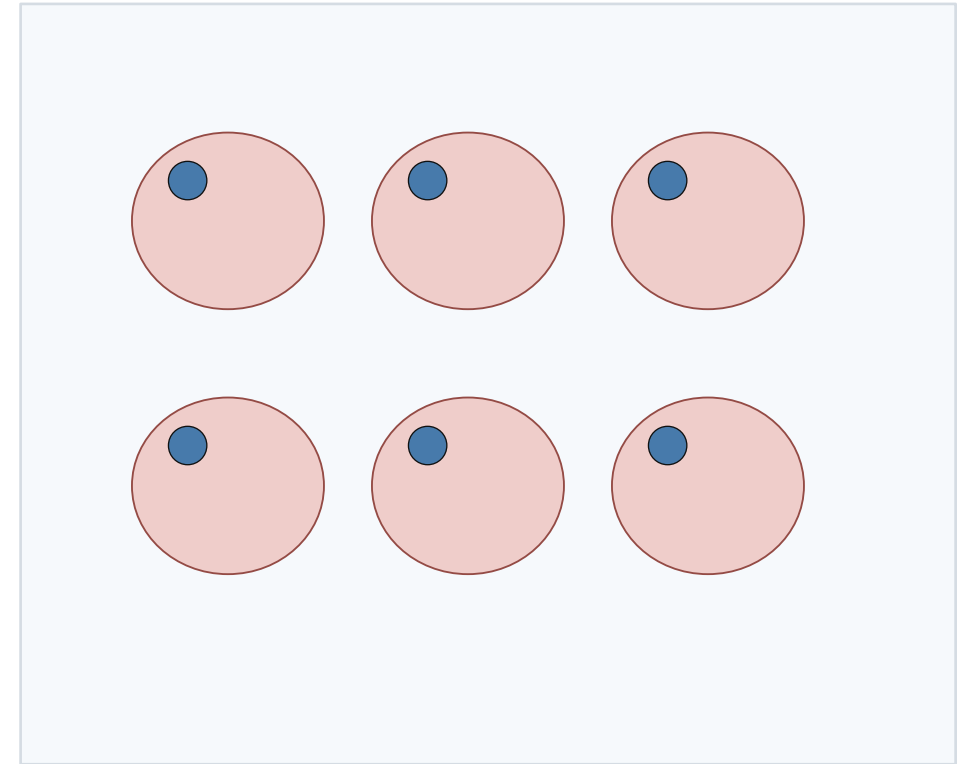
- MTC sometimes produces follicle-like structures.
- Architecture alone may therefore be misleading for cell-lineage assignment.



Schematic; Not a histologic specimen

Neuroendocrine chromatin supports recognition

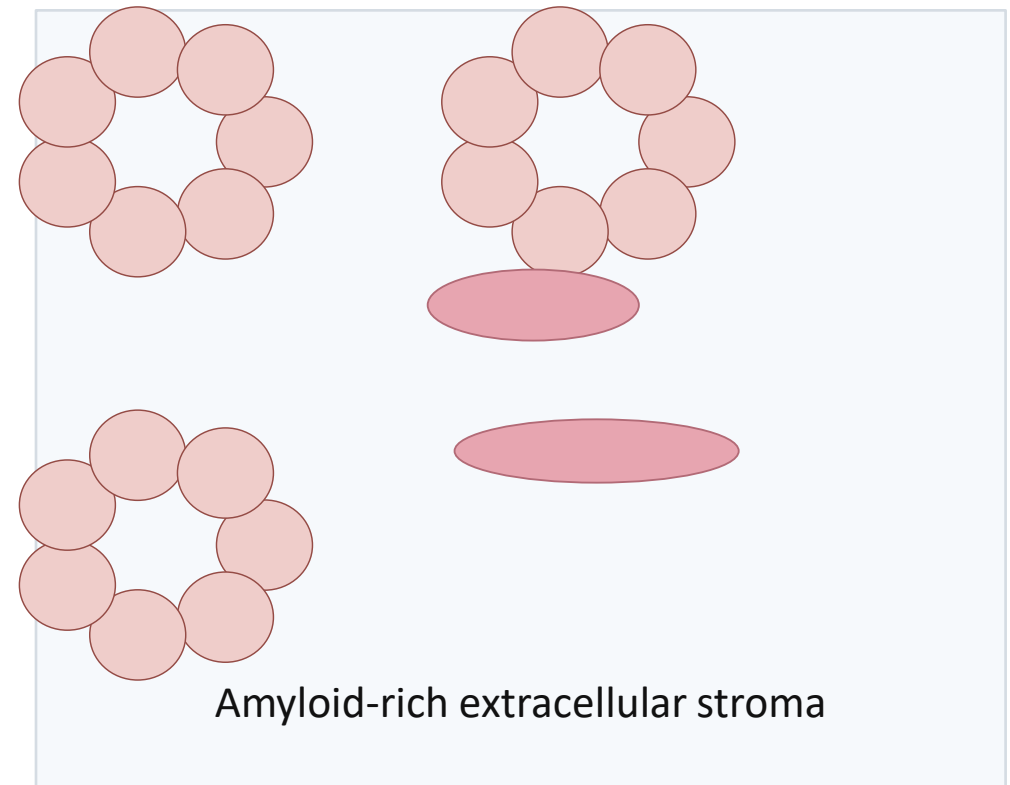
- Stippled nuclear chromatin and round nuclei.
- Nuclear findings support—not independently define—the diagnosis.



Schematic; Not a histologic specimen

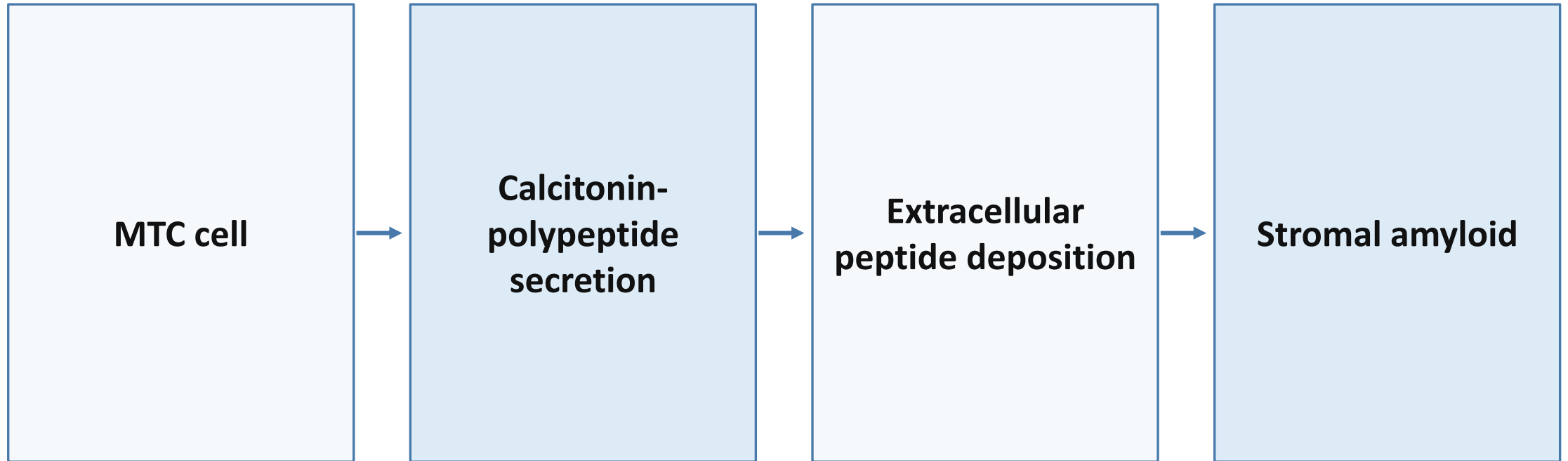
Stromal amyloid is a characteristic clue

- Pink, extracellular amorphous material can lie between tumor-cell nests.
- Amyloid is frequently present but not mandatory in every specimen.



Schematic; Not H&E

The amyloid is derived from calcitonin polypeptides



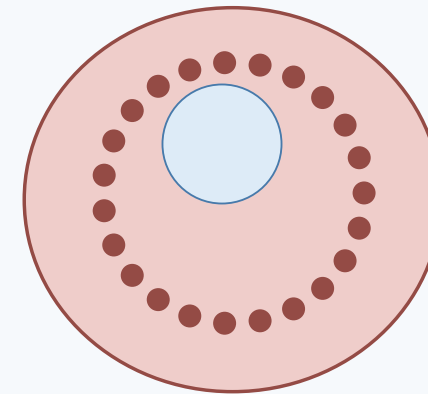
- The defining relation explains the association between calcitonin secretion and stromal amyloid.

Calcitonin is demonstrable in tumor cells and stroma

Neoplastic cells	Amyloid-rich stroma
Calcitonin by immunohistochemistry	Calcitonin can be demonstrated in associated amyloid
Corroborates C-cell neuroendocrine identity	Connects extracellular material to tumor secretion

Electron-dense secretory granules explain endocrine output

- Electron microscopy reveals membrane-bound, electron-dense granules.
- The granules store calcitonin and related secretory peptides.



Secretory granules

Schematic; Not a histologic specimen

Morphologic diagnosis combines several layers of evidence

C-cell phenotype

Variable nests or trabeculae

Neuroendocrine chromatin

Amyloid / calcitonin evidence

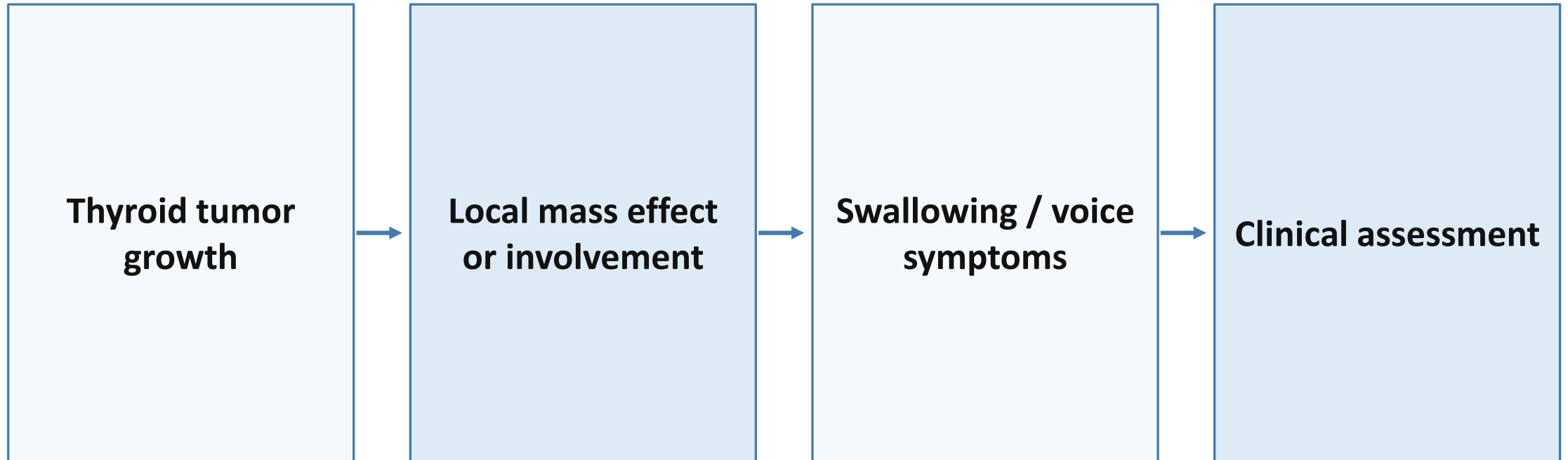
MTC differs from follicular-derived thyroid carcinomas

Follicular-derived carcinomas	Medullary carcinoma
Follicular epithelial lineage	Parafollicular C-cell lineage
Genetic context includes BRAF or RAS pathways	RET activation is prominent
Thyroid hormone lineage	Calcitonin-producing lineage
Papillary nuclear features or follicular invasion	Neuroendocrine cytology; Stromal amyloid

A neck mass is a common sporadic presentation

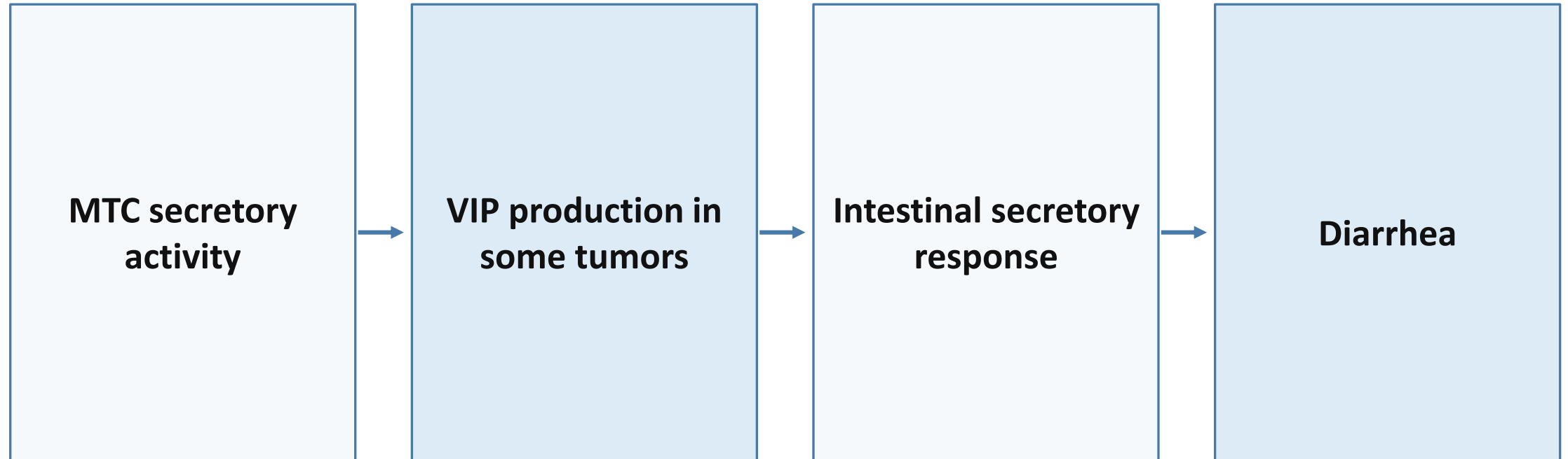
- Patients with sporadic MTC often present with a thyroid or neck mass.
- Some lesions are clinically silent until they enlarge.
- The clinical appearance alone is not sufficient to determine molecular or hereditary subtype.

Dysphagia and hoarseness reflect local effects



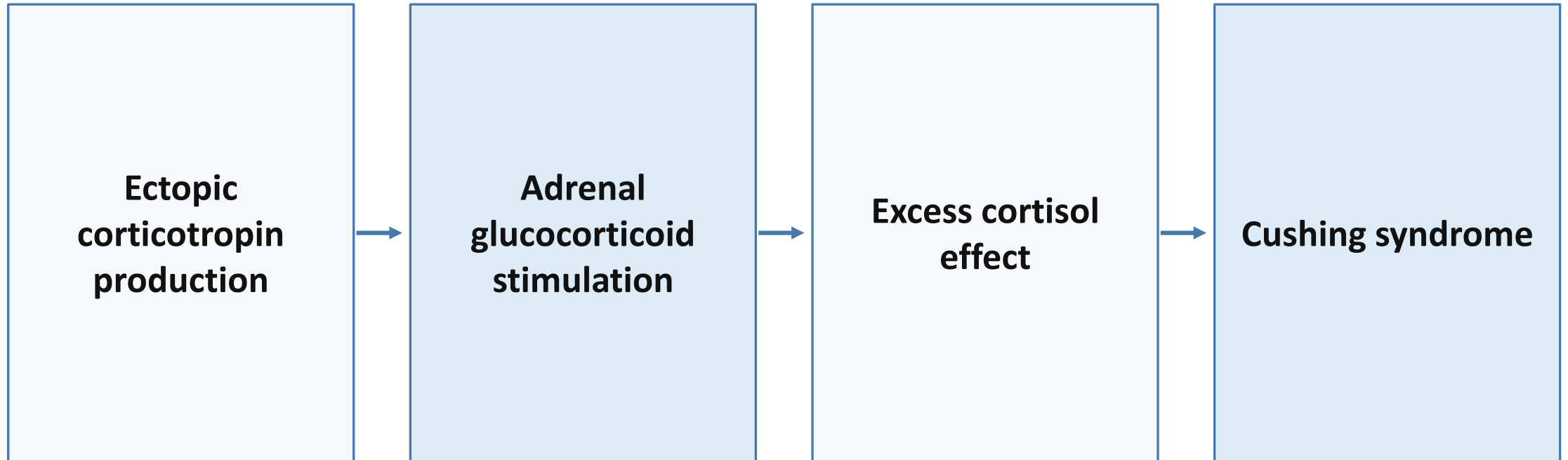
- Dysphagia and hoarseness may accompany a cervical mass.
- These symptoms reflect anatomic consequences rather than peptide secretion.

VIP secretion can produce a diarrheal syndrome



- Diarrhea can be a paraneoplastic clue to medullary carcinoma.
- Most tumors should not be assumed to produce this phenotype.

Corticotropin secretion may cause Cushing syndrome

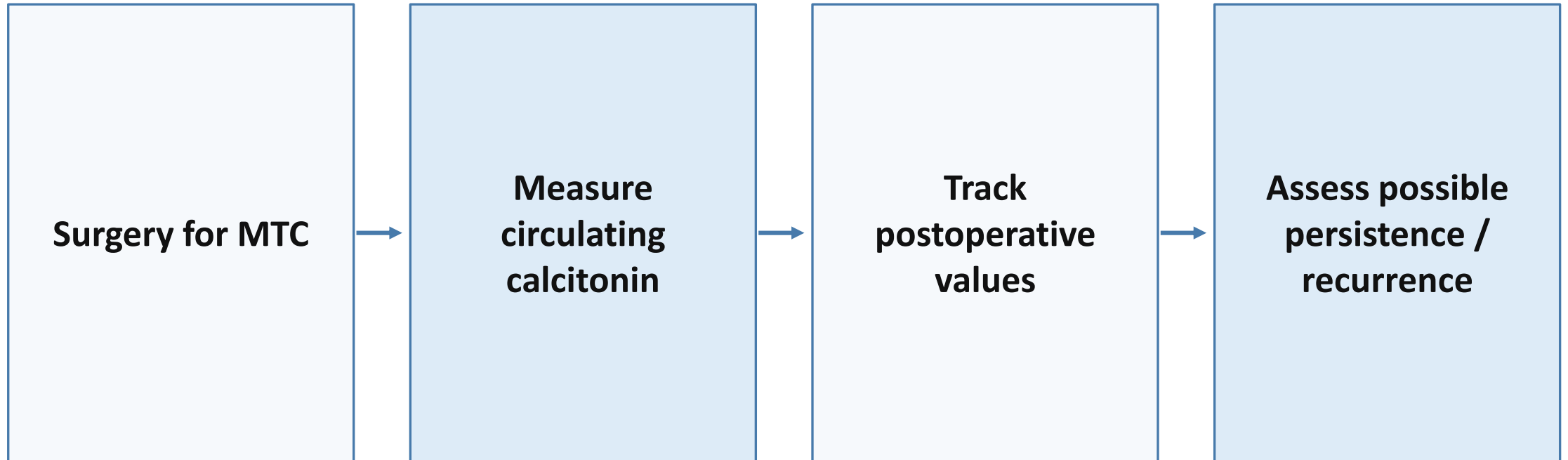


- The presentation is peptide-mediated rather than caused directly by the thyroid mass.

A calcitonin assay has diagnostic relevance

- Calcitonin is a core measurable product of differentiated C-cell tumors.
- Serum calcitonin as important in diagnosis.
- Interpret the laboratory result in the full clinical and pathologic context.

Calcitonin also supports postoperative surveillance



- The role of calcitonin in follow-up.
- Do not substitute unverified cutoffs or kinetics for clinical guidance.

CEA is a complementary tumor-associated marker

- MTC cells may release carcinoembryonic antigen (CEA).
- CEA contributes to presurgical estimation of disease burden.
- CEA is also helpful when calcitonin secretion is unusually absent.

Calcitonin-negative MTC is an important caveat

Typical phenotype: Calcitonin-producing tumor



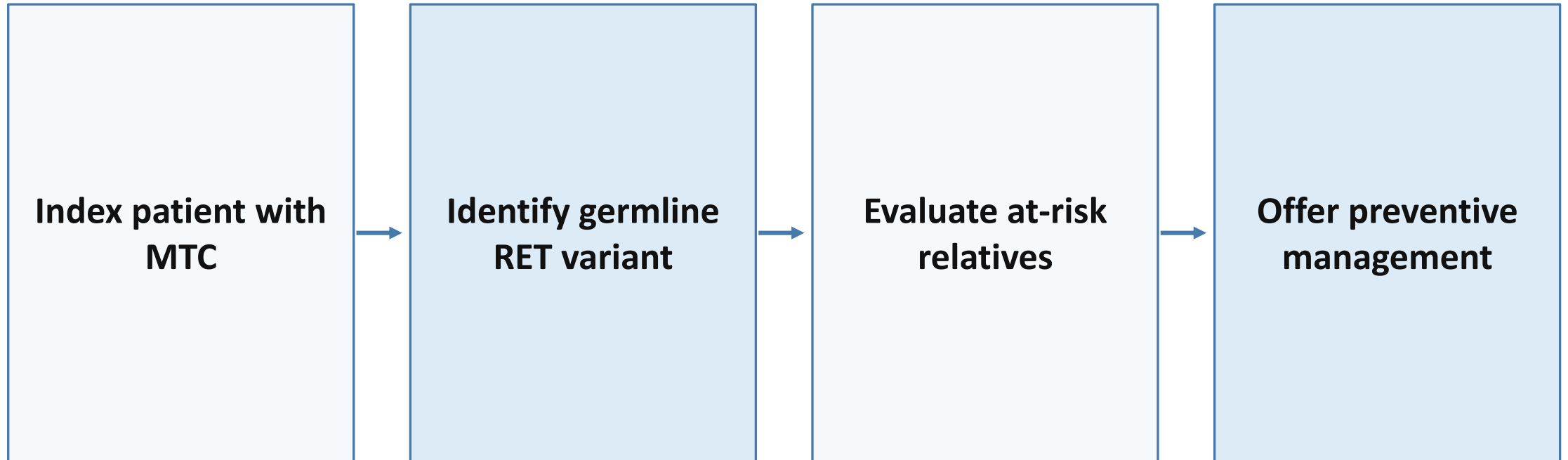
Rare phenotype: Calcitonin-negative tumor

- A negative marker should not be treated as an absolute exclusion.
- CEA and histologic context become especially useful in this setting.

Germline RET testing changes family-level care

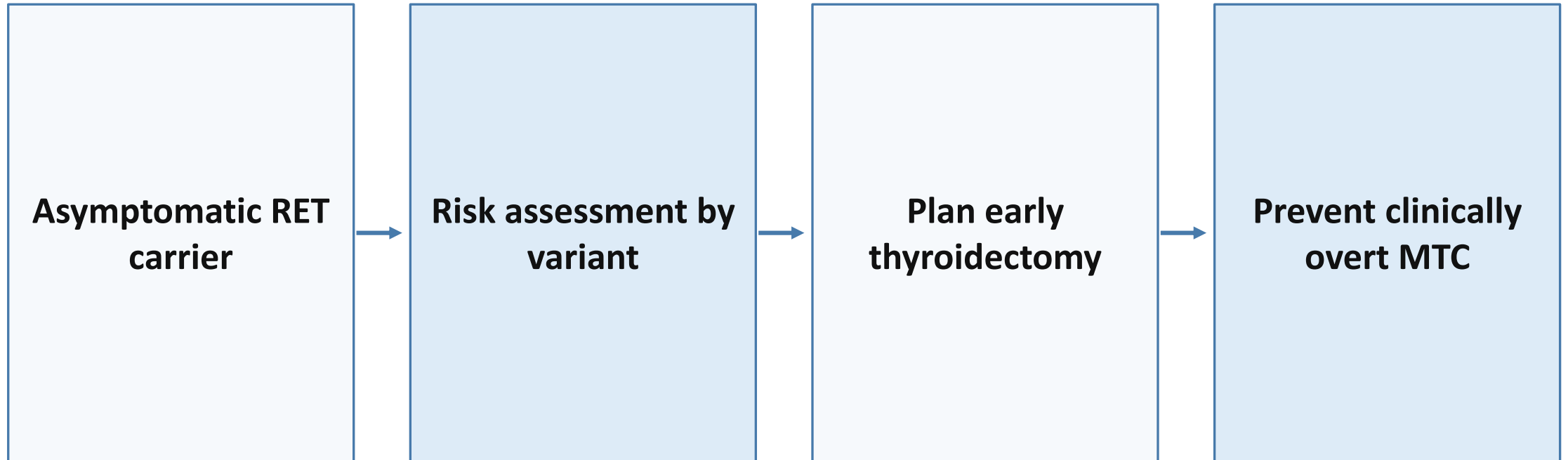
- A 2015 recommendation for germline RET testing in all MTC patients.
- An apparently sporadic tumor may have an inherited predisposition.
- A confirmed germline variant informs family counseling and testing.

Testing relatives turns a tumor diagnosis into prevention



- Screening can identify carriers before a palpable thyroid cancer develops.
- This is distinct from routine postoperative tumor-marker follow-up.

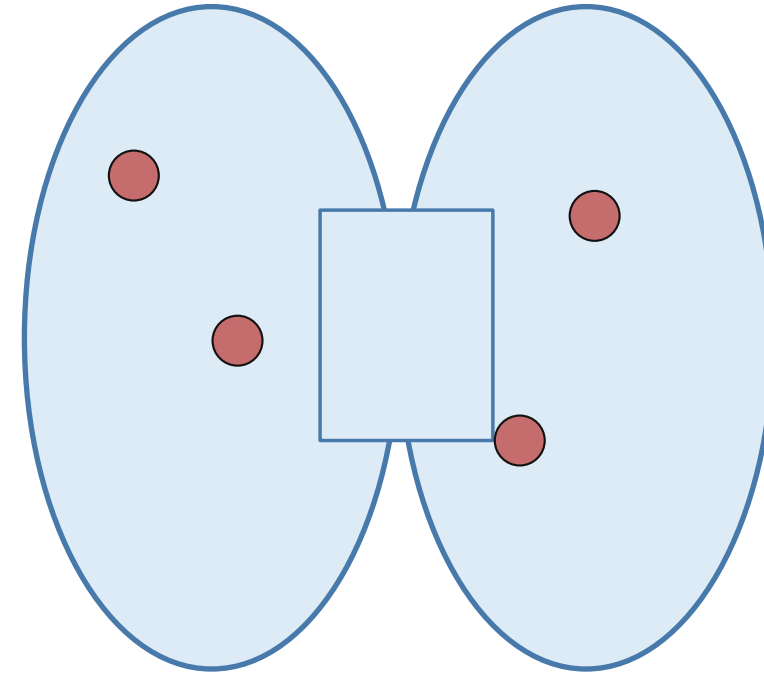
Prophylactic thyroidectomy is mutation-informed



- Operative timing depends on the specific RET mutation.
- No particular age or codon threshold is asserted here without updated guideline verification.

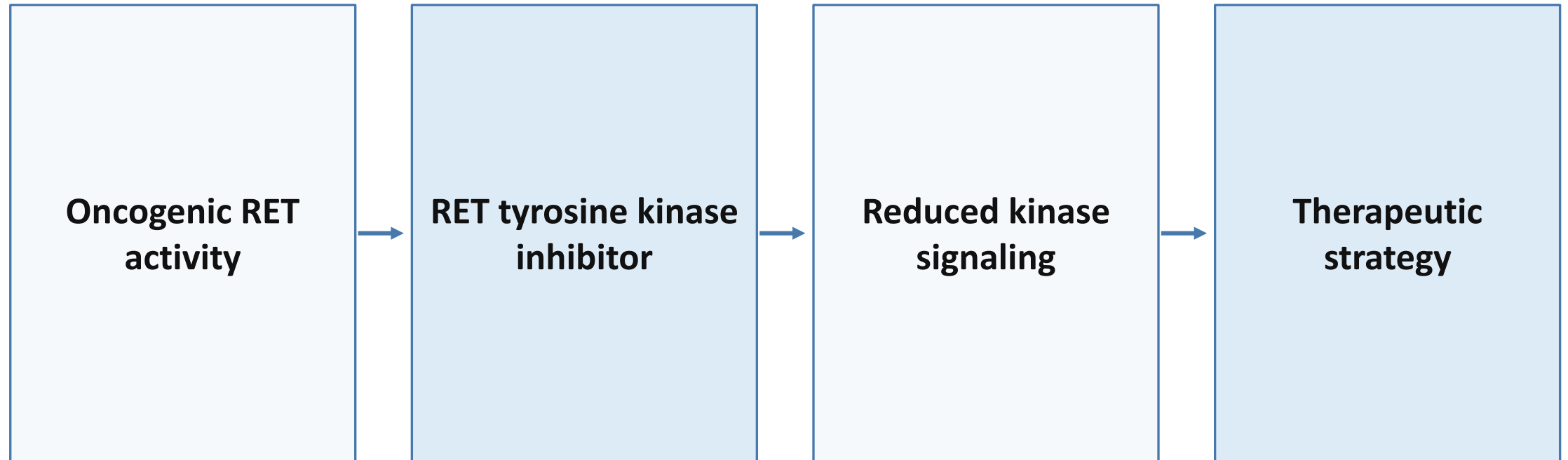
Prophylactic specimens may contain only microscopic disease

- Resected thyroids may show C-cell hyperplasia alone.
- Some contain small medullary microcarcinomas under 1 cm.
- These findings illustrate detection before symptomatic tumor burden develops.



Simplified thyroid schematic

RET inhibition is a molecular treatment principle



- Development and clinical use of small-molecule RET inhibitors.
- This is a mechanism overview, not a treatment-selection guideline.

Case: Solitary nodule in an adult

CASE VIGNETTE

A 52-year-old patient presents with a firm thyroid nodule. Histology shows polygonal neuroendocrine-appearing cells and stromal amyloid.

INTERPRETATION QUESTION

What lineage and key measurable biomarker should be considered?

Medullary thyroid carcinoma of C-cell origin; Calcitonin is the principal biomarker.

Case: Bilateral tumors and C-cell hyperplasia

CASE VIGNETTE

A younger patient has bilateral thyroid foci; C-cell hyperplasia is prominent in the background and contralateral gland.

INTERPRETATION QUESTION

Which molecular and family-level consideration follows?

Consider an inherited MEN2-associated germline RET predisposition and evaluate familial risk.

Case: Mucosal neuromas with a thyroid lesion

CASE VIGNETTE

A patient has multiple oral mucosal neuromas, marfanoid habitus, and a thyroid tumor with calcitonin expression.

INTERPRETATION QUESTION

Which syndrome phenotype is most consistent?

MEN2B, associated with RET activation and medullary thyroid carcinoma.

Case: Peptide-mediated diarrhea

CASE VIGNETTE

A patient with a neck mass develops unexplained secretory diarrhea; The thyroid biopsy shows a neuroendocrine tumor.

INTERPRETATION QUESTION

What paraneoplastic mechanism is supported by the source?

Ectopic production of VIP by some medullary carcinomas.

Integrated clinicopathologic interpretation

Finding	Interpretation
Multifocal MTC + C-cell hyperplasia	Strong hereditary predisposition clue
Nests, stippled chromatin, amyloid	Supports C-cell neuroendocrine carcinoma
Calcitonin and CEA elevation	Biomarkers for disease evaluation
Neuromas / pheochromocytoma	Look for MEN2 syndrome spectrum

What the pathologist should report and communicate

- Establish the neuroendocrine C-cell phenotype using morphology and applicable ancillary findings.
- Describe multiplicity, infiltration, and background C-cell changes where present.
- Flag a possible hereditary phenotype when C-cell hyperplasia or multifocality is identified.
- Communicate the rationale for genetic risk assessment without assuming a specific RET genotype.

Reference and source scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 24: The Endocrine System. Medullary Carcinoma, pp. 992–993.
- Same chapter: Thyroid Carcinomas (parent context); Multiple Endocrine Neoplasia, Type 2 (hereditary context).
- Text adapted for teaching from the supplied robbins.md conversion; no original textbook figures embedded.
- Guideline details, staging and contemporary therapeutic indications have not been independently updated.