Pediatric Medullary Thyroid Carcinoma Associated with MEN-2: Clinical and Laboratory Approach

سرطان مدولاری تیروئید مرتبط با MEN-2 در اطفال: رویکرد بالینی و آزمایشگاهی

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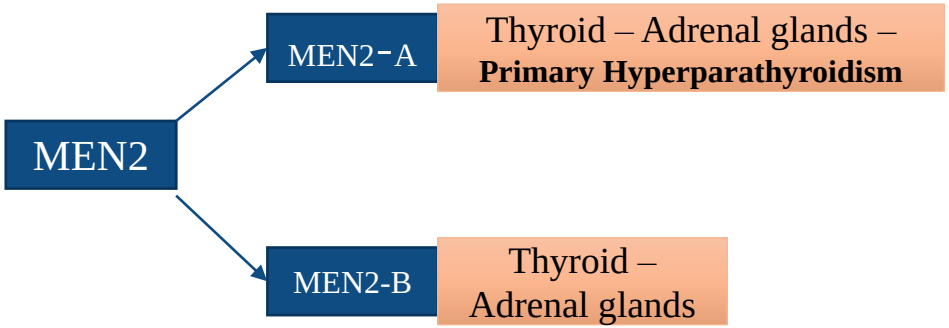
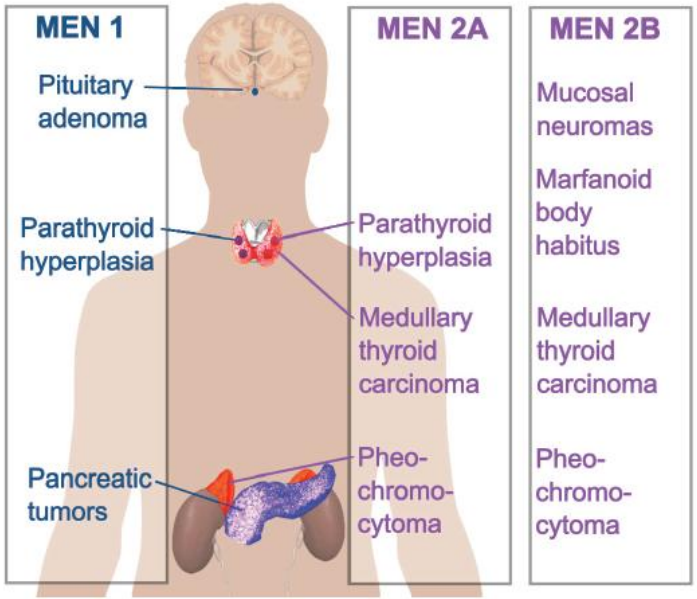
Introduction

Multiple endocrine neoplasia type 2 (MEN2), also known as **Sipple syndrome**, is a group of rare familial cancer syndromes involving multiple endocrine organs, most commonly thyroid, adrenal glands, and parathyroid. MEN2 was first described by Sipple in 1961 when he noticed a high association of bilateral pheochromocytomas with medullary thyroid cancer (MTC)





In both MEN2A and MEN2B, there is an occurrence of multicentric tumor formation in all organs where **RET proto-oncogene** is expressed.

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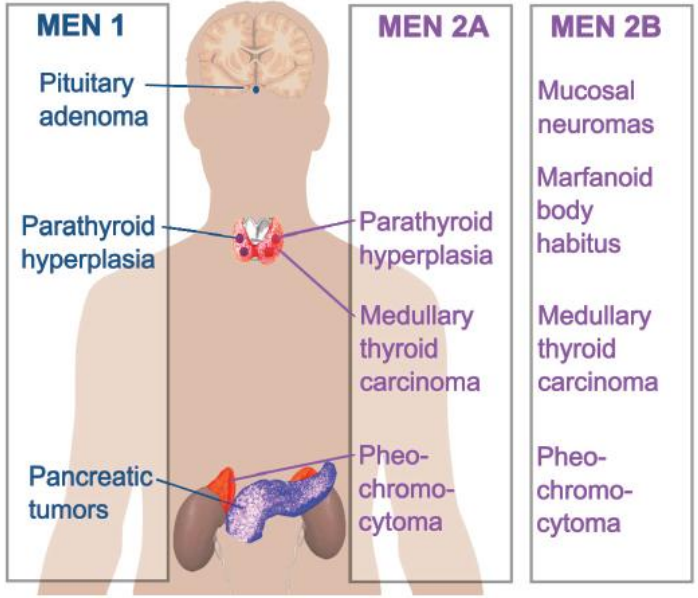
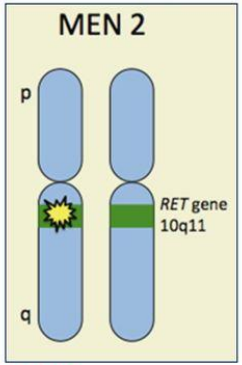
MEN2A subtypes
Classical MEN2A
MEN2A with cutaneous lichen amyloidosis (CLA)
MEN2A with Hirschsprung disease (HD)
Familial medullary thyroid cancer (FMTC)

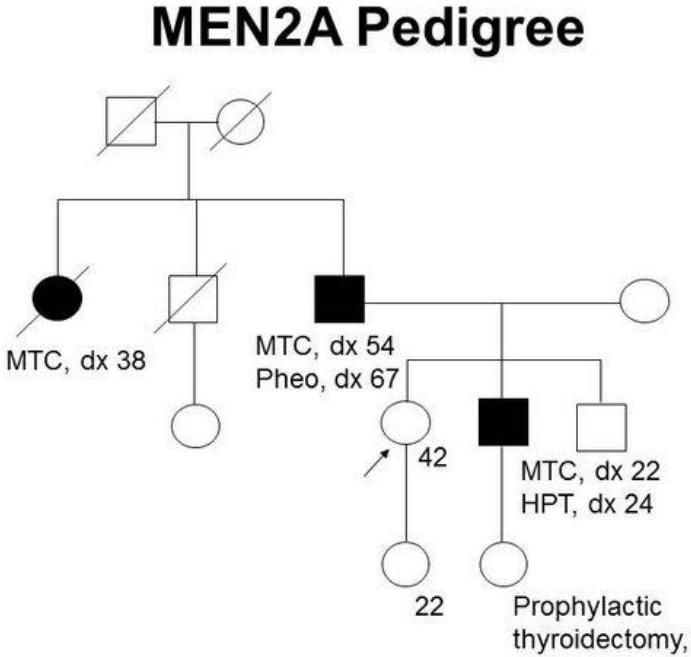


Etiology

Type 2 MEN



- The **RET gene** responsible for type 2 MEN proto-oncogene, located on band 10q11.2
- *RET* leads to hyperplasia of target cells in vivo and tumor development



HPT = hyperparathyroidism; MTC = medullary thyroid cancer; Pheo = pheochromocytoma.

Epidemiology

MEN2 (Multiple Endocrine Neoplasia type 2) is an **autosomal dominant syndrome**, with a high penetrance for MTC (Medullary Thyroid Carcinoma). The estimated prevalence of MEN2 is approximately 1 in 30,000 to 35,000 people worldwide. Within MEN2, there are two subtypes: MEN2A and MEN2B, each with distinct clinical and genetic characteristics.

MEN2A:

•**Prevalence:** 60% to 90% of MEN2 families are affected by MEN2A.

•**Clinical Features:** MEN2A is characterized by MTC, pheochromocytoma (a tumor of the adrenal glands), and hyperparathyroidism (overactive parathyroid glands).

•**MTC:** In MEN2A, MTC usually presents in the first to third decade of life, often as the first sign of the syndrome, and is typically bilateral and multicentric.

MEN2B:

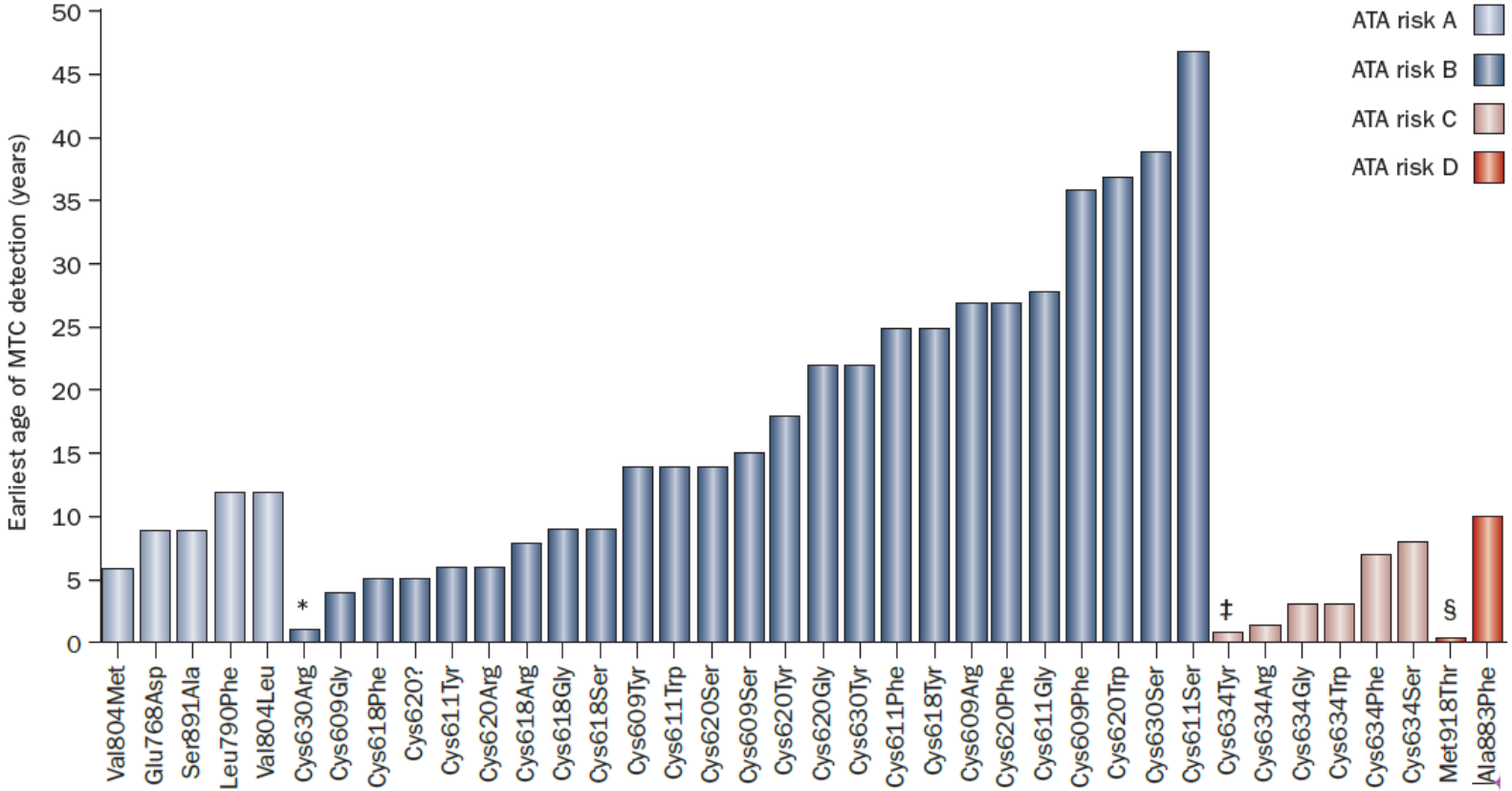
•**Prevalence:** MEN2B affects a smaller portion of MEN2 families, around 5%.

•**Clinical Features:** MEN2B is marked by an earlier and more aggressive form of MTC, which often appears in infancy and may metastasize early.

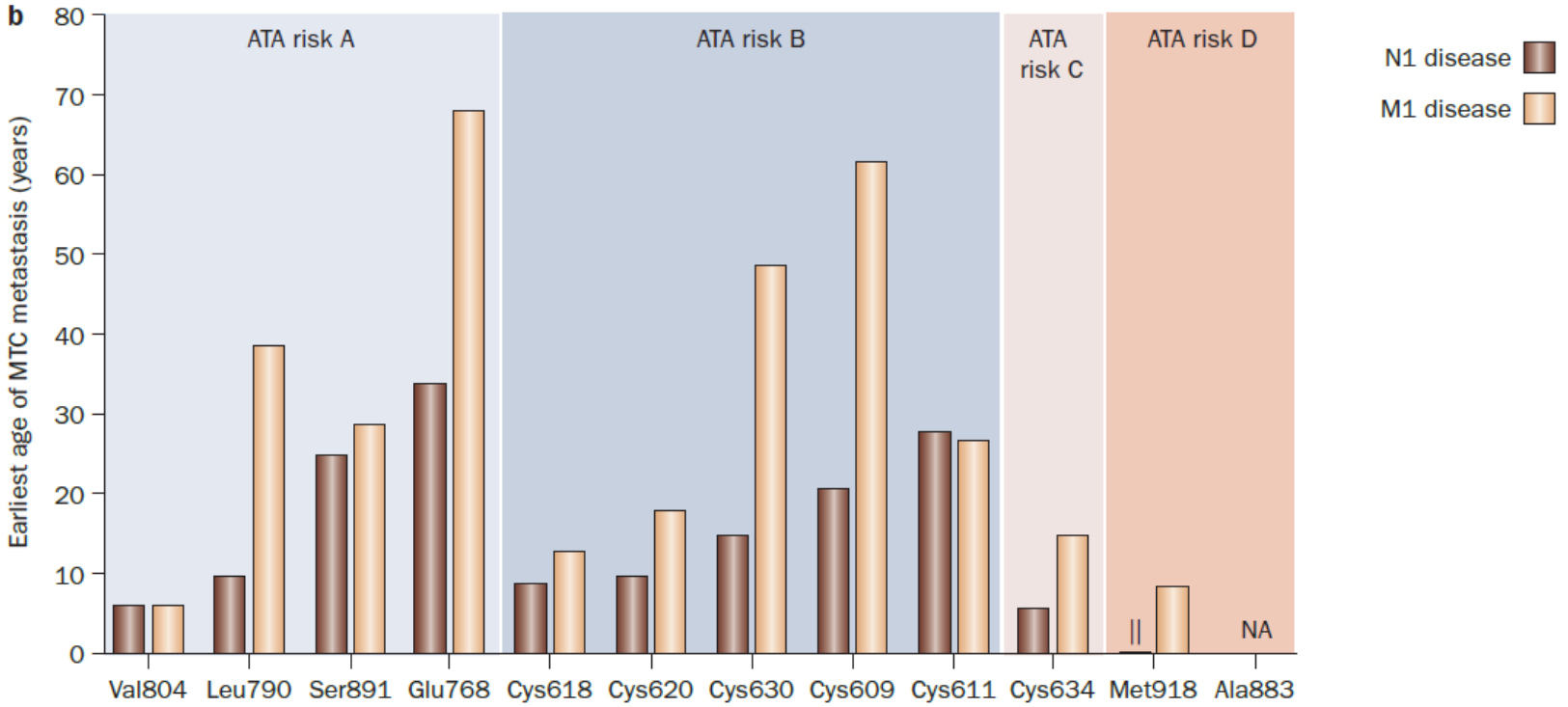
•**MTC:** MEN2B MTC can present in infancy and is highly aggressive.

•**Other Features:** MEN2B may also present with a distinctive facial appearance, including a large nose and a high palate. MEN2B typically does not cause hyperparathyroidism, but it is strongly associated with pheochromocytoma.

Epidemiology (MEN2/MTC)



Epidemiology (MEN2/MTC)



Epidemiology (MEN2/MTC)

RET Mutation	Youngest Age: Spread to Lymph Nodes (N1)	Youngest Age: Spread to Distant Organs (M1)	Comments
C634	6 years	15 years	High risk, metastasis can occur early
M918T	(not shown for N1)	8 months	Extremely aggressive (MEN2B)
Low-risk (e.g. V804, S891)	6–33 years	6–68 years	Metastasis late or very rare

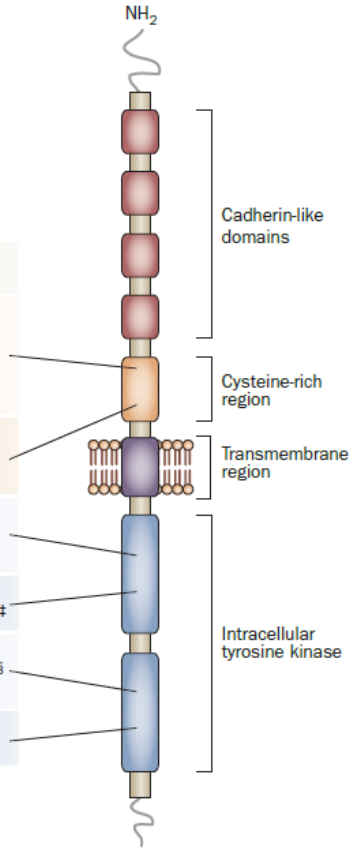
Pathophysiology

RET gene mutations cause MEN2 syndromes, leading to medullary thyroid carcinoma (MTC).

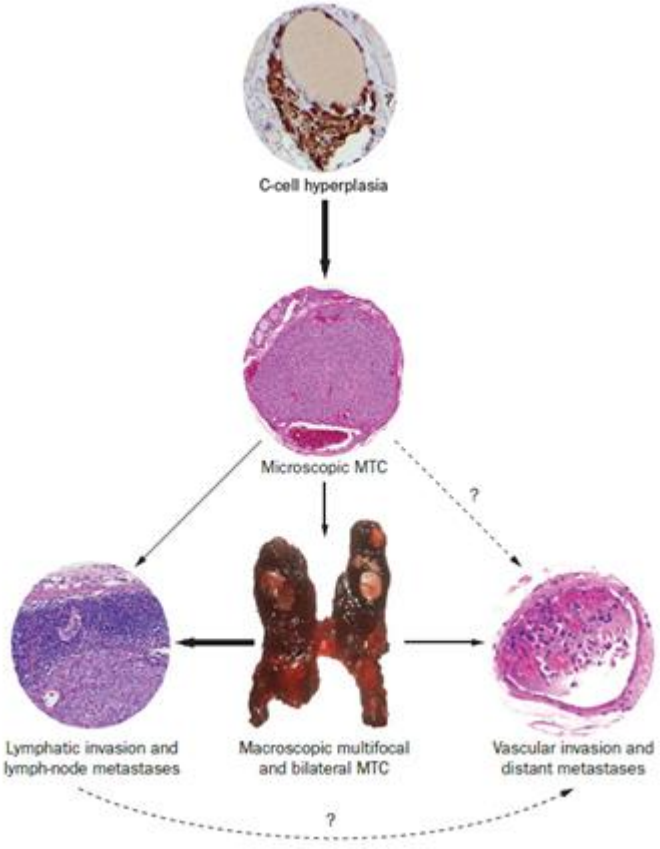
- **Exon 16 (M918T):** Very aggressive, early MEN2B, do screening before 6 months.
- **Exon 11 (C634):** Aggressive MEN2A, screen at 3–5 years.
- **Other exons (10, 13–15):** Milder MEN2A, screen at 5–10 years.

Early risk-adapted surgery saves lives.

Exon, codon and mutation	MTC	+PHEO	+PHPT	+CLA	+HSCR	+MEN2B phenotype	ATA risk	Age at testing*
Exon 10								
C609R/G/F/S/Y	○	○	○		○		B	5 years
C611R/G/F/S/W/Y	○	○	○		○		B	5 years
C618R/G/F/S/Y	○	○	○		○		B	5 years
C620R/G/F/S/W/Y	○	○			○		B	5 years
Exon 11								
C630R/F/S/Y	○		○				B	5 years
C634R/G/F/S/W/Y	○	○	○	○			C	3–5 years
Exon 13								
E768D	○	○					A	5–10 years
L790F	○	○					A	5–10 years
Exon 14								
V804L/M	○	○	○	○			A	5–10 years‡
Exon 15								
A883F	○	○				○	D	<6 months§
S891A	○	○	○				A	5–10 years
Exon 16								
M918T	○	○				○	D	<6 months

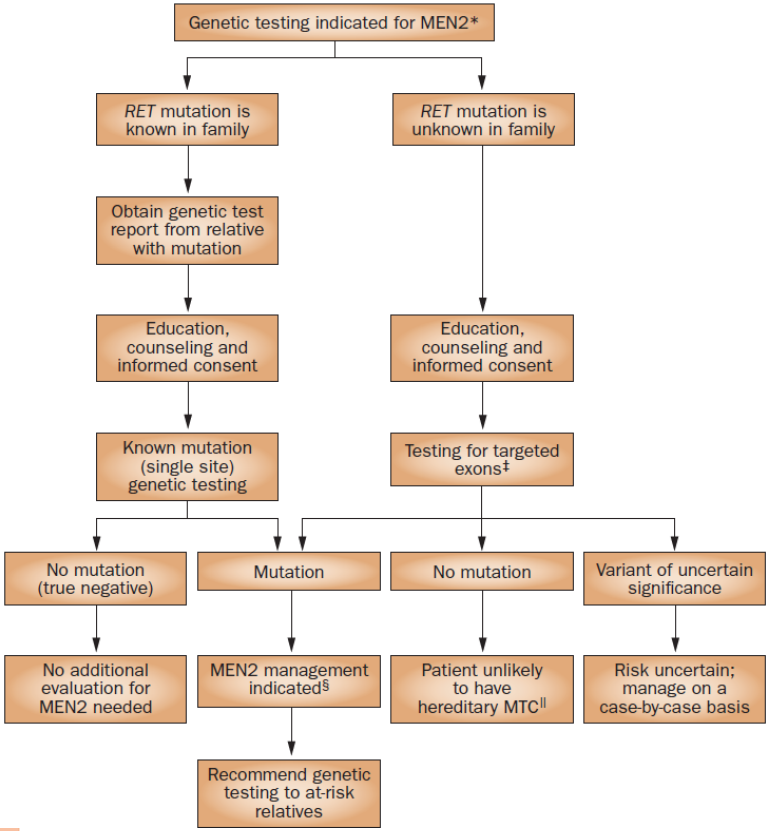


Pathophysiology



This fig. visualizes the pathological sequence in MEN2-related pediatric medullary thyroid carcinoma. It begins with **C-cell hyperplasia**, often identified through screening in RET mutation carriers. This stage progresses to **microscopic MTC**, which is still noninvasive, but can evolve into **macroscopic, multifocal, and bilateral tumors**, a hallmark of hereditary MTC. Solid arrows indicate a high probability of progression from C-cell hyperplasia to lymph-node metastases and larger tumors, notably in RET codon 634 mutations. Distant (vascular) metastasis is rarer in children but possible. The figure highlights the importance of genotype-based early intervention to halt this cascade before metastatic spread occurs.

Lab workup



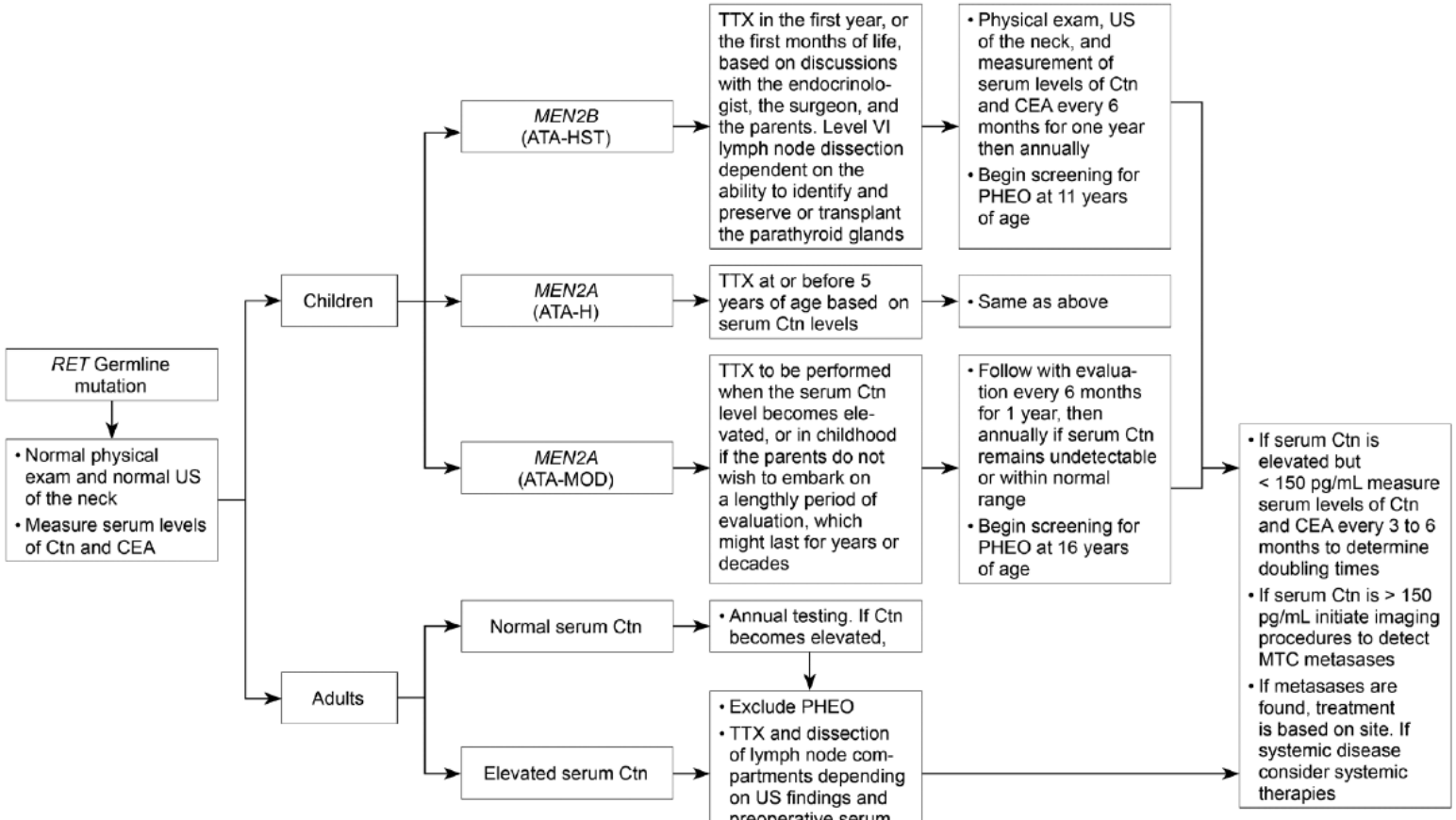
Test	Clinical Purpose	Expected in MEN2/MTC	Clinical Use/Note
Serum Calcitonin (Basal)	MTC marker (C-cell product)	Markedly elevated	Diagnosis, risk stratification, monitoring; rises early in mutation carriers
Stimulated Calcitonin	Early tumor detection in gene carriers	Elevated (more sensitive)	For equivocal basal calcitonin or early screening in children
CEA (Carcinoembryonic Antigen)	Tumor marker	Frequently elevated	Correlates with tumor size/burden; less sensitive than calcitonin
RET Genetic Testing	Confirm MEN2; identify mutation	Pathogenic RET variant	Diagnostic, directs family screening and timing of intervention
Plasma Free Metanephrines	Screen for pheochromocytoma	Markedly elevated if present	Rule out Pheo before any surgery; annual screening for mutation carriers
Serum Ca/PTH	Screen for primary hyperparathyroidism	Elevated if PHPT present	Mainly MEN2A; tested at baseline and as per symptoms
Thyroid Function Tests	General thyroid status	Usually normal in MTC	Not diagnostic for MTC; routine baseline
Chromogranin A	Neuroendocrine tumor marker (adjunctive)	May be elevated	Not specific/sensitive; optional use

Therapeutic approaches

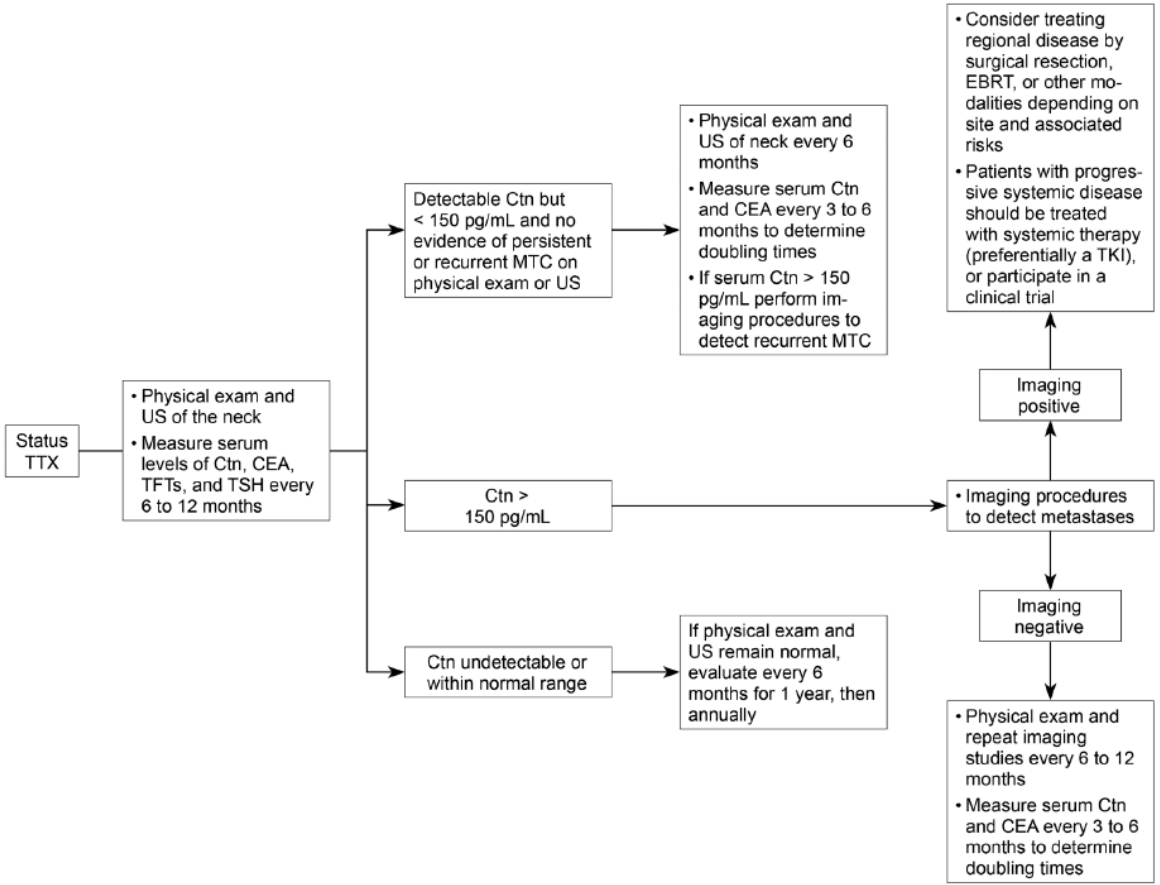
Consider ***5p strategy*** for MEN2/MTC

P	Advanced Focus in MEN2/MTC
Prevention	Universal RET genotyping/variant cascade; at-risk counseling
Prediction	Codon-specific risk: age of onset, penetrance, phenotype
Personalization	Genotype-tailored surgery timing and surveillance
Preemption	Preclinical intervention (thyroidectomy before biochemical or clinical disease)
Precision	Ultra-sensitive biomarkers, molecular imaging, targeted RET inhibition

Therapeutic approaches



Therapeutic approaches



غزل شماره 106 حافظ

تِبت به نازِ طبیبان نیازمند — به هیچ عارضه شخص تو دردمند مباد
مبادوجود نازکت آزرده گزند مباد — جمال صورت و معنی ز امن صحت توست
سلامت همه آفاق در سلامت توست — که ظاهرت دژم و باطنت نژند مباد