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Clinician Management Resource for *RET*

This overview of clinical management guidelines is based on this patient's positive test result for *RET* gene mutation. Unless otherwise stated, medical management guidelines used here are limited to those published in Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma[1]. Please consult the referenced website link for complete details and further information.

Clinical correlation with the patient's past medical history, treatments, surgeries, and family history may lead to changes in clinical management decisions; therefore, other management recommendations may be considered. Genetic testing results and medical society guidelines help inform medical management decision but do not constitute formal recommendations. Discussions of medical management decisions and individualized treatment plans should be made in consultation between each patient and his or her healthcare provider and may change.

SURVEILLANCE CONSIDERATIONS[1,^]	AGE TO START	FREQUENCY
Multiple Endocrine Neoplasia type 2 (MEN2)		
Physical exam	Children with MEN2B (ATA-HST)* or MEN2A (ATA-H)*: At diagnosis	Every 6 months for one year, then annually
	Children with MEN2A (ATA-MOD)*: beginning around age 5 years	Every 6 months for one year, then annually if serum calcitonin remains undetectable or within normal range
	Adults: At diagnosis	Individualized
Cervical ultrasound of the neck	Children with MEN2B (ATA-HST)* or MEN2A (ATA-H)*: At diagnosis	Every 6 months for one year, then annually
	Children with MEN2A (ATA-MOD)*: beginning around age 5 years	Every 6 months for one year, then annually if serum calcitonin remains undetectable or within normal range
	Adults: At diagnosis	Individualized
Measurement of serum levels of calcitonin and carcinoembryonic antigen	Children with MEN2B (ATA-HST)* or MEN2A (ATA-H)*: At diagnosis	Every 6 months for one year, then annually
	Children with MEN2A (ATA-MOD)*: beginning around age 5 years	Every 6 months for one year, then annually if serum calcitonin remains undetectable or within normal range
	Adults: At diagnosis	Every 3-6 months if serum calcitonin is elevated but <150 pg/mL
	For all patients: If serum calcitonin is elevated but <150 pg/mL	Repeat every 3-6 months
Imaging procedures to detect medullary thyroid carcinoma metastases	If serum calcitonin is >150 pg/mL	Individualized
Screening for pheochromocytoma using measurement of free plasma metanephrines and normetanephrines or 24-hour urinary metanephrines and normetanephrines	Children with MEN2B (ATA-HST)* or MEN2A (ATA-H)*: at age 11 years	Individualized
	Children with MEN2A (ATA-MOD)*: at age 16 years	
Screening for hyperparathyroidism including albumin-corrected calcium or ionized serum calcium measurements, with or without serum intact-PTH levels	Children with MEN2A (ATA-H)*: at age 11 years	Individualized
	Children with MEN2A (ATA-MOD)*: at age 16 years	
Adrenal imaging with CT or MRI	Indicated in patients with positive biochemical pheochromocytoma screening results	Individualized

SURVEILLANCE CONSIDERATIONS[1,^]	AGE TO START	FREQUENCY
Prophylactic thyroidectomy	Children with MEN2B (ATA-HST)*: in the first year or first months of life	N/A
	Children with MEN2A (ATA-H)*: at or before age 5 years, or earlier if elevated serum calcitonin levels are detected	
	Children with MEN2A (ATA-MOD)*: when the serum calcitonin level becomes elevated or around age 5 years if parents prefer to avoid a long-term evaluation program	
Total thyroidectomy and dissection of the lymph node compartments depending on ultrasound findings and preoperative serum calcitonin levels	Adults: when the serum calcitonin level becomes elevated and pheochromocytoma has been excluded	N/A
Counseling		
Counsel the patient or surrogate decision maker about the risk that an inherited *RET* mutation may pose to family members	Individualized	Individualized

^ Experienced physicians and surgeons in tertiary care centers should be responsible for the management of children with MEN2A *or* MEN2B.

* Refers to the American Thyroid Association risk categories for aggressive medullary thyroid carcinoma. HST: highest risk, H: high risk, MOD: moderate risk.

1. Wells SA, *et al*. (2015) *Thyroid* 25(6):567-610. https://pubmed.ncbi.nlm.nih.gov/25810047/

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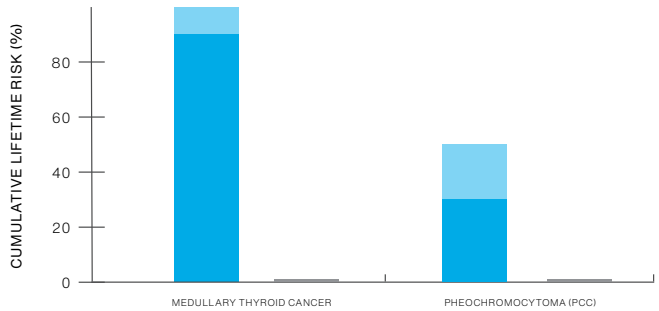
Understanding Your Positive *RET* Genetic Test Result

INFORMATION FOR PATIENTS WITH A PATHOGENIC MUTATION OR VARIANT, LIKELY PATHOGENIC

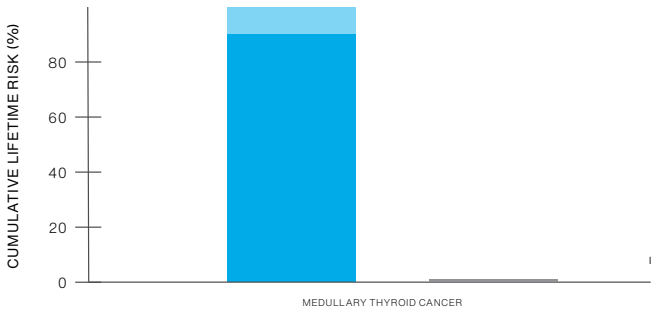
6 Things to Know

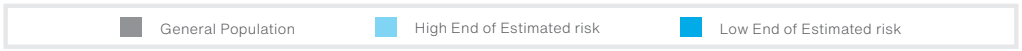
1	*RET* mutation	Your testing shows that you have a pathogenic mutation or a variant that is likely pathogenic in the *RET* gene.
2	*RET*-related conditions	People with *RET* mutations have multiple endocrine neoplasia type 2 (MEN2) or a variant of MEN2 called familial medullary thyroid carcinoma (FMTC). MEN2 is divided into 2 subtypes, MEN2A and MEN2B. Each of these conditions is determined by the specific *RET* mutation and causes slightly different medical concerns.
3	Cancer Risks	Your cancer risks will differ depending on the specific *RET* mutation you have: • MEN2A and MEN2B: increased risk for medullary thyroid cancer and pheochromocytoma (PCC). Thyroid cancer is often diagnosed in childhood or young adulthood. • FMTC: increased risk for medullary thyroid cancer only. People with FMTC are usually diagnosed with thyroid cancer later in life (after age 40) compared to people with MEN2.
4	Non-cancerous tumors and other medical concerns	Subtypes of MEN2 can involve non-cancerous medical concerns: • MEN2A: increased risk for parathyroid overgrowth that can cause hyperparathyroidism and a skin condition known as cutaneous amyloidoses lichen • MEN2B: increased risk for non-cancerous tumors in the mouth (neuromas), non-cancerous tumors known as ganglioneuromas, and skeletal abnormalities • A small number of people with MEN2 or FMTC may also have a condition known as Hirschsprung disease (HD). HD is usually present from birth and can cause blockage in a baby's large intestine.
5	What you can do	The specific *RET* gene mutation you have may determine which subtype you have, and may provide you more information about your specific tumor/cancer risks. Talk to your healthcare provider about which tumors and cancers you are at risk for. Risk management decisions are very personal. There are options to detect cancer early or lower the risk to develop cancer. It is important to discuss these options with your healthcare provider and decide on a plan that works for you.
6	Family	Family members may also be at risk – they can be tested for the *RET* mutation that was found in you. It is recommended that you share this information with your family members so they can learn more and discuss with their healthcare providers.

MEN2A and MEN2B: Lifetime cancer risks*



Familial Medullary Thyroid Carcinoma (FMTC): Lifetime Cancer risks*

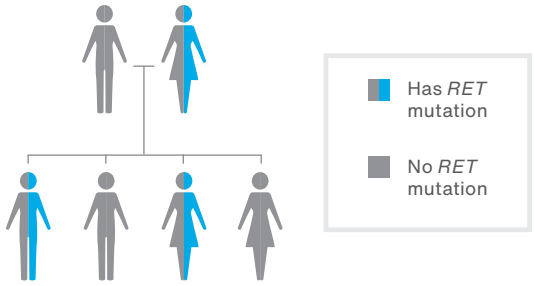




* Because risk estimates vary in different studies, only approximate risks are given. Cancer risks will differ based on individual and family history.

RET Mutations in the Family

There is a 50/50 random chance to pass on a *RET* mutation to each of your children. The image to the right shows that everyone can carry and pass on these mutations, regardless of their sex at birth.



RESOURCES

- Association for Multiple Endocrine Neoplasia Disorders (AMEND) amend.org.uk
- Thyca: Thyroid Cancer Survivors' Association thyca.org
- National Society of Genetic Counselors nsgc.org
- Canadian Society of Genetic Counsellors cagc-accg.ca
- American Multiple Endocrine Neoplasia Support amensuport.org

Please discuss this information with your healthcare provider. The cancer genetics field is continuously evolving, so updates related to your *RET* result, medical recommendations, and/or potential treatments may be available over time. This information is not meant to replace a discussion with a healthcare provider, and should not be considered or interpreted as medical advice.

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