



Cancer Predisposition Clinic

Multiple Endocrine Neoplasia Type 2

Also called: MEN 2, MEN2 syndrome, Sipple syndrome, Mucosal neuroma syndrome

What is multiple endocrine neoplasia type 2?

Multiple endocrine neoplasia type 2 is a genetic condition that increases the risk of developing cancer in the endocrine system. The endocrine system is made up of different glands in the body that secrete hormones. Hormones are important for sending messages in the body. The endocrine system includes the thyroid gland, adrenal gland, pancreas, testes and ovaries.

People with multiple endocrine neoplasia type 2 have an increased risk of developing medullary thyroid cancer (MTC) and pheochromocytomas, which are tumors of the adrenal gland. People with this condition may also develop other types of abnormal growths in endocrine tissues or glands.

There are three subtypes of multiple endocrine neoplasia type 2:

- **Type 2A:** People with this subtype have an increased risk for medullary thyroid cancer and pheochromocytomas. They also have an increased risk for primary hyperparathyroidism, a condition in which the parathyroid glands secrete too much parathyroid hormone. This usually happens because non-cancerous tumors (adenomas) develop in the parathyroid glands, or because the parathyroid gland tissue grows more than normal (hyperplasia). Signs and symptoms of multiple endocrine neoplasia type 2A usually begin in early adulthood.
- **Familial medullary thyroid cancer (FMTC):** People with this subtype have an increased risk of developing medullary thyroid cancer in early or middle adulthood. However, they do not appear to be at risk of having pheochromocytomas or hyperparathyroidism. This subtype is considered a variant of type 2A.
- **Type 2B:** People with this subtype have an increased risk for medullary thyroid cancer and pheochromocytomas. They also have a higher likelihood of developing ganglioneuromas in the digestive tract. Ganglioneuromas are tumors made of nerve cells and ganglion cells, which are special cells that normally support the nerve cells in the body. People with multiple endocrine neoplasia type 2B may also develop non-cancerous growths of the lips and tongue (mucosal neuromas), and they often have a tall, slender body type. Signs and symptoms of multiple endocrine neoplasia type 2B usually begin in infancy or early childhood.

How is multiple endocrine neoplasia type 2 diagnosed?

Multiple endocrine neoplasia type 2A is diagnosed when two or more of the following are seen in a person or among close relatives:

- Medullary thyroid cancer
- Pheochromocytomas
- Parathyroid adenoma/ hyperplasia

Multiple endocrine neoplasia type 2B is suspected when a person has medullary thyroid cancer as well as the presence of some of the following:

- Mucosal neuromas of the lips and tongue
- Distinctive facial features, including an elongated face and protruding lips
- A tall and slender body type
- Medullated corneal nerve fibers (abnormal nerves in the clear covering of the eyeball, which an ophthalmologist can see during an eye exam)

Familial medullary thyroid cancer is diagnosed in families where four or more family members have medullary thyroid cancer but do not have pheochromocytomas, parathyroid adenoma, or parathyroid hyperplasia.

What is the cancer risk for people with multiple endocrine neoplasia type 2?

Nearly all people with multiple endocrine neoplasia type 2 develop some type of endocrine cancer at some point in their lives. The lifetime risks by subtype are listed in the following table:

Subtype	Medullary Thyroid Carcinoma	Pheochromocytoma	Parathyroid Disease
Type 2A	95%	50%	20%-30%
Familial medullary thyroid cancer type	100%	0%	0%
Type 2B	100%	50%	Uncommon

What are other features seen in people with multiple endocrine neoplasia type 2?

Multiple endocrine neoplasia type 2 can affect many areas of the body. People with this condition may have some or all of the following features. These are caused by the growth of tumors or by abnormal levels of hormones made by the tumors. Some people with the condition may have no symptoms, while others may have many of the following symptoms:

- **Medullary thyroid cancer signs and symptoms**
 - A lump or nodule in front of the neck
 - Hoarseness or trouble speaking in a normal voice
 - Swollen lymph nodes, especially in the neck
 - Trouble swallowing or breathing
 - Pain in the throat or neck

- **Pheochromocytoma signs and symptoms**
 - High blood pressure
 - Sudden, severe headache
 - Excessive sweating
 - Racing heartbeat (tachycardia) and palpitations (skipped heartbeats)
 - Feelings of anxiety or feelings of extreme fright
 - Pain in the lower chest or upper abdomen
 - Nausea with or without vomiting
 - Weight loss

- Pale skin
- Feeling hot or unable to tolerate being in the heat
- **Hyperparathyroidism signs and symptoms**
 - Fatigue or weakness
 - Feeling depressed
 - Forgetfulness
 - Bone and joint pain
 - Complaining often of illness with no known cause
 - Fragile bones that easily break (osteoporosis)
 - Kidney stones
 - Increased thirst and urinating too often
 - Pain in abdomen
 - Nausea, vomiting or loss of appetite

What causes multiple endocrine neoplasia type 2?

Multiple endocrine neoplasia type 2 is caused by changes in a gene known as *RET*. Genes carry information telling cells within the body how to function. The *RET* gene helps to control how and when cells grow and divide.

People without multiple endocrine neoplasia type 2 carry two working copies of the *RET* gene in their cells. One copy of *RET* is inherited from the mother and one from the father. Cells from people with multiple endocrine neoplasia type 2 carry one working copy of *RET* and one copy that is changed. This change causes the gene to not work properly. It is called an *RET* mutation.

Nearly all children with multiple endocrine neoplasia type 2A, and about half of children with multiple endocrine neoplasia type 2B, inherit the *RET* gene mutation from a parent who also has the syndrome. Those who do not inherit the *RET* mutation have developed a new *RET* mutation that did not come from a parent. These children have no history of the syndrome in their family. In these cases, the change either happened in an egg or sperm cell when the child was formed or in one of the child's cells during pregnancy. These children are the first in their families to have multiple endocrine neoplasia type 2.

No matter how they acquired the *RET* mutation, people with multiple endocrine neoplasia type 2 have a 50% or 1 in 2 chance of passing it on to their children.

Since people with multiple endocrine neoplasia type 2 have only one working copy of *RET* in their cells, those cells are at risk for growing and dividing uncontrollably, which can cause a tumor. This happens most often in certain cells of the endocrine system, especially thyroid cells. Researchers believe that this is why people with multiple endocrine neoplasia type 2 have a higher risk of developing tumors than people who do not have this condition.

How is the risk of cancer managed for people with multiple endocrine neoplasia type 2?

People with multiple endocrine neoplasia type 2 should be managed by a health care provider who knows this condition well. The goal is to prevent cancer if possible. The goal of screening is finding and treating tumors early to allow the best outcome for patients.

Recommended preventive care for children with multiple endocrine neoplasia type 2:

- Removing the thyroid gland in surgery
 - For children with subtype 2A or the familial medullary thyroid cancer subtype, this surgery depends on several factors, including *RET* gene mutation, serum calcitonin levels, and family preferences.
 - For children with subtype 2B, this surgery should take place as soon as possible after the child's birth, often within the first month of life. In this subtype, health care providers have found thyroid cancer in very young infants.

Recommended screenings for children with multiple endocrine neoplasia type 2 include the following:

- **Annual physical exams** by a health care provider who knows this condition well
- **Annual neck ultrasound and serum calcitonin (blood test)** starting in the first few months of life to ages 3-5 years, depending on the *RET* mutation
- **Annual free plasma metanephrines and normetanephrines blood work** starting at age 8 years, with follow-up imaging through CT or MRI if results are abnormal
- **Annual calcium and vitamin D blood work** starting at age 11 or 16 years, depending on the *RET* mutation

It is possible that recommended care and screenings may change over time as health care providers learn more about multiple endocrine neoplasia type 2. Parents should discuss all screening options for their child with a health care provider who knows this condition well. Because multiple endocrine neoplasia type 2 is a complex condition, it is important that parents seek out an experienced health care provider for their child.

How is genetic testing for multiple endocrine neoplasia type 2 done?

The health care provider may suspect multiple endocrine neoplasia type 2 after looking at a person's medical or family history. In most cases, a health care provider or genetic counselor will ask questions about a person's health and the health of other family members.

The genetic counselor or health care provider will record which family members have developed tumors, what types of tumors and at what ages tumors occurred. From this information they will create a family tree. Health care providers and genetic counselors will look at the family tree to find out:

- If there are more cancers than normal,
- If cancers occurred at younger-than-expected ages, and
- If the types of tumors match up with what might be seen in those with multiple endocrine neoplasia type 2.

If multiple endocrine neoplasia type 2 is suspected in a child or other family members, the health care provider or genetic counselor will likely recommend genetic testing of the *RET* gene.

Diagnostic genetic testing

If the health care provider or genetic counselor suspects that a person has multiple endocrine neoplasia type 2, diagnostic testing may take place as follows:

- A blood sample is collected.
- DNA is isolated from the cells in the sample. A person's genes are made of DNA.
- Both copies of the person's *RET* gene are checked for possible changes. A genetic specialist compares the two copies of the patient's gene to a normal *RET* gene. If there are differences, the specialist decides if these changes might cause multiple endocrine neoplasia type 2.
- If an *RET* mutation is found, the genetic counselor will work with the family in the following ways:
 - To help the family understand the cancer risks of multiple endocrine neoplasia type 2
 - To find out if other family members should consider testing for the mutation
 - To help with decisions about prenatal genetic testing

It is important to remember that genetic testing does not always find a mutation in the *RET* gene for all people with multiple endocrine neoplasia type 2 and a family history of the condition. There may be other types of mutations causing this condition that health care providers do not yet know about. Therefore, a person can still have multiple endocrine neoplasia type 2 even if no *RET* mutation is found.

Prenatal genetic testing

Parents may undergo prenatal testing to find out if the pregnancy is affected with a known *RET* mutation in the family. Testing may take place either before pregnancy occurs or during pregnancy.

People considering prenatal testing should work with a genetic counselor to review the pros and cons of the testing. The genetic counselor can also help parents consider how they wish to handle the results of the testing.

Testing that occurs before pregnancy—Testing that happens before pregnancy is called preimplantation genetic testing (PGT). This special type of genetic testing is done along with in vitro fertilization (IVF). PGT offers a way to test embryos for a known *RET* mutation before placing them into the uterus.

Testing that occurs during pregnancy—Testing can be used to see if a pregnancy is affected with a known *RET* mutation. A doctor gathers cells from the pregnancy in one of two ways:

- **Chorionic villus sampling (CVS)**—during the first trimester (first three months)
- **Amniocentesis**—during the second trimester or later (last six months)

Collected tissue can be checked for the presence of the *RET* mutation identified in the family. Both of these tests carry minor risks and should be discussed with an experienced doctor or genetic counselor.

Special concerns

Genetic testing for multiple endocrine neoplasia type 2 is a complex process. Those thinking about testing should take time to consider the benefits and risks. They should discuss the process with a genetic

counselor before testing is done. If they choose testing, they should review the test results with the health care provider or genetic counselor to be sure they understand the meaning of the results.

Sometimes children or adults with multiple endocrine neoplasia type 2 can feel sad, anxious or angry. Parents who pass on an *RET* mutation to one or more of their children can feel guilty. Some people with an *RET* mutation could have trouble getting disability coverage, life insurance or long-term care insurance in some states. More information about genetic discrimination can be found at www.ginahelp.org.

Are there other special health care needs for children with multiple endocrine neoplasia type 2?

People with multiple endocrine neoplasia type 2 should avoid certain kinds of medicines. These include dopamine D₂ receptor antagonists (for example, metoclopramide and verapride), beta blockers, monoamine oxidase inhibitors, sympathomimetics (e.g., ephedrine) and certain peptide and corticosteroid hormones. It is important to check with a health care provider who is experienced in managing patients with multiple endocrine neoplasia type 2 about the safety of any medicines.

People of any age with multiple endocrine neoplasia type 2 have a higher risk of cancer. They should monitor their health and adopt healthy habits throughout life. It is important to continue to have regular physical checkups and screenings. That way, any cancer can be found early at the most treatable stage.

Other ideas to reduce the risk of cancer:

- Eat a healthy diet with lots of fruits and vegetables
- Get regular exercise
- Avoid smoking or using tobacco products
- Avoid secondhand smoke
- Avoid excess sun exposure and always wear sunscreen, hat and protective clothing when out in the sun

People with multiple endocrine neoplasia type 2 should watch closely for general signs or symptoms that could signal cancer:

- Unexplained weight loss or fever
- Loss of appetite
- Aches, pains, lumps or swelling that cannot be explained

It is important to seek medical help if anything unusual appears.

What other information and resources are there for children with multiple endocrine neoplasia type 2 and their families?

Resources about multiple endocrine neoplasia type 2:

- Genetics Home Reference
(ghr.nlm.nih.gov/condition/multiple-endocrine-neoplasia)
- American Multiple Endocrine Neoplasia Support
(www.amensupport.org)

- National Organization for Rare Disorders
(rarediseases.org/rare-diseases/multiple-endocrine-neoplasia-type)

Other resources:

- Making Sense of Your Genes: A Guide to Genetic Counseling
(www.ncbi.nlm.nih.gov/books/NBK115508/)
- Young People with Cancer: A Parent's Guide
(www.cancer.gov/publications/patient-education/young-people)

Sources:

1. Genetics Home Reference - Multiple endocrine neoplasia type 2
ghr.nlm.nih.gov/condition/multiple-endocrine-neoplasia
2. Gene Reviews – Multiple endocrine neoplasia type 2
www.ncbi.nlm.nih.gov/books/NBK1257/

Developed by:

St. Jude Division of Cancer Predisposition

Updated 5/2020