Multiple Endocrine Neoplasia Type 2

A Guide for Patients and Their Families

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
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Funding provided by generous donors to the
Volunteer Endowment for Patient Support (VEPS) at
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Overview of MEN2

Introduction

The purpose of this booklet is to give you information about the signs, symptoms, diagnosis and treatment of multiple **endocrine neoplasia** type 2 (MEN2). We want to help you better understand the condition – what it means for your health and how it may affect your family.

MEN2 affects 1 out of every 30,000-50,000 people. It is an inherited condition, which means that parents can pass it to their children.

People with MEN2 have a higher chance of having certain types of **tumors** and cancers of endocrine glands. (Read more about the glands of the **endocrine system** in the next section.) People with MEN2 have a higher chance of getting a tumor in at least one of these at some point in their lives:

- **Thyroid gland**
- **Parathyroid glands**
- **Adrenal glands**

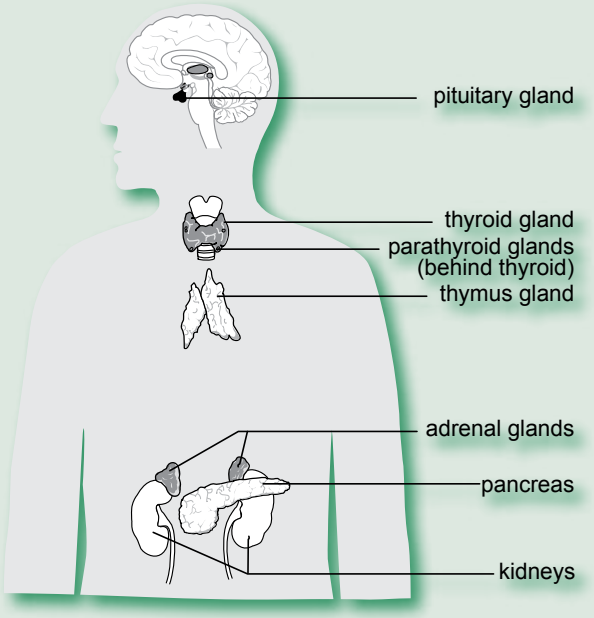
Almost all people with MEN2 will develop a specific type of thyroid cancer called **medullary thyroid cancer (MTC)** – if left untreated. Medullary thyroid cancer can be prevented if MEN2 is diagnosed early.

The parathyroid gland tumors and adrenal gland tumors are usually not cancer, but their growth can cause the glands to become overactive. This leads to changes in the levels of certain **hormones**. The hormone level changes can cause a variety of medical problems.

MEN2 affects people in different ways. Even members of the same family may have different experiences. If you have MEN2, you will need regular checkups and tests.

The Endocrine System

The endocrine system is a collection of glands. It works with the brain to control all of the body's normal functions. This includes getting energy from food, growth, reproduction and sleep.



Glands of the endocrine system
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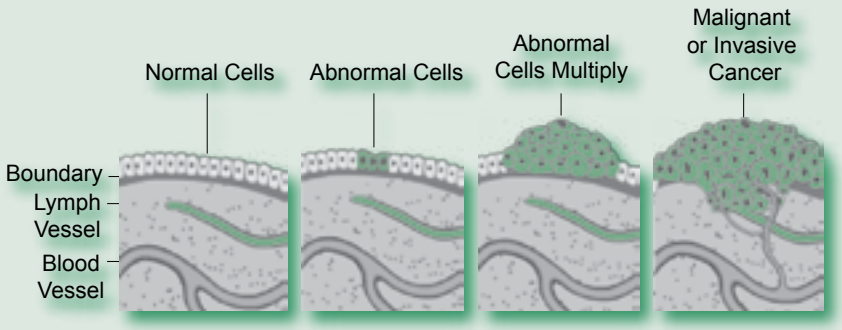
Glands are organs that make hormones, digestive juices, sweat, tears, saliva or milk. Hormones are strong chemicals, and the body makes about 50 different types.

The endocrine glands work by releasing hormones into the bloodstream. Each hormone usually targets only a few of the body's systems. They influence organs and help the body work in a normal way.

Some glands of the endocrine system include:

- Pituitary
- Thyroid
- Parathyroids
- Adrenals
- Pancreas

The glands that are affected in MEN2 are described in more detail in later sections.



Cancer cells growing in the body
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Tumors and Cancer

Many types of **cells** make up the body. Cells are the basic unit of life. Normally, cells grow, divide and make more cells, and this happens in a controlled way. They make more cells only as the body needs them to keep healthy. When cells become old or damaged, they die, and new cells replace them.

A tumor is an abnormal mass of tissue. It happens when cells grow out of control in an abnormal way. A tumor may happen when cells divide more often than they should, or when they do not die when they should.

Tumors can be either **benign**, which means they are not cancer, or **malignant**, which means they are cancer. Cells from a cancerous tumor may invade nearby tissues and spread to other parts of the body. Cells from a benign tumor cannot.

It is important to know that cancer is not just one disease. There are more than 100 different types of cancer. Different types of cancer may need different treatment.

Signs and Symptoms of MEN2

The symptoms of MEN2 vary:

- You may have MEN2 but not any tumors, in which case, you would not have symptoms.
- You may have a tumor but not any symptoms.
- A tumor that makes hormones may cause symptoms; however, they may not start for several years after the tumor first grows.
- Thyroid cancer can sometimes be felt as a growth or nodule in the neck.
- You may have symptoms if a tumor is making too much hormone. The symptoms caused by each tumor type are discussed in later sections.
- Blood tests may show high levels of hormones, which can be a sign of a tumor.

Diagnosis of MEN2

In most cases, **genetic testing** is needed to diagnose MEN2. This special blood test looks for a problem with one of your genes. (To learn more about this, please see page 21.) The test may be positive for MEN2 even if you do not have any medical conditions.

The doctor cannot diagnose MEN2 based on symptoms; medical tests must confirm that you have the condition.

Treatment

The treatment of MEN2 depends on:

- Whether a person has any tumors. Treatment of each tumor type is explained in other sections.
- Age
- Result of genetic testing. This is explained more on page 27.

Even if a person does not have any symptoms, medical tests are recommended. The goal is to find tumors at an early stage. This may prevent medical

problems caused by overactive glands. Detecting the disease early may also help to prevent cancer from growing to an advanced stage.

Frequently Asked Questions About MEN2

If I have MEN2, will I definitely have cancer? Is there anything that can be done to prevent tumors caused by MEN2?

If MEN2 is diagnosed early, medullary thyroid cancer can usually be prevented by removing the thyroid gland.

There isn't a way to prevent adrenal and parathyroid tumors if you have MEN2. Your doctor will want to watch the disease with regular medical tests and checkups. This will help your doctor find tumors early, which can help prevent certain medical problems and advanced cancers.

What is the risk to pass MEN2 on to my children?

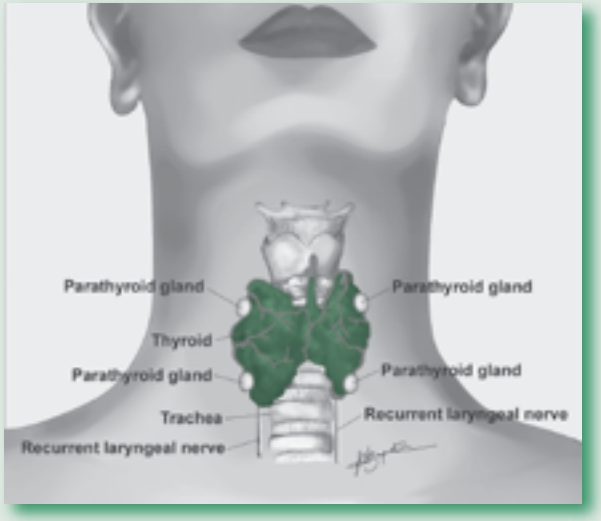
A man or woman with MEN2 has a 1 out of 2 chance to pass MEN2 on to each of their children.

- Boys and girls have an equal chance of inheriting it.
- They have an equal chance of having health problems caused by MEN2.

Parents have some options to reduce the risk of passing MEN2 on to a child. Talk to a genetic counselor about this before getting pregnant.

Signs of MEN2, Diagnosis and Treatment

Thyroid Gland and Medullary Thyroid Cancer (MTC)



The thyroid and parathyroid glands

The thyroid gland is a butterfly-shaped gland in the front part of the neck. It is located at the base of the throat near the trachea (windpipe). Usually you cannot feel the thyroid gland through the skin.

The thyroid plays an important role in a person's well-being. The thyroid uses iodine to help make several hormones. These hormones help to control important body functions like:

- The body's heart rate
- Blood pressure
- Temperature
- Getting energy from food

The thyroid is made up of two cell types: **follicular cells** and **parafollicular cells**. Follicular cells make thyroid hormone, and parafollicular cells, also known as **C-cells**, make a protein called **calcitonin**.

MTC is a cancerous tumor of the C-cells. MTC is the type of thyroid cancer that happens in people with MEN2.

Most people with MEN2 develop MTC at some point during their lives if they are not treated. The subtype of

MEN2 affects the age of diagnosis. (See page 16 for more information).

Although many people with MTC do not develop symptoms, these are warning signs:

- Lump in the neck
- Trouble swallowing
- Trouble breathing
- A hoarse voice
- Frequent diarrhea
- Flushing (feeling hot in the face or arms)

C-cell **hyperplasia** is a condition where there are more C-cells found within the thyroid than usual. This non-cancerous stage happens before MTC, and there are no symptoms.

The rest of the thyroid gland usually works normally in people with MEN2. Most people with MEN2 who still have their thyroid make thyroid hormone normally.

Diagnosis of Medullary Thyroid Cancer

Your doctor may suspect that you have thyroid cancer based on different medical tests, such as:

- Blood tests – MTC is measured in the blood by looking at two proteins: calcitonin and **carcinoembryonic antigen (CEA)**. Calcitonin and CEA are usually higher than normal in people with MTC. People with C-cell hyperplasia may have calcitonin levels that are higher than normal but usually not as high as in patients with MTC.
- Ultrasound – An ultrasound checks if there are any nodules in the thyroid. An ultrasound uses sound waves that bounce off organs to make a picture. Ultrasound may be used to guide a biopsy.
- CT scan – CT scans (also called CAT scans) or MRI scans create detailed pictures of the thyroid or other organs.

Doctors diagnose MTC by looking at tissue under a microscope. Your doctor may do a biopsy using a thin needle to get a sample of the tumor. Or your doctor may take a tissue sample during surgery.

Treatment of Medullary Thyroid Cancer

MTC is treated with surgery. The entire thyroid gland is removed (**thyroidectomy**), and sometimes the **lymph nodes** from the neck are removed (lymph node or neck dissection).

When MEN2 is diagnosed early, many people have the thyroid gland removed before any signs of MTC are present. This is called a **prophylactic** thyroidectomy. See page 27 for more information.

Once the thyroid has been completely removed, people develop **hypothyroidism**. This means that they do no make enough thyroid hormone. People who have had a thyroidectomy must take medicine every day to replace thyroid hormone. They need regular blood tests to monitor the body's thyroid hormone level.

Hypothyroidism is a common condition, and most people live normal lives with it as long as they take the right dose of hormone. Children with hypothyroidism grow and go through puberty normally as long as they receive the right dose. The dose will need to be adjusted regularly as the child grows.

Treatment is unique to each person. Your doctor will look at the location, size and growth of MTC to help you determine your best treatment option.

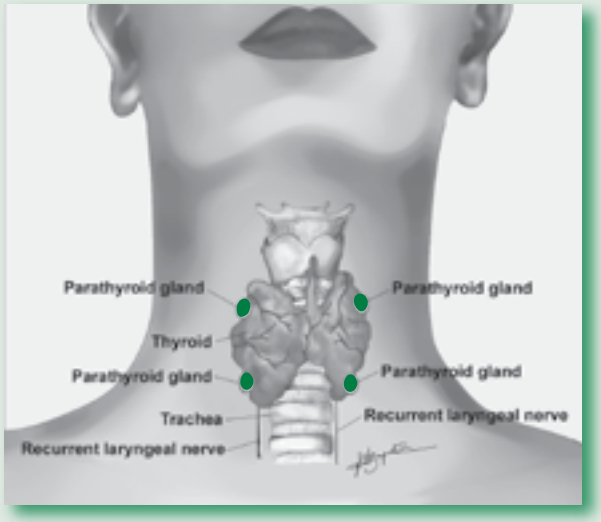
The type of surgery needed and the chance for cure depends on how far MTC has spread outside the thyroid gland. MTC spreads most commonly to lymph nodes in the neck or lymph nodes in the upper middle part of the chest. Like many cancers, MTC can spread to other places in the body, such as the liver, lungs or bones. After surgery, calcitonin and CEA levels in the blood can help determine if the surgery was a success.

- If the thyroid is removed before MTC develops, then the risk of developing MTC is extremely low.
- If MTC is already present, the best chance for a cure is to have surgery before it has spread outside of the thyroid gland.
- If the cancer has spread to lymph nodes in the neck but not beyond, surgery leads to a cure or long-term survival in more than 70 percent of patients.
- If MTC spreads to other places outside of the thyroid, several treatment options may be considered, including:
  - Observation
  - Surgery
  - Radiation
  - Chemotherapy

In some cases, MTC grows slowly over years or even decades. Some patients have had spread of MTC and lived healthy, full lives for more than 30 years. More commonly, the tumor grows slowly but steadily over two to 10 years.

During this time, symptoms, such as diarrhea, may develop. These symptoms can usually be treated. Many patients with MTC live full and enjoyable lives even with relatively extensive cancer.

Parathyroid Glands and Primary Hyperpara-thyroidism



The thyroid and parathyroid glands

The parathyroid glands are pea-sized organs near the back of each corner of the thyroid gland. Although the names are similar, the parathyroid glands are completely different from the thyroid.

Most people have four parathyroid glands, but some people may be missing a gland or have an extra gland. The parathyroid glands make **parathyroid hormone (PTH)**, which controls the balance of **calcium** and phosphorus between the bones, blood and urine. PTH also helps the body make **vitamin D** and maintain the right amount in the body.

Primary hyperparathyroidism (PHPT) happens in as many as 20 percent (1 out of 5) of people with MEN2. The most common age of diagnosis is when a person is in their 30s or older. PHPT is not usually found in children with MEN2.

PHPT is caused by an overgrowth of one or more of the parathyroid glands. The overgrowth of one gland is often called an **adenoma**.

PHPT causes the body to make too much PTH. The

extra PTH tricks the body into thinking that the level of calcium in the blood is too low. As a result, calcium stored in the bones is released into the bloodstream, causing too much calcium in the blood. (This is called **hypercalcemia**.)

While PHPT is usually not a serious condition, over time, untreated PHPT may cause weakness and thinning of the bones. (This is called **osteoporosis**.) In addition, the body moves extra calcium from the blood into the urine, which may cause kidney stones. PHPT may also cause symptoms like having less energy, muscle weakness and bone or joint pain.

Diagnosis of Primary Hyperparathyroidism

Doctors diagnose primary hyperparathyroidism based on blood tests. Usually, the blood (serum) calcium and PTH level are both high.

Treatment of Primary Hyperparathyroidism

PHPT is treated by surgery, and the abnormal parathyroid gland or glands are removed.

Treatment options include:

- Conventional **parathyroidectomy** – The doctor checks all four parathyroid glands during surgery and takes out the most abnormal one.
- Minimally invasive parathyroidectomy – The doctor checks and takes out only one parathyroid gland. This can be done only if the location of the abnormal parathyroid gland is known before surgery. Tests before surgery, such as ultrasound, CT or MRI scan, and/or a special test called a **sestamibi scan**, can determine if the abnormal gland can be found.
- Subtotal parathyroidectomy – The doctor checks all four parathyroid glands, removes 3 ½ glands, and leaves as little as one-half of the most normal gland in place.
- Total parathyroidectomy with parathyroid **autotransplantation** – The doctor removes all four parathyroid glands from the neck and puts a small amount of parathyroid tissue into the arm. The parathyroid tissue stays in the arm and supplies the needed parathyroid hormone.

Treatment of PHPT in people with MEN2 can be different from the treatment of PHPT in people who do not have MEN2. If your doctor thinks you may need surgery again in your neck in the future, he or she may recommend parathyroid autotransplantation no matter how many parathyroid glands need to be removed.

This is to help prevent a condition called **hypoparathyroidism** – not having enough parathyroid hormone. Having more than one surgery in your neck increases the chance of hypoparathyroidism. If you have hypoparathyroidism, then you may have a very low level of calcium in the blood, which could require you to take calcium pills long-term.

Your doctor will discuss your

Frequently Asked Questions About Hyperparathyroidism

Can PHPT come back after surgery?

Yes. You will need regular blood tests to check your parathyroid, calcium and other hormone and vitamin levels. If you never have hyperparathyroidism again, you do not need surgery. If you do get hyperparathyroidism again, you may need more surgery.

options with you.

Adrenal Glands and Pheochromocytoma

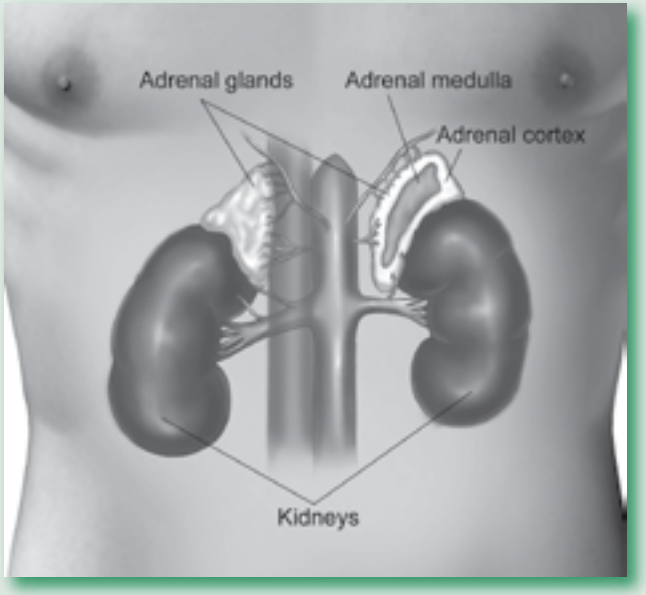
The adrenal glands are triangle-shaped organs near the back of the upper abdomen. There are two adrenal glands: one on top of each kidney. The adrenal glands make hormones that help the body respond to stress and that affect the heart and blood vessels.

Each adrenal gland is divided into an outer cortex and an inner medulla, much like how a hardboiled egg is made up of an outer white part and inner yellow yolk:

- The **adrenal medulla** (inner part) makes hormones known as **catecholamines**, which are "stress hormones." They increase alertness, strength and speed in an emergency. Some examples of catecholamines are:
  - **Epinephrine**, also known as adrenaline
  - **Norepinephrine**, also known as noradrenaline
- The **adrenal cortex** (outer part) makes **steroid** hormones that balance the water and salt in the body and control blood pressure. Some examples of hormones made by the adrenal cortex are:
  - **Cortisol**
  - **Aldosterone**

Up to 50 percent (1 out of every 2) of people with MEN2 can have tumors of the adrenal medulla. A tumor of the adrenal medulla is also called a **pheochromocytoma**. Often, people with MEN2 are diagnosed with this while in their 20s or 30s. Pheochromocytoma can sometimes be the first sign or cause the first symptoms of MEN2.

Pheochromocytomas are rarely cancerous in people with MEN2, but, they cause the levels of stress hormones in the blood to be too high. These may not cause any symptoms, or they may cause symptoms that feel like you are reacting to an emergency. These symptoms might include:



The adrenal glands and kidneys

- High blood pressure
- Sweating for no reason
- Headache
- A rapid or irregular heartbeat
- Dizziness or lightheadedness
- Feelings of anxiety like a panic attack

Pheochromocytomas may develop in both adrenal glands in people with MEN2. This may happen at the same time, or a second tumor may be diagnosed months to several years after the first.

Diagnosis of Pheochromocytoma

Doctors usually diagnose pheochromocytomas based on blood tests or urine tests. The catecholamines, or a related substance called **metanephrines**, are higher than normal.

Once your doctor suspects a pheochromocytoma from blood or urine tests, then he or she will want you to have imaging tests. The imaging tests will

show if the tumor is in the left adrenal gland, right adrenal gland or both.

The most common imaging tests used for pheochromocytomas are **CT scans** or **MRI scans**. **MIBG scans** may also be used. A MIBG scan involves an injection of a low-dose radioactive material. The radioactive material is able to attach to the tumor cells. A device then sees the radioactivity and makes a picture of the tumor cells in the body.

Treatment of Pheochromocytoma

Pheochromocytomas are treated by surgery. Usually the entire adrenal gland with the tumor is removed. This is known as an **adrenalectomy**.

In some cases, the surgeon may be able to spare a portion of the cortex by removing only the tumor within the adrenal medulla.

A **laparoscopic** approach uses smaller cuts and small instruments. This may be possible in some patients and when the tumor is small and only in one adrenal gland. The cuts can be made either from the front or back of the body.

People having surgery to treat pheochromocytoma must take medicines to control their blood pressure before the operation. The medicine is usually an **alpha-blocker**. This helps prevent the person's blood pressure from going too high during the surgery.

If both adrenal glands are completely removed (known as a **bilateral** adrenalectomy), the person has **adrenal insufficiency**. People with adrenal insufficiency must take medicines for the rest of their lives. The medicine is needed to replace the hormones made by the adrenal cortex, which are

Frequently Asked Questions About Pheochromocytomas

If I've had both of my adrenal glands removed, where can I get a medical alert bracelet?

You may purchase medical alert bracelets at many pharmacies, or you may order them online. They come in different styles and prices. Make sure to ask your doctor what should be written on your bracelet.

essential for life. The hormones made by the adrenal medulla are not essential and do not need to be replaced.

People who have had both adrenal glands completely removed are at risk for **adrenal crisis**. An adrenal crisis is caused by not having enough cortisol. This can happen during times of high physical stress, such as a serious illness or injury, such as a major infection or motor vehicle accident. An adrenal crisis is a life-threatening condition, but an injection of cortisol can be life-saving. People who have had both adrenal glands completely removed should wear a medical alert bracelet stating that they have had bilateral adrenalectomy.

Subtypes of MEN2: MEN2A, MEN2B and FMTC

There are three subtypes of MEN2: MEN2A, MEN2B and FMTC (familial medullary thyroid cancer). All three subtypes cause a high risk for MTC, but not all cause the same risk for pheochromocytoma and primary hyperparathyroidism. Also, the age when MTC typically develops and its aggressiveness differs

by subtype.

For people with MEN2A:

- MTC typically develops in adolescence or early adulthood.
- MTC is moderately aggressive.
- There is a high risk for pheochromocytoma (up to 50 percent).
- There is a risk for hyperparathyroidism (up to 20-30 percent).
- Some people have an itchy skin rash on their upper back that does not go away. This is called **cutaneous lichen amyloidosis**. This condition occurs occasionally in people who have a gene mutation of codon 634. (See page 24 for more information about codons.)
- Rarely, a condition called **Hirschsprung disease** happens. Hirschsprung disease is when the large intestine did not develop properly; the nerves do not grow into the colon normally. Hirschsrpung disease is noticed shortly after birth: Children have constipation, which means that bowel movements are difficult. Some children can't have bowel movements at all. The stool creates a blockage in the intestine. Hirschsprung disease usually needs to be treated surgically. The condition is rarely linked to gene mutations of codons 609, 611, 618 and 620. (See page 24 for more information about codons.)

For people with MEN2B:

- MTC typically develops in early childhood.
- MTC is more aggressive than the other MEN2 subtypes.
- There is a high risk for pheochromocytoma (about 50 percent).
- People have distinct physical traits, such as:
  - Small non-cancerous tumors on the lips, tongue and eyelids known as **neuromas**: The tumors make the tongue look bumpy, the lips look larger, and the eyelids to be slightly upturned.
  - Many people also have a thin body build, long arms and legs, flexible joints and foot abnormalities: This body type is often referred to as "**Marfanoid**," but has nothing to do with the condition Marfan syndrome, for which it is named.
- People can have small non-cancerous tumors grow inside the **intestines** known as **ganglioneuromatosis**: This can cause the intestine to become large and irritated.

For people with FMTC:

Frequently Asked Questions About MEN2 Subtypes

How do I know which MEN2 subtype I have?

Any person with a RET gene mutation has MEN2. The subtype can be determined based on your genetic testing results or your family history.

If my parent developed pheochromocytoma, does it mean that I will too?

No. The risk of developing pheochromocytoma varies. Having a parent or other relative with pheochromocytoma does not mean that you will develop one. Similarly, if a parent or other relative does not have a pheochromocytoma, it does not mean that you are not at risk.

- MTC most often does not develop until adulthood.
- MTC tends to be the least aggressive of the MEN2 subtypes.
- The risk for pheochromocytoma and hyperparathyroidism is very low.

It is easy to tell apart people who have MEN2B based on their physical traits and on specific genetic test results. (See page 21 for the section on genetic testing.)

It can be tricky to tell people who have MEN2A apart from those with FMTC. FMTC is like MEN2A but with a much lower risk of developing pheochromocytoma or hyperparathyroidism, and with a form of MTC that develops later in life and is less aggressive.

Genetic tests are helpful to try to determine the risk for pheochromocytoma and hyperparathyroidism. (See page 21 for more information.)

Genetics and Inheritance

The Role of Genes in MEN2

Genes are parts of **DNA** that are found in each of the cells that make up the body. DNA is like the body's instruction manual: It provides the information needed to tell the body how to do everything.

A gene is one part of that instruction manual. Each gene is a code for a particular protein. Each protein has a job it needs to do to help the body work. People get their genes from both of their parents. Every person has two copies of most of their genes: one from their mother, one from their father.

Many genes are responsible for controlling the way the body's cells grow and divide. Genes that encourage the cells to grow and divide faster are called **proto-oncogenes**. The gene that is linked to MEN2 is a type of proto-oncogene. The gene is called the **RET** proto-oncogene.

All tumors and cancer are caused by changes in genes. These changes are called **mutations**. In most people who have cancer, at some point in their lives, a mutation occurred in one cell. It is a random mistake. In people who have MEN2, though, a mutation in one of the RET gene copies is in every cell of the body when they are born. The mutation will be with them throughout their lives. In many cases, it came from a gene that they received from their mother or father.

When a mutation occurs in the RET gene, it is active all of the time: It does not turn itself off when it should. As a result, the cells it controls are more likely to form tumors compared to a person who is born with two normal RET gene copies. The RET gene has its most important role in the cells of the thyroid, parathyroids and adrenal medulla. This is why these are the main types of tumors that happen.

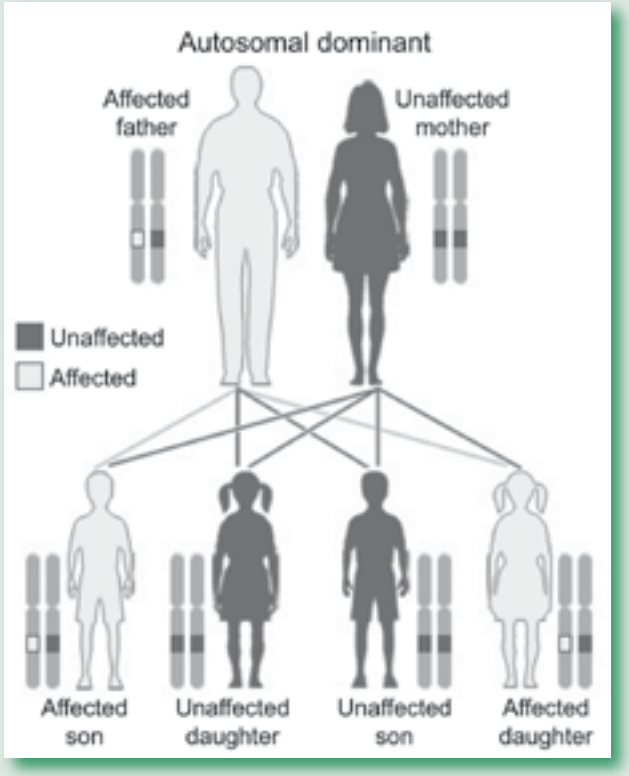
How MEN2 Is Passed on in Families

People with MEN2 have the RET mutation in every cell of the body, including the egg and sperm cells that make babies. Therefore, the mutation may be passed from a parent to a child. People pass on one copy of each gene to a child. Because people with MEN2 have a mutation in only one of the two copies of their RET gene, each child has a 50 percent (1 out of 2) chance of getting the RET gene mutation from their parents.

The second copy of the RET gene is completely normal. So, each child also has a 50 percent chance of getting the normal RET gene copy. A child who inherits the normal RET gene

copy does not have MEN2.

Males and females have an equal chance of inheriting the mutation. Also, the mutation does not skip generations. If a person does not inherit MEN2, they cannot pass it on to their children. This pattern of inheritance is called **autosomal dominant inheritance**.



Genetic inheritance of MEN2
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Genetic Testing for MEN2

Since every cell has the RET gene mutation, it is possible to use a blood sample for genetic testing. Genetic testing involves checking a person's DNA from a blood sample to look for a mutation of the RET gene. This is like an editor reviewing a newspaper for spelling mistakes.

Ninety eight percent of people with MEN2 have a mutation that can be found with genetic testing. Rarely will people with MEN2 have a mutation that current tests cannot detect. When possible, genetic testing should always start in a family member who is known to have MEN2. Doing this ensures that the mutation causing MEN2 in the family can be detected.

There are three possible results from genetic testing:

1. Positive: This result always means that the person has MEN2, even if they have no symptoms or tumors.

2. Negative: If genetic testing is negative, this can mean either:

   - The person does not have MEN2 (if a MEN2 mutation is known in the family)
   - The mutation causing MEN2 cannot be found with current tests, and the person may still have MEN2. Importantly, if a RET gene mutation cannot be detected in an affected member of the family, genetic testing is not helpful for other family members. Talk to a doctor or genetic counselor about this.

3. Uncertain: An uncertain result does not give any information. Talk to a doctor or genetic counselor about what to do next.

RET genetic testing is one of the most important tests for people with MEN2 and their families. Once a mutation has been found in an affected family member, then other family members can have genetic testing for the same mutation. There are several benefits for genetic testing:

- If you are negative, then you do not have MEN2. This may create a sense of relief and may do away with the need for many checkups and tests.
- If you are positive, it can relieve doubt and allow you

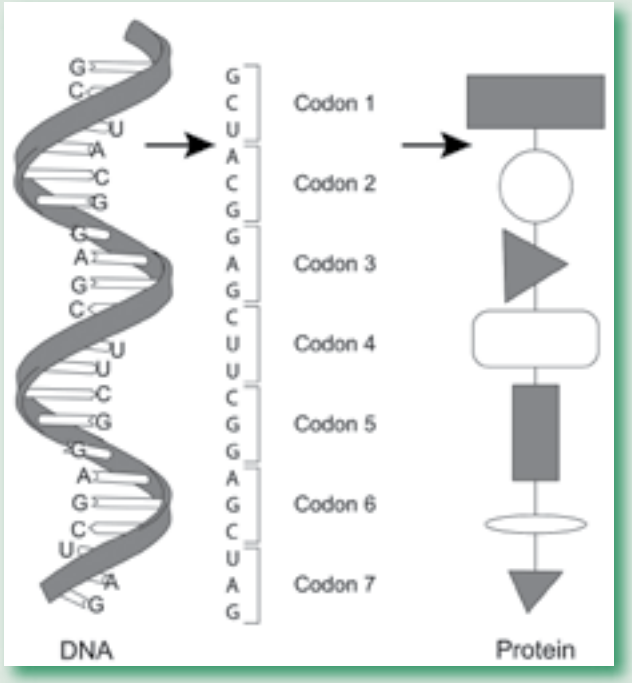
to make informed decisions about the future and your children's future.

- Genetic testing can often predict the MEN2 subtype. MEN2 has **genotype-phenotype correlations**. This means that mutations in certain locations of the RET gene are more likely to be linked to MEN2A. Others are more likely to be linked to FMTC. And two locations are linked to MEN2B. This helps doctors make decisions about treatment. (See page 27 for more information.)

Doctors often describe the location of mutations in terms of a **codon**. DNA is made up of "letters", and each set of three letters is a codon. Codons are numbered in order from the beginning to the end of the gene. Numbering the codons helps define a location in the gene, just like a number on a house tells its location on a street.

The table on page 25 summarizes MEN2 genotype-phenotype correlations.

Genetic testing poses little physical risk since you would just give a simple blood sample; but, the result may have a major affect on your life. Plus, genetic tests reveal information not only about you, but also about your relatives and children. The results may affect family and other personal relationships.



A gene is a segment of DNA that makes a protein. Each set of three letters of the DNA code is known as a codon. A codon makes one piece of a protein.

Frequently Asked Questions About Genetics

If one of my children does not have MEN2, will my other child have MEN2?

The status of one child cannot predict the status of another child. Each child of a person with MEN2 has a 50 percent (1 in 2) chance of having MEN2. The chance is the same for each child.

Where can I go to have genetic testing?

A health care provider must order genetic testing. Most major cities have geneticists or genetic counselors that can talk with you about MEN2. They order genetic tests, too. Ask your doctor to refer you to a local genetic counselor. If there are no genetic counselors in your area, ask your doctor if he or she can order it for you.

How should I tell my children and other family members about MEN2? Can my doctor call my relatives?

Telling your family members about MEN2 is up to you. A doctor cannot call your relatives on your behalf. It can be hard to talk to relatives, especially children, about MEN2. You may ask your doctor or genetic counselor for help if you are having trouble.

People express different emotions when learning that they are at an increased risk of medical conditions and cancer. Some of the risks of genetic testing are:

- Extra stress
- A different view or belief of himself or herself
- Different expectations out of life
- Changed relationships between family members

Some of the benefits of genetic testing are:

- Relief from doubt
- More time to adjust to the diagnosis and plan for the future
- More information to make choices about having children, a career, education, insurance or lifestyle

Summary of Genotype-Phenotype Correlations

RET Codon	MEN2 Subtype	Risk for Pheochromocytoma	Risk for Hyperparathyroidism
609 611 630 768 790 804 891	Usually FMTC	Low	Low
618 620 791	MEN2A or FMTC	Moderate	Low
634	MEN2A	High	Moderate
883 918	MEN2B	High	No increased risk

Genetic Privacy and Discrimination

Because genetic test results hold a wealth of information, privacy is a major concern. In 1996 and 2008, the federal government passed laws to protect a person's privacy concerning the results of genetic tests. These laws include:

- Health Insurance Portability and Accountability Act (HIPAA)
- Genetic Information Nondiscrimination Act (GINA)

It is against the law for insurance companies and employers to discriminate against anyone based on genetic information. For more information about genetic privacy and discrimination, go to the National Human Genome Research Institute (htpp://www.genome.gov).

Genetic Counseling

The decision to have genetic testing is a personal one, and experts stress that it should be voluntary. Many people who are considering genetic testing benefit from meeting with a **genetic counselor**. Genetic counselors are specially trained medical professionals who can help explain MEN2 and the benefits and risks of genetic testing. They help people make informed decisions and help them decide whether they are at a good time in their lives to learn their genetic information.

Genetic counselors and other genetics services can be found using the National Society of Genetic Counselors "Find a Counselor" resource at http://www.nsgc.org or on the National Institute of Health's

Web site (http://www.cancer.gov/search/genetics_services).

Prevention and Screening in MEN2

Prevention of Medullary Thyroid Cancer (MTC)

If MEN2 is diagnosed early, and there are no signs of MTC, then there are two options to prevent or lower the risk of MTC:

- Remove the thyroid gland before any signs of MTC are present. This is called a prophylactic thyroidectomy.
- Monitor the thyroid using ultrasound and blood tests to delay having a thyroidectomy. If MTC is caught early, before it has spread to the lymph nodes, it can usually be cured.

Most doctors agree that at some point, nearly all people with MEN2 will need a thyroidectomy.

In 2009, the American Thyroid Association (ATA) created guidelines to treat people with MEN2. The most common RET codon mutations are sorted into one of four levels: A, B, C and D. The levels determine:

- The age when RET genetic testing should be done
- The age when the thyroid should be checked with ultrasound and calcitonin blood testing
- The age when a thyroidectomy is recommended

The table on page 29 summarizes the ATA guidelines for the most common RET mutations. (Ask your doctor for another list if your mutation is not in this table.) This table reviews advice for patients who are without signs of MTC. For patients with a diagnosis of MTC, there may be different guidelines.

For children and adults with a risk level A or B mutation, the decision to have a thyroidectomy or to delay it can be difficult. Doing a thyroidectomy early may help relieve anxiety about risk for MTC, but then the person must take thyroid hormone replacement medicine every day for the rest of his or her life. Delaying a thyroidectomy has the benefit of not needing to take thyroid hormone replacement medicine, but some people may be nervous about MTC developing. Every person must talk to his or her doctor to decide what is best.

Screening in MEN2

Screening refers to medical tests that are done on a healthy person who has no symptoms. The goal of screening is to detect tumors as early as possible.

Frequently Asked Questions About MEN2 Management

If my child needs a thyroidectomy, how will the surgery affect his or her growth and development?

After a thyroidectomy (surgical removal of the thyroid), medicine must be taken every day to replace the normal function of the thyroid. The dose of the medicine will need to be adjusted as the child grows. Usually, growth and development are normal.

If my child has the thyroid gland removed, what is the chance that he or she will have thyroid cancer? What is the chance of developing thyroid cancer in the future?

It depends. The age of the child and the type of RET gene mutation affect cancer risk. In general, a cure is more likely if the thyroid is removed before cancer has developed or when a cancer is small.

Screening for MEN2 involves blood tests. These measure the levels of the main hormones that are made by MTC, the adrenal medulla and the parathyroid glands. The hormones serve as a signal or tumor marker. If a particular hormone is high, it means that there might be a tumor forming. The following blood tests are recommended at least once a year:

- Calcitonin, which detects MTC
- Free plasma metanephrines, which is the best test to detect pheochromocytomas (Blood should be taken after a person has been lying down in a dark, quiet room for at least 30 minutes.)
- Calcium, which detects hyperparathyroidism
- Intact parathyroid hormone, which also detects hyperparathyroidism

ATA Risk Level	RET Codons	Age to do RET Genetic Testing	Age to Start Checking Thyroid	Age of Thyroidectomy
A	768, 790, 791, 804, 891	By 3-5 years	By 3-5 years	May be delayed*
B	609, 611, 618, 620, 630	By 3-5 years	By 3-5 years	Consider by age 5, but may be delayed*
C	634	By 3-5 years	By 3-5 years	By age 5
D	883, 918	As soon as possible within the first year of life	As soon as possible within the first year of life	As soon as possible within the first year of life

*A thyroidectomy can be delayed as long as:

- The calcitonin level is checked every year and is normal.
- The thyroid ultrasound is checked every year and is normal.
- MTC is not very aggressive in the family.

People with MEN2 need screening for pheochromocytoma and hyperparathyroidism. After a thyroidectomy, calcitonin levels should still be measured. There is a small chance that thyroid cells could be left in the body after a thyroidectomy that could turn into cancer. For people who have been treated and cured of MTC, there is a chance that the cancer could come back or recur.

Early detection and treatment of a cancer **recurrence** is the best chance for long-term cure. This can help avoid medical problems that result from extra hormone levels that these tumors make.

For example, if primary hyperparathyroidism is not treated, bone density decreases over many years. This may raise the risk for breaking a bone. If a pheochromocytoma is not detected, it can cause life-threatening high blood pressure.

Resources and Support

MEN2 requires regular lifelong checkups and tests. The condition can be difficult emotionally, physically and financially. You may worry:

- If you will be able to live your life normally
- That every symptom is caused by a tumor
- About your children and other members of your family

All of these feelings are common. People can do the following things to cope with a

medical condition:

Physically

- **Keep your body healthy**. People who are healthy and have a normal weight tend to recover more easily from surgery. In addition, you lower your risk for other common conditions that happen with poor diet and lack of exercise, such as diabetes, heart disease and other types of cancer.

Emotionally

- **Learn how to manage stress**. Exercise, listen to music, read, meditate or talk to others about what is going on in your life. Make time for fun. Every person should figure out what works best for him or her to relieve stress.
- **Help yourself feel in control**. Some people seek information about MEN2. Others keep a busy schedule and take part in hobbies so that their lives are full of non-medical activities.
- **Know that negative feelings are normal**. You may blame yourself or someone else for what's happening to you or your family. Or you may envy other people's good health. Even people who do not have MEN2 in the family may feel guilty that they are healthy when other people are not. Remember that people do not have control over their genes, and there is nothing that people do or don't do that causes MEN2 tumors to grow. Anger and frustration are also common. Anger is usually a sign of worry or stress that may be taken out on others.
- **Find someone to talk to**. Many people find it helpful to share their feelings with their close family members and friends or a support group. Support groups are particularly helpful when you need to talk to someone outside your family. They may be better able to understand what you're going through.
- **Be hopeful**. Keep in mind that regular checkups can often detect tumors years before symptoms usually start. For people who already have cancer, it is important to remember that having cancer does not necessarily mean that you will die from cancer. Many people live a long time with cancer.
- **Know when to seek help**. Feelings of depression are common for many people. If feelings of sadness or despair seem to take over your life, let your doctor know. Depression is treatable with medicine or counseling. Asking for help is not a sign of weakness.

Legally

- **Know your legal rights**. The Genetic Information Nondiscrimination Act of 2008 and the Health Insurance Portability and Accountability Act (HIPAA) of 1996 protect people against discrimination based on genetic information. HIPAA also protects people with a medical illness from insurance discrimination. The Federal Rehabilitation Act of 1973 and the Americans With Disabilities Act of 1990 are national laws that protect against employers discriminating against people who have disabilities, including certain medical illnesses. The Family and Medical Leave Act allows most workers to take up to 12 weeks of time to deal with certain family and medical problems.

M. D. Anderson Cancer Center Resources

Endocrine Center

The Endocrine Center at M. D. Anderson brings together experts who treat cancers and related diseases of the thyroid, parathyroid and adrenal glands.

713-563-7600

http://www.mdanderson.org/care_centers/endocrine

Clinical Cancer Genetics Program
The Clinical Cancer Genetics Program at M. D. Anderson Cancer Center is dedicated to providing hereditary cancer risk assessment and consultation services.
713-745-7391
toll-free 877-641-0979
http://www.mdanderson.org/departments/ccg/

The Learning Center
The Learning Center is a consumer health library with the latest information on cancer care, support, prevention and general health and wellness issues.
713-745-8063
http://www.mdanderson.org/tlc

Support Programs
Find support programs, get help with advance directives and be inspired by stories of patients who have made the cancer journey.
713- 792-2553
toll-free 800-345-6324
http://www.mdanderson.org/patients_public/support_programs

Place … of wellness
The Place … of wellness is an environment where all persons touched by cancer may enhance their quality of life through programs that complement medical care and focus on the mind, body and spirit.
713-794-4700
http://www.mdanderson.org/departments/wellness

MEN and Endocrine Tumor Web Sites

The Association for Multiple Endocrine Neoplasia Disorders (AMEND)
AMEND is a UK-registered charity committed to supporting all those affected by multiple endocrine neoplasia (MEN) and its associated endocrine growths.
http://www.amend.org.uk

How do I become a patient at M. D. Anderson Cancer Center?

Please call our new patient line at 713-563-4400 for more information about becoming a new patient in the Endocrine Center. For appointments for children 18 years old or younger, please call 713-792-5410.

You may also call askMDAnderson at 877-MDA-6789 or visit our Web site at http://www.mdanderson.org.

Where do I go to learn more?

Please talk to your doctor for more information. You may also contact the genetic counseling program at M. D. Anderson at 713-745-7391 or ccg@mdanderson.org to set up an appointment with a genetic counselor.

Please talk to your social worker for more information about support programs.

The Pheo-Para Alliance
This site gives information to patients and health care providers about pheochromocytomas.
http://www.pheo-para-alliance.org

American Thyroid Association
This organization is focused on thyroid biology and the prevention and treatment of thyroid disorders through excellence and innovation in research, clinical care, education and public health.
http://www.thyroid.org/

ThyCa: Thyroid Cancer Survivors' Association, Inc.
This network of services links thyroid cancer survivors and health care professionals around

the world.
http://www.thyca.org

National Organization for Rare Disorders
NORD is committed to the identification, treatment and cure of rare disorders through programs of education, advocacy, research and service.
203-744-0100
toll-free 800-999-6673
http://www.rarediseases.org

General Cancer Resources

National Cancer Institute
Comprehensive cancer information from the U.S. National Institutes of Health
http://www.cancer.gov

American Society of Clinical Oncology
Get oncologist-approved cancer information from the American Society of Clinical Oncology.
571-483-1780
toll-free 888-651-3038
http://www.cancer.net

I'm Too Young For This!
This foundation works exclusively on the behalf of teens and young adults with cancer who are under the age of 40.
toll-free 877-735-4673
http://www.i2y.com

Rare Cancer Alliance
This group provides information and support to rare cancer patients.
http://www.rare-cancer.org

General Genetics Resources

Genetic Alliance
This non-profit health advocacy organization is committed to transforming health through genetics.
202-966-5557
http://www.geneticalliance.org

The National Society of Genetic Counselors, Inc. (NSGC)
This is a professional membership association for the genetic counseling profession. NSGC has developed a resource link to help consumers in locating genetic counseling services.
http://www.nsgc.org

Genetic Service Learning Center
This interactive site has information about basic genetics, genetic disorders, genetics and society and much more.
http://www.gslc.genetics.utah.edu

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Acknowledgment

We would like to thank the Association for Multiple Endocrine Neoplasia Disorders and the Roberto and Lucy Faith Fund for Endocrine Research for their valuable help and support.

Glossary

Adenoma – a non-cancerous tumor of gland-like tissue.

Adrenal cortex – the outer part of the adrenal gland which makes steroid hormones, such as cortisol and aldosterone.

Adrenalectomy – surgical removal of an adrenal gland.

Adrenal gland – a gland that makes steroid hormones that help control heart rate, blood pressure, and other important body functions. There are two adrenal glands, one on top of each kidney. Each adrenal gland has an outer cortex and inner medulla.

Adrenal crisis – a life threatening situation in which the body does not make enough cortisol. An adrenal crisis can be triggered during times of high physical stress or a serious injury An injection of cortisol can be life-saving.

Adrenal insufficiency – a condition in people who have had both adrenal glands completely removed. People with adrenal insufficiency are at risk for an adrenal crisis.

Adrenal medulla – the inner part of the adrenal gland. It makes catecholamines.

Aldosterone – an essential steroid hormone made by the adrenal cortex that helps control the balance of water and salts in the body.

Alpha-blocker – one of several types of medicines often used to control high blood pressure.

Autosomal dominant inheritance – a type of inheritance pattern. A parent with an autosomal dominant disorder has a 50 percent chance to pass it on to each of his or her children. Inheritance is the same for males and females, and it doesn't "skip" generations.

Autotransplantation – the placement (usually by a surgeon) of a tissue from one site into another.

Benign – not cancerous. A benign tumor may not cause any health problems. Some benign tumors can cause medical problems if they are large or make hormones. A benign tumor cannot spread to other locations in the body.

Bilateral – referring to both the right and left sides of the body or both of a paired organ in the body.

Calcitonin – a hormone produced by the c-cells of the thyroid. Commonly used as a tumor marker for people with medullary thyroid cancer.

Calcium – a mineral found in bones, teeth and many other body tissues.

Carcinoembryonic antigen (CEA) - a substance found in the blood that is used as a tumor marker for certain cancers, including medullary thyroid cancer.

Catecholamines – hormones important in stress responses. High levels cause high blood pressure, headaches, sweating, pounding of the heart, pain in the chest and anxiety. Examples of catecholamines include dopamine, epinephrine (adrenaline) and norepinephrine (noradrenaline).

C-cell – a type of cell in the thyroid that makes the hormone calcitonin.

Cell – a unit that makes up the tissues of the body. The human body contains billions of cells that each has a specific job.

Codon – a segment of a gene that codes for one unit of a protein. The location of gene mutations are often described in terms of the codon that the mutation affects.

Cortisol – an essential steroid hormone made by the adrenal

cortex that helps the body use sugar, fats and protein.

CT or CAT scan – a type of medical test that involves taking a series of X-rays to create a detailed picture of the inside of the body. Also called computed tomography scan, computerized axial tomography scan and computerized tomography.

Cutaneous lichen amyloidosis – an itchy skin rash that occurs occasionally in people who have a mutation of RET codon 634.

DNA – genetic information that is passed down from parent to child.

Endocrine – refers to a type of cell or tissue that makes one or more hormones.

Endocrine system – a collection of glands that regulates and coordinates all the body's normal functions. The endocrine system is made up of the thyroid gland, parathyroid glands, pituitary gland, adrenal glands, endocrine pancreas and other organs.

Epinephrine – see catecholamines.

Follicular cell – a type of cell in the thyroid that makes thyroid hormone.

Ganglioneuromatosis – a condition in which there are many benign tumors arising from nerve tissue. Ganglioneruomatosis in the colon is usually caused by MEN2B.

Gene – a section of DNA that usually contains information for making a particular protein. Genes are passed down from parent to child.

Genetic – refers to information that can be passed on from a parent to a child through genes.

Genetic counselor – a medical professional specially trained to discuss genetic conditions, genetic risks and genetic testing.

Genetic testing – a test usually performed on a sample of blood to look for a mutation in a specific gene. Often used to detect a genetic condition in a person.

Genotype – the genetic makeup of a person; for example, the exact RET gene mutation.

Genotype-phenotype correlation – the ability to predict diseases or traits based on genetic makeup.

Gland – organs that make hormones, digestive juices, sweat, tears, saliva or milk.

Hereditary – a condition that can be passed on from a parent to a child through information contained in genes through sperm or egg cells.

Hirschsprung disease – a disorder in which the large intestine does not develop properly resulting in severe constipation. Symptoms are usually present shortly after birth.

Hormone – a chemical messenger made by endocrine glands. Hormones are secreted into the blood stream and help regulate normal body function.

Hypercalcemia – too much calcium in the body.

Hyperplasia – an abnormal increase in the number of cells in a particular organ. Hyperplasia is not cancerous.

Hypocalcemia – too little calcium in the body.

Hypoparathyroidism – too little production of parathyroid hormone.

Hypothyroidism – too little production of thyroid hormone

Intestine – a long tube-shaped organ that aids in digestion. There is a small intestine and a large intestine. The large intestine is also

known as the colon.

Laparoscopic – refers to surgery done with the aid of a thin, tube-like instrument with a light and a lens for viewing. It allows the surgeon to make a smaller cut than traditional surgery. The smaller cut makes healing faster.

Lymph nodes – a body tissue that filters water and fluid. It helps the body fight off infections. Cancer cells can use the lymph nodes to move through the body.

Malignant – cancerous. A malignant tumor can spread to other locations in the body.

Marfanoid – resembling the condition Marfan syndrome. Marfan syndrome is characterized by a thin body type, the roof of the mouth can be high, long extremities (arms, legs, fingers and toes), joint flexibility and foot abnormalities.

Medullary thyroid cancer – a malignant tumor of the c-cells of the thyroid.

Metanephrines – hormones important in stress responses. High levels cause high blood pressure which can lead to headaches, sweating, pounding of the heart, pain in the chest and anxiety. Examples of metanephrines include metanephrine and normetanephrine. Metanephrines are commonly measured in blood tests to screen for and diagnose pheochromocytomas.

MIBG scan – a test that helps to find hormone-making tumors in the body, such as pheochromocytomas. It involves an injection of a low-dose radioactive material.

MRI scan – a type of medical test that uses radio waves and a powerful magnet to create detailed picture of the inside of the body. Also called magnetic resonance imaging, NMRI and nuclear magnetic resonance imaging.

Mutation – any change in the DNA of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. If they are present in egg or sperm cells, they can be inherited. Certain mutations may lead to cancer or other diseases.

Neoplasia – abnormal cell growth.

Neuroma – a tumor arising from nerve cells.

Norepinephrine – see catecholamines.

Normetanephrine – see metanephrines.

Osteoporosis – weakening or thinning of the bones. People with osteoporosis have fragile bones and are at increased risk to break a bone. Osteoporosis is common and has many causes, one of which is primary hyperparathyroidism.

Pancreas – a tadpole shaped organ located in the abdomen that is involved both in digestion and hormone production.

Parafollicular cell – see C-cell.

Parathyroidectomy – surgical removal of one or more parathyroid glands.

Parathyroid gland – one of the four pea-sized glands found on the back corners of the thyroid. The parathyroid hormone made by these glands regulates calcium and vitamin D levels in the blood.

Parathyroid hormone (PTH) – a hormone made by the parathyroid glands. PTH regulates the balance of calcium and vitamin D in the body.

Phenotype – Unique features

that each person has, such as the chance that they get certain traits or diseases.

Pheochromocytoma – a tumor of the adrenal medulla which usually produces catecholamines and/or metanephrines. Symptoms may include headaches, sweating, pounding of the heart, pain in the chest and anxiety.

Pituitary gland – the "master" endocrine gland. It produces hormones that control other glands. The pituitary gland is located in the brain behind the nose.

Predisposition –a higher chance of having certain conditions.

Primary hyperparathyroidism (PHPT) – a medical condition caused when too much parathyroid hormone is made by one or more of the parathyroid glands. It is usually a non-cancerous condition, but if untreated, PHPT can lead to bone loss, kidney stones and symptoms such as decreased energy, muscle weakness, and bone or joint pain.

Prophylactic – something that prevents a disease from occurring.

Proto-oncogene – a normal gene that is involved in cell growth. Mutations in proto-oncogenes can lead to cancer.

Recurrence – a cancer or tumor that was treated in the past has come back, usually after a period of time during which the disease could not be detected.

RET proto-oncogene – a normal gene that is involved in cell growth. People who are born with a mutation in the RET proto-oncogene have the hereditary condition multiple endocrine neoplasia type 2 (MEN2).

Screening – medical tests that are done on a healthy person with no symptoms. Screening is used to detect a particular medical condition early. Also referred to as surveillance.

Sestamibi scan – a medical test used to find overactive parathyroid glands. It involves an injection of a small amount of a radioactive substance called technetium which collects in overactive glands. A special camera detects the radioactivity to create a picture of where overactive glands are in the body.

Steroid – any of a group of fats that have a similar chemical structure. Steroids occur naturally in the body (such as hormones or cholesterol) or they may be made in the laboratory as medicine.

Subtotal parathyroidectomy – surgical removal of 3 ½ out of the four parathyroid glands. One-half of a parathyroid gland is left in place.

Syndrome – a set of symptoms or medical conditions that occur together, usually caused by one underlying problem.

Thyroid – a small butterfly-shaped gland located at the base of the throat near the trachea (windpipe) that helps control growth and energy.

Thyroidectomy – surgical removal of the thyroid gland.

Total parathyroidectomy – surgical removal of all four parathyroid glands. Usually, the surgeon will put a small amount of parathyroid tissue into the person's arm.

Tumor – an abnormal mass of tissue that results when cells divide and reproduce in an unstructured, abnormal way. A tumor can be malignant or benign.

Vitamin D - a nutrient that helps the body use calcium to make strong bones and teeth. Also called cholecalciferol.

Produced by the Patient Education Office