Multiple Endocrine Neoplasia Type 2 [1]

What is multiple endocrine neoplasia type 2?

Multiple endocrine neoplasia type 2 (MEN2) is a hereditary condition associated with three primary types of tumors: medullary thyroid cancer [2], parathyroid tumors [3], and pheochromocytoma. MEN2 is classified into three subtypes based on clinical features.

- MEN2A, which affects 60% to 90% of MEN2 families
    - Medullary thyroid cancer: 98% to 100% with MEN2A are affected
    - Pheochromocytoma, a typically benign (noncancerous) tumor of the adrenal glands [4]: 50% with MEN2A affected
    - Parathyroid adenoma (benign tumor) or hyperplasia, meaning increased size, of the parathyroid gland: 5% to 10% with MEN2A affected
- MEN2B, which affects 5% of MEN2 families
    - Medullary thyroid cancer: 98% to 100% with MEN2B affected
    - Pheochromocytoma: 50% with MEN2B affected

    - Mucosal neuromas, which is a benign tumor of nerve tissue on the tongue, lips and throughout the gastrointestinal tract: 95% to 98% affected
    - Digestive problems caused by disordered nerves in the gastrointestinal tract: 75% to 90% affected
    - Muscle, joint, and spinal problems: 95% affected
    - Typical facial features, including swollen lips and thick eyelids: 75% to 90% affected

- Familial medullary thyroid cancer (FMTC), which affects 5% to 35% of MEN2 families
    - Medullary thyroid carcinoma only

Sources: Gagel RF, Marx SJ. "Multiple endocrine neoplasia." Williams Textbook of Endocrinology, Chapter 40, 11th ed., Philadelphia, 2008, and Eng C, Clayton D, et al. Grubbs EG, Gagel RF. My, How Things Have Changed in Multiple Endocrine Neoplasia Type 2A! J Clin Endocrinol Metab 100(7):2532-5, 7/2015. PMID: 26151398.

What causes MEN2?

MEN2 is a genetic condition. This means that the cancer risk and other features of MEN2 can be passed from generation to generation in a family. The gene associated with MEN2 is called *RET*. A mutation (alteration) in the *RET* gene gives a person an increased risk of developing medullary thyroid cancer and other tumors associated with MEN2.

How is MEN2 inherited?

Normally, every cell has two copies of each gene: one inherited from the mother and one from the father. MEN2 follows an autosomal dominant inheritance pattern, in which a mutation, a change in the DNA sequence that alters the protein sequence, happens in only one copy of the gene. This means that a parent with a gene mutation may pass along a copy of their normal gene or a copy of the gene with the mutation. Therefore, a child who has a parent with a mutation causing MEN2 has a 50% chance of inheriting that mutation. A brother, sister, or parent of a person who has a mutation also has a 50% chance of having the same mutation. If a child inherits the mutated *RET* gene from an affected parent, there is almost a 100% chance of developing medullary thyroid cancer and lower probabilities of developing other features of this syndrome during his or her lifetime.

Options exist for couples interested in having a child when they know that one of them carries a gene mutation that increases the risk for this hereditary cancer syndrome. Preimplantation genetic diagnosis (PGD) is a medical procedure done in conjunction with in-vitro fertilization (IVF). It allows people who carry a specific known genetic mutation to have children who do not carry the mutation. A woman's eggs are removed and fertilized in a laboratory. When the embryos reach a certain size, one cell is removed and is tested for the hereditary condition in question. The parents can then choose to transfer embryos that do not have the mutation. PGD has been in use for over two decades, and has been used for several hereditary cancer predisposition syndromes. However, this is a complex procedure with financial, physical, and emotional factors to consider before starting. For more information, talk with an assisted reproduction specialist at a fertility clinic.

How common is MEN2?

It is estimated that about one in 30,000 people has MEN2. Most people with MEN2B do not have any family history of the condition. They have a *de novo* (new) mutation in the *RET* gene. Fewer than 5% of people with MEN2A are thought to have a *de novo* mutation in the *RET* gene.

How is MEN2 diagnosed?

FMTC is suspected in families with two or more cases of medullary thyroid cancer and no evidence of parathyroid or adrenal gland problems.

MEN2A is suspected when there are at least two of the three common tumors, such as medullary thyroid cancer, pheochromocytoma, or parathyroid adenoma, in one person or a close relative. Close relatives are generally considered to be parents, siblings, and children. Medullary thyroid carcinoma has been reported in children as young as 2 years of age although it more commonly develops between the ages of 5 and 18 years.

MEN2B is suspected in children with mucosal neuromas, meaning lumps on the tip of the tongue, and typical facial features such as thickened lips of a person with MEN2B. Medullary thyroid cancer can occur very early in childhood.

Genetic testing for mutations in the *RET* gene is available. It is recommended for people with a family history of FMTC, MEN2A, and MEN2B, and anyone diagnosed with medullary thyroid cancer. Mutations in the *RET* gene are found in more than 95% of families with MEN2A or MEN2B, and in more than 85% of families with FMTC. Certified genetic testing laboratories for this condition can be found at www.genetests.org [5].

What are the estimated cancer risks associated with MEN2?

The risk of medullary thyroid cancer in people with MEN2 is nearly 100% for all subtypes.

What are the screening options for MEN2?

Due to the high risk of medullary thyroid cancer**,** *RET* gene testing is recommended for children at risk for any of the MEN2 subtypes. If a mutation is found, the thyroid gland should be surgically removed to prevent cancer from developing. This surgery is recommended by age 3 in children with MEN2B and by age 6 in children with MEN2A or FMTC. The procedure should be performed by a surgeon with experience in both thyroid surgery in children and with the management of medullary thyroid Cancer.

Additional screening recommendations may include:

- Yearly blood tests [6] for ionized calcium and parathyroid hormone levels, beginning in childhood (MEN2A)
- Yearly blood tests for catecholamines and catecholamine metabolites (metanephrine and normetanephrine), beginning in childhood (MEN2A, MEN2B)
- Magnetic resonance imaging [7] (MRI) or computerized tomography [8] (CT or CAT) scan of the abdomen to detect pheochromocytomas, every 4 to 5 years or when abnormal catecholamine or metanephrine levels are detected.

Screening guidelines may change over time as new technologies are developed and more is learned about MEN2. It is important to talk with your doctor about appropriate screening tests.

Learn more about what to expect when having common tests, procedures, and scans [9].

What is the treatment for medullary thyroid cancer that has spread to the lymph nodes of the neck or beyond?

Surgical resection (removal) of lymph nodes in the neck and upper chest, performed by a surgeon experienced with this technique, can result in cure in 10% to 20% of cases where there is spread to neck lymph nodes. Learn more about treatment options for thyroid cancer [10].

Recent studies of drugs that target the *RET* gene have shown promise for the treatment of medullary thyroid cancer that has spread to the lymph nodes, liver, lung or other places in the body. Two of these compounds, vandetanib and cabozantinib, were recently approved by the Food and Drug Administration (FDA) and are available as a treatment option for patients with progressive, metastatic medullary thyroid cancer. The risks and benefits of additional surgery should be discussed with a surgeon or endocrinologist experienced with this disease. Other promising therapies are available through participation in a clinical trial, meaning a research study. To find clinical trials specific to your diagnosis, talk with your doctor or search online

clinical trial databases now [11].

What are the risks associated with pheochromocytoma?

Pheochromocytoma associated with MEN2 is almost always a benign tumor. However, such tumors commonly produce abnormally high levels of adrenalin and noradrenalin and may cause high blood pressure, a rapid or irregular heart rate, tremulousness, meaning tremors or involuntary muscular contractions, and cardiac arrest, meaning sudden death. Medical treatments to prevent these symptoms are highly effective and should be started at the time of diagnosis and before the surgical removal of the tumor. Learn more about adrenal gland tumors [4].

What is the typical treatment for a parathyroid tumor?

Increased production of parathyroid hormone by a benign parathyroid tumor can cause hypercalcemia, meaning high blood calcium, kidney stones, and osteoporosis, meaning the loss of bone mass causing fracture. Surgical removal of the parathyroid tumor often cures the problem. Learn more about parathyroid tumors [3].

Questions to ask the doctor

If you are concerned about your risk of thyroid cancer or other tumors, talk with your doctor. Consider asking the following questions of your doctor:

- What is my risk of developing thyroid cancer?
- What is my risk of developing other types of tumors?
- What can I do to reduce my risk of cancer?
- What are my options for cancer screening?

If you are concerned about your family history and think you or other family members may have MEN2, consider asking the following questions:

- Does my family history increase my risk of developing thyroid cancer?
- Does it suggest the need for a cancer risk assessment?

- Will you refer me to a genetic counselor or other genetics specialist?

- Should I consider genetic testing [12]?

More Information

The Genetics of Cancer [13]

Genetic Testing [12]

What to Expect When You Meet With a Genetic Counselor [14]

Collecting Your Family Cancer History [15]

Sharing Genetic Test Results with Your Family [16]

Additional Resources

Thyroid Cancer Survivors Association
www.thyca.org [17]

American Multiple Endocrine Neoplasia Support
www.amensupport.org/wp/ [18]

Association for Multiple Endocrine Neoplasia Disorders (AMEND)
www.amend.org.uk [19]

American Thyroid Association
www.thyroid.org [20]

International Thyroid Oncology Group (ITOG)
www.itog.org [21]

National Cancer Institute
www.cancer.gov [22]

American Cancer Society
www.cancer.org [23]

Cancer*Care*
www.cancercare.org [24]

To find a genetic counselor in your area, ask your doctor or visit these websites:

National Society of Genetic Counselors
www.nsgc.org [25]

National Cancer Institute
[26]www.cancer.gov/cancertopics/genetics/directory [26]

Links
[1] http://www.cancer.net/cancer-types/multiple-endocrine-neoplasia-type-2
[2] http://www.cancer.net/node/31262
[3] http://www.cancer.net/node/31387
[4] http://www.cancer.net/node/31341
[5] http://www.genetests.org/
[6] http://www.cancer.net/node/24716
[7] http://www.cancer.net/node/24578
[8] http://www.cancer.net/node/24486
[9] http://www.cancer.net/node/24959
[10] http://www.cancer.net/node/19300
[11] http://www.cancer.net/node/24878
[12] http://www.cancer.net/node/24895
[13] http://www.cancer.net/node/24897
[14] http://www.cancer.net/node/24907
[15] http://www.cancer.net/node/30761
[16] http://www.cancer.net/node/24906
[17] http://www.thyca.org/
[18] http://www.amensupport.org/wp/
[19] http://www.amend.org.uk/
[20] http://www.thyroid.org/
[21] http://www.itog.org/
[22] http://www.cancer.gov/
[23] http://www.cancer.org/
[24] http://www.cancercare.org/
[25] http://www.nsgc.org/
[26] http://www.cancer.gov/cancertopics/genetics/directory