Genetic Testing for Patients with Medullary Thyroid Cancer

Most often, medullary thyroid cancer (MTC) does not run in a family; it happens by chance. This is known as sporadic MTC. About 25% of cases (1 out of 4) are hereditary and run in families. There is about a 7% chance that a person with MTC who has no family history of MTC has the hereditary form of MTC. This handout will explain the hereditary form of MTC and genetic testing that your doctor may recommended.

Review of Genes

Genes are found in each of the cells that make up the body. Genes are like the body’s instruction manual. They provide the information needed to tell the body how to do everything. Genes are passed to an individual from their parents, which means the genes are inherited. People who have hereditary MTC are born with a change (a mutation) in a gene called RET.

Overview of MEN2

The hereditary form of MTC is also known as multiple endocrine neoplasia type 2 (MEN2). Almost all people with MEN2 will have MTC at some point during their lives, but there are ways to prevent it. Some people with MEN2 also have a higher chance of having:

- Pheochromocytoma – This is a benign tumor of the adrenal gland. The tumor can cause the levels of stress hormones in the blood to be too high. This may cause symptoms that feel like you are reacting to an emergency.
- Primary hyperparathyroidism – This is a benign disease that affects the parathyroid glands. It can cause the level of calcium in the blood to be too high. Over time, hyperparathyroidism can lead to kidney stones and osteoporosis (weak bones).
- Hirschsprung disease (HD) – This is a condition where the nerves do not grow into the colon normally, causing constipation in babies shortly after birth. The risk to develop HD varies by RET gene mutation.
- Cutaneous lichen amyloidosis (CLA) – This is an itchy skin rash on the upper back that does not go away. The risk to develop CLA varies by RET gene mutation.

There are two subtypes of MEN2:

- MEN2A
- MEN2B

Both subtypes cause a high risk for MTC, but some people with MEN2A have a lower risk of developing pheochromocytoma and hyperparathyroidism than others. This risk varies by RET gene mutation (your medical team will talk with you in more detail about this).
MEN2B is different than MEN2A because it can be recognized based on distinct physical traits. People with MEN2B usually have small non-cancerous tumors on the lips, tongue and eyelids known as neuromas. The neuromas make the tongue look bumpy, the lips look larger and the eyelids to be slightly upturned. Genetic testing will help determine the MEN2 subtype.

**Genetic Testing, Diagnosis and Management of MEN2**

Doctors may suspect MEN2 by reviewing a person’s medical and family history. However, in most cases, a special blood test to look for *RET* gene mutations is needed to diagnose MEN2. This type of test is known as genetic testing.

There are three possible results from *RET* genetic testing:

1. **Positive:** This result means that the person has a *RET* gene mutation associated with MEN2.
2. **Negative:** This result means that a *RET* mutation was not identified and almost always means that a person does not have MEN2.
3. **Uncertain:** This is a rare result and your health care team will talk to you about what this means in your case. An uncertain result (or variant of uncertain significance) does not always rule out MEN2.

*RET* genetic testing is a very accurate test. Over 98% of people with the hereditary form of MTC have a mutation that can be detected in the *RET* gene. It is rare for people with hereditary MTC to have a negative genetic test.

Genetic testing is recommended for persons with MTC. Some benefits of genetic testing include:

- Understanding your risks so that you and your doctor can make a plan to manage your specific health care needs. People with MEN2 need extra checkups and screening exams. These are tests performed when a person has no symptoms. These tests can help detect tumors at their earliest, most treatable stage.

- Knowing if other members of your family could be at risk so that they can make informed decisions about their health:
  - If you have a *RET* gene mutation, then your family members can have genetic testing for the same mutation. In many cases, relatives who test positive have the option to have surgery to remove the thyroid gland to help prevent MTC or thyroid screening so that MTC can be detected at the earliest, most treatable stage.
  - If you do not have a *RET* mutation, then the risk for your family members is very low, and they would not need testing.

**Inheritance**

Inheritance describes how a trait, such as eye or hair color, passes from parent to child. *RET* mutations can be passed to sons and daughters from moms or dads. A parent who has a *RET* gene mutation has a 50% (1 out of 2) chance of passing the mutation on to each child they have. Most people with MEN2 have inherited the *RET* gene mutation from one of their parents.
It is important to discuss genetic testing with a doctor or genetic counselor. If you test positive, your doctor or genetic counselor can help explain your risks and help you identify other people in your family who may need genetic testing.