Hematologic Malignancy Genetic Testing
Information for Patients and their Families

What is a hereditary hematologic malignancy (HHM)?
A hematologic malignancy is a cancer involving the blood. This occurs when cells in the blood grow abnormally, interfering with the ways they are supposed to work. Examples that you may have heard about include leukemia or lymphoma. Hereditary hematologic malignancies (HHM) occur when a person has a genetic change (mutation) that causes their blood cells to be more likely to become cancerous. The mutation can be passed through generations in a family. People with HHM have a higher risk to develop blood cancer, and sometimes other cancers or health problems, as well.

How are hereditary hematologic malignancies inherited?
Hereditary hematologic malignancies can be inherited in one of three ways:

- **Autosomal recessive (AR):**
  Our genes, or DNA, tell the cells in our body how to work correctly. A mutation is a change in a gene that causes it to not work correctly. We have two copies of every autosomal gene - one from our mother and the other from our father. First, HHM can be inherited in an autosomal recessive way. For AR conditions, both copies of a person's gene must have a mutation before they will have the condition. Autosomal conditions occur regardless of whether a person is male or female. Typically, an individual with an AR condition will have inherited one mutation from their mom and one from their dad. Because the mom and dad have another copy of the gene without the mutation, they will usually not show symptoms. For these parents, there is a 25% chance with each pregnancy that the child will inherit both the mom's and the dad's mutations, and therefore, will have the recessive condition. Similarly, for a person with autosomal recessive HHM to have an affected child, their partner would also need to have a mutation in the same gene that causes their HHM. While the risk is low, partner testing is available.

- **Autosomal dominant (AD):**
  HHM can also be inherited in an autosomal dominant way. For AD conditions, having only one copy of a gene mutation is enough to cause symptoms. As stated earlier, autosomal conditions occur regardless of whether a person is male or female. When we have children, we pass down half of our genes. Therefore, if a person has a mutation in one AD gene, there is a 50% risk that each of their children will inherit this mutation and have the condition.

What are some of the genes that increase a person's risk for blood cancer?
Mutations in several genes can lead to an increased risk for blood disorders, including cancer, but usually do not lead to other health problems. Three examples are:

- **RUNX1**
  Mutations in the gene RUNX1 cause familial platelet disorder and increase the risk for myeloid malignancies, such as acute myeloid leukemia.

- **CEBPA and GATA2**
  Mutations in the CEBPA gene or the GATA2 gene also increase the risk for acute myeloid leukemia.
What will genetic testing tell me?

There are three possible results from genetic testing:

**POSITIVE:**
A positive result means that one or more genetic mutations for HHM were identified, confirming a diagnosis. Knowing the specific gene involved tells you how the increased risk for hematologic malignancy in your family was inherited, and can give a doctor insight into the patient’s risk for cancer and other health conditions.

**NEGATIVE:**
A negative result indicates that a genetic mutation was not identified. A negative result may indicate that hereditary hematologic malignancy is not the correct diagnosis. However, it can also mean that the correct gene for HHM in your family was not included on the ordered test, or even that it is not currently known.

**VARIANT OF UNCERTAIN CLINICAL SIGNIFICANCE (VUS):**
The third possible test result is called a Variant of Uncertain Clinical Significance. A gene variant is a genetic difference that could be disease-causing (mutation) or could be a normal finding (benign). More research is needed to determine whether the variant is important or not, and it should usually be treated as a negative result until more information is available. Your doctor may follow up with the laboratory in the future to see if more has been learned.

What are hereditary hematologic malignancy syndromes?

Hereditary hematologic malignancy syndromes are conditions that impact multiple aspects of a person’s body in addition to increasing their risk for blood cancer. Some examples are listed below:

**Bloom syndrome:**
Individuals with Bloom syndrome are at an increased risk for many types of cancers, including lymphoma and leukemia. They also can have many other health problems including, severe growth deficiency, abnormal fat distribution, and hypersensitivity to the sun and radiation. Bloom syndrome is inherited in an autosomal recessive way. In other words, a person has to have two mutations in the BLM gene to have Bloom syndrome.

**Ataxia telangiectasia:**
Ataxia telangiectasia (AT) causes difficulties with movement (ataxia), increased susceptibility to infection, and a higher risk for both leukemia and lymphoma. Symptoms typically begin in early childhood. AT is a recessive condition that occurs when a person has two mutations in the gene ATM.

**Constitutional Mismatch Repair Deficiency Syndrome (CMMRD):**
CMMRD is a recessive condition caused when a person has two mutations in the same cancer-risk gene. Five different cancer-risk genes can cause CMMRD. People with this condition are at an increased risk for many different types of cancer, including lymphoma and leukemia. A family history of colorectal or endometrial cancer may also be present.

Who might need genetic testing for a hereditary hematologic malignancy?

Genetic testing is an important part of establishing the diagnosis of a hereditary hematologic malignancy. Your physician will make the final decision about testing based on your clinical and family history, but some “red flags” suspicious for HHM are listed below:

- Known cancer-risk gene mutation in the family
- Personal or family history of unexplained blood count abnormalities
- Personal or family history of blood cancers
- Personal or family history suggestive for a HHM syndrome. This could include some birth defects, benign tumors, unusual skin pigmentation, or multiple family members with different types of cancer, especially if they occur in a single individual or at an unusually young age.

What will genetic testing tell me?

There are three possible results from genetic testing:
What does a positive result mean for our family?
A positive result is important for your family. Parents, siblings, and children of someone with HHM could have as high as a 50% chance to also have a mutation. For some genes, having only one mutation increases the risk for cancer on its own. Ask your doctor if the gene for HHM in your family falls into this group. If so, close relatives of the person with HHM should consider testing for the mutation(s) to determine if they are at increased risk for cancer themselves. Targeted testing (Familial Mutation Test) is available through Fulgent. The cost is much lower than the cost of genetic panel testing.

How long does it take to receive the results?
Results are usually available in 3 to 4 weeks after the laboratory receives the sample.

Will insurance cover the cost of the testing?
Fulgent accepts all commercial insurance plans. Most insurance companies have specific criteria that they use to determine coverage for genetic testing. Whenever possible, Fulgent will obtain the required prior authorizations. Prior to testing, Fulgent’s insurance specialists will contact you if the anticipated out of pocket cost exceeds $100.

If I have genetic testing, can an employer or health insurance company discriminate against me or my child?
NO. The Genetic Information Nondiscrimination Act (GINA) was signed into law in 2008. It protects Americans from discrimination by an employer or a health insurance company based on genetic information. Importantly, GINA does not offer protections for disability, long term care, or life insurance. It also does not apply to members of the U.S. military or employees of the Federal government, Indian Health Service, or Veterans Health Administration.

Where can I learn more?
Leukemia and Lymphoma Society | www.lls.org
Thinkgenetic | www.thinkgenetic.com