Hereditary Paraganglioma-Pheochromocytoma Genetic Testing
Information for Patients and their Families

What is a hereditary paraganglioma-pheochromocytoma (HPP)?
Paragangliomas and pheochromocytomas are two types of related tumors. A paraganglioma is a tumor that is located near a group of nerve cells called ganglia. A pheochromocytoma is a type of paraganglioma that develops in the adrenal glands. Both paraganglioma and pheochromocytomas develop when cells grow abnormally. In many cases, these tumors are benign, but some will become cancerous if not removed. The majority of paraganglioma and pheochromocytomas arise by chance, but approximately 30% are inherited. Hereditary paraganglioma-pheochromocytoma (HPP) occurs 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 HPP have a higher risk to develop paraganglioma, pheochromocytomas, and sometimes other cancers or health problems, as well.

How is hereditary paraganglioma-pheochromocytoma inherited?
Our genes, or DNA, tell the cells in our body how to work correctly. Cancer-risk genes are genes that can impact whether a cell will begin to grow uncontrollably into cancer. We have two copies of every gene, one from our mother and the other from our father. Hereditary paraganglioma-pheochromocytoma is most commonly inherited in an autosomal dominant way. For dominant conditions, having only one copy of a gene mutation is enough to cause symptoms. In the case of HPP, having one mutation leads to an increased risk for cancer. If a person has a mutation in one gene for HPP, there is a 50% risk that each of their children will inherit this mutation. Siblings, parents, and potentially other relatives could also have the mutation. Importantly, not everyone who has a mutation in a cancer-risk gene will develop cancer, but their chances are higher. For some cancer-risk genes, whether the mutation was inherited from your mother or father impacts your risk for HPP. In these cases, your parents may need to be tested.

While rare, it is possible for a person to have a mutation for a dominant condition that is absent from both of their parents. In this situation, the mutation arose early before they were conceived or born. This is called de novo inheritance. Even after de novo inheritance, if a person has a mutation in one gene for hereditary colorectal cancer, each of their children will have a 50% risk to inherit the mutation.

What are hereditary paraganglioma-pheochromocytoma syndromes?
Hereditary paraganglioma-pheochromocytoma syndromes are conditions that impact multiple aspects of a person’s body in addition to increasing their risk for pheochromocytomas and paragangliomas. Some examples are listed below. Each one is inherited in a dominant way.

Hereditary Paraganglioma-Pheochromocytoma Syndrome (HPPS)
HPPS develops when a person has a mutation in one of six different genes. Other genes for HPPS may be discovered in the future. People with HPPS can have up to an 86% risk to develop a paraganglioma or pheochromocytoma. However, depending on both the gene involved, and whether the mutation was inherited from the mom or the dad, the risk can be lower. Specific genes are also associated with higher or lower chances of the tumors becoming cancerous, so genetic testing can help guide a doctor in how they manage a patient.
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 HPP were identified, confirming a diagnosis. Knowing the specific gene involved tells you how the increased risk for paraganglioma-pheochromocytoma 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 paraganglioma-pheochromocytoma is not the correct diagnosis. However, it can also mean that the correct gene for HPP 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.

Who might need genetic testing for a hereditary paraganglioma-pheochromocytoma?

Genetic testing is an important part of establishing the diagnosis of a hereditary paraganglioma-pheochromocytoma. Your physician will make the final decision about testing based on your clinical and family history, but some *red flags* suspicious for HPP are listed below:

- Known cancer-risk gene mutation in the family.
- Personal or family history of paraganglioma or pheochromocytoma, especially if they are bilateral, reoccur after treatment, or occur below the age of 45 years.
- Personal or family history of benign tumors (neurofibromas), multiple coffee-colored birthmarks (café au lait spots) and/or freckling under the arms or in the groin area.
- Personal or family history of medullary thyroid cancer or hemangioblastoma (especially in the brain or spine).

Multiple Endocrine Neoplasia Type 2 (MEN2)
Mutations in the RET gene cause MEN2. People with this condition are at a higher risk to develop pheochromocytomas and medullary carcinoma of the thyroid, as well as parathyroid disease. The risk for pheochromocytoma is approximately 50%. For MEN2, knowing the specific mutation in a person can help determine the type of MEN2 they have, along with their type's specific risks and related health problems.

Von Hippel Lindau (VHL):
Von Hippel Lindau is caused by a mutation in the VHL gene. People with VHL are at an increased risk for many different types of cancer, including pheochromocytoma, hemangioblasoma, renal cell carcinoma and other neuroendocrine tumors. By age 65 years, almost everyone who has a mutation will eventually develop symptoms.
What does a positive result mean for my family?
A positive result is important for your family, and it is important to share genetic test results whenever possible. Parents, siblings, and children of someone with HPP could have as high as a 50% chance to also have a mutation. Targeted testing (Familial Mutation Test) is available through Fulgent. The cost is much lower than the cost of a 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 your anticipated out of pocket cost exceeds $100.

If I have genetic testing, can my employer or health insurance company discriminate against me?
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?

Pheo Para Troopers | www.pheoparatroopers.org
Children’s Tumor Foundation | www.ctf.org
VHL Alliance | www.vhl.org
Thinkgenetic | www.thinkgenetic.com