Overview

Useful For
Providing a comprehensive evaluation for paraganglioma/pheochromocytoma in patients with a personal or family history suggestive of a hereditary paraganglioma/pheochromocytoma syndrome

Serving as a second-tier test for patients in whom previous targeted gene variant analyses for specific hereditary paraganglioma/pheochromocytoma-related genes were negative

Establishing a diagnosis of a hereditary paraganglioma/pheochromocytoma syndrome in some cases, allowing for targeted cancer surveillance of associated tissues and organs known to be at increased risk for tumor or cancer

Identifying variants within genes known to be associated with increased risk for paraganglioma/pheochromocytoma allowing for predictive testing of at-risk family members

Genetics Test Information
This test includes next-generation sequencing and multiplex ligation-dependent probe amplification to evaluate for the genes listed on the panel.

Sanger sequencing may also be performed to confirm detected variants.

The RET gene is not included in the multiplex ligation-dependent probe amplification (MLPA) portion of the test.

Special Instructions
- Molecular Genetics: Inherited Cancer Syndromes Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)

Method Name
Long-range PCR amplification of targeted genes followed by next-generation sequencing and gene dosage analysis by multiplex ligation-dependent probe amplification (MLPA). Confirmations are performed using polymerase chain reaction (PCR) and Sanger sequencing.

NY State Available
Yes

Specimen

Specimen Type
Varies

Shipping Instructions
Specimen preferred to arrive within 96 hours of collection.

Specimen Required
- Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood
Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

   - Informed Consent for Genetic Testing (T576)
   
   - Informed Consent for Genetic Testing-Spanish (T826)


Specimen Minimum Volume

1 mL

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varies</td>
<td>Ambient (preferred)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frozen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Refrigerated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical and Interpretive

Clinical Information

Paragangliomas and pheochromocytomas (PGL/PCC) are rare, but potentially lethal, neuroendocrine tumors that arise from autonomous ganglia. Tumors located within the adrenal medulla (the largest sympathetic ganglion) are called pheochromocytomas (PCC), while those that stem from either parasympathetic or sympathetic ganglia are designated paragangliomas (PGL).

PCC and sympathetic PGL secrete catecholamines (epinephrine, norepinephrine, or dopamine) and their metabolites. The excess catecholamines result in hypertension, which might be sustained or episodic; however, most patients with sustained hypertension will also occasionally experience episodic "spells" caused by sudden, massive
catecholamine release and characterized by worsened hypertension, palpitations/cardiac arrhythmias, severe headaches, pallor, and sweating. A minority of patients can be largely asymptomatic and might be diagnosed by the incidental discovery of an adrenal mass, or enlarged subdiaphragmatic sympathetic ganglia.

Untreated PGL/PCC has substantial morbidity and mortality, which can be prevented by tumor removal.

PGL/PCC have a germline genetic basis in at least 30% of cases. Pathogenic germline genetic alterations in the following genes are known to predispose to PGL/PCC: RET, VHL, NF1, SDHB, SDHC, SDHD, SDHAF2 (aka SDH5), TMEM127, and MAX. With the exception of the RET kinase, which acquires its tumorigenicity through activating variants, all these genes follow the classical 2-hit model with pathogenic loss of function variants, followed by somatic inactivation of the remaining copy in target organs. RET, VHL, NF1, TMEM127, and MAX predominately cause PCC, while the various SDH genes most often lead to PGL.

Inheritance of these genetic tumor syndromes is autosomal dominant, with the exceptions of SDHD, SDHAF2 (SDH5), and, possibly, MAX, which can show parent-of-origin effects, causing disease almost exclusively when they are paternal in origin. PGL/PCC-specific disease penetrance ranges from approximately 25 to 40% (SDHB) to 80 to 100% (MAX), with exact numbers unknown for some of the genes involved.

While PGL/PCC in general are nonmalignant tumors, malignant PGL/PCC are observed in a significant proportion of patients in most of the predisposing familial tumor syndromes, with the frequency of malignant transformation approaching 50% in SDHB-related tumors. Several of these tumor genes, most notably RET, VHL, NF1, SDHB, and TMEM127, also predispose to a variety of other tumors.

Genetic testing can either proceed gene-by-gene, potentially guided by the clinical pattern of lesions, and biochemical parameters, as most recently outlined in the latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) or, it can be accomplished by screening several genes with a multigene panel.

Reference Values
An interpretive report will be provided.

Interpretation
All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions
Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of a hereditary paraganglioma/pheochromocytoma syndrome or other heritable tumor or cancer risk. For predictive testing of asymptomatic individuals, it is important to first document the presence of a pathogenic variant in an affected family member.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

Technical Limitations:

In some cases, DNA variants of undetermined significance may be identified.
Due to the limitations of next-generation sequencing, small deletions and insertions greater than 8 nucleotides in length will not be detected by this test. If a diagnosis of one of the syndromes on this panel is still suspected, consider full gene sequencing using traditional Sanger methods. Single or multplex deletions as well as whole gene deletions will be detected by multiplex ligation-dependent probe amplification (MLPA).

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

In addition to disease-related probes, the multiplex ligation-dependent probe amplification technique utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

Evaluation Tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly, therefore changes to these algorithms may result in different predictions for a given alteration. Additionally, the predictability of these tools for the determination of pathogenicity is currently not validated.

Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. These and common benign and likely benign variants identified for this patient are available upon request.

Reclassification of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Clinical Reference


Performance

Method Description
Next-generation sequencing is performed to test for the presence of a variant in the MAX, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127, and VHL genes. Additionally, multiplex ligation-dependent probe amplification (MLPA) is used to test for the presence of large deletions and duplications in the MAX, SDHAF2, SDHB, SDHC, SDHD, TMEM127, and VHL genes. All reported alterations detected by next-generation sequencing are confirmed using Sanger sequencing. (Unpublished Mayo method)

**PDF Report**

No

**Day(s) and Time(s) Test Performed**

Performed weekly; Varies

**Analytic Time**

10 weeks

**Maximum Laboratory Time**

12 weeks

**Specimen Retention Time**

Whole Blood: 2 weeks (if available) Extracted DNA: Indefinitely

**Performing Laboratory Location**

Rochester

**Fees and Codes**

**Fees**

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

**Test Classification**

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

**CPT Code Information**

81437

**LOINC® Information**

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Test Order Name</th>
<th>Order LOINC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPGP</td>
<td>Hereditary Pheo/Paraganglioma Panel</td>
<td>In Process</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Result ID</th>
<th>Test Result Name</th>
<th>Result LOINC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA2732</td>
<td>Result Summary</td>
<td>50397-9</td>
</tr>
<tr>
<td>BA2733</td>
<td>Result</td>
<td>82939-0</td>
</tr>
<tr>
<td>BA2734</td>
<td>Interpretation</td>
<td>69047-9</td>
</tr>
<tr>
<td>Result ID</td>
<td>Test Result Name</td>
<td>Result LOINC Value</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>BA2735</td>
<td>Additional Information</td>
<td>48767-8</td>
</tr>
<tr>
<td>BA2736</td>
<td>Specimen</td>
<td>31208-2</td>
</tr>
<tr>
<td>BA2737</td>
<td>Source</td>
<td>31208-2</td>
</tr>
<tr>
<td>BA2738</td>
<td>Released By</td>
<td>18771-6</td>
</tr>
</tbody>
</table>