Introducing the Neurome™
Powered by Personalis®
Innovative Exome Sequencing for Neurology
Clinicians and geneticists have long cared for patients with unexplained neurological disorders. Identifying the cause has been challenging. The diagnostic odyssey can be discouraging and expensive for patients, their families, and caregivers—a time-consuming process that can delay treatment that could help the patient.

Today, whole exome sequencing has made it possible to understand more about the genetic causes of neurological disease. This understanding has driven the discovery of potential targets for new and more effective preventive measures and treatments. 1

Introducing the Neurome™ test, a whole exome sequencing test with analysis specifically focused on neurological disease. With the Neurome’s enhanced clinical exome testing platform and phenotype-driven analysis, determining the cause of a neurological disorder becomes more likely than ever before.

When to Order The Neurome Test

Neurome testing should be considered when:*  
- A patient’s medical history and physical examination suggest a neurological disorder of unknown cause with suspected genetic etiology
- A patient presents with a highly heterogeneous disorder
- Targeted testing fails to identify a diagnosis
- A patient presents with a likely genetic disorder but targeted testing is not available

* Source: www.acmg.net/StaticContent/PPG/Clinical_Application_of_Genomic_Sequencing.pdf

<table>
<thead>
<tr>
<th>TEST CODE</th>
<th>TEST NAME</th>
<th>TEST DESIGNED FOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500</td>
<td>Neurome™ Neurological Exome (Proband)</td>
<td>Patient</td>
</tr>
<tr>
<td>1501</td>
<td>Neurome™ Neurological Exome (Trio)</td>
<td>Patient and parents if necessary to find a causative variant</td>
</tr>
<tr>
<td>1509</td>
<td>Family Testing Supporting Neurome™ Analysis</td>
<td>Other family members for detecting the identified familial variant(s)</td>
</tr>
</tbody>
</table>

Athena Diagnostics Neurome Test services are performed at the laboratory facilities of Personalis.
The Athena Diagnostics Neurome™ test powered by Personalis® is specifically designed to enhance diagnostic yield for clinical care.

The Neurome test is the first whole exome assay with analysis specifically focused on neurological disease. Unlike other exome tests, Personalis’ ACE (Accuracy and Content Enhanced) Exome™ Technology augments a standard exome to sequence regions of the genome missed by conventional exome technologies.

The Neurome test provides a super-charged, neurologically focused investigation—one that obtains superior coverage, optimizes variant detection, and provides the best possible genetic information and insight for neurologists, geneticists, and their patients.

4 Reasons Why The Athena Diagnostics Neurome™ Test Can Make a Difference in the Diagnosis of Neurological Disorders

Personalis’ ACE Exome™ Technology features:

1. A high level of gene finishing available in an exome platform - with more than 6,000 clinically interpretable genes finished (>99% of bases covered at 20x or above) - providing confidence in coverage

2. Inclusion of medically interpretable regions beyond the exome

3. Phenotype-driven analysis for every test ordered by leveraging extensive, up-to-date, curated variant, gene, and phenotype associations

4. Intuitive and actionable reports—created by clinicians for clinicians

The Neurome test can pinpoint the genetic basis of many neurological disorders including:

- Developmental delay (autism, intellectual disability, global developmental delay)
- Hearing loss
- Early-onset dementia
- Hereditary spastic paraplegias
- Familial ALS
- Leukodystrophies
- Epilepsy
- Muscular dystrophies and myopathies
Highest Level of Gene Finishing Available

In an attempt to capture the protein-coding regions of the genome, standard exome sequencing platforms may not achieve complete coverage of many genes. Some entire exons, including many associated with disease, are overlooked. Other variants/exons/regions are not well-covered. In contrast, single-gene tests and gene panel tests generally cover all of the coding bases of a gene, as well as the intron-exon boundaries. To address this challenge, Personalis’ ACE Exome™ Technology was designed to “finish” the biomedically interpretable genes in the exome to a similar standard as single-gene sequencing. As a result, the Neurome test provides a high level of biomedical gene finishing in an exome platform, increasing sensitivity to detect potentially pathogenic variants.

**ARX Coverage Detail**

**FOXG1 Coverage Detail**

**GJB1 Coverage Detail**

Legend:
- Standard Exome Coverage
- With ACE Exome

Example of a Pathogenic Variant That Would Have Been Missed by a Standard Exome

Variant described in Kobayashi et al., Acta Neurol Scand. 201 (2020):359-361
2. **Non-Exonic Interpretable Content**

   While the majority of known pathogenic variants reside within the coding regions of genes, there are many well-characterized pathogenic variants located in introns, UTRs, and promoters—often undetectable using standard exome platforms. In addition to covering the coding bases of a gene and the intron-exon boundaries, the Neurome test includes non-exonic interpretable content not found in standard exomes.

3. **Phenotype-Driven Analysis**

   The Neurome test employs Personalis’ phenotype-driven approach to analysis, which systematically ranks variants based on clinical features and eliminates secondary variants that are unrelated to any of the patient’s clinical features. This approach reduces the likelihood of unrelated findings, which can reduce emotional stress on patients and caregivers.

   Common and unconventional inheritance patterns, such as *de novo* events in recessive disorders, mitochondrial inheritance, and non-penetration, are considered.

   Aneuploidy is detected, and routine assessment for regions of homozygosity provides insight regarding consanguinity and uniparental disomy.

4. **Intuitive and Actionable Reports**

   Each prioritized variant is examined in detail by a clinical team of physicians, genetic counselors, bioinformaticians, and laboratory directors who determine if any of the variants identified are likely to be causally related to the clinical presentation. Results are presented in clear, clinician-friendly reports with key findings summarized on the front page.

   Our genetic counselors are available for consultation with clinicians. We believe that understanding the complexities of disease and genetic variation will inform and benefit future medical management.
Whole exome sequencing using parallel next-generation sequencing technologies provides a new level of diagnostic and treatment possibilities. Once a genetic cause is established, healthcare providers may be able to identify potential treatments, assess the risk of recurrence on subsequent pregnancies, and provide therapeutic guidance and prognosis.1 Ordering the Neurome test is as easy as 1-2-3.

1. Complete the phenotype profile as thoroughly as possible
2. Include patient and family history, previous test results and clinical notes
3. Consult with an Athena Diagnostics genetic counselor for guidance, if desired

The Neurome test requisition form is concise and easy to use—organized by clinical features with fields for patient history and previous test results.

The Neurome Test’s Phenotype-Driven Approach to Testing

The Neurome test platform pairs relevant patient phenotypes with a ranked list of genes for each patient sample to better elucidate the causative variant(s) and eliminate secondary findings. Each patient’s history is considered in detail, including clinical features, pedigree information, and clinical notes to ensure a thorough analysis.

- The report details genetic variants relevant to the reported clinical presentation.
- Interpretation is focused on genes likely to cause human neurological disease based on literature-based databases including OMIM, HGMD, the Personalis disease variant database, and other sources.
- Sanger sequencing or orthogonal, as appropriate to the genomic region and variant type, is performed to confirm reported variants.

“The exome comprises ~1-2% of the genome yet contains ~85% of recognized disease-causing variants.”2
Comprehensive Services from Athena Diagnostics that Go Beyond Results

Genetic Counseling Services

Our team of licensed and board certified genetic counselors is readily available to provide in-depth consultation to clinicians on the nature of the test results, disease inheritance and medical implications for the patient and their family.

Khalida Liaquat, MS, CGC Licensed Genetic Counselor

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Ship overnight at room temperature. *Depending on the number of family members

Client Services Representatives are available from 8:30am to 6:30pm Eastern Time (U.S.). Customers in the U.S. and Canada please call toll free 800-394-4493 or visit us on our website at AthenaDiagnostics.com.


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