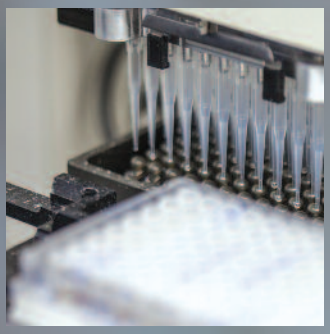
WHOLE EXOME SEQUENCING FOR NEUROLOGICAL DISEASE

Neurome™ Neurological Exome (Proband)

Neurome™ Neurological Exome (Trio)

Family Testing Supporting Neurome™ Analysis



Introducing the Neurome™
Powered by Personalis®
Innovative Exome Sequencing for Neurology

TESTING POWERED BY Personalis®

athena diagnostics®

The More You Know, The More You Can Do

Athena Diagnostics and Personalis introduce the Neurome™ test – an exome specifically focused on neurological disorders.

Adam Medeiros, Associate Scientist, Next Generation Sequencing, Quest Diagnostics

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

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

Athena Diagnostics Neurome Test services are performed at the laboratory facilities of Personalis®

Whole Exome Sequencing for Neurological Disease

Whole Exome Sequencing From Athena Diagnostics Can Make a Difference

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

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

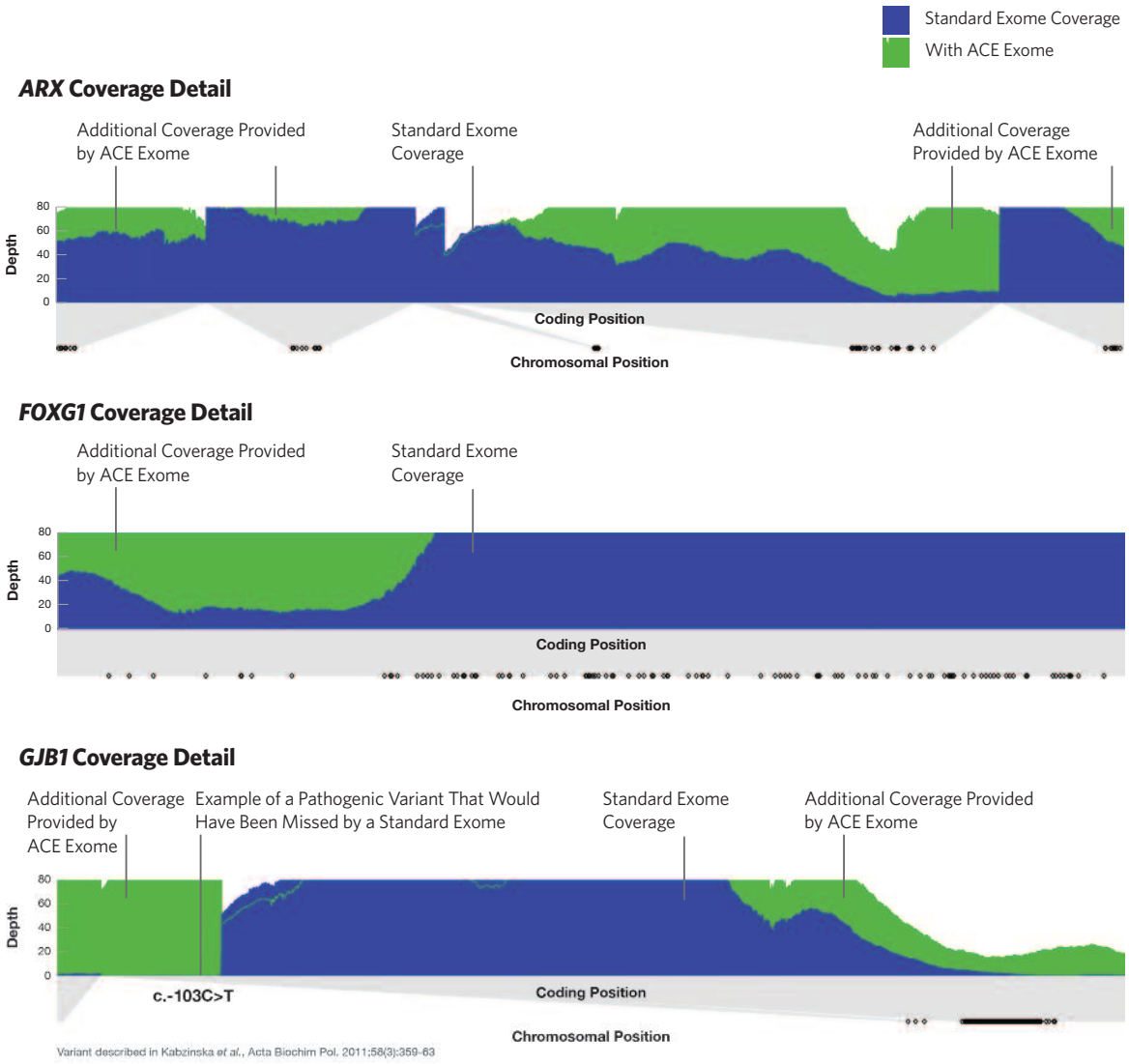
Personalis' ACE Exome™ Technology features:

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

Neurologists and geneticists can rely on the technology of the Athena Diagnostics Neurome, powered by Personalis®.

1. 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.



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

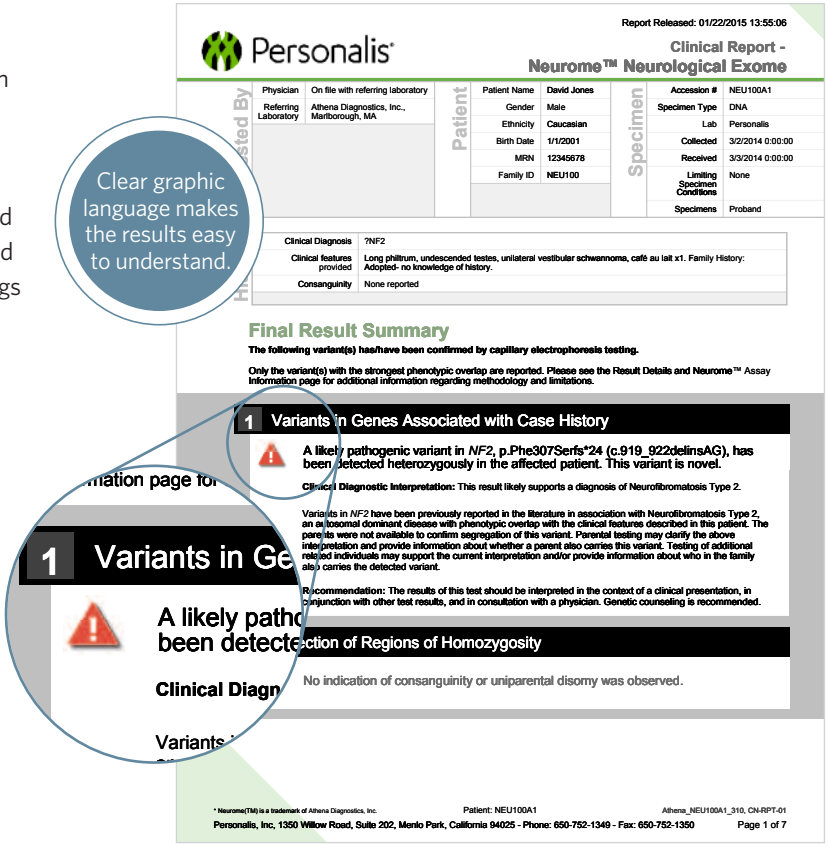
The Neurome test employs Personalis' phenotype-driven approach to analysis, which systematically ranks variants based on clinical features and eliminates secondary variants that are unrelated to any of the patient's clinical features. This approach reduces the likelihood of unrelated findings, which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



"The exome comprises ~1-2% of the genome yet contains ~85% of recognized disease-causing variants."[2]

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 testing method, as appropriate to the genomic region and variant type, is performed to confirm reported variants.

TESTING POWERED BY

Personalis®

Athena Diagnostics Neurome™ Neurological Exome Requisition (February 2015)

Clinical Features for Patient

Please fill in as completely as possible to aid diagnosis. Please provide available clinic notes and pedigree information along with this requisition form.

☐ Environmental History
- ☐ Exposure to lead
- ☐ Exposure to viral agents, specify:
- ☐ History of trauma, specify:
- ☐ Other:

☐ Prenatal/Perinatal History
- ☐ Cystic hygroma/increased NT
- ☐ Oligohydramnios
- ☐ Polyhydramnios
- ☐ Cerebral palsy
- ☐ Complicated delivery, specify:
- ☐ Prematurity, specify:
- ☐ Hypoxic ischemic encephalopathy
- ☐ Other:

☐ CNS/Neurological
- ☐ Abnormal nerve condution velocity, specify:
- ☐ Ataxia
- ☐ Chorea
- ☐ Congenital neuropathy
- ☐ Cranial nerve abnormalities, specify:
- ☐ Dysmyelination, specify:
- ☐ Dystonia
- ☐ Foot drop
- ☐ Motor neuropathy
  - ☐ Proximal
  - ☐ Distal
- ☐ Pes cavus
- ☐ Pressure palsy
- ☐ Recurrent headache/migraine
- ☐ Reduced/absent deep tendon reflexes
- ☐ Sensory neuropathy
- ☐ Sleep apnea
- ☐ Spasticity
- ☐ Stroke/stroke-like episodes
- ☐ Tremor
- ☐ Vocal cord paresis
- ☐ Other:

☐ Seizures/Epilepsy
- ☐ Epileptic encephalopathy
- ☐ Febrile seizures
  - ☐ Dravet syndrome
- ☐ Focal seizures
- ☐ Generalized seizures
  - ☐ Absence
  - ☐ Clonic
  - ☐ Myoclonic
  - ☐ Tonic-clonic
- ☐ Infantile/epileptic spasms
  - ☐ Ohtahara syndrome
  - ☐ West syndrome
- ☐ Status epilepticus
- ☐ Other:

☐ Major Brain Anomalies
- ☐ Agenesis of the corpus callosum
- ☐ Basal ganglia abnormality
- ☐ Brain atrophy
- ☐ Cortical dysplasia
- ☐ Dandy-Walker malformation
- ☐ Encephalocele
- ☐ Holoprosencephaly
- ☐ Hydrocephalus
- ☐ Lissencephaly
- ☐ Molar tooth sign
- ☐ Periventricular leukomalacia
- ☐ Periventricular nodular heterotopia
- ☐ Polymicrogyria
- ☐ Pontocerebellar hypoplasia
- ☐ Subcortical band heterotopia
- ☐ Other:

☐ Developmental Delay
- ☐ Intellectual disability/mental retardation
  - ☐ Mild
  - ☐ Moderate
  - ☐ Severe
- ☐ Developmental regression
- ☐ Fine motor delay
- ☐ Gross motor delay
- ☐ Speech delay
- ☐ Speech articulation difficulties
- ☐ Other:

☐ Behavioral
- ☐ Autism spectrum disorder/autistic features
- ☐ Self-injurious behavior
- ☐ Stereotypic behaviors
- ☐ Other:

☐ Muscular
- ☐ CPK abnormalities, specify:
- ☐ Dysphagia
- ☐ Easy fatigue
- ☐ Exercise intolerance
- ☐ Hypertonia
- ☐ Hypotonia
- ☐ Mobility limitations, specify:
- ☐ Muscle fasciculations
- ☐ Muscle wasting
- ☐ Muscle weakness, specify location:
- ☐ Myotonia

☐ Growth
- ☐ Microcephaly
  - ☐ Std Dev
  - ☐ Progressive/acquired
  - ☐ Congenital
- ☐ Macrocephaly
  - ☐ Std Dev
  - ☐ Progressive/acquired
  - ☐ Congenital
- ☐ Failure to thrive
- ☐ IUGR
- ☐ Obesity
- ☐ Overgrowth
- ☐ Short stature
  - ☐ Std Dev
- ☐ Tall stature
  - ☐ Std Dev
- ☐ Other:

☐ Craniofacial/Dysmorphology
- ☐ Abnormal hair, specify:
- ☐ Cleft lip +/- cleft palate, specify (unit/bilat):
- ☐ Craniosynostosis, specify:
- ☐ Deafness
  - ☐ Congenital
  - ☐ Progressive/acquired
  - ☐ Conductive
  - ☐ Sensorineural
  - ☐ Mixed
  - ☐ Unilateral
  - ☐ Bilateral
- ☐ External ear malformation, specify:
- ☐ Dysmorphic facies, describe:
- ☐ Other:

☐ Skeletal/Limb Abnormalities
- ☐ Contractures
- ☐ Polydactyly
- ☐ Syndactyly
- ☐ Scoliosis
- ☐ Vertebral anomaly
- ☐ Other:

☐ Ophthalmologic
- ☐ Blindness
- ☐ Cataracts
- ☐ Chronic progressive external ophthalmoplegia
- ☐ Coloboma
- ☐ Optic atrophy
- ☐ Ptosis
- ☐ Retinitis pigmentosa
- ☐ Visual impairment
- ☐ Other:

☐ Cardiac
- ☐ Arrhythmia, specify:
- ☐ Cardiomyopathy, specify:
- ☐ Structural heart malformation, specify:
- ☐ Syncope
- ☐ Other:

☐ Genitourinary Abnormalities
- ☐ Renal abnormality, specify:
- ☐ Other genitourinary abnormality:

☐ Abdominal/Gastrointestinal
- ☐ Abdominal wall defect
- ☐ Chronic diarrhea
- ☐ Constipation
- ☐ Pyloric stenosis
- ☐ Recurrent vomiting
- ☐ TE fistula
- ☐ Other:

☐ Skin/Autonomic
- ☐ Abnormal temperature regulation
- ☐ Altered sweating
- ☐ Abnormal nails, specify:
- ☐ Altered skin pigmentation, specify:
- ☐ Other:

☐ Hematologic/Immunologic
- ☐ Specify:

☐ Tumor/Growths:
- ☐ Medullary carcinoma of the thyroid
- ☐ Pheochromocytoma
- ☐ Other tumor type(s) and location(s):

☐ Endocrine/Metabolic
- ☐ Abnormal metabolic testing, specify:
- ☐ Abnormal newborn screen, specify:
- ☐ Adrenal insufficiency
- ☐ Adrenal hyperplasia
- ☐ Cushing syndrome
- ☐ Other abnormal testing:

☐ Test Results
- ☐ Abnormal CT, specify:
- ☐ Abnormal electromyography (EM
- ☐ Abnormal electroencephalography (
- ☐ Abnormal magnetic resonance imaging (MR
- ☐ Muscle biopsy, specify results:
- ☐ Nerve biopsy, specify results:

Requisitions are easy to use, organized by clinical features.

Athena Diagnostics, Inc., 200 Forest Street, 2nd Floor, Marlborough, MA 01752 • 800-394-4493 • Fax 610-271-6085 • AthenaDiagnostics.com

Whole Exome Sequencing for Neurological Disease

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

Athena Diagnostics Neurome Test services are performed at the laboratory facilities of Personalis®

Test Code	Test Name	Specimen Volume Tube Type	Turnaround Time
1500	Neurome™ Neurological Exome (Proband) CPT Code: 81415(1)	Adult: 6-8 mL Pediatrics: (0-3 yrs.): 2-4 mL Whole blood, lavender (EDTA) top tube	10–15 weeks
1501	Neurome™ Neurological Exome (Trio) CPT Codes: 81415(1), 81416* plus additional code(s) if necessary to find a causative variant	Adult: 6-8 mL Pediatrics: (0-3 yrs.): 2-4 mL Whole blood, lavender (EDTA) top tube	10–15 weeks
1509	Family Testing Supporting Neurome™ Analysis CPT Code: 81403	Adult: 6-8 mL Pediatrics: (0-3 yrs.): 2-4 mL Whole blood, lavender (EDTA) top tube	10–15 weeks

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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References: 1. Rabbani B, Tekin M, Mahdieh N. The promise of whole-exome sequencing in medical genetics. *J Hum Genet* 2014;59 5-15.
2. Majewski J, Schwartzentruber J Lalonde E, et al. What can exome sequencing do for you? *J Med Genet* 2011;48:580-589.

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