January 2024

NorthShore University HealthSystem

Neurological Institute

Research Updates

Excellence in Patient Care and Innovative Research

NorthShore
University HealthSystem

NorthShore Neurological Institute is committed to conducting medical research with the goal of helping patients live longer, healthier lives.

The multidisciplinary research staff of neurologists, neurosurgeons, neuroradiologists, neuropsychologists, neuropathologists and a large team of research personnel are engaged in a wide array of clinical studies, often national and international in scope.

These studies involve patient and community volunteers with the goal of better understanding how to diagnose, treat and prevent neurological diseases and conditions.

For an up-to-date list of research studies currently enrolling patients at NorthShore Neurological Institute, go to:
northshore.org/neurological-institute/research-innovation

To learn more about supporting excellence in research at NorthShore Neurological Institute, please contact Danielle Maihofer, Director of Philanthropy at NorthShore University HealthSystem (NorthShore) Foundation, at (224) 364-7614 or dmaihofer@northshore.org.
You can also support NorthShore Neurological Institute by making an online donation at **northshore.org/donate** and selecting NorthShore Neurological Institute from the drop-down menu.

Clinical Trials

For an up-to-date list of clinical trials currently enrolling patients at NorthShore Neurological Institute, go to: northshore.org/nnitrials

The DodoNA Project

The DodoNA Project: DNA Predictions to Improve Neurological Health

Aims: "DodoNA" is a metaphor. Dodona was an oracle of ancient Greece, where priestesses interpreted the rustling leaves of a sacred oak tree to predict the future and to guide actions to improve fate. Just as at Dodona, we can interpret subtle variations in DNA, the "tree of life," to improve neurological health. Specifically, we are developing medical informatics tools to capture standardized data via routine office visits that measure the progression and outcomes of patients with the following neurological disorders: brain tumors, epilepsy, memory disorders, migraine, mild traumatic brain injury, multiple sclerosis, neuropathy, Parkinson's disease, restless legs syndrome and stroke. We are also studying persons who are neurologically healthy but at increased risk for Alzheimer's disease and related brain disorders.

DodoNA is a clinical practice initiative (note-writing and workflow efficiencies) and a quality initiative (best practices). It is also a research initiative. We will invite up to 1,000 subjects for each of the 11 projects (11,000 subjects in total) to provide, via informed consent, a blood sample for DNA extraction and storage. We then will ask permission to associate information in their blood with information in their medical record (for the purposes of developing molecular prognostics and therapeutics).

Principal Investigator: Katerina Markopoulou, MD, PhD
NorthShore Project Number: EH10-139
Contact: Call **(847) 503-4344** with questions regarding the study.

Practice-Based Research

Quality Improvement and Practice-Based Research in Neurology Using the EHR System

Aims: The purpose of this study is to advance quality improvement and practice-based research in neurology using the electronic health record (EHR) system. The Department of Neurology at NorthShore has built into its commercial EHR (called "Epic") structured clinical documentation support (SCDS) and clinical decision support (CDS) tools that standardize care, write progress notes, and capture ~1,000 discrete and cascading fields of neurological data per office visit. The specific aims of this project are to first create a Neurology Practice-Based Research Network by sharing SCDS and CDS tools for 10 common neurological disorders (brain tumors, epilepsy, migraine, mild cognitive impairment, mild traumatic brain injury, multiple sclerosis, neuropathy, Parkinson's disease, restless legs syndrome and stroke) and for brain health (11 projects total) with seven other Neurology Departments nationwide that also use the Epic EHR platform (eight sites total). Secondly, we will individualize medicine at the point of care by conducting pragmatic trials using subgroup-based adaptive designs, comparing the effectiveness of available treatments for common neurological disorders.

Site Principal Investigator: Steven Meyers, MD
NorthShore Project Number: EH14-355
Contact: Call **(847) 503-4344** with questions regarding the study.

Alzheimer's and Memory Disorders

New IDEAS: Imaging Dementia—Evidence for Amyloid Scanning Study (A Study to Improve Precision in Amyloid PET Coverage and Patient Care)

Aims: The goal of the study is to evaluate the utility of beta-amyloid PET for patients with Alzheimer's disease. The study will determine whether beta-amyloid PET imaging affects health outcomes for patients, including short-term outcomes related to changes in management and long-term outcomes of dementia.

Principal Investigator: Chad Yucus, MD
NorthShore Project Number: EH21-277
Contact: Call **(847) 503-4344** with questions regarding the study.

Brain Aneurysm

Humanitarian Use Device: Wingspan Stent System with Gateway PTA Balloon Catheter

Description: This device is used to increase cerebral artery blood flow in patients with intracranial atherosclerotic disease. A stent is placed in the affected area and is deployed by inflation of a very small balloon, which widens the occluded vessel.

Principal Investigator: Shakeel Chowdhry, MD
NorthShore Project Number: EH12-355
Contact: Call **(847) 570-4224** with questions regarding the device.

Humanitarian Use Device: The PulseRider® Aneurysm Neck Reconstruction Device (ANRD)

Description: This device acts as a support for the treatment of unruptured, wide-neck bifurcation aneurysms in the brain. A bifurcation aneurysm is a specific type of aneurysm that arises at the point at which there is a division of one major vessel into two branches.

Principal Investigator: Shakeel Chowdhry, MD
NorthShore Project Number: EH17-313
Contact: Call **(847) 570-4224** with questions regarding the device.

Brain and Spine Tumor

A Phase I study of safety and tolerability of acetazolamide with temozolomide in adults with newly diagnosed MGMT promoter-methylated malignant glioma

Aims: This is a Phase I study that examines the rate of dose-limiting side effects in patients with malignant astrocytoma treated with combination acetazolamide (ACZ) and temozolomide (TMZ). Eligible patients must have histologically proven newly diagnosed, O^6-methylguanine-DNA methyltransferase (MGMT) methylated WHO grade III or IV astrocytoma and be planning to undergo treatment with standard adjuvant TMZ (after completing treatment with TMZ and ionizing radiation).

Principal Investigator: Janardan Khandekar, MD
NorthShore Project Number: EH18-083
Contact: Call **(847) 570-2025** with questions regarding the study.

Brain and Spine Tumor *(continued)*

A Phase II Study of Checkpoint Blockade Immunotherapy in Patients with Somatically Hypermutated Recurrent Glioblastoma

Aims: Glioblastoma multiforme (GBM) is the most aggressive of the primary brain tumors. It remains uniformly lethal, and there are no treatments that extend survival once it recurs. The purpose of this study is to determine whether the combination of ipilimumab and nivolumab can lower the chance of recurrent glioblastoma with elevated mutational burden from growing or spreading after initial therapy failed. For this study, "high mutational burden" is defined as at least 20 mutations on the FoundationOne®CDx test.

Principal Investigator: Bruce Brockstein, MD
NorthShore Project Number: EH21-065
Contact: Call **(847) 570-2025** with questions regarding the study.

Phase II Trial of the Immune Checkpoint Inhibitor Nivolumab in Patients with Recurrent Select Rare CNS Cancers

Aims: The purpose of this study is to determine the efficacy of nivolumab in a variety of recurrent, refractory primary central nervous system (CNS) tumors as measured by disease control rate as confirmed complete response (CR), partial response (PR), or durable stable disease (SD) for at least 6 months.

Principal Investigator: Janardan Khandekar, MD
NorthShore Project Number: EH21-004
Contact: Call **(847) 570-2025** with questions regarding the study.

Phase III Trial of Observation Versus Irradiation for a Gross Totally Resected Grade II Meningioma

Aims: The purpose of this Phase III study is to finally obtain a clear answer to the long-standing question of which treatment route leads to the best clinical outcome for patients with newly diagnosed WHO grade II meningioma. Subjects will be randomly assigned to one of two groups: Group 1 will be observed following surgery, and Group 2 will receive radiation therapy following surgery.

Principal Investigator: Bruce Brockstein, MD
NorthShore Project Number: EH18-270
Contact: Call **(847) 570-2025** with questions regarding the study.

Multiple Sclerosis

An Observational Study of Ocrelizumab-Treated Patients with Multiple Sclerosis to Determine the Incidence and Mortality Rates of Breast Cancer and All Malignancies (Verismo Study)

Aims: The purpose of this study is to assess and characterize the incidence and mortality rates of breast cancer, all malignancies, and the long-term safety regarding serious adverse events (SAEs) among patients with multiple sclerosis (MS) newly exposed to the medication ocrelizumab (OCREVUS®) under routine clinical care.

Principal Investigator: Afif Hentati, MD
NorthShore Project Number: EH20-012
Contact: Call **(847) 503-4044** with questions regarding the study.

A Phase III Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Study to Evaluate the Efficacy and Safety of Fenebrutinib Compared with Teriflunomide in Adult Patients with Relapsing Multiple Sclerosis

Aims: The purpose of this study is to compare the efficacy and safety of the study drug fenebrutinib to the FDA-approved medication teriflunomide (AUBAGIO®) in adult patients with relapsing multiple sclerosis (MS). Primary objectives include measurement of time from baseline to first occurrence of a progression event based on changes in EDSS score, increase in Timed 25-Foot Walk Test, increase in time to complete the 9-hole Peg Test and annualized relapse rate. The pharmacokinetics of fenebrutinib will also be evaluated. Eligible patients with relapsing MS will be randomly assigned (1:1) to one of the two arms. Subjects who complete the initial 96-week-long double-blind treatment phase may be eligible to participate in a 96-week-long open-label fenebrutinib extension phase. Seven patients are expected to be enrolled at NorthShore sites.

Principal Investigator: Afif Hentati, MD
NorthShore Project Number: EH20-357
Contact: Call **(847) 503-4335** with questions regarding the study.

A Randomized, Open Label, Multi-Center, Active-Comparator Study to Assess the Efficacy, Safety and Tolerability of Ofatumumab 20mg SC Monthly Versus Continued Current Therapy in Relapsing-Remitting Multiple Sclerosis After Elevation of Serum Neurofilament Light Levels (SOSTOS)

Aims: The main purpose of this prospective research study is to investigate whether patients without a relapse in the past year would benefit from a switch to ofatumumab versus continued current therapy in a relapsing remitting MS population. The study will also look into whether a preceding elevated serum neurofilament light (NfL) level predicts enhanced benefit from a switch.

Principal Investigator: Carolyn Goldschmidt, DO
NorthShore Project Number: EH22-479
Contact: Call **(847) 503-4335** with questions regarding this study.

Performance and Safety of a Digital Tool for the Unsupervised Self-Assessment of Neuromyelitis Optica Spectrum Disorder

Aims: The study product evaluated is NMOSDCopilot (version 1.0.0) designed and developed by the manufacturer Ad Scientiam. NMOSDCopilot is a Software as a Medical Device (SaMD) consisting of two different components: a mobile application for patients and a web dashboard for clinicians. The version used for this clinical study is an investigational device.

Principal Investigator: Afif Hentati, MD
NorthShore Project Number: EH23-131
Contact: Call **(847) 570-1864** with questions regarding this study.

Neuromuscular Disorders

A Phase III, Multicenter, Open-Label Extension Study of Zilucoplan in Subjects with Generalized Myasthenia Gravis

Aims: The purpose of this research study is to provide access to zilucoplan for subjects with generalized myasthenia gravis (gMG) who have completed a qualifying Ra Pharmaceuticals sponsored zilucoplan study and who wish to continue receiving zilucoplan. This study will also evaluate the long-term efficacy of zilucoplan in subjects with gMG who have completed the qualifying Ra Pharmaceuticals sponsored zilucoplan study.

Principal Investigator: Alexandru Barboi, MD
NorthShore Project Number: EH21-143
Contact: Call **(847) 503-4333** with questions regarding the study.

A Phase II Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Efgartigimod IV in Adult Patients with Post-COVID-19 Postural Orthostatic Tachycardia Syndrome (POTS)

Aims: Efgartigimod is a neonatal Fc receptor (FcRn) antagonist in clinical development for treating autoimmune diseases mediated by immunoglobulin G (IgG) autoantibodies. POTS arising in patients after infection with the SARS-CoV-2 virus (COVID-19) may be caused by pathogenic IgG autoantibodies that lead to autonomic dysfunction. This Phase II study will evaluate the efficacy and safety of efgartigimod in participants with post–COVID-19 POTS.

Principal Investigator: Alexandru Barboi, MD
NorthShore Project Number: EH22-256
Contact: Call **(847) 503-4344** with questions regarding the study.

A Phase II, Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group, Multi-Center Trial to Evaluate the Efficacy, Safety and Tolerability, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of 2 Dose Regimens of ARGX-117 in Adults with Multifocal Motor Neuropathy

Aims: This Phase II clinical trial serves to evaluate the safety and efficacy of two different dose regimens of ARGX-117 versus placebo in participants with multifocal motor neuropathy (MMN) previously stabilized with intravenous immunoglobulin (IVIg). MMN is a rare neuropathy characterized by progressive asymmetric weakness and atrophy without sensory abnormalities. The objectives of the study include evaluating the safety and tolerability of ARGX-117 compared to placebo in adult participants previously stabilized with IVIg and to evaluate the efficacy of ARGX-117 compared to placebo on muscle strength and/or motor function in adult participants previously stabilized with IVIg.

Principal Investigator: Alexandru Barboi, MD
NorthShore Project Number: EH22-033
Contact: Call **(847) 503-4333** with questions regarding the study.

Dr. Alexandru Barboi leads the Neuromuscular Disorders Program at NorthShore Neurological Institute and is Principal Investigator on several clinical trials.

— Dr. Alexandru Barboi,
Section Head,
Neuromuscular Disorders

A Long-Term Extension of ARGX-117-2002 Trial to Evaluate the Long-Term Safety and Tolerability, Efficacy, Pharmacodynamics, Pharmacokinetics, and Immunogenicity of ARGX-117 in Adults with Multifocal Motor Neuropathy (MMN)

Aims: This is an open-label extension trial of ARGX-117-2002. The objectives of the study include evaluating the safety and tolerability of ARGX-117 to evaluate the long-term efficacy of ARGX-117 on muscle strength and/or motor function, arm and hand function, quality of life, and fatigue in adult participants with MMN.

Principal Investigator: Alexandru Barboi, MD
NorthShore Project Number: EH22-333
Contact: Call **(847) 503-4333** with questions regarding the study.

Efficacy and Safety of Pozelimab and Cemdisiran Combination Therapy in Patients with Symptomatic Generalized Myasthenia Gravis

Aims: The primary purpose of this research study is to evaluate the effect of pozelimab and cemdisiran on daily functioning that is impacted by signs and symptoms in patients with symptomatic generalized myasthenia gravis.

Principal Investigator: Alexandru Barboi, MD
NorthShore Project Number: EH21-282
Contact: Call **(847) 503-4333** with questions regarding the study.

Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Efgartigimod in Adult Patients with Post-COVID-19 Postural Orthostatic Tachycardia Syndrome (PC-POTS) Who Completed Study ARGX-113-2104

Aims: The primary objective of this study is to evaluate the long-term safety of efgartigimod in patients with PC-POTS. Secondary objectives include evaluation of the long-term efficacy of efgartigimod in reducing the severity of PC-POTS symptoms and the long-term efficacy of efgartigimod on patient global assessment of symptom experience, fatigue, and cognitive function.

Principal Investigator: Alexandru Barboi, MD
NorthShore Project Number: EH23-132
Contact: Call **(847) 503-4344** with questions regarding this study.

Neuromuscular Disorders *(continued)*

A Phase 3, Multi-Center, Randomized Withdrawal and Long-Term Extension Study of Ampreloxetine for the Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Participants with Multiple System Atrophy

Aims: The primary objective of this study is to evaluate the efficacy and durability of ampreloxetine in participants with multiple system atrophy (MSA) and symptomatic neurogenic orthostatic hypotension (nOH) compared with placebo over a double-blind, randomized withdrawal period of 8 weeks following an open-label period of 12 weeks. Secondary objectives, during the 8-week randomized withdrawal period, include evaluation of the efficacy and durability of ampreloxetine for symptomatic nOH in participants based on the Unified Multiple System Atrophy Rating Scale (UMSARS) Part IV.

Principal Investigator: Alexandru Barboi, MD
NorthShore Project Number: EH23-067
Contact: Call **(847) 503-4344** with questions regarding this study.

Parkinson's Disease and Movement Disorders

Genetic Analysis of Familial Parkinsonism

Aim: The purpose of this study is to identify inherited factors that may cause Parkinson's disease or parkinsonism.

Principal Investigator: Katerina Markopoulou, MD, PhD
NorthShore Project Number: EH16-166
Contact: Call **(847) 503-4333** with questions regarding the study.

The Longitudinal Clinical and Genetic Study of Parkinson's Disease (LONG-PD Study)

Aims: The clinical and genetic factors that influence motor and nonmotor severity, progression and outcomes in Parkinson's disease are unknown. Identification of these factors may allow us to individualize the care of patients and improve neurological health. The Genetic Epidemiology of Parkinson's Disease (GEoPD) consortium clinics care for thousands of patients each year. The purpose of this study is to develop a web-based platform for the capture and sharing of standardized data that measure motor and nonmotor severity, progression and outcomes in Parkinson's disease across 25 global sites—from 18 countries, 5 continents and 4,200 cases. These patients will be followed for 15 years for collaborative research studies. Additionally, DNA will be shared in a central repository to conduct genomic studies of severity, progression and outcomes in Parkinson's disease.

Principal Investigator: Katerina Markopoulou, MD, PhD
NorthShore Project Number: EH15-283
Contact: Call **(847) 503-4334** with questions regarding the study.

The Role of Genetics and Neurophysiology in the Outcomes of Deep Brain Stimulation Surgery

Aims: This retrospective data analysis study aims to assess the contribution of baseline clinical and genetic characteristics to clinical outcomes; to identify, in Parkinson's disease patients who have undergone subthalamic nucleus deep brain stimulation (STN-DBS), patterns of local field potential (LFPs) activity from the subthalamic nucleus (STN) and correlate them with treatment response over serial clinical assessments; and to evaluate associations of patterns of STN LFP activity with clinical outcomes, genetic status, and family history.

Principal Investigator: Katerina Markopoulou, MD, PhD
NorthShore Project Number: EH23-190
Contact: Call **(847) 503-4335** with questions regarding this study.

"In general, the control of Parkinson's disease symptoms is better with deep brain stimulation (DBS) than with medication alone."

— Dr. Katerina Markopoulou, Section Head, Movement Disorders

Spine Surgery

A Multicenter, Prospective, Randomized, Clinical Trial Comparing the Safety and Effectiveness of the BAGUERA®C Cervical Disc Prosthesis to the Mobi-C® Cervical Disc for the Treatment of Patients with Symptomatic Cervical Disc Disease at a Single Level

Aims: The purpose of this study is to evaluate the safety and effectiveness of BAGUERA®C Cervical Disc Prosthesis in treating cervical disc disease at a single level. Subjects will be randomly assigned to one of the two treatment options (BAGUERA®C Cervical Disc Prosthesis or Mobi-C® Cervical Disc) at a 2:1 ratio, and will be evaluated preoperatively, at the time of surgery, at discharge, and at 6 weeks, 3, 6, 12, and 24 months after surgery. Subjects will continue to be followed annually to 7 years to fulfill postapproval study considerations.

Principal Investigator: Michael Musacchio, MD
NorthShore Project Number: EH21-058
Contact: Call **(847) 570-4224** with questions regarding the study.

Spine Surgery *(continued)*

A Multicenter, Prospective, Randomized, Clinical Trial Comparing the Safety and Effectiveness of the BAGUERA®C Cervical Disc Prosthesis to the MOBI-C® Cervical Disc for the Treatment of Patients with Symptomatic Cervical Disc Disease at Two Contiguous Levels

Aims: The purpose of this study is to evaluate the safety and effectiveness of BAGUERA®C Cervical Disc Prosthesis in treating cervical disc disease when implanted at two contiguous levels. Subjects will be randomly assigned to one of the two treatment options (BAGUERA®C Cervical Disc Prosthesis or Mobi-C® Cervical Disc) at a 2:1 ratio and will be evaluated preoperatively, at the time of surgery, at discharge, and at 6 weeks and 3, 6, 12, and 24 months after surgery. Subjects will continue to be followed annually to 7 years to fulfill post-approval study considerations.

Principal Investigator: Michael Musacchio, MD
NorthShore Project Number: EH21-059
Contact: Call **(847) 570-4224** with questions regarding the study.

A Randomized, Single-Blinded, Non-Inferiority Study Comparing AGN1 Local Osteo-Enhancement Procedure (LOEP) SV Kit Treatment of Vertebral Compression Fragility Fractures to Polymethylmethacrylate (PMMA) Bone Cement Treatment

Aims: This is a multicenter, single-blinded, randomized controlled clinical trial evaluating the safety and efficacy of the AGN1 LOEP SV Kit for the treatment of painful vertebral compression fragility fractures (VCFs). The objective of this study is to demonstrate non-inferiority of the AGN1 LOEP SV Kit for the treatment of VCFs to standard-of-care vertebroplasty treatment using bipedicular injection of PMMA bone cement.

Principal Investigator: Michael Musacchio, MD
NorthShore Project Number: EH21-293
Contact: Call **(847) 570-4224** with questions regarding the study.

Long-Term Assessment of the Safety and Performance of the NuVasive Simplify® Disc

Aims: The purpose of this study is to evaluate the long-term 10-year safety and performance of the Simplify Disc when used for cervical disc arthroplasty at one level in the cervical spine C3–C7 in subjects enrolled under the post-approval study as measured by reported adverse events, radiographic outcomes and patient-reported outcomes.

Principal Investigator: Michael Musacchio, MD
NorthShore Project Number: EH22-228
Contact: Call **(847) 570-4224** with questions regarding the study.

Post-Marketing Clinical Follow-Up of an Annular Closure System (Barricaid®)

Aims: The primary objective of this study is to evaluate intra-operative parameters, billing/reimbursement data and post-operative outcomes of patients treated with the Barricaid annular closure device in a real-world setting.

Principal Investigator: Michael Musacchio, MD
NorthShore Project Number: EH22-370
Contact: Call **(847) 570-4224** with questions regarding the study.

Sleep

An Open-Label Study to Evaluate the Long-Term Safety and Effectiveness of Pitolisant in Adult Patients with Idiopathic Hypersomnia Who Completed Study HBS-101-CL-010

Aims: The purpose of the study is to evaluate the long-term safety and effectiveness of pitolisant in adult patients with idiopathic hypersomnia (IH) who have completed the double-blind randomized withdrawal phase of HBS-101-CL-010. Patients who complete study HBS-101-CL-010 will have up to 7 days from the end-of-treatment visit/visit 5 to enroll in this study (HBS-101-CL-011) and begin open-label pitolisant.

Principal Investigator: Thomas Freedom, MD
NorthShore Project Number: EH22-371
Contact: Call **(847) 570-1864** with questions regarding the study.

Stroke

Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2)

Aims: The purpose of this randomized trial is to determine whether the incidence of stroke or death differs between subjects with high-grade asymptomatic carotid stenosis who receive intensive medical management alone, compared to subjects who receive intensive medical management in combination with carotid artery stenting (CAS). The primary endpoint is stroke or death within 44 days after randomization or ipsilateral ischemic stroke thereafter, up to the 4-year follow-up time point.

Principal Investigator: William Ares, MD
NorthShore Project Number: EH22-019
Contact: Call **(847) 570-4224** with questions regarding the study.

See page 7 for more information on this trial.

Stroke *(continued)*

Non-Blinded Data Collection Pilot Study of Acute Stroke Using the BrainPulse™

Aims: The purpose of this pilot study is to collect data from patients experiencing stroke using the BrainPulse device. In the second (current) phase of the study, data will be collected on two groups of patients: those with large vessel occlusion (LVO) acute stroke and those with non-LVO acute stroke. The data collected from the BrainPulse will be compared across these study groups in an attempt to distinguish stroke from other non-stroke conditions that present with similar symptoms and LVO from non-LVO types of strokes. Further assessments will also be made to evaluate whether the BrainPulse device can identify the presence of stroke.

Principal Investigator: Shakeel Chowdhry, MD
NorthShore Project Number: EH19-084
Contact: Call **(847) 570-4224** with questions regarding the study.

Phase 3, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Demonstrate the Efficacy and Safety of Milvexian, an Oral Factor XIa Inhibitor, for Stroke Prevention after an Acute Ischemic Stroke or High-Risk Transient Ischemic Attack LIBREXIA-STROKE

Aims: The main objective of this study is to evaluate if milvexian reduces the risk of ischemic stroke as compared with placebo, to evaluate if milvexian reduces the risk of cardiovascular disease, myocardial infarction, or ischemic stroke, as compared with placebo, and to evaluate if milvexian reduces the risk of ischemic stroke in the first 90 days compared with placebo.

Principal Investigator: Fulvio Roberto Gil, MD
NorthShore Project Number: EH22-478
Contact: Call **(847) 570-1864** with questions regarding this study.

"We're participating in cutting-edge national prospective research trials to improve care for patients with ischemic and hemorrhagic stroke."

— Dr. Shakeel Chowdhry, Neurosurgery Department

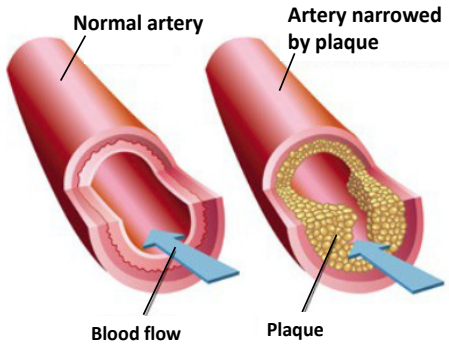
THUNDER: Acute Ischemic Stroke Study with the Penumbra System® including Thunderbolt™ Aspiration Tubing

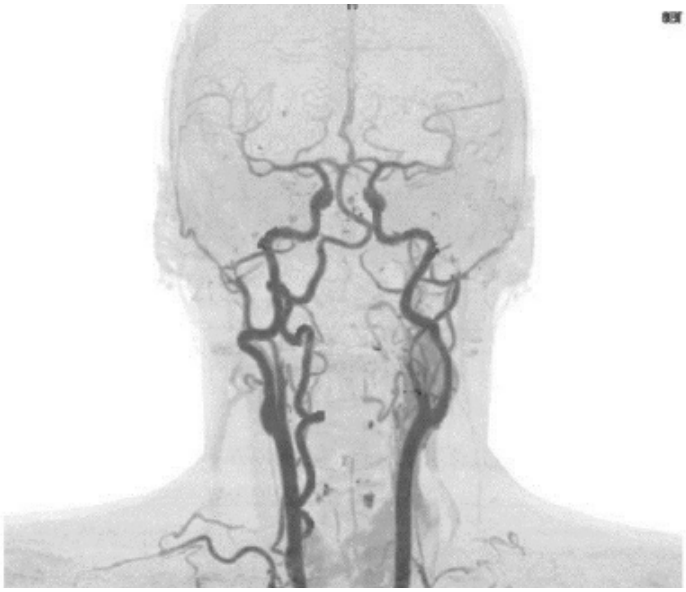
Aims: The objective of this study is to demonstrate the safety and efficacy of the Penumbra System including Thunderbolt Aspiration Tubing in patients with acute ischemic stroke secondary to large vessel occlusion, who are eligible for mechanical thrombectomy. The primary efficacy and safety endpoints are angiographic revascularization of the occluded target vessel at immediate post-procedure as defined by mTICI 2b or higher and occurrence of symptomatic intracranial hemorrhages (sICH) at 24 hours.

Principal Investigator: William Ares, MD
NorthShore Project Number: EH23-219
Contact: Call **(847) 570-4224** with questions regarding this study.

Comparing Surgical Treatment and Intensive Medical Management for Asymptomatic Carotid Stenosis (CREST-2 Trial)

Two carotid arteries, one on either side of the neck, deliver oxygen-rich blood to the brain, head, and neck. Narrowing of one or both carotid arteries (called carotid stenosis) can be caused by accumulation of plaque along the artery walls, which increases the risk of stroke. A stroke can occur either because some plaque, or part of a blood clot that forms on the plaque, breaks off and blocks a blood vessel in the brain. Often, plaque buildup in the carotid artery does not cause any symptoms until it causes a stroke.





Cerebral angiography uses contrast material injected into an artery (usually in the groin), which makes the vessels in the head and neck visible by X-ray, so the amount of artery narrowing can be measured. Ultrasound, or carotid Doppler, uses sound waves to measure the rate of blood flow through the artery.

Images reproduced with permission from "The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study" https://www.crest2trial.org/

Carotid stenosis has typically been treated by either removal of the plaque through an incision in the neck (carotid endarterectomy, or CEA) or by carotid artery stenting (CAS), which involves insertion of a small mesh tube, or stent, to keep the carotid artery open and prevent debris from traveling to the brain. Although these surgical techniques are commonly used and effective at preventing stroke, new advances in medical management may provide a similar benefit. Recent studies have shown that intensive medical management of risk factors—such as high blood pressure, diabetes, and cholesterol—can also significantly reduce stroke risk.

Both CEA and CAS surgical techniques as well as intensive medical management are routinely used standard-of-care treatments for carotid stenosis. The CREST-2 study involves two multi-center clinical trials designed to find out whether intensive medical management alone or combined with either CEA or CAS works best to prevent strokes in people with carotid stenosis.

Approximately 2,480 patients aged 35 years or older with asymptomatic, high-grade stenosis (70–99% artery blockage) will be recruited across approximately 150 sites, including NorthShore. Patients will be assigned to either the CAS or CEA trial (~1,240 patients in each trial), based on clinical criteria. Once assigned, patients will be randomized to either intensive medical management alone or intensive medical management plus CAS or CEA.

(Patients at NorthShore will participate in the CAS trial.)

Medical management may include taking aspirin and other medications to reduce blood pressure and LDL cholesterol. All patients will be provided with support to manage diabetes, cholesterol, weight and physical activity as part of a lifestyle modification program (called INTERVENT), along with help to stop smoking and support from medical specialists as needed.

Patients will be monitored for up to four years with periodic assessments. At some or all of these assessments, imaging and blood test data will be collected and patients will be screened for stroke symptoms and mental abilities.

The primary study outcome will be the number of patients in each study group that experience a stroke or death—either soon after starting the trial or within the four-year follow-up period. Changes in thinking ability and number of strokes at the end of the follow-up period will be recorded, as well as other factors that might affect stroke risk—such as patient age, sex, and narrowing of the carotid over time. Patients will have additional follow-up if they have symptoms of a stroke.

"NorthShore's involvement in the CREST-2 trial reaffirms our dedication to both scientific inquiry and providing the highest level of stroke and cerebrovascular care for our patients. I'm proud to be able to offer participation in this pivotal study to our patients."

— Dr. William Ares,
Neurosurgery Department

For more information on the CREST-2 trial, call: (847) 570-4224

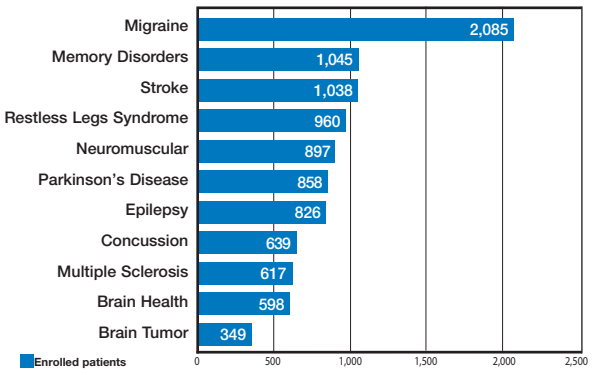
The DodoNA Project

The DodoNA project is one of the major research initiatives of NorthShore Neurological Institute. The purpose of the project is to predict, prevent and halt neurological disorders through the development of DNA-based prognostic tests and therapies. The DodoNA researchers built customized "toolkits" within NorthShore's award-winning Electronic Health Record (EHR) system for each of 10 neurological disorders and a Brain Health cohort that capture and store data from routine office visits. The researchers are also collecting blood and extracting DNA and plasma to be stored in a "biobank." Laboratory scientists are starting our genetic analyses by performing automated DNA sequencing tests, identifying a number of genetic markers in each of the groups. Our statisticians will then determine whether these markers may be significant in identifying disease characteristics or treatment response. With this information, researchers will be in a better position to deliver methods to predict and modify disease. Some descriptive data are shown in the graphs below and on the following pages.

Please note that patient enrollment for migraine, memory disorders, concussion, and stroke is now closed.

Research Update

As of September 2023, we have enrolled 9,912 patients in the DodoNA project, with a target enrollment of at least 1,000 patients for each condition.

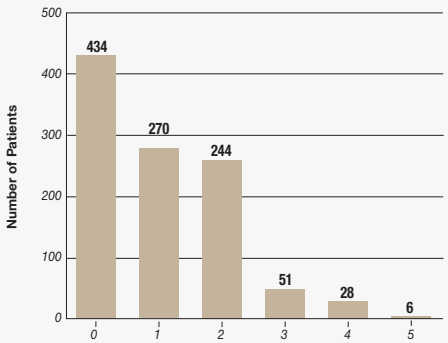


Stroke

Description of 1,038 enrolled patients

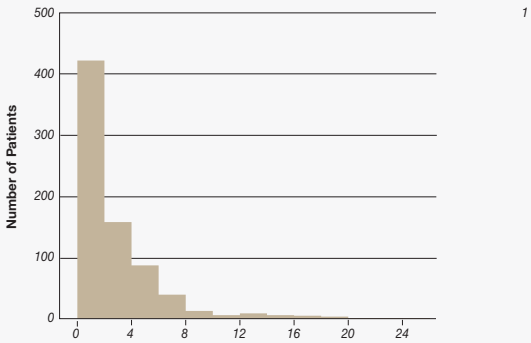
Modified Rankin Index

A global disability scale. 0 = no symptoms; 5 = severe disability. Scores at initial visit are shown.



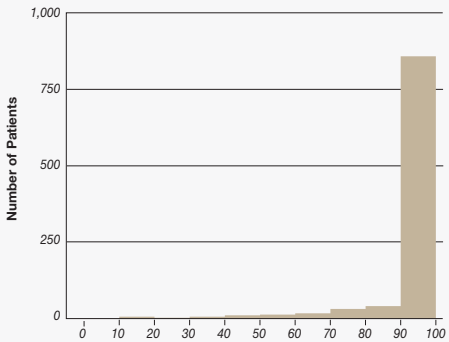
National Institutes of Health Stroke Scale

An objective measure of stroke severity. 0 = no symptoms; 1–4 = mild stroke; 5–15 = moderate stroke. Scores at initial visit are shown.



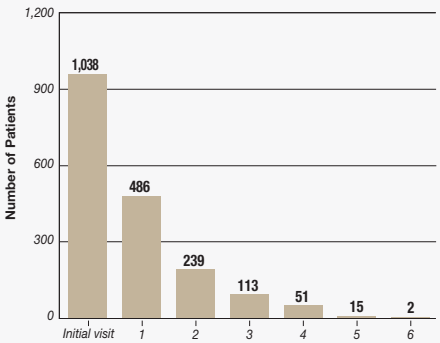
Barthel Index

A measure of performance in activities of daily living (basic activities). 100 = completely independent individual; 0 = completely nonfunctioning individual. Scores at initial visit are shown.



Patient Follow-Up

Numbers of patients evaluated at annual follow-up visits.

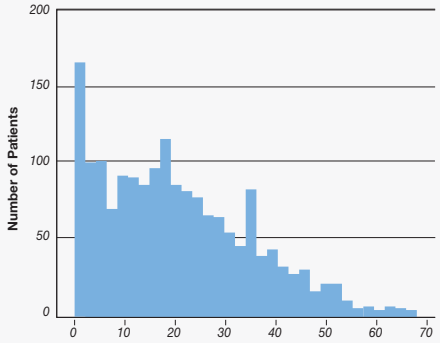


Migraine

Description of 2,085 enrolled patients

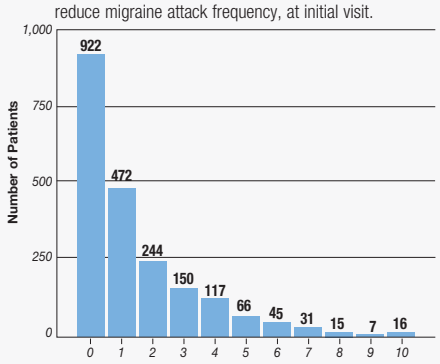
Disease Duration

Measured in years, from year of initial symptom to year of initial visit.



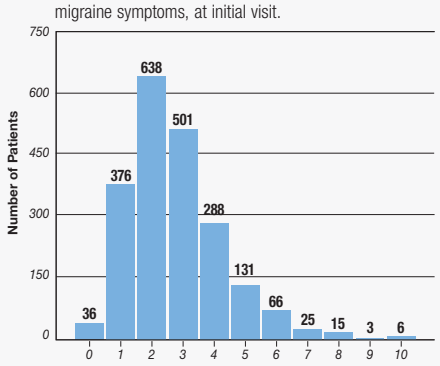
Preventive Medications

Number of patients taking daily preventive medications to reduce migraine attack frequency, at initial visit.



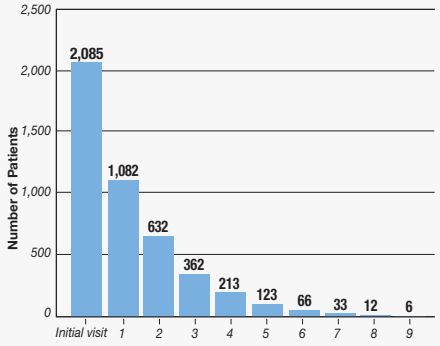
Abortive Medications

Number of patients taking abortive medications to stop migraine symptoms, at initial visit.



Patient Follow-Up

Patients evaluated at annual follow-up visits.



Clinical and Research Insights

Clinical and genetic factors that influence response to CGRP-based migraine preventive medications.

Migraine is an exceptionally common neurological condition that can cause severe disability. In 2018, three new preventive medications were introduced that target CGRP (calcitonin gene-related peptide), which is elevated during migraine headaches. These medications do not work in about a third of people with migraine disease. To understand what factors are associated with efficacy, we used two approaches. First, we reviewed the electronic health records of patients prescribed one of the three medications to identify clinical factors associated with response. Second, we analyzed data from the DodoNA migraine cohort to identify genetic factors associated with response. The DodoNA analyses revealed that genetic variation in two genes affected patient response. A variant in *RAMP1*, which encodes a protein important for CGRP signaling, is associated with decreased responsiveness. In contrast, a variant in *COMT*—which is involved in the degradation of catecholamines—and a higher migraine genetic risk score are associated with increased responsiveness. This work has provided real-world evidence for the importance of clinical as well as genetic factors in response to treatment.

Clinical and genetic factors influence response to CGRP-based preventives

Negative Associations

Prior hospitalization for migraines

≥6 failed preventives

RAMP1 rs12615320 (G)

Positive Associations

Migraine days/month

Female sex

Months on medication

Higher migraine genetic risk score

COMT rs4680 (A)

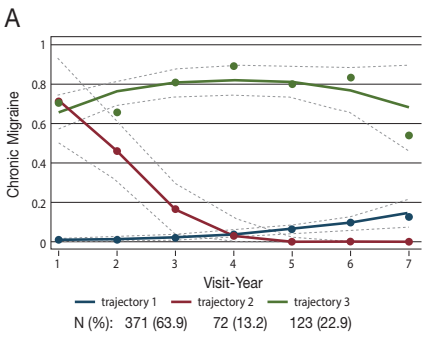
Migraine genetic risk influences patient outcomes.

Migraine can be considered a complex genetic disorder; both genetic variation and environmental factors affect the risk of migraine. We asked whether genetic risk of migraine also affected patient outcomes. We developed a genetic risk score based on genetic variants that have been previously associated with migraine in large genome-wide association studies. We then studied over 2,000 patients in the DodoNA migraine cohort, characterizing their initial-visit clinical features and the longitudinal trajectories. We found that a high-risk score is associated with a decreased age at onset, increased initial-visit severity, increased refractoriness to treatment and a decreased risk of migraine-associated comorbidities.

Patient Genetic Risk	Patient Outcomes
High Risk	▼ Age at onset ▲ Initial-visit severity ▲ Treatment refractoriness ▼ Comorbidity risk

Trajectories of patients with chronic migraine.

Chronic migraine, defined as the occurrence of migraine or other headaches on at least 15 days per month, is highly disabling. We studied the trajectories of people with migraine disease in the DodoNA cohort with respect to chronic migraine. We found evidence for the three trajectories shown in Panel A: (1) stable and low incidence, (2) present at the initial visit but responds to treatment to become low incidence, and (3) stable and high incidence. We then asked whether any of these trajectories are associated with a migraine genetic risk score. In Panel B, bar graphs illustrate that a high-risk score is more often found in trajectory 3, which appears to identify people with migraine disease who are more refractory to treatment.

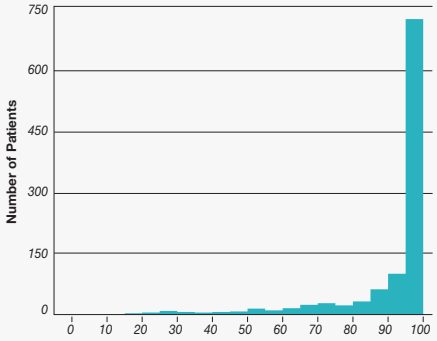


Memory Disorders

Description of 1,045 enrolled patients

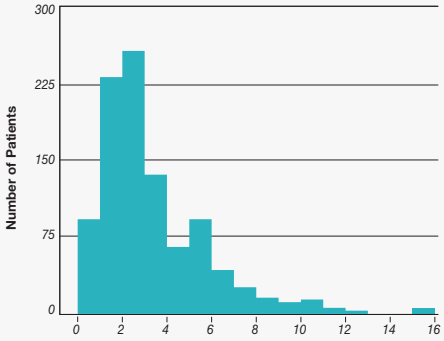
Barthel Index

A measure of performance in activities of daily living (basic activities), at initial visit. 100 = completely independent individual; 0 = completely nonfunctioning individual.



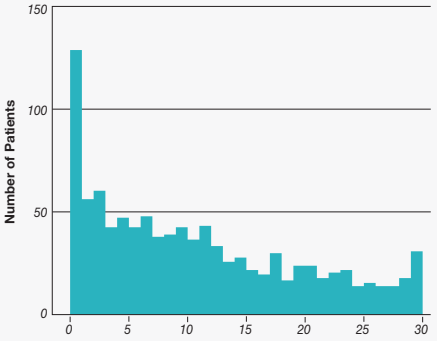
Disease Duration

Measured in years, from year of initial symptom to year of initial visit.



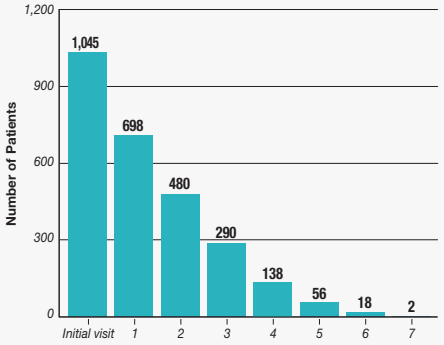
The Functional Activities Questionnaire

A measure of performance in activities of daily living (complex activities), at initial visit. 0 = person with no limitations; 30 = fully dependent individual.



Patient Follow-Up

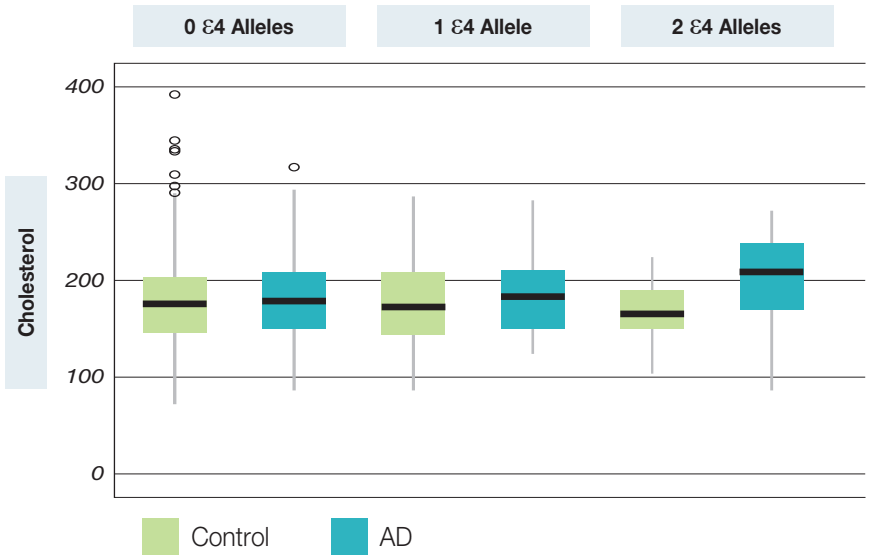
Patients evaluated at annual follow-up visits.



Clinical and Research Insights

Lipid levels in patients who develop Alzheimer's disease (AD).

Many of the over-70 risk loci for Alzheimer's disease, including the apolipoprotein E (APOE) gene, impact lipid metabolism. Although LDL-C plasma levels are elevated in early-onset Alzheimer's disease, the association of lipids with the strongest risk allele, APOE-ε4, and their utility as a biomarker for later-onset Alzheimer's disease and disease progress remains controversial. To gain insight into this issue, we compared lipid levels in members of the DodoNA memory cohort to those in DodoNA patients lacking neurodegenerative disease. The box plots illustrate one of the results of this study and show the distribution of cholesterol levels in DodoNA control subjects and patients with Alzheimer's disease, five years prior to onset, by the number of APOE-ε4 alleles present.

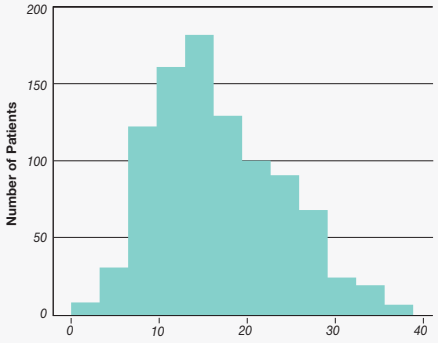


Restless Legs Syndrome

Description of first 960 enrolled patients

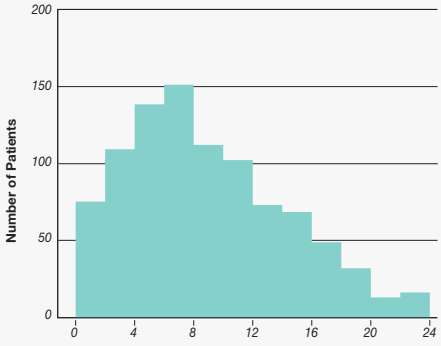
IRLS Score

International Restless Legs Scale (IRLS) rating scale at initial visit. Scores of 0–10 = mild, 11–20 = moderate, 21–30 = severe and 31–40 = very severe.



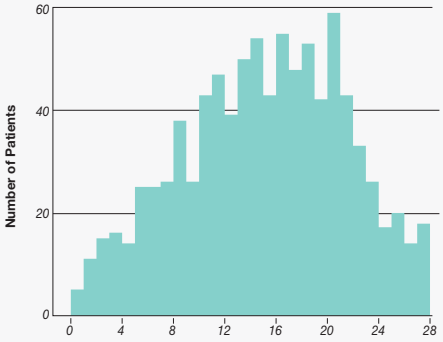
ESS Score

Epworth Sleepiness Scale (ESS), at initial visit. Scores greater than 10 indicate excessive daytime sleepiness.



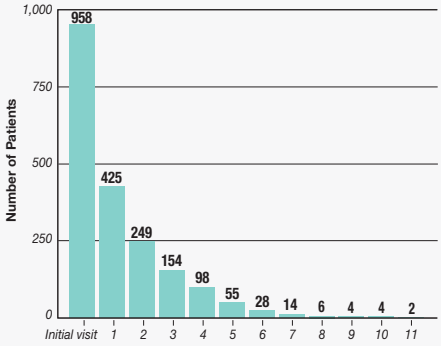
ISI Score

Insomnia Severity Index (ISI) at initial visit. Scores of 15 and over indicate at least moderate severity.



Patient Follow-Up

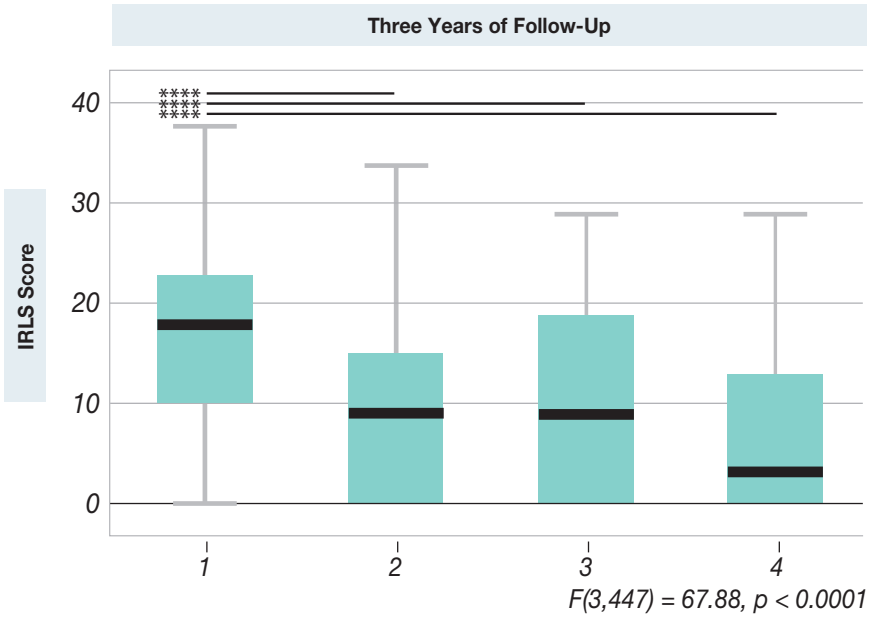
Patients evaluated at annual follow-up visits.



Clinical and Research Insights

Effectiveness of treatment for restless legs syndrome.

In addition to providing insights into the genetic contributions to disease and disease outcomes, analyses of the DodoNA cohort can be used to evaluate quality metrics. One example is illustrated here for the DodoNA sleep cohort, which includes patients with restless legs syndrome. The box plots and associated analyses show that, following treatment at the NNI, scores on the International Restless Legs Scale (IRLS) decline. Compared to initial visit scores, scores are lower on three subsequent annual visits.

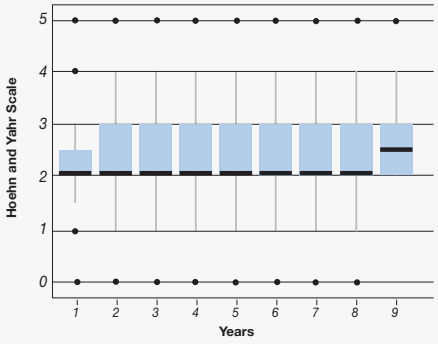


Parkinson's Disease

Description of first 858 enrolled patients

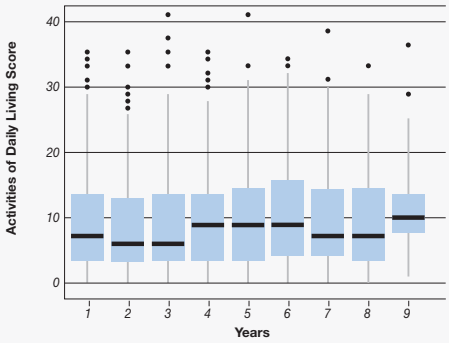
Longitudinal Changes in Hoehn and Yahr Scale

The Hoehn and Yahr scale is a measure of motor impairment; it is an objective measure of disability. As a group, patients' scores have remained largely stable over more than five years.



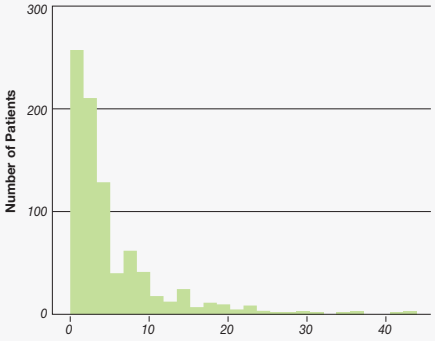
Activities of Daily Living

This scale assesses difficulties in daily activities due to Parkinson's disease, with higher scores reflecting greater difficulty in daily activities.



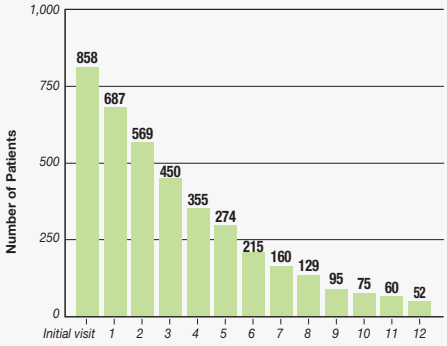
Disease Duration

Measured in years, from year of initial symptom to year of initial visit.



Patient Follow-Up

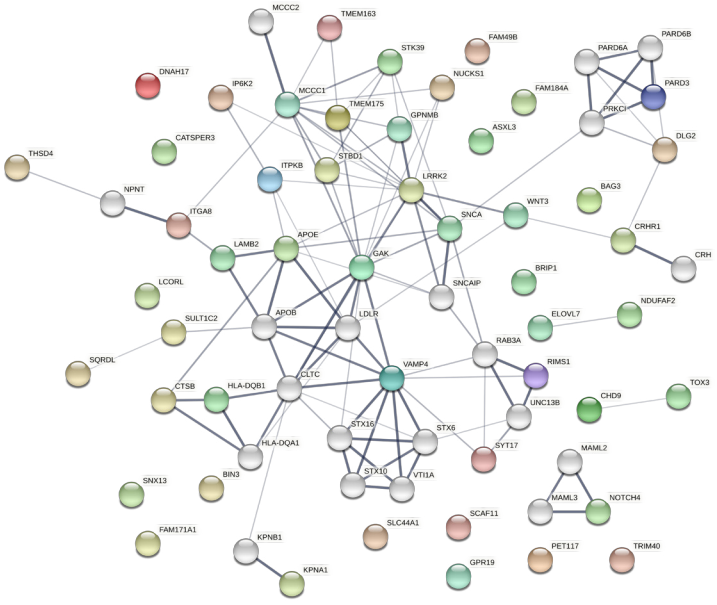
Patients evaluated at annual follow-up visits.



Clinical and Research Insights

Protein-protein interaction network for genes associated with differential presentation of symptoms of Parkinson's disease.

Many studies over the last 20 years have demonstrated that genetic variation impacts the risk of Parkinson's disease. Parkinson's disease presents with a variety of symptoms and can be challenging to diagnose reliably. We evaluated how genetic variation impacts the clinical features that are observed when patients are first diagnosed. By studying patients enrolled in the DodoNA Parkinson's disease cohort, we learned that genetic risk factors for Parkinson's disease do not uniformly affect the clinical presentation. We found that the genes associated with risk are differentially associated with the characteristics seen at the initial clinical diagnosis. This figure shows potential functional protein-protein interactions between the 32 genes identified in our association analysis. Each sphere represents one protein, and the thickness of the lines between the spheres corresponds to the confidence of the interactions. The colored spheres represent the proteins of the genes identified in the association analyses, while the uncolored spheres represent second-shell interactions that reveal indirect interactions among the proteins. For more information, see Markopoulou et al., 2021. *Front. Neurol.* 12:662278. doi: 10.3389/fneur.2021.662278.

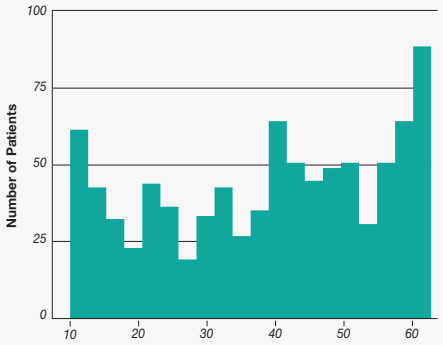


Neuromuscular

Description of first 897 enrolled patients

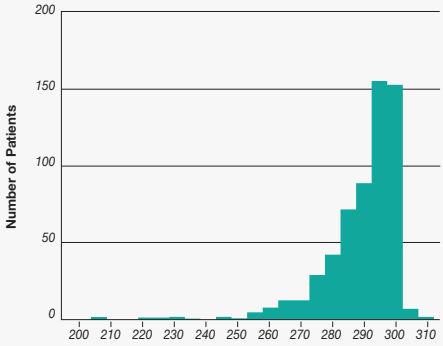
Fatigue Severity Score

This short questionnaire evaluates the effect of fatigue on patients. Scores at initial visit are shown. A total score of less than 36 suggests that a patient may not be suffering from fatigue.



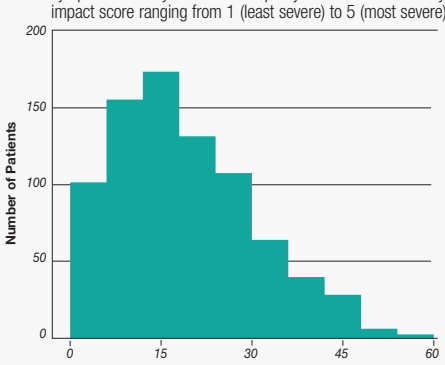
NorthShore Neuropathy Impairment Score

This test was developed by physicians at NorthShore Neurological Institute to parallel severity of involvement and aid in the quantification of disability. Scores are shown from initial visit.



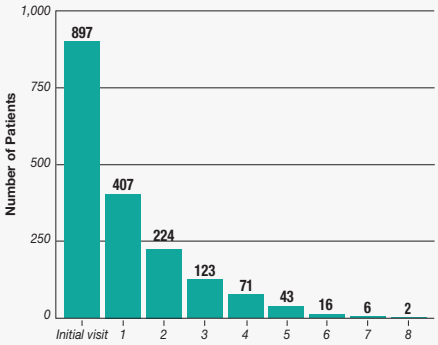
Survey of Autonomic Symptoms

Survey scores shown from initial visit. The survey consists of 11 items in women and 12 in men to measure autonomic symptoms in early diabetic neuropathy. Each item is rated by an impact score ranging from 1 (least severe) to 5 (most severe).



Patient Follow-Up

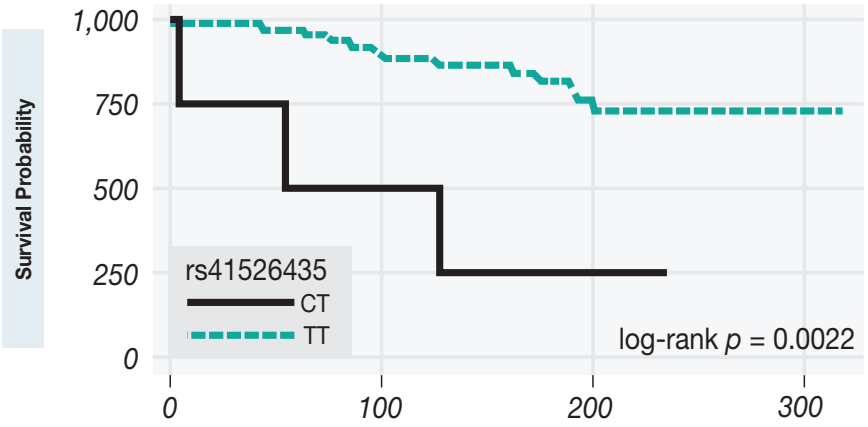
Patients evaluated at annual follow-up visits.



Clinical and Research Insights

A genetic variant is associated with increased risk of mortality in patients with diabetic autonomic neuropathy.

Some patients with diabetes develop diabetic autonomic neuropathy. This condition is associated with increased mortality. To improve outcomes in patients with diabetic autonomic neuropathy, we sought to identify factors that increase mortality risk in these patients. We analyzed data from the DodoNA polyneuropathy toolkit and reviewed the electronic health record. In addition to two clinical characteristics (lower body mass index and the presence of neurogenic orthostatic hypotension), we found that carriers of a genetic variant previously associated with an increased risk of polyneuropathy also had a higher risk of mortality.



Number at Risk

CT	4	(2)	2	(1)	1	(0)	0
TT	64	(6)	50	(7)	23	(0)	1

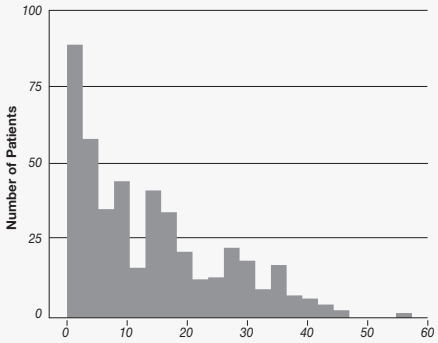
In this study, patients with the genetic variant CT had a higher risk of mortality than those with the TT variant.

Multiple Sclerosis

Description of first 617 enrolled patients

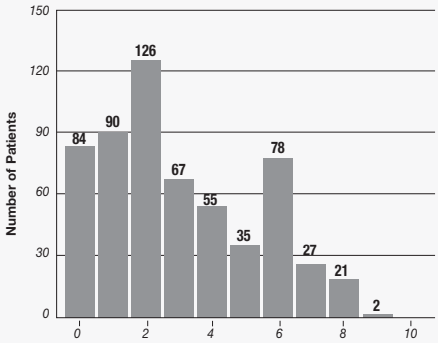
Disease Duration

Measured in years, from year of initial symptom to year of initial visit.



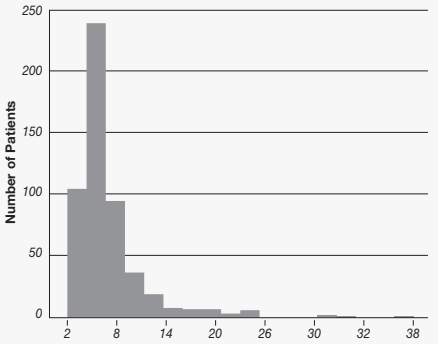
EDSS Step

Expanded Disability Status Scale (EDSS) at initial visit. Higher scores are more severe (e.g., scores of 5 and above indicate increasing difficulty walking).



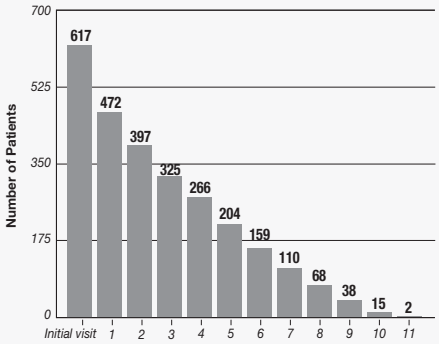
25 ft. Walk

The number of seconds required, on a second attempt, to walk 25 feet, at initial visit.



Patient Follow-Up

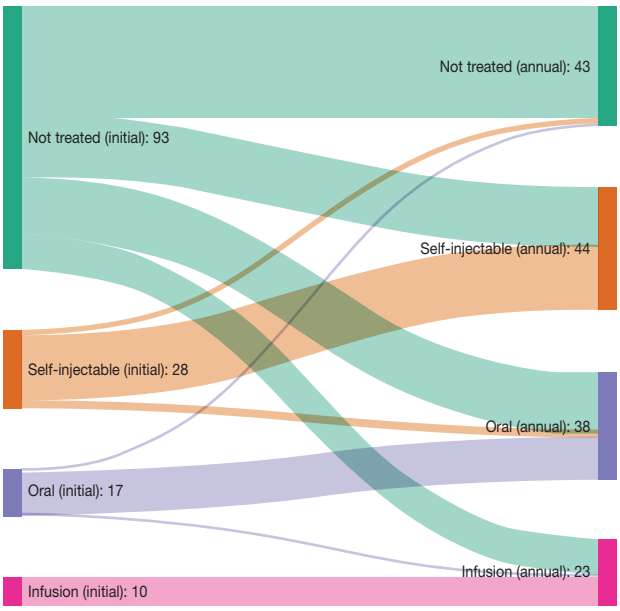
Patients evaluated at annual follow-up visits.



Clinical and Research Insights

Changing immunomodulating medication preferences for the treatment of multiple sclerosis.

DodoNA data can be used to understand trends in patient and clinician preferences for treatment. In this example, we studied trends in the use of immunomodulating medications that are used to treat multiple sclerosis. An analysis of data from the DodoNA multiple sclerosis toolkit provided an understanding of how patient preferences for injectable, oral and infused medications have changed over the past decade. Compared to a study we performed in 2016, we found that patient choices have changed in a way that corresponds to the more varied treatment options in our patient population. The flow (Sankey) diagram presented here illustrates that though many patients still consider injectable medications a first-line agent, oral medications are equally popular in our community-based population.

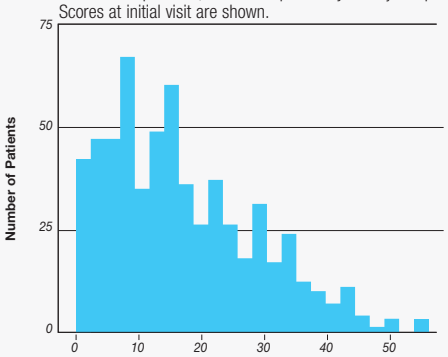


Concussion

Description of first 639 enrolled patients

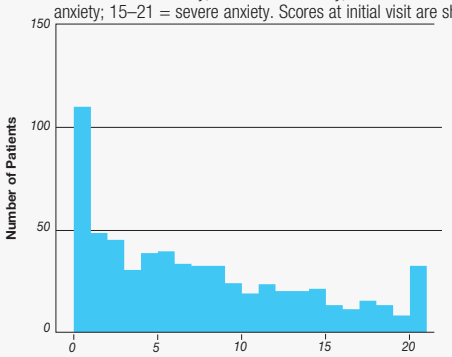
CES-D Score

Screening test to determine depression quotient. 15–21 = mild to moderate depression; over 21 = possibility of major depression. Scores at initial visit are shown.



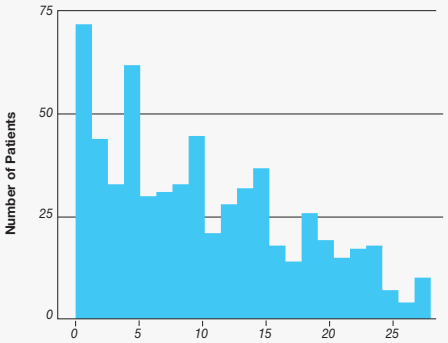
GAD-7 Score

Measuring of generalized anxiety disorder (GAD). 0–4 = minimal anxiety; 5–9 = mild anxiety; 10–14 = moderate anxiety; 15–21 = severe anxiety. Scores at initial visit are shown.



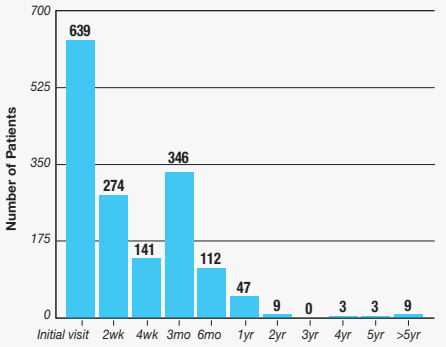
ISI Score

Insomnia Severeity Index (ISI) score at initial visit. Scores of 15 and over indicate at least moderate severity.



Patient Follow-Up

Patients evaluated at annual follow-up visits.

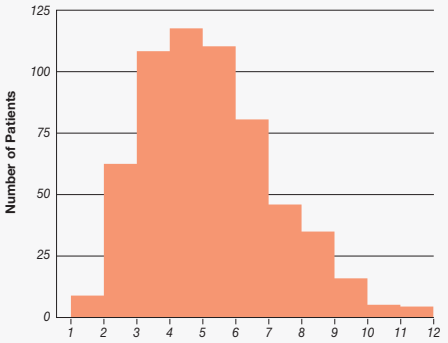


Brain Health

Description of first 598 enrolled patients

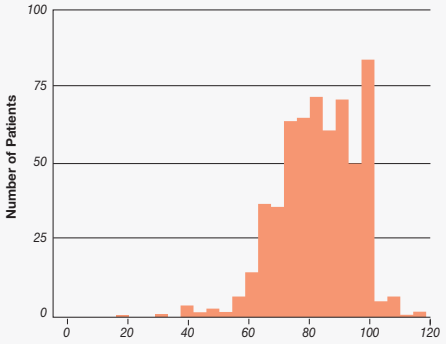
Brain Health Quiz Score

The brain health quiz includes 23 well-defined risk factors for Alzheimer's disease and related disorders. 0 = no risk factors or concerns; 23 = all risk factors and concerns. Scores from initial vist are shown.



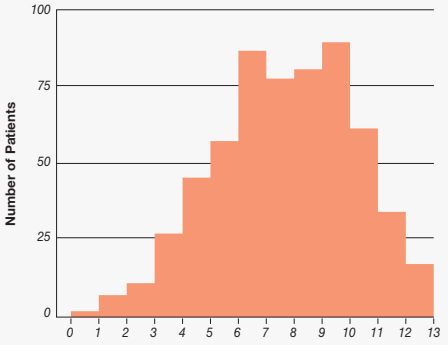
Readiness Questionnaire

The readiness questionnaire indicates readiness to engage in several brain health activities. 100 = very willing for every activity; 0 = very unwilling for all activities. Scores at initial visit are shown.



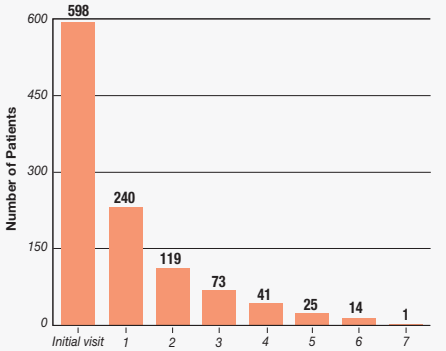
PREDIMED Questionnaire

The PREDIMED questionnaire is a 14-item quiz that defines adherence to the Mediterranean diet. 0–9 = weak adherence; 10–14 = strong adherence. Scores at initial visit are shown.



Patient Follow-Up

Patients evaluated at annual follow-up visits.

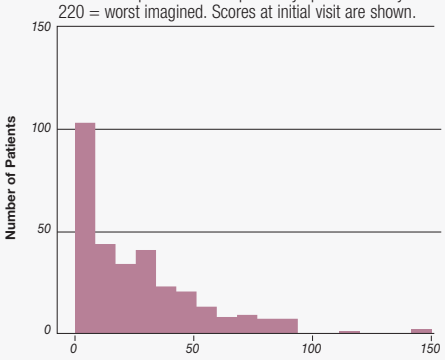


Brain Tumor (primary malignant)

Description of first 349 enrolled patients

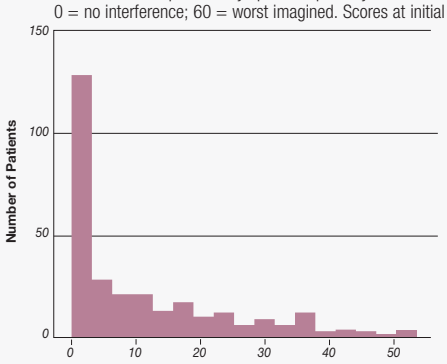
MD Anderson Symptom Inventory—Brain Tumor (Part 1)

Measures a patient's self-reported symptoms severity. 0 = no symptoms; 220 = worst imagined. Scores at initial visit are shown.



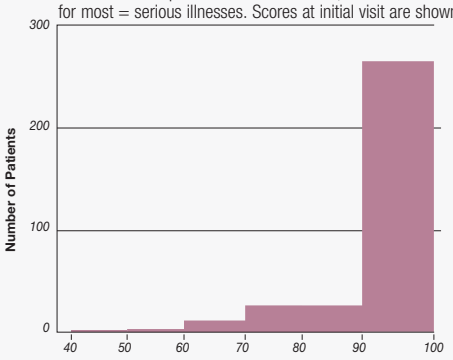
MD Anderson Symptom Inventory—Brain Tumor (Part 2)

Measures how a patient's symptoms reportedly interfere with daily living. 0 = no interference; 60 = worst imagined. Scores at initial visit are shown.



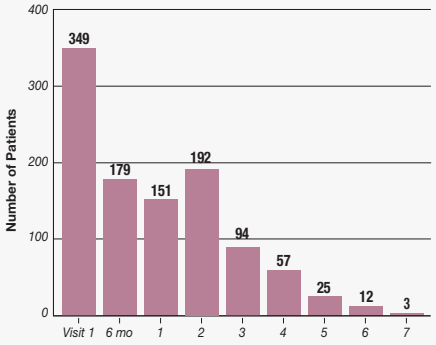
Karnofsky Performance Scale

Classification of functional impairment used to compare effectiveness of different therapies. The lower the score, the worse the survival for most = serious illnesses. Scores at initial visit are shown.



Patient Follow-Up

Patients evaluated at annual follow-up visits.

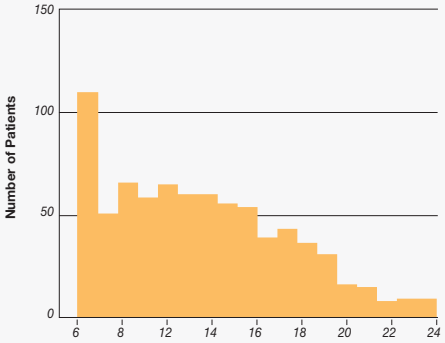


Epilepsy

Description of 826 enrolled patients

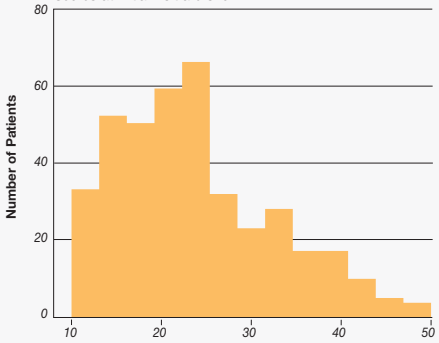
NDDI-E Total Score

The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is a 6-item questionnaire validated to screen for depression in people with epilepsy. Scores at initial visit are shown. Scores greater than 15 indicate depression.



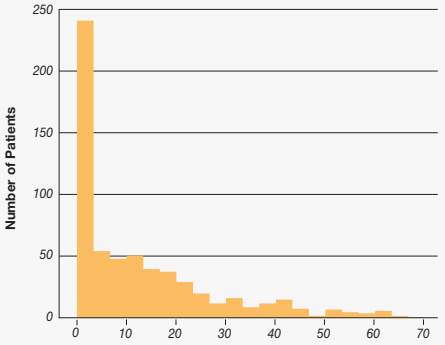
Quality of Life in Epilepsy

Quality of Life in Epilepsy (QOLIE-10-P). Lower scores indicate a greater severity and burden of epilepsy on quality of life. Scores at initial visit are shown.



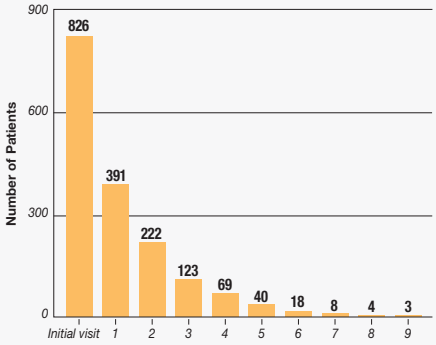
Disease Duration

Measured in years, from year of initial symptom to year of initial visit.



Patient Follow-Up

Patients evaluated at annual follow-up visits.



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A publication of NorthShore Neurological Institute

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