March 2025

Research Updates

Excellence in Patient Care, *Innovation* in Research

Endeavor Health

Endeavor Health

Endeavor Health is committed to conducting medical research with the goal of helping patients live longer, healthier lives.

Endeavor Health Neurosciences Institute is committed to conducting medical research with the goal of better understanding how to diagnose, treat, and prevent neurological diseases and conditions.

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

For an up-to-date list of research studies currently enrolling patients at Endeavor Health Neurosciences Institute, visit:
Neurological Research Institute & Clinical Trials | NorthShore.

To learn more about supporting excellence in research at Endeavor Health Neurosciences Institute, please contact Danielle Maihofer, Director of Philanthropy at NorthShore Hospitals Foundation, part of Endeavor Health, at **(224) 364-7614** or **dmaihofer@northshore.org**.

You can also support Endeavor Health Neurosciences Institute by making an online donation. Visit **Donate to NorthShore Hospitals Foundation** and select Endeavor Health Neurosciences Institute from the drop-down menu.

Clinical Trials

For an up-to-date list of clinical trials currently enrolling patients at Endeavor Health Neurosciences Institute, visit Neurosciences Institute | Endeavor Health

Alzheimer's disease & memory disorders

Principal investigator:
Chad Yucus, MD
Endeavor project number:
EH23-381
Contact:
Call **(847) 503-4344** with questions about this study.
Open to enrollment: **Yes**

Quality improvement PrecivityAD2TM (QUIP II): A survey and clinical utility study of the PrecivityAD2 blood test in the evaluation of cognitive impairment

The purpose of the study is to evaluate the clinical utility of the PrecivityAD2 blood test for assessing cognitive impairment. The study aims to investigate how the PrecivityAD2 test can be used to improve the evaluation and management of cognitive impairment, and to gather data on the performance of this test in real-world clinical settings.

Brain & spine tumor

Principal investigator:
Christopher Trevino, MD
Endeavor project number:
EH18-270
Contact:
Call **(847) 570-2025** with questions about this study.
Open to enrollment: **Yes**

Phase III trial of observation versus irradiation for a gross totally resected grade II meningioma

The purpose of this study is to obtain a clear answer to the longstanding question of which treatment route leads to the best clinical outcome for patients with newly diagnosed, WHO grade II meningioma. Patients will be randomly assigned into one of two groups: After surgical removal of the tumor, Group 1 will be observed and Group 2 will receive radiation therapy.

Principal investigator:
Christopher Trevino, MD
Endeavor project number:
EH21-065
Contact:
Call **(847) 570-2025** with questions about this study.
Open to enrollment: **No**

A phase II study of checkpoint blockade immunotherapy in patients with somatically hypermutated recurrent glioblastoma

Glioblastoma multiforme (GBM) is the most aggressive of the primary brain tumors. It remains uniformly lethal, and there are currently 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 GBM with elevated mutational burden from growing or spreading after initial therapy failed. For this study, an elevated mutational burden is defined as at least 20 mutations on the FoundationOne CDx test.

Principal investigator:
Christopher Trevino, MD
Endeavor project number:
EH18-083
Contact:
Call **(847) 570-2025** with questions about this study.
Open to enrollment: **No**

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

This study 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, O6-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:
Christopher Trevino, MD
Endeavor project number:
Study00000089
Contact:
Call **(847) 570-2025** with questions about this study.
Open to enrollment: **Yes**

Randomized phase II trial of anti-LAG-3 and anti-PD-1 blockade vs. SOC in patients with recurrent glioblastoma

Glioblastoma multiforme is the most aggressive primary brain tumor with a median overall survival of only 16–18 months despite aggressive treatment. Given this bleak prognosis, alternative approaches such as immunotherapy are critically needed. The purpose of this study is to compare the restricted mean survival time for overall survival between patients receiving the combination of relatlimab and nivolumab versus patients receiving standard of care (SOC) chemotherapy with CCNU (lomustine).

Multiple sclerosis

Principal investigator:
Afif Hentati, MD
Endeavor project number:
EH20-357
Contact:
Call **(847) 503-4335** with questions about this study.
Open to enrollment: **No**

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

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. Primary objectives include the amount of time from baseline to first occurrence of a progression event based on changes in a patient's Expanded Disability Status Scale (EDSS) score, increase in their Timed 25-Foot Walk test, increase in their time to complete the Nine-Hole Peg Test and their annualized relapse rate. The pharmacokinetics of fenebrutinib will also be evaluated. Eligible patients with relapsing multiple sclerosis will be randomly assigned, 1:1, to one of the two treatment arms. Patients 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.

Principal investigator:
Carolyn Goldschmidt, DO
Endeavor project number:
EH22-479
Contact:
Call **(847) 503-4335** with questions about this study.
Open to enrollment: **Yes**

A randomized, open-label, multi-center, active-comparator study to assess the efficacy, safety and tolerability of ofatumumab 20 mg SC monthly versus continued current therapy in relapsing-remitting multiple sclerosis after elevation of serum neurofilament light levels (SOSTOS)

The main purpose of this prospective research study is to investigate whether patients with relapsing remitting multiple sclerosis (MS) who have not had a relapse in the past year would benefit from a switch to ofatumumab versus continuing their current therapy. The study will also look into whether an elevated serum neurofilament light (NfL) level before the medication switch predicts enhanced benefit from a switch.

Principal investigator:
Afif Hentati, MD
Endeavor project number:
EH23-131
Contact:
Call **(847) 570-1864** with questions about this study.
Open to enrollment: **Yes**

Performance and safety of a digital tool for the unsupervised self-assessment of neuromyelitis optica spectrum disorder

The study evaluates 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
Endeavor project number:
EH23-324
Contact:
Call **(847) 503-4335** with questions about this study.
Open to enrollment: **Yes**

Master protocol of two independent, randomized, double-blind, phase III studies comparing efficacy and safety of frexalimab (SAR441344) to teriflunomide in adult participants with relapsing forms of multiple sclerosis

The primary objective of this study is to assess the efficacy of frexalimab compared to a daily dose of 14 mg teriflunomide, measured by annualized relapse rate, in participants with relapsing forms of MS. The secondary objective is to assess the efficacy of frexalimab compared to teriflunomide on worsening disability, MRI lesions, cognitive performance, physical function, and quality of life.

Neuromuscular disorders

Principal investigator:
Richard Wlodarski, MD
Endeavor project number:
EH22-333
Contact:
Call **(847) 503-4333** with questions about this study.
Open to enrollment: **No**

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)

This is an open-label extension trial of ARGX-117-2002. The objectives of the study are to evaluate the safety and tolerability of ARGX-117 and 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 adults with multifocal motor neuropathy (MMN).

Principal investigator:
Richard Wlodarski, MD
Endeavor project number:
EH23-132
Contact:
Call **(847) 503-4333** with questions about this study.
Open to enrollment: **No**

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

The primary objective of this study is to evaluate the long-term safety of efgartigimod in patients with postural orthostatic tachycardia syndrome (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:
Richard Wlodarski, MD
Endeavor project number:
EH23-067
Contact:
Call **(847) 503-4344** with questions about this study.
Open to enrollment: **Yes**

A phase III, 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

The aim of this study is to demonstrate the effectiveness and durability of ampreloxetine in reducing symptomatic neurogenic orthostatic hypotension (nOH) in patients diagnosed with multiple system atrophy (MSA). The study also evaluates the safety and efficacy of ampreloxetine in treating nOH in MSA patients. The primary goal is to determine whether ampreloxetine can improve symptoms such as dizziness, lightheadedness and fatigue, which are commonly experienced by MSA patients due to nOH. By investigating the long-term effects of ampreloxetine, the study may provide a potential treatment option for MSA patients who currently have limited therapeutic choices.

Principal investigator:
Richard Wlodarski, MD
Endeavor project number:
EH24-042
Contact:
Call **(847) 503-4333** with questions about this study.
Open to enrollment: **No**

A phase III double-blind randomized placebo-controlled study evaluating efficacy and safety of SAR 445088 in adults with chronic inflammatory demyelinating polyneuropathy (CIDP)

The primary objective of this study is to evaluate the efficacy of riliprubart relative to placebo as measured by the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale.

Principal investigator:
Richard Wlodarski, MD
Endeavor project number:
EH24-078
Contact:
Call **(847) 503-4333** with questions about this study.
Open to enrollment: **No**

A phase III, randomized, double-blind study evaluating efficacy and safety of riliprubart versus intravenous immunoglobulin (IVIg) in participants with chronic inflammatory demyelinating polyneuropathy

The primary objective of this study is to evaluate the efficacy of riliprubart relative to IVIg continuation as measured by the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale.

Parkinson's disease & movement disorders

Principal investigator:
Katerina Markopoulou, MD, PhD
Endeavor project number:
EH15-283
Contact:
Call **(847) 503-4335** with questions about this study.
Open to enrollment: **Yes**

The longitudinal clinical and genetic study of Parkinson's disease (LONG-PD Study)

The clinical and genetic factors that influence motor and non-motor 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 non-motor severity, progression and outcomes in Parkinson's disease across 25 global sites — from 18 countries, five continents, 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
Endeavor project number:
EH16-166
Contact:
Call **(847) 503-4335** with questions about this study.
Open to enrollment: **Yes**

Genetic analysis of familial Parkinsonism

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

Principal investigator:
Katerina Markopoulou, MD, PhD
Endeavor project number:
EH23-190
Contact:
Call **(847) 503-4335** with questions about this study.
Open to enrollment: **Yes**

The role of genetics and neurophysiology in the outcomes of deep brain stimulation surgery

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.

Sleep

Principal investigator:
Thomas Freedom, MD
Endeavor project number:
EH22-371
Contact:
Call **(847) 570-1864** with questions about this study.
Open to enrollment: **No**

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

The purpose of the study is to evaluate the long-term safety and effectiveness of pitolisant in adult patients with idiopathic hypersomnia 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 seven days from the end of treatment Visit/Visit 5 to enroll in study HBS-101-CL-011 and begin open-label pitolisant.

Spine surgery

Principal investigator:
Michael Musacchio, MD
Endeavor project number:
EH21-058
Contact:
Call **(847) 570-4224** with questions about this study.
Open to enrollment: **No**

A multicenter, prospective, randomized clinical trial comparing the safety and effectiveness of BAGUERA®C Cervical Disc Prosthesis to Mobi-C® Cervical Disc in the treatment of patients with symptomatic cervical disc disease at a single level

The purpose of this multicenter, prospective, randomized, controlled non-inferiority study is to evaluate the safety and effectiveness of BAGUERA®C Cervical Disc Prosthesis in the treatment of patients with symptomatic cervical disc disease at a single level.

Principal investigator:
Michael Musacchio, MD
Endeavor project number:
EH21-059
Contact:
Call **(847) 570-4224** with questions about this study.
Open to enrollment: **No**

A multicenter, prospective, randomized clinical trial comparing the safety and effectiveness of BAGUERA®C Cervical Disc Prosthesis to Mobi-C® Cervical Disc in the treatment of patients with symptomatic cervical disc disease at two contiguous levels

The purpose of this multicenter, prospective, randomized, controlled non-inferiority study is to evaluate the safety and effectiveness of BAGUERA®C Cervical Disc Prosthesis in the treatment of patients with symptomatic cervical disc disease at two contiguous levels.

Principal investigator:
Michael Musacchio, MD
Endeavor project number:
EH21-293
Contact:
Call **(847) 570-4224** with questions about this study.
Open to enrollment: **Yes**

A randomized, single-blinded, non-inferiority study comparing AGN1 local osteo-enhancement procedure (LOEP) SV Kit treatment of vertebral compression fragility fractures to PMMA bone cement treatment

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 (VCFFs). The objective of this study is to demonstrate non-inferiority of the AGN1 LOEP SV Kit for the treatment of VCFFs to standard of care vertebroplasty treatment using bipedicular injection of PMMA bone cement.

Principal investigator:
Michael Musacchio, MD
Endeavor project number:
EH22-228
Contact:
Call **(847) 570-4224** with questions about this study.
Open to enrollment: **No**

NuVasive Simplify® Disc

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 patients enrolled under the post-approval study as measured by reported adverse events, radiographic outcomes and patient-reported outcomes.

Principal investigator:
Michael Musacchio, MD
Endeavor project number:
EH24-141
Contact:
Call **(847) 570-4224** with questions about this study.
Open to enrollment: **Yes**

Post-marketing Barricaid® FREEDOM registry

Lumbar discectomy is a surgery for the treatment of a symptomatic, herniated disc. Discectomy is performed to decompress nerve roots compressed by herniated nucleus pulposus. The primary objective of this post-marketing registry study is to evaluate intra-operative parameters of patients treated with lumbar discectomy, with or without the Barricaid® annular closure device to determine the prevalence of patients at higher risk for reherniation and reoperation. The Barricaid® annular closure device is indicated for reducing the incidence of reherniation and reoperation in skeletally mature patients with radiculopathy (with or without back pain) attributed to a posterior or posterolateral herniation.

CLINICAL TRIALS

Stroke & cerebrovascular

Principal investigator:
William Ares, MD
Endeavor project number:
EH22-019
Contact:
Call **(847) 570-4224** with questions about this study.
Open to enrollment: **No**

Carotid revascularization and medical management for asymptomatic carotid stenosis trial (CREST-2)

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

Principal investigator:
Shakeel Chowdhry, MD
Endeavor project number:
EH23-416
Contact:
Call **(847) 570-4224** with questions about this study.
Open to enrollment: **Yes**

Prospective evaluation of the diagnostic accuracy of sine spin non-contrast flat detector CT (FDCT) for the detection of intracranial hemorrhage in stroke patients — an open-label, multicenter, non-inferiority comparison of FDC to multi-detector CT (MDCT) with blinded assessment of outcome events

The primary objective is to evaluate whether non-contrast flat detector CT (FDCT) imaging is non-inferior compared to non-contrast multi-detector CT (MDCT) for the detection and exclusion of intracranial hemorrhages. The secondary objectives are to determine the sensitivity, specificity, positive predictive value and negative predictive value of non-contrast FDCT imaging for the detection of intracranial hemorrhages. The sensitivity of FDCT for the detection of an intracranial hemorrhage within the subset of patients presenting with an isolated infratentorial intracranial hemorrhage will be reported separately. An additional objective is to determine the interrater agreement for non-contrast FDCT imaging regarding the occurrence of intracranial hemorrhages.

Principal investigator:
Mohammad Anadani, MD
Endeavor project number:
EH23-369
Contact:
Call **(847) 618-4430** with questions about this study.
Open to enrollment: **Yes**

Anticoagulation in intracerebral hemorrhage (ICH) survivors for stroke prevention and recovery (ASPIRE)

The goal of this study is to assess the efficacy and safety of apixaban, an anticoagulant, in patients with atrial fibrillation and a recent intracerebral hemorrhage (ICH) to determine if apixaban is superior to aspirin in preventing recurrent hemorrhagic or ischemic stroke or death from any cause. The study also seeks to determine if apixaban, compared with aspirin, results in better functional outcomes as measured by the Modified Rankin Scale.

Principal investigator:
Shakeel Chowdhry, MD
Endeavor project number:
EH22-239
Contact:
Call **(847) 570-1037** with questions about this study.
Open to enrollment: **Yes**

The REpeated ASSEssment of SurvivorS in intracerebral hemorrhage (ICH) study (REASSESS)

The goal of this study is to determine whether surgical clot reduction after intracerebral hemorrhage (ICH) reduces the risk of progressive cognitive decline, if there is a long-term benefit in survival and functional outcome from minimally invasive surgery whether or not cognitive decline occurs, and if expression of inflammatory pathway genes predicts risk of cognitive decline.

Principal investigator:
William Ares, MD
Endeavor project number:
EH23-382
Contact:
Call **(847) 570-1037** with questions about this study.
Open to enrollment: **No**

Product surveillance registry platform base clinical investigation plan (INSPIRE)

The goal of this study is to continue evaluation and periodic reporting of safety and effectiveness of Medtronic market-released products for their intended use, and to obtain real-world performance and safety information from a global network of hospitals, clinics and clinicians intended to represent the range of clinical environments in which Medtronic products are used.

Principal investigator:
William Ares, MD
Endeavor project number:
EH22-328
Contact:
Call **(847) 570-4224** with questions about this study.
Open to enrollment: **Yes**

CHESS — chronic subdural hematoma treatment with embolization versus surgery study

In this prospective, multi-center, randomized, controlled, open-label clinical trial, patients with moderately symptomatic chronic subdural hematoma (CSDH) are randomized in a 1:1 ratio to middle meningeal artery embolization (MMAE) or conventional surgery. The purpose of this study is to collect safety and efficacy data in patients with a moderately symptomatic convexity CSDH. Efficacy objective: Evaluate whether MMAE reduces the proportion of patients requiring rescue surgery or who die within 180 days (+30 days) after MMAE compared to conventional surgery. Safety objectives: Within 180 days (+30 days) of randomization, evaluate the proportion of patients with symptomatic ischemic stroke, serious/life-threatening adverse events, worsening of neurological status, or the development of new disabling neurological symptoms (a decline of 1 point or more on the Markwalder scale), seizures, or cranial neuropathy after MMAE compared to conventional surgery.

Principal investigator:
Fulvio Roberto Gil, MD
Endeavor project number:
EH22-478
Contact:
Call **(847) 570-1864** with questions about this study.
Open to enrollment: **Yes**

Phase III, 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

The main objective of this study is to evaluate if milvexian reduces the risk of ischemic stroke, compared with placebo, and to evaluate if milvexian reduces the risk of ischemic stroke in the first 90 days compared with placebo. Patients participating in the study will receive either milvexian 25 mg or matching placebo twice daily. This is a multicenter study of up to 15,000 participants.

Principal investigator:
William Ares, MD
Endeavor project number:
EH24-227
Contact:
Call **(847) 570-1037** with questions about this study.
Open to enrollment: **Yes**

SEAL™ IT: saccular endovascular aneurysm lattice system interventional pivotal trial

The primary objective of the trial is to document that the safety and effectiveness of the SEAL Embolization System (SES) for the treatment of saccular intracranial aneurysms exceed the objective performance goal to support the FDA premarket approval (PMA) submission. Post-PMA follow-up will continue for five years after the procedure.

Principal investigator:
William Ares, MD
Endeavor project number:
Study00000116
Contact:
Call **(847) 570-4224** with questions about this study.
Open to enrollment: **Yes**

Prospective, open-label, multi-center procedural data collectIon case registry on NeVa VS for cerebral vasospasm management in post SAH patients

This registry is a post-market study of an FDA-Humanitarian Device Exemption (HDE)-approved cerebral vessel dilation device (NeVa VS). Patients participating in this registry were previously deemed to require endovascular intervention for cerebral vasospasm. The objectives of this study are to evaluate the ability of NeVa VS to improve vasospasm, assess trends associated with the use of the NeVa VS, and assess the resource utilization impact of NeVa VS for treatment of cerebral vasospasm secondary to aneurysmal subarachnoid hemorrhage.

Principal investigator:
Daniel Heiferman, MD
Endeavor project number:
Study00000055
Contact:
Call **(630) 527-7343** with questions about this study.
Open to enrollment: **Yes**

Effect of anti-thrombotic therapy on menstruation (ATOM)

Antithrombotic medications are commonly used in the treatment of neurovascular conditions such as stroke prevention and intravascular stent placement. Increased incidence of heavy menstrual bleeding is well documented in the literature in premenopausal patients taking antithrombotic medication. The effects of antithrombotics on premenopausal neurovascular patients have not been investigated. The objective of this prospective and retrospective survey study is to determine the effects of antithrombotic medications on menstruation patterns in premenopausal neurovascular patients.

CLINICAL TRIALS

The DodoNA Project

Principal investigator:
Katerina Markopoulou, MD, PhD
Endeavor project number:
EH10-139
Contact:
Call **(847) 503-4344** with questions about this study.
Open to enrollment: **Yes**

DNA predictions to improve neurological health

“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, in The DodoNA Project (DodoNA), 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. To obtain data, we will invite up to 1,000 patients for each of the 11 projects (11,000 patients 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).

Research Project

VERTEBRAL FRACTURES

Investigating a new resorbable implant for vertebral compression fragility fractures

Globally, approximately 1.4 million vertebral compression fragility fractures are diagnosed every year, most of which are due to osteoporosis.

Vertebral compression fragility fractures (VCFFs) (Fig. 1) can cause chronic, severe back pain affecting quality of life and mental health. If measures such as pain medication, rest or physical therapy do not help, surgical repair may be required.

Painful VCFFs are typically repaired through a minimally invasive procedure using a rigid bone cement — polymethylmethacrylate (PMMA), which is injected into the fractured vertebral body to stabilize it. This procedure has an 80%–90% success rate in reducing pain and restoring function. However, PMMA is non-resorbable and is a permanent implant, which may complicate any future surgeries. In addition, PMMA generates significant heat when setting/curing, which may damage adjacent bone. Once set, the implant material is six to 10 times stiffer than natural bone. The stiffness mismatch between bone and PMMA can affect the biomechanics of adjacent vertebrae, which may be why 18% of patients treated with PMMA experience new VCFFs in adjacent vertebrae within one year of surgery.

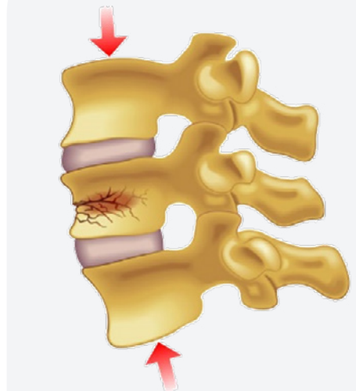


Fig. 1 Vertebral compression fragility fracture (VCFF)

The AGN1 Local Osteo-Enhancement Procedure (LOEP) SV Kit (AGN1, AgNovos Bioscience) is being investigated as an alternative approach to repairing VCFFs. The AGN1 LOEP SV Kit is intended for fixation of pathological fractures of the vertebral body. It uses a different implant material—AGN1, a proprietary biocompatible mix of calcium sulfate/phosphate. After the AGN1 implant material is injected, it hardens in situ to augment the fractured vertebral body, without generating heat. Over time, the AGN1 implant material is resorbed and replaced with new bone. Preclinical studies demonstrated that the AGN1 material provides a similar improvement in strength to PMMA.

Dr. Michael Musacchio

We are conducting a study (Endeavor Health project number EH21-293), led by Dr. Michael Musacchio, to compare the LOEP procedure with the standard PMMA approach. We are evaluating pain reduction and improvement in function, as well as adverse events, device failures, or the need for additional surgery in patients in each treatment group. In the LOEP group, implant resorption and bone formation are also assessed radiographically.

Patients can be included in the study if they are at least 50 years old and meet the following inclusion criteria:

- One or two acute or persistent VCFFs (T1–L5, inclusively) due to diagnosed or presumed osteoporosis (may have asymptomatic, healed VCFFs at any non-target vertebral level)
- VCFF-related pain for up to six months
- No relief from conservative medical therapy (e.g., bed rest, analgesics, physical therapy)
- An Oswestry Disability Index (ODI) score of ≥ 30% at baseline
- Able to provide written informed consent; willing and able to participate in all study procedures

For more information on the study, please call: (847) 570-4224

Research Summaries

MIGRAINE

Clinical & genetic differences may influence response to anti-CGRP migraine medications

Migraine is a common condition, affecting 14%–15% of people worldwide, that can cause significant disability.

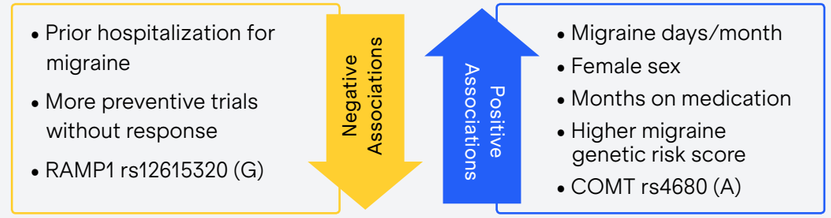
Migraine can be managed by taking medications to stop an attack once it starts (abortives) and/or taking medicines continuously to prevent or reduce the number and severity of migraines (preventives). A molecule called calcitonin gene-related peptide (CGRP), which is produced in the brain and acts to dilate blood vessels and regulate blood flow, is released during migraine attacks. Newer monoclonal antibody–based drugs (Emgality, Ajovy, Aimovig and Vyepti) have been developed to block CGRP activity. In many people, these medications work well to prevent migraines with few side effects; however, in approximately one-third of patients, these drugs do not work.

To understand how clinical and genetic factors may affect patients' response to anti-CGRP medications, we looked at 1,077 patients at Endeavor Health who were diagnosed with migraine and prescribed an anti-CGRP drug. We found that all patients who responded to these medications experienced substantial benefits. The number of migraines per month decreased — especially in patients with higher

initial migraine frequency and in women — and migraine frequency continued to decrease over time. However, in patients who had been hospitalized for migraine or who had not responded to other preventive medications, these medicines were less effective. Looking at genetic differences between patients who did or did not respond, we found that anti-CGRP drugs were more likely to be effective in people with a higher genetic risk for migraine. We also identified variants in two genes — RAMP1 and COMT — that may influence a patient's response. Identifying differences between people who do or do not respond may enable selective prescription of anti-CGRP drugs to patients who are more likely to benefit. This information may also inform development of new medications that are effective in the patients who do not respond to these drugs.

Clinical and genetic factors influence patient response to CGRP-based preventives

Clinical and genetic factors associated with response (blue arrow) or non-response (yellow arrow) to anti-CGRP medications



"Characteristics associated with response to subcutaneously administered anti-CGRP monoclonal antibody medications in a real-world community cohort of persons living with migraine: A retrospective clinical and genetic study." *Headache* 2024 Jan; 64(1): 68-92; Epub 2023, Dec. 10. ©2023, The Authors. doi: 10.1111/head.14655

MIGRAINE

Migraine genetic risk does not strongly affect migraine symptoms or outcomes

Migraine has highly variable characteristics and symptoms, and genetic studies have implicated several underlying pathways. However, the influence of genetic risk on disease symptoms or treatment response is not fully understood.

In this retrospective study, we examined the relationships between a migraine polygenic risk score (PRS) and migraine characteristics in a real-world, treated patient cohort of 1,653 migraine cases with European ancestry at baseline and, in 777 cases, at a one-year follow-up. Participants were recruited as part of The DodoNA Project: DNA Predictions to Improve Neurological Health. Patients were deeply phenotyped by neurologists during extensive interviews using structured clinical documentation tools embedded in the electronic health record to document ~200 discrete data elements that included assessments of migraine-related disability, characteristics, symptoms and changes at follow-up.

We found that a higher genetic risk for migraine correlated with two common migraine symptoms: photophobia (light sensitivity) and stabbing pain. Weaker associations were found between genetic risk and phonophobia (sensitivity to sound), nausea, vomiting and unilateral (one-sided) headache. Genetic risk was not associated with any other migraine symptoms, such as severity, frequency, duration, response to medication or changes at follow-up. This study suggests that in treated patients, non-genetic factors such as lifestyle or environment influence migraine symptoms and disease course more strongly than genetic risk and that genetic susceptibility to migraine does not strongly determine disease course.

Summary of PRS associations identified from covariate-adjusted regression models, using baseline and first annual follow-up data.

Red diamonds mark the PRS estimate for β or odds ratio; blue lines show 95% confidence intervals.

Significant associations ($p < 0.05$) are indicated in bold. An asterisk (*) indicates that the variable retained significance at Q = 0.05.

Key:

MIDAS = Migraine Disability Assessment Test

MSQ = Migraine-Specific Quality of Life Questionnaire

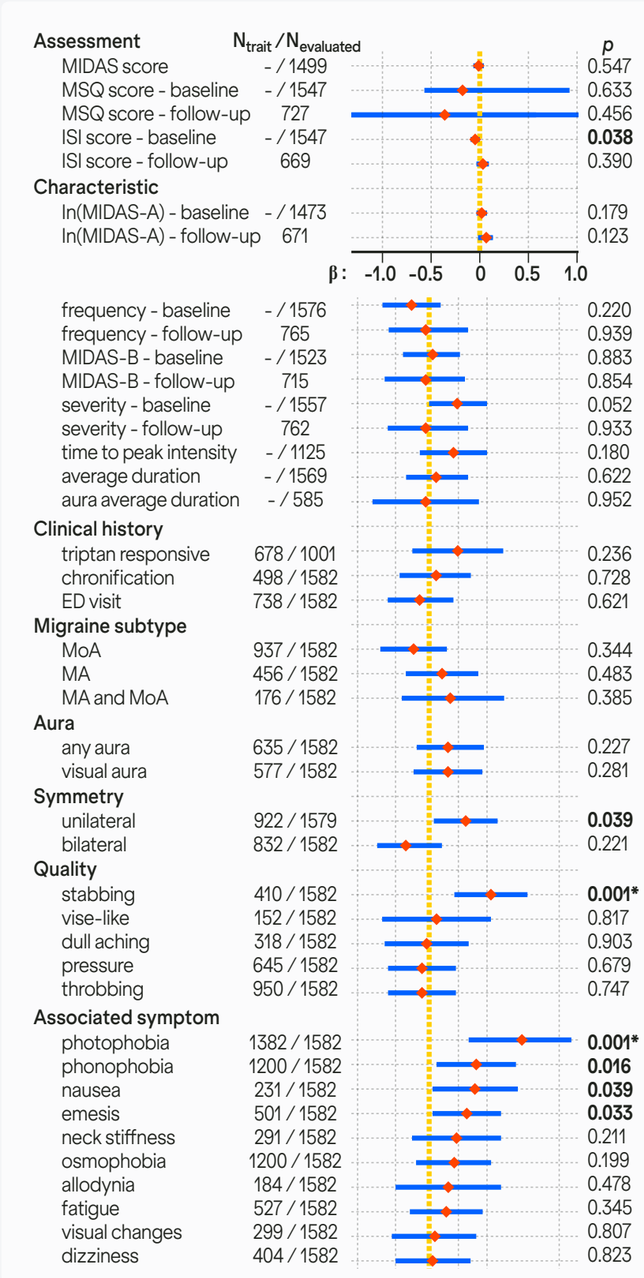
ISI = Insomnia Severity Index

ED = emergency department

MoA = migraine without aura

MA = migraine with aura

MA and MoA = migraine with and without aura



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MIGRAINE

Genetic factors affect age at migraine onset but not risk of chronification

Migraine is a common neurological condition that typically follows an episodic course but can become chronic (i.e., > 15 headache days per month for more than three months) in some people.

Genomic studies have demonstrated that migraine risk is associated with multiple genes involved in diverse functions. We used a composite polygeneic risk score (PRS) to examine how migraine genetic risk is associated with the age at onset of migraine disease and likelihood of chronification. Patients with or without migraine were recruited from two real-world cohorts — The DodoNA Project: DNA Predictions to Improve Neurological Health (DodoNA) and the Genomic Health Initiative (GHI). The DodoNA cohort comprised 1,653 treated migraine cases and 3,460 controls. DodoNA migraine participants were diagnosed using *International Classification of Headache Disorders*, 3rd Edition criteria and were deeply phenotyped by neurologists using a structured data-collection tool in the electronic health record (EHR); control participants had no ICD codes for migraine or any migraine diagnosis. The GHI cohort comprised 2,443 cases and 8,576 controls. GHI migraine cases had ICD codes for migraine, whereas controls did not.

In both cohorts, migraine cases had higher PRS (indicating a higher genetic risk for migraine) than controls. Within cases, a higher PRS was associated with earlier onset of migraine symptoms in men and women in both cohorts. However, genetic risk was not associated with risk of chronification or earlier chronification in any group. These results suggest that genetic risk scores capture susceptibility to migraine, but that other lifestyle or environmental factors affect disease course.

Patients were grouped by PRS-score tertiles (i.e., lowest, middle and highest thirds). In both the DodoNA (A) and the GHI (B) cohorts, a higher PRS (tertiles 2 or 3) was associated with earlier onset of migraine than scores in tertile 1 in females. ***p < 0.001, *p < 0.05, ns = not significant

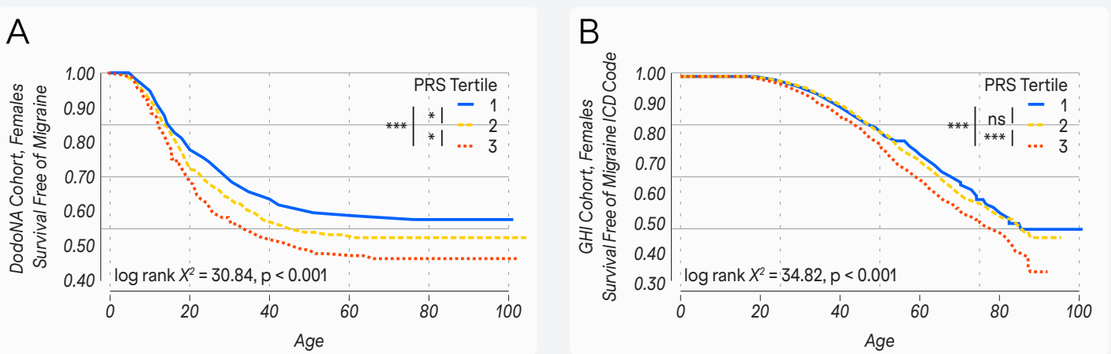


Figure reproduced from "An integrative migraine polygenic risk score is associated with age at onset but not chronification." *J Clin Med.* 2024 Oct 29;13(21):6483. Special Issue: Exploring Recent Advancements in Migraine Treatment: Insights From Clinical Neurology doi: 10.3390/jcm13216483

ALZHEIMER'S DISEASE

Blood lipids affect risk of Alzheimer's disease & mild cognitive impairment

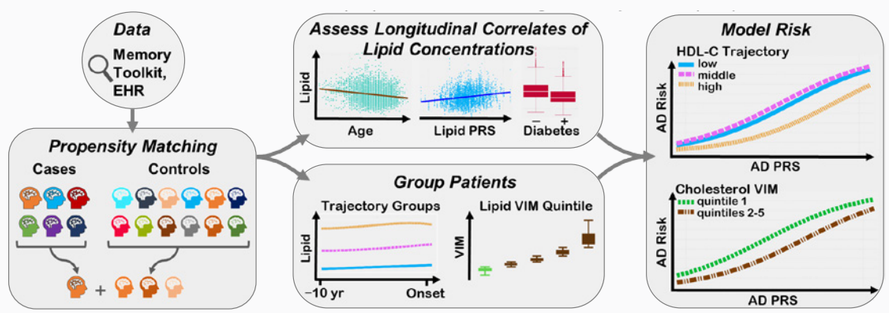
Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder, affecting almost 58 million people globally, including an estimated 6 million in the United States.

Mild cognitive impairment (MCI) typically precedes the onset of dementia but does not always progress to AD. Genetic and biological evidence suggest a central role for lipid dysregulation in AD and other neurodegenerative conditions. In this study, we evaluated whether levels of routinely measured blood lipids (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], non-HDL cholesterol [non-HDL-C], and triglycerides [TG]) or variability in levels of those lipids over the decade prior to symptom onset could help predict risk of AD or MCI. We compared cohorts of patients with and without AD or MCI; those with MCI had been diagnosed for at least five years without progression to AD. Controls were propensity-matched to cases at age of first cognitive symptom by age group, sex, body mass index (BMI), use of cholesterol-lowering medications, race, number of APOE-ε2/ε4 alleles, and patient-reported years of education.

Participants were grouped based on (i) longitudinal lipid-level trajectories and (ii) variability independent of the mean (VIM) for each lipid, over the preceding decade. We then developed models to evaluate the contributions of trajectories and VIM for each lipid type relative to APOE genotype, polygenic risk scores (PRSs) for AD and lipid levels, use of lipid-lowering medications, and comorbidities to AD or MCI risk.

In these models, consistently lower levels of HDL-C (i.e., lowest HDL-C level trajectory) and the lowest VIM quintile of variation (i.e., lowest amount of variability) of non-HDL-C were associated with higher MCI risk. The lowest HDL-C trajectory and the lowest VIM quintile for total cholesterol were associated with higher AD risk. Including lipid trajectory and VIM quintile groups improved the predictive performance of risk models independent of APOE genotype or genetic risk scores for AD or lipid levels. These results provide important real-world perspectives on how longitudinal levels and variation in blood lipid concentrations prior to symptom onset contribute to risk of cognitive decline.

Inclusion of Blood-Lipid Level Trajectories and Variability Improves Risk Models for Alzheimer's Disease (AD) and Stable Mild Cognitive Impairment (MCI)



Models indicated that longitudinal levels of HDL-C and VIM quintile of TC influence risk of AD.

Figure reproduced from "Lipid trajectories improve risk models for Alzheimer's disease and mild cognitive impairment." *J Lipid Res.* 2024 Nov 23:100714. Epub ahead of print. ©2024 The Authors. doi: 10.1016/j.jlr.2024.100714

CARDIAC AUTONOMIC NEUROPATHY

Identifying mortality risk factors in patients with cardiac autonomic neuropathy

Cardiac autonomic neuropathy is caused by damage to autonomic nerves controlling the cardiovascular system and occurs most commonly as a complication of diabetes.

Diagnosis of cardiac autonomic neuropathy (CAN) is based on clinical symptoms and the use of noninvasive autonomic reflex tests that establish the extent and severity of involvement. CAN is associated with cardiovascular disease, chronic kidney disease and increased risk of death; however, there are currently no guidelines to reduce morbidity or mortality due to CAN. The clinical, genetic and co-morbidity factors associated with CAN progression may also be indicators of increased risk of death. We examined whether genetic variants, clinical symptoms and results from autonomic testing at the time of diagnosis were associated with increased mortality.

We reviewed the electronic health record of 124 patients with advanced CAN, 25 of whom had died Group A), and collected data on clinical evaluations, autonomic testing and genetic testing. In a subset of 91 patients, 18 of whom had died (Group B), we collected data using a polyneuropathy toolkit that evaluated neuropathy symptoms as well as depression and sleep. In a second subset of 67 patients, 15 of whom had died (Group C), we examined genetic-risk variants for idiopathic or autonomic neuropathy. In each group, we examined differences between survivors and non-survivors and identified mortality risk factors.

Similar results were seen in each group, suggesting that the subgroups were representative of the entire cohort. A longer duration of diabetes, older age at diagnosis, a lower body mass index (BMI), having had a stroke, cardiac disease, and abnormal sweating (sudomotor) function were associated with an increased risk of death. In Group C, a risk genotype for idiopathic neuropathy, rs147738081-CT, was more often present in non-survivors.

Identifying factors associated with an increased risk of mortality may inform diagnostic testing and prognosis, and improve survival in patients with CAN.

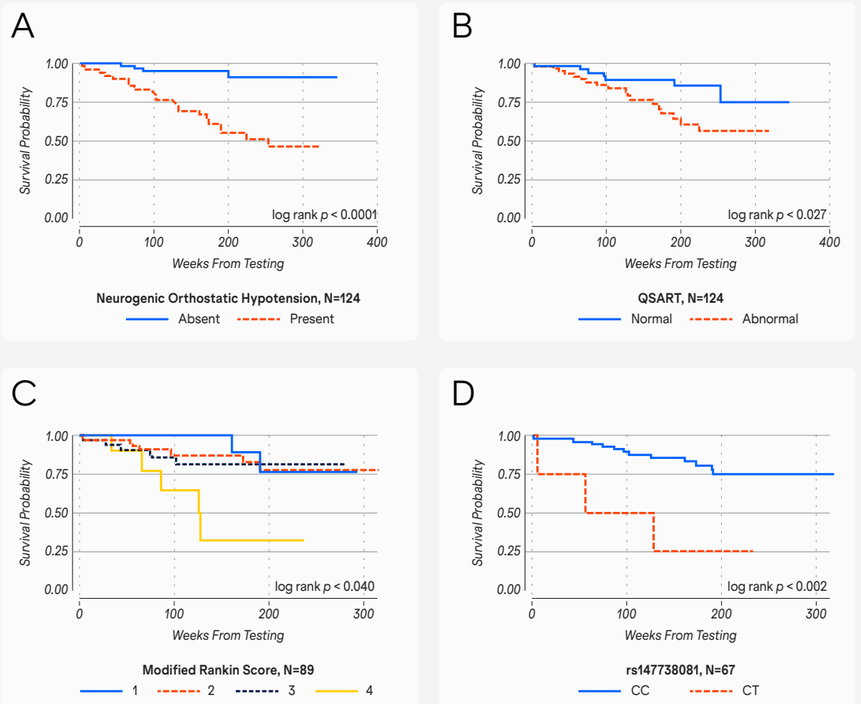
Differences in disease characteristics between surviving and non-surviving CAN patients over the weeks from testing to censure or death:

A — neurogenic orthostatic hypotension

B — abnormalities during a quantitative sudomotor axon reflex test (QSART)

C — Modified Rankin Scale for neurologic disability

D — genotypes at rs147738081



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PARKINSON'S DISEASE

Predicting course, progression & outcomes in Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disease with an insidious onset, a long prodromal phase, and a symptomatic course that includes both motor and non-motor symptoms with variable severity, progression and outcomes.

The goal of this study was to identify predictors of disease course and outcomes by following a cohort of Parkinson's disease (PD) patients over time. Patients were enrolled within five years of initial motor symptom onset across five institutions participating in the Genetic Epidemiology of Parkinson's Disease (GEoPD) consortium. (Patients at Endeavor Health were enrolled as part of The DodoNA Project: DNA Predictions to Improve Neurological Health.) Disease course and progression were then evaluated annually for two to 10 years, and group-based trajectory models were used to identify groups of patients who exhibited similar disease progression. Models were developed for Unified Parkinson's Disease Rating Scale (UPDRS)-III scores, UPDRS-III tremor and bradykinesia-rigidity subscores, Hoehn and Yahr (H&Y) stage, Mini-Mental Status Exam (MMSE) scores, and combined UPDRS-III, H&Y and MMSE scores.

The best-fitting models identified three groups: a relatively benign, slowly progressing course (Group 1); a moderate, intermediately progressing course (Group 2); and a more severe, rapidly progressing course (Group 3). Group allocation remained stable five years after the initial assignment.

Using the combined score (UPDRS-III, H&Y and MMSE scores) model, people in Group 2 were more likely to be male and to have a younger onset age, fewer education years, less pesticide exposure, no reported head injury, and to present initially with an akinetic/rigid subtype than those in Group 1. People in Group 3 were likely to be older at onset, with fewer years or education, less pesticide exposure, and to present with a tremor-predominant subtype than those in Group 1. Persistent freezing, persistent falls and cognitive impairment occurred earlier and more frequently in Group 3, later and less frequently in Group 2, and latest and least frequently in Group 1. Autonomic complications, dysphagia and psychosis occurred more frequently in Groups 2 and 3 than in Group 1.

Modeling disease course using multiple, objective assessments over an extended duration after initial diagnosis identified different courses of PD progression, prognosis and outcomes, which may inform clinical treatment.

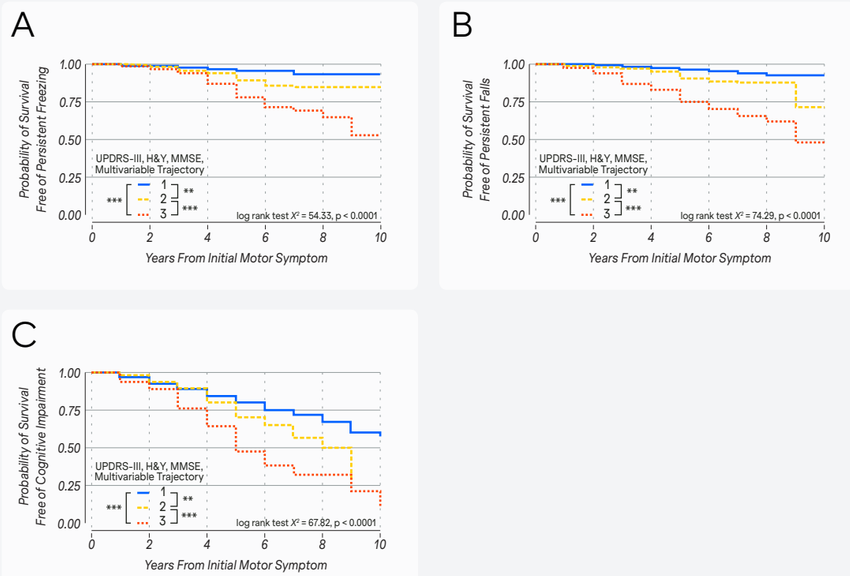
Kaplan-Meier analyses for survival free of clinically significant milestones in Groups 1–3 when three assessments were modeled jointly:

A — persistent freezing

B — persistent falls

C — cognitive impairment

***p < 0.001, **p < 0.01



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