NYU Langone Health

OUR COVID-19 EFFORTS

Read about NYU Langone Health's response to the challenges of the COVID-19 pandemic.
See insert.

Neurology

2020 HIGHLIGHTS

Real-Time Innovation Sustains Quality Care in Neurology Through COVID-19 Response

Realigned Patient Management Enables Safe, Effective Care as New Insights Link Neurological Symptoms to Virus Outcomes

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Pediatric Patient with Puzzling Symptoms Leads Neurologists Toward Translational Discovery

Experts in the Dysautonomia Center Uncover a Rare Disease with Wide-Spanning Clinical Implications

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Cover image: Wireframe polygonal human brain 3D.
RENDERING: GETTY IMAGES

STEVEN L. GALETTA, MD

Philip K. Moskowitz, MD
Professor and Chair of Neurology
Professor of Neurology and Ophthalmology

MESSAGE FROM THE CHAIR

The unexpected arrival of COVID-19 in early 2020 challenged us to make changes in how we approached patient care, but it did not diminish the Department of Neurology's ongoing pursuit of excellence in neurological outcomes for our patients. In fact, it strengthened it.

As the virus proliferated in our region, our team's agility enabled real-time innovation, while new insights uncovered direct neurological impacts of the disease that demanded changes in care and new methods of information sharing. At the same time, we redoubled our emphasis on finding novel treatments for neurological disorders with solutions for complex conditions that eluded prior diagnosis before experts in our centers decoded them.

Across research and clinical care, from diagnosis to treatment, we will continue our push toward new frontiers in neurology, reimagining quality outcomes for the sake of our patients.

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL NEUROLOGY & NEUROSURGERY 2020-21

#6

IN *U.S. NEWS & WORLD REPORT*

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248

NEUROLOGY FACULTY

92K+

OUTPATIENT VISITS IN 2020

During the height of the first wave of the COVID-19 pandemic, multidisciplinary care teams sought therapeutic protocols to treat and prevent complications arising from the disease.
PHOTO: JONATHAN KOZOWYK

Novel Research Sheds Light on COVID-19–Associated Stroke Risk

The COVID-19 pandemic has elicited a global scientific effort to understand the novel disease's transmission, symptom onset, and treatment protocols. Among its associated morbidities is the notable onset of thromboembolic complications, including ischemic stroke, among affected patients. To add to growing anecdotal evidence of ischemic stroke as a complication among COVID-19 cases, NYU Langone Health launched a first-of-its-kind study to examine the association—and uncover potential preventive strategies.

SYMPTOMS INDICATE A DANGEROUS ASSOCIATION

With more than 300,000 confirmed cases of COVID-19 by April 2020, New York State had quickly become a hot spot for the illness. With the novel virus came wide-ranging symptoms, with mounting evidence of affected patients having clinically significant coagulopathy with thromboembolic complications, including ischemic stroke. Moreover, autopsies performed at NYU Langone indicated the presence of clots throughout organ systems, including kidneys, lungs, and the heart.

Acute phase reactants—inflammation markers that increase in the context of infection or injury—have been documented in the setting of other respiratory infections, typically returning to normal range once the illness resolves and the patient recovers. Though it is suspected that such infections accelerate clotting factors through inflammation and direct action on small arteries, there are limited data on the clinical characteristics of thrombotic complications in the context of COVID-19.

With early reports indicating an association between COVID-19 and cerebrovascular disease, a team led by Shadi Yaghi, MD, associate professor in the Department of Neurology and research director of the Center for Stroke and Neurovascular Diseases, identified the critical, unmet need to document the mechanisms and outcomes of patients who have both a stroke and COVID-19.

STRATIFYING STROKE TO COMPARE CAUSE

Dr. Yaghi and team designed a retrospective, observational study examining ischemic stroke in patients with COVID-19 in order to elucidate the characteristics and causes of stroke with this specific etiology. "We set out to answer whether the strokes we are seeing in patients with confirmed cases of COVID-19 are qualitatively different—in cause and course—from pre–COVID-19 cases we saw at the same time last year," notes Dr. Yaghi.

The study, published in May 2020 in *Stroke*, examined all patients admitted for stroke across NYU Langone hospital locations in Manhattan, Brooklyn, and Long Island between March 15, 2020, and April 19, 2020. The primary inclusion criterion was hospital admission for stroke, confirmed by brain imaging. Patients were subsequently divided into three distinct groups: those with ischemic stroke and a confirmed COVID-19 diagnosis, contemporary control patients with stroke but without COVID-19, and patients with ischemic stroke and without COVID-19 from the identical time period in 2019.

Imaging and laboratory variables were evaluated to compare characteristics and subtypes of the stroke cases. These variables included cardiac troponin level (upon admission), C-reactive protein (closest to the time of the stroke), erythrocyte sedimentation rate (closest to the time of the stroke), and D-dimer level (highest level and closest to the time of the stroke).

Among the initial findings was a lower overall number of admissions for stroke during the 2020 COVID-19 pandemic trial period than during the corresponding period of 2019. "This finding aligns with anecdotal reports of patients avoiding hospitals, in spite of stroke symptoms, for fear of contracting COVID-19," says study co-author Jennifer A. Frontera, MD, professor in the Department of Neurology.

The actual number of imaging-confirmed ischemic strokes among patients with confirmed COVID-19 was also low: 32 of 3,556 patients studied, or 0.9 percent—though the researchers acknowledge that the number could under-represent actual patients, since some may have been physically unfit to receive the confirming brain scan.

> *Patients and healthcare workers alike should be aware of the threat of stroke with COVID-19 infection and respond quickly to symptoms of stroke, even in young patients who are not normally at risk."*
>
> **—Jennifer A. Frontera, MD**

PHOTO: JOHN ABBOTT

LOWER CONVENTIONAL RISK, HIGHER COAGULABILITY

Notably, in patients with COVID-19 and ischemic stroke, a majority of strokes were classified as cryptogenic—possibly related to an acquired hypercoagulability—and were associated with increased mortality. These patients were found to have elevated clotting factors, suggesting that one of the causes or triggers of their stroke was related to increased clotting in the setting of COVID-19.

Among those 32 patients with both confirmed stroke and positive COVID-19 status, stroke was the reason for admission in 43.8 percent, and COVID-19 symptoms were the reason for admission in 56.2 percent, with index stroke occurring during the hospital stay. The majority of these strokes—65 percent—were found to be of unknown cause. The patients tended to be younger, with a median age of 63, and were notably less likely to have conventional risk factors, such as hypertension or prior stroke.

"The younger median age could simply reflect that older populations are more susceptible to the competing deleterious effects of COVID-19 and become gravely ill or die from a separate factor before the onset of a stroke," says Dr. Yaghi.

AMONG THE 32 PATIENTS WITH BOTH CONFIRMED STROKE AND POSITIVE COVID-19 STATUS:

REASON FOR ADMISSION:

43.8%
STROKE

56.2%
COVID-19

MEDIAN AGE:

63

65%
OF STROKES
HAD AN UNKNOWN CAUSE

A PATHWAY FOR STROKE PREVENTION

As care teams urgently seek therapeutic protocols to treat and prevent complications arising from COVID-19, Dr. Yaghi and colleagues note that the identification of higher laboratory hyper-coagulability factors, including elevated D-dimer levels, suggests the use of therapeutic anticoagulation could be beneficial in preventing stroke in these patients.

"Our study appears to confirm that this patient population experiences higher rates of thrombotic complications such as ischemic stroke, heart attack, and blood clots," notes Dr. Frontera. "Since these patients also have a significantly higher rate of mortality than the historical and contemporary controls, more research is needed to test the use of anticoagulant protocols to prevent clotting and improve outcomes."

With a therapeutic anticoagulation protocol initiated across NYU Langone in early April 2020, more research is underway to test the safety and efficacy of therapeutic versus prophylactic anti-coagulation in patients with COVID-19 infection and mild to moderate elevation in D-dimer levels. As additional data inform our understanding of the role of anticlotting medications in COVID-19 care protocols, the new research has immediate implications for the evaluation and care of these patients. "Patients and healthcare workers alike should be aware of the threat of stroke with COVID-19 infection and respond quickly to symptoms of stroke, even in young patients who are not normally at risk," adds Dr. Frontera.

Clinicians in the Department of Neurology joined the multi-disciplinary COVID-19 care teams comprising physicians and staff, including Diana Gorga, RN, across NYU Langone Health. They worked tirelessly to manage the influx of patients with COVID-19, as neurologists simultaneously uncovered evidence of COVID-19–related neurological complications that informed tailored approaches to patient management.

PHOTO: JONATHAN KOZOWYK

Real-Time Innovation Sustains Quality Care in Neurology Through COVID-19 Response

Realigned Patient Management Enables Safe, Effective Care as New Insights Link Neurological Symptoms to Virus Outcomes

As the City of New York quickly became one of the country's first COVID-19 epicenters, the continued delivery of quality healthcare depended on a rapid realignment of resources across NYU Langone. In neurology, we shifted to treating the sickest patients diagnosed with COVID-19, while inpatient and outpatient neurological care quickly pivoted to a telemedicine-based model. At the same time, pushing toward innovation, the team uncovered evidence pointing to neurological complications of COVID-19 and the critical role neurologists would play in effectively managing and treating patients with the virus.

With focused and flexible leadership, effective communication, and system-wide collaboration, the Department of Neurology contributed to positive outcomes for patients with COVID-19 while simultaneously maintaining continued quality in neurological care, research, and education.

FIGHTING A NOVEL VIRUS WITH UNPRECEDENTED INNOVATION

As patient units became overtaxed by patients diagnosed with the novel and unpredictable virus, the moment demanded an expeditious shift in our approach to the safe delivery of care, putting our flexibility and ingenuity to the test. "We experienced a complete transformation of our normal course of operations in a single week—it was a period of necessary adaptability and innovation at every level: clinical care, education, and research," says Steven L. Galetta, MD, the Philip K. Moskowitz, MD, Professor and Chair of Neurology and professor of ophthalmology. "It quickly became clear that the battle would be won through innovation, and our team responded with inspiring resilience and compassion."

Such innovation began with necessary shifts in patient management, with a significant number of department faculty and staff redeployed to inpatient units dedicated to the care of patients with COVID-19. "We organized ourselves as a team of individuals contributing to a larger mission," notes Dr. Galetta. Small teams were created to treat patients with COVID-19 in rotating shifts. Staff were assigned specific focus areas to problem-solve the work–life challenges of such extraordinary shifts—wellness, transportation, and child care challenges among them—creating a division of labor and enabling streamlined department-wide communication.

As inpatient care centered on patients with COVID-19, outpatient neurological care shifted to telemedicine, with a rapid acceleration to complete more than 10,000 video visits over the course of 10 weeks. Studies published in June 2020 in *Neurology* and in September 2020 in the *Journal of Neuro-Ophthalmology* combine insights accumulated by the department to document best practices in the use of telemedicine for safe and effective delivery of remote neurological care. The studies note that a robust technology infrastructure and streamlined, sharable documentation and coding are key to performing virtual neurological

examinations that are clinically meaningful. "Beyond the obvious safety benefits of video visits for patients in the context of COVID-19, for some patients with cognitive and movement disorders—for whom transportation and mobility are common challenges—this option has enabled them to be seen more easily for follow-up care," says Dr. Galetta. "As a result, a hybrid of in-person and video visits is likely to become the standard for managing our patients over the long term."

EMERGING EVIDENCE UNCOVERS NEUROLOGICAL LINKS IN SEVERE COVID-19

The neurology team's rapid redeployment to COVID-19 units was critical as the pandemic took hold. When patients with severe disease increasingly exhibited neurological complications, the deep insights of neurologists proved instrumental in discerning symptom patterns and adjusting care plans accordingly. In an analysis of nearly 4,500 admitted patients, neurological complications were seen in more than 800, with the most common abnormality being encephalopathy caused by metabolic disturbances. Stroke was observed in approximately 2 percent of hospitalized patients, likely due to the virus attacking the endothelial cells.

The team has documented some of its findings of neurological involvement in COVID-19 through published research. In a retrospective chart review published in August 2020 in *Stroke*, Dr. Galetta and colleagues reviewed brain MRIs in adult patients admitted to NYU Langone hospitals between March 1, 2020, and May 10, 2020. They compared clinical, laboratory, and functional outcomes of patients with findings of leuko-encephalopathy, cerebral microbleeds, or both—thought to represent various combinations of arterial and venous occlusions coupled with hypoxia—versus patients without these findings. Of the patients who had a brain MRI, 30 percent were found to have leukoencephalopathy, cerebral microbleeds, or both, and the presence of these findings was associated with longer hospitalizations, increased mortality, and poorer functional outcomes at discharge.

A randomized clinical trial is underway at NYU Langone to formally study the effects of anticoagulation in patients critically ill with COVID-19, and the team now has more than 20 active research studies and published reports regarding the neurological effects of COVID-19—with several study grants already funded.

"All told, our findings point to an association between neurological complications of COVID-19 and severe illness," notes Dr. Galetta. "They could provide insight into the pathophysiology of brain damage and encephalopathy observed in this disease as we continue to understand the role of anticoagulation, steroids, and other drugs that can improve treatment and neurological outcomes for COVID-19 patients."

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>
> **—Steven L. Galetta, MD**

PROBING A PANDEMIC'S IMPACT ON PSYCHOSOCIAL WELLNESS

Another body of research has elucidated an area of shared concern for the department since the start of the pandemic: psychosocial wellness. In early May 2020, Dr. Galetta and colleagues administered an anonymous electronic survey to all neurology faculty and staff to assess their psychosocial concerns and the effectiveness of department initiatives to mitigate the impact of the pandemic on psychosocial wellness. Among 130 survey respondents, substantial proportions of both faculty and staff self-reported having increased fear (79 percent), anxiety (83 percent), and depression (38 percent) during the COVID-19 pandemic. The research, published in July 2020 in the *Journal of the Neurological Sciences*, captures the emotional wellness impacts of a provider community at an historic crisis point, underscoring the importance of practitioner wellness both during and beyond the pandemic. The respondents also reported that NYU Langone had provided adequate emotional support and counseling.

Within the Department of Neurology, a range of initiatives focused on employee wellness were recommended and adopted, from virtual social gatherings to conference rooms converted to spaces for therapy sessions. "The pandemic has impacted the lives and minds of our providers," notes Dr. Galetta. "Efforts to support our providers through the evolving crisis have been imperative to promote the resilience we need to care for our patients."

CREATED THROUGH CRISIS, INNOVATIONS WORTH SUSTAINING

Many of the practices initiated throughout the department as the virus first took hold may have a permanent place in specialty best practices moving forward, well beyond another wave of infection. In addition to the benefits of telemedicine for neurologically complex patients, other COVID-19 innovations—such as virtual education events that enabled Department of Neurology faculty to meet conference commitments throughout the pandemic—could be adopted for greater efficiency and enhanced information sharing within the specialty.

"I think what we've done will become an integral component of our ability to communicate," notes Dr. Galetta. "You don't need to travel to be connected to an educational experience you might have missed because you couldn't get to a certain city or medical center." Such a shift could lessen the regionalization of medical education, both internally and externally, Dr. Galetta adds.

"Suddenly internally, everyone can come to grand rounds, and externally you can transmit your educational experience nationwide," he says. "These were necessary innovations that ultimately can contribute to our larger mission: enhancing quality care for the sake of our patients."

10,000+

NEUROLOGICAL VIDEO VISITS COMPLETED IN A SPAN OF 10 WEEKS

New Study Elucidates Mechanisms of COVID-19 Neurological Impact

By the time COVID-19 reached New York City in early 2020, preliminary reports from Asia and Europe had put specialists at NYU Langone on heightened alert for neurological dysfunction among patients with the virus. Subsequent data collected over time have informed a new study showing that one in seven individuals infected with COVID-19 experiences potentially damaging neurological injuries, informing ever-evolving treatment protocols for the virus.

The National Institutes of Health (NIH)–funded study, led by researchers at NYU Grossman School of Medicine, closely followed 606 adult patients diagnosed with COVID-19 who experienced brain complications or other nerve-related medical conditions across NYU Langone between March 10 and May 20, 2020. While no direct invasion or inflammation of the brain or nerves was found, the neurological injuries observed in these patients—from temporary confusion to stroke and seizures—were associated with prolonged low body oxygen levels, electrolyte imbalances, and severe infection or kidney failure. Further, patients with neurological complications were found to have a 38 percent higher risk of dying in hospital; surviving patients had a 28 percent higher risk of requiring long-term or rehabilitation therapy immediately upon discharge.

"The neurological complications seen in COVID-19 are predominantly the secondary effects of being severely ill and suffering from low oxygen levels in the body for prolonged periods," says study lead investigator Jennifer A. Frontera, MD, professor in the Department of Neurology.

Published in October 2020 in *Neurology*, the study also showed that neurological symptoms usually arose within 48 hours of the onset of COVID-19 symptoms. Half of those neurologically affected were over the age of 71, significantly older than the median age of 63 among the other 3,885 patients treated for COVID-19 across NYU Langone hospitals at the time of the study.

"Our results suggest that physicians need to be more aggressive in stabilizing body oxygen levels in patients with COVID-19 as a potentially key therapy for stopping, preventing, and/or possibly reversing neurological problems," says study senior investigator Steven L. Galetta, MD. Approaches to stave off neurological complications by raising blood oxygen levels, including early intubation or use of heart–lung machines (ECMO), continue to inform the investigation of COVID-19 treatment protocols at NYU Langone.

OUR RESULTS SUGGEST THAT PHYSICIANS NEED TO BE MORE AGGRESSIVE IN STABILIZING BODY OXYGEN LEVELS IN PATIENTS WITH COVID-19 AS A POTENTIALLY KEY THERAPY FOR STOPPING, PREVENTING, AND/OR POSSIBLY REVERSING NEUROLOGICAL PROBLEMS.

Together, Horacio Kaufmann, MD (left) and Jose Alberto Palma Carazo, MD, PhD (right) use clinical expertise and basic science to link disparate symptoms with rare dysautonomic diagnoses, aiming to pave the way for more precise treatment protocols.

Pediatric Patient with Puzzling Symptoms Leads Neurologists Toward Translational Discovery

Experts in the Dysautonomia Center Uncover a Rare Disease with Wide-Spanning Clinical Implications

When answers eluded the doctors of a young patient previously hospitalized for acute but disparate autoimmune symptoms, her family approached experts at NYU Langone's Dysautonomia Center to identify the underlying cause and pursue a diagnosis. Through a deliberate analysis combining clinical expertise and basic science research, center experts diagnosed a rarely reported autonomic disorder—providing certainty for the patient's care and treatment and new clues to expand the understanding of autoimmune-associated dysautonomic symptoms.

TROUBLING SYMPTOMS ELUDE A CLEAR CLINICAL PICTURE

With a series of progressively worsening symptoms, the 10-year-old patient had continued to decline while her clinical picture puzzled physicians at another institution searching for an underlying cause.

Symptom onset had begun as a febrile illness with sore throat, facial erythema, and repeated vomiting, and at that point a mild viral illness was suspected. When vomiting and abdominal pain persisted, accompanied by pancreatitis and bladder retention, the patient was admitted to the intensive care unit (ICU) at the other institution. Over the weeks-long course of her stay, unusual symptoms mounted—bladder and bowel paralysis, pupillary paralysis, anhidrosis, tear deficiency, and dry mouth—and a dysautonomic clinical picture began to take shape. Attempted treatment with prednisolone and intravenous immunoglobulin failed to achieve an adequate symptom response.

With autonomic nervous system involvement suspected, the patient's parents were advised to contact Horacio Kaufmann, MD, the Felicia B. Axelrod Professor of Dysautonomia Research in the Department of Neurology and director of the Dysautonomia Center, for consultation. Though the physician treating the patient at that time suspected autoimmune autonomic ganglionopathy (AAG), the symptom profile did not add up to that condition, according to Dr. Kaufmann and colleague Jose Alberto Palma Carazo, MD, PhD, associate professor in the Department of Neurology and assistant director of the Dysautonomia Research Laboratory.

"Though it's not uncommon to see an autoimmune response like AAG in the setting of a flulike infection, those patients typically have severe problems with blood pressure, orthostatic hypotension, and other issues," notes Dr. Kaufmann. "This patient had a range

of autonomic involvement but none of those particular symptoms, so we recommended a treatment protocol to make her well enough to be discharged from the other hospital and seen in our clinic as soon as possible."

DIAGNOSIS BY EXCLUSION DEMANDS A NOVEL DIAGNOSTIC

To prepare for the patient's visit, Dr. Kaufmann and Dr. Palma examined the case symptom by symptom, ruling out conditions to reach a probable cause: an autoimmune response centered in specific muscarinic receptors in the autonomic ganglia. Such receptors are abundant in the nervous system and critical to transmitting nerve signals to activate systems throughout the body. "The prevailing theory was that this patient's condition was caused by a problem with the nerve itself," says Dr. Kaufmann. "But we felt it was a problem with receptors in target organs, not nerves—the keyhole versus the key itself."

The patient's lack of central nervous system involvement pointed to an antibody binding to M3, one of five muscarinic receptors. "Now that we had a suspected cause—an autoimmune process affecting this M3 receptor—we needed to create experiments that could confirm the presence of antibodies and, in particular, characterize the interaction with the M3 receptor," notes Dr. Palma.

The related research of a longtime colleague led Dr. Palma to extend multidisciplinary collaboration beyond the walls of NYU Langone to partner with Salvador Sierra, MD, PhD, whose external laboratory was leading research focused on M3 receptors. Together, the physicians and researchers created tests to identify an antibody blocking activation of M3, as well as to rule out the other receptors' involvement. With the tests complete, the patient presented for examination and diagnostics.

"Our findings supported our theory: Significantly increased levels of antibody were found to bind to M3," says Dr. Palma. The subsequent diagnosis of postganglionic cholinergic dysautonomia (PCD)—a rare disorder of unknown cause described in approximately 10 people—indicated continued therapy with the oral muscarinic receptor bethanechol. A repeat antibody assay found reduced levels of the antibody in the patient, whose symptoms had eased. "That second finding was consistent with our diagnosis, confirming that these antibodies had a relationship with the symptom severity in this patient," adds Dr. Palma.

RARE DISEASE OFFERS BROAD IMPLICATIONS

The path to diagnosis, published in August 2020 in *Annals of Neurology*, represents a translational medicine achievement with tremendous impact, both for this patient and beyond—and is exemplary of the kind of work enabled in part by 30 years of support from the Familial Dysautonomia Foundation. The patient is now feeling well, with the majority of her symptoms resolved. With her definitive diagnosis—a known antibody blocking a receptor that unequivocally caused her disease—it's possible that her future treatment can be refined. "Most autoimmune problems today are treated the same way, with medications that target the immune system," notes Dr. Kaufmann. "But as we further understand these disorders, we may be able to better target this patient's receptors with a more selective therapeutic."

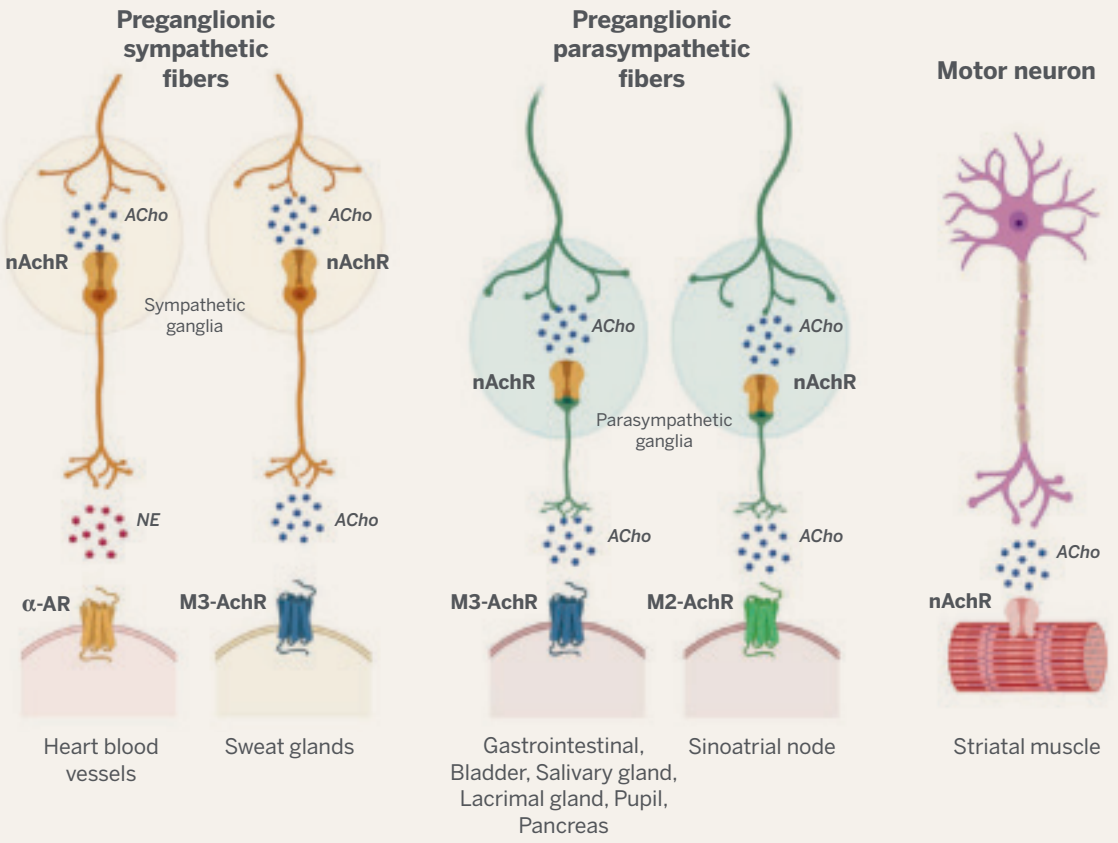
Further, the identification of antibodies as a marker of PCD could be used to rapidly diagnose other patients with the disease—a condition that, with a wide spectrum of clinical presentation, could be underdiagnosed.

"In this case, the translation of medicine happened from the clinic to the lab," concludes Dr. Kaufmann. "When a rare condition like this one comes along, important discovery happens when you can connect a high degree of clinical knowledge to make observations, then bring in the best basic scientists to confirm them." ■

INVESTIGATORS IN THE DYSAUTONOMIA CENTER RECEIVE NEARLY

$3M

IN RESEARCH GRANT FUNDING ANNUALLY



Autonomic and somatic efferent neurons and target organs: Nicotinic acetylcholine receptors (nAchRs) are located in the sympathetic and parasympathetic ganglia and in striatal muscle. Muscarinic acetylcholine (ACho) receptors are located in sweat glands and organs and glands throughout the body (sinoatrial node in the heart, gastrointestinal system, detrusor muscle of the bladder, salivary glands, lacrimal glands, pupillary constrictor muscles, and pancreas). Given the lack of orthostatic hypotension and muscle weakness, the phenotype of postganglionic cholinergic dysautonomia is consistent with selective muscarinic failure, sparing nicotinic acetylcholine and α-adrenergic (α-AR) receptors. NE = norepinephrine.

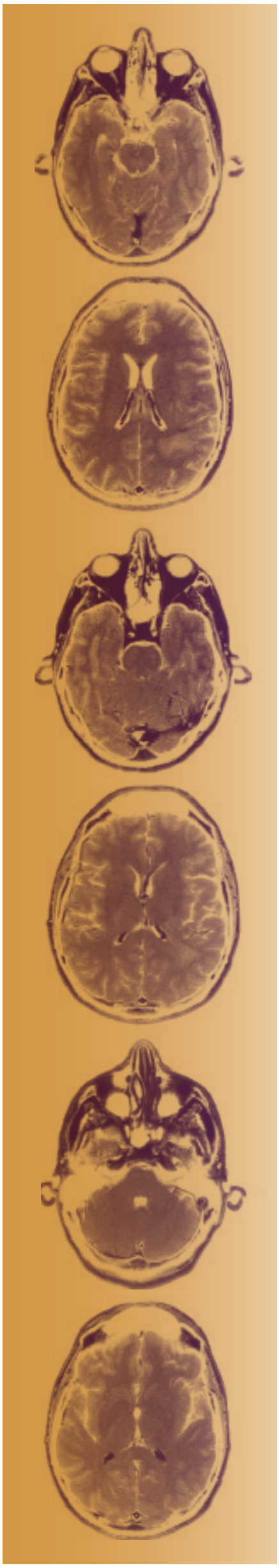


PHOTO: GETTY IMAGES

Before and After Stroke, Insights Reveal Targets for Prevention and Treatment

As experts identify the mechanisms of stroke across different subtypes, NYU Langone researchers continue to seek new insights to enable expanded treatment, as well as more proactive prevention approaches for primary and secondary stroke. With emerging research, advanced imaging, and novel therapies, investigators aim to personalize prevention and treatment by targeting the unique origin and symptoms of stroke in each patient.

IMAGING COULD SHIFT THE CENTER OF ORIGIN IN LACUNAR STROKE

Ad hoc imaging postprocessing, executed by Eytan Raz, MD, PhD, assistant professor in the Department of Radiology, is informing a new understanding of the vascular origins of lacunar strokes—small strokes that occur deep within the brain's structures. Accounting for 15 to 20 percent of ischemic strokes, the subtype has long been thought to originate in thickening of the small arteries of the brain due to untreated hypertension. A two-center study led by Dr. Raz and Shadi Yaghi, MD, associate professor in the Department of Neurology and research director of the Center for Stroke and Neurovascular Diseases, is investigating an alternative theory: that a proportion of these strokes may be related to atherosclerosis that lies within the larger vessel that feeds the smaller perforated vessels.

"The plaque that builds in the brain's large artery is not often associated with narrowing, but in some patients, the plaque can expand and block off these very tiny, hairlike arteries at their origin and cause a stroke," explains Dr. Yaghi. "It's important to identify and treat this plaque to prevent it from blocking more of these small vessels, which may produce more pronounced neurological symptoms."

Lacunar strokes can cause a range of symptoms depending on their involvement of the motor tract and other fibers in the brain, often causing single-sided weakness and significant long-term disability. By visualizing the smaller, more intricate vessels using high-resolution MRI sequences, Dr. Raz and Dr. Yaghi are combining their multidisciplinary expertise to pinpoint the location of lacunar strokes and gain insights that can inform treatment in the acute care setting, focus efforts to prevent a secondary stroke, and—potentially—prevent a primary stroke. This type of crucial stroke research is fostered in part by generous supporters, including Tarsadia Foundation and The Jim and Linda Robinson Foundation.

"When a patient presents with a more profound stroke, we often find imaging evidence of several previously undetected silent strokes, frequently associated with mild cognitive impairment," says Dr. Raz. "Eventually, if we can detect asymptomatic brain artery atherosclerosis at an earlier stage, aggressive intervention might prevent more significant disability down the road."

> *"Eventually, if we can detect asymptomatic brain artery atherosclerosis at an earlier stage, aggressive intervention might prevent more significant disability down the road."*
>
> **—Eytan Raz, MD, PhD**

TREATMENT FOR POST-STROKE FATIGUE COULD ENHANCE FUNCTIONAL OUTCOMES

In patients who experience profound strokes, both ischemic and hemorrhagic, sleepiness is a common and frequent barrier to positive rehabilitative outcomes. Disposition to acute rehabilitation requires patients to participate in a minimum of three hours of rehabilitation activities each day, a threshold reached by only 25.4 percent of patients. Thus, helping more patients—particularly younger patients poised for good outcomes—overcome lethargy and move into acute rehabilitation has become a priority for Jose L. Torres, MD, associate professor in the Department of Neurology. His new research suggests that the novel use of the stimulant drug modafinil can help patients overcome fatigue and reach the endurance benchmark needed to qualify for acute rehabilitation care, which is associated with better functional outcomes and reduced mortality as compared with discharge to other facilities.

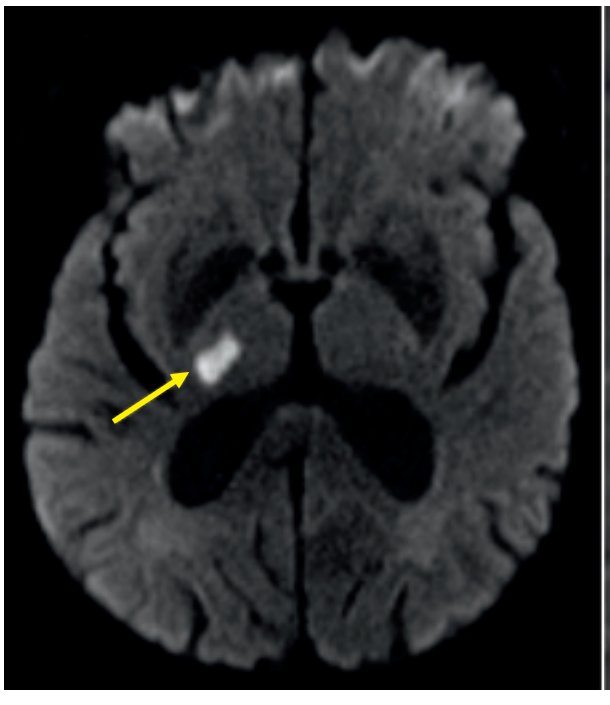
"Lethargy typically improves over time, but this can take several weeks to a month," notes Dr. Torres. "The faster we can get patients to rehab, the better they do. So I searched for an intervention that could help reduce lethargy and fatigue more quickly."

Although amphetamine stimulants have long been tried in these patients, these stimulants are associated with harmful side effects, such as hypertension and seizures. Dr. Torres was encouraged by the documented use of modafinil, a nonamphetamine stimulant that is without side effects in patients with narcolepsy and multiple sclerosis. In a retrospective study of 199 patients, published in 2020 in the *Journal of Stroke and Cerebrovascular Diseases*, he and colleagues found that hospitalized stroke patients who received modafinil were more awake, more equipped to participate in physical and occupational therapy, and twice as likely to be discharged to acute rehabilitation.

Koto Ishida, MD (left), Jose L. Torres, MD (right)

Dr. Torres is working with the National Institutes of Health StrokeNet to develop a randomized, controlled trial with the potential to provide additional evidence of modafinil's efficacy in reducing post-stroke fatigue and lethargy. He is hopeful that modafinil will expand clinicians' available treatment options for patients and enhance the standard of stroke care.

"We've made a lot of progress with acute care interventions for stroke, but we still can't help significant numbers of fatigued patients reach the milestones required for acute rehabilitative care," says Dr. Torres. "I envision modafinil as an add-on therapy that can potentially help these patients overcome their significant lethargy and participate in the rehabilitation activities necessary for them to get better—and ultimately have improved outcomes."



Diffusion-weighted MRI in a patient with an acute stroke shows the infarct in the right thalamus (yellow arrow); and an MRI-based angiography of the brain demonstrates the vessels in the brain, with three-dimensional reconstruction showing the culprit atherosclerotic plaque (red arrows) located in the vicinity of the infarct.

Un Jung Kang, MD

New, Multisystem Insights Reveal Potential Treatment Pathways for Parkinson's Disease

As research elucidates the origins and mechanisms of Parkinson's disease, a multidisciplinary team of NYU Langone researchers is synthesizing those clues in order to diagnose and effectively treat the disease in its earliest stages, before traditional symptoms come to light. With new insights into motor and non-motor symptoms, earlier detection and individualized treatments hold greater promise.

UNCOVERING THE BRAIN CIRCUITRY CHANGES IN PARKINSON'S DISEASE

Two National Institutes of Health (NIH)–funded studies led by Un Jung Kang, MD, the Founders Professor of Neurology, professor in the Department of Neuroscience and Physiology, and director of translational research in the Department of Neurology and Fresco Institute for Parkinson's and Movement Disorders, seek to reveal the dynamic between therapeutic dopamine—the standard of care for patients with the condition—and the brain circuitry behind motor dysfunction.

In the first study, Dr. Kang is mapping cell types in the brain's striatum to investigate how this circuitry influences so-called motor learning, which may underlie the long-duration therapeutic response seen in dopamine-treated patients. "We're discovering that dopamine not only helps patients move better, but also contributes to sustained functional improvement," he says. "We're trying to understand what's behind this gradual buildup of benefit and how long it lasts."

Paradoxically, Dr. Kang and team are also investigating how brain compensation can interfere with dopamine's therapeutic effects. When treatment begins, some patients' brain circuitry, having rewired itself to adapt to dopamine loss, leads to hypersensitive response. "They go from movements that are too slow to uncontrolled movements that interfere with mobility for the opposite reason," notes Dr. Kang. "The rewired brain no longer knows what to do with the dopamine."

> *The idea is that we can eventually test everyone with certain symptoms for this biomarker, treat them early, and suddenly Parkinson's disease is a much more manageable condition."*
>
> **—Un Jung Kang, MD**

By understanding this effect and the cellular-level changes in brain biochemistry, Dr. Kang hopes to fine-tune therapies by combining cell-selective, neuroanatomical, and biochemical approaches to target neurotransmitters beyond dopamine, with greater specificity than surgical therapies such as deep brain stimulation.

NON-MOTOR SYMPTOMS MAY PREDICT DISEASE ONSET

Other research is targeting the effects of Parkinson's disease beyond motor symptoms. Problems with sleep, blood pressure, constipation, and urination have become more prominent in a patient population living longer due to treatment advances. "These symptoms are becoming more troublesome, but we're learning they often begin decades before patients are diagnosed," Dr. Kang says.

One such symptom is rapid eye movement (REM) sleep behavioral disorder (RBD), a condition in which patients' muscle control does not temporarily shut down during REM sleep. Dreams become "enacted," accompanied by activities such as talking or kicking. The disorder itself may not be bothersome unless severe movements injure patients or their bed partners. "However, we're learning that RBD almost always leads to more extensive neurodegeneration, such as Parkinson's disease, Lewy body dementia, or multiple system atrophy," notes Dr. Kang. Similarly, autonomic nervous system abnormalities that manifest as dizziness upon standing, urination problems, or constipation may also foretell Parkinson's disease and related disorders.

The prevalence of gastrointestinal (GI) symptoms in patients with Parkinson's disease, along with recent interest in the initiation of synuclein pathology in the gut and transfer to the brain via the vagus nerve, has prompted Dr. Kang to study detailed GI physiology in patients with Parkinson's disease. He is examining the immunological state and neuro-immune interactions in the gut to understand how immune changes there may contribute to Parkinson's disease, multiple system atrophy, and other disorders. Since the gut microbiome has been shown to differ in patients with Parkinson's disease and other neurological disorders, the team hopes to develop an integrated understanding of how these changes, GI immunity, and GI function collectively contribute to neurodegenerative pathogenesis.

"We're trying to get different disciplines to look at this together to uncover how non-central nervous system–related symptoms might have similar underlying mechanisms to what are traditionally thought to be hallmarks of these neurological disorders," says Dr. Kang.

FINDING A BIOMARKER FOR EARLY DETECTION

A key aim of the research is to pinpoint a biomarker that could correlate with one of these peripheral precursors to Parkinson's disease, enabling earlier diagnosis of the disease. Today, diagnosis is based on clinical presentation and examination—when irreversible disease progression has already occurred. Dr. Kang's research seeks to enable diagnosis decades earlier so therapies can potentially slow the disease before severe symptoms present. One promising biomarker involves an abnormal form of alpha-synuclein, which can accurately identify patients with Parkinson's disease in more than 90 percent of cases and may predict eventual development of neurodegeneration at the prodromal stages.

"The idea is that we can eventually test everyone with certain symptoms for this biomarker, treat them early, and suddenly Parkinson's disease is a much more manageable condition," Dr. Kang observes.

Better understanding of such biomarkers might also help better stratify patients according to their disease pathogenesis, eventually enabling targeting of interventions based on heterogeneous forms of Parkinson's disease. "We may be able to start picking out those patients with higher risk, use a biomarker to narrow them into subtypes, and then intervene before the disease becomes obvious," adds Dr. Kang.

A CLEARER DISEASE PICTURE, DEVELOPED WITH COLLABORATION

Collectively, the research relies on specialists across the clinical spectrum working to understand Parkinson's disease from every angle. Dr. Kang works with NYU Langone sleep specialists, gastroenterologists, dysautonomia specialists, cognitive neurologists, and movement disorder specialists—combining clinical expertise with basic neuroscience, genomics, and immunology. The multisystem approach is linking insights from cutting-edge research into a cohesive blueprint of the root causes and various expressions of Parkinson's disease.

"Today, once patients become 'typical' in presenting with Parkinson's, our options for them are the same," concludes Dr. Kang. "But if we can paint a unique picture of how the disease manifests in each patient, that will unlock new possibilities for future treatment." ■

Disclosure: Dr. Kang is on the scientific advisory board of Amprion, Inc., which is developing the aforementioned biomarker.

NYU Langone Research Seeks to Intervene in Alzheimer's-Associated Brain Changes

New NYU Langone research will investigate the efficacy of promising new therapeutic approaches for Alzheimer's disease and dementia. The projects, funded by the Alzheimer's Association's "Part the Cloud" global research grant program and Microsoft co-founder and philanthropist Bill Gates, targets cellular-level brain changes in an attempt to identify effective interventions.

The first study, led by Dan Iosifescu, MD, associate professor in the Department of Psychiatry, will examine whether "transcranial photobiomodulation" (t-PBM), a noninvasive, light-based brain stimulation technique, can safely and effectively reverse mitochondrial damage seen in the disease. In a phase II clinical trial in 50 individuals with mild cognitive impairment, Dr. Iosifescu will use cognitive tests to study whether the technique improves cognitive function by altering blood flow to the brain. Recent studies suggest cellular mitochondria may undergo early damage in individuals with Alzheimer's disease, and animal models suggest that t-PBM may directly penetrate the brain and stimulate function.

In the second study, Thomas M. Wisniewski, MD, the Gerald J. and Dorothy R. Friedman Professor in the Department of Neurology and director of the Center for Cognitive Neurology, will explore whether CpG oligodeoxynucleotide (ODN)—a chemical compound used in vaccines—can reduce brain changes in mild cognitive impairment and Alzheimer's. Researchers at NYU Langone will test the molecule in Alzheimer's disease for the first time, to determine whether it can boost activity of the brain's primary immune cells. Immune dysregulation is recognized as a critical factor in Alzheimer's disease, and research has linked several genes involved in innate immunity to Alzheimer's.

"Our earlier animal studies have shown significant cognitive benefits and reduced pathology without any evidence of toxicity," says Dr. Wisniewski. "With no current disease-modifying treatments for Alzheimer's disease, this could be among the first."

COVID-19–related Publications from the Department of Neurology

NYU Langone researchers have led many efforts to better understand the impact of COVID-19 across nearly every medical specialty, with 617 publications in 2020. The Department of Neurology contributed to this research with publications that included:

Agarwal S, Conway J, Nguyen V, Dogra S, Krieger P, Zagzag D, Lewis A, Melmed K, Galetta S, Jain R. Serial imaging of virus-associated necrotizing disseminated acute leuko-encephalopathy (VANDAL) in COVID-19. *American Journal of Neuroradiology*. October 22, 2020.

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Awards & Recognition

Steven L. Galetta, MD, was selected as the Daniel M. Jacobson Memorial Lecturer at the North American Neuro-Ophthalmology Society Annual Meeting in 2020 and will deliver the H. Houston Merritt Lecture during the Presidential Plenary Session of the American Academy of Neurology 2021 meeting.

Biyu J. He, PhD, received the Irma T. Hirschl Career Scientist Award and delivered a keynote lecture at the 26th Annual Meeting of the Organization for Human Brain Mapping (OHBM). Dr. He was also appointed a consulting editor for the *Journal of Cognitive Neuroscience*.

Jonathan E. Howard, MD, was given the Clerkship Directors Innovation Award from the American Academy of Neurology.

Koto Ishida, MD, was honored with a 2020 American Academy of Neurology A.B. Baker Teacher Recognition Award.

Zenith Khan, FNP-BC, received the Rising Bruin Recent Alumni Award from the UCLA School of Nursing.

Arielle M. Kurzweil, MD, accepted the Rising Educator Award at NYU Grossman School of Medicine's medical education conference in November 2020.

Arjun V. Masurkar, MD, PhD, was elected to the Steering Committee of the Alzheimer's Disease Cooperative Study.

Arjun V. Masurkar, MD, PhD, **Henrieta Scholtzova, MD, PhD**, and **Thomas M. Wisniewski, MD,** received a $1M grant from the Alzheimer's Association Part the Cloud Program for a phase I trial of CpG ODN to treat Alzheimer's disease.

Mia T. Minen, MD, MPH, received the 2020 Harold Wolff–John Graham Award for Headache/Facial Pain Research from the American Academy of Neurology.

Lawrence C. Newman, MD, was named chair of the American Migraine Foundation.

Janet C. Rucker, MD, was elected secretary of the North American Neuro-Ophthalmology Society Board.

Jose L. Torres, MD, was recognized by the American Academy of Neurology with the Diversity Leadership Award.

Thomas M. Wisniewski, MD, and co-inventors were issued three 2020 U.S. patents related to advancing the treatment of Alzheimer's disease.

ABOUT NYU LANGONE HEALTH

Leader in Quality

NYU Langone's emphasis on continuous improvement inspires teams to continually raise the bar on quality and safety across our growing network in Manhattan, Brooklyn, Queens, Long Island, Staten Island, and Florida. NYU Langone's Tisch Hospital, Kimmel Pavilion, NYU Langone Hospital—Brooklyn, and NYU Langone Hospital—Long Island were awarded an "A" as well as a Top Hospital award as part of the fall 2020 Leapfrog Hospital Safety Grades. NYU Langone Hospitals achieved Five Star ratings on CMS Hospital Compare effective October 2019 and is the only major academic medical center in the New York metropolitan region to attain a Five-Star Quality rating.

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Transforming Medical Education

As COVID-19 has added new urgency to nationwide physician shortages, debt burden, and lack of diversity, we remain committed to our accelerated pathways to the MD degree and full-tuition scholarships regardless of need or merit at the recently renamed NYU Grossman School of Medicine and the new primary-care focused NYU Long Island School of Medicine.

For more information about our physicians, services, and locations, visit **nyulangone.org**

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NYU Langone Health

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Neurology

2020 HIGHLIGHTS

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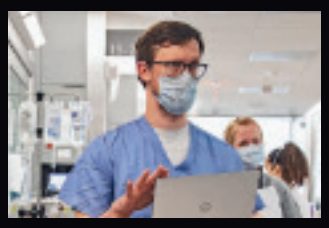

Novel Research Sheds Light on COVID-19–Associated Stroke Risk
See page 1.

Before and After Stroke, Insights Reveal Targets for Prevention and Treatment
See page 8.

New, Multisystem Insights Reveal Potential Treatment Pathways for Parkinson's Disease
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