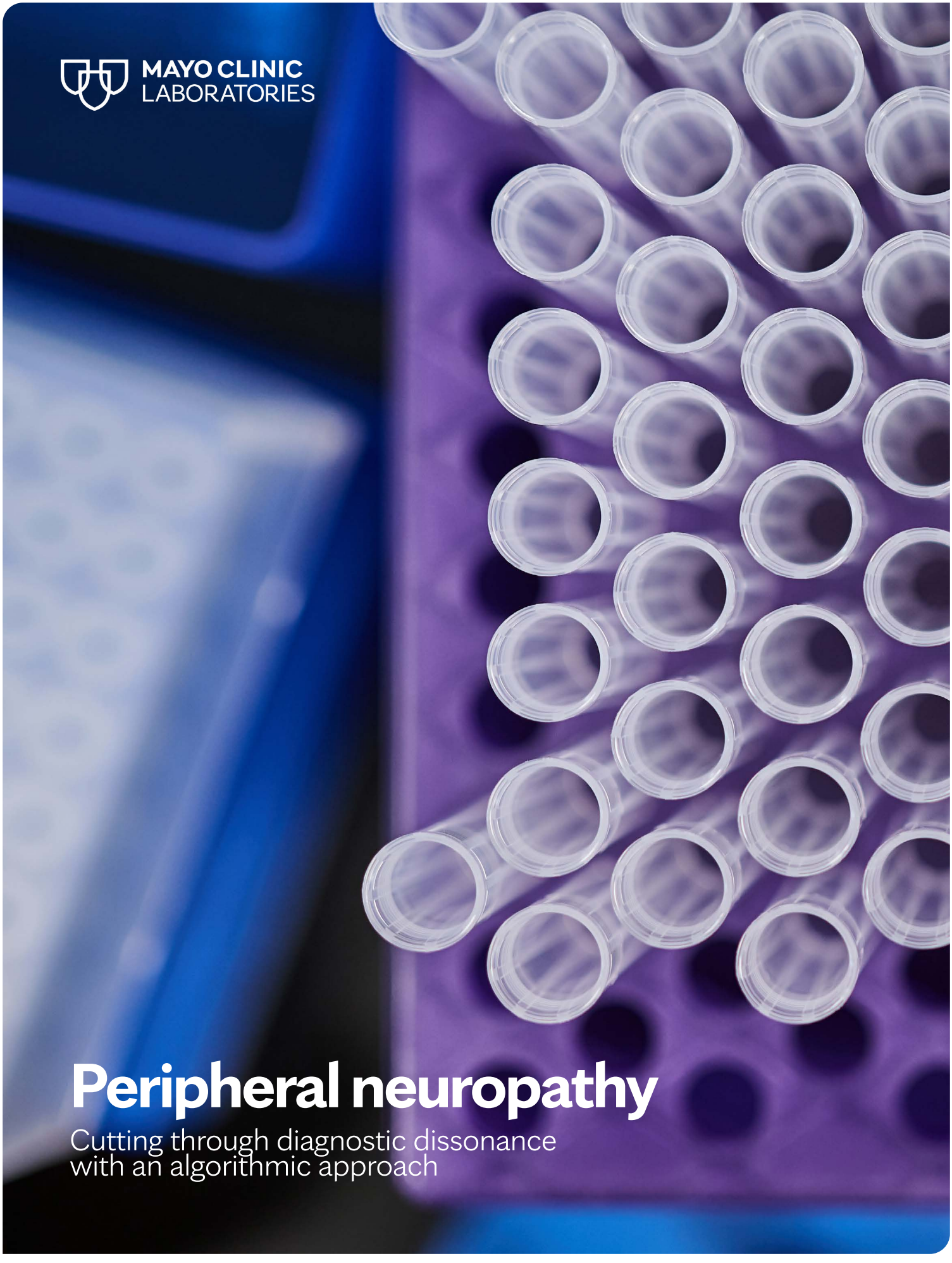


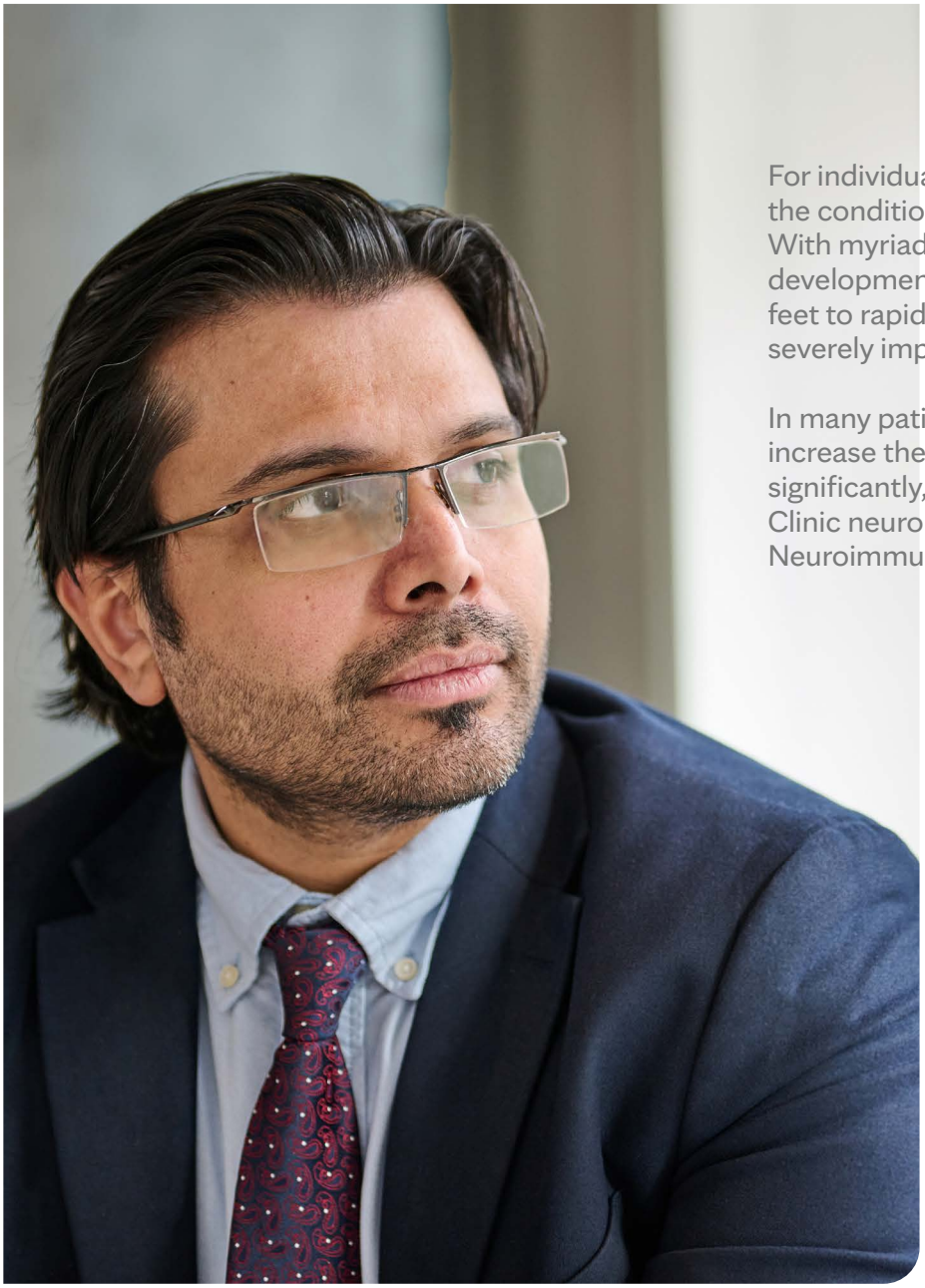
Peripheral neuropathy

Cutting through diagnostic dissonance with an algorithmic approach

Contents

A prevalent, puzzling condition

Peripheral neuropathy is a pervasive, life-altering nerve disorder that affects 2.5% of the global population, and 6% to 30% of seniors.[1,2] More than 100 peripheral neuropathy subtypes have been classified,[3] and while most types are not life-threatening, the illness can cause compounding disability if left untreated.



Divyanshu Dubey, M.B.B.S., Neurology and Laboratory Medicine and Pathology

For individuals impacted by peripheral neuropathy, the condition is often bewildering and disruptive. With myriad causes, presentations range from gradual development of numbness and tingling in hands and feet to rapid-onset weakness and disruption that severely impact movement, strength, and function.

In many patients, neuropathy on its own does not increase the risk of mortality or reduce the lifespan significantly, says Divyanshu Dubey, M.B.B.S., a Mayo Clinic neurologist and co-director of the Clinical Neuroimmunology Laboratory.

"These patients are living long lives with the persistent deficits, or in some cases, progressive deficits. Over time, if you start thinking about statistical comparisons, the disability adjusted for life years can be quite significant," Dr. Dubey says. Although many forms of peripheral neuropathy are not curable, some types are. Others can be effectively managed.

"Among patients with a reversible cause, early diagnosis and intervention is crucial to prevent the condition from progressing to an irreversible stage," Dr. Dubey says.

Unpacking diagnosis to find treatable causes

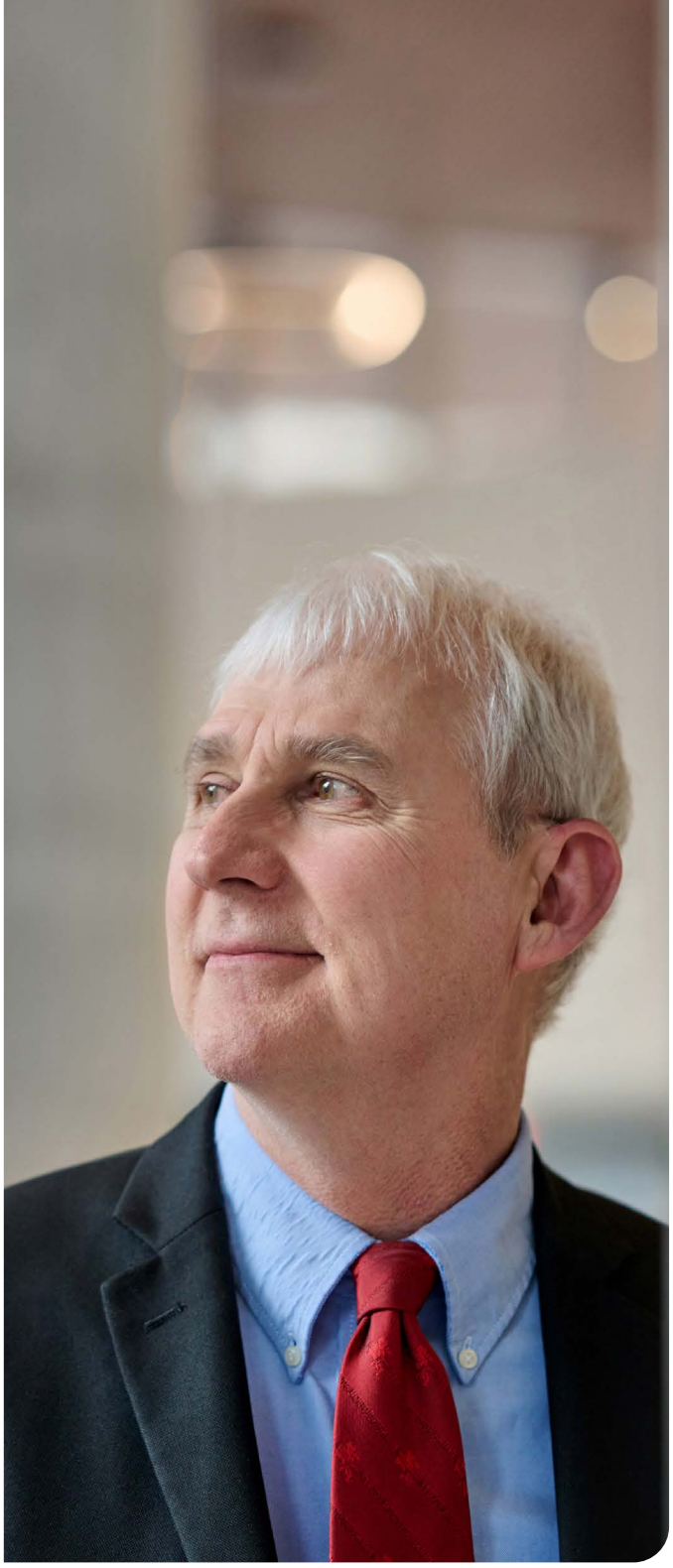
Identifying patients for whom treatment or other interventions are beneficial is crucial. It is not, however, straightforward. Clinical peripheral neuropathy presentations often defy phenotype.

Neuropathy symptoms vary depending on the extent of damage and type of peripheral nerve fiber involved. The condition is categorized by the primary nerve involved: motor, sensory, or autonomic. Despite descriptions such as predominantly sensory, predominantly motor, sensory-motor, and autonomic, most neuropathies affect more than one nerve, and symptoms don't adhere to a clear pattern.

"The big problem is that a lot of these disorders, whether inherited or acquired, overlap with each other," says Mayo Clinic neurologist and neuromuscular specialist Christopher Klein, M.D. "It could be something in the DNA, it could be related to cancer, it could be an autoimmune noncancer-related disorder."

While diabetic neuropathy is the most common peripheral neuropathy, genetic and autoimmune drivers are increasingly being recognized.

Among acquired neuropathies, 10% of cases have autoimmune drivers.[4] Of these, chronic inflammatory demyelinating polyneuropathy (CIDP) is one of the most common treatable types. Caused by a misguided attack of the immune system on peripheral nerves, CIDP is just one of many autoimmune types.



Christopher Klein, M.D., Neurology

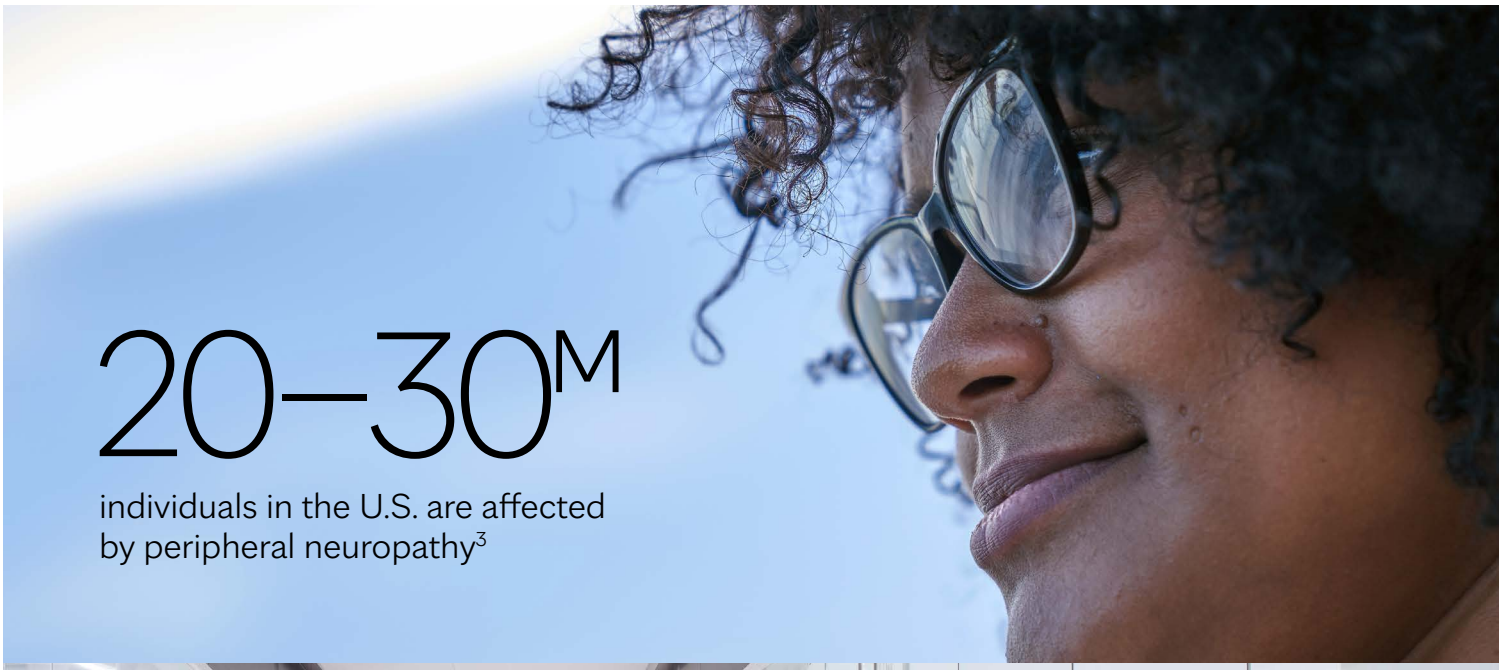
"These make up a small fraction of neuropathies. As physicians, **it is important to make sure we do not miss anything that is treatable or something where we can halt the progression** and limit the disability in these patients' lives."

– Divyanshu Dubey, M.B.B.S.

Research has revealed and continues to reveal antibody associations, as well as genetic connections, and ongoing studies continue to identify antibody-disease connections. In rare instances, an underlying cancer is the cause of the condition, and for these patients, rates of morbidity and mortality are significantly elevated.

The good news for many patients with cancerous and immune-mediated disease is that treatment is often possible, and identifying the specific paraneoplastic condition is becoming easier as a result of advanced laboratory testing[3] (Mayo ID: AIAES).

"Neuropathy is common, but these autoimmune conditions which are associated with or cause the neuropathy are not," Dr. Dubey says.

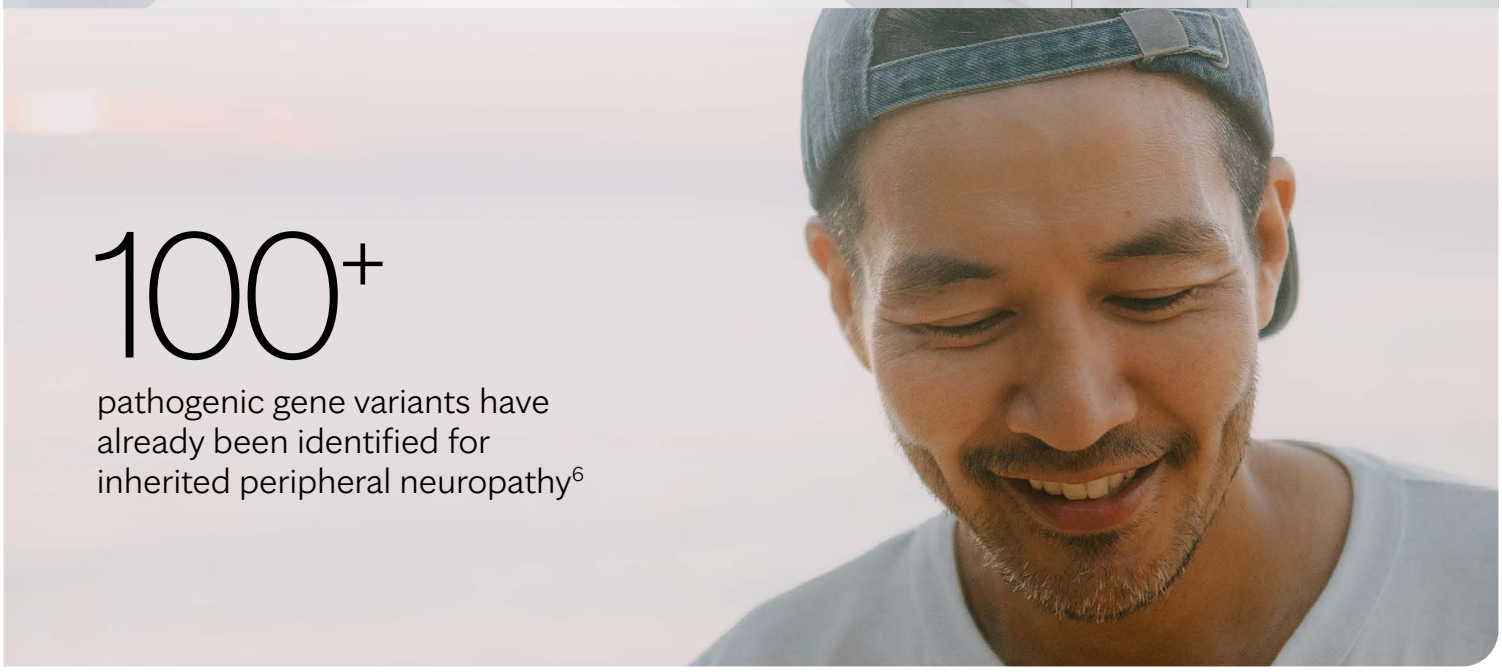


20–30M

individuals in the U.S. are affected by peripheral neuropathy[3]

25–46%

of cases are acquired[5]



100+

pathogenic gene variants have already been identified for inherited peripheral neuropathy[6]

A diagnostic dilemma

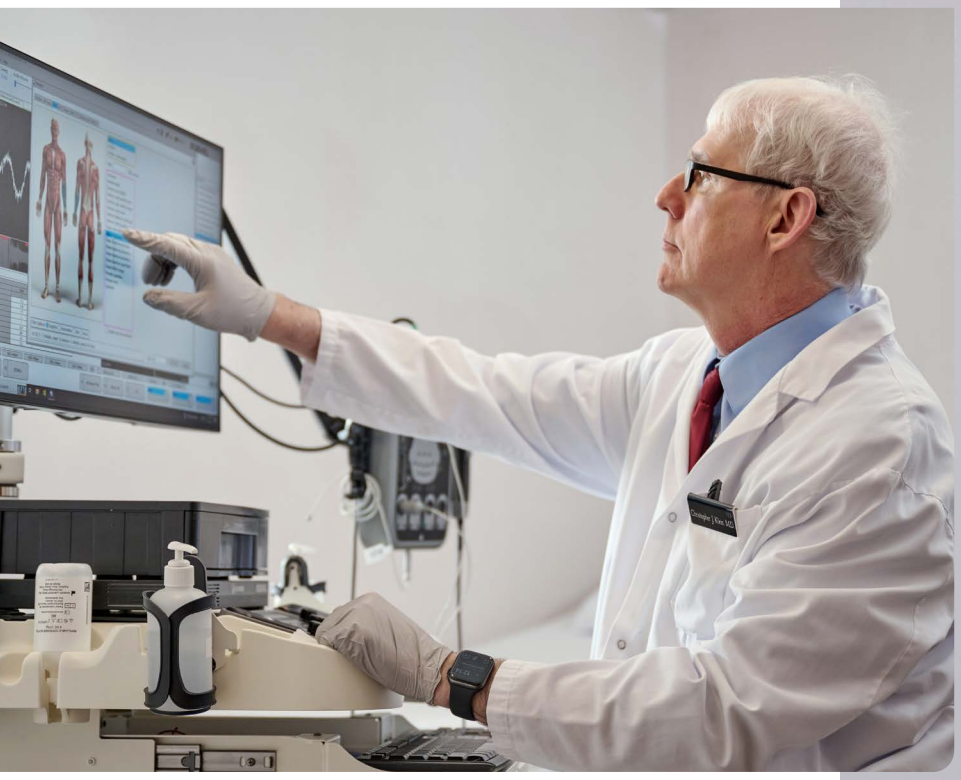
Sorting through the variables to pinpoint the cause of a patient's neuropathy is paramount to successful patient outcomes. Unfortunately, for many patients, diagnosis can take weeks, months, or even years in some cases.

For clear-cut presentations, a clinical exam, comprehensive personal and family medical history, and first-line screening tools can provide primary care physicians with ample evidence to confidently make a diagnosis.

For individuals with unclear cases who progress to the care of a neurologist or neuromuscular specialist, additional testing is often performed to help establish the clinical pattern. Electrodiagnostic testing, such as nerve conduction or needle electromyography (EMG) studies, is often used to assess the nerve structure and function. These tests ascertain if the damage is to the nerve cell's axon (axonal neuropathy) or the myelin sheath surrounding the cell (demyelinating neuropathy).

Electrodiagnostic testing is recommended as part of the diagnostic process for peripheral neuropathies by several medical associations, including the American Association of Neuromuscular and Electrodiagnostic Medicine and the American Academy of Family Physicians.[7]

Under the right circumstances, these tests can be a valuable tool in differentiating the illness and confirming the correct diagnosis. But the right circumstances aren't always present. Even when they are, results from EMGs performed at outside centers can be difficult for ordering physicians to interpret. This challenge was highlighted in 2020 research on the utility of electrodiagnostic studies for the diagnosis of certain peripheral neuropathies.[8]



"At times, in some patients referred to our clinic, I have noticed variability in the performance and interpretation of electrodiagnostic studies. Occasionally, these studies may not offer the level of reliability needed for accurate clinical diagnosis," Dr. Dubey says. "They can be influenced by various factors, including the operator's expertise and the limb's temperature. These factors can affect the results obtained."

The ambiguity of diagnostic tools

In the absence of EMG or as an adjunct, advanced laboratory testing can further define the diagnosis. Lab tests to diagnose peripheral neuropathy have traditionally been structured to align with a patient's clinical disease presentation. So, patients with sensation changes, or radiculopathy, typically receive lab testing of antibodies linked to sensory disorders, whereas patients with motor involvement, or myelopathy, often receive testing for antibodies connected to muscle weakness and movement.

Perplexingly, antibodies can overlap between the sensory and motor presentations, which makes selection of the right lab test for an atypically presenting patient complicated.

"A lot of time it's not known what's the right test," says Dr. Klein, who is also the co-director of Mayo Clinic's Peripheral Nerve Laboratory. "There are some situations where you are pretty sure and can place them into a big group. But every patient is different on how certain I am on how useful the tests are."

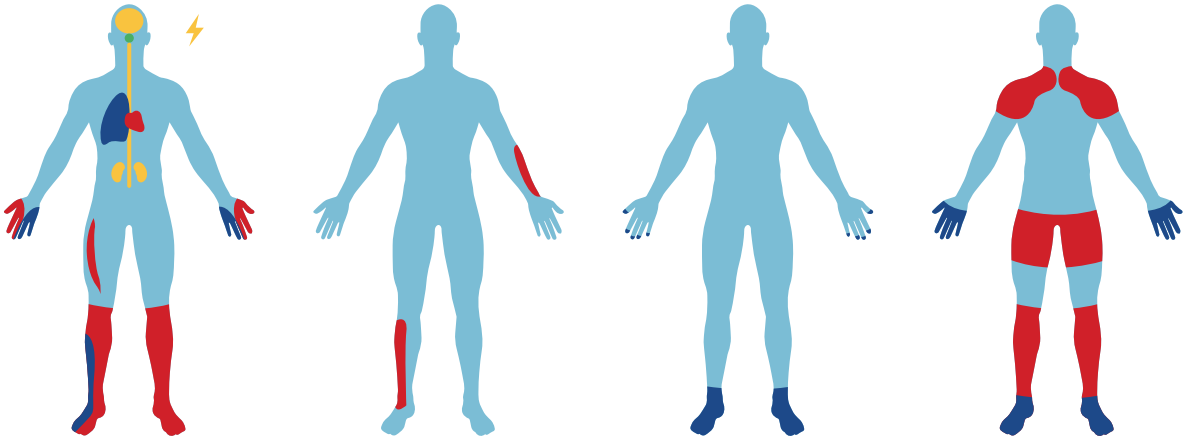
Adding to the confusion over appropriate test utilization is the availability of large, undifferentiated panels.

"One of the challenges with large antibody panels is that they have been generated to capture multiple disease states," says John Mills, Ph.D., co-director of the Clinical Neuroimmunology Laboratory. "If the panel doesn't have specific tests there is an increased risk for generating false-positive results, reducing its positive predictive value and reliability."

Autoimmune subtypes

Demyelinating neuropathy
Subtypes and involvement

CNS SENSORY MOTOR AUTONOMIC PAIN



Systemic vasculitic multifocal

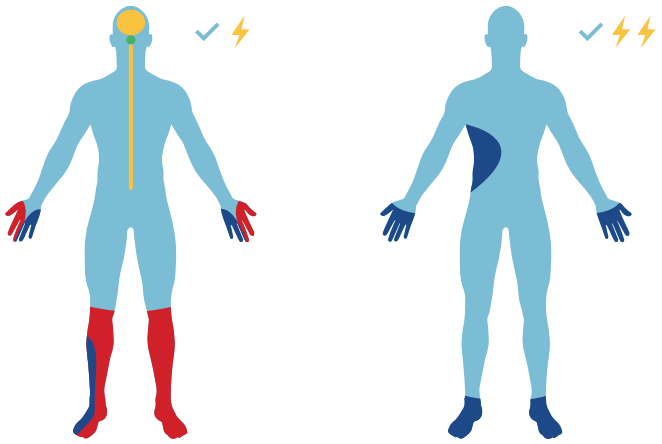
Multifocal motor neuropathy (MMN)

Distal-acquired demyelinating sensory (DADS) neuropathy

Inflammatory demyelinating polyradiculoneuropathies (CIDP, MILLER FISHER, AMAN)

Axonal neuropathy
Subtypes and involvement

CNS SENSORY MOTOR AUTONOMIC PAIN



Neuropathy & polyradiculoneuropathy– symmetric & asymmetric

Small fiber neuropathy & idiopathic pain, autoimmune cases - acute or subacute presentation

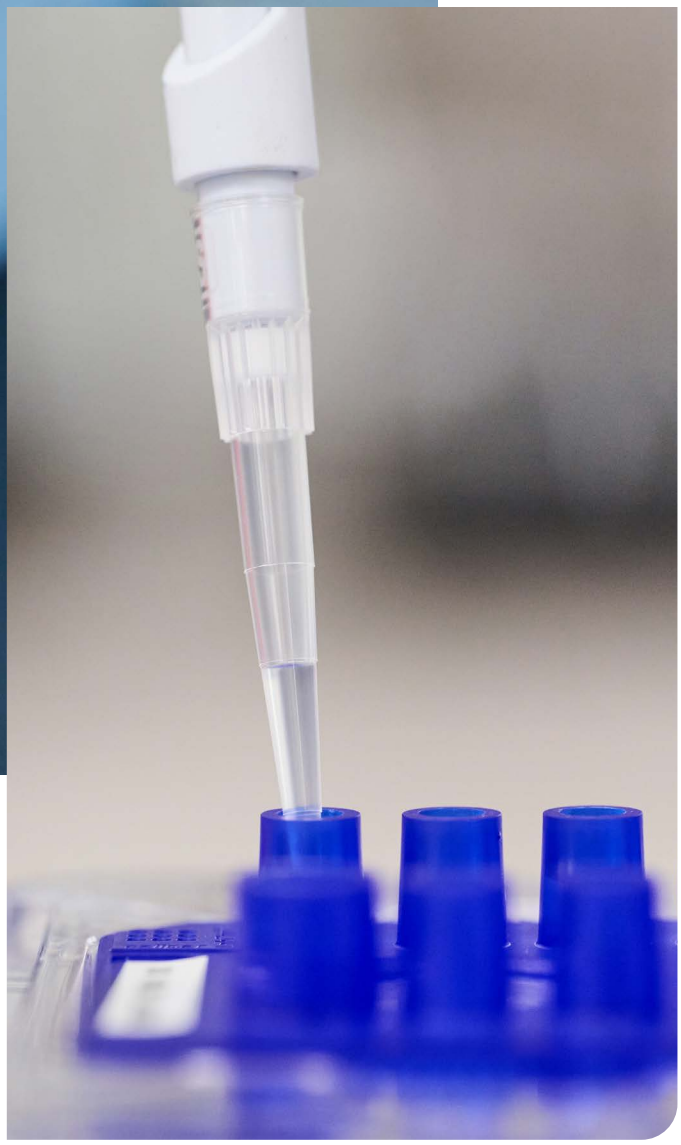
Recasting diagnosis

"The strength of the algorithm is a great equalizer. It takes the most junior person and the most skilled person and puts them on a level playing field for the initial consideration of diagnosis."
– Christopher Klein, M.D.

Dr. Klein in discussion with Neal Niu, Ph.D.

Grounded in and driven by Mayo Clinic's primary value that the needs of the patient come first, Mayo Clinic physicians and scientists have spearheaded a patient-forward approach to peripheral neuropathy diagnosis that eliminates the guesswork.

"I've been working in this area since I was 21 years old," Dr. Klein says. "I am 60 years plus now, and this is one of the most hopeful things I've seen in terms of helping physicians of different skill levels expedite their patient's diagnosis."



In late 2024, the neuroimmunology and neurogenetics laboratory team at Mayo Clinic released updated versions of the acquired peripheral neuropathy and hereditary peripheral neuropathy testing algorithms. These guidelines holistically direct test ordering for patients suspected of having autoimmune or genetic causes for their condition and are designed to yield definitive answers and faster diagnoses.

Selecting the right test for the right patient increases the pre-test probability by preventing false positives, Dr. Dubey says. "False-positive tests can unfortunately lead to either excessive, unnecessary testing or administration of immunotherapy that is not warranted."

Additionally, to help reduce misdiagnosis of CIDP, Mayo Clinic test developers designed a digital tool to guide test ordering.

According to internal Mayo Clinic research, inaccurate, overdiagnosis of CIDP exacerbates the economic burden of IVIg treatment in the U.S. and delays appropriate treatment in half of those patients who initially receive IVIg but are found to have a different diagnosis.[9,10,11,12]

The CIDP calculator helps physicians navigate between classic CIDP, atypical CIDP, and mimic disorders by identifying red flags associated with mimics. While most types of classic CIDP respond to first-line IVIg therapy, certain atypical variants are treatment refractory.

Clinical Laboratory Technician Caileen Hughes observes samples processed on a liquid handler as part of autoimmune axonal neuropathy testing.

"We're pretty confident that these tests and the algorithms are faithful to our belief in getting the right patient to the right test. That is a very important concept and by doing that, **we can get patients to the best care,**" Dr. Klein says.

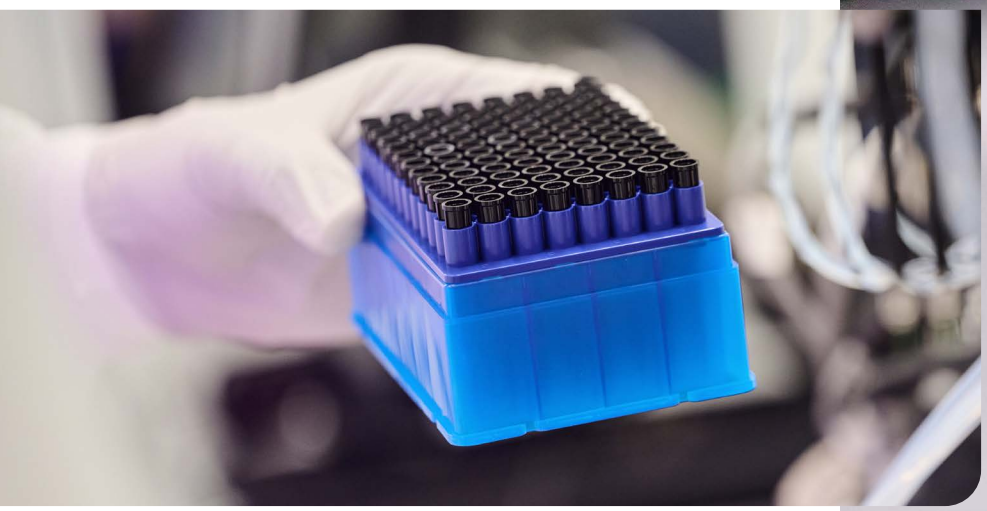
Meaningful, patient-focused testing

Since the establishment of the Clinical Neuroimmunology Laboratory at Mayo Clinic in the mid-1980s, Mayo Clinic neurology specialists have propelled excellence in the autoimmune peripheral neuropathy testing space. The intersection of research, practice, and test development is the engine that launches new discoveries into practice.

"Since most of us are clinicians and there is a clinical connection in each of our groups, we are in constant learning mode," Dr. Dubey says.

"We continue to learn about what is going on in our space, whether that is in the form of patients we see in our clinic or reviewing the literature."

When antibodies are discovered, either by Mayo Clinic scientists or outside researchers, they are evaluated for their clinical relevance and, if appropriate, incorporated into Mayo Clinic Laboratories' autoimmune testing portfolio.



The antibody neurofascin-155 (NF155), which is one of the biomarkers associated with CIDP-like presentation that responds poorly to IVIg,[13] is an example of a target identified outside of Mayo Clinic but incorporated into CIDP testing (Mayo ID: CIDP and Mayo ID: DMNES).

"Our first step was reviewing NF155 autoimmune nodopathy and convincing ourselves there's enough literature to support that this should be a Mayo Clinic offering," Dr. Dubey says. "Then we do pre-verification work to test enough cases to understand whether what we are seeing out there in the literature is consistent with what we are experiencing on our clinical side. And when we are convinced from all angles, those antibodies are validated and entered onto these panels."

Ensuring that every antibody in the panel has high specificity for peripheral neuropathy is essential to designing clinically meaningful testing, Dr. Mills says.

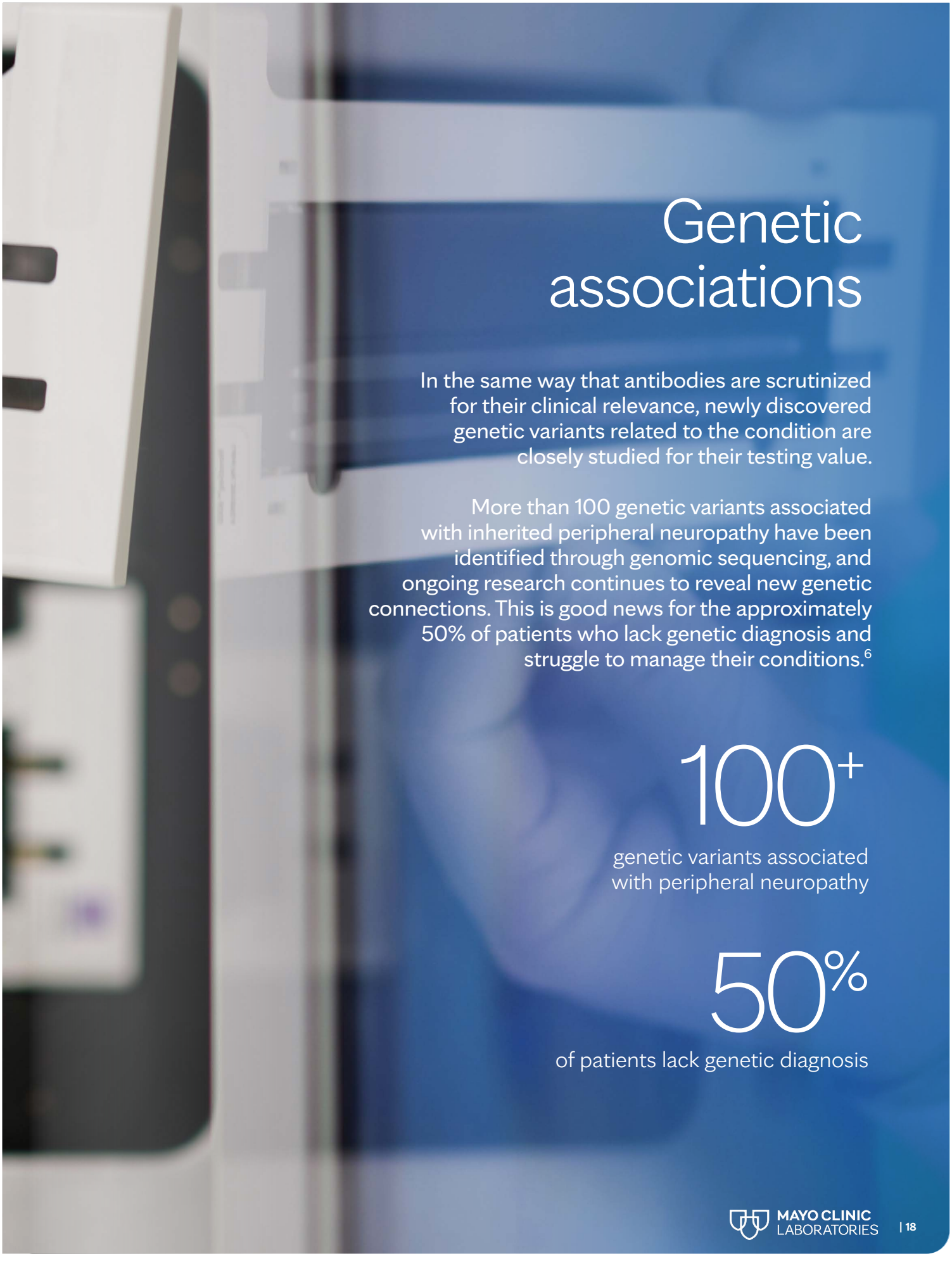
"With every analyte we provide, everything is backed by a clinical study," Dr. Mills says. "These are analytes with proven clinical utility, with a lot of peer-reviewed literature support, and they are all actionable. The treatment and approach to manage these patients when they have one of these antibodies is well-defined." To that end, antibodies that lack sufficient specificity in the context of a large panel and risk generating false-positive results are excluded or removed.

For instance, voltage gated potassium channel (VGKC) antibodies were excluded from Mayo Clinic Laboratories' autoimmune axonal peripheral neuropathy evaluation (Mayo ID: AIAES) based on research reporting 85% of VGKC-positive cases were negative upon reflex testing.[14]

"We are constantly assessing our panels, and we will remove or modify poor performing tests because we know they may actually add more diagnostic confusion than they do answers," Dr. Mills says. "We strive to ensure that when we do include something in our panel, it's a reliable test result."

Ganglioside antibody testing is a recent addition in the autoimmune testing space at Mayo Clinic (Mayo ID: GAES). Ganglioside antibodies are related to several serious but treatable disorders, such as Guillain-Barrè syndrome and its variants Miller Fisher syndrome, Bickerstaff brainstem encephalitis, multifocal motor neuropathy (MMN), and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM).

John Mills, Ph.D., co-director of the Clinical Neuroimmunology Laboratory, and Rachel Tyler, clinical laboratory technician, discuss patient samples placed in the flow cytometer.



Genetic associations

In the same way that antibodies are scrutinized for their clinical relevance, newly discovered genetic variants related to the condition are closely studied for their testing value.

More than 100 genetic variants associated with inherited peripheral neuropathy have been identified through genomic sequencing, and ongoing research continues to reveal new genetic connections. This is good news for the approximately 50% of patients who lack genetic diagnosis and struggle to manage their conditions.[6]

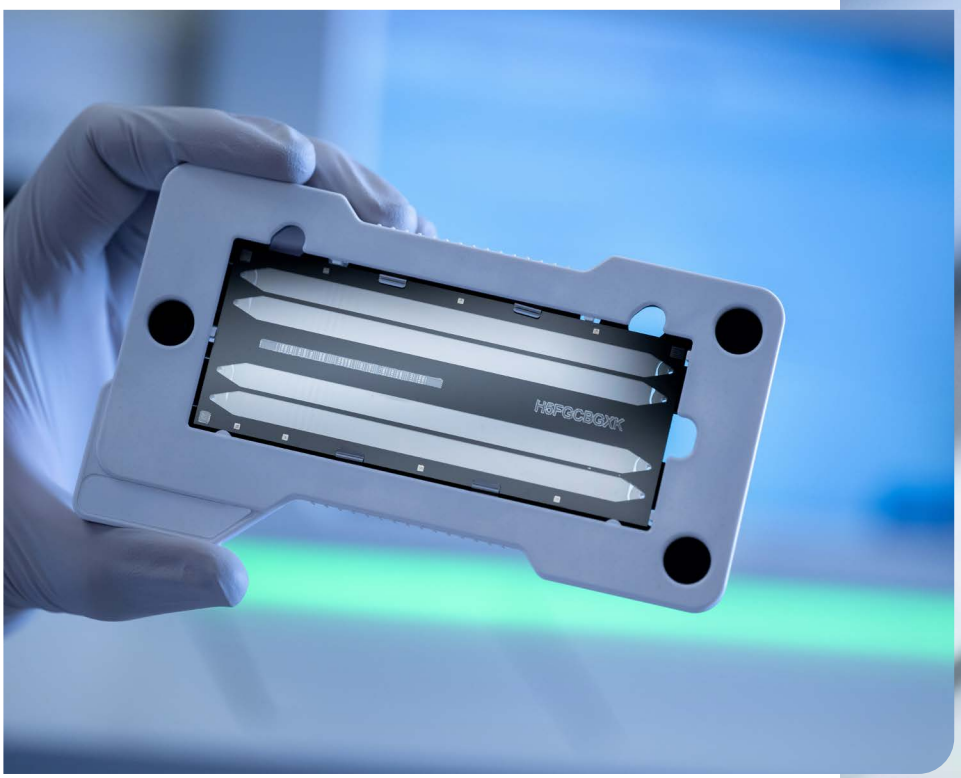
100+

genetic variants associated with peripheral neuropathy

50%

of patients lack genetic diagnosis

At Mayo Clinic, research into genetic affiliations at both genome and exome levels continually provides new targets to investigate, says Dr. Klein.



"This area moves so quick," Dr. Klein says. "(Advanced sequencing) will allow us to find a type of mutation, which are called repeat expansions, historically missed by other sequencing platforms."

Among neuropathies associated with repeat expansions are certain sensory ataxias, which are caused by axonal damage. Implementation of testing to correctly diagnose ataxia has been a priority for Mayo Clinic test developers, and the lab now offers a hereditary ataxia gene panel (Mayo ID: ATAXP), testing for Friederich's ataxia (Mayo ID: AFXN), and spinocerebellar ataxia (Mayo ID: SCAP).

"We suspect we are going to find other repeat expansions missed by routine sequencing, so that 40% of missed axonal neuropathies may be whittled down to a much smaller number," Dr. Klein says.

When new discoveries are made, such as the 2020 finding that variation in the *SORD* gene can cause atypical Charcot-Marie-Tooth disease,[15] they are quickly validated and implemented (Mayo ID: SORD).

At Mayo Clinic, advanced technologies evaluate for genetic variation associated with inherited peripheral neuropathy. Offerings include single gene analysis of *PMP22*, which is linked to 70%–80% of all hereditary neuropathies (Mayo ID: PMPDD), and a comprehensive next-generation sequencing panel that analyzes more than 180 genes with known associations to inherited peripheral neuropathies (Mayo ID: PEPAN).

"In our panel design, we include systemic neuropathies, metabolic-related neuropathies, and some other genetic disorders that present with peripheral neuropathy symptoms, which are really the core of our design to make it useful," says Neal Niu, Ph.D., a molecular genetics researcher at Mayo Clinic. "Our panel provides more of a phenotype-driven clinical evaluation; it's not just confirming a particular bucket of specific genetic disorders."

Neal Niu, Ph.D., reviews next-generation sequencing data with clinical laboratory technician Travis Anderson.

Answers with impact

Each year, peripheral neuropathy testing available at Mayo Clinic Laboratories **delivers thousands of life-changing answers to patients** both local to Mayo Clinic and around the world. For these patients, receiving answers after months and even years of misdiagnosis provides a clear path forward.

One such patient searched for answers for more than 10 years before Mayo Clinic Laboratories testing revealed he had neurofascin-155 (NF155) autoantibodies causing his severe progressive neuropathy.

Prior to an accurate diagnosis, the patient was misdiagnosed as having carpal tunnel syndrome and spinal compression, for which he underwent surgery. When he transferred care to Mayo Clinic, he received a diagnosis of CIDP and was treated with IVIg, but the treatment failed. Next, he received high-dose steroids and underwent plasmapheresis, which helped a bit, but the blood exchange was arduous.

The failure of IVIg to combat the patient's symptoms prompted his Mayo Clinic neurologist to look more deeply. That investigation pointed to new research on the role of NF155 antibodies, which are found in just 4% to 18% of patients with CIDP.

A sample of the patient's blood was evaluated though a Mayo Clinic Laboratories antibody test, which uses flow cytometry to confirm NF155-type CIDP. Flow cytometry is a sophisticated laboratory technique that provides more specific test results. The test result was positive.

"That was remarkable," says the patient's physician. "It was the answer that we knew was in front of us, but we could never grab hold of it."

Knowing a patient is positive for the NF155 antibody is crucial because it points to an alternative therapy, which is often the immune-suppressing medication rituximab.

"NF155 autoimmune nodopathy can be a progressive disease if not treated appropriately," Dr. Dubey says. "Patients can have lasting deficits that, at some point, become permanent."

Life-changing answers

A different patient, a teenager, had experienced seemingly random symptoms, including tremor and atypical foot structure, for most of his life. Electrodiagnostic testing in the form of a nerve conduction study came back inconclusive. The patient received whole genome testing, but genetic sequencing did not detect any obvious variation related to peripheral neuropathy.

A member of the young patient's care team suggested a more thorough genetic evaluation, and the patient's sample was sent to Mayo Clinic Laboratories. Single gene testing of the *PMP22* and *SORD* genes revealed the teen's condition was a type of Charcot-Marie-Tooth disease cause by *SORD* variation. Clinical trials are currently underway for targeted treatments of *SORD* neuropathy. These medications aim to combat the destructive process caused by the gene defect and prevent symptoms from occurring or worsening.

In another instance, a young woman who'd suffered from peripheral neuropathy symptoms for most of her life, and had previously been diagnosed with Charcot-Marie-Tooth disease, wanted children but did not want to pass on the genetic condition to her offspring. The patient sought a second opinion at Mayo Clinic. Her care team, which included Dr. Klein, thought her nerve conduction studies pointed to an acquired cause. Autoimmune testing was ordered, and results were positive for IgG 4 nodopathy, an autoimmune type that could be treated.

"We got her on a treatment and now she's got five children."

– Christopher Klein, M.D.

For patients who do receive a genetic diagnosis, results can be useful to guide both personal and family healthcare decisions.

"Those diagnoses translate into the care for family members, brothers, sisters, and even for younger generations who are thinking about screening to access potential treatments," Dr. Niu says.

For instance, in the case of hereditary systemic amyloidosis, such as ATTR-amyloidosis, molecular therapies are available that can stop peripheral neuropathy symptoms from getting worse.

"As part of our philosophy, we always pay attention to and emphasize those lab testings that can be useful to treat the patient," Dr. Niu says.

Powering innovation

The integration between the clinical practice at Mayo Clinic and test developers in the Department of Laboratory Medicine and Pathology at Mayo Clinic drives testing innovation at Mayo Clinic Laboratories. Teams of practicing neurologists, lab medicine scientists, and researchers work collaboratively to convert new discoveries into novel testing approaches that meet a patient need.

"A strength in our approach, which I've seen from having done this for so long, is the combination of players," Dr. Klein says. "Whether it is somebody like John Mills, who is an extraordinary laboratorian and familiar with extremely technical details and validation issues, or Div Dubey, who is a great clinician but also a great laboratory scientist, or Neal Niu, who is also a wonderful laboratory scientist, and then our client support team and their ability to get patients to the right test; it takes a very strong team with divergent skill sets to allow all this to work."

The multidisciplinary, patient-first approach means that the most important clinical needs remain at the forefront.

"What makes our service really stand out is that we start with a clinical question we want to answer," Dr. Niu says. "It is through close collaboration with our neuromuscular clinic and clinical geneticists that we carve out the core question that our panel will be aiding to address."

Viewing test development through the lens of physicians and their patients aligns with Mayo Clinic's emphasis on prioritizing patient needs, says Dr. Dubey.

"We gather from our experience and expertise and then try to apply what we've learned to these tests to best serve the patients we see," he says. "That has led not only to success for us in the lab, but success for us in our ability to provide good foundational care for patients day in and day out."

Resources

Testing algorithms

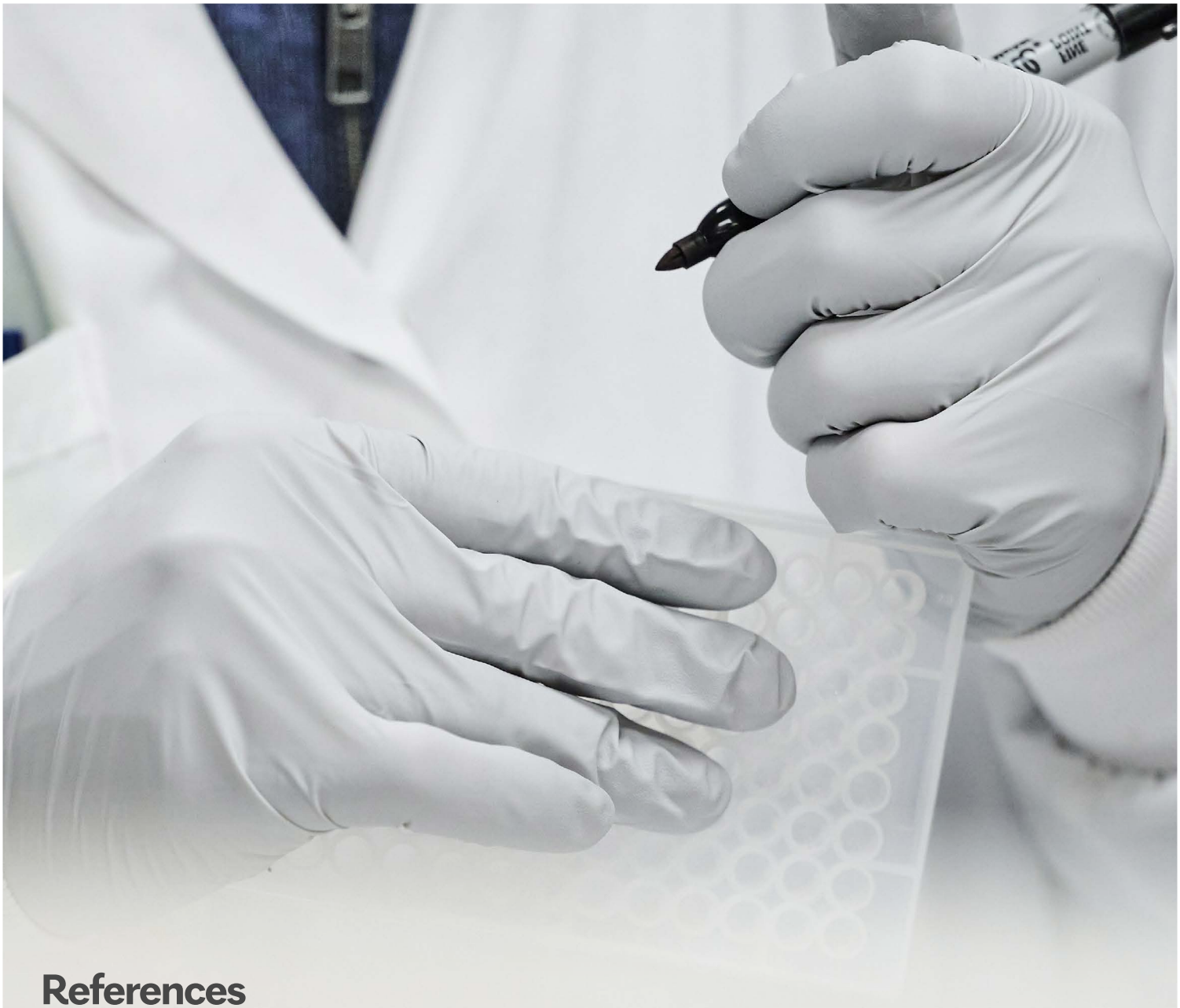
The use of testing algorithms to guide test ordering is essential to ensure the right patient receives the right test. Our algorithms for acquired neuropathy and hereditary neuropathy combine the unsurpassed expertise of Mayo Clinic physicians and scientists, emerging research, and leading-edge testing methodologies to guide the test ordering process.

- Acquired neuropathy diagnostic algorithm
- Hereditary peripheral neuropathy diagnostic algorithm

Peripheral neuropathy testing

View our testing to identify peripheral autoimmune neuropathy with axonal or demyelinating causes, as well as next-generation sequencing to help establish whether a peripheral neuropathy is genetic in nature.

- View testing



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