The Promise of Gene Therapy for Neuropathy and Rare Diseases

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Gene Therapy: What is it and Why Does it Matter to Patients?

Gene therapy is a way to use genes to prevent, treat, or cure medical conditions or diseases by inactivating, repairing, or replacing a gene. For example, "gene therapy works by adding new copies of a broken gene, or by replacing a defective or missing gene in a patient's cells with a healthy version of that gene." The scientific concept of using a gene to change the course of a disease is nearly 50 years old, but translating the science at the lab bench to gene therapy at the patient's bedside is still in the early stages of innovation.

Gene therapy products use gene therapy techniques to address medical conditions or diseases in patients. To date, approved gene therapy products focus on diseases or conditions that have a genetic component and have few, if any, treatment options, and in many cases, the disease or condition is considered to be rare, that is, affecting fewer than 200,000 patients in the U.S. Still a new approach to fighting disease, the first gene therapy product — for young patients with a form of leukemia — was only approved for use in the U.S. in 2017.

The promise of gene therapy is immense, especially for patients who have no other treatment options. According to the American Society of Gene + Cell Therapy, more than 2,000 gene therapies are in development worldwide. As of December 2023, more than 30 gene therapy products have been approved by the U.S. Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER). If this rate of development continues, in the next ten years, an estimated 750,000 to 1 million patients will have access to more than 60 gene therapy products in the U.S.

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For patients with neuropathy, currently available treatments are limited and tend to be focused on relieving symptoms, not on halting the process of nerve degeneration. Researchers and clinicians are hopeful that gene therapy products can create new options for treating certain kinds of neuropathy, such as inherited peripheral neuropathy (IPN), which is caused by genetic mutations in more than 100 genes. A 2023 survey conducted by the Neuropathy Action Foundation (NAF) also shows that patients with immune mediated neuropathies such as Guillain–Barre Syndrome (GBS), Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN) overwhelmingly hope that a gene therapy for their condition is on the horizon.

Innovative Therapies Need Innovative Policy Approaches to Ensure Access

Cell and gene therapy science continues to evolve and will bring more innovative products to the market. For patients to access these innovative therapies, however, innovative policies will also be required. While patients in the U.S. currently face a range of barriers in accessing medical interventions that can prevent, slow, or stop disease progression, cell and gene therapies represent a shift in clinical options for addressing health conditions and diseases from palliative to curative. The policy environment will need to adapt to the different clinical options gene therapy products present, as well as the higher initial price points of these therapies, in several ways. Three interrelated adaptations will be foundational to ensuring patient access: 1) Centering patient and family input, 2) Assessing value appropriately, and 3) Creating new payment models.

Centering Patient and Family Input

Perhaps the most crucial adaptation policies addressing access to gene therapy products will

require is centering the experience of patients living with the condition or disease for which the gene therapy product is used. Consider that more than 90% of rare diseases do not have any FDA-approved treatments, and of course, a person doesn't have to have a rare disease to have a lack of treatment options. For example, "there are no standard treatments for hereditary neuropathies." Clinicians can offer interventions to relieve symptoms, such as physical therapy or pain medications, but patients still face a range of health issues that affect their activities of daily living. A person with an inherited peripheral neuropathy (IPN) lives with progressive nerve damage that causes pain, loss of sensation, muscle weakness, and atrophy, all of which can, in turn, create loss of function, such as walking or using their arms. Some patients with severe disease can have difficulty speaking, swallowing, or breathing as the neuropathy causes the muscles that control these functions to weaken.

Payers determine whether, under what circumstances, and at what price to cover medical interventions. But if a patient is facing lifelong deterioration, such as is the case for many people with neuropathy, the way a patient or family thinks about a medical intervention is likely to be different from the way a payer or a clinician thinks. As gene therapy products come to market, policies will need to adapt by prioritizing patient preferences when it comes to coverage decisions. In current medical practice, shared decision-making occurs when clinicians and patients collaborate to make choices that align patient values with clinical evidence and are considered evidence-based. Shared decision-making at its best is patient-centered and focuses on a patient's (and sometimes a family's) preferences about whether to use a medical intervention and which one might work best considering the patient's unique medical and non-medical circumstances. For example, a patient might prefer a medication that is delivered through a portal instead of needing to take multiple pills on a strict schedule throughout the day. Or a patient and their family might choose a medical intervention that enables the patient to walk a few steps versus relieving pain but reducing mobility. Families might also prioritize interventions that minimize informal caregiver burdens or reduce burdens siblings might experience from a particular patient intervention, including stigma.

As payers make coverage decisions about gene therapy products, however, they are unlikely to prioritize or even consider these patient-driven preferences and are likely to use the same criteria they currently use to determine the "value" of an intervention. Cost and cost-effectiveness, as measured by whether the clinical benefits of an intervention justify the cost, are the primary considerations for coverage, utilization management restrictions, and benefit design, such as patient cost-sharing requirements from the point of view of payers. It makes sense that maximizing clinical and economic benefits while minimizing costs is a payer's perspective, but it does not make sense that access to innovative medical interventions should be decided solely by payers with little to no patient input. Patients, family members, advocates, and other stakeholders are already working to include patient and family preferences in coverage and cost decision models. For example, the "Patient-Driven Values in Healthcare Evaluation (PAVE) Center at the University of Maryland developed, in collaboration with patient stakeholders, a framework of condition-agnostic, patient-identified value elements." As more gene therapy products become available, efforts to center patient and family input will be an essential component of assessing the value of gene therapy products appropriately.

Assessing Value Appropriately

Cost-effectiveness analysis (CEA) is one of the most common methods for assessing the value of a medical intervention. This analytical framework considers several value elements, such as short and long-term costs, costs compared to available treatments, and clinical effectiveness as measured by specific endpoints (e.g., progression-free survival, event-free survival, or elimination or reduction of damaging effects of condition at particular time intervals). However, this approach to assessing value has several shortfalls. First, most CEAs are from the healthcare sector or payer perspective and take

only their value elements into account. In a review of more than 7,000 CEA studies conducted between 1974 and 2018, almost 75% had a healthcare sector or payer perspective. Of these value assessments, the perspective included only monetary costs associated with treatment and usually included only immediate medical costs, not future medical costs or costs avoided due to the medical intervention. Second, the same review showed CEAs "rarely included unrelated medical costs and impacts on non-healthcare sectors." If such costs were included, they were almost always related to productivity or patient transportation.

Assessing value appropriately would mean making patient and family value elements integral to the cost-effectiveness analysis. "Even though it is known that patients value specific aspects of treatment differently," value assessments do not sufficiently engage patients in the assessment process, and the inputs, as well as final value elements chosen in a CEA, are seldom patient-centered. As previously mentioned, patients and their families may prioritize one medical intervention over another because of the effects on family members. However, while "an important health consequence, spillover health effects on family members and informal caregivers of patients…is also often omitted" from value assessments.

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Policies must change to assess value appropriately as more gene therapy products come to market. For patients with limited or no treatment options, gene therapy could provide their only possible pathway to slowing their disease or eliminating symptoms; a new gene therapy product might also provide relief to family members not currently included in most value assessments but is undoubtedly valuable to that patient. Assessing value appropriately by including the full range of outcomes and preferences important to people living with the condition the gene therapy product is meant to treat will become even more critical as interventions continue to be made available to patients. For example, in December 2023, the FDA approved the first gene therapies to treat patients with sickle cell disease, a chronic, life-shortening, inherited blood disorder. These treatments could replace the current standard of care, which includes blood transfusions multiple times a year and frequent emergency department or hospital stays to support patients during episodes of extreme pain. The patient and family value elements affecting those living with sickle cell disease would go well beyond cost-effectiveness. As such, gene therapy products will require alternative approaches to assessing value appropriately.

The Innovation and Value Initiative (IVI) is already working with various stakeholders to improve the "transparency, patient-centeredness, and relevance of value assessment to real-world decisions." IVI has published nine principles for value assessment in the U.S., including sustaining authentic patient-centricity, for example, by including patients and patient preferences in priority setting and model creation, and supporting health equity by including the patient and family preferences of diverse communities and experiences. Modifying the current approach to value assessments to incorporate equity considerations is particularly important for gene therapy products as a number of patients who would benefit from such therapies have been historically marginalized, whether because of their race or ethnicity, their income level or where they live. Advocates are already proposing changing value assessments to incorporate the effects of a medical intervention on equity. Distributional cost-effective analysis (DCEA) includes measures to quantify the effects of an intervention on equity. DCEA is just one approach that could be used to assess the value of gene therapy appropriately.

Creating New Payment Models

The most immediate change to the policy environment necessary to ensure patient access to gene therapy products is creating new payment models. To date, gene therapy products available in the U.S. have initial costs ranging from $300,000 to $3 million. For comparison, the average spending of a person in the top 1% of spending in the U.S. in 2021 was about $165,000 for the year. It is not just the cost but the unpredictability of which patients may incur such costs, the timing of those costs, and the uncertainty of measuring outcomes of gene therapy products that create problems current payment policy models need to be designed to address. To ensure patient access, payment models will need to adapt to each of these risks.

Managing the Risk of Unpredictable Patient Uptake

Both private and public payers in the U.S. assume risk for only a subset of possible patients in any given year. A health insurer providing coverage to an organization's employees and retirees only needs to estimate costs for those limited number of enrollees. A health insurer determines its risk for covering medical services based on the previous year's experiences, both in terms of utilization and prior cost of care, and sets its premiums accordingly. If the health insurer does not accurately predict both the number of people who may need gene therapy and the cost of each of those therapies, the premiums collected will not cover the medical expenses of the insured group.

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State Medicaid programs generally assume the risk of health costs only for people who enroll in the program in their state. However, unlike health insurers, Medicaid programs are required to provide health coverage to certain groups, including people with severe, debilitating, or disabling conditions, which can include many people living with rare or inherited diseases. In the case of sickle cell disease, Medicaid pays for about half of the hospitalizations and emergency department visits for people with the disease. Since Medicaid programs tend to cover higher need, and higher expense patients currently, it is likely Medicaid programs would have a higher risk for covering gene therapy products than would private payers. In the case of a gene therapy product, this risk is further compounded for Medicaid programs because they generally only cover care provided within the geographic confines of their state. Gene therapy is so innovative, a Medicaid program might need to send patients out-of-state to receive treatment at a medical center that is providing the gene therapy.

Managing the Risk of Upfront Costs

Patients tend to incur medical costs over the course of months or even years. Accordingly, over time, private and public payers can spread reimbursement to providers, whether medical offices, hospitals, or pharmacies. Current payment models are not designed to manage the risk of an upfront cost in the hundreds of thousands or millions of dollars for hundreds or thousands of patients. Yes, payers can manage the costs of a few patients with high costs in a year, but combining the risk of unpredictable patient uptake with the higher upfront costs of gene therapy products is likely to destabilize current payment policy models, which in turn could radically diminish patient access to these innovative therapies.

Managing the Risk of Uncertain Outcomes

Private payers, such as health insurers or employers, and public payers, such as Medicaid or Medicare, decide which medical services, medications, and devices to pay for and what price they will agree to pay. Ideally, these decisions are guided by the latest available evidence related to whether and how well a particular medical intervention works for a particular disease or condition. Though public payers have less latitude in these decisions than private payers, gene therapy products present similar dilemmas to both payers. The starkest example of the risk of uncertain outcomes for gene therapy is the case where a payer incurs a high upfront cost for a product that is expected to cure a disease, but the gene therapy does not cure the disease.

Payment Policy Approaches to Improve Access to Gene Therapy

Options to address the cost, timing, and predictability risks outlined above include:

- Basing payment on agreed-upon outcomes
- Spreading costs out over time
- Sharing risk across multiple payers

Basing payment for gene therapy products on agreed-upon outcomes, also referred to as outcomes-based agreements, value-based payments, and alternative payment models, is a payment policy approach both private and public payers can use to lower the risk of upfront costs and uncertain outcomes. With this model, the payer provides a portion of the cost of the gene therapy product when the patient first uses it but only pays the remainder of the cost if and when the patient reaches certain clinical milestones. While most attractive to payers, this policy approach requires assessing "clinical value" appropriately, most significantly by centering patient and family input. This approach is the least likely to ensure patient access or equitable access to treatment as different payers will have different assessments of value.

Spreading costs out over time, also called amortization models or annuity payments, allows payers to pay a portion of the total cost of the gene therapy product over months or years. This approach reduces the risk of unpredictable patient uptake, at least somewhat, because it allows payers to pay for only the patients they have currently enrolled and only for that month's "portion" of the complete gene therapy treatment. These models can also be combined with the outcomes-based agreements described above. This payment policy approach balances the needs of payers to manage upfront costs and risks with gene therapy product companies' need to be paid for innovative products. This approach is likely to support reasonable patient access to innovative therapies.

Sharing risk across multiple payers, for example, across health insurers or across a group of state Medicaid agencies, allows private or public payers to manage the risks of unpredictable patient uptake and the high upfront costs of gene therapy. Kate McEvoy, the executive director of the National Association of Medicaid Directors, summarized the current payment policy mismatch: "The key argument is whether the investment in curative therapies would offset future costs. But it will be extraordinarily difficult for the state programs to solve this on their own." It will be difficult for any single payer or entity to address payment for gene therapies – and therefore patient access – independently.

In response to the concerns of public payers, in particular, the state Medicaid agencies that are most likely to enroll patients needing gene therapy products, the Centers for Medicare and Medicaid Services (CMS) has proposed a new payment policy model called The Cell & Gene Therapy Access Model. While individual state Medicaid agencies have been negotiating value-based arrangements with drug makers since 2018 – Oklahoma was the first – the new, voluntary CMS model would allow multiple

state Medicaid agencies to structure, coordinate, and negotiate price agreements with gene therapy product makers. Additionally, CMS will provide technical assistance to states executing these complex agreements. This payment policy approach could address all three risks listed previously related to making innovative gene therapies accessible to patients, but it is the most difficult to implement. Still, as Medicaid agencies are the most likely to provide health coverage to patients who could benefit from gene therapy in the future, it is promising that CMS is already laying the groundwork for this kind of adaptive payment policy.

The Future of Gene Therapy Product Access for Patients

The increasing availability of innovative gene therapy products creates new questions for health care payers and policymakers about what should be covered, for which patients, and at what price. In the case of gene therapy products, though, the primary barrier is the current mismatch between need and availability. While the thousands of gene therapies currently being investigated may produce more than 50 products reaching nearly a million patients in the next decade, that leaves millions more patients who still need treatment, not just amelioration of their symptoms. More than 20 million people living in the U.S. have peripheral neuropathy, just one form of neuropathy. While gene therapy products may eventually become available to slow the progression or even cure peripheral neuropathy, much more research and development will be necessary to reach this goal.

To support the development of gene therapy products, policies addressing cost, risk, and outcomes will need to be altered or created anew. Ensuring patient access will require policy approaches that center patient and family input, assess value appropriately, and develop new payment models. The treatment future for patients is bright, as long as advocates can continue their efforts to create payment policies that ensure patients can access innovations.

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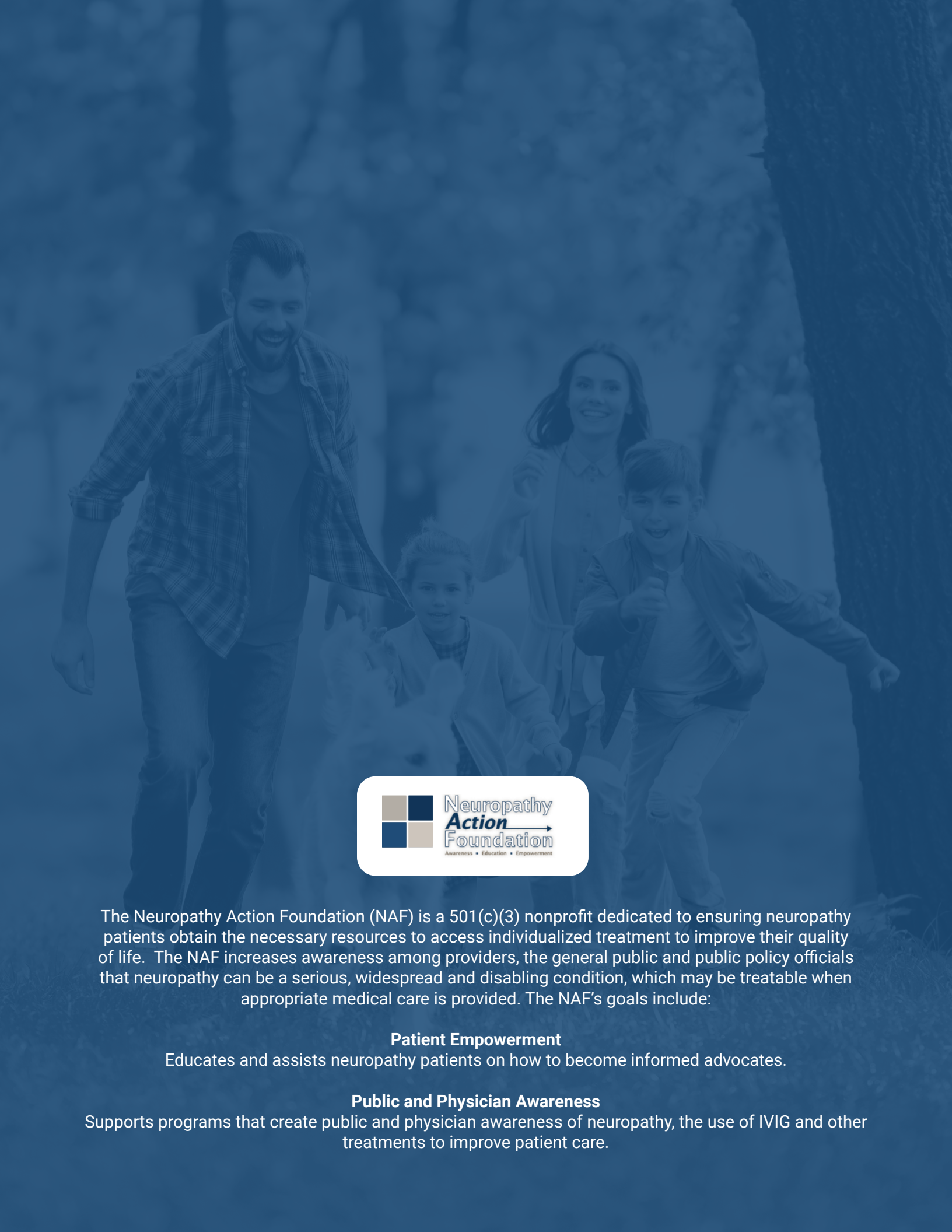

The Neuropathy Action Foundation (NAF) is a 501(c)(3) nonprofit dedicated to ensuring neuropathy patients obtain the necessary resources to access individualized treatment to improve their quality of life. The NAF increases awareness among providers, the general public and public policy officials that neuropathy can be a serious, widespread and disabling condition, which may be treatable when appropriate medical care is provided. The NAF's goals include:

Patient Empowerment
Educates and assists neuropathy patients on how to become informed advocates.

Public and Physician Awareness
Supports programs that create public and physician awareness of neuropathy, the use of IVIG and other treatments to improve patient care.