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# Parkinson's Disease Monitor & Commentary

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*Practical Analysis on Today's Findings in Parkinson's Disease*

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## *From the editor...*

ANDREW D. SIDEROWF, MD

Research unraveling the biology of Parkinson's disease (PD) has identified an array of proteins that may be relevant to diagnosis, prognosis, and treatment. In this issue, two articles in this area of research are reviewed by our invited experts. Both see promise but ultimately remain circumspect: Dr. Kevin Biglan, from the University of Rochester, acknowledges the potential for α synuclein as a biomarker, while Dr. Claire Henchcliffe, of Weill Cornell Medical College, remains open to the potential for leucine-rich repeat kinase-2 (LRRK2) to become a target of therapy.

In contrast, gene therapy for PD may be closer to clinical application. In reviewing the results of a sham-controlled trial in patients, Dr. Tanya Simuni of Northwestern University calls the findings a proof of principle. However, she points out that the therapy targets the symptoms, not the underlying pathophysiology. Maybe better gene targets will be the answer, and to that end, Dr. Vivianna Van Deerlin from my own institution is favorably impressed with a study that associates genetic mutations in the histocompatibility region with an increased risk of PD. However, she sees a long road to validation of specific gene targets.

Secondary analyses of a major multicenter study looking at evidence for non-motor symptom control with the MAO B inhibitor rasagiline are evaluated by Dr. Daniel Weintraub, also from the University of Pennsylvania. He characterizes these analyses as provocative in regard to demonstrating protection against disease progression. Lastly, we ask Dr. Nabila Dahodwala, who is also from my center, to look at a study suggesting that there are substantial racial disparities in PD care in the United States. She notes that this is not the first set of data that has made this assertion.

In our new sections, Dr. Jayne Wilkinson steps into the Q&A corner to talk about the role of telehealth in PD, while I spar with Dr. Michael Okun of the University of Florida about the viability of gene therapy as an alternative to deep brain stimulation for the current generation of patients with PD.

This issue is representative of the mix of clinical and experimental studies and topics we try to cover in *PD Monitor & Commentary*. As always, comments and suggestions are welcome. Please feel free to reach me at info@delmedgroup.com.

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**NEW: CONTROVERSIES IN PD AND Q&A WITH JAYNE R. WILKINSON, MD**

PD Monitor & Commentary

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Dr. Kevin Biglan, Dr. Nadia Dahodwala, Dr. Claire Henchcliffe, Dr. Tanya Simuni, Dr. Vivianna Van Deerlin, and Dr. Jayne Wilkinson have nothing to disclose.

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# In This Issue

## Commentaries



## Q&A with Jayne R. Wilkinson, MD



## Controversies in PD

# AAV2-GAD gene therapy for advanced Parkinson's disease: A double-blind, sham-surgery controlled, randomized trial.

**First Author and Institution:**
Peter A. LeWitt, MD, Wayne State University, Detroit, Michigan.

**Citation:**
*Lancet Neurology.* 2011;10:309-319.

**Objective:**
Assess effect of bilateral delivery of adeno-associated viral vector (AAV2)-glutamic acid decarboxylase (GAD) therapy for treatment of Parkinson's disease (PD).

**Type of Study:**
Multicenter, double-blind, sham-controlled, surgical trial.

**Result:**
The group receiving gene therapy showed significantly greater improvement in motor scores over baseline relative to those in the sham-surgery group at the end of 6 months of follow-up.

**Conclusion:**
In a small but controlled trial, the efficacy of AAV2-GAD surgery in the absence of serious adverse events supports the promise of gene therapy in neurological diseases.

In the treatment of PD, gene therapy has the potential to address key molecular steps in the disease pathogenesis. In previous experimental and then open-label clinical studies in which the GAD gene was inserted into the subthalamic nucleus, improvement in movement symptoms has been reported.

In this double-blind, phase-2, randomized, sham-controlled trial, 22 patients were randomized to receive the GAD gene delivered by the AAV2 and 23 patients received the same bilateral stereotaxic procedure but without active therapy. All patients had had symptomatic PD for at least 5 years. The primary outcome measure was change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) 6 months after the procedure.

The off-medication UPDRS scores decreased (improved) in both groups relative to baseline, but were significantly greater in those receiving the AAV2-GAD therapy relative to the sham group (-8.1 versus -4.7; $P$=0.04). When a score reduction of -9.0 points was employed as a cut-off, improvement was achieved in 50% of those who received the gene therapy versus 14% of those treated with the sham procedure. Adverse events were slightly more common in those treated with gene therapy, but these were generally mild and resolved. The most common were headache (seven versus two patients) and nausea (six versus two patients).

The results support the benefit observed previously in open-label studies and encourage a larger clinical trials program. The results also suggest that gene therapy to alter neurochemical systems is feasible and may provide an alternative to conventional drug therapy.

**Commentary:**

**Tanya Simuni, MD**
**Director, Parkinson's Disease and Movement Disorders Center**
**Northwestern University**
**Chicago, Illinois**

*This study provides an important proof of principle for the concept of employing gene therapy in progressive neurological diseases, and, as the authors suggest, supports a larger study to further explore this approach.*

*The major strength of this study was that it was sham-controlled. We know from previous experiences in PD and other neurological disorders that there can be a significant placebo effect from treatment. In fact, this study did show significant improvement in UPDRS scores from baseline in both groups. However, it is important to recognize that the effect of the gene therapy was limited to an improvement in symptoms. Neither the current data nor the hypothesis regarding the effect of the gene therapy predicts any significant change in the natural history of the disease.*

*Relative to deep brain stimulation, which has been available for almost 15 years, the advantage of gene therapy is that it does not require any implantation of hardware. We do not, of course, yet know anything about long-term safety. Ultimately, while these data are promising, the real need is for therapies that will address the underlying disease mechanism and will lead to disease modification rather than treatment of the symptoms, but a demonstration of benefit and safety with gene therapy is very important.* ■

# Detection of elevated levels of α-synuclein oligomers in CSF from patients with Parkinson disease.

**First Author and Institution:**
Takahiko Tokuda, MD, PhD, Kyoto Prefectural University of Medicine, Kyoto, Japan.

**Citation:**
*Neurology.* 2010;75:1766-1772.

**Objective:**
Evaluate α-synuclein as a biological marker of Parkinson's disease (PD).

**Type of Study:**
Prospective, controlled comparison using ELISA.

**Result:**
Levels of α-synuclein oligomers and the oligomers/total α-synuclein ratio in the cerebrospinal fluid (CSF) had sensitivity and specificity for PD.

**Conclusion:**
Even in patients with mild and early PD, increased levels of α-synuclein provide good sensitivity for distinguishing patients from individuals without PD, suggesting this may be clinically useful.

The early symptoms of PD include an array of nonspecific complaints such as depression, constipation, and hyposmia. Motor symptoms develop only after advanced stages of neuronal loss in the substantia nigra, and these can be generated by pathologies other than PD. A readily measurable biomarker may facilitate both early identification of PD and early initiation of therapy.

Based on evidence that soluble oligomers of α-synuclein are elevated in the brains of individuals with PD and other synucleinopathies, this study was conducted to determine whether α-synuclein could be a useful biomarker for identifying patients with PD. The levels of α-synuclein oligomers and the oligomers/total α-synuclein ratio were measured in the CSF of individuals with PD, progressive supranuclear palsy, Alzheimer's disease, and age-matched controls without a neurologic disease.

Relative to the 28 controls without a neurologic disease, the 32 patients with PD had highly significant increases in α-synuclein oligomers and the oligomers/total α-synuclein ratio ($P<0.0001$). While the oligomer levels provided a sensitivity of 75% and a specificity of 87.5% for a diagnosis of PD, the ratio provided a sensitivity of 89.3% and a specificity of 90.6%. The oligomer levels were also significantly higher in patients with PD than in the 35 patients with Alzheimer's disease ($P<0.001$), and the 18 patients with progressive supranuclear palsy ($P<0.05$).

The data led to the conclusion that α-synuclein demonstrates promise for the diagnosis of PD and possibly for presymptomatic screening in high-risk patients.

**Commentary:**

**Kevin M. Biglan, MD, MPH**
**Associate Professor of Neurology**
**Director, NPF Center of Excellence**
**Clinical Director, MIND Unit**
**University of Rochester School of Medicine and Dentistry**
**Rochester, New York**

*This study demonstrates that α-synuclein is a sensitive and specific biomarker when comparing patients with PD to normal controls. This is a critical and necessary first step for the evaluation of a potential biomarker in PD. However, it is not clear from this study that measuring α-synuclein is a useful tool to distinguish patients with PD or any other synucleinopathy from another type of pathology in patients with ambiguous symptoms early in the course of illness. In addition, while the authors contend that levels of α-synuclein may correlate with PD stage and duration of illness, variability in α-synuclein expression with disease severity is not well supported in the cross-sectional results and will need additional validation.*

**This study demonstrates that α-synuclein is a sensitive and specific biomarker when comparing patients with PD to normal controls.**

*Although the methodology used to evaluate α-synuclein in the series of studies performed by this group is appropriate, the conclusions may be strong for the data provided. While α-synuclein may ultimately be a useful biomarker in PD, it is not yet clear from these or other published data that measuring α-synuclein will be a meaningful diagnostic marker or surrogate measure in future clinical trials.* ■

# Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease.

**First Author and Institution:**
Taye H. Hamza, MSc, New York State Department of Health Wadsworth Center, Albany, New York.

**Citation:**
*Nature Genetics.* 2010;42:781-785.

**Objective:**
Identify genetic markers of Parkinson's disease (PD).

**Type of Study:**
Genome-wide association study (GWAS) comparing patients and controls.

**Result:**
In addition to replicating previous associations, this study found a new genetic association between the human leukocyte antigen (HLA) region and sporadic and late-onset PD.

**Conclusion:**
A genetic link between PD and the HLA region, which is involved in the inflammatory response, offers a new direction for PD pathogenesis and treatment targets.

The initial gene mutations associated with PD, such as SNCA (4q21) and MAPT (17q21.1), were based on Mendelian evaluations of familial groups. These are valuable for identifying causative genetic mutations in high-risk populations, but may not be useful for understanding mechanisms of sporadic and late-onset PD. GWAS undertaken without case selectivity looking for genetic differences across the entire genome are potentially more appropriate for identifying previously unrecognized genetic links in cases where familial associations are weak.

In this study, GWAS was performed in 2,000 individuals with PD and 1,986 unaffected controls. All of the cases and controls were Americans of European ancestry and from the same geographic areas. More than 800,000 single nucleotide polymorphisms (SNPs) were evaluated. All analyses were adjusted for age and gender.

While the GWAS reaffirmed strong associations with genes previously implicated in the risk of PD, a new genetic association was identified in chromosome 6p21.3, which is known to be important to the HLA system. The variant most strongly associated with PD was rs3129882 in intron 1 of the HLA-DRA. It was a particularly strong predictor of sporadic and late-onset PD, and PD in men.

This finding invites a variety of new theories about the pathogenesis of PD.

**Commentary:**

**Vivianna M. Van Deerlin, MD, PhD**
**Associate Professor of Pathology and Laboratory Medicine**
**University of Pennsylvania**
**Philadelphia, Pennsylvania**

*This is a well-performed study, but it is important to recognize that it is one piece of a larger puzzle. The suggestion that some change in the major histocompatibility complex has a role in PD creates a hypothesis, but this now sets the stage for the important work of replicating the results, creating the models of biological activity, and conducting studies to demonstrate that there is an inflammatory mechanism involved in PD development. I think the findings are very interesting and have the potential to provide an important new direction of research, but I would not put a lot of stock into the one variant that the researchers emphasized, since the GWAS simply points to an area of interest without specifying the actual mechanism. There are numerous confounding factors and a high likelihood that multiple risk alleles are involved in several regions. In fact, the authors of this study did find that an increasing number of risk alleles in the HLA region, as well as other previously identified risk genes such as SNCA, MAPT, and GAK, provide a stronger association with PD than any one single allele, which supports the finding that PD is due to multiple cumulative risk factors.*

**This is a well-performed study, but it is important to recognize that it is one piece of a larger puzzle.**

*I think the study was technically well performed, including an effort to select cases with long-duration PD to reduce the likelihood of misdiagnosed cases and using older controls to increase the likelihood of excluding individuals with latent PD, but the work must now be further replicated and translated into clinical or pathological relevance.* ■

# Inhibitors of leucine-rich repeat kinase-2 protect against models of Parkinson's disease.

**First Author and Institution:**
Byoung Dae Lee, MD, Johns Hopkins University School of Medicine, Baltimore, Maryland.

**Citation:**
*Nature Medicine.* 2010;16:998-1000.

**Objective:**
Evaluate inhibitors of leucine-rich repeat kinase-2 (LRRK2) mutations to prevent neurodegeneration in Parkinson's disease (PD).

**Type of Study:**
Series of studies in experimental models.

**Result:**
LRRK2-induced neurodegeneration is kinase dependent and can be prevented by kinase inhibitors.

**Conclusion:**
The study advances evidence that neurotoxicity induced by LRRK2 activity is a mechanism of PD in patients with a genetic susceptibility. Drug therapy may halt this process.

PD associated with LRRK2 mutations does not differ from idiopathic PD by any clinical or neurochemical characteristics. It has been hypothesized that treatment of LRRK2 mutations, which produce neurotoxicity, might prevent or reverse PD in susceptible individuals.

In a series of in vitro experiments and animal model studies, the goal was to identify inhibitors of LRRK2 activity that leads to neurodegeneration, as a strategy for providing neuroprotection in PD. In the first step, 84 kinase and phosphatase inhibitors were screened for their ability to reduce LRRK2 autophosphorylation and LRRK2-mediated phosphorylation of myelin basic protein. Eight inhibitors were selected that produced substantial inhibition for both substrates. Further experiments were conducted to evaluate the direct effects of these inhibitors on LRRK2 relative to other kinases, such as Raf. Finally, the authors used a herpes simplex virus (HSV) amplicon-based mouse model of PD, in which wild type or mutant LRRK2 DNA could be delivered into the striatum, with mutant LRRK2 delivery leading to dopamine neuronal loss in the substantia nigra. Two LRRK2 inhibitors identified in the previous experiments (GW5074 and indirubin-3'-monooxime) were administered intraperiotoneally to test for their ability to prevent neurotoxicity in vivo. Both protected against loss of dopamine neurons caused by G2019S mutant LRRK2.

This series of studies confirms that inhibitors of LRRK2 kinase activity can be identified, and that these inhibitors protect against LRRK2 activity both in vitro and in vivo, providing a basis for clinical LRRK2 inhibitor development.

**Commentary:**

**Claire Henchcliffe, MD, DPhil**
**Associate Professor of Neurology**
**Weill Cornell Medical College**
**New York, New York**

*LRRK2 is the most common genetic cause of autosomal-dominant PD (1.6% of PD cases with sporadic PD, and in the Ashkenazi population, 18% of sporadic and 30% of familial PD cases). This makes LRRK2 an important potential target for treatment. How the mutations act to cause neuronal damage in PD is unknown, but evidence suggests that kinase overactivity is key. Therefore, individuals with LRRK2 mutations would seem to be excellent candidates for "personalized" clinical intervention based upon this target (and ultimately for attempting prevention through preclinical intervention).*

*This study, although a brief communication, is supplemented by almost 30 pages of carefully ordered experiments, examining in vitro effects of potential LRRK2 inhibitors at the biochemical level (kinase activity), cellular level (primary cortical neurons transfected with LRRK2), and in vivo in a highly interesting mouse PD model. Candidate compounds were whittled down to ultimately provide proof of principle that LRRK2 kinase inhibition can indeed provide neuroprotection in this mouse model of PD. Of course, there are a number of issues needing clarification, particularly, how well does screening kinase inhibitors work when we do not know the kinase's true physiologic substrate? The mouse model in this study is based upon introduction of viral (HSV)-mediated gene delivery into the striatum, with presumed retrograde transport into the substantia nigra. It will therefore be interesting to see if the results can be replicated in other LRRK2 models. As a first step, however, these data are cause for optimism, and will rightly encourage expanded efforts.* ■

# A double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study): Prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and non-motor outcomes.

**First Author and Institution:**
Olivier Rascol, MD, PhD, Toulouse University Hospital, Toulouse, France.

**Citation:**
*Lancet Neurol.* 2011;10:415-423.

**Objective:**
Provide secondary analyses from a large study of rasagiline for Parkinson's disease (PD).

**Type of Study:**
Double-blind, placebo-controlled, multicenter trial with early- versus late-start comparison.

**Result:**
In the placebo-controlled phase, rasagiline treatment was associated with a decreased need for additional antiparkinsonian therapy. Relative to a late start, early-start rasagiline provided better long-term Unified Parkinson's Disease Rating Scale (UPDRS) scores for activities of daily living (ADL).

**Conclusion:**
Early-start rasagiline, compared with delayed initiation, improves long-term functional outcomes in patients with PD. ADL scores may better capture disease progression than motor performance scores.

The previously published ADAGIO study randomized 1,176 patients to initial therapy with rasagiline, a monoamine oxidase (MAO) B inhibitor, or placebo, switching the placebo subjects to the MAO B inhibitor at 36 weeks. Early-start rasagiline, which was administered either as a 1-mg or 2-mg daily dose, met all study endpoints for the UPDRS score at the 1-mg dosage, consistent with a disease-modifying effect.

In this secondary analysis, one of the primary goals was to evaluate the effect of rasagiline treatment on UPDRS subscores and on non-motor symptoms.

Of the multiple findings reported, the 1-mg dose of rasagiline was found to provide a 59% reduction in the hazard ratio of starting an additional antiparkinsonian medication relative to placebo at 36 weeks ($P$=0.0002). The protection was almost exactly the same for the 2-mg dose.

Both doses significantly improved UPDRS motor subscores and ADL subscores, and the 1-mg dose also improved the mentation subscore at 36 weeks compared with placebo.

Both doses were associated with less fatigue at 36 weeks versus placebo, and the 1-mg dose was associated with better non-motor experiences of daily living. At 72 weeks, the early-start group had better ADL subscores with the 1-mg dose than the delayed-start group.

The study also found rates of disease progression, as measured by UPDRS total score, to be less than anticipated in the placebo group. Specifically, those with the lowest baseline UPDRS scores progressed more slowly than those with the highest baseline scores.

For comparisons of disease progression, the authors conclude that ADL scores may be more useful than conventional UPDRS motor scores.

**Commentary:**

**Daniel Weintraub, MD**
**Associate Professor of Psychiatry and Neurology**
**University of Pennsylvania**
**Philadelphia, Pennsylvania**

*This secondary analysis generated a number of provocative preliminary findings. While the previously reported ADAGIO study results raised the possibility that rasagiline might slow progression of PD, these new findings are helpful by showing that patients may be able to delay the need for a second antiparkinsonian drug. The support this study provides for non-motor benefits from rasagiline, including reduction of fatigue, is also clinically relevant.*

*This preliminary evidence for benefit on non-motor symptoms strengthens the role of rasagiline as a first-line agent in PD. However, there are several important limitations of the study. While these results are consistent with non-motor benefits associated with several other dopaminergic drugs, patients had low baseline scores for non-motor symptoms overall. It is also important to note that the UPDRS instrument has not been validated to detect changes in non-motor symptoms. While it should be kept in mind that these were secondary or post-hoc analyses that are best understood as hypothesis generating, these data from a very well-conducted trial are helpful for encouraging the studies that would provide validation.* ■

# Racial and social disparities in Parkinsonism.

**First Author and Institution:**
J. Patrick Hemming, MD, University of Maryland, Baltimore, Maryland.

**Citation:**
*Archives of Neurology.* 2011;68:498-503.

**Objective:**
Assess racial and socioeconomic disparities in presentation of Parkinson's disease (PD).

**Type of Study:**
Cross-sectional data collected at a single center.

**Result:**
Disease severity and disability from PD increase as income and education level fall. African-Americans have greater disability than whites even after controlling for income and education.

**Conclusion:**
The reasons for the disparities in disease severity for individuals of African-American race, low income, and less education should be identified and addressed to improve outcomes.

Disparities in the care of many diseases have been observed on the basis of race or socioeconomic status. The causes of these disparities are generally considered to be multifactorial and may include access to care and awareness or perceptions about the value of care. Differences in the management of PD on the basis of race have not been well studied.

In the current investigation, disability and disease severity measures were compared by race, income, and educational level in a tertiary hospital with a movement disorders center. The population included 1,159 patients with parkinsonism, of whom 93.4% were white and 6.1% were African-American. Approximately 80% had a diagnosis of PD. The annual income was greater than $50,000 in 61.2%, and 62.7% had completed college.

Greater disability was observed in African-Americans relative to whites on the Unified Parkinson's Disease Rating Scale (UPDRS) (53.0 versus 42.8; $P<0.001$). African-Americans were also less likely to be prescribed dopaminergic medications (20.6% versus 41.1%; $P=0.01$). The difference was greatest for newer medications. Lower income and lower education levels were also associated with greater disease severity and disability. Racial differences in disability persisted after controlling for these variables.

Disparities between disease severity and the likelihood of receiving specific treatments were observed when stratifying patients by race, education, and income. According to the authors, complex factors preclude a conclusion that care is administered differently on the basis of these variables alone. Identification of the source of these disparities is essential for correcting outcome differences.

**Commentary:**

**Nabila Dahodwala, MD**
**Assistant Professor**
**Department of Neurology**
**University of Pennsylvania**
**Philadelphia, Pennsylvania**

*This is a well-performed descriptive study that helps to draw attention to a potential problem in the optimal management of patients with PD. Although the data suggesting that there are disparities in care among patients with PD stratified by race, education, or income remain relatively limited, such disparities are well documented in many other diseases. These data provide a basis for clinicians to consider and discuss barriers to care, including socio-economic obstacles. However, one of the problems is that the source of these disparities remains undetermined, so it is not clear what strategies are needed to eliminate these inequities. It could be an issue of patient attitudes about treatment, physician biases, or how physicians and patients communicate about different treatment options, or it might be a product of the structure of the health care system and the way that referrals are made. One consideration in assessing these data is that the study was conducted at a tertiary center, which may limit the relevance to other types of settings where patients receive care. Less than 30% of individuals with PD are treated at specialty centers, and we do not know if the disparities are better or worse among the patients who are not referred to tertiary care.*

*While this study is important for increasing awareness of the problem, clearly we now need studies that will explain why these differences in care exist. Once we understand the causes, we can begin to address the underlying problems.* ■

Q&A

WITH

**Jayne R. Wilkinson, MD**
Associate Clinical Director
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Assistant Professor of Clinical Neurology
University of Pennsylvania
Philadelphia, Pennsylvania

**Question:** What are the practical applications of telehealth for patients with Parkinson's disease (PD)?

**Answer:** Telehealth is a broad term used to describe the delivery of health-related services via telecommunication technologies. This rapidly expanding and innovative field has received an immense amount of attention throughout the world as its numerous merits and seemingly endless possibilities to revolutionize medical care delivery systems are explored and developed. From transmitting vital signs and other health-related data over a period of time, to a live, face-to-face video encounter with your patient, the possible applications of this technology are innumerable. The many advantages—including cost-effectiveness, increased access, and patient-centered care—have quickly brought telehealth to the attention of leadership in the medical community, insurance industry, and beyond.

Telehealth is an innovative solution to many of the challenges faced by both providers and patients in the field of PD. The largest challenge lies in access to care; obtaining quality, multidisciplinary care is often limited by geography. As a neurological subspecialty, fellowship-trained movement disorder neurologists are more concentrated in urban areas and tend to practice in close proximity to other specialists utilized in caring for these patients (such as physiatrists, speech pathologists, and geriatric psychiatrists). This leaves more rural, less densely populated areas relatively underserved. Additionally, patients' symptoms often limit access to care. As mobility decreases and caregiver burden increases, traveling to a provider's office can be more challenging than is often realized.

Telehealth has many interesting applications. Within large healthcare systems, such as the Veterans Affairs Medical Center, a subspecialist at a larger centralized site can perform consultations by way of video conferencing with patients and/or providers at distant sites. This reduces travel times and costs for patients and allows medical facilities to capitalize on the investment of hiring subspecialists; similarly, subspecialists can focus their practice in their area of expertise and interest. It is efficient, it is cost-effective, and reports indicate both providers and patients enjoy equal satisfaction compared to in-person visits.

Home-based video technologies even allow patients to undergo evaluation and management in the comforts of their own home. Clearly, video conferencing has limitations, including the inability to physically examine patients, but much is gained from taking a patient history, simple observation, and visual inspection. For example, patients who have intermittent symptoms such as tremor or dyskinesia that are difficult to determine by history could be observed directly and management could be directed appropriately. For the same reasons, telehealth allows patients with PD to enhance their care by increasing access to additional specialists needed to treat the myriad of associated symptoms such as depression, speech/swallowing difficulties, and falls. Telehealth could provide a means to administer resources such as nursing, cognitive-behavioral therapy, Lee-Silverman Voice Treatment, and even physical therapy.

Telehealth in PD easily encompasses more than telemedicine, which refers specifically to clinical services. There are numerous opportunities to extend educational materials and information with these technologies. Home devices can upload instructional videos, publications, and web links. Questionnaires can be implemented, with data returning to the provider in an organized, useful format. Support groups and other psychosocial resources can also be orchestrated more easily if they are more accessible, and decentralized medical centers can "dial-in" to hosting medical centers. Telehealth may also provide a means to conduct some aspects of clinical trials and facilitate research.

Physicians writing prescriptions for medicine will remain the cornerstone for most disease management. However, telehealth will allow these physicians to be anywhere in the world and provide comprehensive care and numerous resources for their patients. What makes telehealth in PD uniquely innovative is both its solution to care-access challenges and its wide applicability to clinical, educational, and other aspects of comprehensive care.

# Controversies in PD

## PRO Opinion

**Andrew D. Siderowf, MD**

*Associate Professor of Neurology*
*Parkinson's Disease and*
*Movement Disorders Center*
*University of Pennsylvania*
*Philadelphia, Pennsylvania*

Gene therapy has captured the imagination of many in the medical community as a potential curative treatment for PD as well as for other challenging disorders. The great question has always been: Can it live up to its promise? In the case of PD, a reasonable measure of success would be whether gene therapy can prove itself to be at least as useful as DBS.

DBS has been available for over a decade as a treatment for advanced PD and a number of studies have confirmed its effectiveness. As an example, Weaver and colleagues in the VA cooperative study showed that DBS is clearly superior to best medical therapy based on traditional clinical outcomes.[1] In another study, Deuschl and colleagues demonstrated a similar superiority to medical therapy on measures of health-related quality of life.[2] Again analyzing the VA cooperative study data, Follett and colleagues showed that DBS targeting either the subthalamic nucleus or globus pallidus pars interna is effective, but there are some important differences both in safety and treatment effects for the two sites.[3]

However, these same reports have raised significant safety concerns about DBS. In the VA cooperative study, approximately 40% of subjects who had DBS also had at least one adverse experience.[1] Subtle cognitive decrements were observed in subjects who had stimulation of the subthalamic nucleus, in particular.[3] In addition, long-term follow-up of patients after DBS shows that clinical benefit tends to decline over time.

Gene therapy has the potential to address the limitations of DBS, and there is recent evidence it has begun to justify the lofty expectations that have been placed on it. In a randomized, double-blind trial, LeWitt and colleagues showed that implanting the gene for glutamic acid decarboxylase (GAD) improved clinical symptoms in patients with advanced PD.[4] Although the magnitude of the clinical benefit was modest, this study is important because it shows that gene therapy can have clinical efficacy when tested in a rigorously conducted clinical trial. (See page 3 for a summary of and commentary on the LeWitt study.)

In another study, Marks and colleagues explored the effectiveness of delivery of the gene for neurturin for patients with advanced PD.[5] Neurturin is a naturally occurring structural and functional analogue of glial-cell-derived neurotrophic factor (GDNF). In theory, neurturin possesses the kind of biological activity that would be expected in a disease-modifying treatment. The primary analysis of this study showed that neurturin gene therapy produced the same effects as placebo at the prespecified 12-month primary outcome analysis. However, the study continued for another 6 months, and at 18 months of follow-up, the benefit of gene therapy appeared to be increasing relative to placebo. This is a very intriguing result because it suggests precisely the type of improvement that would be expected from a disease-modifying treatment.

Undoubtedly, DBS has revolutionized the care of patients with advanced PD. However, in spite of a full portfolio of well-conducted studies, there is scant evidence that DBS alters long-term outcomes. Recent evaluations of gene therapy, described above, show that it can be effective when tested in the most rigorous trial settings, and suggest that molecules like neurturin have the potential to change the natural history of the disease.

Unlike DBS, gene therapy is not a mature technology; it is still growing and improving. As understanding of PD improves, it is likely that better molecular treatments for PD, using gene therapy as a delivery system, will offer greater immediate clinical benefits than are currently possible, as well as neuroprotective effects. This combination will make gene therapy clearly preferable to DBS.

At the rate that technology moves in the 21st century, it is an entirely reasonable proposition that the next generation of gene-therapy innovations will arrive in time for the current generation of patients with PD.

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# The Question: Will gene therapy for Parkinson's disease (PD) be a viable alternative to deep brain stimulation (DBS) for the current generation of patients?

## CON Opinion

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Hailed as a major breakthrough for PD research, investigators from multiple institutions throughout the United States recently published an important paper on gene therapy in *Lancet Neurology* (see page 3).[1] The study was a double-blind, sham-controlled, randomized trial, and was one of the largest of its type to be performed in actual patients with PD. Although the results were not as robust as what has been observed with DBS stimulation and with other therapies, the door seems to have swung open for the possibility for gene-therapy approaches in PD.[2,3]

Motor scores on the United Parkinson's Disease Rating Scale (UPDRS) were used as the primary outcome. Sixty-six patients were included in the study, and 23 were assigned to receive sham surgery and 22 assigned to gene-therapy infusion. What is interesting about this study was that the investigators designed a completely sham procedure in order to be sure that there was a difference between the gene-therapy group and the sham-operated group. The motor scores improved by 8 points in the gene-therapy group, and by nearly 5 points in the sham group. This was a significant difference favoring the gene-therapy group. Only 21 sham-surgery patients and 16 gene-therapy patients of the original 66 were analyzed for primary outcomes, meaning that the study was smaller than one may have hoped for, as several patients were excluded from the analysis due to misplaced catheters or mechanical failures. Importantly, the adverse event and safety profile was reported as excellent, with the most common side effect being headache (seven patients in the gene-therapy group and only two in the sham group complained of this symptom).

Although the results of this study were positive, patients should not come away with false impressions and with false hopes. This type of gene therapy was targeted as a symptomatic approach to address levodopa-responsive PD issues. It was not designed as a neuroprotective approach, nor was it a disease-modifying approach. The benefits were mainly mild improvements in the motor symptom scale score. Although the therapy group fared better than the sham group, gene therapy did not perform better than DBS performed in the same target (as reported by other recent studies).[2,3]

The future of gene therapy for PD we hope will be bright. The lessons from early studies such as the one published in *Lancet Neurology* should point us in the right direction. Larger numbers of patients will need to be examined, outcomes optimized, and safety documented. Additionally, there are basic science questions remaining to be answered, such as "How long will viral-mediated gene expression last?" The transplant trials in patients with PD taught us important lessons, including the appearance of delayed complications (one of which, runaway dyskinesia, proved to be a limiting issue for continuation of the therapy), and we must be careful to document the presence or absence of long-term, delayed adverse events with gene therapy.

Hopefully, gene-therapy approaches can be modified to address nonmedication-responsive symptoms of PD. Remember, this current gene-therapy approach was aimed at achieving symptomatic improvement of levodopa-responsive PD symptoms. The field, however, remains in desperate need of therapies targeting both motor and non-motor symptoms that are resistant to levodopa and other therapies. These symptoms include but are not limited to walking, balance, speech, swallowing, cognition, mood, and sexual dysfunction.[4]

We remain very encouraged about gene therapy and its possibilities for future use in patients with PD. But the therapy in its current form will not replace DBS for addressing levodopa-responsive symptoms and response fluctuations in PD.

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