**The Phosphodiesterase 10 Positron Emission Tomography Tracer, [18F]MNI-659, as a Novel Biomarker for Early Huntington Disease**

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**IMPORTANCE** In Huntington disease (HD) striatal neuron loss precedes and predicts motor signs or symptoms. Current imaging biomarkers lack adequate sensitivity for assessing the early stages of HD. Developing an imaging biomarker for HD spanning the time of onset of motor signs remains a major unmet research need. Intracellular proteins whose expression is altered by the mutant huntingtin protein may be superior markers for early HD stages.

**OBJECTIVE** To evaluate whether [18F]MNI-659 (2-(2-(3-(4-(2-[18F]fluoroethoxy)phenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-4-isopropoxyisoindoline-1,3-dione), a novel phosphodiesterase 10 positron emission tomography (PET) ligand, is a sensitive marker for striatal changes in early HD.

**DESIGN, SETTING, AND PARTICIPANTS** A cohort of individuals with HD, including premanifest (pre-HD) or manifest with motor signs (mHD), underwent clinical assessments, genetic determination, [18F]MNI-659 PET imaging, and brain magnetic resonance imaging. Age-matched healthy volunteers (HVs) also received clinical assessments and PET and magnetic resonance imaging.

**MAIN OUTCOMES AND MEASURES** Binding potentials (BPn ds) were estimated for brain regions of interest, specifically within the basal ganglia, and compared between participants with HD and the HVs and correlated with markers of HD severity and atrophy of basal ganglia nuclei.

**RESULTS** Eleven participants with HD (8 mHD and 3 pre-HD) and 9 HVs participated. Ten of 11 HD participants had known huntingtin CAG repeat length, allowing determination of a burden of pathology (BOP) score. One individual with HD declined CAG determination. All participants with mHD had relatively early-stage disease (4 with stage 1 and 4 with stage 2) and a Unified Huntington’s Disease Rating Scale (UHDRS) total Motor subscale score of less than 50. The HD cohort had significantly lower striatal [18F]MNI-659 uptake than did the HV cohort (mean, −48.4%; P < .001). The HD cohort as a whole had a reduction in the basal ganglia BPnd to approximately 50% of the level in the HVs (mean, −47.6%; P < .001). The 3 pre-HD participants had intermediate basal ganglia BPn ds. Striatal [18F]MNI-659 uptake correlated strongly with the severity of disease measured by the clinical scale (UHDRS Motor subscale; R = 0.903; P < .001), the molecular marker (BOP; R = 0.908; P < .001), and regional atrophy (R = 0.667; P < .05).

**CONCLUSIONS AND RELEVANCE** As a promising striatal imaging biomarker, [18F]MNI-659 is potentially capable of assessing the extent of disease in early mHD. Furthermore, [18F]MNI-659 may identify early changes in medium spiny neurons and serve as a marker to predict conversion to mHD. Additional studies with larger, stratified cohorts of patients with HD and prospective studies of individuals with pre-HD are warranted.

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Early disease detection provides a window of opportunity to evaluate initial disease processes and potentially intervene before significant tissue destruction. However, for several degenerative brain conditions, including Huntington disease (HD), significant cell loss exists before the emergence of identifiable signs or symptoms. Nuclear imaging has been shown to have the potential to detect changes in brain biomarkers at an earlier stage in neurodegenerative diseases than can be detected by the clinician. For illnesses involving changes in the brain striatal nuclei, such as HD, several imaging biomarkers have been evaluated. Phosphodiesterase 10 (PDE10) is a particularly promising marker of early striatal neuron changes. We conducted a study in early HD using a novel positron emission tomography (PET) radiotracer, [18F]MNI-659 (2-(2-(3-(4-(2-[18F]fluoroethoxy)phenyl)-7-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)-4-isoproxyisindoline-1,3-dione).

Alterations in striatal neurons underlie disease pathology in a wide range of brain disorders, from neurodegenerative conditions such as HD to mental illnesses such as addiction. Accurate clarification of the extent and timing of these changes would be beneficial in understanding and treating these diseases. Phosphodiesterase 10 is a promising candidate biomarker of striatal function. Cyclic nucleotide PDEs are ubiquitously expressed, but individual PDE genes display tissue specificity. Unlike most PDE gene families, the PDE10 family consists of only one gene and gene product with 2 coexpressed splice variants, present almost exclusively in the striatum. Phosphodiesterases function by degrading cyclic nucleotides, thus playing roles in many diverse cellular functions. Inhibitors of PDE10 are in development for several diseases including schizophrenia, cognitive dysfunction, and hyperkinetic movement disorders. In HD mouse models, inhibition of PDE10 normalizes molecular abnormalities and, furthermore, slows loss of MSNs.

Medium spiny neurons are among the earliest neurons lost in HD, and substantial loss occurs before the onset of motor abnormalities. As a marker of MSN loss, PDE10 is an excellent candidate for biomarker development owing to its high level of expression, striatal specificity, and expression within the cell body and throughout cellular compartments. Furthermore, in mouse models of HD, PDE10 is among the first proteins to be downregulated in MSNs, perhaps due to direct interference of PDE10 expression by the mutant huntingtin protein. A previous in vitro study identified [18F]MNI-659 as a potential PET radiotracer with high specificity for PDE10. This has been confirmed in vivo in non-human primates. Studies in healthy volunteers (HVs) have shown highly specific uptake in the striatum, good test-retest reliability, accurate estimation of striatal binding potentials by a noninvasive method, and acceptable whole-body radiation dosimetry with no identified safety concerns. In the studies presented here, we evaluated [18F]MNI-659 PET imaging as a biomarker of human striatal PDE10 expression in HD across early disease stages.

### Methods

#### Study Population

The study procedures were approved by the New England Institutional Review Board. Written informed consent was obtained from all research participants, and they received a stipend. Individuals were recruited for this study through local neurologists and the Institute for Neurodegenerative Disorders’ clinical database. Twenty individuals were enrolled, including 9 HVs and 11 participants with HD: 3 with premanifest HD (pre-HD) and 8 with manifest HD (mHD). Participants were considered as pre-HD if they had genetic confirmation of an expanded trinucleotide repeat (>39 CAG repeats on chromosome 4p16.3) in the range expected for HD and no apparent motor manifestations specific for HD (ie, a Unified Huntington’s Disease Rating Scale [UHDRS] Motor subscale [UHDRS-M] score of 0 ascertainment by a movement disorders specialist). Individuals with mHD met International Statistical Classification of Diseases, 10th Revision, diagnostic criteria for symptomatic HD. Two of the 8 patients with mHD exhibited psychiatric manifestations and subtle motor changes without chorea. Participants were aged 18 years or older and were considered medically stable by the clinical investigators. The HV participants had no history of neurologic disease and no current neurologic symptoms. All participants underwent a complete physical and neurologic examination before the study including medical history, electrocardiogram, blood hematology and chemistry testing, and urinalysis. Caffeine ingestion was restricted for 24 hours before imaging and the HVs had no nicotine exposure for 6 months before imaging. Although neither caffeine nor nicotine is known to interfere with PDE10 measurements, these pharmacologic agents were restricted in this early study because they could theoretically affect PDE10 measurements. Brain magnetic resonance imaging (MRI) was obtained on all participants. Individuals with HD were evaluated using the UHDRS-M, the Total Functional Capacity (TFC) scale, and a UHDRS diagnostic confidence level. All clinical assessments were performed by the investigator. The HD stage was assigned according to the TFC scale (stage 0, pre-HD; stage 1, TFC score 11-13; stage 2, TFC score 7-10; stage 3, TFC score 3-6, and stage 4, TFC score 1-2). The diagnostic confidence levels include 0 (normal), 1 (<50% clinical confidence), 2 (50%-89% clinical confidence), 3 (90%-98% clinical confidence), and 4 (>99% clinical confidence), with 4 representing “motor abnormalities that are unequivocal signs of HD,” and 3 representing “motor abnormalities that are unequivocal signs of HD.” For the pre-HD group, the predicted time to a clinically definite HD diagnosis was determined by the formulas of Langbehn et al. Clinically definite HD was defined in the present study as a score of 4 on the UHDRS diagnostic confidence level. The burden of pathology (BOP) (age × [CAG repeats – 35.5]), which estimates the genetic burden adjusted for age, was calculated for both the mHD and pre-HD participants.

#### ([18F]MNI-659 PET Imaging

The clinical doses of [18F]MNI-659 were prepared in the radiochemistry laboratory at Molecular NeuroImaging, LLC,
New Haven, Connecticut. The radiolabeling with $^{18}$F was accomplished by reacting $^{18}$F fluoride with the MNI-659 labeling precursor, followed by purification and formulation into a solution containing ascorbic acid, polysorbate 80, ethanol, and normal saline as previously described. Participants received a target dose of 5 mCi (±0.5 mCi) of $[^{18}F]MNI$-659 and a mass dose of no more than 5 μg over a 3-minute infusion period.

All participants completed brain imaging after injection of $[^{18}F]MNI$-659 immediately followed by serial dynamic imaging (HR+ PET camera; Siemens). Serial, dynamic 3D PET images were acquired for 6 frames of 30 seconds, 4 of 1 minute, and 4 of 2 minutes, followed by 5-minute frames for a total imaging time of up to 90 minutes. Images were reconstructed in a 128 × 128 matrix (zoom, 2) with an iterative reconstruction algorithm (ordered subset expectation maximization, 4 iterations, 16 subsets), a post hoc Gaussian filter of 5 mm, and corrections for randoms, scatter, and attenuation.

**Magnetic Resonance Imaging**

Magnetic resonance images were obtained using a 1.5-T scanner with a 3-dimensional T1-weighted magnetization-prepared rapid gradient-echo sequence (Espree; Siemens). The MRIs were used to generate anatomy-based regions of interest (ROI) for analysis of regional $[^{18}F]MNI$-659 binding. Basal ganglia nuclei volumes were estimated by manually delineating structure margins followed by summation of pixels from all levels in which the nucleus was visible. The volumes presented are the total bilateral volumes for each structure.

**Image Analysis**

For each participant, PET images were co-aligned with the brain MRI to generate anatomy-based ROI for analysis of regional $[^{18}F]MNI$-659 binding. The cerebellum was used as a reference region. Standard uptake values were calculated for the basal ganglia nuclei (globus pallidus, caudate, putamen, and striatum [ie, caudate + putamen]) and the cerebellum normalizing to the injected dose, as well as the participant’s weight and height. The data presented are the mean of both sides. Binding potentials were determined as previously described using the simplified reference tissue method with the cerebellar cortex as reference tissue. In addition, striatal binding potential (BPnd) was estimated as a ratio of $[^{18}F]MNI$-659 uptake in the striatal volume of interest to uptake in the cerebellar volume of interest. Notably, BPnd and standard uptake value ratios are unitless measures of signal concentration or intensity within the volume determined on MRI—not total uptake within an ROI. Therefore, a reduction in these measures would largely be independent of and in addition to ROI volume loss.

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<th>HD Stage</th>
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<th>UHDRS-M Score</th>
<th>TCS</th>
<th>UHDRS Behavioral</th>
<th>TFC</th>
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Abbreviations: BOP, burden of pathology; HD, Huntington disease; HV, healthy volunteer; NA, not applicable; ND, not done; TCS, total chorea subscore; TFC, Total Functional Capacity; UHDRS-M, Motor subscale of the Unified Huntington’s Disease Rating Scale.

* Included in the HD cohort were both premanifest HD (HD-06, HD-09, and HD-10) and manifest HD (all other HD cases). Both groups were similar for mean age (46.1 HV vs 46.5 HD) and other characteristics (see text), except for the preponderance of women in the HD group. For the HD cohort, from the UHDRS are presented the total Motor subscale score (UHDRS-M; maximum score, 124), the TCS (maximum score, 28), the behavioral assessment (maximum score, 88), and the TFC (maximum score, 13). The BOP could not be calculated for HD-01, who declined genetic testing.
Results

Participant Characteristics
Twenty individuals completed $^{[18F]}$MNI-659 PET imaging. The HV group comprised 5 men and 4 women with a mean age of 46.1 years (range, 28.9-70.7 years). The HD participants included 2 men and 9 women with a mean age of 46.5 years (range, 19.9-67.1 years). The demographic and clinical characteristics are provided in the Table. The ages of the HV and HD cohorts were similar. The mean UHDRS-M score for the HD group was 18.5 (range, 0–48). The mean BOP score for the 10 HD participants with known CAG repeats was 347.7 (range, 220-646). Six of the 8 mHD participants had a UHDRS diagnostic confidence level of 4 (ie, >99% confidence). The other 2 mHD participants had subtle, nonspecific motor symptoms. On the basis of the TFC scores, 4 mHD participants had stage 1 HD (TFC score, 11-13) and 4 had stage 2 (TFC score, 7-10). The 3 pre-HD individuals had UHDRS-M scores of 0 and diagnostic confidence levels of 0 or 1. None of these 3 pre-HD participants had motor signs, but 1 had nonspecific behavioral symptoms. Of the 3 pre-HD and 2 mHD participants with a diagnostic confidence level of 0, 1, or 2, the predicted time to clinically definite symptomatic conversion (ie, the time to >50% annual risk of conversion) was 5 to 10 years for participant HD-10, 10 to 15 years for patients HD-06 and HD-07, and 15 to 20 years for patients HD-08 and HD-09.

MRI Analysis
Total volumes for the caudate, putamen, globus pallidus, striatum, and basal ganglia were measured (eTable in the Supplement). As expected, based on previous studies of nuclear volumes in early HD, the caudate nucleus showed the greatest mean reduction in volume. In addition, as expected in a cohort of individuals with early HD, the mean reductions in volumes were modest (<11% mean reduction in the mHD cohort). The volumes of the nuclei in the HV cohort were comparable to the volumes reported in HV cohorts in other published studies. The mean volume losses in the nuclei were less pronounced than volumes reported in other studies of patients with mHD and more closely resembled late pre-HD cohorts, even though most participants in this cohort had mHD. However, mHD in the present study was more clinically mild than in most comparative mHD groups. This finding supports the assertion that the mHD cohort in the present study represented patients spanning the early stages of HD.

PDE10 PET Imaging
All participants underwent 90 minutes of PET imaging following injection of $^{[18F]}$MNI-659. The mean radioactivity injected was 4.79 mCi (range, 4.42-5.05 mCi) and the mean mass dose was 0.22 μg (range, 0.080-0.390 μg). There was rapid $^{[18F]}$MNI-659 distribution and high retention throughout the basal ganglia. No technical failures occurred in the present study and all participants who received the injection completed the study. Imaging using $^{[18F]}$MNI-659 PET was generally well tolerated by the HV and HD participants. Three adverse events were possibly related to the radiopharmaceutical injection procedures or scanning procedures: headache (n = 2) and nausea (n = 1); all were rated as mild and resolved spontaneously.

The uptake of $^{[18F]}$MNI-659 was high in all basal ganglia nuclei (globus pallidus > putamen > caudate). Figure 1 shows a typical pattern of uptake in 3 planes in an HV participant, with intense uptake specifically in these nuclei and very low signals in other brain regions. The progression of loss of signal within the basal ganglia can be seen clearly in the 4 images presented in Figure 2. The pre-HD participant in Figure 2 had a reduced signal compared with the HV; the 2 individuals with mHD had a further reduced signal, especially HD-11, who had the highest BOP and UHDRS-M scores and lowest TFC score among the participants.

The large reduction in the mean (SD) basal ganglia BPnD between the HV and HD groups was statistically significant (HV, 2.88 [0.50] and HD, 1.51 [0.83]; P < .001 by a 2-tailed t test), as well as selectively within the mean striatum (HV, 2.79 [0.52] and HD, 1.44 [0.81]; P < .001 by a 2-tailed t test). Figure 3 demonstrates that this difference existed to a similar extent and was significant in each of the 3 basal ganglia subnuclei, with the 3 HD individuals clustering among those in the HD cohort with the least signal loss. Despite the small number of participants, the mean reduction in striatal BPnD in the mHD compared with...
the pre-HD participants was statistically significant (mHD, 1.15 [0.68]; pre-HD, 2.21 [0.67]; P < .05). The 2 mHD individuals with diagnostic certainty scores of 2 or less also had less signal loss compared with the other mHD participants, all of whom had diagnostic certainty scores of 4. All of the mHD participants had basal ganglia uptake lower than the lowest of the HVs.

Loss of specific striatal biomarkers assessed by PET imaging should correlate with loss of striatal volume determined by MRI. Published pathologic and imaging studies5,25,42-44 show that the loss of caudate volume is the most sensitive marker of early regional atrophy in HD. Loss of [18F]MNI-659 uptake in the caudate correlates with reduction in MRI volume (eFigure in the Supplement). In the present cohort, reduction in [18F]MNI-659 uptake was more pronounced than caudate volume loss. Nine of the 11 participants with HD had [18F]MNI-659 loss greater than 1 SD below the mean of our HV cohort, including all of those with mHD. In contrast, only 5 of the 11 HD participants had a caudate volume that was greater than 1 SD below the HV mean. The mean caudate volume loss of the HD cohort relative to the HV cohort was −14.3% (21.6%) compared with a caudate loss of [18F]MNI-659 uptake of −49.2% (30.8%). For the striatum as a whole, the mean volume loss in the HD cohort was −11.4% (19.5%) compared with a loss of −48.4% (30.4%; P < .001) of [18F]MNI-659 uptake. As expected, the loss of striatal volume correlated with the loss of [18F]MNI-659 uptake (R = 0.667; P < .05).

We considered the possibility that the changes in signal observed between these groups derived from the expected differences in nuclei volume owing to HD-associated atrophy. This effect would be most pronounced in smaller or narrower structures, such as the putamen tail, and less in larger, more spherically shaped regions. We estimated the atrophy-related signal loss differences in the putamen in 4 participants spanning the range of disease severity. The signal loss differences never exceeded more than 3% between 3 individuals (HV-03, HD-02, and HD-10). For HD-11, clearly the most affected individual in our cohort, there was a signal loss difference ranging from approximately 7% in the globus pallidus to approximately 19% in the caudate compared with the HV. Although this is notable in the patient with more extreme volume loss, it cannot account for the degree of reduction in [18F]MNI-659 uptake observed in the present study.

Within the HD cohort as a whole (mHD and pre-HD), the decrease in [18F]MNI-659 PET binding demonstrated a strong inverse correlation with cellular pathology as estimated by BOP (Figure 4A) (R = 0.908; P < .001). Furthermore, the PDE10 loss also strongly correlated with the clinical measure of severity, the UHDRS-M score (Figure 4B) (R = 0.903; P < .001). Among the
HVs, there may have been a weak inverse correlation of the striatal signal with age (approximately −0.7%/y; R = 0.659; P = 0.54), but this does not account for the correlations seen with BOP (which corrects for age) or the UHDRS-M scores. With the development of a larger HV database, BPnd in each group could be age adjusted to further refine the observed correlations.

Discussion

Identification of sensitive and reliable biomarkers of disease progression and severity remains an unmet need for several neurodegenerative diseases, including HD, to facilitate basic research and hasten drug development.5-6 Standard MRI assessments, such as volumetrics, have revealed regional volume loss in early pre-HD.5,25-27,42,46 However, while the average regional volume loss can be relatively large in pre-HD, the measure is variable and has significant overlap with healthy controls even through stage 2 HD. Other MRI methods such as diffusion tensor imaging and MR spectroscopy, may be more useful as early HD biomarkers.4,47 but are still in the early stages of evaluation. Changes in striatal markers revealed by nuclear imaging (PET and single-photon emission computed tomography) have been reported6-48-52 for the dopamine D2 receptor, glucose metabolism, and the γ-aminobutyric acid-a receptor, as well as more complex patterns of change in regional glucose metabolism ratios.53 Of these, D2 receptor binding was found to correlate well with the product of age and CAG repeat length,43 but was not a good predictor of conversion to mHD.52 The current biomarkers are inadequate for the reliable early detection and prediction of conversion to mHD, which is a necessity for the development of disease-modifying drugs in pre-HD cohorts.54

As a promising biomarker to detect early HD, PDE10 PET imaging with [18F]MNI-659 correlated strongly with markers of disease severity in this small sample. Several possible reasons exist for this potential superiority over prior imaging agents. First, preclinical studies29-33,35-60 indicated that PDE10 loss is not just linear to neuron loss in the striatum, but also that the mutant huntingtin protein may directly interfere with PDE10 expression, perhaps on levels of both transcription and protein expression. Second, unlike receptors, PDE10 is expressed throughout the perikarya and the processes.8-10 Third, previous studies34 have revealed that [18F]MNI-659 possesses excellent brain penetration, signal to background, and test-retest reliability. The loss of basal ganglia [18F]MNI-659 binding in HD demonstrated in the present study further supports the specificity of the ligand for PDE10.

Although the HD population in the present study represents mild disease from stage 0 through stage 2, the findings show that [18F]MNI-659 and PET imaging can clearly detect loss of striatal PDE10, a biomarker of the MSN pathology expected among individuals with HD. The majority of the observed signal must derive from striatal MSNs; however, an additional contribution from other, smaller populations of cells within these regions, such as interneurons, cannot be excluded. The degree of loss seen in this relatively early HD group, to a mean of approximately 50% of the loss in the control group, is striking when viewed relative to other published imaging biomarkers.4-6,25-27,42,43,45-53 Although with larger sample sizes we might expect some overlap between mild mHD and HV groups, the full separation between these 9 HV participants and 8 mHD individuals in the present study is notable. The correlation with both BOP and the burden of motor symptoms suggests that [18F]MNI-659 PET has the potential to be a useful progression biomarker for early HD and may be superior to other imaging approaches reported.4-6,25-27,42,43,45-53

A different, distinct PDE10 PET tracer ([18F]-JNJ42259152) was recently reported61 to reveal a large reduction in striatal signal in HD. In contrast to our study, the study by Ahmad and colleagues61 did not find any correlations between observed PDE10A tracer binding and clinical disease severity measures. Although this finding supports our conclusion that PDE10 is a robust and sensitive marker of striatal abnormalities in HD, the primary strength of the present study is that [18F]MNI-659 PET correlates strongly with clinical and molecular markers of HD disease severity. Several possibilities exist for this discrepancy, including use of a different tracer, the smaller HD cohort in the Ahmad et al study, or a more clinically advanced cohort in the Ahmad et al study that did not include individuals with pre-HD. Such a finding might be predicted if PDE10 loss reaches a very low level by clinically moderate disease (ie, a “floor effect”).

Although the number of participants with pre-HD in the present study was too small to make definitive conclusions, it is interesting to speculate on these individuals relative to each other and the other 2 groups (ie, HV and mHD). Given that the 3 pre-HD participants were approximately the same age, the participant with the greater CAG repeat length would be predicted to be the first to convert to mHD, consistent with the...
lower striatal $B_{\text{Pnd}}$. It may be that $[\text{18F}]$MNI-659 uptake is lower in individuals with pre-HD in general than in age-matched HVs, but drops into the mHD range near conversion to mHD. The small cohort sizes and lack of prospective imaging data are limitations of the present study. A larger number of participants and prospective observation will be required to test these hypotheses. Further studies will also be required to correlate findings obtained with the use of $[\text{18F}]$MNI-659 PET with specific clinical features or with other imaging biomarkers and to develop methods to reliably identify a population of individuals near the time of conversion for inclusion in clinical trials.

Conclusions

The sensitivity and reliability of $[\text{18F}]$MNI-659 PET for basal ganglia PDE10 in the HV and HD cohorts in this preliminary study demonstrate that this is a promising biomarker for longitudinal studies in pre-HD and mHD, as well as for rapid evaluation of potential HD therapeutics. Furthermore, since many neurologic and psychiatric diseases involve dysfunction within the striatal nuclei, this PET imaging biomarker may have value for studies across a range of brain diseases.

REFERENCES

Call for Papers

JAMA Neurology is announcing a new journal feature, Clinical Challenge, which will be published quarterly, under the section editorship of Lawrence S. Honig, MD, PhD. The goal of this feature is to present short clinical problems to challenge readers to arrive at the correct diagnosis from a small data set, including images. Readers will see a short clinical synopsis and relevant images or laboratory information allowing them to exercise their diagnostic skills. Actual correct diagnosis and a brief discussion will be available on the following page of the journal or on the Discussion tab online. The overall format of this feature will be like that of the current highly successful feature What is Your Diagnosis?, which has been running since January 2011, available on the web quarterly, only online. Clinical Challenge will be the successor to this feature but will be an integral journal section, viewable interactively online and in the print version of the journal, and indexed like other articles. JAMA Neurology welcomes submissions to this feature, for which any submission should include a maximum of up to 3 authors. The format must include (1) a paragraph introducing and describing the clinical case (no more than 250 words); (2) 1 to 3 figures including imaging, electrophysiological, and/or other laboratory data; (3) 4 multiple-choice potential answers for diagnosis; and (4) a paragraph of discussion (no more than 600 words) disclosing the actual diagnosis (confirmed by conclusive tissue pathology, genetic, or other test), and including up to 10 references. We invite submissions through the standard JAMA Neurology submissions process.