The Food and Drug Administration (FDA) recently approved $[^{123}I]$ioflupane ($[^{123}I]$-fluoropropyl-β-CIT), a dopamine transporter (DAT) radioligand, for SPECT to "assist in the evaluation of adult patients with suspected parkinsonian syndromes (PS)." This permits physicians to prescribe $[^{123}I]$ioflupane SPECT scans as part of clinical practice. Advertisements encourage clinicians to order this and patients to request such scans. The key questions for neurologists are as follows: Do $[^{123}I]$ioflupane SPECT scans provide useful data beyond clinical evaluation? Does this information improve patient care?

SPECT measurement of the striatal uptake of $[^{123}I]$ioflupane reflects the integrity of terminal fields of nigrostriatal neurons. People with Parkinson disease (PD) have reduced striatal uptake. In fact, such scans may be more sensitive than the clinical examination to detect nigrostriatal defects. However, loss of striatal DAT occurs in most degenerative PS, including multisystem atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal disease (CBD). Thus, in individual cases, reduced striatal uptake of $[^{123}I]$ioflupane does not distinguish these different conditions. Most clinical studies focused on whether these scans reliably discriminate PS from disorders that clinically resemble PS but without striatal DAT deficiency.

Multiple studies report that DAT SPECT can distinguish PS from essential tremor (ET). ET is chosen as the comparator disorder for many studies since it has normal striatal DAT. The first published study compared DAT SPECT with initial and 6-month follow-up clinical evaluations by movement disorders experts. The goal was to determine whether SPECT predicts the follow-up clinical diagnosis. The subjects had either PS or other various nondegenerative conditions including ET. Imaging correctly identified 23 of 25 with PS, demonstrating that SPECT is almost as good as the follow-up examination. One might argue that DAT SPECT saves 6 months to make the correct diagnosis.

In this issue of Neurology®, de la Fuente-Fernández questions the clinical utility of $[^{123}I]$ioflupane SPECT. He analyzed 2 clinical studies submitted to the FDA by GE Healthcare, the manufacturer of $[^{123}I]$ioflupane. The first compared $[^{123}I]$ioflupane SPECT in normal controls with people with PS or ET. The second study compared baseline and 36-month follow-up clinical evaluations by movement disorders experts with SPECT scans. de la Fuente-Fernández calculated sensitivity, specificity, and positive and negative predictive values for the SPECT assuming that clinical diagnoses were "truth" and did the same calculations for the SPECT data. He found nearly identical diagnostic accuracy of clinical diagnosis and SPECT and suggested that the SPECT findings were redundant. This straightforward analysis demonstrates the limited clinical utility of DAT SPECT. This is not surprising since the gold standard for these studies was clinical diagnosis.

So what are we to do? First, let’s return to the key questions. In these studies, $[^{123}I]$ioflupane SPECT did not provide utility beyond clinical diagnoses. More importantly, relying on these scans rather than neurologic follow-up may have risk. Several years’ follow-up of people with negative DAT SPECTs reveals that some develop idiopathic PD or another PS. If the clinician relied on SPECT for diagnosis, these people would not be treated. Similarly, patients with dopa-responsive dystonia may develop parkinsonism but with normal striatal DAT. Reliance on DAT SPECT could cause clinicians to miss this condition that dramatically responds to levodopa. DAT SPECT could lead to other misdiagnoses. Can we

**To scan or not to scan**

DaT is the question
confirm diagnosis of psychogenic parkinsonism by a normal SPECT, as some suggest. A normal scan does not exclude alternative diagnoses such as dystonic tremor, ET, or drug-induced parkinsonism. Importantly, these scans also do not distinguish among degenerative PSs (i.e., PD vs MSA, PSP, or CBD)—trying to determine, at an early stage, which patients respond to dopaminergic drugs, or at later stages, which respond to deep brain stimulation (DBS). Would a neurologist withhold a trial of a dopaminergic medication based upon a SPECT scan? The response to dopaminergic medication is one of the most clinically relevant outcomes in clinical practice. A 1-month trial of levodopa with a follow-up visit would be a far less expensive alternative than [123I]ioflupane SPECT. Indeed, a conservative estimate indicates that the SPECT scan would cost 5 times more than a short-term trial of levodopa. Thus, the value of [123I] ioflupane SPECT for clinical decision-making remains unclear.

DAT SPECT may, however, have sound uses. Can [123I]ioflupane SPECT help determine how to treat a patient with an asymmetric resting tremor who has not responded to high-dose levodopa? This person may be a candidate for DBS, but should one target the thalamus as would be appropriate for ET, or either the subthalamic nucleus or internal pallidum as done routinely for PD? An abnormal [123I]ioflupane SPECT may reveal a nigrostriatal defect consistent with PD. However, this does not distinguish PD from MSA, and MSA does not respond to DBS. A long-term clinical study is needed to determine whether DAT SPECT scan can help decision making, as opposed to offering moral support to the clinician. While these scans can help define more homogenous groups for research, this use limits generalizability of the study. Finally, since DAT SPECT may be more sensitive to detect a nigrostriatal defect than clinical examination, such scans in an appropriate population at high risk for PD could identify candidates for treatment to forestall disease onset, if such a proven intervention were available.

As clinicians, we must act responsibly. If a test does not improve patient care and alter what we do for them, then we should not order it. Any test has potential undesirable consequences, such as diagnostic inaccuracies leading to inappropriate treatment, lost opportunity for treatment, or subsequent unnecessary follow-up tests. The clinical utility of each new test ought to be evaluated. In this case, the evidence suggests that clinical diagnosis and follow-up may be far more important than relying on [123I]ioflupane SPECT to diagnose and treat PD.

DISCLOSURE
Dr. Perlmuter serves on scientific advisory boards for American Parkinson Disease Association, Dystonia Medical Research Foundation, Missouri Chapter of the Dystonia Medical Research Fund, Greater St. Louis Chapter of the APDA; serves on the editorial board of Neurology<sup>®</sup>; has received honoraria for grant reviews from the Parkinson Disease Study Group; receives research support from Express Scripts, the NIH, the Huntington Disease Society of American Center of Excellence, the Michael J Fox Foundation, CHDI (formerly HiQ Foundation), McDonnell Center for Higher Brain Function: Greater St. Louis Chapter of the American Parkinson Disease Association, American Parkinson Disease Association, APDA Advanced PD Research Center at Washington University, and BJH Foundation; and has provided expert testimony in a medico-legal case. Dr. Eidelberg serves on scientific advisory boards for and has received honoraria from the Thomas Hartman Foundation for Parkinson’s Research, Inc., the Michael J Fox Foundation, and the Bachmann-Strauss Dystonia and Parkinson Foundation; has served as a consultant for Neurologix, Inc. and Merck & Co., Inc.; serves on the editorial board of Annals of Neurology and as Associate Editor for the Journal of Neuroscience, is listed as coinventor of patents re: Markers for use in screening patients for nervous system dysfunction and a method and apparatus for using same; has received research support from the NIH (NINDS, NCRR, NIDCD, NIAID), High Q Foundation, the Dana Foundation, and the Bachmann-Strauss Dystonia and Parkinson Foundation; and has served as an expert in medico-legal cases.

REFERENCES