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To the Editor**:** In their study on the use of florbetapir for positron emission tomographic (PET) imaging of brain β-amyloid,[1] Dr. Clark and colleagues submitted to JAMA median values for PET scan reader scores but withheld critical individual reader score data that Avid Radiopharmaceuticals submitted to the Food and Drug Administration (FDA) on September 17, 2010. FDA analyses of these data show substantial inter-reader variability among independent, extensively trained readers of the florbetapir-PET scans for individuals in the autopsy cohort,[2] emphasizing that florbetapir-PET imaging fails to provide an accurate and reliable assessment of amyloid burden.

The primary endpoint for the autopsy cohort was the correlation between the amyloid burden in the brain as measured by florbetapir-PET, using a pre-specified semi-quantitative visual rating scale (0-4) and cortical amyloid burden by pathology using quantitative immunohistochemistry (IHC). The published measurement of the amyloid burden for this correlation was the median rating of 3 expert independent readers who underwent extensive training, a process that the authors acknowledge "is not likely to be replicated in clinical settings.[1]" Therefore, data on the inter-reader variability for the 3 independent readers is crucial to evaluating the potential clinical utility of florbetapir-PET.

Independent FDA analysis of the data regarding florbetapir-PET scoring by the individual readers for the 35 subjects who underwent autopsy revealed substantial inconsistency among the readers, with sensitivities of 55%, 85%, and 90% and specificities of 80%, 100% and 100%.[2] This analysis assumed that a semi-quantitative score of 0 or 1 was a negative test and a score of 2 to 4 was a positive test, consistent with the authors' approach.

In 8 of 20 autopsy subjects (40%) who had positive IHC for amyloid, at least 1 reader's scoring of the florbetapir-PET scans differed from that of the other 2 readers by 2 or 3 points on the 5-point scale.[3]

The study implemented florbetapir-PET in a rigorously controlled setting with well-trained readers, using patient populations at 2 extremes of the spectra for both age and health. However, despite these optimal conditions, the test yielded disparate results when looking at the analysis of the individual readers. If widely deployed in the real-world setting, with more variability in reader training and skill and in the patient population for whom florbetapir-PET presumably is intended, the performance of the test will most likely be worse. For these reasons, in our opinion the FDA should not approve florbetapir for diagnosis of Alzheimer's disease.

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[1] Clark CM, Schneider JA, Bedell BJ, et al. Use of florbetapir-PET for Imaging β-amyloid pathology. *JAMA*. 2011;305(3);275-283.

[2] Food and Drug Administration. FDA advisory committee briefing document: Peripheral and Central Nervous Systems Drugs Advisory Committee; statistical review and evaluation. December 20, 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240265.pdf. Accessed January 31, 2011.

[3] Food and Drug Administration. FDA advisory committee briefing document: Peripheral and Central Nervous Systems Drugs Advisory Committee; draft clinical review. December 20, 2010. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM240265.pdf. Accessed January 31, 2011.