November 7, 2012

Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244-1850

RE: National Coverage Analysis (NCA) for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431N)

Dear Dr. Hutter, Ms. Burton, and Mr. Caplan:

Piramal Imaging SA (a wholly owned subsidiary of Piramal Enterprises) appreciates the opportunity to comment on the topic regarding beta amyloid positron emission tomography (PET) in dementia and neurodegenerative disease. In this letter, we aim to provide additional evidence that demonstrate the value of beta amyloid PET imaging for physicians as well as patients and their families.

Piramal Imaging is dedicated to developing innovative imaging technologies and bringing new PET tracers to the market after having acquired Bayer Healthcare’s proprietary molecular imaging PET tracer portfolio in April 2012. The most advanced program is Florbetaben, an F\(^{18}\) labeled beta amyloid PET tracer that recently completed Phase 3 clinical trial.

The prevalence and the burden of Alzheimer’s disease (AD) are widely recognized and highlighted by Congress in its passage of the National Alzheimer’s Project Act.\(^1\) Health and Human Services further underscored the imperative for timely and accurate diagnosis of Alzheimer’s disease in the National Plan.\(^2\) Among the research community, imaging experts and clinicians have spearheaded the project, Alzheimer’s Disease Neuroimaging Initiative (ADNI), the NIH’s largest public-private partnership on brain research that aims to define and predict the onset and progression of Alzheimer’s disease.\(^3\) Piramal Imaging is proud and committed to partake in the collective effort to tackle the challenges in the diagnosis and treatment of Alzheimer’s.

Among the current diagnostic tools used in the evaluation of AD, amyloid PET imaging is unique in its ability to detect brain amyloid pathology. There is wide consensus that amyloid deposition in the brain is one of the earliest and most important pathological hallmarks of the disease. An imaging agent that tracks amyloid deposits thus holds a significant promise as a new tool for the evaluation of AD. The merit of such an imaging...
agent was recently validated by the FDA through its approval of Florbetapir. Amyloid imaging represents a significant advance in the complex diagnostic assessment of AD. Neuropsychological tests probe for phenotypes manifested far downstream from the disease origin, whereas CT, MRI and FDG-PET are a step closer as they reveal the presence of neuronal injury, which can be caused by AD or other conditions. Only amyloid PET imaging reveals brain amyloid pathology, which is directly associated with AD. While CSF $\text{A}\beta_{42}$ levels similarly provide evidence for amyloid in the brain, the test requires lumbar puncture, an invasive and sometimes painful procedure that diminishes the diagnostic utility of this test.

Even as we demonstrate the contribution and value of amyloid imaging to AD diagnosis, we are acutely aware and acknowledge its current limitations. We are in agreement with many expert clinicians that the boundaries for the use of amyloid PET imaging should be set as follows:

- It should not be used as a screening tool in patients with no symptoms of cognitive decline
- It should not be used for cases where a physician can make a confident diagnosis based on the clinical features and profiles of the patient
- A positive scan does not establish a diagnosis of AD or other cognitive disorder

**Improving the Accuracy of Current Diagnosis for Alzheimer’s Disease**

The effectiveness of the current diagnostic work-up for AD can be assessed through the overall sensitivity and specificity numbers, as described in detail below. The results show a large variation in both the sensitivity and the specificity of the assessments and, in particular, a rather low average specificity number, which suggests an elevated rate of false positive diagnosis. They partly reflect the current challenges in AD diagnosis: difficulties in diagnosing AD in the early stages and differentiating it from other etiologies. Amyloid PET Imaging - through the application of a negative scan - can help physicians exclude AD as an underlying cause thus reducing the number of false positive diagnosis. Looking forward, the 2011 NIA-AA guideline officially recognized and defined the early stages of AD that exist prior to the appearance of dementia symptoms. The new diagnostic criteria certainly pose challenges for the current symptom-based clinical diagnosis.

Currently a clinically meaningful diagnosis of AD is conducted largely through a diagnostic workup involving medical history and physical exams, lab tests, neurological examination, neuropsychological tests, and structural and functional imaging. Definitive diagnosis is achieved only through histopathological examination postmortem.
It is important to acknowledge the progress made in the diagnosis of AD thus far. As we gain deeper insights into the disease symptoms and progression, the diagnostic criteria and techniques have undergone continuous improvements. Yet, if we were to take stock of our current capabilities, there is still more to be achieved. In an attempt to quantify the effectiveness of the dementia diagnosis, the Quality Standards Subcommittee of the American Academy of Neurology (AAN) conducted a review of studies where the diagnostic value of the standard clinical assessment could be meaningfully measured. The average sensitivity of the studies was 81% (range 49% to 100%), and specificity was 70% (range 47-100%) for “Probable AD”. It is worth noting that the numbers indicate the performance of an entire series of evaluations (the diagnostic workup) repeated over a period of years.

The wide range of sensitivity/specificity numbers and the low specificity score suggest a few problems: first, despite a standard clinical guideline, clinical judgments vary in their robustness for making a correct diagnosis; second, the low specificity score of 70% suggests that the number of false positives is high. In other words, many non-AD cases are falsely diagnosed as AD. It seems that when there are uncertainties involved, physicians rather err on the side of giving positive AD diagnosis thus initiating treatment. While this may ensure timely treatment for those who are truly AD patients, the consequences of incorrect treatments for non-AD patients cannot be ignored. As shown by Mendez et al, treating a fronto-temporal dementia patient with AD symptomatic therapeutics could exacerbate the conditions. Moreover, failure to treat depression because it was misdiagnosed as AD means lost opportunities for patients whose conditions could have been improved.

The sensitivity and specificity numbers are also consistent with the known challenges in AD diagnosis: early diagnosis and differential diagnosis of AD. For example, it is difficult to distinguish Mild Cognitive Impairment (MCI) from dementia, as they share similar clinical features and the differentiation rests solely on whether the cognitive impairment affects a person’s ability to perform daily activities. Thus this is a highly subjective clinical judgment; secondly, it is challenging to isolate AD as the underlying cause when a number of other etiologies, such as frontotemporal dementia (FTD) or Lewy Body Dementia (DLB), are present and can have similar clinical manifestations.

In light of the difficulties in ruling out AD as an underlying cause for dementia, amyloid imaging provides an important tool adjunct to the current diagnostic workup. In the Florbetapir label approved by the FDA, a negative scan means that amyloid is absent and thus increases the physician’s confidence in ruling out AD. Thus a negative amyloid PET scan could help improve the accuracy of the final diagnosis by reducing the probability of false positive diagnosis.
Furthermore, mounting evidence indicates that AD pathologic process begins years before dementia symptoms appear.\textsuperscript{15} The acknowledgement of this body of evidence culminated in the revision of the 1984 guideline with the introduction of two new diagnostic criteria: “MCI due to AD” and “Preclinical AD” in the 2011 NIA-AA guideline. With more nuanced definitions of the early stages of AD when symptoms are difficult to observe through conventional clinical assessment, the clinical and research communities together must look for a diagnostic tool that is best suited for detecting the early stage of AD. This may also entail more advanced analysis of the segmental distribution of amyloid plaques as well as the quantification of amyloid deposits in the brain.

After all, the early stage of AD is where the therapeutic treatments, disease modifying or symptom targeting, are most effective and provide the most benefits for the individual patient and the society as a whole. We acknowledge that current clinical evidence does not support the use of amyloid imaging as a confirmative diagnostic tool of AD. What is undisputed is the value of a negative amyloid scan for improving the diagnostic accuracy of AD, a usage that is approved by the FDA. Its clinical application would give physicians more confidence in their final diagnosis. Faced with the mounting burden of an aging society in the US where the late stage AD accounts for 44% of all AD patients, and the total cost of care for late stage AD is almost 10 times that of the early stage\textsuperscript{16,17}, the quest for the most reliable diagnostic procedure and comprehensive diagnostic workup regimen must move in parallel with, if not ahead of, the quest for the best treatment for Alzheimer’s disease.

**Improved Diagnostic Accuracy Leads to Better Patient Management**

*Current therapeutics for AD are effective in managing symptoms and thus provide tangible benefits for AD patients. Consequently, an accurate diagnosis as early as possible is clinically meaningful by way of initiating the right treatment for AD patients and preventing unnecessary treatments and their associated adverse effects for non-AD patients. In addition to the therapeutic impact, earlier and accurate diagnosis satisfies the psychological and emotional need to know for patients and their families in order to help them plan and prepare for the future.*

Even though no disease modifying drugs are available to cure AD at present, certain therapeutics have proven to be effective in delaying cognitive decline, reducing behavioral problems, and in the long term delaying nursing home placement. Cholinesterase inhibitors have been shown to improve memory and other cognitive functions.\textsuperscript{18,19,20,21} Moreover, treatments have shown benefits for AD patients who exhibit behavioral symptoms such as aggression, hallucinations, wandering or sleeping
difficulties and have reduced caregiver burden as a result.\textsuperscript{22, 23, 24} In studies that have examined the long term effects of cholinesterase inhibitors, results indicate that drug treatment leads to a delay in the need for nursing homes of 18 months on average.\textsuperscript{25} Recognizing the therapeutic value of these treatments, most Medicare Part D sponsors provide coverage for them, including the Part D program’s largest plans UnitedHealth and Humana.

Given the recognized benefits of these prescription treatments for AD, improvement in the accuracy of the diagnosis can indeed lead to better health outcomes for patients. Specifically, this is achieved on two levels: first, as a result of increased number of correct diagnosis, more patients will receive AD therapeutics that help improve their conditions; second, an accurate diagnosis as early as possible will also reduce or avoid the number of unnecessary treatments and their associated adverse effects for non-AD patients.

In addition to the therapeutic impact that amyloid PET imaging may bring, early and accurate diagnosis has intrinsic values for patients and their families. A number of studies have explored their perspectives. In a study of 314 people, 79\% respondents stated that they would want to know early in life if there were a genetic test that predicted whether they would eventually develop AD, even in the absence of a preventative measures or treatment for the disease.\textsuperscript{26} Genetic testing aside, it is worth noting that when asked what they would do with the diagnostic information, respondents pointed to planning, for example, signing advance directives, spending more time with family, getting their finances in order, and etc. In a US study of 200 patients 65 years or older assessing the attitudes of patients regarding the disclosure of AD diagnosis, 92\% respondents would want to be told if they had AD, and the top three reasons were advance/financial planning, to get a second opinion, and to understand/explain symptoms.\textsuperscript{27} Most recently, in an international survey of 2678 people across five countries including the US, Harvard School of Public Health and Alzheimer Europe examined public perception and awareness of Alzheimer’s disease and aimed to identify the views of the general public on the value of diagnosis.\textsuperscript{28} The results not only confirmed previous findings about patients’ and their families’ desire to know, but also found significant public interest in predictive testing. Approximately two thirds of respondents said that, they would get a medical test which would tell them whether they would get Alzheimer’s disease before they had symptoms. These studies reveal a strong demand from patients and their families for the knowledge of an accurate diagnosis, even in the absence of an immediate therapeutic impact.

With aforementioned data and evidence, we believe there is a significant unmet medical need in the clinical diagnosis and overall assessment of Alzheimer’s disease that can
be addressed by beta amyloid PET imaging. Its clinical contribution and value are significant to clinicians, patients, and their caregivers.

We sincerely hope CMS will consider all evidence and provide coverage for the appropriate use of beta amyloid PET scans as a diagnostic tool for the purpose of estimating beta amyloid density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease or other causes of cognitive decline.

We also believe that a complete and fair evaluation of the extensive preclinical and clinical explorative work undertaken is an essential step to encourage the continued development of innovative approaches to in vivo diagnostic imaging.

With a strong commitment to improving the quality of life of patients suspected and/or diagnosed with Alzheimer’s disease, we look forward to working with CMS throughout the NCA process to discuss any of the evidence presented here and provide additional information that may be of help for your consideration. Please feel free to contact Dr. Ludger Dinkelborg, Ph.D., at ludger.dinkelborg@piramal.com.

Sincerely,

Ludger Dinkelborg
Managing Director
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REFERENCES:

7. Ibid.


