ResearchersAgainstAlzheimer's

August 2, 2013

Louis B. Jacques, M.D.
Director
Coverage and Analysis Group
Office of Clinical Standards and Quality
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

VIA ELECTRONIC DELIVERY

Re: Proposed Decision Memo for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431N)

Dear Dr. Jacques:

A little more than one year ago, our government set the bold, ambitious and necessary goal of preventing and treating Alzheimer's disease by 2025. In the year-plus since our nation ratified the first-ever National Plan to Address Alzheimer's disease, a number of departments and agencies throughout the government have demonstrated their commitment to the plan and its goals by the boldness of their actions. We applaud this effort.

As a group of more than 350 of the nation's leading Alzheimer's scientists and clinician researchers, we believe strongly this goal is within reach. However, to succeed, every resource and proven tool that is available in the public and private sector must be marshaled, toward this end. Although we all support the practice of evidence-based medicine, we need to advance the field even as we deliver the highest possible standard of care.

We write to you as members of **ResearchersAgainstAlzheimer's** – a group of scientists, researchers, and clinicians who work on the front lines of the nation's fight against Alzheimer's. We are witnessing in our labs and clinics the progress that is underway to find a better means of treating or preventing this disease, and we are confident that many breakthroughs will materialize over the coming years. That said, we also recognize just how challenging today's environment is for patients, who are entitled to the best care possible, and for physicians, who seek every means to bring diagnostic clarity, hope and appropriate, safe and effective treatments to aging Americans who face the onset of dementia.

Today, the Centers for Medicare & Medicaid Services (CMS)has a unique opportunity to advance the care and health outcomes of a narrow subset of patients who will benefit from an advanced imaging technology: Beta Amyloid Positron Emission Tomography imaging, or PET Aβ. However, last month CMS issued a proposed coverage decision that runs counter to the goal of ensuring every patient receives quality and efficient care, another core goal of our National Plan**. ResearchAgainstAlzheimer's requests that CMS reconsider and revise this proposed decision. Specifically, we request that CMS issue a National Coverage Determination for PET Aβ imaging for carefully defined patients with difficult-to-diagnose memory disorders, especially as described by the Appropriate Use Criteria (AUC) issued by the Amyloid Imaging Task Force (AIT).**

Never has the need been greater to determine the underlying causes of dementia and to deliver the best evidence-based care to Medicare beneficiaries. According to current estimates, only about half of all dementia patients ever receive a diagnosis of dementia. An accurate diagnosis is fundamental to providing appropriate treatment and care for any condition, including those that may lack an abundance of, or even any, disease-modifying treatments. An accurate diagnosis is also vital to well-informed research efforts.

The Importance of Beta Amyloid

The question before CMS at present is what coverage level is appropriate for an FDA-approved diagnostic that when used with PET imaging technology is able to detect levels of beta amyloid in the brain of patients being evaluated for dementia. While not all researchers agree with the "amyloid hypothesis," a definitive diagnosis of Alzheimer's during autopsy is not possible absent the presence of beta-amyloid.[1] Specifically, the radiopharmaceutical Amyvid before CMS is FDA-approved to:

> Estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations.[2]

As CMS itself recognized in its proposed coverage policy, this drug and corresponding imaging technology can be quite valuable in aiding in the diagnosis of memory-impaired patients

[1] http://www.webmd.com/alzheimers/news/20110118/beta-amyloid-may-identify-alzheimers-disease
[2] See FDA Amyvid Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202008s000lbl.pdf

presenting with complex and difficult-to-diagnose cases where, absent such information, a physician is largely left to speculation. Unfortunately, despite recognizing this value and benefit, the agency proposed to provide coverage only to a narrow subset of patients under the highly restrictive Coverage with Evidence Development (CED) policy. Importantly, patients who are scanned under these circumstances will, in most cases, not be told the results of their testing. While we agree that additional data should and must be collected to better understand the value of the technology, restricting all coverage to CED is de facto non-coverage given the tremendous amounts of time, cost, and other resources necessary to implement a CED study.

If existing technologies were able to provide accurate and precise diagnoses of memory disorders today, this would be a non-issue. But the reality is that there is a dearth of such technologies, as evidenced by the unacceptably high numbers of patients who go undiagnosed or inaccurately diagnosed. One recent study by Kirson et al presented at the Alzheimer's Association International Conference earlier this month, has found that substantial misdiagnosis of Alzheimer's patients with other forms of dementia or Parkinson's Disease results in "substantial excess costs."[3] By detecting a fundamental indicator of Alzheimer's disease or the absence of such proteins, a beta amyloid imaging test is able to support superior diagnosis of a subset of dementia patients that otherwise present a confounding clinical presentation. And once such a diagnosis is made, the patient and his or her family should then have access to the latest evidence-based care and treatments available – appropriate to their underlying disease pathology.

It is particularly disappointing that in issuing its proposed coverage policy, CMS appears to have completely disregarded the consensus of a leading group of Alzheimer's researchers and clinicians that, under the auspices of the AIT, developed an evidence-based set of Appropriate Use Criteria (AUC) that would limit use of the technology to a narrow cohort of patients. Specifically, the task force determined that PET Aβ was appropriate only for:

- Patients with persistent or progressive unexplained MCI;
- Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation; and
- Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age). [4]

In addition, the AUC also stipulates clearly a sizeable segment of the population for whom the use of such a diagnostic is inappropriate, <u>making clear that the tool is to be used sparingly and judiciously.</u>

Improving Diagnosis and Health Outcomes

[3] See: Kirson, et al. DT-02-04, presented at AAIC 2013, Boston, MA July 2013
[4] See:
http://www.alz.org/research/downloads/appropriate_use_criteria_for_amyloid_pet_alz_and_dem_january_2013.pdf

If the proposed policy is not amended, we are concerned that the misdiagnosis of Alzheimer's disease, as found in the recent immunotherapy phase 3 trials (20% not Alzheimer's), will preempt non-Alzheimer's patients from being properly treated. For example, vascular dementia, which is caused by stroke, and frontotemporal dementia, which is caused by atrophying of the brain's frontal and temporal lobes, are very different than Alzheimer's disease in how they are managed, and treated, yet can be hard to diagnose based solely on clinical presentation. The line between Alzheimer's and frontotemporal dementia is one such case in point that speaks to the need for greater coverage of – and beneficiary access to – PET Aβ. Absent access to more precise diagnostic tools, the situation could result in patients with frontotemporal dementia being treated as if they had Alzheimer's despite evidence that some Alzheimer's medications are potentially harmful to such patients.[5]

If a PET Aβ scan reveals little to no evidence of beta amyloid, the test results would help physicians to rule out Alzheimer's as the cause of a patient's dementia and direct their efforts toward other causes. For example, the absence of beta amyloid should result in consideration of alternate diagnoses including depression, and, in some cases of patients with atypical cognitive impairment who are amyloid negative, it may be appropriate to undertake a trial of antidepressant medication.

If the test indicates a high-level of beta amyloid, that result coupled with additional information, can aid a physician in making a diagnosis of likely Alzheimer's disease and treating the patient accordingly. For some patients, this could include treatment with medications available today to address the symptoms of the disease, leading to improved overall health outcomes. Greater physician confidence in the diagnosis of or exclusion of Alzheimer's disease can result in better medication management. An amyloid-positive PET result that raises confidence in the diagnosis of AD – coupled with additional information – is likely to result in early and appropriate use of specific medication for symptomatic treatment of AD.

Conclusion

ResearchersAgainstAlzheimer's urges CMS to reconsider its proposed decision memo on PET Aβ imaging and to issue a National Coverage Determination that covers the difficult-to-diagnose cohort of dementia patients as outlined in the Appropriate Use Criteria developed by the Amyloid Imaging Task Force. This action is warranted based on the science and available evidence, and is critical to improving care for dementia patients as well as enhancing and expanding our body of knowledge of all forms of dementia. We would be very pleased to discuss this course forward with you at any time and to provide any further information you may request or require. Thank you for your careful reconsideration of this decision.

[5] See: http://memory.ucsf.edu/ftd/matters/memantine

Sincerely,

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