TESTIMONY

of the

American Academy of Neurology

before the

U.S. House of Representatives

Committee on Energy and Commerce

Subcommittee on Health

Re: “Innovation Saves Lives: Evaluating Medicare Coverage Pathways for Innovative Drugs, Medical Devices, and Technology”

Presented by: Natalia Rost, MD, MPH, FAAN, FAHA

July 18, 2023

Summary

- The American Academy of Neurology is the world's largest neurology specialty society representing more than 40,000 neurologists and clinical neuroscience professionals. Our members are dedicated to promoting the highest quality patient-centered neurologic care. Our membership represents the main medical professional treating patients with Alzheimer's disease.
- Our experience working with CMS and relevant stakeholders on the national coverage decision for monoclonal antibody treatments for Alzheimer's disease can shed light on lessons learned and opportunities for improvement to further promote patient access to innovative treatments that are both safe and effective.
- The AAN first engaged with CMS two years ago after the FDA granted accelerated approval for Aducanumab, the first treatment approved in this new class of drugs. We provided feedback on how the coverage determination for this product should be constructed, many of which were incorporated into CMS's final determination
- However, the AAN was concerned with two key aspects of CMS's determination. First, given additional drugs in development in the same class, we were concerned that the determination applied to all new monoclonal antibody treatments for Alzheimer's. Second, we were concerned CMS did not outline how a drug could be removed from this coverage determination if there was demonstrated clinical benefit.
- Due to these concerns, the AAN submitted an initial reconsideration request to CMS in February of 2023 following the publication of evidence relating to the safety and efficacy of lecanemab. After that submission, we engaged directly with the agency to refine our request and provide them actionable recommendations. That work, as well as conversation with other key stakeholders, resulted in the AAN submitting an amended reconsideration request to CMS on June 12, 2023.
- That amended request had two key focal points. The first was asking CMS to remove a subset of patients identified by the AAN's subject matter experts as having peer-reviewed evidence demonstrating the safety and effectiveness of lecanemab from their coverage determination. The second was asking CMS to create an "off ramp" by which new subsets of patients could be removed from the coverage determination as new studies demonstrated that lecanemab was also safe and effective for them.
- The AAN is grateful to CMS for engaging in constructive dialogue with relevant stakeholders throughout this process and we hope it will result in positive changes for the benefit of our patients with neurologic disorders, their families, and their communities.
- As the Subcommittee considers how to ensure patients have access to innovative therapies, the AAN hopes they will look at additional barriers to access. These include the physician workforce shortage, increased use of utilization management tools by Medicare Advantage plans, and the high cost of these drugs.

Written Testimony

First, let me thank Chairwoman Rodgers, Ranking Member Pallone, Chairman Guthrie, Ranking Member Eshoo, and the members of this Subcommittee for inviting me here to represent the American Academy of Neurology on this important topic.

My name is Dr. Natalia Rost. I am a Vascular Neurologist, Chief of the Stroke Division at the Massachusetts General Hospital Department of Neurology and Professor of Neurology at Harvard Medical School. I am a clinician-scientist with internationally recognized expertise in vascular neurology, neuroimaging of cerebrovascular disease, and big-data science applications to personalized clinical outcome prediction in acute stroke.

I am Principal Investigator of the DISCOVERY study, an innovative national clinical research network funded jointly by the NINDS/NIA to address post-stroke cognitive impairment and dementia in diverse US populations. I serve as a Fellow of the American Academy of Neurology (AAN) and American Heart Association (AHA), former President of the Boston AHA Board (2014-2016), immediate Past Scientific Chair of the 2022 NINDS Alzheimer's Disease-Related Dementias Summit, immediate Past Chair of the AAN Science Committee, and I also serve as Associate Editor of the journal *Stroke*.

Among my professional accomplishments, I am particularly proud of my career-long service to the AAN, where I currently serve as President Elect and Vice Chair of the Committee on Public Engagement. I appreciate the opportunity to testify today.

The American Academy of Neurology (AAN) is the world's largest neurology specialty society representing more than 40,000 neurologists and clinical neuroscience professionals. The AAN is dedicated to promoting the highest quality patient-centered neurologic care. A neurologist is a

physician with specialized training in diagnosing, treating, and managing disorders of the brain and nervous system. These disorders affect one in six people and include conditions such as multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease, stroke, migraine, epilepsy, traumatic brain injury, ALS, and spinal muscular atrophy.

For years, the disorders our profession treated had little hope of a cure. Today science has progressed to the point where we have innovative therapies that can slow or stop the progress of many of the conditions we treat, giving new hope to our patients and their families. This continued innovation underscores the importance of the topic we are discussing today, and the Academy applauds the Subcommittee for investigating the ways we can ensure Medicare beneficiaries have access to these new therapies.

One such area where we have seen innovation bring potential hope is the development of monoclonal antibody treatments for Alzheimer's disease. This relentlessly progressive neurodegenerative disorder affects nearly 6.7 million Americans. As the primary medical specialty that treats this disease, our members know all too well the burden that it places on our patients and their families. We fully understand the promise these new treatments hold and know that, while they will not provide a cure, any delay in the progression of Alzheimer's disease could bring additional months or years of peace to millions of Americans.

However, we also remain concerned about the potentially deadly side effects these drugs can cause. The potential for swelling or bleeding of the brain is a risk physicians and their patients will have to weigh, but they can only accurately do so with the appropriate data. That is why when the Centers for Medicare and Medicaid Services (CMS) began deliberations on how to cover these new treatments, we were eager to provide our expertise.

The AAN has been engaged on issues surrounding monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease for more than two years. The goal of the AAN's advocacy has always been to ensure appropriate access to these new therapies for patients in need. Shortly after the accelerated approval of aducanumab in the summer of 2021, the Academy participated in the National Coverage Analysis initiated by CMS to investigate appropriate coverage for aducanumab for the Medicare population. The AAN submitted comments and met with the Coverage Analysis Group at CMS to contribute to that analysis and was ultimately proud to have been cited extensively throughout the resulting National Coverage Determination (NCD). Many of the AAN's recommendations relating to study protocol requirements, care-team design, and loosening of site-of-service limitations were ultimately incorporated into the final NCD.

However, there was one key disagreement the AAN had with the proposed NCD. I will read key sections directly from our comment letter, submitted on February 4, 2022, elaborating on this topic. I will note that this letter was submitted prior to the release of lecanemab's Phase III trial results (appendix 1).

"[T]he AAN is concerned that this NCD is being applied to the entire class of monoclonal antibodies (mAbs) directed against amyloid for the treatment of AD. While aducanumab is currently the only approved therapy of its kind, there are multiple therapies in various stages of the approval process that work through the same mechanism but for which the full body of evidence is not currently publicly available. The AAN is concerned that results from trials in progress for upcoming therapies may demonstrate evidence of meaningful clinical benefits that will not warrant the same restrictions as proposed in this NCD.

The AAN believes that the Coverage with Evidence Development (CED) included in this determination is prudently designed to investigate the safety and effectiveness of these therapies. However, should further study of aducanumab, or any other mAb, yield clinically meaningful results in the treatment of AD, a mechanism must be in place to remove that therapy from the constraints of this NCD and allow widespread access as quickly as possible. **As such, the AAN requests that an "off-ramp" be created within this NCD that would allow for a therapy demonstrating safety and effectiveness to be reconsidered without the need to restart the NCA/NCD process."**

Unfortunately, the AAN's concerns have ultimately come to pass. CMS' decision to implement a class-wide determination and the lack of a nimble process to update the NCD as evidence emerges for impacted products and sub-populations has necessitated a need for further reconsideration of the existing coverage policy.

In February of 2023, following the publication of evidence[1] relating to the safety and efficacy of lecanemab, the AAN sent a letter to CMS broadly asking CMS to open a reconsideration process of the existing NCD so that it could be updated to reflect newly available evidence on lecanemab to ensure appropriate coverage. Following submission of that request, the AAN engaged directly with the agency to refine our request and provide the agency with actionable recommendations (Appendix 2). The result of those conversations, as well as conversations among other key stakeholders, culminated in the amended reconsideration request we submitted to CMS on June 12 of this year (Appendix 3).

[1] Christopher H. van Dyck et al., Lecanemab in Early Alzheimer's Disease, NEW ENGLAND J. MED. (Nov. 29, 2022)

This amended reconsideration request reflects not only the clinical judgment of key subject matter experts within the Academy but also the feasibility of the policy proposed given the existing coverage landscape. Put simply, the AAN has identified a subset of patients for whom there is conclusive peer-reviewed evidence available demonstrating the safety and effectiveness of lecanemab and recommends those patients be removed from the CED requirements to ensure access outside of the existing study requirement. Not only would this relieve these patients from any burdens associated with study participation, but it would also create the clear "off-ramp" that is needed to ensure that CED is not indefinite, nor required of all Medicare beneficiaries, regardless of available evidence. As evidence is gathered on other patient populations, these criteria could be adjusted efficiently to broaden access. We are grateful to CMS for engaging in a constructive dialogue with us throughout this process and we hope it will result in positive changes for the benefit of our patients with neurologic disorders, their families, and their communities. We believe that our experience in providing feedback and working with stakeholders throughout this process can shed light on lessons learned and opportunities for improvement to further promote patient access to innovative treatments that are both safe and effective.

In addition to restrictions imposed by CMS, the AAN is concerned about additional issues that could further restrict access to this innovative treatment. First and foremost, among those concerns is access to a neurologist that can properly diagnose and treat this disease. The United States is facing a physician shortage of between 54,100 and 139,000 physicians by 2034 that will likely be exacerbated by rising rates of physician burnout and early retirement due to the COVID 19 pandemic. One in six Americans live with a brain or nervous system condition, and as our nation's population continues to age the burden of these diseases will continue to grow. **If**

Congress wants to ensure that patients suffering from Alzheimer's Disease can access these innovative treatments, they need to commit to supporting the current neurology workforce and finding ways to expand the number of physicians in the cognitive specialties. The AAN recently submitted a response to a Request For Information from the Senate Health, Education, Labor, and Pensions Committee outlining ways Congress can do that, which you can find attached here in appendix 4.

We are also concerned by restrictions on coverage that could be imposed by the Medicare Advantage (MA) program. The share of Medicare eligible beneficiaries enrolled in MA plans has increased dramatically over the years, with nearly half of the eligible population enrolled in an MA plan[2]. Many of these plans still use restrictive utilization management tools, such as prior authorization requests and step therapy protocols, that can severely impact a patient's ability to access the care their physician prescribes in a timely manner. While we are encouraged by a recent proposed rule from CMS that would reform the prior authorization process in MA plans, we note that the rule would not cover drugs in the Part B program**. We urge Congress to consider legislation that would ensure the growing number of Americans enrolled in MA plans will also have access to this innovative treatment.**

Finally, the AAN is concerned that the high cost of this treatment could provide an additional barrier to access for many Americans. The sale price for lecanemab has been set at $26,500 per year, well above the price range recommended by the Institute for Clinical and Economic Review (ICER). With out-of-pocket costs to patients potentially reaching $6,000 per year, that puts access to this drug out of reach for many Medicare beneficiaries. **The AAN's position**

[2] Meredith Freed et al, Medicare Advantage in 2022: Enrollment Update and Key Trends, Kaiser Family Foundation (August 25, 2022)

statement on prescription drug prices lays out the ways we believe Congress can address this issue—including expanded price negotiation authority for Medicare, transparency requirements, and importation. You can find the entire position statement attached here in appendix 5. We urge the Subcommittee to also consider this important barrier to access as you explore ways to ensure Medicare beneficiaries have access to new and innovative treatments.

I would like to reiterate the AAN's gratitude to the Subcommittee for inviting me here today and to CMS for their continued willingness to work with the Academy to find the best path forward to promote coverage of these new therapies to help our members deliver the best possible care to their patients in need. We look forward to continuing our engagement with the Subcommittee on this important issue.

Appendix 1

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February 4, 2022

Tamara Syrek Jensen, JD
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RE: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease [CAG-00460N]

Dear Ms. Syrek Jensen,

The American Academy of Neurology (AAN) is the world's largest neurology specialty society representing more than 38,000 neurologists and clinical neuroscience professionals. The AAN is dedicated to promoting the highest quality patient-centered neurologic care. A neurologist is a physician with specialized training in diagnosing, treating, and managing disorders of the brain and nervous system. These disorders affect one in six people and include conditions such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease, stroke, migraine, epilepsy, traumatic brain injury, ALS, and spinal muscular atrophy.

The AAN is grateful to the Centers for Medicare and Medicaid Services (CMS) for its diligent response to aducanumab's approval and the agency's attention to the need to ensure that Medicare beneficiaries have access to safe and effective treatments. We understand and appreciate the decision to launch a National Coverage Analysis (NCA) in response to the approval of aducanumab and note that the time and effort required to reach a National Coverage Determination (NCD) is substantial. The AAN appreciates the opportunity to comment on this NCD and notes that we have been engaged with regulators and stakeholders throughout the aducanumab approval and coverage determination process. The AAN's primary objective in responding to this request for comment is to ensure that patients suffering from AD have access to the best possible care and that the search for curative therapies is supported.

Application of NCD to the Entire Class

The AAN notes that we have provided comment to the Food and Drug Administration (FDA)[1] prior to the approval of aducanumab and to

[1] AAN Comments to FDA Advisory Committee on Aducanumab Labeling | October 22, 2020

CMS during the NCA[2] requesting that proof of amyloid biomarker abnormalities should be required for treatment and that treatment should be limited to patients with a diagnosis of mild Alzheimer's disease or mild cognitive impairment (MCI) due to AD (Mini-Mental Status Exam between 24-30 and Clinical Dementia Rating of 0.5). The AAN has also worked to expand access to amyloid positron emission tomography (PET) imaging to confirm amyloid positivity to help identify patients for whom these therapies may be effective. This NCD realizes many of the AAN's priorities. These include coverage of PET to confirm amyloid positivity for prospective patients, limitation of coverage to patients with mild cognitive impairment or mild AD, further clinical trials to confirm clinical benefit, and more inclusive trial data to reflect the diverse patient population affected by AD.

However, the AAN is concerned that this NCD is being applied to the entire class of monoclonal antibodies (mAbs) directed against amyloid for the treatment of AD. While aducanumab is currently the only approved therapy of its kind, there are multiple therapies in various stages of the approval process that work through the same mechanism but for which the full body of evidence is not currently publicly available. The AAN is concerned that results from trials in progress for upcoming therapies may demonstrate evidence of meaningful clinical benefits that will not warrant the same restrictions as proposed in this NCD.

The AAN believes that the Coverage with Evidence Development (CED) included in this determination is prudently designed to investigate the safety and effectiveness of these therapies. However, should further study of aducanumab, or any other mAb, yield clinically meaningful results in the treatment of AD, a mechanism must be in place to remove that therapy from the constraints of this NCD and allow widespread access as quickly as possible. **As such, the AAN requests that an "off-ramp" be created within this NCD that would allow for a therapy demonstrating safety and effectiveness to be reconsidered without the need to restart the NCA/NCD process.** Criteria should be developed to determine which therapies no longer need to be constrained by the CED. The AAN believes that criteria may include clinically meaningful differences in decline on the Clinical Dementia Rating Sum of Boxes (CDR-SB), decreased decline on a cognitive screen, and improvement on a functional screen. The AAN notes that CMS should not view the above criteria as a comprehensive list, but rather as being representative of the types of tools CMS should consider when evaluating the performance of these therapies and welcomes the opportunity to engage with the agency regarding the appropriateness of criteria.

Should the FDA approve a new amyloid therapy that is proven to be safe and clinically effective, the AAN is deeply concerned that patients may be denied access while waiting for this NCD to be altered or otherwise be limited to accessing the newly approved product through a trial under the proposed CED. Since the approval of aducanumab in June 2021, the AAN believes that providers have demonstrated their ability to make decisions jointly with their patients on whether a new drug is appropriate for each given circumstance. Should each new amyloid therapy start from a position of extremely limited coverage, regardless of demonstrated benefit, patients without the means to access care under the NCD will effectively be barred from accessing treatment. **The AAN requests that this NCD be**

[2] AAN provides comments to CMS on coverage for aducanumab | August 9, 2021

limited to only aducanumab while establishing a process to allow new therapies in this class to be individually judged on their safety and effectiveness.

Coverage with Evidence Development (CED)

The AAN notes that we have voiced concerns over the process that resulted in the approval of aducanumab. We are grateful to CMS for the thought and intention behind requiring CED for its use. This tool will allow CMS to gather additional data on aducanumab that will be integral in informing care decisions in the future. The following are suggestions that the AAN has regarding the implementation of CED to maximize its investigative reach while minimizing disruption to patients and providers.

Hospital-Based Outpatient Setting:

One of the AAN's most pressing concerns with the proposed NCD is the requirement that provision of these therapies be restricted to "hospital-based outpatient settings." While the AAN agrees that close monitoring and access to an adequately trained care team are critical, the "hospital-based outpatient setting" is not the only setting where this therapy can be safely administered. The AAN believes that the proposed requirement would restrict access to care in many clinical practices. A significant portion of trialists in aducanumab's phase three trials, as well as ongoing trials for other mAbs, do not work in this strictly defined setting. Many operate in infusion centers, private practices with robust clinical research centers, or within a large medical center, but not necessarily on a floor or unit that is categorically defined as a hospital outpatient department. **It is critical for patient access and trial integrity that the "hospital-based outpatient setting" requirement be revised to include infusion centers and other settings not strictly designated as a hospital outpatient department.** The AAN believes that rather than implementing this limitation, the agency should focus on ensuring that services are provided by clinicians and staff with expertise in the treatment of AD and promoting communication between the treating clinician and the infusion center to ensure that patients do not receive the mAb when they have amyloid-related imaging abnormalities (ARIA) or another contraindication.

The AAN believes that the first year of treatment is the highest risk for the development of ARIA, so infusions should be provided in an infusion center during this period. After the first year of infusions, we would support flexibility to allow for provision within a home infusion setting, as eligible patients may have transportation challenges and could benefit from the ability to receive home infusion therapy. While a patient is receiving care at home, they should continue to receive care and be monitored by a care team member who has received training in monitoring and caring for patients receiving this class of drug. Care should be given by a physician who can identify appropriate patient populations to receive this medication. This includes coordination of screening studies, including baseline magnetic resonance imaging (MRI), detection of beta-amyloid, and appropriate cognitive evaluations. Appropriate care also includes coordinating ongoing management of the patient as they receive therapy, monitoring for clinical and radiographic signs of ARIA, and general monitoring of the patient's health and wellbeing.

Research Questions:

The AAN fully supports the proposed research questions in this NCD. These questions are well designed to fill gaps in existing data to help patients and providers make appropriate treatment decisions.

Validated Cognitive and Functional Instruments in CED Trials:

The following are examples of instruments that the AAN believes are effective in the measurement of cognitive and functional decline in patients with AD. This list is not necessarily comprehensive but is intended to demonstrate potential considerations for CMS when evaluating instruments:

- Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)
- Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL)
- Alzheimer's Disease Cooperative Study Instrumental Activities of Daily Living (ADCS-iADL)
- Zarit Burden Interview (ZBI)
- Mini-Mental Status Exam (MMSE)
- Montreal Cognitive Assessment (MoCA)
- Katz Index of Independence in Activities of Daily Living (ADL)
- Lawton Instrumental Activities of Daily Living Scale (IADL)
- Functional Activities Questionnaire (FAQ)
- Neuropsychiatric Inventory (NPI)
- Global Clinical Dementia Rating (Global CDR)
- Clinical Dementia Rating Sum of Boxes (CDR-SB)

Clinically Meaningful Improvement:

Alzheimer's disease and associated dementia can lead to many challenges for patients and caregivers. Therefore, meaningful improvement may take many forms. It is also notable that aducanumab, and likely other mAbs that are yet to be approved, do not purport to reverse cognitive decline but instead slow its progression. Stabilization, improvement, or meaningful slowing of decline in cognitive function and independent functioning, both in the community and at home, are the most meaningful outcomes for patients receiving these treatments. These outcomes can be measured by using standardized dementia scales and other functional measures. Examples of dementia scales the AAN would recommend include MMSE, MOCA, CDR-SB, Katz ADL, and Lawton IADL. Due to varying rates of decline among the patient population, even using objective scales, it might be difficult for a patient being treated to tell if their decline is occurring less quickly on therapy. Therefore, insight from the treating physician is necessary. **It is critical that CMS not be overly restrictive in its trial approval criteria as trialists may aim to study a variety of qualitative and quantitative measurements for determining meaningful benefit.**

<u>Patient Criteria:</u>

Inclusion Criteria

The AAN is grateful to CMS for their recommendations, consistent with our advocacy, to limit coverage to patients with proven amyloid positivity and those suffering from MCI due to AD or mild AD dementia.

We appreciate the decision by CMS to allow for coverage of an amyloid PET scan to confirm amyloid positivity. However, limiting coverage to one scan per patient may have the unintended consequence of reducing access for patients who may develop amyloid positivity later in their disease progression. There may also be other circumstances in which the clinician believes an additional scan is warranted. Such circumstances include but are not limited to technical issues with tracer, movement artifact, development of new cognitive symptoms, or the initial scan being done when the patient is not symptomatic. Therefore, the AAN believes that the agency should account for these circumstances and allow clinicians covered by the CED to exercise their professional judgment to request coverage in cases in which an additional scan may be necessary.

Exclusion Criteria:

The AAN recommends that patients should be excluded if their baseline MRI shows four or more microhemorrhages or evidence of superficial siderosis. However, the AAN advises caution in the broadness of exclusion criteria that may prevent trialists from responsibly studying the effect of these new therapies on patients with certain comorbidities. As an illustrative example, 30 percent of patients with AD have concurrent vascular dementia. Patients with anything more than minimal vascular changes on the initial MRI have been excluded from relevant clinical trials in the past. The AAN believes that the frequency of this concurrence may warrant the inclusion of patients with vascular burden in the trial population. The AAN believes that it is prudent to make decisions on the exclusion of these patient populations at the individual trial level with specific consideration of contraindications that may signify a higher risk of ARIA-H or other harmful side-effects.

Health Disparities:

The AAN has fervently advocated for improving the representation of diverse populations in clinical trials. We agree wholeheartedly with CMS' description of the inequity inherent in the research and treatment of AD in Black and Hispanic patient populations. **As such, the AAN recommends that each trial be required to demonstrate the methodology for recruiting and retaining diverse participant populations, as supported by health care institutions around the world and in the USA in alignment with National Institutes of Health standards, including Guiding Principles for Ethical Research[3] and Ethics in Clinical Research.[4] In support of this effort, CMS should work to address disparities based on geography, race, and other socio-economic factors by providing resources to address barriers to trial participation for historically underrepresented populations.**

One such barrier is the potentially prohibitive cost-sharing a patient may be responsible for voluntarily agreeing to participate in these trials that have inherent risks to the

[3] Guiding Principles for Ethical Research | March 16, 2016
[4] Patient Recruitment: Ethics in Clinical Research | October 21, 2021

participant. Furthermore, the AAN has concerns that the likelihood of high out-of-pocket costs will skew access to these trials and, by extension, these therapies towards an unrepresentative patient population. Additionally, the AAN believes that CMS must account for the challenges associated with a double-blind, randomized control trial if patients are responsible for different cost-sharing amounts depending on their receipt of the therapy or the placebo. **Finally, CMS should structure coverage of trial costs to limit financial barriers to participation for patients with limited financial resources due to the impacts that they may have on participant representativeness.**

The AAN appreciates the opportunity to comment on this proposed NCD and the continued dialogue between CMS and the AAN. Our members care for the millions of Alzheimer's patients enrolled in Medicare and are grateful for the thoughtful consideration of these issues. AAN member experts are eager to continue lending expertise to CMS as this NCD is finalized. If you have any questions regarding these comments or seek further input, please contact Matt Kerschner, Director, Regulatory Affairs at mkerschner@aan.com or Max Linder, Government Relations Manager at mlinder@aan.com.

Sincerely,

Orly Avitzur, MD, MBA, FAAN
President, American Academy of Neurology

Appendix 2

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February 02, 2023

Tamara Syrek Jensen, JD
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RE: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease [CAG-00460N]

Dear Ms. Syrek Jensen,

The American Academy of Neurology (AAN) is the world's largest neurology specialty society representing more than 38,000 neurologists and clinical neuroscience professionals. The AAN is dedicated to promoting the highest quality patient-centered neurologic care. A neurologist is a physician with specialized training in diagnosing, treating, and managing disorders of the brain and nervous system. These disorders affect one in six people and include conditions such as multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease, stroke, migraine, epilepsy, traumatic brain injury, ALS, and spinal muscular atrophy.

The AAN is requesting that the Centers for Medicare and Medicaid Services (CMS) begin a reconsideration process for the National Coverage Determination (NCD) published on April 7, 2022, regarding monoclonal antibodies directed against amyloid for the treatment of Alzheimer's Disease (CAG-00460N)[1]. Specifically, the AAN believes that CMS should begin a focused expedited review of the NCD as it pertains to lecanemab (brand name Leqembi). CMS guidance states that a reconsideration request may be granted in circumstances in which the request includes "[a]dditional scientific evidence that was not considered during the most recent review along with a sound premise by the requester that new evidence may change the NCD decision."[2]

Under the current NCD, all monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (mAbs) are subject to Coverage with Evidence Development (CED) requirements upon being granted

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[1]National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N), Centers for Medicare & Medicaid Services (Apr. 7, 2022), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=305 (Apr. 2022 Alzheimer's Decision Memo).

[2] 78 Fed. Reg. At 48167

approval by the Food and Drug Administration (FDA)[3]. The NCD specifies that therapies in this class that are approved based on evidence of efficacy from a change in a surrogate endpoint, as is consistent with the Accelerated Approval Pathway,[4] are only covered in the context of randomized controlled trials. Therapies approved based on evidence of efficacy from a direct measure of clinical benefit may be covered in CMS approved or NIH supported prospective comparative studies.[5][6] In this NCD, and in guidance issued by CMS on the CED requirements, CMS stated that as further evidence becomes available that supports consideration of a change in the coverage status of the item or service, a revised NCD could be expedited.[7][8]

In explaining the purpose of the NCD requirements, CMS noted that "(t)o date, no large, pivotal RCT, or set of RCTs, of an antiamyloid mAb has been completed, with a trial report published in the peer-reviewed medical literature demonstrating a clear (non-conflicting) improved health outcome (i.e., a meaningful clinical benefit in terms of slowing in the decline of cognition and function) for Medicare beneficiaries with AD."[9] CMS further noted that "clear evidence about the clinical benefits and harms of any drug in this antiamyloid mAb class is needed for Medicare beneficiaries with early AD to make, along with their physicians and trusted advisors, informed decisions about whether the treatment is appropriate for them."[10]

Although the AAN has not taken a position on whether lecanemab ought to receive traditional FDA approval, there is consensus among the AAN's member experts and leadership who have reviewed the phase III data that the CLARITY AD trial was well-designed, and its findings are clinically and statistically significant. The AAN concurs with CMS that at the time of the NCD's release, critical questions remained regarding the efficacy of mAb products for the treatment of Alzheimer's Disease. These critical questions were summarized in three specific questions to be addressed through CED. The AAN's answers to those questions and the AAN's interpretation of recently released data are as follows:

a. Does the antiamyloid mAb meaningfully improve health outcomes (i.e., slow the decline of cognition and function) for patients in broad community practice?

   The phase III data from the CLARITY AD trial was published in the *New England Journal of Medicine (NEJM)* on January 5, 2023.[11] The AAN concurs with the authors of the paper, entitled "Lecanemab in Early Alzheimer's Disease" that treatment with lecanemab, "resulted in moderately less decline on measures of

[3] Section I.A. Apr. 2022 Alzheimer's Decision Memo
[4] Section I.B.1 Apr. 2022 Alzheimer's Decision Memo
[5] Section I.B.2 Apr. 2022 Alzheimer's Decision Memo
[6] Sections I.B.3-5 Apr. 2022 Alzheimer's Decision Memo
[7] Apr. 2022 Alzheimer's Decision Memo
[8] Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development, Centers for Medicare & Medicaid Services (Nov. 20, 2014) https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27
[9] Apr. 2022 Alzheimer's Decision Memo
[10] Apr. 2022 Alzheimer's Decision Memo
[11] Christopher H. van Dyck et al., Lecanemab in Early Alzheimer's Disease, NEW ENGLAND J. MED. (Nov. 29, 2022)
("Van Dyck et al.")

cognition and function than placebo." The AAN notes that Alzheimer's disease and associated dementia can lead to many challenges for patients and caregivers. Therefore, meaningful improvement may take many forms. Stabilization, improvement, or meaningful slowing of decline in cognitive function and independent functioning, both in the community and at home, are the most meaningful outcomes for patients receiving these treatments. The AAN believes the findings of the phase III trial are indicative of meaningful improvement. Data presented showed therapeutic benefit on not just surrogate endpoints, such as amyloid clearance, but also cognitive endpoints including the slowing of cognitive dysfunction and a decrease in the decline of activities of daily living. The AAN believes these findings support the need for broader access to lecanemab than currently permitted under the NCD.

b. Do benefits, and harms such as brain hemorrhage and edema, associated with use of the antiamyloid mAb, depend on characteristics of patients, treating clinicians, and settings?

   The AAN believes that, upon further study, patient factors such as disease stage and preexisting level of function will be associated with benefits of treatment and that patient populations that are reflective of the trial populations are likely to derive the same amount of mean benefit. The AAN also believes that certain patient factors are likely to lead to distinct side effect profiles. Preexisting microbleeds, use of anti-coagulants, and the presence of at least one ApoE4 gene variant may indicate higher risk for ARIA-related complications. The AAN is eager for additional study on this class of therapies, and lecanemab specifically, but believes that existing information provides a framework to reasonably stratify benefits and risk.

   In relation to how benefits and harms depend on the treating clinician and setting, the AAN believes that facilities should be appropriately licensed, with trained personnel to administer the medication and monitor patients during infusions. Care should be overseen by trained physicians with experience in treating Alzheimer's disease patients and the expertise needed to monitor for the adverse events associated with this medication, including ARIA E and ARIA H. It is also critical to promote communication between the treating clinician and the infusion center to ensure appropriate adjustments are made to the plan of care should ARIA or other contraindications arise or worsen.

c. How do the benefits and harms change over time?

   The AAN shares CMS' commitment to ensuring patients are receiving the most appropriate and effective treatments possible and that those considerations incorporate the harms and benefits of FDA-approved products over time. However, the AAN believes that this question is not reasonably able to be answered given the existing body of published evidence. The AAN does believe that, while the data indicates that incidence of isolated ARIA H does not decrease with time, the incidence of mixed ARIA is more common in the first six months of treatment.

Although this question cannot be fully elucidated at this time and warrants further study, the AAN does not believe absence of longitudinal data should be sufficient reason for the agency to restrict access to a treatment for patients in dire need, with no other FDA-approved treatment options to meaningfully impact disease progression. There is clear unmet need for the Alzheimer's disease population and the AAN does not believe that it is appropriate to substantially limit patients' access to therapy solely based on this criterion.

Alternatively, CMS could explore how best to work with both the FDA and the manufacturer to ensure that appropriate post-market surveillance occurs and to ensure that the NCD is updated in a timely manner if persuasive evidence emerges indicating either increased risk of adverse events or diminished benefit over time. The AAN believes that real world use of the drug can be a helpful longitudinal tool to further establish how benefits and harms change over time. The AAN will be eager to continue to collaborate with regulators to ensure that patients are receiving optimal care as this data is reported.

Throughout the National Coverage Analysis (NCA) and NCD processes, the AAN repeatedly raised concerns regarding the potential unintended consequences of applying this NCD to the entire class of mAbs for the treatment of Alzheimer's disease. The AAN is concerned that absent a reconsideration of the NCD, patients who could benefit from lecanemab will be denied access, due to restrictions found in the NCD, leading to irreversible disease progression that could have been slowed with treatment. At the time of the release of the NCD, aducanumab (brand name Aduhelm) was the only approved therapy of its kind that would be subject to the NCD, and the available data did not persuasively demonstrate meaningful clinical benefit for patients affected by Alzheimer's disease. Given these facts, the AAN believed that the NCD was broadly appropriate at the time. However, as of January 6, 2023, lecanemab has been granted accelerated approval by the FDA.[12] Although traditional approval is pending and the FDA has not yet considered the phase III data, as noted above, the AAN believes that data from the phase III CLARITY AD trial provides persuasive evidence that indicates meaningful direct clinical benefit, which upon traditional approval would warrant reconsideration of the NCD.

Although the AAN is supportive of modifying the NCD, we would also like to note the substantial impact that broadened coverage of lecanemab is expected to have on the health care system at large. Given the sizable patient population for whom lecanemab may be prescribed, the AAN does believe that pressure will mount on providers and patients alike. There will be a need for additional resources for neurologists and their support staff to accommodate the substantial increase in infusion and monitoring services for these patients and the AAN has already begun identifying and developing resources for our members and their patients to this end. Additionally, the AAN notes that our members have expressed concerns relating to the costs associated with this medication and the impact that this will have both on patient access and on the broader healthcare system. Neurologists seek to provide high-value care for patients with neurological disease at the lowest cost possible and

[12] FDA Grants Accelerated Approval for Alzheimer's Disease Treatment, U.S. Food and Drug Administration (Jan. 6, 2023) https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment

we welcome the opportunity to serve as a resource to promote access to high-value medications.

To summarize, the AAN believes that the phase III data from the CLARITY AD trial indicating a direct clinical benefit warrants a focused expedited reconsideration of the existing coverage policy as it applies to lecanemab, as it would have been impossible for CMS to consider this highly relevant data at the time that the NCD was published. We believe to promote patient access to therapy, that it would be appropriate for this reconsideration to occur so that a revised decision can be released with an effective date concurrent with a potential traditional approval of lecanemab. Furthermore, the AAN believes that a similar approach could be applied to future products which meet the standard set by the phase III data published in NEJM.

The AAN appreciates the opportunity to engage on this issue and for the continued dialogue between CMS and the AAN. The AAN was heavily involved in the NCA that preceded this NCD and submitted official comments[13] on the proposed decision memo with the intent to aid CMS in establishing prudent coverage policy for this class of therapies. The AAN wishes to reiterate our gratitude to CMS for its diligent response and attention to the need to ensure that Medicare beneficiaries have access to safe and effective treatments. We understand and appreciate that the time and effort required to reach a NCD is substantial. Our members care for the millions of Alzheimer's patients enrolled in Medicare and are grateful for the thoughtful consideration of these issues. The AAN's member experts are eager to continue lending expertise to CMS. If you have any questions regarding these comments or seek further input, please contact Matt Kerschner, Director, Regulatory Affairs at mkerschner@aan.com or Max Linder, Government Relations Manager at mlinder@aan.com.

Sincerely,

Orly Avitzur, MD, MBA, FAAN
President, American Academy of Neurology

[13] American Academy of Neurology Proposed National Coverage Determination Comment Letter (Feb. 4 2022) https://www.aan.com/siteassets/home-page/tools-and-resources/practicing-neurologist--administrators/aducanumab/2022.02.04-final-aan-amyloid-ncd-comments.pdf?epiprojects=13

Appendix 3

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June 12, 2023

Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: Formal Reconsideration Request: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease [CAG-00460N]

Dear Ms. Syrek Jensen,

The American Academy of Neurology (AAN) is the world's largest neurology specialty society representing more than 40,000 neurologists and clinical neuroscience professionals. The AAN is dedicated to promoting the highest quality patient-centered neurologic care. A neurologist is a physician with specialized training in diagnosing, treating, and managing disorders of the brain and nervous system. These disorders affect one in six people and include conditions such as multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease, stroke, migraine, epilepsy, traumatic brain injury, ALS, and spinal muscular atrophy.

The AAN is submitting an amended request that the Centers for Medicare and Medicaid Services (CMS) formally reconsider the National Coverage Determination (NCD) published on April 7, 2022, regarding monoclonal antibodies directed against amyloid for the treatment of Alzheimer's Disease (CAG-00460N)[1]. Specifically, the AAN believes that CMS should reconsider the NCD as it pertains to lecanemab (brand name Leqembi). This letter updates our request submitted on February 2, 2023, based on an ongoing collaborative effort between the AAN and CMS to determine the most appropriate coverage policy for this therapy. This letter contains our full recommendations and refines our request based on the AAN's understanding, through virtual meetings and email communications with CMS, of CMS' commitment to moving forward with Coverage with Evidence Development (CED) requirements for lecanemab and our mutual interest in ensuring that patients receive coverage under the least restrictive

[1]National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N), Centers for Medicare & Medicaid Services (Apr. 7, 2022), https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=305 (Apr. 2022 Alzheimer's Decision Memo).

policy feasible. This reconsideration request is based on the AAN's assessment of recently published evidence as well as the clear unmet need for Alzheimer's patients to have access to appropriate therapies. CMS guidance states that a reconsideration request may be granted in circumstances in which the request includes "[a]dditional scientific evidence that was not considered during the most recent review along with a sound premise by the requester that new evidence may change the NCD decision."[2]

Background

Under the current NCD, all monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (mAbs) are subject to CED requirements upon being granted approval by the Food and Drug Administration (FDA)[3]. The NCD specifies that therapies in this class that are approved based on evidence of efficacy from a change in a surrogate endpoint, as is consistent with the Accelerated Approval Pathway,[4] are only covered in the context of randomized controlled trials. Therapies approved based on evidence of efficacy from a direct measure of clinical benefit may be covered in CMS approved or NIH supported prospective comparative studies.[5][6] In this NCD, and in guidance issued by CMS on the CED requirements, CMS stated that as further evidence becomes available that supports consideration of a change in the coverage status of the item or service, a revised NCD could be expedited.[7][8]

In explaining the purpose of the CED requirements, CMS noted that "(t)o date, no large, pivotal RCT, or set of RCTs, of an antiamyloid mAb has been completed, with a trial report published in the peer-reviewed medical literature demonstrating a clear (non-conflicting) improved health outcome (i.e., a meaningful clinical benefit in terms of slowing in the decline of cognition and function) for Medicare beneficiaries with AD."[9] CMS further noted that "clear evidence about the clinical benefits and harms of any drug in this anti-amyloid mAb class is needed for Medicare beneficiaries with early AD to make, along with their physicians and trusted advisors, informed decisions about whether the treatment is appropriate for them."[10]

The AAN is formally requesting that this NCD be reconsidered and amended should lecanemab be granted traditional approval by the FDA to ensure broader and more equitable access for appropriate patients. There is consensus among the AAN's member experts and leadership who have reviewed the phase III data that the CLARITY AD trial was well-designed, and its findings are clinically and statistically significant. The AAN recognizes the existence of gaps in the available body of literature and that CMS seeks to answer three key

[2] 78 Fed. Reg. At 48167
[3] Section I.A. Apr. 2022 Alzheimer's Decision Memo
[4] Section I.B.1 Apr. 2022 Alzheimer's Decision Memo
[5] Section I.B.2 Apr. 2022 Alzheimer's Decision Memo
[6] Sections I.B.3-5 Apr. 2022 Alzheimer's Decision Memo
[7] Apr. 2022 Alzheimer's Decision Memo
[8] Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development, Centers for Medicare & Medicaid Services (Nov. 20, 2014) https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27
[9] Apr. 2022 Alzheimer's Decision Memo
[10] Apr. 2022 Alzheimer's Decision Memo

questions using the CED requirements laid out within the NCD, but the AAN does not believe CED is appropriate for all patients who may receive this treatment.

Proposed Coverage with Criteria Framework

AAN subject matter experts have reviewed the CED requirements under the current NCD and currently available data, including the data published in the *New England Journal of Medicine* (NEJM), and determined that upon traditional approval, patients matching the below criteria should be able to receive lecanemab without being required to participate in registry-supported prospective comparative studies. The AAN believes it is appropriate that patients not meeting the below criteria but who are likely to receive benefit from treatment receive lecanemab in the context of a prospective comparative study. However, the AAN firmly believes that CED should not be a long-term solution and that the goal of this coverage policy should be to identify the most appropriate patients for this class of therapies and expeditiously transition them from being subjected to CED requirements to receiving broad, equitable, and unfettered coverage as long as they meet evidence-based criteria. Furthermore, the AAN believes it is critical for CED to have a predetermined timeline for interim data analysis, and if that analysis demonstrates that the study endpoints have been met, that the CED should be stopped and full coverage be established.

The AAN is proposing a two-pronged coverage schema under which a subset of Medicare beneficiaries would have access to lecanemab without being subject to CED (which we refer to as the "coverage with criteria" population) and a second population of patients would be subject to CED requirements. The AAN believes that patients should be covered under CED if they meet any of the below exclusion criteria and their provider reasonably believes that the patient is likely to derive meaningful clinical benefit. The AAN's proposed coverage framework is described below:

Proposed Coverage with Criteria: Patient Characteristics:

- Diagnosis: Mild Cognitive Impairment (MCI) due to Alzheimer's disease–- intermediate likelihood:
    - Meet the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to Alzheimer's disease – intermediate likelihood
    - Report a history of subjective memory decline with gradual onset and slow progression over the last 1 year before treatment initiation; must be corroborated by an informant, or
- Diagnosis: Mild Alzheimer's disease dementia:
    - Meet the NIA-AA core clinical criteria for probable Alzheimer's disease dementia

Proposed Coverage with Criteria: Inclusion Requirements (all of the following must be met):

- Objective impairment in memory or thinking corroborated on bedside (e.g., MMSE, MoCA) or formal neuropsychological testing with minimal impairment in day-to-day function
- Positive biomarker for brain amyloid pathology via CSF or PET

- Male or female participants aged greater than or equal to (>=) 50 and less than or equal to (<=) 90 years, at the time of informed consent
- Mini mental state examination (MMSE) score >=22 at treatment initiation and baseline
- Body mass index (BMI) greater than (>)17 and less than (<) 35 at treatment initiation
- Have an identified care partner (defined as a person able to support the participant for the duration of the therapy)

Proposed Coverage with Criteria: Exclusion Conditions:

- Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's Alzheimer's disease
- History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of treatment initiation
- Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with the patient's ability to adhere to the monitoring regimen
- Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (example in skull and cardiac devices other than those approved as safe for use in MRI scanners)
- Evidence of other clinically significant lesions on brain MRI at treatment initiation that could indicate a dementia diagnosis other than Alzheimer's disease
- Other significant pathological findings on brain MRI at treatment initiation, including but not limited to: more than 4 microhemorrhages (defined as 10 millimeter [mm] or less at the greatest diameter); a single macrohemorrhage > 10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts that are <1 centimeter [cm] at their greatest diameter need not be exclusionary)
- Any immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during treatment
- APoe4 Homozygote positivity
- Participants with a bleeding disorder that is not under adequate control (including a platelet count < 50,000 or international normalized ratio [INR] > 1.5 for participants who are not on anticoagulant treatment, example, warfarin)
- Patients who are on anticoagulant therapy
- Any other medical conditions (example, cardiac, respiratory, gastrointestinal, renal disease) which are not stable and adequately controlled, or which in the opinion of the provider could affect the patient's safety
- Patients with autosomal dominant AD, including trisomy 21

Although we are not recommending that they be excluded, careful consideration should be made by the provider for patients with prior exposure to anti-amyloid mAb therapy.

AAN Response to CED Questions

Currently, Medicare coverage for lecanemab is limited by CED. The AAN makes this reconsideration request with the goal of mitigating any undue restrictions on access resulting from the CED policy. The AAN believes it is of the utmost importance to critically evaluate the current body of evidence as it pertains to the CED questions. It is the AAN's belief that the three CED questions laid out within the NCD have been sufficiently answered for the proposed "coverage with criteria" patient population, and we therefore believe that these patients should not have their access to this therapy limited by the constraints of CED. Our reasoning for each of these questions, as stated in our letter dated February 2, 2023, with minor clarification, are as follows.

a. Does the antiamyloid mAb meaningfully improve health outcomes (i.e., slow the decline of cognition and function) for patients in broad community practice?

   The phase III data from the CLARITY AD trial was published in the NEJM on January 5, 2023.[11] The AAN concurs with the authors of the paper, entitled "Lecanemab in Early Alzheimer's Disease" that treatment with lecanemab, "resulted in moderately less decline on measures of cognition and function than placebo." The AAN notes that Alzheimer's disease and associated dementia can lead to many challenges for patients and caregivers. Therefore, meaningful improvement may take many forms. Stabilization, improvement, or meaningful slowing of decline in cognitive function and independent functioning, both in the community and at home, are the most meaningful outcomes for patients receiving these treatments. The AAN believes the findings of the phase III trial are indicative of meaningful improvement. Data presented showed therapeutic benefit on not just surrogate endpoints, such as amyloid clearance, but also cognitive endpoints including the slowing of cognitive dysfunction and a decrease in the decline of activities of daily living. The AAN does not believe there is adequate reason to doubt the applicability of these results to the proposed "coverage with criteria" population, as that population very closely mirrors the patient population of the CLARITY AD trial. The AAN believes these findings support the need for broader access to lecanemab than currently permitted under the NCD.

b. Do benefits, and harms such as brain hemorrhage and edema, associated with use of the anti-amyloid mAb, depend on characteristics of patients, treating clinicians, and settings?

   The AAN believes that this question has been satisfactorily answered, by existing data for lecanemab, for the patient population included in our proposal for "coverage with criteria." The AAN believes that these patients would receive a similar amount of mean benefit from treatment as the trial population, with similar safety profiles, and therefore should be removed from CED. However, the AAN believes that, upon further study, for patients outside of the "coverage with criteria" population (e.g.,

[11] Christopher H. van Dyck et al., Lecanemab in Early Alzheimer's Disease, NEW ENGLAND J. MED. (Nov. 29, 2022)

those with an excluded condition), patient factors such as disease stage and preexisting level of function may be associated with varied benefits of treatment. The AAN also believes that certain patient factors are likely to lead to distinct side effect profiles. Preexisting microbleeds, use of anti-coagulants, and the presence of at least one ApoE4 gene variant may indicate higher risk for ARIA-related complications. The AAN is eager for additional study on this class of therapies, and lecanemab specifically, but believes that existing information provides a framework to reasonably stratify benefits and risk. This distinction among patient populations is the basis for our request to remove the proposed patients from the CED requirement, as we believe that the safety and efficacy questions for these patients have been addressed.

In relation to how benefits and harms depend on the treating clinician and setting, the AAN believes that facilities should be appropriately licensed, with trained personnel to administer the medication and monitor patients during infusions. Regardless of the mechanism for coverage, care should be overseen by trained physicians with experience in treating Alzheimer's disease patients and the expertise needed to monitor for the adverse events associated with this medication, including ARIA E and ARIA H. It is also critical to promote communication between the treating clinician and the infusion center to ensure appropriate adjustments are made to the plan of care should ARIA or other contraindications arise or worsen.

c. How do the benefits and harms change over time?

The AAN believes this question has been satisfactorily answered, by existing data on lecanemab, for the patient population we propose for "coverage with criteria." The AAN also notes that this is an open-ended question and could be interpreted to mean that 10 or more years of follow-up is needed for a final answer. The AAN believes any CMS-approved CED trial must include an agreed-upon length of follow-up at which time an interim analysis can be performed to determine if this question is satisfactorily answered for the CED population or a subset thereof.

The AAN shares CMS' commitment to ensuring patients receive the most appropriate and effective treatments possible and that those considerations incorporate the harms and benefits of FDA-approved products over time. The AAN acknowledges that this question is not reasonably able to be answered for the proposed CED population given the existing body of published evidence. The AAN does believe that, while the data indicates that incidence of isolated ARIA H does not decrease with time, the incidence of mixed ARIA is more common in the first six months of treatment.

Although this question cannot be fully elucidated at this time for the CED population, and warrants further study, the AAN does not believe absence of longitudinal data should be sufficient reason for the agency to restrict access to a treatment for patients in our proposed "coverage with criteria" population, as there are no other FDA-approved treatment options to meaningfully impact disease progression. There is clear unmet need for the Alzheimer's disease population and the AAN does not

believe that it is appropriate to substantially limit patients' access to therapy solely based on this criterion.

The AAN is eager to continue to work with the FDA, CMS, and other stakeholders to monitor developments in the published evidence as this therapy is administered. This includes the AAN's continued collaboration in exploring how best to develop and operationalize the registry-supported prospective comparative studies required for coverage of this therapy for patients outside of the proposed "coverage with criteria" population. Furthermore, the AAN believes that real-world use of the drug can be a helpful longitudinal tool to further establish how benefits and harms change over time. The AAN will be eager to continue to collaborate with regulators to ensure that patients are receiving optimal care as this data is reported.

Rationale for Reconsideration Request

Throughout the National Coverage Analysis (NCA) and NCD processes, the AAN repeatedly raised concerns regarding the potential unintended consequences of applying this NCD to the entire class of mAbs for the treatment of Alzheimer's disease. The AAN is concerned that absent a reconsideration of the NCD, patients who could benefit from lecanemab will be denied access, due to restrictions found in the NCD, leading to irreversible disease progression that could have been slowed with treatment. At the time of the release of the NCD, aducanumab (brand name Aduhelm) was the only approved therapy of its kind that would be subject to the NCD, and the available data did not persuasively demonstrate meaningful clinical benefit for patients affected by Alzheimer's disease. Given these facts, the AAN believed that the NCD was broadly appropriate at that time. However, as of January 6, 2023, lecanemab has been granted accelerated approval by the FDA.[12] Although traditional approval is pending and the FDA has not yet fully considered the phase III data, as noted above, the AAN believes that data from the phase III CLARITY AD trial provides persuasive evidence that indicates meaningful direct clinical benefit, which upon traditional approval would warrant reconsideration of the NCD for appropriate patients. The AAN believes that CMS should take this opportunity to implement the "off-ramp" to full coverage recommended by the AAN in our comments[13] in order to facilitate adjustments to this NCD as quickly as possible, as evidence is gathered.

This reconsideration is critically necessary in order to mitigate the substantial limitations on access to this therapy inherent in the existing CED design. The AAN understands the importance of thorough and accurate evidence gathering to address gaps in existing data on the safety and efficacy of this therapy for certain patient populations and thus the need for CED requirements for those patients. However, requiring participation in a registry-supported prospective comparative study for patients who meet our "coverage with criteria" population will represent a substantial barrier for providers and patients alike. The AAN

[12] FDA Grants Accelerated Approval for Alzheimer's Disease Treatment, U.S. Food and Drug Administration (Jan. 6, 2023) https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment

[13] American Academy of Neurology Proposed National Coverage Determination Comment Letter (Feb. 4 2022) https://www.aan.com/siteassets/home-page/tools-and-resources/practicing-neurologist--administrators/aducanumab/2022.02.04-final-aan-amyloid-ncd-comments.pdf?epiprojects=13

acknowledges the initiative announced recently to develop a "nationwide CMS-facilitated portal" in order to address the existing gap in technical infrastructure to support the existing coverage policy.[14] However, the AAN believes that the announced web-portal is unlikely to address many of the underlying issues inherent to requiring registry participation as a condition of coverage for all patients. The AAN has significant concerns related to the burdensome nature of the CED requirements for institutions that would seek to participate and anticipates that complying with a registry-supported study will likely be a lengthy and complex process. Data collection and reporting requirements are likely to dampen participation and may be exclusionary for smaller community practices for whom study participation may be infeasible. Furthermore, it is the understanding of the AAN that, at present, no such study has been approved by CMS that could leverage a registry to fulfill CMS' commitment to "broader coverage using the framework we announced last year, under coverage with evidence development, on the same day [as traditional approval]."[15] The AAN is committed to addressing these operational concerns to the best of our ability but notes that there are significant and time-consuming challenges that will assuredly need to be addressed before any registry supported study can effectively implement the CED requirements. For all the reasons described in this letter, the AAN believes that CMS should adopt our recommendation for "coverage with criteria" so patients for whom the benefit and safety profile has been well established are eligible for lecanemab in the normal course of care.

Conclusion

Although the AAN is supportive of modifying the NCD, we would also like to note the substantial impact that broadened coverage of lecanemab is expected to have on the health care system at large. Given the sizable patient population for whom lecanemab may be prescribed, the AAN does believe that treatment challenges will mount for providers and patients alike. There will be a need for additional resources for neurologists and their support staff to accommodate the substantial increase in infusion and monitoring services for these patients and the AAN has already begun identifying and developing resources for our members and their patients to this end. Additionally, the AAN notes that our members have expressed concerns relating to the costs associated with this medication and the impact that this will have both on patient access and on the broader healthcare system. Neurologists seek to provide high-value care for patients with neurological disease at the lowest cost possible and we welcome the opportunity to serve as a resource to promote access to high-value medications.

To summarize, the AAN believes that the phase III data from the CLARITY AD trial indicating a direct clinical benefit warrants a focused expedited reconsideration of the existing coverage policy as it applies to lecanemab, as it would have been impossible for CMS to consider this highly relevant data at the time that the NCD was published. While the AAN believes that registry-supported prospective comparative studies may be an appropriate context for coverage for certain patients, the patients described above in the "coverage with

[14] CMS announces plan to ensure availability of new Alzheimer's drugs (Jun. 1. 2023) https://www.cms.gov/newsroom/press-releases/cms-announces-plan-ensure-availability-new-alzheimers-drugs
[15] CMS Statement on FDA Accelerated Approval of Lecanemab (Jan. 6 2023) https://www.cms.gov/newsroom/press-releases/cms-statement-fda-accelerated-approval-lecanemab

criteria" framework should not be limited in their access given the existing evidence demonstrating lecanemab's safety and efficacy.

The AAN strongly encourages and is committed to working with CMS and all stakeholders to ensure, if our framework is accepted, that evidence is expeditiously evaluated, and patients are able to transition from being subject to CED to receiving coverage with criteria as appropriate. Furthermore, the AAN believes that a similar approach could be applied to future products which meet or exceed the evidentiary standard set by the phase III data published in NEJM. The AAN believes that CMS should proactively consider how the AAN's proposed framework could be applied expeditiously and appropriately to additional forthcoming products that may seek FDA approval.

The AAN appreciates the opportunity to engage on this issue and for the continued dialogue between CMS and the AAN. The AAN was heavily involved in the NCA that preceded this NCD and submitted official comments[16] on the proposed decision memo with the intent to aid CMS in establishing prudent coverage policy for this class of therapies. The AAN wishes to reiterate our gratitude to CMS for its diligent response and attention to the need to ensure that Medicare beneficiaries have access to safe and effective treatments. We understand and appreciate that the time and effort required to reach a NCD is substantial. Our members care for the millions of Alzheimer's patients enrolled in Medicare and are grateful for the thoughtful consideration of these issues. The AAN's membership is eager to continue lending expertise to CMS. If you have any questions regarding these comments or seek further input, please contact Matt Kerschner, Director, Regulatory Affairs and Policy at mkerschner@aan.com or Max Linder, Government Relations Manager at mlinder@aan.com.

Sincerely,

Carlayne E. Jackson, MD, FAAN
President, American Academy of Neurology

[16] American Academy of Neurology Proposed National Coverage Determination Comment Letter (Feb. 4 2022) https://www.aan.com/siteassets/home-page/tools-and-resources/practicing-neurologist--administrators/aducanumab/2022.02.04-final-aan-amyloid-ncd-comments.pdf?epiprojects=13

Appendix 4

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March 20, 2023

The Honorable Bernie Sanders
Chair, Senate HELP Committee
332 Dirksen Senate Office Building
Washington, D.C. 20510

The Honorable Bill Cassidy, M.D.
Ranking Member, Senate HELP Committee
455 Dirksen Senate Office Building
Washington, D.C. 20510

Dear Chair Sanders and Ranking Member Cassidy, M.D., and the Senate Health, Education, Labor and Pensions Committee:

The American Academy of Neurology (AAN) is the world's largest neurology specialty society representing more than 40,000 neurologists and clinical neuroscience professionals. The AAN is dedicated to promoting the highest quality patient centered neurologic care. We thank you for the opportunity to respond to this Request for Information (RFI) regarding health care workforce shortages.

A neurologist is a physician with specialized training in diagnosing, treating, and managing disorders of the brain and nervous system. These disorders affect one in six people and include conditions such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease, stroke, migraine, epilepsy, traumatic brain injury, ALS, and spinal muscular atrophy.

The United States is facing a shortage of between 54,100 and 139,000 physicians by 2034[1] that will likely be exacerbated by rising rates of physician burnout and early retirement due to the COVID19 pandemic. In addition, the population of Americans over 65 years old is expected to double to 95 million by 2060,[2] and a dramatic rise in neurodegenerative disease is expected with incidence of stroke rising 20% by 2030,[3] prevalence for Parkinson disease doubling by 2040,[4] and incidence of dementia doubling by 2050.[5] Based on these projections, we should anticipate a marked increase in demand for neurologic care. Neurology is an incredibly complex field that is in a renaissance period given recent opportunities for advancement in research and treatment.

For neurologic patients with chronic conditions, there is often no “one size fits all” course of treatment. Prompt access to care is essential to minimize risks of dangerous complications and side effects. Patients in rural areas are particularly impacted by lack of access to neurologic care. Studies also show that patient care also benefits when physicians are racially and/or ethnically concordant.[6] The American Academy of Neurology (AAN) is firmly committed to embracing the diversity of our members, staff, organization, profession, and, ultimately, the patient communities we serve.

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[1] https://www.aamc.org/news-insights/press-releases/aamc-report-reinforces-mounting-physician-shortage
[2] https://www.prb.org/resources/fact-sheet-aging-in-the-united-states/
[3] https://pubmed.ncbi.nlm.nih.gov/23697546/
[4] https://pubmed.ncbi.nlm.nih.gov/23436720/
[5] https://pubmed.ncbi.nlm.nih.gov/25984581/
[6] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2772682

Addressing the workforce shortage in healthcare will require several points of intervention. **AAN recommends several avenues outlined below to address the workforce shortage.** We recognize this is not an exhaustive list and we look forward to continuing to work with the committee to ensure access to neurologic care for all patients.

Bolstering the Existing Workforce

The AAN supports measures to strengthen and support the existing neurology workforce.

Overly Burdensome Administrative Requirements

Administrative burdens like prior authorization and step therapy contribute to physician burnout and hinder patient access to care. On average physicians and staff spend 2 days a week completing prior authorizations.[7] Typically, addressing the burden of prior authorization requires the hiring of additional full-time employees, causing more issues with workforce shortages and for many is not sustainable. The AAN supports policies that seek to reduce unnecessary constraints on patient access to physician directed care and allow physicians to spend their time with patients rather than completing administrative tasks. The AAN supports the following legislation that seek to decrease unnecessary administrative burdens that hinder patient access to care:

- One of the most widely supported bipartisan pieces of legislation in the last Congress, the Improving Seniors' Timely Access to Care Act would establish an electronic prior authorization (ePA) program; standardize and streamline the PA process for routinely approved services; reduce the amount of time an insurer is allowed to consider such requests; and ensure that they are reviewed by qualified medical personnel.
- The Gold Card Act will help reduce the burdens of prior authorization in Medicare Advantage by streamlining processes and giving physicians who had prior authorization requests for prescriptions and treatments approved at least 90% of the time a "gold-card" exemption status. These improvements will benefit many neurologic patients who require timely access to care for their chronic conditions.
- The AAN also supports the Safe Step Act (S. 652), which addresses the growing burden of step therapy protocols for employer sponsored health plans by: ensuring employer plans are offering a clear step therapy exceptions request process, requiring employer plans to respond to a step therapy exception request within 24–72 hours, and outlining circumstances in which a step therapy exception request should be granted.

AAN is appreciative of ongoing efforts to bring about value-based care; however, the Merit-based Incentive System (MIPS) in its current form falls sort of its intention. This system has added burdens on the part of practices, without sufficient increases in benefits. Many providers have been able to reach the performance benchmarks set out for them, yet there is uncertainty on whether the metrics used to assess processes and outcomes ultimately changed care delivery in a significant way. MIPS puts too much emphasis on an individual clinician's role in the healthcare system in respect to cost and holds clinicians responsible for expenditures that they may have no control over. Practices spend just short of an estimated 4 hours per week per physician on MIPS reporting.[8] There is great concern that increased administrative requirements and compliance burdens contribute to burnout, further exacerbating problems with the inadequate supply of clinicians in the workforce.

[7] https://www.ama-assn.org/system/files/prior-authorization-survey.pdf
[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8796897/

Appropriately Valuing Neurologic Care

Recently, the AAN responded to a Request for Information (RFI) regarding MACRA and actions Congress could take to stabilize the Medicare payment system. That feedback encompasses a variety of recommendations to reform the Medicare physician payment system.

AAN recognizes the financial pressures of the Medicare system and the importance of finding a financially stable solution. Given this, we are concerned about the unsustainable nature of the temporary fixes to combat conversion factor cuts, and the financial impacts of statutory PAYGO requirements. However, we remain supportive of requests to Congress to offset the cost of the temporary relief measures by appropriating funds to the Medicare Physician Fee Schedule. We also request an inflation update to the Medicare conversion factor from Congress, similar to what exists for nearly every other area of the health care sector, to aid patient access to care and stability of neurology practices serving all communities. On March 15th, the Medicare Payment Advisory Commission (MedPAC) submitted recommendations to Congress calling for an annual physician payment update tied to the Medicare Economic Index. Although this update accounting for 50% of the MEI[9] is a much needed step in the right direction, the AAN believes that the full effects of medical inflation need to be accounted for to promote practice sustainability and to safeguard the neurology workforce. In addition, AAN is supportive of permanent payment parity for Evaluation and Management (E/M) services for established patients delivered via real-time interactive audiovisual technology, as well as regular review of E/M codes. Appropriately valuing neurologic care is critical in bolstering the existing workforce and not deterring future neurologists from the field.

Importance of the Physician-Led Care Team

As demand for neurological services increases, the workload on those providing care will grow. The AAN strongly supports physician-led neurology care teams that recognize the accepted scope(s) of practice for each member of the care team. The AAN supports the integration of neurology specific trained advanced practice providers into the physician-led care team as part of a robust team to manage the high workload.

Mental Health and Burnout

An estimated 60% of neurologists experience at least one symptom of burnout.[10] There are many factors that increase the risk of burnout, including hours worked, nights on call, number of patients seen, and clerical work per week.[11] Burnout and related emotional exhaustion can be expected to increase as demand for neurologic care rises. The AAN is supportive of reducing unnecessary administrative burden that impacts burnout as well as investments in physician mental health.

The AAN supported the Dr. Lorna Breen Health Care Provider Protection Act that that provided mental health support through grants to programs encouraging health care providers to seek treatment and improve mental health. **The AAN asks that similar measures to support physician mental health continue to be championed in the 118th Congress.**

Building the New Workforce

The AAN is supportive of efforts to increase the incoming neurology workforce in addition to bolstering the existing one.

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[9] https://www.medpac.gov/document/march-2023-report-to-the-congress-medicare-payment-policy/
[10] https://n.neurology.org/content/88/8/797
[11] https://n.neurology.org/content/88/8/797

Training and Residency

New physician training is important to ensure an adequate supply of neurologists. Currently, trainees are not guaranteed exposure to neurology, and the Accreditation Council for Graduate Medical Education does not mandate that all residents complete a clinical neurology rotation, nor does it specify core competencies in neurologic disease.[12] The AAN recognizes the need to encourage medical students to consider neurology when choosing a specialty, and supports policies that seek to bolster the physician workforce pipeline.

Access to federally-funded residency slots is crucial to maintaining the neurology pipeline. The AAN supports policies, like the Resident Physician Shortage Reduction Act, that seek to increase the number of graduate medical education (GME) residency slots available. The Academy was encouraged to see an increase in residency slots for the first time in nearly 20 years, but recognizes that more access is needed to address the physician pipeline. Recent allocation of GME slots did not reach neurology. The AAN supports future funding for additional residency slots and encourages policies that allow for the allocation of a portion of the new residency slots to neurology.

Medical students take on an average of $200,000 of student loan debt on top of any pre-medical student loans,[13] which influences the decision on which specialty to practice and location of practice thereby impacting physician supply. Anticipated medical student debt is a barrier to entry for many undergraduate students, who may choose other fields over medicine to protect their financial future. For many students, taking on such large debts is simply not feasible. The AAN supports programs and legislative solutions that would decrease debt burden on our nation's physicians, such as:

- The Pediatric Subspecialty Loan Repayment Program (PSLRP), implemented by the Health Resources and Services Administration (HRSA), which provides loan repayment for pediatric medical subspecialists, pediatric surgical specialists, and child mental health professionals who care for children in underserved areas. Increased funding is essential to promote the program's growth and success in encouraging residents to practice in underserved areas.
- The Resident Education Deferred Interest (REDI) Act (S. 704/H.R. 1202), decreases the burden of student loans on medical students and residents by allowing borrowers to qualify for interest-free deferment on their student loans while serving in a medical or dental internship or residency program. The AAN supports the adoption of this legislation, or a similar legislative solution.

International Medical Graduates

International medical graduates (IMGs) make up 31.5% of active neurologists. However, non-US IMG resident physicians training in the US on J-1 visas are required to return to their home country for two years after their residency has ended before they can apply for a work visa or a green card. The Conrad 30 program provides 30 waivers per state to allow these physicians to remain in the US without having to return home for two years if they agree to practice in a medically underserved area for three years. **With communities across the country facing physician shortages, the Conrad 30 program helps physicians who are educated and trained in the US continue to care for patients.** The AAN asks that improvements continue to be made to the program, including creating a process to gradually increase the number of waivers while requiring additional employment protections. **The Healthcare Workforce Resilience Act would provide stability for foreign-born physicians that are critical to the neurology workforce by reallocating 15,000 visas for physicians and 25,000 visas for nurses to practice in the United States**. This

[12] https://www.acgme.org/Specialties

[13] https://www.ama-assn.org/medical-residents/medical-residency-personal-finance/say-goodbye-physician-residency-and-medical

legislation was introduced last congress and the AAN urges that similar measures be introduced and enacted in the 118th Congress.

Conclusion

While these avenues are priorities for the AAN in addressing the workforce shortage, we recognize that this is not a comprehensive list. **We look forward to continuing to work with the Committee to improve access to neurologic care for all patients.** If you have any questions or requests for additional information, please contact Madeline Turbes, Health Policy Manager, at mturbes@aan.com, or Kelly McCone, Senior Congressional Affairs Manager, at kmccone@aan.com.

Sincerely,

Orly Avitzur, MD, MBA, FAAN
President, American Academy of Neurology

POSITION STATEMENT:

PRESCRIPTION DRUG PRICES

AMERICAN ACADEMY OF NEUROLOGY®

Background Information

The American Academy of Neurology (AAN) is a professional association of more than 34,000 neurologists and neuroscience professionals dedicated to providing the best possible care for patients with neurologic conditions including Alzheimer's disease, Parkinson's disease, stroke, epilepsy, ALS, multiple sclerosis, traumatic brain injury, and headache. One in six people live with a brain or nervous system condition and the annual cost of treating neurologic disorders in the United States is more than $500 billion. As state and federal policymakers consider new ways to address the rising costs of prescription drugs, it is important for the AAN to establish an official position on the issue to advocate effectively for its members.

Description of Issue

Prescription drug prices are high and continue to increase, which is concerning for patients, prescribers, payers, and policymakers. Between 2013 and 2015, spending on prescription drugs increased by 20 percent in the United States[1] with nearly 50 percent of Americans using at least one prescription drug in a given month.[2] Drugs that treat complex, chronic conditions like Parkinson's disease, epilepsy, and migraine, and specialty drugs which may require special handling or administration, such as those used for multiple sclerosis, are particularly expensive. Spending on specialty medications has increased by $54 billion since 2011 and now accounts for more than 70 percent of all prescription spending growth.[3] Two multiple sclerosis medications, Copaxone and Tecfidera, accounted for $1.9 billion in Medicare Part D catastrophic coverage in 2015 with an average monthly price of $5,600 each. This reflects an 84 percent increase in the price of Copaxone from 2010 to 2015.[4] These prices directly impact patients and their treating providers as they work together to treat neurologic illness.

There are three distinct cost challenges. Each are quite different and will require different solutions: 1) massive increase in the pricing of previously low-cost generic drugs used to treat common disorders without obvious increases in cost of production or distribution; 2) massive increase in the pricing for high-priced generic and brand name drugs used to treat serious disorders that are not protected by the Orphan Drug Act; 3) the high cost of new medications used to treat rare disorders as defined by the Orphan Drug Act, understanding the economic factors involved in rare-disease drug development.

The AAN Position

Action must be taken to ensure that prescription medications are accessible for patients with complex, chronic neurologic conditions. Potential solutions should be affordable, simple, and transparent.[5] Cost-containment efforts must also address the burden on the entire health care system as high prescription drug prices may be shifted and absorbed in ways that negatively impact patient and prescriber access to important medications.

Areas of Support

Price Negotiation

The AAN supports proposals that would give federal agencies the authority to negotiate contracts with manufacturers of covered Part D drugs. Price negotiation would allow the government to leverage its purchasing power in an effort to obtain prescription drugs at a lower price, bringing savings to the health care system and consumers. The AAN would especially support proposals that increase competition among drug manufacturers and ultimately promote access to more affordable medications.

Transparency

The AAN supports proposals that promote transparency in prescription drug pricing. Disclosure of pricing information, including how drugs are priced, the prices paid by insurers, and the prices paid by consumers, would provide important information that could lower costs for patients and for the entire health care system. Recent efforts by Johnson & Johnson[6] and Merck[7] to disclose pricing practices model the type of transparency that could bring down costs across the industry.

The AAN would also support proposals that prohibit direct-to-consumer advertising of prescription drugs, as passed by the American Medical Association House of Delegates.[8]

Importation

The AAN supports proposals that allow for the reimportation of the same high quality prescription drugs from Canada when prices for those prescriptions are less expensive than in the United States. Many specialty drugs are priced significantly higher in the United States than in other countries. The average monthly price of Copaxone is 287 percent greater in the United States than in Switzerland.[9] While recent Congressional proposals on reimportation were defeated[10], it is important to continue considering this opportunity as a cost control measure.

Rationale

Neurologists seek to provide high-value care for patients with neurological disease at the lowest cost possible. This is specifically of interest as neurologists aim to reduce their resource use as part of the Quality Payment Program, or MACRA. However, many therapies for neurological disease are among the most expensive in the United States. Neurologists are also limited by few, if any therapies available in a particular class of medications. For example, the recently approved therapies for Duchenne Muscular Dystrophy and Spinal Muscular Atrophy are expected to cost $500,000 and $750,000 in the first year of treatment, respectively.[11] Given the limited options to seek less expensive therapies in clinic, mechanisms are needed to reduce the cost of these important medications, or support methods of paying for the treatment of these disorders outside the standard reimbursement process. Such cost reductions will improve the quality of life for many patients with neurologic disease.

Position Statement History

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