<u>**VIA ELECTRONIC SUBMISSION**</u>

Chiquita Brooks La-Sure
Administrator
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

August 11, 2021

RE: National Coverage Analysis (NCA) Tracking Sheet for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N)

Dear Administrator La-Sure,

The Robert J. Margolis, MD Center for Health Policy at Duke University (the "Duke-Margolis Center" or the "Center") appreciates the opportunity to comment on the Centers for Medicare and Medicaid Services (CMS) National Coverage Analysis (NCA) Tracking Sheet for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. The Duke-Margolis Center analyzes evidence across the spectrum of health policy and supports the triple aim of better care, better health, and lower costs. A core mission is to increase the value of biomedical innovation. Our experts are engaged in policy research and development efforts to improve the processes, resources, and infrastructure needed at CMS to ensure efficient and appropriate access to new and innovative technologies.

The Duke-Margolis Center appreciates the opportunities for substantive public comments that CMS is seeking throughout multiple stages of this very consequential NCA process. Alzheimer's Disease (AD) affects an estimated 6 million Americans. This number is expected to triple by 2060, massively increasing the disease burden on the American healthcare system.[1] Current AD treatment models are largely fragmented, reactive, and impose heavy costs on families and Medicaid for supportive care. Some promising patient-focused "memory clinics" and whole-person care models have demonstrated improvements in patient experience and reduced complications, but they are not widely accessible or well supported by traditional fee-for-service payment policies.

Previous pharmacologic treatments for AD have only targeted symptoms. There is an urgent need for access to effective treatments for patients and respective caregivers of early-stage AD and the mild cognitive impairment (MCI) that precedes it. Aducanumab is the first disease modifying treatment approved for patients with MCI and early-stage AD. Further, there are a range of additional monoclonal antibodies (mAbs) treatments in pivotal studies with promising effects on reducing beta-amyloid protein ("amyloid") plaques associated with the neurodegeneration that causes AD.[2] There is a real possibility that more mAbs as well as other AD treatments progressing through clinical development will be approved in the next few years.

Based on the evidence compiled at the time of accelerated approval, significant uncertainties remain about the "reasonable and necessary" use of aducanumab for Medicare beneficiaries. These reflect the FDA advisory committee's assessment that prespecified analyses of the suspended pivotal trials did not reliably show slowing of cognitive decline and showed amyloid related imaging abnormality (ARIA) related safety concerns. There are outstanding questions about the FDA's accelerated approval decision

based on an ex-post reanalysis of trial results emphasizing an apparent association of amyloid plaque reduction, a surrogate endpoint, with an incremental slowdown in cognitive decline. Consequently, more definitive evidence on the safety and effectiveness of aducanumab would be extremely valuable to Medicare beneficiaries with AD and their caregivers.

First, further evidence validating the relationship of amyloid plaque reduction to slowing of cognitive decline is important for advancing this field. As we describe below, it is feasible to develop such evidence in the near term. Moreover, as is often the case with new technology accelerated approvals, there are several other key evidence gaps that complicate assessments of "reasonable and necessary" use:

- Limited evidence on outcomes that matter to patients: Clinical research metrics like slower decline in cognitive scores and promising surrogate endpoints are accepted for accelerated approval studies in AD. But most relevant for "reasonable and necessary" decisions is whether the treatment has a clinically meaningful impact in practice. For example, measures like "complete response rates" are used as markers for likely clinical outcome benefit in some cancer treatments, but patients value measures that translate into prolongation of survival and quality of life outcomes. AD patients and their caregivers want slower cognitive decline, but mainly because of the impact on quality of life, including enjoyment and engagement, ability to live independently, and ability to perform activities of daily living without assistance. These key outcomes can be quantified through existing measures used in clinical practice. Because drugs and many nonpharmacologic therapies can influence quality of life outcomes, and because patient circumstances are diverse, the capacity to assess the impact of new treatments on such outcomes in real-world care settings is unlikely to come through traditional pivotal clinical trials. They can, however, be developed through real-world experience.

- Limited evidence on the treatment effects across different subgroups of Medicare patients, which can inform treatment decisions and monitoring for particular patients: In the pivotal aducanumab trials, pre-specified subgroup analyses were conducted to determine if there are any notable trends or risk factors based on race or presence of a biomarker for AD risk that can inform likelihood of treatment success. These analyses were inconclusive. There is limited evidence on how these or other criteria could help inform patient selection, beyond the eligibility criteria for the trial, and inform what patient characteristics impact treatment success. Further evidence development is needed on treatment effects across subgroups of Medicare patients to inform patient selection, disease progression management, safety risks and ongoing monitoring activities, which can be derived from real-world evidence (RWE).

Unfortunately, CMS had limited ability to coordinate with product developers, patient advocates, providers, and other payers and stakeholders to determine how to address these issues prior to the approval of aducanumab. This reflects many factors. One is very limited CMS resources: expert staff support for such analyses at the Centers for Clinical Standards and Quality (CCSQ) has declined in recent years despite the explosion in advanced technology development. It is also likely a function of regulatory structures and authorities. On the one hand, FDA has received extensive bipartisan support to increase its expert review resources, to implement accelerated approval and breakthrough pathways, and to develop RWE methods and infrastructure to help address post-market questions related to safety and effectiveness. On the other hand, there have been few or no corresponding changes at CMS, and limited guidance for coordination across CMS, FDA, and NIH to plan ahead to develop the infrastructure that could help inform the adoption and use of these new technologies.

Nonetheless, given the importance of AD, it is critical that CMS use its available resources and collaborations with stakeholders to develop the best foundation possible for the current coverage decision for this new treatment class. We expect CMS will receive extensive and thoughtful comments on whether aducanumab should be covered or not based on the current evidence. For the reasons outlined below, we think CMS should undertake a thorough review guided by a special process through its Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) and expand opportunities for further public input and emerging evidence from relevant ongoing AD mAb therapy studies as that effort proceeds. Given the gaps in evidence, we expect that Coverage with Evidence Development (CED) should be an important part of the final coverage decision.

The limited evidence to support "reasonable and necessary" use of aducanumab suggests that CMS may face the difficult decision of limiting access to many patients and physicians who would support aducanumab treatment based on the available evidence. Alternatively, CMS could provide broader access with substantial uncertainty about whether beneficiaries are receiving a meaningful clinical benefit. This option could raise questions about whether increased resources devoted to disease-modifying therapies should also be made available for expanded access to other, evidence-based nonpharmaceutical interventions that can improve quality of life and potentially slow AD progression.

Given the importance of the process leading to a proposed NCD in the coming months, and its likely relevance beyond aducanumab, our comments focus on steps CMS and stakeholders can take now to reduce uncertainty associated with the "reasonable and necessary" determination for coverage for aducanumab, other mAb treatments, and other AD therapies that may be approved. We believe there is too much at stake in this disease area for the status quo to continue. CMS should support translating drug development and approval to "reasonable and necessary" use for AD patients and stakeholders by accelerating evidence development, and by advancing changes in payment policies to support timely reforms in AD care.

Our comments reflect the following framing principles on how CMS should proceed with this important NCA process:

1) CMS should ensure that the scope and breadth of coverage and any coverage requirements for aducanumab also consider relevant evidence on "class effects" coming from near-term clinical studies of other amyloid targeting mAbs that are contributing to the growing evidence base of this class of therapies.

2) Given the ongoing clinical studies and untapped opportunities for post-market RWE development in this space, coverage decisions should support evidence development in areas that are highly relevant to the well-being of Medicare beneficiaries with MCI and early AD who may be treated with mAbs. This type of evidence can be developed in real-world studies that can be supported through CED and stakeholder collaboration.

3) Coverage for treatment with mAbs for AD should be aligned with steps by CMS to support better care models for beneficiaries at risk and amid AD progression. Such person-centered models should include a coordinated approach that supports improving evidence-based approaches for:
   - screening,
   - timely diagnosis,

- access to clinically appropriate pharmaceutical and nonpharmaceutical interventions to manage disease progression and functional capacity,
- ongoing monitoring to anticipate and prevent complications,
- effective complication management, and
- addressing the many social and behavioral factors that influence quality of life for AD patients and their caregivers.

Such models exist now, including high-quality "memory clinics" and care coordination programs. However, they are not widely or equitably available. AD cannot be managed effectively through a fragmented care system that pays unevenly, if at all, for the combination of treatments and supports that have the most impact for individual patients and their caregivers. The inadequacies of fragmented AD care models will be exacerbated with likely further progress in the development of AD treatment and supportive technologies like remote monitoring and telehealth. CMS could consider coverage restricted to patients who have access to person-centered care models for AD therapies. But taking such a step alone would be inconsistent with stated CMS priorities to provide all beneficiaries with access to well-coordinated, effective comprehensive care, in a manner that reduces health inequities.

Below we address CMS's questions in the NCA:

Which health outcomes are important, and what degree of improvement in them is meaningful for patients receiving treatment? What characteristics of patients with Alzheimer's disease are important to optimizing the likelihood of positive health outcomes from treatment?

Aducanumab represents the first accelerated approval of an AD treatment using amyloid plaque reduction, a surrogate endpoint expected to achieve an incremental reduction in the rate of cognitive decline. As we have described above, there are a range of important health outcomes relevant to "reasonable and necessary" mAb therapy for AD. Here, we describe our recommendations for improving the evidence on such outcomes. While CMS has limited authority and resources to develop better evidence, there are important steps that CMS can take during its NCD process and beyond it, to advance reasonable and necessary care for AD. In particular:

1) Support FDA and sponsor efforts to implement, enroll, and complete the Phase IV study to validate the surrogate endpoint and strengthen the evidence on aducanumab's impact on cognitive decline.

   Timely development of evidence to validate the clinical impact of amyloid plaque reduction is a high priority. Right now, especially ahead of the completion of the Medicare NCD, coverage for potentially eligible patients is very limited and uneven. It is unfortunate that the required Phase IV randomized trial for aducanumab does not have an infrastructure in place to enable rapid enrollment and completion, since there appear to be many patients willing to participate. However, there are clinical studies on other amyloid targeting mAb therapies that are contributing evidence on the validity of amyloid plaque reduction as a surrogate endpoint for slower cognitive decline. Consequently, it is possible that emerging evidence will lead to more certainty about the clinical validity of this surrogate endpoint in the coming months.

   CMS can take steps to encourage effective design and speedy implementation of the trial by:

a. conveying key questions like those posed in this NCA to the sponsor and researchers involved in the trial, to the extent they are feasible to address,
b. identifying ways in which readily-available Medicare data (e.g., on hospital, home health, post-acute, and nursing home utilization) could augment the trial design and analysis,
c. facilitate broad awareness of and participation in the trial to Medicare beneficiaries, and
d. clarify coverage of the routine and associated costs of care associated with the trial, including PET and MRI scans and other ancillary services needed (within CMS authority now).

Given the expected additional accelerated approvals in this space, any activities that CMS undertakes in parallel to this NCA process can also help assure that such confirmatory phase IV trials, for aducanumab and other AD mAb therapies, are conducted and completed efficiently and support future coverage assessments.

2) Account for and support ongoing efforts to advance the validation of amyloid plaque reduction as a surrogate marker for decline of cognitive impairment, and guide further evidence development on the impact of AD mAb therapies on the rate of decline in cognitive impairment.

Prior to finalizing the NCD, CMS can use expert consultation or convening to help assure that the NCA considers developing evidence on this surrogate marker. This could involve independent expert metanalysis to integrate study results and optimize evidence development on the validity of amyloid plaque reduction as a surrogate endpoint for slower cognitive decline for the class of mAb therapies.

In particular, there are three pivotal studies underway involving other AD mAb therapies that have and will continue to contribute valuable evidence on the relationship between amyloid plaque reduction and cognitive decline progression in the coming months. All three pivotal studies are using validated endpoints pertaining to dementia progression (CDR-SoB) and other cognitive tests as primary or secondary effectiveness outcomes. They are also evaluating amyloid plaque reduction. These clinical trials are already showing suggestive evidence that mAb class therapies can decrease amyloid plaques and relevant proteins, with an impact on cognitive function decline. Preliminary results from the Gantenerumab and Lecanemab clinical trials demonstrate a decrease in plaque buildup and cognitive decline, and the Donanemab trial demonstrated reduction in plaque buildup and slower declines in cognitive testing.[3] These studies, and potentially others underway now, could provide additional short-term evidence on whether amyloid plaque reduction is a valid surrogate endpoint.

3) Support and facilitate the development of a CED infrastructure that could develop RWE on additional key health outcomes that are challenging to assess in traditional randomized clinical trials (RCTs).

While RCTs should yield more evidence on impact on cognitive decline that is relevant to the AD mAb therapy coverage decision, there are other outcomes relevant to the well-being of Medicare beneficiaries with MCI and early AD who may be treated with mAbs:
- functional and quality of life outcomes, including independent living, ability to perform activities of daily living, absence of depression, caregiver quality of life, and decreased emergency room visits and complications,

- adverse event and complication rates, influenced by management and monitoring, and,
- subgroup effects across various types of Medicare patients (due to genomics, demographics, comorbidities, preferences and circumstances) that can inform optimal treatment choice.

These outcomes are certainly affected by changes in cognitive status, but the magnitude of the impact may be influenced by many other care interventions and patient factors. At the same time, it is challenging to develop practically relevant evidence on these outcomes using typical clinical trials with specifically defined care settings, populations, and experimental assessments. Instead, this type of evidence can be developed in real-world studies that can be supported through CED and stakeholder collaboration.

Addressing these questions about the impact of mAb therapies will generally require larger and more diverse populations and are harder to conduct through RCTs. As we have noted, we encourage facilitating feasible and meaningful RCTs as quickly as possible, including as part of a Phase IV study. Given the incremental effect sizes and heterogeneity of AD patients, randomization is likely to be particularly important for reliable evidence on the size of treatment effects for both surrogate endpoints and key trial endpoints. Some commenters have suggested alternatives to standard RCT randomization methods, such as regionally-based access models or "waiting lists." These may be challenging to implement and sustain alongside broader access, leading some to call for CMS to limit coverage to further RCTs only.

Given the limitations of RCTs, there are important questions that are feasible to address through real-world studies that could be supported through CED as part of the NCD. This could include some randomized studies. While randomization to treatment or placebo may be difficult, real-world randomization may be more feasible for issues that are less likely to be perceived as infringing patient preferences given existing evidence. For example, greater equipoise may exist for such issues as dosing or duration of therapy and comparative effectiveness, if and when additional treatments are approved.

Methods for observational analysis are improving. Using such approaches as propensity score matching and target trial designs, coupled with attention to data reliability and fitness for the study, observational methods can yield reliable results on a growing range of questions. RWE on differences in patients' medical history, course of disease, and safety for subgroups of AD patients can help target AD treatment use to those likely to benefit. RWE can also help determine which providers and care models lead to effective use of AD therapies (pharmaceutical and non-pharmaceutical).[4] Such evidence can inform clinician-patient decision making and guide further coverage decisions.

Registries or other observational study platforms can mitigate the costs and burdens of the data collection and study participation. There are several existing registries that could be a starting point, and many companies with data and analytic expertise that could potentially support virtual platforms. These observational studies could track different patient subgroups' progress with propensity matching or historical or other controls and generate evidence on safety profiles. Such a process would generate more evidence on the course, predisposing factors, and impacts of interventions on ARIAs, advancing the use of mAb treatments.

We understand that CMS does not have the authority or resources to directly support this type of data infrastructure – a recurrent challenge in addressing key post-market issues for Medicare beneficiaries involving new technologies. Prior successful CED initiatives have relied on stakeholder collaborations, including infrastructure and study funding from NIH, leadership from specialty societies and other clinical organizations, electronic data collection from willing providers, and support from private-sector

data infrastructure and analysis collaborators. In the AD space, patient organizations, including the Alzheimer's Association and US Against Alzheimer's, have already contributed to evidence development for AD that is meaningful to patients. While challenging, CMS's steps toward addressing these issues now may be helpful not only for the current coverage decision, but also to improve the capacity and infrastructure for addressing the likely substantial questions to come involving whether any future AD treatment is reasonable and necessary.

CMS can be a critical partner in such evidence development activities, and can help assure that they are relevant, synergistic, and efficient. In particular:

- CMS can support the use of meaningful measures in AD treatment studies by building on approaches already adopted to collect data for quality improvement. For example, CMS could explore the feasibility of extending the standardized data that it routinely collects for quality improvement in post-acute care (PAC), which include important cognitive and functional measures. Standard approaches for key electronic data reporting could also reduce the cost of adhering to diverse prior authorization or diverse reporting requirements required for coverage and payment.
- CMS could promote consistent adoption and use of well-developed measures in clinical practice relevant to patient functional outcomes to augment the cognitive measures used in research studies – for example, the Montreal Cognitive Assessment (MoCA) test for patients with mild cognitive impairment, and the Activities of Daily Living (ADL) assessment for patients with early-stage AD.

As our comments suggest, these efforts should be undertaken thoughtfully, with attention to the cost and burden of data collection versus the benefits resulting from evidence using the data. Any CED requirements should include a clear description of the expected results and of the circumstances that would reduce or conclude the need for CED data collection.

What issues of equity and inclusion must be accounted for in the diagnosis and treatment of Alzheimer's disease?

Inequities exist today in AD diagnosis, treatment, monitoring, and progression. Diagnosis rates for Black and Hispanic patients are lower than White patients, even though they have a higher incidence and prevalence rate of Alzheimer's-related dementia. Further, Black and Hispanic populations report higher levels of discrimination when seeking care for AD, as well as higher rates of reported caregiver discrimination. Dually eligible Medicaid and Medicare recipients not only have a higher prevalence of Alzheimer's, but also have more comorbidities and concomitant medications that increase their complication rates. Clinical trials typically have underrepresented such patients.[5] Rural patients are also less likely to be diagnosed and treated.

Without complementary steps, an NCD for AD mAb therapies could exacerbate inequities in access to AD care, especially if coverage is tightly limited. The AD mAb treatment trials have relied on specialized treatment centers with diagnostic tools and capabilities that are in limited supply. This includes access to the diagnostic positron emission tomography (PET) scans to confirm eligibility, which is currently covered only in clinical trials, as well as access to neuropsychologist or geriatric expertise for ongoing management. CMS currently only covers PET scans in clinical trial participation. Such specialized AD treatment centers are not readily accessible for most Medicare beneficiaries.

Moreover, the cost of these additional services on top of drug costs may be substantial, and traditional Medicare covers only 80%. With current expectations about mAb pricing, cost will be a significant

barrier to equitable access for beneficiaries in traditional Medicare without supplemental coverage. As we describe in the next section, alternative payment models, such as milestone payments, outcome-based contracts, or other forms of risk-sharing arrangements, could help increase and support equitable access while encouraging the development of useful additional evidence.

Non-pharmaceutical care management can have a significant impact on patient experience and outcomes, especially since drug therapies to date have had only limited impacts, and inequities exist here too. For example, to participate in recent trials participants need to already have a "reliable" informant or caregiver. More generally, AD patients benefit from care navigators and whole-person care programs that can help them get access to other covered and uncovered services including behavioral health programs, occupational therapy, social services, caregiver assistance, and community supports that lead to better quality of life and other outcome improvements.

These challenges highlight the need to take steps now to redesign payments for AD treatments. Ideally, AD care models should support equitable access to all effective diagnostic testing and treatment options, including nonpharmaceutical treatments, and help patients and their caregivers get the best combination of services for their particular needs. Such comprehensive care models exist, with some evidence that they not only lead to better outcomes but may also lower long-term costs associated with AD treatment and management. They are also likely to be better equipped to manage AD treatment and possible complications. However, they require an alternative, more person-centered approach to payment than fee-for-service. In the absence of complementary policy steps to enhance the availability of better care models for AD patients, urban, wealthier, non-minority patients will likely have greater access if coverage is limited to randomized clinical trials or "memory clinic" centers of excellence.

What health care providers should be included as part of the patient's treatment team? Should medical specialists be included in the care team of patients receiving treatment? If so, which specialists should be included in the care? In what setting(s) should treatment and care be given?

An effective care model for AD, especially with coverage for new mAb therapies, would include the following:

1. Patient screening, diagnosis and eligibility determination through:
   - Timely assessment
   - Efficient use of diagnostic PET scans (and potentially other emerging diagnostic modalities, such as beta amyloid blood tests, if clinical evidence supports their approval and use)
2. Appropriate regular evaluation and management in consultation with a specialized provider with expertise in AD care and mAb use, including support for management of ARIAs to avoid significant or long-term complications, and
3. Appropriate counseling and decision-making support about the initiation, adjustment, and termination of mAb therapy.

Primary care providers are generally not equipped to provide such support, and there is limited availability of specialized "memory centers" around the country that could provide these services. Furthermore, considerable evidence and experience with innovative, technology-enabled models for AD care show that drug prescribing and monitoring is only one aspect of a comprehensive and effective care program. Effective, patient-centered AD care should also rely on care coordination and integration that incorporates evidence-based nonpharmaceutical interventions such as occupational therapy programs and support services that can keep the patient at home longer and decrease caregiver stress,

improve quality of life, and potentially slow cognitive decline – potentially at a significantly lower cost compared to drug therapy. Indeed, with access to care models that provide additional resources that could be used for drug treatment or some of these other interventions, many patients may prefer the latter until the evidence base on the mAb treatments improves. This is another reason why CMS should accelerate its key strategic goal of increasing beneficiary access to alternative payment models for advanced primary care and comprehensive care, including telehealth support from specialists to frontline providers to increase access to care in rural and other undeserved areas.

The alternative payment models are consistent with current promising Medicare pilots and programs like Primary Care First, Independence at Home, and accountable care organizations. Clinicians or provider groups receive at least part of their payment in a risk-adjusted per-person amount, which gives them more flexibility to provide the specific services that are most needed by a patient, even if not covered by Medicare. At the same time, they are accountable for improving outcomes for the populations they serve, including better patient/caregiver experience and quality of care, fewer days in care away from home, and lower total costs. Such alternative payment models could help collect needed data on important patient outcomes, such as ability to live independently, that the new AD mAb therapies are be expected to improve. The alternative payment models can also support partnerships between providers and manufacturers to share risks related to uncertainty about the impact of mAb treatment, where payments would be greater when patient populations achieve better outcomes.

While some private payers have concluded so far that the current evidence on mAb therapy does not support coverage, some other private payers and Medicare Advantage plans are also exploring alternatives to Medicare's standard "ASP+6%" payment system. For example, payment might be based on continuation (e.g., no or lesser payments for patients who terminate treatment early due to safety issues or progression) or partial capitation (e.g., drug payments reduced or capped above some level of spending in the population). Some payers have also proposed an "accelerated approval" payment rate that could be increased after evidence improves and/or full approval occurs, which would be difficult to implement under current Part B payment rules. CMS should explore ways in which it can support private plans in implementing innovative contracting alternatives to traditional Part B payment, or potentially even pilot such models.

These payment reforms are not easy to implement quickly, but could improve access to mAb therapies as well as other available or emerging AD therapies. They would also advance a needed shift of AD-related care from fragmented, reactive, and uneven access to more person-centered approaches. Now is the time to advance these models, both to inform the current NCA and to provide a stronger foundation for efficient access to effective therapies in the future.

In conjunction with the NCA for aducanumab and other amyloid targeting mAb therapies, CMS should also consider short-term steps to update its coverage of amyloid PET scanning. CMS has determined that PET amyloid-beta imaging is not reasonable and necessary for the diagnosis or treatment of illness, except to help diagnose AD in clinically difficult cases.[6] Per the current NCD for Amyloid PET, one scan will be covered per patient through CED clinical trials that meet certain requirements. Only patients involved in clinical trials will be eligible for covered PET scans, and only if CMS determines that the results of the PET scans lead to improved health outcomes.[7] We recommend CMS reevaluate coverage criteria for diagnostic amyloid PET to conform to appropriate uses of diagnostic PET scans for decisions regarding mAb therapy use. More specifically, in the short term, CMS should revise its PET NCD to provide clarity that it will conform to local coverage decisions on mAbs by Medicare Administrative Contractors ahead of the completion of the NCD. CMS should also assess the feasibility of including a code for whether the test result was a positive screen for amyloid plaque. Such data collection may

facilitate coverage decisions for particular beneficiaries, and can also improve the evidence on appropriate screening methods. Then, as part of the mAb NCA process, the PET NCD should be updated to match the final mAb NCD. CMS should also determine whether special coverage considerations will also be needed for other tests, for example, diagnostic blood tests in development that may be headed to the FDA for authorization in the coming months.

Conclusion

The burden of disease of AD on the Medicare population is substantial and it is projected to get worse. Aducanumab is the first disease-modifying treatment that shows promise of slowing the rate of cognitive decline that is characteristic of AD; more AD mAb therapies may be approved soon. However, current clinical evidence on the safety and efficacy of aducanumab has raised important questions for the "reasonable and necessary" coverage determination for Medicare beneficiaries with MCI and early stage AD.

This situation is another reminder that CMS needs updated resources and authorities to help anticipate and manage the coverage and post-market evidence needs that arise as a result of the successes of accelerated and breakthrough approvals. The increasing pace of development of technologies that influence serious diseases "upstream" that may have important long-term effects, presents opportunities for learning more and creating more value from such products after approval. This NCA process is timely and appropriate, but also challenging.

We appreciate the intense efforts at CMS to seek input and engage the public and private sector in conducting its NCA. While opinions differ about what CMS should decide, there is a deep commitment across all stakeholder groups to use this opportunity to improve evidence and care for all Americans touched by AD. Given the potentially substantial implications for the care of Medicare beneficiaries, not to mention the potentially significant implications for Medicare spending, we hope that CMS will undertake a thorough process involving MEDCAC, potential research funders such as the National Institute on Aging and the Patient-Centered Outcomes Research Institute, as well as patient advocates, private payers, providers and other stakeholders, to reach a coverage determination that includes the effective use of CED and thoughtful consideration of appropriate and equitable access for beneficiaries outside of the CED process. In addition, the NCA process should recognize that evidence on this class of treatments will evolve in the coming months with expected clinical study reports involving other AD mAb therapies.

We believe evidence development should be a key component of this coverage analysis and determination, as it is critical not only for an effective NCD now but also to allow CMS to improve care and the evidence base ahead of future coverage decisions in the AD space. Our recommendations to improve evidence include not only options for CED, but also steps that CMS can take in the short term during the NCA process to closely assess emerging evidence on amyloid plaque reduction as a validated surrogate marker and to encourage a timely and informative Phase IV study. In addition, CMS should implement timely conforming changes to its policies for PET coverage for diagnosing AD.

Moreover, CMS can play an important role in promoting standardized, efficient data collection and analysis related to AD, including consistent use of meaningful measures related to functional outcomes, quality of life, independence, use of supportive care, and complications. CMS leadership on data and meaningful measures enables not only better evidence but also better care models for AD patients that

incorporate evidence-based pharmaceutical and non-pharmaceutical therapies, and that help reduce inequities.

With both pharmacologic and nonpharmacologic innovations in care, there is an increasingly urgent need for CMS's support for better care models for AD. Barriers to access and inequities in current care models will become more pronounced as more such innovations are developed. Accordingly, CMS should advance alternative payment models that promote greater care coordination and mitigate barriers to access to care. Moreover, alternative payment models, by basing financial risk of treatments on observed outcomes, can promote greater evidence development, better patient and disease management, and downstream technological improvements.

Ultimately, any coverage decision should help patients, clinicians, and caregivers get the information and care systems to make the best treatment decisions for their needs. As this NCA process unfolds over the coming months, we look forward to opportunities to update and refine our recommendations to support the NCA process, based on the evolving evidence on mAb therapies and on the best approaches to include them in coverage and in better care models for AD patients.

The Duke-Margolis Center and our colleagues appreciate CMS's consideration of our comments.

Sincerely,

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