June 7, 2024

Comments on Food and Drug Administration's Draft Guidance: "Early Alzheimer's Disease: Developing Drugs for Treatment" (FDA-2013-D-0077)

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, submits the below comments on the Food and Drug Administration's (FDA's) Draft Guidance, "Early Alzheimer's Disease: Developing Drugs for Treatment," published in the *Federal Register* on March 12, 2024.

The goal of the draft guidance is "to assist sponsors in the clinical development of drugs for the treatment of the stages of sporadic Alzheimer's disease (AD) that occur before the onset of overt dementia" (or early Alzheimer's disease).[1] The draft details the agency's current thinking on the selection criteria for clinical trial enrollment and the selection of endpoints for clinical trials in this population.[2] To this end, the draft guidance defines what the agency considers to be the three stages of early Alzheimer's disease:[3]

- Stage 1 includes patients "with characteristic pathophysiological changes of AD but no evidence of clinical impact." Importantly, the guidance clarifies that this stage describes patients who are "truly asymptomatic with no subjective complaint, [or] functional impairment…"
- Stage 2 describes patients who already have "subtle detectable abnormalities on sensitive neuropsychological measures or subjective complaints of mild cognitive symptoms but no functional impairment."
- Stage 3 describes patients who generally have "more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment," corresponding roughly to "mild cognitive impairment."
- The guidance does not address Stages 4 through 6, which include patients with overt dementia.

Public Citizen agrees that research is needed to develop treatments that provide patients living with Alzheimer's disease, including those at the early symptomatic stages, clinically meaningful benefits. We also agree that is important for patients who experience early symptoms to have access to reliable diagnostic tools that will allow them and their caregivers to make informed decisions about prevention and treatment strategies. The draft guidance, however, raises three main areas of concern. We urge the FDA to revise the final guidance to fully address these concerns.

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[1] Food and Drug Administration. Draft guidance. Early Alzheimer's disease: developing drugs for treatment. March 12, 2024. https://www.fda.gov/media/110903/download. Accessed June 7, 2024.
[2] *Id*. PDF p. 9.
[3] *Id.* PDF p. 6.

1. The proposed definition of early Alzheimer's disease and the reliance on biomarkers as both a diagnostic tool and a measure of benefit

The draft guidance states that because "the scientific understanding of AD has evolved," the clinical criteria that have historically been used for enrollment in trials may need to be replaced with the "use of biomarkers reflecting underlying AD pathophysiological changes".[4] These biomarkers (not directly defined in the draft guidance but presumably including the Alzheimer' disease biomarker amyloid beta) are described as preceding "often by many years or even decades, the development of clinically evident findings…."

The draft guidance not only expects that evidence from these biomarkers will "establish the reliable diagnosis of subjects in trials of early AD" but also argues that they "may be an appropriate measure" to help address the challenge of demonstrating "a clinically meaningful benefit" in clinical trials involving asymptomatic individuals at the proposed earliest stages of Alzheimer's disease.[5]

We are concerned about the limited view that the draft guidance takes about the causes of Alzheimer's disease and the importance of biomarkers. At present, there is no scientific consensus about the causes of Alzheimer's disease. According to the National Institute on Aging, Alzheimer's disease can be influenced by multiple genes in combination with environmental and lifestyle factors.[6] Specifically, evidence is lacking that the accumulation of amyloid beta is necessarily the cause of Alzheimer's disease or that targeting amyloid beta is sufficient or even necessary to delay or reverse disease progression at any stage of the disease. Available data from recent clinical trials involving drugs that target amyloid beta to treat Alzheimer's disease (such as aducanumab, lecanemab, or donanemab)[7,8,9] have not demonstrated meaningful clinical improvement for patients. These drugs are associated with serious adverse events such as amyloid-related imaging abnormalities, cerebral hemorrhage**,** and a decrease in whole brain

[4] *Id.* PDF p. 5.
[5] *Id.* PDF p. 7, 10.
[6] National Institute on Aging. Alzheimer's disease genetics fact sheet. Last reviewed March 1, 2023. https://www.nia.nih.gov/health/genetics-and-family-history/alzheimers-disease-genetics-fact-sheet. Accessed June 7, 2024.
[7] Public Citizen. Testimony before the FDA's peripheral and central nervous system drugs Advisory Committee regarding aducanumab for the treatment of Alzheimer's disease. November 6, 2020. https://www.citizen.org/wp-content/uploads/2556.pdf. Accessed June 7, 2024.
[8] Public Citizen. Testimony before the FDA's peripheral and central nervous system drugs Advisory Committee regarding lecanemab for the treatment of Alzheimer's disease. June 9, 2023. https://www.citizen.org/article/testimony-before-the-fdas-peripheral-and-central-nervous-system-drugs-advisory-committee-regarding-lecanemab-for-the-treatment-of-alzheimers-disease/. Accessed June 7, 2024.
[9] Public Citizen. Outrage of the month: FDA approval of lecanemab for Alzheimer's disease. August 2023. https://www.citizen.org/article/outrage-of-the-month-fda-approval-of-lecanemab-for-alzheimers-disease/. Accessed June 7, 2024.

volume and cortical thickness.[10] Instead, biomarkers may represent a marker of the disease, not a causal factor.[11,12]

This is of particular concern, because aducanumab and lecanumab received accelerated and traditional approval, respectively, by the FDA, even though these drugs failed to achieve accepted clinically meaningful outcomes. This also set a problematic precedent regarding the required treatment effects amyloid lowering drugs need to demonstrate for approval. For this reason, in the final guidance Public Citizen strongly encourages the FDA to require prespecified outcome measures of what will be considered clinically meaningful for clinical trials of drugs targeting Alzheimer's disease.[13,14]

Public Citizen believes that the focus on biomarkers (such as amyloid beta) is premature, especially as a "reliable" diagnostic tool in otherwise asymptomatic individuals.[15,16] For instance, research suggests that not all patients with a clinical diagnosis of Alzheimer's disease have amyloid beta buildup, and many individuals with amyloid beta buildup will never develop Alzheimer's disease or experience clinically detectable cognitive decline.[17,18] Even among apolipoprotein E4 (*APOE4*) homozygotes, who are known to have a higher lifetime risk of developing Alzheimer's disease and often to have higher levels of biomarkers, about 12% do not have detectable amyloid beta.[19]

Public Citizen is concerned that classifying "truly asymptomatic" individuals as patients with Stage 1 Alzheimer's disease and thereby eligible for enrollment in clinical trials does not serve patients' needs and instead puts them at considerable risk of overdiagnosis and overtreatment. For instance, it has been estimated that the proposed criteria could classify over 40 million adults in the United States to be in the stage 1 category. Most of these adults would never

[10] Widera E. Who gets to decide on what it means to have Alzheimer's disease? *J Am Geriatr Soc*. 2024;1-3.
[11] *STAT News*. The maddening saga of how an Alzheimer's 'cabal' thwarted progress toward a cure for decades. June 25, 2019. https://www.statnews.com/2019/06/25/alzheimers-cabal-thwarted-progress-toward-cure/. Accessed June 7, 2024.
[12] Kumar A, Nemeroff CB, Cooper JJ, et al. Amyloid and tau in Alzheimer's disease: biomarkers or molecular targets for therapy? Are we shooting the messenger? *Am J Psychiatry*. 2021;178(11):1014-1025.
[13] Liu KY, Schneider LS, Howard R. The need to show minimum clinically important differences in Alzheimer's disease trials. *Lancet Psychiatry*. 2021;8(11):1013-1016.
[14] Liu KY, Thambisetty M, Howard R. How can secondary dementia prevention trials of Alzheimer's disease be clinically meaningful? *Alzheimers Dement*. 2023;19(3):1073-1085.
[15] Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. *Alzheimers Dement*. 2018;14(8):981-988.
[16] Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446.
[17] Kumar A, Nemeroff CB, Cooper JJ, et al. Amyloid and tau in Alzheimer's disease: biomarkers or molecular targets for therapy? Are we shooting the messenger? *Am J Psychiatry*. 2021;178(11):1014-1025.
[18] Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA*. 2015;313(19):1924-38.
[19] Fortea J, Pegueroles J, Alcolea D, et al. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. *Nat Med*. 2024;1-8.

develop the disease and would therefore not benefit from treatments.[20,21] Research also has shown that the detection of amyloid beta tends to be associated with an increase in inappropriate use of Alzheimer's drugs; when amyloid beta was not detected, drug use in patients did not substantially decrease.[22]

Our concern about overdiagnosis and inappropriate use of medications in millions of asymptomatic adults is compounded by the fact that blood tests for biomarkers are less invasive, less expensive, and more accessible than magnetic resonance imaging of the brain and thus are likely to be more widely used.[23,24]

The draft guidance also has concerning resemblances to the revised criteria on the diagnosis and staging of Alzheimer's disease proposed by the Alzheimer's Association.[25] The Alzheimer's Association receives considerable financial support from pharmaceutical companies, which could benefit from a broader definition of Alzheimer's disease and a broader market for their drugs. Moreover, one-third of the members of the Alzheimer's Association workgroup were directly employed by industry, and another third had substantial financial conflicts of interest.[26]

2. The proposed criteria for the duration of clinical trials and the selection of clinical endpoints

The draft guidance acknowledges that clinical trials with a duration of two years or less in subjects with early Alzheimer's disease may not be sufficient to "establish a clinically meaningful treatment effect in early AD due to the minimal or absent cognitive and functional deficits seen in those stages of the disease" and that in clinical trials involving subjects with asymptomatic early-stage Alzheimer's disease many of the tools "used to measure functional impairment in patients with later dementia stages… would not be sensitive to detect subtle functional changes in early AD."[27]

For this reason, the draft guidance states that the FDA is willing to consider "endpoints based on cognitive assessments or surrogate endpoints, which may allow for shorter trial durations as a

[20] Widera E. Who gets to decide on what it means to have Alzheimer's disease? *J Am Geriatr Soc*. 2024;1-3.
[21] Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. *Alzheimers Dement*. 2018;14(8):981-988.
[22] Langa KM, Burke JF. Preclinical Alzheimer disease-early diagnosis or overdiagnosis*? JAMA Intern Med*. 2019;179(9):1161-1162.
[23] *New York Times*. Apparently healthy, but diagnosed with Alzheimer's? March 23, 2024. https://www.nytimes.com/2024/03/04/health/alzheimers-amyloid-diagnosis.html. Accessed June 7, 2024.
[24] *Los Angeles Times*. Inside the plan to diagnose Alzheimer's in people with no memory problems — and who stands to benefit. February 14, 2024. https://www.latimes.com/science/story/2024-02-14/inside-controversial-plan-to-diagnose-alzheimers-in-people-without-symptoms. Accessed June 7, 2024.
[25] Alzheimer's Association. Revised criteria for diagnosis and staging of Alzheimer's disease. https://aaic.alz.org/diagnostic-criteria.asp. Accessed June 7, 2024.
[26] Widera E. Who gets to decide on what it means to have Alzheimer's disease? *J Am Geriatr Soc*. 2024; 1-3.
[27] Food and Drug Administration. Draft guidance. Early Alzheimer's disease: developing drugs for treatment. March 12, 2024. https://www.fda.gov/media/110903/download. Accessed June 7, 2024.

basis for approval in the earliest stages of AD."[28] Importantly, the draft guidance states that the FDA may accept such surrogate endpoints for accelerated approval of a drug, even if these are endpoints that "do not directly measure clinical benefit but that are considered reasonably likely to predict clinical benefit."[29]

Given the willingness to allow the inclusion of individuals with early Alzheimer's disease in clinical trials (which, as discussed above, could include millions of individuals, many of whom will never experience cognitive decline), Public Citizen urges that the draft guidance be revised to ensure that all clinical trials are based on scientific principles serving the interests of this vulnerable patient population. Specifically, the FDA should ensure that the clinical trials are designed and appropriately powered to provide evidence about whether a drug has measurable and clinically meaningful benefits that outweigh the adverse effects associated with the treatment. The FDA should not allow sponsors to shorten the duration of trials or use surrogate endpoints without *a priori* convincing evidence that the surrogate endpoint is reasonably likely to predict clinical benefit.

3. Insufficient guidance for the development of drugs for early Alzheimer's disease

For the final guidance, Public Citizen urges the FDA to consider and include additional context for the development of drugs for early Alzheimer's disease.

For example, the *APOE* gene influences an individual's risk of Alzheimer's disease.[30] A person who carries the *APOE4* gene (about 15-25% of the population) has a higher risk of developing Alzheimer's disease, especially if the individual has two copies of this gene (about 2-5% of the population).[31] Given the increased risk for carriers of the *APOE4* gene, it is concerning that recent clinical trials with drugs targeting amyloid beta (such as lecanemab and donanemab)[32,33] indicate that such drugs are associated with less benefit and an increased risk of adverse effects in *APOE4* homozygotes.[34] The final guidance document should advise sponsors on how to address potential safety concerns for people who carry the *APOE4* gene and how best to include them in clinical trials.

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[28] *Id.* PDF p. 8.
[29] *Id.* PDF p. 7.
[30] Fortea J, Pegueroles J, Alcolea D, et al. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. *Nat Med*. 2024;1-8.
[31] National Institute on Aging. Alzheimer's disease genetics fact sheet. Last reviewed March 1, 2023. https://www.nia.nih.gov/health/genetics-and-family-history/alzheimers-disease-genetics-fact-sheet. Accessed June 7, 2024.
[32] *Worst Pills, Best Pills News*. Lecanemab for Alzheimer's disease: do not use. October 2023. https://www.worstpills.org/newsletters/view/1556. Accessed June 7, 2024.
[33] Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512-527.
[34] *STATNews*. Alzheimer's risk gene APOE4 may cause a distinct form of the disease, study suggests. May 6, 2024. https://www.statnews.com/2024/05/06/alzheimers-disease-research-apoe4-gene-risk-factor/. Accessed June 7, 2024.

Rates of dementia vary across racial and ethnic groups; Black individuals have a higher prevalence of dementia, including from Alzheimer's disease, than Whites.[35] Moreover, some research suggests that Alzheimer's disease may have different causes and biomarkers in Black and Hispanic individuals than in White individuals. For example, the effect of the *APOE4* gene may be different in Black and Hispanic individuals than in White individuals, and biomarkers other than amyloid beta may be more relevant.[36,37] As non-White subjects are often not adequately represented in clinical trials, the final guidance document should address considerations for ensuring adequate representation.

Classifying "truly asymptomatic" individuals as having Stage 1 Alzheimer's disease based on biomarkers alone also has serious ethical implications. In revising the draft guidance, the FDA should carefully consider the lack of compelling evidence for a favorable benefit-risk ratio for the early diagnosis and treatment of asymptomatic patients. At present, as previously stated, there is no evidence to suggest that drugs targeting biomarkers delay, halt, or reverse Alzheimer's disease at any stage of the disease. Many of those who would be diagnosed by "Stage 1 criteria" will never develop Alzheimer's disease or require treatment. To the contrary, the clinical trials conducted for aducanumab, lecanemab, and donanemab have established that drugs targeting amyloid beta are associated with substantial harm, as discussed above.[38] Moreover, to date, little is known on whether and how the demonstrated adverse events (such as amyloid-related imaging abnormalities) influenced the cognitive or functional outcomes in these trials.[39] Absent compelling evidence from clinical trials, there is no reason for healthy, asymptomatic individuals to be treated for Alzheimer's disease, especially given the potential for considerable harms and costs from years to decades of treatment.[40] The concerns include psychological trauma and potential discrimination in employment and health insurance.[41]

Finally, the final guidance should place more emphasis on the importance of addressing known risk factors and nonpharmacologic approaches to Alzheimer's disease, which have been found to be effective even in individuals with a genetic susceptibility for Alzheimer's disease, such as

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[35] Matthews KA, Xu W, Gaglioti AH, et al. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015-2060) in adults aged ≥65 years. *Alzheimers Dement*. 2019;15(1):17-24.

[36] *STAT News*. In the whitewashed world of Alzheimer's research, one scientist is on a quest to understand the diversity of brains. March 30, 2023. https://www.statnews.com/2023/03/30/alzheimers-research-lisa-barnes-brains/. Accessed June 7, 2024.

[37] Fortea J, Pegueroles J, Alcolea, et al. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. *Nat Med*. 2024;1-8.

[38] Widera E. Who gets to decide on what it means to have Alzheimer's disease? *J Am Geriatr Soc*. 2024; 1-3.

[39] Thambisetty M, Howard R. Conveying Risks of Harm in Alzheimer Disease by Amyloid Lowering. JAMA. 2024 May 6.

[40] *New York Times*. Apparently healthy, but diagnosed with Alzheimer's? March 23, 2024. https://www.nytimes.com/2024/03/04/health/alzheimers-amyloid-diagnosis.html. Accessed June 7, 2024.

[41] *Los Angeles Times*. February 14, 2024. Inside the plan to diagnose Alzheimer's in people with no memory problems — and who stands to benefit. https://www.latimes.com/science/story/2024-02-14/inside-controversial-plan-to-diagnose-alzheimers-in-people-without-symptoms. Accessed June 7, 2024.

APOE4 gene carriers.[42,43] The *Lancet* Commission recently highlighted 12 modifiable risk factors for dementia, including hypertension, hearing impairment, depression, lack of physical activity, obesity, diabetes, smoking, excessive alcohol consumption, and air pollution.[44]

Thank you for the opportunity to comment on this draft guidance, which addresses important public health issues.

Sincerely,

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[42] Centers for Disease Control and Prevention. Reducing Risk of Alzheimer's Disease. Last reviewed: September 13, 2022. https://www.cdc.gov/aging/publications/features/reducing-risk-of-alzheimers-disease/index.htm. Accessed June 7, 2024.
[43] Neuffer J, Wagner M, Moreno E, et al. Association of LIfestyle for BRAin health risk score (LIBRA) and genetic susceptibility with incident dementia and cognitive decline. *Alzheimers Dement*. 2024; 1-10.
[44] Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413-446.