



**Aducanumab for Alzheimer’s Disease
Summary of Public Comments on Draft Report**

June 30, 2021

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#	Comment	ICER Response
Manufacturers		
Biogen		
1.	When conducting comparative effectiveness analysis and economic modeling, data should be pooled only when adjustments are made for differences within the datasets. In particular, to pool data from different trials without adjusting for known relevant differences such as duration of follow-up, exposure to the target treatment dose, etc., may lead to biased results.	While we appreciate that there are differing views on how to interpret the discrepant results between ENGAGE and EMERGE, there is no <i>a priori</i> reason to believe the results of one trial over the other. It is as likely that the results from ENGAGE are true (and perhaps more likely given prior failures of drugs in this class) as it is that the EMERGE results are true. Blending the results seems like the fairest approach in this situation, though we recognize that the true effect of aducanumab may not be the average of the results of the two trials. Furthermore, we present pooled data from multiple scenarios including the opportunity-to-complete population, and the post-Protocol Version 4 population, which accounts for many of the known relevant differences between ENGAGE and EMERGE, and we also present scenarios that focus on the results of EMERGE being true; if, in fact, the results of ENGAGE are true, then the therapy has no value.
2.	All methodological assumptions in a cost-effectiveness analysis need to be balanced and justified. When assumptions are made, base assumptions should be realistic and tested in extensive scenario analysis.	We completely agree. We have conducted extensive sensitivity and scenario analyses. Further, we have presented additional scenario analyses from what were published in the Draft Evidence Report.
3.	Technology assessments should incorporate unique societal considerations of the disease state being assessed.	We used best-available evidence to capture the impact beyond that of the health system perspective. We included caregiver quality of life, caregiver time spent caregiving, caregiver direct medical costs, and patient productivity. Further, we presented the modified societal perspective as a co-base-case for all our analyses.
4.	Appropriate disease-specific value thresholds should be utilized in the economic model. For example, ICER's quality-adjusted life-year (QALY) thresholds (\$100K-\$150K) are too low for Alzheimer's disease and should be adjusted to capture the devastating disease burden, lack of treatments, and other contextual considerations.	We do not suggest one specific threshold or one specific formula in estimating a fair price. Rather we present a range of threshold prices from \$50,000-\$200,000 per outcome gained. We are aware of the literature suggesting higher thresholds for more severe illnesses with high unmet need, and understand that this literature suggests lower thresholds for less severe illnesses with lower unmet need. Because you are recommending a higher threshold for Alzheimer's disease, we would be interested to know which conditions you feel we should evaluate using a lower threshold. Instead of listing winners and losers, we allow for deliberation: our voting panels can determine what may be appropriate across a wide range of field-supported thresholds.

Eli Lilly and Company		
1.	<p>We were encouraged to see ICER include in the draft evidence report on aducanumab (Section 5) a short list of potential benefits and contextual considerations beyond those captured in the traditional cost-effectiveness paradigm that may affect overall judgments of long-term value for money provided by treatments for AD. A more comprehensive benefit list was articulated by a special ISPOR task force in 2018 and includes a number of additional value elements of particular relevance in AD. These include:</p> <ul style="list-style-type: none"> • (1) “scientific spillover,” the value of research and innovation in an area of high unmet medical need on future generations regardless of immediate health gains; • (2) “insurance value,” the benefit to healthy persons of physical and financial risk protection provided by effective new treatments; • (3) “severity of disease,” the greater value placed by society on treating more severe diseases; and • (4) “distributional equity,” addressing the disproportionate impact of disease on different groups and communities, including those defined by age, gender, race/ethnicity, socioeconomic status, and educational level. 	<p>The value assessment field continues to develop methods that comprehensively measure harms and benefits of treatments. ICER’s current Value Assessment Framework features aspects of “severity of disease” and “distributional equity,” through our Potential Benefits and Contextual Considerations section. We view scientific spillover and insurance value as emerging domains that need further testing. We ask our voting panels if domains outside those covered are important in their long-term value judgments. As we continue to test new domains, the field should also wrestle with the opportunity costs and face head-on the situations where we may be willing to trade more health lost to gain health in the treated population versus in other treated populations where we are not willing to make such a trade.</p>
2.	<p>These additional value elements are missing in the standard “cost per QALY” framework. Given the critical importance of many of these factors in AD, we disagree with ICER’s approach of defaulting to the “frequently cited” willingness-to-pay thresholds of \$50K, \$100K and \$150K per QALY gained for base-case analyses and in “fair price” calculations. AD, in particular, has been called out, along with metastatic cancers, as one of the most “severe” illnesses with high unmet need, for which use of a higher threshold would be appropriate. While asking the members of the California Technology Assessment Forum (CTAF) voting body to consider additional contextual considerations when assessing the value of treatments for AD is appropriate, we feel that anchoring such judgments to traditional (and controversial) cost-per-QALY benchmarks is problematic.</p>	<p>We do not suggest one specific threshold or one specific formula in estimating a fair price. Rather we present a range of threshold prices from \$50,000-\$200,000 per outcome gained. We are aware of the literature suggesting higher thresholds for more severe illnesses with high unmet need, and understand that this literature suggests lower thresholds for less severe illnesses with lower unmet need. Because you are recommending a higher threshold for Alzheimer’s disease, we would be interested to know which conditions you feel we should evaluate using a lower threshold. Instead of listing winners and losers, we allow for deliberation: our voting panels can determine what may be appropriate across a wide range of field-supported thresholds.</p>
3.	<p>We commend ICER for responding to several important points that were raised consistently by multiple stakeholders in response to the initial Scoping Document on aducanumab reported in November 2020. In particular, we applaud the formal adoption of both health care system and societal perspectives as base-case comparative cost-</p>	<p>Thank you. We have used best-available evidence to inform the inputs in our model and have attempted to be as comprehensive as possible. If you are aware of high-quality evidence that we are not using, please provide a specific citation of that evidence and we will review it for potential inclusion in our review.</p>

	<p>effectiveness analyses and the consequent inclusion of costs and benefits from both patient and caregiver perspectives. On the other hand, we remain concerned that in its current form ICER’s cost-effectiveness model may still significantly underestimate the full extent of the costs of AD from both of these perspectives. For example, ICER’s current model does not include out-of-pocket expenditures paid by patients and family members for medical care, long-term care and formal care, which can be substantial, particularly in later stages of disease. Furthermore, caregiver costs captured in ICER’s model reflect only the opportunity cost of time spent caregiving and neglect other spill-over costs attributable to reduced health and well-being of the caregiver and other family members.</p>	
4.	<p>Another concern with the current model is that it likely significantly underestimates the quality-of-life impact of AD on both patients and caregivers due to the choice of utilities used in modeling. The patient utility values used in ICER’s model are derived from a study using generic health-related quality-of-life instruments (i.e., EQ-5D and HUI3) that are broadly criticized as inappropriate in AD in that they are insensitive to changes in disease progression and having substantial ceiling effects and poor inter-rater reliability. This same study was used for estimates of caregiver quality-of-life, despite the fact, as noted by the authors of the draft report, that these utilities “did not vary by AD disease severity” – a fact that demonstrates a lack of face validity for this use and further reinforces our concerns about the scores.</p> <p>We propose that using values derived from direct utility elicitation studies or, alternatively, mapping from more sensitive disease-specific measures such as the Quality of Life Alzheimer’s Disease scale (QOL-AD) to utility scores could provide more reliable and credible estimates.</p>	<p>We have searched for multiple estimates for patient and caregiver quality of life, and have engaged numerous stakeholder groups for these data. We believe we are using the best-available evidence to date. If you are aware of high-quality evidence that we are not using, please provide a specific citation of that evidence and we will review it for potential inclusion in our review.</p>
5.	<p>As a final point, we note that ICER chose to conduct sensitivity analyses only from the health care system perspective. In light of the importance of and uncertainty around, both indirect costs of care and caregiver quality-of-life impacts as noted above, we suggest ICER include sensitivity analyses from the societal perspective in order to understand the effects of uncertainty on these and other caregiver-related variables on cost-effectiveness estimates.</p>	<p>We have now included results from the societal perspective (in addition to the results from the health care system perspective) for sensitivity and scenario analyses.</p>
Genentech		
1.	<p>Capture the holistic value of aducanumab by describing key secondary clinical endpoints from</p>	<p>We agree that discussion of secondary clinical endpoints is an important part of evaluating the</p>

	<p>ENGAGE/EMERGE, in addition to primary endpoints, in the Comparative Clinical Effectiveness section.</p> <p>Recommendation: The Comparative Clinical Effectiveness section should include a detailed discussion of secondary clinical endpoints from ENGAGE/EMERGE trials, including Mini-Mental State Exam (MMSE), Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13), Alzheimer’s Disease Cooperative Study Scale for Activities of Daily Living in Mild Cognitive Impairment (ADCS-ADL-MCI), and Neuropsychiatric Inventory 10 (NPI-10).</p>	<p>clinical effectiveness of aducanumab and have done so with a summary in the Evidence Report and detailed discussion in the Report Supplement. The ICER report structure has been streamlined and as per the new structure, this type of detailed information is typically placed in the Report Supplement. Direct links to the Report Supplement are embedded into the Evidence Report to facilitate easy access to this information from the main body.</p>
2.	<p>Adopt a more comprehensive approach to estimating patient/caregiver burden in the societal perspective by adding scenarios that include health-related quality of life (HRQoL) beyond a single, primary caregiver and that reflect the broader productivity impacts for patients and their caregivers.</p> <p>Recommendation: A scenario analysis should be added that incorporates additional caregiver utility decrements to reflect instances where an AD patient has more than one informal caregiver, including secondary caregivers. Additionally, the approach to modeling caregiver societal costs should be updated to include broader productivity impacts (e.g., absenteeism, presenteeism) and non-market productivity losses (e.g., volunteer activities, secondary childcare, and eldercare) for multiple caregivers per AD patient.</p>	<p>The evidence used to inform the societal perspective in our model is for a primary caregiver who was assumed to be responsible for the vast majority of patient care. Our model uses best-available evidence and this evidence focused on a single primary caregiver. Assumptions not founded upon evidence would have to be made if additional caregivers were included in the model, alongside the potential overlap in contributions across caregivers. The evidence we identified was not as granular as suggested by this comment. For future responses, please share citation(s) for more actionable recommendations so that we may review the evidence for potential inclusion in our analysis.</p>
3.	<p>Leverage equity-informative value assessment methods to incorporate health equity considerations into the appraisal of aducanumab.</p> <p>Recommendation: Explore and apply formal health equity-informative methodology (e.g. distributional cost-effectiveness analysis [DCEA]) to the value assessment of aducanumab.</p> <p>If formal equity-informative methods of cost-effectiveness are not feasible for ICER at this time, we recommend that ICER conduct extensive scenario analyses to (1) benchmark the level of inequality in AD patients relative to the other diseases; and (2) consider how differences in timing of diagnosis across subgroups impacts treatment effect. Furthermore, ICER should describe the important variation in family spillover effects across key vulnerable subgroups based on race/ethnicity and other social determinants of health in the main body of the report.</p>	<p>Many institutions, including ICER, are exploring adaptations to cost-effectiveness analysis (e.g., MCDA, DCEA, etc.). There is extensive methodological work that still needs to be refined and developed. ICER’s Value Assessment Framework includes flexibilities built into that framework for deliberation that can include key other benefits and contextual considerations (e.g., equity). Finally, if a therapy causes net harm, this may result in additional harms to vulnerable populations.</p>

Patient Organizations

Alliance for Aging Research

1.	<p>ICER’s made-up “modified societal perspective” does not cut it. However, ICER’s method of disease burden analysis incorporates direct medical costs into its model and relegates the costs of health effects to family caregivers or work loss for family members related to care needs for loved ones with AD to its subjective “modified societal perspective” as a “co-base-case analysis.” ICER states that the rationale for this additional analysis is due to “the large impact of AD on caregivers,” which makes it seem as though it would better account for the caregiver perspective. Instead, the modified societal perspective that ICER invented penalizes the caregiver for the productivity and economic impacts of keeping a loved one at home, as captured in report summary and comment:</p> <ul style="list-style-type: none">• “In addition, keeping a patient in earlier AD states longer, which delays the transition to long-term care, can increase productivity losses for the caregiver...This highlights the complexities of capturing caregiver perspectives in the modified societal perspective in that caregivers may prefer to keep loved ones at home, rather than in a long-term care facility, although doing so may increase the negative financial impact on the caregiver.” <p>This statement illustrates the tension inherent in the assumptions underlying ICER’s value assessment framework, even under the modified societal perspective proposal, illustrating its inherent weakness and inability to truly account for the family caregiver perspective. From a patient, family caregiver, and societal perspective, there is significant value to prolonging independence and identity that is not reflected in medical costs or solely captured in caregiving burden. Slowing the progression of AD means prolonging independence and identity, both lowering caregiver burden in earlier stages of the disease and providing immense intrinsic value to patients and their families that outweighs opportunity costs lost elsewhere. If this value is not reflected in the value assessment, that is a shortcoming of the model in accurately capturing and incorporating value, not of patients and caregivers in valuing non-monetary outcomes. If value assessment fails to accurately capture value to those who benefit from the therapeutic, then the exercise is incomplete.</p>	<p>The burden of the primary caregiver is included in our analysis. Changes in caregiver burden associated with aducanumab were, unfortunately, marginal at best due to the current evidence around aducanumab’s net health benefit. The failure of a treatment in demonstrating net health benefit is not a failure of the value assessment framework. Additionally, ICER has a Value Assessment Framework that includes flexibilities built into that framework for deliberation that can include key other benefits and contextual considerations (e.g., equity, severity, unmet need, etc.) that may not be possible to incorporate in the cost-effectiveness model.</p>
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2.	<p>The use of cost-effectiveness assessment to judge therapeutic value from a payer’s perspective, and technical issues using quality-adjusted life years (QALYs) renders the approach problematic. The QALY has significant limitations when dealing with complex diseases such as AD, as they do not recognize value driven by public health improvement, transformation, or even societal value. These issues are not unique to AD, although the characteristics of AD and the ecology of care around people with AD highlight these issues.</p>	<p>ICER follows common academic and health technology assessment standards by using the cost per QALY gained, but also presents cost per life year gained and cost per evLYG. The QALY is the gold standard for measuring how well a medical treatment improves and lengthens patients’ lives and has served as a fundamental component of cost-effectiveness analyses in the United States and around the world for more than 30 years. ICER has a Value Assessment Framework that includes flexibilities built into that framework for deliberation that can include key other benefits and contextual considerations (e.g., equity, severity, unmet need, etc.) specific to Alzheimer’s disease that may not be possible to incorporate in the cost-effectiveness model.</p>
3.	<p>ICER’s evaluation of the cost-effectiveness of aducanumab in the draft evidence report inappropriately pooled the data of the ENGAGE and EMERGE trials without adjusting for the number of people titrated to a higher dose for the different time periods. Fewer trial participants had the opportunity in ENGAGE to receive high-dose treatment than the patients in EMERGE. By not adjusting, ICER’s approach provides an inaccurate picture of the value of the treatment. In its July 2021 public meeting on aducanumab, we request that ICER address why it selected this approach instead of properly analyzing the updated sponsor data submitted to the FDA.</p>	<p>While we appreciate that there are differing views on how to interpret the discrepant results between ENGAGE and EMERGE, there is no <i>a priori</i> reason to believe the results of one trial over the other. The scientific method begins by assuming an intervention has no effect (no harms and no benefits), also known as the null hypothesis. Conventional scientific approaches place the onus on an intervention, through evidence generation and corresponding analyses, to demonstrate alternatives to the null. Biostatistics, epidemiology, and pharmacoeconomic good practices all argue for best-available evidence approaches in assessing an intervention’s benefits and harms.</p> <p>As the Evidence Report communicates, we support approaches that synthesize evidence across all comparable trials to quantify benefits and harms of aducanumab. In the case of aducanumab, it is as likely that the results from ENGAGE are true (and perhaps more likely given prior failures of drugs in this class) as it is that the EMERGE results are true. Blending the results seems like the fairest approach in this situation, though we recognize that the true effect of aducanumab may not be the average of the results of the two trials. Moreover, we present scenarios that focus on the results of EMERGE being true; if, in fact, the results of ENGAGE are true, then the therapy has no value.</p> <p>We look forward to addressing this issue and discussion about it during the public meeting.</p>
4.	<p>To accurately assess the value of Alzheimer’s disease treatments, Milliman’s report outlines an alternative, equitable value assessment framework for use in AD that accounts for the ecosystem that surrounds people with AD, including the impact treatments may</p>	<p>Thank you for sharing this white paper with us. Many institutions are exploring adaptations to cost-effectiveness analysis (e.g., MCDA, DCEA, etc.) as well as this report by Milliman. There is extensive methodological work that still needs to be refined and</p>

	<p>have on ameliorating social ills such as racial disparities. The principles include that such a framework should:</p> <ul style="list-style-type: none"> • Utilize metrics that, when appropriate, apply the same standards regardless of age or socioeconomics, • Capture the health-related value of AD treatments not only for patients but also for their family caregivers, and • Appropriately account for changes in non-health outcomes and issues of community value related to AD patients and their caregivers. 	<p>developed before potential application. Further, ICER has a Value Assessment Framework that includes flexibilities built into that framework for deliberation that can include key other benefits and contextual considerations (e.g., equity) that may not be able to be incorporated into the cost-effectiveness analysis.</p>
Alzheimer’s Association		
1.	<p>In its effort to evaluate the cost effectiveness of aducanumab, ICER assumed blended efficacy of the ENGAGE and EMERGE trials. We dispute and question ICER’s approach. EMERGE met its prespecified primary outcome and found in the high dose aducanumab group a 22% reduction in decline on the CDR-SB--an outcome that was evident even under the situation of early trial cessation.</p> <p>The argument made by ICER that “the primary outcome of CDR-SB, while a validated scale, is not used frequently in clinical practice and thus the minimal clinically important difference has not been established” is misconstrued.</p>	<p>While we appreciate that there are differing views on how to interpret the discrepant results between ENGAGE and EMERGE, there is no <i>a priori</i> reason to believe the results of one trial over the other. The scientific method begins by assuming an intervention has no effect (no harms and no benefits), also known as the null hypothesis. Conventional scientific approaches place the onus on an intervention, through evidence generation and corresponding analyses, to demonstrate alternatives to the null. Biostatistics, epidemiology, and pharmacoeconomic good practices all argue for best-available evidence approaches in assessing an intervention’s benefits and harms.</p> <p>As the Evidence Report communicates, we support approaches that synthesize evidence across all comparable trials to quantify benefits and harms of aducanumab. In the case of aducanumab, it is as likely that the results from ENGAGE are true (and perhaps more likely given prior failures of drugs in this class) as it is that the EMERGE results are true. Blending the results seems like the fairest approach in this situation, though we recognize that the true effect of aducanumab may not be the average of the results of the two trials. Furthermore, we present scenarios that focus on the results of EMERGE being true; if, in fact, the results of ENGAGE are true, then the therapy has no value.</p> <p>With respect to the CDR-SB, our review of the literature and discussion with multiple experts revealed no consensus on what a clinically relevant difference in the scores would be, and several experts had concerns that the differences seen in EMERGE were too small to be clinically meaningful.</p>
2.	<p>ICER has mischaracterized the ARIA-E and ARIA-H data and mis-interpreted the weight given to it</p>	<p>Although we agree that the data from the clinical trials show that the majority of ARIA cases were</p>

	<p>compared with the potential benefits of the therapy. ICER notes that 41.3% of participants experienced ARIA-E and ARIA-H compared with 10.3% in the placebo arm; that 74.0% of ARIA-E cases in the high-dose aducanumab arm and 89.7% of cases in the placebo arm were asymptomatic; and that most ARIA-E symptoms and MRI findings were mild or moderate in severity and transient (98% resolved) in the high-dose aducanumab arm. These data simply do not support ICER’s conclusion that taking aducanumab has a “high certainty of harm.”</p> <p>ARIA is a manageable side effect of treatment and is far less threatening than complications of many routinely used therapies for other conditions, including cancer. The FDA’s rigorous review of any potential treatment significantly weights the safety but does so in the context of the full data package and in the context of expert guidance. This guidance, and the routine management of ARIA, has been adopted by multiple beta amyloid trials. The Alzheimer’s Association Research Roundtable Workgroup developed recommendations on detecting and monitoring amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials to protect participants, guide clinicians, and ensure that this research can continue. The FDA--whose mission is to protect public health--has adopted guidance, built upon these recommendations, for reasonable management of ARIA.</p>	<p>asymptomatic or mild in severity and mostly resolved, the fact remains that ARIA occurs in a substantial proportion of patients treated with aducanumab, particularly in ApoE+ subjects. Our wording in the Evidence Report that there is certainty of harm with treatment with aducanumab is meant to reflect that all patients given aducanumab are at risk of harm from treatment and that, as demonstrated in the clinical trials, a certain proportion of patients will experience harm.</p>
3.	<p>The misunderstanding and misrepresentation of the scientific evidence surrounding aducanumab has a dramatic effect on ICER’s assumption of the value attributed to the drug, as measured by the assumed QALY gain. For example, using only the evidence from EMERGE rather than the blended data from both ENGAGE and EMERGE would result in a significantly higher assessed gain in QALY from aducanumab, resulting in a cost-effectiveness price about three times higher. Using the data for participants who received the highest dose of aducanumab in EMERGE, the QALY gain would likely be even greater. Such a dramatic difference underscores our concern about using blended data for this analysis, especially since it could have a profound effect on whether patients will have access to the drug.</p>	<p>The scientific method begins by assuming an intervention has no effect (no harms and no benefits), also known as the null hypothesis. Conventional scientific approaches place the onus on an intervention, through evidence generation and corresponding analyses, to demonstrate alternatives to the null. Biostatistics, epidemiology, and pharmacoeconomic good practices all argue for best-available evidence approaches in assessing an intervention’s benefits and harms.</p> <p>As the Evidence Report communicates, we support approaches that synthesize evidence across all comparable trials to quantify benefits and harms of aducanumab. As a scenario analysis, we present the incremental cost-effectiveness ratios and value-based prices assuming only the EMERGE trial evidence. However, as explained in detail in the report, we cannot simply disregard the ENGAGE trial. We blend the estimates between ENGAGE and EMERGE in our base-case analysis rather than selecting one trial over the other. If we selected one trial over the other for</p>

		the base case, the estimates from ENGAGE (and not necessarily EMERGE) may have been selected.
4.	It should be noted that this significant QALY difference is only over the interpretation of the scientific data. ICER's threshold analysis still relies on a rigid, inflexible, narrow--and in our view, outdated--formula that looks solely at direct patient costs instead of a valuation more appropriately suited to therapies for Alzheimer's disease and the long-term value of such a therapy. Alzheimer's disease presents unique issues and challenges to traditional cost-effectiveness analyses. While ICER acknowledges some of these challenges--and does attempt to include a broader "modified societal perspective" in the report--we are troubled that a more serious effort was not made to account for the full range of value that an Alzheimer's therapy would bring or the effect this failure might have on patient access to the drug.	ICER has a Value Assessment Framework that includes flexibilities built into that framework for deliberation that can include key other benefits and contextual considerations (e.g., equity, severity, unmet need, etc.). Further, we have used best-available evidence to inform the inputs in our model and have attempted to be as comprehensive as possible. If you are aware of high-quality evidence that we are not using, please provide a specific citation of that evidence and we will review it for potential inclusion in our review.
5.	ICER's formulation fails to take into account the value of what is truly important to those living with the disease and their caregivers. A systematic review of studies found that patients and caregivers value outcomes such as maintaining an individual's independence and identity--that is, observable effects on their daily life. While ICER incorporates cognitive test scores from the clinical trials on aducanumab in determining cost-effective pricing, these scores can only be faint proxies for what individuals and caregivers truly value: the impact on how they are able to live on a day-to-day basis. ICER does not incorporate these values into the assessment.	We heard from a broad variety of stakeholders that patient-important outcomes include maintaining independence and identity; a summary of these conversations are reflected in the Patient Perspectives section of our report. In the economic analyses, these outcomes are broadly captured by the use of different patient utilities for different states of disease. Finally, the Potential Other Benefits and Contextual Considerations section of the report also attempts to capture outcomes that may not be fully captured in the clinical trial outcomes and economic analyses, and we ask the voting panel to consider these types of outcomes in their deliberations of value and the value votes during the public meeting.
6.	Alzheimer's places a huge burden on caregivers. If ever there was a disease or condition for which the value of a drug to caregivers must be taken into account, Alzheimer's disease is it. The care required of family and friends of those living with the disease is more intense and broader in scope than for caregivers of those with other conditions. Compared with other caregivers, dementia caregivers have twice as many substantial emotional, financial, and physical difficulties. Depression is significantly higher. They are twice as likely to say their health has worsened as a result of caregiving. And, those who contribute to the care of someone with dementia are 28% more likely than other adults to eat less or go hungry because they cannot afford food. A drug therapy that slows the progression of Alzheimer's disease--extending the period of time	We have attempted to be as comprehensive as possible given available evidence in including impact on caregivers including caregiver quality of life, caregiver time spent, and caregiver health impact. We have used best-available evidence to inform the inputs in our model and have attempted to be as comprehensive as possible. If you are aware of high-quality evidence that we are not using, please provide a specific citation and we will review it for potential inclusion. Further, ICER uses a Value Assessment Framework , and there are flexibilities for deliberation of other benefits and contextual considerations that are important to consider. Finally, the effect on reducing caregiver impact is related to the effect of the treatment modeled. When a treatment is not effective or is only marginally effective, the downstream effects will also be limited.

	<p>when individuals with the disease remain in a stage where they have some level of independence and an ability to significantly contribute to their own care--provides an enormous value to caregivers, which must be taken into account in cost-effectiveness analyses. ICER's modified societal perspective includes medical and productivity costs of the primary caregiver--but does not fully account for what caregivers value and the value a drug would bring to caregivers, such as a reduction in distress and burden. In fact, the additional QALY gain under the modified societal perspective appears to be only about 0.005. Other analyses have found the QALY gain attributable to caregiver value significantly higher, indicating that ICER is not taking into account the full and true value to caregivers.</p>	
7.	<p>The unmet need for those living with Alzheimer's and those who will develop Alzheimer's is critical. No disease modifying treatments exist, and for more than a decade there have been a series of initially promising but ultimately ineffective potential disease modifying therapies. Aducanumab represents a real advance for those affected by this devastating disease</p> <p>- It is not a cure, nor even the most successful possible therapy. But it would provide as many as several years of positive benefits for a devastating disease that places an enormous burden on caregivers--and for which there is no alternative. In other words, addressing an unmet need has value in and of itself and should be accounted for.</p>	<p>We fully agree that there is a tremendous unmet need for a disease-modifying therapy to counteract the devastating effects of Alzheimer's disease. However, after careful consideration of the data, we are not convinced that aducanumab represents a real advance, and if the results from ENGAGE were true, the treatment would not provide any benefit to patients at all and expose them to potential harm. Additionally, since there is no standard method to capture the value of unmet need in clinical or economic analyses, we include this point in the Contextual Considerations portion of the report and ask the panelists to consider this in their deliberations on treatment value during the public meeting.</p>
8.	<p>Rarely is a first-of-its-kind treatment--for any condition--a panacea or cure-all. But it often does spur the research into and development of additional and better therapies. For example, approval and coverage of the first reductase inhibitor for lowering LDL cholesterol--and thus delaying the onset of heart disease, the leading cause of death in the United States--spurred the development of at least six additional therapies. There were questions surrounding the effectiveness of the first treatment for HIV, but AZT's approval and coverage stimulated the scientific community to develop additional treatments and combination therapies that have now resulted in a nearly two-thirds decline in the number of HIV deaths since 2000. Even with Alzheimer's disease, approval of the first symptomatic treatment (tacrine) led to the development and approval of better and safer symptomatic drugs.</p> <p>This innovation value is crucial for people living with Alzheimer's and future generations of individuals</p>	<p>We agree that innovation is critical in finding effective treatments for Alzheimer's disease. However, it is also possible that approval and use of unproven and/or ineffective therapies may stifle, rather than spur, innovation. In the case of Alzheimer's disease, there is debate about whether targeting beta-amyloid is the most effective mechanism for treatment and premature approval of a drug such as aducanumab on the basis of a surrogate marker that has yet to be linked conclusively to improvements in clinical outcomes, may lead to development of more drugs targeting amyloid. If, in fact, amyloid is not the main or only causal pathway for Alzheimer's disease, then there will be a tremendous amount of time and money spent on less effective or ineffective therapies that could be directed towards other targets that may ultimately yield greater clinical benefits.</p> <p>In terms of the capturing the value of innovation, although this cannot be measured directly, we do include this in our Contextual Considerations section,</p>

	<p>who will develop Alzheimer’s. Without the first, there cannot be the second or third or fourth, each improving on the earlier treatments. We recognize this value cannot be measured in terms of short-term patient costs, but we oppose the systematic exclusion of innovation from determinations of value.</p>	<p>and this is part of the value discussion and votes during the public meeting.</p>
<p>9.</p>	<p>Even without a disease-modifying therapy, the benefits of an early diagnosis of Alzheimer’s are well-known. Early diagnosis allows individuals with the disease and their caregivers to better manage medications, build a care team, manage comorbidities, receive counseling and other support services, create advance directives, and address driving and safety concerns. Studies have also shown that health and long-term care costs are lower among people diagnosed earlier. Unfortunately, too many individuals with Alzheimer’s are diagnosed too late—if they are diagnosed at all. Many primary care physicians say they doubt the value of diagnosing a condition for which there are no treatments, and nearly half of primary care physicians in one survey say they sometimes choose not to even assess an individual’s cognition because, if the individual is eventually diagnosed, treatment options are limited. The approval and coverage of a disease-modifying therapy for Alzheimer’s would drive earlier diagnosis and thus accrue benefits, even if the direct effect of the drug were limited.</p> <p>This is of particular importance among diverse populations. Evidence suggests Blacks and Hispanics on average are diagnosed at a much later stage than Whites. This raises profound health equity concerns around access to care, quality of care, and financial burden. As the first-of-its-kind treatment, aducanumab’s value in driving earlier diagnosis should not be ignored, and this value should be taken into account.</p>	<p>We agree that the availability of an effective disease-modifying therapy for Alzheimer’s disease would have beneficial effects on the current situation of under- and delayed diagnosis of Alzheimer’s disease, particularly in minority populations. However, as we have stated in the report, we believe that the current evidence is not sufficient to support that aducanumab is an effective treatment for Alzheimer’s disease, and from conversations with experts, it is not at all clear that the availability of this drug would spur dramatic changes in clinical practice. Additionally, because Black and Hispanic patients were not well-represented in the clinical trials (Black patients made up less than 1% of the clinical trial population; Hispanic patients around 3%), any differential efficacy and harms of the drug in these populations are not clearly known. Finally, the high price of aducanumab has the potential to widen disparities if access to the drug is limited by affordability.</p>
<p>10.</p>	<p>In addition to the potentially greater value of an earlier diagnosis that the approval and coverage of aducanumab may have on traditionally underserved populations, the treatment itself could have tremendous value in addressing the disproportionate impact of Alzheimer’s. Blacks are about twice as likely and Hispanics are about one and a half times as likely as Whites to develop Alzheimer’s. In other words, relatively, this drug could have a greater value on the Black and Hispanic communities than the White population. ICER’s formula does not take into account the value of reducing health disparities between those who are at higher risk of developing Alzheimer’s and those who are not.</p>	<p>We agree that an effective therapy would potentially reduce the burden of Alzheimer’s disease on underserved communities, and we have noted this in the report in the Potential Other Benefits section. However, use of an ineffective therapy could cause significant harm to these communities, both in terms of potential side effects and financial harm. Given that the evidence of efficacy for aducanumab is far from clear, and that Black and Hispanic patients were woefully underrepresented in clinical trial populations, the impact of aducanumab on addressing health inequities may be limited.</p>

Institute for Patient Access		
1.	<p>The draft evidence report cites the total costs of Alzheimer’s to be at least \$500 billion annually, which is likely an understatement of the actual costs. According to the Alzheimer’s Association, the direct health care costs alone are projected to be \$355 billion in 2021. A study in the AJMC confirms this estimate, finding that the direct health care costs for treating Alzheimer’s in 2020 were \$305 billion. A substantial share of these costs, 49% according to a May 2021 Milliman report, are related to long-term residential nursing care. These costs impose significant financial burdens on families but also on state governments, as Medicaid will ultimately bear a large share.</p> <p>In addition to these costs, caregivers provide nearly \$257 billion in unpaid care to people living with Alzheimer’s and other dementias as of 2020. These costs are based on the 15.3 billion hours of unpaid assistance that caregivers must provide patients every year and imply total annual costs in excess of \$600 billion – 20% larger than the number cited in the report. And even this cost estimate is incomplete because it does not account for the many costs of the disease that are difficult to quantify.</p>	<p>We appreciate the updated citations with the most recent estimates of direct health costs and caregiver costs due to Alzheimer’s disease. We have updated the report to reflect these new estimates and citations.</p>
2.	<p>These cost estimates do not account for the emotional burden on caregivers. According to a 2017 survey from the Alzheimer’s Association, 64% of those caring for someone with Alzheimer’s or dementia felt “isolated or alone” in the task. More than four in every five (84%) said they needed “more help with caregiving, especially from other family members.” These stresses ultimately impact caregiver’s health, with surveys showing that caregivers experience higher rates of physical and emotional stress and depression. They even report declines in cognition themselves.</p> <p>As Alzheimer’s patients often have multiple caregivers, these caregiver burdens significantly expand the number of people experiencing negative consequences from this disease. The severity and pervasiveness of these burdens demonstrates that it is essential for a cost-effectiveness model to incorporate the full costs borne by caregivers even if it is challenging to quantify them. Without an accurate assessment of these burdens, the model will significantly undervalue the benefits of any efficacious treatment.</p>	<p>We have attempted to be as comprehensive as possible given available evidence in including impact on caregivers, including caregiver quality of life, caregiver time spent, and caregiver health impact. We have used best-available evidence to inform the inputs in our model and have attempted to be as comprehensive as possible. If you are aware of high-quality evidence that we are not using, please provide a specific citation and we will review it for potential inclusion. The time spent by caregivers has been included in our model and is large in magnitude. A full description of these inputs and their values can be found in the Report Supplement.</p>

3.	<p>The cost estimates reviewed above look at the disease’s cost from an annual basis. When discussing the financial burden of a degenerative disease, however, it is important to explicitly recognize that the costs are incurred for many years and will increase over time as the degeneration worsens. In short, an estimation of costs is incomplete if it does not incorporate the lifetime burden of the disease (appropriately discounted into the present value).</p>	<p>Our cost-effectiveness model employs a lifetime time horizon and accounts for disease worsening over time and is presented in the present value.</p>
4.	<p>Loss of identity is one of the more devastating and terrifying aspects of Alzheimer’s and other forms of dementia. Patients struggle to maintain their self-worth while having to accept the inevitable cognitive decline and realization that they will become a burden on loved ones.</p> <p>Here, as with many of Alzheimer’s burdens on patients and caregivers, the methodologies to quantify impact are underdeveloped. Nevertheless, when it comes to Alzheimer’s and dementia, not incorporating these impacts will lead to a vast underestimation of the benefits provided by an efficacious treatment.</p>	<p>As mentioned in this comment, these downstream impacts are related to the efficacy of the treatment. We agree that an efficacious treatment would be incredibly valuable. When a treatment is not effective or is only marginally effective, the downstream effects will be limited. Further, ICER uses a Value Assessment Framework, and there are flexibilities for deliberation of other benefits and contextual considerations that are important to consider.</p>
National Alliance for Caregiving		
1.	<p>ICER should note in the Draft Report when reviewers lack the information needed to assess caregiver strain and quality of life, caregiver health impact, and the caregiver's ability to provide care. Noting limitations more clearly will assist advocates and sponsors in understanding the opportunities to collect additional, meaningful evidence in the ongoing monitoring of existing treatments. This may also incentivize sponsors to collect and identify this data in the development of future clinical trials.</p>	<p>We agree that evidence gaps will be an important issue when ICER makes recommendations for policy in the Final Evidence Report and Meeting Summary.</p>
2.	<p>The tools and models used to assess the value of health technologies have been slow to align their methodologies with a person-centered and health equity lens. This is especially detrimental in the evaluation of treatments for conditions such as Alzheimer’s and dementia where the impact on the family caregiver is extensive. Among other methodological limitations, the QALY does not include the essential caregiver perspective.</p> <p>Family caregiving dynamics are best understood as a constellation, rather than a dyad and increasingly involves a system of family, friends and neighbors providing medical and social support to a recipient. In its 2021 report, the Alzheimer’s Association found that as many as 30% of older adults with dementia had three or more unpaid caregivers. In evaluating</p>	<p>In our co-base-case modified societal perspective, we incorporate the quality of life of the caregivers. Secondly, the evidence used to inform the societal perspective in our model overwhelmingly was for a single primary caregiver. Changes in caregiver burden associated with aducanumab were, unfortunately, marginal at best due to the current evidence around aducanumab’s net health benefit. The failure of a treatment in demonstrating net health benefits is not a failure of the Value Assessment Framework. Our model uses best-available evidence and this evidence focused on a single primary caregiver. Assumptions not founded on evidence would have to be made if additional caregivers were included in the model.</p>

	<p>treatment for certain diseases, such as Alzheimer's Disease, where the impact on the family is significant, the base case modeled should accurately count the number of involved caregivers, and be inclusive of the caregiver time spent caregiving, caregiver quality of life and caregiver direct medical costs.</p> <p>Value assessors such as ICER need more nuanced models and measures that can incorporate novel aspects of value essential to patients and caregivers, especially in complex, progressive, and not yet curable conditions and where treatment could provide value other than the extension of life.</p>	
3.	<p>The timing and duration of ICER's Draft Report public comment period disincentivizes stakeholders from participating. The current period is limited to four or five weeks and ends before a treatment's Prescription Drug User Fee Act (PDUFA) action date. Key stakeholders such as caregiver advocates, patient advocates, and researchers with relevant input may lack resources to mobilize their networks and provide useful comments in this short timeframe. The current timeframe asks stakeholders to provide input despite uncertainty around whether or not a drug will be approved for use and what indication.</p> <p>Effectiveness and safety of a medicine are essential inputs in the determination of its value. Stakeholders, including family caregivers who are concerned about the safety and efficacy of a particular medicine for their loved one, are asked to comment without the benefit of knowing the FDA's decision and therefore cannot respond to the reality of a treatment's actual approved use. Extension of ICER's public comment period on Draft Reports would engender trust with patient and caregiver advocates by creating a genuine dialogue wherein stakeholders can incorporate additional understandings gained from the FDA's determination.</p>	<p>We recognize that data are often limited for new treatments. However, patients, clinicians, and insurers are still faced with decisions about how to best use these treatments once they are approved for use. Thus, we view comparative effectiveness research and economic modeling as important ways to identify key inputs that impact the effectiveness and cost of a new treatment. Our report highlights the limitations of these data as well.</p>
4.	<p>For the first question on making judgments of overall long-term value for money, consider the addition of the following:</p> <ul style="list-style-type: none"> • Add "Magnitude of the lifetime impact on caregivers' capacity to partner in care for the individual patients of the condition being treated" • Add "Magnitude of the lifetime impact on caregivers' own health as a result of their care of individual patients of the condition being treated" 	<p>We agree that Alzheimer's disease has a tremendous impact on caregivers, including caregiver health. Our economic analyses account for caregiver burden and thus this aspect of treatment with aducanumab should be considered by the panel with the existing voting questions.</p>

5.	<p>For the question on the relative effects of aducanumab plus supportive care versus supportive care alone, the Draft Question offers “Caregivers’ quality of life and/or ability to achieve major life goals related to education, work, or family life” as consideration. Caregiver quality of life and ability to achieve major life goals should not be presented together as these measure different items. We would recommend focusing on evidence-based considerations that can be measured through validated clinical outcome assessment tools and that speak to the caregiver’s ability to partner in care. This may include:</p> <ul style="list-style-type: none"> • Caregivers’ strain related to intensity of care • Caregiver’s health and wellness • Caregiver’s quality of life 	<p>We appreciate the additional clarification of the components of caregiver impact for Alzheimer’s disease. We believe that these issues can be discussed by the panel with the existing question, and plan to discuss all aspects of caregiver impact in the public meeting and in the Final Evidence Report and Meeting Summary.</p>
Partnership to Improve Patient Care		
1.	<p>ICER is conducting this assessment far too early to produce accurate and useful results. A consistent concern PIPC and many others have presented to ICER is that it conducts assessments at too early a juncture to have accurate inputs for its models, and, as a result its results are often incomplete or incorrect. This assessment is particularly worrisome, as ICER’s timeline is so condensed that it is requiring commenters to submit feedback prior to aducanumab being approved by the FDA. ICER already delayed the assessment once to align with FDA’s changing timeline, and it would be prudent to delay the comment deadline until after approval. Conducting the assessment prior to approval, and requiring stakeholders to comment prior to the approval, forced both ICER and stakeholders to make inferences and deal in conjecture. This puts an undue burden on stakeholders and undermines the credibility of the assessment that will be referenced by payers.</p> <p>In this case specifically, it is also very likely that we will have additional reliable data about this drug upon the conclusion of additional trials.</p>	<p>We recognize that data are often limited for new treatments. However, patients, clinicians, and insurers are still faced with decisions about how to best use these treatments once they are approved for use. Thus, we view comparative effectiveness research and economic modeling as important ways to identify key inputs that impact the effectiveness and cost of a new treatment. Our report highlights the limitations of these data as well.</p>
2.	<p>ICER significantly underestimated the impact on caregiver burden in evaluating treatments for Alzheimer’s Disease.</p> <p>Alzheimer’s disease puts a particularly large burden on caregivers and accrues a multitude of societal care costs. The National Institute for Health and Care Excellence, NICE, which ICER leans heavily on for its approach to value assessment, has already included caregiver utility in its cost-effectiveness models for</p>	<p>We agree that Alzheimer’s disease places a particularly large burden on caregivers and accrues substantial societal care costs. We have noted this in our Patient Perspectives section and have included the best estimates of caregiver utilities that we could find in the literature in the economic models. Should better estimates of caregiver burden become available before the Final Evidence Report’s publication, we would be glad to incorporate them.</p>

	<p>diseases such as Alzheimer’s Disease, multiple sclerosis, and Parkinson’s disease.</p> <p>When ICER does look at caregiver burden, it appears to drastically underestimate it.</p>	
3.	<p>ICER continues to rely on the Quality-Adjusted Life Year (QALY), which is known to devalue the lives of older adults.</p> <p>As PIPC has consistently stated – the use of the QALY in ICER’s models is inappropriate, as the QALY discriminates against older adults, patients, and people with disabilities. This is widely recognized as a problem with the QALY. In fact, in 2019, the National Council on Disability, an independent federal agency, published a report finding that the use of the QALY would be contrary to United States civil rights laws and disability policy. The use of this metric is particularly concerning in an assessment of treatments for Alzheimer’s disease, as it is a condition that generally impacts older adults.</p>	<p>ICER follows common academic and health technology assessment standards by using the cost per QALY gained, but also presents cost per life year gained and cost per evLYG. The QALY is the gold standard for measuring how well a medical treatment improves and lengthens patients’ lives and has served as a fundamental component of cost-effectiveness analyses in the United States and around the world for more than 30 years.</p> <p>A recent legal analysis found that the QALY does not disadvantage patients who have a disability or a chronic condition that is not curable:</p> <ul style="list-style-type: none"> • https://icer.org/wp-content/uploads/2021/02/ICER-Analyses-and-Payer-Use-of-Cost-effectiveness-Results-Based-on-the-QALY-and-evLYG-Are-Consistent-With-ADA-Protections-for-Individuals-With-Disabilities.pdf.
4.	<p>ICER’s model underestimates the probability of patients being admitted to long-term care facilities, which is a major driver of costs and burden related to Alzheimer’s Disease.</p> <p>Transition into long-term care facilities is a very common outcome for patients and people with disabilities with Alzheimer’s Disease. The set of probabilities used in the ICER model seems quite conservative compared to other data points. As ICER’s source is over twenty years old, we would posit it is now out of date. A more recent study suggests that the probability of transitioning to long-term care is much higher than those estimates used in the ICER model.</p>	<p>Thank you for providing a citation for this comment. We could not identify the numbers provided in this public comment in the referenced citation. The detail in the public comment said, “A more recent study suggests that the probability of transitioning to long-term care is much higher than those estimates used in the ICER model. Examples of this discrepancy include 16% a year in moderate Alzheimer’s disease as compared to 11% used in ICER’s model and over 32% in severe Alzheimer’s disease as compared to just 23% used in the ICER model.” However, the reference states, “Rates of institutionalization at age 65 years ranged from 0% for normal cognition through mild AD to 1% for moderate AD, and 30% for severe AD patients.” Using these numbers, our model would have higher rates of institutionalization for MCI, mild AD, and moderate AD. Our point estimate is slightly lower for severe AD; however, we vary these inputs in sensitivity analyses. Collectively across all these health states, we would have higher estimates of long-term care using our current estimates than if we were to use the suggested estimates from the referenced citation.</p>
Society for Women’s Health Research		
1.	<p>ICER assumed blended efficacy of the ENGAGE and EMERGE trials when working to evaluate cost-effectiveness of aducanumab. Further, ICER’s argument that “the primary outcome of CDR-SB,</p>	<p>Our review of the literature and discussion with multiple experts revealed no consensus on what a clinically relevant difference in the scores would be and several experts had concerns that the differences</p>

	<p>while a validated scale, is not used frequently in clinical practice and thus the minimal clinically important difference has not been established” is not accurate. FDA’s guidance on the development of drugs for the treatment of early-stage disease specific to AD recommends CDR-SB as just one potential approach to evaluate cognitive and functional change in individuals with MCI. We reiterate that even small changes can be clinically meaningful for patients and their caregivers, and must be taken into account.</p>	<p>seen in EMERGE were too small to be clinically meaningful.</p>
2.	<p>ICER’s characterization that taking aducanumab has a “high certainty of harm” is not aligned with the evidence related to the ARIA-E and ARIA-H data, particularly as it relates to the benefits of the therapy.</p>	<p>Although we agree that the data from the clinical trials show that the majority of ARIA cases were asymptomatic or mild in severity and mostly resolved, the fact remains that ARIA occurs in a substantial proportion of patients treated with aducanumab, particularly in ApoE+ subjects. Our wording in the report that there is certainty of harm with treatment with aducanumab is meant to reflect that all patients given aducanumab are at risk of harm from treatment and that, as demonstrated in the clinical trials, a certain proportion of patients will experience harm.</p>
3.	<p>Because ICER assumed blended efficacy of ENGAGE and EMERGE, the calculation of quality of life years (QALY) was skewed inappropriately. Had ICER used only evidence from EMERGE, a higher assessed QALY would have resulted- with the Alzheimer’s Association indicating that it would result “in a cost effectiveness price about three times higher.”</p>	<p>As a scenario analysis, we present the incremental cost-effectiveness ratios and value-based prices assuming only the EMERGE trial evidence. However, as explained in detail in the report, we cannot simply disregard the ENGAGE trial. We blend the estimates between ENGAGE and EMERGE in our base-case analysis rather than selecting one trial over the other. If we selected one trial over the other for the base case, the estimates from ENGAGE (and not necessarily EMERGE) may be selected. The evidence is too uncertain at this time to confidently select one trial over the other.</p>
4.	<p>Further, QALY should incorporate a more flexible formula that appropriately values quality of life years, beyond direct patient costs. SWHR would have liked to have seen a broader range of value that this therapy would bring to a patient and their caregiver. Given this, we reiterate our Value Assessment Principles for consideration: Value assessments should account for diversity in patients, including sex and genders; in addition to measuring clinical outcomes, value assessment frameworks should account for what matters most to patients, caregivers, and society, while recognizing that these values vary and change across patient populations; value assessments should take into consideration the long-term benefits of a therapy; and value assessments should use a range of high-quality evidence to demonstrate improvement in outcomes.</p>	<p>ICER would have also been encouraged by a stronger improvement in health gains or cost offsets associated with aducanumab based on the current evidence. Such gains are desperately needed for patients, families, and caregivers. The burden of the primary caregiver is included in our analysis. Changes in caregiver burden associated with aducanumab were, unfortunately, marginal at best. ICER has a Value Assessment Framework that includes flexibilities built in for deliberation that can include key other benefits and contextual considerations (e.g., equity, severity, unmet need, etc.).</p>

	Unfortunately, it does not appear that ICER incorporated these principles broadly into its draft evidence report for aducanumab. We are specifically concerned that this was not the case related to the burden of caregiving.	
Us Against Alzheimer's		
1.	In our review of ICER's evidence report, it appears that several relevant costs were omitted, including: out-of-pocket costs incurred by the patient or caregiver for medical care, transportation, home adaptations, in-home paid caregiving, and adult day care services.	The evidence we identified to inform the costs (from both perspectives) in our analysis was not as granular as suggested by this comment. If Us Against Alzheimer's is aware of a specific source that provides this level of detail, please share the citation and we will review it for potential inclusion in our analysis.
2.	Additionally, the model framework assumes a single primary caregiver. We know that AD takes a toll on the entire family and that often times there are many caregivers, including working-age and school-aged caregivers involved who may miss out on career opportunities, earned wages, and/or education. Our colleagues at the Alzheimer's Association estimate that there are, on average, nearly two caregivers for every person living with the disease. Including more comprehensive costs for the primary caregiver as well as costs for the secondary and tertiary caregiver(s) would provide in a more accurate reflection of the true burden of AD.	The evidence used to inform the societal perspective in our model overwhelmingly was from a single primary caregiver. Our model uses best-available evidence and this evidence focused on a single primary caregiver. Changes in caregiver burden associated with aducanumab were, unfortunately, marginal at best due to the current evidence around aducanumab's net health benefit. The failure of a treatment in demonstrating net health benefits is not a failure of the value assessment framework. Assumptions not founded on evidence would have to be made if additional caregivers were included in the model.
3.	<p>The source selected for this important model cost input has several limitations.</p> <p>Quoting the study authors directly "Study limitations include that estimates are for a single geographic population, which in 2010 was 86% white. Olmsted County age- sex- and racial-distributions are also similar to these [Minnesota/Upper Midwest] geographic regions; however, Olmsted County residents exhibit higher income and education... While no single geographic area is representative of all others, the under-representation of minorities and the fact that essentially all medical care is delivered by few providers compromises the generalizability of our study findings to different racial and socio-economic groups and different health care environments."</p> <p>The County of Olmstead has a population with less racial and ethnic diversity than the nation, as well as a higher-than-average mean education level. It is also worth noting that the Mayo Clinic health system is located in this county and provides a different type of healthcare than the majority of the US experiences. Simply stated, Olmstead County, MN is not nationally</p>	We agree that the source we are using has limitations, but it was the best-available evidence we identified. Suggestions for other sources of evidence are appreciated, and we will happily review them for potential inclusion in the report if provided a citation.

	representative and costs data from this county should not be the sole source for these critical model cost inputs.	
4.	In addition to concerns that this study is not nationally representative, the cost estimates from this study also appear to be very low. For example, in another study by Aigbogun et. al. published in 2019, in individuals with Dementia and AD per person, per year medical costs ranged from \$32,640 (no behavioral disturbance) to \$42,284 (with behavioral disturbance). In contrast, the Olmstead Country study reported costs in the prevalent population (most severe group) as only \$11,678 per year. The lower cost estimates from Leibson et. al. are in part due to not including pharmacy costs. ICER only minimally accounted for these costs by adding costs of anti-dementia treatments into the model. In the same study, Aigbogun et. al. reported pharmacy costs ranging from \$4,105 to \$4,447 per year with high rates of several classes of medications not accounted for in the current ICER model. Utilization of several classes of medications have been shown to increase with disease severity including anti-depressants, anti-psychotics, and opioids as rates of symptoms and associated diagnoses increases.	Thank you for providing us the Aigbogun citation. We were not aware of this piece of literature before and have now extensively reviewed it. The challenge with that paper is that it is not stratified by disease severity, but is rather stratified by behavioral disturbances. If the same value for health care costs was used for all alive health states, then the model would not capture the potential cost savings associated with a treatment that could keep a patient in a less costly (likely corresponding to a less severe) health state. We continue to use our cost estimates from the Draft Evidence Report to allow for cost savings for keeping patients in less severe health states longer. We do incorporate a large standard error on these values to capture the wide uncertainty and possible range of these costs in sensitivity analyses.
5.	Finally, accurate accounting of costs by disease stage is particularly important when you have a treatment with a smaller relative treatment effect over a longer period of time. It is also worth noting that the Olmstead County study also was only for people with dementia and did not break down costs into moderate or severe AD. The approach used by ICER to leverage the data from Leibson et. al. to assist in estimating direct medical cost multipliers by model disease stages is not unreasonable in the absence of another study. If a source of costs with each model defined disease stage is not available, it would be reasonable to use these costs multipliers developed from Leibson et. al.. However, if used, these cost multipliers should be applied to more nationally representative and complete medical costs data.	We continue to review the literature as this review progresses and will update our analysis with best-available evidence as we identify them. Suggestions for other sources of evidence are appreciated, and we will happily review them for potential inclusion in the report if provided a citation.
Economists		
Paul Langley		
1.	That is, your reports lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of measurement theory in confusing ordinal scales with interval and ratio scales. While you might view these reports and the application of lifetime incremental cost-per-QALY calculations and the	ICER follows common academic and health technology assessment standards by using the cost per QALY gained. The QALY is the gold standard for measuring how well a medical treatment improves and lengthens patients' lives and has served as a fundamental component of cost-effectiveness analyses in the United States and around the world for more than 30 years.

<p>application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. The QALY, as you have been informed on a number of occasions, is a mathematically impossible construct with a paper in F1000Research and a letter to Value in Health pointing this out.</p> <p>I would like to draw to your attention the assertion above that multiattribute utility instruments have ratio measurement properties. I think you misunderstand what ratio property means particularly as all direct and indirect preference instruments can produce negative responses or states worse than death.</p> <p>You need to be clear on what a ratio scale actually means. Belief in the QALY as a mathematical construct must rest on a belief that any preference scale, for either direct or indirect values or utilities, has a true zero. If this condition is not met, under any circumstance, then the preference scale is, at best, an interval scale although this has to be proved.</p> <p>The overarching criticism, however, is that your modelling and subsequent recommendations for pricing and patient uptake are entirely imaginary constructs. In short, the proposed 'evidence' you bring to the table to evaluate Aducanumab is invented through assumption driven lifetime simulations that fail the standards of normal science. Your standard defense of these criticisms is that this methodology is the one everyone else has pursued for the past 30 years in health technology assessments</p>	
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