



**Lecanemab for Early Alzheimer’s Disease:
Response to Public Comments on Draft Evidence Report**

March 1, 2023

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#	Comment	ICER Response
Manufacturers		
Biogen		
1.	<p>Biogen supports a consistent approach to evaluating the cost-effectiveness of beta amyloid antibodies in Early AD, utilizing the latest data in a manner which recognizes the relative strength of the evidence.</p> <p>In particular, the clinical evidence supporting different treatment paradigms is expected to expand significantly in the near future, including the possibility for dosing at longer intervals (i.e., less frequent dosing). These treatment paradigms could be significantly more cost-effective and return even more value to society than the base-case currently studied. This hypothesis is of significant interest to all stakeholders and could be easily explored in an extended series of scenario analyses.</p> <p>Biogen welcomes the possibility for further updates of ICER’s analyses as new data become available, both for the clinical efficacy of treatments and also with new studies quantifying the immense cost and quality-of-life burden Alzheimer’s disease places on our society.</p>	<p>We recognize that relevant new data may become available after we complete an evidence report. We have established processes to update our assessments. Those policies can be found on our website. Further, we will be putting this model into our Interactive Modeler™ alongside the posting of our final evidence report. The Interactive Modeler is a user-friendly web-based interface that is a modifiable rendering of the actual ICER analytic model used to produce this report. The user is able to update model inputs and dynamically calculate updated findings.</p>
2.	<p>ICER’s value assessment does not fully capture AD’s devastating disease burden, lack of treatments, and other contextual considerations. ICER’s use of low willingness-to-pay thresholds does not reflect the value of AD treatments to society.</p> <p>A key part of ICER’s value assessment framework is the value assigned to quality-of-life gains from therapies. In an ISPOR panel in 2021, Professor Charles Phelps emphasized the need for willingness-to-pay (WTP) thresholds which are adjusted to reflect society’s preference to invest in healthcare directed at the most severe diseases. Specifically, when assessing the value of AD treatments to society:</p> <p><i>“Supposing that the ratio of willingness to pay at consumption is 3, income consumption is \$50K, and the utility elasticity versus health consumption are identical: combining those, crank that up to Alzheimer’s disease and [willingness to pay] climbs readily to \$500,000 or more.”</i></p> <p>A methodological framework underpinning this statement was published by Phelps and Lakdawalla (2021), which suggests a WTP threshold of up to \$600,000 per QALY for AD, which is four times higher than the values currently used by ICER in its health-benefit price benchmark recommendation.</p> <p>At a minimum, we would welcome scenario analyses which explore WTP thresholds up to the levels suggested above, with appropriate context given.</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 specific conditions you feel we should evaluate using a lower threshold.</p>
3.	<p>The societal co-base case in ICER’s report does not fully reflect the extraordinary circumstances faced by AD patients and caregivers. AD is a devastating disease, whose diagnosis leads to significant</p>	<p>The evidence used to inform the societal perspective in our model is for a primary caregiver who was assumed to be</p>

	<p>fear, anxiety and uncertainty for patients, their families and caregivers. This impact on quality-of-life is significantly magnified, with many patients having up to three caregivers. Although it is difficult to fully capture these impacts using current models and data sources, it is clear that the current assumption of impact on a single caregiver is almost certainly an underestimate. For that reason, Biogen would welcome further scenario analysis which estimates the value of therapy under the assumptions of multiple caregivers, particularly for patients at later stages of disease.</p>	<p>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, if you are aware of a more comprehensive citation, please share that citation for more actionable recommendations so that we may review the evidence for potential inclusion in our analysis.</p>
Eisai Co., Ltd		
1.	<p>Treatment Discontinuation Rate: ICER's Markov models fail to account for the loss of accrued treatment benefit and QALYs from treatment discontinuation or patient drop-out hence introduces bias in the estimation of clinical effectiveness.</p> <p>Tangible differences in discontinuation rates between interventions should not result in equivalent QALY gains, since patients who discontinue treatment, stop accruing benefits (QALYs) and incur additional costs tied to disease progression: ICER's assessment is accordingly inaccurate. ICER uses a 6.9% discontinuation rate for lecanemab and a 30.5% discontinuation rate for a comparative intervention, yet both treatments are shown to provide a 3.71 increase in QALYs. While the ICER report inflated clinical effectiveness and QALYs gained, the report, at the same time, deflated the cost estimation associated with potentially increased expenditures for diagnostic tests, earlier entry to long-term care, increased caregiver burden, healthcare provider visits, as well as costs associated with declines in QOL and lost productivity. Therefore, ICER's cost effectiveness estimations are likely to have been systematically errored based on an overestimation of the value of the comparative product relative to lecanemab. In effective treatments, however, treatment persistence improves the patient's QOL and wellbeing and results in additional QALY gain.</p> <p>In randomized clinical trials, any discontinuation or attrition rate greater than 20% is likely to pose serious threats to the validity and generalizability of study results. Different rates of discontinuation in a control and treatment arm can lead to the loss of randomness and equality between arms, introducing a form of selection bias. Importantly, if the patient dropout rate is higher in the treatment group than in the control group, this overestimates a treatment's effectiveness and corresponding cost-effectiveness. This is because the costs of treatment only came from the patients who remained in the trial, making the treatment appear more cost-effective than if the analysis</p>	<p>We asked manufacturers of each drug to confirm that the efficacy evidence reported from the trials included individuals that did and did not discontinue treatment, and thus the efficacy evidence was appropriate for the entire cohort, rather than only for those who remained on treatment.</p> <p>Further, in the draft report, we did caveat in numerous places regarding the number of optimistic assumptions that were required to generate draft report results for donanemab. On January 19th, Eli Lilly & Co. announced a Complete Response Letter for accelerated approval of donanemab, and thus we have removed donanemab from this assessment and results for donanemab will no longer be presented as part of this assessment.</p>

	<p>included all patients, since clinical benefits are overcounted, but treatment costs undercounted. It is important to note that the Oxford Center of Evidence-Based Medicine (EBM) uses a follow-up rate of 80% as a threshold to differentiate between “high” and “low” randomized trials in their “Levels of Evidence”.</p> <p>Recommendation: Incorporate the probability of treatment failure for each patient and conduct sensitivity analyses to determine how different treatment failure assumptions impact cost-effectiveness. Separately consider overall patient discontinuation and adverse event-related discontinuation rates, as these can have disparate impacts on the costs and benefits.</p>	
2.	<p>Modeling Choice: ICER’s use of a Markov method to model AD does not account for the heterogeneous, nonlinear progression of AD.</p> <p>Markov models are an outdated method that do not fully reflect the complexity of AD and fail to capture patient heterogeneity and disease progression. Markov models simulate disease progression over time by dividing the patient population into discrete health states with constant transitions between states occurring at regular intervals. The probability of transitioning between states is typically based on estimates of the disease’s natural history and treatment effectiveness from a particular time segment. Consequently, these models assume that all patients are identical to the population average. In the real world, individual patients may experience varying progression of their disease and respond differently to treatment according to their unique baseline clinical and demographic characteristics. An excellent alternative to Markov models is Archimedes condition-event simulation (CES), a computer-based simulation that accounts for individual heterogeneity as well as changes in risk profile over time. This method allows the probability of disease progression to vary over a lifetime, realistically reflecting the natural history of disease and therapeutic outcomes, and has been validated using longitudinal, real-world data. The CES approach is more flexible and considers a wide variety of factors, such as patient-specific characteristics, disease stage interactions, patient, time-varying attributes, broader treatment outcome measures (including treatment discontinuation and persistence), and resource utilization.</p> <p>Recommendation: Introduce alternative modeling approaches as sensitivity analyses or revise the model in this assessment and use patient level simulations to account for the complex, heterogeneous, and nonlinear progression of AD, additional benefits of treatment persistence, the loss of QALYs from patient discontinuations, and the cost of treatment failure.</p>	<p>Markov models are widely and commonly used to model disease progression in AD. A strength of our Markov modeling approach over some patient simulation models is that we use direct patient outcome evidence rather than using surrogate endpoints to extrapolate patient outcomes.</p>
3.	<p>Transition Probabilities: The source for ICER’s transition probabilities, the National Alzheimer’s Coordinating Center (NACC) dataset, is not representative of the patient population. Data from the National Alzheimer’s Coordinating Center (NACC) have been widely used in research studies; however, depending</p>	<p>The source we use for transition probabilities was authored by colleagues at Biogen, the co-developer of lecanemab. They previously provided us this source as a recommendation for natural history</p>

<p>on their use, the data have several limitations including bias, incompleteness, lack of standardization, and lack of relevance to current clinical practice. 1) Though the NACC data set includes a wide range of information (<i>e.g.</i>, demographics, medical history, cognitive and functional assessments, and genetic data), it is based on a convenience sample of participants from the NACC network, subjecting it to selection bias. As the patients included in the data set may differ in important ways from those not included, the data may not be representative of the broader population of AD patients, limiting generalizability. 2) NACC data may also have missing or incomplete information as it only includes data collected by the participating clinical research centers, which can shape the reliability of the results. 3) In addition, the data are collected from multiple sources using a variety of methods and may not be standardized across all centers (<i>e.g.</i>, differing protocols/methods for data collection/reporting). This can introduce inconsistency, potentially further impacting the validity of the results. 4) Finally, the NACC data may not be up to date, as these are collected at various points in time and the most recent data may not reflect current practices or advances in the field. This can reduce its relevance for current research questions. Overall, the NACC data limitations vastly increase the probability of erroneous conclusions in a value assessment.</p> <p>The AD Neuroimaging Initiative (ADNI) is the preferred database for determining transition probabilities because it incorporates more centers across the US and Canada with a standardized diagnostic protocol. ADNI additionally excludes non-AD causes of dementia and focuses on <i>amnestic</i> mild cognitive impairment (MCI), which changes the likelihood of transitioning to AD.¹ ADNI has been the chosen data set for discrete event simulation, which has been used to develop well-validated equations that accurately model the full spectrum of disease progression and the effects of disease modifying treatments for the early stages of AD. Recommendation: Use the ADNI database instead of NACC data for determining transition probabilities, at least as a sensitivity analysis.</p>	<p>transition probabilities for Alzheimer’s disease. It is obviously tricky for ICER to implement manufacturer requests on such data when co-manufacturers provide conflicting suggestions.</p>
<p>4. ICER’s source for utilities, Neumann <i>et al.</i> 1999, is 24 years out of date with advances in AD research and clinical practice. A fundamental problem with applying Neumann <i>et al.</i> to determine outcomes is that the paper is so old that it not only uses a completely different definition of disease progression, but it also uses a definition of MCI so different that it would be unrecognizable today. Neuman <i>et al.</i> apply a completely different version of the Clinical Dementia Rating (CDR) scale than today’s standard (<i>e.g.</i>, defining 7 CDR states [normal, questionable, mild, moderate, severe, profound, terminal], whereas the <i>current</i> CDR defines 5 states [normal, very mild, mild, moderate, severe]). Additionally, the definition of MCI has dramatically evolved over</p>	<p>As stated in our report, the utility estimates from Landeiro et al. did not stratify the utilities by care setting (long-term care versus community) and did not provide utilities for the caregivers of the patients. Therefore, using the utility estimates from Landeiro would have to require numerous assumptions and additional sources to be able to have utility estimates for individuals that live in the community, individuals that live in long-term care, caregivers of individuals that live in the community, and</p>

the past 20 years (Neumann *et al.* define MCI due to AD as a CDR of 0.5 [uncertain dementia rating]). Therefore, the use of Neumann utilities is highly problematic, especially given that its scales and disease states (and utilities assigned to them) do not align with the disease states in ICER's economic model – heightening inaccuracies from the overlap between states. Furthermore, additional problems lie within ICER's interpretation of Neumann *et al.* 1999. The utility scores in this publication correspond to a CDR of 1, 2 and 3, respectively, and scores are also provided for a CDR of 4 (profound) and 5 (terminal). ICER omitted the last 2 data points and effectively assumed that no patient would progress beyond a CDR of 3. This approach of initially utilizing a scale of 7 CDR states from Neumann *et al.* and then omitting the last two states to interpret it into 5 CDR states is highly problematic from a scientific standpoint and will lead to inaccurate conclusions.

ICER uses the HUI Mark (HUI2) utility index rather than the most commonly used health-related quality of life (HRQOL) measure in AD, the EuroQol 5-Dimension (EQ-5D) utility index. ICER noted that HUI2 utility estimates from the cross-sectional Neumann *et al.* (1999) study were “comparable” to a recent systematic literature review, Landeiro *et al.* 2020, using EQ-5D. This is not accurate, as the magnitude of differences and construct validity, including responsiveness of these instruments in AD, are simply not comparable. Even between HUI2 and HUI3, QOL scores differ significantly, highlighting the need for caution in comparing studies using different HRQOL measures. Considering the strengths and limitations of HUI2 and EQ-5D, ICER should use a single, standardized utility index for cost-effectiveness analysis. The HUI2 may be more sensitive to change in AD stage, but is not specifically tailored for AD, thus not all dimensions are suitable for describing AD. In addition, its dimensions are not independent of one another, making it inadequate for representing AD. The few published reports on HUI validity in AD have mixed findings. While Neumann *et al.* (2000) showed that HUI discriminated across dementia stages, Naglie *et al.* (2006) found no significant associations between either patient or proxy-rated scores and measures of cognition or physical function. The EQ-5D utility index has demonstrated the best combination of feasibility, reliability, and validity in patients with AD and dementia, unlike inconsistencies observed for the HUI. In contrast, Li *et al.* (2018) found that biased estimates calculated from the proxy-rated HUI scores (as in Neumann *et al.* 1999) for people with dementia, led to poorer cost-effectiveness.

Recommendation: Adopt utility estimates from Landeiro *et al.* 2020. This robust meta-analysis uses utilities from multiple studies using EQ-5D, aligning it with current advances in AD and making it representative of the patient experience. Of the included studies, 3 reported utilities with a weighted mean of 0.8 for patients with MCI, twelve studies reported a weighted mean of 0.74 for patients with mild dementia, 9 studies reported a

caregivers of individuals that live in long-term care.

Figure 2 of the Landeiro source provides a depiction of the mean EQ-5D by disease severity state. However, it does not provide the demographics of the individuals (caregiver or patient) completing the EQ-5D. Thus, without knowing the baseline utility, we are unable to calculate a disutility for each health state using this pooled data.

We understand the uncertainty around the utility estimates for each category, and thus we varied each of these inputs across a wide range in sensitivity analyses. As shown in the results from our one-way sensitivity analysis, the range for each of our utility estimates for each level of disease severity includes the point estimate from Figure 2 in the Landeiro source.

	<p>weighted mean of 0.59 for patients with moderate dementia, and 8 reported a weighted mean of 0.36 for patients with severe dementia. Curiously, ICER does not attempt a scenario analysis of this alternate source, dismissing it as “comparable” to Neumann <i>et al.</i> – a paper that is decades older and fails to use the same diagnostic standards.</p>	
5.	<p>Lecanemab demonstrated a reduced clinical decline of 27% in the overall trial population, a clinically meaningful result. ICER states that there is disagreement about the clinical meaningfulness of the magnitude of change in CDR-SB in the lecanemab trial. It is important to note that the Clarity AD study demonstrated a reduced clinical decline of 27%. This breakthrough has been recognized by independent patient advocates and should not be understated. The study confirms that lecanemab can meaningfully change the course of the disease for people in the earliest stages of AD. The results show lecanemab will provide patients more time to participate in daily life, improve QOL, activities of daily living and their independence. It could mean many more months of recognizing their spouse, children, and grandchildren. Treatments that deliver tangible benefits to those living with early AD and at risk for further disease progression are as valuable as treatments that extend the lives of those with other terminal diseases.</p> <p>There has been a continuing focus on what constitutes a Minimal Clinically Important Difference (MCID) in AD. An MCID quantifies the smallest change in an outcome that <i>patients perceive as beneficial</i> and results in a <i>change in patient management</i>. It is an <i>individual, within-patient change</i> in a clinical outcome assessment and is different from a between-group treatment effect measured in randomized clinical trials. In early AD, the ability to <i>maintain a healthy, active, engaged, and independent life</i> is considered meaningful from the <i>patient perspective</i>. Experts caring for patients with AD generally consider a treatment effect of 20%-30% as clinically meaningful. The thresholds that ICER references are mostly defined in late-stage patient populations, and MCIDs vary for each instrument as well as according to disease stage or severity. An MCID of 1-2 points in CDR-SB has been challenged in the context of MCID and early-stage AD, as the values have been largely benchmarked on the range of meaningful change estimates across MCI due to AD and full dementia stages. Further, Cohen <i>et al.</i> suggest that the NACC database used in the study may not represent the broader AD population, due to differences in patient characteristics and enrollment procedures. In addition, the diagnostic criteria for MCI due to AD did not reflect current clinical practice: a substantial population was not biomarker-verified, so it is uncertain if some patients truly had MCI due to AD.</p> <p>Recommendation: Consider the results from the pivotal trial, Clarity AD, particularly from the patient perspective, as lecanemab demonstrated a clinically meaningful reduction in clinical decline.</p>	<p>We appreciate the discussion around MCID and its use. It would be helpful in assessing whether the magnitude of benefit is clinically meaningful if manufacturers provided analyses of the percentage of patients who experience decreases in an outcome measure beyond a prespecified endpoint (percentage achieving a clinically important decline, for instance) in the placebo and treatment groups. However, we currently only have access to aggregate measures, such as mean change in an outcome. While changes in aggregate outcomes will potentially obscure changes in individual patients that are above or below the MCID, unless changes in the assessed outcome measure are very non-normally distributed, the mean change can tell us something about the overall clinical relevance of the change.</p> <p>We also note that statistically significant changes to an outcome can be a result of clinically meaningful changes or a large sample size, or both. Declining 27% slower than before is not inherently clinically meaningful; what matters is how this impacts life. While we acknowledge that there is not universal agreement on MCIDs for the outcome measures used in the lecanemab studies, discussion of MCID is relevant because on average, the benefit isn't as large as what is published in the literature to be clinically meaningful for CDR-SB. Comparison to MCID can help those assessing the data in understanding the magnitude of benefits for patients. Furthermore, establishment of MCIDs benefits patients, family members, caregivers, and health-care systems by pushing clinical trial sponsors to power trials not just on statistically significant</p>

		differences but clinically relevant ones as well. ¹
6.	<p>ICER’s assessment underestimates caregiver burden: broadening the model to include caregiver QALYS, productivity and healthcare costs should have more considerable impact on the model as showcased by Ito <i>et al.</i></p> <p>Ito <i>et al.</i> - similar to ICER’s assessment - conducted an analysis of a treatment that would delay the progression of dementia in individuals with MCI from both a healthcare system and societal perspective. This included patient productivity, caregiver productivity, and caregiver health care costs. Even with the use of a hypothetical treatment with a much lower incurred QALY gain than in ICER’s assessment (0.225 QALYs), the spillover effect of QALYs, healthcare costs, and productivity costs for caregivers substantially improved the cost per QALY between the healthcare vs. societal perspectives (\$192K/QALY vs. as low as \$74K/QALY). Nonetheless, outputs of these 2 perspectives in ICER’s assessment were extremely similar. Other recent studies have shown that, with the consideration of caregiver costs and QOL effects in AD economic evaluation, the cost-effectiveness of an AD treatment improves substantially. ICER’s analysis has failed to evaluate costs and benefits beyond the patient.</p> <p>Recommendation: Account for disease heterogeneity and a more comprehensive analysis of the societal perspective to provide a more accurate assessment of the societal and economic impact of beta-amyloid antibody treatments for Early AD.</p>	<p>In our model, treatment results in approximately one more year lived in early AD (MCI due to AD and mild AD), and approximately six fewer months lived in later AD (moderate AD and severe AD). Prolonging time in MCI due to AD and mild AD is still associated with an impact on caregivers as measured by an impact on quality of life, health care costs, and time spent caregiving. This treatment is not restoring to a health state that doesn’t involve caregiver time spent. Therefore, this treatment delays and slightly shortens time in more severe AD health states, but prolongs time in early AD, which is still characterized by impacts to caregiver quality of life, health care costs, and time spent. Reversing AD would reduce caregiver impact dramatically, but that isn’t what this treatment does.</p>
Eli Lilly & Co.		
1.	<p>Lilly urges ICER to reduce its population and utility estimates to more accurately reflect the myriad factors that impact uptake of new therapies in the U.S.</p> <p>Data from a recent literature review showed that people aged 60 and older with amyloid-positive mild cognitive impairment (MCI) or mild dementia due to AD represent 8.2 percent of the global population (Gustavsson et al., 2022). Applying this percentage to data from the latest Medicare Enrollment Report for people aged 60 and older, who will represent approximately 95% of Americans receiving amyloid-targeting therapies, suggests a total eligible Medicare population of 4.5 million people across the U.S. That number, however, would be further reduced based on the diagnostic barriers and potential treatment contraindications for amyloid-targeting therapies, as well as the prevailing uptake rates for new medicines. For example, a meta-analysis of studies in the U.S. found that only 39.3% of those with dementia receive a diagnosis (Lang et al., 2017) and emerging data suggests that a far fewer percentage of patients with MCI may seek care, while a study of participants eligible to be enrolled in clinical trials of aducanumab for AD</p>	<p>ICER's analyses of potential budget impact are intended to provide an alert if the anticipated cost to the overall health care system has the potential to exceed specific growth targets due to high incremental costs and/or population size.</p> <p>ICER’s analyses of potential budget impact are not intended to estimate expected uptake, rather they are intended to provide an alert to health care payers and others when an intervention has the potential to cause a rapid increase in spending, so that they can proactively plan for and manage such increases in spending to ensure that access and affordability to new interventions are sustainable over time.</p> <p>We state in numerous places our practices for modeling uptake.</p>

	<p>found that a large percentage of Medicare beneficiaries would have been ineligible based on established trial exclusion criteria (Anderson et al., 2021). Further, ICER’s assumption of 100% uptake within 5 years is not based on existing evidence, as no medicine or class of medicine has ever reached a rate of 100%. On average, the uptake of an evidence-based intervention in clinical practice can take 17 years before it becomes part of a routine practice, with a variety of oft-cited systemic factors impeding adoption (Medlinskiene et al, 2021). Given the identified barriers and the well-known factors that negatively affect uptake, amyloid-targeting therapies will be available to a substantially smaller initial patient population than ICER has assumed in its draft report. Lilly strongly urges ICER to reduce its estimates of the total eligible population to no more than 4.5 million adults aged 60 and older in the U.S. and to modify the utilization estimate to a range between 1.7 and 2 million adult patients (Gillis et al, 2022), reflecting a maximum uptake rate of 44% in the early post-approval period.</p>	
2.	<p>Lilly urges ICER to use a base case threshold of \$250,000 to \$400,000/quality-adjusted life year (QALY)</p> <p>We are encouraged by ICER’s recognition of the “the enormity of the societal costs in AD” and its attempt to present a societal perspective as a co-base case. It is widely recognized that the healthcare system perspective adopted by ICER as its typical base case for cost-effectiveness (CE) analysis (CEA), by focusing on direct medical costs, fails to account for much of the burden of AD (Lin and Neumann, 2021). This burden includes elevated severity/disability, health inequities, full costs of institutionalization and family impacts. Therefore, in calculating its health benefit price benchmarks, ICER should use a base case threshold of \$250,000 to \$400,000/QALY, which better reflects the severity and societal impacts of AD as supported by recent scholarship on the topic.</p> <p>Instead of considering “acuity of need” and “severity of the condition” as merely contextual factors, ICER should consider these factors explicitly in its CE thresholds, in line with recent advances in economic evaluation (Lakdawalla and Phelps, 2020; 2021). The recent work of Lakdawalla and Phelps on Generalized Risk-Adjusted Cost-Effectiveness Analysis (GRACE) makes the case that the interaction of severity/disability with uncertainty/risk aversion would imply a higher CE threshold, based on willingness to pay from a healthcare sector perspective: “[...] cost-effectiveness decision thresholds should be about 5 times higher for severe Alzheimer’s disease than for peptic ulcer disease” (Lakdawalla and Phelps, 2020; 2021).</p> <p>GRACE is a formalization of “augmented CEA” as outlined in the “value flower” from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Special</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 specific conditions you feel we should evaluate using a lower threshold.</p>

	<p>Task Force on Value Assessment Frameworks (Lakdawalla et al., 2018). While conventional CEA using the QALY will be the key driver for many new medicines, the “health risk protection” component of the “insurance value” petal in the ISPOR value flower can be very important in cases of severe disability or poor health. Shafrin et al. analyzed a new medicine in non-small cell lung cancer and concluded: “89.8% of the total value of new lung cancer treatments comes from the willingness to pay [that] healthy individuals place on generous insurance coverage” (Shafrin et al., 2021).</p> <p>The point is that not only would patients and their caregivers benefit from the availability of a new AD treatment, but all persons at risk for AD would be better off (Shafrin et al., 2021). Prados et al. have constructed a long-term population-level model of the aggregate impact of a new AD drug that would reduce clinical progression by 30%. They project that the “societal value” between 2021 and 2041 would be \$2.64 trillion for those with AD, but “the value of insurance for the unaffected is \$4.52 trillion or \$18,399 on average per person” (Prados et al., 2022). We recognize that there is more work to be done to determine how to incorporate this formally into economic evaluation but ignoring it as merely an “other benefit” would be a substantial omission.</p>	
3.	<p>One recent study by Ito et al. determined the CE of a hypothetical treatment for AD improved substantially, falling from \$192,000 per QALY gained when considering only patient healthcare costs to \$107,000 per QALY gained when including healthcare costs and QALY impacts for both patients and caregivers. When the same study analyzed both healthcare and non-healthcare factors, the CE ratio fell further, from \$183,000 per QALY gained for patients alone to \$74,000 per QALY gained when considering both patients and caregivers. We hope that ICER’s assessment of amyloid-lowering disease modifying therapies will incorporate many of the methods of this study, which was co-authored by ICER Founder and President, Steven D. Pearson, MD, MSc. Ito et al. relied on caregiver utility data from outside the U.S. rather than the caregiver utilities used by ICER in its review of aducanumab (Ito et al., 2021; Neumann et al., 1999), which even ICER has acknowledged lack face validity. Lilly urges ICER to use alternative measures of quality of life for patients and caregivers, including the Belger et al. studies presented at ISPOR in May 2022 (Belger et al., 2022).</p>	<p>These treatments result in approximately one more year lived in early AD (MCI due to AD and mild AD), and approximately six fewer months lived in later AD (moderate AD and severe AD). Prolonging time in MCI due to AD and mild AD is still associated with an impact on caregivers as measured by an impact on quality of life, health care costs, and time spent caregiving. This treatment is not restoring to a health state that doesn’t involve caregiver time spent. Therefore, this treatment delays and slightly shortens time in more severe AD health states, but prolongs time in early AD, which is still characterized by impacts to caregiver quality of life, health care costs, and time spent. Reversing AD would reduce caregiver impact dramatically, but that isn’t what this treatment does.</p> <p>The Belger studies presented at ISPOR in May 2022 were not used in the model for numerous reasons, including: not yet published or peer-reviewed, appropriateness of using time trade-off for eliciting utilities for a caregiver, challenges of respondent disentangling patient experience from caregiver experience, not a</p>

		<p>clear mapping to our health states and setting of care, small sample, and the importance and limited information around the framing of the questions.</p> <p>The Belger utilities were used in a scenario analysis.</p>
4.	<p>Ito et al. argued the limitations of conventional CEA in AD when accounting for caregiver impacts justifies the use of different willingness-to-pay thresholds than those typically used:</p> <p>Although the application of different CE thresholds from a health care and a societal perspective is uncommon in published CE analyses, it has been mentioned that using a different threshold according to perspective might be more appropriate (Claxton et al., 2021). The widely varying results seen in our scenarios highlight this concern, raising the question of whether a perspective inclusive of caregiver effects should be compared with a different (i.e., lower) threshold. There is also an argument about the need for a different CE threshold for severe diseases and conditions, such as AD. Recent literature (Lakdawalla and Phelps, 2020) has suggested a CE of 5 times annual per capita consumption (\$50,000-\$80,000), implying that a range of \$250,000 to \$400,000 could be appropriate. (Ito et al., 2021)</p> <p>Ito et al. did not, however, offer an approach for including caregiver and other societal effects, instead they conclude: “[...] the appropriate methods and values are not well established.” While this is true, we would suggest that as a first approximation they could take a net monetary benefit (NMB) approach to incorporating CE thresholds into the societal perspective by applying the following four steps:</p> <ol style="list-style-type: none"> i. Per Lakdawalla and Phelps (2020), accounting for insurance value implies a CE threshold range of \$250K to \$400K per QALY in conditions like AD. ii. For the healthcare system perspective, then apply this range of thresholds to the QALY gains in calculating the varying NMB for different annual AD drug treatment costs. (For a given CE threshold, NMB converts the cost-per-QALY-gained analysis into a cost-benefit analysis, i.e., with health benefits also in monetary terms.) iii. To expand to the modified societal perspective, revise this healthcare system NMB by (a) adjusting for any other cost differences, such as caregiver burden, and (b) adjusting for QALY gains for caregivers by using the standard population CE threshold range of \$100,000 to \$150,000 per QALY 	<p>Thank you; however, 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. Instead of us specifying the threshold based on the condition, we allow for deliberation: our voting panels can determine what may be appropriate across a wide range of field-supported thresholds.</p>

	<p>for differences in caregiver disutility. For varying annual treatment cost levels, we could then see how the modified societal NMB varies.</p> <p>The “fair” or “economically justifiable” price from a modified societal perspective would be where NMB equals zero for different threshold levels for patients and for caregivers. The result would be a matrix of societal economically justifiable prices for different combinations of patient and caregiver thresholds.</p>	
<p>GE Healthcare</p>		
<p>1.</p>	<p>We recommend ICER acknowledge and recognize the benefits of early diagnostics to identify amyloid pathology consistent with AD.</p> <p>The ICER Draft Evidence Report states “the hallmark of AD is the progressive accumulation of beta-amyloid protein plaques and neurofibrillary tangles of phosphorylated tau protein in the brain.” (Rajmohan R et al. 2017)</p> <p>A positron emission tomography beta amyloid (amyloid PET or PET Aβ) scan is a minimally invasive diagnostic imaging procedure that can detect levels of amyloid accumulation in the human brain. Studies conducted on the use of amyloid PET scan for patients with cognitive impairment have demonstrated the impact on both changes in diagnosis and patient management (Shea YF et al. 2018, Rabinovici GD et al. 2019).</p> <p>Additionally, PET Aβ can exclude Alzheimer’s disease, prevent potential misdiagnosis, avoid unnecessary procedures or treatments, and monitor the impact of therapeutic interventions for patients presenting with symptoms of dementia. (Kim Y et al. 2018; Shailendra MT et al. 2021, Hunter et al. 2015)</p> <p>Other benefits of PET Aβ include informing changes in clinical management, such as medication adjustments and counseling on safety and future planning to potentially avoiding unnecessary risks or costs. (Rabinovici GD et al. 2019). Additional evidence supports the contribution of PET Aβ to delay institutionalization, lower mortality and reduce care costs. (Maurik IS et al. 2022)</p>	<p>We agree that patients who will be treated with anti-amyloid therapies need confirmation of amyloid in their brain. We have also updated our report in the Background section to discuss that amyloid PET scans can be useful for both diagnosis and treatment monitoring.</p>
<p>2.</p>	<p>We recommend ICER include all the FDA approved beta amyloid positron emission tomography (PET) radiopharmaceuticals: Flutemetamol F-18; Florbetapir F-18; and Florbetaben F-18 where PET amyloid use is noted, when not referenced in a specific study.</p> <p>The ICER Draft Evidence Report on beta-amyloid antibodies defines Beta-amyloid as: “Beta-amyloid (Aβ) plays a key role in</p>	<p>We have updated the report and supplement to include all radiopharmaceuticals for PET amyloid where applicable.</p>

	<p>the pathogenesis of Alzheimer’s disease and can be imaged in vivo using F-florbetapir PET.”</p> <p>Currently, the FDA has approved three F-18 products (Flutemetamol F-18; Florbetapir F-18; and Florbetaben F-18) which are being used in New IDEAS: Imaging Dementia – Evidence for Amyloid Scanning Study under the CMS Coverage with Evidence Development Study (registered on Clinical Trials.gov NCT04426539). New IDEAS is an observational, open label, longitudinal cohort study on PET Aβ to evaluate the association between PET Aβ and patient centered outcomes in a clinically diverse population with cognitive impairment. The draft ICER evidence report (p 68) states ‘beta-amyloid can be imaged in vivo using ‘florbetapir PET’. This is not accurate given three FDA approved Aβ PET radiopharmaceuticals are available: Flutemetamol F-18; Florbetapir F-18; and Florbetaben F-18</p>	
3.	<p>We recommend the ICER model be based on a patient population that is confirmed to be amyloid positive.</p> <p>The cost-effectiveness analysis of the ICER Draft Evidence Report describes the population included in the model as: “a hypothetical cohort of individuals with MCI due to AD or mild AD receiving either the intervention or comparator treatments.” A more appropriate assumption is for the model to include the confirmation of “amyloid positivity” with the use of biomarkers to identify evidence of amyloid pathology consistent with AD before initiation of any therapy. Previous evidence has demonstrated in a cohort of MCI and dementia patients that were selected based on PET amyloid appropriate use criteria, 35.6% of patients had a change in diagnosis after the PET scan (25.1% from AD to non-AD and 10.5% from non-AD to AD and that 36.1% of patients who were considered to be due to AD after clinical workup turned out to be amyloid negative. (Rabinovici GD et al. 2019)</p>	<p>Thank you. We have clarified that the population in our model are those with confirmed amyloid positivity, and more clearly stated that patients will have amyloid positivity confirmed by a reliable method prior to determining eligibility for treatment.</p>

#	Comment	ICER Response
Patients/ Patient Groups		
Alzheimer's Association		
1.	<p>1.0 Background</p> <p>We note the overall negative tone of this report and that it seems to have been based on skepticism about lecanemab's approval. Now that it has received accelerated approval by the Food and Drug Administration (FDA), we urge ICER to update the final paragraph of this section and reconsider its tone.</p>	<p>We have updated the description in the Executive Summary and Background to reflect the approval of lecanemab.</p> <p>Our assessment of lecanemab's overall net health benefit is based upon an evidence-based analysis of both the benefits and harms of lecanemab. We continue to have concerns that on the whole, the benefits of lecanemab may not outweigh the potential harms and thus stand by our original assessment and evidence rating of promising but inconclusive.</p>
2.	<p>3.0 Comparative Clinical Effectiveness</p> <p>We note that the report fails to acknowledge that the clinical efficacy of these treatments is significant <i>in addition to</i> the benefits of background concomitant Alzheimer's therapies. Table 3.1, Baseline Characteristics and Cognitive Measures, does offer that more than 50 percent of trial participants for both lecanemab and donanemab were on background therapies while participating in the trials. We encourage ICER to explicitly recognize that the results of these trials are significant above and beyond the current standard of care with these older medications.</p>	<p>We have clarified that supportive care includes non-disease modifying drugs in Section 3.</p>
3.	<p>Uncertainty and Controversies</p> <p>The Alzheimer's Association disagrees with ICER's statement that adequate data do not exist to demonstrate the association between amyloid removal and treatment effect. First, the FDA approved lecanemab based on such data, which had also been previously published in a journal. Second, data presented at the Clinical Trials on Alzheimer's Disease (CTAD) 2022 conference on gantenerumab's negative trial results demonstrate that if amyloid cannot be removed adequately from the brain there is no treatment effect. Finally, the analysis conducted by the Division of Pharmacometrics at the FDA and the presentation, "Advances in amyloid lowering therapeutics, what questions remain?" by Dr. Yaning Wang at the Alzheimer's Association International Conference 2022 demonstrate that amyloid removal is related to impact on disease progression. There is an extremely low probability that these relationships happen by chance when looking across amyloid targeting treatments.</p>	<p>We respectfully disagree that there is conclusive evidence to demonstrate the association between amyloid removal and treatment effect. A 2021 meta-analysis of all anti-amyloid therapies (and a 2022 update) failed to find an association between amyloid removal and improvement in cognition, though these did not include the most recent data from CLARITY-AD.² The manufacturers of lecanemab have patient level data from at least three Phase III trials (including two trials of aducanumab) where they could show at the patient level across two therapies whether there is association between amyloid removal and cognitive benefit. This hasn't been published and would be broadly helpful in understanding the strength of evidence for the amyloid hypothesis.</p>
4.	<p>With regard to ICER's perspective on the use of aggregate measures, the Alzheimer's Association respectfully notes that the very purpose of mean outcome measurements in clinical</p>	<p>We appreciate the discussion around MCID and its use. We note that statistically significant changes to an outcome can be a</p>

	<p>trials are to understand whether the results would be generalizable: an average response to a treatment can be assumed—to an extent—to have an effect on a segment of the population. Furthermore, there are many reasons not to apply individual patient analysis in instances such as this, as individual change could create additional bias in the results. We therefore disagree that MCID analysis would be beneficial to helping to understand from a value perspective how these treatments will impact the broader population.</p>	<p>result of clinically meaningful changes or a large sample size, or both. Declining 27% slower than before is not inherently clinically meaningful; what matters is how this impacts life. While we acknowledge that there is not universal agreement on MCIDs for the outcome measures used in the lecanemab studies, discussion of MCID is relevant because on average, the benefit isn't as large as what is published in the literature to be clinically meaningful for CDR-SB. Comparison to MCID can help those assessing the data in understanding the magnitude of benefits for patients. Furthermore, establishment of MCIDs benefits patients, family members, caregivers, and health-care systems by pushing clinical trial sponsors to power trials not just on statistically significant differences but clinically relevant ones as well.¹</p>
5.	<p>As we have noted in the past, ICER's economic analysis fails to do justice to the beneficial societal impact of these treatments. While a "modified societal perspective" is included, the failure to incorporate it into a single economic analysis continues to leave the impression that it is an afterthought, is not really of importance, and can (or should) be ignored. Furthermore, many elements of social value continue to be excluded, even though it has been demonstrated that severity of disease, insurance value, and adherence-improving factors can be quantified and included in value determinations for Alzheimer's therapies. Given the responsibility that ICER has accepted in conducting this analysis, it is incumbent upon ICER to seek out and include as many relevant elements of social value as possible.</p>	<p>We include a modified societal perspective, but also present this modified societal perspective as our co-base-case analysis.</p> <p>We include patient productivity, caregiver time spent, caregiver quality of life, and caregiver health care costs in our modified societal perspective. Additionally, we discuss other benefits and contextual considerations in the report. We will also discuss other benefits and contextual considerations during our public meeting.</p>
6.	<p>We also continue to be concerned that even the elements ICER does include in the "modified societal perspective" are undervalued. A project on evaluating the cost-effectiveness of hypothetical Alzheimer's treatments funded by the National Institute on Aging in which ICER participated concluded, "When using the broadest societal perspective, with all estimated caregiver productivity and QALY gains included," the QALY was 2.5 times greater than the health care sector perspective that included only patient clinical outcomes and health care costs. Yet, in ICER's current analysis, the QALY under the societal</p>	<p>These treatments result in approximately one more year lived in early AD (MCI due to AD and mild AD), and approximately six fewer months lived in later AD (moderate AD and severe AD). Prolonging time in MCI due to AD and mild AD is still associated with an impact on caregivers as measured by an impact on quality of life, health care costs, and time spent caregiving. This treatment is not restoring to a health state that doesn't involve caregiver time spent.</p>

	<p>perspective relative to the health care-only perspective was just two percent higher for lecanemab and 70 percent higher for donanemab. This wide difference suggests ICER is not evaluating the caregiver gains from an Alzheimer’s treatment as robustly as it should.</p>	<p>Therefore, this treatment delays and slightly shortens time in more severe AD health states, but prolongs time in early AD, which is still characterized by impacts to caregiver quality of life, health care costs, and time spent. Reversing AD would reduce caregiver impact dramatically, but that isn’t what this treatment does.</p>
<p>Black Women’s Health Imperative</p>		
<p>1.</p>	<p>Under-representation of African Americans in Clinical Trials & Alzheimer’s Research</p> <p>The Black Women’s Health Imperative agrees with ICER’s observation that Black and Hispanic underrepresentation in clinical trials serves as a societal disadvantage – as treatment effects remain unknown, thus contributing to health inequities.</p> <p>Despite controversy about the efficacy and safety of aducanumab, it was accelerated by the FDA. Two trials organized by Biogen Inc. for its drug Aduhelm (generic name is aducanumab), the first Alzheimer’s drug approved in almost two decades, were among those with the lowest Black representation. Only 19 people, or 0.6%, of 3,285 participants in its two final-stage trials identified themselves as Black.</p> <p>Biogen’s partner, Eisai Co., says its Phase III trial of an experimental Alzheimer’s drug, lecanemab, enrolled 4.5% Black and 22.5% Hispanic individuals in the U.S. portion of the trial – an increase from numbers it achieved in its second-stage trial.</p> <p>African Americans age 65 and older make up <i>only</i> ~9% of the U.S. population and represent 13.8% of persons with Alzheimer’s disease and other dementias (AD). There remain important gaps in medical literature (and research), and consequently, understanding of factors that influence Alzheimer’s disease among African Americans.</p> <p>Black women (in particular) had the highest prevalence (15.1%) of AD and related dementias (ADRDs) among nearly 5 million people (aged 65 years and older) diagnosed in 2014. Several well-established AD risk factors (e.g., genetics, sociodemographics, vascular conditions) could not fully explain these racial disparities.</p> <p>In an environmental study for determining whether racial/ethnic disparities in Alzheimer’s disease (AD) risk may be explained by ambient particles (PM_{2.5}), Diana Younan, et al concluded that PM_{2.5} may contribute to racial/ethnic disparities in AD risk, and finding that its associated increase in AD risk was stronger in Black women.</p> <p>The lack of high-quality biologic data on large numbers of racial and ethnic minorities poses critical barriers to progress in understanding whether the mechanisms and processes of</p>	<p>We agree with the points made here about health inequities in AD and appreciate the information and references provided. We have updated our report to better reflect these inequities, including additional information in the Background and Patient and Caregiver Perspectives section, and also adding a Sample Diversity Rating in Section 3 the Evidence Report, which highlights that although the CLARITY-AD trial was more diverse than other similar trials of early AD patients, it still isn’t reflective of the overall population of AD patients in the US. The lack of diversity in clinical trials both impact generalizability of results and is inappropriate given the high burden of illness and need for effective disease-modifying treatments.</p>

	Alzheimer’s disease operate the same or differently in racial and ethnic minorities and, if so, how - particularly in the high-risk African American population.	
2.	<p>Diagnosis & Treatment of Alzheimer’s in African Americans</p> <p>Researchers, led by Keenan Walker, PhD., from the NIA Intramural Research Program, found that Black study participants showed higher rates of cognitive impairment, particularly on measures of processing speed, executive function, and language, compared with white participants. Black participants also had higher rates of hypertension and diabetes, potential risk factors for Alzheimer’s and related dementias. The research team found that neuropsychiatric symptoms were also more likely to occur in diagnosed Black participants than in white participants with a similar diagnosis. After accounting for demographic factors and education, Black participants were roughly twice as likely as white participants to experience delusions and hallucinations. Black participants were also more likely to have other symptoms, including agitation/aggression, loss of inhibition, irritability, motor disturbances, and abnormal sleep, behavioral, and appetite/eating changes.</p> <p>Investigators from the NIA Intramural Research Program see their results as further evidence that Black patients often have to present with more severe clinical presentations to warrant a diagnosis of dementia from physicians than white patients. This is consistent with numerous studies that showed Black individuals were not being diagnosed with Alzheimer’s or related dementias or seeking treatment until the disease process was more advanced. Investigators are not yet clear on the reasons behind these findings but substantiates the need for addressing racial disparities in Alzheimer’s disease and related dementias treatment, especially to avoid delayed diagnoses that could have major adverse consequences for patients and their families.</p>	We appreciate the information and references provided and have updated our Background and Patient and Caregiver Perspectives sections to better reflect the concerns raised in this comment.
3.	<p>Overcoming Barriers to Equity</p> <p>Findings from two national surveys conducted by the Alzheimer’s Association show that Black Americans reported the highest level of discrimination in dementia health care followed by Native Americans, Asian Americans, and Hispanic Americans. With projected increases in Alzheimer’s disease among these populations, it is more important to address care inequities. The surveys show that among non-White caregivers, half or more say they have also faced discrimination when navigating health care settings for their care recipient. Their top concern being that providers or staff do not listen to what they are saying because of their race, color, or ethnicity. This concern was especially high among Black caregivers (42%), followed by Native American (31%), Asian American (30%), and Hispanic (28%) caregivers. Fewer than 1 in 5 White caregivers (17%) expressed this view.</p>	We appreciate the information and references provided, and have updated the Patient and Caregiver Perspectives section to better reflect the concerns of caregivers raised in this comment.

	<p>Findings from the Alzheimer’s Association surveys indicate that, despite ongoing efforts to address health and health care disparities in Alzheimer’s and dementia care, there is still much work to do. Based on these findings, paths forward should prepare the workforce to care for a racially and ethnically diverse older adult population; increase diversity among providers for dementia care; and engage, recruit and retain diverse populations in Alzheimer’s research and clinical trials. The Black Women’s Health Imperative supports these recommendations.</p>	
<p>4.</p>	<p>Caregiving & Alzheimer’s Disease</p> <p>When compared with White caregivers, Black caregivers are more likely to provide more than 40 hours of care per week (54.3% versus 38.6%) and are also more likely to care for someone with dementia (31.7% versus 11.9%). Black dementia caregivers were found to be 69% less likely than White caregivers to use respite services.</p> <p>In 2021, the 11.3 million family and other unpaid caregivers of people with Alzheimer’s or other dementias provided an estimated 16 billion hours of unpaid help. This number represents an average of 27.1 hours of care per caregiver per week, or 1,413 hours of care per caregiver per year. With care valued at the average of the state minimum wage and the median hourly cost of a home health aide, the estimated economic value of care provided by family and other unpaid caregivers of people with dementia across the United States was \$271.6 billion in 2021. The chronic stress of caregiving may be associated with an increased incidence of hypertension and a number of physiological changes that could increase the risk of developing chronic conditions, including high levels of stress hormones, impaired immune function, slow wound healing and coronary heart disease.¹⁴</p> <p>To help reduce the physiological and financial strains of caregiving, the Black Women’s Health Imperative recommends efforts to raise awareness in Black communities about the <i>Improving HOPE for Alzheimer’s Act</i>, signed into law in December 2020, to increase caregiver-provider collaboration related to dementia care planning.</p>	<p>We appreciate the information and references provided and have updated the Patient and Caregiver Perspectives section to better reflect the concerns of caregivers raised in this comment.</p>
<p>California Chronic Care Coalition</p>		
<p>1.</p>	<p>The ICER methodology utilizes what we believe is an excessively narrow focus on the value, assessed in monetary terms, of a patient’s life if given additional years of mental acuity as a result of this treatment being successful. Because Alzheimer’s patients tend to be of a comparably older age, traditional value-of-life measures tend to skew against them. Also, measures that focus on alleviation of direct medical costs are greatly insufficient in recognizing the wide-ranging costs that go beyond health system costs of care. It is critical that any value assessment recognize the unique nature of Alzheimer’s disease and that potential treatment can’t be compared, for example, to a hip replacement or a cardiac stent. Alzheimer’s is, after all, a</p>	<p>Throughout our assessment, we use the equal value life year (evLY), which evenly measures any gains in length of life, regardless of the treatment’s ability to improve patients’ quality of life. In other words, if a treatment adds a year of life to a vulnerable patient population – whether treating individuals with Alzheimer’s disease, cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLYG as a</p>

	<p>chronic condition – often patients will battle this disease for years, even decades, as the disease progresses and ultimately takes their life.</p> <p>The possibility of bringing additional years of cognitive health, and slow disease progression, for an individual carries extraordinary value and significantly reduces the burdens on caregivers.</p>	<p>different treatment that adds a year of life for healthier members of the community.</p> <p>Further, we did seek out input from patients and advocacy groups throughout our review and we believe that our report highlights their insights and concerns. Though it is not possible to include all of these insights into our cost-effectiveness model itself, these quantitative assessments are only one part of our report. We focus considerable attention on the data available, its limitations as well as key insights from all concerned groups including patients and their advocates. Presenting these data, along with insights from patients and other interested parties along with the quantitative results are all necessary to inform policymakers about how best to consider new therapies. The comparative clinical effectiveness, quantitative evaluation, other benefits, and contextual considerations sections of our report all feature prominently in the ICER value framework to inform all decision making by our panels.</p>
2.	<p>Patients afflicted with dementia incur average lifetime care costs from the time of diagnosis of almost \$360,000. The lion's share of these costs won't be absorbed by public or private health systems, but rather by the patient's family. We believe the ICER study fails to recognize the tremendous, physical, emotional and financial (loss of revenue and employment opportunities in addition to direct medical and maintenance costs) burdens that caregivers assume. Many caregivers are individuals, predominantly women, in their 40s and 50s who are sacrificing their prime earning years to provide care for a loved one. Absences from the workforce, lower incomes and loss of productivity must all be fully accounted for in assessing the value of a treatment. Just in California, Alzheimer's caregivers provide 881 million hours of unpaid care, representing an enormous amount of productive labor that is not engaged in the wage-earning workforce.</p>	<p>Thank you for this comment and we agree that there is a heavy economic impact on caregivers of persons with dementia. However, nothing suggests these costs will be reduced with a therapy like lecanemab that is not curative but that marginally slows the progression of the disease, as persons with dementia will still require caregiving.</p>
3.	<p>There is a societal benefit as well that should not be disregarded. Addressing the ravages of Alzheimer's disease will, simultaneously, affect this nation's challenges related to health equity and persistent disparities. Research from the National Institute on Aging tells us that older African Americans and older Hispanic Americans have disproportionate affliction rates from Alzheimer's than older white individuals. Similarly, Americans with lower incomes, less education, and who live in rural areas also have a higher incidence rate.</p>	<p>We agree and look forward to a therapy that addresses the ravages of AD.</p>

	Research in recent years has provided the tools to quantify the value in addressing these caregiver and societal burdens and we would strongly encourage ICER to utilize that scholarship in formulating its final report	
4.	<p>Finally, we believe that it is essential to apply a broad historical context in evaluating the value of emerging Alzheimer’s treatments. For decades, there have been no Alzheimer’s disease treatments that slow the damage that causes symptoms and prolongs mental acuity. Thus, this disease has been one of the most severe and devastating in our society in terms of causing irreversible decline in its patients and enormous burdens on caregivers, without hope of improvement prior to death. The success of beta-amyloid antibodies in clinical trials delivers something more than just a new medical treatment, but rather a lifeline where none had previously existed and a stepping stone toward even more effective therapies. These qualities bring significant and tangible value and should be incorporated in any assessment of this treatment.</p> <p>Preventing this increasing stress on families, on communities, on our health care and social services systems, and on society as a whole is dependent on medical science’s success in developing effective treatments for a disease that is as cruel as it is expanding in the number of patients it claims. As with other diseases such as cancer and HIV/AIDS, treatment effectiveness will be enhanced in each subsequent iteration of scientific discovery, but those new generations of therapies will be slowed if not halted altogether if value assessments of current treatments are flawed and do not incentivize continued research and development.</p>	We agree that the results from CLARITY-AD represent an advance in treatment for such a devastating disease, but that advance is a small one - clinical experts disagree on whether a 27% slowing of cognitive decline is clinically relevant. We have attempted to encapsulate both the advance and the uncertainty in the benefit/harm ratio in our evidence rating (Promising but inconclusive).
Global Alzheimer’s Platform Foundation		
1.	<p>The scientific evidence supporting Leqembi is robust and demonstrates significant benefit to patients.</p> <p>The most informative clinical trial of an antibody directed toward beta amyloid aggregates in patients with Alzheimer’s disease completed to date is the Clarity AD study, a phase 3 trial of lecanemab (now Leqembi) conducted in 1795 patients with mild AD. This trial demonstrated a highly significant effect of lecanemab to slow the rate of disease progression over 18 months on the primary clinical outcome measure, the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB). The CDR-SB is a validated composite measure of the most important cognitive and functional deficits experienced by patients with mild AD. The scale is completed by an experienced clinician and assesses cognitive deficits in Memory, Orientation, Judgement and Problem Solving and functional deficits in Community Affairs, Home Activities and Hobbies, and Personal Care. These are the general areas of cognition and function that are recognized as most important to patients with AD, their loved ones, and experienced clinicians; the observed improvement shown with lecanemab is clinically relevant and meaningful. As with all drug</p>	We agree that the results from CLARITY-AD represent an advance in treatment for such a devastating disease but a small one. We note that statistically significant changes to an outcome can be a result of clinically meaningful changes or a large sample size, or both. Declining 27% slower than before is not inherently clinically meaningful and clinical experts disagree on whether the slowing of decline seen in CLARITY-AD is clinically meaningful. Additionally, assessment of the overall net health benefit of a treatment involves assessing the balance between potential benefits and potential harms. In the case of lecanemab, we have concerns about the harms of ARIA, particularly since real-world monitoring may not be as stringent as that in the clinical trial and with the three recently reported deaths in patients taking lecanemab. While we agree that there will be individual responses

<p>treatments, response to lecanemab varied such that the slowing of progression was smaller than average in some patients and larger in others. Individual patients with their clinicians will need to determine the extent to which their own response to treatment is above their threshold for meaningful benefit; those who experience, and report sufficient benefit should not be denied treatment because some patients experience little or no benefit.</p> <p>The efficacy of lecanemab is also supported by positively meeting two key secondary endpoints. The Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-Cog) very precisely measures patient deficits in the ability to learn and remember, the ability to speak and understand language, and the ability to perform common motor activities (e.g. drawing or writing) as desired by the patient. The ADAS-Cog has been shown to track the progressive loss of cognitive function in AD and has been accepted as a primary endpoint in previous AD clinical trials. Lecanemab showed a highly significant effect to delay the loss of cognitive function as measured by the ADAS-Cog.</p> <p>Another secondary outcome, the Alzheimer’s Disease Cooperative Study – MCI – Activities of Daily Living (ADCS-MCI-ADL) scale measures the extent to which patients require assistance from another person such as a family member or caregiver to complete their daily activities. To score this scale, a trained clinician asks the patient and family member about how the patient performs activities such as using household appliances, making their own meals, selecting their own clothes, shopping, handling money and being left alone. Independence in these activities is important to patients and to their family. Lecanemab treated patients remained significantly more self-sufficient and independent in these activities compared to placebo treated patients, an effect that is clinically meaningful.</p> <p>As with all drugs, there were adverse events associated with lecanemab and other antibodies directed against amyloid aggregates. The most concerning are amyloid related imaging abnormalities (ARIA), either with edema (ARIA-E) or with microhemorrhage (ARIA-H). ARIA is detected by Magnetic Resonance Imaging (MRI) brain scans and usually does not cause symptoms, although headache, dizziness, vision changes, nausea or seizures can occur and usually resolve on their own; more serious, life-threatening symptoms are very rare. The prescribing information for lecanemab advises monitoring for ARIA with MRI scans early in treatment (4 scans, one pretreatment and 3 through week 14 of treatment), and also provides guidance on whether to continue dosing or to suspend treatment if ARIA is detected. Used as directed lecanemab should be safe for the vast majority of eligible patients.</p> <p>In short, the quantitative data supporting Leqembi conclusively shows that it provides meaningful clinical benefit and that it will</p>	<p>to the drug, we continue to have concerns that on the whole, the benefits of lecanemab may not outweigh the potential harms</p>
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	offer many patients a significant delay in the devastating deficits in cognition and in the activities of daily living that plague patients and families living with Alzheimer’s.	
2.	<p>The ICER Report demonstrates a negative bias from a lack of scientific rigor and clinical experience.</p> <p>It is our understanding that the team that the drafted the Report was devoid of Board-Certified Neurologists or other scientific professionals that conduct Alzheimer’s research or treat Alzheimer’s patients routinely. The Report identifies two respected professionals that consulted with the drafters; however, such a structure does not appear to have infused into the process the scientific and clinical insights needed to create a model that captures the value of a disease modifying therapy for Alzheimer’s disease.</p>	ICER approaches reviews by employing and engaging experts who are skilled in evidence-based medicine systematically reviewing and synthesizing a body of evidence. Domain experts are consulted throughout the process and are not limited to those who were engaged to provide expert review. Such input is vital to our reports, but we believe that experts in evidence-based medicine are best able to provide an unbiased look at the therapies we review.
3.	<p>First, the Report suggests on page 11 that the “Minimal Clinically Important Difference” (MCID) for the Clinical Dementia Rating—Sum of Boxes is 1-2 points. The Report goes on to cite studies that many have said are not relevant to the required change in 18-month study tracking MCI patients. The Report also fails to cite and acknowledge the writings of many researchers that assert a change of .4-.5 is a Minimal Clinical Important Difference. We think the Report should acknowledge the majority opinion on what constitutes MCID and run their model to reflect an alternate cut-off of around .5.</p> <p>Second, the Report suggests on page 11 that there are no MCID for the secondary endpoints that were recorded for Activities of Daily Living. These are validated and routinely used measures to assess how patients feel and function as compared to healthy individuals. The slowing of deficit in this area by as much as 30 percent is substantial. To suggest, that there is no method for recognizing that they data showed MCID for these measures demonstrates a lack of understanding of Alzheimer’s clinical practice--and the value to patients and society. The Report must undertake the hard work of thoughtfully valuing the significant changes in ADLs and not trivializing the benefit Leqembi provides in significantly slowing the functional declines patients experience with this disease.</p> <p>In conclusion, GAP strongly encourages ICER to revamp its model to accurately reflect Leqembi’s benefits and what matters most to patients and their families. The current draft Report misses the mark.</p>	<p>We appreciate the conversation around MCIDs for the relevant AD scales. We would be happy to review any published sources which support a different MCID for CDR-SB. During our literature search, we did not identify sources that cited a 0.4-0.5 difference in the CDR-SB as the MCID for patients with MCI or mild AD. The source we cite³ was based on a cohort of patients from the National Alzheimer's Coordinating Center Uniform Data and stratified MCID by disease severity. In addition, clinical experts who reviewed our report, who were neurologists or geriatricians with expertise in diagnosing and treating AD, did not dispute our characterization of the MCID for CDR-SB. Finally, even if the commonly accepted MCID for CDR-SB was 0.5, the changed seen in CLARITY-AD (-0.45) would still not exceed MCID.</p> <p>In terms of MCIDs for the ADCS-MCI-ADL and ADCOMS, our systematic review of the literature did not yield any citations where MCID for these scales was assessed. We do not make any conclusions that MCID cannot be determined for these scales, only that we did not find any relevant sources. Therefore, we make no conclusions in the report about whether changes in those scales in the CLARITY-AD trial are clinically relevant. Again, we welcome the opportunity to review any sources that contain MCID values for these scales.</p>

Healthy Men Inc.		
1.	<p>The Current Assessment Algorithms Have A Dangerous And Inappropriate Age Bias.</p> <p>There is no question that AzD is a very complex condition and there is much yet to learn about its pathophysiology and its clinical management. As people around the globe live longer, the potential for developing AzD and length of managing AzD will also increase. The central traditional value assessment used by ICER, and other organizations, is the quality-adjusted life year (QALY). There have been numerous reviews, analyses and expert comments over the years that have pointed out technical, philosophical and sometimes ethical, criticisms of the QALY; these are well known to ICER and are beyond the scope of our comments. In the case of AzD, HMI, as well as others patient advocacy and clinical practice believe because AzD is primarily a condition afflicting older persons with QALY's heavy reliance on economic metrics structured for individuals much earlier in life the tool is not fully applicable as currently structured and applied. In an ethical and sociologic context, applying the current formulas imposes a significant and stigmatizing age-bias on the assessment process that is most inappropriate. HMI believes that approaches other than the traditional QALY must be applied to any evaluation of the value of a treatment for this devastating disease. HIM is not aware of any such algorithms for assessing the value of treatments for conditions that are seen in older persons. We, and other experts, believe that until such an adjusted and tailored assessment tool is accepted any analysis of value, such as the one proposed by ICER, is meaningless and worse is tainted by ageism.</p>	<p>We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment.</p> <p>Throughout our assessment, we use the equal value life year (evLY), which evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. In other words, if a treatment adds a year of life to a vulnerable patient population – whether treating individuals with Alzheimer's disease, cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLYG as a different treatment that adds a year of life for healthier members of the community. Therefore, the evLY removes the potential for bias between diseases in life extension.</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>
2.	<p>The Analytic Approach Does Not Adequately Include Caregiver and Family Economic Factors.</p> <p>Current analytic approaches used by ICER do not take into account quality and cost metrics for caregivers. This is of fundamental importance to assessing the value of a therapeutic entity or approach. The analysis of AzD is an example of a complex condition that has substantial persona and financial impacts on the afflicted individual as well as the caregivers. It</p>	<p>We include patient productivity, caregiver uncompensated time spent, caregiver health care costs, and caregiver quality of life. In addition to those features included in our co-base-case modified societal perspective analysis, we richly discuss other benefits and contextual considerations.</p>

	<p>should be particularly noted that caregivers are people, caregiving is stressful both mentally and physically, thus consideration of the potential impact of adverse mental and physical health problems because of ineffective patient treatment modalities <i>must</i> be accounted for. Leaving these assessments out of the equation simply provides not only a incomplete picture of value but also misleads payors who cover healthcare costs not only the patient but, as is most frequently the case, their family member caregivers. ICER’s assessments for AzD are an unfortunate excellent example of this methodologic deficiency.</p>	
3.	<p>Great Care Is Needed To Make Every Effort To Properly Characterize Value Of These Treatments Or Important Incremental Private Sector Investment In This Area Of R&D Will Be Curtailed Or Halted.</p> <p>It is essential that research into these areas continue and that both public and private entities have sufficient societal support for their work and financial support for their work. It is obvious that unless private business who have the brunt of the financial exposure in discovery, research, development, and commercialization of marketable medications have confidence in their ability to price products they bring to market in a way that fully accounts for the investment, uncertainty and risks of work in this complex and uncertain area they will simply pull-back. This cannot be allowed. HIM urges all organizations who conduct cost-effectiveness analysis, formulary management and clinical care guidelines to appreciate the level of risk, not only in the development cycles of products for AzD but also the risks associated with market entry of these products and an important component of their utility analysis. To not consider industry and academic institution incentives to work in this area is completely self-defeating to the advancement of basic and applied research as well as access to a steady-stream of improved treatments.</p>	<p>We agree that it is important to properly characterize the value of treatments. Except, perhaps, in the most ultra-rare conditions, we disagree that the price of therapies should be based on the cost of development. We believe that pricing to value maximizes current and future health.</p>
<p>Institute for Patient Access</p>		
1.	<p>With respect to lecanemab, the report cites an inaccurate range regarding the treatment’s efficacy, concluding that the impact could be “small” or “substantial.” Such uncertainty regarding lecanemab’s efficacy is inconsistent with the Phase III trial results and should not be used as justification to undervalue the drug’s benefits.</p> <p>The primary outcome for the lecanemab Phase III trial was the change from baseline in the Clinical Dementia Rating-Sum of Boxes (CDR-SB). The results of the trial demonstrated that the patients who received lecanemab performed better on this test than those who received a placebo. Further, the patients receiving lecanemab met the trial’s secondary goals, which included reducing toxic plaques within the brain and a slower decline on three other memory and function measures.</p> <p>These improvements in outcomes are not small. The Alzheimer’s Association, in response to lecanemab’s results, said that the</p>	<p>ICER’s evidence ratings judge the <u>net</u> health benefits of lecanemab. Net health assesses the balance between the potential clinical benefit as well as the potential harms from the drug. While the primary outcome showed a small benefit in terms of slowing of decline, there is uncertainty around whether the change in CDR-SB will result in a clinically meaningful benefit to patients. Additionally, lecanemab is associated with infusion reactions as well as ARIA as possible harms. Taken together, along with the lack of long-term data and prior studies that did not show a correlation between amyloid removal and slowing of cognitive decline, there is substantial uncertainty about the</p>

	<p>treatment “has the potential to change the course of the disease in a clinically meaningful way.” Specific benefits for patients include more time at or near their full abilities, allowing them to remain independent and participate in future health care decision. The ability to maintain one’s sense of self is also a critical benefit.</p> <p>A University of Chicago working paper by Philipson and Ling (2022) quantifies the large value enabled by treatments that slow Alzheimer’s progression. According to the authors, delaying the progression of Alzheimer’s from mild to moderate by between six months and three years provides between \$212 billion and \$1.3 trillion in benefits over the next 10 years. With respect to direct health care costs, delaying Alzheimer’s progression can reduce expenditures by “\$34,249 and non-market costs by caregivers by \$7,882.”</p> <p>Despite both the positive results from the Phase III trial and the benefits in terms of reduced health care spending and improved patient and caregiver outcomes, the report rates lecanemab promising but inconclusive. This rating significantly understates lecanemab’s efficacy in delaying disease progression and the tremendous value delayed progression offers patients, their caregivers and the broader community.</p>	<p>net health benefit of lecanemab. Our evidence rating of “Promising but Inconclusive” reflects this uncertainty of a range from net harm (e.g., if the risks of ARIA are greater in real world practice than in the clinical trial) to substantial net benefit (e.g., if longer term data demonstrate that longer use of lecanemab is associated with greater slowing of cognitive decline).</p> <p>Our approach in the economic model is similar to that of Philipson and Lang. We also monetize health and societal factors and evaluate quality-adjusted life expectancy. They model a one-year delay in progression from mild to moderate AD, which is not observed for this specific treatment we are modeling. Further, they include no treatment-related costs.</p>
2.	<p>The Costs of Alzheimer’s Are Higher Than the Estimates Cited in the Draft Evidence Report.</p> <p>The draft evidence report states the “direct and indirect costs of health care related to AD are estimated to be around \$500 billion annually.” This is likely an understatement.</p> <p>According to the Alzheimer’s Association, the direct health care costs alone are projected at \$321 billion in 2022. A study in the AJMC confirms this estimate finding the direct health care costs for treating Alzheimer’s in 2020 was \$305 billion and expected to grow to over \$1 trillion. A substantial share of these costs, 49% according to a Milliman report, are related to long-term residential nursing care.</p> <p>In addition to these costs, caregivers provide nearly \$271 billion in unpaid care to people living with Alzheimer’s and other dementias. These figures imply total annual costs around \$600 billion, approximately 20% more than the number cited in the report. And this cost estimate is still incomplete because it does not account for the many costs that are difficult to quantify.</p>	<p>Our original source was an estimate of indirect and direct costs from 2017; we have updated our estimate to be in line with the most recent Alzheimer’s Association Facts and Figures report.</p>
3.	<p>According to a survey from the Alzheimer’s Association, 64% of respondents caring for someone with Alzheimer’s or dementia felt “isolated or alone,” and more than four in every five (84%) said they needed more help with caregiving, especially from other family members.” These stresses impact caregivers’ health, with surveys showing that caregivers experience higher</p>	<p>We include patient productivity, caregiver uncompensated time spent, caregiver health care costs, and caregiver quality of life. In addition to those features included in our co-base-case modified societal perspective analysis, we richly discuss other benefits and contextual considerations.</p>

	<p>rates of stress, depression and even report declines in cognition themselves.</p> <p>Importantly, Alzheimer’s caregivers endure a larger burden compared to caregivers for other diseases. According to a survey by Home Care Assistance, “dementia caregivers were seven times more likely to experience daily physical, emotional and mental exhaustion from caregiving than non-dementia caregivers.” Dementia caregivers were also three times more likely to “feel extreme stress from their caregiving responsibilities than other types of caregivers.”</p> <p>As Alzheimer’s patients will 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 despite the difficulty in quantifying them. Without an accurate assessment of these burdens, ICER’s model will significantly undervalue the benefits from any efficacious treatment.</p>	<p>However, these treatments result in approximately one more year lived in early AD (MCI due to AD and mild AD), and approximately six fewer months lived in later AD (moderate AD and severe AD). Prolonging time in MCI due to AD and mild AD is still associated with an impact on caregivers as measured by an impact on quality of life, health care costs, and time spent caregiving. This treatment is not restoring to a health state that doesn’t involve caregiver time spent. Therefore, this treatment delays and slightly shortens time in more severe AD health states, but prolongs time in early AD, which is still characterized by impacts to caregiver quality of life, health care costs, and time spent. Reversing AD would reduce caregiver impact dramatically, but that isn’t what this treatment does.</p>
4.	<p>The cost estimates reviewed look at the disease’s cost from an annual basis. However, when discussing the financial burden of a degenerative disease, it’s necessary to recognize that the costs are incurred for many years and will increase over time as degeneration worsens. Consequently, an accurate understanding of the costs is incomplete without considering the lifetime burden of the disease (appropriately discounted into the present value).</p> <p>According to Jutkowitz et al., “the discounted cost of care for a person with dementia was \$321,780 (2015 dollars)” over each patient’s lifetime. The Alzheimer’s Association estimates that in 2020 dollars, lifetime costs that cover just the direct care expenditures equate to \$373,527.</p> <p>Of course, people not living with Alzheimer’s or other forms of dementia will also require direct health care expenditures over their lifetimes. For this reason, the study also accounted for the additional discounted lifetime costs of an Alzheimer’s patient compared to someone not living with dementia. Evaluated on this “additional cost basis,” the excess lifetime health care costs of an Alzheimer’s patient are \$184,500 higher than a patient not living with dementia. Again, these are direct health care costs only, and do not include the impacts on caregivers. Across the 6.2 million people currently living with Alzheimer’s, these</p>	<p>Our cost-effectiveness model, for both the health care sector perspective and the modified societal perspective are from the lifetime time horizon to capture the lifetime economic impact of this disease. Our economic model is predicting lifetime costs that cover just the direct cost expenditures of approximately \$400,000 (see table 4.3 in the Evidence Report). From the societal perspective, this is upwards of \$700,000 over the lifetime time horizon (see table 4.4 in the Evidence Report). Therefore, our economic model is suggesting an even higher lifetime economic burden than the sources you cite.</p> <p>The original estimate of \$500 billion direct and indirect costs was from a manuscript published in 2017; we have updated the estimated costs in the Background section to the most recent estimates found in the 2022 Alzheimer’s Facts and Figures report.</p>

	<p>additional costs imply that the present value of Alzheimer’s excessive direct health care costs are over \$1.1 trillion.</p> <p>A disproportionate share of the financial burden from this disease will be directly borne by families. Families will incur 70% of the total cost burden (\$225,140), compared to Medicaid, which will incur 14% (\$44,090) and Medicare, which will incur 16% (\$52,540).</p> <p>In light of these costs, IfPA fears that the \$500 billion cost estimate cited in the report may be an inaccurate basis from which to judge the benefits of effective treatments.</p>	
5.	<p>Accounting for Patients’ “Loss of Self” and Alzheimer’s Less Tangible Costs</p> <p>Loss of identity is one of the more devastating and terrifying aspects of Alzheimer’s and other forms of dementia. The ability to maintain one’s self-worth while having to accept the inevitable cognitive decline, along with the realization that you will become a burden on your loved ones, is a common struggle for patients diagnosed with Alzheimer’s.</p> <p>According to the aforementioned Alzheimer’s Association survey, “a full 70% of the 1,502 adult participants feared being unable to care for themselves and live independently as they aged....” Alzheimer’s patients also commonly experience depression, have thoughts of suicide and experience a poorer quality of life even before the disease robs them of their memories.</p> <p>The methodologies to accurately quantify these subjective impacts 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 efficacious treatment.</p>	<p>We thank you for this insight into the impact of AD on patients. We have attempted to describe how the disease affects patients in our Patient and Caregiver Perspectives and the Potential Other Benefits and Contextual Consideration sections of the report.</p>
6.	<p>Explicitly Accounting for Alzheimer’s Disproportionate Impact on Communities of Color is Essential</p> <p>As the draft evidence report mentions, Alzheimer’s imposes a disproportionate impact on communities of color. According to the Alzheimer’s Association, “African Americans are about two times more likely than whites to have Alzheimer’s and other dementias, [but] they are only 34% more likely to have a diagnosis. Hispanics are about one and one-half times more likely than whites to have Alzheimer’s and other dementias, but they are only 18% more likely to be diagnosed.” Communities of</p>	<p>We agree that AD has a disproportionate impact on communities of color and have tried to address the issue throughout the report, including in the Patient and Caregiver Perspectives section, as well as through our Sample Diversity Rating in Section 3 of the Evidence Report, and our calculation of the Health Improvement Disparities Index (HIDI) in the Potential Other Benefits and Contextual Considerations section.</p>

	<p>color have a higher risk of developing this devastating disease and, because it is discovered later, have higher average medical costs.</p> <p>Even still, racial and ethnic minorities are underrepresented in clinical trials – for Alzheimer’s drugs specifically and across disease states broadly. Of studies that reported ethno-racial information, according to a systematic review, the participation rate for racial and ethnic minorities in dementia prevention clinical trials was only 25.6%. This disproportionately low participation translates to lack of knowledge, risks associated with generalizability of findings and also lost benefits associated with clinical trials participation. Despite these shortcomings, ICER’s review heavily relies on clinical trials data – as opposed to waiting for FDA approval and real-world patient experience. As a result, ICER’s results inadequately capture the benefit effective treatments could have on communities of color.</p> <p>The disproportionate burden of Alzheimer’s borne by communities of color means that an efficacious treatment will be particularly valuable for these demographic groups. Such a benefit cannot be understated.</p>	<p>Also, in July 2022, we launched an initiative to evaluate health technology assessment methods that support health equity. The project will culminate in a White Paper and a series of public dissemination efforts in March 2023.</p>
7.	<p>IfPA would also like to comment about the structure of this assessment of Alzheimer’s disease interventions. IfPA has previously commented about the pitfalls associated with ICER initiating an assessment ahead of the FDA – as the designated federal agency – completing its drug review, yet those concerns are worth reiterating.</p> <p>Without the Phase III trial results, the efficacy of any drug cannot be determined – either positively or negatively. Further, without federal approval, a final indication and a manufacturer list price, any determination of value can only be based on assumptions – not facts. Timing aside, ICER has redefined the scope of this review multiple times since it was first announced over a year ago. Multiple edits to both the timeline and the interventions of interest make meaningful participation in the process difficult. In short, this assessment, which spurred a prolonged investment of time and resources by stakeholders, was premature.</p>	<p>ICER recognizes the importance of having its review be available at the time a product is approved. That is when prices are set and when clinicians and patients need to make decisions about using a therapy.</p> <p>We agree that the timeline and scope of this review changed multiple times. This was done to maximize access to appropriate data for a therapy that was likely to receive accelerated approval.</p> <p>We note that both the Draft Report and this Report include Phase III trial results.</p>
National Minority Quality Forum		
1.	<p>In NMQF’s view, the work of the Institute for Clinical and Economic Review (ICER) is an excellent example of how the scales can be set so that financial risk mitigation takes precedence over patient risk mitigation. As a nonprofit, non-governmental entity that strives to align healthcare spending with available dollars, ICER makes recommendations about the cost benefit of novel therapies and devices. Fundamental to</p>	<p>We respectfully disagree with this statement. The cost-effectiveness analyses are only one part of this report. It also includes a detailed review of the existing literature as well as input from stakeholders highlighting potential other benefits of these agents as well as key</p>

	<p>every one of ICER’s assessments is the application of its benchmark cost thresholds as tools to help it distinguish high-value from low-value care. A medication that is inferior in its medical benefit, but whose cost meets ICER’s long-term money value and short-term affordability valuation could be designated high value compared to a more clinically effective but more costly medication. In the comparisons, the more costly, clinical effective medications could be rated as low value in the ICER assessment. ICER conveniently ignores the fact that clinical effectiveness and lowering of patient risk are inextricably linked, and cost does not and should not mediate that relationship. ICER’s recommendations promote a healthcare system in which structural inequalities are an acceptable by-product of its legal and policy framework. In making these recommendations, ICER offers no advice to require payers and providers in the public and private sectors to consent patients to this care limitation.</p>	<p>contextual factors that should be considered by policymakers.</p> <p>We also note that ICER has concluded that some very expensive therapies are cost-effective because they were so clinically effective. Expensive therapies that are only marginally effective and thus not cost-effective lead to decreased population health by consuming resources out of proportion to their benefits.</p>
2.	<p>The need for health technology assessment processes through the lens of mitigating patient risk vs financial risk is an incomplete conversation. Value assessment that assigns a higher valence to financial risk mitigation are, at the moment, a pragmatic reality. As such, NMQF assumes a duty to engage in conversations with ICER as part of our commitment to the U.S. health equity movement in an effort to improve patient access to timely and appropriate high-quality healthcare. The following comments are offered in service to this objective.</p> <p>Our overarching concern is that the methodology undergirding ICER’s value assessments are based upon data sets that are incomplete, biased and serve to create and perpetuate harm to specific populations, and to American society writ large. They reflect NMQF’s perspective, as well as articulated perspectives of organizational partners which whom we collaborate, including Us Against Alzheimer’s, the Partnership to Improve Patient Care, and the Global Liver Institute.</p> <p>The National Minority Quality Forum joined several organizations in 2020 to review the existing literature about value assessment and its implications for health inequity. The report noted that value assessments are largely based on population-level averages and rarely report results specific to minorities. Also, the metric for determining cost effectiveness, known as a quality-adjusted life year (QALY), assigns a lower value to the lives of patients with disabilities and chronic conditions. The report also recognized that the underlying health utilities that are used alongside the QALY as part of the algorithm for cost effectiveness are typically derived from homogeneous Caucasian non-Hispanic populations. Utility designs also may not incorporate outcomes that matter to patients, including social determinants of health that too often drive disparity in health among various subpopulations.</p> <p>Quality Adjusted Life Years (QALYs) are, and are intended to be, a biased metric that assigns differential value to certain</p>	<p>We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment.</p> <p>Throughout our assessment, we use the equal value life year (eVLY), which evenly measures any gains in length of life, regardless of the treatment’s ability to improve patients’ quality of life. In other words, if a treatment adds a year of life to a vulnerable patient population – whether treating individuals with Alzheimer’s disease, cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same eVLYG as a different treatment that adds a year of life for healthier members of the community. Therefore, the eVLY removes the potential for bias between diseases in life extension.</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</p>

	<p>population or patient cohorts. The QALY is understood to reflect a utility value (quality of life) between 1 (perfect health) and 0 (dead). Therefore, years of life x utility value = the # of QALYs. Value assessments are largely based on population-level averages which underrepresent the quantifiable experiences of underserved and under-included populations.</p> <p>Value/health technology assessment processes that are conducted with foreknowledge of the limitations of the data sets are unacceptable. These data sets rarely report results specific to populations defined as minorities in the United States. NMQF, therefore opposes the use of QALYs in any model or Health Technology Assessment (HTA) to assess value of treatments</p>	<p>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>
Partnership to Fight Chronic Disease		
1.	<p>Importance of Not Undervaluing Alzheimer’s Disease Treatments</p> <p>We recognize the significant impact that value assessments will have on people’s access to therapies. The risks of undervaluing treatments for Alzheimer’s disease are particularly acute given the critical need for new treatments, the progressive nature and long duration of illness, and major health disparities affecting both patients and their caregivers. Alzheimer’s disease has wide-ranging disease burdens dominated not by medical system costs but involving large amounts of care predominately borne by individuals and their families. In fact, only 16 percent of the enormous costs of Alzheimer’s disease are paid for by the health care system whereas the social care costs and informal care or indirect costs amount to 84 percent of the total.</p> <p>Although the draft report acknowledges the enormous societal costs associated with Alzheimer’s disease, the assessment consistently excludes elements that enhance the value of the therapy under review, including failing to consider research supporting broader views on value, undervaluing delaying disease progression, and grossly underestimating caregiver burden. Given the high stakes involved, we urge you to consider making needed adjustments to reflect more closely the full value treatments that delay progression of Alzheimer’s disease offer.</p>	<p>We include patient productivity, caregiver uncompensated time spent, caregiver health care costs, and caregiver quality of life. In addition to those features included in our co-base-case modified societal perspective analysis, we richly discuss other benefits and contextual considerations.</p> <p>However, these treatments result in approximately one more year lived in early AD (MCI due to AD and mild AD), and approximately six fewer months lived in later AD (moderate AD and severe AD). Prolonging time in MCI due to AD and mild AD is still associated with an impact on caregivers as measured by an impact on quality of life, health care costs, and time spent caregiving. This treatment is not restoring to a health state that doesn’t involve caregiver time spent. Therefore, this treatment delays and slightly shortens time in more severe AD health states, but prolongs time in early AD, which is still characterized by impacts to caregiver quality of life, health care costs, and time spent. Reversing AD would reduce caregiver impact dramatically, but that isn’t what this treatment does.</p>
2.	<p>ICER has publicly commented in support of restricting access to these new therapies, prior to conducting this analysis or even the availability of clinical trial results. Within value assessment modeling, hundreds if not thousands of judgment calls are made in terms of studies to use, assumptions to accept or reject, weights to place on evidence, and criteria to include or exclude. In the aggregate, particularly when made with a bias toward undervaluing benefits, those decisions can amount to a</p>	<p>We are uncertain what this is referring to. ICER has not suggested restricting access to lecanemab (or donanemab).</p>

	<p>substantial difference. Explicit and implicit biases toward undervaluing benefits raise serious concerns and should be addressed proactively and transparently before finalizing this analysis given the potential to negatively affect patient access. We strongly urge ICER to consider these ramifications while reviewing and responding to the issues raised in this letter and issues raised by others that draw attention to areas where either the burden of Alzheimer’s disease or the benefits of treatment are underestimated or otherwise not fully captured in ICER’s draft report.</p>	
3.	<p>Consider Value Framework Enhancements</p> <p>Several experts have noted the limitations of current value assessment frameworks, particularly in their application to Alzheimer’s disease given its “uniquely complex and widespread burden—and resulting potential for therapeutic value—that is not fully captured ...” We strongly encourage ICER to consider this research and recommended approaches to capture more fully the burden of illness and benefits of slowing disease progression:</p> <ul style="list-style-type: none"> • Health economists Tomas Philipson and Yier Lang analyzed the value of innovations slowing the progression of Alzheimer’s disease and, specifically, slowing progression from mild to moderate disease by six months to three years assuming that half of mild AD patients can be treated. Their analysis estimates the value at \$212 billion to \$1.274 trillion for the US population over the next 10 years. Further, they estimate per-capita costs from a one-year delay in progression from mild to moderate AD reduces health care costs by \$34,249 and additional caregiver costs by \$7,882. • Milliman also analyzed the challenges of assessing the full value of treatments for Alzheimer’s disease and weaknesses in existing approaches. They note several flaws in current approaches and suggest solutions to address them that include capturing both the full burden of illness and the resulting benefits from treatments that delay disease progression. • Other experts have commented on the limitations of current assessment frameworks as they apply to the unique, wide-spread burdens of Alzheimer’s disease and need for assessments that reflect this value. Without incorporating broader considerations, traditional value assessments like that included in the draft report, miss the significant “hidden” burden of disease ranging from 60.7 percent of total costs for mild disease to 72.5 percent as disease progresses. 	<p>Our approach is similar to that of Philipson and Lang. We also monetize health and societal factors and evaluate quality-adjusted life expectancy. They model a one-year delay in progression from mild to moderate AD, which is not observed for this specific treatment we are modeling. Further, they include no treatment-related costs.</p> <p>The Millian publication suggests capturing effects on caregivers (which we do in our co-base-case modified societal perspective analysis) and suggests alternatives to potential biases of the QALYs (which we do with our evLY outcome).</p> <p>Our value assessment also includes discussion around other benefits and contextual considerations.</p>

<p>4.</p>	<p>Abandon the Unrealistic Assumption of the Single Caregiver</p> <p>ICER’s draft report equates caregiver hours per month to caregiver hours per patient, which grossly undervalues the caregiving burden even in early stages of disease. The assumption that all people living with Alzheimer’s disease, even in its earlier stages only need one caregiver is both unrealistic and offensive to people caring for these individuals. This assumption also fails to align with research ICER’s draft report cites in support of caregiving hours considered. In Robinson et al. 2020, even for people with MCI, one in three reported having more than one caregiver and more than one in five had four or more caregivers. For people living with mild Alzheimer’s disease in the study, nearly 45 percent had two or more caregivers and nearly thirty percent had four or more. This reality more closely correlates with research on caregiving by the Alzheimer’s Association and others that estimate 6.9 million people live with Alzheimer’s disease in the US yet “more than 11 million people provide caregiving” for people with Alzheimer’s disease and other dementias.</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.</p>
<p>5.</p>	<p>Alzheimer’s disease also has a profound impact on caregivers that grows exponentially given the progressive disability involved in disease progression that occurs over years. Yet, by choosing to exclude these disutilities in the draft report’s base-case analysis, ICER fails to account adequately for the caregiving burden and health care cost escalation associated with progression of Alzheimer’s disease. This is a significant flaw given the focus of these treatments on delaying progression. Consideration of these factors would aid in providing a more complete picture of value from slowing disease progression and reflect real-world burden of illness.</p>	<p>We did not exclude these disutilities in the base-case analysis. We present our modified societal perspective as a co-base-case analysis. In this analysis, we capture the disutilities for the caregiver.</p>
<p>6.</p>	<p>Research also confirms that the disparate impact of Alzheimer’s disease on people of color extends to their caregivers. Compared to white caregivers, Black caregivers are more likely to provide more than 40 hours a week of care. Hispanic, Black and Asian American dementia caregivers report higher care demands, less usage of outside help and formal service use, and greater depression compared with White caregivers. ICER’s draft report does not account for the disparate experiences of patients and caregivers nor does it adequately account for the system’s reliance on low-wage or no-wage labor. In so doing, the draft report ignores the “systemic disparities affecting racial, ethnic, and economic subgroups and fails to capture full value.” We urge ICER to consider conducting and including subgroup analyses on the impact of Alzheimer’s disease on different racial and ethnic groups as well as the potential impacts of treatments on health disparities.</p>	<p>We agree that AD has a disproportionate impact on communities of color and have tried to address the issue throughout the report, including in the Patient and Caregiver Perspectives section, as well as through our Sample Diversity Rating in Section 3 of the Evidence Report, and our calculation of the Health Improvement Disparities Index (HIDI) in the Potential Other Benefits and Contextual Considerations section.</p> <p>Also, in July 2022, we launched an initiative to evaluate health technology assessment methods that support health equity. The project will culminate in a White Paper and a series of public dissemination efforts in March 2023.</p>

7.	<p>QALYs and evLYs Are Crude Measures that Discriminate Against Older Patients</p> <p>Alzheimer’s disease is predominately a disease of aging and many affected have comorbidities. QALYs involve assumptions about age, comorbidities, and disabilities that puts these individuals at a discriminatory disadvantage in terms of the value of their lives and worthiness of treatment. Both the QALY and evLY use years of life as a quantifier of value which by definition assign less value to interventions that treat older people. As researchers have noted, for “all measures based on added years of life” interventions for younger populations have larger effects than interventions for the old. The use of these metrics is particularly misplaced given the burden of Alzheimer’s disease, though a disease predominately affecting older adults, is a heavy one borne by society at large.</p> <p>In a separate section of the draft report, the authors reject the use of a higher cost-effectiveness threshold for Alzheimer’s disease treatments and describe ICER’s rationale as wishing to avoid picking “winners and losers” and having “some patients viewed as worth ‘less’” than others. QALYs and evLYs starts with the premise that treatments for older people generate less value and those patients are by definition worth “less” to treat. Accordingly, the QALY and evLY should be rejected as well.</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> <p>Throughout our assessment, we use the equal value life year (evLY), which evenly measures any gains in length of life, regardless of the treatment’s ability to improve patients’ quality of life. In other words, if a treatment adds a year of life to a vulnerable patient population – whether treating individuals with Alzheimer’s disease, cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLYG as a different treatment that adds a year of life for healthier members of the community. Therefore, the evLY removes the potential for bias between diseases in life extension.</p>
RetireSafe		
1.	<p>Other health care conditions may place limitations on a patient’s ability to engage in normal daily life activities. Alzheimer’s, by contrast, inevitably takes everything away from the person afflicted – physical activity, social connectivity, communication capabilities, the most basic abilities to care for oneself. It is a disease of unparalleled severity that mentally and physically devastates its victims. Just as the disease robs its patients of mental cognition, independence and, eventually, life itself, it also robs our society of the value these individuals can bring whether through productivity or the imparting of wisdom and insights collected over the course of a life. And it is important to note that Alzheimer’s is unique that, while fatal, it is often not a</p>	<p>We thank you for this insight into the impact of AD on patients. We have attempted to describe how the disease affects patients in our Patient and Caregiver Perspectives and the Potential Other Benefits and Contextual Consideration sections of the report.</p>

	<p>short term illness or even one with a determined course – the disease can span decades.</p> <p>Conventional value assessment tools do not capture this colossal loss and, conversely, they don't capture the broad scope of benefits gained if a beta-amyloid antibody treatment can delay or slow this loss of cognition.</p>	
2.	<p>Similarly, we believe the draft evidence report understates the value of reducing the burden on those who provide care for Alzheimer's patients. Anyone who has known those who have provided care for someone afflicted with Alzheimer's can attest that this is a full-time, exhausting, even debilitating task – one that also exacts a financial toll. More than 11 million Americans provide unpaid care for people with Alzheimer's and other types of dementia. In 2021, caregivers provided an estimated 16 billion hours of care with a monetary valuation of over \$270 billion. The difficulty of their work leads to higher rates of illness and injury, financial difficulties, and shorter lifespans.</p>	<p>We agree completely. We include patient productivity, caregiver time spent caregiving, caregiver quality of life decrements, and caregiver health care costs in our co-base-case analysis from the modified societal perspective.</p>
3.	<p>What needs to be measured here is not just the impact on the individual caregiver (and there are often more than one per patient), but the broader loss to our society. Many caregivers for over-65 Alzheimer's patients are adult children in their 40s and 50s who would normally be engaging in the most productive years of their working lives. Their skills are lost to the workforce because of the unpaid services they are providing to their loved ones. Even caregivers who are at normal retirement age are unable to participate in volunteer activities that benefit their communities. If one is to look at the value of an Alzheimer's treatment through a comprehensive lens, the assessment must include the benefits of redirecting these caregiver years into the workforce and the larger community.</p>	<p>We monetize time spent caregiving using the average hourly wage in the United States. We do not use a different hourly wage for those who are employed or not employed. We do not use a different hourly wage for time off from work versus time off from volunteer activities. All caregiver time spent caregiving was monetized using the average hourly wage for those working in the United States.</p>
<p>Society for Women's Health Research (SWHR)</p>		
1.	<p>Concern with Missing Information Pertaining to Patient and Caregiver Perspectives</p> <p>SWHR appreciates that ICER took the time to speak with individuals—13 people with Alzheimer's disease and five caregivers—about the challenges associated with caring for persons with Alzheimer's disease. This perspective is critical to making an informed assessment about value.</p> <p>As ICER notes, these individuals emphasized “challenges with diagnosis, experience of coping with the diagnosis and a new way of living, impact on caregiver quality of life, treatment concerns and goals, and financial impacts and disparities.” While each of these areas may provide critical insight and context for life with Alzheimer's disease, it does not appear that these conversations touched upon these individuals' perceptions of value of the specific treatments under consideration; conversations appeared to be kept a higher level (e.g., thoughts</p>	<p>We appreciate that AD has a vast impact on patients and caregivers and that there are a wide variety of impacts the disease has and the potential impact of treatment that may not be captured within the limited number of informal interviews within this report. The Patient and Caregiver Perspectives section is meant to be a summary of the informal interviews, which were not exhaustive and not meant to replace formal research into the impact of the disease and the potential value of a therapy to all patients. We welcome additional research into this topic to include in any future reports.</p>

	<p>on receiving regular infusions, accessibility issues, insurance coverage).</p> <p>ICER shares in its report, “In terms of anti-amyloid therapies, both people living with [Alzheimer’s disease] and caregivers were interested in any treatment that would help slow disease progression.” When it comes to navigating life with a disease, such as Alzheimer’s, additional choice alone could be a valuable outcome for patients. To gain a truer understanding of the value patients assign to specific anti-amyloid therapies, SWHR would encourage ICER to engage in a deeper discussion with Alzheimer’s disease patients and caregivers about what these new treatments could mean for them in light of the evidence that has been shared thus far, including whether their decision to take such a treatment would be impacted by the stage of disease and how much risk they would be willing to tolerate for such a treatment. In the absence of this information from conversations, it could be presumptive to assign patient value to these treatments.</p>	
2.	<p>ICER’s Approach to ARIA</p> <p>SWHR is concerned about ICER’s characterization of ARIA and would direct ICER to the Alzheimer’s Association’s May 2021 comments on ICER’s Aducanumab for Alzheimer’s Disease: Effectiveness and Value Draft Evidence Report. As the Alzheimer’s Association stated, “ICER has...misinterpreted the weight given to [ARIA-E and ARIA-H data] compared with the potential benefits of the therapy,” asserting that “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.”</p>	<p>Our report details the rates of ARIA, including symptomatic ARIA, as they occurred in clinical trials. Our characterization of ARIA and the risks of treatment are based on these data. In fact, the FDA label for lecanemab states that “serious and life-threatening events, including seizures and status epilepticus, rarely can occur” and “events of intracerebral hemorrhage, including fatal events, in patients taking LEQEMBI have also been reported in other studies”.⁴ Whether or not the risks associated with ARIA are more or less severe in comparison to treatments for other conditions is not relevant, as clinicians and patients are weighing the potential harms and benefits for treatment of AD and not other conditions.</p>
3.	<p>Alzheimer’s disease is a fatal degenerative brain disease that affects the parts of the brain that control thought, memory, and language. To say that it is a challenging and devastating diagnosis for both patients and their caregivers is a gross understatement. While risk with any given treatment should certainly be assessed, SWHR is concerned that ICER’s report presents ARIA’s risk in an imbalanced manner—centering its recommendation on the potential of net harm from ARIA and minimizing both patient choice and Alzheimer’s disease as a fatal disease.</p> <p>By ICER’s own admission, “the net health benefits of lecanemab in patients with early Alzheimer’s disease may be small or even</p>	<p>As mentioned above, we report on ARIA based on data from the clinical trials, which included reports of severe and symptomatic ARIA. While the FDA guidance describes that enhanced surveillance for ARIA is needed within the first 14 weeks of treatment and when to discontinue dosing of lecanemab, the label also states that “There is no experience in patients who continued dosing through symptomatic ARIA-E or through asymptomatic, but radiographically severe, ARIA-E. There is</p>

	<p>substantial.” For those battling Alzheimer’s disease progression, these study results—and the glimmer of hope of a disease-modifying treatment—cannot afford to be eclipsed. Further, as noted by the Alzheimer’s Association in its letter, the U.S. Food and Drug Administration has adopted guidance for reasonable management of ARIA.</p>	<p>limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data in dosing patients who experienced recurrent ARIA-E.”⁴ We continue to be concerned that in real world practice, without the rigorous follow-up and monitoring that occurs within a clinical trial, that the consequences of ARIA may be greater than seen in the clinical trial. The three reported deaths in patients taking lecanemab only serve to heighten those concerns and we feel that clinicians and patients should be adequately informed about the potential harms prior to deciding whether to pursue therapy.</p>
<p>UsAgainstAlzheimer’s</p>		
<p>1.</p>	<p>The report bases its assessment of value on Quality Adjusted Life Years (QALY) and Equal Value of Life Years Gained (evLYG) models, which are inherently limited in scope and have been roundly criticized as being discriminatory against people with disabilities and chronic diseases. What’s more, the analysis does not acknowledge the limitations and biases in those models. As the National Council on Disability noted in its report <i>Quality Adjusted Life Years and the Devaluation of Life with Disability</i> (2019), QALY measures place a lower value on treatments which extend the lives of people with chronic illnesses and disabilities, creating discriminatory effects and having been found to violate the Americans with Disabilities Act. ICER should not use an analysis based on QALYs at all, and move toward more comprehensive, less discriminatory models than the evLYG as well. To the extent that ICER uses evLYG in its models, it must be clear throughout on the limitations and inherent bias of this metric.</p>	<p>We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment.</p> <p>Throughout our cost-effectiveness assessment, we use the equal value life year (evLY), which evenly measures any gains in length of life, regardless of the treatment’s ability to improve patients’ quality of life. In other words, if a treatment adds a year of life to a vulnerable patient population – whether treating individuals with Alzheimer’s disease, cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLYG as a different treatment that adds a year of life for healthier members of the community. Therefore, the evLY removes the potential for bias between diseases in life extension.</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-</p>

		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.
2.	We appreciate the ICER research team’s engagement with the Alzheimer’s community and its willingness to consider the experiences of those living with AD. We were pleased that you conducted some discussions with a limited number of stakeholders and referenced our What Matters Most™ research in the draft report. However, we see room for improvement in terms of the robustness of your research with these most-critical stakeholders. The results of a small number of interviews are obviously anecdotal, and not in alignment with the FDA Patient-Focused Drug Development (PFDD) guidance on rigorous attainment of feedback from such stakeholders. Therefore, these results have limited value in understanding what drug improvements matter most to patients and the degree of importance those improvements hold. Beyond lacking robustness, the evidence also did not appear to impact the model assumptions in any way. If it did, this should be explained clearly.	<p>We appreciate that AD has a vast impact on patients and caregivers and that there are a wide variety of impacts the disease has and the potential impact of treatment that may not be captured within the limited number of informal interviews within this report. The Patient and Caregiver Perspectives section is meant to be a summary of the informal interviews, which were not exhaustive and not meant to replace formal research into the impact of the disease and the potential value of a therapy to all patients. We welcome additional research into this topic to include in any future reports.</p> <p>The model was impacted by which clinical outcome to model alongside the standard outcomes that are modeled (e.g., QALYs, evLYs, LYs). For this review, the clinical outcome was time outside of long-term care based on feedback from patients and caregivers that is an important outcome for them. Additionally, the model structure was based on disease progression, which was the important target for treatments as reported by patients.</p>
3.	The annual cost thresholds of \$150,000 and \$200,000 are arbitrary; ICER’s analysis should acknowledge this and note the tremendous costs to society of untreated Alzheimer’s that have been shown in many economic analyses that do not limit themselves to a QALY/evLYG-style model.	We state the economic burden of Alzheimer’s disease throughout the report and we present numerous thresholds. The cost-effectiveness model outcomes also explicitly show the tremendous costs to society and the health care system of Alzheimer’s disease.
4.	There is no acknowledgement of the increasing extent of the burden with disease progression, such as financial and consumer fraud and other abuse. In general, the ‘loss of abilities’ goes well beyond a disabilities calculation and includes loss of jobs and income, increased need for legal services, in-home health	Patient productivity losses, uncompensated time spent caregiving, patient and caregiver health care costs, and quality of life decrements for the patient and caregiver

	services, and reduced quality of life for both the diagnosed person and often the caregiver.	are all included in our analysis from the modified societal perspective.
5.	<p>There are several flaws in your section about the magnitude of change from treatment. The terms “minimal clinically important difference” (MCID) and “minimum important difference” (MID) are important to patients, and they are misused.</p> <ol style="list-style-type: none"> While there is passing recognition in the draft report that MCID relates to change <u>within</u> a specific patient, you still create a table that appears to equate between-group change with MCID. In the text, you assert that “when averaged in aggregate it can provide context for the magnitude of changes overall.” ICER should not conflate within-person and between group changes, and generally apply the same level of statistical and methodological rigor to this section as it seeks to apply to the rest of its analysis. The table on MCID, in addition to being misleading on within-person versus between-group changes, also appears to misuse a single study to state the MCID on the Clinical Dementia Rating—Sum of Boxes (CDR-SB). MCID is inherently centered on the minimal change that is significant to the patient, but that single study was anchored on clinician opinion, without asking patients. The statement that a the MCID on CDR—SB must be >1 point lacks face validity. A change of .5 on any of the “boxes” in the CDR is the difference between independence and at least partial dependence. It is inconceivable that, if anyone had asked patients, they would not find that difference important. 	<p>We appreciate the discussion around MCID and its use. We note that statistically significant changes to an outcome can be a result of clinically meaningful changes or a large sample size, or both. Declining 27% slower than before is not inherently clinically meaningful; what matters is how this impacts life. While we acknowledge that there is not universal agreement on MCIDs for the outcome measures used in the lecanemab studies, discussion of MCID is relevant because on average, the benefit isn’t as large as what is published in the literature to be clinically meaningful for CDR-SB. Comparison to MCID can help those assessing the data in understanding the magnitude of benefits for patients. Furthermore, establishment of MCIDs benefits patients, family members, caregivers, and health-care systems by pushing clinical trial sponsors to power trials not just on statistically significant differences but clinically relevant ones as well.¹</p> <p>During our literature search, we did not identify sources that cited a 0.5 difference in the CDR-SB as the MCID for patients with MCI or mild AD. The source we cite {Andrews, 2019, 25} was based on a cohort of patients from the National Alzheimer’s Coordinating Center Uniform Data and stratified MCID by disease severity. In addition, clinical experts who reviewed our report, who were neurologists or geriatricians with expertise in diagnosing and treating AD, did not dispute our characterization of the MCID for CDR-SB. Finally, even if the commonly accepted MCID for CDR-SB was 0.5, the changed seen in CLARITY-AD (-0.45) would still not exceed MCID.</p>
6.	The reviewers of the draft report are esteemed <u>clinical</u> experts. However, there was no external review by even a single health economist.	We previously reviewed the economic model and our prior report with a world economic expert. Changes since then were primarily clinical in nature, hence the clinical

		experts. Additionally, the model was shared with all relevant manufacturers.
7.	We were able to identify questionable practices, such as the lack of a “limitations” section, and saw many apparent opinions conveyed which did not reference specific citations.	ICER commonly uses the “Uncertainties and Controversies” sections to discuss limitations.
8.	Data, for instance on disease-level input into the model, do not appear to have been systematically selected to avoid or limit bias.	There are numerous points within our assessment where stakeholders can and do suggest alternative sources, with the public comments being one of them. For future reviews, if you have a specific citation to share, please share that with us and we will review.
9.	Key data in the report are extremely dated, including use of 1999 patient and caregiver disutilities. Health systems have dramatically changed, longevity has shifted, and newer understandings of the wide range on impacts (on diagnosed individuals and caregivers) have emerged. A more transparent acknowledgement of this limitation, as was done in your Aduhelm report, would better serve the public.	We have expanded our discussion around the limitations of the current utility evidence within the “Uncertainties and Controversies” section of section 4 of our report.
10.	Caregiver settings considered in the report should be listed as a limitation. The complex ecosystem is comprised of senior apartments, retirement communities, respite care, senior co-ops, congregational settings, nursing homes, dementia/Alzheimer’s care units, assisted living facilities, active seniors, adult day care, independent living and personal home care, to name a few. The specific caregiver setting and its unique impact on the patient and the caregiver is deserving of a much deeper review.	These would be great data to incorporate if this level of granularity existed in the data.
11.	Similarly, just as there is such complexity around the caregiving ecosystem, family caregiving also generally involves many care providers.. ICER should take into account research showing that there is generally more than one care partner for each person living with Alzheimer’s.	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.
12.	You note a concern for ARIA real-world occurrences and complications, which we share. The limited research conducted by ICER was not robust enough to identify risk/benefit for a treatment with potential for ARIA. We propose (i) development of comprehensive real-world data to develop an evidence base that tracks clinical use and is coupled with (ii) clear guidelines for informed, shared clinical decision-making to assess benefit and	We agree there should be more information about ARIA and agree that there should be mechanisms to collect real-world data - the Alzheimer’s Network for Treatment and Diagnostics (ALZ-NET) registry is one such example and we hope that clinicians using lecanemab will enroll in the registry. We

	<p>risk choices at the patient level as well as appropriate use recommendations for imaging.</p>	<p>also agree that shared decision-making should take place and encourage the appropriate clinical societies to include shared decision-making and appropriate recommendations for imaging in their clinical guidelines.</p>
<p>UsAgainstAlzheimer's (Coalition Comment)</p>		
<p>1.</p>	<p>To begin, there is nearly unanimous consensus that Quality Adjusted Life Years (QALYs) discriminate against people with disabilities (including those with Alzheimer's disease) by placing a lower value on their lives and undervaluing outcomes that are life-changing. Specifically, QALY weights are constructed in a way that discriminates against older and disabled people and inadequately weights quality of life beyond the average of the entire (generally Caucasian) population. ICER should not use QALYs in its models, period.</p> <p>Utilizing the Equal Value of Life Year Gained, (evLYG) measure also is not an adequate solution. This measure undervalues quality of life improvements, ignores clinical knowledge, and takes no account of the priorities and values of diverse constituents. At bare minimum, ICER must explicitly acknowledge the limitations and biases of both these models.</p>	<p>We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are also only one component of the value assessment.</p> <p>Throughout our cost-effectiveness assessment, we use the equal value life year (evLY), which evenly measures any gains in length of life, regardless of the treatment's ability to improve patients' quality of life. In other words, if a treatment adds a year of life to a vulnerable patient population – whether treating individuals with Alzheimer's disease, cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLYG as a different treatment that adds a year of life for healthier members of the community. Therefore, the evLY removes the potential for bias between diseases in life extension.</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>

2.	<p>Also, the draft report comes dangerously close to misleading readers about the minimal clinically important differences (MCID) on various scales. There is no consensus on what those MCIDs are, as this term should be patient-centric and nobody has asked patients. Further, even if there were consensus, the data presented are between-group differences, while MCID is intended to capture within-individual differences.</p>	<p>We appreciate the discussion around MCID and its use. We note that statistically significant changes to an outcome can be a result of clinically meaningful changes or a large sample size, or both. Declining 27% slower than before is not inherently clinically meaningful; what matters is how this impacts life. While we acknowledge that there is not universal agreement on MCIDs for the outcome measures used in the lecanemab studies, discussion of MCID is relevant because on average, the benefit isn't as large as what is published in the literature to be clinically meaningful for CDR-SB. Comparison to MCID can help those assessing the data in understanding the magnitude of benefits for patients. Furthermore, establishment of MCIDs benefits patients, family members, caregivers, and health-care systems by pushing clinical trial sponsors to power trials not just on statistically significant differences but clinically relevant ones as well.¹</p>
3.	<p>The analysis for AD provides a key opportunity for ICER to incorporate equity in its analysis. The Phase III clinical trial for lecanemab included robust data on Hispanic populations, though representation in Black populations was less robust. The clinical trial data and established prevalence data should permit ICER to extrapolate key findings and evaluate how access to therapies that slow the progression of AD have a societal value in different communities. ICER may consider issues such as disparities in what stage of the disease individuals are diagnosed, extension of life years in populations where onset of disease often occurs earlier, and other factors in meaningfully incorporating equity into the AD pricing assessment.</p>	<p>We agree that AD has a disproportionate impact on communities of color and have tried to address the issue throughout the report, including in the Patient and Caregiver Perspectives section, as well as through our Sample Diversity Rating in Section 3 of the Evidence Report, and our calculation of the Health Improvement Disparities Index (HIDI) in the Potential Other Benefits and Contextual Considerations section.</p> <p>Also, in July 2022, we launched an initiative to evaluate health technology assessment methods that support health equity. The project will culminate in a White Paper and a series of public dissemination efforts in March 2023.</p>
4.	<p>Finally, we urge ICER to take into account research showing that there is generally more than one care partner for each person living with Alzheimer's disease. The current report makes heavy</p>	<p>The evidence used to inform the societal perspective in our model is for a primary caregiver who was assumed to be</p>

	<p>use of data from a 1999 study on disutilities for a single caregiver. Health systems have dramatically changed, longevity has shifted, our understanding of the greater prevalence of Alzheimer’s across minority populations has grown, and the recognition of the wide range on impacts (on diagnosed individuals and multiple caregivers) has become widely embraced. We ask that you include a more robust information set to underpin your analysis and acknowledge that these shifts limit the relevance of research done almost 25 years ago. Generally, we recommend that the report follow best practices for research and include a section on limitations of the work.</p>	<p>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.</p> <p>We discuss limitations in the sub-sections titled, “Uncertainties and Controversies”. We have expanded our discussion around the limitations of the current utility evidence within the “Uncertainties and Controversies” section of section 4 of our report.</p>
<p>Voices of Alzheimer’s</p>		
<p>1.</p>	<p>The Patient Perspective is Paramount However, we are disappointed to learn that the information gathered from people living with Alzheimer’s did not seem to have been fully understood or incorporated by all evaluators. This is a missed opportunity to gain a deeper understanding of the needs and priorities of people living with the Alzheimer’s and to make more informed decisions about the value of treatments.</p> <p>We recommend that the organization take steps to ensure that the input from people living with the Alzheimer’s and care partners is required reading for all evaluators. This could include providing training on how to understand and interpret the perspectives of people living with Alzheimer’s, as well as incorporating their input into evaluations and decision-making processes. In addition, it’s important to remember that people living with the disease and care partners have a unique and valuable perspective that cannot be replicated by any other group. By taking these steps, the ICER can ensure that the voices of people living with the Alzheimer’s are truly heard and that their needs are fully taken into account as part of this and future value assessments.</p>	<p>We appreciate that AD has a vast impact on patients and caregivers and that there are a wide variety of impacts the disease has and the potential impact of treatment that may not be captured within the limited number of informal interviews within this report. The Patient and Caregiver Perspectives section is meant to be a summary of the informal interviews, which were not exhaustive and not meant to replace formal research into the impact of the disease and the potential value of a therapy to all patients. We welcome additional research into this topic to include in any future reports.</p>
<p>2.</p>	<p>ICER Should Consider What Matters Most to Patients For those living with the Alzheimer’s, care partners, and families, activities of daily living (ADLs) and quality of life (QoL) are of paramount importance. Measures of ADLs and QoL can provide important insights into the real-world impact of the disease. They can also help to identify areas where treatments along with other support may be particularly valuable to improve the quality of life for people living with Alzheimer’s and their families.</p>	<p>We agree completely. Measures of QoL and ADL were used in our economic model, and people living with Alzheimer’s and their care partners were engaged throughout the assessment.</p>

	<p>Therefore, it is important that the organization's methodology gives great weight to the value of these measures. This could include using validated tools and instruments to assess ADLs and QoL, as well as incorporating the perspectives of people living with Alzheimer's and care partners into the evaluation process. Additionally, the organization should consider using multiple sources of data to gather information about ADLs and QoL, such as interviews, surveys, and observation.</p>	
3.	<p>Moreover, it's important to incorporate the patient-centered outcome measures that are most meaningful to the people living with Alzheimer's. The organization should consider including measures of patient-reported outcomes (PROs) such as the Patient-Reported Outcomes Measurement Information System (PROMIS) and the European Quality of Life-5 Dimensions (EQ-5D) which are widely used in the research community and can provide a more comprehensive understanding of the patient's experience.</p> <p>For those living with the disease, care partners and families, activities of daily living and quality of life are of paramount importance when it comes to understanding and valuing the impact of new treatments. It is important that the organization's methodology for this and future evaluations gives sufficient consideration to the value of these measures and incorporates patient-centered outcome measures that are most meaningful to the people living with Alzheimer's.</p>	<p>The economic model uses utility evidence derived from the Health Utilities Index Mark II. The HUI:2 is a commonly used patient-reported outcome instrument to calculate utility weights in the Alzheimer's disease population because cognition is a separate attribute.</p> <p>A recent systematic review reported the mean EQ-5D for individuals with Alzheimer's disease. As shown in the results from our one-way sensitivity analysis, the range for each of our utility estimates for each level of disease severity <i>includes</i> the mean EQ-5D reported in the recent systematic review source. The mean EQ-5D from the recent systematic review was not used in our report because it did not stratify the utilities by care setting (long-term care versus community) and did not provide utilities for the caregivers of the patients. Therefore, using the utility estimates from the recent systematic review would require numerous assumptions and additional sources to be able to have utility estimates for individuals that live in the community, individuals that live in long-term care, caregivers of individuals that live in the community, and caregivers of individuals that live in long-term care. It also did not provide the demographics of the individuals (caregiver or patient) completing the EQ-5D. Thus, without knowing the baseline utility, we are unable to calculate a disutility for each health state using this pooled data.</p>
4.	<p>We Must Act Urgently</p> <p>The proposed value assessment will impact access to new treatments for patients, and so it is critical the ICER understands and acts with urgency. The patient community calls on ICER to act in reconsidering its framework for assessing these and future Alzheimer's treatments. As these treatments are only effective</p>	<p>Alzheimer's is a devastating disease and we all hope for a truly effective therapy. We also believe that even with a marginally effective therapy, there will be many patients who desperately desire access to treatment, and so we understand the urgency you express.</p>

<p>for those in the earlier stages of AD, time is of the essence. It is critical we have a patient-centered approach to treatment value so patients who need these therapies the most are able to benefit.</p>	
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#	Comment	ICER Response
Other		
Partnership to Improve Patient Care (PIPC)		
1.	<p>ICER underestimates the probability of patients being admitted to a long-term care facility, which is a major driver of cost for Alzheimer’s Disease.</p> <p>Transition into long-term care facilities is a common outcome for AD patients. The set of probabilities used in the ICER model are quite conservative and are derived from a source that is over 20 years old. A more recent study based on longitudinal data from the National Alzheimer’s Coordinating Committee (NACC) uniform data set suggests that the probability of transitioning to long-term care is much higher than represented in the ICER model. The NACC uniform data set followed 18,000 patients for an average of 10 years between 2004 and 2014. This data was not available when ICER’s chosen source, which followed only 1,000 patients in the early 1990s, was published.</p> <p>The more recent source suggests 16% a year transition to long-term care facilities in moderate AD as compared to 11% used in the ICER model and over 32% in severe ADs compared to just 23% used in the ICER model. Given how important a driver of longer-term costs admission of patients to long-term care is, updating this data with the more recent and rigorous source would likely show greater long-term costs savings from delaying progression to later stages of AD.</p>	<p>Thank you for providing us citations for potential other sources to incorporate in our work. In the source you shared by Davis et al., we read the following, “The estimated risk of institutionalization and death increased with age and severity state. 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.” Therefore, we believe our model is using a higher rate of institutionalization for MCI, mild, and moderate AD than this source suggests. For severe AD, we are using 26%, but 30% is within our range used in the sensitivity analyses. For less severe health states, we also vary widely the probability of transitioning to long-term care widely through sensitivity analyses.</p>
2.	<p>ICER underestimates caregiver burden.</p> <p>Taking solely a health care system perspective as a base case is not appropriate. The only perspective represented in the assessment should be the societal perspective. If ICER’s goal is to capture an accurate picture of costs associated with disease and benefits of treatment then it is imperative that a broader societal perspective is used, which incorporates components like caregiver burden, lost productivity, and human cost of social support. The National Institute for Health and Care Excellence (NICE) in the United Kingdom, which ICER leans heavily on for its approach to value assessment, has already included caregiver utility in its base-case cost-effectiveness models for diseases where informal caregiver burden is known to be high, such as AD, Multiple Sclerosis and Parkinson’s disease. It is also the recommended perspective for cost-effectiveness models of the United States’ second panel on cost-effectiveness, and the International Society for Pharmacoeconomics and Outcomes Research.</p>	<p>The modified societal perspective is our co-base-case. We do not take solely a health care system perspective as a base case.</p>

3.	<p>More than 11 million family members and other caregivers provided an estimated 15.3 billion hours of unpaid care to patients with Alzheimer’s or other dementia every year in the United States, putting these caregivers at risk for negative mental, physical, and emotional outcomes. As patients moved from mild to severe Alzheimer’s, the financial, physical, psychosocial, social, and personal strain as measured by the Modified Caregiver Strain Index (MCSI) increased from an average score of 9.0 to 17.5 (out of a maximum of 26), indicating a substantial increase in caregiver impact.</p> <p>In contrast, when ICER does include caregiver disutility, ICER’s assessment assumes a very marginal impact, suggesting the impact on caregiver’s quality-of-life is just a few percentage points from 0.08 to 0.10, when a patient progresses to severe Alzheimer’s. The paper this data was taken from states in its discussion section that its key limitations were both that the majority of those surveyed were paid rather than unpaid caregivers, and that the tool used to measure the quality-of-life changes on caregivers was not designed for that purpose. The reality is, those two limitations make it a poor source for ICER’s assessment. Alternative sources of caregiver utility loss in AD show significantly larger effects on overall cost-effectiveness, with a recent review of over sixty cost-effectiveness studies in AD concluding that on average the inclusion of caregiver burden led to about a 20% improvement in cost-effectiveness ratios.</p>	<p>Our caregiver-specific model inputs demonstrate the increased impact on caregivers as disease severity increases. We have added to the “Uncertainties and Controversies” section of section 4 of our report additional details around the limitations of the current utility evidence available. We also vary the utility estimates widely in our sensitivity analysis.</p> <p>Related to the impact of inclusion of caregiver burden on improvement in cost-effectiveness ratios, this is entirely dependent on how effective the drug is.</p>
4.	<p>Another review suggested that, when caregiver costs were included, 11% of interventions previously considered not to be cost-effective became cost-effective. When caregiver utility was also included, an additional 37% moved from being above to being below the stated cost-effectiveness threshold. Conversely, the effect in the ICER model of moving from healthcare to an inclusion of caregiver burden improves the cost-effectiveness ratio by just 6%. Given this reality, it is safe to assume that if any of these alternative sources of caregiver utility were used in the ICER assessment, the cost-effectiveness of either treatment would be higher with caregiver utility included.</p>	<p>This treatment results in approximately one more year lived in early AD (MCI due to AD and mild AD), and approximately six fewer months lived in later AD (moderate AD and severe AD). Prolonging time in MCI due to AD and mild AD is still associated with an impact on caregivers as measured by an impact on quality of life, health care costs, and time spent caregiving. This treatment is not restoring to a health state that doesn’t involve caregiver time spent. Therefore, this treatment delays and slightly shortens time in more severe AD health states, but prolongs time in early AD, which is still characterized by impacts to caregiver quality of life, health care costs, and time spent. Reversing AD would reduce caregiver impact dramatically, but that isn’t what this treatment does.</p>
5.	<p>ICER continues to use the QALY, which is inherently biased against older adults, which is the primary population of need when evaluating treatments for AD.</p>	<p>We appreciate the concerns about relying solely on QALYs. They are not used in the assessment of the comparative net health benefit: see Figure 3.1 for more details on the ICER Evidence Rating Matrix. They are</p>

	<p>Multiple studies have shown that cost-effectiveness models that use the QALY discriminate against people with chronic illnesses and disabilities. The United States has a thirty-year, bipartisan track record of opposing the use of the QALY and similar discriminatory metrics and establishing appropriate legal safeguards to mitigate their use. Section 504 of the Rehabilitation Act ensures that people with disabilities will not be “excluded from participation in, be denied the benefits of, or otherwise be subjected to discrimination,” under any program offered by any Executive Agency, including Medicare. Title II of the Americans with Disabilities Act (ADA) extended this protection to programs and services offered by state and local governments. Based on the ADA’s passage in 1990, in 1992 the Secretary of the U.S. Department of Health and Human Services (HHS) established that it would be a violation of the ADA for state Medicaid programs to rely on cost-effectiveness standards, as this could lead to discrimination against people with disabilities. The equal value of life year metric similarly undervalues treatments for conditions affecting older adults due to its emphasis on life extension and predicted life years. In response to this, several alternate ways of measuring health benefit have been developed, are under development, or are being tested.</p> <p>The most recent work shows that due to diminishing returns, traditional cost utility methods overvalue treatments for mild illnesses and undervalue treatments for highly severe illnesses, like AD, and as a result we are underpaying for severe illnesses by factors of 4-5 or more. ICER should be evolving away from use of outdated, discriminatory methods and metrics, and using outcome measures based on the most up to date science.</p>	<p>also only one component of the value assessment.</p> <p>Throughout our assessment, we use the equal value life year (evLY), which evenly measures any gains in length of life, regardless of the treatment’s ability to improve patients’ quality of life. In other words, if a treatment adds a year of life to a vulnerable patient population – whether treating individuals with Alzheimer’s disease, cancer, multiple sclerosis, diabetes, epilepsy, or a severe lifelong disability – that treatment will receive the same evLYG as a different treatment that adds a year of life for healthier members of the community. Therefore, the evLY removes the potential for bias between diseases in life extension.</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>
6.	<p>Where possible, ICER should put greater weight on cross-validation with other published models, which tend to suggest that the ICER model underestimates health gain for interventions that slow progression in AD.</p> <p>A recent model developed in Scandinavia, based on Sweden’s AD registry data suggests that a therapy that slows progression from mild AD by 25% would result in about 0.73 QALYs gained per patient treated. This is roughly double what the ICER model estimates for the effect of a drug that reduces risk of progression from mild AD by 31%.</p> <p>Another open-source model with a slightly more conservative approach suggested that a drug that slowed progression from</p>	<p>In every report, we have a section titled “Prior Economic Models” that is entirely dedicated to cross-validation with other published models.</p> <p>It is inappropriate to compare the results from two separate models and only look at one single input, as you are doing here with the results and QALYs gained. For the Scandinavia model, the population was different than ours (100% MCI). Our health gains are even more favorable than theirs if we mirror their population characteristics.</p>

	<p>mild AD by 20% would generate on average about a 0.35 QALY gain, which is about the same as that generated in the ICER model for a 31% efficacy. These other studies should offer a check on the validity of ICER's assessment, and they suggest that ICER's model underestimates health gain.</p>	<p>The same thing is true with the study you shared by Green and colleagues. That patient population is 100% pre-dementia. Our health gains are even more favorable than theirs if we mirror their population characteristics.</p> <p>These other studies did offer a check on the validity of ICER's assessment, and if anything, they could be suggesting we are slightly overestimating health gain.</p>
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