The Value of Innovation Delaying the Progression of Alzheimer's Disease in the US[1]

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Executive Summary

Despite the large disease burden imposed by Alzheimer's disease (AD), little quantitative evidence exists on the aggregate value stemming from innovation slowing the progression of the disease. To fill this gap, this paper uses the existing evidence base to assess the value of medical innovation aimed at slowing the progression of AD. We find that slowing the progression from mild to moderate AD by 0.5 to 3 years has a value of $212 billion to $1,274 billion for the US population over the next 10 years, assuming 50% of mild AD patients can be treated. This total value is attributable to 27 percent of the health gains to AD patients and caregivers, 59 percent of reduced market-based health care spending, and 13 percent of reduced time needed for informal care by care givers. In terms of per-capita costs, we find that a one-year delay from mild AD to moderate AD reduces health care costs by $34,249 and non-market costs by caregivers by $7,882. It also leads to an increase in patient and caregiver quality adjusted life years (QALYs) by 0.16. With 3.3 million mild AD patients in 2022 predicted to grow to 14.6 million in 2032, we find the aggregate value of such a one-year delay ranges from $73.3 billion to $637 billion at $100,000 per QALY. This large value demonstrates the importance of delaying AD progression and ought to further encourage relevant innovation efforts.

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Section 1: Introduction

Alzheimer's disease imposes a large disease burden in the US and the world. In the US, it is reported that 6.5 million people aged 65 and older suffer from dementia due to AD, and the number is projected to be 12.7 million by 2050 (Alzheimer's Association, 2022a). Such prevalence of Alzheimer's and other dementia leads to an estimated national cost of $321 billion for formal care in 2022 (ibid). An additional annual cost from unpaid informal caregiving is estimated to be $276.1 billion, based on 16 billion hours of unpaid care in 2021 (ibid). In an earlier study, Zissimopoulos et al. (2014) estimates there will be 9.1 million Alzheimer's patients in the group age 70 and older by 2050, yielding a total cost of $1.5 trillion.

Globally, it is estimated that 32.3 million people are clinically diagnosed with Alzheimer's disease, while 416.4 million people suffer from Alzheimer's disease over its entire spectrum, including preclinical and prodromal Alzheimer's disease (Gustavsson et al., 2022). The global cost of Alzheimer's disease was estimated to be $957.6 billion in 2015, and projected to be $2.54 trillion in 2030 and $9.12 trillion in 2050 (Jia et al., 2018). For dementia, where Alzheimer's disease is a major cost, the global cost in 2019 reached $1.3 trillion, and is projected to exceed $2.8 trillion by 2030 (WHO, 2021). Wimo et al. (2018) estimates the global cost of dementia to be more than $1 trillion in 2018, with 40% of the cost from informal caregiving. It is estimated that globally 82 billion hours were devoted to informal care for dementia in 2015, equivalent to more than 40 million full time workers, which is expected to grow to 65 million by 2030 (ibid).

Innovation to help reduce this burden has been slow to emerge but recent developments provide more promise. Aducanumab, one of the first approved targeted therapies for Alzheimer's disease by Biogen, showed significant efficacy in terms of both clinical and biomarker results in one of its Phase III trials, though discrepancies exist in another trial (Tolar et al., 2020; Lin et al., 2021). Simulations based on Aducanumab also suggest delay of moderate AD from 0.07 to 2.58 years (Lin et al., 2021; Herring et al., 2021). Donanemab by Eli Lilly significantly slowed the decline of AD on a combined cognitive and functional measure in its Phase II trial with early-stage Alzheimer's patients (Mintun et al., 2021). Lecanemab by Eisai also received priority review from the FDA (Eisai, 2022), and a simulation based on Lecanemab implies a delay of moderate AD by 3.13 years (Monfared et al., 2022). In September 2022, Eisai announced its topline results from its phase III trial of lecanemab, noting that lecanemab met the primary endpoint and reduced clinical decline.

The value of public policy attempting to stimulate or enhance these innovative developments to reduce the burden of AD depends on the value of slowing the progression of the disease. To help guide these efforts, this paper assesses the quantitative value of innovations delaying the transition from mild to moderate Alzheimer's disease potentially enabled by future diagnostic and treatment innovation.

Our main findings are that if innovation delaying the onset of moderate AD by 0.5 to 3 years would yield and aggregate value of $212 - $1,274 billion over the next 10 years, assuming 50% mild AD patients are treated and $100,000 per QALY gained. Of this aggregate value, 27 percent is due to the health gains of AD patients, 59 percent is for reduced market-based health care spending, and 13 percent is due to reduced time needed for informal care by care givers.

Section 2: Methodology

The methodology consists of calculating the annual value of prolonging the onset of moderate AD and then applying that annual value to the length of time the onset is extended. The annual value is broken down in three components consisting of the value of health gains of patients, the reduced health care cost, and the reduced care giver burden.

We consider innovations that delay the onset of moderate AD by 0.5 to 3 years. This range corresponds to the estimated lengths of delay in simulations like Boustani et al. (2022) (0.452 years) and Monfared et al. (2022) (3.13 years). Thus, we multiply 0.5 to 3 by the annual benefits of such delays. Reduced health care and care giver burden costs per year are given by the cost difference between mild and moderate AD, while health gains are calculated by the gains in QALYs valued at standard monetary values, which we here assume to be $100,000 per QALY. For example, assuming the annual cost difference between mild and moderate AD is $10,000 for market-based care and $12,000 for non-market care per year, and QALYs in the mild AD stage are 0.2 higher than in the moderate AD stage, innovations yielding a half-year delay will have a total value of $21,000, with $5,000 from market-based care, $6,000 from non-market care, and $10,000 from QALYs gained.

2.1 Definition of mild and moderate AD

AD is characterized by the accumulation of amyloid and tau protein in the brain, causing cognitive and functional impairment and hence dementia. The continuum of AD spans from an asymptomatic stage known as preclinical to mild cognitive impairment (MCI) to severe impairment. MCI is a clinical stage associated with subtle cognitive changes that do not impact daily activities. Dementia due to AD is clinically diagnosed when there is impairment of at least two cognitive domains (memory, language, executive function, and visuospatial function) and these deficits significantly interfere with the ability of the patient to function independently at work or at home. Patients transition through the stages of dementia due to AD – mild, moderate and severe – at varying rates. The rest of this paper will use "mild AD" and "moderate AD" as short hand for "mild dementia due to AD" and "moderate dementia due to AD" (Aisen et al., 2017; Albert et al., 2011; Dubois et al., 2021; Jack et al., 2011; Jack et al., 2018; McKhann et al., 2011; Sperling et al., 2011;).

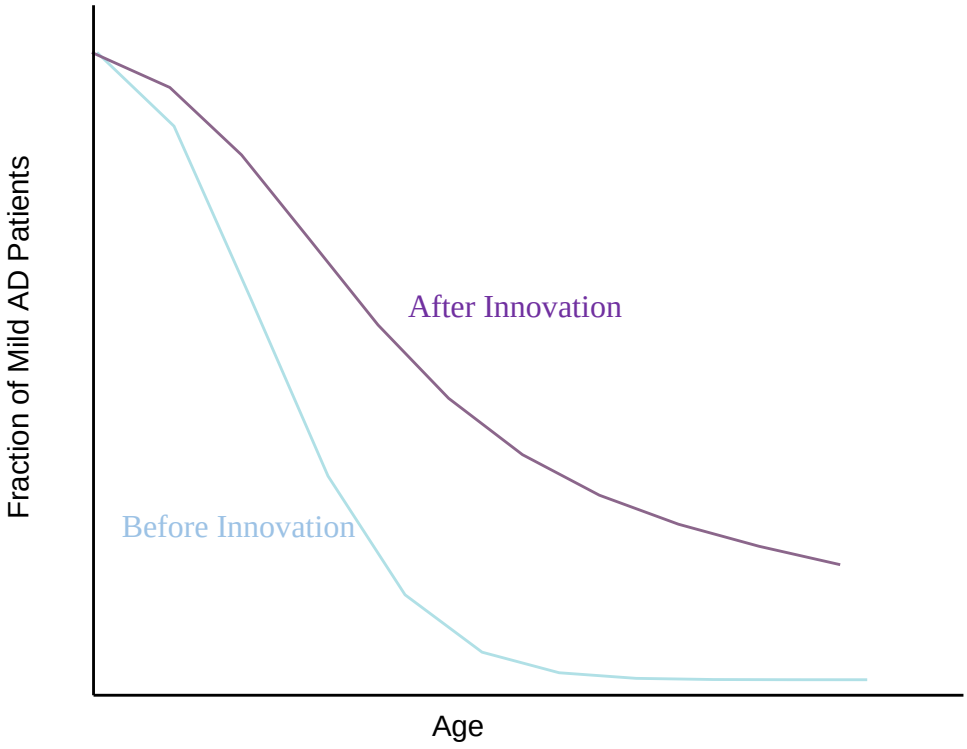
Common measurements of AD severity include tests and scales like Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), which assigns scores to cognitive performances and sometimes functional performances. Wimo et al (2020) suggest a MMSE score between 21 to 30 indicates mild AD, 10 to 20 indicates moderate AD, and 0 to 9 indicates severe AD. Both Herring et al (2021) and Monfared et al (2022) used CDR-SB, and categorized a score between 0.5 and 4 for MCI, between 4.5 and 9 for mild AD and between 9.5 and 15.5 for moderate AD. Clinical trials for Aducanumab considered both MMSE and CDR-SB and reported consistent results (Lin et al., 2021).

2.2 Transitions from mild to moderate AD

The transitioning from mild to moderate AD may conceptualized by survival functions in the mild AD stage as shown in Figure 1, where the two curves represents the fractions of mild AD patients with and without innovation. Assuming innovations successfully extend mild AD, the fraction of people with mild AD at each age would be higher with innovation, making the with-innovation curve be above the without-innovation curve. At each age, the gap between the two curves indicates the fraction delayed by innovation.

Another way to interpret the innovation effect is to focus on the fraction of mild AD patients and examine the ages, where an elder age with the same fraction of mild AD patients indicates a delay in transitioning to moderate AD. In other words, per a certain fraction of mild AD patients, more years in the mild stage are earned by innovation, and the threshold age to achieve each fraction is delayed. This interpretation corresponds to multiple simulation literature investigating innovation effects in delaying the transition between mild and moderate AD. We follow this interpretation and assume hypothetical innovation with delay ranging from 6 months to 3 years. The average time in the mild state turns out to be the integral or area under the survival function so that an increase of the average time by 0.5 to 3 years means the higher survival curve has a larger area under it.

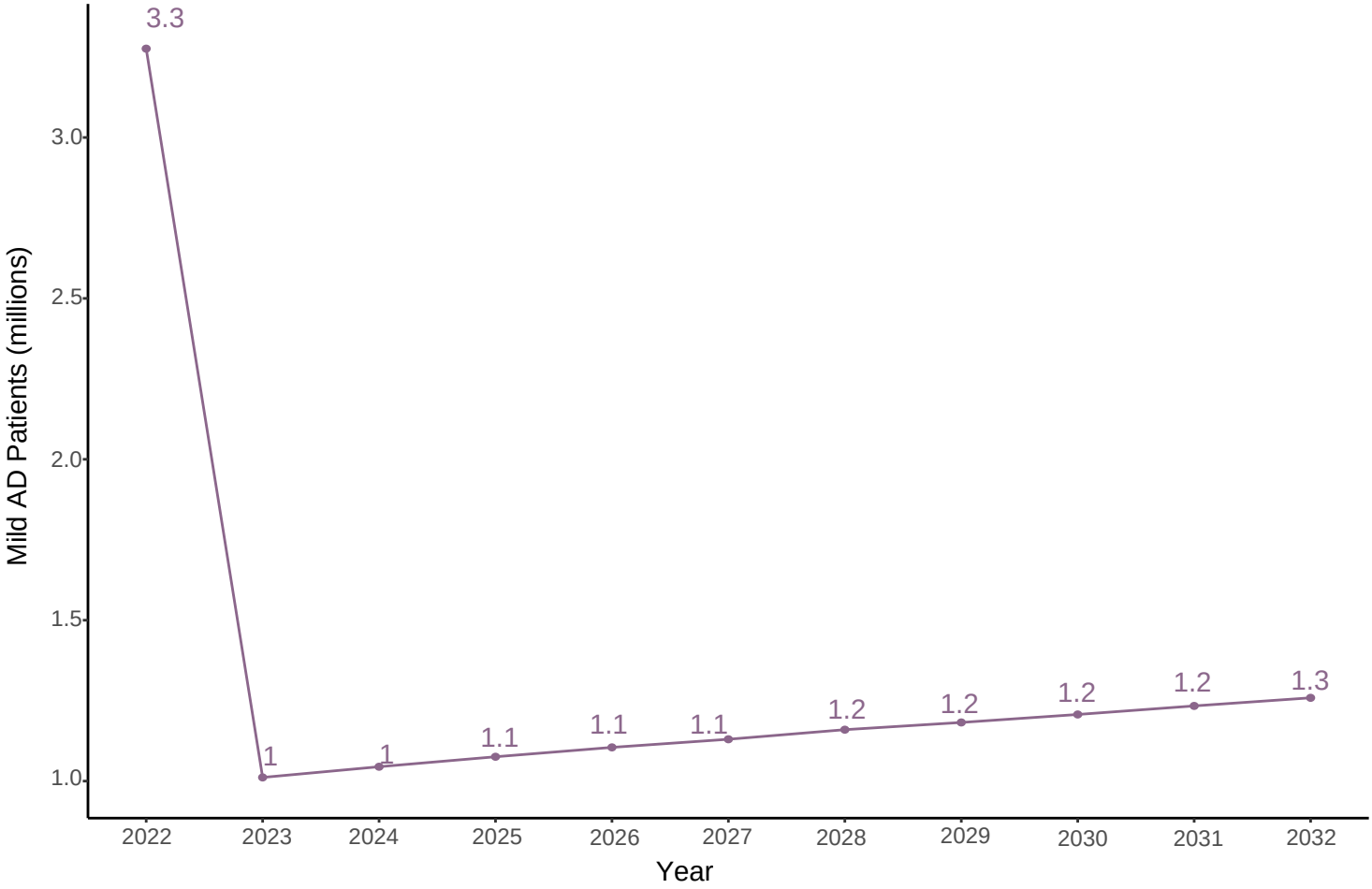
Figure 1: Fraction of Mild AD Patients Before and After Innovation



2.3 The size of the population that may potentially be delayed in its transition

We first estimate the hypothetical number of patients able to receive such innovative therapies. Given the focus on mild AD patients progressing to moderate AD, we first estimate the total number of mild AD patients from 2022 to 2032 and assume a fraction of patients can be treated for availability and eligibility concerns, since treatment provisions should be limited at the beginning and some patients may be reluctant to accept new treatments for concerns like side effects. To calculate the total number of mild AD patients in the next ten years, we first calculate the current number of mild AD patients as of 2022 by multiplying the total 6.5 million AD patients in the US by the estimated percentage of 50.4% of mild AD patients, yielding approximately 3.3 million (Yuan et al., 2021; Alzheimer's Association, 2022a). For years starting in 2023, we estimate the incidence of mild AD, the additional number of new mild AD occurrences in each year, by multiplying the forecasted MCI population in the previous year by a transition rate to mild AD of 12.5%, with a midpoint of 10% to 15% (Alzheimer's Association (2022b)). For example, for every 100 MCI patients in year 1 with a transition of 12.5% to mild AD, 12.5 new mild AD patients would be added in year 2. The MCI population in each year is estimated by multiplying the prevalence estimates of MCI as fractions of each age group by the projected population in each age group. For example, Petersen et al. (2018) estimates MCI patients take up 6.7% of the 60 to 64 age group and 8.4% of the 65 to 69 age group and supposes only the two age groups are in consideration and both groups have 10 million people. The total number of MCI patients in that year is approximately 1.5 million. Using the prevalence in Petersen et al. (2018) and the projected population in U.S. Census Bureau (2014), the total cumulative number of mild AD patients since 2022 to 2032 exceeds 14.6 million (Figure 2).

Figure 2: Estimated New Mild AD Patients by 2032 (Incidence per year)



Note: cumulative number of mild AD patients by 2022 and new incidences of mild AD patients for each later year

We assume 50% mild AD patients would be treated over the course of ten years, with 25% and 75% treatment rates considered for sensitivity analysis, leading to 7.3 million, 3.7 million and 11 million patients receiving treatment respectively. We understand 50% may be an overestimation of the proportion receiving treatment due to amyloid positivity and contraindications, so we perform the same analysis for 25% in the sensitivity section. In addition, we also consider a more complicated method of determining treatment assignment: according to Hlávka et al. (2022), 1 million diagnosed mild AD patients will be eligible for innovative therapies in 2022, and contingent on the number of visits required, which can adversely affect the number of patients in treatment as more frequent visits may deter getting treatments. It is estimated that at least 35.3% of eligible patients can receive treatment in the first five years. We calculate the ratio between actual mild AD patients above and eligible mild AD patients reported in Hlávka et al. (2022) and apply the ratio to the total number of mild AD patients across the ten years to determine the eligible mild AD patients. Considering 35.3% would be the lower bound of the proportion and actual proportion receiving treatment may be higher, we apply the 48.6%, a slightly higher estimate by the same authors, to all eligible mild AD patients by 2027 for treated patients by 2032 as the treatment would take place in the span of five years, yielding 1.3 million treated patients.

Since such innovative therapies would highly likely influence the MCI population as well, we also estimate the effect on MCI patients of their progression to mild AD. Similarly, we estimate incidences of MCI to 2032. According to Alzheimer's Association (2022a), approximately 5 million patients of MCI exist in the US, which is likely an underestimate due to the early onset of MCI. As a review paper suggests, MCI incidence rates are 2.25% for the age group between 75 to 79 years old, 4.09% for individuals aged 80 to 84, and 6.01% for individuals over 85 years old (Gillis et al., 2019). We again use the projected population by age, and multiply the population in each age group by corresponding incidence rates as the new cases in each age group in the specific year. These new cases across age groups are then summed as the new MCI case for the next year. For example, assuming there are 1 million people in each age group from 75 to over 85 years old in year

1, we estimate 22,500 new MCI cases to be created in the age group of 75 to 79 years old, 40,900 cases for the 80 to 84 years old age group, and 60,100 cases for the eldest group. The three groups yield a total count of new cases of 123,500, which will be attributed as the new incidences in year 2. For 2022, we use the cumulative total number of 5 million MCI cases reported in Alzheimer's Association (2022a). Following this calculation, a total number of 17 million MCI cases would exist until 2032.

Section 3: The Impact of Innovation on Market Based Care

We define market-based care to be care incurred with monetary transactions, sometimes defined as formal care (Gustavsson et al., 2011). Following this definition, we estimate the difference in the cost of market-based care between mild and moderate AD patients and multiply the difference by the number of years delayed in mild AD stages.

Table 1 below exhibits market-based cost estimates for mild and moderate AD from literature with a few modifications. While Prados et al. (2022) is a simulation study, we borrow two sets of ratios from their calculations for imputation: first, we divide their reported 2021 USD values by the corresponding values in the original paper to arrive at intertemporal ratios of cost; second, we borrow the ratios between moderate and mild AD costs they calculated based on Gustavsson et al. (2011). With the intertemporal ratio, we translated market-based costs in Gustavsson et al. (2011) to 2021 USD values. With the latter ratios, we imputed moderate AD cost for Robinson et al. (2020). Since Prados et al. (2022) only focus on medical costs excluding community care lost, we cannot directly use the costs reported. Using weights based on the moderate AD population in community and residential settings in Gustavsson et al. (2011) and Prados et al. (2022) (67% in community and 33% in residential), we also calculated the weighted average of costs in moderate AD stage.

As shown in Table 1, both Gustavsson et al. (2011) and Robinson et al. (2020) use MMSE to define AD stages while Leon et al. (1998) and Michaud et al. (2017) use CDR or its equivalent. Mild AD is defined as MMSE larger than 20, and its associated market-based costs are $15,973 and $31,099 per patient respectively from Gustavsson et al. (2011) and Robinson et al. (2020), whose difference may come from the time gap and the additional FAQ threshold applied in Robinson et al. (2020). Between the studies utilizing CDR, mild AD is defined as CDR between 0.5 and 1 in Leon et al. (1998) and equaling 1 in Michaud et al. (2017), with per patient annual market-based cost of $12,192 and $6,317 respectively. While the cost difference appears counterintuitive, this difference may be explained by the small sample (132 patients) and the zero cost for long-term care in Michaud et al. (2017) (no mild AD patient is institutionalized), which can be a major component in mild AD market-based cost.

Similarly, moderate AD is also defined by MMSE and CDR equivalents across the studies. Gustavsson et al. (2011) maps moderate AD to a MMSE score between 10 and 20, and reports market-based costs of $16,585 for community patients and $128,034 for residential patients. Since Robinson et al. (2020) does not consider moderate AD and its cost is imputed based on Gustavsson et al. (2010), it follows that moderate AD is also given by a MMSE score between 10 and 20. With imputed values, Robinson et al. (2020) suggests market-based costs for moderate AD are $32,291 and $249,282 for community and residential patients. With CDR, unlike mild AD, Leon et al. (1998) and Michaud et al. (2017) unify on a score equaling 2 for moderate AD, and report market-based costs of $23,448 and $21,866 per patient. Though the numbers are similar, estimates in Michaud et al. (2017) may still be considerably smaller given inflation, which possibly can be attributed to the small sample size.

Gustavsson et al. (2011), Michaud et al. (2017) and Robinson et al. (2020) share similar percentage increases from mild to moderate AD of around 240%, though the magnitudes of costs are much smaller in Michaud et al. (2017). In other words, market-based cost triples when progressing from mild to moderate AD. Leon et al. (1998) reports a 92.3% increase from mild to moderate AD, possibly due to the gap in time compared to the other studies.

To arrive at the cost difference between mild and moderate AD, we use the average cost across studies for each stage, among which weighted averages are used for studies distinguishing between community and residential costs. For conservativeness of our estimates, we include Leon et al. (1998) to result in smaller cost differences. Prados et al. (2022), however, is not included due to its simulation nature and focus on only

medical cost. 2021 USD values are used when available. The average cost for mild AD is $16,395 and $50,644 for moderate AD, yielding an 209% increase and a difference of $34,249 per year per patient.

With the reported difference, we now calculate the cost saved by delaying progression to moderate AD by innovation. At the lower end of a 6-month delay, $17,124.5 would be saved per patient. Considering a 1-year delay, the numbers double to $34,249. Assuming 50% mild AD patients receive treatments in the ten years, $251.5 billion can be saved for a 1-year delay and $125.7 billion for a half-year delay in total. For a 3-year delay, $102,747 per patient and $754.4 billion in aggregate can be saved, respectively.

Since Medicare mostly covers market-based health expenses (Alzheimer's Association, 2021), we consider the effect of such innovation on Medicare through cost saved on market-based spendings. According to Alzheimer's Association (2022a), Medicare covers approximately 45% of the total medical payments by patients with AD and other dementia in 2022. Since this percentage is calculated using aggregate spending by dementia patients, there would be no need to consider the fraction of patients with Medicare within AD. Assuming the 45% is identical for AD and other dementia patients, a 6-month delay would save Medicare $7,706 per patient, and $15,412 per patient for a 1-year delay. Following the assumption that 50% of AD patients can be treated, the total amount saved for Medicare would range from $56.6 billion to $339.5 billion for delays of 6 months to 3 years.

Among the literatures in consideration, two also cover the MCI population, as presented in Table A1 in appendix. Notably, while no patient in the MCI or mild AD stages live in long-term care facilities in the sample of Michaud et al. (2017), long-term care cost is $0 for mild AD patients but not MCI patients, leading to a negative cost difference progressing from MCI to mild AD. Hence, we calculated cost difference both with and without long-term care, which yield both positive cost differences from MCI to mild AD after averaging across papers. For conservative estimates, we use the cost difference considering long-term care in the following value calculations. At a 1-year delay, $1,844 would be saved per patient, and such value ranges from $922 to $5,532 per patient as the delay ranges from 6 months to 3 years. Similarly, assuming 50% of the MCI patients receive such innovative treatment, $7.8 billion to $47 billion would be saved from market-based cost for delays from 6 months to 3 years.

Table 1: Market-based Cost for mild and moderate AD from literature (annual per patient)

Study	AD Stage Definition	Mild AD Cost	Moderate AD Cost	Cost Difference	Note
Leon et al. (1998)	Mild: CDR: 0.5 -1 Moderate: CDR =2	$12,192	$23,448 (92.3% increase)	$11,256	NA
Gustavsson et al. (2011)	Mild: MMSE: >20 Moderate: MMSE: 10-20	Community: $10,597 ($15,973 in 2021 USD)	Community: $11,003 ($16,585 in 2021 USD; 4% increase) Residential: $84,942 ($128,034 in 2021 USD; 700% increase) Weighted Average: $53,363 (234% increase)	Community: $406 Residential: $74,345 Weighted Average: $37,390	Hospitalization cost imputed the same for all patients
Michaud et al. (2017)	Mild: DS: 4-5 (Equivalent to CDR=1) Moderate: DS: 8-9 (Equivalent to CDR=2)	$6,317	$21,866 (246% increase)	$15,549	NA
Robinson et al. (2020)	Mild:MMSE ≥ 20 and FAQ ≥ 6 Moderate: not considered	$27,972 ($31,099 in 2021 USD)	Not Considered (Imputed in 2021 USD Community: $32,291; 4% increase; Residential: $249,282; 702% increase) Weighted Average:	Imputed: Community: $1,192 Residential: $218,182 Weighted Average: $72,799	Include market-based costs for both patients and caregivers

			$103,898 (234% increase)		
Average	**/**	**$16,395**	**$50,644 (209% increase)**	**$34,249**	**/**
Prados et al. (2022)	Not specified	$17,184	Community: $17,591 (2% increase) Residential: $19,709 (14.7% increase) Weighted Average: $18,290 (6.4% increase)	Community: $407 Residential: $2,525 Weighted Average: $1,106	Calculated based on cost ratio in Gustavsson et al. (2011) and mild AD cost in Robinson et al. (2020); Only consider medical cost from patients

Note: 2021 USD values and imputed values are calculated based on Prados et al. (2022);
CDR: Clinical Dementia Rating; MMSE: Mini-Mental State Examination; DS: Dependence Scale; FAQ: Functional Activities Questionnaire; Residential patients: patients in residential care institutions; Community patients: "At-home" patients not institutionalized

Section 4: The Impact on Informal Care

Similarly, we now investigate the cost difference between mild and moderate AD patients from non-market care (Table 2), essentially caregiver burden. Since non-market care mostly consists of unpaid caregiving, we can use 2021 USD values and imputed values from Prados et al. (2022). The mild and moderate AD stages are defined in the same metrics as with market-based cost. For mild AD with MMSE larger than 20, Gustavsson et al. (2010) reports $15,328 for non-market cost while Robinson et al. (2020) reports $25,697. For mild AD defined by CDR between 0.5 and 1 or equaling 1, Leon et al. (1998) reports non-market costs of $6,216 and Michaud et al. (2017) reports $5,813.

As for moderate AD, with MMSE scores between 10 and 20, Gustavsson et al. (2010) suggests non-market costs of $20,073 for community patients and $10,730 for residential patients. Similarly, the imputed values for Robinson et al. (2020) suggest $33,651 for community patients and $17,988 for residential patients. The higher non-market cost for community patients is intuitive: as patients become institutionalized, the patients substitute paid caregiving for unpaid informal care by family and friends. For moderate AD defined by CDR scores equaling 2, Leon et al. (1998) suggests per patient costs of $6,648 and Michaud et al. (2017) suggests $32,463, without distinguishing between community and residential patients.

Unlike market-based cost, Gustavsson et al. (2011) and Robinson et al. (2020) no longer share the same trend with Michaud et al. (2017), but instead with Leon et al. (1998) with percentage increases around 10%. The extremely large increase observed in Michaud et al. (2017) may be owed to its much lower cost for mild AD, since its moderate AD cost is similar to Robinson et al. (2020) in magnitude.

As with market-based care, we estimate the average cost for mild AD to be $13,264, and $21,146 for moderate AD, yielding a difference of $7,882. Since two of the four studies used replacement methods and the other two used opportunity cost, the averages are also the weighted averages in terms of valuation methods, potentially alleviating biases stemmed in valuation methods like lower wages for women.

Similarly, considering a 6-month delay, each patient would save $3,941 from non-market care. Considering a 1-year delay, the per patient cost saved would be $7,882. Assuming 50% of mild AD patients are treated in the next ten years, a total of $57.9 billion can be saved for a 1-year delay and $28.9 billion for a half-year delay. $23,646 can be saved per patient from non-market cost for a 3-year delay, and $173.6 billion in total.

As for MCI patients, as shown in Table A1, $9,711 can be saved per patient by delaying progression to mild AD by 1 year. For 6-month and 3-year delays, the values become $4,855.5 and $29,133 per patient. By the assumption that 50% MCI patients can be treated, a total of $41.3 billion to $247.6 billion can be saved from non-market cost for delays ranging from 6 months to 3 years.

Table 2: Non-market Cost for mild and moderate AD from literature (annual per patient)

Study	AD Stage Definition	Mild AD Cost	Moderate AD Cost	Cost Difference	Method
Leon et al. (1998)	Mild: CDR: 0.5 -1 Moderate: CDR =2	$6,216	$6,648 (7% increase)	$432	Caregiver time loss with replacement method
Gustavsson et al. (2011)	Mild: MMSE: >20 Moderate: MMSE: 10-20	Community: $11,631 ($15,328 in 2021 USD)	Community: $15,231 ($20,073 in 2021 USD; 31% increase); Residential: $8,142 ($10,730 in 2021 USD; -30% increase) Weighted Average: $16,990 (10.8% increase)	Community: $3,600 Residential: -$3,489 Weighted Average: $1,662	Time and production loss with opportunity cost method; 2021 USD values from Prados et al. (2022)
Michaud et al. (2017)	Mild: DS: 4-5 (Equivalent to CDR=1) Moderate: DS: 8-9 (Equivalent to CDR=2)	$5,813	$32,463 (458% increase)	$26,650	Unpaid caregiving with replacement method
Robinson et al. (2020)	Mild:MMSE ≥ 20 and FAQ ≥ 6 Moderate: Not considered	$22,944 ($25,697 in 2021 USD)	Not considered (Imputed in 2021 USD Community: $33,651, 31% increase; Residential: $17,988, -30% increase) Weighted Average: $28,482 (10.8% increase)	Imputed: Community: $7,954 Residential: -$7,709 Weighted Average: $2,785	Indirect non-medical cost for caregivers with opportunity cost method; Imputed values from Prados et al. (2022)
Average	**/**	**$13,264**	**$21,146**	**$7,882**	**/**

Note: 2021 USD values and imputed values are calculated based on Prados et al. (2022);CDR: Clinical Dementia Rating; MMSE: Mini-Mental State Examination; DS: Dependence Scale; FAQ: Functional Activities Questionnaire; Residential patients: patients in residential care institutions; Community patients: "At-home" patients not institutionalized; Replacement method: Estimating cost of purchasing the same care from the market; Opportunity cost method: Estimating the forgone wages of caregivers by dedicating time to caregiving

Section 5: The impact of the delay on improved health outcomes

In addition to reducing cost of care for AD, delay in AD progression can further benefit patients and their caregivers by raising health outcomes as measured by QALYs. As reductions in Quality of Life (QoL) constitute another aspect of caregiver burden, we consider innovation effect on caregivers in conjunction with patients. Table 3 shows the QoL associated with each AD stage from literature. Using the same weights as above (67% community and 33% residential), we also calculate the weighted average of moderate AD QoLs when an overall score is unavailable.

Except Oremus et al. (2014), all studies share similar patient QoLs in both mild and moderate AD stages, while QoLs in Oremus et al. (2014) are systematically higher. This may be because QoLs in Oremus et al. (2014) were not estimated directly on the US population, but on a Canadian sample with US population weights applied. Thus, we calculate both average QoLs with and without Oremus et al. (2014) but use the averages without Oremus et al. (2014) for conservative estimates.

With a 6-month delay to moderate AD, a patient would gain 0.081 QALY, while 0.0025 QALY would be lost for caregivers, resulting in a total QALY improvement of more than 0.07 QALY per patient. If innovation can delay moderate AD by 1 year, the QALY improvement would double to more than 0.15 QALY. Considering the average VSLY approximating $490,000 reported in Philipson and Durie (2021), a comprehensive literature review on VSLY estimates across studies, as an upper bound, with a range of $100,000 to $490,000 per QALY, a 6-month delay would be valued from $7,850 to $38,465 per patient. For a 1-year delay, the range becomes

$15,700 to $76,930 per patient; for a 3-year delay, the range becomes $47,100 to $230,790. At the benchmark of $100,000 per QALY and assuming 50% of mild AD patients are treated, $115.3 billion can be gained for a 1-year delay, $57.6 billion for a half-year delay and $345.8 billion for a 3-year delay. Though $490,000 is close to the average in Philipson and Durie (2021), it drastically exceeds the value per QALY traditionally adopted by governments, indicating possible underestimation of cost-effectiveness in evaluating innovation, since VSLY should represent the value of a full QALY.

As exhibited in Table A1, utility score decreases by 0.05 for patients and 0.01 for caregivers when progressing from MCI to mild AD. Using $100,000 per QALY, this indicated that a total of $6,000 can be gained per patient for a 1-year delay, and $3,000 to $18,000 for delays of 6 months to 3 years. With the highest value of $490,000 per QALY, the range becomes $14,700 to $88,200 per patient. Assuming 50% patients are treated, the total value gained from QoL improvement varies from $25.5 billion to $749.7 billion, depending on the length of delay and the value per QALY.

Table 3: QoL Differences in literature

Study	AD Stage Definition	Mild AD QoL	Moderate AD QoL	QoL Difference	Note
Neumann et al. (1998)	Mild: CDR = 0.5 or 1 Moderate: CDR = 2	Patient: Community: 0.68 Residential: 0.71 Caregiver: Community: 0.86 Residential: 0.86 Weighted Average: Patient: 0.69 Caregiver: 0.86	Patient: Community: 0.54 Residential: 0.48 Caregiver: Community: 0.86 Residential: 0.88 Weighted Average: Patient: 0.52 Caregiver: 0.87	Patient: Community: -0.14 Residential: -0.23 Caregiver: Community: 0 Residential: 0.02 Weighted Average: Patient: -0.17 Caregiver: 0.01	Instrument: HUI:2, AD stage definition from subsequent studies
Neumann et al. (1999)	Mild: CDR = 1 Moderate: CDR = 2	Patient: 0.69 Caregiver: 0.87	Patient: 0.53 Caregiver: 0.87	Patient: -0.16 Caregiver: 0	Instrument: HUI:2
Leon et al. (2000)	Mild: CDR: 0.5 -1 Moderate: CDR = 2	Overall: 0.7 Community: AMC: 0.69 MCO: 0.67 Residential: Assisted Living:0.74 Nursing Home: 0.71	Overall: 0.53 Community: AMC: 0.53 MCO: 0.56 Residential: Assisted Living:0.56 Nursing Home: 0.48	Overall: -0.17 Community: AMC: -0.16 MCO: -0.11 Residential: Assisted Living: -0.18 Nursing Home: -0.23	Patient utility; Instrument: HUI:2
Oremus et al. (2014)	Mild: FAST stage 4 Moderate: FAST stage 5	0.89	0.82	-0.07	Patient utility; Instrument: EQ-5D; US population weights applied to Canadian results
Landeiro et al. (2020)	Mild: CDR-SB: 4.5 -9 Moderate: CDR-SB: 9.5-15.5	0.74	0.59	-0.15	Patient utility; Multiple Instruments; AD stage definition from subsequent studies; Numbers are most used estimates
Average	/	**Patient: 0.74** **Caregiver: 0.865**	**Patient: 0.6** **Caregiver: 0.87**	**Patient: -0.14** **Caregiver: 0.005**	/
Average without Oremus et al. (2014)	/	**Patient: 0.705** **Caregiver: 0.865**	**Patient: 0.543** **Caregiver: 0.87**	**Patient: -0.162** **Caregiver: 0.005**	/

Note: CDR-SB: Clinical Dementia Rating Scale-Sum of Boxes; CDR: CDR-SB: Clinical Dementia Rating; HRQoL: health-related quality of life; HUI:2: Health Utilities Index Mark II; EQ-5D: EuroQol five-dimensional; FAST: Functional Assessment Staging; TTO: Time Trade-Off; VAS: Visual Analog Scale; AMC: Academic Medical Center; MCO: Managed Care Organization

Section 6: Sensitivity Analysis

We consider the change results from varying several parameter values.

6.1 Ranges of Annual Cost Differences

We start by evaluating how variations of cost differences affect the value of innovation. We consider such variations within 20% deviations from the abovementioned average cost differences for both market-based and non-market care as well as the QALY improvements. Deviations in the cost difference estimates translate into a range of $27,399 to $41,099 per patient per year difference for market-based cost, and a range of $6,306 to $9,458 for non-market cost. Similarly, the deviations translate into a range of QoL difference from approximately 0.13 to 0.19, yielding a range of QALY improvements from $12,560 to $18,840 per patient using a value of $100,000 per QALY. The per patient values of delaying AD progression considering sensitivity are presented in Table 4. As the value per QALY increases, the percentage of QALY improvements within the total value of innovation increases as well, though market-based cost saved still takes up the largest proportion unless the highest value per QALY of $490,000 is employed.

In the same manner, we estimate the values for MCI patients under sensitivity (Table 5). For a 1-year delay, the value per patient in total ranges from $14,044 to $21,066 at $100,000 per QALY. For 6-month delays, the range becomes $7,022 to $10,533 at $100,000 per QALY; for 3-year delays, the ranges are $42,132 to $63,198 at $100,000 per QALY.

Table 4: Value of Innovation per patient

Delay	VQALY	Baseline				20% Higher				20% Lower				Percentage		
		Market-based	Non-market	QALY improvement	Total	Market-based	Non-market	QALY improvement	Total	Market-based	Non-market	QALY improvement	Total	Market-based	Non-market	QALY improvement
0.5	100,000	$17,124.5	$3,941.0	$7,850.0	$28,915.5	$20,549.4	$4,729.2	$9,420.0	$34,698.6	$13,699.6	$3,152.8	$6,280.0	$23,132.4	59.2%	13.6%	27.1%
	150,000	$17,124.5	$3,941.0	$11,775.0	$32,840.5	$20,549.4	$4,729.2	$14,130.0	$39,408.6	$13,699.6	$3,152.8	$9,420.0	$26,272.4	52.1%	12.0%	35.9%
	490,000	$17,124.5	$3,941.0	$38,465.0	$59,530.5	$20,549.4	$4,729.2	$46,158.0	$71,436.6	$13,699.6	$3,152.8	$30,772.0	$47,624.4	28.8%	6.6%	64.6%
1	100,000	$34,249.0	$7,882.0	$15,700.0	$57,831.0	$41,098.8	$9,458.4	$18,840.0	$69,397.2	$27,399.2	$6,305.6	$12,560.0	$46,264.8	59.2%	13.6%	27.1%
	150,000	$34,249.0	$7,882.0	$23,550.0	$65,681.0	$41,098.8	$9,458.4	$28,260.0	$78,817.2	$27,399.2	$6,305.6	$18,840.0	$52,544.8	52.1%	12.0%	35.9%
	490,000	$34,249.0	$7,882.0	$76,930.0	$119,061.0	$41,098.8	$9,458.4	$92,316.0	$142,873.2	$27,399.2	$6,305.6	$61,544.0	$95,248.8	28.8%	6.6%	64.6%
1.5	100,000	$51,373.5	$11,823.0	$23,550.0	$86,746.5	$61,648.2	$14,187.6	$28,260.0	$104,095.8	$41,098.8	$9,458.4	$18,840.0	$69,397.2	59.2%	13.6%	27.1%
	150,000	$51,373.5	$11,823.0	$35,325.0	$98,521.5	$61,648.2	$14,187.6	$42,390.0	$118,225.8	$41,098.8	$9,458.4	$28,260.0	$78,817.2	52.1%	12.0%	35.9%
	490,000	$51,373.5	$11,823.0	$115,395.0	$178,591.5	$61,648.2	$14,187.6	$138,474.0	$214,309.8	$41,098.8	$9,458.4	$92,316.0	$142,873.2	28.8%	6.6%	64.6%
2	100,000	$68,498.0	$15,764.0	$31,400.0	$115,662.0	$82,197.6	$18,916.8	$37,680.0	$138,794.4	$54,798.4	$12,611.2	$25,120.0	$92,529.6	59.2%	13.6%	27.1%
	150,000	$68,498.0	$15,764.0	$47,100.0	$131,362.0	$82,197.6	$18,916.8	$56,520.0	$157,634.4	$54,798.4	$12,611.2	$37,680.0	$105,089.6	52.1%	12.0%	35.9%
	490,000	$68,498.0	$15,764.0	$153,860.0	$238,122.0	$82,197.6	$18,916.8	$184,632.0	$285,746.4	$54,798.4	$12,611.2	$123,088.0	$190,497.6	28.8%	6.6%	64.6%
2.5	100,000	$85,622.5	$19,705.0	$39,250.0	$144,577.5	$102,747.0	$23,646.0	$47,100.0	$173,493.0	$68,498.0	$15,764.0	$31,400.0	$115,662.0	59.2%	13.6%	27.1%
	150,000	$85,622.5	$19,705.0	$58,875.0	$164,202.5	$102,747.0	$23,646.0	$70,650.0	$197,043.0	$68,498.0	$15,764.0	$47,100.0	$131,362.0	52.1%	12.0%	35.9%
	490,000	$85,622.5	$19,705.0	$192,325.0	$297,652.5	$102,747.0	$23,646.0	$230,790.0	$357,183.0	$68,498.0	$15,764.0	$153,860.0	$238,122.0	28.8%	6.6%	64.6%
3	100,000	$102,747.0	$23,646.0	$47,100.0	$173,493.0	$123,296.4	$28,375.2	$56,520.0	$208,191.6	$82,197.6	$18,916.8	$37,680.0	$138,794.4	59.2%	13.6%	27.1%
	150,000	$102,747.0	$23,646.0	$70,650.0	$197,043.0	$123,296.4	$28,375.2	$84,780.0	$236,451.6	$82,197.6	$18,916.8	$56,520.0	$157,634.4	52.1%	12.0%	35.9%
	490,000	$102,747.0	$23,646.0	$230,790.0	$357,183.0	$123,296.4	$28,375.2	$276,948.0	$428,619.6	$82,197.6	$18,916.8	$184,632.0	$285,746.4	28.8%	6.6%	64.6%

Table 5: Value of Innovation per patient (MCI)

Delay	VQALY	Baseline				20% Higher				20% Lower				Percentage		
		Market-based	Non-market	QALY improvement	Total	Market-based	Non-market	QALY improvement	Total	Market-based	Non-market	QALY improvement	Total	Market-based	Non-market	QALY improvement
0.5	100,000	$922.0	$4,855.5	$3,000.0	$8,777.5	$1,106.4	$5,826.6	$3,600.0	$10,533.0	$737.6	$3,884.4	$2,400.0	$7,022.0	10.5%	55.3%	34.2%
	150,000	$922.0	$4,855.5	$4,500.0	$10,277.5	$1,106.4	$5,826.6	$5,400.0	$12,333.0	$737.6	$3,884.4	$3,600.0	$8,222.0	9.0%	47.2%	43.8%
	490,000	$922.0	$4,855.5	$14,700.0	$20,477.5	$1,106.4	$5,826.6	$17,640.0	$24,573.0	$737.6	$3,884.4	$11,760.0	$16,382.0	4.5%	23.7%	71.8%
1	100,000	$1,844.0	$9,711.0	$6,000.0	$17,555.0	$2,212.8	$11,653.2	$7,200.0	$21,066.0	$1,475.2	$7,768.8	$4,800.0	$14,044.0	10.5%	55.3%	34.2%
	150,000	$1,844.0	$9,711.0	$9,000.0	$20,555.0	$2,212.8	$11,653.2	$10,800.0	$24,666.0	$1,475.2	$7,768.8	$7,200.0	$16,444.0	9.0%	47.2%	43.8%
	490,000	$1,844.0	$9,711.0	$29,400.0	$40,955.0	$2,212.8	$11,653.2	$35,280.0	$49,146.0	$1,475.2	$7,768.8	$23,520.0	$32,764.0	4.5%	23.7%	71.8%
1.5	100,000	$2,766.0	$14,566.5	$9,000.0	$26,332.5	$3,319.2	$17,479.8	$10,800.0	$31,599.0	$2,212.8	$11,653.2	$7,200.0	$21,066.0	10.5%	55.3%	34.2%
	150,000	$2,766.0	$14,566.5	$13,500.0	$30,832.5	$3,319.2	$17,479.8	$16,200.0	$36,999.0	$2,212.8	$11,653.2	$10,800.0	$24,666.0	9.0%	47.2%	43.8%
	490,000	$2,766.0	$14,566.5	$44,100.0	$61,432.5	$3,319.2	$17,479.8	$52,920.0	$73,719.0	$2,212.8	$11,653.2	$35,280.0	$49,146.0	4.5%	23.7%	71.8%
2	100,000	$3,688.0	$19,422.0	$12,000.0	$35,110.0	$4,425.6	$23,306.4	$14,400.0	$42,132.0	$2,950.4	$15,537.6	$9,600.0	$28,088.0	10.5%	55.3%	34.2%
	150,000	$3,688.0	$19,422.0	$18,000.0	$41,110.0	$4,425.6	$23,306.4	$21,600.0	$49,332.0	$2,950.4	$15,537.6	$14,400.0	$32,888.0	9.0%	47.2%	43.8%
	490,000	$3,688.0	$19,422.0	$58,800.0	$81,910.0	$4,425.6	$23,306.4	$70,560.0	$98,292.0	$2,950.4	$15,537.6	$47,040.0	$65,528.0	4.5%	23.7%	71.8%
2.5	100,000	$4,610.0	$24,277.5	$15,000.0	$43,887.5	$5,532.0	$29,133.0	$18,000.0	$52,665.0	$3,688.0	$19,422.0	$12,000.0	$35,110.0	10.5%	55.3%	34.2%
	150,000	$4,610.0	$24,277.5	$22,500.0	$51,387.5	$5,532.0	$29,133.0	$27,000.0	$61,665.0	$3,688.0	$19,422.0	$18,000.0	$41,110.0	9.0%	47.2%	43.8%
	490,000	$4,610.0	$24,277.5	$73,500.0	$102,387.5	$5,532.0	$29,133.0	$88,200.0	$122,865.0	$3,688.0	$19,422.0	$58,800.0	$81,910.0	4.5%	23.7%	71.8%
3	100,000	$5,532.0	$29,133.0	$18,000.0	$52,665.0	$6,638.4	$34,959.6	$21,600.0	$63,198.0	$4,425.6	$23,306.4	$14,400.0	$42,132.0	10.5%	55.3%	34.2%
	150,000	$5,532.0	$29,133.0	$27,000.0	$61,665.0	$6,638.4	$34,959.6	$32,400.0	$73,998.0	$4,425.6	$23,306.4	$21,600.0	$49,332.0	9.0%	47.2%	43.8%
	490,000	$5,532.0	$29,133.0	$88,200.0	$122,865.0	$6,638.4	$34,959.6	$105,840.0	$147,438.0	$4,425.6	$23,306.4	$70,560.0	$98,292.0	4.5%	23.7%	71.8%

6.2 Total Number of Treated Patients

As mentioned above, we impose different assumptions on how many mild AD patients can be treated in the next ten years, translating into a range of 1.3 million to 11 million treated patients. The aggregate value of such innovation delaying AD progression can be seen in Table 6. Note since all deviations are systematic across components, the proportions of each gain within the total value of innovation would remain identical, and the same as the proportions for the individual-level value, at each value per QALY. For example, assume the gains from market and non-market cost saved and QALY improvements are $10,000 each adding up to a sum of $30,000, each component would take up to one-third of the total gains. Consider a systematic deviation of 20% to all the components. The gain from each component would be $12,000 leading to a sum of $36,000, yet the proportion of each component is still one-third. Relating variations in the treated population to the value compositions, Figure 3 below exhibits the compositions for values gained with 50% treated patients at $100,000 per QALY. When different treated populations and value per QALY are in consideration, the overall upward trends remain. The magnitudes are larger the more treated patients or the higher value per QALY.

We also estimate the aggregate values for MCI delay to mild AD (Table 7). Assuming 50% MCI patients can be treated by 2032, a 1-year delay to mild AD would yield a total value of $149.2 billion at $100,000 per QALY. For 6-month delays, the values become half at $74.6 billion at $100,000 per QALY; for 3-year delays, the values are $447.7 billion at $100,000 per QALY.

Figure 3: Value of Delay by Length: 50% Treated Patients at $100,000 per QALY

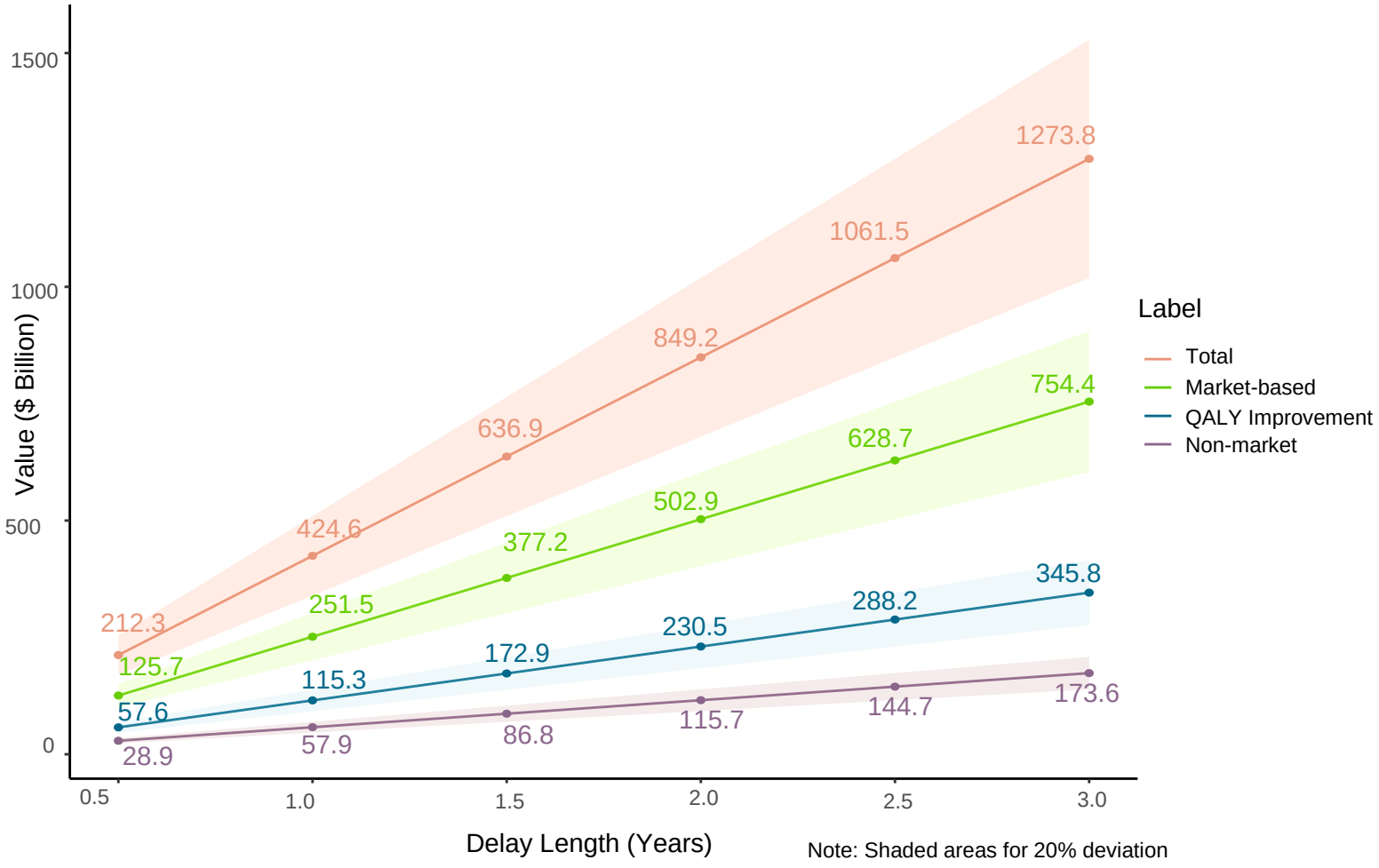


Table 6: Value of Innovation in Total

Delay	VQALY	Total ($ billion) 1.3 million treated patients			Total ($ billion) 50%; 7.3 million treated patients			Total ($ billion) 25%; 3.7 million treated patients			Total ($ billion) 75%; 11 million treated patients		
		Baseline	20% Higher	20% Lower	Baseline	20% Higher	20% Lower	Baseline	20% Higher	20% Lower	Baseline	20% Higher	20% Lower
0.5	100,000	$36.6	$44.0	$29.3	$212.3	$254.8	$169.8	$106.2	$127.4	$84.9	$318.5	$382.1	$254.8
	150,000	$41.6	$49.9	$33.3	$241.1	$289.3	$192.9	$120.6	$144.7	$96.4	$361.7	$434.0	$289.3
	490,000	$75.4	$90.5	$60.3	$437.1	$524.5	$349.7	$218.5	$262.2	$174.8	$655.6	$786.7	$524.5
1	100,000	$73.3	$87.9	$58.6	$424.6	$509.5	$339.7	$212.3	$254.8	$169.8	$636.9	$764.3	$509.5
	150,000	$83.2	$99.8	$66.6	$482.2	$578.7	$385.8	$241.1	$289.3	$192.9	$723.4	$868.0	$578.7
	490,000	$150.8	$181.0	$120.6	$874.2	$1,049.0	$699.3	$437.1	$524.5	$349.7	$1,311.2	$1,573.5	$1,049.0
1.5	100,000	$109.9	$131.8	$87.9	$636.9	$764.3	$509.5	$318.5	$382.1	$254.8	$955.4	$1,146.4	$764.3
	150,000	$124.8	$149.7	$99.8	$723.4	$868.0	$578.7	$361.7	$434.0	$289.3	$1,085.0	$1,302.0	$868.0
	490,000	$226.2	$271.4	$181.0	$1,311.2	$1,573.5	$1,049.0	$655.6	$786.7	$524.5	$1,966.9	$2,360.2	$1,573.5
2	100,000	$146.5	$175.8	$117.2	$849.2	$1,019.0	$679.4	$424.6	$509.5	$339.7	$1,273.8	$1,528.6	$1,019.0
	150,000	$166.4	$199.7	$133.1	$964.5	$1,157.4	$771.6	$482.2	$578.7	$385.8	$1,446.7	$1,736.1	$1,157.4
	490,000	$301.6	$361.9	$241.3	$1,748.3	$2,098.0	$1,398.7	$874.2	$1,049.0	$699.3	$2,622.5	$3,147.0	$2,098.0
2.5	100,000	$183.1	$219.7	$146.5	$1,061.5	$1,273.8	$849.2	$530.8	$636.9	$424.6	$1,592.3	$1,910.7	$1,273.8
	150,000	$208.0	$249.6	$166.4	$1,205.6	$1,446.7	$964.5	$602.8	$723.4	$482.2	$1,808.4	$2,170.1	$1,446.7
	490,000	$377.0	$452.4	$301.6	$2,185.4	$2,622.5	$1,748.3	$1,092.7	$1,311.2	$874.2	$3,278.1	$3,933.7	$2,622.5
3	100,000	$219.7	$263.7	$175.8	$1,273.8	$1,528.6	$1,019.0	$636.9	$764.3	$509.5	$1,910.7	$2,292.9	$1,528.6
	150,000	$249.6	$299.5	$199.7	$1,446.7	$1,736.1	$1,157.4	$723.4	$868.0	$578.7	$2,170.1	$2,604.1	$1,736.1
	490,000	$452.4	$542.9	$361.91	$2,622.5	$3,147.0	$2,098.0	$1,311.2	$1,573.5	$1,049.0	$3,933.7	$4,720.5	$3,147.0

Table 7: Value of Innovation in Total (MCI)

Delay	VQALY	Total ($ billion) 50%; 7.3 million treated patients			Total ($ billion) 25%; 3.7 million treated patients			Total ($ billion) 75%; 11 million treated patients		
		Baseline	20% Higher	20% Lower	Baseline	20% Higher	20% Lower	Baseline	20% Higher	20% Lower
0.5	100,000	$74.6	$89.5	$59.7	$ 37.3	$44.8	$29.8	$111.9	$134.3	$89.5
	150,000	$87.4	$104.8	$69.9	$ 43.7	$52.4	$34.9	$131.0	$157.2	$104.8
	490,000	$174.1	$208.9	$139.2	$ 87.0	$104.4	$69.6	$261.1	$313.3	$208.9
1	100,000	$149.2	$179.1	$119.4	$ 74.6	$89.5	$59.7	$223.8	$268.6	$179.1
	150,000	$174.7	$209.7	$139.8	$ 87.4	$104.8	$69.9	$262.1	$314.5	$209.7
	490,000	$348.1	$417.7	$278.5	$174.1	$208.9	$139.2	$522.2	$626.6	$417.7
1.5	100,000	$223.8	$268.6	$179.1	$111.9	$134.3	$89.5	$335.7	$402.9	$268.6
	150,000	$262.1	$314.5	$209.7	$131.0	$157.2	$104.8	$393.1	$471.7	$314.5
	490,000	$522.2	$626.6	$417.7	$261.1	$313.3	$208.9	$783.3	$939.9	$626.6
2	100,000	$298.4	$358.1	$238.7	$149.2	$179.1	$119.4	$447.7	$537.2	$358.1
	150,000	$349.4	$419.3	$279.5	$174.7	$209.7	$139.8	$524.2	$629.0	$419.3
	490,000	$696.2	$835.5	$557.0	$348.1	$417.7	$278.5	$1,044.4	$1,253.2	$835.5
2.5	100,000	$373.0	$447.7	$298.4	$186.5	$223.8	$149.2	$559.6	$671.5	$447.7
	150,000	$436.8	$524.2	$349.4	$218.4	$262.1	$174.7	$655.2	$786.2	$524.2
	490,000	$870.3	$1,044.4	$696.2	$435.1	$522.2	$348.1	$1,305.4	$1,566.5	$1,044.4
3	100,000	$447.7	$537.2	$358.1	$223.8	$268.6	$179.1	$671.5	$805.8	$537.2
	150,000	$524.2	$629.0	$419.3	$262.1	$314.5	$209.7	$786.2	$943.5	$629.0
	490,000	$1,044.4	$1,253.2	$835.5	$522.2	$626.6	$417.7	$1,566.5	$1,879.8	$1,253.2

Section 7: Conclusion

We estimate the value of AD innovation delaying progression by evaluating the cost and utility differences between moderate and mild AD stages, and apply the differences to hypothetical innovation assumed to postpone progression to moderate AD. We assume the delay to vary from 6 months to 3 years. For a 1-year delay, we estimate $34,249 would be saved from market-based cost, $7,882 from non-market care, and $15,700 would be gained from QALY per patient with a value of $100,000, where market-based cost takes up 59.2% of the total value, non-market takes up 13.6%, and QALY improvements take up 27.1%. Assuming that 50% of mild AD patients in the next ten years can be treated, the aggregate value of delaying AD progression by 1 year would be approximately $424.6 billion. Considering different lengths of delay, values per QALY and total numbers of treated patients, the total value of such innovation ranges from $29.3 billion to $4,720.5 billion. As a higher value per QALY is used, the proportion of gains from QALY improvements increases in conjunction, yet market-based cost saved remains to be the major source of value unless an upper bound of $490,000 is applied.

Considering MCI patients, assuming 50% of the patients can receive the innovation treatment, a 1-year delay would bring a total value of $149.2 billion, at $100,000 per QALY. The aggregate value would be $74.6 billion if the delay is only 6-month and $447.7 billion if the delay is 3 years. Assuming all 17 million patients can receive the innovative treatment and achieve a 3-year delay, such innovation would bring a total value of $895.3 billion at the same value per QALY, and a total of $2,088.7 billion at the maximum value of $490,000 per QALY.

The estimated results also shed light on future policy designs. First, pharmaceutical companies should be further encouraged for such innovation, where cost effectiveness thresholds may be correspondingly adjusted compared to other drugs. Second, since the total value of such innovation would largely depend on the number of treated patients, easier access to such innovative therapies should be provided for a larger population of treated patients and hence higher values. Third, access to AD diagnoses should be improved as well, such that more patients can be treated at earlier AD stages where higher values from treatment would be gained.

Section 8: Discussion and Limitations

There exist several limitations in this study. First, our estimates of values can be largely conservative, by not considering delaying progression to later stages of AD. As severity elevates, the delay from moderate to severe AD should generate substantial values from avoiding costs for severe AD, which are not considered here. At the same time, in our analysis, the impact of such therapy on the duration of moderate and severe AD is not accounted for, which would generate another significant saving if the delay to moderate AD can further reduce time in moderate and severe AD. Aware of the conservativeness of our estimates, our estimated values should reflect the value of such interventive therapies alone, potentially aiding authorities with cost-efficiency evaluations and subsequent decisions.

In addition to alternative progressions, there remain other components in valuation of AD drugs that we did not touch upon. First, Prados et al. (2022) employed the ISPOR value flower to consider more aspects of an Alzheimer's treatment's potential value, such as its insurance value for people with and without the disease. Second, Lakdawalla and Phelps (2021) added diminishing returns to health in the standard cost-effectiveness method, which shows that valuation of drugs can be prone to patient beliefs, and the cost-effectiveness thresholds should be varying contingent on disease severity. Lastly, though we considered caregiver burden, many of the papers here assume one caregiver, which may not necessarily be a family member to the patients. Park et al. (2021) shows that in addition to just caregivers, AD would also have substantial spillover effects on patients' families.

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Appendix

Table A1: Cost difference for MCI and mild AD from literature (annual per patient)

Type	Study	AD Stage Definition	MCI	Mild AD	Difference	Note
Market-based cost	Michaud et al. (2017)	MCI: DS: 1-3 (Equivalent to CDR=0.5) Mild: DS: 4-5 (Equivalent to CDR=1)	Long-term care included: $7,685 Long-term care not included: $4,550	$6,317 (Long-term care included: -17.8% increase Long-term care not included: 38.8% increase)	Long-term care included: -$1,368 Long-term care not included: $1,767	Mild AD patients have $0 cost for long-term care in this sample
Market-based cost	Robinson et al. (2020)	MCI: MMSE ≥ 24 and FAQ < 6 Mild: MMSE ≥ 20 and FAQ ≥ 6	$23,424 ($26,043 in 2021 USD)	$27,972 ($31,099 in 2021 USD; 19.4% increase)	$4,548 ($5,056 in 2021 USD)	
	Average	**/**	**Long-term care included: $16,864 Long-term care not included: $15,297**	**$18,708**	**Long-term care included: $1,844 Long-term care not included: $3,412**	**In 2021 USD**
Non-market cost	Michaud et al. (2017)	MCI: DS: 1-3 (Equivalent to CDR=0.5) Mild: DS: 4-5 (Equivalent to CDR=1)	$548	$5,813 (960.8% increase)	$5,265	
Non-market cost	Robinson et al. (2020)	MCI: MMSE ≥ 24 and FAQ < 6 Mild: MMSE ≥ 20 and FAQ ≥ 6	$10,380 ($11,540 in 2021 USD)	$22,944 ($25,697 in 2021 USD; 121% increase)	$12,564 ($14,157 in 2021 USD)	
	Average	**/**	**$6,044**	**$15,755**	**$9,711**	**In 2021 USD**
QoL	Neumann et al. (1999)	MCI: CDR=0.5 Mild: CDR = 1	Patient: 0.73 Caregiver: 0.88	Patient: 0.69 Caregiver: 0.87	Patient: -0.04 Caregiver: -0.01	Instrument: HUI:2
QoL	Landeiro et al. (2020)	MCI: CDR-SB < 4.5 Mild: CDR-SB: 4.5 -9	0.80	0.74	-0.06	Patient utility; Multiple Instruments; AD stage definition from subsequent studies; Numbers are most used estimates
	Average	**/**	**Patient: 0.77 Caregiver: 0.88**	**Patient: 0.72 Caregiver: 0.87**	**Patient: -0.05 Caregiver: -0.01**	