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# The value of earlier initiation of anti-amyloid therapy for Alzheimer's disease

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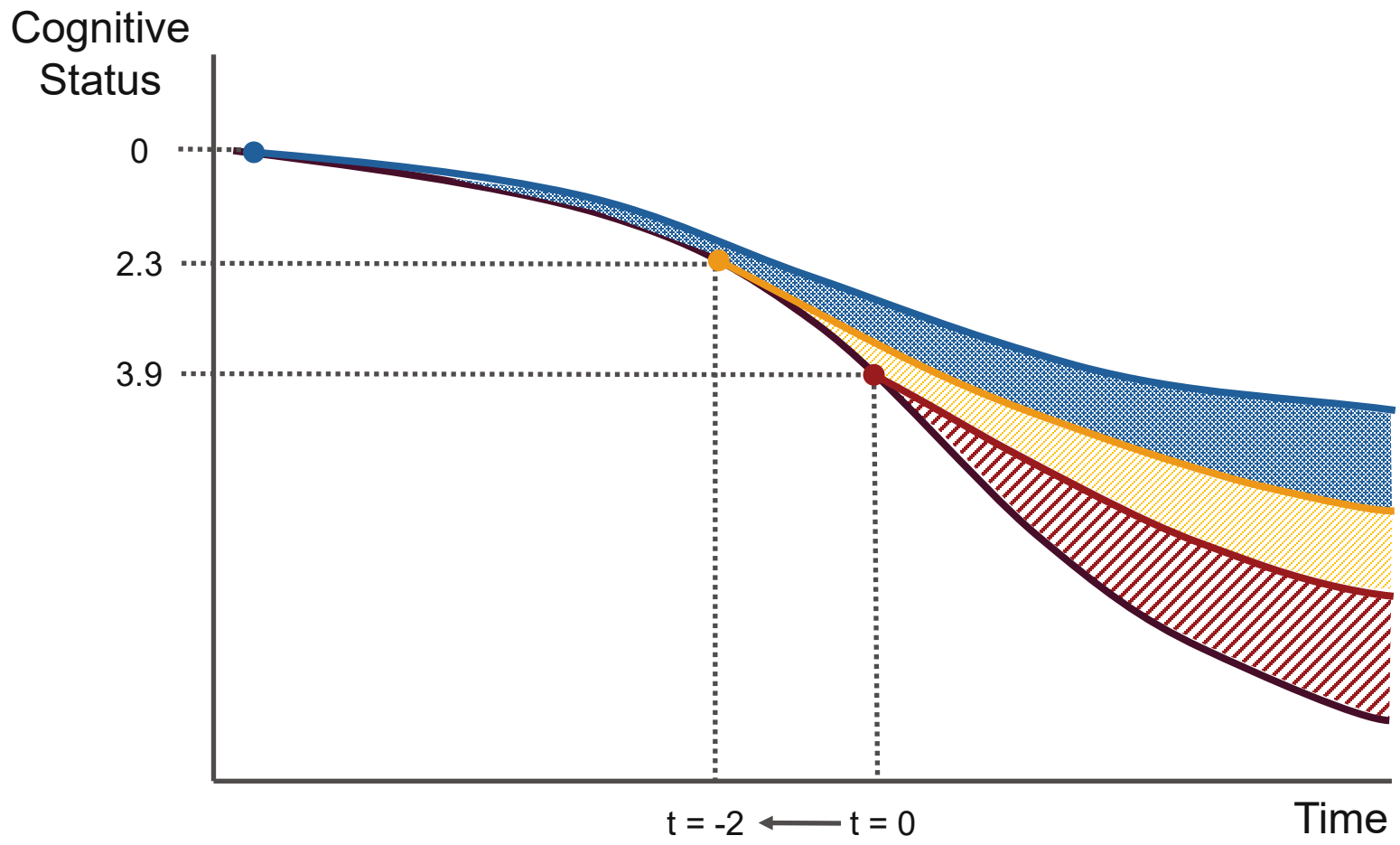
***This presentation includes preliminary research findings that have not yet undergone peer-review.***

# Scenarios for cognitive decline as a cohort ages




## Presymptomatic Treatment

Treatment initiated before cognitive symptoms present, after positive biomarker test

## 2-Year Earlier Treatment

Treatment initiated 2 years earlier, consistent with improved cognitive/biomarker monitoring and timely diagnosis

## Treatment

Donanemab treatment administered at baseline cognitive status in pivotal clinical trial

## Status quo

Cognition declines over time without treatment

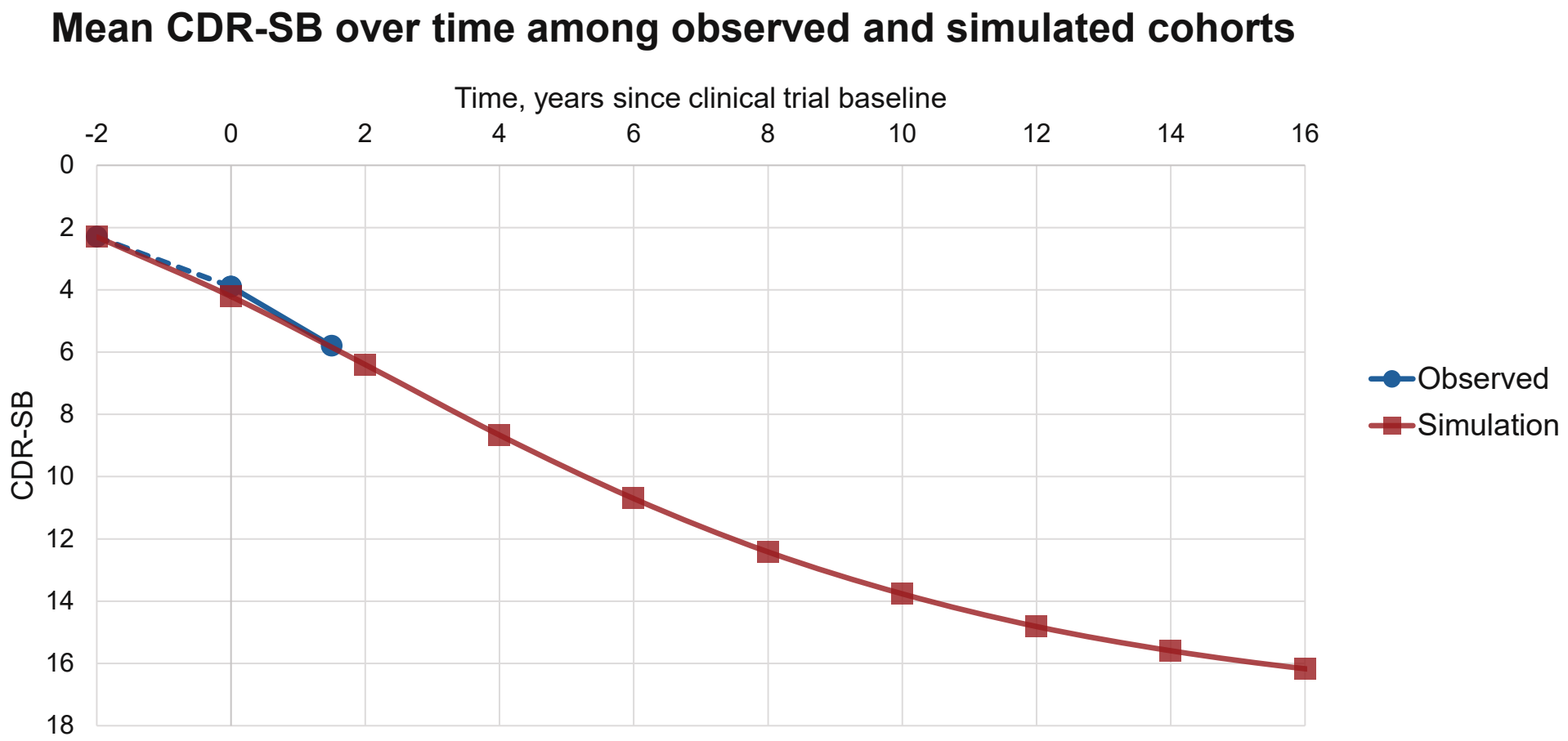
Notes: Cohort based on the TRAILBLAZER-ALZ 2 trial. Cognitive status measured using Clinical Dementia Rating – Sum of Boxes (CDR-SB) score. This score is based on interviewing a patient and their care partner and measuring 6 domains. Scores range from 0 to 18, with 0 representing no impairment. Scores of 0.5 to 4.0 correspond to “questionable cognitive impairment to very mild dementia.”

# Overview of Methods

- **Data: Health and Retirement Study (HRS)**
  - Nationally representative survey of Americans aged 51+
  - Ongoing since 1992, surveys respondents every 2 years through the end of their life
  - Detailed information on wide range of health and economic topics
    - Health behaviors, conditions, cognition, functional limitations, formal/informal care, nursing home entry, economic resources
- **Microsimulation: The Future Elderly Model (FEM)[2]**
  - Established, well validated[3,4] dynamic microsimulation of older Americans' life-course outcomes
  - Estimated using HRS data, supplemented with additional sources
    - Alzheimer's Disease Neuroimaging Initiative (ADNI) data used for modeling CDR-SB among an amyloid positive population
    - Medicare Current Beneficiary Survey data used for modeling medical spending
- **Use microsimulation to extend the outcomes and time horizon of the trial**
  - Using HRS, construct a cohort resembling the TRAILBLAZER-ALZ 2[1] study participants
    - Select HRS respondents based on trial inclusion criteria, reweight to match placebo group characteristics (see Appendix)
  - Using FEM, simulate the cohort's remaining life-course under status quo and treatment scenarios
    - Simulate, for each year of life, individuals' cognitive status, chronic disease incidence, functional limitations, nursing home entry, informal care hours, work and earnings, medical costs, and quality of life (QALYs)


1. Sims et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023;330(6):512-527.
2. Health Policy Simulation. USC Schaeffer Center for Health Policy & Economics. Accessed November 20, 2025. https://schaeffer.usc.edu/programs/center-for-health-policy-and-economics/health-policy-simulation/
3. Leaf et al. Predicting quantity and quality of life with the Future Elderly Model. *Health Economics*. 2021;30(S1):52-79.
4. Wei et al. Using dynamic microsimulation to project cognitive function in the elderly population. *PLoS ONE*. 2022;17(9):e0274417.

# The simulated trajectory of cognitive status without treatment matches the observed trial placebo group




Notes: CDR-SB, Clinical Dementia Rating – Sum of Boxes. "Observed" line shows the mean CDR-SB score among the TRAILBLAZER-ALZ 2 placebo group at baseline and 76 weeks. The "Observed" point at $t$ = -2 is estimated based on a cohort of Alzheimer's Disease Neuroimaging Initiative (ADNI) participants selected and reweighted to match the clinical trial population. The "Simulation" line shows the average CDR-SB score among surviving cohort members in each year of the simulation. The simulation proceeds in 2-year time steps. CDR-SB is governed by a transition model estimated among ADNI participants with at least 24 months follow-up and amyloid and tau pathology at baseline (see Appendix).

# Simulated treatment effects are based on clinical trial results

## Treatment parameters

| Parameter (X) | Description | Scenarios | | | |
|---|---|---|---|---|---|
| | | Status quo | Baseline Tx | 2Yr Earlier Tx | Presymptom. Tx |
| Treatment initiation | Initiate treatment in year X | No Tx | t = 0 | t = -2 | t = CU[a] |
| Treatment effect | Slow CDR-SB increase by X% | 0% | 29% | 29% | 46%[b] |
| Treatment duration | Apply CDR-SB slowing for X years | 0 | Lifetime | Lifetime | Lifetime |
| Symptomatic ARIA | 12-week disutility for X% of cohort | 0% | 6% | 6% | 6% |
| Treatment discontinuation due to AE | No treatment effect for X% of cohort | 0% | 13% | 13% | 13% |

Abbreviations: CU, cognitively unimpaired; CDR-SB, Clinical Dementia Rating Sum of Boxes; ARIA, amyloid-related imaging abnormalities; AE, adverse event.
Notes: Treatment parameters are based on results from the TRAILBLAZER-ALZ 2 trial.[1]
a. t = CU represents the most recent HRS wave the individual was observed as CU (i.e., no more than 2 years before symptoms); mean age = 68.
b. Treatment first lowers the probability of transitioning from CU to mild cognitive impairment by 37%. After individuals transition into cognitive impairment, treatment slows CDR-SB progression by 46%. This rate of slowing is based on the reported effect among individuals with mild cognitive impairment and low-medium tau pathology from TRAILBLAZER-ALZ 2.[2]

1. Sims et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023;330(6):512-527.
2. Mintun et al. Donanemab in Early Symptomatic Alzheimer's Disease: Efficacy and Safety in TRAILBLAZER-ALZ 2, a Phase 3 Randomized Clinical Trial. Presented at: AAIC 2023.

# Treatment extends the number and proportion of life-years spent living in the community

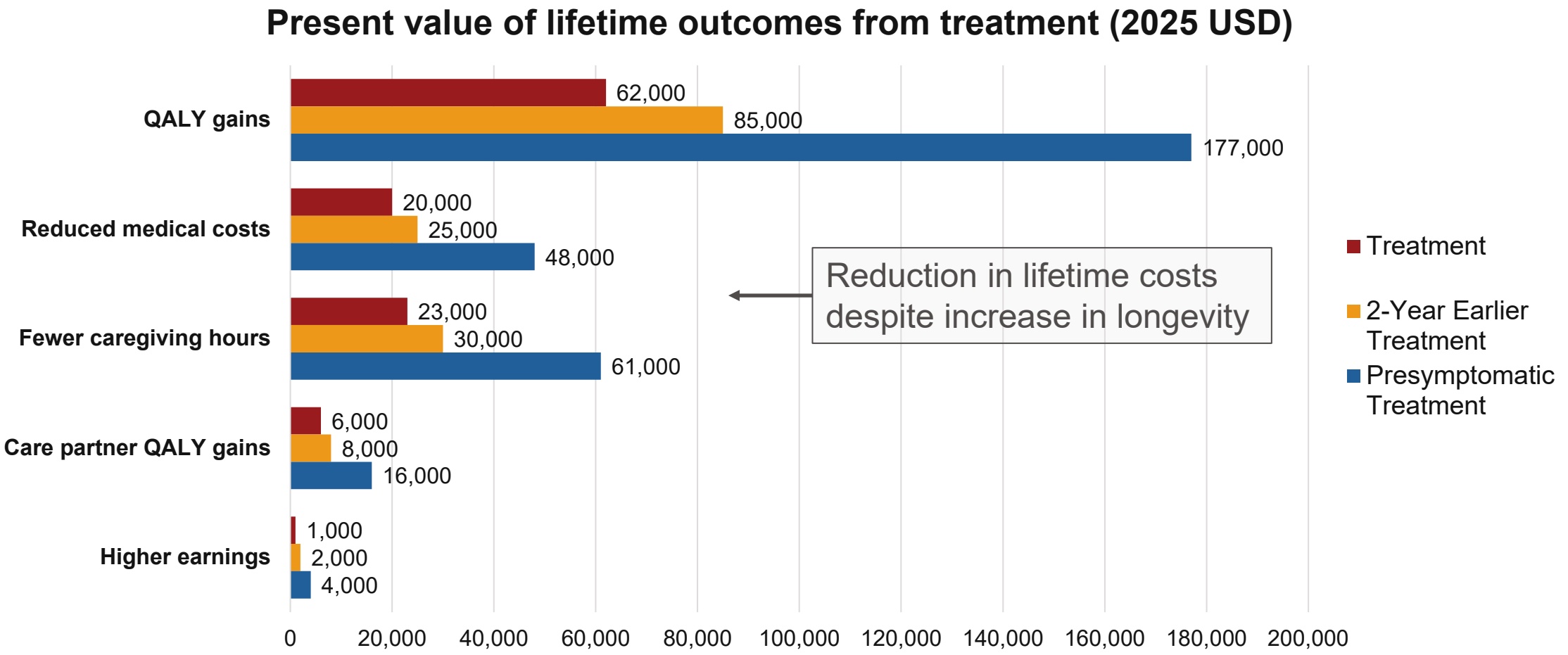
## Average remaining lifetime outcomes under status quo and treatment scenarios

| Scenario | Remaining lifetime outcomes | | | |
|---|---|---|---|---|
| | Life-years | QALYs | Years in the community | Years working |
| Status quo, mean age = 71 at baseline | 14.7 | 6.7 | 12.1 | 2.0 |
| Difference from status quo[a] | | | | |
| Treatment | +0.34 | +0.56 | +0.67 | +0.07 |
| 2-Year Earlier Treatment | +0.47 | +0.75 | +0.87 | +0.11 |
| Presymptomatic Treatment | +1.0 | +1.7 | +1.8 | +0.23 |

Notes: Years in the community refers to years living not in a nursing home. Treatment and 2-Year Earlier Treatment simulations start at t = -2, when the cohort mean age = 71. The Treatment scenario initiates treatment at t = 0 (mean age = 73); 2-Year Earlier Treatment initiates treatment at t = -2 (mean age = 71). Presymptomatic Treatment simulation starts from the most recent HRS wave the individual was observed cognitively unimpaired (cohort mean age = 68), and initiates treatment immediately.

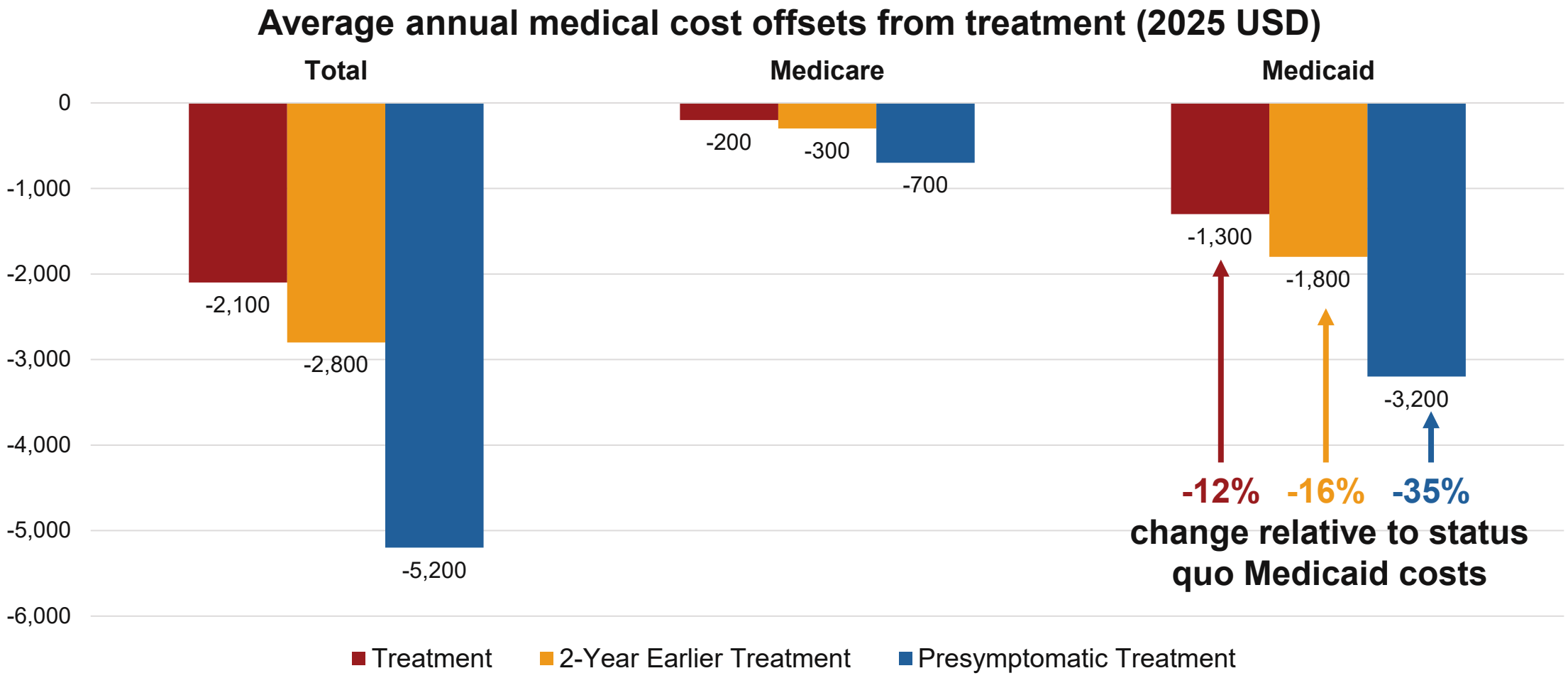
a. For Treatment and 2-Year Earlier Treatment scenarios, the difference is relative to the status quo levels shown in the first row, from simulations beginning in t = -2. The Presymptomatic Treatment scenario begins at varying times before t = -2, depending on when the respondent was last cognitively unimpaired, and so their status quo levels differ and start from earlier baseline ages; their status quo levels are not shown in the table.

# Treatment generates societal value from quality-of-life gains, medical cost offsets, and reduced burden on care partners



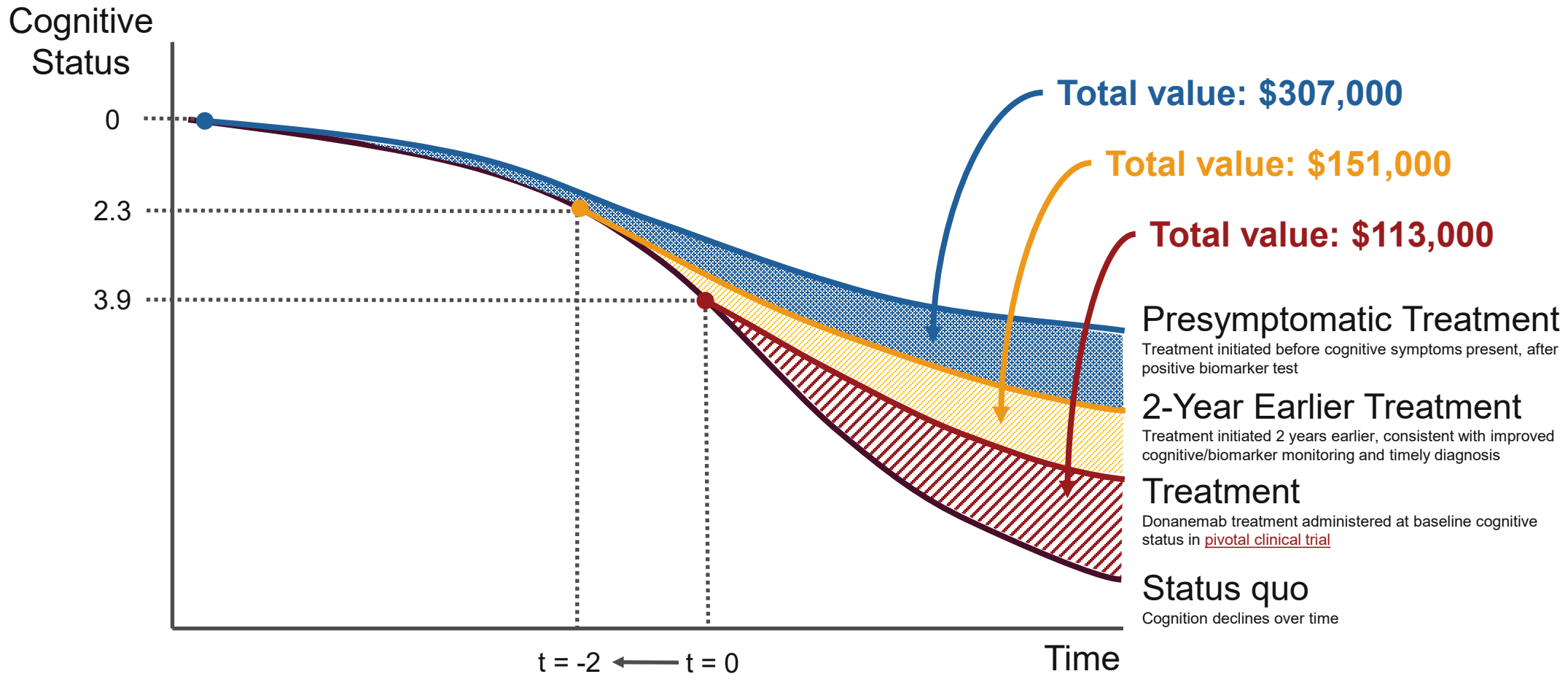

Notes: Present value discounted to the year of treatment initiation using a 3% discount rate. Values rounded to the nearest thousand. QALY gains valued using the Generalized Risk Adjusted Cost Effectiveness (GRACE) framework. **Medical costs do not include costs of screening, treatment, or monitoring.** Informal caregiver hours valued at $34/hour. Caregiver disutility estimates come from Lin et al. (2023) and depend on number of caregivers and stage of dementia.

# Presymptomatic treatment could reduce individuals' annual Medicaid costs by up to 35%




Notes: **Medical costs do not include costs of screening, treatment, or monitoring.** Annual medical costs calculated as the total remaining lifetime medical cost divided by the number of life-years lived. Total includes out-of-pocket costs. Values are rounded to the nearest hundred.

# Presymptomatic treatment could generate up to $307,000 in value over a patient's remaining lifetime

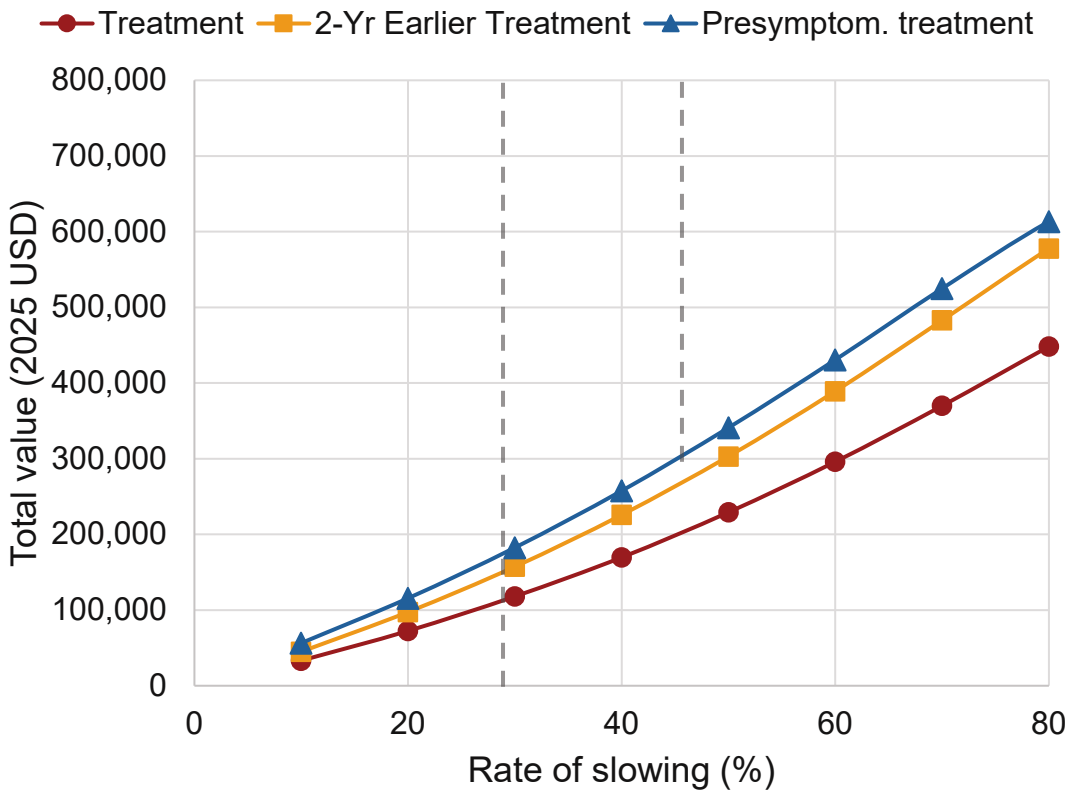



Notes: Total value is the sum of the present value of lifetime outcomes: QALY gains, reduced medical costs, higher earnings, fewer caregiving hours, and caregiver QALY gains. Total value does not include the costs of screening, treatment, and monitoring. Values are rounded to the nearest thousand. Cognitive status measured using Clinical Dementia Rating – Sum of Boxes (CDR-SB) score. Scores range from 0 to 18, with 0 representing no impairment. Scores of 0.5 to 4.0 correspond to "questionable cognitive impairment to very mild dementia."

# Total value depends on key parameter assumptions

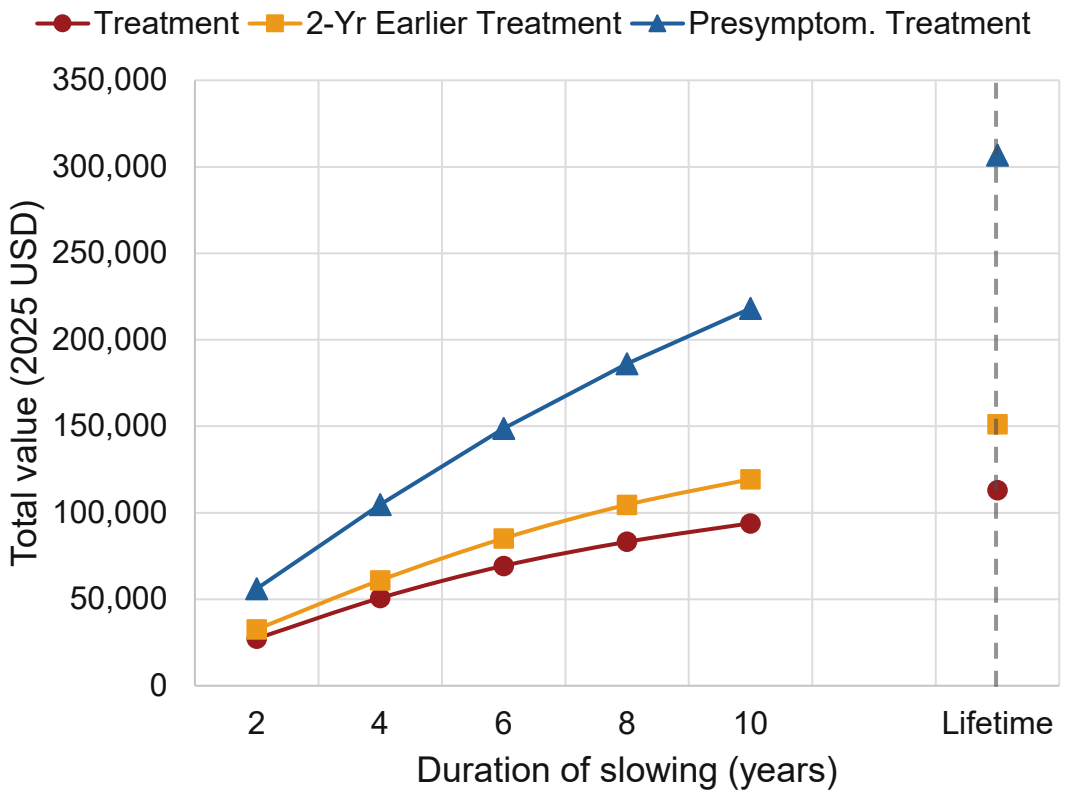
## Total value of treatment under alternative treatment parameters

### Varying treatment effect magnitude




Note: Dashed lines show the values used in the main analyses. All scenarios use lifetime treatment duration.

### Varying treatment effect duration




Note: Dashed line shows the value used in the main analyses. Rate of slowing is the same as in the main analyses.

# Conclusion

- **Treatment with donanemab shows meaningful value for patients, their care partners, and society**
  - Largest benefits from improving patient quality of life and reducing burden on care partners
  - Medical cost offsets despite increase in longevity, driven by reductions in nursing home use
- **Initiating treatment earlier could substantially increase value**
  - Initiating treatment 2 years earlier than the clinical trial baseline generates 34% more value
  - Next generation treatments initiated in presymptomatic stage could generate triple the value
- **Benefits described here must be weighed against costs of screening, treatment, and monitoring**

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# Appendix

# Clinical Dementia Rating – Sum of Boxes (CDR-SB)

| CDR-SB Score | Disease Severity | Global CDR Score |
|---|---|---|
| 0 | Unimpaired | 0 (normal) |
| 0.5 – 4.0 | Questionable cognitive impairment to very mild dementia | |
| 0.5 – 2.5 | Questionable impairment | 0.5 (very mild) |
| 3.0 – 4.0 | Very mild dementia | |
| 4.5 – 9.0 | Suggests mild dementia | 1 (mild) |
| 9.5 – 15.5 | Suggests moderate dementia | 2 (moderate) |
| 16.0 – 18.0 | Suggests severe dementia | 3 (severe) |

Adapted from Eisai and O'Bryant S, et al. Arch Neurol. 2008;65(8):1091–5.

# Cohort of Americans selected and reweighted to match the clinical trial population

## HRS respondents age 60-85 in 2010-2020, compared to clinical trial

| | All HRS respondents | Simulation cohort | | Clinical trial[a] |
|---|---|---|---|---|
| | | HRS selected | Reweighted | |
| Age (SD) | 70.0 (6.9) | 73.9 (8.0) | 73.0 (7.9) | 73.0 (6.2) |
| Male | 46% | 48% | 43% | 42.6% |
| White | 84% | 65% | 92% | 92.1% |
| 13+ years of education | 55% | 37% | 73% | 72.8% |
| CDR stage 0.5 | 35% | 87% | 62% | 61.2% |
| CDR-SB (SD) | 1.0 (2.4) | 2.2 (2.4) | 3.9 (2.6) | 3.9 (2.1) |
| CDR-SB, 2 years earlier | 0.8 | 0.8 | 2.3 | 2.3[b] |
| Respondent-wave obs. | 64,409 | 7,234 | 7,234 | |
| Unique respondents | 18,342 | 7,234 | 7,234 | |

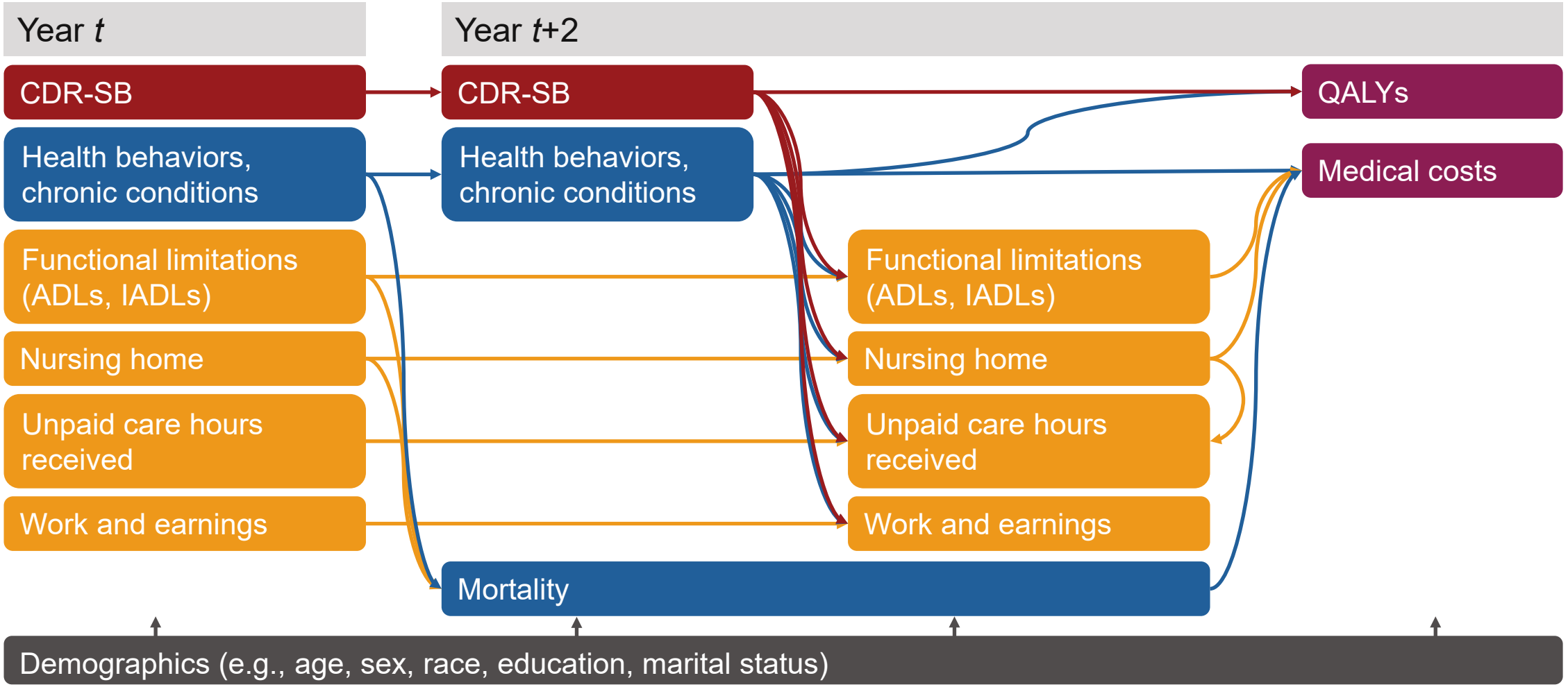
Notes: CDR-SB, Clinical Dementia Rating – Sum of Boxes. Simulation cohort selected based on trial inclusion criteria for MMSE, schizophrenia/chronic psychosis, recent cancer, and memory decline. First and second columns use HRS sample weights. Reweighted simulation cohort used entropy balancing to match the clinical trial population.

a. Reported baseline characteristics of the placebo group in the TRAILBLAZER-ALZ 2 study.

b. Estimated from a cohort of ADNI participants, selected and reweighted to match clinical trial; included as matching variable in cohort reweighting.

# The simulation proceeds in 2-year steps; individuals' characteristics in year *t* predict their outcomes in *t*+2

## Overview of relationship between key FEM components




Notes: All transition models are estimated based on the longitudinal relationships observed in HRS data; CDR-SB model estimated using data from ADNI among an amyloid positive population. Cross-sectional models predict QALYs and medical costs in each simulation step based on the transitioned outcomes.

# CDR-SB Transition Model

- **Data: Alzheimer's Disease Neuroimaging Initiative**

- **Transition model estimated among sample with:**
  - At least 24 months of follow-up
  - Likely amyloid and tau pathology at baseline
    - P-tau$_{181}$/A$\beta_{42}$ ratio ≥ 0.0395, based on thresholds in Hansson et al. (2018)[1] and Smith et al. (2025)[2]

**CDR-SB transition model**

| | CDR-SB |
|---|---|
| Age (years, 2-year lag) | 0.017 |
| | (0.012) |
| Male | -0.014 |
| | (0.182) |
| White | 0.655 |
| | (0.440) |
| CDR-SB (2-year lag) spline, <4.5 | 1.647 |
| | (0.069) |
| CDR-SB (2-yaer lag) spline, 4.5+ | 1.007 |
| | (0.076) |
| Constant | -1.354 |
| | (1.019) |
| N | 765 |

Notes: Standard errors in parentheses. OLS model with current CDR-SB as the outcome.


1. Hansson et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression. Alzheimer's & Dementia. 2018;14(11):1470-81.
2. Smith et al. Clinical Performance of the Elecsys CSF pTau181/Aβ42 Ratio for Concordance with Tau-PET in Two Independent Cohorts. Neurology and Therapy. 2025;14(5):2011-31.