EE454

SHIFTING THE CURVE: Valuing Healthcare Utilization across Preclinical and Symptomatic Alzheimer's Disease

Jackson Dooley and Daniel Gautieri | SiteRx | New York, NY, USA

INTRODUCTION

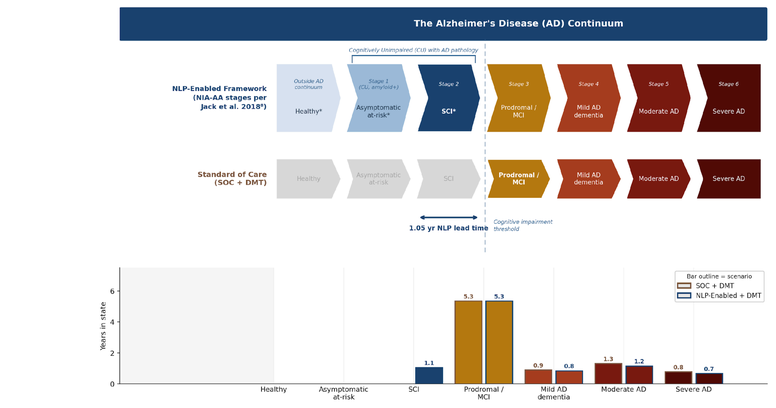
Alzheimer's disease (AD) does not begin when memory fails: pathological changes accumulate for years before any objective decline is detectable, a preclinical stage – Subjective Cognitive Impairment (SCI) – that sits upstream of where both clinical practice and economic evaluation currently engage. Disease-modifying therapies (DMTs), now approved and reimbursed, show the greatest benefit when initiated early; yet standard of care anchors clinical entry at Mild Cognitive Impairment (MCI), because routine care lacks an established mechanism to identify SCI-stage patients before symptoms crystallize. Conventional cost-effectiveness models compound this gap: calibrated to symptomatic disease with high costs and measurably reduced utilities, they omit SCI entirely (utility ≈ 0.865; state cost ~$14K/yr), leaving the full economic value of upstream intervention unquantified. This analysis fills that gap by coupling a validated NLP classifier – applied to de-identified EHR notes across SiteRx's longitudinal network (4,000+ providers, 36 states) – with a five-state Markov model spanning the complete AD continuum, enabling cost-effectiveness analysis at a stage conventional models cannot access.

OBJECTIVES

Standard cost-effectiveness models anchor clinical entry at MCI or later, where costs are high, utilities are measurably reduced, and the benefit of intervention is intuitive. Shifting entry upstream to SCI creates a fundamental tension: patients are relatively unimpaired (utility ≈ 0.865), state costs are low ($14K/yr), yet treatment (including a $26,500/yr DMT) begins earlier and runs longer. A model that values earlier entry must therefore justify higher near-term expenditure against benefits that materialize slowly, in a population that does not yet look sick. Reconciling earlier identification with a framework for valuing a relatively unimpaired stage – one built around symptomatic disease – is the core methodological challenge this analysis addresses.

This research proposes a framework that couples a validated NLP classifier (applied to de-identified EHR notes from SiteRx's Data Platform, a longitudinal, real world data repository sourced from community-based EHR network spanning 4,000+ primary care and neurology providers across 36 states) – with a five-state Markov model spanning the full AD continuum from SCI through severe disease, enabling cost-effectiveness analysis at an entry point conventional models do not reach.

METHODS



* Healthy and Asymptomatic at-risk: modeled background states, not directly NLP-detected. SCI: EHR/NLP symptom-defined — clinically corresponds to NIA-AA Stage 2: amyloid+ confirmation not required. Time-in-state: Green et al. 2019 (Alzheimers Dement 2019;15:1309–21). NLP lead time = 1.05 yr (empirical median). Late-stage compression = 12%. SOC arm = SOC+DMT (lecanemab, CLARITY-AD RR=0.69). NIA-AA stages: Jack CR Jr, et al. Alzheimers Dement. 2018;14(4):535–562.

Figure 1. Detection Framework: NLP-Enabled vs. SOC across the Alzheimer's Disease Continuum. Chevron rows show pipeline entry points per framework. NIA-AA biological stage mapping from Jack et al. 2018.[8] Bottom bars: time-in-state by scenario (Green et al. 2019[4]; NLP lead time 1.05 yr, compression 12%).

NLP Pipeline

Cohort: 79,863 ICD-10 G31.84 (MCI) patients and 157,512 matched controls (2:1, age × sex), SiteRx EHR network (2009–2024).

Pipeline: 7-bucket regex classifier (93 patterns) applied to de-identified clinical notes via OpenSearch. Domains: memory complaints, word-finding difficulty, functional changes, mood/sleep, caregiver-reported changes, and objective testing language.

Operating Point: NLP-positive if any fragment in the 5-year lookback window (ending 90 days pre-MCI code) reaches the SCI bucket; SCI signal captured via NLP patterns in routine notes, not structured fields. ConText negation/speculation filter[5] applied post-hoc.

Economic Model

Markov Structure: Five states – SCI/Preclinical, MCI, Mild AD, Moderate AD, Severe AD – annual cycle; time-in-state from Green et al. 2019.[4] Three scenarios evaluated:

Scenario	Entry Point	DMT
SOC, No DMT	MCI	None
SOC + DMT	MCI	Lecanemab (CLARITY-AD[6]; relative risk [RR]=0.69)
NLP-Enabled + DMT	SCI (35.8%) + MCI (64.2%)	Lecanemab

Costs: State costs from Green et al.[4] 2019 (societal perspective, inflated to 2024 USD). SCI $14K/yr (model assumption). DMT: lecanemab $26,500/yr. NLP screen: $50/pt. Blood-based biomarker (BBM) confirmation: $220/pt. Probabilistic Sensitivity Analysis (PSA) N=5,000, seed=42; Beta prior (ESS=50); LogNormal relative risk (RR) [0.59, 0.81]; Expected Value of Perfect Information (EVPI) at $150K Willingness-To-Pay (WTP).

RESULTS

NLP-enabled detection of SCI-stage signals in routine EHR notes – a median of 1.05 years before MCI diagnosis – shifts the cost-effectiveness of early AD intervention.

NLP Validation

Of 79,863 future MCI patients, 35.8% had a detectable SCI-stage signal in routine EHR notes a median of 1.05 years (interquartile range [IQR] 0.54–2.16 yr) before formal diagnosis. Positive Predictive Value (PPV) 64.2%: nearly 2 in 3 NLP-flagged patients progressed to MCI or worse. Full lead-time distribution available as supplemental Figure 2.

Table 1. NLP Validation Performance (Post-ConText, SCI Threshold)

Metric	Point Estimate	95% Bootstrap Confidence Interval (CI)
Sensitivity	0.358	[0.355, 0.361]
Specificity	0.899	[0.897, 0.900]
PPV	0.642	[0.638, 0.646]
NPV	0.734	[0.733, 0.735]

N(MCI)=79,863; N(controls)=157,512. Bootstrap N=10,000. NPV = Negative Predictive Value. Deployment uncertainty captured separately in PSA Beta prior.

High specificity (89.9%) keeps false-positive referral rates low. Tight bootstrap confidence intervals confirm classifier stability across the full 237K-patient cohort.

Economic Model

NLP-Enabled + DMT shifts 35.8% of patients 1.05 years upstream into the SCI state (utility 0.865; cost $14K/yr), compressing late-stage disease by 12% relative to SOC. Time-in-state breakdown by scenario available as supplemental Figure 3.

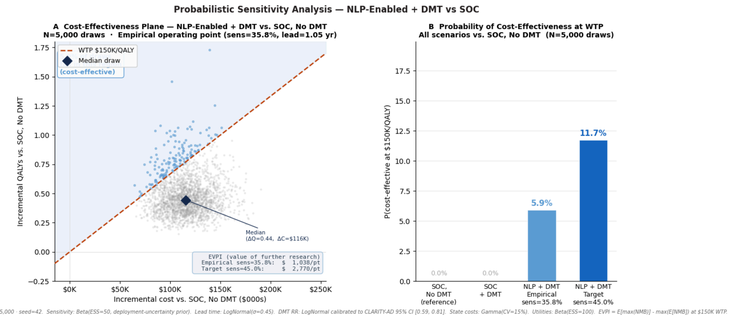
Table 2. Three-Scenario Economic Summary (Base Case)

Scenario	Life-Yrs	Disc. QALYs	Lifetime Cost	ICER vs. SOC, No DMT
SOC, No DMT	8.06	4.94	$198,012	Reference
SOC + DMT	8.34	5.17	$315,332	$515,731/QALY
NLP-Enabled + DMT	9.07	5.38	$314,162	$262,234/QALY

ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life Year. Screening + BBM: $81/patient. Discount rate 3%. Societal perspective.

NLP-Enabled+DMT is simultaneously cheaper and more effective than SOC+DMT – a near-dominant result. The same DMT works harder when started at SCI rather than MCI, cutting the ICER by 49% ($516K → $262K/QALY) and adding a full life-year (8.06 → 9.07 yrs) at essentially identical total spend.

Probabilistic Sensitivity (PSA)



PSA: N=5,000 · seed=42. Sensitivity: Beta(ESS=50, deployment-uncertainty prior). Lead time: LogNormal(σ=0.45). DMT RR: LogNormal calibrated to CLARITY-AD 95% CI [0.59, 0.81]. State costs: Gamma(CV=15%). Utilities: Beta(ESS=100). EVPI = E[max(NMB)] - max(E[NMB]) at $150K WTP.

Figure 4. PSA: Cost-Effectiveness (CE) Plane and P(CE) Bar Chart (N=5,000 draws, seed=42). Left: incremental CE plane (NLP+DMT vs. SOC, No DMT) with shaded CE region and WTP slope. Right: P(cost-effective at $150K WTP) by scenario.

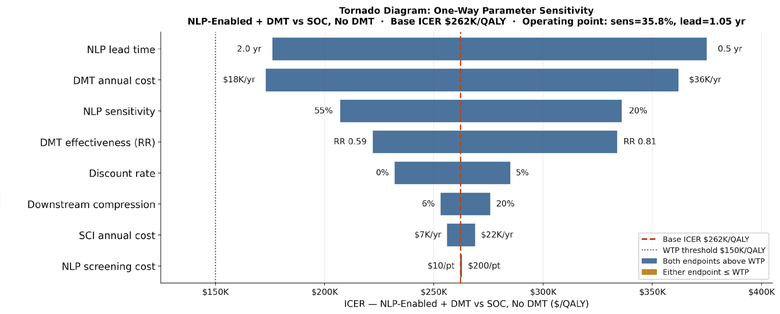
Table 3. Probabilistic Sensitivity Analysis

Metric	Empirical (sens=35.8%)	Target (sens=45%)
P(NLP+DMT CE at $150K WTP)	5.6%	11.6%
P(SOC+DMT CE at $150K WTP)	0.0%	0.0%
Median ΔQALY (NLP+DMT vs SOC)	0.443	0.497
Median ΔCost (NLP+DMT vs SOC)	$115,560	$115,151
EVPI (per patient at WTP)	$1,045	$2,751

SOC+DMT is never cost-effective at $150K WTP. NLP+DMT's probability of CE nearly doubles (5.6% → 11.6%) with a 9-point sensitivity gain – and EVPI more than doubles ($1,045 → $2,751 per patient), quantifying the return to improving the classifier.

SENSITIVITY ANALYSIS

One-Way (Tornado)



NLP screening cost: $50/pt base case (range $10–$200/pt); ICER shift <$1K — immaterial vs. DMT cost ($26.5K/yr). NLP-Enabled + DMT vs SOC, No DMT; sens=35.8%, lead=1.05 yr, compression=12%.

Figure 5. Tornado Diagram: One-Way Parameter Sensitivity. NLP-Enabled+DMT vs. SOC, No DMT. Base ICER $262,234/QALY. WTP $150K/QALY dashed. Lead time and DMT cost drive the widest ICER ranges. NLP screening cost ($50/pt base; range $10–$200/pt) shifts ICER by <$1K and is immaterial vs. DMT cost ($26.5K/yr).

Full one-way parameter sensitivity ranges available as Supplemental Table S4.

Table 4. Conditions for NLP+DMT Cost-Effectiveness at $150K/QALY WTP

Pathway	Required Value	vs. Current ($26,500/yr, 1.05 yr)
DMT price reduction alone	≤$15,793/yr	−40% of current
Lead-time extension alone	≥2.54 yr	2.4× empirical
Joint (illustrative)	~$20K/yr + ~1.8 yr	−25% price + 1.7× lead time

CONCLUSION & OUTLOOK

This analysis establishes that routine EHR language carries a measurable, economically meaningful AD staging signal that current care systematically ignores. NLP-enabled early detection cuts the ICER by 49% ($516K → $262K/QALY); NLP+DMT is simultaneously cheaper and more effective than SOC+DMT. Cost-effectiveness at $150K WTP is within reach: a 40% DMT price reduction or 2.4× lead-time improvement suffices (Table 5). As payers and the Centers for Medicare & Medicaid Services (CMS) develop coverage frameworks for approved DMTs, the defining gap is not efficacy but who gets identified, when, and at what cost. The SiteRx Data Platform is positioned to anchor that answer – through multi-site validation, embeddings-based classifier refinement, and biomarker-coupled screening – in partnership with DMT manufacturers, plasma biomarker platforms, and payers evaluating upstream AD coverage. As NLP-enabled early detection moves from research to routine practice, stakeholders who build adaptive partnerships now will be best positioned to capture clinical and economic value of intervening earlier across the AD continuum.

REFERENCES

1. Institute for Clinical and Economic Review. Lecanemab for Early Alzheimer's Disease: Effectiveness and Value. Final Evidence Report. April 2023.
2. Tahami Monfared AA, et al. A path to improved Alzheimer's care. Neurol Ther. 2023;12(3):863–881.
3. Handels R, et al. New IPECAD open-source model framework for the health technology assessment of early Alzheimer's disease treatment. Value Health. 2025;28(4):511–518.
4. Green C, et al. Assessing cost-effectiveness of early intervention in Alzheimer's disease: An open-source modeling framework. Alzheimers Dement. 2019;15(10):1309–1321.
5. Harkema H, et al. ConText: negation detection algorithm. J Biomed Inform. 2009;42(5):839–851.
6. van Dyck CH, et al. Lecanemab in Early Alzheimer's Disease (CLARITY-AD). N Engl J Med. 2023;388(1):9–21.
7. Aye S, et al. Optimising Alzheimer's disease diagnosis and treatment. J Prev Alzheimers Dis. 2024;11:928–942.
8. Jack CR Jr, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535–562.

Disclosures: Dooley J and Gautieri D are employees of SiteRx. No external funding declared.

Jackson Dooley, Sr. Commercial Strategy Analyst, SiteRx | jdooley@siterx.com **Daniel Gautieri, VP of Data & Strategy Services, SiteRx** | daniel@siterx.com

PLEASE VISIT OUR SITE ON SUPPLEMENTAL FOR MORE ABOUT SITERX AND THESE FIGURES.