

Calibrating a POINTER-Referenced Cognitive Slope Effect to Conversion Risk Across Cohorts: A Joint Modeling Analysis

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KEY TAKEAWAY: A POINTER-referenced cognitive-slope benchmark (+0.029 SD/year) was used to illustrate a framework for translating cognitive-slope differences into clinically interpretable progression-risk metrics. Resulting estimates varied across cohorts, modeling assumptions, and biomarker/genotype enrichment groups

INTRODUCTION

U.S. POINTER reported a more favorable annual rate of global cognitive change for a structured multidomain lifestyle intervention relative to a self-guided program. However, a standardized cognitive-slope difference is difficult to interpret for clinicians and policy makers.

Objective
To develop and illustrate a framework for translating a published cognitive-slope benchmark into clinically interpretable progression-risk metrics in external cohorts.

Study design

External-cohort translation analysis using ADNI, A4, and LEARN. No lifestyle intervention was administered in these cohorts; the analysis explored how a hypothetical POINTER-sized slope shift could map onto clinical outcomes under explicit modeling assumptions.

POINTER benchmark
Counterfactual slope shift: +0.029 SD/year in cohort-standardized mPACC/PACC-compatible cognition.

Workflow schematic

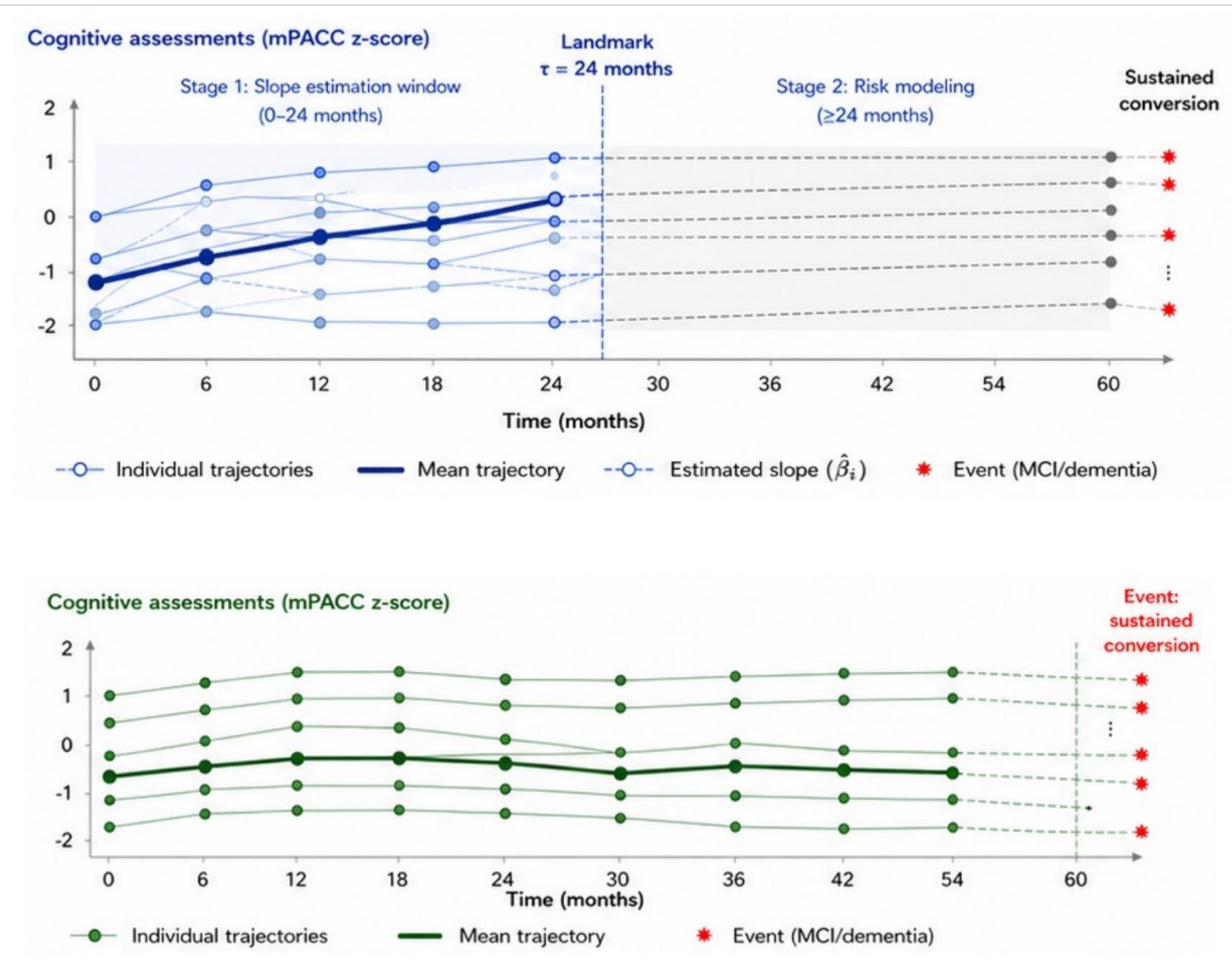


Figure 1. Landmark analysis uses early slope; joint modeling uses repeated trajectories & event time jointly.

Outcome

Clinical endpoint was sustained conversion to MCI or dementia, defined as the first diagnostic change confirmed at the subsequent visit. Cognitive endpoint was cohort-standardized mPACC/PACC-compatible score.

METHODS

Analytic frameworks

Framework	Risk set / data use	Clinical interpretation
Landmark Cox	CN at Month 24; 0-24 mo slope	Transparent early-change estimand
Joint model	CN at baseline; repeated measures to Month 84	Latent slope linked to event risk

A4 landmark caution
A4 landmark sample was small (124 participants); 123 entered through the Month 12 to <24 fallback window rather than a true Month 24-36 visit.

Cohort risk structure

Cohort	Baseline CN N/events	Joint N/events	Amyloid+
ADNI	540 / 86	486 / 86	44.8%
A4	1169 / 410	1064 / 410	95.1%
LEARN	538 / 87	505 / 87	0.8%

A4 and LEARN represent contrasting amyloid-risk settings. ADNI contains both amyloid-positive and amyloid-negative participants and was therefore used for subgroup and economic scenario analysis.

Primary translated measures

For each cohort and framework, the observed-slope scenario was compared with a shifted-slope scenario in which individual cognitive slope was hypothetically shifted by +0.029 SD/year. Measures included HR, 5-year risk difference (RD), translated model-based number needed to treat (NNT), and 5-year restricted mean survival time (RMST) difference. NNT represents a translated model-based metric, not a directly observed treatment effect.

ADNI economic threshold analysis

Economic analyses were scenario-based threshold calculations, not within-trial economic evaluations. Base incremental 2-year delivery cost was \$400/person; sensitivity scenarios used \$600 and \$800. WTP thresholds were \$100,000 and \$150,000 per case prevented.

ADNI subgroups: overall, APOE4+, amyloid+, and APOE4+ & amyloid+.

RESULTS

Cohort-level clinical translation

Cohort	Model	HR	5-year RD	NNT	RMST
ADNI	Landmark	0.972	0.31 pp	322.9	0.062 mo
ADNI	Joint	0.831	1.26 pp	79.1	0.297 mo
A4	Landmark	0.998	0.06 pp	1755.6	0.013 mo
A4	Joint	0.917	3.04 pp	32.9	1.242 mo
LEARN	Landmark	0.996	0.08 pp	1282.3	0.020 mo
LEARN	Joint	0.833	2.25 pp	44.5	0.617 mo

Joint ADNI	Joint A4	Joint LEARN
1.26 pp	3.04 pp	2.25 pp
NNT 79.1; RMST +0.297 mo	NNT 32.9; RMST +1.242 mo	NNT 44.5; RMST +0.617 mo

Landmark estimates were small, especially in A4 and LEARN. Joint models yielded directionally consistent translated estimates, although the translated individual-level delays remained modest.

ADNI subgroup translation

ADNI group	Joint HR	5-year RD	NNT	RMST
Overall	0.831	1.26 pp	79.1	0.297 mo
APOE4+	0.831	1.95 pp	51.2	0.488 mo
Amyloid+	0.816	1.70 pp	58.8	0.395 mo
APOE4+ & amyloid+	0.775	2.65 pp	37.7	0.723 mo

Highest-risk ADNI subgroup

The APOE4+ & amyloid+ subgroup showed the largest translated estimates: RD 2.65 percentage points, NNT 37.7, and RMST +0.723 months.

Target-population sensitivity

ADNI analysis	HR	RD	NNT	RMST
Main joint	0.831	1.26 pp	79.1	0.297 mo
POINTER-weighted joint	0.877	0.86 pp	116.0	0.241 mo

Reweighting ADNI toward published U.S. POINTER parent-trial marginals attenuated, but did not reverse, the translated estimates.

ECONOMIC TRANSLATION

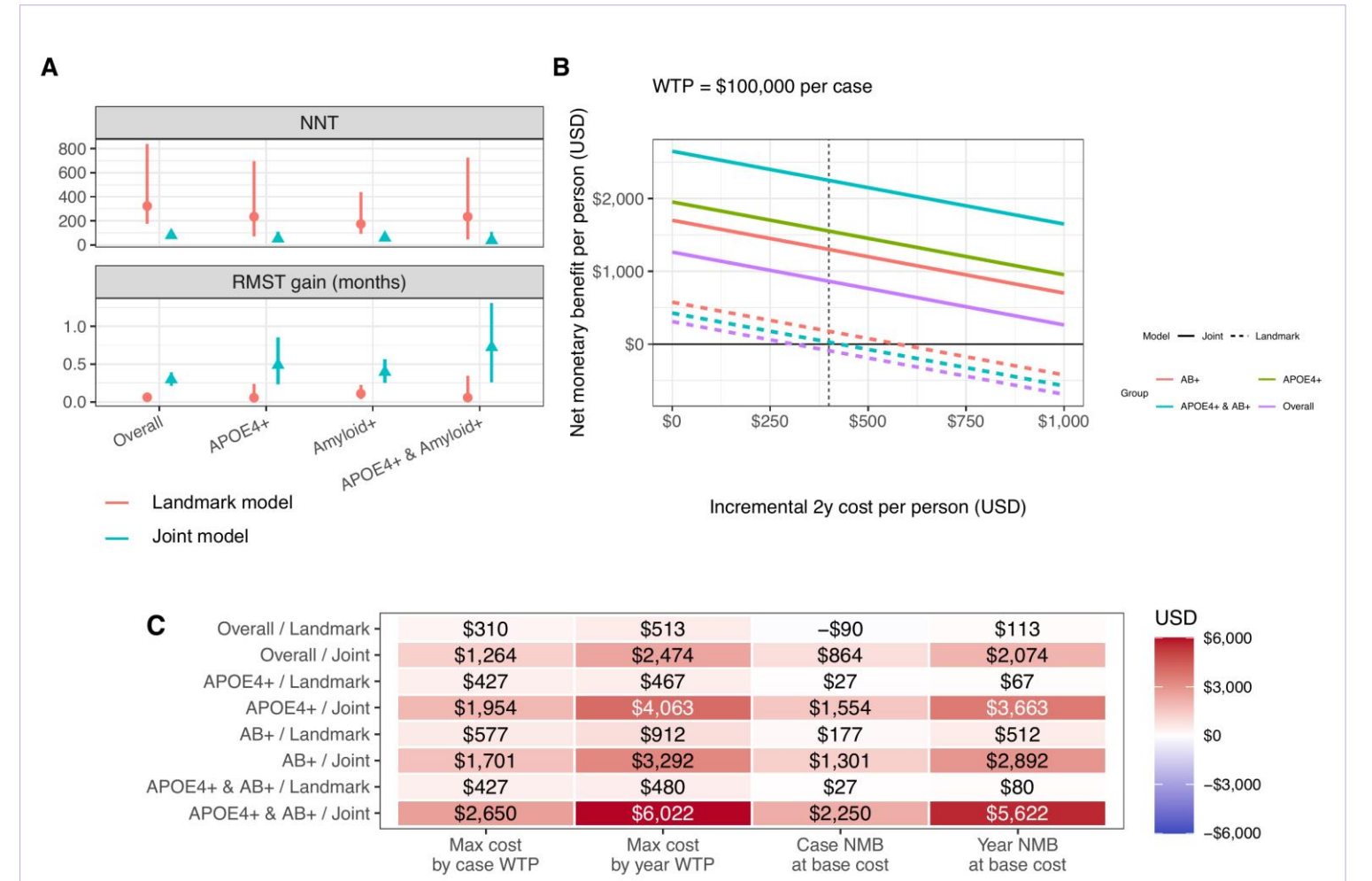


Figure 2. ADNI subgroup clinical translation and threshold-based net monetary benefit.

Scenario-based economic summaries

Joint-model group	Max cost by case WTP	Case NMB at \$400
Overall	\$1,264	+\$864
APOE4+	\$1,954	+\$1,554
Amyloid+	\$1,701	+\$1,301
APOE4+ & amyloid+	\$2,650	+\$2,250

All joint-model ADNI groups produced NMB estimates above zero under the assumed cost and willingness-to-pay threshold scenarios. The largest threshold margin was observed in the APOE4+ & amyloid+ group.

CONCLUSIONS

- 1. Translation framework**
This study demonstrates a framework for translating cognitive-slope differences into clinically interpretable progression-risk metrics.
- 2. Cohort and model sensitivity**
Resulting estimates were sensitive to cohort characteristics and modeling assumptions.
- 3. Enrichment and risk structure**
Biomarker and genetic enrichment influenced the magnitude of translated metrics.
- 4. Counterfactual interpretation**
These findings represent counterfactual model-based translations rather than direct evidence of intervention effects.

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