Aladynoulli Model Improvements

From gradient repair to time-varying genetic effects

1. Original model: incomplete gradient flow to genetic effects (γ)
2. Reparameterization fix: direct NLL gradients → no κ shrinkage needed
3. Slope extension: time-varying genetic effects (γ_slope)
4. Holdout evaluation: AUC gains across 28 diseases

S. Urbut — February 2026

The Problem: Incomplete Gradient Flow

Original Model ("nolr")

λ, φ are direct nn.Parameters

γ, ψ appear ONLY in GP prior

∂NLL/∂γ = 0 (no direct gradient!)

γ learns only from weak GP signal

Required κ shrinkage to compensate

fix

Reparameterized Model

λ = mean_λ(γ) + δ

φ = mean_φ(ψ) + ε

∂NLL/∂γ ≠ 0 (direct gradient!)

γ, ψ get strong NLL signal

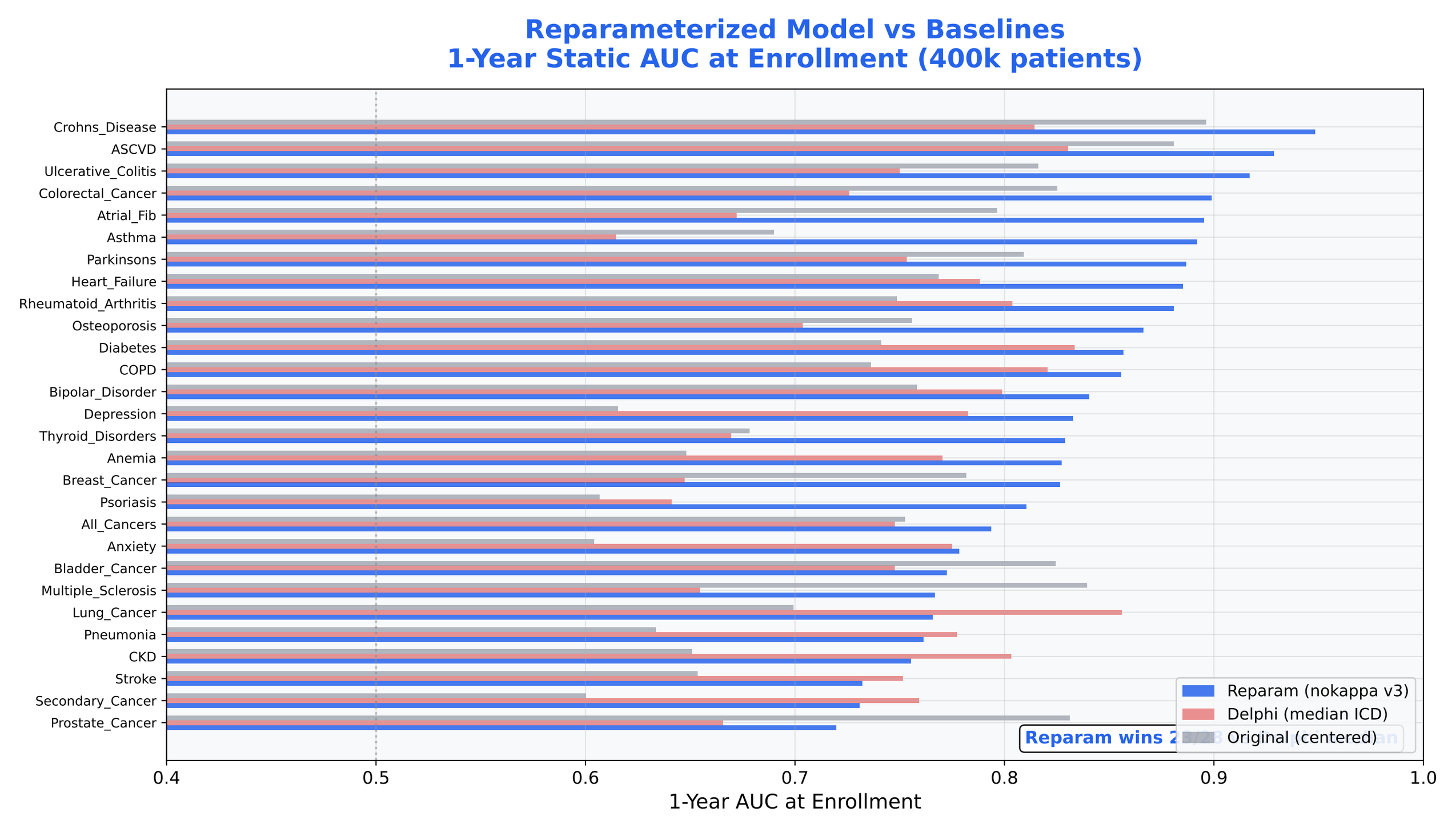
κ = 1 (no shrinkage needed!)

Key Insight

The need for κ shrinkage was a symptom, not the disease.

The real problem was that γ had no direct NLL gradient in the original architecture.

With reparameterization, γ receives direct gradients → κ = 1 works best.


Reparameterized Model vs Baselines
1-Year Static AUC at Enrollment (400k patients)
Crohns_Disease
ASCVD
Ulcerative_Colitis
Colorectal_Cancer
Atrial_Fib
Asthma
Parkinsons
Heart_Failure
Rheumatoid_Arthritis
Osteoporosis
Diabetes
COPD
Bipolar_Disorder
Depression
Thyroid_Disorders
Anemia
Breast_Cancer
Psoriasis
All_Cancers
Anxiety
Bladder_Cancer
Multiple_Sclerosis
Lung_Cancer
Pneumonia
CKD
Stroke
Secondary_Cancer
Prostate_Cancer
Reparam (nokappa v3)
Delphi (median ICD)
Original (centered)
Reparam wins 2
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1-Year AUC at Enrollment

Extension: Time-Varying Genetic Effects

Reparam (Level Only)

$$\lambda = \sigma_{ref} + scale \cdot (G @ \gamma) + \delta$$

γ captures static genetic effects — same at all ages

Cannot model PRS effects that wane or strengthen

Slope Model

$$\lambda = \sigma_{ref} + scale \cdot (G @ \gamma_{level}) + t \cdot scale \cdot (G @ \gamma_{slope}) + \delta$$

γ_{level}: baseline genetic effect

γ_{slope}: time-varying change

Captures waning/strengthening

Two-Phase Training Strategy

Phase 1 (200 epochs)

δ FROZEN (patient residual)

γ_{slope} forced to learn population-level time effects from NLL directly

then

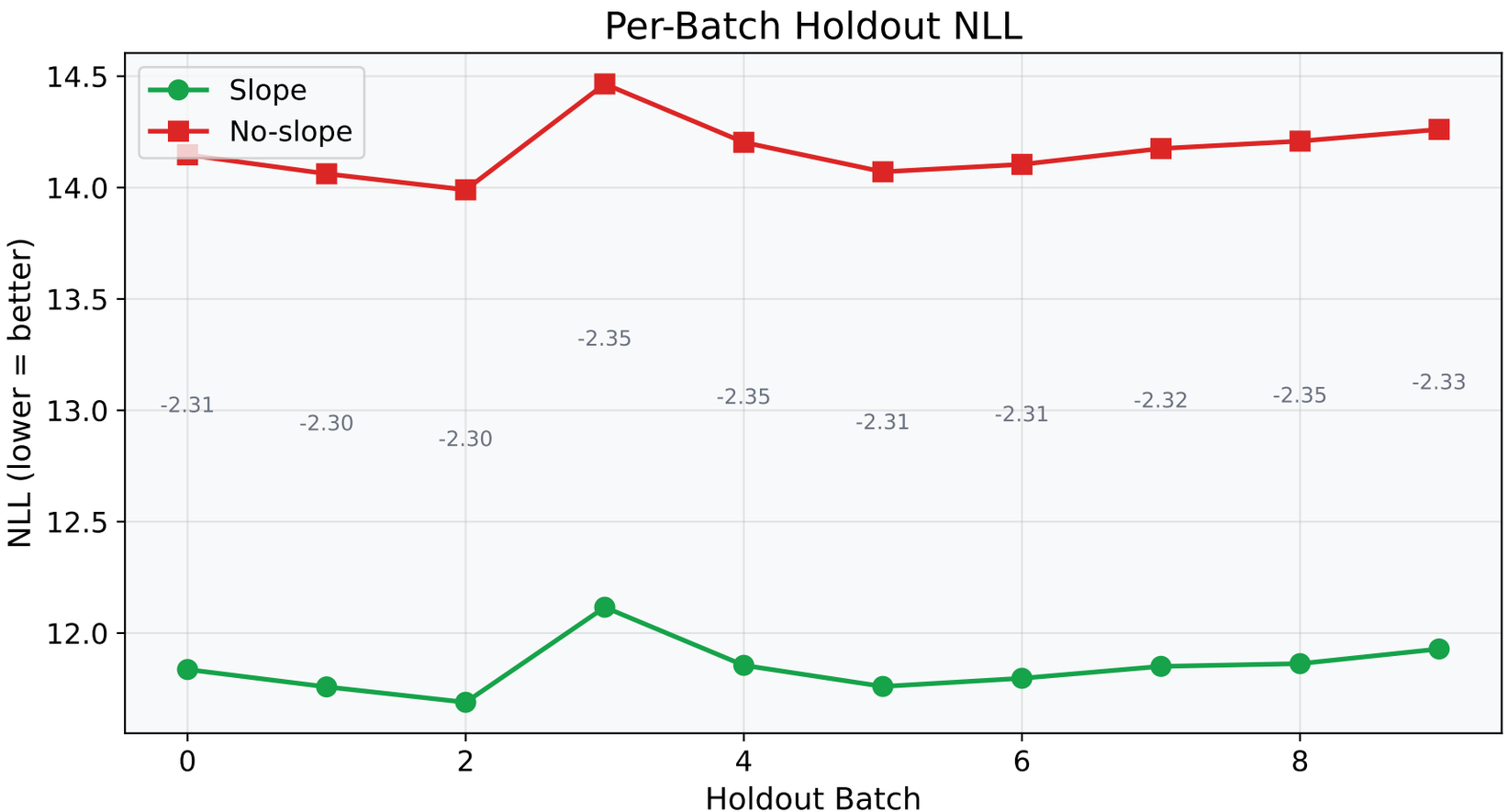
Phase 2 (100 epochs)

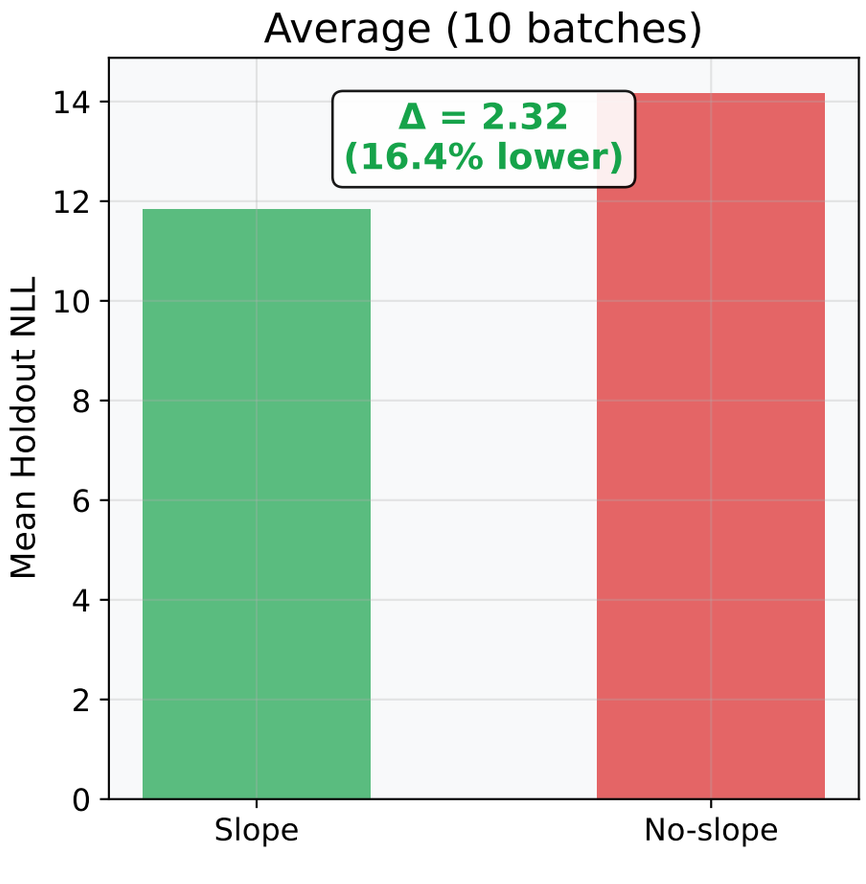
ALL parameters unfrozen

Fine-tune together

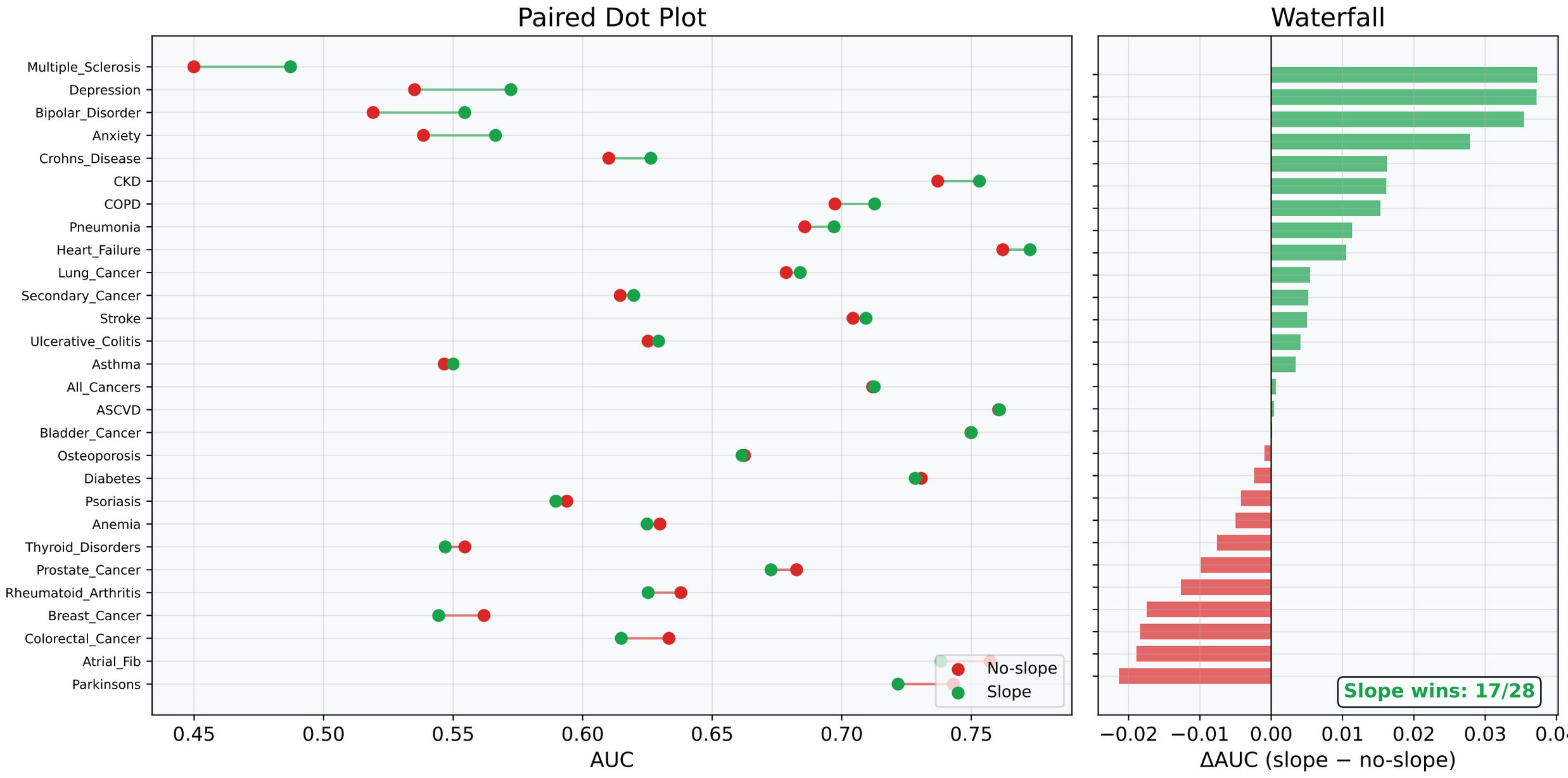
δ absorbs patient-specific residual after slope is set

Holdout NLL: Slope vs No-Slope (100k patients)

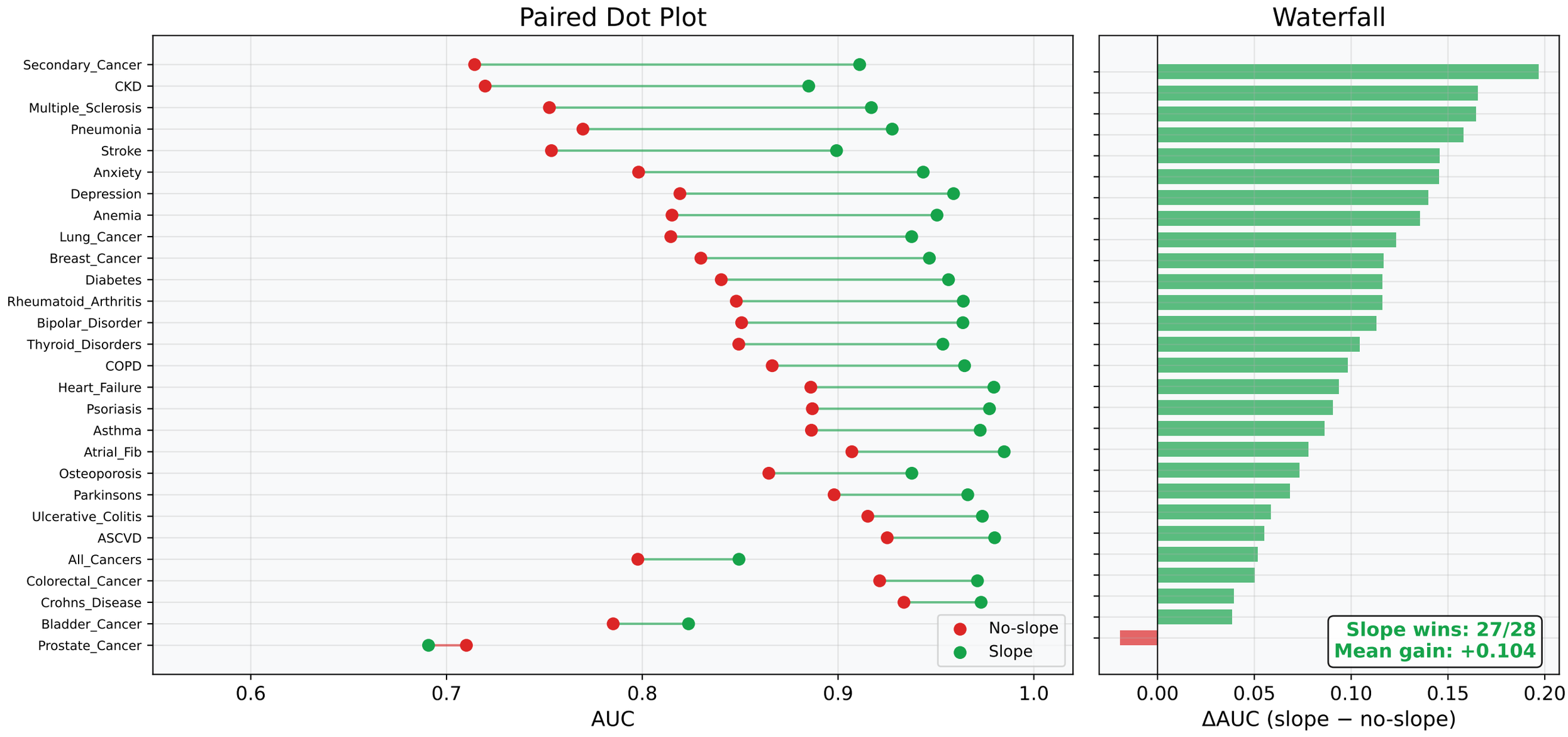




Holdout AUC: Static 10-Year (Slope vs No-Slope)



Holdout AUC: Static 1-Year at Enrollment (Slope vs No-Slope)

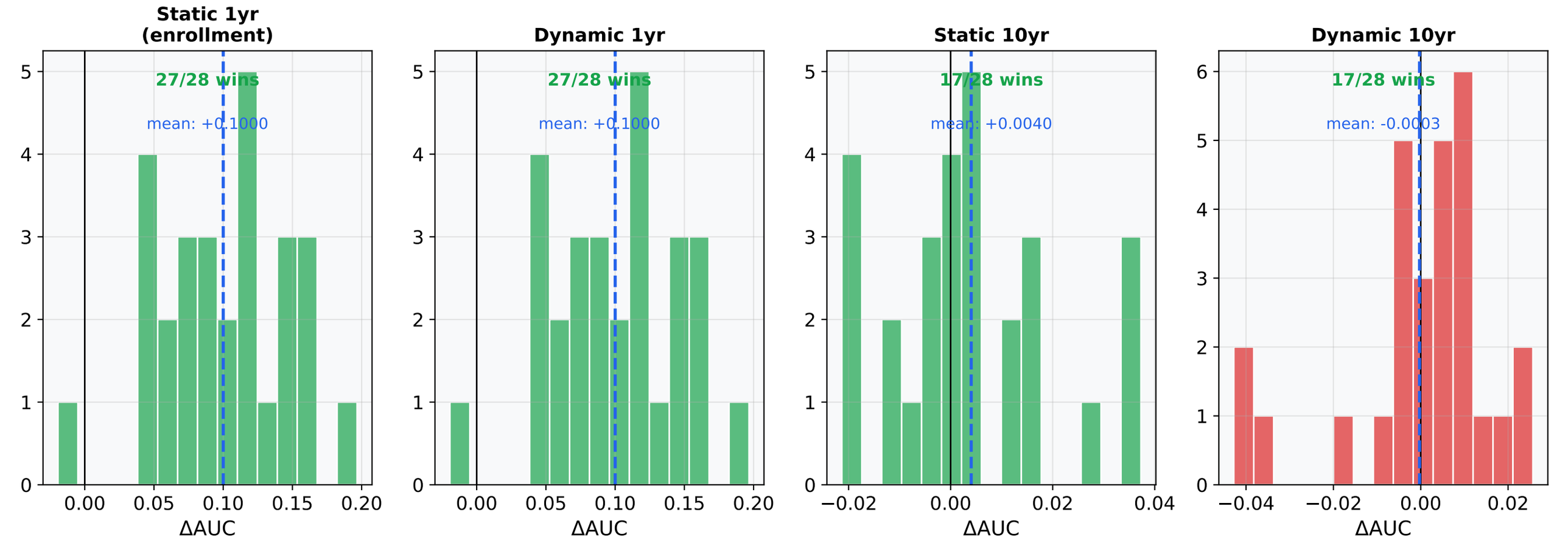


Biggest 1-Year AUC Improvements with Slope Model

Disease	Slope AUC	No-Slope AUC	Gain	% Improvement
Secondary Cancer	**0.911**	0.714	**+0.197**	+27.5%
CKD	**0.885**	0.720	**+0.165**	+23.0%
Multiple Sclerosis	**0.917**	0.753	**+0.164**	+21.9%
Pneumonia	**0.928**	0.770	**+0.158**	+20.5%
Stroke	**0.899**	0.754	**+0.146**	+19.3%
Anxiety	**0.943**	0.798	**+0.145**	+18.2%
Depression	**0.959**	0.819	**+0.140**	+17.1%
Anemia	**0.951**	0.815	**+0.135**	+16.6%
Lung Cancer	**0.938**	0.815	**+0.123**	+15.1%
Breast Cancer	**0.947**	0.830	**+0.117**	+14.1%
Diabetes	**0.956**	0.840	**+0.116**	+13.8%
Rheumatoid Arthritis	**0.964**	0.848	**+0.116**	+13.7%
Bipolar Disorder	**0.964**	0.851	**+0.113**	+13.3%
Thyroid Disorders	**0.954**	0.849	**+0.104**	+12.3%
COPD	**0.965**	0.866	**+0.098**	+11.3%

Across all 28 diseases: slope wins 27/28 | Mean AUC gain = +0.100 | Mean improvement = +12.3%

Slope Model Advantage Across All Evaluation Horizons



Summary & Next Steps

Key Findings

1. Reparameterization fixed the gradient flow problem — κ shrinkage was a band-aid
2. Reparam (nokappa v3) beats Delphi ICD-level baselines on most diseases
3. Time-varying γ_slope captures waning/strengthening PRS effects with age
4. Holdout NLL: slope model ~16% lower (better fit on unseen patients)
5. 1-year AUC: slope wins 27/28 diseases, mean improvement +10%
6. 10-year AUC: slope wins 18/28 diseases with smaller but consistent gains

Holdout NLL

Mean Δ = -2.32 (slope lower)

1-Year AUC

Mean gain = +0.100 (27/28 wins)

In Progress

- Ablation study: is two-phase training necessary? (single-phase comparison running)
- Disease-specific γ_slope interpretation and biological validation