ALADYNOULLI: A Bayesian Framework for Genomic Discovery and Clinical Prediction

Disease Signatures, Individual Trajectories, and Drug Discovery

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Outline

1. **The problem**: Disease complexity across 348 conditions over a lifetime
2. **The model**: `ALADYNOULLI` — signatures, trajectories, genetics
3. **Identifiability**: Non-centered parameterization for genetic effects
4. **Discovery**: Consistent signatures across 3 biobanks (700K+ patients)
5. **Heterogeneity**: Different pathways to the same diagnosis
6. **Genetics**: 151 GWAS loci, rare variants, heritability
7. **Prediction**: Rigorous LOO framework, outperforming established scores
8. **Applications**: Patient stratification, trial design, drug targets

The Problem: Disease Doesn’t Happen in Isolation

A real patient’s journey:

- Rheumatoid arthritis at age 45
- Hypertension at 48
- Myocardial infarction at 52

Traditional approaches:

- Treat each disease in isolation
- Miss the underlying metabolic-inflammatory process
- Separate risk models for each condition
- Cannot share information across related diseases

What we need:

- Model **all 348 diseases** jointly
- Capture **temporal dynamics** across the lifespan
- Integrate **genetics** directly
- Share information across **related conditions**
- Provide **interpretable** biological structure
- **Predict** future disease risk

The Model: ALADYNOULLI

Core equation — mixture of probabilities:

$$\pi_{idt} = \sum_{k=1}^{K} \underbrace{\theta_{ikt}}_{\text{individual loading}} \cdot \underbrace{\text{sigmoid}(\phi_{kdt})}_{\text{signature-disease association}}$$

Individual trajectories $(\lambda \to \theta)$:

$$\lambda_{ik} \sim \mathcal{GP}\left(r_k + \mathbf{g}_i^\top \Gamma_k,\ \Omega_\lambda\right)$$

- $\mathbf{g}_i$: 36 PRS + sex + 10 PCs
- Γ_k: genetic effects on signature k
- Ω_λ: temporal smoothness

Disease signatures (ϕ):

$$\phi_{kd} \sim \mathcal{GP}(\mu_d + \psi_{kd},\ \Omega_\phi)$$

- μ_d: population baseline prevalence
- ψ_{kd}: signature-disease strength
- Ω_ϕ: temporal smoothness

Key: Diseases conditionally independent given signatures — correlations mediated through shared biology.

Ensuring Identifiable Genetic Effects

The identifiability challenge:

In the standard formulation, λ_{ikt} is a free parameter that directly enters the likelihood. The optimizer fits data by adjusting λ directly, so Γ_k receives only weak gradient signal through the GP prior (scaled by $W = 10^{-4}$).

Non-centered (reparameterized) formulation:

$$\lambda_{ikt} = \underbrace{r_k + \mathbf{g}_i^\top \Gamma_k}_{\text{genetic mean}} + \underbrace{\delta_{ikt}}_{\text{residual}}$$

- δ (not λ) carries the GP prior
- Γ_k now flows through the NLL via chain rule
- κ fixed at 1 (not jointly identifiable

Simulation evidence (N=1000, D=50, K=5):

	Centered	**Non-centered**
γ recovery (r)	0.80	**0.95**
γ gradient norm	$\sim$0.01	$\sim$0.5
κ behavior	drifts	fixed $= 1$

Key insight: In the centered model, only $\kappa \cdot \Gamma$ enters the likelihood, so κ and Γ trade off. Fixing $\kappa = 1$ and reparameterizing resolves this.

Both models fit the data equally well (same NLL); the difference is in γ recovery

ALADYNOULLI vs. Traditional Approaches

Feature	**Traditional / Topic Models**	ALADYNOULLI
Diseases modeled	1 at a time	**348 jointly**
Temporal dynamics	Static snapshot	**Age-varying GP**
Genetic integration	Post-hoc	**In the model**
Prediction type	Retrospective	**Prospective**
Rare diseases	Insufficient data	**Borrows strength**
Patient description	Risk score (1 number)	**Signature profile**
Bias correction	None	**IPW via likelihood**
Data required	Labs, biomarkers	**ICD codes only**

Simulation: Parameter Recovery

Synthetic data:

- $N = 10{,}000$ individuals, $D = 20$ diseases
- $T = 50$ time points (ages 30–79), $K = 5$ signatures
- $P = 5$ genetic covariates
- Ground truth Γ_k, ϕ_{kd}, ψ_{kd} known

Recovery results:

- Signature composition: **ARI = 0.843**, **NMI = 0.943**
- Temporal trajectories accurately reconstructed
- Genetic effects recovered

The model recovers ground truth structure from realistic synthetic data

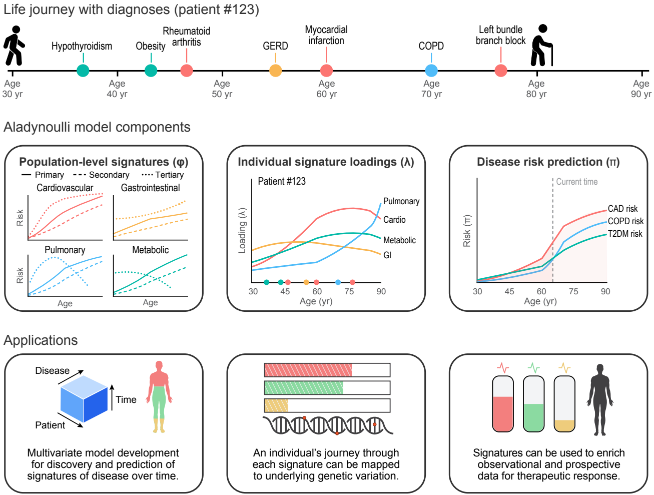
What is learned vs. fixed at prediction:

Parameter	Discovery	Prediction
ϕ_{kdt} (signatures)	Learned	**Fixed**
ψ_{kd} (offsets)	Learned	**Fixed**
Γ_k (genetics)	Learned	**Fixed**
κ (calibration)	Fixed $= 1$	Fixed $= 1$
δ_{ikt} (individual)	Learned	**Learned**

$$\lambda_{ikt} = r_k + \mathbf{g}_i^\top \Gamma_k + \delta_{ikt}$$

Only individual residuals (δ) are fit at prediction time — population biology is frozen from training.

Model Overview



Life journey with diagnoses (patient #123)

Aladynoulli model components

Population-level signatures (φ)

Individual signature loadings (Λ)

Disease risk prediction (π)

Applications

Multivariate model development for discovery and prediction of signatures of disease over time.

An individual's journey through each signature can be mapped to underlying genetic variation.

Signatures can be used to enrich observational and prospective data for therapeutic response.

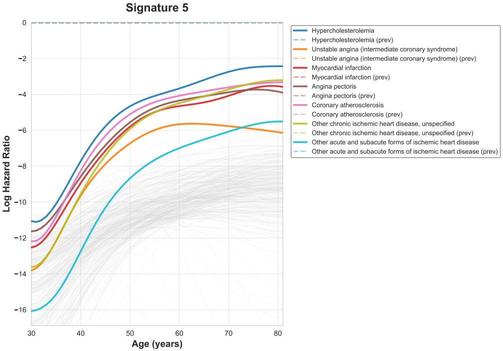
Top: Patient timeline. *Middle:* Signatures (ϕ), loadings (θ), risk (π). *Bottom:* Applications.

Three Independent Biobanks

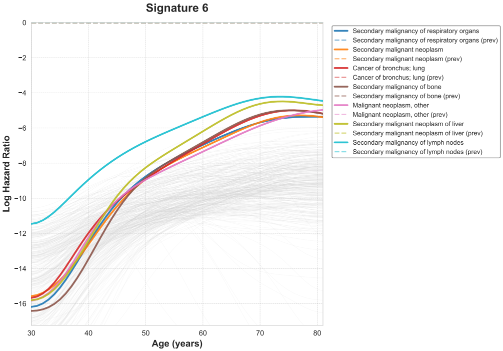
	UK Biobank	Mass General Brigham	All of Us
N	427,239	48,069	208,263
Follow-up	Up to 52 years	∼30 years	∼6 years
EHR from	∼1980	∼1990	∼2018
Country	UK	USA (Boston)	USA (national)
Diseases	348	346	348
Genetics	Array + imputed	Array	WGS + array

Despite different populations, healthcare systems, and data collection — signatures are remarkably consistent.

Disease Signatures: Temporal Patterns



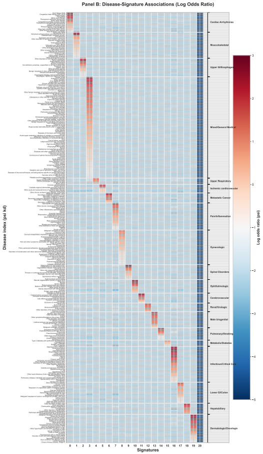
Ischemic Cardiovascular (Sig 5)

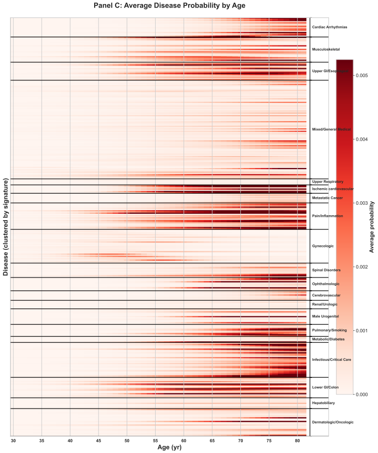


Metastatic Cancer (Sig 6)

Age-dependent log hazard ratios (ϕ_{kdt}) for diseases within each signature. Each line $=$ one disease. UKB, pooled across 40 batches.

Disease–Signature Associations (ψ) and Predicted Hazards





ψ_{kd}: Signature–disease association strength

Predicted age-specific disease hazards ($\bar{\pi}$)

348 diseases × 21 signatures. Diseases ordered by primary signature assignment.

21 Disease Signatures — Clinically Interpretable

Example signatures:

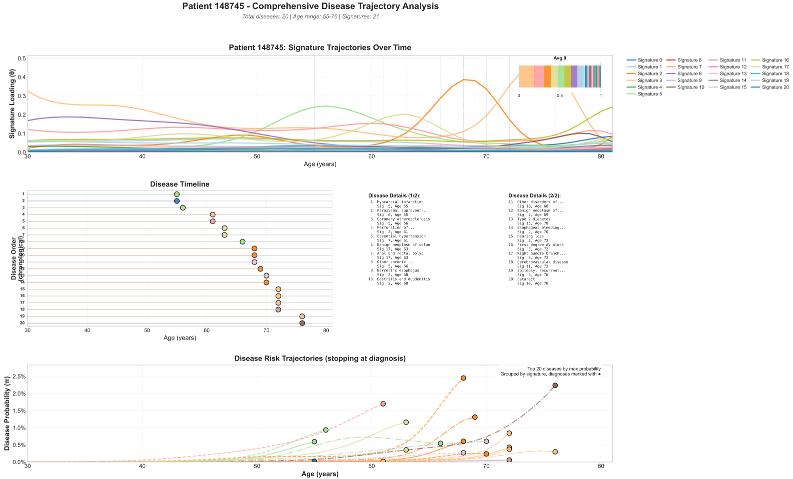
- **Sig 5**: Ischemic cardiovascular (CAD, MI, hyperlipidemia)
- **Sig 6**: Metastatic cancer
- **Sig 15**: Metabolic/diabetes
- **Sig 7**: Pain/inflammatory/metabolic
- **Sig 8**: Gynecologic
- **Sig 14**: Pulmonary/smoking
- **Sig 21**: Health (low-incidence across conditions)

Cross-biobank consistency:

- Median composition preservation: **80%**
- UKB–MGB: 83.8%
- UKB–AoU: 78.2%
- Temporal patterns replicate across cohorts
- Disease ordering within signatures preserved

→ **These are real biological processes, not statistical artifacts.**

Individual Trajectories: A Real Patient



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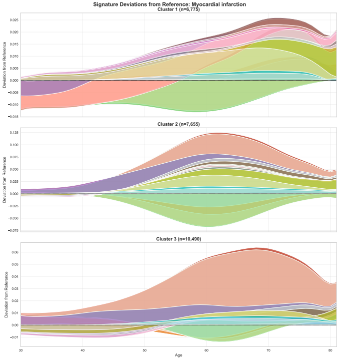
Disease Details (1/2):
 1. Myocardial infarction
    Sig  5, Age 55
 2. Paroxysmal supraventr...
    Sig  0, Age 55
 3. Coronary atherosclerosis
    Sig  5, Age 56
 4. Perforation of...
    Sig  3, Age 61
 5. Essential hypertension
    Sig  7, Age 61
 6. Benign neoplasm of colon
    Sig 17, Age 63
 7. Anal and rectal polyp
    Sig 17, Age 63
 8. Other chronic...
    Sig  5, Age 66
 9. Barrett's esophagus
    Sig  2, Age 68
10. Gastritis and duodenitis
    Sig  2, Age 68
```

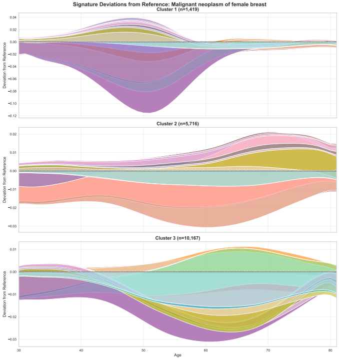
```
Disease Details (2/2):
11. Other disorders of...
    Sig 13, Age 68
12. Benign neoplasm of...
    Sig  2, Age 69
13. Type 2 diabetes
    Sig 15, Age 70
14. Esophageal bleeding...
    Sig  2, Age 70
15. Hearing loss
    Sig  3, Age 72
16. First degree AV block
    Sig  3, Age 72
17. Right bundle branch...
    Sig  3, Age 72
18. Cerebrovascular disease
    Sig 11, Age 72
19. Epilepsy, recurrent...
    Sig  3, Age 76
20. Cataract
    Sig 10, Age 76
```

Patient 148745 (20 diseases, ages 55–76). *Top:* Signature loadings (θ) over time. *Middle:* Disease timeline. *Bottom:* Predicted disease probabilities (π).

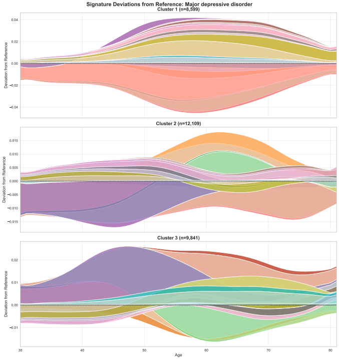
Disease Heterogeneity: Multiple Pathways to the Same Diagnosis



MI clusters



Breast cancer clusters



Depression clusters

Deviations from population reference for 3 patient clusters within each disease.

Same diagnosis, different signature profiles → different biology.

Same Diagnosis, Different Biology

Patients with MI, breast cancer, or depression cluster into distinct subgroups:

Myocardial infarction:

- Early-onset ($\leq$55): higher, faster Sig 5 rise
- Late-onset ($\geq$70): gradual, multi-signature
- Cohen's d up to 2.82 between clusters

Breast cancer:

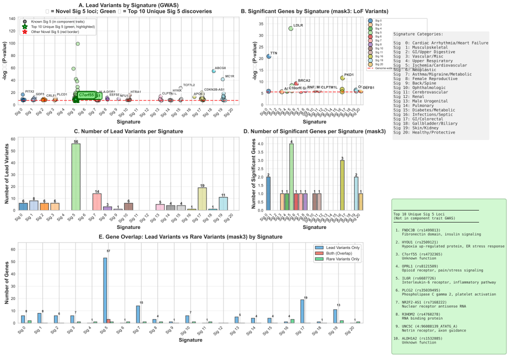
- Gynecologic signature dominant: $C_{1,8}^{\text{SIG}} = 4.25$
- Pain/inflammatory subtype: $C_{2,7}^{\text{SIG}} = 2.53$

Why this matters for drug discovery:

- Different subtypes → different mechanisms
- Different mechanisms → different targets
- **PRS patterns differ** between clusters
- Same drug may work for one subtype but not another
- Trial enrichment: enroll the right biology

$p \leq 1 \times 10^{-8}$ for 95% of cluster comparisons

Genetic Architecture of Disease Signatures



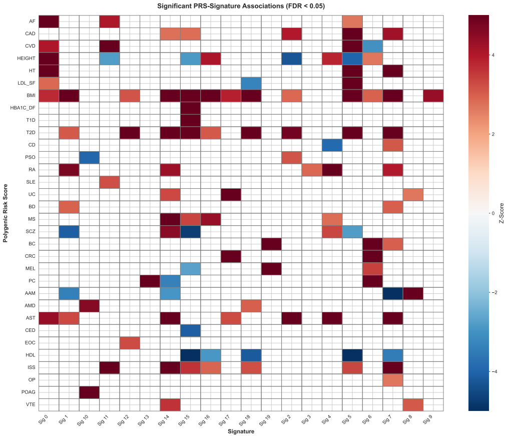
Signature Categories:

Sig 0: Cardiac Arrhythmia/Heart Failure
Sig 1: Musculoskeletal
Sig 2: GI/Upper Digestive
Sig 3: Vascular/Misc
Sig 4: Upper Respiratory
Sig 5: Ischemia/Cardiovascular
Sig 6: Neoplastic
Sig 7: Asthma/Migraine/Metabolic
Sig 8: Female Reproductive
Sig 9: Back/Spine
Sig 10: Ophthalmologic
Sig 11: Cerebrovascular
Sig 12: Renal
Sig 13: Male Urogenital
Sig 14: Pulmonary
Sig 15: Diabetes/Metabolic
Sig 16: Infections/Septic
Sig 17: GI/Colorectal
Sig 18: Gallbladder/Biliary
Sig 19: Skin/Kidney
Sig 20: Healthy/Protective

Top 10 Unique Sig 5 Loci
(Not in component trait GWAS)

1. FNDC3B (rs1499813)
   Fibronectin domain, insulin signaling
2. HYOU1 (rs2509121)
   Hypoxia up-regulated protein, ER stress response
3. C7orf55 (rs4732365)
   Unknown function
4. OPRL1 (rs8121509)
   Opioid receptor, pain/stress signaling
5. IL6R (rs6687726)
   Interleukin-6 receptor, inflammatory pathway
6. PLCG2 (rs35039495)
   Phospholipase C gamma 2, platelet activation
7. NR2F2-AS1 (rs7168222)
   Nuclear receptor antisense RNA
8. R3HDM2 (rs4760278)
   RNA binding protein
9. UNC5C (4:96088139_ATATG_A)
   Netrin receptor, axon guidance
10. ALDH1A2 (rs1532085)
   Unknown function

GWAS lead variants + RVAS genes per signature



Significant PRS–signature associations

151 GWAS loci + 18 rare variant genes across 21 signatures. 116 PRS–signature associations (FDR < 0.05).

Genetic Discovery: Common and Rare Variants

Common variant GWAS:

- **151 genome-wide significant loci** across 21 signatures
- Sig 5 alone: 56 loci (LPA, APOE, PCSK9)
- TCF7L2 → metabolic signature
- GDF5 → musculoskeletal
- HTRA1, CFH → ophthalmologic
- **23 loci in Sig 5 not found** in single-trait GWAS

Rare variant associations:

- 18 unique genes (Bonferroni-corrected)
- *LDLR*, *APOB*, *LPA* → Sig 5
- *TTN* → heart failure ($p = 10^{-21}$)
- *TET2* → critical care/inflammation
- *BRCA2* → Sig 16

Heritability exceeds component diseases:
Sig 5 $h^2 = 0.041$ (observed scale)
vs. MI $h^2 = 0.013$, CAD $h^2 = 0.029$

Joint multi-disease modeling detects pleiotropic effects too weak for single-trait GWAS.

Biological Validation: FH and CHIP Carriers

Familial hypercholesterolemia (FH):

- FH carriers (*LDLR*/*APOB*/*PCSK9*)
- Higher rate of pre-event Sig 5 rise
- OR = 1.63, p = 0.017
- Validates: Sig 5 captures CV risk pathways

Clonal hematopoiesis (CHIP):

- DNMT3A carriers: 1.97-fold enrichment in Sig 16 before leukemia/MDS
- 81.1% rising trajectories vs. 68.5% non-carriers
- TET2 carriers: enriched in Sig 16 before CV and inflammatory outcomes

Signatures capture known biology — independent validation via genetically defined high-risk groups.

PRS–Signature Associations: Genetics Drive Trajectories

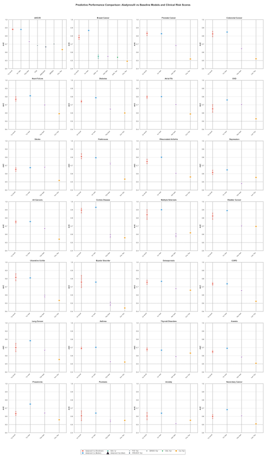
116 significant PRS–signature associations (FDR < 0.05):

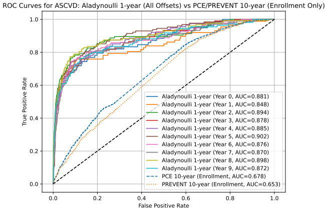
PRS	Signature	γ	Z-score
Coronary artery disease	Sig 5 (Ischemic CV)	0.153	27.2
LDL cholesterol	Sig 5 (Ischemic CV)	0.071	22.7
Type 2 diabetes	Sig 15 (Metabolic)	0.154	58.3

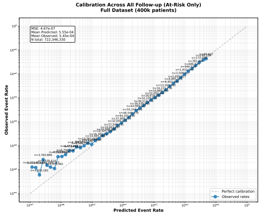
Genetic effects are directly in the model (Γ_k in the GP mean for λ):

- Not post-hoc associations — genetics shape individual trajectories from the start
- Enables genetically-informed risk prediction from birth
- PRS clusters within disease subtypes confirm biological relevance (Fig. 4D)

Predictive Performance Across 28 Diseases







Left: AUC across 28 diseases. *Right:* ASCVD ROC + calibration.

Rigorous Prospective Evaluation Framework

Leave-one-out cross-validation:

- 400K individuals in 40 batches of 10K
- For each batch: pool ϕ, ψ, Γ from the other 39
- Predict on the held-out batch
- **No information leakage**: held-out batch never contributes to pooled parameters

Temporal censoring:

- At each prediction time t, only data up to t is used
- Individual δ re-estimated at each timepoint
- Simulates real clinical deployment

LOO robustness (40 batches):

- LOO vs. full-pool predictions: $r = 0.995$
- Mean AUC difference: ≤ 0.0001
- Maximum AUC difference: ≤ 0.0015
- 99.6–100% within 0.01 AUC threshold

Evaluation at multiple horizons:

- **Dynamic 1-year**: predictions at enrollment $+ 0, 1, \ldots, 9$ years
- **Static 10-year**: single prediction at enrollment
- Each score evaluated at its designed horizon

No single batch dominates — generalizes

Prediction: Outperforming Established Risk Scores

Dynamic 1-year predictions (median AUC):

- ASCVD: **0.879**
- Breast cancer: **0.867**
- Atrial fibrillation: **0.801**
- Heart failure: **0.811**
- Parkinson's: **0.796**
- Diabetes: **0.846**

All via leave-one-out cross-validation, strictly prospective, no temporal leakage.

Head-to-head (each at its designed horizon):

ASCVD	**Horizon**	**AUC**
ALADYNOULLI (dynamic)	1yr	**0.879**
ALADYNOULLI (enrollment)	1yr	0.881
ALADYNOULLI (enrollment)	10yr	0.733
PCE	10yr	0.683
PREVENT	10yr	0.667

Breast Ca.	**Horizon**	**AUC**
ALADYNOULLI (dynamic)	1yr	**0.867**
ALADYNOULLI (enrollment)	1yr	0.782
GAIL	1yr	0.549

Using only ICD codes — no labs, biomarkers, or questionnaires required.

Calibration and Robustness

Calibration:

- MSE $= 4.67 \times 10^{-7}$
- Mean predicted: 5.55×10^{-4}
- Mean observed: 5.45×10^{-4}
- 722M patient-time observations
- Log-log calibration plot shows tight alignment

Robustness checks:

- **Reverse causation**: excluding 1–6 months of pre-enrollment events → AUC drop $<$1%
- **Washout periods**: 1–2 year washouts maintain strong performance
- **IPW**: UK Biobank participation bias corrected; ϕ correlation > 0.999
- **High-risk subgroups**: RA patients 0.694, BC patients 0.689 for 10yr ASCVD

Applications for Drug Discovery

1. **Patient stratification for trials:**
   - Signature profiles identify **biological subtypes**
   - Enroll patients with the **right mechanism**
   - Reduce heterogeneity → larger treatment effects
2. **Novel target identification:**
   - 23 loci in Sig 5 missed by single-trait GWAS
   - Candidates: *WWP2*, *C1S*, *HYOU1*, *EHBP1*
   - Rare variants pinpoint causal genes
3. **Dynamic biological profiling:**
   - Signature loadings update with new diagnoses
   - Real-time biological patient state
   - Monitor treatment response via trajectory changes
4. **Digital twin matching:**
   - Match patients by **shared biology**, not diagnosis
   - MI via inflammatory pathway $\neq$ MI via lipid pathway
5. **Drug repurposing:**
   - Signatures shared across diseases → repositioning
   - 348 diseases: side effect profiles built in

Practical: Fast, Deployable, Interpretable

Transfer learning:

- Fix population parameters (ϕ, ψ, γ; $\kappa = 1$) from UKB training
- Fit only individual δ (residual trajectories) for new patients
- **0.05 seconds per patient**
- 10,000 patients in 8 minutes
- No retraining needed for new cohorts

Data requirements:

- **Only ICD codes** from standard EHR
- No labs, biomarkers, or questionnaires
- Works across healthcare systems (UK, US)

Interpretability:

- Every prediction decomposable into signature contributions
- Clinician can see *why*: “70% of this patient’s ASCVD risk is driven by the inflammatory signature”
- Not a black box

Available now:

- Code: `https://surbut.github.io/aladynoulli2/`
- App: `http://aladynoulli.hms.harvard.edu`
- Open source, all parameters exportable

Summary

`ALADYNOULLI`: **Unified Discovery + Prediction**

1. **21 disease signatures** consistent across 3 biobanks, 700K+ patients
2. **Non-centered parameterization** ensures identifiable genetic effects (γ recovery $r = 0.95$)
3. **Heterogeneity within diagnoses** — different pathways, different targets
4. **151 GWAS loci + 18 rare variant genes** — enhanced genetic discovery
5. **Heritability exceeds component diseases** — signatures capture shared biology
6. **Outperforms PCE, PREVENT, GAIL** across 28 diseases using only ICD codes
7. **Calibrated**, robust to washout, reverse causation, and selection bias
8. **Fast transfer learning**: 0.05 sec/patient, fix $\phi/\psi/\gamma$, learn only δ

For drug discovery: Patient stratification by biology, not diagnosis.
For risk prediction: Dynamic, multi-disease, genetically informed.

Thank you

Questions?

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