Sarah M. Urbut

Massachusetts General Hospital & Broad Institute

January 27, 2026

Traditional Approach

- Study one disease at a time
- Simple risk factors (age, sex)
- Static models
- Misses biological complexity

Reality

- Diseases co-occur in patterns
- Shared biological pathways
- Risk evolves over lifetime
- Need to **borrow strength** across diseases

Example

Metabolic syndrome: Hypertension, Type 2 Diabetes, and Coronary Artery Disease don't appear randomly—they cluster together in time and share genetic basis.

Traditional Models

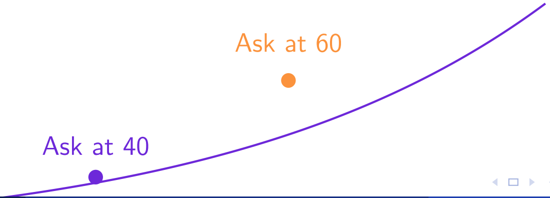
Cox Proportional Hazards:

$$h(t|\mathbf{X}) = h_0(t)\exp(\beta^T\mathbf{X})$$

- Relative risk is constant over time
- Doesn't capture life course dynamics
- When you ask matters!

Why This Is a Problem

- Same individual, different ages → different risk
- Genetic effects manifest differently across life course
- Need dynamic, time-varying models



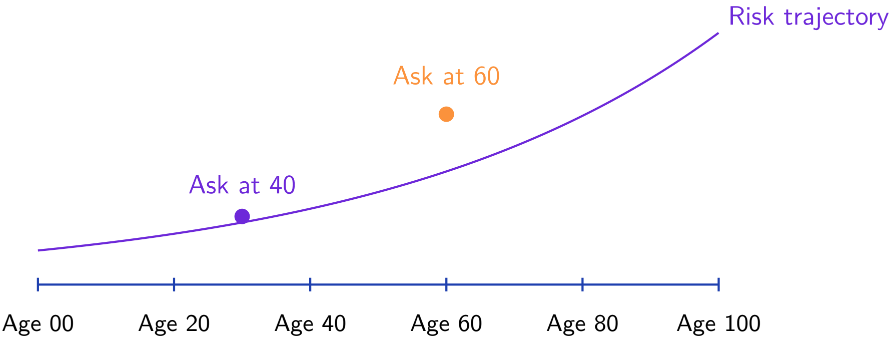
What We Have

- **Longitudinal EHR**: Diagnoses over time for millions of patients
- **Genetics**: PRS for multiple diseases
- **Complex patterns**: Diseases co-occur, evolve, interact

What We Need

1. **Discover latent patterns** of disease co-occurrence
2. **Model time-varying trajectories** for individuals
3. **Integrate genetics** to inform individual risk
4. **Predict future disease** while learning biology

Solution: Bayesian hierarchical model



Same individual, different answers

The question changes as we move through life

The Bayesian Philosophy

$$\mathbb{P}(\text{Model} \mid \text{Data}) \propto \mathbb{P}(\text{Data} \mid \text{Model}) \cdot \mathbb{P}(\text{Model})$$

Prior

Population knowledge

Disease signatures from all patients

Patterns

Likelihood

Individual data

This patient's diagnoses over time

Diagnoses

Posterior

Updated beliefs

Personalized risk prediction

Updated

Continuous updating as we walk through the lifetime

The Key Insight

Diseases don't occur independently—they cluster in **signatures** representing shared biological pathways

Example Signatures

Metabolic Signature:

- Type 2 Diabetes
- Hypertension
- Coronary Artery Disease
- Obesity

Inflammatory Signature:

- Rheumatoid Arthritis
- Inflammatory Bowel Disease
- Psoriasis

Why This Matters

- **Borrow strength**: Learn from similar patients
- **Predict multiple diseases**: Learn signature, predict all
- **Biological interpretation**: Signatures have genetic basis
- **Efficiency**: Don't model each disease separately

The Core Idea: Mixture Model

For individual i, disease d, at time t:

$$\pi_{i,d,t} = \kappa \cdot \sum_{k=1}^{K} \theta_{i,k,t} \cdot \text{sigmoid}(\phi_{k,d,t})$$

Breaking It Down

- $\theta_{i,k,t}$: How much does individual i load on signature k at time t? **(Individual-specific)**
- $\phi_{k,d,t}$: How strongly is disease d associated with signature k at time t? **(Population-level)**
- Multiple signatures can contribute

Key Innovation

This is a **mixture of probabilities**, not probability of mixture

Why this matters:

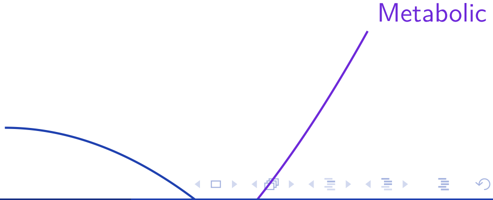
- Enables direct risk prediction
- Unlike topic models (allocation-based)
- Multiple signatures contribute to same disease

Individual Signature Loadings Change Over Time

Each individual's association with signatures evolves:

$$\theta_{i,k,t} = \frac{\exp(\lambda_{i,k,t})}{\sum_{k'=1}^{K} \exp(\lambda_{i,k',t})}$$

- Softmax ensures $\sum_k \theta_{i,k,t} = 1$ (proper mixture)
- $\lambda_{i,k,t}$ evolves smoothly over time



Why Time-Varying Matters

- Young person: Low metabolic signature loading

We Model $\lambda_{i,k,t}$ as a Gaussian Process

$$\lambda_{i,k} \sim \mathcal{GP}\left(\text{mean function}, K_\lambda\right)$$

Why GP?

- Ensures **smooth trajectories** over time (no wild jumps)
- Flexible—can capture any smooth function
- Handles irregular observation times
- Natural for longitudinal data

But what's the mean function?

This is where **genetics comes in!**

Genetics Modify the Mean Trajectory

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

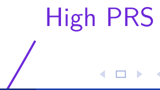
Components

- r_k: Population baseline for signature k
- $\mathbf{g}_i$: Individual's PRS vector
- Γ_k: **How genetics affect signature k (learned!)**
- K_λ: Temporal smoothness

Why This Matters

High CAD PRS?

- $\Gamma_{\text{metabolic}}$ tells us how this shifts your metabolic signature trajectory
- Higher genetic loading → earlier/stronger signature activation
- This provides **biological interpretation**



Signature-Disease Associations Are Shared

$$\phi_{k,d} \sim \mathcal{GP}\left(\mu_d + \psi_{k,d}, K_\phi\right)$$

- μ_d: Disease baseline (population prevalence)
- $\psi_{k,d}$: How strongly signature k associates with disease d
- **Learned from all patients** (not individual-specific)
- Time-varying: associations can change over life course

Example

Metabolic signature strongly associated with:

- T2D: $\psi_{\text{metabolic,T2D}} = +2.3$
- CAD: $\psi_{\text{metabolic,CAD}} = +1.8$
- Cancer: $\psi_{\text{metabolic,Cancer}} = +0.1$

Why This Works

- **Borrow strength**: Learn patterns from millions
- **Interpretability**: Signatures have clear meaning
- **Efficiency**: Shared parameters across all individuals

The Likelihood: Discrete-Time Survival

For individual i, disease d:

$$\ell_{i,d} = \sum_{t<E_{i,d}} \log(1-\pi_{i,d,t}) + Y_{i,d,t}\log(\pi_{i,d,t}) + (1-Y_{i,d,t})\log(1-\pi_{i,d,t})$$

At Risk

Before event time
Person hasn't gotten disease yet
$(1-\pi)$ terms

Event

Disease occurs at time t
$\log(\pi)$ contribution

Censored

Person leaves study
Last observation at $E_{i,d}$
$(1-\pi)$ at enrollment

Why This Matters

Properly handles censoring (critical for EHR data!)
and enables **direct prediction** (unlike topic models)

Individual Disease Probability

$$\pi_{i,d,t} = \kappa \cdot \sum_{k=1}^{K} \theta_{i,k,t} \cdot \text{sigmoid}(\phi_{k,d,t})$$

Individual Component (Time-Varying)

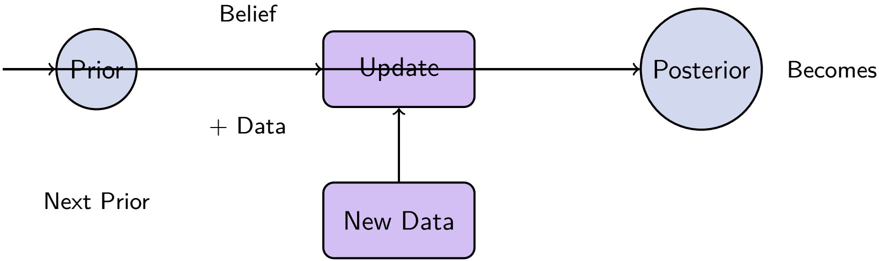
$$\theta_{i,k,t} = \text{softmax}(\lambda_{i,k,t})$$

$$\lambda_{i,k} \sim \mathcal{GP}(r_k + \mathbf{g}_i^\top \Gamma_k, K_\lambda)$$

Population Component (Shared)

$$\phi_{k,d} \sim \mathcal{GP}(\mu_d + \psi_{k,d}, K_\phi)$$

Genetics + Population Patterns + Time = Personalized Risk



Belief

Prior

Update

Posterior

Becomes

+ Data

Next Prior

New Data

Key Insight

At each time point t, we observe new diagnoses and update our beliefs about future risk:

$$\mathbb{P}(\pi_{i,d,t} \mid \text{Data up to } t) \propto \mathbb{P}(\text{Data up to } t \mid \pi_{i,d,t}) \cdot \mathbb{P}(\pi_{i,d,t})$$

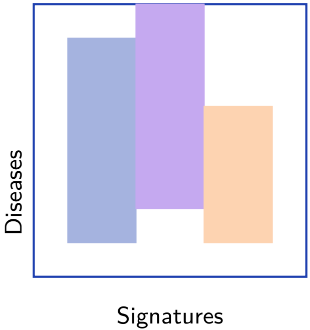
This is what happens naturally—we continuously learn from data

Learned Signatures

- Latent patterns of disease co-occurrence
- Each signature has characteristic timing
- Some signatures activate early, others later in life
- Genetics inform individual predisposition

Example Patterns

- **Metabolic** → early adulthood onset
- **Inflammatory** → mid-life activation
- **Cancer** → age-dependent patterns

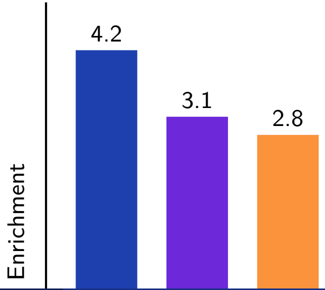


Signature-Disease Matrix

Key Findings

- Cardiovascular PRS → strongly associated with metabolic signature
- Psychiatric PRS → associated with neuro/psychiatric signatures
- Genetic correlations reveal shared architecture

PRS-Signature Associations



ASCVD Predictions

- **10-year:** Aladynoulli 0.737 vs PCE 0.683

  +**7.9**% improvement
- **30-year:** Aladynoulli 0.708 vs PREVENT 0.650

  +**9.0**% improvement

vs Cox Baseline

- Parkinson's: +35.2%
- CKD: +33.2%
- Stroke: +31.6%
- ASCVD: +16.3%

vs Delphi-2M

- Outperforms on 15/28 diseases
- Largest gains: Parkinson's (+35%), CKD (+33%)

Dynamic Risk Assessment

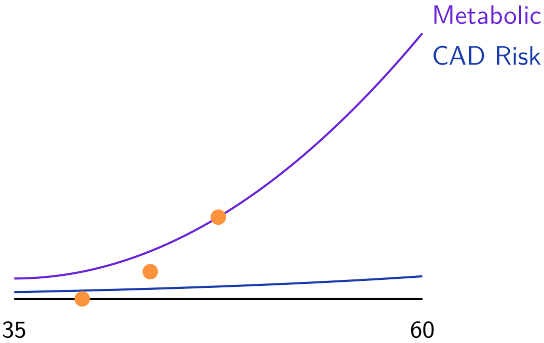
Model updates predictions as patients age and develop conditions

Patient Timeline

- Age 35: Enrollment
- Age 40: Hypertension
- Age 45: Type 2 Diabetes
- Age 50: Coronary Artery Disease
- Age 55: Ongoing monitoring

Signature Evolution

- Metabolic signature loading increases over time
- Genetic predisposition (PRS) influences trajectory
- Risk predictions continuously updated



Posterior beliefs evolve as new information arrives

✓ Unified Framework

Simultaneous genomic discovery and clinical prediction

↗ Dynamic

Properly models lifetime risk evolution with Bayesian updating

⊗ Interpretability

Signatures provide biological meaning through genetic architecture

⊙ Scalable

Works across diseases and biobanks

Bayesian framework enables both discovery and prediction

Integration

- Imaging (CAC, CT-coronary)
- AI-enhanced features (ECG, TTE)
- Multi-omics data

Applications

- Intervention modeling (digital twins)
- Personalized screening
- Drug repurposing

$$\heartsuit \qquad \langle\rangle \qquad \star$$

Thank You!

□ surbut@mgh.harvard.edu

○ aladynoulli.hms.harvard.edu

Collaborators: P. Natarajan, G. Parmigiani, A. Gusev, and team