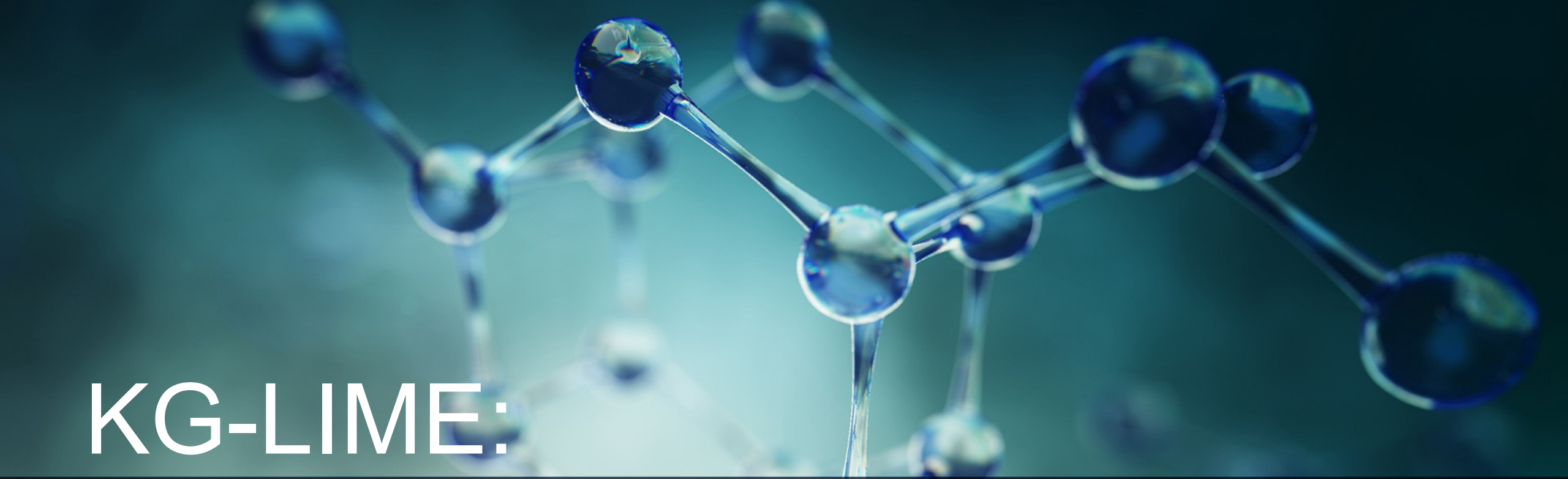

# KG-LIME:

## Predicting Individualized Risk of Adverse Drug Events for Multiple Sclerosis Disease-Modifying Therapy

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JOURNAL ARTICLE

# KG-LIME: predicting individualized risk of adverse drug events for multiple sclerosis disease-modifying therapy

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## Abstract

### Objective

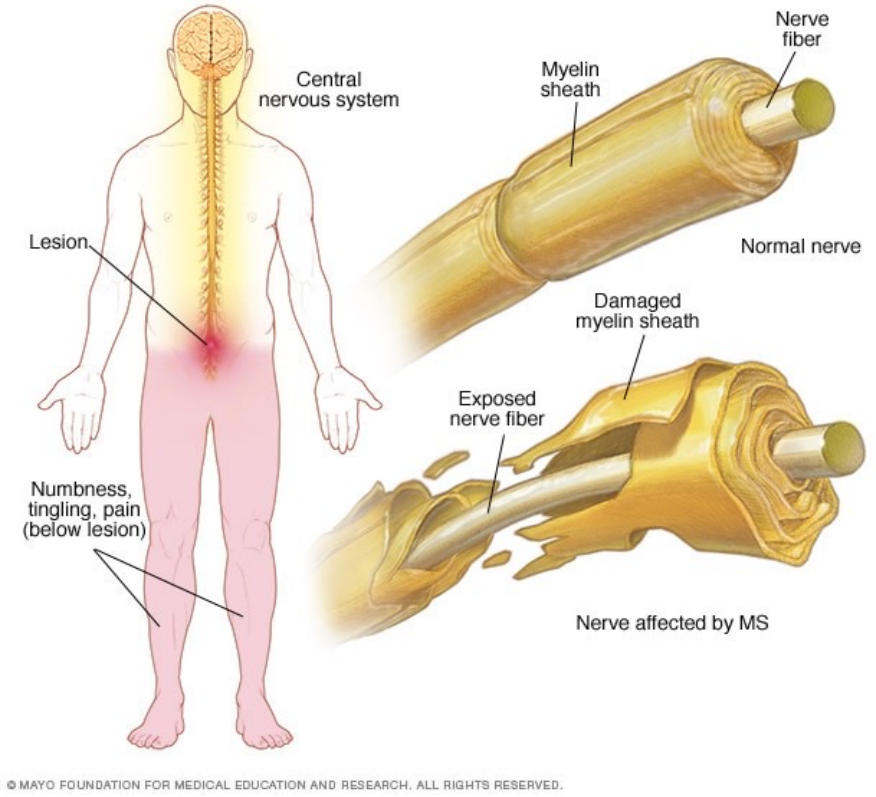
The aim of this project was to create time-aware, individual-level risk score models for adverse drug events related to multiple sclerosis disease-modifying therapy and to provide interpretable explanations for model prediction behavior.

### Materials and Methods

We used temporal sequences of observational medical outcomes partnership common data model (OMOP CDM) concepts derived from an electronic health record as model features. Each concept was assigned an embedding representation that was learned from a graph convolution network trained on a

# Background

- Multiple sclerosis (MS) is an **inflammatory and demyelinating autoimmune disease** of the central nervous system
- Symptoms include
  - Muscle weakness
  - Tremor
  - Neuropathy
  - Cognitive issues
- Third most common cause of disability in U.S. among individuals aged 15 to 50 (>2.8 million worldwide)



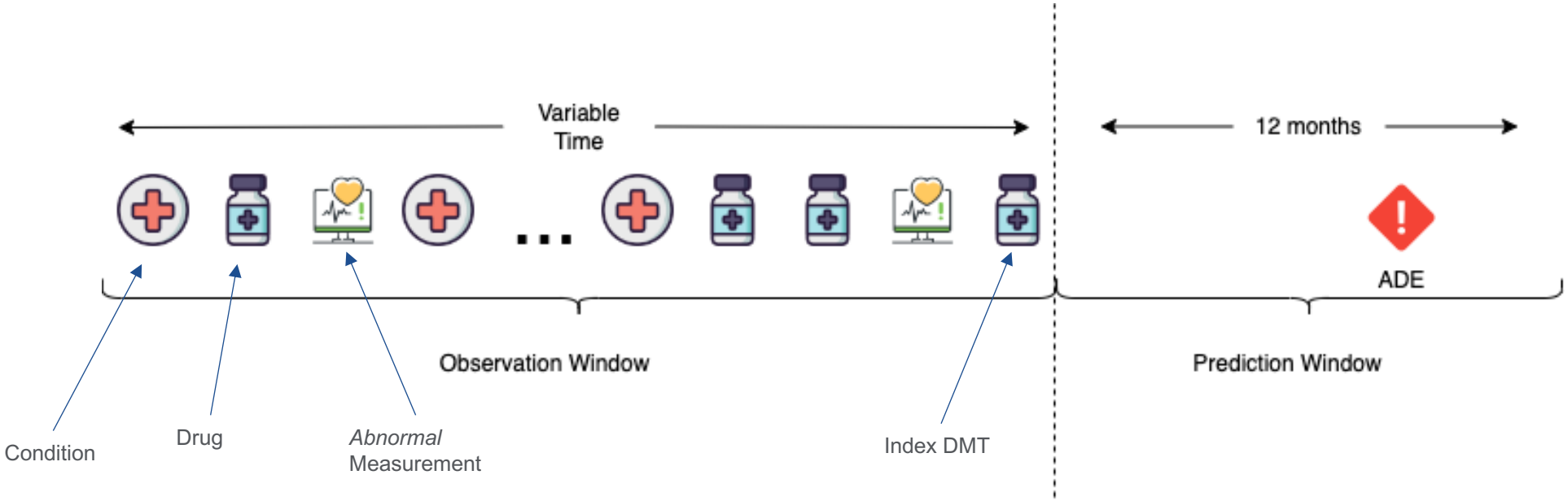

Multiple sclerosis - Symptoms and causes. *Mayo Clinic*

# Disease-modifying Therapy (DMT)

- Slow progression of relapsing MS through **immunosuppressive** drugs
- Moderate efficacy
  - beta-interferons
  - glatiramer acetate
- High efficacy
  - alemtuzumab
  - natalizumab
  - ocrelizumab
- Tradeoff between efficacy and **adverse drug effects (ADEs)**


# Study Aims

- Build ADE risk score prediction models for FDA-approved MS drugs using time series of EHR OMOP concepts
- Append interpretation layer at end of models

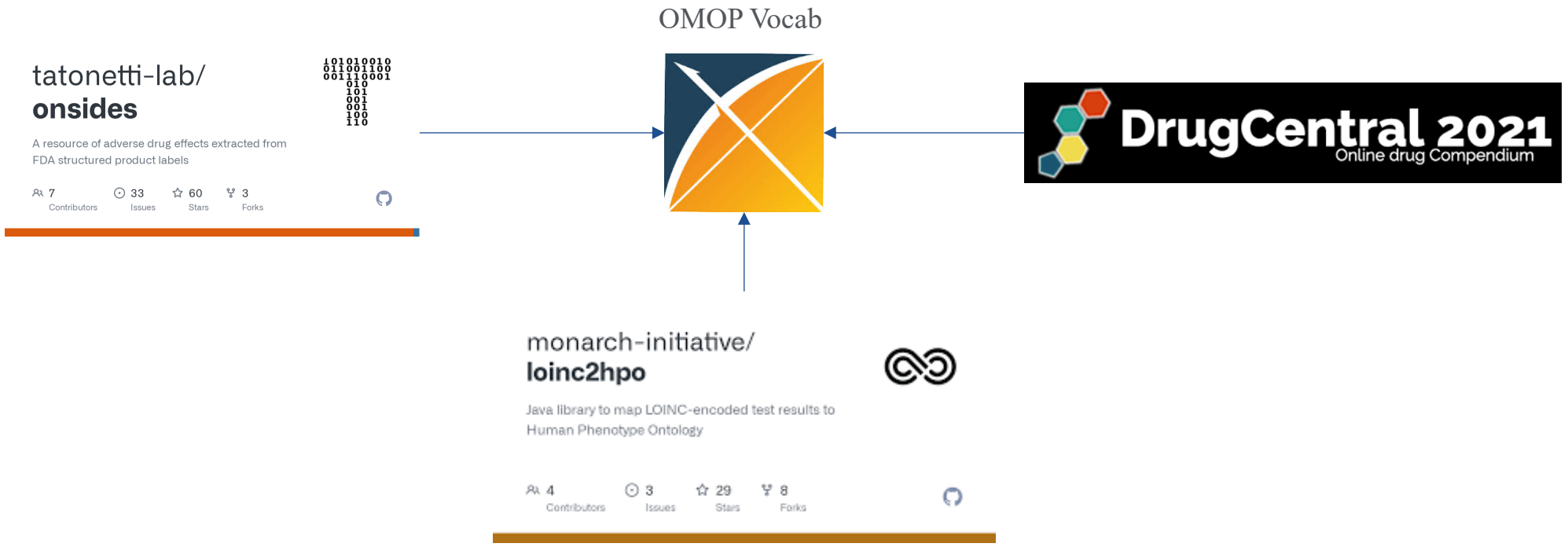



How should models represent OMOP concepts?

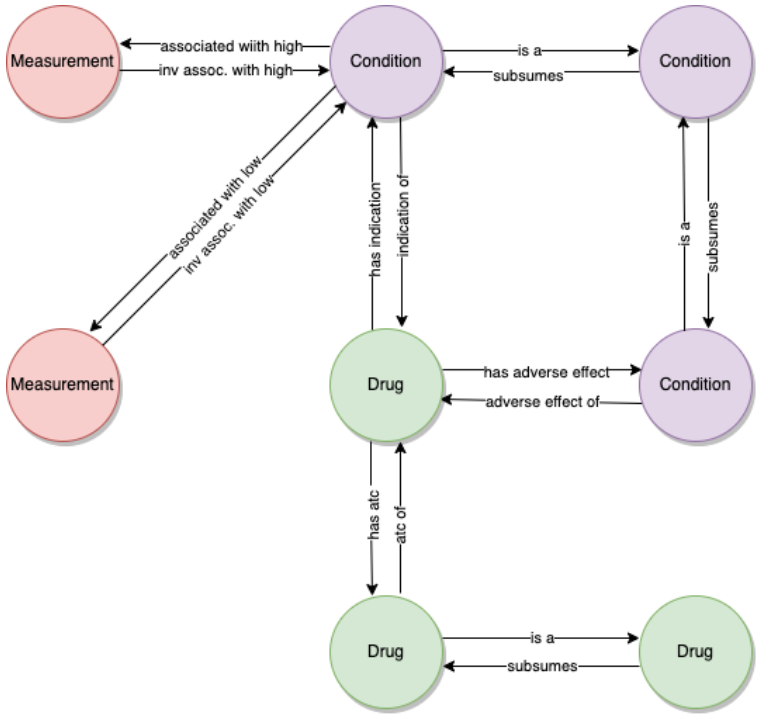
**Graph Embeddings**

# Representing Concepts in a Graph

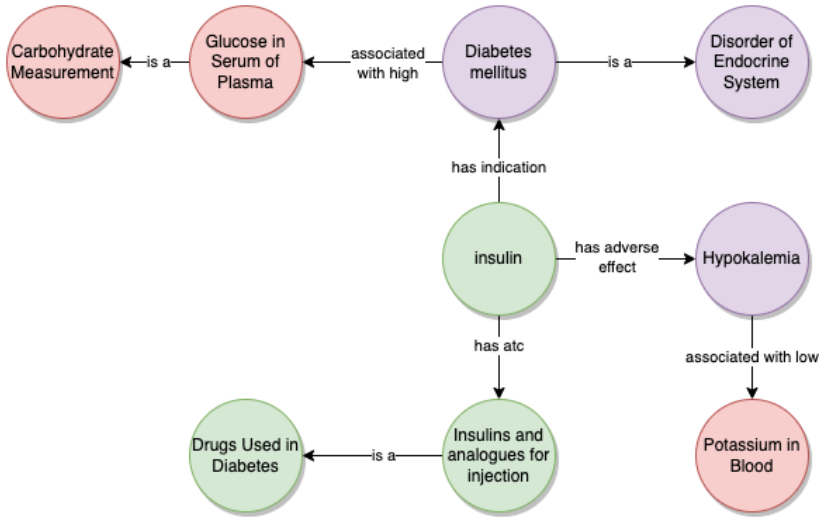
- Integrate ontologies into a combined knowledge graph (KG) with OMOP vocabulary as backbone
  - Each node is a standard OMOP concept



# Representing Concepts in a Graph



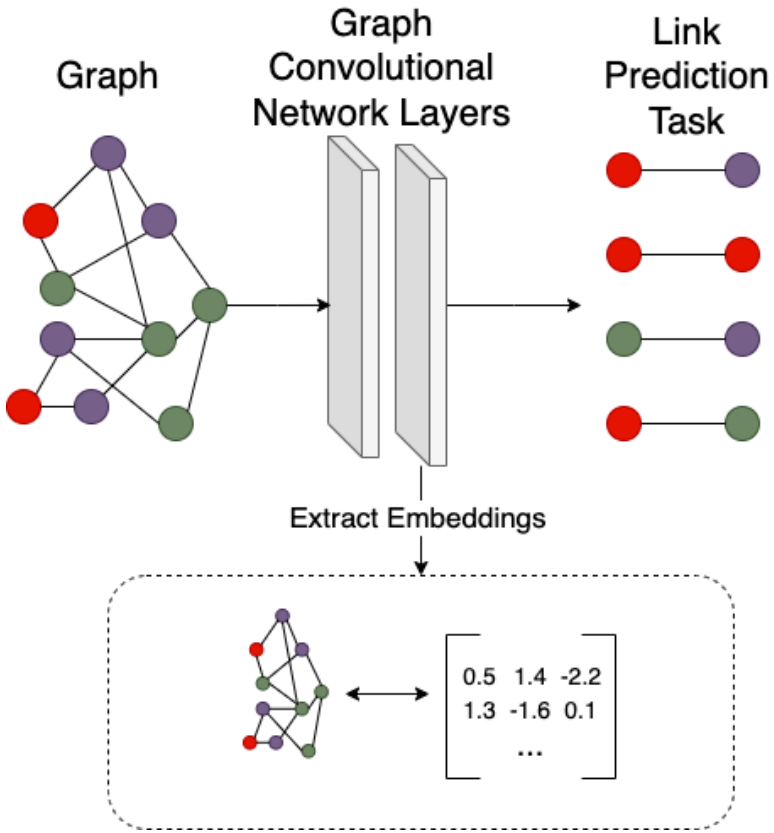

**(a) Metagraph**




**(b) Insulin Subgraph**

- 12,676 nodes
- 186,494 edges
- 6 edge types (and inverses)

# Graph Embeddings

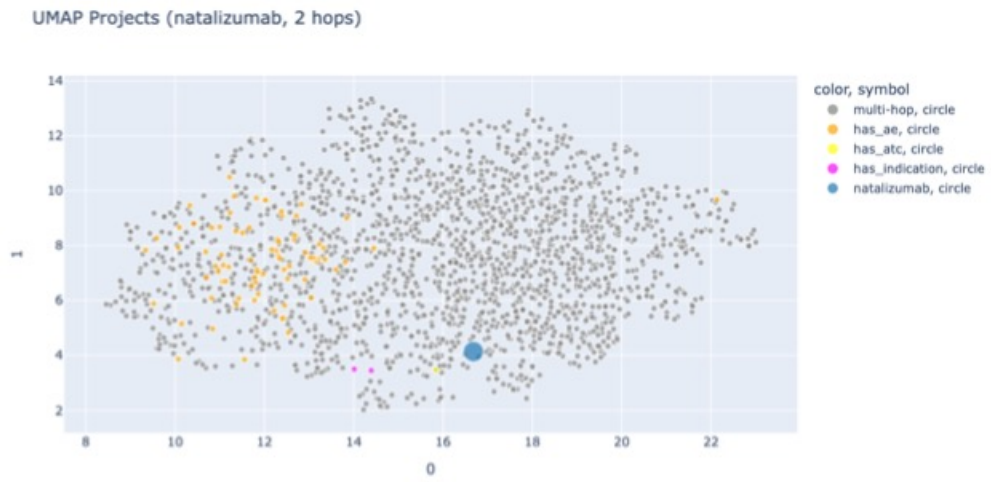


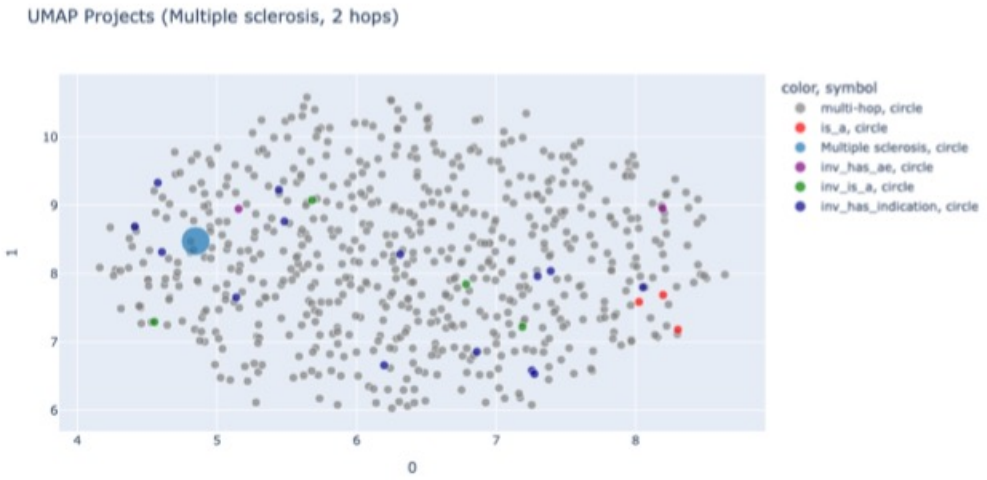

- **Graph Convolution Network (GCN)** learns embedding representations of nodes via link prediction task
- "Similar" nodes have "similar" representations

# Graph Embeddings

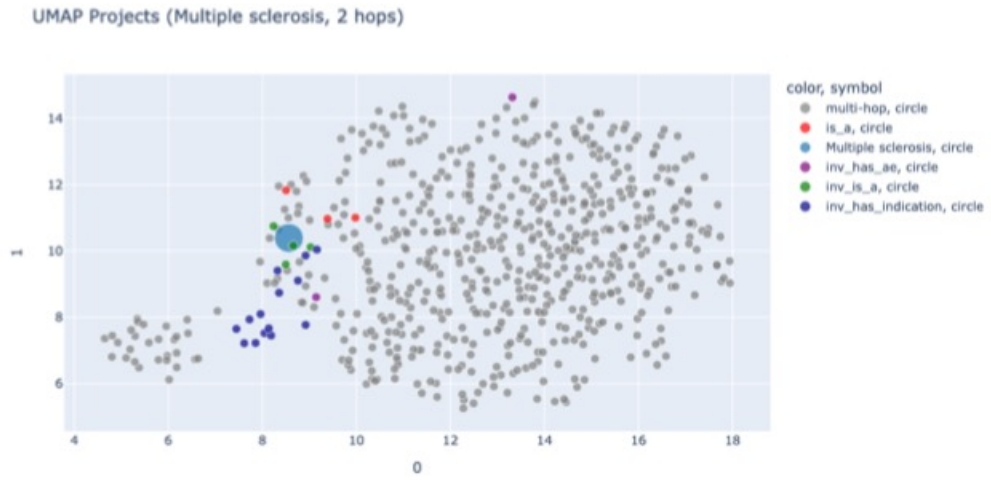
- Embeddings of concepts with similar relationships group up following training


Training

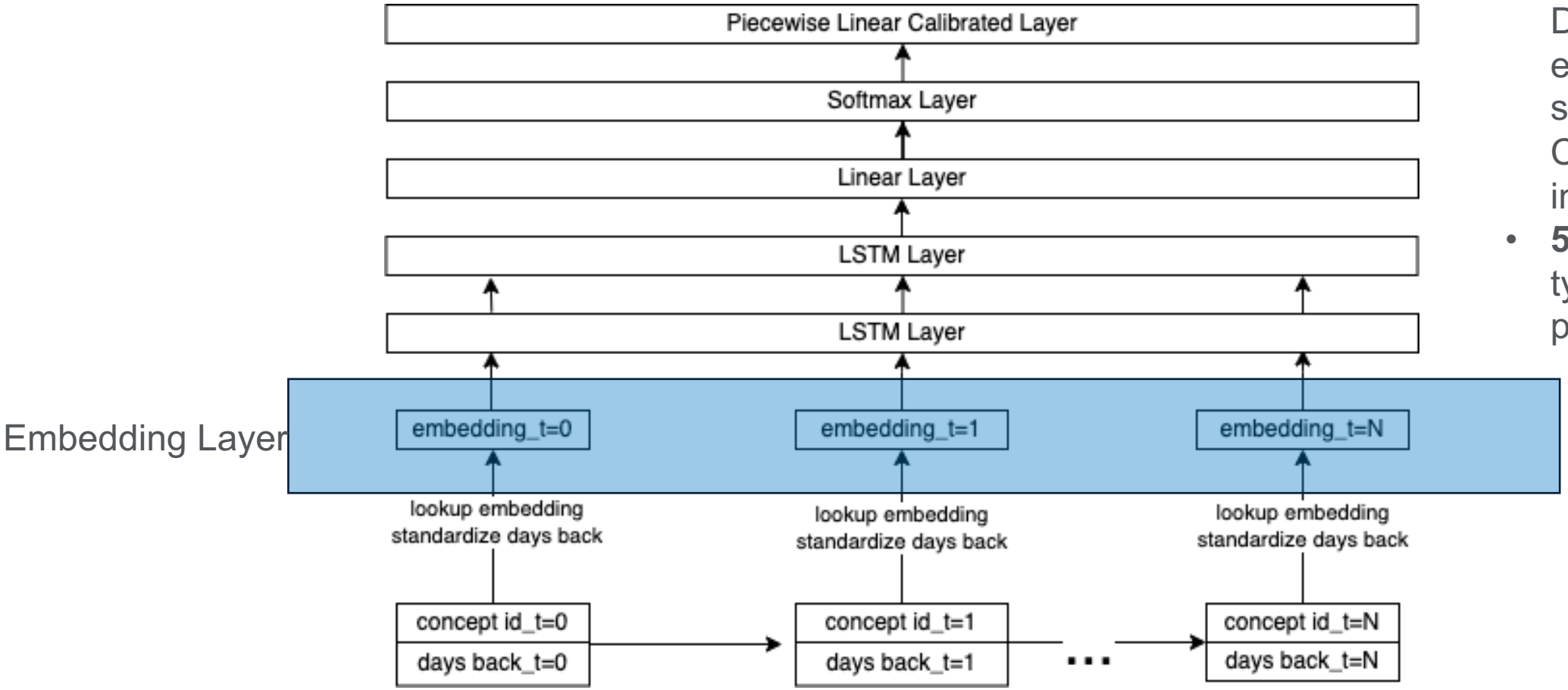



Training



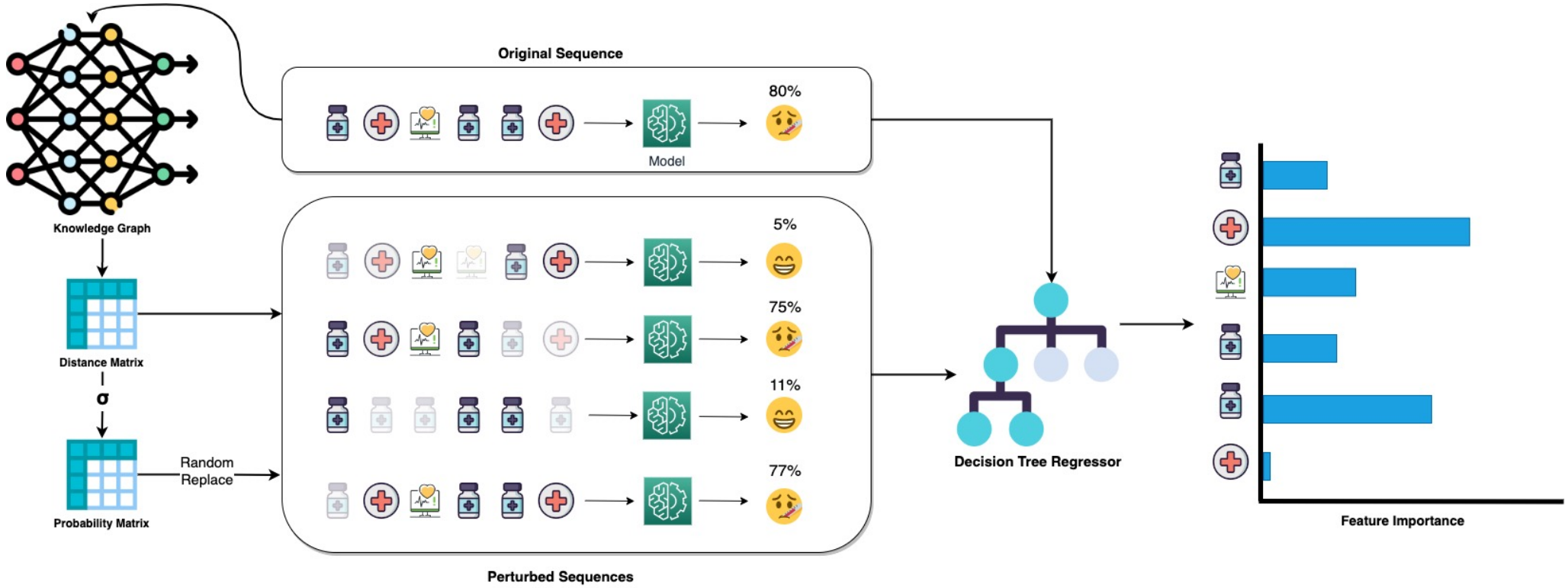
# ADE Prediction LSTM Model




- Trained on **11,589** DMT drug exposure sequences from CUIMC OMOP instance
- **56** adverse effect types were predicted

# Interpretation with KG-LIME

- Modified the Local Interpretable Model-Agnostic Explanations (LIME) framework to utilize Knowledge Graph



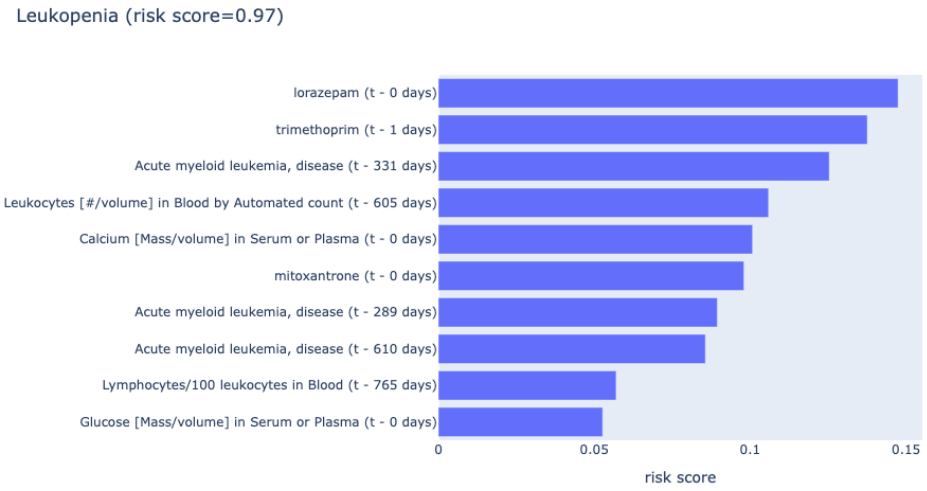
# ADE Prediction Results

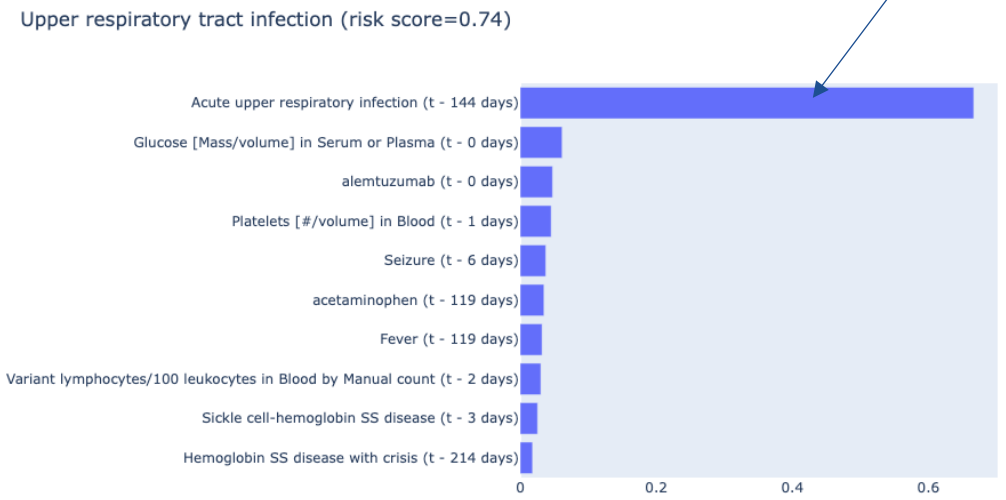
| Adverse effect | AUC | % Positive | AUC-PR | Sensitivity at 90% specificity | Sensitivity at 70% specificity | Sensitivity at 50% specificity | Precision at 90% recall | Precision at 70% recall | Precision at 50% recall | Brier score |
|---|---|---|---|---|---|---|---|---|---|---|
| **Neutropenia** | 0.98 | 6.8 | 0.86 | 0.98 | 0.98 | 0.99 | 0.68 | 0.84 | 0.93 | 0.02 |
| Sepsis | 0.96 | 5 | 0.51 | 0.95 | 0.98 | 1 | 0.37 | 0.52 | 0.6 | 0.03 |
| **Leukopenia** | 0.95 | 6.5 | 0.72 | 0.92 | 0.94 | 0.96 | 0.5 | 0.62 | 0.79 | 0.03 |
| **Anemia** | 0.95 | 13.1 | 0.82 | 0.84 | 0.93 | 0.96 | 0.42 | 0.86 | 0.86 | 0.04 |
| **Thrombocytopenia** | 0.94 | 6.7 | 0.74 | 0.88 | 0.91 | 0.94 | 0.33 | 0.75 | 0.88 | 0.03 |
| Pneumonia | 0.94 | 4.9 | 0.5 | 0.83 | 0.9 | 0.93 | 0.24 | 0.43 | 0.59 | 0.03 |
| Hypertension | 0.93 | 16.9 | 0.82 | 0.85 | 0.93 | 0.95 | 0.6 | 0.78 | 0.89 | 0.08 |
| Pruritus | 0.92 | 2.9 | 0.51 | 0.77 | 0.89 | 0.92 | 0.1 | 0.41 | 0.53 | 0.02 |
| Pyrexia | 0.91 | 4.6 | 0.7 | 0.84 | 0.89 | 0.92 | 0.21 | 0.6 | 0.86 | 0.03 |
| Vomiting | 0.91 | 3.6 | 0.5 | 0.81 | 0.93 | 0.95 | 0.15 | 0.27 | 0.6 | 0.03 |
| Bronchitis | 0.9 | 1.7 | 0.17 | 0.75 | 0.78 | 0.84 | 0.06 | 0.13 | 0.19 | 0.02 |
| Diarrhea | 0.9 | 4.6 | 0.43 | 0.76 | 0.86 | 0.94 | 0.12 | 0.36 | 0.51 | 0.03 |
| Urinary tract infection | 0.9 | 6.7 | 0.52 | 0.7 | 0.88 | 0.94 | 0.16 | 0.33 | 0.45 | 0.04 |
| Insomnia | 0.89 | 4.8 | 0.42 | 0.69 | 0.91 | 0.95 | 0.13 | 0.25 | 0.53 | 0.03 |
| Rash | 0.88 | 5.3 | 0.45 | 0.78 | 0.86 | 0.93 | 0.11 | 0.44 | 0.51 | 0.04 |
| Nausea | 0.88 | 4.8 | 0.37 | 0.68 | 0.9 | 0.95 | 0.15 | 0.25 | 0.32 | 0.04 |
| Influenza | 0.87 | 0.5 | 0.03 | 0.48 | 0.61 | 0.72 | 0.01 | 0.02 | 0.02 | 0.01 |

* Remaining adverse effects not shown

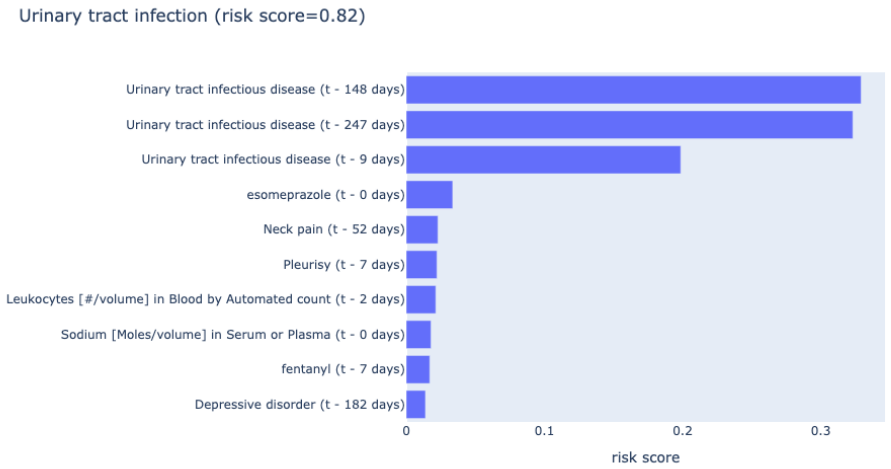
- Mean AUC across all adverse effects was 0.77 ± 0.15
- Adverse effects dealing with low blood cell counts were among highest performing

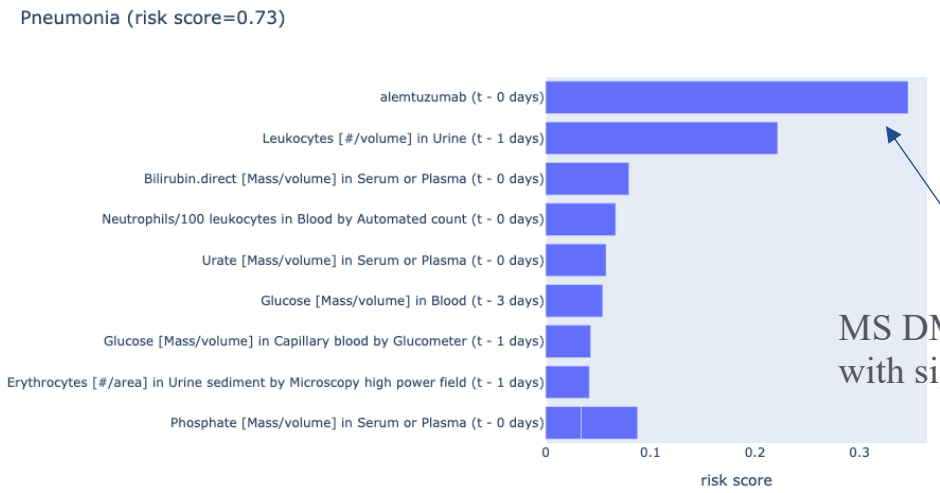
# KG-LIME Individual Explanations



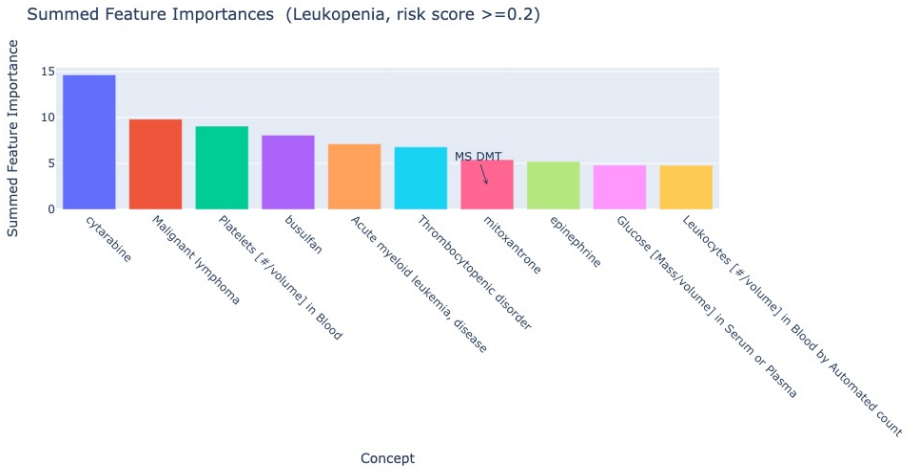

PMH is often strong predictor



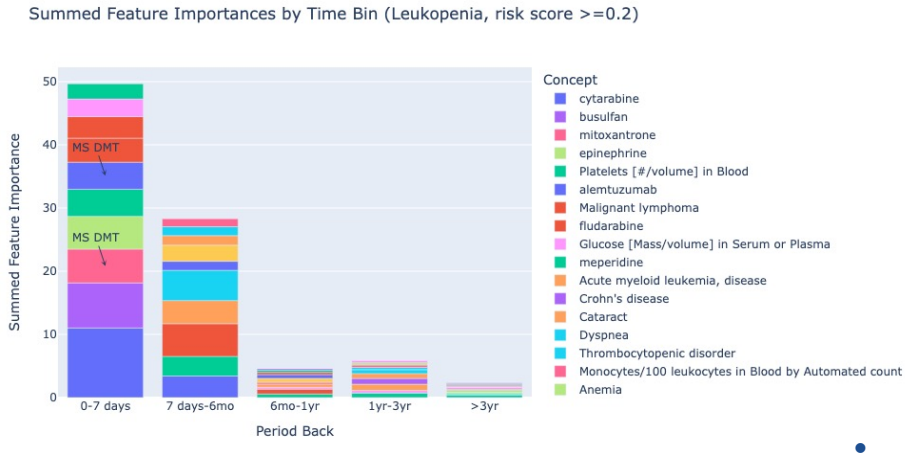




MS DMT appears with signal

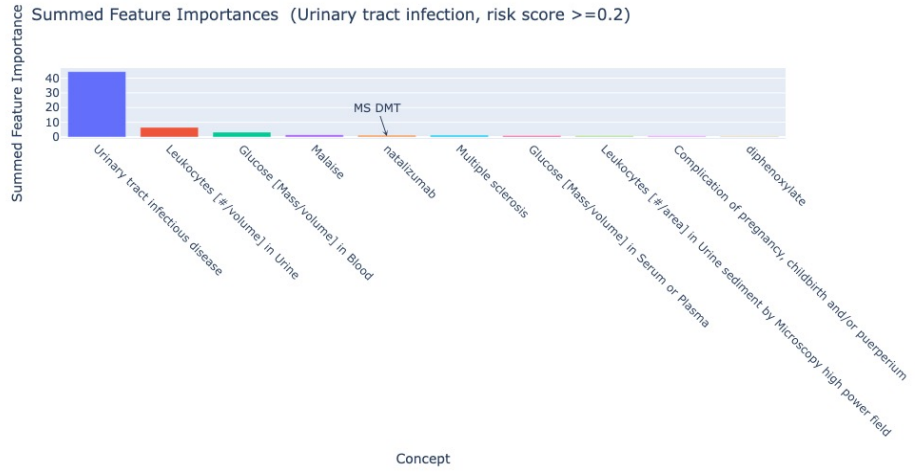
# KG-LIME Global Explanations



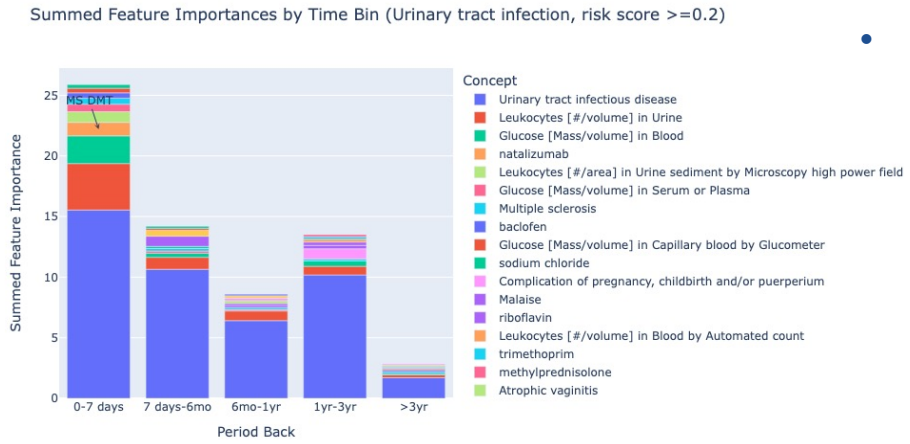

**(a) Leukopenia**




**(b) Leukopenia Over Time**




**(c) Urinary Tract Infection**




**(d) Urinary Tract Infection Over Time**

- Recent concepts have strongest influence
- MS DMT is often important, follows literature

# Conclusion

- Ontology-derived graph embeddings can be used for ADE prediction
- KG-LIME can provide feature importances
- Limitations
  - Arbitrary time window of 12 months
  - Extremely rare events were not able to be predicted
  - Gaps in EHR record (e.g. patients receiving care elsewhere)

# Special Thanks

- Dr. Nicholas Tatonetti
- T-Lab
- Columbia Department of Biomedical Informatics