NCATS Improving Health Through Smarter Science

An application of studying FAERS data to Enhance Drug Safety and Treatment Outcomes in Rare Diseases

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Overview of Rare Diseases and Drug Safety

Patients Affected

300M

Over 300 million patients worldwide are affected by rare diseases, with 95% lacking treatment.

Orphan Drugs Approved

1,268

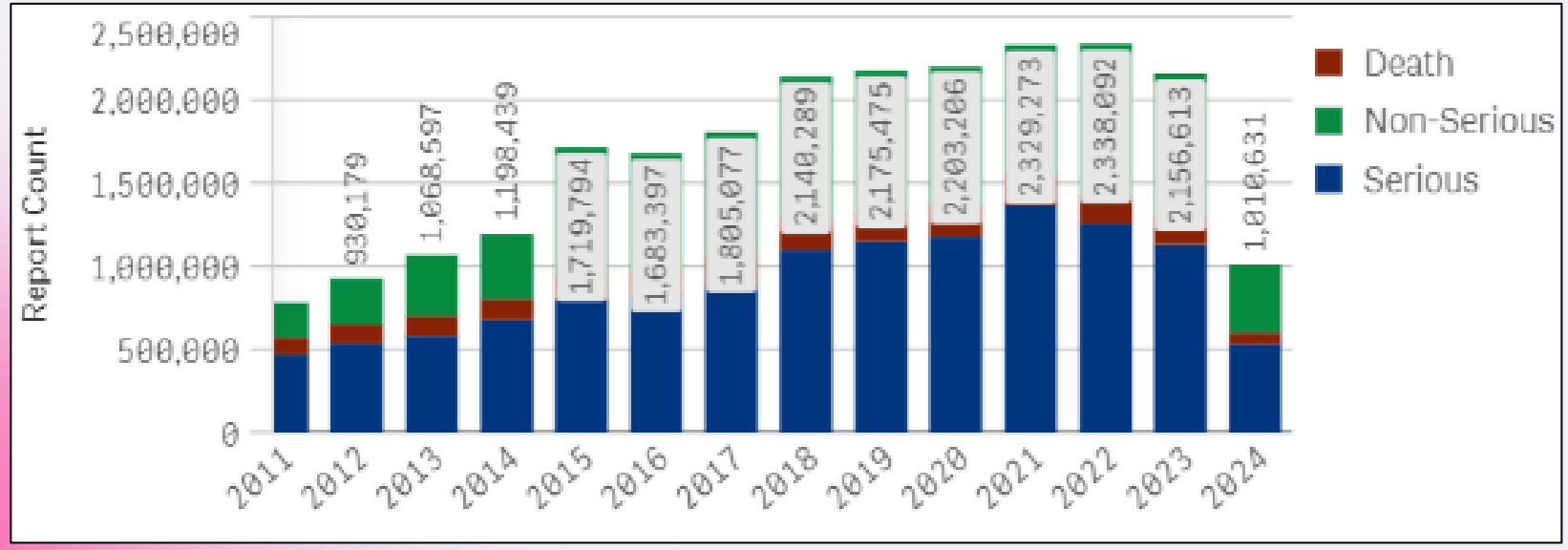
The FDA has approved 1,268 orphan drugs for rare conditions, emphasizing the need for drug safety assessment.

Adverse Drug Events

29M

Understanding adverse drug events (ADEs) in rare diseases is crucial for improving patient safety and treatment outcomes.

Trends in Adverse Drug Events Over Time



Total adverse event reports

29,153,222

Total adverse event reports submitted to FAERS

Serious reactions

16,130,758

Reports involving serious reactions (excluding death)

Deaths

2,650,057

Deaths linked to drug-related adverse events

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Problem Statement

Challenges:

- ❑ Adverse drug events (ADEs) are often underreported, especially in the context of rare diseases, resulting in limited knowledge about the true safety profile.
- ❑ Adverse events often arise post-approval and are harder to detect due to the rarity of the disease, making it critical to have a robust system to track and analyze these events.

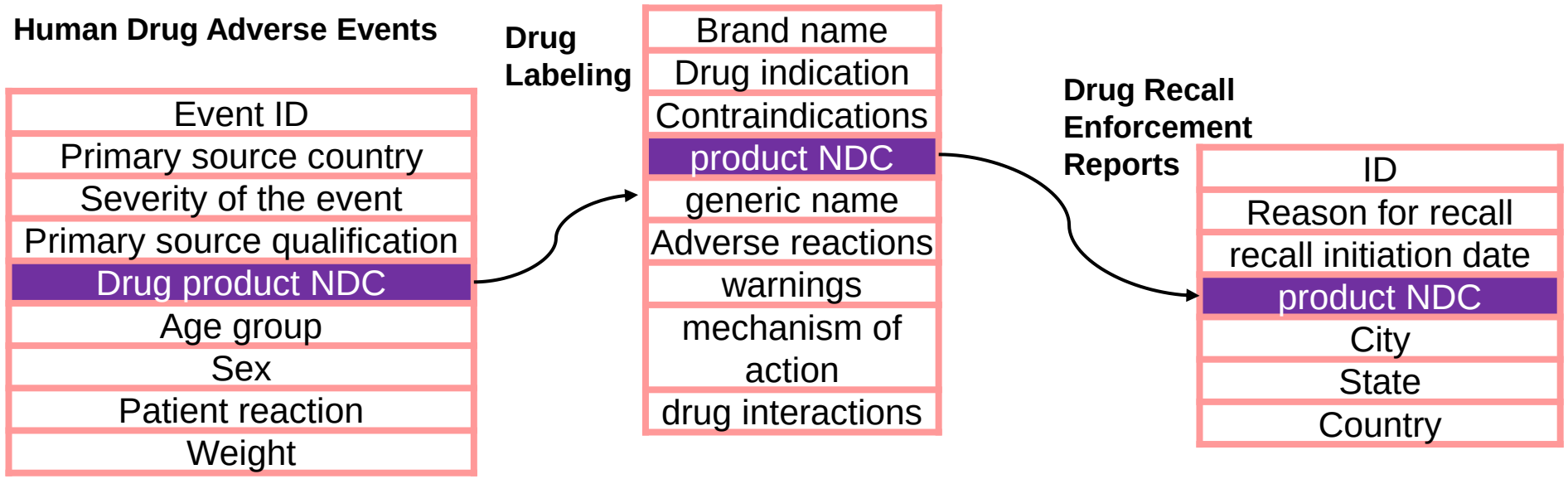
Purpose of Our Study:

- ❑ Systematically collecting adverse drug events (ADEs) from FAERS for rare diseases
- ❑ Presenting the ADEs in a knowledge graph named ADE4RD to support pharmacovigilance studies in rare diseases

Overview of FAERS (FDA Adverse Event Reporting System)

openFDA

- FAERS is a key public resource for tracking adverse drug events (ADEs) reported by healthcare providers, patients, and drug manufacturers.

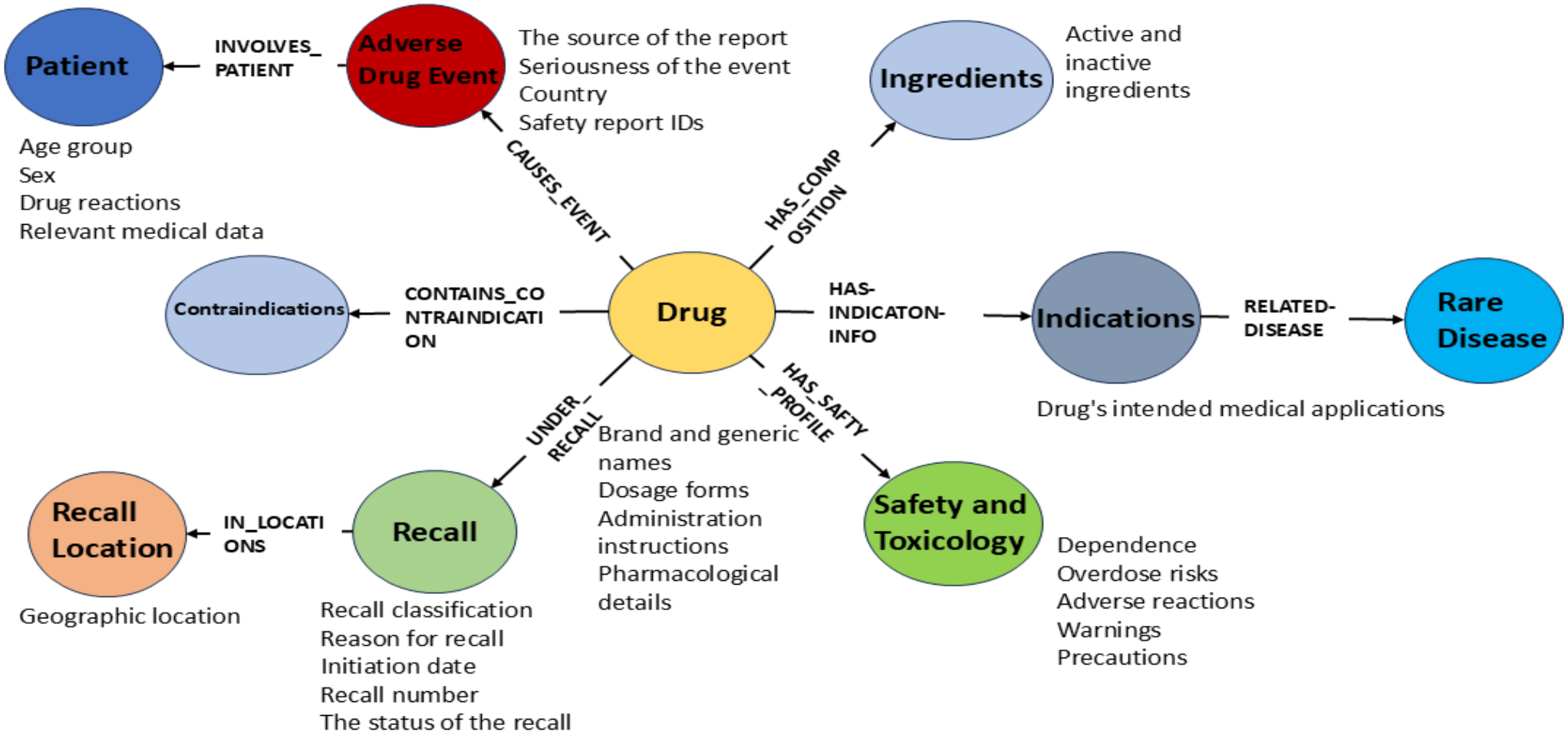


Mappings Adverse drug events to Rare Diseases

- Mapped orphan drug designations from the FDA to the rare diseases listed in the GARD database.
- Integrated ADE data with the GARD database to better understand adverse events in the context of rare diseases.

Orphan designation	Mapped rare diseases
Treatment of retinopathy of prematurity	Retinopathy of prematurity (GARD ID: 0005695)
treatment of idiopathic pulmonary fibrosis	Idiopathic pulmonary fibrosis (GARD ID: 0008609)
treatment of cutaneous variants of porphyria (which includes treatment and prevention of cutaneous manifestations of disease)	Porphyria (GARD ID: 0010353)

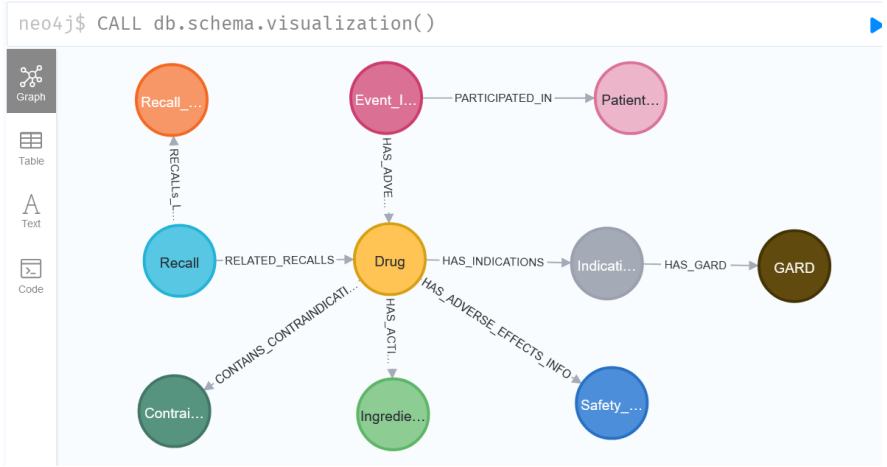
Data Model for ADE4RD



Knowledge Graph Statistics

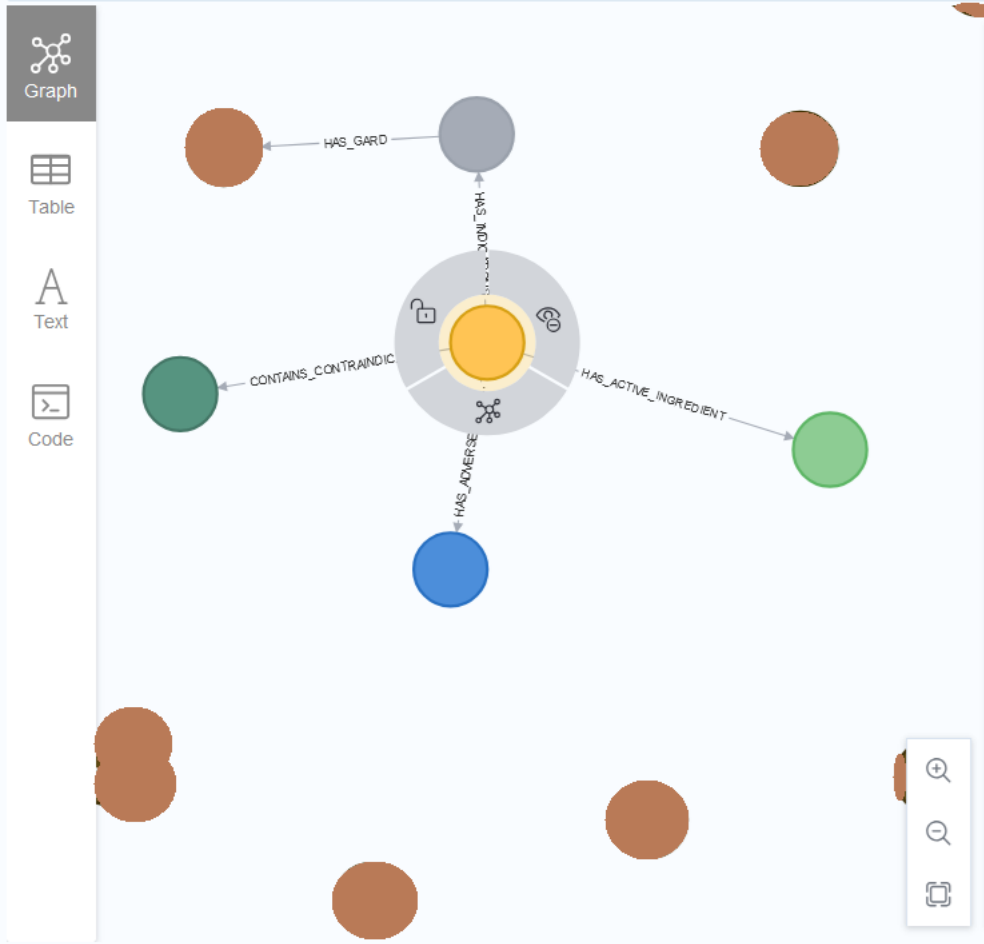
Key Statistics:

- Nodes: 17,833 total nodes representing various entities like drugs, diseases, ADEs, etc.
- Edges: 19,617 edges, representing relationships between different entities in the model.



Classes	# nodes
Patient	6,375
Recall Location	29
Drug Recall	509
Adverse Drug Event	6,375
Drug	830
Safety and Toxicology	830
Drug Ingerdients	830
Contraindications	830
Indications	830
Rare disease	395

```
neo4j$ MATCH (n:Gard) RETURN n LIMIT 25
```



Node properties

Drug

	22]
openfda_pharm_class_cs	[Anti-Inflammatory Agents, Non-Steroidal [CS]]
openfda_pharm_class_epc	[Nonsteroidal Anti-inflammatory Drug [EPC]]
openfda_pharm_class_moa	[Cyclooxygenase Inhibitors [MoA]]
openfda_product_ndc	[53489-478,53489-479]
openfda_product_type	[HUMAN PRESCRIPTION DRUG]
openfda_route	[ORAL]
openfda_spl_id	[3567b400-08be-4012-89c0-e9f57fc8873e]
openfda_spl_set_id	[a47e4259-d44b-4b7b-b517-841cb6840982]

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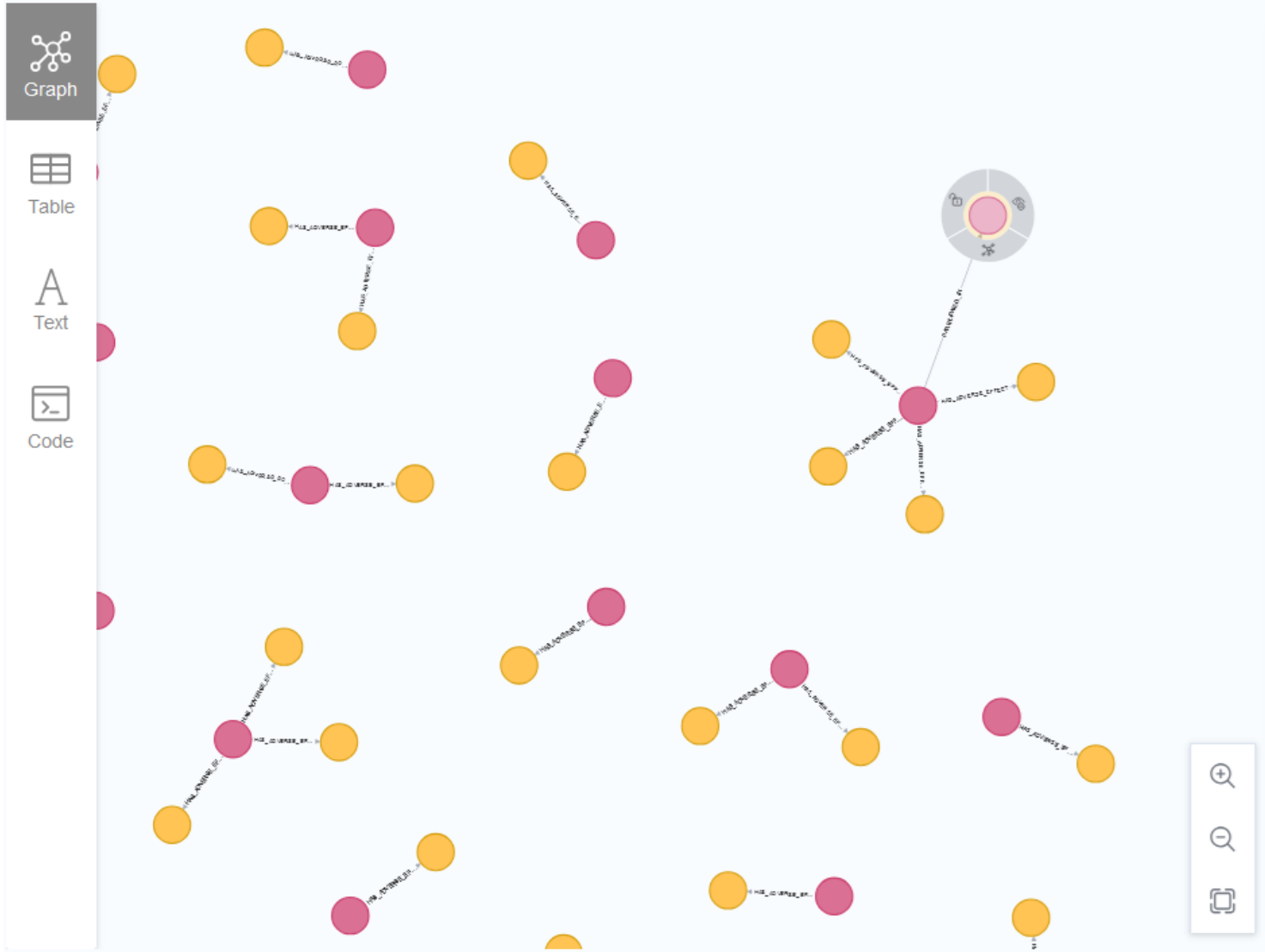
```
neo4j$ MATCH p=()-[r:HAS_ADVERSE_EFFECT]→() RETURN p
```



Node properties

Patient_Information

patient_patientonsetage	78
patient_patientonsetageunit	801
patient_patientsex	2
patient_reaction	[Dyspnoea,Thrombocytopenia,Pain,Cytopenia,Pulmonary embolism,Pancreatic neoplasm,Pneumonia]
patient_summary	{'narrativeincludeclinical': 'CASE EVENT DATE: 201901'}

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Case Study 1: Assessing Drug Safety of Orphan Drugs

To analyze ADEs linked to orphan drugs in a single year (2019) and assess the severity of these events.

Total ADEs related to rare diseases in 2019

6,375

Out of which, serious ADEs: 3,201

Number of recalls associated with drugs for rare diseases

509

Total number of drugs used to treat rare diseases

334

Case Study 2: Top Orphan Drugs with ADEs

Top 10 Orphan Drugs:

Used a Cypher query to extract the top 10 orphan drugs with highest number of reported ADEs from the knowledge graph

Cypher Query 1

```
MATCH (n:Event_Information)-[r:HAS_ADVERSE_EFFECT]-(m:Drug)
WITH DISTINCT n, m.openfda_generic_name AS generic_name
WITH generic_name, COUNT(DISTINCT n) AS event_count
RETURN generic_name, event_count
ORDER BY event_count DESC
LIMIT 10
```

Drug generic names	# Adverse Events	Rare diseases	GARD IDs
ADALIMUMAB	1918	non-infectious anterior uveitis	GARD:0021260
APREMILAST	652	behcet's disease	GARD:0000848
METHOTREXATE, METHOTREXATE SODIUM	407	osteogenic sarcoma	GARD:0007284
PREDNISONE	373	Chronic inflammatory demyelinating polyneuropathy	GARD:0006102
GABAPENTIN	293	Amyotrophic lateral sclerosis	GARD:0005786
ETANERCEPT	278	active polyarticular-course juvenile rheumatoid arthritis	
AFLIBERCEPT	275	Retinopathy of prematurity	GARD:0005695
DUPILUMAB	190	Bullous pemphigoid	GARD:0005972
IBRUTINIB	174	Lymphoma	GARD:0020548
CYCLOPHOSPHAMIDE	159	Systemic sclerosis	GARD:0009748

Discussion

FAERS Data Limitations:

- ❑ FAERS relies on voluntary reporting, which may lead to underreporting or inconsistent data quality.
- ❑ Self-reported data can introduce biases, such as inaccurate or incomplete information.

Future Directions:

- ❑ Use large language models (LLMs) and natural language processing (NLP) techniques to improve data reliability and consistency.
- ❑ Data Integration: Incorporate more comprehensive datasets (e.g., clinical trials, literature) to enhance safety analysis.
- ❑ AI and ML: Utilize AI techniques to predict and detect adverse events in real time.
- ❑ Repurposing Drugs: Explore drug repurposing opportunities by analyzing safety data across diseases.

Acknowledgments and Q&A

Acknowledgments:

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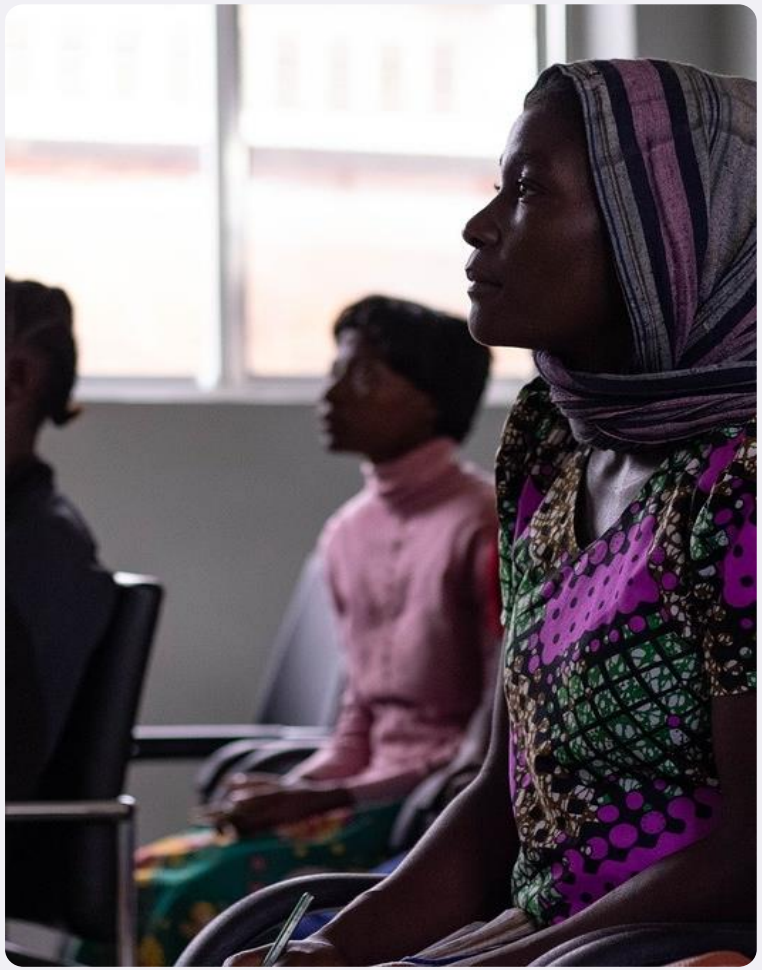

Q&A

Open the floor for questions and discussion.