# Biomedical Knowledge Graph: Build & Usage

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  - Biomedical KG construction
  - Entity Event KG model



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  - Semantic Health Data
     Platform
  - Biomedical NLP

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# Agenda

- Semantic UMLS knowledge graph
- Augmenting baseline UMLS KG with clinicaltrials.gov
- Knowledge extraction Biomedical NLP
- Information Retrieval: Knowledge Based Query
- Entity Event Model of Health Data
- Summary

## **Biomedical Knowledge Sources**

NIH U.S. National Library of Medicine

ClinicalTrials.gov



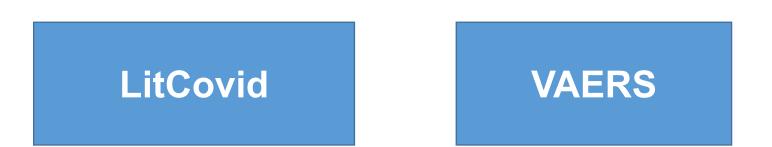
UMLS









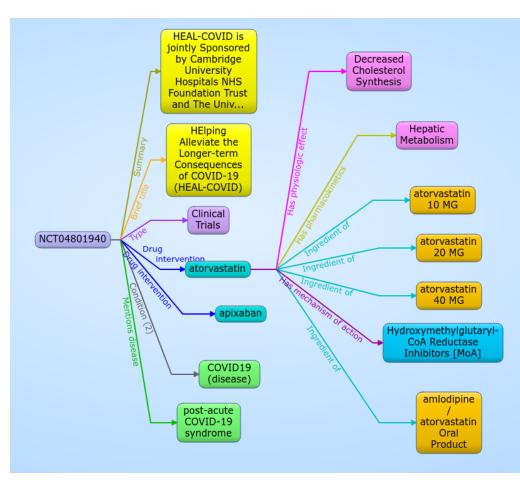




### **Biomedical Knowledge Sources**

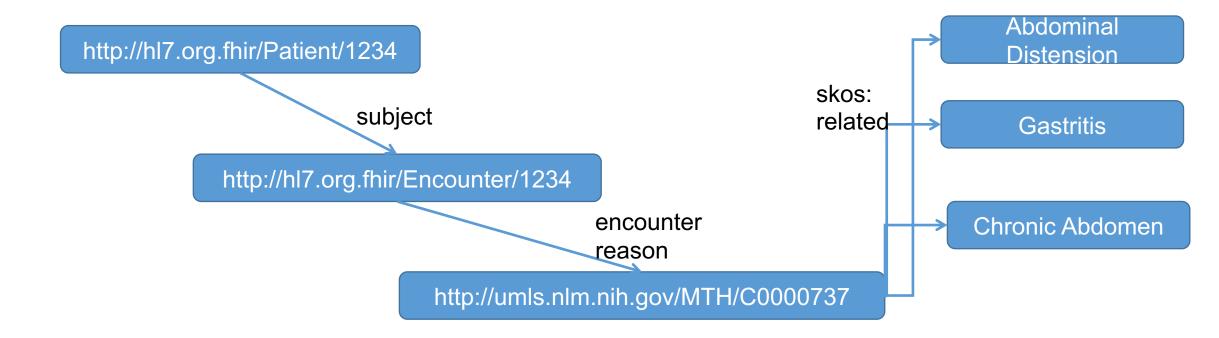
### CONNECT DISPARATE BUT RELATED SOURCES OF BIOMEDICAL KNOWLEDGE

- ClinicalTrials.gov
- Drugbank
- RxNORM
- SIDER

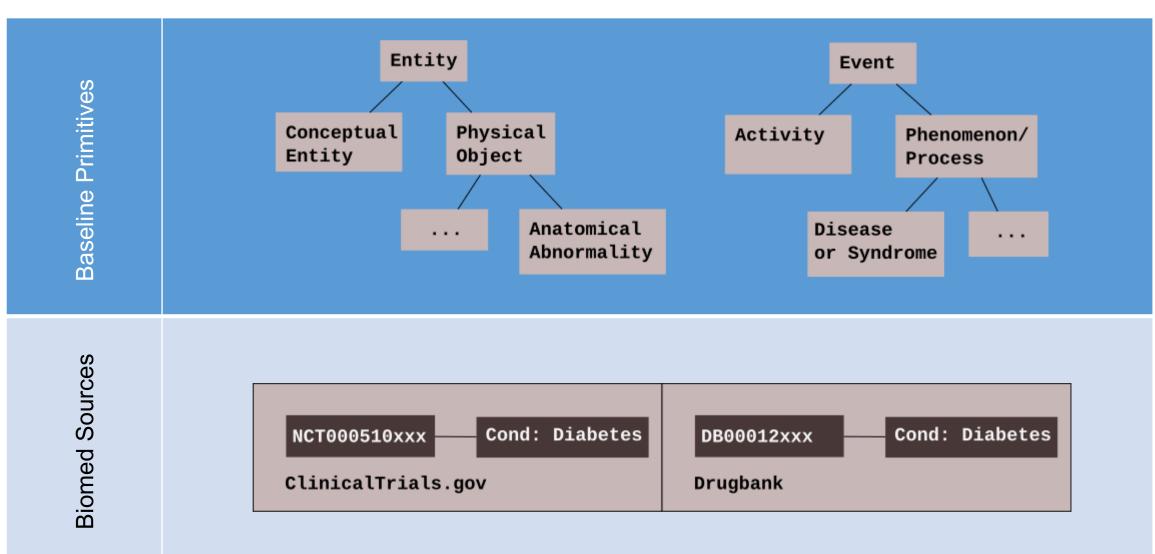


**Biomedical Knowledge Sources** 

CONNECT HEALTH DATA TO KNOWLEDGE GRAPH



# **Baseline KG**



### UMLS: COMPONENTS

- Unified Medical Language System (UMLS) is a long-term project of the NLM (National Library of Medicine) which involves mapping biomedical concepts across multiple sources using a concept unique identifier (CUI) to normalize concepts and organize concepts across 54 broad semantic type categories called the semantic network.
- Three components of UMLS
  - Metathesaurus
  - Semantic Network
  - Specialist Lexicon and Lexical tool

### UMLS: METATHESAURUS

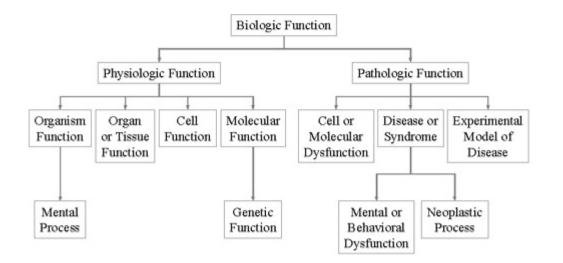
• Over 100 vocabularies, code sets, and thesauri, or "source vocabularies" are brought together to create the Metathesaurus. Terms from each source vocabulary are organized by meaning and assigned a concept unique identifier (CUI).

Term	Source Vocabulary
Atrial fibrillation	ICD-9-CM
AF	NCI Thesaurus
AFib	MedDRA
Atrial fibrillation (disorder)	SNOMED Clinical Terms
atrium; fibrillation	ICPC2-ICD10 Thesaurus



### UMLS: SEMANTIC NETWORK

 The Semantic Network consists of semantic types and semantic relationships. Semantic types are broad subject categories, like Disease or Syndrome or Clinical Drug. Semantic relationships are useful relationships that exist between semantic types. For example: Clinical Drug treats Disease or Syndrome.



### UMLS: RELATIONSHIPS

### Hierarchical

**PAR:** has parent relationship

CHD: has child relationship

**RB:** has broader relationship

**RN:** has narrower relationship

**RO:** Relationship other than RB/RN

### Synonymous or Qualifier Relationships

AQ: Allowed Qualifier

QB: Can be qualified by

**RL:** Synonymous

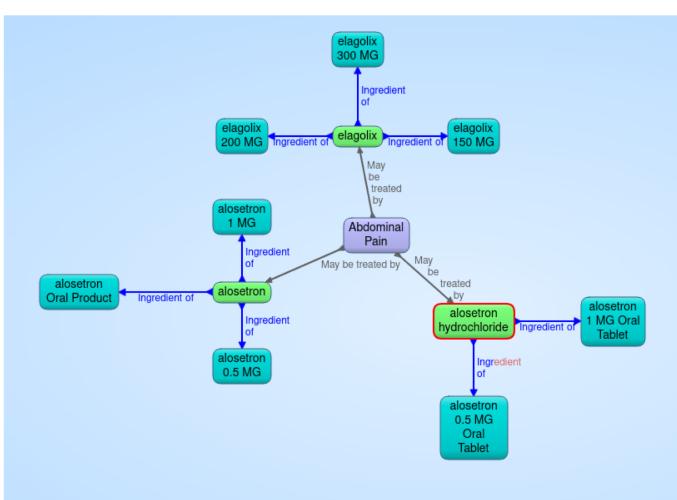
**RQ:** Related and possibly Synonymous

SY: Source asserted Synonymy

RU: Related, unspecified

### UMLS: RELATIONSHIPS OTHER THAN SYNONYMOUS OR HIERARCHICAL

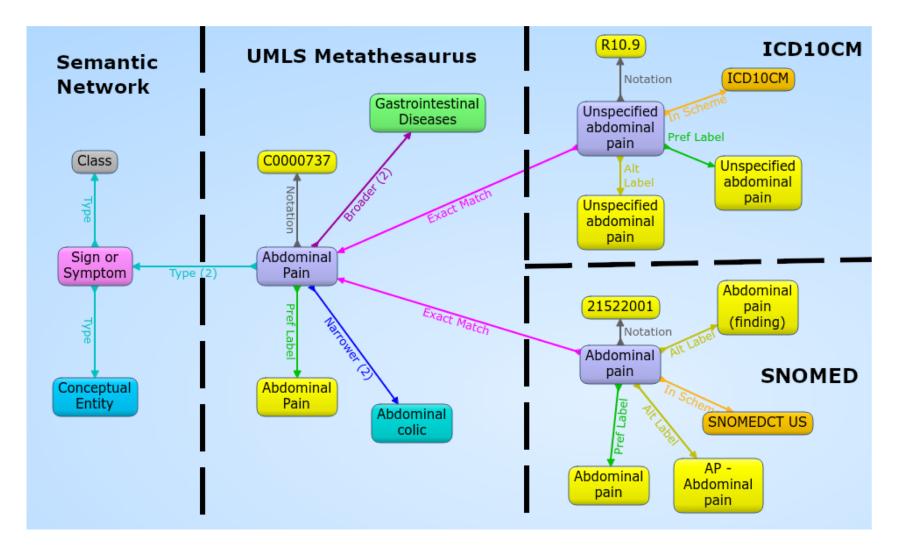
 The UMLS Metathesaurus also imports a host of relationships from the source vocabulary which is not hierarchical or synonymous or semantic in nature. These relatioships connect concepts of same or different semantic type. For example, "ingredient of" relationship can connect a concept of pharmacologic substance to a concept of clinical drug. Following screen shot shows an example of such a network built from these types of relationships.



# Simple Knowledge Organization System (SKOS)

- A semantic web framework for use of thesauri, vocabularies and controlled taxonomies
- FAIR representation of domain knowledge.
- Can potentially share over distributed environment using semantic web principles
- Extensible
- Concepts from different sources can be organized into separate concept schemes and linked together based on semantic similarity

## **SKOS Representation of UMLS**



# **SKOS Representation of UMLS**

 The UMLS sources including the Metathesaurus (abbreviated MTH) are represented as skos:ConceptScheme. The concepts imported from the source will link to the skos:ConceptScheme resource using skos:inScheme property. Below is an example of skos:ConceptScheme definition for Medical Subject Heading (abbreviated MSH) and an example of a MeSH concept linked to the defined ConceptScheme class:

<http://umls.nlm.nih.gov/2021AA/MSH> rdf:type skos:ConceptScheme .

<http://umls.nlm.nih.gov/MSH/D015746> skos:inScheme <http://umls.nlm.nih.gov/2021AA/MSH> .

- The UMLS concepts are imported as skos:Concepts and each have unique URI's that identify the source vocabulary and the corresponding code used in source vocabulary. For example, <<u>http://umls.nlm.nih.gov/MTH/C0000737> rdf:type skos:concept.</u>
   <a href="http://umls.nlm.nih.gov/MSH/D015746>">http://umls.nlm.nih.gov/MSH/D015746>">http://umls.nlm.nih.gov/MSH/D015746></a> rdf:type skos:concept.
- The skos:exactMatch property links UMLS concepts across different ConceptSchemes or UMLS sources:

;; Concept of Abdominal Pain in MSH scheme is same as Abdominal Pain in Metathesaurus with CUI C0000737 <<u>http://umls.nlm.nih.gov/MSH/D015746> skos:exactMatch <<u>http://umls.nlm.nih.gov/MTH/C0000737</u>>.</u>

# **SKOS Representation of UMLS**

- The PAR/RB and CHD/RN relationships from UMLS Metathesaurus are interpreted as skos:broader and skos:narrower relationships respectively.
   <a href="http://umls.nlm.nih.gov/MTH/C0000737">http://umls.nlm.nih.gov/MTH/C0476288</a>.
   <a href="http://umls.nlm.nih.gov/MTH/C0000737">http://umls.nlm.nih.gov/MTH/C0476288</a>.
- Each imported skos:Concept will also have a skos:prefLabel property set to preferred term imported from UMLS per source.
   <a href="http://umls.nlm.nih.gov/MTH/C0000737">http://umls.nlm.nih.gov/MTH/C0000737</a>> skos:prefLabel "Abdominal Pain".
   <a href="http://umls.nlm.nih.gov/MSH/D015746">http://umls.nlm.nih.gov/MTH/C0000737</a>> skos:prefLabel "Abdominal Pain".
- In addition to setting the skos:prefLabel property, SKOS import will also set skos:altLabel and skos:notation properties to alternative terms and code used in the source respectively for the concerned concept:

<http://umls.nlm.nih.gov/MSH/D015746> skos:altLabel "Pain, Abdominal" . <http://umls.nlm.nih.gov/MSH/D015746> skos:altLabel "Colicky Pain" . <http://umls.nlm.nih.gov/MSH/D015746> skos:notation "D015746" .

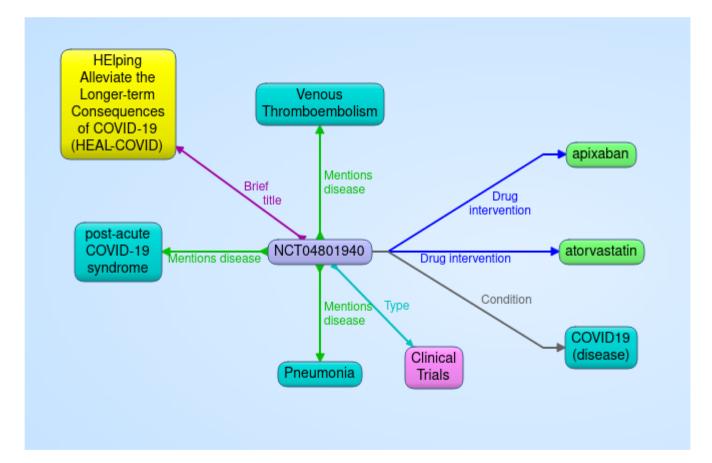
# **Augmenting Baseline KG - ClinicalTrials.gov**

### CLINICAL TRIALS KNOWLEDGE GRAPH

- ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. It is a resource provided by the US National Library of Medicine (NLM). Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study.
- The dataset is distributed as a set of XML files containing detailed information on studies including recruiting information, eligibility criteria and clinical outcomes. Each ClinicalTrials.gov record presents summary information about a study protocol and includes the following:
  - Disease or Condition
  - Intervention (for example, the medical product, behavior or procedure being studied)
  - Title, description and design of the study
  - Requirements for participation (eligibility criteria)
  - Locations where the study is being conducted
  - Contact information for the study locations
  - Outcomes of the study if available
  - Summary of adverse events experienced by study participants

### Augmenting Baseline KG - ClinicalTrials.gov

### LINKEDCT REPRESENTATION OF CLINICAL TRIALS DATA



h dhim_Brody	
<intervention></intervention>	
<intervention_type>Drug</intervention_type>	
<intervention_name>Amoxicillin - high dose dual therapy</intervention_name>	
<pre><description>Eradication with Amoxicillin 1000mg + 500 mg + 1000mg + 500mg, for 15 days.</description></pre>	
<arm_group_label>Treatment with high-dose amoxicillin + esomeprazole 40mg</arm_group_label>	
<intervention></intervention>	
<intervention_type>Drug</intervention_type>	
<intervention_name>Pylera</intervention_name>	
<description>Eradication with Pylera, for 10 days.</description>	
<arm_group_label>Treatment with Pylera (r) + esomeprazole 40mg</arm_group_label>	
<intervention></intervention>	
<intervention_type>Drug</intervention_type>	
<intervention_name>Esomeprazole 40mg</intervention_name>	
<description>Esomeprazole 40mg, twice a day.</description>	
<arm_group_label>Treatment with Pylera (r) + esomeprazole 40mg</arm_group_label>	
<arm_group_label>Treatment with high-dose amoxicillin + esomeprazole 40mg</arm_group_label>	
<pre>celigibility&gt;</pre>	

<condition\_browse>
 <!-- CAUTION: The following MeSH terms are assigned with an imperfect algorithm -->
 <mesh\_term>Infections</mesh\_term>
 <mesh\_term>Communicable Diseases</mesh\_term>
 <mesh\_term>Helicobacter Infections</mesh\_term>
 <mesh\_term>Gastritis</mesh\_term>

</condition\_browse>

### BIOMEDICAL NLP - METHOD

- The description and summary fields in clinicaltrials.gov data are unstructured and as a result, we need to
  perform bio-medical Named Entity Recognition (NER) on the fields of interest and in addition, normalize the
  identified entities using UMLS Concept Identifiers or CUI.
- Thus entity resolution is a two step process
  - first step involving entity recognition of types disease, drug or gene in the free-text
  - second step involving lookup of UMLS CUI associated with the entity.



### BIOMEDICAL NER - BIOBERT

- BioBERT (Bi-Directional Encoder Representations from Transformers for Biomedical Text Mining) is a pretrained language representation model for biomedical domain. We will be using a BioBERT model which is fine-tuned for biomedical NER for the purpose of entity identification in free-text.
- BioBERT is pre-trained on biomedical domain corpora (PubMed abstracts and PMC full-text articles). Following table represents datasets used for fine-tuning BioBERT for each of the NER usecases:

Dataset	Entity Type	Number of Annotations
NCBI-disease	disease	6881
BC4CHEMD	drug/chem	79842
BC2GM	gene/protein	20703

### **BIOMEDICAL NER - BIOBERT**

Result:

🛑 Genes/Proteins 🛑 Diseases 🛑 Drugs/Chemicals 🛑 Species 🛑 Mutations 🛑 miRNAs 🛑 Pathways

BACKGROUND Vaccine-related thrombosis and thrombocytopenia syndrome (TTS) is a rare life-threatening syndrome reported after vaccination against COVID-19. CASE REPORT We describe a case of 56-year-old postmenopausal, obese woman with hypothyroidism and hyperlipidemia, who presented to the Emergency Department (ED) with fluctuating mental status and left-side weakness for 5 days. She received her first and second dose of mRNA-1273 vaccine (Moderna) at 12 and 8 weeks, respectively, prior to presentation. She was found to have multiple hemorrhages and infarcts on a computed tomography (CT) scan of the head. She was intubated in the ED for airway protection and mechanically ventilated. Magnetic resonance angiogram and venogram showed multiple infarcts in right frontal, parietal, and left parietal lobes, along with occlusion of left-side transverse sinus, sagittal sinuses, and left internal jugular vein, suggesting cerebral venous sinus thrombosis (CVST). Despite anticoagulation, her clinical condition continued t

#### Result in PubAnnotation JSON:

Copy JSON to clipboard

"project": "BERN",

"sourcedb": "",

"sourceid": "23259d89ae3d303bb444a220b2bdc3267128d66f13dc5c5f021423e9-Thread-4005404",

"text": "BACKGROUND Vaccine-related thrombosis and thrombocytopenia syndrome (TTS) is a rare life-threat ening syndrome reported after vaccination against COVID-19. CASE REPORT We describe a case of 56-year-old po stmenopausal, obese woman with hypothyroidism and hyperlipidemia, who presented to the Emergency Department

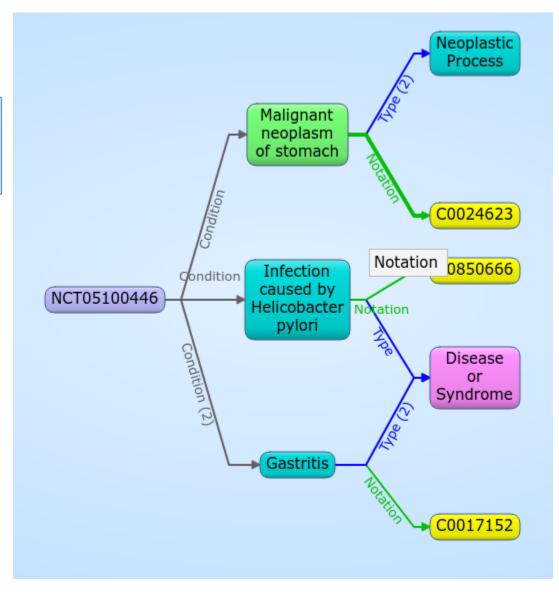


### BIOMEDICAL ENTITY NORMALIZATION

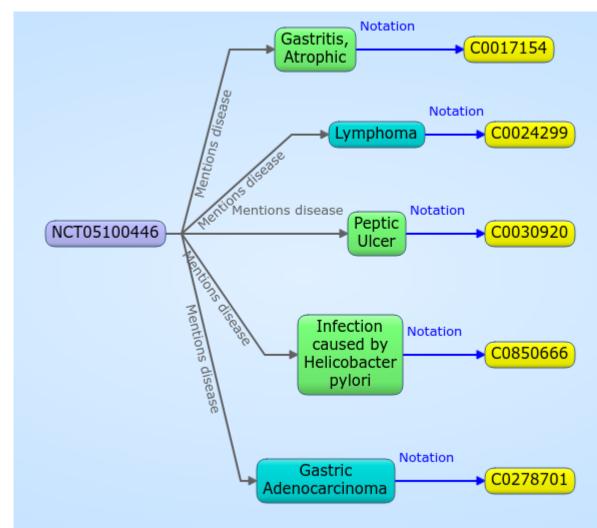
- Each entity identified by NER model needs to be resolved to it's corresponding identifier in the target vocabulary or ontology.
- Following table is a list of tools available for purpose of entity normalization based on type of entity:

Normalizer	Entity Type
GNormPlus	Gene
tmChem	Chemical
tmVar	Mutation
MetaMap	All UMLS Semantic Types
DNorm	Disease
SR4GN	Species

<condition>Helicobacter Pylori Infection</condition> <condition>Gastritis</condition> <condition>Gastric Cancer</condition>



H. pylori infection is associated with active chronic gastritis in every colonized patient, what may consequently lead to peptic ulcer disease, atrophic gastritis, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma.

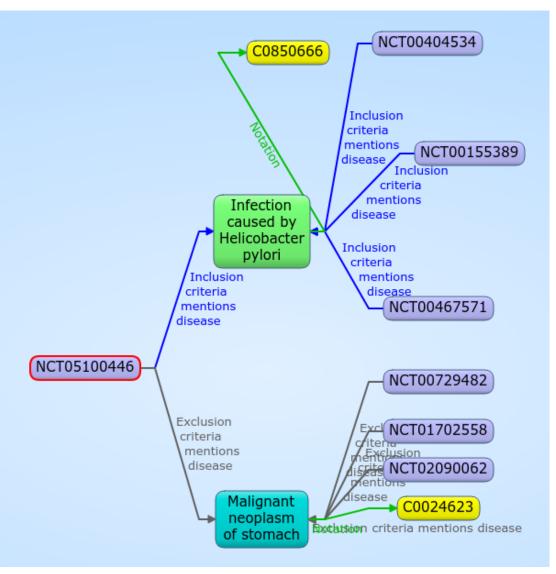


Inclusion Criteria:

- Documented Helicobacter pylori infection
- Age equal or greater to 18 years
- Recent (6months) upper digestive endoscopy
- Ability to consent to participate in the study

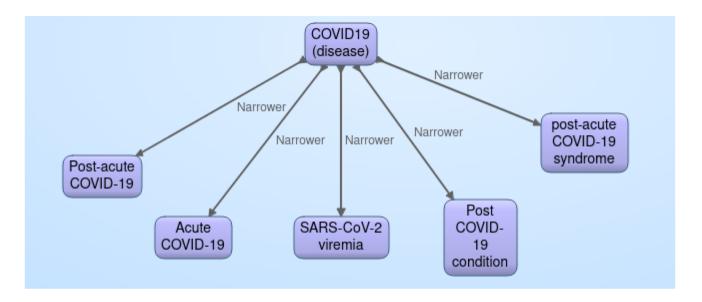
Exclusion Criteria:

- Documented allergy to any of the available drugs
- Contraindications to any of the available drugs
- Antibiotics use for the last 4 weeks
- Previous gastric cancer
- Previous gastric surgery
- Pregnancy
- Breastfeeding



# Query for all child concepts of UMLS Concept with CUI C5203670 which is the concept of COVID-19 disease in UMLS.

```
select distinct ?cond ?cond_label where {
    umls:C5203670 skos:narrower ?cond .
    ?cond skos:prefLabel ?cond_label .
```



# Query for trials related to covid-19 or trials that mention covid19..

```
select ?title ?cond label where {
 #Sub-query to collect covid and it's child concepts in UMLS-SKOS
                                                                                                                                                                        title
  select distinct ?cond where {
   {umls:C5203670 skos:narrower ?cond .}
                                                                                                              Risk Factors Worsening COVID19 for Out-patient With Home Monitoring
   UNION
   {BIND(umls:C5203670 AS ?cond)}
                                                                SaRS-Cov-2 Antibodies Following Exposure to Coronavirus Disease 2019 (COVID-19) and/or Vaccination in Nursing Homes
 ?trial :mentions_disease|linkedct-rel:condition ?cond .
                                                                               Anti COVID 19 Hyperimmune Intravenous Immunoglobulin (C-IVIG) Therapy for Severe COVID-19 Patients
 ?cond skos:prefLabel ?cond label.
 ?trial linkedct-rel:brief title ?title .
                                                                                                           Convalescent Plasma Transfusion in Severe COVID-19 Patients in Jamaica
limit 50
                                                                         Natural History of Systemic and Nasal Mucosal Immunity to Influenza and SARS-CoV-2 in Adults After Vaccination
                                                                                        Safety, Tolerability, and Pharmacokinetics of SAB-185 in Ambulatory Participants With COVID-19
```

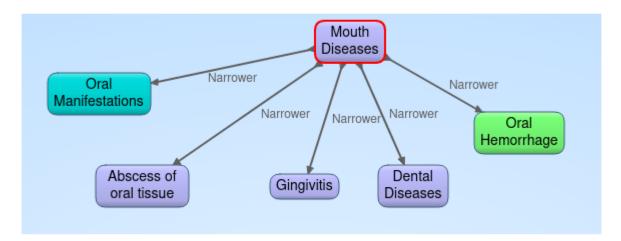
The Salivary Raman COVID-19 Fingerprint

### COVID-19 TRIALS DEALING WITH ORAL SIDE-EFFECTS

# Query for all child concepts of UMLS Concept with CUI C0026636 which is the concept of mouth disease in UMLS

select distinct ?cond ?cond\_label where {
 umls:C0026636 skos:narrower ?cond .
 ?cond skos:prefLabel ?cond\_label .

} limit 25



### COVID-19 TRIALS DEALING WITH ORAL SIDE-EFFECTS

# Query for trials related to covid-19 or trials that mention covid19..

```
select distinct ?trial ?title {
 #sub-guery for narrower concepts of COVID-19 disease
   select distinct ?cond where {
    {umls:C5203670 skos:narrower ?cond .}
    UNION
    {BIND(umls:C5203670 AS ?cond)}
 #sub-query for narrower concepts of mouth diseases
   select distinct ?oral cond where {
    {umls:C0026636 skos:narrower ?oral cond .}
    UNION
    {BIND(umls:C0026636 AS ?oral cond)}
 ?trial rdf:type umls:C0008976.
 ?trial :mentions disease|linkedct-rel:condition ?cond .
 ?trial :inclusion_criteria_mentions_disease|linkedct-rel:condition ?oral_cond .
 ?trial linkedct-rel:brief title ?title .
```

### Title

Oral Manifestations of Coronavirus Disease 2019(COVID-19) :a Multicentre Study

Evaluation of Dental Emergency Treatments During COVID19 Crisis

Proper Nutrition And Its Relation To Oral Diseases In Covid -19 Era

Oral Manifestation of COVID 19 Patient: A Cross Sectional Study on Egyptian Population

Oral Side Effects of COVID-19 Vaccine

Familial Mediterranean Fever and Behçet: Analysis Before and After Covid19 Pandemic

Oral Manifestation in Patients With SARS-CoV2 Infection.

the Prevalence of Oral Manifestation in Patients With SARS-CoV2 Infection

### Use-Case: Patient Health Data Connected to Biomedical Knowledge ENTITY EVENT KNOWLEDGE GRAPH

### Entity Event Knowledge Graph for Powerful Health Informatics

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Abstract—This paper introduces the Entity-Event Knowledge Graph (EEKG) model for clinical data stored in graph databases. We describe how the EEKG model dramatically simplifies the representation of patient data, facilitates temporal queries, enables a 360 view of patients and promotes scalability by partitioning patient data into shards. We solved the practical problem that not all clinical data and life science knowledge can be sharded. The solution is to federate each individual shard with common shared data in a knowledge graph. One such shared data source is the UMLS (Unified Medical Language System) knowledge base, which contains genetic, drug clinical trials and Metathesaurus data that we link to individual patient records. We report on several use cases including EMR patient retrieval, matching patients with clinical trials, patient control group selection, and care quality measures.

Keywords—entity-event model, knowledge graph, distributed graph database, umls skos knowledge graph, clinical trials knowledge base

#### I. INTRODUCTION

We describe an EMR and Analytics data system based on

(NLM) project that integrates multiple sources of biomedical knowledge, vocabulary and standards [3]. We report on several use cases including EMR patient retrieval, matching patients with clinical trials, patient control group selection, and care quality measures.

#### II. METHOD

In this section, we will describe our approach to building an EEKG model based on patient health data and linking it to a biomedical knowledge graph constructed from multiple sources of biomedical knowledge bases such as UMLS and the clinicaltrials.gov dataset [6]. For the purpose of this demonstration we will use synthetic patient data generated using an open-source project called Synthea [2]. Patient health data concepts will be linked to a knowledge graph by normalizing concepts to standard vocabulary which in this case will be the UMLS Metathesaurus.

#### A. Entity-Event Model

The Entity-Event (EE) model is a method of data organization for information stored in a graph database. By



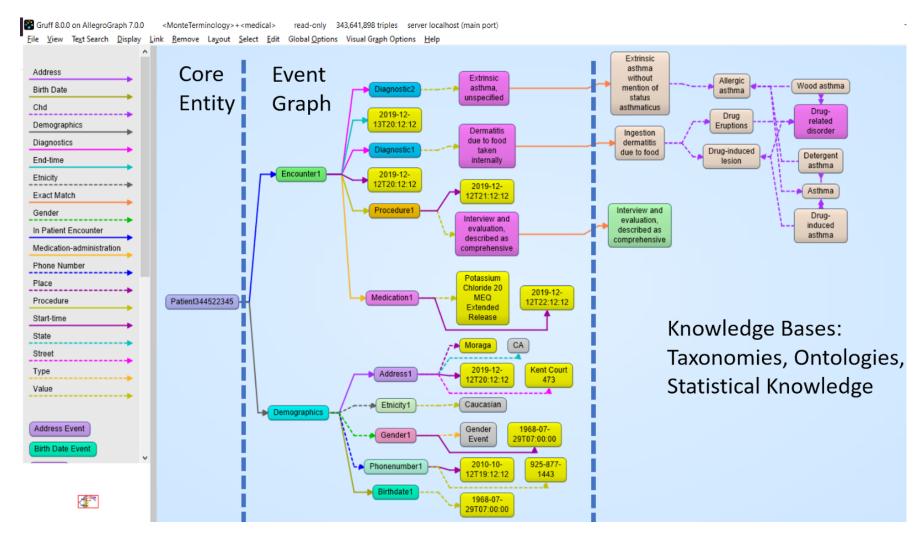
# Use-Case: Patient Health Data Connected to Knowledge Graph ENTITY-EVENT KNOWLEDGE GRAPH

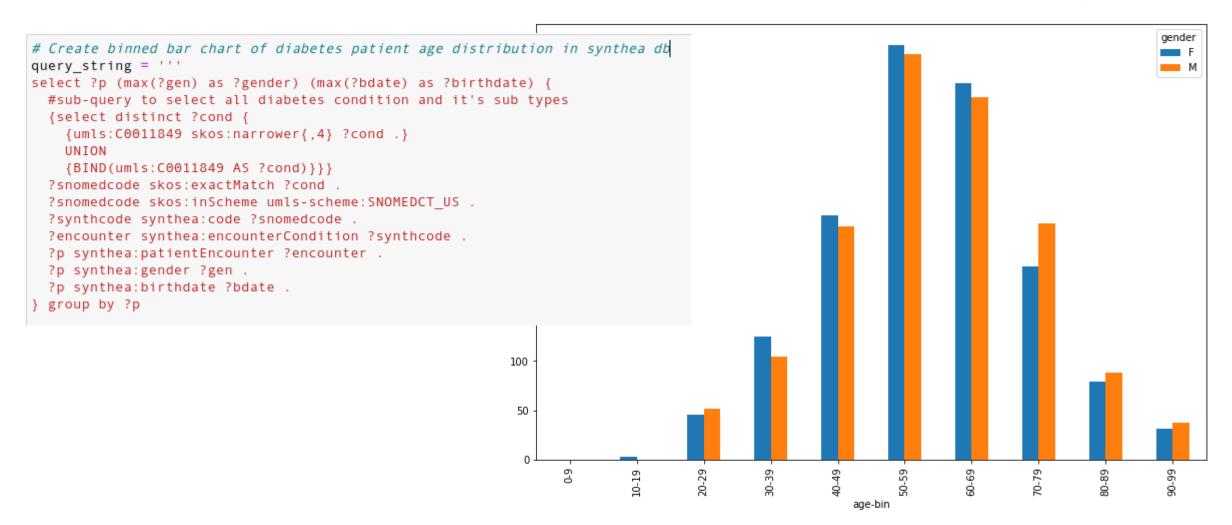
- Patient data is typically represented as a hierarchical tree.
- At the top of the tree is the patient as the core entity. The next level of the tree consists of events and sub-events.
- Usually the top level events are inpatient and outpatient encounters with sub-events such as diagnostics, observations, medication orders, procedures and vital signs.
- Each of these event objects have a similar shape because they all have a main type and an associated start and, optionally, end time.
- Their other properties distinguish them from other events: Encounters have providers, medications have dosages, observations have values, and so on, but they all have start times

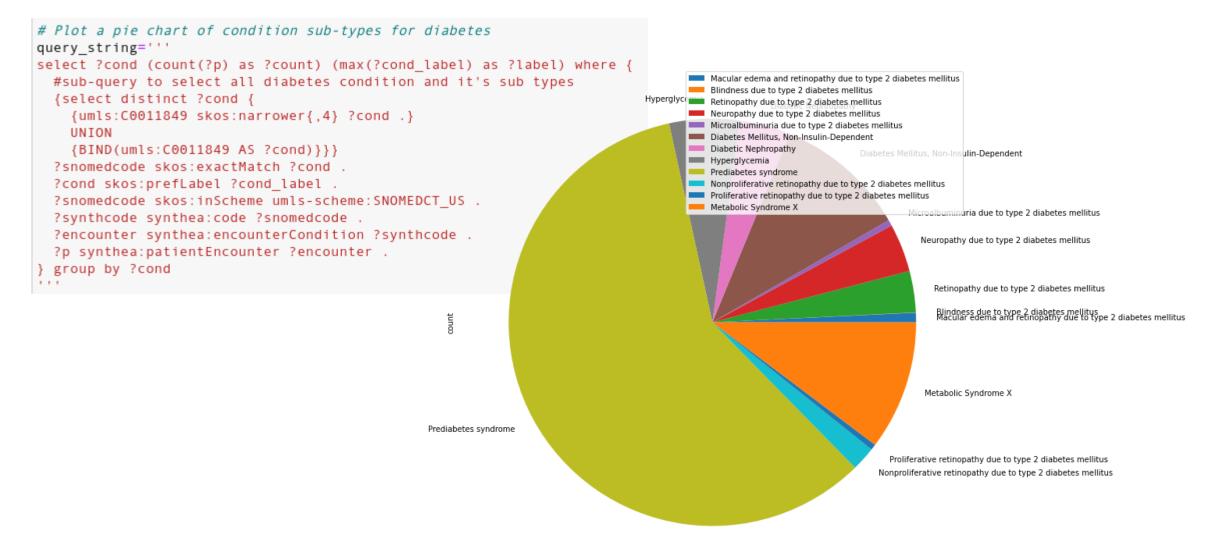


### **Use-Case: Patient Health Data Connected to Knowledge Graph**

### ENTITY-EVENT KNOWLEDGE GRAPH MODEL FOR HEALTH DATA







SPARQL query to fetch diabetic patients based on conditions specified for NQF-

59 quality measure

select ?patient (max(?obsDate) as ?obsDate) {

select ?category (count(?category) as ?count) {

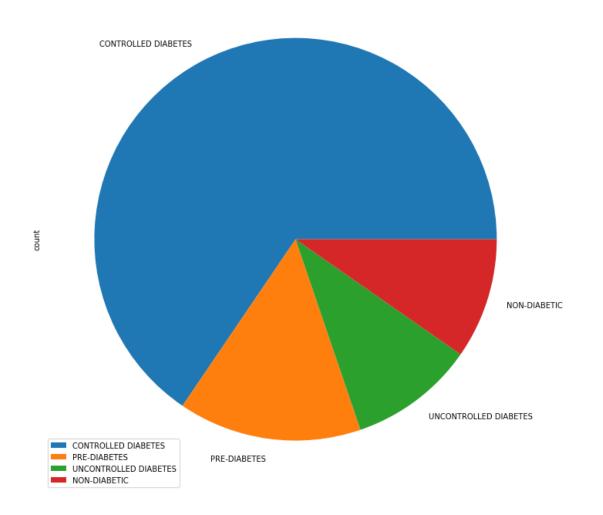
```
# sub-query for office visit
      select ?patient (max(?ovDate) as ?ovDate) {
       # sub-query for diagnosis
          select ?patient (max(?diagnosisDate) as ?diagnosisDate) {
               {umls:C0011849 skos:narrower{,4} ?cond .} UNION {BIND(umls:C0011849 AS ?cond)}
               ?snomed skos:exactMatch ?cond; skos:inScheme umls-scheme:SNOMEDCT_US .
               ?condition rdf:type synthea:Condition; synthea:code ?snomed;
                          synthea:startDateTime ?diagnosisDate FILTER (?diagnosisDate > "2018-06-01T00:00:00+00:00"^^xsd:dateTime).
               ?patient rdf:type synthea:Patient; synthea:patientCondition ?condition .
          } group by ?patient
       ?patient synthea:patientEncounter ?officeVisit; synthea:birthdate ?dob .
      ?officeVisit synthea:code/skos:notation "162673000"; synthea:startDateTime ?ovDate .
       bind(year(?ovDate) - year(?dob) - if(month(?ovDate) < month(?dob) || (month(?ovDate) = month(?dob) && day(?ovDate) < day(?dob)),1,0) as ?age
      filter (?ovDate > "2020-06-01T00:00:00+00:00"^^xsd:dateTime && ?age >= 18 && ?age <=75)
      } group by ?patient
    ?patient synthea:patientObservation ?obs .
    ?obs synthea:startDateTime ?obsDate; synthea:code/skos:notation "4548-4" .
   filter (?obsDate > "2020-06-01T00:00:00+00:00"^^xsd:dateTime)
  } group by ?patient
?patient synthea:patientObservation ?obs .
?obs synthea:startDateTime ?obsDate; synthea:code/skos:notation "4548-4"; synthea:value ?alc .
BIND (COALESCE (
                                                                          # categorize the A1C level
  IF(xsd:float(?alc) >= 8.0, "CRITICALLY HIGH", 1/0),
 IF(xsd:float(?alc) >= 7.0, "UNCONTROLLED DIABETES", 1/0),
 IF(xsd:float(?alc) >= 6.0, "CONTROLLED DIABETES", 1/0),
 IF(xsd:float(?alc) >= 5.7, "PRE-DIABETES", 1/0),
 IF(xsd:float(?alc) >= 0.0, "NON-DIABETIC", 1/0),
  "NO MEASUREMENT") as ?category)
} Group by ?category
```

# Use-Case: Patient Health Data Connected to Knowledge Graph ENTITY-EVENT KNOWLEDGE GRAPH

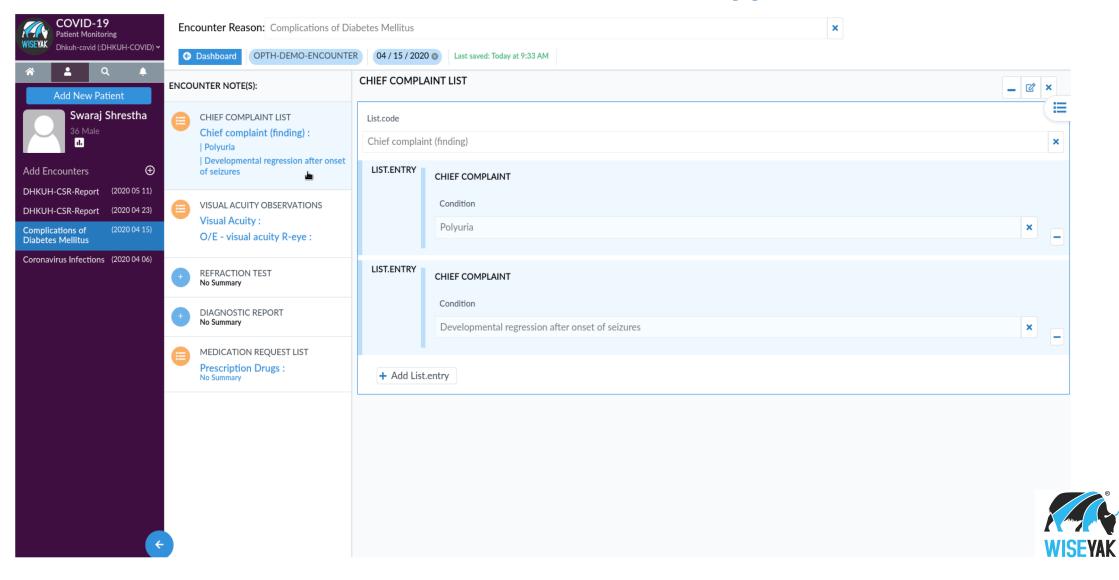
- 360 view of patient journey
- Descriptive analytics of Individual and Aggregated Patient Journey
- Temporal Analytics
- Easily scale to millions of patients and billions of RDF triples
  - Allegrograph FedShard
  - Shard using patient with each shard federated with a shared KG
- Knowledge-based data science



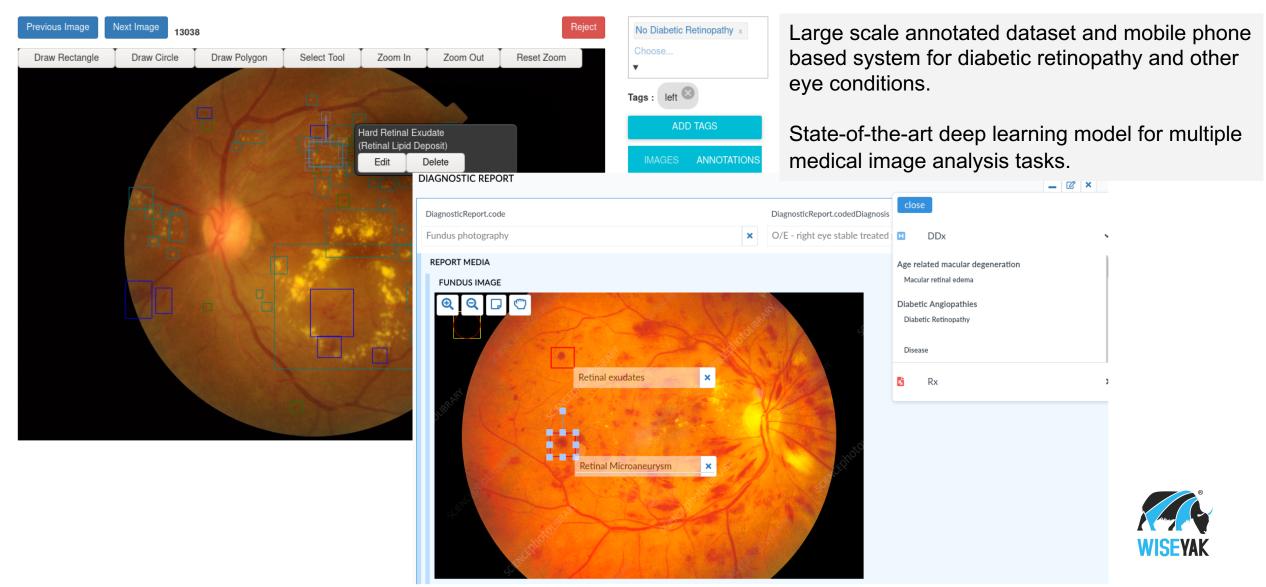
SPARQL query to fetch diabetic patients based on conditions specified for NQF-59 quality measure



# **Use-Case: Clinical Decision Support**



### **Use-Case: Clinical Decision Support**



### **Use-Case: Clinical Decision Support**



☐ Mobile phone based non mydriatic camera

☐ Attached to iphone

Permits image capture and upload to server





# Summary

- Semantic representation of UMLS improves it usability and interoperability beyond it's common use-cases.
- Lot of value in linking disparate but related sources of biomedical knowledge and making it FAIR in the process
- Linking health data to knowledge graph enables powerful healthcare informatics and analytics
- Biomedical knowledge becomes accessible and usable in clinical applications/workflows.