End of fellowship presentation - May 19th, 2017

# Investigating the Coverage of Disease Concepts across SNOMED CT and the Disease Ontology… …and other projects

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U.S. National Library of Medicine




# Agenda

- Specific Project: Coverage of disease concepts across SNOMED CT and DO
  - Introduction
  - Methods and Results
  - Discussion
  - Conclusion – Practical Contribution
- Shout-outs to other projects
  - Leveraging lexical features of concept names using DL – Application to QA in SNOMED CT
  - Harmonizing user defined phenotypic variables across studies in dbGaP
  - MeSHgram: A tool for visual browsing of PubMed
  - A toolkit to extend TCGA queries to fetch analogous sequence data from NCBI datasets

# Investigating coverage of disease concepts in SNOMED CT and DO

# Introduction

## SNOMED CT

- Largest clinical terminology (over 300,000 concepts)
- About 100,000 concepts in “Clinical findings” hierarchy
- Integrated in UMLS
- *March 2016 US edition used in this study. Converted to OWL using script provided.*

## Disease Ontology (DO)

- Part of OBO. Widely used in the research domain.
- 6931 *active* disease concepts
- ***Not integrated in UMLS.*** Some concepts mapped to SNOMED CT via “obo:hasDbXref”.
- *August 2016 release used in this study. Available in OWL format.*

- ***Interoperability is critical for translational research***

# *Methods* - Overview

- Establishing a reference set of mappings
  - Apply semantic constraints on existing mappings from DO to SNOMED CT
  - Find additional mappings lexically
- Characterizing DO concepts not mapped to SNOMED CT
  - Distribution of mapped vs. unmapped concepts by top-level hierarchies in DO
  - Analysis of connected components of unmapped concepts
  - Manual review of semantic “differentia” for unmapped concepts
- Comparing the hierarchical organization based on mapped concepts

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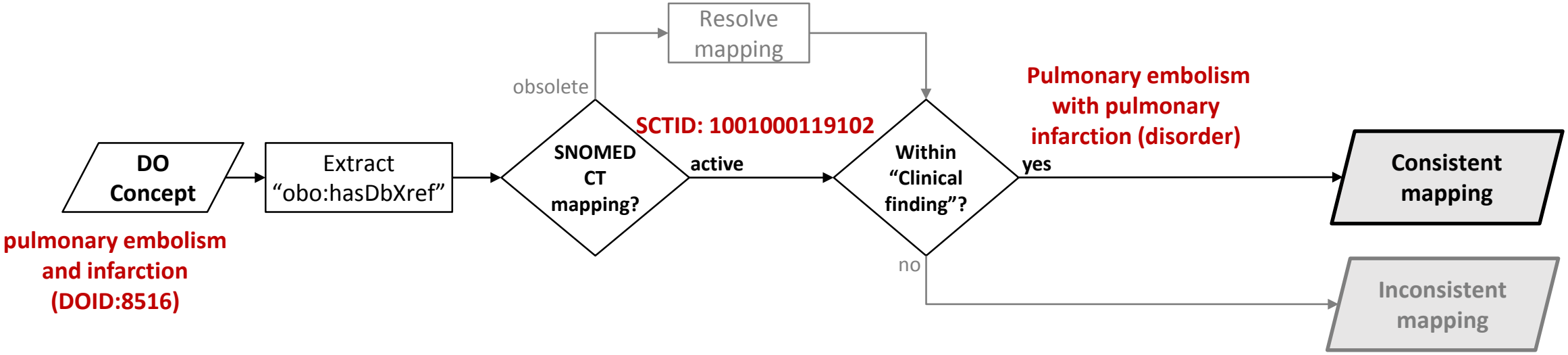
# *Methods* - Establishing a reference list of mappings (Semantic Constraint)

- Some DO concepts have “mappings” to SNOMED CT through “obo:hasDbXref”
- *Semantic constraint* - Mappings outside “Clinical Findings” hierarchy in SNOMED CT are considered semantically inconsistent



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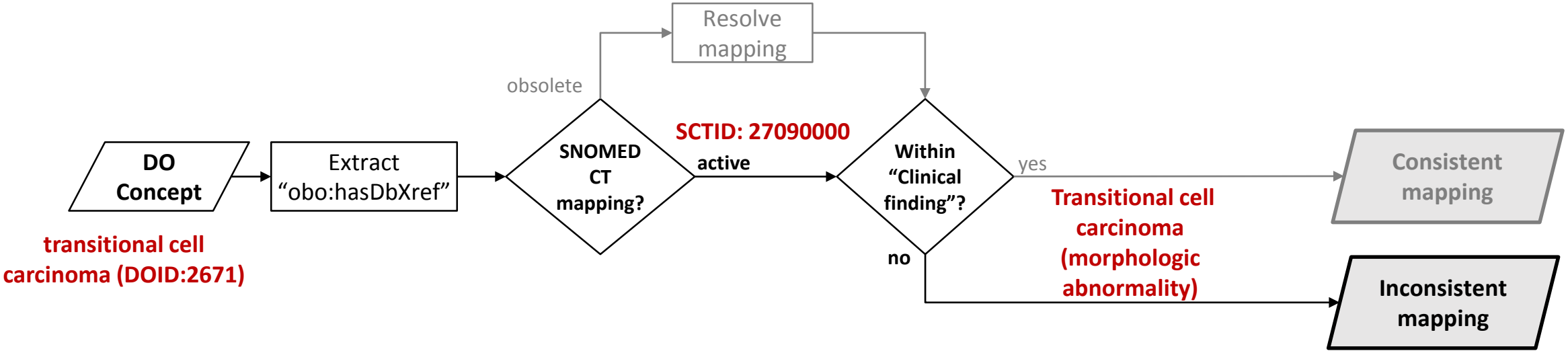
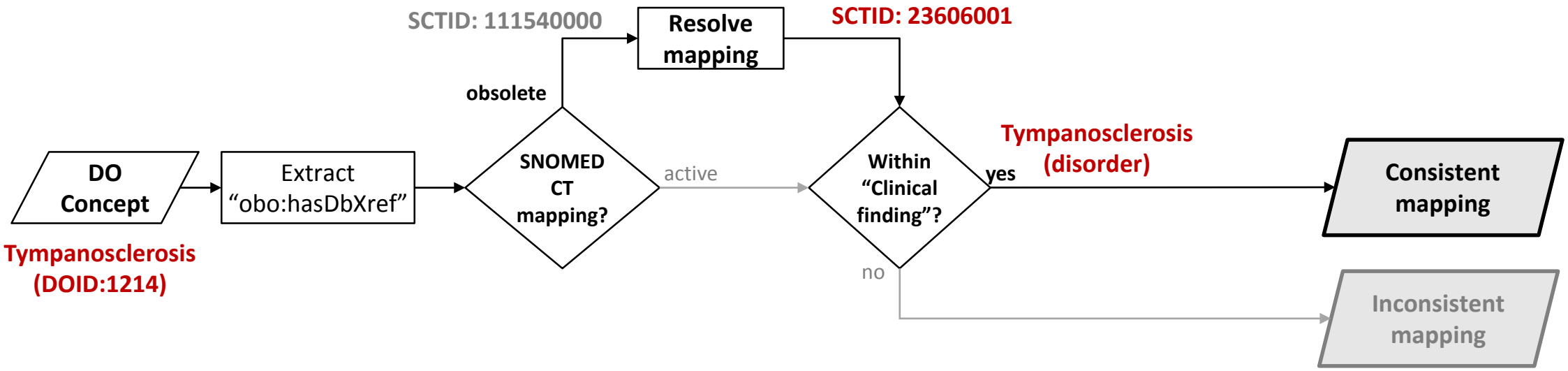


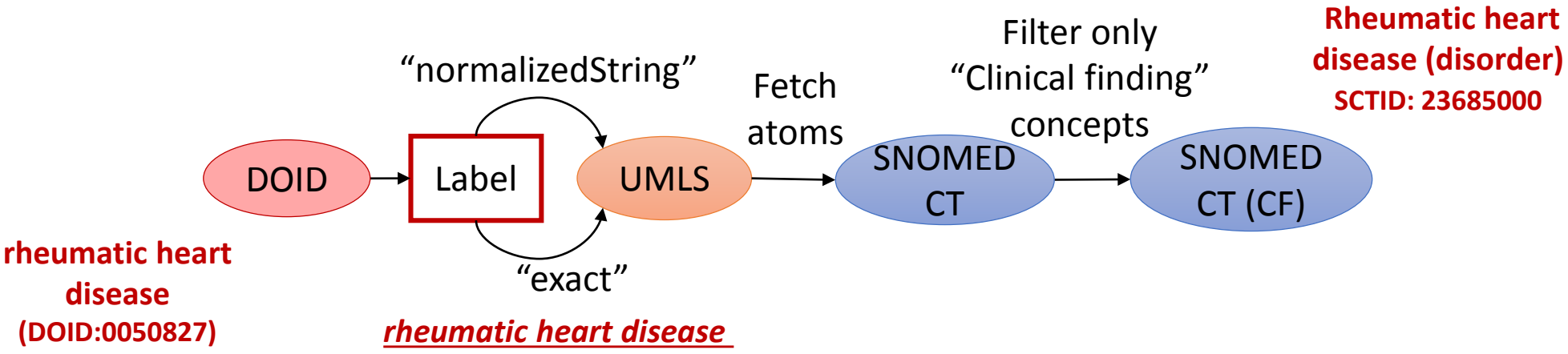
# *Methods* - Establishing a reference list of mappings (Semantic Constraint)

- Some DO concepts have “mappings” to SNOMED CT through “obo:hasDbXref”
- *Semantic constraint* - Mappings outside “Clinical Findings” hierarchy in SNOMED CT are considered semantically inconsistent
- Resolve mappings to obsolete SNOMED CT concepts

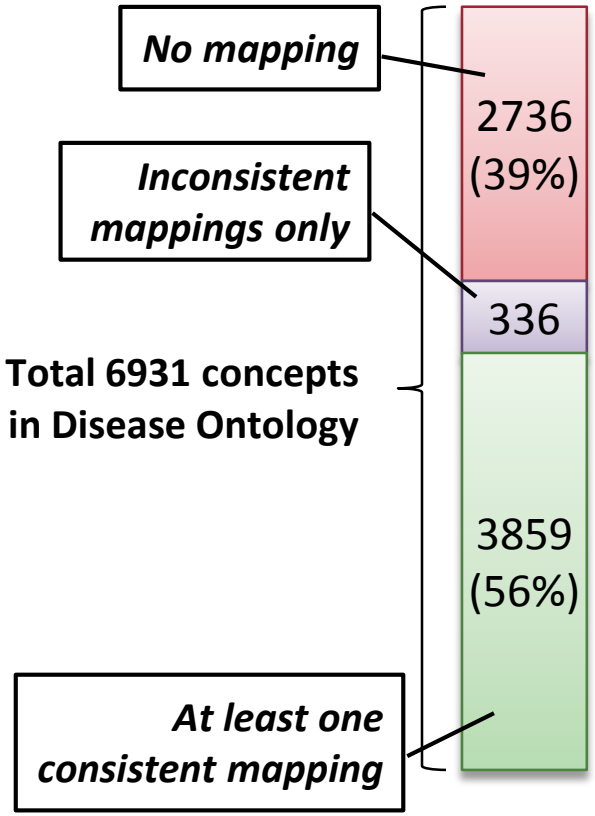


# *Methods* - Establishing a reference list of mappings (Lexical mappings)

- Find additional mappings to SNOMED CT via UMLS concepts lexically
- Leveraging synonymy within UMLS
- UMLS Rest API for string match based on label of DO concept



# *Results* - Establishing a reference list of mappings (Semantic Constraint)



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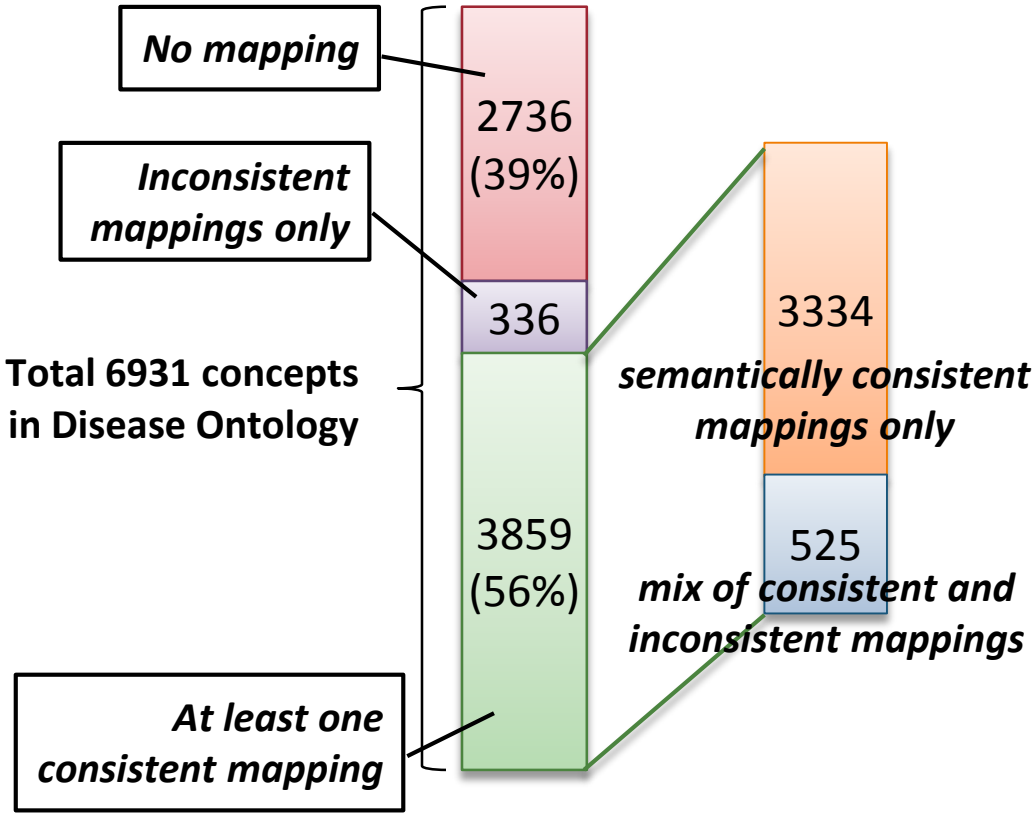

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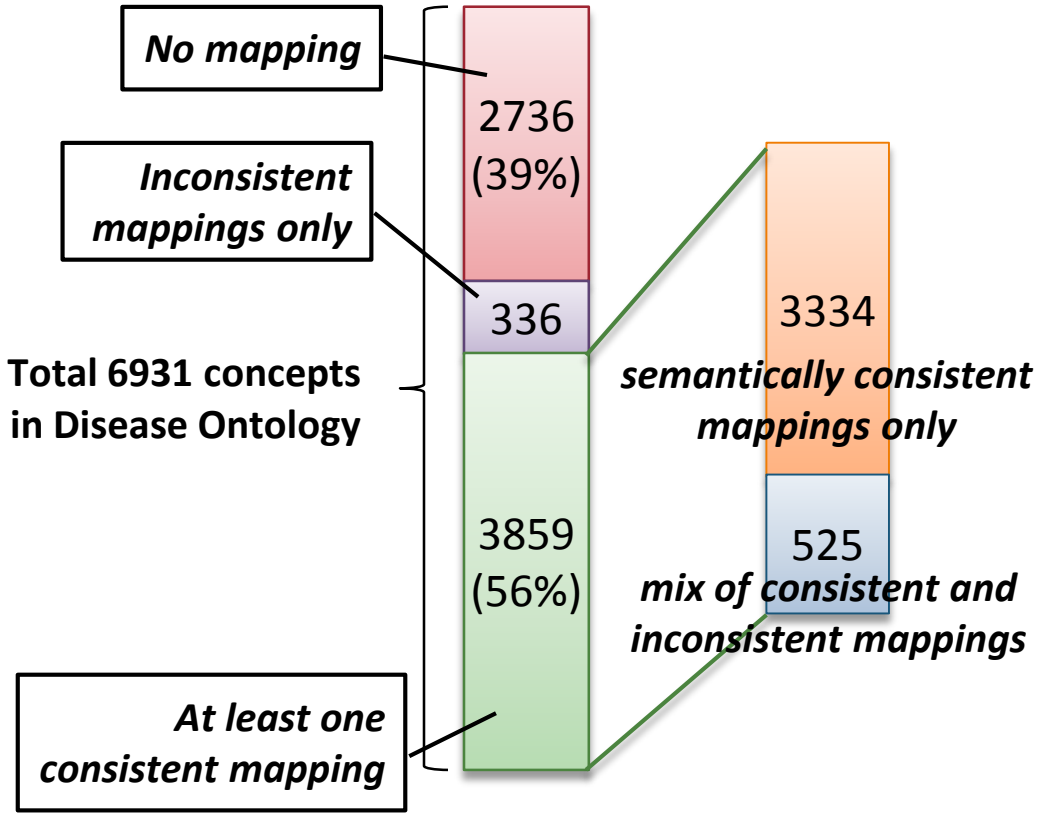
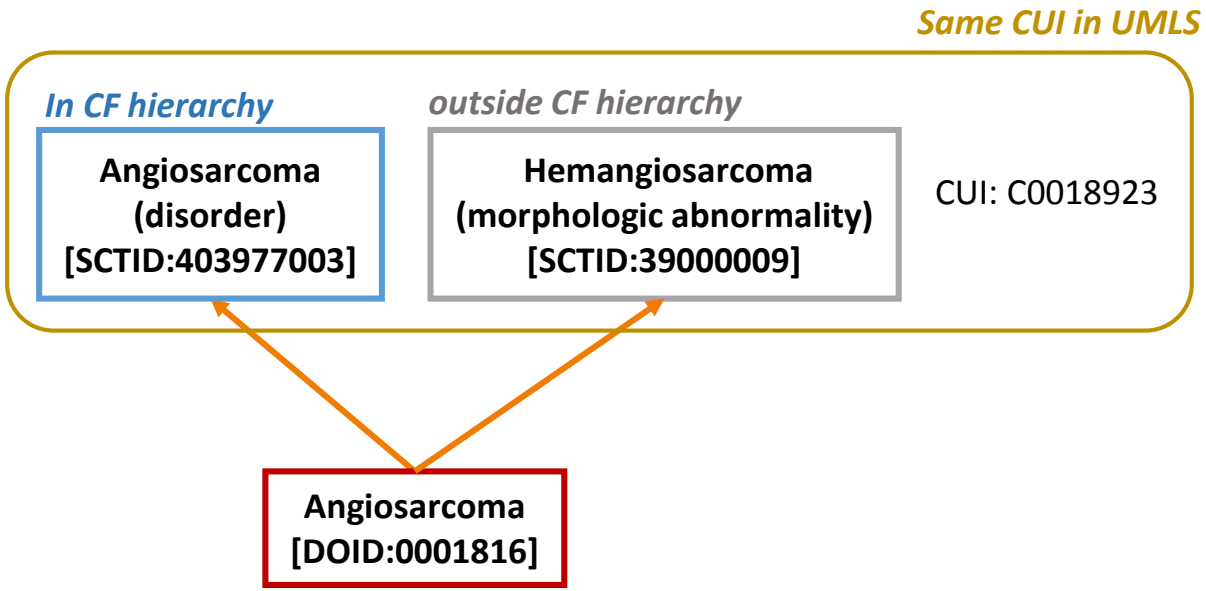



- 525 Concepts mapped with consistent and inconsistent mappings
- All of them were identified to be mapped to disorder and associated morphology
- Most had same UMLS CUI



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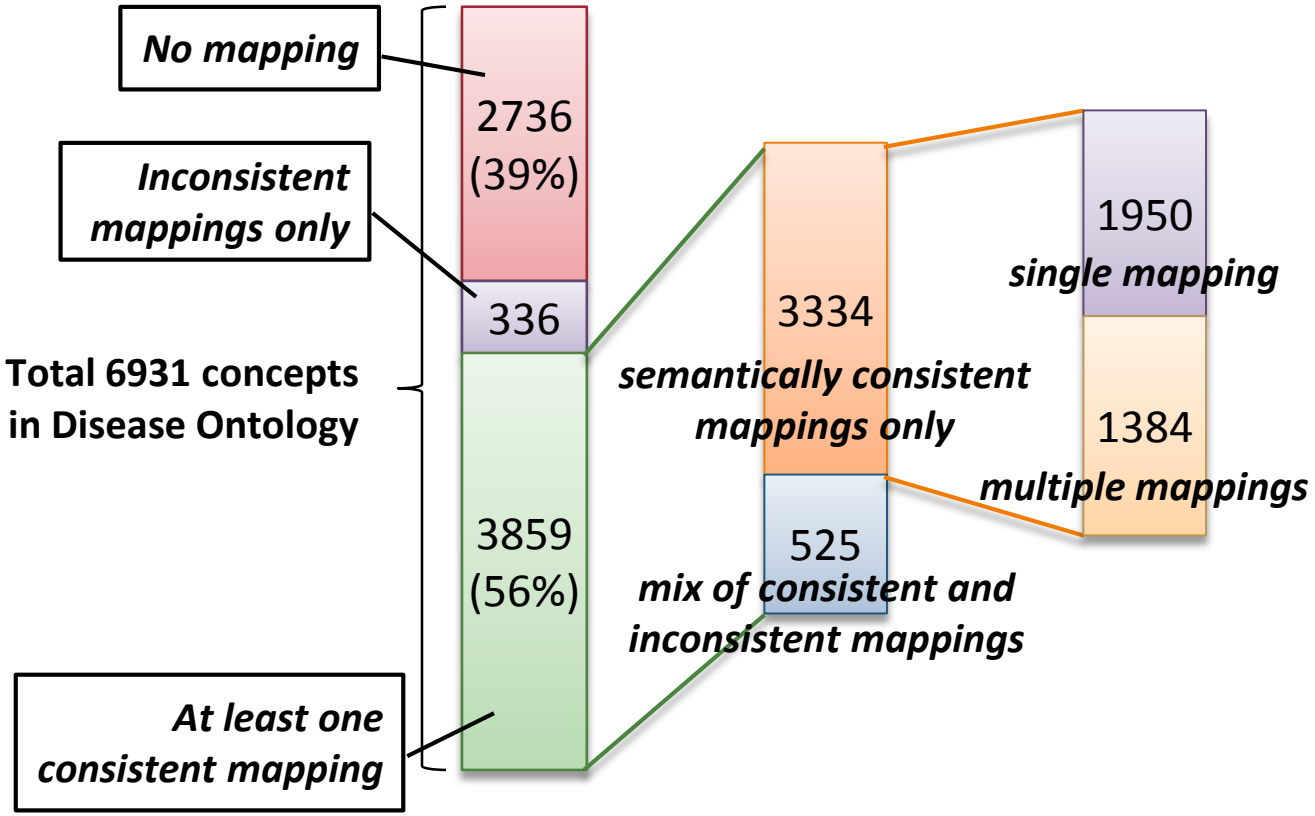

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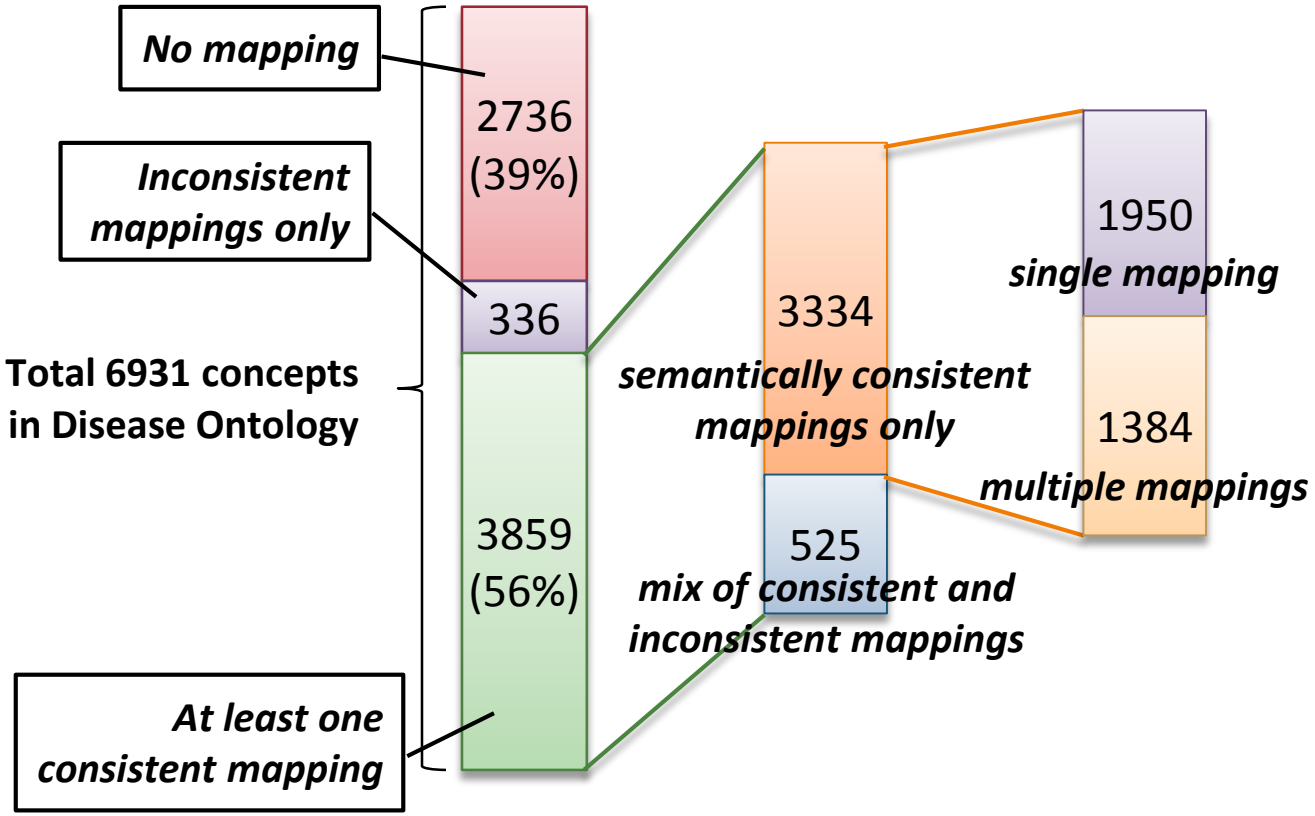
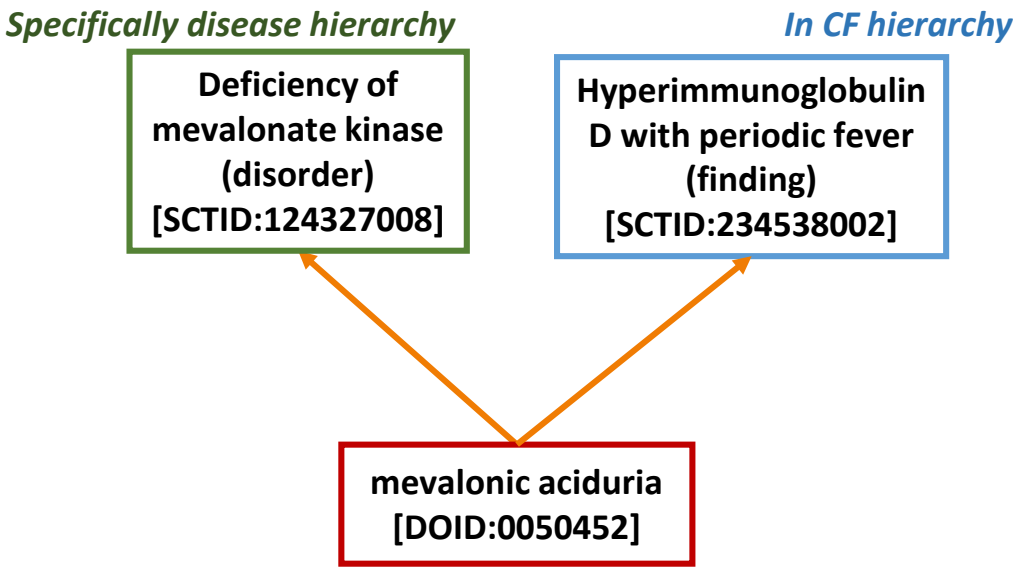



- 1384 concepts with multiple mappings that are all consistent
- 110 of these are mapped to disorder and associated finding
- 1274 concepts with multiple mappings within same hierarchy



# *Results* - Establishing a reference list of mappings (Lexical Mappings)

- 3072 DO concepts (44% of total)
  - 336 concepts with only inconsistent mappings
  - 2736 with no mapping
- Found mappings for **619 additional concepts**

- ***2453 (35%) DO concepts remain unmapped***

# *Methods* - Overview

- Establishing a reference set of mappings
  - Apply semantic constraints on existing mappings from DO to SNOMED CT
  - Find additional mappings lexically
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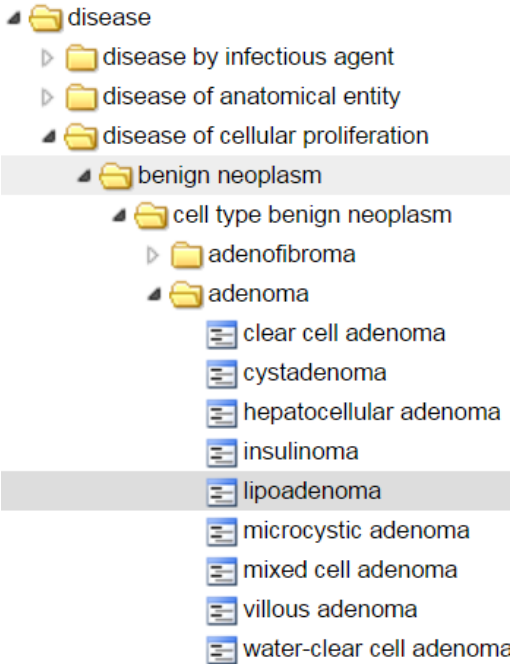
  - Distribution of mapped vs. unmapped concepts by top-level hierarchies in DO
  - Analysis of connected components of unmapped concepts
  - Manual review of semantic “differentia” for unmapped concepts
- Comparing the hierarchical organization based on mapped concepts

# *Methods* - Characterizing unmapped concepts (Distribution)

- Find the top level ancestor for each concept
- Plot the distribution of mapped versus unmapped concepts at the top level hierarchy in DO




*Source:* disease-ontology.org

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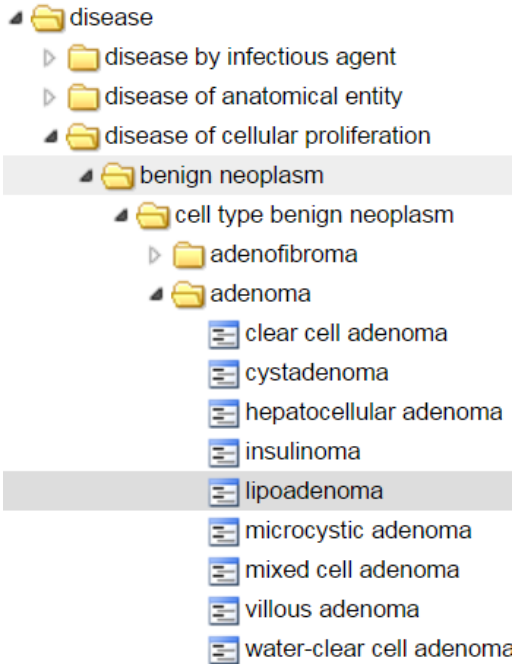
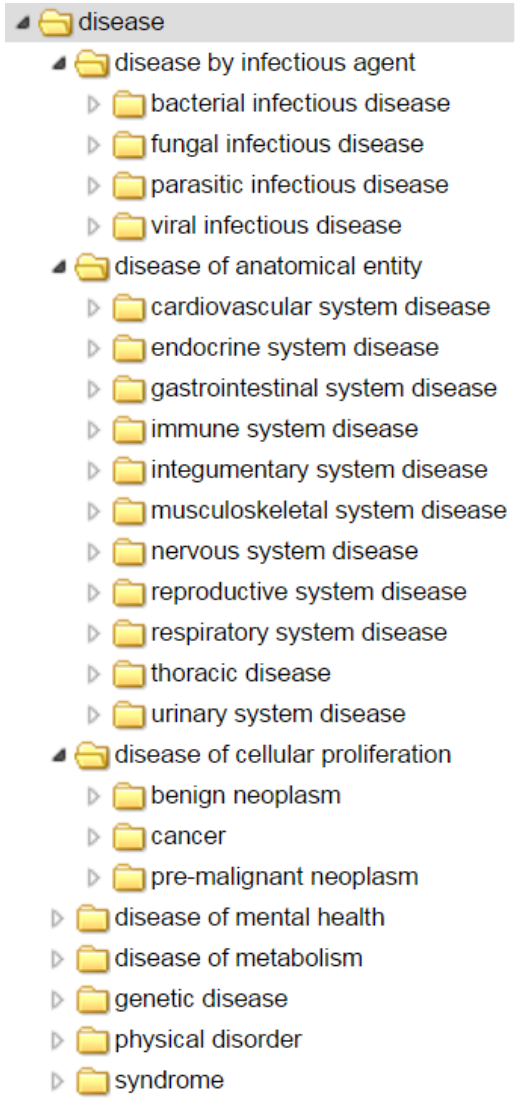
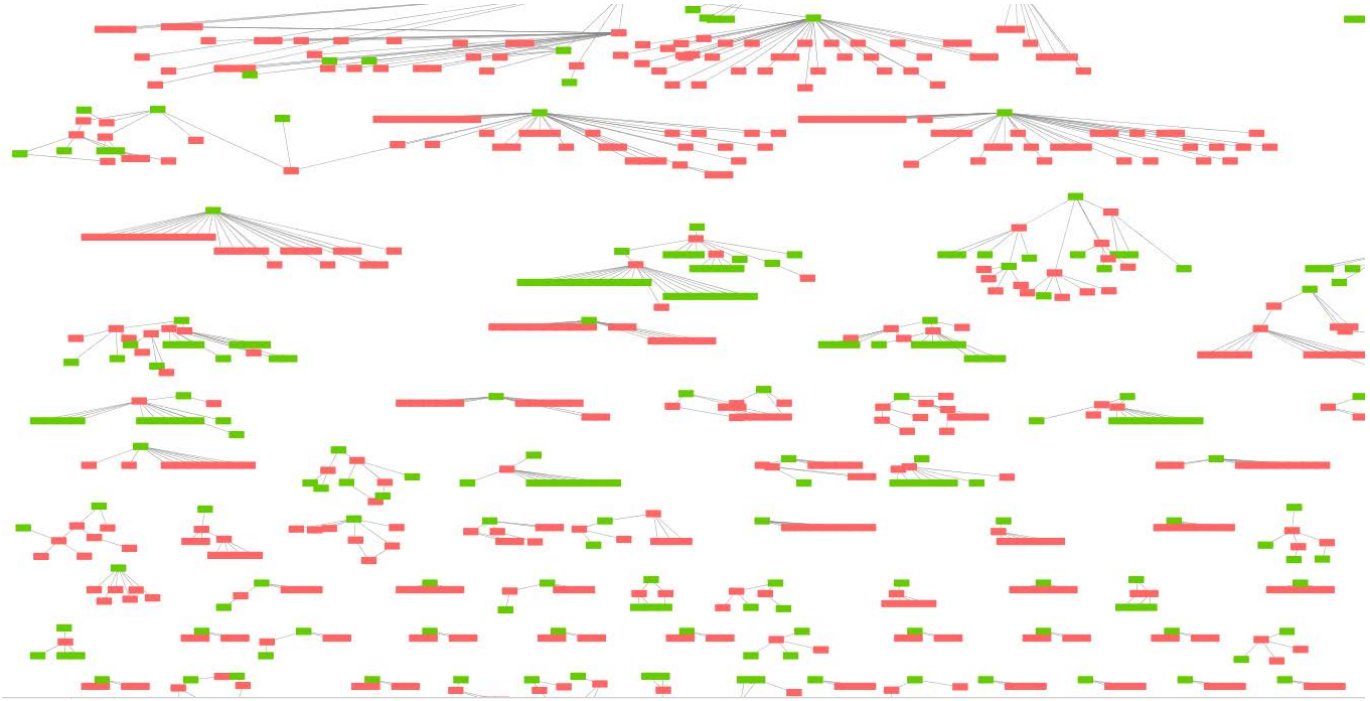



*Source*: disease-ontology.org

# *Methods* - Characterizing unmapped concepts (Structural)

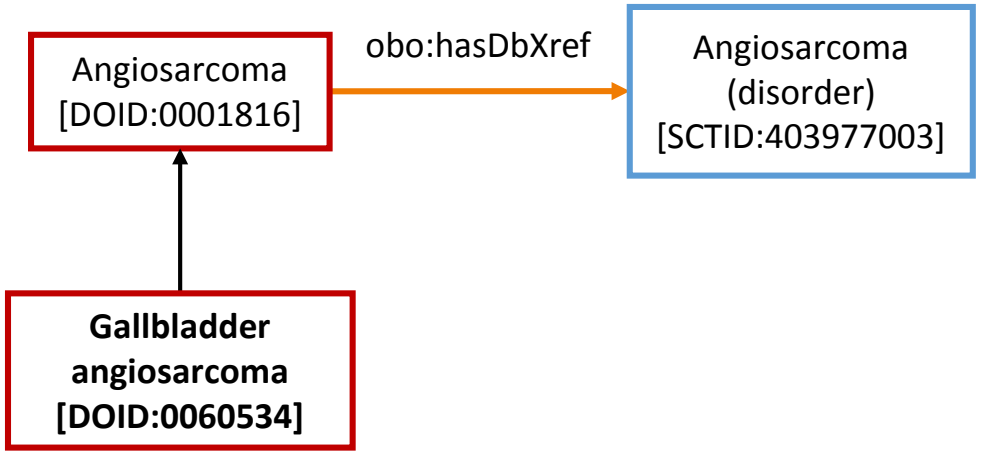
- Analyzing connected components on unmapped concepts
- Create graph of unmapped concepts with immediate (mapped or unmapped) parents and children
- Identify patterns among connected components generated



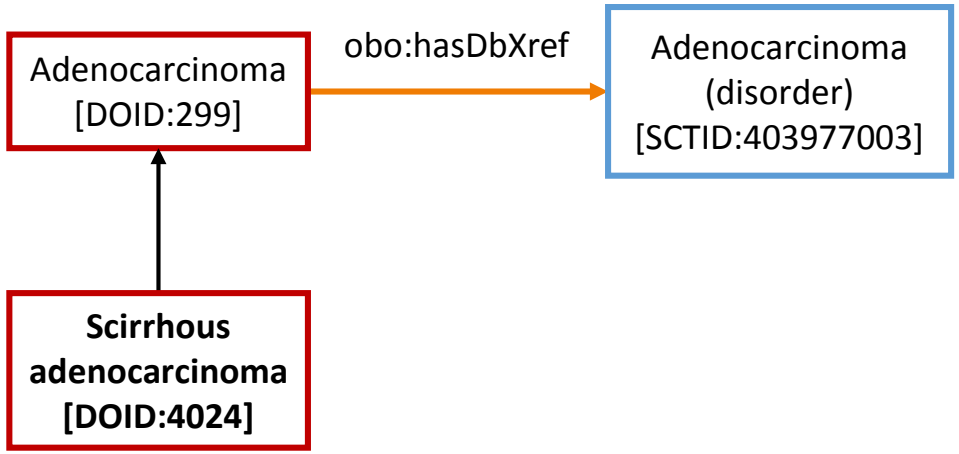
Visualization in Cytoscape

# *Methods* - Characterizing unmapped concepts (Semantic)

- Understand why some DO concepts are unmapped
- Applied to completely unmapped sub-hierarchies and leaves only
- Manually review the semantic "differentia" in comparison with parents

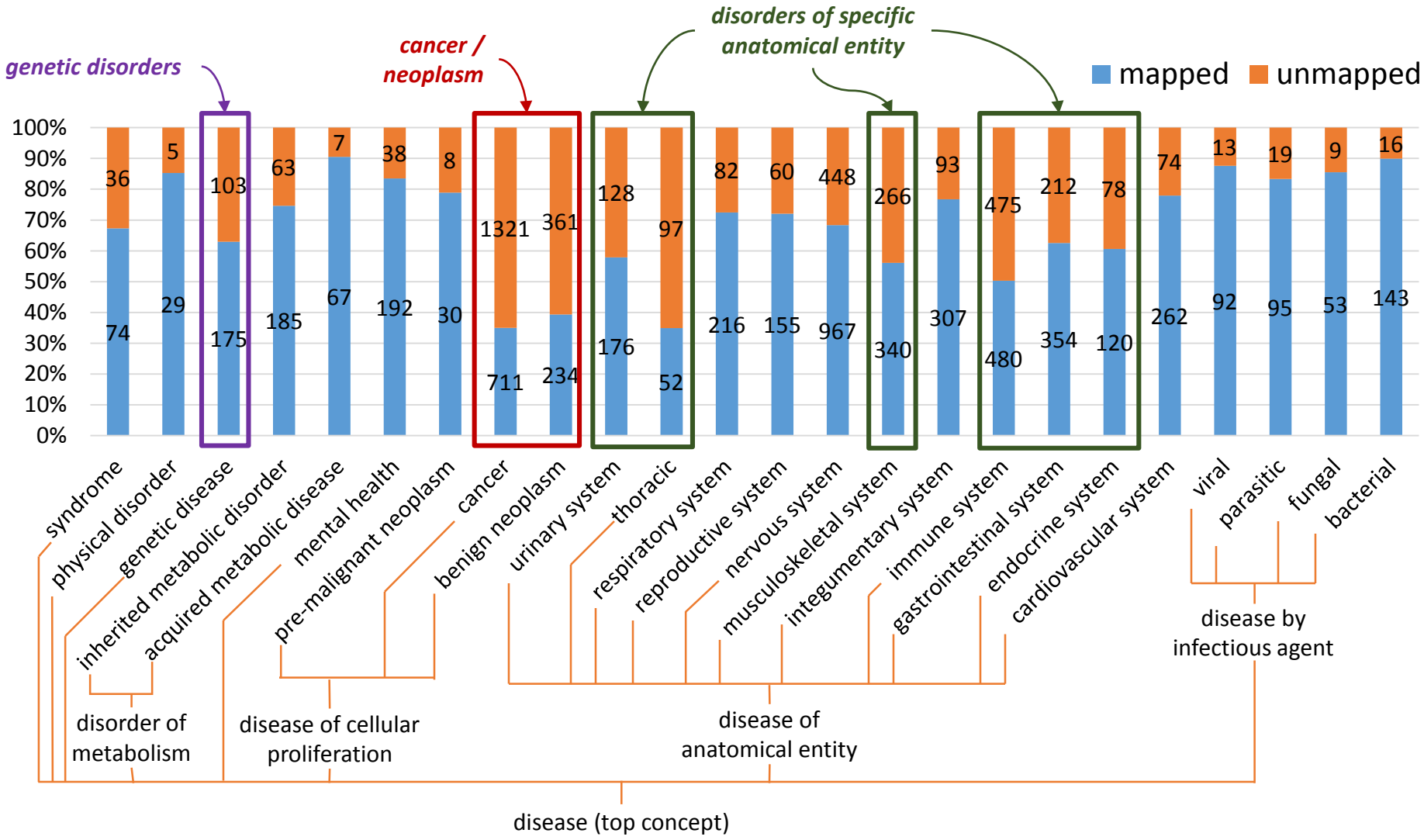



anatomic site



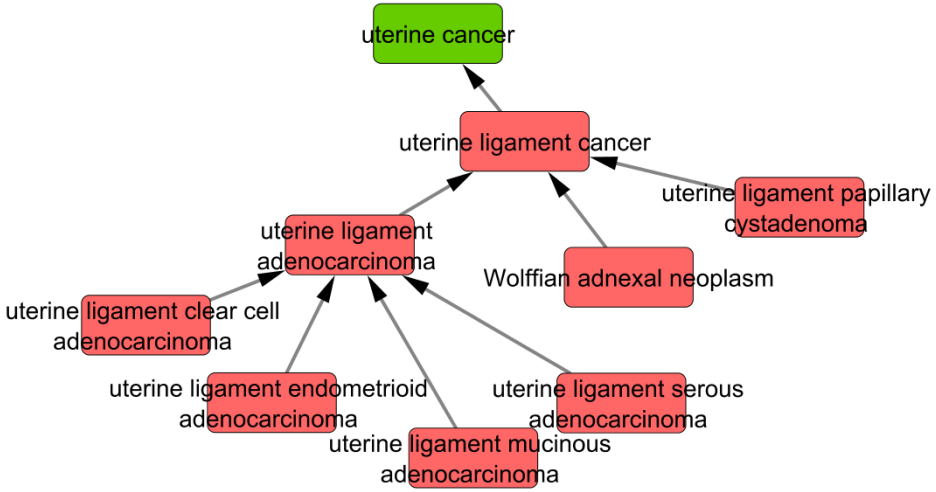

specific morphology

# *Results* - Characterizing unmapped concepts (Distribution)

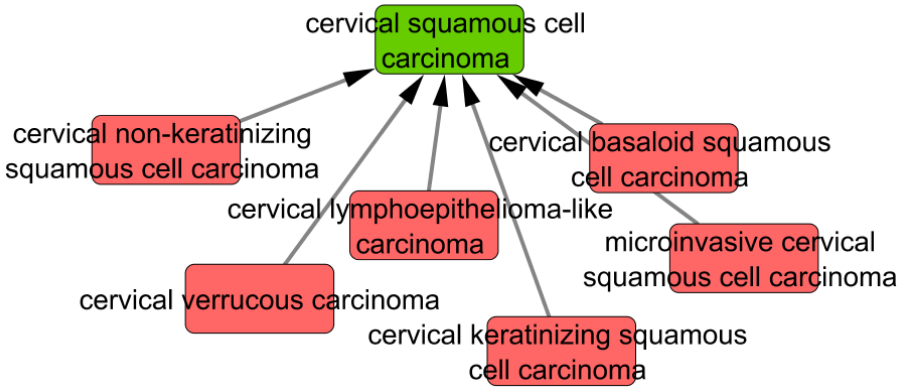


# *Results* - Characterizing unmapped concepts (Structural)

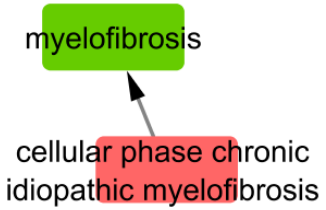
- Patterns among connected components



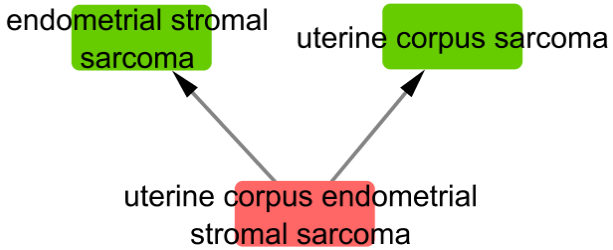

743 concepts (30.3%) within entirely unmapped subhierarchies of a mapped parent




1064 (43.4%) unmapped leaves of a single parent

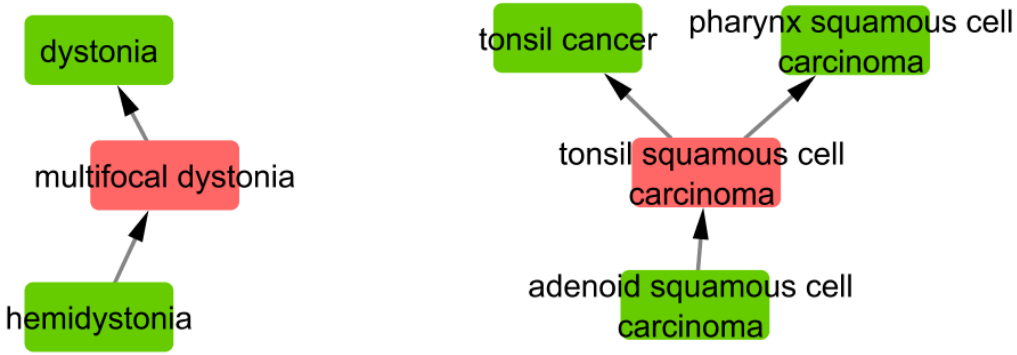



214 (9%) single parents




187 (8%) multiple parents

Single unmapped leaves




246 unmapped intermediary concepts

# *Results* - Characterizing unmapped concepts (Semantic)

- 2207 concepts - sub-hierarchies and leaves only (90% of 2453 unmapped)

| Type of semantic granularity | Count | % |
|---|---|---|
| **specific morphology** (e.g. ***follicular*** dendritic cell sarcoma) | 831 | 37.65 |
| **morphology and anatomic site** | 520 | 23.56 |
| **specific subtype X** (e.g. spinocerebellar ataxia ***type 1***) | 253 | 11.46 |
| **anatomic site** (e.g. ***intramuscular*** hemangioma) | 147 | 6.66 |
| **morphology and period of onset** | 61 | 2.76 |
| **period of onset** (e.g. ***pediatric*** osteosarcoma) | 45 | 2.04 |
| **chromosomal location and anomaly** | 45 | 2.04 |
| **complex syndrome** (e.g. agnathia-otocephaly complex) | 42 | 1.90 |
| **other generic subtypes** | 42 | 1.90 |
| **organism** (e.g. ***screw worm*** infectious disease) | 30 | 1.36 |
| ***others*** | *191* | *8.65* |
| Total | 2207 | |

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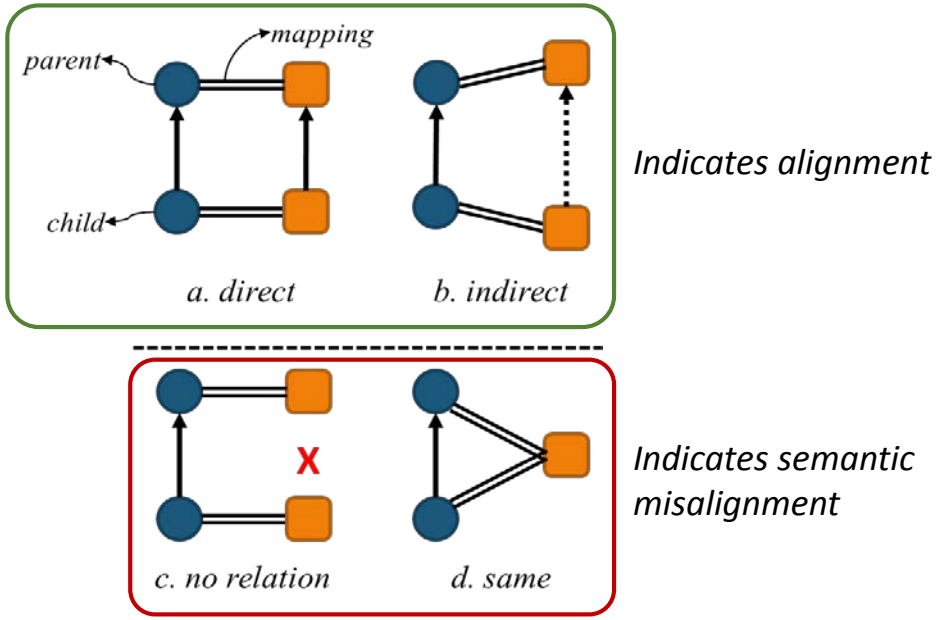
# *Methods* - Comparing hierarchical organization

- Identify differences in the hierarchical organization of SNOMED CT and DO based on the mapped concepts
- Compare the parent-child pairs with relation between corresponding mapped concepts
- Applied in both directions (i.e. from DO to SNOMED CT and vice versa)

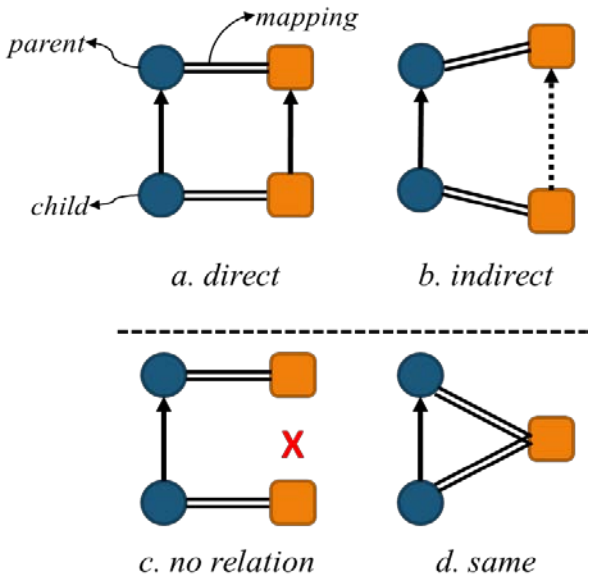



*Indicates alignment*

*Indicates semantic misalignment*

# *Results* - Comparing hierarchical organization

- There is a lot of “confusion” regarding the hierarchical organization of concepts
- Multiple mappings are largely responsible




| Mapping direction | Type (a) or (b) only | Type (c) or (d) only | (a or b) & (c or d) | Total pairs |
|---|---|---|---|---|
| DO to SNCT | 1198 [28%] | 1075 [25%] | 1978 [48%] | 4233 |
| SNCT to DO | 1842 [32%] | 2792 [48%] | 1138 [20%] | 5772 |

# Discussion

- DO has 2453 potentially “new” concepts for UMLS
  - Adding some semantic differentia
- Pre- vs. Post-coordination of concepts
  - Responsible for some of the concepts being unmapped in DO
- Multiple mappings are not good for interoperability
  - Further work needed to formulate rules to resolve such mappings
- Characterizing concepts based on hierarchical relation between the two ontologies
  - Further work needed to identify specific causes for semantic misalignment

***Limitation***

- Inclusion in the “Clinical Findings” hierarchy was the only validation criteria for existing mappings

# Conclusion – Practical Contribution

- When using both DO and SNOMED CT
  - “Better” set of mappings
    - Removal of invalid mappings
    - Additional mappings through lexical match
- Choosing between DO and SNOMED CT
  - Characterization of specific content in DO
    - Semantic categorization
    - Hierarchical organization

# Publications/presentations

- **Raje S, Bodenreider O.** Investigating the coverage of diseases across biomedical research and clinical ontologies. [abstract]. *Proceedings of the AMIA Joint Summits on Translational Science 2017*

- **Raje S, Bodenreider O.** Interoperability of Disease Concepts in Clinical and Research Ontologies – Contrasting Coverage and Structure in the Disease Ontology and SNOMED CT. *Stud Health Technol Inform (Proc Medinfo) 2017 (selected)*

# Other projects

# List of other projects

- Leveraging Lexical Features of Concept Terms for Quality Assurance in SNOMED CT using Description Logics
- Harmonizing User-defined Phenotypic Variables using Latent Semantic Analysis (LSA) to Improve Data Discoverability in dbGaP

*NCBI Hackathons:*

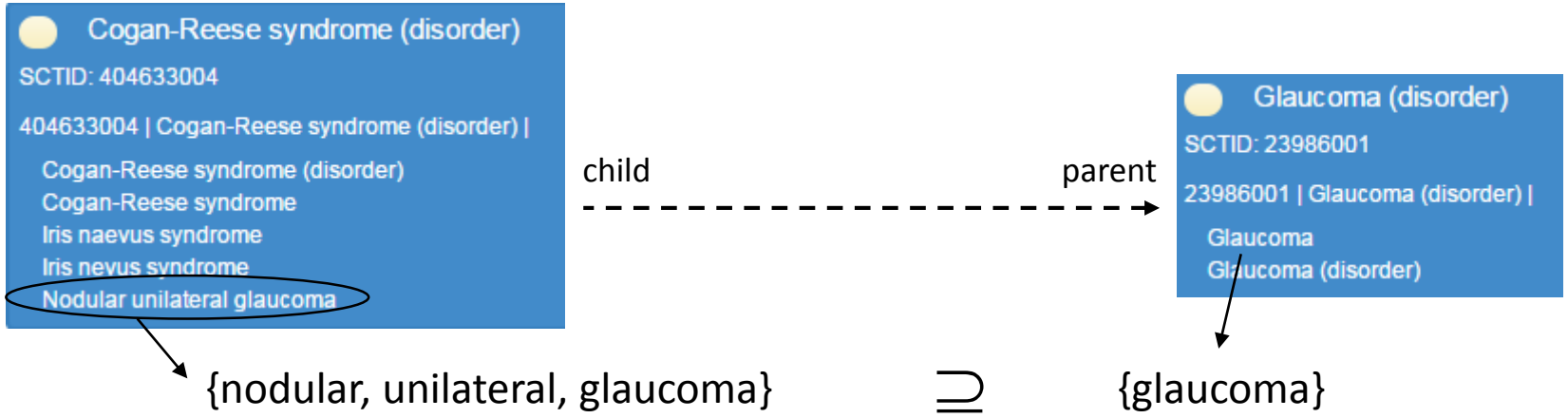
- MeSHgram: An Open Source Tool to Visually Browse Co-occurrence of MeSH Terms in PubMed
- A search tool to extend TCGA queries to automatically identify analogous genomic data from dbGaP

# Leveraging Lexical Features using Description Logics

- Identify potential missing hierarchical relation in SNOMED CT

**Bodenreider O.** Identifying missing hierarchical relations in SNOMED CT from logical definitions based on the lexical features of concept names. *Proc. of 6th Intl. Conf. on Bio. Ontology (ICBO 2016)*

- Lexical semantics




- Extended to include synonyms and lexical constraints based on shallow parsing
- Applied to *almost* all of SNOMED CT

# Leveraging Lexical Features using Description Logics

- Create logical definitions for concepts based on lexical features
- Represent using Description Logics (DL)
- Infer hierarchy “automatically” using ELK reasoner

Chronic pansinusitis (disorder)
SCTID: 88850006
88850006 | Chronic pansinusitis (disorder) |
Chronic pansinusitis
Chronic pansinusitis (disorder)

child → parent

Pansinusitis (disorder)
SCTID: 195790000
195790000 | Pansinusitis (disorder) |
Pansinusitis
Pansinusitis (disorder)

{chronic, pansinusitis} $\supseteq$ {pansinusitis}

Annotations
rdfs:label
Pansinusitis (disorder)

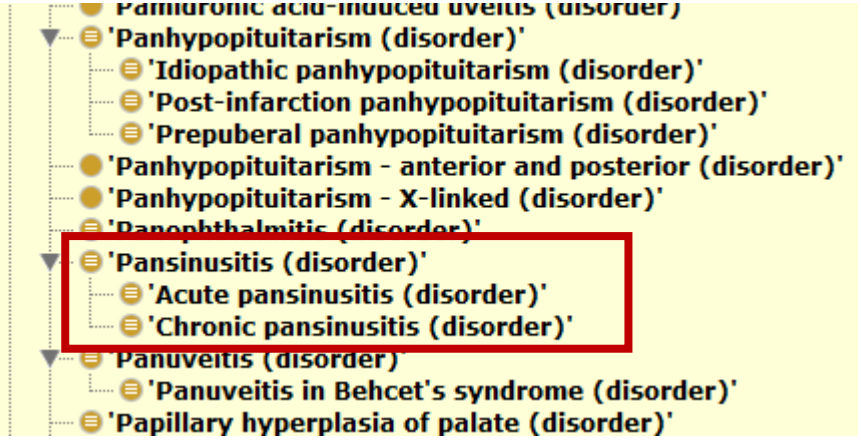
Description: 'Pansinusitis (disorder)'

Equivalent To
T_disorder
and (has_head some pansinusitis)

Annotations
rdfs:label
Chronic pansinusitis (disorder)

Description: 'Chronic pansinusitis (disorder)'

Equivalent To
T_disorder
and (has_head some pansinusitis)
and (has_mod some chronic)



# Leveraging Lexical Features using Description Logics

- Filter out relations present in original hierarchy of SNOMED CT (transitively closed)
- Remaining relations are identified as potentially missing

| SNCT ID | Label | FSN only | | | with synonyms | | |
|---|---|---|---|---|---|---|---|
| | | Total relation inferred | Not present in SNOMED CT | % | Total relation inferred | Not present in SNOMED CT | % |
| **123037004** | **Body Structure (body structure)** | 24835 | 8666 | 34.89 | 45316 | 15170 | 33.48 |
| **404684003** | **Clinical Finding (finding)** | 56698 | 10674 | 18.83 | 79306 | 18235 | 22.99 |
| **71388002** | **Procedure (procedure)** | 31818 | 6981 | 21.94 | 48873 | 13467 | 27.56 |

- Preliminary study completed for hierarchies “Disorder of head (disorder)” and “Operative procedure on head (procedure)”

**Raje S, Bodenreider O.** Identifying potentially missing hierarchical relations in SNOMED CT based on lexical features – Impact of synonyms and lexico-syntactic constraints. [abstract] *AMIA Annu Symp Proc 2017 (submitted)*

# Harmonizing user-defined phenotypic variables in dbGaP

- NCBI's Database of Genotypes and Phenotypes (dbGaP) – Largest collection of genomic and epigenomic data
- Over 220,000 variables in dbGaP (as per latest stats https://www.ncbi.nlm.nih.gov/projects/gap/summaries/cgi-bin/summary.cgi?)
- Group user-defined phenotypic variables based on the variable descriptions
  - "weight", "weight of subject", "weight of participant", "how much does the patient weigh?"
  - "participant gender", "gender", "gender: male, female", "male or female?", "sex"
  - "how many cigarettes per day did you average over all the time you smoked?", "cigarettes: average # smoked per day", "average number of cigarettes smoked per day"

- **Reused data from previous NCBI study**
  - 20635 total variables (all variables associated with the PhenX toolkit)
  - PhenX toolkit is "a catalog of recommended, standard measures of phenotypes"
  - Manually identified PhenX IDs and LOINC codes for each variable

# Harmonizing user-defined phenotypic variables in dbGaP

- Simple lexical similarity based methods (such as Hamming or Levenshtein distance) was not enough. (Good precision but very poor recall)
- Used Latent Semantic Analysis (LSA) to compute pairwise similarity score between all variables.

- Manually evaluated identified "duplicates" for 10% of variables (randomly chosen).
- 96% precision when all 3 evaluators mark valid (kappa = 0.07)
- Compared our groupings with groups based on existing LOINC and PhenX IDs
  - Confusion due to semantic versus lexical information
  - "sex" and "gender"; "age of participant" and "age of participant at first diagnosis"

**Amos L, Raje S, Kimura M, *et. al.*** Harmonizing User-defined Phenotypic Variables using Latent Semantic Analysis (LSA) to Improve Data Discoverability in dbGaP [poster]. *AMIA 2017 (submitted)*

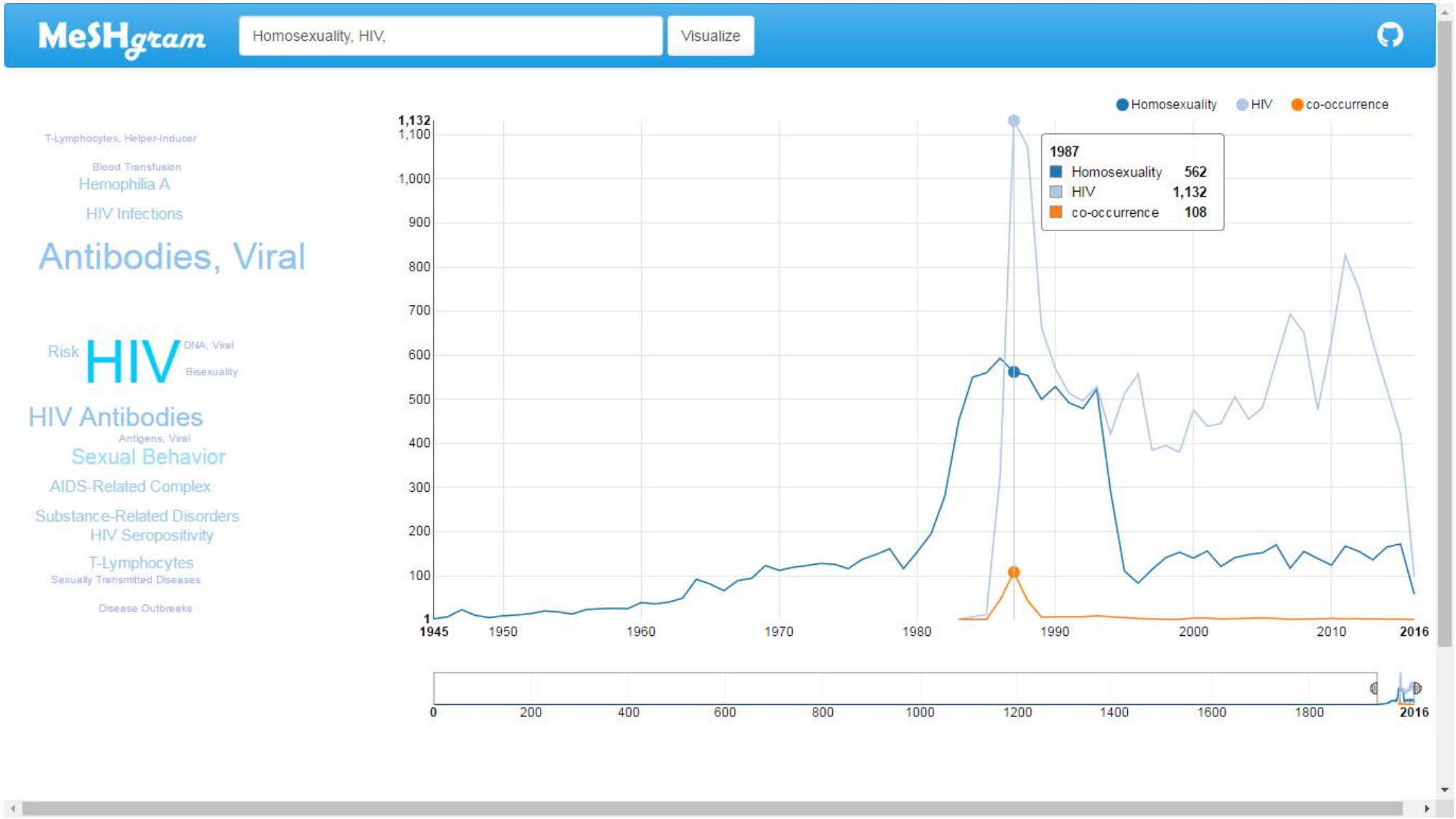
# MeSHgram

- A tool to visually browse co-occurrence of MeSH terms in PubMeb
- Use the MeSH terms associated with PubMed articles to visualize co-occurrence over time
  - Processed NLM PubMed corpus (approx. 24.5 mil. citations) from 1809 to 2016.
  - Extracted the MeSH terms for all citations
  - Ignore MeSH “stop words” when calculating co-occurence
- *Applications:*
  - Visual browsing / querying of PubMed
  - Support meta-analysis
  - Hypotheses generation, medical research activity, etc..

**Raje S, Bhupatiraju RT, Hosny A, Busby B.** Investigating the coverage of diseases across biomedical research and clinical ontologies. [poster] *AMIA Annu Symp Proc 2017 (submitted)*

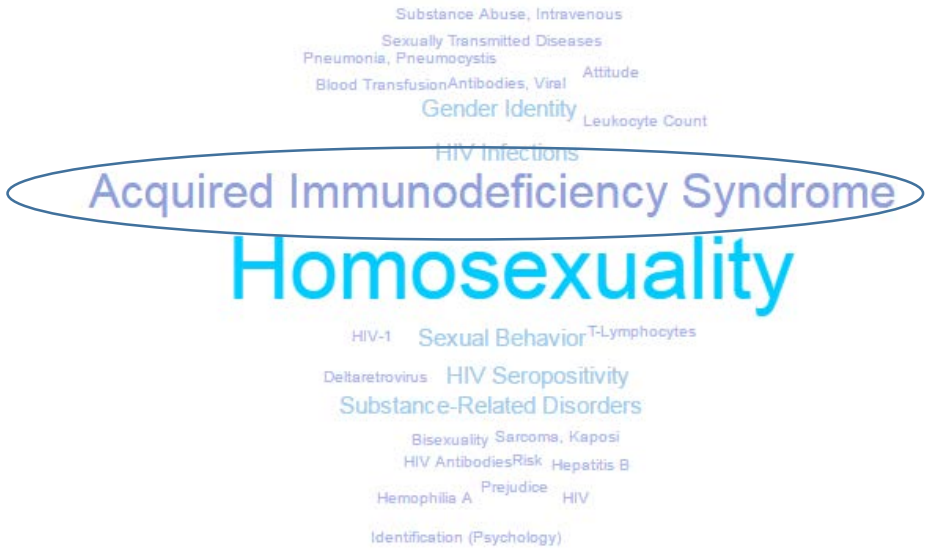
https://github.com/NCBI-Hackathons/Visualizing_MeSH_Term_Interaction_Over_Time

# MeSHgram – Case-study of HIV and Homosexuality



# MeSHgram – Homosexuality through the ages

1960-1970 – Psychology → 1980-1995 – Classical Pathology → 2000-2010 – Sociology


# Extending TCGA queries to fetch analogous data from NCBI databases

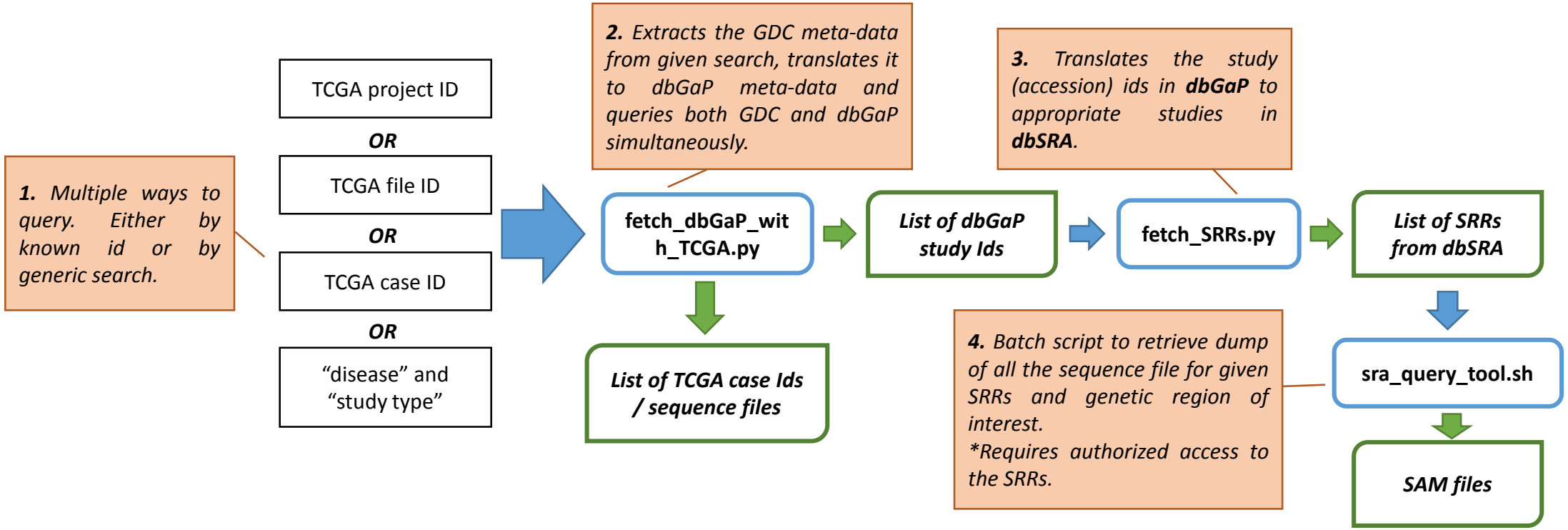
- TCGA: The Cancer Genome Atlas (now part of Genomic Data Commons) from NCI
  - Over 270,000 samples
- dbGaP: Database of Genotypes and Phenotypes
- SRA: Sequence Read Archive stores the sequence data
  - Over 2 million samples *(not all human)*

- Software toolkit to find analogous genomic data (sequence files) using TCGA queries

**Wagner EK, Raje S, Amos L *et al.*** Extending TCGA queries to automatically identify analogous genomic data from dbGaP. *F1000Research* 2017, **6**:319 (doi: 10.12688/f1000research.9837.1)

https://github.com/NCBI-Hackathons/TCGA_dbGaP

# Extending TCGA queries to fetch analogous data from NCBI databases




**Wagner EK, Raje S, Amos L *et al.*** Extending TCGA queries to automatically identify analogous genomic data from dbGaP. *F1000Research* 2017, **6**:319 (doi: 10.12688/f1000research.9837.1)

https://github.com/NCBI-Hackathons/TCGA_dbGaP

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Medical Ontology Research

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*& LHC*

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*Ben Busby, NCBI*

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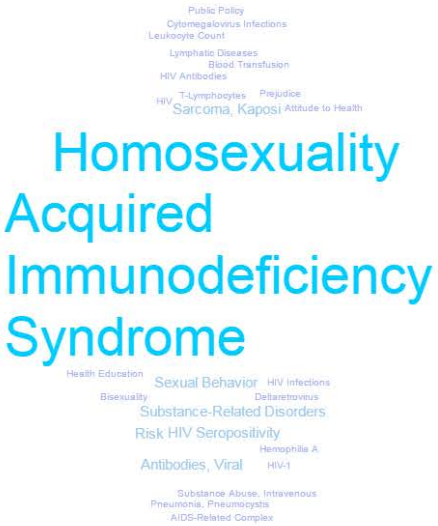
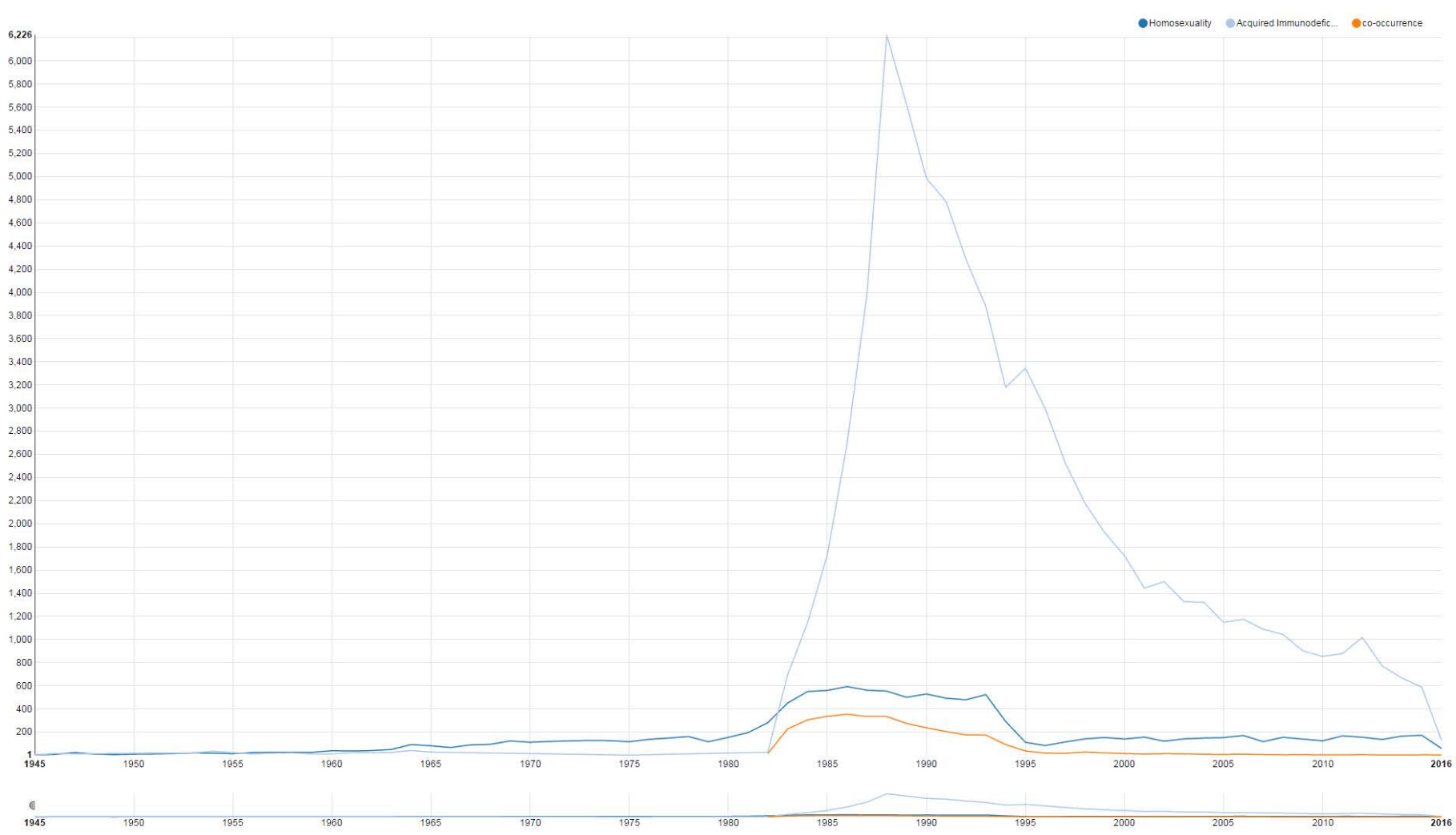
U.S. National Library of Medicine


Public Policy
Cytomegalovirus Infections
Leukocyte Count
Lymphatic Diseases
Blood Transfusion
HIV Antibodies
HIV
T-Lymphocytes
Prejudice
Sarcoma, Kaposi
Attitude to Health
Homosexuality
Acquired Immunodeficiency Syndrome
Health Education
Sexual Behavior
HIV Infections
Bisexuality
Deltaretrovirus
Substance-Related Disorders
Risk
HIV Seropositivity
Hemophilia A
Antibodies, Viral
HIV-1
Substance Abuse, Intravenous
Pneumonia, Pneumocystis
AIDS-Related Complex


Homosexuality
Acquired Immunodefic...
co-occurrence
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6,000
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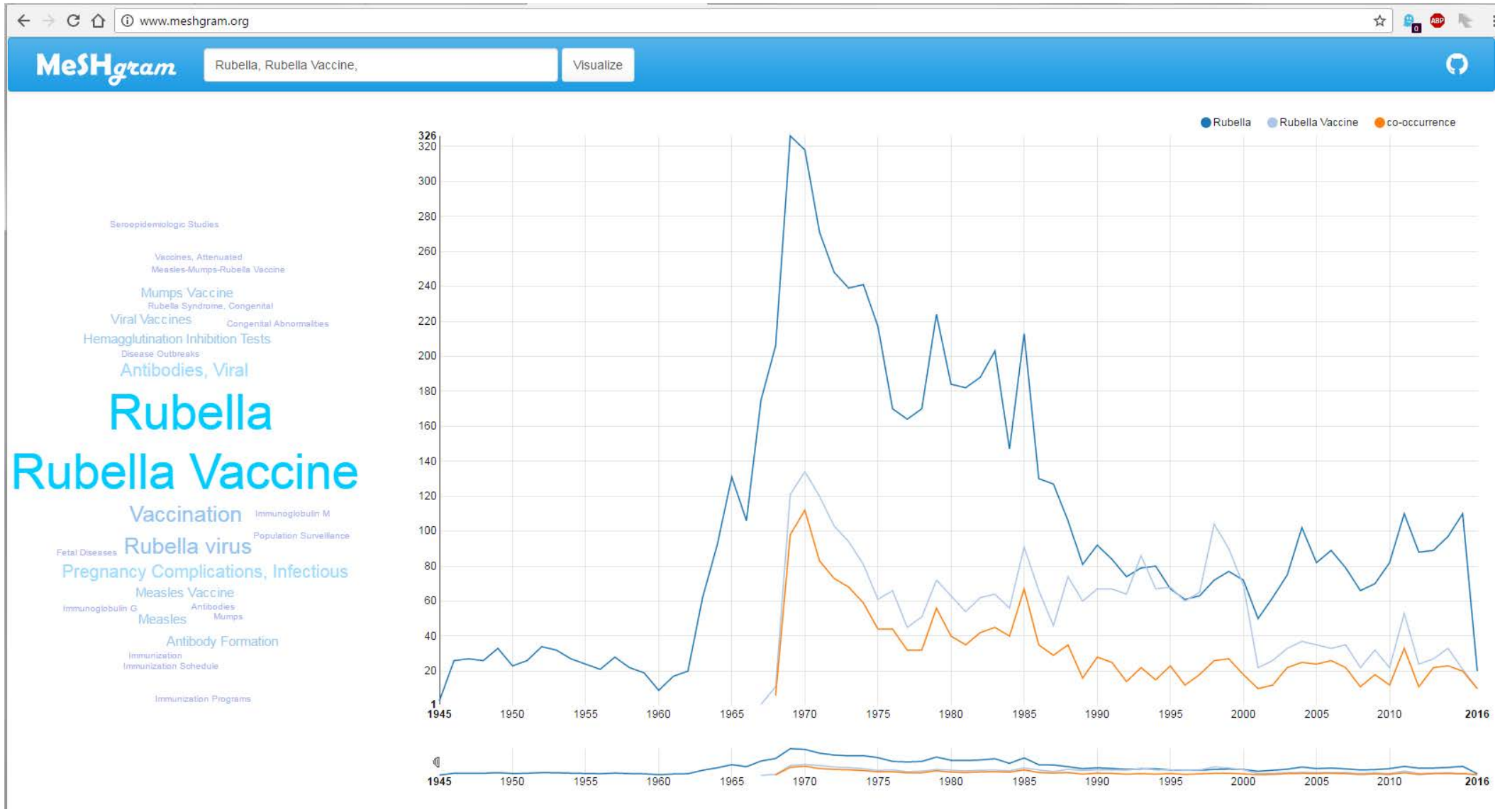
www.meshgram.org
MeSHgram
Rubella, Rubella Vaccine,
Visualize
Seroepidemiologic Studies
Vaccines, Attenuated
Measles-Mumps-Rubella Vaccine
Mumps Vaccine
Rubella Syndrome, Congenital
Viral Vaccines
Congenital Abnormalities
Hemagglutination Inhibition Tests
Disease Outbreaks
Antibodies, Viral
Rubella
Rubella Vaccine
Vaccination
Immunoglobulin M
Population Surveillance
Fetal Diseases
Rubella virus
Pregnancy Complications, Infectious
Measles Vaccine
Immunoglobulin G
Antibodies
Measles
Mumps
Antibody Formation
Immunization
Immunization Schedule
Immunization Programs
Rubella
Rubella Vaccine
co-occurrence
326
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260
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180
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