From Symptoms to Diseases – Creating the Missing Link

Heiner Oberkampf[1;2], Turan Gojayev[1;3], Sonja Zillner[1;4], Dietlind Zühlke[5], Sören Auer[3;5], and Matthias Hammon[6]

1Siemens AG, Corporate Technology, Germany
2Software Methodologies for Distributed Systems, University of Augsburg, Germany
3Institute for Applied Computer Science, University of Bonn, Germany
4School of International Business & Entrepreneurship, Steinbeis University, Germany
5Fraunhofer Institute for Intelligent Analysis and Information Systems, Germany
6Department of Radiology, University Hospital Erlangen, Germany

Disease Centric View on Patient Data

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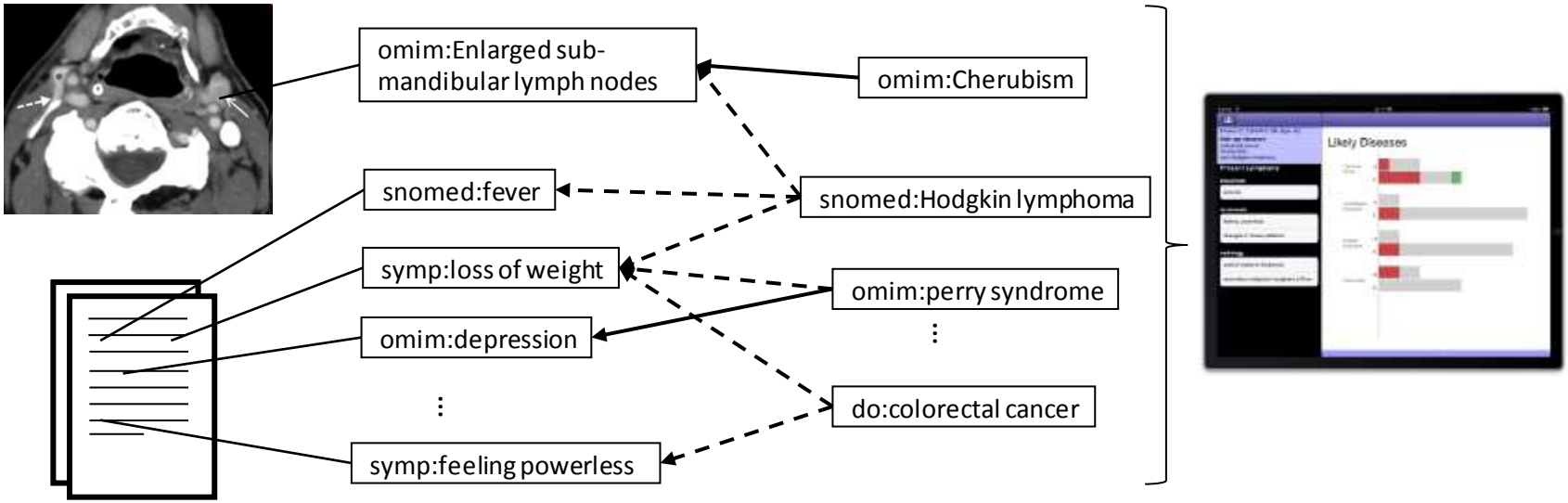
unstructured clincal data | **annotations with symptoms** | **related diseases** | **ranking of likely diseases**



Disease Centric View on Patient Data

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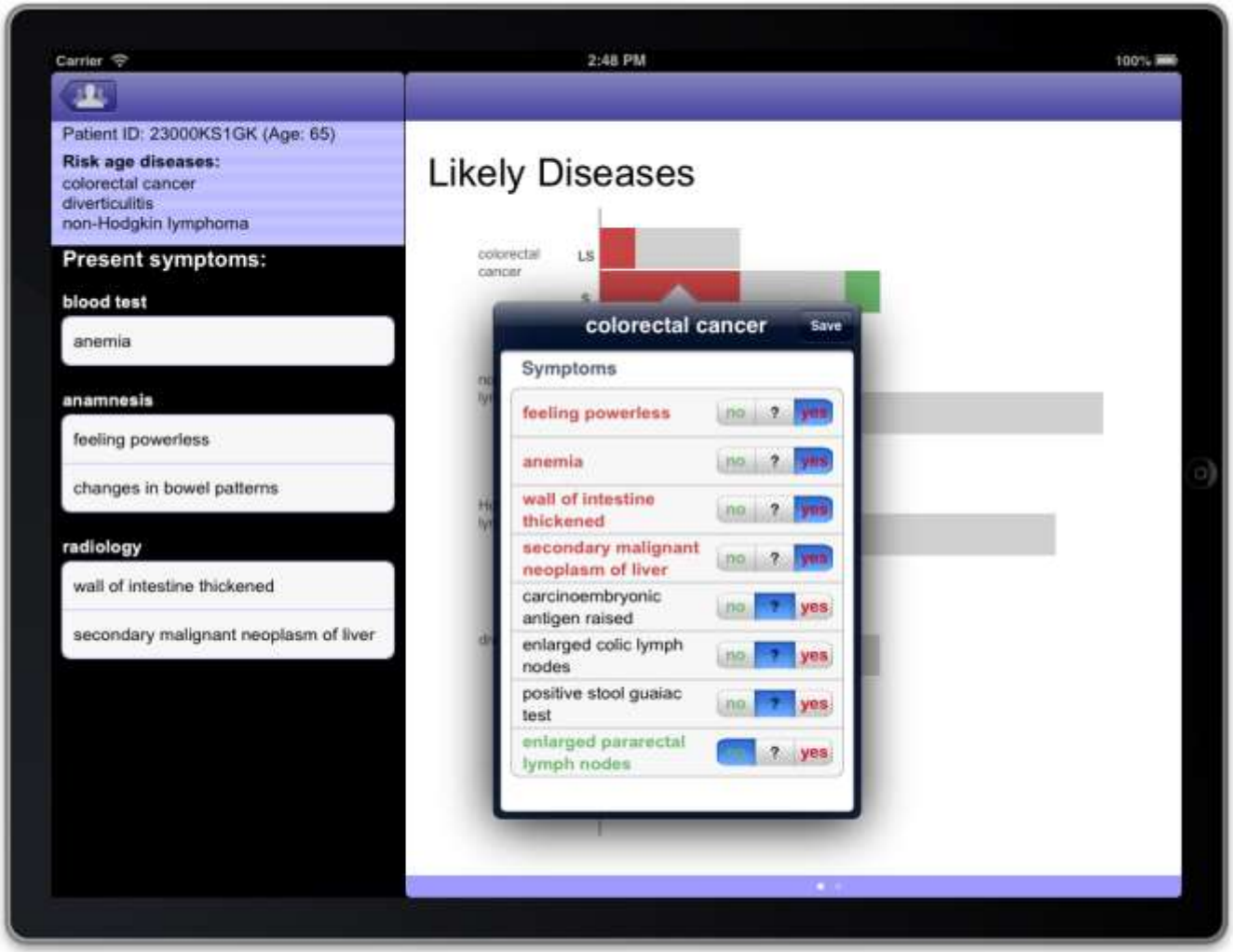
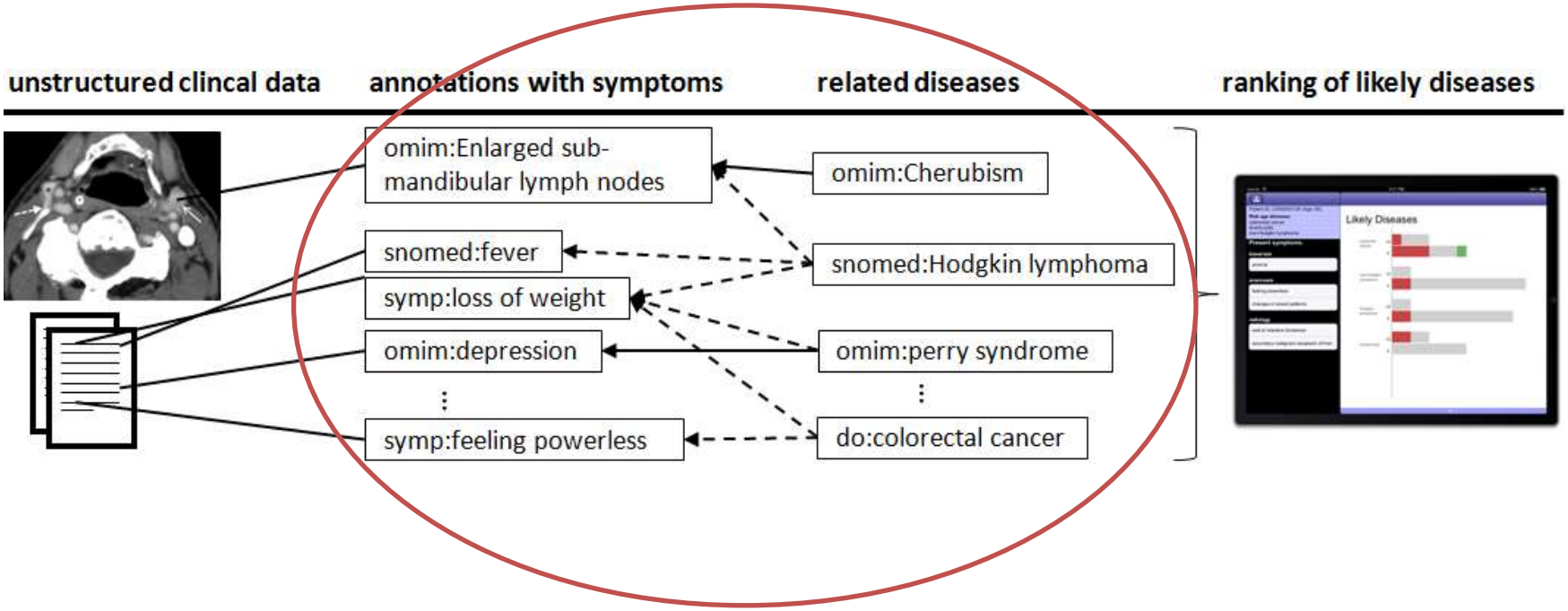


Challenge



- Disease and Symptoms *and* relations between them
- Only integrated information from *different ontologies* can provide the complete picture

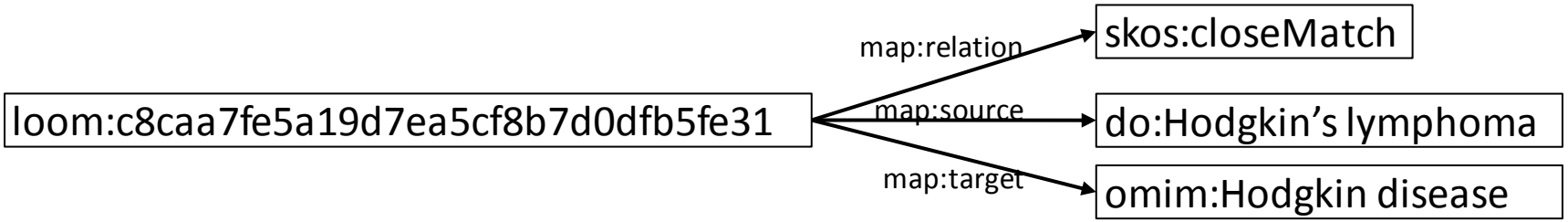
BioPortal[1]

- Ontologies
  - 400+ different ontologies
  - ~ 6 mio entities
  - 2600+ distinct object properties used in triples
- Mappings
- Metadata
- Service
  - REST-full API[2]
  - SPARQL endpoint[3]

1) http://bioportal.bioontology.org/
2) http://data.bioontology.org/
3) http://sparql.bioontology.org

BioPortal Mappings

- 6 Mapping Resources:
  - UMLS-CUI: Based on the UMLS Concept Unique Identifier
  - LOOM: Automatically generated mappings based on lexical similarity
  - OBO-XREF: Mappings for terms with same xref attribute
  - REST: User submitted mappings
  - …
- Can be used without additional preprocessing
- Mapping Types: skos:exactMatch, skos:closeMatch, skos:relatedMatch, owl:sameAs, rdfs:seeAlso



Human Disease Ontology[1]

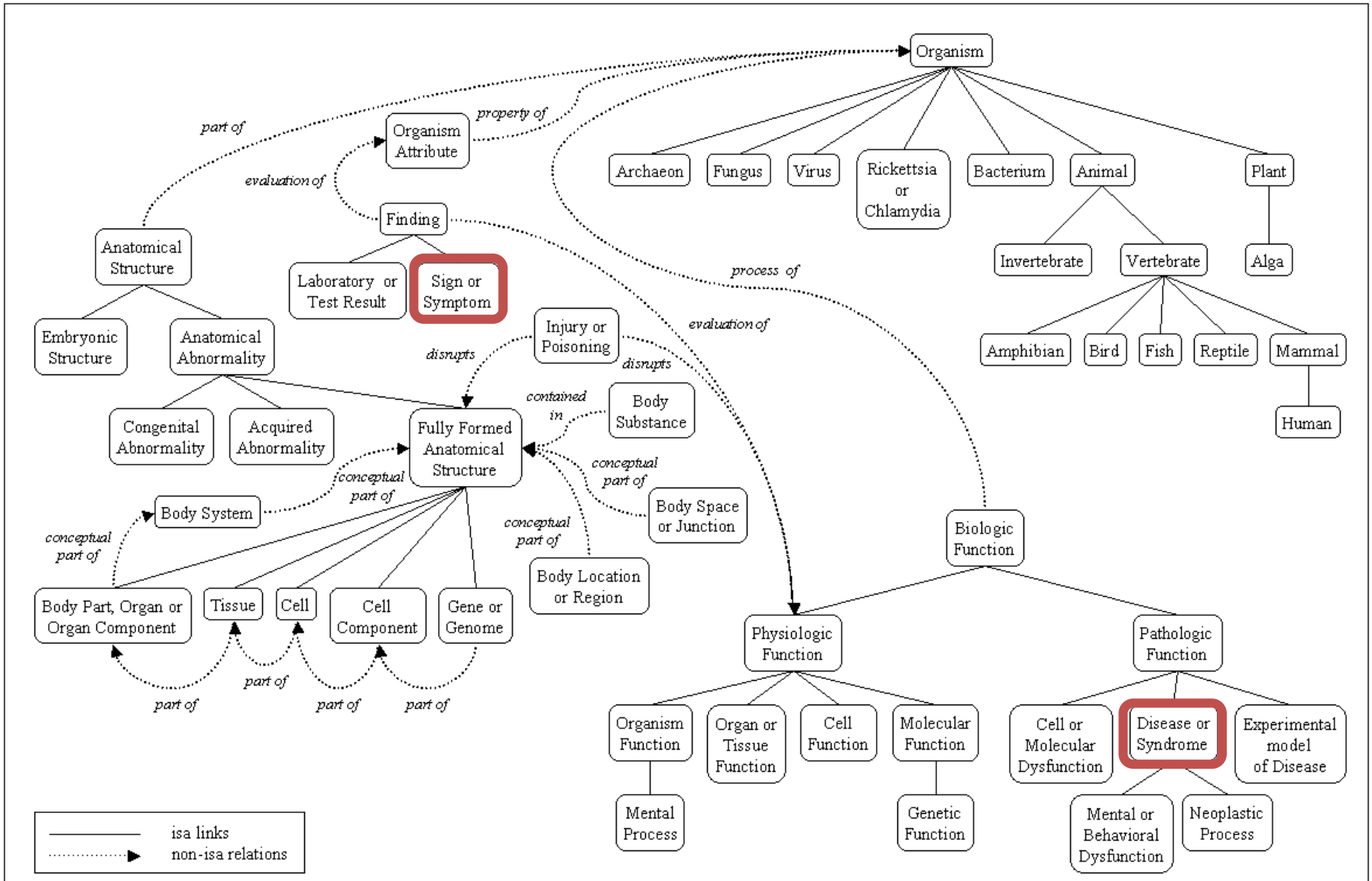
- 8,681 classes
- Utilized as reference by major biomedical databases
- Labels and textual definitions
- Part of the OBO Foundry[2]
- Available links to:
  - MeSH
  - ICD
  - NCIs thesaurus
  - SNOMED CT
  - OMIM

1) http://disease-ontology.org/
2) http://www.obofoundry.org/

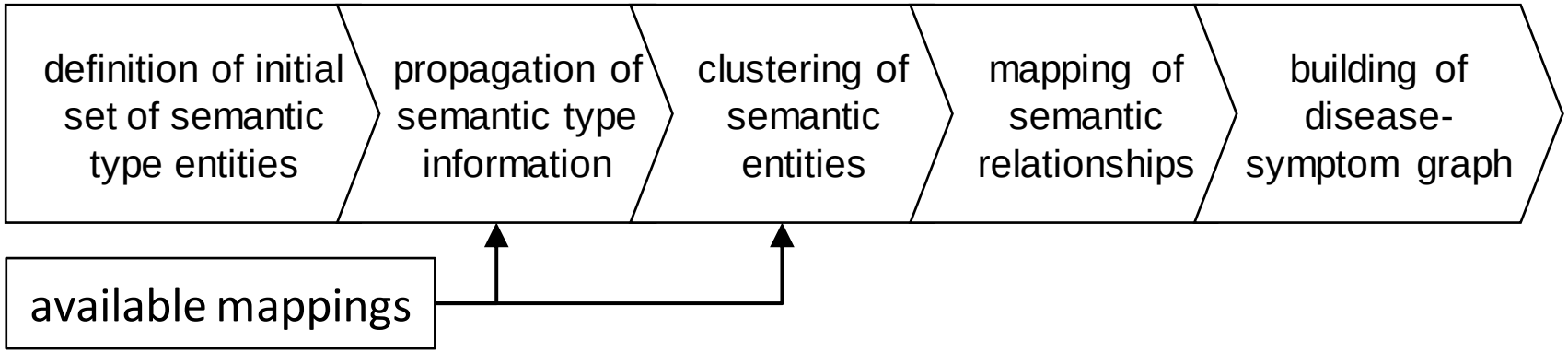
Unified Medical Language System (UMLS)

- Metathesaurus:
  - SNOMEDCT Systematized Nomenclature of Medicine – Clinical Terms
  - ICD10CM International Classification of Diseases, Version 10 – Clinical Modification
  - ICD10 International Classification of Diseases, Version 10
  - ICD9CM International Classification of Diseases, Version 9 – Clinical Modification
  - MDR Medical Dictionary for Regulatory Activities
  - RCD Read Codes, Clinical Terms Version 3 (CTV3)
  - OMIM Online Mendelian Inheritance In Man
  - ICPC2P International Classification of Primary Care – 2 Plus
  - CST Coding Symbols for a Thesaurus of Adverse Reaction Team
  - AIR Artificial Intelligence Rheumatology Consultant System Ontology
  - MEDLINEPLUS Medline Plus Health Topics
  - ICPC International Classification of Primary Care
  - MSH Medical Subject Headings
  - NDFRT National Drug File – Reference Terminology
  - …
- Semantic Network

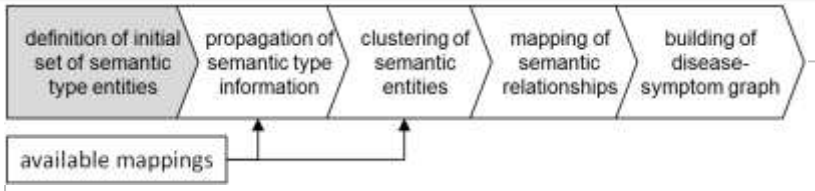
UMLS Semantic Network



Five Steps of Our Approach



Definition of Initial Sets



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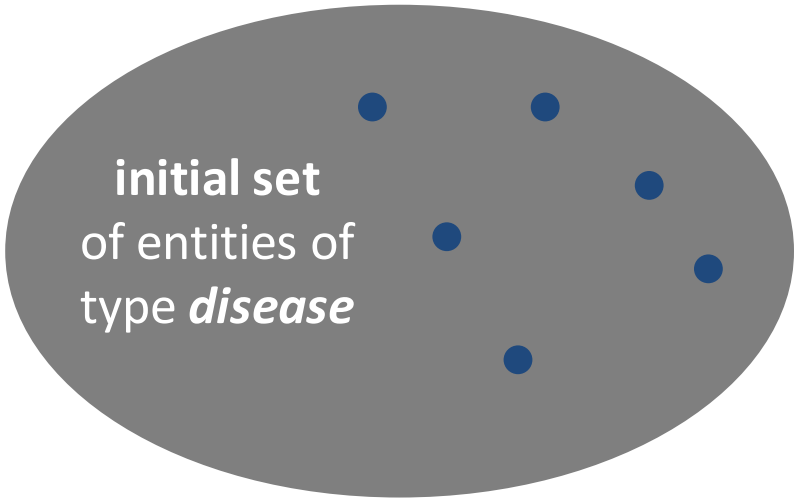
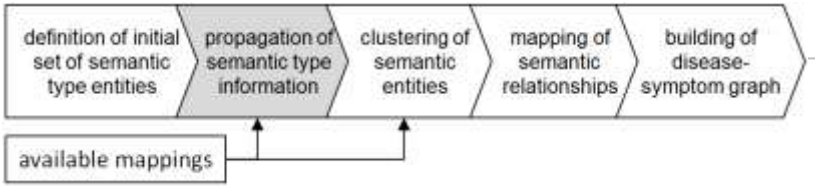
Disease entities:

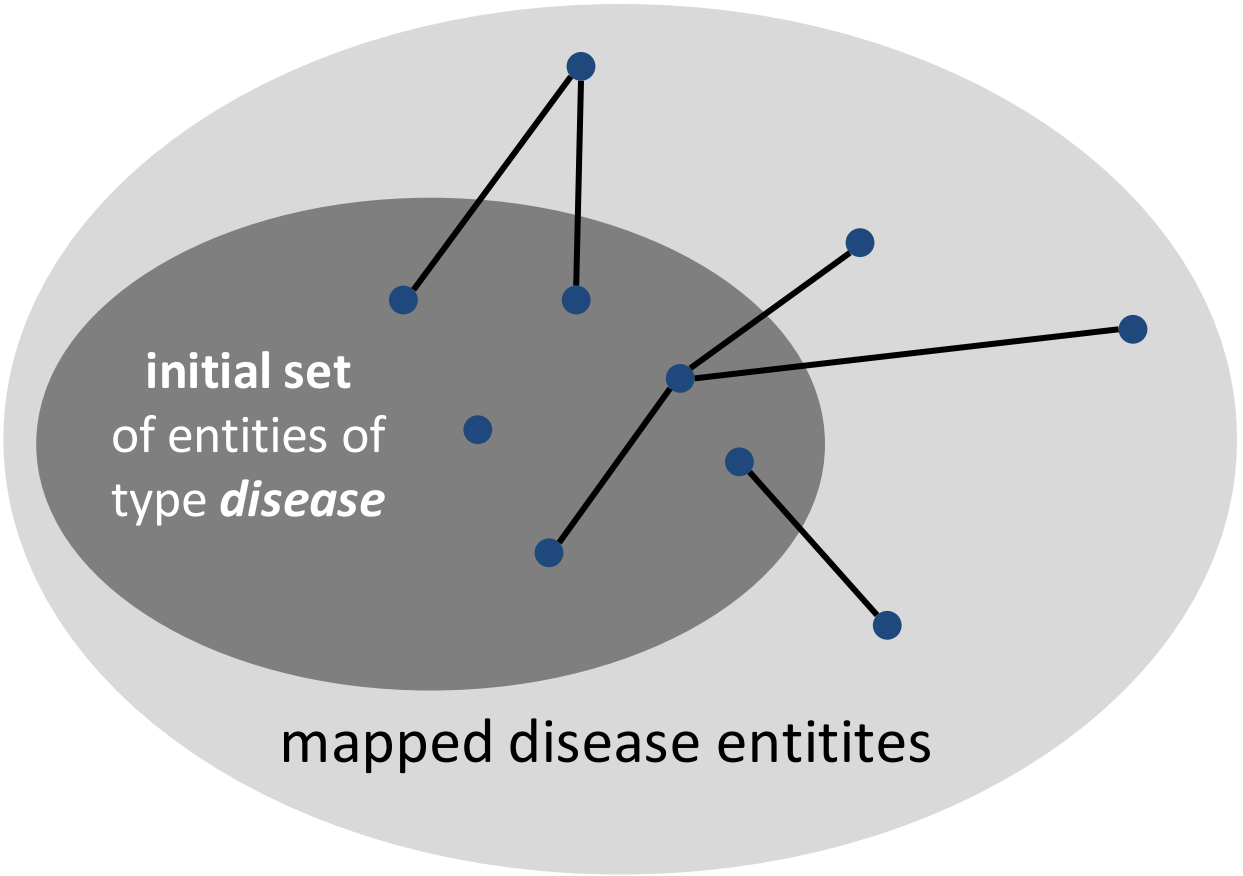
- UMLS entities of type T047 *disease or syndrome*
- Human Disease Ontology



For symptom entities we used UMLS entities of type „sign or symptom“ and the Symptom Ontology (SYMP) http://purl.obolibrary.org/symp.owl

Propagation of Semantic Types





Disease Entities in BioPortal

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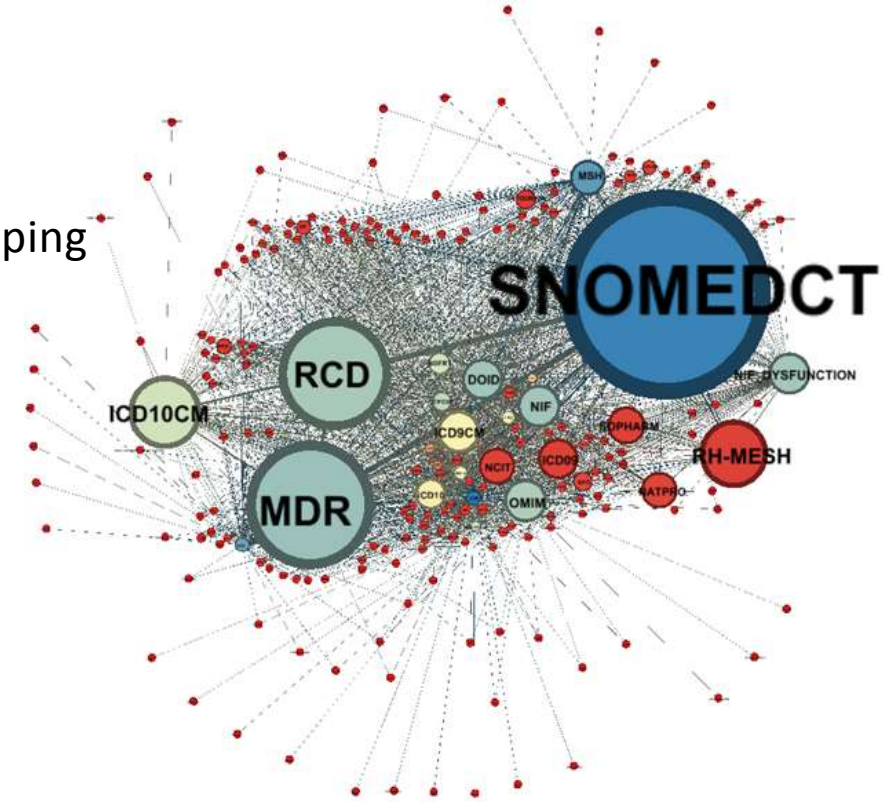
- Start:
  - 18 ontologies
  - 153,223 initial disease entities
    - 123,736 have at least one mapping
- Result:
  - 219 ontologies
  - 247,683 disease entities



Symptom Entities in BioPortal

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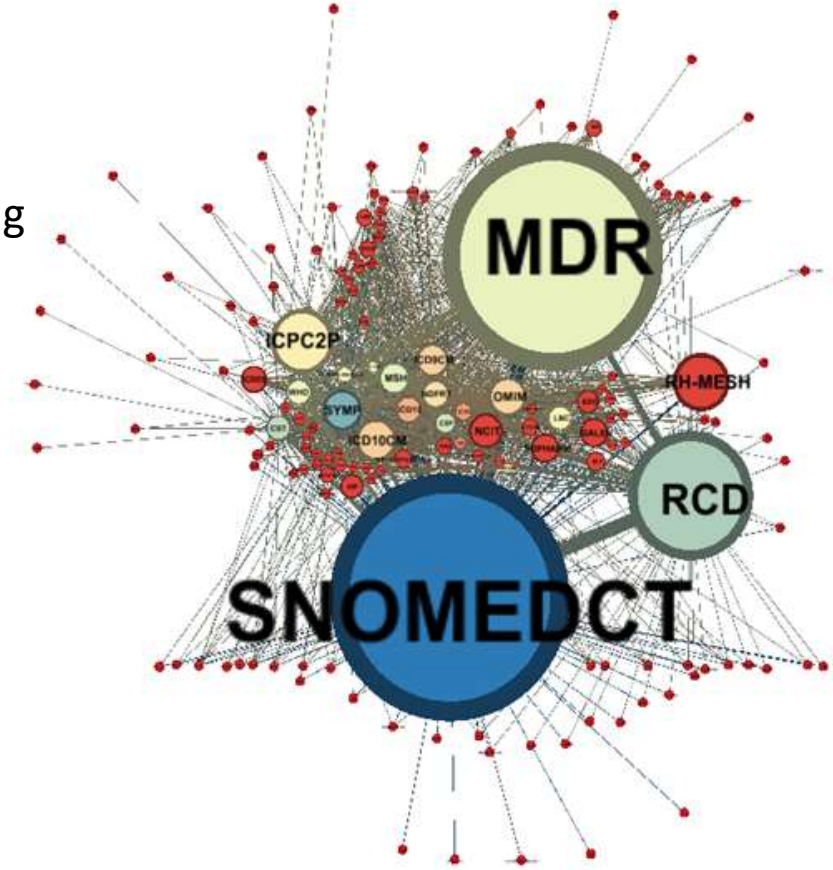
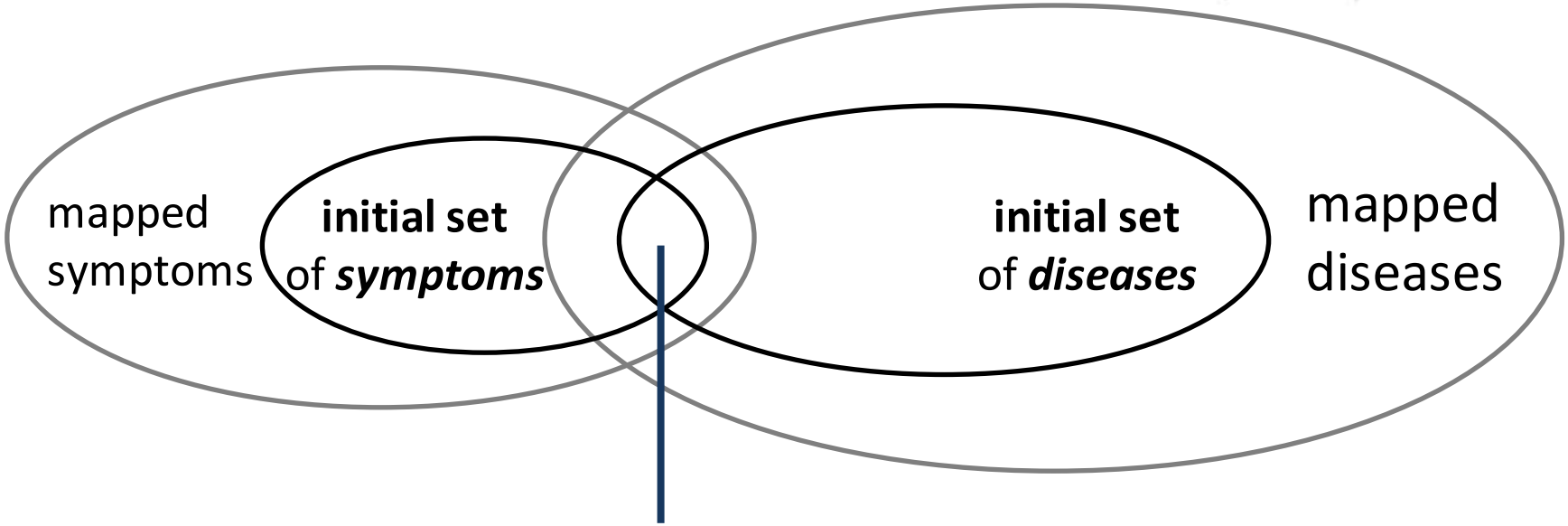
- Start:
  - 18 ontologies
  - 14,971 initial symptom entities
    - 11,882 have at least one mapping
- Result:
  - 161 ontologies
  - 34,088 symptom entities



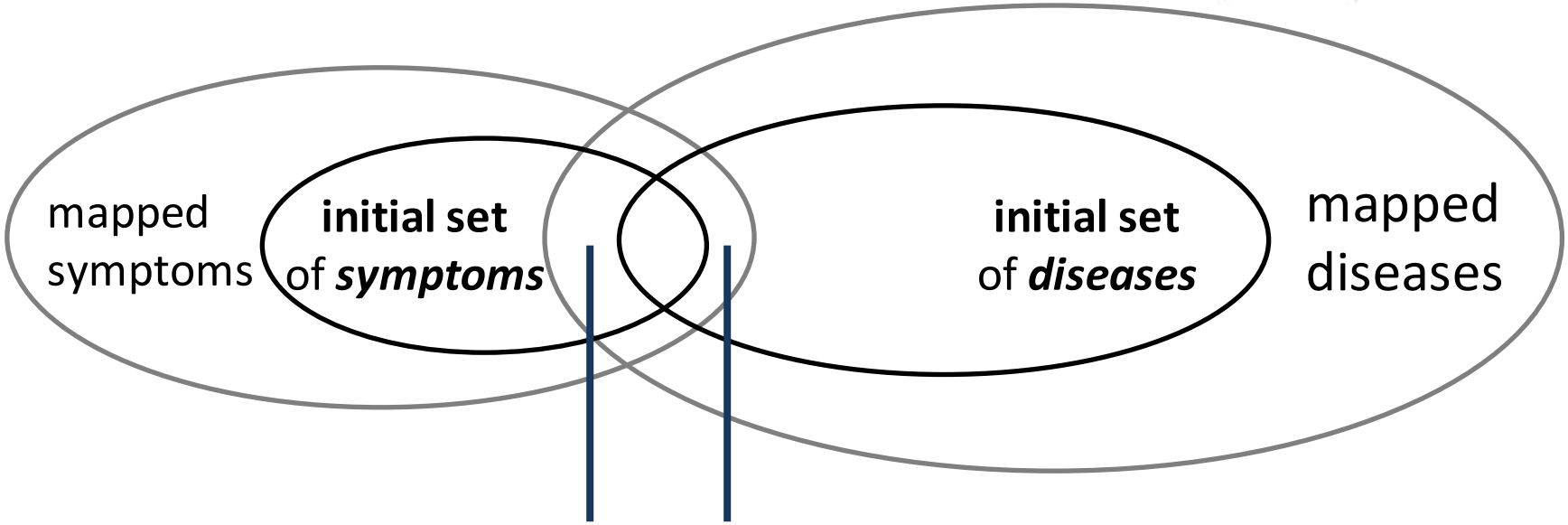
Overlap of Disease and Symptom Sets



- Manual classification of 471 classes in the overlap of initial sets by clinical expert:
  - 189 diseases: removed from symptom set (e.g. *migraine*)
  - 234 symptoms: remove from disease set (e.g. *dry mouth disorder*)
  - 48 both (not decidable): keep in both sets (e.g. *eating disorder*)

Complete classication results are available at http://goo.gl/CFgFVx

Overlap of Disease and Symptom Sets

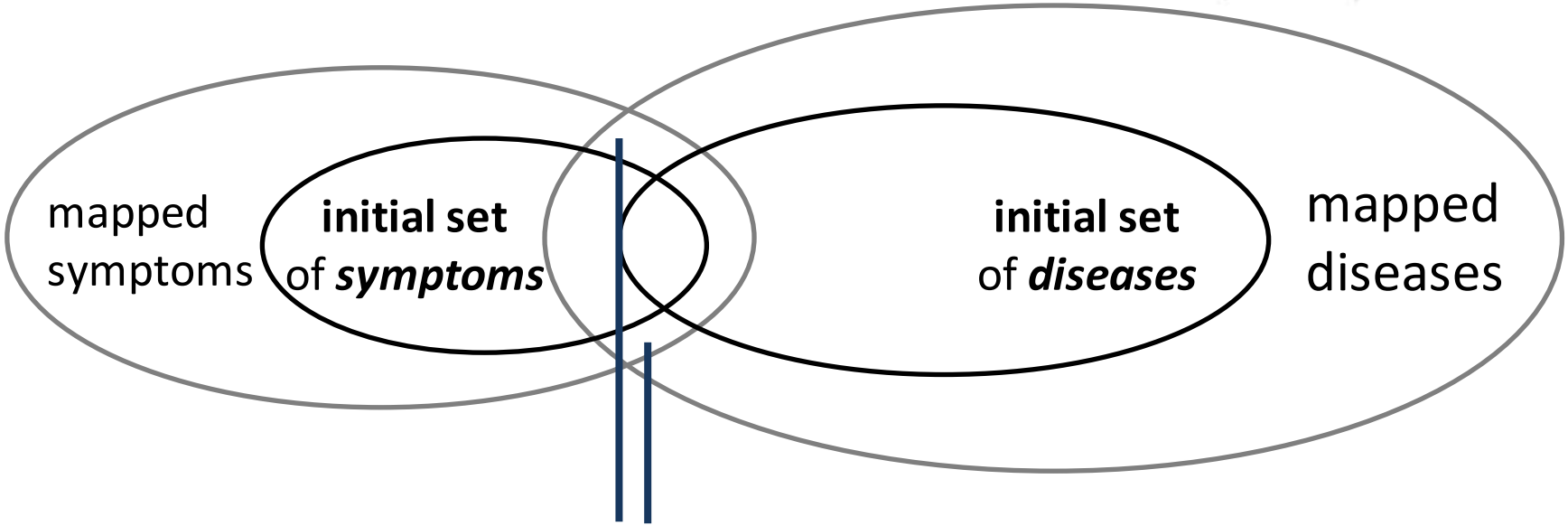


Classified as symptoms:
removed from diseases

Classified as diseases:
removed from symptoms

Complete classication results are available at http://goo.gl/CFgFVx

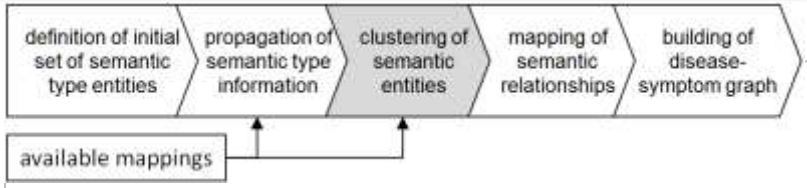
Overlap of Disease and Symptom Sets



- Automatic classification of 5139 classes in the overlap of mapped sets:
  - 2847 diseases: remove from symptom set
  - 2292 symptoms: remove from disease set

Complete classication results are available at http://goo.gl/CFgFVx

Clustering



- Initial approach: Maximal connected components
  - largest cluster with 70,000+ entities
- Adapted approach: Keep distinctions of source ontologies
  - largest disease cluster: 64 entities
  - largest symptom cluster: 57 entities
  - many 1-entity clusters

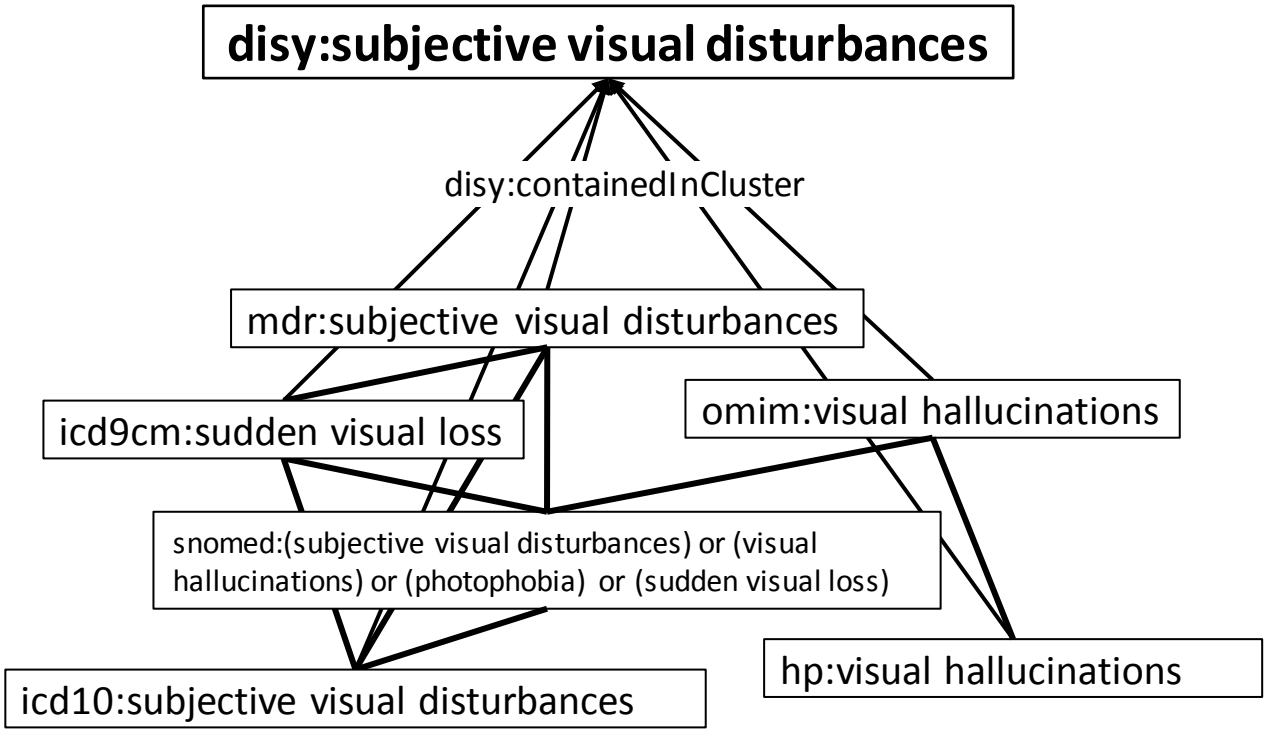
Diseases Clusters:

	UMLS	LOOM	All
clusters	167,970	113,165	102,990
max cluster size	20	53	64
1-entity-clusters	135,313	70,820	62,562

Symptom Clusters:

	UMLS	LOOM	All
clusters	16,416	13,000	11,530
max cluster size	18	53	57
1-entity-clusters	13,243	9,491	8,010

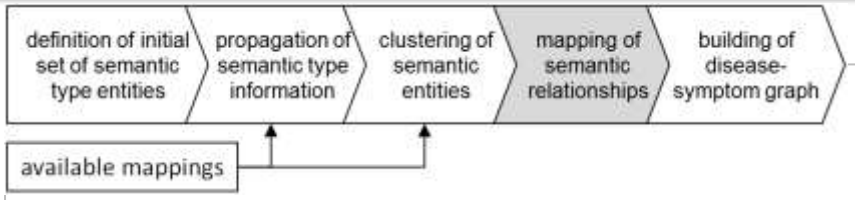
Example: Symptom Cluster

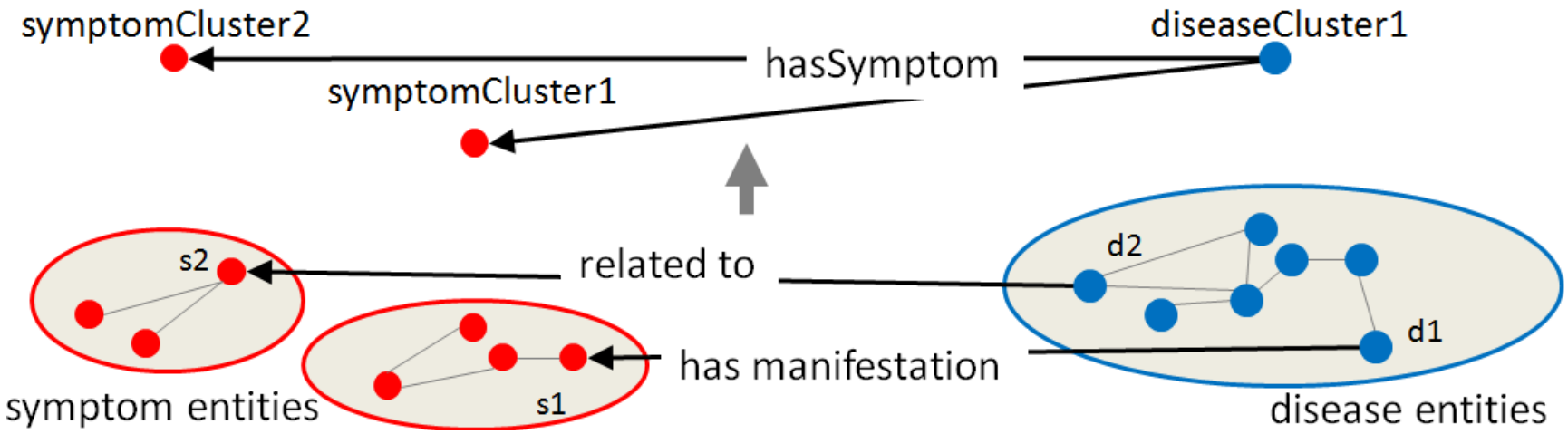


cluster

entities from different ontologies with mappings

Mapping Object Properties





Relations between Diseases and Symtpoms

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2474	MDR:SIB
1463	rdfs:subClassOf
1346	RCD:SIB
1114	OMIM:has_manifestation
737	WHO:SIB
398	MSH:SIB
369	MEDLINEPLUS:SIB
330	ICD9CM:SIB
324	ICD10CM:SIB
268	MDR:classified_as
149	CSP:SIB
146	MSH:mapped_to
127	MDR:classifies
79	SNOMEDCT:may_be_a
66	WHO:RN
48	CSP:RN
47	MEDLINEPLUS:related_to
31	WHO:RB
28	MSH:RO
21	CSP:RB
18	CSP:RO
15	SNOMEDCT:associated_morphology_of
9	SNOMEDCT:same_as
8	SNOMEDCT:is_alternative_use
4	SNOMEDCT:replaces
3	SNOMEDCT:cause_of
3	SNOMEDCT:interprets
2	SNOMEDCT:replaced_by
2	ICPC2P:replaced_by
2	ICPC2P:replaces
1	SNOMEDCT:occurs_after
1	SNOMEDCT:associated_finding_of
1	SNOMEDCT:occurs_before

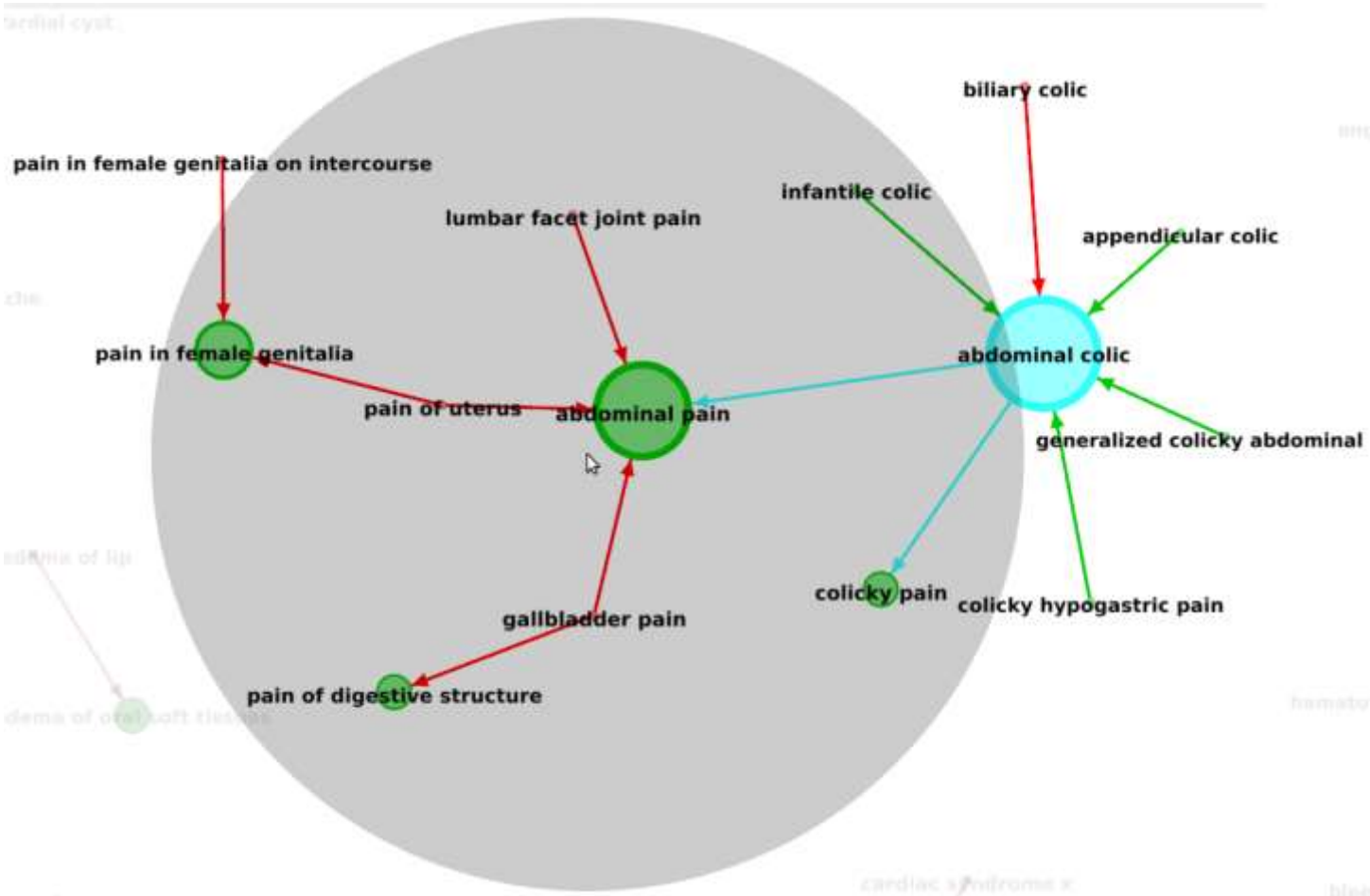
looked for triples

```
?disease ?p ?symptom .
```

obtained 33 properties

Subclass Relations

- Example: SNOMED CT



Mapping Object Properties

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sibling

- MDR/SIB
- RCD/SIB
- WHO/SIB
- MSH/SIB
- MEDLINEPLUS/SIB
- ICD9CM/SIB
- ICD10CM/SIB
- CSP/SIB

hasSymptom

- OMIM/has_manifestation
- MEDLINEPLUS/related_to
- SNOMEDCT/cause_of

RN

- WHO/RN
- CSP/RN

rdfs:subClassOf

- WHO/RB
- CSP/RB

RO

- CSP/RO
- MSH/RO

skos:exactMatch

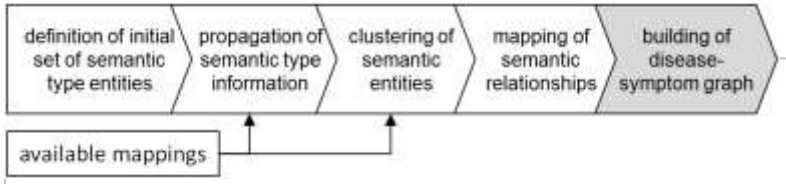
- SNOMEDCT/same_as
- MSH/mapped_to

replaces

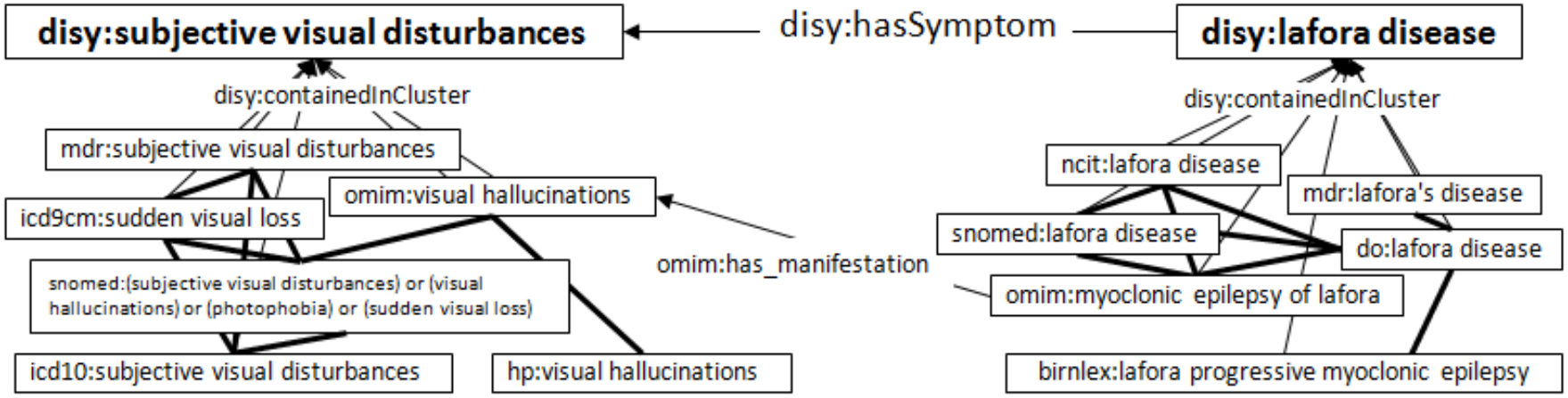
- SNOMEDCT/replaces
- ICPC2P/replaces

SNOMEDCT/replaced_by
SNOMEDCT/occurs_before
SNOMEDCT/occurs_after
SNOMEDCT/may_be_a
SNOMEDCT/is_alternative_use
SNOMEDCT/associated_finding_of
SNOMEDCT/associated_morphology_of
SNOMEDCT/interprets
MDR/classified_as
MDR/classifies
ICPC2P/replaced_by

Disease-Symptom Cluster Graph

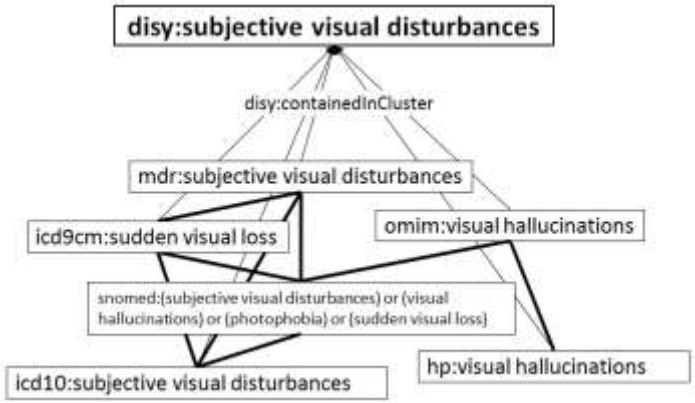


- **Initially:** 1114 distinct disease entities related to 345 symtom entities.
- **Cluster Graph:** 5960 diseases entities related to 3615 symtom entities.



Evaluation of Clusters

- Evaluated, whether all entities in a cluster are about the same disease (symptom) and thus correctly represented by the cluster.
- Checked the preferred labels of entities and cluster.



	disease	symptom
evaluated clusters	100	100
max. cluster size	28	36
max. distinct labels	15	18
correct clusters	**91**	**86**
clusters with wrong entities	**9**	**14**

Evaluation: Cluster-level Relations

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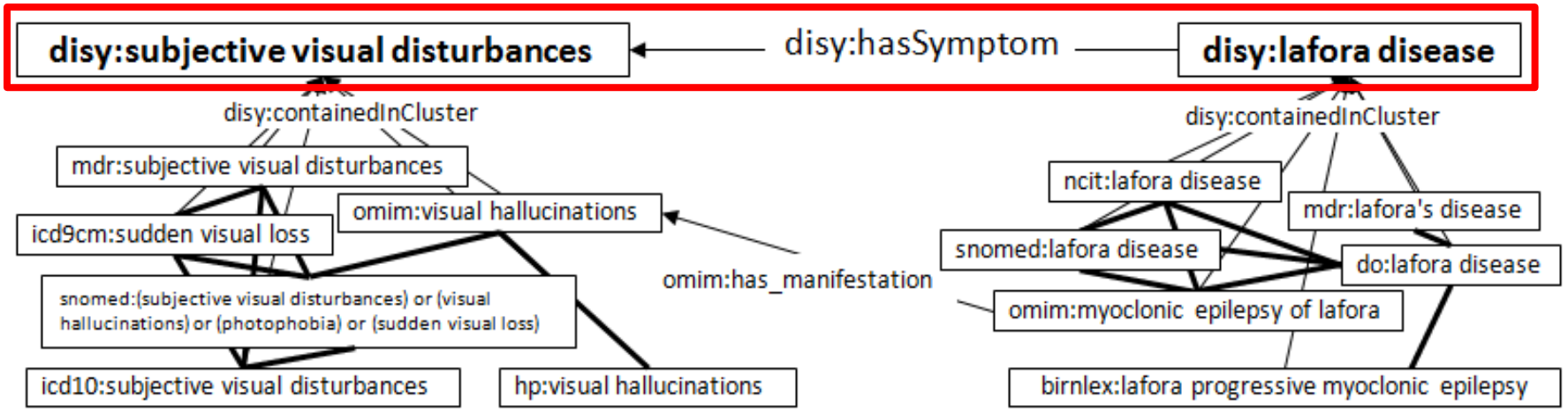
- Randomly selected 500 cluster level relations out of all 2531 relations of the cluster graph.
- All were evaluated as correct.



Conclusion

- Clear picture on available disease-symptom relations
- Only few of the found disease-symptom relations
  - … and only few of them are useful are usefull for our application scenario.
- Clustering can be enhanced:
  - Allow overlapping clusters to reduce number of 1-entity clusters
  - use some clustering metric involving number and type of mappings
- Try the approach on other semantic types
- Cluster graph is a good resource for
  - identification of further disease-symptom relations by annotation of their textual definitions.
  - idetification of disease entities in other LOD resources

Questions?

Contact:

Heiner Oberkampf
OSTHUS GmbH
heiner.oberkampf@osthus.com
www.osthus.com