Short course – Summer 2008
Biomedical Ontology in Practice

June 9-11, 2008

Biomedical Ontology in Practice

Olivier Bodenreider

Lister Hill National Center
for Biomedical Communications
Bethesda, Maryland - USA

Objectives

- Learn about biomedical ontologies
  - History
  - Design principles, formalisms and tools
  - What are they?
  - What are they used for?
- Work with biomedical ontologies
  - Search
  - Analyze
  - Extend
  - Use for data integration

Agenda

Monday, June 9	Introduction to Biomedical Ontologies	Design Principles, Formalisms and Tools for Biomedical Ontologies	Biomedical Ontologies - Content and structure - Function
Tuesday, June 10	Interfaces to Biomedical Ontologies	Searching and Analyzing Biomedical Concepts	Contrasting Biomedical Ontologies
Wednesday, June 11	Critical Analysis of Biomedical Ontologies	Extending Biomedical Ontologies	Using Biomedical Ontologies for Data Integration

References Bio-ontology courses

- Barry Smith, U. Buffalo / NCBO
  - http://ontology.buffalo.edu/smith/Ontology_Course.html
- Stefan Schulz, U. Freiburg, Germany / KR-MED 2008 tutorial
  - http://www.kr-med.org/2008/index.html

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June 9, 2008 – Session #1

Introduction to Biomedical Ontologies

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Outline

- Historical perspective
- Introduction to biomedical terminologies through an example
- Biomedical terms as names for biomedical classes
- Terminological relations as a surrogate for ontological relations

Historical perspective

Why biomedical terminologies?

- To support a theory of diseases
- To classify diseases
- To support epidemiology
- To index and retrieve information
- To serve as a reference

To support a theory of diseases

- Hippocrates
  - Dismisses superstition
  - Four humors
    - Blood
    - Phlegm
    - Yellow bile
    - Black bile
- Thomas Sydenham (1624-1689)
  - *Medical observations on the history and cure of acute diseases* (1676)

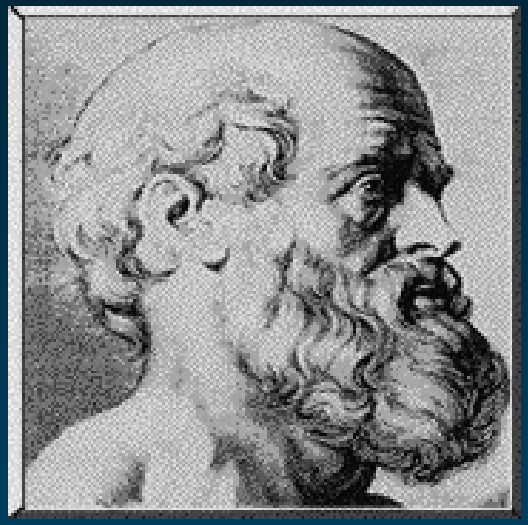
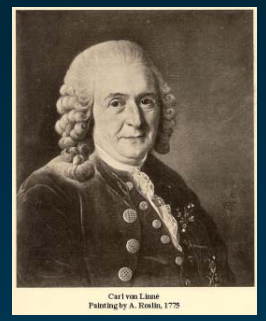


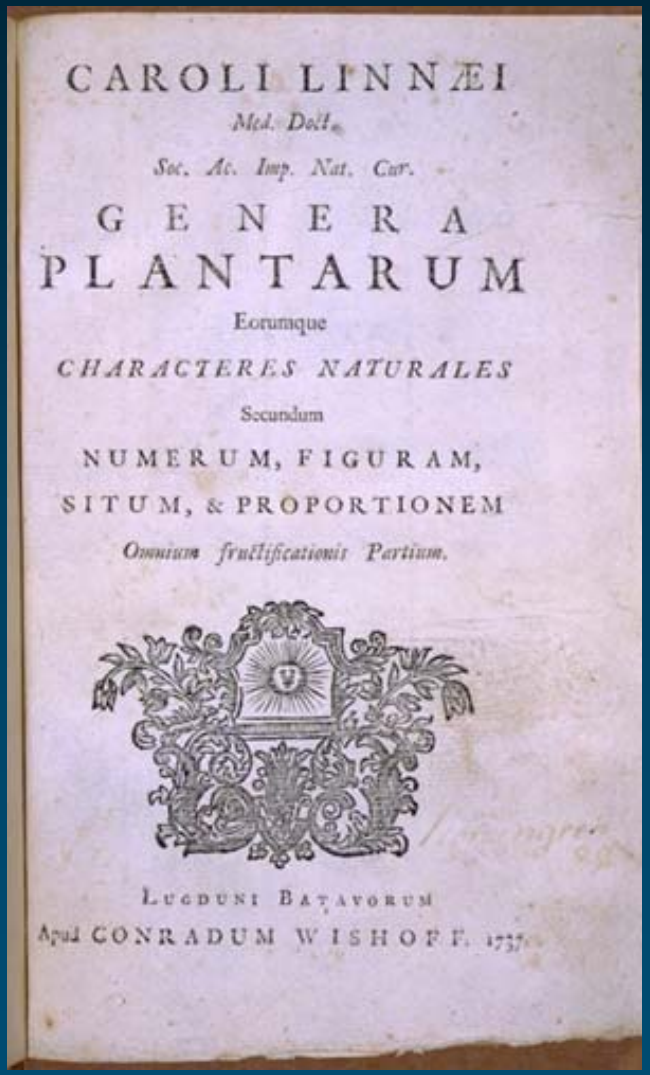
Figure 36 Thomas Sydenham (1624–1689)

To classify diseases (and plants)

- Carolus Linnaeus (1707-1778)
  - *Genera Plantarum* (1737)
  - *Genera Morborum* (1763)
- François Boissier de La Croix a.k.a. F. B. de Sauvages (1706-1767)
  - *Methodus Foliorum* (1751)
  - *Nosologia Methodica* (1763/68)
- William Cullen (1710-1790)
  - *Synopsis Nosologiae Methodicae* (1785)



From plants...



CAROLI LINNÆI

Med. Doct.

Soc. Ac. Imp. Nat. Cur.

GENERA PLANTARUM

Eorumque

CHARACTERES NATURALES

Secundum

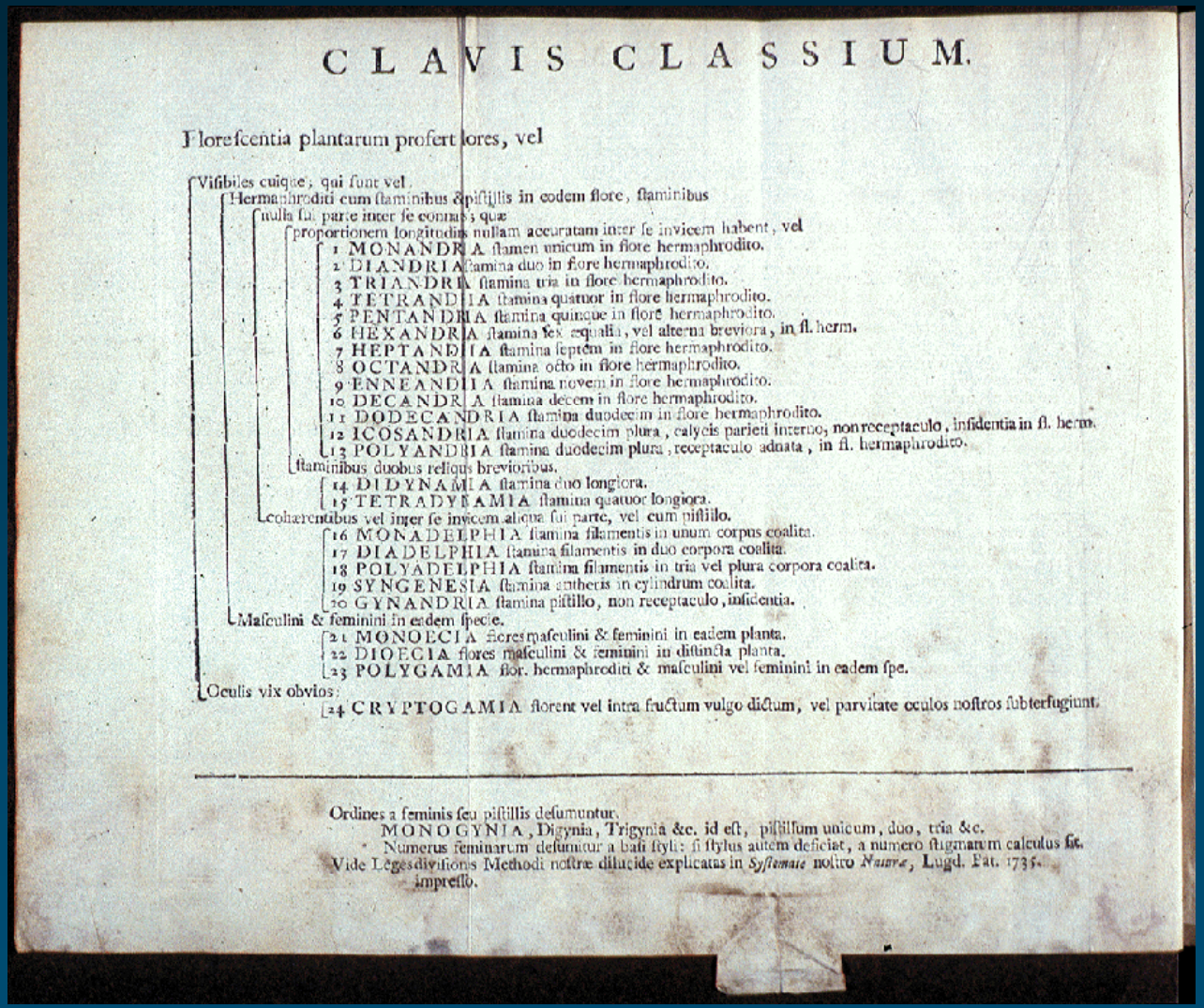
NUMERUM, FIGURAM,

SITUM, & PROPORTIONEM

Omnium fructificationis Partium.

LUGDUNI BATAVORUM

Apud CONRADUM WISHOFF. 1737.



CLAVIS CLASSIUM.

Floreſcentia plantarum profert flores, vel

Viſibiles cuique, qui ſunt vel
- Hermaphroditi cum ſtaminibus & piſtillis in eodem flore, ſtaminibus
  - nulla ſui parte inter ſe connatis; quæ
    - proportionem longitudinis nullam accuratam inter ſe invicem habent, vel
      1. MONANDRIA ſtamen unicum in flore hermaphrodito.
      2. DIANDRIA ſtamina duo in flore hermaphrodito.
      3. TRIANDRIA ſtamina tria in flore hermaphrodito.
      4. TETRANDRIA ſtamina quatuor in flore hermaphrodito.
      5. PENTANDRIA ſtamina quinque in flore hermaphrodito.
      6. HEXANDRIA ſtamina ſex æqualia, vel alterna breviora, in fl. herm.
      7. HEPTANDRIA ſtamina ſeptem in flore hermaphrodito.
      8. OCTANDRIA ſtamina octo in flore hermaphrodito.
      9. ENNEANDRIA ſtamina novem in flore hermaphrodito.
      10. DECANDRIA ſtamina decem in flore hermaphrodito.
      11. DODECANDRIA ſtamina duodecim in flore hermaphrodito.
      12. ICOSANDRIA ſtamina duodecim plura, calycis parieti interno, non receptaculo, inſidentia in fl. herm.
      13. POLYANDRIA ſtamina duodecim plura, receptaculo adnata, in fl. hermaphrodito.
    - ſtaminibus duobus reliquis brevioribus.
      14. DIDYNAMIA ſtamina duo longiora.
      15. TETRADYNAMIA ſtamina quatuor longiora.
    - cohærentibus vel inter ſe invicem aliqua ſui parte, vel cum piſtillo.
      16. MONADELPHIA ſtamina filamentis in unum corpus coalita.
      17. DIADELPHIA ſtamina filamentis in duo corpora coalita.
      18. POLYADELPHIA ſtamina filamentis in tria vel plura corpora coalita.
      19. SYNGENESIA ſtamina antheris in cylindrum coalita.
      20. GYNANDRIA ſtamina piſtillo, non receptaculo, inſidentia.
  - Maſculini & feminini in eadem ſpecie.
    21. MONOECIA flores maſculini & feminini in eadem planta.
    22. DIOECIA flores maſculini & feminini in diſtincta planta.
    23. POLYGAMIA flor. hermaphroditi & maſculini vel feminini in eadem ſpe.
- Oculis vix obvios:
  24. CRYPTOGAMIA florent vel intra fructum vulgo dictum, vel parvitate oculos noſtros ſubterfugiunt.

Ordines a feminis ſeu piſtillis deſumuntur.
MONOGYNIA, Digynia, Trigynia &c. id eſt, piſtillum unicum, duo, tria &c.
Numerus feminarum deſumitur a baſi ſtyli: ſi ſtylus autem deficiat, a numero ſtigmatum calculus fit.
Vide Leges divifionis Methodi noſtræ dilucide explicatas in *Syſtemate* noſtro *Naturæ*, Lugd. Bat. 1735. impreſſo.

… to diseases

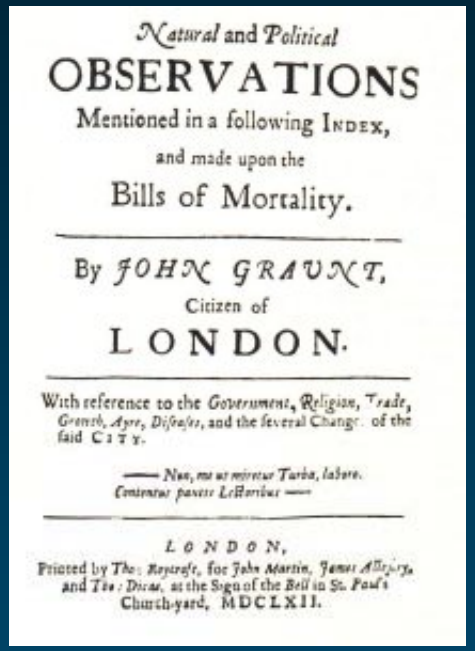
- Four categories (W. Cullen)
  - Fevers
  - Nervous disorders
  - Cachexias
  - Local diseases

> "The distinction of the genera of diseases, the distinction of the species of each, and often even that of the varieties, I hold to be a necessary foundation of every plan of physic, whether dogmatical or empirical."
> – William Cullen, Edinburgh, 1785
> *Synopsis Nosologia Methodicae*

(Cited by Chris Chute)

To support epidemiology

- John Graunt (1620-1674)
  - Analyzes the vital statistics of the citizens of London
- William Farr (1807-1883)
  - Medical statistician
  - Improves Cullen's classification
  - Contributes to creating ICD
- Jacques Berthillon (1851-1922)
  - Chief of the statistical services (Paris)
  - Classification of causes of death (161 rubrics)



Natural and *Political*

OBSERVATIONS

Mentioned in a following INDEX,

and made upon the

Bills of Mortality.

By *JOHN GRAUNT*,

Citizen of

LONDON.

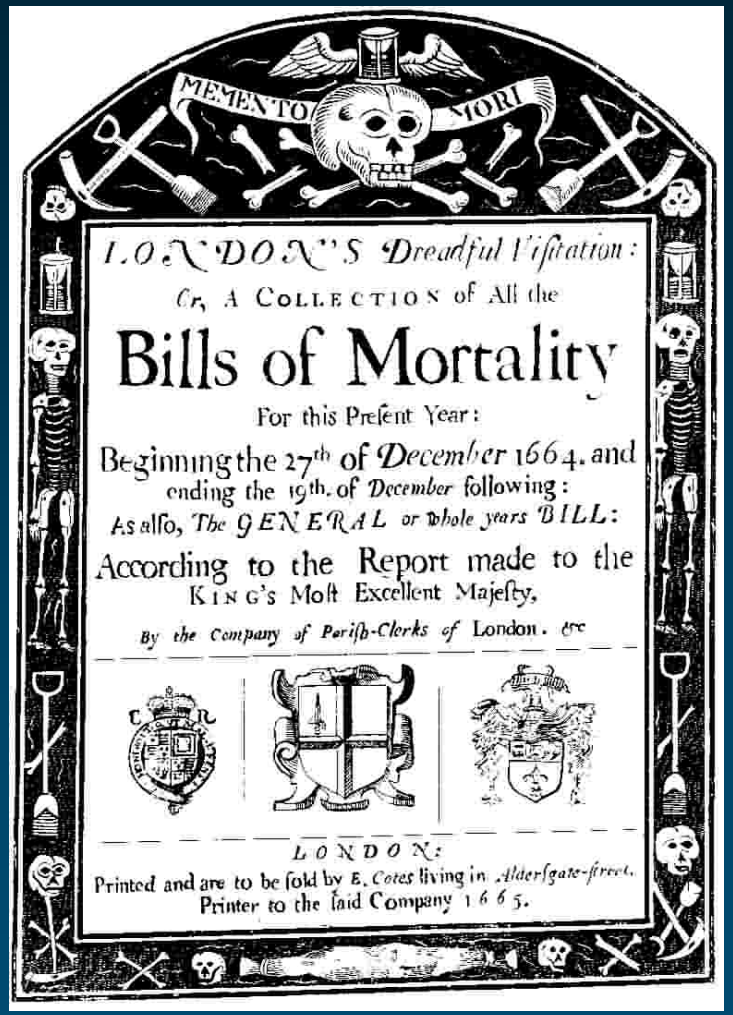
With reference to the *Government*, *Religion*, *Trade*, *Growth*, *Ayre*, *Diseases*, and the several Changes of the said CITY.

—— Non, me ut miretur Turba, labore.
Contentus paucis Lectoribus ——

LONDON,

Printed by *Tho: Roycroft*, for *John Martin*, *James Allejtry*, and *Tho: Dicas*, at the Sign of the *Bell* in St. *Paul's* Church-yard, MDCLXII.

London Bills of Mortality



A generall Bill for this present year, ending the 19 of December 1665. according to the Report made to the KINGS most Excellent Majesty.

By the Company of Parish Clerks of London, &c.

The Diseases and Casualties this year.

Abortive and Stilborne	617	Executed	21	Palsie	30
Aged	1545	Flux and Small Pox	655	Plague	68596
Ague and Peaver	5257	Found dead in streets, fields, &c.	2[illegible]	Plannet	6
Appoplex and Suddenly	116	French Pox	86	Plurisie	15
Bedrid	10	Frighted	23	Poysoned	1
Blasted	5	Gout and Sciatica	27	Quinsie	35
Bleeding	16	Grief	46	Rickets	157
Bloody Flux, Scowring & Flux	185	Griping in the Guts	1238	Rising of the Lights	397
Burnt and Scalded	8	Hangd & made away themselves	7	Rupture	34
Calenture	3	Headmouldshot & Mouldfallen	14	Scurvy	1[illegible]7
Cancer, Gangrene and Fistula	56	Jaundies	1[illegible]	Shingles and Swine pox	2
Canker, and Thrush	1[illegible]1	Impostume	227	Stores, Ulcers, broken and bruised	
Childbed	625	Kild by severall accidents	46	Limbs	82
Chrisomes and Infants	1258	Kings Evill	86	Spleen	14
Cold and Cough	68	Leprosie	2	Spotted Feaver and Purples	1929
Collick and Winde	134	Lethargy	14	Stopping of the stomack	33[illegible]
Consumption and Tissick	48[illegible]8	Livergrown	2[illegible]	Stone and Strangury	[illegible]8
Convulsion and Mother	2036	Meagrom and Headach	12	Surfet	[illegible]
Distracted	5	Measles	7	Teeth and Worms	2614
Drouse and Tympany	1476	Murthered and Shot	9	Vomiting	5[illegible]
Drowned	5[illegible]	Overlaid & Starved	45	Wenn	[illegible]

Christned: Males	5114	Buried: Males	48568	Of the Plague	68596
Females	4853	Females	48737		
In all	9967	In all	97[illegible]		

Increased in the Burials in the 130 Parishes and at the Pest-house this year — 79009
Increased of the Plague in the 130 Parishes and at the Pest-house this year — 68590

Limitations of existing classifications

"The advantages of a uniform statistical nomenclature, however imperfect, are so obvious, that it is surprising no attention has been paid to its enforcement in Bills of Mortality. Each disease has, in many instances, been denoted by three or four terms, and each term has been applied to as many different diseases: vague, inconvenient names have been employed, or complications have been registered instead of primary diseases. The nomenclature is of as much importance in this department of inquiry as weights and measures in the physical sciences, and should be settled without delay."

– William Farr

First annual report.

London, Registrar General of England and Wales, 1839, p. 99.

To index and retrieve information

- Biomedical literature
  - MEDLINE (15M citations from 4600 journals)
  - Manually indexed
  - Medical Subject Headings (MeSH)
- Genome
  - Model organism databases (Fly, Mouse, Yeast, …)
  - Manually / semi-automatically curated
  - Gene Ontology

MEDLINE and MeSH

1: J Hist Neurosci. 2004 Mar;13(1):91-101. Related Articles, Links

MetaPress

Black bile and psychomotor retardation: shades of melancholia in Dante's Inferno.

Widmer DA.

Memorial Sloan-Kettering Cancer Center, New York, NY 10017, USA. widmerd@mskcc.org

The history of melancholy depression is rich with images of movement retardation and mental dysfunction. The recent restoration of psychomotor symptoms to the diagnostic terminology of affective disorder is not novel to the students of medieval melancholia. The move back to the biology of this psychomotor dysfunction with the technical advances in brain imaging in recent years only echoes centuries-old writings on the centrality of movement changes in the depressive condition. The Inferno, the first cantica of Dante Alighieri's Commedia, has a wonderful abundance of allusions to the importance of psychomotor symptoms in describing the depressed individual. Slowed steps, garbled speech, frozen tears, these and many other images keep the physical manifestations of psychomotor suffering in the forefront of the reader's mind. Considering Medieval and Renaissance writings on melancholy suffering, it is fitting that Dante shows a bodily illness reflected in the hellish torments visited on the damned. From the souls of the sullen to those of the violent, the panorama of psychomotor symptoms plays a prominent role in the poem as well as in the medical and literary prose of succeeding centuries.

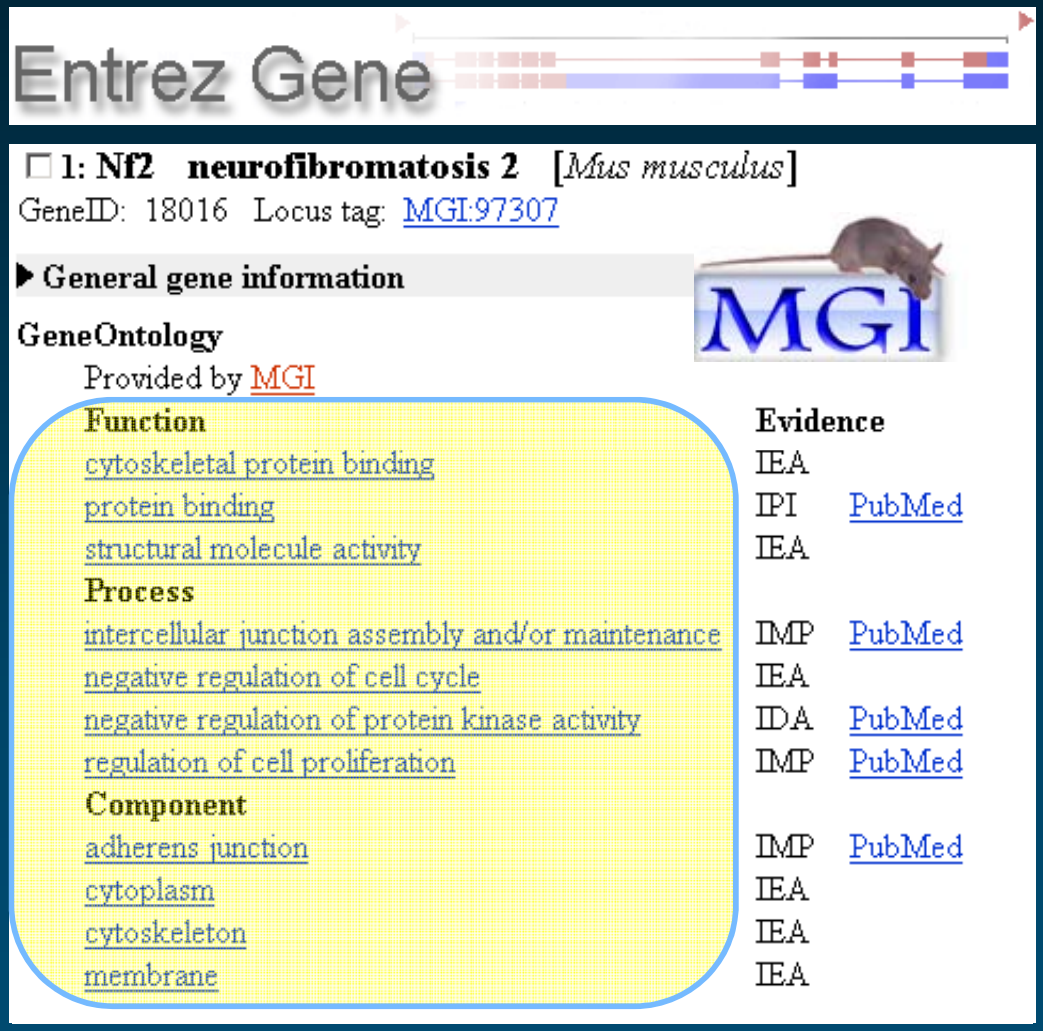
MeSH Terms:

- Depressive Disorder/history*
- History of Medicine, Medieval
- Human
- Italy
- Literature, Medieval/history*
- Medicine in Literature*
- Poetry/history*
- Psychomotor Disorders/history*

PubMed

National Library of Medicine NLM

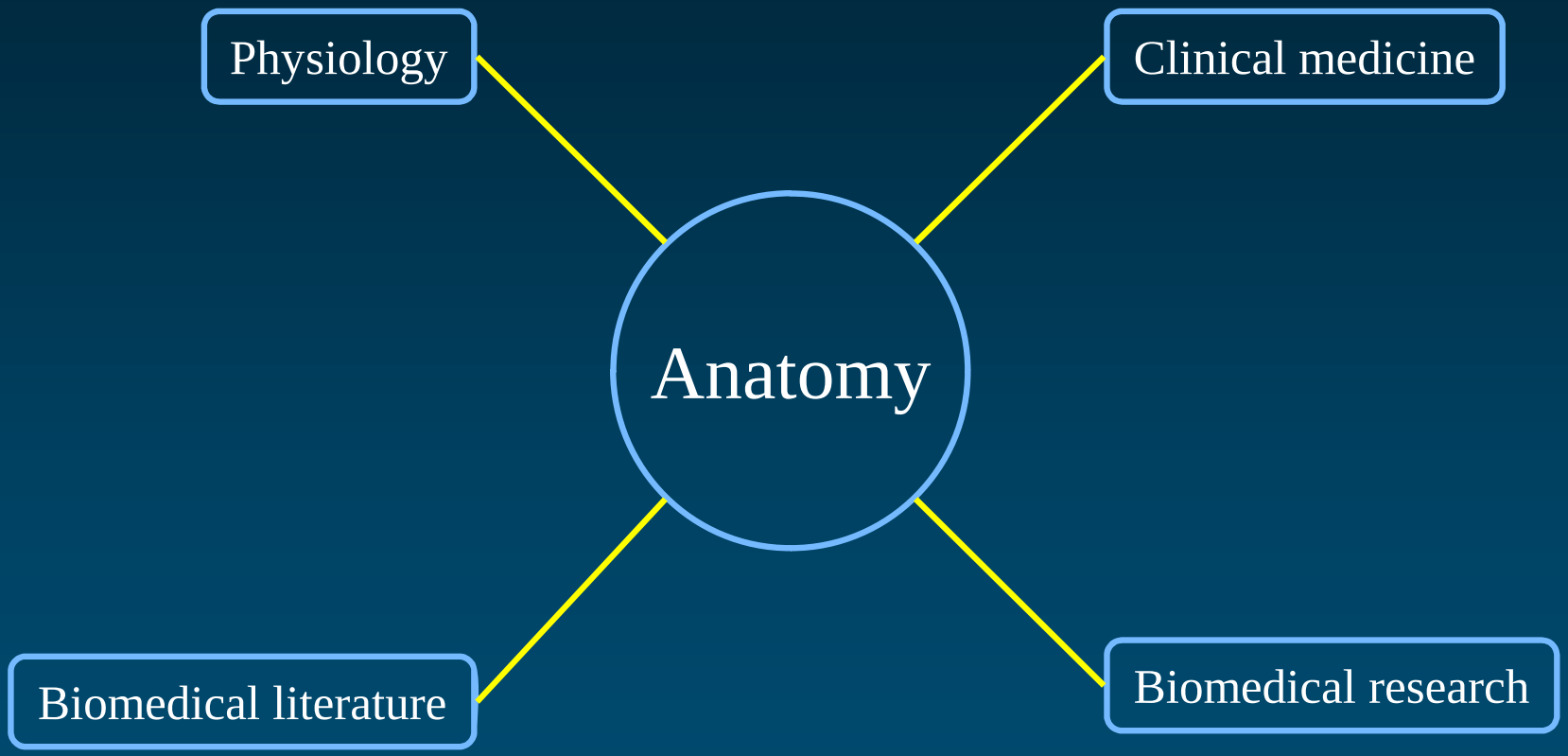
Mouse Genome Database and GO



To serve as a reference

- Reference terminology/ontology
  - Universally needed
  - Developed independently of any purposes
  - Reusable by many applications
- Examples
  - VA National Drug File (NDF)
  - Foundational Model of Anatomy (FMA)
  - SNOMED CT

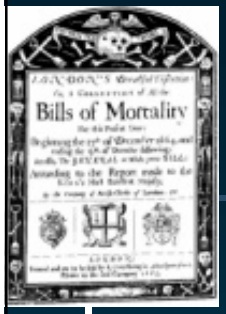
Anatomy in Biomedicine



Administrative terminologies

- Coding patient records
  - International Classification of Primary Care (ICPC)
  - SNOMED
  - Read Codes
- Reporting claims to health insurance companies
  - Current Procedural Terminology (CPT)
  - International Classification of Diseases (ICD-9 CM)
  - Healthcare Common Procedure Coding System (HCPCS)

[Bodenreider, BIB 2006] *(courtesy of J. Rogers)*



History of Medical Ontologies

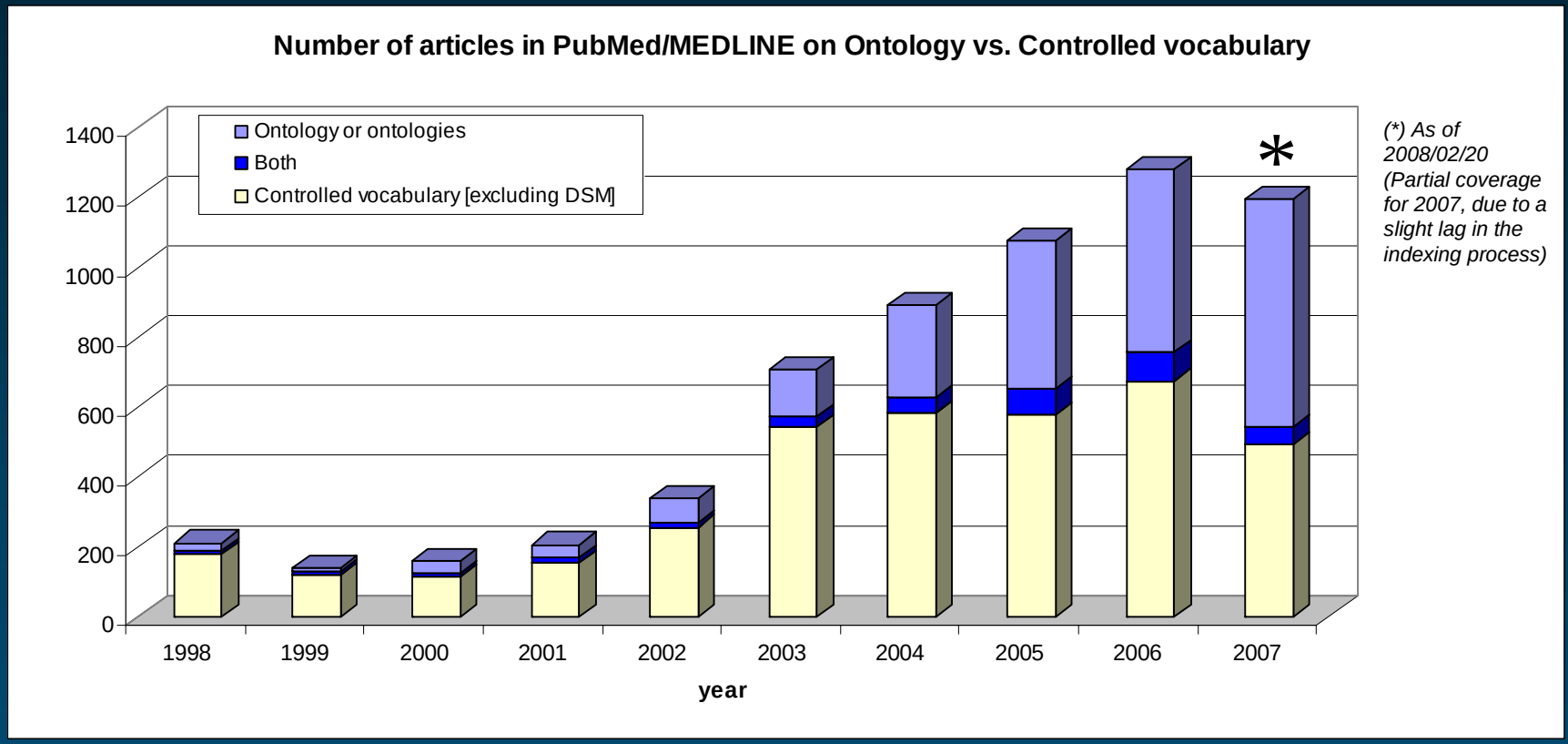
Synopsis Nosologiae Methodicae

SNOP
CPT
OPCS
EmTree
MeSH
ICD
ICD9
FMA
GALEN
DM&D
UMLS
OPCS3
OPCS4
OPCS4.3
CTV3
READ
ICPC
SNOMED International
SNOMED-CT
SNOMED-2
SNOMED-RT
MESH

1603 1700 1785 1855 1900 1975 1985 1995 2005

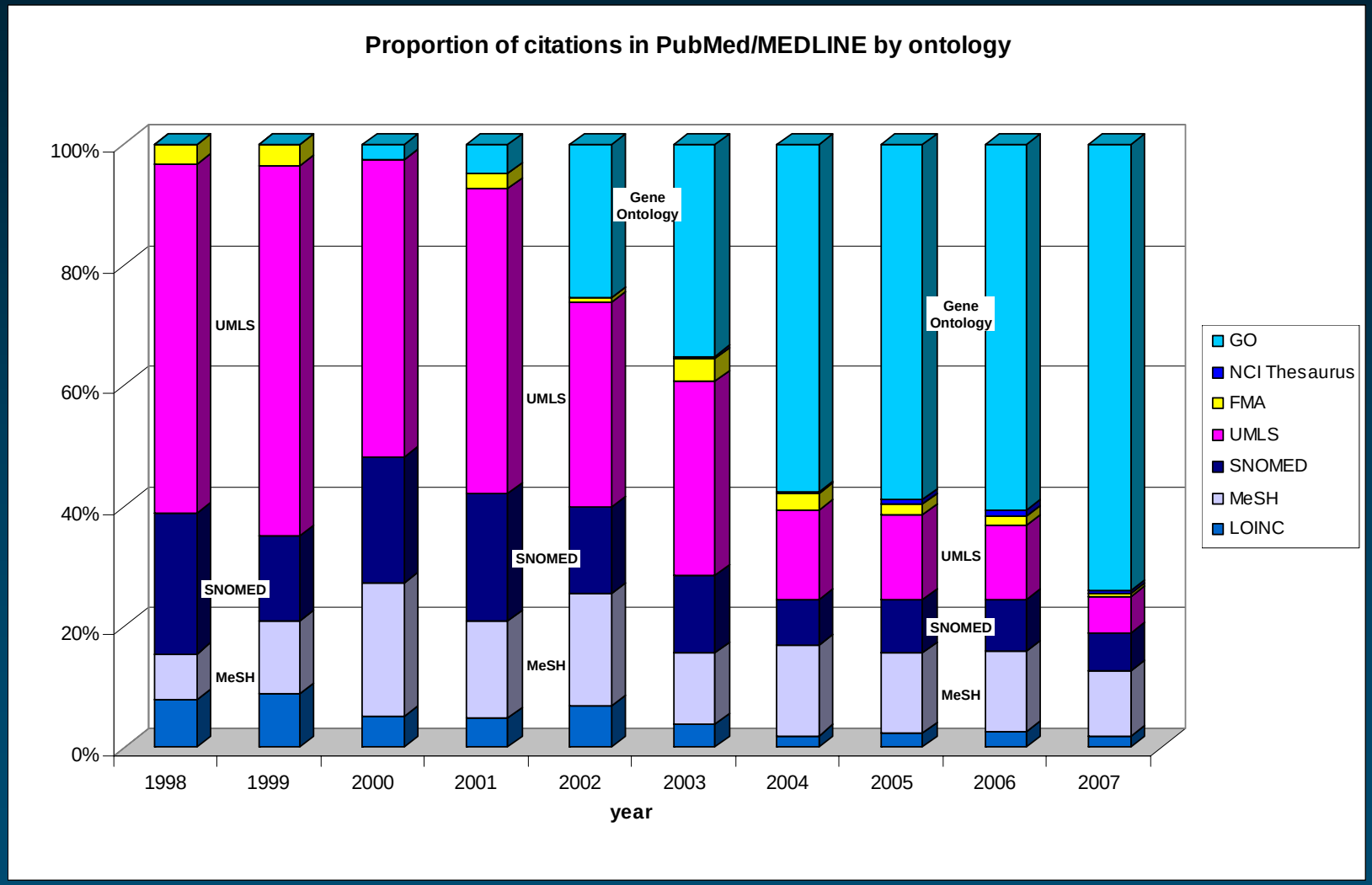
NLM

Biomedical ontology in PubMed



[Bodenreider, YBMI 2008]

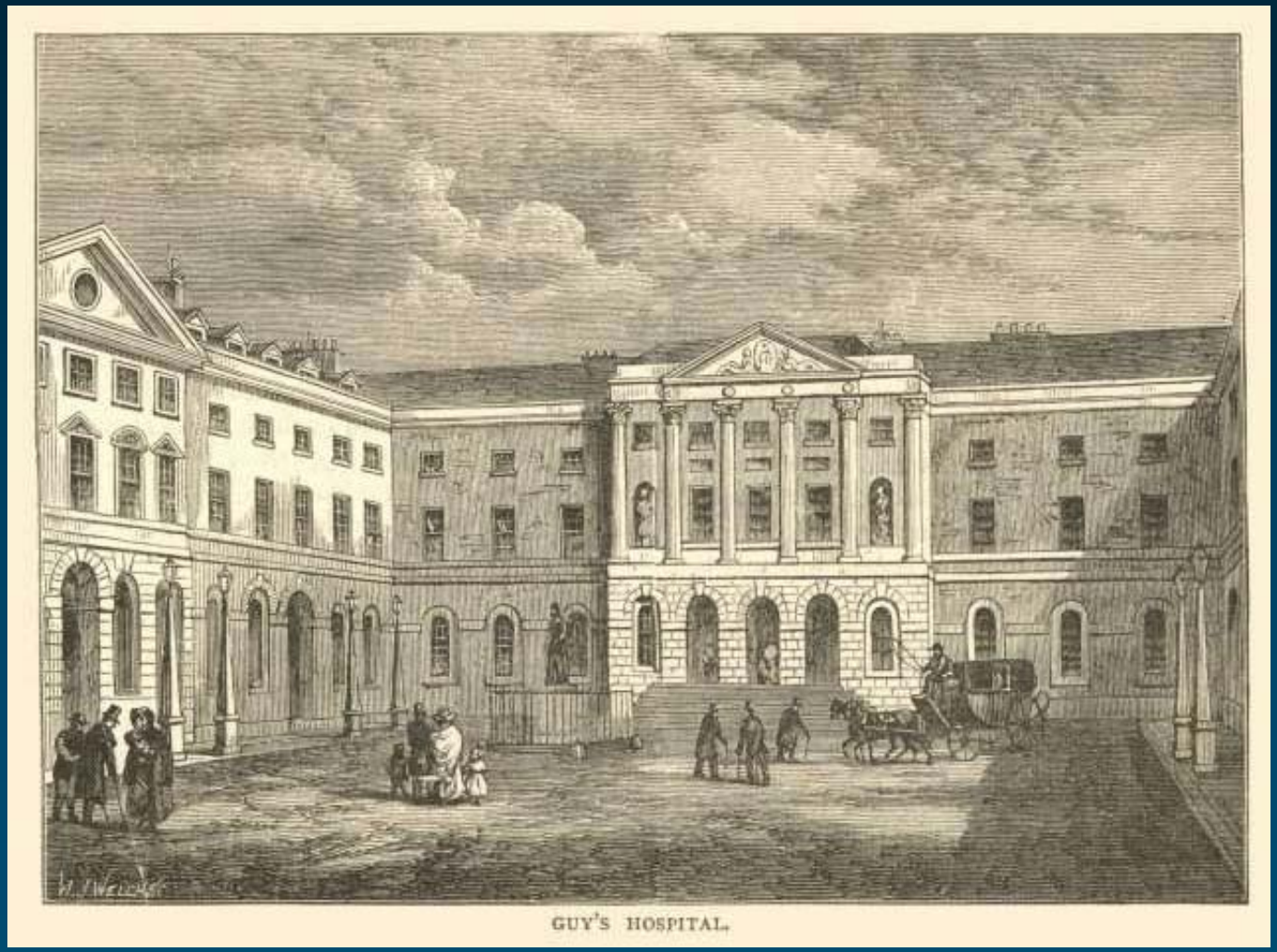
Biomedical ontologies in PubMed



[Bodenreider, YBMI 2008]

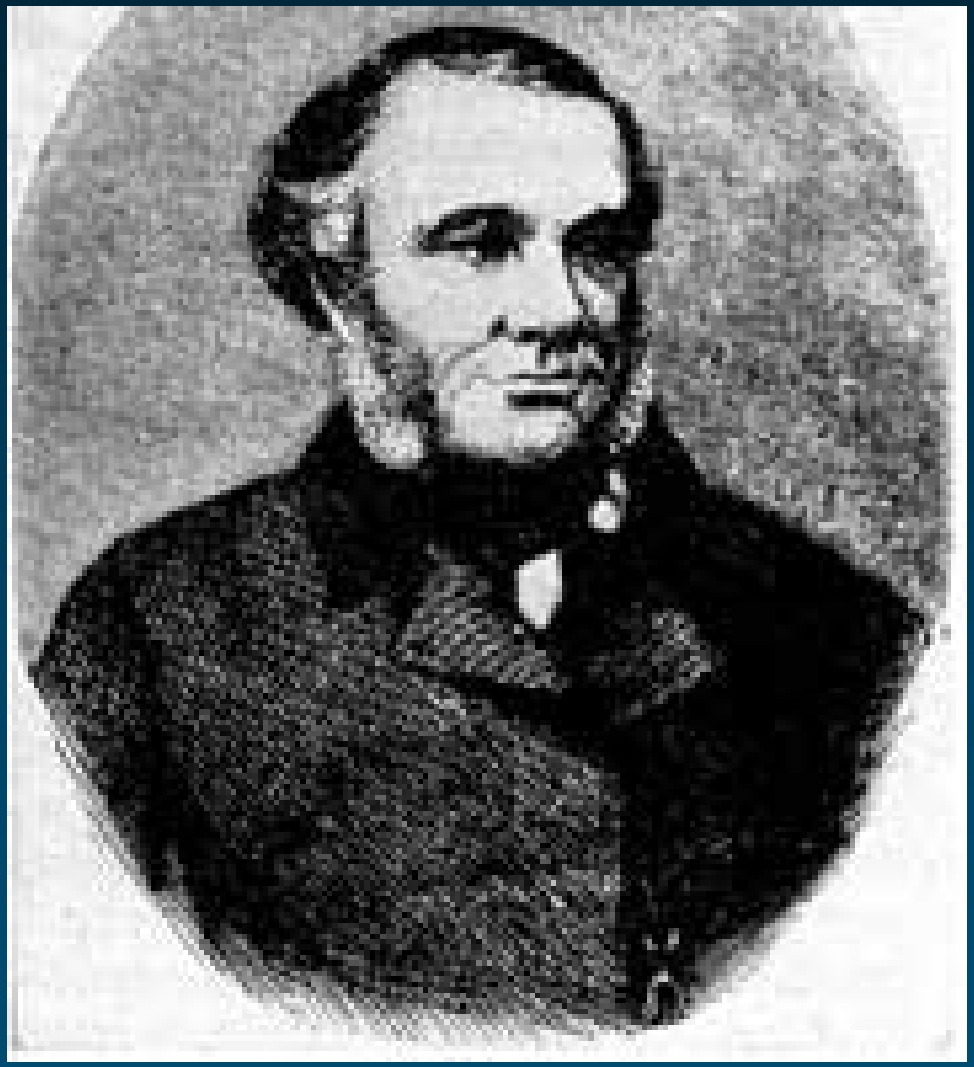
Introduction to biomedical terminologies through an example

Guy's Hospital, London



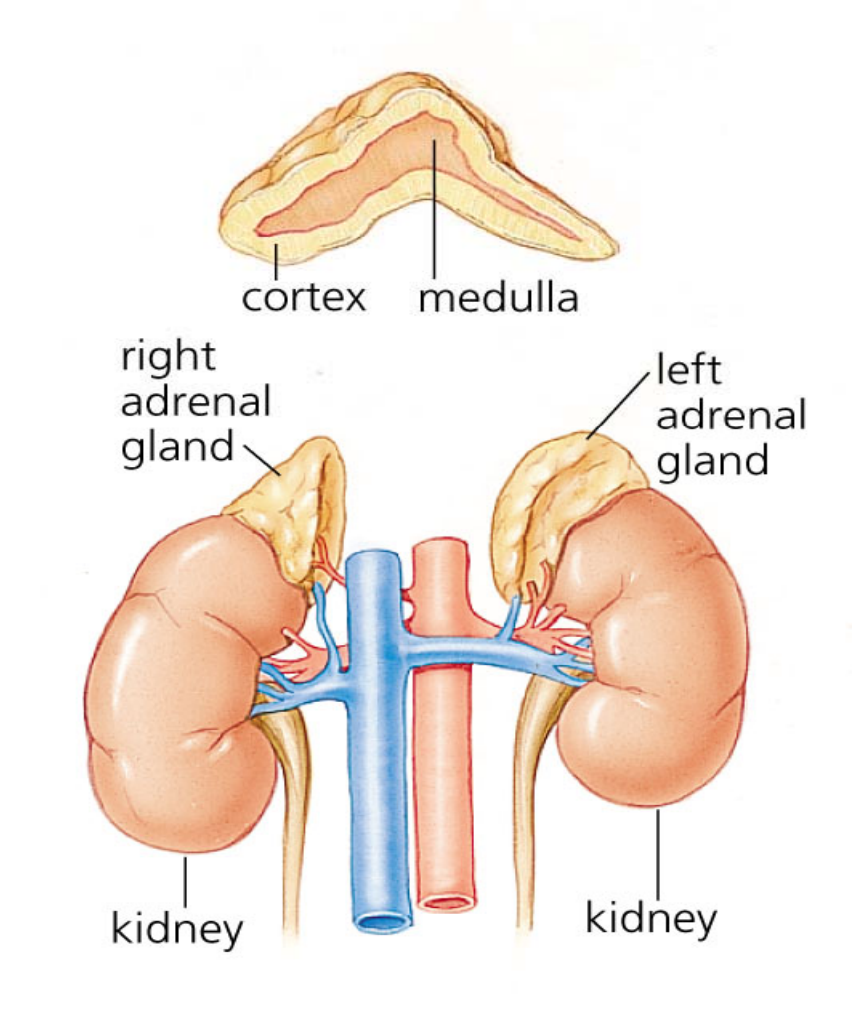
GUY'S HOSPITAL.

Thomas Addison (1795-1860)



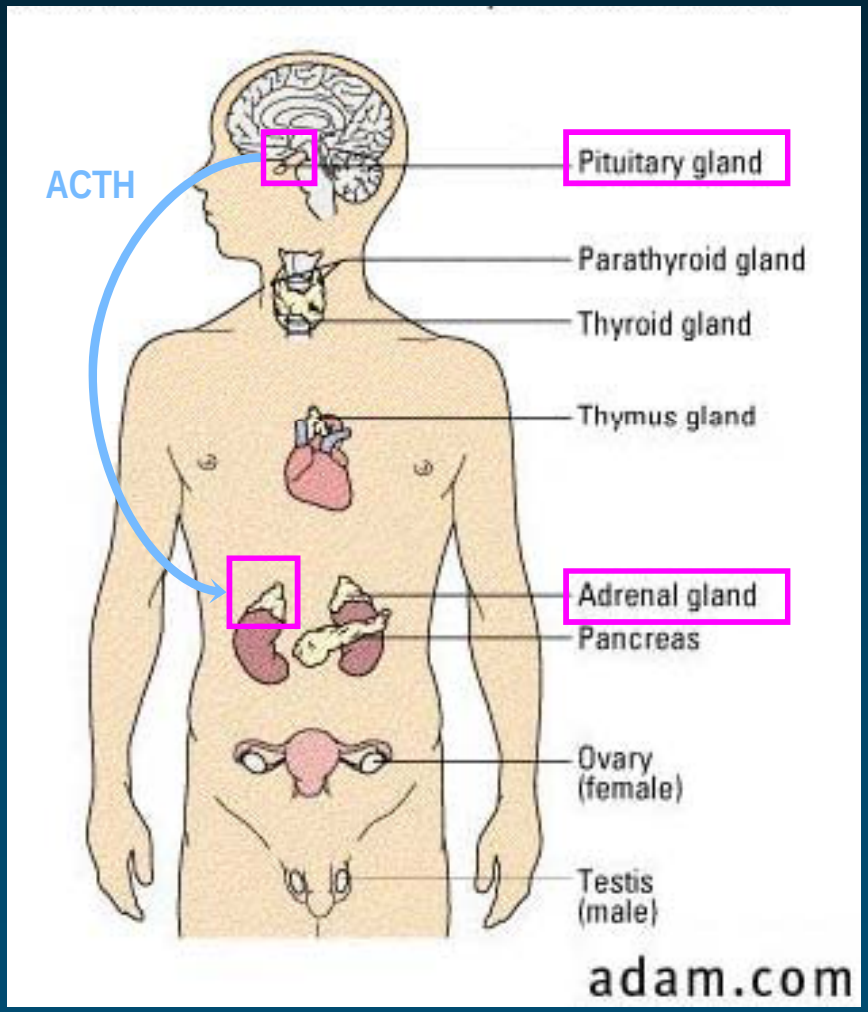
Addison’s disease

- Addison's disease is a rare endocrine disorder
- Addison's disease occurs when the adrenal glands do not produce enough of the hormone cortisol
- For this reason, the disease is sometimes called chronic adrenal insufficiency, or hypocortisolism



Adrenal insufficiency Clinical variants

- Primary / Secondary
  - Primary: lesion of the adrenal glands themselves
  - Secondary: inadequate secretion of ACTH by the pituitary gland
- Acute / Chronic
- Isolated / Polyendocrine deficiency syndrome



Addison's disease: Symptoms

- Fatigue
- Weakness
- Low blood pressure
- Pigmentation of the skin (exposed and non-exposed parts of the body)
- …

AD in medical vocabularies

- Synonyms: different terms
  - Addisonian syndrome — eponym
  - Bronzed disease — symptoms
  - Addison melanoderma — symptoms
  - Asthenia pigmentosa — symptoms
  - Primary adrenal deficiency — clinical variants
  - Primary adrenal insufficiency — clinical variants
  - Primary adrenocortical insufficiency — clinical variants
  - Chronic adrenocortical insufficiency — clinical variants
- Contexts: different hierarchies

Internal Classification of Diseases

CHAPTER 4

Endocrine, nutritional and metabolic diseases (E00-E90)

Disorders of other endocrine glands (E20-E35)

E27 Other disorders of adrenal gland

E27.0 Other adrenocortical overactivity
Overproduction of ACTH, not associated with Cushing's disease
Premature adrenarche
Excludes1: Cushing's syndrome (E24.-)

E27.1 Primary adrenocortical insufficiency
Addison's disease
Adrenocortical insufficiency NOS
Autoimmune adrenalitis
Excludes1: Addison only phenotype adrenoleukodystrophy (E71.428)
amyloidosis (E85)
tuberculous Addison's disease (A18.7)
Waterhouse-Friderichsen syndrome (A39.1)

E27.2 Addisonian crisis
Adrenal crisis
Adrenocortical crisis

E27.3 Drug-induced adrenocortical insufficiency
Code first (T36-T50) to identify drug

E27.4 Other and unspecified adrenocortical insufficiency

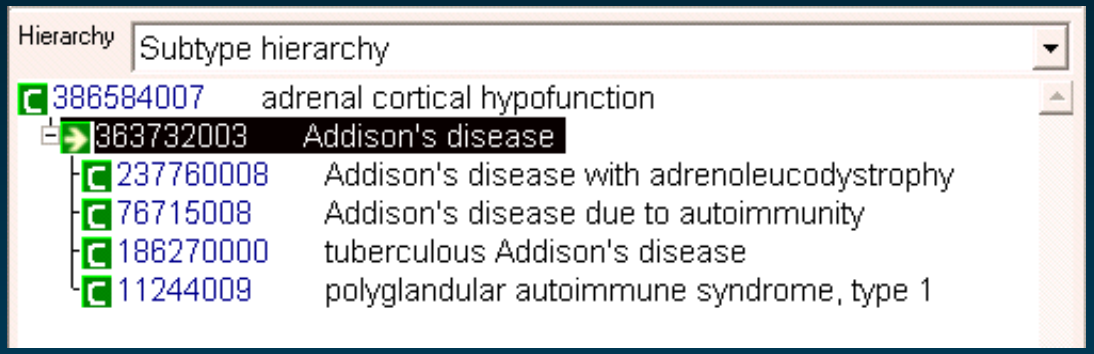
Medical Subject Headings

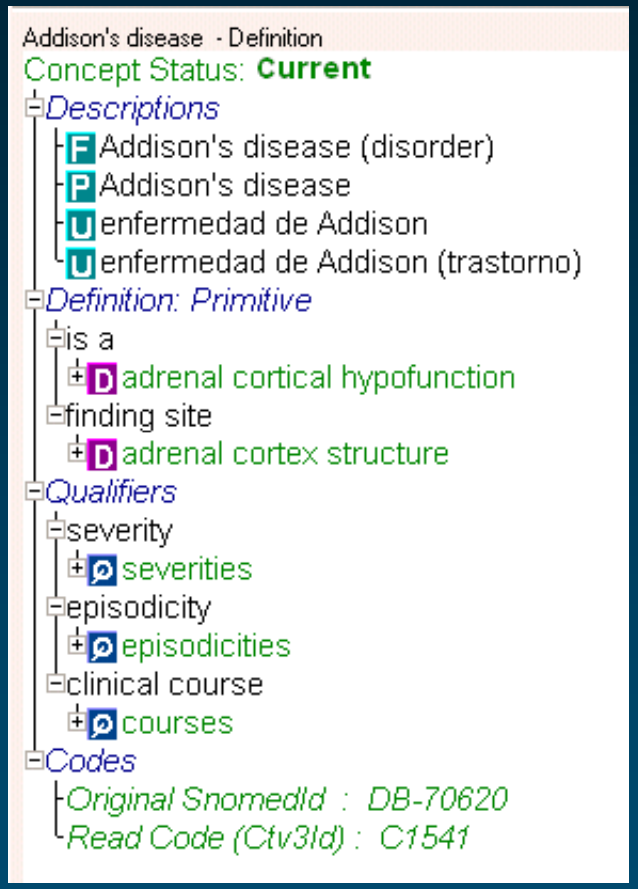
MeSH Tree Structures

Endocrine Diseases [C19]
- Adrenal Gland Diseases [C19.053]
  - Adrenal Gland Hypofunction [C19.053.264]
    - Addison's Disease [C19.053.264.263]
    - Adrenoleukodystrophy [C19.053.264.270]
    - Hypoaldosteronism [C19.053.264.480]

Immunologic Diseases [C20]
- Autoimmune Diseases [C20.111]
  - Addison's Disease [C20.111.163]
  - Anemia, Hemolytic, Autoimmune [C20.111.175]
  - Anti-Glomerular Basement Membrane Disease [C20.111.190]
  - Antiphospholipid Syndrome [C20.111.197]
  - Arthritis, Rheumatoid [C20.111.199] +
  - Autoimmune Diseases of the Nervous System [C20.111.258] +

SNOMED CT


Hierarchy
Subtype hierarchy
386584007 adrenal cortical hypofunction
363732003 Addison's disease
237760008 Addison's disease with adrenoleucodystrophy
76715008 Addison's disease due to autoimmunity
186270000 tuberculous Addison's disease
11244009 polyglandular autoimmune syndrome, type 1


Addison's disease - Definition
Concept Status: Current
Descriptions
Addison's disease (disorder)
Addison's disease
enfermedad de Addison
enfermedad de Addison (trastorno)
Definition: Primitive
is a
adrenal cortical hypofunction
finding site
adrenal cortex structure
Qualifiers
severity
severities
episodicity
episodicities
clinical course
courses
Codes
Original SnomedId : DB-70620
Read Code (Ctv3Id) : C1541

Biomedical terms as names for biomedical classes

Terms reflecting valid classes

- Pulmonary anthrax
- BRCA1 protein
- Coronary artery
- Coronary artery bypass
- …

- Non-insulin dependent diabetes mellitus
- Non-Hodgkin lymphoma
- Non-steroidal anti-inflammatory drugs
- Non-opioid analgesics
- Non-invasive medical procedure

Issues

- Multiple terms for a class
- Multiple classes for a term
- Presence of non-ontological features in terms
- Composite terms

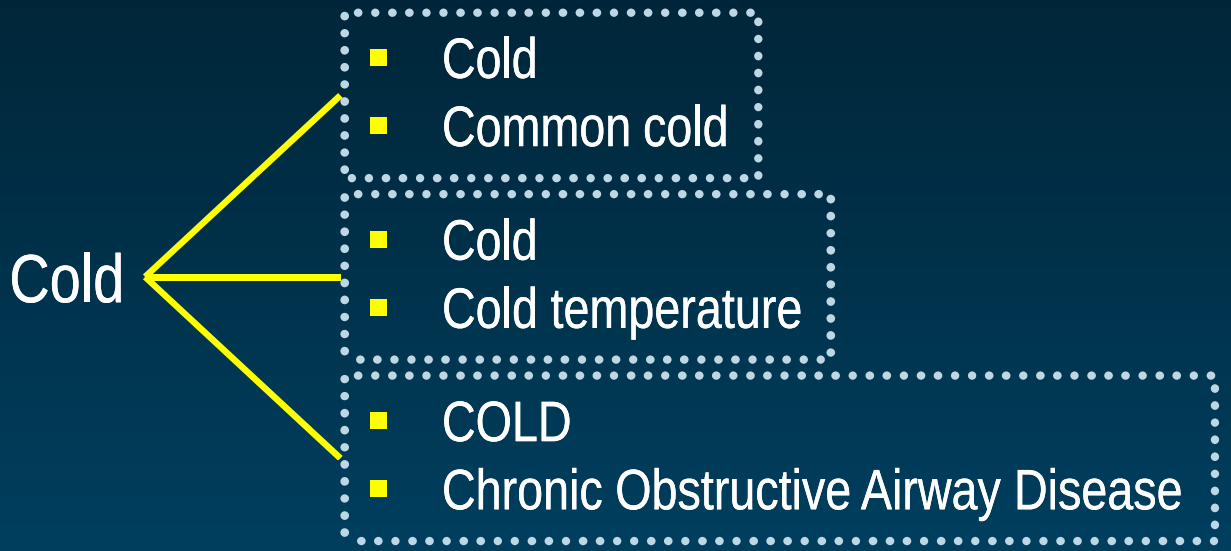
Multiple terms for a class

- Synonymy
  - Left coronary artery
  - LCA
  - Arteria coronaria sinistra
  - Addison's disease
  - Primary adrenocortical insufficiency
- "Clinical synonymy" (vs. identity)
  - Abdominal swelling
  - Swollen abdomen
  - Posttransfusion hepatitis
  - Posttransfusion viral hepatitis
  - Addison's disease
  - Primary adrenocortical insufficiency

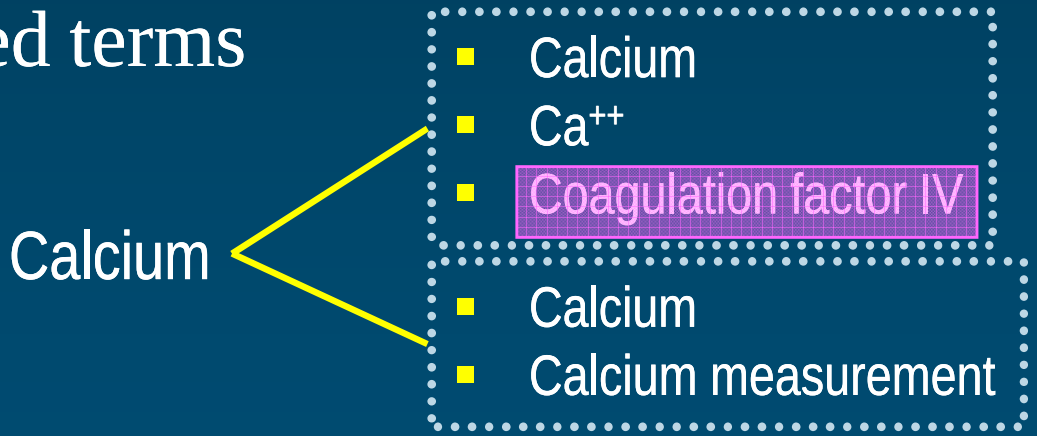
vs. Waterhouse-Friderichsen Syndrome

Multiple classes for a term

- Polysemy



- Truncated terms



Non-ontological features in terms

- Epistemological features
  - Gallbladder calculus without mention of cholecystitis
  - Diarrhea of presumed infectious origin
  - Replacement of unspecified heart valve
  - …

Ontology vs. Epistemology

- Ontology
  - Invariants in reality
    - Classes (universals)
    - Relations between them
  - Theory of reality

- Epistemology
  - Knowledge about such entities
  - Perception of reality

Bone metastasis

Bone metastasis
diagnosed by CT scan

Bone metastasis
diagnosed by Tc99m bone scintiscan

Composite terms

- Sentence-like terms
  - Several classes and their relations
  - May contain epistemological features

- Tuberculosis of adrenal glands, tubercle bacilli not found (in sputum) by microscopy, but found by bacterial culture

More composite terms

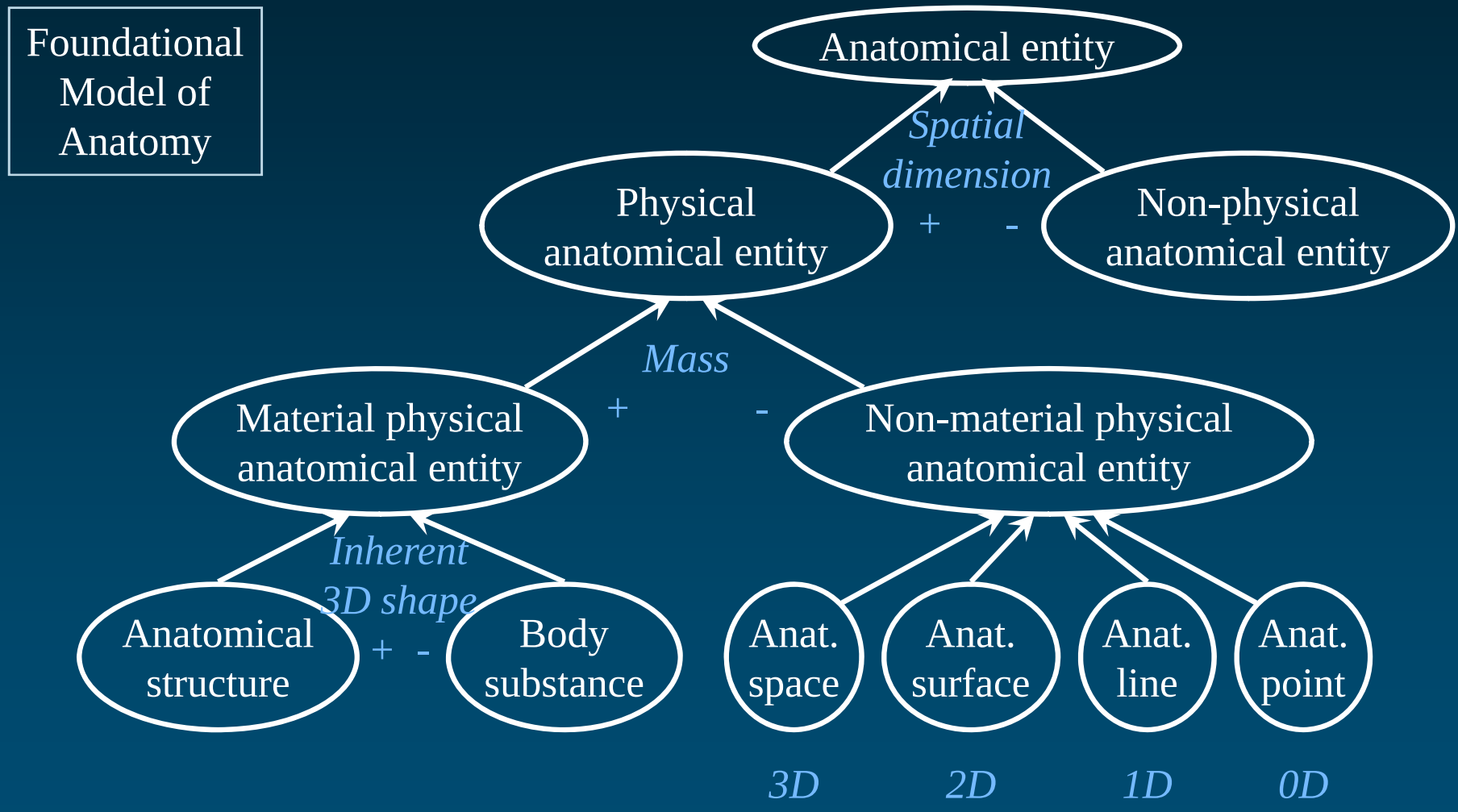
- Nontraffic accident involving being accidentally pushed from motor vehicle, except off-road motor vehicle, while in motion, not on public highway, driver of motor vehicle injured
- Determine whether the elder patient and caretaker have a functional social support network to assist the patient in performing activities of daily living and in obtaining health care, transportation, therapy, medications, community resource information, financial advice, and assistance with personal problems
- Telephone call by a physician to patient or for consultation or medical management or for coordinating medical management with other health care professionals (eg, nurses, therapists, social workers, nutritionists, physicians, pharmacists); complex or lengthy (eg, lengthy counseling session with anxious or distraught patient, detailed or prolonged discussion with family members regarding seriously ill patient, lengthy communication necessary to coordinate complex services of several different health professionals working on different

Terminological relations as a surrogate for ontological relations

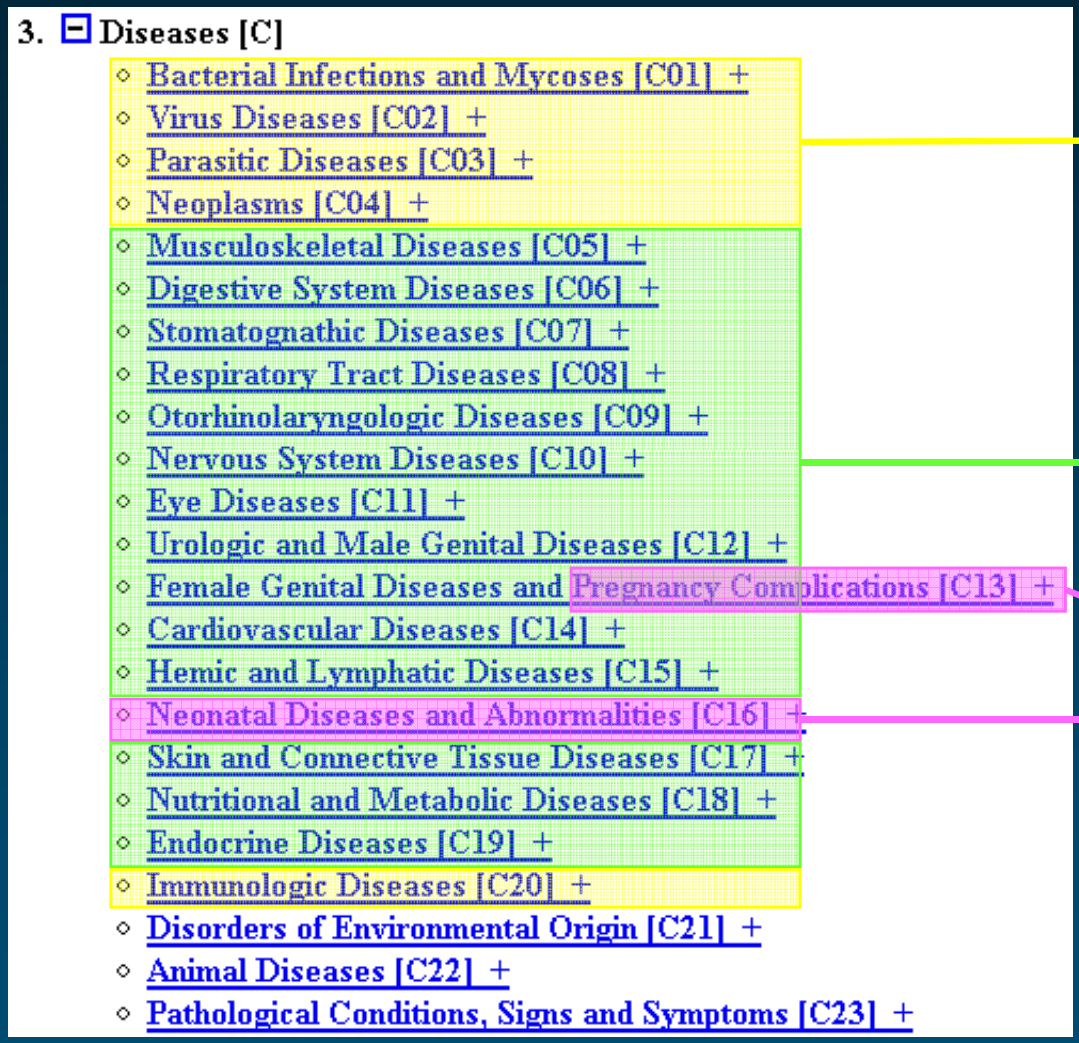
Issues

- Lack of explicit classificatory principle
- Underspecification of the relations
- Thesaurus relations
- Limited depth in hierarchies “by design”

Explicit classificatory principle



No explicit classificatory principle

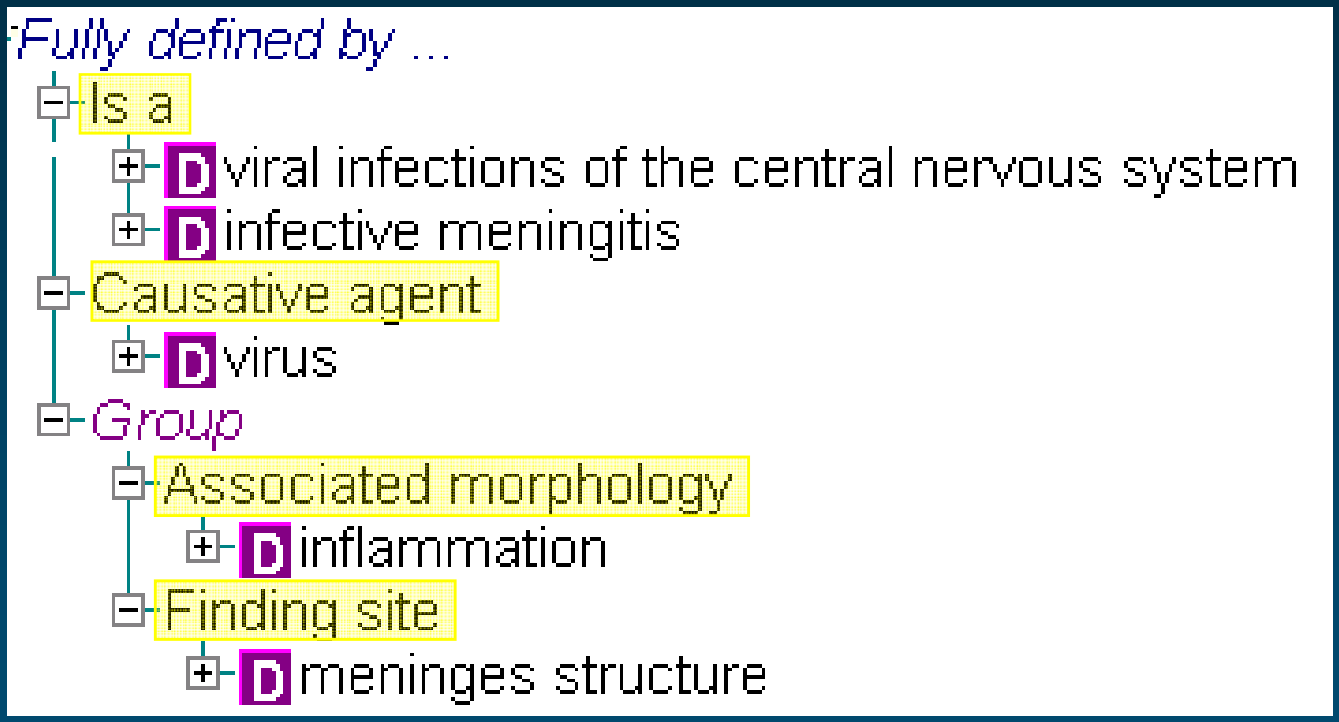


1. Certain infectious and parasitic diseases
2. Neoplasms
3. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
4. Endocrine, nutritional, and metabolic diseases
5. Mental and behavioral disorders
6. Diseases of nervous system
7. Diseases of the eye and adnexa
8. Diseases of the ear and mastoid process
9. Diseases of circulatory system
10. Diseases of respiratory system
11. Diseases of digestive system
12. Diseases of the skin and subcutaneous tissue
13. Diseases of the musculoskeletal system and connective tissue
14. Diseases of the genitourinary system
15. Pregnancy, childbirth, and the puerperium
16. Certain conditions originating in the newborn (perinatal) period
17. Congenital malformations, deformations and chromosomal abnormalities
18. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
19. Injury, poisoning and certain other consequences of external causes
20. External causes of morbidity
21. Factors influencing health status and contact with health service

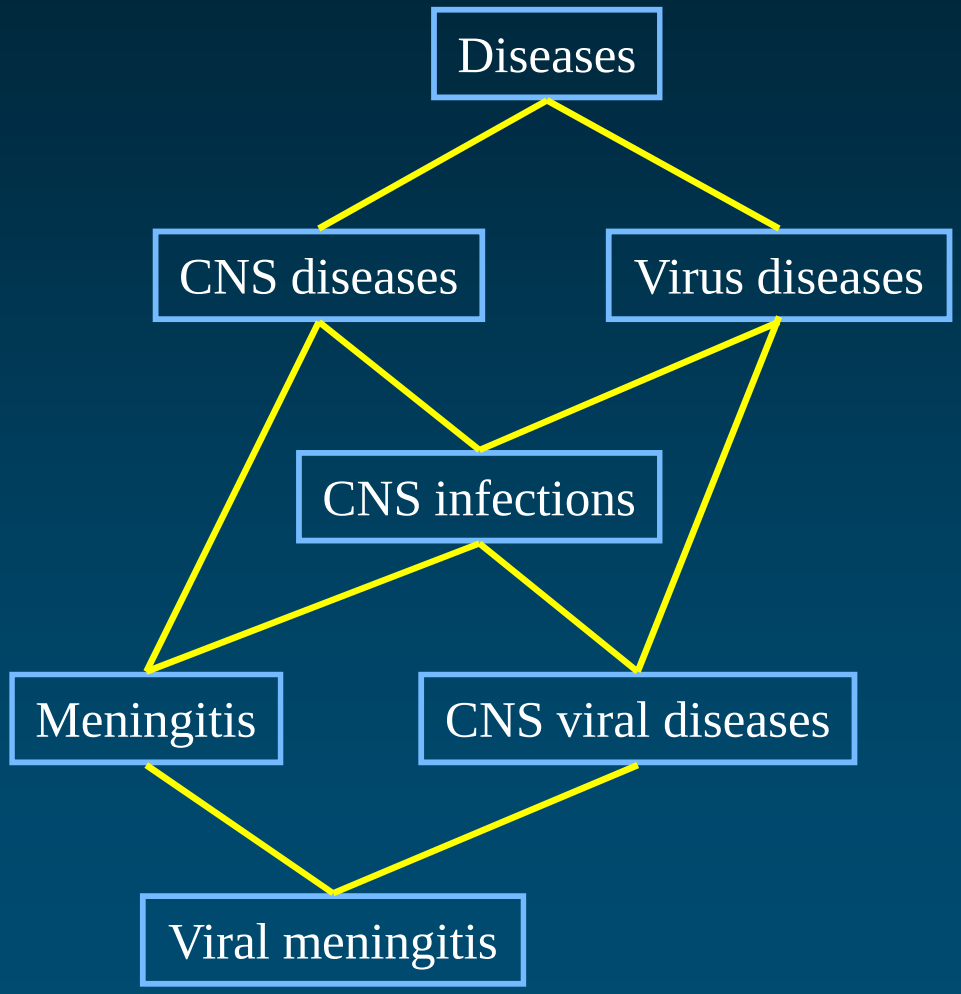
- Attribute
- Body structure
- Clinical finding
- Context-dependent categories
- Environments and geographical locations
- Events
- Observable entity
- Organism
- Pharmaceutical / biologic product
- Physical force
- Physical object
- Procedure
- Qualifier value
- Social context
- Special concept
- Specimen
- Staging and scales
- Substance

Fully specified relations

Viral meningitis in SNOMED CT



Underspecification of the relations



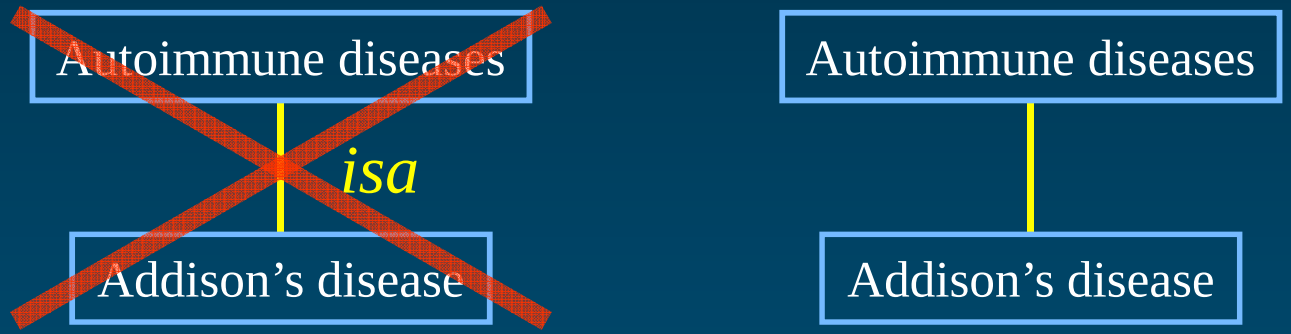
parent

isa ?

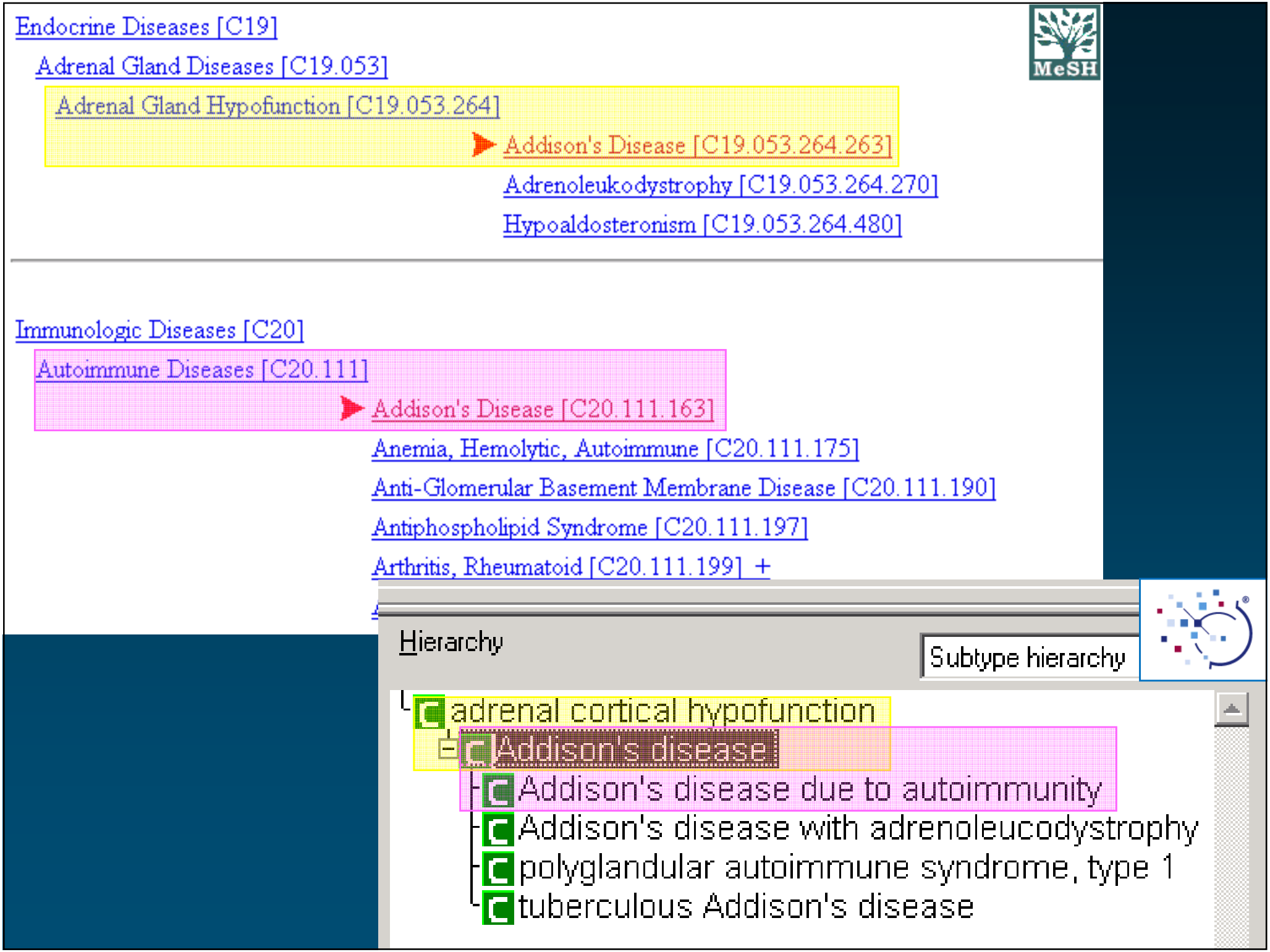
child

Thesaurus relations

- Addison's disease
  - Due to auto-immunity in 80% of the cases
  - Other causes include tuberculosis



Relations used to create hierarchical structures
vs. hierarchical relations


Endocrine Diseases [C19]
Adrenal Gland Diseases [C19.053]
Adrenal Gland Hypofunction [C19.053.264]
Addison's Disease [C19.053.264.263]
Adrenoleukodystrophy [C19.053.264.270]
Hypoaldosteronism [C19.053.264.480]
Immunologic Diseases [C20]
Autoimmune Diseases [C20.111]
Addison's Disease [C20.111.163]
Anemia, Hemolytic, Autoimmune [C20.111.175]
Anti-Glomerular Basement Membrane Disease [C20.111.190]
Antiphospholipid Syndrome [C20.111.197]
Arthritis, Rheumatoid [C20.111.199] +
MeSH
Hierarchy
Subtype hierarchy
adrenal cortical hypofunction
Addison's disease
Addison's disease due to autoimmunity
Addison's disease with adrenoleucodystrophy
polyglandular autoimmune syndrome, type 1
tuberculous Addison's disease

Accidents in MeSH

Environment and Public Health [G03]

Public Health [G03.850]

Accidents [G03.850.110]

Accident Prevention [G03.850.110.060] +

Accidental Falls [G03.850.110.085]

Accidents, Aviation [G03.850.110.185]

Accidents, Home [G03.850.110.205]

Accidents, Occupational [G03.850.110.250] +

Accidents, Radiation [G03.850.110.285]

Accidents, Traffic [G03.850.110.320]

Drowning [G03.850.110.500] +

Limited depth in hierarchies “by design”

- Term identifier (code) used to record the position in the hierarchy
  - Limited number of digits available
  - May hide part of the structure
- Terminologies: ICD, SNOMED, …

E84 Cystic fibrosis

Includes: mucoviscidosis

E84.0 Cystic fibrosis with pulmonary manifestations

Use additional code to identify any infectious organism present, such as:
Pseudomonas (B96.5)

E84.1 Meconium ileus in cystic fibrosis

Excludes1: meconium ileus not due to Cystic fibrosis (P75)

E84.2 Cystic fibrosis with gastrointestinal manifestations

Excludes2:meconium ileus in cystic fibrosis (E84.1)

E84.8 Cystic fibrosis with other manifestations

Cystic fibrosis in ICD

E84 Cystic fibrosis

Includes: mucoviscidosis

E84.0 Cystic fibrosis with pulmonary manifestations

Use additional code to identify any infectious organism present, such as:
Pseudomonas (B96.5)

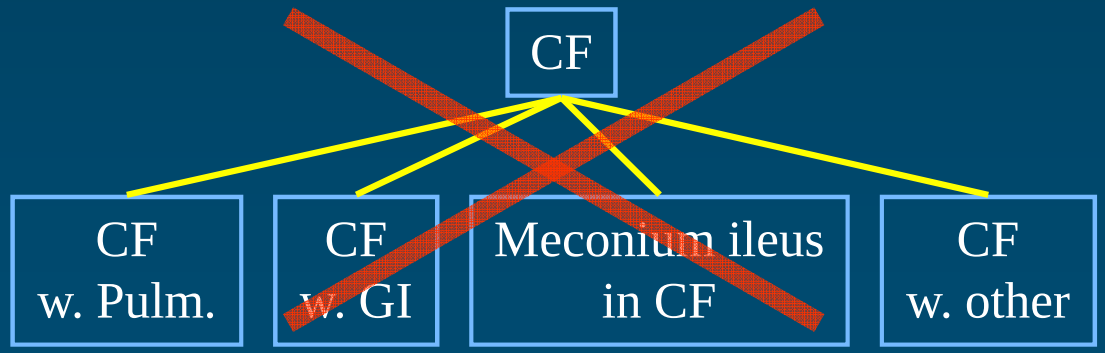
E84.1 Meconium ileus in cystic fibrosis

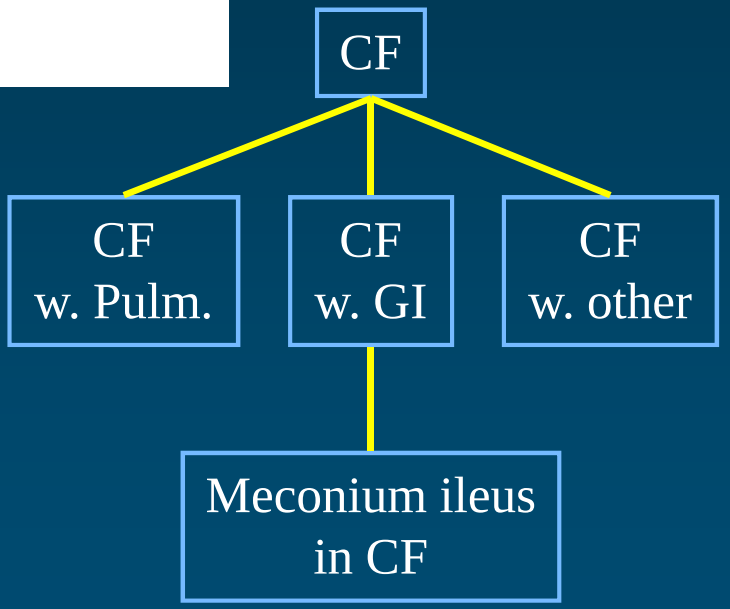
Excludes1: meconium ileus not due to Cystic fibrosis (P75)

E84.2 Cystic fibrosis with gastrointestinal manifestations

Excludes2:meconium ileus in cystic fibrosis (E84.1)

E84.8 Cystic fibrosis with other manifestations





Conclusions

Conclusions ☹

- Biomedical terms
  - reflect some aspects of biomedical reality
    - Although the primary concern of terminology is naming, not reflecting reality
  - often convey additional features (e.g., epistemology)
- Biomedical terminology tends to offset part of the complexity
  - but often reflects utility

Conclusions ☺

- Biomedical terminologies can help populate biomedical ontologies
- Resources needed
  - Linguistic analysis of terms
  - Statistical analysis of terms in a corpus / annotation database (dependence relations)
  - Manual curation

Agenda

Monday, June 9	Introduction to Biomedical Ontologies	Design Principles, Formalisms and Tools for Biomedical Ontologies	Biomedical Ontologies - Content and structure - Function
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Short course – Summer 2008
Biomedical Ontology in Practice

June 9, 2008 – Session #2

Design Principles, Formalisms and Tools for Biomedical Ontologies

Olivier Bodenreider

Lister Hill National Center
for Biomedical Communications
Bethesda, Maryland - USA

Overview

- Definitions
  - Ontologies vs. other artifacts
  - Kinds of ontologies
- Some principles of formal ontology
  - Top-level categories
  - Categories of relationships
- Formalisms and tools

Definitions

Introduction

Ogden-Richards

Definitions

- The *What* question
  - Objects in the world
    - With their properties
    - With their relations to other objects
  - Also: events, processes, and states
- Explicit specification of a conceptualization
  - Support software applications
- Domain ontology reflects
  - Underlying reality
  - Theory of the domain

Examples of use

- Natural language processing
- Access to heterogeneous sources of information (e.g., Semantic Web)
- Systems engineering

- Interoperability

Ontology vs. other artifacts

- Ontology
  - Defining types of things and their relations
- Terminology
  - Naming things in a domain
- Thesaurus
  - Organizing things for a given purpose
- Classification
  - Placing things into (arbitrary) classes
- Knowledge bases
  - Assertional knowledge

[Smith, KR-MED 2006]
[Chute, JAMIA 2000]

(Controlled) Terminology

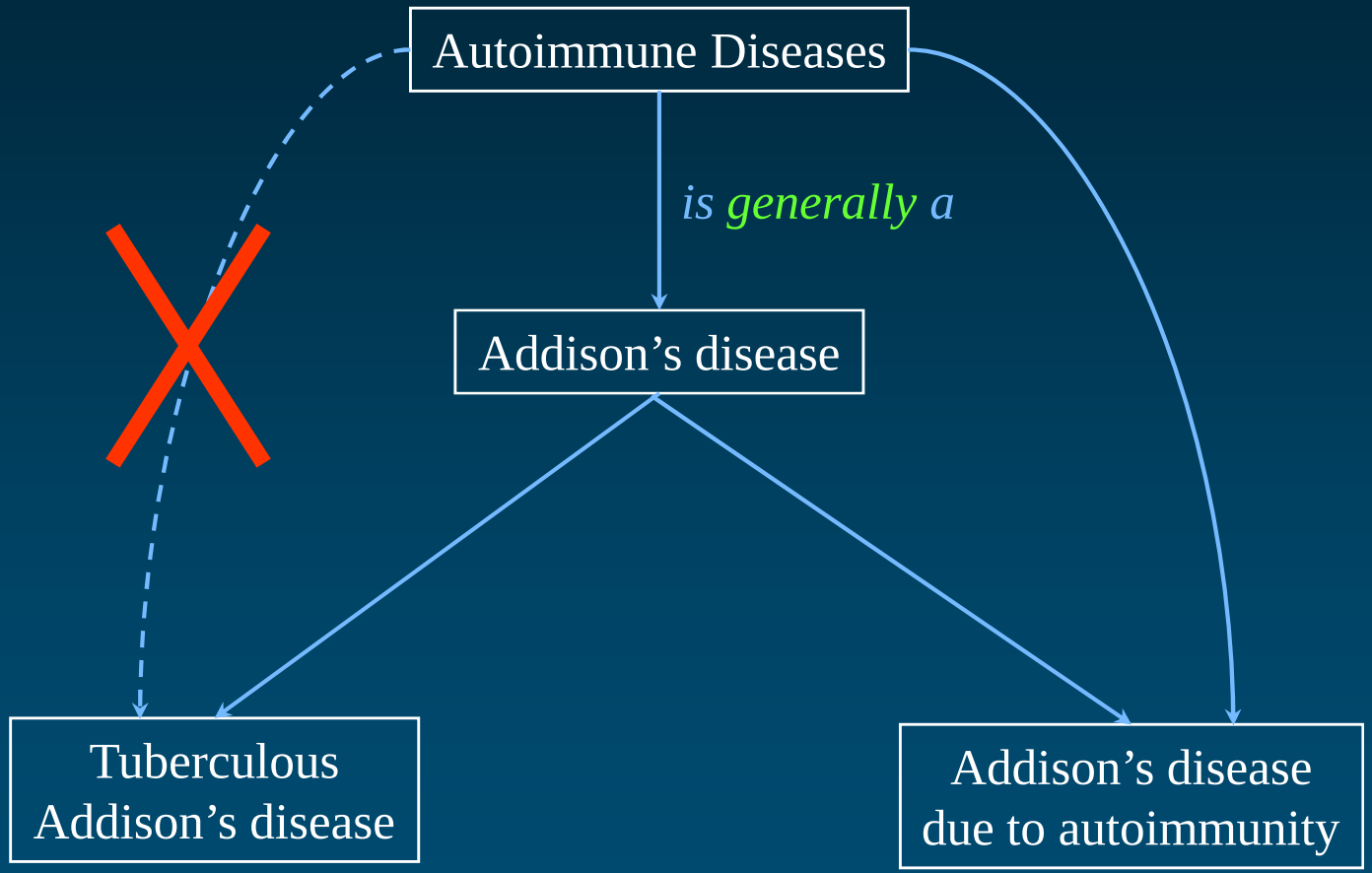
- Objective: naming things
- Example: Current Procedural Terminology (CPT)
- Shared understanding
  - Agreement on what terms to use
  - Utility-driven (arbitrary)

Telephone call by a physician to patient or for consultation or medical management or for coordinating medical management with other health care professionals (eg, nurses, therapists, social workers, nutritionists, physicians, pharmacists); complex or lengthy (eg, lengthy counseling session with anxious or distraught patient, detailed or prolonged discussion with family members regarding seriously ill patient, lengthy communication necessary to coordinate complex services of several different health professionals working on different

Thesaurus

- Objective: organize things for a purpose
  - e.g., information retrieval
    - Organization by relatedness
- Example: Medical Subject Headings (MeSH)
  - Indexing/retrieval of biomedical articles
- Relations used in hierarchies
  vs. hierarchical relations

Thesaurus vs. ontology



Classification

- Objective: placing things into classes
- Characteristics
  - Single inheritance (tree)
  - Idiosyncratic inclusion/exclusion criteria

E10 **Insulin-dependent diabetes mellitus**

[See before E10 for subdivisions]

Includes: diabetes (mellitus):
- brittle
- juvenile-onset
- ketosis-prone
- type I

Excludes: diabetes mellitus (in):
- malnutrition-related (E12.-)
- neonatal (P70.2)
- pregnancy, childbirth and the puerperium (O24.-)

glycosuria:
- NOS (R81)
- renal (E74.8)

impaired glucose tolerance (R73.0)

postsurgical hypoinsulinaemia (E89.1)

Classification

- Characteristics (continued)
  - Everything must be classified, including
    - When there is no specific slot (NEC)
    - When there is insufficient information (NOS)

E84	**Cystic fibrosis**
	Includes: mucoviscidosis
E84.0	**Cystic fibrosis with pulmonary manifestations**
E84.1	**Cystic fibrosis with intestinal manifestations**
	Meconium ileus+ (P75*)
	Excludes: meconium obstruction in cases where cystic fibrosis is known not to be present (P76.0)
E84.8	**Cystic fibrosis with other manifestations**
	Cystic fibrosis with combined manifestations
E84.9	**Cystic fibrosis, unspecified**

Knowledge Bases

- Objective: represent knowledge needed for a given application
- Example: drug knowledge bases
- Assertional knowledge
  - Vs. definitional knowledge in ontologies
  - Often probabilistic
- Examples of assertions
  - Indications of a drug
  - Signs and symptoms of a disease

Fuzzy borders

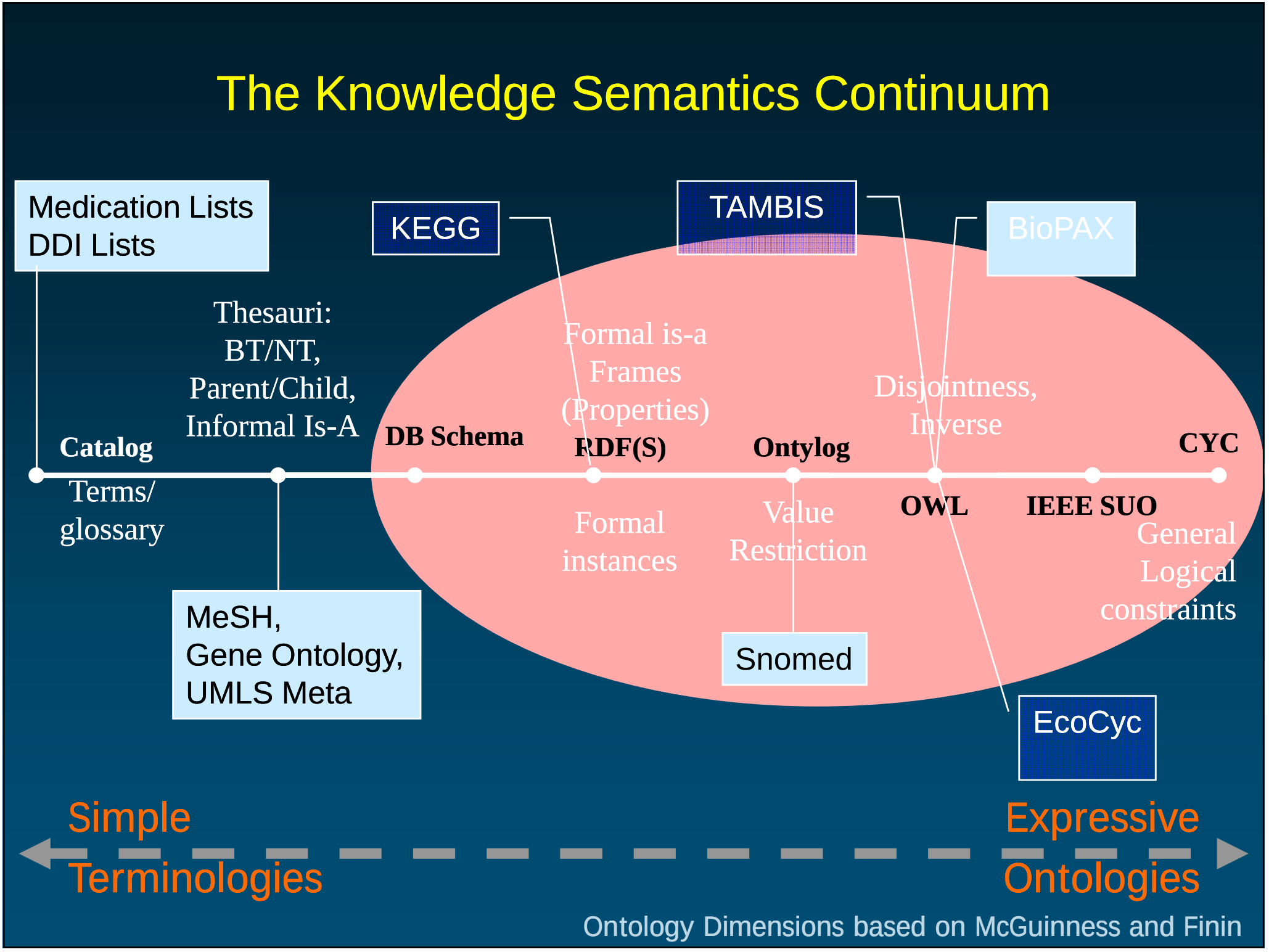
- Some ontologies also collect names
  - FMA
- Some terminologies also provide formal definitions
  - SNOMED CT
- Some terminologies/ontologies include both definitional and assertional knowledge
  - SNOMED CT

Types of resources

- Lexical resources
  - Collections of lexical items
  - Additional information
    - Part of speech
    - Spelling variants
  - Useful for entity recognition
  - UMLS SPECIALIST Lexicon, WordNet
- Ontological resources
  - Collections of
    - kinds of entities (substances, qualities, processes)
    - relations among them
  - Useful for relation extraction
  - UMLS Semantic Network, BioTop

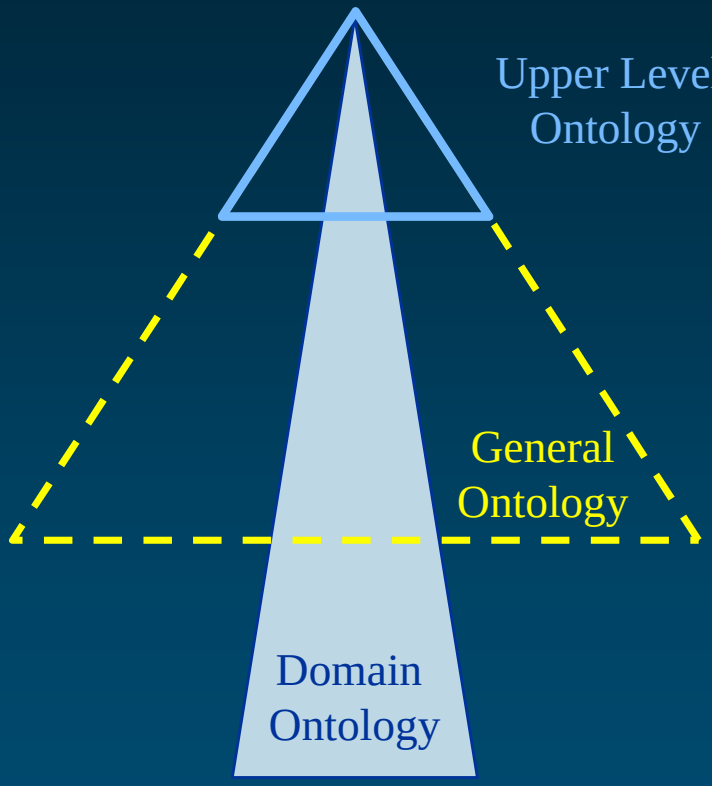
- Terminological resources
  - Collections lexical items + identifiers
    - Useful for entity resolution
      - UMLS Metathesaurus

The Knowledge Semantics Continuum



Ontology Dimensions based on McGuinness and Finin

Kinds of ontologies



Application ontologies

Ontology-related issues

- Creation
- Merging
- Alignment
- Validation

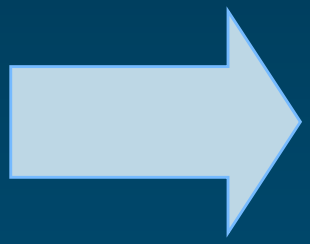
Formal Ontological Principles

Formal ontological distinctions

- Universal vs. individual
- Continuant vs. occurent
- Independent vs. dependent

Universal vs. Individual

- Universal = *category*
- Synonyms
  - Kind, Type, (Class)
- Examples
  - eyeball
  - blood pressure
  - conference



instantiation

- Individual = *instance*
- Synonyms
  - Particular, Token
- Examples
  - my right eyeball
  - my blood pressure (132/79)
  - AMIA Annual Symposium 2003

Continuant vs. Occurrent

- Continuant = *Continues to exist through time*
- Synonyms
  - Substance
- Examples
  - tennis racquet
  - mitochondrion
  - insulin production

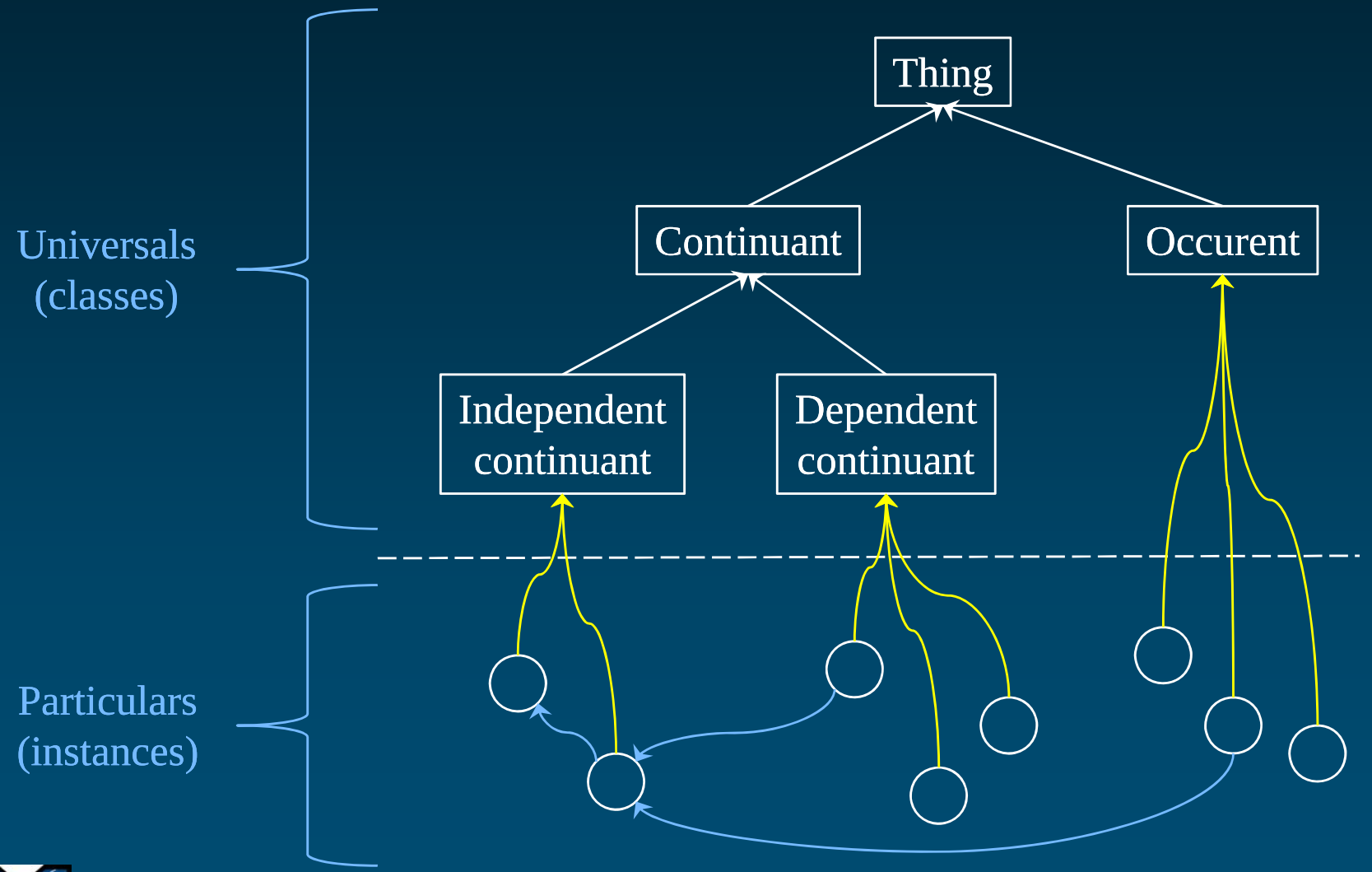
- Occurrent = *Unfolds through time*
- Synonyms
  - Process
- Examples
  - tennis tournament
  - metabolism
  - producing insulin

Independent vs. Dependent

- Independent = *Can exist without support from other entities*
- Examples
  - virus
  - molecule
  - plant

- Dependent = *Require support from other entities for its existence*
- Examples
  - viral infection
  - DNA binding
  - food

Formal ontology Upper level



Formal ontological distinctions

- Basic distinctions in many top-level ontologies
  - Generic: BFO, DOLCE
  - Biomedical: BioTop, UMLS Semantic Network
- Condition the relations between various types of entities
  - Relations
    - Between instances (e.g., *part_of* [at time])
    - Between classes (e.g., *isa*, *part_of* [atemporal])
    - Between one instance and one class (*instance_of*)

[Smith, Genome Biology 2005]

Formal ontology in practice

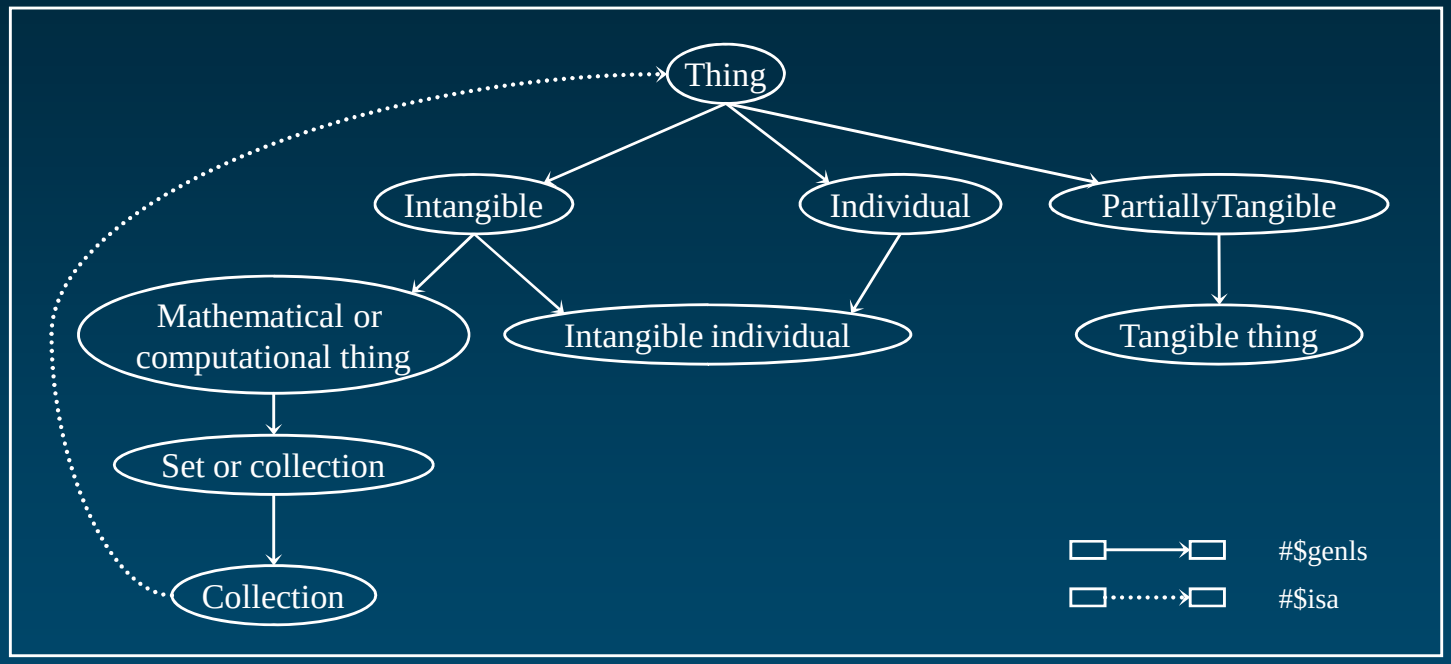
- Provides foundational classes and relations
  - Upper level ontologies
  - Relation ontology
- Provides a framework for analyzing entities and relations

Examples

General ontologies

- OpenCyc
  - General ontology
  - Cycorp, Inc (D. Lenat & al.)
  - Over 1M hand-coded assertions
  - http://www.opencyc.org
- WordNet
  - Electronic lexical database
  - Princeton University (G. Miller & al.)
  - Over 100,000 synsets
  - http://wordnet.princeton.edu/

Top level in OpenCyc



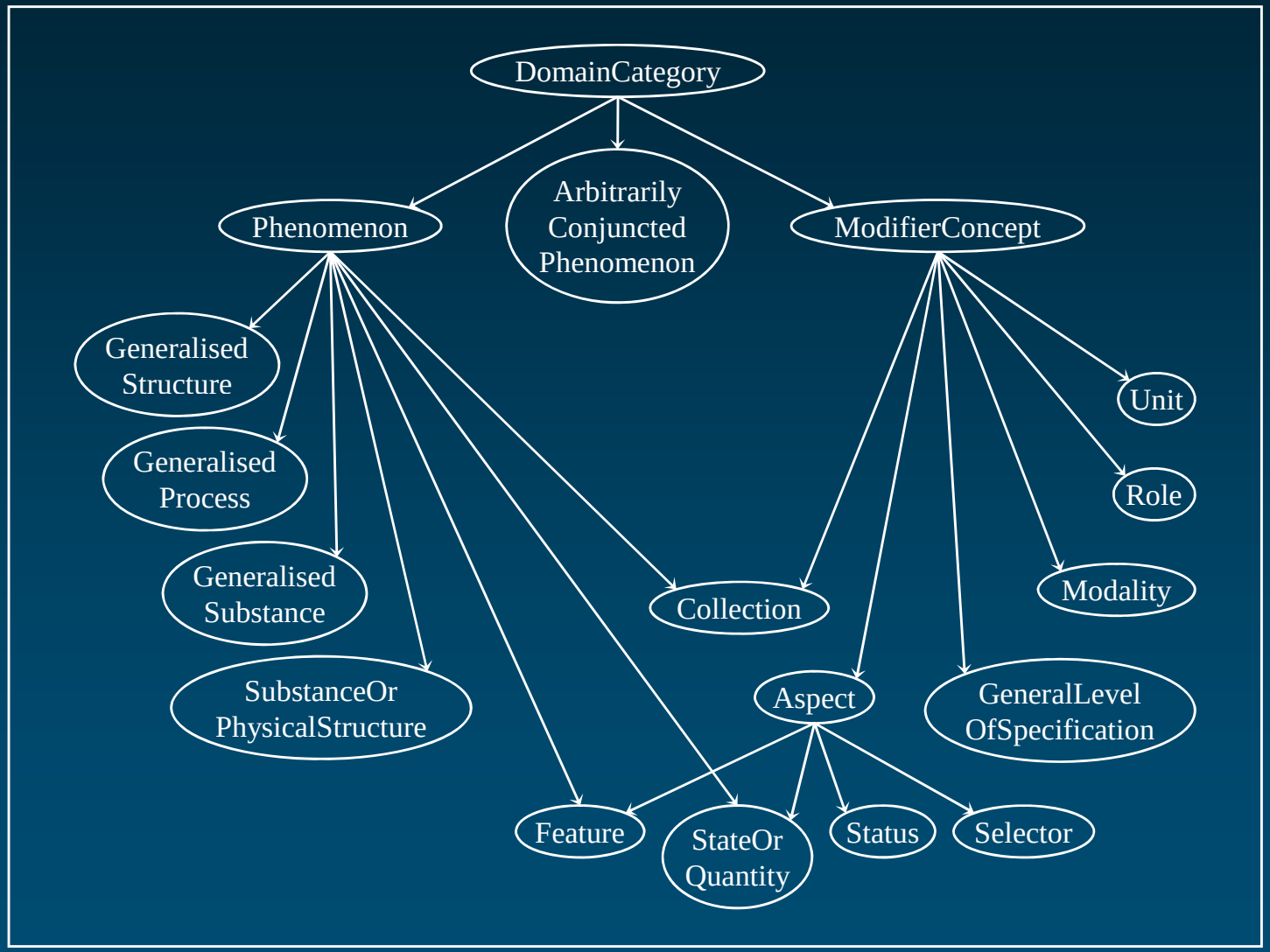
Top level in WordNet

Abstraction
Activity
Entity
Event
Group
Location
Natural phenomenon
Possession
Psychological feature
Shape
State

GALEN

- Generalised Architecture for Languages, Encyclopaedias, and Nomenclatures in Medicine
- European Union project (A. Rector & al.)
- Over 25,000 concepts (primitives)
- http://www.opengalen.org

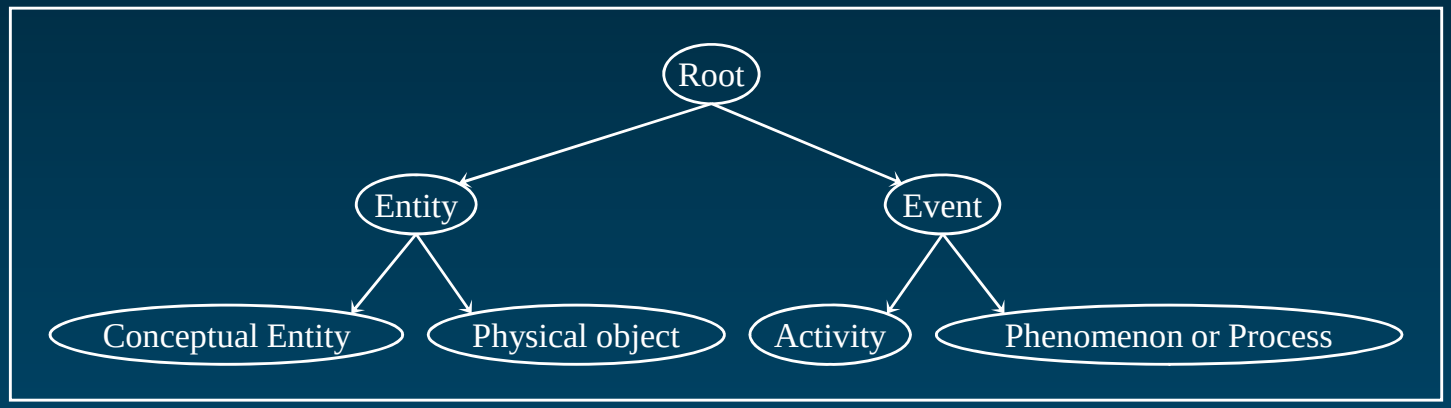
Top level in GALEN



UMLS Semantic Network

- Definitional knowledge in the biomedical domain
- NLM (A. McCray & al.)
- Content
  - 135 semantic types
  - 54 types of relationship
  - 6700 semantic relations
- http://semanticnetwork.nlm.nih.gov

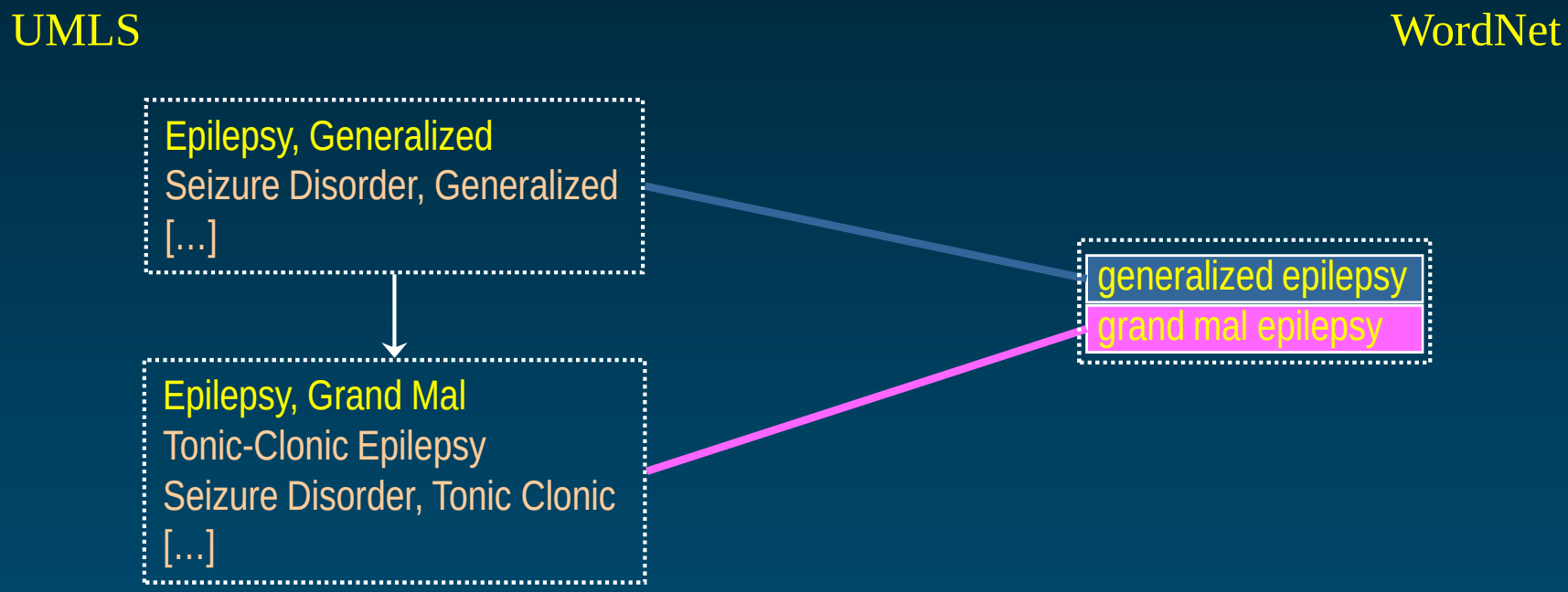
Top level in the Semantic Network



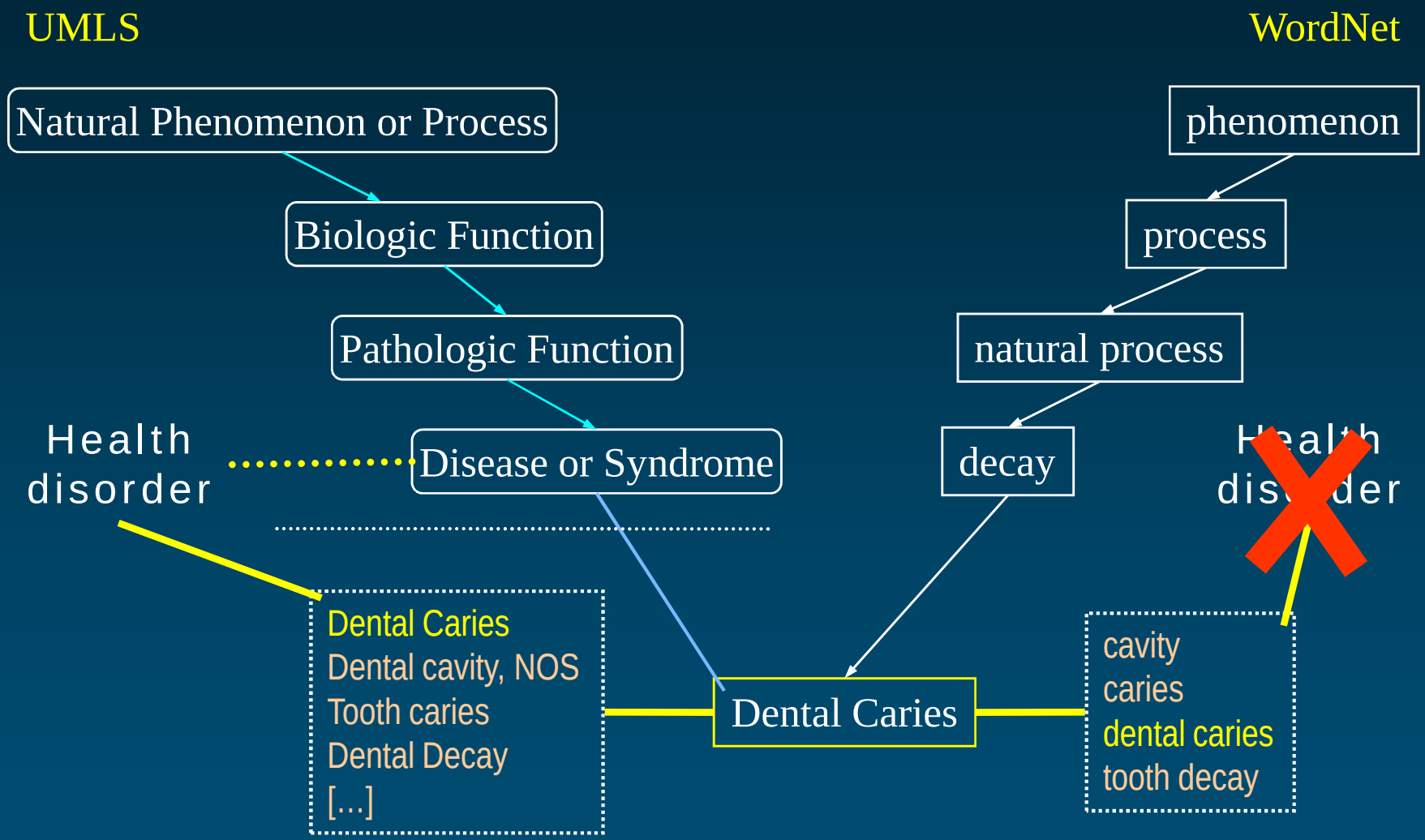
Differences between ontologies

Examples

Granularity, plesionymy



Differing categorization



Formalisms and Tools

Ontology and Formalism

- Frames
- Description logics
  - OWL DL
- First-order logic

- OBO Format
  - Conversion to OWL DL

Tools for ontology developers

- Protégé
  - Publicly available
  - Frames and DL
  - Classifier
  - Supports many file formats (import/export)
  - Large community of users
  - Well supported
  - http://protege.stanford.edu/

http://protege.stanford.edu/

- OBO-Edit
  - Specific to the biomedical/OBO community
  - Simpler than Protégé (“tool for biologists”)
  - http://oboedit.org/

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Short course – Summer 2008
Biomedical Ontology in Practice

June 9, 2008 – Session #3

"High-Impact" Biomedical Ontologies

A Structural Perspective

Olivier Bodenreider

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for Biomedical Communications
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Overview

- Structural perspective [J. Cimino, YBMI 2006]
  - What are they (vs. what are they for)?
- "High-impact" biomedical ontologies
  - International Classification of Diseases (ICD)
  - Logical Observation Identifiers, Names and Codes (LOINC)
  - SNOMED Clinical Terms
  - Foundational Model of Anatomy
  - Gene Ontology
  - RxNorm
  - Medical Subject Headings (MeSH)
  - NCI Thesaurus
  - Unified Medical Language System (UMLS)

International Classification of Diseases

ICD Characteristics (1)

- Current version: ICD-10
- Type: Classification
- Domain: Disorders
- Developer: World Health Organization (WHO)
- Funding: WHO
- Availability
  - Publicly available: No
  - Repositories: UMLS [ICD9-CM in NCBO BioPortal]
- URL: http://www.who.int/classifications/icd/en/

ICD Characteristics (2)

- Number of
  - Concepts: 12,318
  - Terms: 1 per concept (tabular)
- Major organizing principles:
  - Tree (single inheritance hierarchy)
  - No explicit classification criteria
    - Idiosyncratic inclusion/exclusion mechanism
  - .8 slots for Not elsewhere classified (NEC)
  - .9 slots for Not otherwise specified (NOS)
- Formalism: Proprietary format

ICD Top level

Chapter	Blocks	Title
I	A00-B99	Certain infectious and parasitic diseases
II	C00-D48	Neoplasms
III	D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
IV	E00-E90	Endocrine, nutritional and metabolic diseases
V	F00-F99	Mental and behavioural disorders
VI	G00-G99	Diseases of the nervous system
VII	H00-H59	Diseases of the eye and adnexa
VIII	H60-H95	Diseases of the ear and mastoid process
IX	I00-I99	Diseases of the circulatory system
X	J00-J99	Diseases of the respiratory system
XI	K00-K93	Diseases of the digestive system
XII	L00-L99	Diseases of the skin and subcutaneous tissue
XIII	M00-M99	Diseases of the musculoskeletal system and connective tissue
XIV	N00-N99	Diseases of the genitourinary system
XV	O00-O99	Pregnancy, childbirth and the puerperium
XVI	P00-P96	Certain conditions originating in the perinatal period
XVII	Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities
XVIII	R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
XIX	S00-T98	Injury, poisoning and certain other consequences of external causes
XX	V01-Y98	External causes of morbidity and mortality
XXI	Z00-Z99	Factors influencing health status and contact with health services
XXII	U00-U99	Codes for special purposes

ICD Example

- Idiosyncratic inclusion/exclusion criteria

E10 **Insulin-dependent diabetes mellitus**

[See before E10 for subdivisions]

Includes: diabetes (mellitus):
- brittle
- juvenile-onset
- ketosis-prone
- type I

Excludes: diabetes mellitus (in):
- malnutrition-related (E12.-)
- neonatal (P70.2)
- pregnancy, childbirth and the puerperium (O24.-)

glycosuria:
- NOS (R81)
- renal (E74.8)

impaired glucose tolerance (R73.0)

postsurgical hypoinsulinaemia (E89.1)

ICD Example

- Not elsewhere classified (NEC)
- Not otherwise specified (NOS)

E84	**Cystic fibrosis**
	Includes: mucoviscidosis
E84.0	**Cystic fibrosis with pulmonary manifestations**
E84.1	**Cystic fibrosis with intestinal manifestations**
	Meconium ileus+ (P75*)
	Excludes: meconium obstruction in cases where cystic fibrosis is known not to be present (P76.0)
E84.8	**Cystic fibrosis with other manifestations**
	Cystic fibrosis with combined manifestations
E84.9	**Cystic fibrosis, unspecified**

Logical Observation Identifiers, Names and Codes (LOINC)

LOINC Characteristics (1)

- Current version: 2.22 (Dec. 2007)
- Type: Controlled terminology*
- Domain: Laboratory and clinical observations
- Developer: Regenstrief Institute
- Funding: NLM
- Availability
  - Publicly available: Yes
  - Repositories: UMLS
- URL: www.regenstrief.org/loinc/loinc.htm

LOINC Characteristics (2)

- Number of
  - Concepts: 50k active codes (2.18)
  - Terms: n/a*
- Major organizing principles:
  - No hierarchical structure among the main codes
  - 6 axes
    - Component (analyte [+ challenge] [+ adjustments])
    - Property
    - Timing
    - System
    - Scale
    - [Method]
- Formalism: “DL-like”

LOINC Example

- *Sodium:SCnc:-Pt:Ser/Plas:Qn*
  [the molar concentration of sodium is measured in the plasma (or serum), with quantitative result]

Axis	Value
Component	Sodium
Property	SCnc – Substance Concen-tration (per volume)
Timing	Pt – Point in time (Random)
System	Ser/Plas – Serum or Plasma
Scale	Qn – Quantitative
Method	--

SNOMED Clinical Terms

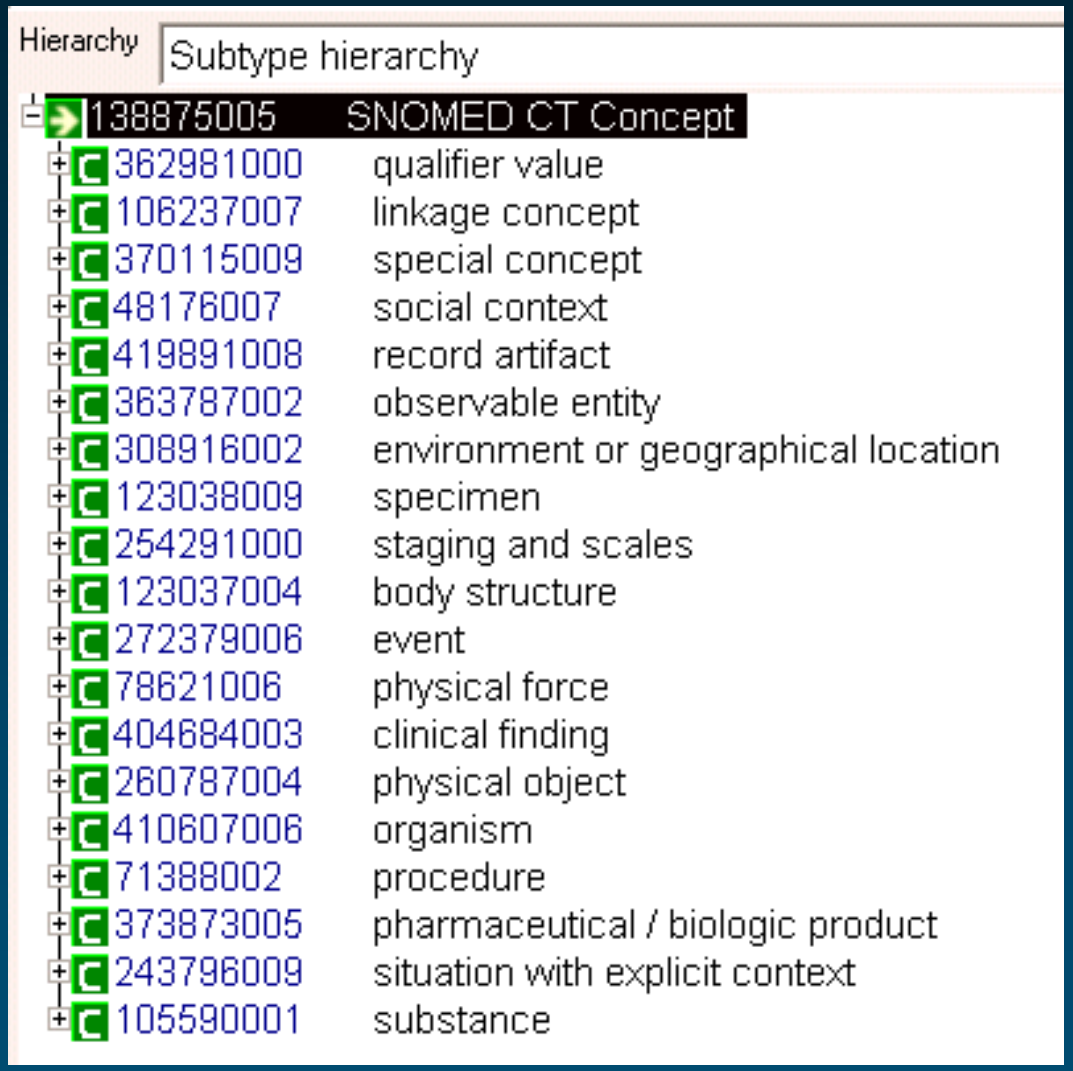
SNOMED CT Characteristics (1)

- Current version: January 31, 2008 (2 annual releases)
- Type: Reference terminology / ontology
- Domain: Clinical medicine
- Developer: IHTSDO
- Funding: IHTSDO
- Availability
  - Publicly available: Yes* (in member countries)
  - Repositories: UMLS
- URL: http://www.ihtsdo.org/

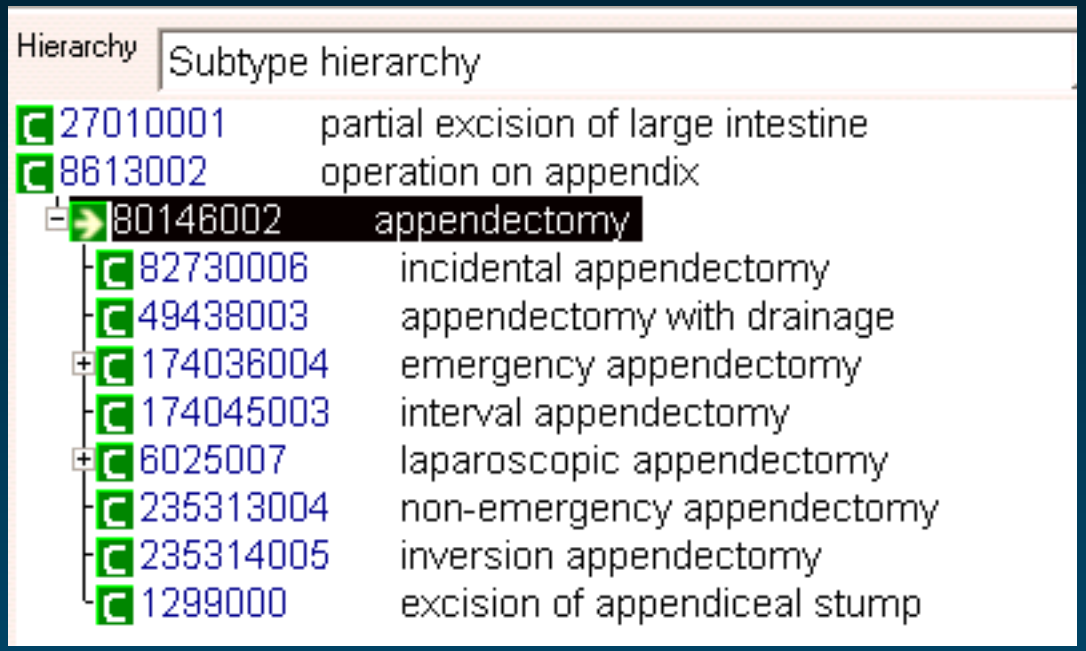
SNOMED CT Characteristics (2)

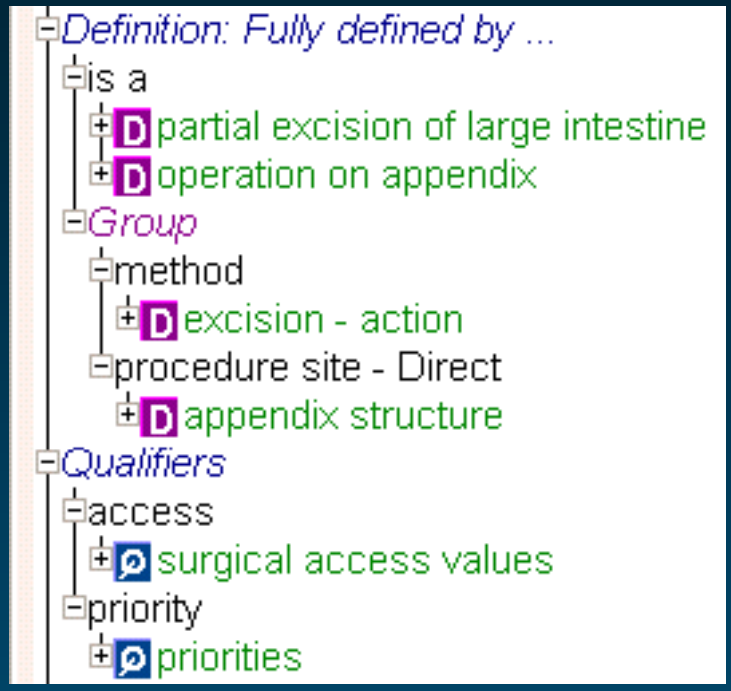
- Number of
  - Concepts: 311,313 active concepts (Jan. 31, 2008)
  - Terms: 794,061 active “descriptions”
- Major organizing principles:
  - Utility for clinical medicine (e.g., assertional + definitional knowledge)
  - Model of meaning (incomplete)
  - Rich set of associative relationships
  - Small proportion of defined concepts (many primitives)
- Formalism: Description logics (KRSS)

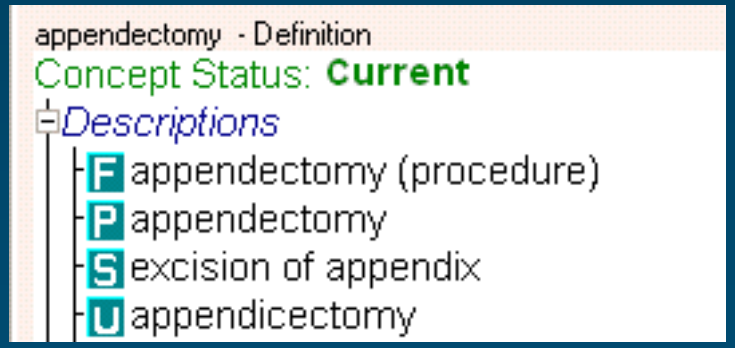
SNOMED CT Top level



SNOMED CT Example







Foundational Model of Anatomy

FMA Characteristics (1)

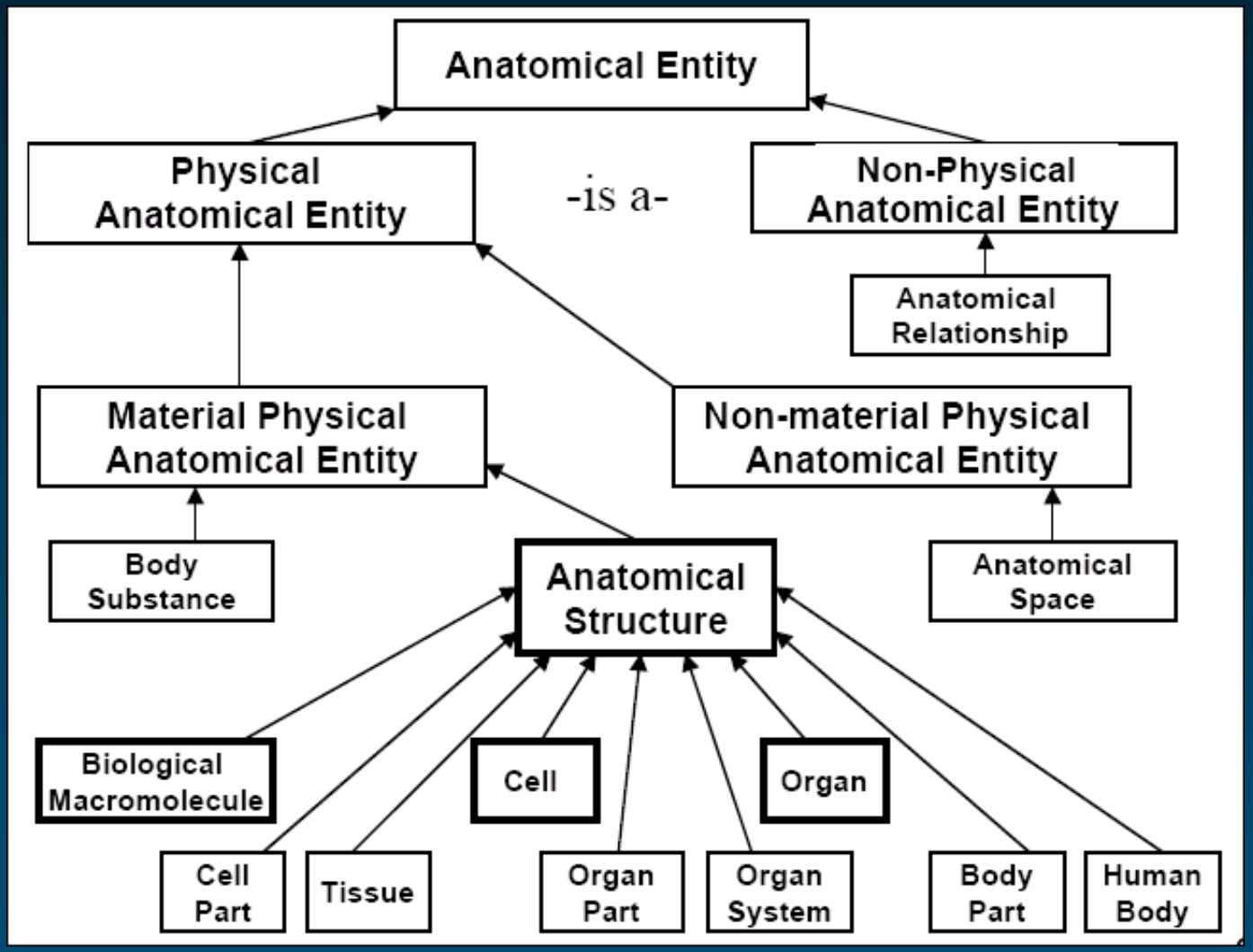
- Current version: ? (no fixed release schedule)
- Type: Ontology
- Domain: Anatomy (anatomical structures)
- Developer: U. Washington, Department of Biological Structure
- Funding: NLM (grants and contract) and others
- Availability
  - Publicly available: Yes
  - Repositories: [UMLS] / OBO / NCBO BioPortal
- URL: http://fma.biostr.washington.edu/

FMA Characteristics (2)

- Number of
  - Concepts: ~72k
  - Terms: ~1.5 / concept
- Major organizing principles:
  - Explicit classificatory criteria
  - Distinct *isa* and *part_of* hierarchies
  - Additional spatial relations (e.g., adjacency)
  - Multiple levels of granularity (organism to sub-cellular)
- Formalism: Frames (Protégé)
  - Conversion to OWL Full and OWL DL available

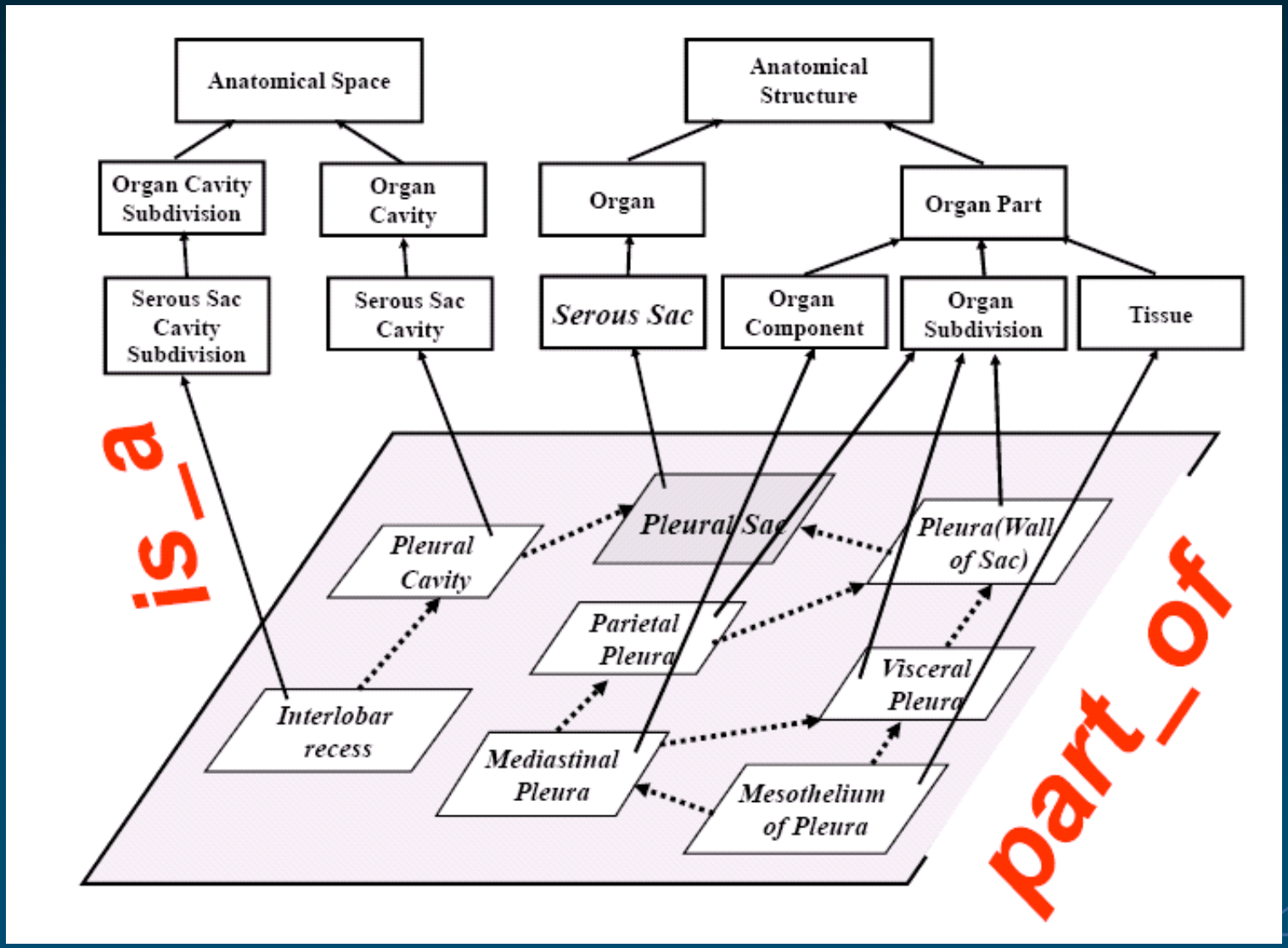
FMA Top level

(Courtesy of C. Rosse)

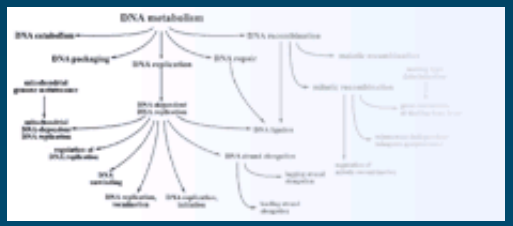


FMA Example

(Courtesy of C. Rosse)



Gene Ontology



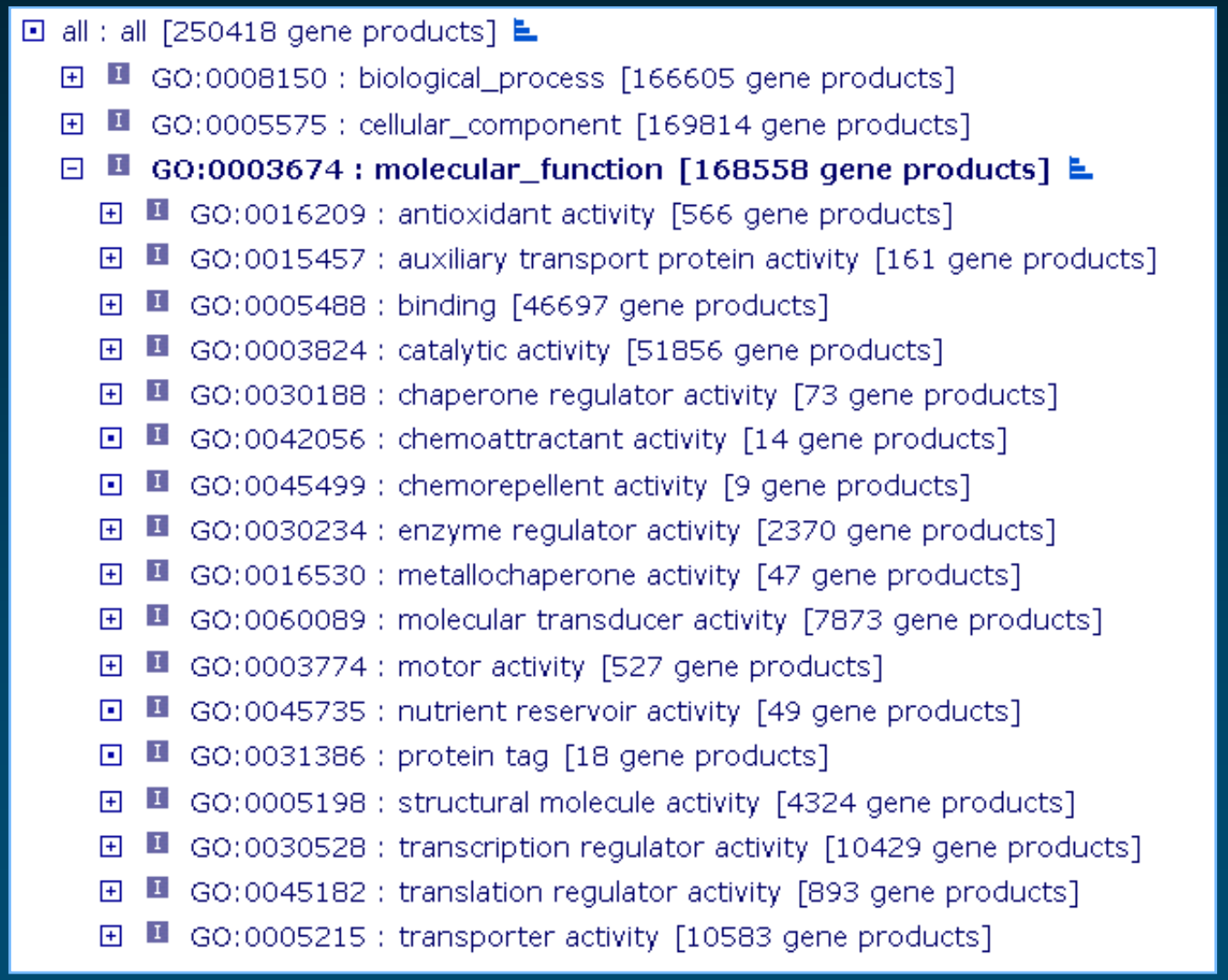
Gene Ontology Characteristics (1)

- Current version: n/a (daily/monthly releases)
- Type: Controlled vocabulary
- Domain: Molecular biology
- Developer: GO Consortium
- Funding: NIH (grants)
- Availability
  - Publicly available: Yes
  - Repositories: UMLS / OBO / NCBO BioPortal
- URL: http://www.geneontology.org/

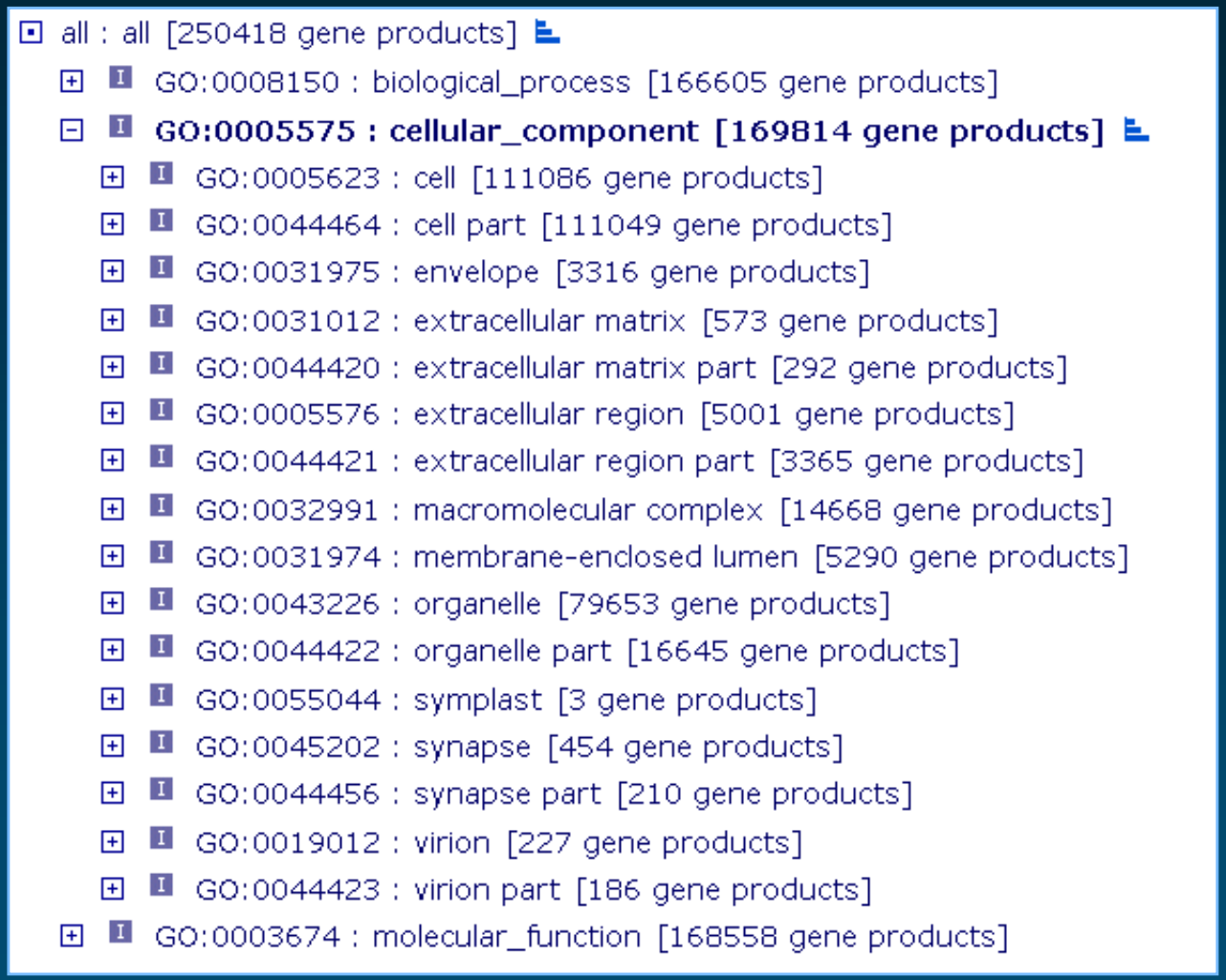
Gene Ontology Characteristics (2)

- Number of
  - Concepts: 22,546 (Jan. 2, 2007)
  - Terms: 2.15 per concept
- Major organizing principles:
  - 3 major hierarchies
    - Molecular function
    - Cellular component
    - Biological process
  - Relations (within hierarchies): *isa*, *part_of*, *regulates*
  - No relations between concepts across hierarchies
- Formalism: OBO format

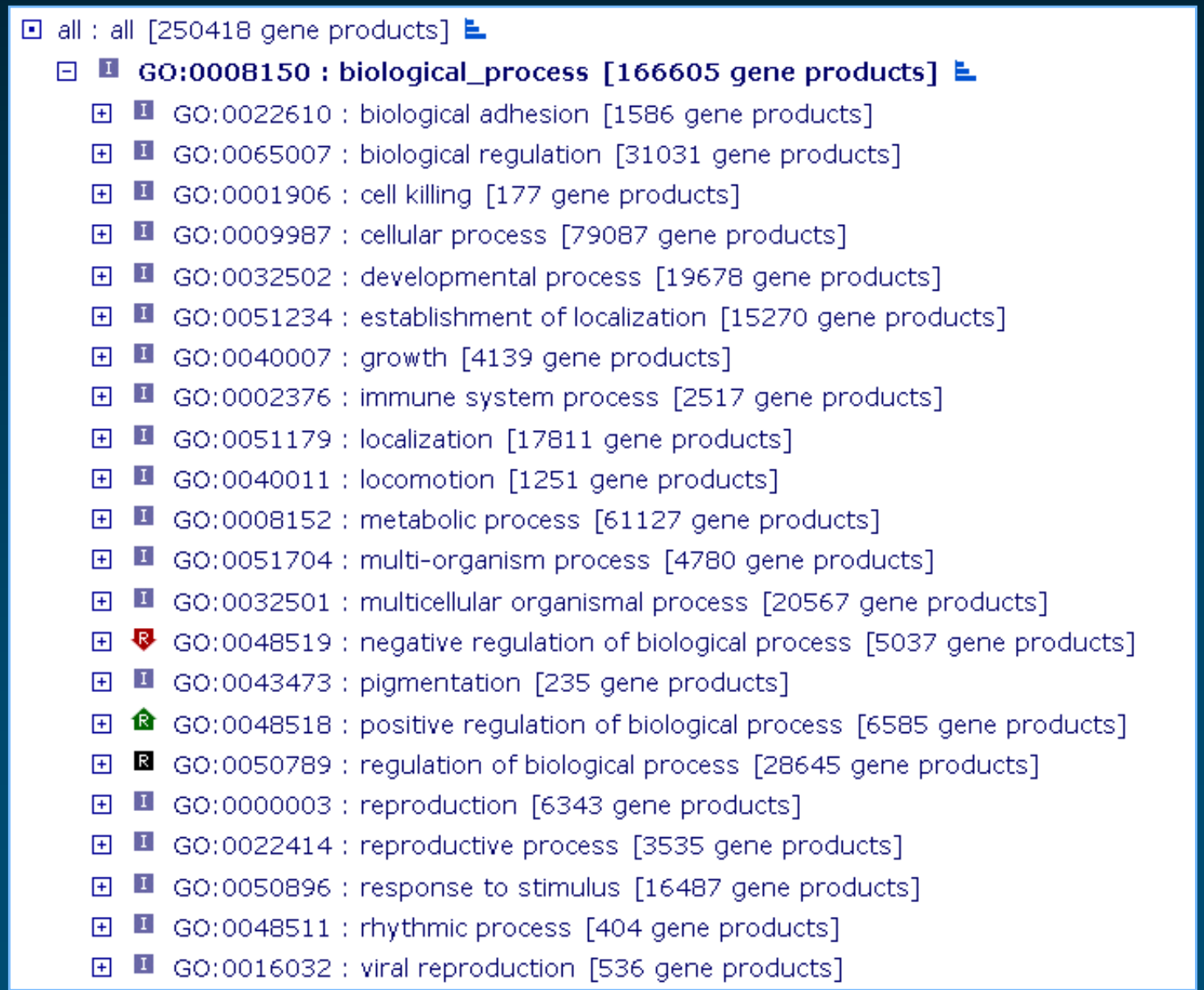
Gene Ontology Top level (MF)



Gene Ontology Top level (CC)

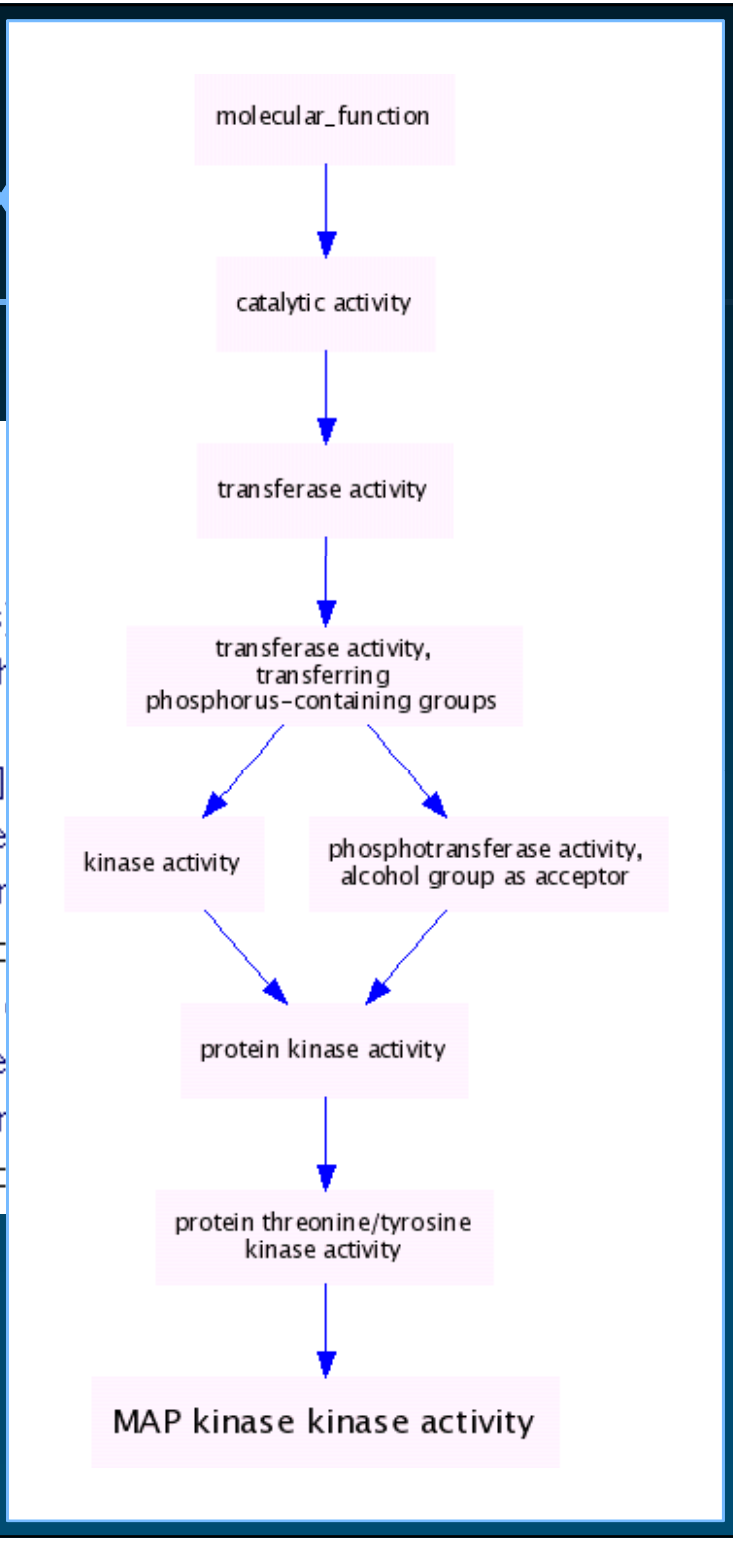


Gene Ontology Top level (BP)



Gene Ontology Ex

- all : all [250418 gene products]
  - GO:0003674 : molecular_function [168558 gene products]
    - GO:0003824 : catalytic activity [51856 gene products]
      - GO:0016740 : transferase activity [15763 gene products
        - GO:0016772 : transferase activity, transferring phosph
          products]
          - GO:0016301 : kinase activity [6093 gene products]
            - GO:0004672 : protein kinase activity [3504 gene
              - GO:0004712 : protein serine/threonine/tyrosir
                - **GO:0004708 : MAP kinase kinase activit**
          - GO:0016773 : phosphotransferase activity, alcohol
            - GO:0004672 : protein kinase activity [3504 gene
              - GO:0004712 : protein serine/threonine/tyrosir
                - **GO:0004708 : MAP kinase kinase activit**



NLM

RxNorm

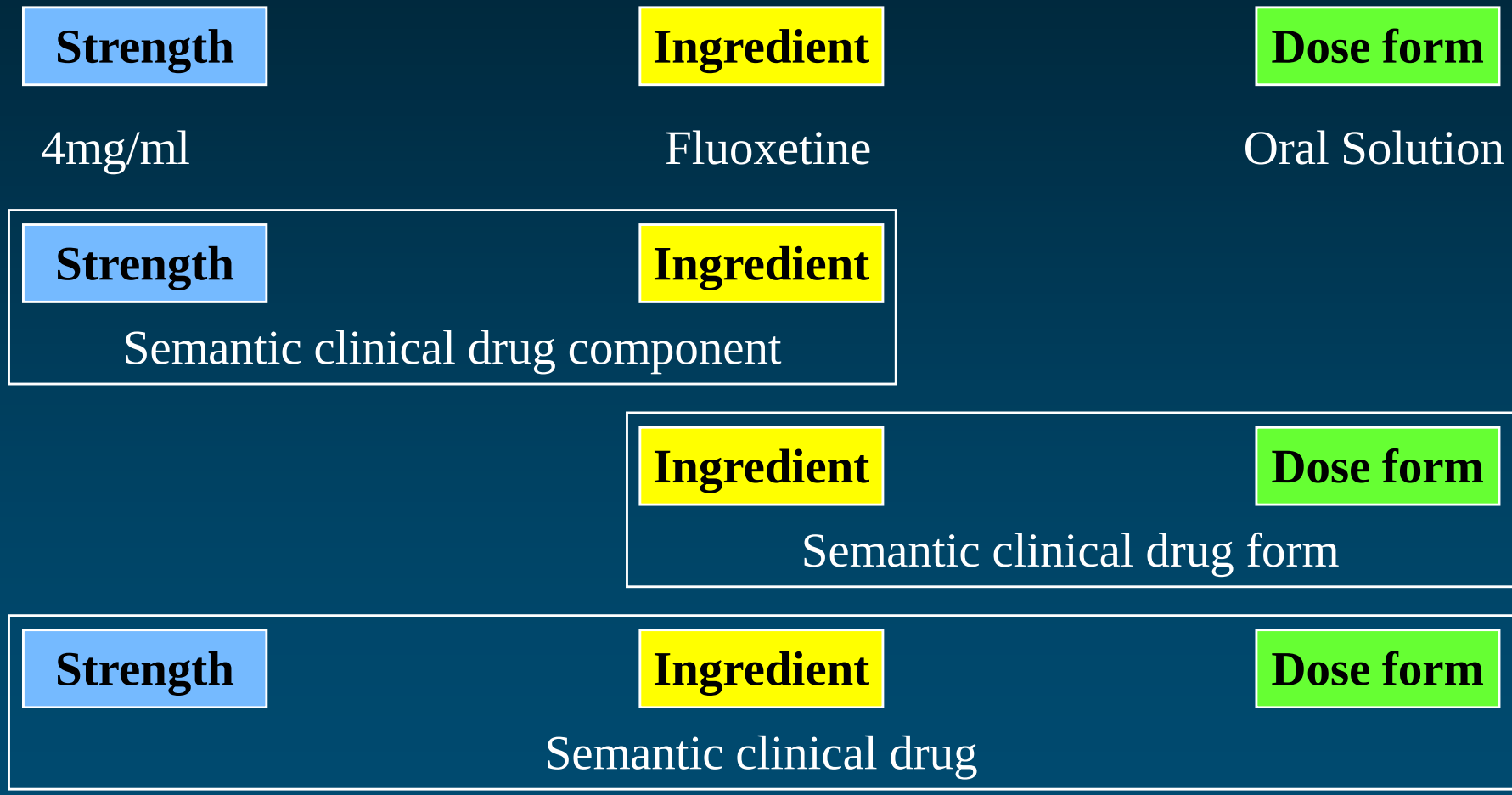
RxNorm Characteristics (1)

- Current version: June 2, 2007 (monthly releases)
- Type: Controlled terminology
- Domain: Drug names
- Developer: NLM
- Funding: NLM
- Availability
  - Publicly available: Yes*
  - Repositories: UMLS
- URL: http://www.nlm.nih.gov/research/umls/rxnorm/

RxNorm Characteristics (2)

- Number of
  - Concepts: 93k
  - Terms: 105k
- Major organizing principles:
  - Generic vs. brand
  - Combinations of Ingredient / Form / Dose
  - No hierarchical structure
  - Links to all major US drug information sources
  - No clinical information
- Formalism: UMLS RRF format

RxNorm Normalized form

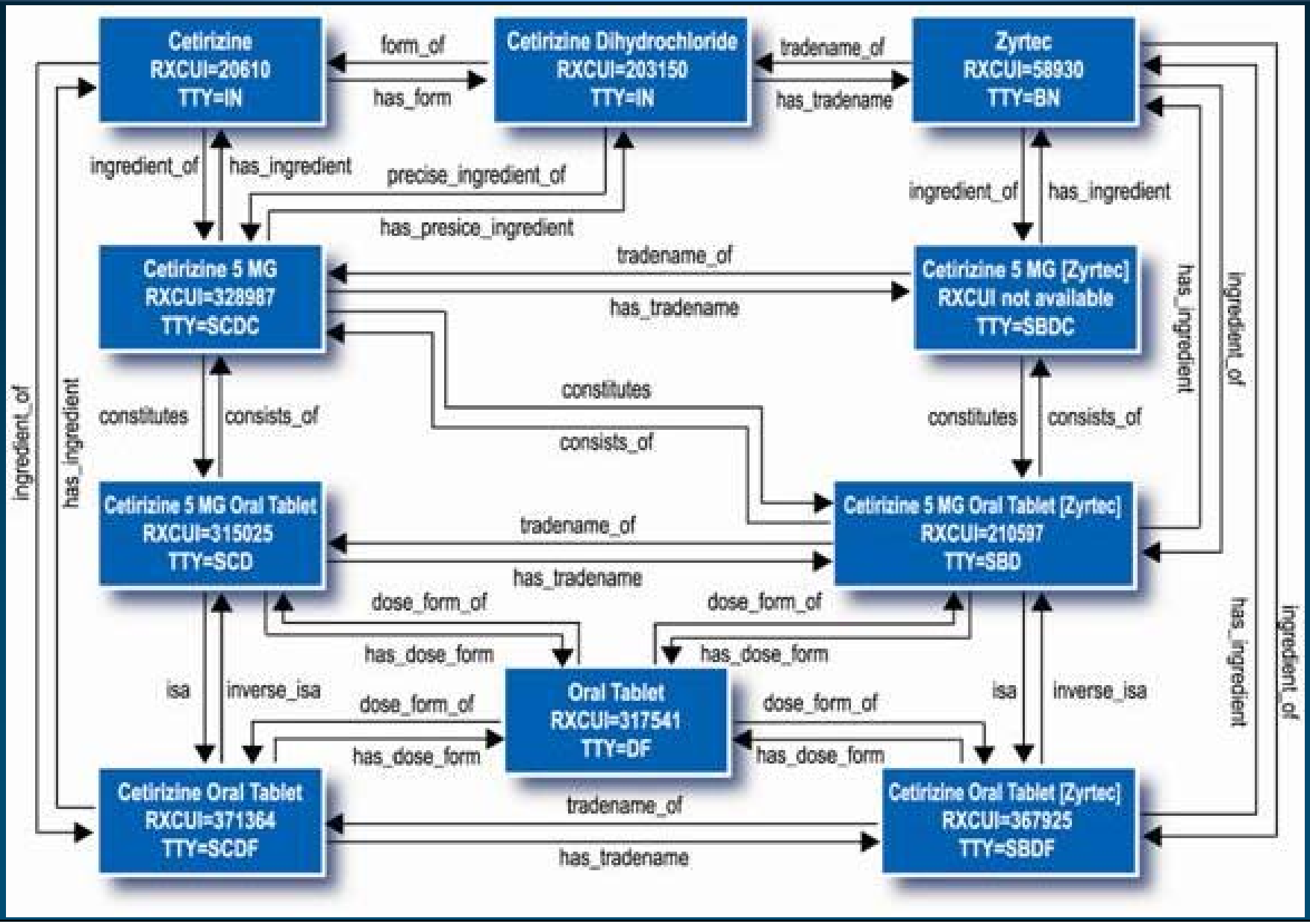


Rx Norm Generic *vs.* Brand

- Generic
  - Ingredient (IN)
  - Clinical drug form (SCDF)
  - Clinical drug component (SCDC)
  - Clinical drug (SCD)
- Brand
  - Brand name (BN)
  - Branded drug form (SBDF)
  - Branded drug component (SBDC)
  - Branded drug (SBD)

tradename_of

RxNorm Relations among drug entities



Medical Subject Headings (MeSH)

MeSH Characteristics (1)

- Current version: 2008 (yearly releases)
- Type: Thesaurus / Controlled vocabulary
- Domain: Biomedicine
- Developer: NLM
- Funding: NLM (Library Operations)
- Availability
  - Publicly available: Yes
  - Repositories: UMLS / NCBO BioPortal
- URL: http://www.nlm.nih.gov/mesh/

MeSH Characteristics (2)

- Number of
  - Concepts: 24,767 descriptors (2007)
  - Terms: 7.5 per descriptor
- Major organizing principles:
  - Descriptor + entry terms
    (also: Qualifiers, Supplementary concepts)
  - Thesaurus relations (RB/RN/RO)
- Formalism: Thesaurus / Proprietary XML DTD

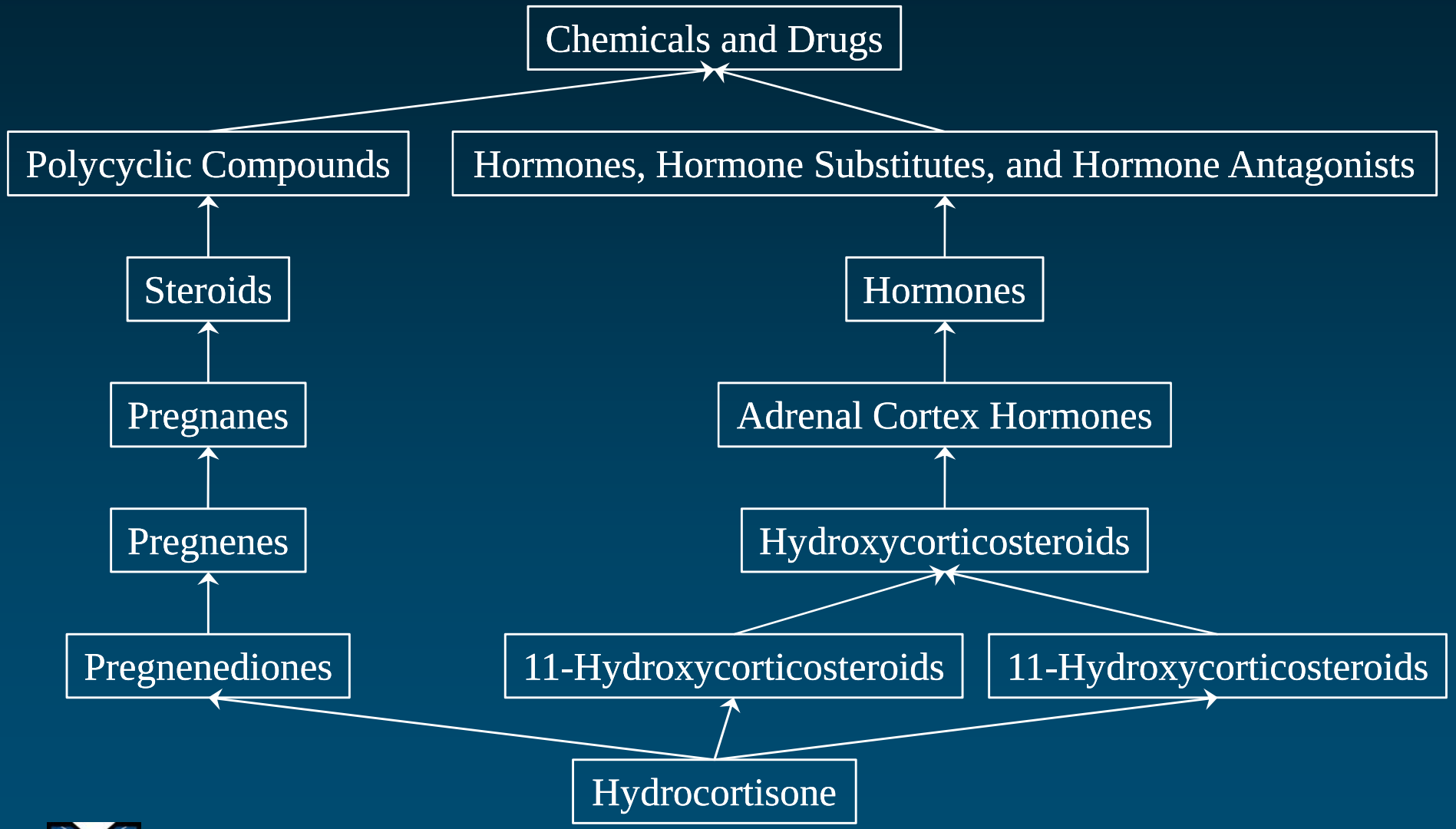
MeSH Top level

1. Anatomy [A]
2. Organisms [B]
3. Diseases [C]
4. Chemicals and Drugs [D]
5. Analytical, Diagnostic and Therapeutic Techniques and Equipment [E]
6. Psychiatry and Psychology [F]
7. Biological Sciences [G]
8. Natural Sciences [H]
9. Anthropology, Education, Sociology and Social Phenomena [I]
10. Technology, Industry, Agriculture [J]
11. Humanities [K]
12. Information Science [L]
13. Named Groups [M]
14. Health Care [N]
15. Publication Characteristics [V]
16. Geographicals [Z]

MeSH Example (terms)

MeSH Heading	Hydrocortisone
Tree Number	D04.808.745.745.654.600
Tree Number	D06.472.040.585.353.476
Tree Number	D06.472.040.585.478.392
Scope Note	The main glucocorticoid secreted by the ADRENAL CORTEX. Its synthetic counterpart is used, either as an injection or topically, in the treatment of inflammation, allergy, collagen diseases, asthma, adrenocortical deficiency, shock, and some neoplastic conditions.
Entry Term	11-Epicortisol
Entry Term	Cortifair
Entry Term	Cortisol
Entry Term	Cortril
Entry Term	Epicortisol
Entry Term	Hydrocortisone, (11 alpha)-Isomer
Entry Term	Hydrocortisone, (9 beta,10 alpha,11 alpha)-Isomer

MeSH Example (hierarchies)



NCI Thesaurus

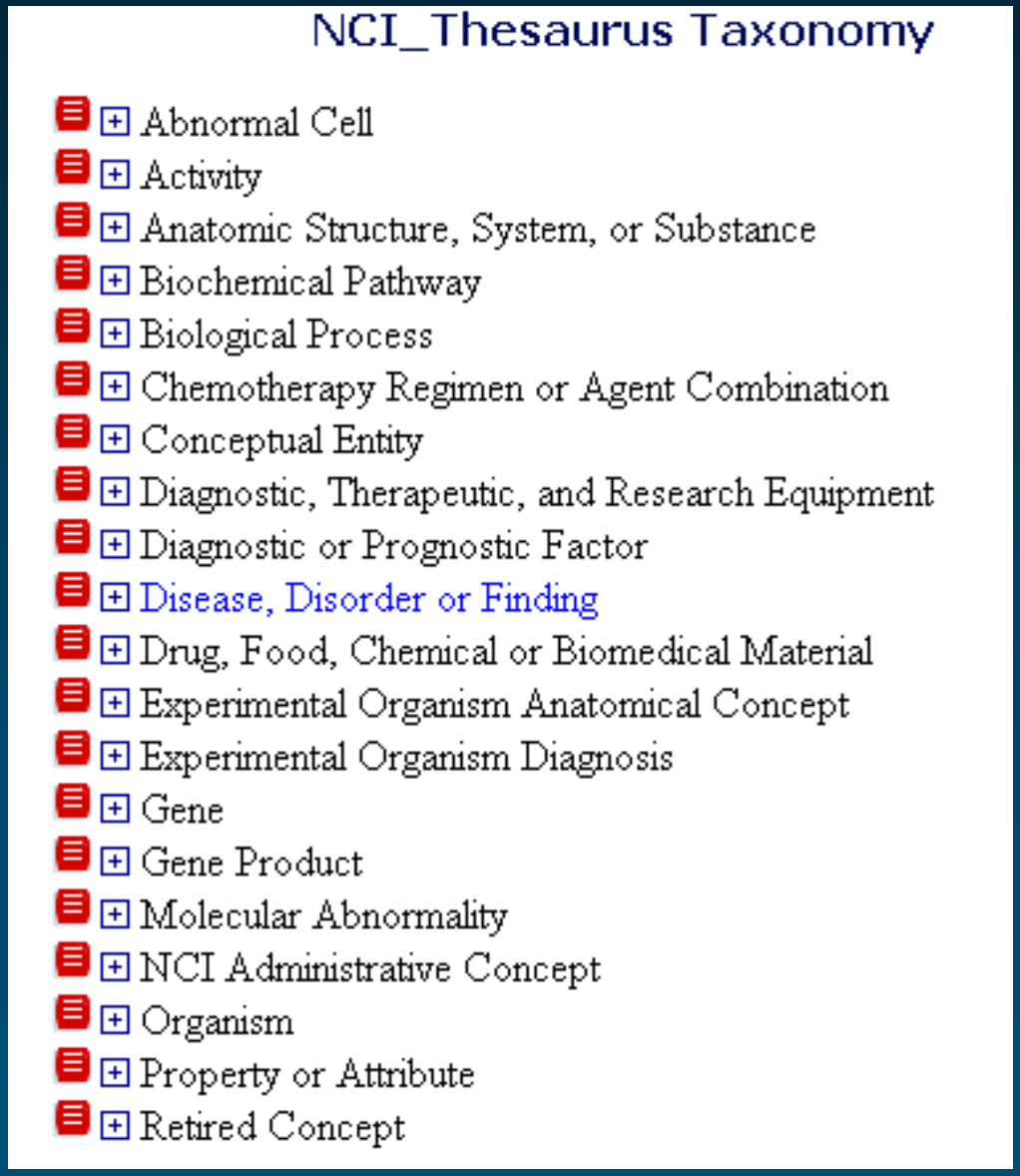
NCI thesaurus Characteristics (1)

- Current version: 08.04d (~monthly releases)
- Type: Controlled terminology / ontology
- Domain: Cancer
- Developer: NCI Center for Bioinformatics
- Funding: NCI
- Availability
  - Publicly available: Yes
  - Repositories: UMLS / OBO / NCBO BioPortal
- URL: http://nciterms.nci.nih.gov/

NCI thesaurus Characteristics (2)

- Number of
  - Concepts: 58,868 (2007_05E)
  - Terms: 2.68 per concept
- Major organizing principles:
  - Subsumption hierarchy
  - Rich set of associative relationships
  - Small proportion of defined concepts (many primitives)
  - Links to many external resources
- Formalism: OWL Lite

NCI thesaurus Top level



NCI thesaurus Example

Concept Details

URI: http://nciterms.nci.nih.gov:80/NCIBrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&code=C2919
Version: June 2007 (07.06d)

Prostate Adenocarcinoma

Identifiers:

name	Prostate_Adenocarcinoma
code	C2919

Relationships to other concepts:

Disease_Has_Finding	Invasive Lesion
Disease_Has_Abnormal_Cell	Adenocarcinoma Cell
Disease_Has_Normal_Tissue_Origin	Prostatic Epithelium
Disease_May_Have_Finding	Serum Prostate Specific Antigen Increased
Disease_Has_Finding	Carcinomatous Component Present
Disease_Excludes_Abnormal_Cell	Neoplastic Smooth Muscle Cell
Disease_Excludes_Abnormal_Cell	Malignant Squamous Cell
Disease_Has_Primary_Anatomic_Site	Prostate Gland
Disease_Has_Associated_Anatomic_Site	Male Reproductive System
Disease_Excludes_Abnormal_Cell	Malignant Stromal Cell
Disease_Has_Associated_Anatomic_Site	Prostate Gland
Disease_Has_Normal_Cell_Origin	Epithelial Cell

Superconcepts:

- Adenocarcinoma
- Common Carcinoma
- Invasive Prostate Carcinoma

Subconcepts:

- Acinar Prostate Adenocarcinoma
- Metastatic Prostatic Adenocarcinoma
- Moderately Differentiated Prostate Adenocarcinoma
- Poorly Differentiated Prostate Adenocarcinoma
- Prostate Adenocarcinoma with Focal Neuroendocrine Differentiation
- Prostate Ductal Adenocarcinoma
- Stage III Prostate Adenocarcinoma
- Stage II Prostate Adenocarcinoma
- Stage I Prostate Adenocarcinoma
- Well Differentiated Prostate Adenocarcinoma

Information about this concept:

DEFINITION	
	Synonym with source data
	Synonym with source data
	Synonym with source data
	Preferred_Name
	Semantic_Type
	Synonym
	Synonym
	Synonym
	Unified Medical Language System Concept Identifier

Unified Medical Language System (UMLS)

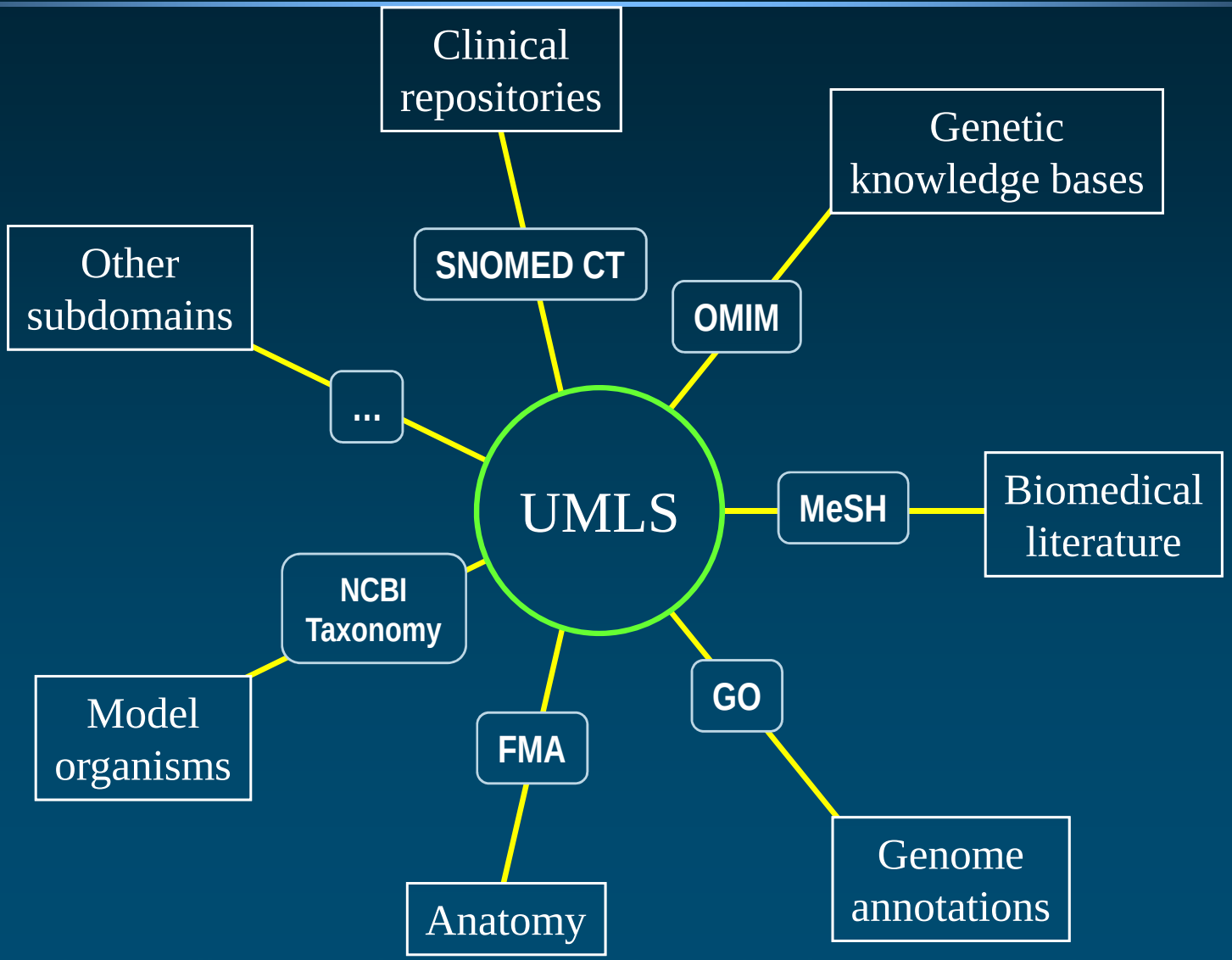
UMLS Characteristics (1)

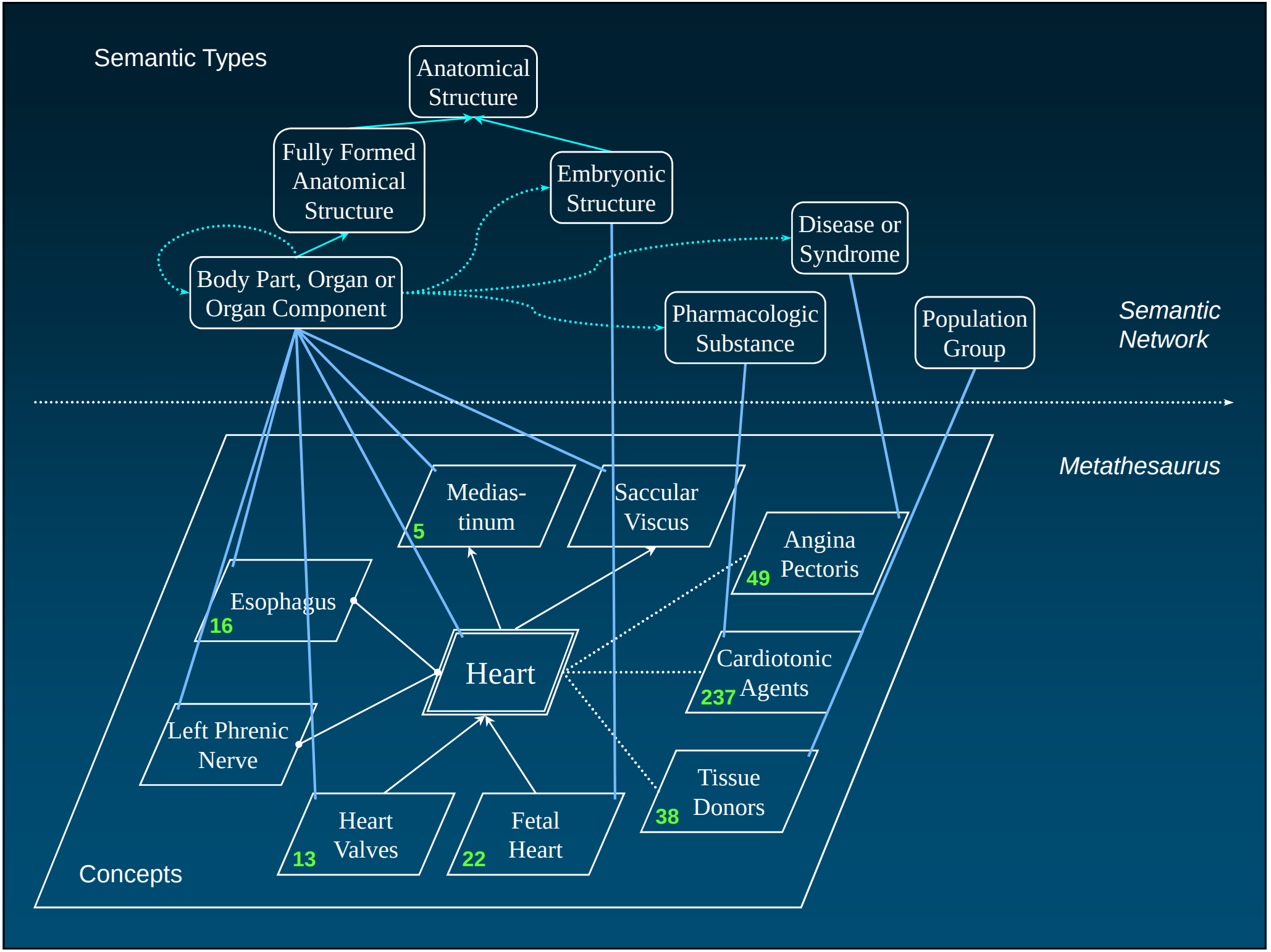
- Current version: 2008AA (2-3 annual releases)
- Type: Terminology integration system
- Domain: Biomedicine
- Developer: NLM
- Funding: NLM (intramural)
- Availability
  - Publicly available: Yes* (cost-free license required)
  - Repositories: UMLS
- URL: http://umlsks.nlm.nih.gov/

UMLS Characteristics (2)

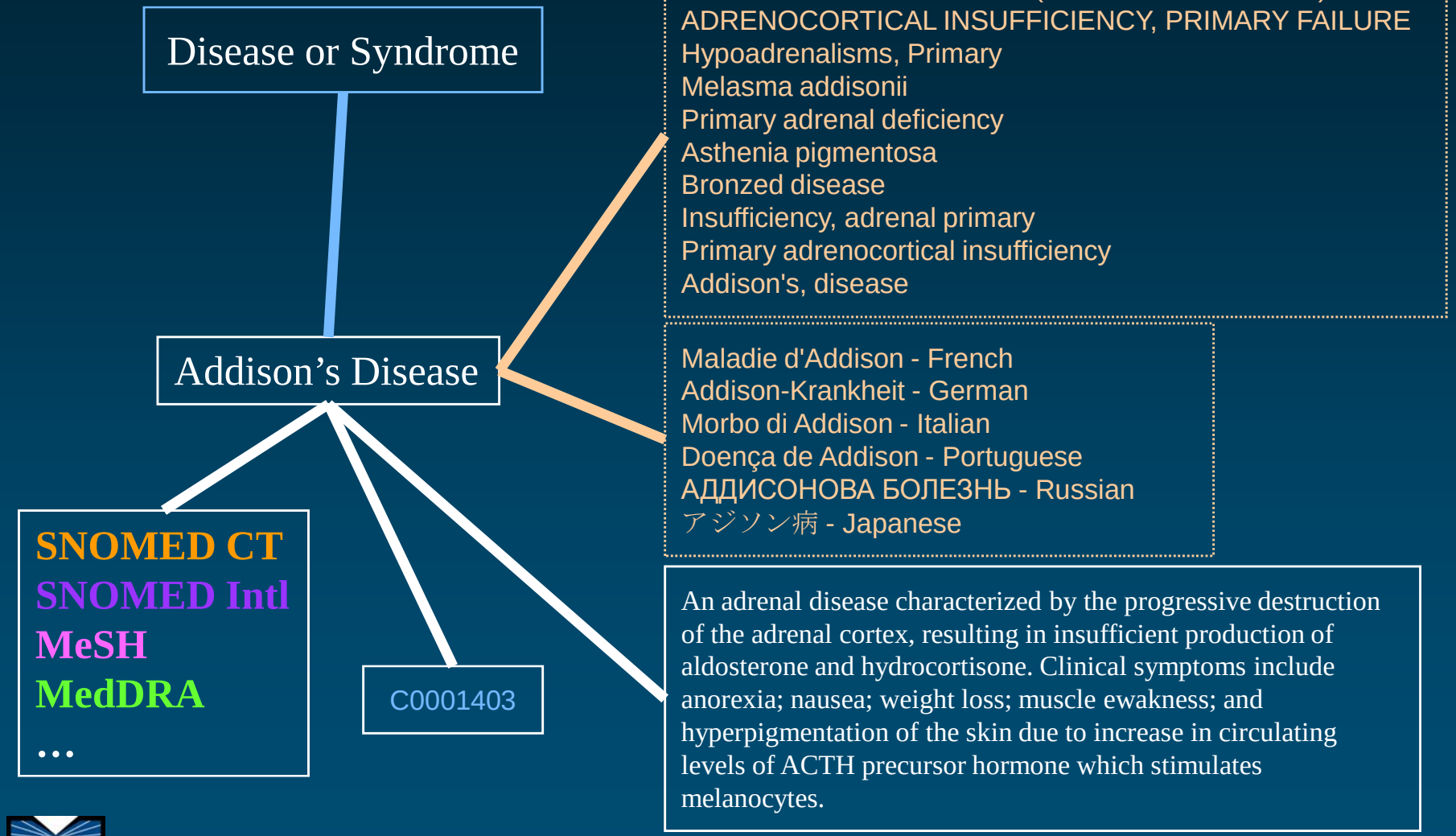
- Number of
  - Concepts: 1.5M (2008AA)
  - Terms: ~6M
- Major organizing principles (Metathesaurus):
  - Concept orientation
  - Source transparency
  - Multi-lingual through translation
- Formalism: Proprietary format (RRF)

UMLS Integrating subdomains



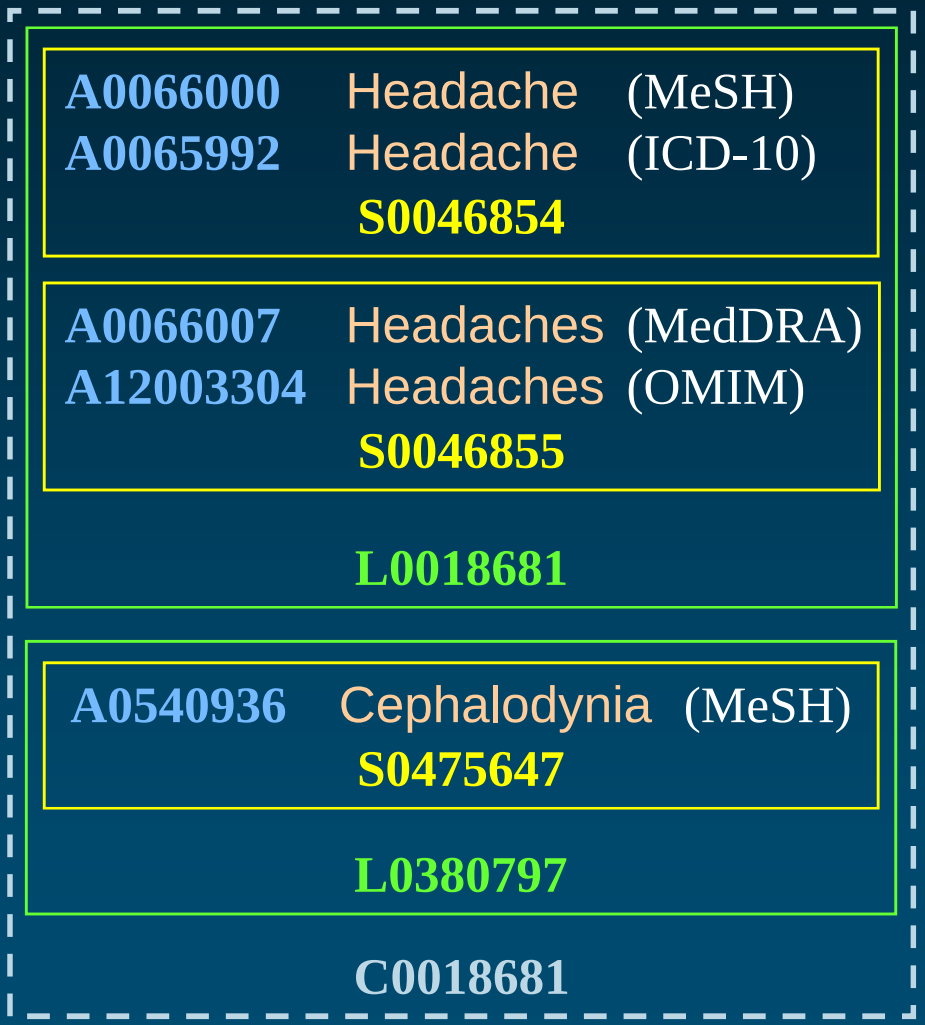

Semantic Types
Anatomical Structure
Fully Formed Anatomical Structure
Embryonic Structure
Disease or Syndrome
Body Part, Organ or Organ Component
Pharmacologic Substance
Population Group
Semantic Network
Metathesaurus
Medias-tinum
5
Saccular Viscus
Angina Pectoris
49
Esophagus
16
Heart
Cardiotonic Agents
237
Left Phrenic Nerve
Tissue Donors
38
Heart Valves
13
Fetal Heart
22
Concepts

Addison's Disease: Concept



Metathesaurus Concepts (2007AB)

- Concept (~ 1.4M) CUI
  - Set of synonymous concept names
- Term (~ 5.3 M) LUI
  - Set of normalized names
- String (~ 5.9M) SUI
  - Distinct concept name
- Atom (~ 7.2M) AUI
  - Concept name in a given source



Recap

Name	Scope	# concepts	Median	Subs. Hier	Version
SNOMED CT	Clinical medicine (patient records)	310,314	2	yes	July 31, 2007
LOINC	Clinical observations and laboratory tests	46,406	3	no	Version 2.21 (no “natural language” names)
FMA	Human anatomical structures	~72,000	?	yes	(not yet in the UMLS)
Gene Ontology	Functional annotation of gene products	22,546	1	yes	Jan. 2, 2007
RxNorm	Standard names for prescription drugs	93,426	1	no	Aug. 31, 2007
NCI Thesaurus	Cancer research, clinical care, public information	58,868	2	yes	2007_05E
ICD-10	Diseases and conditions (health statistics)	12,318	1	no	1998 (tabular)
MeSH	Biomedicine (descriptors for indexing the literature)	24,767	5	no	Aug. 27, 2007
UMLS .	Terminology integration in the life sciences	1,4 M	2	n/a	2007AC (English only)

[Bodenreider, YBMI 2008]

Agenda

Monday, June 9	Introduction to Biomedical Ontologies	Design Principles, Formalisms and Tools for Biomedical Ontologies	Biomedical Ontologies - Content and structure - Function
Tuesday, June 10	Interfaces to Biomedical Ontologies	Searching and Analyzing Biomedical Concepts	Contrasting Biomedical Ontologies
Wednesday, June 11	Critical Analysis of Biomedical Ontologies	Extending Biomedical Ontologies	Using Biomedical Ontologies for Data Integration

Short course – Summer 2008
Biomedical Ontology in Practice

June 9, 2008 – Session #4

Biomedical Ontologies in Action

A Functional Perspective on Biomedical Ontologies

Olivier Bodenreider

Lister Hill National Center
for Biomedical Communications
Bethesda, Maryland - USA

Overview

- Functional perspective [Bodenreider, YBMI 2008]
  - What are they for (vs. what are they)?
- "High-impact" biomedical ontologies
- 3 major categories of use
  - Knowledge management (indexing and retrieval of data and information, access to information, mapping among ontologies)
  - Data integration, exchange and semantic interoperability
  - Decision support and reasoning (data selection and aggregation, decision support, natural language processing applications, knowledge discovery).

Knowledge management

Knowledge management

Annotating data and resources

Terminology in ontology

- Ontology as a source of vocabulary
  - List of names for the entities in the ontology (ontology vs. terminology)
- Most ontologies have some sort of terminological component
  - Exceptions: GALEN, LOINC
- Not all surface forms represented
  - Often insufficient for NLP applications
  - Large variation in number of terms per concept across ontologies

Annotating data

- Gene Ontology
  - Functional annotation of gene products in several dozen model organisms

- Various communities use the same controlled vocabularies
- Enabling comparisons across model organisms
- Annotations
  - Assigned manually by curators
  - Inferred automatically (e.g., from sequence similarity)

GO Annotations for Aldh2 (mouse)

GO Annotations in Tabular Form (Text View) (GO Grap

Category	Classification Term	Evidence
Molecular Function	aldehyde dehydrogenase (NAD) activity	IEA
Molecular Function	oxidoreductase activity	IEA
Molecular Function	oxidoreductase activity	IEA
Cellular Component	mitochondrion	IDA
Biological Process	metabolic process	IEA
Biological Process	oxidation reduction	IEA

http:// www.informatics.jax.org/

GO ALD4 in Yeast

GO Annotations

*All **ALD4** GO evidence and references*

*View Computational GO annotations for **ALD4***

Molecular Function

Manually curated

- aldehyde dehydrogenase (NAD) activity (IDA, IMP, ISS)
- aldehyde dehydrogenase [NAD(P)+] activity (IDA)

Biological Process

Manually curated

- ethanol metabolic process (IMP)

Cellular Component

Manually curated

- mitochondrial nucleoid (IDA)
- mitochondrion (IMP, ISS)

High-throughput

- mitochondrion (IDA)

SGD

http://db.yeastgenome.org/

NLM

GO Annotations for ALDH2 (Human)

Function						
GO:0016491	oxidoreductase activity	interpro	IEA	IPR015590	UniProt	9606
GO:0016491	oxidoreductase activity	interpro	IEA	IPR016160	UniProt	9606
GO:0016491	oxidoreductase activity	interpro	IEA	IPR016162	UniProt	9606
GO:0016491	oxidoreductase activity	interpro	IEA	IPR016161	UniProt	9606
GO:0016491	oxidoreductase activity	spkw	IEA	KW-0560	UniProt	9606
GO:0004029	aldehyde dehydrogenase (NAD) activity	1306115	TAS		PINC	9606
GO:0004030	aldehyde dehydrogenase [NAD(P)+] activity	8903321	TAS		PINC	9606
GO:0009055	electron carrier activity	8903321	TAS		UniProt	9606
GO:0004029	aldehyde dehydrogenase (NAD) activity	enzyme	IEA	1.2.1.3	UniProt	9606

http://www.ebi.ac.uk/GOA/

Indexing the biomedical literature

- MeSH
  - Used for indexing and retrieval of the biomedical literature (MEDLINE)
- Indexing
  - Performed manually by human indexers
    - With help of semi-automatic systems (suggestions) e.g., Indexing Initiative at NLM
  - Automatic indexing systems

MeSH MEDLINE indexing

1: Anesth Analg. 2008 Jun;106(6):1813-9.

Related Articles, Links

Full Text Anesth Analg

Free cortisol in sepsis and septic shock.

Bendel S, Karlsson S, Pettilä V, Loisa P, Varpula M, Ruokonen E; Finnsepsis Study Group.

Collaborators (26)

Department of Intensive Care, Kuopio University Hospital, PL 16222 Kuopio, Finland. Stepani.Bendel@kuh.fi

BACKGROUND: Severe sepsis activates the hypothalamopituitary axis, increasing cortisol production. In some studies, hydrocortisone substitution based on an adrenocorticotropic hormone-stimulation test or baseline cortisol measurement has improved outcome. Because only the free fraction of cortisol is active, measurement of free cortisol may be more important than total cortisol in critically ill patients. We measured total and free cortisol in patients with severe sepsis and related the concentrations to outcome. METHODS: In a prospective study, severe sepsis was defined according the American College of Chest Physicians/Society of Critical Care Medicine criteria. Blood samples were drawn within 24 h of study entry. Serum cortisol was analyzed by electrochemiluminescence immunoassay. The Coolens method was used for calculating serum free cortisol concentrations. RESULTS: Blood samples were collected from 125 patients, of whom 62 had severe sepsis and 63 septic shock. Hospital mortality was 21%. Calculated free serum cortisol correlated well with serum total cortisol ($r = 0.90$, $P < 0.001$). There was no difference in the total cortisol concentrations in patients with sepsis and septic shock (728 +/- 386 nmol/L vs 793 +/- 439 nmol/L, $P = 0.44$). Nonsurvivors had higher calculated serum free (209 +/- 151 nmol/L) and total (980 +/- 458 nmol/L) cortisol concentrations than survivors (119 +/- 111 nmol/L, $P = 0.002$, and 704 +/- 383 nmol/L, $P = 0.002$). Depending on the definition, the incidence of adrenal insufficiency varied from 8% to 54%. CONCLUSIONS: Clinically, calculation of free cortisol does not provide essential information for identification of patients who would benefit from corticoid treatment in severe sepsis and septic shock.

MeSH MEDLINE indexing

MeSH Terms:

- Adrenal Cortex Function Tests
- Adrenal Insufficiency/blood*
- Adrenal Insufficiency/drug therapy
- Adrenal Insufficiency/mortality
- Adult
- Biological Markers/blood
- Female
- Finland/epidemiology
- Hospital Mortality
- Humans
- Hydrocortisone/blood*
- Hydrocortisone/therapeutic use
- Kaplan-Meiers Estimate
- Male
- Predictive Value of Tests
- Prospective Studies
- Sepsis/blood*
- Sepsis/drug therapy
- Sepsis/mortality
- Severity of Illness Index
- Shock, Septic/blood*
- Shock, Septic/drug therapy
- Shock, Septic/mortality
- Treatment Outcome

Substances:

- Biological Markers
- Hydrocortisone

MeSH MEDLINE indexing

1: Expert Opin Investig Drugs. 2008 Apr;17(4):497-509. Related Articles, Links

Expert Opinion Full text article at www.expertopin.com

Replacement therapy for Addison's disease: recent developments.

Lovås K, Husebye ES.

University of Bergen, Institute of Medicine, Section of Endocrinology, 5021 Bergen, Norway.
Kristian.lovas@helse-bergen.no

BACKGROUND: The hormone deficiencies in Addison's disease (primary adrenal insufficiency) are conventionally treated with oral glucocorticoid and mineralocorticoid replacement but the available therapies do not restore the physiological hormone levels and biorhythm. Despite such treatment these patients self-report impaired health-related quality of life (HRQoL) and recent research has indicated increased mortality. OBJECTIVE/METHODS: We review the literature and recent developments in replacement therapy. RESULTS/CONCLUSION: Patients with Addison's disease require mineralocorticoid replacement, i.e., fludrocortisone 0.05 - 0.20 mg once daily. Starting doses of glucocorticoids should be 15 - 20 mg for hydrocortisone or 20 - 30 mg for cortisone acetate, divided into two or three doses, and preferentially weight-adjusted. There are indications that the synthetic glucocorticoids have undesirable metabolic long-term effects, which make them less suitable as first-line treatment. Timed-release hydrocortisone tablets and continuous subcutaneous hydrocortisone infusion are promising new treatment modalities. Studies of replacement with the adrenal androgen dehydroepiandrosterone (DHEA) in adrenal failure have shown inconsistent benefit on HRQoL. DHEA, or possibly testosterone replacement is likely to be beneficial for selected groups of patients with Addison's disease but this remains to be shown. We here give our opinion of the best treatment and future direction of research in this area.

MeSH MEDLINE indexing

MeSH Terms:

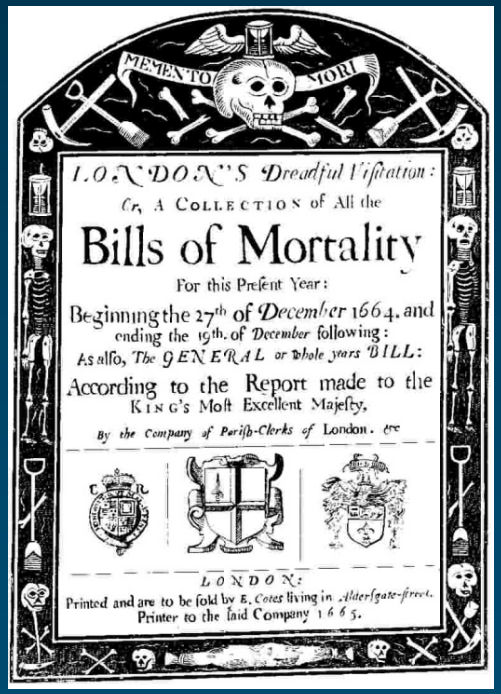
- Addison Disease/blood
- Addison Disease/drug therapy*
- Androgens/administration & dosage*
- Androgens/therapeutic use
- Dosage Forms
- Drug Administration Routes
- Drug Administration Schedule
- Glucocorticoids/administration & dosage*
- Glucocorticoids/adverse effects
- Glucocorticoids/blood
- Glucocorticoids/deficiency
- Hormone Replacement Therapy*
- Humans
- Mineralocorticoids/administration & dosage*
- Mineralocorticoids/adverse effects
- Mineralocorticoids/blood
- Mineralocorticoids/deficiency
- Quality of Life
- Treatment Outcome

Substances:

- Androgens
- Dosage Forms
- Glucocorticoids
- Mineralocorticoids

ICD9-CM Coding clinical data

- ICD9-CM
  - Used for coding clinical data e.g., for billing purposes
- Other uses of ICD
  - Morbidity and mortality reporting worldwide

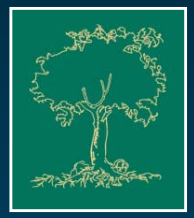


Knowledge management

Accessing biomedical information

Resources for biomedical search engines

- Synonyms
- Hierarchical relations
- High-level categorization
- Co-occurrence information
- Translation

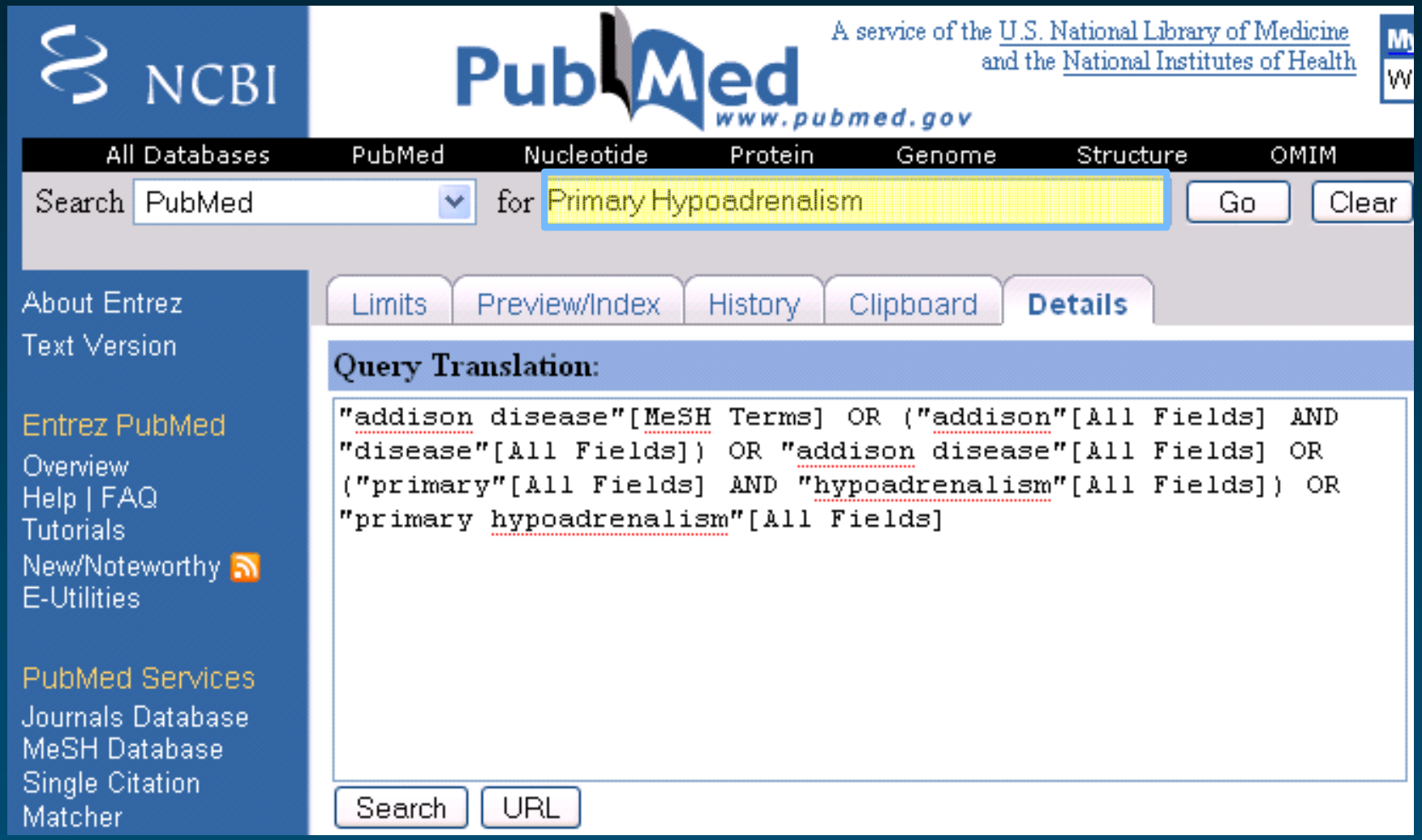


MeSH “synonyms” MEDLINE retrieval

- MeSH entry terms
  - Used as equivalent terms for retrieval purposes
  - Not always synonymous
- Increase recall without hurting precision

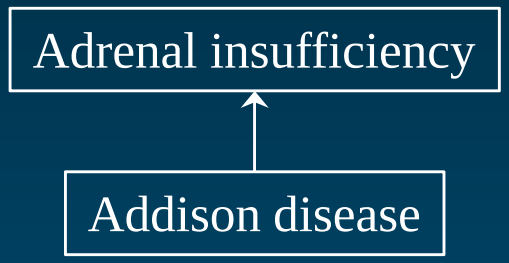
MeSH Heading	Addison Disease
Entry Term	Addison's Disease
Entry Term	Primary Adrenal Insufficiency
Entry Term	Primary Adrenocortical Insufficiency

MeSH “synonyms” MEDLINE retrieval



MeSH hierarchies MEDLINE retrieval

- MeSH “explosion”
  - Search for a given MeSH term and all its descendants
  - A search on Adrenal insufficiency also retrieves articles indexed with Addison disease



NCBI

PubMed www.pubmed.gov

A service of the U.S. National Library of Medicine and the National Institutes of Health

My NCBI

Welcome olivier_bodenreider. [Sign Out]

All Databases | PubMed | Nucleotide | Protein | Genome | Structure | OMIM | PMC | Journals | Books

Search PubMed for "adrenal insufficiency"[MeSH Terms] Go Clear Advanced Search (beta) Save Search

Limits | Preview/Index | History | Clipboard | Details

Display Summary Show 20 Sort By Send to

All: 8994 Review: 1069

Items 1 - 20 of 8994 Page 1 of 450 Next

1: Bendel S, Karlsson S, Pettilä V, Loisa P, Varpula M, Ruokonen E; Finnsepsis Study Group. Related Articles, Links

Free cortisol in sepsis and septic shock.

Anesth Analg. 2008 Jun;106(6):1813-9.

PMID: 18499615 [PubMed - indexed for MEDLINE]

2: Luboshitzky R, Qupti G. Related Articles, Links

Corticosteroids for septic shock.

N Engl J Med. 2008 May 8;358(19):2069; author reply 2070-1. No abstract available.

PMID: 18467975 [PubMed - indexed for MEDLINE]

• • •

12: Løvås K, Husebye ES. Related Articles, Links

Replacement therapy for Addison's disease: recent developments.

Expert Opin Investig Drugs. 2008 Apr;17(4):497-509. Review.

PMID: 18363515 [PubMed - indexed for MEDLINE]

NLM

Co-indexing

gopubmed®

Searching is now sorted!

http://www.gopubmed.com/

cox-2

what

- Top categories
  - Chemicals and Drugs [992]
    - Cyclooxygenase 2 [517]
    - Cyclooxygenase 2 Inhibitors [289]
    - Prostaglandins [358]
    - Prostaglandin-Endoperoxide Synthases [667]
    - NF-kappa B [138]
    - RNA, Messenger [222]
    - Anti-Inflammatory Agents [414]
    - more
  - biological_process [851]
    - cyclooxygenase pathway [305]
    - more
  - Biological Sciences [960]
    - Up-Regulation [166]
    - more
  - Diseases [781]
    - Inflammation [192]
    - more
  - Organisms [398]
  - Techniques and Equipment [809]
  - molecular_function [483]
  - Anatomy [778]
  - Named Groups [285]
  - cellular_component [307]
  - Natural Sciences [661]
  - Technology, Industry, Agriculture [147]
  - Psychiatry and Psychology [386]

NLM

Knowledge management

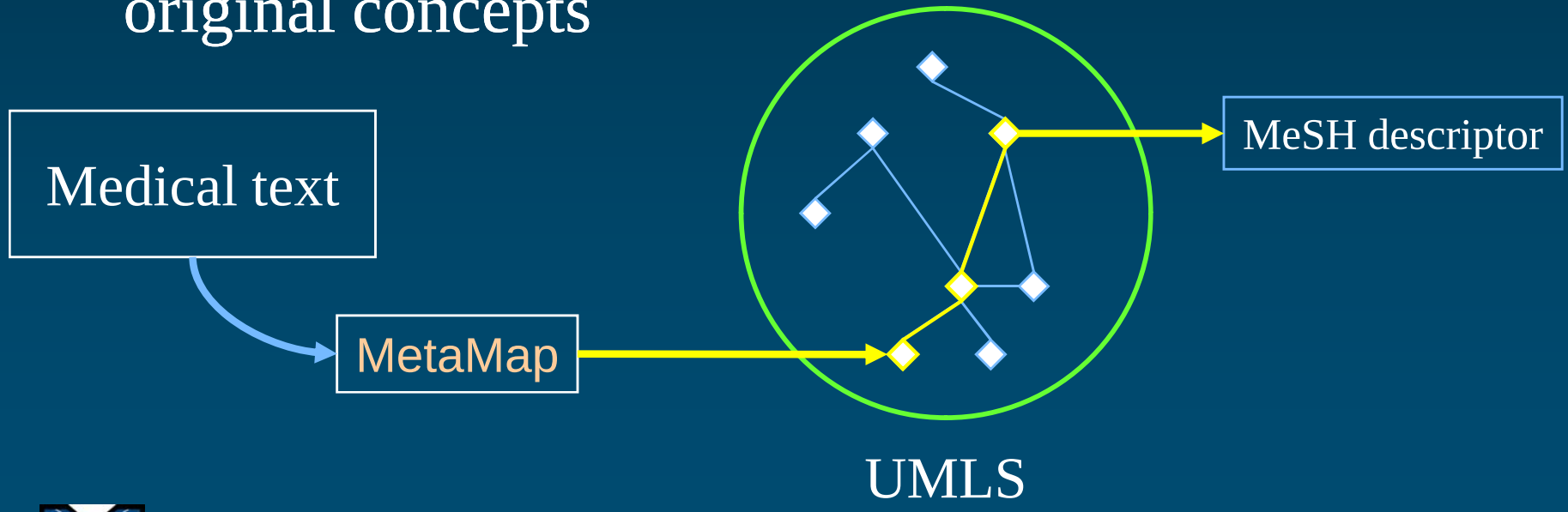
Mapping across biomedical ontologies

Reusing information

- Clinical information coded with SNOMED CT
  - Mapped to ICD9-CM and CPT for billing purposes
  - Mapped to ICD-O for epidemiology purposes
- Existing mapping tables crated by terminology developers as an incentive to use SNOMED CT

Reusing tools

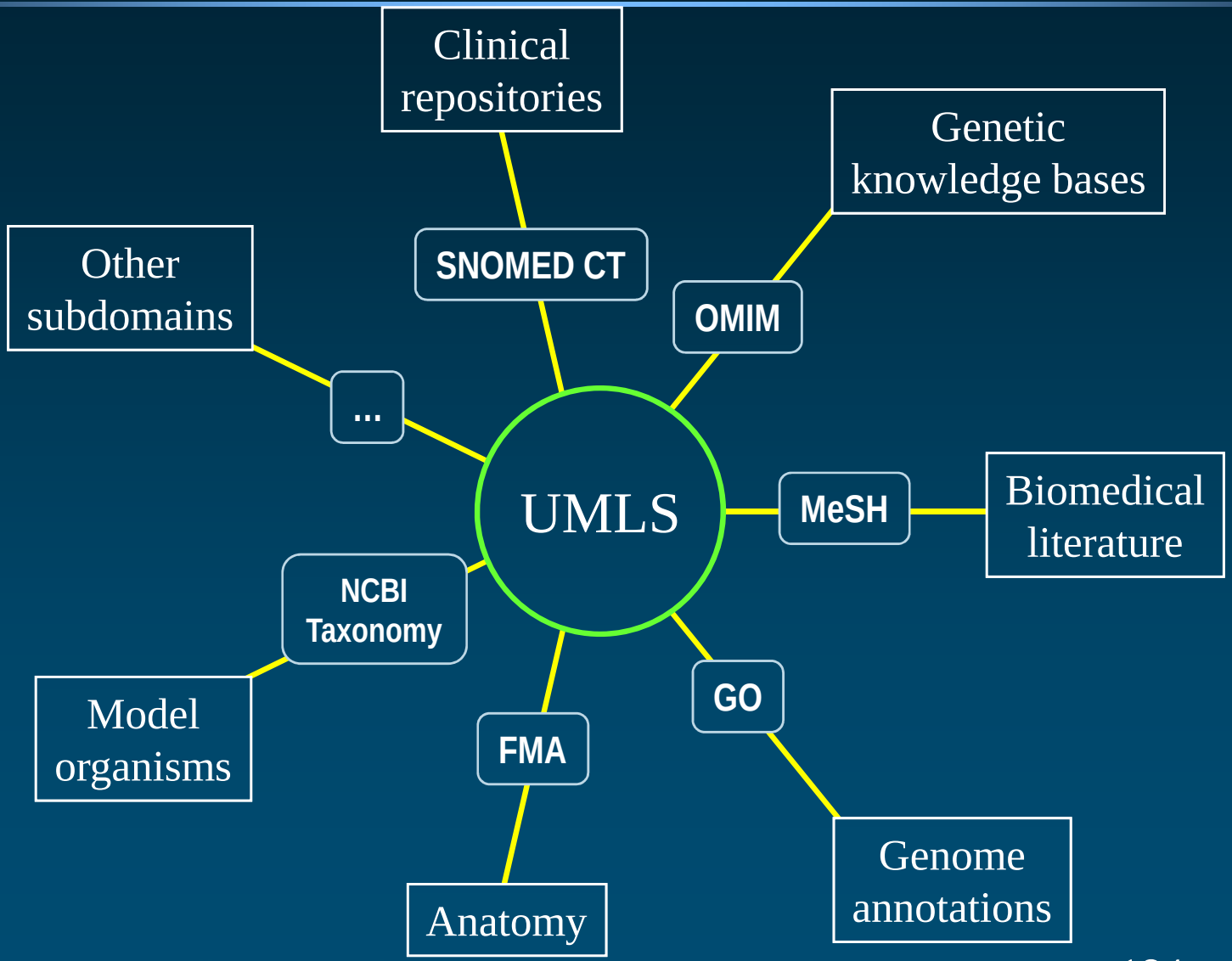
- For noun phrases extracted from medical texts, map to UMLS concepts [Aronson & al., *AMIA*, 2000]
- Then, select from the MeSH vocabulary the concepts that are the most closely related to the original concepts



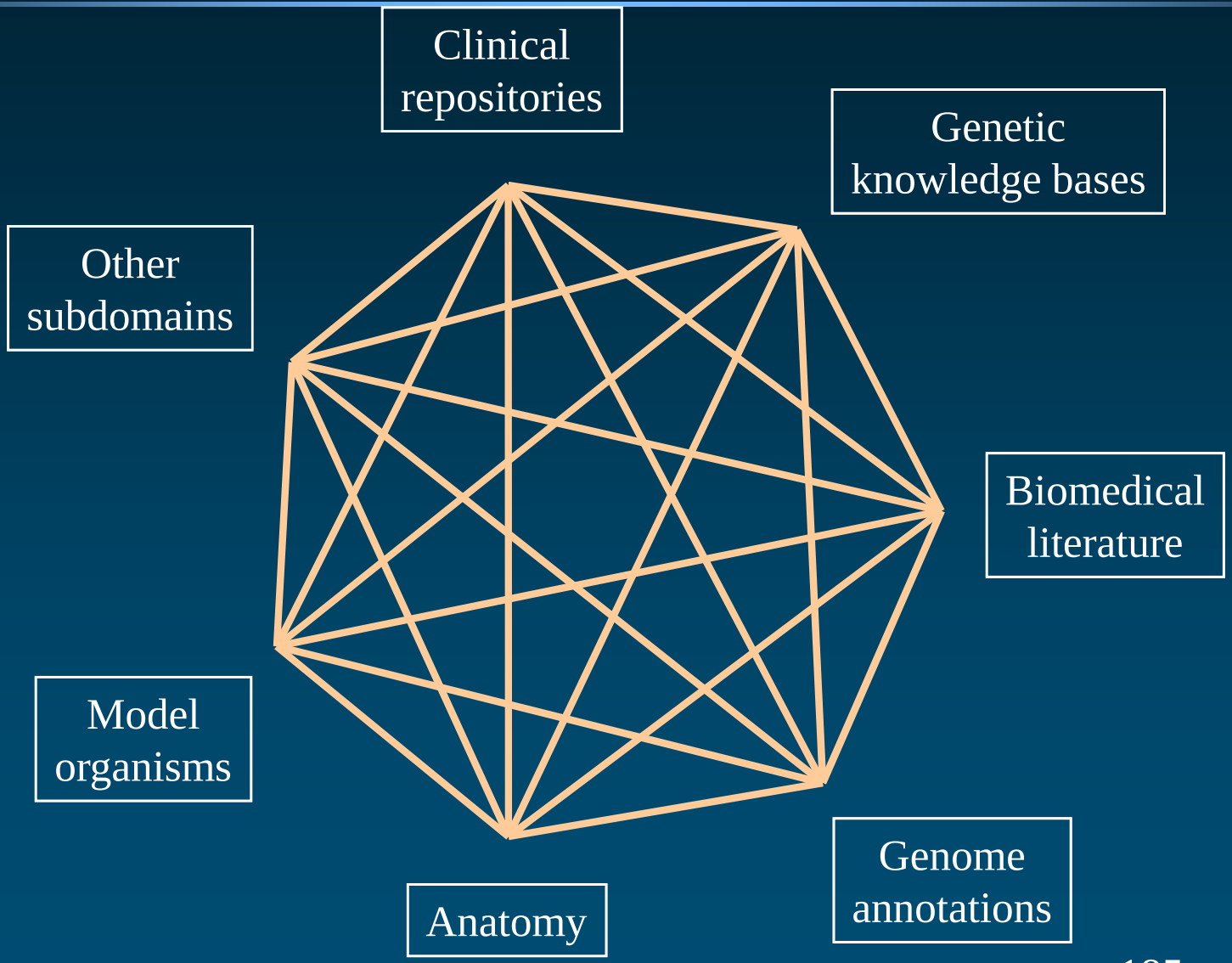
Terminology integration systems

- Terminology integration systems (UMLS, RxNorm) help bridge across vocabularies
- Uses
  - Information integration
  - Ontology alignment
  - Medication reconciliation

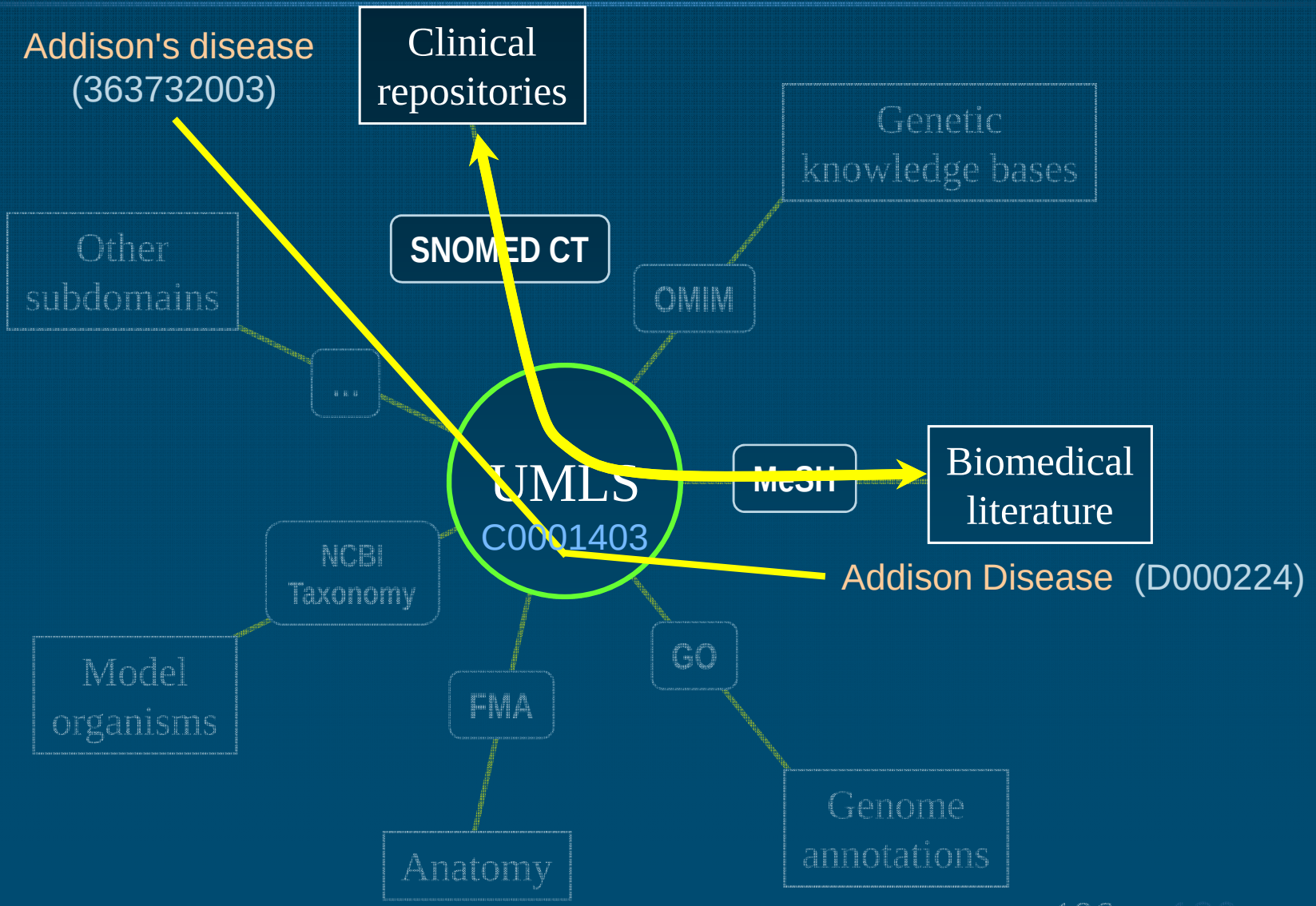
Integrating subdomains



Integrating subdomains



Trans-namespace integration



Data integration, exchange and semantic interoperability

Data integration, exchange and semantic interoperability

Information exchange
and semantic operability

“Standards”

- Ontologies help standardize patients data
  - Facilitate the exchange of data across institutions
  - Help connect “islands of data” (silos)

- LOINC
  - Exchange of laboratory data
  - In conjunction with HL7 messaging

Semantic interoperability projects BRIDG

- Biomedical Research Integrated Domain Group
  - Information model for clinical research
  - Interoperability between clinical trials information systems
  - Ontologies provide value sets to the information model

Semantic interoperability projects CDA

- Clinical Document Architecture (CDA R2)
  - Formal representation of clinical statements
    - Clinical observations
    - Medication administration
    - Adverse events
  - Associate an information model (HL7 RIM) with terminologies (LOINC, SNOMED CT, RxNorm)

Semantic interoperability projects caCORE

- Cancer Common Ontologic Representation Environment
  - Infrastructure developed to support an interoperable biomedical information system for cancer research
  - Uses the NCI Thesaurus as a component

Data integration, exchange and semantic interoperability

Information and data integration

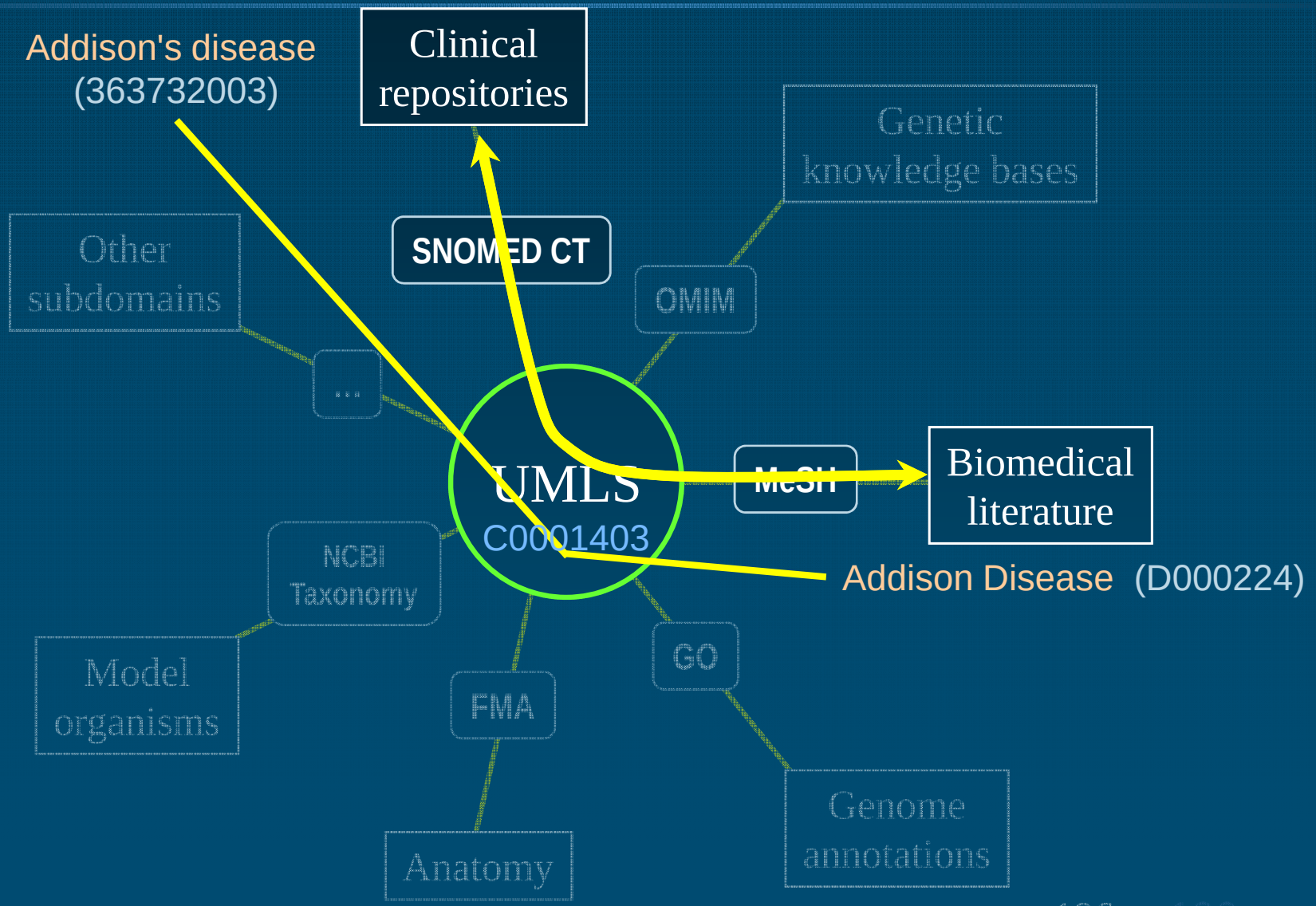
Approaches to data integration

- Warehousing
  - Sources to be integrated are transformed into a common format and converted to a common vocabulary
  - Normalization through ontologies (e.g., GO annotations)
- Mediation
  - Local schema (of the sources)
  - Global schema (in reference to which the queries are made)
  - Ontologies help define the global schema and map between local and global schemas (OntoFusion, ARIANE)

Ontologies and integration

- Terminology integration systems help bridge across terminolgies and the domains they represent
- Mappings across ontologies enable the integration of namespaces in the Semantic Web

Trans-namespace integration



Decision support and reasoning

Data selection

- The structure of biomedical ontologies helps define groups of values from a high-level value
  - Vs. enumerating all possible values
- Useful for data selection in clinical studies
- ICD is used pervasively for this purpose
  - E.g., Study on supraventricular tachycardia (SVT), based on 2 high-level ICD codes
- Similarity with the definition of value sets for use in the information model

Data aggregation

- Ontologies help partition/aggregate data in data analysis
  - Clinical studies: Study a variable in groups of patients corresponding to the top level categories in ICD
  - Biology studies: Functional characterization of gene expression signatures with high-level concepts from the Gene Ontology
    - Recent trend: co-clustering

Decision support

- Clinical decision support
  - Ontologies help normalize the vocabulary and increase the recall of rules
  - Ontologies provide some domain knowledge and make it possible to create high-level rules (e.g., for a class of drugs rather than for each drug in the class)
- Other forms of decision support
  - Based on automatic reasoning services for OWL ontologies (e.g., grading gliomas with NCIt)

Natural language processing applications

- Ontologies provide background domain knowledge for NLP applications
  - Question answering
  - Document summarization
  - Literature-based discovery
- The UMLS is often used, but other specific resources have been developed

Knowledge discovery

- By standardizing the vocabulary in a given domain, ontologies are enabling resources for knowledge discovery through data mining
- Less frequently, the structure of the ontology is leveraged by data mining algorithms
- Example of available datasets
  - ICD-coded clinical data (in conjunction with non-clinical information, e.g., environmental data)
  - Annotation of gene products to the GO (function prediction)

Barriers to usability of biomedical ontologies

Availability

- Many ontologies are freely available
- The UMLS is freely available for research purposes
  - Cost-free license required
- Licensing issues can be tricky
  - SNOMED CT is freely available in member countries of the IHTSDO
- Being freely available
  - Is a requirement for the Open Biomedical Ontologies (OBO)
  - Is a de facto prerequisite for Semantic Web applications

Discoverability

- Ontology repositories
  - UMLS: 143 source vocabularies
    (biased towards healthcare applications)
  - NCBO BioPortal: ~100 ontologies
    (biased towards biological applications)
  - Limited overlap between the two repositories
- Need for discovery services

Formalism

- Several major formalism
  - Web Ontology Language (OWL) – NCI Thesaurus
  - OBO format – most OBO ontologies
  - UMLS Rich Release Format (RRF) – UMLS, RxNorm
- Conversion mechanisms
  - OBO to OWL
  - LexGrid (import/export to LexGrid internal format)

Ontology integration

- *Post hoc* integration , form the bottom up
  - UMLS approach
  - Integrates ontologies “as is”, including legacy ontologies
  - Facilitates the integration of the corresponding datasets
- Coordinated development of ontolgoies
  - OBO Foundry approach
  - Ensures consistency *ab initio*
  - Excludes legacy ontologies

Quality

- Quality assurance in ontologies is still imperfectly defined
  - Difficult to define outside a use case or application
- Several approaches to evaluating quality
  - Collaboratively, by users (Web 2.0 approach)
    - Marginal notes enabled by BioPortal
  - Centrally, by experts
    - OBO Foundry approach
- Important factors besides quality
  - Governance
  - Installed base / Community of practice

Agenda

Monday, June 9	Introduction to Biomedical Ontologies	Design Principles, Formalisms and Tools for Biomedical Ontologies	Biomedical Ontologies - Content and structure - Function
Tuesday, June 10	Interfaces to Biomedical Ontologies	Searching and Analyzing Biomedical Concepts	Contrasting Biomedical Ontologies
Wednesday, June 11	Critical Analysis of Biomedical Ontologies	Extending Biomedical Ontologies	Using Biomedical Ontologies for Data Integration

Short course – Summer 2008
Biomedical Ontology in Practice

June 10, 2008 – Session #1

Interfaces to Biomedical Ontologies

Olivier Bodenreider

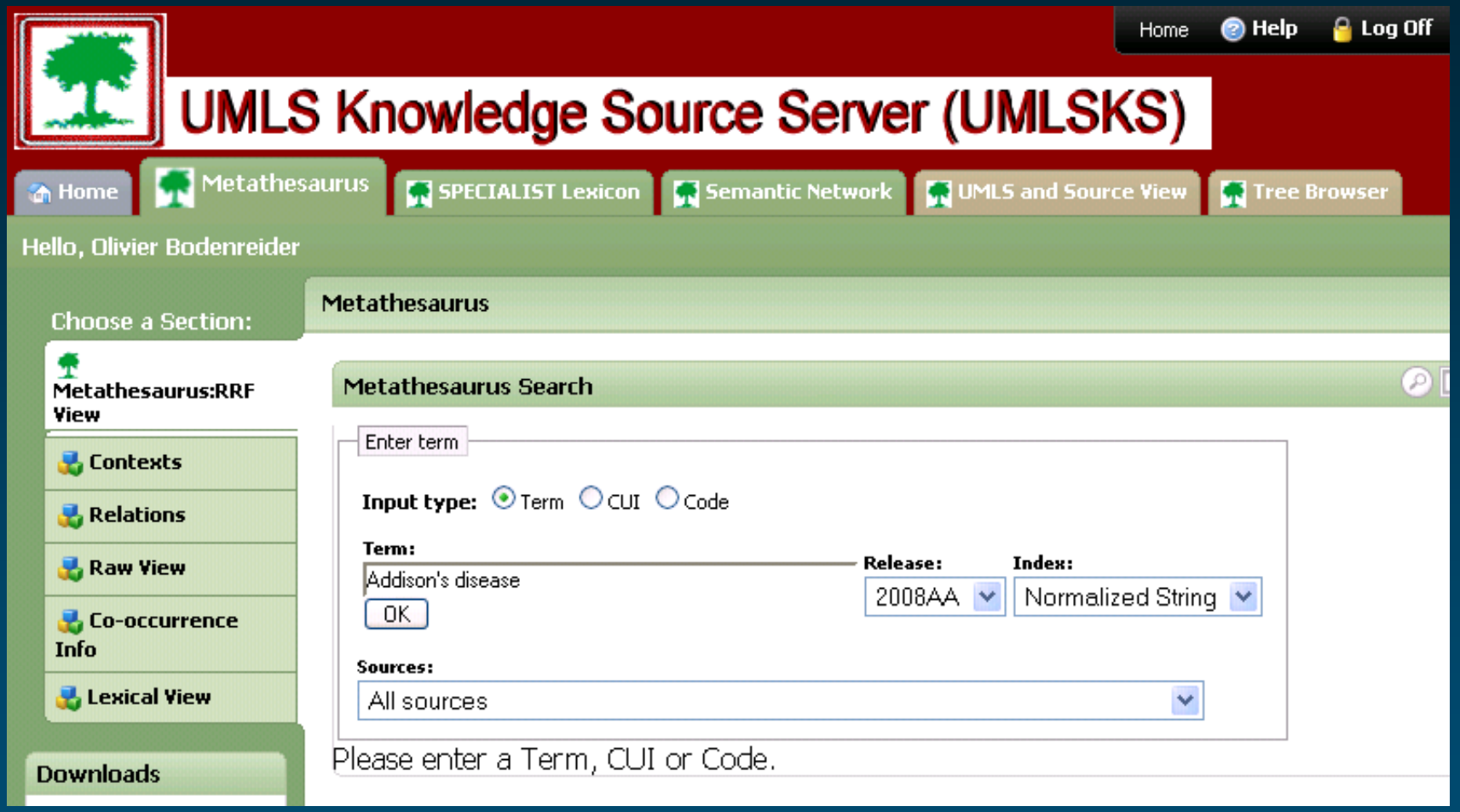
Lister Hill National Center
for Biomedical Communications
Bethesda, Maryland - USA

Overview

- Graphical interfaces
  - UMLS Knowledge Source Server
  - NCBO BioPortal
  - NCI Thesaurus
  - MeSH browser
  - Foundational Model of Anatomy (FMA) Explorer
  - Gene Ontology AmiGO
  - ICD-10 online
  - RxNav (RxNorm)
  - […]
- Application Programming Interfaces

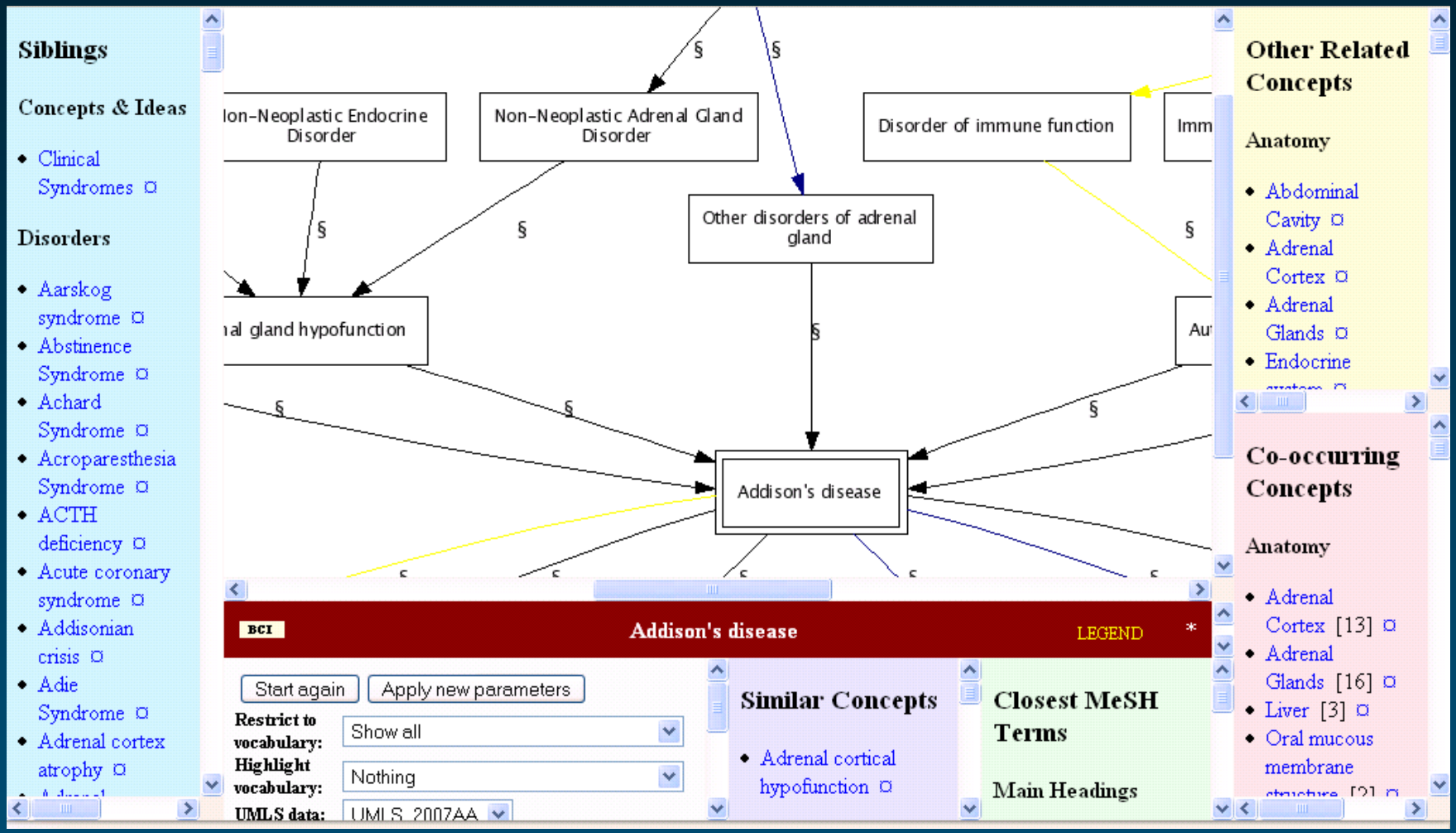
Graphical interfaces

UMLS Knowledge Source Server



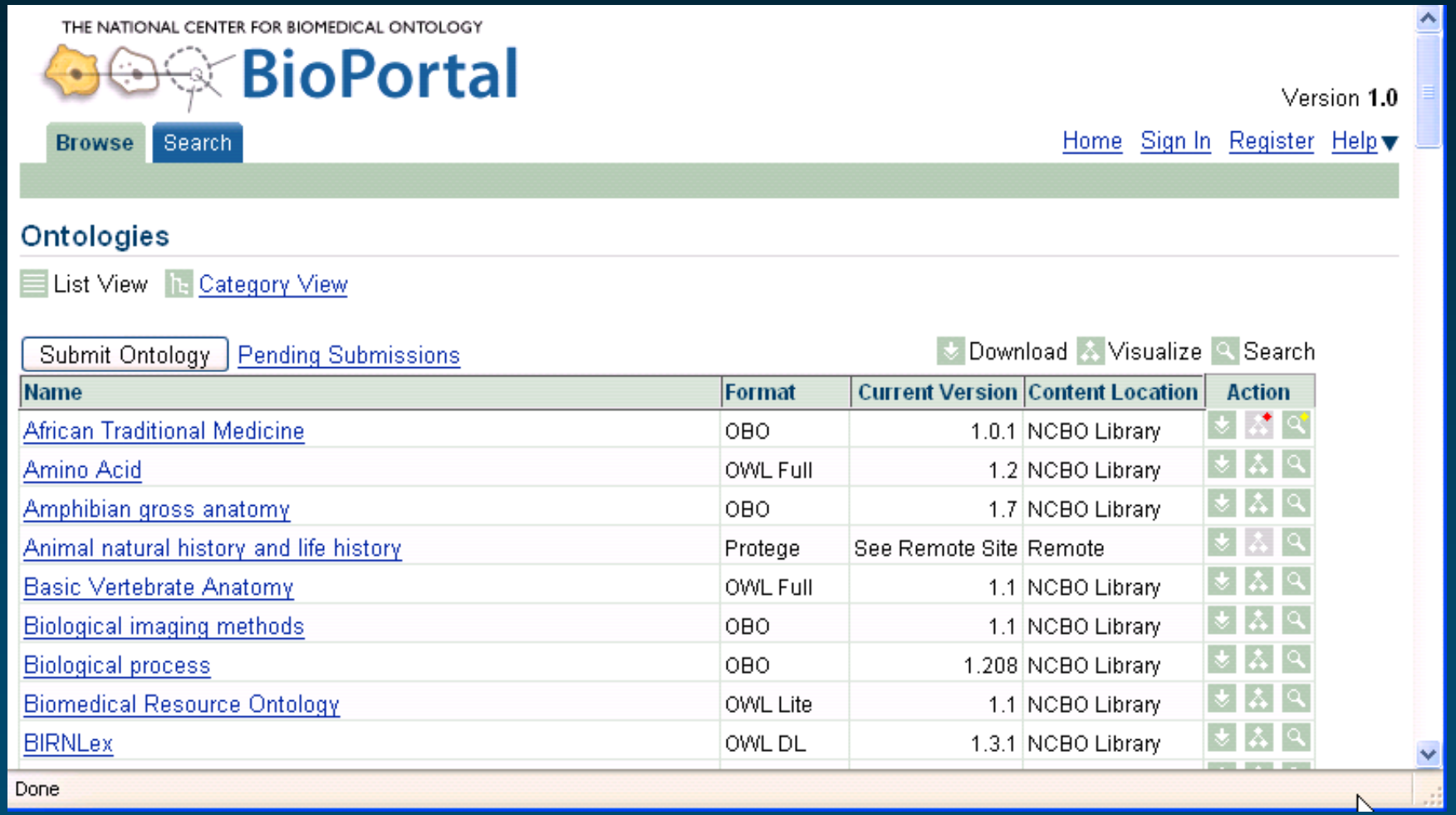
http://umlsks.nlm.nih.gov/

UMLS Semantic Navigator



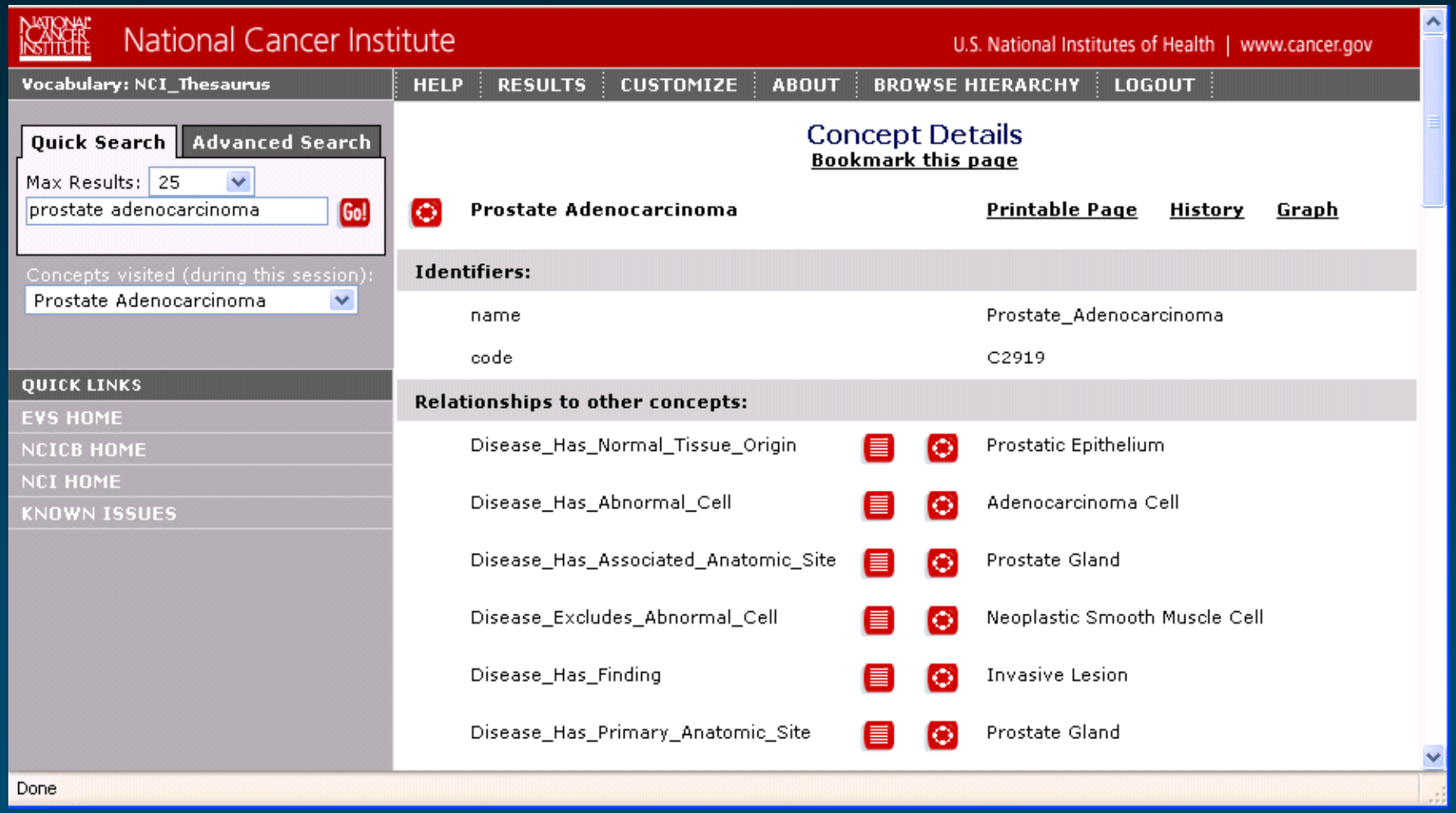
http://mor.nlm.nih.gov/perl/semnav.pl

NCBO BioPortal



http://www.bioontology.org/tools/portal/bioportal.html

NCI Thesaurus (EVS Server)



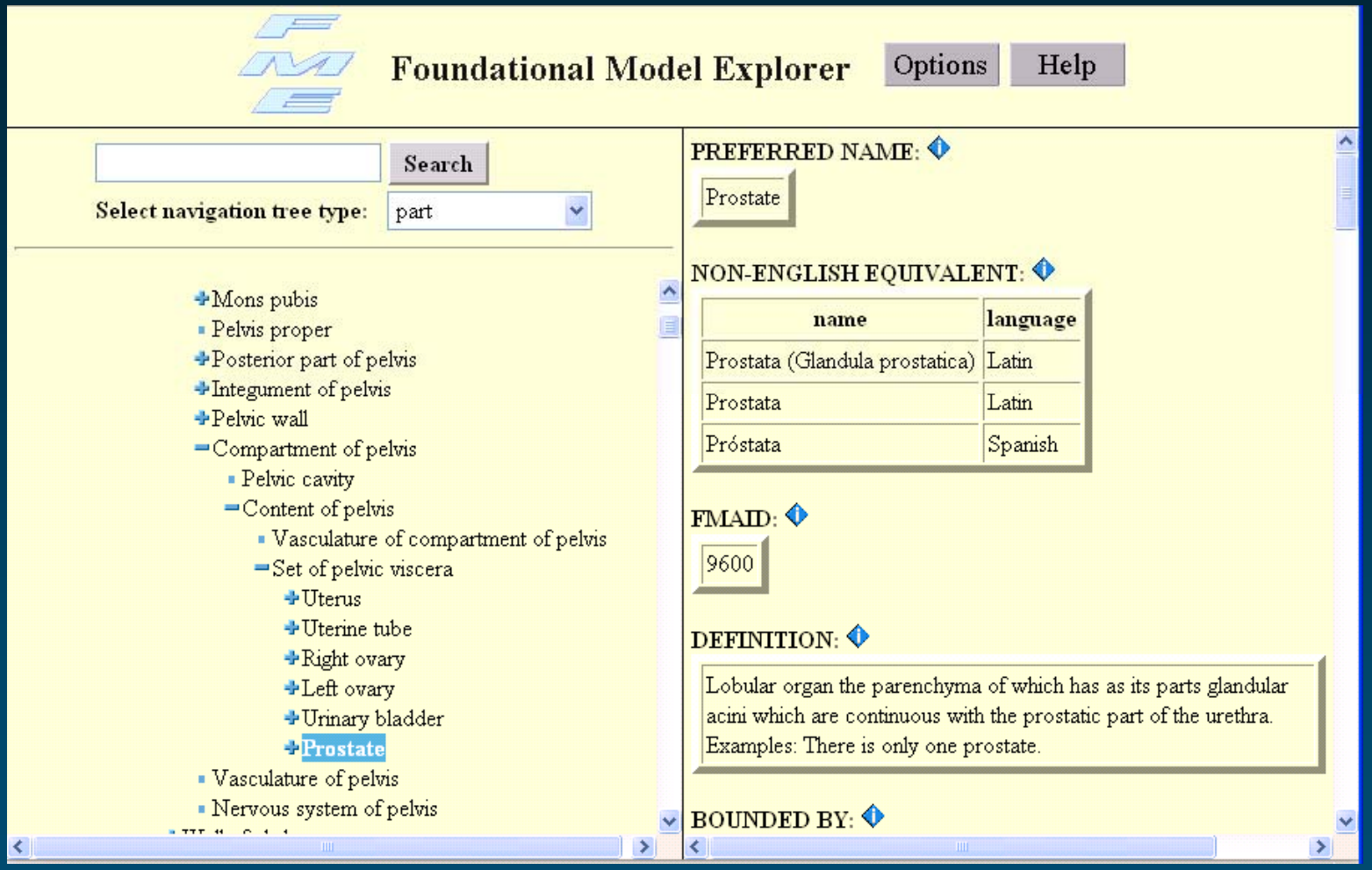
http://nciterms.nci.nih.gov/NCIBrowser/SearchConcept.do

MeSH Browser

MeSH Heading	Prostatic Neoplasms
Tree Number	C04.588.945.440.770
Tree Number	C12.294.260.750
Tree Number	C12.294.565.625
Tree Number	C12.758.409.750
Annotation	coordinate IM with histological type of neoplasm (IM); note PROSTATIC ADENOMA see PROSTATIC HYPERPLASIA is also available
Scope Note	Tumors or cancer of the PROSTATE.
Entry Term	Cancer of Prostate
Entry Term	Cancer of the Prostate
Entry Term	Neoplasms, Prostate
Entry Term	Neoplasms, Prostatic
Entry Term	Prostate Cancer
Entry Term	Prostate Neoplasms
Entry Term	Prostatic Cancer
See Also	Prostate-Specific Antigen
See Also	Prostatic Hyperplasia
Allowable Qualifiers	BL BS CF CH CI CL CN CO DH DI DT EC EH EM EN EP ET GE HI IM ME MI MO NU PA PC PP PS PX RA RH RI RT SC SE SU TH UL UR US VE VI
Entry Version	PROSTATIC NEOPL
Date of Entry	19990101
Unique ID	D011471

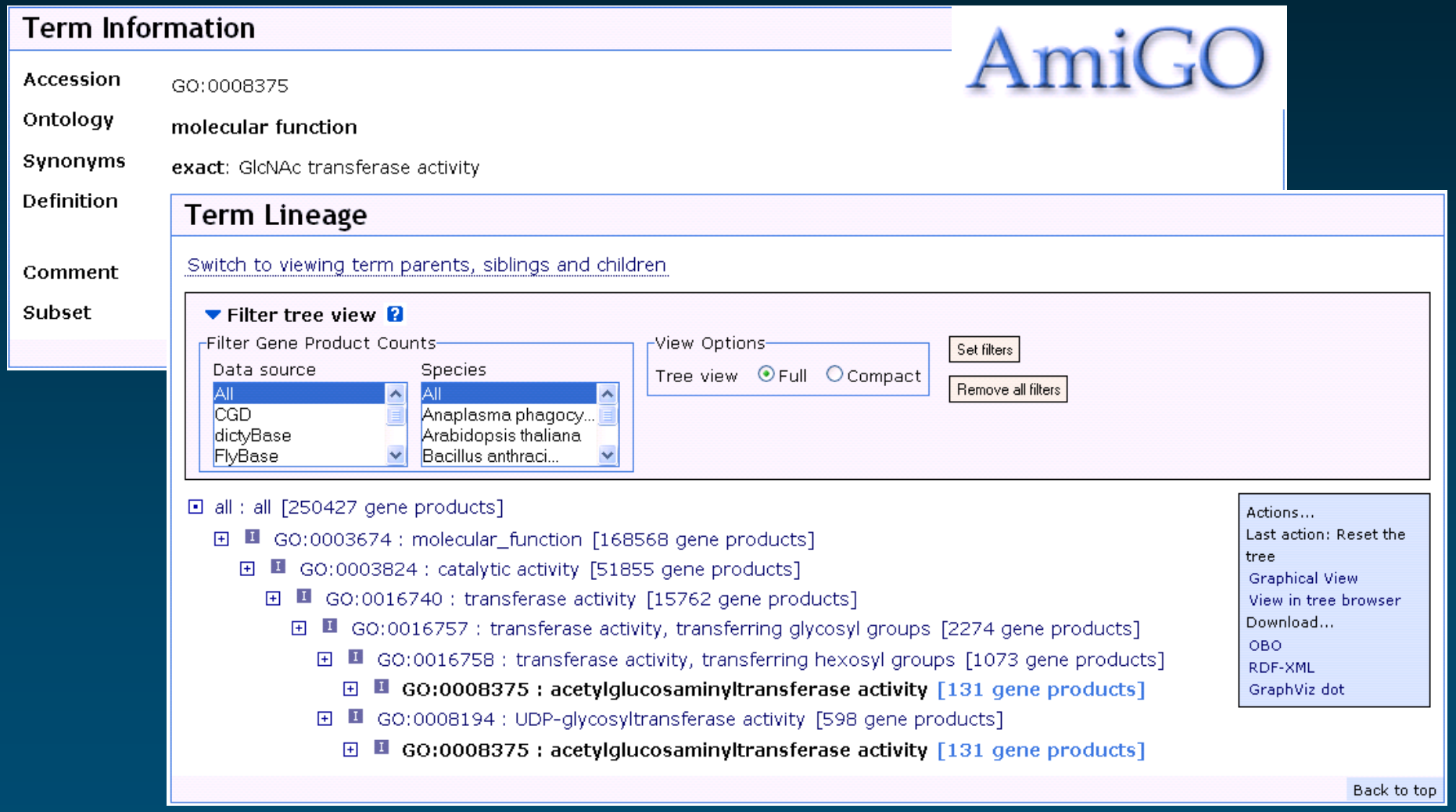
http://www.nlm.nih.gov/mesh/MBrowser.html

Foundational Model of Anatomy



http://sig.biostr.washington.edu/projects/fm/FME/

Gene Ontology AmiGO



NLM

http://www.geneontology.org/

SNOMED CT University of Sydney

Viral meningitis (disorder)

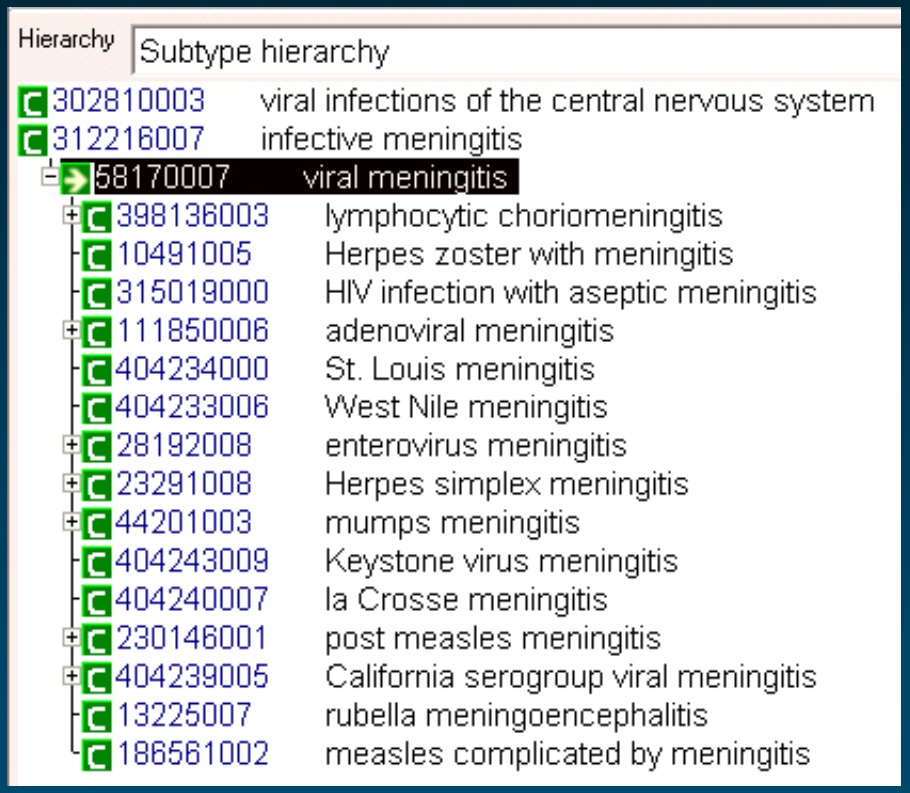
CONCEPT					
Concept ID	Fully Specified Name	Concept Status	CTV3ID	SNOMED ID	Is Primitive
58170007	Viral meningitis (disorder)	Current (0)	Xa9B5	DE-30020	Fully defined (0)

DESCRIPTIONS and SYNONYMS						
	Description ID	Term	Description Status	Description Type	Language Code	Initial Capital Status
1	96672018	Viral meningitis	Current (0)	Preferred (1)	en	Capitalization meaningless (0)
2	96673011	Aseptic meningitis, viral	Current (0)	Synonym (2)	en	Capitalization meaningless (0)
3	96674017	Abacterial meningitis	Current (0)	Synonym (2)	en	Capitalization meaningless (0)
4	96677012	Aseptic meningitis	Non-Current (1)	Synonym (2)	en	Capitalization meaningless (0)
5	96676015	Viral meningitis NOS	Non-Current (1)	Synonym (2)	en	Capitalization meaningless (0)
6	96675016	Viral meningitis, NEC	Non-Current (1)	Synonym (2)	en	Capitalization meaningless (0)

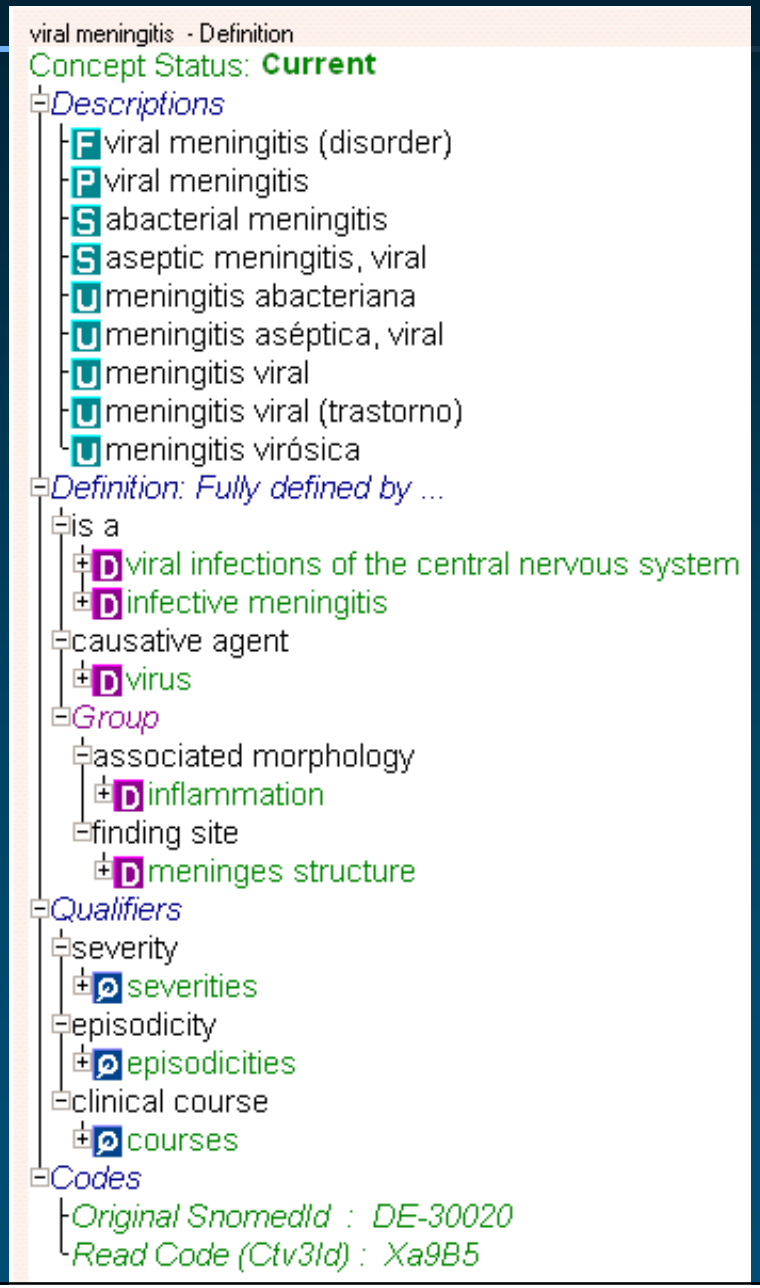
PARENTS		
	Concept ID	FSN for Parent Concept (This Concept IS A)
1	302810003	Viral infections of the central nervous system (disorder)
2	312216007	Infective meningitis (disorder)

http://www.it.usyd.edu.au/~hitru/sct/A1.cgi

SNOMED CT CliniClue

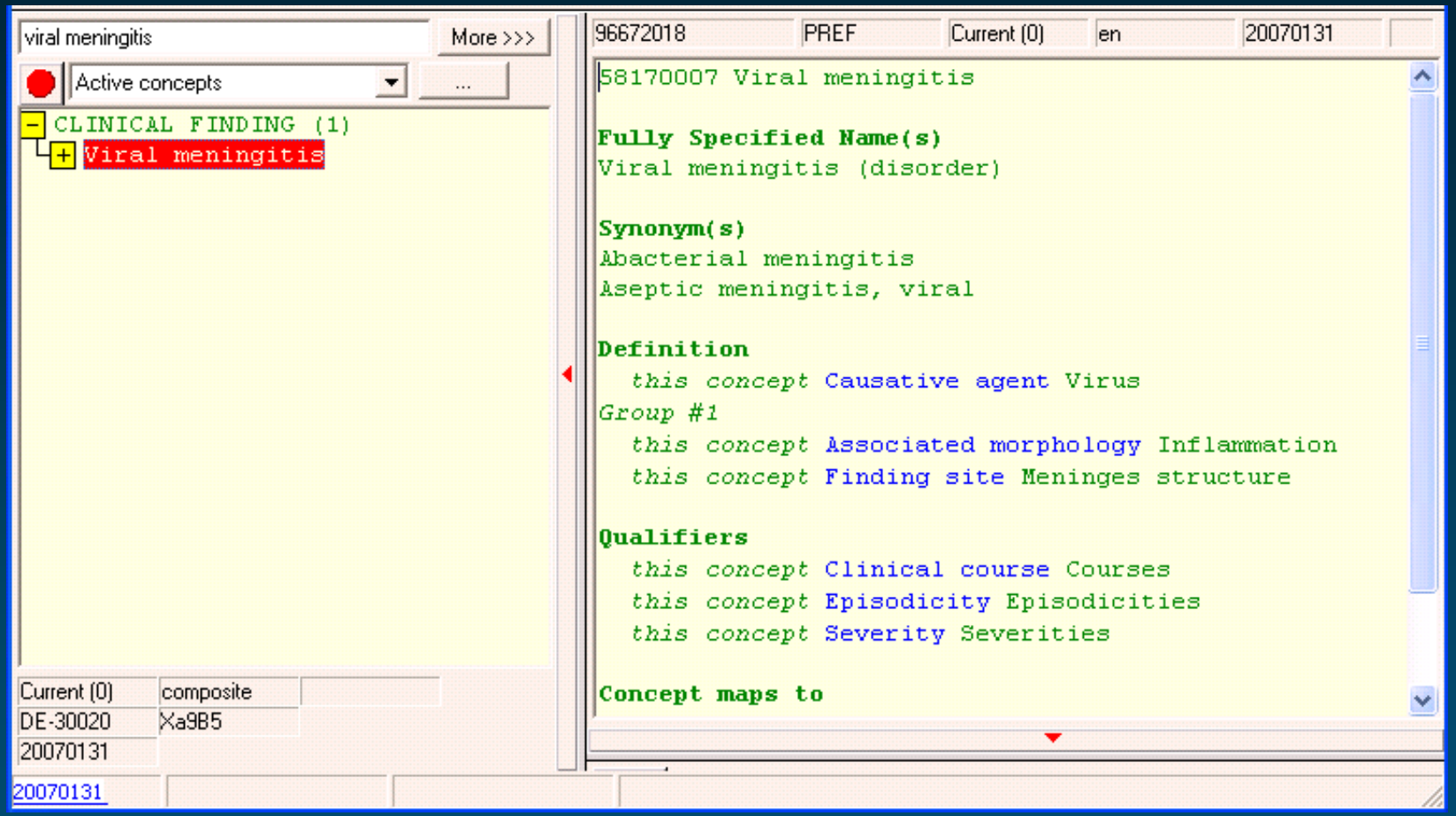


www.cliniclue.com/



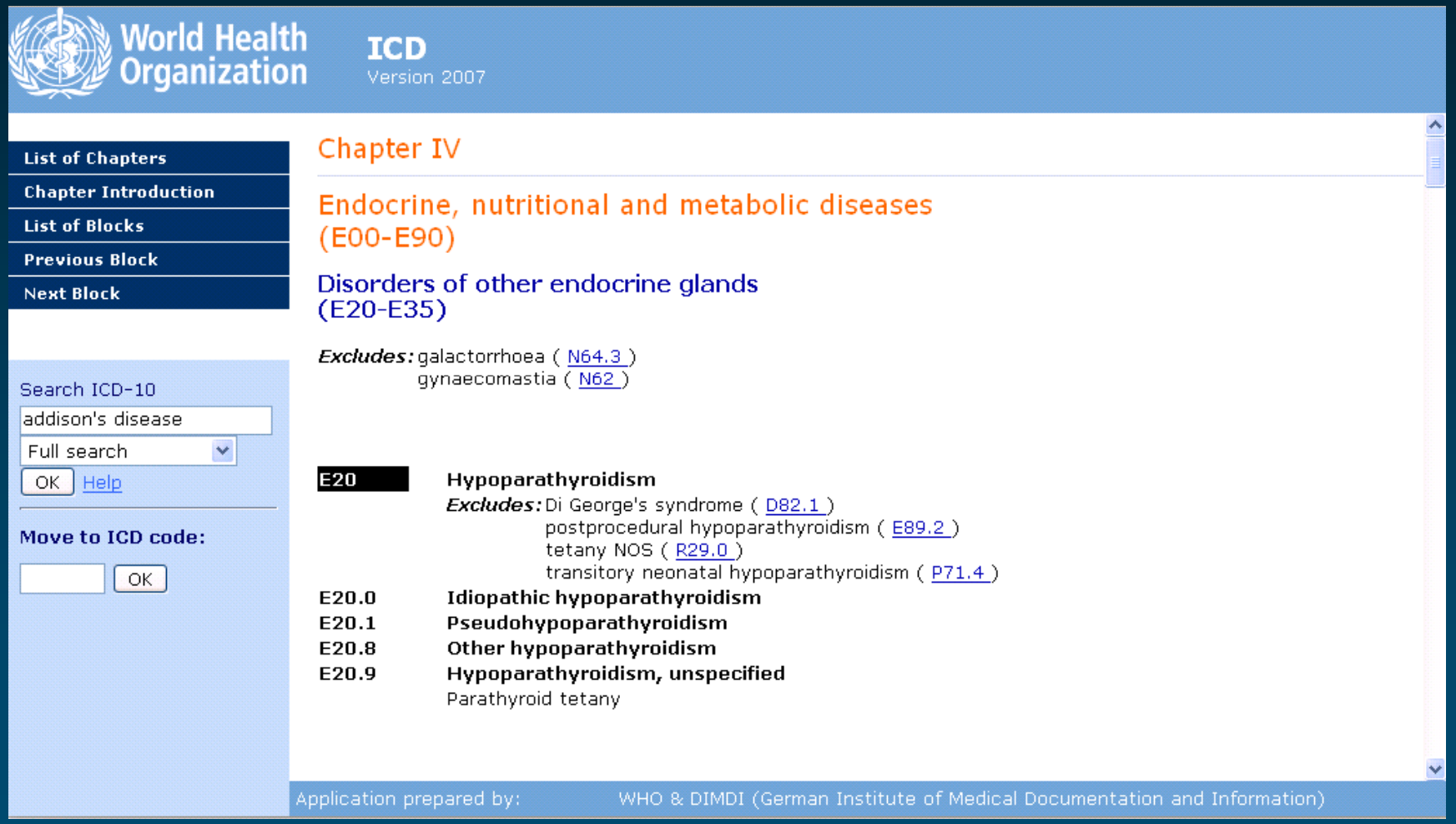
NLM

SNOMED CT SNOB



http://snob.eggbird.eu/

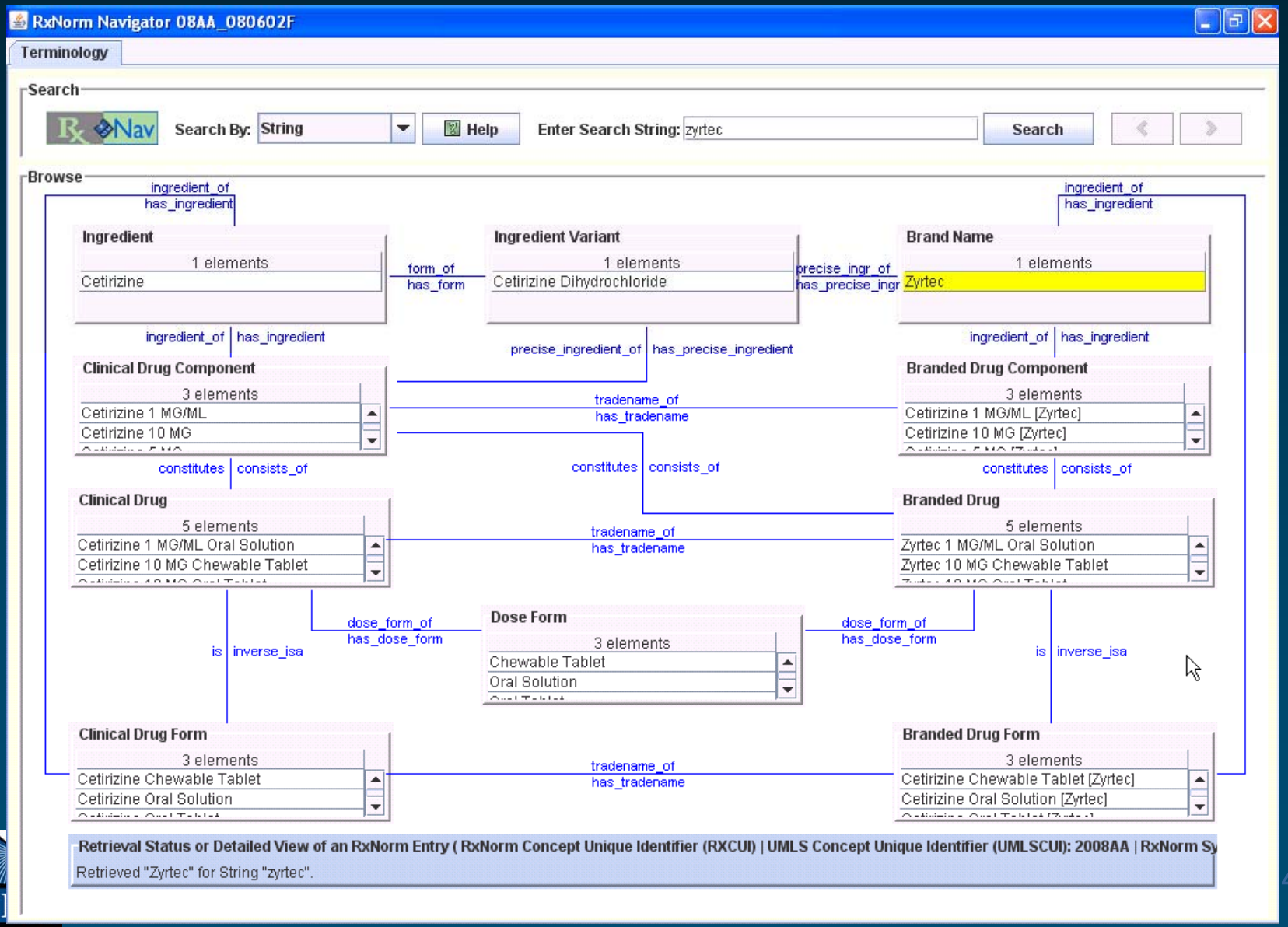
ICD-10



http://www.who.int/classifications/apps/icd/icd10online/

RxNav (RxNorm)

http://mor.nlm.nih.gov/download/rxnav/



Application Programming Interfaces

Application Programming Interface

- Expose resources in such a way that they can be integrated in programs
  - Programming “against” a resource
- Standard protocols for communication
  - Web services (SOAP, REST)
- Standard libraries for programming
- Focus on content, not message

UMLSKS Web Service API

- UMLSKS http://umlsks.nlm.nih.gov/
  - Developer's Guide > Webservice Operations
- WSDL available
- API give access to all 3 knowledge sources
- Licensing issues
  - Granting ticket and Single-use tickets

UMLSKS Web Service API Example

```
ConceptIdGroup findCUIByNormString
    (ConceptIdNormStringRequest request);
```

Argument: ConceptIdNormStringRequest

This class contains the arguments that further restrict the behavior of the call.

```
setCasTicket (String s)
    - Single-use ticket returned by the AuthorizationPort webservice
setRelease (String s)
    - UMLS release of interest
setSearchString (String s)
    - input search string
setSABs (String[] array)
    - set of source abbreviations to search
setLanguage (String s)
    - language restriction
setIncludeSuppressibles (boolean b)
    - true if suppressible strings are included in the search
setCVF (long l)
    - Bit flag for the content view to search
```

Return: ConceptIdGroup

Other APIs to terminology systems

- NCBO BioPortal
  http://www.bioontology.org/docs/bioportal/development/web_services.html
- OLS - Ontology Lookup Service
  http://www.ebi.ac.uk/ontology-lookup/WSDLDocumentation.do
- RxNorm
  http://mor.nlm.nih.gov/download/rxnav/RxNormAPI.html

Applications based on WS APIs

- UMLSKS API
  - UMLSKS
    http://umlsks.nlm.nih.gov/
- RxNorm API
  - RxNav
    http://mor.nlm.nih.gov/download/rxnav/rxnav.jnlp
  - MyMedicationList
    http://mml.nlm.nih.gov/MyMedicationList.jnlp

Agenda

Monday, June 9	Introduction to Biomedical Ontologies	Design Principles, Formalisms and Tools for Biomedical Ontologies	Biomedical Ontologies - Content and structure - Function
Tuesday, June 10	Interfaces to Biomedical Ontologies	Searching and Analyzing Biomedical Concepts	Contrasting Biomedical Ontologies
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Short course – Summer 2008
Biomedical Ontology in Practice

June 10, 2008 – Session #2

Searching and Analyzing Biomedical Concepts

Olivier Bodenreider

Lister Hill National Center
for Biomedical Communications
Bethesda, Maryland - USA

Exercise 1

- What are the Clinical Drug Components for Zyrtec? (RxNav)

Exercise 2

- What are the parts of the Aorta? (FMA)

Exercise 3

- What are the parents of Hodgkin's disease in SNOMED CT?
  - Try SNOMEDCTID: 118599009
- What is its associated morphology?

Exercise 4

- What are the various meanings of IL-2? (UMLS)

Exercise 5

- What are the pharmacologic actions of Zyrtec? (MeSH)

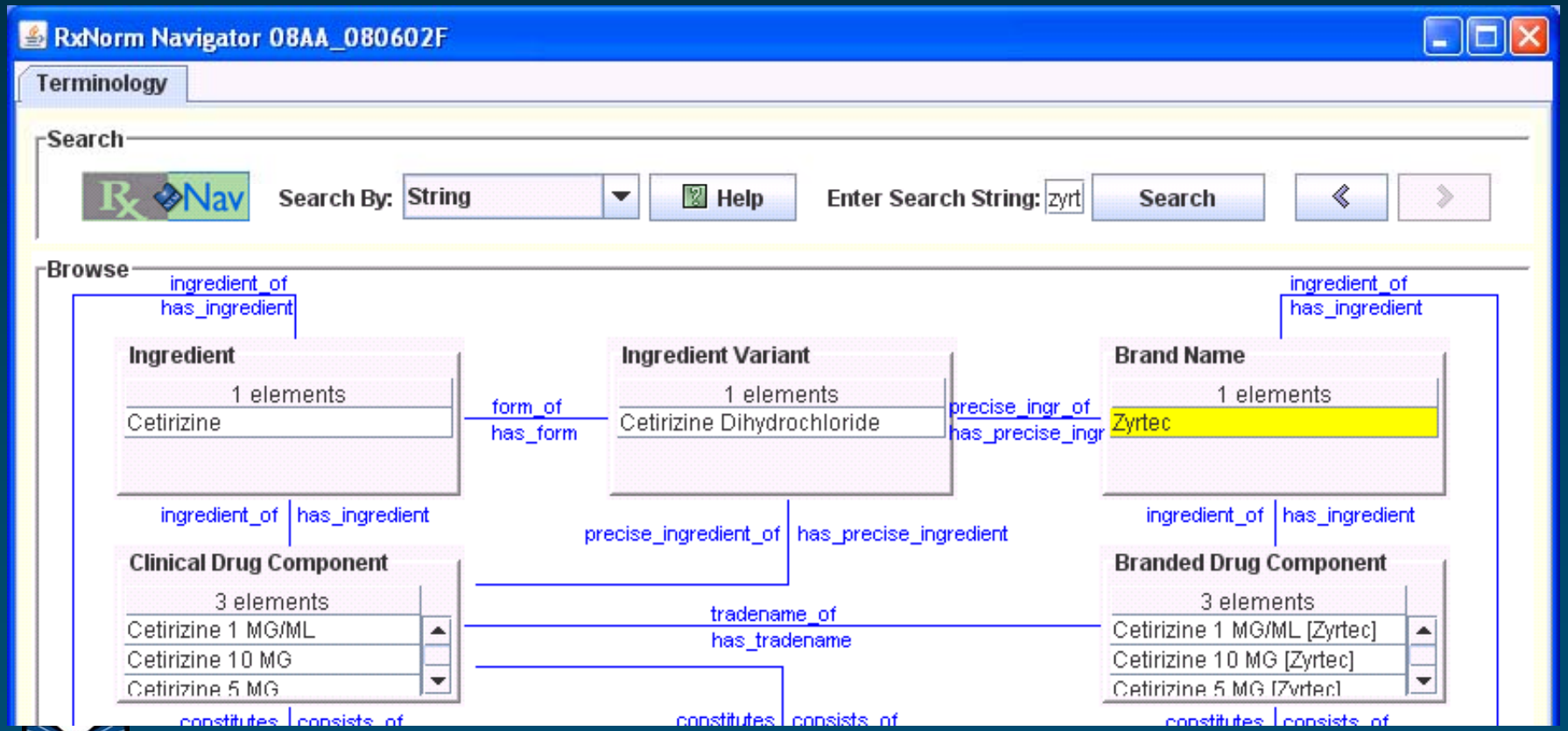
Exercise 6

- What are some synonyms for Schwannoma? (NCI Thesaurus)

Solutions

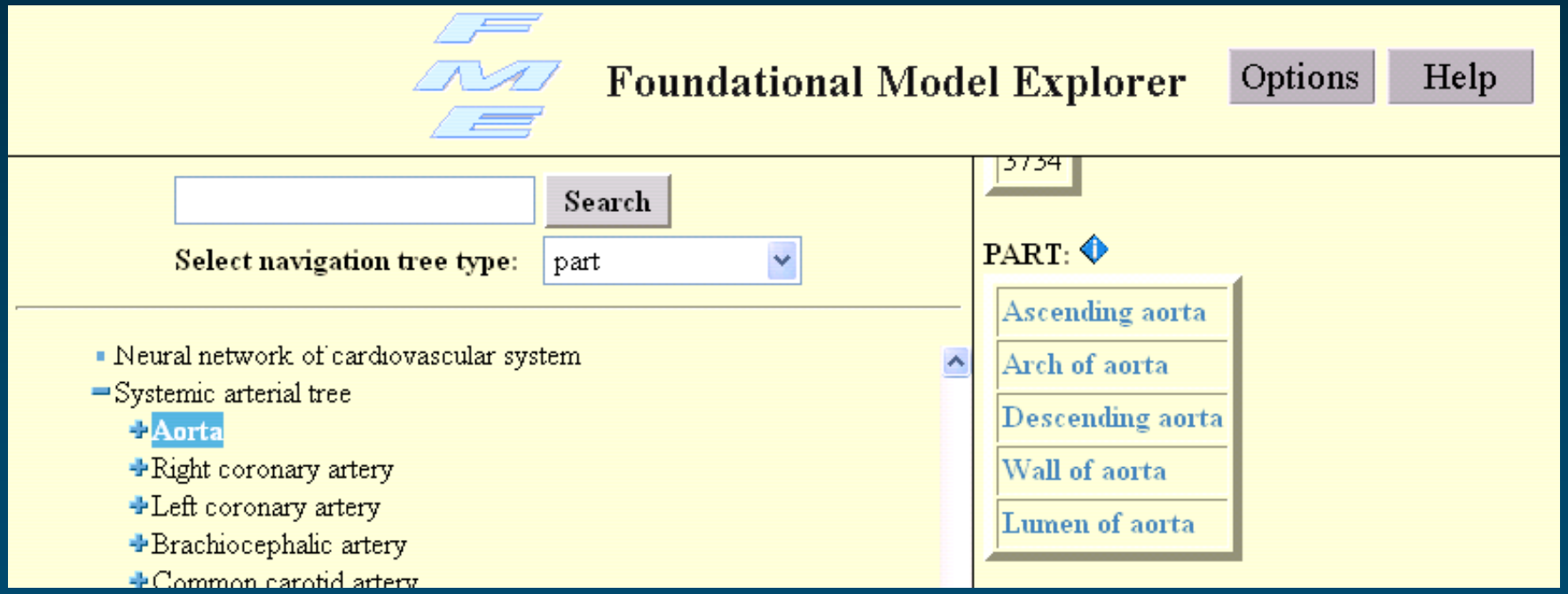
Exercise 1

- What are the Clinical Drug Components for Zyrtec? (RxNav)



Exercise 2

- What are the parts of the Aorta? (FMA)



Exercise 3

- What are the parents of Hodgkin's disease in SNOMED DT?
  - Try SNOMEDCTID: 118599009
- What is its associated morphology?

CONCEPT

Concept ID	Fully Specified Name	Concept Status	CTV3ID	SNOMED ID	Is Primitive
118599009	Hodgkin's disease (disorder)	Current (0)	B61..	DC-F1000	Fully defined (0)

PARENTS

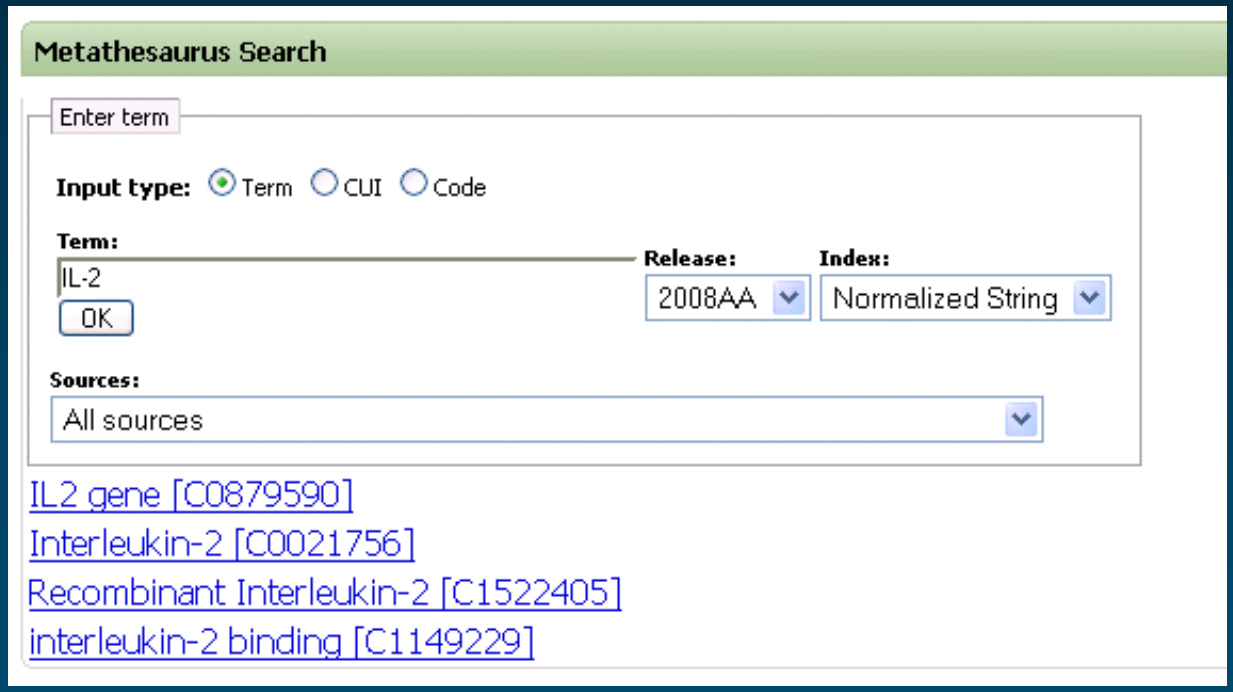
	Concept ID	FSN for Parent Concept (This Concept IS A)
1	118600007	Malignant lymphoma (disorder)

ATTRIBUTES

	Concept ID	FSN for Target Concept	Relationship Type	Values
1	288526004	Episodicities (qualifier value)	Episodicity (attribute)	{New episode; Ongoing episode; Old episode; Undefined episodicity; Other episode RCGP; First episode}
2	128930002	Hodgkin lymphoma - category (morphologic abnormality)	Associated morphology (attribute)	{Hodgkin lymphoma, lymphocyte-rich; Hodgkin lymphoma, no ICD-O subtype; Hodgkin lymphoma, lymphocyte depletion, diffuse fibrosis; Hodgkin lymphoma, nodular sclerosis, cellular phase; Hodgkin lymphoma, mixed cellularity; Hodgkin lymphoma, nodular sclerosis, grade 2; Hodgkin lymphoma, nodular sclerosis, grade 1; Hodgkin sarcoma [obs]; Hodgkin lymphoma, nodular sclerosis; Hodgkin lymphoma, nodular lymphocyte predominance; Hodgkin lymphoma, lymphocyte depletion, reticular; Hodgkin granuloma [obs]; Hodgkin lymphoma, lymphocyte depletion}

Exercise 4

- What are the various meanings of IL-2? (UMLS)



Exercise 5

- What are the pharmacologic actions of Zyrtec? (MeSH)

Pharm. Action	Anti-Allergic Agents
Pharm. Action	Histamine H1 Antagonists, Non-Sedating

Exercise 6

- What are some synonyms for Schwannoma? (NCI Thesaurus)

Preferred_Name	Schwannoma
Semantic_Type	Neoplastic Process
Synonym	Neurilemmoma
Synonym	Neurinoma
Synonym	Schwannoma
Synonym	schwannoma

What to look for

- Search modalities
  - Spelling correction / auto-completion / normalization
  - Word combinations (AND/OR)
- Visualization
  - Graph vs. (forest of) trees
- Navigation
- What properties are displayed

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Short course – Summer 2008
Biomedical Ontology in Practice

June 10, 2008 – Session #3 / June 11, 2008 – Session #1

Contrasting and Critiquing Biomedical Ontologies

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Lister Hill National Center
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Bethesda, Maryland - USA

Exercise #1

- Hodgkin's disease
  - NCI Thesaurus
  - SNOMED CT

Exercise #2

- Prostate
  - FMA
  - SNOMED CT

Exercise #3

- Cetirizine
  - MeSH
  - SNOMED CT

Solutions

Solutions

Exercise #1

Exercise #1

- Hodgkin's disease
  - NCI Thesaurus
    - Using the NCI browser (EVS)
      http://nciterms.nci.nih.gov/
  - SNOMED CT
    - Using the online browser from U. Sydney
      http://www.cs.usyd.edu.au/~hitru/sct/A3.cgi

Hodgkin's disease in NCIt (1)

URI: http://nciterms.nci.nih.gov:80/NCIBrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&code=C9357
Version: April 2008 (08.04d)

Hodgkin Lymphoma

Identifiers:	
name	Hodgkin_s_Lymphoma
code	C9357
Relationships to other concepts:	
Disease_Has_Primary_Anatomic_Site	Hematopoietic and Lymphatic System
Disease_Has_Normal_Tissue_Origin	Lymphoid Tissue
Disease_Excludes_Normal_Cell_Origin	Myeloid Cell
Disease_Excludes_Normal_Cell_Origin	Plasma Cell
Disease_Has_Abnormal_Cell	Reed-Sternberg Cell
Disease_Has_Associated_Anatomic_Site	Hematopoietic and Lymphatic System
Disease_Has_Normal_Cell_Origin	Mature Lymphocyte
Disease_Has_Primary_Anatomic_Site	Lymphatic System

Superconcepts

- Common Hematopoietic Neoplasm
- Lymphoma

Hodgkin’s disease in NCIt (1)

Information about this concept:	
ALT_DEFINITION	NCI-GLOSS|A malignant disease of the lymphatic system that is characterized by painless enlargement of lymph nodes, the spleen, or other lymphatic tissue. It is sometimes accompanied by symptoms such as fever, weight loss, fatigue, and night sweats.
DEFINITION	NCI|A lymphoma, previously known as Hodgkin's disease, characterized by the presence of Reed-Sternberg cells. There are two distinct subtypes: nodular lymphocyte predominant Hodgkin lymphoma and classical Hodgkin lymphoma. Hodgkin lymphoma has a bimodal age distribution, and involves primarily lymph nodes. Current therapy for Hodgkin lymphoma has resulted in an excellent outcome and cure for the majority of patients.
ICD-O-3_Code	9650/3
Preferred_Name	Hodgkin Lymphoma
Semantic_Type	Neoplastic Process
Synonym	HL
Synonym	Hodgkin Lymphoma
Synonym	Hodgkin's Disease
Synonym	Hodgkin's Lymphoma
Synonym	Hodgkin's disease
Unified Medical Language System Concept Identifier	C0019829

Comments on Hodgkin's disease in NCIt (1)

- Search term: "Hodgkin's disease"
  - Not found, although "Hodgkin's disease" is listed as a synonym
  - Search on "hodgkin", select "Hodgkin lymphoma"
- Parent classes
  - Common hematopoietic neoplasm
    - Not an ontological category
    - Would be better represented through an associative relation (e.g., along the lines of "*has_prevalence* high prevalence")
    - *Isa* overloading

Comments on Hodgkin's disease in NCIt (2)

- Associative relations
  - For cancers, anatomy and morphology are foundational relations
  - Here
    - Anatomy : *Disease_Has_Primary_Anatomic_Site* Hematopoietic and Lymphatic System
    - Morphology: not directly represented (indirectly through *Disease_Has_Normal_Cell_Origin* Mature Lymphocyte)

Hodgkin's disease in SNOMED CT (1)

CONCEPT

Concept ID	Fully Specified Name	Concept Status
118599009	Hodgkin's disease (disorder)	Current (0)

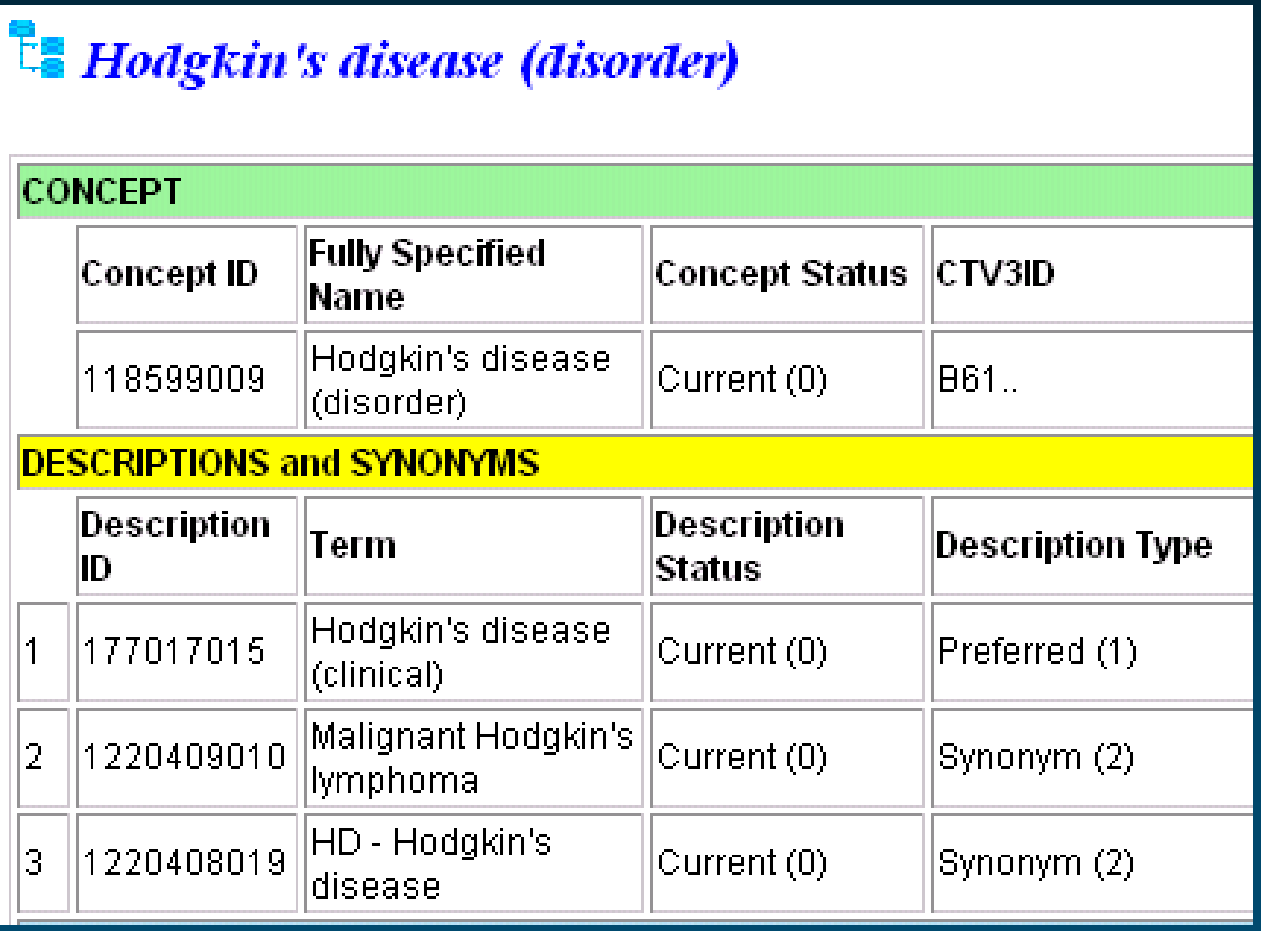
PARENTS

	Concept ID	FSN for Parent Concept (This Concept
1	118600007	Malignant lymphoma (disorder)

ATTRIBUTES

	Concept ID	FSN for Target Concept	Relationship Type
1	288526004	Episodicities (qualifier value)	Episodicity (attribute)
2	128930002	Hodgkin lymphoma - category (morphologic abnormality)	Associated morphology (attribute)

Hodgkin's disease in SNOMED CT (2)



Hodgkin's disease (disorder)

CONCEPT

Concept ID	Fully Specified Name	Concept Status	CTV3ID
118599009	Hodgkin's disease (disorder)	Current (0)	B61..

DESCRIPTIONS and SYNONYMS

	Description ID	Term	Description Status	Description Type
1	177017015	Hodgkin's disease (clinical)	Current (0)	Preferred (1)
2	1220409010	Malignant Hodgkin's lymphoma	Current (0)	Synonym (2)
3	1220408019	HD - Hodgkin's disease	Current (0)	Synonym (2)

Comments on Hodgkin's disease in SNOMED CT (1)

- Search term: "Hodgkin's disease"
  - Not found, although "Hodgkin's disease" is listed as a synonym
    - Search result: "Hodgkin lymphoma, nodular sclerosis, grade 1 (morphologic abnormality)"
  - Search on "lymphoma", navigate down from "Malignant lymphoma"
  - "hodgkin's disease" is ambiguous
    - Hodgkin lymphoma, no ICD-O subtype (morphologic abnormality)
    - Hodgkin's disease (disorder)
  - "Malignant lymphoma, Hodgkin's"
    - NB: lymphoma is always malignant
- Parent classes
  - Malignant lymphoma (clinical) [OK]

Comments on Hodgkin's disease in SNOMED CT (2)

- Associative relations
  - For cancers, anatomy and morphology are foundational relations
  - Here
    - Anatomy : not directly represented (indirectly through descendant concepts, e.g., Hodgkin's disease of intrathoracic lymph nodes)
    - Morphology: *Associated morphology* Hodgkin lymphoma - category

Hodgkin's disease NCIt vs. SNOMED CT (1)

- Shared synonyms: NCIt 1/2, SNOMED CT 1/3
  - Hodgkin's disease
- Shared relations
  - *Isa*
    - NCIt: Lymphoma
      - Definition: "malignant (clonal) proliferation of B-lymphocytes or T- lymphocytes which involves the lymph nodes, bone marrow and/or extranodal sites. This category includes Non-Hodgkin lymphomas and Hodgkin lymphomas."
    - SNOMED CT: Malignant lymphoma
    - Same UMLS concept (CUI: C0024299)

Hodgkin's disease NCIt vs. SNOMED CT (2)

- Shared relations: Associative relations
  - Anatomy
    - In NCIt, but not in SNOMED CT
  - Morphology
    - In SNOMED CT, but not in NCIt
      - Only indirectly, though cell type
  - Cell type
    - Only in NCIt

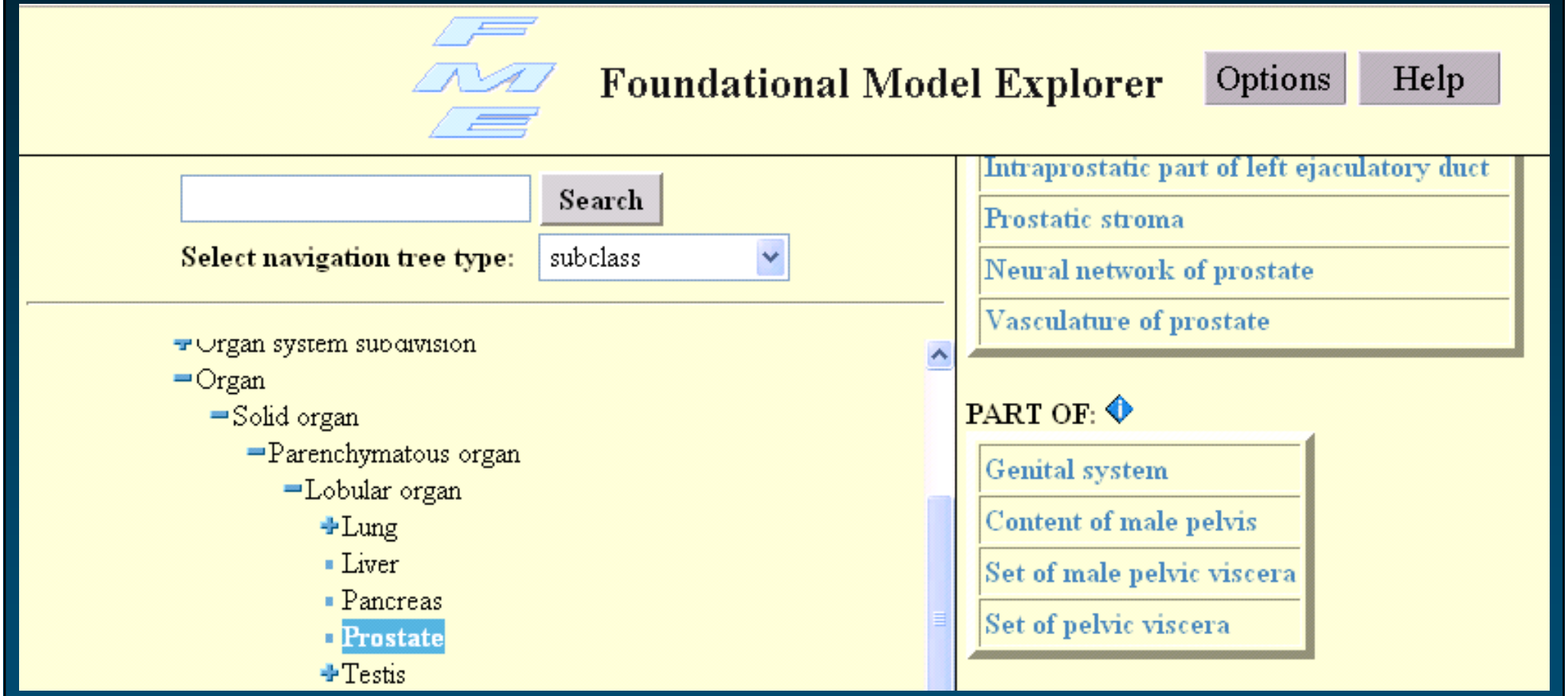
Solutions

Exercise #2

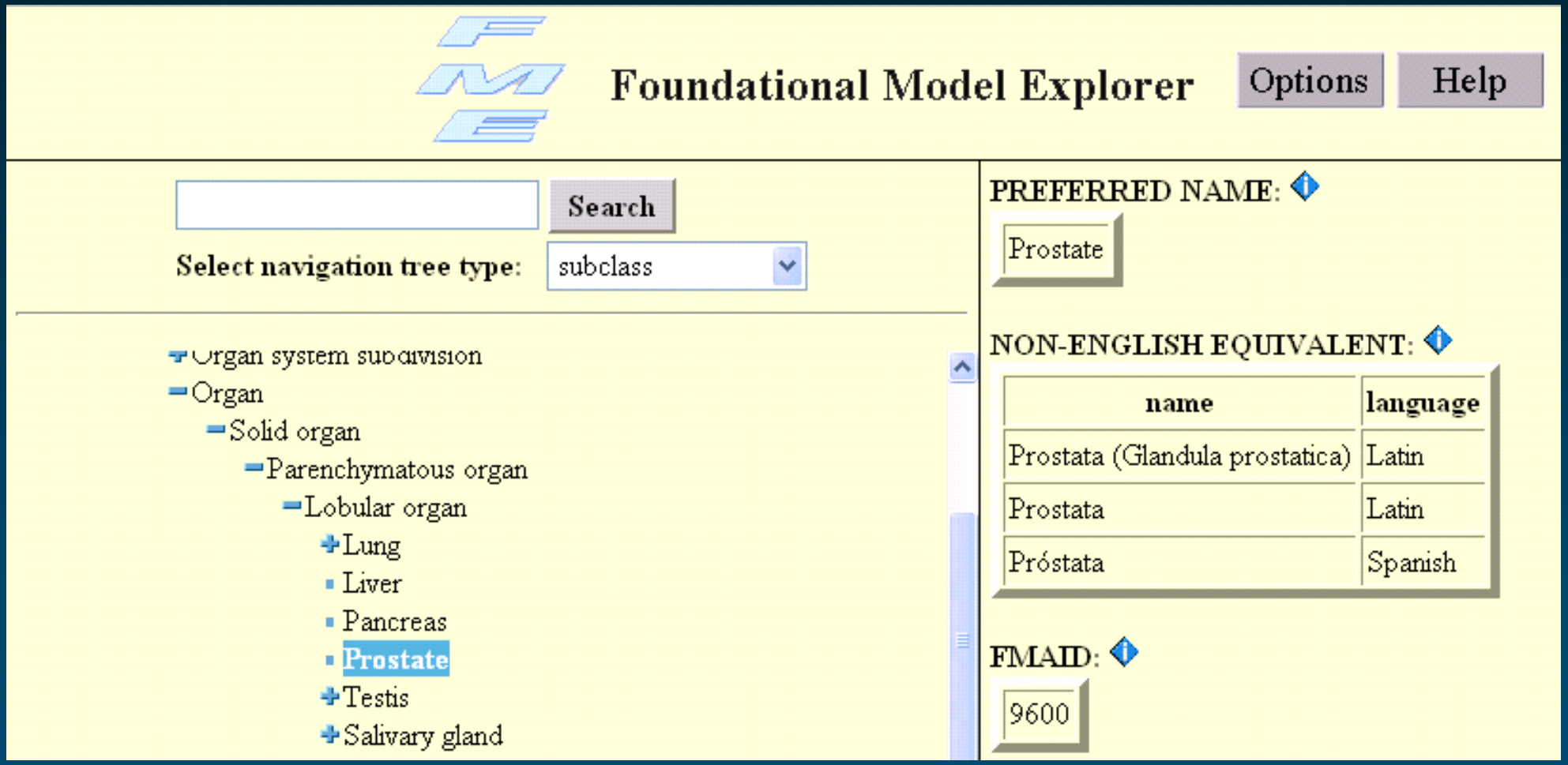
Exercise #2

- Prostate
  - FMA
    - Using the Foundational Model Explorer
      http://sig.biostr.washington.edu/projects/fm/FME/
  - SNOMED CT
    - Using the online browser from U. Sydney
      http://www.cs.usyd.edu.au/~hitru/sct/A3.cgi

Prostate in FMA (1)



Prostate in FMA (2)



Comments on Prostate in FMA

- No synonyms in English
  - Latin and Spanish synonyms
- Hierarchies
  - *Isa*: Lobular organ
  - *Part_of*: Set of pelvic viscera
- Associative relations
  - *Lymphatic drainage*
  - No spatial relations

Prostate in SNOMED CT (1)

435 results found for prostate:

Previous Next

#	Concept ID	Fully Specified Name	Preferred Terms and Synonyms
1	9713002	Prostatitis (disorder)	Inflammation of prostate- Prostatitis [PT]- Prostatitis, NOS
2	11441004	Prostatism (disorder)	Prostatism [PT]- Prostatism, NOS
3	41216001	Prostatic structure (body structure)	Prostatic structure [PT]- Prostate- Prostate, NOS
4	181422007	Entire prostate (body structure)	Entire prostate [PT]- Prostate

CONCEPT

Concept ID	Fully Specified Name
181422007	Entire prostate (body structure)

DESCRIPTIONS and SYNONYMS

	Description ID	Term
1	280451017	Entire prostate
2	280452012	Prostate

PARENTS

	Concept ID	FSN for Parent Concept (This Concept IS A)
1	310536002	Male internal genital organ (body structure)
2	41216001	Prostatic structure (body structure)
3	300443000	Entire male genital organ (body structure)

Prostate in SNOMED CT (2)

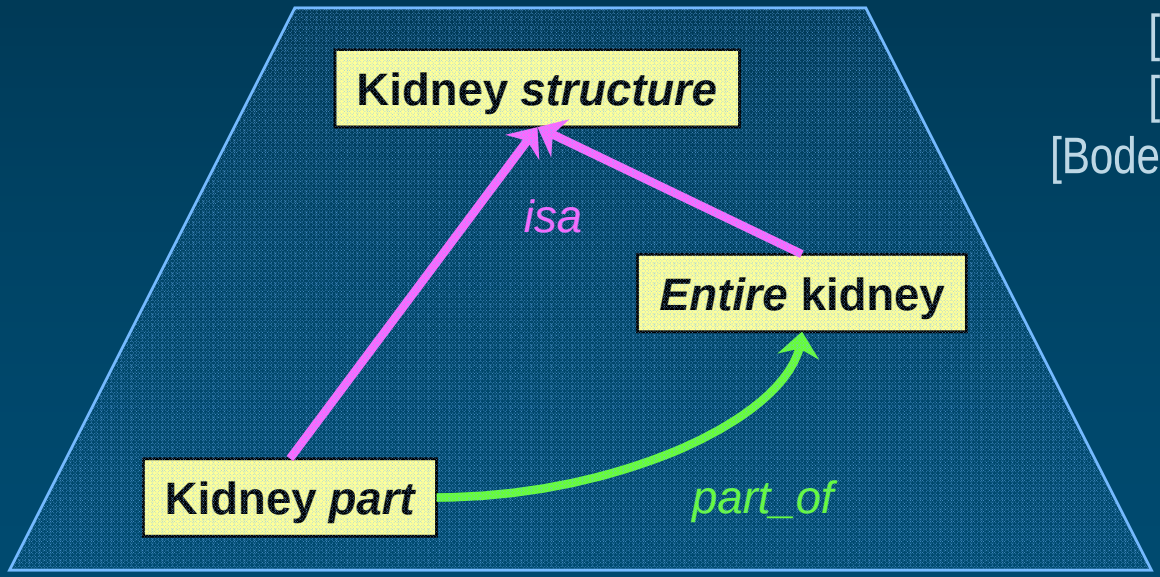
ATTRIBUTES			
	Concept ID	FSN for Target Concept	Relationship Type
1	118760003	Entire viscus (body structure)	Part of (attribute)
2	245461005	Entire urinary tract (body structure)	Part of (attribute)
3	362265004	Entire male internal genitalia (body structure)	Part of (attribute)
4	362267007	Entire lower male genitourinary tract (body structure)	Part of (attribute)
5	362717004	Entire minor pelvis (body structure)	Part of (attribute)
6	362206001	Entire lower genitourinary tract (body structure)	Part of (attribute)
7	361340001	Entire male genital system (body structure)	Part of (attribute)
8	302553009	Entire abdomen (body structure)	Part of (attribute)

Comments on Prostate in SNOMED CT

- "Ambiguous" term
  - Entire prostate
  - Prostatic structure
- Structure-Entire-Part representation of anatomical entities in SNOMED CT
  - Reification of *part_of*
  - Enables mereological inference through *isa* hierarchy
  - Not intuitive

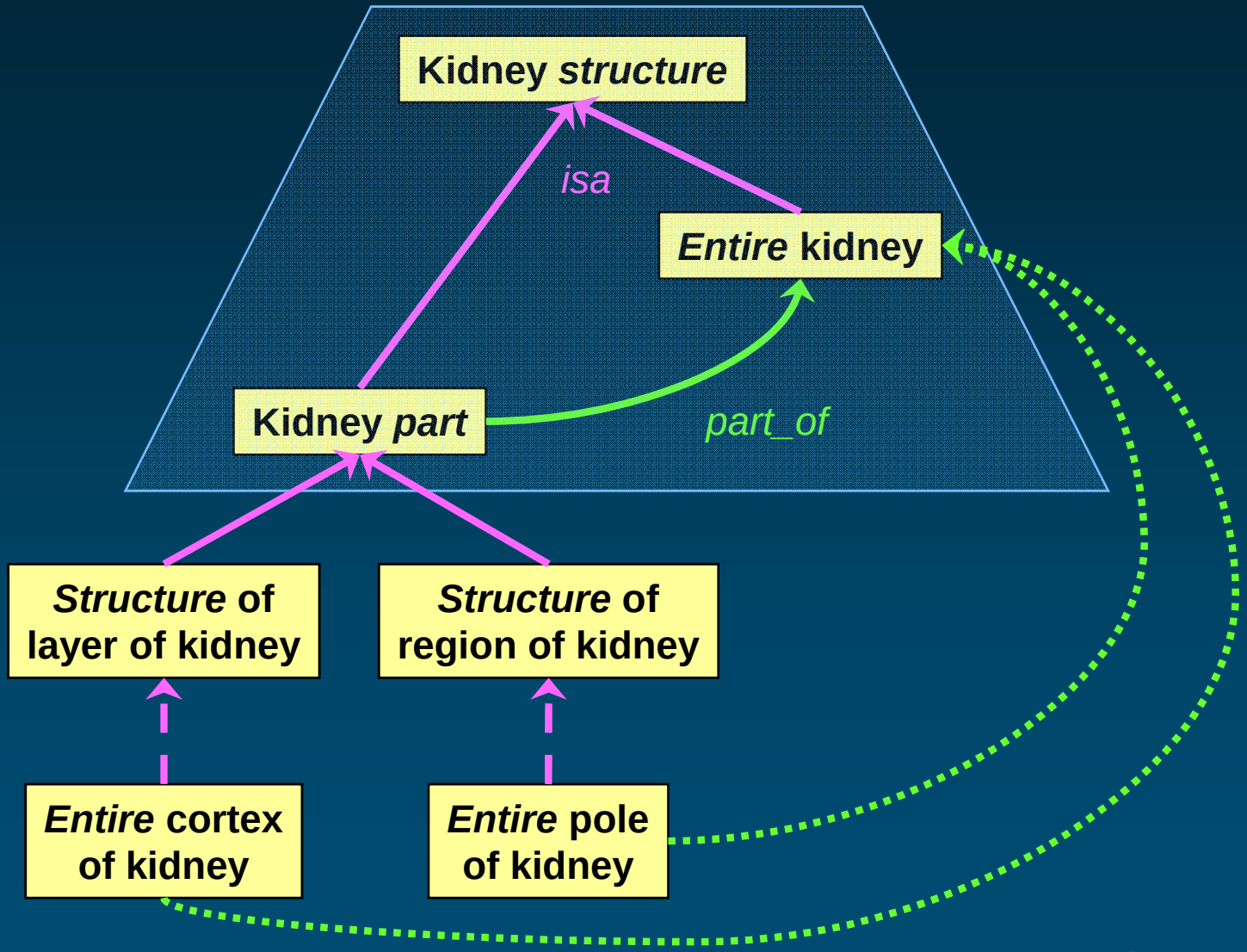
Structure-Entire-Part (SEP) triples

- S – The entity or any of its parts — **X *structure***
- E – The entire anatomical entity — ***Entire* X**
- P – Any parts of the anatomical entity — **X *part***



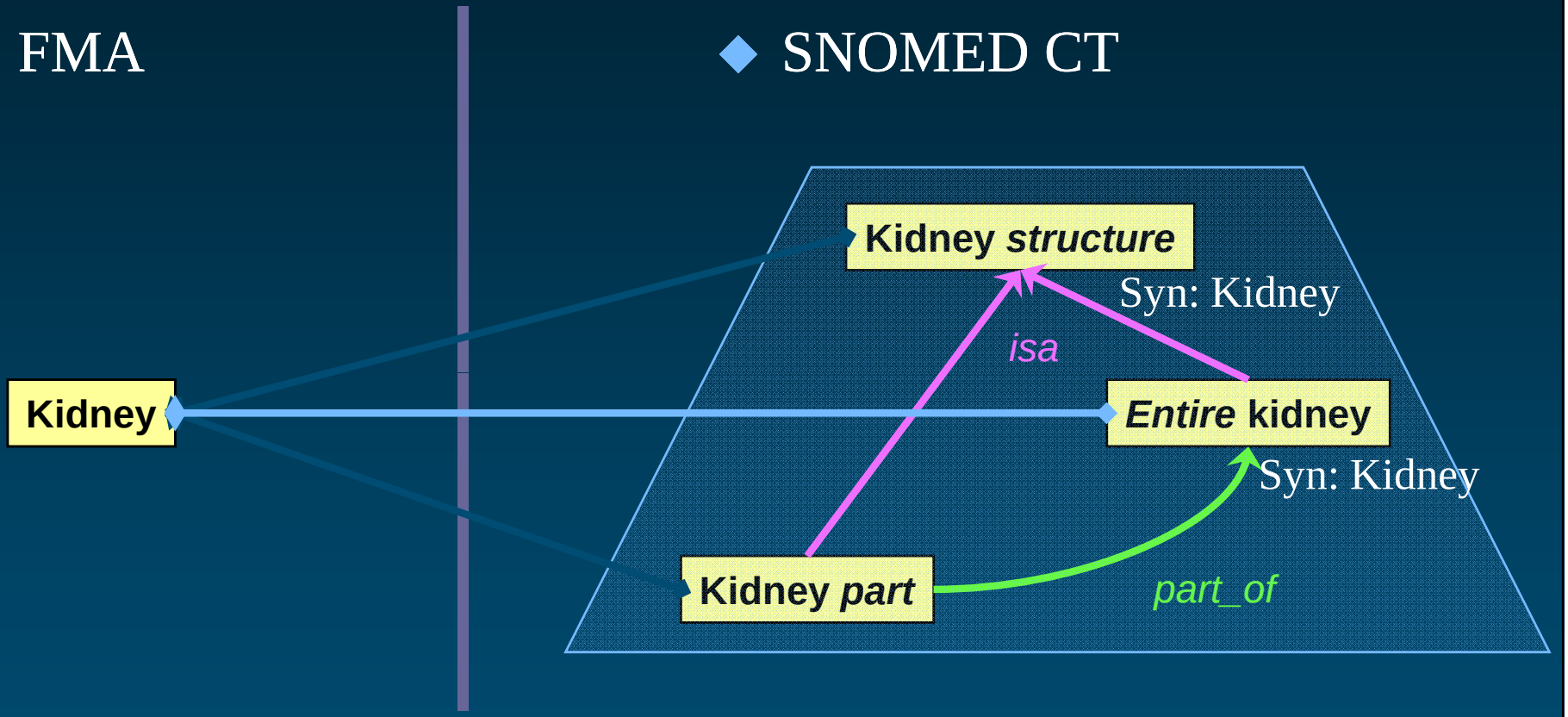
[Schulz & al., 1997]
[Schulz & al., 1998]
[Bodenreider et al, 2006]

Mereological inference through *isa*



FMA mapping goes to *Entire*

- FMA
- SNOMED CT



Prostate FMA vs. SNOMED CT

- Shared synonyms: FMA 1/1, SNOMED CT 1/2
  - Prostate
- Shared relations
  - *Isa*: no
    - FMA
      - Lobular organ
    - SNOMED CT
      - Prostatic structure
      - Male internal genital organ
      - Entire male genital organ

Prostate FMA vs. SNOMED CT

- Shared relations
  - *Part of*: almost
    - FMA
      - Genital system
      - Content of *male* pelvis
      - Set of male pelvic viscera
      - Set of pelvic viscera
    - SNOMED CT
      - Entire minor pelvis
      - Entire *male* genital system
      - …

Solutions

Exercise #3

Exercise #3

- Cetirizine
  - MeSH
    - Using the MeSH browser
      http://www.nlm.nih.gov/mesh/MBrowser.html
  - SNOMED CT
    - Using the online browser from U. Sydney
      http://www.cs.usyd.edu.au/~hitru/sct/A3.cgi

Cetirizine in MeSH (1)

Entry Term	(2-(4-((4-Chlorophenyl)phenylmethyl)-1-piperazinyl)ethoxy)acetic Acid
Entry Term	Alerlisin
Entry Term	Aliud Brand of Cetirizine Dihydrochloride
Entry Term	Alpharma Brand of Cetirizine Dihydrochloride
Entry Term	AWD.pharma Brand of Cetirizine Dihydrochloride
Entry Term	Azupharma Brand of Cetirizine Dihydrochloride
Entry Term	Basics Brand of Cetirizine Dihydrochloride
Entry Term	Cetalerg

• • •

Entry Term	Voltric
Entry Term	Wolff Brand of Cetirizine Dihydrochloride
Entry Term	Wörwag Brand of Cetirizine Dihydrochloride
Entry Term	Zetir
Entry Term	Zirtek
Entry Term	Zyrtec

Cetirizine in MeSH (2)

Heterocyclic Compounds [D03]

Heterocyclic Compounds, 1-Ring [D03.383]

Piperazines [D03.383.606]

Hydroxyzine [D03.383.606.515]

Cetirizine [D03.383.606.515.200]

Pharm. Action	Anti-Allergic Agents
Pharm. Action	Histamine H1 Antagonists, Non-Sedating

Comments on Cetirizine in MeSH

- 45 entry terms
  - Various generic and brand names
  - Chemical formula
  - Code (P-071)
- Hierarchy
  - *Isa*: Piperazines [chemistry]
- Pharmacologic action
  - Anti-Allergic Agents
  - Histamine H1 Antagonists, Non-Sedating

Cetirizine in SNOMED CT (1)

15 results found for cetirizine:

Previous Next

#	Concept ID	Fully Specified Name	Preferred Terms and Synonyms
1	108655000	Cetirizine (product)	Cetirizine [PT]
2	372523007	Cetirizine (substance)	Cetirizine [PT]

Cetirizine (substance)

CONCEPT					
Concept ID	Fully Specified Name	Concept Status	CTV3ID	SNOMED ID	Is Primitive
372523007	Cetirizine (substance)	Current (0)	XUVwU	F-61523	Primitive (1)

DESCRIPTIONS and SYNONYMS						
	Description ID	Term	Description Status	Description Type	Language Code	Initial Capital Status
1	1211057019	Cetirizine	Current (0)	Preferred (1)	en	Capitalization meaningless (0)

PARENTS		
	Concept ID	FSN for Parent Concept (This Concept IS A)
1	372624008	Non-sedating antihistamine (substance)

CHILDREN		
	Concept ID	FSN for Child Concept
1	108656004	Cetirizine hydrochloride (substance)

Cetirizine in SNOMED CT (2)

CONCEPT

	Concept ID	Fully Specified Name	Concept Status	CTV3ID
	108655000	Cetirizine (product)	Current (0)	x01Dq

DESCRIPTIONS and SYNONYMS

	Description ID	Term	Description Status	Description Type
1	173189012	Cetirizine	Current (0)	Preferred (1)

PARENTS

	Concept ID	FSN for Parent Concept (This Concept IS A)
1	349956006	Non-sedating antihistamine (product)

ATTRIBUTES

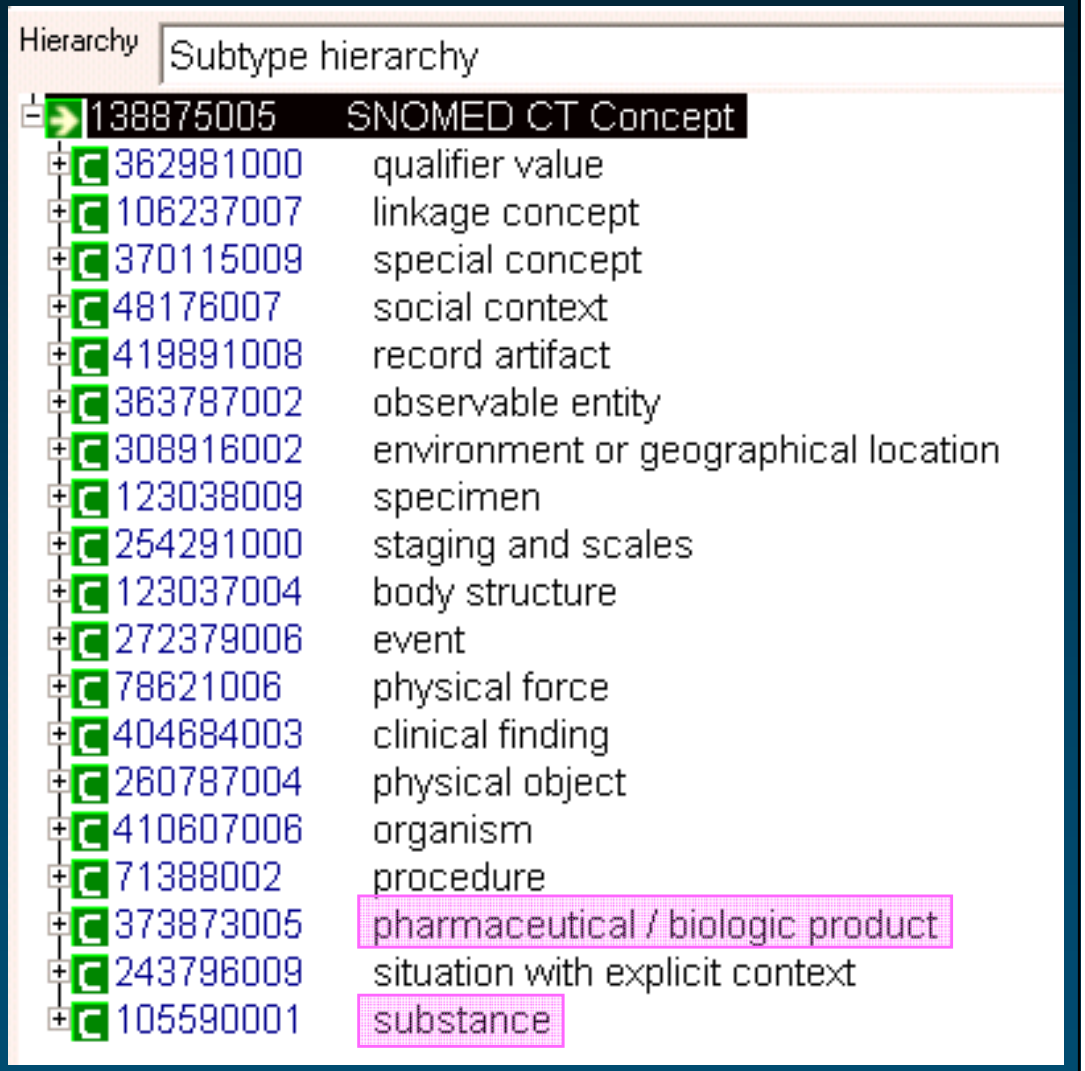
	Concept ID	FSN for Target Concept	Relationship Type	
1	372523007	Cetirizine (substance)	Has active ingredient (attribute)	{Cetirizine hydroc

CHILDREN

	Concept ID	FSN for Child Concept
1	320818006	Cetirizine dihydrochloride 10mg tablet (product)
2	320820009	Cetirizine dihydrochloride 1mg/1mL s/f liquid (product)
3	371746005	Cetirizine dihydrochloride 5mg tablet (product)
4	375571002	Cetirizine hydrochloride 5mg tablet (product)
5	375572009	Cetirizine hydrochloride 10mg tablet (product)
6	375573004	Cetirizine hydrochloride 5mg/5 mL syrup (product)
7	400462001	Cetirizine hydrochloride+pseudoephedrine hydrochloride (product)
8	409491005	Cetirizine hydrochloride 5mg chewable tablet (product)
9	409492003	Cetirizine hydrochloride 10mg chewable tablet (product)

Comments on Cetirizine in SNOMED CT

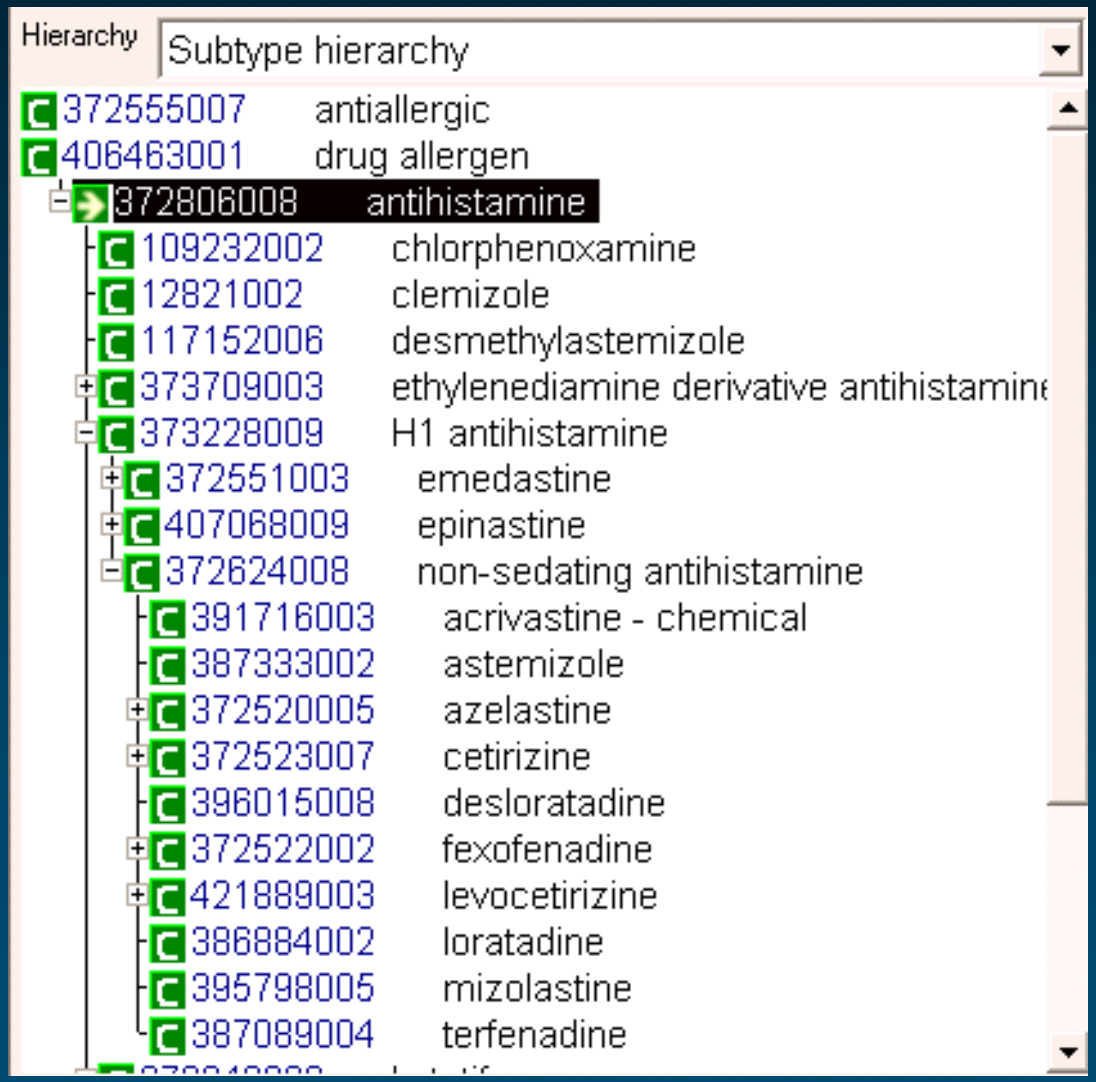
- Ambiguous term
  - Cetirizine (product)
  - Cetirizine (substance)
- Hierarchy
  - *Isa*: Non-sedating antihistamine (substance) [pharmacologic action]
- No associative relations



Cetirizine MeSH vs. SNOMED CT (1)

- Shared synonyms: MeSH 1/45, SNOMED CT 1/1
  - Cetirizine
- Shared relations: none
  - MeSH:
    - *Isa*: <chemistry>
    - Associative: <pharmacologic action>
  - SNOMED CT
    - *Isa*: < pharmacologic action>
    - Associative: none

Cetirizine MeSH vs. SNOMED CT (2)



Summary

- Differing representations
  - Not necessarily inconsistent
  - Consistency may be difficult to assess automatically
- Often due to idiosyncratic representation in one ontology
- Hindrance to ontology alignment and evaluation methods relying on shared relations

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Short course – Summer 2008
Biomedical Ontology in Practice

June 9, 2008 – Session #2

Extending Biomedical Ontologies

Olivier Bodenreider

Lister Hill National Center
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Bethesda, Maryland - USA

Overview

- Corpus terminology
- Identify terms in biomedical text (in reference to the UMLS)
- Identify additional terms
- Place these terms in UMLS hierarchies

[Bodenreider, ACL 2002]

Tiny corpus One MEDLINE abstract

1: Anesth Analg. 2008 Jun;106(6):1813-9.

Related Articles, Links

Full Text Anesth Analg

PMID: 18499615

Free cortisol in sepsis and septic shock.

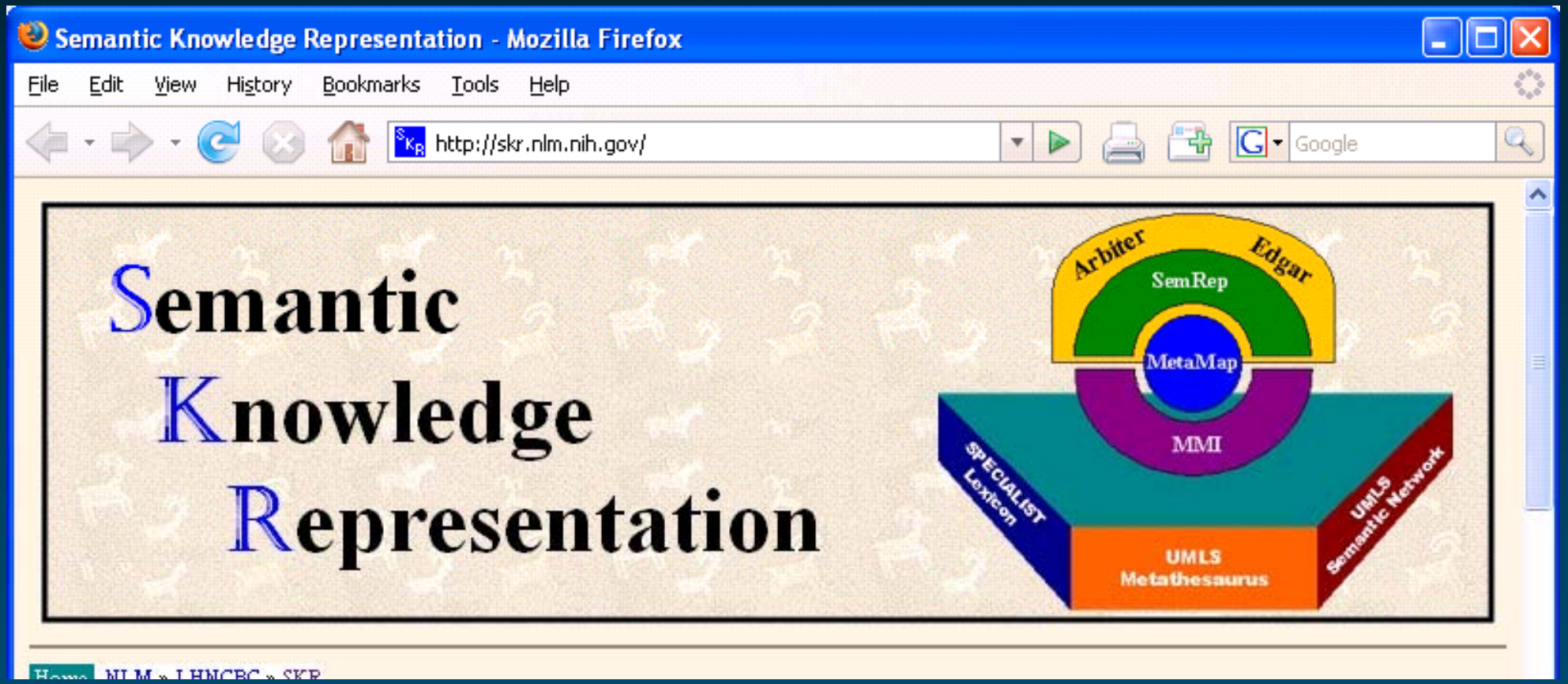
Bendel S, Karlsson S, Pettilä V, Loisa P, Varpula M, Ruokonen E; Finnsepsis Study Group.

Collaborators (26)

Department of Intensive Care, Kuopio University Hospital, PL 16222 Kuopio, Finland. Stepani.Bendel@kuh.fi

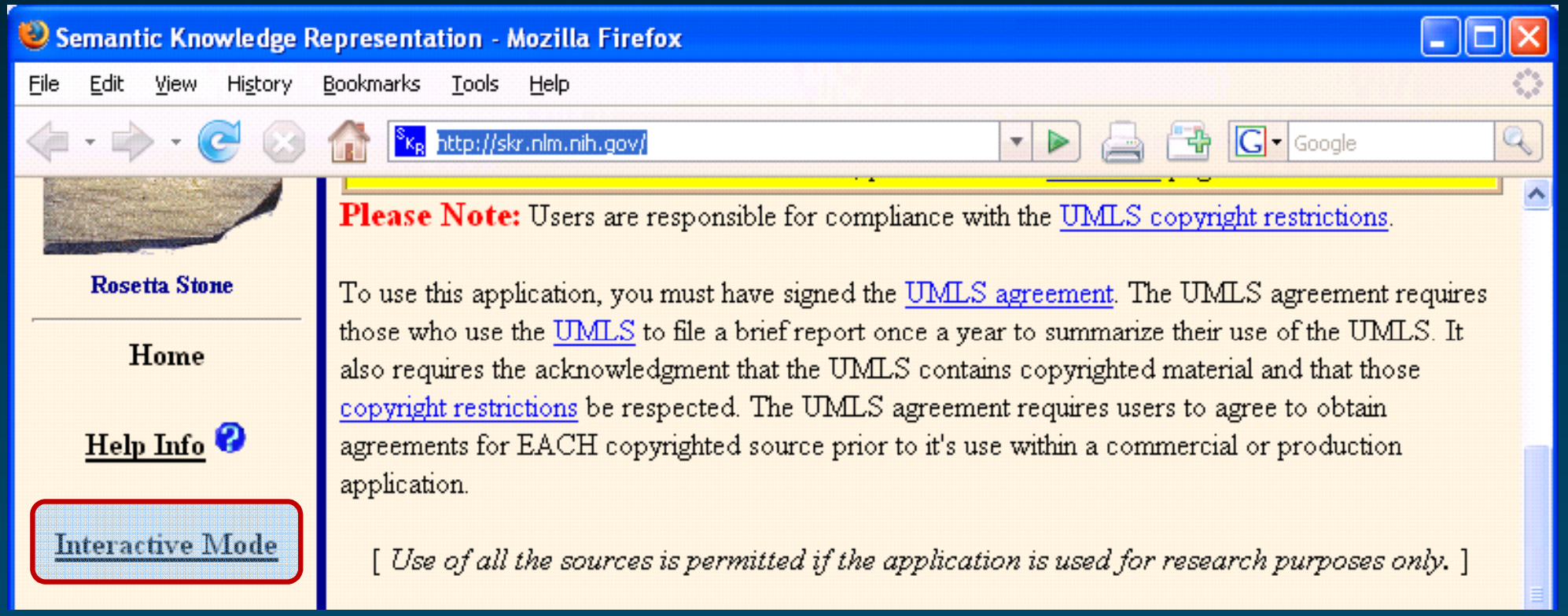
BACKGROUND: Severe sepsis activates the hypothalamopituitary axis, increasing cortisol production. In some studies, hydrocortisone substitution based on an adrenocorticotropic hormone-stimulation test or baseline cortisol measurement has improved outcome. Because only the free fraction of cortisol is active, measurement of free cortisol may be more important than total cortisol in critically ill patients. We measured total and free cortisol in patients with severe sepsis and related the concentrations to outcome. METHODS: In a prospective study, severe sepsis was defined according the American College of Chest Physicians/Society of Critical Care Medicine criteria. Blood samples were drawn within 24 h of study entry. Serum cortisol was analyzed by electrochemiluminescence immunoassay. The Coolens method was used for calculating serum free cortisol concentrations. RESULTS: Blood samples were collected from 125 patients, of whom 62 had severe sepsis and 63 septic shock. Hospital mortality was 21%. Calculated free serum cortisol correlated well with serum total cortisol ($r = 0.90$, $P < 0.001$). There was no difference in the total cortisol concentrations in patients with sepsis and septic shock (728 +/- 386 nmol/L vs 793 +/- 439 nmol/L, $P = 0.44$). Nonsurvivors had higher calculated serum free (209 +/- 151 nmol/L) and total (980 +/- 458 nmol/L) cortisol concentrations than survivors (119 +/- 111 nmol/L, $P = 0.002$, and 704 +/- 383 nmol/L, $P = 0.002$). Depending on the definition, the incidence of adrenal insufficiency varied from 8% to 54%. CONCLUSIONS: Clinically, calculation of free cortisol does not provide essential information for identification of patients who would benefit from corticoid treatment in severe sepsis and septic shock.

Identify UMLS concepts with MetaMap

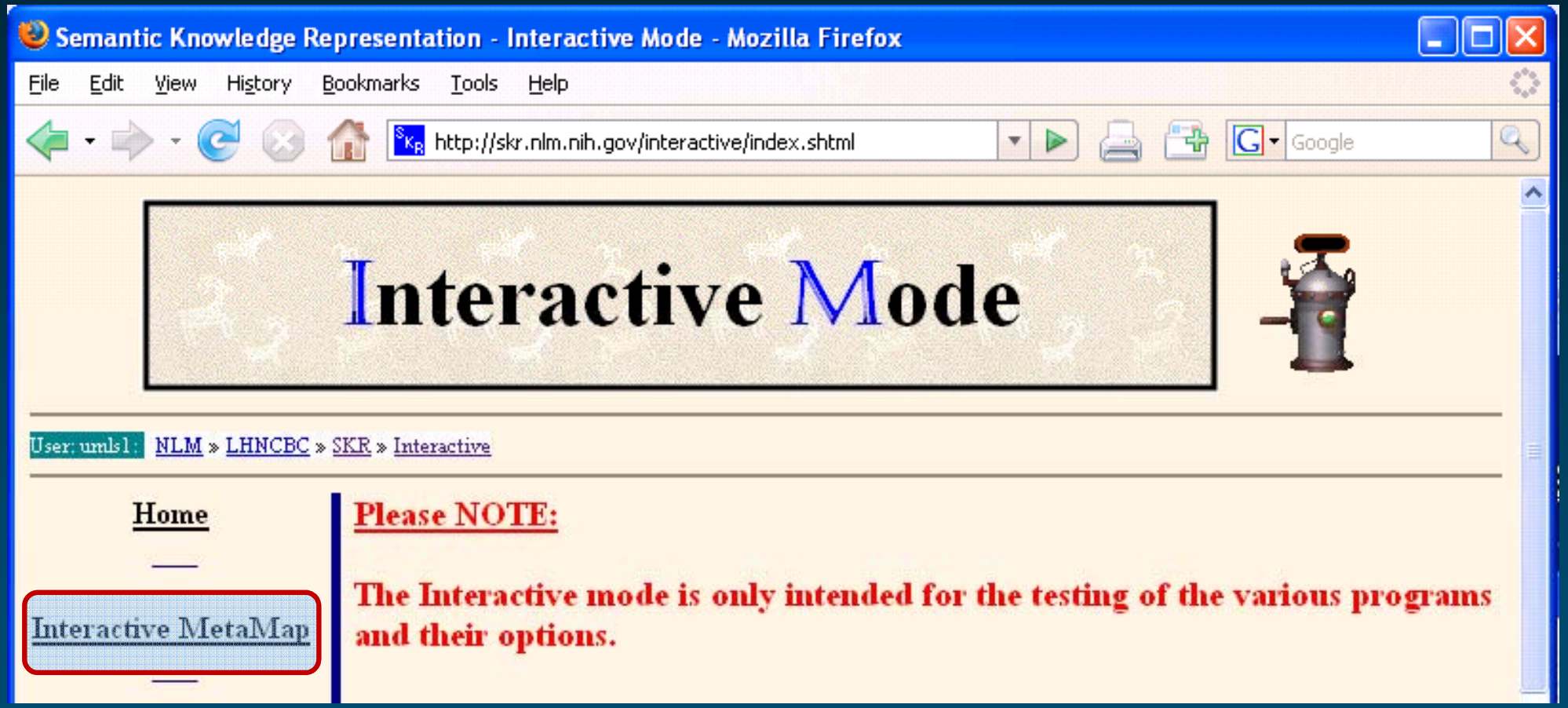


http://skr.nlm.nih.gov/

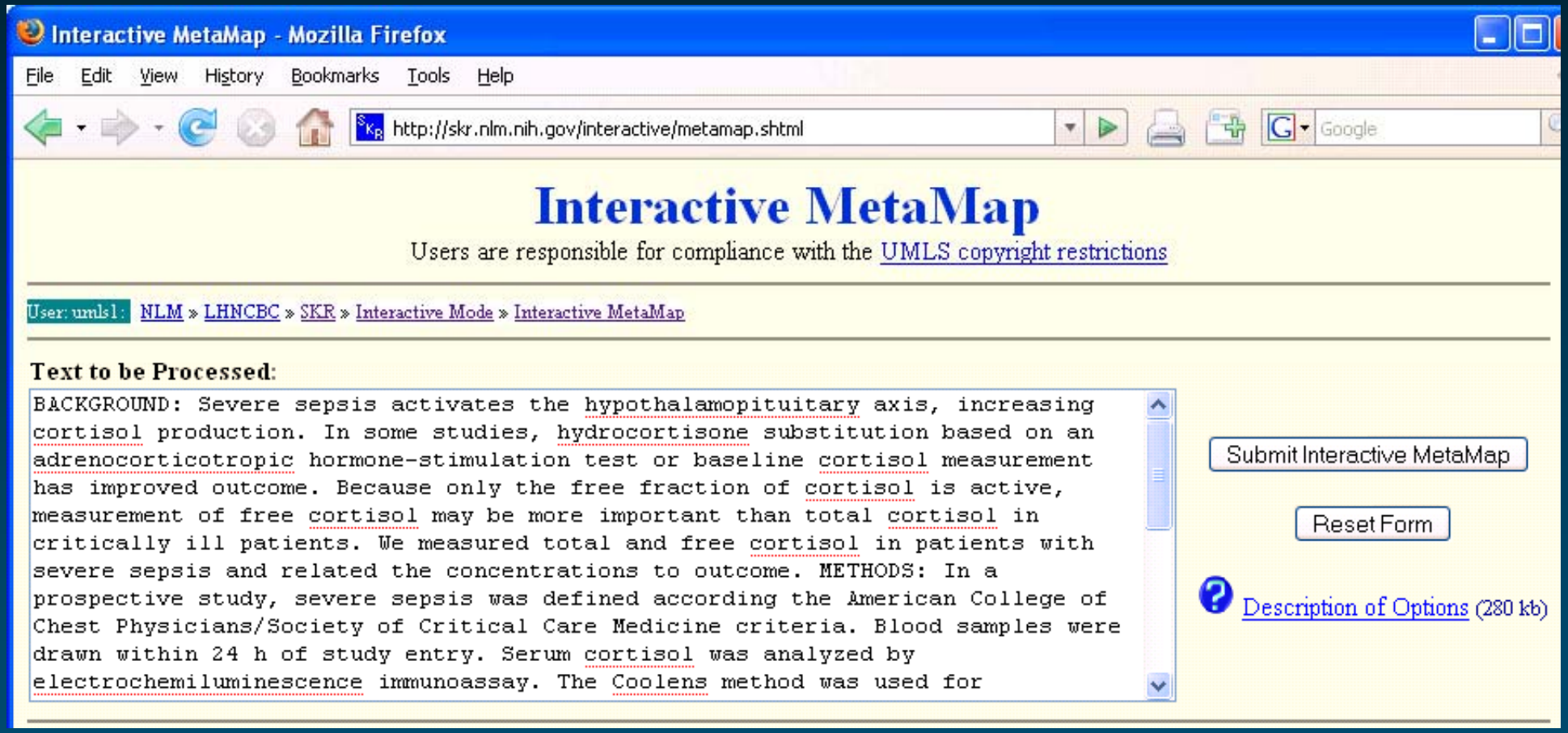
Interactive mode



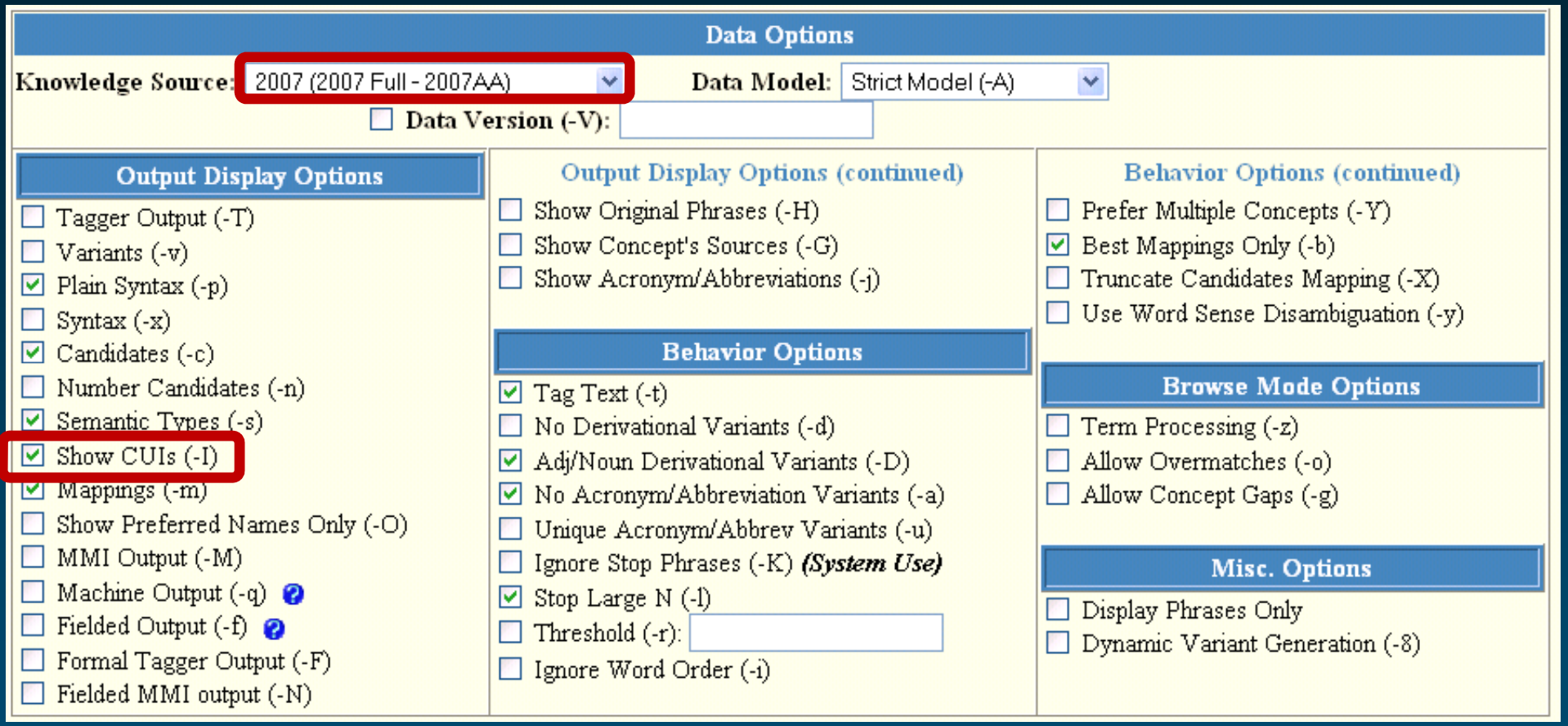
Interactive MetaMap



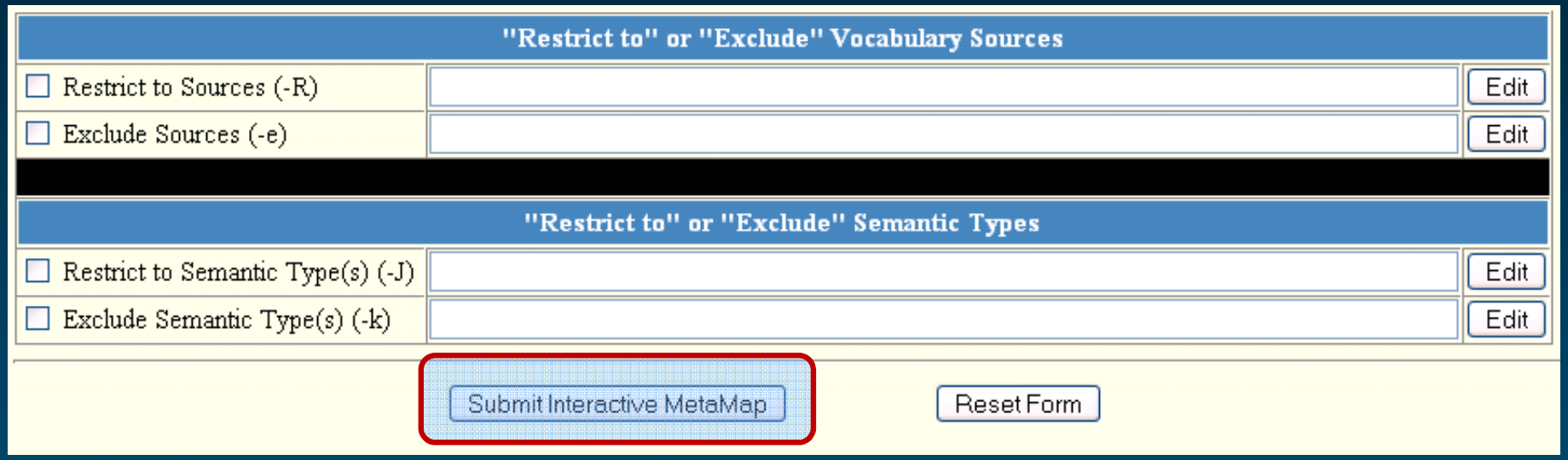
Paste abstract



Select options



Run MetaMap


"Restrict to" or "Exclude" Vocabulary Sources
Restrict to Sources (-R)
Edit
Exclude Sources (-e)
Edit
"Restrict to" or "Exclude" Semantic Types
Restrict to Semantic Type(s) (-J)
Edit
Exclude Semantic Type(s) (-k)
Edit
Submit Interactive MetaMap
Reset Form

Output

```
Processing 00000000.tx.1: BACKGROUND: Severe sepsis activates the hypothalamopituitary
axis, increasing cortisol production.
```

```
Phrase: "Severe sepsis"
>>>>> Phrase
severe sepsis
<<<<< Phrase
>>>>> Candidates
Meta Candidates (8):
  1000 C1719672:Severe Sepsis [Disease or Syndrome]
   861 C0036690:Sepsis (Septicemia) [Disease or Syndrome]
   861 C0243026:Sepsis (Systemic infection) [Disease or Syndrome]
   861 C1090821:Sepsis [Invertebrate]
   789 C0333534:Septic [Functional Concept]
   694 C0205082:Severe [Qualitative Concept]
   694 C1519275:SEVERE (Severe Adverse Event) [Finding]
   694 C1561581:Severe (Allergy Severity - Severe) [Finding]
<<<<< Candidates
>>>>> Mappings
Meta Mapping (1000):
  1000 C1719672:Severe Sepsis [Disease or Syndrome]
<<<<< Mappings
```

Suggest term candidates

- Not recognized by MetaMap ay all
- Partially identified by MetaMap
- Missing terms in a concept

Suggest placement in UMLS

- Use a browser
- Identify close parent
- Examine its children
- Assess placement by comparing with potential siblings

Possible new terms (1)

- Hypothalamopituitary axis
  - Concept exists: C0678897, but missing exact (neoclassical) synonym
    - hypothalamic pituitary axis
    - hypothalamus hypophysis axis
    - hypothalamus-pituitary axis
- American College of Chest Physicians
  - Similar to other American Colleges (e.g., American College of Physicians ())
  - Integrate as a child of Professional Organization or Group (C1522486)
  - NB: instance, cannot be a child of ACP

Possible new terms (2)

- Free cortisol
  - Identified as a substance (C0443476), not a laboratory procedure / test result
    - Cortisol, free measurement (C0236401)
- Coolens method
  - Missing term / concept
  - Method for estimating (not measuring directly) the free fraction of cortisol

Possible new terms (3)

- Electrochemiluminescence immunoassay
  - Missing concept
  - Create as a child of Chemiluminescence assay (C0201709)
- Nonsurvivors
  - Survivors exists as a concept (C0206194)
  - Create as a child of Patients (C0030705)

Agenda

Monday, June 9	Introduction to Biomedical Ontologies	Design Principles, Formalisms and Tools for Biomedical Ontologies	Biomedical Ontologies - Content and structure - Function
Tuesday, June 10	Interfaces to Biomedical Ontologies	Searching and Analyzing Biomedical Concepts	Contrasting Biomedical Ontologies
Wednesday, June 11	Critical Analysis of Biomedical Ontologies	Extending Biomedical Ontologies	Using Biomedical Ontologies for Data Integration

Short course – Summer 2008
Biomedical Ontology in Practice

June 11, 2008 – Session #3

Using Biomedical Ontologies for Data Integration

Olivier Bodenreider

Lister Hill National Center
for Biomedical Communications
Bethesda, Maryland - USA

Overview

- Motivation
- Some practical considerations and issues
  - Integration approaches
  - Concept repositories
  - Using existing mappings
  - Creating mappings through the UMLS
  - Comparing semantic descriptions
- Thinking outside the integration box

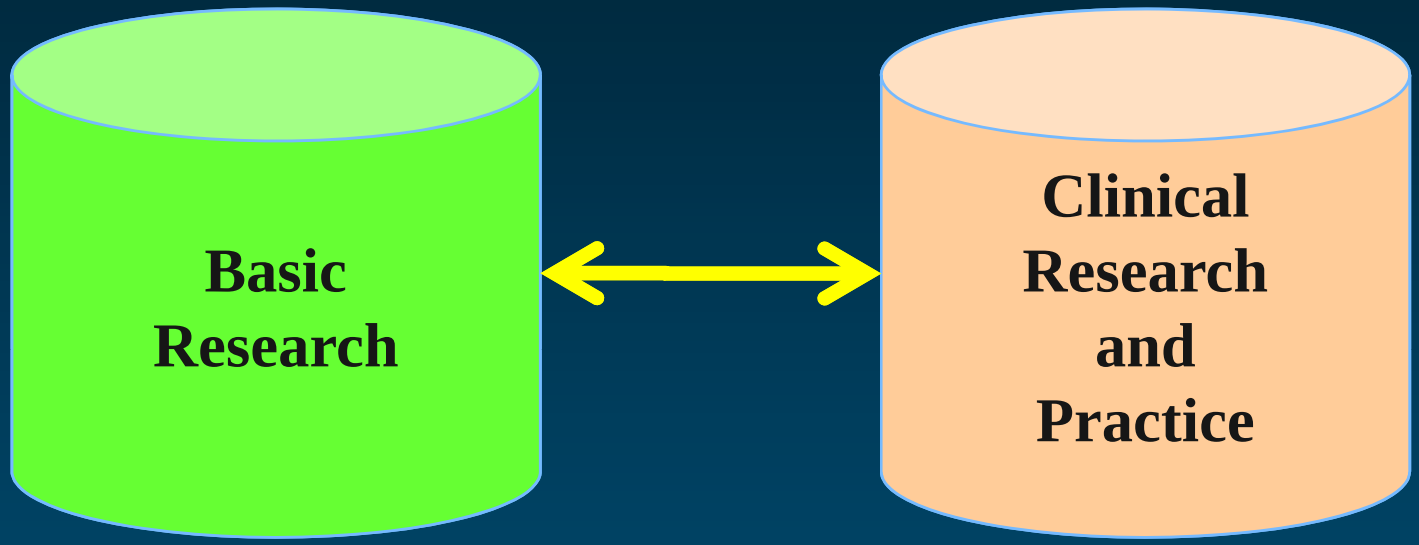
Motivation

Motivation Translational research

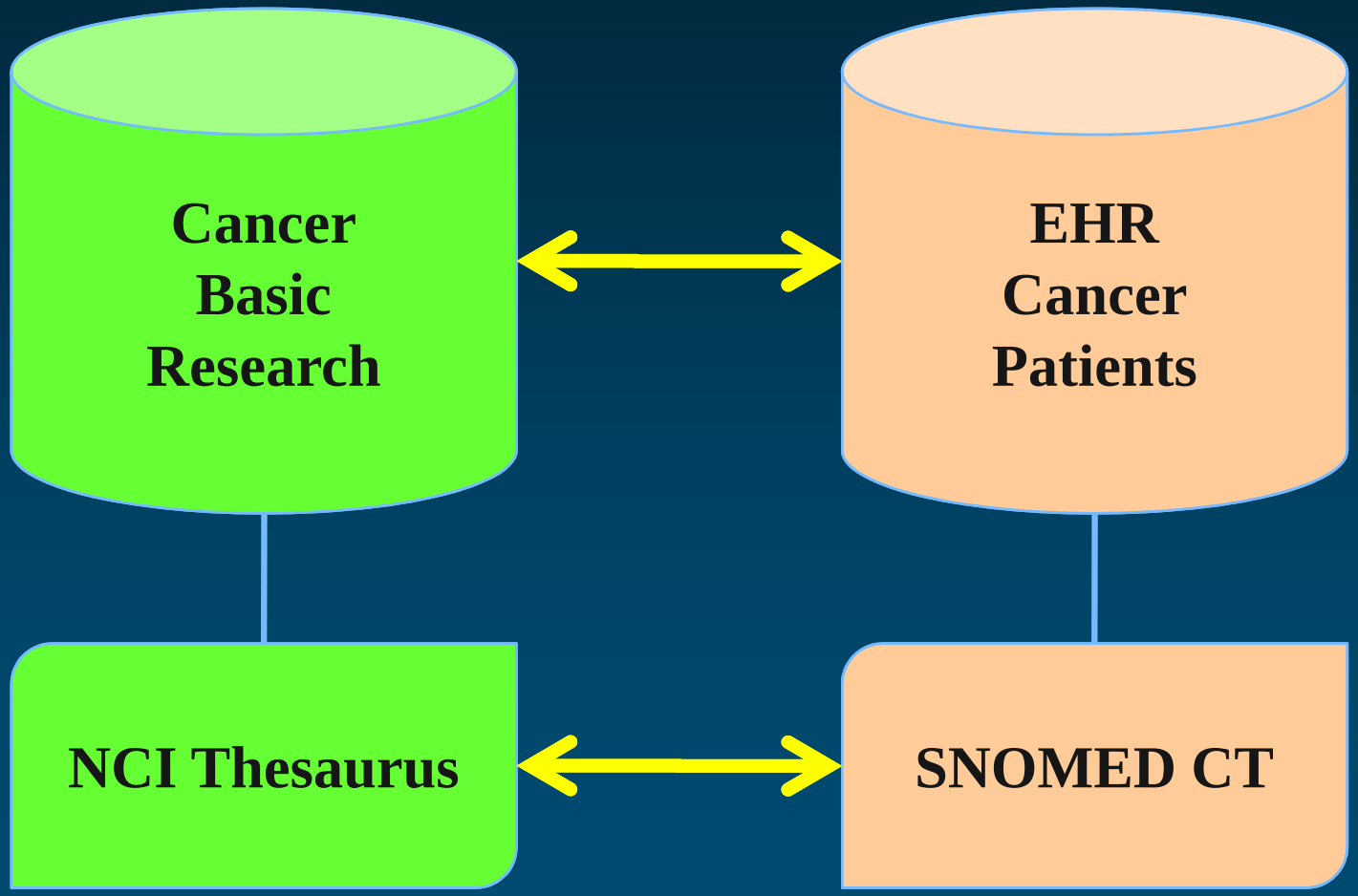
- "Bench to Bedside"
- Integration of clinical and research activities and results
- Supported by research programs
  - NIH Roadmap
  - Clinical and Translational Science Awards (CTSA)
- Requires the effective integration and exchange and of information between
  - Basic research
  - Clinical research

Translational research NIH Roadmap

Motivation Translational research



Terminology and translational research



Some practical considerations and issues

Integration approaches

Approaches to data integration

- Warehousing
  - Sources to be integrated are transformed into a common format and converted to a common vocabulary
  - Normalization through ontologies (e.g., GO annotations)
- Mediation
  - Local schema (of the sources)
  - Global schema (in reference to which the queries are made)
  - Ontologies help define the global schema and map between local and global schemas (OntoFusion, ARIANE)

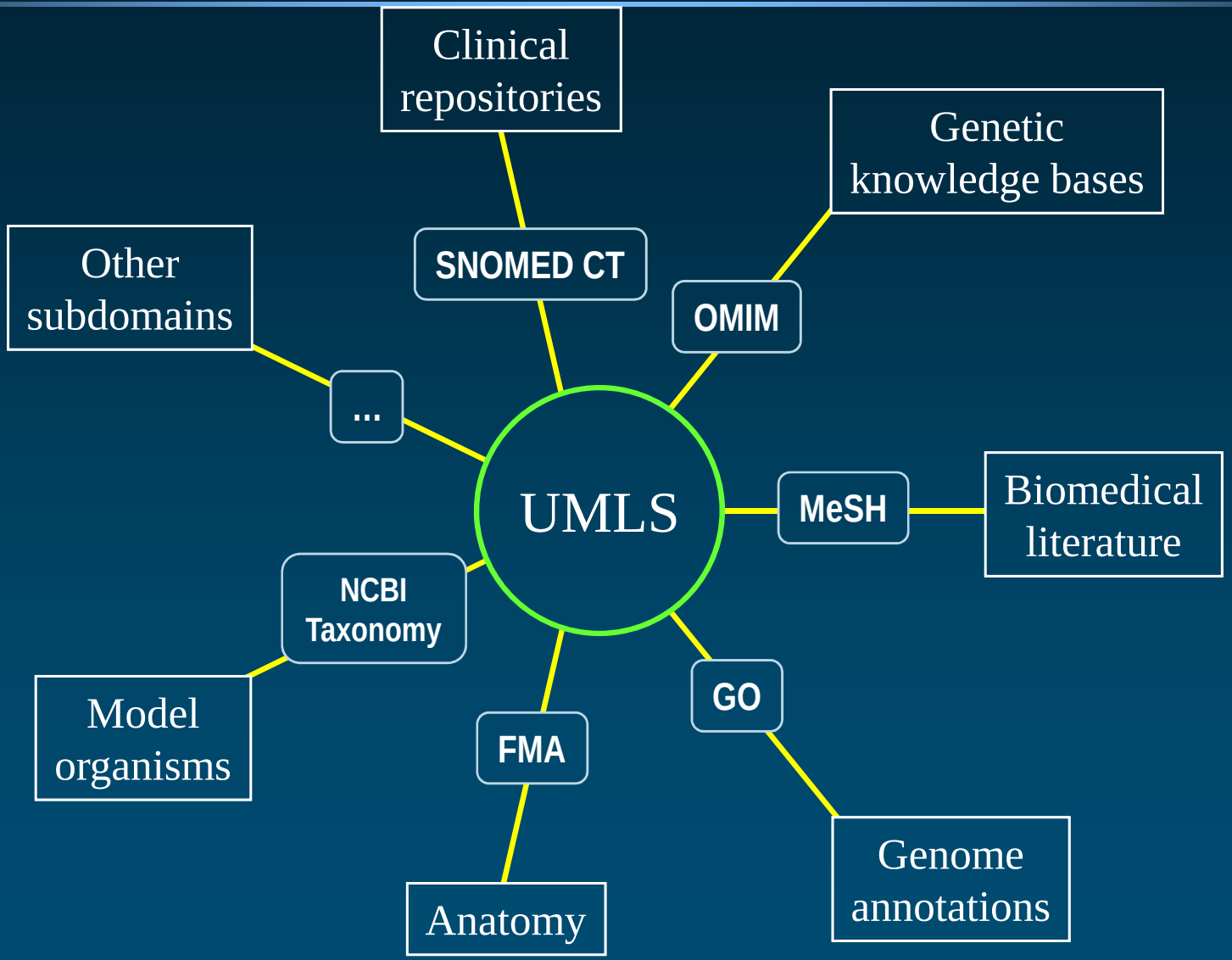
Some practical considerations and issues

Concept repositories

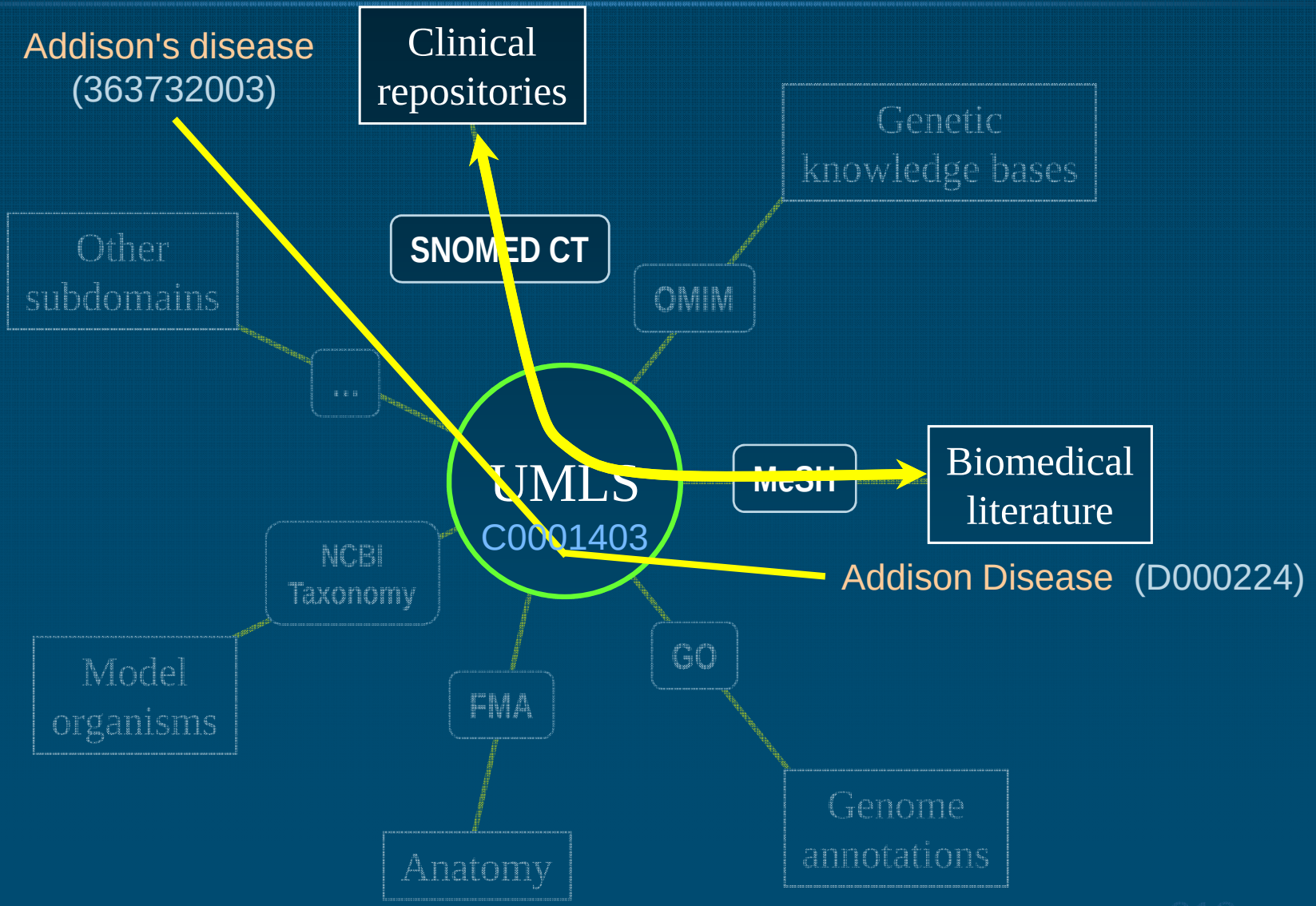
(Integrated) concept repositories

- Unified Medical Language System
  http://umlsks.nlm.nih.gov
- NCBO's BioPortal
  http://www.bioontology.org/tools/portal/bioportal.html
- Open Biomedical Ontologies (OBO)
  http://obofoundry.org/
- caDSR
  http://ncicb.nci.nih.gov/NCICB/infrastructure/cacore_overview/cadsr

Integrating subdomains



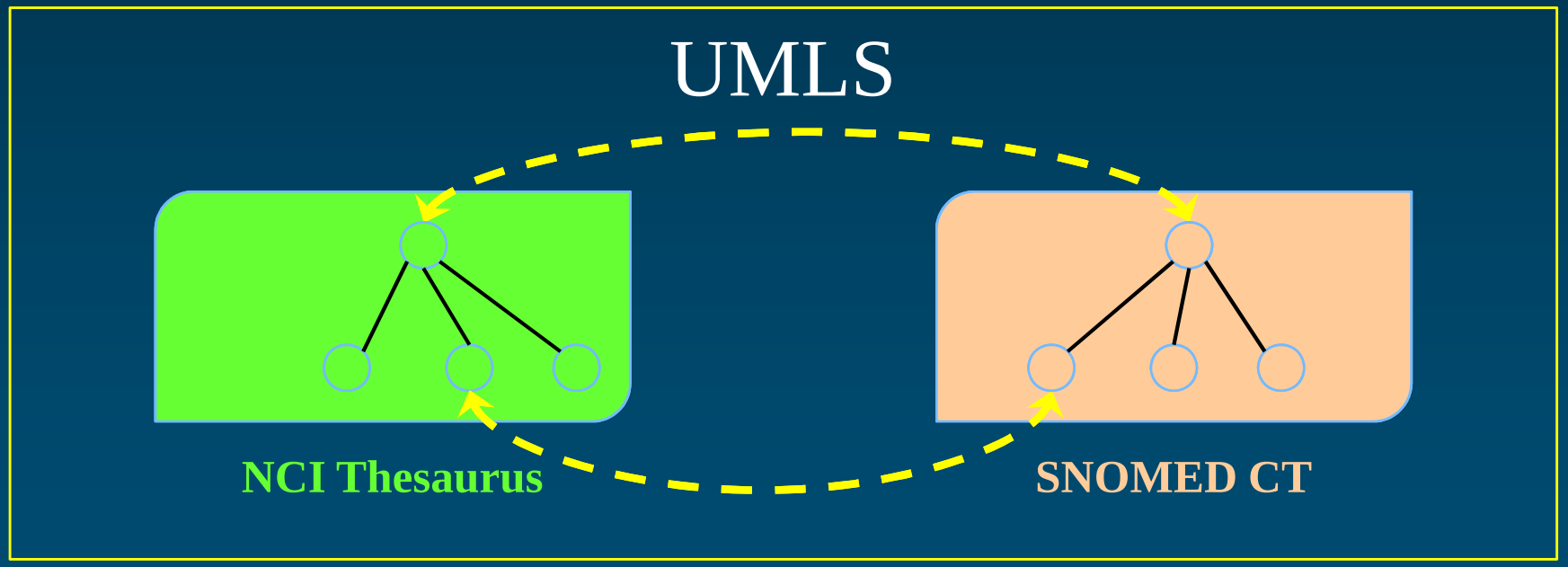
Trans-namespace integration



Some practical considerations and issues

Mappings

Mappings



Mappings

- Created manually
  - UMLS
- Created automatically
  - BioPortal

- Key to enabling semantic interoperability
- Enabling resource for the Semantic Web

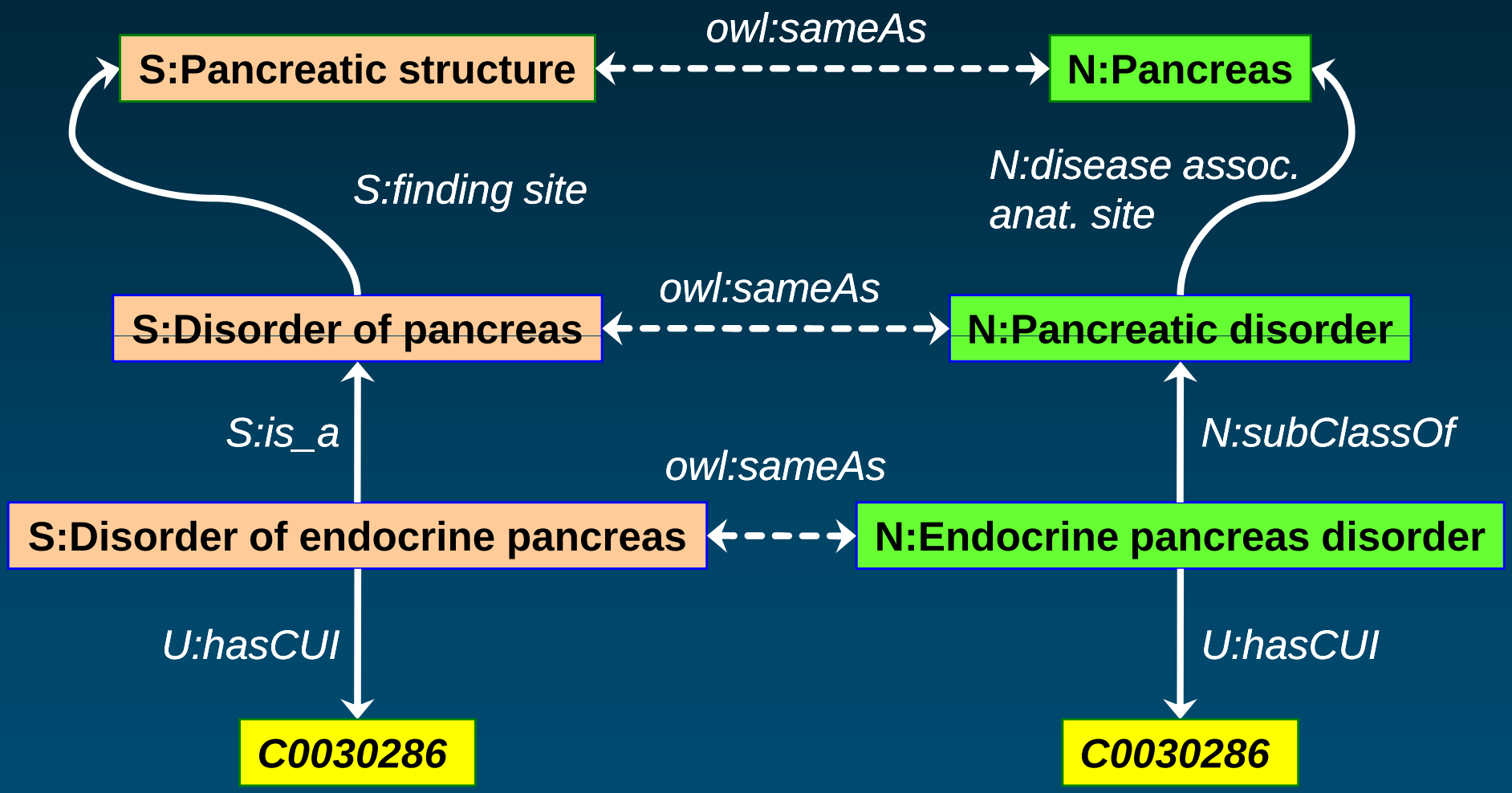
Quality of mappings

- Created for a purpose
  - Reusability issues
- Generally unidirectional
  - Mapping from ontology 1 to ontology 2
  - Not necessarily reversible

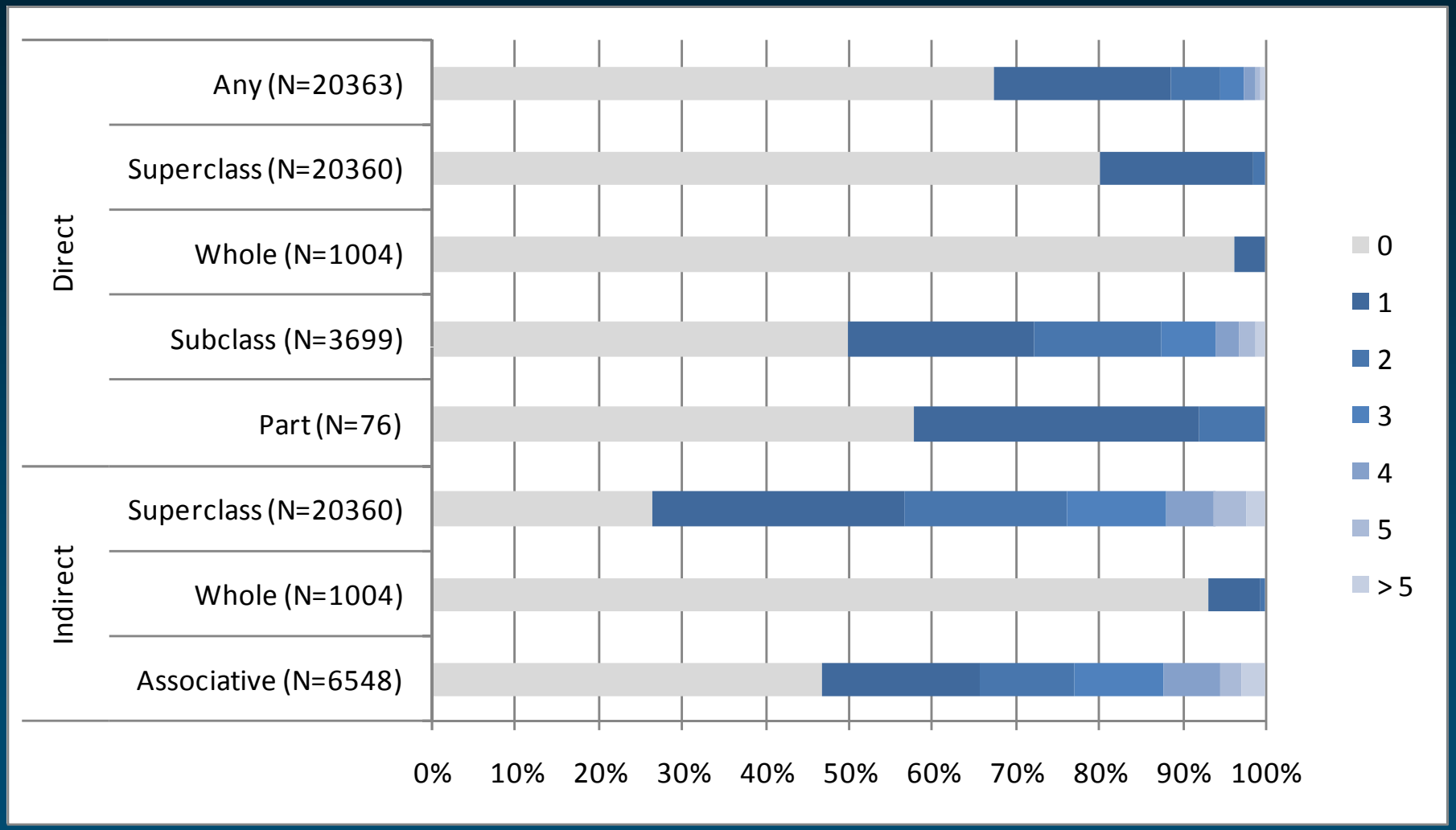
Some practical considerations and issues

Comparing semantic descriptions

Semantic descriptions Consistent



SNOMED CT/NCI Thesaurus
Limited consistency



Comparing formal definitions

- Relatively small proportion of relata in common between equivalent concepts from NCIt and SNOMED CT
- Large number of primitive concepts in NCIt and SNOMED CT (70-80%)
- Insufficient for effectively comparing definitions
  - Could not be used for validating the mapping provided by the UMLS

[Bodenreider, KRMED 2008]

Exercises

Exercise #1

- Check the equivalence (shared relata) between these 2 concepts:
  - NCI Thesaurus: N:Endocrine pancreas disorder
  - SNOMED CT: S:Disorder of endocrine pancreas

Exercise #2

- Find a correspondence in SNOMED CT for the LOINC term: *Sodium:SCnc:-Pt:Ser/Plas:Qn* [the molar concentration of sodium is measured in the plasma (or serum), with quantitative result]

Axis	Value
Component	Sodium
Property	SCnc – Substance Concen-tration (per volume)
Timing	Pt – Point in time (Random)
System	Ser/Plas – Serum or Plasma
Scale	Qn – Quantitative
Method	--

Comments on exercise #2

- Difficult in the absence of a search mechanism on the values of the relations
- Large number of underspecified descriptions in SNOMED CT
- 2 separate concepts for plasma and serum concentrations of sodium in SNOMED CT
- Property, time and scale not represented in SNOMED CT

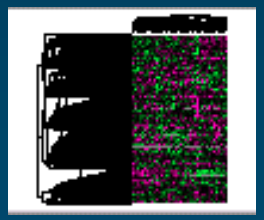
Thinking outside the integration box

The Butte approach

Integrating genomic and clinical data

Genomic data

Clinical data



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Title:	Aging and cognitive impairment: hippocampus		
DataSet type:	gene expression array-based (RNA / in situ oligonucleotide)		
Summary:	Analysis of hippocampi from aged learning-impaired animals on the last day of training in the Morris water maze (MWZ) or 21 days post-training. The MWZ task is a dorsal hippocampal-dependent task. Results provide insight into the molecular basis of aging-related cognitive impairment.		
Platform:	GPL341: Affymetrix GeneChip Rat Expression Set 230 Array RAE230A		
Citation:	Rowe WB, Blalock EM, Chen KC, Kadish I et al. Hippocampal expression analyses reveal selective association of immediate-early, neuroenergetic, and myelinogenic pathways with cognitive impairment in aged rats. J Neurosci 2007 Mar 21;27(12):3098-110. PMID: 17376971		
Sample organism:	Rattus norvegicus	Platform organism:	Rattus norvegicus
Feature count:	16923	Value type:	count
Series:	GSE5666	Series published:	03/15/2007
Last GDS update:	04/27/2007		

Coded discharge summaries

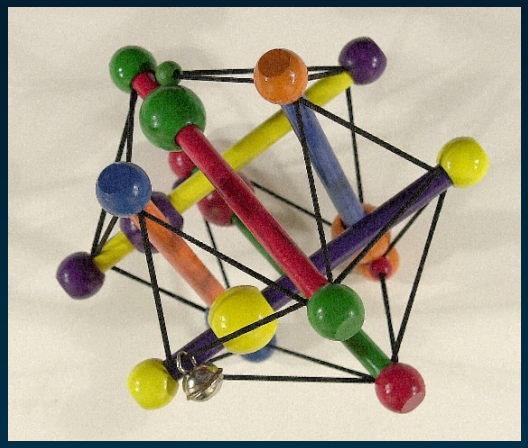
Laboratory data

Upregulated genes

Diseases (extracted from text)

References

- Dudley J, Butte AJ "Enabling integrative genomic analysis of high-impact human diseases through text mining." *Pac Symp Biocomput* 2008; 580-91
- Chen DP, Weber SC, Constantinou PS, Ferris TA, Lowe HJ, Butte AJ "Novel integration of hospital electronic medical records and gene expression measurements to identify genetic markers of maturation." *Pac Symp Biocomput* 2008; 243-54
- Butte AJ, "Medicine. The ultimate model organism." *Science* 2008; 320: 5874: 325-7



Medical Ontology Research

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