II INTERNATIONAL SUMMER SCHOOL

Rare disease and orphan drug registries

New paradigm for a clinical taxonomy applied to Rare Diseases

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Setting up a RD registry project

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Creating a Global Rare Disease Patient Registry linked to a Rare Diseases Biorepository Database: Rare Disease - HUB (RD – HUB)

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The chronological Steps

- bioethical and legal issues
- **vocabulary, thesaurus, classification,**
- **data considerations,**
- technical issues,
- e-CRF,
- **standardization,**
- dataharvest,
- quality control, datamonitoring, datamanagement,
- **Interoperability**

Vocabulary, data elements

Standardized vocabulary, terminology, codes and diagnoses

Recommendations:

- Standardize questions
- Find commonalities across all rare diseases
- Provide guidance to advocacy groups
- Established a central data store of questions
- Develop a “minimal common registry model”
- Strive for electronic health record standardization.

Source: Contemp Clin Trials. 2010; 31(5): 394–404.

Data elements

A DE refers to information that describes a piece of data to be collected in a study. It does not include the data themselves (e.g. gender)

Source: http://metadata-tds.org/11179/#A1 and http://www.nlm.nih.gov/cde/glossary.html#examples

Data elements

Name - The name of the DE (a code may be used in addition).
Definition - An explanation of the nature, scope, or meaning of the DE.
Query/Instructions – Instructions on how to respond to a question, instructions on how to conduct a laboratory test, ..
Representation – The way the data is represented
Provenance - Information describing the history or origin of a DE, and its scientific validity (references to journal articles, vocabularies or data Standards, review process, validation, owner or creator, or other information).
Value Set - The set of possible values or responses.

Source: http://metadata-tds.org/11179/#A1 and http://www.nlm.nih.gov/cde/glossary.html#examples

Common Data elements (1)

Common Data Element (CDE):
A data element that is *common* to *multiple* data sets *across* different studies/registries.
Commonality may be intentional or not.
CDEs are dedicated to improve data quality, promote data sharing, and interoperability.

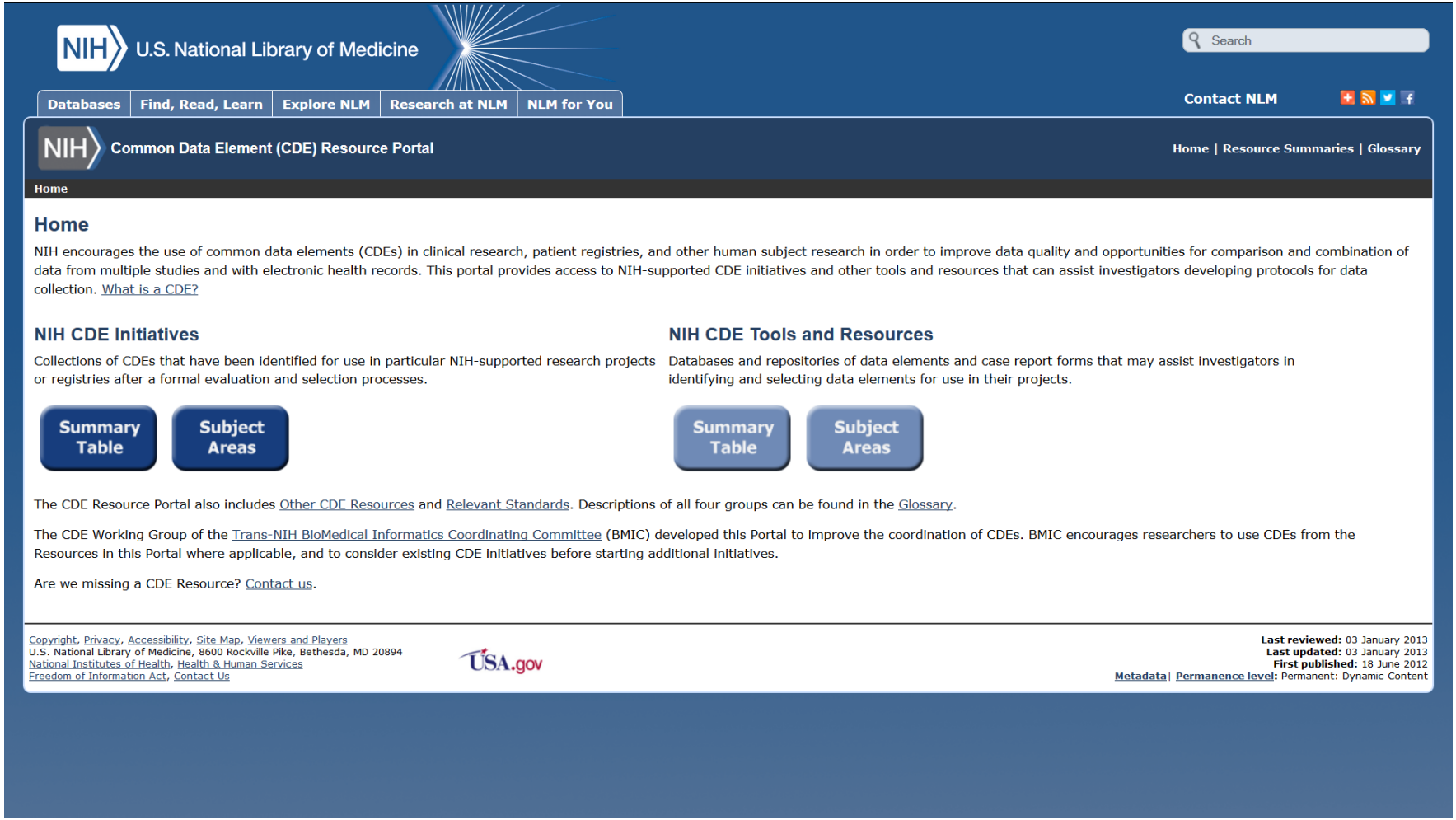
Source: http://metadata-tds.org/11179/#A1 and http://www.nlm.nih.gov/cde/glossary.html#examples

Common Data elements (2)

Universal - CDEs that may be used in studies/registries, regardless of the specific disease or condition of interest, (demographic information, medical history,..)
Domain-specific - CDEs designed and intended for use in studies of a particular topic, disease or condition, such as rare diseases. Some are broadly applicable, other more specific.
Required - CDEs required (or expected), for institutional policy to be collected for *all* subjects in studies of a particular type.
Core - CDEs required (or expected) for particular classes of studies.

Source: http://metadata-tds.org/11179/#A1 and http://www.nlm.nih.gov/cde/glossary.html#examples

A Common Data Elements portal

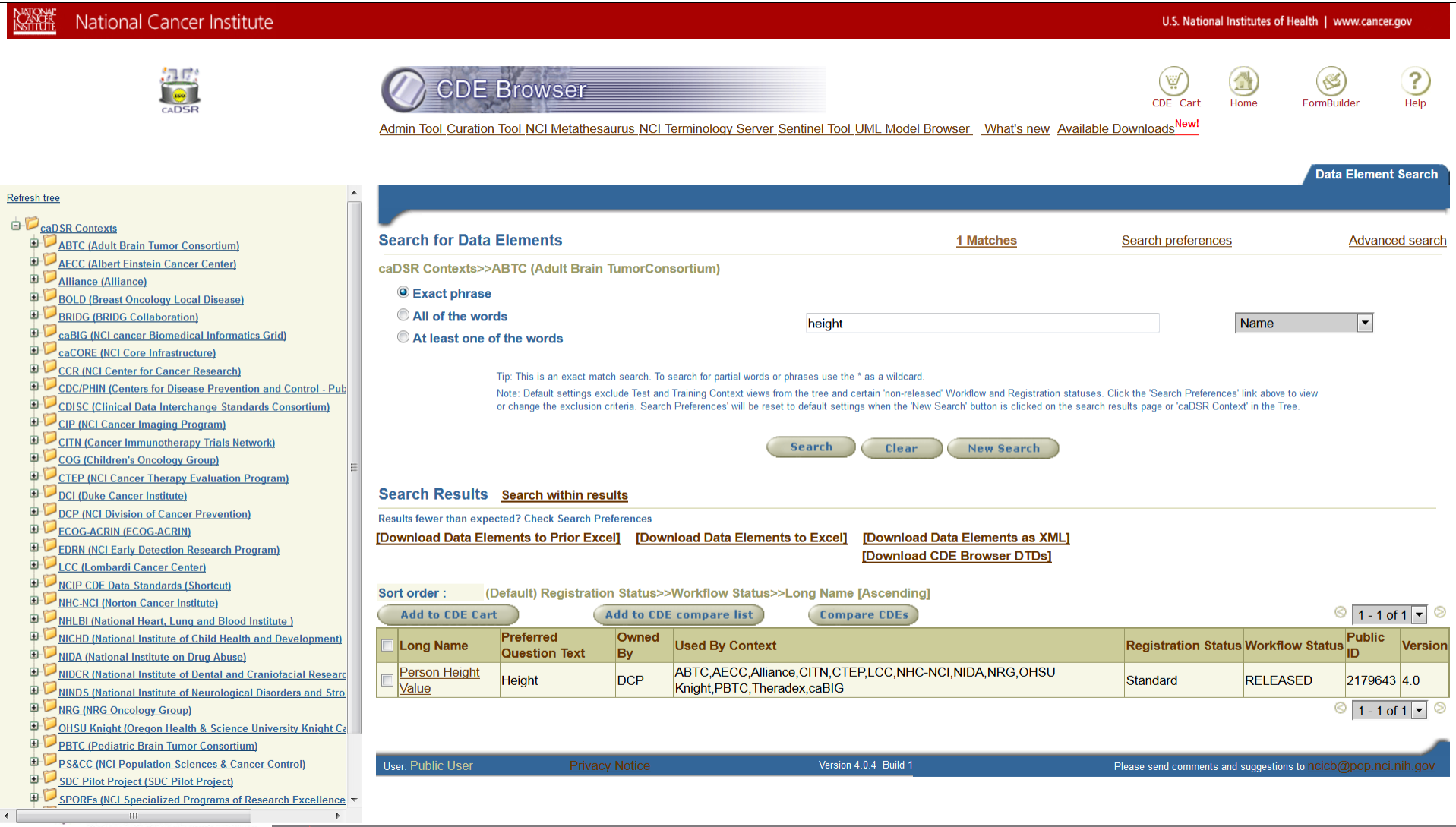


Source: http://metadata-tds.org/11179/#A1 and http://www.nlm.nih.gov/cde/glossary

ORDR GRDR CDEs

Element Number	Element Name	Question Text	Element Definition	Permissible Values	Data Source	Link to Data Source	Elements selected as "Required" by the steering committee are marked √
Current Contact Information							
1	Date of registry record	Date report is filled out or registry information is updated	A date or date and time value.	Non-enumerated Display Format YYYY/MM/DD	International Organization for Standards (ISO) HL7 DT data type (http://www.hl7.org/)	http://www.iso.org/iso/support/faqs/faqs_widely_used_standards/widely_used_standards_other/date_and_time_format.htm http://www.hl7.org/	√
2	First name of patient	Patient First Name as recorded in birth certificate or passport	A word or group of words indicating a person's first (personal or given) name; the name that precedes the surname. Synonym = Given Name.	Name as appears in official documents e.g. passport and birth certificate	HL7 ST data type	(http://www.hl7.org/)	√
3	Last name of patient	Patient Last Name	A means of identifying an individual by using a word or group of words indicating a person's last (family) name. Synonym = Last Name, Surname.	Name as appears in official documents e.g. passport and birth certificate	HL7 ST data type	(http://www.hl7.org/)	√
4	Middle name of patient	Patient Middle Name	A means of identifying an individual by using a word or group of words indicating a person's middle name.	Name as appears in official documents e.g. passport and birth certificate or NA	HL7 ST data type	(http://www.hl7.org/)	√
5	Patient address: street	Street name	A component of an address that specifies a location by formatted concatenation of street/thoroughfare address components as described by a derivation rule.	Text	HL7 ST data type	http://www.hl7.org/	√

CDE browser (1)



CDE browser (2)

National Cancer Institute — U.S. National Institutes of Health | www.cancer.gov

caDSR — CDE Browser — Back — Help

Data Element | Data Element Concept | Value Domain | Classifications | Usage | Data Element Derivation | Admin Info

Data Element Details

Public ID:	2179643
Version:	4.0
Long Name:	Person Height Value
Short Name:	PRSN_HT_VAL
Preferred Question Text:	Height
Definition:	The number that describes the vertical distance of an individual.
Value Domain:	Height Value
Data Element Concept:	Person Height
Context:	DCP
Workflow Status:	RELEASED
Origin:	CSAERS:Chemoprevention Serious Adverse Event System
Registration Status:	Standard
Direct Link:	https://cdebrowser.nci.nih.gov/CDEBrowser/search?elementDetails=9&FirstTimer=0&PageId=ElementDetailsGroup&publicId=2179643&version=4.0

Reference Documents

Document Name	Document Type	Document Text	Context	URL
Height	Preferred Question Text	Height	DCP	
CRF TEXT	Alternate Question Text	Height Measure	caBIG	
6671-TA	Alternate Question Text	Patient height	DCP	
NIDA CTN PhenX Body Mass Index	Alternate Question Text	Record standing height in meters (or centimeters) or inches	NIDA	

Alternate Names and Definitions

Alternate Names

Name	Type	Context	Language
caBIG	USED_BY	caBIG	ENGLISH
PRSN_HT_VAL	USED_BY	caBIG	ENGLISH
CTEP	USED_BY	CTEP	ENGLISH
AECC	USED_BY	AECC	ENGLISH
NHC-NCI	USED_BY	NHC-NCI	ENGLISH
PRSN_HT_VAL	USED_BY	AECC	ENGLISH
CITN	USED_BY	CITN	ENGLISH
		BTC	ENGLISH

https://cdebrowser.nci.nih.gov/CDEBrowser/search?elementDetails=9&FirstTimer=0&PageId=ElementDetailsGroup&publicId=2179643&version=4.0

Metadata (1)

The term **metadata** refers to "data about data".
The term is used for two fundamentally different types.
Structural metadata is about the design and specification of data structures and is more properly called "data about the *containers* of data";
Descriptive metadata, on the other hand, is about individual instances of application data, the data *content*.
In this case, a useful description would be "data about data content" or "content about content" it is thus a *metacontent*

Metadata (2)

- Metadata (or *metacontent*) are defined as the data providing information about one or more aspects of the data, such as:
  - Means of creation of the data;
  - Purpose of the data;
  - Time and date of creation;
  - Creator or author of the data;
  - Location on a computer network where the data are available…

Metadata (3)

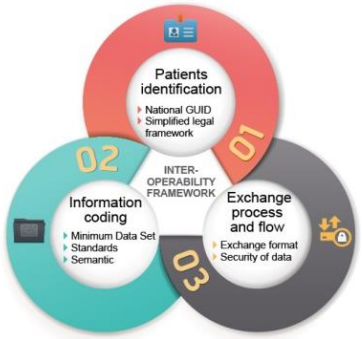
- For example:
- an image may include metadata that describes how large the picture is, the color depth, the image resolution,..
- when the image was created.

Minimum data set

Minimum data set

Definition: a minimum *set of common data elements* (CDEs) agreed for mandatory collection and reporting at a given level (local, regional, national, international,..).
It includes common data elements that are also comprised in other minimum data sets.
A MDS is contingent upon an agreement to collect uniform data and to supply it as part of the collection.
It does not preclude agencies and service providers from collecting additional data to meet their own specific needs.

The French RD Minimum data set



A methodology for a minimum data set for rare diseases to support national centers of excellence for healthcare and research

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ABSTRACT

Background Although rare disease patients make up approximately 6–8% of all patients in Europe, it is often difficult to find the necessary expertise for diagnosis and care and the patient numbers needed for rare disease research. The second French National Plan for Rare Diseases highlighted the necessity for better care coordination and epidemiology for rare diseases. A clinical data standard for normalization and exchange of rare disease patient data was proposed. The original methodology used to build the French national minimum data set (F-MDS-RD) common to the 131 expert rare disease centers is presented.

Methods To encourage consensus at a national level for homogeneous data collection at the point of care for rare disease patients, we first identified four national expert groups. We reviewed the scientific literature for rare disease common data elements (CDEs) in order to build the first version of the F-MDS-RD. The French rare disease expert centers validated the data elements (DEs). The resulting F-MDS-RD was reviewed and approved by the National Plan Strategic Committee. It was then represented in an HL7 electronic format to maximize interoperability with electronic health records.

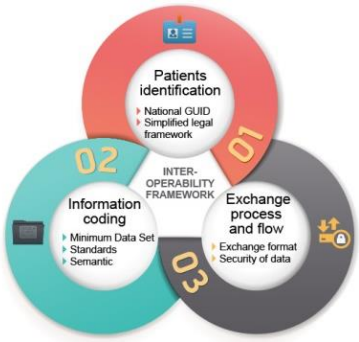
Results The F-MDS-RD is composed of 58 DEs in six categories: patient, family history, encounter, condition, medication, and questionnaire. It is HL7 compatible and can use various ontologies for diagnosis or sign encoding. The F-MDS-RD was aligned with other CDE initiatives for rare diseases, thus facilitating potential interconnections between rare disease registries.

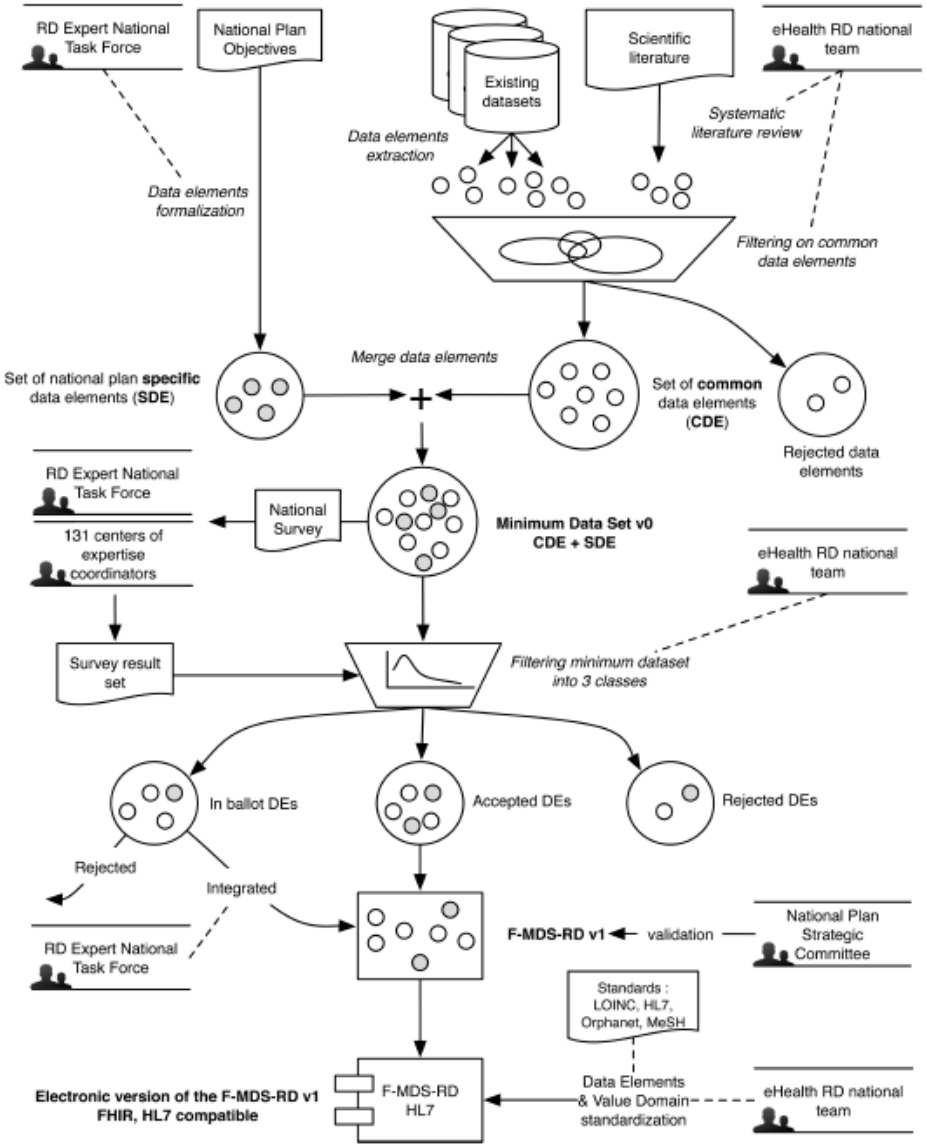
Conclusions The French F-MDS-RD was defined through national consensus. It can foster better care coordination and facilitate determining rare disease patients' eligibility for research studies, trials, or cohorts. Since other countries will need to develop their own standards for rare disease data collection, they might benefit from the methods presented here.

often lacking. Rare diseases have been identified as a public health priority in Europe. Many EU countries have launched national plans to promote rare diseases care and research.[9 10] Since 2004, the French authorities together with field experts, patients' associations, and other stakeholders have implemented two consecutive rare disease national plans. The first plan (2005–2009) fostered the implementation of a network of 131 rare disease centers of expertise distributed throughout French territory[11] and focused on groups of diseases (rare renal diseases, rare pulmonary diseases, rare developmental defects, etc). Each center of expertise consisted of one or more medical units mainly located in university hospitals. A complementary network of 501 units was connected to this first set of centers to better cover the different areas closer to patients' residences. This rare disease network aimed at building a nation-wide continuum of care for these chronic and disabling diseases. To support clinicians' rare disease care and research activities, an IT infrastructure has been funded by the second national plan for rare diseases (2011–2014).[12] This national information system promotes information exchange tools that can be integrated within the current local or national information systems to avoid data re-entry. Rare disease patients are often barely identifiable within hospital information systems because of the lack of standardized rare disease coding, as well as a lack of systematized data collection at a national level such as used for the Global Rare Diseases Patient Registry and Data Repository (GRDR) common data elements (CDEs) of the US initiative.[13] A first objective is to identify patients in the rare disease care network to help build a seamless continuum of care across expert centers and reduce overall costs. Making rare disease-associated activity detectable is essential for the expert centers so they can submit claims for rele-

Source: Choquet et al, JAMIA 2014

The F-MDS-RD methodology diagram





Source: Choquet et al, JAMIA 2014

Data standards definition

Consensual specifications for the representation of data from different sources or settings.
Necessary for the sharing, portability, and reusability of data.
Enable to reconcile the requirements of varied investigators and data users with the need for common standards.

Include specifications for

- data fields (variables)
- and value sets (codes) : encode the data within these fields.

French RD Minimum data set

BNDMR
French Rare Disease Data Repository

RD MDS v1.09
French National Rare Diseases Minimum Data Set

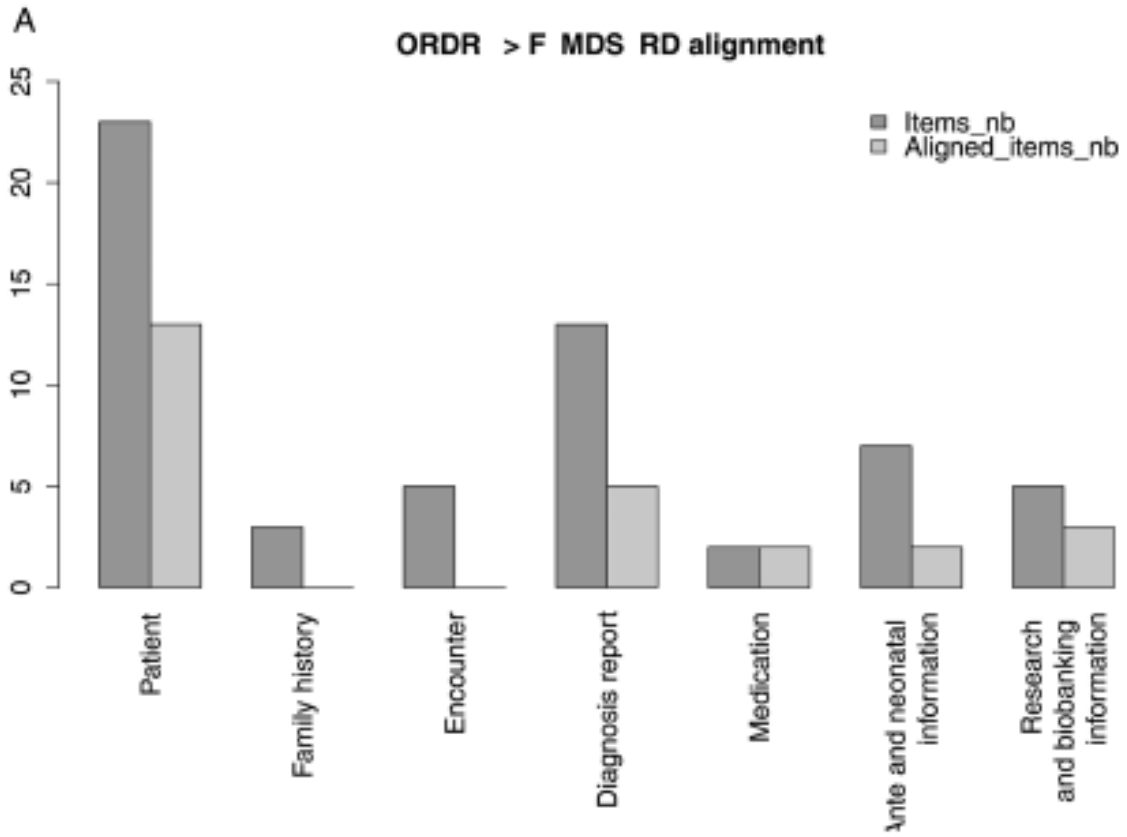
Item group	Item #	Item concept	Definition	Content coding
1. Consent	1.1	Patient consent	Does the patient give his/her consent for information to be stored in a computer data management system?	Yes - LA33-6
	1.2	Patient's non-opposition for data reuse	Was the patient duly informed that part of his/her de-identified data, will be used for public health purposes, and that he/she did not express his/her opposition?	Yes - LA33-6 No - LA32-8
	1.3	Consent by legal guardian	Is the consent given by the patient's legal guardian?	Yes - LA33-6 No - LA32-8
2. Patient identification	2.1	National rare disease identifier	GUID (Global Unique Identifier) allowing the unique identification of patients between BaMaRa and BNDMR (de-identified).	String (automatically generated)
	2.1 bis	National rare disease identifier	National Rare Disease Identifier allowing the unique identification of patients between BaMaRa and BNDMR.	String (automatically generated)
	2.2	Health national identifier	Patient identifier subject to the discretion of the CNIL: unique national identifier allowing future connections with the French patient medical file (DMP).	String (automatically generated)
	2.3	Patient's local hospital identifier	Local hospital identifier.	String
3. Personal information	3.1	Patient's patronymic name (surname at birth)	Patient's patronymic name (surname at birth).	String
	3.2	Patient's commonly used last name	Patient's commonly used last name.	String
	3.3	Patient's first name	Patient's first name as specified on the birth certificate or identity card.	String
	3.4	Patient's date of birth	Patient's date of birth as recorded on the birth certificate.	Date
	3.5	Patient's gender	Patient's gender.	Female - LA3-6 Male - LA2-8 Undetermined - LA18959-9 Unknown (for the fœtus) - LA4489-6
	3.6	Fœtus (if applicable)	Information recorded for a fœtus if appropriate.	Yes - LA33-6 No - LA32-8
	3.7	City of birth	Patient's city of birth.	City code
	3.8	Country of birth	Patient's country of birth.	Country code
	3.9	City de residence	Patient's city of residence.	City code
	3.10	Country of residence	Patient's country of residence.	Country code

Data Alignment

Is the set of data elements collected compatible with other resources?

Alignment ORDR vs F-MDS-RD

Figure 2 Number of common data elements between US Office of Rare Diseases Research (ORDR) (GRDR CDEs) and F-MDS-RD (from US CDE to French CDE). CDE, common data elements; F-MDS-RD, French national minimum data set for rare diseases; GRDR, Global Rare Diseases Patient Registry and Data Repository; nb, numbers.

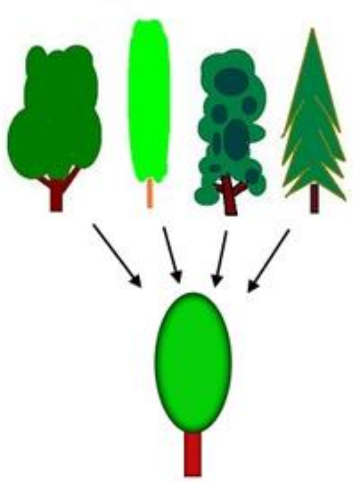


Terminology

Terminology

- *The science of both techniques or ideas they represent*

- Find *terms* that describe *concepts* of interest
- A *term* is a linguistic expression of a concept
- A *concept* identifies a notion; It is preset.
- A *domain* is a fixed network of concepts.



Characteristics of a terminology

- In a specialized field, matches a domain
- Responds to a need for a specific application
- Entries of a terminologies are *terms*
- Identifiers, codes are associated to the entries
- Definitions are provided.

Terminologies (1)

Several RD terminologies with distinct objectives.

- *OMIM* catalogues all the known diseases with a genetic component, a comprehensive, authoritative compendium of human genes and genetic phenotypes.
- *Orphanet* is a thesaurus of signs and symptoms for use by clinicians.
- *Human Phenotype Ontology* enables computational analysis of human disease manifestations. It aims to provide a standardized vocabulary of phenotypic abnormalities encountered in human disease

OMIM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OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh. Its official home is omim.org.
Using OMIM
Getting Started
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Last updated on: 12 Sep 2014
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Genes & Expression
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Homology
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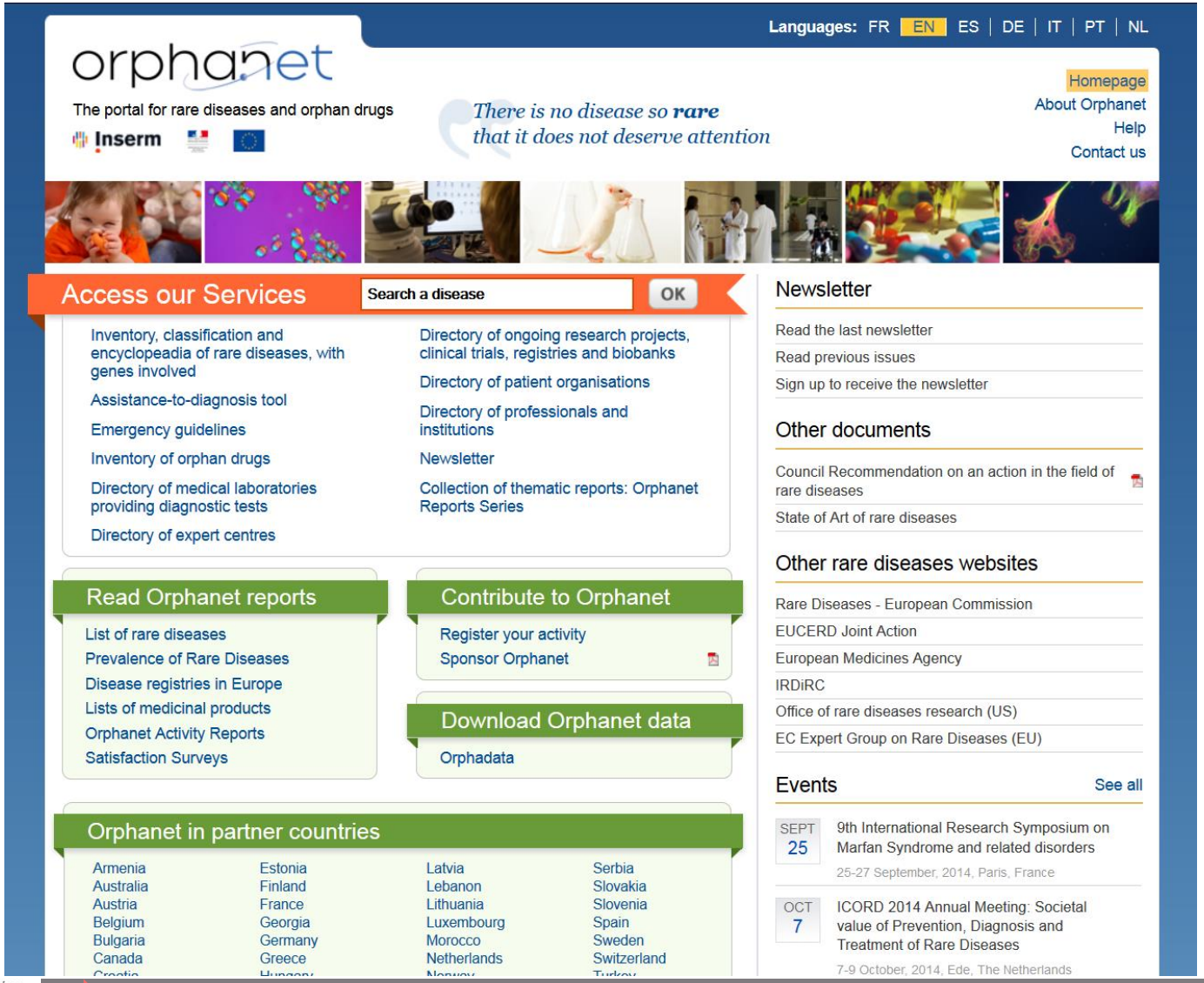
Proteins
POPULAR
PubMed
Bookshelf
PubMed Central
PubMed Health
BLAST
Nucleotide
Genome
SNP
Gene
Protein
FEATURED
Genetic Testing Registry
PubMed Health
GenBank
Reference Sequences
Gene Expression Omnibus
Map Viewer
Human Genome
Mouse Genome
Influenza Virus
Primer-BLAST
NCBI INFORMATION
About NCBI
Research at NCBI
NCBI News
NCBI FTP Site
NCBI on Facebook
NCBI on Twitter
NCBI on YouTube

ORPHANET


Languages: FR EN ES DE IT PT NL
orphanet
The portal for rare diseases and orphan drugs
Inserm
There is no disease so rare that it does not deserve attention
Homepage
About Orphanet
Help
Contact us
Access our Services
Search a disease
OK
Inventory, classification and encyclopeadia of rare diseases, with genes involved
Assistance-to-diagnosis tool
Emergency guidelines
Inventory of orphan drugs
Directory of medical laboratories providing diagnostic tests
Directory of expert centres
Directory of ongoing research projects, clinical trials, registries and biobanks
Directory of patient organisations
Directory of professionals and institutions
Newsletter
Collection of thematic reports: Orphanet Reports Series
Read Orphanet reports
List of rare diseases
Prevalence of Rare Diseases
Disease registries in Europe
Lists of medicinal products
Orphanet Activity Reports
Satisfaction Surveys
Contribute to Orphanet
Register your activity
Sponsor Orphanet
Download Orphanet data
Orphadata
Orphanet in partner countries
Armenia
Australia
Austria
Belgium
Bulgaria
Canada
Estonia
Finland
France
Georgia
Germany
Greece
Latvia
Lebanon
Lithuania
Luxembourg
Morocco
Netherlands
Serbia
Slovakia
Slovenia
Spain
Sweden
Switzerland
Newsletter
Read the last newsletter
Read previous issues
Sign up to receive the newsletter
Other documents
Council Recommendation on an action in the field of rare diseases
State of Art of rare diseases
Other rare diseases websites
Rare Diseases - European Commission
EUCERD Joint Action
European Medicines Agency
IRDiRC
Office of rare diseases research (US)
EC Expert Group on Rare Diseases (EU)
Events
See all
SEPT 25
9th International Research Symposium on Marfan Syndrome and related disorders
25-27 September, 2014, Paris, France
OCT 7
ICORD 2014 Annual Meeting: Societal value of Prevention, Diagnosis and Treatment of Rare Diseases
7-9 October, 2014, Ede, The Netherlands

Human Phenotype Ontology

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- Documentation
  - Defining HPO Terms
  - Annotation guide
  - How to collaborate
  - Legal issues
- HPO people

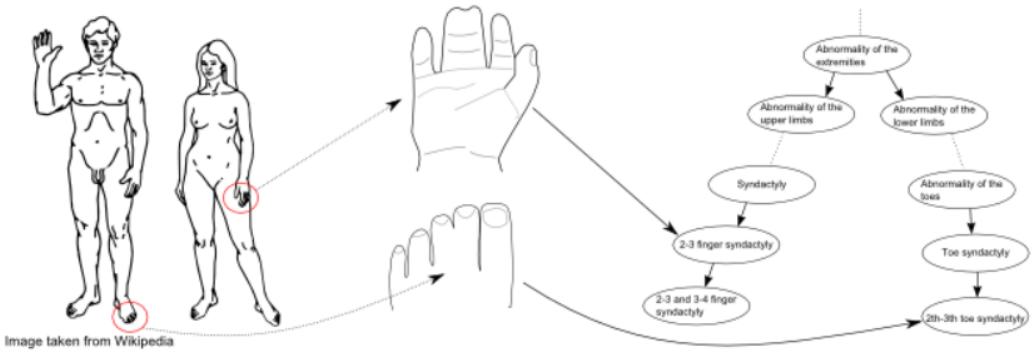


Image taken from Wikipedia

Human Phenotype Ontology > Human Phenotype Ontology Website

... *news* ...

An ontology is a computational representation of a domain of knowledgebased upon a controlled, standardized vocabulary for describing entities and the semantic relationships between them. The Human Phenotype Ontology (HPO) aims to provide a standardized vocabulary of phenotypic abnormalities encountered in human disease. Terms in the HPO describes a phenotypic abnormality, such as *atrial septal defect*.

The HPO was initially developed using information from Online Mendelian Inheritance in Man (OMIM), which is a hugely important data resource in the field of human genetics and beyond. The HPO is currently being developed using information from OMIM and the medical literature and contains approximately 10,000 terms. Over 50,000 annotations to hereditary diseases are available for download or can be browsed using the PhenExplorer.

The HPO is now being developed in collaboration with members of the OBO Foundry (Open Biological and Biomedical Ontologies), and logical definitions for HPO terms are being developed using PATO and a number of other ontologies including the FMA, GO, ChEBI, and MPATH. The HPO can be used for clinical diagnostics in human genetics (Phenomizer), bioinformatics research on the relationships between human phenotypic abnormalities and cellular and biochemical networks, for mapping between human and model organism phenotypes, and for providing a standardized vocabulary for clinical databases, among many other things. There exists a webpage for every HPO-term.

The HPO project encourages input from the medical and genetics community with regards to the ontology itself and to clinical annotations.

Monarch Initiative

Model organisms are a cornerstone of biomedical research to investigate biological processes, test gene-based disease hypotheses, and develop and test disease treatments. The HPO team is a member of the Monarch Initiative, which is developing computational and semantic resources and software to allow cross-species phenotype analysis, and to integrate information from multiple organisms including phenotypic similarity, network analysis, gene expression and function, and genomics. One such tool for using phenotypic similarity between human disease and mouse models of disease is the Exomiser.

monarch INITIATIVE

Terminologies (2)

- *PhenoDB* enables quick entry of phenotypic features by clinicians (or health care providers).
- *Elements of Morphology* is a glossary of state of the art definitions for phenotypic features.

Data considerations

- What different categories of data are needed from what sources?
- How to make useful research data maximally available?
- What CDEs' or metadata elements are needed?
- What are the key quality control issues to tackle?
- What are new challenges and opportunities arise due to « omics » or « Big data » types?

Nosology, nomenclature, classification

Nosology

- At the end of the XVII century, in parallel to the efforts of the naturalists and biologists, to the progress of taxonomy and systematic, a similar trend emerged in medicine: arranging and classifying diseases.
- *nosology* studies the distinctive characteristics allowing to define and classify diseases.
- Different from *nosography* which describes diseases
- *Nomenclatures* and *classifications* have emerged at that time.

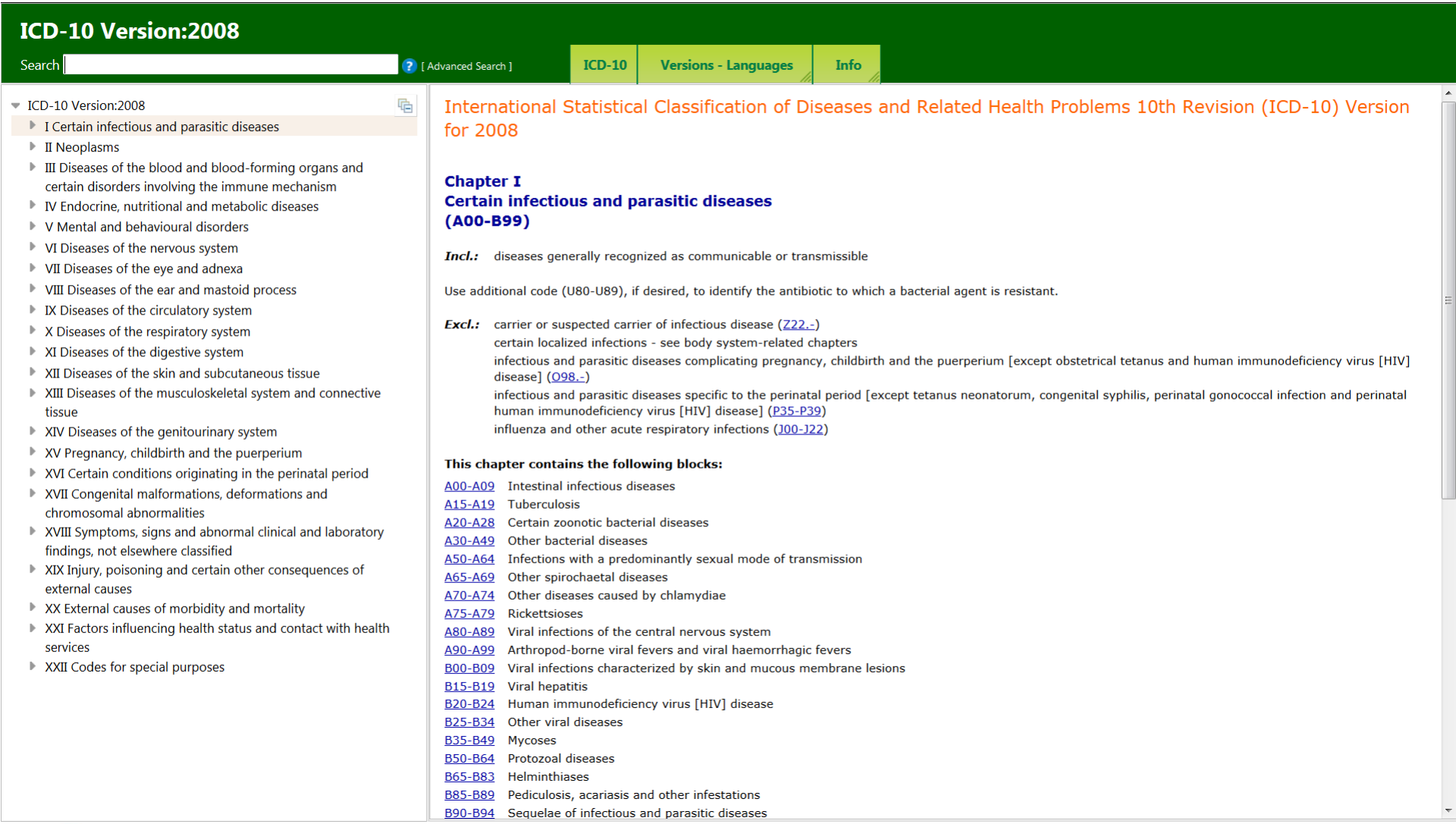
Nomenclature

- It is an inventory of the terms used to designate objects in a collection.
- A *nomenclator* was a roman slave accompanying a judicial candidate who discreetly indicated to him the citizens of interest to greet.
- Brings together a set of terms, sufficiently rich and elaborate, methodically arranged, in order to describe the status of an individual.
- No implicit arrangement of terms.
- No explicit definition of terms.

Classification

- The objective followed by the creator of a classification models the classification structure.
- The international classification of diseases (ICD-10) has an *epidemiological* orientation, when SNOMED CT has a *clinical* orientation.
- Brings closer and orders words that have a semantic relationship.
- Relationships between vocabulary terms are ordered according to their meaning proximity (synonymy) or parentage (hierarchy).
- The choice of a classification determines subsequent selection of relevant documents for the user.

ICD-10


ICD-10 Version:2008
Search
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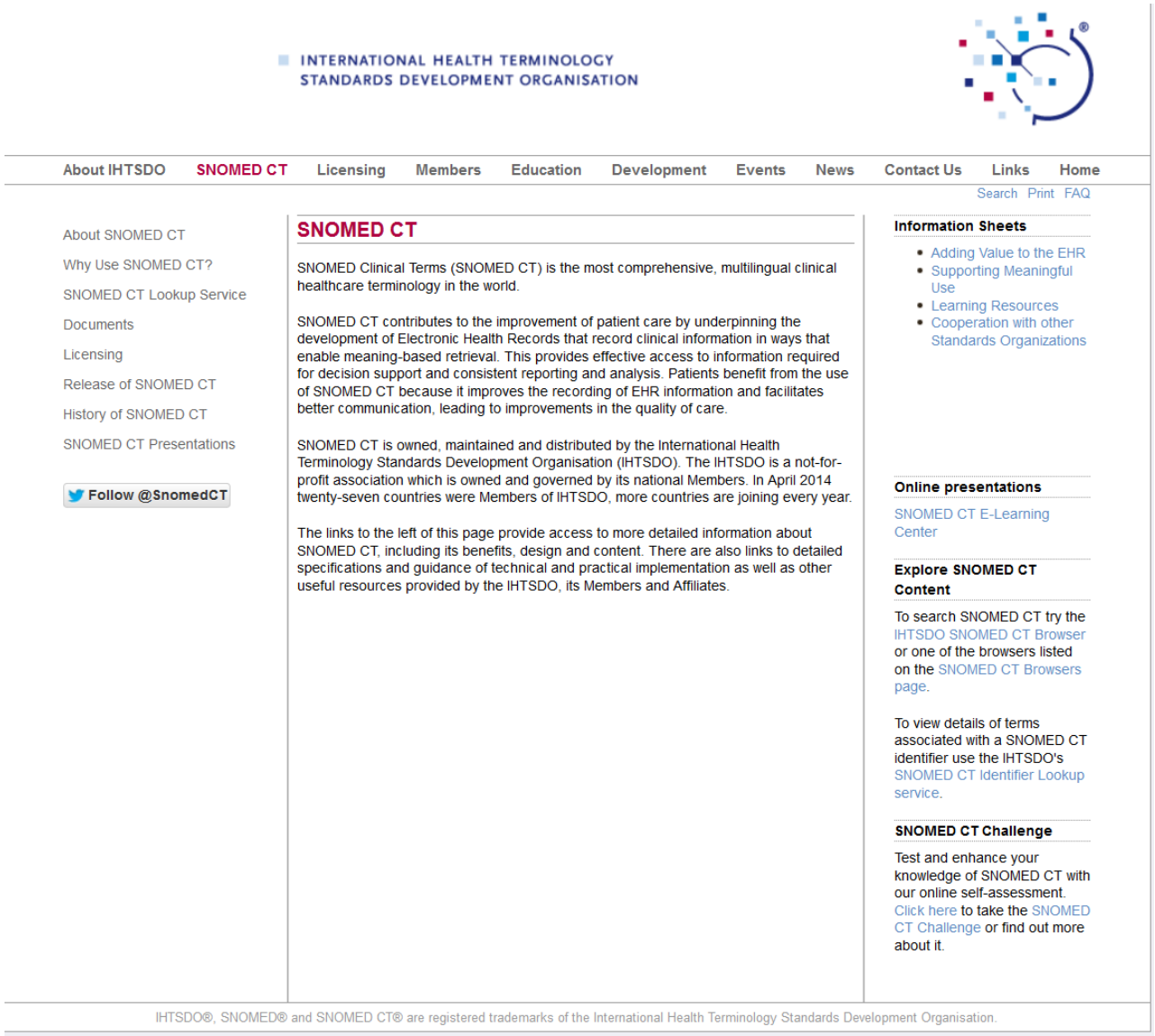
ICD-10
Versions - Languages
Info
ICD-10 Version:2008
I Certain infectious and parasitic diseases
II Neoplasms
III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
IV Endocrine, nutritional and metabolic diseases
V Mental and behavioural disorders
VI Diseases of the nervous system
VII Diseases of the eye and adnexa
VIII Diseases of the ear and mastoid process
IX Diseases of the circulatory system
X Diseases of the respiratory system
XI Diseases of the digestive system
XII Diseases of the skin and subcutaneous tissue
XIII Diseases of the musculoskeletal system and connective tissue
XIV Diseases of the genitourinary system
XV Pregnancy, childbirth and the puerperium
XVI Certain conditions originating in the perinatal period
XVII Congenital malformations, deformations and chromosomal abnormalities
XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
XIX Injury, poisoning and certain other consequences of external causes
XX External causes of morbidity and mortality
XXI Factors influencing health status and contact with health services
XXII Codes for special purposes
International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2008
Chapter I
Certain infectious and parasitic diseases
(A00-B99)
Incl.: diseases generally recognized as communicable or transmissible
Use additional code (U80-U89), if desired, to identify the antibiotic to which a bacterial agent is resistant.
Excl.: carrier or suspected carrier of infectious disease (Z22.-)
certain localized infections - see body system-related chapters
infectious and parasitic diseases complicating pregnancy, childbirth and the puerperium [except obstetrical tetanus and human immunodeficiency virus [HIV] disease] (O98.-)
infectious and parasitic diseases specific to the perinatal period [except tetanus neonatorum, congenital syphilis, perinatal gonococcal infection and perinatal human immunodeficiency virus [HIV] disease] (P35-P39)
influenza and other acute respiratory infections (J00-J22)
This chapter contains the following blocks:
A00-A09 Intestinal infectious diseases
A15-A19 Tuberculosis
A20-A28 Certain zoonotic bacterial diseases
A30-A49 Other bacterial diseases
A50-A64 Infections with a predominantly sexual mode of transmission
A65-A69 Other spirochaetal diseases
A70-A74 Other diseases caused by chlamydiae
A75-A79 Rickettsioses
A80-A89 Viral infections of the central nervous system
A90-A99 Arthropod-borne viral fevers and viral haemorrhagic fevers
B00-B09 Viral infections characterized by skin and mucous membrane lesions
B15-B19 Viral hepatitis
B20-B24 Human immunodeficiency virus [HIV] disease
B25-B34 Other viral diseases
B35-B49 Mycoses
B50-B64 Protozoal diseases
B65-B83 Helminthiases
B85-B89 Pediculosis, acariasis and other infestations
B90-B94 Sequelae of infectious and parasitic diseases

SNOMED CT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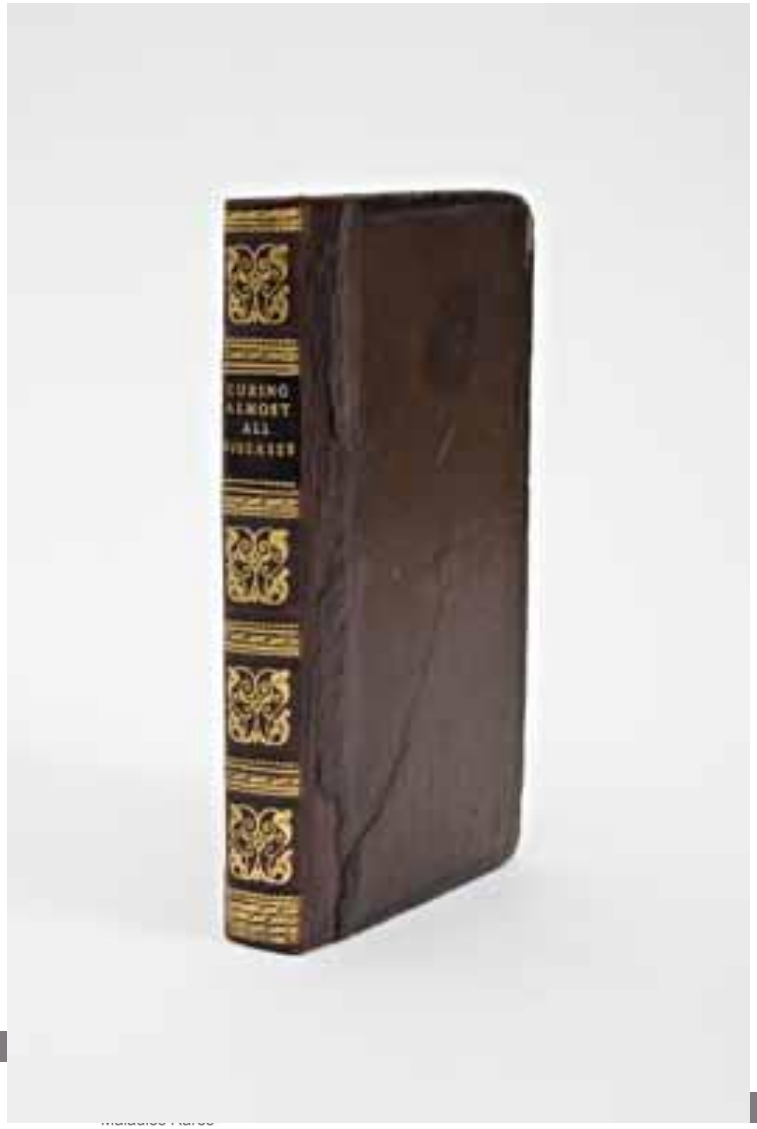
First medical classifications



1626-1689 :
Thomas SYDENHAM
medical documentation
"Opera Universa".

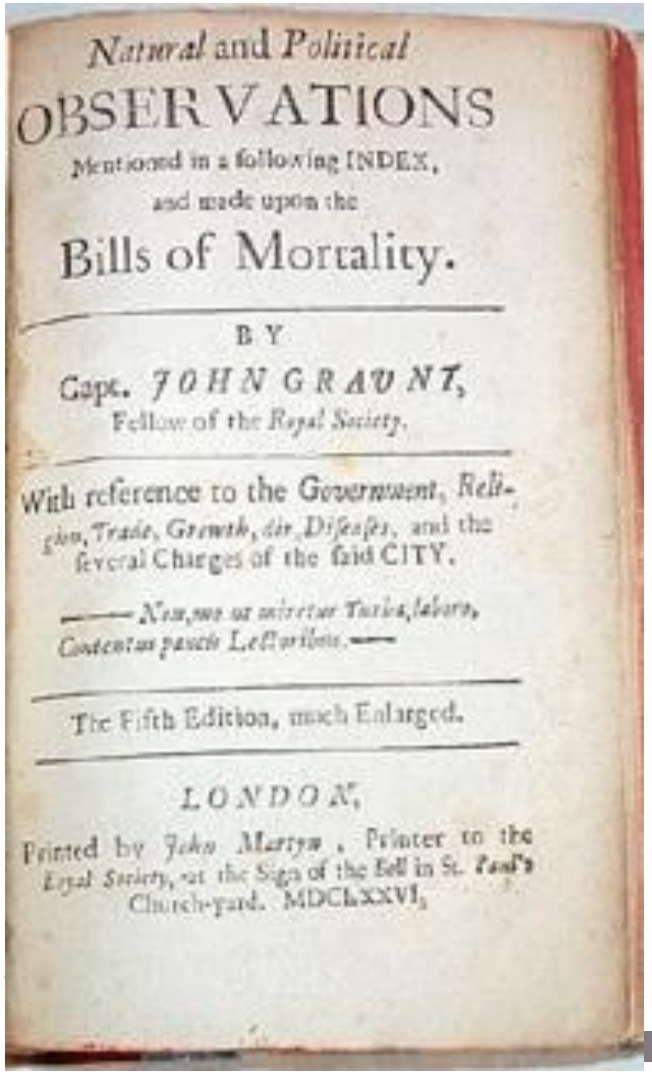
1662 : John GRAUNT

- First work of modern epidemiology

describes the causes of mortality before age of 6,

in London

J. GRAUNT 1662
causes of infant mortality



Natural and *Political*

OBSERVATIONS

Mentioned in a following INDEX,

and made upon the

Bills of Mortality.

BY

Capt. JOHN GRAUNT,

Fellow of the *Royal Society*.

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

—— *Non, nec ut mirentur Turba, laboro,*
Contentus paucis Lectoribus. ——

The Fifth Edition, much Enlarged.

LONDON,

Printed by *John Martyn*, Printer to the *Royal Society*, at the Sign of the Bell in St. *Paul's* Church-yard. MDCLXXVI.

Chrisoms
Convulsion
Rachitism
Prematurity
Mortinatality
Hepatomegaly
Overlaid
Smallpox, chickenpox, measles
Gravel
Stranguary

BOISSIER DE SAUVAGES 1763
classification : class and order

SYNOPSIS CLASSIUM *ET ORDINUM.*

CLASSIS I. *VITIA.*

Symptomata cutanea levidentia, vel mechanicis Chirurgiae auxiliiscuranda.

Ordo I. *Maculae*, coloris nativi mutationes.

Ordo II. *Efflorescentiae*, tumores humorales exigui gregales.

Ordo III. *Phymata*, tumores humorales folitarii.

Ordo IV. *Excrescentiae*, tumores à folidis adauctis.

Ordo V. *Cystides*, tumores capfulati fluido referti.

Ordo VI. *Ectopiae*, tumores à partibus à fuâ fede dimotis.

1785 : William CULLEN published his "Synopsis Nosologiae Methodicae".

A statistical approach for a systematic classification

- 1853, the congress of statistics in Brussels, according to a proposal of Achille Guillard, statistician and botanist, (who introduced the term *demography*) decided that « it was necessary to set up a uniform nomenclature of the causes of death »
- Marc d'Espine and William Farr were in charge to present a project of nomenclature for the 1855 congress.

International classification of diseases

1855 : William FARR (1807-1883)
Proposed his classification of causes of death.

1893 : Jacques BERTILLON (1851-1922)

- international classification

of the causes of death
1900 : 1st revision
of Bertillon's classification
International Classification of Diseases
(ICD) decennal revision

The difficulty of classifying: methods and tools

Difficulties of nosology

- Several difficulties to apply: the absence of a definition of medical terminology,
- No consensus on medical definitions,
- Inappropriate evolutionary adaptation,
- Lack of universality of the language: use of synonyms, proper nouns, eponyms, acronyms
- Cognitive sciences bring their support including language support to understand the organization of medical language.
- Paradigm, syntagm, pragmatics.

Contribution of linguistic: paradigm

- For linguists a *paradigm* is a set of terms that may lay in a point of a speech chain.
- In a sentence the paradigmatic relationship is a *vertical* relationship.
- Thus, in the example below, the following indicative terms have between them a relationship of interchangeability.
- She gives bread
  work
  ideas
  life

Medical language: paradigm

- One chooses an object in the list of paradigms.
- This choice is inconsequential to the foregoing.
- A paradigmatic change may change the meaning of a sentence (even makes it meaning anything!).
- The paradigms are mutually exclusive and are just lists.
- A directory is of the order of a paradigm.

Medical language: syntagm

- Syntagm is borrowed from the Greek
  - 'suntagma', set of arranged things,
  - and 'tassein' the science of the laws of classification.
- In a sentence the syntagmatic relationships organize an horizontal combinatorial.
- Each element is determined by its place on the basis of the preceding and following terms.

Medical language: syntagm

- "She gives life to her children”.
- If you replace “she" by "us", we must also change the verb form and the possessive pronoun.
- Thus, a syntagmatic change calls into question the ability of a sentence to mean something.
- Syntagms combine to carry a meaning.
- A novel is of the order of a syntagm.

Pragmatics

- A complementary semantic dimension is provided by the analysis of the meaning of the medical language conveyed by the context of its production.
- It is called *pragmatics*.

Building classifications taxonomy, systematics

Organizing a classification

- The organization of classifications is a function of the model that is defined for structuring knowledge.
- It requires a model *a priori*.
- The model should be based on a clear, reliable and reproducible organizational principle.
- Each term of the classification must be defined precisely, unambiguously.
- is endowed with information anything that reduces uncertainty.
- The model must be based on reproducible operating criteria. Thus, the same objects must be classified in the same way.

Pyrame de Candolle (1778-1841)

- 1813 Swiss botanist, created the term *taxonomy* in his "elementary theory of Botany or exposition of the principles of the natural classification and art to describe and study the plants",
- to designate in his "theory of classifications" both the method and what he described as a “basis for philosophical Botany”.

(Mémoires et souvenirs, Livre III, § 11)

Taxonomy

- Taxonomy would origin from the Greek
- ταξινομία *taxis*, 'placement', 'putting into order'
- (and indirectly from the Sanskrit; taksh = 'prune', 'do', 'train')
- and *nomos,* "law"
- It describes and defines the taxa

Taxon

- Conceptual entity that is supposed to gather all living organisms sharing some taxonomic or defined diagnostic characters.
- These characters are considered homogeneous according to their taxonomic rank, their 'weight', their taxonomic value relative to the assessment of systematists.
- The species is the basic taxon of the systematic classification.

Systematics

- Inseparable from the taxonomy
- Systematics is designed to *count* and *categorize* taxa, in a certain order, based on various principles.
- Refers to both the method used ("phylogenetic systematics") and the result (the "Systematics of fungi")

Representing classifications

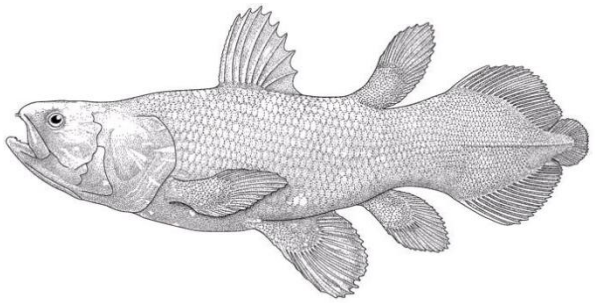
Representing classifications

- Represented as a tree from a root including all beings live existing or having existed, to the individuals.
- Each node in the tree defines a taxon that groups all sub-taxa that generates the node.
- The classical systematics is based on the internal hierarchy of taxa according to criteria of 'morphological' similarity and supposed affinities.
- Subsequently, and especially from the work of Lamarck and Darwin, this order also gave a dimension of evolution.
- Given the limits of genealogy, *phylogeny* then has grown up particularly in the second half of the 20th century.

Phylogenetic systematics

- *Phylogenetic systematics* has developed from a reconstruction method known as *cladistics*, initiated by Hennig in 1950.
- Schematically this method is based on evolutionary relationships for which the fundamental criterion for the choice of classification is that it must strictly reflect the phylogeny, i.e. the *degree of relatedness* between species.

For example, one can show that the Coelacanth is closer to humans than to a sardine!



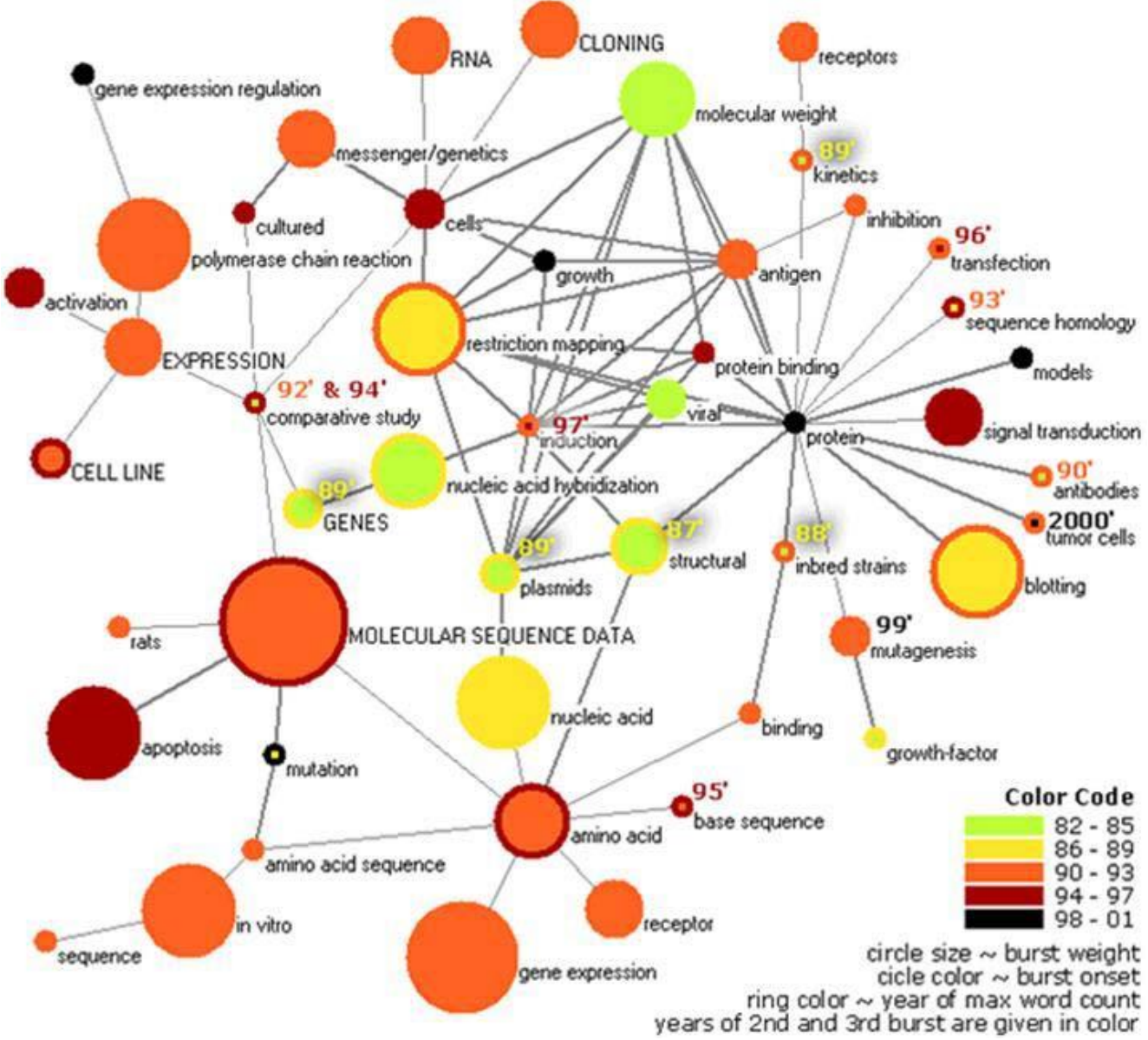
Cladogram and cladistics

- A *cladogram* is a 'phylogenetic tree' illustrating the distribution of characters that optimize the hypotheses of homology.
- A *clade* or 'branch' contains an ancestor and all its descendants.
- A *cladistic* is a phylogenetic classification which, in principle, must includes only clades.
- A *cladistic analysis* is a method of analyzing characters.

Phylogenetic trees

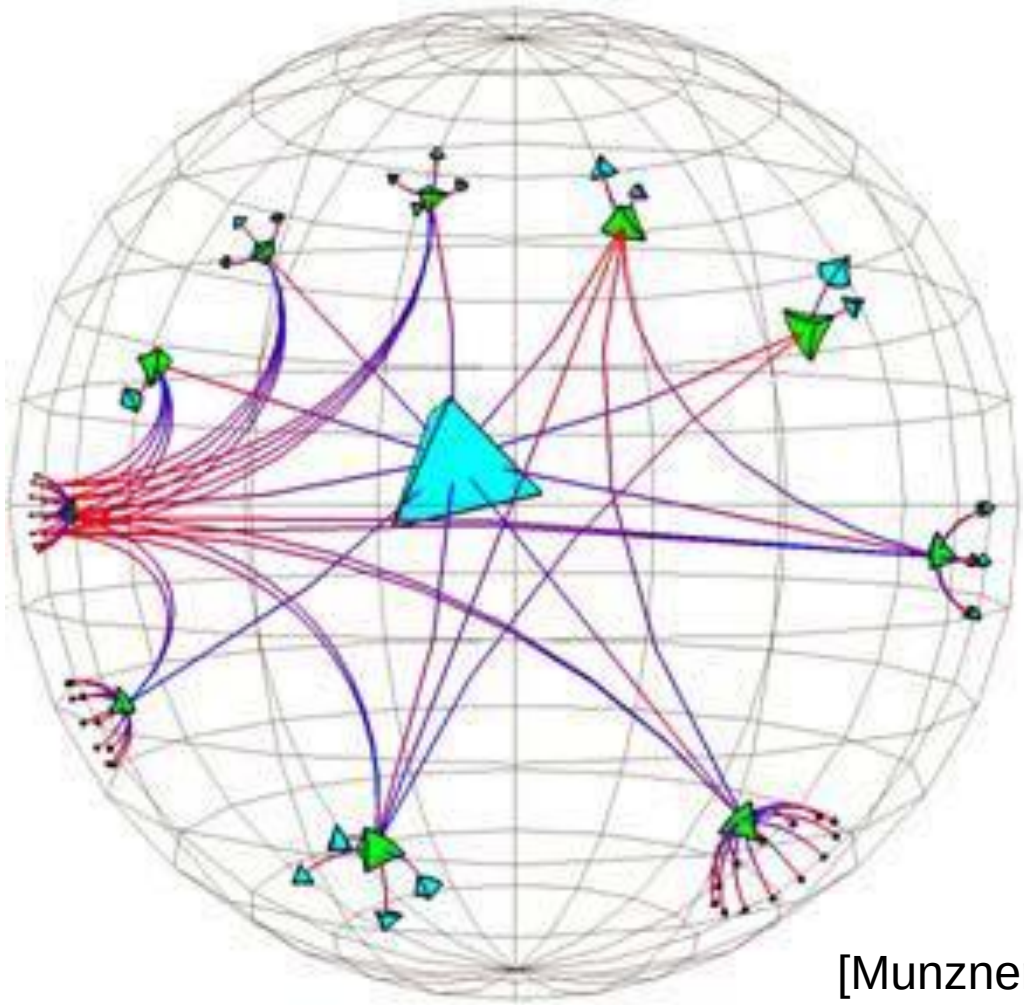
One describes three major types of construction of these trees:

- The *cladistic* approach seeks to determine a branch-specific characters, who "sign" a matching.
- The *phenetic* approach is based on measurements of distance between taxa (e.g. assessed by counting the differences in DNA sequences) without trying to make a phylogenetic interpretation.
- The *probabilistic* approach which uses most often molecular models of the evolution of the characters.



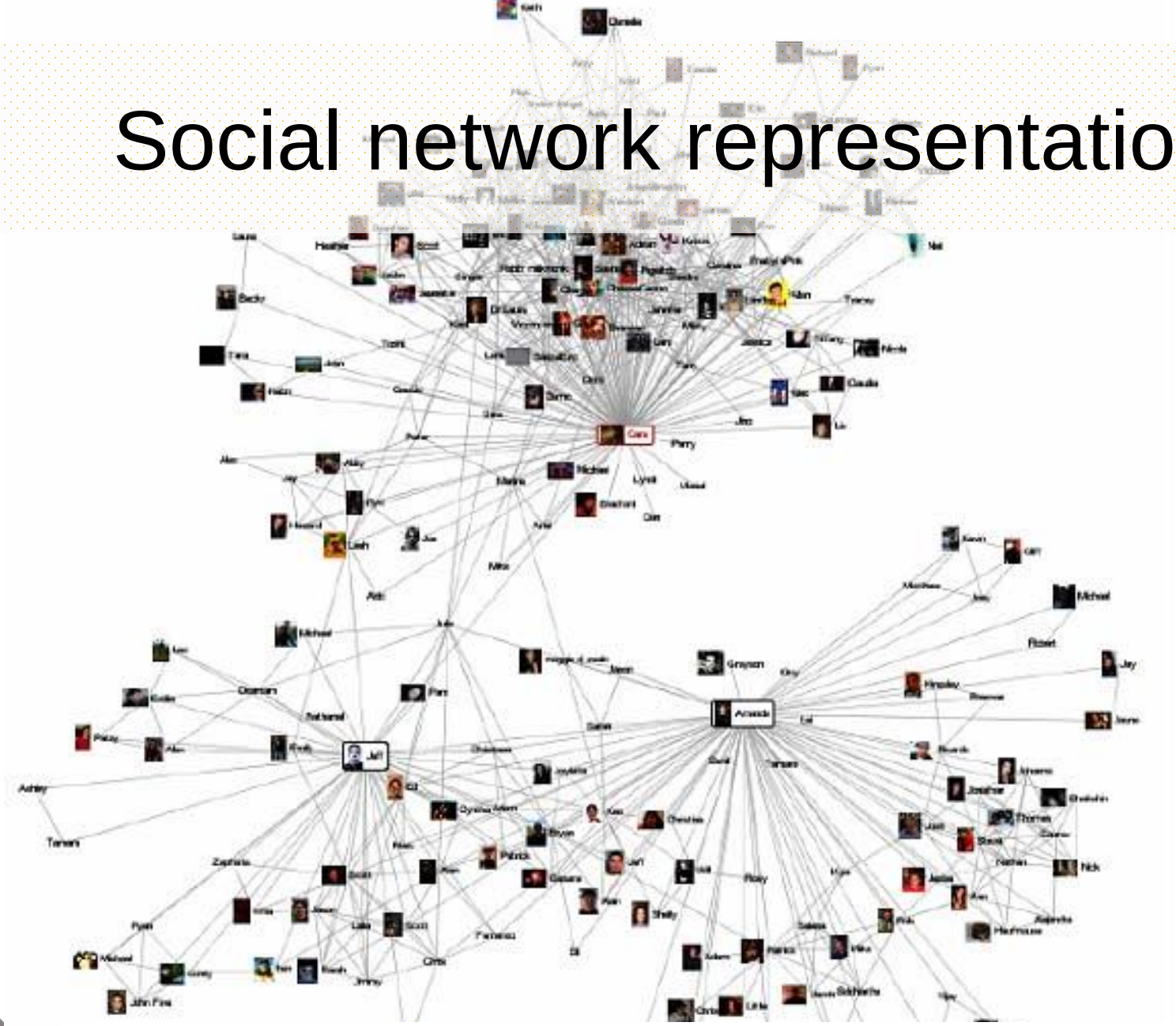
Graph of the 50 most frequent words of the 10% most cited PNAS articles [Mane & Borner, 2004].

Representation of a network of internet pages



[Munzner & Burchard, 1995].

Social network representation



Interest for revealing underlying structures, particularly the connex and strongly connex components. [Heer & Boyd, 2005].

The occlusion phenomenom

- As soon as the size of a graph or the links density increases, a tangled web of links appears.
- Then, it becomes very difficult for the user to explore the graph visually and to interact with its constituent parts.
- This phenomenon of *occlusion* occurs especially in case of large graphs.
- techniques of matrix representations are here of interest.

Arborescent representations

- A tree is a connected *acyclic graph* (its form evokes the branching of the branches of a tree).
- A tree is a specific graph where each element has more than one father.
- The result of the positioning of the tree nodes depends on the geometry used:
  - either Euclidean geometry,
  - or hyperbolic geometry.

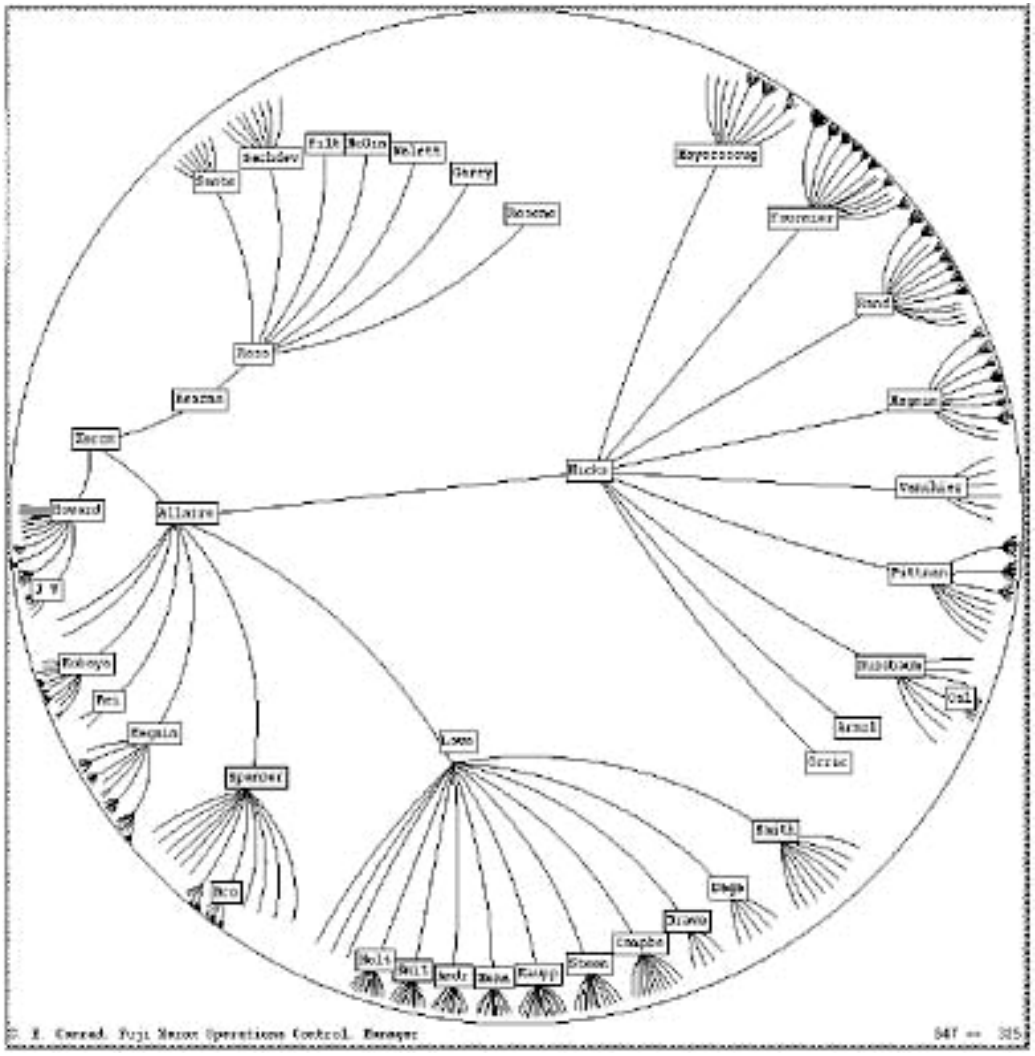
[van Wijk *et al.*, 2003].

Hyperbolic trees

- In case of large hierarchies, a map space is often too narrow.
- One must then choose between the level of details and an overall vision.
- A distribution of entities radially in a space with a hyperbolic geometry responds in part to this goal.
- In this geometry the plan is strictly defined inside the limits of a disc whose boundary is called horizon.
- The lines are the arcs of circles orthogonal to the boundary of the disk.

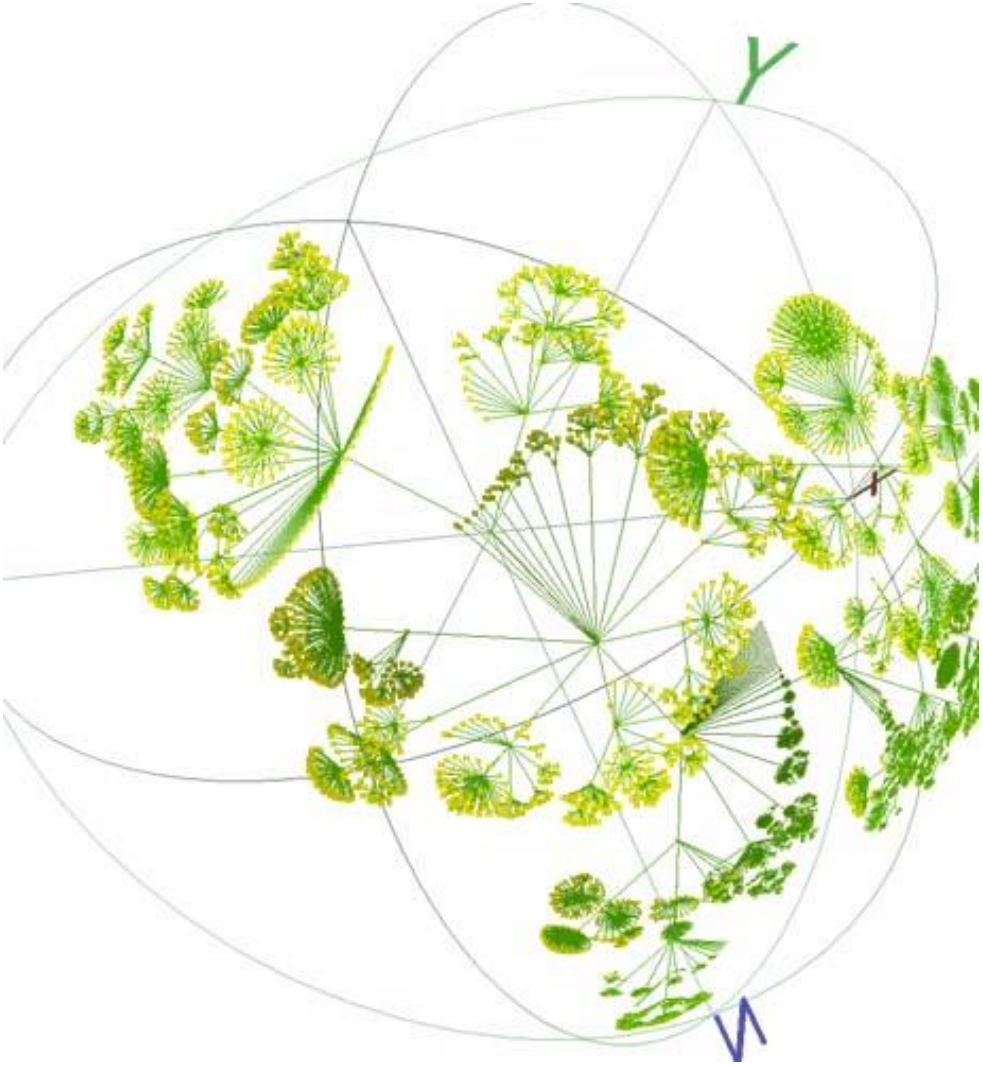
[Lamping *et al.*, 1995].

Hyperbolic hierarchical browser



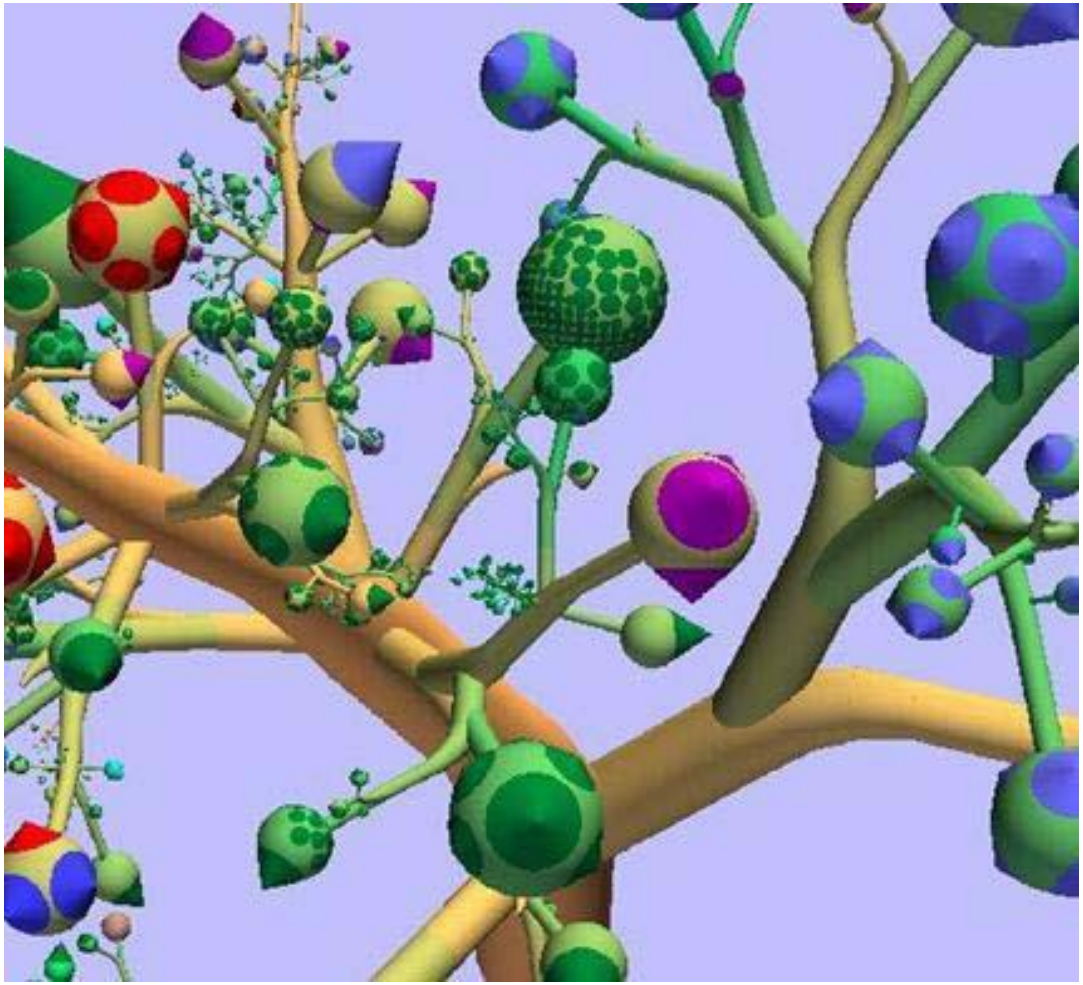
Representation of a hierarchy with an hyperbolic geometry [Lamping, 1995]

3D hyperbolic hierarchical browser



Representation of a hierarchy using an hyperbolic geometry [Hughes *et al.*, 2004].

« Botanic »visualization



Representation of hierarchies using a 3D virtual metaphore [Kleiberg *et al.*, 2001].

Sharing a common language, ontology

Sharing the same language

Having the same language in common enables sharing :

- Common symbols and concepts (syntax)
- Agreement on their meaning (semantic)
- Classification of concepts (taxonomy)
- Associations and relationships between concepts (Thesaurus)
- Rules and knowledge about wich relationships are allowed and make sense (Ontology)

Representing knowledge

- ***Ontology*** is a philosophical study of the nature of being, existence or reality, as well as the basic categories of beings and their relationships.

- an ontology is *an explicit and formal specification of a shared conceptualization.*

  (T Gruber 1993)

- What does that mean?

Ontology

- An ontology is the *specification* of a *conceptualization* of a domain of knowledge
- The *conceptualization* of a domain refers to a choice of description of a domain (natural taxonomy)
- The *specification of this conceptualization* refers to the formal description which will be developed, that will be transposable and computer usable (formalization, logical rules..).
- An ontology is a thus a computational representation of a domain of knowledge based upon a controlled, standardized, vocabulary for describing entities and the semantic relationships between them. (HPO, OntoOrpha)
- It is a network of concepts expressed in a given language with a given syntax.

The roles of an ontology

- On the computer side:
  - define/provide a *formal semantic* for information that allows its management by a computer
- On the human being side :
  - define/provide an *interpretative semantic* of a domain of the real world based on a consensus and enabling to link the computer exploitable content to its signification for humans.

Composition of an ontology

An ontology is composed of:

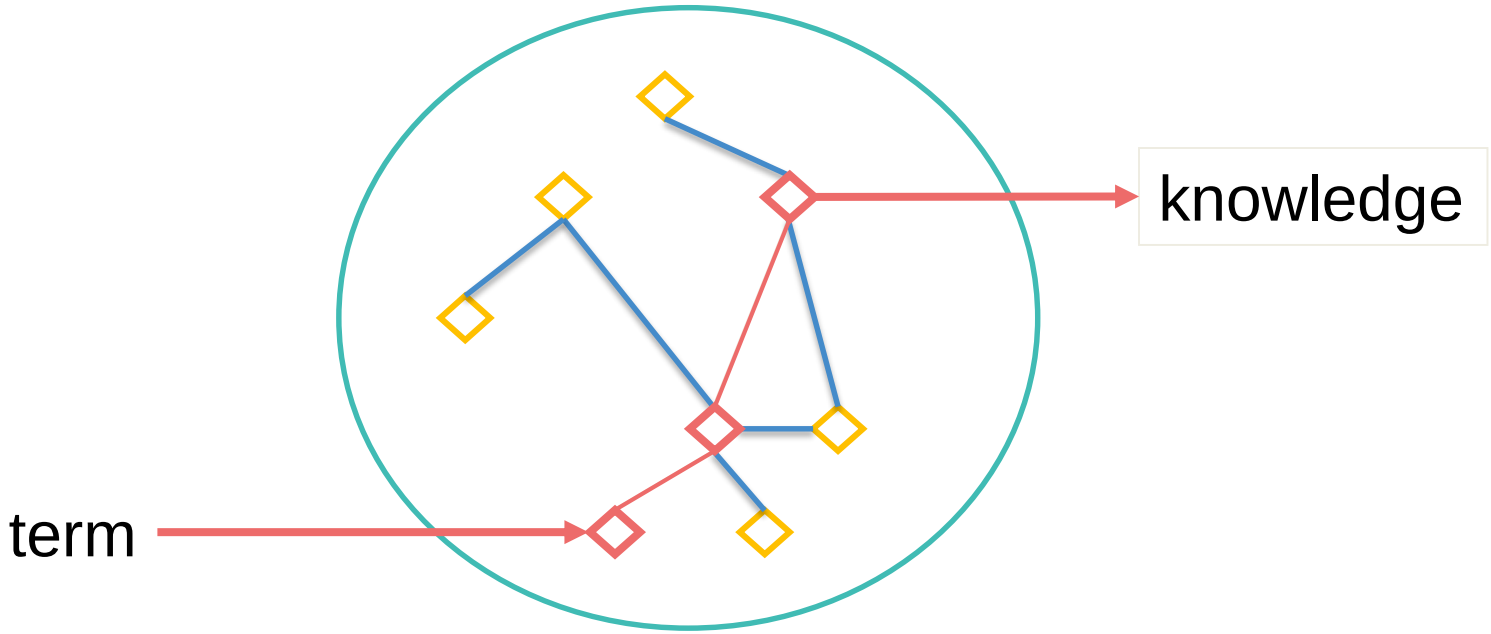
- *Classes* which represent concepts
- *Attributes* which are name –value pairs
- *Relations* are specific attributes, the values of which are objects of classes
- *Rules* represent constraints between relations and attributes that specify allowed values.

Composition of an ontology

- Classes, relations and constraints, put together, can support *statements* or *assertions*
- An *axiom* describes knowledge that cannot be represented simply by other components.
- *Instances* describe the individuals that constitute an ontology (either: people, animals, plants,..or abstract individuals, numbers, words,..)

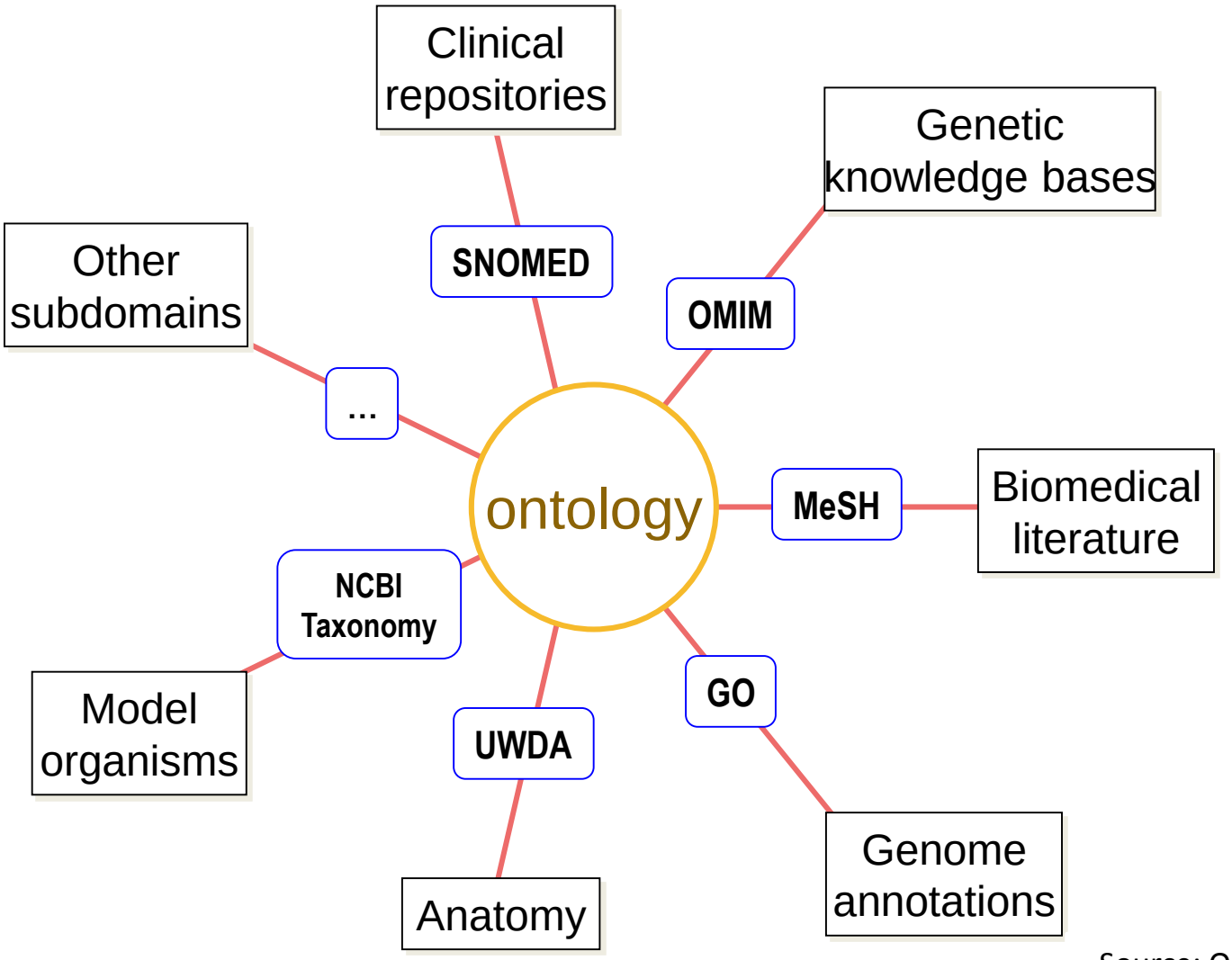
From facts to knowledge

- Mapping terms to concepts
- Visualizing concept spaces
- Navigating concept spaces



Source: O Bodenreider, National Library of Medicine,

Ontology: Integrating subdomains



Source: O Bodenreider, NLM

Terminology vs Ontology

- Terminological resources
  - Collections of terms (e.g., controlled vocabularies)
  - Useful for indexing and annotating
  - MeSH, GO
- Ontological resources
  - Collections of
    - kinds of entities (substances, qualities, processes)
    - relations among them
  - Useful for reasoning
  - UMLS Semantic Network, SNOMED CT

Source: O Bodenreider, National Library of Medicine, Lister Hill National Center for Biomedical Communications

Human Phenotype Ontology

Home | News | HPO Browser | Tools | Downloads | Citing HPO | Who uses HPO? | Documentation

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- Who uses HPO?
- Documentation
  - Defining HPO Terms
  - Annotation guide
  - How to collaborate
  - Legal issues
- HPO people

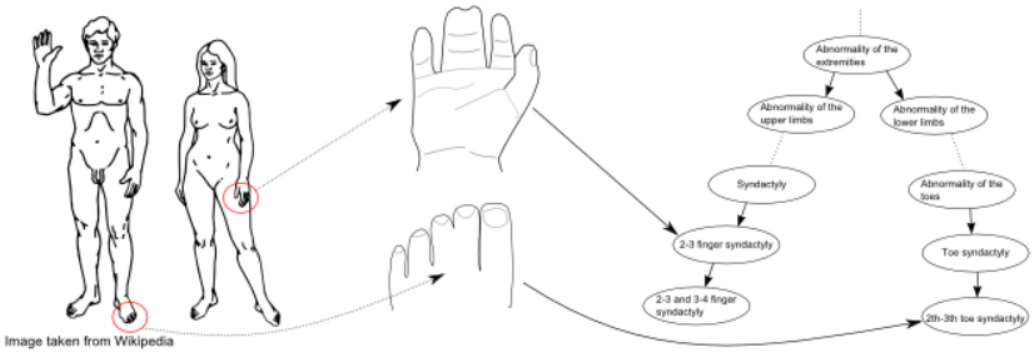

Image taken from Wikipedia

Human Phenotype Ontology > Human Phenotype Ontology Website

... *news* ...

An ontology is a computational representation of a domain of knowledgebased upon a controlled, standardized vocabulary for describing entities and the semantic relationships between them. The Human Phenotype Ontology (HPO) aims to provide a standardized vocabulary of phenotypic abnormalities encountered in human disease. Terms in the HPO describes a phenotypic abnormality, such as *atrial septal defect*.

The HPO was initially developed using information from Online Mendelian Inheritance in Man (OMIM), which is a hugely important data resource in the field of human genetics and beyond. The HPO is currently being developed using information from OMIM and the medical literature and contains approximately 10,000 terms. Over 50,000 annotations to hereditary diseases are available for download or can be browsed using the PhenExplorer.

The HPO is now being developed in collaboration with members of the OBO Foundry (Open Biological and Biomedical Ontologies), and logical definitions for HPO terms are being developed using PATO and a number of other ontologies including the FMA, GO, ChEBI, and MPATH. The HPO can be used for clinical diagnostics in human genetics (Phenomizer), bioinformatics research on the relationships between human phenotypic abnormalities and cellular and biochemical networks, for mapping between human and model organism phenotypes, and for providing a standardized vocabulary for clinical databases, among many other things. There exists a webpage for every HPO-term.

The HPO project encourages input from the medical and genetics community with regards to the ontology itself and to clinical annotations.

Monarch Initiative

Model organisms are a cornerstone of biomedical research to investigate biological processes, test gene-based disease hypotheses, and develop and test disease treatments. The HPO team is a member of the Monarch Initiative, which is developing computational and semantic resources and software to allow cross-species phenotype analysis, and to integrate information from multiple organisms including phenotypic similarity, network analysis, gene expression and function, and genomics. One such tool for using phenotypic similarity between human disease and mouse models of disease is the Exomiser.

monarch INITIATIVE

OntoOrpha

ICBO: International Conference on Biomedical Ontology
July 28-30, 2011 · Buffalo, NY, USA

OntoOrpha: An Ontology to Support the Editing and Audit of Knowledge of Rare Diseases in ORPHANET

Ferdinand Dhombres[1,2,3,4], Pierre-Yves Vandenbussche[1,5], Ana Rath[2], Marc Hanauer[2], Annie Olry[2], Bruno Urbero[2,6], Rémy Choquet[1,2], Jean Charlet[1,2,3,7]

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[3]Sorbonne Universitiés, UPMC, Paris, France
[4]Service de Gynécologie-Obstétrique et Centre de Diagnostic Prénatal de l'Est Parisien, Hôpital Armand Trousseau, AP-HP, Paris, France
[5]Mondeca, Paris, France
[6]INSERM DSI – Langedoc-Roussillon, Montpellier, France
[7]AP-HP – Assistance Publique, Hôpitaux de Paris, Paris, France

Abstract. ORPHANET is the reference information portal on rare diseases and orphan drugs for healthcare professionals and for general audience. After ten years of evolution, current ORPHANET tools cannot support efficiently the edition, update and data sharing processes demanded by a constantly growing rare diseases knowledge. In order to improve the editing workflow, we are conducting research to build and use a rare diseases knowledge base in an *ontology-based architecture* that complies with the W3C standards of the semantic web: OWL, RDF, SPARQL and SKOS. Our ontology design approach is based on both domain expertise (in rare diseases and in knowledge engineering) and knowledge extraction from our relational database. The current version of OntoOrpha comprises over 11,000 classes

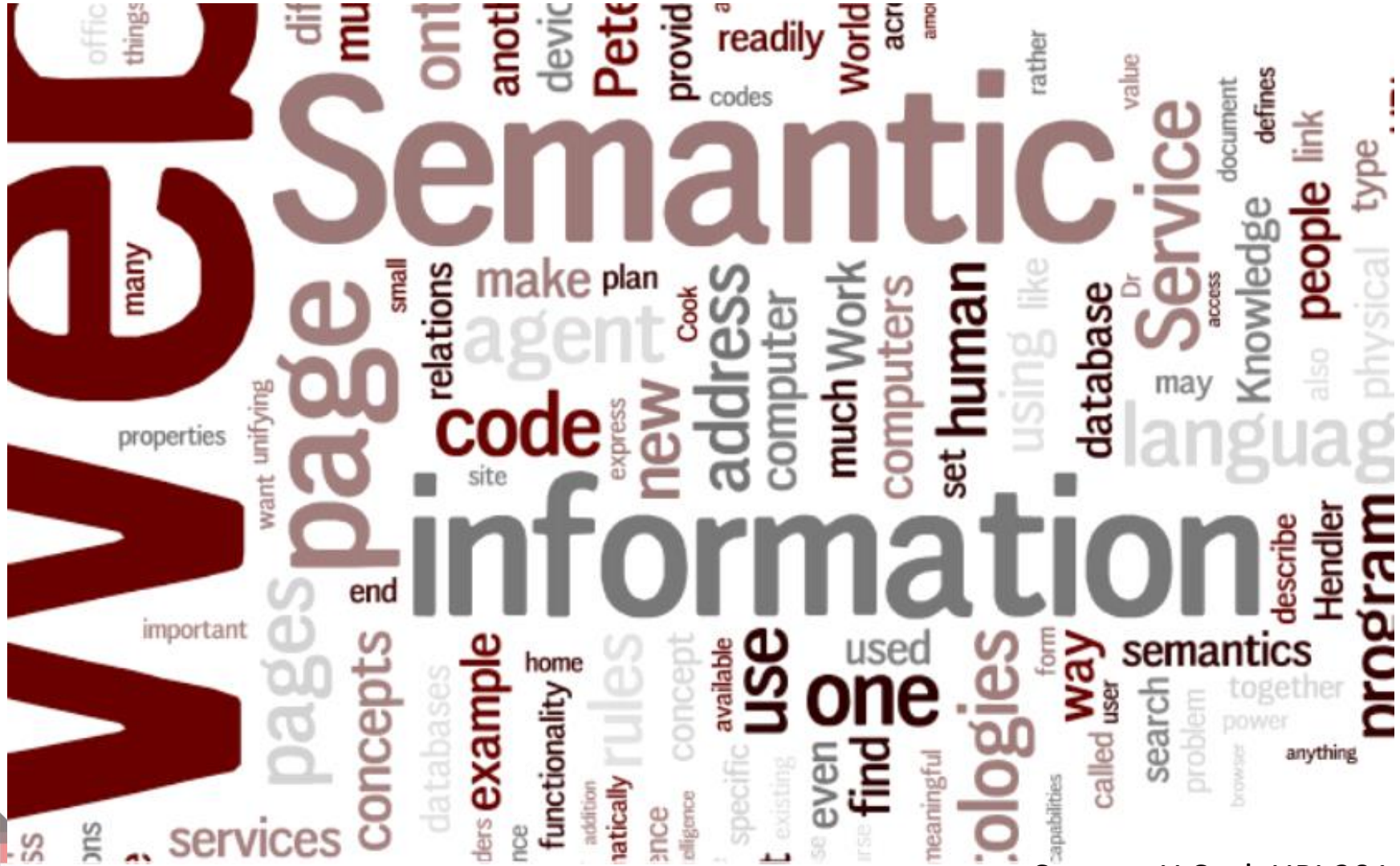
Expected utility of ontologies

- Pragmatic approaches for knowledge-based systems and semantic web
- create and maintain knowledge bases reusable
- Interoperability between knowledge-based systems
- Information system, conceptual vocabulary database, repository
- conceptual vocabulary for labelling and indexing documents
- Resource Description Framework models and Linking Open Data

Ontology: examples of uses

- Aid to differential or etiologic diagnosis
- Aid to research or aggregation of information
- Support quality control of knowledge
- Support semantic interoperability
- Assistance to the evolution of editorial methods
- Support generation of classifications

Ontology and computer sciences



Source: H Sack HPI 2014

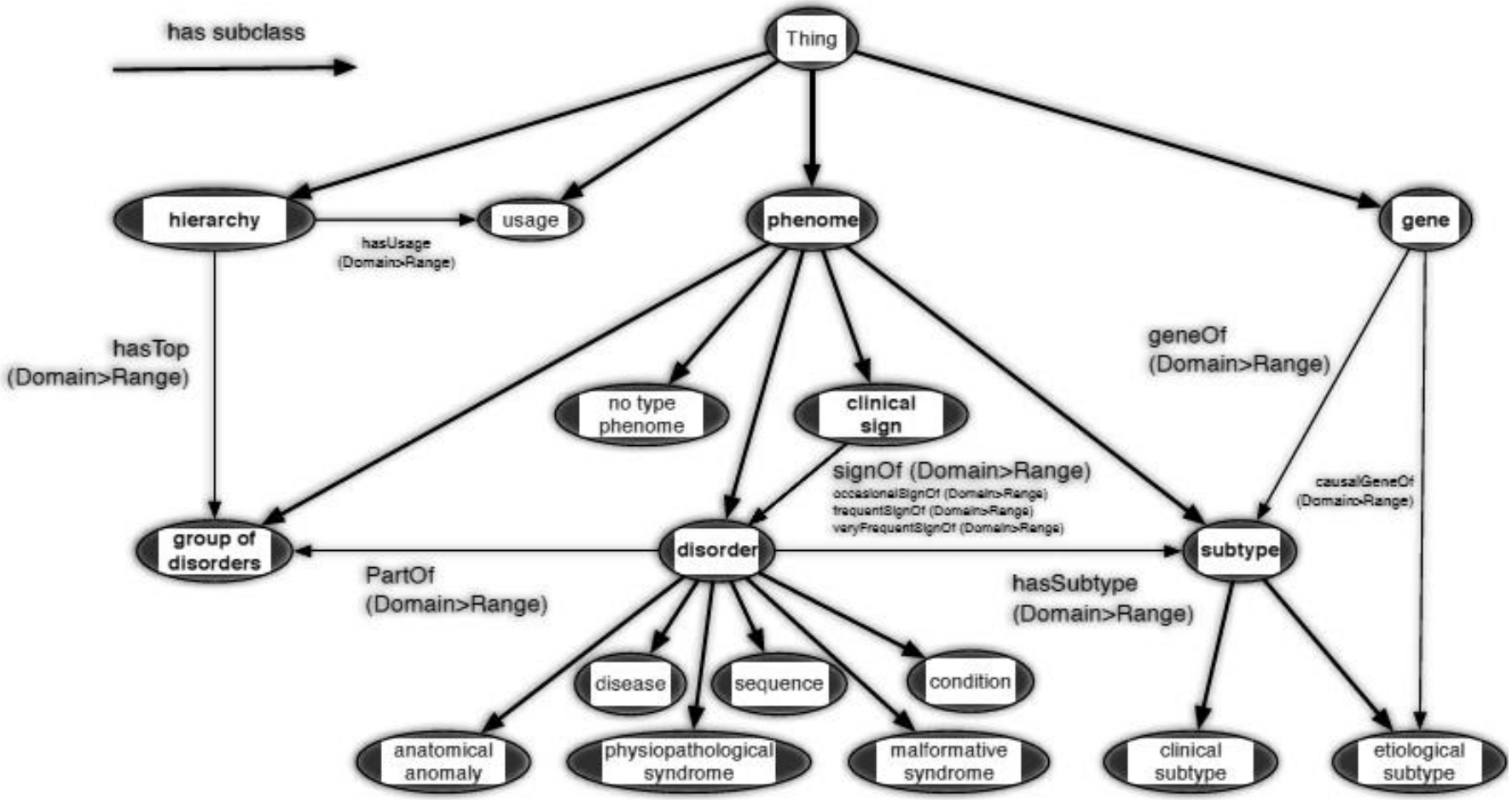
Ontology languages (1)

- **OWL**
  - The **Web Ontology Language** (**OWL**) is a family of knowledge representation languages or ontology languages for authoring ontologies or knowledge bases.
  - The languages are characterized by formal semantics and RDF/XML-based serializations for the Semantic Web.
  - The **Resource Description Framework** (**RDF**) is a family of World Wide Web Consortium (W3C) specifications originally designed as a metadata data model

Ontology Languages (2)

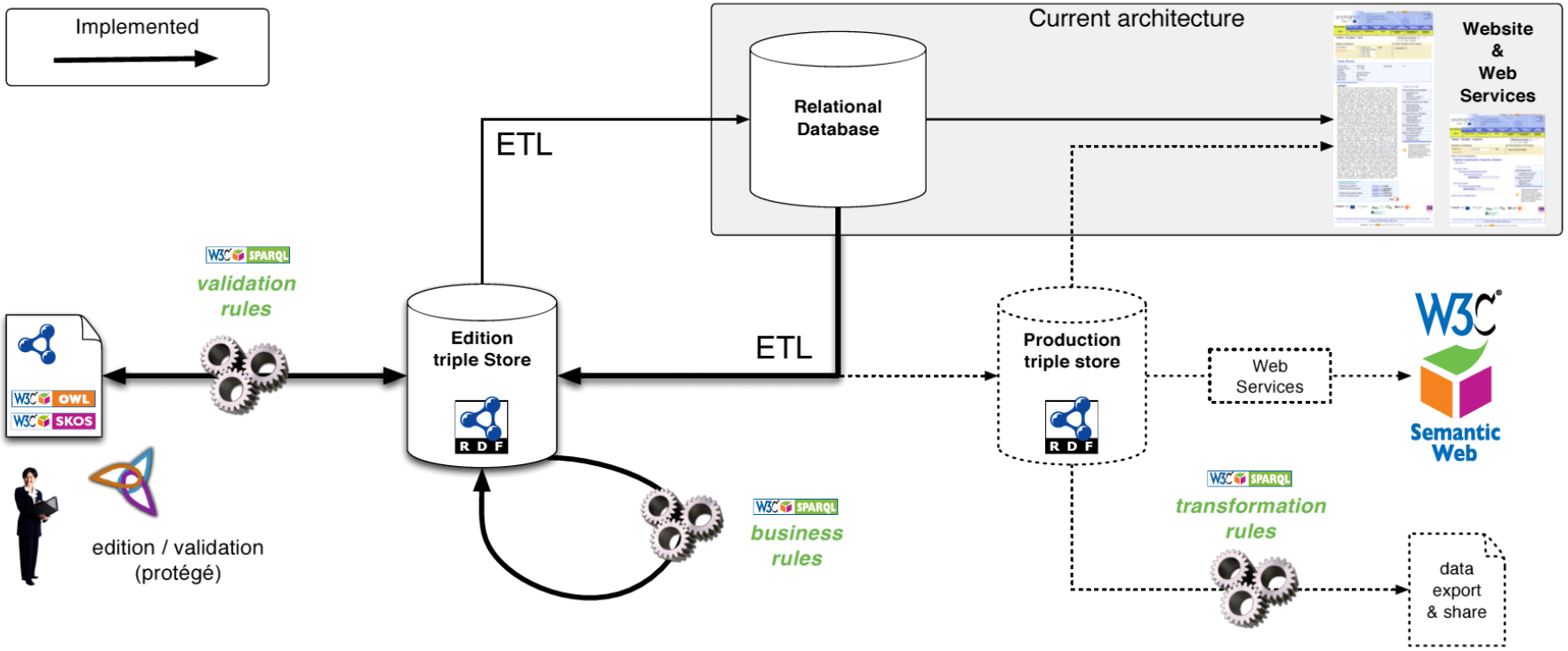
- **PROTEGE**
  - **Protégé** is a free, open source ontology *editor* and a *knowledge acquisition system*.
  - It provides a graphic user interface to define ontologies.
  - It also includes deductive classifiers to validate that models are consistent and to infer new information based on the analysis of an ontology.

Core RD ontology



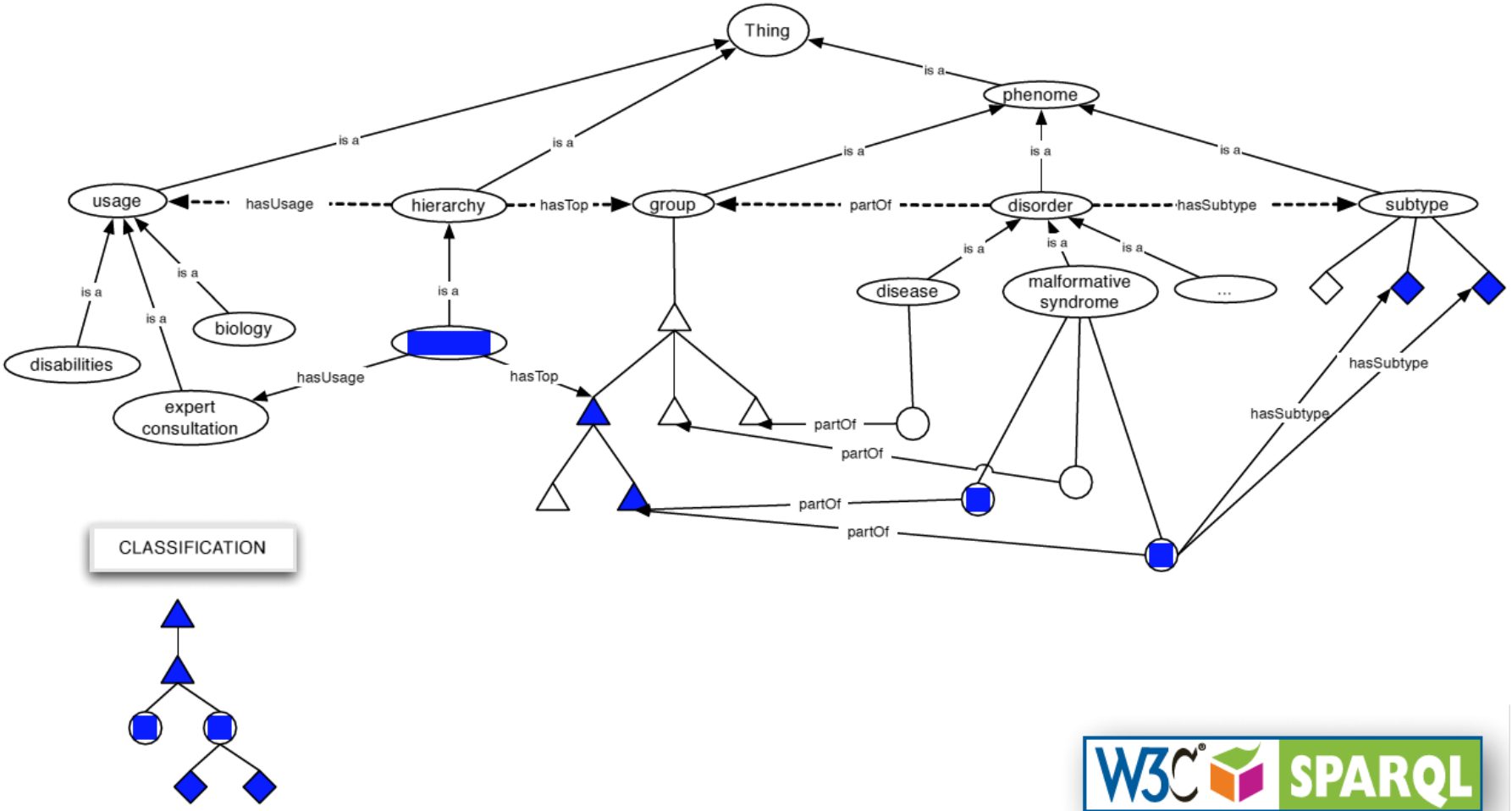
Source: F Dhombres 2012

Generating a RD ontology



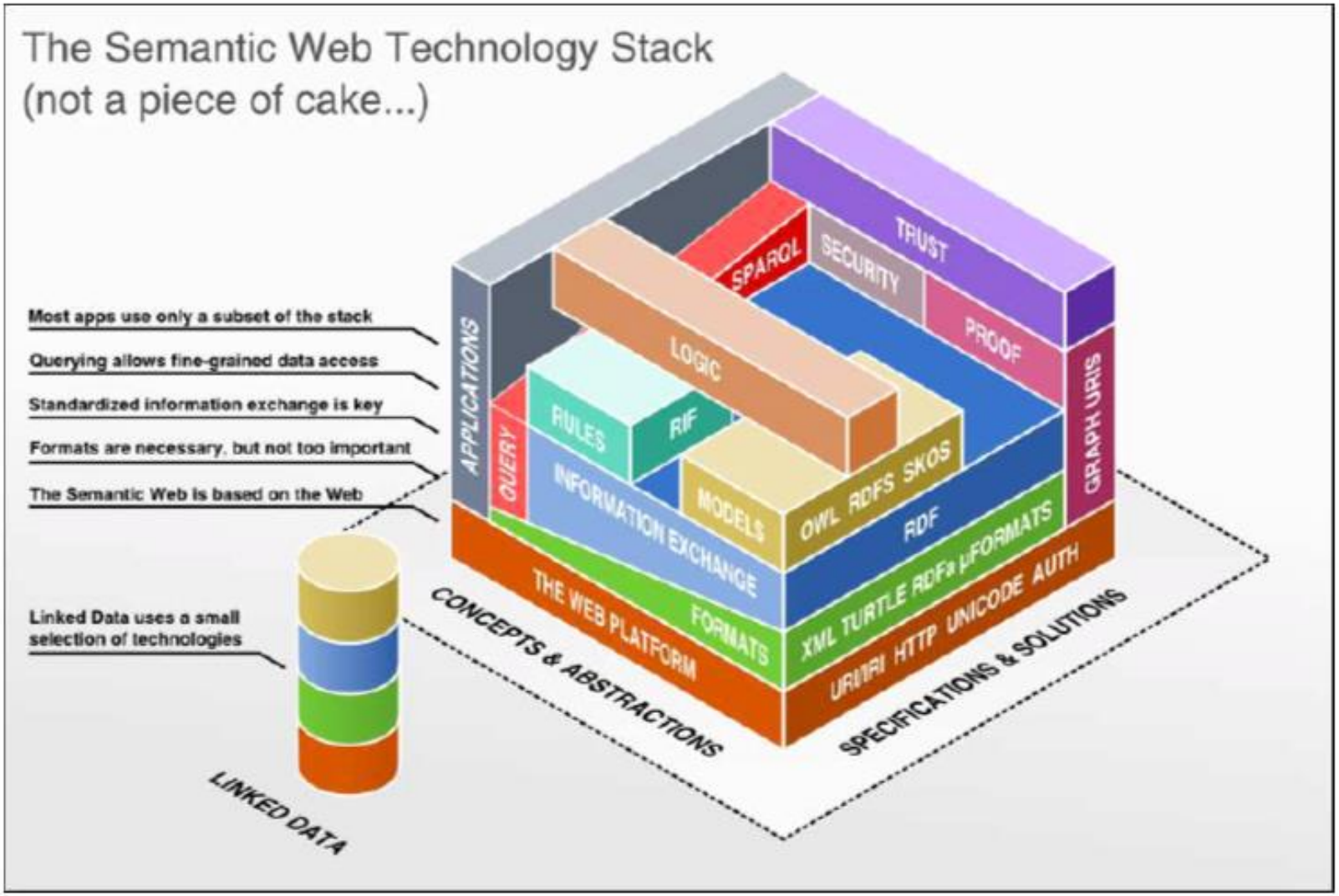
Source: F Dhombres 2012

A support for generating classifications



Source: F Dhombres 2012

Ontology and computer sciences



Source: H Sack HPI 2014

Standardization

Standardization

- A Need to standardize for:
  - The exchanged content (semantic, syntax)
  - The exchange services
  - The technical means of communication and transport
  - The safety devices

- The use of standards also helps:
  - discarding artifacts (data elements, or information models)
  - qualifying content (coding item)

Standards of transcoding

Choose the standards to transcode the information

In the view of increasing interoperability

Standards for transcoding (1)

- Standardization: the use of standards to discard artifacts (data elements, or information models) and qualify content (coding item)
- Standards for information models/data elements:
  - SNOMED (3.5, CT)
  - HL7
  - openEHR (EN 13606)

Standards for transcoding (2)

- Terminologies/Classifications:
  - Clinical Terms : LOINC, SNOMED CT
  - Orphan drugs : RxNorm, ATC, Thériaque, Vidal, Orphanet
  - Diagnosis RD: Orphanet, OMIM,
  - Signs : HPO (ICD10, signs to be validated)
  - Genes : OMIM, GenATLAS, Ensembl
  - Medical and administrative data messages: HL7 v2, v3

CDEs in the GRDR and transcoding

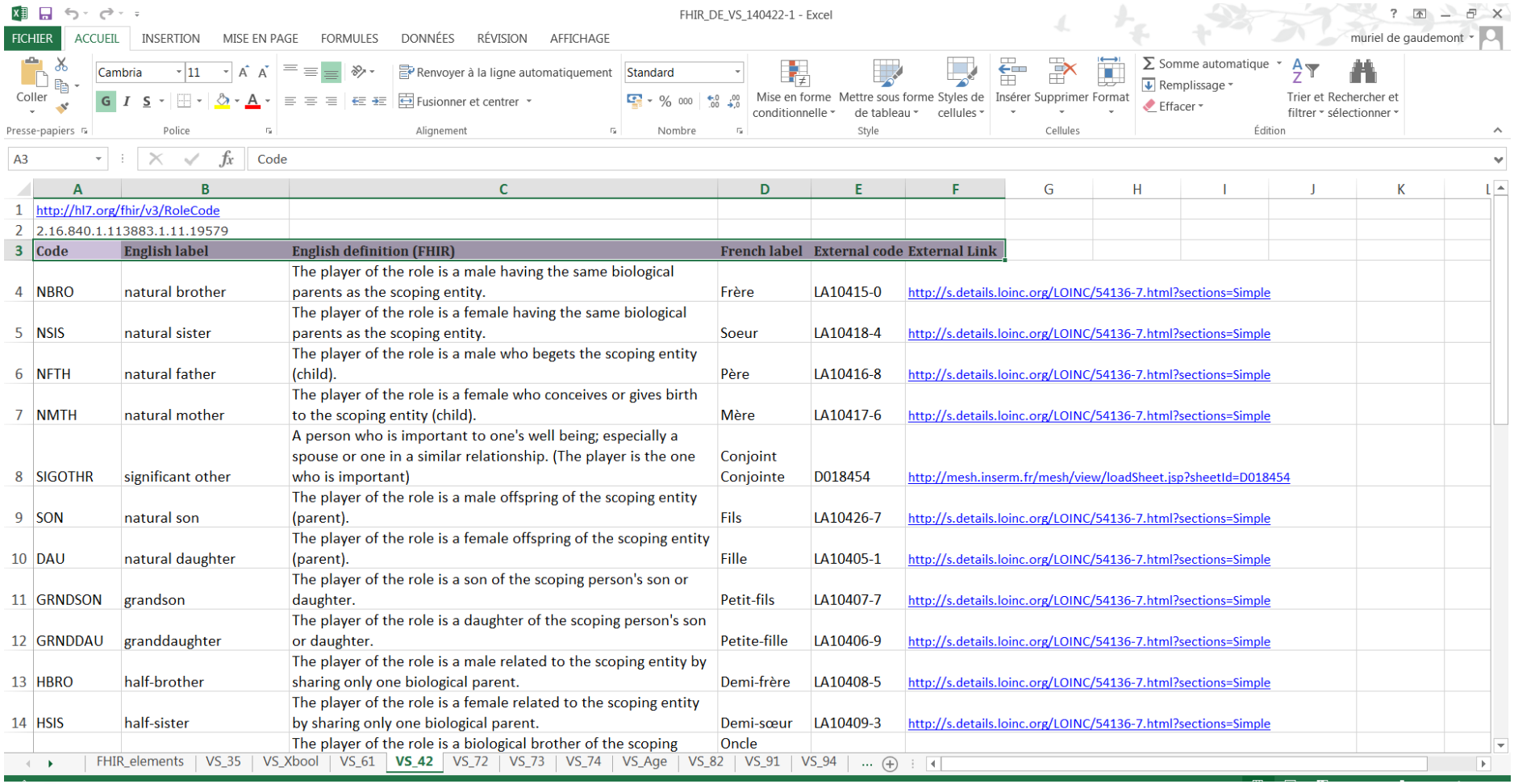
ORDR/GRDR Registry Model Common Data Elements (CDEs)
Updated 08-16-2013
CDEs collected for the **GRDR** are designated by a **GRDR** number e.g. GRDR001, GRDR002, etc.
CDEs used by the registries to generate the GUID ID are designated GUID

Item #	Item Concept	Question Text	Comments	Response Categories	Variable Structure	Reference Categories	Reference Categories Link (if applicable)	Recommended Degree of Requirement
15	Registrar	Is data entered by anyone other than the participant?		Yes No		1-Yes 2-No	LOINC Yes/No	Required
16	Name of Registrar	Name of person entering data in the registry			Sting		HL7 ST data type	Required
17	GRDR008 Record of Self Completion	Did the participant provide the information for this registry update?		Yes No Refused Don't know	Integer	1 – Yes 2 – No 3 – Refused 4 – Don't know	LOINC Yes/No/Refused/Don't Know	Required
				Self Parent (biologic, adoptive, or step) Grandparent Spouse		1 - Self 2 - Parent (biologic, adoptive, or step) 3 - Grandparent 4 - Spouse		

ORDR Model Data Elements | GUID Elements Appendix | Age to Height Appendix

http://www.grdr.info/index.php?option=com_content&view=article&id=3&Itemid=13

The F-MDS-RD standardization



	A	B	C	D	E	F
1	http://hl7.org/fhir/v3/RoleCode					
2	2.16.840.1.113883.1.11.19579					
3	**Code**	**English label**	**English definition (FHIR)**	**French label**	**External code**	**External Link**
4	NBRO	natural brother	The player of the role is a male having the same biological parents as the scoping entity.	Frère	LA10415-0	http://s.details.loinc.org/LOINC/54136-7.html?sections=Simple
5	NSIS	natural sister	The player of the role is a female having the same biological parents as the scoping entity.	Soeur	LA10418-4	http://s.details.loinc.org/LOINC/54136-7.html?sections=Simple
6	NFTH	natural father	The player of the role is a male who begets the scoping entity (child).	Père	LA10416-8	http://s.details.loinc.org/LOINC/54136-7.html?sections=Simple
7	NMTH	natural mother	The player of the role is a female who conceives or gives birth to the scoping entity (child).	Mère	LA10417-6	http://s.details.loinc.org/LOINC/54136-7.html?sections=Simple
8	SIGOTHR	significant other	A person who is important to one's well being; especially a spouse or one in a similar relationship. (The player is the one who is important)	Conjoint Conjointe	D018454	http://mesh.inserm.fr/mesh/view/loadSheet.jsp?sheetId=D018454
9	SON	natural son	The player of the role is a male offspring of the scoping entity (parent).	Fils	LA10426-7	http://s.details.loinc.org/LOINC/54136-7.html?sections=Simple
10	DAU	natural daughter	The player of the role is a female offspring of the scoping entity (parent).	Fille	LA10405-1	http://s.details.loinc.org/LOINC/54136-7.html?sections=Simple
11	GRNDSON	grandson	The player of the role is a son of the scoping person's son or daughter.	Petit-fils	LA10407-7	http://s.details.loinc.org/LOINC/54136-7.html?sections=Simple
12	GRNDDAU	granddaughter	The player of the role is a daughter of the scoping person's son or daughter.	Petite-fille	LA10406-9	http://s.details.loinc.org/LOINC/54136-7.html?sections=Simple
13	HBRO	half-brother	The player of the role is a male related to the scoping entity by sharing only one biological parent.	Demi-frère	LA10408-5	http://s.details.loinc.org/LOINC/54136-7.html?sections=Simple
14	HSIS	half-sister	The player of the role is a female related to the scoping entity by sharing only one biological parent.	Demi-sœur	LA10409-3	http://s.details.loinc.org/LOINC/54136-7.html?sections=Simple
			The player of the role is a biological brother of the scoping	Oncle		

Interoperability

Interoperability

- Ability attached to multiple systems or components to exchange information and to use the information thus exchanged.
- Interoperability is *semantic* if the information exchanged is interpretable by systems, without distortion of meaning from one system to another, and without alteration of meaning in the long term.

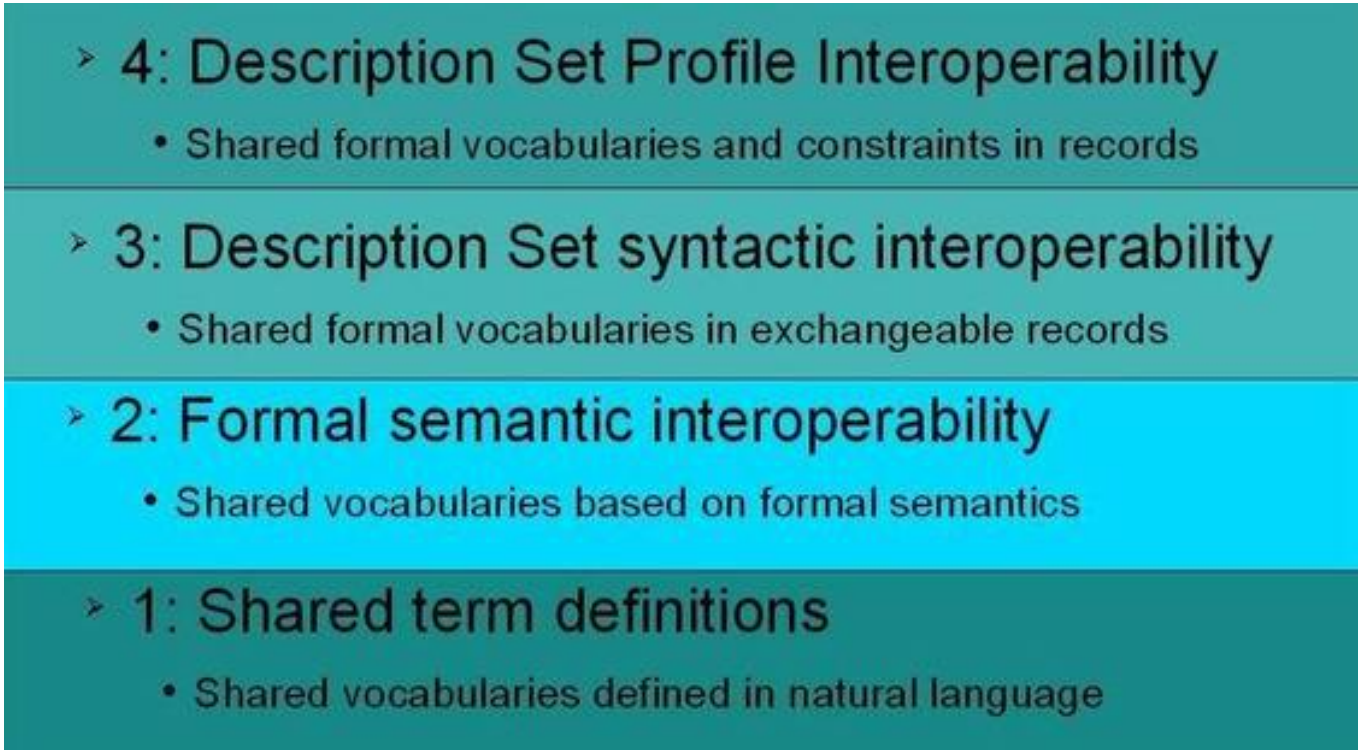
Semantic interoperability

- How to build RD semantic repositories and adhere to their professionals use?
- How to facilitate coding information for RD?
- How to pass RD information without loss of meaning?
- How to maintain RD repositories?

Semantic interoperability

- Data characterization : structured or not, and depending on the use, individual or collective
- Model of representation of information
- Choice of repositories (nomenclature of acts, diagnoses, drugs, medical devices,...),
- Repositories of patient identifiers, identification of professionals, directories,.. and their maintenance
- Semantic consistency and data representation are crucial for the development of hospital information systems, as well as information exchange
- Maintenance of repositories interoperability framework based on international standards.

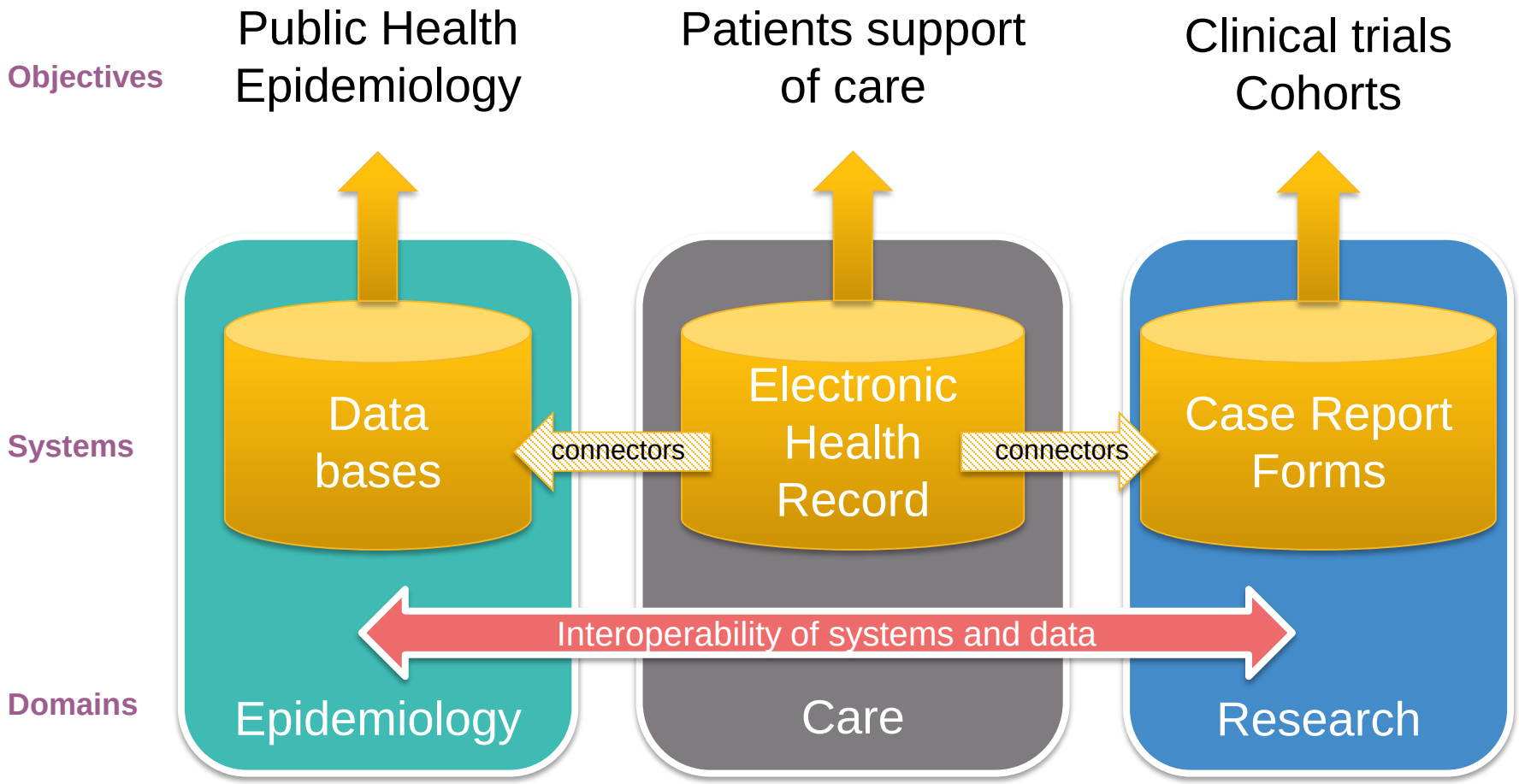
Metadata interoperability



http://dublincore.org/metadata-basics/

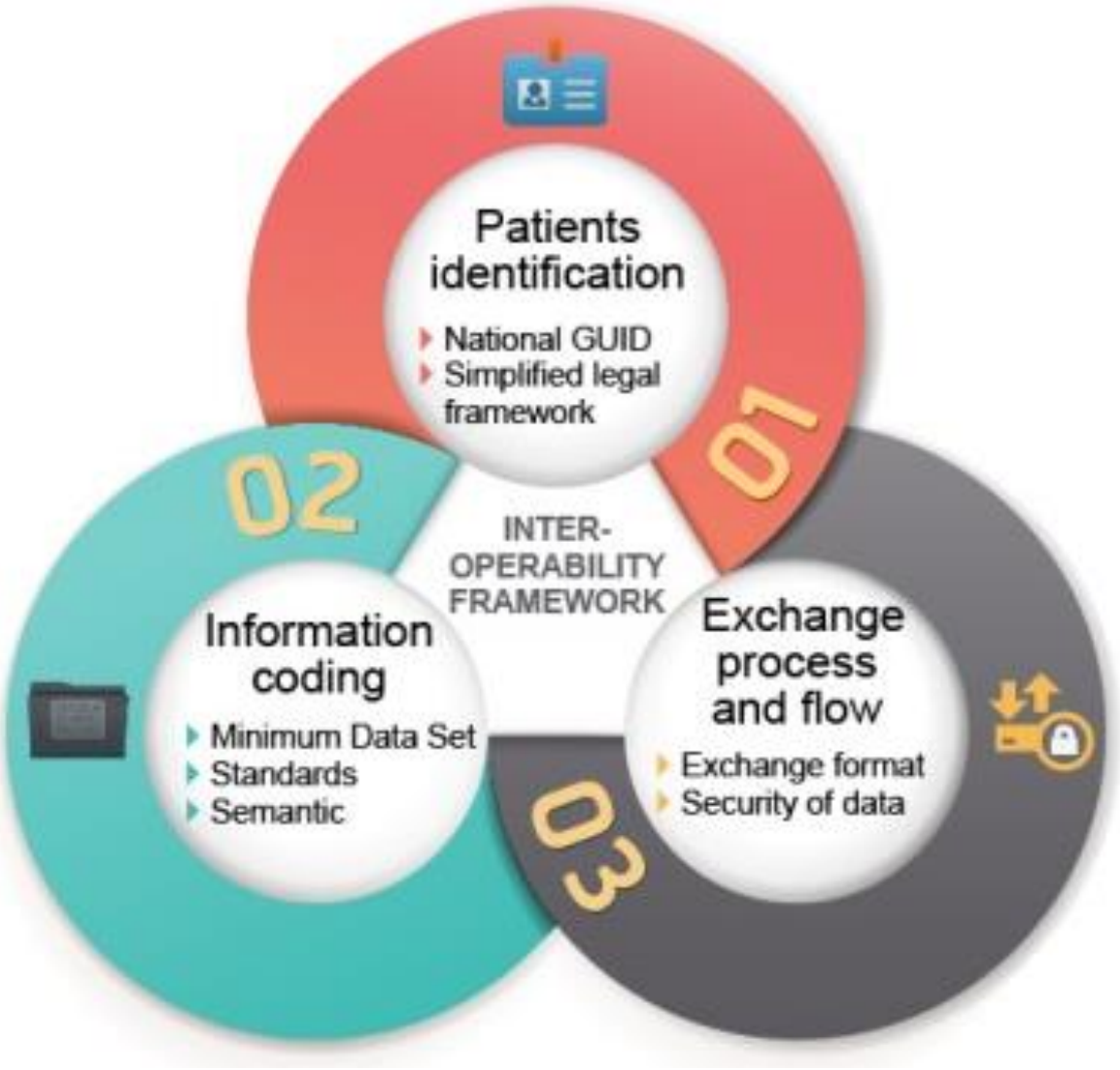
The EHR model of the BNDMR the interoperability framework

Domains, systems, objectives and interoperability

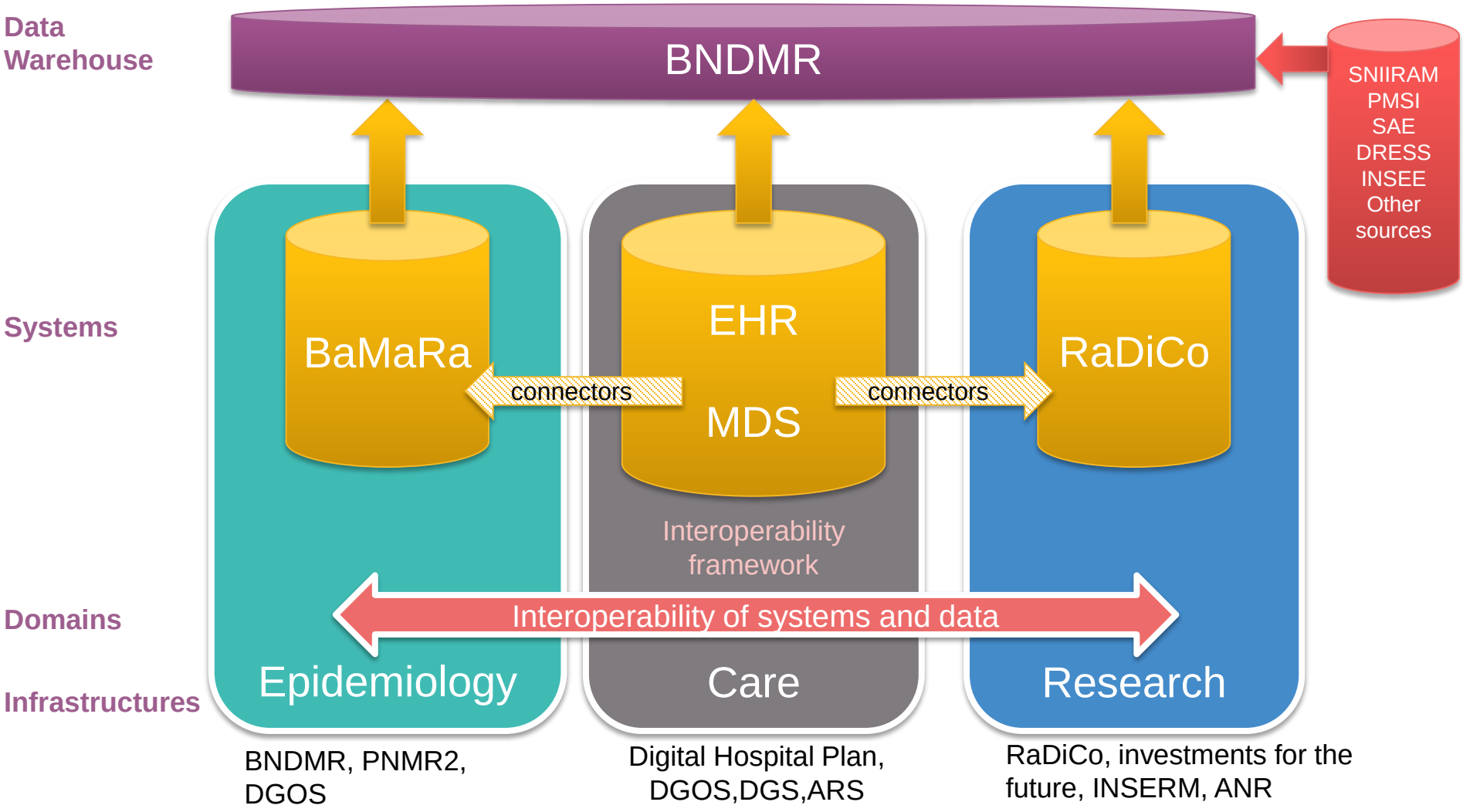


Source: BaMaRa 2013

An interoperability framework for RD



BNDMR



BNDMR : *National Data Bank for Rare Diseases;* BaMaRa*: Rare Diseases Database;* EHR*: Electronic Health Record;* MDS *: Minimum Data Set ;* RaDiCo *: Rare Disease Cohorts;* SNIIRAM *: Information system of the Health Care Insurance;* PMSI *: Activity based Payment Information System;* SAE *: Hospitals Annual Statistics ;* DRESS *: Direction for research, studies, evaluation and statistics of the Ministry of Health;* INSEE *: National Institute for statistics and economic studies.*
Source : Landais P, Choquet R, BaMaRa 2014

Interoperability

- It is based on standards and / or controlled vocabularies that promotes communication with other information systems.

- For information technology or systems engineering services interoperability allows information exchange

- Interoperability of data and systems is crucial for exchanging information

Some standards for interoperability

- Terminologies : LOINC, ICD-10, SNOMED, …
- Medical and administrative data messages: HL7 v2, v3
- Dematerializing medical documents: CDA (HL7 v3)
- Services of terminologies: CTS 2 (HL7 + OMG)
- Communication et archiving of images: DICOM
- Clinical research: CDISC, Bridg and HL7 v3

Standards for clinical research (3)

Two great forums for clinical research data standards:

- the Clinical Data Standards Interchange Consortium (CDISC)

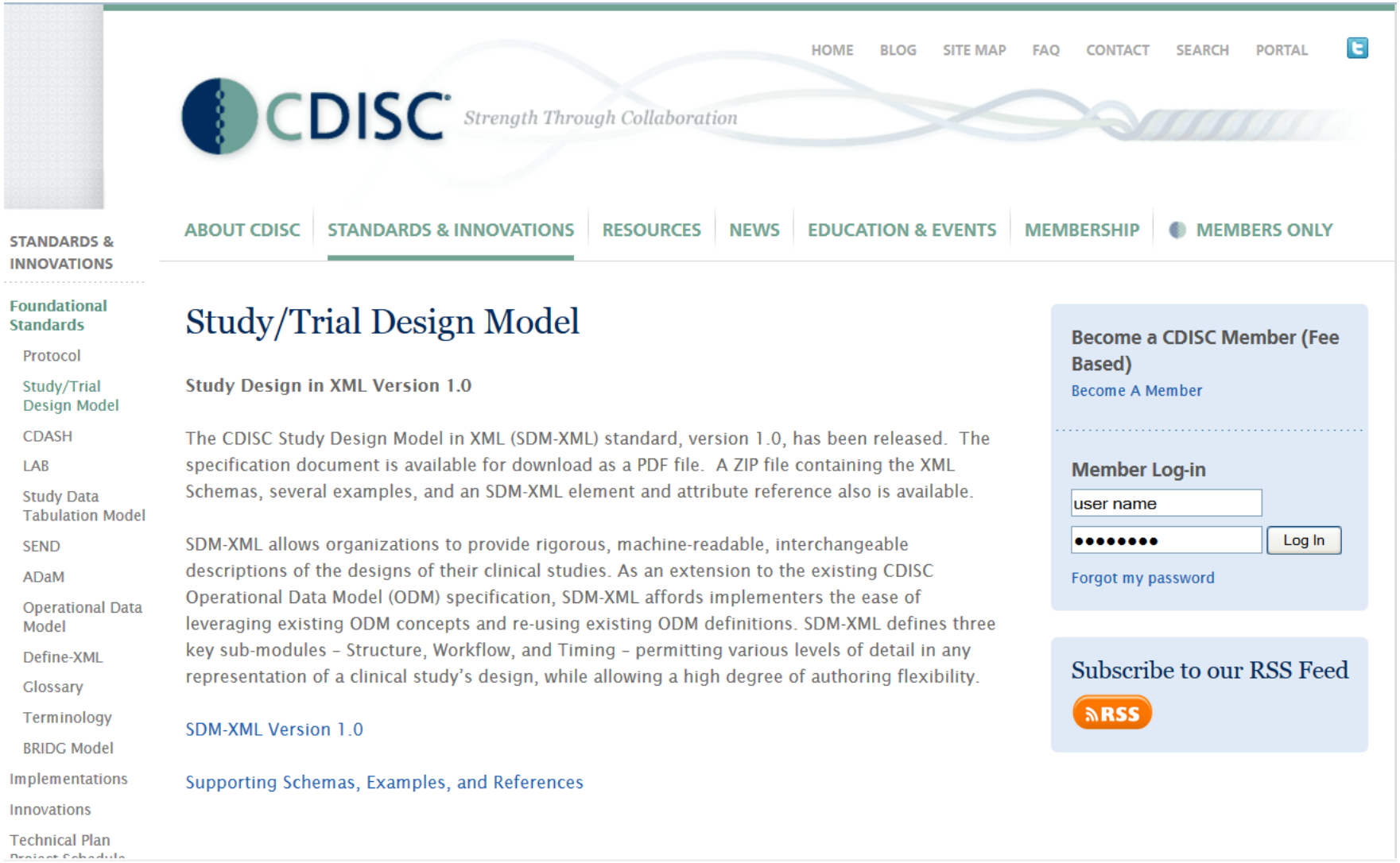
- the Regulated Clinical Research (RCRIM) Technical Committee of Health Level Seven (HL7). HL7 version 3 relies upon a very abstract information model, the Reference Information Model (RIM). It is broad and flexible enough to address any messaging need in the healthcare domain.

Richesson RL, Krischer J. J Am Med Inform Assoc 2007;14:687-696

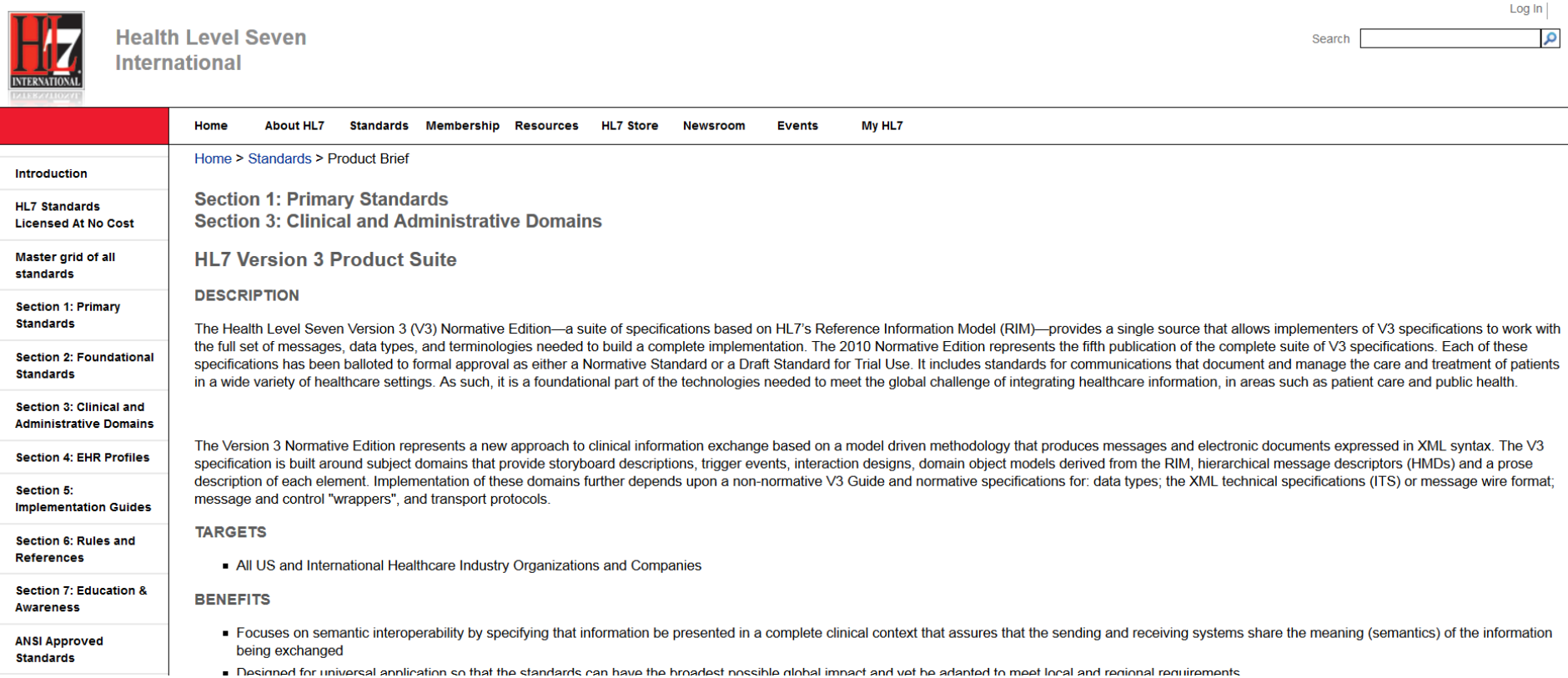
C DISC

http://www.cdisc.org/

C DISC


HOME BLOG SITE MAP FAQ CONTACT SEARCH PORTAL
CDISC
Strength Through Collaboration
ABOUT CDISC
STANDARDS & INNOVATIONS
RESOURCES
NEWS
EDUCATION & EVENTS
MEMBERSHIP
MEMBERS ONLY
STANDARDS & INNOVATIONS
Foundational Standards
Protocol
Study/Trial Design Model
CDASH
LAB
Study Data Tabulation Model
SEND
ADaM
Operational Data Model
Define-XML
Glossary
Terminology
BRIDG Model
Implementations
Innovations
Technical Plan
Study/Trial Design Model
Study Design in XML Version 1.0
The CDISC Study Design Model in XML (SDM-XML) standard, version 1.0, has been released. The specification document is available for download as a PDF file. A ZIP file containing the XML Schemas, several examples, and an SDM-XML element and attribute reference also is available.
SDM-XML allows organizations to provide rigorous, machine-readable, interchangeable descriptions of the designs of their clinical studies. As an extension to the existing CDISC Operational Data Model (ODM) specification, SDM-XML affords implementers the ease of leveraging existing ODM concepts and re-using existing ODM definitions. SDM-XML defines three key sub-modules – Structure, Workflow, and Timing – permitting various levels of detail in any representation of a clinical study's design, while allowing a high degree of authoring flexibility.
SDM-XML Version 1.0
Supporting Schemas, Examples, and References
Become a CDISC Member (Fee Based)
Become A Member
Member Log-in
user name
Log In
Forgot my password
Subscribe to our RSS Feed
RSS

Health Level Seven



Health Level Seven International

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- Introduction
- HL7 Standards Licensed At No Cost
- Master grid of all standards
- Section 1: Primary Standards
- Section 2: Foundational Standards
- Section 3: Clinical and Administrative Domains
- Section 4: EHR Profiles
- Section 5: Implementation Guides
- Section 6: Rules and References
- Section 7: Education & Awareness
- ANSI Approved Standards

Home > Standards > Product Brief

Section 1: Primary Standards
Section 3: Clinical and Administrative Domains

HL7 Version 3 Product Suite

DESCRIPTION

The Health Level Seven Version 3 (V3) Normative Edition—a suite of specifications based on HL7's Reference Information Model (RIM)—provides a single source that allows implementers of V3 specifications to work with the full set of messages, data types, and terminologies needed to build a complete implementation. The 2010 Normative Edition represents the fifth publication of the complete suite of V3 specifications. Each of these specifications has been balloted to formal approval as either a Normative Standard or a Draft Standard for Trial Use. It includes standards for communications that document and manage the care and treatment of patients in a wide variety of healthcare settings. As such, it is a foundational part of the technologies needed to meet the global challenge of integrating healthcare information, in areas such as patient care and public health.

The Version 3 Normative Edition represents a new approach to clinical information exchange based on a model driven methodology that produces messages and electronic documents expressed in XML syntax. The V3 specification is built around subject domains that provide storyboard descriptions, trigger events, interaction designs, domain object models derived from the RIM, hierarchical message descriptors (HMDs) and a prose description of each element. Implementation of these domains further depends upon a non-normative V3 Guide and normative specifications for: data types; the XML technical specifications (ITS) or message wire format; message and control "wrappers", and transport protocols.

TARGETS

- All US and International Healthcare Industry Organizations and Companies

BENEFITS

- Focuses on semantic interoperability by specifying that information be presented in a complete clinical context that assures that the sending and receiving systems share the meaning (semantics) of the information being exchanged
- Designed for universal application so that the standards can have the broadest possible global impact and yet be adapted to meet local and regional requirements

HL7 and standards

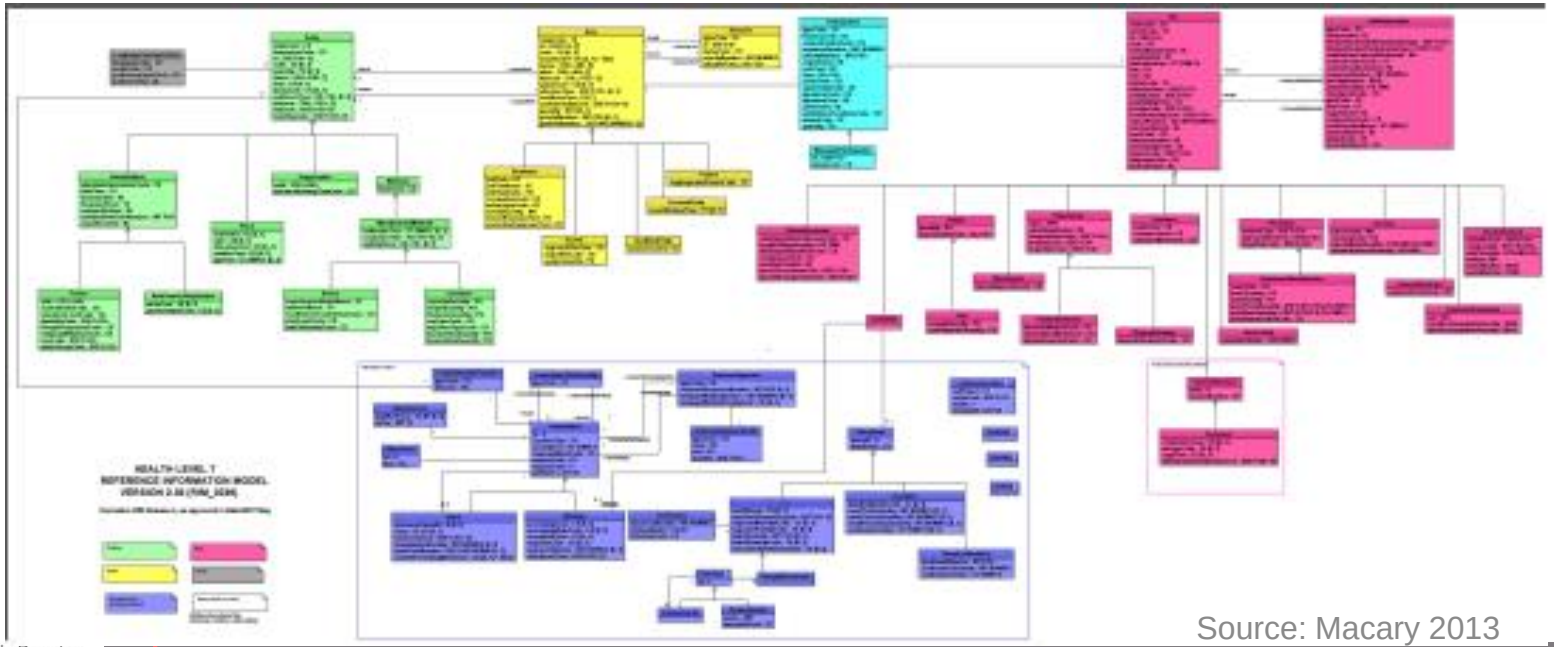
- HL7 V2:
  - A corpus of messages for dematerialised inter-application data exchange.
- HL7 V3,
  - Foundations:
    - A base of data types (51 in Release 1, 60 + in Release 2)
    - A reference information model: the RIM
    - resources of vocabularies (concepts, coding systems and sets of values)
  - A corpus of messages for the exchange of data
  - CDA: a XML format for dematerializing medical records
  - Services of terminologies (CTS)

HL7 V3

The Health Level Seven normative edition
is a suite of specifications
based on HL7' Reference Information Model (RIM).
It provides a single source that allows implementers of V3 specifications to work with a full set of messages, data types, and terminologies needed to build a complete implementation.

Reference Information Model (RIM)

- An object model covering all trade in health (~ 60 classes)
- clinical, medico-technical, administrative, financial, insurance data
- the root of all models and all HL7 v3 structures
- the ultimate source of all information exchanged in the V3
- standard ISO (TC 215) messages
- Coupled to the vocabulary and data types

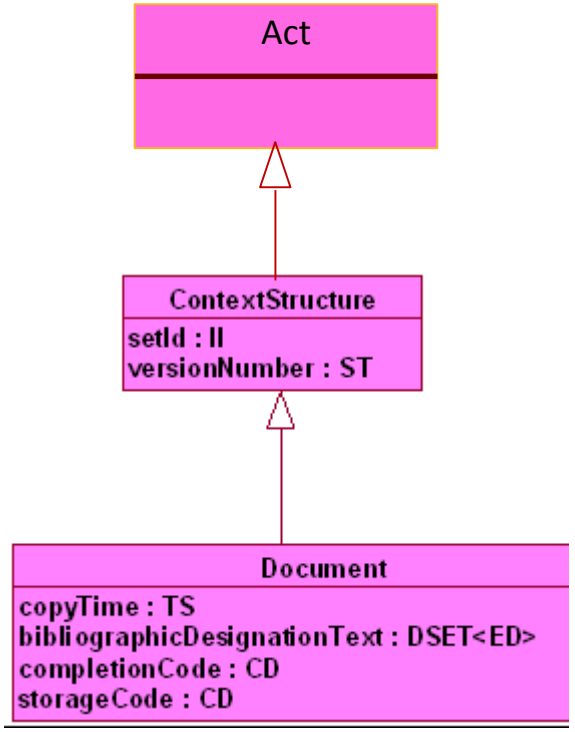


Source: Macary 2013

Clinical Document Architecture

The HL7 v3 standard for dematerializing medical documents

- 6 Characteristics of an electronic medical document:
  - Persistence
  - Stewardship
  - Potential for authentication
  - Linked to a context
  - Wholeness
  - Human readability



The general class for electronic documents

BRIDG

- The Biomedical Research Integrated Domain Group (BRIDG) (2005)
- Aim : linking the CDISC data reporting models with the HL7 RIM (Reference Information Model).
- The BRIDG model is a domain analysis model of protocol-driven biomedical and clinical research,
- developed to provide a comprehensive conceptual model of the clinical research domain
- a basis for harmonization across information model standards.

Navigating ontologies and knowledge bases

Semantic web

- More recently, the semantic web is associated with the principles of taxonomy and ontology.
- It represents any hierarchical organization of topics or concepts used for taxonomies or classifications, or for navigation in a portal,
- Such an approach offers rich and promising prospects for managing the complexity of medical information and its sharing.

Visualizing and navigating biomedical ontologies and knowledge bases

- *SemNav* and *GeneNav*
- Two examples of navigation through UMLS and Gene ontology, respectively.

Source: O Bodenreider, National Library of Medicine,
Lister Hill National Center for Biomedical Communications

MeSH

- Medical subject headings
- A tool to index documents
- Allows searches for information
- Includes synonyms, reporting relationships and associations
- http://www.nlm.nih.gov/mesh/

Medical Subject Headings

NIH U.S. National Library of Medicine

Search

Databases | Find, Read, Learn | Explore NLM | Research at NLM | NLM for You

Contact NLM

Medical Subject Headings

MeSH Home | About MeSH | MeSH Browser | MeSH Files | MeSH on Demand | Staff | Suggestions

Home > Library Catalogs and Services > MeSH

MeSH Browser

- Online searching of MeSH vocabulary
- About the MeSH Browser
- Suggestions for authors' keywords

All About MeSH

- MeSH Fact Sheet
- Publications and presentations by MeSH staff
- Introduction to MeSH
- Information from Previous Years

Obtaining MeSH

- Download electronic copies.
- Lists of Annual Changes to MeSH.
- MeSH on Demand.

MeSH Vocabulary Suggestions

- MeSH vocabulary suggestions

What's New

NEW!

- 2014 MeSH Files Available

Related Efforts

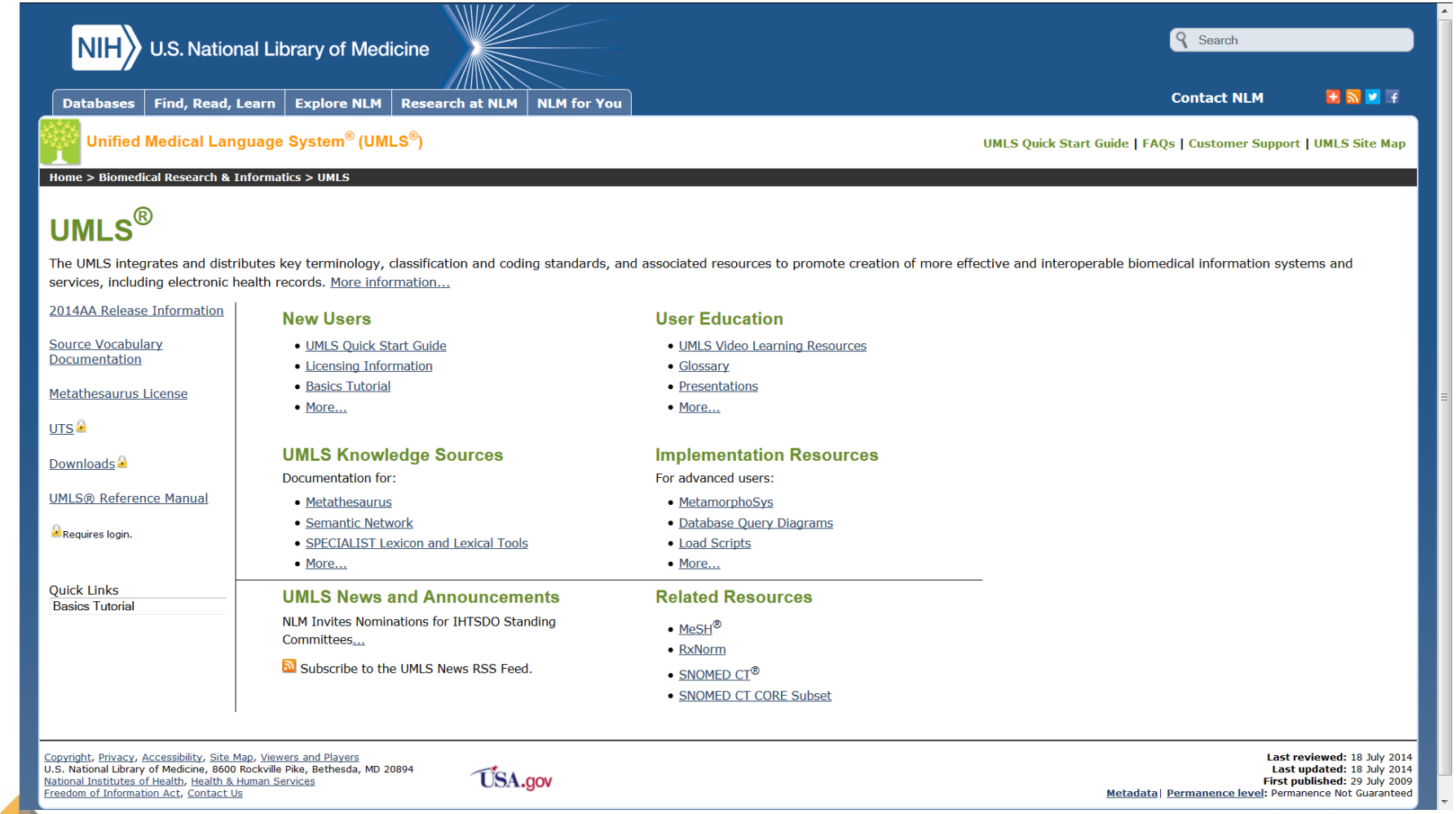
- Unified Medical Language System (UMLS®)
- NLM Classification
- RxNorm
- DailyMed

MeSH Staff

- Biographies and email
- Publications and presentations

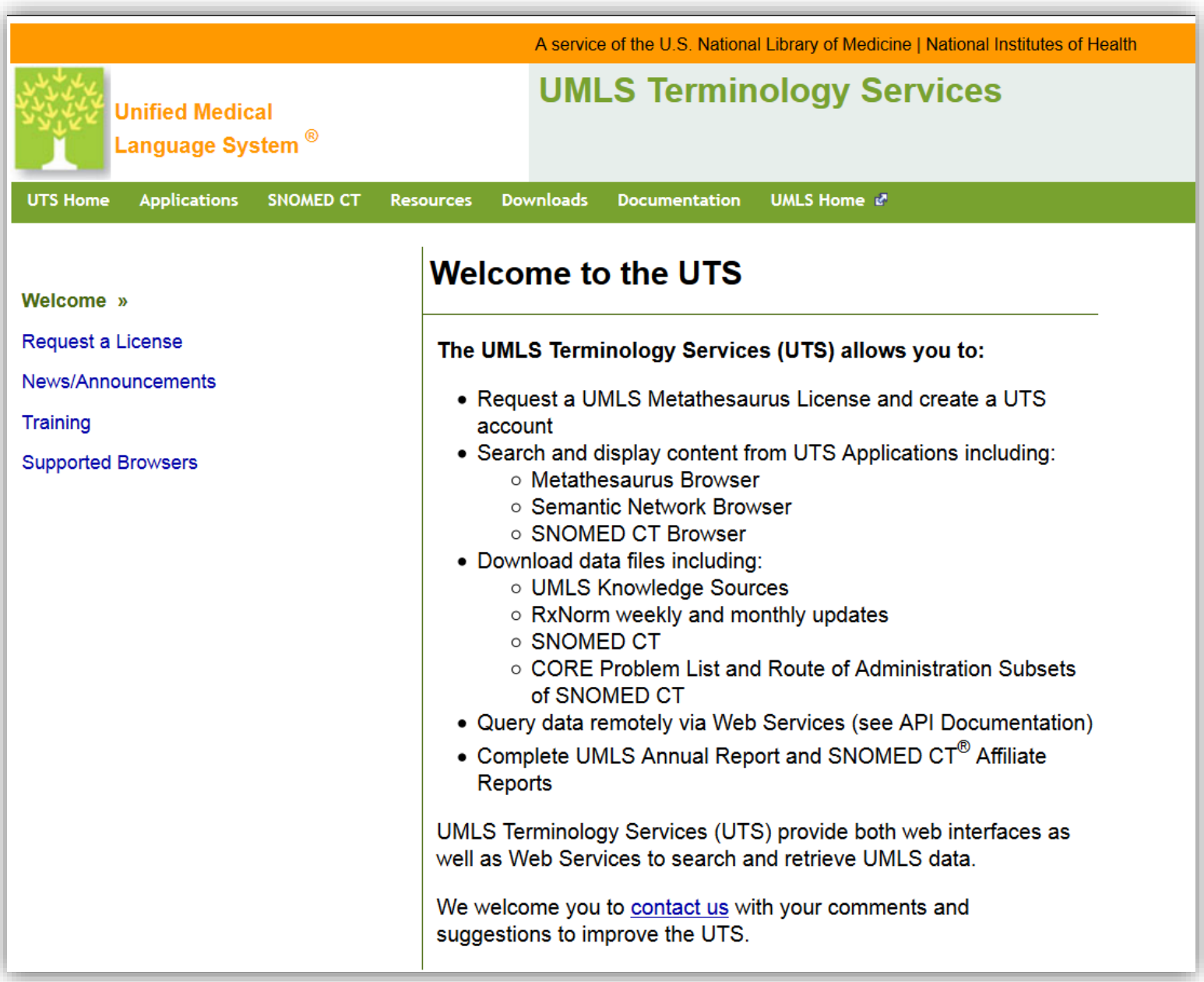
Last reviewed: 01 August 2014
Last updated: 01 August 2014
First published: 01 September 1999

UMLS - metathesaurus



Unified Medical Language System

- Developed at NLM since 1990
- Integrates some 60 terminological resources
  - Clinical vocabularies (including specialties)
  - Core terminologies (anatomy, drugs, med. devices)
  - Administrative terminologies, standards
- Integration
  - Synonymous terms are clustered in a concept
  - Hierarchies (trees) are combined in a graph structure


A service of the U.S. National Library of Medicine | National Institutes of Health
Unified Medical Language System ®
UMLS Terminology Services
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UMLS Home
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Training
Supported Browsers
Welcome to the UTS
The UMLS Terminology Services (UTS) allows you to:
Request a UMLS Metathesaurus License and create a UTS account
Search and display content from UTS Applications including:
Metathesaurus Browser
Semantic Network Browser
SNOMED CT Browser
Download data files including:
UMLS Knowledge Sources
RxNorm weekly and monthly updates
SNOMED CT
CORE Problem List and Route of Administration Subsets of SNOMED CT
Query data remotely via Web Services (see API Documentation)
Complete UMLS Annual Report and SNOMED CT® Affiliate Reports
UMLS Terminology Services (UTS) provide both web interfaces as well as Web Services to search and retrieve UMLS data.
We welcome you to contact us with your comments and suggestions to improve the UTS.

Gene Ontology

- Developed by the GO Consortium
- Several components
  - Ontology (~11,000 concepts)
    - Molecular functions
    - Cellular components
    - Biological processes
  - Gene products (~125,000)
  - Associations between Gene products and GO concepts (~357,000)

SemNav and GenNav

- SemNav: UMLS browser
  - UMLS browser
  - Entry point: biomedical term
  - Display related concepts
  - Display properties of interconcept relationships
  - Allow navigation among concepts
- GenNav : GO browser
  - GO browser
  - Entry point: GO term or gene product name/symbol
  - Display related GO terms and gene products
  - Display properties of term/term and term/gene product relationships
  - Allow navigation between GO terms and gene products

Source: O Bodenreider, National Library of Medicine,
Lister Hill National Center for Biomedical Communications

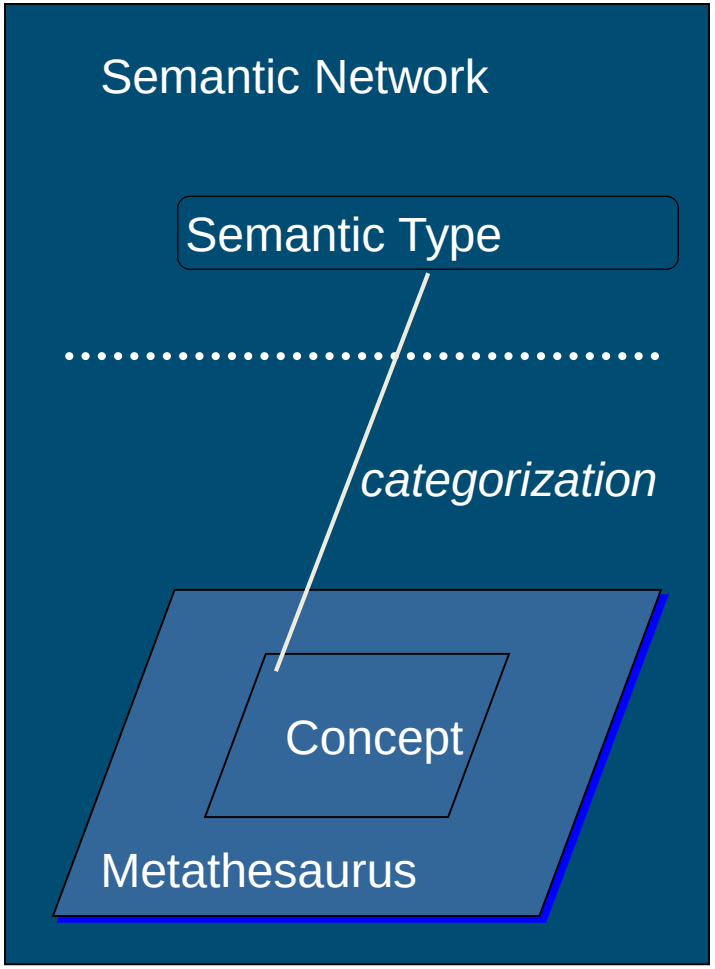
Terminology integration
Terms

Duchenne muscular dystrophy	MeSH, SNOMED CTV3, Jablonski, CRISP, DxPlain, MedDRA, LOINC
Duchenne's muscular dystrophy	COSTAR
Duchenne de Boulogne muscular dystrophy	Jablonski
Duchenne type progressive muscular dystrophy	SNOMED
pseudohypertrophic muscular dystrophy	MeSH, CTV3 SNOMED
X-linked recessive muscular dystrophy	Jablonski
severe generalized familial muscular dystrophy	SNOMED

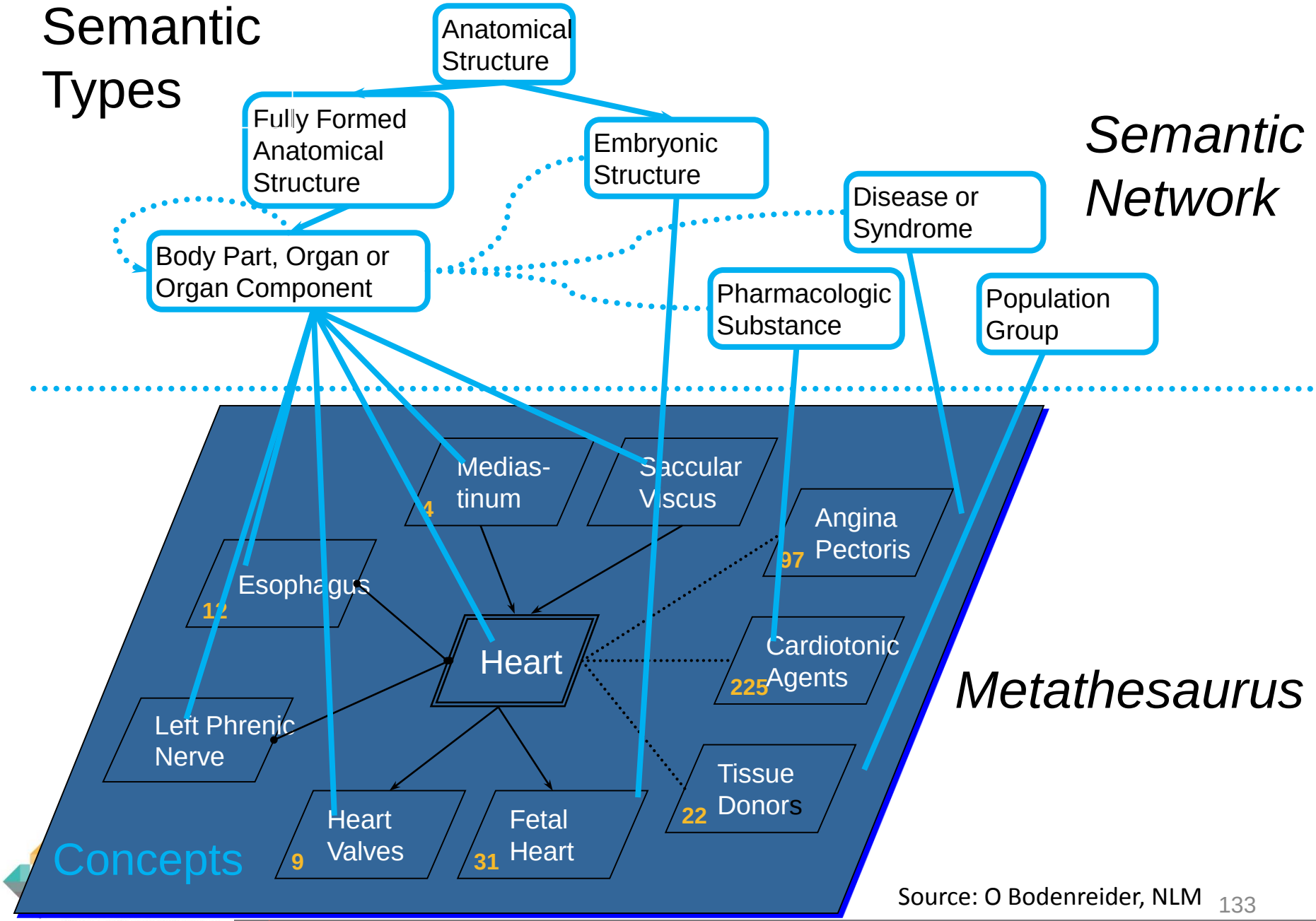
Source: O Bodenreider, National Library of Medicine,
Lister Hill National Center for Biomedical Communications

UMLS

- Two-level structure
  - Semantic Network
    - 134 Semantic Types (STs)
    - 54 types of relationships among STs
  - Metathesaurus
    - 800,000 concepts
    - ~10 M inter-concept relationships
  - Link = categorization



Source: O Bodenreider, National Library of Medicine,
Lister Hill National Center for Biomedical Communications



Source: O Bodenreider, NLM

UMLS Browser

Amino Acids, Peptides, and Proteins [D12]
- Proteins [D12.776]
  - Contractile Proteins [D12.776.210]
    - Muscle Proteins [D12.776.210.500]
      - Actinin [D12.776.210.500.095]
      - Actins [D12.776.210.500.100]
      - Actomyosin [D12.776.210.500.154]
      - Calsequestrin [D12.776.210.500.220]
      - Dystrophin [D12.776.210.500.250]
      - Myogenic Regulatory Factors [D12.776.210.500.570] +
      - Myoglobin [D12.776.210.500.588]
      - Myosins [D12.776.210.500.600] +
      - Parvalbumins [D12.776.210.500.750]
      - Ryanodine Receptor Calcium Release Channel [D12.776.210.500.800]
      - Tropomyosin [D12.776.210.500.895]
      - Troponin [D12.776.210.500.910] +

Amino Acids, Peptides, and Proteins [D12]
- Proteins [D12.776]
  - Cytoskeletal Proteins [D12.776.220]
    - Adenomatous Polyposis Coli Protein [D12.776.220.040]
    - Dystrophin [D12.776.220.250]
    - Intermediate Filament Proteins [D12.776.220.475] +
    - Microfilament Proteins [D12.776.220.525] +
    - Microtubule Proteins [D12.776.220.600] +
    - Spectrin [D12.776.220.980]
    - Talin [D12.776.220.985]
    - Vinculin [D12.776.220.990]

BNDMR
Banque Nationale de Maladies Rares

SemNav

Relationships
of **Dystrophin** (C1)
Amino Acid, Peptide, or Protein
Biologically Active Substance
to **Muscular Dystrophy, Duchenne** (C2)
Disease or Syndrome

Metathesaurus Relationships

C1 *otherwise related to* C2

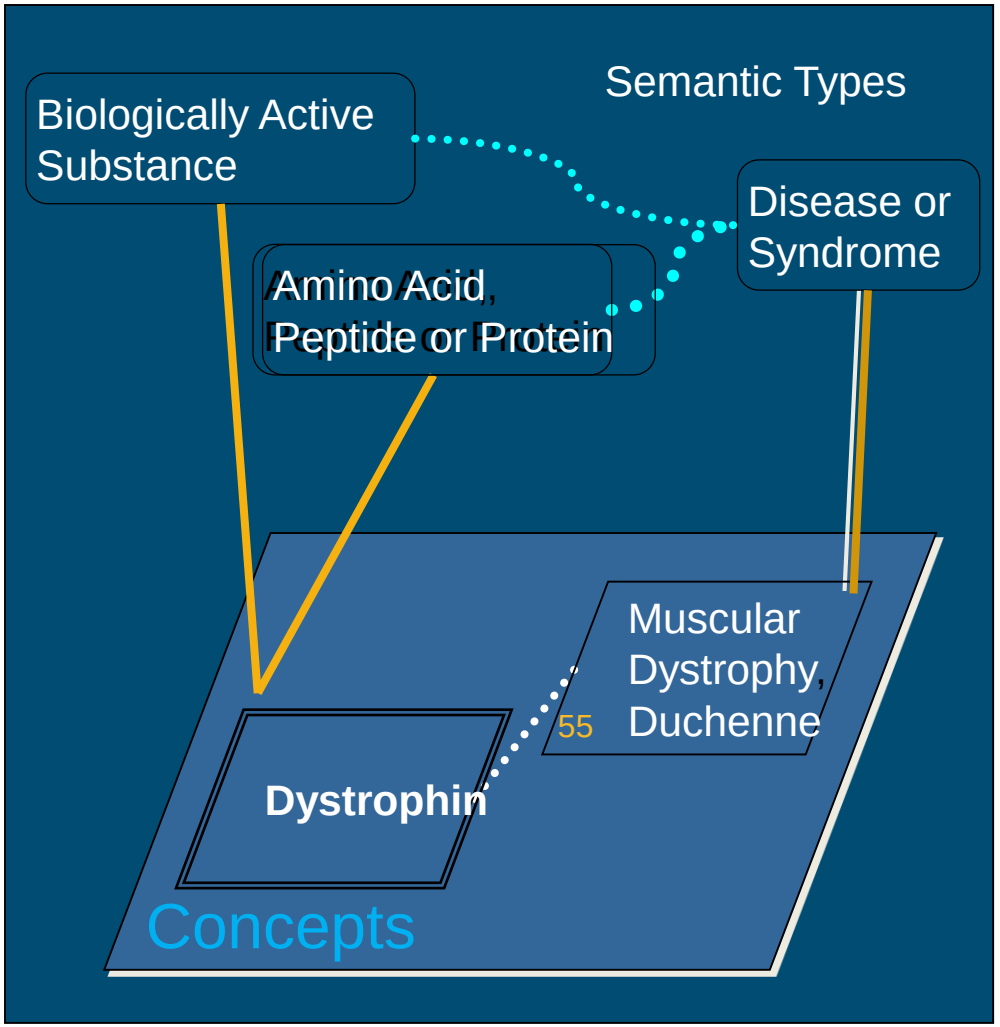
not defined	• MeSH

C1 *co-occurs with* C2

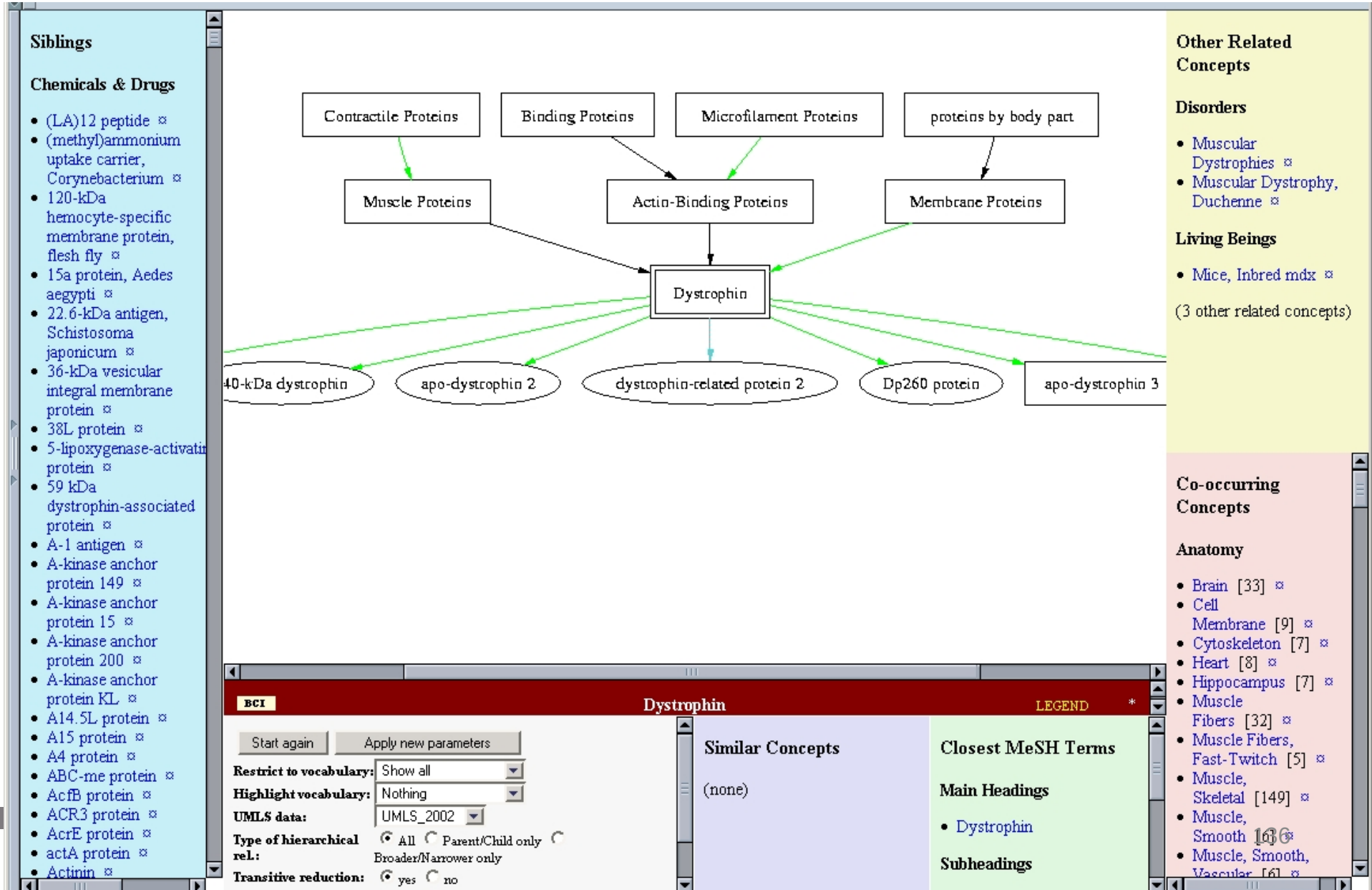
Frequency = 55	• MEDLINE

Semantic Network Relationships

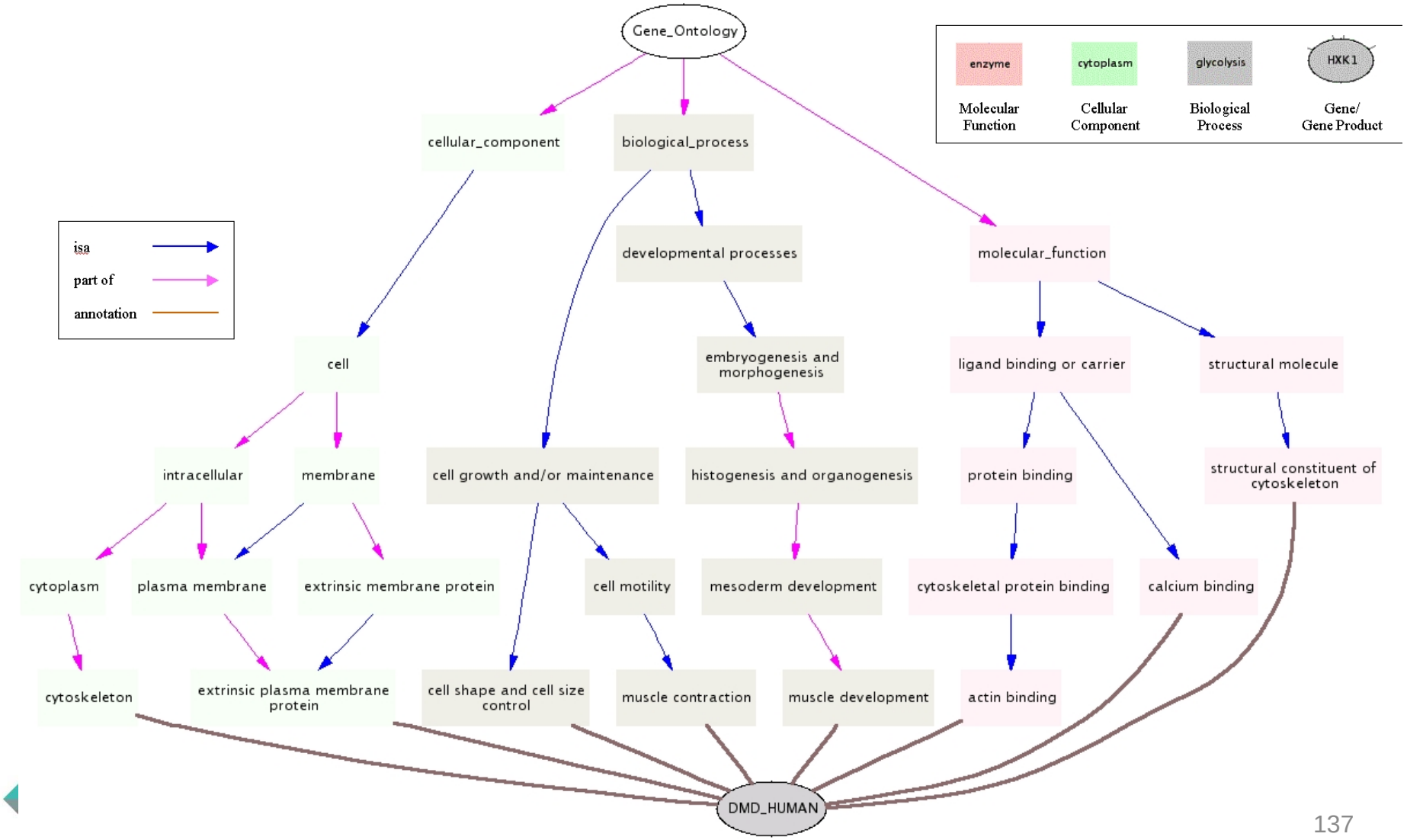
Amino Acid, Peptide, or Protein	• affects • causes	*Disease or Syndrome*
Biologically Active Substance	• affects • causes • complicates • produced_by	*Disease or Syndrome*



SemNav


Siblings
Chemicals & Drugs
(LA)12 peptide
(methyl)ammonium uptake carrier, Corynebacterium
120-kDa hemocyte-specific membrane protein, flesh fly
15a protein, Aedes aegypti
22.6-kDa antigen, Schistosoma japonicum
36-kDa vesicular integral membrane protein
38L protein
5-lipoxygenase-activatin protein
59 kDa dystrophin-associated protein
A-1 antigen
A-kinase anchor protein 149
A-kinase anchor protein 15
A-kinase anchor protein 200
A-kinase anchor protein KL
A14.5L protein
A15 protein
A4 protein
ABC-me protein
AcfB protein
ACR3 protein
AcrE protein
actA protein
Actinin
Contractile Proteins
Binding Proteins
Microfilament Proteins
proteins by body part
Muscle Proteins
Actin-Binding Proteins
Membrane Proteins
Dystrophin
40-kDa dystrophin
apo-dystrophin 2
dystrophin-related protein 2
Dp260 protein
apo-dystrophin 3
Other Related Concepts
Disorders
Muscular Dystrophies
Muscular Dystrophy, Duchenne
Living Beings
Mice, Inbred mdx
(3 other related concepts)
Co-occurring Concepts
Anatomy
Brain [33]
Cell Membrane [9]
Cytoskeleton [7]
Heart [8]
Hippocampus [7]
Muscle Fibers [32]
Muscle Fibers, Fast-Twitch [5]
Muscle, Skeletal [149]
Muscle, Smooth [6]
Muscle, Smooth, Vascular [6]
BCI
Dystrophin
LEGEND
Start again
Apply new parameters
Restrict to vocabulary: Show all
Highlight vocabulary: Nothing
UMLS data: UMLS_2002
Type of hierarchical rel.: All Parent/Child only Broader/Narrower only
Transitive reduction: yes no
Similar Concepts
(none)
Closest MeSH Terms
Main Headings
Dystrophin
Subheadings

Gene Ontology



GeneNav

AmiGO

Search GO:

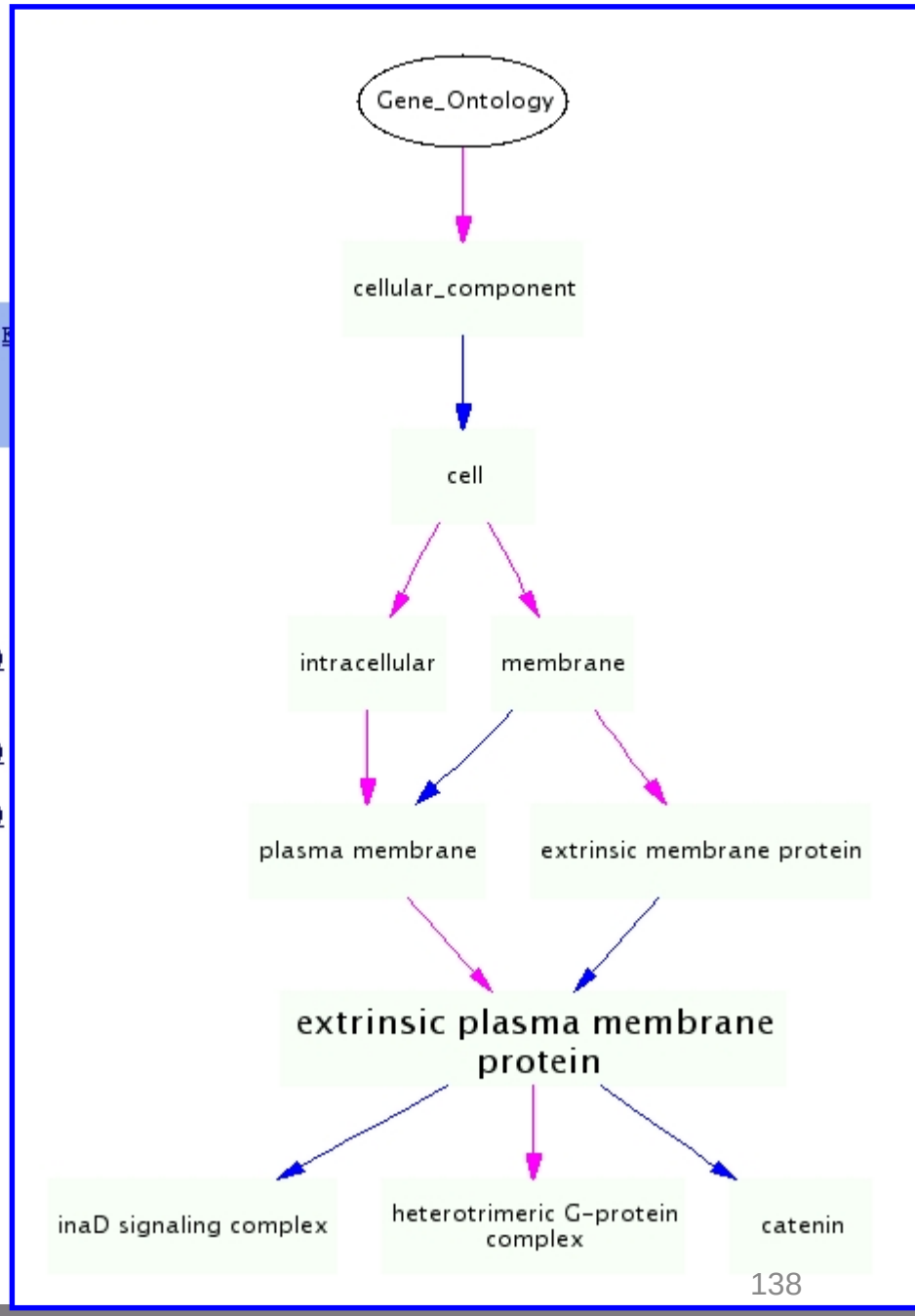
Top Docs Gene Ontology GO Links GO Summary

Terms Gene Products

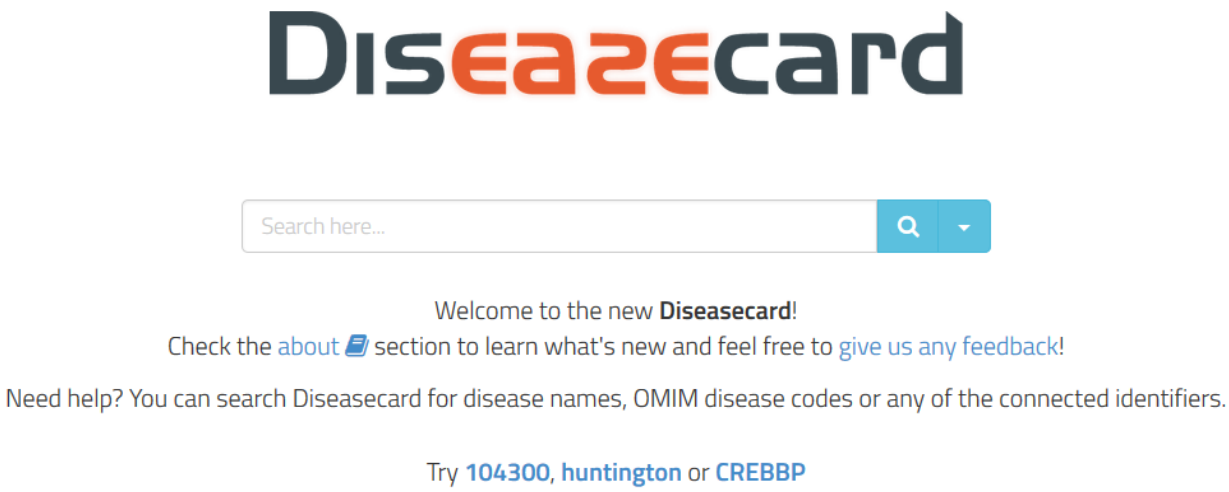
- GO:0003673 : Gene_Ontology (33650)
  - GO:0008150 : biological_process (24768)
  - GO:0005575 : cellular_component (17255)
    - GO:0005623 : cell (14268)
      - GO:0005622 : intracellular (12771)
        - GO:0005886 : plasma membrane (2273)
          - **GO:0019897 : extrinsic plasma membrane protein (56)**
      - GO:0016020 : membrane (4511)
        - GO:0019898 : extrinsic membrane protein (58)
          - **GO:0019897 : extrinsic plasma membrane protein (56)**
        - GO:0005886 : plasma membrane (2273)
          - **GO:0019897 : extrinsic plasma membrane protein (56)**
  - GO:0003674 : molecular_function (23707)

Get this GO tree as RDF XML.
Get this data as a GO flat file.

Get a bookmarkable url of this GO tree.

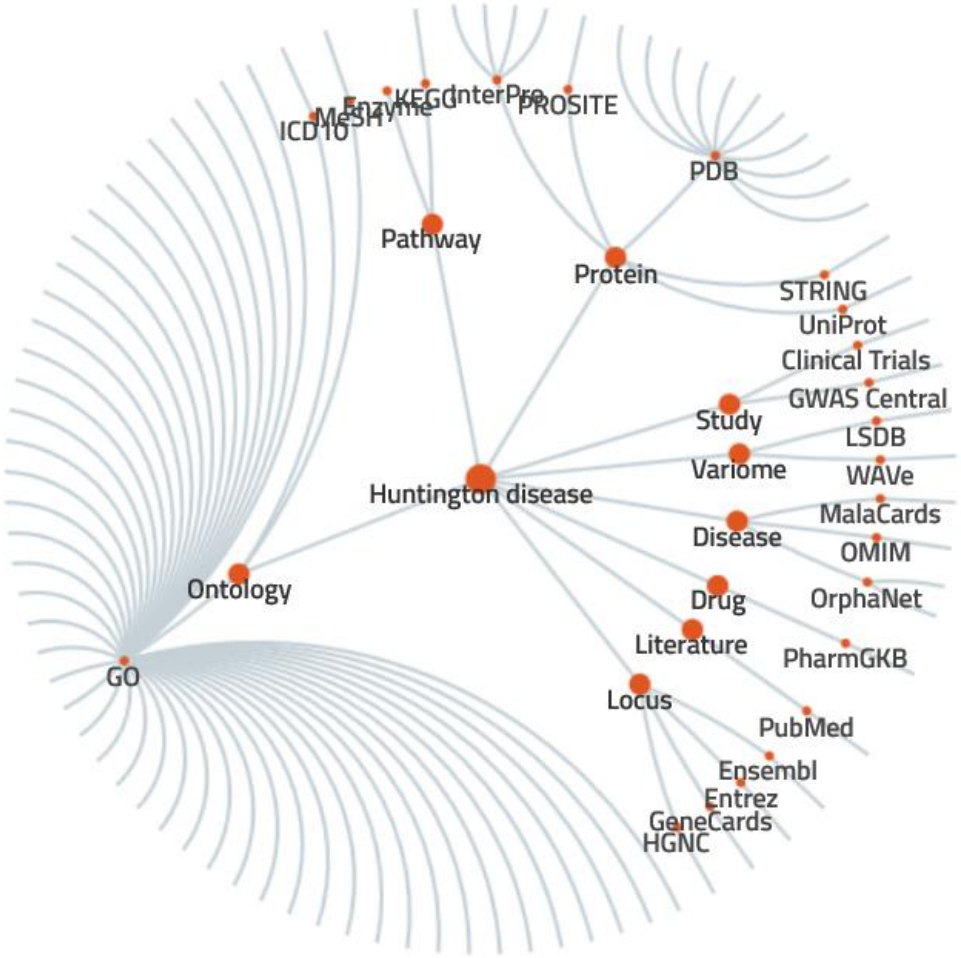


Diseasecard

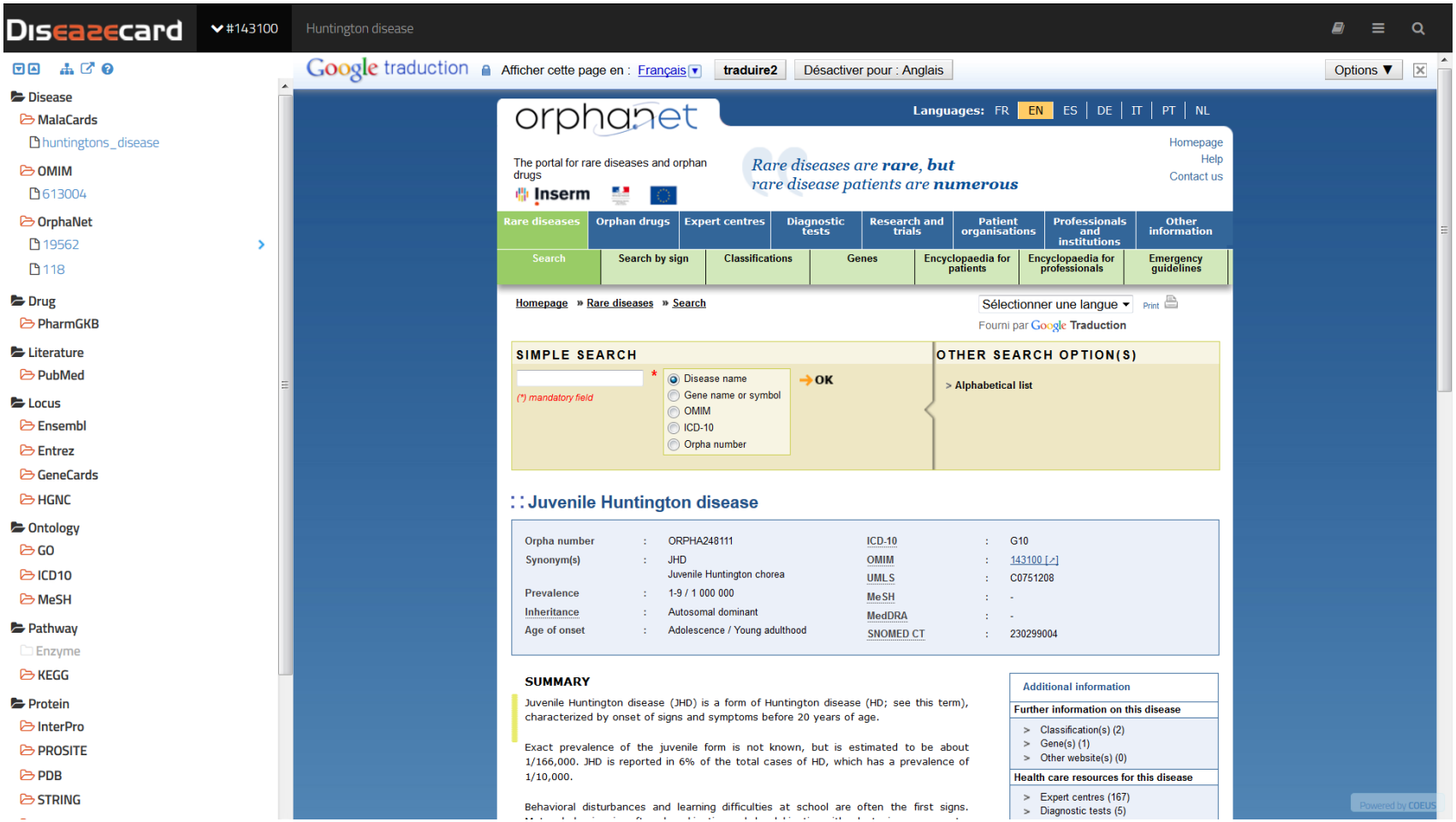


- bioinformatics.ua.pt/diseasecard

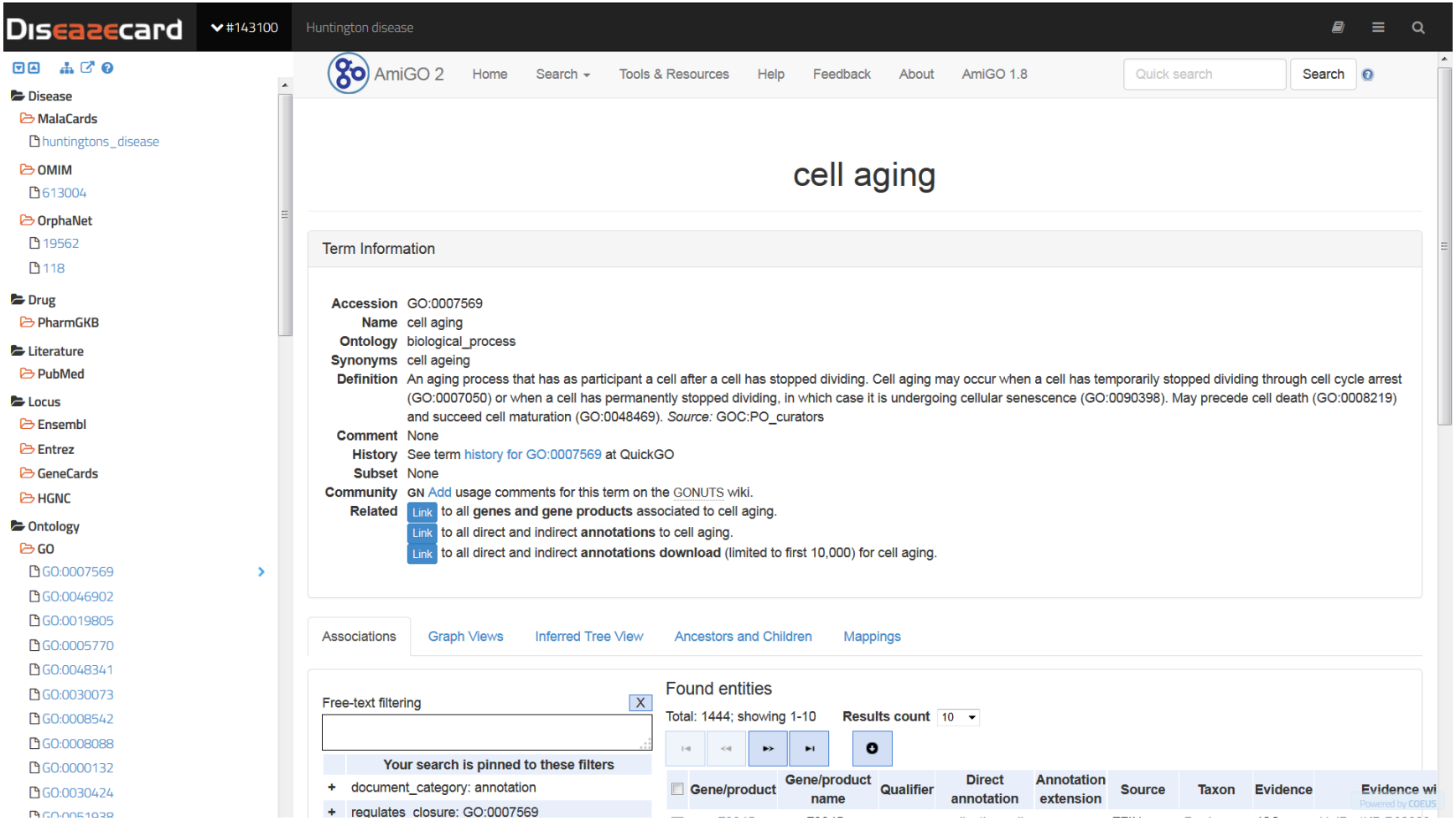
Disease card: representation of RD



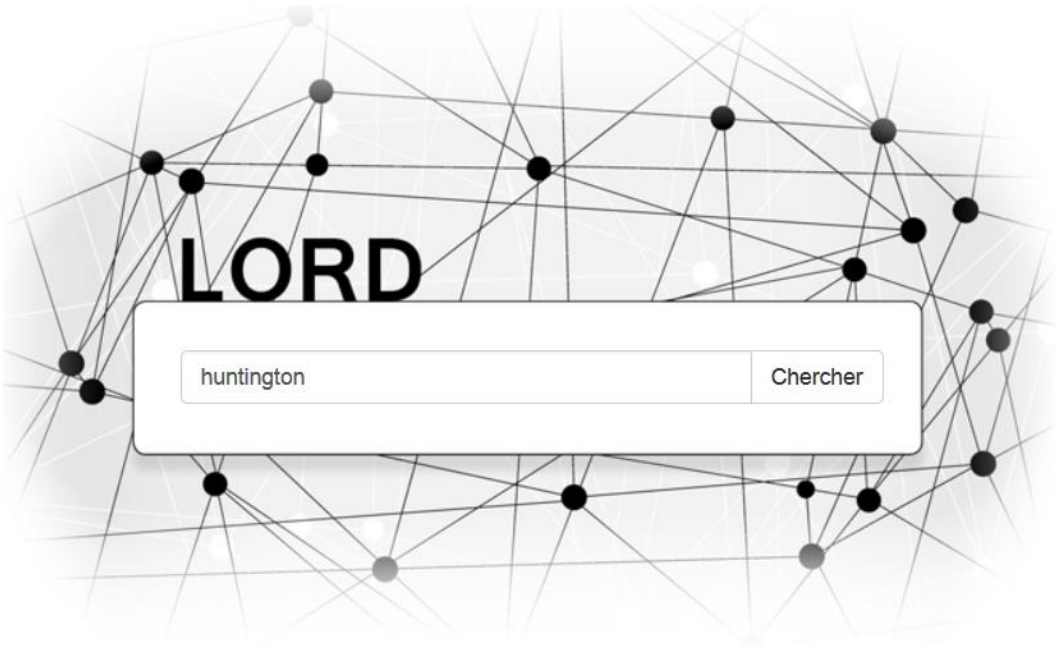
Diseasecard



Diseasecard

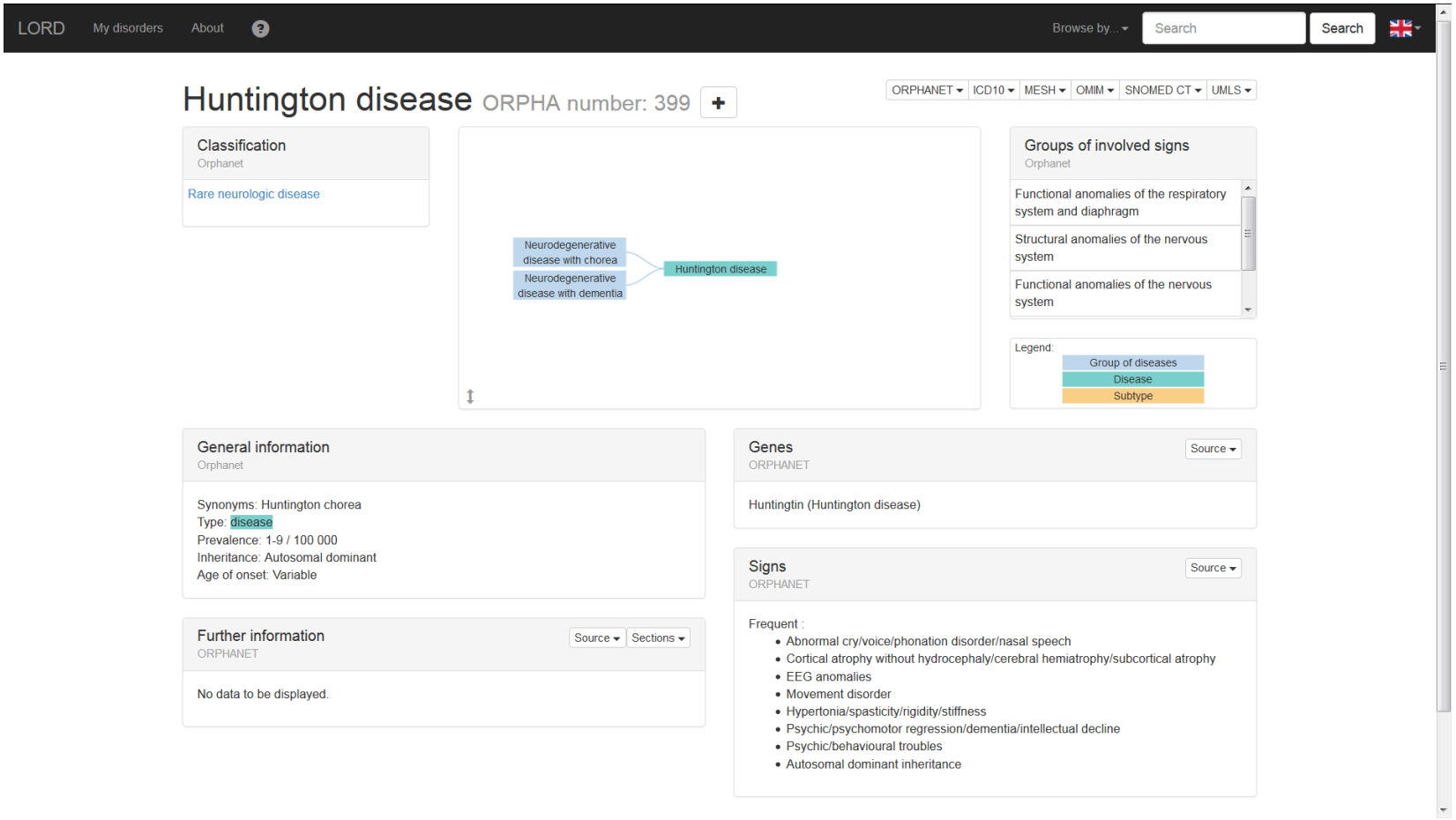


LORD

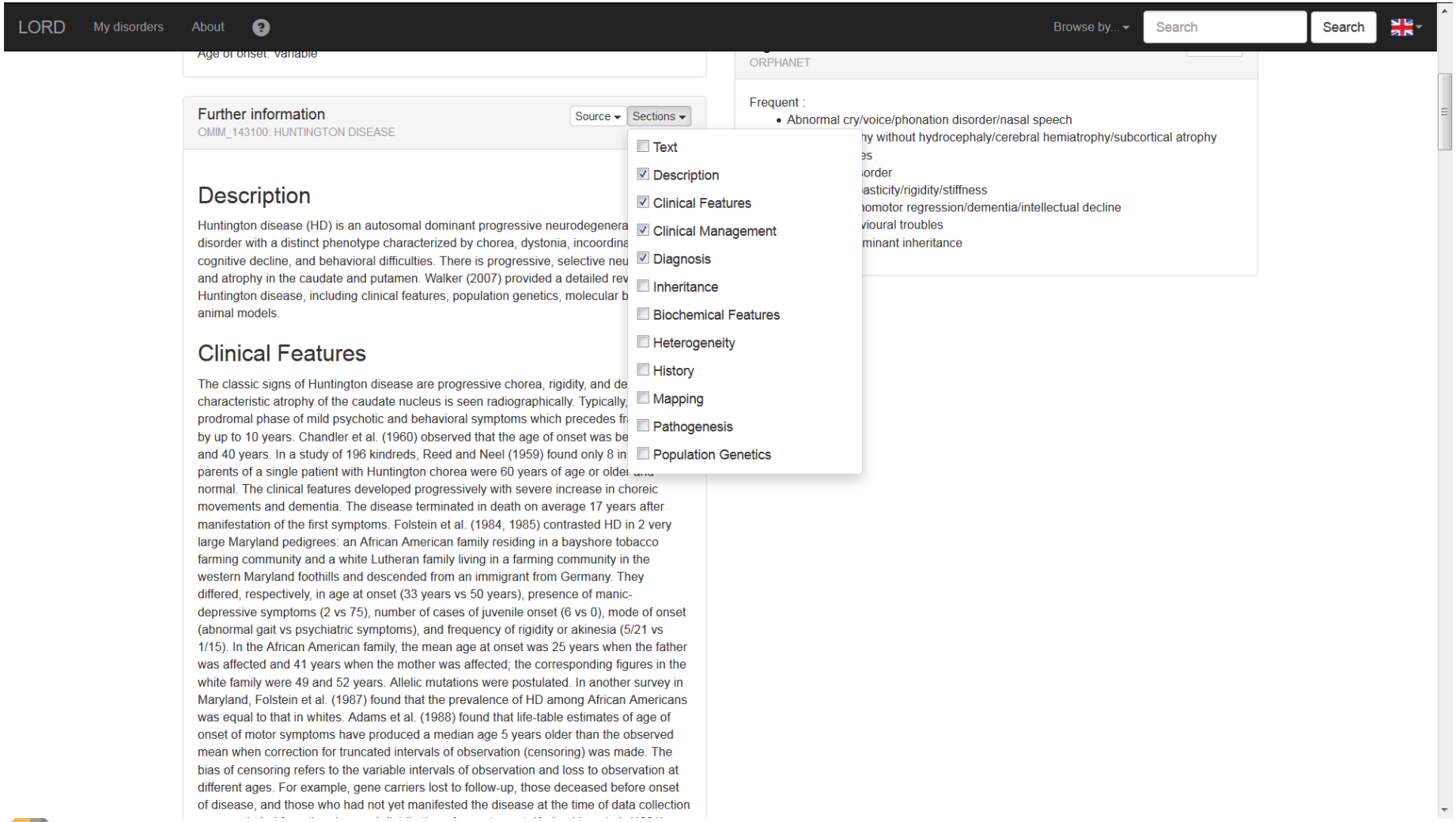


lord.bndmr.fr

LORD


LORD
My disorders
About
Browse by...
Search
Search
Huntington disease ORPHA number: 399
ORPHANET
ICD10
MESH
OMIM
SNOMED CT
UMLS
Classification
Orphanet
Rare neurologic disease
Neurodegenerative disease with chorea
Neurodegenerative disease with dementia
Huntington disease
Groups of involved signs
Orphanet
Functional anomalies of the respiratory system and diaphragm
Structural anomalies of the nervous system
Functional anomalies of the nervous system
Legend:
Group of diseases
Disease
Subtype
General information
Orphanet
Synonyms: Huntington chorea
Type: disease
Prevalence: 1-9 / 100 000
Inheritance: Autosomal dominant
Age of onset: Variable
Genes
ORPHANET
Source
Huntingtin (Huntington disease)
Signs
ORPHANET
Source
Frequent :
Abnormal cry/voice/phonation disorder/nasal speech
Cortical atrophy without hydrocephaly/cerebral hemiatrophy/subcortical atrophy
EEG anomalies
Movement disorder
Hypertonia/spasticity/rigidity/stiffness
Psychic/psychomotor regression/dementia/intellectual decline
Psychic/behavioural troubles
Autosomal dominant inheritance
Further information
ORPHANET
Source
Sections
No data to be displayed.

LORD


LORD
My disorders
About
Browse by...
Search
Search
Age of onset: Variable
ORPHANET
Frequent :
• Abnormal cry/voice/phonation disorder/nasal speech
Further information
OMIM_143100: HUNTINGTON DISEASE
Source
Sections
Text
Description
Clinical Features
Clinical Management
Diagnosis
Inheritance
Biochemical Features
Heterogeneity
History
Mapping
Pathogenesis
Population Genetics
Description
Huntington disease (HD) is an autosomal dominant progressive neurodegenera
disorder with a distinct phenotype characterized by chorea, dystonia, incoordina
cognitive decline, and behavioral difficulties. There is progressive, selective neu
and atrophy in the caudate and putamen. Walker (2007) provided a detailed rev
Huntington disease, including clinical features, population genetics, molecular b
animal models.
Clinical Features
The classic signs of Huntington disease are progressive chorea, rigidity, and de
characteristic atrophy of the caudate nucleus is seen radiographically. Typically,
prodromal phase of mild psychotic and behavioral symptoms which precedes fr
by up to 10 years. Chandler et al. (1960) observed that the age of onset was be
and 40 years. In a study of 196 kindreds, Reed and Neel (1959) found only 8 in
parents of a single patient with Huntington chorea were 60 years of age or older
normal. The clinical features developed progressively with severe increase in choreic
movements and dementia. The disease terminated in death on average 17 years after
manifestation of the first symptoms. Folstein et al. (1984, 1985) contrasted HD in 2 very
large Maryland pedigrees: an African American family residing in a bayshore tobacco
farming community and a white Lutheran family living in a farming community in the
western Maryland foothills and descended from an immigrant from Germany. They
differed, respectively, in age at onset (33 years vs 50 years), presence of manic-
depressive symptoms (2 vs 75), number of cases of juvenile onset (6 vs 0), mode of onset
(abnormal gait vs psychiatric symptoms), and frequency of rigidity or akinesia (5/21 vs
1/15). In the African American family, the mean age at onset was 25 years when the father
was affected and 41 years when the mother was affected; the corresponding figures in the
white family were 49 and 52 years. Allelic mutations were postulated. In another survey in
Maryland, Folstein et al. (1987) found that the prevalence of HD among African Americans
was equal to that in whites. Adams et al. (1988) found that life-table estimates of age of
onset of motor symptoms have produced a median age 5 years older than the observed
mean when correction for truncated intervals of observation (censoring) was made. The
bias of censoring refers to the variable intervals of observation and loss to observation at
different ages. For example, gene carriers lost to follow-up, those deceased before onset
of disease, and those who had not yet manifested the disease at the time of data collection

Acknowledgments (1)

- This work was developed in the context of the BNDMR program, part of the 2nd French National Program for Rare Diseases;
- Acknowledgments to F Dhombres, J Charlet, O Bodenreider and C Angin.

Acknowledgments (2)

To the members of the French task force for rare diseases, Second Rare Diseases Plan.

National coordinators of the rare diseases reference centers

Members of the rare diseases competence centers

Members of the national working group for the rare disease Minimun data Set

Members of the BNDMR team (Rare Diseases National Database)

Members of the National Rare Diseases Cohorts (RaDiCo) program

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