Rare Diseases
Nomenclature and classification
For codification purposes

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Improved codification for rare diseases is cited as a priority in the Council Recommendation on an action in the field of rare diseases (2009)

Need for coding RD

- **Make RD visible** in order to:
  - Have sound epidemiological data
  - Document the natural history of RD
  - Identify patients from health records for clinical research
  - Bring clinical data to research
- Different systems are using **different terminologies**
  - **Need for inter-operability**
  - **RD are poorly represented in ICD10, SNOMED-CT and other terminologies**
- Need **to have a common language** to allow for sharing clinical data between health care centres and databases and registries:
  - Patients are rare and scattered
  - Significant amounts of data are necessary to perform research

Rare diseases, an European priority

- A continuous work on policies for RD
  - Rare Diseases Task Force (2004-2009)
  - European Union Committee of Experts on Rare Diseases (EUCERD) (2010-2013) and EUCERD-JA (2013-2015)
  - Commission Expert Group on Rare Diseases (CEGRD) (2014 onwards)
- A database for RD that becames European and global
  - Orphanet (EU co-funded since 2000)
- A dedicated nomenclature for RD
  - ORPHA nomenclature
  - Preparing ICD11

Orphanet nomenclature usage

Recommendations

In the context of the improvement of codification for rare diseases being cited as a priority in the Council Recommendation on an action in the field of rare diseases, the Commission Expert Group on Rare Diseases recommends the following:

1. The lack of data about rare diseases, due to the absence of codes for most rare diseases, deserves a special effort in epidemiology to make rare diseases more visible in the healthcare systems, in parallel with the ongoing process to incorporate codes for rare diseases in ICD and SNOMED-CT, as this process will not provide full results before several

5. On this basis, MSs should consider adding Orpha codes to their country's health information system and explore the feasibility and resources needed to do so. Rare diseases codification should be included in MS National Plan for Rare Diseases.

3. The Orpha codes should be further promoted within the development process of WHO's ICD11, in order to allow a seamless transition of RD classifi… from Orpha codes to ICD-11 when the latter is finally released.

4. MSs interested in using the Orph… …ng party to define the optimal strategy and the … …s effort should involve representatives … …plore the details and reach a consens… …e key stakeholders of the eHealth com… …int Research Centre Registration Platfo… …ations involved in the development of so… …atient organisations.

5. On this basis, MSs … …ng Orpha codes to their country's health information system … …e feasibility and resources needed to do so. Rare diseases codification s… …e included in MS National Plan for Rare Diseases.

6. Interested MSs together with the Commission should seek possibilities to support, at EU level, the implementation process of the identified solutions.

Orphanet is the only structured nomenclature specific for RD

- ICD-10: 550 specific codes for RD
- SNOMED-CT: around 40% of Orphanet entries
  - T0 mapping exercise, 2015
  - Collaboration ongoing
- OMIM: 57 % exact matchs with Orphanet nomenclature
- In all these nomenclatures:
  - RD are mixed up with common diseases or genetic traits/conditions

RD-ACTION objectives

- To continue **implementation of the policy priorities** identified in Council Recommendation 2009/C151/02 and the Commission Communication (COM 2008 679) on RD, with a view to ensuring the sustainability of the recommended priority actions, and to support the work of the Commission Expert Group on Rare Diseases by gathering expertise and producing data necessary to its action.

Contribute to solutions to ensure an appropriate **codification** of rare diseases in health information systems

Support the further development and sustainability of **the Orphanet database** on rare diseases which is run by a large consortium of European partners and is the biggest global repository of information about rare diseases.

Key-word: Integration

- Epidemiology, public health:
  - Codification in MS
    - Recommendations & guidelines
    - Master file
- Care & Research
  - Common standards, interoperability
- Orphanet & ERNs

→ Towards European commonalities

Interoperability

Care
Health Information System (EHRs)

Research
Registries/Cohorts

Orphanet central nomenclature

Genes
- HGNC
- OMIM
- UniProt
- Reactome
- Ensembl
- Genatlas
- IUPHAR

Phenotypes

Disabilities

Terminologies
- OMIM
- ICD10/11
- UMLS
- MedDRA
- SNOMED

orphanet

www.orpha.net

Needs at EU level

Definition of a common level of interoperability
&
Codification standards

ORPHANET NOMENCLATURE

Orphanet RD nomenclature

ORPHA number	Preferred label	Synonyms
ORPHA:93545	Renal or urinary tract malformation	CAKUT
		Congenital anomalies of kidney and urinary tract
ORPHA:216	Neuronal ceroid lipofuscinosis	NCL
ORPHA:586	Cystic fibrosis	CF
		Mucoviscidosis
ORPHA:355	Gaucher disease	Acid beta-glucosidase deficiency
		Glucocerebrosidase deficiency
ORPHA:77259	Gaucher disease type 1	Non-cerebral juvenile Gaucher disease

- The only clinical terminology specific for rare diseases
- Unique, stable ORPHA number
- Definitions
- 8 languages (En, Fr, Es, It, Nl, De, Pt, Pl)
- Peer-reviewed publications only (2 cases<RD<1/2000)

Search for a **rare disease**

Search
Search by sign
Classifications
Genes
Disability
Encyclopaedia for patients
Encyclopaedia for professionals
Emergency guidelines
Sources/procedures

Disease name *

Search

(*) mandatory field

- (•) Disease name
- ( ) OMIM
- ( ) Gene name or symbol
- ( ) Orpha number
- ( ) ICD-10

Usher syndrome

Suggest an update

Disease definition

Usher syndrome (US) is characterized by the association of sensorineural deafness (usually congenital) with retinitis pigmentosa and progressive vision loss.

ORPHA:886

Synonym(s):

Retinitis pigmentosa-deafness syndrome

USH

Prevalence: **1-9 / 100 000**

Inheritance: **Autosomal recessive**

Age of onset: **Infancy, Neonatal**

ICD-10: **H35.5**

OMIM: 276900 276901 276902 276904 500004 601067 602083 602097 605472 606943 611383 612632 614504 614869 614990

UMLS: **C0271097**

MeSH: **D052245**

GARD: 7843

MedDRA: **10063396**

RD classification

- **Why?** → Improve information
  Epidemiology and statistics studies
- **How?** → Organized by medical specialties
- **Particularity** → Systemic disorders

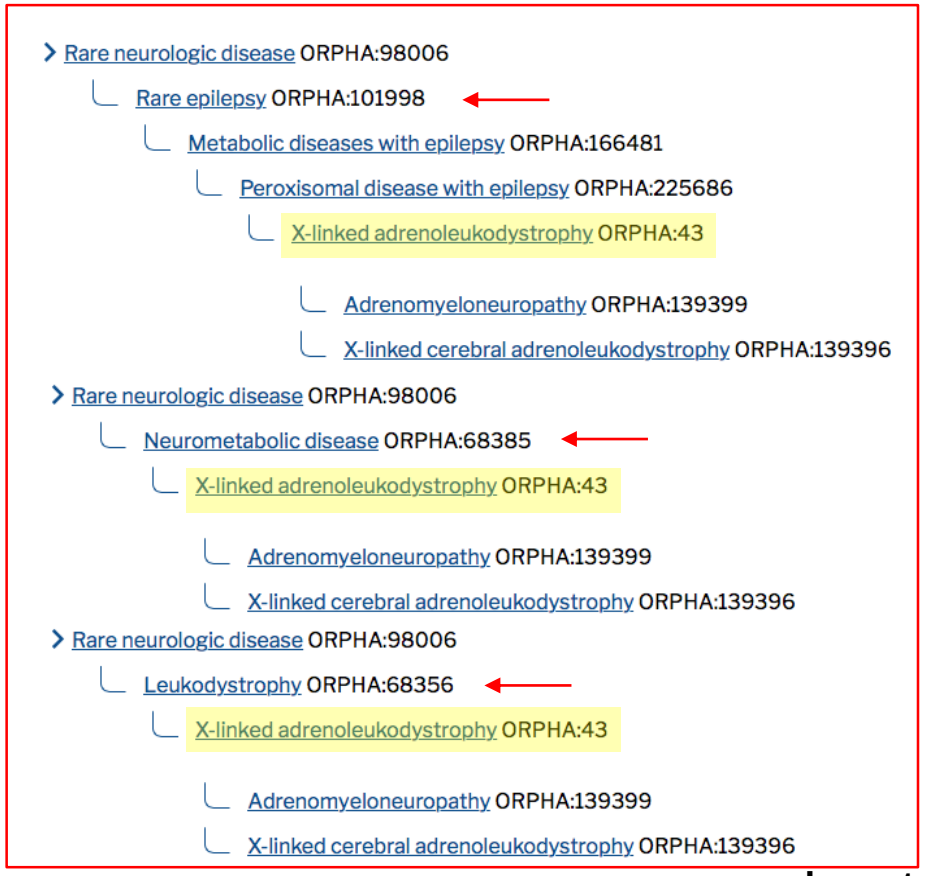
Multi- classification

Multi-dimensional

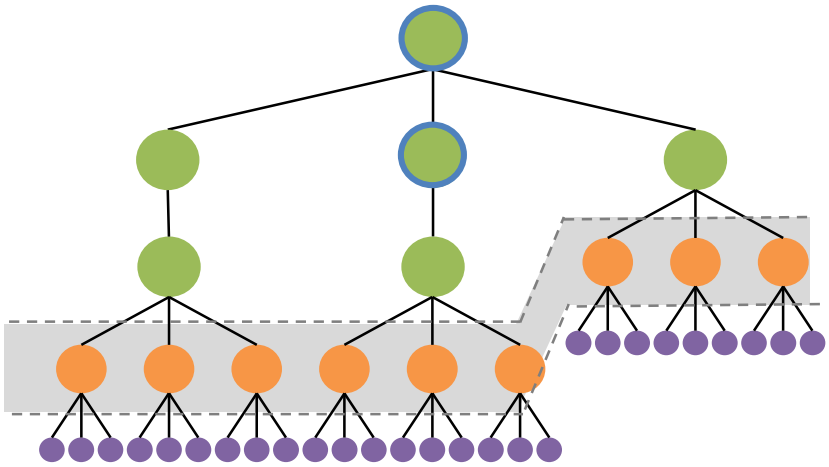
X-linked adrenoleukodystrophy

- Orphanet classification of rare inborn errors of metabolism
- Orphanet classification of rare genetic diseases
- Orphanet classification of rare neurological diseases
- Orphanet classification of rare endocrine diseases
- Orphanet classification of rare infertility disorders

Multi-hierarchical



Logical structure



Group

Category: clinically heterogeneous

Clinical group: clinically homogeneous

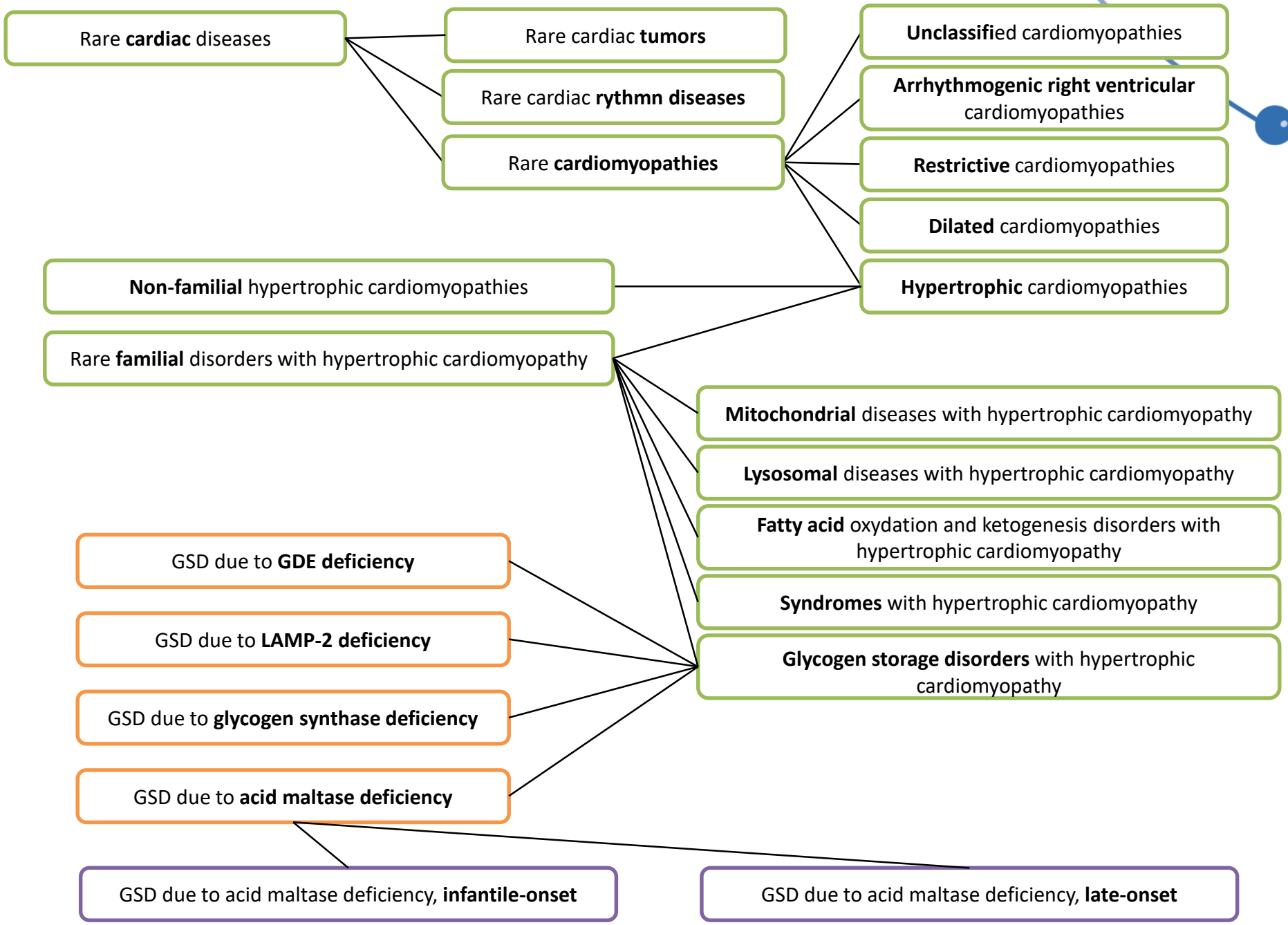
Disorder:

- Disease, clinical syndrome, malformation syndrome, morphological anomaly, biological anomaly, particular clinical situation

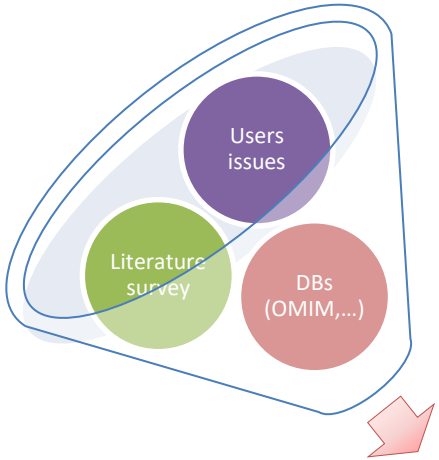
Subtype:

- Clinical, etiological, histopathological

- Every entity is **meaningful**
- Entities are **disjointed**
- **Parts** are added to form the **wholes**
- **Transitivity** applies at every level


Rare **cardiac** diseases
Rare cardiac **tumors**
Rare cardiac **rythmn diseases**
Rare **cardiomyopathies**
Unclassified cardiomyopathies
Arrhythmogenic right ventricular cardiomyopathies
Restrictive cardiomyopathies
Dilated cardiomyopathies
Hypertrophic cardiomyopathies
Non-familial hypertrophic cardiomyopathies
Rare **familial** disorders with hypertrophic cardiomyopathy
Mitochondrial diseases with hypertrophic cardiomyopathy
Lysosomal diseases with hypertrophic cardiomyopathy
Fatty acid oxydation and ketogenesis disorders with hypertrophic cardiomyopathy
Syndromes with hypertrophic cardiomyopathy
Glycogen storage disorders with hypertrophic cardiomyopathy
GSD due to **GDE deficiency**
GSD due to **LAMP-2 deficiency**
GSD due to **glycogen synthase deficiency**
GSD due to **acid maltase deficiency**
GSD due to acid maltase deficiency, **infantile-onset**
GSD due to acid maltase deficiency, **late-onset**

Update process



Orphanet DB verification, literature search, expert advice

Verification of prevalence, database and classification consistency

Decision
Disease committee

Qualify the demand

Creation

Modification

New entry

Reject

+ info

Nomenclature

Obsolescence

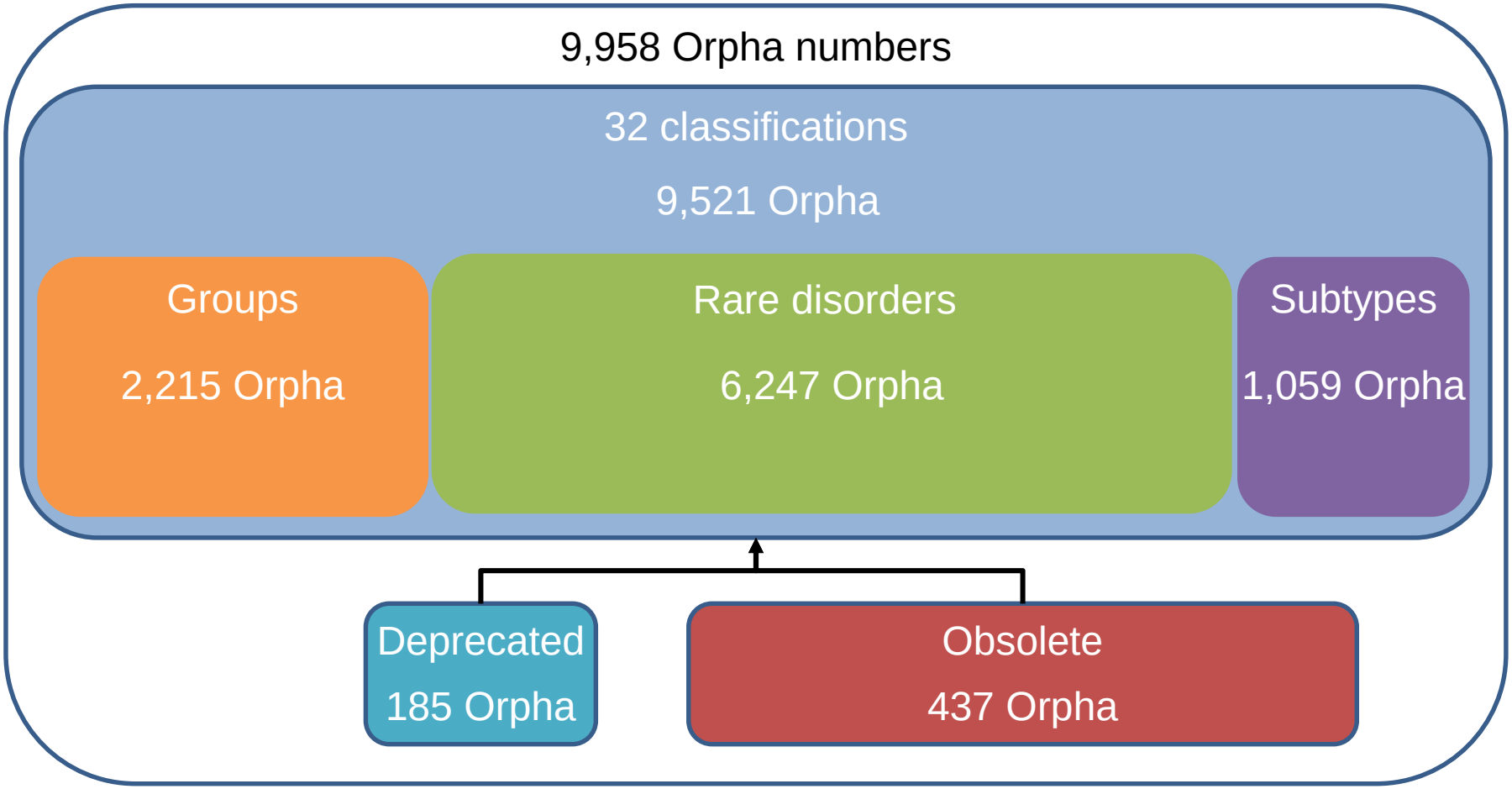
Deprecation

Expert advice

Impact on the inventory → New Orpha numbers, Status modification

Impact on the classification → New hierarchy including new orpha numbers consitency inter- and intra-classification

Some figures



Mappings with other terminologies

Terminology	mapped	RD
ICD-10	Manually	All
OMIM	Manually	4,390
Snomed-CT	Manually	3,800
GARD	Semi-automatically	2,998
UMLS	Semi-automatically	2,885
MeSH	Semi-automatically	1,763
MedDRA	Semi-automatically	1,224

Qualifier	
E	exact mapping (the terms and the concepts are equivalent)
NTBT	narrower term maps to a broader term
BTNT	broader term maps to a narrower term
W	incorrect mapping (two different concepts)
ND	not yet decided/unable to decide

ICD10 codes only :	
Specific code	The term has its own code in the ICD10
Inclusion term	The term is included under a ICD10 category and has not its own code
Index term	The term is oncluded in ICD10 index and refers to one more general code
Attributed code	The term does not exist in ICD10 and a code was attributed by Orphanet

Coding perspective

Orpha number	Preferred label	Synonyms	Typology	Status	ICD-10	Definition/relationship
ORPHA:93545	Renal or urinary tract malformation	CAKUT Congenital anomalies of kidney and urinary tract	Category	_	_	_
ORPHA:216	Neuronal ceroid lipofuscinosis	NCL	Clinical group	_	E75.4	Yes
ORPHA:586	Cystic fibrosis	CF Mucoviscidosis	Disease	_	E84.0 E84.1 E84.8 E84.9	Yes
ORPHA:355	Gaucher disease	Acid beta-glucosidase deficiency Glucocerebrosidase deficiency	Disease	_	E75.2	Yes
ORPHA:1245	BIDS syndrome	Amish brittle hair syndrome Trichothiodystrophy type D	Disease	Deprecated	_	moved to Trichothiodystrophy
ORPHA:77259	Gaucher disease type 1	Non-cerebral juvenile Gaucher disease	Subtype	_	E75.2	yes
ORPHA:101042	Taussig-Bing syndrome		Subtype	Obsolete	_	Refered to Double outlet right ventricle with subpulmonary ventricular septal defect

Orpha Code

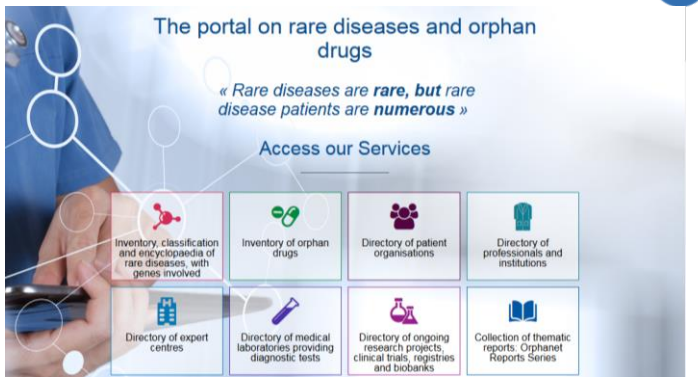
=

Orpha numbers used to be assigned to a patient within an information system

Users and information media

Health professionals
Patients
Public health stakeholders

→ Information on a specific disorder



R&D
Public health stakeholders
HIS

→ Computational use subset of disorders/data

R&D

→ Computational analysis logical inference

ordo
Orphanet Rare Disease Ontology

Similarities and differences

orphanet

Updated daily

- Orpha numbers in use
- **deprecated** disorders

orphadata

xml format

Updated monthly

- Orpha numbers in use
- **deprecated** disorders

ordo

Orphanet Rare Disease Ontology

owl format

Updated bi-annually

- Orpha numbers in use
- **deprecated** disorders
- **obsolete** disorders

- Versioning with change log

RD-ACTION

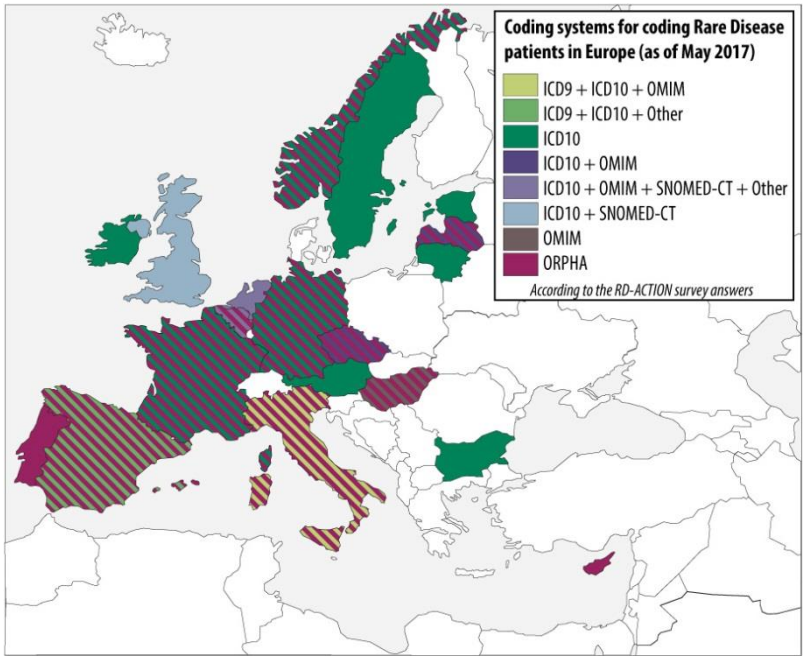
IMPLEMENTING ORPHA CODIFICATION

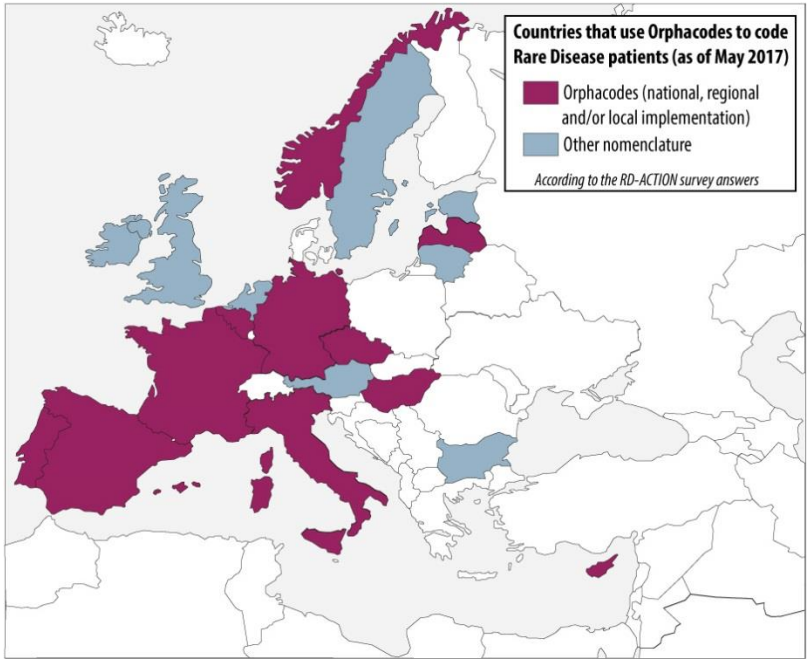
Implementation of rare disease patient coding across member states: SoA

✓**Survey of current codification situation in MS 2016:**

http://www.rd-action.eu/wp-content/uploads/2016/01/framework-survey-interpretation.pdf

✓**Survey of current codification situation in MS 2017:**
http://www.rd-action.eu/wp-content/uploads/2016/01/framework-survey-interpretation.pdf





✓Review document of existing technical implementations for RD coding of MS

http://www.rd-action.eu/wp-content/uploads/2016/06/677024_D5.1_INTEGRATED_FINAL_2.pdf

What else can we learn from that?

- The introduction of a new coding system without guidelines and regulation may not be sufficient to succeed.
- The use of classifications is strongly dependent on the use case.
- There should be a balance between national system requirements and international demand for data on rare diseases.
- Giving strict rules for coding of rare diseases could restrict the national possibilities but will enhance the international comparability.

How to make coded data exploitable at the EU level?

- Data should be collected in routine settings so all patients can be captured

- Data should be collected in a unified way
  - Agreed list of Orphacodes to be used (Master file)
  - Coding guidelines that do not interfere with national regulations (as much as possible) but standardize the data collection so that it serves the international use case

- ✓ Standard procedure and guide for the coding with Orphacodes & The set of clear objectives and coding rules propositions for RD at EU level

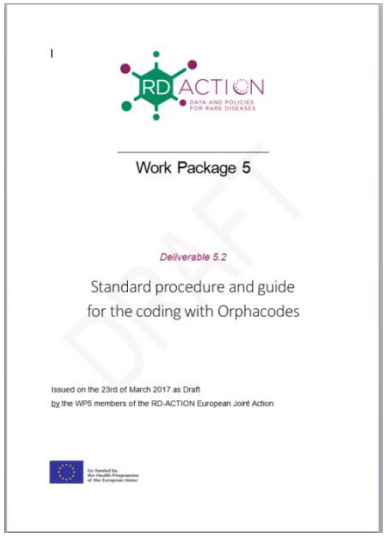
  http://www.rd-action.eu/wp-content/uploads/2017/05/D5.2_Standard-procedure-and-guide_final.pdf

This document provides information about the use cases of coding Rare Diseases, the coding process, reference methods for the implementation of the Orphanet nomenclature into Health Systems and the technical requirements.

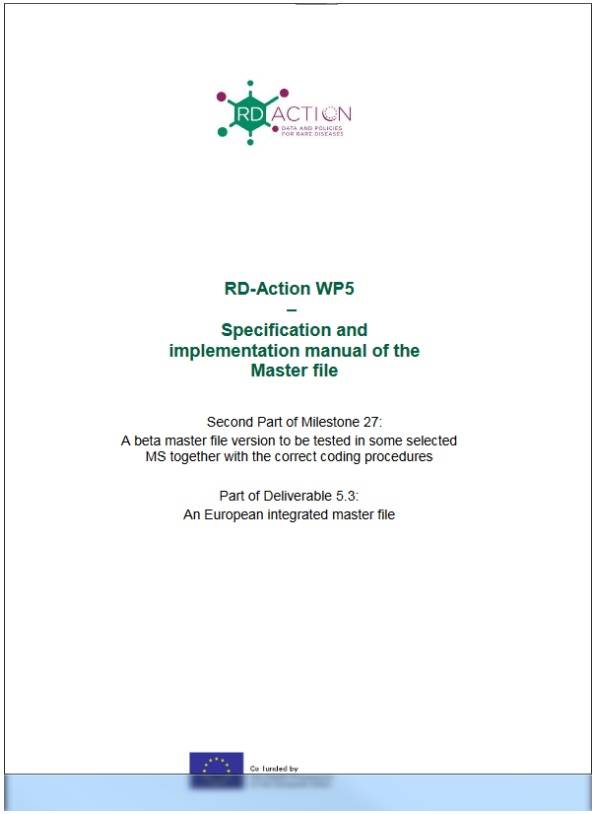
- ✓ Defines common objectives for coding RD
- ✓ Provides guidance and standard procedures for coding RD

International rules and guidelines for coding rare diseases

- **Guideline 1** - Several tools and strategies could be set at MS level to produce data or statistics for RD, nevertheless each country should set this strategy accordingly to a standard principle of maximizing exhaustiveness as well as possible re-use of existing data collections
- **Guideline 2** - Code the data in a way that the reporting can compile to the granularity of the international recommended list of Orphacodes ("master file"-granularity). If no further national needs for reporting are necessary, use the codes from the "master file" directly.
- **Guideline 3** - Whenever possible capture the information of the diagnostic assertion for all RD cases. Use the Options "Suspected rare disease", "Confirmed rare disease" and "Undetermined diagnosis". Additional options might be helpful.
- **Guideline 4** – Although rare disease registries (disease, population or patient based) should promote the use of data standards to increase interoperability of their data, they should not be the only instruments upon which the EU strategy to produce health statistics for RD at population level relies.
- **Guideline 5** - Update your coding resource according to the internationally agreed cycle in order to have the most recent coding file and to ensure comparability.
- **Guideline 6** - If Orphacodes are used together with another national coding system for morbidity coding, the two systems should be linked in a standardized way to ensure that code combinations are standardized and the coding effort for the user is minimized.



The Master file and the Manual



✓Specifications of a master file taking into account existing implementation and strategies of MS

✓A beta master file version to be tested in some selected MS together with the correct coding procedures

The Master file is intended to:

✓Provide a standard for coding RD (minimal level of standardisation)

✓Support consistency across MS

✓Allow different national coding practices

✓Enable international statistical retrieve and aggregation (interoperability)

THANK YOU!