Patients with Undiagnosed Rare Diseases
The EUCERD perspective

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INSERM US14 / Orphanet, Paris, France

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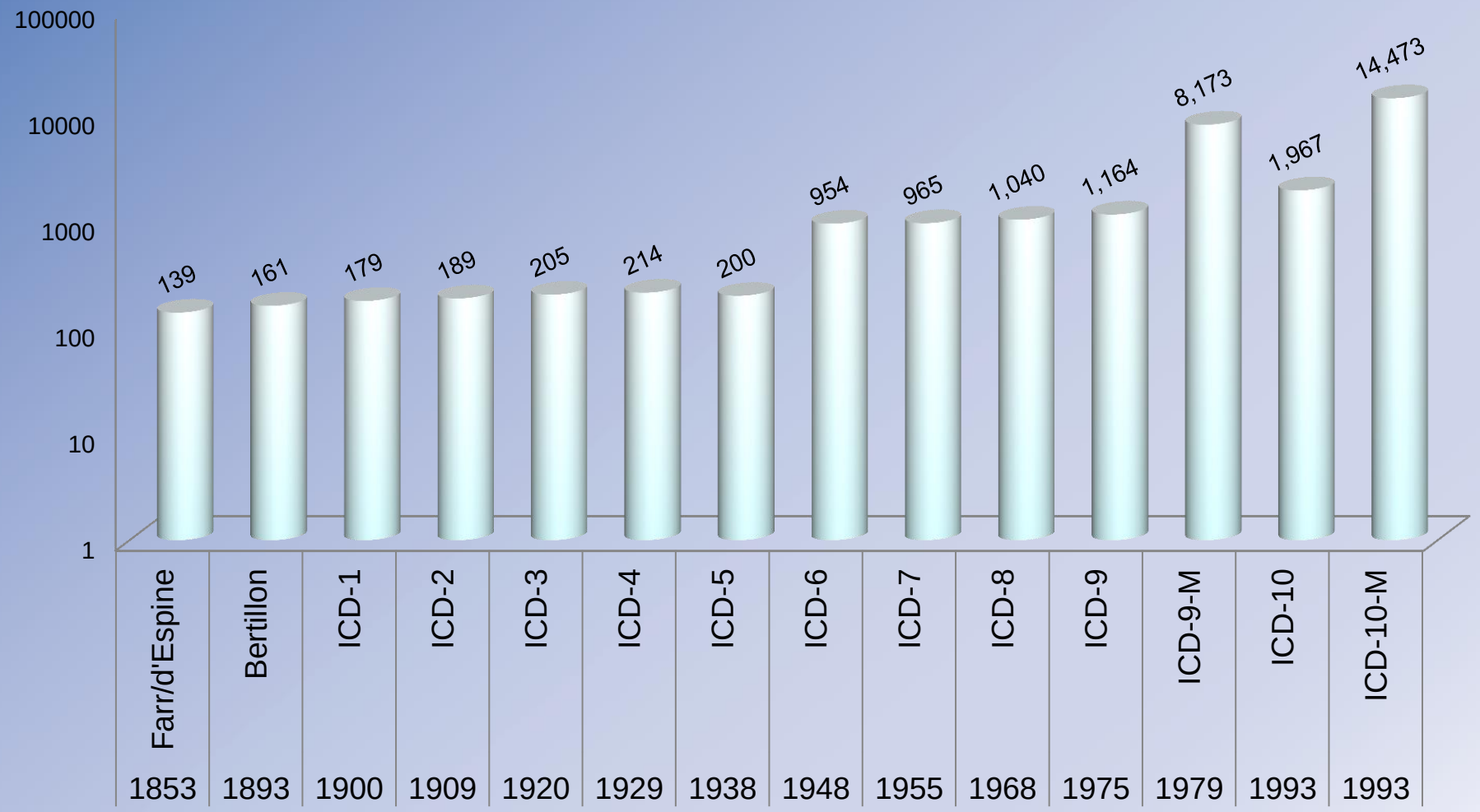
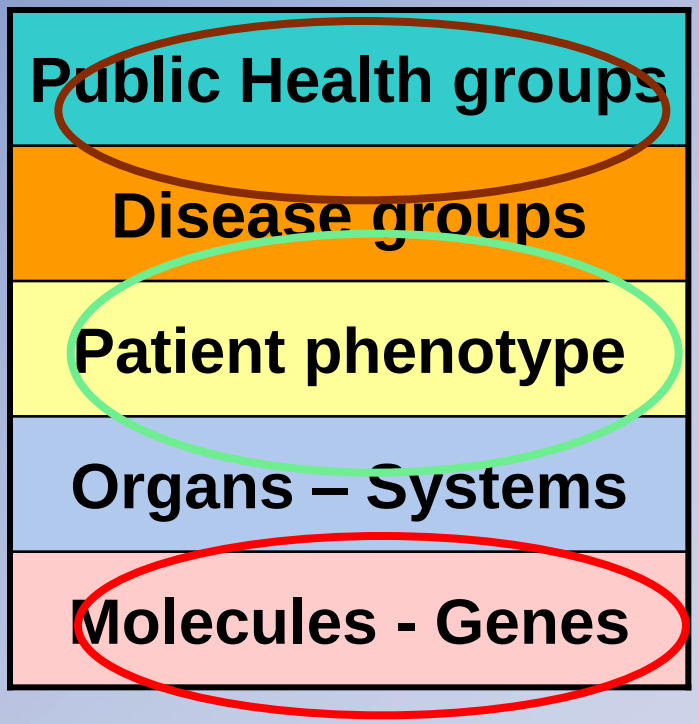
When is a patient diagnosed/undiagnosed?

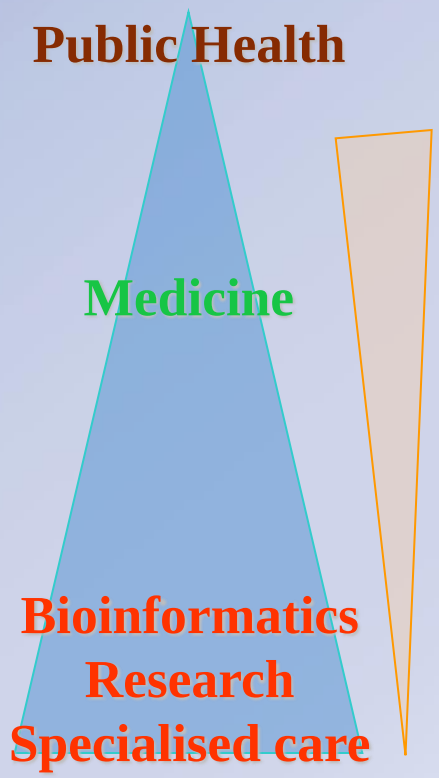
- Making a diagnosis is putting a name on a clinical situation so as
  - To inform the patient of the prognosis and consequences of his disease
  - To propose appropriate management
  - To be able to communicate with other healthcare professionals
  - To identify an entity for clinical research and/or for administrative reasons
- It is very much dependent on
  - the level of knowledge in general
  - the level of investigation performed

The International Classification of Diseases



Levels of entity definitions





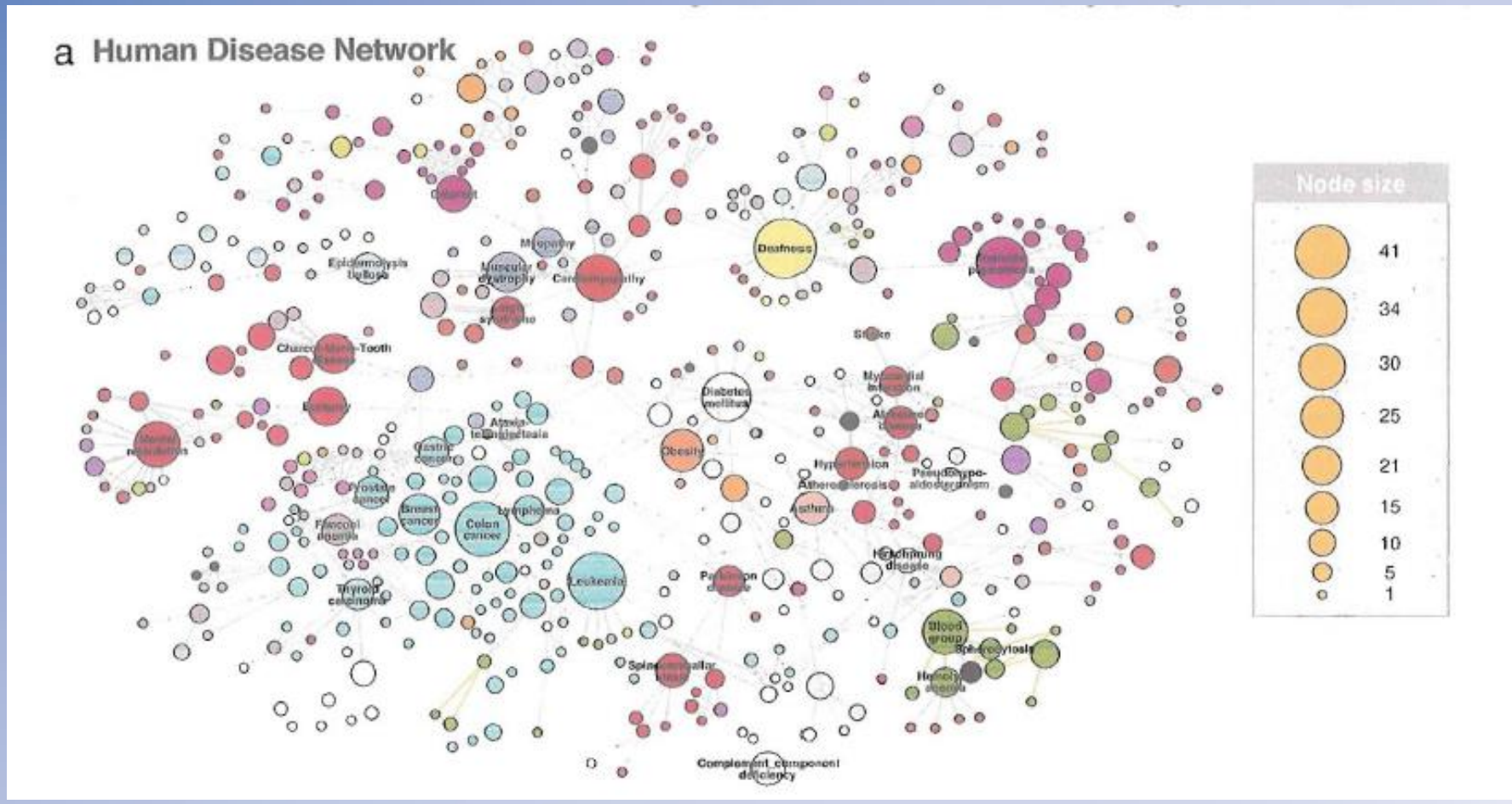
Disease: concept linked to type of use

- Recognisable set of signs and symptoms
  - Clinical approach
- Entity due to a unique mechanism
  - Physiopathological approach
- Entity with a unique evolution and prognosis
  - Approach by natural history
- Entity reponding to a specific treatment
  - Pragmatic approach in relation with an intervention
- Entity with a specified etiology
  - Biological approach

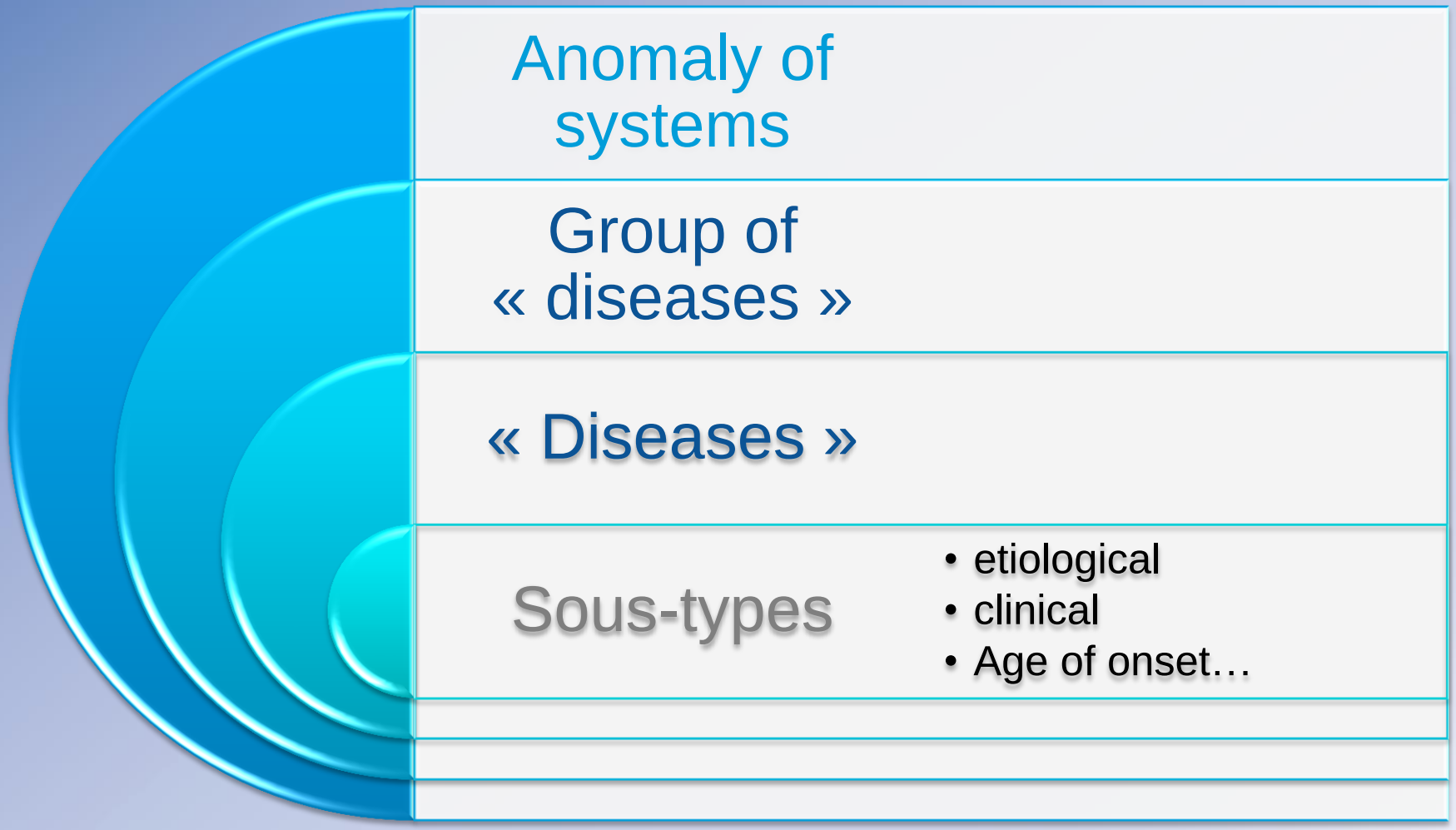
The modular nature of diseases…

- Many phenotypes overlap

- They cluster in family of diseases


a Human Disease Network
Node size
41
34
30
25
21
15
10
5
1
Deafness
Stroke
Diabetes mellitus
Obesity
Hypertension
Atherosclerosis
Asthma
Colon cancer
Breast cancer
Leukemia
Lymphoma
Blood group
Complement component deficiency

There is a nosological continuum



Types of undiagnosed patient (1)

- Clinical entity never observed before / despite extensive search
  - Search in syndrome databases: negative
  - Biochemical and molecular investigation: negative
- But assignable to a broad clinical group
  - Multiple malformation syndrome
  - Neuromuscular disease
    - ✓ Limb-girle muscular dystrophy not linked to any known gene

Types of undiagnosed patient (2)

- NO diagnosis but
  - No expert knowledge
  - No systematic search in syndrome databases
  - No biochemical nor molecular investigation
- Experience of Dyscerne (EC project)
  - Database of undiagnosed patients with dysmorphic syndromes
  - Cases submitted to a panel of experts
  - Most advices were to further investigate

Suggestions

- Undiagnosed patients should benefit from advances in science
- They should be refered to centres of expertise (CoE) to benefit from the best possible investigation

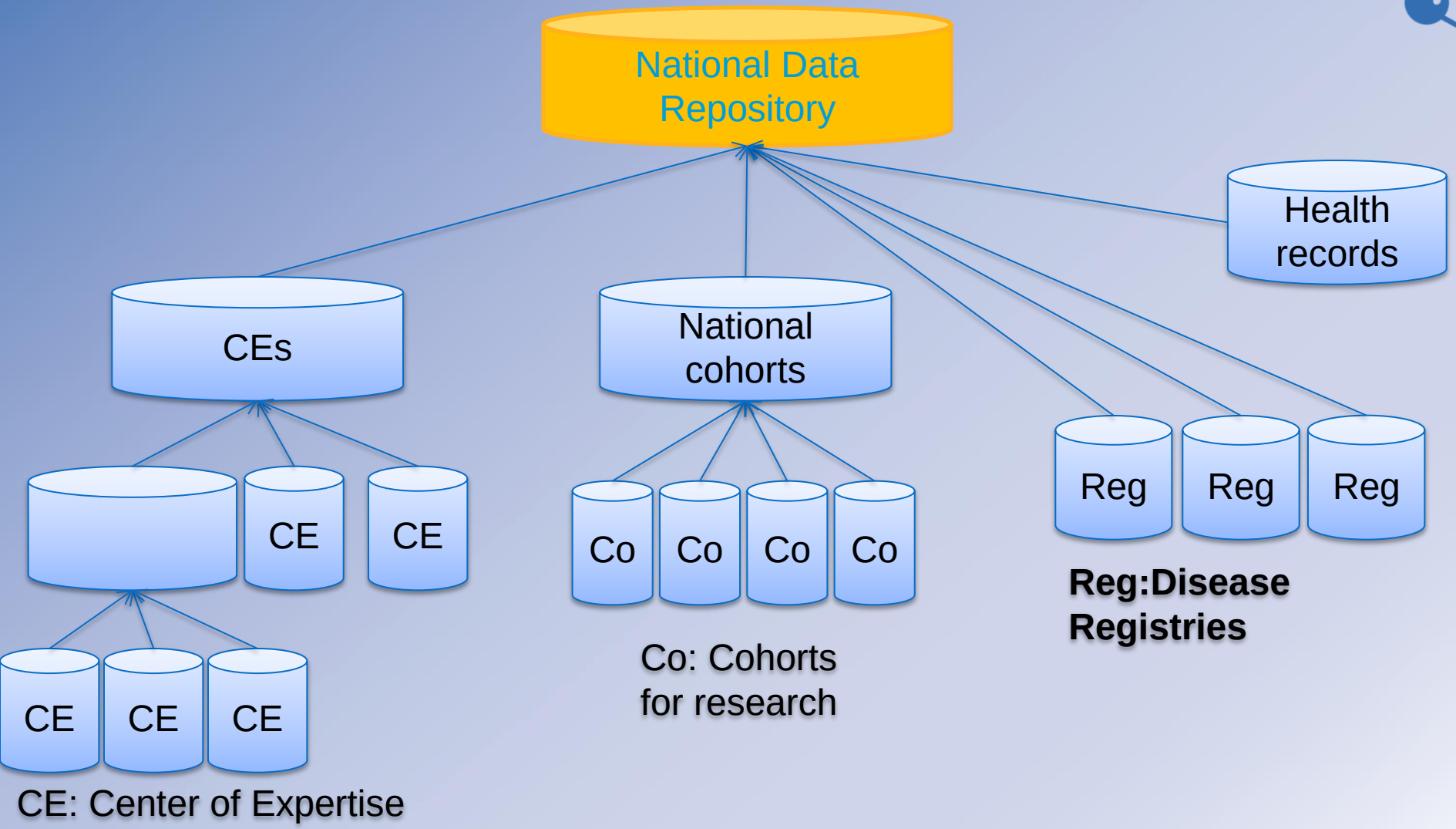
If So

- They will be described in the database of these centres, with their fuzzy diagnosis (group)
- The easiest way to establish a registry of these patients for clinical research is to build it by aggregation of data from the CoE

Other sources of Data on undiagnosed patients

- Research-oriented datasets
  - Disease registries
  - Cohorts
  - National RD registries
- Care-oriented datasets
  - Electronic Patient Records

French National Data Repository Project



Key factors of Success

- Do not request clinicians to register twice their data
  - They are too busy
- Use existing computerized systems at clinical level or establish a system at that level

- Make systems interoperable
  - Common phenome descriptors
    - ✓ HPO and ICHPT
  - Common nomenclature of diseases
    - ✓ Orpha codes
- Provide open access to data

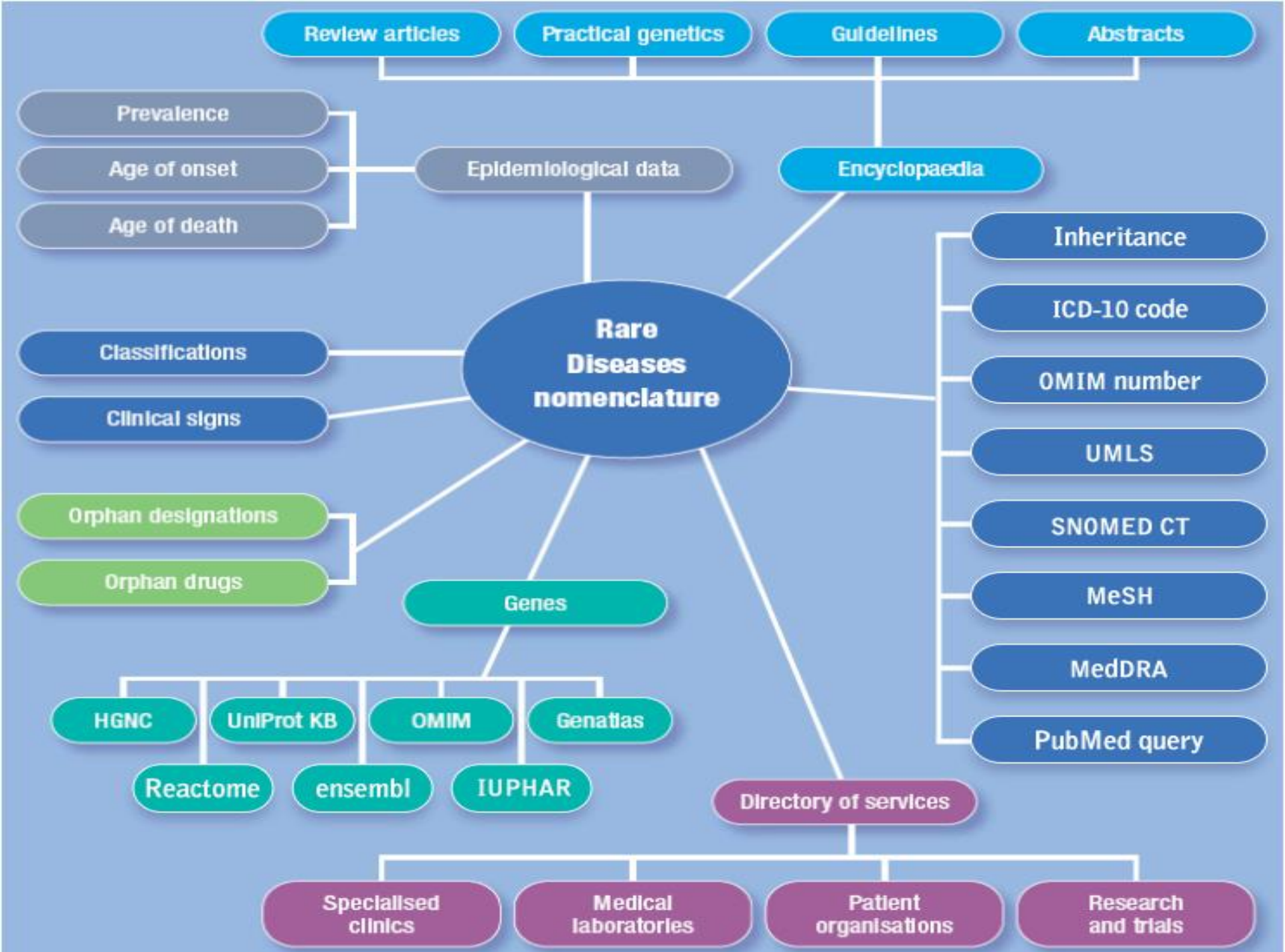
Orphanet Terminology of Diseases

- Comprehensive list of rare diseases
  - Identity card + genes
  - **Unique Orpha number**
    - ✓ **Stable what ever is the evolution of knowledge**
    - ✓ **Linked to parent and child disease in every classification**
  - Files available at www.orphadata.org
  - **Suitable to code clinical activity / lab activity in information systems**

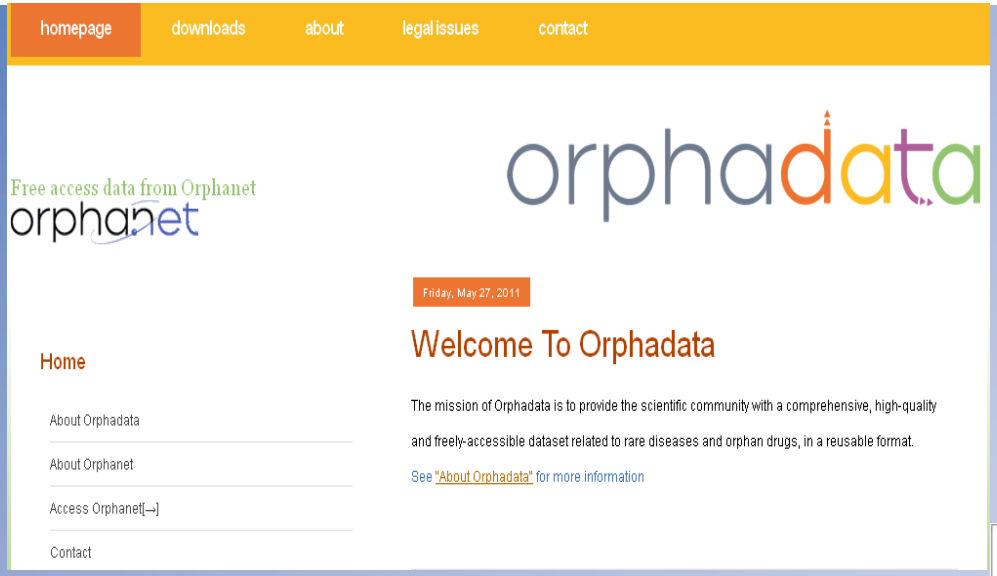
- Classifications of rare diseases
  - List of all published classifications
  - Visualisation of each classification
  - Possibility to click at any level to have detailed information

Orpha codes for all levels of uncertainty

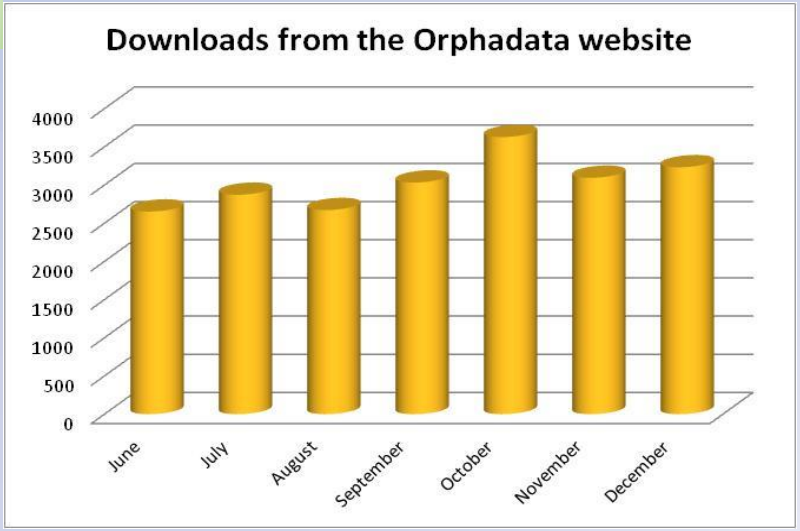
- Dysmorphic syndrome
  - Short stature syndrome
  - Craniosynostosis syndrome
- Intellectual deficit syndrome
- Multisystemic disease
- Rare neurological disease
  - Leukodystrophy
  - Genetic ataxia
  - Medular disease
  - Neuromuscular disease
  - …….


Review articles
Practical genetics
Guidelines
Abstracts
Prevalence
Age of onset
Age of death
Epidemiological data
Encyclopaedia
Inheritance
ICD-10 code
OMIM number
UMLS
SNOMED CT
MeSH
MedDRA
PubMed query
Classifications
Clinical signs
Rare Diseases nomenclature
Orphan designations
Orphan drugs
Genes
HGNC
UniProt KB
OMIM
Genatlas
Reactome
ensembl
IUPHAR
Directory of services
Specialised clinics
Medical laboratories
Patient organisations
Research and trials

www.orphadata.org



- Re-usable format



Thank you for your attention

I look forward to discussing with you