European Commission
Directorate-General for Health and Food Safety (DG SANTE)

ITHACA

ITHACA Board Meeting

2020 December 10 – 12

Satellite Meetings : Friday Dec. 11th

WG 9 ID

From 9 to 10:50 AM

European Reference Networks

(WG9) Work Groups / Satellite Meetings : Friday December 11th

Time Slot (Virtual Zoom Rooms)	W9 : Intellectual Disability Chair : Tjitske Kleefstra /Dagmar Wieczorek	SPEAKER PM contact : Anne Hugon
9h00	WG ID Goals	Tjitske Kleefstra
9h20	SNW1 ID	Tjitske Kleefstra
9h40	SNW2 PMID	Sylvia Huisman
10h00	Sys ID up Date	Christiane Zweier
10h20	WG ID project forecast	Tjitske Kleefstra
10h40 - 10h50	Discussion for Y 4-5 Future objectives	All attendees

⇨ Feel free to invite ERN and external experts

Experts can be:

- 1/ unrelated to ITHACA
- 2/ non-european (UK…)
- 3/ Patient organisation

On the Excell sheet, next slide 4,
we would like you to help us to fill up
your Medical specialty and/or your field of interest
*****
Please send an email to anne.hugon@aphp.fr

Medical specialty:

- Neuropediatrician; pediatric neurologist; Pediatric Geneticist; Physical and Rehabilitation Medicine; Ophthalmologist; Gastropediatrician; Psychiatrist; Endocrinologist; Dental Surgeon; Sex Specialist; Psychologist; Occupational Therapist; Public Health Physician; Speech-Language Pathologist; Patients organisations ; Ethical issues

Field of interest to complete

European Reference Network
for rare or low prevalence complex diseases
Network Intellectual Disability and Congenital Malformations (ERN ITHACA)

Members list WGWG 9 ID diagnosis and management

Role	Name	HCP	Country	SNW2 P	SNW1 a	SNW3 D	medical Specialty/ interest field
Chair	Tjitske Kleefstra	Nijmegen	NL				
Chair	Dagmar Wieczorek	Dusseldorf	DE				
Member	Christiane Zweier	Erlangen	DE				
Member	Cyril Mignot	Paris (APHP PSL)	FR		1		clinical Geneticist and pediatrician ID
Member	Delphine Héron	Paris (APHP PSL)	FR		1		clinical Geneticist and pediatrician Coordinator of Expert Center Rare ID
Member	Livia Garavelli	Reggio Emilia	IT				pediatric genetist
Member	Gijs Santen	Leiden	NL				
Member	Kai Muru	Tartu	EE				
Member	Malgorzata Szmyt	Olsztyn	PL				
Member	Malgorzata Pawlowicz	Olsztyn	PL				
Member	Maria Antonietta Mencarelli	Siena	IT				
Member	Maria Francesca Bedeschi	Milano	IT	**1**			genetist
Member	Livia Garavelli	Emilia	IT				
Member	Nadia Bahi-Buisson	Paris (APHP NCK)	FR	**1**			pediatric neurologist - Spécialized in PIMD
Member	Solveig Heide	Paris (APHP PSL)	FR				clinical Geneticist and pediatrician
Member	Stefania Bigoni	Ferrara	IT			1	
Member	Lina Cardoso Ramos	Coimbra	PT				clinical Geneticist
Member	Isabelle Maystadt	Namur - Gosselies	Be				clinical Geneticist
Member	Sylvia Huisman	Amsterdam	NL	**Chair**			pediatric neurologist - Spécialized in PIMD
Member	Vincent des Portes	Lyon HCL	FR		1		pediatric neurologist, Expert in ID, Coordinator of DefIScience
Member	Karolina Śledzińska	Gdansk	PL				
Member	Zeynep Tümer	Copenhaguen	DK				
Member	Marie Hully	Paris (APHP NCK)	FR	**1**			pediatric neurologist - Spécialized in PIMD
Guest	Perrine Charles	Paris (APHP PSL)	FR		1		Clinical Geneticist expert in Adult ID
Member	Esther Bakker-van Gijssel	Nijmegen	NL		1		
Guest	Marie Christine Rousseau	Paris (APHP)	FR	**1**			Physical and Rehabilitation Medicine - Spécialized in PIMD
Guest	Billette de Villemeur	Paris (APHP TSL)	FR	**1**			pediatric neurologist - Spécialized in PIMD
Member	Joyce Geelen	Nijmegen	NL	**1**			pediatrician specialised in developmental and congenital disorders
Member e-	Carole Herman	Paris	FR				e-Pag
Member e-	Dorica Dan	Zalau	HU				e-Pag
Member e-	Katarzyna Swieczkowska	Gdansk	PL	**1**			e-Pag
Member e-	Inés Fernández Ulibarri	Mainz	DE				e-Pag community
Guest PO	Marie Christine Teznas du Montcel	Paris	FR	**1**			GPF Groupe Polyhandicap France - Présidente

we would like you to help us to fill up your Medical specialty and/or your field of interest

Please send an email to anne.hugon@aphp.fr

We need
Neuropediatrician
pediatric neurologist
Pediatric Geneticist
Physical and Rehabilitation Medicine
Ophthalmologist
Gastropediatrician
Psychiatrist
Endocrinologist
Dental Surgeon
Sex Specialist
Psychologist
Occupational Therapist
Public Health Physician
Speech-Language Pathologist
Patients organisations
Ethical issues

your contact for WG 9 ID Anne HUGON , Project Manager & Coordination Officer (ERN) ITHACA
06 68 96 91 07 / +33 1 40 03 23 39 / anne.hugon@aphp.fr

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Web site page : WG 9 ID diagnosis and management

☆ WORKPACKAGE LEADS

Dr Tjitske. Kleefstra (Nijmegen)

Dr Dagmar Wieczorek (Dusseldorf)

KEY OBJECTIVES

To deal with rare genetic IDs, improve our knowledge and understanding of these disorders, which number in the thousands but are poorly known for the most part.
Description

Deliverables

https://ern-ithaca.eu/missions/wg-id-diagnosis-and-management/

EXPERT CONSENSUS

Develop a web-based rare ID gene database and wiki to provide access to information on genetic causes of ID. Create and make accessible an ID gene database connected to clinical information and interacting with Orphanet (M36).

2019 Dusseldorf Challenges WP9: ID (Tjitske & Dagmar)

- Collaborate with Registry WG to define ILIAD minimum ID dataset and ILIAD scope of genes
- SYSID synergy/integration with ORPHANET (cf **Christiane Zweier's talk**)
- Implementation of an English version of INSERM report on ID on the web site (collaboration with national French ID network)

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WG 9 ID - Launch 3 projects for the next 2 years
Diagnosis and management of intellectual disability

Discussion

- Propose 3 separate working groups
- Identify potential partners ,
  - need experts out of the genetic circle of ITHACA
  - including in the other ERNs (Epicare, NMD...)
- Provisional roadmap
- Transversal recommandation could be based on Raoul's experience (WG4) and on the means proposed by the European community (help in writing and organizing meetings.)
- **Developping a specific dataset for ID patients in ILIAD**

Recommendations of good practice for the management of mentally disabled adults	**Good practice recommendations for the management of children with profound intellectual impairment and multiple disabilities**	**Recommendations of good practice on strategies for diagnosing intellectual disability, applicable in Europe**
	Launch oct 20 *Sylvia Huisman*	

Recommendations of good practice for the management of mentally disabled adults

Recommendations of good practice for the management of mentally disabled adults

- **Based publications to edit practical/recommandation**

- Sullivan, William F., et al. "**Primary care of adults with intellectual and developmental disabilities: 2018 Canadian consensus guidelines**." Canadian Family Physician 64.4 (2018): 254-279.
- "**Constructing a health assessment questionnaire for people with intellectual disabilities: A cognitive interview study.**" Journal of Applied Research in Intellectual Disabilities 33.3 (2020): 345-353.
- Bakker-van Gijssel, Esther J., et al. "**Development of a health assessment instrument for people with intellectual disabilities: a Delphi study**." Family practice 35.5 (2018): 599-606.
- Bakker-van Gijssel, ESTHER J. **A pro-active health assessment instrument for people with intellectual disabilities**. Towards reducing health inequities. Diss. [Sl: sn], 2018.
- Lunsky, Yona, et al. "**Primary care of adults with developmental disabilities in Ontario.**" *Healthc Q* 17.3 (2014): 11-3.

Others ideas

Implementation of an English version of INSERM report on ID on the web site (collaboration with national French ID network)

Identify needs and partners → **Draft production and SNW meeting** → **1st production & revision** → **Final proposition to be discuss** → **Final publication dissemination**

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Recommendations of good practice on strategies for diagnosing intellectual disability, applicable in Europe

- Beyond the simple "array + genome“ make proposal: initial assessment, systematic check-up after genetic diagnosis, attitude for patients without a diagnosis …

Sylvia Huisman PIMD SNW
Good practice recommendations for the management of children with profound intellectual impairment and multiple disabilities

Good practice recommendations for the management of children with profound intellectual impairment and multiple disabilities

- **Focusing on genetic causes - but these recommendations could be relevant to all patients with profond, severe and multiple disabilities**
- Set a subnetwork group (SNW**)** on profound intellectual and multiple disabilities
- Based on the PNDS Polyhandicap (French National Diagnostic and Care Protocols (NDCPs) on PIMD profound intellectual and multiple disabilities) published in may 2020 – English Translation is in progress
- To Agree on a EU specific definition
- To Edit practical/recommendation (specific management fact sheets)

october 20
- Identify needs and partners

January 20
- Draft production and SNW meeting

July 21
- 1st production & revision

January 22
- Final proposition to be discuss

June 22
- Final publication dissemination

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Network
Intellectual Disability and Congenital Malformations (ERN ITHACA)

SNW2 PMID – Goals – ITHACA's Scope : PIMD / Polyhandicap

Group leader - Sylvia Huisman, ID physician

ITHACA PM contact - Anne Hugon

Project PIMD / produce Good practice recommendations, Transversal recommendations

- Good practice recommendations for health care of children with profound intellectual and multiple disabilities
- Good practice recommendations for daily care and support of children with profound intellectual and multiple disabilities.

- Starting from rare (genetic) causes, directing towards generic recommendations relevant to all individuals with PIMD
- Medical, rehabilitative, and socio-educational care
- To guide professional care in European countries and to empower families to receive optimal care

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SNW2 PMID – Goals – ITHACA's Scope : PIMD / Polyhandicap

Goals

- Identifying specific group of people based on their characteristics (directly or indirectly related to cerebral functioning) and needs
- Holistic approach with balanced focus on physical and mental (emotional) health and well-being
- Optimal support of development and quality of life of individuals with PIMD and the ones whom they closely relate to

Points of attention

- Early signs, (proactive) care and treatment options
- Developmentally appropriate approach, communication and (by proxy) decision making
- Multidisciplinary collaboration
- Goal attainment and life path dedicated care
- Organization of continuous care, coordination and longitudinal follow-up

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SNW2 PMID – Goals – ITHACA's Scope : PIMD / Polyhandicap

Target audience

- Medical, rehabilitative, and socio-educational care professionals
- Lay version for parents and daily caregivers

Cover the Period from Birth to 25 yrs

- argument to include transition period > Good practice recommendations for children and adolescents with PIMD.

SNW2 PMID – Goals – ITHACA's Scope : PIMD / Polyhandicap

Working group and task assignment

- 10 persons from various disciplines and 2 ePAG members/patient advocates
- At least 4, 5 countries FR, NL, DE, ES or IT to agree on a EU specific definition/position
- Invite 1 expert representative per country/HCP
- Collaborate with Patient Organisation
- Rely on professional and specialist' societies (ex: EPNS The European Paediatric Neurology Society https://www.epns.info)

Methods, immediate actions

- Collecting of existing recommendations and national guidelines, establish a consensus and propose a definition
- A minimum of consensus with 4 countries?

SNW2 PMID – Goals – ITHACA's Scope : PIMD / Polyhandicap

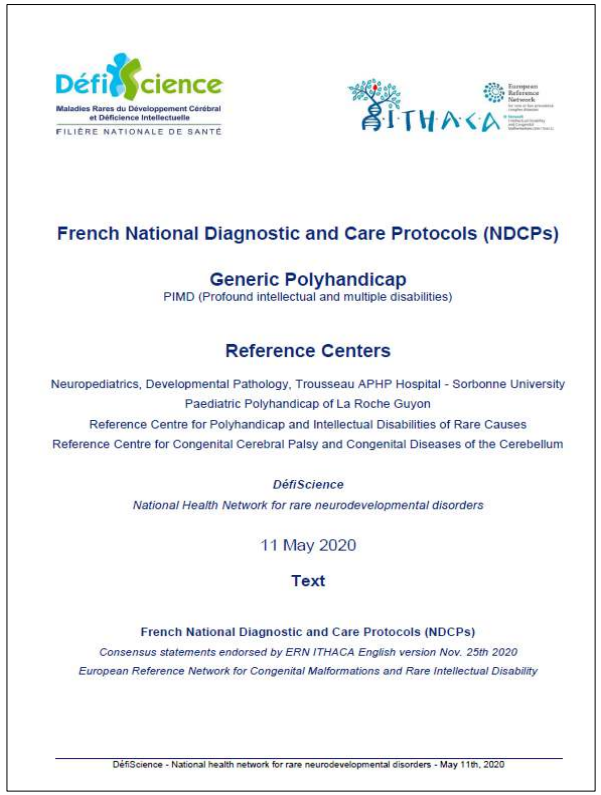
Prepare Draft Project
Tree format, online/web-based version?

Send to all HCP, with a survey

- What parts are or are not applicable in your country?
- What is missing?
- What needs to be changed?
- What needs to be added?

SNW2 PMID – Pre-existing guidelines on PIMD/Polyhandicap

French guidelines, translated engl nov 2020
National Diagnostic and Care Protocols (NDCPs)



DéfiScience
Maladies Rares du Développement Cérébral et Déficience Intellectuelle
FILIÈRE NATIONALE DE SANTÉ

ITHACA

French National Diagnostic and Care Protocols (NDCPs)

Generic Polyhandicap
PIMD (Profound intellectual and multiple disabilities)

Reference Centers

Neuropediatrics, Developmental Pathology, Trousseau APHP Hospital - Sorbonne University
Paediatric Polyhandicap of La Roche Guyon
Reference Centre for Polyhandicap and Intellectual Disabilities of Rare Causes
Reference Centre for Congenital Cerebral Palsy and Congenital Diseases of the Cerebellum

DéfiScience
National Health Network for rare neurodevelopmental disorders

11 May 2020

Text

French National Diagnostic and Care Protocols (NDCPs)
Consensus statements endorsed by ERN ITHACA English version Nov. 25th 2020
European Reference Network for Congenital Malformations and Rare Intellectual Disability

DéfiScience - National health network for rare neurodevelopmental disorders - May 11th, 2020

Pre-existing guidelines

- Valid sources to build on abstract,
- These guidelines largely integrated and implemented the same concepts and explanations

- **Define a general definition/classification and common**
- Terminology of this specific group of people
- PIMD term and general definition

≠ except for ‘the signs of autism’

- Netherlands sign of autism not used in this context
- Italy, Poland use of behaviour
- Roumania quite similar but no official definition

Dutch guidelines, nl 2020

Federatie Medisch Specialisten

Spastische cerebrale parese bij kinderen

Deze richtlijn is tot stand gekomen op initiatief van Nederlandse Vereniging van Revalidatieartsen
© 2012 - 2020 Richtlijnendatabase is een product ondersteund door het Kennisinstituut van de Federatie van Medisch Specialisten

https://www.nvk.nl/
https://vsop.nl/

What is the situation in other countries ?
We did not receive any other National guidelines
What do you think ?

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SNW2 PMID – Definition

The Home of Polyhandicap /PIMD

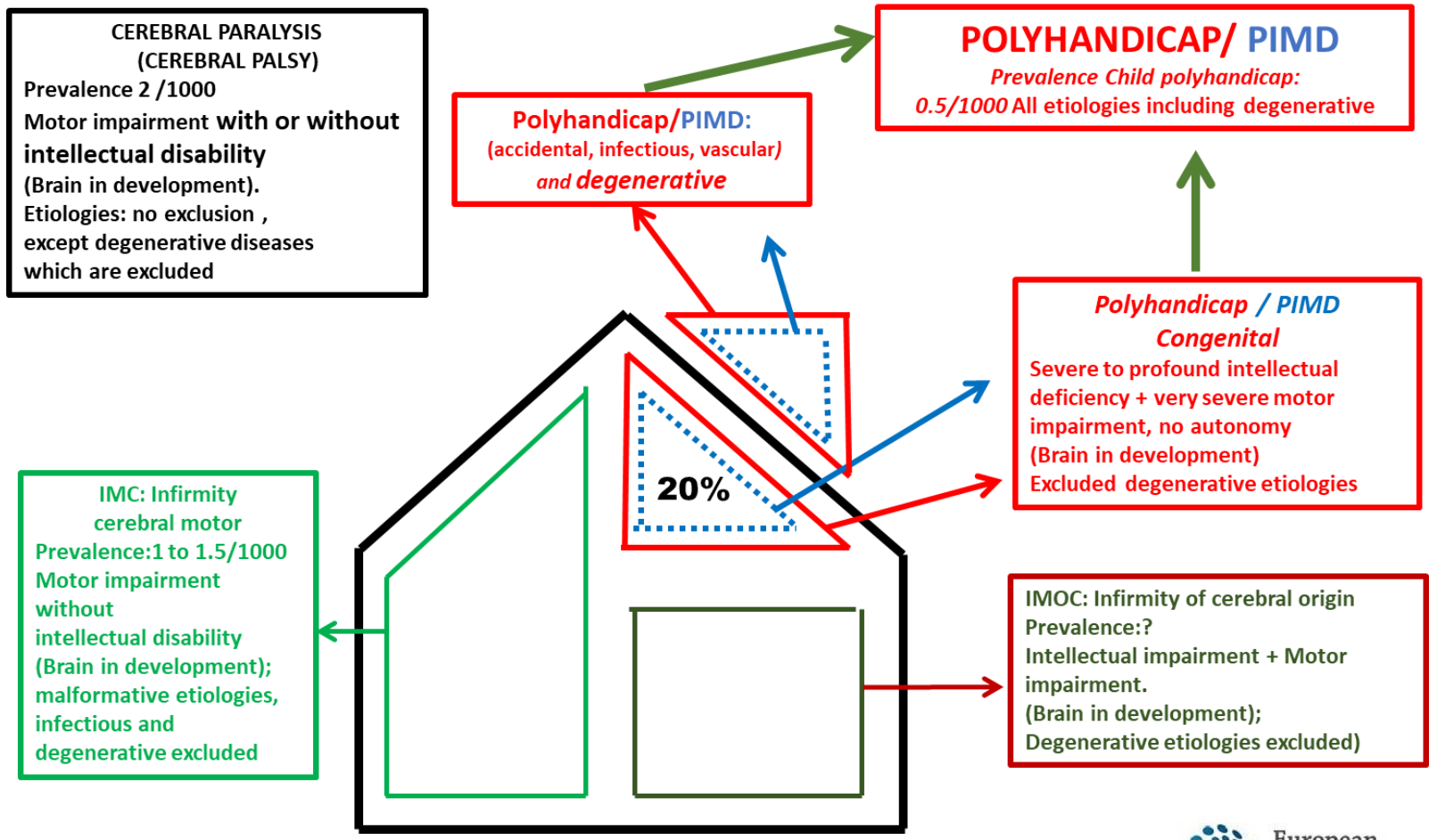
(starting from rare (genetic) causes)

Rare diseases in the scope of ITHACA: PIMD / Polyhandicap

The prevalence of polyhandicap is 0.50 per 1,000, so it is not uncommon. However, the etiologies of polyhandicap are by and large rare diseases, diagnosed or not. Multiple brain lesions and their consequences on growth and secondary repercussions on various organs are sufficiently characteristic for this situation of severe disability, from birth or early childhood, to be declared as a true pathological entity in a national summary document.

Problem of linguistic and terminology

PIMD Profound intellectual and multiple disabilities



The place of polyhandicap among neurological disabilities with motor impairment

Pr Gérard Ponçot

Collect EU definition from each countries, taking the basic point from the French guideline definition

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SNW2 PMID - A starting point

The official French definition of polyhandicap has been updated by decree N°2017-982 of May 9, 2017 on the nomenclature of social and medico-social establishments and services accompanying disabled or chronically ill individuals. This text was incorporated as soon as it was published in the Code of Social Action and Families and describes the population concerned:

- "Individuals with an early or developmental brain dysfunction resulting in severe, multiple, and progressive disturbances in motor, perceptual, and cognitive capacities and the construction of relationships with the physical and human environment, and a situation of extreme physical, mental, and social vulnerability in which some individuals may present, either temporarily or permanently, signs of autism".

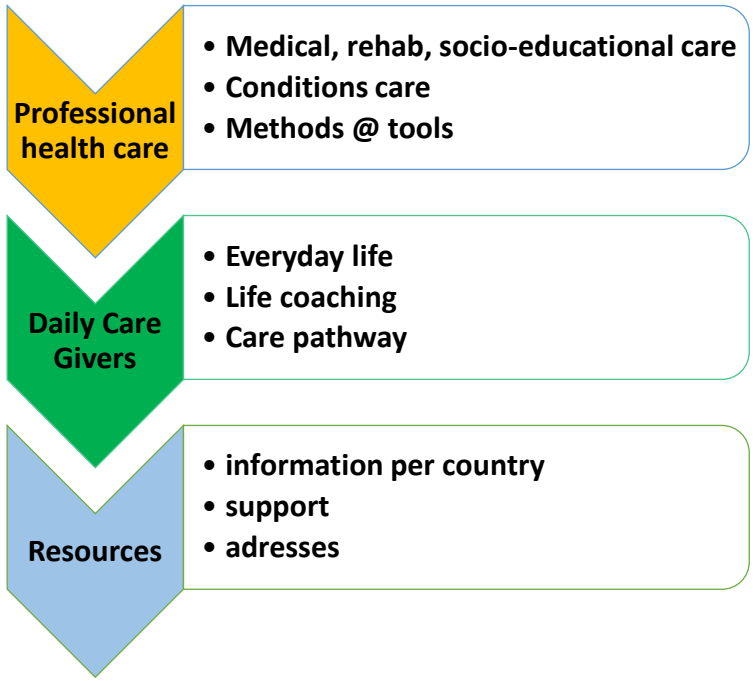
- This official recognition of severe and multiple disabilities (**lack of independent walking, no meaningful oral language, profound intellectual disability**) should make it possible to provide more appropriate responses to the needs of the people thus identified. It highlights the situation of vulnerability caused by severe and early brain injury, usually before the age of two years. Since 1989, the date of the first "official" definition, other definitions have circulated, which are intended to be more complete or more positive or to include etiological elements.

- The precise **aetiology of a polyhandicap is only known in 70 to 80% of cases**: when it is known, the cause is prenatal (65 to 80% of cases), essentially genetic, including progressive neurological diseases, perinatal (10 to 15% of cases), mostly linked to extreme prematurity, or post-natal (10 to 15% of cases).

- These brain disorders always have multiple consequences, which remain progressive throughout life: multiple neurological (somatic and intellectual), orthopaedic, digestive, respiratory, sensory, bone, and other disorders *(See Appendix 4 in connection with the definition Chapter, Table 1: Polyhandicap, medical aspects)*. Behavioural disorders are frequent (30 to 40%). Pain is also a part of the daily life of these individuals. The perceptive, sensitive, and affective capacities of these people, their skills, and their appetite for communication must be considered to optimize the care they receive and their quality of life.

Collect EU definition from each countries, taking the basic point from the French guideline definition
Propose a first definition arranged in the steering group and a starting classification

SNW2 PMID – Classification tree proposition



Professional Health Care

Medical, rehabilitative, and socio-educational care	Conditions for optimal care and follow-up	Methods and tools
• Etiologies and diagnosis • Clinical signs and treatment • Cognitive, communicative, motor functioning • Development, behaviour and quality of life	• Developmentally appropriate approach, communication and (by proxy) decision making • Multidisciplinary collaboration • Goal attainment and life path dedicated care • Organization of continuous care, coordination and longitudinal follow-up	• Classification systems • Pain assessment tools • Behavioral assessment tools • Communications tools • Neuro-orthopaedic devices • Tools to support hospitalisations

Daily Care Givers (layman version)

Everyday life	Life coaching (Organisation life path)	Care pathway (patient journey)
• Specific recommendations • Therapeutic education and the promotion of health • Life path and support • Health decision making • Participation and quality of life	• Early childhood (0 to 6 years) • Childhood and adolescence (7 to 12 years old) • The transition from childhood to adulthood (13 to 20 years old)	• Information transmission and networking • Family support • Team of professionals and support staff Professionals • Health networks, reference centres, and other organizations .

Resources international and per country

• information (publication)	• support	addresses

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SNW2 PMID – Discussion & wrap up

Provisional roadmap

October 20
- Launch meeting
- Identify needs and partners

December 20
- Draft production of project
- Presentation Board members

Next TC on January ?
16:30-17:30
Jan 4th
Jan 8th
Jan 11th
Jan 15th

January 21
- First proposition to be discuss (reco and classification)

April 21
- validation of recommandation
- validation of the classification

June 21
- publication on e-support web site
- dissemination

- Dissemination, and update policy
- Practical appointments: timeline development recommendations, task assignments for the participants, searching representatives of missing disciplines, coordination, administrative support, meeting schedule

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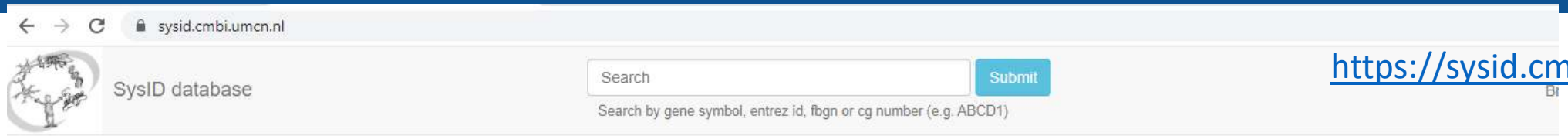
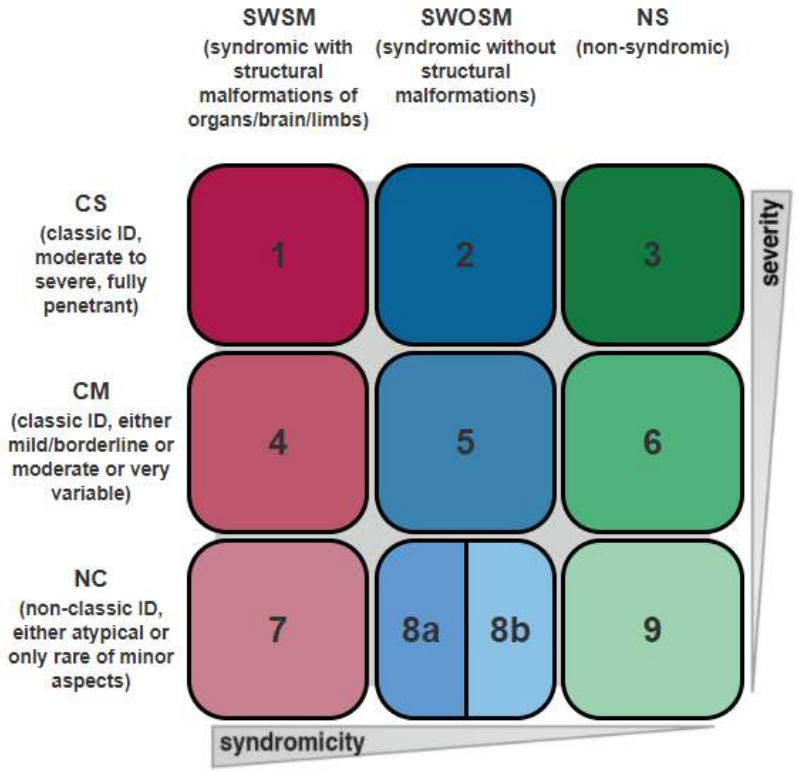
SysID database – up dates/ news

https://sysid.cmbi.umcn.nl/



- Overview
- Human gene info
- Fly gene info
- Disease info
- Orthology
- Neuronal screen
- Wing screen
- Transcription factors
- Motifs
- Autism candidate genes (SFARI)



Letter	Feature(s) or organ system
A	short stature
B	microcephaly
C	lethality
E	epilepsy
F	overgrowth/macrocephaly
G	progression/regression
H	neurological symptoms
I	malignancies
J	immunological anomalies
K	endocrine anomalies
L	L1: brain malformations L2: non-structural MRI anomalies
M	metabolic/mitochondrial anomalies
N	obesity
O	vegetative anomalies
P	behavioral anomalies
Q	myopathy (or muscular anomalies)
R	blood cell anomalies
S	ectodoermal anomalies
T	eye anomalies
U	U: skeletal anomalies Ua: limb anomalies Ub: vertebral/skull anomalies Uc: clefts
V	cardiac malformations
W	urogenital and renal anomalies
X	other malformations

With the latest update on 31st July 2020 SysID currently contains: 1366 primary ID genes, 1189 candidate ID genes

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SysID - database

- Latest update November 2020 (update every 3-4 months):
  - 1396 confirmed ID genes
  - 1218 candidate ID genes
- Per gene: contains information on associated diseases, accompanying phenotypes and inheritance patterns plus short clinical synopsis

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SysID – ITHACA - ORPHANET

WG: ID

- European ID/NDD specific reference list
- improving patient care and centricity

Gene based perspective

Disease based perspective

- Cleaning up and moving SysID
- Acc. phenotypes into HPO terms
- Links to variant databases

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Status with Orphanet

- Discussion on curation and integration ongoing
- Organisatory/financial questions between ITHACA and Orphanet solved
- some discrepancies between curation/nomenclature/definition of NDDs between SysID and Orphanet still need to be solved
- Some delay due to staff members gone

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Status SysID

- Database needs to be moved from the Nijmegen Server by March 2021
- Currently exploring other server options
- Bernt Popp (project partner in Leipzig) is currently building a new, tidied-up and more slender version of the database: «SysNDD» as an intermediate solution
- Aims: curation of all data and re-formatting to prepare and facilitate future integration into Orphanet
- Translation of accompanying phenotypes to HPO terms
- Automatic adaption of disease names to current OMIM nomenclature
- BUT…….

We need expert help for manual re-curation….

- …of data from more than 10 years

- → checking gene classification and where appropriate re-classification (3 categories: confirmed, likely candidate and candidate)
- →checking and revising associated diseases and phenotypes and adding new data and literature links where appropriate

- Manual with criteria for classification and for clinical curation will be provided
- Curation interface with random selection of «gene packages» for curation per expert

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Volunteers

- Please contact me asap:

christiane.zweier@insel.ch

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WG 9 ID - Grant Description

WP9	D9.1	Develop a web-based rare ID gene database and wiki to provide access to information on genetic causes of ID	Create and make accessible an ID gene database connected to clinical information and interacting with Orphanet	Data sets	Public	28 Feb 2022	Pending

part.

- **Description of work** Collate information on rare ID genes and make them publicly available to the medical and scientific community, along with information regarding the clinical manifestations and links to the corresponding Orphanet descriptions.
- **Deliverables** D9.1: Develop a web-based rare ID gene database and wiki to provide access to information on genetic causes of ID. Create and make accessible an ID gene database connected to clinical information and interacting with Orphanet (M36).

- **Insertion of SysID in the ORPHAnet ecosystem in progress**
- **NOT in DELIVERABLES for very important in ERN strategies**

  Prepare ID specific section of ILIAD (if necessary)
  Coordinated with WP5
  General statement on day care and health prevention for adults with ID
  General statement for day care for patients with severe/profound disabilities with ID

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WG ID projet forecast
Discussion for Y 4-5 Future objectives

- Next meeting 2021
- Points to summarize for the afternoon plenary session
  - xxxx

Do not hesitate to send your feed back
Thankyou for your participation

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