The European consensus guideline for Phelan-McDermid syndrome

Conny van Ravenswaaij-Arts,
University Medical Centre Groningen, Netherlands

on behalf of the
European PMS guideline consortium
https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline

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

UNIEK: UMCG Center of Expertise for NeuroDevelopmental Disorders

Multidisciplinary care for:

- Diagnostics in NDD
- CHARGE syndrome
- Phelan-McDermid syndrome
- Chromosome 6 disorders

European Reference Network
ITHACA

Conflicts of interest

- This project was administratively supported by ERN-ITHACA, ERN-ITHACA is partly co-funded by the EU Health Programme
- Funding for the consensus meeting was obtained from the EU Horizon 2020 research and innovation programme under the EJP RD COFUND-EJP N° 825575
- Individual consortium member were not paid for their contributions to the guideline
- Nothing else to declare

1. How it all started

- Since 2015 UMCG is an EU-accredited Centre of Expertise for PMS
- 2018 Dutch guideline for 22q13 deletion syndrome
- 2020 ERN - ITHACA's request for European guidelines
- Email to all known professionals involved in PMS research, all ITHACA members and PMS support organisations within Europe

→ European consortium

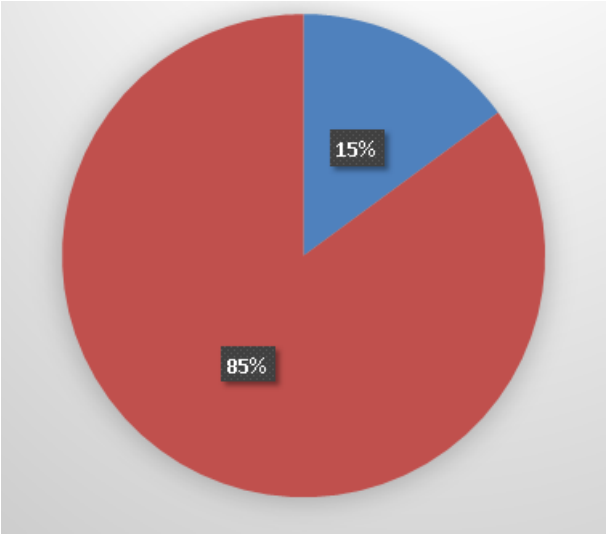
- Administrative support by ITHACA (Klea Vyshka)
- First online meeting on PMS awareness day 22-10-2020

2. Patient participation

- Worldwide survey to explore the needs of families
- Patient representative in each working group
- Teams meetings of patient representatives
- Feed back on all chapters of the guideline
- Represented in organising committee of final consensus meeting (June 2022, Groningen)

3. The methods used

- AGREE II: www.agreetrust.org
- Define who are the patients and users of the guideline
- Perform a bottleneck analysis to decide
  - Based on expert opinions
  - Based on parental survey
  - E.g.: *Do professionals have enough knowledge about PMS in order to deliver appropriate care?*



4. Who are the patients?
Phelan-McDermid syndrome

- *SHANK3*-related:
  - Deletion 22q13.3, including *SHANK3*
  - Pathogenic variant in *SHANK3*

- *SHANK3*-unrelated:
  - Deletion 22q13, not including *SHANK3*

4. For whom is the guideline? Professionals

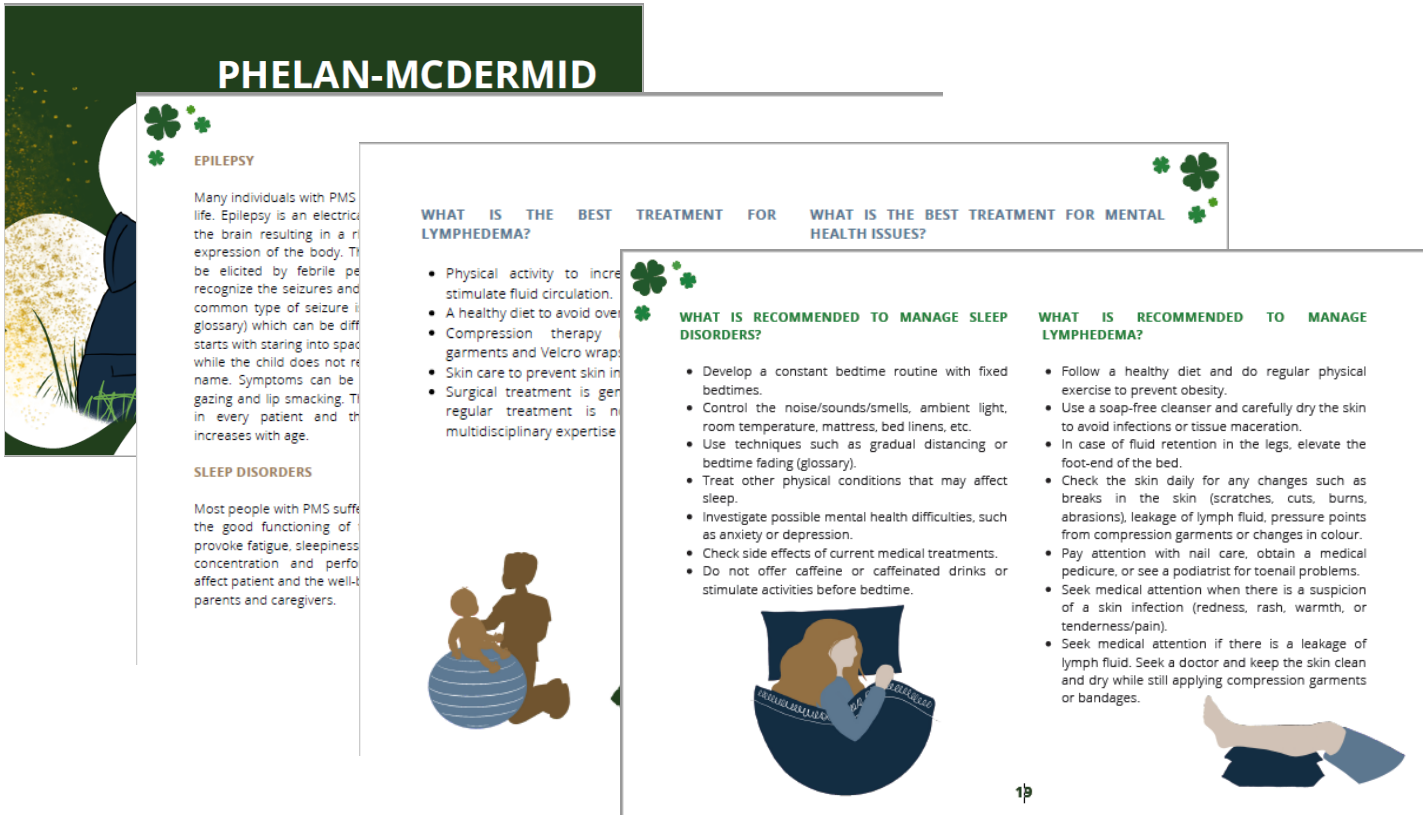
European Journal of Medical Genetics

Supports *open access*

Phelan-McDermid syndrome; towards a European consensus guideline

Edited by Dr. Conny Van Ravenswaaij-Arts, Dr. Sarah Jesse, Dr. Maria Clara Bonaglia, Dr. Ingrid DC van

4. For whom is the guideline?
Lay version for families



5. What are the main topics?

- AGREE II: www.agreetrust.org

- Define who are the patients and users of the guideline

- Perform a bottleneck analysis
  A. Review of literature
  B. Parental survey
  C. Expert opinion

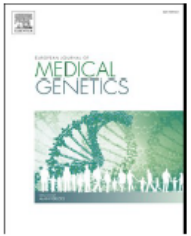
  → selection of **topics** for the guideline

5A. Selection of topics based on review

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg



Definition and clinical variability of *SHANK3*-related Phelan-McDermid syndrome

Michael Schön [a,*], Pablo Lapunzina [b], Julián Nevado [b], Teresa Mattina [c], Cecilia Gunnarsson [d], Kinga Hadzsiev [e], Chiara Verpelli [f], Thomas Bourgeron [g], Sarah Jesse [h], Conny M.A. van Ravenswaaij-Arts [i], the European Phelan-McDermid syndrome consortium [i,1], Raoul C. Hennekam [j]

5A. Clinical signs

Sign / Symptom	22q13.3 deletions (%)		*SHANK3* variants (%)		Sign / Symptom	22q13.3 deletions (%)		*SHANK3* variants (%)	
Development					**External phenotype**				
Developmental delay	493/504	(98%)	48/50	(96%)	Dolichocephaly	84/319	(26%)	2/28	(7%)
Speech impairment	507/572	(88%)	31/44	(70%)	Long eyelashes	149/312	(48%)	19/39	(49%)
Neurology					Down-slanting fissures	16/74	(22%)	3/10	(30%)
Seizures (one or more)	148/542	(27%)	14/53	(26%)	Periorbital fullness	69/239	(29%)	7/39	(18%)
Hypotonia	333/451	(74%)	42/51	(82%)	Ptosis	62/286	(22%)	2/28	(7%)
Structural brain anomalies	118/223	(53%)	12/42	(29%)	Epicanthal folds	122/378	(32%)	8/39	(21%)
Senses					Ear anomalies	232/492	(47%)	16/41	(39%)
Vision disturbances	70/316	(22%)	9/34	(26%)	Wide nasal bridge	156/349	(45%)	15/42	(36%)
Strabismus	59/243	(24%)	4/28	(14%)	Broad nose	169/349	(48%)	15/40	(38%)
Hearing loss	32/372	(8%)	3/29	(10%)	Short philtrum	22/138	(16%)	0/21	(0%)
Increased pain tolerance	204/314	(65%)	38/48	(79%)	Thin upper vermillion	15/56	(27%)	3/11	(27%)
Behaviour					Thick lower vermillion	4/44	(9%)	5/21	(24%)
ASD	162/282	(57%)	26/33	(79%)	Malocclusion	109/297	(37%)	10/29	(34%)
Hyperactivity	33/112	(29%)	21/29	(72%)	Retrognathia	29/115	(25%)	0/31	(0%)
Aggression	50/267	(19%)	18/49	(37%)	Pointed chin	154/309	(50%)	18/29	(62%)
Self-injury	10/80	(13%)	8/27	(30%)	Large fleshy hands	180/392	(46%)	11/28	(39%)
Sleep disorder	62/237	(26%)	24/46	(52%)	Clinodactyly 5th finger	79/405	(20%)	10/28	(35%)
Internal organs					2-3 Syndactyly of toes	65/232	(28%)	5/11	(45%)
Gastro-oesophageal reflux	31/122	(25%)	5/29	(17%)	Sandal gap	30/56	(54%)	6/9	(7%)
Cardiac anomalies	49/387	(13%)	3/46	(7%)	Small / malformed nails	138/438	(32%)	13/29	(45%)
Freq. airway infections	75/280	(27%)	15/47	(32%)	Lymphedema	29/270	(11%)	0/34	(0%)
Urogenital problems	9/62	(15%)	0/24	(0%)	Eczema	48/225	(21%)	14/46	(30%)
Renal abnormalities	20/137	(15%)	0/17	(0%)	Hypohidrosis	31/84	(37%)	2/24	(8%)
Growth					Hyper-extensible joints	4/18	(22%)	6/10	(60%)
Short stature (≤ P3)	37/392	(9%)	4/41	(10%)					
Tall stature (≥ P98)	84/392	(21%)	3/41	(7%)					
Macrocephaly (≥ P98)	55/329	(17%)	6/39	(15%)					
Microcephaly (≤ P3)	53/329	(16%)	5/52	(10%)					

5B. Selection of topics based on parental survey

Contents lists available at ScienceDirect

European Journal of Medical Genetics

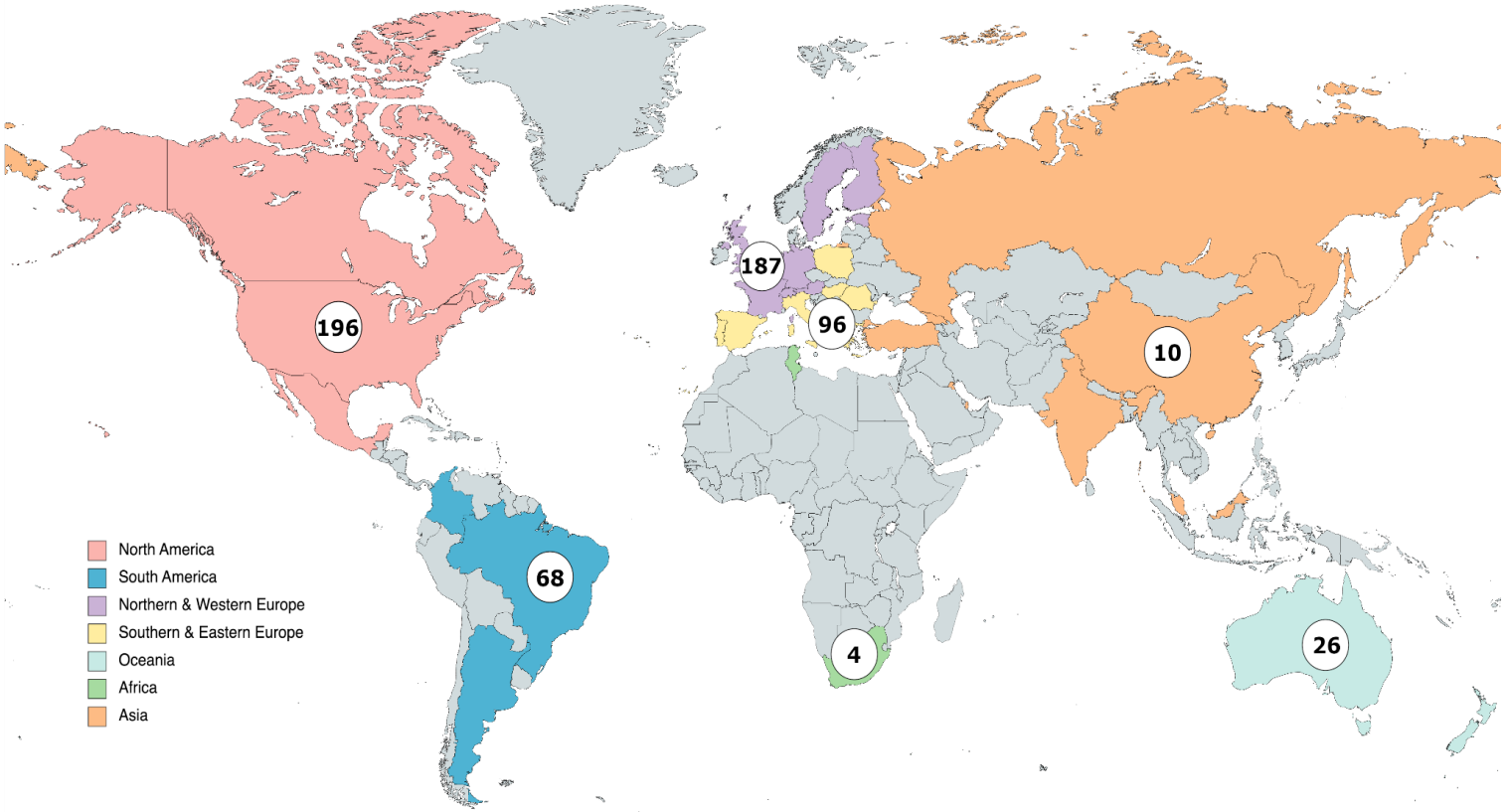
journal homepage: www.elsevier.com/locate/ejmg

Check for updates

Parental perspectives on Phelan-McDermid syndrome: Results of a worldwide survey

Annemiek M. Landlust [a,b,1,*], Sylvia A. Koza [b,1], Maya Carbin [c], Margreet Walinga [b], Sandra Robert [d], Jennifer Cooke [e], Klea Vyshka [f], the European Phelan-McDermid syndrome consortium

5B. worldwide survey



5B. Parental survey

- 10 languages; 35 countries
- Completed by 587 caregivers, mainly being parents (98%)

- Median age at completion survey 12 years (0-60)
- Median age at diagnosis 3 years (0-59)
- 56% female 44% male

- Near normal IQ/mild delay 10%
- Moderate delay 19%
- Severe delay 71%

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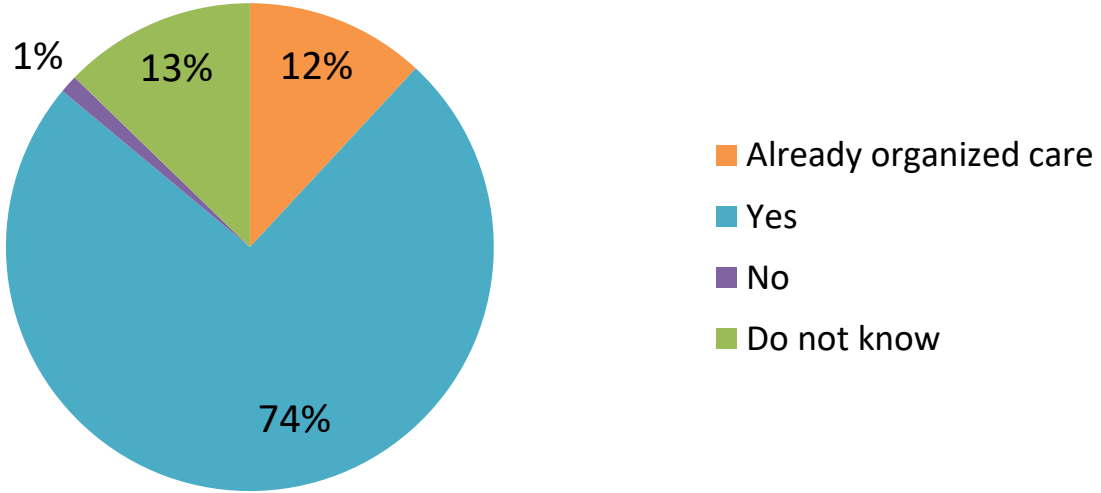
Microcephaly (≤ P3)	53/329	(16%)	5/52	(10%)					

57% in survey

5B. Opinion on the usefulness of the guideline

Would a PMS guideline help to better organize and personalize care? (n=587)



5. The main topics → working groups

- Introduction: Definition and clinical overview of PMS
- Genetic counselling, including ring chromosome 22
- Communication, language and speech problems
- Chewing, swallowing and gastrointestinal problems

		AT DIAGNOSIS	0-2 YEARS	2-12 YEARS	12-16 YEARS	>16 YEARS
HEART AND LUNGS	Cardiac ultrasound					
	Congenital abnormalities (including TI- tricuspid insufficiency, ASD- atrial septal defect, PDB- Persistent ductus Botalli)	Consult cardiology: ECG, US (<2 years) if indicated.				
	Recurrent upper airway infections					

- Mental health issues
- Organization of care

5. Task of working groups:

- Write a chapter with:
  - Introduction: what is the chapter about?

→ Fundamental questions

→ Search and selection of literature sources

→ Conclusions from literature

→ Recommendations

  - References & other sources

6. How consensus was reached

- Each chapter was reviewed at least twice
  - by the members of the European consortium
  - including patient representatives
  - and discussed at Teams meetings every 6 weeks
- Final consensus meeting
  - in Groningen (June 2022)
  - 30 participants, including 5 patient representatives, representing 12 European countries
  - Fine-tuning of the text of the recommendations and voting until consensus was reached (hybrid)

6. How consensus was reached

7. Recommendations

https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline

Link to all PMS guidelines materials

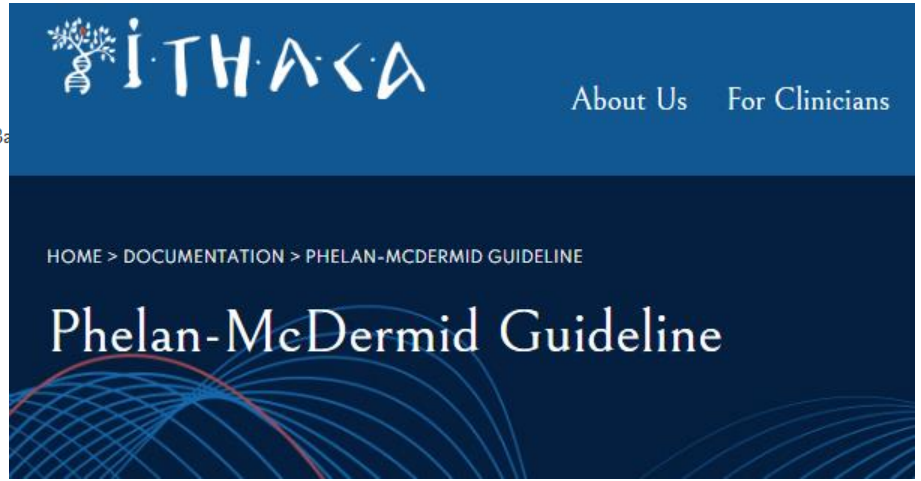
8. Clinical synopsis

Phelan-McDermid syndrome; towards a European consensus guideline

Edited by Dr. Conny Van Ravenswaaij-Arts, Dr. Sarah Jesse, Dr. Maria Clara Bonaglia, Dr. Ingrid DC van Ba

12 extensive papers:

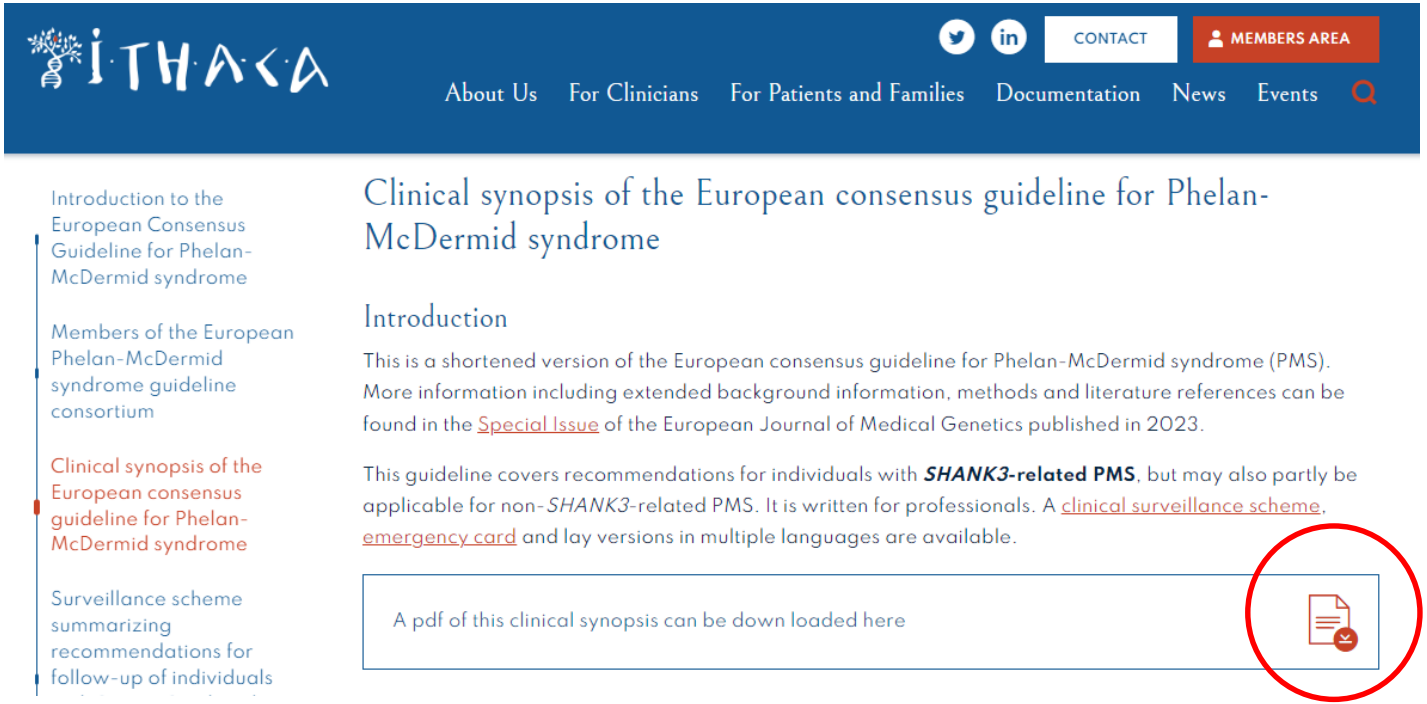
- Good background information
- Not practical



Website with:

- **Clinical synopsis**
- Surveillance scheme
- Emergency card

8. Clinical synopsis



https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline

The EU-PMS Consortium

Sirpa Ala-Mello
Norma Alhambra Jiménez
Britt Marie Anderlid
Stephanie Andres
Emmelien Aten
Ruí Barbosa Guedes
Inge van Balkom
Clara Bonaglia
Thomas Bourgeron
Griet van Buggenhout
Monica Burdeus Olavarrieta
Maya Carbin
René de Coo
Jenny Cooke
Robert Damstra
Stella di Domenico
Agnies van Eeghen
Gareth Evans
Kristiana Gordon
Andreas Grabrucker
Cecilia Gunnarson
Kinga Hadzsieu

Raoul Hennekam
Sarah Jesse
Sarina Kant
Larissa Kerecuk
Sylvia Koza
Els de Kuiper
Annemiek Landlust
Pablo Lapunzina
Claire Leblond-Manry
Eva Loth
Sahar Mansour
Anna Maruani
Teresa Mattina
Ausra Matulevicienė
Natasha Mikusky
Julian Nevado Blanco
Susanne Parker
Flaviano Pinna
José Ramón Fernández
Conny van Ravenswaaij-Arts
Sandra Robert
Romina Romanielle

Cristina Rusu
Michael Schön
Carlo Sala
Antonia San José Cáceres
Kamile Siauryte
Annelies Smit
Daphne Stemkens
Dominque Stiefsohn
Ann Swillen
Anne Claude Tabet
Roberto Toro
Alison Turner
Chiara Verpelli
Stephane Vignes
Aline Vitrac
Annick Vogels
Klea Vyshka
Margreet Walinga
Sabrina van Weering

The guideline's website

https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline

Questions?

contact us:
c.m.a.van.ravenswaaij@umcg.nl
michael.schoen@uni-ulm.de