# The European consensus guideline for Phelan-McDermid syndrome

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SCAN ME

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

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## 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

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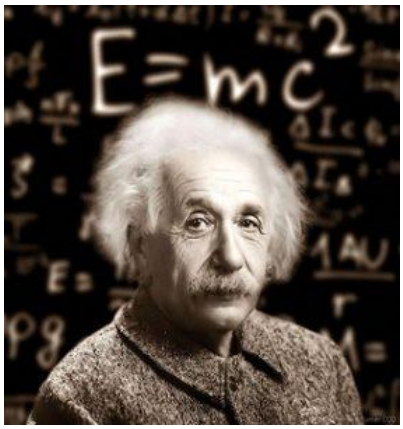
## Donde es Ulm?

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## The PMS centre in Ulm

Phelan-McDermid-Gesellschaft e.V.

Interdisziplinäre Spezialsprechstunde für Betroffene mit Phelan McDermid-Syndrom (Deletionssyndrom 22q13)

PD Dr. med. Sarah Jesse
Oberärztin
Kontakt

**Interdisziplinäre Phelan-McDermid-Sprechstunde**

**Neurologische, urologische, orthopädische, kardiologische Anliegen sowie Teilnahme an Patientenstudien**

Hier erfolgt die individuell notwendige Diagnostik und Therapie sowie Vorstellung in der Klinik für **Neurologie, Universitätsklinikum Ulm, RKU Oberer Eselsberg 45, 89081 Ulm**

**bei Frau PD Dr. Jesse**

Terminkoordination über die Telefonnummer 0731-177-5243 oder per email: sarah.jesse@uni-ulm.de

**Psychiatrische Anliegen/Verhaltensauffälligkeiten**

Die individuell notwendige Diagnostik und Therapie sowie Unterstützung im sozialen Bereich erfolgt durch die **Kinder- und Jugendpsychiatrie, Universitätsklinikum Ulm, Krankenhausweg 3, 89075 Ulm**

Terminkoordination über die Telefonnummer 0731/500 61636

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## 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

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## Towards a European consensus guideline

1. How it all started
2. Patient/parent participation
3. The methods used
4. For whom is the guideline?
5. **What are the main topics?**
   - parental survey and clinical definition of PMS
6. How consensus was reached
7. [The recommendations]
8. **Clinical synopsis, Surveillance Scheme & Emergency Card**
9. Lessons learned

Intro

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# 1. How it all started

- Since 2015 UMCG is an 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



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# 1. How it all started

- Dutch guideline translated into English
- Feedback asked on main content and approach
- Working groups formed for each PMS-related topic
- Administrative support by ITHACA (Klea Vyshka)
- First online meeting on PMS awareness day 22-10-2020




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6. How consensus was reached
7. The recommendations, a few examples
8. Clinical synopsis, Surveillance Scheme & Emergency Card
9. Lessons learned

Intro | Participation

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## 2. Patient participation

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

Intro | Participation

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Intro | Participation

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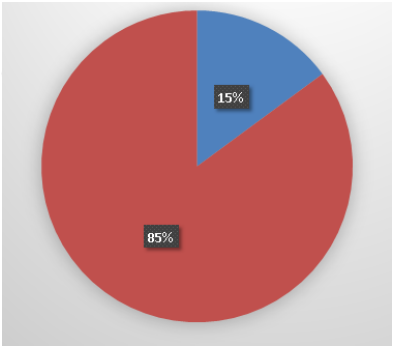
## 3. The methods used

- 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?*




Intro | Participation | Methods

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## 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*
- Deletion 22q13.3:
  - Simple terminal deletion
  - Translocation
  - Ring chromosome 22



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## 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


Intro | Participation | Methods | For whom

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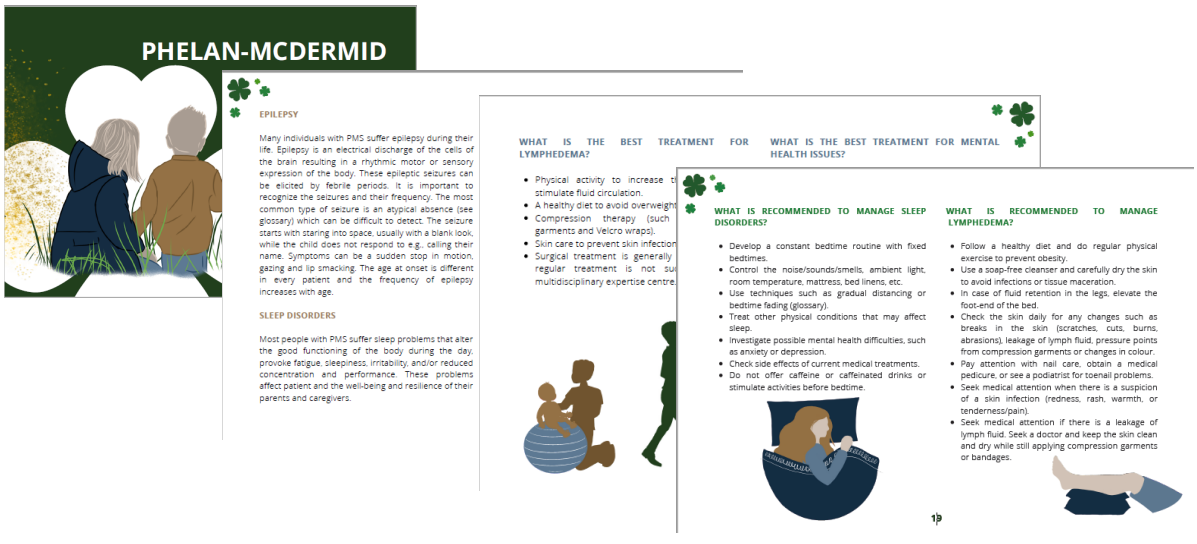
## 4. For whom is the guideline? Lay version for families




Intro | Participation | Methods | For whom

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## Towards a European consensus guideline

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## 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
  - Parental survey
  - Review of literature: clinical definition of PMS

→ selection of **topics** for the guideline



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## 5. Selection of topics based on parental survey

Contents lists available at ScienceDirect

European Journal of Medical Genetics

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

### 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



## 5. Selection of topics based on review

Contents lists available at ScienceDirect

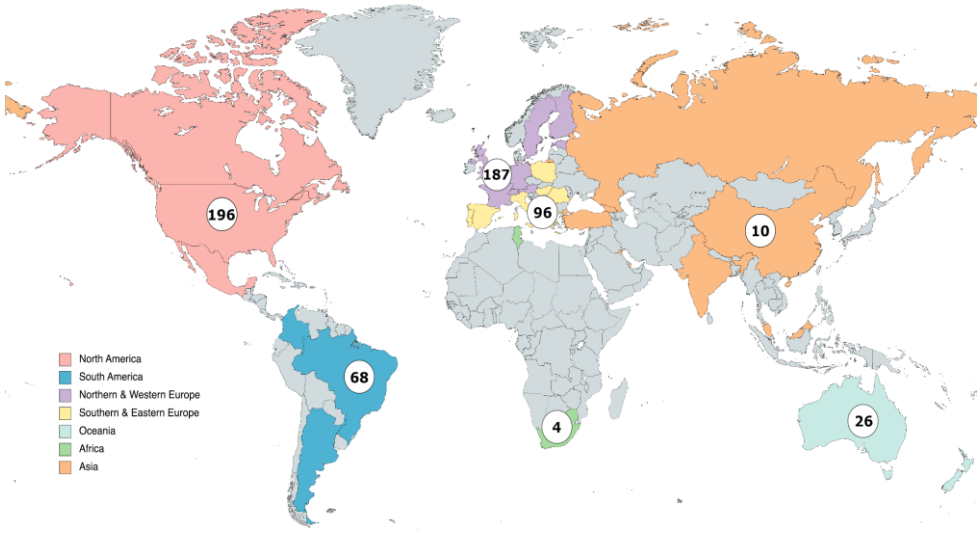
European Journal of Medical Genetics

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]

# A worldwide survey



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# 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

- 33% North America: 30% US
- 48% Europe: 7% Spain 1% Portugal
- 12% South America: 11% Brazil
- Oceania 4%; Asia 2%, Africa 1%

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



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## How many are known?

**Epidemiology**

Numbers from Netherlands, Spain, Portugal Germany, Austria, Switzerland, UK, Ireland, France, Italy, Hungary, Belgium, Sweden, Lithuania

More than 1000 (less than 10 % known)

Some do better (the Dutch way)

At least 1 in 30.000



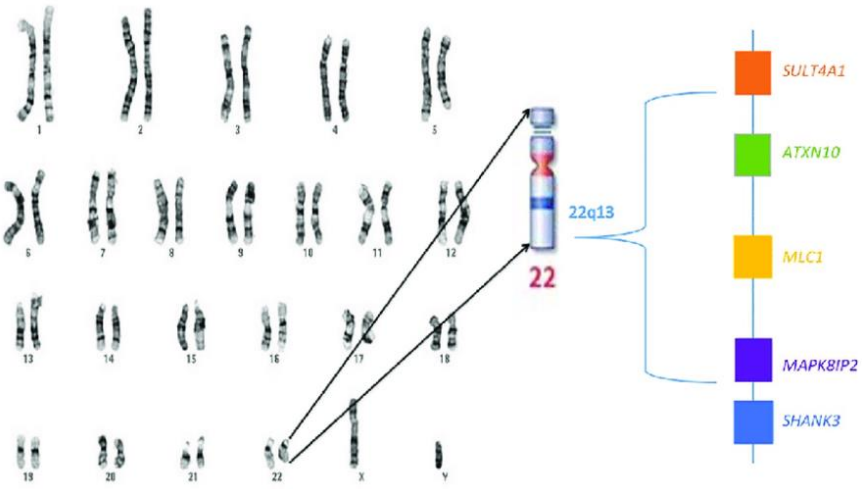
## What is PMS?

**Definition:**

PMS-*SHANK3* related: either deletion 22q13 or pathogenic/likely pathogenic variant of *SHANK3*

Ziats et al., 2019

## What is PMS?




Ziats et al., 2019

Intro | Participation | Methods | For whom | Topics

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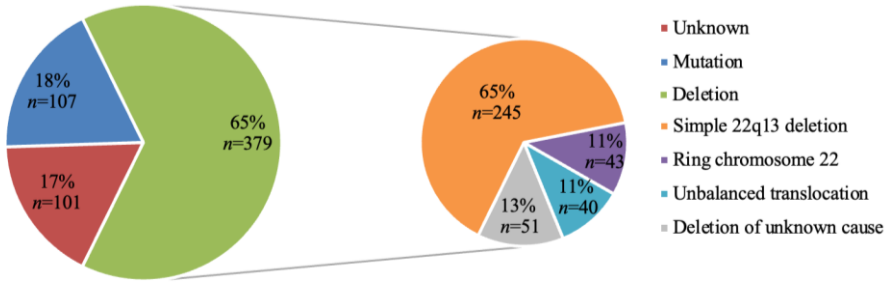
## Survey: genetics

Cause of PMS (*n*=587)




SHANK3 variants in Parental survey: 22%
Literature: 8%

Intro | Participation | Methods | For whom | Topics

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## Importance correct diagnosis and counselling

Every child with a developmental delay should receive proper genetic counselling



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## The clinical signs

**Genotype-phenotype correlations**

It is important to know the genotype because:

1) Deletions and variants have partly different phenotypes
2) Ring chromosomes: increased risk for certain types of tumours
3) Translocation: increased risk for recurrence



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# 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%) | | | |

57% in survey



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# Comparison per age group

| Problem/symptom | 0-4 years (n=86) | 5-12 years (n=227) | 13-18 years (n=119) | >18 years (n=156) |
|---|---|---|---|---|
| Epilepsy | 9% | 19% | 23% | 43% |
| Sleeping problems | 41% | 55% | 62% | 73% |
| Mood problems | 16% | 23% | 42% | 54% |
| Loss of skills | 30% | 44% | 51% | 64% |
| Lymphedema | 6% | 5% | 13% | 15% |



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## Survey: stress in parents

**Table 4**
Mean scores (0–3 Likert scale) and percentage extremely stressful scores on items GSSS (n = 507) and extra added item 15.

| | Topic item | Mean (0–3 Likert scale) | Percentage (%) "extremely stressful" |
|---|---|---|---|
| 1.10 | A genetic diagnosis causing tension within the immediate and extended family | 0.94 | 11.1 |
| 2. | People staring when I go out in public with my child | 1.12 | 9.9 |
| 3. | Having to make extensive preparations for my child before leaving the house | 1.39 | 16.2 |
| 4. | Having to explain my child's condition to new people I meet | 1.42 | 13.8 |
| 5. | Sleep deprivation, due to my child's sleeping patterns | 1.58 | 29.8 |
| 6. | Getting my child's complex needs met through social services | 1.81 | 30.5 |
| 7. | Not having access to professionals who have knowledge about child's condition | 1.82 | 32.7 |
| 8. | Going to see professionals who are not knowledgeable about my child's genetic syndrome | 1.93 | 36.6 |
| 9. | An educational placement that does not meet all of my child's needs | 1.93 | 37.3 |
| 10. | The large amount of effort required to help my child reach developmental milestones (e.g. sitting up, self-feeding) | 1.94 | 33.2 |
| 11. | Not being able to fully relax at home, as I need to attend to my child 24 h a day | 1.96 | 36.5 |
| 12. | Having to be constantly vigilant about my child's state of health in case of a sudden change | 2.03 | 39.7 |
| 13. | Arranging care (e.g. babysitting, respite) that is suitable for my child | 2.08 | 43.6 |
| 14. | *Not knowing what is bothering my child due to limited communication possibilities* | *2.42* | *61.2* |
| 15. | Worrying about the future for my child because of the lack of specialist services once they reach adulthood | 2.56 | 68.1 |

Intro | Participation | Methods | For whom | Topics

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## How is a life with PMS?

**Natural history**

Pregnancy: normal

Newborns: hypotonia

Infancy/childhood: delayed milestones

Adolescence: mental health, regression, seizures

Adulthood: little known, no reduced life expectancy

**COVID-19**: vaccination most likely more important than in general population

Intro | Participation | Methods | For whom | Topics

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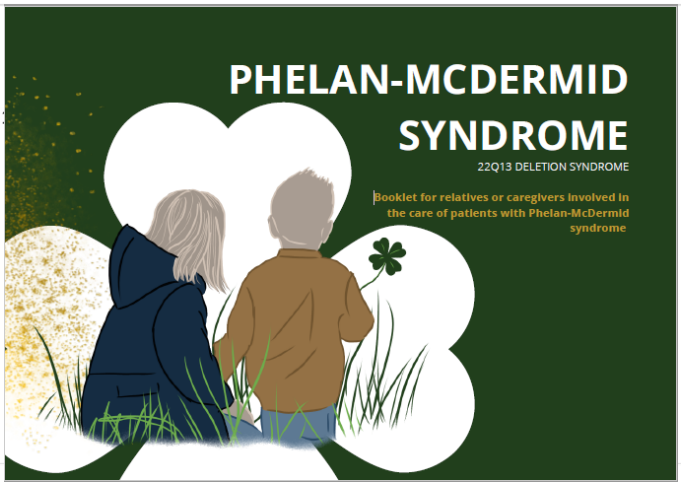
## Survey: communication




Intro | Participation | Methods | For whom | Topics

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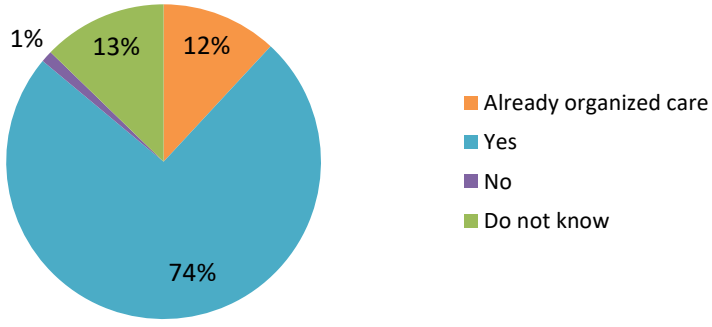
## Opinion on the usefulness of the guideline

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




Intro | Participation | Methods | For whom | Topics

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## 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 |
| Sensory dysfunction |
| Epilepsy |
| Sleep Disorders |
| Lymphedema |
| Mental health issues |
| Organization of care |



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## 5. What about other topics → surveillance scheme

Clinical features that were not regarded as “big issues” or for which general, non-specific PMS guidelines were appropriate, were not reviewed in depth, but were included in the surveillance scheme.

Example:

| | | 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 | | | | | |



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## 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



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## 5. Example: Lymphedema

- Fundamental questions
  - How often does lymphedema occur in PMS and what is known about the origin and pathogenesis?
  - What is the best management for lymphedema in individuals with PMS?
  - Are there options for early diagnosis and early management?
- Conclusions from literature
  - Primary lymphedema may occur in up to 25% of individuals with PMS, due to a deletion 22q13.3
  - The mechanism causing lymphedema in PMS is unknown
  - Lymphedema in PMS can be treated using existing general management guidelines, taking the functioning of the PMS patients into account
- Recommendations
  - The health care provider should pay attention to the possible development of lymphedema in individuals with a 22q13 deletion and start treatment when needed.
  - Refer individuals with PMS with lymphedema impacting daily functioning to a lymphedema centre of expertise for further investigations and treatment



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## 6. How consensus was reached

- Each chapter was reviewed at least twice
  - by the members of the European consortium
  - Patient representatives were actively invited
  - 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)



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## 6. Why are most recommendations precise, but not detailed?

- The good clinical practise guideline should be workable for professionals. If there are too many recommendations, there is a risk that the guideline will not be used.
- Care should always be personalised. Therefore, sometimes we state “it should be discussed with parents…” Instead of “the doctor should do [this or that] …”
- The guideline hopefully will be endorsed by and therefore should be applicable to many different countries. This has legal implications: a doctor can only deviate from the guideline when a good motivation is given.



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## 6. How consensus was reached: the june 2022 meeting




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## 7. Recommendations: which shall we discuss?

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| |
|---|
| Genetic counselling |
| Ring chromosome 22 |
| Communication, language and speech problems |
| Chewing, swallowing and gastrointestinal problems |
| Sensory dysfunction |
| Epilepsy |
| Sleep Disorders |
| Lymphedema |
| Mental health issues |
| Organization of care |
| Clinical Trials |



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## 7. Recommendations: Genetic counseling

- All individuals with PMS and their parents should be referred for genetic counselling. [genotype – phenotype; recurrence risk]
- After a diagnosis of PMS has been made, further genetic studies should be performed for proper genetic counselling.
- Follow-up of individuals with PMS should include a check whether genetic work-up has been complete and up-to-date.
- In subsequent pregnancies, the parents of the child with PMS should be offered prenatal diagnostic testing.



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## 7. Recommendations: Ring chromosome 22

- In an individual with a ring chromosome 22, personalised monitoring for potential NF2-tumours should be discussed with the patient or their representatives.
- In an individual with a ring chromosome 22, cerebral imaging (MRI) is recommended at the age of 14 to 16 years, if not already available. In case of obvious hearing loss discuss with the patient or their representatives repeating of the MRI.

*(supported by OncoDefi)*



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## 7. Recommendations: Communication

- Hearing should be checked in every individual with PMS at the time of diagnosis and subsequently put into surveillance according to national guidelines.
- Every individual with PMS should be assessed by a specialized multidisciplinary team to evaluate all factors that may influence communication, speech and language.
- Preverbal and verbal communicative skills and cognitive development should be thoroughly evaluated in individuals with PMS prior to intervention and treatment.
- Parents of individuals with PMS should be counselled by a specialist on supporting, facilitating, and stimulating communication, language and speech from an early age on.
- Use of augmentative and alternative communication (AAC) tools is recommended to facilitate communication for individuals with PMS when communication is limited.



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## 7. Recommendations: Gastrointestinal

- Both gastroesophageal reflux and constipation should be considered if behavioural changes are observed in individuals with PMS.
- In individuals with PMS, evaluation of faecal incontinence is advised. Somatic causes should be excluded, and behavioural modifications should be considered.
- For treatment of gastroesophageal reflux, diarrhoea and constipation in individuals with PMS, refer to general national or international guidelines.
- If zinc deficiency is present in an individual with PMS, dietary zinc supplementation should be considered.
- A referral to a pre-verbal speech therapist for chewing and swallowing disorders should be considered.



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## 7. Recommendations: Altered sensory function

- Caregivers and health care providers should be aware that individuals with PMS often have a reduced responsiveness to sensory stimuli such as pain, sudden sounds and heat. After every (suspected) trauma or physical incident the individual should be carefully examined.
- Every individual with PMS needs to be screened for hearing and visual disturbances at the time of diagnosis and subsequently put under surveillance according to national guidelines.
- Sensory integration functioning should be checked in every person with PMS using a validated screening instrument. If altered sensory function is present a sensory integration therapist should be consulted.
- In case of behavioural changes in individuals with PMS, evaluation of possible causes should include a search for pain and altered sensory function. The use of a validated non-verbal pain scale is recommended.



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## 7. Recommendations: Epilepsy

- In every individual with PMS, irrespective of age, caregivers should be alert for seizures and epilepsy.
- In every individual with PMS in whom seizures are suspected but EEG studies are nonconclusive, overnight prolonged EEG studies should be considered.
- Brain imaging, preferably by MRI, is advised in every individual with PMS who has epileptic seizures, and indicated when new neurological signs and symptoms, including seizures, occur.
- A paediatric neurologist or neurologist should be involved in the therapy for epilepsy.
- Anticonvulsant treatment of epilepsy in individuals with PMS should be provided according to national guidelines.



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## 7. Recommendations: Sleep problems

- Every individual with PMS and sleep problems should be evaluated for somatic, and/or environmental and/or neuropsychiatric causes.
- Mental health conditions co-occurring with sleep problems in individuals with PMS need to be investigated and treated.
- In individuals with PMS with sleep problems, sleep hygiene should be evaluated, and caregivers should be supported in establishing a structured approach (behavioural interventions).
- If sleep problems persist despite appropriate interventions, the individual with PMS should be referred to a specialist experienced in sleep problems or a specialist sleep centre.



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## 7. Recommendations: Lymphedema

- The health care provider should pay attention to the possible development of lymphedema in individuals with a 22q13 deletion, including ring chromosome 22, and start treatment (e.g., compression bandages and garments, skincare and advice) when needed.
- Refer individuals with PMS with lymphedema impacting daily functioning to a lymphedema centre of expertise for further investigations and treatment.



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## 7. Recommendations: Mental Health 1/2

- At diagnosis for individuals with PMS a comprehensive evaluation should be made of factors influencing mental health, which include physical, psychiatric, psychological, developmental, communicative, social, educational, environmental, and economic domains, and general wellbeing as informed by caregivers.
- In individuals with PMS cognitive and socio-emotional level, communication, adaptive and sensory functioning should be assessed at diagnosis using appropriate tools, which may include a Functional Behavioural Assessment.
- In individuals with PMS a baseline measurement of individual functioning and skill level is useful, preferably in early childhood.



## 7. Recommendations: Mental Health 2/2

- Monitor behavioural status regularly including mood, affect, communication, interests and day/night routines in every individual with PMS, especially at important changes in daily environment, allowing early recognition of behavioural changes.
- Individuals with PMS who demonstrate noteworthy behavioural changes should be physically examined and evaluated for the presence of medical issues, including physical signs of abuse.
- If concerns are raised regarding mental health, functioning and behaviour of an individual with PMS, a psychiatric assessment is indicated to determine (comorbid) diagnoses, considering the developmental level of the individual.

## 7. Recommendations: Organisation of care

- Every person with PMS should receive PMS-specific care by a dedicated expert team.
- A coordinating professional should initiate and monitor the multidisciplinary care. The multidisciplinary team should be established based on the surveillance scheme.
- For every person with PMS, specific care needs and the responsible professionals should be recorded in the medical record and the individual care plan.
- For every teenager with PMS the transition from paediatric to adult care should be timely initiated, monitored and documented.
- Caregivers of individuals with PMS should be informed abut the PMS patient registry when established



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## 7. Recommendations: Organisation of Care




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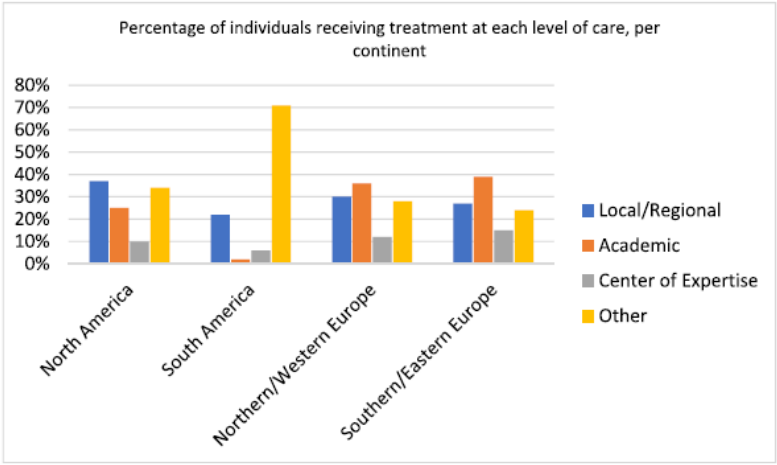
## Survey: access of care



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## Survey: Number of specialists involved in the care

Median number of specialists in the past: 7 specialists, range 1-13

Median number of specialist at the time of the survey: 4 specialists, range 1-10



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## 7. Recommendations: Clinical trials

**Clinical trials**

- IGF-1: successful (the „US drug“)
- Insulin intranasal: successful (the „European drug“)
- Oxytocin: failed

**Consensus**

Enrolment in a clinical treatment trial may be considered and discussed with individuals with PMS (if possible) or their representatives.



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## Towards a European consensus guideline

1. How it all started
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6. How consensus was reached
7. The recommendations
8. Clinical synopsis, Surveillance Scheme & Emergency Card
9. Lessons learned



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# 8. Clinical synopsis

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 Ba

12 extensive papers:

- Good background information
- Not practical

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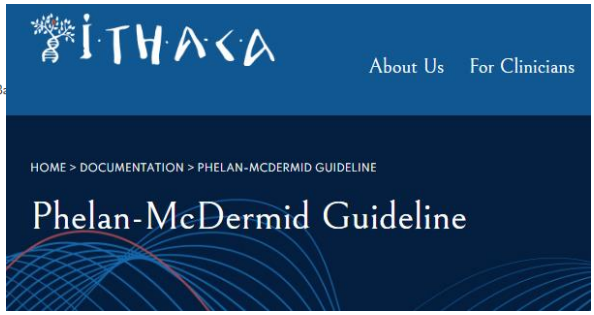
Website with:

- Clinical synopsis
- Surveillance scheme
- Emergency card




Intro | Participation | Methods | For whom | Topics | Consensus | Recommendations | Practical

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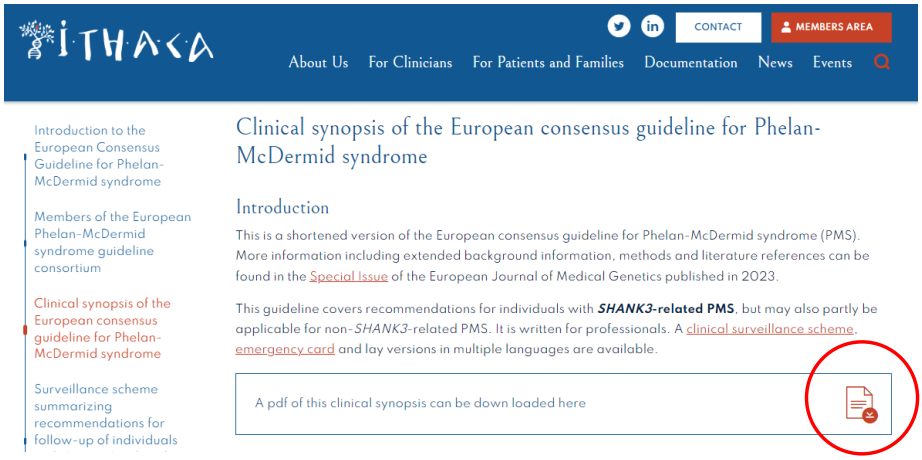
# 8. Clinical synopsis

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Intro | Participation | Methods | For whom | Topics | Consensus | Recommendations | Practical

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# 8. Clinical synopsis: example

## PMS due to a ring chromosome 22

For detailed background information see Koza et al., EJMG 2023

Few genotype-phenotype relationships have been reported. However, certain clinical characteristics distinguish Phelan-McDermid syndrome due to a ring chromosome 22 from a simple deletion 22q13.3. A ring chromosome 22 confers increased risk of NF2-related schwannomatosis (formerly neurofibromatosis type 2) and atypical teratoid rhabdoid tumours associated with the tumour suppressor genes NF2 and SMARCB1, respectively, both located on chromosome 22. The prevalence of PMS due to ring chromosome 22 is estimated at 10-20%, while the risk of developing a tumour although not fully known is estimated at 2-4%. However, those who do develop them, often have multiple tumours.

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### European consensus recommendations concerning ring chromosome 22

- In an individual with a ring chromosome 22, personalized monitoring for potential NF2-tumors should be discussed with the patient or their representatives[1].
- In an individual with a ring chromosome 22, cerebral imaging (MRI) is recommended at the age of 14 to 16 years, if not already available. In case of obvious hearing loss discuss with the patient or their representatives repeating of the MRI[2].



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# 8. Surveillance scheme

## Surveillance scheme summarizing recommendations for follow-up of individuals with *SHANK3*-related Phelan-McDermid syndrome (PMS)

A pdf of this scheme can be down-loaded here

For background information see Special issue EJMG

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| | | AT DIAGNOSIS | 0-2 YEARS | 2-12 YEARS | 12-16 YEARS | >16 YEARS |
|---|---|---|---|---|---|---|
| GENETICS | Genetic counselling of relatives to discuss:<br>- phenotype PMS<br>- Recurrence risk: FISH and karyotyping (also to exclude ring 22)<br>- reproductive options<br>- family support groups | | | | | |
| | Referral to (PMS) centre of expertise (CE) for follow-up, general updates on PMS, participation in research, collecting data and providing (new) information to families. | | Yearly | Every 2 years | Every 2 to 3 years | Every 3 to 5 years |



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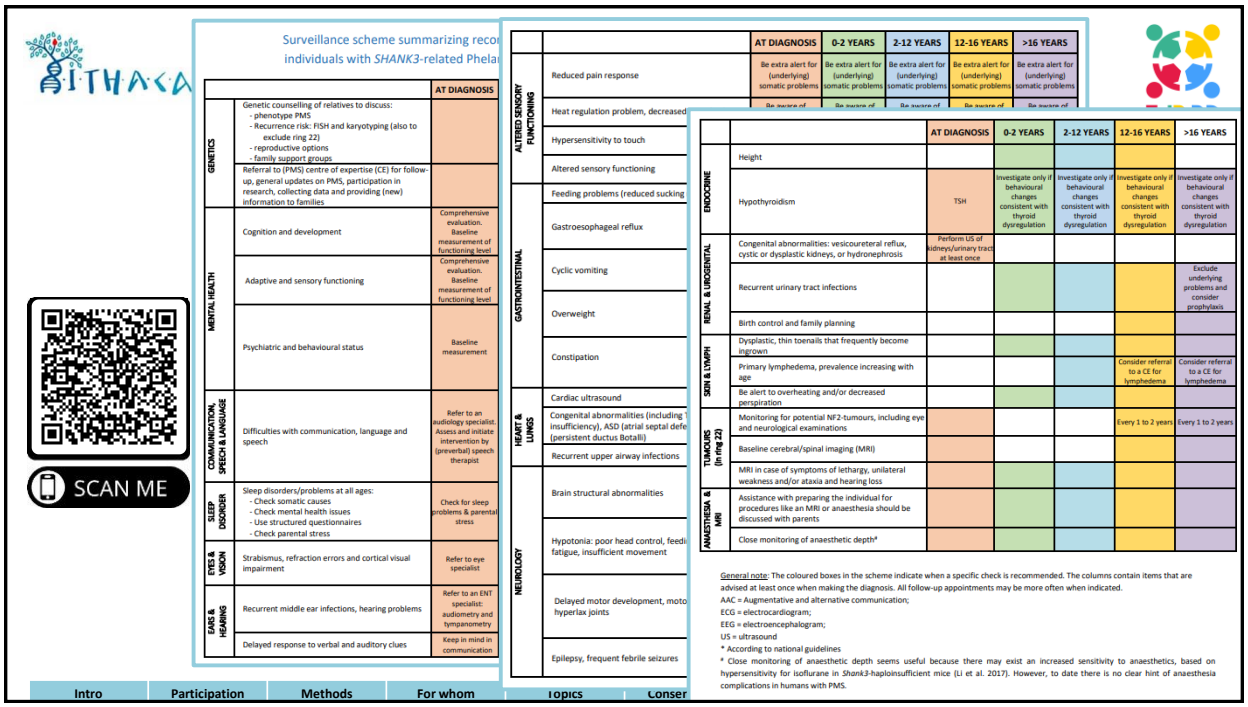


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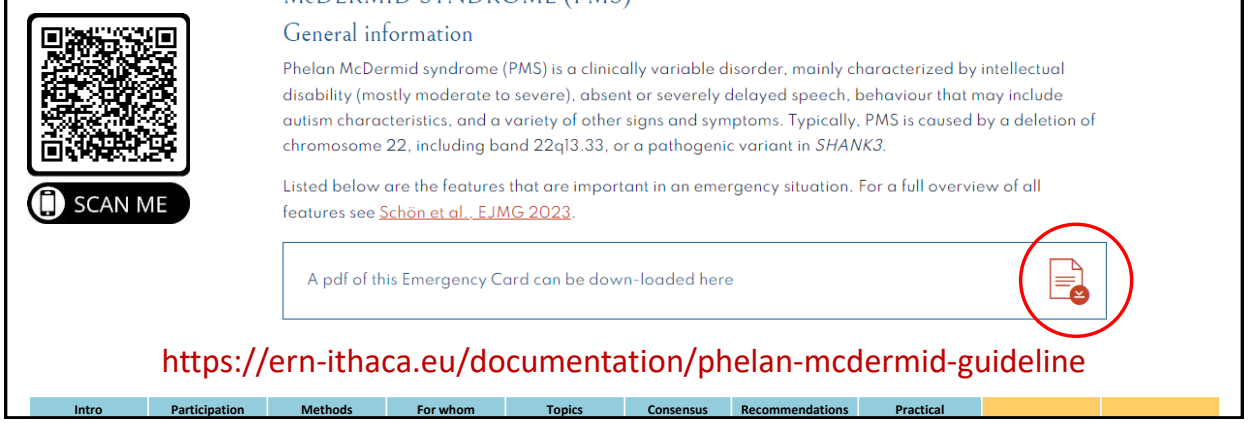
# 8. Emergency Card




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

Intro | Participation | Methods | For whom | Topics | Consensus | Recommendations | Practical

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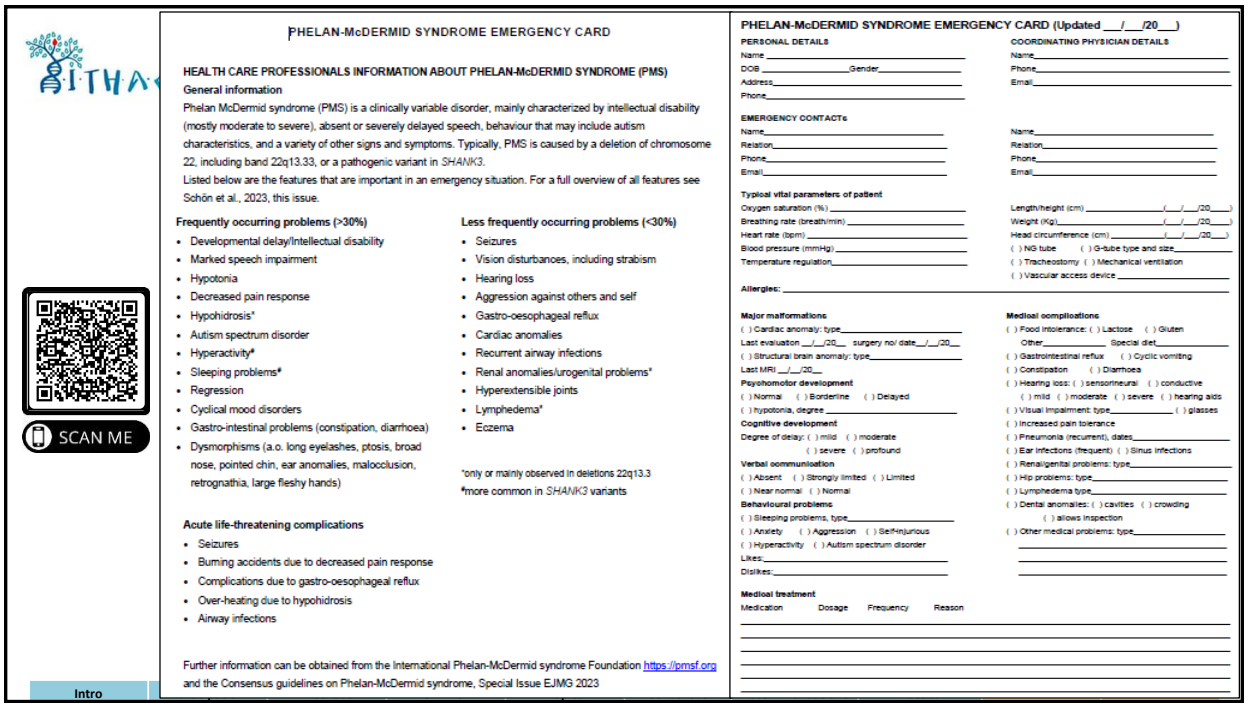

PHELAN-McDERMID SYNDROME EMERGENCY CARD

**HEALTH CARE PROFESSIONALS INFORMATION ABOUT PHELAN-McDERMID SYNDROME (PMS)**

**General information**

Phelan McDermid syndrome (PMS) is a clinically variable disorder, mainly characterized by intellectual disability (mostly moderate to severe), absent or severely delayed speech, behaviour that may include autism characteristics, and a variety of other signs and symptoms. Typically, PMS is caused by a deletion of chromosome 22, including band 22q13.33, or a pathogenic variant in *SHANK3*.

Listed below are the features that are important in an emergency situation. For a full overview of all features see Schön et al., 2023, this issue.

**Frequently occurring problems (>30%)**

- Developmental delay/Intellectual disability
- Marked speech impairment
- Hypotonia
- Decreased pain response
- Hypohidrosis*
- Autism spectrum disorder
- Hyperactivity#
- Sleeping problems#
- Regression
- Cyclical mood disorders
- Gastro-intestinal problems (constipation, diarrhoea)
- Dysmorphisms (a.o. long eyelashes, ptosis, broad nose, pointed chin, ear anomalies, malocclusion, retrognathia, large fleshy hands)

**Less frequently occurring problems (<30%)**

- Seizures
- Vision disturbances, including strabism
- Hearing loss
- Aggression against others and self
- Gastro-oesophageal reflux
- Cardiac anomalies
- Recurrent airway infections
- Renal anomalies/urogenital problems*
- Hyperextensible joints
- Lymphedema*
- Eczema

*only or mainly observed in deletions 22q13.3
#more common in *SHANK3* variants

**Acute life-threatening complications**

- Seizures
- Burning accidents due to decreased pain response
- Complications due to gastro-oesophageal reflux
- Over-heating due to hypohidrosis
- Airway infections

Further information can be obtained from the International Phelan-McDermid syndrome Foundation https://pmsf.org and the Consensus guidelines on Phelan-McDermid syndrome, Special Issue EJMG 2023

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**PHELAN-McDERMID SYNDROME EMERGENCY CARD (Updated ___/___/20___)**

**PERSONAL DETAILS**
Name _____
DOB _____ Gender_____
Address_____
Phone_____

**COORDINATING PHYSICIAN DETAILS**
Name_____
Phone_____
Email_____

**EMERGENCY CONTACTs**
Name_____
Relation_____
Phone_____
Email_____

Name_____
Relation_____
Phone_____
Email_____

**Typical vital parameters of patient**
Oxygen saturation (%) _____
Breathing rate (breath/min) _____
Heart rate (bpm) _____
Blood pressure (mmHg) _____
Temperature regulation_____

Length/height (cm) _____/___/___/20____)
Weight (Kg)_____/___/___/20____)
Head circumference (cm) _____/___/___/20____)
( ) NG tube ( ) G-tube type and size_____
( ) Tracheostomy ( ) Mechanical ventilation
( ) Vascular access device _____

**Allergies:** _____

**Major malformations**
( ) Cardiac anomaly: type_____
Last evaluation __/__/20__ surgery no/ date__/__/20__
( ) Structural brain anomaly: type_____
Last MRI __/__/20__
**Psychomotor development**
( ) Normal ( ) Borderline ( ) Delayed
( ) hypotonia, degree _____
**Cognitive development**
Degree of delay: ( ) mild ( ) moderate
( ) severe ( ) profound
**Verbal communication**
( ) Absent ( ) Strongly limited ( ) Limited
( ) Near normal ( ) Normal
**Behavioural problems**
( ) Sleeping problems, type_____
( ) Anxiety ( ) Aggression ( ) Self-injurious
( ) Hyperactivity ( ) Autism spectrum disorder
Likes:_____
Dislikes:_____

**Medical treatment**
Medication Dosage Frequency Reason

**Medical complications**
( ) Food intolerance: ( ) Lactose ( ) Gluten
Other_____ Special diet_____
( ) Gastrointestinal reflux ( ) Cyclic vomiting
( ) Constipation ( ) Diarrhoea
( ) Hearing loss: ( ) sensorineural ( ) conductive
( ) mild ( ) moderate ( ) severe ( ) hearing aids
( ) Visual impairment: type_____ ( ) glasses
( ) Increased pain tolerance
( ) Pneumonia (recurrent), dates_____
( ) Ear infections (frequent) ( ) Sinus infections
( ) Renal/genital problems: type_____
( ) Hip problems: type_____
( ) Lymphedema type_____
( ) Dental anomalies: ( ) cavities ( ) crowding
( ) allows inspection
( ) Other medical problems: type_____

Intro

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Intro | Participation | Methods | For whom | Topics | Consensus | Recommendations | Practical | Lessons

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## 9. Lessons learned (presented at a European meeting)

- Start with parental/patient survey
- Ensure good coordination (time!)
- Starting with a (translated) national guideline can be helpful
- Multidisciplinary working groups, including a patient representative
- Regular online meetings on fixed days/time
- Publication and implementation plan
- Have someone in your team with experience in writing guidelines (advisory member)
- **Do you have a national guideline on a rare NDD? Consider converting it to a European guideline !**



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## The guideline's website

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

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# Questions?

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