DEM-CHILD

Natural History Studies in Rare Diseases
Challenges and Opportunities

DZKJ German Center for Child and Adolescent Health

KINDER | UKE

Universitätsklinikum Hamburg-Eppendorf

UKE HAMBURG

Disclosures

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- Honoraria for speaker fees from BioMarin Pharmaceutical Inc., and for consultations from Regenxbio Inc. and Neurogene Inc
- Principal Investigator in the BMN 190 clinical trials funded by BioMarin Pharmaceutical Inc.
- Scientific Advisor Latus Tx

Challenges:

- Limited number of patients
- Phenotype variability
- Need for reliable clinical outcome measures
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- Use of natural history control data in clinical trials – can it be done?

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Natural History Studies in Rare Diseases require International Collaboration

DEM-CHILD NCL Patient Database: Founding Consortium and Collaborators

European DEM-CHILD Founders

DEM-CHILD

SEVENTH FRAMEWORK PROGRAMME

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PGIMER, Chandigarh

DEM-CHILD Database: Collaborating centers and projects

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DEM-CHILD Database: Aims

International DEM-CHILD Database

- To improve early diagnosis of NCLs
- To optimise standard of care for patients
- To collect precise natural history data of ALL NCL types
- To establish evaluation tools and outcome measures for experimental therapies

Ethic approval:

- DEM-CHILD database is in line with European Dataprotection Guidelines
- Non-exclusive data sharing with third parties (scientists and industry, also outside EU)

  in order to support development of various therapies as much as possible
- Collection and sharing of patient samples with third parties – Virtual Biobank

DEM-CHILD Database: Harmonization of data collection and sharing

DEM-CHILD Database Structure

- Online database – RedCap System
- Multi-site use of database infrastructure
- Every site agrees to DB User Agreement
- Every site can add items to be collected specifically for this site
- Data safety
  - Audit trail
  - Data storage on two different servers with emergency power supply
  - Backup of entire dataset every 24 hours

Ongoing work:

DZKJ German Center for Child and Adolescent Health

- Enabling parents to directly feed data into the database
- Database expansion
  - ➢ Collection of Natural History Data for additional lysosomal and pediatric neurodegenerative diseases

DEM-CHILD DB User Agreement

- To ensure protection of patient rights

  Consent forms, compliance with local ethic regulations etc.

- To ensure data safety

  Password protection, patient codes etc.

- To ensure data quality

  Data quality remains solely at the data entering site

- To ensure data ownership

  Ownership remains solely at the data entering site

DEM-CHILD DB: Type of data collected – Static data

Static Data

- Gender
- Family history
- Pregnancy / Perinatal history
- Psychomotor development
- Medical history
- Diagnostic summary
- Neurologic findings
- Experimental therapy studies

Static data can be collected **retrospectively** using

- Patient charts
- Parent interviews

Language	
Was INITIAL LANGUAGE DEVELOPMENT NORMAL?	(•) yes ( ) no
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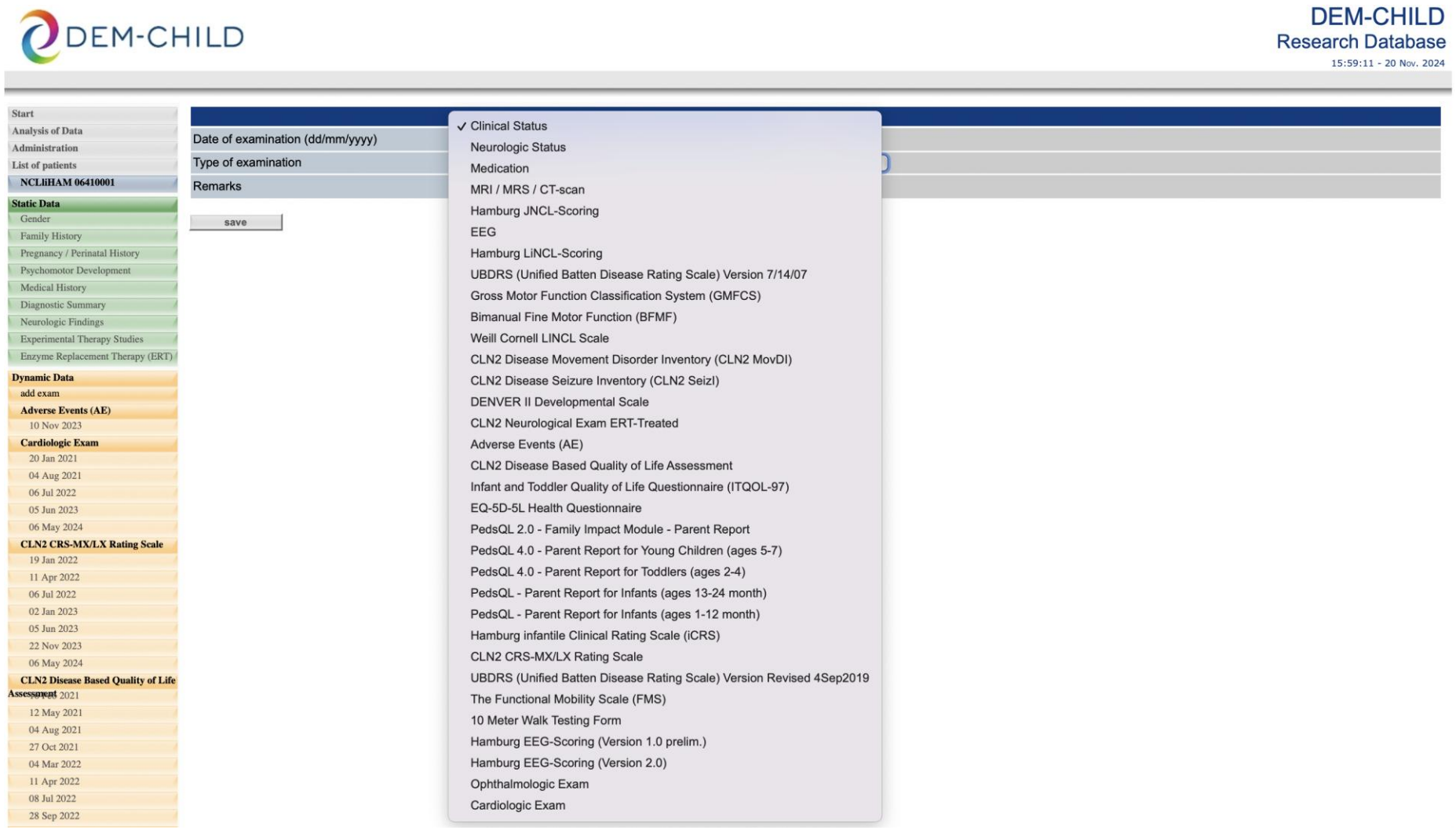
TPP activity measured in dried blood spots?	(•) yes ( ) no
TPP dried blood spots value / unit	0,01
TPP activity in dried blood spots is	( ) normal ( ) questionable (•) abnormal
Patient MATERIAL AVAILABLE?	[ ] DNA [x] fibroblasts [ ] lymphocytes [ ] tissue specimen [ ] dry blood spots
if tissue specimen available please specify	UKE Hamburg

Virtual biorepository: Prevention of repetitive invasive sample collection if possible

DEM-CHILD DB: Type of data collected – Dynamic data



Dynamic data are collected **prospectively**

- Related to patient‘s age / date of examination

DEM-CHILD DB: Type of data collected – Dynamic data

HAMBURG INFANTILE NCL-SCORING, Nickel et al., unpublished	
Gross Motor Function (GMF)	Reset answ 3 (age appropriate function) 2 (developmental delay present but no regress of function) 1 (regress of function noted, INDEPENDENT active function present) 0 (total loss of active function) *Interim checked*
Fine Motor Function (FMF)	Reset answ 3 (age appropriate function) 2 (developmental delay present but no regress of function) 1 (regress of function noted, INDEPENDENT active function present) 0 (total loss of active function) *Interim checked*
Expressive Language	Reset answ 3 (age appropriate function) 2 (developmental delay present but no regress of function) 1 (regress of function noted, language PRESENT (may be language-residues only) 0 (total loss of expressive language) *Interim checked*
Communication & Interaction	Reset answ 1 (age appropriate) 0 (pathologic) *Interim checked*
Visual Attention	Reset answ 1 (age appropriate) 0 (pathologic) *Interim checked*
Agitation & Irritability	Reset answ 1 (age appropriate) 0 (pathologic) *Interim checked*
Seizures	Reset answ 1 (age appropriate) 0 (pathologic) *Interim checked*
Feeding	Reset answ 1 (age appropriate) 0 (pathologic) *Interim checked*
Sleep	Reset answ 1 (age appropriate) 0 (pathologic) *Interim checked*

HH iNCL SCORING STATIC COMPONENT	
Individual max. GMF function reached:	< = 6m head control in lying position < = 6m rolls, turns < = 6m sits, with support < = 12m sits, no support < = 12m crawls, scrabbles, changes position from lying to sitting < = 12m stands, with support < = 12m walks, with support < = 18m stands, no support < = 18m changes position to stand, no support < = 18m walks, no support < = 24m runs well, rarely falls < = 24m climbs stairs up/down, no support (1 step at a time) < = 36m pedals tricycle, wheeler < = 36m climbs stairs up/down, no support (alternating feet)
First decline of GMF function at age:	years months or date month: year:
Individual max. FMF function reached:	< = 6m hand-to-mouth function (comforts self with hand/thumb/pacifier) < = 6m reaches for toys/faces with either hand < = 12m transfers from one hand to the other < = 12m combined use of hands (bangs two cubes) < = 12m grabs object and lets them fall < = 12m thumb-finger grasp < = 18m begins to build a cube tower < = 18m grabs objects coordinated (lifts cup to mouth to drink, spoon to eat) < = 24m turns pages of book (one at time) < = 24m scribbles with crayon < = 24m eats with fork/spoon < = 36m cuts with scissors < = 36m opens and closes bottle < = 36m washes hands < = 36m eats and drinks by itself
First decline of FMF function at age:	years months or date month: year:
Individual max. expressive language reached:	< = 6m cooing, going, laughing, vowel sounds (oooh, eeeh, aaahh) < = 12m sound production (with tone variation) < = 12m babbles/jabbers (unintelligible speech) < = 12m monosyllables < = 12m min. one or two specific words at 12m (mama, dada, "nana" for banana), may be unclear < = 18m clear, specific meaningful words (word count: min. of 2-4 at 18m) < = 18m "need word" (up, more..) < = 24m more words every month < = 24m expressive word: count min. of 10 words at 24m < = 24m (receptive word count: min. 200+ at 24m) < = 24m me/mine < = 24m min. two-word sentence/grouping at 24m < = 36m word count: min. 300-400 at 36m < = 36m min. 3-4 words sentences/grouping at 36m < = 36m asks "why" questions < = 36m in/on/under
First decline of expressive language at age:	years months or date month: year:

Dynamic data are collected **prospectively**

- Related to patient's age / date of examination

Clinical Trial Design and Endpoints: Challenges in Rare Diseases

Challenges:

- Limited number of patients
  - International Collaboration
- Phenotype variability
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CLN1 disease – phenotype variability

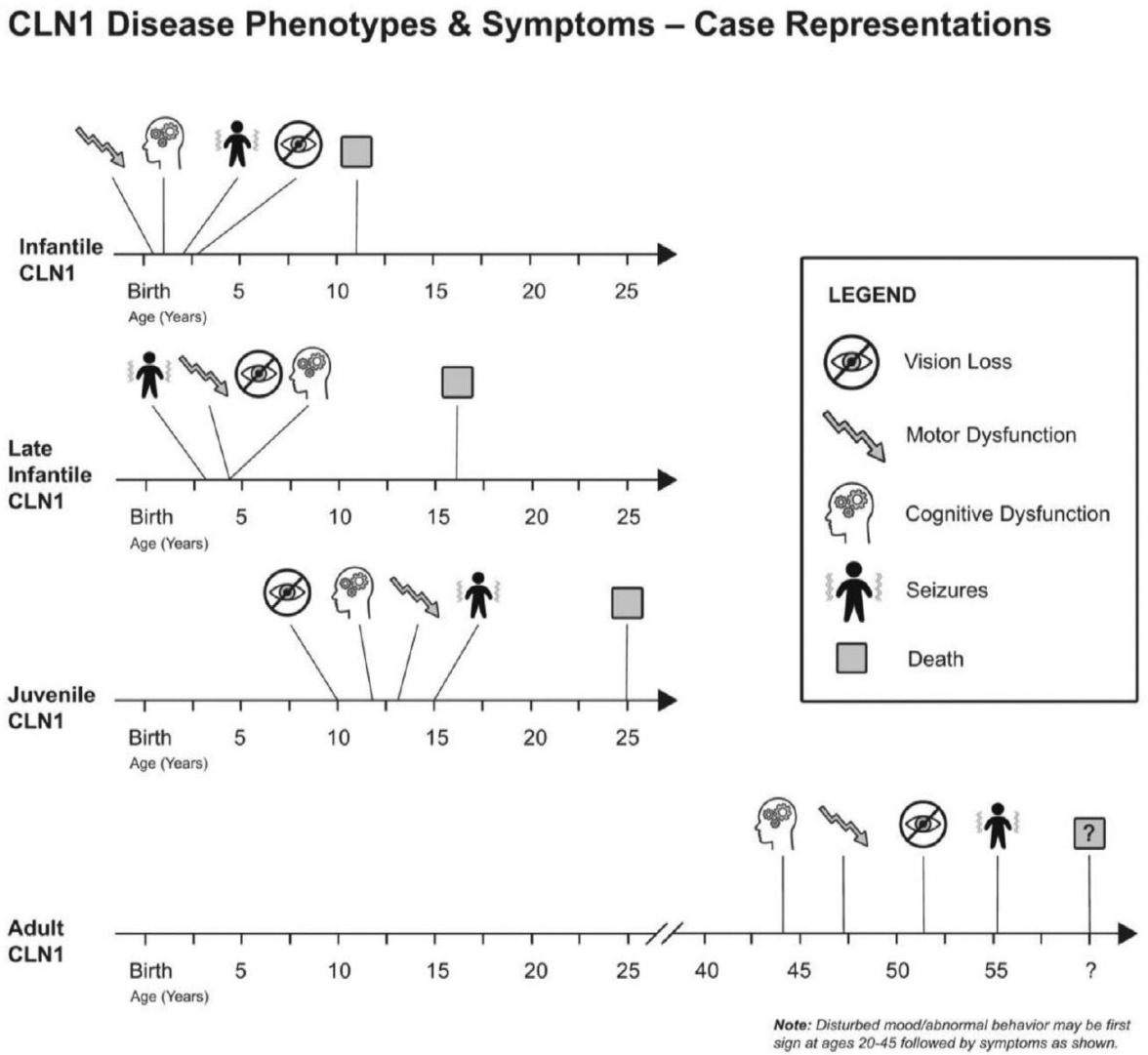


FIGURE 1. Examples of CLN1 disease phenotypes and symptom progressions. The ages at symptom onset depicted here are derived from clinical experience and published data and are intended to represent *sample* cases. The specific occurrence, order, and age at symptom onset are variable. Figure adapted from Miriam Nickel, MD.

CLN1 – maximum psychomotor development level

	Majority of developmental milestones achieved	
Functions	infantile	juvenile
Gross Motor Function	✗	✓
Fine Motor Function	✗	✓
Language	✗	✓
Cognition	(✗)	✓
Vision	✓	✓

CLN1 disease – phenotype variability

	Majority of developmental milestones achieved		Age at key aspects of disease	
Functions	infantile	juvenile	infantile	juvenile
Gross Motor	✗	✓		
Fine Motor	✗	✓		
Language	✗	✓		
Cognition	(✗)	✓		
Vision	✓	✓		
Start of decline			17m	133m (11y)
Seizures			25m	247m (21y)
Start of vision loss **- blindness**			19m 30m	133m (11y) 206m (17y)
Diagnosis			25m	-
End of life			111m (9y)	> 408m (34y)
Disease duration			94m	206m (17y)

CLN1 disease – phenotype variability

Tools for Possible Outcome Measures		
	infantile	juvenile
Denver II	✓	✗
Bayley III	✓	✗
WISC / WPPSI	✗	✓ *
Vineland	✗	✓
	✗	
UBDRS	✗	✓
HHJNCL	✗	✓
HHLiNCL	✗	✗
HHiCRS	✓	✗
GaitRite	✗	✓
Clinical Global Impression,..	✓	✓
Seizures: **Diaries, Apps,..**	✓ * *	✓
Vision: **Visual acuity, OCT, ERG**	✓	✓
QoL: **PedsQL, sleep questionnaires,..**	✓	✓
MRI	✓	✓
Lab Biomarkers (PPT1, NFL)	✓	✓

*depending on stage of disease, vision impairment prevents subtests that rely on visual assessments

* * depending on stage of disease seizure may become more stable over time

WPPSI ages: 4,0-7,7y
WISC ages: 6-16y
Vineland ages: 3-21y (adaptive behaviour)
CGI clinical global impression
PGI parental/patient global impression

… and if so – HOW?

Both phenotypes cause challenges:

Juvenile:

- all developmental milestones are reached
- all quantifiable clinical scorings and test batteries (neurocognitive,..) possible
- valid natural history data therefore exist

BUT – very slowly progressive therefore long duration of potential trial

Infantile:

- most milestones are never reached
- developmental level low
- clinical scoring challenging

BUT - fast progressive and therefore quick efficicacy results

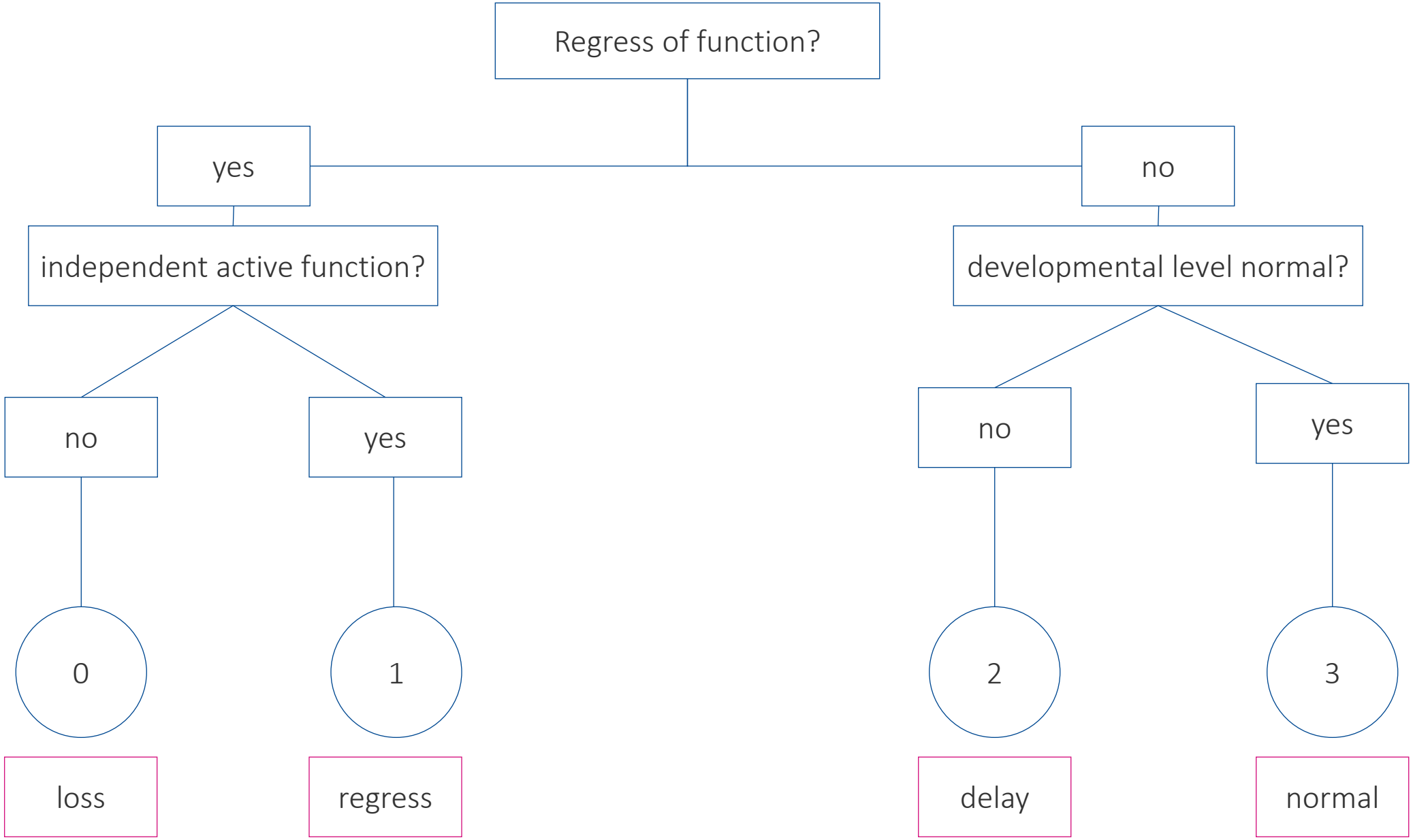
CLN1 disease – clinical rating scale for infantile phenotype

Development of an adapted clinical rating scale for quantitative description of disease severity and progression for use in infantile degenerative diseases.

Requirements:

- Easy and quick to use
- Retrospective data analysis and prospective clinical evaluations
- Focus on functional relevant outcome parameters
- Excellent inter-rater-reliability

CLN1 disease – clinical rating scale for infantile phenotype



CLN1 disease – clinical rating scale for infantile phenotype

Main functional domains:

> max. of 9 points

SCORE	GROSS MOTOR FUNCTION (GMF)	FINE MOTOR FUNCTION (FMF)	EXPRESSIVE LANGUAGE
3	age-appropriate function	age-appropriate function	age-appropriate function
2	developmental delay present but no regress of function	developmental delay present but no regress of function	developmental delay present but no regress of function
1	regress of function noted, independent active function present	regress of function noted, independent active function present	regress of function noted, language present (may be language-residues only)
0	total loss of active function	total loss of active function	total loss of expressive language function

CLN1 disease – clinical rating scale for infantile phenotype

Six „add-on“ clinical meaningful categories: > max. of 6 points

SCORE	COMMUNICATION & INTERACTION	VISUAL ATTENTION	IRRITABILITY & AGITATION	SEIZURES	SLEEP	FEEDING
1	age appropriate	age appropriate	age appropriate	no seizures	age appropriate	age appropriate
0	pathologic	pathologic	pathologic	seizures	pathologic	pathologic

>> Overall total score: max. of 15 points

Clinical Trial Design and Endpoints: Challenges in Rare Diseases

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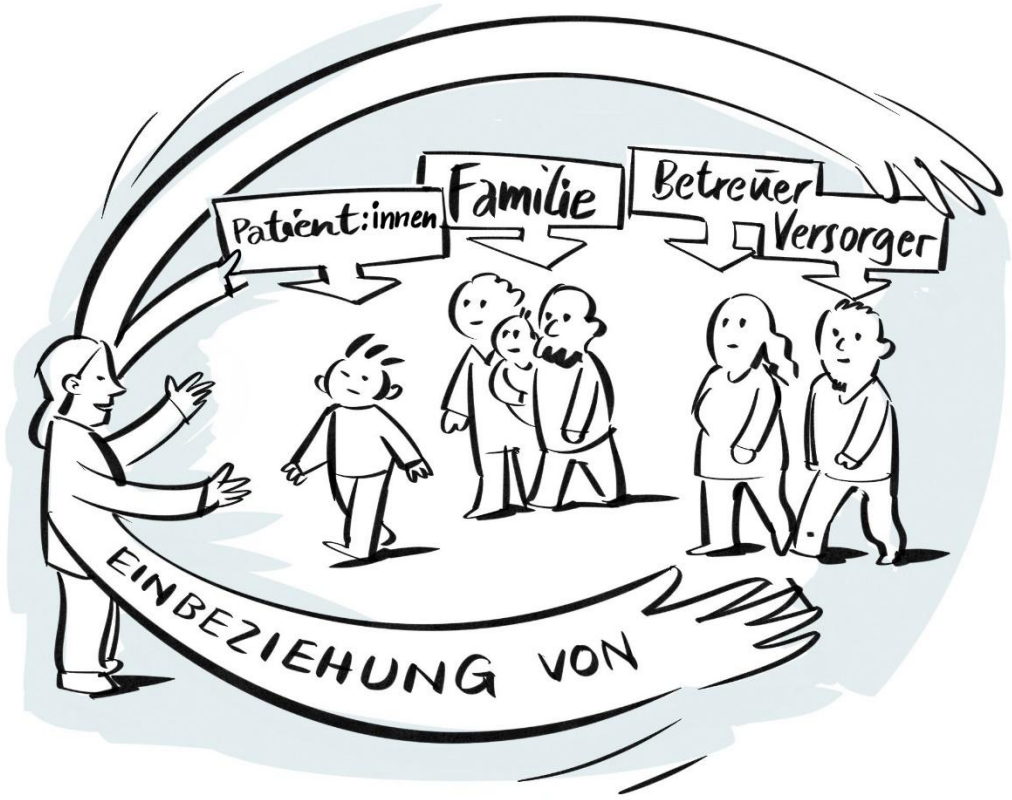
„Nothing about them without them.“



What is PPPI?

- Patient-Parent-Public Involvement
- Research „with“ or „by“ patients, parents or members of the public rather than „about“ them
- Inclusion of potential „recipients“ of healthcare, medical care or social care
- PPPI is a cross-cutting issue

PPPI – Harmonization of data collection and sharing

International NCL DEM-CHILD Database

- To improve early diagnosis of NCLs
- To optimise standard of care for patients
- To collect precise natural history data of ALL NCL types
- To establish evaluation tools and outcome measures for experimental therapies

PPPI Feedback:

- Natural history data should be used as controls in clinical trials to prevent placebo controls
- Collaboration with regulatory agencies
- Collaboration with pharmaceutical companies
- Parents should have the possibility to directly feed data into the database

Static data: Psychomotor development

Static data can be collected **retrospectively** using

- Patient charts
- Parent interviews

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At what age was no more language present or no verbal contact possible?	years months or date month: year:

PPPI Feedback:

- Do parents and clinicians mean the same when answering these questions?
- Do we miss asking about important symptoms and problems?

PPPI Feedback:

- Prevention of repetitive invasive sample collection if possible

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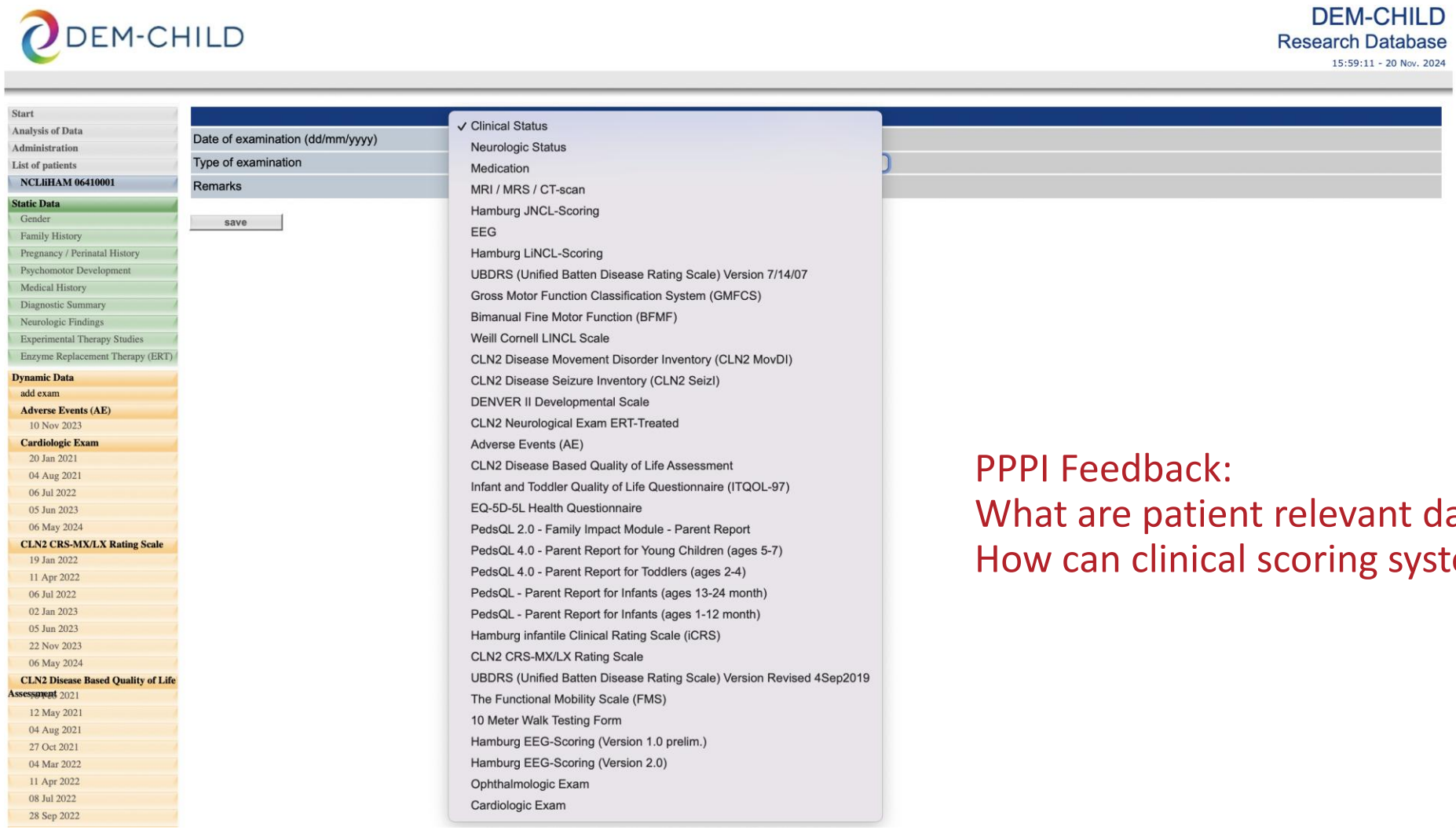
Virtual biorepository

PPPI - Type of data collected – Dynamic data



PPPI Feedback:
What are patient relevant data?
How can clinical scoring systems be improved?

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DEM-CHILD Database:
CLN2 Natural History Data used as Control Data in Phase 1/2 Clinical Trial

Lessons learned

- International Collaboration

	DEM-CHILD dataset (n=67)	WCMC dataset (n=66)
Core data cohort, n	41	0
Comparison cohort 1, n	21	12
Comparison cohort 2, n	5	54

Of the 74 patients in the DEM-CHILD dataset, 67 patients had clinical scoring data available and formed the DEM-CHILD core data and comparison cohorts.

Nickel M…..Schulz A . Lancet Child Adolesc Health 2018;2:582-90

DEM-CHILD Database:
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Lessons learned

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- Data Harmonisation – early engagement of regulatory bodies
- Data should show homogeneity in disease phenotype

CI: confidence interval

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- Data should allow to rate disease progression quantitatively

Rate of decline
2.04 units/year (SD±1.08)
n = 41

CI: confidence interval
Nickel M …..Schulz A. Lancet Child Adolesc Health 2018;2:582-90

Lessons learned

- International Collaboration
- Data Harmonisation – early engagement of regulatory bodies
- Data should show homogeneity in disease phenotype
- Longitudinal and cross-sectional data should match
- Data should allow to rate disease progression quantitatively
- Successful audits by EMA and FDA
  - Source verification
    - Important cross-reference of data from questionnaires with data from medical charts
  - Data safety
    - Audit trail
    - Data storage on two different server with emergency power supply
    - Backup of entire dataset every 24 hours

Use of independent natural history control data to advance therapy development in rare diseases is possible!!!!!

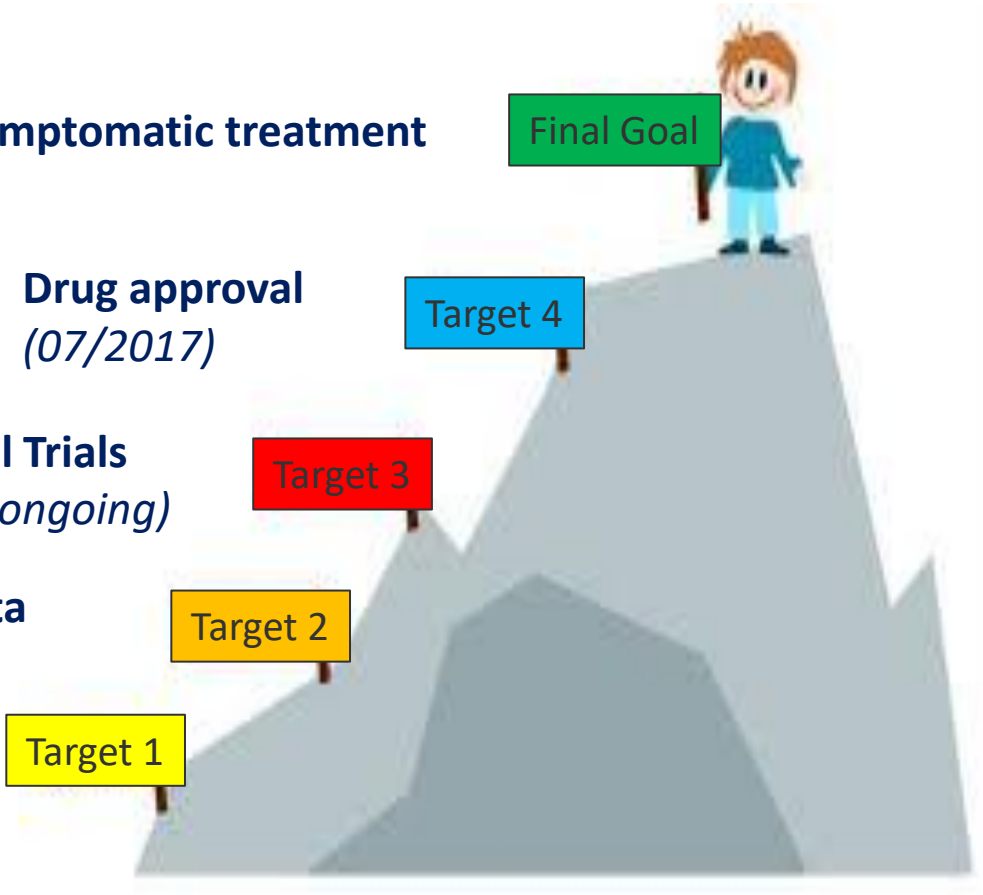
EARLY pre-symptomatic treatment

Drug approval
(07/2017)

Clinical Trials
(2013-ongoing)

Collection of natural history data
(2000-ongoing)

Pre-clinical testing in the CLN2 dog
(2010-2012)



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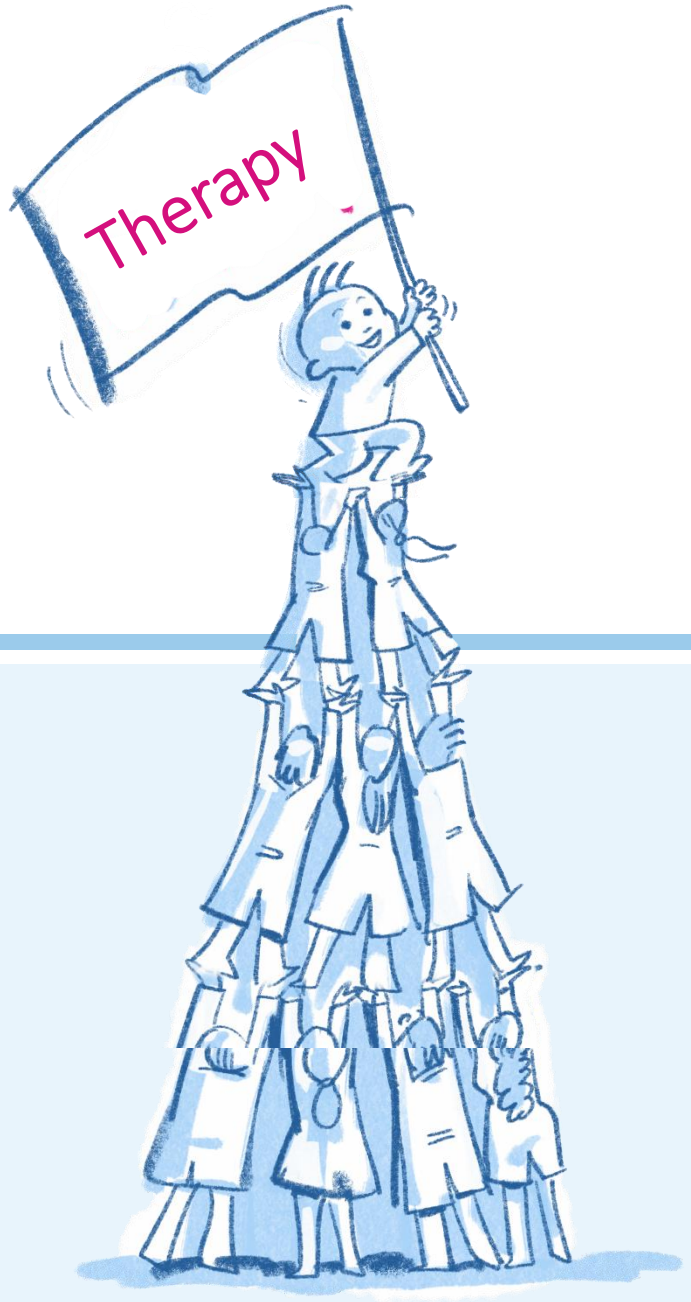

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