Mitteldeutsches Kompetenznetz Seltene Erkrankungen

CrescNet

European Reference Network
for rare or low prevalence complex diseases
Network Endocrine Conditions (Endo-ERN)

Natural History vs Real World Data

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F. Hundertwasser, 2010

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Disclosures

Research funded by Novo-Nordisk, Pfizer, BioMarin, Lilly

Receives honoraria for seminars by Roche, Novo-Nordisk, QED, BioMarin, Lilly

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Achondroplasia: condition or disease?

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Natural History Data

AIM:

The Lifetime Impact of Achondroplasia Study in Europe (LIAISE; NCT03449368) to quantify the burden of achondroplasia among individuals across all ages

COHORT:

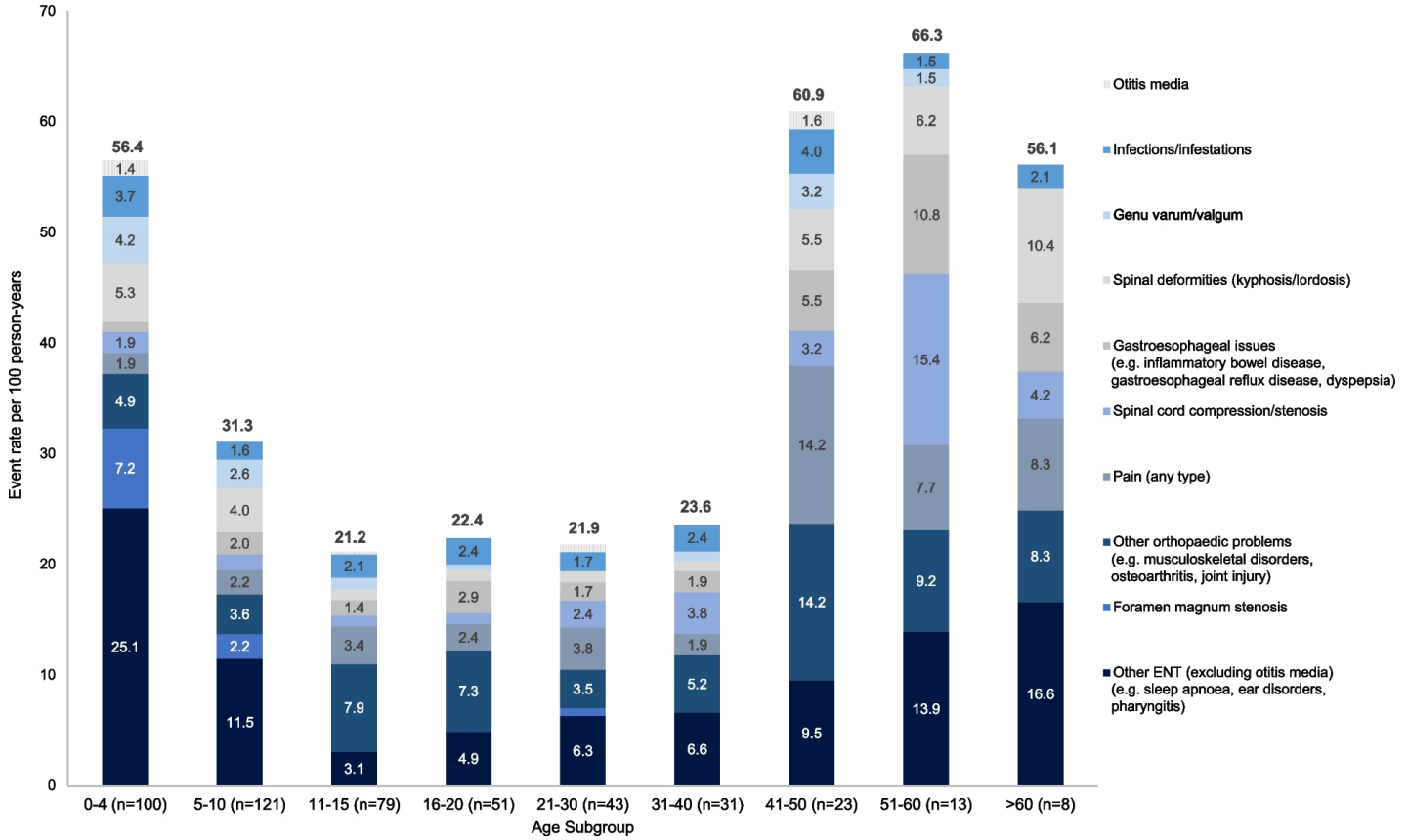
186 study patients mean age of 21.7 ± 17.3 years (range 5.0–84.4)

METHOD:

- Demographic, clinical and healthcare resource use data from medical records
- Patient-reported outcomes questionnaires at the time of enrolment (quality of life [QoL], pain, functional independence, work productivity activity impairments)

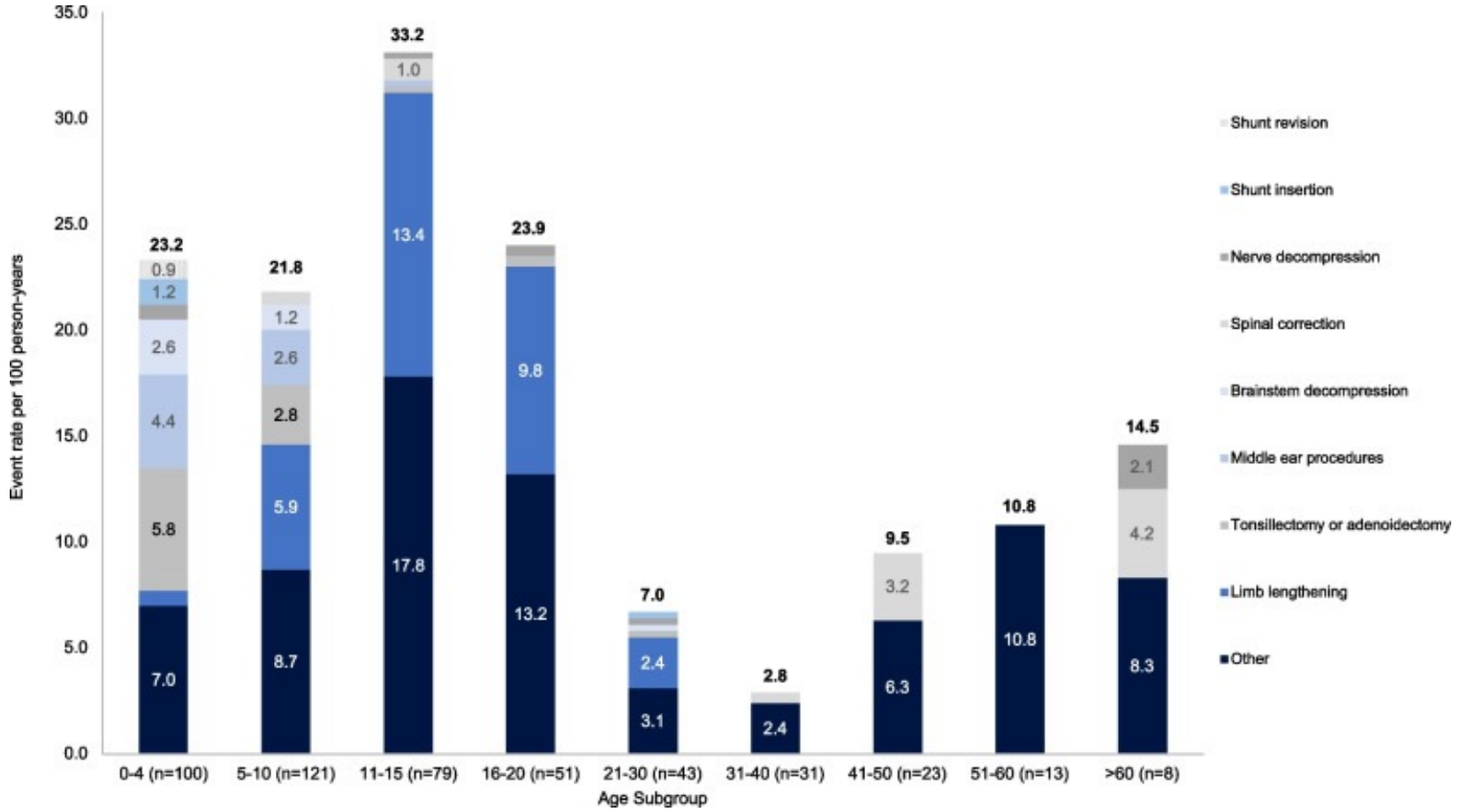
Complications and healthcare resource use

In total, 94.6% of patients reported 66.6 events per 100 patient-year



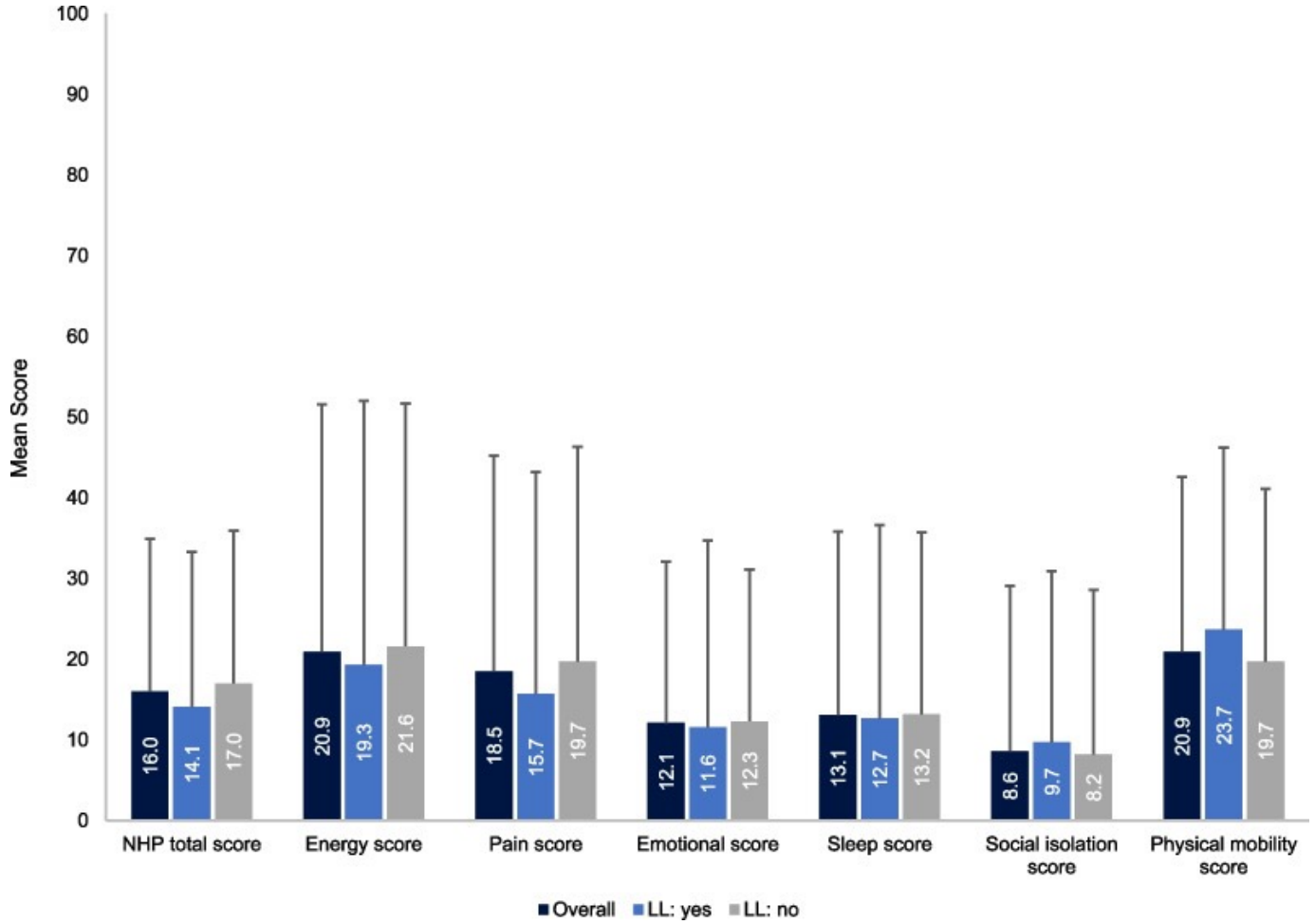
Surgical Burden

72.0% of individuals had undergone at least one surgical procedure.
event rate 21.5 per 100 person-years



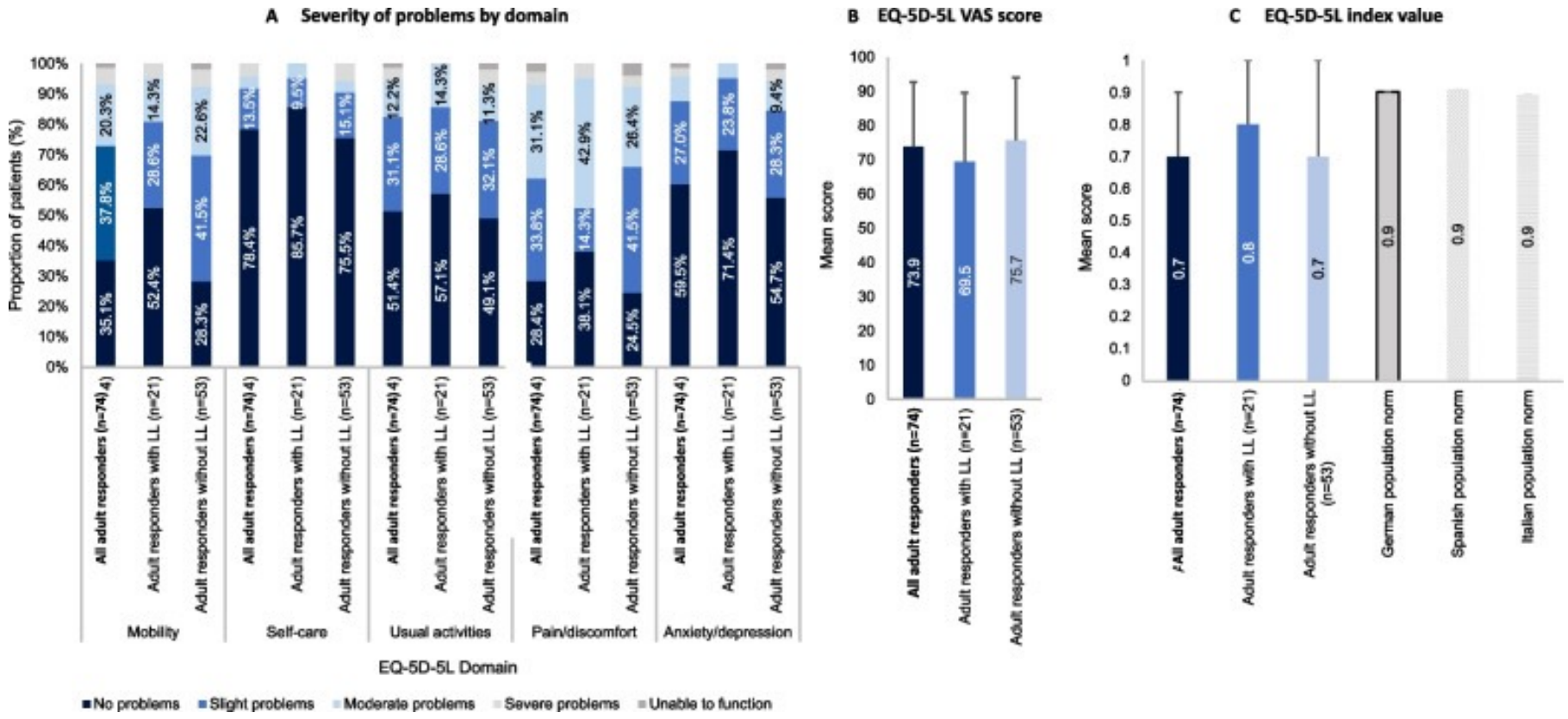
Quality of Life

Self-reported scores were typically higher than parent-reported scores



Quality of Life –adults

Negatively impacted domains: physical mobility, energy and pain



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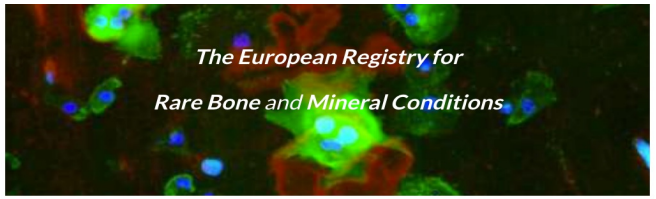

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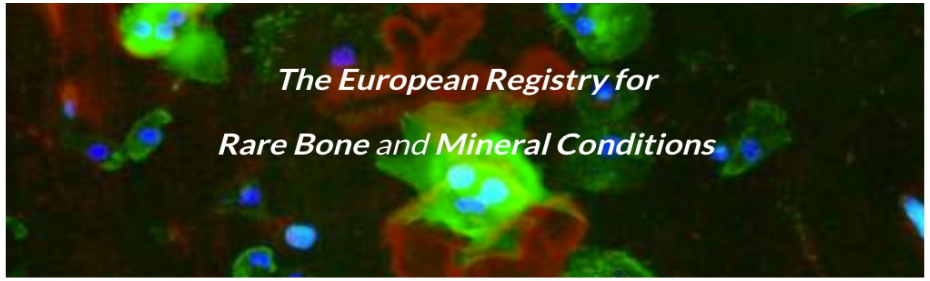
The e-REC platform monthly new referrals of rare endocrine and bone conditions are reported

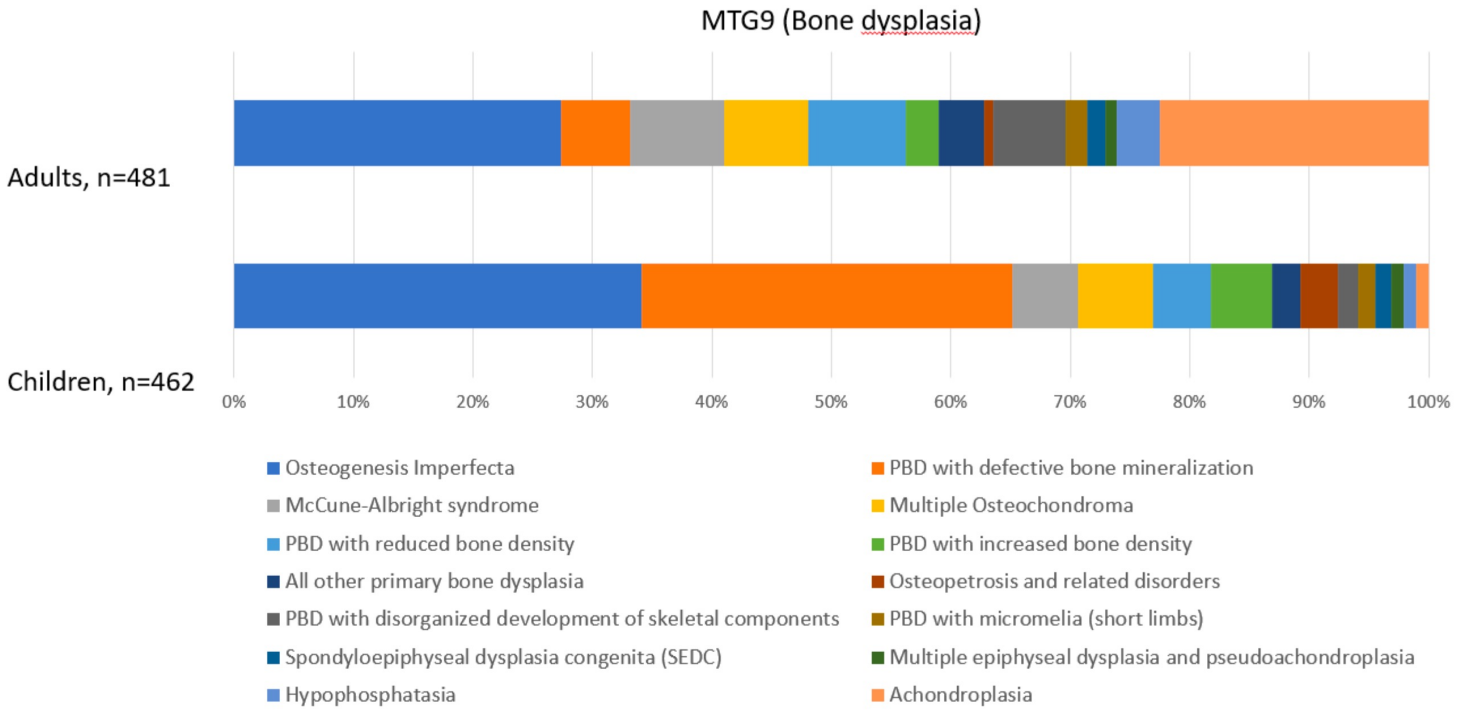
BONE DYSPLASIA

Condition	Suspected Cases - Child (< 18)	Confirmed Cases - Child (< 18)
Osteogenesis Imperfecta [ORPHA666]	0	0
McCune-Albright syndrome [ORPHA562]	0	0
Achondroplasia [ORPHA15]	0	0



7/2018 to 12/2022 reported new referrals with achondroplasia

<18y.	N of centers	28
	patients	462
>18y.	N of centers	22
	patients	481



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Available natural history data will be evaluated by prospective standardized monitoring

- ✓ Co-morbidities including cervico-medullary compression, spinal stenosis, sleep apnea, bone deformities
- ✓ Current treatment for complications related to ACH is surgical intervention (foramen magnum decompression, spinal surgery, limb lengthening, etc.)
- ✓ Medical treatment until final adult height.

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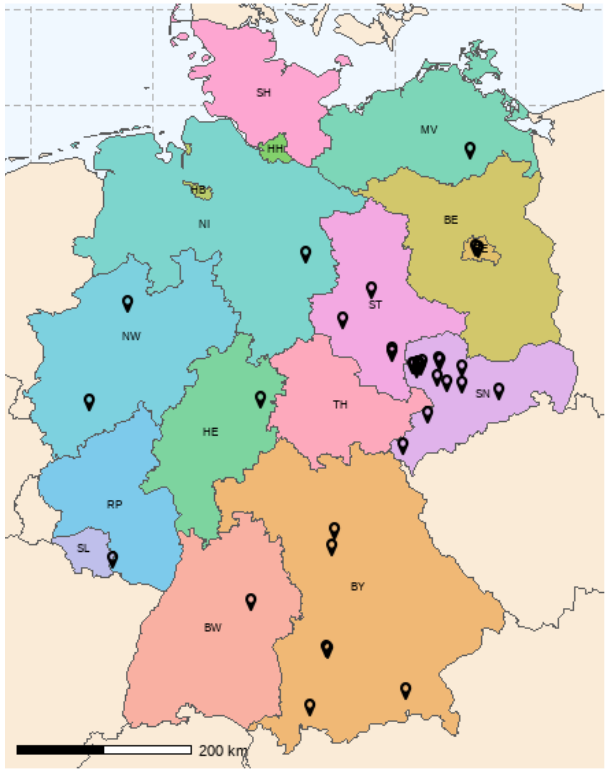
Consensus on principles of management for achondroplasia (8 specialities & PAG from 7 countries)

Name	Speciality	Country
Alves, Inês	PAG	Portugal
Baujat, Genevieve	Genetics	France
Bedeschi, Maria Francesca	Genetics	Italy
Brizola, Evelisa	Genetics	Italy
Cheung, Moira	Ped. Endocrinologist	UK
Fredwall, Svein	Internal med	Norway
Hagenäs, Lars	Ped. Endocrinologist	Sweden
Innig, Florian	Patient Advocacy Group (PAG)	Germany
Kunkel, Philip	Neurosurgeon	Germany
Lampe, Christian	Neuropediatrician	Germany
Milrad, Josef	Neuropediatrician	Sweden
Mohnike, Klaus	Ped. Endocrinologist	Germany
Mordenti, Marina	Genetics	Italy
Mortier, Geert	Genetics	Belgium
Offiah, Amaka	Radiologist	UK
Palm, Katja	Ped. Endocrinologist	Germany
Quitman, Julia	Psychologist	Germany
Sessa, Marco	PAG	Italy



Cormier-Daire et al. The first European consensus on principles of management for achondroplasia. *Orphanet J Rare Dis* 2021;16(1):333.

https://crescnet.org/ (University of Leipzig). This network has been developed by the Medical Faculty of the University of Leipzig.

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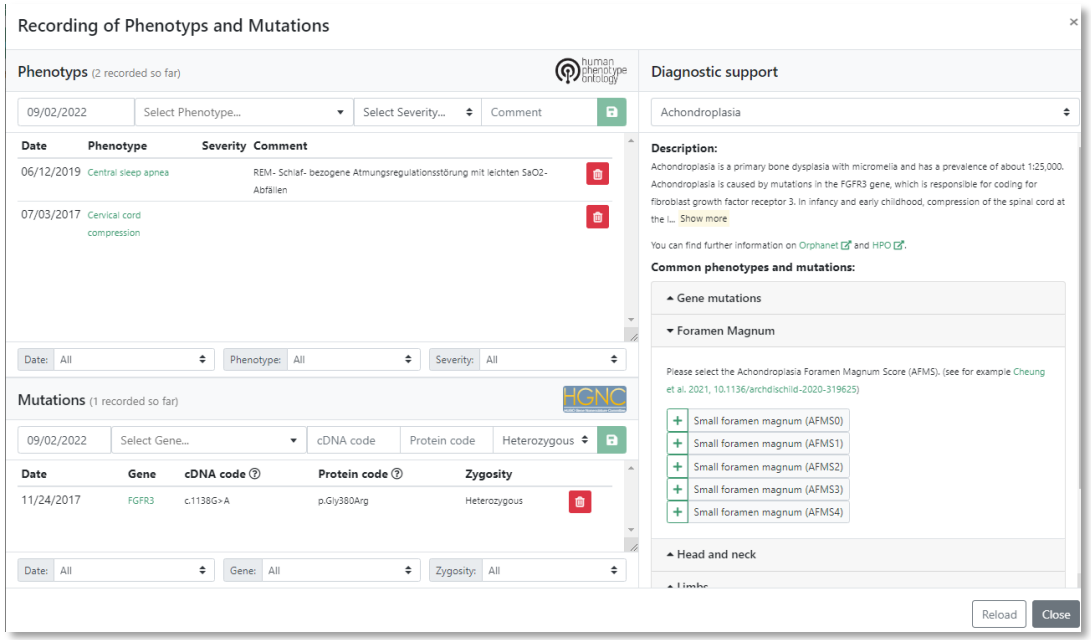
Real world evidence monitoring

Achondroplasia-specific modified version of CrescNet

Structured data collection

- Enrolment after care givers consent
- Standardized items:
  - Human Phenotype Ontology (HPO),
  - Logica Observation Identifiers Names and Codes (LOINC®)
- Documentation of clinical findings during visit, `real-time´
- Self-reporting of questionnaires
  - Milestones
  - QoL (quality of life)

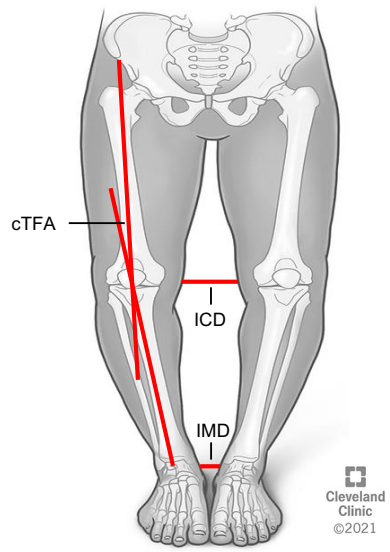


https://crescnet.org/ (University of Leipzig). This network has been developed by the Medical Faculty of the University of Leipzig and is dependent on financial donations and support in order to be able to fulfill its associated tasks.

Real world evidence monitoring

Orthopaedic findings (gibbus, etc.)

Measurement of the Intercondylar Distance, the Intermalleolar Distance and the Clinical Tibiofemoral Angle[1]



Intercondylar Distance (ICD)

Measurement of the distance between the two medial femoral condyles with the inner ankles or medial foot edges just touching in neutral joint position.

Unit: cm (centimetre)

Tool: Measuring tape

Intermalleolar Distance (IMD)

Measurment of the distance between the two medial malleoli in neutral joint position.

Unit: cm (centimetre)

Tool: Measuring tape

clinical Tibiofemoral Angle (cTFA)

Measurement of the acute intersection angle of the anatomical frontal longitudinal axes of the thigh (spina iliaca anterior superior to the middle of the patella) and lower leg (middle of the patella to the middle of the ankle joint) in neutral joint position.

Unit: ° (Grad)

Tool: Goniometer / Protractor

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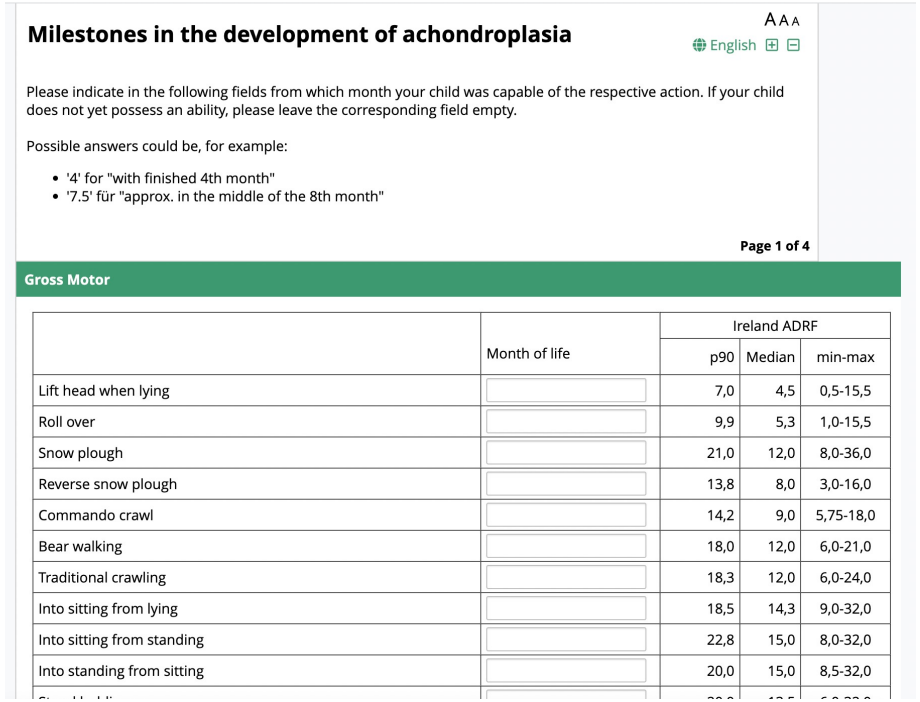
Standardized documentation during patient visits – auxology documentation



Milestones in the development of achondroplasia

AAA English

Please indicate in the following fields from which month your child was capable of the respective action. If your child does not yet possess an ability, please leave the corresponding field empty.

Possible answers could be, for example:

- '4' for "with finished 4th month"
- '7.5' für "approx. in the middle of the 8th month"

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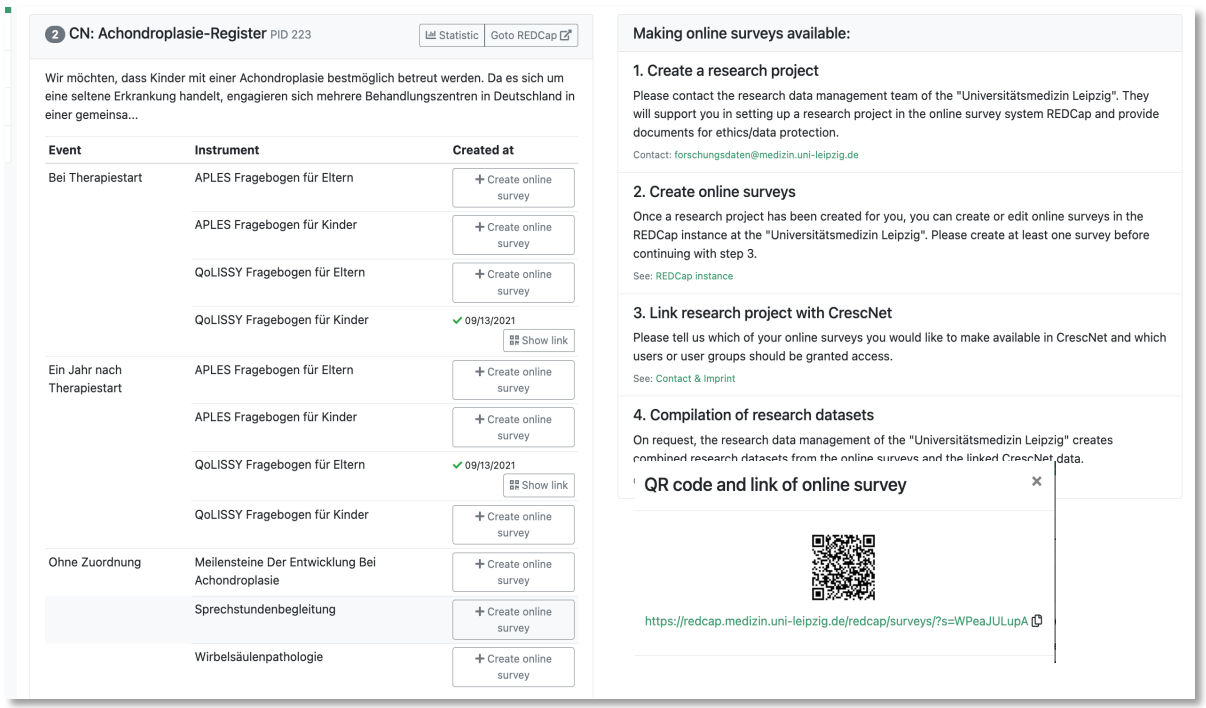
Gross Motor

	Month of life	Ireland ADRF		
		p90	Median	min-max
Lift head when lying		7,0	4,5	0,5-15,5
Roll over		9,9	5,3	1,0-15,5
Snow plough		21,0	12,0	8,0-36,0
Reverse snow plough		13,8	8,0	3,0-16,0
Commando crawl		14,2	9,0	5,75-18,0
Bear walking		18,0	12,0	6,0-21,0
Traditional crawling		18,3	12,0	6,0-24,0
Into sitting from lying		18,5	14,3	9,0-32,0
Into sitting from standing		22,8	15,0	8,0-32,0
Into standing from sitting		20,0	15,0	8,5-32,0



2 CN: Achondroplasie-Register PID 223 — Statistic | Goto REDCap

Wir möchten, dass Kinder mit einer Achondroplasie bestmöglich betreut werden. Da es sich um eine seltene Erkrankung handelt, engagieren sich mehrere Behandlungszentren in Deutschland in einer gemeinsa...

Event	Instrument	Created at
Bei Therapiestart	APLES Fragebogen für Eltern	+ Create online survey
	APLES Fragebogen für Kinder	+ Create online survey
	QoLISSY Fragebogen für Eltern	+ Create online survey
	QoLISSY Fragebogen für Kinder	✓ 09/13/2021 Show link
Ein Jahr nach Therapiestart	APLES Fragebogen für Eltern	+ Create online survey
	APLES Fragebogen für Kinder	+ Create online survey
	QoLISSY Fragebogen für Eltern	✓ 09/13/2021 Show link
	QoLISSY Fragebogen für Kinder	+ Create online survey
Ohne Zuordnung	Meilensteine Der Entwicklung Bei Achondroplasie	+ Create online survey
	Sprechstundenbegleitung	+ Create online survey
	Wirbelsäulenpathologie	+ Create online survey

Making online surveys available:

1. Create a research project

Please contact the research data management team of the "Universitätsmedizin Leipzig". They will support you in setting up a research project in the online survey system REDCap and provide documents for ethics/data protection.

Contact: forschungsdaten@medizin.uni-leipzig.de

2. Create online surveys

Once a research project has been created for you, you can create or edit online surveys in the REDCap instance at the "Universitätsmedizin Leipzig". Please create at least one survey before continuing with step 3.

See: REDCap instance

3. Link research project with CrescNet

Please tell us which of your online surveys you would like to make available in CrescNet and which users or user groups should be granted access.

See: Contact & Imprint

4. Compilation of research datasets

On request, the research data management of the "Universitätsmedizin Leipzig" creates combined research datasets from the online surveys and the linked CrescNet data.

QR code and link of online survey

https://redcap.medizin.uni-leipzig.de/redcap/surveys/?s=WPeaJULupA

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Patient demographics

		N=
All registered in CrescNet		258 (131 f)
Foramen magnum surgery		19
Limb lengthening		12
Vosoritide treatment		87
Start of treatment	H-SDS (German reference)	-4.9
	H-SDS (Merker et al.)	0.42
	BMI-SDS	1.68
	Chron. age	9.89 y.
	Bone age	8.79 y.
Treatment duration		**0.75 y.**

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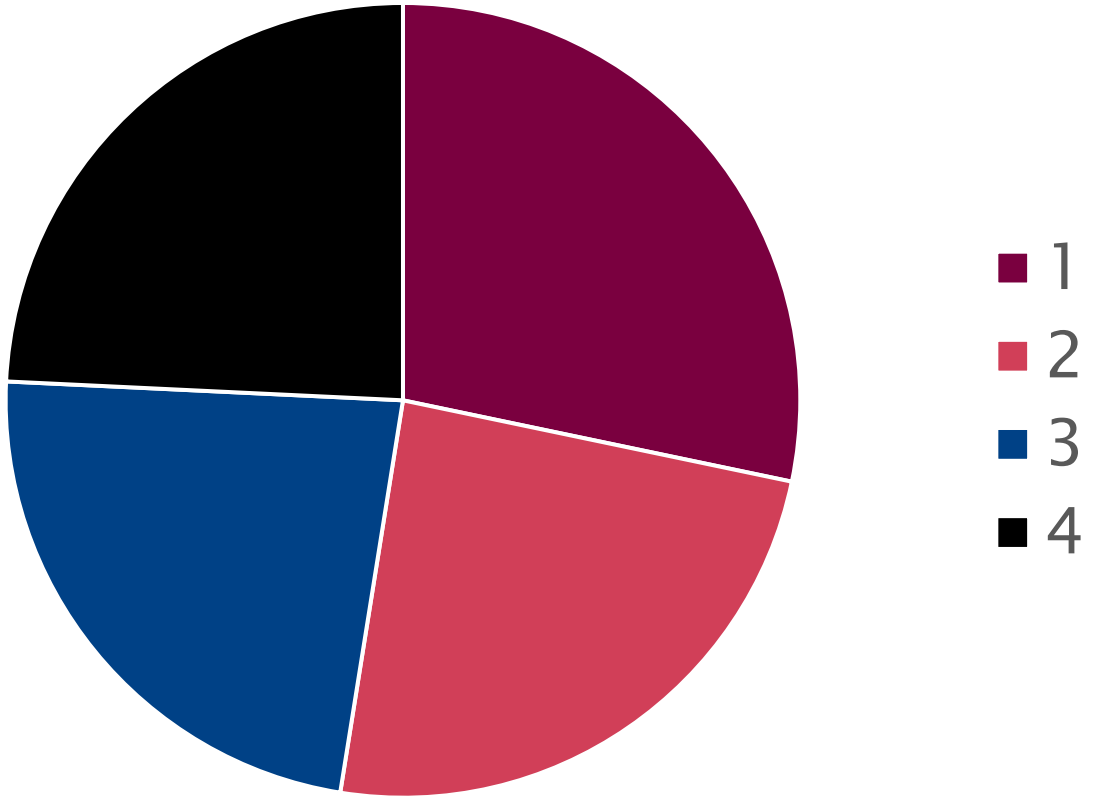
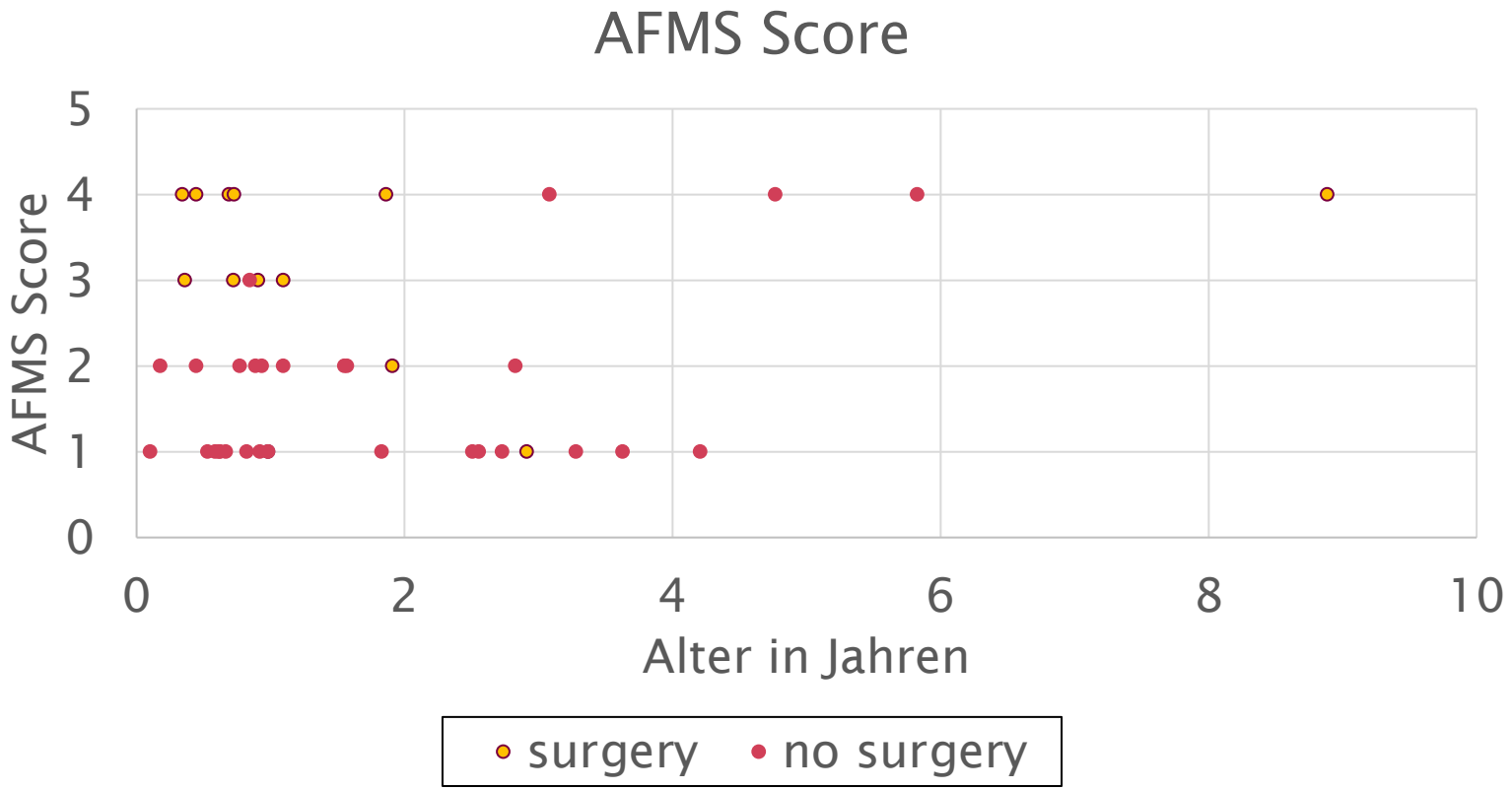
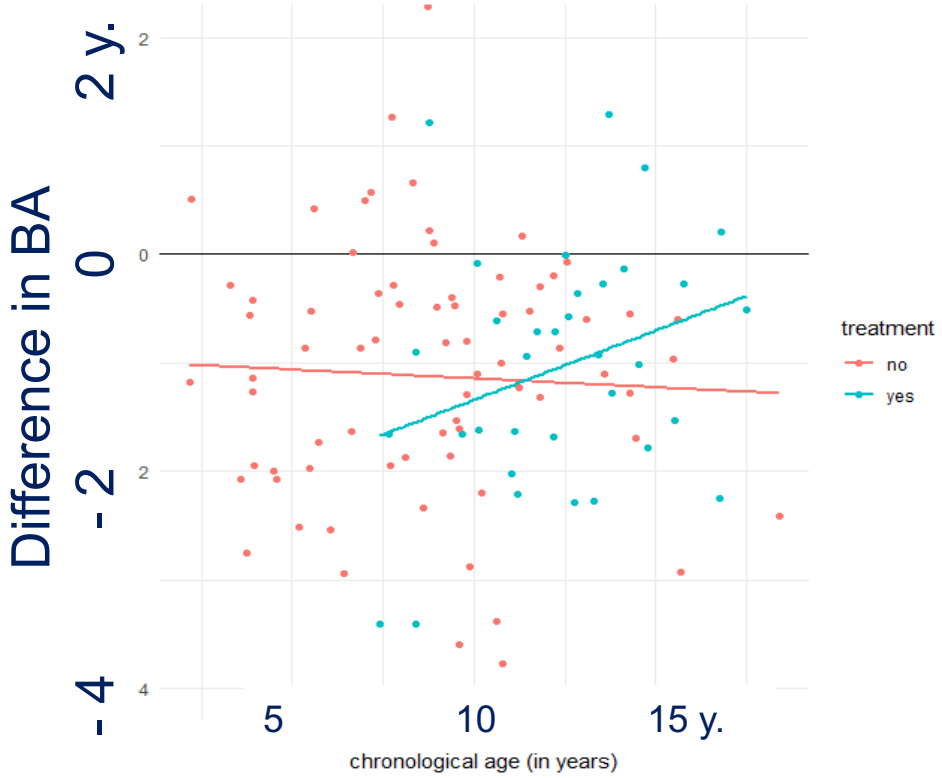
AFMS-Score (N=93)




AFMS Score
AFMS Score
0
1
2
3
4
5
0
2
4
6
8
10
Alter in Jahren
surgery
no surgery

Bone age (Greulich/ Pyle)



Chron. age (years)

	N=110
>1 years retarded	54 (49.1%)
+/- 1y.	51 (46.4%)
≥ 1 y. accelerated	5 (4.55%)

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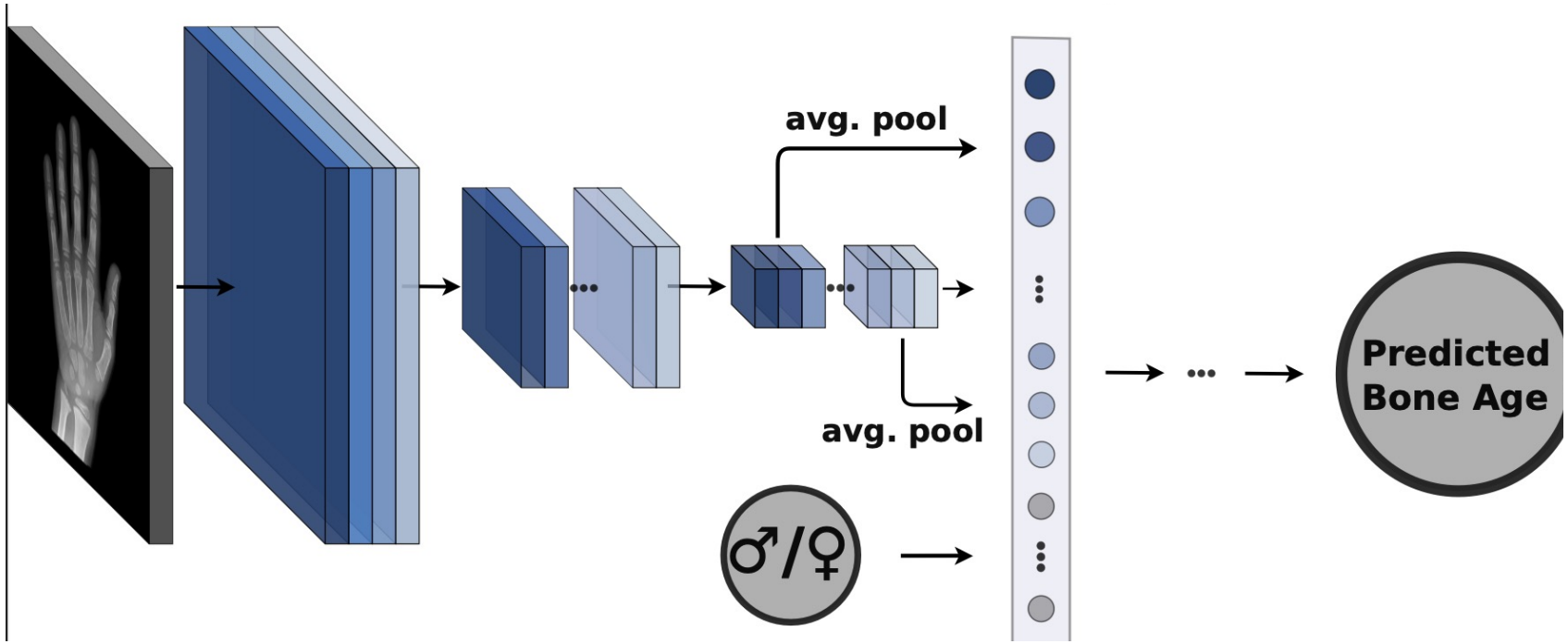
Bone age in bone dysplasia determined by prior-free deep learning (pilot project S. Rassmann, Univ. Bonn)



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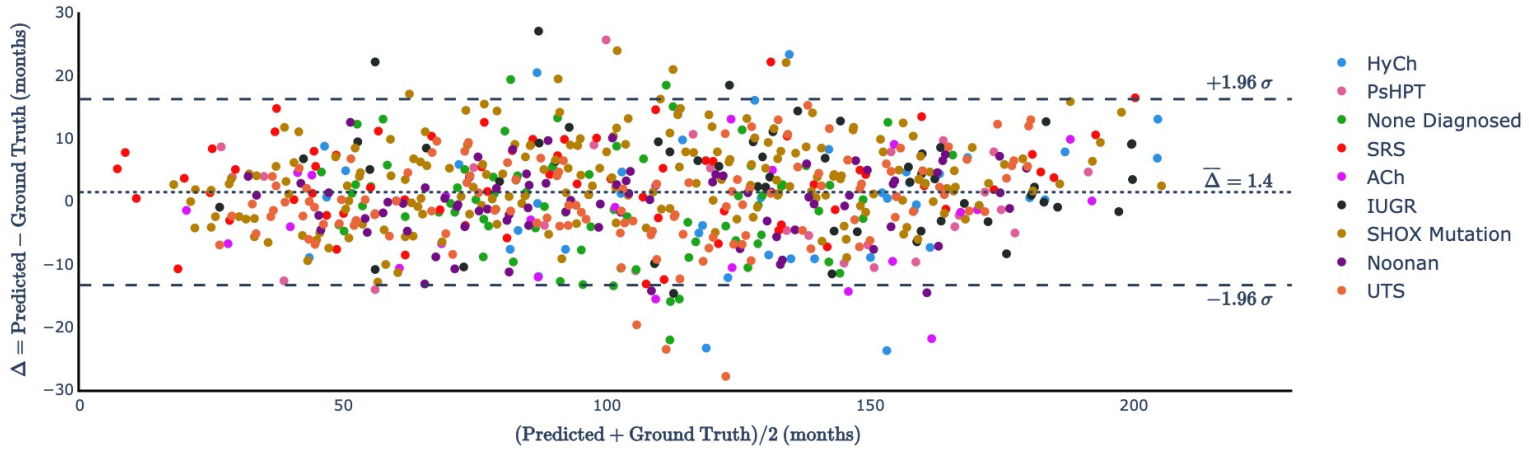
Blant-Altmann-Plot



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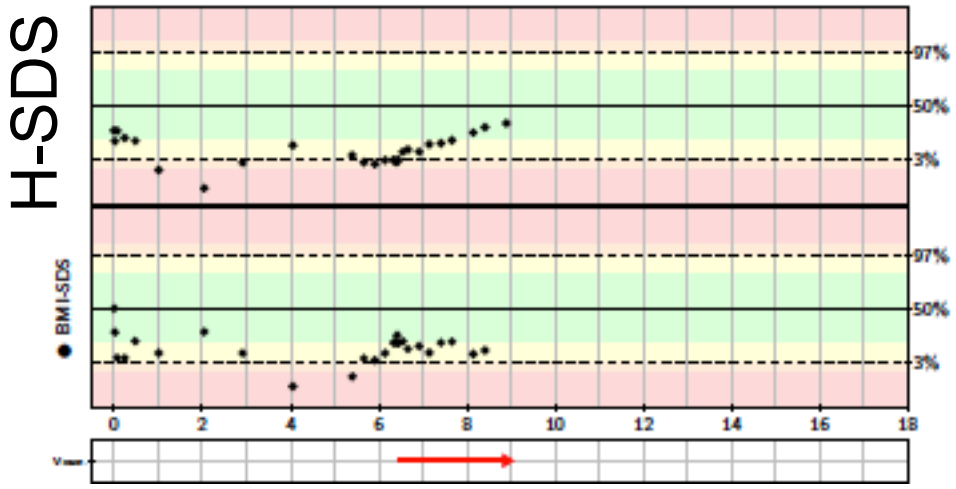
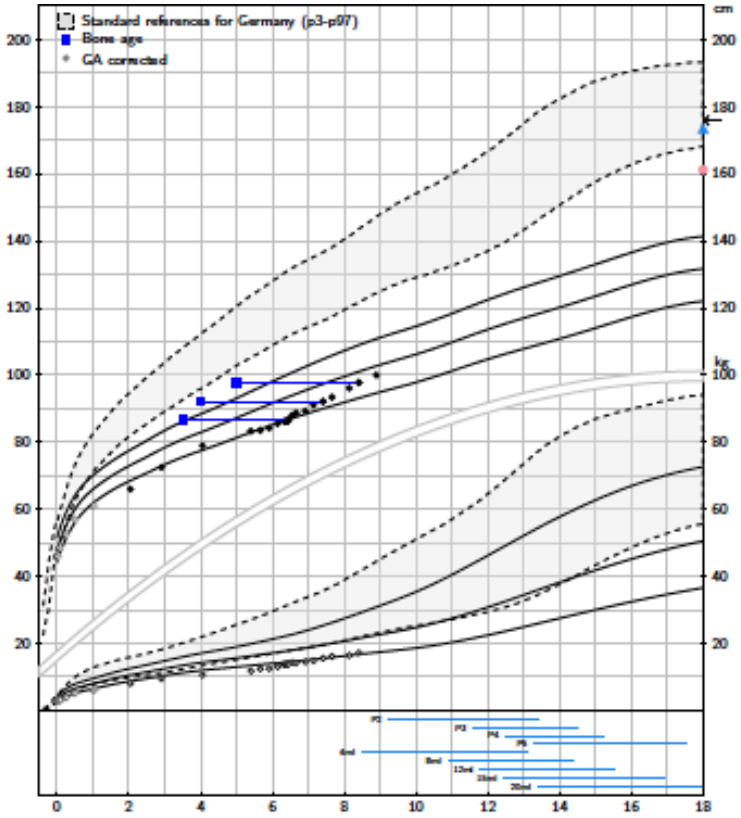
Graphical Visualization – CrescNet©

Disease-related references

Merker A et al.: *Growth in achondroplasia: Development of height, weight, head circumference, and body mass index in a European cohort.* Am J Med Genet Part A. 2018; 176A: 1723-1734.





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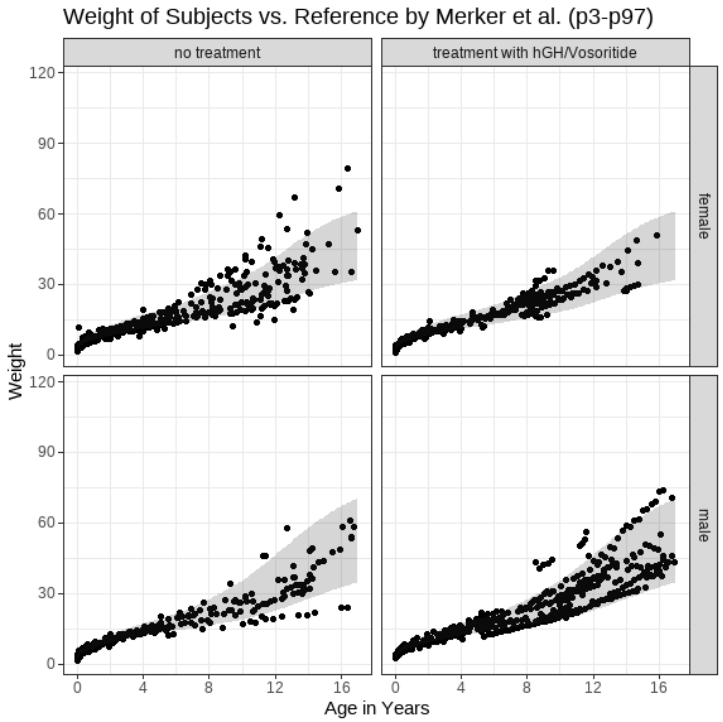
Results | Height and weight



Data from Otto-von-Guericke University (OvGU) Magdeburg, Germany

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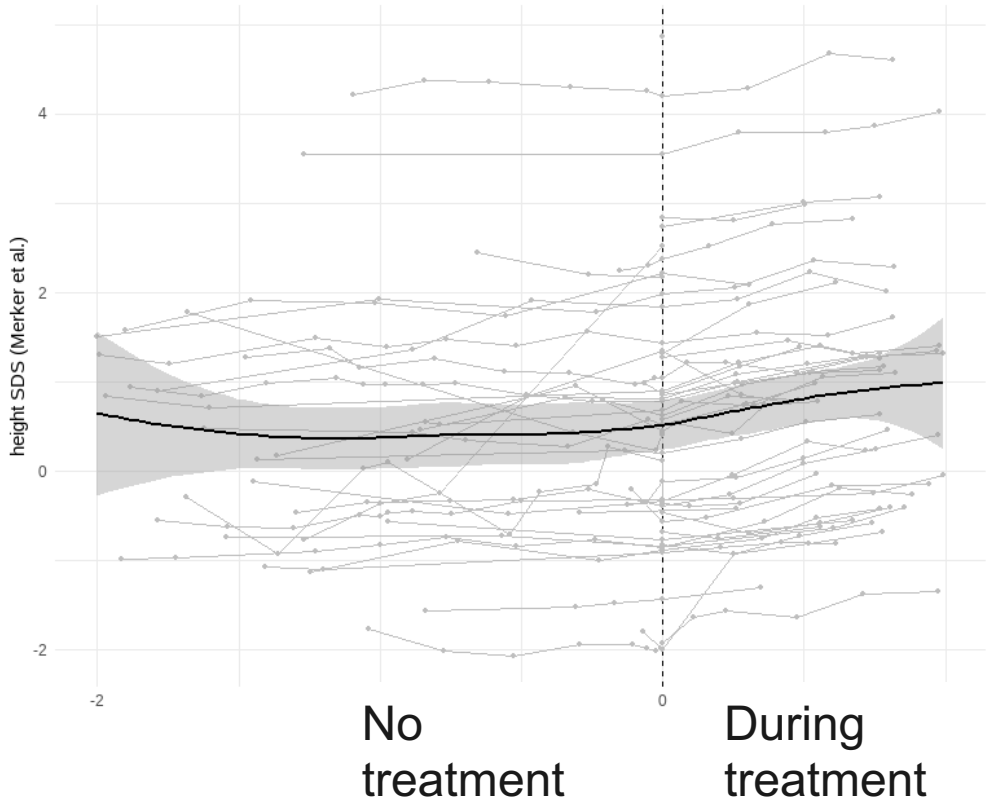
Results | Height SDS vs Treatment



Calculated as Achondro-specific Height-Standard Deviation Score (SDS), data from OvGU Magdeburg, Germany, since 10/2021

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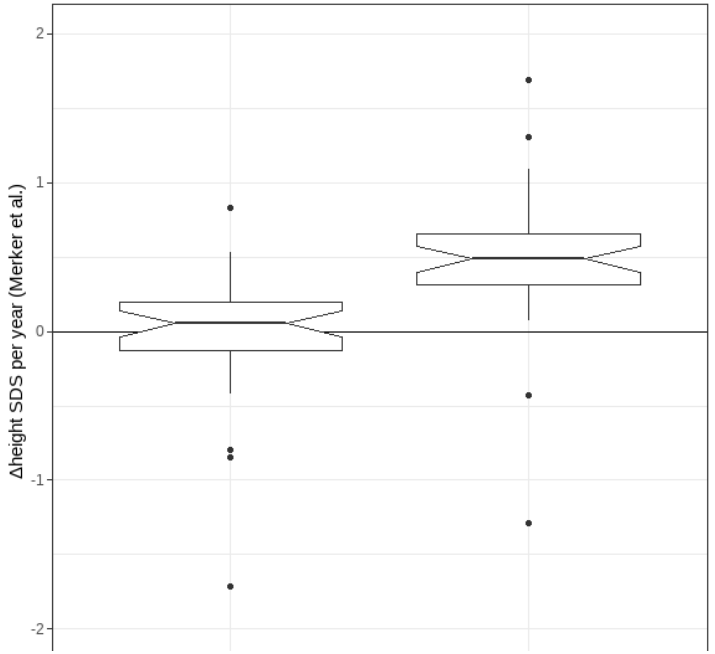
Results | ΔHeight SDS per year vs before and during 1 year treatment



Data from Otto-von-Guericke University (OvGU) Magdeburg, Germany, since 10/2021

Conclusions in RWE

- ✓ Prospective standardized monitoring by real-time data collection enables evaluation of standard of care (SoC)
- ✓ QR-code to patients for documentation of milestones, mobility and pain score (STEMS), QoL-questionnaires
- ✓ Severity of co-morbidities :AFMS-Score of cervico-medullary compression, bone deformities (intercondylar distance, intermaleolar distance, tibiofemoral angle)
- ✓ Bone age:
  - Retardation >> acceleration
  - Low accuracy of Greulich/ Pyle method in bone dysplasia
- ✓ Response to vosoritide: 1st year ΔH-SDS equals 0.5 SDS