Nordiskt center för genterapi mot Metakromatisk leukodystrofi (MLD)

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NORDISKT CENTER FÖR GENTERAPY MOT MLD

Current Qualified Treatment Centers

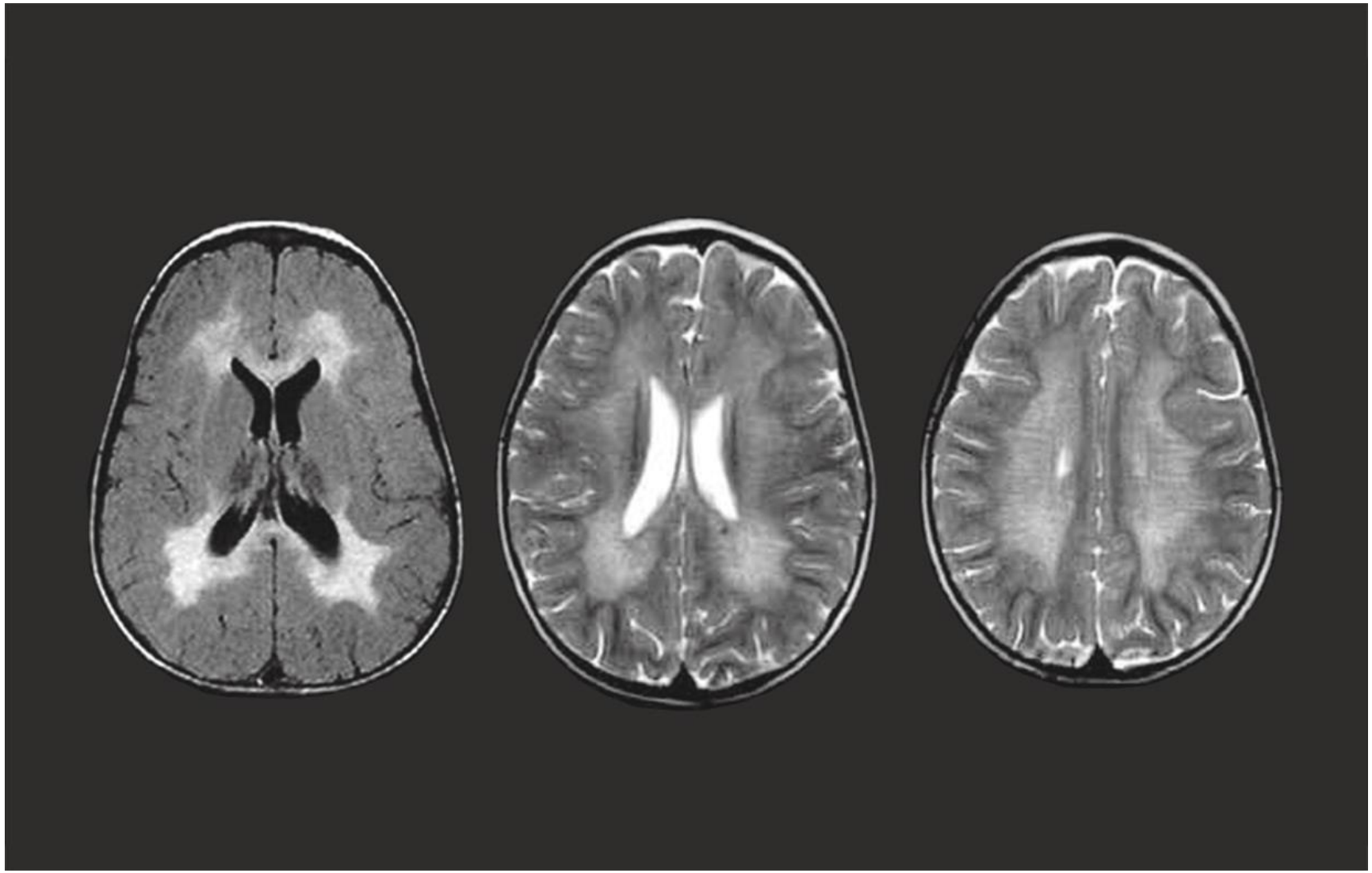
Libmeldy

AUTHORISED
This medicine is authorised for use in the European Union.

Autologous CD34+ cells encoding ARSA gene

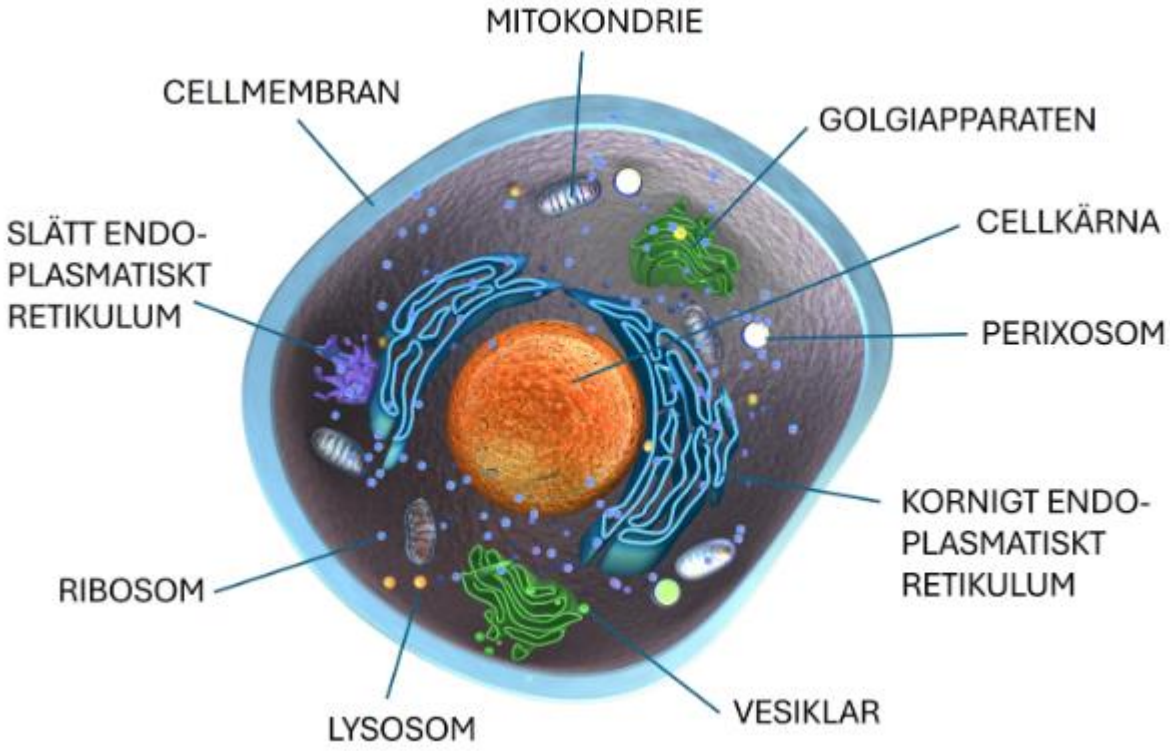
Dominik Turkiewicz, överläkare inom onkologi, Josefina Dykes, medicinskt ansvarig för blodstamceller vid Medicinsk service, Maria Forsgren, överläkare inom barnmedicin, och Erik Eklund, överläkare inom barnmedicin, har arbetat tillsammans för att genomföra den första genterapin mot MLD vid Skånes universitetssjukhus.

Metakromatisk Leukodystrofi (MLD)

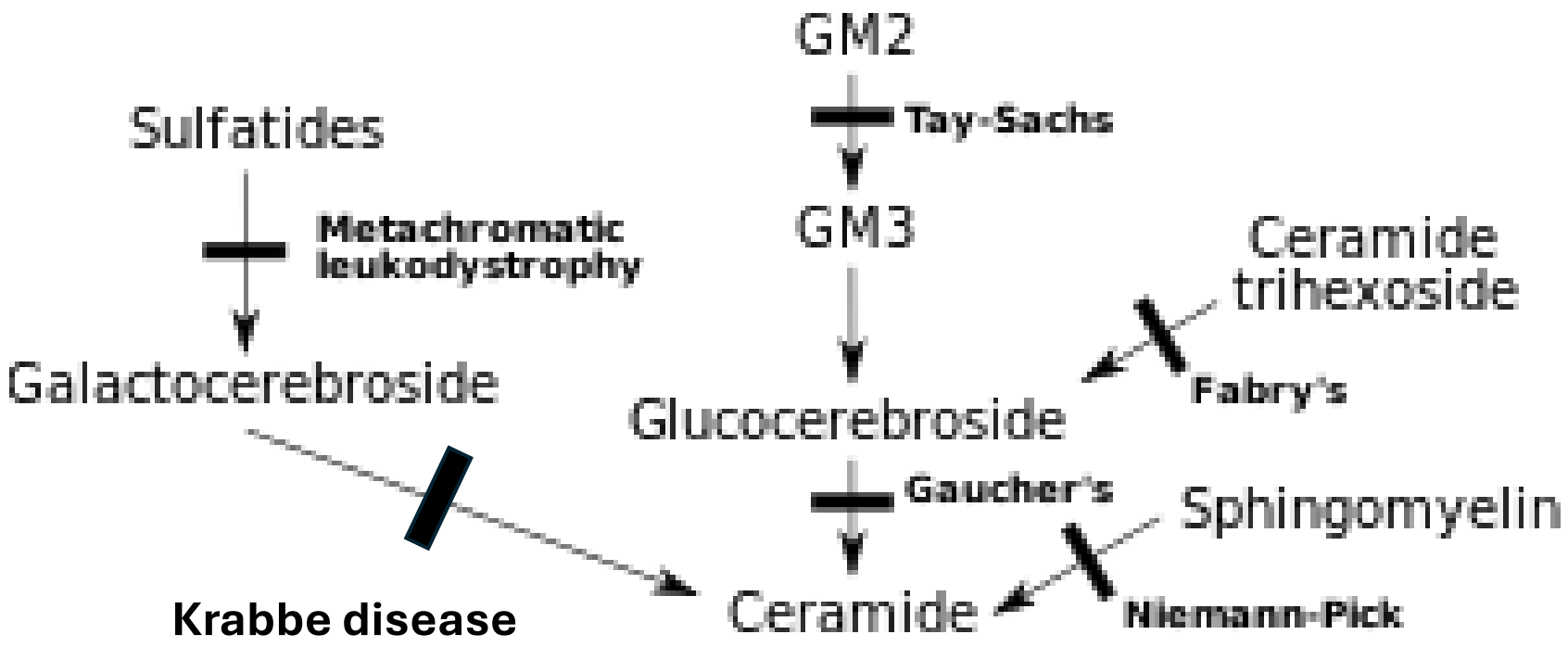


MLD i korthet

- Lysosomal sjukdom
- (1)-2/100,000 födda i Norden
- Patogena varianter in ARS-genen (Arylsulfatas A)
- Kan inte bryta ner sulfatider i myelinproducerande celler i hjärnan (men också perifera nerver, lever, galla, njurar).
- Ansamling av sulfatider → demyelinisering



Sphingolipidoses



(After Knud Krabbe, Danish neurologist)

Fyra subtyper: late infantile (LI), early juvenile (EJ), late juvenile (LJ) och adult.

LI < 2,5 år, EJ 2,5-6 år, LJ 6-16 år, adult >16 år

Sen infantil form: LI

- Vanligaste formen
- Debut innan 2,5 års ålder med motorikproblem, spasticitet och/ eller neuropati
- Snabbt progredierande med förlust av talfunktion, muskelfunktion, syn
- Överlever i snitt 5 år efter diagnos

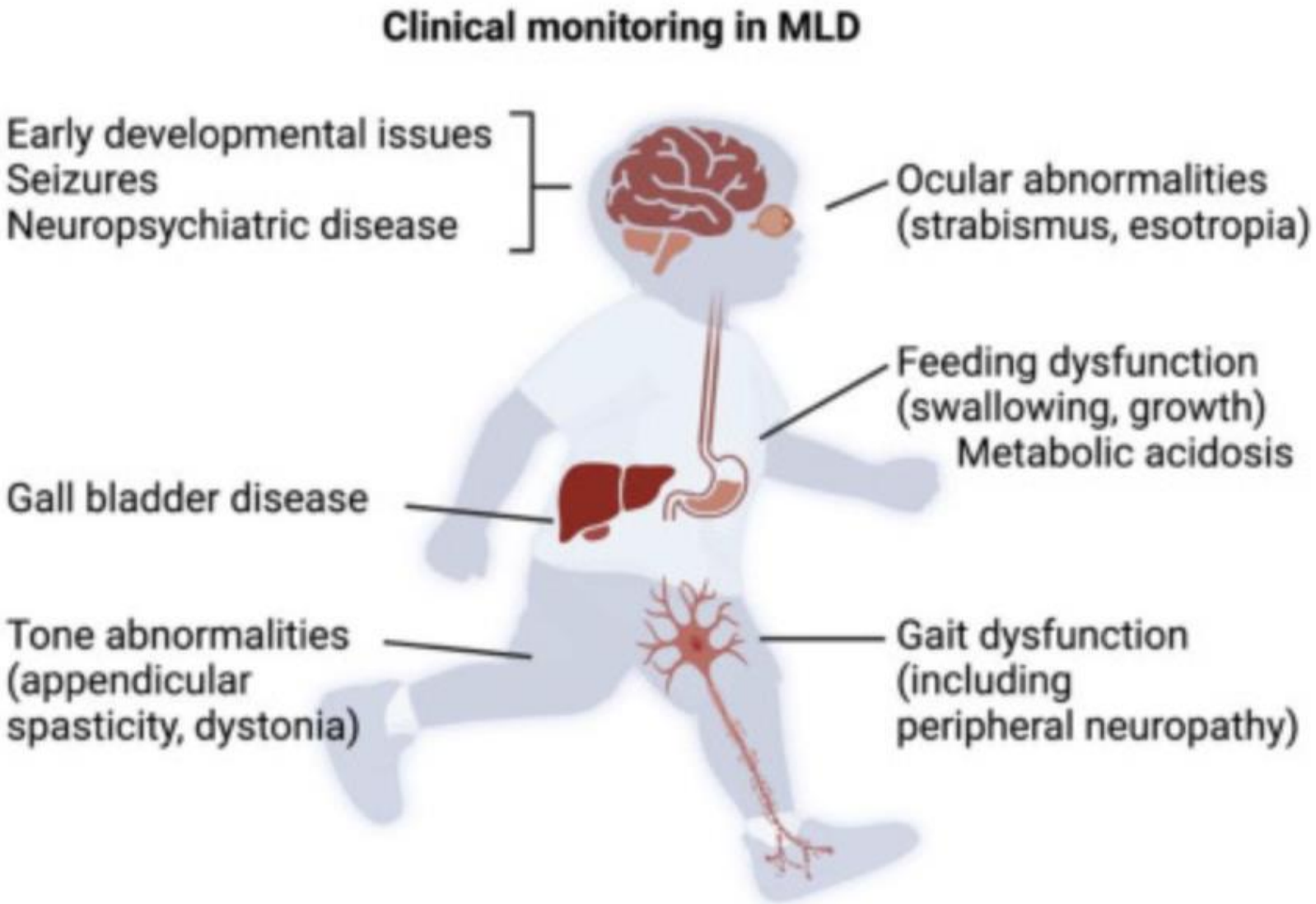
Juvenil form (EJ + LJ)

- Debut mellan 3-16 år(tidig 3-6, sen 7-16)
- Beteendeförändringar
- Hälta, motorikproblem
- Överlevnad mindre än 20 år efter symptomdebut

Vuxenform

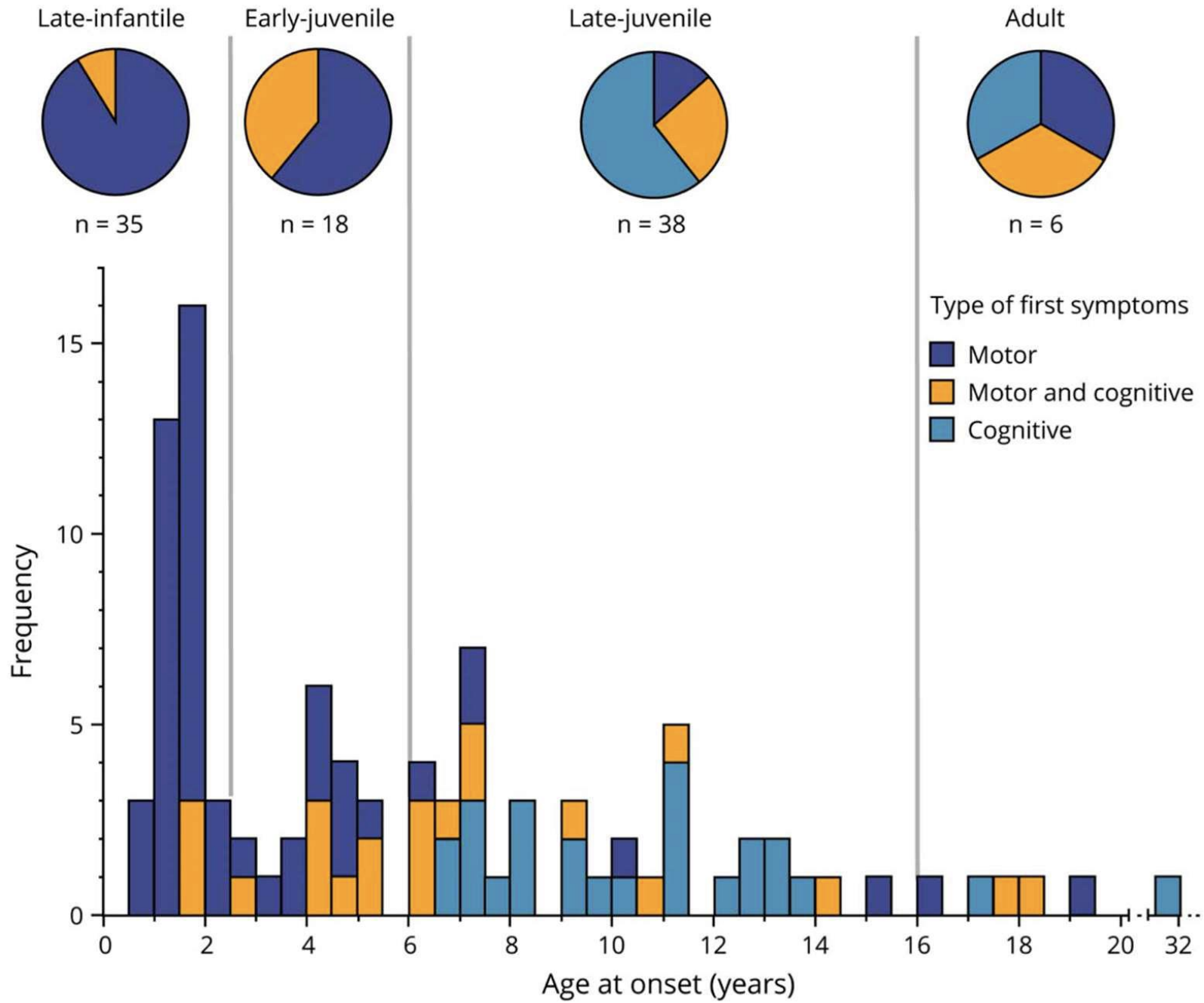
Debut efter 16 år långsamt
Beteende och psykiatriska symptom, missbruk,
inlärningssvårigheter
Psykotiska symptom
Går i skov och tappar succesivt
Kan över leva flera decennier

A.



Adapted from Adang et al, 2024, Cytotherapy

” Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States”


Late-infantile
Early-juvenile
Late-juvenile
Adult
n = 35
n = 18
n = 38
n = 6
Type of first symptoms
Motor
Motor and cognitive
Cognitive
Frequency
0
5
10
15
0
2
4
6
8
10
12
14
16
18
20
32
Age at onset (years)

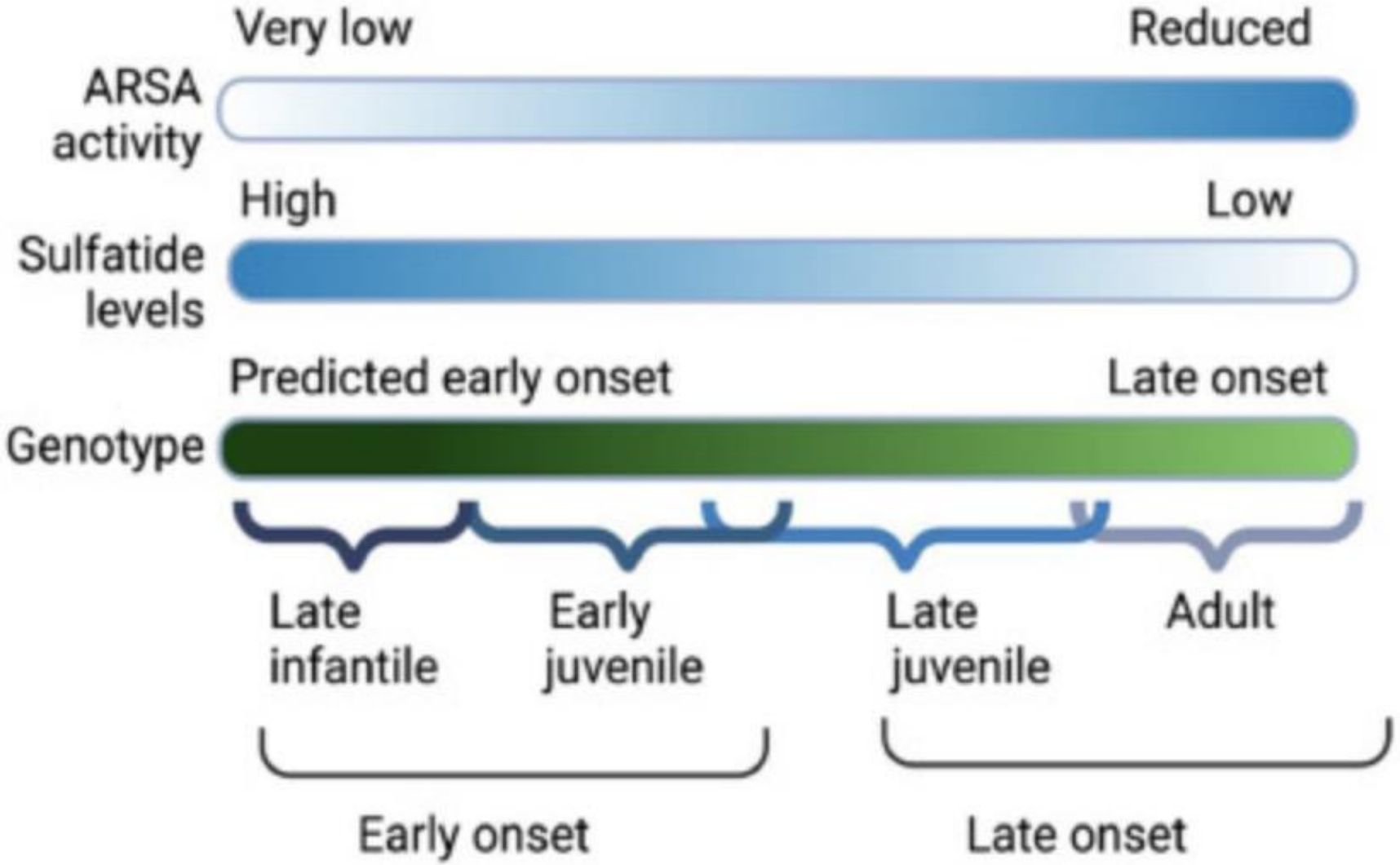
Hur ställer vi diagnosen?

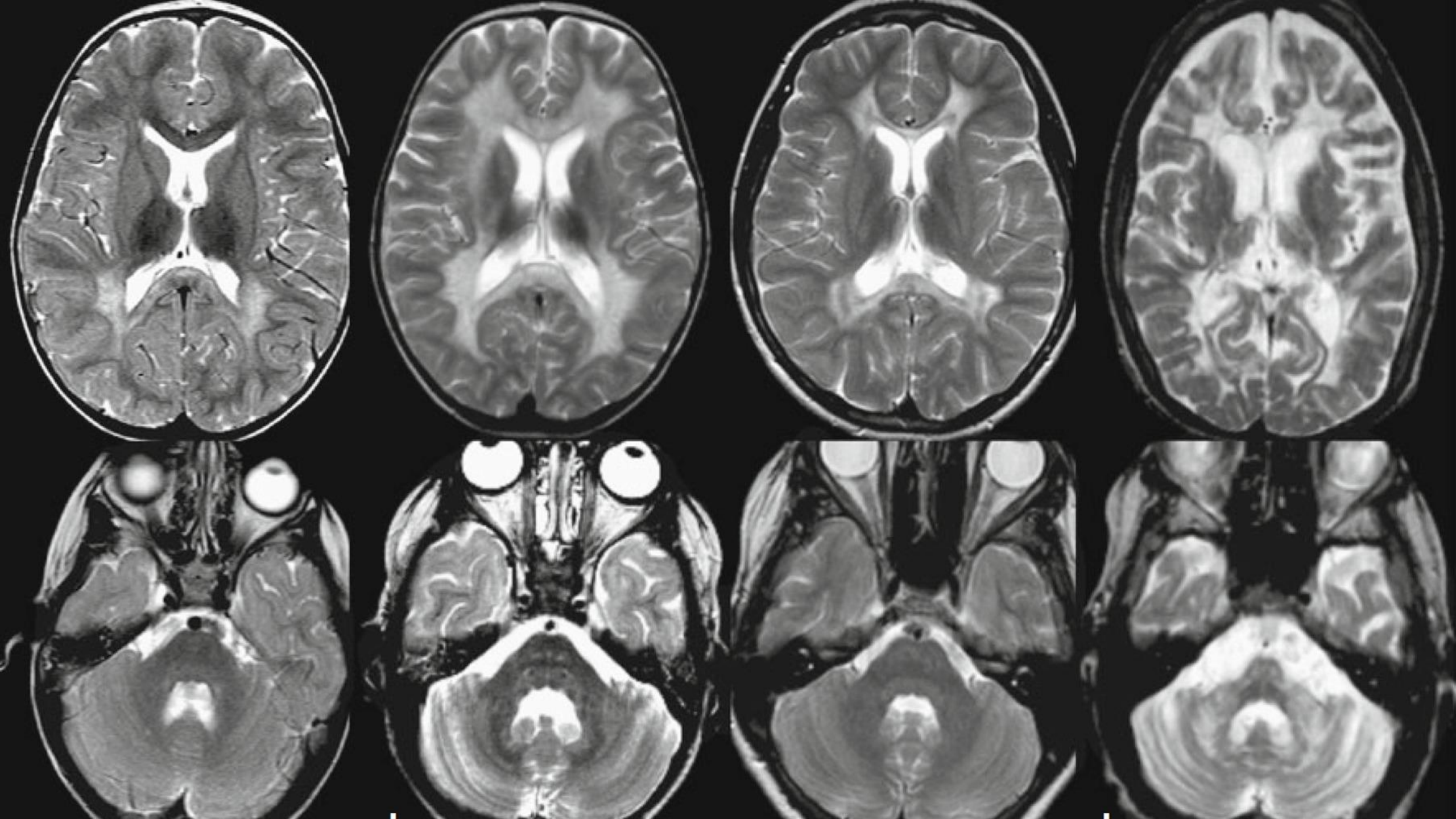
- ARSA enzymaktivitet (leukocyter el fibroblaster)
- Urin sulfatider
- Genetik (pseudo-brist)

- Magnetkameraundersökning
- Neurografi

< 1%

5-20 %


Very low
Reduced
ARSA activity
High
Low
Sulfatide levels
Predicted early onset
Late onset
Genotype
Late infantile
Early juvenile
Late juvenile
Adult
Early onset
Late onset



Tidigare standard of care (SoC)

- LJ och vuxen – HSCT
- LI och EJ – stödjande, symptomatisk

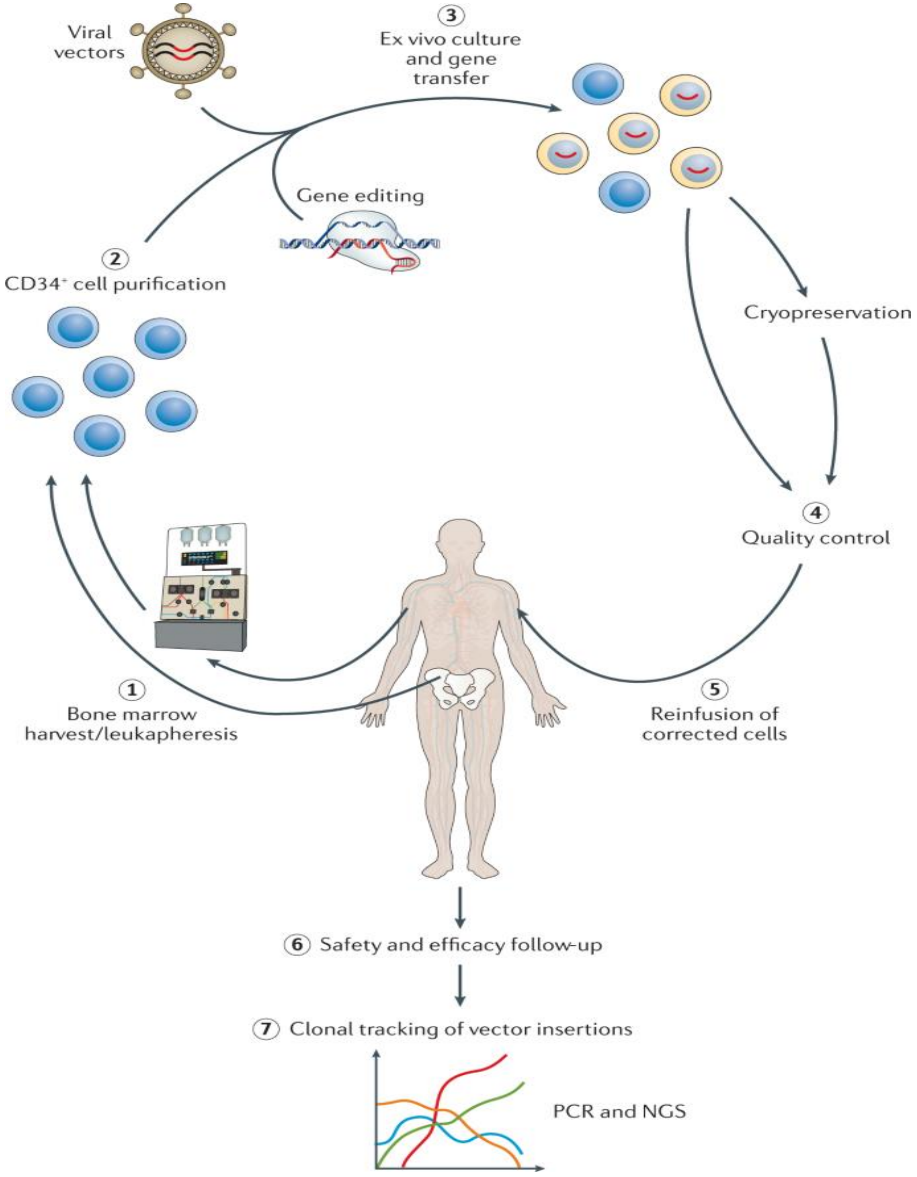
The Lancet
Volume 399, Issue 10322, 22–28 January 2022, Pages 372-383

Articles

Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access

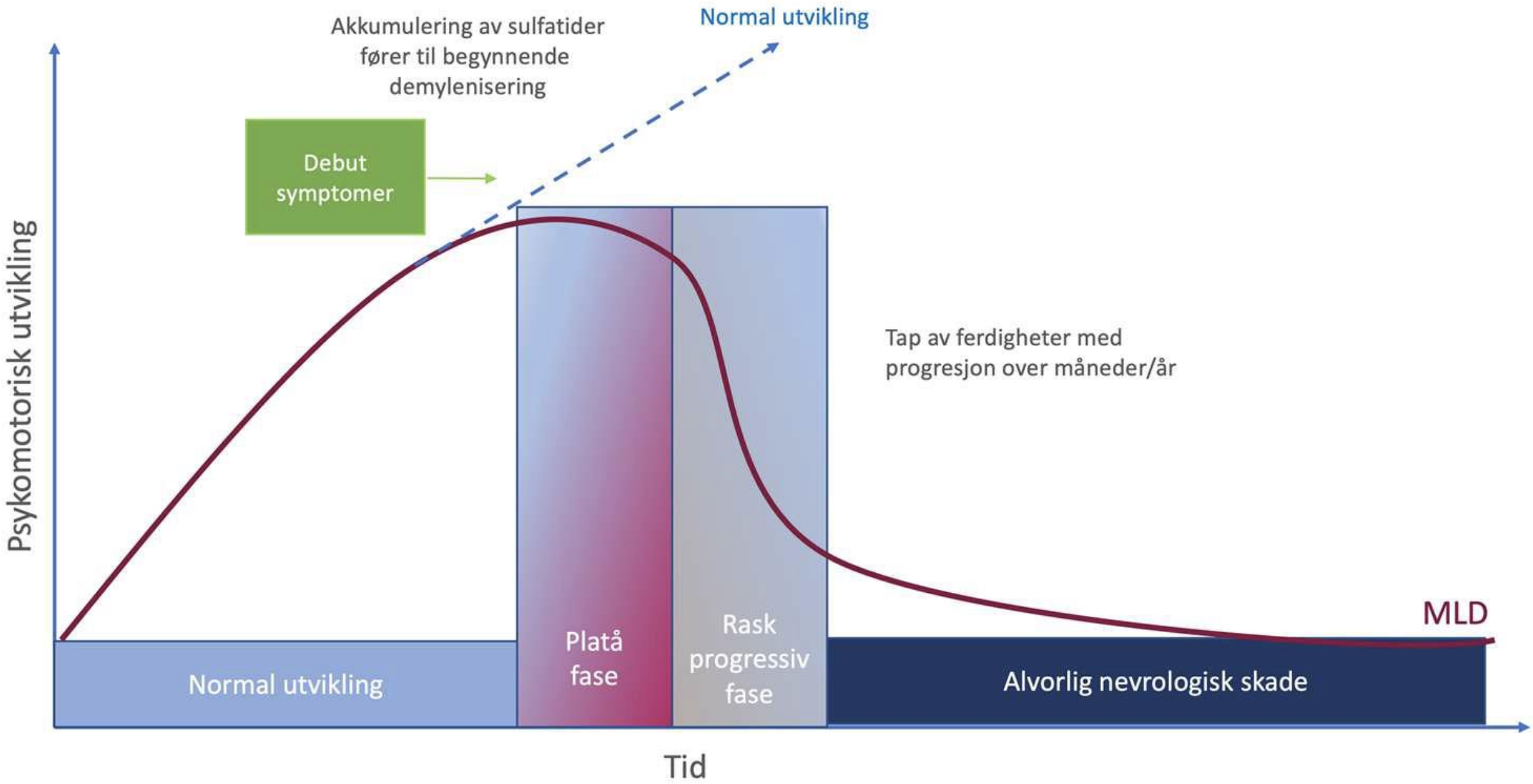
Francesca Fumagalli MD [a b c *], Valeria Calbi MD [a b *], Maria Grazia Natali Sora MD [c], Maria Sessa MD [a p], Cristina Baldoli MD [e], Paola Maria V Rancoita PhD [j k], Francesca Ciotti MSc [b], Marina Sarzana MSc [b], Maddalena Fraschini MSc [b], Alberto Andrea Zambon MD [c], Serena Acquati PhD [a], Daniela Redaelli MSc [a], Vanessa Attanasio MSc [a], Simona Miglietta MSc [a], Fabiola De Mattia MSc [a], Federica Barzaghi MD [a b], Francesca Ferrua MD [a b], Maddalena Migliavacca MD [a b], Francesca Tucci MD [a b], Vera Gallo MD [a b]…Prof Alessandro Aiuti MD [a b k †]

Ex vivo gen-terapi med autologa stem celler (CD34-pos)



TID TILL AKTIV ENZYMPRODUKTION I HJÄRNAN

6-12 MÅNADER


Akkumulering av sulfatider fører til begynnende demylenisering
Normal utvikling
Debut symptomer
Psykomotorisk utvikling
Tap av ferdigheter med progresjon over måneder/år
MLD
Normal utvikling
Platå fase
Rask progressiv fase
Alvorlig nevrologisk skade
Tid

Vilka behandlas idag?

Presymptomatisk LI och EJ

Tidig symptomatisk EJ

Presymptomatisk - definition

No signs of CNS symptoms

MR-changes and neurography patologies as well as polyneuropathy may be ok.

Gall bladder polyposis ok

Early symptomatic EJ

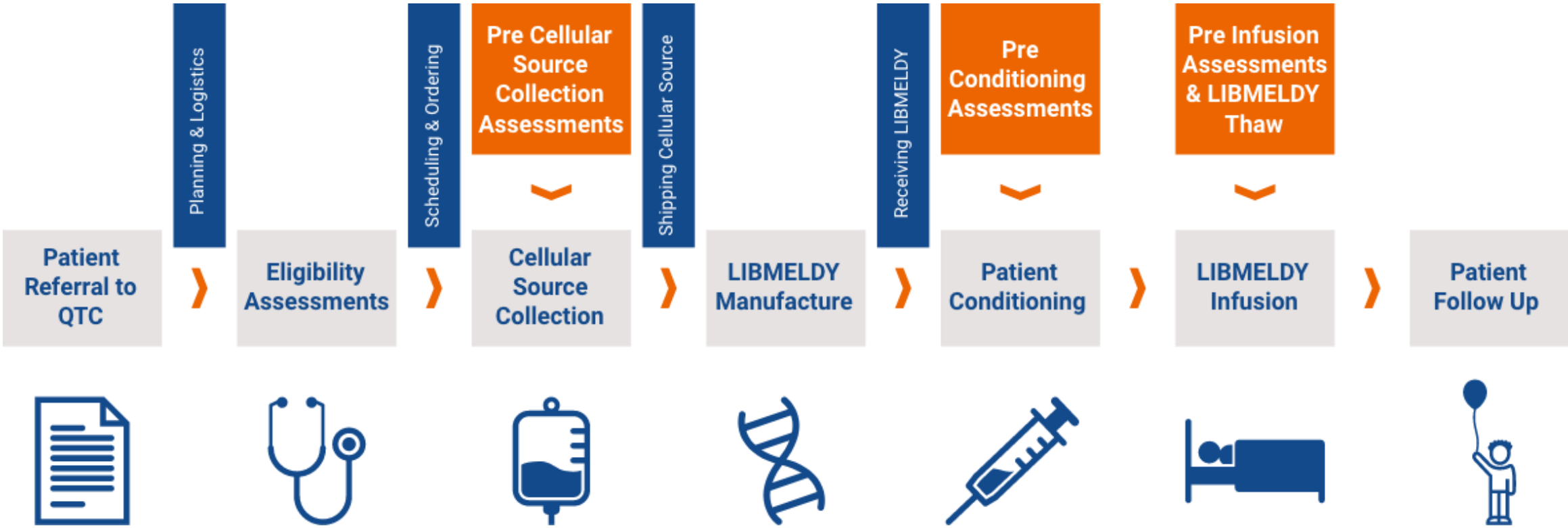
+ IQ > 85

Gross Motor (GMFC-MLD)	
M0	Walking without support with quality and performance normal for age
M1	Walking without support but with reduced quality of performance, i.e. instability when standing or walking
M2	Walking with support; walking without support not possible (fewer than 5 steps)
M3	Sitting without support **and** locomotion such as crawling or rolling; walking with our without support not possible
M4	Sitting without support but no locomotion **or** sitting without support not possible, but locomotion such as crawling or rolling
M5	No locomotion nor sitting without support, but head control is possible
M6	Loss of any locomotion as well as loss of any head and trunk control
Expressive Language (ELFC-MLD)	
E0	Communicates in complete sentences at a quality and performance normal for age
E1	Communicates in complete sentences with reduced quality of performance for age
E2	Cannot communicate complete sentences, but able to use 2 word phrases
E3	Cannot communicate 2-word phrases, but able to use single, meaningful words/ideas
E4	Complete loss of expressive language

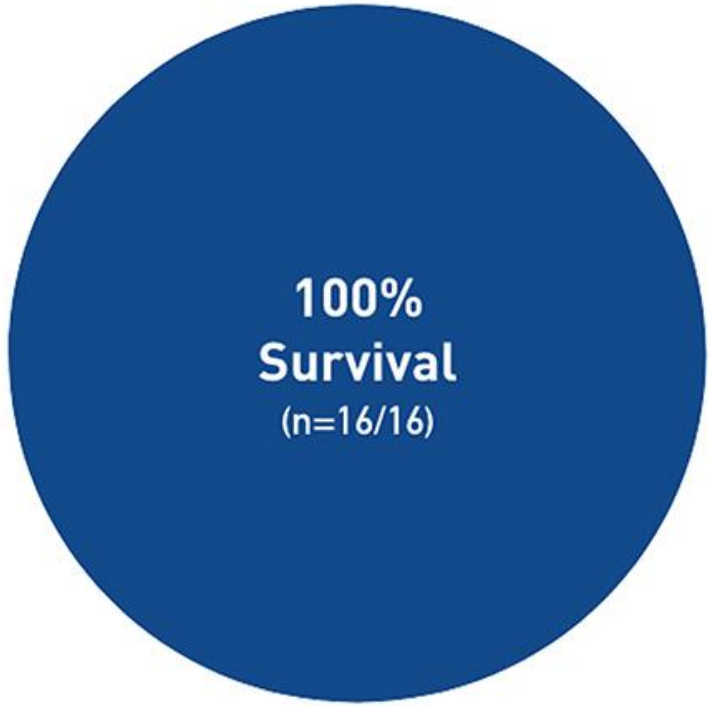
Tid är hjärna!

- Få (om några) LI-MLD patienter som är diagnostiserade kliniskt är behandlingsbara.
- Syskon till indexfall
- Mildare MLD
- SCREENING!!!

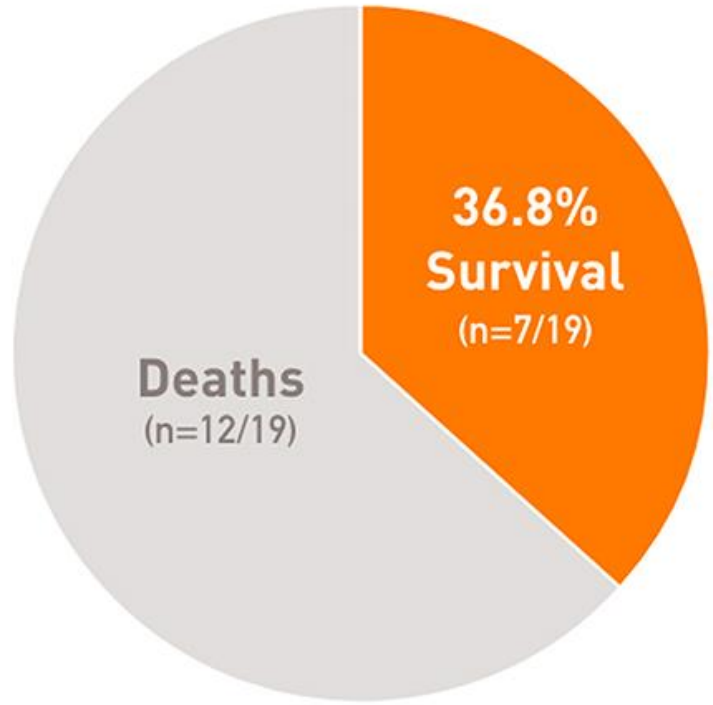
Process


Patient Referral to QTC
Planning & Logistics
Eligibility Assessments
Scheduling & Ordering
Pre Cellular Source Collection Assessments
Cellular Source Collection
Shipping Cellular Source
LIBMELDY Manufacture
Receiving LIBMELDY
Pre Conditioning Assessments
Patient Conditioning
Pre Infusion Assessments & LIBMELDY Thaw
LIBMELDY Infusion
Patient Follow Up

Libmeldy



Natural history

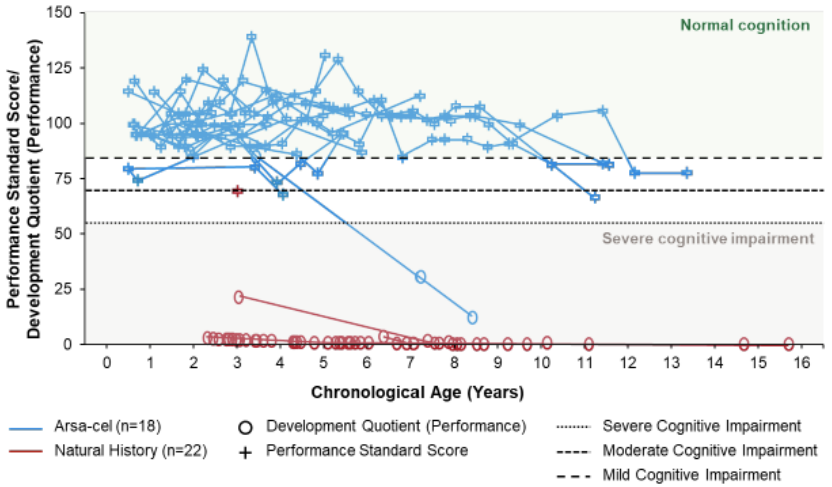


100% survival in LI patients treated with Libmeldy, with an median follow up of 3 years post-treatment (range 0.99 – 7.51)

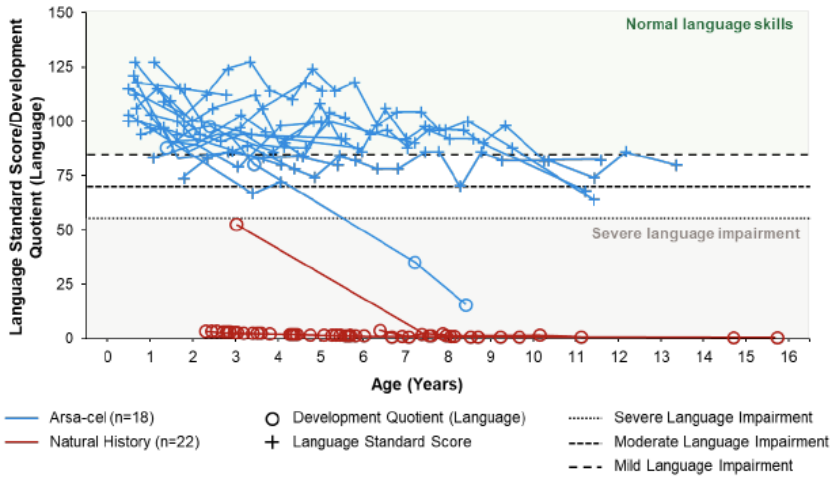
36.8% survival (7/19) in untreated LI patients in the natural history cohort at the time of this analysis

Pre-symptomatic Late Infantile (PSLI) vs. LI Natural History

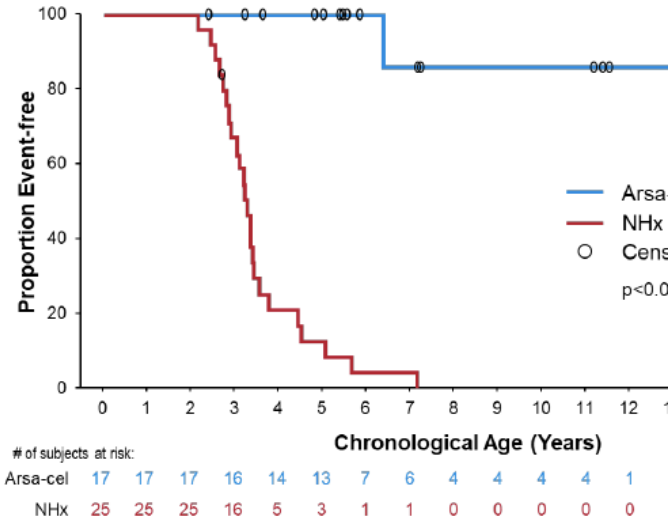
Performance Standard Score / Developmental Quotient



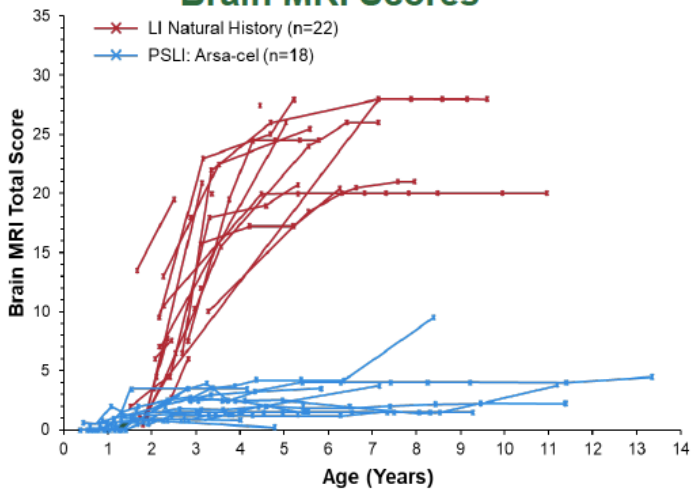
Language Standard Scores / Developmental Quotient



Severe Speech Impairment Free Sur

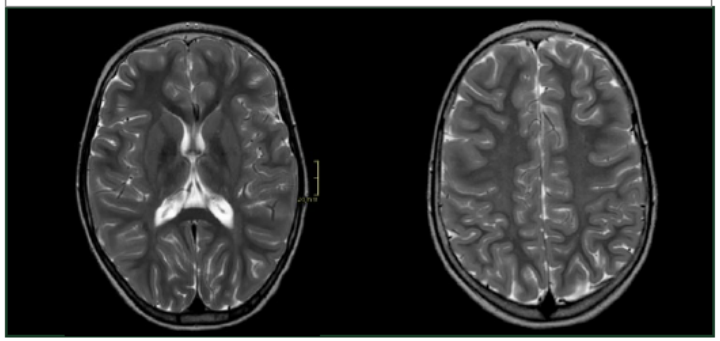


Brain MRI Scores

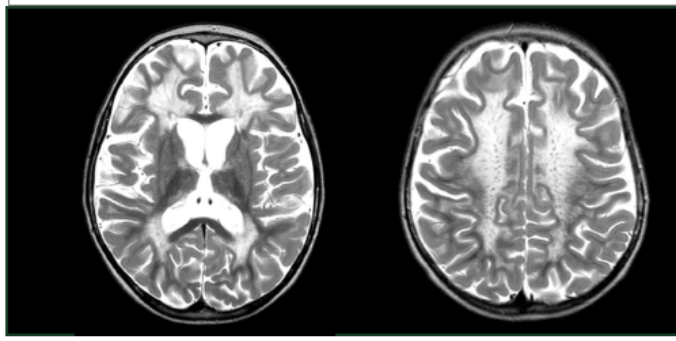


Brain MR Imaging

PSLI Treated Pt.
Age: 10 y.o. – 9 yrs post-GT



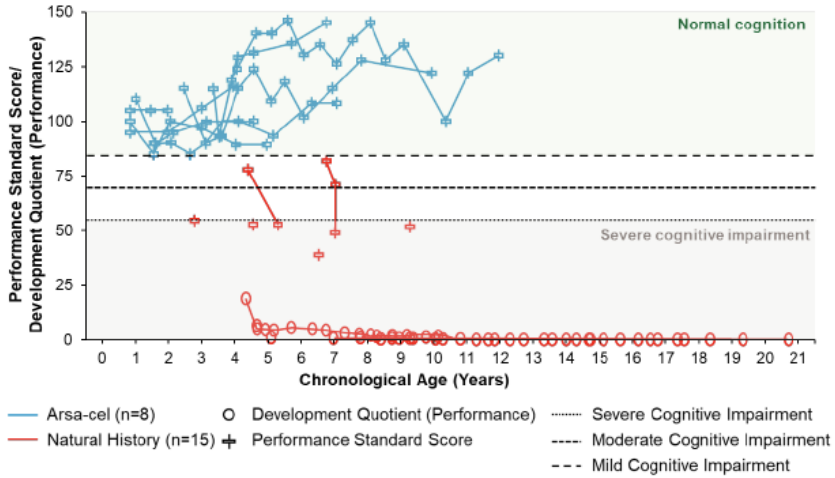
LI Untreated Sib
Age: 56 m.o. – 38 mo post-onset



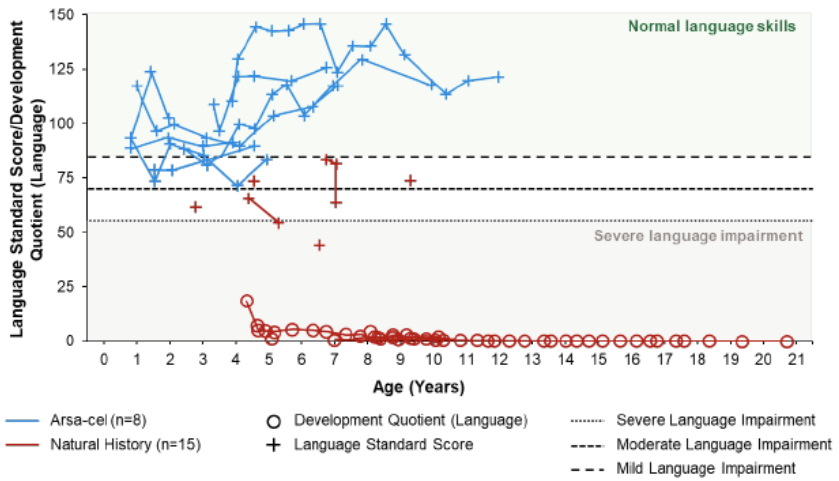
Fumagalli et al, 2024.

Pre-symptomatic Early Juvenile (PSEJ) vs. EJ Natural History

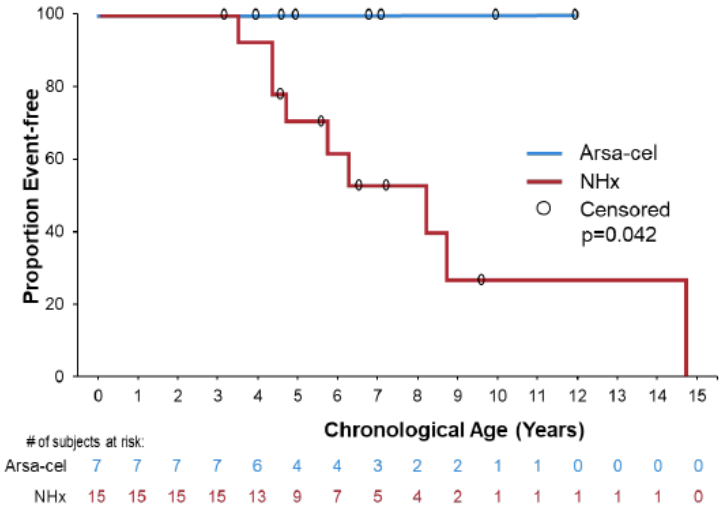
Performance Standard Score / Developmental Quotient



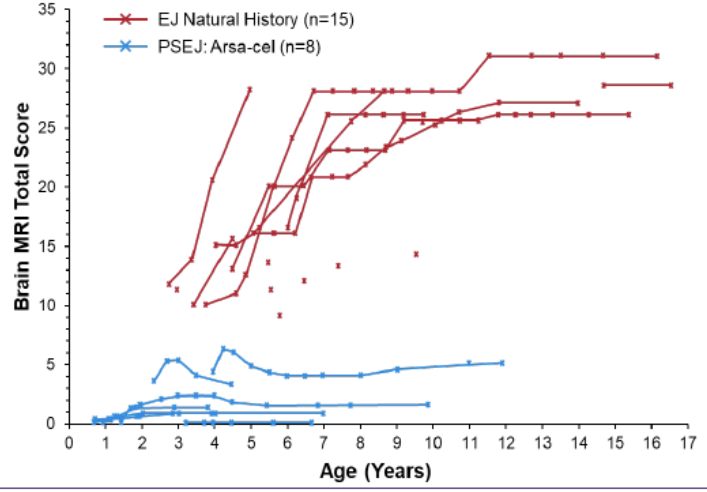
Language Standard Scores / Developmental Quotient



Severe Speech Impairment Free Survival

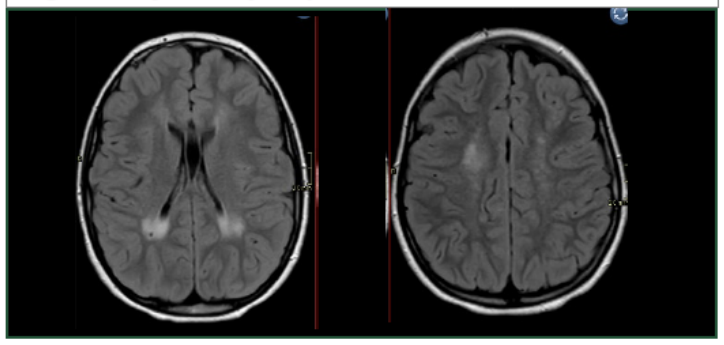


Brain MRI Scores

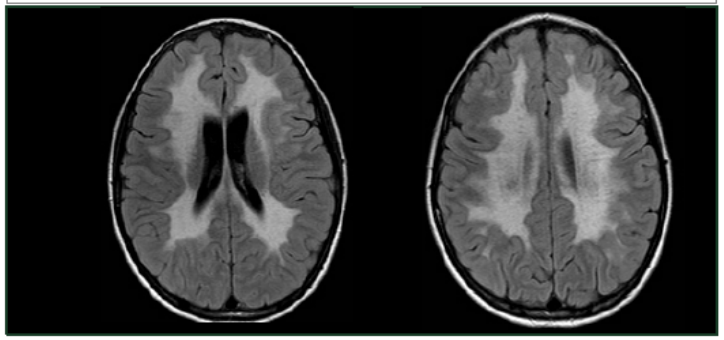


Brain MR Imaging

PSEJ Treated Pt.
Age: 11 y.o. 7 yrs post-GT



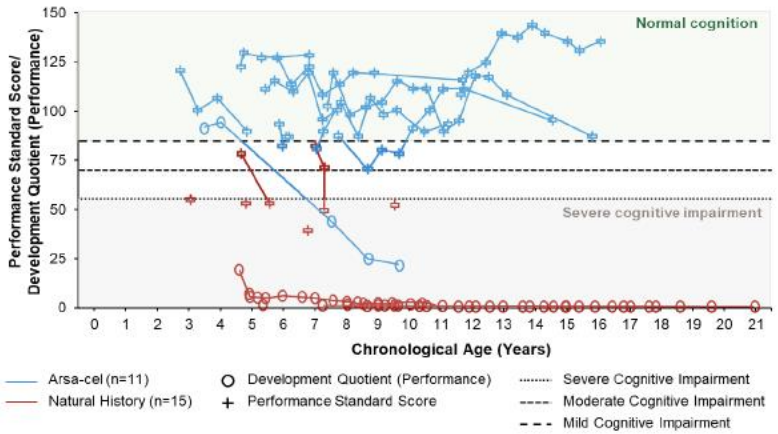
EJ Untreated
Age: 8 y.o.



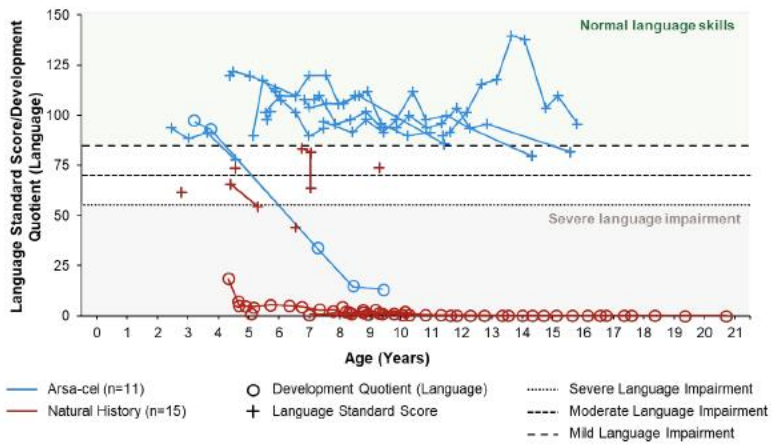
Fumagalli et al, 2024.

Early-Symptomatic Early Juvenile (ESEJ) vs. EJ Natural History

Performance Standard Score / Developmental Quotient



Language Standard Scores / Developmental Quotient



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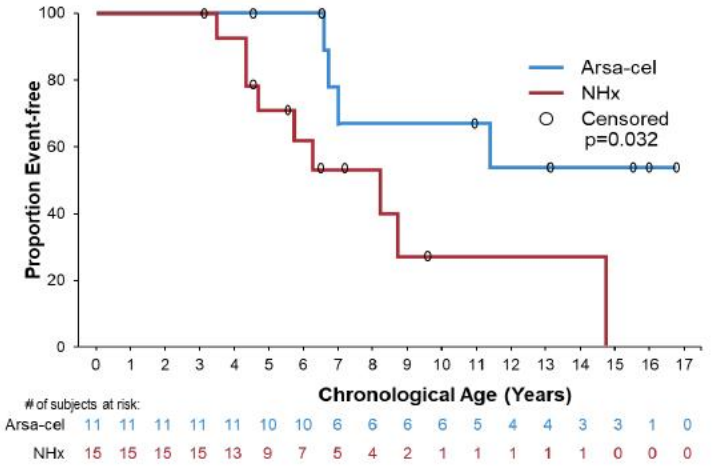
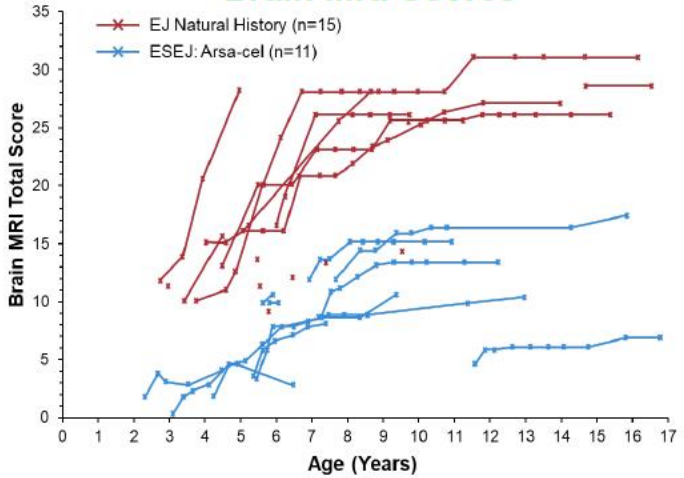
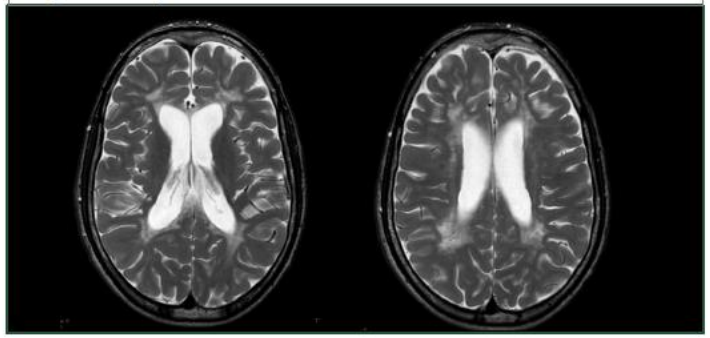


Brain MRI Scores

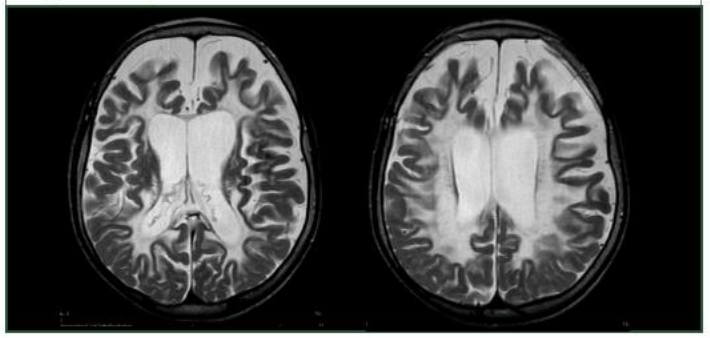


Brain MR Imaging

ESEJ Treated Pt
Age: 14 y.o.



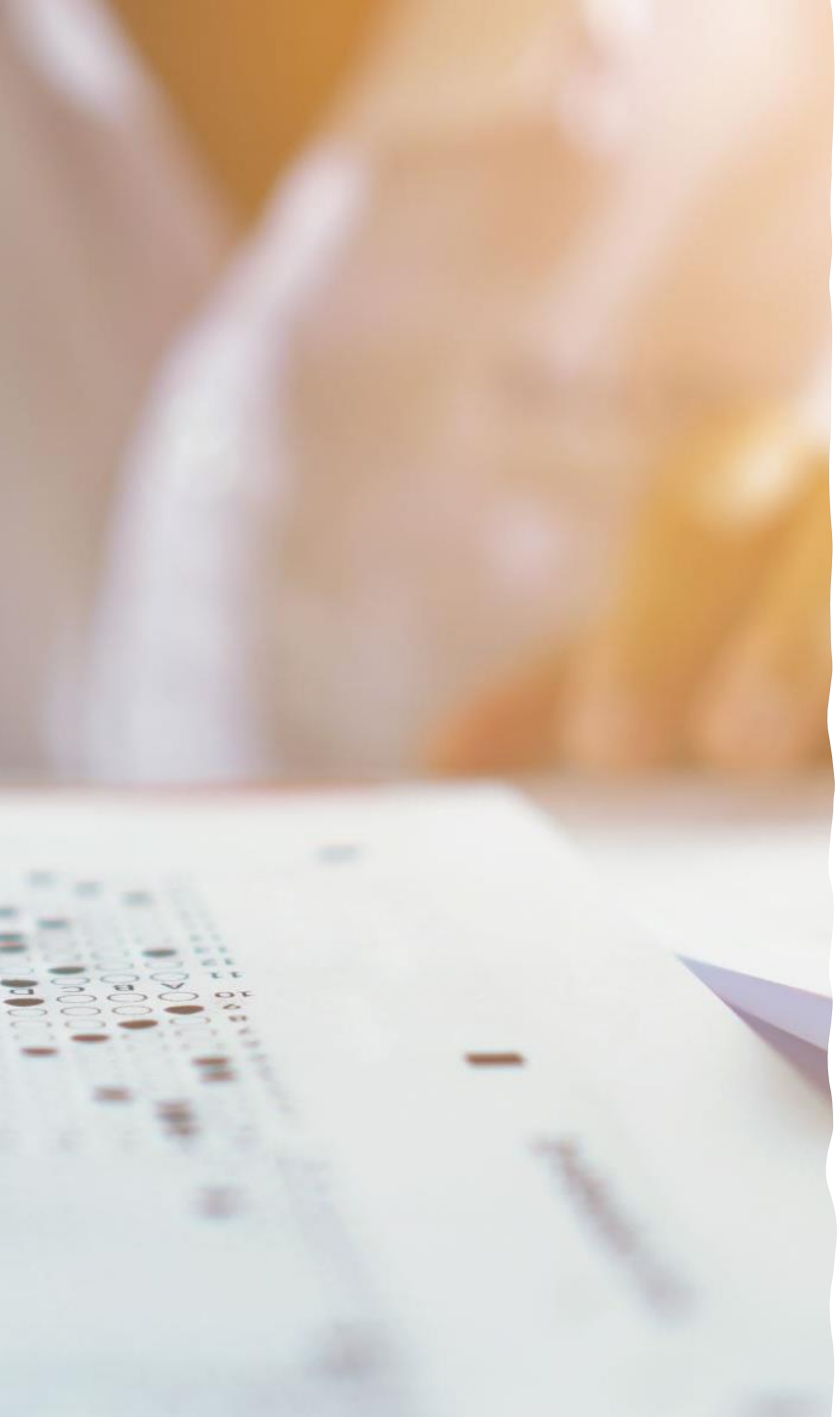
EJ Untreated
Age: 14 y.o.



Fumagalli et al, 2024.

Första patienten

- Pojke född 2016 in Norge. Friska föräldrar, ej släkt
- 2020 första symptom av tilltagande ostadighet.
- Patogena varianter i ARSA (c.465+1G>A/1283C>T), kraftigt reducerad ARSA aktivitet, och förhöjda urin-sulfatides. Diagnos EJ MLD.
- MR: MLD-Loes score 5. Neurografi visar polyneuropathy. IQ 92. Kan gå utan support



Första patienten

- Libmeldy godkändes i Norge Juni 2023.
- GMFC-MLD 1, IQ 92, MR Loes 14.
- Diskuterad i MLDi i juli
- Cellskörd I aug -23 efter mobilisering med G-CSF.
- Celler klara och transplanterades i slutet av oktober -23

Första patient:

- ARSA aktivitet i WBC, 4 veckor efter transplantation: 300 % av normal aktivitet (innan beh < 5 %)
- Motorisk funktion initial lite sämre- nutritionen sämre- spasticitetsutveckling på immobilisering
- 6 mån efteråt förbättrad
- Nu ånyo gångare

Sedan ytterligare 3 patienter

- Pojke född juli-25. Fångades i nyföddhetscreeningen. LI
  - Cellskörd vid knappt 3 mån ålder.
- Pojke född -20. Debut april -26 av ostadighet, spasticitet.
  - Diagnos i juni -26, EJ
  - Cellskörd juli- får tillbaka sina celler om ca 1 vecka
- Pojke född april-26. Fångades i nyföddhetsscreeningen. LI
  - Cellskörd förra veckan. Planerad återgivning om ca 5 v

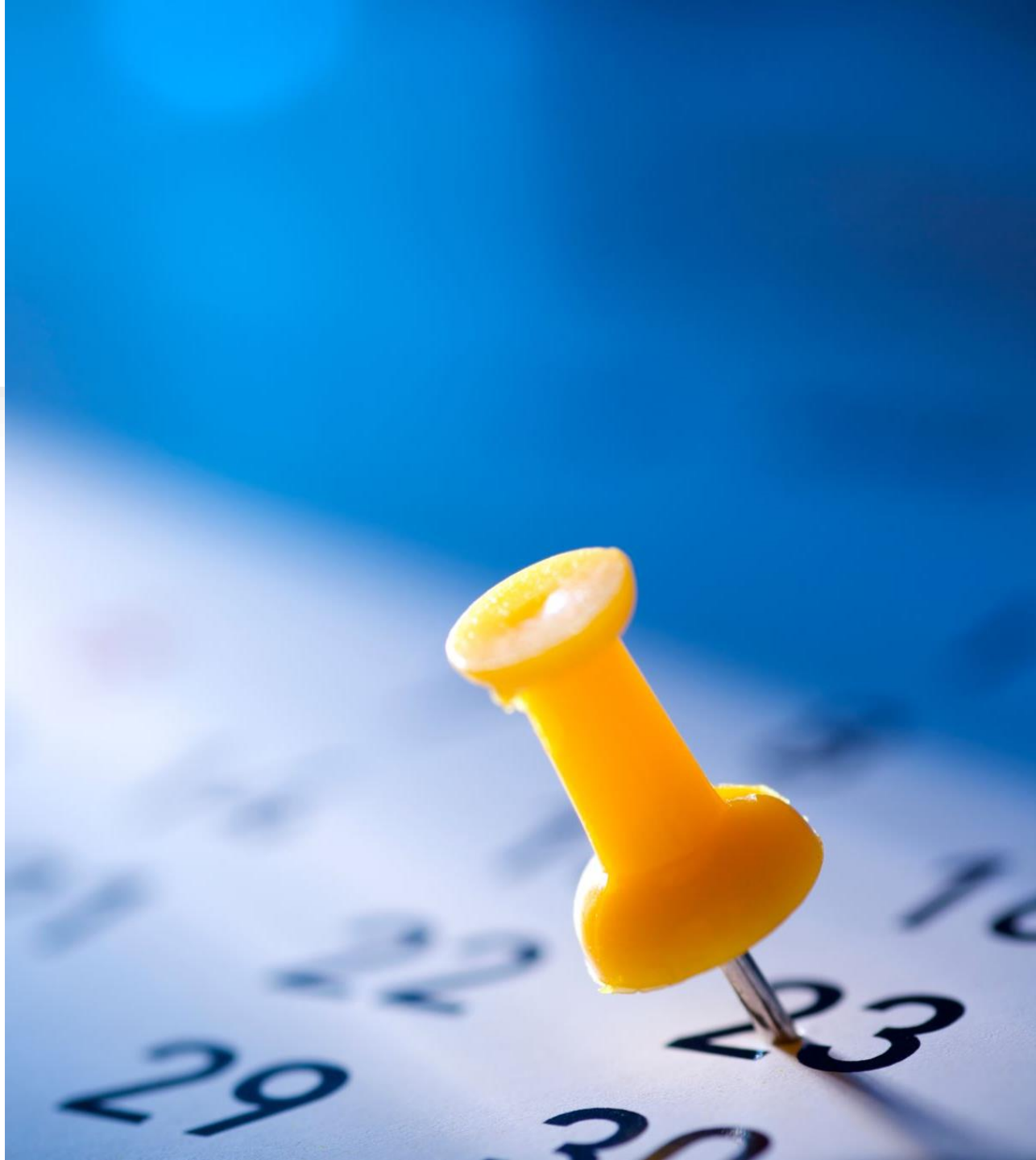
Treatment eligibility panel

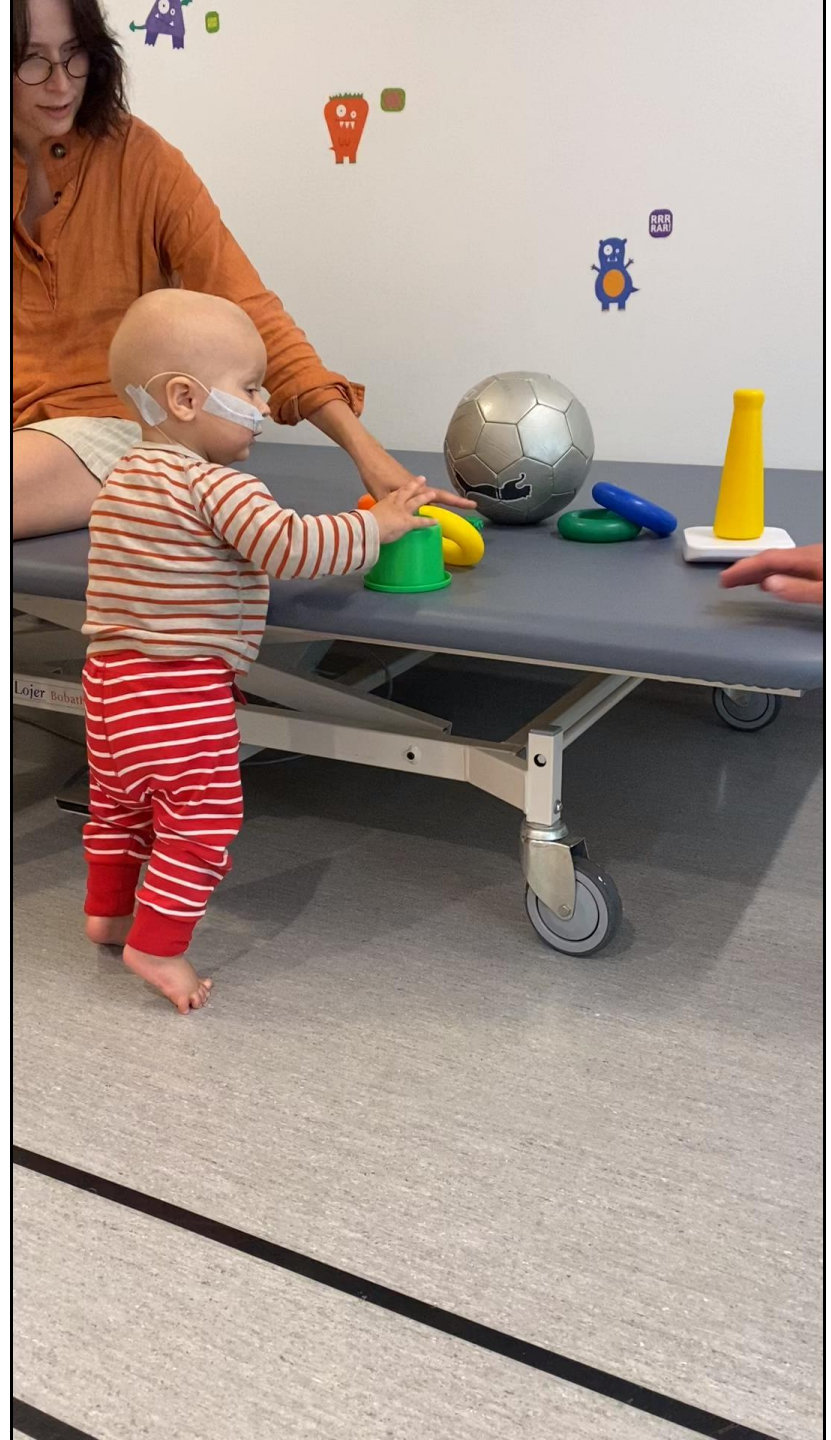
Determining which patients might benefit from treatment and which do not, can be difficult. Therefore, an international MLD treatment eligibility expert panel can be consulted.

Sverige
Expertråd utsett av NT-rådet

Screening i Sverige

- Startar nästa månad!




RRR
RAR!

TACK!

- Maria.jerlhagenforsgren@skane.se