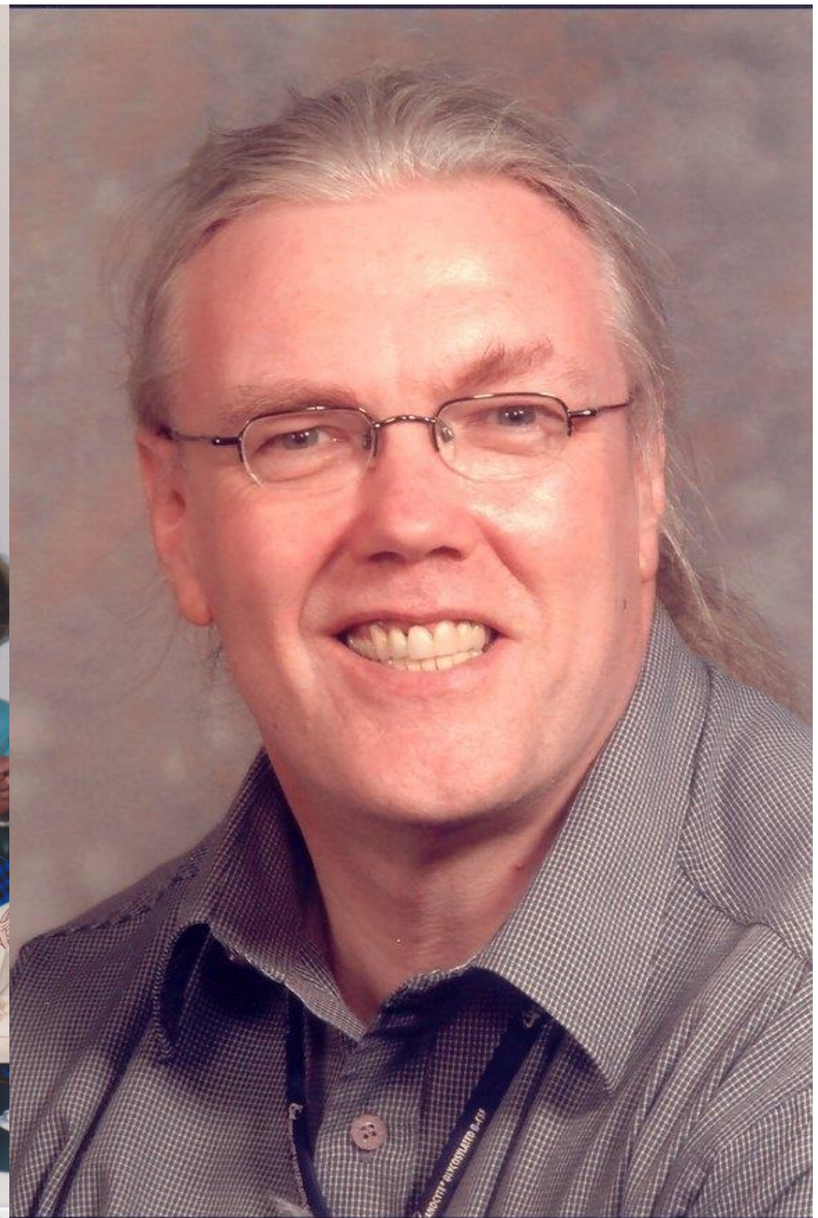
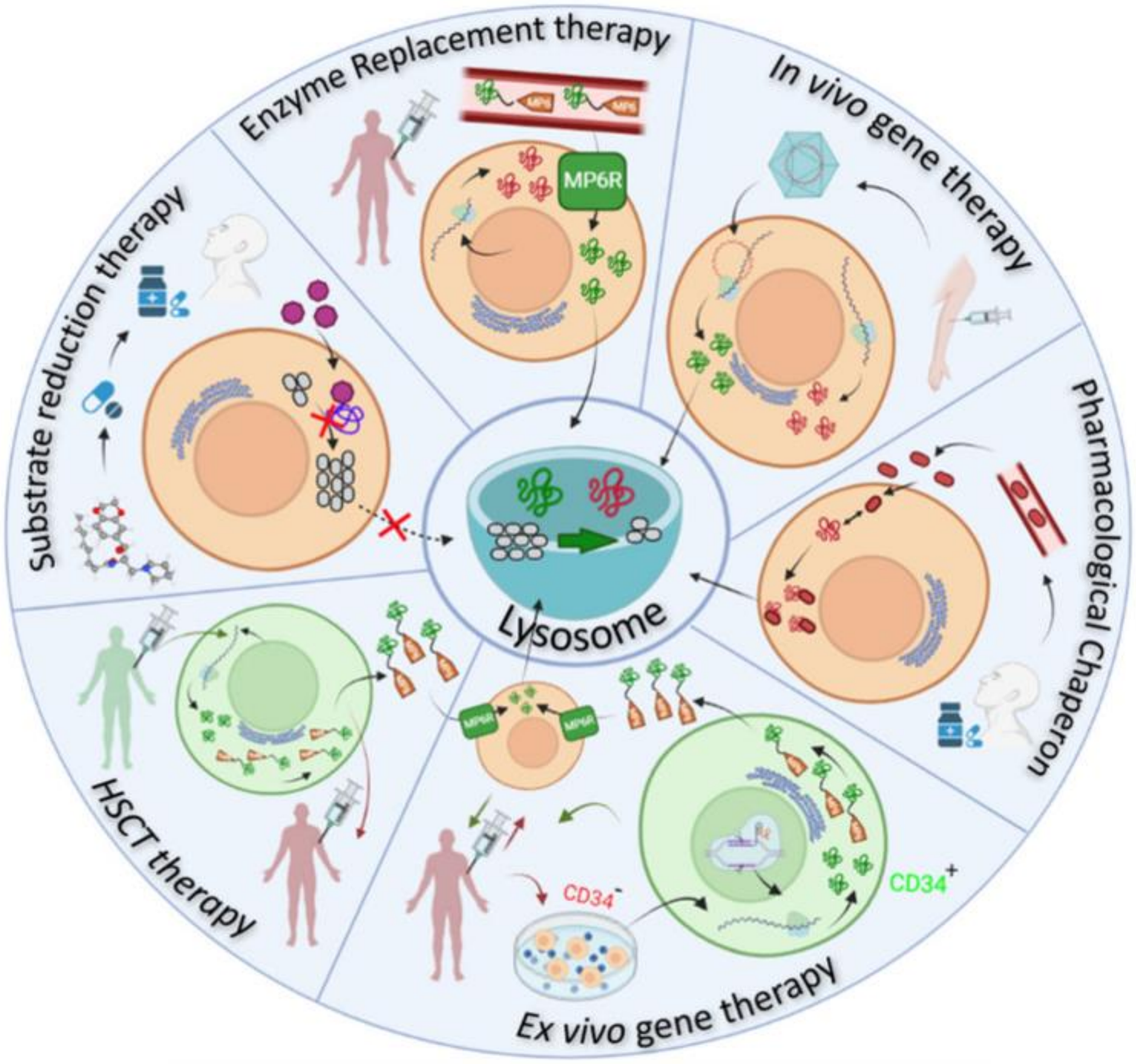
Recent advances in the treatment of lysosomal disorders and their implications to the laboratory

ERNDIM 2024

Maria Jose de Castro, MD PhD
Consultant in Paediatric Inherited Metabolic Disorders
Willink Unit, Manchester centre for Genomic Medicine

The unconventional Professor… Ed Wraith

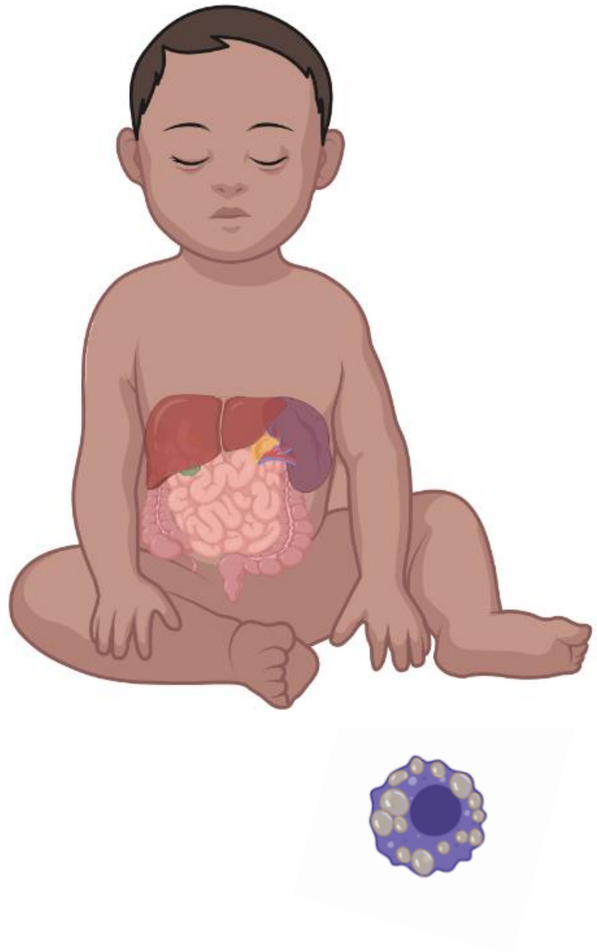




Therapeutic approaches in lysosomal storage disorders. Fernandez-Pereira C et al. Biomolecules. 2021 Dec; 11(12): 1775.

WOLMAN DISEASE

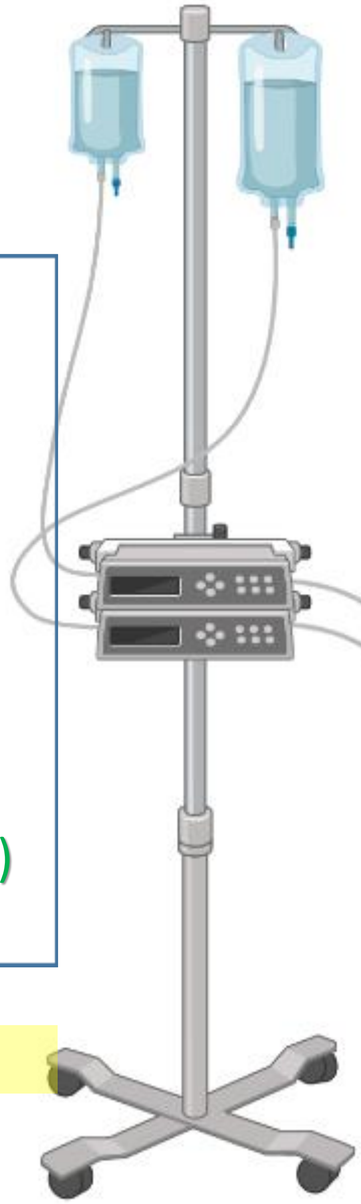
- Lysosomal Storage Disorder due to lysosomal acid lipase deficiency
- Most severe form of LAL-D (early onset and rapid progression)
- Failure to thrive, vomiting, diarrhoea, and hepatosplenomegaly
- Without treatment, infants do not survive beyond 6 months of age
- Sebelipase alfa (Kanuma®) binds to the mannose 6-phosphate receptor and the macrophage mannose receptor and is internalized into the lysosome, catalysing the hydrolysis of cholesteryl and triglyceride esters



KANUMA ® CLINICAL TRIALS

WOLMAN DISEASE VITAL (n=9)	WOLMAN DISEASE CL08 (n=10)
Kanuma® 1-3 mg/kg weekly	Kanuma® 1-5 mg/kg weekly
	Faster dose scalation
	More severe patients
Kaplan-Meier estimates of survival being 67% (to 12 months) and 56% (to 4 years)	Kaplan-Meier estimates of survival being 90% (to 12 months) and 80% (to 3 years)

HYPOTHESIS: Sickest patients may benefit from more frequent dosing



Burton BK, et al. Sebelipase alfa in children and adults with lysosomal acid lipase deficiency: Final results of the ARISE study. J Hepatol. 2022 Mar;76(3):577-587.

Intensive sebelipase alfa (Kanuma®) regimen rescues infants with severe Wolman disease

de Castro MJ, Jones SA, Ghosh A et al.

Wolman disease (WD) is a rare disorder caused by a deficiency in the enzyme lysosomal acid lipase (LAL) that leads to rapid accumulation of lipids in the organs

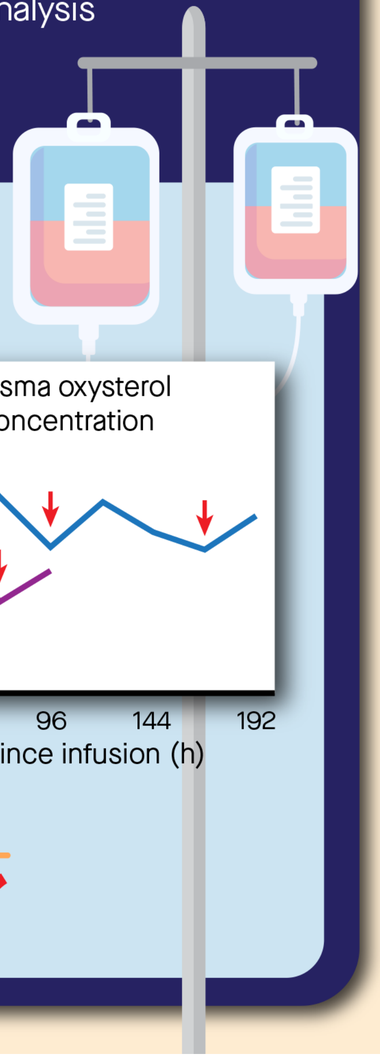
It can cause vomiting, diarrhea, organ enlargement, adrenal gland calcification, and death within the first 6 months of life

The drug Kanuma® improved outcomes in 3 infants with severe WD when administered **twice weekly** at a **high dose**

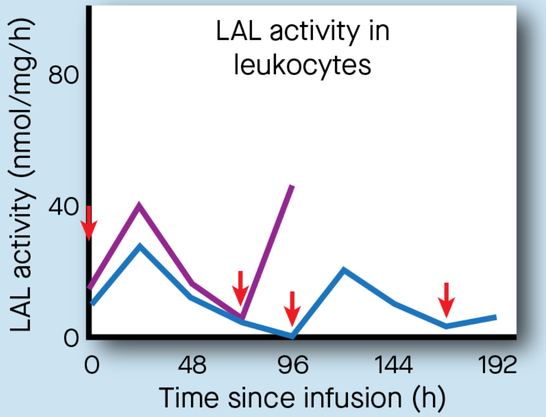
3 patients with severe WD

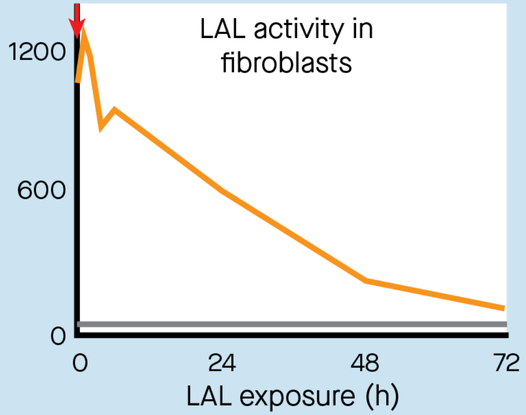
Kanuma® infusion (5 mg/kg 2× weekly)

LAL/oxysterol lipid analysis



Short-term post-dosing **increase in LAL enzyme activity** was associated with the **release of stored lipids**



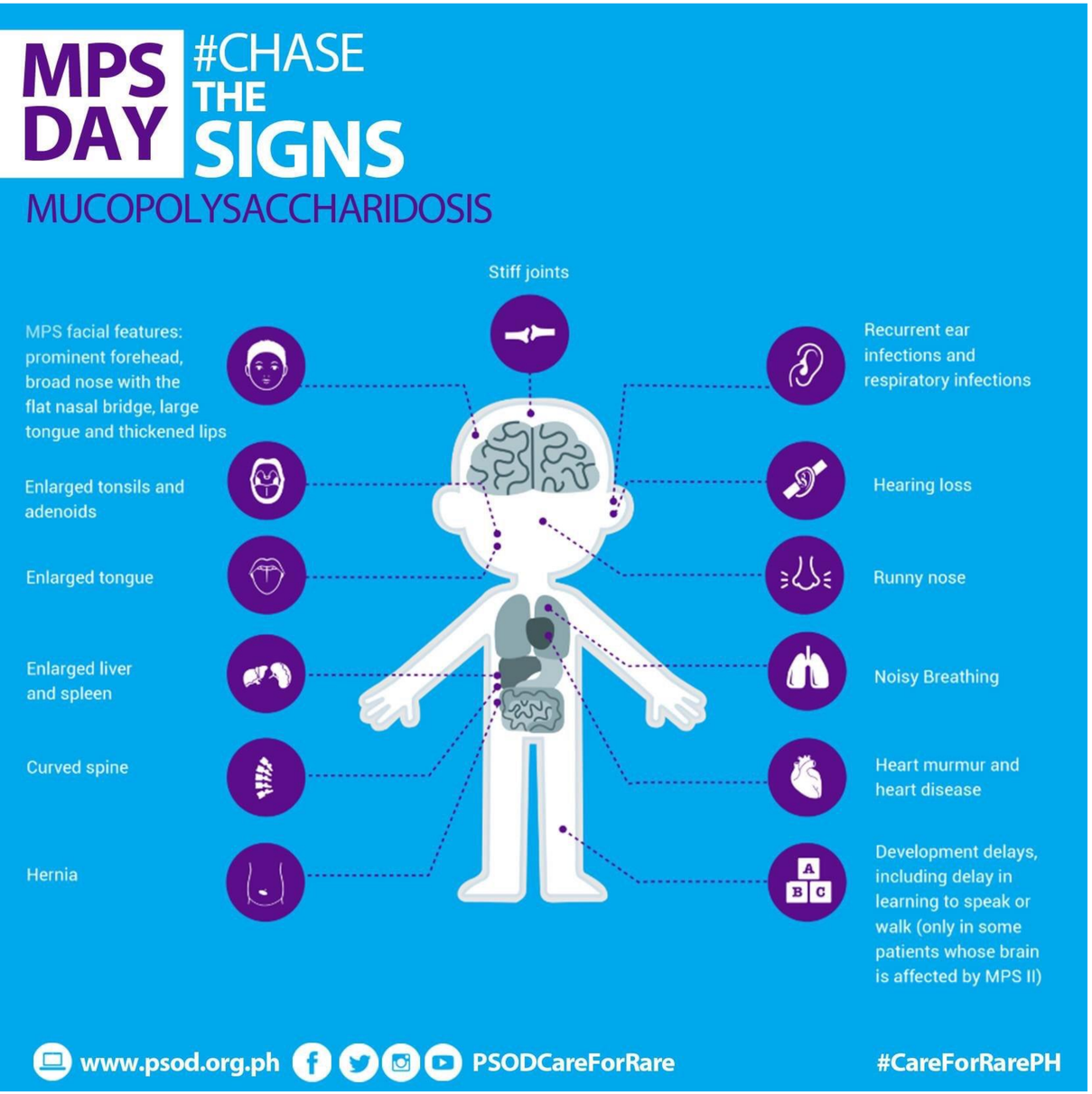


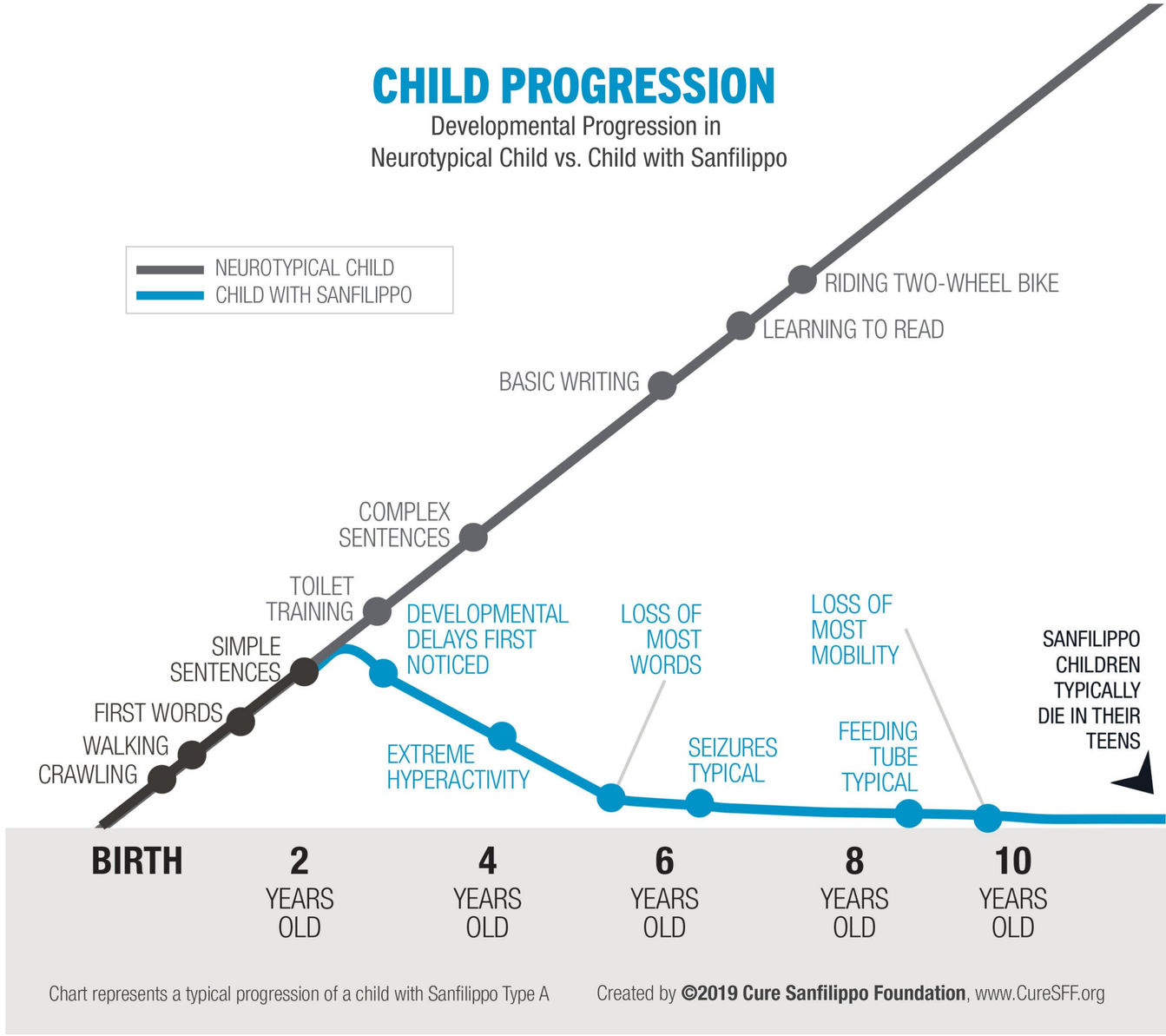
Patient 1 — Patient 2 — Patient 3 ↓ Kanuma® infusion

5 mg/kg twice weekly dosing was **well tolerated** and **effective,** improving clinical condition in all 3 patients ✓

This work was funded by the LALD Spanish Society (AELALD)

NEURONOPATHIC MUCOPOLYSACCHARIDOSIS



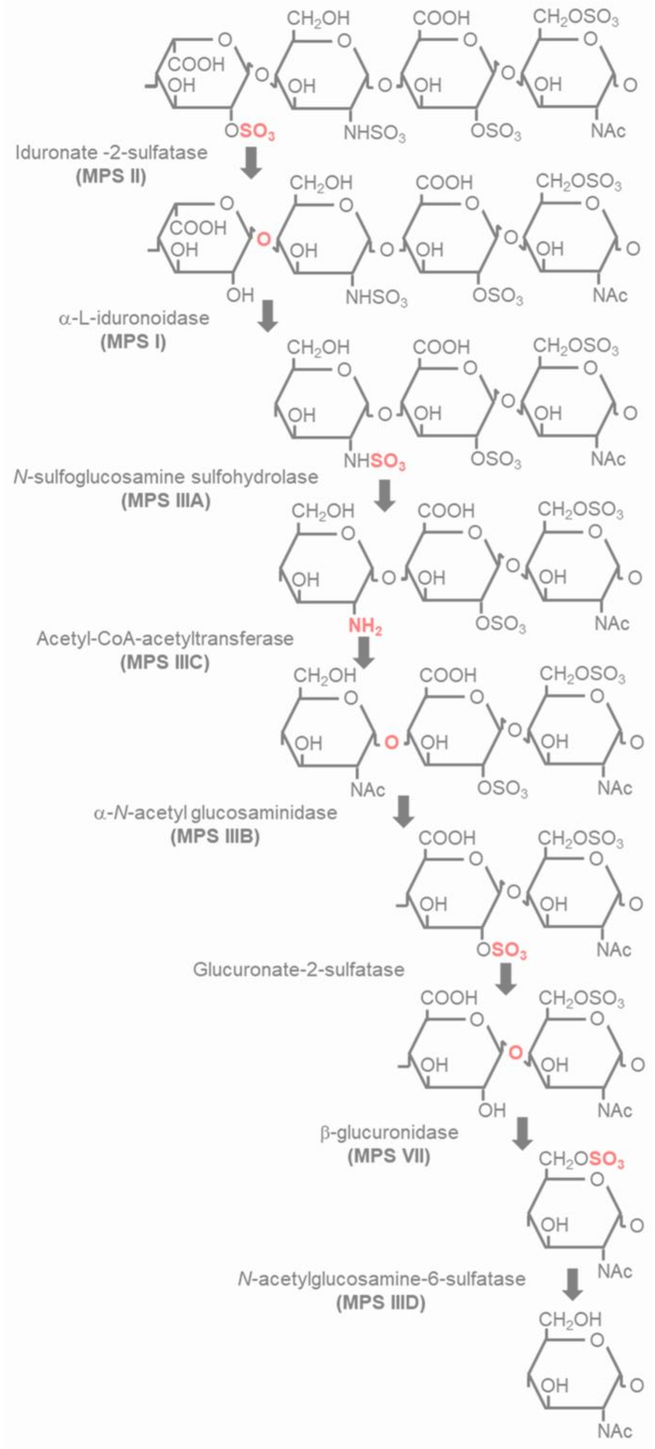


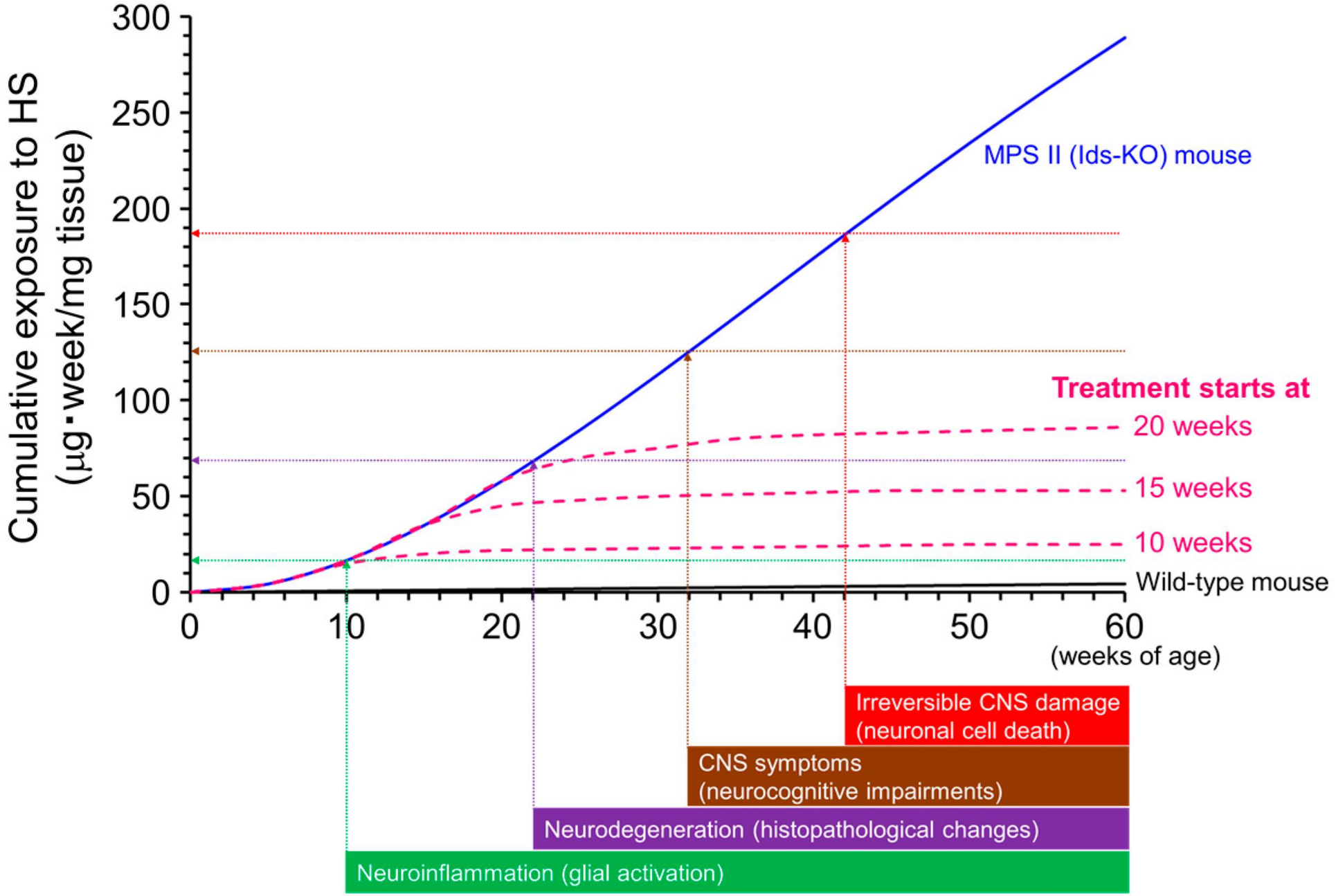
FDA meeting “Developing biomarkers to support accelerated approval in rare diseases”

- Feb 2024 discuss failure of most trials/programs in neuronopathic MPS
- Leading experts and FDA agree heparan sulphate is a reasonable surrogate endpoint
- In animal models CSF HS levels correlate with:
    - - brain tissue HS
    - - pathological and clinical outcomes
- FDA accelerated approval pathway will provide patients access to life-saving therapies

A need for new assays have emerged

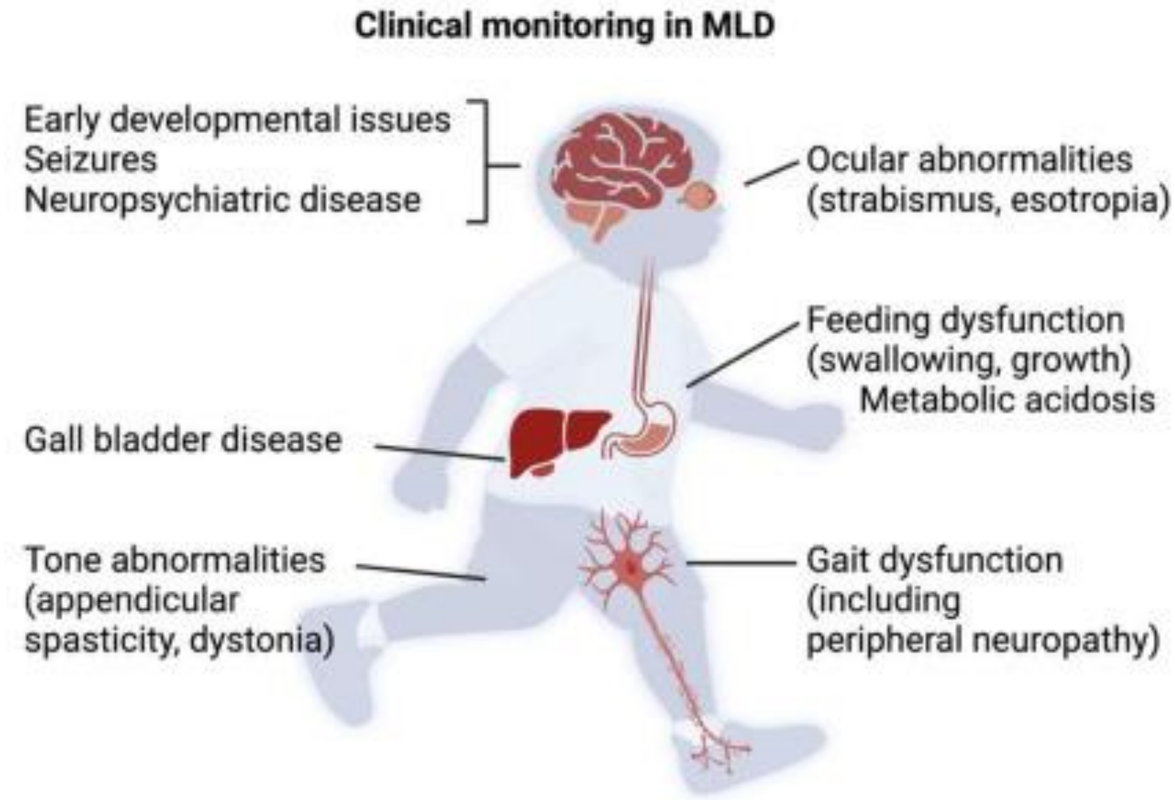
- CSF heparan sulfate (normal ranges according to age) and CSF enzyme activity
- Equivalence of the different assays
- Interpretation of CSF HS levels:
  - cumulative exposure
  - % reduction
  - % normalisation



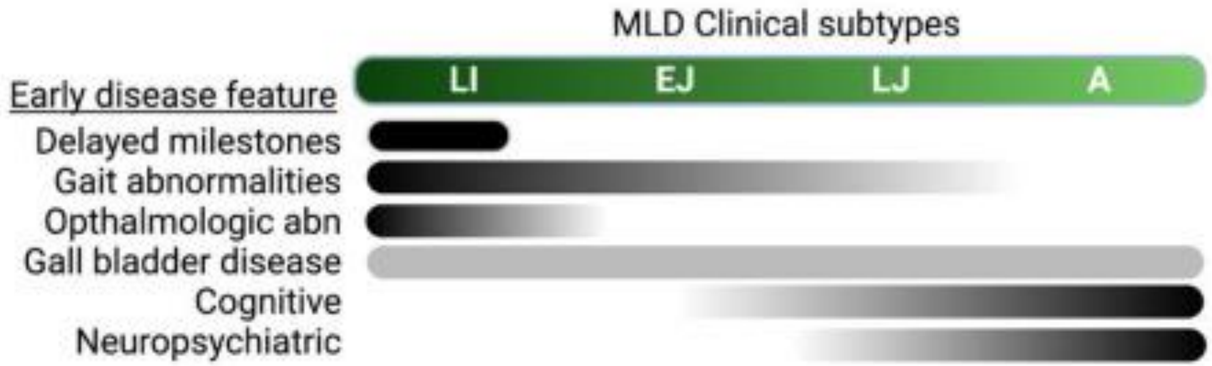

Cumulative exposure to HS
(μg·week/mg tissue)
300
250
200
150
100
50
0
0
10
20
30
40
50
60
(weeks of age)
MPS II (Ids-KO) mouse
Treatment starts at
20 weeks
15 weeks
10 weeks
Wild-type mouse
Irreversible CNS damage
(neuronal cell death)
CNS symptoms
(neurocognitive impairments)
Neurodegeneration (histopathological changes)
Neuroinflammation (glial activation)

Metachromatic leukodystrophy

A.



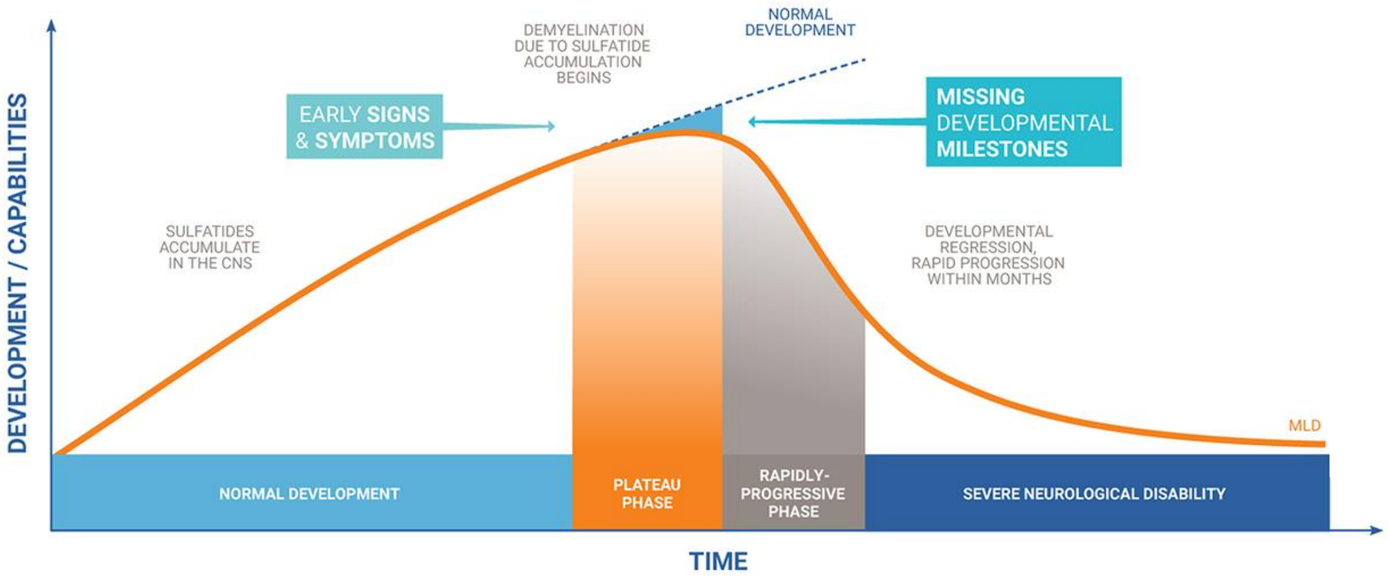
B.



Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States. Adang A. et al. Cytotherapy. 2024 Jul;26(7):739-748.

Libmeldy

- First LSD gene therapy approval
  - Funded despite the price tag
  - Highly effective but for minority of patients
  - Only in the pre/oligo-symptomatic scenario



NEWS

Home | War in Ukraine | Cost of Living | Coronavirus | Climate | UK | World | Business | Politics | Tech | Science

Health

Libmeldy: World's 'most expensive' drug recommended for NHS use

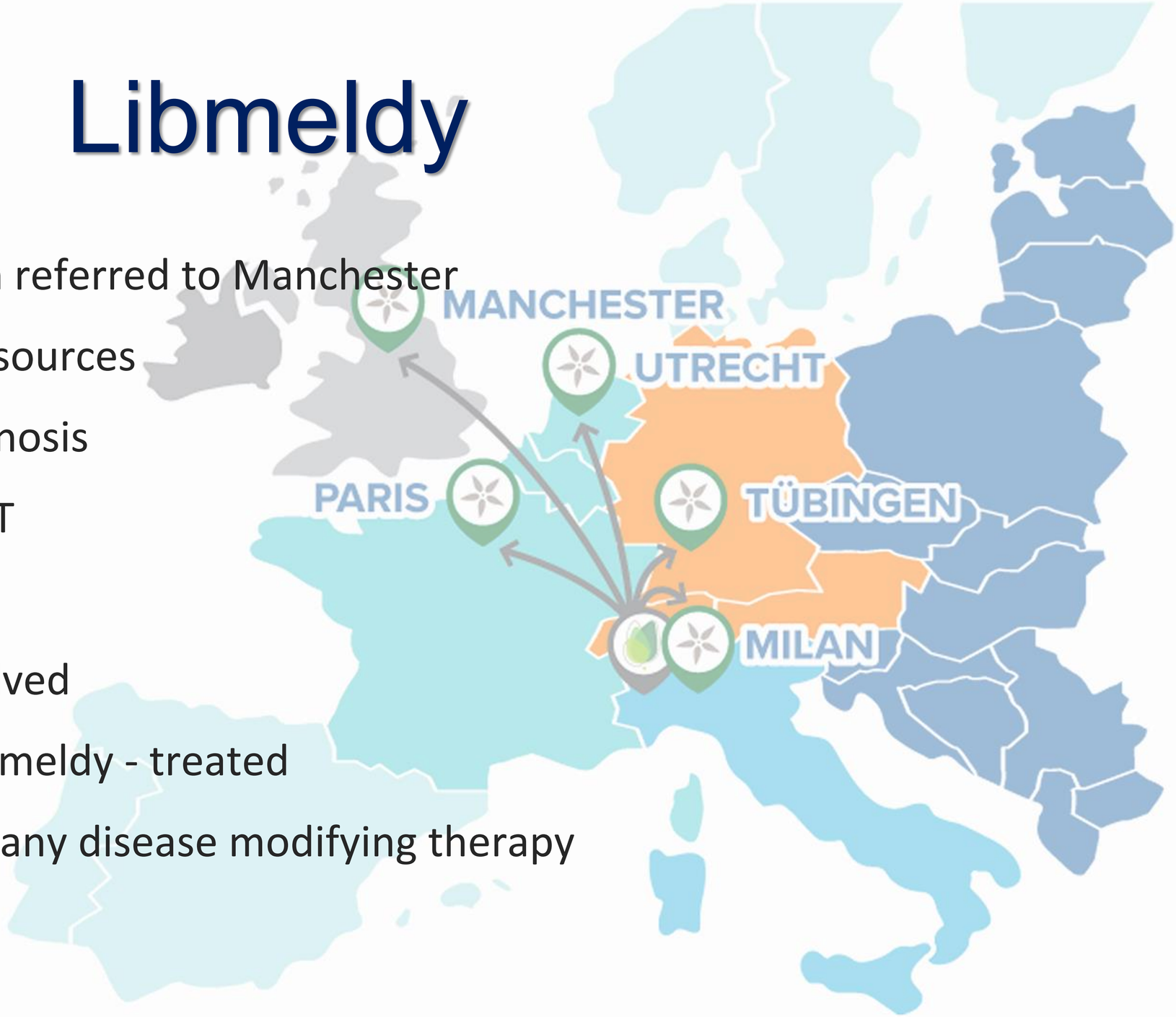
By Jim Reed
Health reporter

4 February

Caption

Libmeldy

- 19 newly diagnosed children referred to Manchester
  - Referred from a variety of sources
  - Usually within days of diagnosis
- All urgently assessed by MDT
  - Virtually or in person
  - Often with local team involved
- 4 suitable and eligible for libmeldy - treated
- 15 therefore not eligible for any disease modifying therapy



Libmeldy

NBS should be developed in paralell to clinical trials

Pre-pilot study design

Phase 1

Assay Validation

- Adapt sulphatide and ARSA assays (Gelb) to Waters Xevo-TQS
- Validate assay performance to ISO15189
- Reference ranges for normal, MLD, siblings and ARSA pseudo-def
- Determine screen cutoff levels for the pre-pilot

Phase 2

Pre-Pilot study

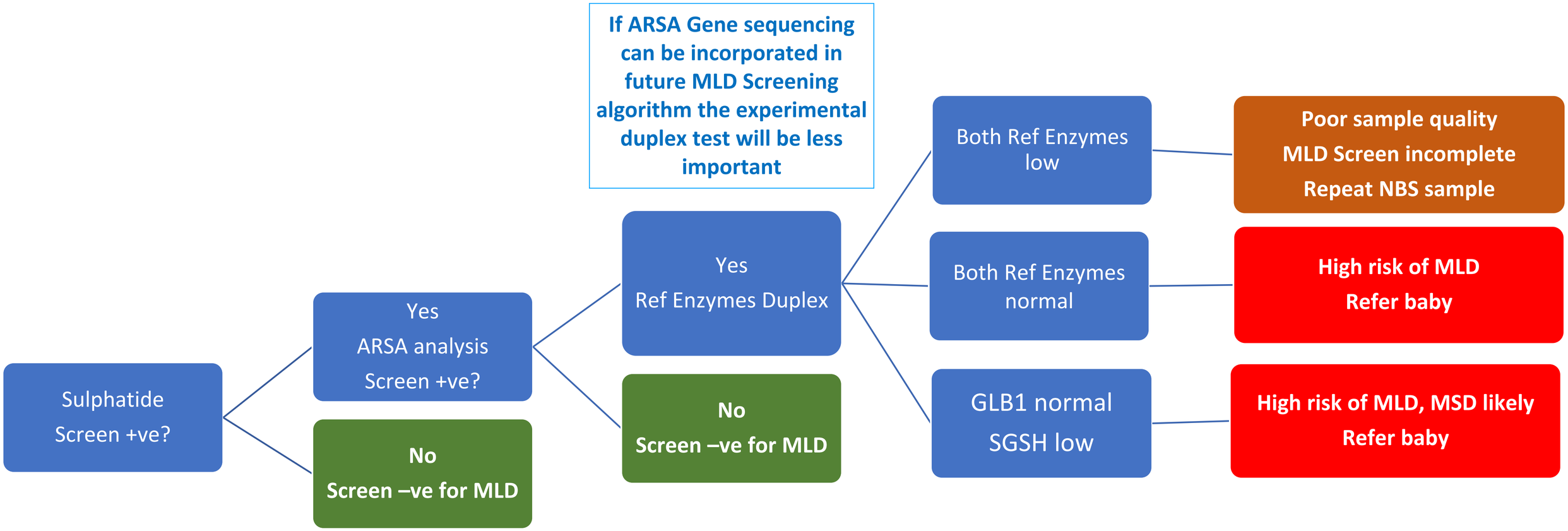
- Run up to 5000 random de-identified baby bloodspots, MLD and siblings using the 2-tier test algorithm

Outcome +

Recommendations

- Were cutoff levels effective
  - detecting the MLD samples as true positives?
  - were there any false positives?
- Can screening results predict MLD phenotype?
- Recommend a screening test algorithm and screening cutoff levels for future pilot studies
- Publication

Libmeldy



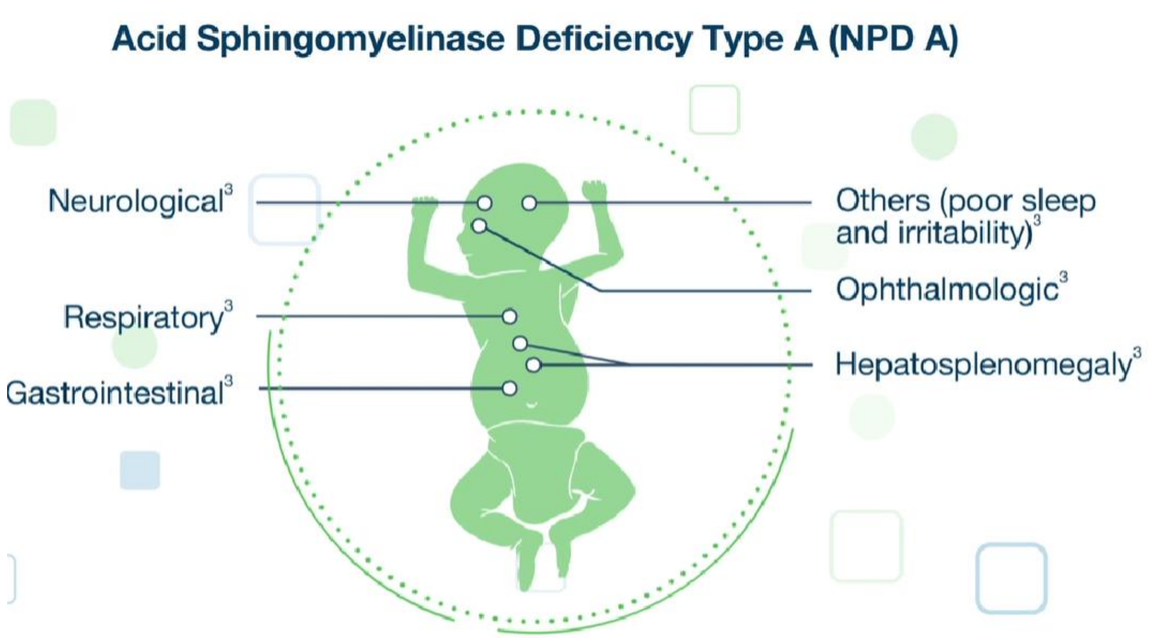
- Toward newborn screening of metachromatic leukodystrophy: results from analysis of over 27,000 newborn dried blood spots. X Hong, et al. Genet Med. 2021 Mar;23(3):555-561.- Improving newborn screening test performance for metachromatic leukodystrophy: Recommendation from a pre-pilot study that identified a late-infantile case for treatment. Wu HY et al. Mol Genet Metab. 2024;142(1):108349

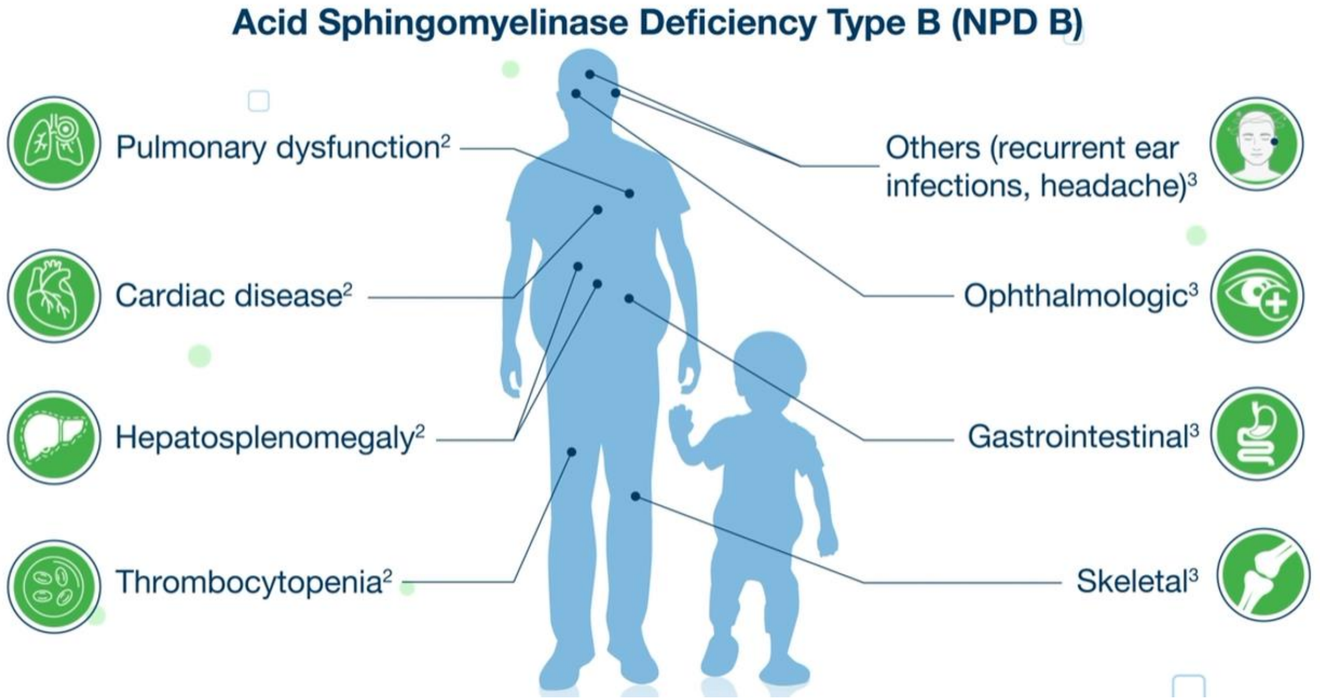
A serendipitous finding…

NBS study ID	C16:0-S (nmol/L)	ARSA (umol/h)	ARSA % of Envir control mean	ARSA gene sequencing finding
A200	150	0.042	**4%**	**Homozygous c.465+1G>A, pathogenic** c.854+82G>A (VUS) Homozygous 5 Benign variants

- 10 month old when genetics were available
- Decision to de-identify baby for follow up supported by NHSE and authorised by MFT Trust
- Attended first clinic at 11 Month
  - healthy, clinical examination normal
  - ARSA enzyme and genetic tests confirmed the MLD diagnosis
  - qualify for Gene therapy
  - 2nd child in the family – first born unaffected

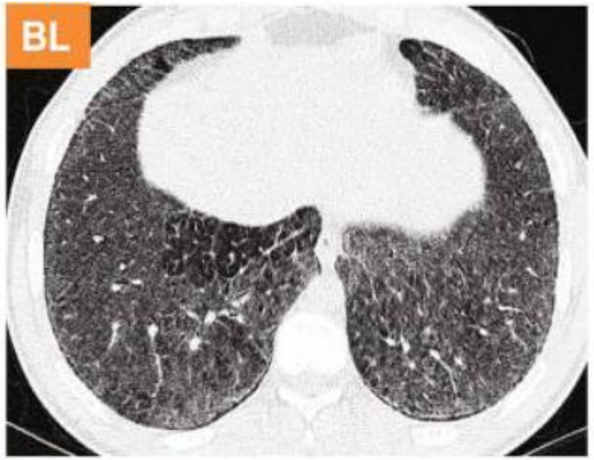
ASMD

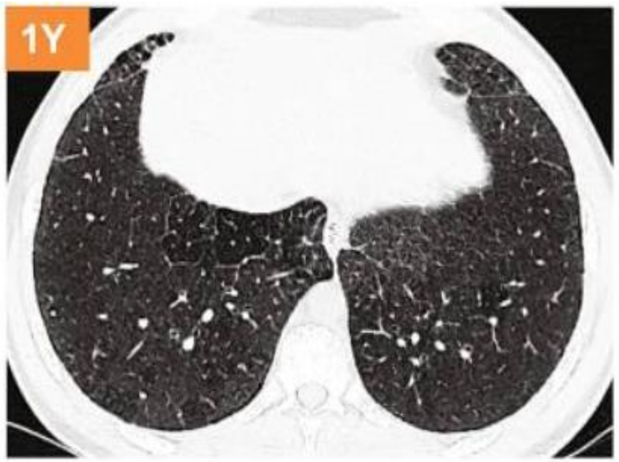

Acid Sphingomyelinase Deficiency Type A (NPD A)
Neurological[3]
Respiratory[3]
Gastrointestinal[3]
Others (poor sleep and irritability)[3]
Ophthalmologic[3]
Hepatosplenomegaly[3]

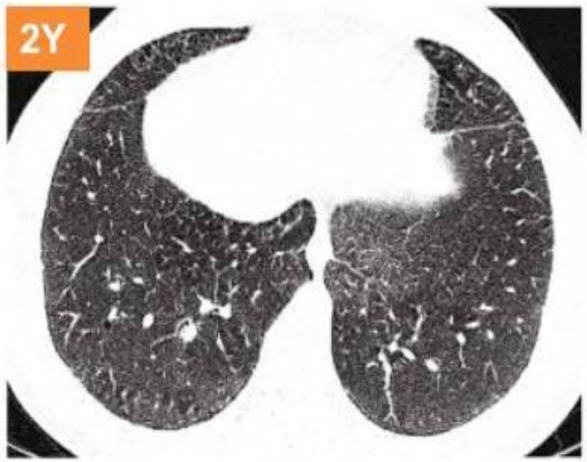

Acid Sphingomyelinase Deficiency Type B (NPD B)
Pulmonary dysfunction[2]
Cardiac disease[2]
Hepatosplenomegaly[2]
Thrombocytopenia[2]
Others (recurrent ear infections, headache)[3]
Ophthalmologic[3]
Gastrointestinal[3]
Skeletal[3]

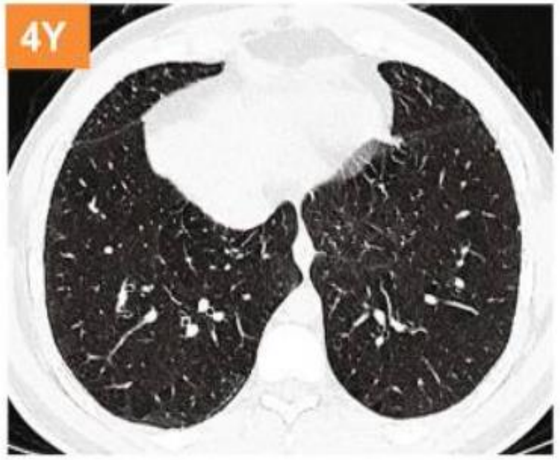
Olipudase alfa

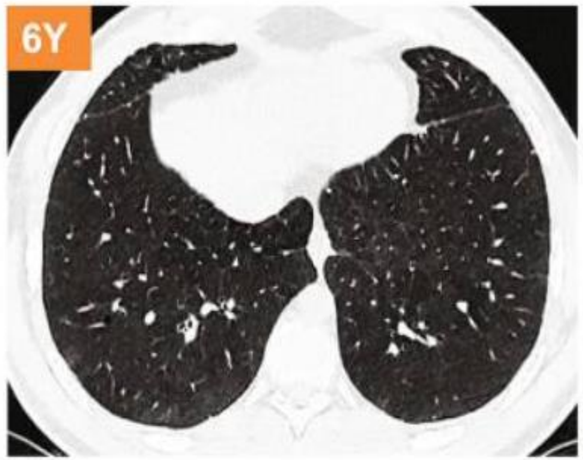
- Highly effective for peripheral aspects of the disease











Ground Glass Appearance Score	
Baseline (BL)	2.33
1 year (1Y)	1.625
2 year (2Y)	1.25
4 year (4Y)	0
6 year (6Y)	0

Olipudase alfa enzyme replacement therapy for acid sphingomyelinase deficiency (ASMD): sustained improvements in clinical outcomes after 6.5 years of treatment in adults. Lachmann R. et al. Orphanet J Rare Dis. 2023; 18: 94.

Editorial

https://doi.org/10.1038/s41591-024-03227-9

Every baby deserves access to genetic screening

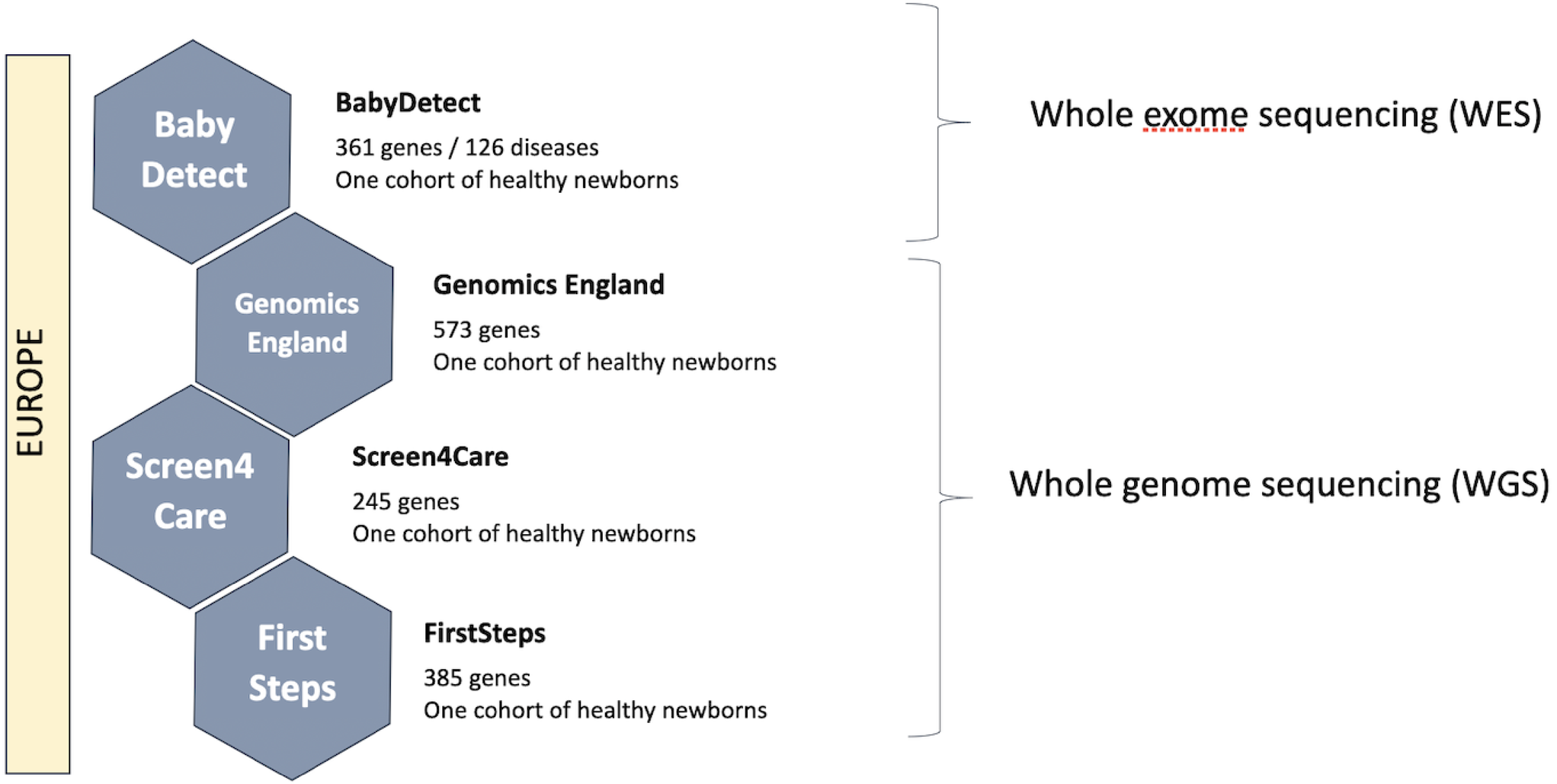
Genomics-based newborn screening has the potential to revolutionize healthcare, but new solutions are needed to ensure that the benefits are equitably available.

Early disease diagnosis has become ever more a priority in healthcare, and many argue that there is no better time than at the very start of life. In July 2024, Genomics England, which has been at the forefront of integrating genomics into a country's national healthcare system, announced the enrollment of the first baby in the Generation study, its flagship newborn genetic screening program that aims before receiving a diagnosis. Early detection also opens the path to early intervention, which is typically associated with better outcomes. Recent advances in technologies such as molecular therapies and gene editing are also paving the way for personalized genetic therapies developed for individual patients in record time[4,5].

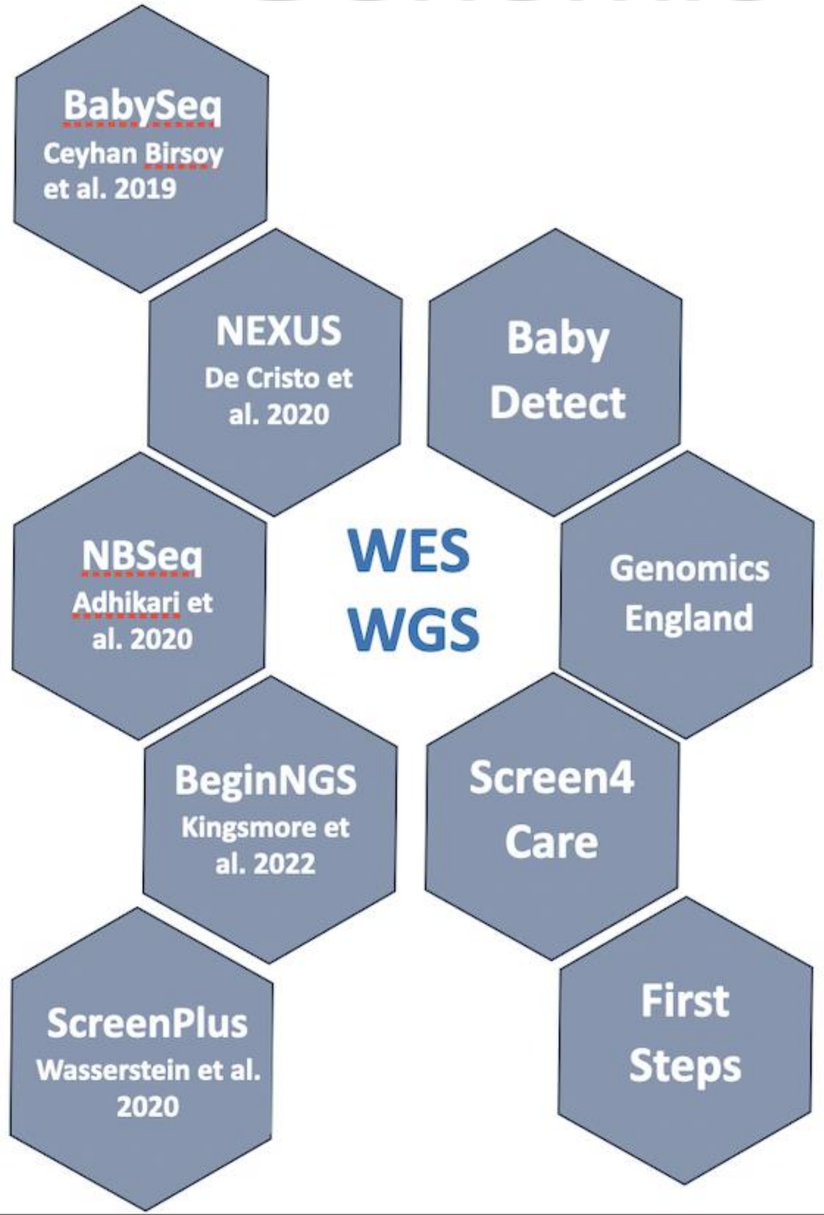
Nation-wide genetic screening, available to all newborns, could in principle also be a tool to narrow the disparities that exist in today's healthcare systems, providing to every family information about their baby's health, regardless of socioeconomic and geographical factors. Designing genomics-based newborn screening programs that bring benefit equitably to the population is, however, that evidence is gathered in cohorts that are representative of the national demographic, and that the public is involved in the decision-making starting from the study design. The second iteration of the BabySeq project has moved in that direction, and the study was set up with the collaboration of a community advisory board of mothers from various community healthcare centers serving families from diverse ethnic and socioeconomic backgrounds. The Generation study in the UK was also designed following extensive consultations with various stakeholders, including bioethicists and patient advocates, once again highlighting the importance of public dialogue during the setting up of initiatives that will have wide impacts

Genomic newborn screening

Genomic newborn screening

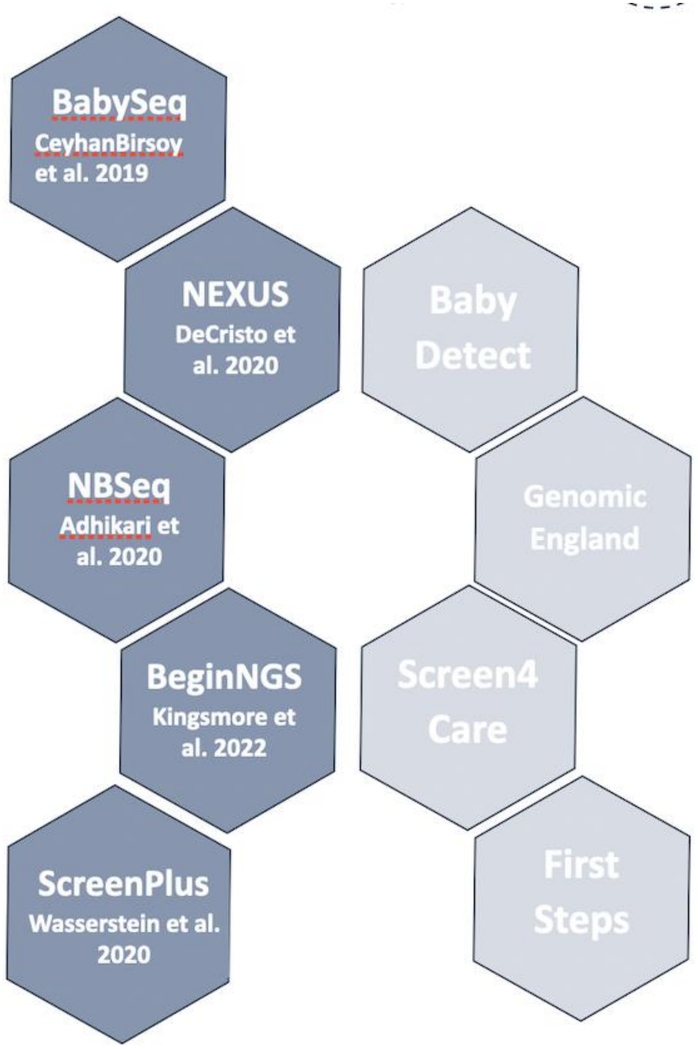


Genomic newborn screening



Principles used to choose genes and conditions in the Genomics England program	
A	There is strong evidence that the genetic variant(s) causes the condition and can be reliably detected. Where appropriate, there may be a confirmatory test that can establish whether or not the child has the condition
B	A high proportion of individuals who have the genetic variant(s) would be expected to have symptoms that would have a debilitating impact on quality of life if left undiagnosed. The impact on quality of life should consider factors such as the testimony of patients and families affected including social and environmental factors, and QALYs where available
C	Early or pre-symptomatic intervention for the condition has been shown to lead to substantially improved outcomes in children, compared with intervention after the onset of symptoms. The intervention would normally be initiated in early childhood (by age 5); and could either cure, delay or modify the course of the condition
D	Conditions screened for are only those for which the interventions are equitably accessible for all. This incorporates input from NHS England and other relevant clinical and commissioning bodies

Genomic newborn screening



Main conclusions

- 2nd tier test for diseases in which the biochemical diagnosis is feasible
- Reduce false positives
- Prognostication
- 1st tier test for disorders in which no biochemical test is possible

At this point GNBS must act as an adjunct to traditional biochemical NBS, rather than as a replacement

Genomic Sequencing as a First-Tier Screening Test and Outcomes of Newborn Screening. Cheng M, et al. JAMA Netw Open. 2023; 6(9): e2331162.

Table 2.

Patients With G6PD Deficiency, Congenital Hypothyroidism, Isolated HTT and Amino Acid, Organic Acid, and Fatty Acid Oxidation Disorders

Diseases	Cases detected by both (n = 343)	Undetected cases		All (N = 445)
		Biochemical NBS (n = 20)	Genetic NBS (n = 82)	
G6PD deficiency	318	10	0	328
Male	272	10	0	282
Female	46	0	0	46
Congenital hypothyroidism and isolated HTT	10	8	76	94
Congenital hypothyroidism	4	2	24	30
Isolated HTT	6	6	52	64
Amino acids, organic acids, and fatty acid oxidation disorders	15	2	6	23
Methylmalonic acidemia, cbIC Type	4	1	0	5
Primary carnitine deficiency	4	0	1	5
Phenylketonuria	3	0	0	3
Isobutyryl-CoA dehydrogenase deficiency	1	0	1	2
Short chain acyl-CoA dehydrogenase deficiency	1	0	1	2
Medium-chain acyl-coenzyme A dehydrogenase deficiency	1	0	0	1
Methylmalonic acidemia, cbIA type	1	0	0	1
Carnitine palmitoyltransferase II deficiency	0	0	1	1
Maple syrup urine disease, type II	0	0	1	1
Multiple acyl-CoA dehydrogenase deficiency	0	0	1	1
Citrin deficiency	0	1	0	1

Abbreviations: HTT, hyperthyrotropinemia; NBS, newborn screening.