X-linked adrenoleukodystrophy

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Very-long chain fatty acids (VLCFAs)

Definition: Fatty acids with a chain-length of **≥20 carbons**

- **C22 and C24:** found throughout the body
- **C≥26 or ultra long-chain FAs (ULCFAs):** found in specific tissues, including the skin, retina, meibomian gland, testis, and brain

Form: Present in sphingolipids, glycerophospholipids, and other forms of lipids including w-O-acyl-ULCFAs

Function: Skin barrier formation, liver homeostasis, myelin maintenance, spermatogenesis, retinal function and anti-inflammation

Kihara A. Biomol Ther (Seoul). 2014 Mar; 22(2): 83–92.

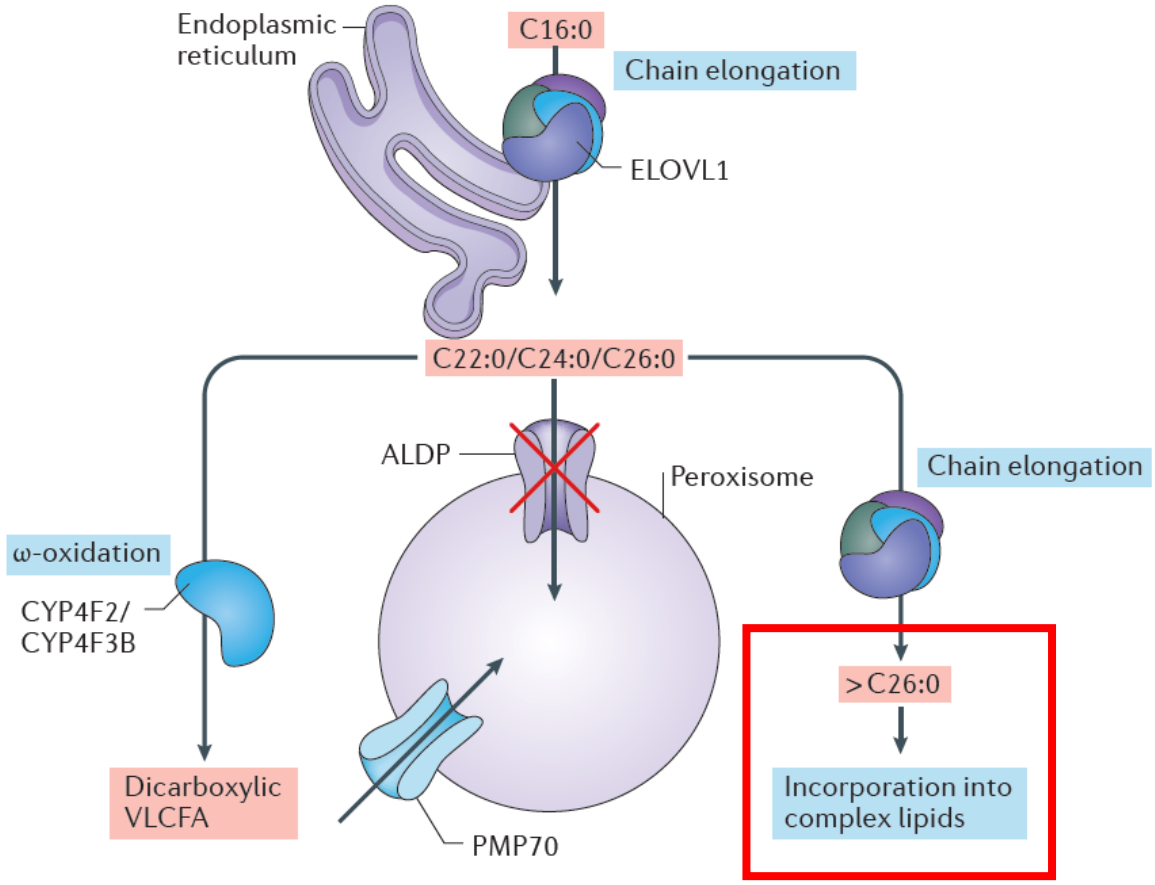
Metabolism of fatty acids

Size class	Number of carbons	Site of catabolism	Membrane transport
Short chain	2–4	Mitochondrion	Diffusion
Medium chain	4–12	Mitochondrion	Diffusion
Long chain	12–20	Mitochondrion	Carnitine cycle
Very long chain	>20	Peroxisome	Unknown

John WB; Marek HD. Medical biochemistry Fifth edition : Elsevier Health Sciences, 2019.

Adrenoleukodystrophy (ALD)

- Rare **X-linked disorder of peroxisomal oxidation** due to **mutations in *ABCD1***
- Leading to high levels of VLCFA in the plasma that **accumulate in**
  - **White matter of the brain**
  - **Spinal cord**
  - **Adrenal cortex**



Abbr:

ELOVL, Elongation of very long chain fatty acids protein;

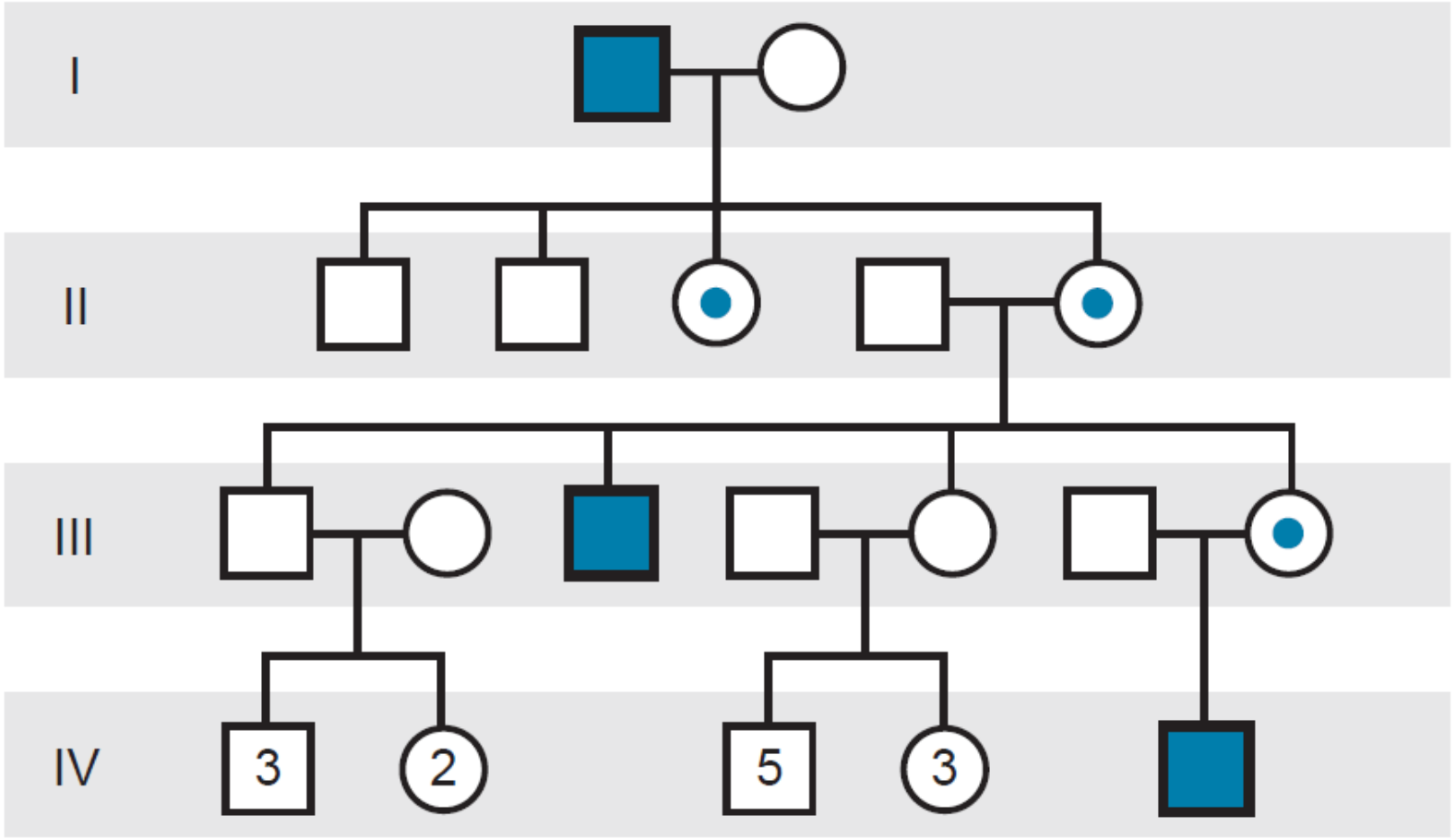
ALDP, Adrenoleukodystrophy protein;

ABCD1, ATP binding cassette subfamily D member 1

Zhu J, et al. Endocr Rev. 2020 Aug 1;41(4):577-93.

Kemp S, et al. Nat Rev Endocrinol. 2016 Oct;12(10):606-15.

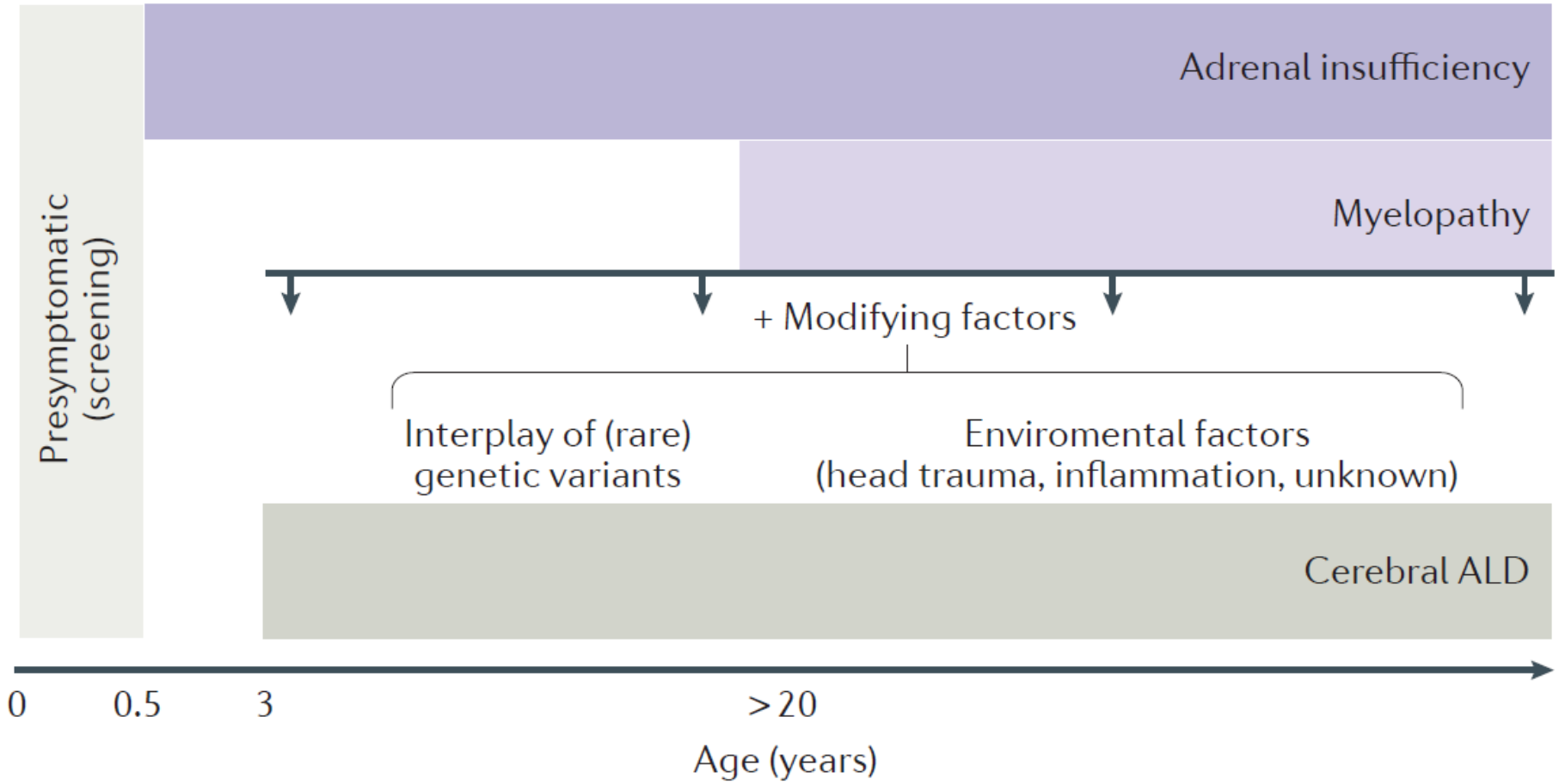
X-linked recessive inheritance



Chapter 7 Patterns of Single-Gene Inheritance. Thompson & Thompson Genetics in Medicine 8th Ed

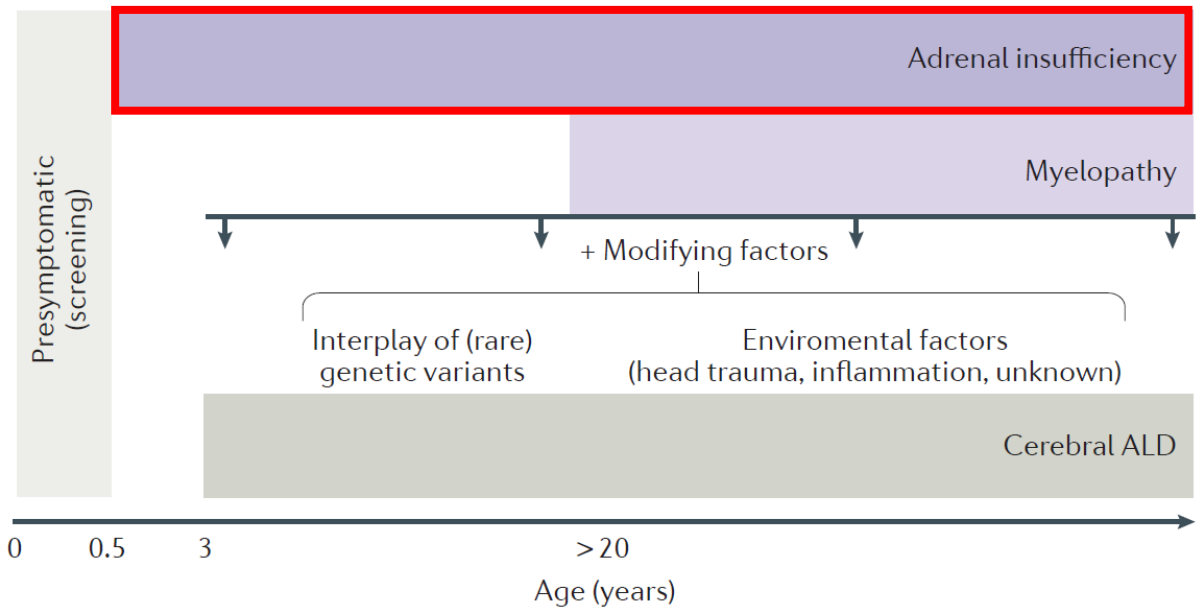
Clinical manifestation

Clinical spectrum of ALD in men



Kemp S, et al. Nat Rev Endocrinol. 2016 Oct;12(10):606-15.

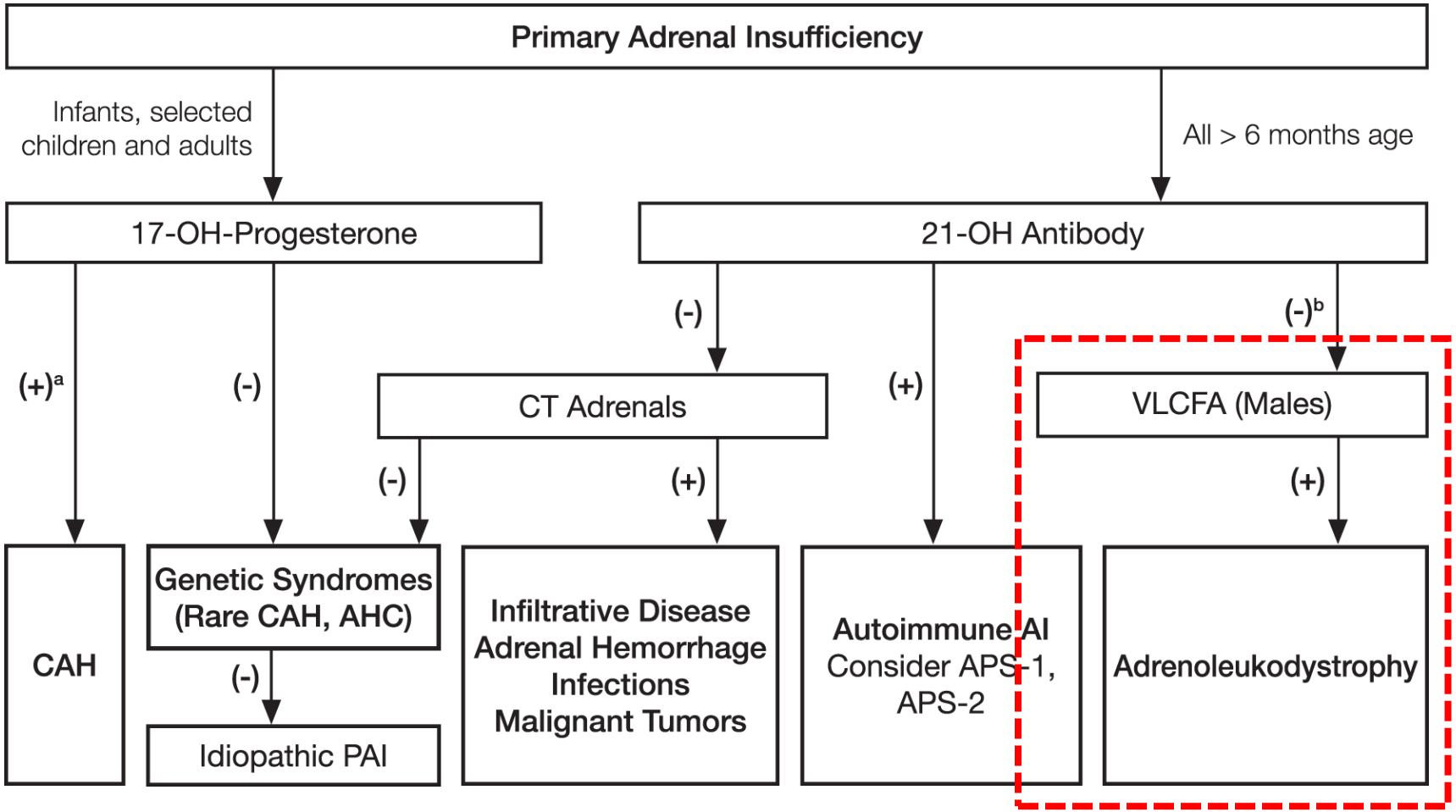
Adrenal insufficiency



- Lifetime prevalence: 80%
- Initial manifestation of ALD: 38%
- Earliest onset: 5 weeks of life (subclinical AI)
- Peak incidence: 3–10 years of age
- Mineralocorticoid deficiency: only 50%
- Account for 4-35% of idiopathic AI

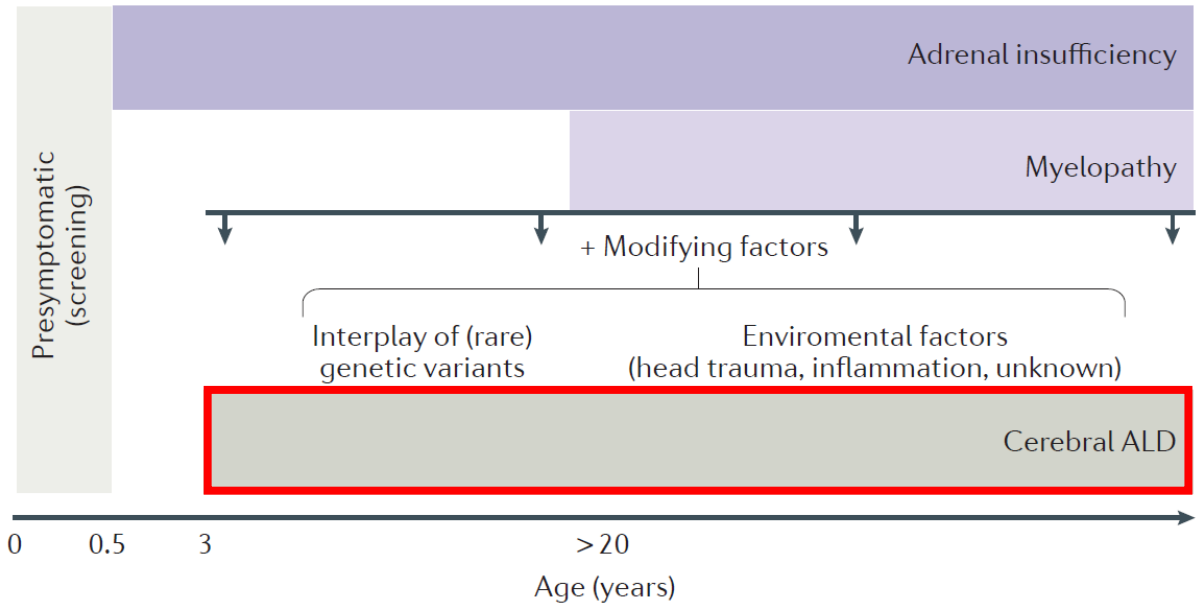
1) Kemp S, et al. Nat Rev Endocrinol. 2016 Oct;12(10):606-15. 2) Zhu J, et al. Endocr Rev. 2020 Aug 1;41(4):577-593.

Algorithm for the diagnostic approach to the patient with PAI



Bornstein SR, et al. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89.

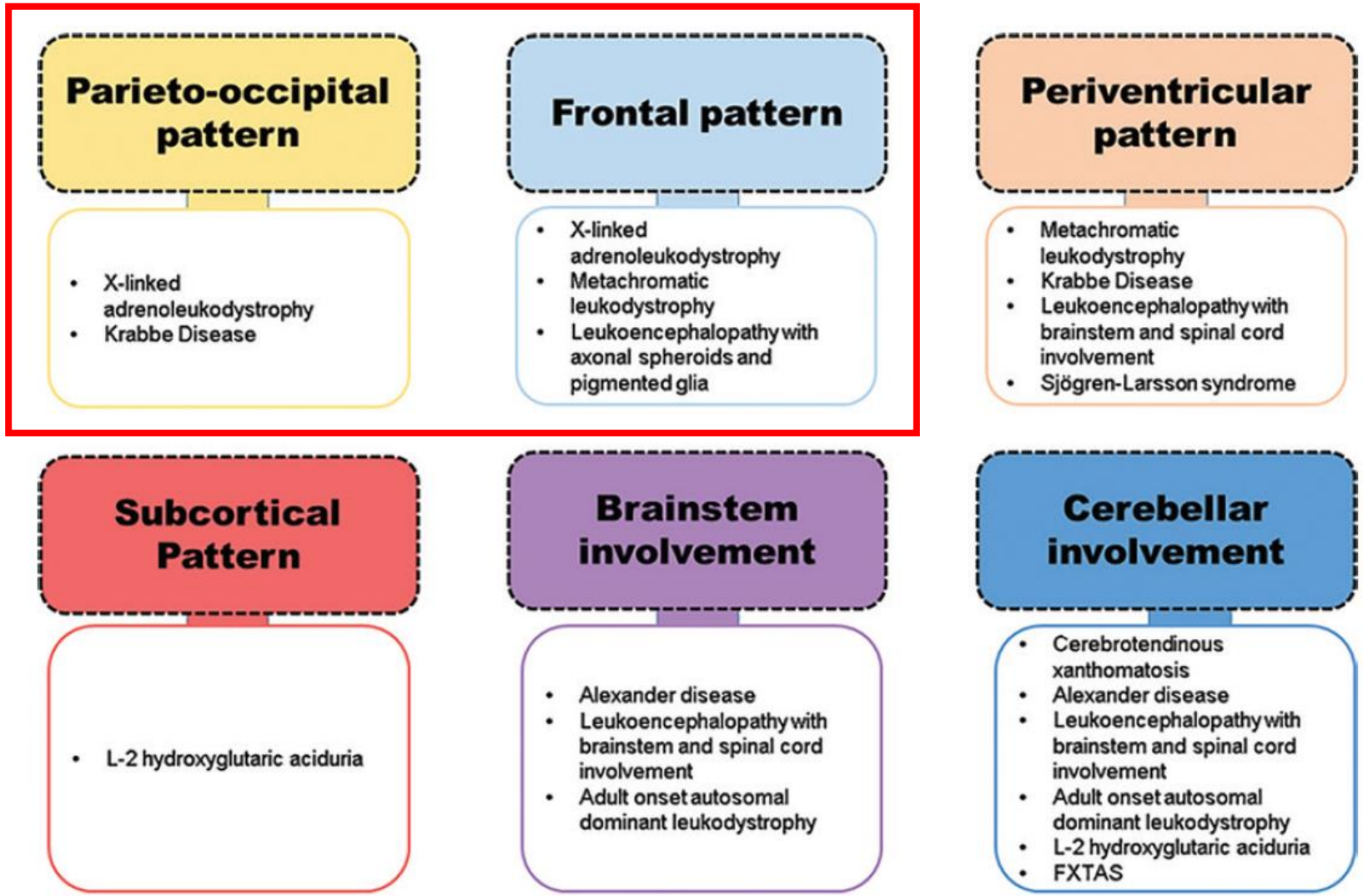
Cerebral ALD



- Affects 1/3 of boys with ALD
- Onset: 4–12 years (peak age at 7 years)
- Rare after 15 years of age
  - Adolescence 4–7%
  - Adulthood 2–5%
- Manifestations
  - 1st manifestation: Radiographic finding
  - Cognitive and behavioral abnormalities, cortical blindness, central deafness, quadriparesis, seizures
- Prognosis (if untreated)
  - Progressive with rapid neurological decline and total disability by 6 months to 2 years
  - Death within 5–10 years after diagnosis

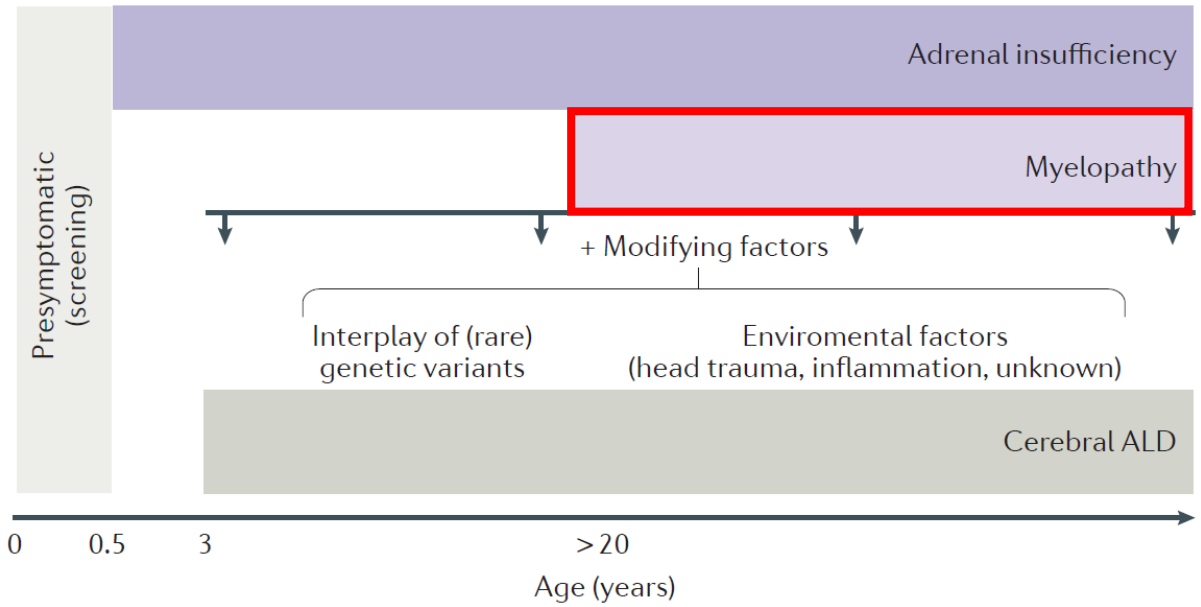
1) Kemp S, et al. Nat Rev Endocrinol. 2016 Oct;12(10):606-15. 2) Zhu J, et al. Endocr Rev. 2020 Aug 1;41(4):577-593.

White matter involvement patterns



Resende LL, et al. RadioGraphics 2019; 39:153–168

Myelopathy



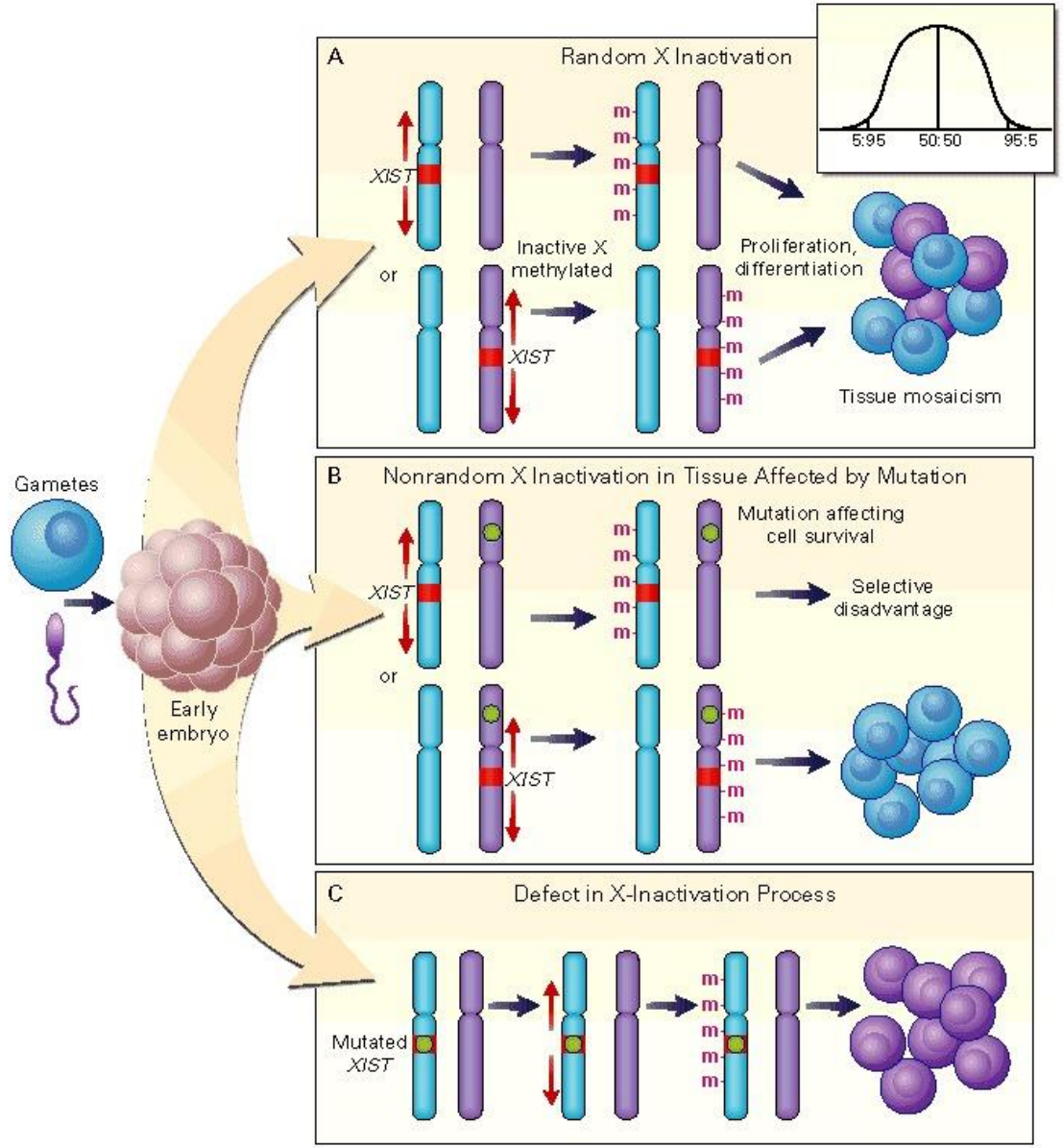
- Onset: 20–40 years (median of 28 years)
- Manifestations
  - 1st manifestation: Peripheral neuropathy
  - Spinal cord dysfunction: progressive stiffness and weakness of the legs (spastic paraparesis), sensory ataxia, abnormal sphincter control, and sexual dysfunction
- 27–63% develop cerebral involvement, 10–20% associated with rapid neurologic decline
- T2-weighted MRI: spinal cord atrophy

1) Kemp S, et al. Nat Rev Endocrinol. 2016 Oct;12(10):606-15. 2) Zhu J, et al. Endocr Rev. 2020 Aug 1;41(4):577-593.

Woman with ALD?

Mechanisms leading to a skewed pattern of X-inactivation in females

A. Random X inactivation
B. Nonrandom X inactivation in tissue affected by mutation
C. Defect in X-inactivation process



Abbr: XIST, X-inactivation–specific transcript gene

Jennifer MP, Huntington FW. N Engl J Med 1998; 338:325-328.

Woman with ALD

- Onset: typically ≥30 years
- Myelopathy similar to men
- Neuropathic pain (generally not present in males)

  20% who are ≤40 years

  90% who are ≥60 years
- Conventional imaging does not show abnormalities
- Milder and slower progression compared to men

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Diagnosis

Measurement of very long chain fatty acids (1)

- Screening test
- 3 VLCFA parameters
  1) ↑ C26:0
  2) ↑ C26:0 to C22:0 ratio
  3) ↑ C24:0 to C22:0 ratio

- Samples should be collected after a 4 to 14 hour fast
- False positives (case reports)
  - Ketogenic diet for Tx of epilepsy
  - Liver insufficiency
  - Diabetic ketoacidosis

Moser HW, Moser AB, Frayer KK, et al. Neurology. 1981;31(10):1241–1249.
Moser AB, Kreiter N, Bezman L, et al. Ann Neurol. 1999;45(1):100–110.

Measurement of very long chain fatty acids (2)

- Not distinguish between ALD and other peroxisomal disorders

↑ VLCFA levels or

abnormal ratios of VLCFA

↓

Genetic testing

- 15% of women with ALD have normal VLCFA levels

Any woman with

symptoms of myelopathy

↓

Genetic testing

Moser AB, Kreiter N, Bezman L, et al. Ann Neurol. 1999;45(1):100–110.

Genetic testing

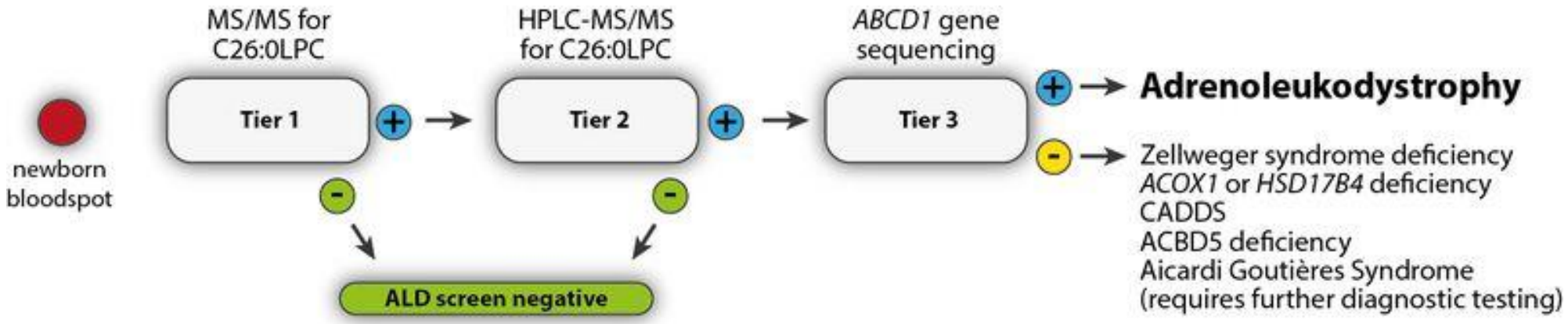
- Confirmatory test
- >800 nonrecurrent ABCD1 mutations have been described
- De novo mutation rate: 5-19%
- No correlation exists between *ABCD1* mutation and X-ALD phenotype

Moser AB, Kreiter N, Bezman L, et al. Ann Neurol. 1999;45(1):100–110.

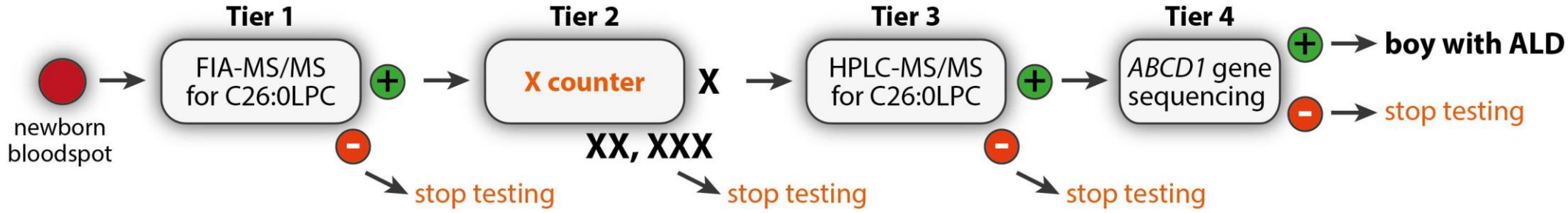
O'Neill GN, Aoki M, Brown RH Jr. Neurology. 2001;57(11):1956–1962.

Newborn screening

United states

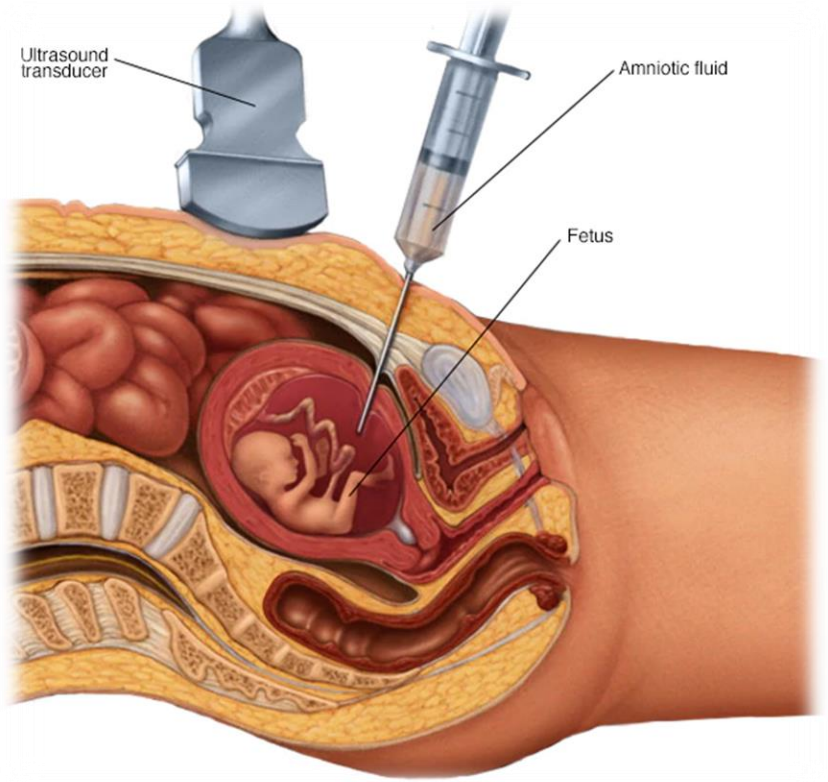


Netherlands



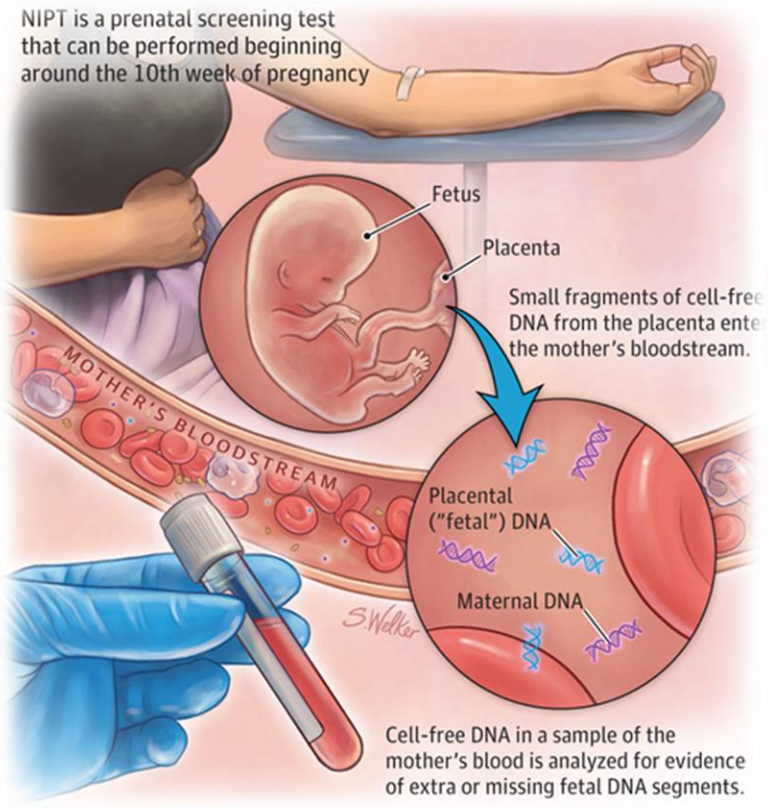
Pre-natal diagnosis

Amniocentesis



Future

Noninvasive prenatal testing (NIPT)



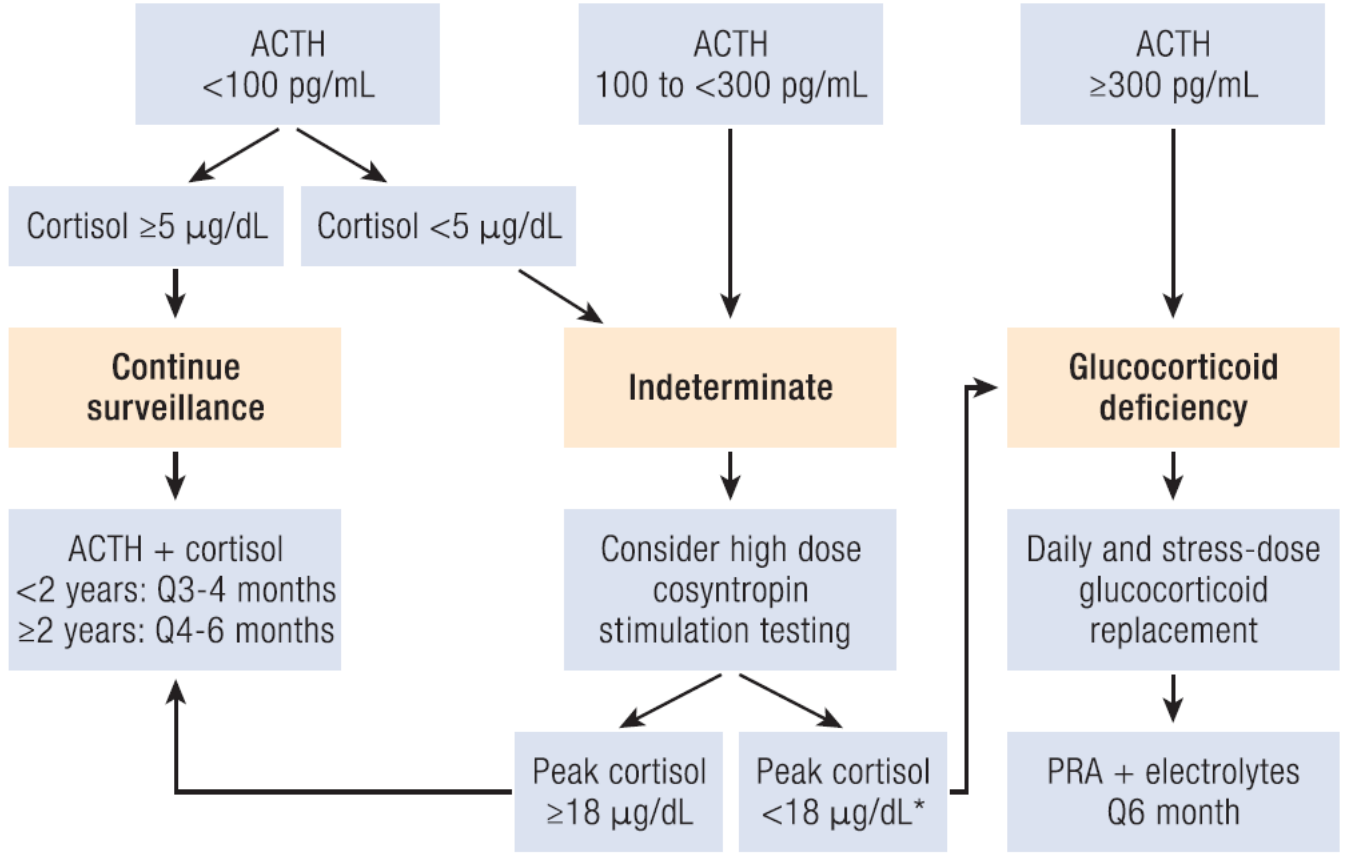
https://www.mayoclinic.org

Surveillance of asymptomatic individuals

Surveillance of asymptomatic individuals

Adrenal insufficiency

- ACTH and cortisol
  - At diagnosis of ALD
  - <2 years: q 3–4 months
  - ≥2 years: q 4–6 months
- PRA and electrolytes
  - After diagnosis of AI, q 6 months



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Surveillance of asymptomatic individuals

Adrenal insufficiency	Cerebral ALD	Myelopathy
• **ACTH and cortisol** - At diagnosis of ALD - <2 years: q 3–4 months - ≥2 years: q 4–6 months • **PRA and electrolytes** - After diagnosis of AI, q 6 months	• **Brain MRI** - 2–36 months: q 1 year - 3–10 years: q 6 months - 10–18 years: q 1 year	• **Clinical neurologic assessment** - q 1 year

Zhu J, et al. Endocr Rev. 2020 Aug 1;41(4):577-593.

Treatment

Treatment

Adrenal insufficiency	Cerebral ALD	Myelopathy
• Chronic glucocorticoid replacement therapy • Chronic mineralocorticoid replacement, if needed • Stress-dose steroids for acute physiologic stress • No current curative therapy	• Hematopoietic stem-cell transplant (HSCT) • Gene therapy (clinical trials)	• Supportive care • Does not appear to be impacted by a history of HSCT for cerebral ALD • No curative therapy

Zhu J, et al. Endocr Rev. 2020 Aug 1;41(4):577-593.

Treatment for cerebral ALD

	HSCT	Gene therapy (in clinical trials)
Pros	- **Arrests progression** of neurologic disease in **early stage childhood cerebral ALD (CCALD)** - Improved survival outcomes **(5-year, 95% transplanted vs. 54% untransplanted)**	- Arrests progression of neurologic disease - Brain MRI and neurological outcomes in the short term are comparable to HSCT - **No risk of GVHD**
Cons	- Not effective in advanced cerebral ALD - Requires matched stem cell donor - Risk of acute mortality, failure of engraftment, and GVHD	- Risk of failure of engraftment - Theoretical risk of insertional oncogenesis - Unknown long-term outcomes

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HSCT for cerebral ALD

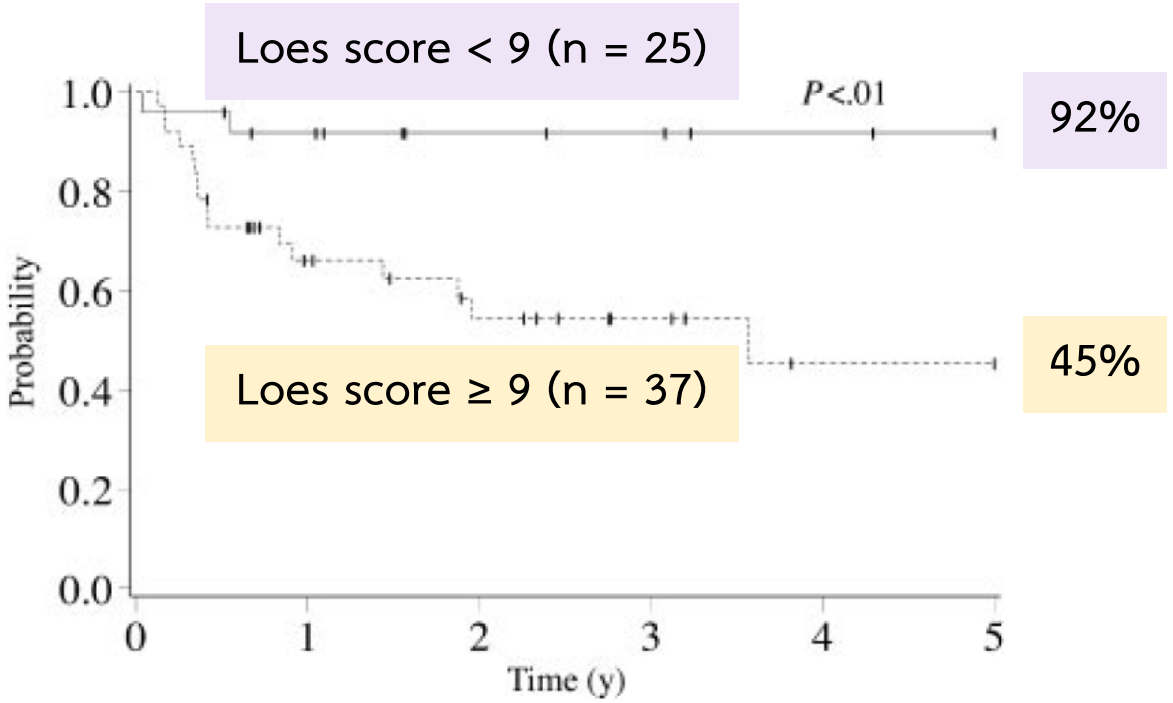


Figure 2. Kaplan-Meier estimate of survival for cerebral X-linked adrenoleukodystrophy following hematopoietic cell transplantation by number of neurologic deficits and MRI severity score before transplantation. Solid line indicates patients with 0 to 1 neurologic deficits and MRI severity score less than 9 (n = 25). Dashed line indicates patients with 2 or more neurologic deficits or MRI severity score 9 or greater (n = 37). Ticks on probability lines indicate dates of censoring at last follow-up.

Loes MRI severity score

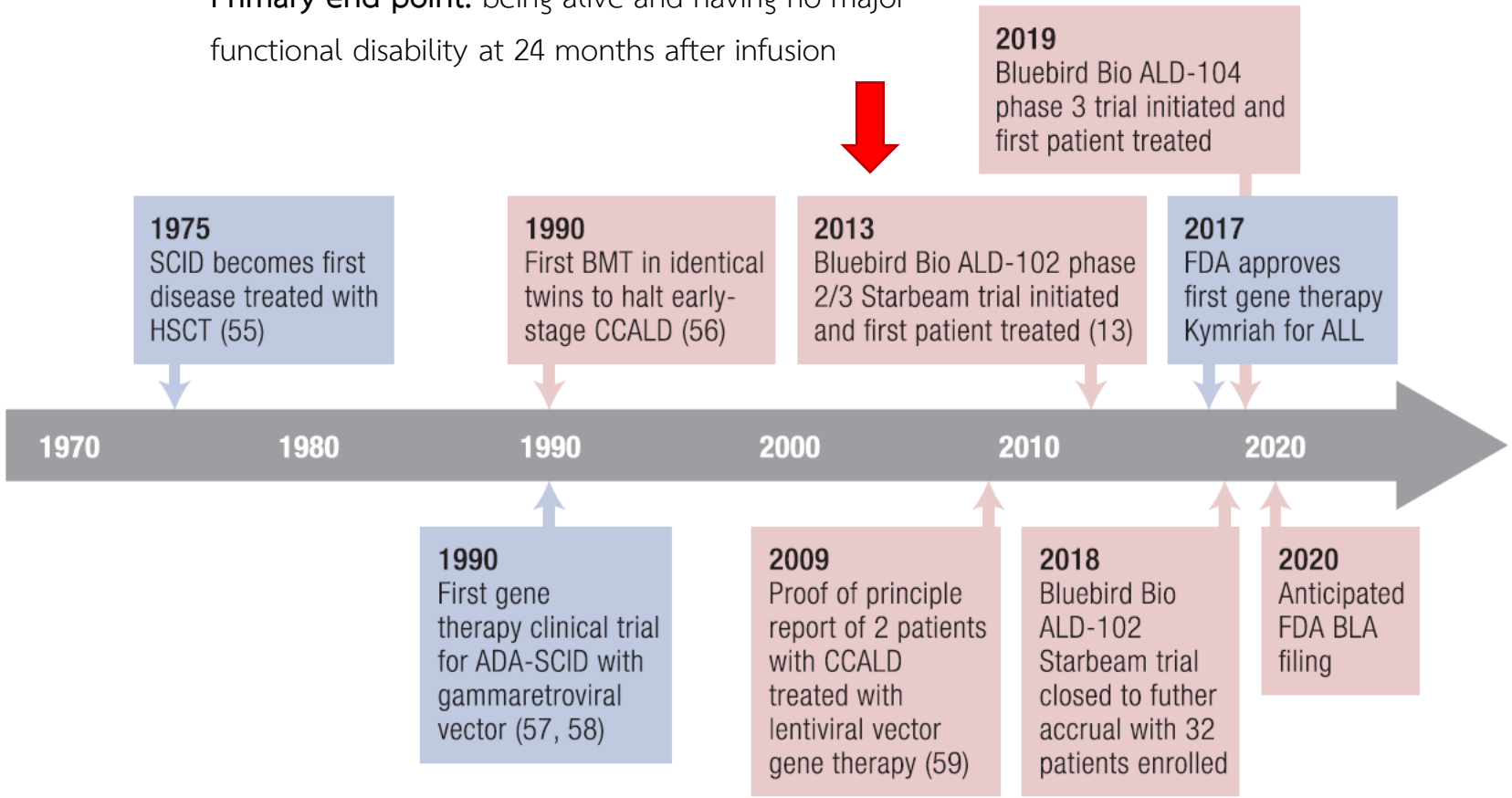
Parieto-occipital WM (maximum 4) **Anterior temporal WM** (maximum 4) **Frontal WM** (maximum 4) • Periventricular • Central • Subcortical • Local atrophy	**Visual pathway** (maximum 4) • Optic radiation • Meyer's loop • Lateral geniculate body • Optic tract
Corpus callosum (maximum 5) • Splenium • Body • Genu • Splenium atrophy • Genu atrophy	**Auditory pathway** (maximum 4) • Medial geniculate body • Brachium of inferior colliculus • Lateral lemniscus • Pons
Basal ganglia (maximum 1)	**Projection fibers** (maximum 2) • Internal capsule • Brainstem
Cerebellum (maximum 2) • White matter • Atrophy	**Global atrophy** (maximum 4) • Mild • Moderate • Severe • Brainstem

Each region is scored as 0 if normal, 0.5 if unilateral involvement is present, and 1 if the lesion or atrophy is bilateral. The maximum severity score is 34; a score of ≥1 is considered abnormal. WM – white matter.

Peters C, Charnas LR, Tan Y, et al. Blood. 2004;104(3):881–888.

Gene therapy for CCALD timeline

Primary end point: being alive and having no major functional disability at 24 months after infusion



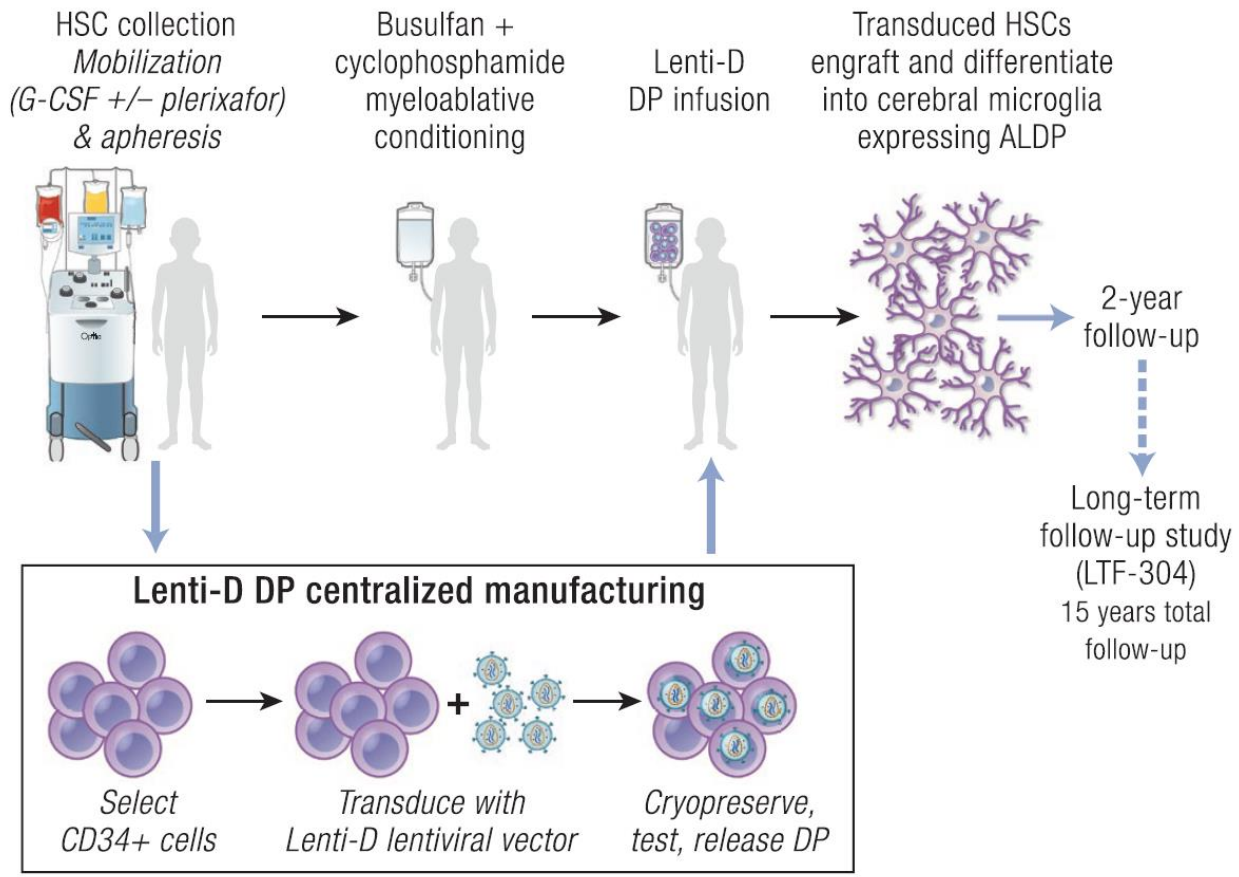
Abbr:

ADA, adenosine deaminase; ALL, acute lymphoblastic leukemia;
BLA, biologics license application; BMT, bone marrow transplant;
SCID, severe combined immunodeficiency

Zhu J, et al. Endocr Rev. 2020 Aug 1;41(4):577-593.

Gene therapy

Treatment protocol for the gene therapy study utilized in the Bluebird Starbeam ALD-102 trial



Results of phase 2-3 safety and efficacy study

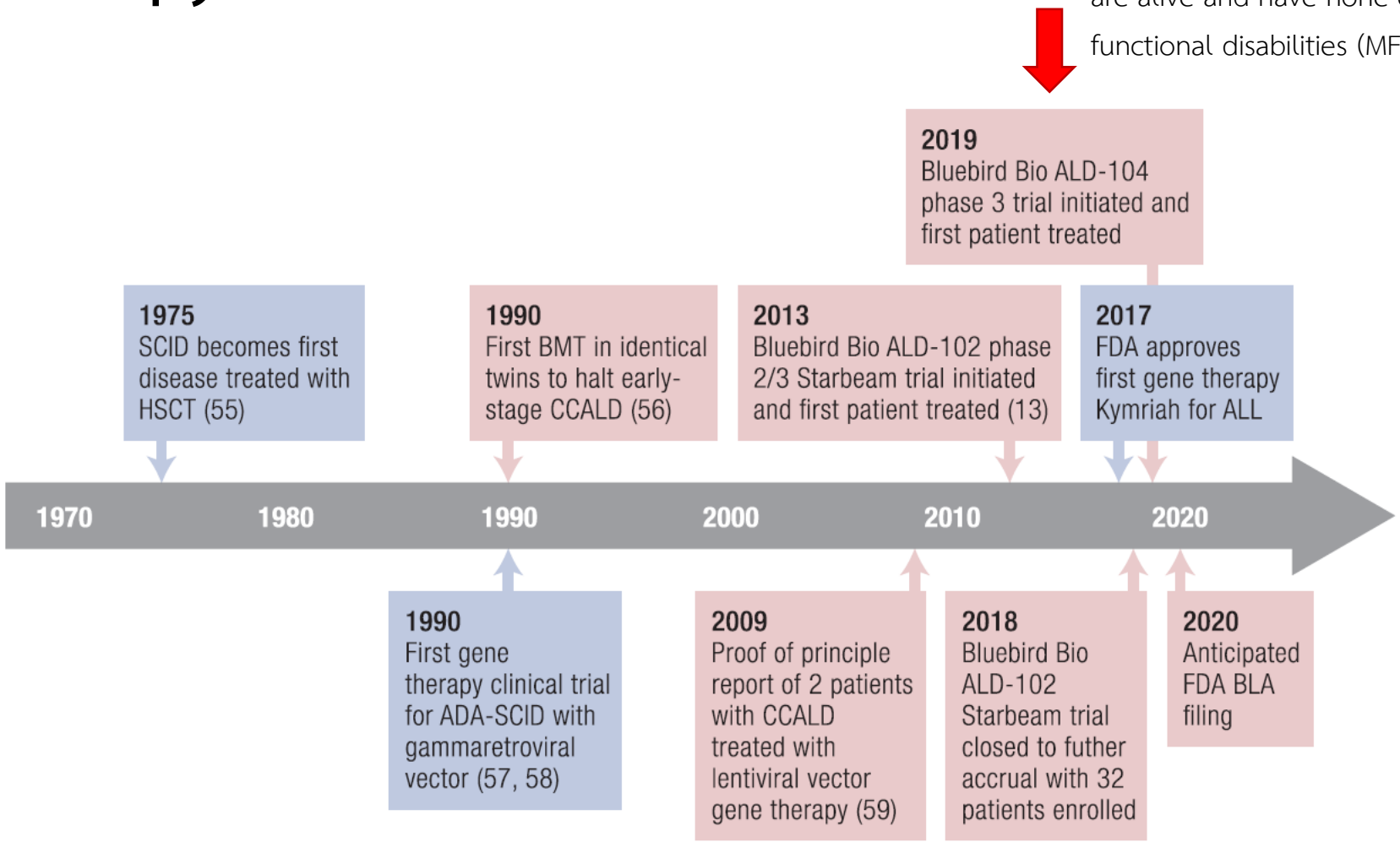
- 17 boys received Lenti-D gene therapy
- Median F/U 29.4 months (range, 21.6-42.0)
- All the patients had
  - Gene marked cells after engraftment, with no evidence of preferential integration near known oncogenes or clonal outgrowth
  - Measurable ALD protein
- No treatment-related death or GVHD
- 15 of the 17 patients (88%) were alive and free of major functional disability, with minimal clinical symptoms
- One patient, who had had rapid neurologic deterioration, had died from disease progression
- Another patient, who had had evidence of disease progression on MRI, had withdrawn from the study to undergo allogeneic stem cell transplantation and later died from transplantation-related complications

Zhu J, et al. Endocr Rev. 2020 Aug 1;41(4):577-593.

Eichler F, et al. N Engl J Med. 2017 Oct 26;377(17):1630-1638.

Gene therapy for CCALD timeline

Primary end point: proportion of subjects who are alive and have none of the 6 major functional disabilities (MFDs) at Month 24



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