Fast Tracks in Slow Conditions: Biomarkers in Rare Disease Clinical Trials

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Learning Objectives

Define biomarkers and surrogate endpoints

Understand validation principles

Explore heparan sulfate as a case example

Discuss advantages, limitations, and regulatory aspects

What is a Biomarker?

An objective, measurable indicator of biological processes

Examples:

Blood pressure,

hemoglobin A1C,

troponin,

prostate specific antigen

Classes of Biomarkers

- Diagnostic

  Is there disease?

- Prognostic

  How bad is it?

- Predictive

  Which treatment for this patient?

- Therapy response

  Is the treatment helping?

Troponin: a diagnostic biomarker for myocardial infarction (heart attack)

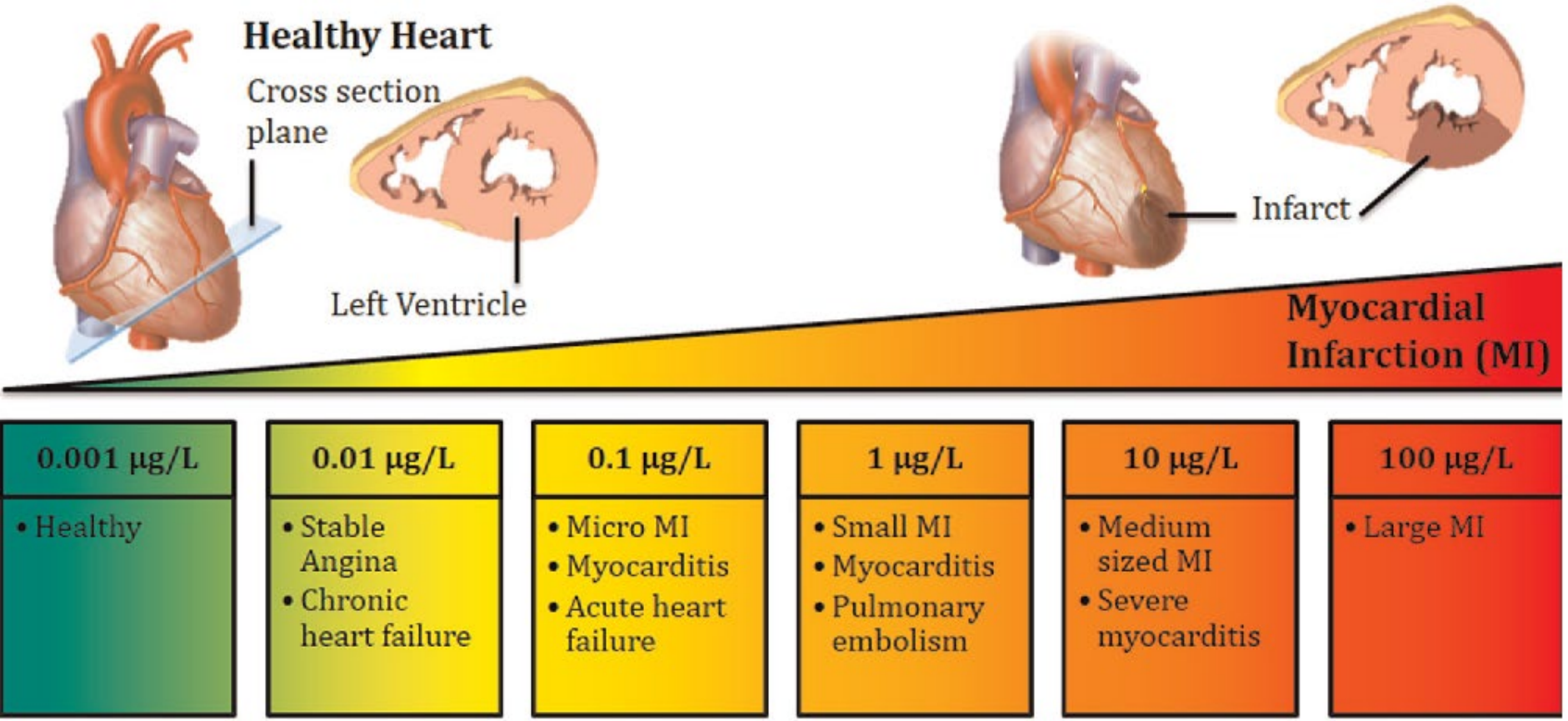
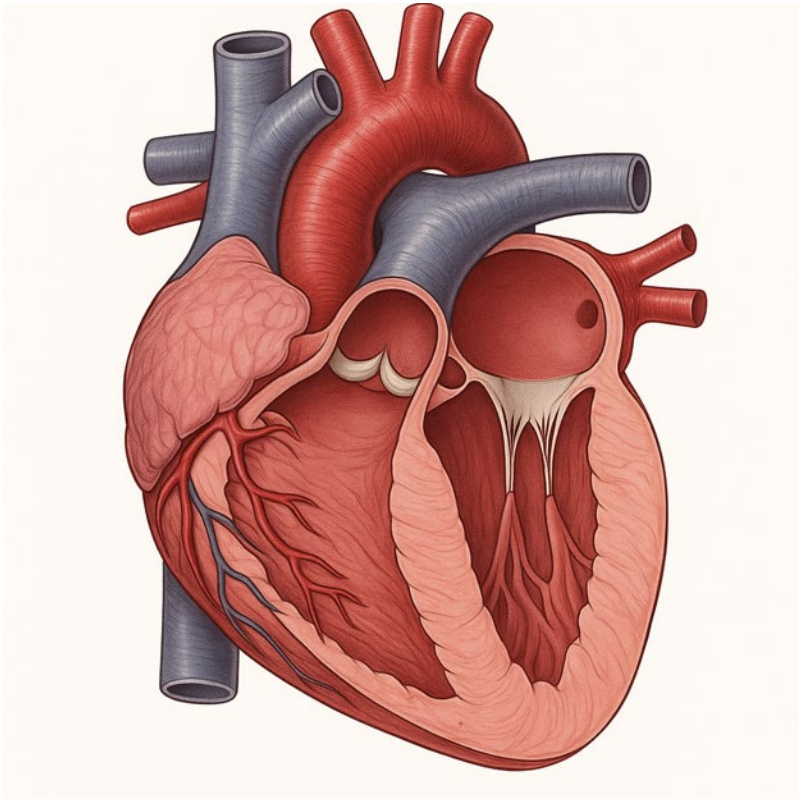


Figure from Fathil et al, Biosens Bioelectron, 2015

Natriuretic peptide: a prognostic biomarker



BNP is released by the heart in response to increased wall stretch and pressure

The higher it is, the worse the heart disease and the more likely a person is to have an episode of heart failure

Also used as a diagnostic biomarker

HER2 (Human Epidermal Growth Factor Receptor 2)
a predictive biomarker

Identifies which breast cancer patients are likely to respond to **HER2-targeted therapy**

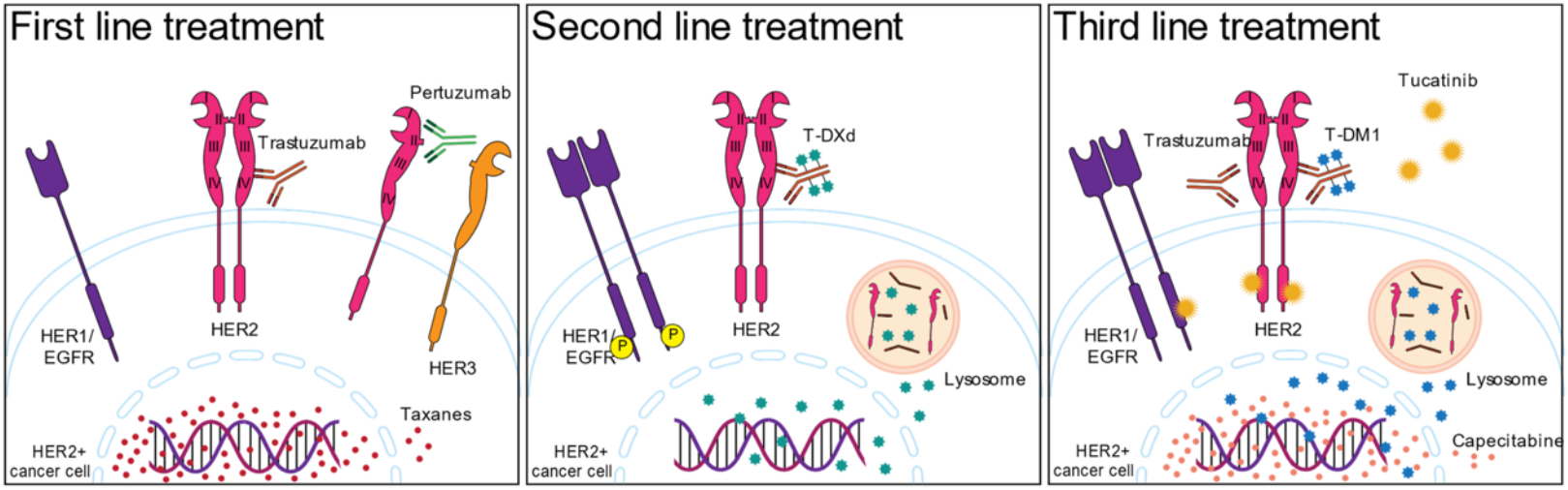


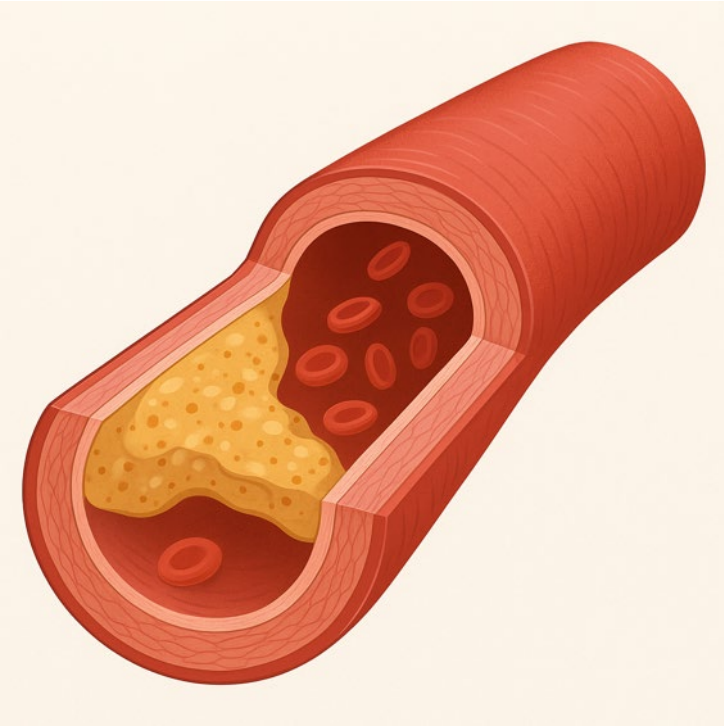
Figure source: Mercogliano, *Cancers* **2023**

HER2-positive breast cancers:
Grow faster
Are more likely to metastasize
Historically had poorer outcomes before targeted therapies existed

Low-density lipoprotein (bad cholesterol): *a therapeutic response biomarker*

Reducing LDL-C correlates strongly with reduced cardiovascular events and mortality

Taking a statin medication lowers LDL



Why Biomarkers Matter

• Enable early detection and personalized therapy

• Reduce trial cost and duration

• Provide objective endpoints

Surrogate Endpoints

Substitute biomarkers for clinical outcomes

Predicts benefit on survival or function

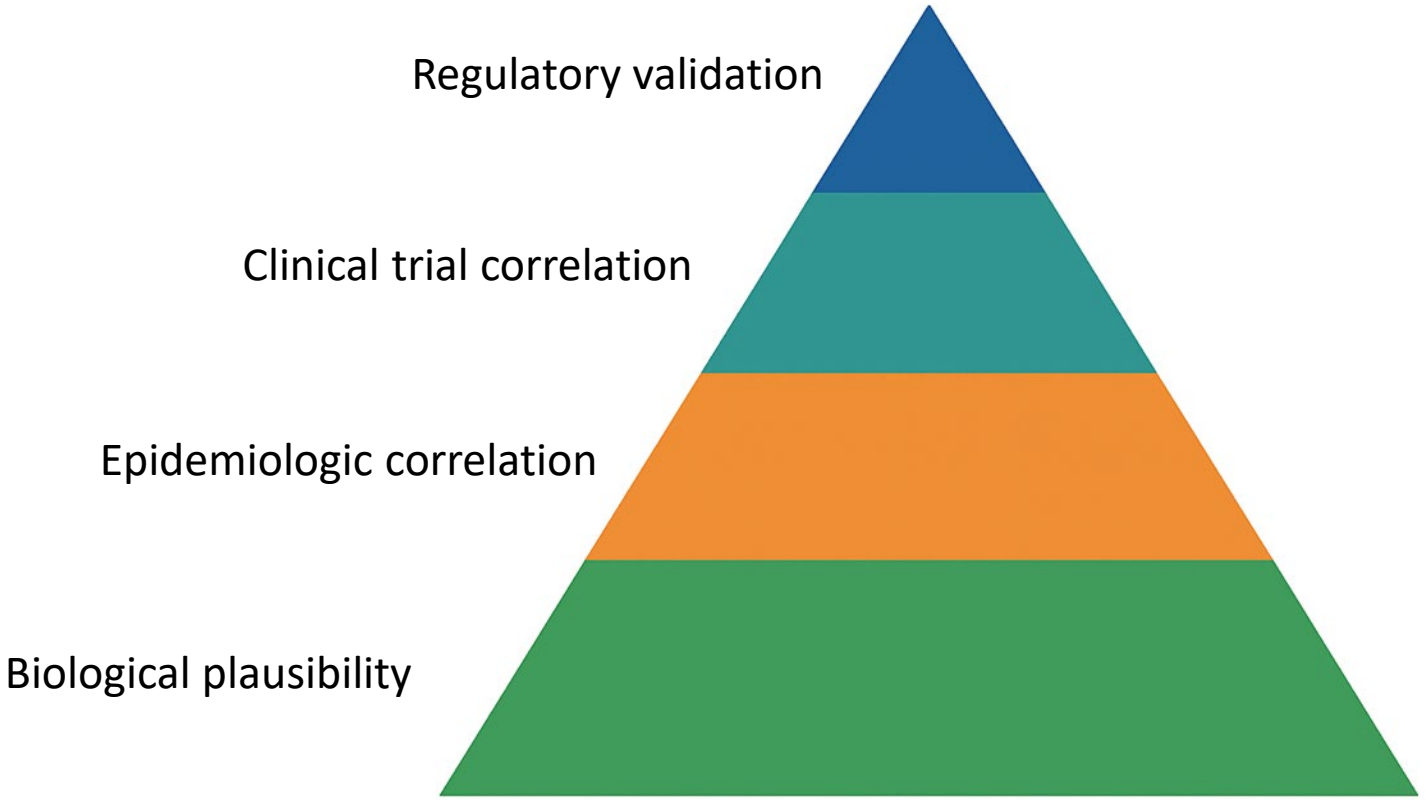
Example: testing whether a drug lowers blood glucose and assuming that if it does, there will be fewer complications of diabetes (kidney failure, vision loss, amputations)

Thriva.co

Advantages of Surrogates

- Faster and smaller trials
- Can be more ethical in serious disease
- Early efficacy signal

Surrogate Marker Validation Pyramid



Prentice criteria for a surrogate endpoint

	Principle	Example of LDL
1	Treatment affects clinical outcome	**Criterion 1:** Statins reduce cardiovascular events → ☑
2	Treatment affects surrogate	**Criterion 2:** Statins lower LDL-C → ☑
3	Surrogate associated with clinical outcome	**Criterion 3:** Lower LDL-C correlates with fewer events → ☑
4	Surrogate fully mediates treatment effect	**Criterion 4:** The reduction in LDL-C fully explains (mediates) statins' effect on events → ☑

Limitations of Surrogates

- Correlation ≠ causation
- May mislead
- Requires careful validation

Phenylketonuria (PKU) and phenylalanine

- Before the 1960s, a major cause of intellectual disability was PKU
- After PKU was identified, it was discovered that if phenyalanine is withheld from the diet, newborns will not develop ID

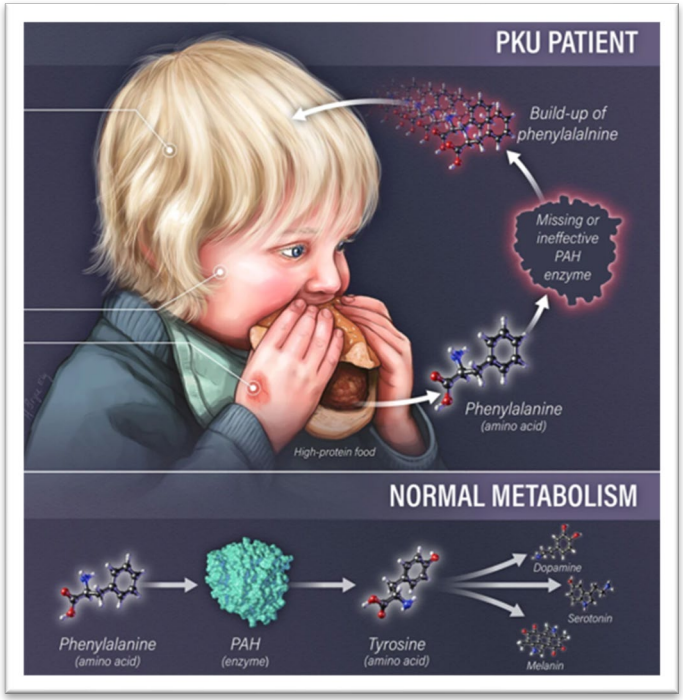
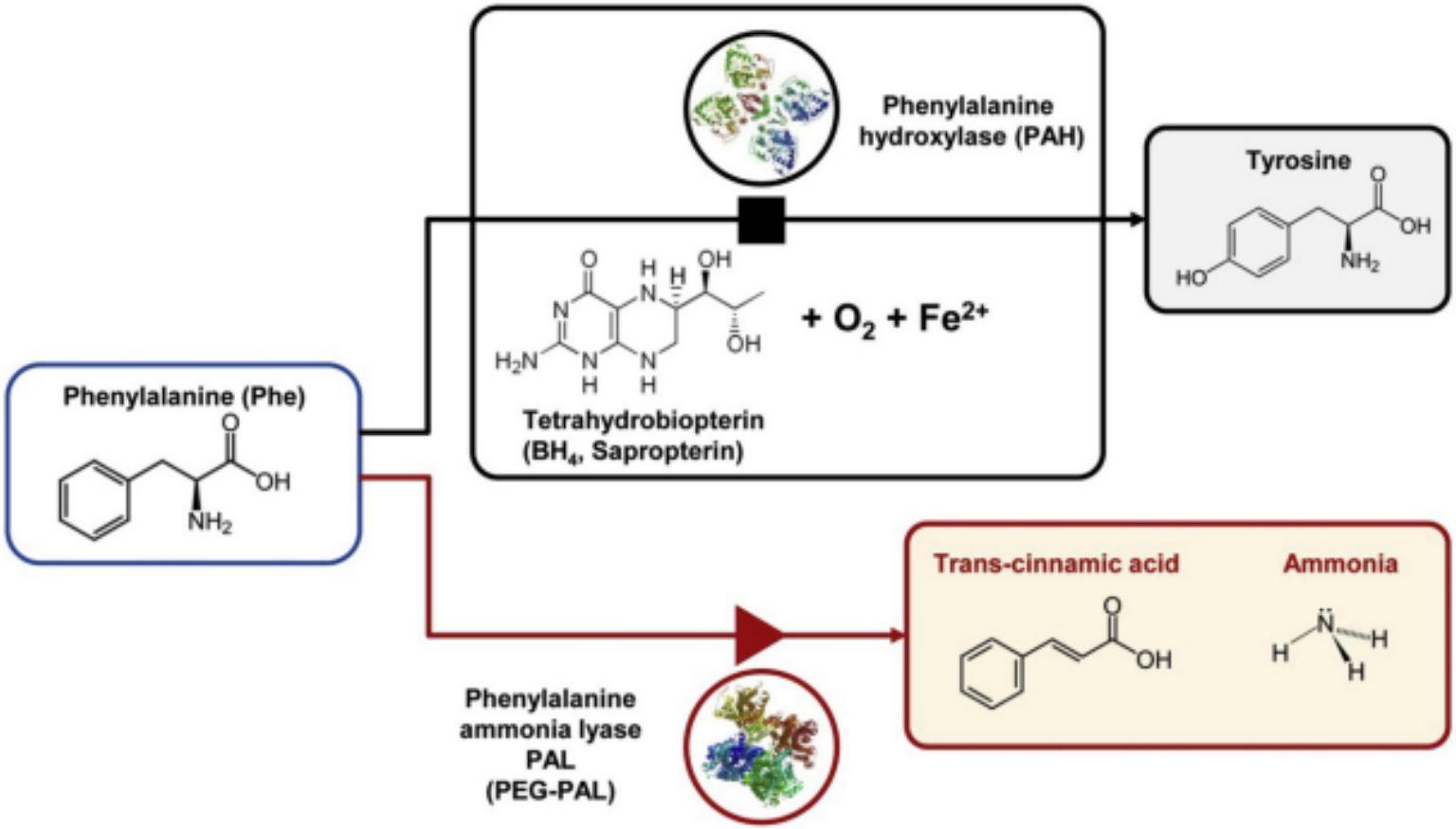


Image source: Hannah Ely, https://www.hbely.com/work/pkuposter


Phenylalanine hydroxylase (PAH)
Tyrosine
Phenylalanine (Phe)
+ O_2 + Fe^{2+}
Tetrahydrobiopterin
(BH_4, Sapropterin)
Trans-cinnamic acid
Ammonia
Phenylalanine ammonia lyase PAL (PEG-PAL)

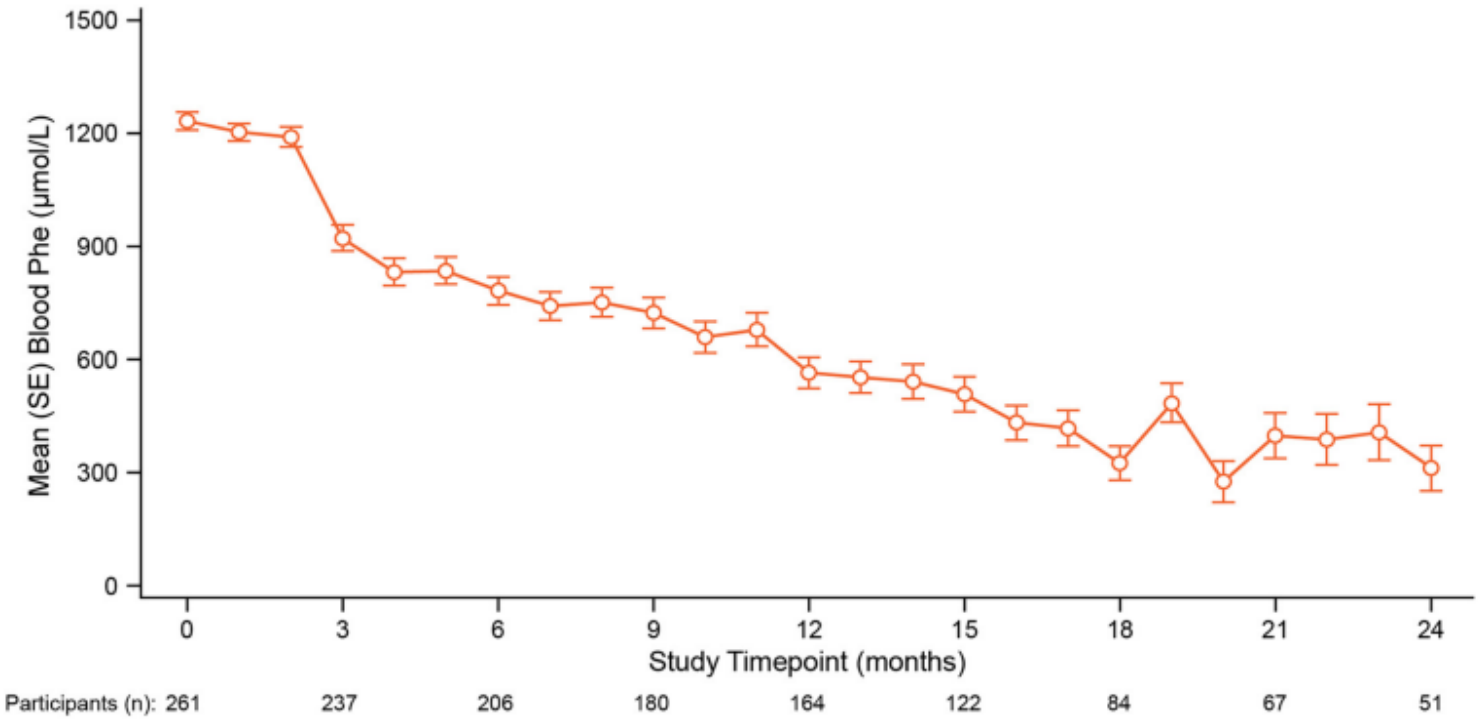


Fig. 3. Mean blood Phe concentration over time (intent-to-treat population; $N = 261$). Sample size reflects participants with data available at study timepoint and who have reached study timepoint at data cut; study is ongoing. Error bars represent standard error. SE, standard error.

"The primary endpoint was change in blood phenylalanine concentration, an established surrogate reasonably likely to predict clinical benefit."
(Source: FDA Palynziq approval letter and review documents)

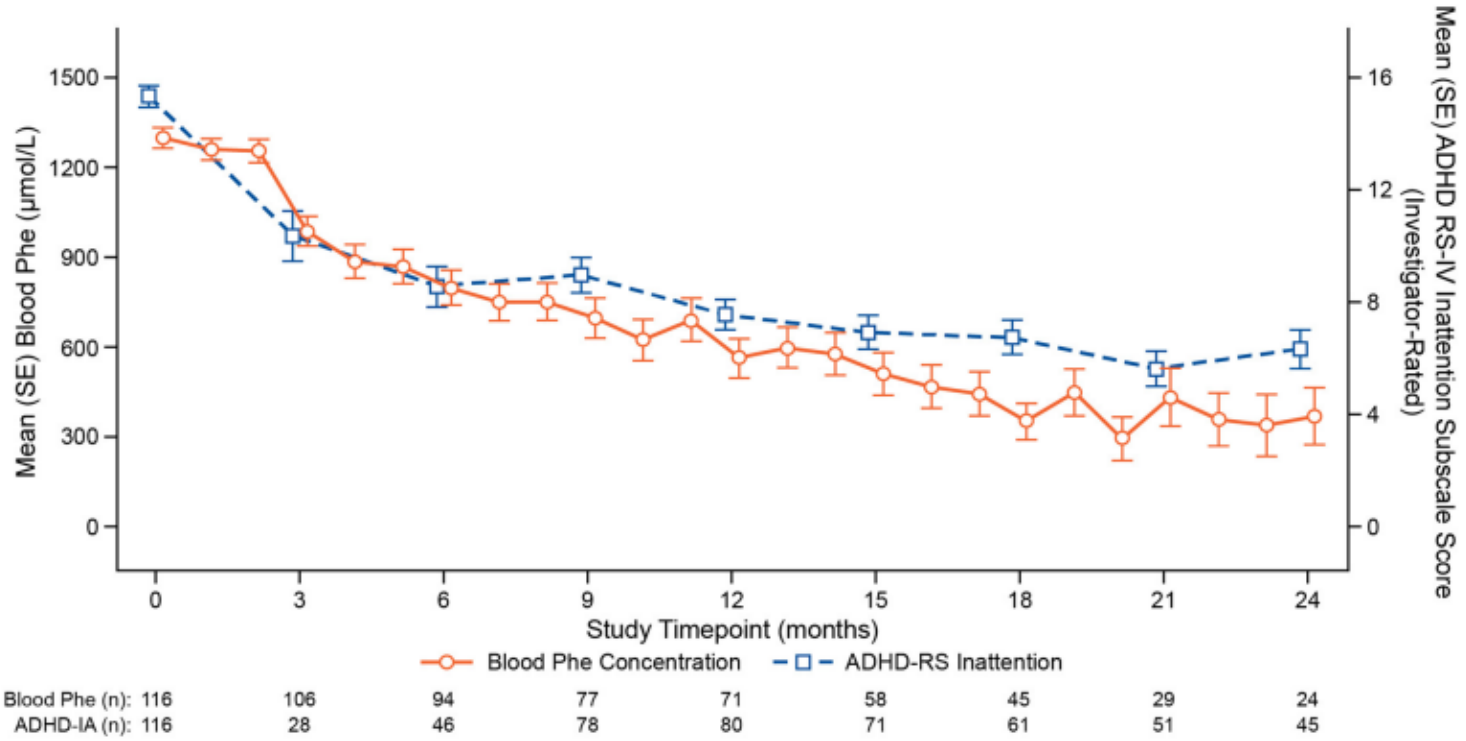
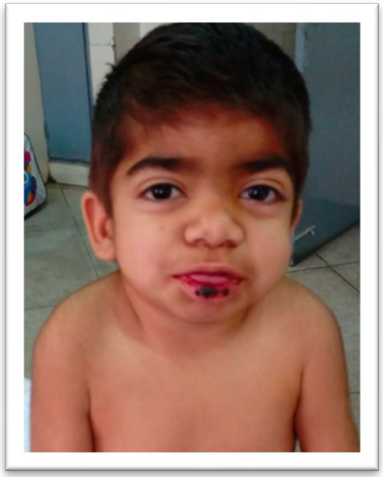
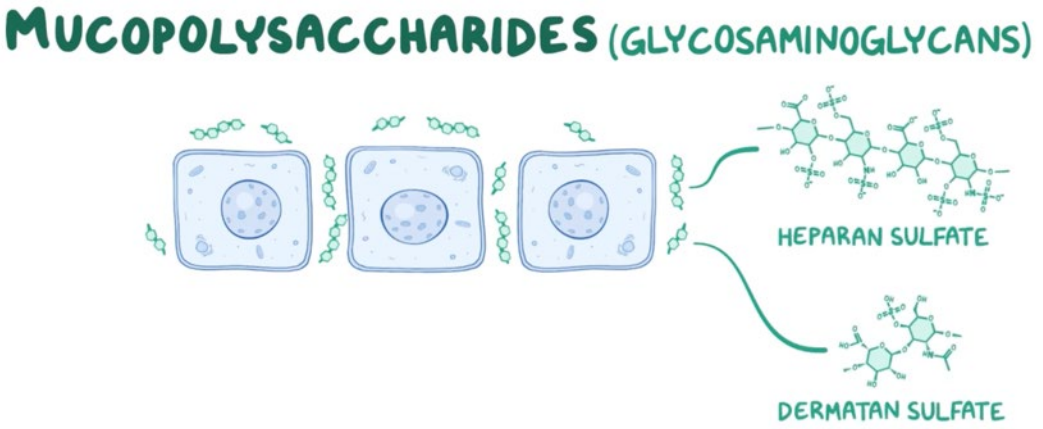


Fig. 5. Blood Phe concentration and investigator-rated ADHD RS-IV IA scores in participants with baseline scores > 9 (inattention subgroup, $N = 116$). Sample size reflects participants with data available at study timepoint and who have reached study timepoint at data cut; study is ongoing. ADHD RS-IV IA, Attention Deficit Hyperactivity Disorder Rating Scale IV inattention subscale; SE, standard error.

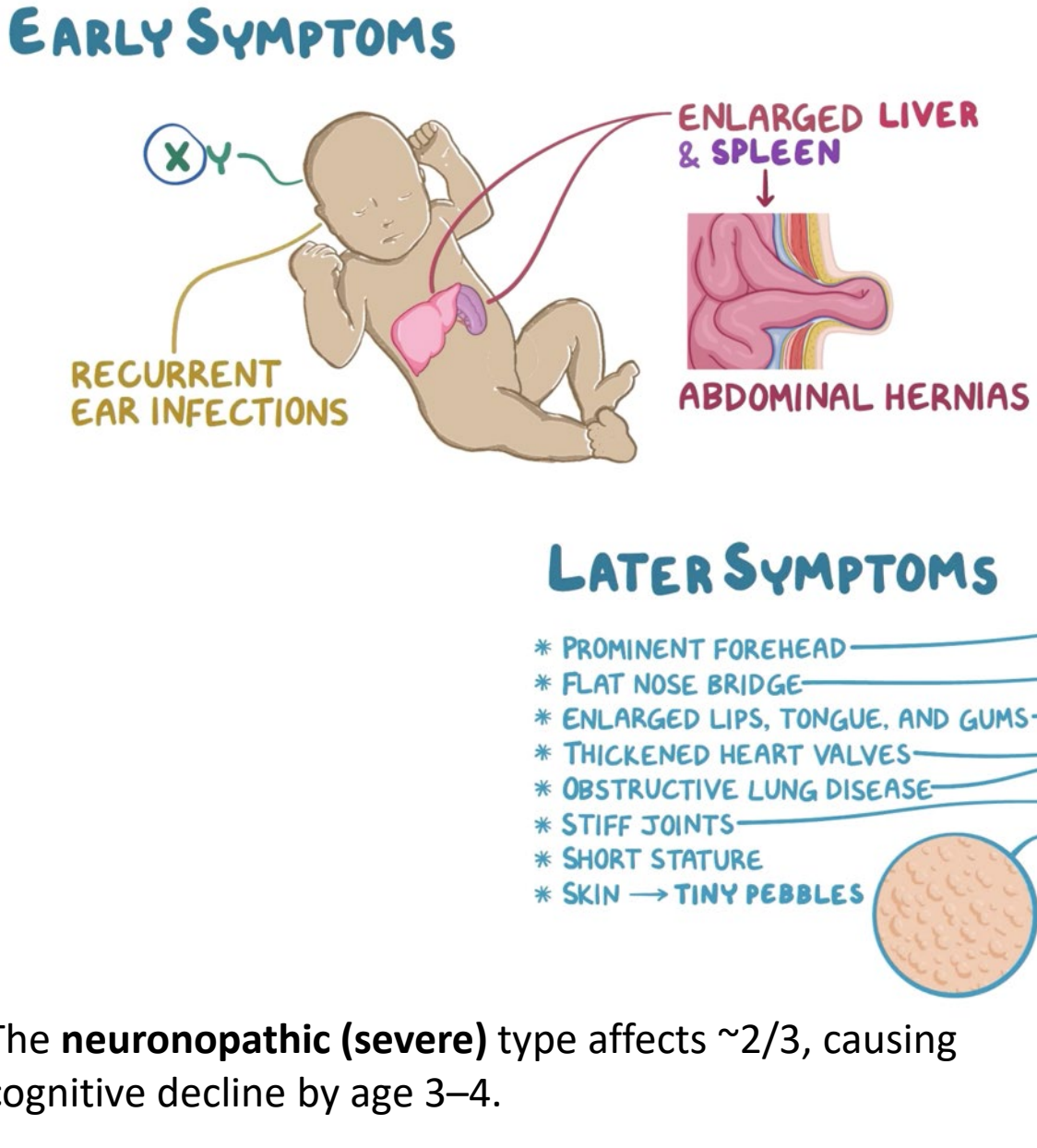
Mucopolysaccharidosis type 2 (Hunter syndrome)





Osmosis.org

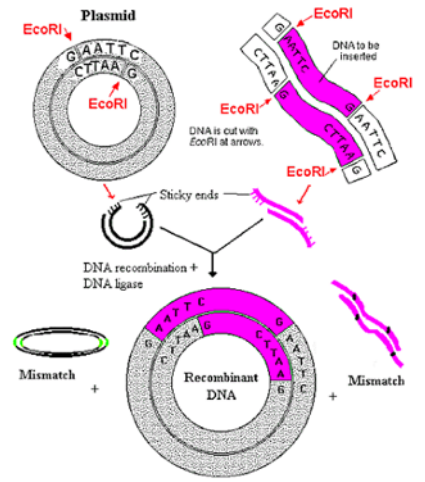
https://doi.org/10.1136/bcr-2018-226518



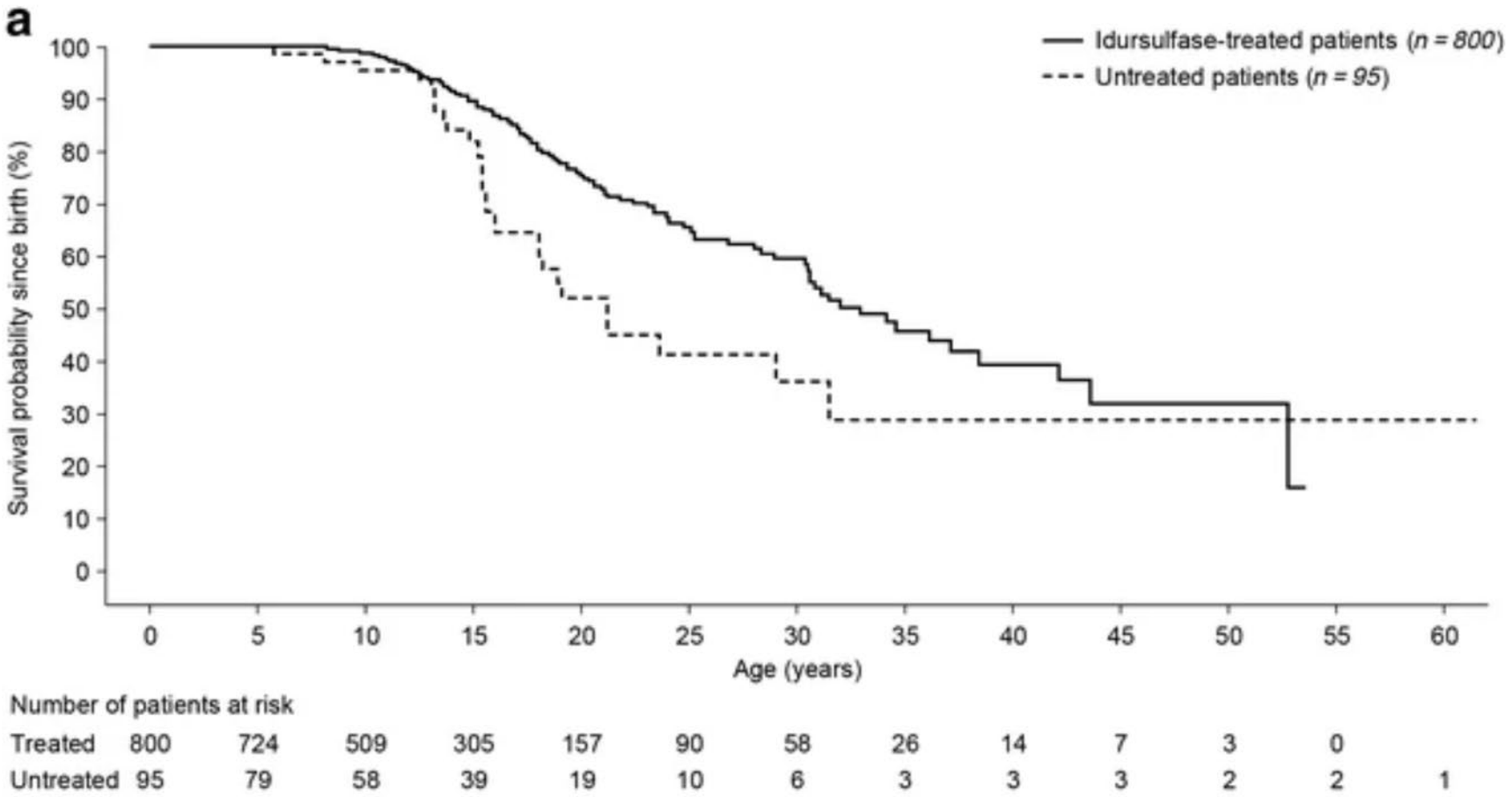
The **neuronopathic (severe)** type affects ~2/3, causing cognitive decline by age 3–4.

Source: osmosis.org

A gene for the desired protein is cloned into a plasmid and then transfected into host cells, which then mass-produce the product in bio-reactors. After harvesting, purification, and quality checks, the drug is ready to be distributed

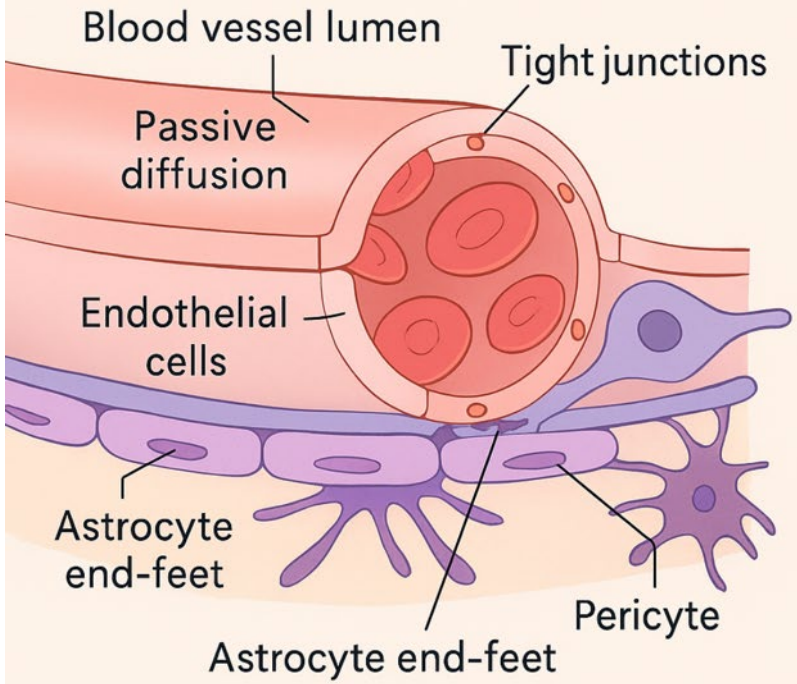


Inserting a DNA Sample into a Plasmid



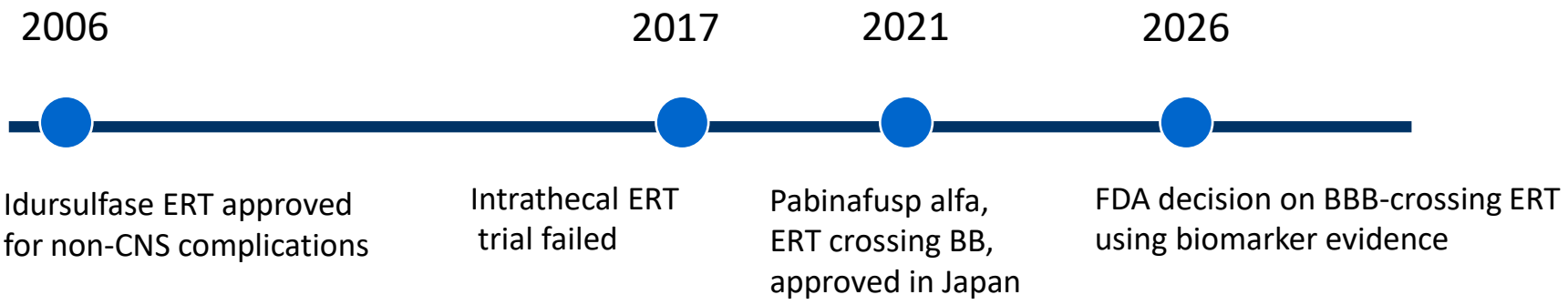
Burton et al., JIMD, 2017

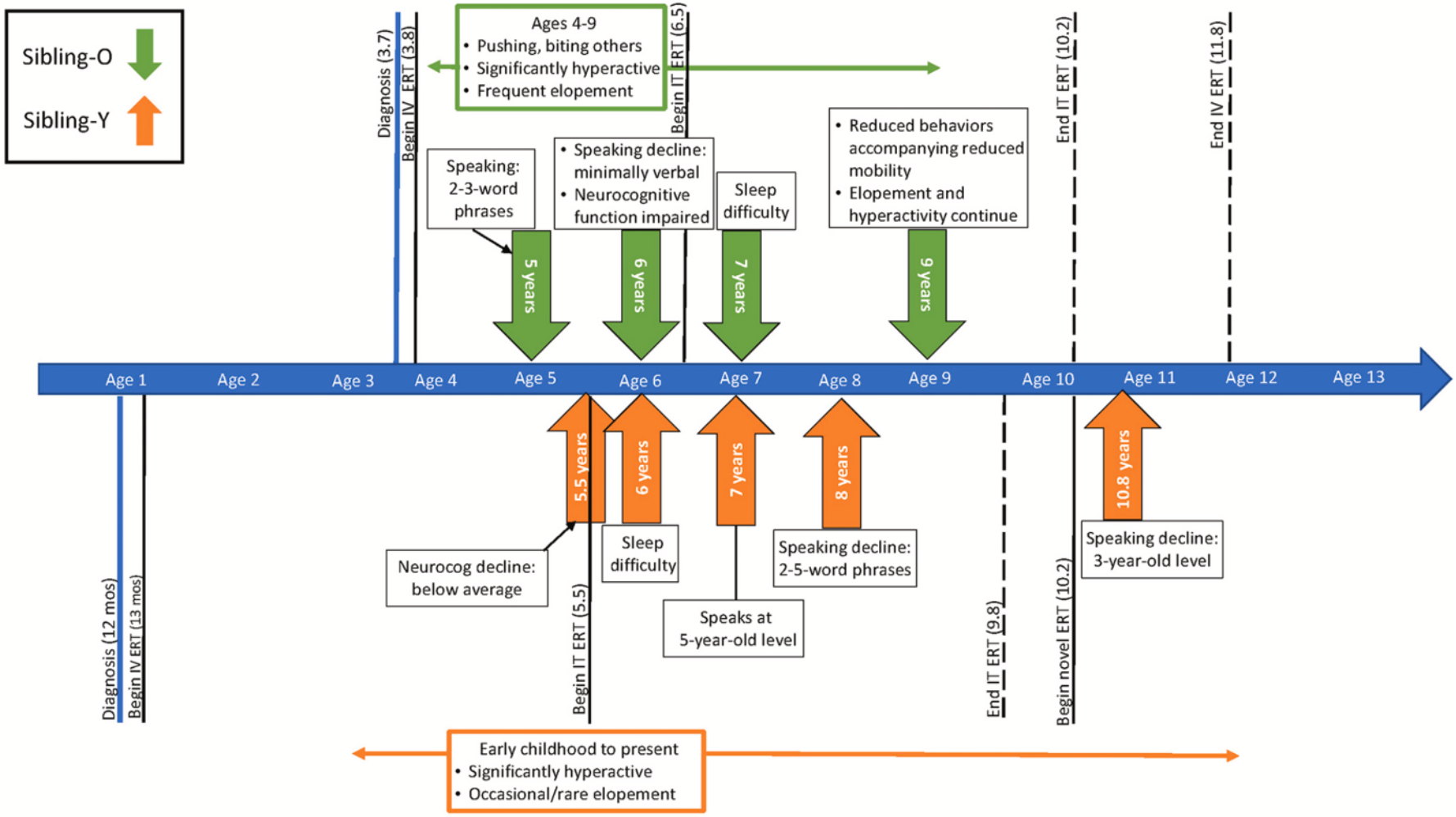
BLOOD-BRAIN BARRIER



Crosses BBB?	
Lipid-soluble molecules	✓ Yes — Passive diffusion
Glucose amino acids	✗ No — Carrier-mediated transport
Large/charge molecules	✗ No — Carrier-mediated transport
Proteins	✗ No
Pathogens	✗ No

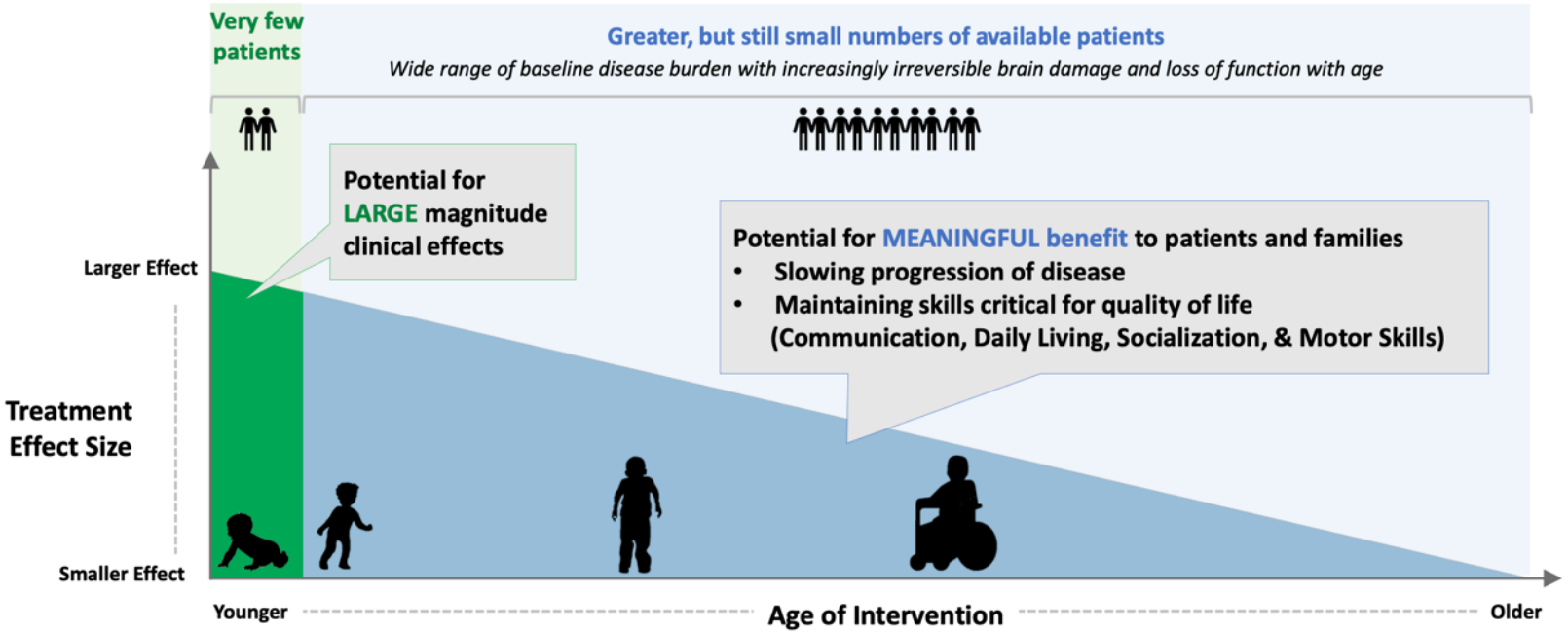
The evolution of treatment for MPS 2





Grant et al, Molecular Genetics and Metabolism Reports 30 (2022)

Demonstrating Effectiveness in Clinical Trials for Neuronopathic MPS Children is Challenging



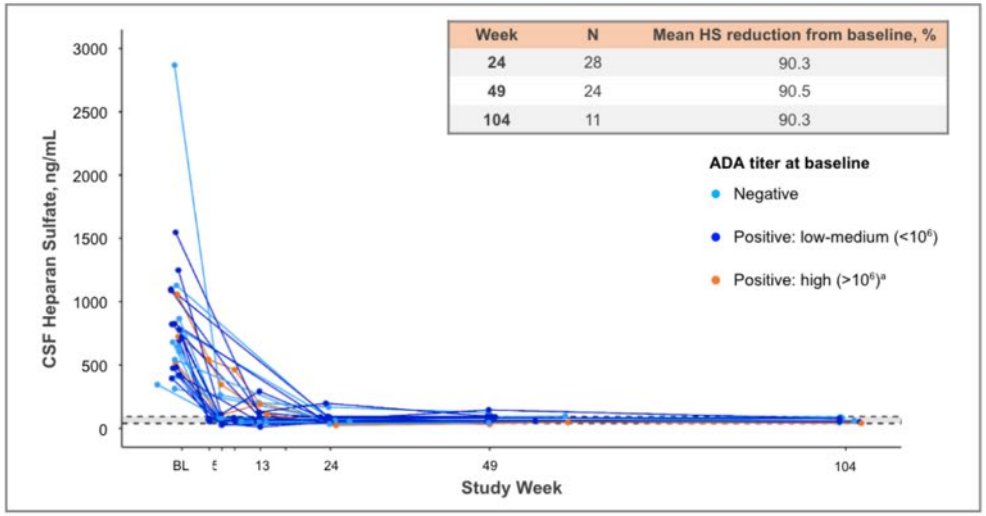
Demonstrating evidence of effectiveness for therapies in neuronopathic MPS is **extremely challenging** given the low prevalence, baseline disease burden of children at time of entry into clinical trials and long timespan of symptom evolution

Slide created by Dr. Cara O'Neill

CSF Heparan Sulfate Reduction with Weekly IV DNL310

RESULTS: BIOMARKERS

CSF HEPARAN SULFATE



Week	N	Mean HS reduction from baseline, %
24	28	90.3
49	24	90.5
104	11	90.3

Normal levels of CSF HS[b] were achieved and sustained over time, including in those with pre-existing high ADA

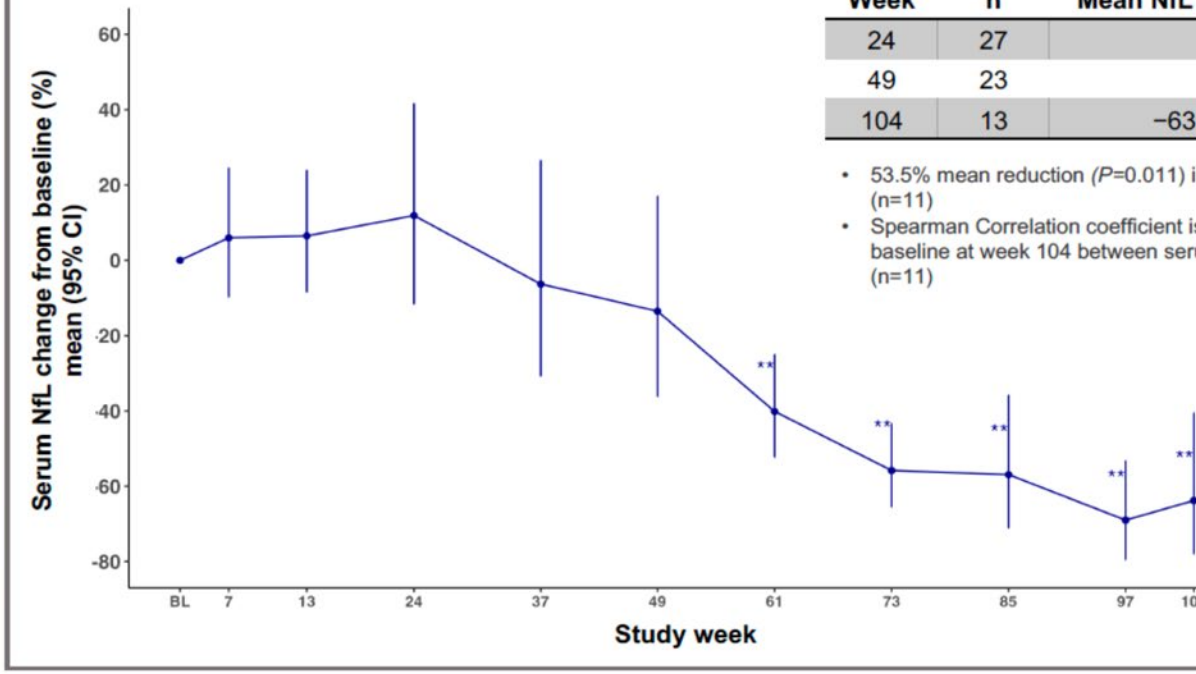
Data cutoff: 2 Mar 2023. ADA, anti-drug antibody; BL, baseline; CSF, cerebrospinal fluid; HS, heparan sulfate.
[a]3 participants had high baseline ADA titer; [b]CSF HS was measured as a sum of the disaccharides D0A0, D0A6, D0S0, and D2S6 by mass spectrometry after enzymatic digestion. Preliminary normal range (10th-90th percentile) was based on analysis of CSF from healthy adults (n=30; median [range] age, 52 [18-80] years); 39.1-92.51 ng/mL. Total CSF GAG levels are similar in adults and children.[1]

1. Hendriksz CJ, et al. *Mol Genet Metab Rep.* 2015;5:103-106.

Data presented at the WORLD Symposium, San Diego, CA (Feb 2024)

Data presented by J. Muenzer

Serum Neurofilament Light Chain (NfL) Reduction with Weekly IV DNL310



Week	n	Mean NfL change from BL, %
24	27	+11.9
49	23	−13.5
104	13	−63.8 (**P<0.001)

- 53.5% mean reduction (P=0.011) in CSF NfL at week 104 (n=11)
- Spearman Correlation coefficient is 0.76 for the change from baseline at week 104 between serum NfL and CSF NfL (n=11)

Data presented at the WORLD Symposium, San Diego, CA (Feb 2024)

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Is Heparan Sulfate a Good Enough Biomarker to Prove a New Drug Works to Improve Neuro Outcomes?

- HS measured in CSF is only coming from the **brain**, not other organs
- Higher CSF HS levels corresponds with **greater neurological impairment**
- Concentrations decrease after therapy.
- **Neurocognitive and adaptive behavior were overall stabilized** during therapy in a Phase 2 trial *(eg., Mol Ther 2021, 272:378–2386.)*
  - **However,** reductions in CSF HS don't yet predict a defined amount of clinical benefit.
  - **Patients with advanced neurological injury**, even if CSF HS decreases, **measurable clinical improvement may not occur**

The verdict by the FDA?

- CSF heparan sulfate is an acceptable surrogate endpoint measure for consideration of **"Accelerated Approval"**

- **Accelerated Approval pathway** allows the FDA to approve a drug **based on a surrogate or intermediate clinical endpoint** that is *reasonably likely* to predict a genuine clinical benefit when measuring a clinical outcome is very slow, or difficult due to small numbers.
  - The disease must be very serious.
  - Past example: **HIV drugs** were approved based on **viral load reduction** rather than waiting for data on AIDS-related deaths.
  - Companies must conduct **confirmatory trials** to verify the predicted clinical benefit.
  - If those trials fail to show benefit, the FDA can **withdraw approval**.

Conclusions and Future Directions

Biomarkers are indispensable tools in medicine and science, but they are not all equal

We must never forget that we don’t treat biomarkers: we treat to improve quantity and quality of life.

Using only 1 biomarker is simple and inexpensive, but developing the ability to integrating multiple biomarkers may increase their power

If national regulators could work together and harmonize their procedures, this would speed up drug decisions and reduce costs