Overview of Therapeutic Approaches for MPS

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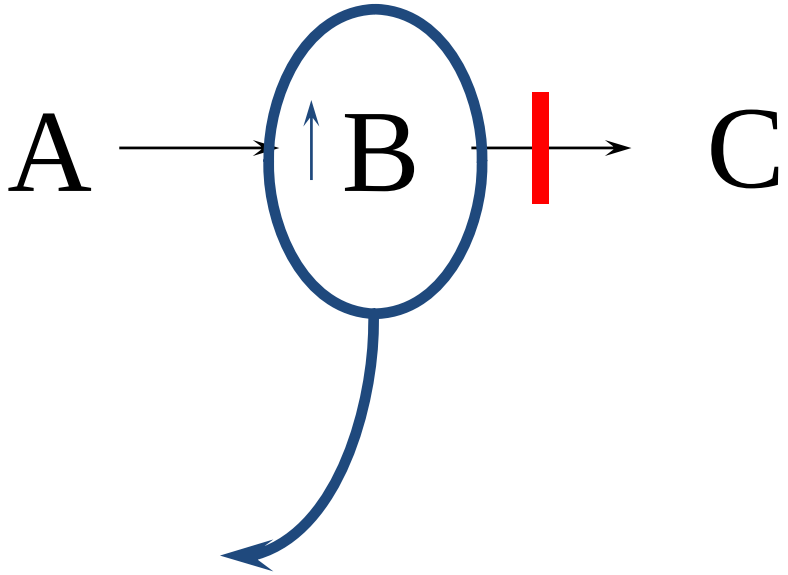
A
B
C

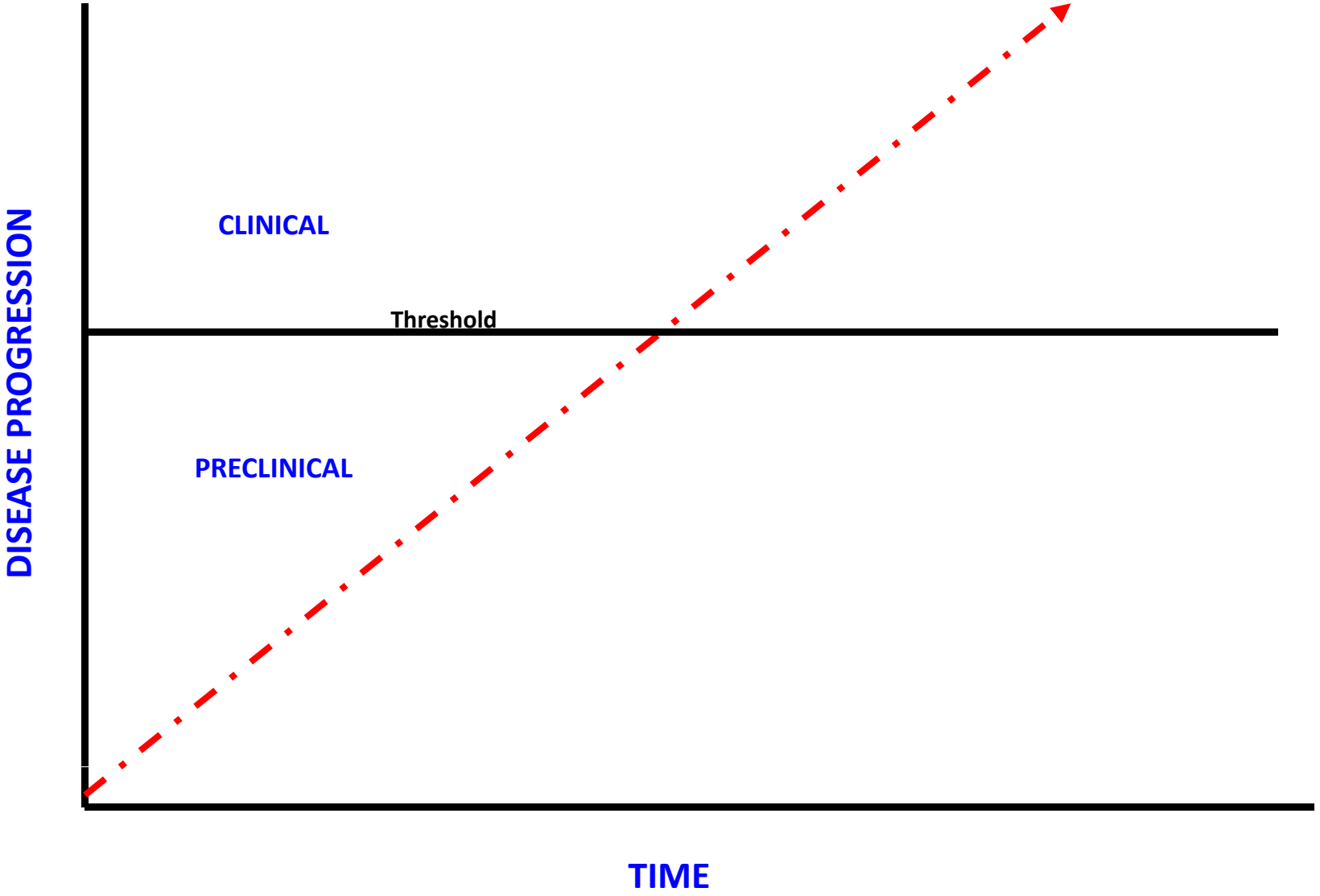


glycosaminoglycans

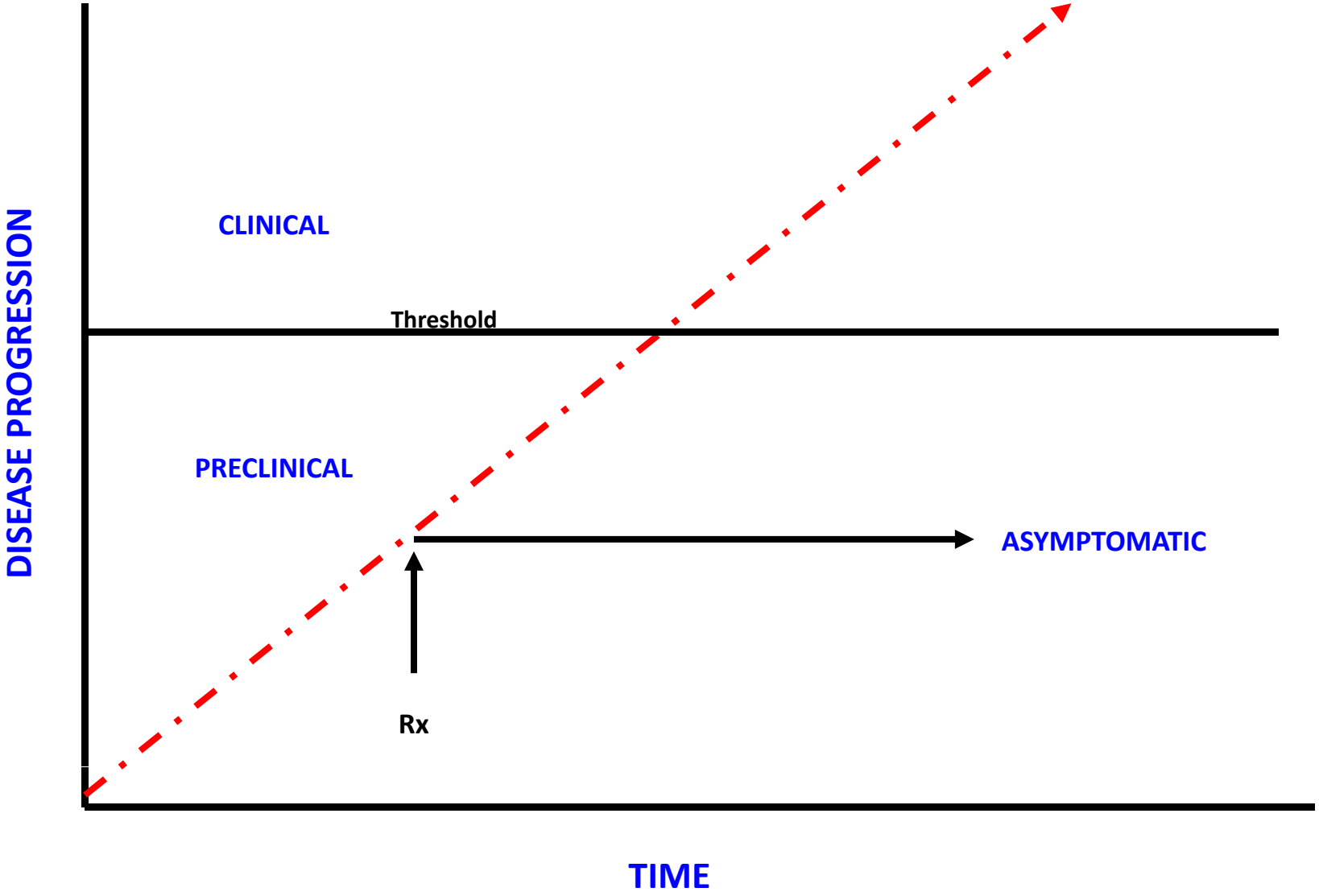
Principles of therapy

- Key attention so far has been reduction in lysosomal storage
- Less attention has been paid to the effects of storage (downstream)
- Very important but little researched is the large amount of multi-disciplinary supportive care required

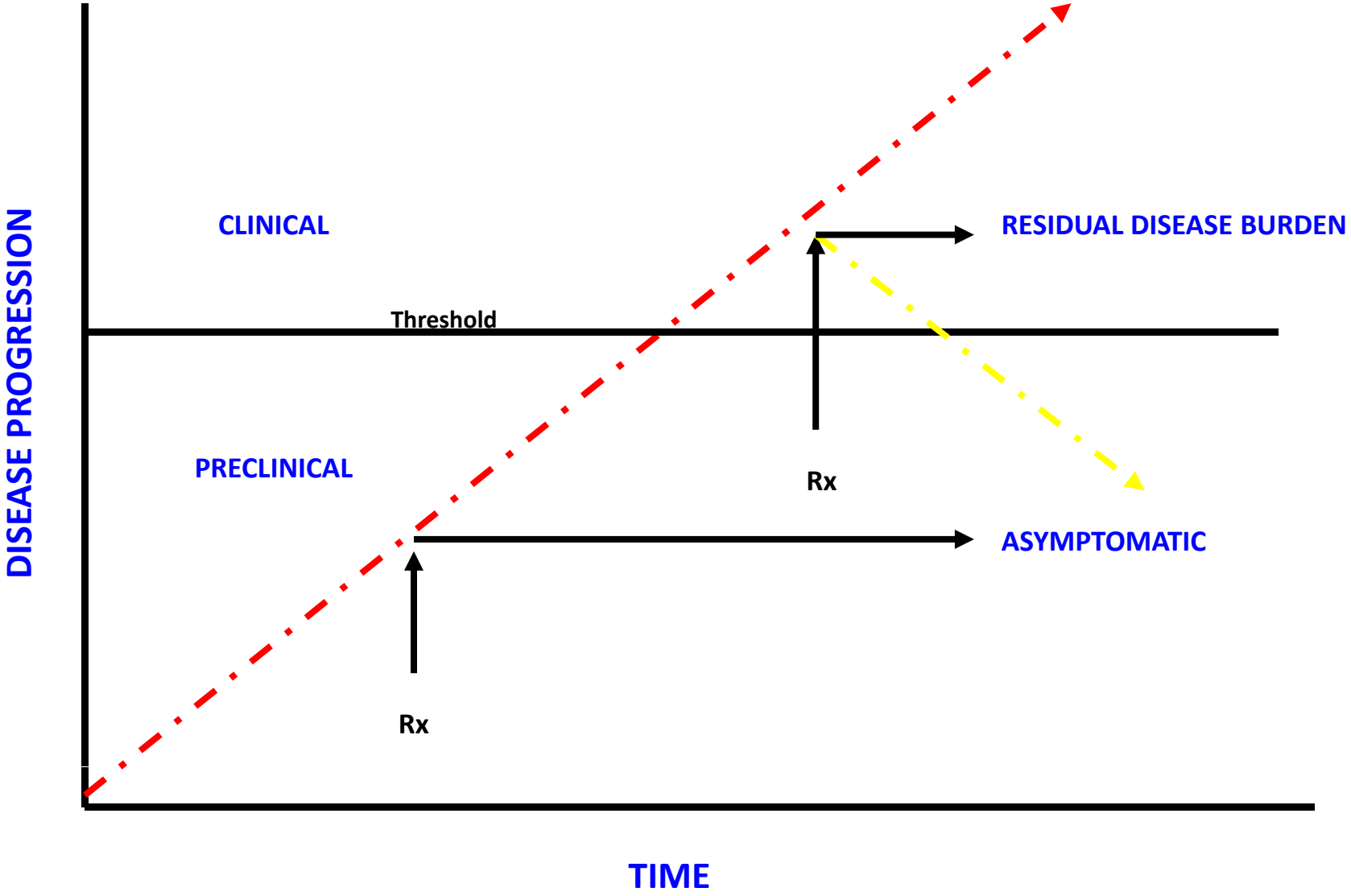
Disease Progression



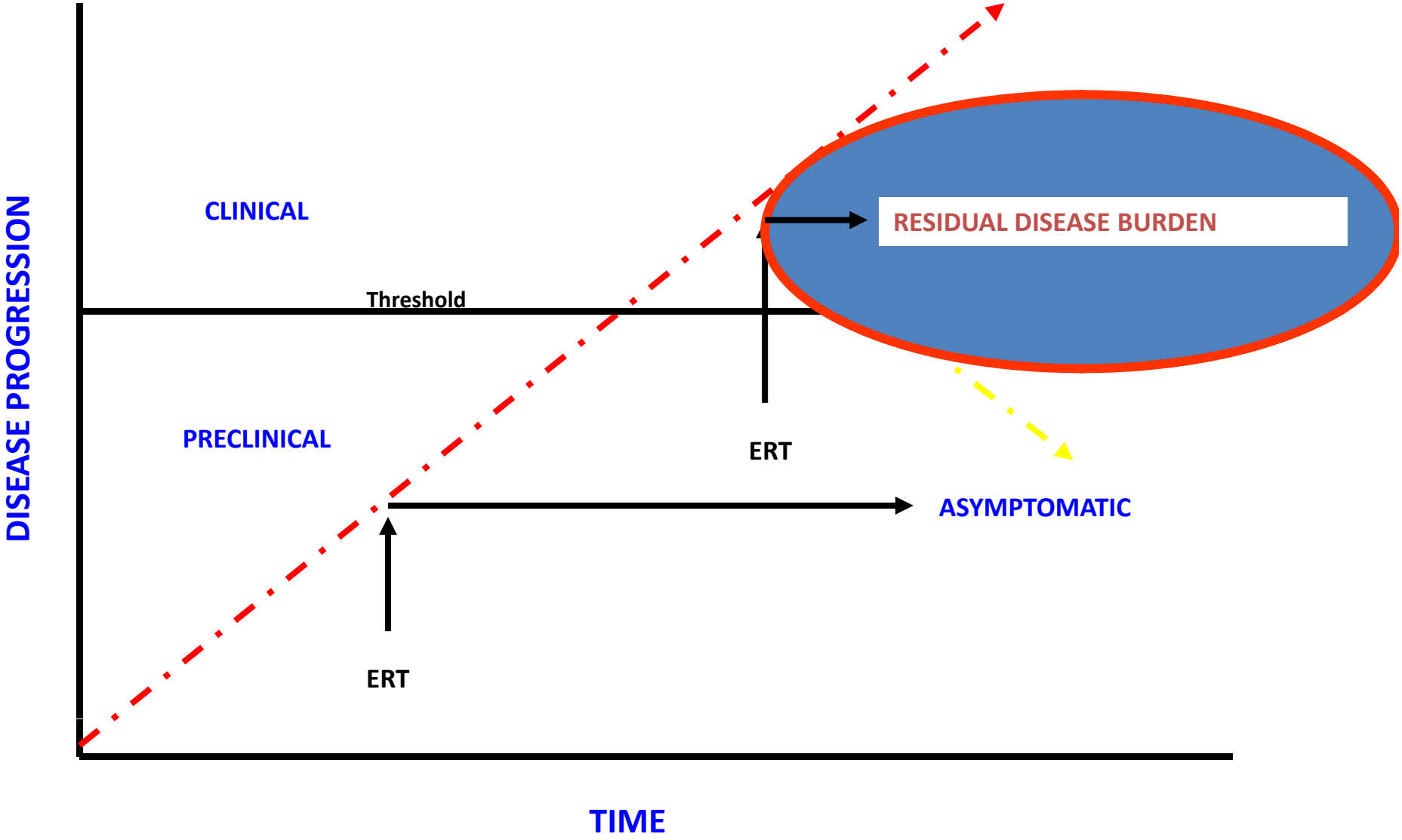
Therapeutic response to Rx



Therapeutic response to Rx



Therapeutic response to ERT

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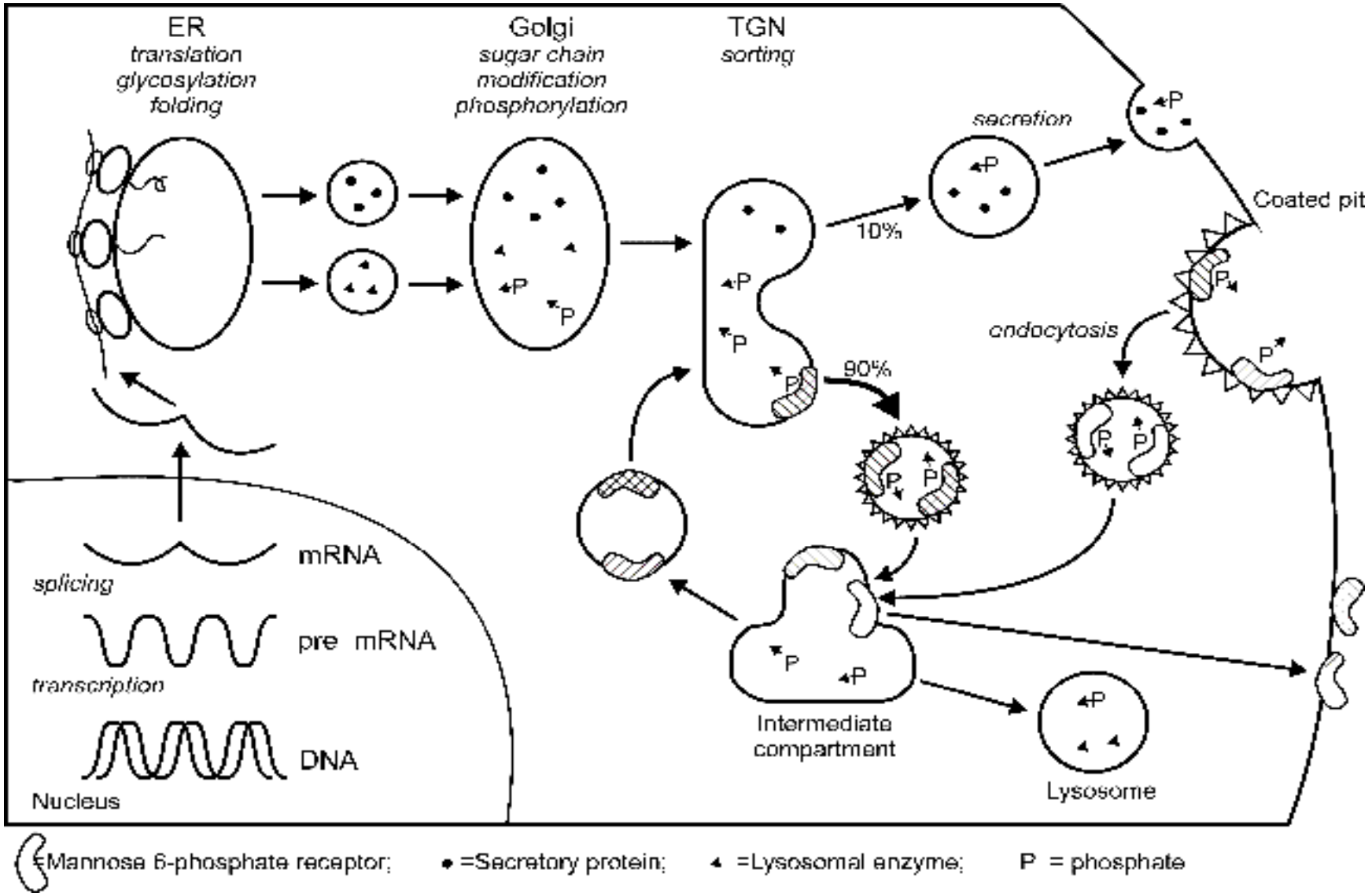
Concept

- Cross-correction (Neufeld in 1970s)
- Applies to a variety of techniques (including HSCT, gene therapy)
- Ideally suited for recombinant enzyme technology



Courtesy of Ans Van der Ploeg

Treatment options in LSDs

- Supportive/ palliative care

- Enzyme replacement therapy
- Bone marrow transplantation (HSCT)
- Substrate reduction therapy

- Chaperone therapy
- Gene therapy

What can ERT do well?

- Soft tissues with good blood supply and high turnover of cells
  - Liver
  - Spleen
  - Bone marrow derived cells
  - Cardiac muscle
  - Soft tissue around joints

What can ERT NOT do?

- Reach tissues with slow turnover and poor blood supply
  - Cardiac valves
  - Cartilage
  - Bone
  - Cornea

- Cross the BBB (currently used therapies)

BUT…

- Increasing evidence of bone effect if treatment begun BEFORE significant bone disease present

Advantages of ERT

- Safe
- Effective (relatively)
- Administration relatively low-tech
- Can be given in home/ school environment

Disadvantages of ERT

- Ongoing therapy
- Huge financial burden
- Invasive therapy (regular venepuncture)
- No brain treatment
- Not complete cure
- Infusion associated reactions
- Immunological response to drugs

Bone marrow transplantation

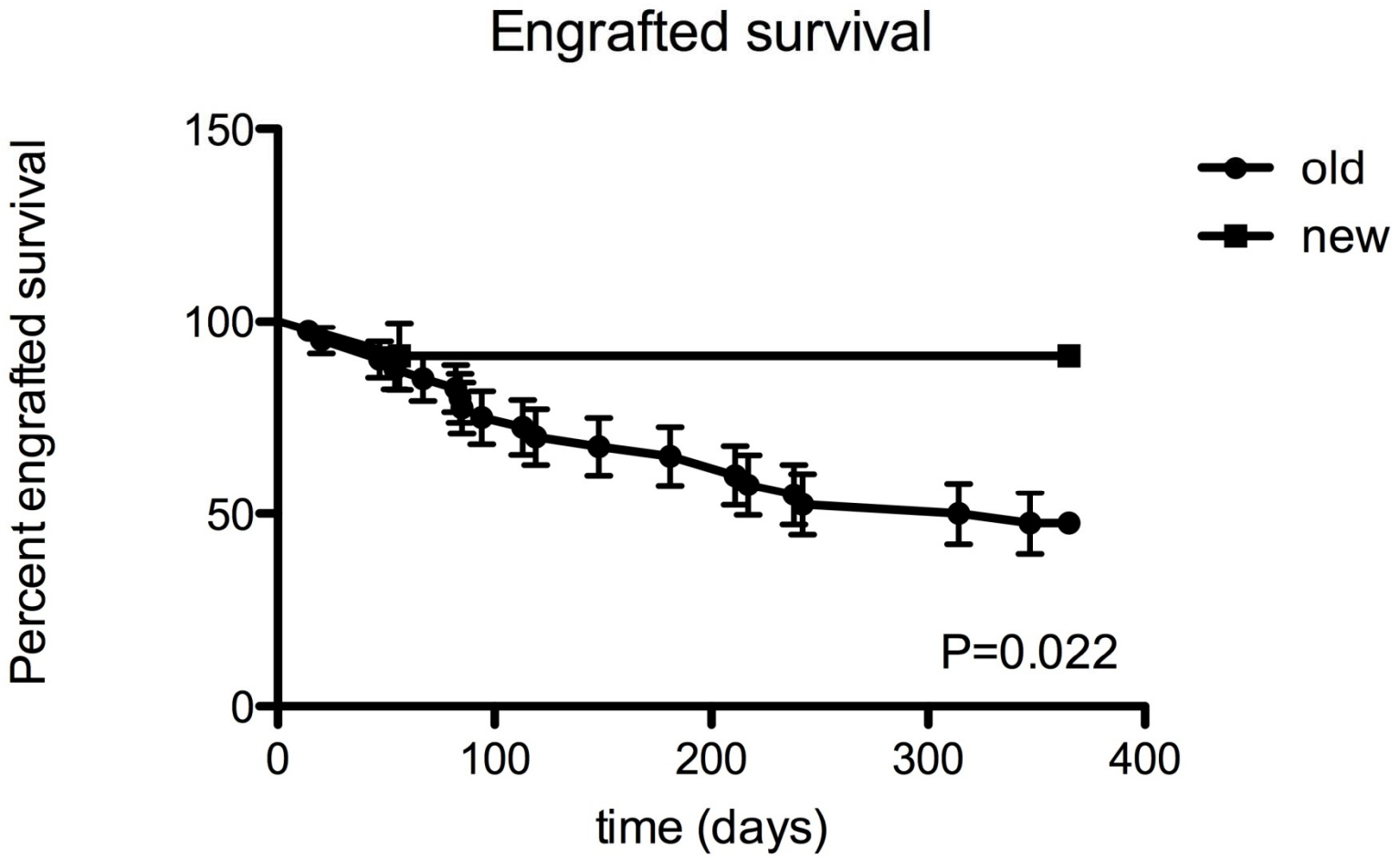
- Mainstay of treatment in many countries for MPS I – Hurler
- Can also be effective in MPS VI, but ERT (as?) effective also so not standard care
- Utility of BMT in MPS II, III and IV much less clear – must be viewed as experimental at least

Advantages of BMT

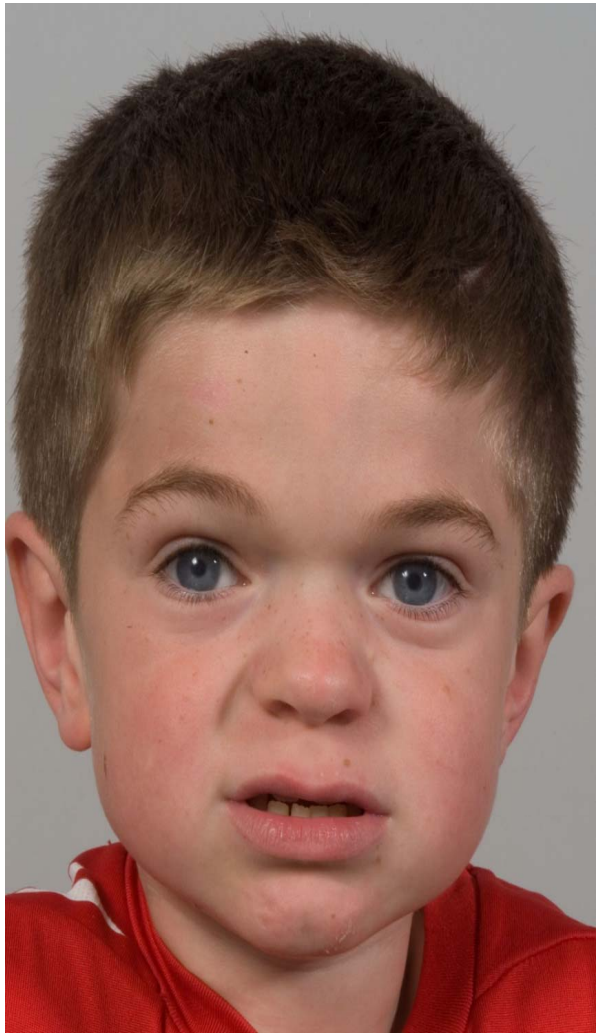
- One-off treatment
- Effective
- Treats the brain disease
- Less expensive

Disadvantages of BMT

- Availability of service and/ or donors
- Residual disease occurs
- Risk of death
- Late effects?


Engrafted survival
Percent engrafted survival
150
100
50
0
0
100
200
300
400
time (days)
old
new
P=0.022

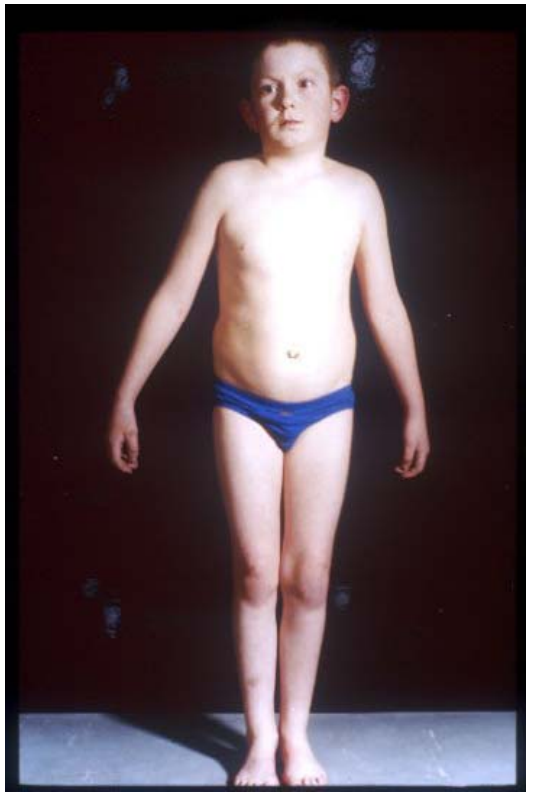
HSCT – MPS I



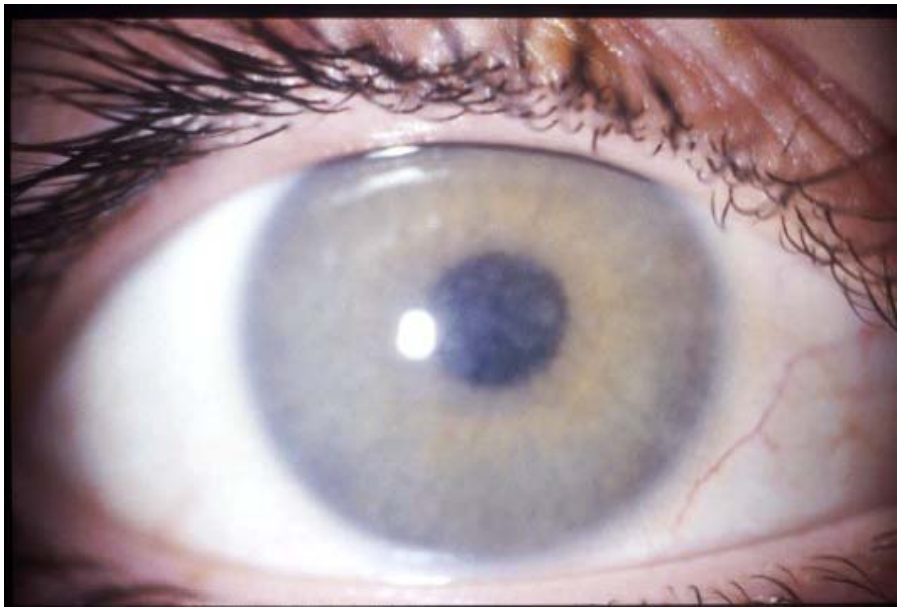
HSCT - residual disease burden

Brain

- Mild to moderate learning difficulties
- Age at transplant is important



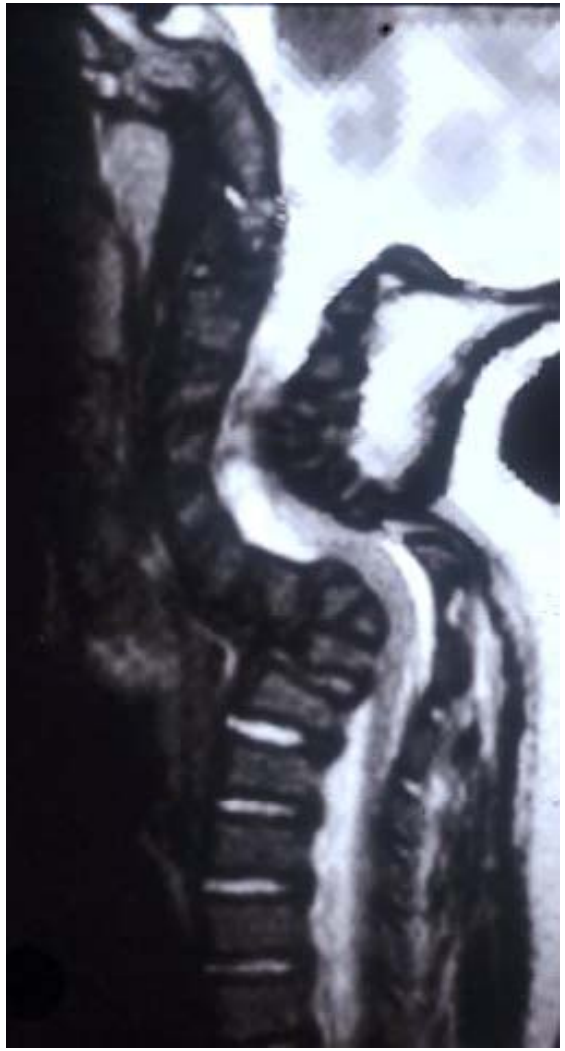
HSCT - residual disease burden



Eye

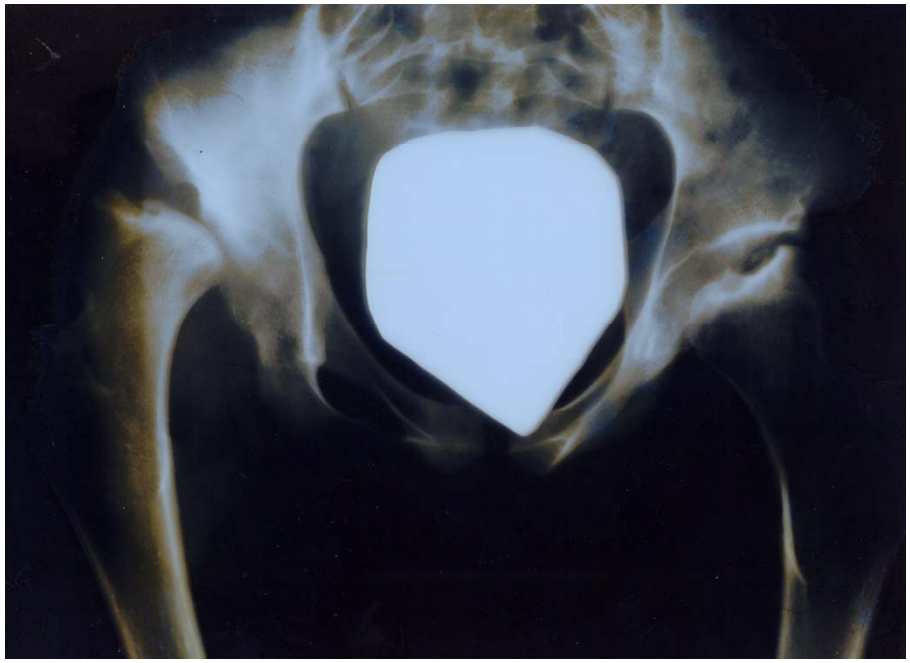
- Corneal clouding
- Retinal degeneration – night blindness (ERGs)

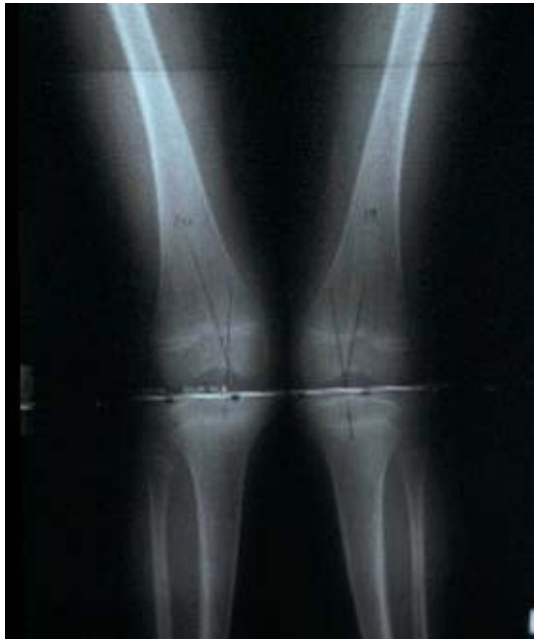
HSCT - residual disease burden

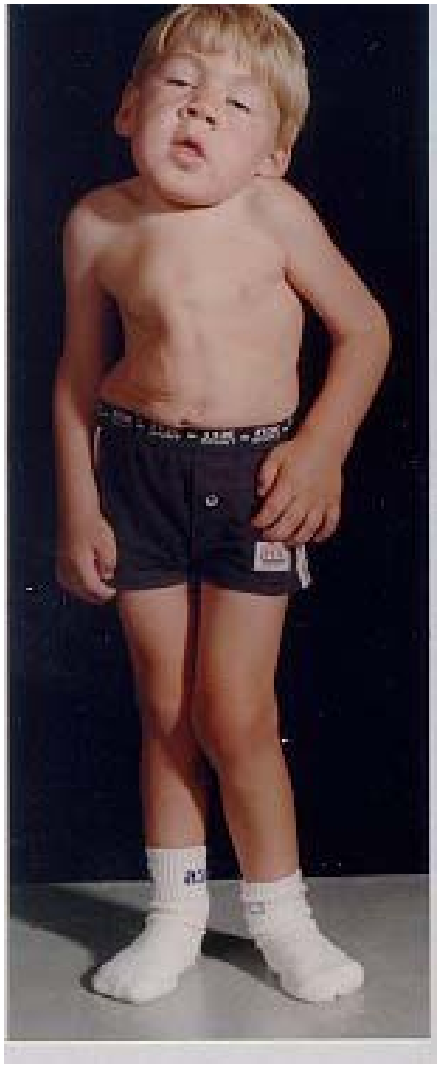


Skeleton

- Kyphoscoliosis
- Genu valgum
- Hip dysplasia







Follow Up, Post BMT

- **Early SCT clinics**
- **From 6 months dedicated MPS long term multidisciplinary clinic for transplanted children**
- **Standardised assessments - ENT, radiology, cardiac**
    - **metabolic**
    - **transplant**
    - **orthopaedic surgeon**
    - **spinal surgeon**
    - **endocrine**
    - **Neuropsychology**
    - **patient support groups**

Summary

- Current therapies aimed at replacing the missing enzyme
- Neither approach perfect
- Residual disease is important and needs managed
- Need to think more about other strategies, and not just about storage……