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Rare and Genetic Disease Network

CME/CE

Mucopolysaccharidosis I

Treating MPS I

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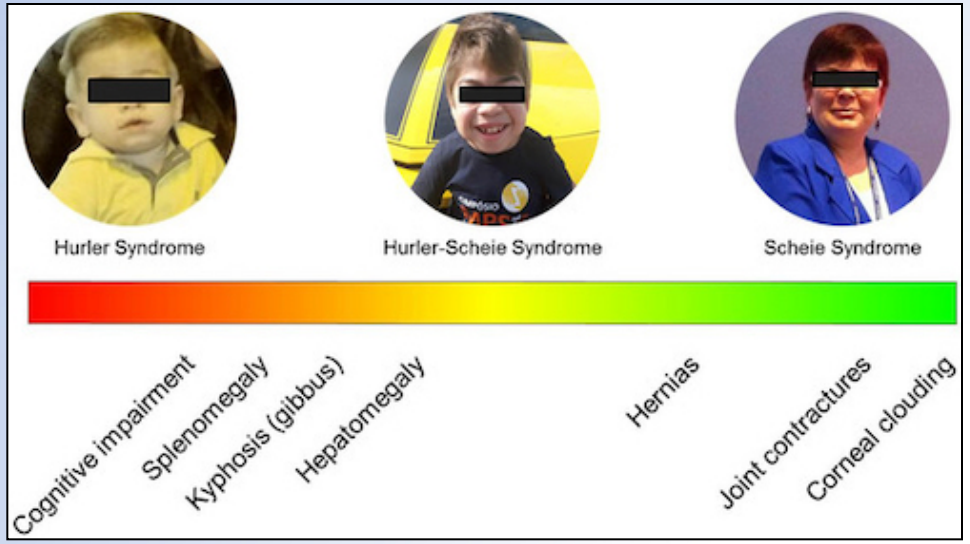
What is MPS I?

Mucopolysaccharidosis I (MPS I)

- Lysosomal “storage disease”
- Mutations in α-L-iduronidase (*IDUA)* gene, leading to:
  - increased glycosaminoglycans (dermatan sulphate and heparan sulphate)
- An autosomal recessive disease
- Disease severity and symptom onset varies
  - Two subtypes
    - Hurler syndrome (Severe MPS I, or MPS IH)
    - Attenuated MPS I (previously Scheie, or Hurler-Scheie syndrome
- 1 in 100,000 births (Severe MPS I)
- 1 in 500,000 births (Attenuated MPS I)



Jameson et al. *Cochrane Rev.* 2016; CD009354. Kabuska et al. *Diagnostics.* 2020;10: 161. Mucopolysaccharidosis type I. US National Library of Medicine website.

Team Approach: Multiple Systems Affected

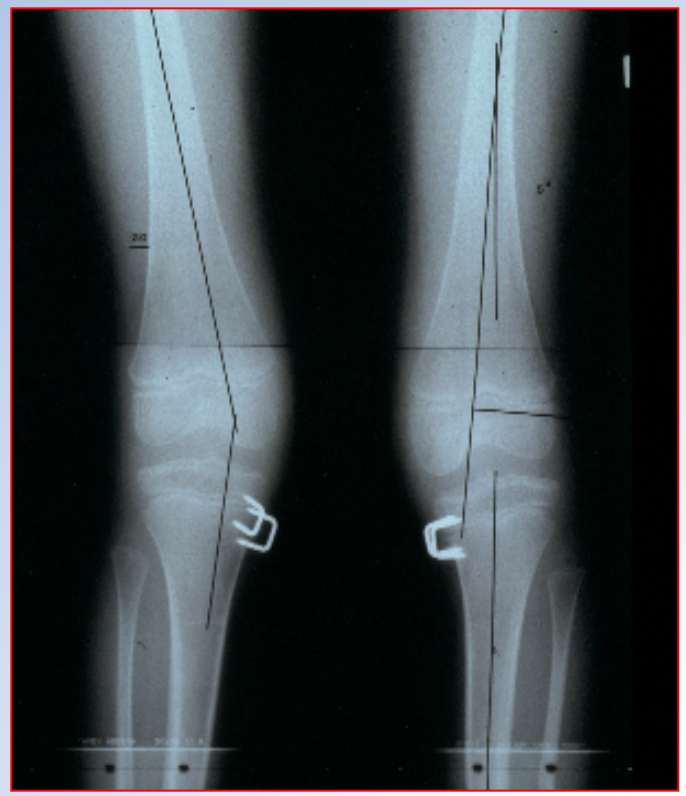
- **Neurologic**
  - Developmental delay (Hurler), hydrocephalus
- **Pulmonology/Airway**
  - Snoring, difficult intubations, apnea
- **Cardiology**
  - Cardiomyopathy, valvular changes
- **GI**

  hernias, hepatosplenomegaly
- **Ophthalmology**
  - Cornea clouding, retinal degeneration
- **Hearing**
  - Recurrent ear infections, sensorineural loss

Symptoms/complications	Percentage of patients ≤2 y of age with symptom
Coarse facies	98
Valvular disease	95
Corneal clouding	90
Hepatomegaly	84
Upper airway obstruction → OSA	82
Kyphosis gibbus	75
Joint contractures	72
Hernia	70
Dysostosis multiplex	70
Cognitive impairment	60
Enlarged tongue	60
Splenomegaly	60
Eustachian tube obstruction → otitis media	55
Hip dysplasia	42
Genu valgum	38
Reactive airway disease	37
Scoliosis	35
Carpal tunnel syndrome	25
Pes cavus	18
Glaucoma	10
Heart failure	3
Cor pulmonale	2

Team Approach: Multiple Systems Affected

- **Musculoskeletal (dysostosis multiplex)**
  - Abnormal bone and cartilage development
  - Joint stiffness
  - Abnormal growth, despite therapy
  - Lower extremity and spine abnormalities
    - Kyphosis
    - Abnormal acetabulum, femurs
    - Valgus deformities of the knees
  - Vertebral bodies are hypoplastic, show anteroinferior beaking
  - Cervical instability, spinal cord compression
  - Carpal issues tunnel prominent



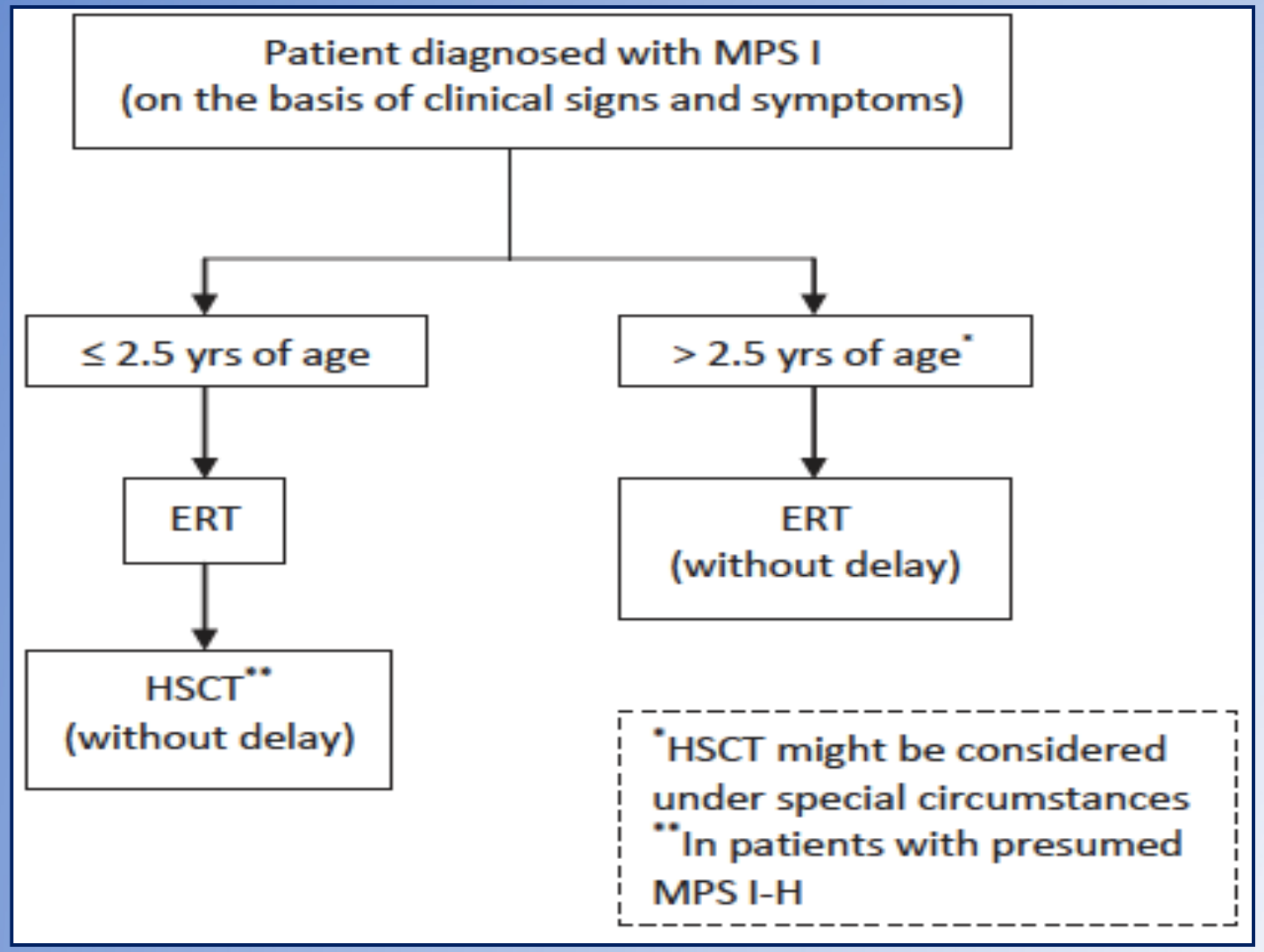
Sakura R, Bollu PC. *StatPearls.* 2020. Figure provided by Dr. Orchard.

Treatment Options

- Allogeneic hematopoietic stem cell transplantation
  - The gold standard for severe MPS I
- Enzyme replacement therapy
  - Used as monotherapy for severe and attenuated MPS I
  - Has been used as adjunct therapy with HSCT for severe MPS I
  - Laronidase is the only FDA approved ERT
- Treatments under investigation
  - Intrathecal ERT
  - ERT with fusion protein to direct enzyme to the brain
  - Gene therapies

Adapted from Meikle P et al. *JAMA.* 1999;281:249-254.

Treatment Options



De Ru et al. *Orphanet J Rare Dis.* 2011..

HCT; Survival over time

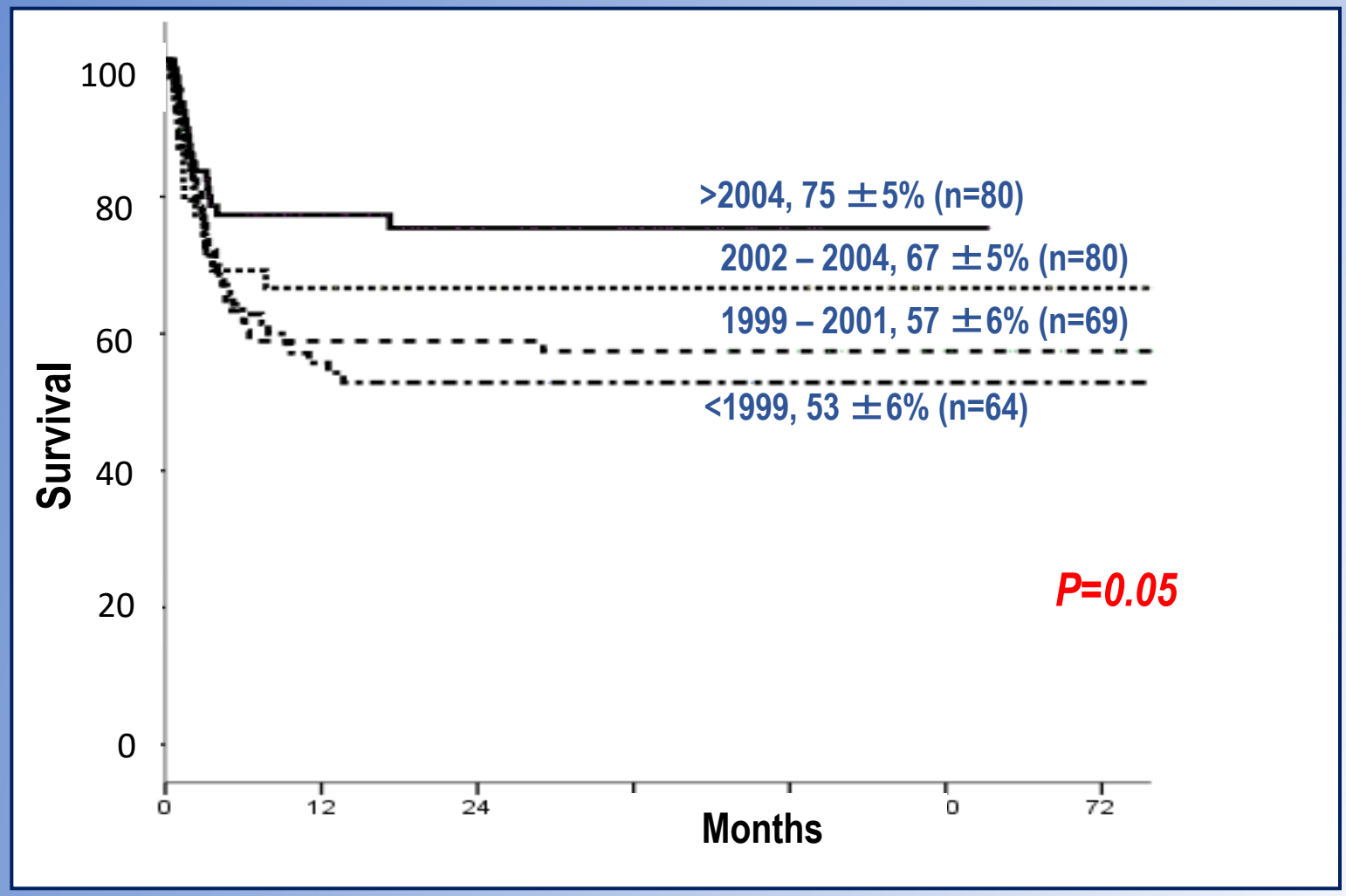


Figure adapted from Boelens et al. *Blood* 2013; 121: 3981-3987.

Survival of Severe MPS I by age at HCT

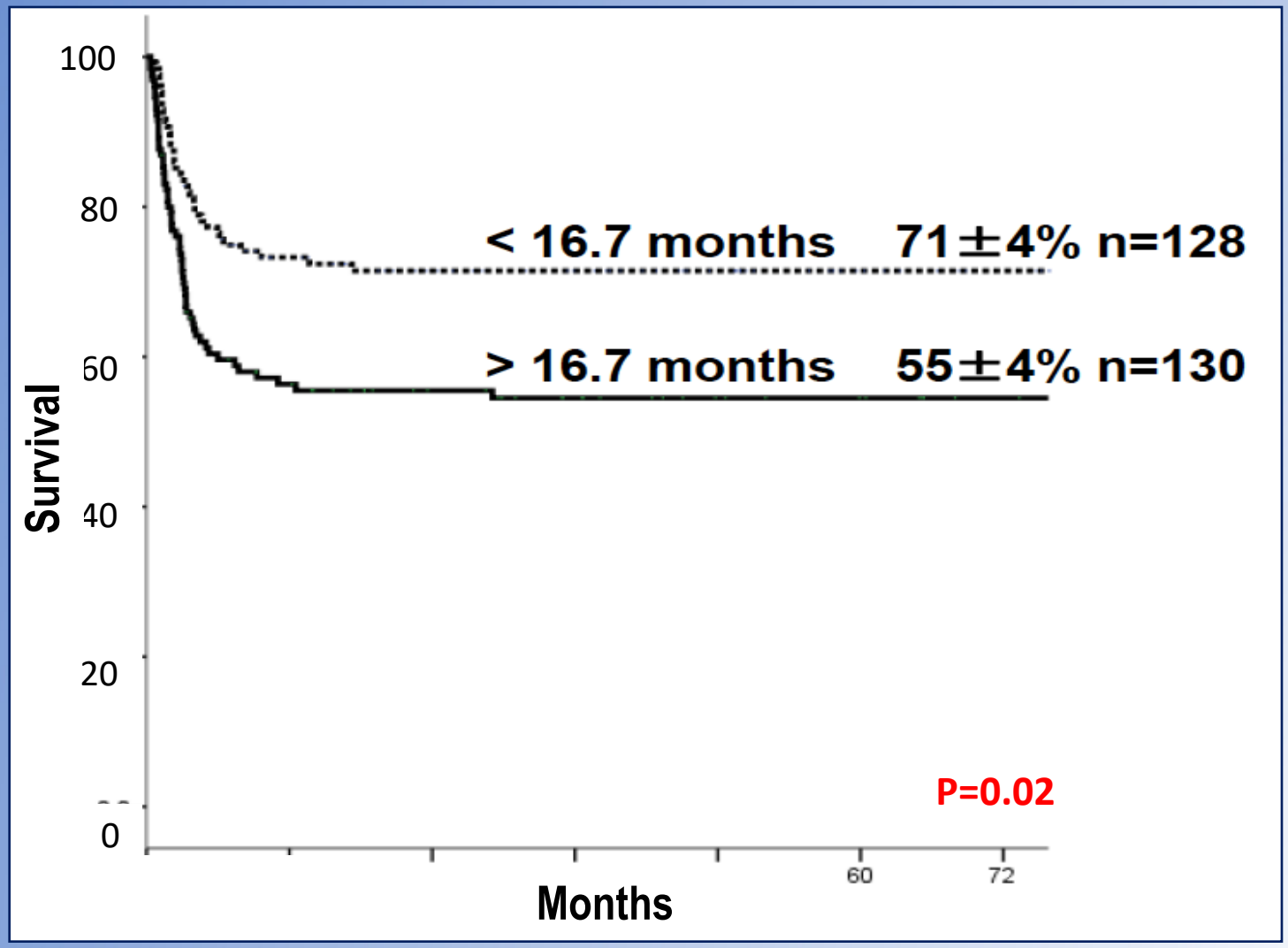
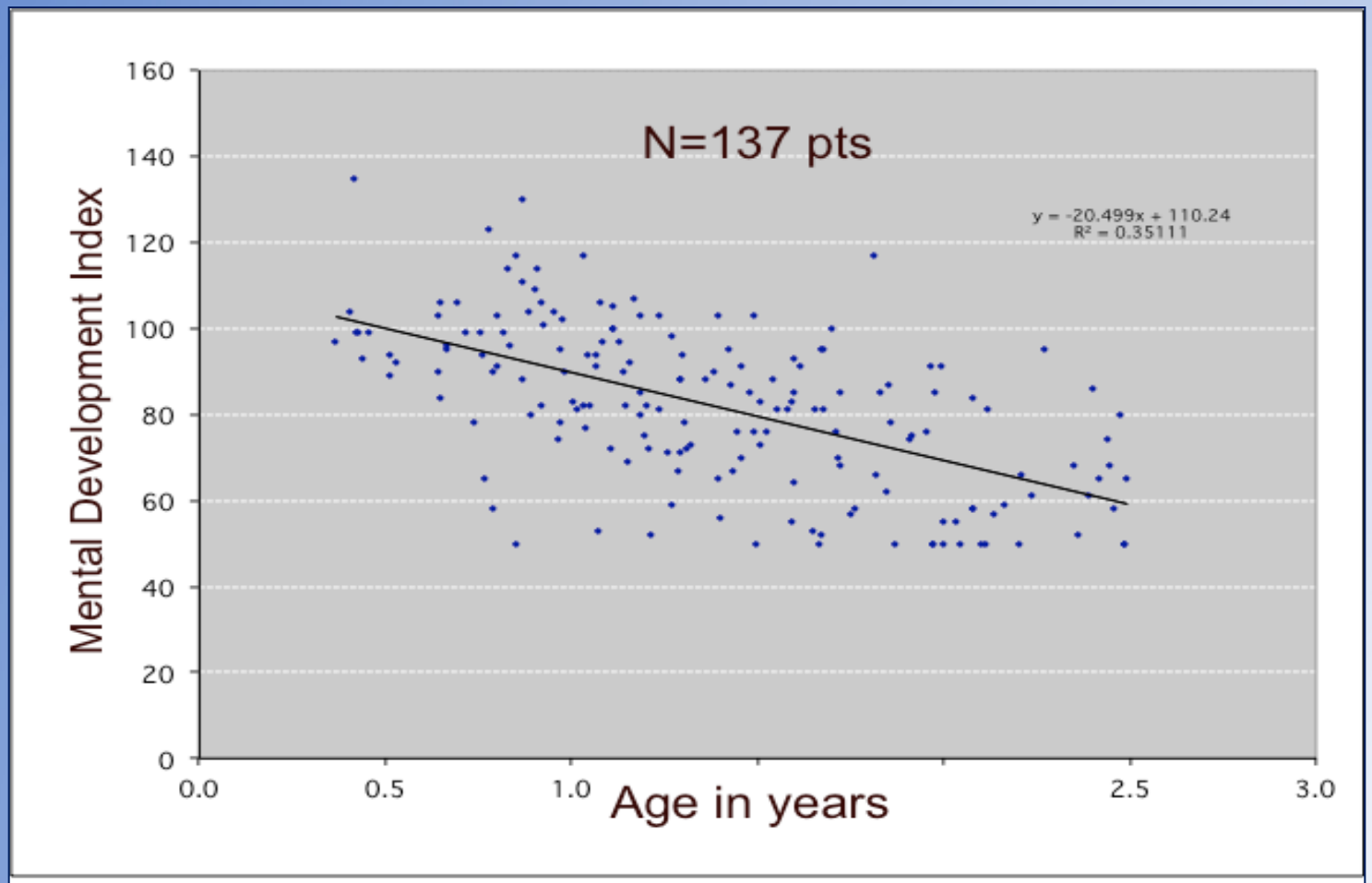


Figure adapted from Boelens et al. *Blood* 2013; 121: 3981-3987.

Cognition: Untreated Severe MPS I Patients



Neurologic Decline in Untreated MPSIH:

Figure adapted from Krivit et al. *Current Opin Neurol* 1999; 12: 167-176. Note MPS IH refers to severe MPS I or MPS I - Hurler

Neurologic Outcomes Following HCT

	NL (>85 IQ)	Mild (70-85)	Severe (<55 IQ)
Pre	56.9%	26.6%	16.5%
Post	**26.9%**	28.3%	**44.9%**

Factors

Male – P = 0.04

Low Baseline IQ – P = 0.009

Older Age at BMT – P = 0.009

TBI based Regimen – P = 0.03

Aldenhoven et al. *Blood* 2015;125: 2164-2172.

Orthopedic Outcomes Following HCT

Growth Failure (GF): Height <2 SD

At last follow-up (6.9 ± 5.1 yr post HCT) - 71% with GF

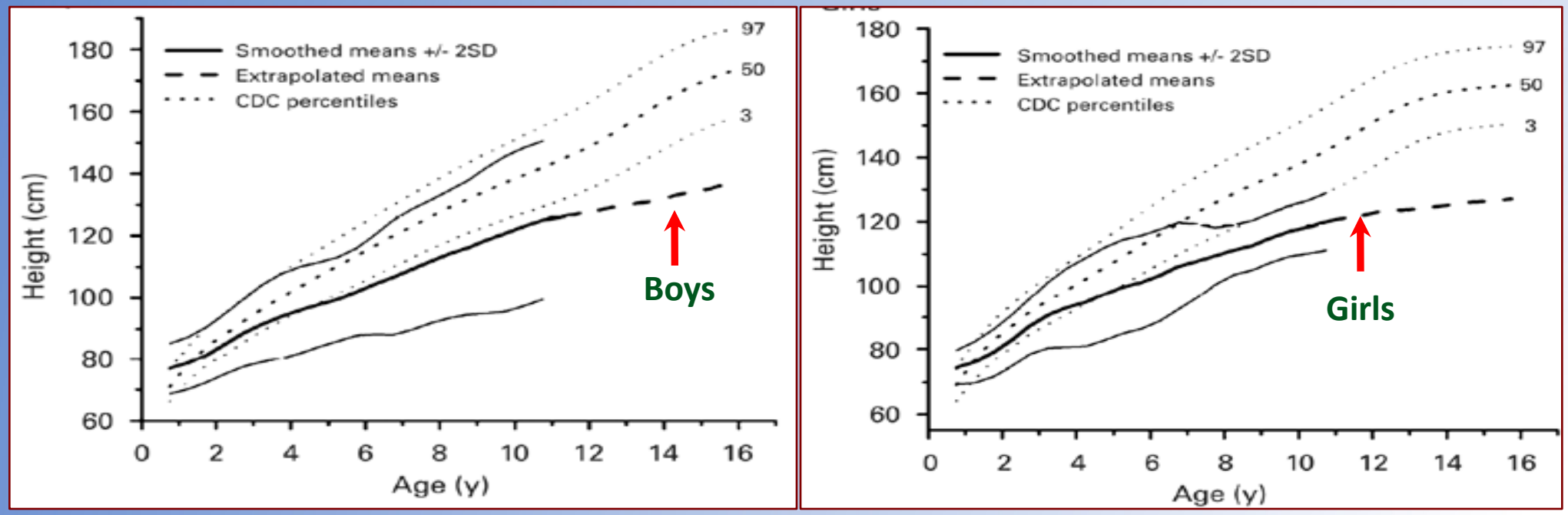


Figure adapted from Polgreen et al. *BMT* 2008; 41: 1005-1011.

Surgical Risks Following HCT

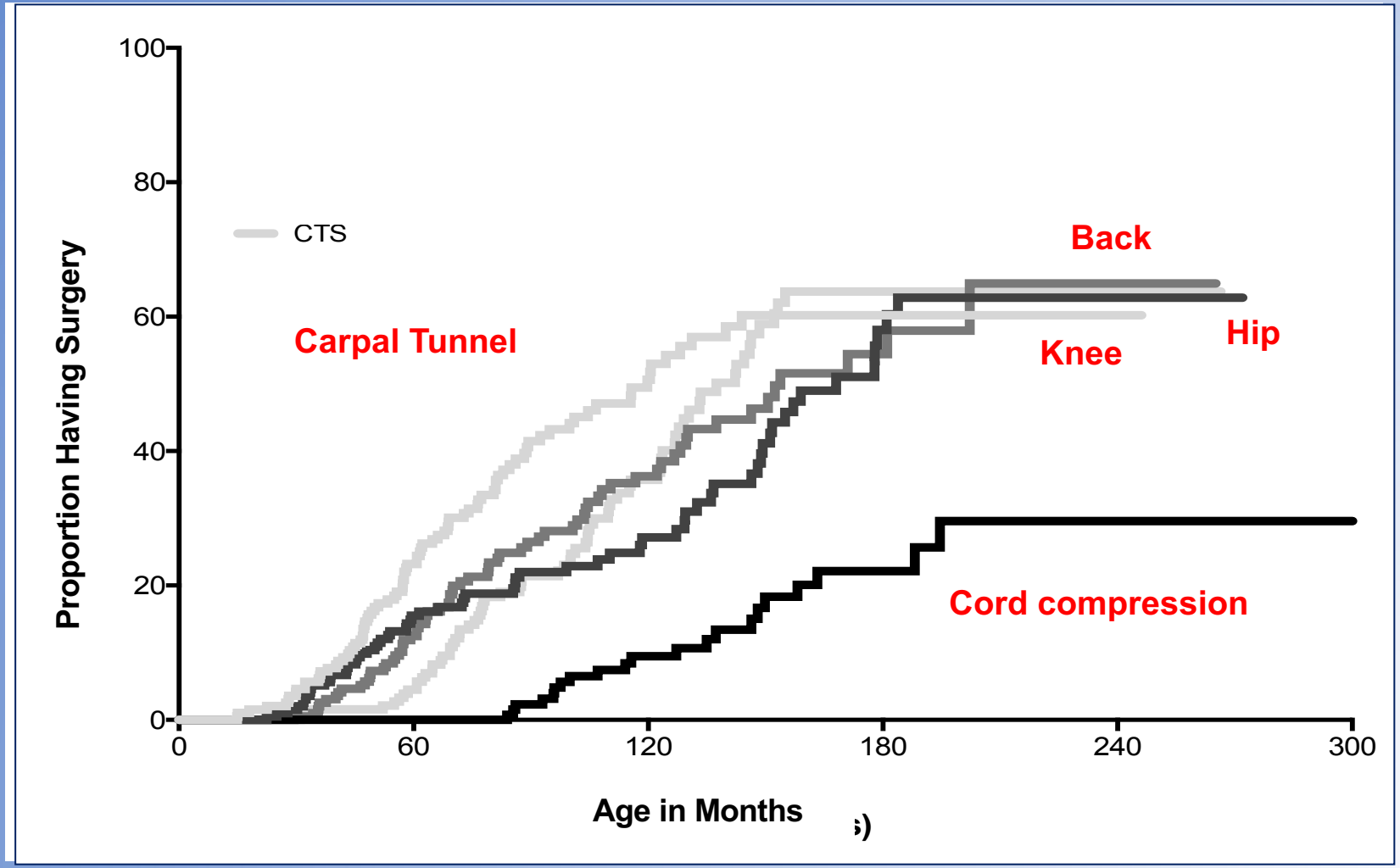


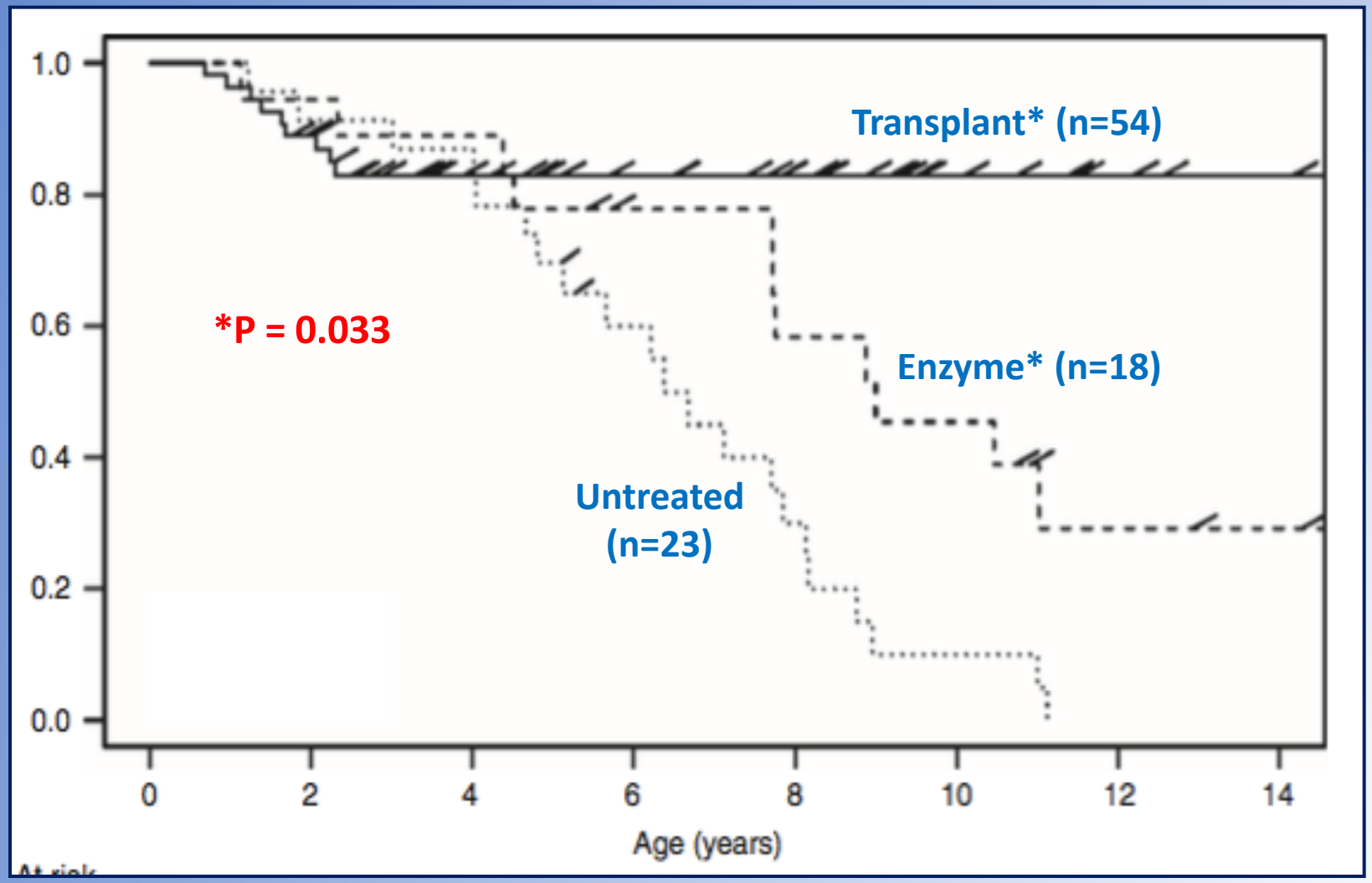
Figure adapted from Aldenhoven et al. *Blood* 2015;125: 2164-2172.

Enzyme Replacement Therapy

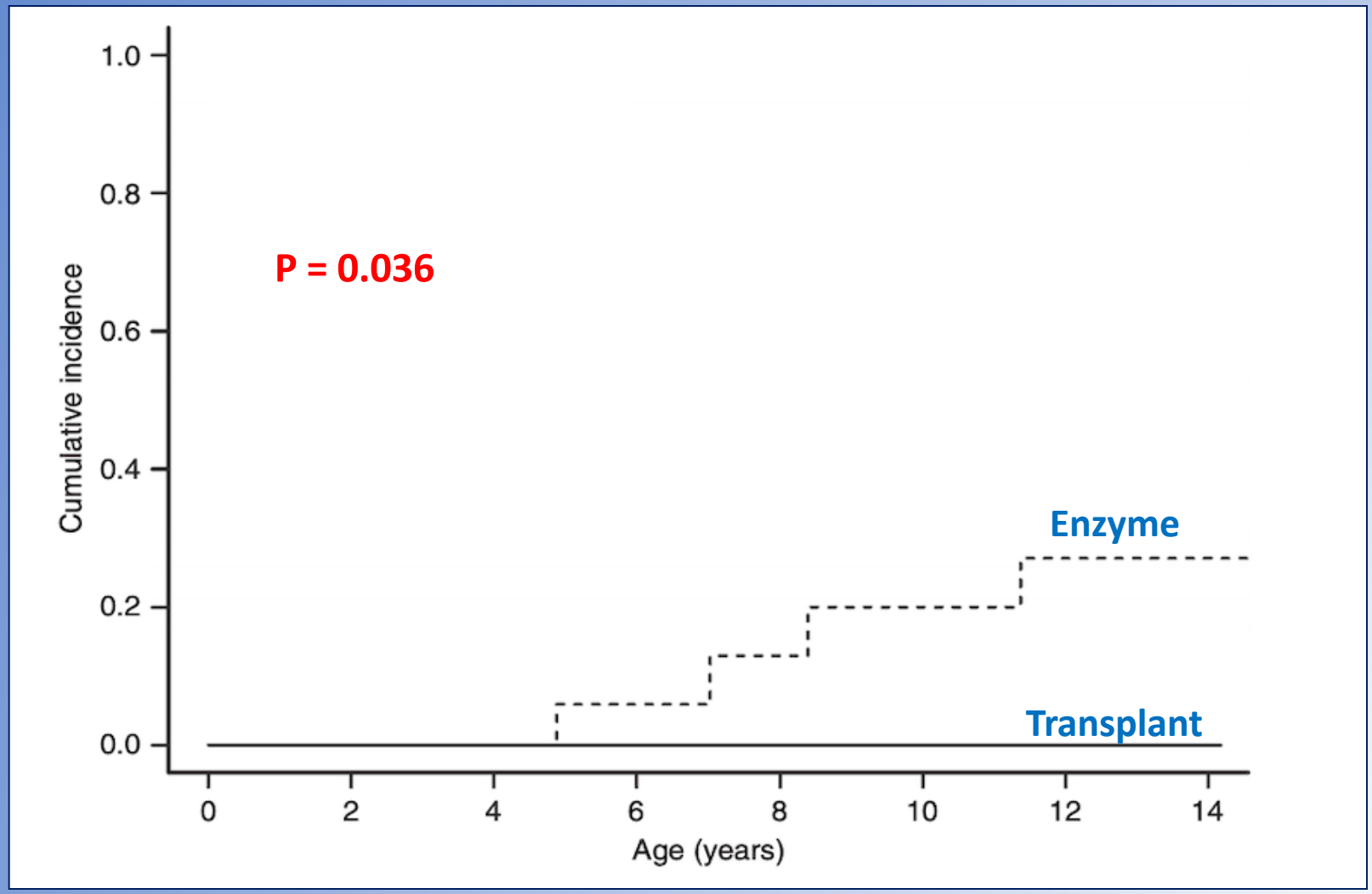
- Laronidase is FDA-approved ERT based on phase 3 clinical trial
- Pros
  - Cochrane review concluded drug is effective
  - Improves forced vital capacity (FVC) and six minute walk test (6MWT)
  - Reduces GAGs and hepatomegaly
  - Well tolerated
- Cons
  - Only improves peripheral symptoms
  - Weekly infusions
  - Expensive ($200,000-$300,000/yr for the life of the patient)

Wraith et al. *J Pediatr/* 2004; 144:581-588. Jameson et al. *Cochrane Databases Syst Rev.* 2019; 6: CD009354.

Comparison; Severe MPS I Survival by Therapy



Development of hydrocephalus by therapy



Clinical Pearls

- MPS I is a genetic degenerative disorder
- Treatment requires a multidisciplinary approach
- Treatment dependent on severity
- Gold standard is HSCT for severe MPS I; higher risk
- Weekly IV ERT the standard of care for attenuated MPS I patients
- Neither transplantation or ERT curative; other therapies being explored
- Since these treatments can dramatically reduce or stop disease progression, early detection (i.e., newborn screening) can have a profound impact on the person's quality of life (and their families). These topics will be covered in modules 3 and 4 of this program.