UMC Utrecht

# Hematopoietic Cell Transplantation in Lysosomal Storage Diseases; Optimizing Safety and Efficacy

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Jan 2015

# Research Program

## Hematopoietic Cell Transplantation

### A. U-DANCE-project

(Utrecht Dendritic Cells against Cancer)

1) Individualized Conditioning: Predictable IR
2) Development of Adjuvant Immunotherapies (cord blood-derived)

4PostDocs, 3PhDs, 2 Technicians
Co-PI: Stefan Nierkens

### B. HCT in Rare Diseases

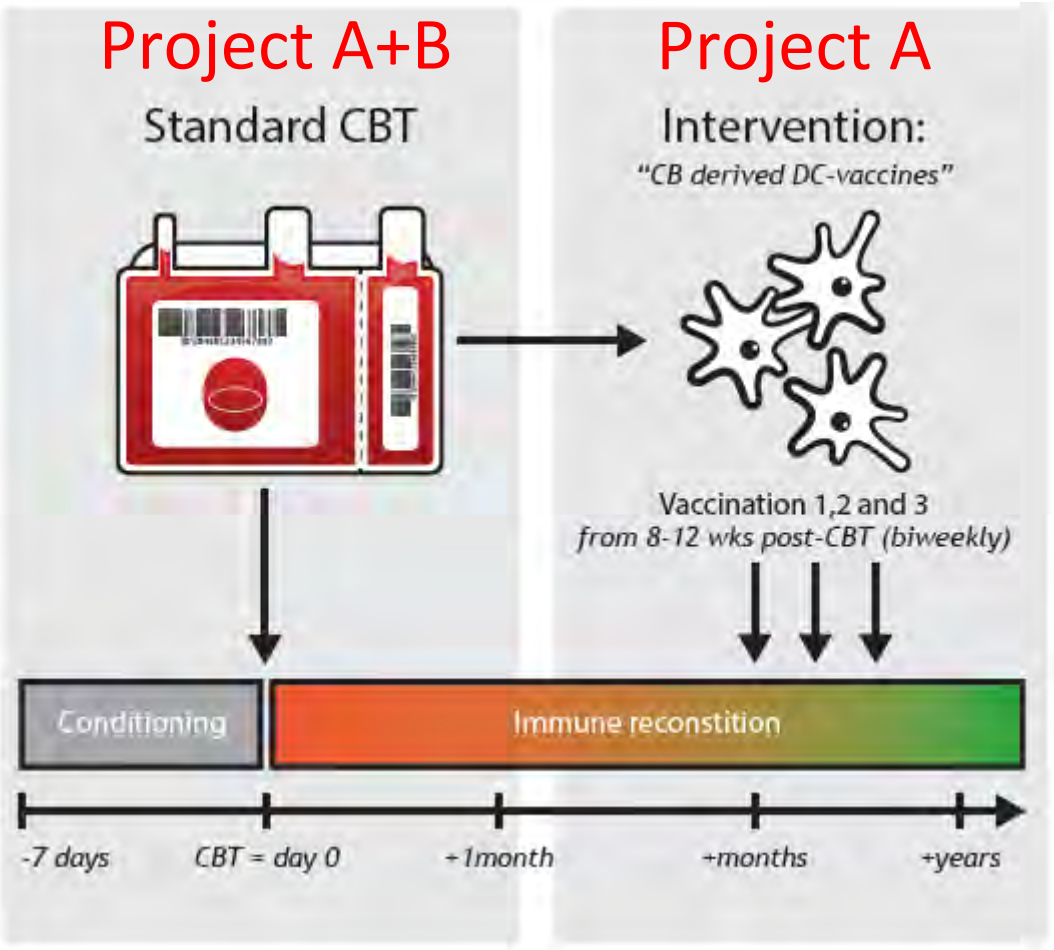
(Focus on Lysososmal Storage Diseases)

1) Identifying Predictors for Outcome (Short and Long Term)
2) Future Strategies

2PhDs, International Network

# Unrelated Cord Blood Central Theme in Research Program

## How to Increase Safety and Efficacy?



# Challenges in HCT

1. **Reducing the toxicity of HCT:**
    1. Short term toxicity
    2. Long term toxicity

2. **Better disease control**

Balancing Optimal disease control and reduced toxicity

# How to make HCT more efficient and safer?

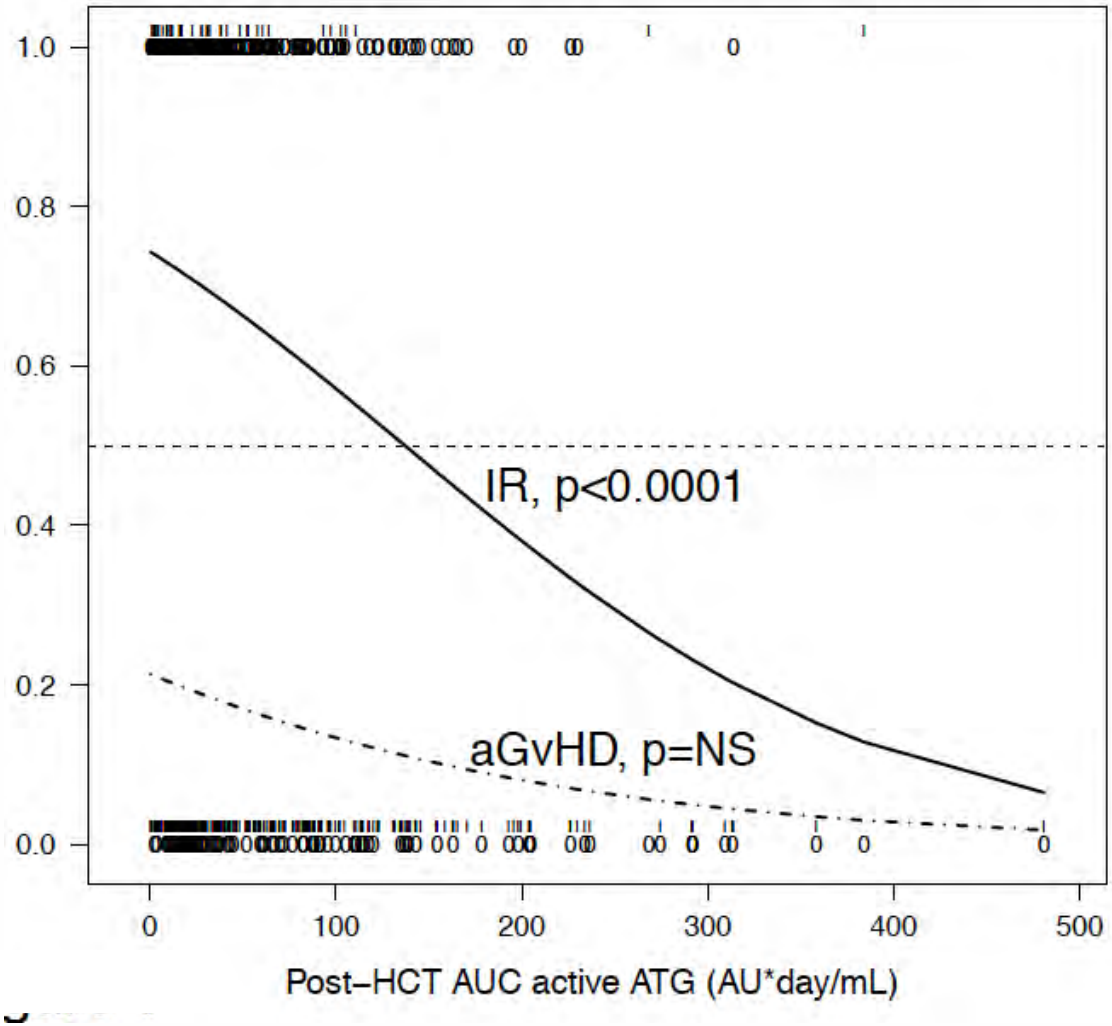
1. **Cord blood transplantation (CBT)**
    1. Lower relapse (Eapen 2007, Brunstein 2010, Milano 2015)
    2. Prompt availability
    3. Mismatch OK

2. **Individualized conditioning (PKPD): <u>predictable Immune-Reconstitution</u>**

3. **1 + CB-derived DC vaccination**

4. **Advanced immunomonitoring**

# Post-HCT exposure of active ATG is associated with IR but not with prop. on aGvHD



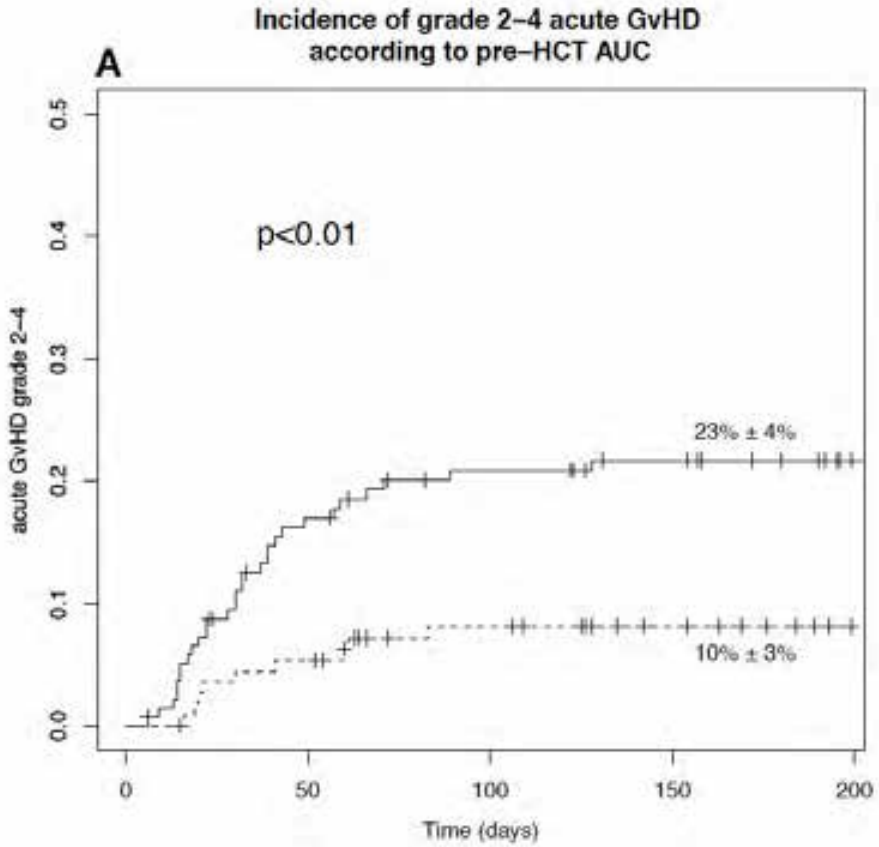

Collaboration:

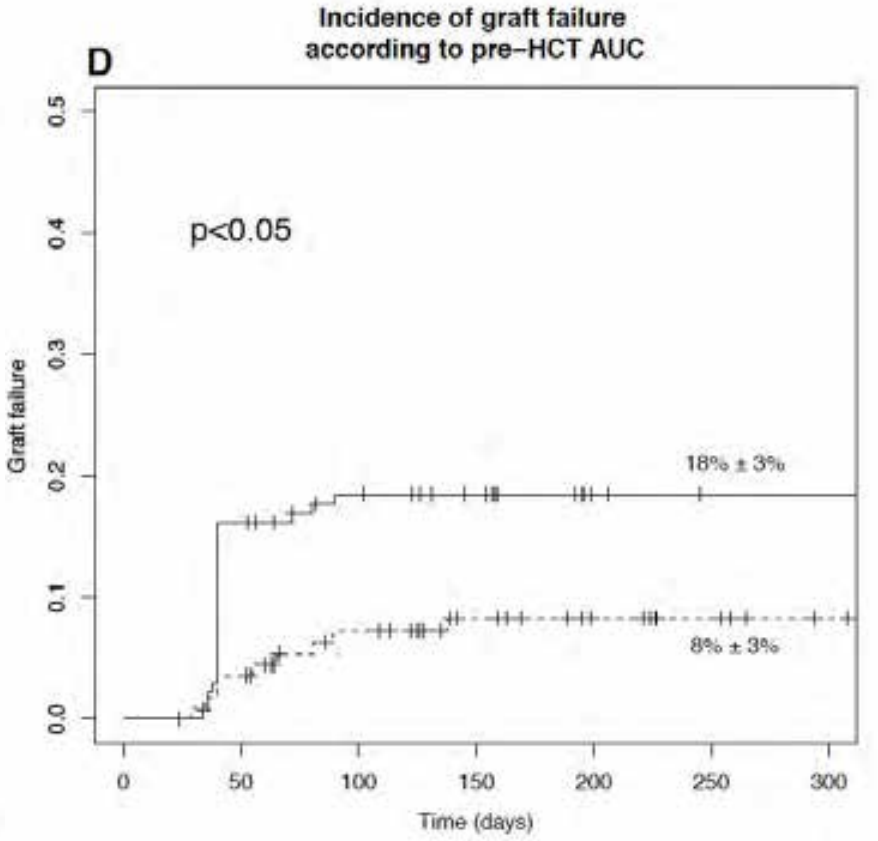
Ped. BMT Program in Leiden
-Robbert Bredius
-Arjan Lankester
-Wouter Kollen
-Dorien Bresters
-Frans Smiers, Lynn Ball

LACDR

Prof Catherijne Knibbe
Prof Meindert Danhof

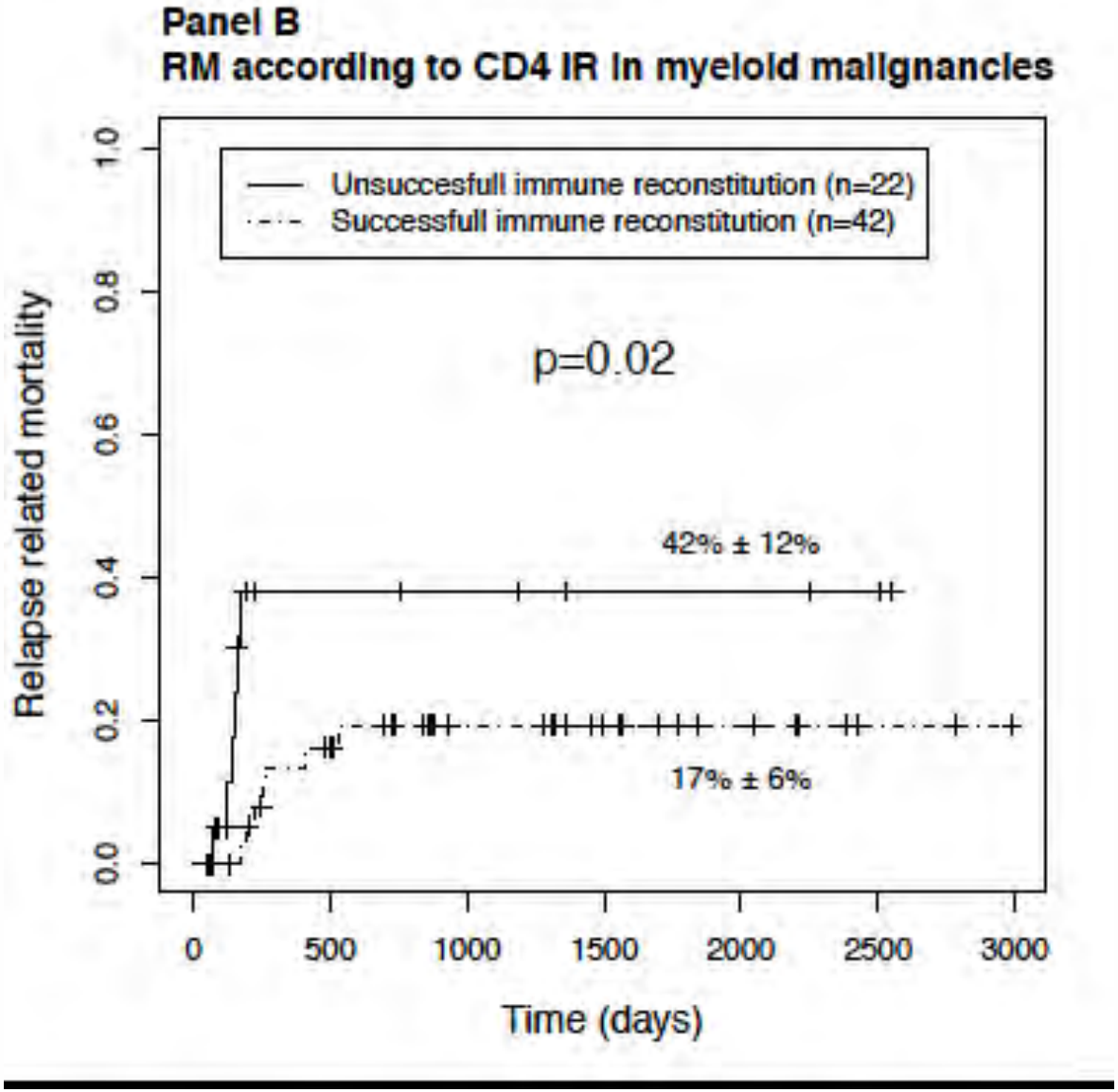
# Pre-HCT ATG-exposure (< > 40 AU*day/mL) is associated with Prop. on aGvHD and Graft-Failure



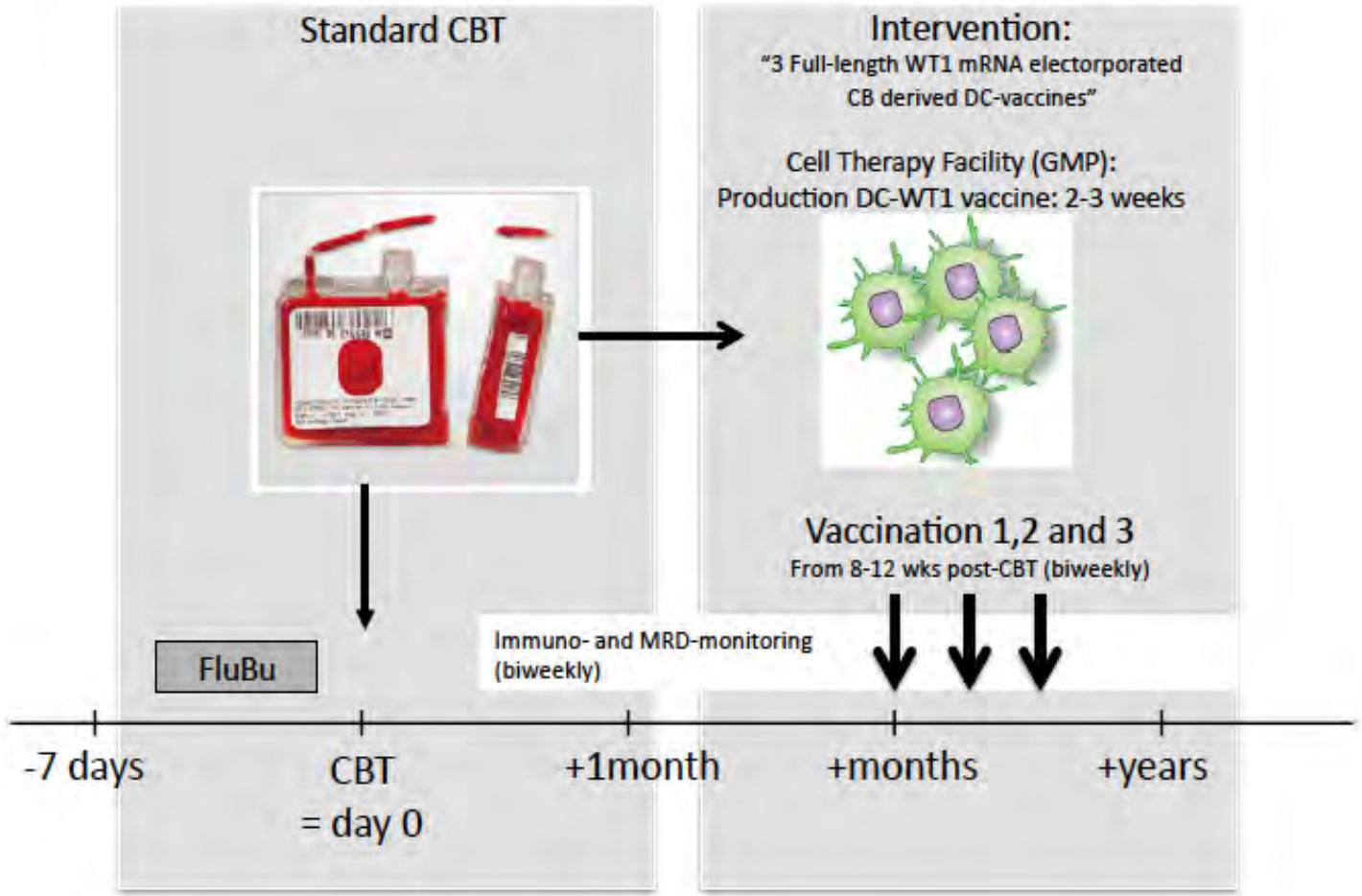




Lancet Hematology; Revisions

# Prop on Relapse is associated with CD4+ Reconstitution in Myeloid Malignancies



# 3. Pre-Clinical to Clinical Protocol (Phase 2)
# Draft *"AML protocol" >>> move to clinic in 2015*



# Lab Boelens/Nierkens

**Applied**

Project A

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Coco de Koning
Charlotte van Kesteren (PKPD)
Max van Noesel (PMC)
DCOG.GOSH.GPOH

Section Applied LTI
Theme: Tumor Immunology

U-DANCE
Utrecht - Dendritic Cells Against Cancer

AOMDOM

Kika
kinderenkankervrij

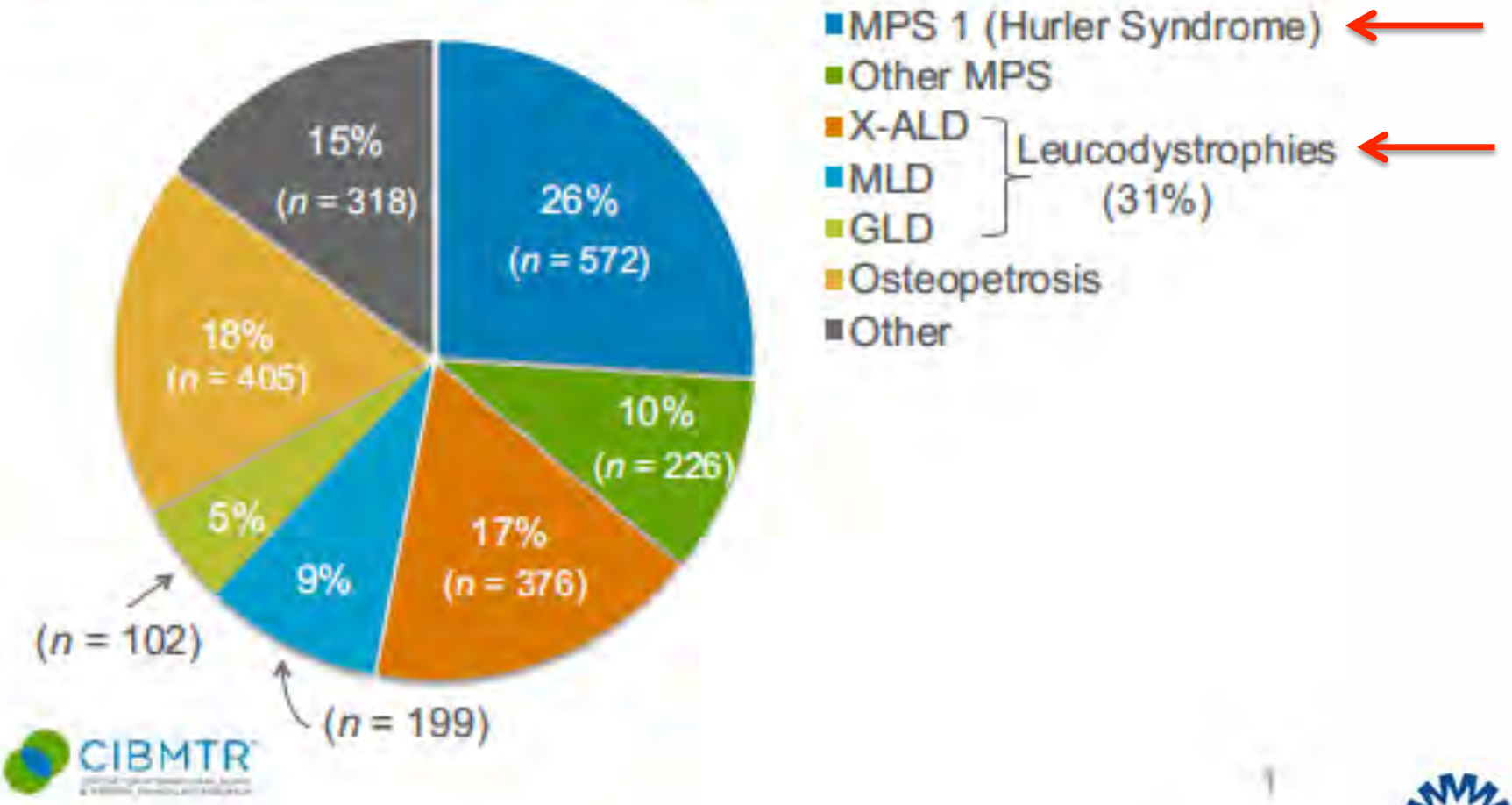
ZonMw

Villa Joep!
Het fonds tegen Neuroblastoom kinderkanker

Vrienden
Wilhelmina Kinderziekenhuis

Project B

# Allogeneic Transplants for Inborn Errors of Metabolism Registered with CIBMTR, 1980-2013



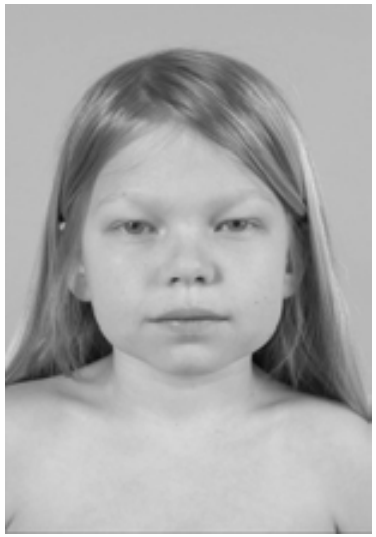

>2000 HCTs since early 80s

# 1. Hurler syndrome: MPS-1

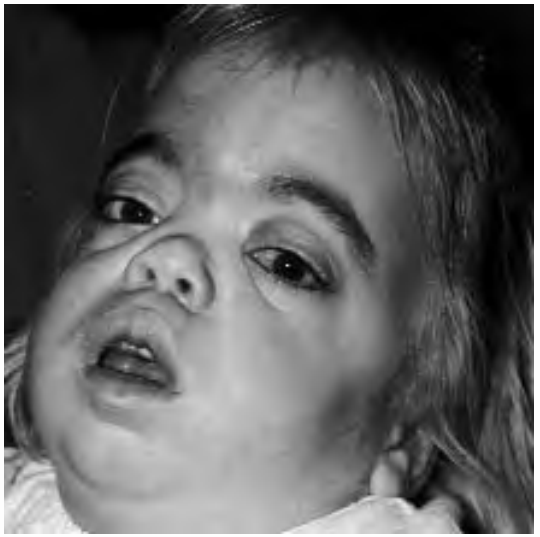
IDUA deficiency → GAG accumulation

MPS type I

‘Mild’ ‘Severe’



Scheie
9 years old

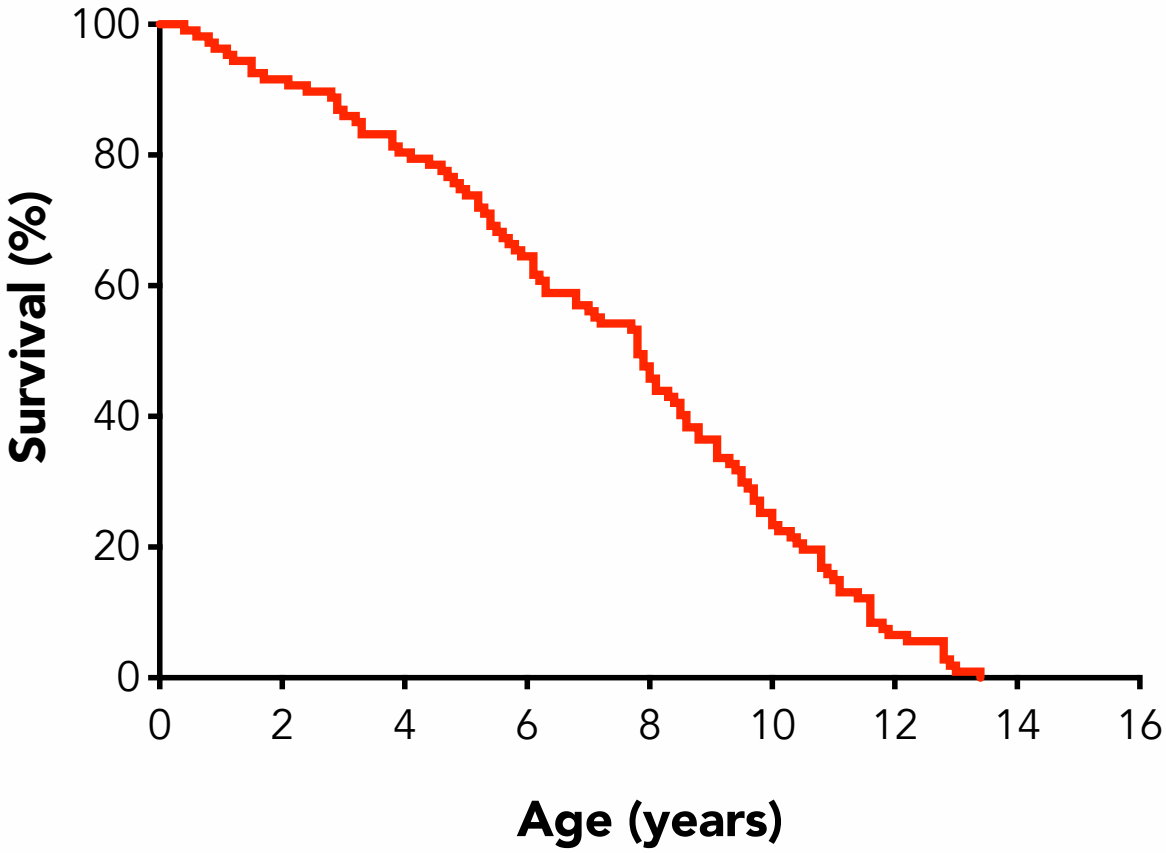


Hurler
6 years old

- Mental retardation
- Orthopedic complications
- Blindness and deafness
- Cardio-respiratory failure
- Premature Death

# Hurler syndrome:

# No HCT - No survival

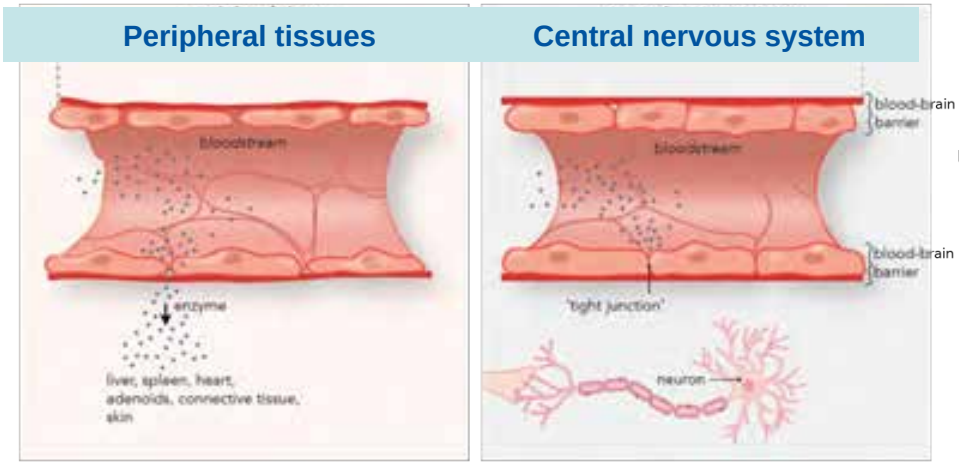


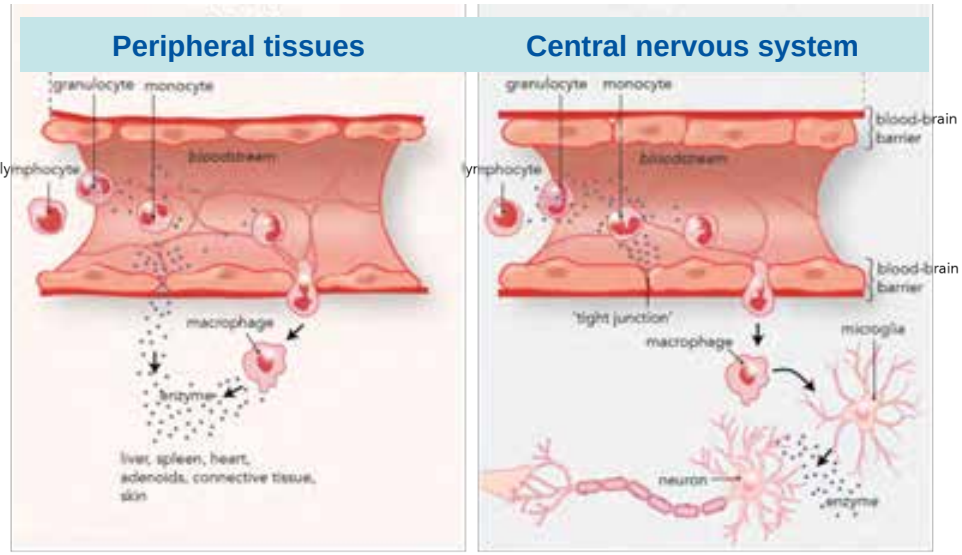
# Treatment options

Universitair Medisch Centrum Utrecht

## Since 2003
**Enzyme replacement therapy**

## Since 1980
**Hematopoietic cell transplantation**



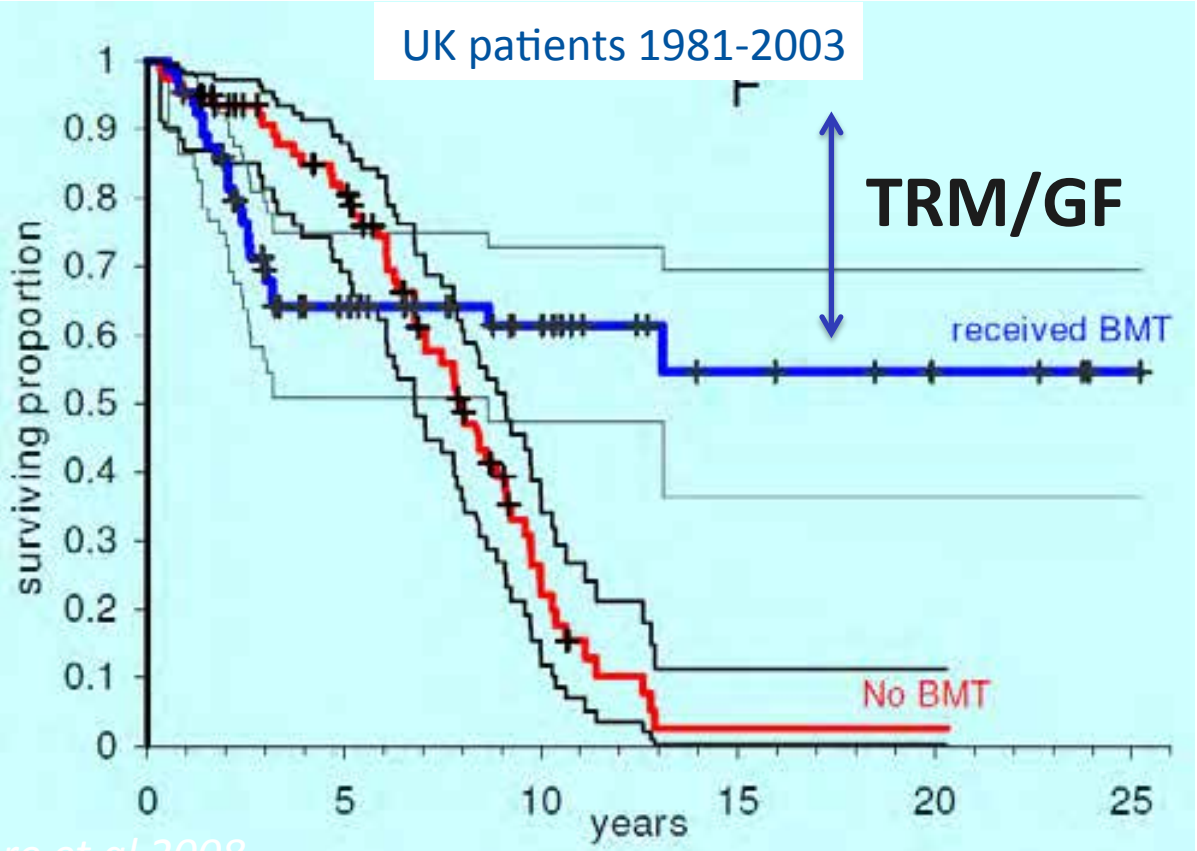




**<u>No</u> CNS involvement: Scheie**

**CNS involvement: Hurler**

*Aldenhoven et al. BBMT. 2008*

# Successful HCT influences long term survival of Hurler Syndrome patients




*N=67*

*N=129*

*Moore et al 2008*

# How to optimize the outcomes?

## Studies on SCT in Hurler's Syndrome since 2004

1. Outcomes of HCT for MPS I in Europe (1994-2004): a risk factor analysis: *BMT 2007 (N=146)*
   - *Predictors graft-failure: T-cell depletion, RIC*
   - *Predictor higher EFS: Busulfan with "therapeutic drug monitoring"*

2. HCT in combination with Enzyme Replacement Therapy in patients with Hurler syndrome: *BMT 2006*
   - *No impact, but poor performing patients became eligible for BMT*

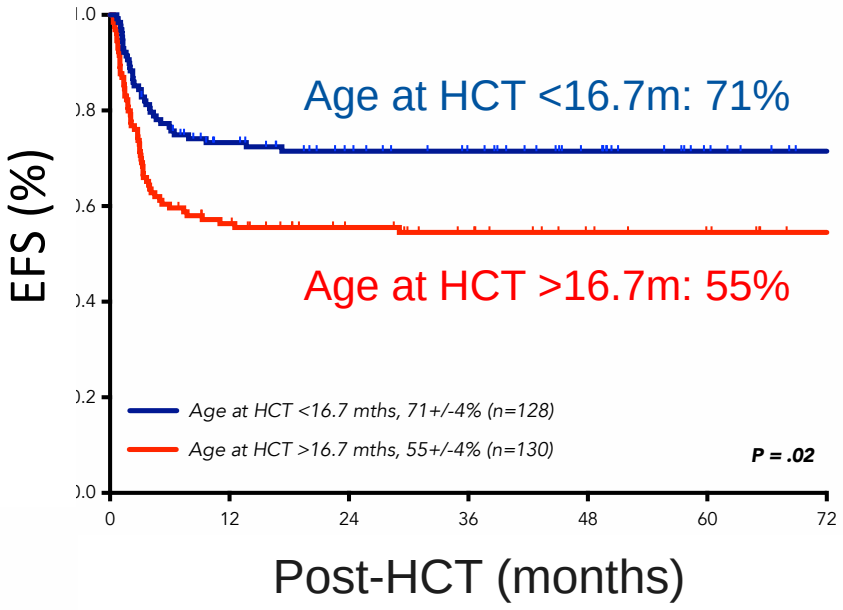
3. Outcomes of Cord blood transplantation for Hurler syndrome: an EUROCORD / DUKE Collaborative study: *BBMT 2009 (n=93)*
   - *Predictor higher EFS: BuCy, interval Dx-CBT < 4.5mths, 6/6 CBU*

# 4. Survival & graft outcome – predictors

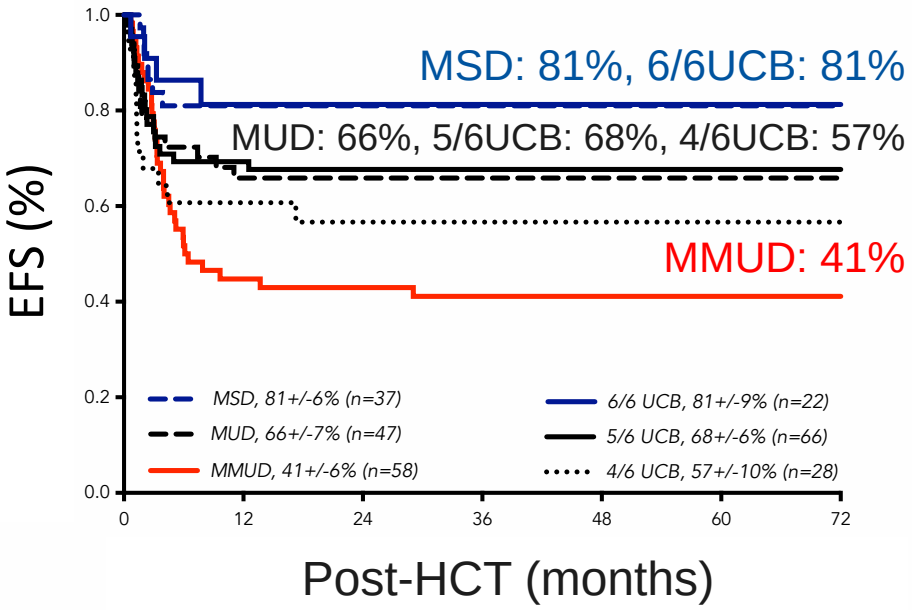
Duke University, Minnesota, CIBMTR, EUROCORD, EBMT

N=258 Hurler syndrome after myeloablative HCT 1995-2007: all sources

## Age at HCT




## Source / HLA matching




*Boelens et al. Blood. 2013*

# Full Donor Chimerism (>95%)

N=258 (incl 116 CBs)

| | UCB | UD | TCD-UD | idSIB |
|---|---|---|---|---|
| **Full donor chimerism** (%) | **92** | **74** | **47** | **70** |
| Mixed 50- 95% donor | 7 | 17 | 26 | 20 |
| Mixed <50% donor | <1 | 9 | 26 | 10 |
| **Normal enzyme level** (%) | **98** | **66** | **50** | **56** |

Cord blood significantly associated with higher full donor chimerism & normal enzyme levels ($p < 0.01$)

# New EBMT guidelines - HCT in IEM

- Donor hierarchy
  1. Non-carrier MSD

     Or Identical UCB (6/6 intermediate resolution)

     Or Identical MUD (10/10 high-resolution typing)
  2. Mismatched UCB

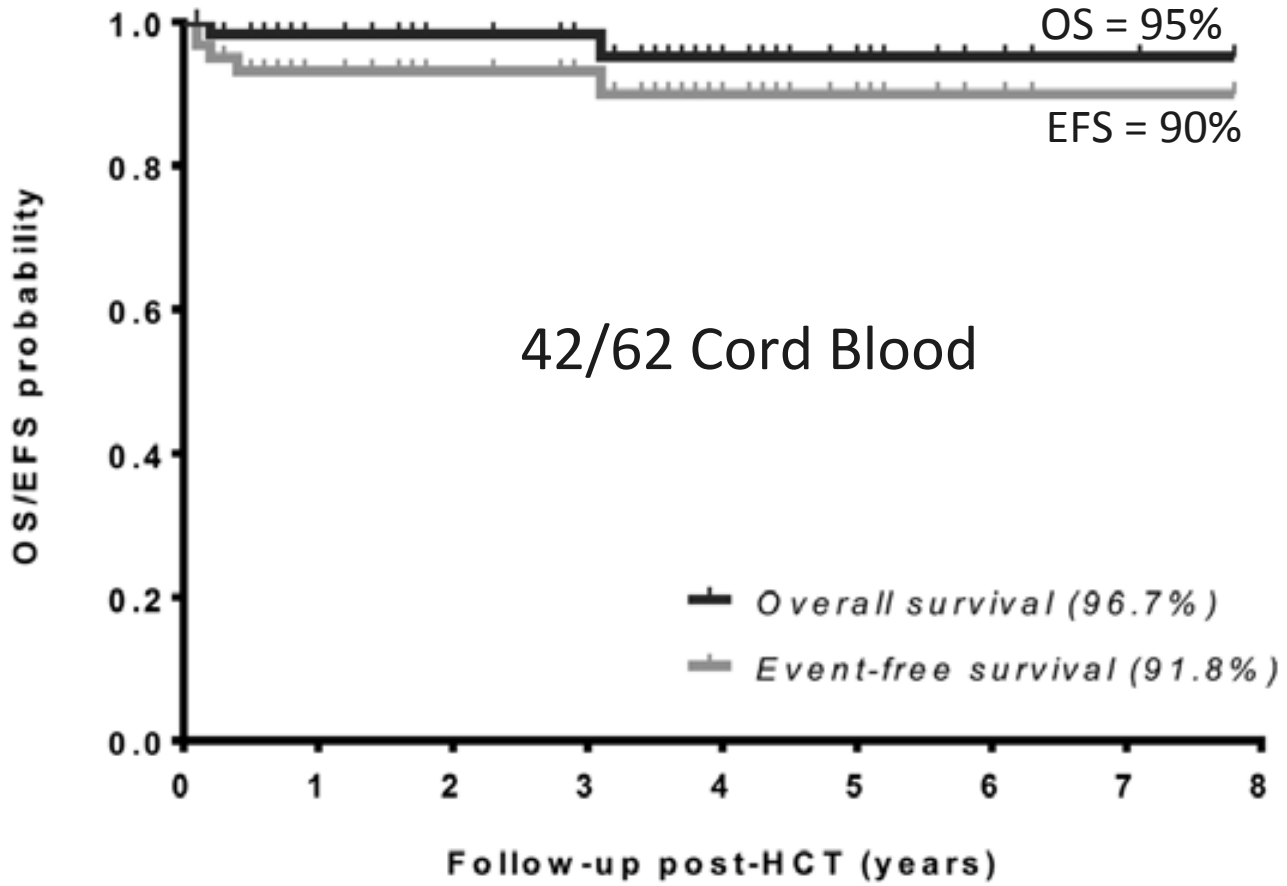
- Conditioning regimen
  - Myeloablative: Bu/Cy (2008) or Flu/Bu (2012)
  - Bu drug monitoring recommended

*Boelens et al. HCT - The EBMT Handbook. 2012*

# Utrecht / Manchester Data Since 2006 (n=62)

## BuCy (29) and FluBu (33)

Med.age @ HCT = 13 mths



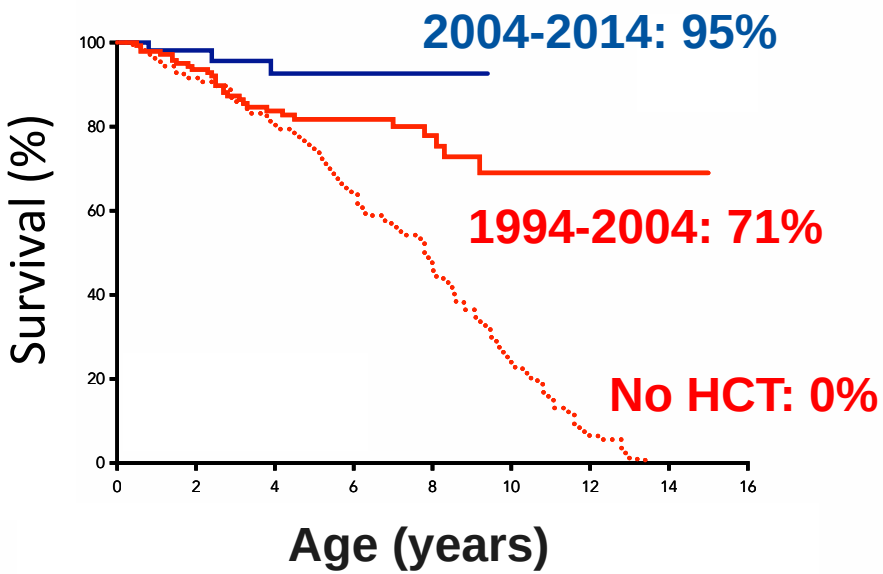

42/62 Cord Blood

Note:
Low GvHD
No VOD
<5% cGvHD

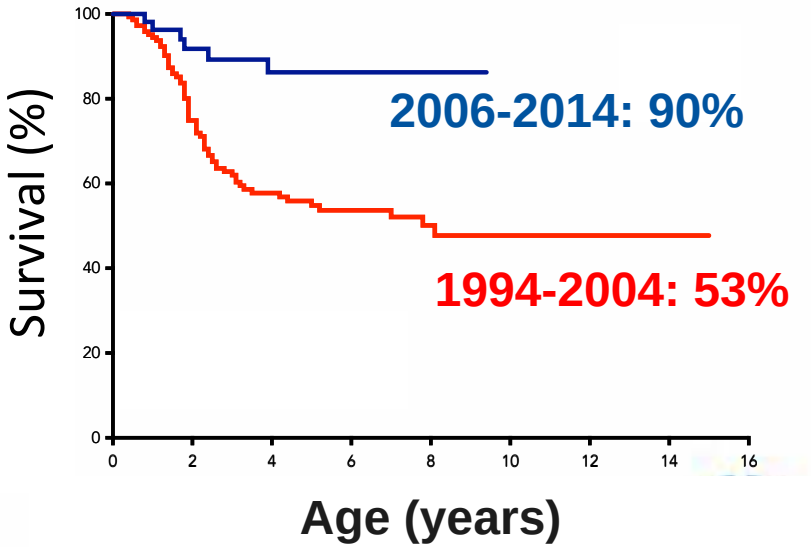
# Improved safety and efficacy

- N=62 MPS-patients
- HCT EBMT guidelines 2006-2014 (Manchester/Utrecht)

## Overall survival



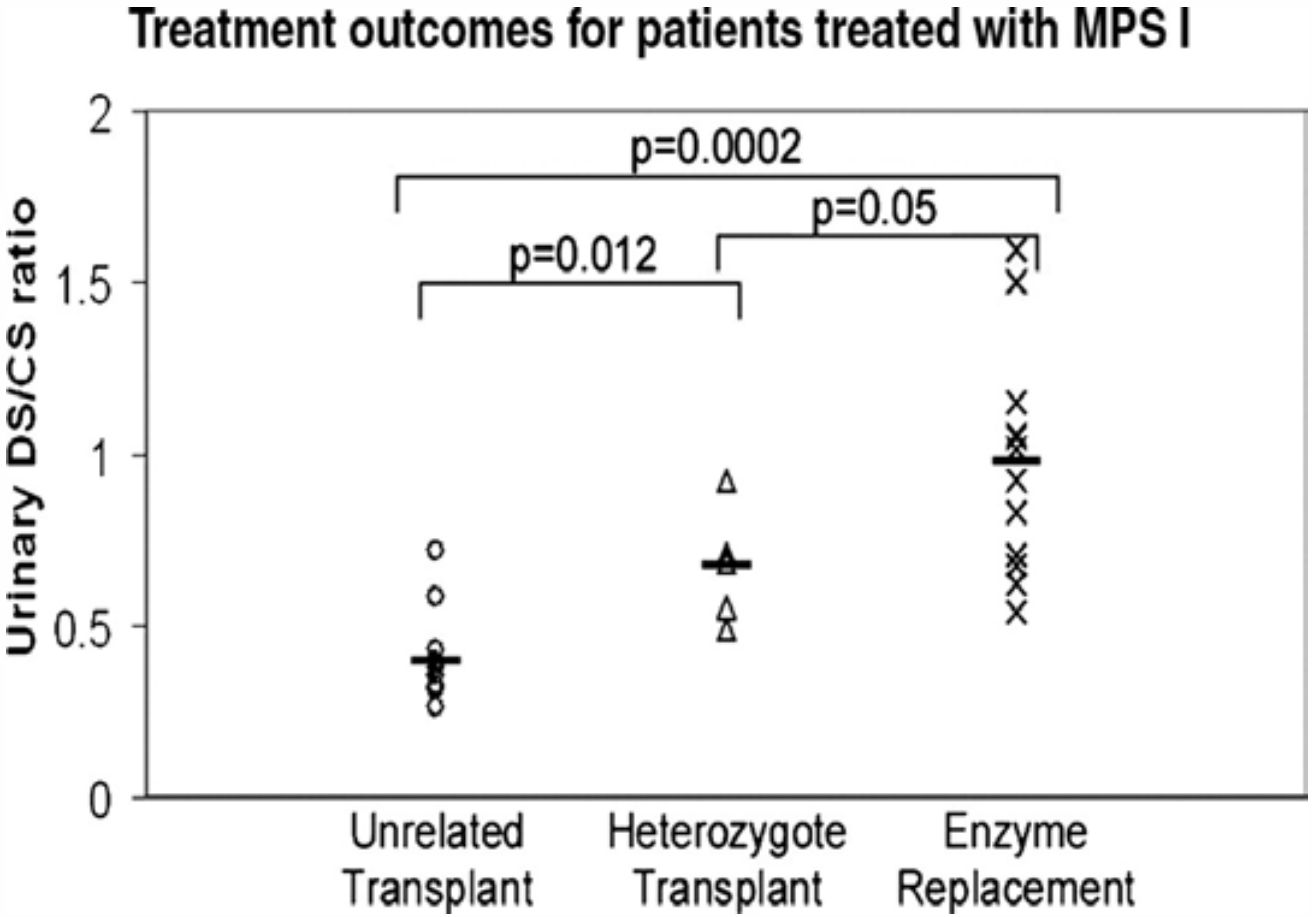

## Event-free survival (after 1st HCT)




*Aldenhoven et al. BBMT. 2015*

# Urinary GAG excretion (DS/CS-ratio)

## Influence of treatment




*Wynn et al. J Pediatr. 2009*

# Long term outcome Hurler syndrome post-HCT




High variability between Hurler patients post-HCT

Explanation?

# International collaboration

## Identifying predictors for Late Outcomes

## N=217 Hurler syndrome

Age at HCT 16 (2-47) months

Follow-up age 9 (3-23) years

*Aldenhoven et al. Blood. 2015*

# How to collect these data?

Mieke Aldenhoven:

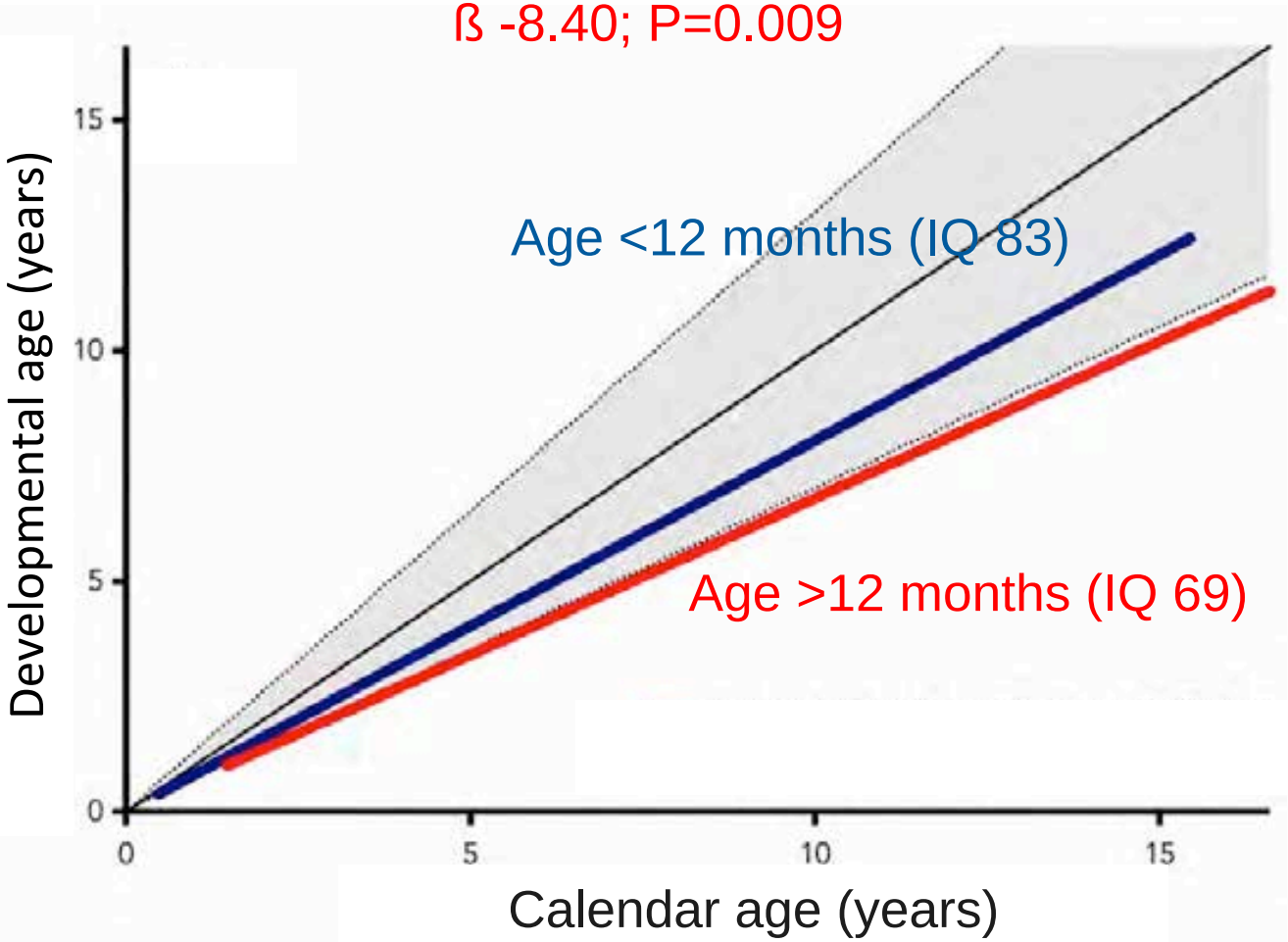
Visited all (larger) centers in USA and Europe to collect data

PhD: 15th of Jan 2015

# Neurodevelopmental outcome: Predictors

## Age at HCT

ß -8.40; P=0.009




## Baseline IQ

ß -8.58; P=0.009

## TBI

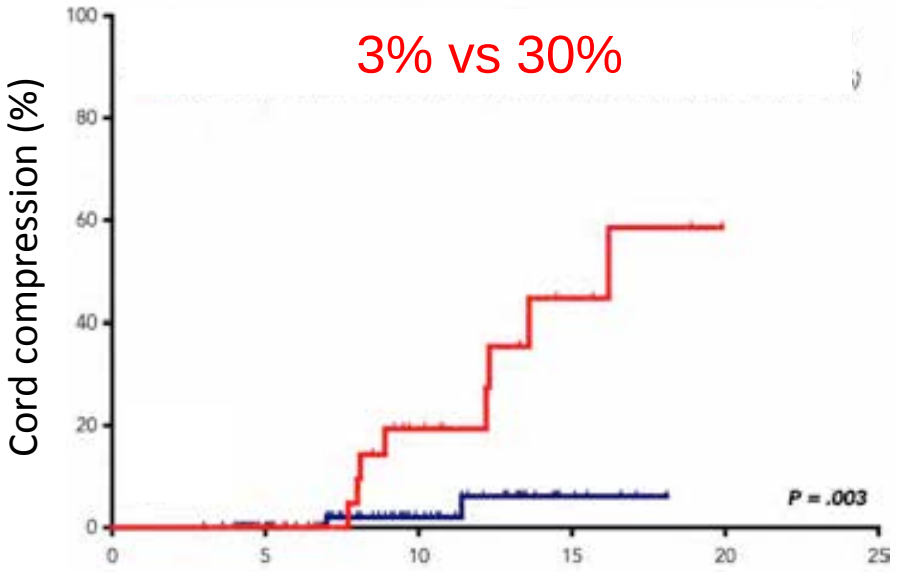
ß -9.90; P=0.03

*Aldenhoven et al. Blood 2015*

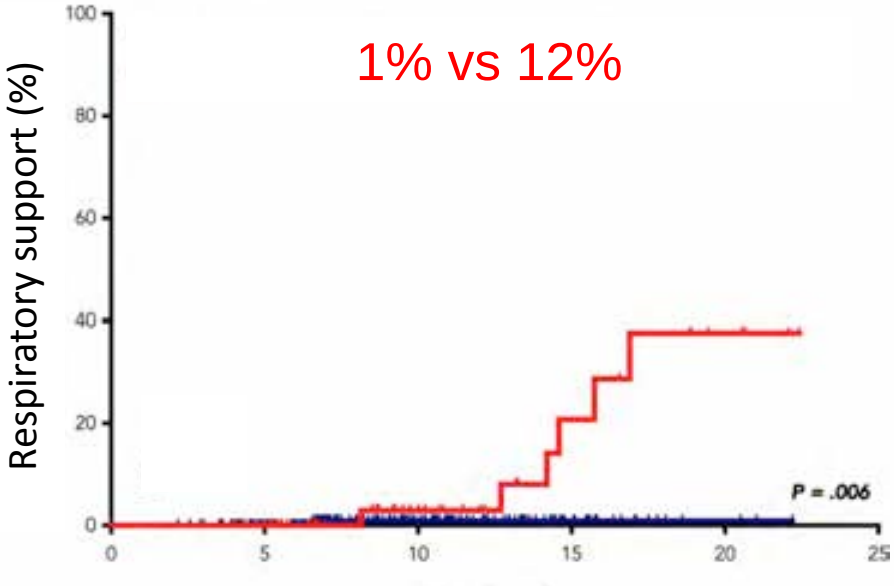
# Enzyme level Post-HCT

## Predictor for Outcomes

Cord compression




Respiratory support




## Multi-system effect

*Aldenhoven et al. Blood. 2015*

# Outcome of cord blood transplantation for leukodystrophies

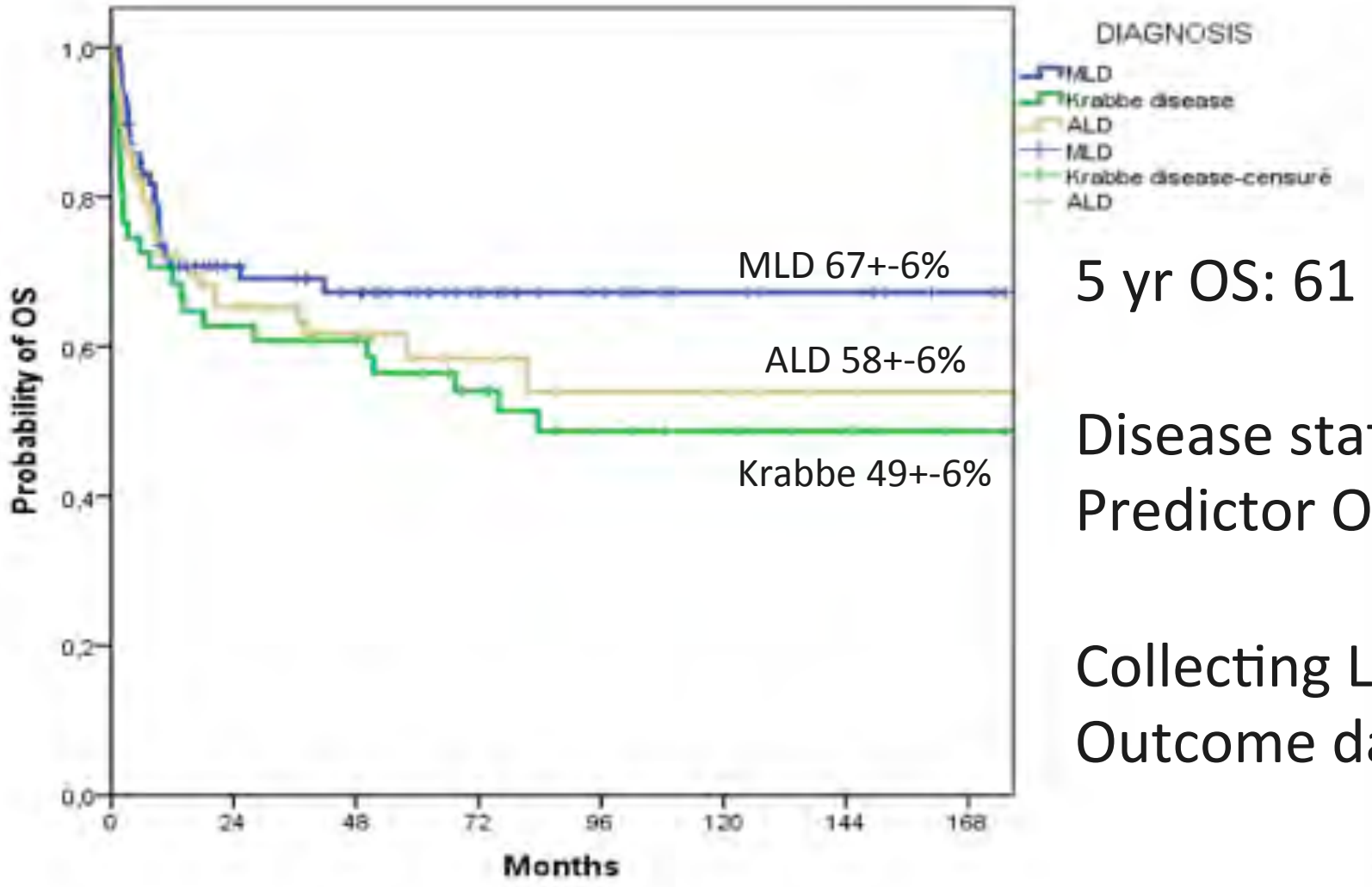
JOINT EUROCORD, EBMT and Duke University

(Working Party Inborn Errors)

STUDY 2014

*Janna Hol; J.J. Boelens, MD PhD*

# OS according to Leukodystrophy (n=220)
# Duke, EBMT, Eurocord




5 yr OS: 61 +-3%

Disease status
Predictor OS

Collecting Late
Outcome data

# In summary: Hurler and HCT

- No fatal disease
- Improved safety & efficacy: >95% engrafted survival
  - Cord Blood Preferred Cell Source
- Age & enzyme level predictors for late outcomes
- Future:
  - Newborn screening!
  - Genetherapy: increasing the enzyme levels (supranormal)
    - MLD, X-ALD, MPS-3, (MPS-1)

# EUROCORD TEAM 2013

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Vanderson Rocha
MD PhD
Scientific Director

Eliane Gluckman MD
FRCP
Project Leader

Agnès Devergie
MD

Chantal Kenzey
Data Manager

Fernanda Volt, MT

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MD

# Acknowledgements


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- **University Medical Center Utrecht, the Netherlands**
  - JaapJan Boelens, Peter van Hasselt, Mieke Aldenhoven
- **Royal Manchester Children's Hospital, UK**
  - Rob Wynn, Ed Wraith, Jean Mercer
- **Our lady's Hospital for Sick Children, UK**
  - Anne O'Meara
- **Ospedale San Gerardo, Monza, Italy**
  - Antillio Rovelli
- **Great Ormond Street Hospital, UK**
  - Paul Veys
- **University of Minnesota, USA**
  - Paul Orchard, Elsa Shapiro, Teresa Kivisto
- **Duke University, USA**
  - Joanne Kurtzberg, Vinod Prasad
- **All other participating transplantation centers**

# Acknowledgements


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Caroline Lindemans
Ariane de Wildt (datamanager)
Corinne Gerhardt (datamanager)
Marco Valkenburg (JACIE-officer)

**Immunology:**
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Wietse Kuis

**Adult HCT:**
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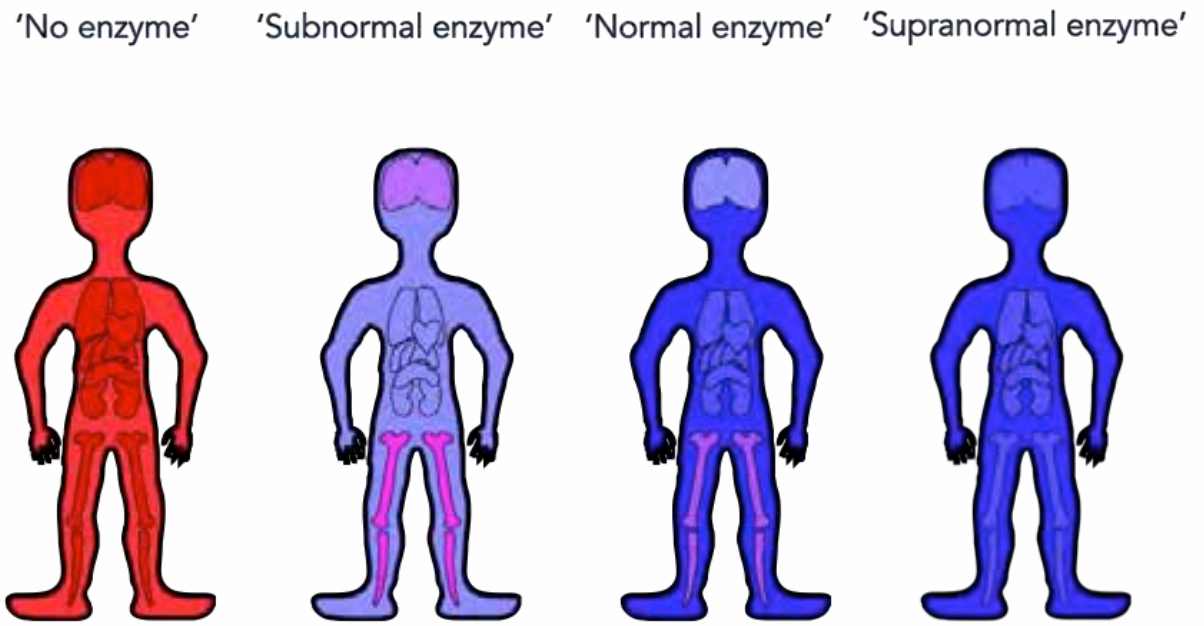
Eefke Petersen
Moniek de Witte
Datamanagers

**Section APPLIED LTI (Tumorimmunologie)**
Jurgen Kuball
Jeanette Leusen
Erik Spierings
Niels Bovenschen
Stefan Nierkens


# 1. Newborn screening

## Challenge: phenotype prediction

# 2. Gene therapy?




*No HCT* *HCT* *Gene therapy?*

# In summary

1. With Individualized Conditioning and Adjuvant

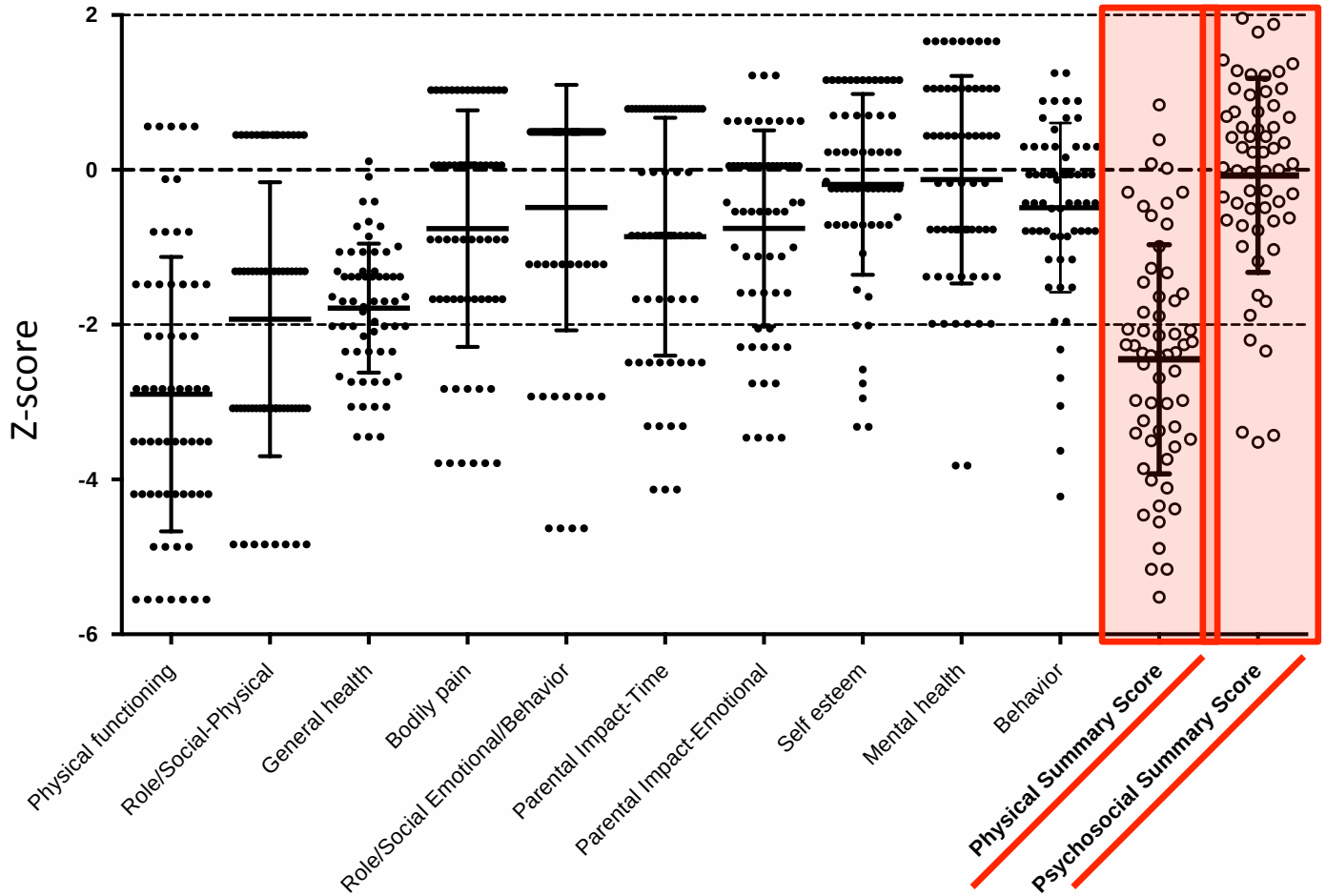
   Immunotherapies: Better Disease Control

2. HCT in Lysosomal Storage Diseases:

   –Improved Safety and Efficacy

   –Newborn Screening and Genetherapy for Further improvement

# Quality of Life




Physical health: mean z-score -2.5 (SD 1.5)

Psychosocial health: mean z-score -0.1 (SD 1.3)

-Post-HCT enzymes Predictor

*Aldenhoven et al. Submitted*