Public Donation and Family Banking: Cord Blood Options

Joanie Y. Hare, MD
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Recorded: February 9, 2017 1

Learning Objectives

- State the rationale in counseling patients about cord blood options
- Differentiate between transplant medicine and regenerative medicine as it relates to umbilical cord blood
- Discover resources available for you, your organization, and ultimately your patients, about umbilical cord blood donation and storage

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Disclosures

The following planners and speakers have no financial disclosures.

Name	Role in activity
Joanie Hare, MD	Speaker
Nicole Heino	Planner
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Disclosures

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Cbr® From AMAG Pharmaceuticals

Counseling Patients is Key in Cord Blood Banking

Joanie Y. Hare, MD

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What to Ask?

- Has the obstetrician (OB) discussed cord blood options?
  - Patients seek credibility/endorsement from their OB
  - Nurse can reinforce discussion
  - Nurse can support mom's decision
  - Nurse can answer questions

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What is Cord Blood?

- Cord blood is the blood that remains in the umbilical cord and placenta and can be collected once the cord is clamped and cut
- Cord blood contains hematopoietic cells like those found in bone marrow

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Cord Blood Preservation Options

Public Donation	Family Banking	Sibling Directed	Do Nothing
Added to Be The Match Registry® if requirements are met	Cord blood stored for family's personal use	Available to families with a sibling (in some cases a parent) with medical need	Discarded as medical waste
No cost to donor	Storage/processing fee	Offered at little or no cost to eligible families	
Used for any child or adult in need	Cord Tissue banking	Stored for family's personal use	

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Public and Family Banking

Public Donation	Family Banking

• Cord blood unit (CBU) belongs to public cord blood bank
• Used for any child/adult in need
• No cost to donate
• HLA typed prior to registry listing
• Highest cell count CBUs are processed/stored
	• CBU belongs to family
	• Most directed allogeneic/ autologous use in children
	• Storage/processing fee
	• HLA typed when needed
	• Most CBUs stored for:
	  • traditional use
	  • future use in new areas
	  • regenerative medicine

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What Information Should I Provide?

Public Donation	Family Banking

• Health assessment prior to donation
  – Cord blood bank initiates and complies with FDA regulation
• Singleton birth
• > 34 weeks gestation
• Defined accredited delivery location, unless a kit collection
  – Limited kit donations
	• Health assessment with enrollment
	• Singleton/multiple births
	• Any delivery location
	• Payment options available to make affordable for all families

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Sibling in Need

- CBUs can be saved for a sibling, and in some cases a parent, with medical need
- Sibling-directed donation offered at little/no cost to eligible families
- Parents need to have conversation with sibling's physician
- Parents need to contact participating public cord blood bank or family bank
- Another option
  Newborn Possibilities Program
  http://www.cordblood.com/benefits-cord-blood/family-cord-bloods

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Do Nothing

- In many areas, public cord blood donation is not available
- Parents may decide that neither public donation nor family banking is right for them
- If not collected, discarded as medical waste
- Provide support for family's decision

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Benefits of Cord Blood

Public Donation

- Only 30% of patients have family match
- CB does not need to match as closely as other stem cell sources
- Fewer post transplant immune complications
- Immediately available for patient in need

Family Banking

- Research has shown that a well-matched sibling is the best donor source of stem cells
- Growing scientific evidence supports future potential for regenerative medicine
- Clinical trials are studying cord blood stem cells for cellular therapy in disease conditions
- May be a more serious consideration for families with medical history, ethnic minorities, or mixed ethnicity

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Common Questions

- **Patients often ask about these topics:**
  - Cord blood does not contain embryonic stem cells
  - Cord blood is rich in blood-forming cells
  - Patients have options
  - Collection process is completely safe for mother and baby
  - Donation is not available everywhere
  - Not all public cord blood units are stored
  - If unit is placed on registry, no transplant information is shared (donor and recipient never meet)
  - Cord blood stored in family bank cannot be transferred to public bank at this time

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Delayed Cord Clamping

- Providers may prefer a short delay of 30-60 seconds
  - See ACOG Committee Opinion No. 624 for details
  - For public donation and family banking, do not interfere with standard-of-care for baby/mother

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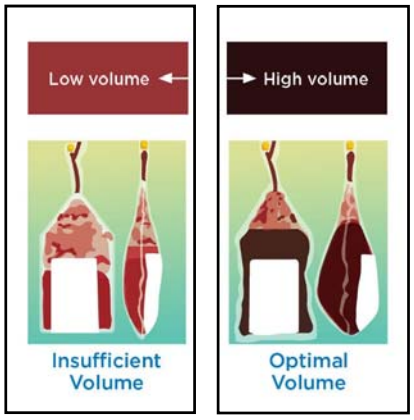
Public Cord Blood Collection

- Optimal volume is critical for a successful transplant
- The darker the color, the higher the volume



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Cord Blood Collection

- Best practices include:
  - Clamp cord as close to baby as possible
  - No contamination
  - Use smallest sample necessary for hospital testing
  - Minimize manipulation of cord and placenta
  - Allow enough time for cord to blanch
  - Accurate, complete labeling

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Additional Resources

- American Academy of Pediatrics official policy statement, Cord Blood Banking for Potential Future Transplantation
- American College of Obstetricians and Gynecologists (ACOG) Committee Opinion on Umbilical Cord Blood Banking, Committee Opinion on Delayed Cord Blood Clamping and FAQs about cord blood donation.
- American Medical Association ethical guidelines for physicians about umbilical cord blood
- American Society for Blood and Marrow Transplantation position statement and committee report on cord blood collection and preservation and a guide for parents
- Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, Cord Blood Information

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Additional Resources

- Parents Guide to Cord Blood
  - www.parentsguidecordblood.org
- To learn more about:
  - Be The Match
    - www.BeTheMatch.org/cord
  - Cord Blood Registry:
    - www.cordblood.com
  - Cord Blood Registry:
    - "Cord blood banking legislation"
    - http://www.cordblood.com/benefits-cord-blood/umbilical-cord-blood-banking/cord-blood-banking-legislation

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Cord Blood Transplantation: Past, Present & Future

Joanne Kurtzberg, MD

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Joanne Kurtzberg, MD
Duke University Medical Center

CORD BLOOD TRANSPLANTATION:
PAST, PRESENT, AND THE FUTURE

Why Cord Blood?

- CB contains stem and progenitor cells of blood and other lineages.
- CB is immunologically tolerant and can be transplanted without full HLA matching, increasing access to transplantation for patients lacking matched adult donors.

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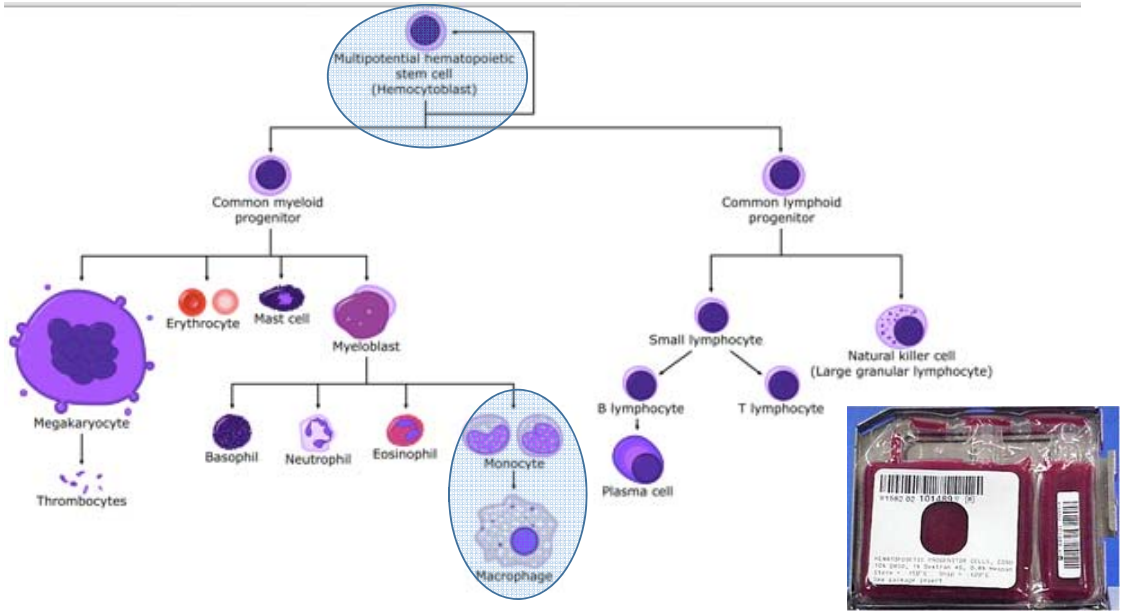
Types of Cells in Cord Blood



- 1988 – 1st Cord Blood Transplant
- MRD for Fanconi Anemia
- A&W 27 years later

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Umbilical Cord Blood Transplant History

- 1st Transplant, France 1988 – Matched Related Donor (MRD)
- 1st unrelated donor cord blood bank(CBB), NYBC 1992
- 1st unrelated transplant, Duke 1993
- Netcord: Established 1997
- NMDP center for cord blood established 1999
- Now >35,000 transplants and >160 banks worldwide
- Public Inventory ~180K US, 700K worldwide
- Private Inventory ~4M worldwide
- Legislation: CW Bill Young Cell Transplantation Program
  - Coordinating centers, registry, outcomes database
  - NCBI banking network
- Regulations: Guidance for FDA Licensure 10/20/2011
- Now 7 licensed CBBs in the USA
- ~4-5,000 transplants annually around the world

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Cord Blood Banking

- Public – Donation for public use
  - No cost to donor
  - Regulated
  - High standards
- Private – Saved at a $$ for the family
  - Charge to the family
  - Non-Regulated
  - Variable standards

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Manufacturing and Administration of CBUs

- Collection
- Manufacturing
  - + / – RBC, volume reduction
  - Ancillary testings samples (mom and baby)
  - Storage in LN or vapor
- Unit Selection
- Thawing and administration
  - "To wash or not to wash"

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Banking Specifications

- Banking Specifications
  - >900M Total Nucleated Cell Count (TNCC)
  - >1.25M viable CD34 cells
  - CFU growth
  - Viability >90% (Trypan Blue)
  - Negative Sterility
  - Negative Donor Screening Tests and Questionnaires
  - Negative hemoglobinopathy screen

Key Observations about UCBT

- Cord blood could substitute for bone marrow as a donor for Hematopoetic Stem Cell Transplant (HSCT) for all standard allogeneic indications
  - Hematological malignancies, marrow failure, immunodeficiencies, hemoglobinopathies, certain inherited metabolic diseases
- Cell dose matters and single cord blood unit may be on the cusp or too small for larger individuals
- HLA matching also matters, but lesser matches can be utilized when higher cell doses are administered
- Immune reconstitution is delayed
- Graft versus Host Disease (GvHD) is decreased as compared to adult HSCT sources
- Results are comparable to MRD and MUD
- Relapse may be lower post CBT versus other HSCT sources

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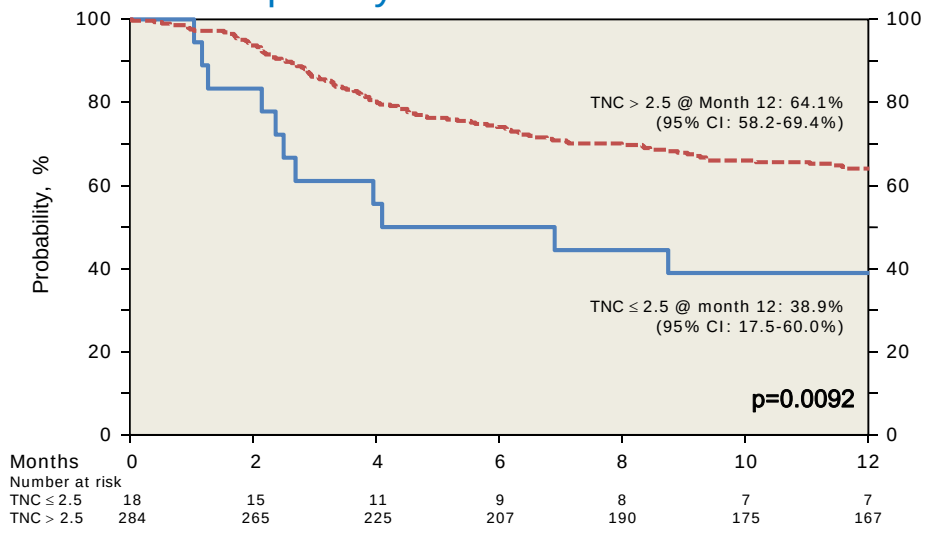
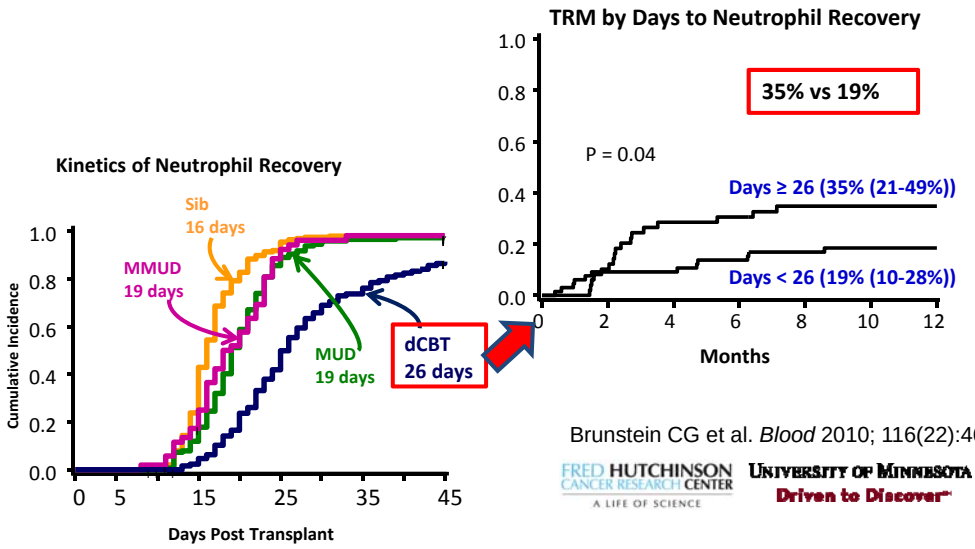
Overall Survival All Patients
- Total pre-cryo nucleated cell dose -



Kurtzberg J et al, *Biol Blood Marrow Transplant* 2013; 19:2

The Impact of Low Cell Dose in CBT



Brunstein CG et al. *Blood* 2010; 116(22):4693-9

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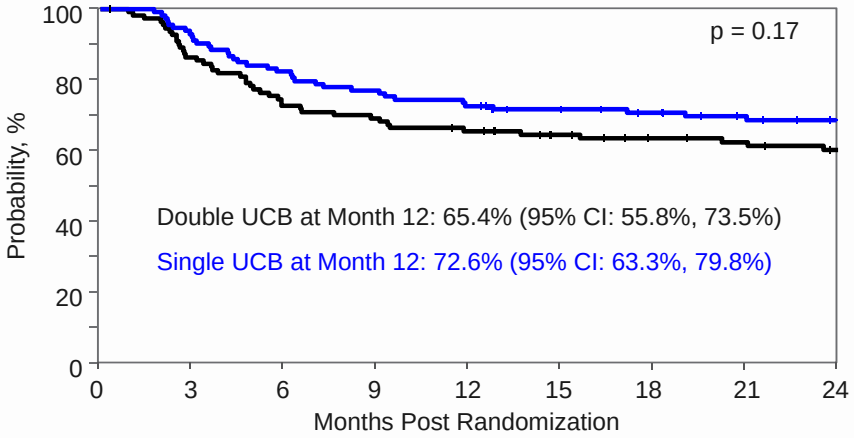
BMT-CTN 0501: DC vs SC in HM after MA therapy in Children: Overall Survival



Number at risk

Double UCB	111	95	80	76	71	64	59	57	54
Single UCB	113	103	93	87	82	75	71	66	63

Wagner JE, N Engl J Med 2014

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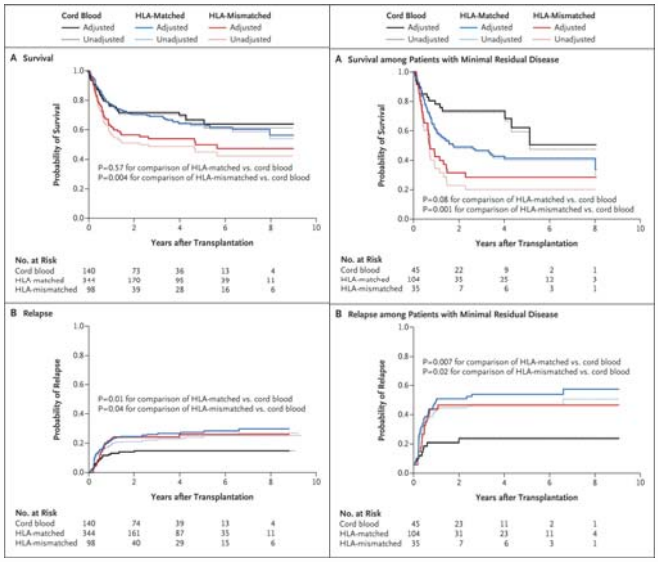
UCBT offers superior protection against relapse in adults with hematological malignancies undergoing UD HSCT



Comparison of UCB, MUD, mmMUD on DSF in 582 patients.

Milano F et al. N Engl J Med 2016;375:944-953.

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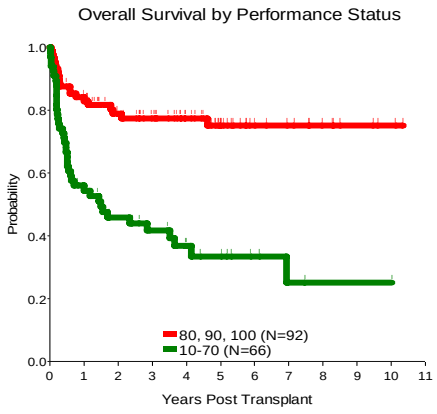
Patient Selection

- Malignancies
  - AML
  - ALL
  - MDS, secondary AML
- Non Malignancies
  - Metabolic
    - Extent of disease progression
    - Newborn screening
  - Immunodeficiency diseases
  - Hemoglobinopathies
  - Marrow Failure



Prasad VK et al., Blood. 2008;112(7):2979-89

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Non-malignant Diseases Transplanted

Adenosine Deaminase	Adrenoleukodystrophy	Alpha-mannosidosis
Autoimmune Encephalitis	Bare Lymphocyte Syndrome	Batten Disease
Chronic Granulomatous Disease	Combined Immune Deficiency Syndrome	Common Variable Immune Deficiency Disease
Chediak-Higashi Disease	Congenital Hypoplastic Anemia	Crohn's Disease
DOCK8 Deficiency	DiGeorge Syndrome	Diamond Blackfan Anemia
Dyskeratosis Congenita	Familial Erythrophagocytic Lymphohistiocytosis	Fanconi Anemia
GM1 Gangliosidosis	Glanzmann's Thrombasthenia	Hemophagocytic Lymphohistiocytosis
Hemolytic Anemia/PIEZO1	Hunter Syndrome	Hurler Scheie Syndrome
Hurler Syndrome	Hyper IGM Syndrome	Hypophosphatasia
I Cell Disease	IPEX	Kostman's Neutropenia
Krabbe Disease	Leukocyte Adhesion Deficiency	Lesch-Nyhan Syndrome
Lymphocyte Signaling Deficit	Maroteaux-Lamy Syndrome	Metachromatic Leukodystrophy
Nezelof's Syndrome	Niemann-Pick Disease Type B	Omenn's Disease
Osteopetrosis	Paroxysmal Nocturnal Hemoglobinuria	PNP Deficiency
Pelizaeus Merzbacher Disease	SCID	Sandhoff Disease
Sanfilippo Type A and B	Severe Aplastic Anemia	Shwachman-Diamond Syndrome
Sickle Cell Anemia	Sideroblastic Anemia	Tay Sachs Disease
Thalassemia Major	Wiskott-Aldrich Syndrome	ZAP70 Deficiency

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Selection of CBU Graft

- Total Nucleated Cell Count (TNCC)
  - ≥3x10e7/kg for malignancies
  - ≥5x10e7/kg for non-malignancies
  - Per BMT-CTN 0501, 1 CBU is optimal
- CD34 (bank dependent)
  - ≥2x10e5/kg
- HLA match
  - No more than 1 MM at each loci
    - A, B, DRB1 and C (if possible)
  - Match DRB1 over class I

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Prior to Start of Conditioning Therapy

- Complete workup
- Control infections
- Obtain informed consent
- Confirm donor and ship CBU to TC
- Place central line
- Consider G-tube (metabolic patients)
- Simulate for TBI (if indicated)

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Selection and Administration of CBU

- For Metabolic diagnoses
  - Screen for carrier state in donor
  - Test enzyme level
- Make sure a full match is not autologous CB
- Favor accredited banks
- Favor RBC depleted CBUs
- Bank should have a release assay (on a segment) for potency
- Thaw and wash CBU before administration

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Conditioning

- Total body irradiation (TBI)
  - For Heme Malignancies
    - Flu/Cy/TBI
  - Some centers use Bu based regimens for AML
- Non-TBI
  - Bu/Cy or other Bu based regimen
  - Obtain busulfan PK
  - +/- ATG
- Use MAC not RIC

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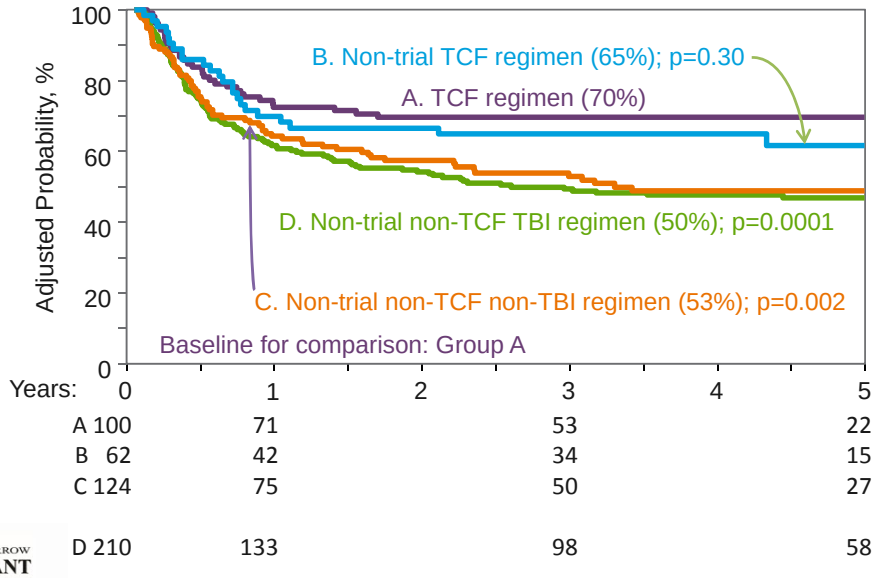
Overall Survival

Adjusted for disease, disease status, CMV serostatus, age



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Eapen M et al., Blood 2016

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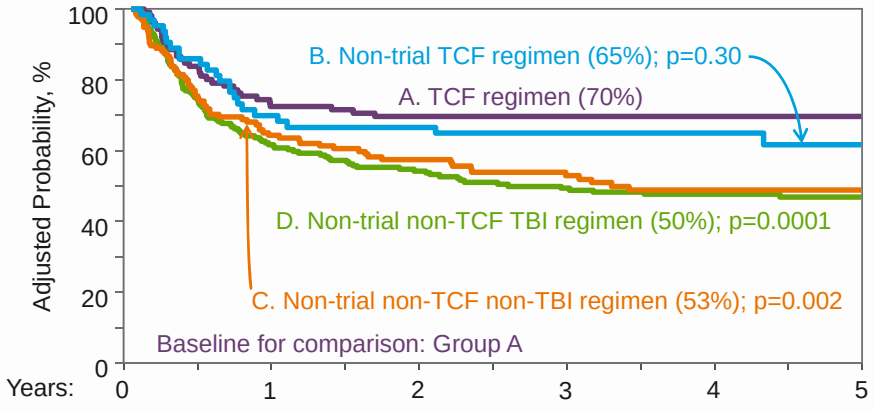
Overall Survival

Adjusted for disease, disease status, CMV serostatus, age



Years:	0	1	2	3	4	5
A	100	71		53		22
B	62	42		34		15
C	124	75		50		27
D	210	133		98		58

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Eapen M et al., Blood 2016

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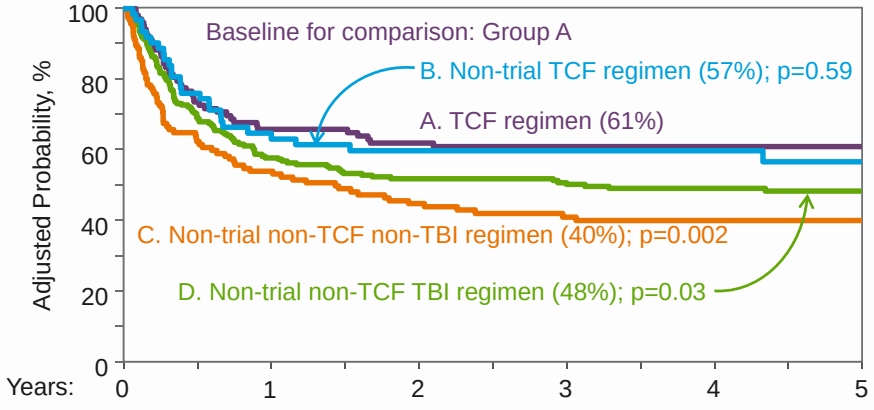
Leukemia-free Survival

Adjusted for disease status, CMV serostatus, age



Years:	0	1	2	3	4	5
A	100	65		46		20
B	61	38		31		14
C	122	67		42		31
D	208	118		92		55

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GvHD prophylaxis

- Cyclosporine (CYA)
- Tacrolimus (FK)
- Mycophenolic acid (MMF)
- Steroids
- Antithymocyte Globulin (ATG)
- CYA or FK/MMF
  - MMF to 45-60 days
  - CYA or FK to 9 months, then taper

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Supportive Care

- Nutrition support
  - TPN or enteral
- IVF
- IVIG
- G-CSF
- Anti virals, antifungals until CD4 >200/uL
- Monitoring (CMV, Adeno, HHV-6, EBV)
- Granulocytes
  - Parental, G-mobilized, irradiated

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Engraftment Syndrome and GvHD

- Engraftment Syndrome (fever, erythroderma)
  - Short steroid pulse
    - Load 2mg/kg, then 1mg/kg q12h x 3days, then taper over 5-10 days
- Acute GvHD
  - Steroids
  - Change from CYA to FK or reverse or MSCs if available
  - 2nd or 3rd line agents
- Chronic GvHD

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Long Term Follow-Up – Late effects

- Skeletal Growth
- Gonadal Failure
- Thyroid
  - Hypo/hyper/Ca
- Osteoporosis
- Cardiac function
- Pulmonary function
- Dentition
- Cognitive

Teeth of an 8 year old child who was conditioned with BuCyATG in the first month of life.

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Expanded Cord Blood Product for BMT

Cord Blood Cells Expanded in Nicotinamide

Cord Blood Unit

↓

CliniMACS separation: Enrichment of $CD133^+$ cells

Cultured fraction (CF)		Non-cultured fraction (NF)
The CD133 positive cell fraction - Cultured for 3 weeks using NAM technology	+	The CD133 negative cell fraction - Kept frozen till the day of transplantation

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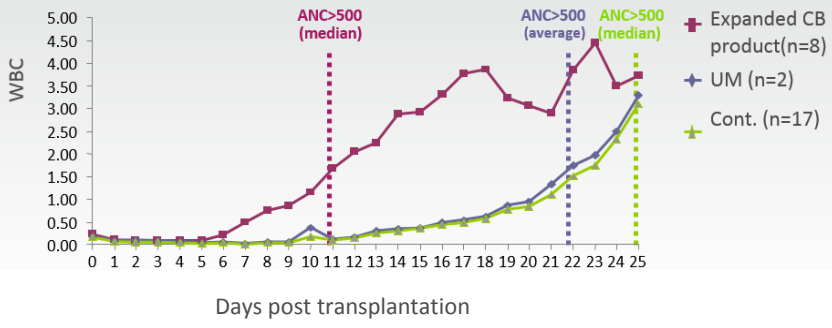
Expanded Cord Blood (CB) Product Rapid Engraftment Shortens Hospitalization

Avg. hospitalization days

- Patients engrafted with expanded CB product: 23.5 (**Day 14** post transplant discharge)
- Patients engrafted with the UM CBU: 40 (**Day 31** post transplant discharge)
- Duke control cohort (n=17) average 36 (**Day 24** post transplant discharge)

Rapid PB WBC Reconstitution in Patients Engrafted with Expanded CB product



Horwitz M et al J Clin Invest. 2014;124(7):3121–3128.

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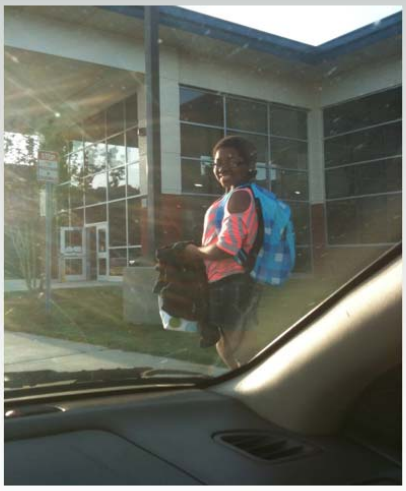
The first SCD patient transplanted with Expanded CB Product



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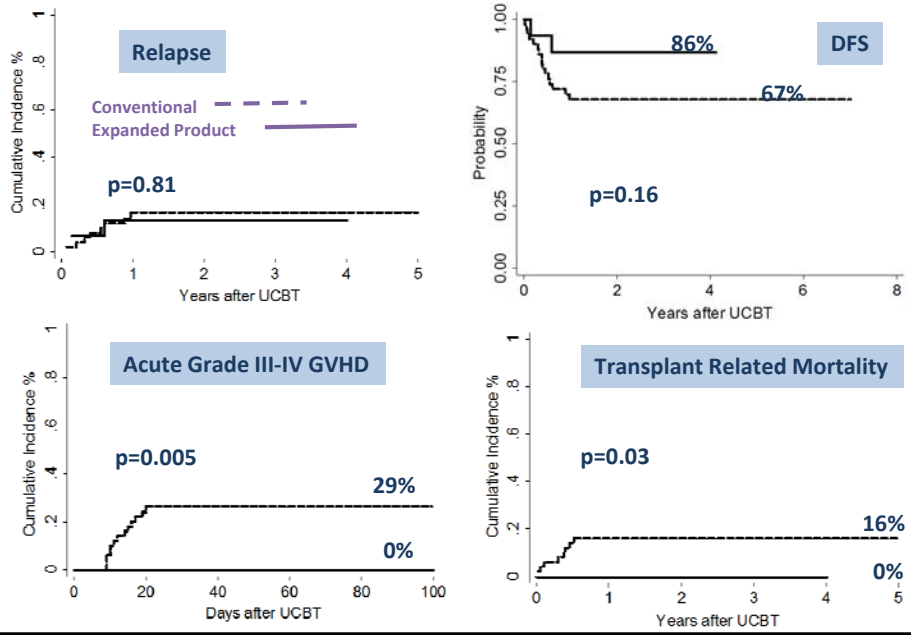
Support with off-the-shelf Notch-expanded UCBT improves outcomes – Colleen Delaney



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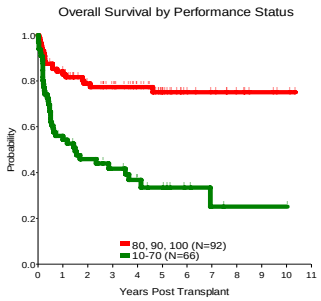
Diseases Treated (N=>350)
Median follow-up 10.3 years

- Krabbe Disease
- Metachromatic Leukodystrophy
- Adrenoleukodystrophy
- Mucopolysaccharidoses
- Hurler, Hunter, Sanfilippo
- Neimann Pick Disease
- Maroteau Lamy
- PMD
- Batten Disease
- Others



Prasad VK et al., Blood. 2008;112(7):2979-89

- Unrelated cord blood donor
- Myeloablative chemotherapy
- Average 56 day hospitalization
- 12-18 month recovery
- Risk of GvHD and TRM

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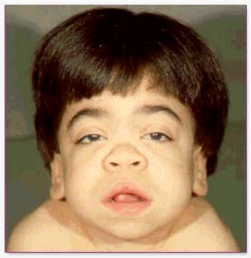
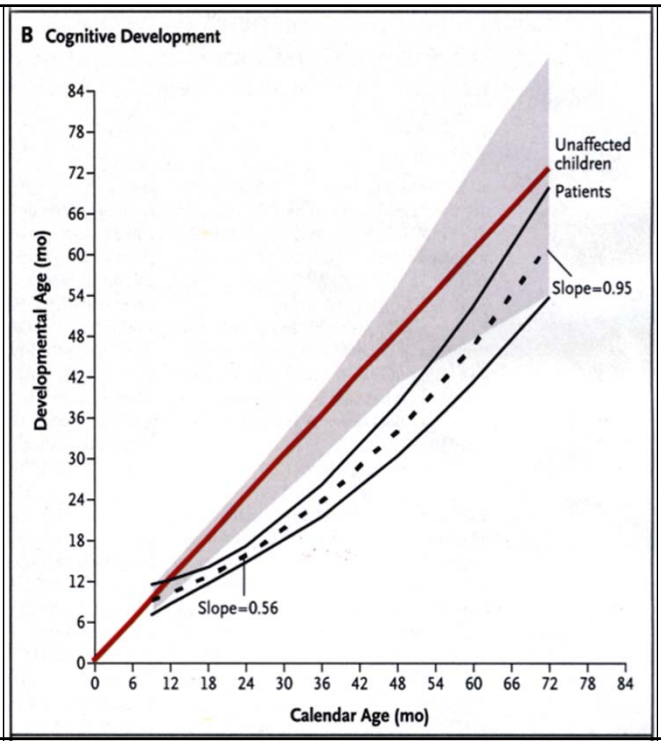


Coarse Facial Features
Courtesy of E. Kakkis, M.D.



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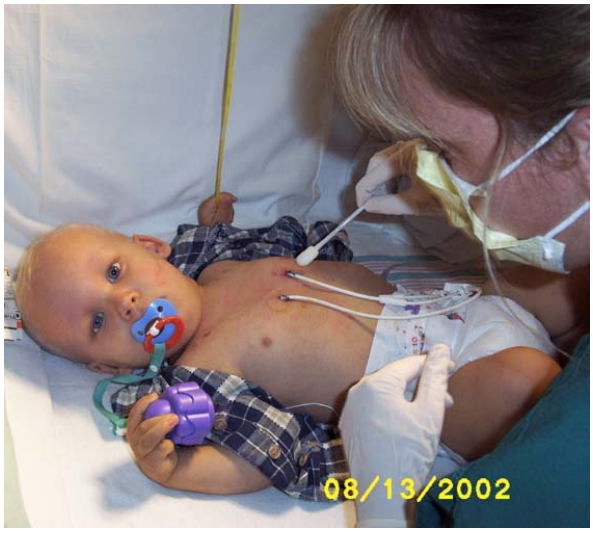
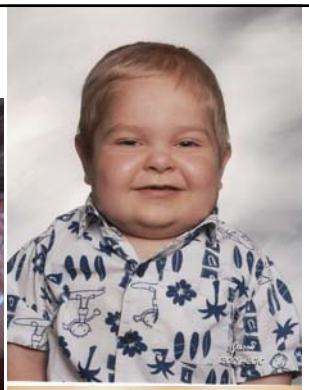
MA chemotherapy is required for engraftment





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Two Brothers Transplanted for Late Infantile Krabbe Disease

UCBT age 11 months

UCBT age 2.5 months

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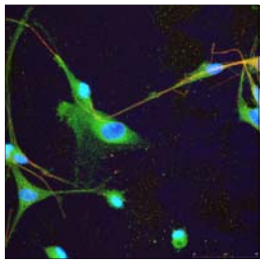
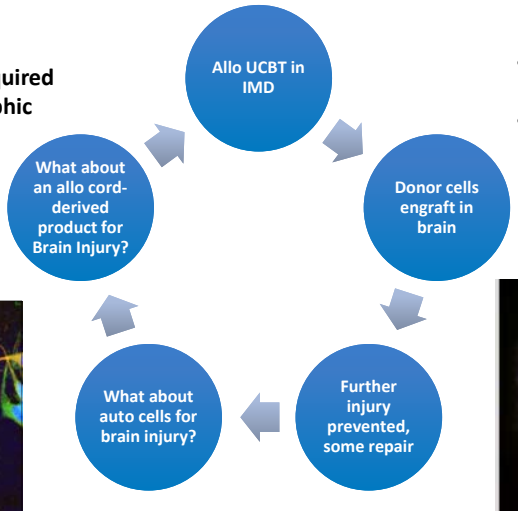
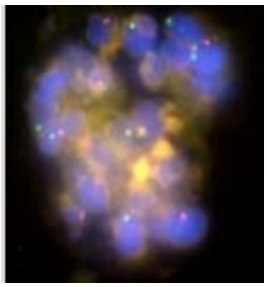
Rationale

- **Engraftment not required**
- **MOA paracrine/trophic**





- **Engraftment required, MA chemotherapy**
- **MOA enzyme replacement**



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Autologous UCB Trials at Duke

- Safety
  - Cryopreserved UCB, 184 patients
  - Sun et al, Transfusion, 2010
- HIE Study "Babybac"
  - Fresh, VR, RR, UCB
  - Cotten et al, J Peds, 2014
- Congenital Hydrocephalus
  - Multiple doses of auto UCB
  - Sun et al, Pediatric Research, 2015
- HLHS/ECMO
  - Fresh and cryopreserved
- CP
  - Cryopreserved
- Autism
  - Cryopreserved
  - 25 patient safety/endpoint finding study in progress

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Allogeneic Cord Derived Therapies

Ongoing:

DUOC-01

Acute Stroke in Adults

Non HLA Matched
ABO/Rh matched
Race matched
3 sites
10 patients treated

Sibling CP

15 patients treated

Planned:

Best donor Autism Phase II
Allogeneic CP Phase II
Cord Tissue MSCs Autism Phase I
MSC versus CB Autism Phase II

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THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Feasibility of Autologous Cord Blood Cells for Infants with Hypoxic-Ischemic Encephalopathy

C. Michael Cotten, MD[1], Amy P. Murtha, MD[2], Ronald N. Goldberg, MD[1], Chad A. Grotegut, MD[2], P. Brian Smith, MD[1], Ricki F. Goldstein, MD[1], Kimberley A. Fisher, PhD[1], Kathryn E. Gustafson, PhD[3], Barbara Waters-Pick, BS, MT(ASCP)[4], Geeta K. Swamy, MD[2], Benjamin Rattray, MD[1], Siddhartha Tan, MD[5], and Joanne Kurtzberg, MD[6]

J Pediatr 2014;164:973-9).

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Survival with 1 year Bayley III scores > 85 in 3 domains

	Cells N = 28 N (%)	Cooled only N = 66 N (%)	p
Survival with all 3 Bayley domain scores ≥ 85	18 (64)	25 (38)	0.04
Bayley < 85 at one year (among survivors)*	9 (35)	23 (48%)	0.33

Next: Multi-center Randomized, placebo controlled, Phase II study
120-160 babies
10 centers

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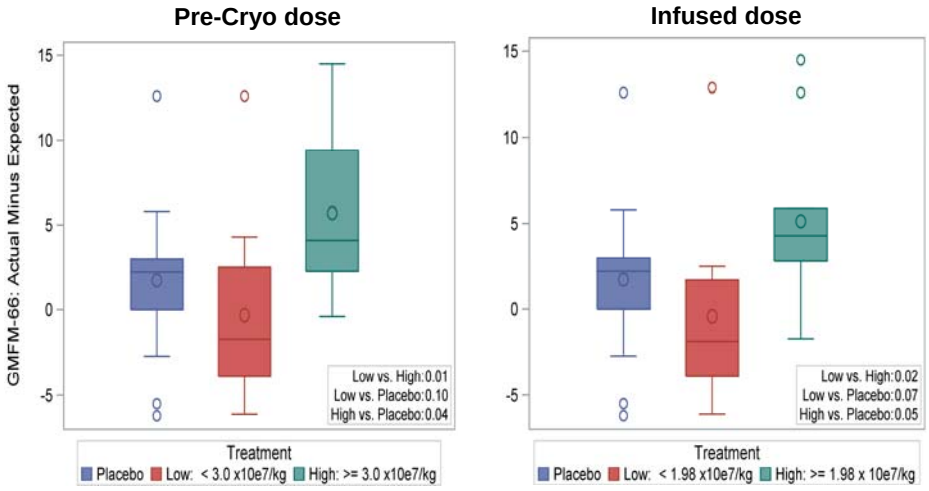
Cotten CM et al., J Pediatr. 2014; 164(5):973-979

CP-AC: Observed – Expected Change

- **≥ 2 year olds (n=38)**



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In Summary

- The CB journey is 27 years young
- CB increases access to HSCT for patients lacking matched donors
- Cord Blood Preparedness:
  - Emerging cell engineering technology promised to reduce TRM and further improve outcomes
  - Expertise in UCBT will improve outcomes
- Emerging applications in cell expansion and regenerative medicine offer promising therapy for babies and children with unmet medical needs

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THANKS!

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