Advisory Council for Blood Stem Cell Transplantation

September 25th, 2020

Why We Can Not Let Cord Blood Transplant Become a Lost Art:

Excellent Outcomes and the Unmet Medical Needs of Our Increasingly Diverse Nation

Filippo Milano, MD, PhD
Director Cord Blood Transplant Program
Fred Hutchinson Cancer Research Center
University of Washington, School of Medicine

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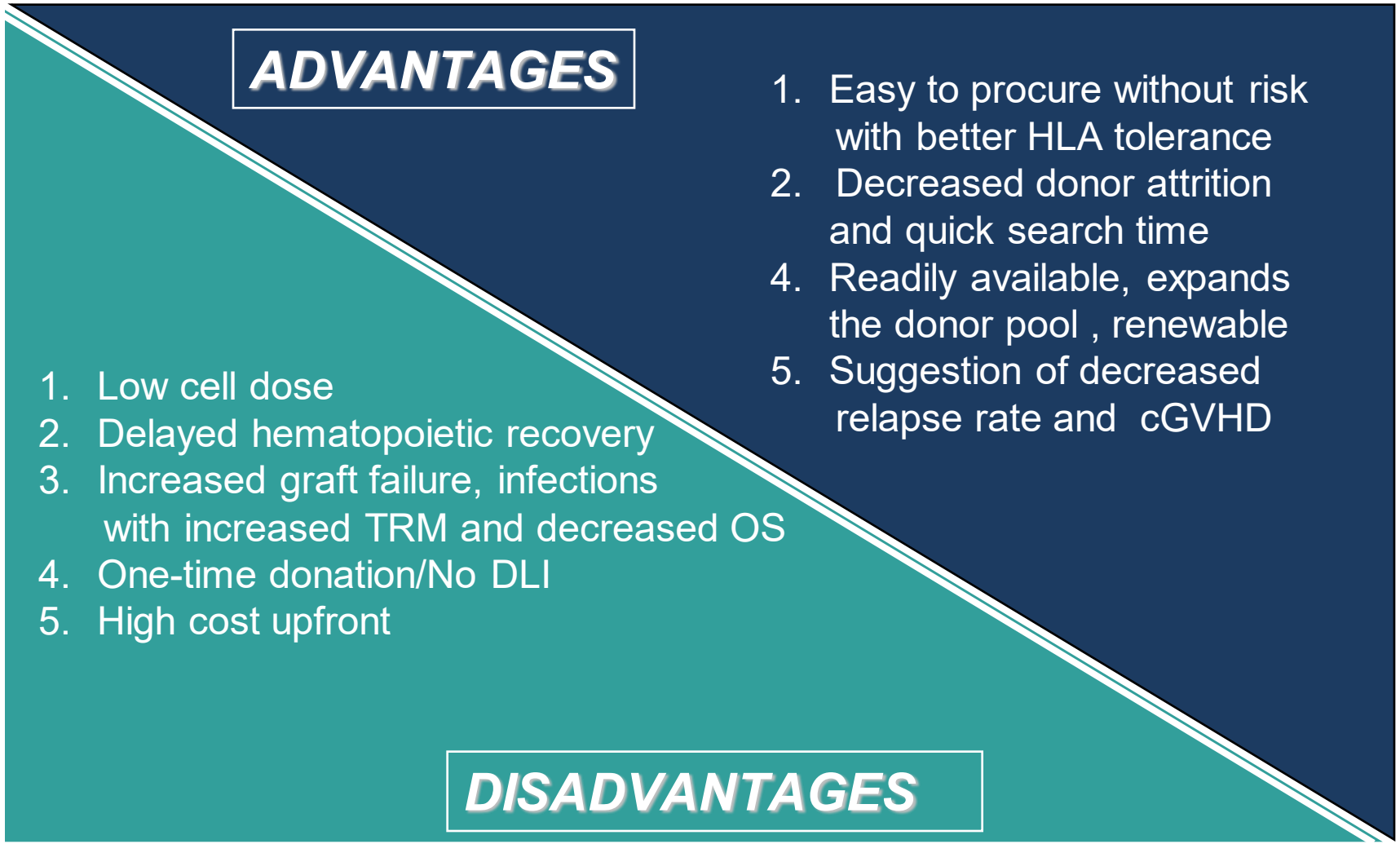
CURES START HERE

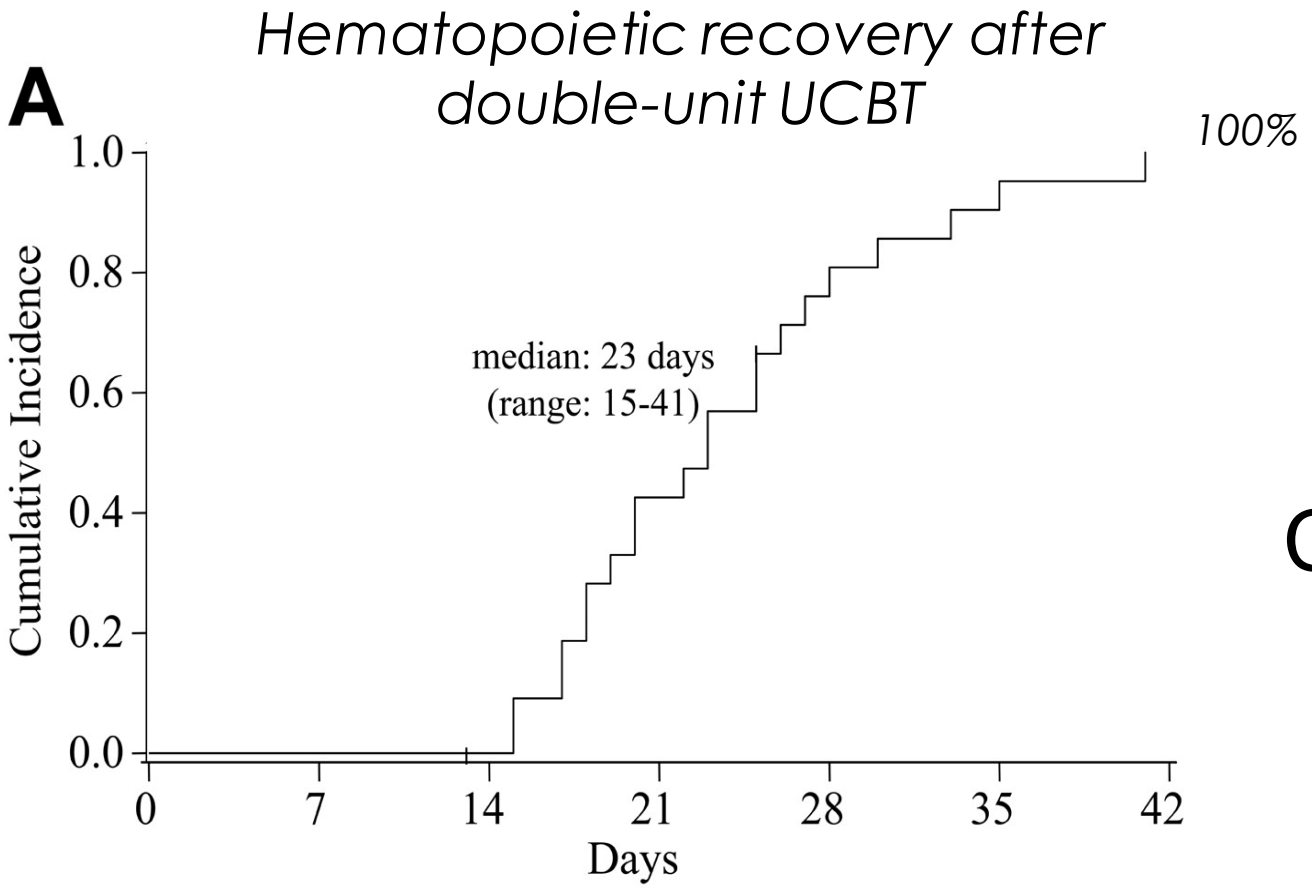
Cord Blood Transplantation



Barrier #1: Real or Perceived?

DELAYED HEMATOPOIETIC RECOVERY

Overcoming the Cell Dose Obstacle and Removing the Barrier to Engraftment



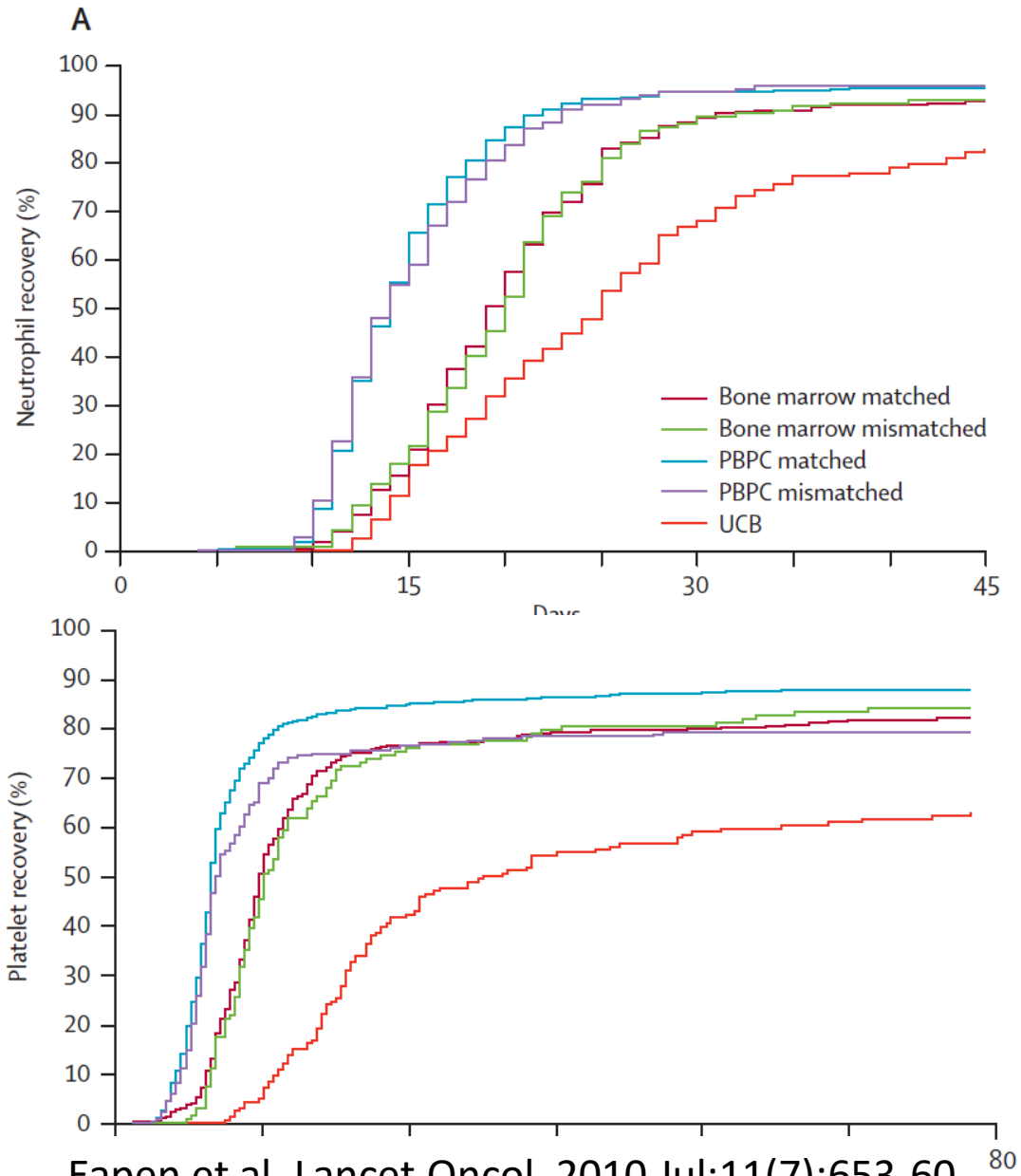
University of Minnesota

DOUBLE UNIT

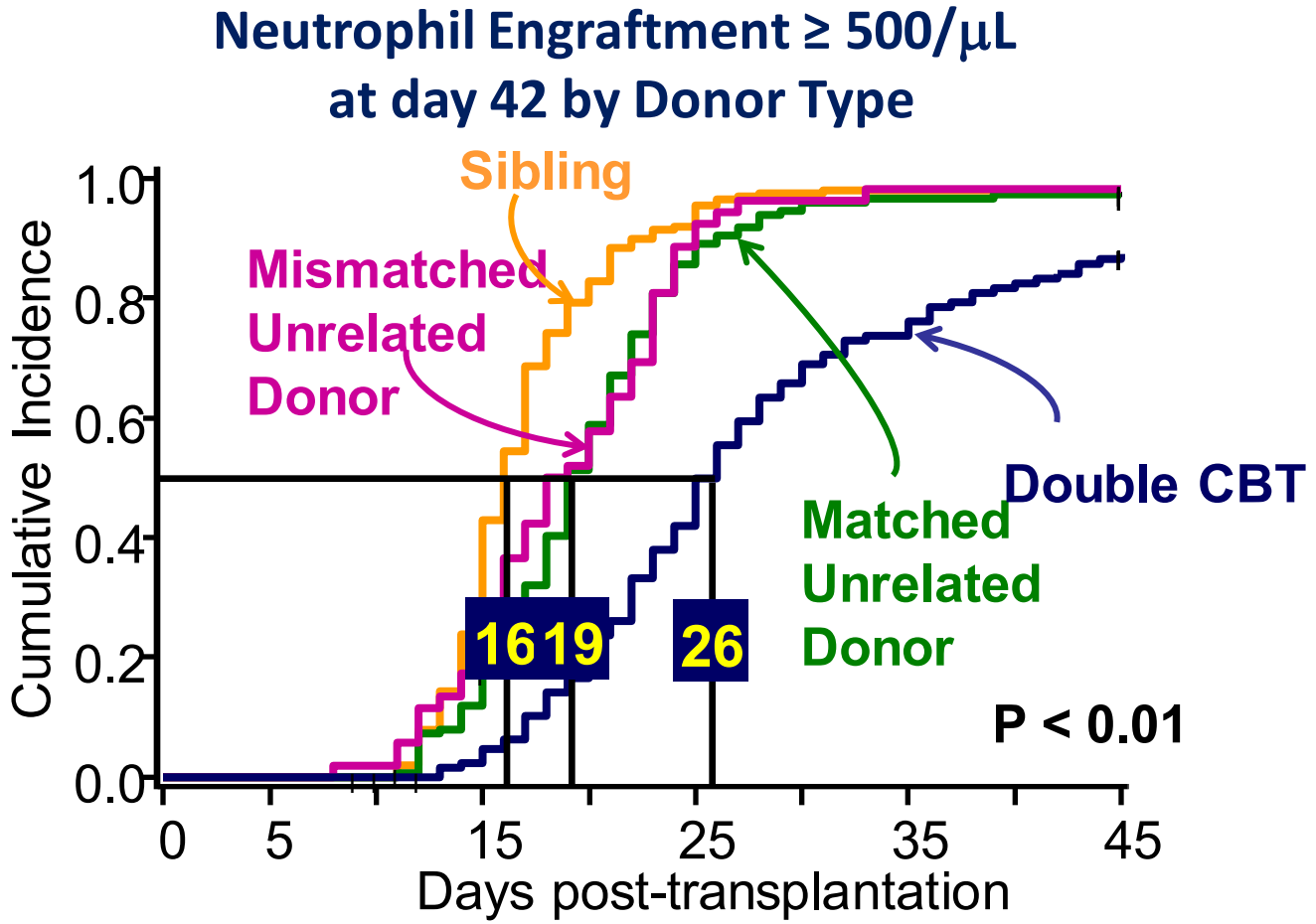
Cord Blood Transplantation

Barker, J. N. et al. Blood 2005;105:1343-1347

BUT: Continued Delay in Time to Hematopoietic Recovery



Eapen et al. Lancet Oncol. 2010 Jul;11(7):653-60

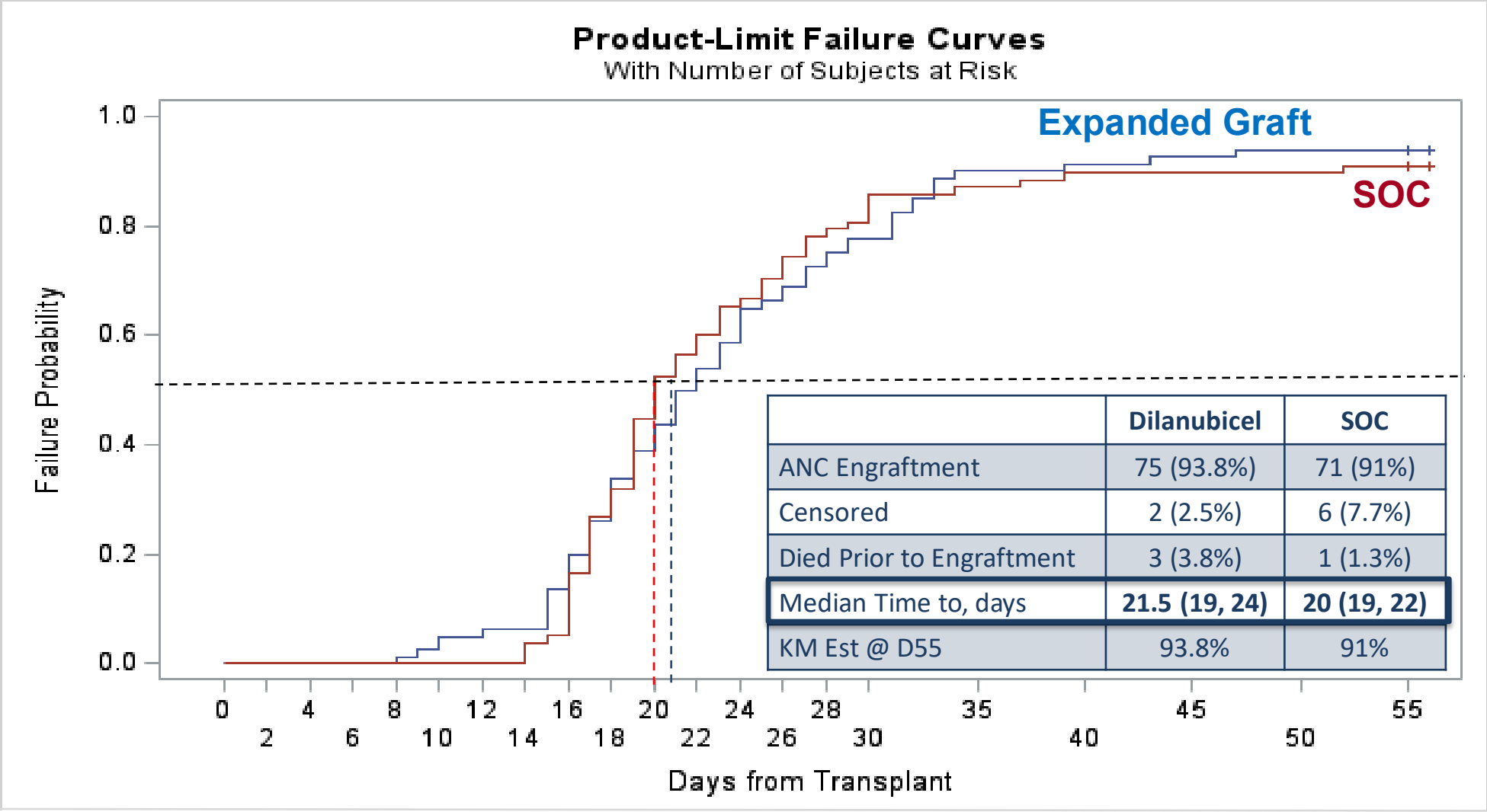


Brunstein et al Blood. 2010 Nov 25;116(22):4693-9

Expansion Technologies to Overcome Engraftment Delay

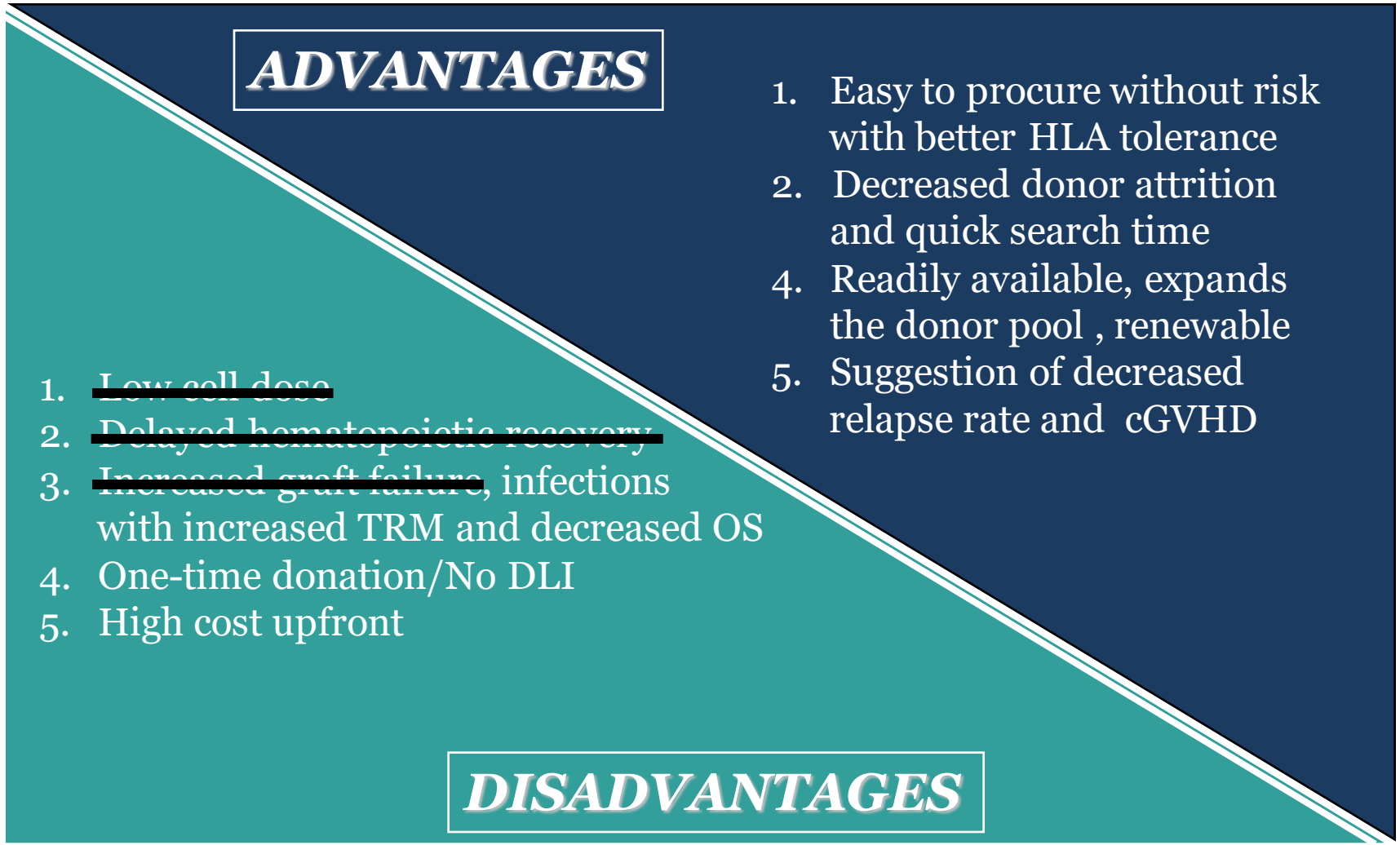
Approach	$CD34^+$ cell fold expansion	Median infused (10^6) $CD34^+$/kg, range	Day to ANC engraftment Median (range)	Group
Expansion				
Notch-ligand fresh	164 (41-471)	6 (0.93-13)	11 days	Delaney et al
Notch-ligand Universal donor off-the shelf	-	5 (3-11)	19 days	Delaney et al.
MSCs co-culture	30.1 (0 - 137.8)	1.81 (0.09–9.88)	15 days	Shpall et al
SR1: fresh + T cell addback	330 (67–848)	17.5 (1.4-48.3)	15 days	Wagner et al.
Nicotinamide: : fresh + T cell addback	72 (16–186)	3.5 (0.9-18.3)	13 days	Horwitz et al
Homing				
CD26/DPP-4 inhibition	-	-	21 days (13-50)	Farag et al[89]
C3a priming	-	-	7 days (6-26)	Brunstein et al
PGE2 exposure	-	-	17.5 days (14-31)	Cutler et al
Fucosylation	-	-	17 days (12-34)	Popat et al

Time to Neutrophil Recovery Has Improved Over Time: Results from a Recent Randomized Controlled Study



	Dilanubicel	SOC
ANC Engraftment	75 (93.8%)	71 (91%)
Censored	2 (2.5%)	6 (7.7%)
Died Prior to Engraftment	3 (3.8%)	1 (1.3%)
Median Time to, days	**21.5 (19, 24)**	**20 (19, 22)**
KM Est @ D55	93.8%	91%

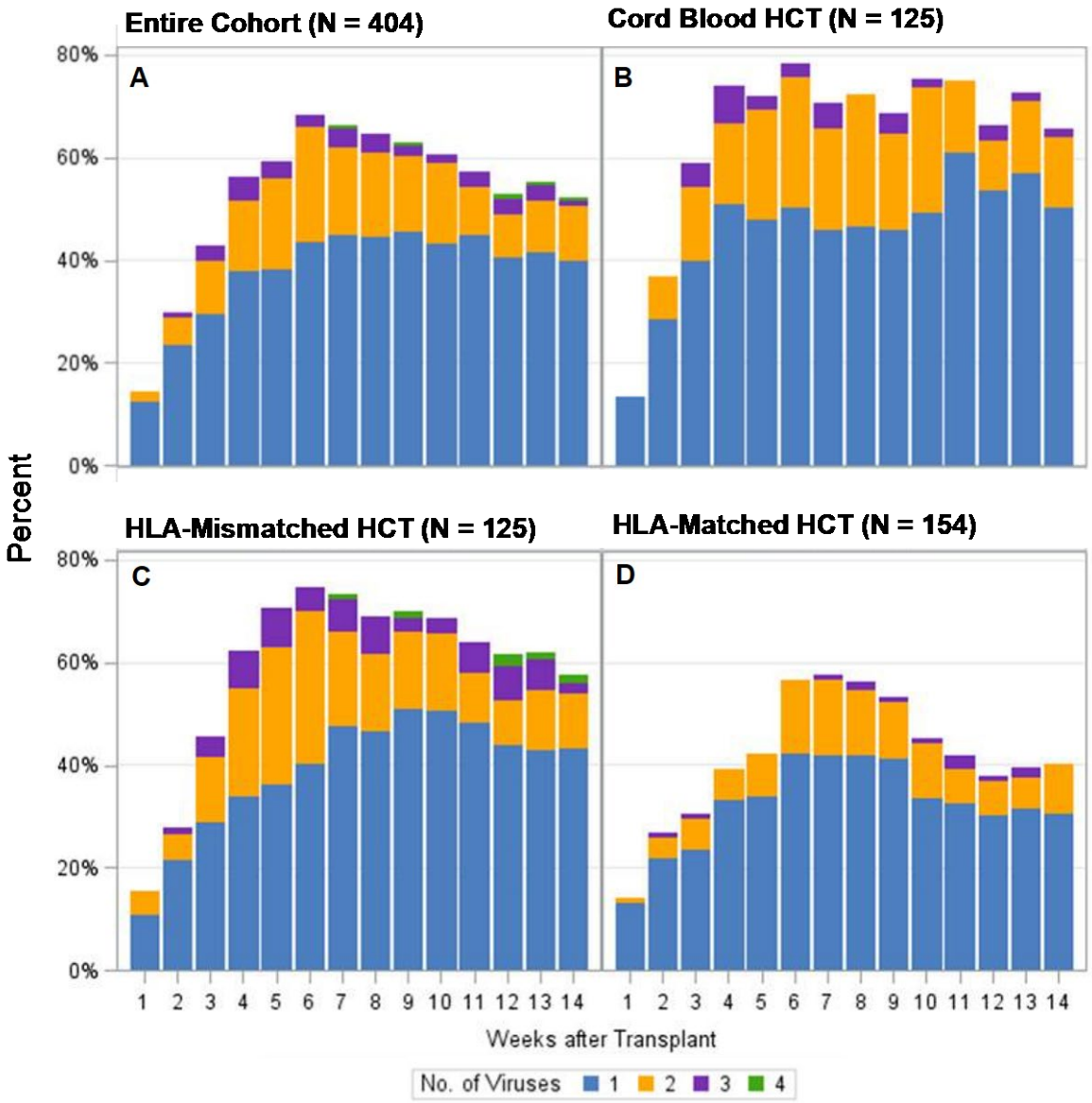
Cord Blood Transplantation



Barrier #2: Real or Perceived

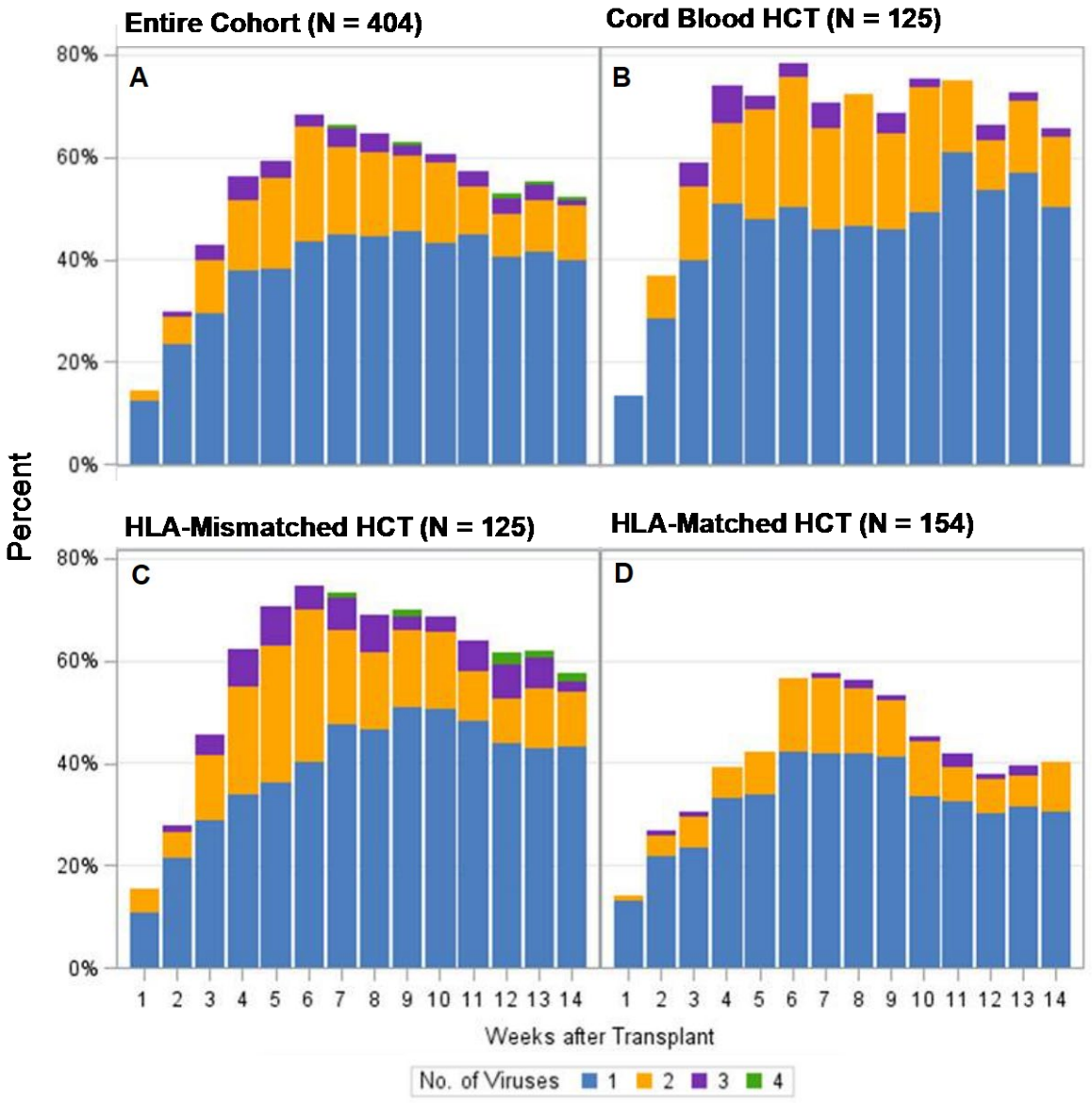
(VIRAL) INFECTIONS

CONCURRENT DETECTION of MULTIPLE dsDNA VIRUSES



Hill et al. Clin Infect Dis. 2018 Jan 18;66(3):368-375

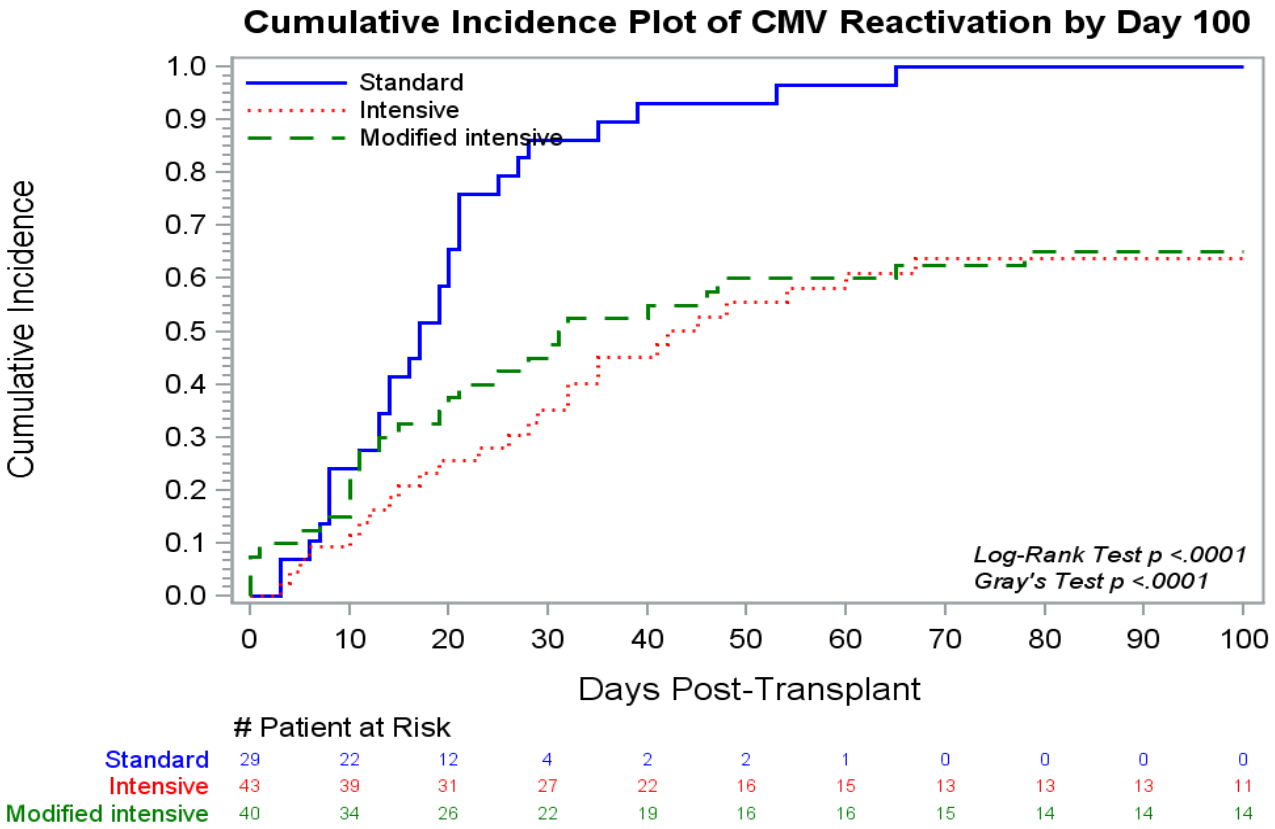
Risk Factors for Multiple Viruses



	Adjusted Hazard Ratios (95% CI)		
Risk Factor	≥2 Viruses	≥3 Viruses	≥4 Viruses
Age ≤21 years	--	--	3 (1.7-5.5)
HCT category Matched Mismatched Cord blood	 Ref 2.1 (1.8-2.4) 2.6 (2.2-3.1)	 Ref 3 (2.4-3.7) 3.2 (2.4-4.2)	 Ref 7.3 (4.1-13) 3.4 (1.6-7.2)
Myeloablative conditioning	--	1.5 (1.2-1.8)	4.4 (2.5-7.7)
Acute GVHD, grade 3-4	2.2 (1.6-3)	--	--
Adjusted for age, sex, HCT comorbidity index, HCT type, conditioning regimen, GVHD, CMV serostatus			

Hill et al. Clin Infect Dis. 2018 Jan 18;66(3):368-375

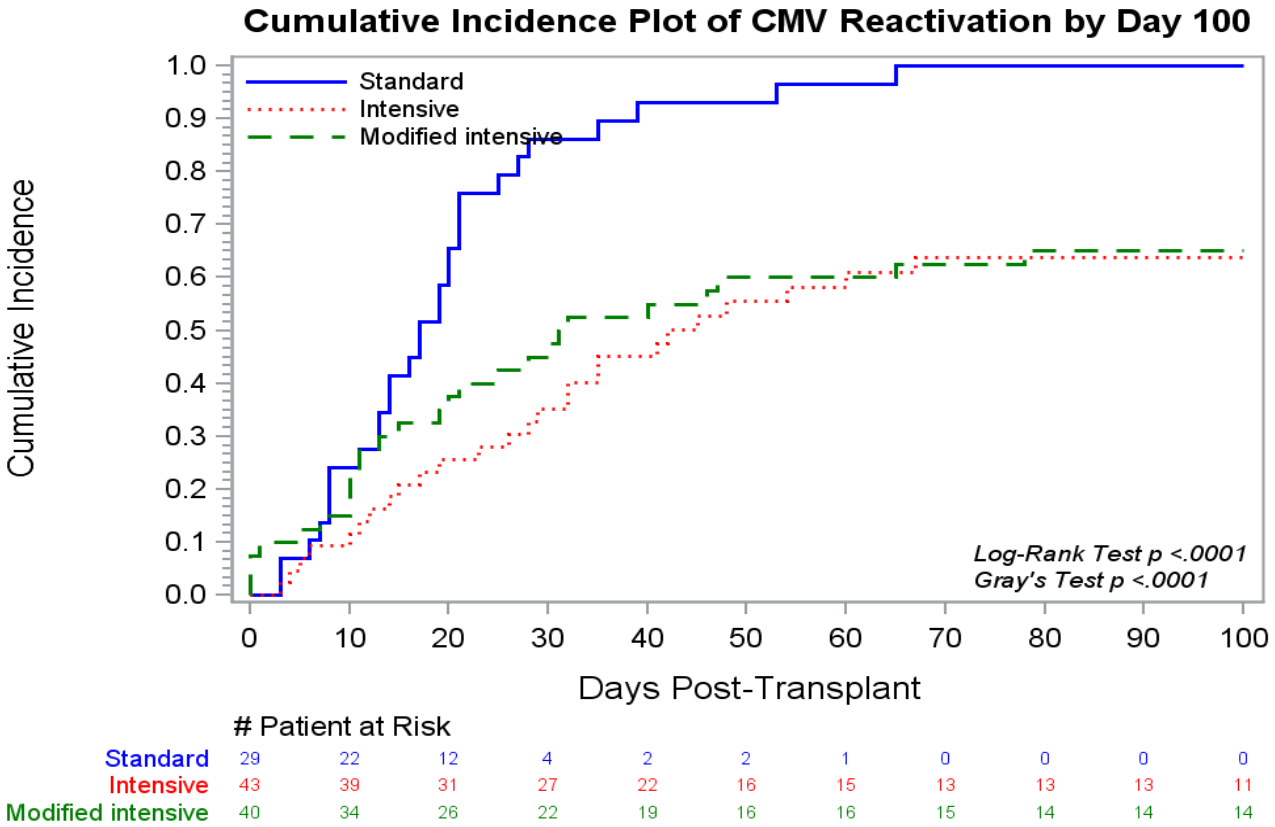
CMV reactivation rate

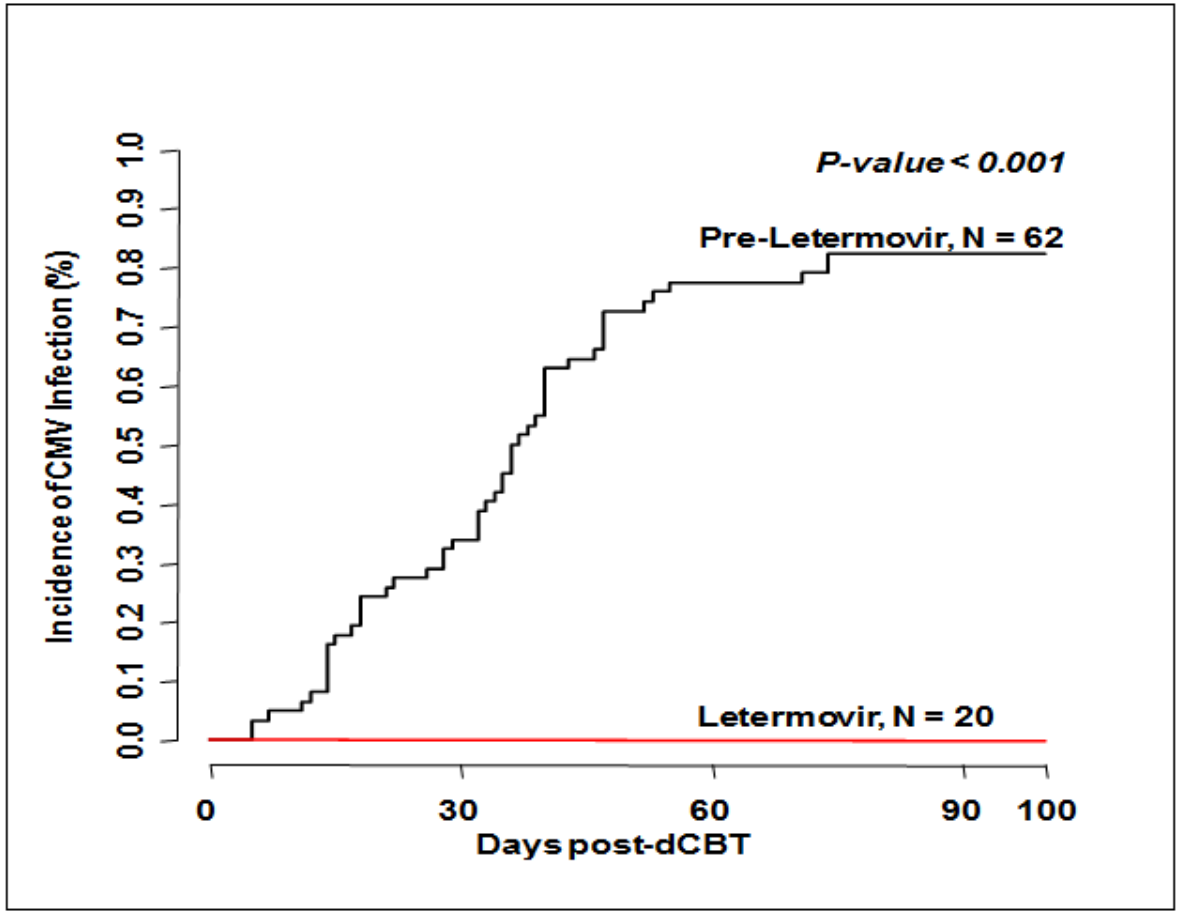


Hill et al. Biol Blood Marrow Transplant. 2018 Oct;24(10):2094-2100

CMV reactivation rate

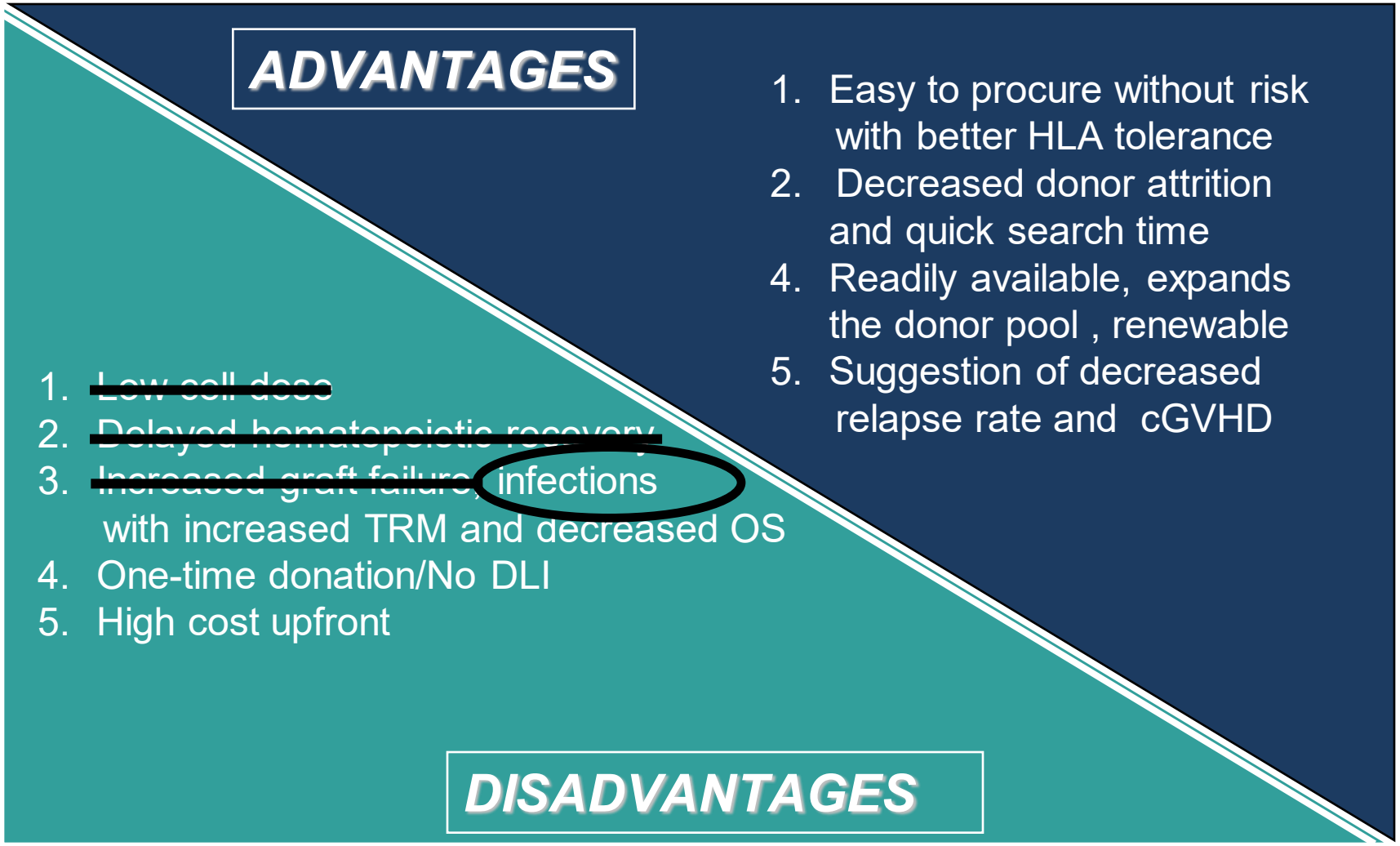
Introduction of Newer Anti-Virals





Lau et al. Late Breaking Abstract TCT 2020

Cord Blood Transplantation



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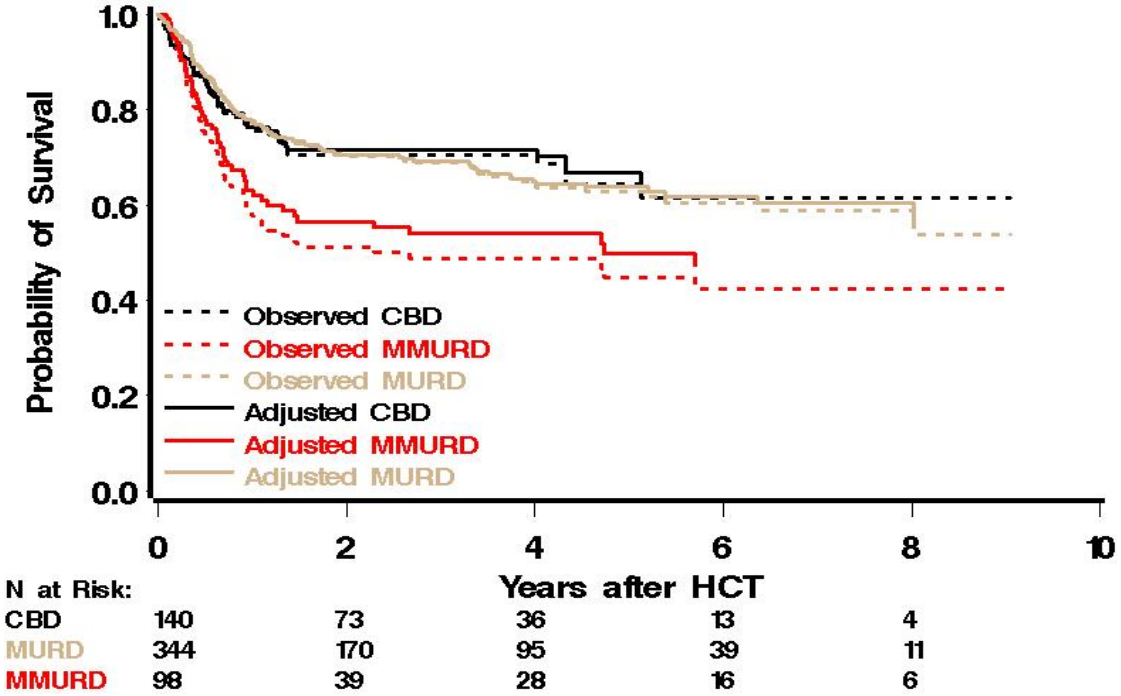
Barrier #3: Real or Overlooked

CLINICAL OUTCOMES
&
GRAFT VERSUS HOST DISEASE

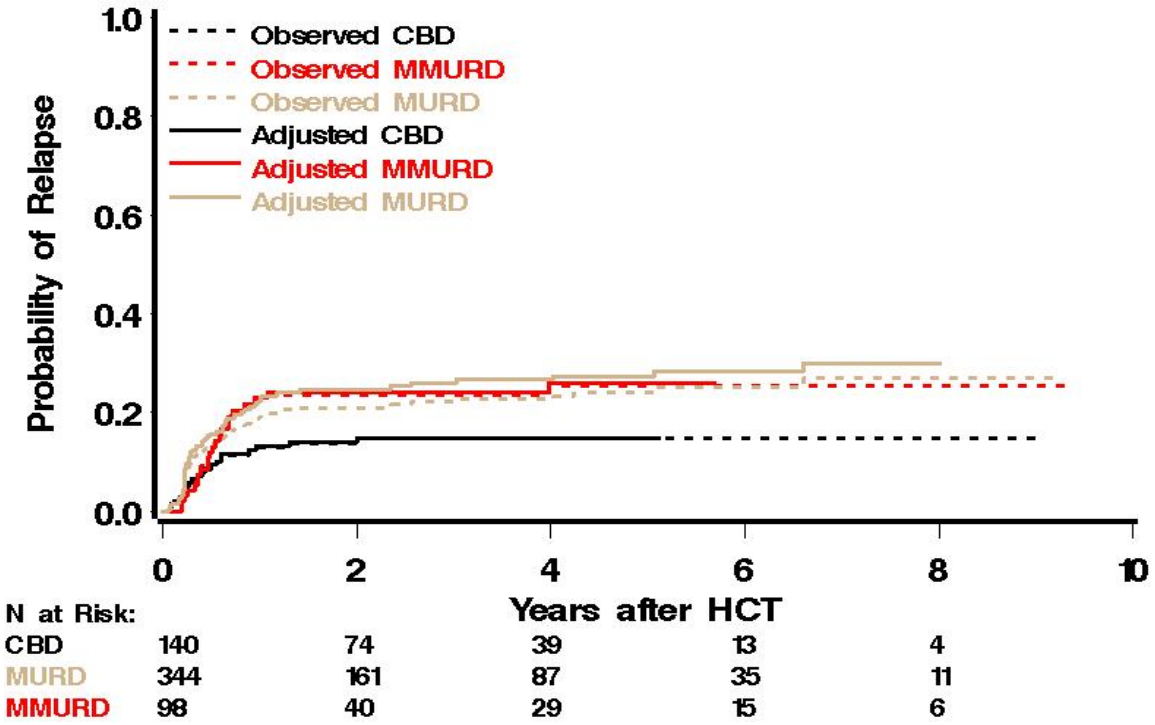
Clinical outcomes: Overall Survival & Relapse

Overall survival at 4 years



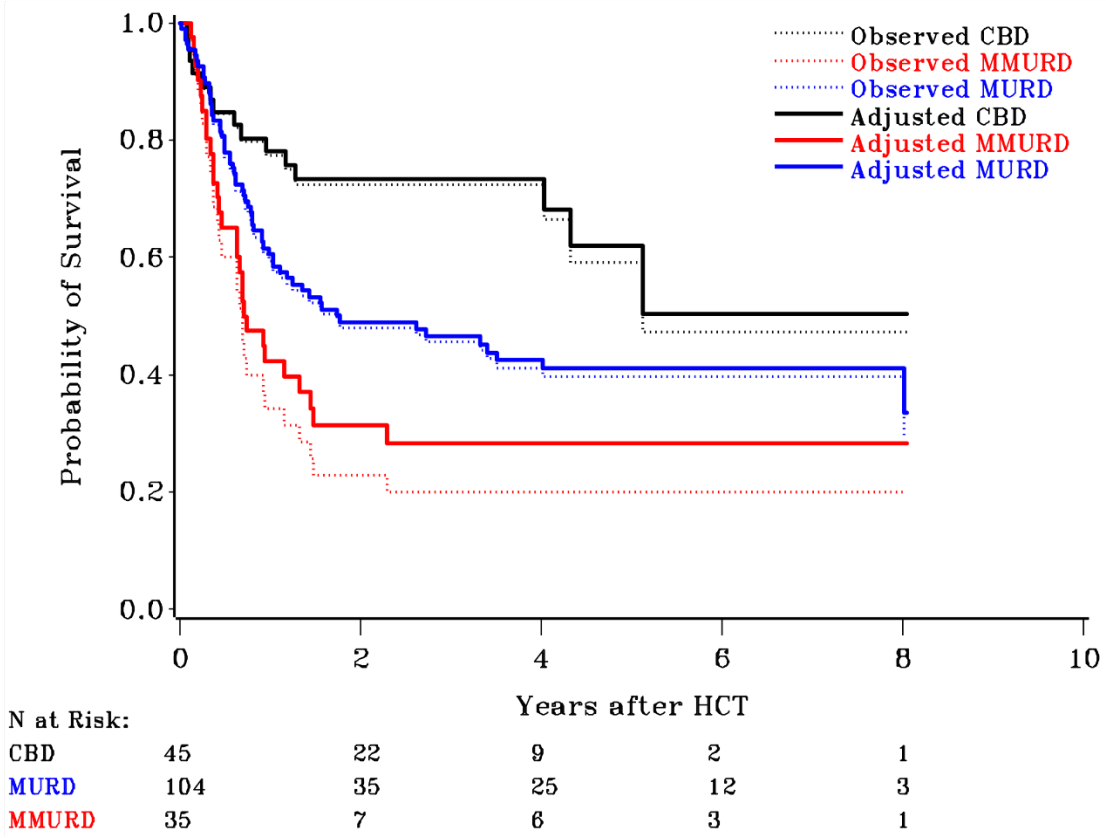
CBT	71%
MURD	63%
MMURD	49%

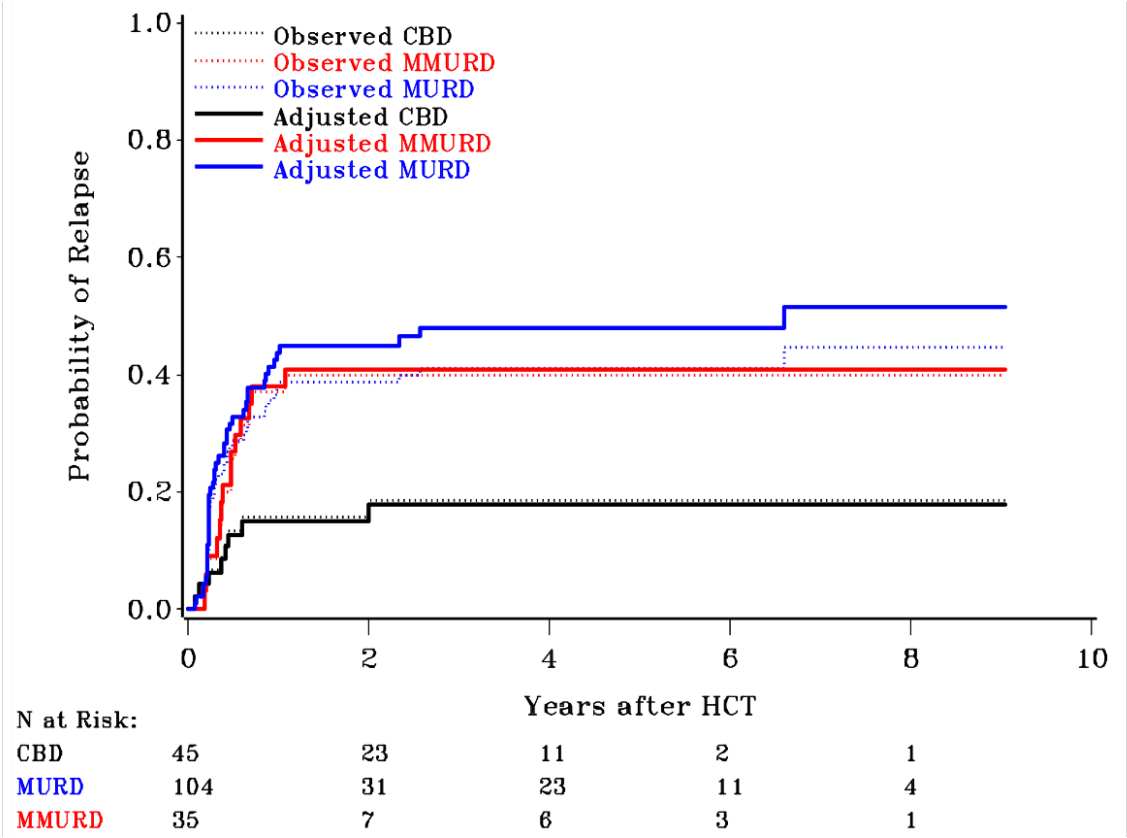
Relapse at 4 years



CBT	15%
MURD	24%
MMURD	25%

Overall Survival & Relapse in MRD+ patients





CBT	67%
MURD	40%
MMURD	20%

CBT	19%
MURD	44%
MMURD	40%

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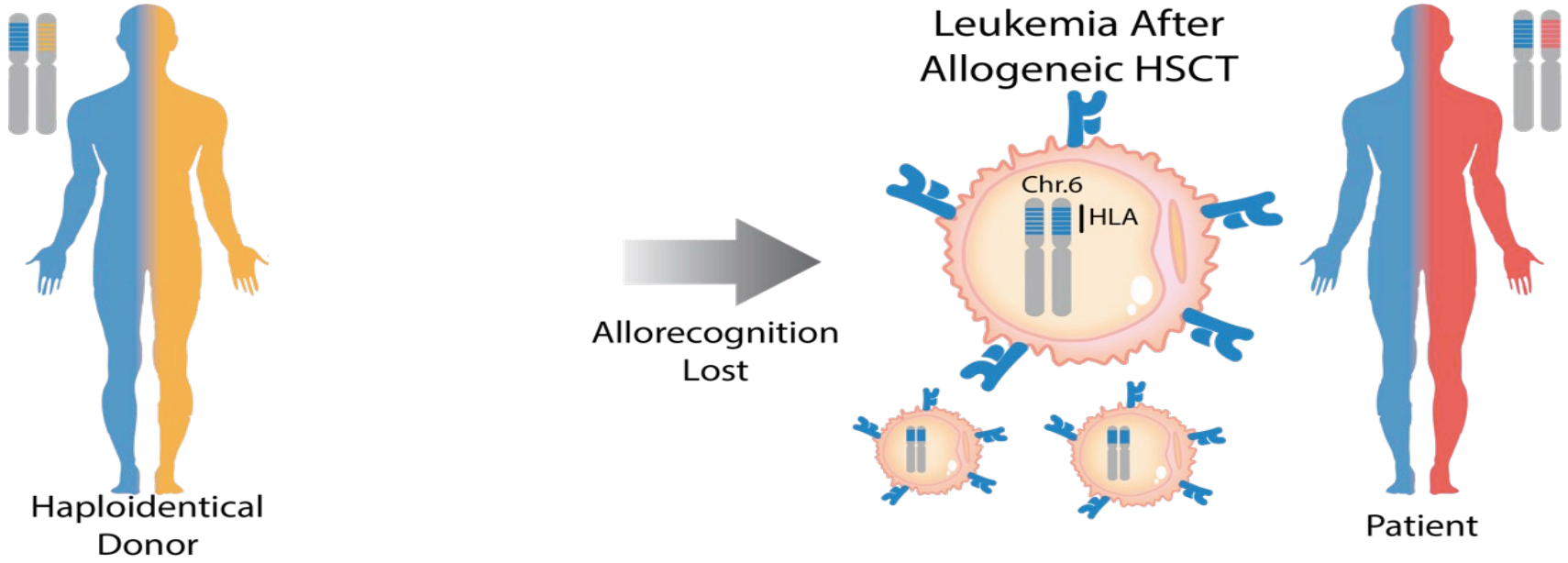
Molecular Mechanism and Immunological Consequences of HLA Loss



- Loss of the entire HLA complex (both class I and class II)
- Genomic mechanism (irreversible)
- Occurs only in leukemia cells, and rapidly becomes clonally prevalent
- Loss is counterbalanced by duplication of the other haplotype (expression level unchanged)

Vago, N Engl J Med, 2009; Toffalori, Blood, 2012
Crucitti, Leukemia, 2015; Ahci and Toffalori, Blood, 2017

Dr. Vago at the TCT
2/20 at 10:30 am Mechanism of Relapse after Transplantation

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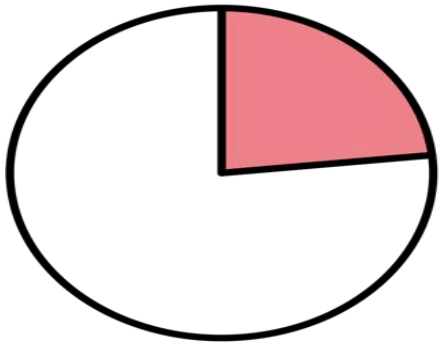
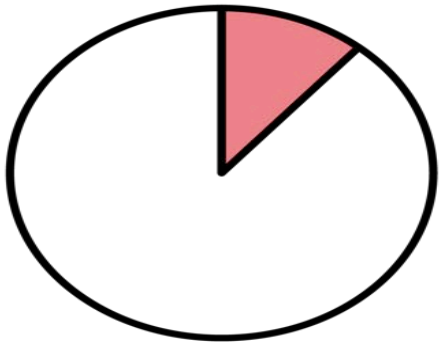
Results: Incidence of HLA Loss

Haplo
5-6 HLA mm
n=155



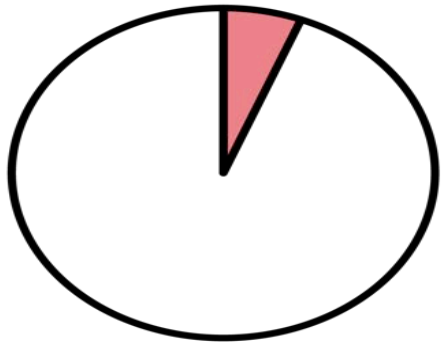
HLA loss
n=38 (**24%**)

MMUD
3-4 HLA mm
n=110



HLA loss
n=12 (**11%**)

MUD
1-2 HLA mm
n=111



HLA loss
n=7 (**6%**)

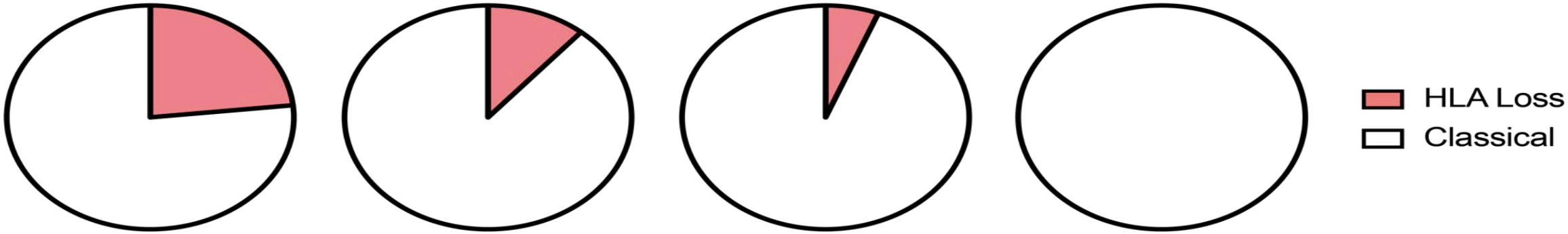
Results: Incidence of HLA Loss

Haplo
5-6 HLA mm
n=155

MMUD
3-4 HLA mm
n=110

MUD
1-2 HLA mm
n=111

CBT
4-6 HLA mm
n=49



HLA loss
n=38 (**24%**)

HLA loss
n=12 (**11%**)

HLA loss
n=7 (**6%**)

HLA loss
n=0 (**0%**)

Chronic GVHD Severity and Function Status after Alternative Donor Hematopoietic Cell Transplantation

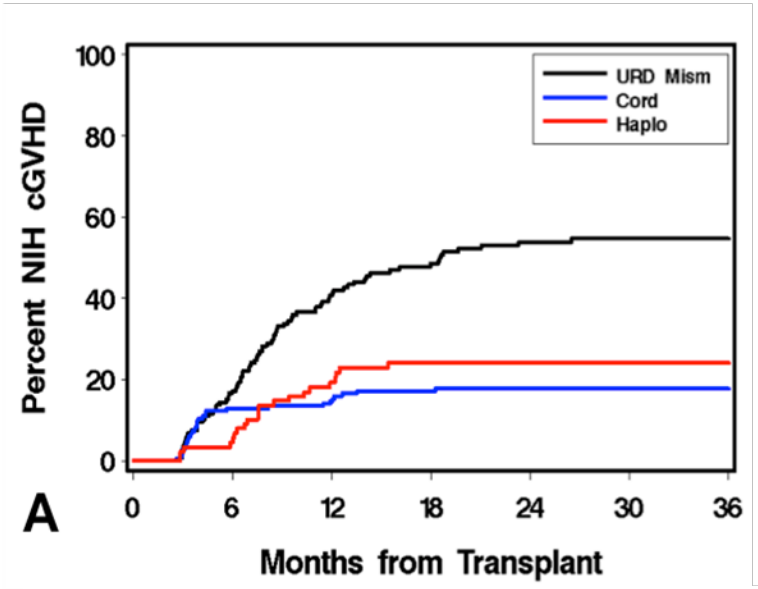
- Retrospective study
- All patients > 18 y/o
- First alternative donor hematopoietic cell transplant for any diagnosis in Seattle between 2006 to 2015

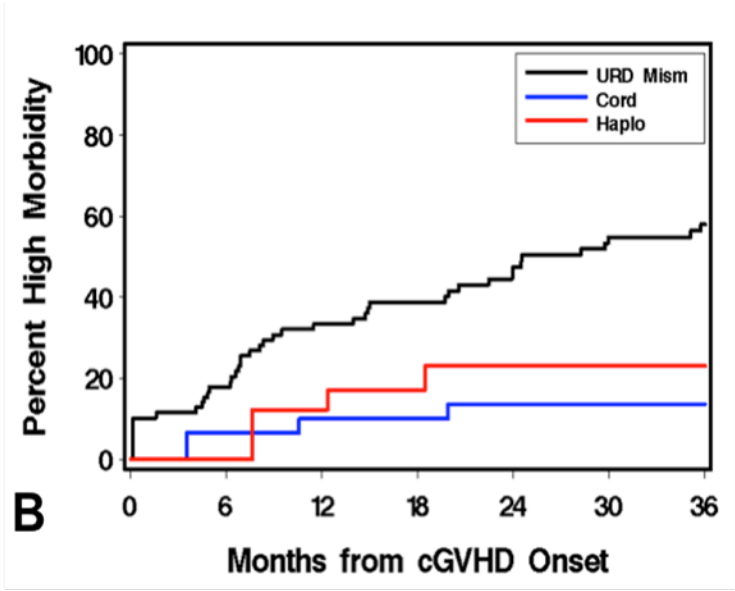
Alternative hematopoietic cell donors included:

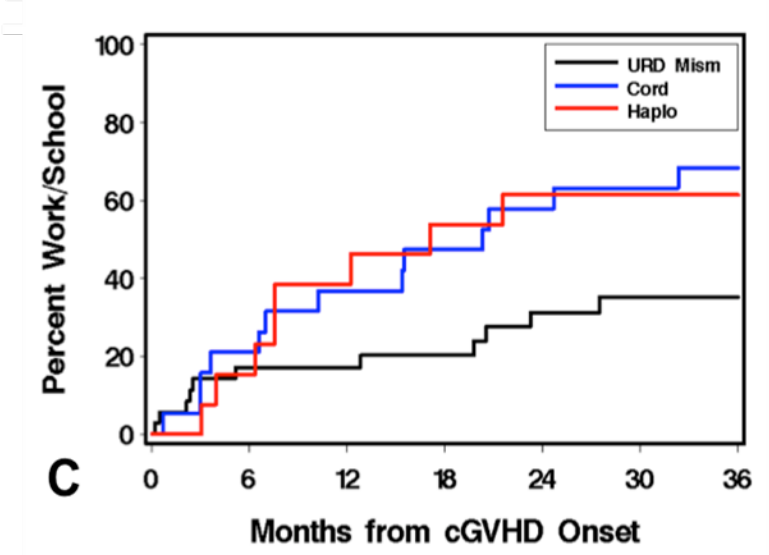
- 1 allele mismatched unrelated adult mobilized blood (n=145)
- Cord blood unrelated (single or double) (n=163)
- Haploidentical related bone marrow or mobilized peripheral blood (n=88)

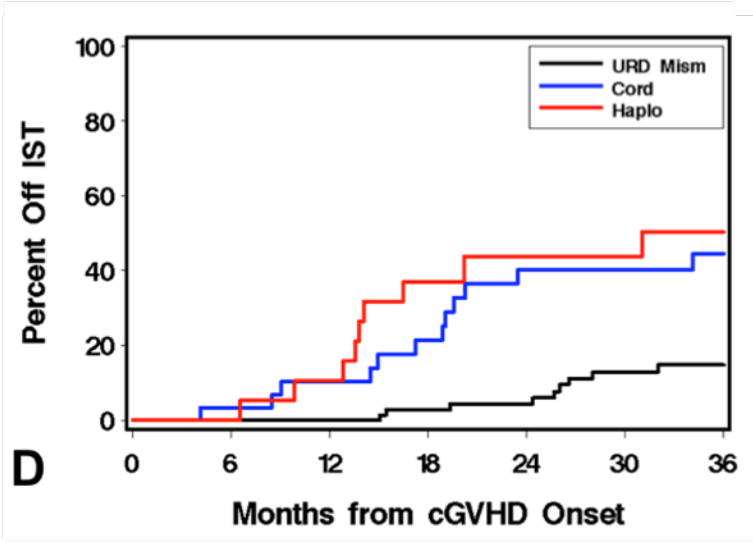
Fatobene G. Hematologica 2019 Apr;104(4):835-843

Distribution of chronic GVHD Manifestations associated with severe morbidity

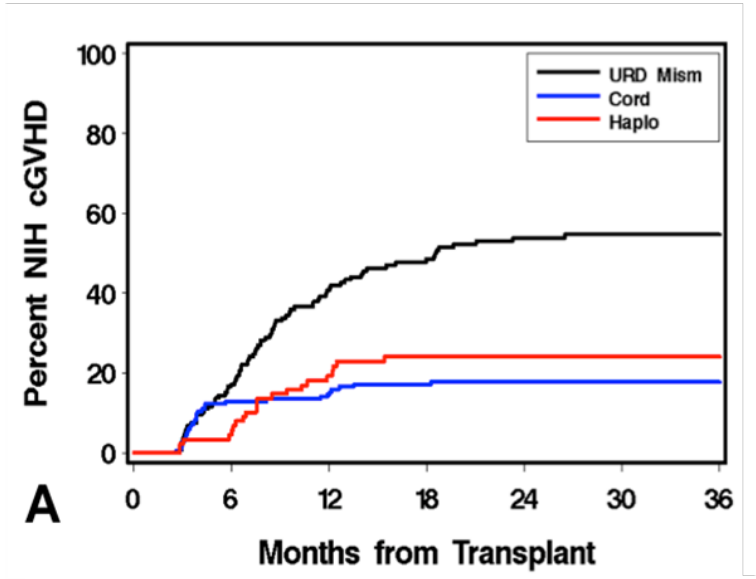


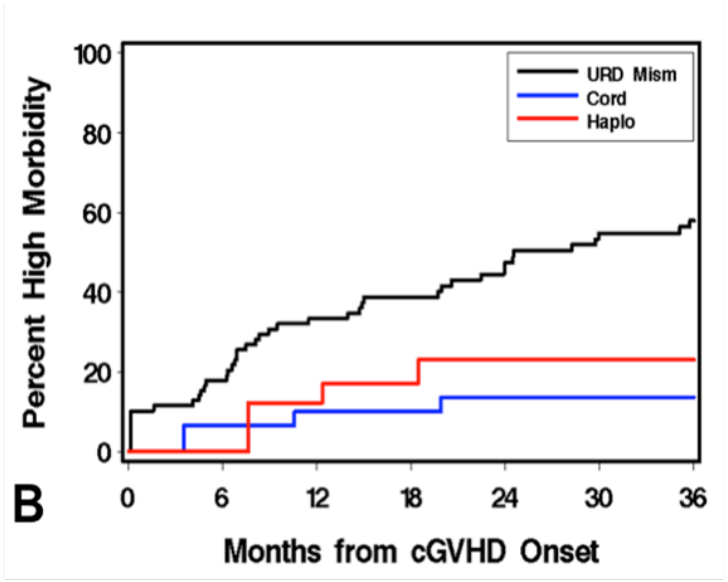


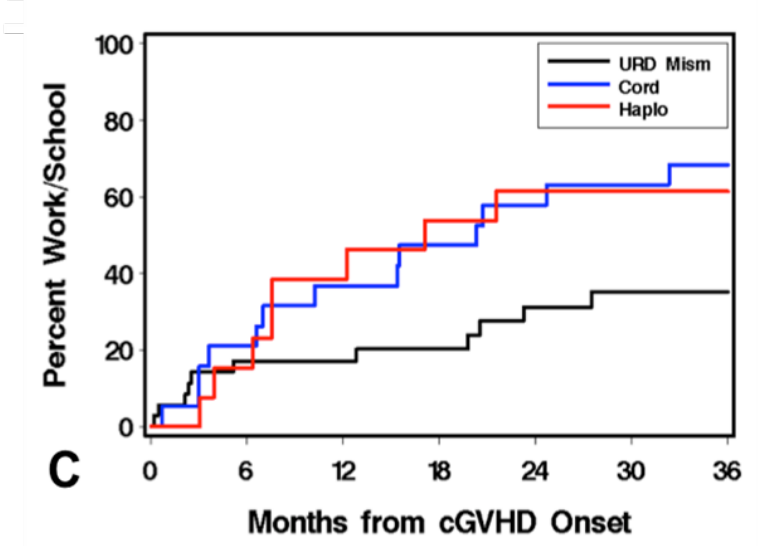


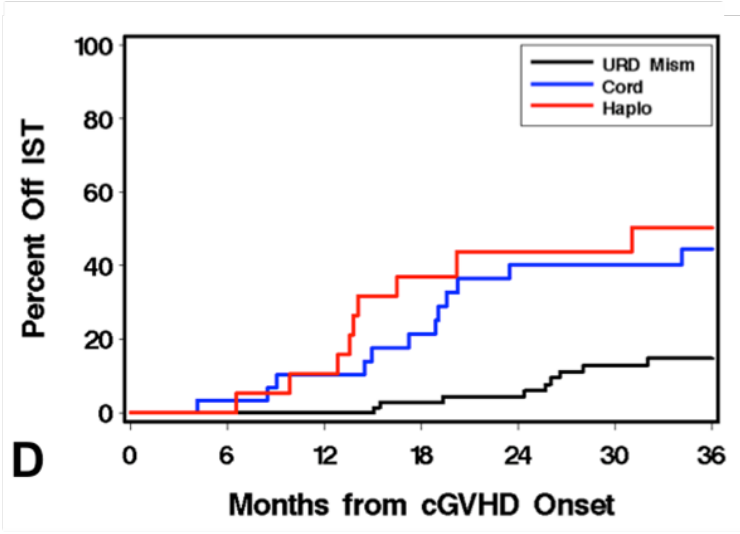


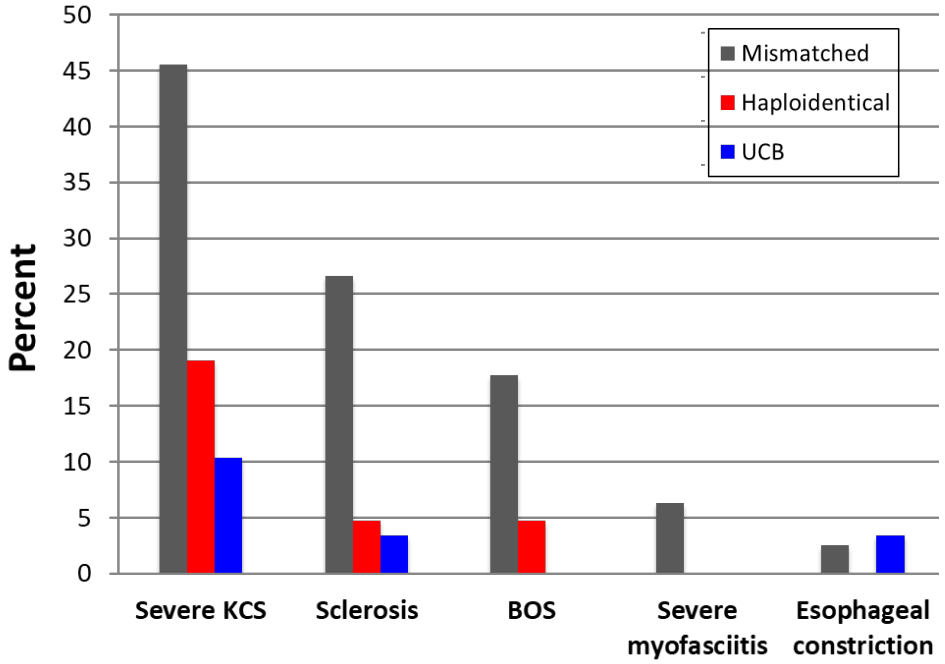
Distribution of chronic GVHD Manifestations associated with severe morbidity



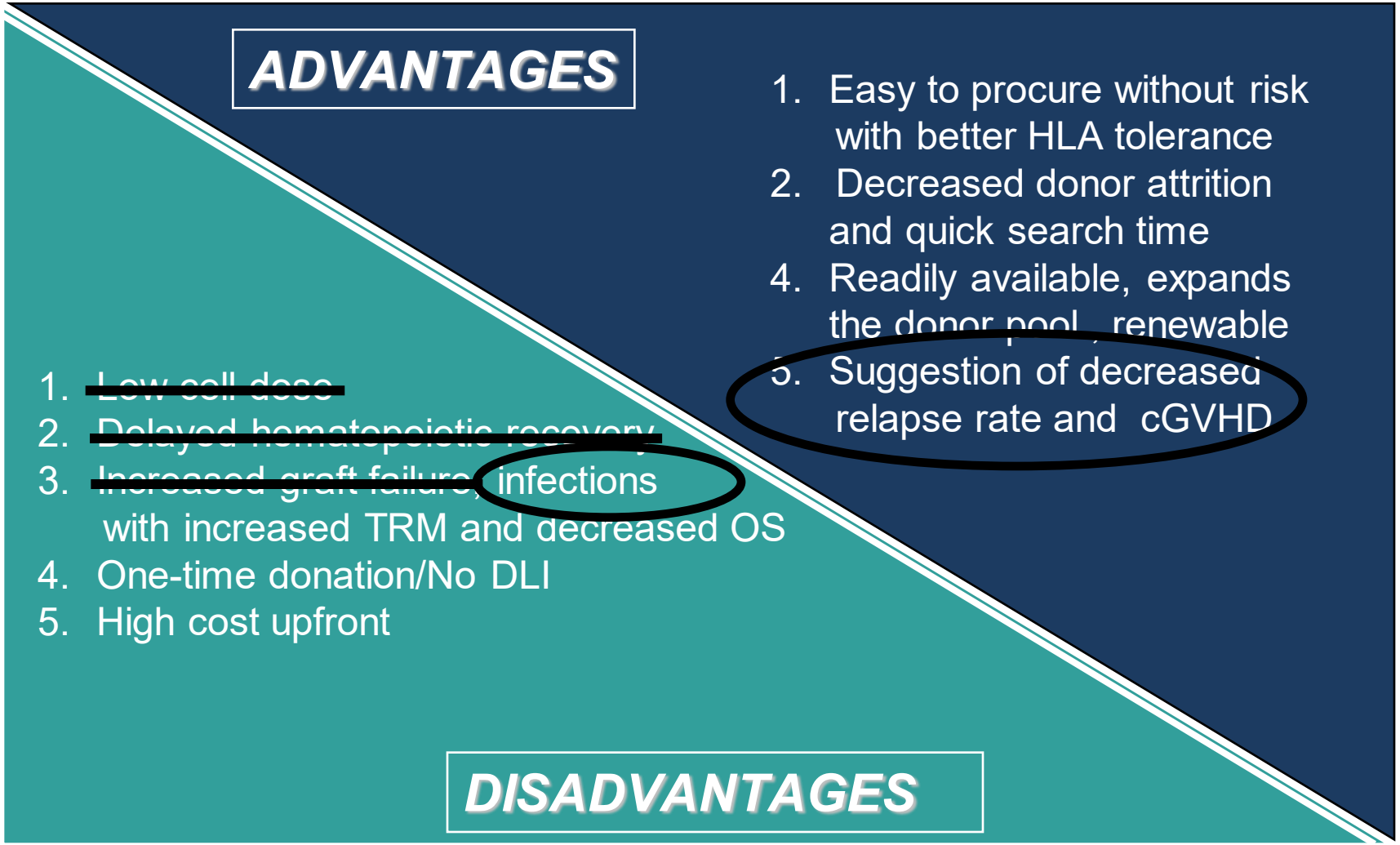








Cord Blood Transplantation



CONCLUSIONS

- Outcomes after myeloablative CBT have improved significantly in the last two decades and are comparable to outcomes with MUD and haplo
- **ENGRAFTMENT & PRIMARY GRAFT FAILURE ARE NO LONGER A BARRIER IN MYELOABLATIVE CBT**
- Graft manipulation remains important – but it is no longer needed to enhance hematopoietic recovery
- We have not yet realized the full potential of CBT. Outstanding clinical outcomes cannot be ignored especially in high-risk and pediatric patients
- Higher risk for viral infections remains a limitation but the use of new drugs is promising

So…. Why the Decline in the Number of CBT?

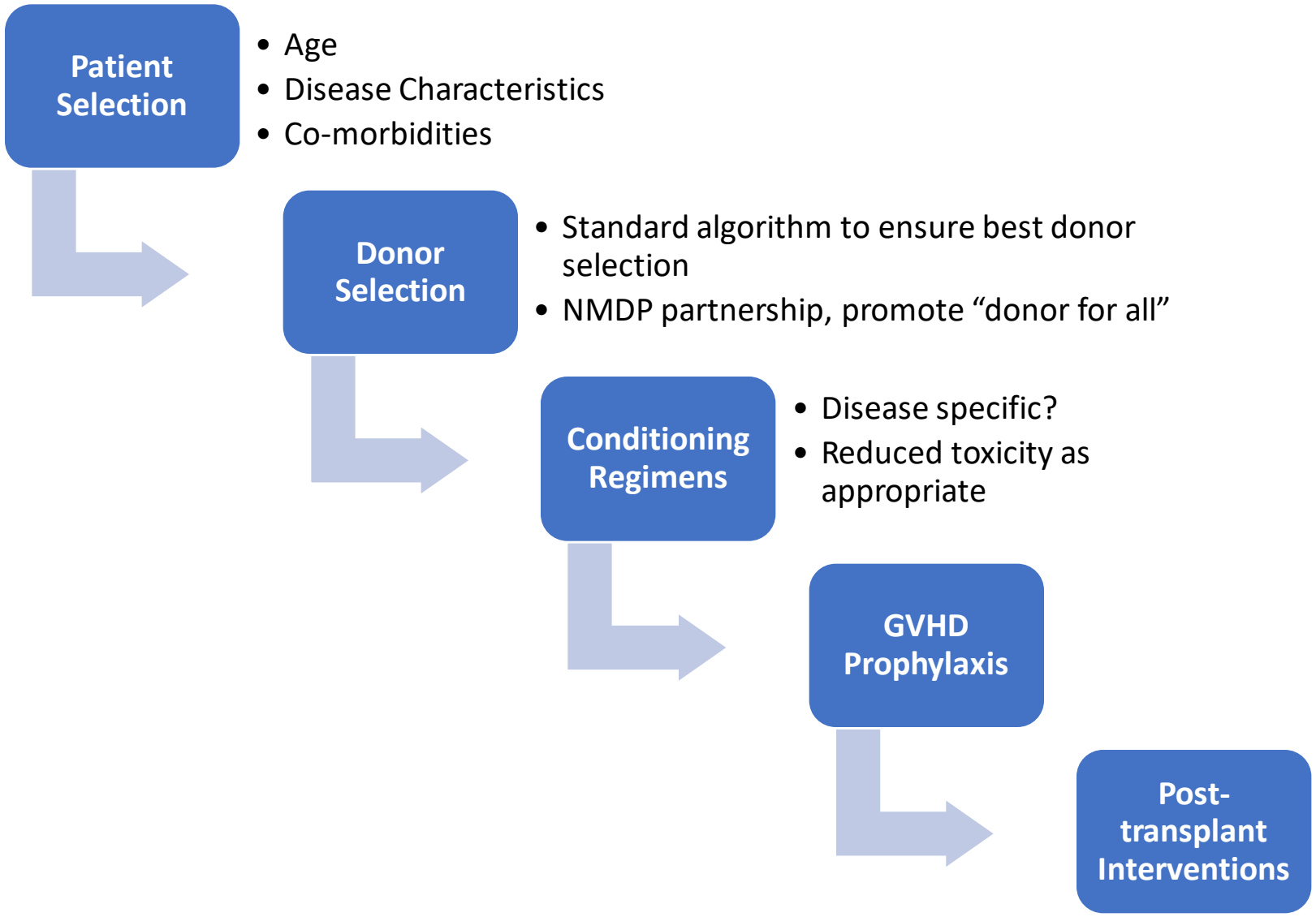
When and Why SHOULD a Physician Choose a CB Donor?

1. Donor AVAILABILITY (50% identified MUD/MMUD are unavailable or unwilling)
2. CB donors for HCT are going to be increasingly important as the diversity of the population increases, making MUDS/MMUDS more difficult (and costly and lengthy) to identify for a given patient
3. Lower relapse rates – thus, optimal donor in setting of MRD/disease
4. Less cGVHD
5. Lower relapse/cGVHD = improvement in long term QOL and reduced cost overall
6. Faster time to donor identification = faster time to transplant

What we need to do first…

- We should not be deaf and blind on what is happening around us, but at the same time we need to defend/sustain a very important stem cell source:
  - Real barriers:
    - most centers do not do enough HCT to do CB and other type of transplants and are forced to decide where to focus.
    - Lack of rigorous pre-clinical science to understand the unique biology of CB that will support the use of CB.
- Reinforce the importance of prospective and retrospective collaborative studies.
- Facilitate data sharing among CBT centers.
- Create a common sample repository

How Do We Facilitate/Increase Adoption of CBT*: Immediate Intervention Opportunities



Overall Goals:

1. Keep it simple, so those with less experience can and will participate
2. Focus first on interventions that we can do as a community (i.e., may need to wait to introduce graft engineering ONCE we know where this is needed in CBT (engraftment? relapse?)
3. Importance of ancillary studies/repositories to answer other questions: e.g., immune reconstitution

*Not versus haplo, but in addition to haplo

CBT Guidelines

Creating CBT Guidelines

Achieve consensus around Cord Blood Transplant practice guidelines to guide optimal practice.

We are not there yet if we don’t solve other problems first