Calling All Super Heroes

Evolution of adult donor stem cell products over the history of the NMDP and implications for current practices

Speakers:

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Disclosures

The following faculty and planning committee staff have no financial disclosures:

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Name	Institution	Disclosure
Misty Evans DNP	Sarah Cannon Blood and Marrow Transplant Program; Vanderbilt University	Jazz Pharmaceuticals Honorarium for Speakers Bureau

Learning objectives

At the conclusion of this session, attendees will be able to:

- ✓ Assess the effectiveness of current and past stem cell product collection methods
- ✓ Describe bone marrow product collection quality over time
- ✓ Distinguish donor characteristics between donors who donate peripheral blood stem cells in one day versus two days

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One versus Two Day Apheresis in Unrelated Donors

Jack W. Hsu, MD
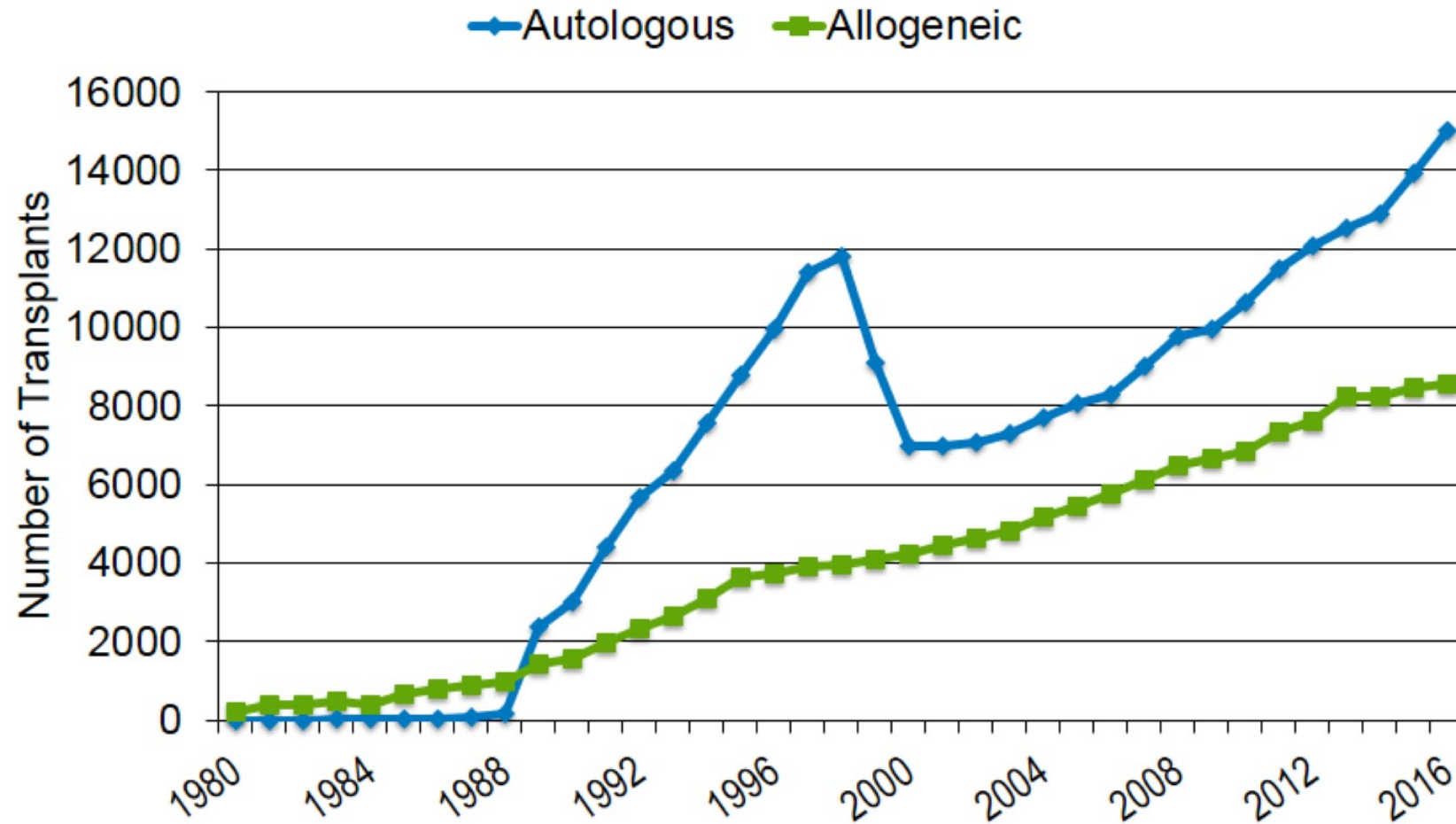University of Florida

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Background

✓ Number of allogeneic transplants have steadily increased since 1980.

✓ Since 2006, most common donor source is from matched unrelated donors.

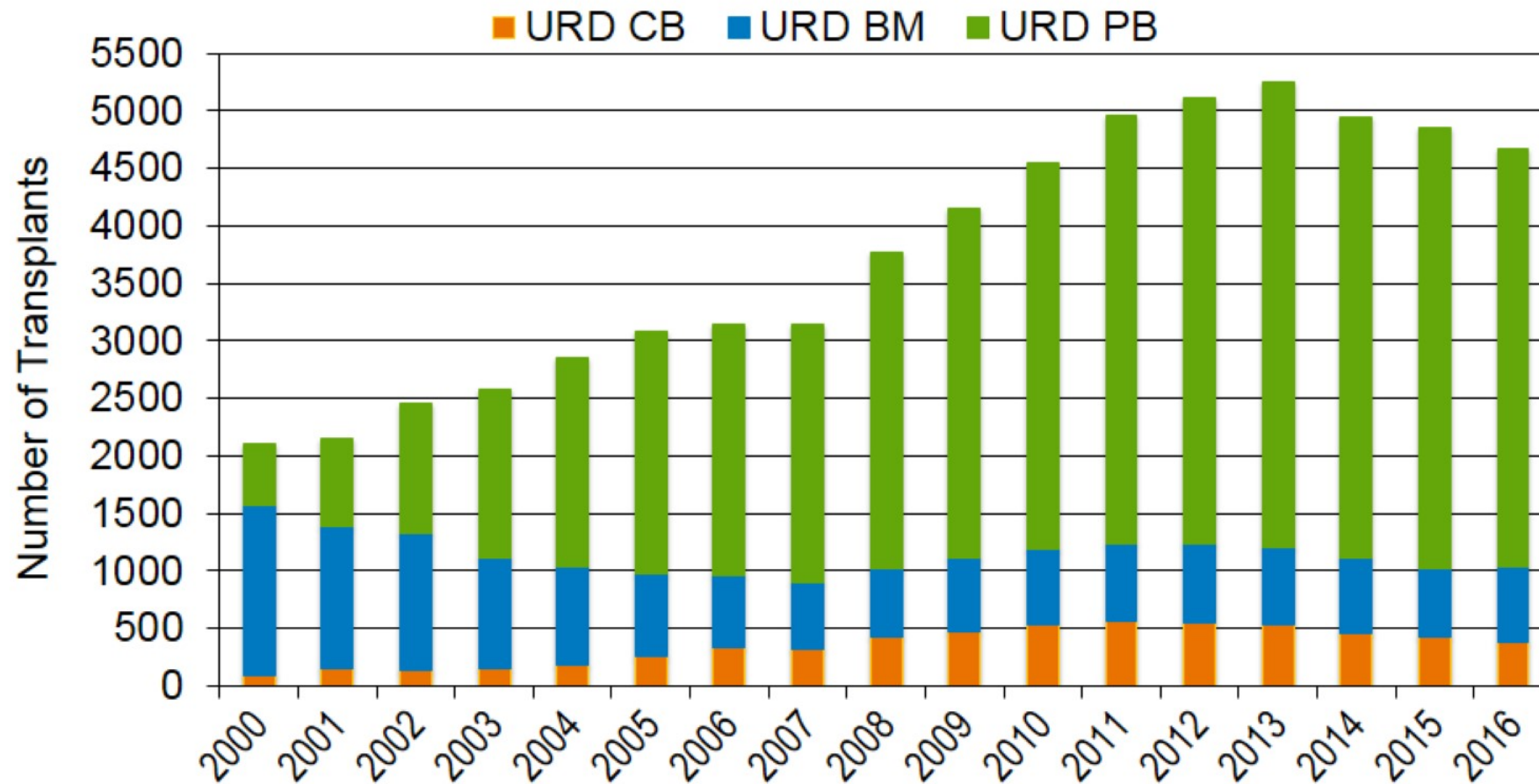✓ Most common method for collecting stem cells is by peripheral blood.

Annual Number of HCT Recipients in the US by Transplant Type

Allogeneic HCT Recipients in the US, by Donor Type
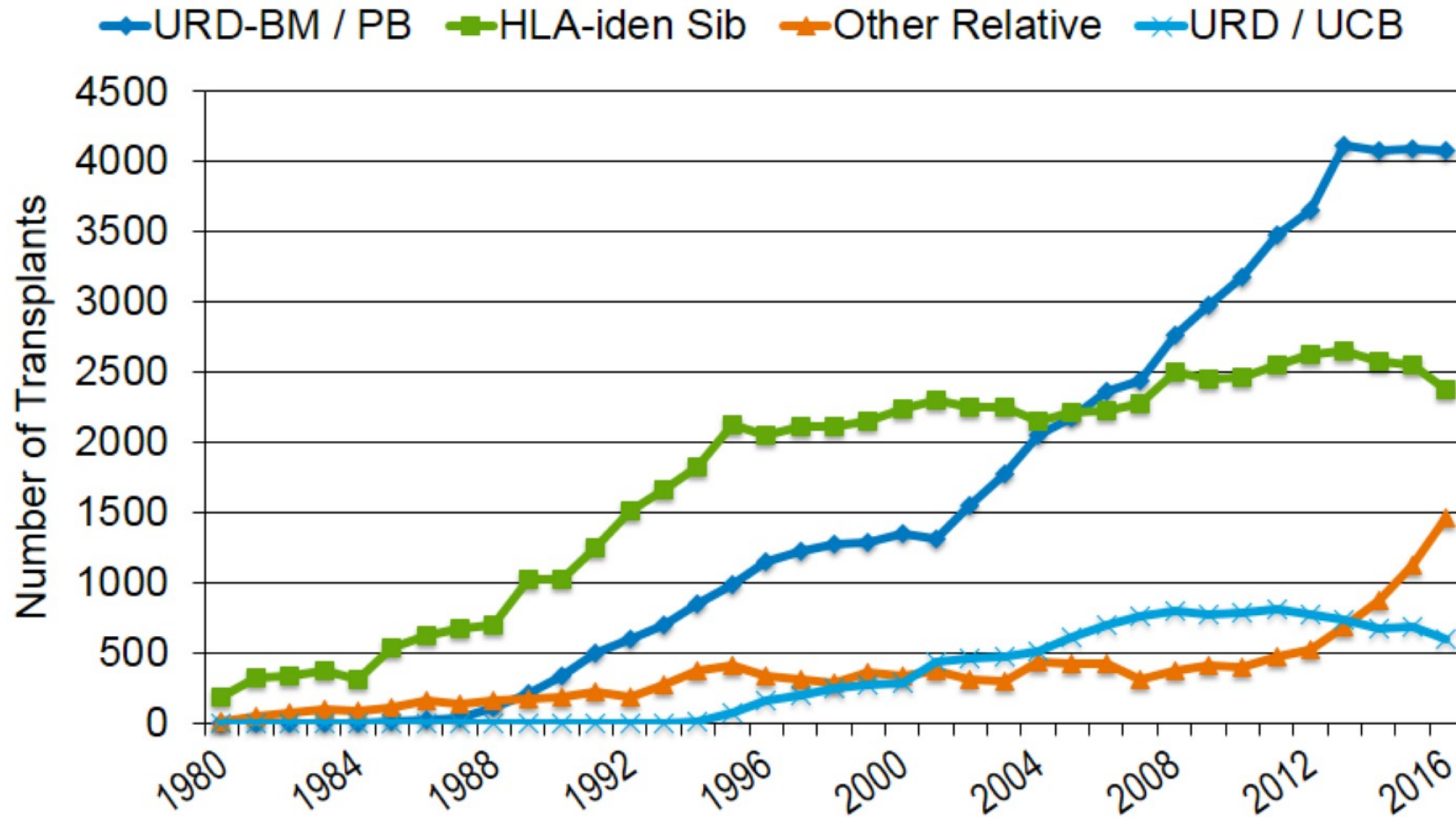
Differences Between PBSC vs. BM

- Recipient[1]

  - Decreased risk of graft rejection with PBSC donors.

  - Increased risk of chronic GVHD with PBSC donors.

  - No difference in survival.

- Donors[2]

  - BM donors were more likely to experience grade 2 to 4 toxicities at 1 week and pain at 1 week and 1 month after the procedure.

  - BM donors experienced slower recovery, with 3% still not fully recovered at 24 weeks, whereas 100% of PBSC donors had recovered.

[1] Anasetti C, Logan B, Lee SJ, et al. NEJM. 2012; 367(16): 10.
[2] Pulsipher MA, Chitphakdithai P, Logan BR, et al. Blood. 2013; 121(1): 197.

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NMDP PBSC Collection Procedures

✓ Donors receive GCSF for 5 days

Donor Weight (kg)	Filgrastim Dosing			Dose Range (ucg/kg/d)
	300 ucg	480 ucg	Total (ucg/day)	
45–60	2	0	600	13.3–10.0
61–78	1	1	780	12.8–10.0
79–90	3	0	900	11.4–10.0
91–96	0	2	960	10.5–10.0
97–108	2	1	1080	11.1–10.0
109+	4	0	1200	−11.1

"Filgrastim-Mobilized Peripheral Blood Stem Cells for Allogeneic Transplantation with Unrelated Donors, V27" Dr. John Miller

NMDP PBSC Collection Procedures

✓ Donors undergo apheresis for 1 (90%) or 2 (10%) days

Recipient Weight (kg)	Volume Processed (L)	Procedure
< 35	12	Single 12L apheresis
36–45	15	Single 15L apheresis
46–55	18	Single 18L or two 12L apheresis
56–65	22	Single 22L or two 12L apheresis
> 65	24	Single 24L or two 12L apheresis

"Filgrastim-Mobilized Peripheral Blood Stem Cells for Allogeneic Transplantation with Unrelated Donors, V27" Dr. John Miller

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Questions about Unrelated Donor Apheresis

✓ For 2 day collections, GCSF administration on day 6 is not specified.

✓ Most donors do not receive GCSF on day 6.

Primary Endpoints

- ✓ Toxicity
  - ✓ Fatigue
  - ✓ Insomnia
  - ✓ Dizziness/Syncope
  - ✓ Anorexia
  - ✓ Nausea
  - ✓ Vomiting
  - ✓ Rash/Local site reactions
  - ✓ Fever
- ✓ Pain
- ✓ Recovery Time

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Secondary Endpoints

✓ Apheresis yield on day 1 of apheresis vs. day 2 of apheresis for donors who underwent apheresis for tow days.

Baseline Characteristics

	One-Day Collection, N (%)	Two-Day Collection, N (%)	p-value
Number of donors	20004	2344	
Number of centers	100	84	
Median # collections/center/ year (Range)	275 (1-1837)	162 (3-1837)	<0.01
Fact Accreditation (June 2018)	16330 (90)	1823 (92)	0.01
Male/Female	6589 (33)/13415 (67)	1268 (54)/1076 (46)	<0.01
Median Weight, kg (Range)	83.0 (40.8-179.2)	75.9 (37.0-160.1)	<0.01
Body Mass Index (kg/m^2)			<0.01
Underweight, <18.5	120 (1)	35 (1)	
Normal, 18.5-24.9	6369 (32)	1010 (43)	
Overweight, 25-29.9	7590 (38)	776 (33)	
Obese, 30+	5914 (30)	522 (22)	
Unknown	11 (N/A)	1 (N/A)	

Baseline Characteristics (cont.)

	One-Day Collection, N (%)	Two-Day Collection, N (%)	p-value
Race			<0.01
Caucasian	14505 (73)	1728 (74)	
Hispanic	1745 (9)	251 (11)	
African / African American	821 (4)	88 (4)	
Asian / Pacific Islander	1052 (5)	123 (5)	
Native American	169 (1)	22 (1)	
Multiple races / Other	1449 (7)	124 (5)	
Unknown / Declined	263 (1)	8 (<1)	
Age at donation			<0.01
18 to 29	9600 (48)	837 (36)	
30 to 39	5227 (26)	649 (28)	
40 to 49	3607 (18)	571 (24)	
50+	1570 (8)	287 (12)	
Median (Range)	31 (18-62)	35 (18-61)	<0.01

Apheresis Characteristics

	One-Day Collection, N (%)	Two-Day Collection, N (%)	p-value
Blood processed Day 5			<0.01
Small, <12 L	1014 (5)	258 (11)	
Standard, 12-18 L	4978 (25)	1972 (84)	
Large, 18 L ≤	14006 (70)	113 (5)	
Unknown	6 (N/A)	1 (N/A)	
Median (Range)	20 (2-35)	12 (1-26)	<0.01
Blood processed Total			<0.01
Small, <12 L	1014 (5)	2 (<1)	
Standard, 12-18 L	4978 (25)	75 (3)	
Large, 18 L ≤	14006 (70)	2263 (97)	
Unknown	6 (N/A)	4 (N/A)	
Median (Range)	20 (2-35)	24 (10-45)	<0.01

Apheresis Characteristics (cont.)

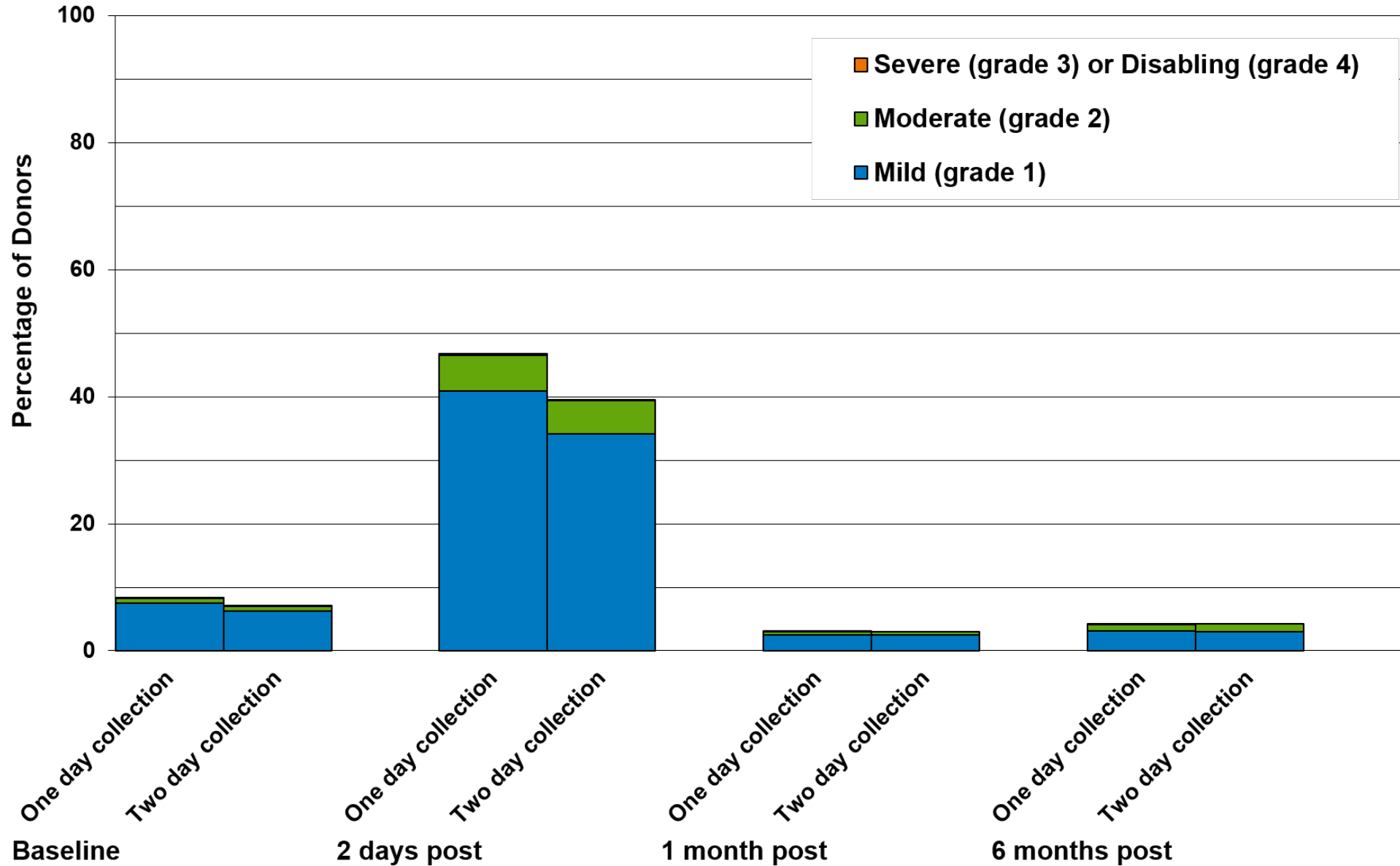|	One-Day Collection, Median (Range)	Two-Day Collection, Median (Range)	p-value
Pre-apheresis Day 5 (x10^9/L)			
Platelets	219 (20-548)	229 (50-503)	<0.01
Neutrophils	32.6 (2.5-104)	29.2 (4.5-82.5)	<0.01
Mononuclear cells	6.2 (0.5-38.1)	5.9 (0.6-30.4)	<0.01
CD34+ cells	84.2 (0.9-16,000)	58.2 (0.3-13,000)	<0.01
Pre-apheresis Day 6 (x10^9/L)			
Platelets		144 (52.0-349)	
Neutrophils		35.2 (3.7-80.4)	
Mononuclear cells		5.2 (0.7-45.7)	
CD34+ cells		50.2 (0.3-12,000)	

Requested vs. Collected Cell Counts in the Product on Day 5 of filgrastim

	One-Day Collection, N (%)	Two-Day Collection, N (%)	p-value
Number of donors	10272	868	
Number of centers	94	67	
Collected target CD34+	8429 (82)	142 (16)	<0.01

Clinical Outcomes (Univariate Analysis)

	One-Day Collection, N (%)	Two-Day Collection, N (%)	p-value
Hospitalization	238 (1)	135 (6)	<0.01
Citrate Toxicity			
Day 5	7268 (36)	1212 (52)	<0.001
Overall	7268 (36)	1348 (58)	<0.001
Central Line Placement			
Day 5	1713 (9)	149 (6)	
Overall	1713 (9)	187 (8)	0.34
Mononuclear cells (x10^6)			
Day 5 Median (Range)	54.3 (2.8-323.7)	34.2 (0.6-211.1)	<0.01
Total Median (Range)	54.3 (2.8-323.7)	63.1 (9.8-283.1)	<0.01
CD34+ cells (x10^6)			
Day 5 Median (Range)	669.5 (7.9-5967)	308.0 (18.3-2167)	<0.01
Total Median (Range)	669.5 (7.9-5967)	547.8 (37.0-3089)	<0.01

Highest Skeletal Pain Experienced
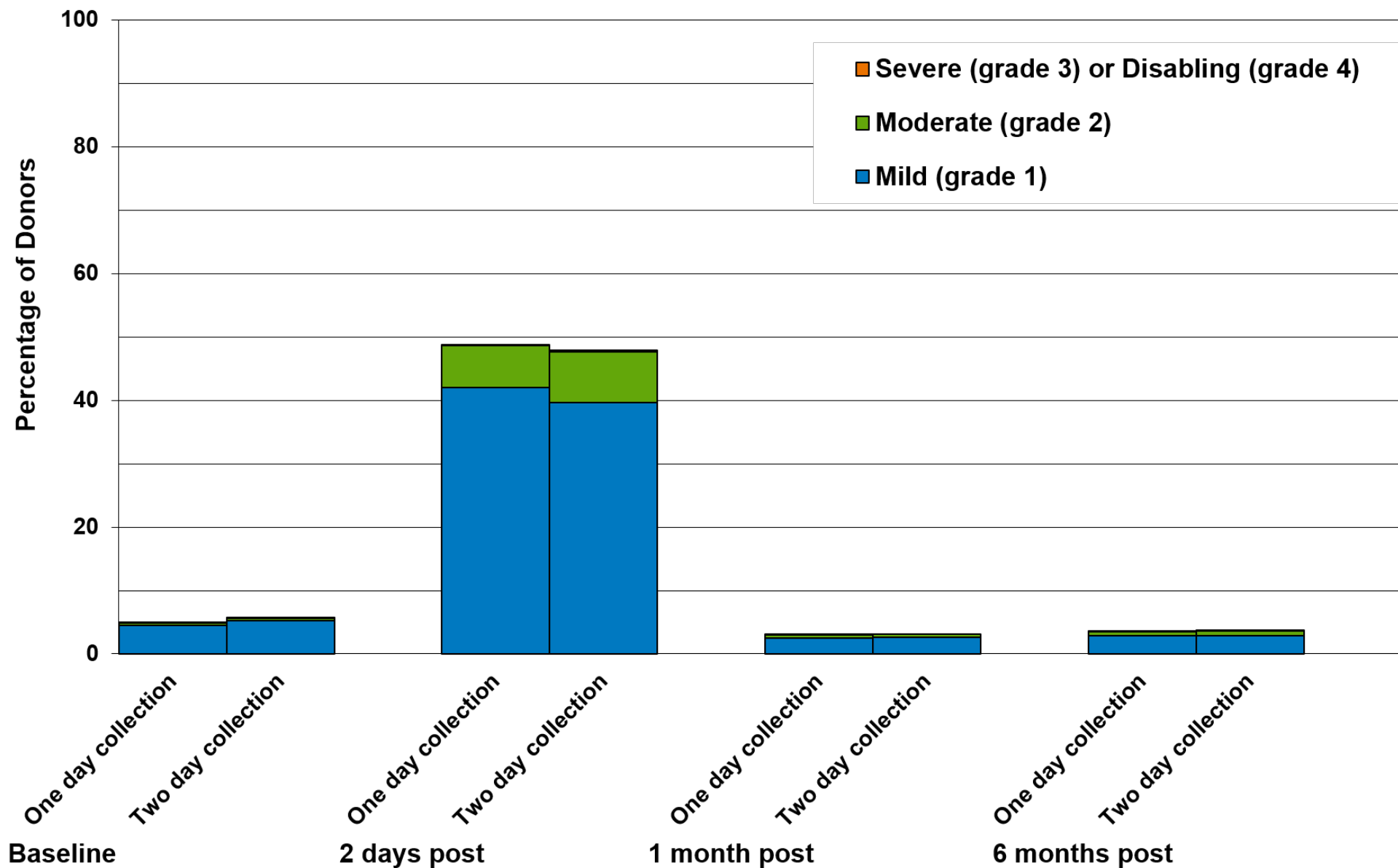
Apheresis (Univariate Analysis)

	One-Day Collection, Mean (SD)	Two-Day Collection, Mean (SD)	p-value
Platelets (x10^9/L)			
Day 5 Pre-apheresis	225.1 (53.7)	235.5 (56.1)	<0.01
Day 5 Post-apheresis	117.4 (38.6)	147.3 (42.7)	<0.01
Change (Post – Pre)	-107.6 (42.3)	-88.1 (38.6)	<0.01
Mononuclear Cells (x10^9/L)			
Day 5 Pre-apheresis	6.7 (3.0)	6.3 (2.6)	<0.01
Day 5 Post-apheresis	4.3 (2.6)	4.5 (2.7)	<0.01
Change (Post – Pre)	-2.4 (2.9)	-1.8 (2.9)	<0.01
CD34$^+$ Cells (x10^6/L)			
Day 5 Pre-apheresis	102.1 (174.2)	83.99 (289.4)	<0.01

CD34+ Cell Yields (Day 1 vs. Day 2)

	Day One Collection	Day Two Collection	p-value
CD34+ Cells (x10^6/L)			
N	2337	2336	
Median (SD)	23.8 (21.2)	28.7 (17.9)	<0.01

Multivariate Analysis (Skeletal Pain)

Variable	N	2 day follow-up		1 month follow-up		6 month follow-up	
		RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
# days apheresis							
1 day	18181	Reference (1.00)		Reference (1.00)		Reference (1.00)	
2 days	2230	0.9 (0.7-1.2)	0.54	0.82 (0.5-1.5)	0.53	1.13 (0.7-1.8)	0.60
Gender							
Male	13089	Reference (1.00)					
Female	7322	1.63 (1.4-1.9)	<0.01				
Age							
18 to 29	9363	Reference (1.00)		Reference (1.00)			
30 to 39	5382	1.3 (1.1-1.5)	<0.01	1.29 (0.8-2.0)	0.26		
40 to 49	3900	1.3 (1.1-1.6)	<0.01	2.12 (1.4-3.3)	<0.01		
50+	1766	1.1 (0.9-1.4)	0.33	0.95 (0.5-2.0)	0.89		

Multivariate Analysis (Skeletal Pain cont.)

Variable	N	2 day follow-up		1 month follow-up		6 month follow-up	
		RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
BMI							
Underweight/ Normal (< 24.9)	6905	Reference (1.00)					
Overweight (25 - 29.9)	7598	1.14 (1.0-1.3)	0.09				
Obese (30+)	5908	1.42 (1.2-1.7)	<.01				
Central line on day 5 or 6							
No						Reference (1.00)	
Yes						2.49 (1.7-3.7)	<.01

Multivariate Analysis (Body Toxicity)

Variable	N	2 day Follow-up		1 month Follow-up		6 month Follow-up	
		RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
# days apheresis							
1 day	18183	Reference (1.00)		Reference (1.00)		Reference (1.00)	
2 days	2230	1.29 (1.1-1.6)	<.01	0.78 (0.4-1.5)	0.46	1.13 (0.7-1.8)	0.60
Gender							
Male	13089	Reference (1.00)		Reference (1.00)			
Female	7322	2.09 (1.9-2.4)	<.01	2.09 (1.5-3.0)	<.01		
Age							
18 to 29	9365	Reference (1.00)					
30 to 39	5382	1.47 (1.3-1.7)	<.01				
40 to 49	3900	1.47 (1.3-1.7)	<.01				
50+	1766	1.35 (1.1-1.7)	<.01				

Multivariate Analysis (Body Toxicity cont.)

Variable	N	2 day Follow-up		1 month Follow-up		6 month Follow-up	
		RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
BMI							
Underweight/ Normal (< 24.9)	6907	Reference (1.00)					
Overweight (25 - 29.9)	7598	1.10 (1.0-1.3)	0.18				
Obese (30+)	5908	1.41 (1.2-1.6)	<.01				
Central line on day 5 or 6							
No						Reference (1.00)	
Yes						1.79 (1.1-2.9)	0.02

Multivariate Analysis (Body Toxicity cont.)

Variable	N	2 day Follow-up		1 month Follow-up		6 month Follow-up	
		RR (95% CI)	P-value	RR (95% CI)	P-value	RR (95% CI)	P-value
CD34+ cells (x10^6) collected day 5							
< 423	4761					Reference (1.00)	
423- 631.2	4734					0.70 (0.4-1.1)	0.13
631.2-906	4662					0.64 (0.4-1.0)	0.07
>906	4581					0.43 (0.3-0.8)	<0.01
Volume blood processed on day 5							
0 L – < 12L	1061					Reference (1.00)	
12 L– < 18L	5954					0.44 (0.2-0.8)	<0.01
≥18 L	11723					0.53 (0.3-1.0)	0.04

Conclusions

✓ No clinically significant difference in skeletal pain or body toxicity between 1-day vs. 2-days of apheresis.

✓ Decreased hospitalization and citrate toxicity associated with 1-day vs. 2-days of apheresis.

✓ Decreased body toxicity associated with increased volume of whole blood processed.

✓ Increased CD34+ cell yields on 2nd day of apheresis with 2-day collections.

Questions?

The Quality of Harvested Bone Marrow for Transplantation Has Decreased Over Time - Implications & Solutions

Nicole L Prokopishyn PhD
University of Calgary, Calgary, AB Canada

2018-11-09

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Bone Marrow – An Essential Stem Cell Source

✓ Preferred cell source for specific disease indications in adults (*e.g.,* Aplastic Anemia)

✓ For the majority of pediatric transplants

✓ When the benefits of a decreased risk of chronic graft versus host disease (cGVHD) outweigh other considerations

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Decreased Bone Marrow Usage in Unrelated Allogeneic Transplants

- With the advent of G-CSF mobilized peripheral blood stem cells (PBSC)
- Significant decrease in the utilization of BM has occurred at many transplant centers.
- Use of BM as the HSC source has declined from 100% in the early 1990s to 19% in 2017 in the unrelated donor setting

Transplants by Cell Source
Unrelated Donor Transplants Facilitated by NMDP/Be The Match
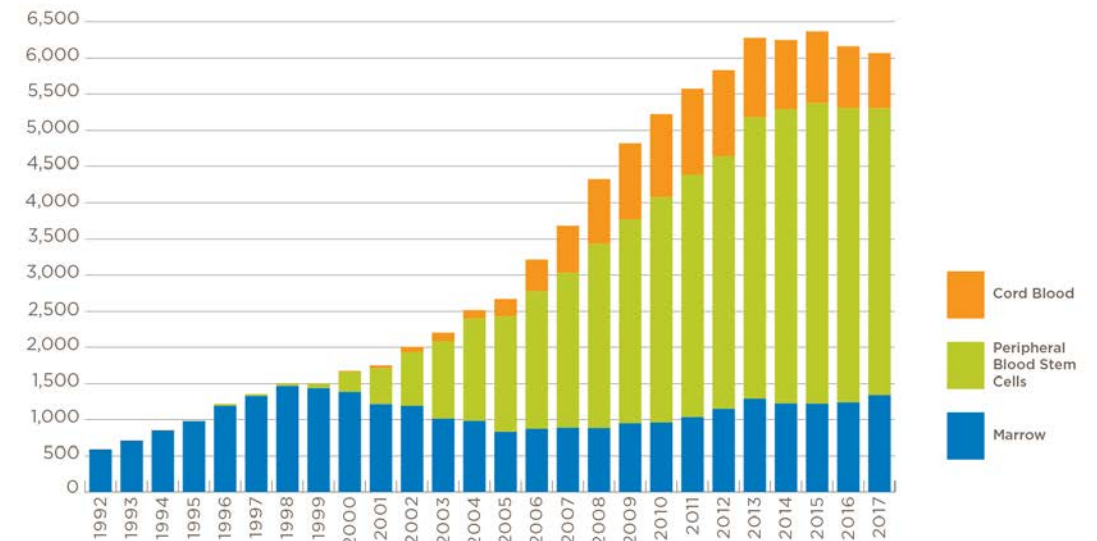
Source: National Marrow Donor Program/Be The Match FY 2017

Bone Marrow – Possible Implications of Declined Use

- ✓ Decreased harvester and harvest team experience

- ✓ Difficulties maintaining competency

- ✓ Difficulties with proper assessment of BM harvest metrics with performance of limited procedures

  - ✓ Total nucleated cell (TNC) dose collected as compared to target dose

  - ✓ Quality of BM collected

  - ✓ Adverse reactions in donors following collection

Accreditation standards have specific requirements to help maintain quality in bone marrow harvests

✓ Minimum of 1 BM harvest per year average in the accreditation cycle

    ✓ Minimum of 3 BM harvests in the accreditation cycle of 3 years

✓ Perform quality assessment of collection procedures

✓ Implement standardized protocols

✓ No specific requirements for:

    ✓ Individual harvester procedures per year

    ✓ Harvester and staff training

    ✓ Collection technique

Bone Marrow – An Essential Stem Cell Source

- ✓ Preferred cell source for specific disease indications in adults (*e.g.,* Aplastic Anemia)
- ✓ For the majority of pediatric transplants
- ✓ When the benefits of a decreased risk of chronic graft versus host disease (cGVHD) outweigh other considerations

The Study

✓ Study Population - domestic unrelated first-time BM donors, with products collected by NMDP centers from 1994-2016. Over 15,000 harvests were analyzed

✓ Marrow was collected in an operating room from the posterior iliac crests under general or regional anesthesia following NMDP standards.

    ✓ NMDP standards require that no more than 20 mL/kg (donor weight) of marrow be aspirated, the duration of anesthesia should not exceed 150 minutes, and the duration of the collection should be less than 120 minutes

✓ All data utilized were reported by collection centers to the NMDP/CIBMTR at time of collection/transplant.

✓ The number of collections per center per time period was calculated using the number of collections reported to NMDP in this population.
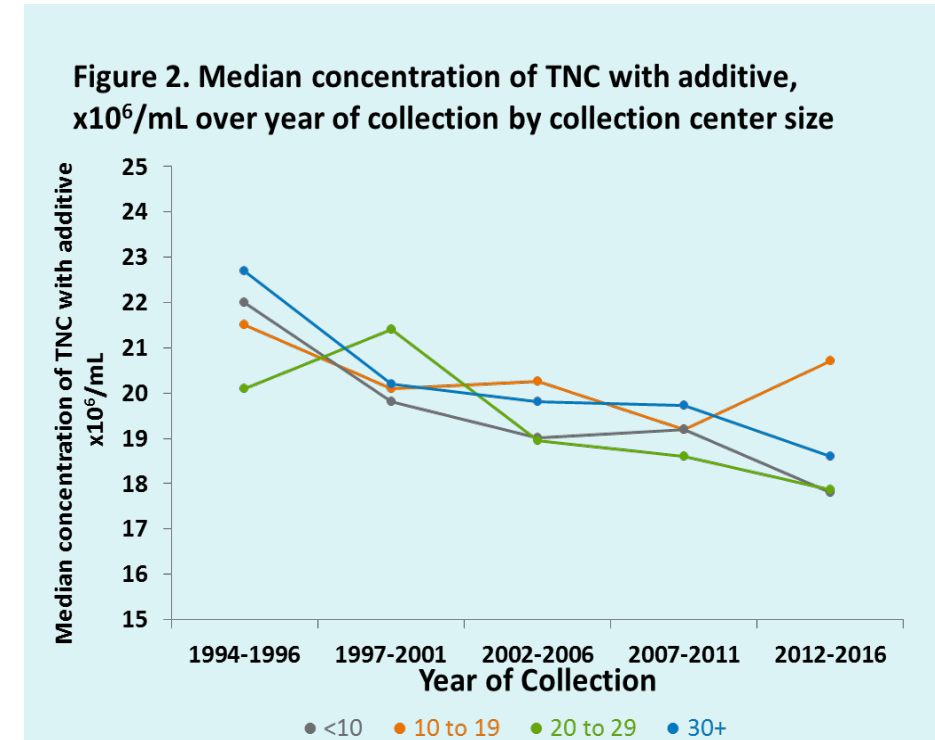
The Study

✓ Primary outcome of this study is the examination of TNC collected per milliliter (TNC/mL) of BM, as an estimate of HSC product quality. TNC/mL for each harvest was calculated based on TNC in the product and the volume (mL) of final product including additives.

✓ Population was analyzed over 5 time periods: 1994 – 1996, 1997 – 2001, 2002 – 2006, 2007 – 2011, and 2012-2016.

✓ Donor characteristics, including of sex, age, and Body Mass Index (BMI), as well as collection volume, were compared between time-periods

✓ Collection centers were subdivided based on collection center volume based on the number of collections performed per harvest center per time period
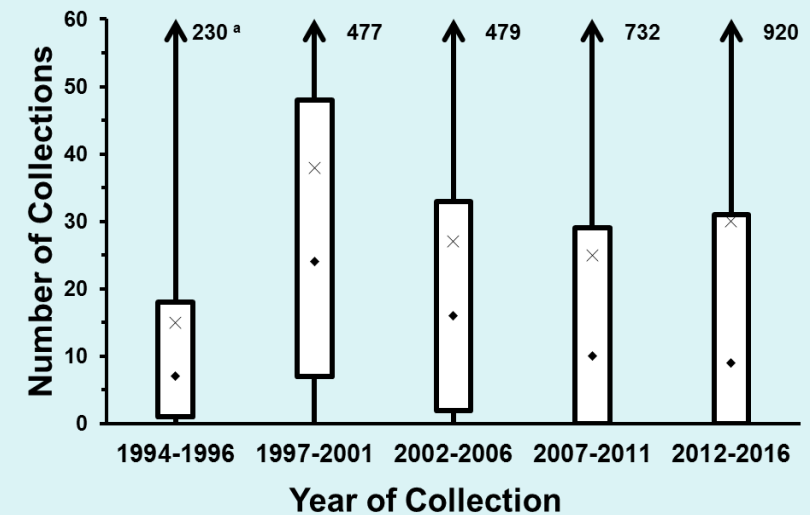
Decreased Bone Marrow Quality Over Time

Significant decline in the concentration of TNC in the product over time, from 21.8 TNC x 10^6/mL in the earliest era (1994-1996) to 18.7 TNC x10^6/mL in the most recent time era (2012-2016) (Ratio of Means 0.83, p<0.001)

Figure 2. Median concentration of TNC with additive, x10^6/mL over year of collection by collection center size

Median concentration of TNC with additive x10^6/mL

● <10   ● 10 to 19   ● 20 to 29   ● 30+

Year of Collection

Higher Volume Centers Have Higher Quality Bone Marrow Harvests

Centers performing 30 or more collections per era having a significantly positive association with BM quality compared to centers performing less than 30 collections in an era
 (Ratio of Means 1.02, 95% CI

1.01-1.04)

Figure 1. Number of collections at collection center by year of collection.

Donor Characteristics Also Impacting BM Quality Over Time

✓ Reduction in BM Quality Over Time:

    ✓ Donor race was associated with a reduction of BM quality over time,

        ✓ Hispanic, African/African American, Asian Pacific Islander all having significantly lower TNC/ml when compared to Caucasians (Ratio of Means 0.98, 95% CI 0.96-0.99; Ratio of Means 0.85, 95% CI 0.84-0.87; Ratio of Means 0.90, 95% CI 0.88-0.92; respectively).

    ✓ Donor Age

        ✓ Older donors had a lower BM quality as compared to the youngest donors aged 18 to 29.

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Donor Characteristics Also Impacting BM Quality Over Time

✓ Donor Factors Associated with Increased BM Quality Over Time:

    ✓ Female donors had higher quality BM as compared to male donors

      (Ratio of Means 1.04, 95% CI 1.03-1.06)

    ✓ Heavier donors had higher quality as compared to lighter donors.

        ✓ The heaviest donor group, weighing more than 83kg, had a Ratio

          of Means of 1.14 compared to the lightest donors weighting 69kg

          or less (95% CI 1.12-1.16).

Collection Center Volume Impacts BM Quality Over Time

✓ The number of BM collections at a center per era was also associated with BM quality, with centers performing 30 or more collections per era having a significantly positive association with BM quality compared to centers performing less than 30 collections in an era (Ratio of Means 1.02, 95% CI 1.01-1.04).

Conclusions

✓Quality of BM harvests has decreased over time.

✓Collection centers collecting smaller numbers of BM per year collected lower quality BM products.

✓Decline in BM quality persisted even though centers select more optimal donors in recent eras.

Where do we go from here?

✓ What exact factors are responsible for this significant decrease in BM quality?

    ✓ Harvester experience

    ✓ Harvest technique

    ✓ Center protocols

✓ What is the impact of this decline in BM quality has on transplant outcomes?

Thank you!