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All Donors and Patients: Safety and Ethical Challenges?

COI

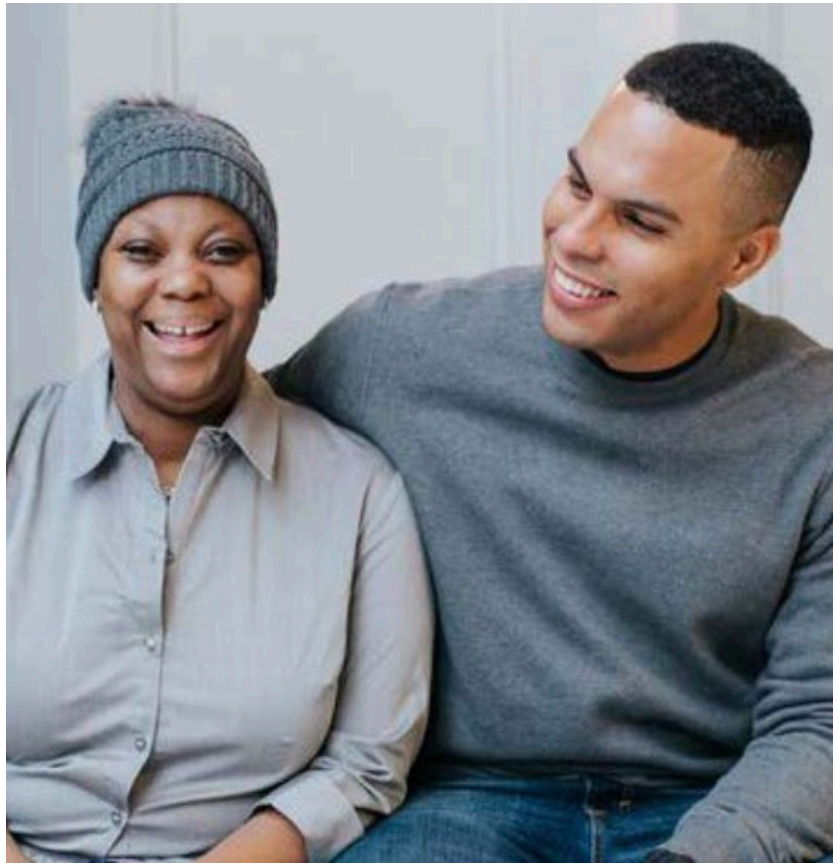
- None to disclose

Agenda

- RD studies
- Current state of RD and TC interactions
- WMDA Survey about RD services to registries
- Challenging cases RDs
- Updates on long-term follow-up of URDs
- Final Thoughts

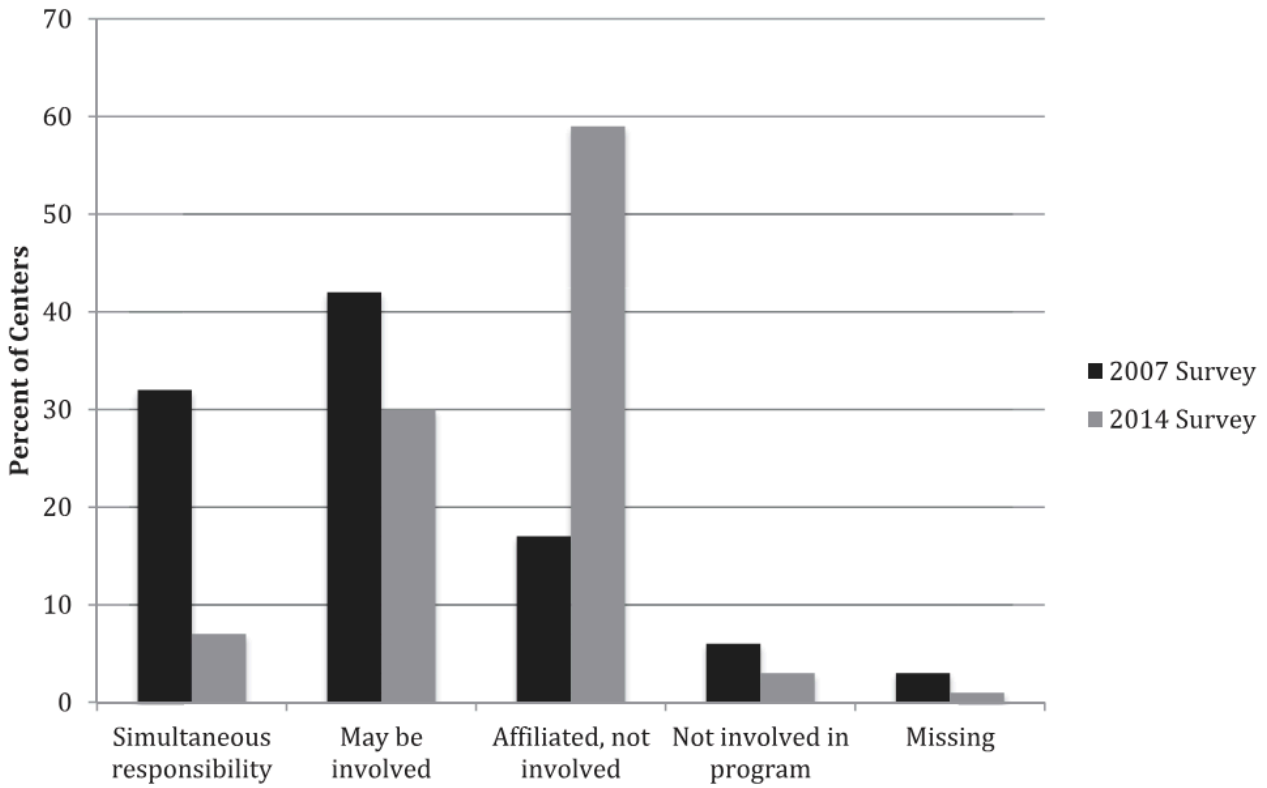
Background

- Registries of volunteer URDs have stringent policies and standard practices in place to ensure both donor and patient safety.
- In contrast to URDs, there is heterogeneity in donor center processes and external oversight for RDs and the experience and outcomes of RDs are not as well known.



Understanding RD practices at the TC

- A 2007 TC Survey from the Donor Health Safety Working Committee of the CIBMTR found that in over **70%** of US Centers, the same physician cared for both the RD and recipient.
- The led to a practice change which included consensus recommendations and regulations by FACT and JACIE.
- A follow-up survey in 2014 showed a huge improvement with 62% of centers separating RD and recipient care.



Anthias et al. 2016

RD-SAFE

- This prospective observational study focused on the differences in nature, severity and duration of 11,942 recruited URD and RDs aged 18–60 years between January 2010- July 2014.
- BM was collected at 37 transplant and 78 NMDP centers, and PBSCs were collected at 42 transplant and 87 URD centers in North America.

Pulsipher et al, 2019

RDs have increased pain and toxicity compared to URDs

RDs had increased risk of moderate and severe pain and toxicities with collection.

RDs were at increased risk of persistent toxicities and non-recovery from pain at one year.

RDs with more *significant comorbidities* were at especially high risk for grade 2-4 pain and non-recovery from toxicities at one year.

Pulsipher et al, 2019

SAEs were also more prevalent in RDs compared to URDs

A total of 12 SAEs were confirmed in 12 (0.71%) of the 1680 donors. Of these, 5 SAEs occurred in 404 BM donors (1.24%), and 7 occurred in 1276 donors (0.55%) of PBSC.

By comparison, SAE rates in URDs are reported to be 0.99% for BM and 0.31% for PBSC.

SAEs are especially relevant in donors at extremes of age or with comorbid medical conditions, situations more likely to be observed in RDs rather than URDs.

Seftel et al, 2021

WMDA RD subgroup in Pillar 3

- To ascertain what RD services *registries* currently offer, a survey was sent via the WMDA monthly newsletter and sent to all 85 WMDA registries.
- Clinicians involved in donor care were asked to complete the survey.
- There was a 50.6% response rate with 43 completed responses from 39 different registries. There were 10 partial responses, which were not including in the results reporting.
- This survey provided valuable insights into the similarities and differences between URD and RD care in areas such as consent process, eligibility and suitability criteria, follow-up care, and RD-specific challenges.

Current vs. Planned/Future RD Services

RD service provided	Current	Future
Counselling/assessment of RDs before HLA typing	51.2%	14%
Arranging HLA typing in your own country	72.1%	16.3%
Arranging HLA typing in other countries	58.1%	18.6%
Facilitating the stem cell donation at your collection centers	76.7%	20.9%
Facilitating the workup and/or medical clearance only	27.9%	14%
Transportation of RD cells	53.5%	11.6%
Providing post-donation follow-up of RDs	53.5%	20.9%

Key Messages from the Survey

MOST REGISTRIES REPORTED THAT THEIR ELIGIBILITY AND SUITABILITY CRITERIA FOR RDS ARE *SIMILAR* TO THOSE FOR URDS, BUT THERE ARE SOME DIFFERENCES.

ONE NOTABLE DIFFERENCE IS THE UPPER LIMIT OF DONOR AGE, WITH MANY REGISTRIES ALLOWING RDS OVER 60 YEARS OLD.

SOME REGISTRIES ALSO ADOPT A MORE LENIENT APPROACH TO RD CLEARANCE.

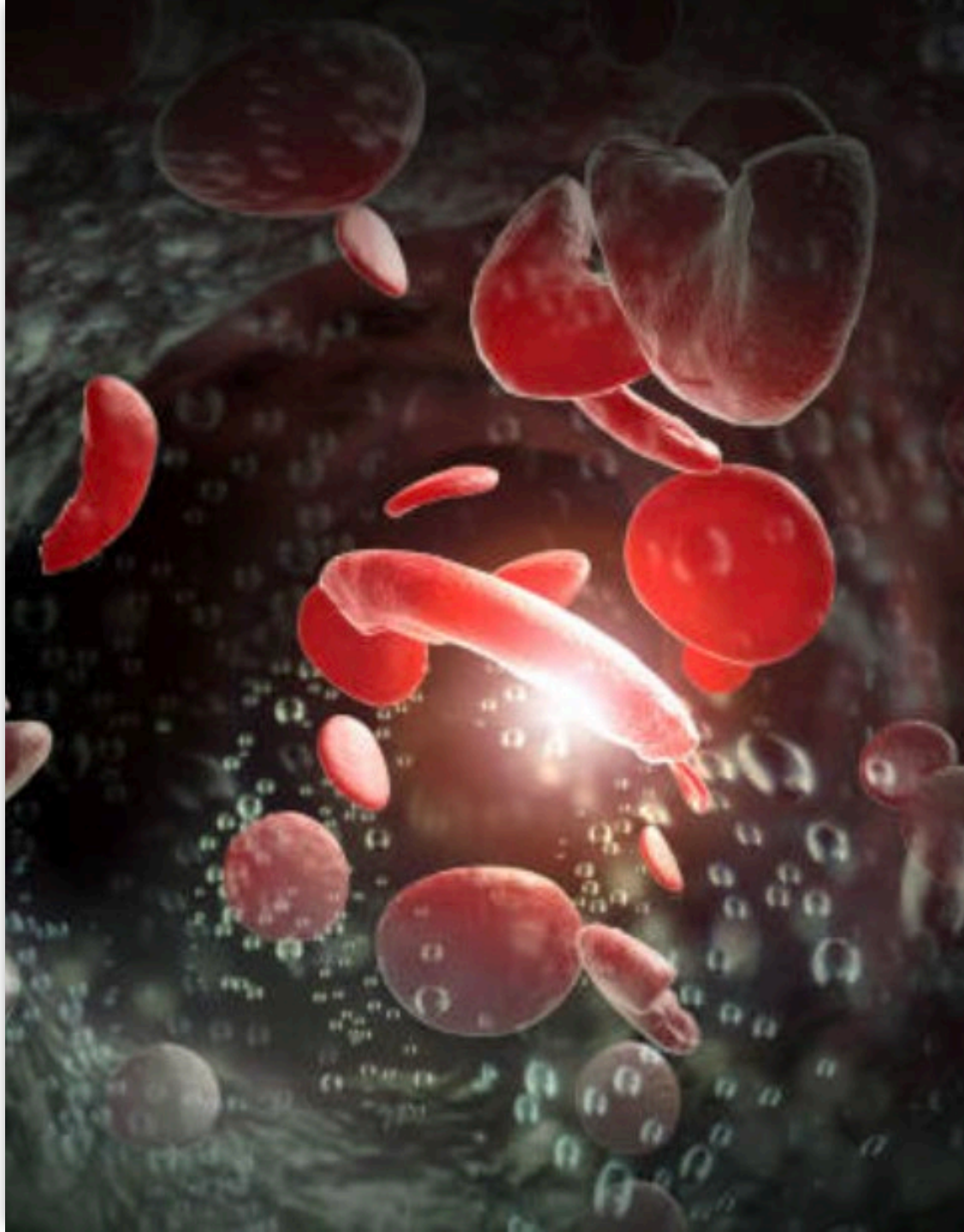
REGISTRIES GENERALLY FOLLOW THE SAME CONSENTING PROCEDURE AS FOR URDS, EXCEPT WHEN CONSENTING MINORS.

MOST REGISTRIES CONDUCT RD FOLLOW-UP SIMILARLY TO URDS.

Unique circumstances for RDs

SABMR: mobilizing SC trait donors

- Sickle cell anemia is a hemoglobinopathy and affects the shape of red blood cells.
- According to WMDA Donor Suitability Wiki guidelines: "**There is no evidence of clinically significant sickling during mobilized PBSC collection in those with sickle cell trait. However, clumping of sickle cells has been observed during post-collection processing. In these circumstances, it is advisable that donors with sickle cell trait should donate by BM**."
- As many donors of West and Central African ancestry have SC trait and it is difficult at times to attain BM, mobilized PBSC has been the preferred stem cell source. SABMR done 4 cases and has had no issues with exacerbation of a SC crisis in the donor.
- To prevent this, the donor received oxygen throughout the procedure.



Difficulties with RD Care

- One common theme from the WMDA survey was the amount of time it takes to complete workup and clearance due to older donors' more extensive medical histories and health conditions that require additional testing and attention to detail.

Heart Disease in a RD

- 50 yo F, hx of symptomatic paroxysmal atrial fibrillation of unclear cause for the past 12 years.
- No known hx of coronary artery disease. Normal LVEF.
- Had tolerance issues with several antiarrhythmic medications including sotalol, propafenone, and amiodarone.
- At the time of donation evaluation donor was prescribed flecainide, unclear if donor was taking regularly, and continued to have breakthrough episodes.
- Donor reported using Digoxin and diltiazem as needed for rate control.
- She was also prescribed Eliquis to reduce risk of cardioembolic stroke; but reported only taking Eliquis PRN after experiencing an episode of hemoptysis 2 years prior.
- Cardiology had recommended ablation although donor unable to proceed due to lack of insurance.
- Due to the paroxysmal nature of donor atrial fibrillation and lack of strict compliance with medications for rate control and anticoagulation, this donor was deferred for NMDP facilitation of collection.

Difficult family relationships

- The survey also revealed recurrent ethical dilemmas surrounding RDs, such as the feeling of obligation a RD might have to donate for a family member.

- A 58 yo female had difficult and seemingly toxic familial relationships – all siblings were estranged from the donor.
- Donor's brother died post-transplant.
- Donor had a difficult time with her brother's death. AN provided emotional support to the donor and referred her to psychology.

Misunderstanding of the donation process

A 59 year old female (ex-smoker) RD developed lung cancer shortly after donation and died 7 months post donation.

After death, AN was contacted by the partner of the donor who complained to AN as they felt that the donor might have been treatable if the lung cancer was picked up by AN before the donor developed symptoms.

The partner was very distressed and contacted us to complain on several occasions as well as contacting WMDA.

Other complicating factors with RDs

RDs may not understand why they are deferred and would be inclined to accept an above average risk of donation-related adverse event.

Communication between the RD and patient outside of transplant center and donor center oversight and this can lead to confusion and miscommunication.

Concerns about current RD practices

- Assessment of potential RD health before HLA typing is necessary both to prevent delays to the transplant recipient by reducing deferrals at the point of donor medical evaluation
- Also doing so will reduce potential distress or guilt to the RD by being canceled after they are known to be HLA-matched.

Other concerns with RDs

Plerixafor or other mobilization agents

- Some centers use plerixafor off-label for RDs and it is not well documented.
- NMDP recently amended our IND to allow for plerixafor use in specific cases, however we will be monitoring all donors who receive it (both URDs and RDs) for adverse events.

LTFU

- The recent TC survey (Anthias, et al., 2016), found that 96% of centers perform short-term follow-up (1–4 weeks post donation), only 23% continue follow-up to 5 years and 14% to 10 years.
- The WMDA registry survey found that most registries perform RD follow-up similar to URD.

LTFU study

- The study consisted of BM or PBSC URDs who underwent a collection between July 1, 1999, and October 1, 2010.
- After donors provided informed consent, they completed biennial phone surveys to report malignancy, autoimmune, or thrombotic (MAT) events until study completion.
- The study was closed to accrual on September 30, 2015, and follow-up phone call surveys were completed on September 30, 2020.
- 21653 donors were included in the final analyses; BM donors were considered the control.
- BM donors median follow-up was 9 years and PBSC donors was 7 years.

Filgrastim **did not** increase MAT events in PBSC donors

	Filgrastim-Mobilized PBSC Donors			Unstimulated Bone Marrow Donors				
	Person -years	*No. of events*	*Incidence rate[a]*	*Person -years*	*No. of events*	*Incidence rate[a]*	*Rate ratio (95% CI)*	*p-value*
Myeloid	118712	3	2.53	72641	3	4.13	0.61 (0.12, 3.03)	0.55
Lymphoid	118649	17	14.33	72572	10	13.78	1.04 (0.48, 2.27)	0.92
Other cancers	116213	535	460.36	70553	368	521.59	0.88 (0.77, 1.00)	0.05
Thrombosis	117977	156	132.23	72172	95	131.63	1.01 (0.78, 1.30)	0.95
Autoimmune	116566	449	385.19	71269	262	367.62	1.03 (0.89, 1.21)	0.66

Study conclusions

- The results of this study provide strong evidence that donors who receive filgrastim are not at increased risk of these events compared to BM donors.
- This study provides reassurance to current donors undergoing stem cell mobilization as well as to those considering joining stem cell registries such as the NMDP.

Conclusions

- Based on the survey results and the lack of guidelines or standardization for RDs, there is clearly an unmet need for guidance and standardization of RD management and care.
- Evidence clearly shows that RDs are at higher risk of AEs compared to URDs.
- We encourage Registries to follow the same standards for RDs as they do for URDs.

Other aspects of RD care that need to be addressed

- What about RDs who are minors?
- How much is too much when pushing for a RD?
- How do registries handle when the TC pushes back?
- What about when the donor pushes back?

Thank you.

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