

Rare blood: programs in Europe and the impact of demographic changes

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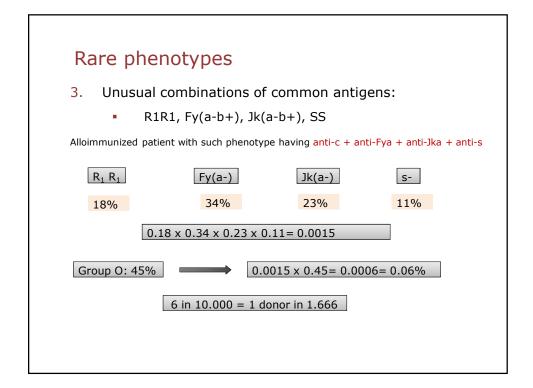
What is Rare blood?

- A blood type is rare when more than 200 donors must be screened to find one compatible donor
- When only 1 person in 1,000 shares the same uncommon phenotype
- If only 1 person in 10,000 → very rare

Rare phenotypes

- 1. Negative for a high frequency antigen (HFA)
 - Up to 189 high-frequency blood group antigens have been recognized by the ISBT
 - → Homozygosity for a recessive gene, e.g. Kp(b-)
 - → Inheritance of an "inhibitor" gene, e.g. Lu(a-b-)
- 2. Absence of a whole protein "Null" phenotypes
 - Rh_{null}, K₀

Rare Gems



Rare phenotypes and Ethnicity



There are certain ethnic groups where certain blood types are more common:

- U-, Fy(a-b-) and Js(b-) \rightarrow African descent
- Jk(a-b-) → Polynesian and Finnish
- Di(b-) → Hispanics (Latino Americans)
- Kp(b-) and Vel → Caucasians
- Jr(a-) and Co(a-b-) → Roma people
- Dr(a-) → Russian Jews
- In(b-) → Indian, Pakistani, Iranian

How can we find rare blood donors?

- > Through screening programs
- ➤ Former patients identified as lacking a highprevalence antigen because of the presence of the corresponding alloantibody in their serum → can be recruited as rare donors
- ➤ Testing family members of these patients
 Especially siblings → 25% chance of inheriting the same rare phenotype

Screening for rare donors

- Using serological methods
- → Mass screening for high-prevalence antigen negative donors
- Often dependent on limited availability of antisera from patients
- Monoclonal antibodies can be used for some antigens

Routine extended typing strategies

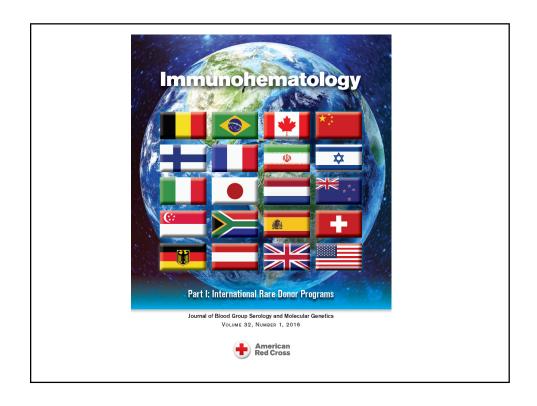
- Routine Rh typing (D, C, c, E, e) facilitates the detection of r'r', r"r", Rh_{null}, D-- and other Rh variants
- Cellano typing of all K+ donations
- Extended phenotyping of repeat blood donors (Fya, Fyb, Jka, Jkb, M, N, S and s) increase availability of RBCs negative for multiple common antigens

Screening for rare donors

- Using genotyping methods
- Molecular basis of almost all rare blood group phenotypes known
- Molecular blood group screening approaches can be used to test large numbers of donors economically for several rare blood group alleles (KEL*02, KEL*04, YT*01, CO*01, LU*02, VEL and JR*01)
- Several commercial blood group genotyping platforms available

Unfortunately, it is not always meaningful to screen for every rare blood group \rightarrow e.g. O_h (Bombay), Rh_{null} or the K_0 phenotypes





Rare blood donor Programs in Europe

Common traits:

 All donors donate on a voluntary basis and no incentives are given to rare blood donors



- When rare blood is needed, there is an increasing tendency to use of fresh unit from one of the available rare donors rather than a thawed unit
- Shortage of rare donors with non-Caucasian phenotypes

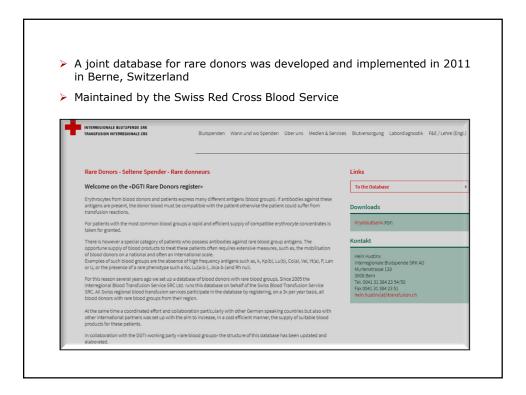
The DGTI Rare donor program



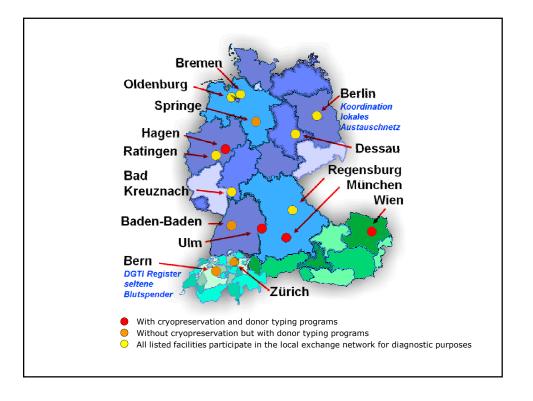


Arbeitsgruppe Seltene Blutgruppen German Rare Donor Program

 The Working Party on Rare Donors of the German Society of Transfusion Medicine and Immunohematology (DGTI) represents the German-speaking countries of Switzerland, Germany and Austria.



Stand: July 2018 Blood Service			DRK Blutspendedienst West Zentrum Hagen +48-(0)2331-807-0 +48-(0)2331-807-151 -48-(0)731-150-610;-506;-536				Österreichisches Rotes Kreuz Institut Wien +43(1)58-900 +43(1)58-900-262							
Tel: Fax:		Institut Ulm +49-(0)731-150-610;-600;-536												
Blood group				0	Ι.	A		0		Α.)		A
system	ISBT number	Phaenotype	D+	D-	D+	: D-	D+	D-	D+	D-	D+	D-	D+	D-
MNS	002	U-, S-s-												
		U-, S-s-, Fy(a-b-)												
P1PK/Globosid	003/028	p (PP1Pk-, Tja-)									4		3	
		P-												3
Rh	004	Rh _{null}				5			111	DEL				
		D	6			1								
		CCddee		5				15		5		10		4
		ccddEE		4				10		4		2		6
		CCDDEE	2				5		3					
		CCddEE												
Lutheran	005	Lu(b-)	3	4			7	2			6			
		Lu(a-b-), In(Lu)												
		LU:-8												
Kell	006	Kell _{null}		1		1		1					2	
		KK	6	6			2	2			10			1
		Kp(b-)	10	9			7	5			15		4	
		Js(b-)												
Duffy	008	Fy(a-b-)	6	2			10	3						
Kidd	009	Jk(a-b-)												
Diego	010	Di(b-)	-			-								
Yt	011	Yt(a-)	6	4	_	₩	17	9	3	_	5			-
Dombrock	014	Do(a-)		-		-			_		\vdash			
		Do(b-)	+	-	-	-	-		-		_			—
	1	Gy(a-)	+	-		-	-		-		_		_	-
Colton	015	Hy- / Joa- Co(a-)	2	5	_	-	3	11	1	2	20		2	_
Cotton	015	Co(a-b-)	2	5	-	-	3	-11	1	2	20		2	-
Landsteiner-	1	CO(a-D-)	+	-	 	+	1	_	1	_		_		-
Wiener	016	LWa-			I		I		1		ı		l	
	1	LW(a-b-)	1		†		1							_
Hh	018	hh (Bombay)	5					Pleas	e call!					_
Kx	019	Kx-					_		T					
Gerbich	020	Ge-2	1	1	t	1	1							-
JR	032	Jr(a-)			1		1	1						
Lan	033	Lan -	4		1				2					
Vel	034	Vel -	7	9	_	_	19		7		2		2	_



High-throughput molecular methods have been developed and implemented

Jungbauer, C & M Hobel, C & W M Schwartz, D & R Mayr, W. (2011). High-throughput multiplex PCR genotyping for 35 red blood cell antigens in blood donors. Vox sanguinis. 102. 234-42.

Portegys J, Rink G, Bloos P, Scharberg E, A, Klüter H, Bugert P: Towards a Regional Registry of Extended Typed Blood Donors: Molecular Typing for Blood Group, Platelet and Granulocyte Antigens. Transfus Med Hemother 2018;45:331-340.

> 1100 donors with rare blood types are listed in the DGTI database

The Finnish national rare donor program



- Managed by the national blood service and reference laboratory
- Operative for over 30 years
- In 2010 → implemented a program for freezing RBCs

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Blood types globally rare but more common in Finland: \gt Jk(a-b-) \gt LW(a-) \gt P^k
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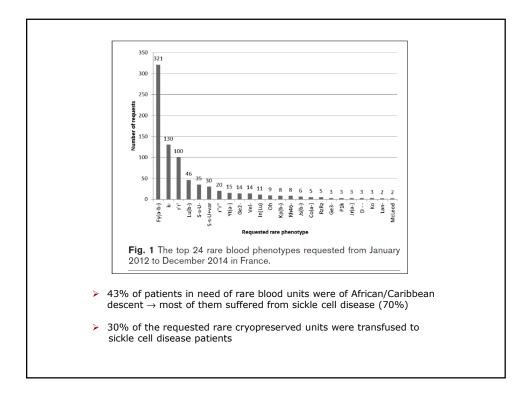
- Represented in the donor database and in the stock of frozen RBC units \rightarrow available internationally
- Aprox. 130 donors with rare blood types in the registry
 → 70 active donors

The French national rare blood program



- National rare blood donor database implemented in the late 1960s
- Early $1980s \rightarrow The National Rare Blood Bank was set-up$
- > Facility located in Créteil
- Co-managed by the Immunohematology Reference Laboratory of the CNRGS and the French National Blood Service (EFS)
- ➤ Currently → 6539 cryopreserved blood units

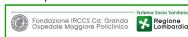
Up to 12,929 individuals with a rare blood phenotype or genotype are listed in the rare blood national registry, including donors and patients



Country	Rare phenotype	ABO/Rh/K	Alloantibodies	Number of RBC units provided
Belgium	Yt(a-)	O, D-C-E-c+e+; K-	Anti-Yta, anti-Lua	2
Belgium	Sec- (RNRN, RH:-46)	O, E-c-; K-	Anti-Sec, anti-E	2
Germany	Fy(a-b-)	O, D+C-E-c+e+; K-	Anti-Fy3 suspected	3
Germany	Fy(a-b-)	O, D+C-E-c+e+; K+	Anti-Fy3, anti-C, anti-E, anti-s, anti-P1	3
Germany	S-s-U-	O, D+C-E-c+e+; K-	Anti-U, anti-M	1
Germany	S-s-U-	B, D+C-E-c+e+; K-	Anti-U	11
Germany	rr	O, D-C+E-c-e+; K-	Anti-D, anti-c, anti-S	8
Iceland	D	O, D+C-E-c-e-; K-	Anti-Hr _o	2
Monaco	Fy(a-b-)	A, D+C-E-c+e+; K-	Anti-Fy3, anti-A1, anti-E, anti-C, anti-Fy³, anti-Jk³, anti-Lu³, antibody to a high-prevalence antigen of undetermined specificity	2 autologous units for elective surge (no possibility to cryopreserve RBC units in Monaco)
Sweden	S-s-U-	A, D+C-E-c+e+; K-	Anti-U	2
Sweden	S-s-U-	A, D-C-E-c+e+; K-	Anti-U, anti-D	1
Switzerland	GE:-2,3	O, D+C-E+c+e+; K-	Anti-Ge2	2
Switzerland	P_1^{k}	A, D+C+E+c+e+	Anti-P	3
Switzerland	O _h (Bombay)	O _h , D+C+E-c+e+; K-	Anti-H	1
United Kingdom	D	O, D+C-E-c-e-; K-	Anti-Hr ₀	1

The Lombardy Rare Donor Program (LORD-P)

 Established in 2005 as the first regional rare donor program in Italy → a network of 15 blood transfusion services coordinated by the Immunohaematology Reference Laboratory of the Ca' Granda Ospedale Maggiore Policlinico in Milan



- Extensive typing of selected blood donors (age 18-55, history of two or more previous donations)
 - ightarrow 10.040 active donors with a rare combination of common antigens
 - \rightarrow 579 donors negative for high-prevalence antigens
 - \rightarrow 48 donors with rare Rh phenotype
- The LORD-P registry and blood bank of frozen RBC units has contributed to resolving planned and urgent transfusion needs of immunized patients throughout the country

LORD-P

Intigen/phenotype	Number of donors
Yt(a-)	196
Fy(a-b-)	140
k-	129
Co(a-b+)	56
Lu(b-)	44
CCdee (r'r')	31
ccdEE (r"r")	9
CCDEE (R _z R _z)	6
Kp(b-)	5
Fy(a-b-) Js(b-)	4
PP1P ^k -	2
D	2
Js(b-)	1
Co(a-b+) Yt(a-)	1
GE:-2	1
Total	627

 Since 2010, another regional rare donor program established at the Blood Transfusion Center of Ragusa Hospital in Sicily.

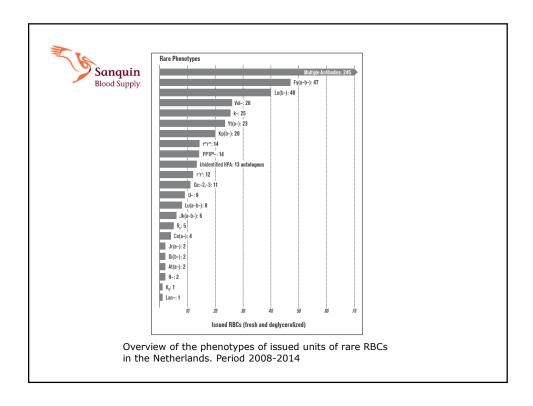


Includes a nationally organized rare donor program in the Netherlands

• In 2006 o Sanquin Bank of Frozen Blood (SBFB), originally part of the European Bank of Frozen Blood of the Council of Europe



- Aprox. 1300 frozen rare blood units stored at the SBFB
- 900 active rare donors, negative for a high-prevalence antigen



The Spanish program for rare blood donors

- Created in 2005 as a cooperative group of 5 Blood Transfusion Centers (BTCs) involved in the management of rare blood phenotypes
- Supported by the Spanish Society of Blood Transfusion (SETS) ⇒ Established a Working Party on rare blood

Bask Country
Navarra

Aragón

- Currently, a network of 8 BTCs
- → 5 collecting and cryopreserving rare blood units
- \rightarrow 3 providing a list of rare blood donors

Inventory of cryopreserved units of rare blood - 2018 AB+ AB-B+ Total **ISBT** Phenotype KEL:-2 79 кк 41 20 93 236 KEL:-4 Kp(a+b-) 28 3 35 64 1 6 137 Lu(a+b-) LU:-2 16 6 79 70 1 172 LU:-1.-2 Lu(a-b-) 7 9 19 PP1Pk-Tj(a-) 12 39 2 72 VEL:-1 Vel -16 13 FY:-1, -2 Fy(a-b-) 8 9 33 52 1 103 JK:-1, -2 Jk(a-b-) 5 3 8 CO: -1 Co(a-) 8 8 38 9 63 2 DI:-2 Di(b-) 24 26 YT:-1 Yt(a-) 2 5 29 14 50 JR:-1 Jr(a-) 5 9 11 29 ЈМН-ЈМН-6 2 8 LAN:-1 2 8 Lan -6 MNS:-3,-4 S- s-1 6 3 11 MNS:-5 8 1 12 Bombay(Oh) 8 8 5 r'r' 25 30 r"r" 8 7 16 Rz Rz 3 5 8 -D-/-D-5 14 1061

- \rightarrow More than 900 donors identified with rare blood types
- \rightarrow Integrated into the International Rare Donor Panel (IRDP) in 2009

Rare blood units distributed through International requests

Country	Rare Phenotype	Antibody	Units
Portugal	- D-	Anti-Rh17	1
Norway	K_0	Anti-Ku	1
Israel	Vel -	Anti-Vel	1
Sweden	Di(b-)	Anti-Di ^b	5
Sweden	Jr(a-)	Anti-Jra	1
UK	Jr(a-)	Anti-Jra	4
Japan	PP1Pk-	Anti-PP1Pk	8
Iran	Rh _{null}	Anti-Rh29	2
	· · · · · · · · · · · · · · · · · · ·	TOTAL	23

Period 2010-2017

Rare blood units imported -Period 2010-2017

Country	Rare Phenotype	Antibody	Units
Germany Japan	K ₀	Anti-Ku	2
France	(R ^N R ^N , RH:-46)	Anti-Sec, anti-E	2
		ТО	TAL 4

	Age	History	ABO	IH study	Rh	Antibody	R ^N Phenotype
Patient haemolytic crisis	18	SCD Transfused No extended phenotype	B+	Panaglutinine Auto - DAT -	D+ C+ c- E- e+w	Anti-Sec (anti-Rh46)	Rh:32,-46

- \rightarrow Antibody unreactive with D-- and $\mathrm{Rh}_{\mathrm{null}}\,\mathrm{RBCs}$
- \to The patient has been transfused on 5 occasions in the last 6 years with a total of 11 blood units: 6 D--, 1 Rh_null, 3 R^NR^N
 - RH:-46 phenotype is extremely rare in Caucasians
 - Incidence about 1% in Africant descent population

The United Kingdom program for rare blood donors

- The UK national rare donor panel (NRDP) was first established in 1952
- In 1967, coinciding with the development of the WHO International Rare Donor Panel (IRDP), the IBGRL revised and updated the NRDP
- Late $1970s \rightarrow \text{Mass}$ screening program initiated at the National Blood Service South London center
- Serological screening using microplate methodology
- Aimed to identify donors negative for high-prevalence antigens
- ▶ Developed over the years → largest source of rare donors in the UK
- Samples from donors identified as having a rare phenotype are sent to the IBGRL for confirmation testing

The current UK NRDP consists of approx. 2000 active donors

- A selection of rare units are frozen and stored at the UK National Frozen Blood Bank (NFBB) → situated at the NHSBT Liverpool center
- Donations are sent to the NFBB from all the NHSBT centers across England but also from the Scottish and Welsh blood services
- ➤ Upon freezing, units are stored between -60°C and -80°C → shelf life of 10 years
- For some extraordinary rare phenotypes, the units may be kept beyond the assigned expiry date
- > The NFBB has approximately 600 frozen rare units



This area is restricted to authorized professional users only; users should enter their username and password in the login box.

Click here to search for a rare donor

Blood Centre staff and other professionals requiring information regarding donors of a specific rare blood group should contact:

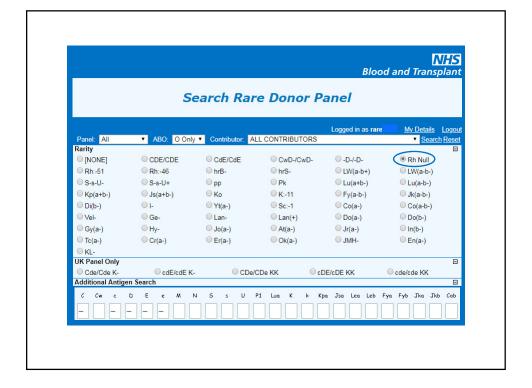
Nicole Thornton: <u>nicole.thornton@nhsbt.nhs.uk</u>

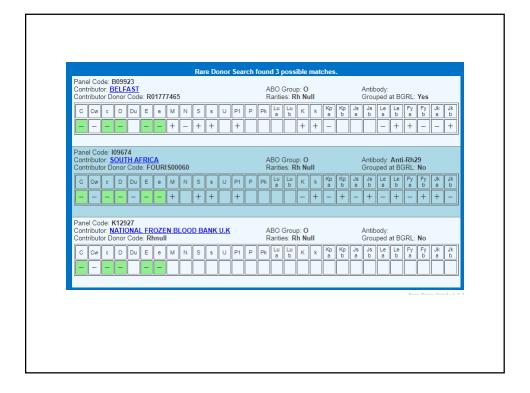
Phone: +44 (0) 117 921 7587 FAX: +44 (0) 117 912 5796



>8000 registries of blood donors with a rare phenotype

- 60 centers
- 27 countries





Impact of demographic changes

- ▶ Due to increasing migration, blood collection establishments are increasingly required to supply blood for patients from different ethnic backgrounds
- ▶ People from minority groups are generally less actively involved in the blood supply than people from the native population
- ▶ Different ethnic groups can differ in blood group antigen expression, which can cause alloimmunisation if donor and patient are not from the same ethnic background

Common West African RBC phenotype: D+ C- E- c+ e+, K- k+, S- s+, Fy(a-b-), Jk(a+b-) → 30-40% of African donors → 1:1000 Caucasian donors The less common blood groups pose challenges especially if a patient requires regular blood transfusions



Genetic blood disorders

- ▶ Sickle-cell disease (SCD)
- ▶ Thalassemia



- Sickle-cell anaemia mostly affects people of African origin
- · Thalassemia is more common among Mediterranean people
- ▶ The incidence of alloimmunization to RBC antigens in patients with SCD has been reported to range from 30% to 40%, which is markedly higher than what is seen in the general population (roughly 2-5%)

▶ To explore the problems associated with migration and minority populations, the Missing Minorities (MIMI) Project was initiated by the European Blood Alliance in 2012

Diversity and Equality in Health and Care (2016) 13(1): 138-145 2016 "Missing Minorities – A survey based description of the current state of minority blood donor recruitment across 23 countries"

Demographic Data

Percentage of people from minority groups with a different blood genotype varied greatly among countries

- $\blacksquare \ France \rightarrow 25\%$
- Spain \rightarrow 16%
- England & North Wales → 14%
- Netherlands \rightarrow 12%
- ▶ Many blood services were not able to provide data on the representation of minority groups in their donor database
- Minorities mostly underrepresented

It is of utmost importance that people from minority groups with different extended red cell typing are represented in the blood donor base. Diversifying the donor base is necessary to ensure that all persons in need of blood products have an equal chance of finding matching products

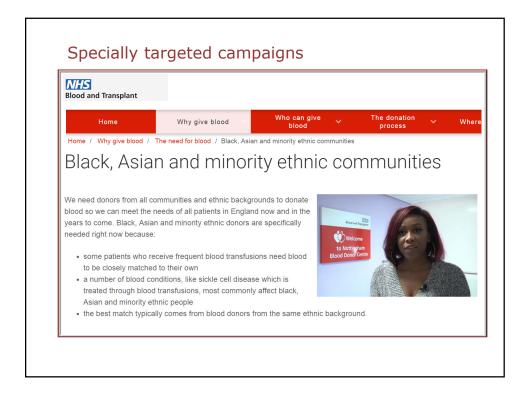


Methods used to recruit minority donors

- Social media and local television
- Recruitment in religious organisations (e.g. mosques) or minority organisations
- Recruitment using individual spokespersons from specific minority groups
- Leaflets

Obstacles to minority recruitment

- High deferral percentage
- Socio-cultural issues
- Problems regarding the language barrier
- Hard to reach target audience





Second-generation Africans needed in particular

As a result of increasing immigration, other Western countries have begun to take similar action, too.

"Immigration into Finland is so far relatively low compared to many other European countries, but in the Helsinki region especially, a significant and increasing proportion of the population is of African origin. By active recruiting, we aim to be better prepared for future needs," says Ekblom-Kullberg.



The Blood Service hopes to get new blood donors especially among people of African origin who were born in Finland, so-called second-generation Africans. Blood donors must be able to fill in the health questionnaire in Finnish, Swedish or English. Donors who were born or lived in a malarial area under the age of 5 will be tested for malaria antibodies the first time.





2 year old Zainab Mughal is battling neuroblastoma.
To support her through her treatments for this aggressive cancer,
Zainab must receive blood transfusions.

HOWEVER, Zainab cannot receive blood from donors who have the Indian B antigen as she is Indian B antigen-negative. 96% of people have the Indian B antigen. The greatest chance of finding compatible blood for Zainab is in people

of Indian, Pakistani and Iranian heritage.

If you have this heritage, and you are **blood Type O or A**, you can help by donating at any blood drive and telling our staff of your heritage and to **tag your blood donation** so that your blood will receive this additional antigen testing.



Thank you for your attention