CareForum 2022

The WellSky® Conference

Blood and Biotherapies state of the industry & when rare blood requests go overseas

9/11/2022

CareForum 2022

The WellSky® Conference

Today's speakers

Margaret Keller, PhD
Executive Director, National Laboratories, and Senior Director, American Rare Donor Program
American Red Cross

Aaron Winkelmann
Vice President & General Manager
WellSky Blood & Biotherapies

Objectives

- Describe the mission of the American Rare Donor Program
- Define what is “rare”
- Provide statistics about the current state of the program
- Describe the process of requesting and obtaining rare blood products
- Describe what happens when blood cannot be found within the United States
- Use a case to illustrate when rare blood needs go overseas

American Rare Donor Program

- The mission of the American Rare Donor Program (ARDP) is to register, educate and engage rare donors and facilitate identifying blood products of rare phenotypes to meet the needs of alloimmunized patients
- ARDP was formed in 1998 by merging the AABB Rare Donor File and the American Red Cross Rare Donor Registry, both of which were created in the 1960s by Tibor Greenwalt
- There are currently 90 members (87 in US, 3 non-US)

ARDP Rare Donor Criteria

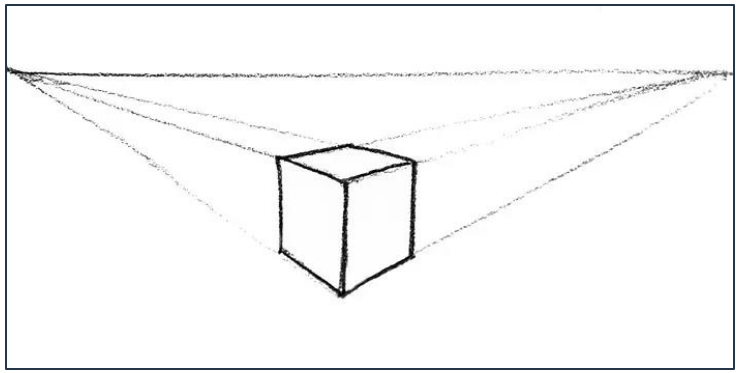
- Negative for high-prevalence antigen, any ABO/Rh
  - < 1/1000

"HiPrev Rare"

- Negative for multiple common antigens
  - Set 1- R_1, R_2, R_0, or rr; K-; AND
    - Fy(a-) or Fy(b-); Jk(a-) or Jk(b-); S- or s-
  - Set 2- R_1, R_2, or rr; K-; Fy(a-b-)

"PhenoRare"

- Homozygous, hemizygous or compound heterozygous for *RHCE* variants
- IgA Deficient

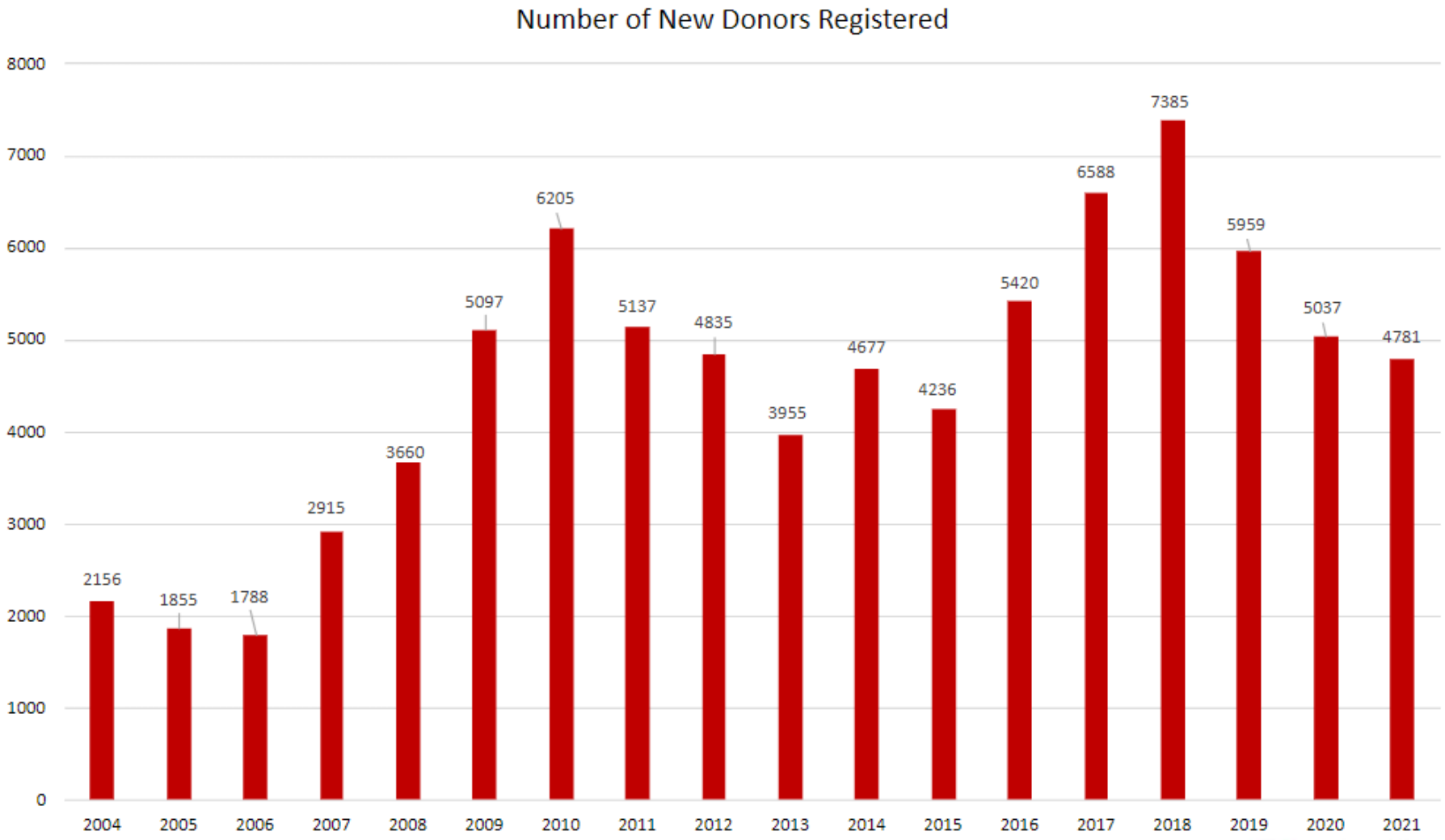


r	D-	c+	e+	C-	E-
R0	D+	c+	e+	C-	E-
R1	D+	c-	e+	C+	E-
R2	D+	c+	e-	C-	E+

AABB IRL Standard

- 5.2 American Rare Donor Program
- All laboratories shall participate in the ARDP system by performing at least one of the following functions on an annual basis:
    1) Ship 15 units to other participating laboratories through the ARDP
    2) Screen at least 1000 donors for high-prevalence antigens
    3) A combination of shipping at least 7 units to other participating laboratories through the ARDP and screening at least 500 donors for high-prevalence antigens
    4) Provide antisera (or for non-collecting facilities, provide resources) to another ARDP member laboratory or IRL for use in screening donors for high- or low-prevalence antigens for the purpose of identifying rare donors
    5) Perform at least one family study to identify rare donors
- 5.2.1 All laboratories shall register donors (as of the effective date of this edition of IRL Standards) with a current or subsequent donation identified as lacking a high prevalence antigen(s).
- 5.2.2 Donor center-based laboratories shall also register at least 10 donors in the ARDP on an annual basis. Standards 5.2 and 5.2.1 applies

Rare donor submissions, 2004-2021

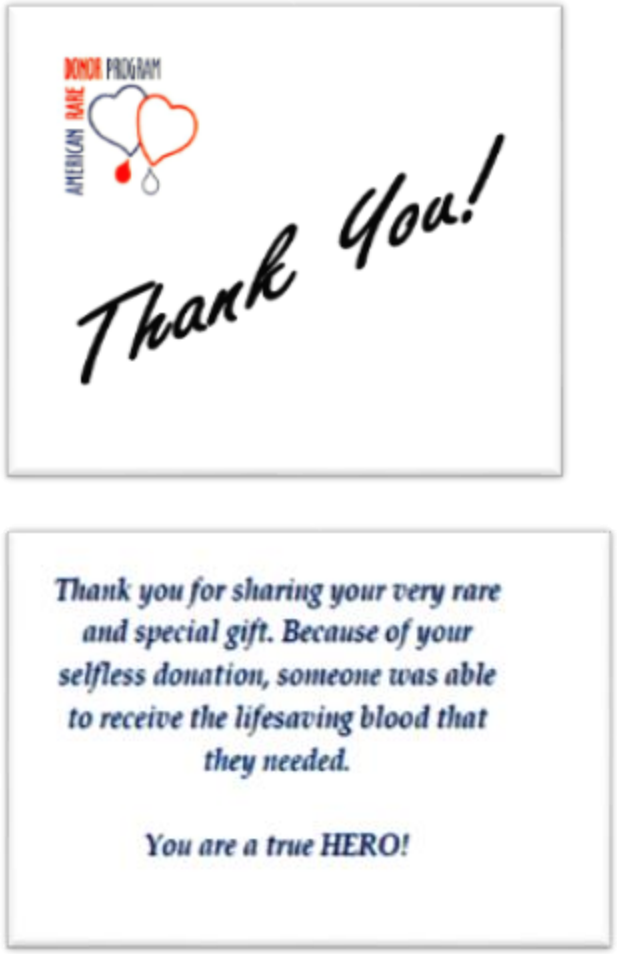


Staying connected with rare donors

Sympathy Card

Cannot Donate Now

TY: Recruited Donor



Growth and retention of rare donors

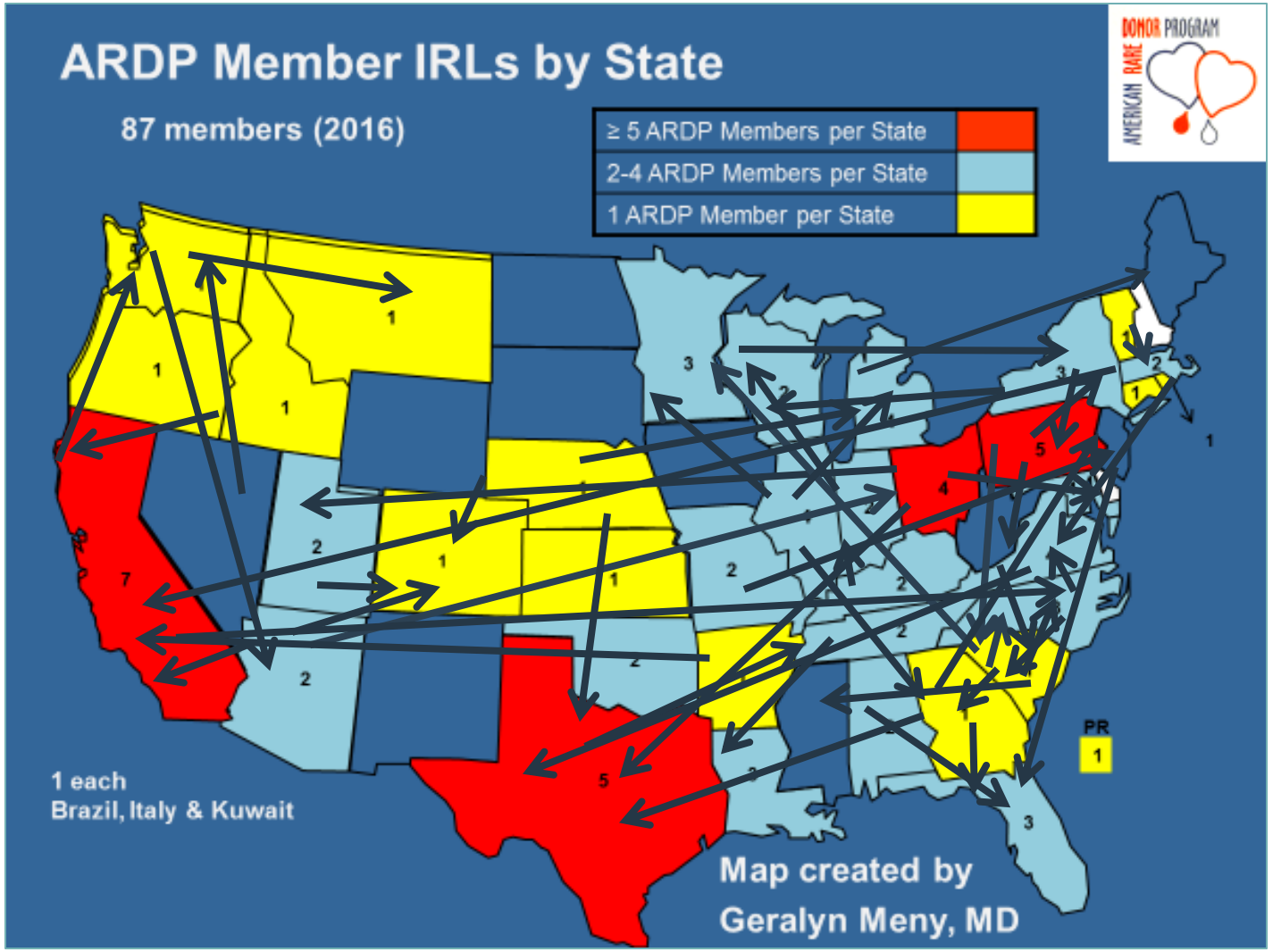
Year	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
# of Active donors	41,003	44,544	47,344	50,919	54,199	58,463	63,970	70,515	76,015	80,941
# of Donors Deactivated	1,282	1,448	1,585	1,864	1,624	1,567	2,688	2,237	2,615	1,837
# of New Donors Registered	5,137	4,835	3,955	4,677	4,236	5,420	6,588	7,385	5,959	5,037
Retention Rate (%)	97	97	97	96	97	97	96	97	97	98

Key Take-aways

- There was a 50% increase in active donors (41,003 in 2011 and 80,941 in 2020)
- An average of 5,323 new donors were registered yearly and an average of 1,875 donors were inactive (97% retention rate)
- The predominant reason a donor was inactive was inaccurate contact information (83%)

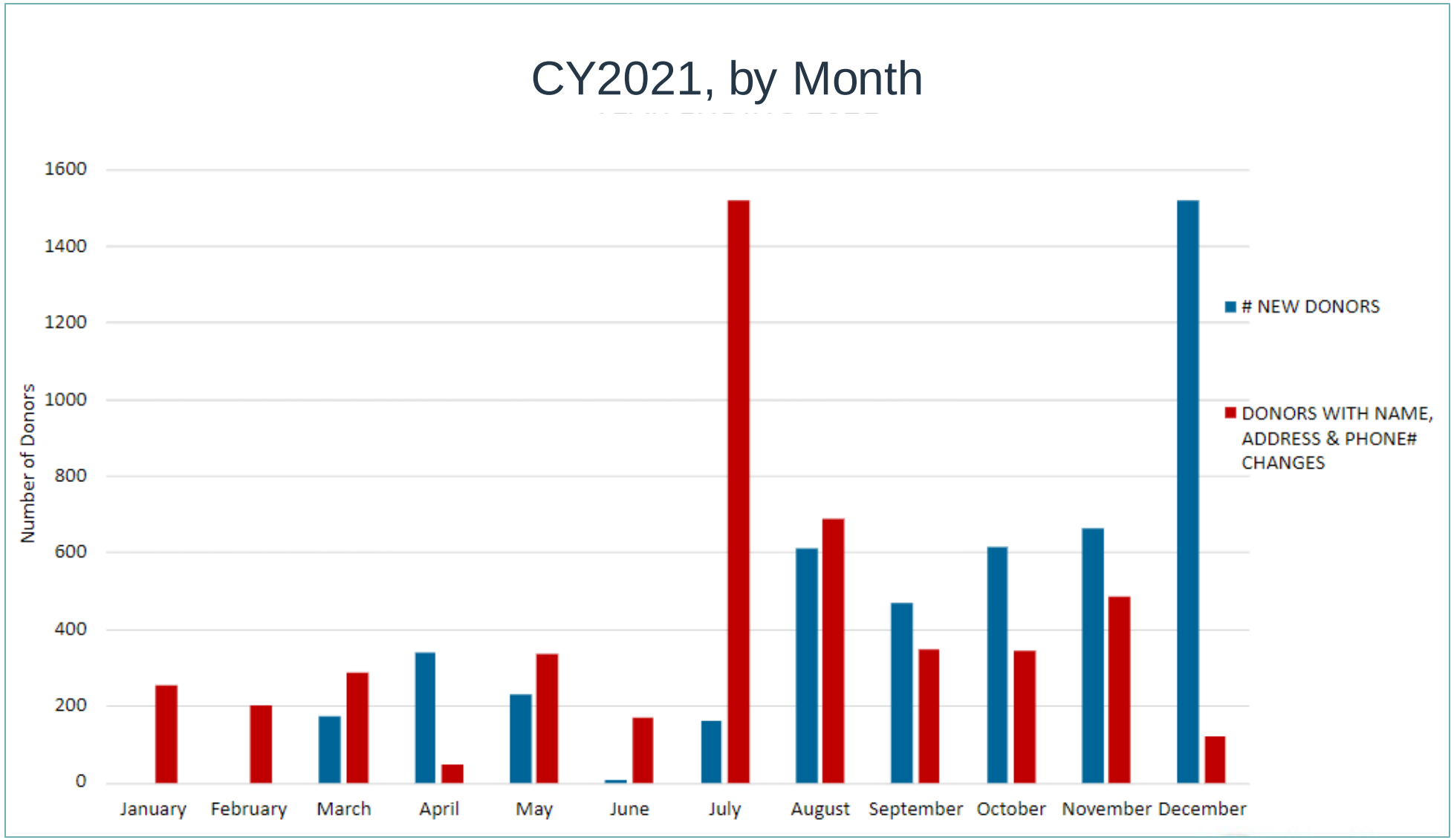
Kavitsky V. *et al., Transfusion* 2021;61(S3):31A

Staying connected: Donor movement

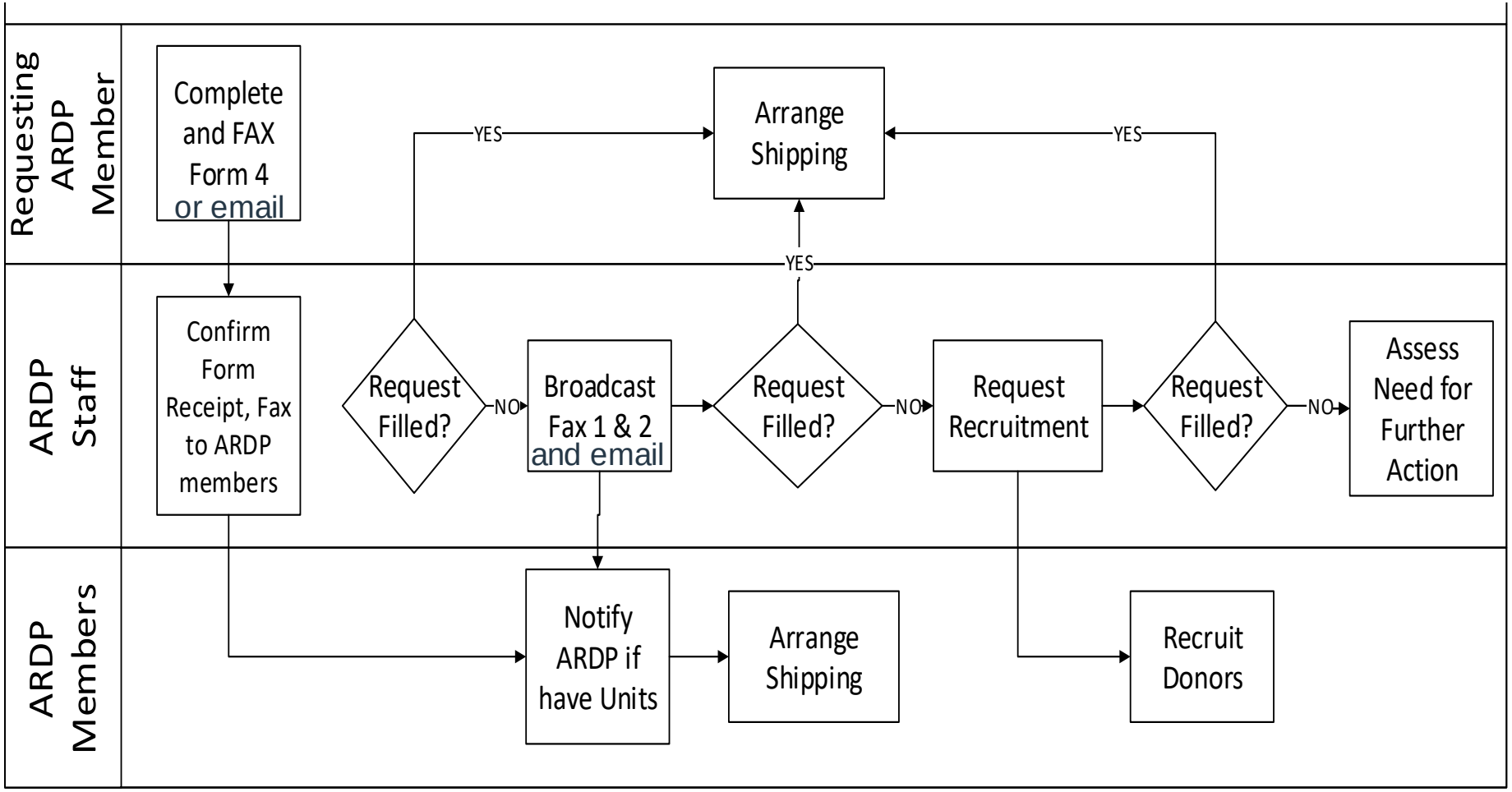


Manigly, M, Fludd, DR, Nance, SJ. Rare Donor Engagement with American Rare Donor Program (ARDP) *Transfusion* 2017;57(S3):225a.

Additions and movements of rare donors

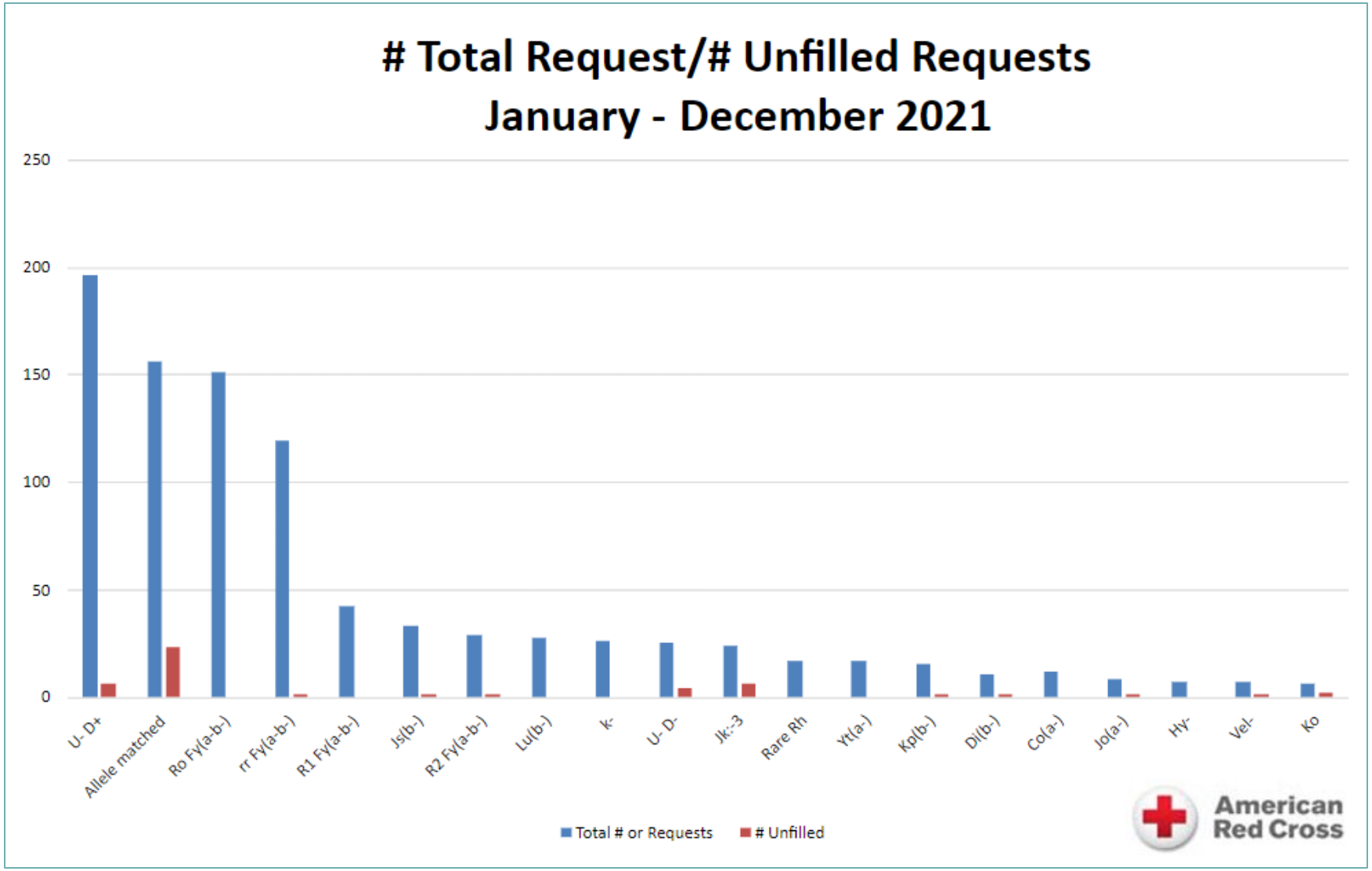


Requesting rare blood products

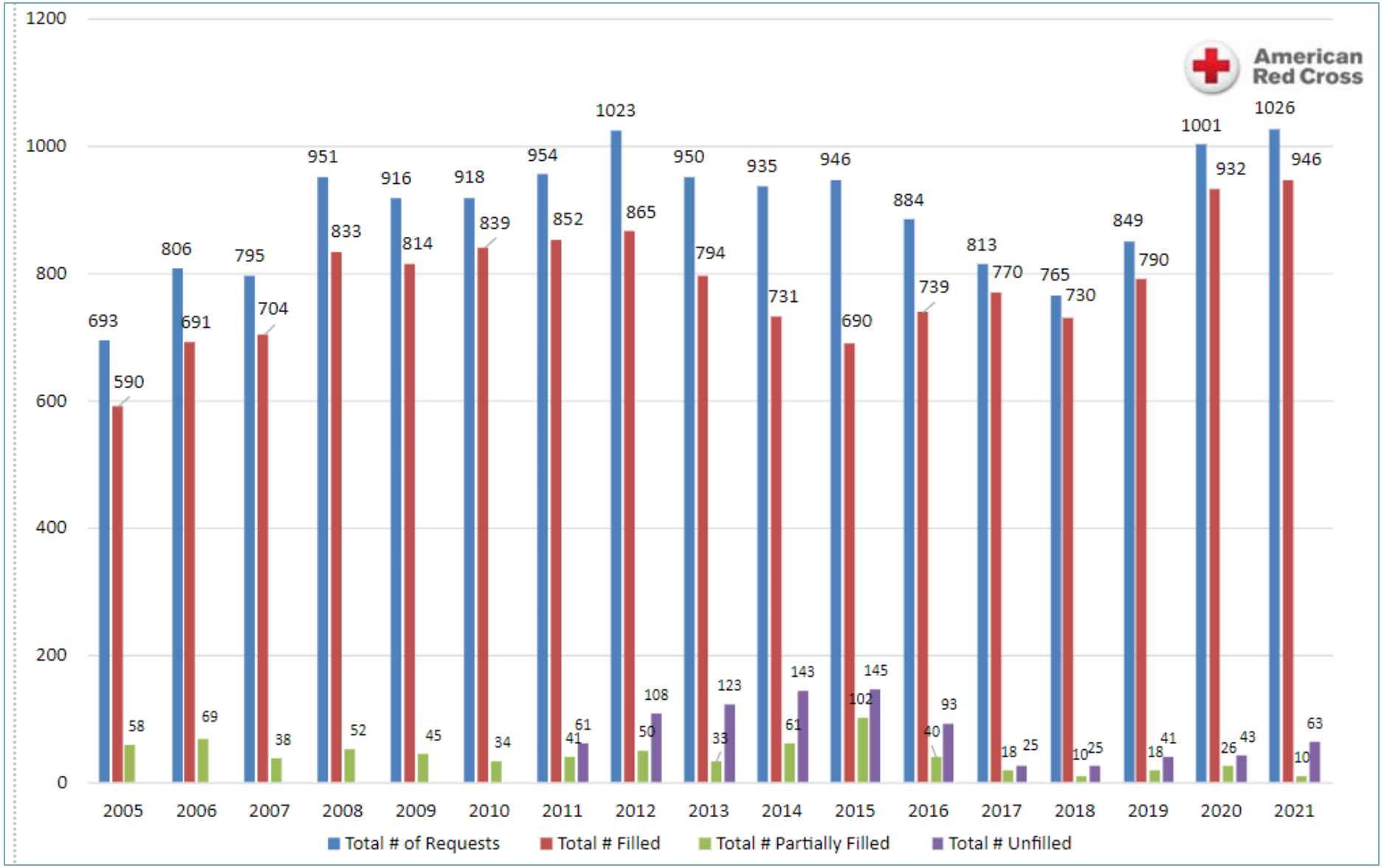


*New web-based portal will allow members to submit requests and respond to open requests as well as register/manage rare donors

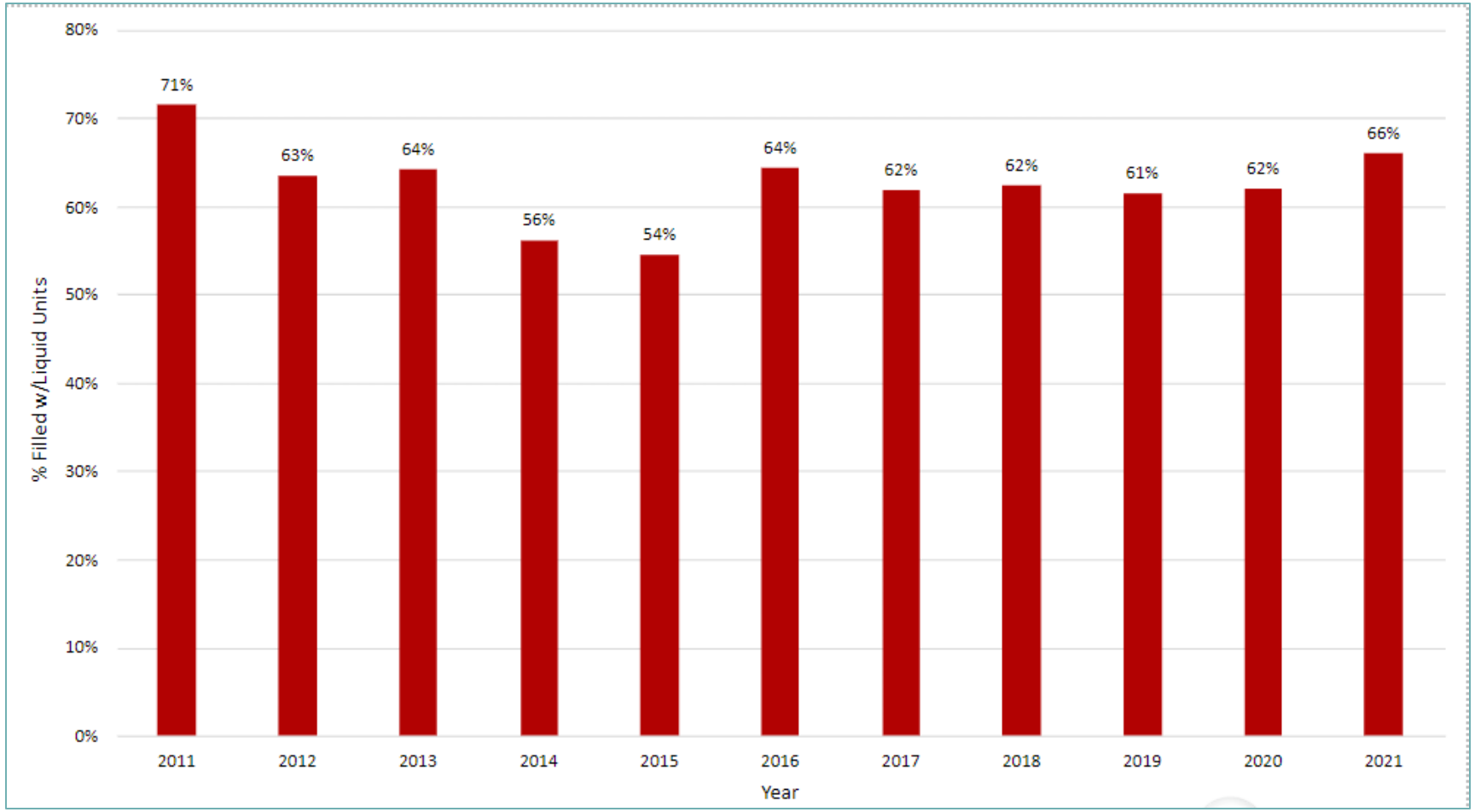
Rare requests, by phenotype and fill rate



Requests and fill rate, 2005-2021



Red cell requests by product status: liquid (vs frozen)

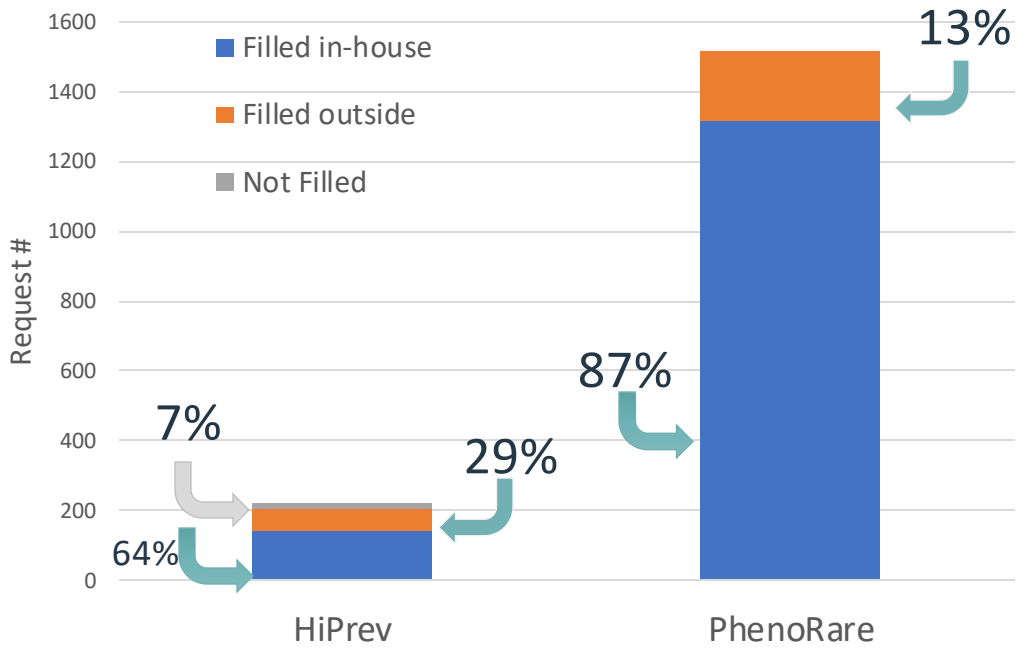


A broader look at rare donors in the US

- Not all rare donors are in the ARDP
- Not all rare blood needs require the ARDP
- A survey was sent to US ARDP members in 2021
  - Rare requests received, HiPrev and PhenoRare
  - Rare requests filled in-house
  - Donors by phenotype

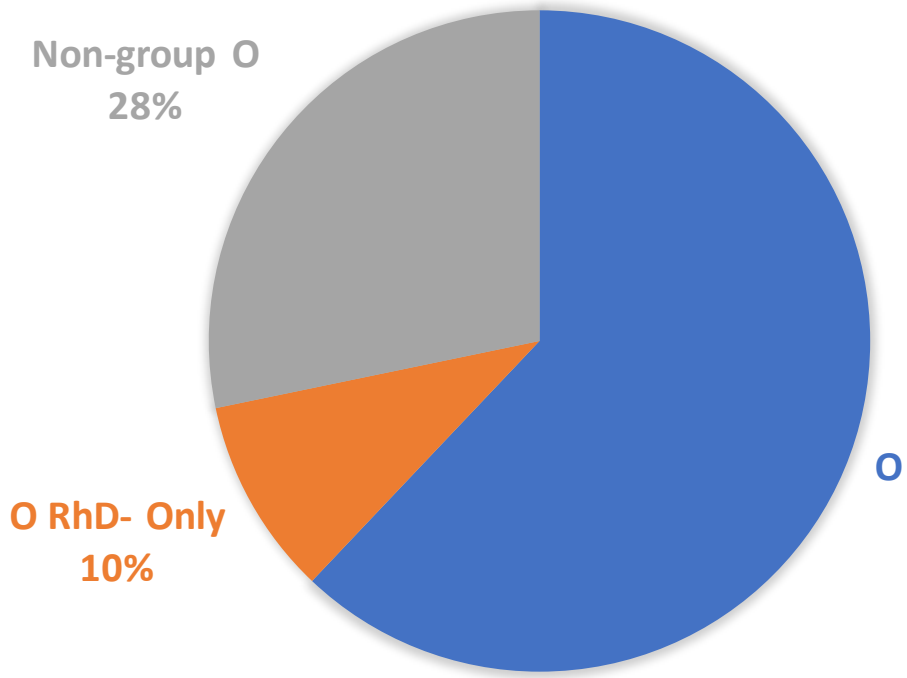
Nance S. *et al., Transfusion* 2021;61(S3):17A.

Many rare blood needs are managed locally



Nance S. *et al.*, *Transfusion* 2021;61(S3):17A.

HiPrev rare donors, by ABO/RH

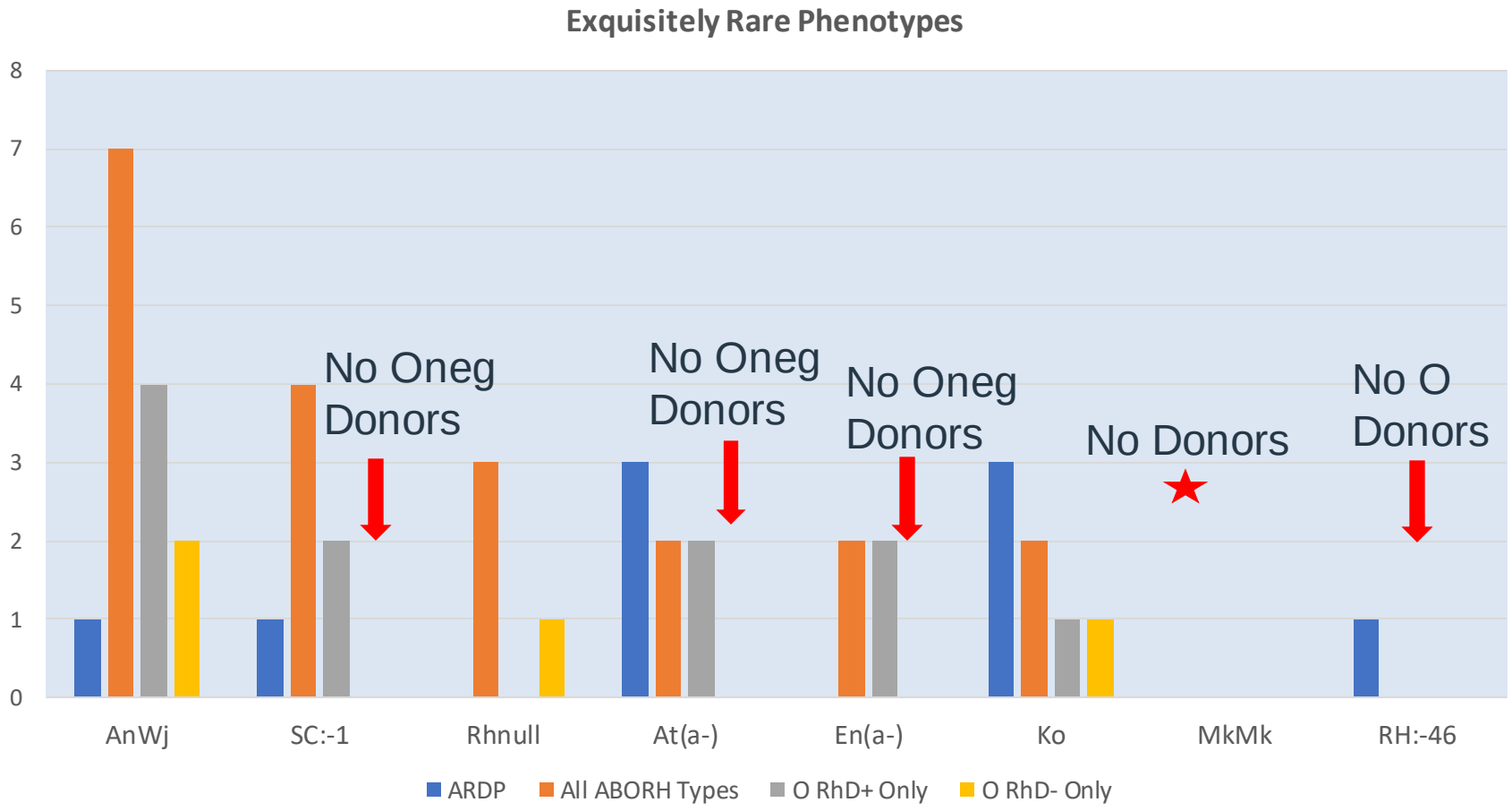


vs 7% of US population

vs 40% of US population

Nance S. *et al., Transfusion* 2021;61(S3):17A.

There's rare, then there's exquisitely rare



Nance S. *et al., Transfusion* 2021;61(S3):17A.

Exquisitely rare donors, as donors and possible future patients

- Exquisitely rare donors are defined as those phenotypes with less than 10 Group O donors registered in the ARDP
- The ARDP member IRL can contact the donor and describe their rare blood type and encourage autologous donation followed by allogeneic donation to build up the number of units of their rare type
- The donor could be able to access their units in the future.
- The IRL can provide donor with customized letter based on template developed by ARDP that they can provide to their physician who can order autologous donation.
- When the donor donates, the IRL can give the manufacturing facility instructions to
  - Freeze the red cells and extend the expiration date to 30 years

When no blood is found in the US…

- ARDP staff schedule a conference call
  - ARDP staff
  - ARDP Medical Directors
  - Requesting Facility
    - Transfusion Medicine Physician, IRL supervisor
  - Hospital Clinical Team
    - Transfusion Medicine Physician, Blood Bank Supervisor
    - May include OB, Neonatologist, Hematologist, Surgeon
  - Agenda
    - Clinical Update
    - ARDP Update
    - Options/Process/Logistics
    - Next Steps

One option: International importation

The International Rare Donor Panel (IRDP) was conceived under a joint World Health Organisation (WHO) and ISBT initiative in 1965 to facilitate the rapid location and exchange of rare blood between countries.

The panel currently contains details of rare donors from 27 contributing countries and also frozen unit inventories from frozen blood banks around the world. The compilation and maintenance of the IRDP is carried out by the Red Cell Reference department of the IBGRL in Bristol, UK.

ISBT International Society of Blood Transfusion

https://www.nhsbt.nhs.uk/ibgrl/services/international-rare-donor-panel/

International import process

- ARDP documents the following:
  - That no or insufficient number of domestic units are available
  - Required testing has been investigated and/or performed (MMA, siblings, autologous donation)
  - Autologous donation has been ruled out
- ARDP works with requesting facility and clinical team to obtain
  - Physician authorization
  - Patient consent
- ARDP files IND (Investigational New Drug) application
- FDA approval process for units collected/tested outside the US

Documenting the search

Documenting ARDP Search of U.S. Facilities for Rare Blood Units Prior to Importing

Patient Information

Patient Name: _____

ABO/Rh type: _____ Phenotype requested: _____

Diagnosis: _____ # of units requested: _____

Physician. Approving request: _____

Antibody(s) identified by (facility): _____

Blood Request Information

Number of matching donors in the ARDP system: _____

Number of units recently provided: _____

Date of and response to ARDP rare FAX: _____

Donor recruitment: _____

_____

Non-ARDP facilities contacted: _____

Autogeneic donation: _____

Patient's siblings:

NOTE: content is excerpted

Investigational New Drug (IND or eIND)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Individual Patient Expanded Access
Investigational New Drug Application (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0814
Expiration Date: May 31, 2022
See PRA Statement on last page.

1. Patient's Initials

2. Date of Submission *(mm/dd/yyyy)*

3.a. Initial Submission

☐ Select this box if this form is an initial submission for an individual patient expanded access IND, and complete only fields 4 through 8, and fields 10 and 11.

3.b. Follow-Up Submission

☐ Select this box if this form accompanies a follow-up submission to an existing individual patient expanded access IND, and complete the items to the right in this section, and fields 8 through 11.

Investigational Drug Name

Physician's IND Number

4. Clinical Information

Indication

Brief Clinical History *(Patient's age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy, reason for request, including an explanation of why the patient lacks other therapeutic options)*

5. Treatment Information

Investigational Drug Name

Name of the entity that will supply the drug *(generally the manufacturer)*

NOTE: content is excerpted

Physician authorization & patient consent

To: ARDP Manager/Director
700 Spring Garden St.
Philadelphia, PA 19123
Fax: (215-451-2538)

I am aware that my patient_____ requires blood products of the rare phenotype. _____ As domestic products are not available, I am aware that international imported products are necessary. I understand that international imported products are considered "untested" and must be utilized for patient _ only and must be tracked for this patient. Units not used for this patient are to be destroyed. I confirm that the above patient and/or the individual with power of attorney, has been notified of the untested nature of the international imported products.

The transfusion need for patient_____ is expected to be_____ per _____

This product should be hand delivered to:
List specific blood bank contact name
Name:
Address:
Floor and room number:
Cell phone number:

Physician _____

Date _____

American Rare Donor Program/American Red Cross
700 Spring Garden Street
Philadelphia, PA 19123

CONSENT FORM
Patient Consent for Importing Rare Blood Products from International Locations

PURPOSE

We ask you to give consent for transfusion of rare blood products from international locations for your use. By importing these products, we hope to support your care by providing blood products prescribed by your physician. Hospital staff will be provided this form for consent purposes. The American Rare Donor Program staff and the American Red Cross are responsible to search for this rare blood product internationally.

PROCEDURES
If you provide consent, the American Rare Donor Program and American Red Cross staff will search international facilities for rare blood products not available in the USA in sufficient quantity to support your transfusion needs. The American Rare Donor Program and American Red Cross staff will have access to the data to support your rare blood transfusion needs. Results of obtaining blood for you and other patients for whom rare blood is not available in the USA will be presented in a summary report with identifying information anonymized for presentation.

RISKS AND BENEFITS
Rare bloods imported from international sources have donor qualification criteria as determined by each country including the blood donation questionnaire, infectious disease specific testing and blood test manufacturers. While this rare blood will meet the release criteria of the country of export, it should be considered not tested by FDA requirements. Importation from international locations carries the risk of transportation delays and blood product breakage, possibly resulting in discard of the rare blood. This would result in no blood product being available for you.
If you decline consent, rare blood products may not be available for transfusion.

ALTERNATIVE TO PARTICIPATION
If you decline this rare blood imported from international sources, blood products may not be available for transfusion and you may require medical management for blood transfusion needs.

What if I am injured by the transfusion of imported blood products?
If you suffer physical injury as a direct result of your participation in this activity, the facility named below will assume responsibility for making immediate medical care available to you. There is no provision for monetary compensation to you at the expense of the facility named below or the American Red Cross or the American Rare Donor Program for incidences such as lost wages, disability, injury, or discomfort resulting from such physical injury. To contact us regarding further information concerning treatment and payment of medical expenses in the event of an injury, please see the following contact information.

NOTE: content is excerpted

Other required information and considerations

- Infectious Disease Testing
- Photo of Unit
- Transport
  - Courier, Broker
  - Timing
- Ship directly to the hospital
- Planning for how to receive the unit
  - Labeling, computer system etc.

When Rare Blood Requests Go Overseas

Victoria Kavitsky[1], BS, Margaret A Keller[1,2], PhD, Joan L. Maurer[1], BS, SBB(ASCP), Dexter A. Facey[1], MBA, MT and Sandra J. Nance[1], MS, MASCP, MT(ASCP) SBB
(1)American Rare Donor Program, Philadelphia, PA,
(2) American Red Cross National Laboratories, Philadelphia, PA

American Red Cross

DONOR PROGRAM AMERICAN RARE

DONOR PROGRAM AMERICAN RARE

- We performed a query of the ARDP donor database from CY2015 through CY2020.
  - Each request was evaluated for phenotype, # of units, and whether the request was filled or cancelled
  - The phenotypes were compared against
    - the number of donors in the ARDP
    - the number of donors globally, based on a recent survey conducted by the ISBT Working Party on Rare Donors

Kavitsky V. *et al., Transfusion* 2021;61(S3):80A

Rare requests, CY2015-CY2020

Of the 5,303 requests received by ARDP, 32 units were sourced internationally for 14 requests for red blood cell units for 10 patients

- All but one of the phenotypes include a high prevalence antigen

  Half were for phenotypes with no donors registered
- En(a-) units were imported for 2 patients when only 8 donors were reported globally
- Nine countries supplied units for these 10 patients
- Japan, Switzerland, Canada and Spain supplied units for more than 1 patient and 2 countries supplying multiple phenotypes

Kavitsky V. *et al., Transfusion* 2021;61(S3):80A

Imports, CY2015-2020

ABO/Rh	Phenotype	# of Requests	# of Units Requested	# of US Donors Registered*	# of Global Donors **	Source Country
O pos	D--	1	2	7	136	Japan (2)
O pos	D-- K-	2	3	7		Japan (3)
O neg	E- c- K- Jk(a-)	1	1	15	N/A	Switzerland (1)
O pos	En(a-)	2	3	0	8	Canada (1) Qatar (1)
B pos	En(a-)	1	2	0	N/A	Canada (2)
A pos	In(b-) E-	2	11	0	N/A	Australia (1) UK (2)
O neg	JK: -3	2	4	0	285	Finland (6)
O pos	Ko- Fy(b-) Jk(a-) S-	1	2	0	116	Japan (2)
A pos	Vel- C^{W}-	1	12	56	N/A	Spain (2) Switzerland (2)
O pos	Vel- E-	1	6	65	N/A	France (3) Spain (2) Switzerland (2)

Other outcomes of international searches

- Three patient requests for At(a-) units lacking 2 to 5 common antigens
  - At(a-) unit was found in the UK
  - At(a-) unit and an AUG_{null} unit were found in France
  - The requests were cancelled by the treating hospital's clinical team
- Request for 2 units lacking AnWj and K antigens
  - One unit was identified in the UK
  - Instead of importing that unit, an *In(Lu)* phenotype unit was sourced from the US
- A request for two E- hr^S- RH allele-matched units
  - A unit was unable to be sourced domestically or internationally

Case of patient with anti-Jk3

- 85 year old woman
- Myelodysplastic syndrome
- Group O RhD negative
- Hb 6.3g/dL
- Requiring long-term transfusion support using Jk(a-b-) units

The Kidd Blood Group System

- ISBT symbol: JK
- ISBT number: 009
- Gene: SLC14A1 (Solute carrier family 14, member 1), encodes urea transporter
- Number of Kidd antigens: 3
  - Jk^a, Jk^b (antithetical antigens)
  - Jk3
- Anti-Jk3 seen in patients with Jk(a-b-) or null phenotype
  - Null phenotype is recessive and caused by variety of mutations
  - Anti-Jk3 associated with hemolytic transfusion reactions and hemolytic disease of the fetus and newborn (HDFN)

Jk(a-b-) phenotype

- Jk(a-b-) is more common in Finnish and Polynesians
- Finnish Red Cross has 200 rare donors in their registry
- They had screened 99,000 donors in 2009 on PK7300 and found 22 new Jk(a-b-) donors
- At the time of the request, they had
  - 23 active Jk(a-b-) donors
  - 19 frozen Jk(a-b-) units
- They made five shipments of 8 units from 5 donors
- Units were both fresh and thawed ACP215 units
- Several shipping challenges were experienced including a lost shipment

Sareneva IM *et al. Vox Sang* 2021

BLOOD COMPONENT	RED CELLS, CRYOPRESERVED, THAWED
UNIT NUMBER	Y00031313835200D
DATE OF DONATION	25.4.2013
DATE OF THAWING	22.3.2021
DATE OF SHIPMENT	23.3.2021

CERTIFICATE

Blood is exclusively collected from voluntary and non remunerated donors in Finland by the Finnish Red Cross Blood Service (FRC BS) regional and local centres, which are approved and inspected by Finnish Medicines Agency (license number Dnro 2562/20.20.01/2012, current license number LL Dnro FIMEA/2020/003510).

Donor selection, donor examination, blood collection and processing are done in compliance with

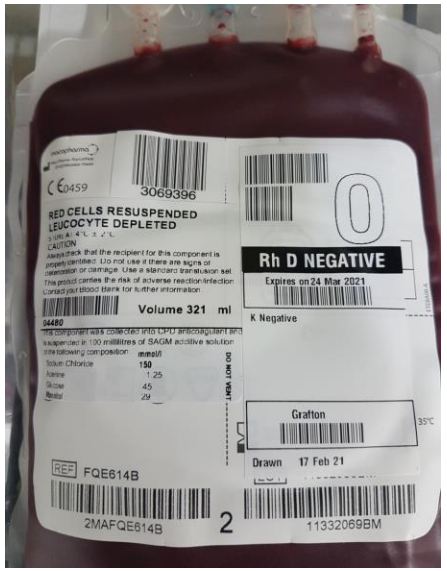
- Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003, setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC
- Commission Directive 2004/33/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.
- Act on Blood Service Activities (197/2005)
- National regulations of the Ministry of Social Affairs and Health concerning Blood Service Activities (258/2006)
- Guide to the preparation, use and quality assurance of blood components. Strasbourg: Council of Europe, current edition. Council of Europe Recommendation R(95)15.

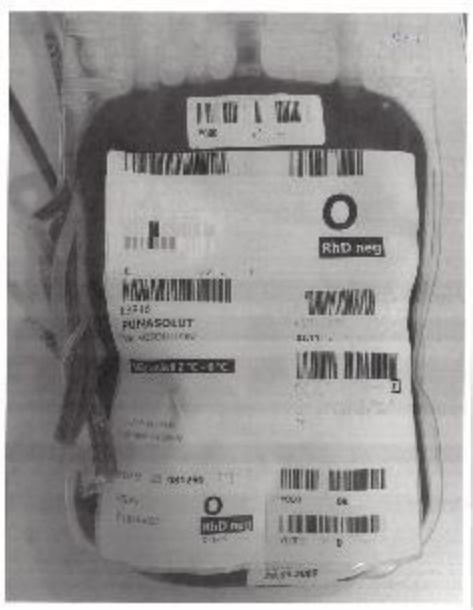
The data of the blood donation can be found and communicated due to an identification number (donation number) printed on the label of the bag.

Donated blood has been controlled and complies with the following criteria:

- negative for HBsAg (detection level < 0,5 IU/ml HB antigen)
- negative for HIV-antigen, anti-HIV 1 and 2 antibodies
- negative for anti-HCV antibodies
- negative for Syphilis marker
- non-reactive for HCV-RNA (detection level < 5000 IU/ml/donation)
- non-reactive for HIV-1-RNA (detection level < 10^4 IU/ml/donation)
- non-reactive for HBV-DNA

O Neg Jk(a-b-)





Rare donors: Challenges and opportunities

- Challenges
  - Admixture and high-prevalence antigen negative phenotypes
  - Logistics
  - Product Shelf-life
- Opportunities
  - Social media
  - Population-based genomic testing

Conclusions

- The American Rare Donor Program works with its members to fulfill the rare blood needs of alloimmunized patients
- Member centers screen blood donors and submit rare donors to the program
- ARDP connects with donors and updates their location and may connect them to a new donor center, if applicable.
- If ARDP cannot source units from within the US, we work with the clinical team to evaluate other options including international importation
- There is a complex process that is followed to import blood from outside of the US that involves patient consent, physician authorization, and FDA approval
- The number of rare donors in the US is growing, but so too is the number of requests for rare blood submitted to the ARDP

CareForum 2022

The WellSky® Conference

Thank you.

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Executive, National Laboratories
American Red Cross Biomedical Services
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Learn more about WellSky Blood & Biotherapies

Request a consultation today!

WellSky