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Integration of red cell genotyping into the blood supply chain: a population-based study

Willy A Flegel, MD, **Jerome L Gottschall, MD**, and **Gregory A Denomme, PhD**

Department of Transfusion Medicine, Clinical Center, National Institutes of Health, Bethesda, MD, Department of Pathology, Medical College of Wisconsin, and Diagnostic Laboratories, BloodCenter of Wisconsin, Milwaukee, WI, USA

Abstract

Background—When problems with compatibility arise, transfusion services often perform time-consuming serologic testing to locate antigen-negative red cell units for safe transfusion. New technologies enabled red cell genotyping for all clinically relevant blood group antigens. We performed mass-scale genotyping and provided access to a large red cell database to meet the demand for antigen-negative red cell units beyond ABO and Rh.

Methods—A red cell genotype database was established in 2010. Hospitals were given online access to a web-based antigen query portal in 2013 to find antigen-negative units in their inventories.

Findings—Genotype data were analyzed for 43,066 blood donors covering a set of 42 clinically relevant red cell antigens. Requests were filled for 5661 of 5672 patient encounters (99.8%) requiring antigen-negative red cell units in a multi-ethnic and multi-racial population. Red cell genotyping met the demand for antigen-negative blood in 5339 of 5672 (95%) patient encounters, while 333 remaining requests were filled using serologic data. In a pilot phase, seven community and rural transfusion services searched their local inventories using an online antigen query portal.

Interpretation—Red cell genotyping has the potential to transform the way antigen-negative red cell units are provided. An antigen query portal may reduce the need to ship blood or perform serologic screening. The wealth of genotype data, easily accessible online, facilitates the supply of

Address for correspondence: Gregory A Denomme, PhD, FCSMLS(D), Diagnostic Laboratories, BloodCenter of Wisconsin, 638 N 18th Street, P.O. Box 2178, Milwaukee, WI 53201-2178, phone: 414-937-6440, fax: 414-937-6404, greg.denomme@bcw.edu.

Authorship contribution: GAD coordinated red cell genotyping, and collected and summarized the data. JLG contributed to the content of the discussion. GAD and WAF conceptualized the study, analyzed the data, and wrote the manuscript.

Conflict of interest disclosure: GAD is the inventor of European patents on red cell genotyping owned by Canadian Blood Services. WAF & JLG do not have a conflict of interest relevant to this article.

affordable antigen-negative red cell units for patient safety. Physicians may recognize these new efficiencies for patient transfusion support.

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Introduction

Blood group antigens are polymorphic, and alloimmunization to these antigens complicates red cell transfusion and clinical care during pregnancy. Patients who are alloimmunized require antigen-negative red cell units. In chronically transfused patients, matching of the antigens between the red cell unit and the patient, in the absence of alloantibodies, can be an effective way to limit alloimmunization and avoid acute or delayed hemolytic transfusion reactions.[1–4] In the setting of stem cell therapy, delayed red cell engraftment complications due to alloimmunization can be obviated.[5–7] This prophylactic matching can be accomplished by serologic testing[8,9] or by red cell genotype ‘dry’ matching.[10]

When problems with compatibility beyond ABO and Rh arise, tertiary care centers traditionally search their inventories and perform time-consuming serologic testing on site to locate antigen-negative red cell units. The skills and resources required are beyond the capability of smaller hospitals and often of large hospital transfusion services. Then, the responsibility for locating antigen-negative red cell units falls on the regional blood center which can provide an inventory encompassing the entire supply chain from blood centers to transfusion institutions.

For 20 years, blood centers have used molecular techniques to screen blood for blood-borne infectious disease markers. More recently, similar molecular techniques have become available for red cell genotyping as the molecular basis has been established for the clinically relevant blood group antigens.[11–12] Methods vary in complexity and feasibility for high-throughput application. Several available molecular methods can identify a greater number of antigens than can be determined by any blood group serology.[10,13,14] Red cell genotyping provides an opportunity to integrate antigen testing into other molecular testing of blood donors,[15,16] and has been applied to a limited degree outside of the US for routine typing and labeling of blood since 2002.[17]

Several models of mass-scale donor red cell genotyping have been published since 2008. Notably, a multi-center study[18,19] reported a ‘fill-fraction’ exceeding 90% for common antigen-negative requests. Red cell genotyping involving 3400 to more than 21,000 donors have been also reported[17,20–22] and may be more wide-spread among large blood centers than presently reflected in the literature. The basic academic research on molecular immunohematology, which began around 1990 and culminated approximately 10 years ago, is rendered into practice today.

Red cell genotyping could contribute to an efficient supply of antigen-negative red cell units when performed by mass-scale testing. We implemented a high-throughput red cell genotyping process and integrated the data with the inventory database throughout the blood

supply chain. We monitored the ability to meet the demand for compatible blood over 3 years.

Materials and Methods

Blood donor inclusion criteria

Two groups of whole blood donors were included in the study. All self-declared African American, Asian, Hispanic, and Native American blood donors were eligible regardless of their ABO and Rh type or history of donation. In addition, blood donors who were group O, A and B, regardless of the Rh phenotype, were eligible for inclusion only if they had a history of at least 3 donations in the previous 3 years, with one donation in the previous 12 months at BloodCenter of Wisconsin. The blood donors gave informed consent, and the BloodCenter of Wisconsin's Institutional Review Board approved the retrospective red cell phenotype and genotype review (BCW12-27).

For the purposes of this study, we analyzed all blood donor samples collected in 4 years from 2010 to 2013, antigen-negative red cell units supplied from 2011 to 2013, and blood requests filled using an online web-based portal from May to December 2013.

Blood group alleles and predicted phenotypes

Red cell genotyping was done using a nanofluidic microarray system as described previously.[23,24] Thirty-two single nucleotide polymorphisms (SNPs) predicted 42 blood group antigens[24]: C, E, c, e, V, hr^S, VS, hr^B, Crawford; M, N, S, s, U; Lu^a, Lu^b, Lu8, Lu14; K, k, Kp^a, Kp^b, Js^a, Js^b; Fy^a, Fy^b; Jk^a, Jk^b, Jk3; Di^a, Di^b; Yt^a, Yt^b; Sc1, Sc2; Do^a, Do^b, Hy, Jo^a; Co^a, Co^b; and Cr^a. Specific combinations of SNPs predicted C, c, e, U, Fyb and Jk variant blood group antigens.[25–32] Another 14 antigens were identified by phenotyping: He, 'N', P1, P^k, f, C^w, Go^a, Le^a, Le^b, Wr^a, Xg^a, H, Tc^a, and Vel.

Red cell genotype database

Genotype results were electronically transferred to a database where a computer algorithm translated the genotype data into alleles with predicted blood group phenotypes. The data were parsed with blood donor demographic information and existing serologic phenotypes. Red cell genotypes could be displayed with historical genotypes (predicted phenotypes) and serologic phenotypes using a standard blood establishment computer system (LifeTrak; Mediware Information Systems, Oak Brook, IL).

Antigen query portal

Seven hospital-based transfusion services were given access to the BloodCenter of Wisconsin's secure online web-based antigen query portal on May 1, 2013. A set of 14 common and clinically relevant antigens could be queried: C, E, c, e, C^w, M, N, S, s, K, Fy^a, Fy^b, Jk^a, and Jk^b, which was arranged on the basis of the frequency of requests and the expected prevalence of the antigens in the generally small inventories of transfusion services. The antigen query portal was designed to transmit blood group antigen information associated with the red cell unit using its identification number (ISBT 128; International

Council for Commonality in Blood Banking Automation, San Bernardino, CA) without personal health information.

The operator at the transfusion service scanned the red cell unit identification numbers into an electronic file, and indicated the antigen requirements and number of units requested. The blood center output file returned to the transfusion service displayed the red cell unit identification numbers of the oldest units in their inventory matching the request. The system provided an option to electronically forward unfilled or partially filled requests to BloodCenter of Wisconsin for shipment of compatible blood. Prior to transfusion, all red cell units identified by their historical phenotype or genotype were confirmed by serology either at the blood center or transfusion service. All transfusion services ensured that the antigen-negative red cell units were crossmatch-compatible in accordance with standard operating procedures.

Patient encounter

For the purpose of this study, a blood center-patient encounter was defined as an event when one or more red cell units were requested for a patient at a specific time. Requests for a patient could come from different hospitals over time.

Role of the funding sources

The work was supported by unrestricted grants from BloodCenter of Wisconsin Diagnostic Laboratories Strategic Initiative and the Intramural Research Program of the NIH Clinical Center. The funding programs did not participate in the study design, collection, analysis, interpretation, or in writing the report. GAD had access to the original data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

A red cell database was established at our blood center on July 17, 2010 encompassing donors genotyped from January 2, 2010. It comprised 42 blood group antigens that were genotyped and an additional 14 antigens that continued to be tested by serology.[24] We described the database for blood donor antigens and monitored the ability to meet the demand for antigen-negative red cell units over 3 years from January 1, 2011 to December 31, 2013.

Blood donor antigen database

No more than 28 antigens were known by phenotype for any blood donor before 2010, representing the serologic phenotype database accumulated since 1985 (Table 1). In the 4 years since, at least 36 antigens were determined in 41,280 of 43,066 (96%) red cell genotyped donors, with a minimum of 26 antigens for all genotyped donors. Red cell genotyping generated nearly 1.67 million results with a total of 728,482 antigen-negative genotypes obtained in 4 years compared to 133,086 antigen-negative phenotypes accumulated over nearly 3 decades of testing. The phenotype-genotype concordance rates ranged from 80.7% to 100% (median 99.6%, mean 98.0%).[24] It was not possible to calculate

the negative predictive value because discrepant results were not entered into our clinical database.

Antigen-negative blood supply

The ability to complete antigen-negative red cell unit requests was examined for 3 years subsequent to the establishment of the red cell genotype database (Table 2).[33] Using the combined genotype and serologic phenotype information, we identified 15,072 of the 15,106 (99.8%) red cell units needed for 5661 of 5672 (99.8%) patient encounters (Table 2). Requests ranged from 1 to 10 antigens per red cell unit. There were no cases of acute or delayed hemolytic transfusion reactions recognized due to the antigen requirements specified. No adverse reactions or alloimmunizations due to unmatched antigens were reported to the blood center. From 2011 to 2013, we thawed and deglycerolized 83 of 15,106 (0.6%) frozen units for patients in hospitals served by BloodCenter of Wisconsin, and supplied 134 (0.9%) red cell units that were defined as ‘rare’ by the American Rare Donor Program (ARDP)[33] to 25 patients. Only 34 red cell units had to be imported from other blood centers for 11 patients, because the antigen-negative red cell units were not readily available at the time of the request. These data represented the complete antigen-negative red cell unit supply for the hospitals served by our blood center.

Using the 42 antigens represented in our red cell genotype database, we were able to fill 14,357 of 15,106 (95%) requests for antigen-negative red cell units from hospitals served by BloodCenter of Wisconsin (Table 2). Only 749 of 15,106 (5.0%) red cell units, representing 333 of 5672 (5.9%) patient encounters, required serologic phenotyping (Table 3), because the antigens involved are not currently part of the red cell genotyping process. For hospitals elsewhere in the US, the red cell genotype database could fill 1080 of 1199 (90.8%) requests (Table 2), with another 198 units provided by serologic phenotyping (Table 3).

Screening red cell units by serology for any of the 42 antigens was phased out as red cell genotyping data was accrued, and has not been used since 2011. We continued to use serologic phenotype data for the steadily decreasing number of blood donors who remained active and were not red cell genotyped.

Antigen query portal

A web-based interface was established to allow hospital-based transfusion services to search their own inventories for antigen-negative red cell units. They were given access to query for those antigen-negative red cell units most likely present in their inventories based on the small size of their inventories. One hospital participated in the pilot project and six community hospitals joined after the query portal was implemented. The hospitals represented facilities with 25 to 201 beds, with 4 hospitals located more than 140 miles from BloodCenter of Wisconsin. For the eight months ending in 2013, a total of 71 red cell units were found in the local hospital inventories for 52 requests from seven hospitals. Beginning in 2014, the program was offered to all transfusion services within our supply chain.

Patient encounters

We had 5672 patient encounters from hospitals served by our blood center (Table 2). There were 1623 patients involved in 3 years (Table 4). The number of patient encounters ranged from 1 to 64 and their distribution was highly skewed (median 1.5, 75%-percentile 2.5, mean 3.49), because 877 patients were encountered only once.

Discussion

When antigen-negative red cell units are needed, blood centers commonly screen red cell units by serologic methods. This time-consuming and labor-intensive process was abandoned by our blood service in 2011 after implementation of red cell genotyping, which transformed the supply of antigen-negative red cell units at our blood center. Larger numbers of red cell units with much more antigen data were made available using red cell genotyping, when compared with conventional serologic phenotyping (Table 1). With 4 years of high-throughput red cell genotyping, we achieved a 5-fold increase in available antigen information over that obtained in almost 30 years of phenotyping.

Our database, including genotype and residual phenotype data, ensured that enough red cell units were available to meet the demand for compatible blood in our region 99.8% of the time. In the remaining 11 of 5672 (0.2%) cases requiring 34 red cell units, providing antigen-negative red cell units was challenging because red cell units were retrieved from other blood centers, a costly and time-consuming process that can be further minimized with sufficiently large genotype databases. Our genotype database included all non-Caucasian blood donors to provide antigen-negative red cell units to patients with sickle cell disease on chronic transfusion programs and to freeze red cell units with rare blood types for long-term storage. Extending the network of red cell genotyped blood to other blood centers will facilitate rapid access to compatible blood for safer transfusions in regions beyond our catchment area. Virtual networks of red cell genotyped donor databases, which can be web-based ‘in the cloud’, will eventually complement previously proposed centralized recipient databases.[34] At the time we implemented red cell genotyping, there was no FDA approved test available in the US. However, the FDA approved a comparable test in 2014 (PreciseType HEA; Immucor, Norcross, GA). Currently, there are no publications of studies which use sequencing. In the future, red cell genotype databases from many blood centers could become a virtual inventory made available for querying compatible blood.

Patients with alloantibodies require blood that is negative for the cognate antigen for safe transfusion. Red cell genotyping is a technology whereby DNA-based techniques are used to evaluate genes for the particular single and multiple nucleotide substitutions, deletions, insertions, and gene conversions that determine the expression of red cell antigens. Red cell genotyping, as a new routine technology at the blood center, increases the availability of blood typed for clinically relevant blood group antigens. This study was concluded in 2013 and described the initial 4 years of applying mass-scale genotype screening that has been instituted as a routine process at BloodCenter of Wisconsin in 2010 and is continuing since as described previously.[24]

The identification of antibodies to distinct antigens of high-prevalence decreases the quality of transfusion support in patients;[35] blood donor screening using molecular methods resolved this supply issue by 2008.[20] Our red cell genotyping covered three of the most frequently involved high prevalence antigens, Kp^b, Lu^b, and Yt^a. The fourth antigen, Vel, could not be genotyped at the inception of our program because its gene was only identified in 2013.[36–38] All antigen-negative red cell units provided on the basis of a phenotype (Table 2) could be determined by red cell genotyping. Based on their clinical relevance in our patient population, the high-prevalence Vel antigen and the C^w antigen are the next targets to be included in our red cell genotyping process.

Access to red cell genotype information for blood in hospital inventories via an online web-based antigen query portal may provide efficiencies in the supply of antigen-negative red cell units which can be captured by any participating hospital. The ability to search and utilize hospital inventories avoids delays associated with shipping blood, reduces the number of blood group phenotypings performed at transfusions services, and limits the necessity to ship antigen-negative red cell units from blood centers. However, the traditional blood supply chain may prevail at many blood centers for a while. Physicians should be made aware of the new efficiencies for patient transfusion support because they control the demand for antigen-negative red cell units.

The cost and return on investment of red cell genotyping requires careful consideration. Genotyping enables a mass-scale approach to red cell antigen matching that cannot be offered by any phenotyping alone. Since our red cell genotyping is a seamless end-to-end process within the blood center,[24] the efficiencies and impact on the movement of red cell units, database value, and low hands-on-time can be included in cost evaluations. A cost efficacy analysis[39] should capture the benefit to the patient and long-term value of maintaining sufficient red cell units with a genotype, as compared to the costs of establishing the process initially. Red cell genotyping of blood donors on a mass-scale, combined with real-time inventories shared between blood centers and transfusion services, could provide a supply of antigen-negative red cell units at a level that cannot technically and economically be attained using current database structures and conventional phenotyping.

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GAD is the inventor of European patents on red cell genotyping owned by Canadian Blood Services. WAF & JLG do not have a conflict of interest relevant to this article.

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Research in context

Evidence before this study

A literature search revealed more than 10 studies detailing red cell genotyping among blood donors. No publication documented the extent to which the accrued data of red cell genotypes enabled the supply of antigen-negative red cell units for an entire state with a large number of hospitals. There was no published web-based portal allowing hospitals to identify red cell units in their inventory using an online search of the blood center's red cell genotype database.

Added value of this study

We showed that blood donor genotype data covering a set of 42 clinically relevant red cell antigens represented 1,667,026 data points including 728,482 antigen-negative genotypes. We were able to phase out serologic screening of red cell units for any of these antigens within one year after red cell genotyping began, while 5661 of 5672 (99.8%) of clinical requests were filled for an entire region with a multi-ethnic population. Hospital transfusion services identified antigen-negative red cell units in their local inventories using an online antigen query portal.

Implications of all the available evidence

The integration of available red cell genotype databases at various blood centers with a web-based portal accessible for hospitals constitutes a novel approach to supply affordable antigen-negative blood. Mass-scale red cell genotyping combined with internet 'cloud'-based informatics can transform the way antigen-negative blood is provided for patient safety at a level that cannot be technically and economically attained using current database structures and conventional phenotyping. Physicians may recognize these new efficiencies for patient transfusion support.

Table 1

Blood donors with phenotypes or genotypes for 42 blood group antigens at the end of 2013

Number of antigens*	Number of donors and antigens tested			
	by phenotype only†		by genotype‡	
	Donors (n)	Antigens (n)	Donors (n)	Antigens (n)
1	20147	20147	0	0
2	12013	24026	0	0
3	7016	21048	0	0
4	7850	31400	0	0
5	5222	26110	0	0
6	2990	17940	0	0
7	2221	15547	0	0
8	3830	30640	0	0
9	2367	21302	0	0
10	1535	15350	0	0
11	899	9889	0	0
12	805	9660	0	0
13	1432	18616	0	0
14	1656	23184	0	0
15	914	13710	0	0
16	691	11056	0	0
17 to 25	678	12479	0	0
26 to 28	6	160	5	137
29 to 33	0	0	364	11688
34	0	0	878	29852
35	0	0	539	18865
36	0	0	3916	140976
37	0	0	1260	46620
38	0	0	21144	803472
39	0	0	995	38805
40	0	0	1033	41320
41	0	0	7853	321973
42	0	0	5079	213318
Total	72272	322264	43066	1667026
Donors not tested§	523302	na	595720	na

*Antigens as listed Materials and Methods.

†Antigen phenotype records were tabulated since 1985. Because of annual donor attrition, more than 98% of donors with phenotypes are from 1991 to 2013. There were an additional 23,731 confirmatory phenotypes tests based on previously known red cell genotype results (data not shown).

‡Red cell genotyping records began January 2, 2010; among the 202,275 donors in 2010 – 2013 we genotyped 43,066 donors (21.3%).

§The total number of individual whole blood donors at BloodCenter of Wisconsin since 1985 was 638,786.

na not applicable

Table 2

Supply of antigen-negative red cell units other than ABO and RhD by BloodCenter of Wisconsin (BCW) from 2011 to 2013.*

	Supplied in Wisconsin						Supplied elsewhere in the US					Total	
		Red cell units from inventory				From sources other than BCW		Red cell units from inventory					
Antigens required (n)	Patient encounters (n)	Genotype only (n)	Including phenotype (n)	Total (n)	Genotype only (%)	(n)	Patient encounters (n)	Genotype only (n)	Including phenotype (n)	Total (n)	Genotype only (%)	Patient encounters (n)	Units (n)
1	1528	3473	88	3561	97.5 %	0	8	18	6	24	75.0 %	1536	3585
2	1628	4458	186	4644	96.0 %	0	17	71	0	71	100 %	1645	4715
3	1415	4128	203	4331	95.3 %	5†	27	68	0	68	100 %	1442	4399
4	452	1126	70	1196	94.1 %	0	60	146	2	148	98.6 %	512	1344
5	342	675	88	763	88.5 %	7†	169	345	5	350	98.6 %	511	1113
6	118	196	64	260	75.4 %	1†	84	129	25	154	83.8 %	202	414
7	73	106	49	155	68.4 %	0	27	36	14	50	72.0 %	100	205
8	30	61	0	61	100 %	0	30	48	10	58	82.8 %	60	119
9	0	0	0	0	na	0	10	4	12	16	25.0 %	10	16
10	0	0	0	0	na	0	4	0	5	5	0 %	4	5
Rare‡	86	134	1	135	99.3%	21§	626	1080	119	1199	90.1 %	712	1334
Total	5672	14357	749	15106	95.0 %	34	1062	1945	198	2143	90.8 %	6734	17249

*In these 3 years, there were no unfilled requests in Wisconsin and only one request for a patient with the rare phenotype E-Di(b-), which was partially filled.

†The 13 red cell units with common phenotypes were: 5 C-e-Jk(b-); 6 C-e-K-S-Jk(b-); 1 E-K-Fy(a-b-)Co(b-); 1 C-e-S-K-Fy(b-)Jk(a-).

‡Rare phenotypes as defined by the American Rare Donor Program[33] with or without additional antigen requirements.

§The 21 red cell units with rare phenotypes were: 10 E-Di(b-); 4 E-U-; 2 E-K-U-; 2 U-; 1 E-K-S-Jk(b-)Yt(a-); 1 ‘N’-; and 1 H-(Bombay).

na not applicable

Table 3

List of blood group antigens that were phenotyped but not genotyped

Antigen*	Red cell units supplied 2011 – 2013		
	In Wisconsin		Elsewhere in the US
	From BCW	From other blood centers	
He	–	–	2
'N'	–	1	–
P1	16	–	5
P^k	–	–	2
f†	–	–	–
C^w	680	–	80
Go^a	–	–	15
Le^a	19	–	15
Le^b	29‡	–	17
Wr^a	–	–	42
Xg^a	4	–	–
H	–	1	–
Tc^a	–	–	1
Vel	1	–	19
Total	749	2	198

*All antigens could be genotyped as previously detailed.[24]

†Lack of the f antigen expression can be deduced by a negative phenotyping result for the c or e antigens.

‡29 units of Le(a-b-) phenotype

na, not applicable

Table 4

Number of antigens required for patients in hospitals served by BCW

Antigens required	Patients
1	612
2	519
3	292
4	98
5	54
6	13
7	9
8	1
Rare*	25
Total	1623

* Rare phenotypes (see footnote to Table 2).