REPORT

Transfusion practices for patients with sickle cell disease at major academic medical centers participating in the Atlanta Sickle Cell Consortium

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The Atlanta Sickle Cell Consortium represents more than 2600 pediatric and adult patients with sickle cell disease (SCD) in the metropolitan Atlanta, Georgia, area receiving care at four major locations, each providing comprehensive care 24 hours a day, 7 days a week. Both transfusion services that support these sites use two levels of prospective phenotype matching to decrease the rates of alloimmunization. Although exact rates are unknown and are currently under investigation, alloimmunization occurs infrequently with the exception of chronically transfused SCD patients, who represent the minority of active SCD patients. With increasing availability, red blood cell genotyping will be used in the near future both for determination of predicted patient phenotypes and for provision of genotypically matched donor units. *Immunohematology* **2012;28:24–6.**

SCD have been cured through matched sibling bone marrow transplants with a 96 percent disease-free survival rate; the first successful unrelated cord blood transplant for SCD was also performed at CHOA. In fiscal year 2010, there were a total of 1402 inpatient hospitalizations (ECH, 605; SR, 500; HS, 297) and 7155 outpatient Aflac clinic visits (ECH, 2272, SR, 2622, HS, 2261) among all sites.

Once these patients reach adulthood (age 18 and older), their SCD care is most often transitioned to the Georgia Comprehensive Sickle Cell Center at Grady Health System (GHS), which was the first 24-hour comprehensive primary-

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CHOA and Grady SCD Policies

- Phenotype all SCD patients for major blood groups
  - C/c, E/e, K, Fya/Fyb, Jka/Jkb, S/s
- For non-alloimmunized patients, prophylactically match for Rh (D, C/c, E/e) and K
- For sensitized patients who have produced clinically significant RBC antibodies:
  - RBCs for transfusion are Rh (D, C/c, E/e), K, Fy^a, and Jk^b specific and must also be negative for any other antigens to which the patient has produced alloantibodies if clinically significant
  - At GHS for patients >16, also match for S
- Units must also be leukoreduced and HbS negative

Outcomes with Prospective Antigen Matching Protocols

TABLE 5. Studies evaluating alloimmunization and matching for RBC antigens

Reference	Number of patients/transfusions	Percentage alloimmunized/number of alloantibodies per 100 units transfused
	Matching ABO, D only	
Ambruso et al.[4]	85/1,941	34%/3.4
Rosse et al.[5]	1,044/—*	18-31% (27% in study group)/—
Vichinsky et al.[7]	107/—	30%/—
Aygun et al.[9]	140/3,239† (pediatric and adult patients)	37%/2.8†
Castro et al.[10]	351/8,939†	29%-35%/3.8†
Sakhalkar et al.[11]	387/14,263†	31%/1.7†
	Matching extended beyond ABO, D, including C, E, K	
	Number of patients/transfusions	Percentage alloimmunized/rate, alloantibodies per 100 units transfused
Vichinsky et al.[13]	Extended matching for C, E, K 61/1,830	8-11%/0.5
Sakhalkar et al.[11]	Extended matching for C, E, K 113/2,345	5%/0.26
	Matching extended beyond ABO, D, in addition to C, E, K	
	Number of patients/transfusions	Percentage alloimmunized/rate, alloantibodies per 100 units transfused
Tahhan et al.[8]	Extended matching to K, C, E, S, Fy^a, Fy^b 40/—	0/—

* Bar notes data not provided or available.
† Different from results for present report, Table 4, $p < 0.00005$.

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LaSallle-Williams M. Transfusion 2011, 51: 1732-1739

Outcomes with Prospective Extended Antigen Matching Protocols

- LaSalle-Williams *et al* published their experience with extended RBC antigen matching in a cohort of 99 patients from 1993-2006
  - Only 34% of units were exactly matched for all antigens
    - C/c, E/e, K, Fy^a mismatched in <2%
  - 7 patients developed an alloantibody (7% or 0.1%/100 units)

TABLE 4. Alloimmunization in patients treated with extended matching protocol*

Period, reference	Patient group	Matching	Percentage of patients immunized	Rate (antibodies/100 units transfused)
Before 1978 (control), Ambruso et al.[4]	Chronic transfusions n = 85	ABO, D	34%	3.4
1979-1983, Ambruso et al.[4]	Chronic transfusions n = 12	Extended matching All had previously received ABO, D	25%	0.3
1983-1990, Ambruso et al.[22]	Chronic transfusions n = 13	Extended matching only	8%	0.08
1993-2006, Present report	Chronic and intermittent n = 99	Extended matching	All—7%† Eliminate D mosaic—4%†	0.10† 0.06†

* Patients described in each period group were analyzed spearately and not included in the summary for any other group.
† Different from historical control, $p < 0.00005$.

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Compliance with Prospective Antigen Matching Protocols

- Osby *et al* published the results of a CAP Proficiency Testing Survey and Educational Module from 2003
  - Of the 1182 labs who participated
    - 37% performed a complete red cell antigen phenotype prior to transfusion
    - Approximately 1/3 of responders would issue ABO/Rh compatible, C-E-K-matched units
- Afenyi-Annan and Brecher published the results of a survey to 50 academic medical centers in 2004

TABLE 1. Prophylactic antigen matching 37 academic medical centers

	Antigen						
	C	c	E	e	K	k	Fy[a]
Number	25	15	27	15	26	3	1
Percent	68	41	73	41	70	8	3

Osby M. *Arch Pathol Lab Med* 2005, 129: 190-193
Afenyi-Annan A. *Transfusion* 2004, , 44: 619-620

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Compliance with Prospective Antigen Matching Protocols

- Afenyi-Annan *et al* formally surveyed medical directors and laboratory supervisors of transfusion services at each of the NIH funded Comprehensive Sickle Cell Centers
  - 36/49 (73.5%) response rate
  - 80.6% of centers performed pre-transfusion red cell antigen phenotyping
  - In regards to prospective antigen matching,
    - 77.1% prospectively matched
    - 11.4% matched following antibody development
    - 8.6% did not perform antigen matching

TABLE 3. Antigen matching at CSCCs (n = 31)

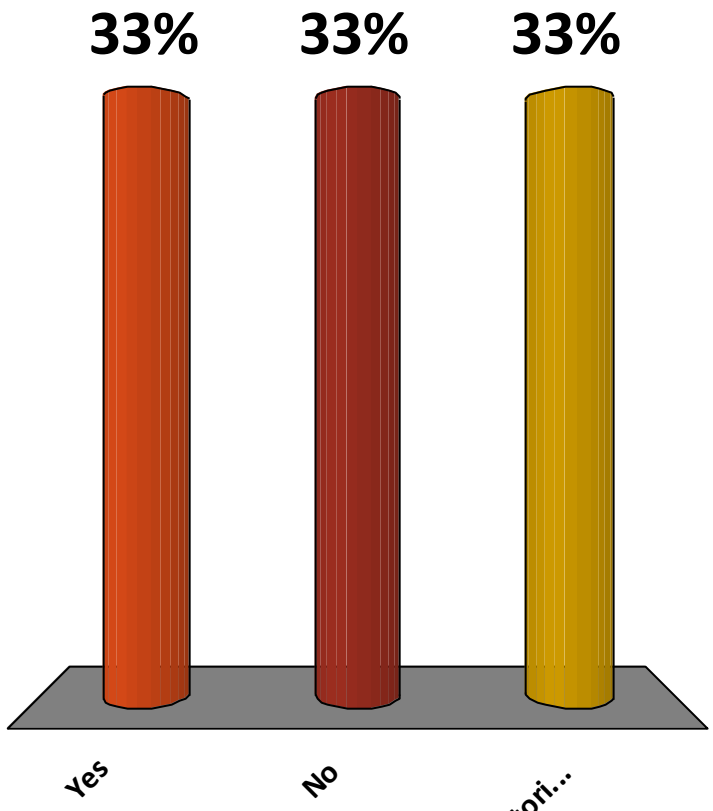
	Antigen												
	C	c	E	e	K	k	Fy^a	Fy^b	Jk^a	Jk^b	S	s	M/N
Number	29	23	29	20	30	6	5	2	3	3	3	2	1/1
Percent	94	74	94	65	97	19	16	7	10	10	10	7	3/3

- When surveyed if consensus existed on selection of blood products and use of phenotypically matched RBCs, 60% and 68.5% disagreed

Afenyi-Annan A. *Transfusion* 2007 , 47: 2089-2097

Do you routinely phenotype any new SCD patient?

1. Yes
2. No
3. Obtain historical phenotype from reference lab / other transfusion service



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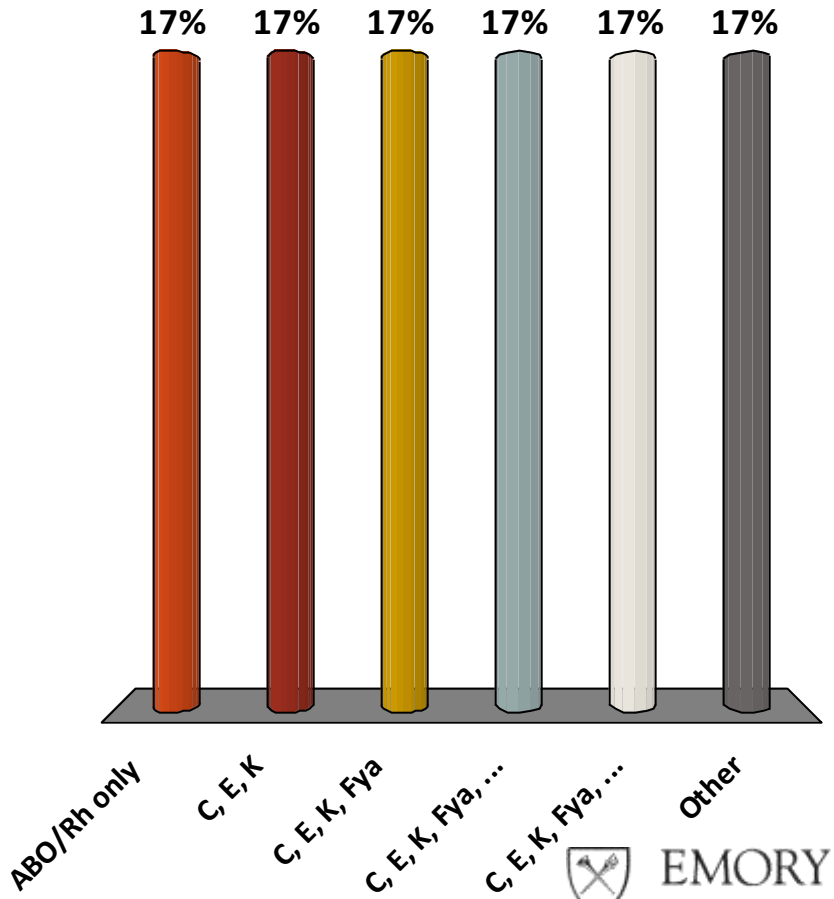
For non-alloimmunized patients, my BB/transfusion service matches for

1. ABO/Rh only
2. C, E, K
3. C, E, K, Fy^a
4. C, E, K, Fy^a, Jk^b
5. C, E, K, Fy^a, Jk^b, S
6. Other



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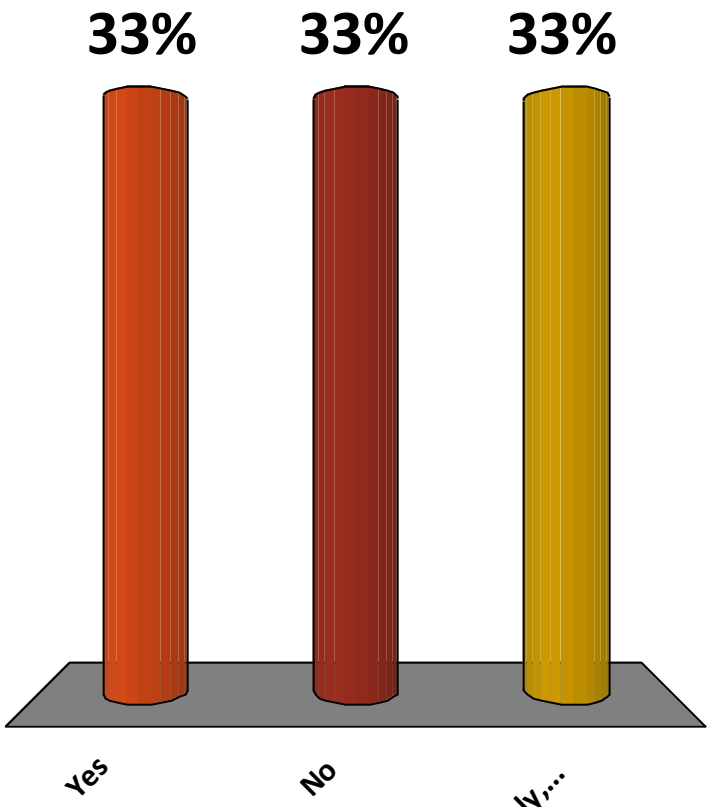
Red Blood Cell Genotyping in Sickle Cell Disease

My BB/ transfusion service has started genotyping SCD patients?

1. Yes
2. No
3. Not routinely, only in select cases



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Introduction to RBC Molecular Testing

- During the past 10-15 years, experimental immunohematology laboratories have implemented molecular methods to identify specific SNPs in the many genes that encode blood group antigens
  - To date, genes encoding 28 of the 29 established blood group systems have been cloned and sequenced; only the encoding of the P system remains to be resolved
- In addition, there has been the development of several different mass-scale genotyping technologies to perform high-throughput blood group prediction with the goal of mainstream application

Application of RBC Molecular Testing

Table 3. Application and Implementation of Molecular Technologies

Donor center

Genotype RBC products

- Product for special patient populations, such as sickle cell disease patients
- Products for patients with multiple alloantibodies
- *RHD* genotyping donors who are D-negative

Reference laboratory

- Reagent RBCs for antibody detection
- Genotype to determine dosage of RBC antigens
- Resolution of typing discrepancies
- Genotype to predict presence or absence of an antigen when no antisera exists
- Determination if new antibody is an autoantibody or alloantibody
- Resolution of unusual serological findings

Transfusion service

Genotype patients

- Recently transfused patients
- Patients with autoantibodies
- D type of the patient to predict need for RhIg or D-negative products

Providing genotyped matched products

- Patients with SCD
- Patients with thalassemia
- Patients with AIHA
- Chronically transfused patients

Prenatal testing

- *RHD* type to predict need for RhIg
- Genotype fetal DNA to predict risk for HDFN

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Hillyer CD. *Transfusion Medicine Reviews* 2008 , 22: 117-132

Application of RBC Molecular Testing in SCD Example

- Wilkinson et al recently published a feasibility study to determine if RBC components drawn from predominantly white donors could provide antigen matched products for molecular typed SCD patients
  - SCD patients were typed with HEA Beadchip, BioArray Solutions

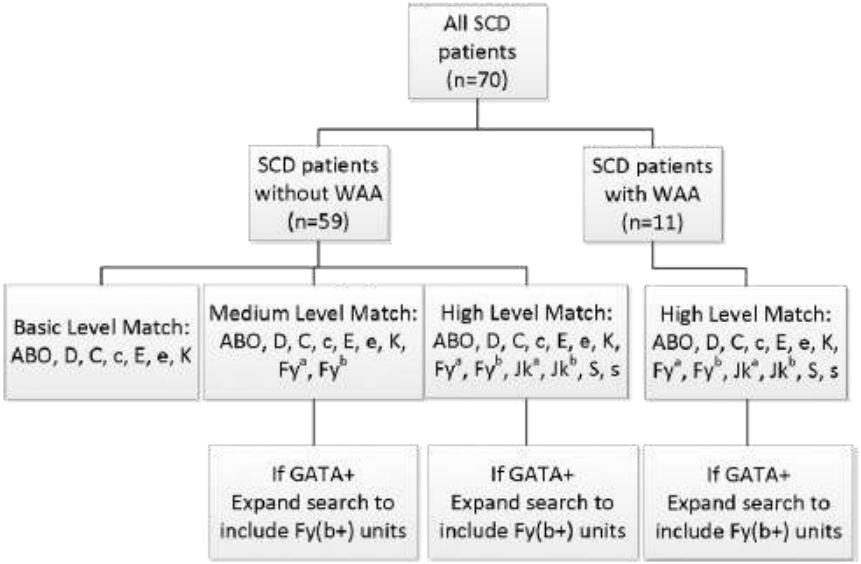

Fig. 1. RBC inventory query matching algorithm for SCD patients. WAA = warm autoantibody.

Wilkinson K. *Transfusion* 2012 , 52: 381-388

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Application of RBC Molecular Testing in SCD Example

TABLE 3. Mean number of RBC components available in PSBC's inventory by RBC antigen match level and by SCD patient characteristics

	Basic-level match, ABO, D, C, c, E, e, K	Mid-level match, ABO, D, C, c, E, e, K, Fy^a, Fy^b	High-level match, ABO, D, C, c, E, e, K, Fy^a, Fy^b, Jk^a, Jk^b, S, s
All patients (n = 70)	96.2 (37-100)	34.0 (1-100)	16.3 (0-100)
All patients; if GATA+, then Fy(b+) components allowed	N/A	90.4 (11-100)	37.4 (0-100)
With five negative antigens	94.6 (41-100)	27.4 (11-100)	19.3 (5-71)
With five negative antigens; if GATA+, then Fy(b+) components allowed	N/A	100 (100-100)	54.9 (29-100)
With six negative antigens	94.9 (37-100)	25.3 (1-82)	6.0 (0-16)
With six negative antigens; if GATA+, then Fy(b+) components allowed	N/A	84.3 (11-100)	21.7 (0-37)
With negative antigens	96.2 (54-100)	20.9 (10-82)	1.6 (0-3)
With seven negative antigens; if GATA+, then Fy(b+) components allowed	N/A	86.4 (54-100)	8.4 (0-11)

Data are reported as mean (range). Inventory size is approximately 4300 with approximately 335 antigen-typed products.

- The *FY**01N.01 allele encodes the Duffy null phenotype due to a change in the promoter region, also known as the *GATA* mutation
  - Fy^b negative patients with the *GATA* mutation typically do not make anti-Fy^b when transfused with Fy^b positive components
- Knowledge of the patient's *GATA* status expands the inventory of antigen matched products

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Wilkinson K. *Transfusion* 2012 , 52: 381-388

Creation of a Registry SCD Patients within the Atlanta Sickle Cell Consortium

REDCap™ Introduction

- REDCap™ (Research Electronic Data Capture) is a secure, web-based application for building and managing online surveys and databases
- REDCap™ provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages
- Additional features include a built-in project calendar, scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields

REDCap™ Introduction

- REDCap™ Consortium is composed of 566 active institutional partners from CTSA, GCRC, RCMI and other institutions in 51 countries
  - Currently in production use or development build-status for more than 61,000 projects with over 80,000 users spanning numerous research focus areas

http://project-redcap.org/

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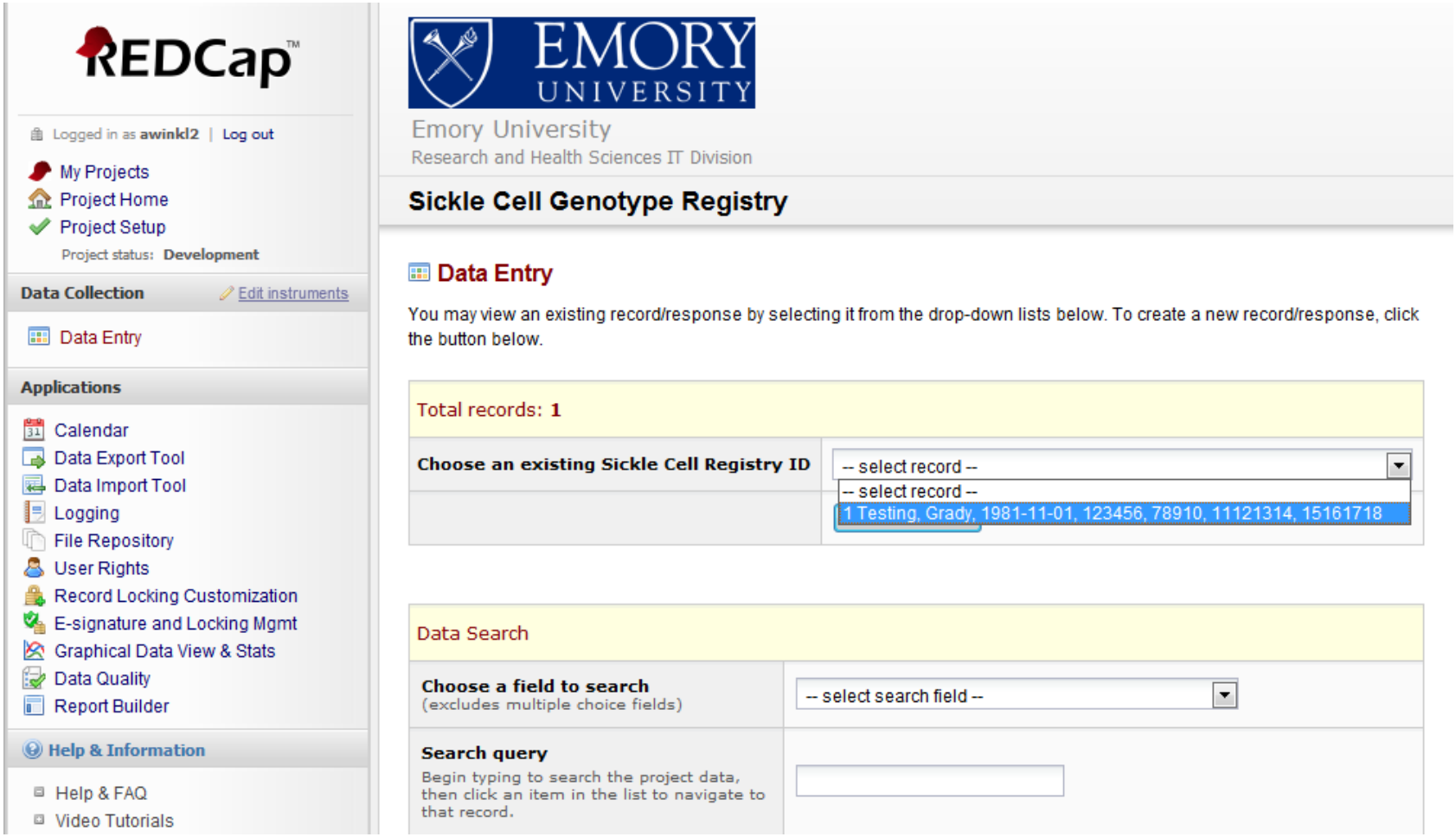

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Sickle Cell Registry ID **1** Testing, Grady,

Data Collection Instrument	Basic Info (1)	Transfusion 1 (2)	Transfusion 2 (3)	Transfusion 3 (4)	Transfusion 4 (5)	Transfusio 5 (6)	Transfusion 24 (25)	Transfusion 25 (26)	Disposition (27)
Demographics	●								
Past Medical History	●								
Sickle Cell Disease Treatment	●								
Red Blood Cell Phenotype	●								
Red Blood Cell Genotype	●								
Alloimmunization Profile	●								
Post Transfusion Complications	●								
Transfusion Episode Details		●	●	●	●	●	●	●	
Transfusion History Summary									●
Patient Status and Follow-Up									●

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Sickle Cell Registry ID	1
Last Name * must provide value	
First Name * must provide value	
Middle Initial/Name	
Clinical Sites (check all that apply)	☑ GHS-Grady Health System ☑ CHOA-Egleston ☐ CHOA-Hughes Spalding ☐ CHOA-Scottish Rite ☐ CNMC-Children's National Medical Center ☐ EUH-Emory University Hospital ☐ EUHM-Emory University Hospital Midtown ☐ Other
Grady MRN	
Egleston MRN	
Date of Birth * must provide value	M-D-Y
Gender	○ Male ○ Female reset value
Race	○ Black ○ Hispanic ○ Asian ○ White ○ Other reset value

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Sickle Cell Disease Clinical Complications		
Avascular necrosis	○ No ○ Yes	reset value
Acute Chest Syndrome	○ No ○ Yes	reset value
Stroke or TIA	○ No ○ Yes	reset value
Pulmonary Hypertension	○ No ○ Yes	reset value
Pneumonia	○ No ○ Yes	reset value
Priapism	○ No ○ Yes	reset value
Splenic Sequestration	○ No ○ Yes	reset value
Splenectomy	○ No ○ Yes	reset value
Hyperhemolysis	○ No ○ Yes	reset value
Iron Overload	○ No ○ Yes	reset value
Iron Diagnostic(s)	☐ Ferriscan ☐ Liver biopsy ☐ Cardiac T2* MRI ☐ Other ☐ None	
Vitamin D Deficient	○ No ○ Yes	reset value
Vitamin D Replacement	○ No ○ Yes	reset value

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Basic Phenotype				
RhC Phenotype	Positive	Negative	Not tested	reset valu
Rhc Phenotype	Positive	Negative	Not tested	reset valu
RhE Phenotype	Positive	Negative	Not tested	reset valu
Rhe Phenotype	Positive	Negative	Not tested	reset valu
K Phenotype	Positive	Negative	Not tested	reset valu
k Phenotype	Positive	Negative	Not tested	reset valu
Fy(a) Phenotype	Positive	Negative	Not tested	reset valu
Fy(b) Phenotype	Positive	Negative	Not tested	reset valu
Jk(a) Phenotype	Positive	Negative	Not tested	reset valu
Jk(b) Phenotype	Positive	Negative	Not tested	reset valu
S Phenotype	Positive	Negative	Not tested	reset valu
s Phenotype	Positive	Negative	Not tested	reset valu
Extended Phenotype				
Kp(a) Phenotype	Positive	Negative	Not tested	reset valu
Js(a) Phenotype	Positive	Negative	Not tested	reset valu
M Phenotype	Positive	Negative	Not tested	reset valu
N Phenotype	Positive	Negative	Not tested	

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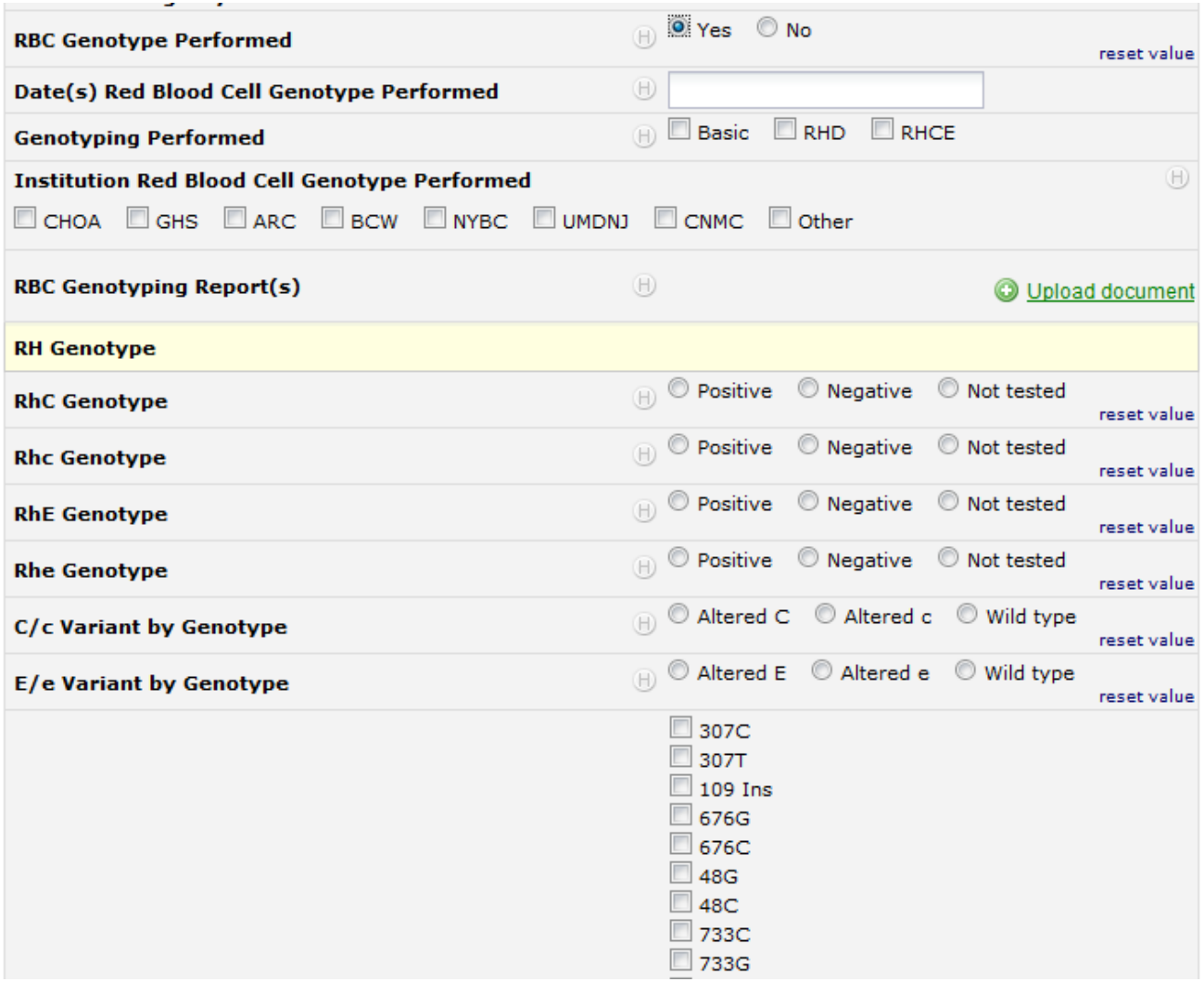

RBC Genotype Performed	(H) ◉ Yes ○ No reset value
Date(s) Red Blood Cell Genotype Performed	(H)
Genotyping Performed	(H) ☐ Basic ☐ RHD ☐ RHCE
Institution Red Blood Cell Genotype Performed	(H) ☐ CHOA ☐ GHS ☐ ARC ☐ BCW ☐ NYBC ☐ UMDNJ ☐ CNMC ☐ Other
RBC Genotyping Report(s)	(H) Upload document
RH Genotype	
RhC Genotype	(H) ○ Positive ○ Negative ○ Not tested reset value
Rhc Genotype	(H) ○ Positive ○ Negative ○ Not tested reset value
RhE Genotype	(H) ○ Positive ○ Negative ○ Not tested reset value
Rhe Genotype	(H) ○ Positive ○ Negative ○ Not tested reset value
C/c Variant by Genotype	(H) ○ Altered C ○ Altered c ○ Wild type reset value
E/e Variant by Genotype	(H) ○ Altered E ○ Altered e ○ Wild type reset value
	☐ 307C ☐ 307T ☐ 109 Ins ☐ 676G ☐ 676C ☐ 48G ☐ 48C ☐ 733C ☐ 733G

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Anti-D	NA	Identified	reset value
D Variant Antibody	NA	Identified	reset value
Anti-C	NA	Identified	reset value
Anti-c	NA	Identified	reset value
Anti-E	NA	Identified	reset value
Anti-e	NA	Identified	reset value
e Variant Antibody	NA	Identified	reset value
Anti-f	NA	Identified	reset value
Anti-Cw	NA	Identified	reset value
Anti-V	NA	Identified	reset value
Anti-K	NA	Identified	reset value
Anti-Kp(a)	NA	Identified	reset value
Anti-Js(a)	NA	Identified	reset value
Anti-Js(b)	NA	Identified	reset value
Anti-M	NA	Identified	reset value
Anti-N	NA	Identified	reset value
Anti-S	NA	Identified	reset value

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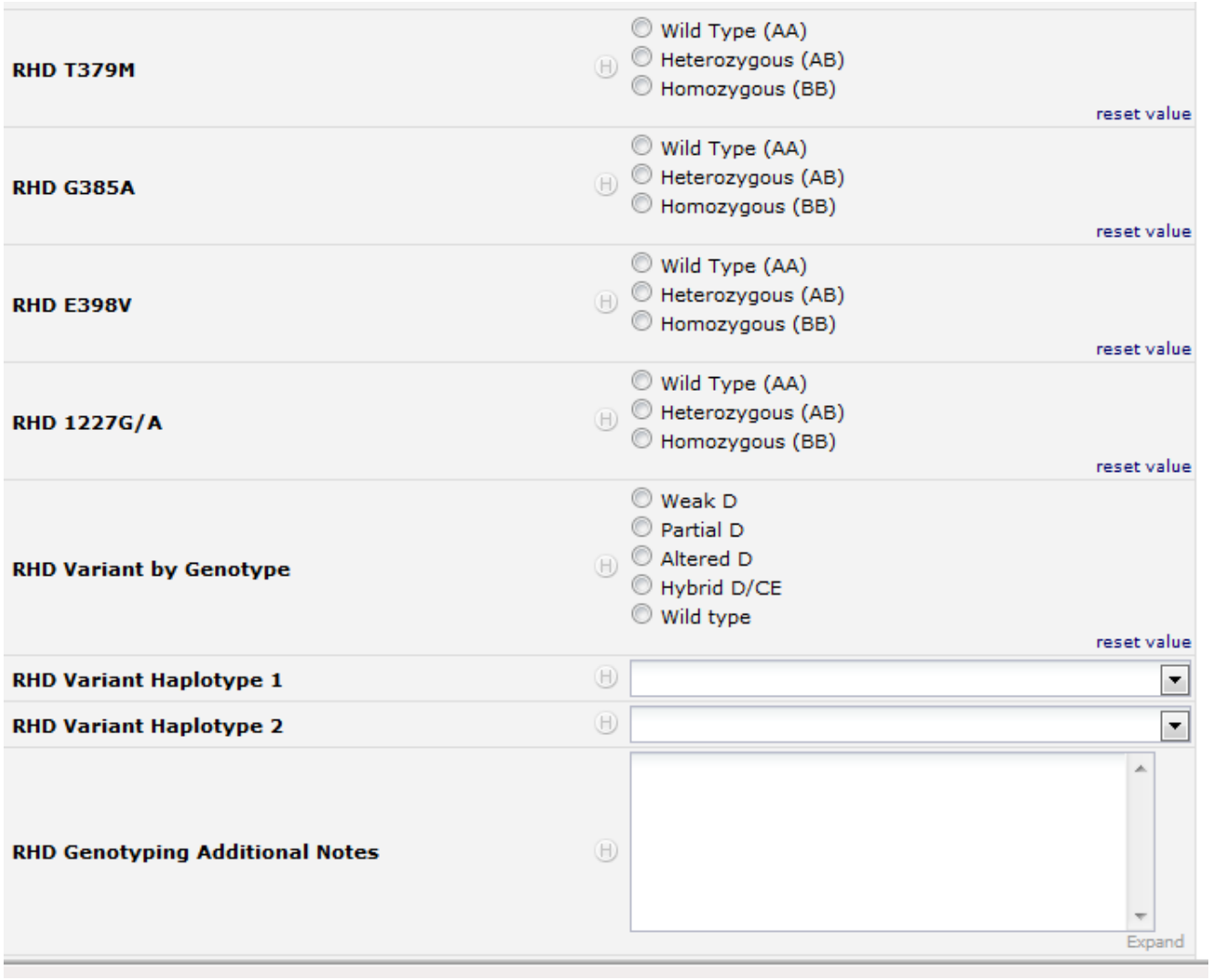

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Sickle Cell Registry ID	1
Transfusion Episode Date	M-D-Y
Transfusion Interval	days in between transfusions
Transfusion Type	○ Simple ○ Automated Exchange ○ Manual Exchange reset value
Transfusion Indication	☐ No acute event ☐ Acute symptomatic anemia ☐ Aplastic crisis ☐ Acute splenic sequestration ☐ Acute hepatic sequestration ☐ Acute stroke ☐ Acute chest syndrome ☐ Acute multiorgan failure ☐ Infection ☐ Preoperative transfusion elective surgery (uncomplicated) ☐ Prevention of stroke ☐ Acute pain crisis ☐ Priapism ☐ Pregnancy ☐ Vaso-occlusive crisis ☐ Vaso-occlusive crisis with WBC > 20,000 ☐ Other
New Alloantibody Formation	○ Yes ○ No reset value new allo associated with transfusion episode

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1. Unit Number	whole blood donor number
Unit Product Code	
Aliquot or Unit?	○ Aliquot ○ Unit reset value
Unit Anticoagulant/Preservative Solution	○ CPD ○ CPDA-1 ○ AS reset value
Aliquot/Unit Volume (ml)	Default volumes for full units: CPDA = 250 ml AS=320 ml
Unit Length of Storage (days)	
Leukoreduced	○ Yes ○ No reset value
Unit ABO Type	○ O ○ A ○ B ○ AB reset value
Unit RhD Type	○ Negative ○ Positive reset value
Antigen Matching Method	☐ Phenotype ☐ Genotype
Level of Antigen Match	○ ABO and Rh ○ Rh (C/c, E/e) and Kell Matched ○ Rh (C/c, E/e), Kell, Fya and Jkb Matched ○ Rh (C/c, E/e), Kell, Fya, Jkb Matched and Antigen Negative for Clinically Significant Alloantibodies ○ Rh (C/c, E/e), Kell, Fya, Jkb, and S Matched (GMH) ○ Rh (C/c, E/e), Kell, Fya, Jkb, S, Matched and Antigen Negative for Clinically Significant Alloantibodies (GMH) ○ Rh (C/c, E/e), Kell, Fya, Jka/Jkb (CNMC) ○ Rh (C/c, E/e), Kell, Fya, Jka/Jkb, Matched and Antigen Negative for Clinically Significant Alloantibodies (CNMC) ○ Rh (C/c, E/e), Kell, Fya, Jka/Jkb, S/s (CNMC) ○ Rh (C/c, E/e), Kell, Fya, Jka/Jkb, S/s, Matched and

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Questions?

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