NHS Blood and Transplant

Haemoglobinopathy Transfusion in the UK: Could it be state of the art?

Dr Sara Trompeter

Consultant Haematologist UCLH and NHSBT

The HAEM-MATCH consortium

Leads:

Sara Trompeter

Will Astle

Simon Stanworth

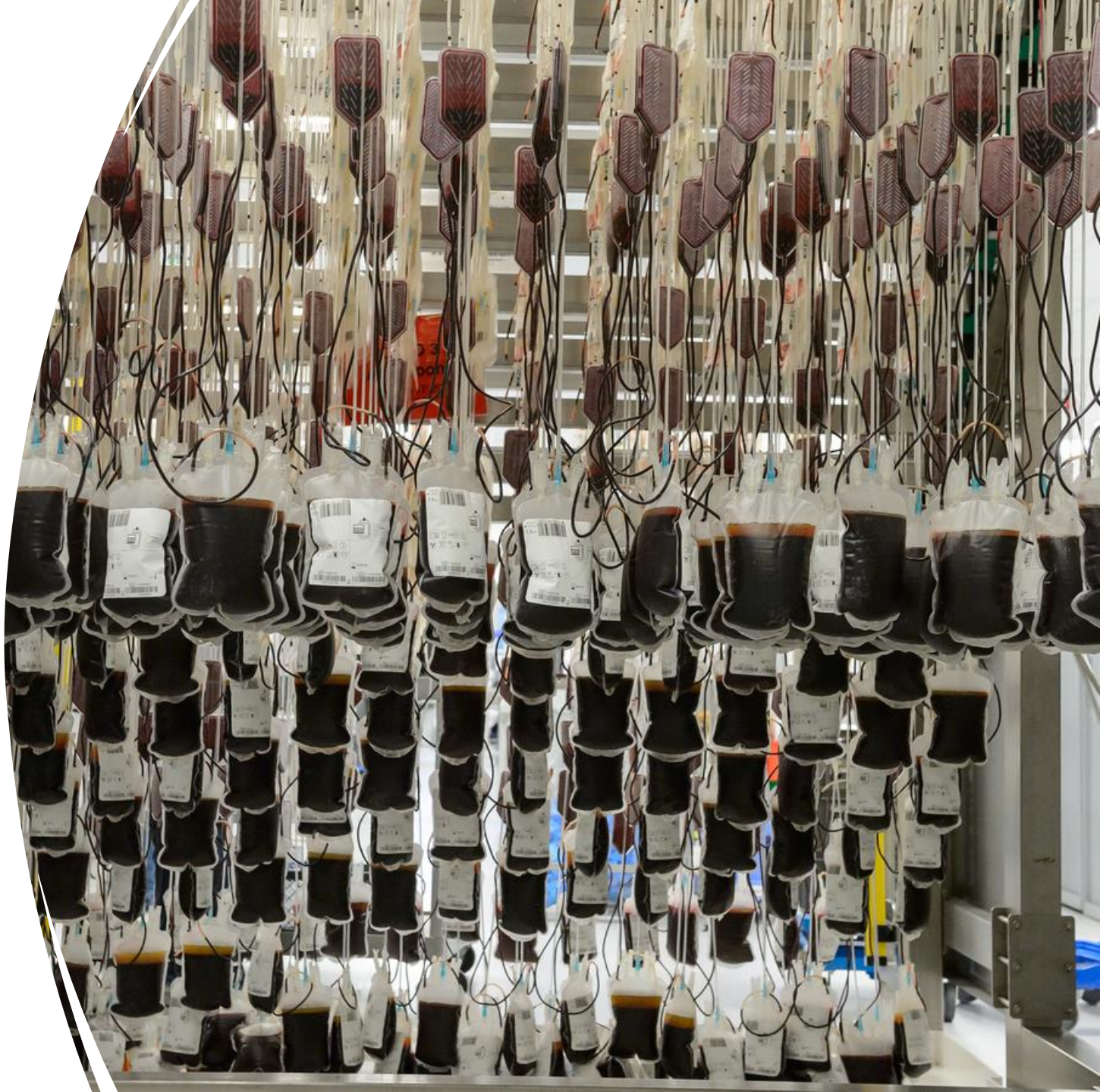
Core members:

- Rekha Anand
- Ian Britton
- Nick Gleadall
- Shane Grimsley
- Edwin Massey
- Mike Murphy
- John Ord
- Willem Ouwehand
- Jo Sell
- Fiona Regan
- Nicole Thornton
- Charlotte Washington

NHS Blood and Transplant

Aim of talk

- What is the current practice of transfusion in haemoglobinopathies in the UK?
- Blood grouping and alloimmunisation, an illustrated case of what happens when things go wrong…
- What do guidelines say?
- Precision transfusion medicine
- What is the HAEM-MATCH programme?



Current practice in transfusion in haemoglobinopathies in the UK

- In the UK there are approximately 14,000 patients with sickle cell disease (SCD) and 1,000 with thalassaemia (THAL).
- For many patients, their lives are defined by access to and the need for red cell transfusion, delivered in an emergency or as part of a long-term transfusion programme.

National Comparative Audit of Blood Transfusion in SCD

- 84 hospitals, 1290 cases
- 75% of cases came from 18 hospitals
- 91% of patients had HbSS
- 60% of patients had Ro phenotype
- 4528 transfusion episodes
- 84% of transfusion episodes were elective
- 2/3 transfusions simple top up, remainder mostly automated red cell exchange
- Stroke prevention accounted for 42% (1913/4528) of all transfusion and 65% (1290/1990) of all transfusions for children
- For acute transfusion episodes, 30% given for anaemia, 18% for acute chest syndrome

TRANSFUSION MEDICINE
Official Journal of the British Blood Transfusion Society
British Blood Transfusion Society

ORIGINAL ARTICLE

National comparative audit of blood transfusion: 2014 audit of transfusion services and practice in children and adults with sickle cell disease

Sara Trompeter, Paula Bolton-Maggs, Kate Ryan, Farrukh Shah, Lise Estcourt, Gavin Cho, David Rees, Derek Lowe, Baaba Davis

First published: 17 December 2019 | https://doi.org/10.1111/tme.12655 | Citations: 2

Haemoglobinopathy Survey

- Alloimmunisation prevalence was 17%
- R_or 59.8%
- Mean blood requirement p.a.
  - Automated exchange 7-weekly, 66 units
  - manual exchange 4-weekly 38 units
  - simple transfusion 4-weekly 30 units
- Guidelines on pheno/genotyping not met
- Access to care was sporadic

Received: 17 April 2020 | Revised: 8 September 2020 | Accepted: 28 September 2020
DOI: 10.1111/tme.12732

ORIGINAL ARTICLE

TRANSFUSION MEDICINE WILEY

The haemoglobinopathy survey: The reality of transfusion practice in sickle cell disease and thalassaemia in England

Sara Trompeter[1,2] | Lise Estcourt[3,4] | Ana Mora[5] | Esther Wong[5] | David Collett[6] | Paula Bolton-Maggs[7,8] | Debbi Poles[8] | Alison Deary[5] | Alison Watt[8]

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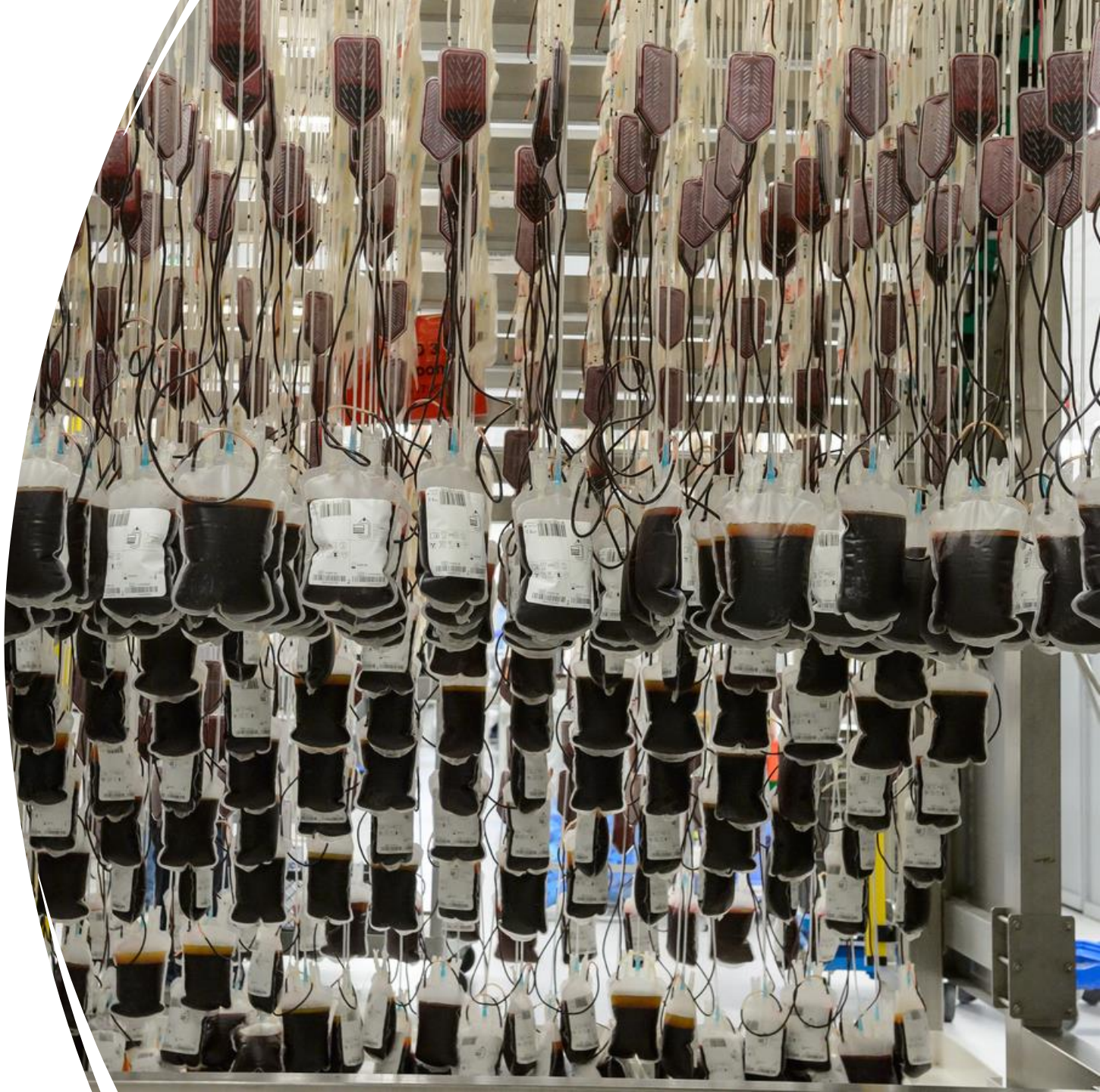
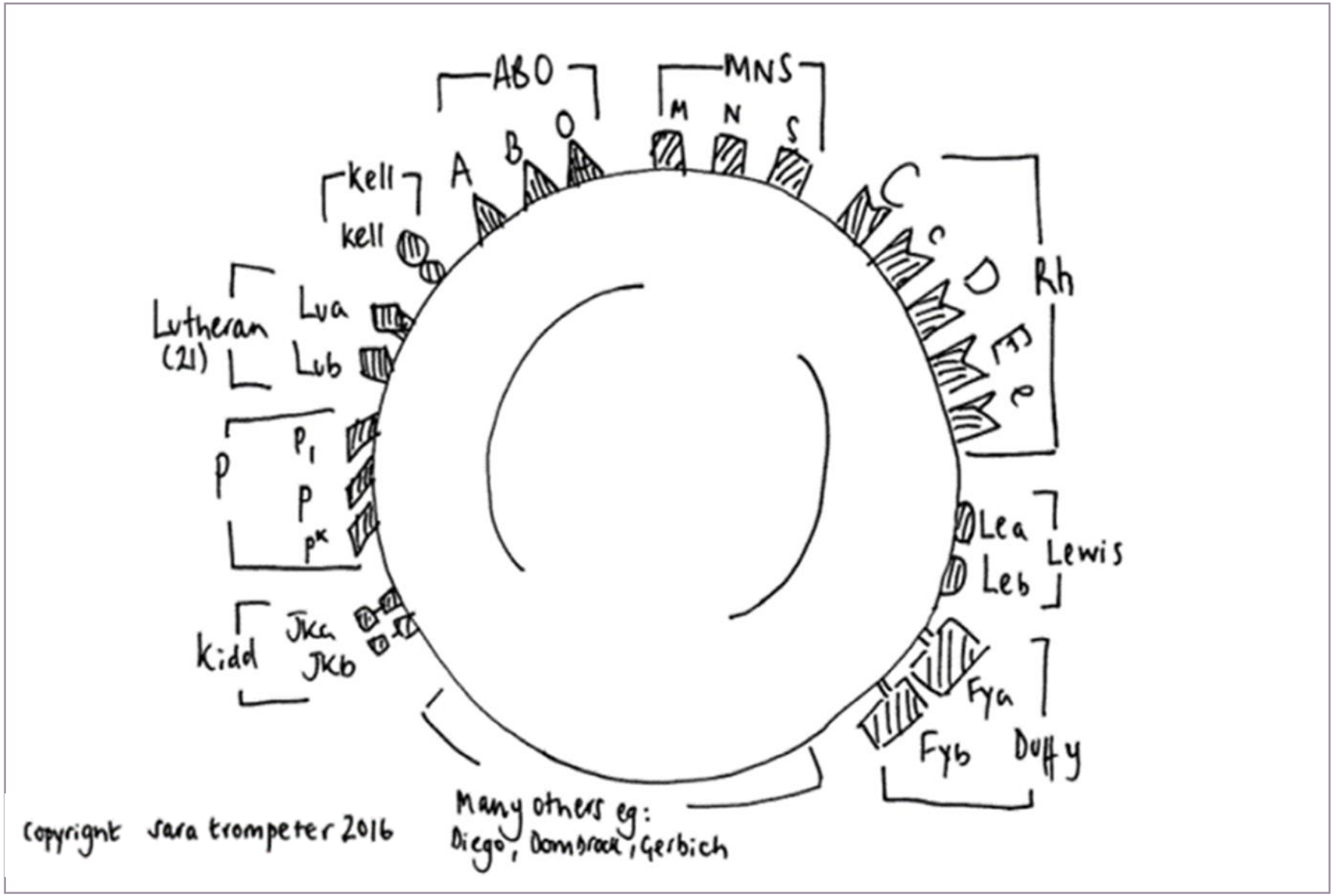
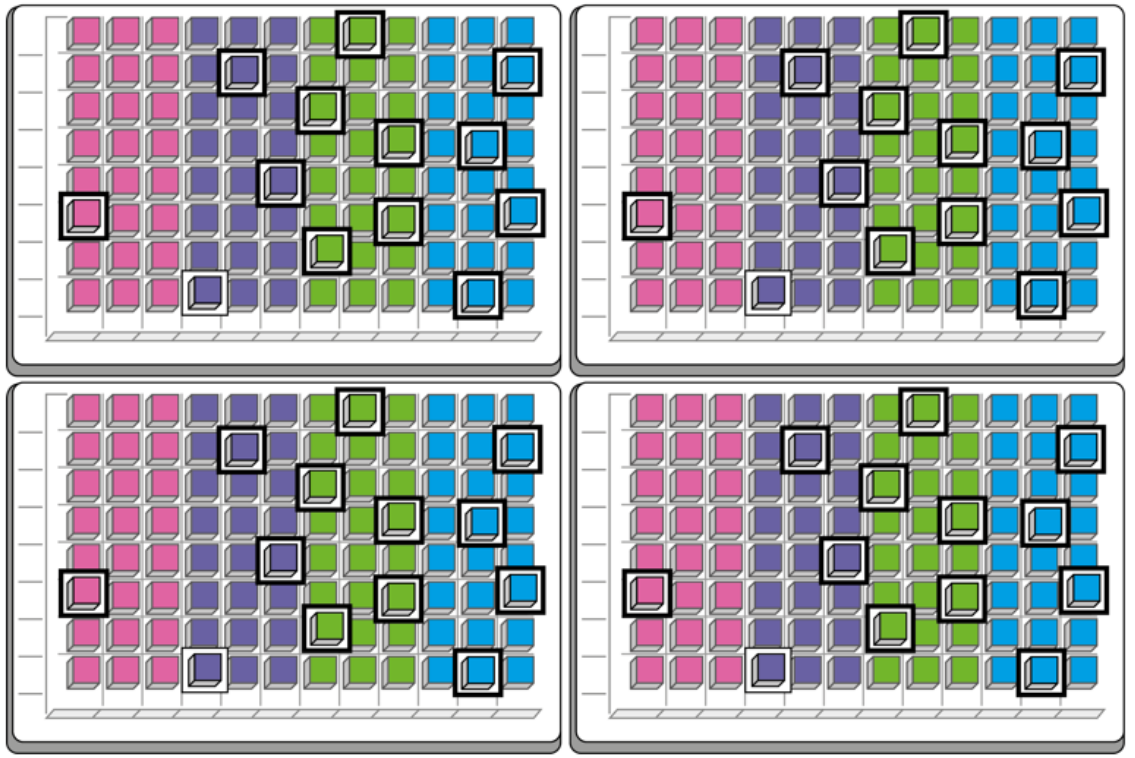


Blood Groups and Antibody formation (alloimmunisation)



	Genotype	Phenotype
Definition	The inherited genes of the blood group	The observed characteristics if the red cell antigen when detected on the surface of the rbc
Process	Uses genetics	Uses antibodies
Cost	££££	££
Variants detected?	YES	NO
Can do if transfused in last 3/12?	YES	NO

But…. New advances make rapid cost effective genotyping a reality



Transfusion basics - Genotypes and Phenotypes

What issues arise when a patient forms an antibody?

- They may become very unwell and destroy the blood you have just given them

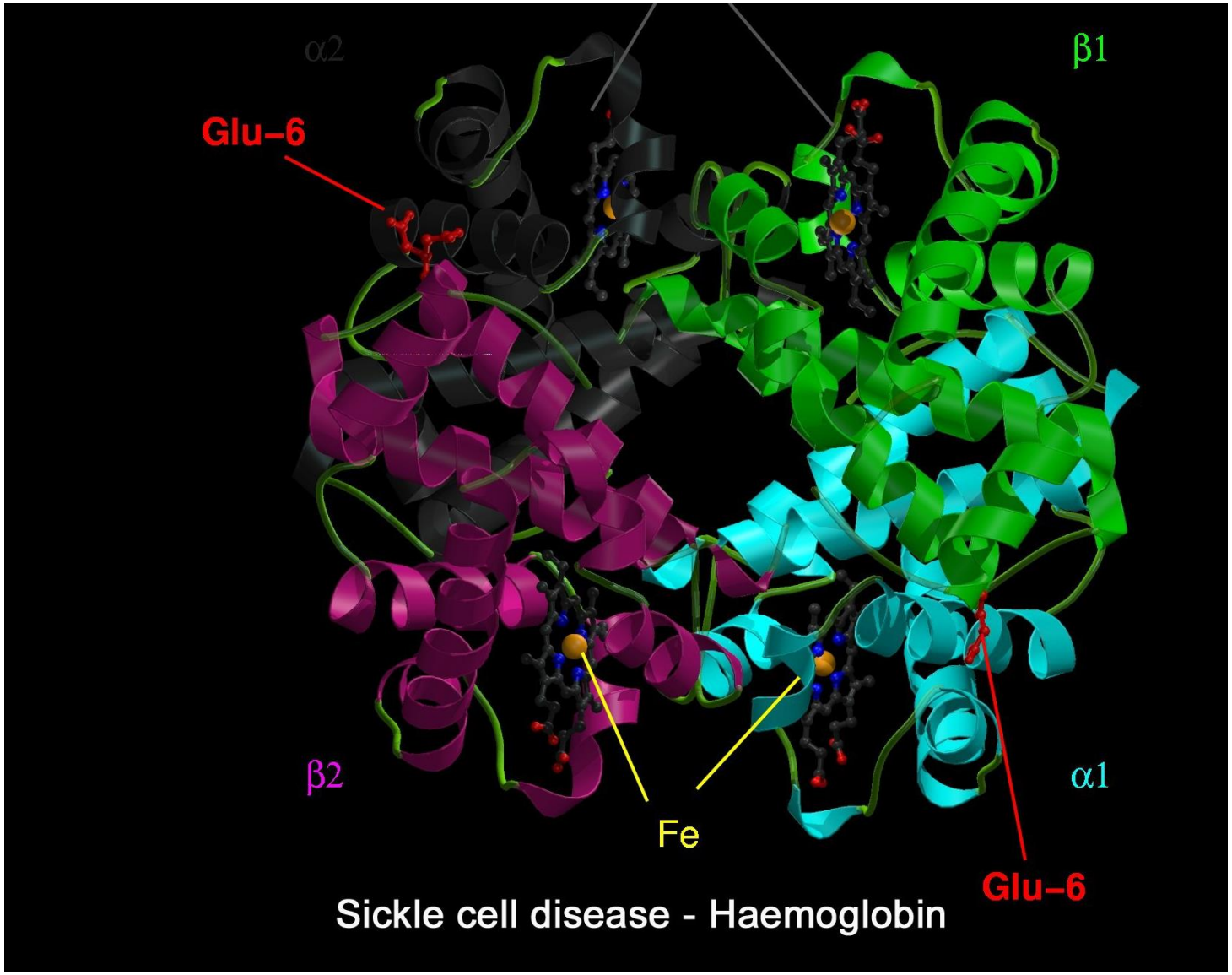
- It becomes harder to find suitable units for them

- Delay in transfusion or receive insufficient units or be “untransfusable”

- Major morbidity and death

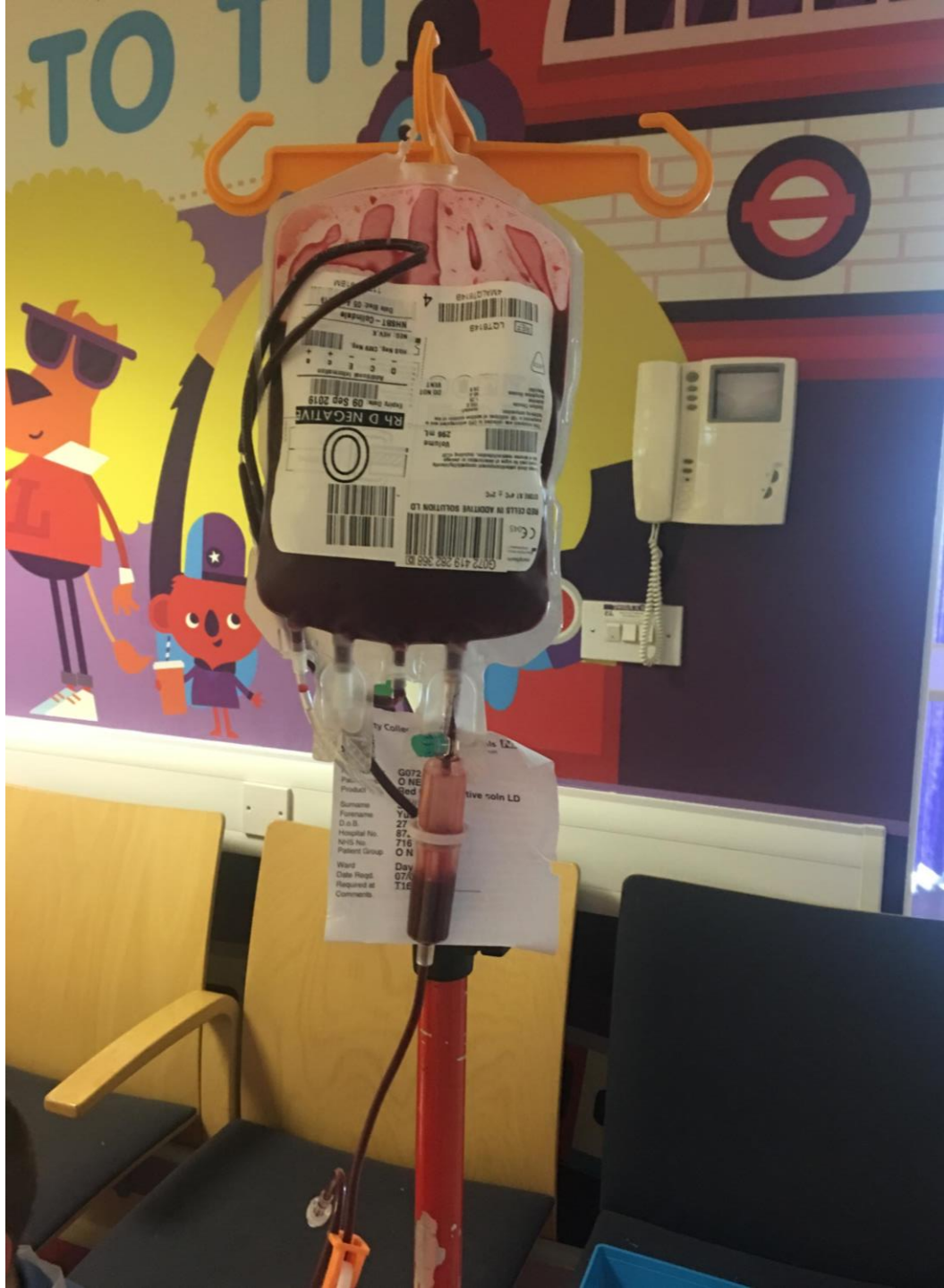
Case history

- 46 year old woman
- HbSS
- Mild disease
- Has breast cancer
- Didn’t tolerate treatment
- Came to a specialist centre that could manage the sickle and cancer together



Case history: Transfusion history

- DHTR 2005
- Anti-Jkb, Anti-K antibodies with DHTR post 4 unit transfusion for THR
- Anti Ce and Anti s noted November 2016
- R1R2 phenotype
- Rh D variant, Rh e variant, RhC variant,
- Recent: one unit transfusion post breast operation with no DHTR (August 2016)



Case history:initial treatment

- Referred to sickle and oncology specialist centre so as to ascertain whether can have chemotherapy i.e. can control SCD sufficiently
- Decision made to give supportive care only, given transfusion complexities
- Tolerates chemotherapy well
- And then: BRCA2 - recommendation now is for bilateral oopherectomy and mastectomy

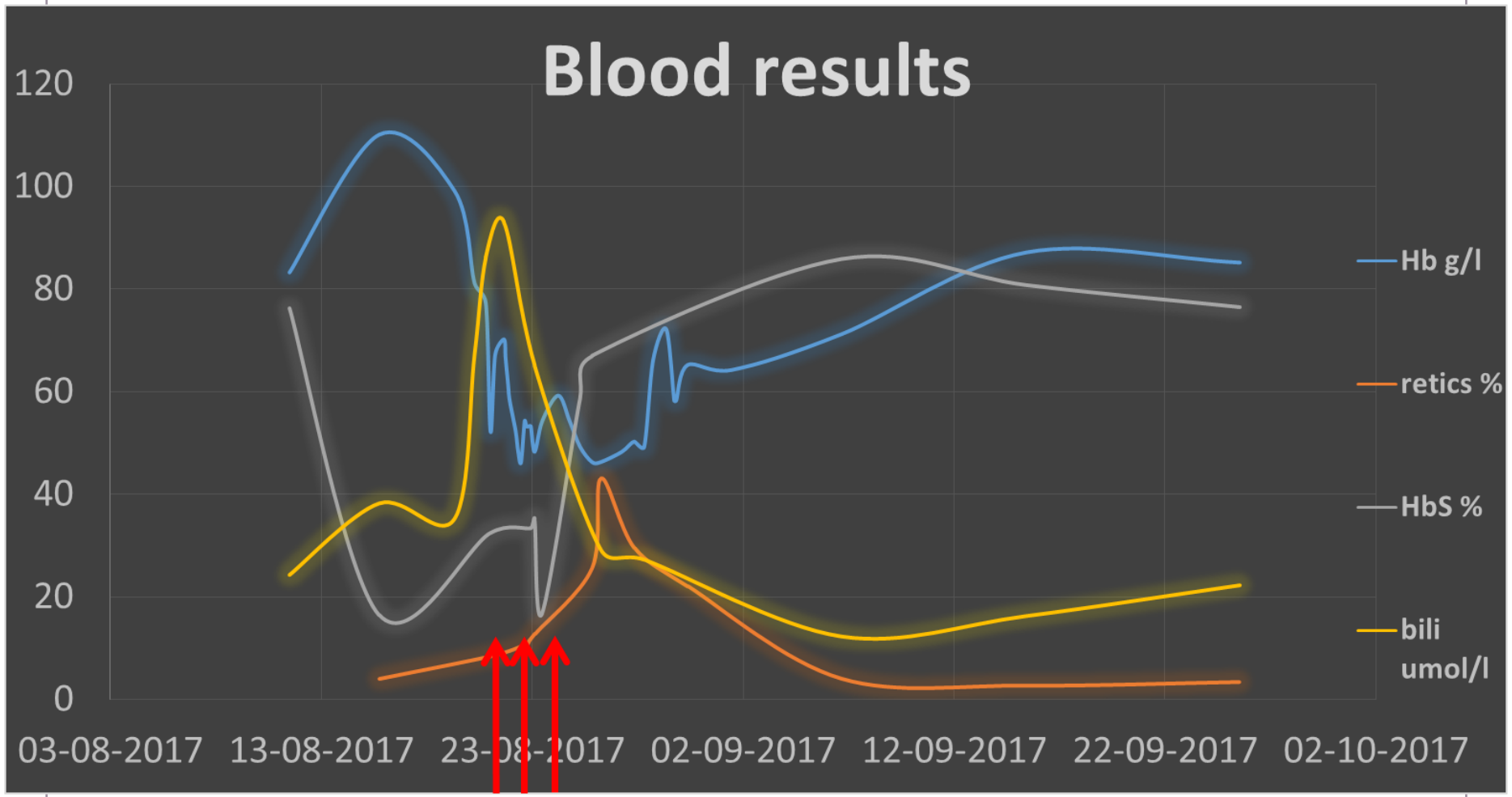
Case history: perioperative plan

- Plan is for an automated exchange
- ivIg preoperatively and methylprednisolone
- Letters/email to immunohaematology consultants
- Blood arrives at the hospital
- Has automated exchange uneventfully

Case history: The blood transfusion reaction

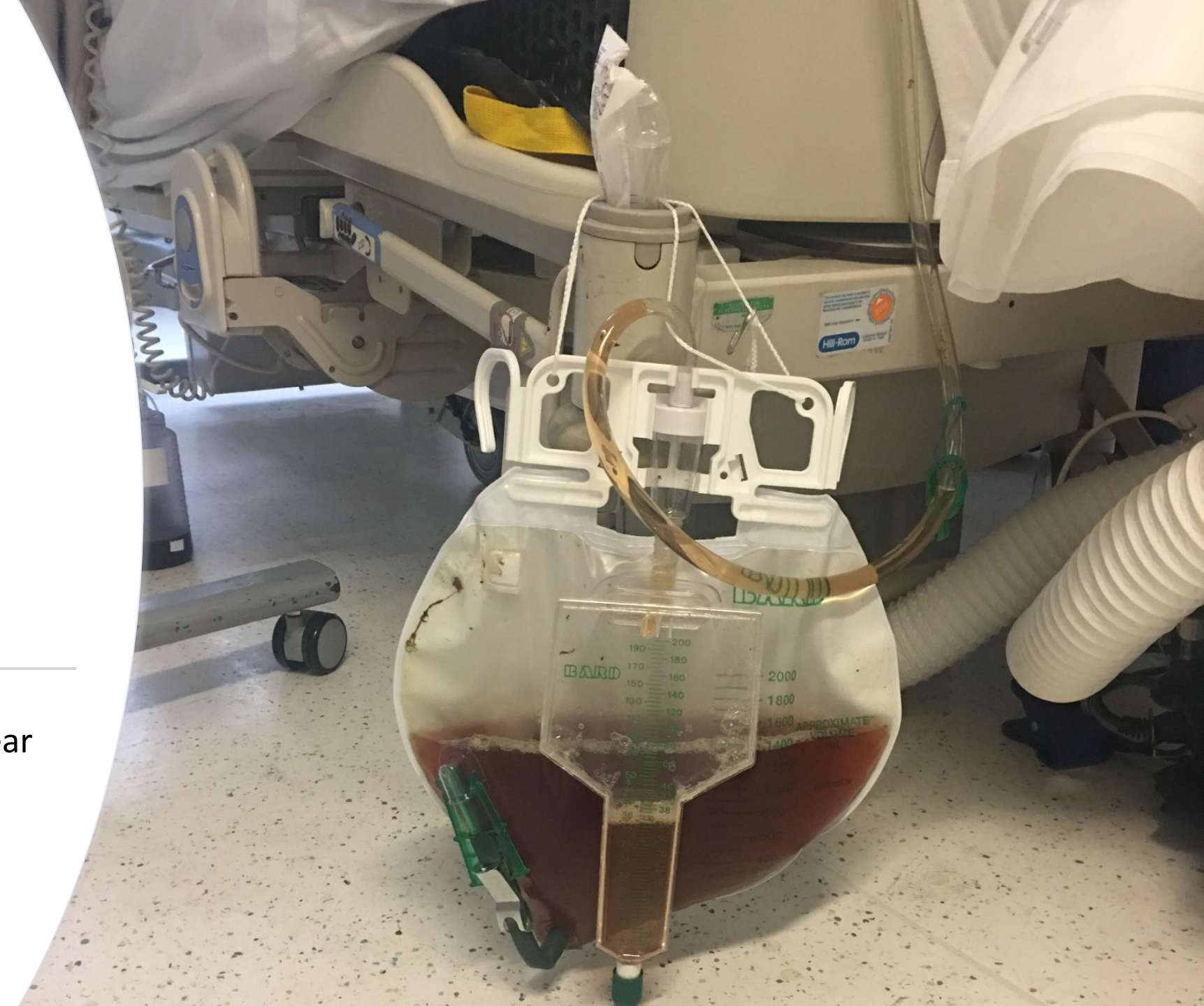
- 48 hours later, haemoglobin in the urine
- Urine only contains HbA, so it is a delayed haemolytic transfusion reaction
- She had anti Ce and a D variant to which there was no demonstrable antibody
- She had been given Orr

- HbS post exchange was 12%, Hb 100g/l


Blood results
120
100
80
60
40
20
0
03-08-2017
13-08-2017
23-08-2017
02-09-2017
12-09-2017
22-09-2017
02-10-2017
Hb g/l
retics %
HbS %
bili umol/l

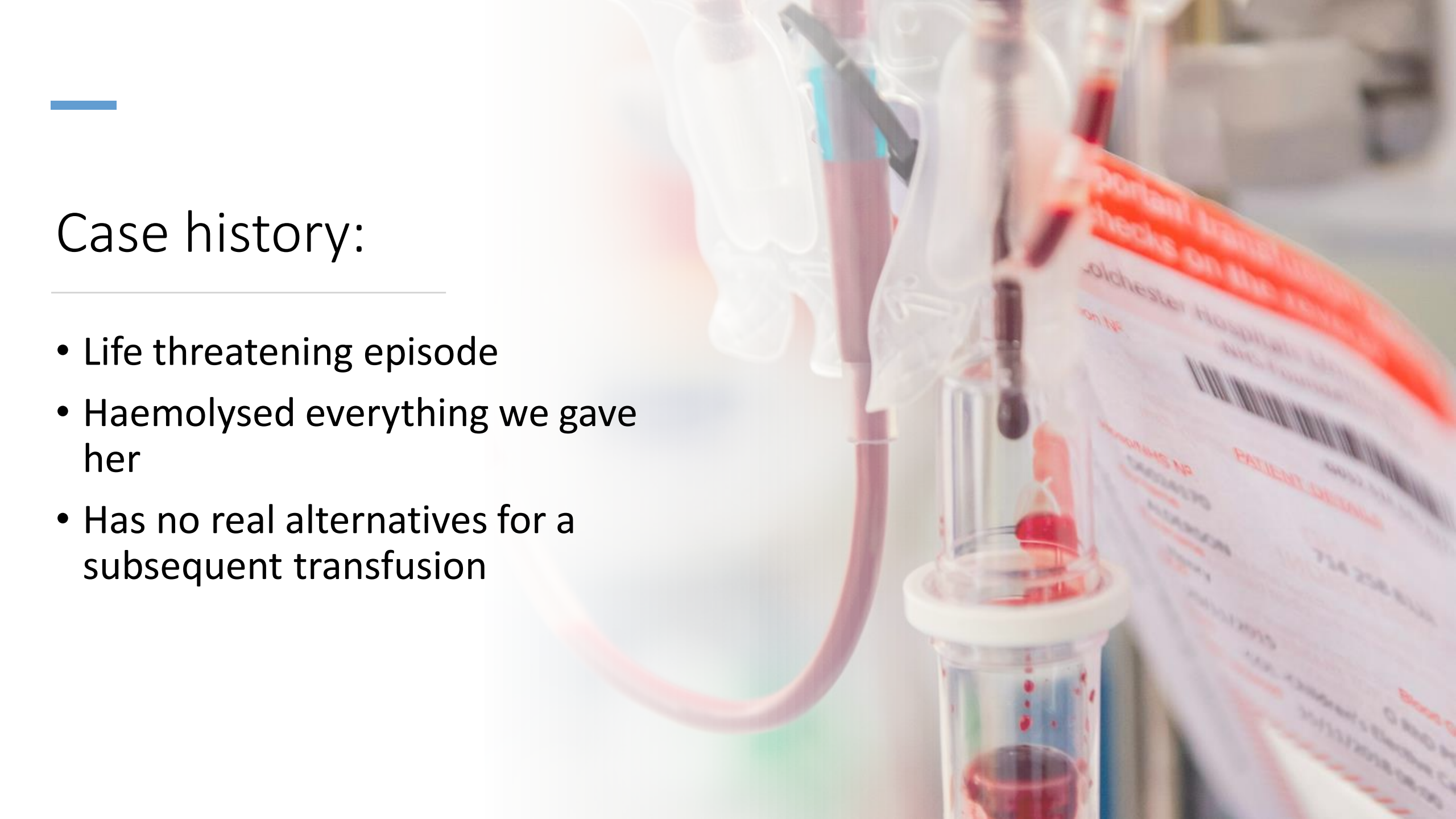
Case history: and eventually….

Haemolysis settles, urine runs clear



Case history:

- Life threatening episode
- Haemolysed everything we gave her
- Has no real alternatives for a subsequent transfusion



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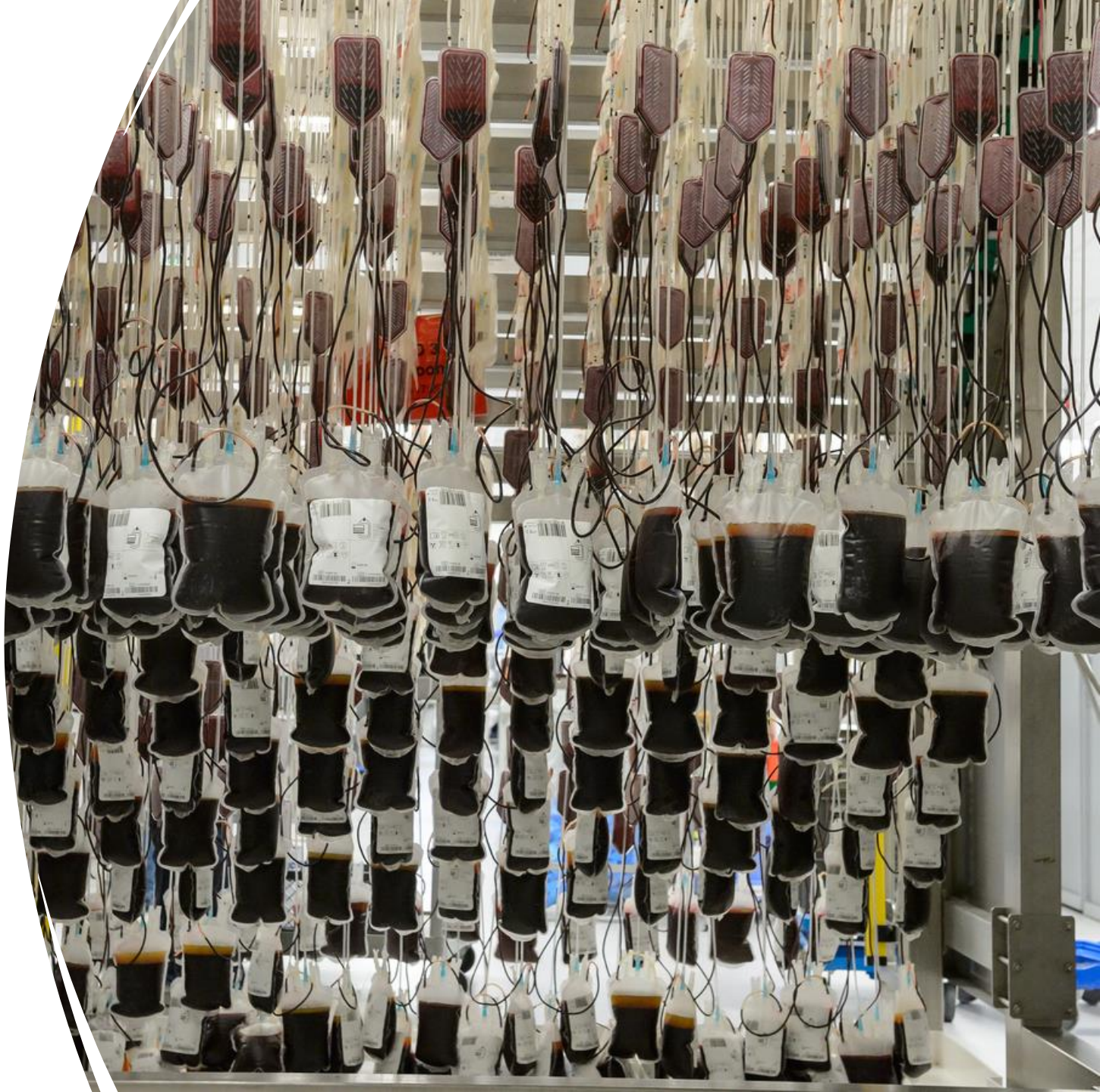

What do the guidelines say?

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

British Society for Haematology

Guideline | Free Access

Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion

Bernard A. Davis, Shubha Allard, Amrana Qureshi, John B. Porter, Shivan Pancham, Nay Win, Gavin Cho, Kate Ryan, on behalf of the British Society for Haematology

First published: 18 November 2016 | https://doi.org/10.1111/bjh.14383 | Citations: 37

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Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects

Bernard A. Davis, Shubha Allard, Amrana Qureshi, John B. Porter, Shivan Pancham, Nay Win, Gavin Cho, Kate Ryan, on behalf of the British Committee for Standards in Haematology

First published: 07 November 2016 | https://doi.org/10.1111/bjh.14346 | Citations: 35

REVIEW

Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline

Veerle Compernolle,[1] Stella T. Chou,[2] Susano Tanael,[3] William Savage,[4] Jo Howard,[5] Cassandra D. Josephson,[6] Isaac Odame,[7] Christopher Hogan,[8] Gregory Denomme,[9] and Nadine Shehata,[3,10] for the International Collaboration for Transfusion Medicine Guidelines

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support

Stella T. Chou,[1] Mouaz Alsawas,[2] Ross M. Fasano,[3] Joshua J. Field,[4] Jeanne E. Hendrickson,[5,6] Jo Howard,[7,8] Michelle Kameka,[9] Janet L. Kwiatkowski,[1] France Pirenne,[10] Patricia A. Shi,[11] Sean R. Stowell,[3] Swee Lay Thein,[12] Connie M. Westhoff,[13] Trisha E. Wong,[14] and Elie A. Akl[15]

Conclusions: The majority of panel recommendations were conditional due to the paucity of direct, high-certainty evidence for outcomes of interest. Research priorities were identified, including prospective studies to understand the role of serologic vs genotypic red cell matching, the mechanism of HTRs resulting from specific alloantigens to inform therapy, the role and timing of regular transfusions during pregnancy for women, and the optimal treatment of transfusional iron overload in SCD.

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty of the evidence identified for many of the questions. The included studies did not measure the potential burden of blood transfusion, which include emotional distress, time required to undergo transfusion, associated loss of income, and patients' concerns about transfusion. The guideline panel acknowledged that several recommendations have "moderate resource implications" associated with them because of the cost of transfusion and the requirement for exchange transfusion in certain patient scenarios.

First published online 21 January 2020

bjh guideline

Position paper on International Collaboration for Transfusion Medicine (ICTM) Guideline 'Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline'

Sara Trompeter,[1] Edwin Massey,[2] and Susan Robinson[3] on behalf of the Transfusion Task Force of the British Society of Haematology Guidelines Committee

[1]University College London NHS Foundation Trust and NHS Blood and Transplant, London, [2]NHS Blood and Transplant, Bristol and [3]Guys and St Thomas' NHS Foundation Trust, London, UK

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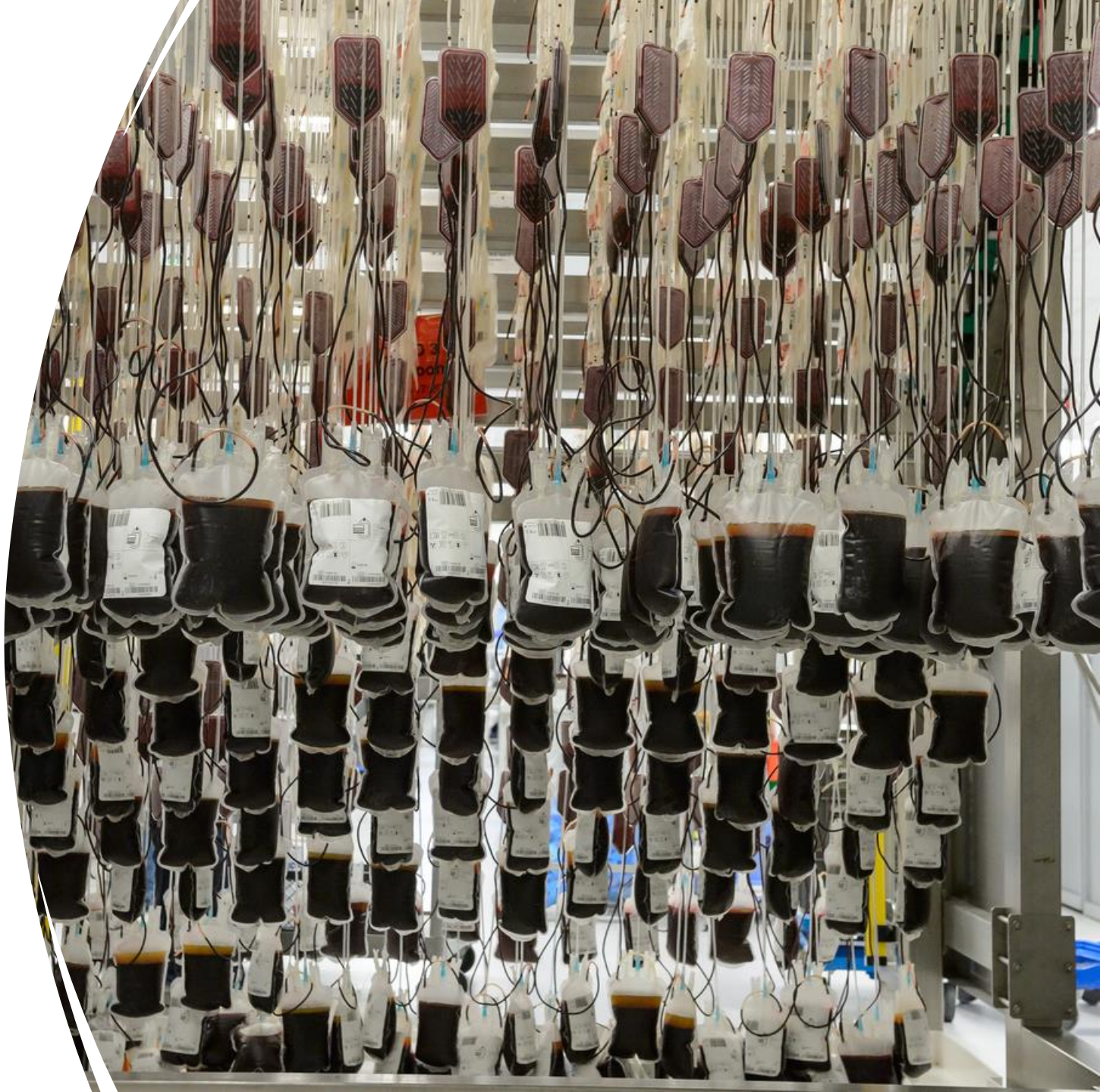


Primary Prevention

- Principles
  - Don’t transfuse unless you have to
    - Optimise sickle care: hydroxyurea
  - Communication between clinical and laboratory staff
  - If someone is needing transfusions frequently, consider regular exchange programme
  - Matching of units
    - Ideal approach
    - Pragmatic Approach
    - Precision Transfusion Medicine

Precision transfusion medicine: the current not precise approach

Donor testing

- Algorithms
- Protocols

Blood specificity

- Fully typed
- Moderately typed
- Basic typing

Patient requirements

- Highly specific
- Moderately specific
- Not very specific at all

Most decision are human based
Little uniformity
Labour intensive
Unlikely to have extended phenotypes frequently available

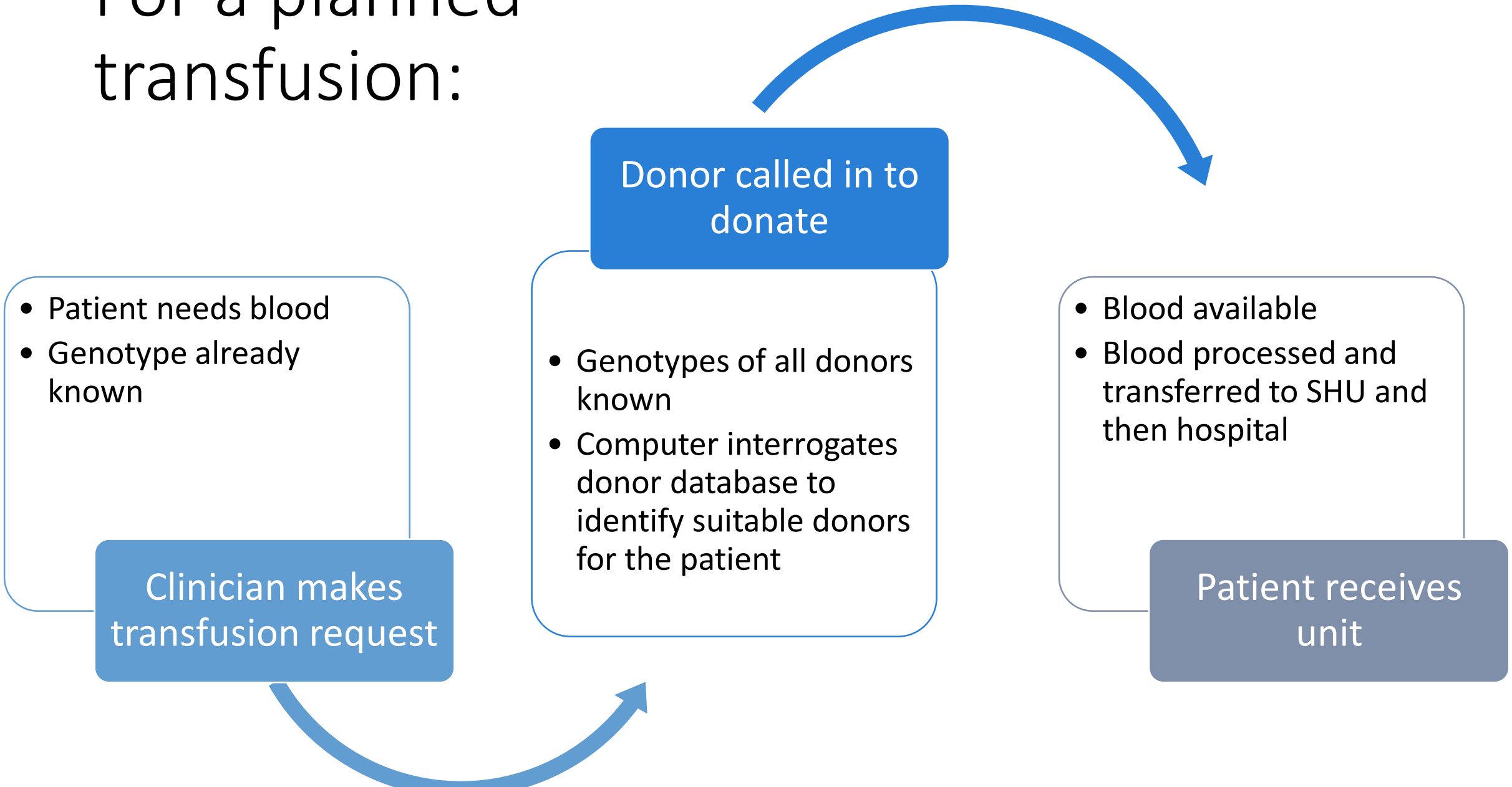
Primary prevention: Precision Transfusion Medicine

- Extensive donor pool
  - Fully red cell genotyped
  - Full spectrum of red cell genotypes that match the need of the patient population
- Targeted intelligent blood donation
  - Electronic linkage between donation and need
  - Pulling in donors when needed
- Patients all red cell genotyped

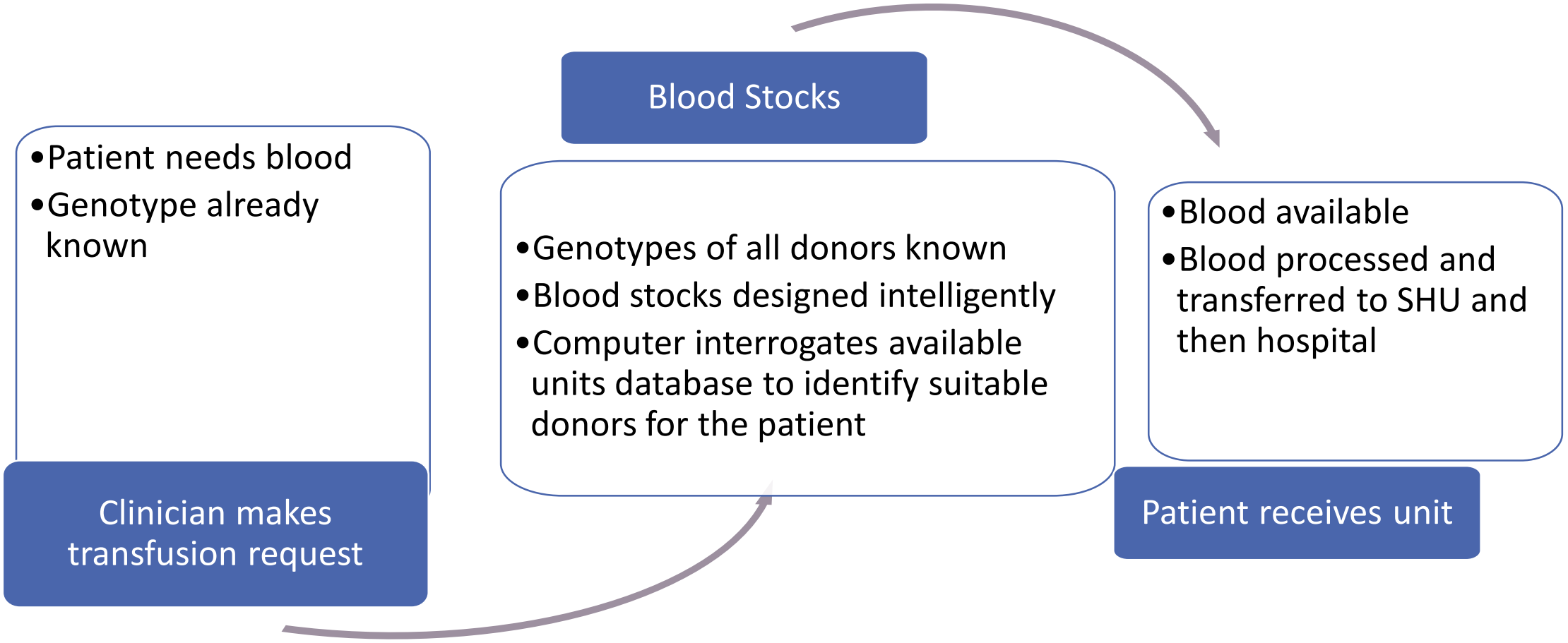
Primary prevention: Precision Transfusion Medicine – is this possible?

- You need
  - Large transfusion database on which to build algorithm
  - Full connectivity between systems
  - AI and ML
  - A donor and recipient panel that are fully genotypws

For a planned transfusion:



For an emergency transfusion:



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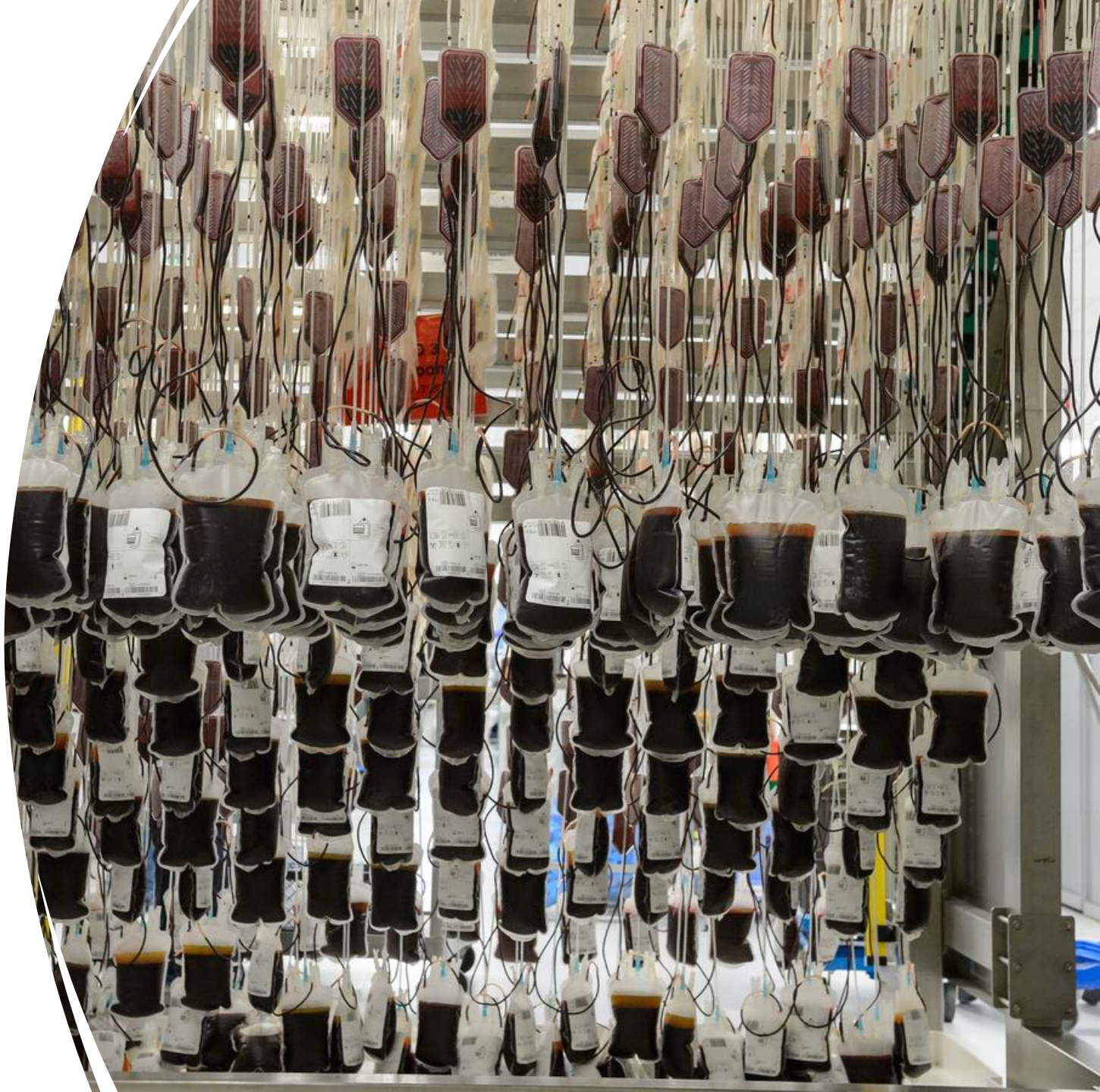
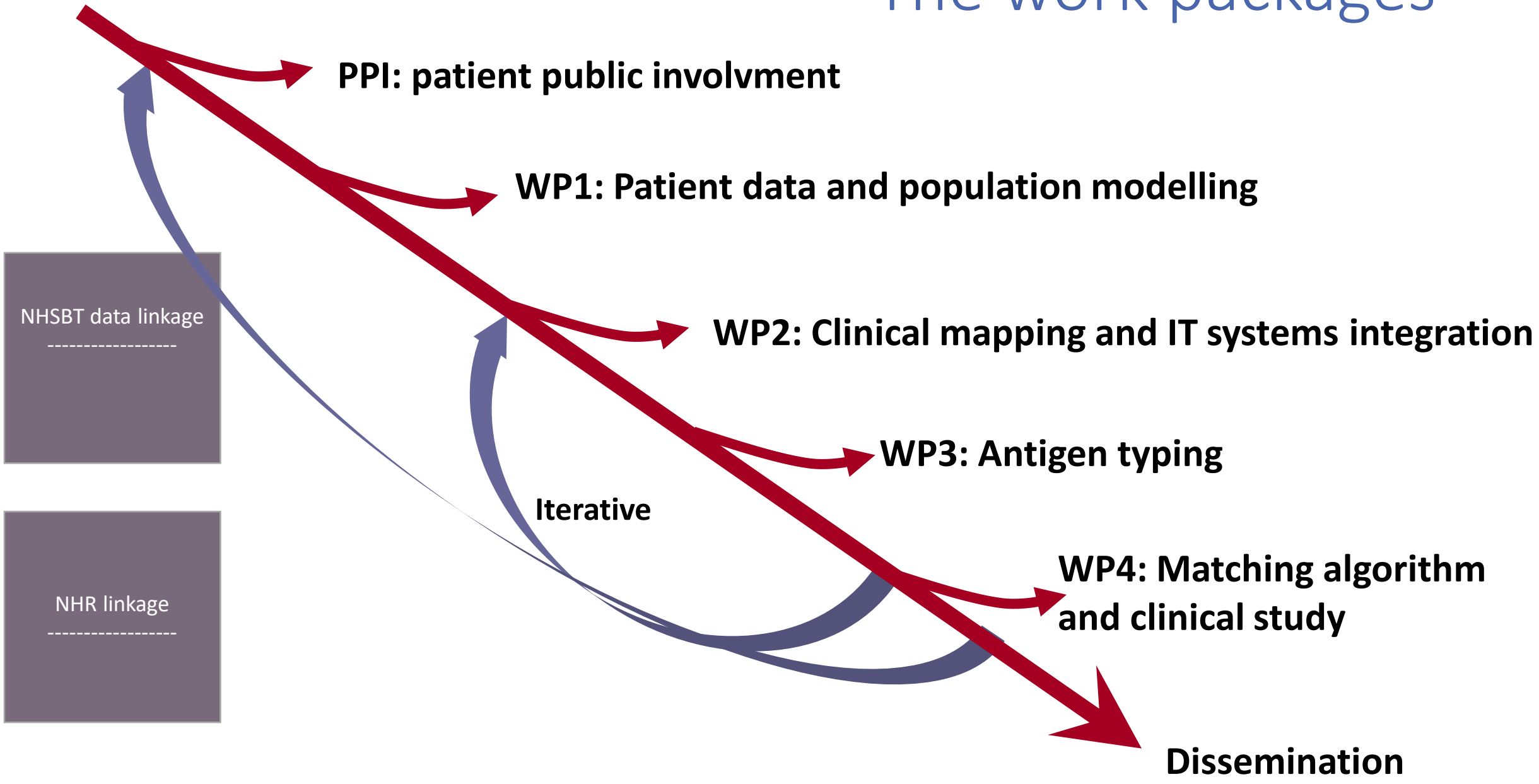
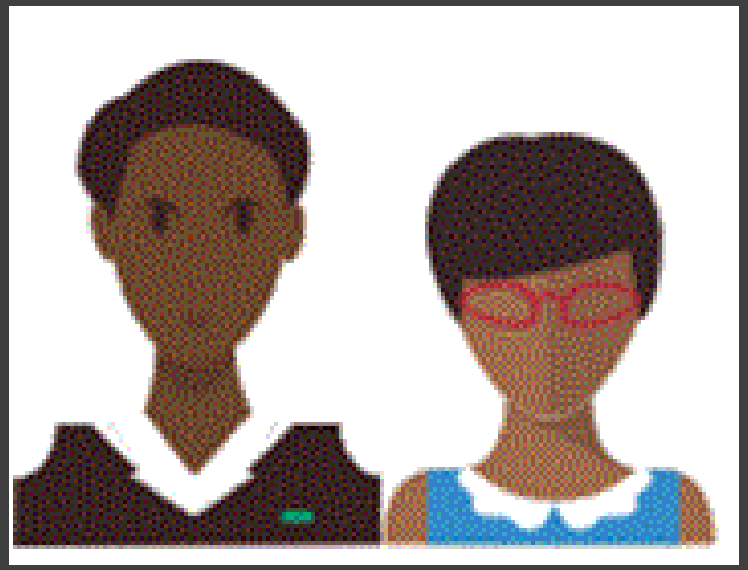


HAEM-MATCH programme : overview

- Four interrelated packages) to define a process of better (extended) matching of patients to donated red cell units for transfusion, to improve outcomes for patients with sickle cell disease
- We believe that extended donor and patient antigen typing could enable routine timely and cost-effective automated extended antigen matching in sickle cell disease
- The potential benefits would include reducing delays in transfusion, reducing risks of alloimmunisation and transfusion reactions, streamlining the allocation of units for difficult to match patients and making regular transfusions available to those who currently cannot have them

The work packages



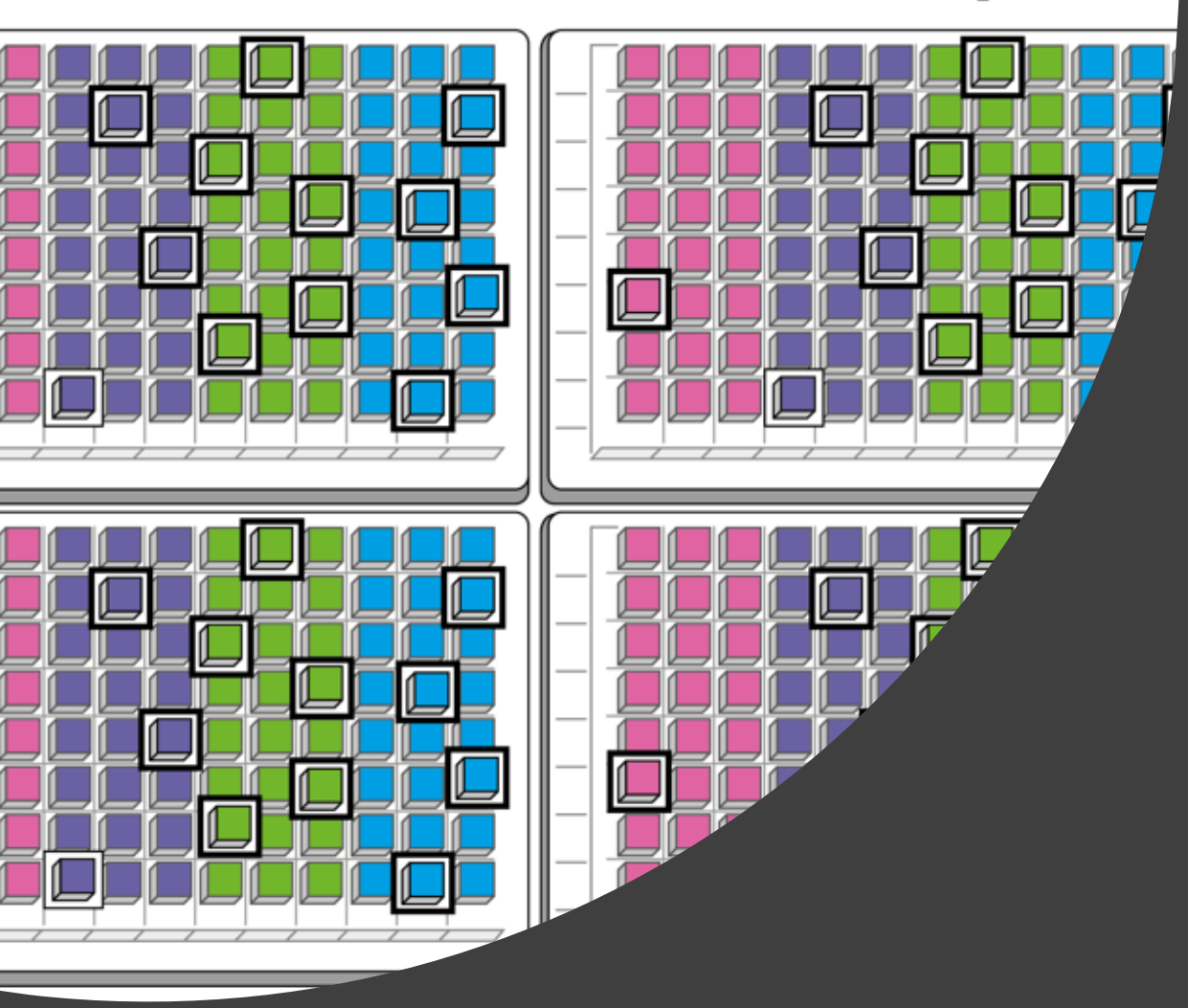


HAEM-MATCH Work Package 1

- A database of a large representative population of patients with SCD
- To establish the transfusion history and current standards of matching

HAEM-MATCH: Work Package 2

- To map the pathway from the clinical decision to transfuse a patient with sickle cell disease to the patient receiving his/her transfusion
- To enable better connectivity between the key IT systems in NHSBT; between NHSBT and the National Haemoglobinopathy Registry (NHR) and between the hospital and NHSBT and vice versa
- To ensure that all patient data that is transmitted is stored appropriately and safety

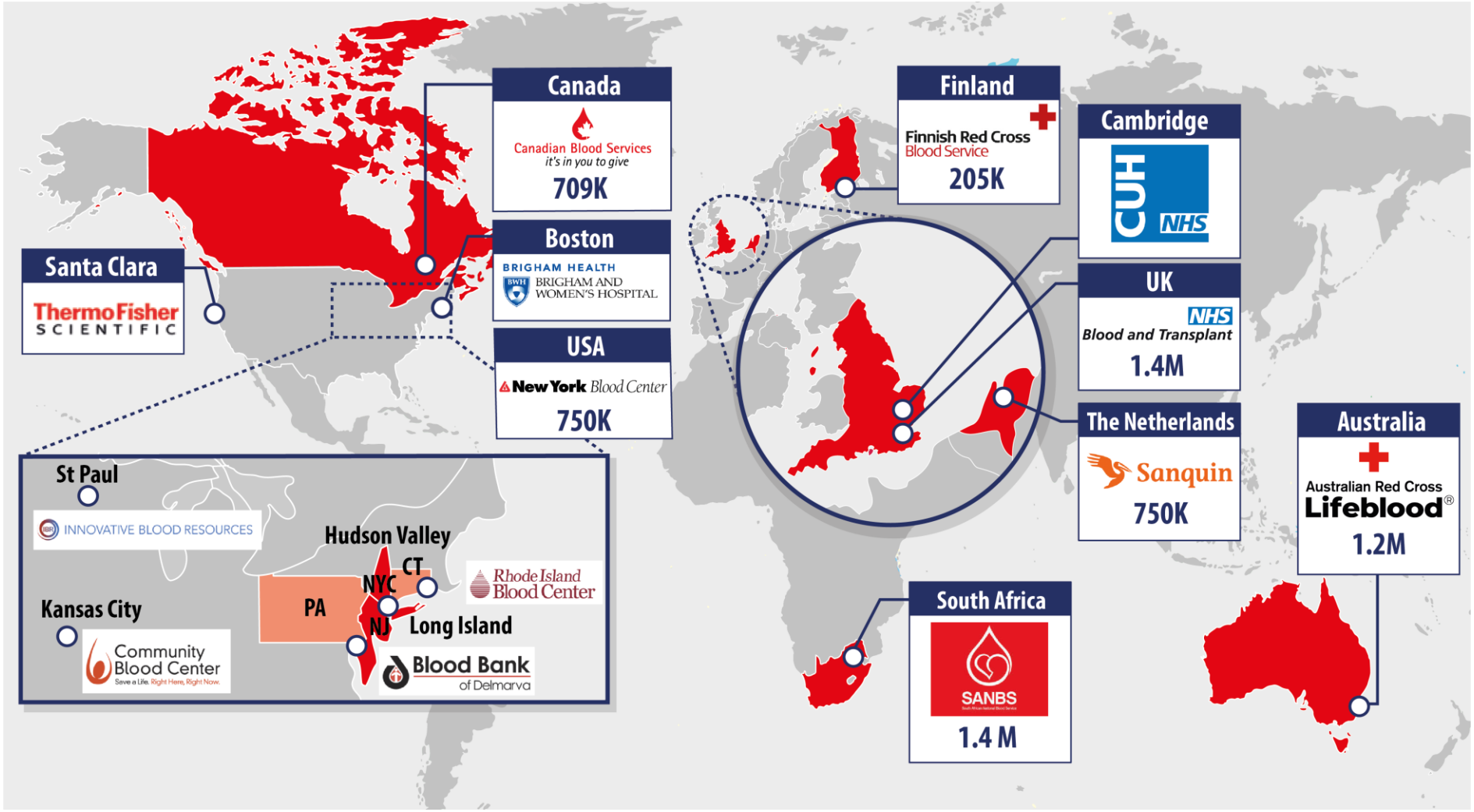


Work Packages 3 & 4

- To explore the role of various antigen typing platforms for donors and patients, including by genetic testing

- To develop a clinical study protocol, to include a better red cell antigen matching algorithm for patients with sickle cell disease and the impact on blood donor recruitment strategy

The Blood transfusion Genomics Consortium



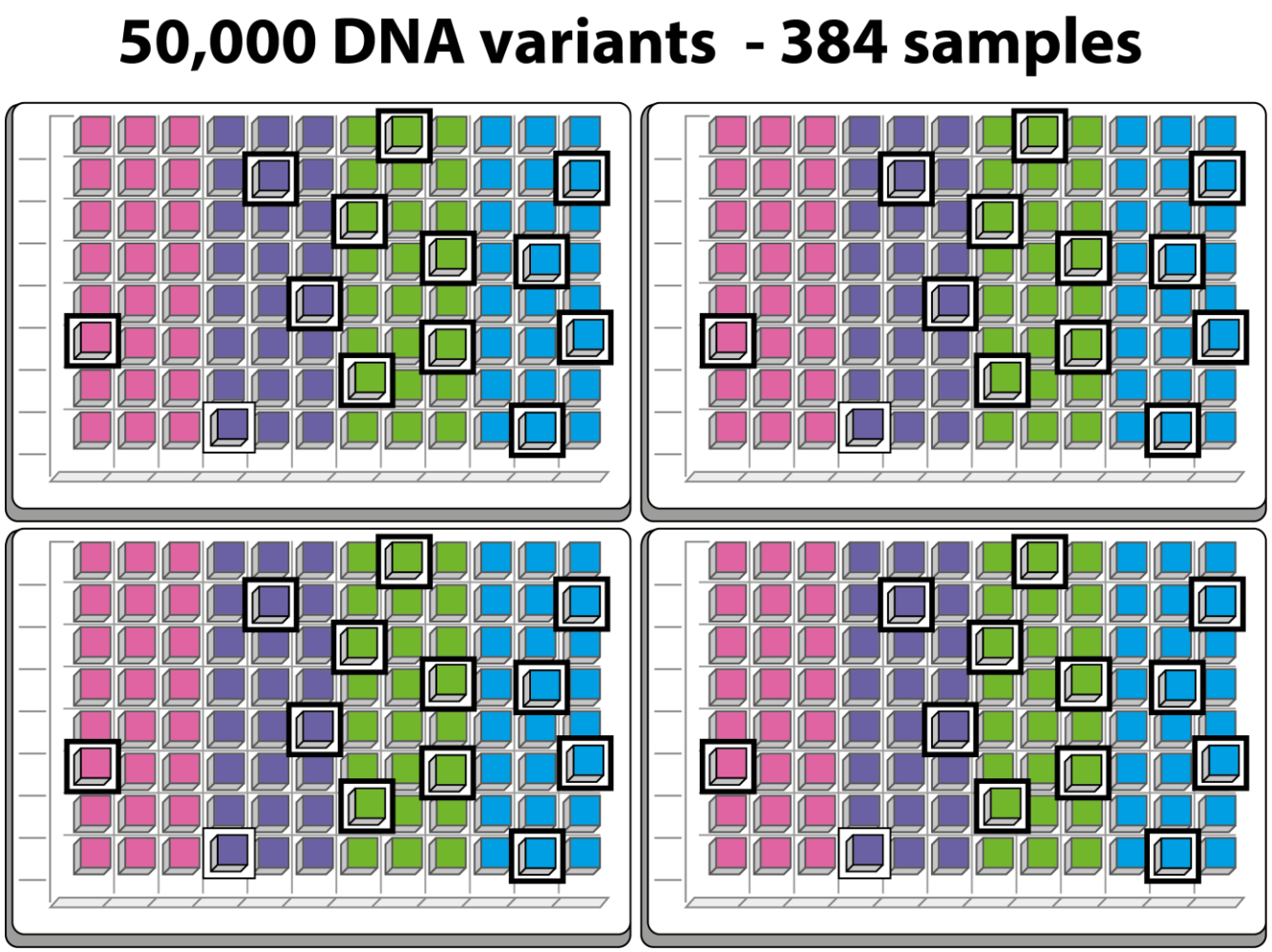
Blood transfusion Genomics Consortium

Principal Investigators

James Daly
Ute Jentsch
Will Kruka
Andrea Harmer
Bill Lane
Celina Montemayor
Willem H Ouwehand
Jukka Partanen
Ellen v.d. Schoot
Connie Westhoff

- Aim to develop a universal array for blood type genotyping

New Transfusion Genotyping Array



Developed by Nick Gleadall

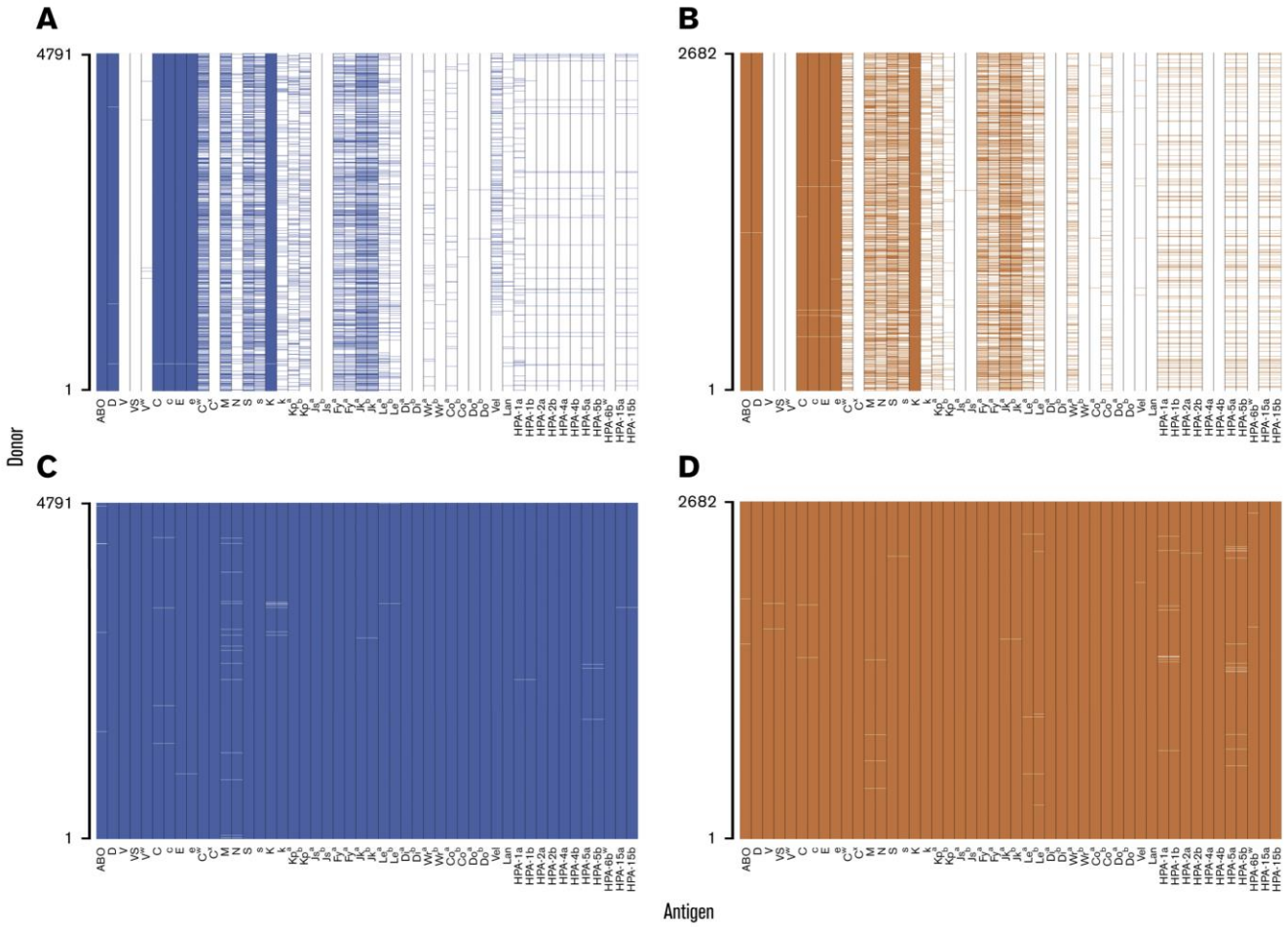
Array Characteristics

- Probes DNA variants relevant to transfusion & transplantation
- The same array content will be used by the REDS consortium in the USA
- The array generates:
  - Blood group types
  - HLA, HPA and HNA types
  - Donor health and product quality information

The 384-format: One GENETITAN-MC instrument processes 8 plates/week generating typing results for **3,008 donor** and 64 QC samples

Genetic Blood Typing

- Accurate calling of most red cell antigens relevant to transfusion
- £11.25/sample: the NHS currently pays £480/sample
- 5 million typed within 3 years in Our Future Health study
- 1 million will be NHSBT donors
- Large pool of donors/non-donors to identify for rare types



Taken from Gleadall, N.S.*et al.*, **Development and validation of a universal blood donor genotyping platform: a multinational prospective study**

Collaboration with Sanquin

- The Dutch blood service Sanquin are a little more advanced
- We plan to collaborate and hope to adapt some of their ideas for matching for application by NHSBT
- Joost van Sambeeck has developed a framework for optimal matching in his PhD thesis

- bloodTyper, Translate the genetic codes of blood grouping into blood groups
- bloodStocker, Prioritise rare blood for difficult to transfuse patients and call in donors on the basis of genotype
- bloodMatcher, Provide a high degree matching of blood units
-
- bloodLinker, Allow direct ordering of specific blood units for specific patients

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- Manuel Gomes
- Ellen van der Schoot
- Shantanu Kaushikkar
- Michaela van der Schaar
- Connie Westhoff
- Sara Trompeter

Informatics – AI NiHR Application

bloodTyper	bloodStocker	bloodMatcher	bloodLinker
• Translate the genetic codes of blood grouping into blood groups	• Prioritise rare blood for difficult to transfuse patients and call in donors on the basis of genotype	• Provide a high degree matching of blood units	• Allow direct ordering of specific blood units for specific patients

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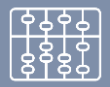
Future Possibilities

- HaemMatch will focus initially on SCD and collect data on thalassaemia
- Other transfusion dependent patient populations:
  - MDS, other transfusion dependent cohorts
  - Dynamic integration of elective transfusion schedules into blood matching system
- Automatic donor invitations for rare blood types

A monumentally collaborative approach will be needed to make this a reality

Database: Large haemoglobinopathy centres / database build/ information transfer / link to NHSBT data on donors and recipients

Genotyping: fast throughput cost effective genotyping of patients and donors/ informatics to translate genetic codes into blood groups



Informatics: linking different systems / pulling donors in for appointments and allocating their units to specific recipients

Feasibility study

Clinical Trials

NHS
Blood and Transplant

Thank you