

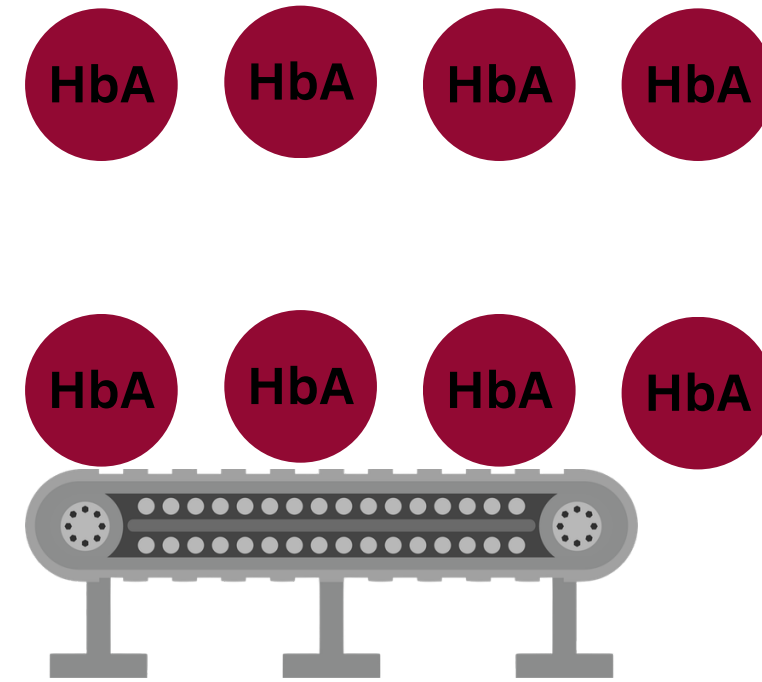
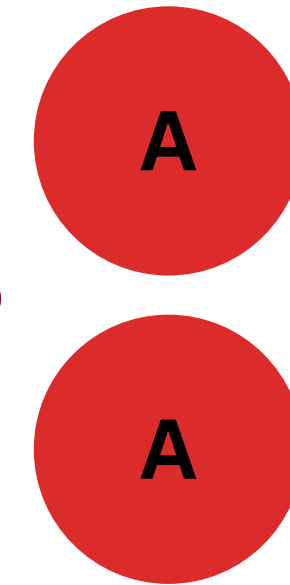
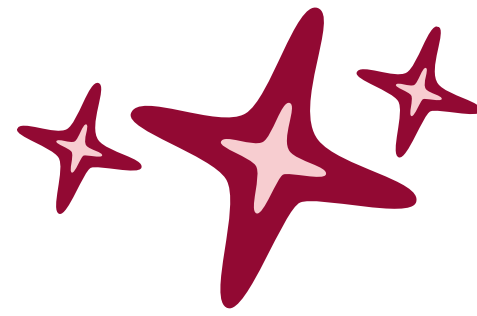


GENE THERAPY FOR SICKLE CELL DISORDERS AND THALASSAEMIA

Dr Amy Cooper
Haemoglobinopathy QI Fellow



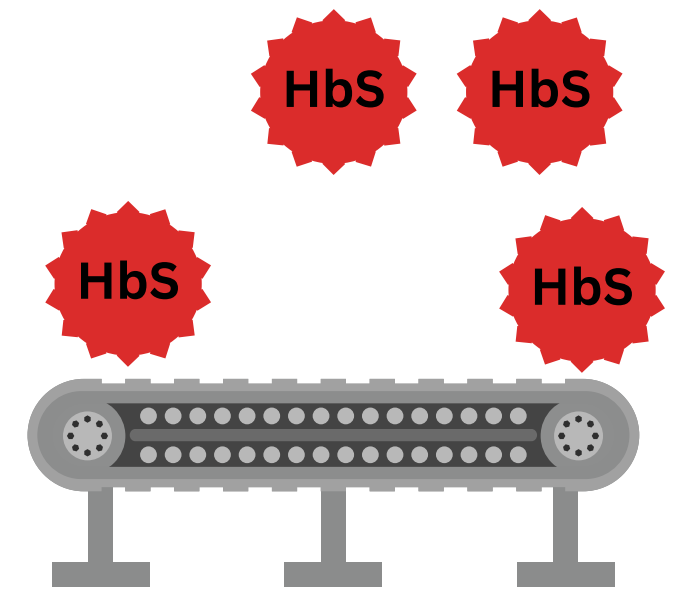
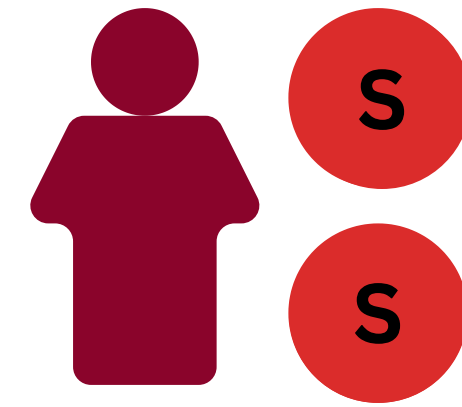
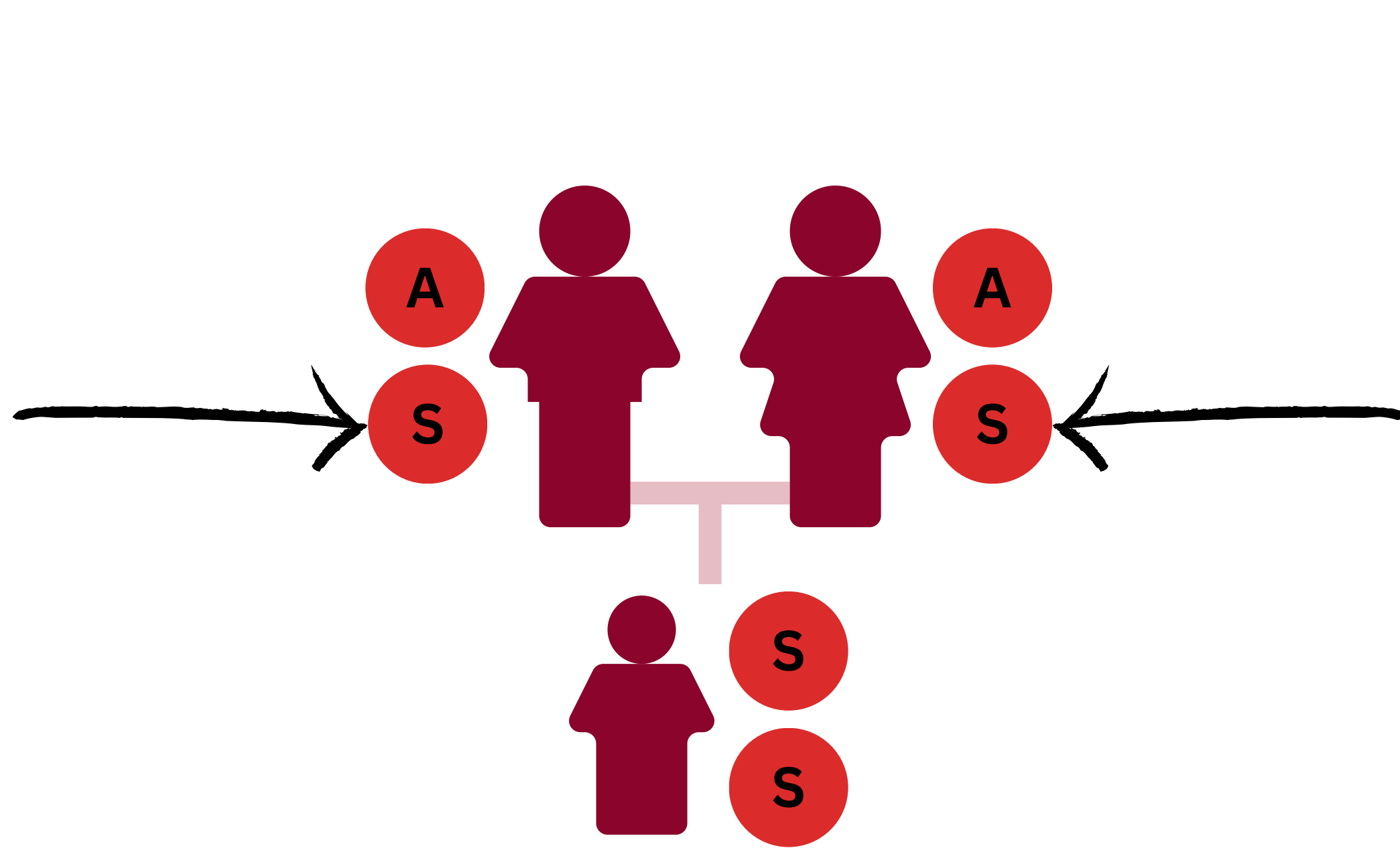
RED CELLS



- Red cells are blood cells which travel around the body in the blood stream
- They are filled with proteins called haemoglobin which carry the oxygen
- Haemoglobin is made by the two genes which are inherited - one from each parent
- Most people have the same kind of haemoglobin - HbA.

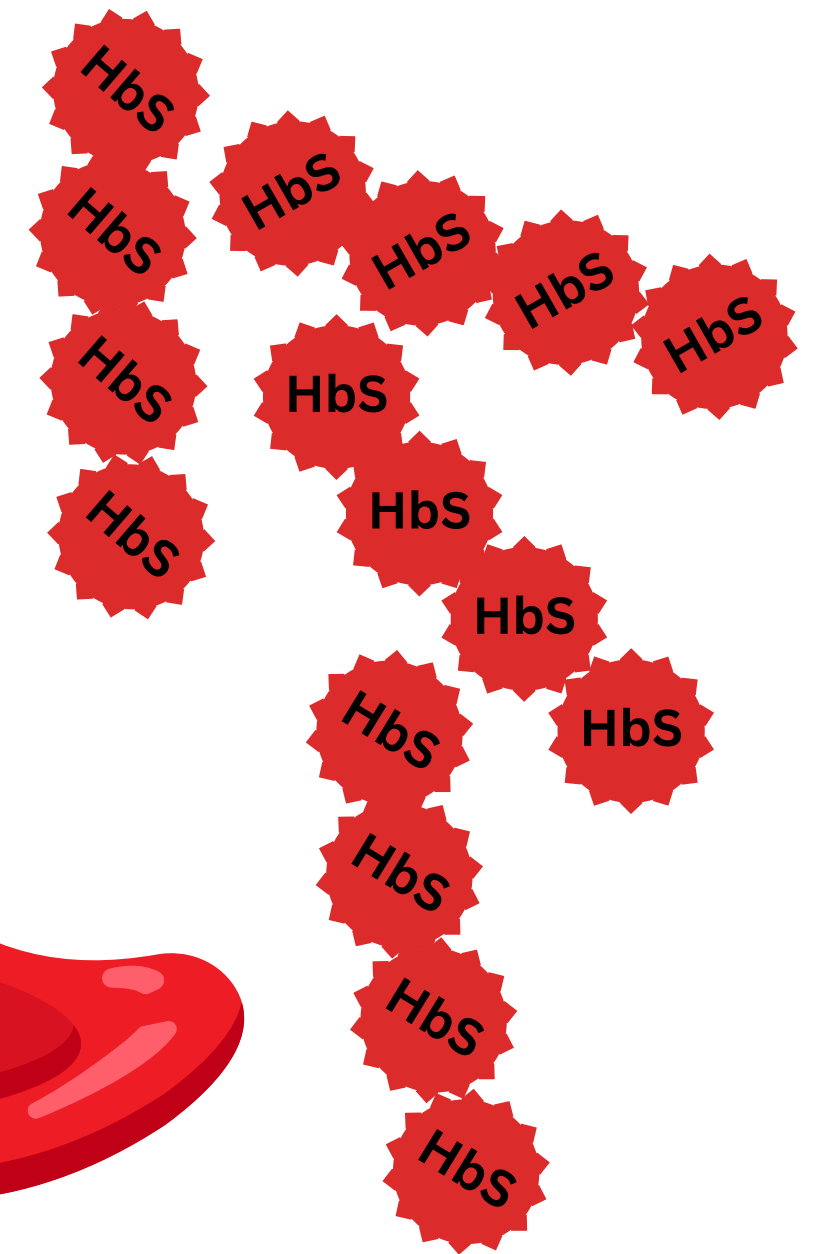
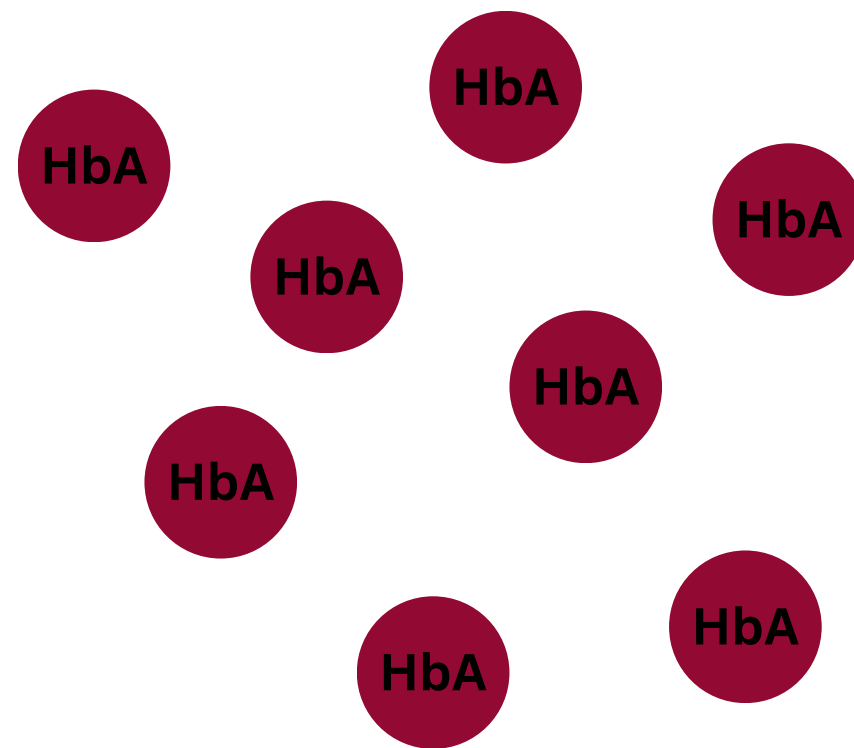


SICKLE CELL ANAEMIA



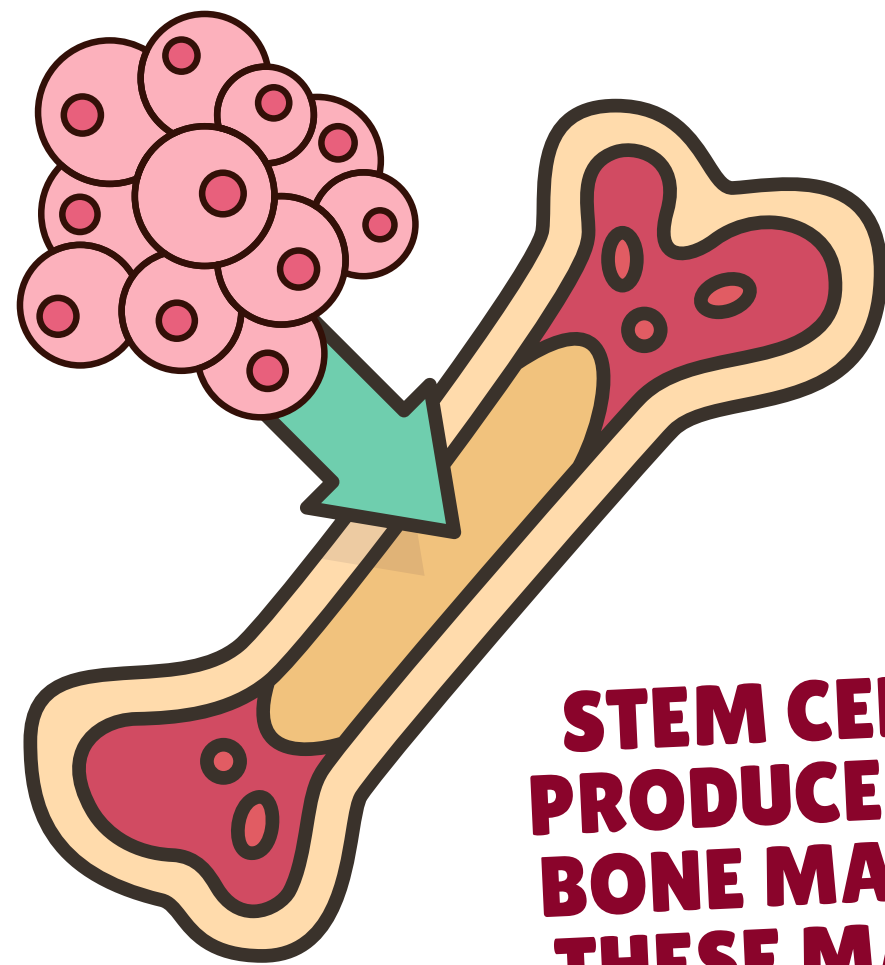
SICKLE CELL ANAEMIA

WHY DO CELLS SICKLE?

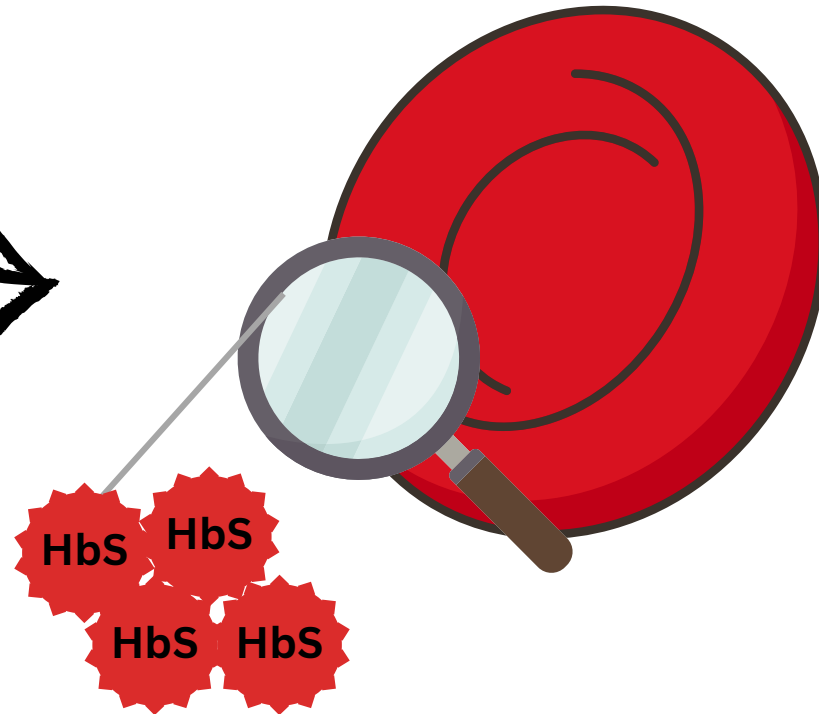
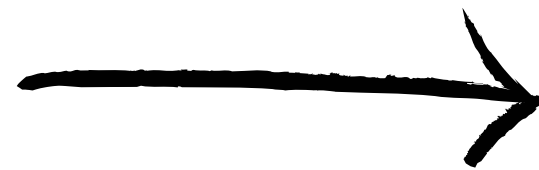


SICKLE CELL ANAEMIA

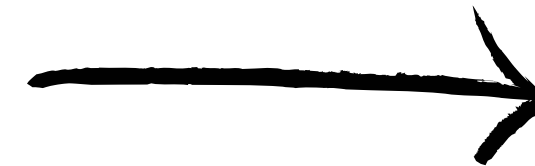
WHERE DO SICKLE CELLS COME FROM?



STEM CELLS ARE PRODUCED IN THE BONE MARROW – THESE MAKE RED CELLS, WHITE CELLS AND PLATELETS

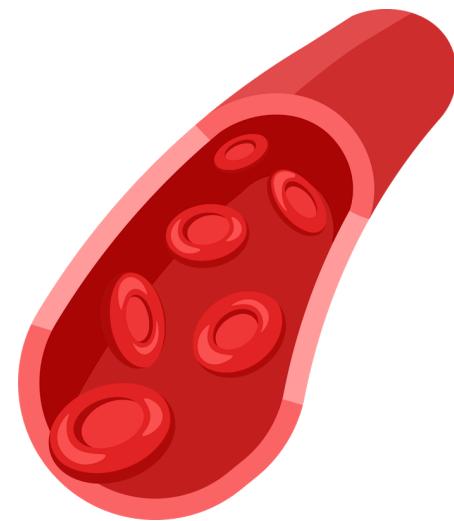


RED CELLS ARE MADE – FILLED WITH SICKLE HAEMOGLOBIN



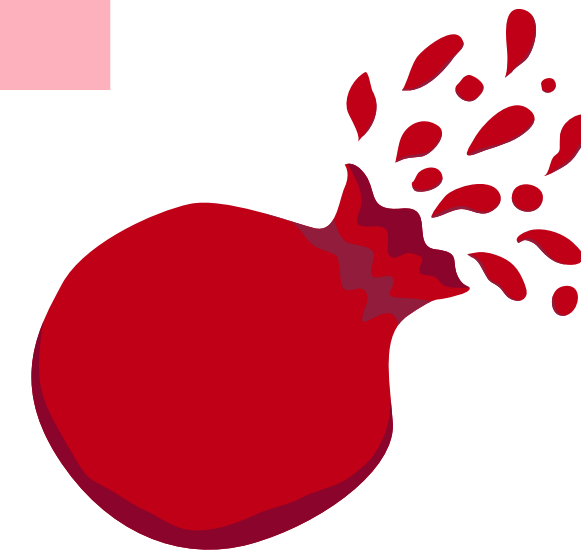
CELLS BECOME SICKLE SHAPED WITHIN 10 DAYS

WHAT DO SICKLED CELLS DO IN THE BODY?



VESSEL BLOCKAGES

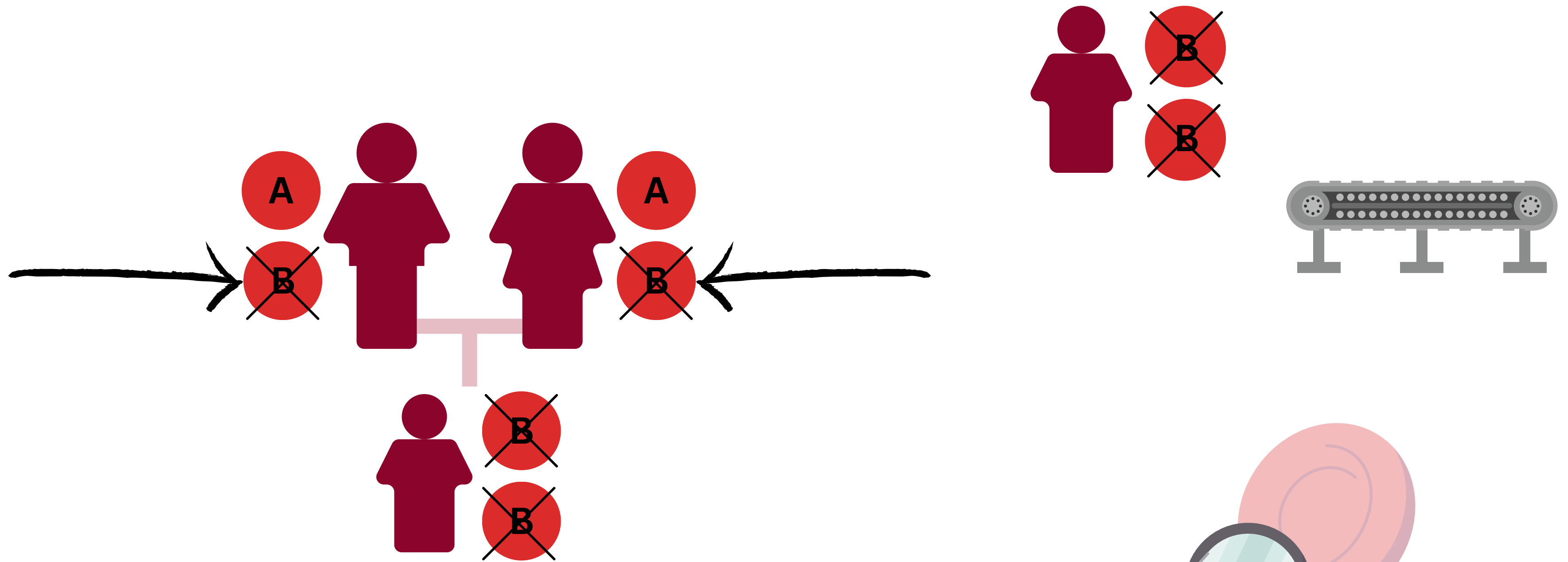
Sickle cells block small vessels, causing severe pain and background organ damage



CELL BREAKDOWN

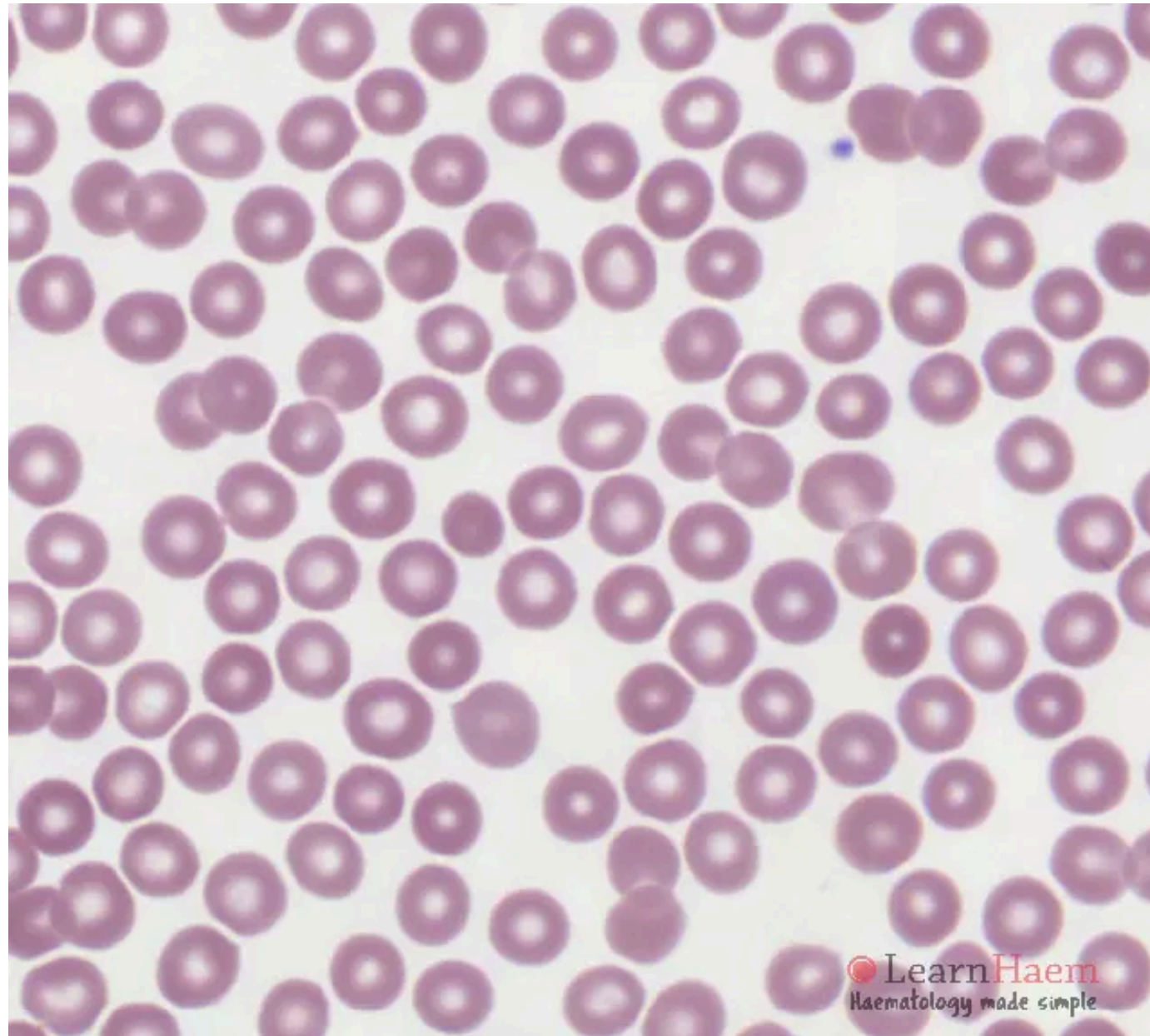
Sickle cells are destroyed quickly by the body as it recognises them as abnormal.

BETA THALASSAEMIA

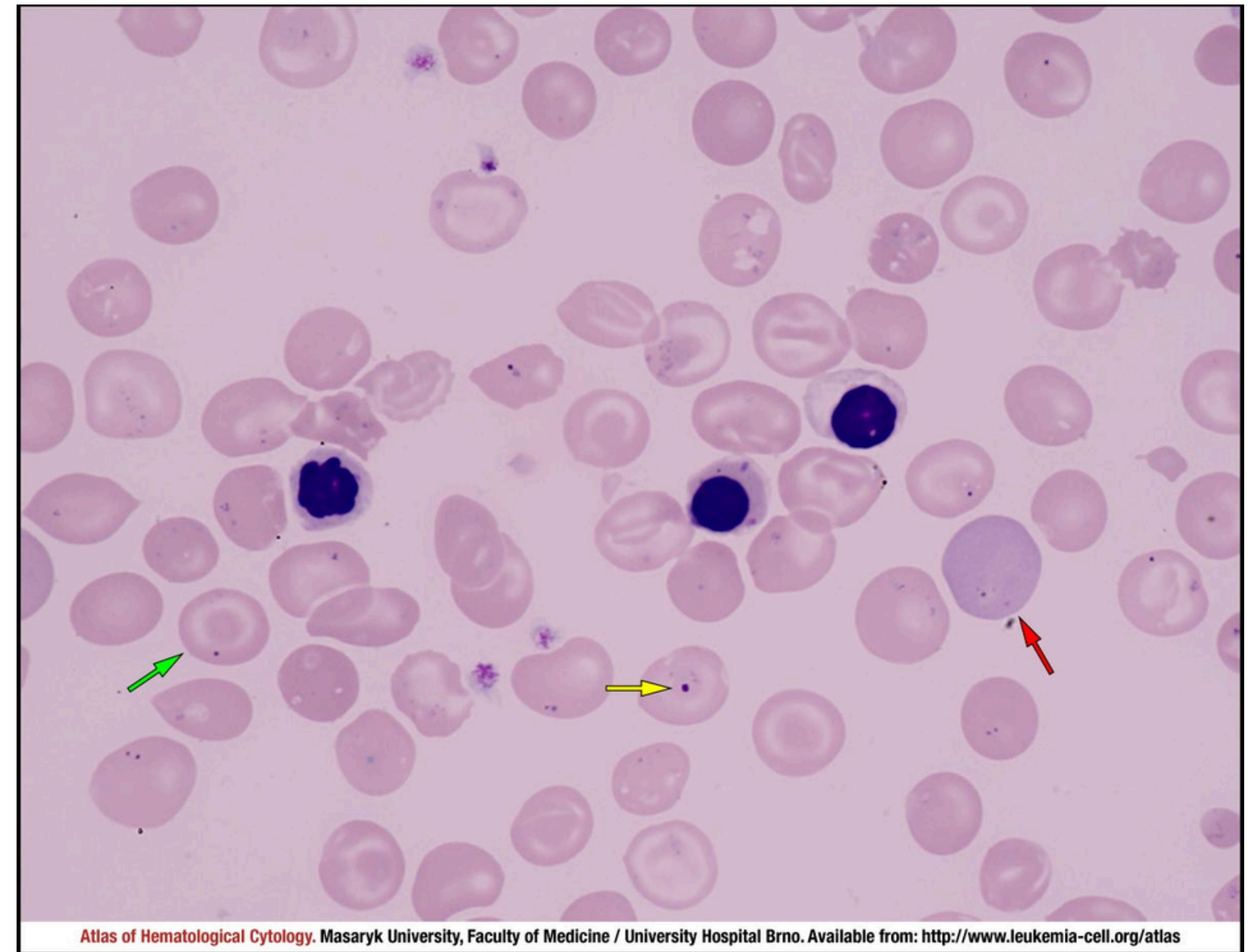
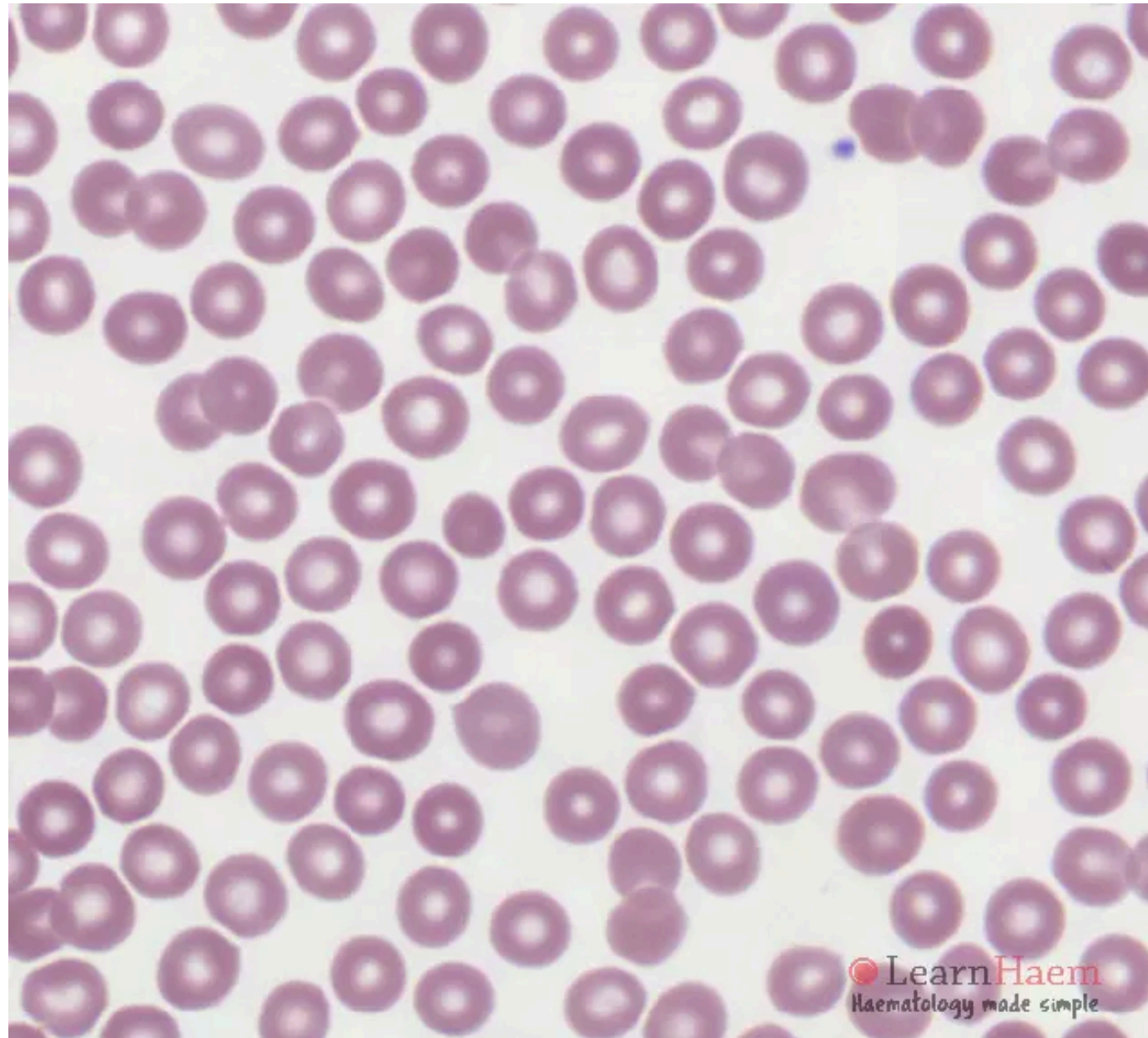


HbF

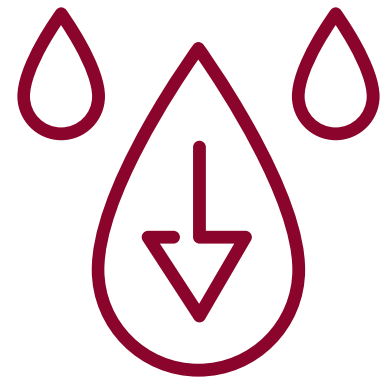
BETA THALASSAEMIA



BETA THALASSAEMIA

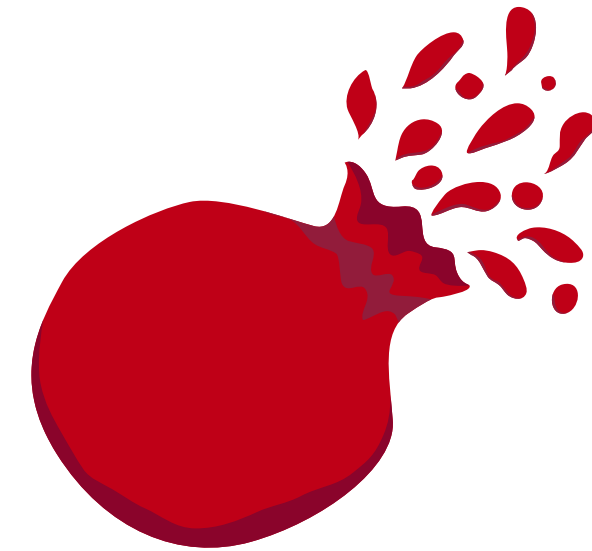


WHY IS THALASSAEMIA A PROBLEM?



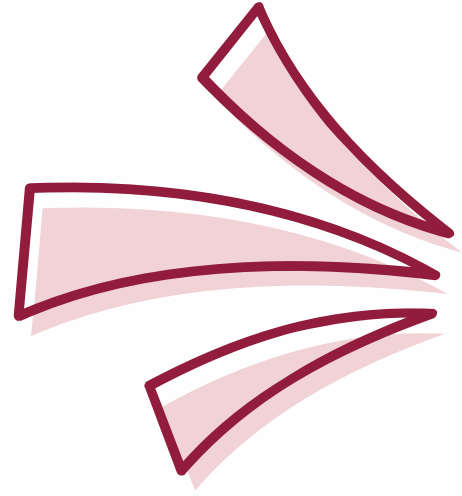
NOT ENOUGH HAEMOGLOBIN

Although there is some haemoglobin, it is only made in small amounts and is not enough to make the cells healthy.



CELL BREAKDOWN

Thalassaemia red cells are destroyed quickly by the body as they are an unusual size and shape.



CURATIVE OPTIONS?

1

Stem cell transplant is available in the UK for sickle cell disorders and thalassaemia, and is a potential cure





WHY DO WE OFFER CURATIVE OPTIONS?

- Sickle cell disorders and thalassaemia can cause acute and chronic organ damage
- Life expectancy remains shortened despite recent advances
- Impact of living with haemoglobinopathies on wellbeing and quality of life can be significant



WHO IS ELIGIBLE FOR TRANSPLANT? SICKLE CELL

1

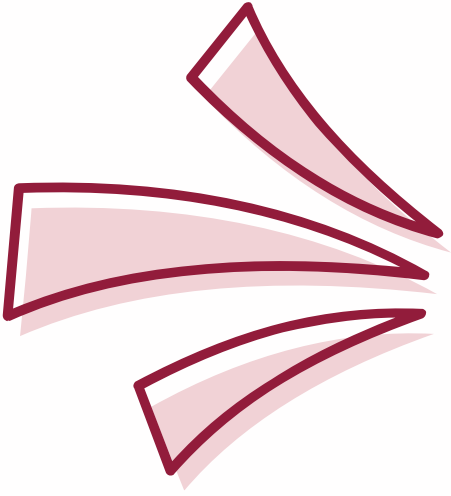
Patients with organ damage related to sickle cell disease

2

Patients on regular red cell exchange transfusions

3

Patients who have severe complications such as acute chest syndrome and stroke



WHO IS ELIGIBLE FOR TRANSPLANT? THALASSAEMIA

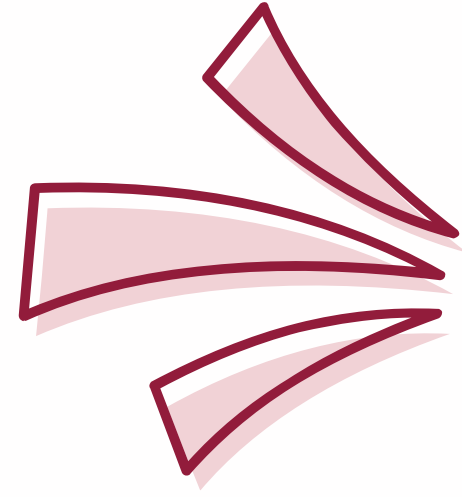
2

Patients with
transfusion dependent
thalassaemia

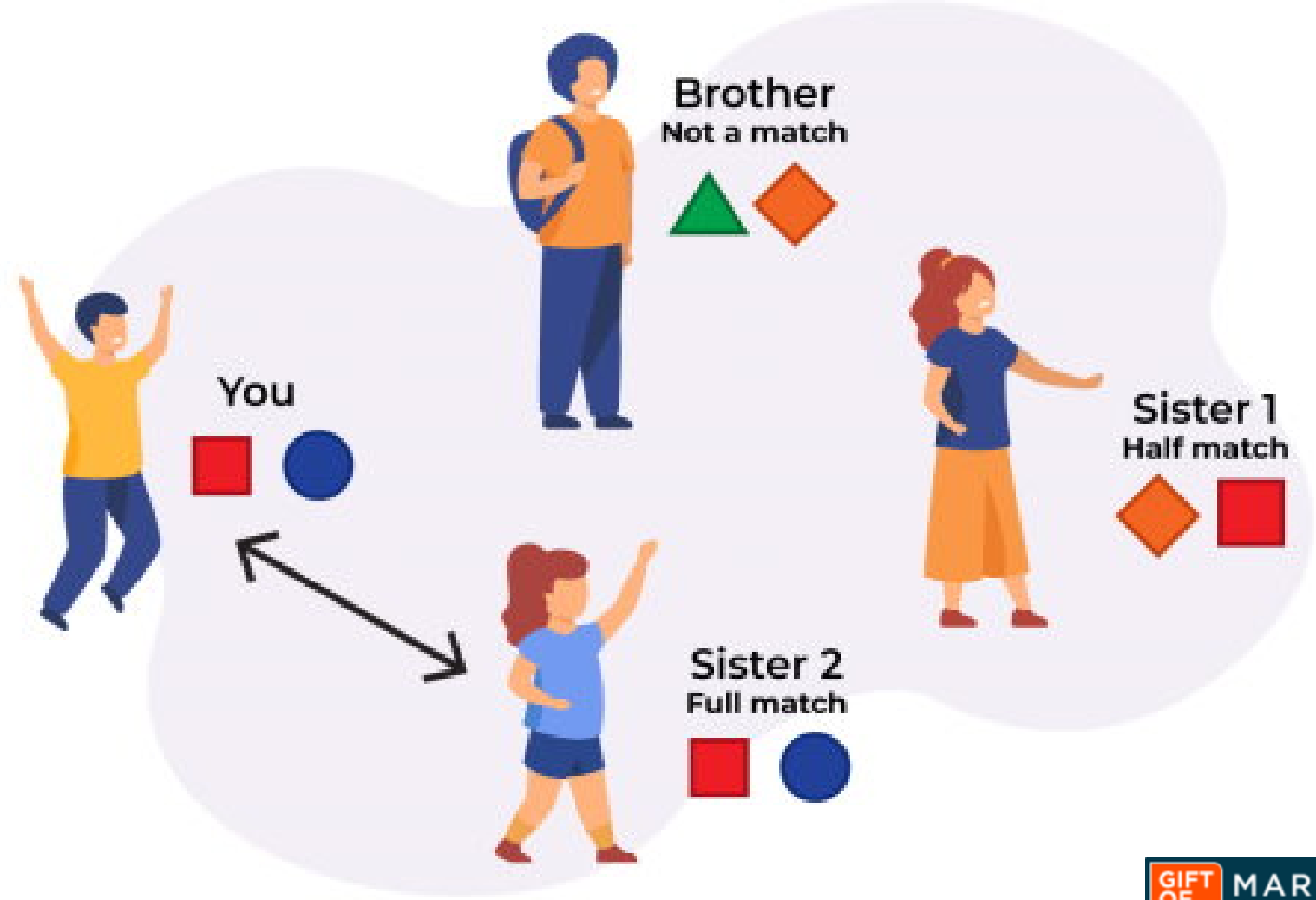
Usually children,
although now also
available for adults in UK

3

Must have a fully
matched sibling
donor



TYPES OF MATCH





CURATIVE OPTIONS?

1

Stem cell transplant is available in the UK for sickle cell disorders and thalassaemia, and is a potential cure

2

Patients need a 10/10 sibling match to be eligible to have a transplant on the NHS

3

So what else is available if you don't have a sibling match?

OCTOBER 2020



NOBELPRISET I KEMI 2020
THE NOBEL PRIZE IN CHEMISTRY 2020



KUNGL.
VETENSKAPS-
AKADEMIEN
THE ROYAL SWEDISH ACADEMY OF SCIENCES



Photo: Halbauer/Forell

Emmanuelle Charpentier



Photo: UC Berkeley/Doudna Lab

Jennifer A. Doudna

"för utveckling av en metod för genomeditering"

"for the development of a method for genome editing"

#nobelprize



8TH AUGUST 2024

sky news

Gene therapy costing over £1.6m is approved for NHS patients with inherited blood disorder

The medicines watchdog is allowing the treatment on the NHS - after securing a discount on the normal price - and says it "could represent a potential cure" for people with a condition called beta-thalassaemia.

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First gene-editing therapy may cure blood disorder

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The Guardian

UK

Society Law Scotland Wales Northern Ireland

This article is more than 1 year old

NHS to offer 'life-changing' gene therapy for blood disorder thalassaemia


Treatment may be offered to hundreds with severe form of disease, most often found in people of Mediterranean, Asian and Middle Eastern heritage

Advertisement



South West
**Haemoglobinopathy
Coordinating Centre**

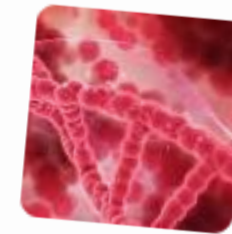
31ST JANUARY 2025


 Imperial College Healthcare NHS Trust

World-first gene-editing treatment for blood disorders including sickle cell disease approved for use in the NHS

The National Institute for Health and Care Excellence (NICE) has today approved a gene-editing treatment for use with NHS patients over the age of 12 with a...

31 Jan 2025

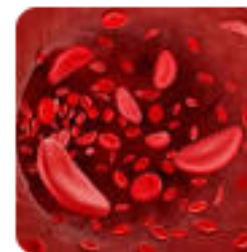



 The Guardian

'Groundbreaking' sickle cell disease treatment approved for NHS use in England

Clinical trials find one-time gene therapy exa-cel offers 'functional cure' in 96.6% of patients.

31 Jan 2025



 London Evening Standard

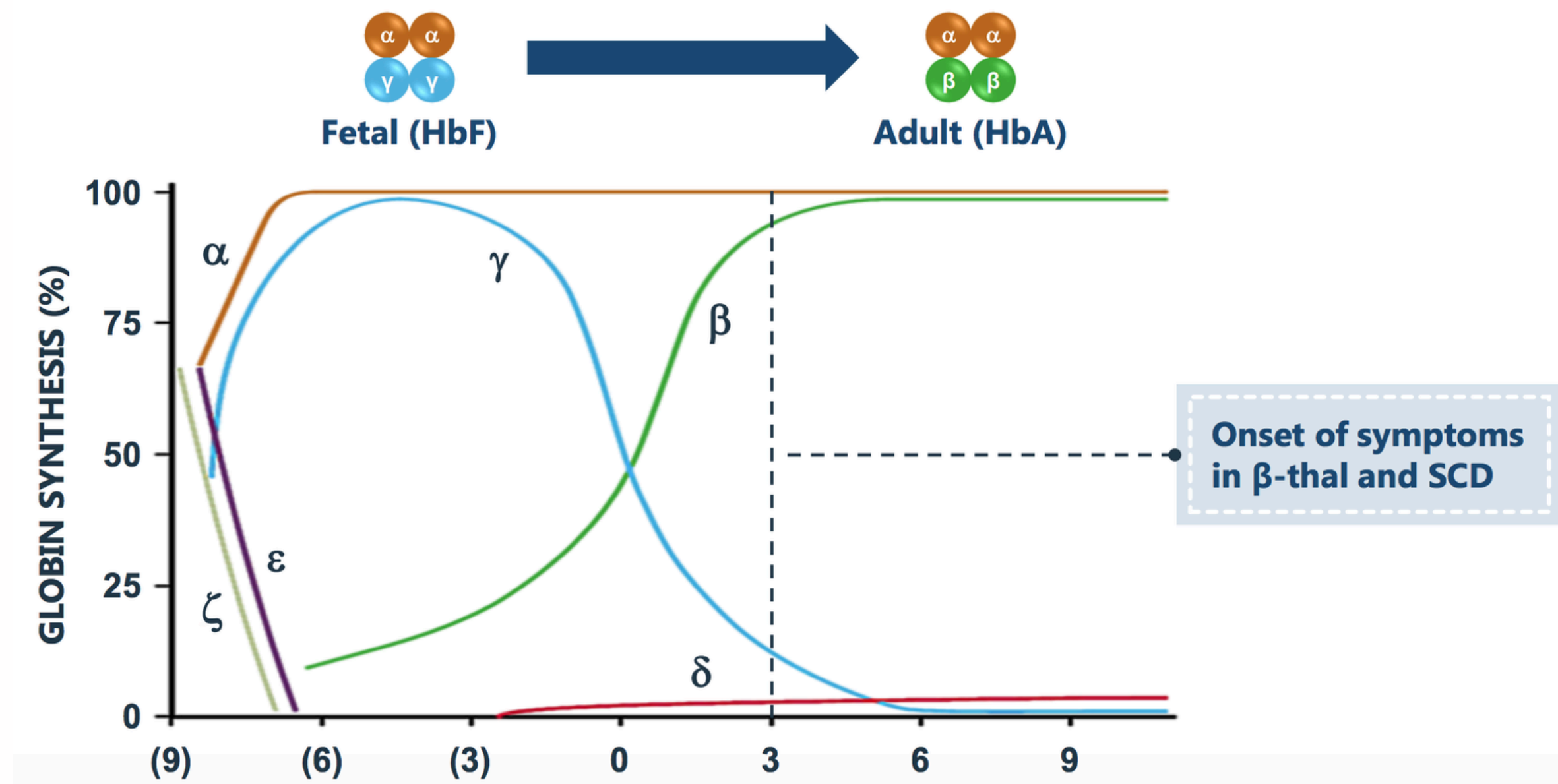
Sickle cell patients share delight over approval of new treatment

Health officials have approved a £1.65 million treatment for some NHS patients.

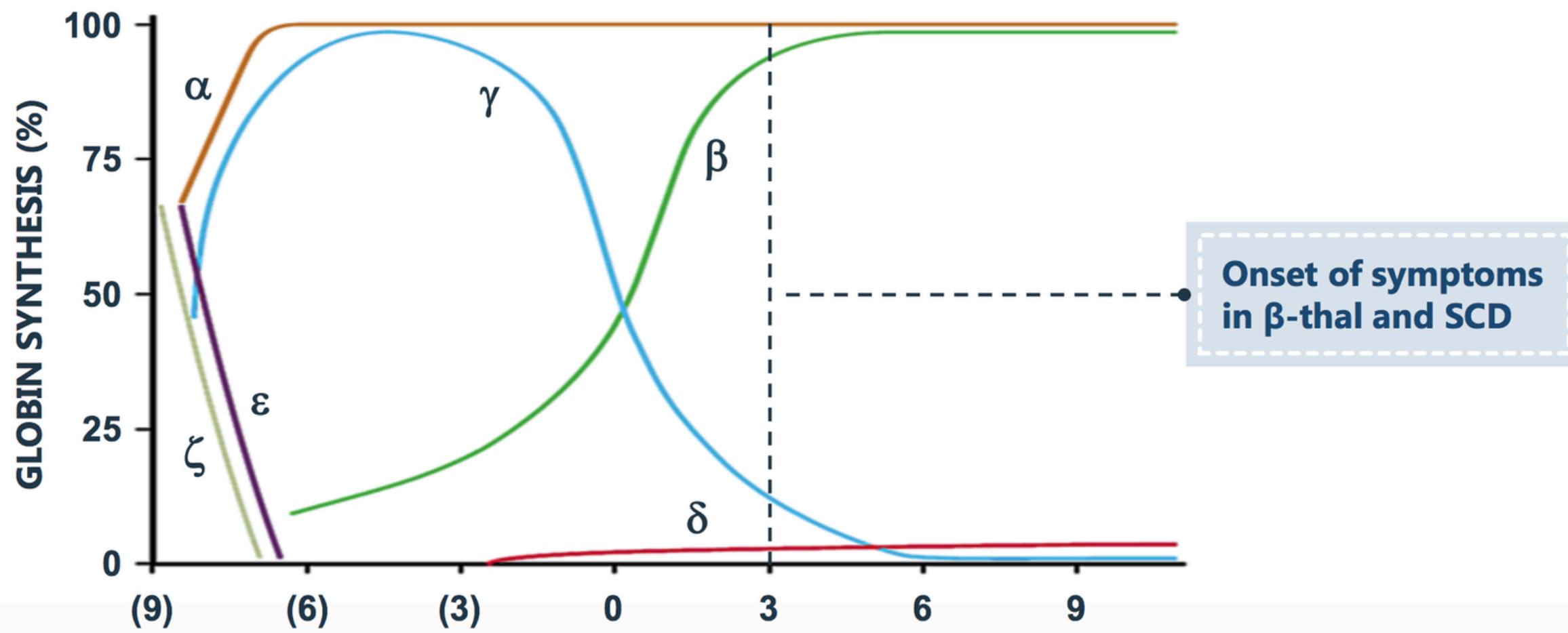
31 Jan 2025



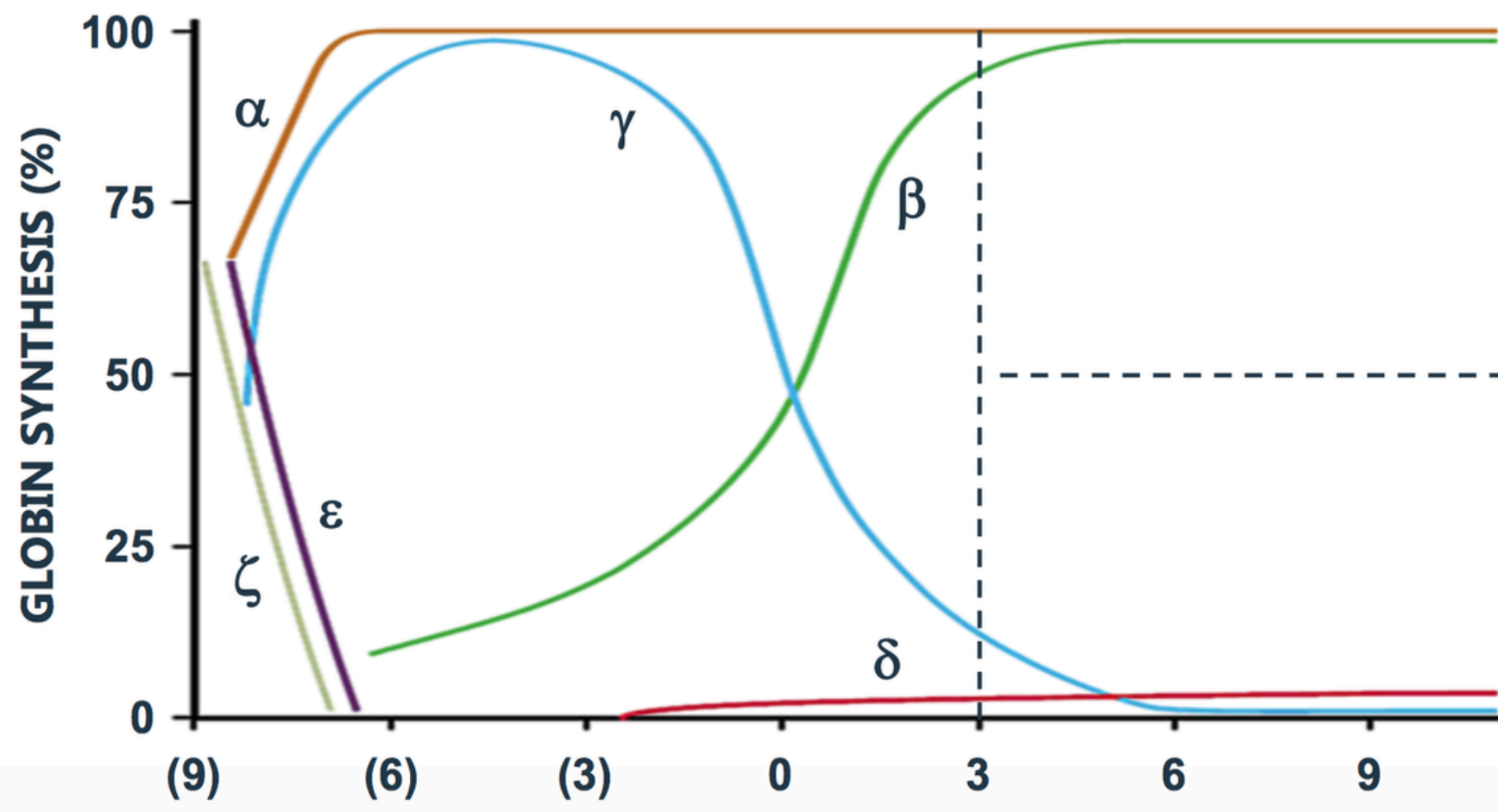
WHAT DOES GENE THERAPY TARGET?



WHAT DOES GENE THERAPY TARGET?

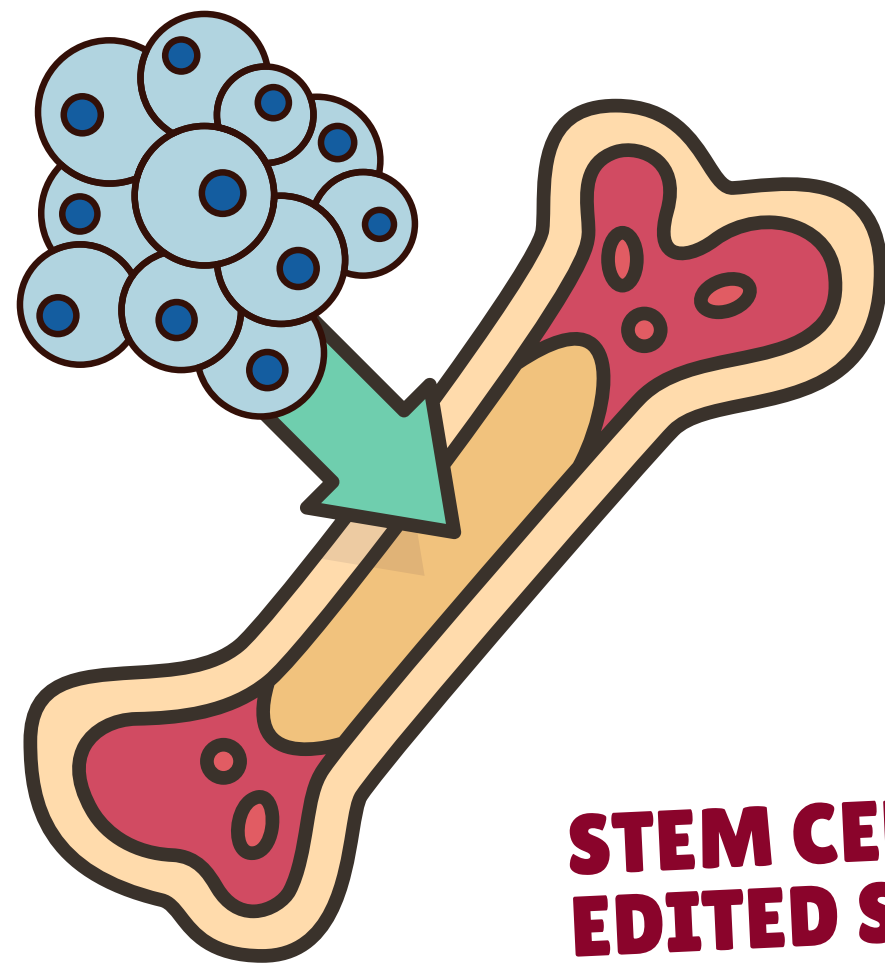


WHAT DOES GENE THERAPY TARGET?

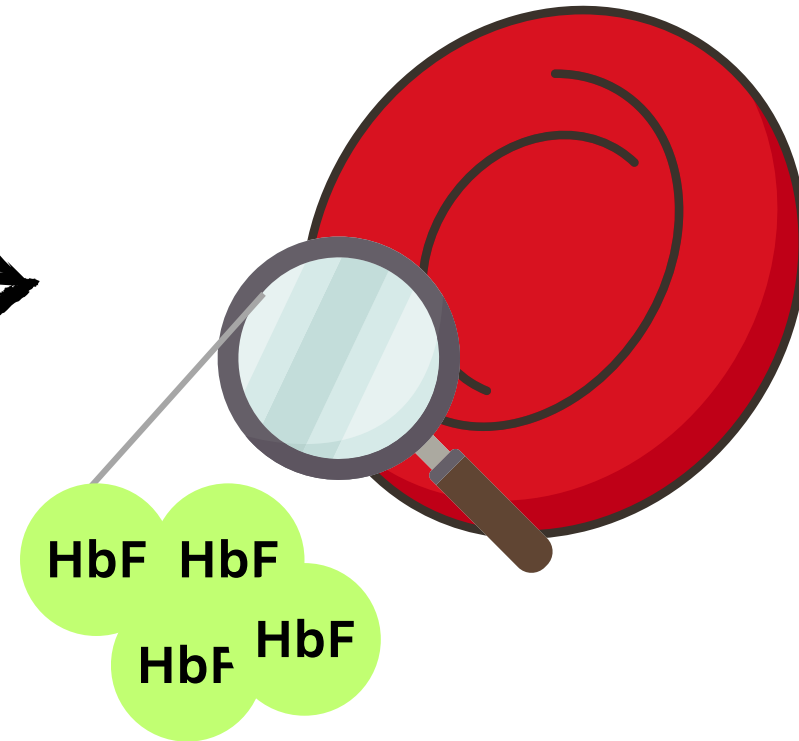


GENE THERAPY

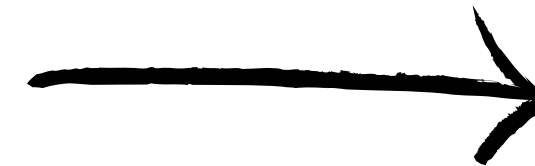
HOW DOES IT WORK?



STEM CELLS ARE EDITED SO THEY MAKE MORE HbF



RED CELLS ARE NOW FILLED WITH GOOD AMOUNTS OF HEALTHY 'BABY' HAEMOGLOBIN



CELLS SURVIVE FOR LONGER, LESS ANAEMIA



A NOTE ON 'CURE'

This treatment is hoped to be a functional cure - i.e. the symptoms of the condition are treated, but not the underlying genetic problem.



Design

Phase 1 / 2, international, multicenter, open-label, single-arm study (NCT03655678)

Phase 1 / 2, international, multicenter, open-label, single-arm study (NCT03745287)

Target enrollment

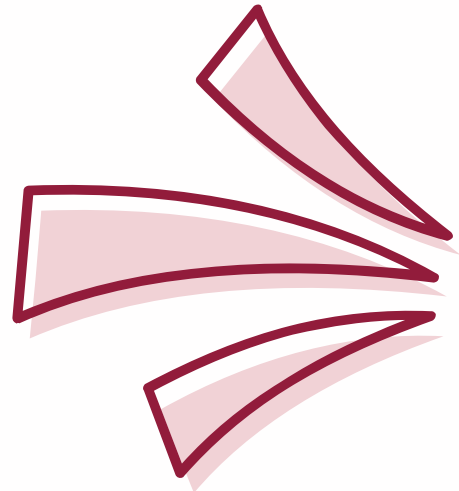
45 patients aged 12 to 35 years with TDT, including β^0 / β^0 genotypes, defined as a history of at least 100 mL/kg/year or 10 units/year of pRBC transfusions in the previous 2 years

45 patients aged 12 to 35 years with severe SCD and a history of ≥ 2 vaso-occlusive crises per year over the previous 2 years

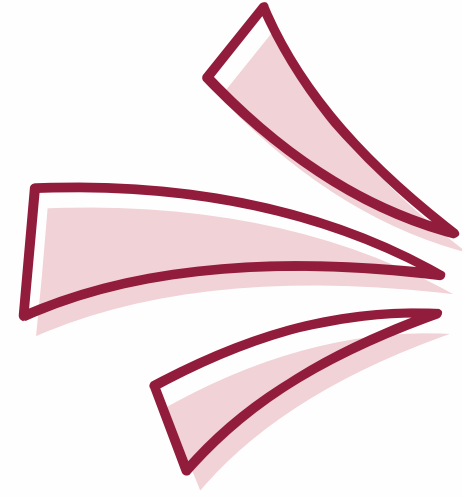
Primary endpoints

Proportion of patients achieving sustained transfusion reduction of 50% for at least 6 months starting 3 months after CTX001 infusion

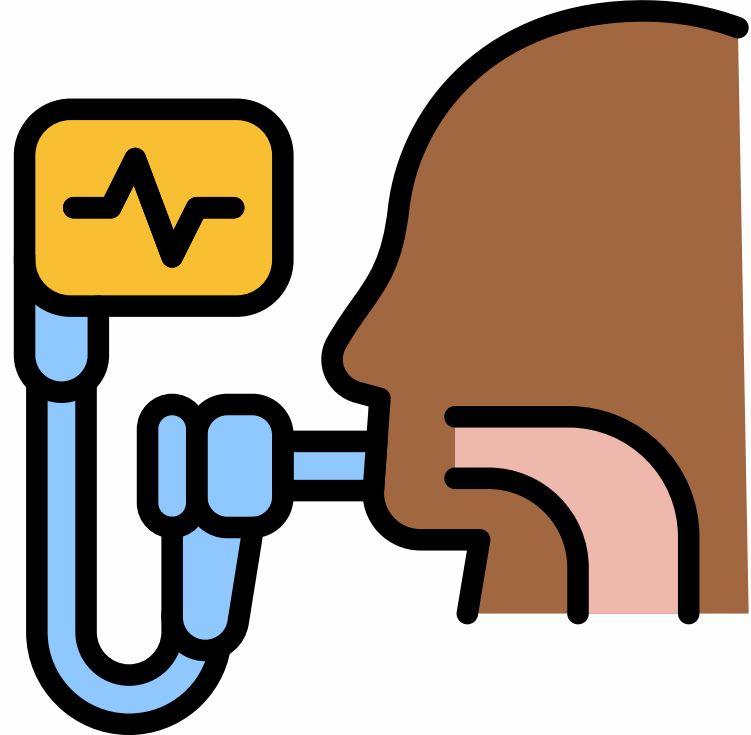
Proportion of patients with HbF $\geq 20\%$ sustained for at least 3 months starting 6 months after CTX001 infusion



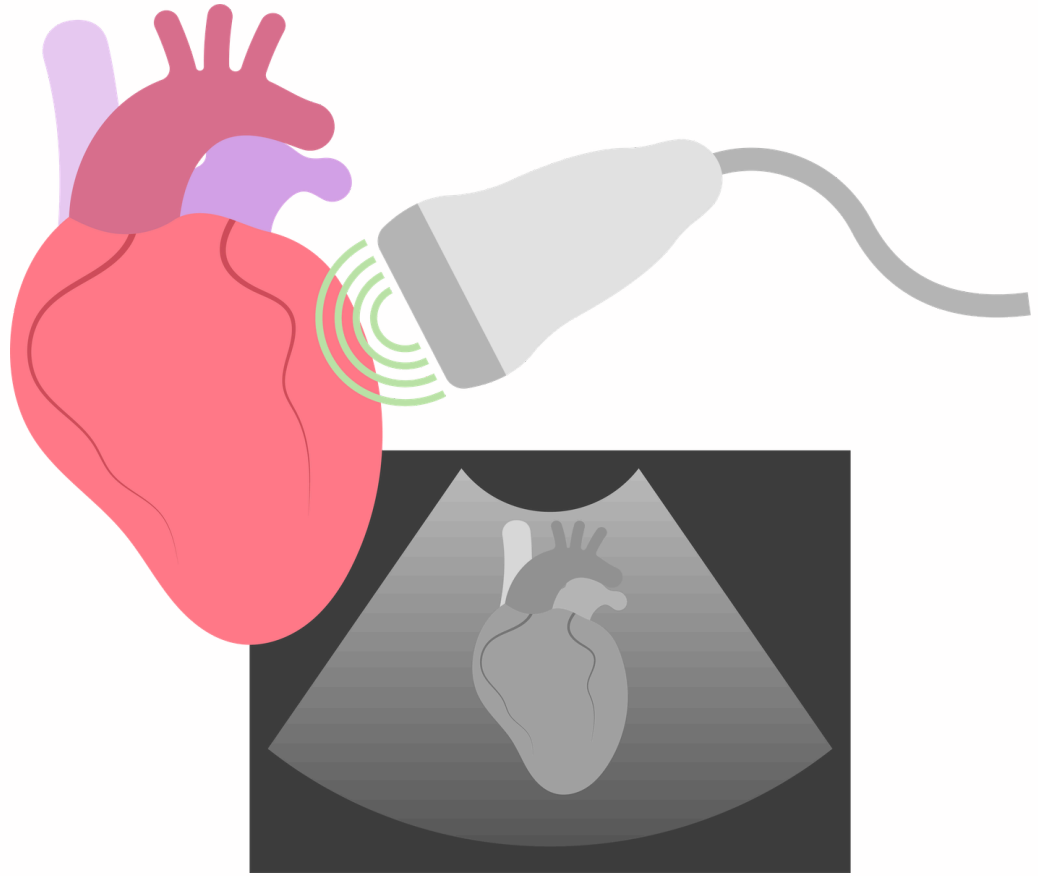
GENE THERAPY PROCESS



GENE THERAPY PROCESS



**EXTENSIVE WORK UP IS
REQUIRED TO DETERMINE A
PATIENT'S FITNESS FOR THE
PROCEDURE**



Please fill in the below if the patient is being referred for Casgevy gene therapy	
Question/Patient has the following:	Answer
Documented homozygous β -thalassaemia (including β^0/β^0 , β^0/β^0 -like, or non- β^0/β^0 -like genotype) or compound heterozygous β -thalassaemia including Haemoglobin E/ β -thalassaemia and a history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the prior 2 years.	<input type="checkbox"/> Yes, <input type="checkbox"/> No
Karnofsky performance status of $\geq 80\%$ for patients ≥ 16 years of age OR Lansky performance status of $\geq 80\%$ for patients < 16 years of age.	<input type="checkbox"/> Yes, <input type="checkbox"/> No
Known and available fully matched HLA related donor	<input type="checkbox"/> Yes, <input type="checkbox"/> No
Prior allogeneic HSCT	<input type="checkbox"/> Yes, <input type="checkbox"/> No
Patients with associated α -thalassaemia with > 1 alpha deletion or alpha multiplications. Patients with sickle cell β -thalassaemia variant	<input type="checkbox"/> Yes, <input type="checkbox"/> No
Clinically significant and active bacterial, viral, fungal, or parasitic infection as determined by the attending physician	<input type="checkbox"/> Yes, <input type="checkbox"/> No
White blood cell count $< 3 \times 10^9/L$ or platelet count $< 50 \times 10^9/L$ not related to hypersplenism	<input type="checkbox"/> Yes, <input type="checkbox"/> No
History of a significant bleeding disorder	<input type="checkbox"/> Yes, <input type="checkbox"/> No
Any prior or current malignancy or myeloproliferative disorder or a significant immunodeficiency disorder	<input type="checkbox"/> Yes, <input type="checkbox"/> No
Advanced liver disease defined as: Aspartate transaminase (AST), alanine transaminase (ALT) $> 3 \times$ the upper limit of normal (ULN), or conjugated bilirubin value $> 2.5 \times$ ULN, or: a) Baseline prothrombin time (International Normalized Ratio; INR) $> 1.5 \times$ ULN, or b) History of cirrhosis or any evidence of bridging fibrosis on a prior liver biopsy, if available c) Patients with active hepatitis infection d) Patients with history of chronic hepatitis infection are also excluded unless liver biopsy within 3 months prior to or at screening shows no evidence of bridging fibrosis or cirrhosis e) Liver iron content (LIC) ≥ 15 mg Fe/g dry weight on R2 or T2* MRI of liver unless liver biopsy within three months prior to or at screening shows no evidence of bridging fibrosis or cirrhosis	<input type="checkbox"/> Yes, <input type="checkbox"/> No a) <input type="checkbox"/> Yes, <input type="checkbox"/> No b) <input type="checkbox"/> Yes, <input type="checkbox"/> No c) <input type="checkbox"/> Yes, <input type="checkbox"/> No d) <input type="checkbox"/> Yes, <input type="checkbox"/> No e) <input type="checkbox"/> Yes, <input type="checkbox"/> No
A cardiac T2* < 10 ms by MRI or left ventricular ejection fraction (LVEF) $< 45\%$ by echocardiogram	<input type="checkbox"/> Yes, <input type="checkbox"/> No
Baseline estimated glomerular filtration rate < 60 mL/min/1.73 m ²	<input type="checkbox"/> Yes, <input type="checkbox"/> No, <input type="checkbox"/> Pending
Diffusion capacity of the lungs for carbon monoxide (TLCO) $< 50\%$ of predicted (corrected for haemoglobin and/or alveolar volume)	<input type="checkbox"/> Yes, <input type="checkbox"/> No, <input type="checkbox"/> Pending

Translates to:

- Ferriscan
 - o +/- liver biopsy
- Echo
- ECG
- Lung function testing
- Bloods
- Genetic testing
- Possible intensification of treatment to meet eligibility



GENE THERAPY PROCESS

**EACH CASE IS DISCUSSED WITH
A NATIONAL PANEL OF EXPERTS
BEFORE PROCEEDING**



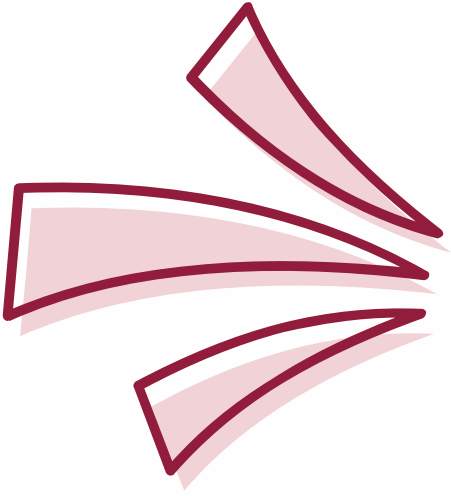


GENE THERAPY PROCESS

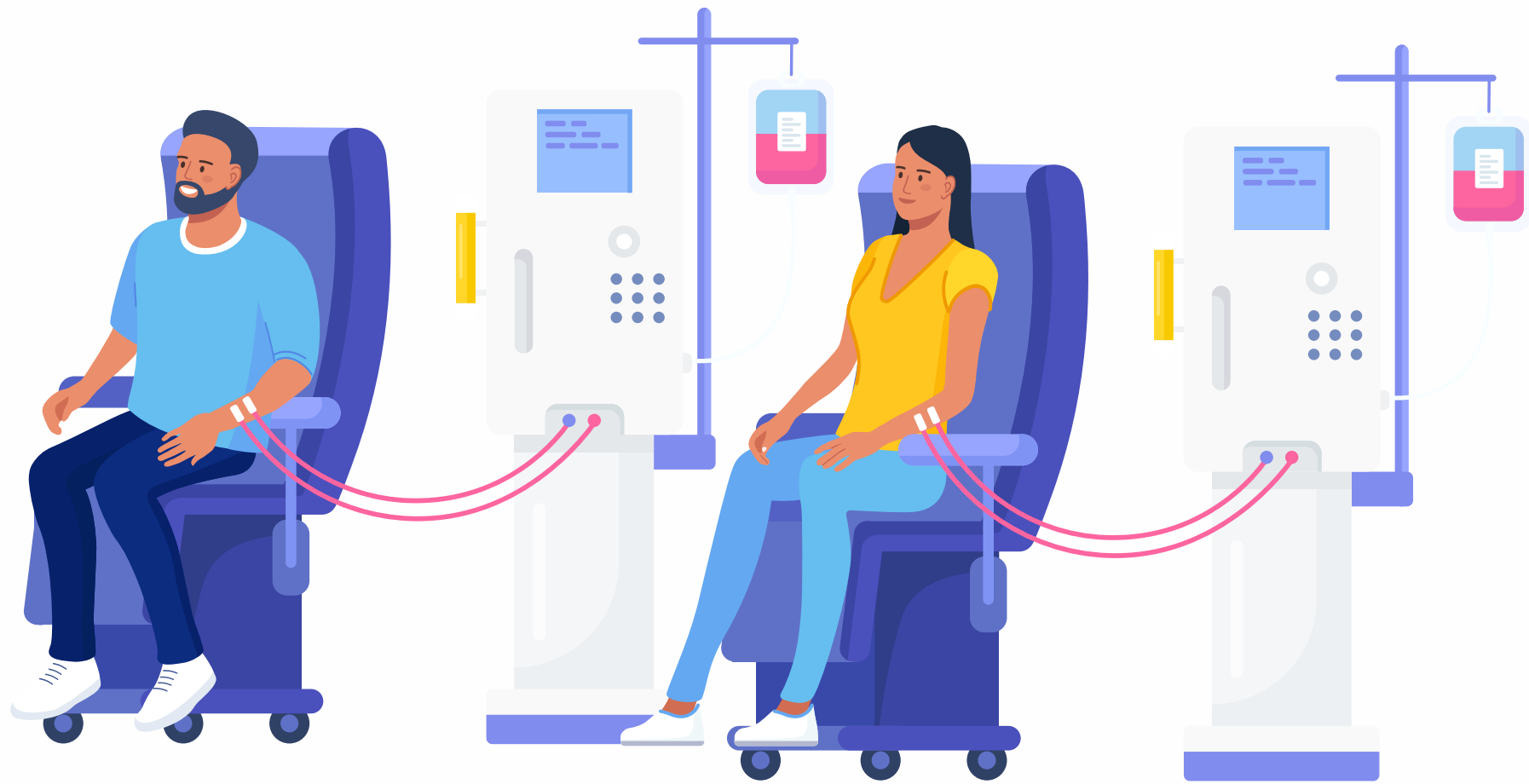


**THE PATIENT MEETS THE
CELLULAR THERAPY TEAM TO
DISCUSS THE PROCESS IN
EXTENSIVE DETAIL
(CURRENTLY BASED IN LONDON)**

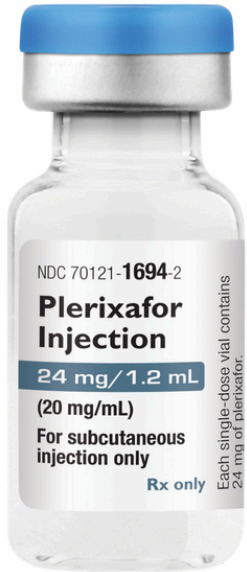




GENE THERAPY PROCESS



THE PATIENT HAS THEIR OWN STEM CELLS COLLECTED READY FOR EDITING. EXTRA 'RESCUE' CELLS ARE ALSO COLLECTED





GENE THERAPY PROCESS



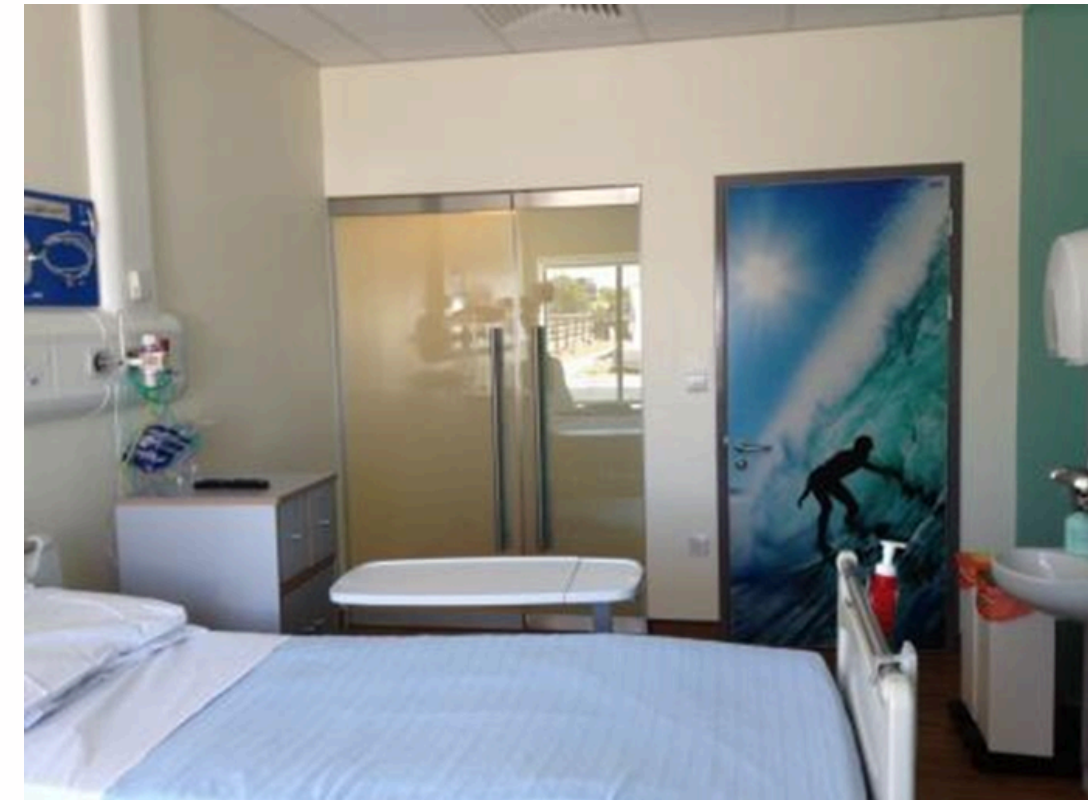
**STEM CELLS ARE EDITED IN THE
MANUFACTURING SITE**

TAKES UP TO 6 MONTHS



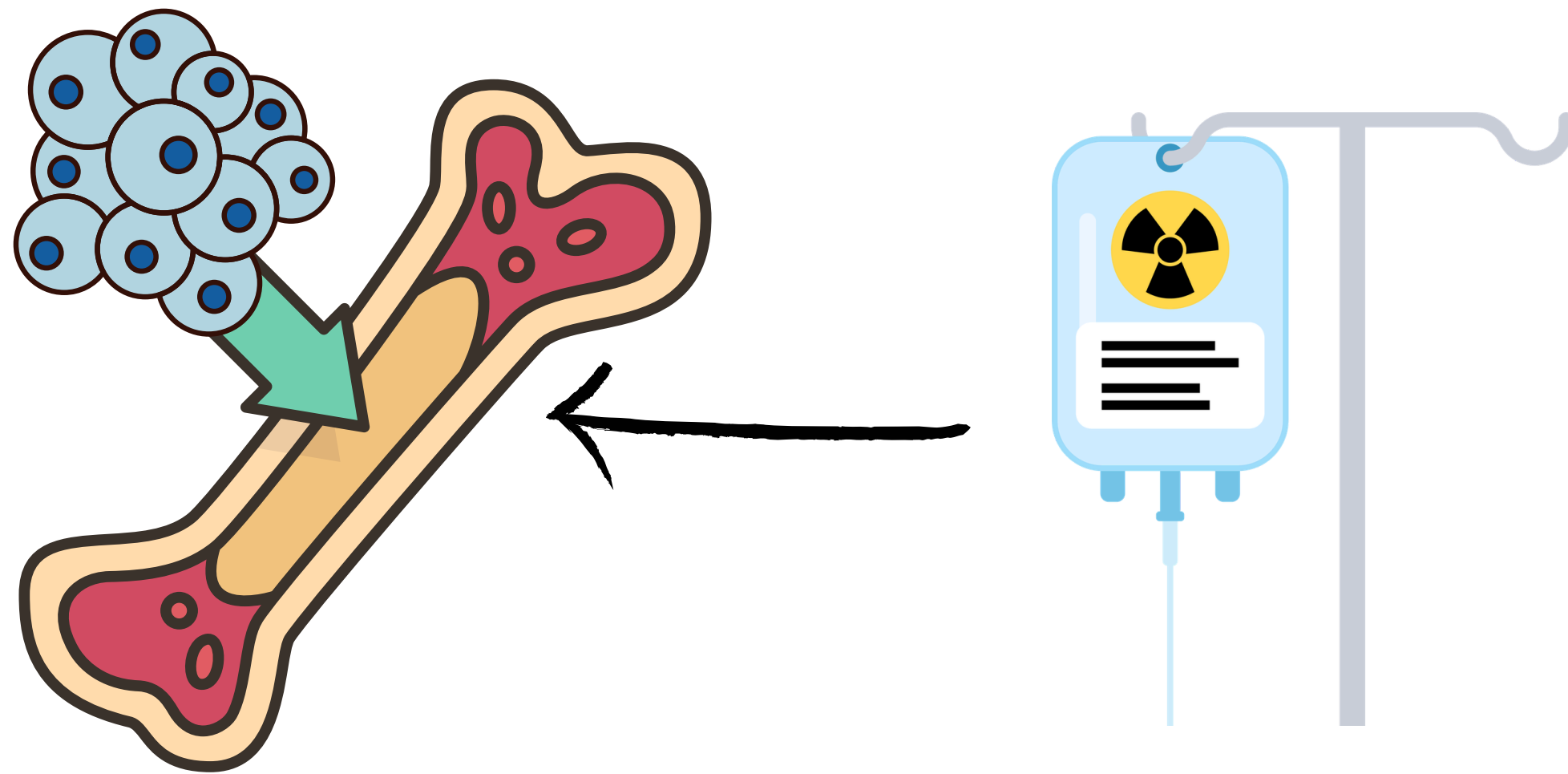
GENE THERAPY PROCESS

**ADMISSION TO HOSPITAL –
AROUND 1 WEEK BEFORE THE
STEM CELLS ARE GIVEN BACK**

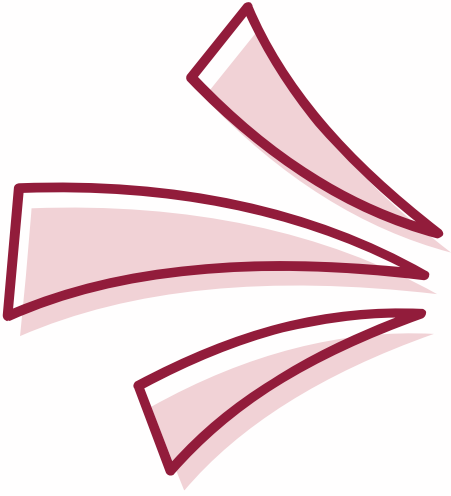


GENE THERAPY PROCESS

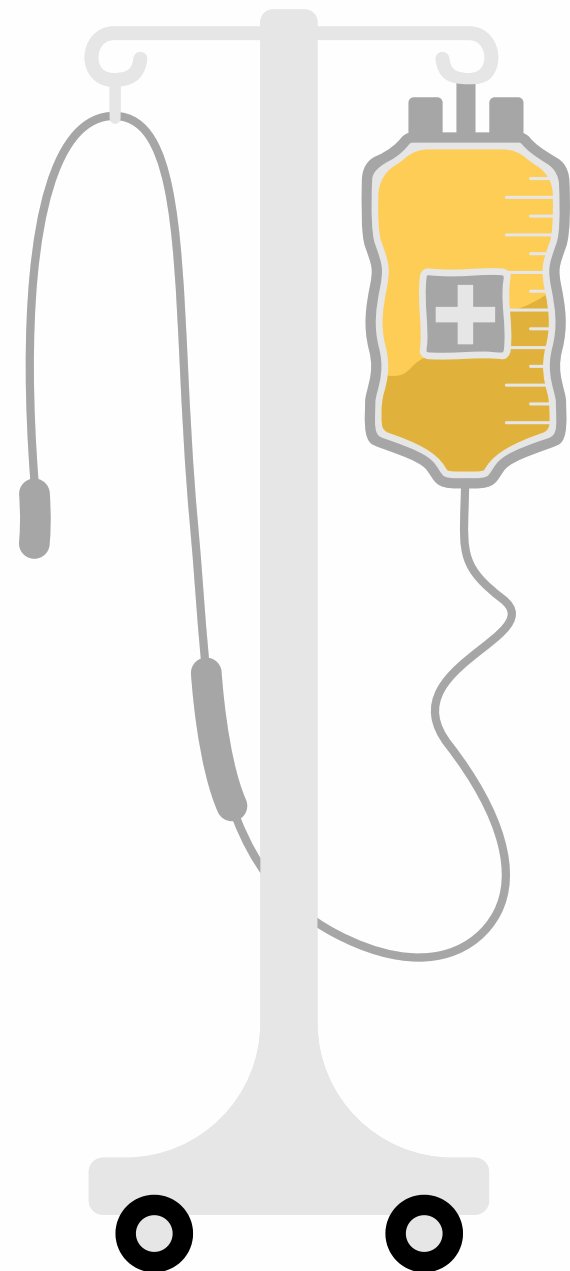
HOW DOES IT WORK?



TO MAKE ROOM FOR THE EDITED STEM CELLS, THE NATIVE CELLS MUST BE ELIMINATED. TOXIC TREATMENTS (OFTEN STRONG CHEMOTHERAPIES) ARE USED TO DO THIS



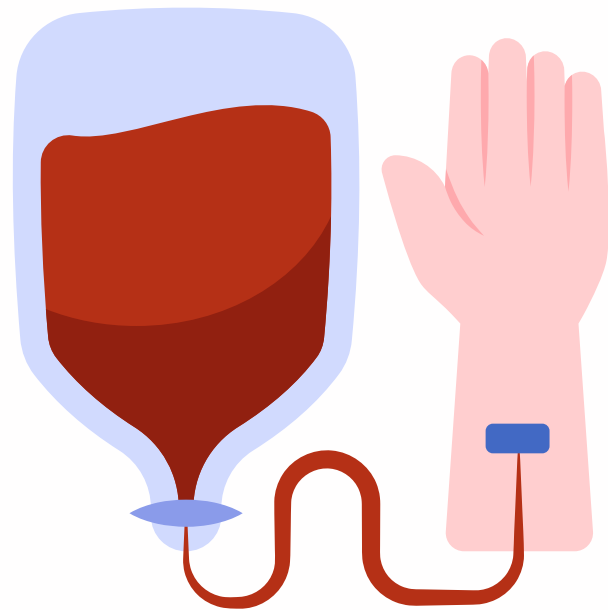
GENE THERAPY PROCESS



**"DAY ZERO" – EDITED STEM
CELLS ARE GIVEN BACK TO THE
PATIENT**

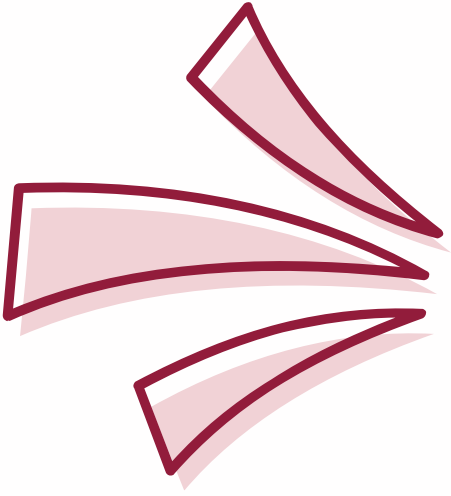


GENE THERAPY PROCESS



AFTER STEM CELLS ARE GIVEN, THEY NEED 4–6 WEEKS TO START WORKING. DURING THIS TIME, THE PATIENT HAS VERY LOW BLOOD COUNTS.

THEY WILL LIKELY REQUIRE TRANSFUSION AND ARE VERY SUSCEPTIBLE TO SERIOUS INFECTION.



GENE THERAPY PROCESS

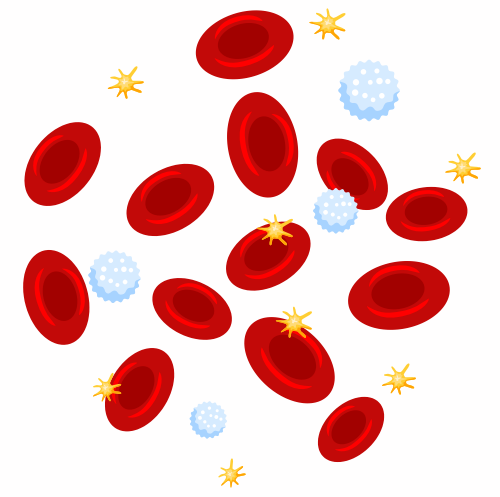


**AROUND 4–6 WEEKS AFTER
STEM CELLS ARE GIVEN,
PATIENTS CAN BE DISCHARGED.**

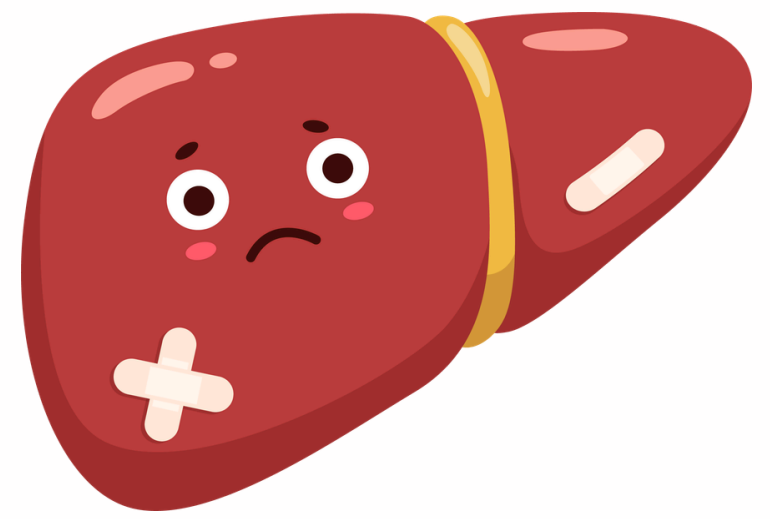
CLOSE FOLLOW UP IS REQUIRED



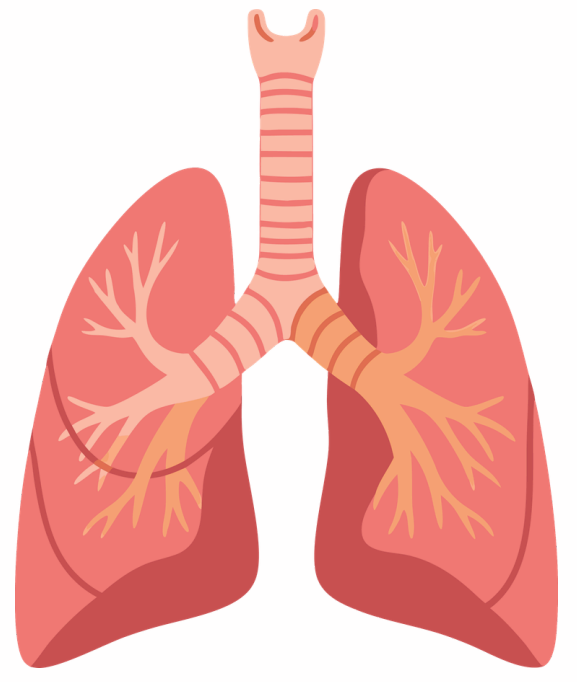
SIDE EFFECTS



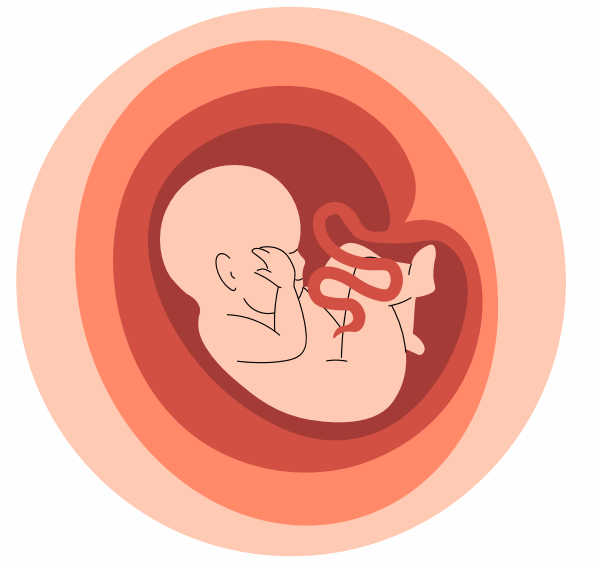
Side effects related to low blood counts - sepsis, bleeding



Veno-occlusive disease of the liver



Some respiratory complications reported



Long term impacts on fertility

THALASSAEMIA – OUTCOMES

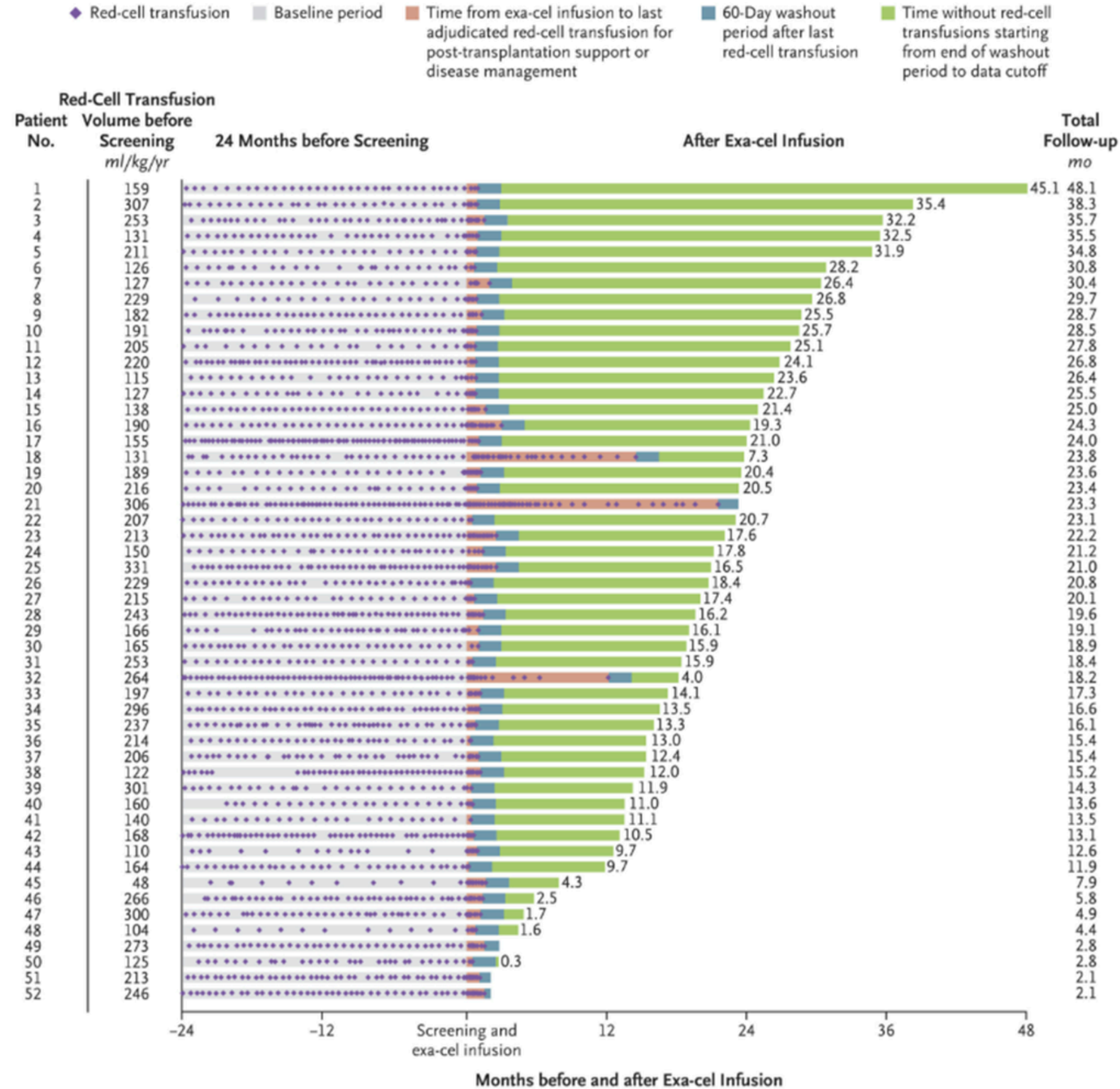
- **Primary Endpoint:**

Proportion of patients who achieved transfusion independence for at least 12 consecutive months.

- **Transfusion independence:**

haemoglobin level of ≥ 90 g/L without red-cell transfusion for at least 12 consecutive months

THALASSAEMIA – OUTCOMES



- 32/35 (91%) patients achieved transfusion independence
- Mean time to no longer requiring transfusions – 35 days from exa-cel infusion

SICKLE CELL – OUTCOMES

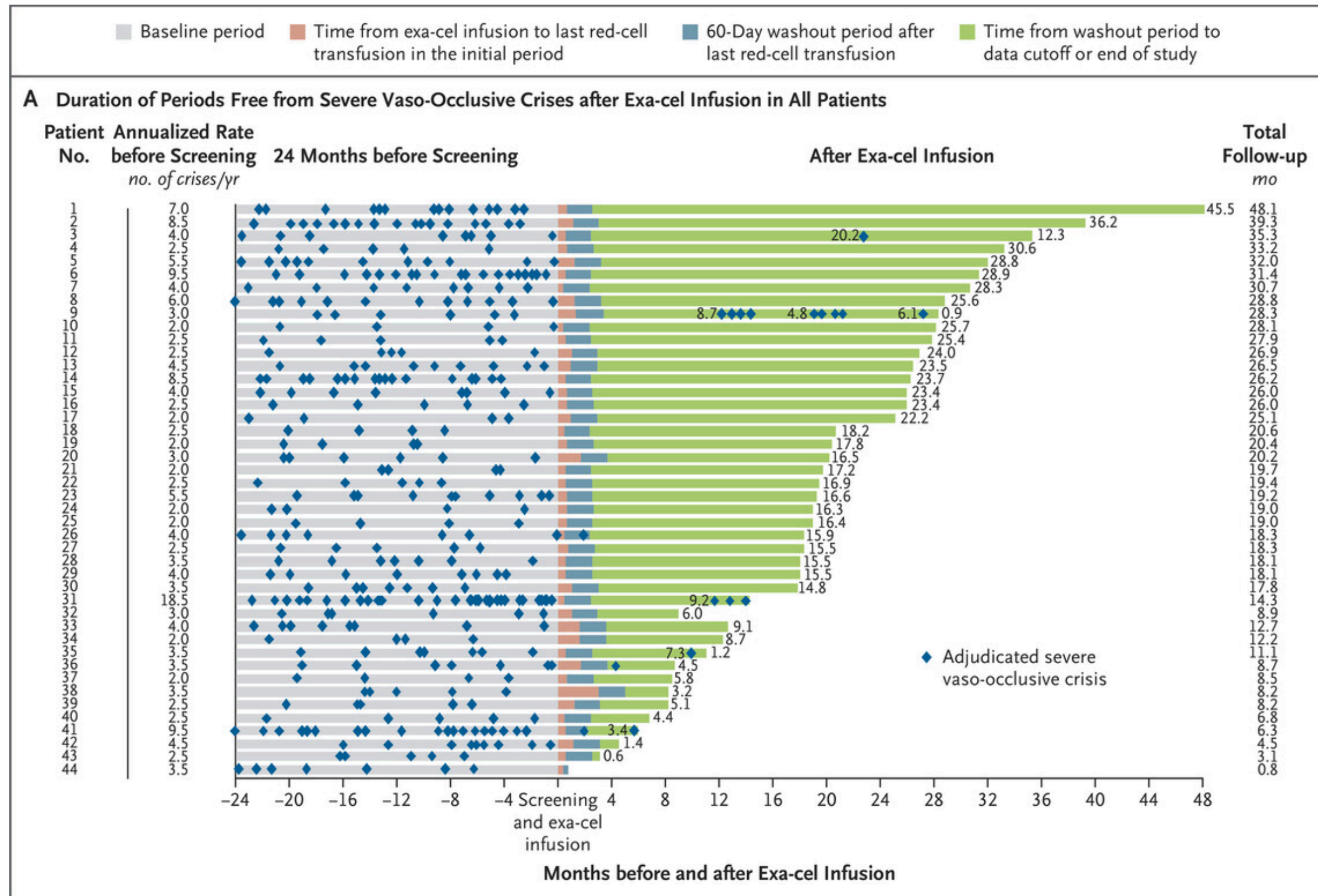
- **Primary Endpoint:**

Proportion of patients who achieved freedom from severe painful crisis for at least 12 months

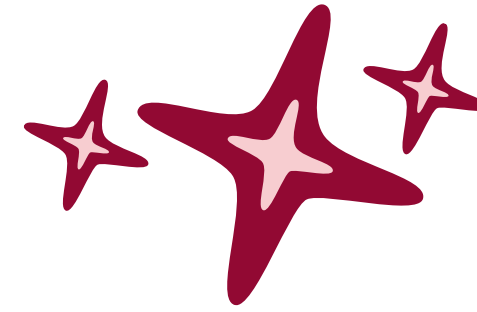
- **Severe painful crisis:**

An event of acute pain which led to a visit to a medical facility and needed opiates OR acute transfusion OR acute chest syndrome OR priapism for over 2 hours OR splenic sequestration

SICKLE CELL – OUTCOMES



SUMMARY



- Gene therapy is a hopeful development for people living with thalassaemia and sickle cell disorders
- Currently very early days
- Rigorous process to confirm eligibility
- Currently need to travel to London for tests and treatment