Brigham and Women's Hospital
Founding Member, Mass General Brigham

Hot Topics in Hematology: Gene Therapies for Hemoglobinopathies and Hemophilia

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DISCLOSURES

Please state any/all financial disclosures for past 24 months.

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Images
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OBJECTIVES

Introduce gene therapies for inherited hematologic disorders

Discuss indications, mechanism of action, and clinical data supporting gene therapy for:

- Sickle cell disease
- Beta-thalassemia
- Hemophilia A/B

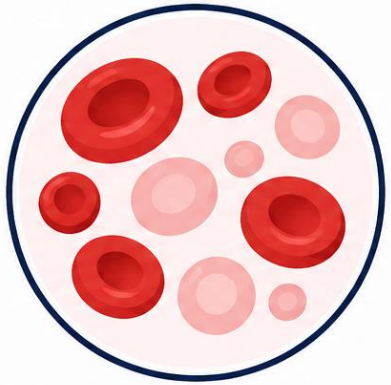
Highlight current barriers and need for innovation in gene therapy to improve tolerability, affordability, and accessability

Inherited blood disorders and the promise of gene therapy

Genetic disorders amenable for gene therapy

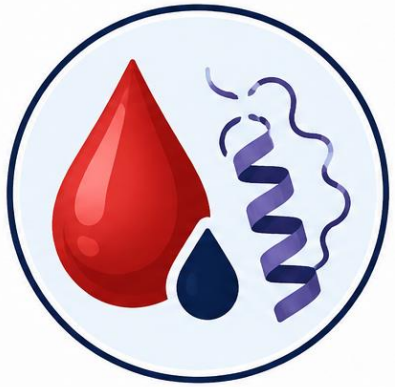
SICKLE CELL DISEASE

Autosomal recessive
Mut in HBB gene
Recurrent VOEs



BETA-THALASSEMIA

Autosomal recessive
Ineffective erythropoiesis
Transfusion dependence

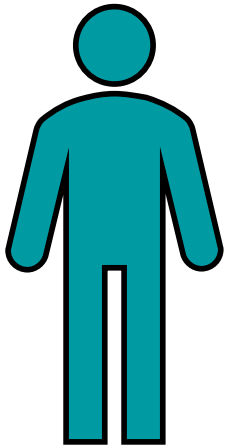


HEMOPHILIA

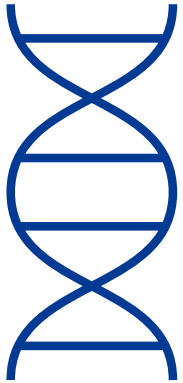
X-linked
Deficiency of FVIII (A) or FIX (B)
Bleeding

Hemoglobinopathies: ex-vivo gene editing and autologous hematopoietic cell transplantation

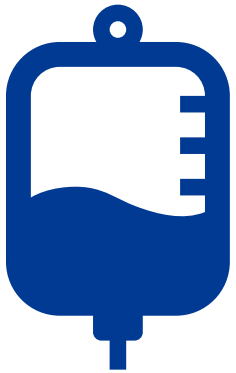
Ex-vivo gene therapy: a promising new paradigm



Autologous stem cell collection



Gene editing

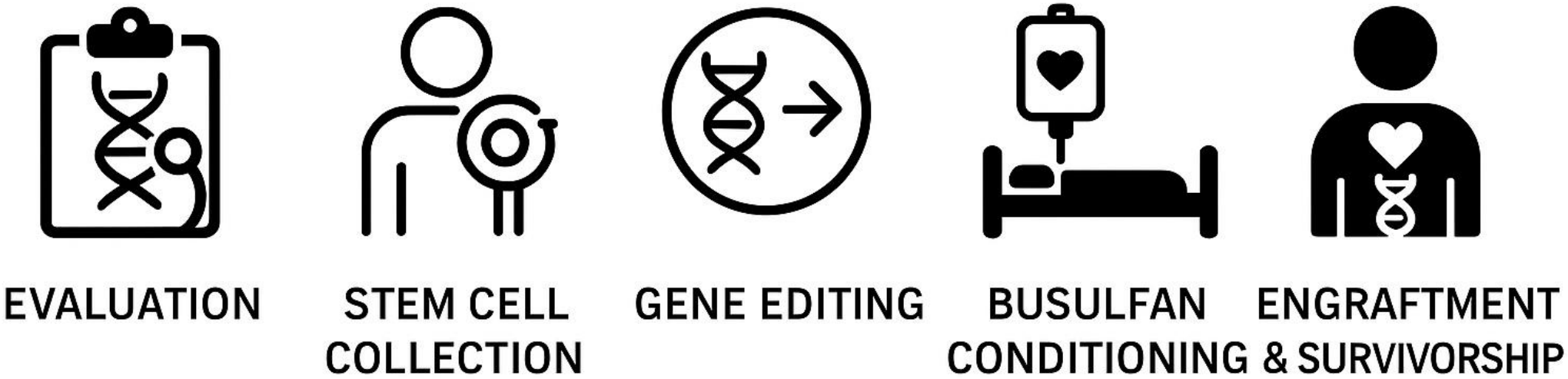


Preparative regimen

Restoration of red blood cells

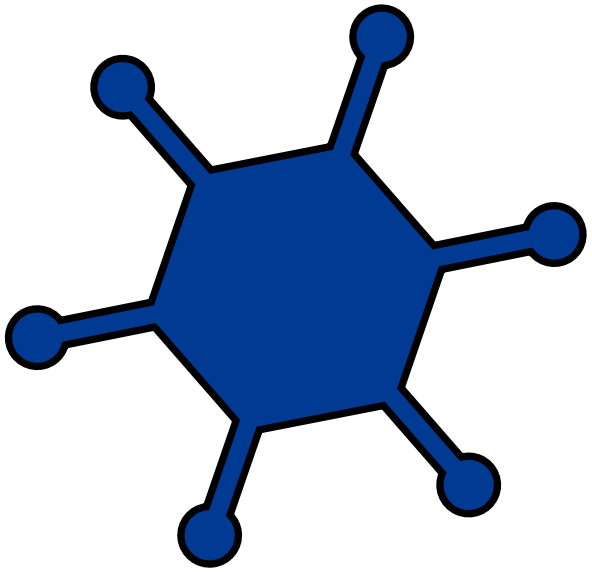
Promise: no risk of graft-versus-host disease

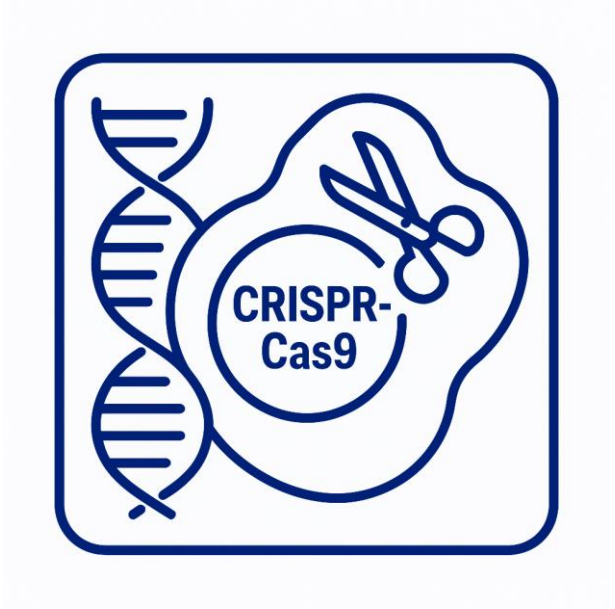
Journey for gene therapy for hemoglobinopathies

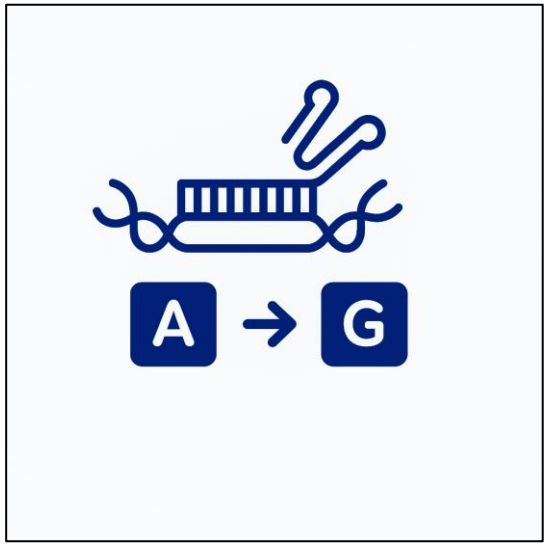


Icons created with the assistance of GPT5 (Open AI)

Gene therapy: multiple approaches to gene editing







Icons created with the assistance of GPT5 (Open AI)

Sickle cell disease

Case of patient with sickle cell disease

Autosomal recessive
Mut in HBB gene
Recurrent VOEs

KN is a 25 year old woman with HbSS disease who presents to her primary care physician for post-discharge follow-up. In the past 24 months, she has hospitalized eight times for acute pain in back, chest, arms, and legs related to vaso-occlusive events. She has a history of acute chest and osteonecrosis of the R hip. She has received several blood transfusions in her life. She takes her hydroxyurea religiously and is currently on a dose of 2000mg QD. She has no other medical history and has never experienced a stroke. She lives with her mom and sister. Her sister has sickle cell trait. The sister has never been tested to be a stem cell donor. The appropriate next best step is:

A) Increase the hydroxyurea to 3000mg QD
B) Increase her long-acting opioid
C) Refer to hematology/BMT for transplant & gene therapy consideration
D) Send to a chronic pain specialist for opioid induced hyperalgesia

Points of emphasis

Autosomal recessive
Mut in HBB gene
Recurrent VOEs

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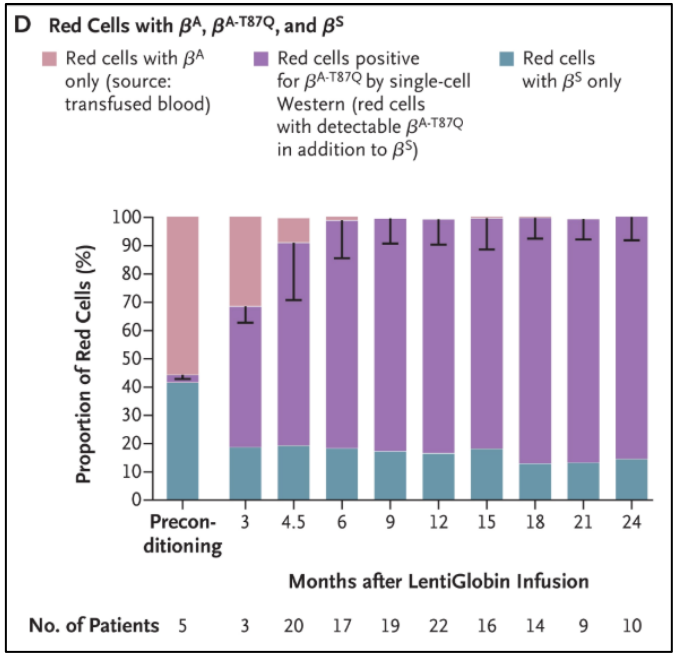
Severe disease despite HU needs transformative therapy

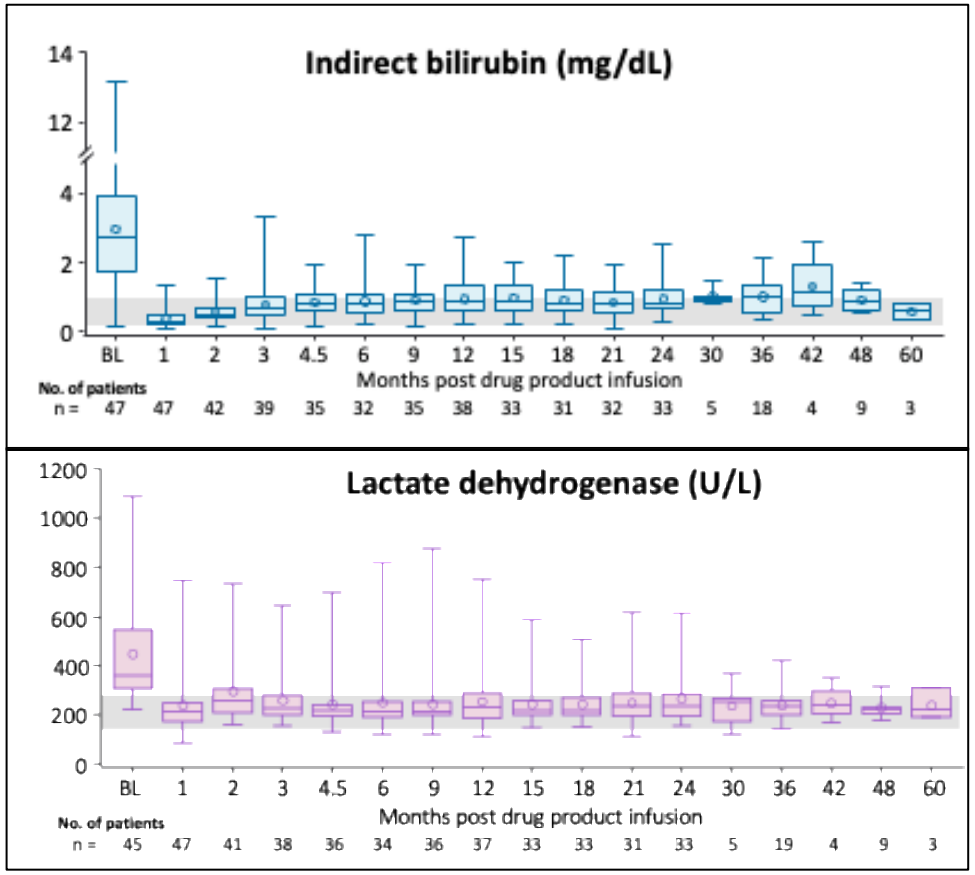
- Autosomal recessive
- Mut in HBB gene
- Recurrent VOEs

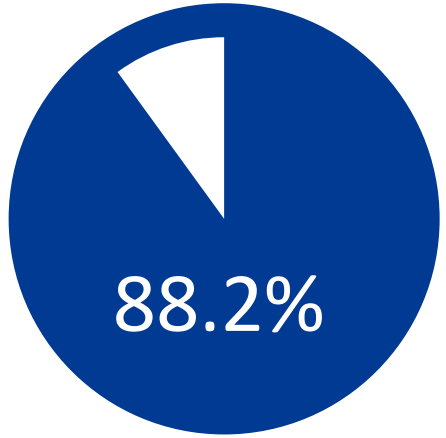
- Recurrent VOEs (pain crises, acute chest, priapism)
- End organ damage: osteonecrosis, pHTN, nephropathy, hepatopathy
- Cerebrovascular accident / vasculopathy
- Iron overload
- Allosensitization

SCD and Gene Therapy

Lovotibeglogene-autotemcel: FDA approved





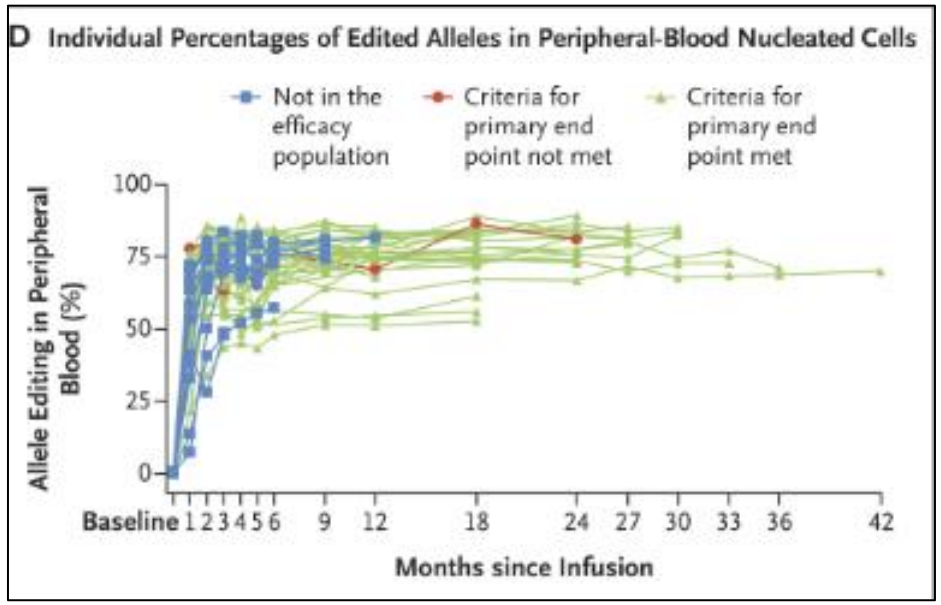


Complete resolution of vaso-occlusive events

Mechanism	Lentiviral vector that inserts modified B-globin gene that blocks HbS polymerization and reduces HbS levels

Kanter et al, NEJM 2022;

Exagamglogene autotemcel: FDA approved



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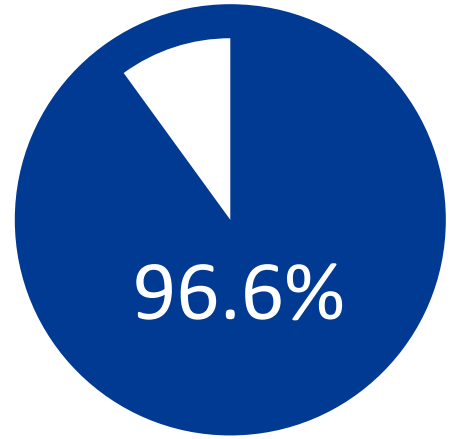
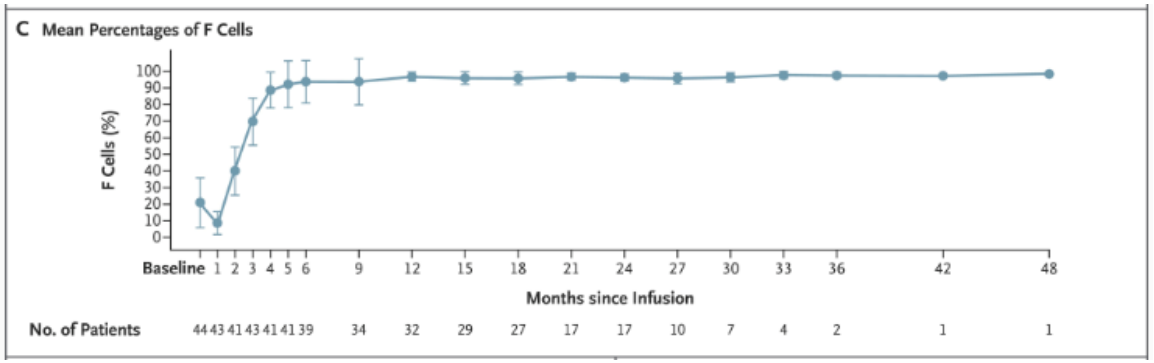


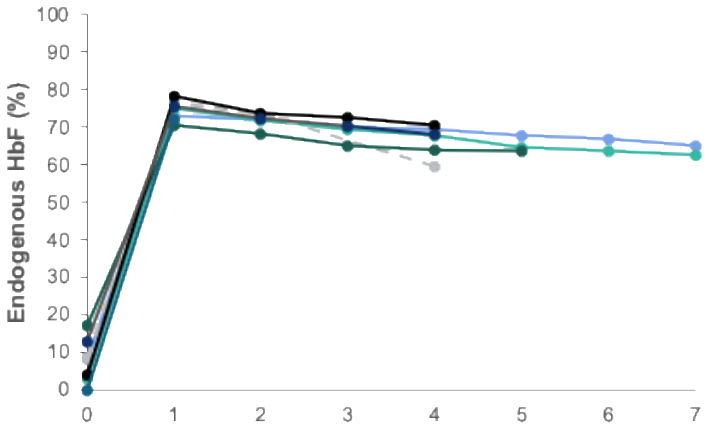


Mechanism	CRISPR/CAS9 based disruption of erythroid specific enhancer region of BCL11a gene and induction of fetal hemoglobin

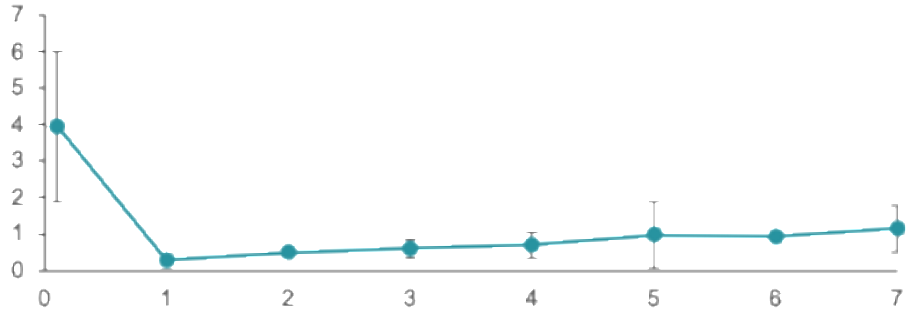
Frangoul et al, NEJM 2024

BEAM 101: clinical trial enrollment complete

Fetal hemoglobin (%)



Indirect bilirubin (mg/dL ± SD)



Improvements?

Median collections: 1

Median days to neutrophil engraftment: 17

Mechanism	Base editing to disrupt HBG1 & 2 promoter sites to eliminate BCL11a binding sites and induction of fetal hemoglobin

Reasons for caution with gene therapy

Unknown efficacy to halt or reverse end-organ disease

Potential for therapy related myeloid neoplasms

Need for busulfan and dramatic effects (infertility/death)

Difficulties of mobilization and collection – especially with increasing age

Financial constraints: $$$

Return to our case question

Autosomal recessive
Mut in HBB gene
Recurrent VOEs

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D) Send to a chronic pain specialist for opioid induced hyperalgesia

Key points for gene therapy for SCD

Autosomal recessive
Mut in HBB gene
Recurrent VOEs

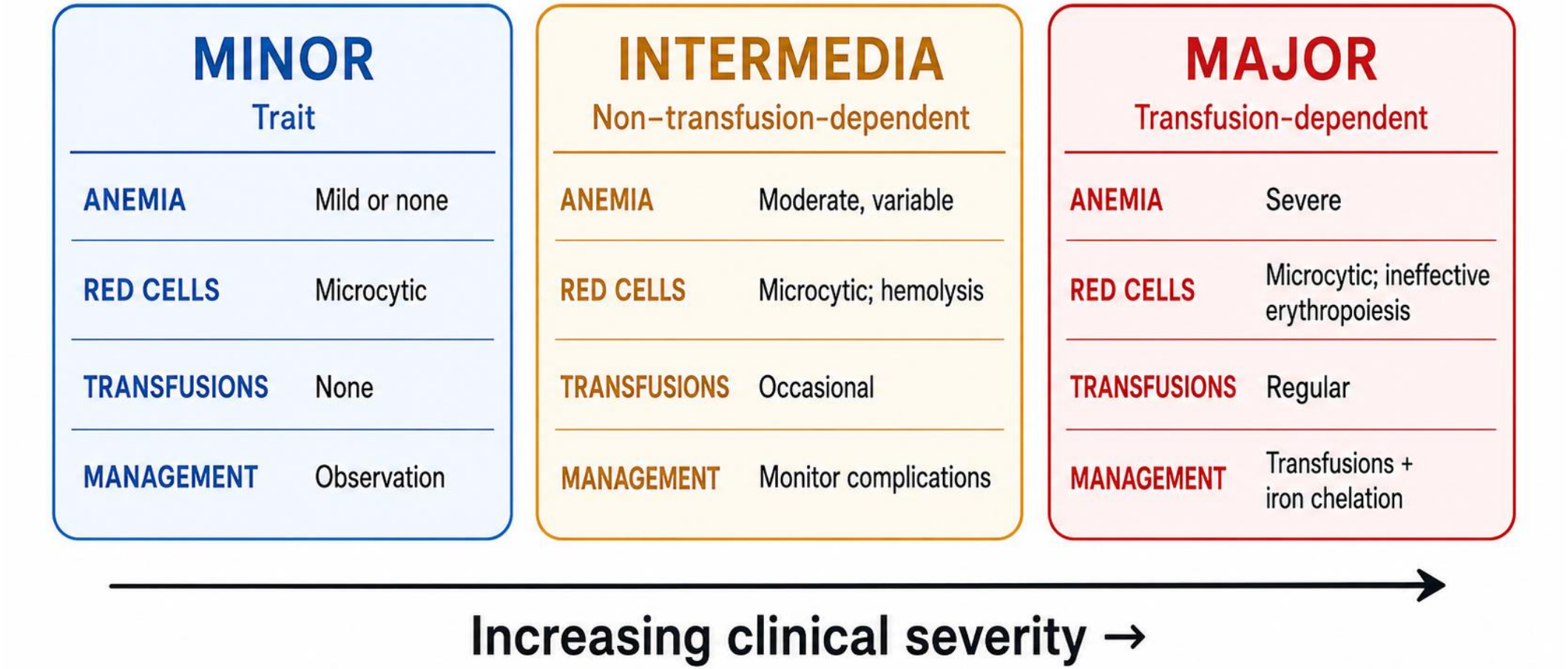
- 2 FDA approved gene therapy products: Exa-cel and Lovo-cel
- Reduces serious vaso-occlusive events
- Improves quality of life
- Not an established cure like allogeneic HCT

Barriers:

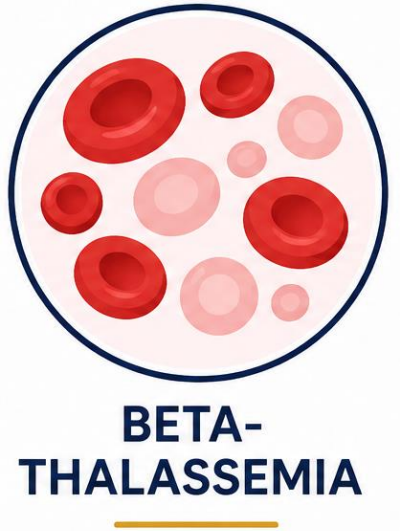
- Difficult to mobilize and collect:
- Requirement of myeloablative conditioning
- Tethered to authorized treatment centers
- $$$

Beta-thalassemia

Beta-thalassemia: spectrum of illness



Case of patient with beta-thalassemia

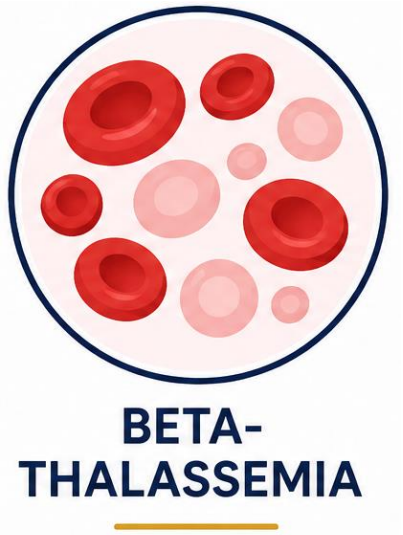


Autosomal recessive
Ineffective erythropoiesis
Transfusion dependence

MC is a 18 year old woman with beta-thalassemia who presents to her primary care physician for usual care. She moved last month and has not established hematology follow-up. In the past 2-3 years, has become more transfusion dependent. She now needs 1 unit of blood per month. Prior to moving, she was started on an iron chelator for iron overload. She is unhappy with current quality of life. She wants to see what else can be done for her disease. The next best step is:

A) Refer for a clinical trial
B) Start an erythropoietin stimulating agent (ESA)
C) Increase frequency of transfusions and number of units
D) Refer to hematology/BMT for transplant & gene therapy consideration

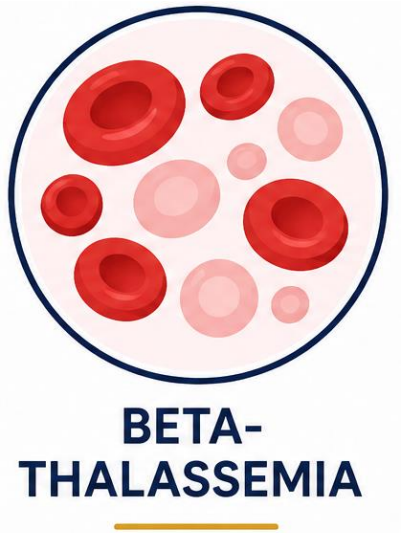
Case of patient with beta-thalassemia



Autosomal recessive
Ineffective erythropoiesis
Transfusion dependence

MC is a 18 year old woman with **beta-thalassemia major** who presents to her primary care physician for usual care. She sees a hematologist once every other year. **In the past 3 years, has become more transfusion dependent and is now receiving 1 unit of blood monthly** to maintain her Hb. Last year, **she started an iron chelator for iron overload**. She is unhappy with current quality of life and wants to see what else can be done for her disease.

Transfusion dependent thalassemia merits action



- Autosomal recessive
- Ineffective erythropoiesis
- Transfusion dependence

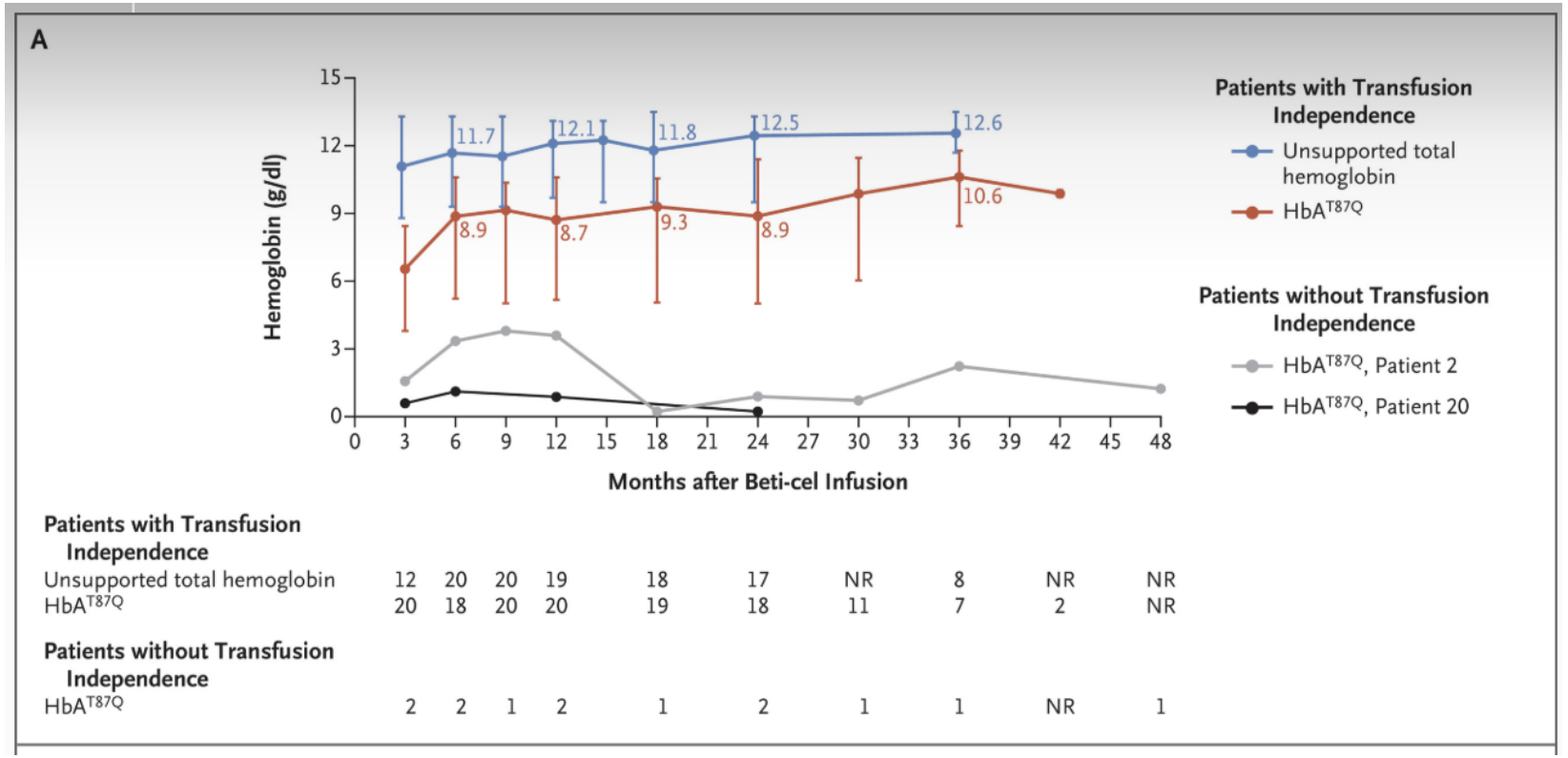
Transfusion dependent

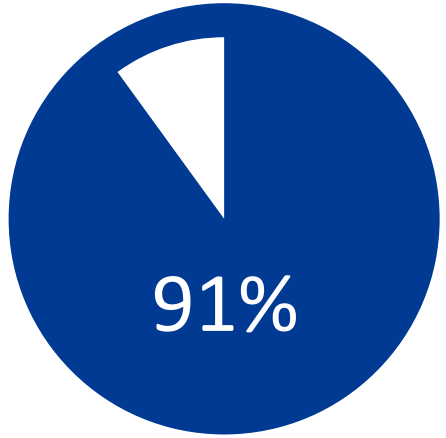
History of at least 10 units of pRBC per year for 2 years

Iron overload often present; most patients on iron chelator

Thalassemia and Gene Therapy

Betibeglogene autotemcel: FDA approved

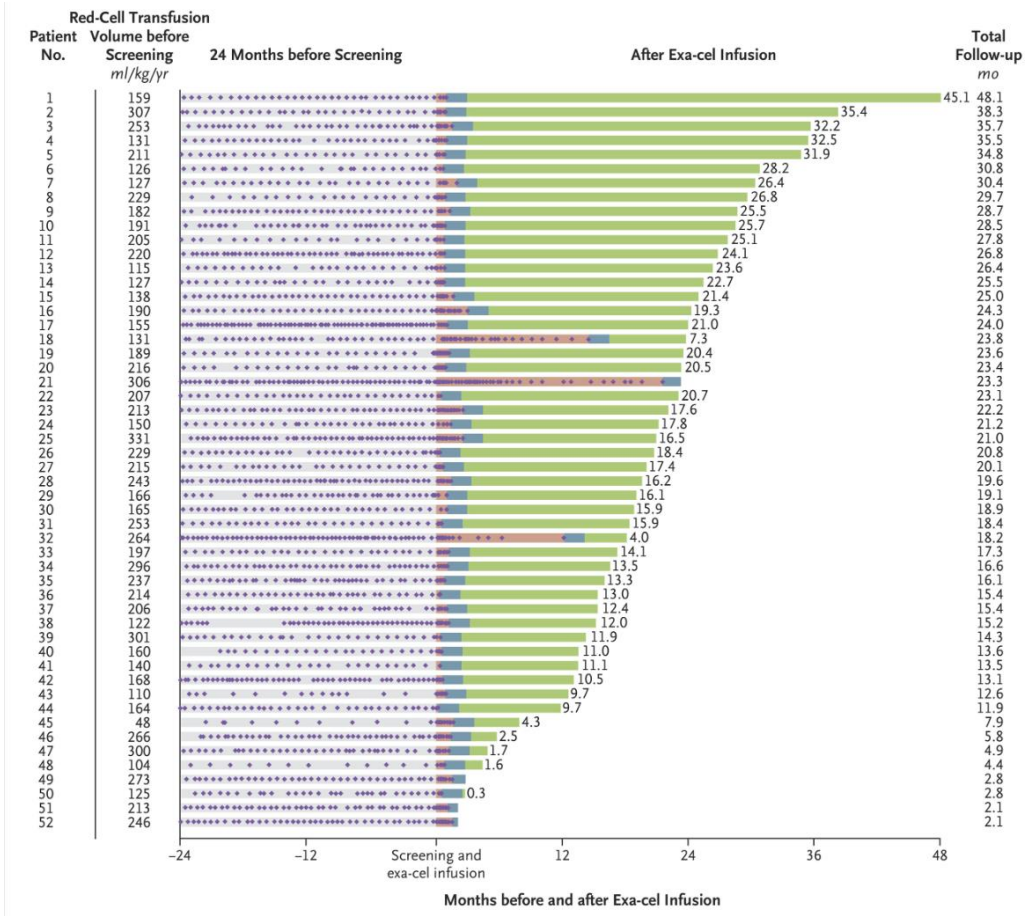




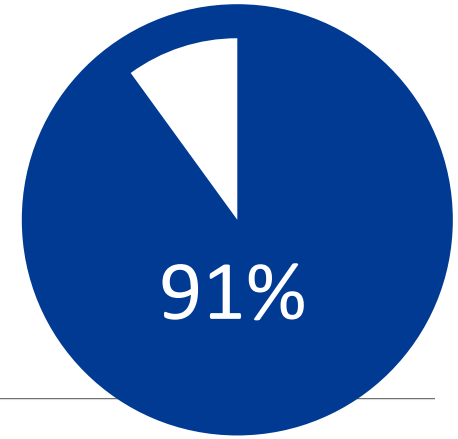
Achieved transfusion independence

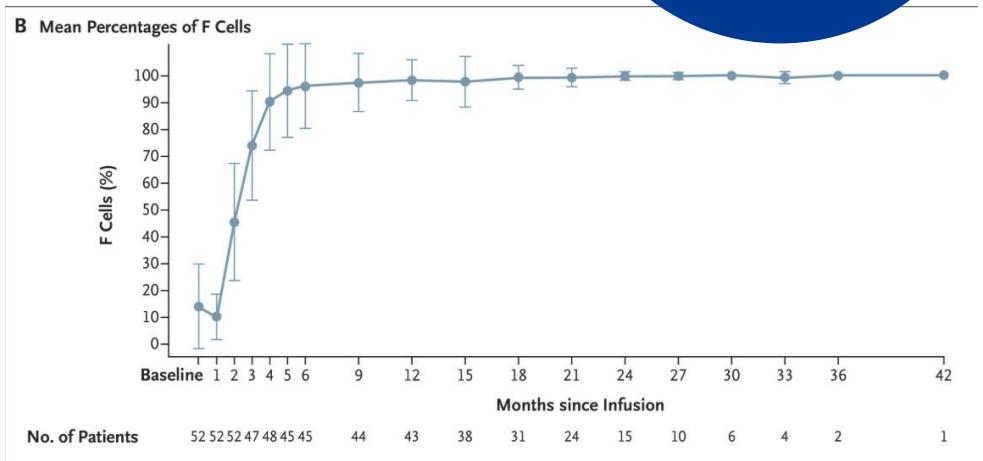
Mechanism	Lentiviral vector that inserts modified B-globin gene that blocks HbS polymerization and reduces HbS levels

Exagamglogene autotemcel: FDA approved



Achieved transfusion independence





Mechanism	CRISPR/CAS9 based disruption of erythroid specific enhancer region of BCL11a gene and induction of fetal hemoglobin

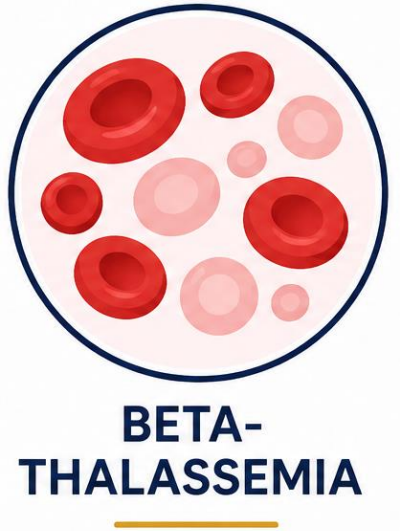
Reasons for caution with gene therapy

Potential for therapy related myeloid neoplasms

Need for busulfan and dramatic effects (infertility/death)

Financial constraints: $$$

Case of patient with beta-thalassemia



Autosomal recessive
Ineffective erythropoiesis
Transfusion dependence

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A) Refer for a clinical trial
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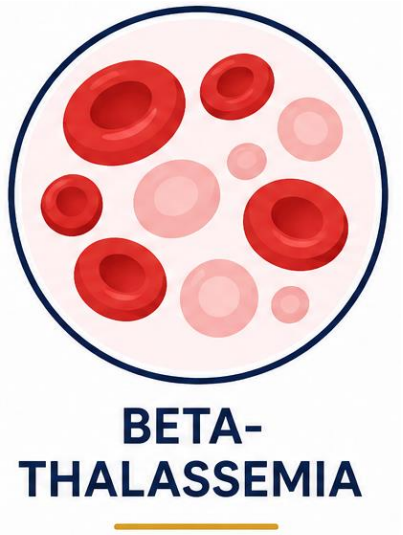
C) Increase frequency of transfusions and number of units
D) Refer to hematology/BMT for transplant & gene therapy consideration

Key points for gene therapy for B-thalassemia



Autosomal recessive
Ineffective erythropoiesis
Transfusion dependence

- 2 FDA approved gene therapy products: Exa-cel and Beti-cel
- Eliminates transfusion dependence
- Improves quality of life

Barriers:

- Requirement of myeloablative conditioning
- Tethered to authorized treatment centers
- Limited manufacturing availability
- $$$

Future directions with gene therapy for hemoglobinopathies

- Long term efficacy and safety data for gene therapies
- Make conditioning for GT less toxic
- Comparative and cost-effectiveness: HCT and GT
- Pursue the promise of in-vivo gene therapy
- Formally evaluate decision making
- Augment our supportive care offerings for our vulnerable patients

Hemophilia A/B

Case of patient with hemophilia

X-linked
Deficiency of FVIII (A) or FIX (B)
Bleeding

CB is a 40 year old man with Hemophilia A. As child, he had a history of recurrent hemarthroses. His factor level was always consistently < 1%. He has been on prophylactic recombinant factor VIII replacement (infusions multiple times per week) since childhood. In his medical history, he has untreated hepatitis C infection without evidence of cirrhosis. On last evaluation, he had not developed antibody titers to FVIII. He has discussed with his hematologist a strong desire to discontinue prophylactic factor infusions because he is tired of getting frequent infusions. A previous trial off factor replacement resulted in recurrent R hemarthrosis. You counsel him to consider:

A) Stay on current factor replacement – it cannot be that bad
B) Switch to a recombinant factor VIII product with a longer half-life
C) Stop factor replacement and start emicizumab
D) Treat his hepatitis C and refer for gene therapy consideration
E) Administer gene therapy to cure his hemophilia

Case of patient with hemophilia

X-linked
Deficiency of FVIII (A) or FIX (B)
Bleeding

CB is a 35 year old man with **Hemophilia A** As child, he had a **history of recurrent hemarthroses**. His **factor level was always consistently < 1%.** He has been on prophylactic **recombinant factor VIII replacement** (infusions multiple times per week) since childhood. **In his medical history, he has untreated hepatitis C infection without evidence of cirrhosis.** On last evaluation, he had **not developed antibody titers to FVIII**. He has discussed with his hematologist a strong desire to discontinue prophylactic factor infusions because he is tired of getting frequent infusions. A previous trial off factor replacement resulted in recurrent R hemarthrosis.

Review of hemophilia

HEMOPHILIA A
Factor VIII deficiency

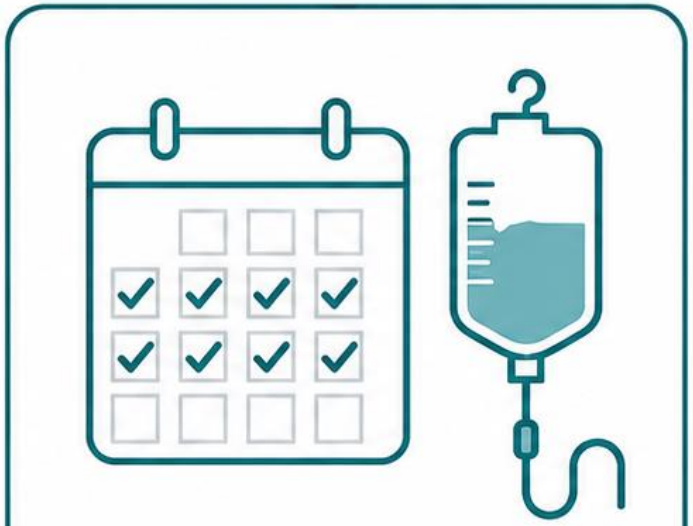
INHERITANCE	X-linked recessive
LABS	↑ aPTT; normal PT
BLEEDING	Hemarthroses; deep-tissue bleeding
SEVERE DISEASE	Factor VIII activity <1%
TREATMENT	Factor VIII replacement
OTHER THERAPY	Desmopressin for mild disease

HEMOPHILIA B
Factor IX deficiency

INHERITANCE	X-linked recessive
LABS	↑ aPTT; normal PT
BLEEDING	Hemarthroses; deep-tissue bleeding
SEVERE DISEASE	Factor IX activity <1%
TREATMENT	Factor IX replacement
OTHER NAME	Christmas disease

Clinical severity is determined by factor activity

Limitations of factor replacement



Frequent Infusions

Ongoing treatment burden

Difficult Venous Access

Repeated access can be challenging

Inhibitor Development

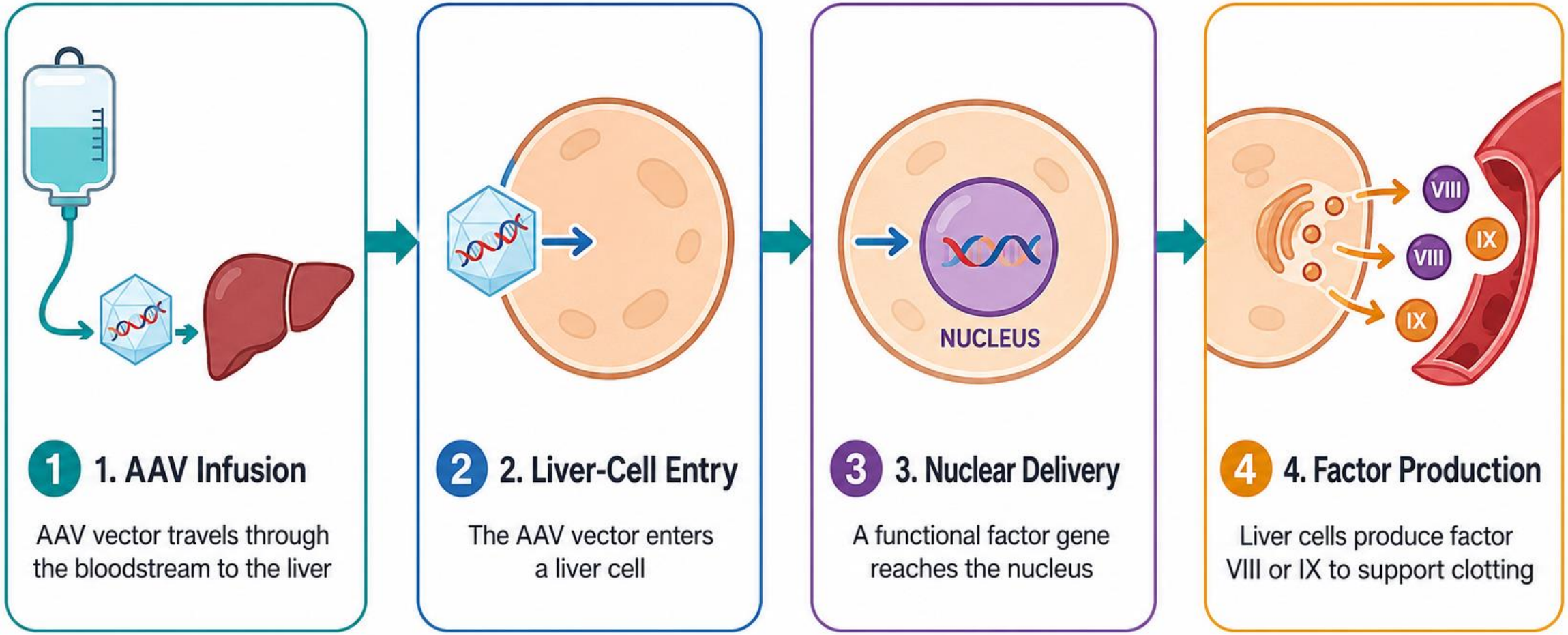
Antibodies can block factor activity

A rationale for durable factor production

Icons created with the assistance of GPT5 (Open AI)

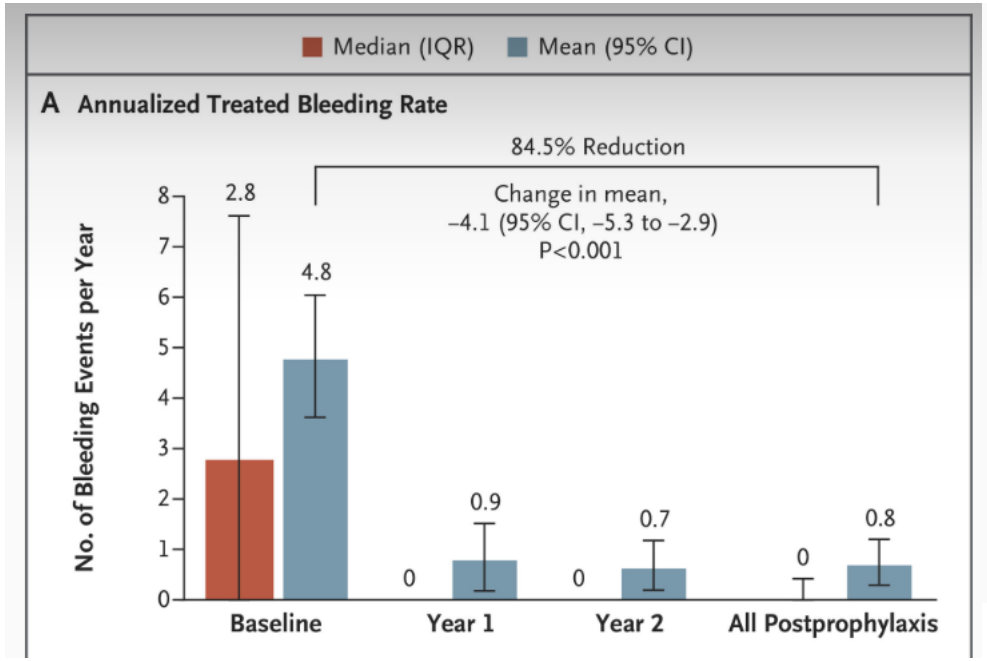
Hemophilia and Gene Therapy: in-vivo gene editing

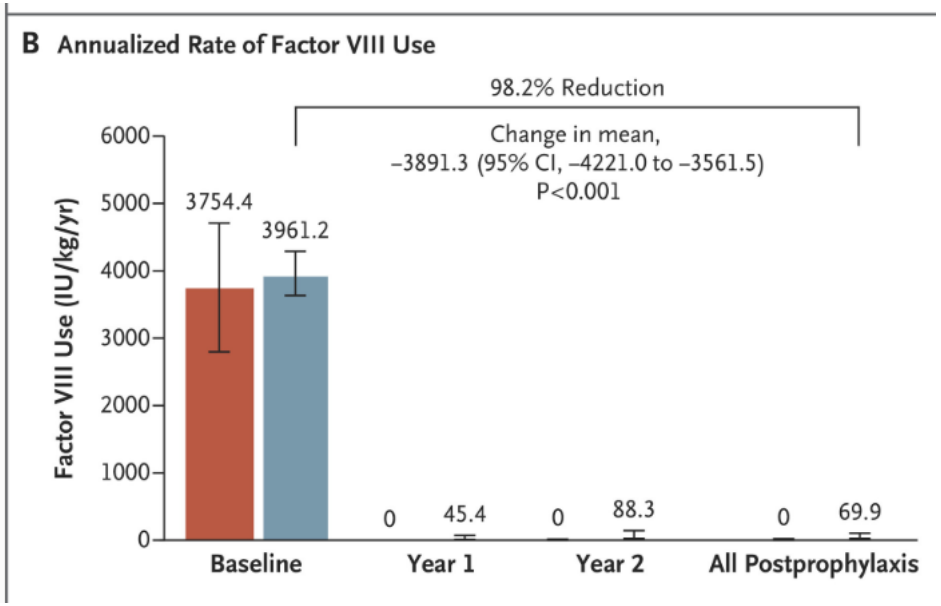
Hemophilia gene therapy: basic mechanism of action



Icons created with the assistance of GPT5 (Open AI)

Valoctocogene roxaparvovec: FDA approved for HemA





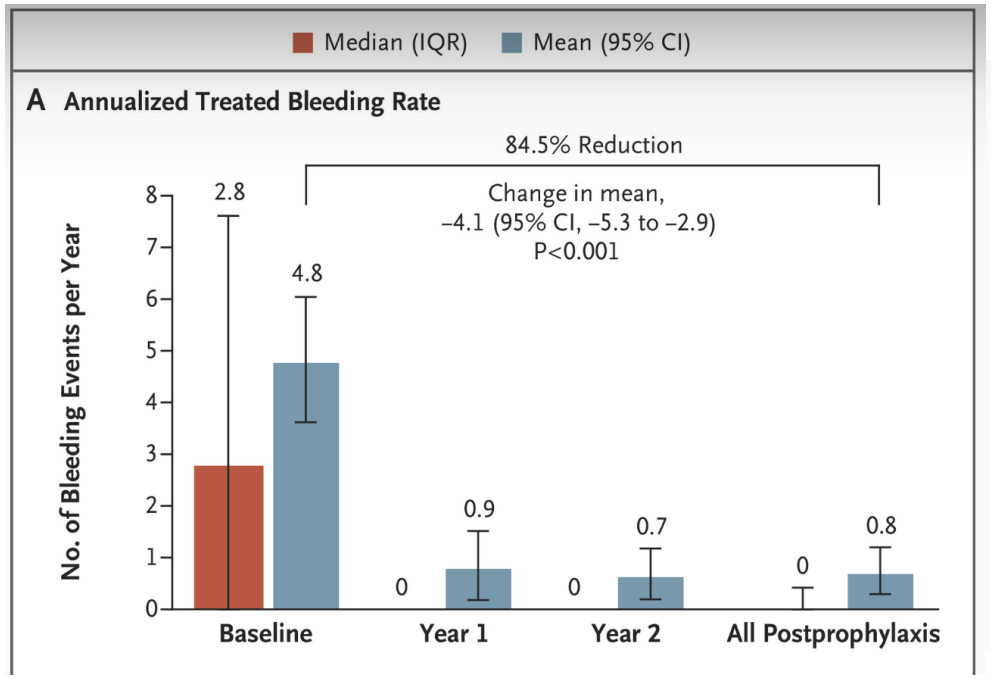
84%

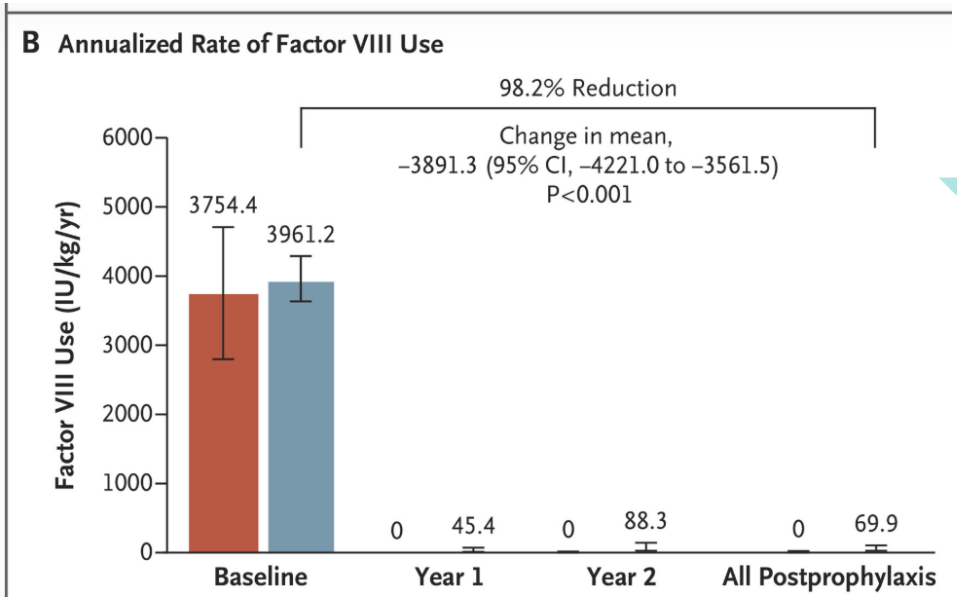
Decease in annualized bleeding rate

Mechanism	Adeno-associated viral vector that transfers a B-domain deleted human FVIII coding sequence into hepatocytes providing endogenous FVIII production

Mahlangu et al, NEJM 2023;

Etranacogene dezaparvovec: FDA approved for HemB





84%

Decease in annualized bleeding rate

Mechanism	Adeno-associated viral vector that transfers the Padua factor IX variant (R338L) into hepatocytes providing endogenous Padua factor IX production

Reasons for caution with gene therapy

Most with liver injury; up to 20% require corticosteroids, need monitoring

Patients with active liver disease or antibodies to viral vector not eligible

Patients with factor inhibitors unlikely to benefit

Long term durability not known; median factor level at 5 years ~ 5%

Cost: $$$ for x1 infusion

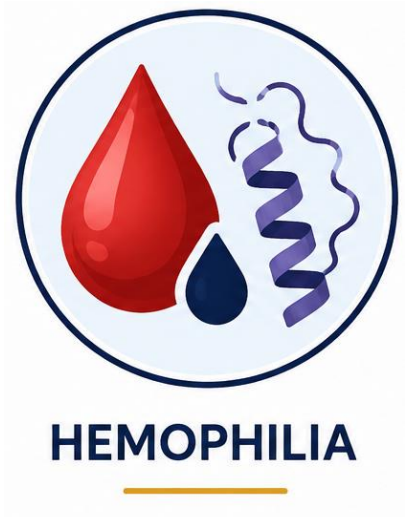
Case of patient with hemophilia

X-linked
Deficiency of FVIII (A) or FIX (B)
Bleeding

CB is a 40 year old man with Hemophilia A. As child, he had a history of recurrent hemarthroses. His factor level was always consistently < 1%. He has been on prophylactic recombinant factor VIII replacement (infusions multiple times per week) since childhood. In his medical history, he has untreated hepatitis C infection without evidence of cirrhosis. On last evaluation, he had not developed antibody titers to FVIII. He has discussed with his hematologist a strong desire to discontinue prophylactic factor infusions because he is tired of getting frequent infusions. A previous trial off factor replacement resulted in recurrent R hemarthrosis. You counsel him to consider:

A) Stay on current factor replacement – it cannot be that bad
B) Switch to a recombinant factor VIII product with a longer half-life
C) Stop factor replacement and start emicizumab
D) Treat his hepatitis C and refer for gene therapy consideration
E) Administer gene therapy to cure his hemophilia

Key points for gene therapy for B-thalassemia



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Deficiency of FVIII (A) or FIX (B)
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- 2 FDA approved gene therapy products:
- Greatly reduce bleeding events
- Eliminates dependence on factor replacement
- Improves quality of life

Barriers:

- Liver toxicity, monitoring, and steroids for some
- Durability a long-term concern
- Those with inhibitors cannot currently benefit
- $$$

MOC REFLECTIVE STATEMENT

Gene therapies for inherited hematologic conditions such as sickle cell disease, beta-thalassemia, and hemophilia are promising and can powerfully control disease manifestations

Limitations exist:

- For hemoglobinopathies: difficulty of stem cell collection and adverse effects of chemotherapy impose profound limitations on accessibility
- For hemophilia: uncertainties around durability and immunogenicity pose concerns
- For all: affordability is a key issue

Future iterations of gene therapy may address these!

Thank you!
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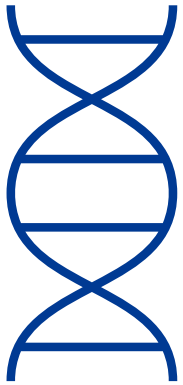

Gene therapy