

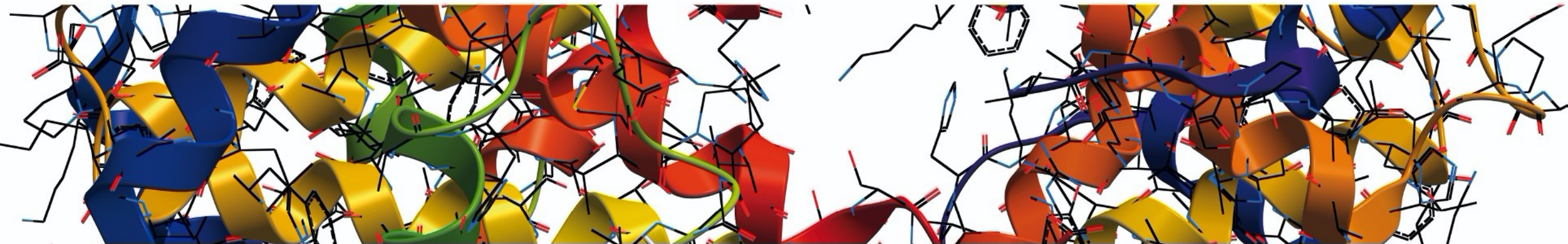
AGGIORNAMENTO SU DIAGNOSI E TERAPIA DELLE EMOGLOBINOPATIE

Ferrara, 4 luglio 2025 | Hotel Ferrara

La drepanocitosi oggi

Vincenzo voi

SSD Centro Microcitemie e malattie rare ematologiche.
Dipartimento di Scienze Cliniche e Biologiche. Università di
Torino.
AOU San Luigi Gonzaga. Orbassano (TO)



Disclosure

Company	Advisory Board - Consultancy	Principal Investigator	Sub-Investigator	Research Support	Employee	Stockholder	Speaker's Bureau	Other
Novartis	X		X					
Celgene			X					
Add Medica	X	X						X
Vertex	X							
Pfizer	X	X						
Novo-Nordisk	X	X						
Forma		X	X					

Di cosa parleremo?

Entità del fenomeno

Riconoscere il fenomeno

Perché è importante
riconoscerlo

Criticità

Generalità sulla gestione

Attualità

Prospettive

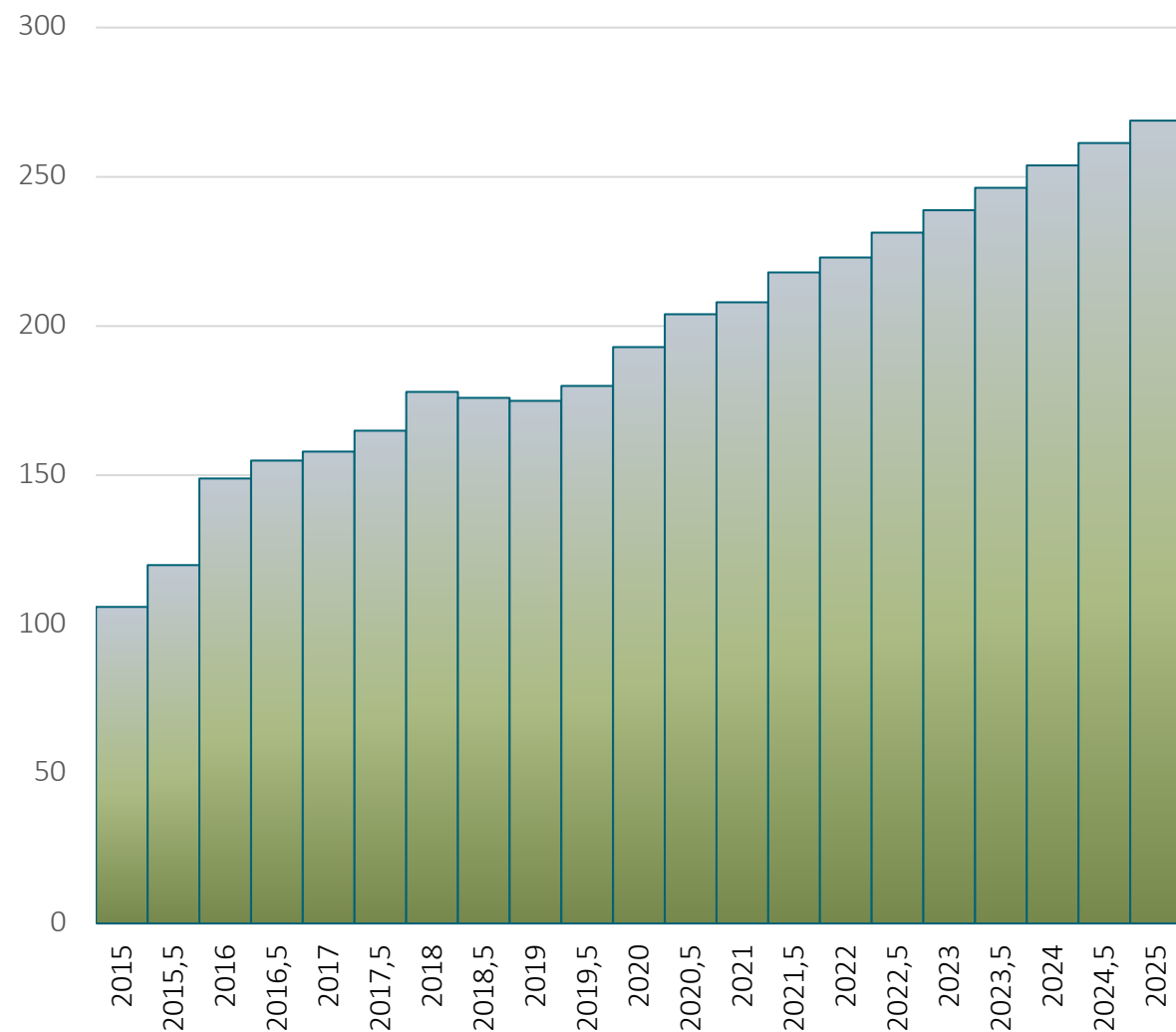
Riflessioni

Entità del fenomeno

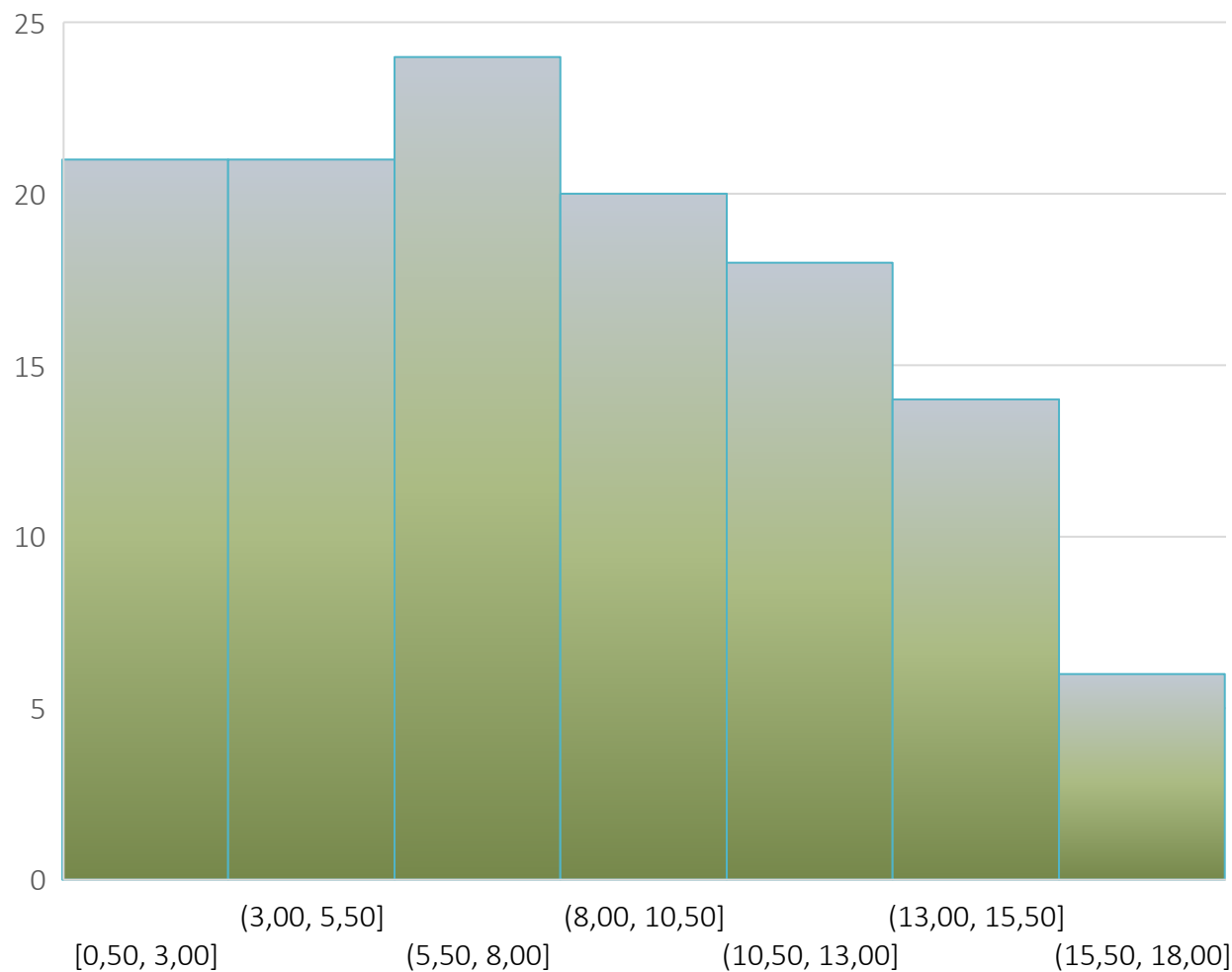
Incidenza

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Numero pazienti seguiti presso il centro negli ultimi 7 anni (conteggio semestrale)



Distribuzione età pazienti pediatrici seguiti presso il Centro N° 153



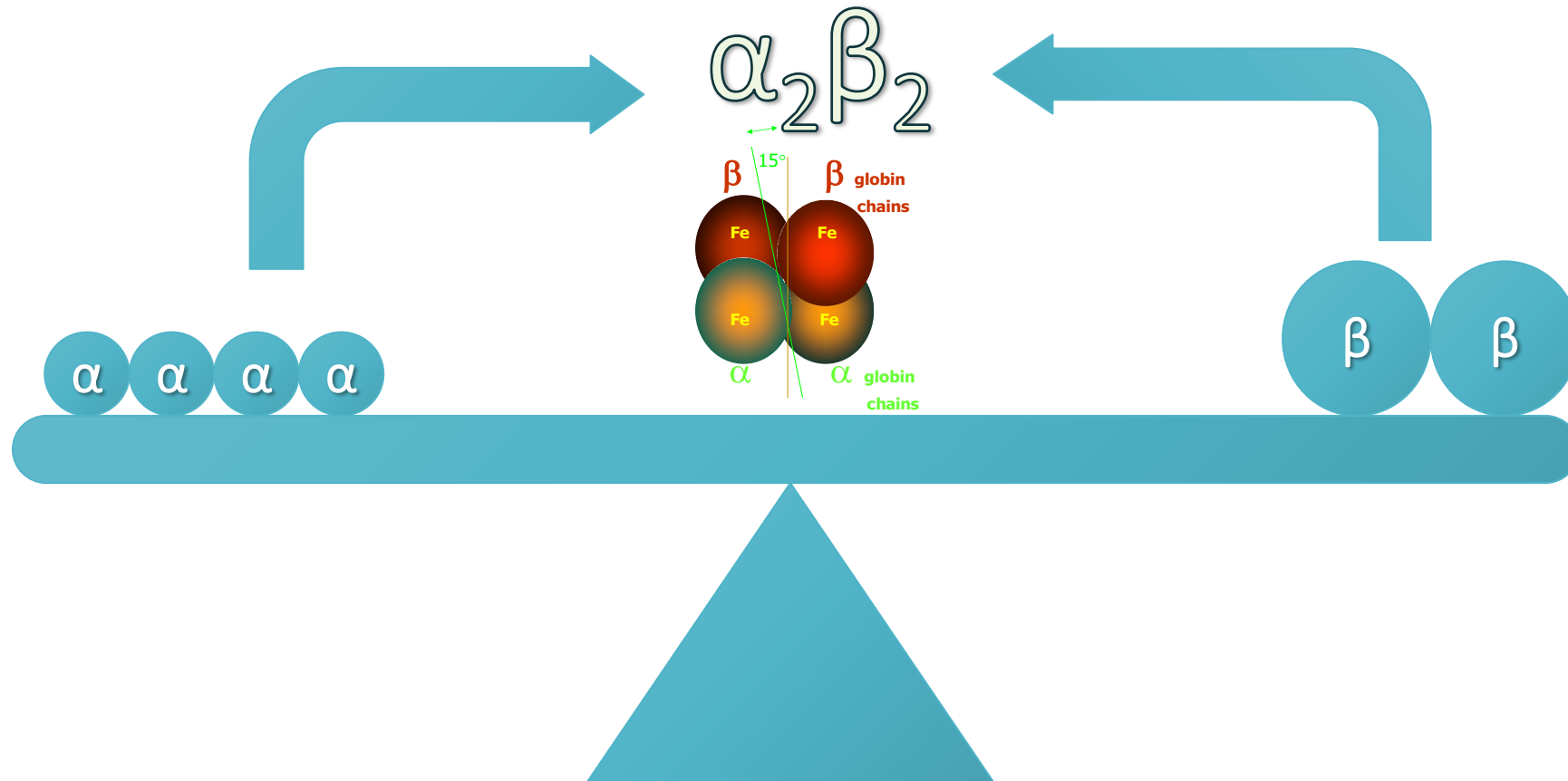
Riconoscere il fenomeno

Diagnosi

Fisiopatologia

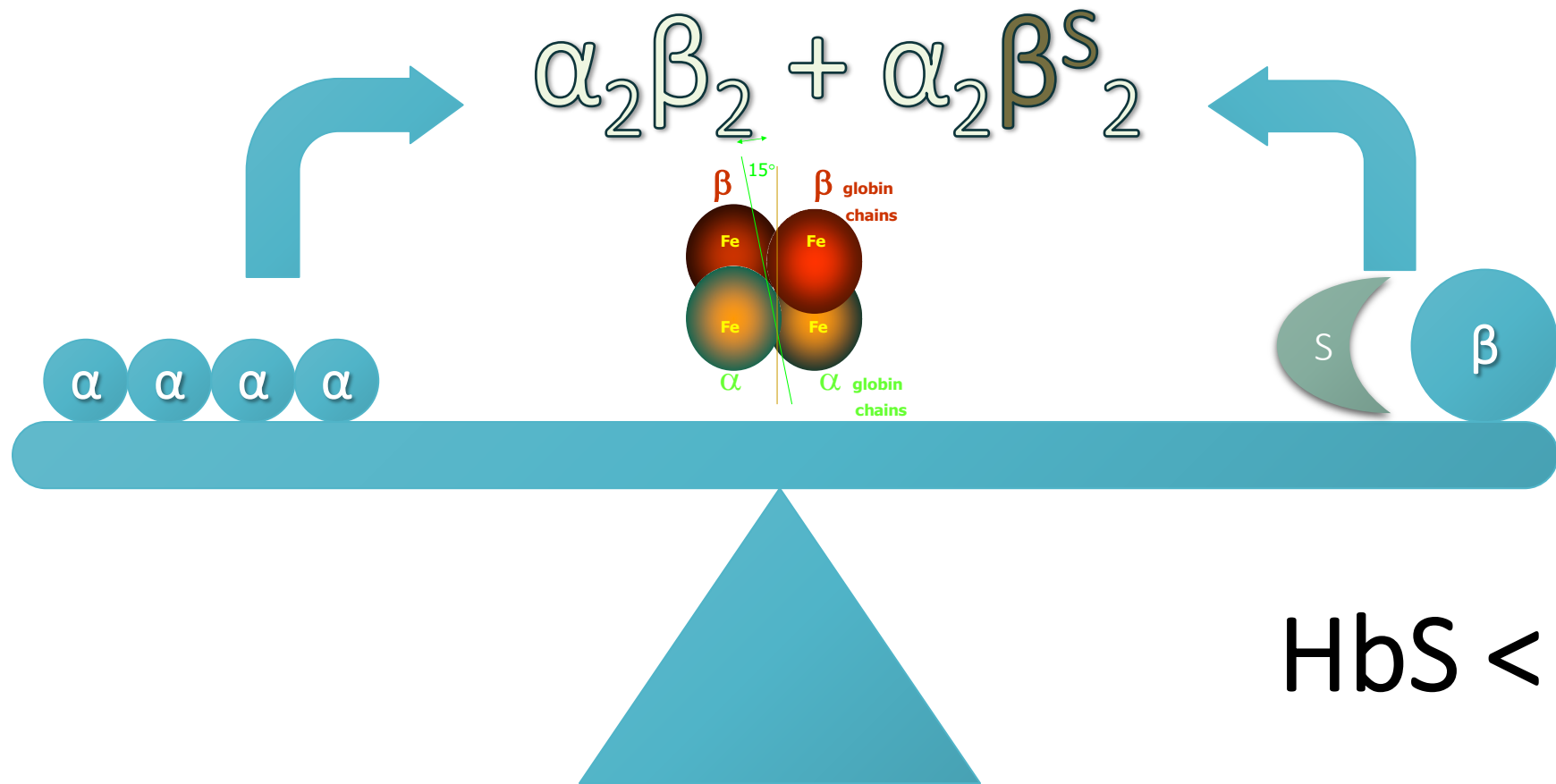
➡ Eritropoiesi

➡ Equilibrio di sintesi di catene α /non α [$\beta+\gamma$]

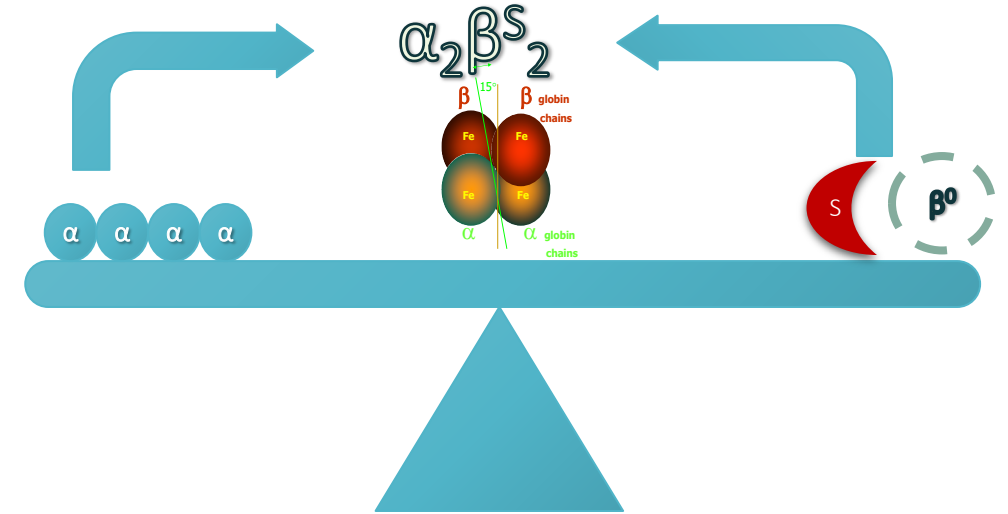
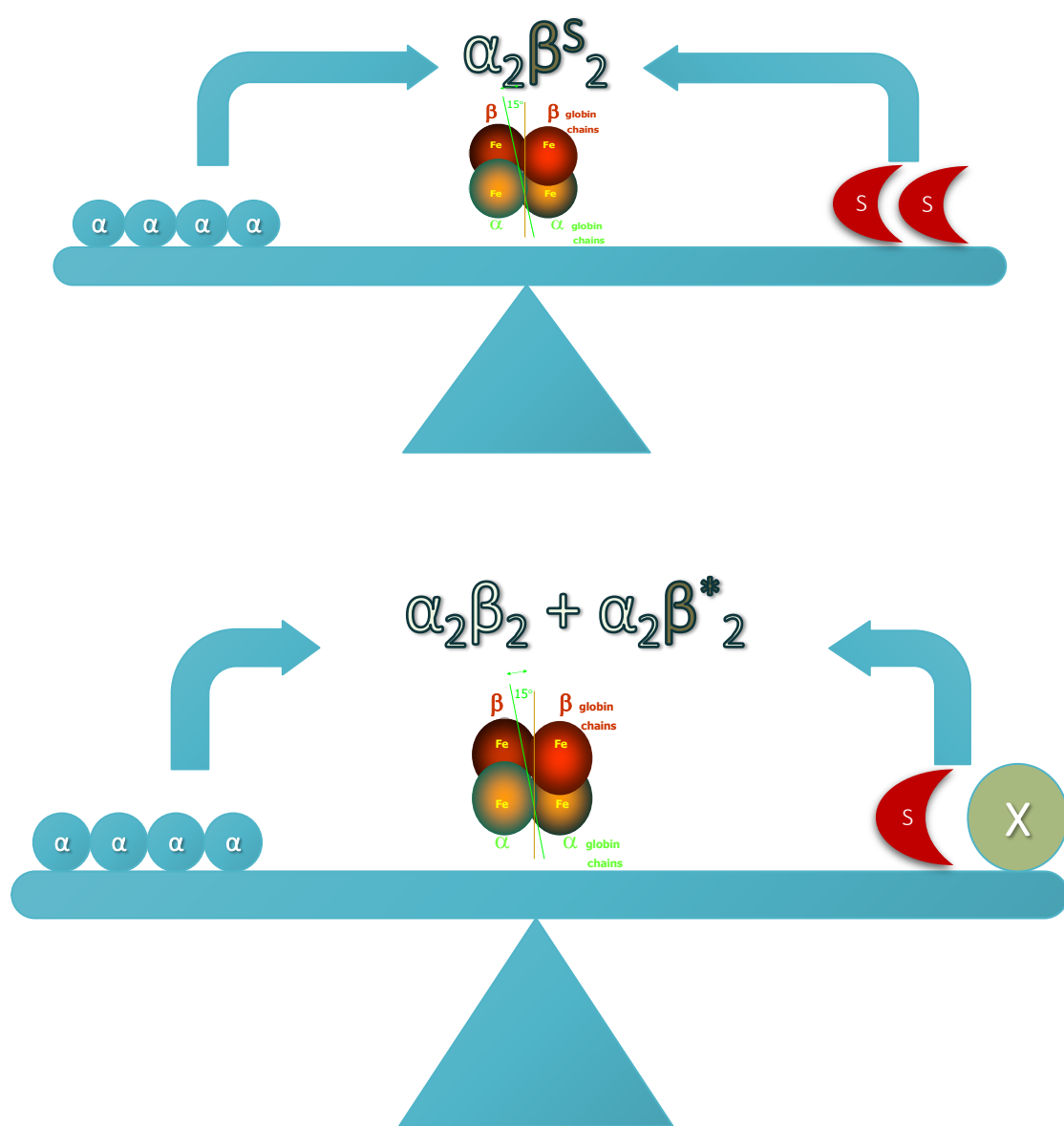


Fisiopatologia

➡ Drepanocitosi eterozigote



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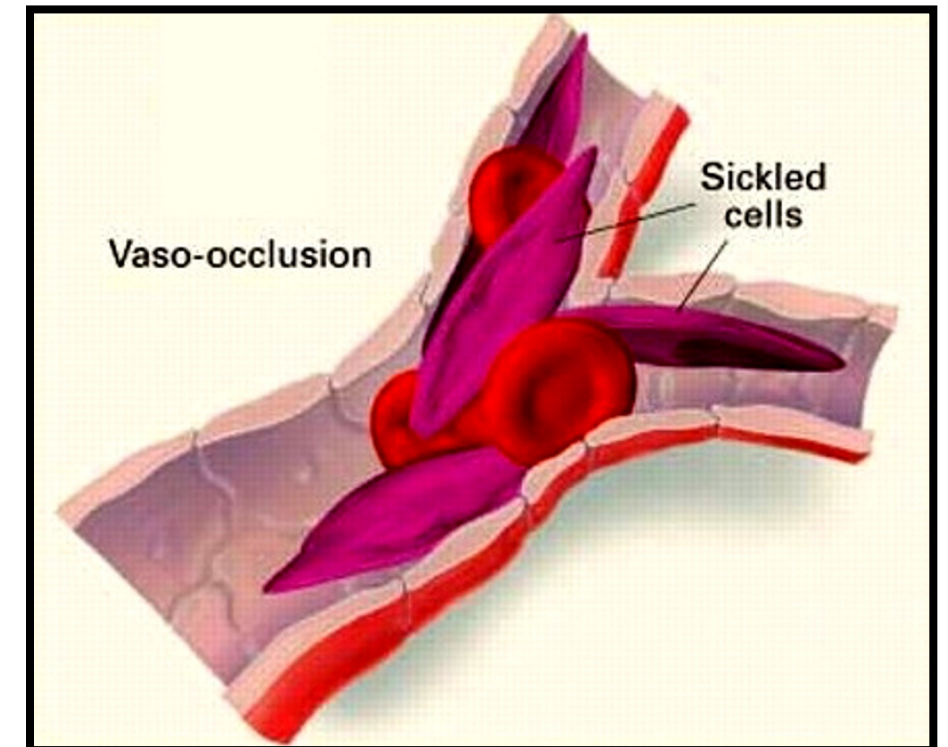
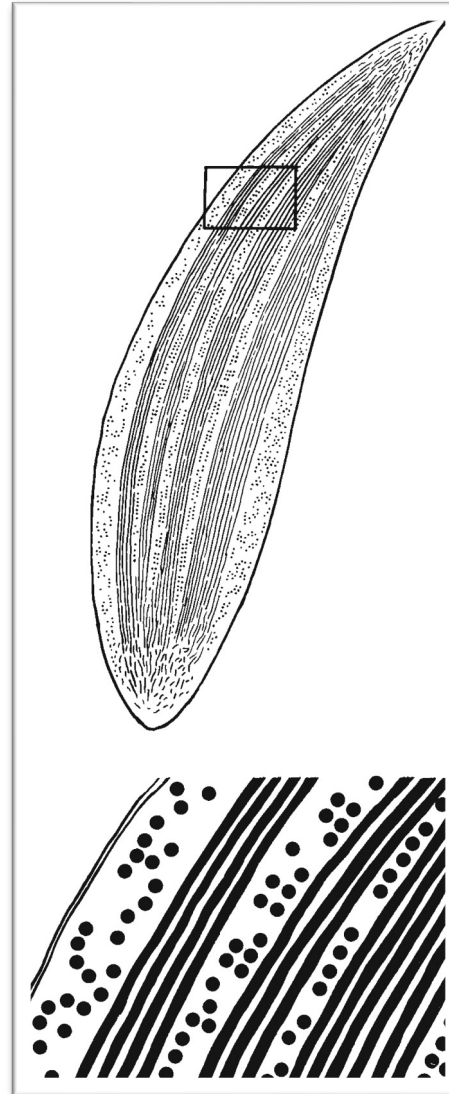
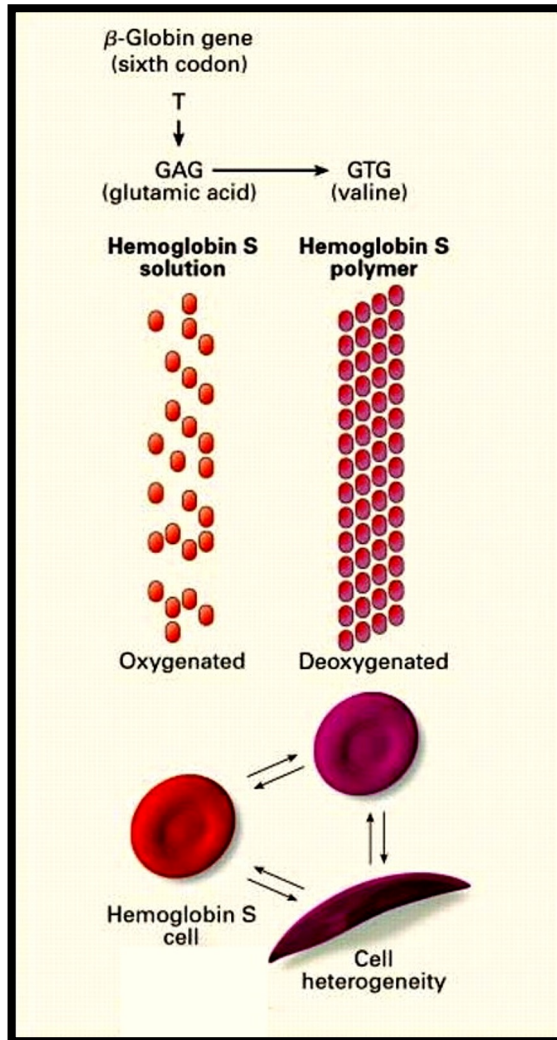


$$HbS + (HbX) > 50\%$$

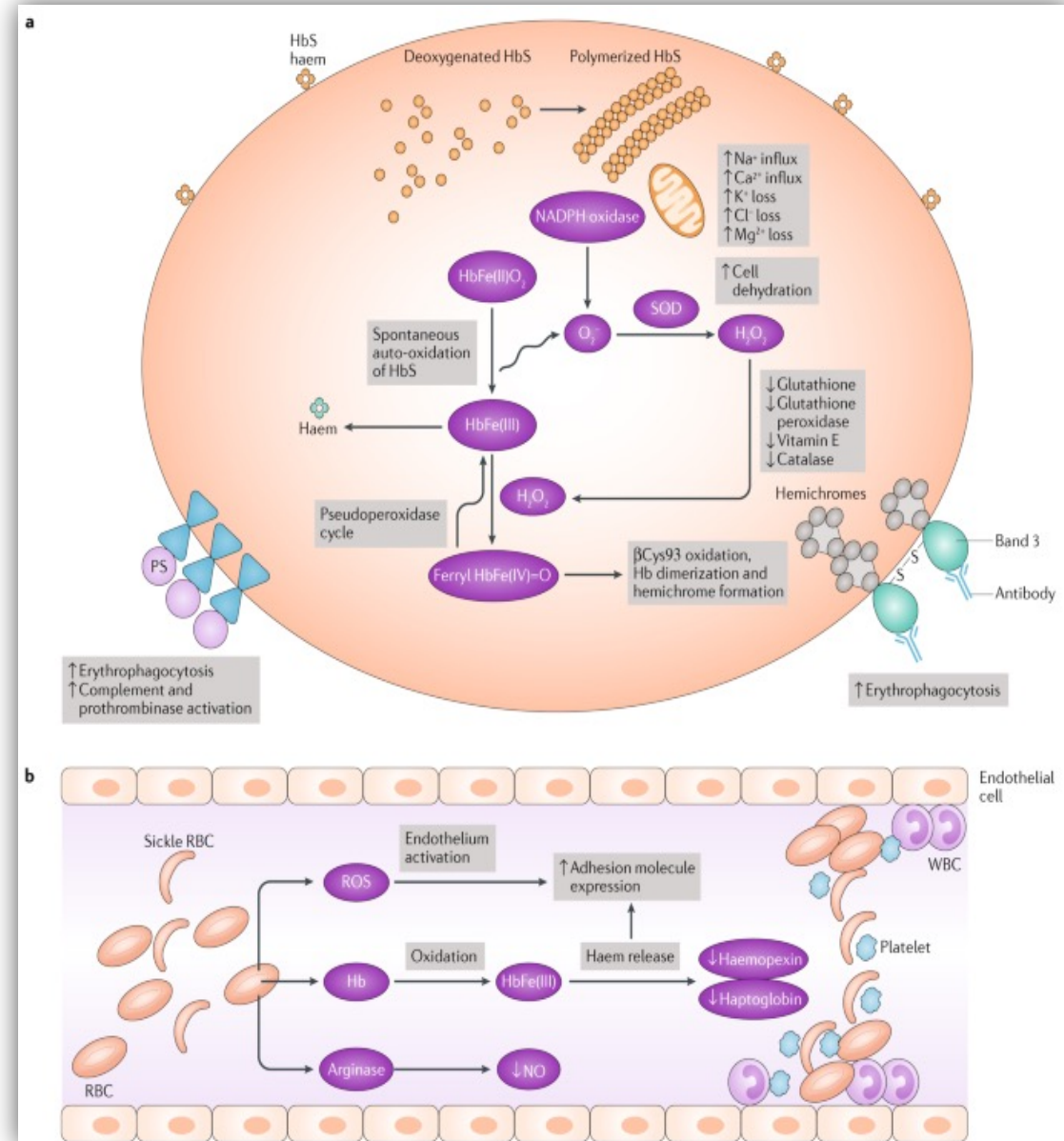
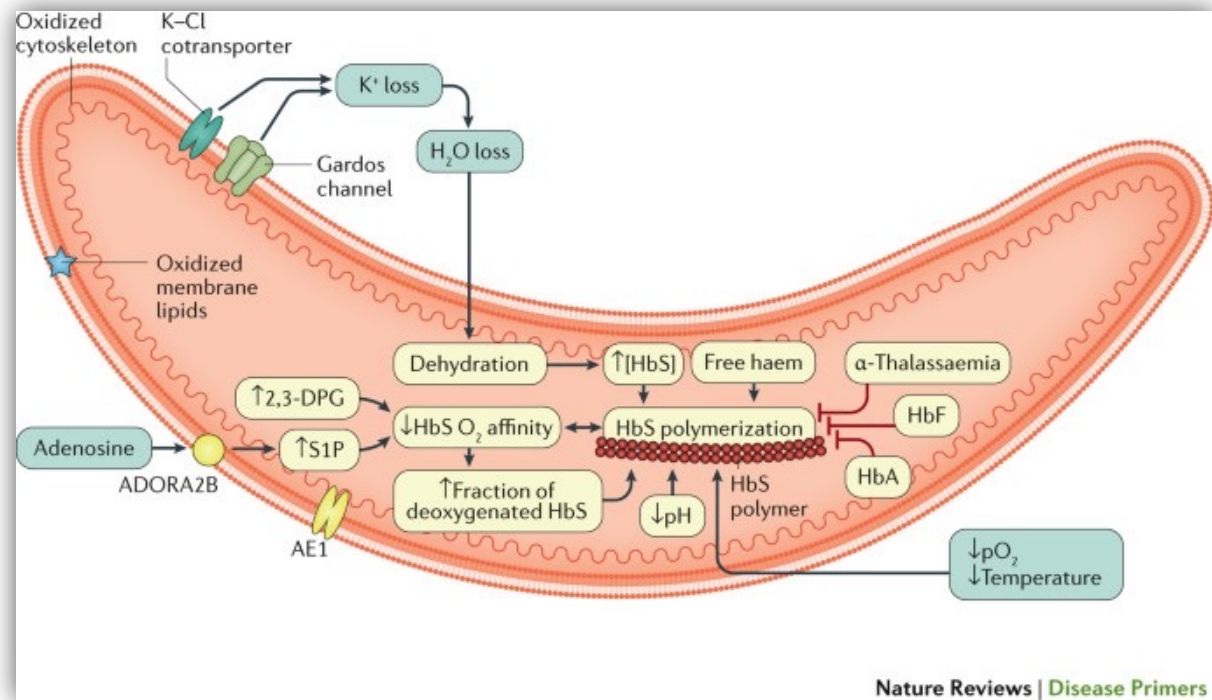
Clinica

Fisiopatologia

SICKLING



MULTIFACTORIAL DISFUNZIONE



SOMMARIO



Morfologia eritrocitaria

Ossidazione e disidratazione



Emolisi

Disidratazione – Rilascio di Eme libero – Attivazione del DAMP



Disfunzione endoteliale

Sovraespressione delle molecole di adesione – Attivazione e adesione dei leucociti – Carenza di NO – Vasocostrizione



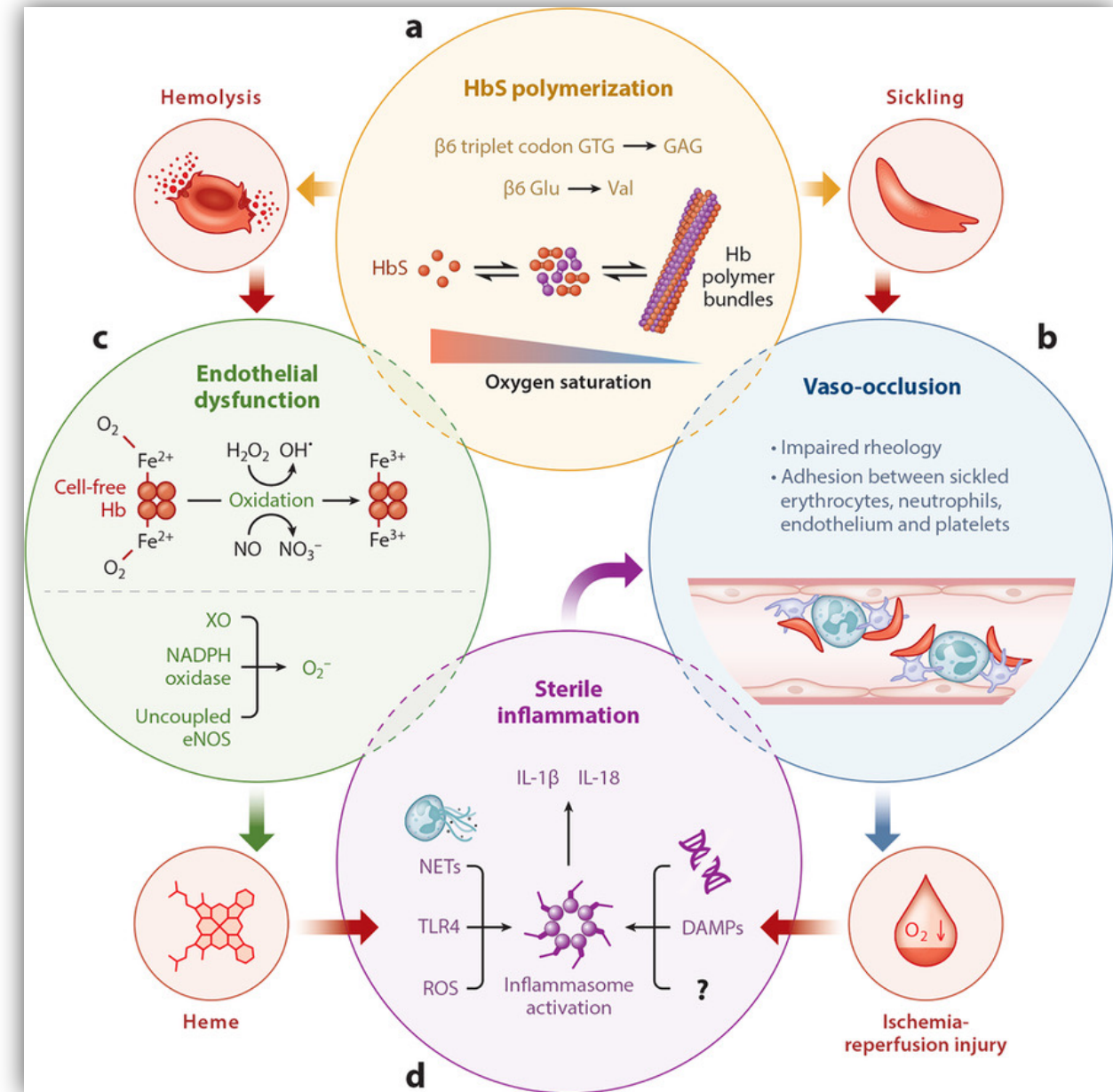
Attivazione del Sistema immunitario

Citochine infiammatorie – Attivazione del complemento



Disfunzione della coagulazione

Adesione delle piastrine – Coagulazione

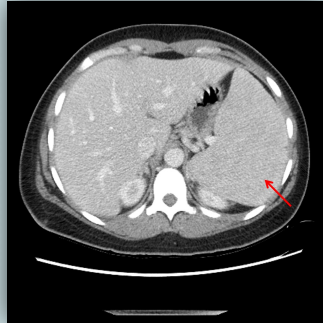


COMPLICAZIONI

ACUTE

Emolisi

Vaso-occlusione

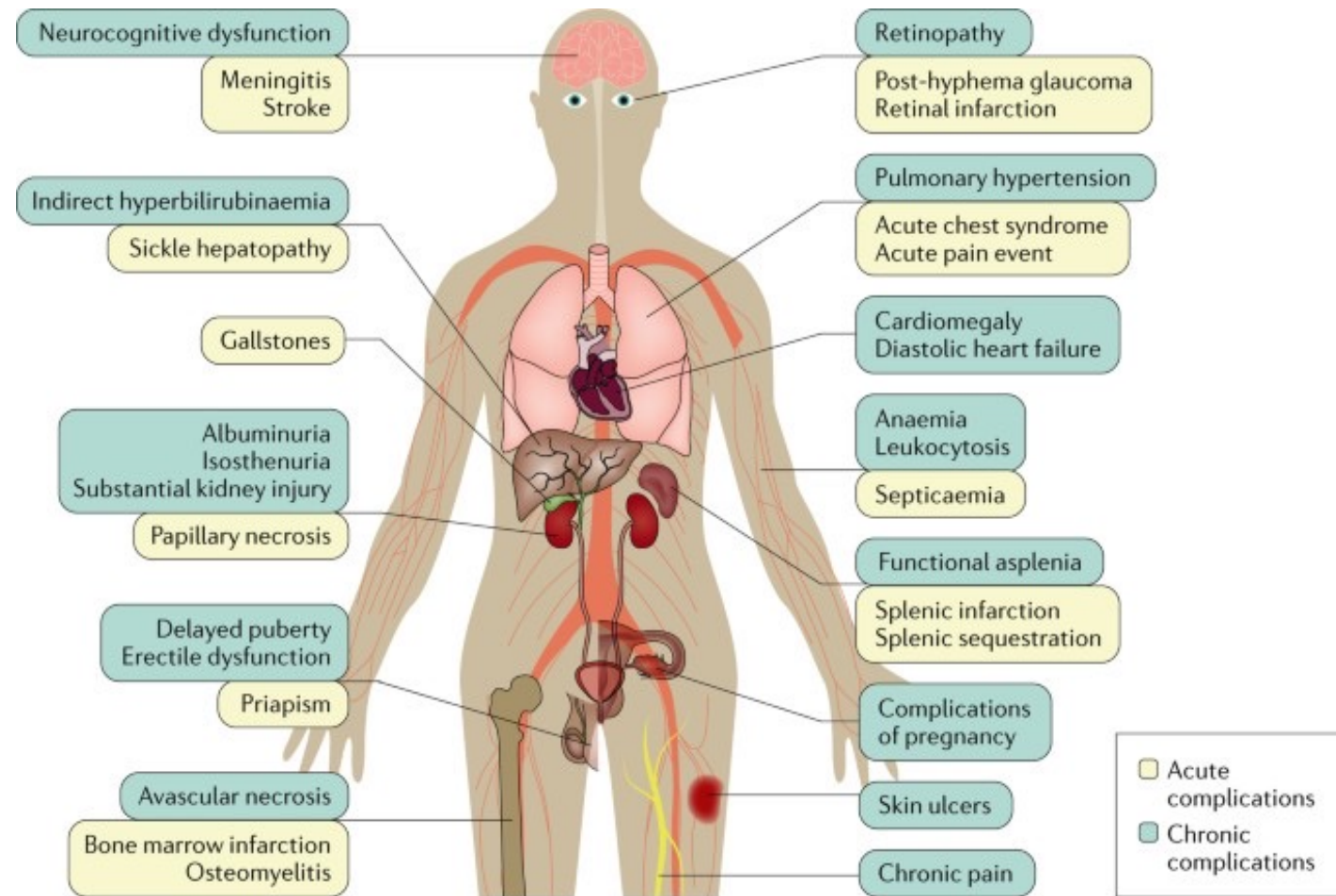


CRONICHE

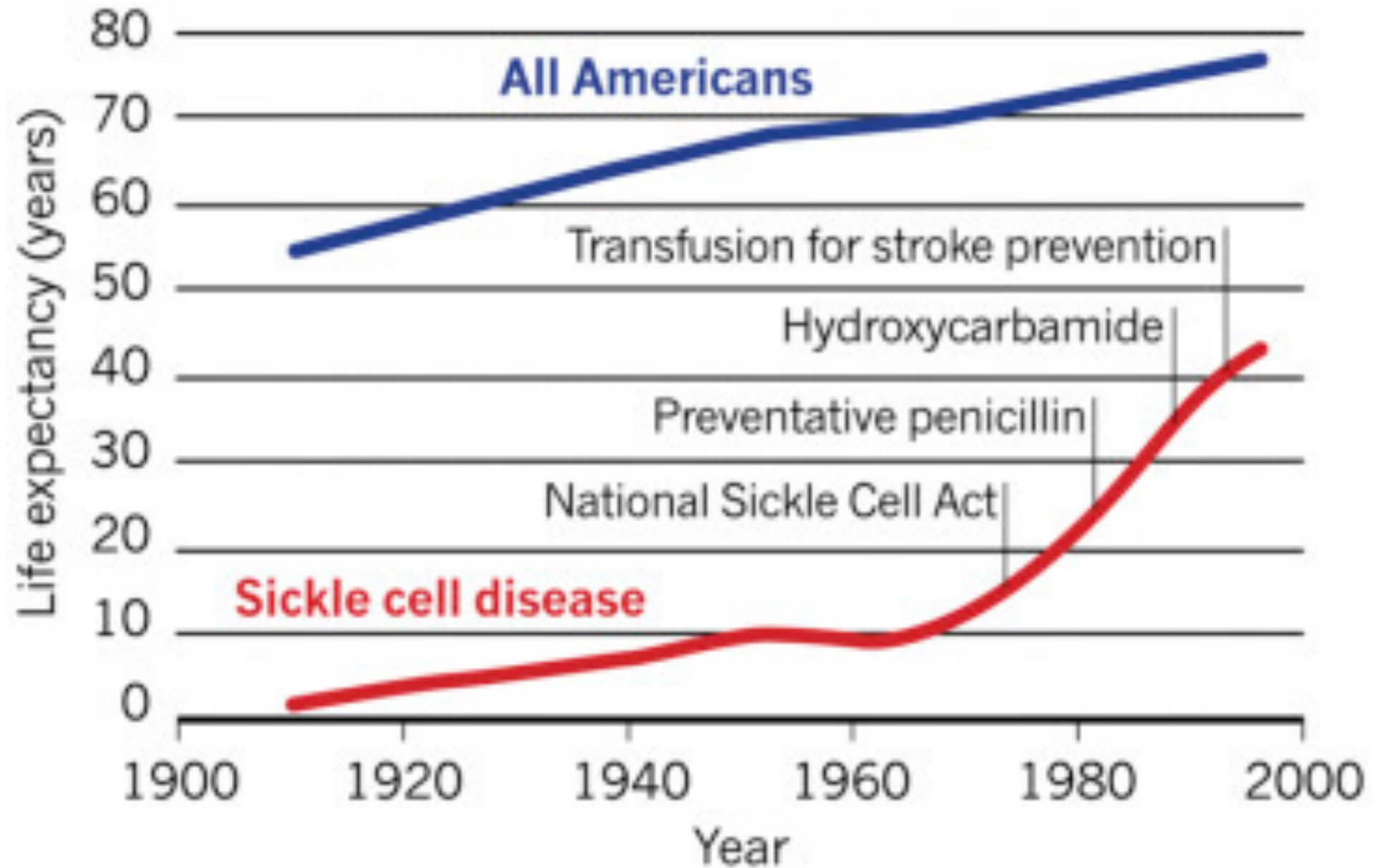
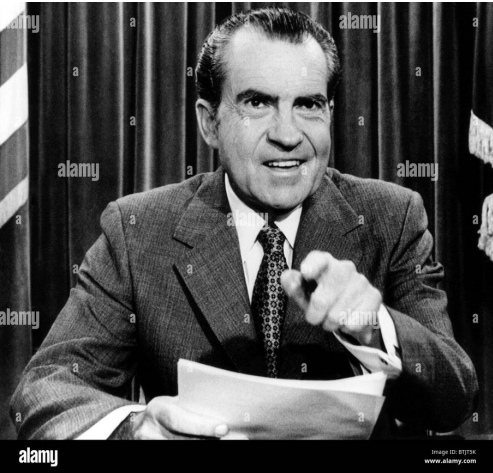
Ipossia cronica

Ipo-perfusione – Riperfusione

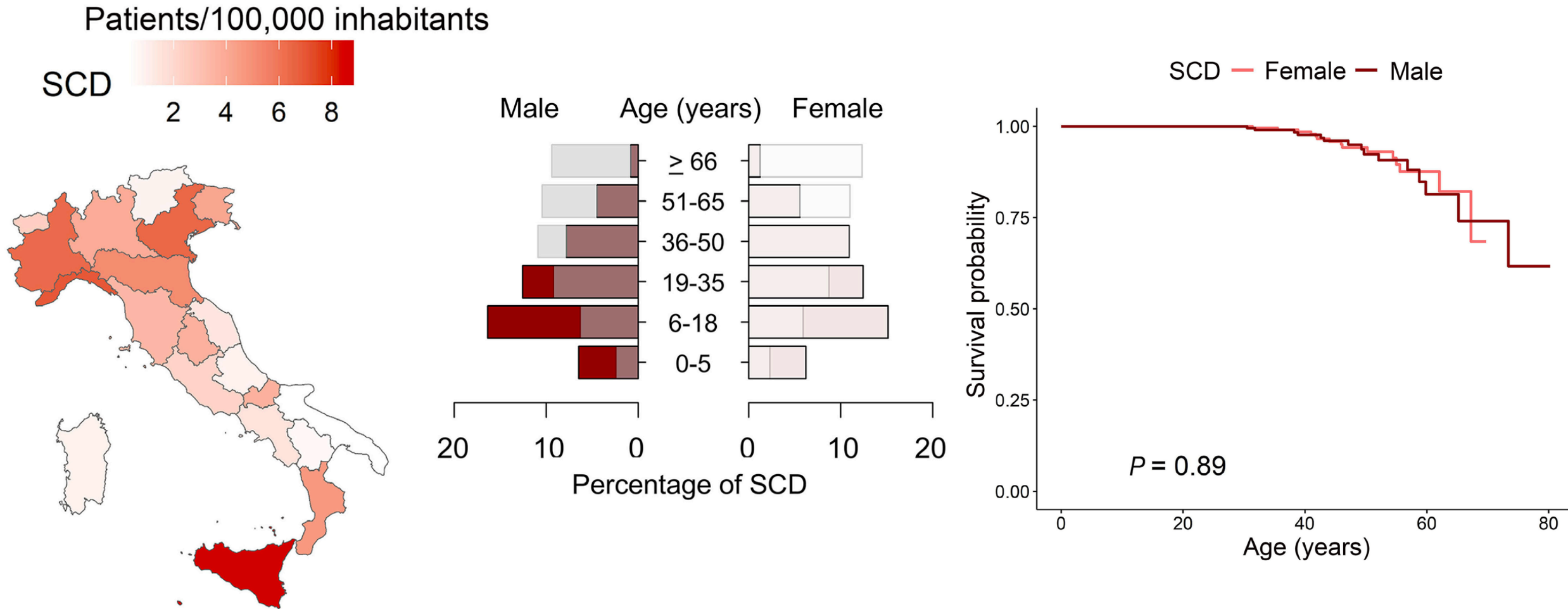
Danno endoteliale



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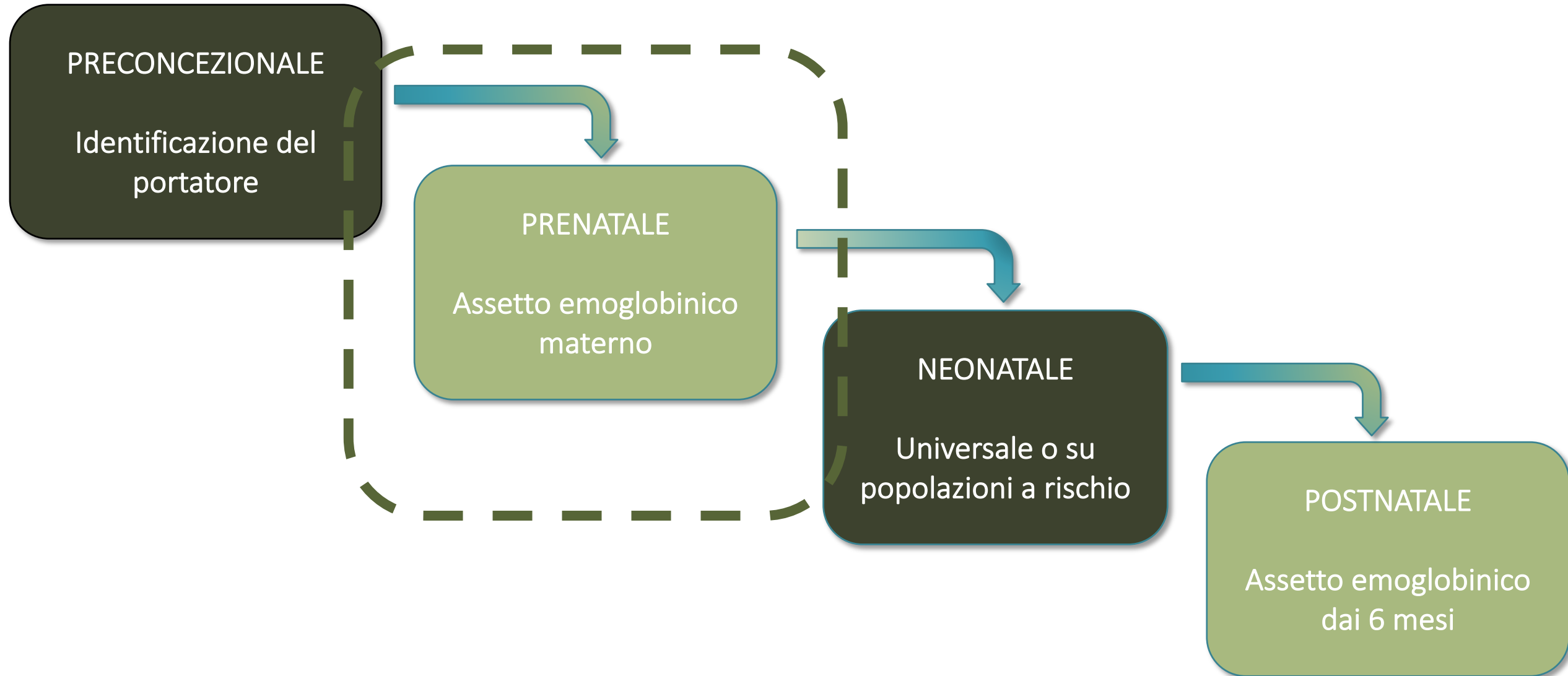


Realtà attuale e prospettive di vita

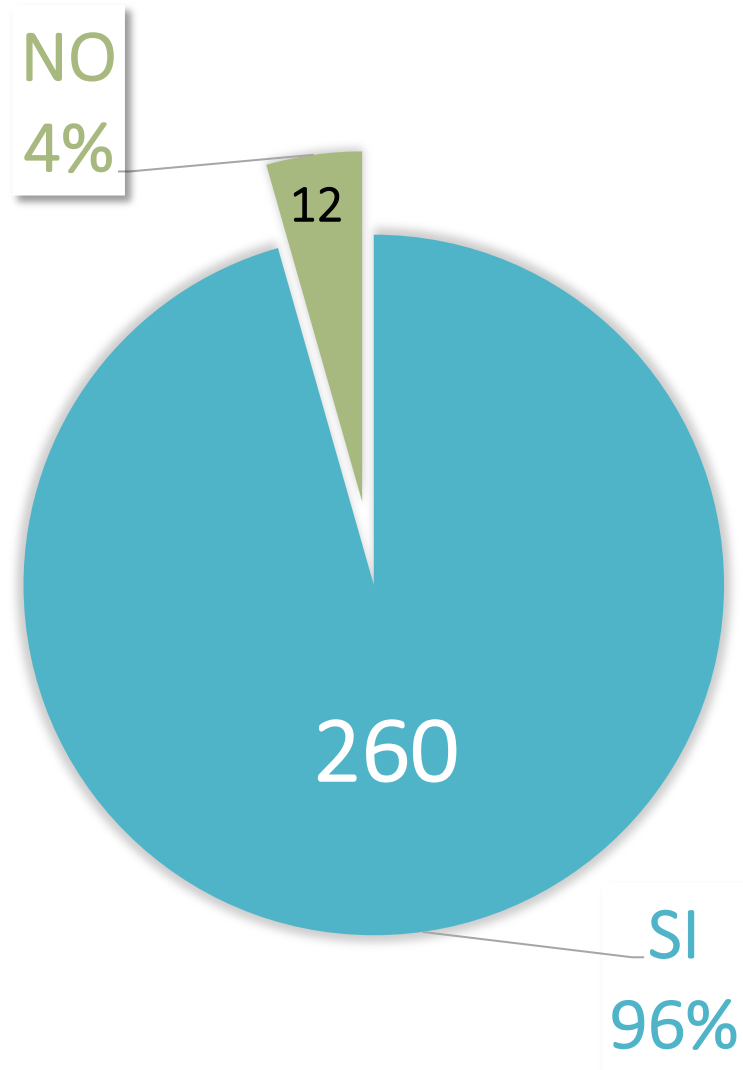


Gianesin et al. Haematologica. 2025

Identificazione del problema



STUDIO PILOTA OSP. MAURIZIANO



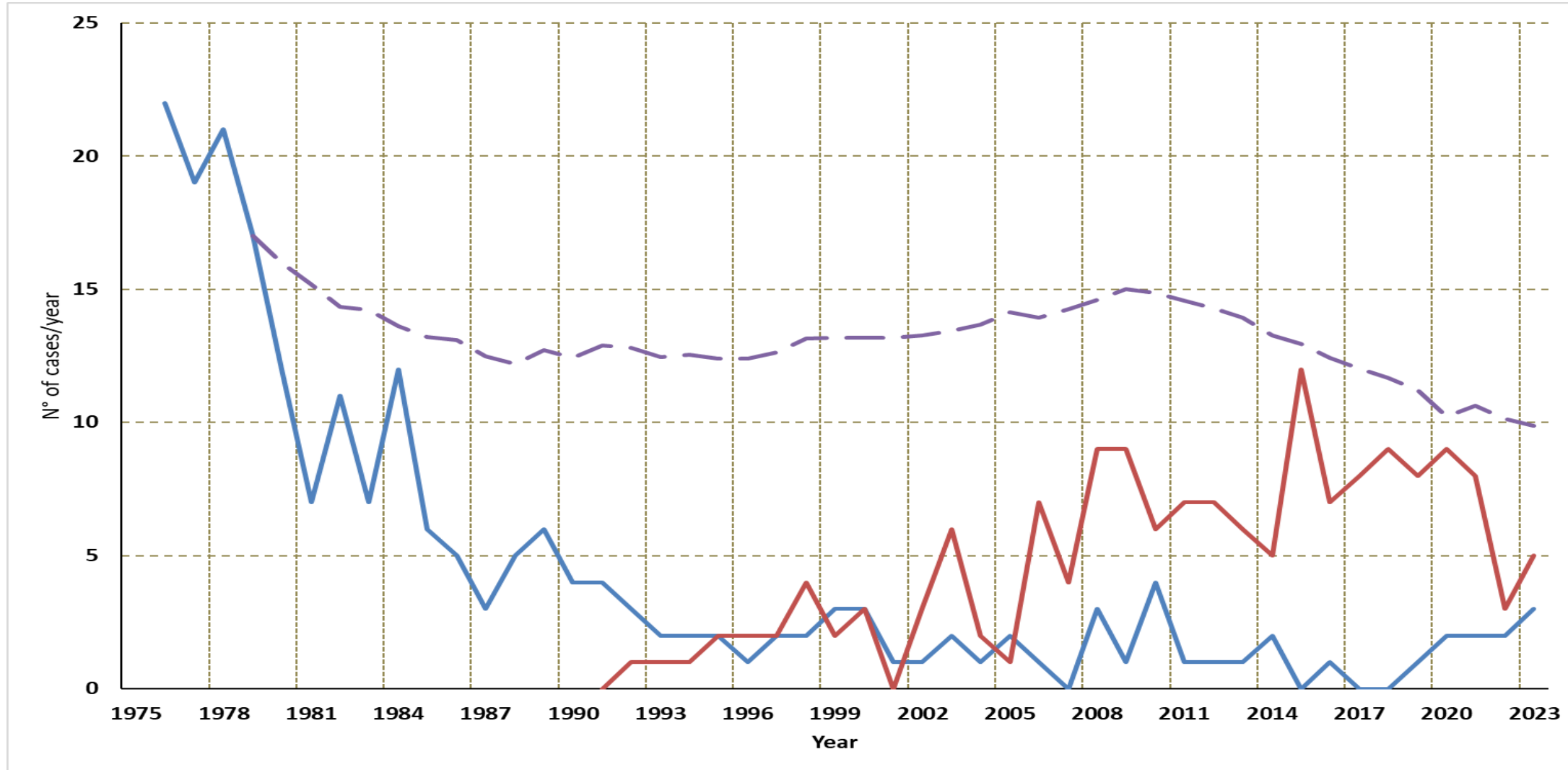
SCREENING PRENATALE

- 260 (96%) madri hanno aderito allo screening prenatale
- 12 (4%) NON hanno aderito

I. Stigliano. University of Turin, personal data. 2022

AGGIORNAMENTO SU DIAGNOSI E TERAPIA DELLE EMOGLOBINOPATIE

Regional incidence of TDT and SCD in Piemonte



Generalità sulla gestione

Attualità e prospettive

Drepanocitosi

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DIAGNOSI

Terapia iniziale:
Profilassi ATB

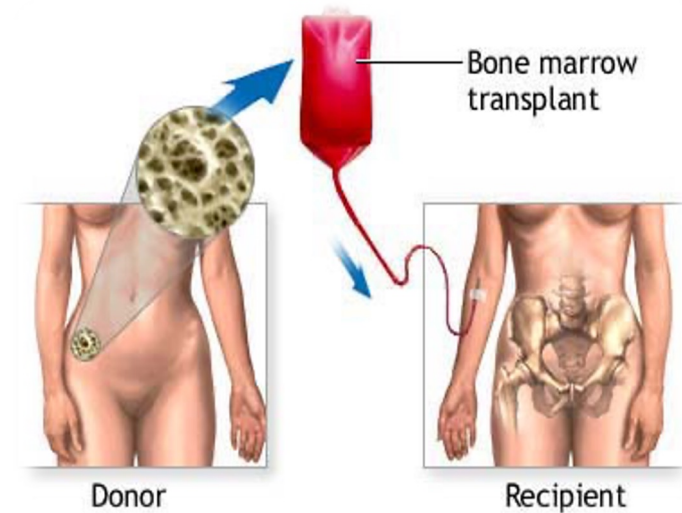
Ac. Folico
Vit D

Educazione
Parentale



TCD
 $Pz < 15aa$

Follow up
Regolare



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STEP 01

- Oral Paracetamol
- Oral FANS (Ibuprofen)
- Nonpharmacological

STEP 02

- Oral FANS
- Mild opioid
Codeine + paracetamol
- Medium potency
(Oral Tramadol)

STEP 03

- Medium potency
opioids (tramadol) IV
- FANS IV (ketorolac)












STEP 04

- Morphine IV (bolus & Continuous infusion)
- FANS IV

STEP 05

- Morphine IV (bolus & Continuous infusion)
- FANS IV
- Ketamine
- Deep Sedation

Comparative pain scale chart (pain assessment tool)

										
0	1	2	3	4	5	6	7	8	9	10
Pain Free	Very Mild	Discomforting	Tolerable	Distressing	Very Distressing	Intense	Very Intense	Utterly Horrible	Excruciating Unbearable	Unimaginable Unpeakable
No Pain Feeling perfectly normal	Minor Pain Nagging, annoying, but doesn't interfere with most daily living activities. Patient able to adapt to pain psychologically and with medication or devices such as cushions.			Moderate Pain Interferes significantly with daily living activities. Requires lifestyle changes but patient remains independent. Patient unable to adapt pain.			Severe Pain Disabling; unable to perform daily living activities. Unable to engage in normal activities. Patient is disabled and unable to function independently.			

TRATTAMENTO
DEL DOLORE

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IDROSSIUREA

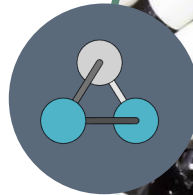
Preventative Treatment



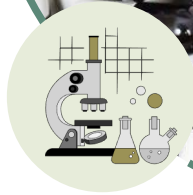
Safety and Efficacy in Children



Mechanism of action



Confirmed Efficacy in Adults:



Underutilization in High-Resource Countries:



TERAPIA TRASFUSIONALE

TOP – UP transfusion

Easy to perform
Avoid Hyper viscosity ($Hb > 10$)



Manual Eritroexchange (MEEEX)

Easy to do
Minimum skill required
Not applicable if Hb is low ($Hb < 8$)



Automated Eritroexchange (EEX)

Not always available
Gold standard



EMERGING DRUGS – AVAILABLE IN OTHER COUNTRIES



CRIZANLIZUMAB

MoAb anti P-selectin
Not available in Italy
and Europe



VOXELOTOR

Inhibition of HbS
polymerization
Approved in Italy
(CCN)



ETAVOPIVAT MITAPIVAT

Pyruvate Kinase
Activators
(Phase 2-3 trials)



L-Glutamine

Amino acid
Not available/approved
in Europe

THE FUTURE IS OPEN

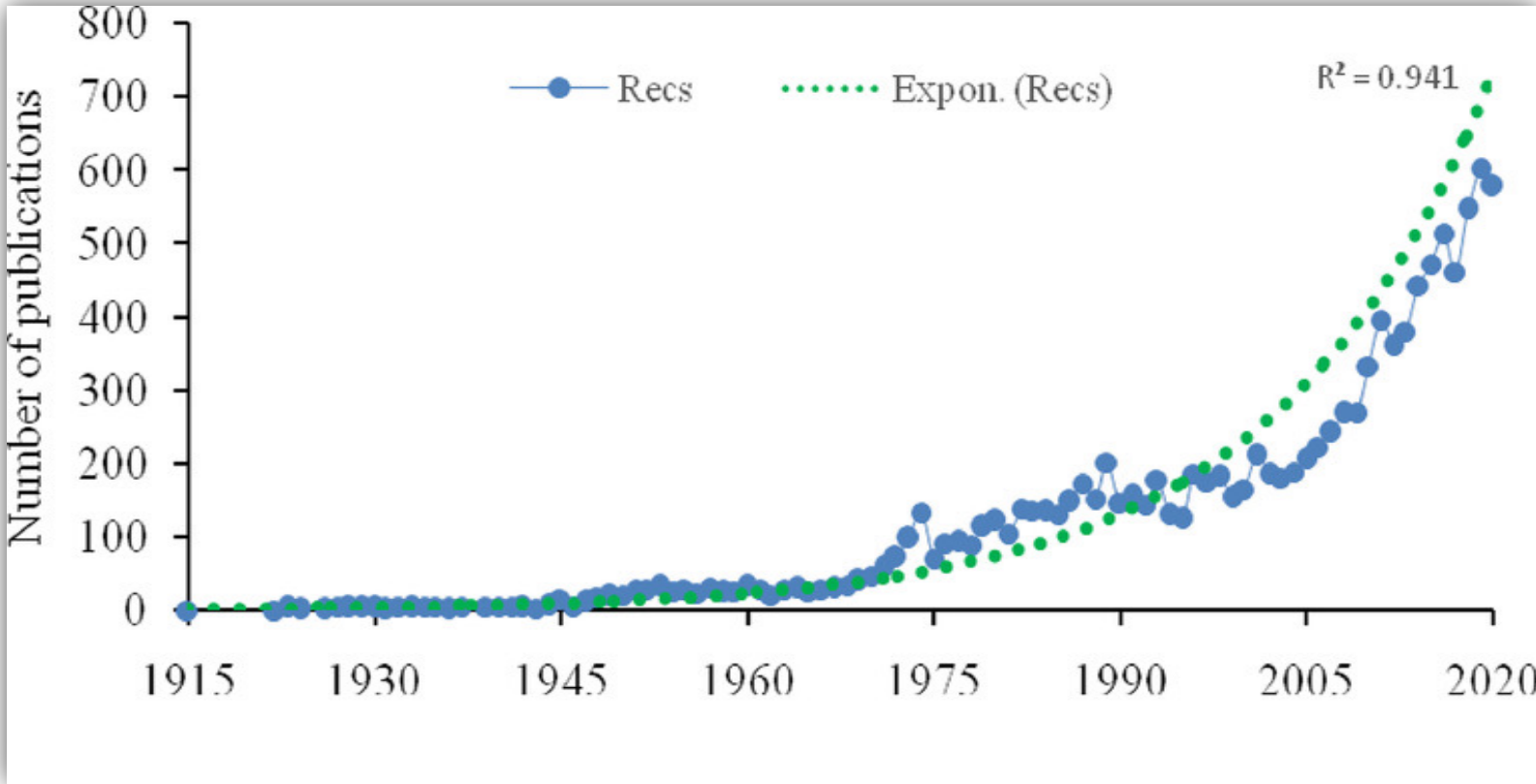
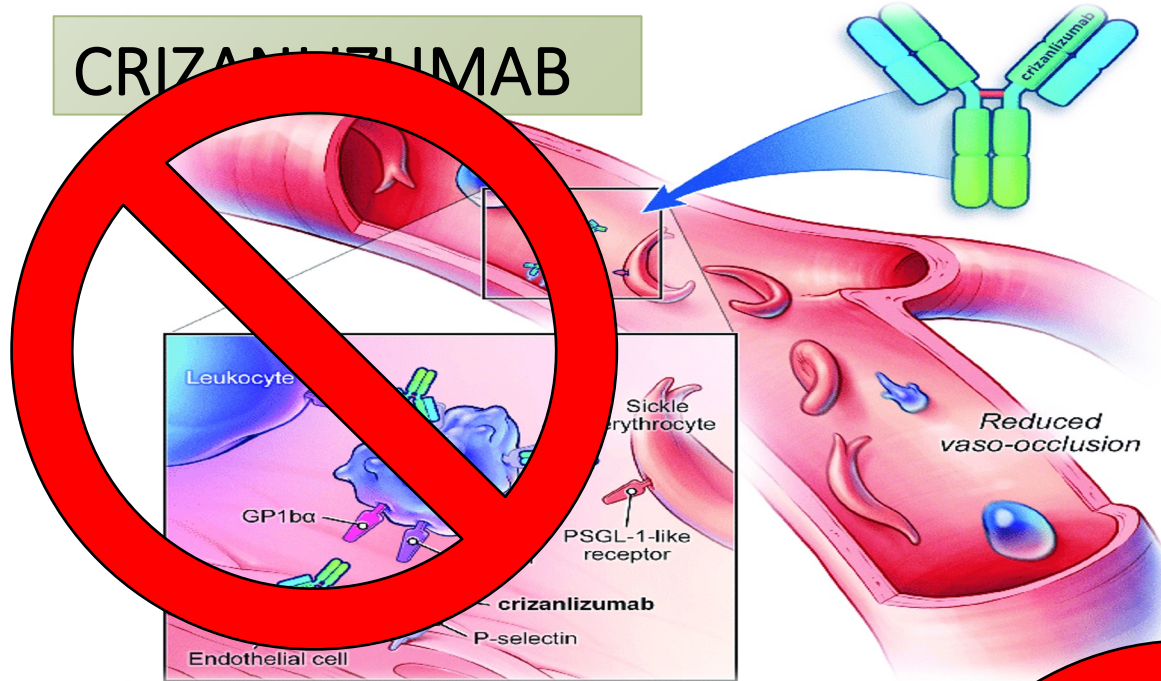


Table 1 | Emerging treatment approaches for sickle cell disease

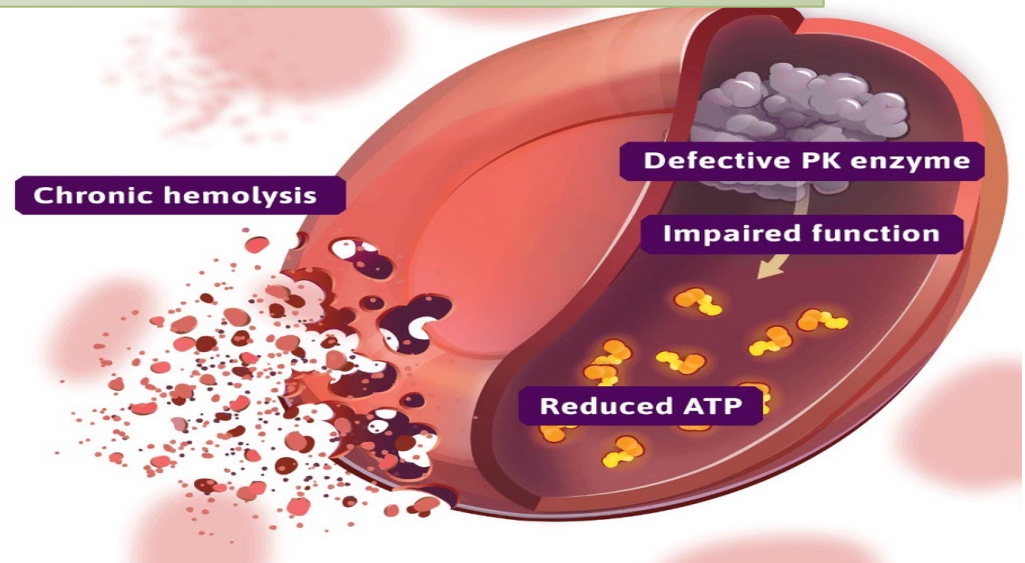
Therapy (previous name)	Mechanism	Advantages	Limitations	Refs
FDA approved				
L-Glutamine	Increases NADH levels and, as a result, cellular antioxidant activity	Oral formulation available; reduced the frequency of acute complications	Phase III trial results not yet published	273
Phase III study				
Rivipansel (GMI-1070)	Pan-selectin inhibitor	Can reduce the duration of pain crises, shorten hospital stays and decrease the amount of opioid pain medication	Currently available only in intravenous formulation; phase III trial results not yet available	254
Hydroxycarbamide	Increases expression of HbF	Reduces frequency of acute pain events, acute chest syndrome and transfusions in infants and adults	Disproportionate perceptions of carcinogenicity, teratogenicity and reduced fertility	144, 151
Prasugrel	Platelet inhibitor	Hypothesized to reduce the duration of vaso-occlusive crises; seems to be well tolerated at both therapeutic and supratherapeutic doses	Phase III study results not significant	152, 274
Vepoloxamer (MST-188)	Enhances microvascular blood flow	Hypothesized to reduce the duration and severity of acute pain crises	Phase III study results showed no effect*	275
L-Arginine	NOS substrate	Significantly reduced the severity of vaso-occlusive crises in Phase II studies	Phase III trial results not yet available	276, 277
N-Acetylcysteine	Antioxidant	Oral administration	Phase III study results showed no effect	278
Magnesium sulfate	Multimodal	Vasodilator, anti-inflammatory and pain reliever activities	Phase III study results showed no effect	279
Transfusions for silent cerebral infarcts	Erythrocyte transfusion	Significantly reduced the incidence of ischaemic stroke recurrence in children	Cumbersome to move into general practice	213
Transfusions for stroke prevention	Erythrocyte transfusion	Significantly reduced the incidence of first stroke in children with high cerebral artery blood flow	Follow-up study showed that it was not safe to stop regular transfusions after 30 months	208, 209
Transfusions changing to hydroxycarbamide	Increases expression of HbF	Efficacious for primary stroke prophylaxis	Not clearly superior to chronic transfusion for secondary stroke prophylaxis	211, 280
GBT440 ¹	HbS polymerization inhibitor	Well tolerated; proof of concept with improved oxygen delivery to tissues and marked reduction in circulating sickle erythrocytes	Phase III trial results not yet available	281
Phase II study				
Crizanlizumab (SelG1)	P-selectin inhibitor	Reduced the incidence of acute complications by 45–63%	Monthly intravenous infusions required	149
Inhaled NO	Pulmonary vasodilator	Provides NO to correct decreased bioavailability	Phase II trial showed no effect on the duration or severity of vaso-occlusive pain crises	282
Sildenafil	PDE5A inhibitor	FDA-approved for pulmonary hypertension and erectile dysfunction	Phase II trial terminated early owing to increased frequency of acute pain events	283
Sanguinate ¹	Improves tissue oxygen levels	Hypothesized to prevent vaso-occlusive crises and leg ulcers	Limited data	284
Sevuparin (DF02) ¹	Enhances microvascular blood flow	Might decrease erythrocyte adhesion and favour normal blood flow and reduce the risk of vaso-occlusion	Limited data	285
Phase I study				
Pomalidomide	Increases expression of HbF	Well tolerated; increases HbF and total Hb levels; anti-inflammatory effects	Limited data	286
IMR-687 ¹	PDE9A inhibitor	Preclinical data indicate decreased sickling, neutrophil adhesiveness and vaso-occlusion	Limited data	287
SCD-101	HbS polymerization inhibitor	Natural product	Limited data	288
Gene insertion	Lentiviral vectors	Insertion of genes encoding anti-sickling engineered β -globins	Unknown long-term risks; unclear whether curative or only ameliorative	248

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CRIZANLIZUMAB



ETAVOPIVAT - MITAPIVAT



VOXELOTOR



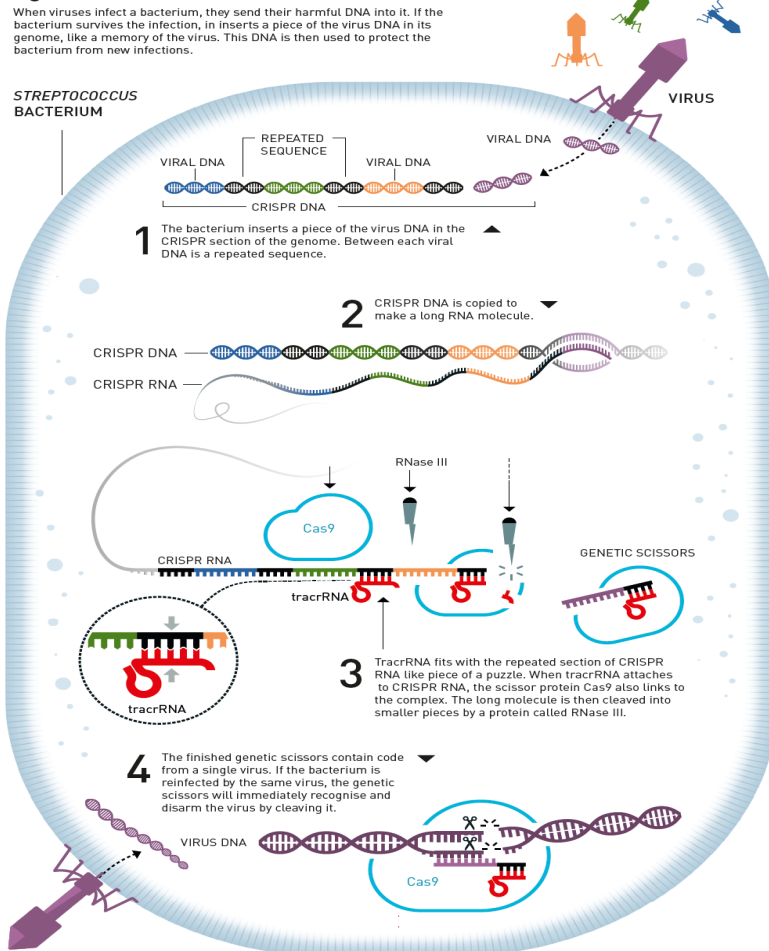
TERAPIA GENICA GENE EDITING- CRISPR CAS9

www.nobelprize.org

Streptococcus' natural immune system against viruses: CRISPR/Cas9

When viruses infect a bacterium, they send their harmful DNA into it. If the bacterium survives the infection, it inserts a piece of the virus DNA in its genome, like a memory of the virus. This DNA is then used to protect the bacterium from new infections.

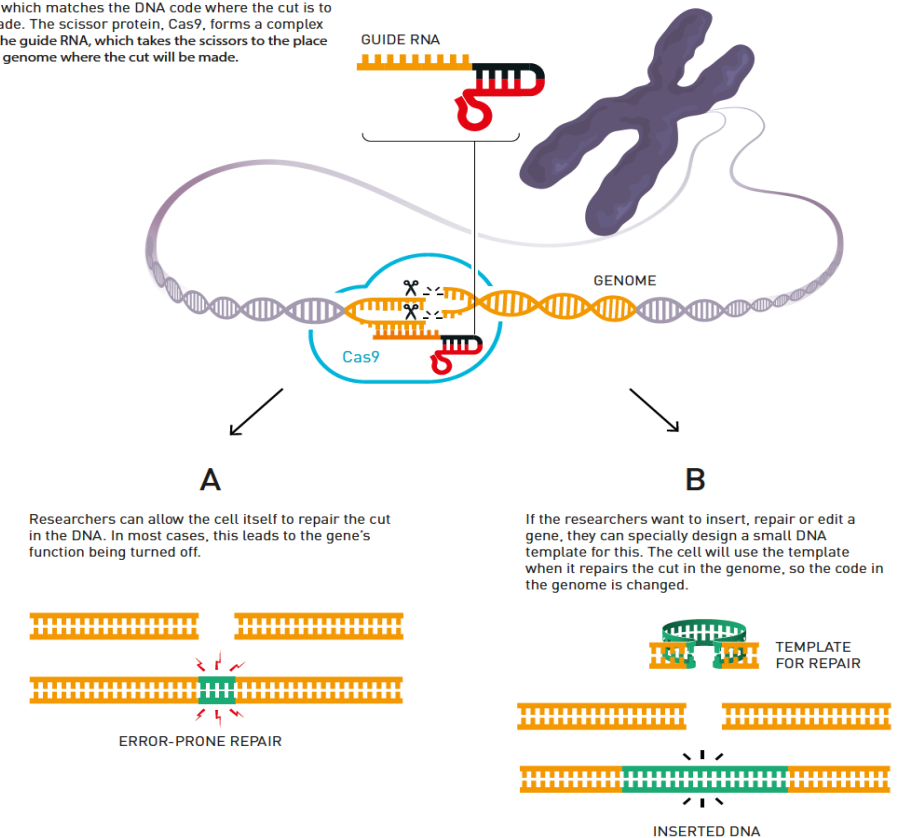
**STREPTOCOCCUS
BACTERIUM**



©Johan Jarnestad/The Royal Swedish Academy of Sciences

The CRISPR/Cas9 genetic scissors

When researchers are going to edit a genome using the genetic scissors, they artificially construct a guide RNA, which matches the DNA code where the cut is to be made. The scissor protein, Cas9, forms a complex with the guide RNA, which takes the scissors to the place in the genome where the cut will be made.



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luglio 2025

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Protocollo Exa-Cell[®] – – Vertex

HbF

- riduce morbidità e mortalità

BCL11A

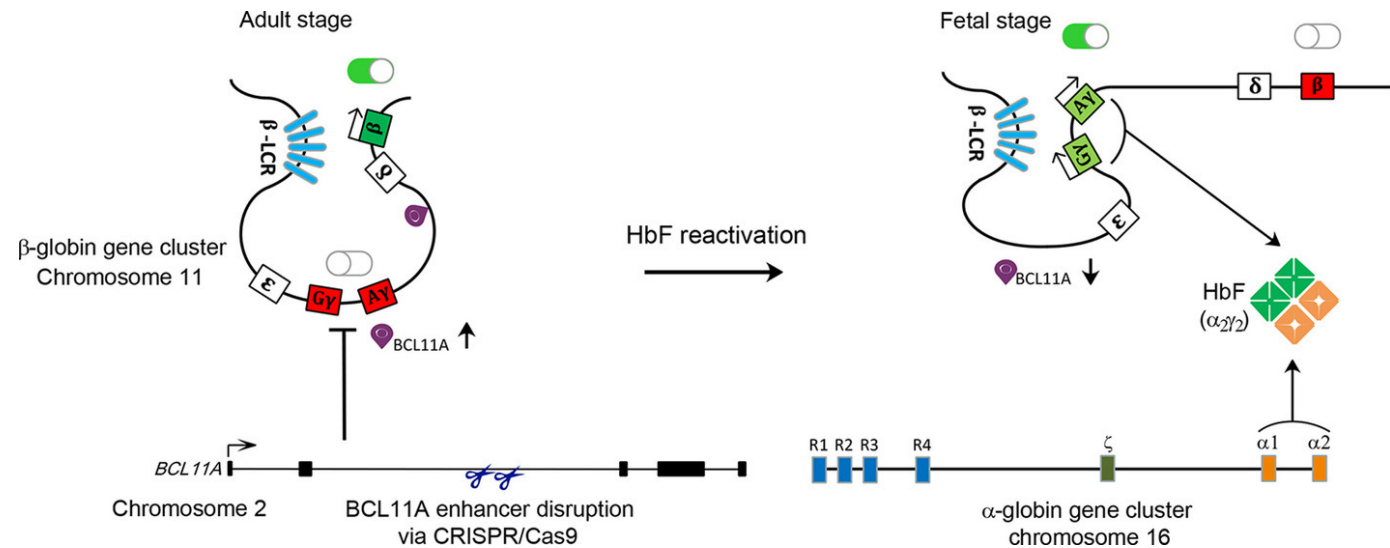
- sopprime HbF alla nascita

Ex vivo editing

- di BCL11A per ridurre l'espressione

Aumento HbF

- Riduzione VOC e fabbisogno trasfusionale



Stage 1

Stage 2

Stage 3A/ Stage 3B

Stage 4A/ Stage 4B

Open-label rollover trial

Screening

CD34+ HSPCs collected (G-CSF & plerixafor for TDT; plerixafor for SCD)

Cells returned ready for use

Conditioning chemotherapy (busulfan)

Exa-cel infusion

Neutrophil engraftment and discharge

Follow-up to Month 24 after exa-cel infusion

Additional follow-up CLIMB-131

Central manufacturing facility

CRISPR-Cas9 editing

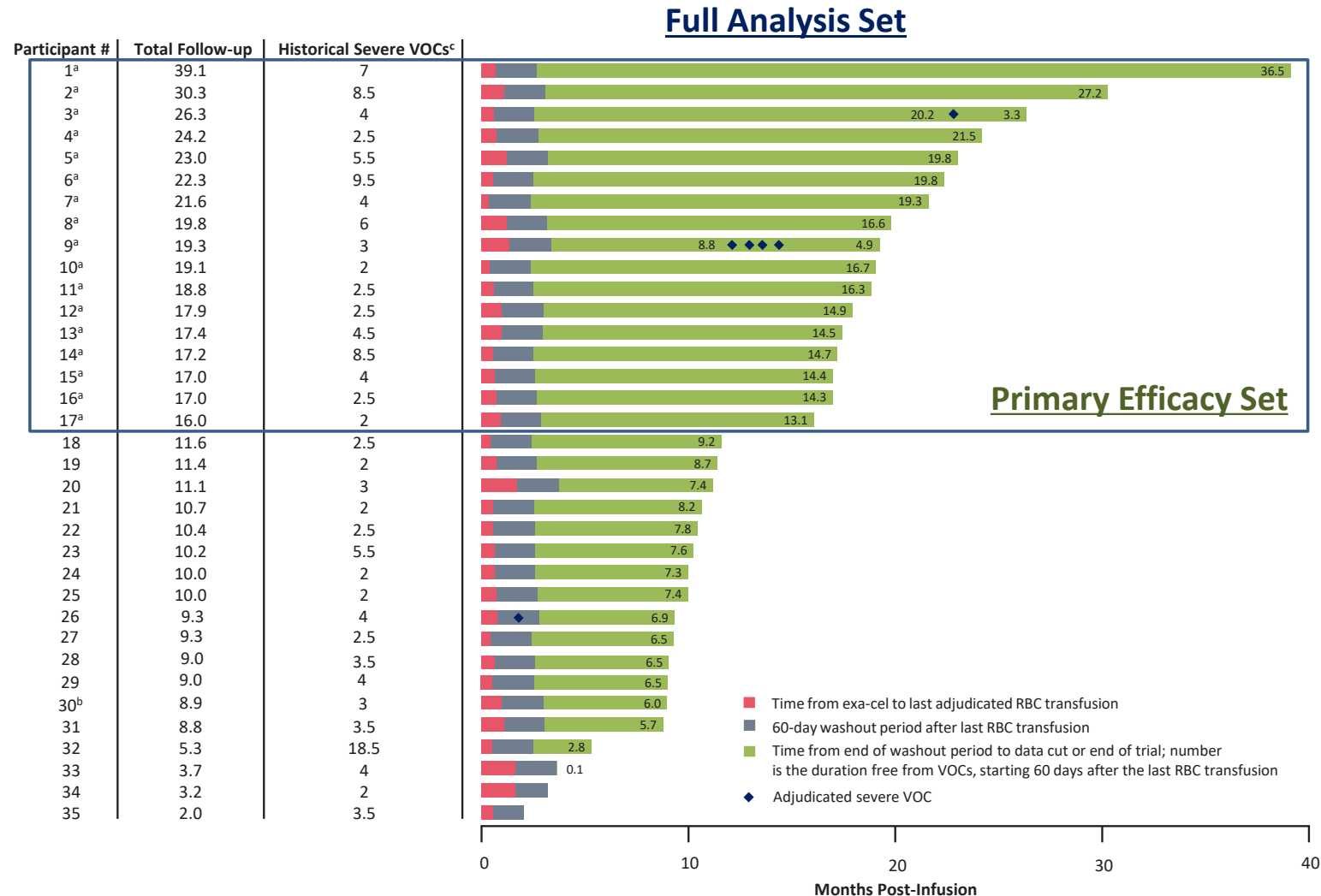
Enrichment

Cells frozen; release testing

Courtesy of Vertex Pharmaceuticals

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SCD: Participants Who Achieved Freedom from VOC (VF12) Maintained VOC-Free From 13.1 Months to 36.5 Months



- For participants achieving VF12, duration of VOC-free was 13.1 to 36.5 months (mean 18.7 months)
 - Participants **stopped transfusions** after a mean of 22.5 days
- One participant did not achieve VF12 but achieved HF12
 - Participant had multiple **complex comorbidities**, including a history of chronic pain
- 15 of 16 participants remained **VOC-free** through follow-up
 - One participant had a **VOC** in the setting of a parvovirus **infection** 22.8 months after exa-cel infusion
 - Participant **fully recovered** and has been **VOC-free** since

Each row in the figure represents an individual participants. All VOCs were adjudicated by the Independent Adjudication Committee.

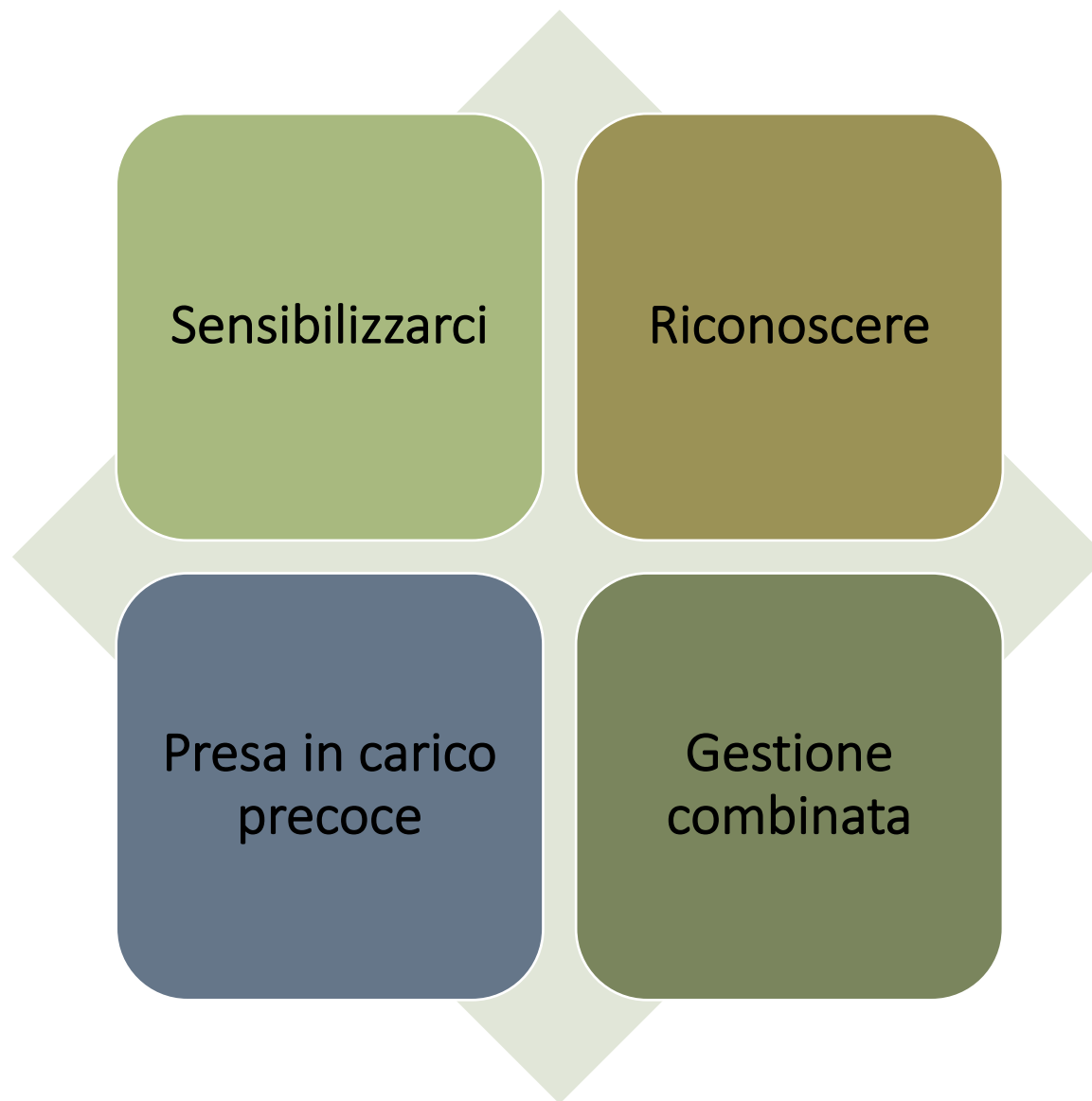
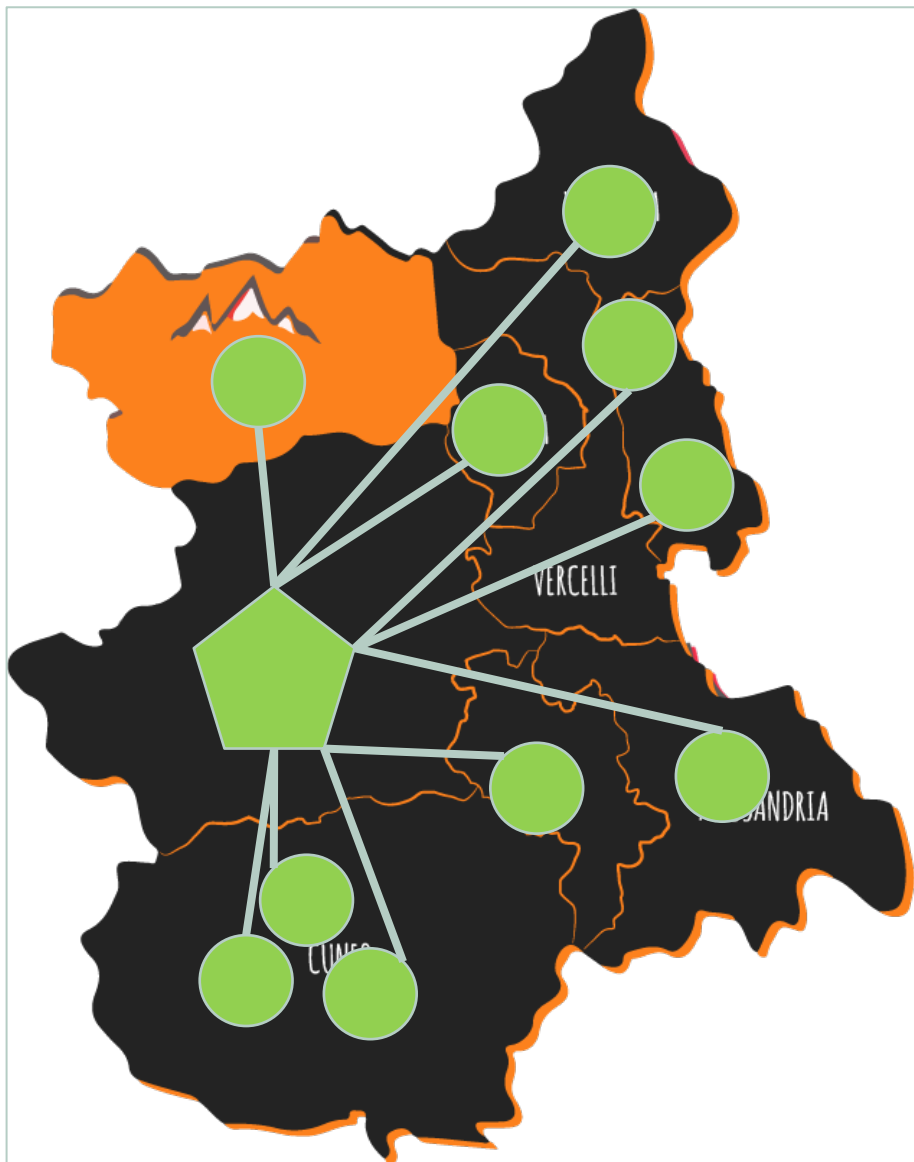
^aParticipants evaluable for the primary endpoint; ^bDeath from respiratory failure due to COVID-19 infection; ^cPre-trial severe VOCs annualized over 2 years.

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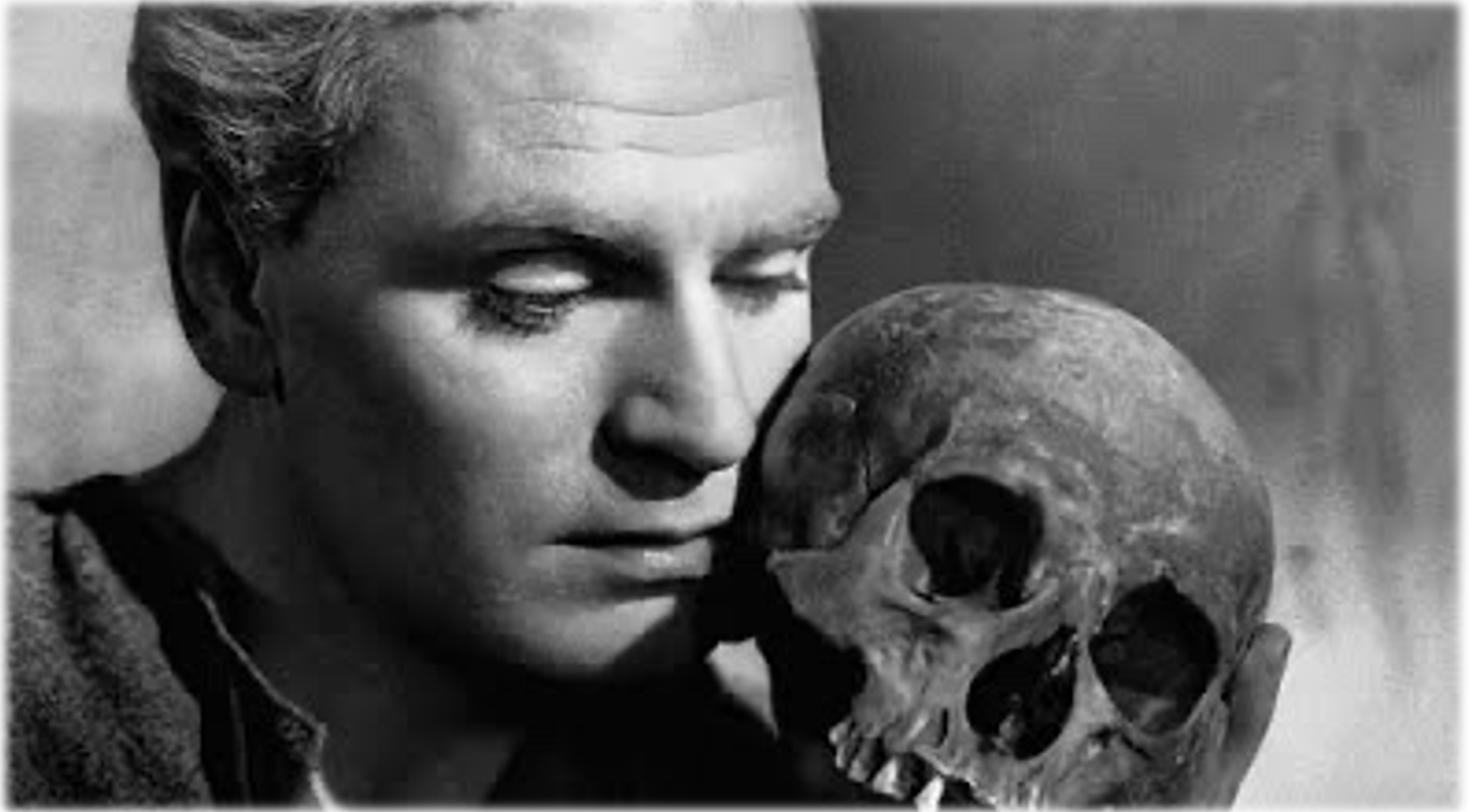


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