Aggiornamento su diagnosi e terapia delle emoglobinopatie

La drepanocitosi oggi

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Obiettivi

Diagnosi e diagnosi differenziale delle varie forme di drepanocitosi (Sickle Cell Disease, SCD)

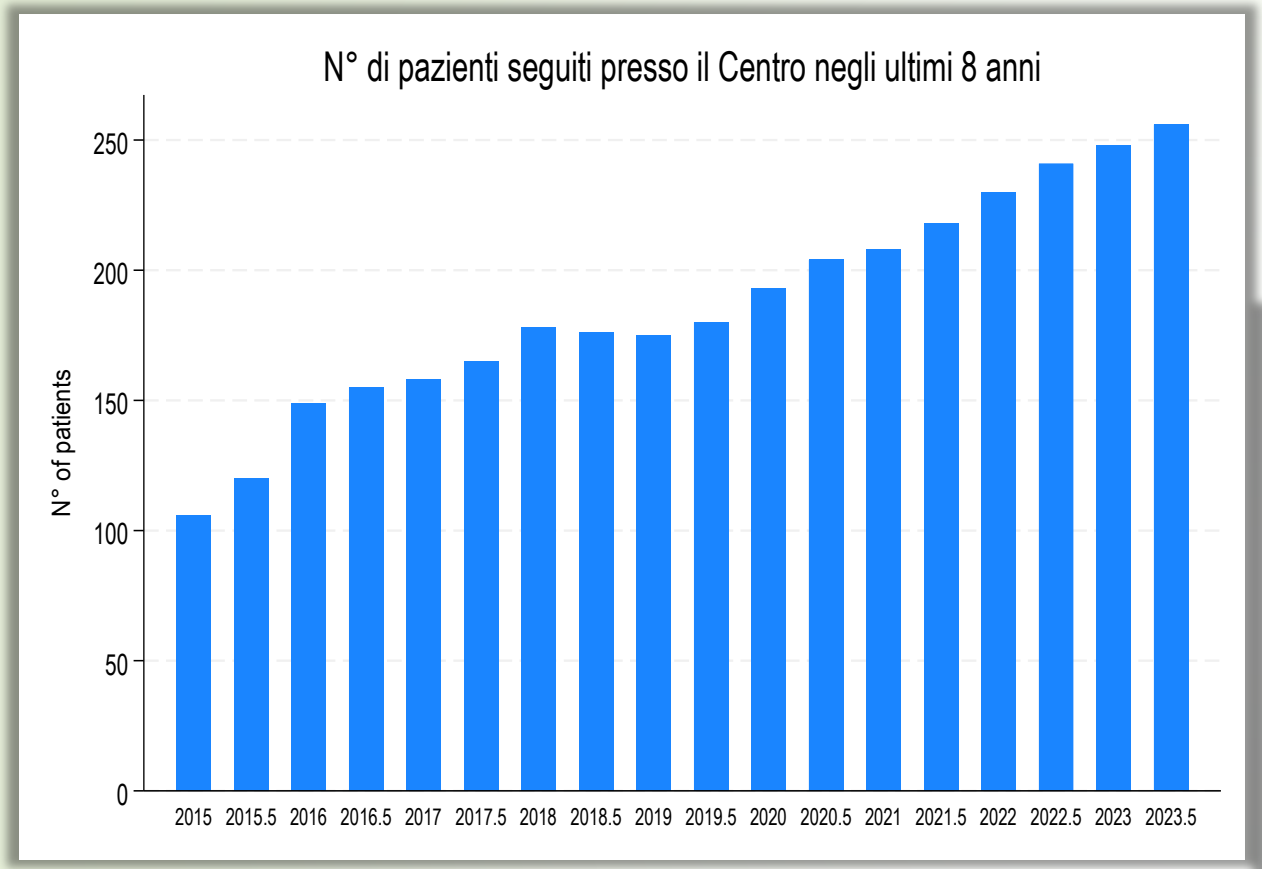
Quali sono le **ragioni** per cui oggi si parla di prevenzione in SCD

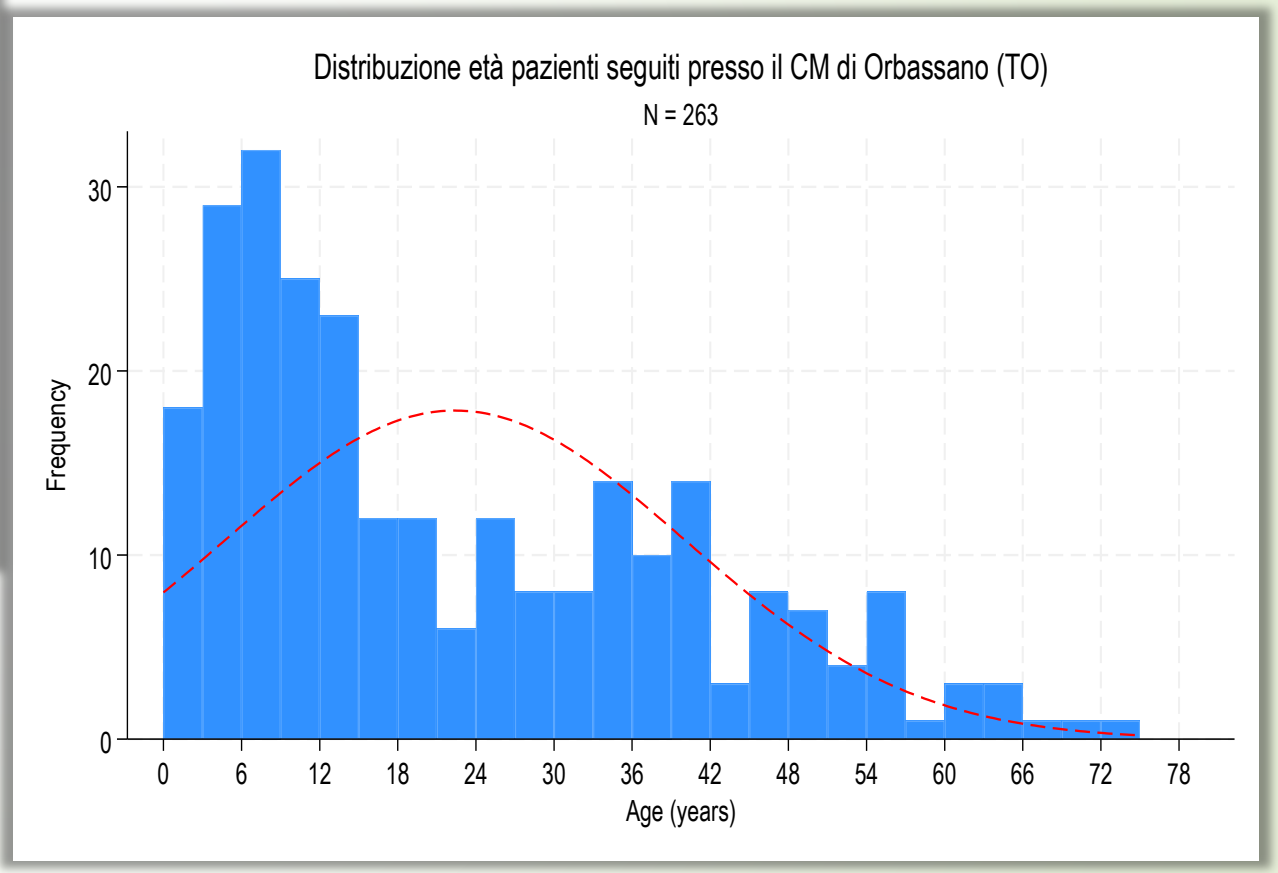
Quali sono le criticità per cui oggi è in discussione la prevenzione

Quali sono le criticità delle criticità

Entità del fenomeno

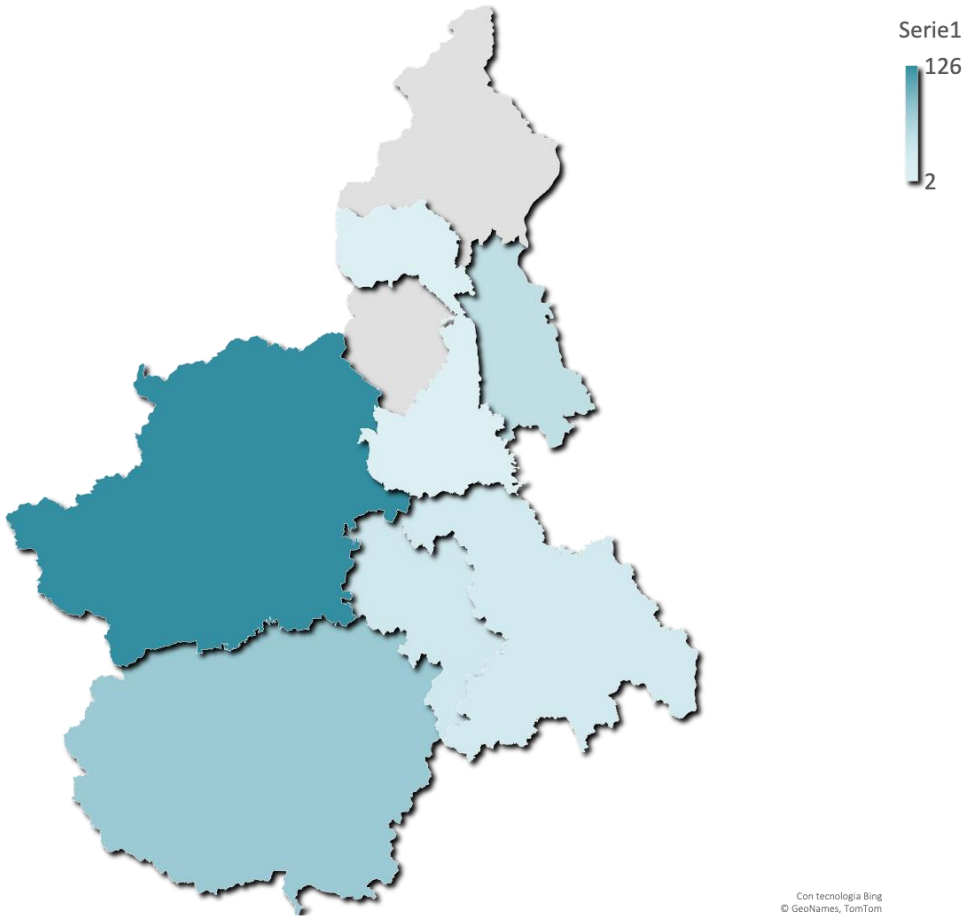
Incidenza





V. Voi. 2024. Personal Data

Prevalenza SCD in Piemonte (2023)



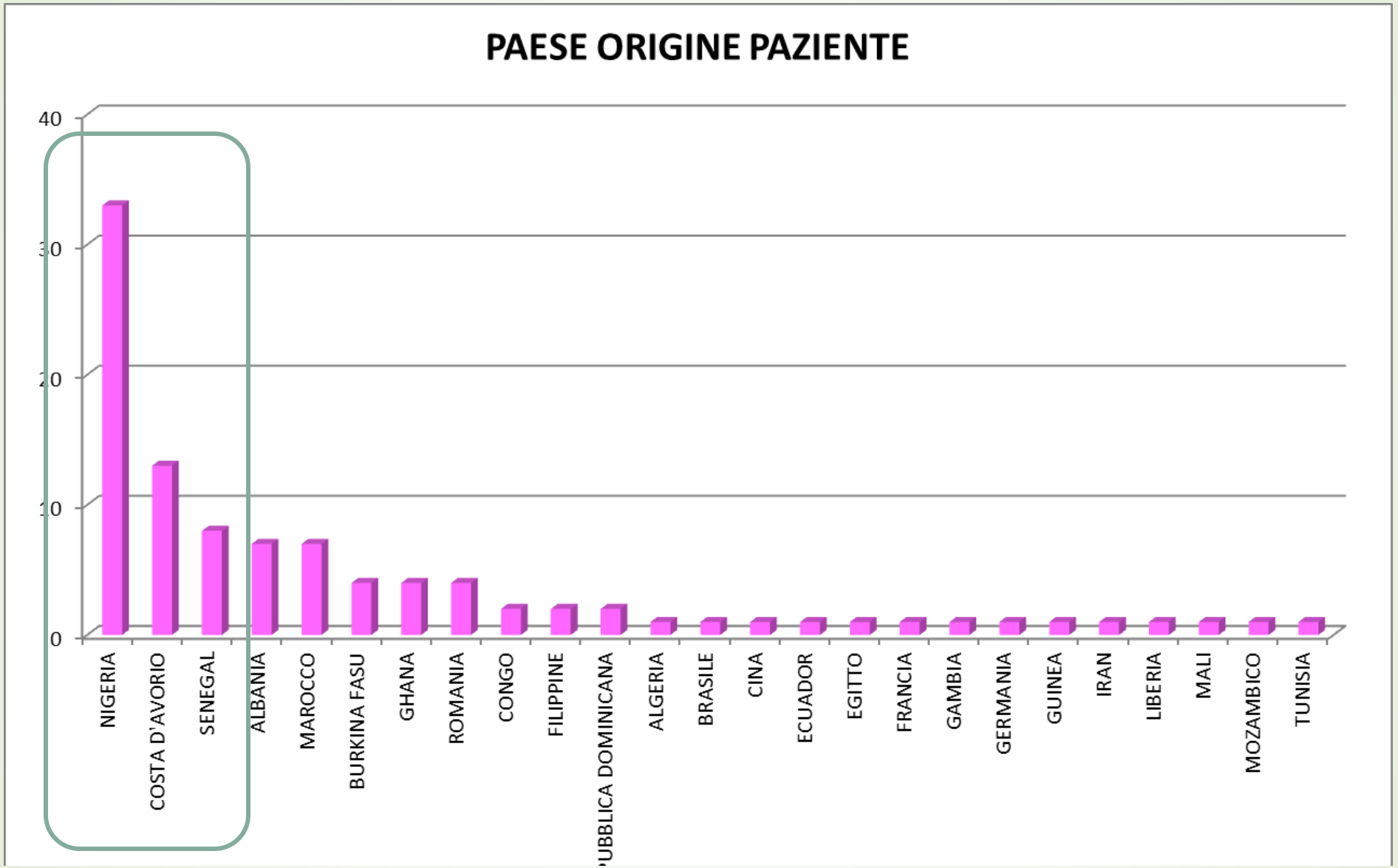
Prevalenza SCD in Europa / Italia (2023)

	HbA (%)	HbS (%)	HbC (%)	HbF (%)	HbA_2 (%)	Clinical Course	Prevalence (%)*
Normal	95–98%	0	0	<1%	<3·5%	..	..
Trait conditions							
Sickle trait HbAS	55–65%	30–40%	0	<1%	<3·5%	Benign	1–8%
Haemoglobin C trait	55–65%	0	30–40%	<1%	<3·5%	Benign	1–3%
β-thalassaemia trait	90–95%	0	0	1–3%	>3·5%	Benign	1–2%
Disease conditions							
Sickle cell anaemia	0	80–95%	0	5–15%	<3·5%	Severe	50–60%
Sickle-C disease	0	50–55%	40–45%	<3%	<3·5%	Moderate	25–30%
S/β⁰ thalassaemia	0	80–90%	0	5–15%	>3·5%	Severe	1–3%
S/β⁺ thalassaemia†	10–25%	70–80%	0	<3%	>3·5%	Mild	5–10%
S/Other (Hb variant)	0	50–60%	0	Variable	<3·5%	Variable	1–2%

Trait conditions refer to beta globin heterozygous states, while disease conditions refer to compound heterozygous or homozygous states. Concomitant alpha-thalassaemia can coexist with all of these conditions and affects the ratio of HbA to HbS or HbC, as shown by the range of values for each haemoglobin listing. Sickle cell genotypes are shown with the typical haemoglobins present on electrophoresis, clinical course, and prevalence. The sickle/other disease conditions typically have 50–60% HbS with 20–45% of a variant haemoglobin such as HbD, HbE, or HbO_{Arab}. Thalassaemic trait and disease also feature microcytosis with low mean corpuscular volume *Prevalence refers to persons living in the USA, Caribbean, UK, and Europe; the haemoglobin trait percentages refer to the general population and the disease percentages refer to sickle cell patient cohorts. †S/β⁺ thalassaemia in the USA, Caribbean, UK, and northern Europe typically has 10–25% HbA, but more mild and severe forms of β⁺ thalassaemia have been identified, particularly in southern Europe. Accurate prevalence figures from high burden regions such as sub-Saharan Africa are not available. HbA=. HbS=sickle haemoglobin. HbC=haemoglobin C. HbD=haemoglobin D. HbE=haemoglobin E. HbF=fetal haemoglobin. HbO_{Arab}=haemoglobin OArab.

***Table* 1: Common forms of sickle cell disease and related haemoglobinopathies by genotype**

Ware. Lancet, 2017 - V. Voi. Personal Data, 2017



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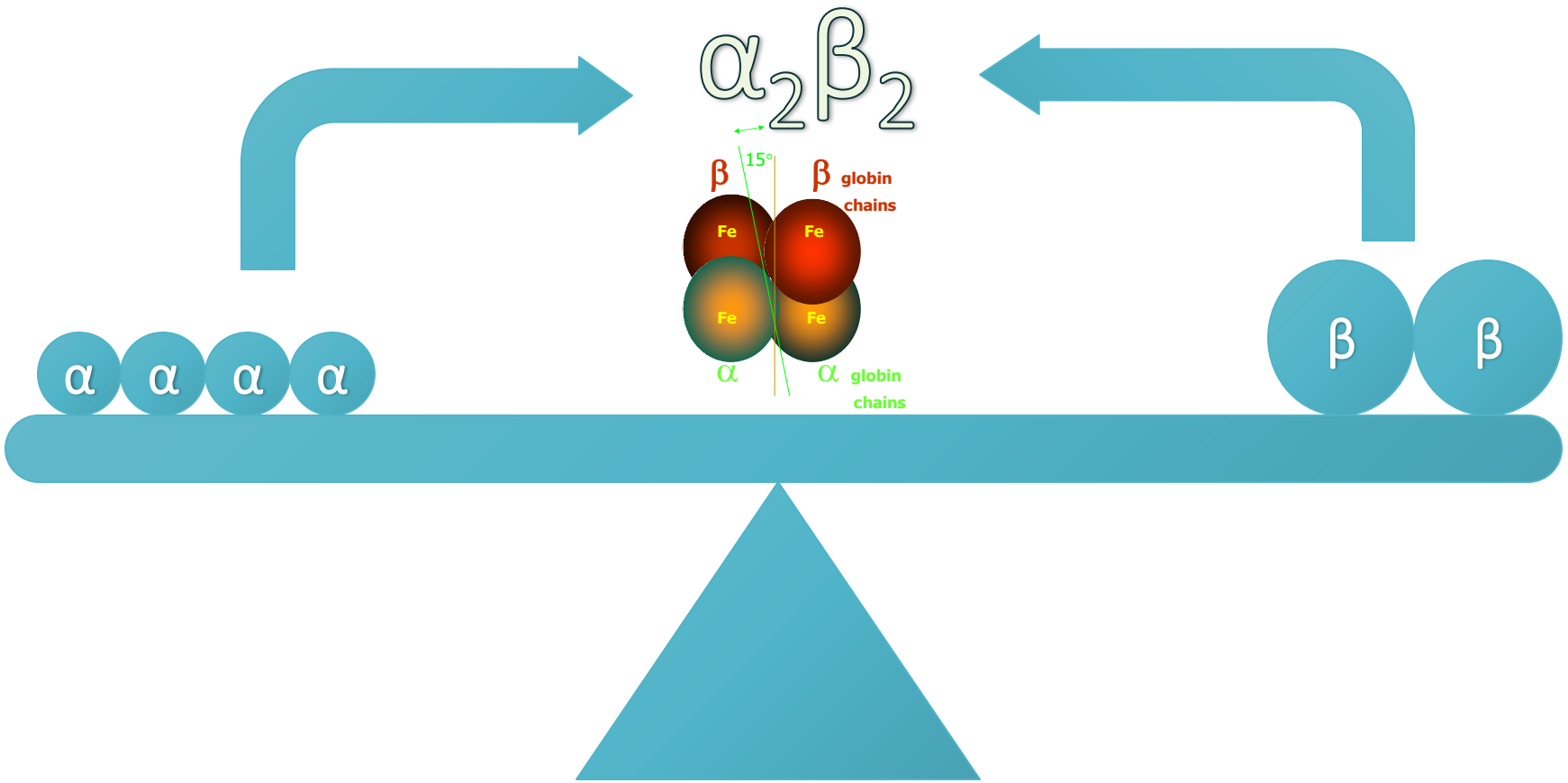
Riconoscere il fenomeno

Diagnosi

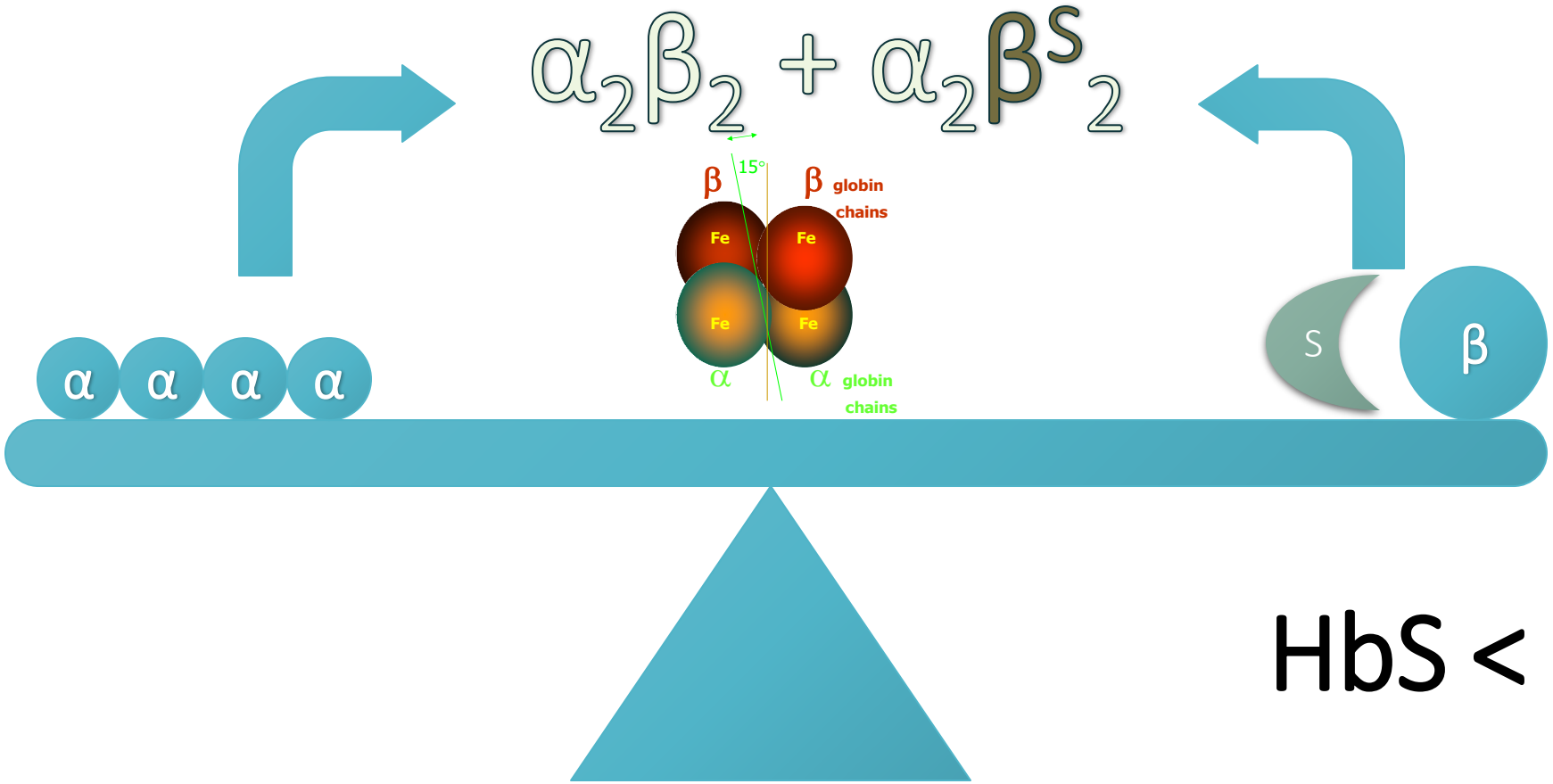
Fisiopatologia

- Eritropoiesi
  - Equilibrio di sintesi di catene **α/non α** [β+γ]

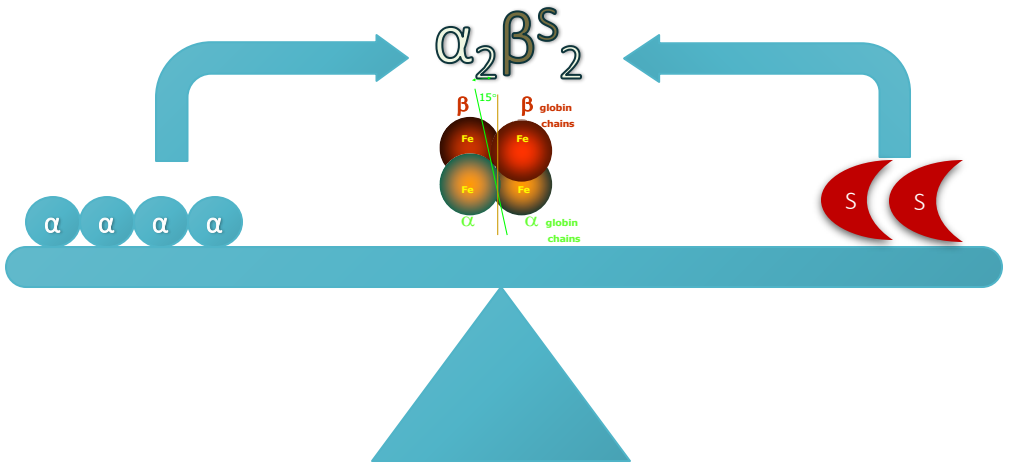


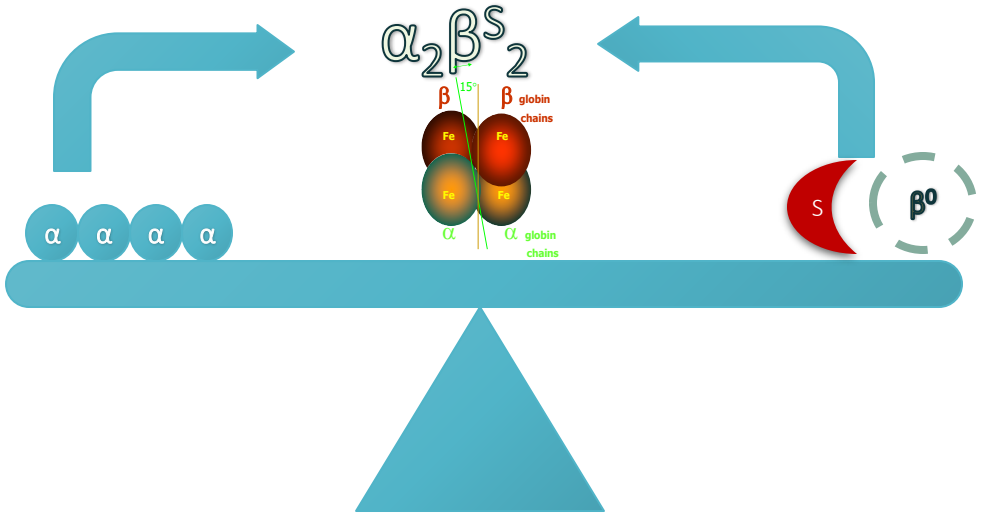
Fisiopatologia

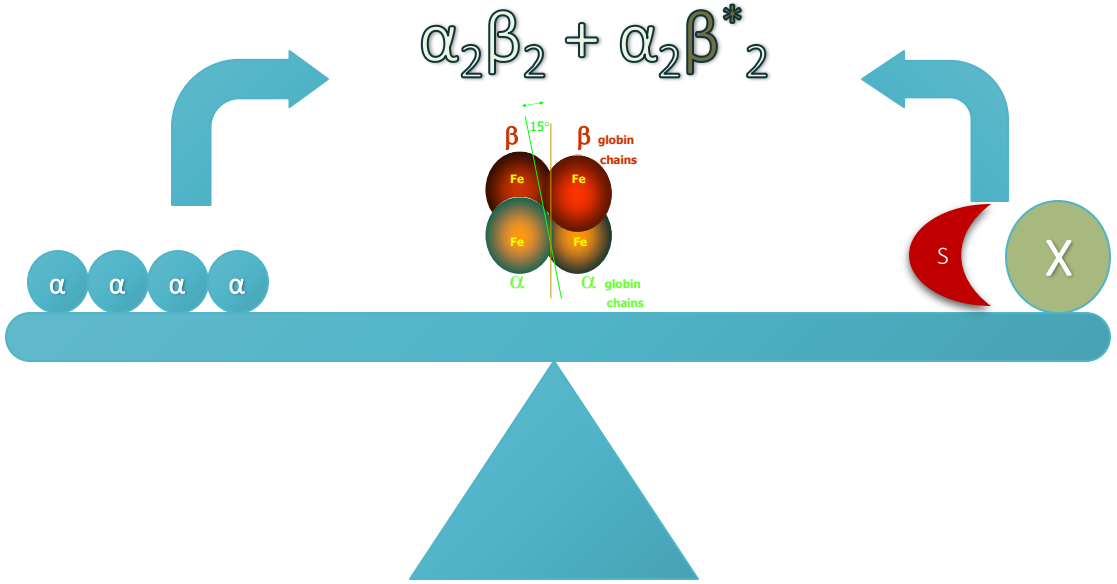
- Drepanocitosi eterozigote



HbS < 50%





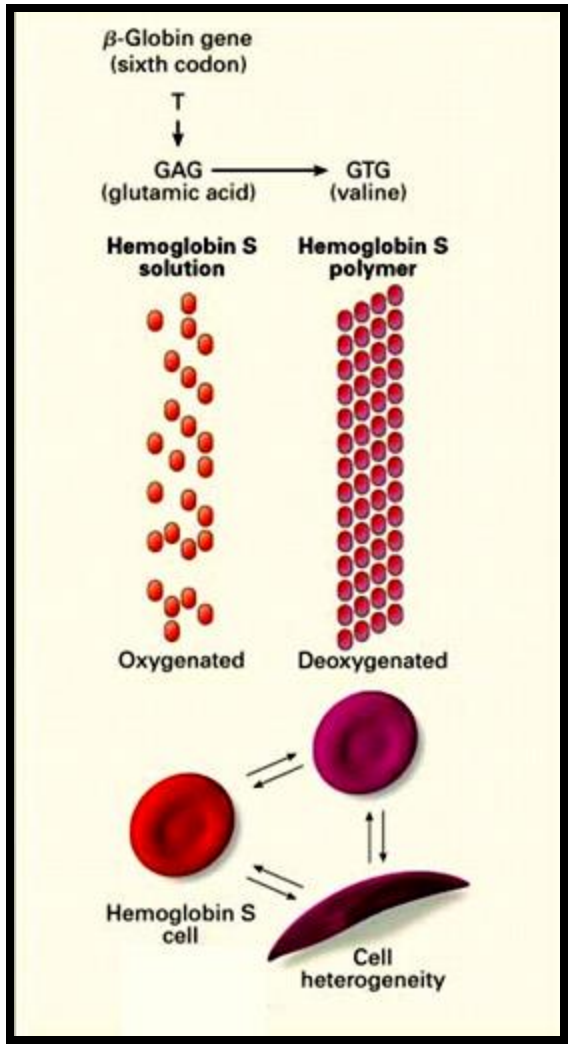


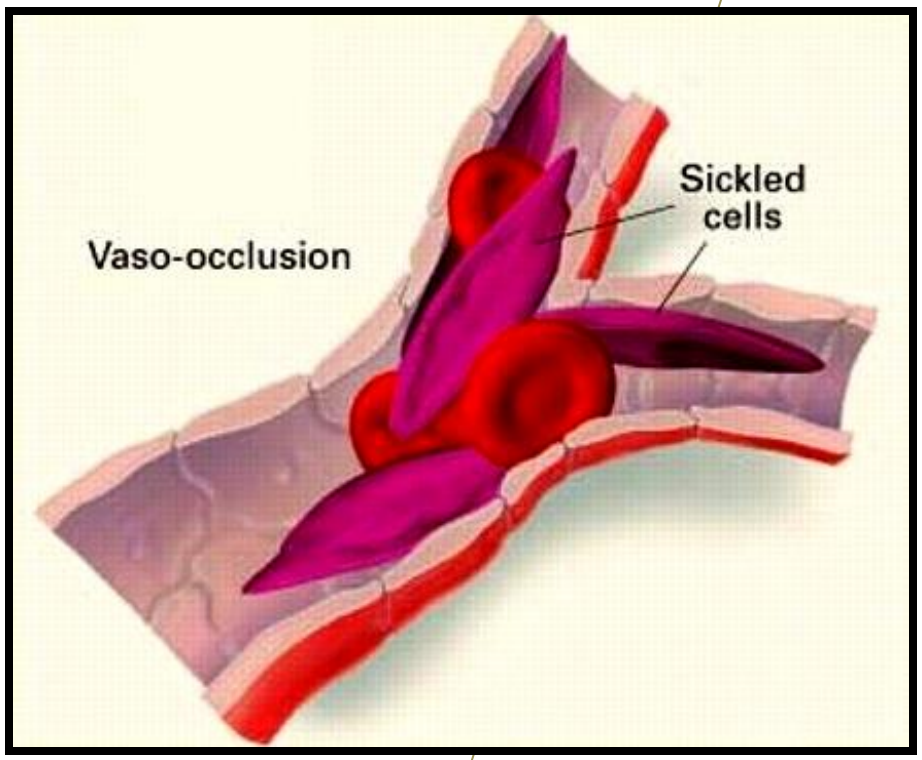
$$\boldsymbol{HbS + (HbX) > 50\%}$$

Fisiopatologia e Clinica

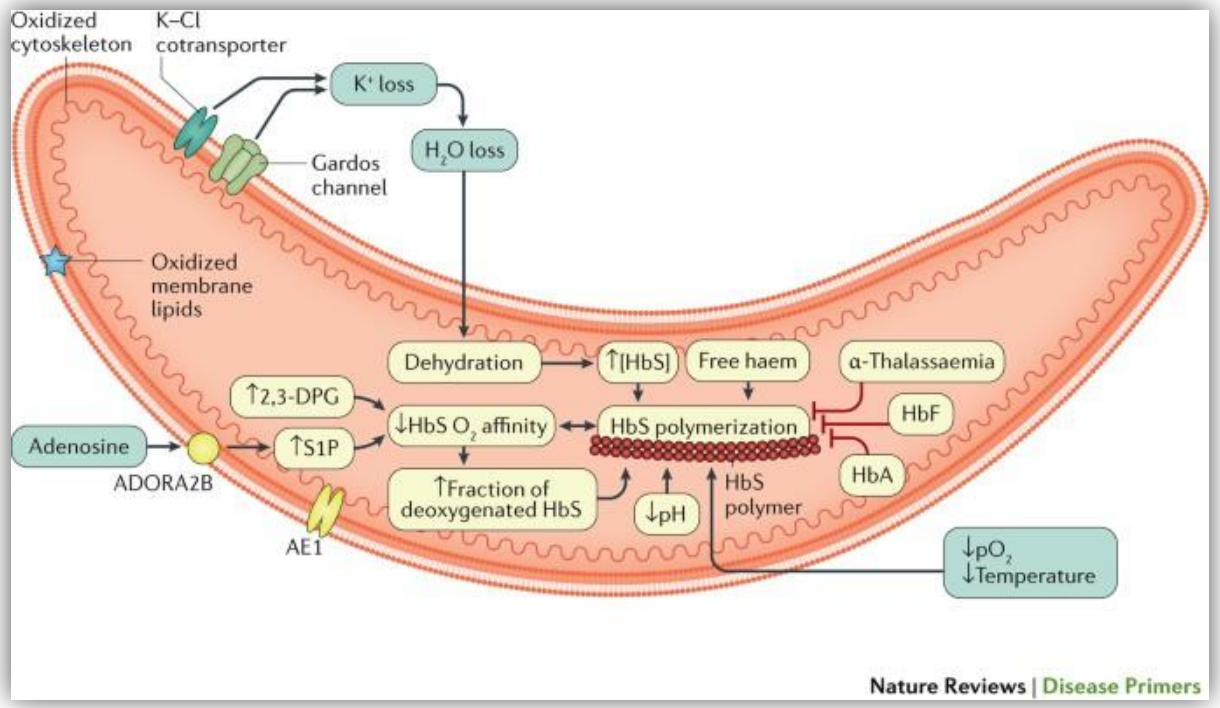
Che cosa preveniamo?

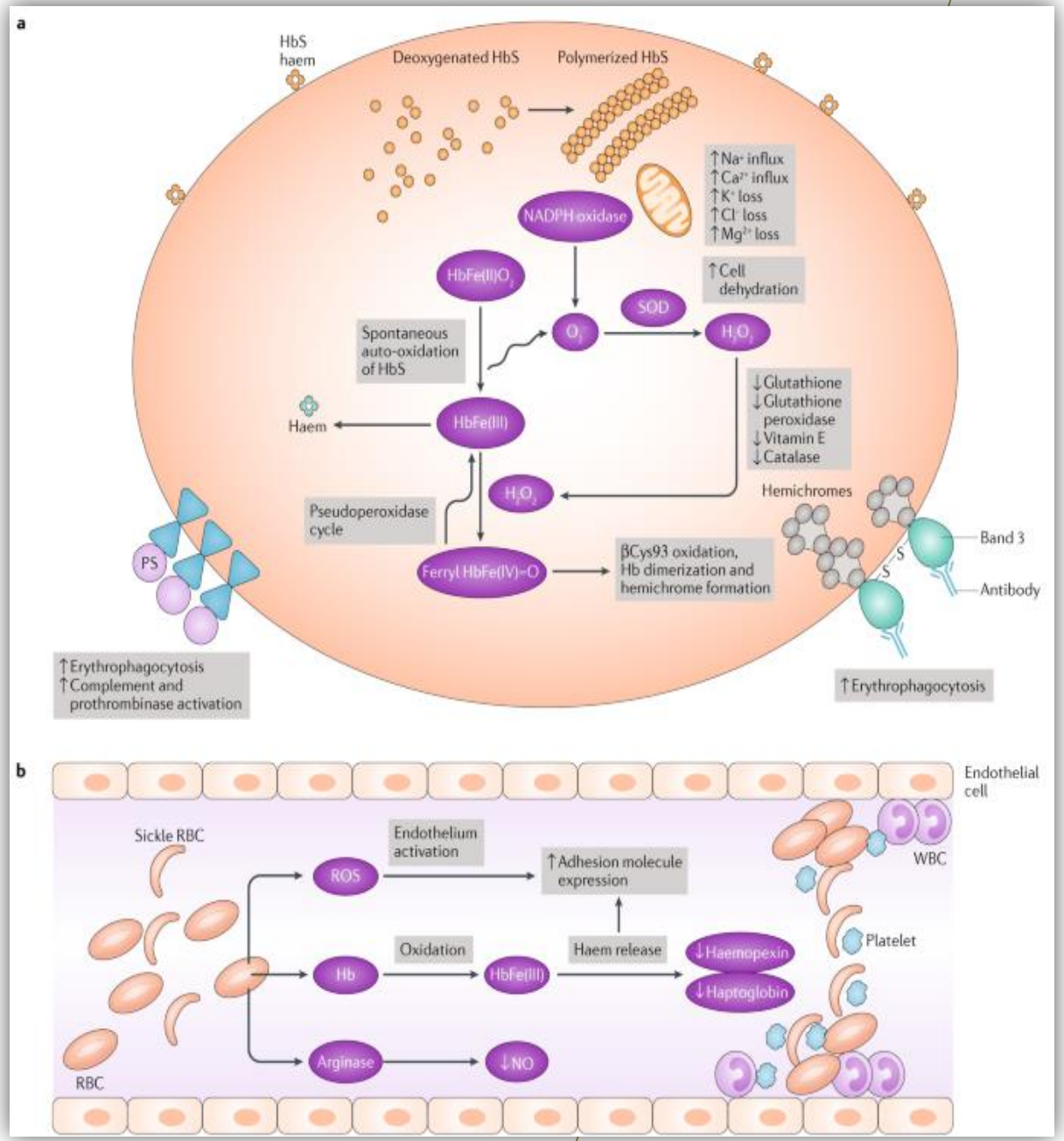
SICKLING


β-Globin gene
(sixth codon)
T
GAG
(glutamic acid)
GTG
(valine)
Hemoglobin S
solution
Hemoglobin S
polymer
Oxygenated
Deoxygenated
Hemoglobin S
cell
Cell
heterogeneity


Vaso-occlusion
Sickled
cells

MULTIFACTORIAL DISFUNZIONE





SOMMARIO

Morfologia eritrocitaria

Ossidazione e disisratazione

Emolisi

Disidratazione – Rilascio di Eme libero – Attivazione del DAMP

Disfunzione endoteliale

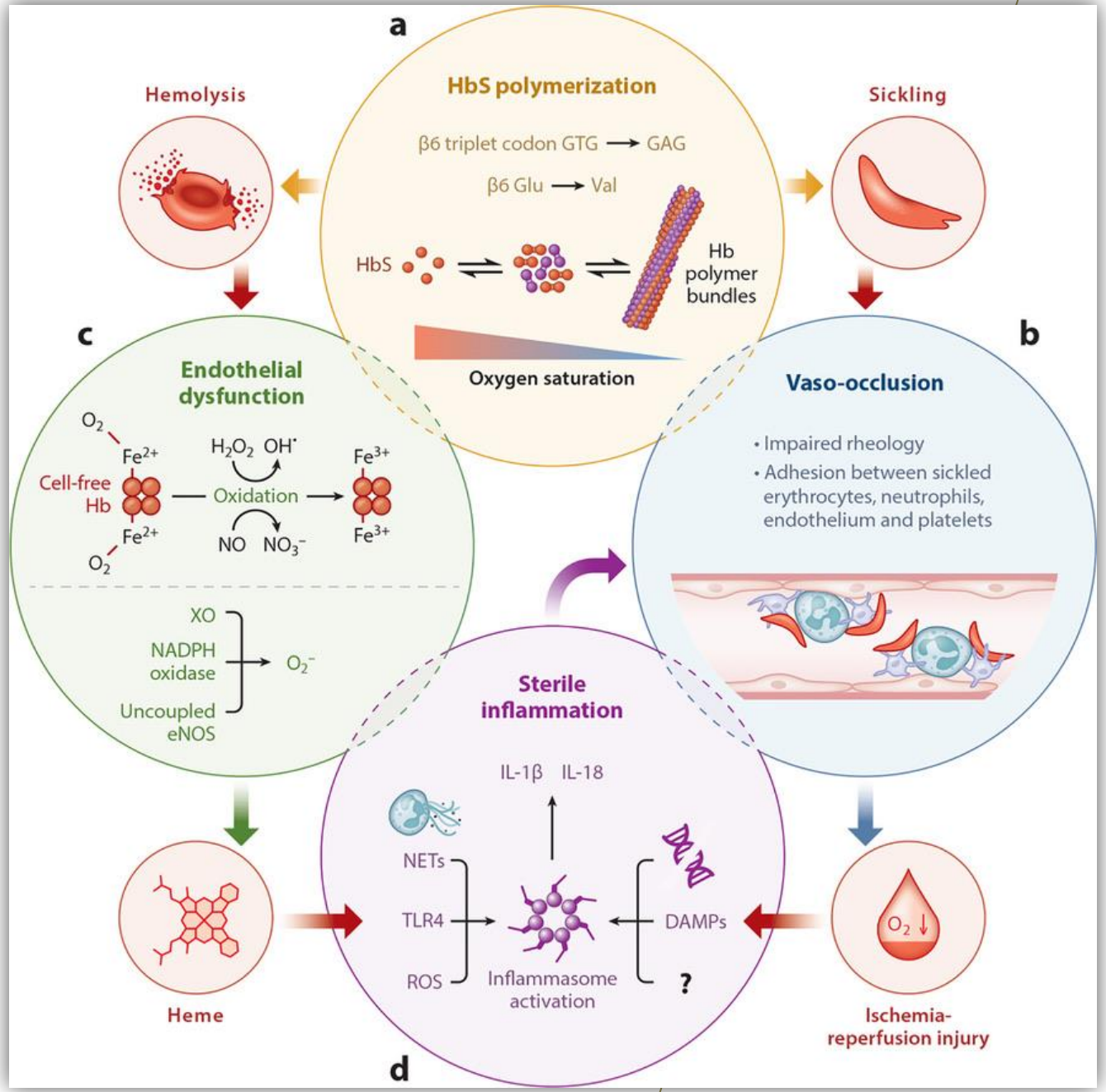
Sovraespressione delle molecole di adesione - Attivazione e adesione dei leucociti - Carenza di NO - Vasocostrizione

Attivazione del Sistema immunitario

Citochine infiammatorie - Attivazione del complemento

Disfunzione della coagulazione

Adesione delle piastrine - Coagulazione



Cosa preveniamo?

Quadro clinico generale

Complicazioni Acute

Più comuni

1. **INFEZIONI** — Batteriemia - Sepsi - Polmonite - Osteomielite
2. **Dolore Acuto – VOC** — Dattilite - Priapismo - Dolore osseo
3. **DANNO D'ORGANO** — Stroke- Sindrome toracica acuta (ACS) - Infarto splenico
4. **ANEMIA ACUTA** — Sequestro splenico - Iperemolisi

Ware 2017 et al, NEJM 2018 – mod.

Complicanze croniche

Rene

Ipostenuria, iperfiltrazione, glomerulosclerosi, albuminuria, insufficienza renale cronica

Cuore – Polmoni

Patologia restrittiva, ostruttiva. Ipertensione polmonare, cardiomiopatia restrittiva

SNC

Stroke, Emorragia, Lesioni Silenti, ritardo cognitivo

Fegto – Milza

Colestasi, insufficienza epatica, ipersplenismo

App. Visivo – uditivo

Retinopatia, cataratta, ipoacusia

Scheletro

Infarti ossei, crolli vertebrali, osteoporosi, osteopenia

App. riproduttivo

Impotenza, infertilità, aborti ripeuti

Che presente hanno?

Attualità clinica

Gestione

Profilassi antibiotica

Bambini: quotidiana nei bambini fino ai 15 anni + antibiotico tempestivo se febbre elevata

Adulti: antibiotico tempestivo se febbre elevata

Terapia specifica

Idrossiurea

Terapia trasfusionale

Follow up regolare

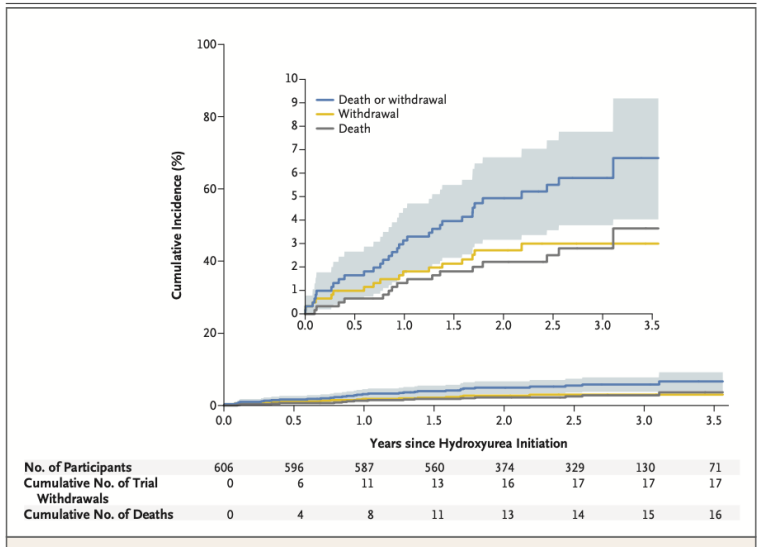
Ogni 1 -4 mesi

Hydroxyurea

Trattamento Preventivo

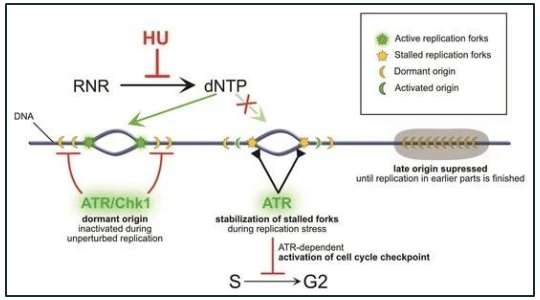
Ware, R. E. (2015).
Hematology Am Soc Hematol Educ Program 2015: 436-443.

Efficace e sicuro nei bambini

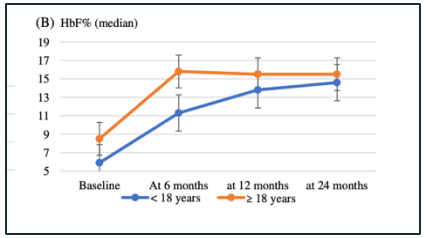


No. of Participants	606	596	587	560	374	329	130	71
Cumulative No. of Trial Withdrawals	0	6	11	13	16	17	17	17
Cumulative No. of Deaths	0	4	8	11	13	14	15	16

Meccanismo di azione



Efficace negli adulti:



Ancora poco e male utilizzato

Nonostante i suoi comprovati benefici, l'HU è significativamente sottoutilizzata nel trattamento della SCD nei paesi ad alte risorse.

Terapia Trasfusionale

TOP – UP transfusion

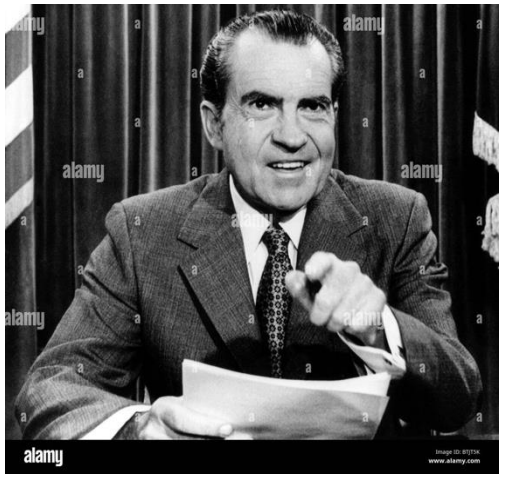
Easy to perform
Avoid Hyper viscosity (Hb > 10)

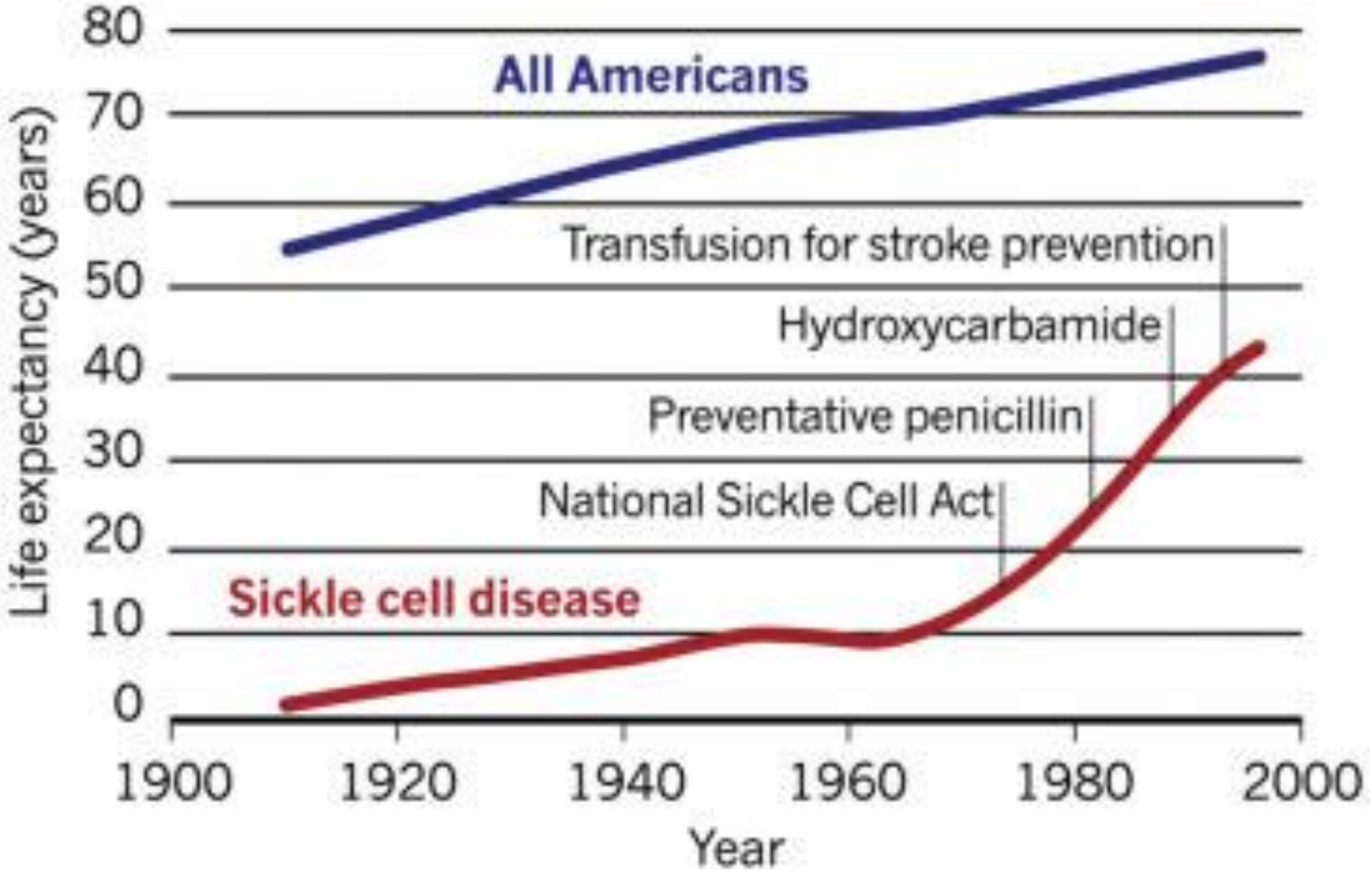
Manual Eritroexchange (MEEX)

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

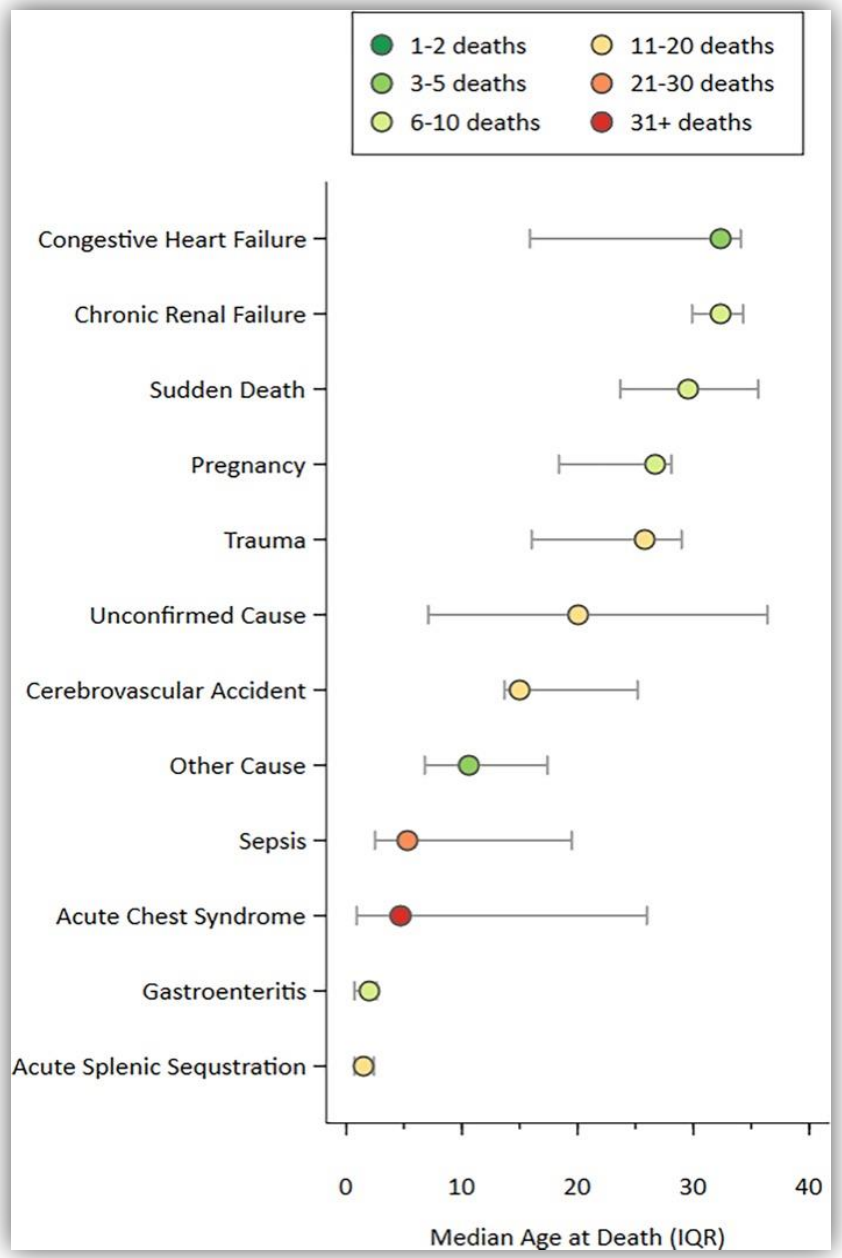
Automated Eritroexchange (EEX)

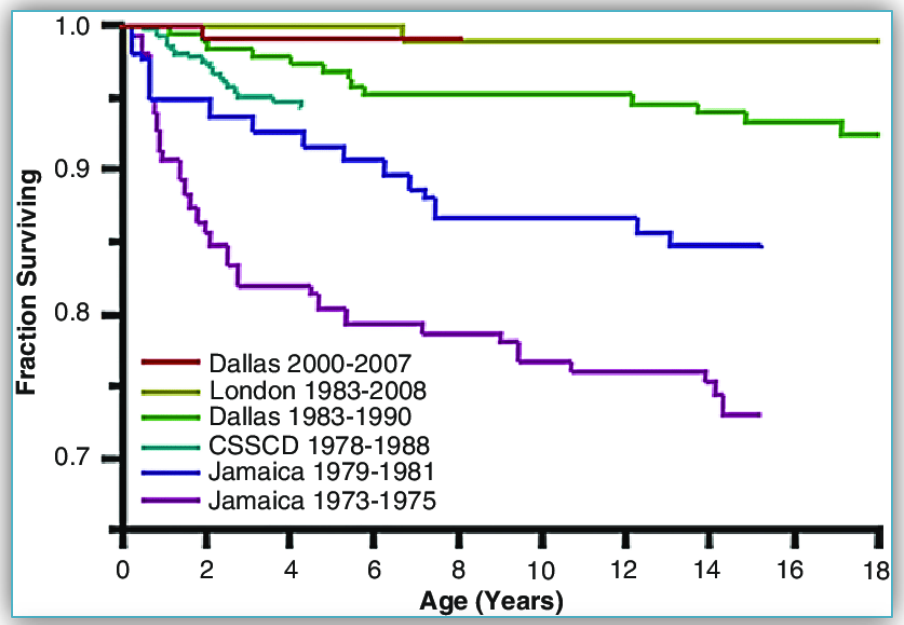
Not always available
Gold standard

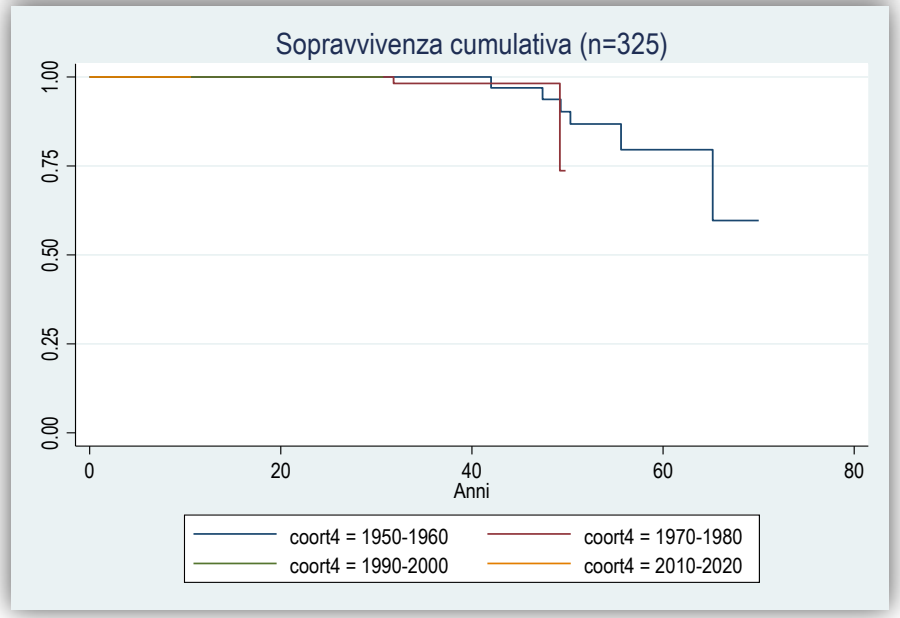


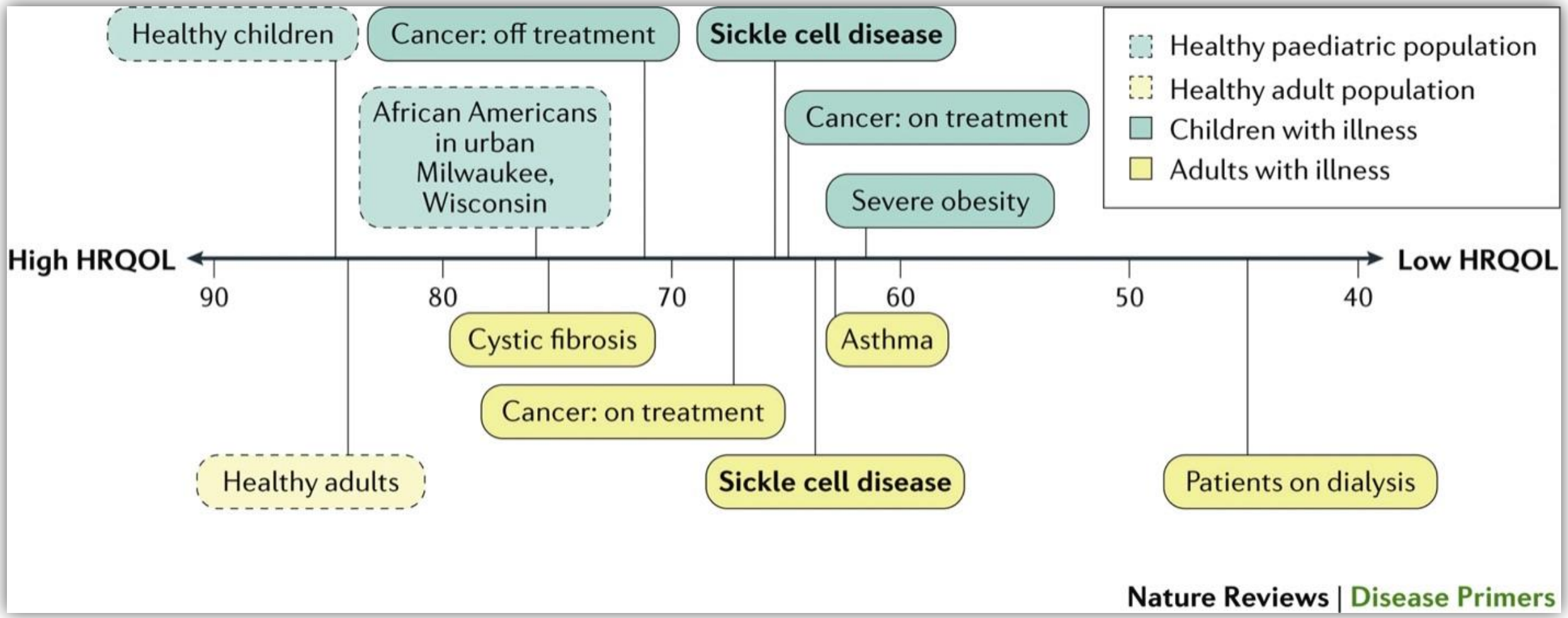


Abboud et al. 2019

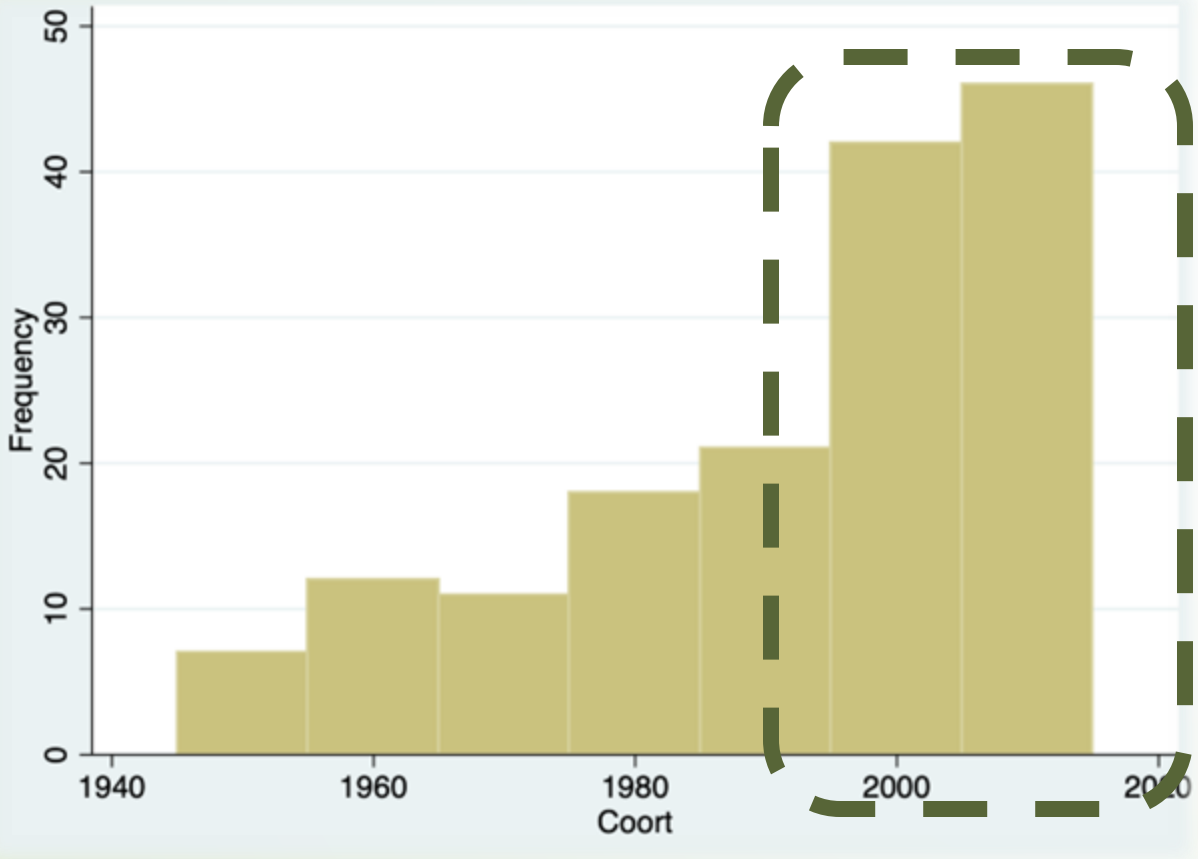

1-2 deaths
3-5 deaths
6-10 deaths
11-20 deaths
21-30 deaths
31+ deaths
Congestive Heart Failure
Chronic Renal Failure
Sudden Death
Pregnancy
Trauma
Unconfirmed Cause
Cerebrovascular Accident
Other Cause
Sepsis
Acute Chest Syndrome
Gastroenteritis
Acute Splenic Sequstration
0
10
20
30
40
Median Age at Death (IQR)

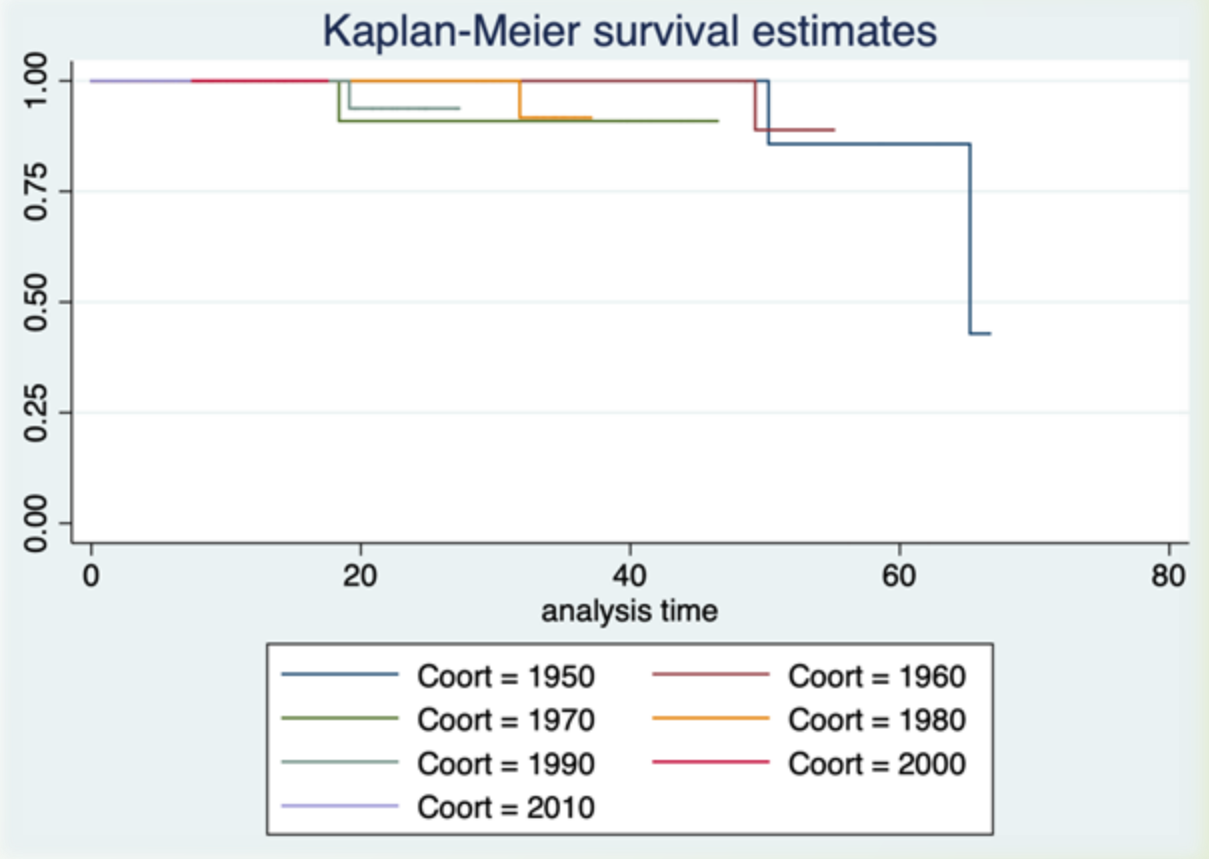

1.0
0.9
0.8
0.7
Fraction Surviving
Dallas 2000-2007
London 1983-2008
Dallas 1983-1990
CSSCD 1978-1988
Jamaica 1979-1981
Jamaica 1973-1975
0
2
4
6
8
10
12
14
16
18
Age (Years)


Sopravvivenza cumulativa (n=325)
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
Anni
coort4 = 1950-1960
coort4 = 1970-1980
coort4 = 1990-2000
coort4 = 2010-2020


Healthy children
Cancer: off treatment
Sickle cell disease
African Americans in urban Milwaukee, Wisconsin
Cancer: on treatment
Severe obesity
Healthy paediatric population
Healthy adult population
Children with illness
Adults with illness
High HRQOL
Low HRQOL
90
80
70
60
50
40
Cystic fibrosis
Asthma
Cancer: on treatment
Healthy adults
Sickle cell disease
Patients on dialysis
Nature Reviews | Disease Primers

Realtà attuale e prospettive di vita





V. Voi. 2022. Personal Data

Che futuro ci aspetta?

Prospettive e innovazione

Il futuro è aperto

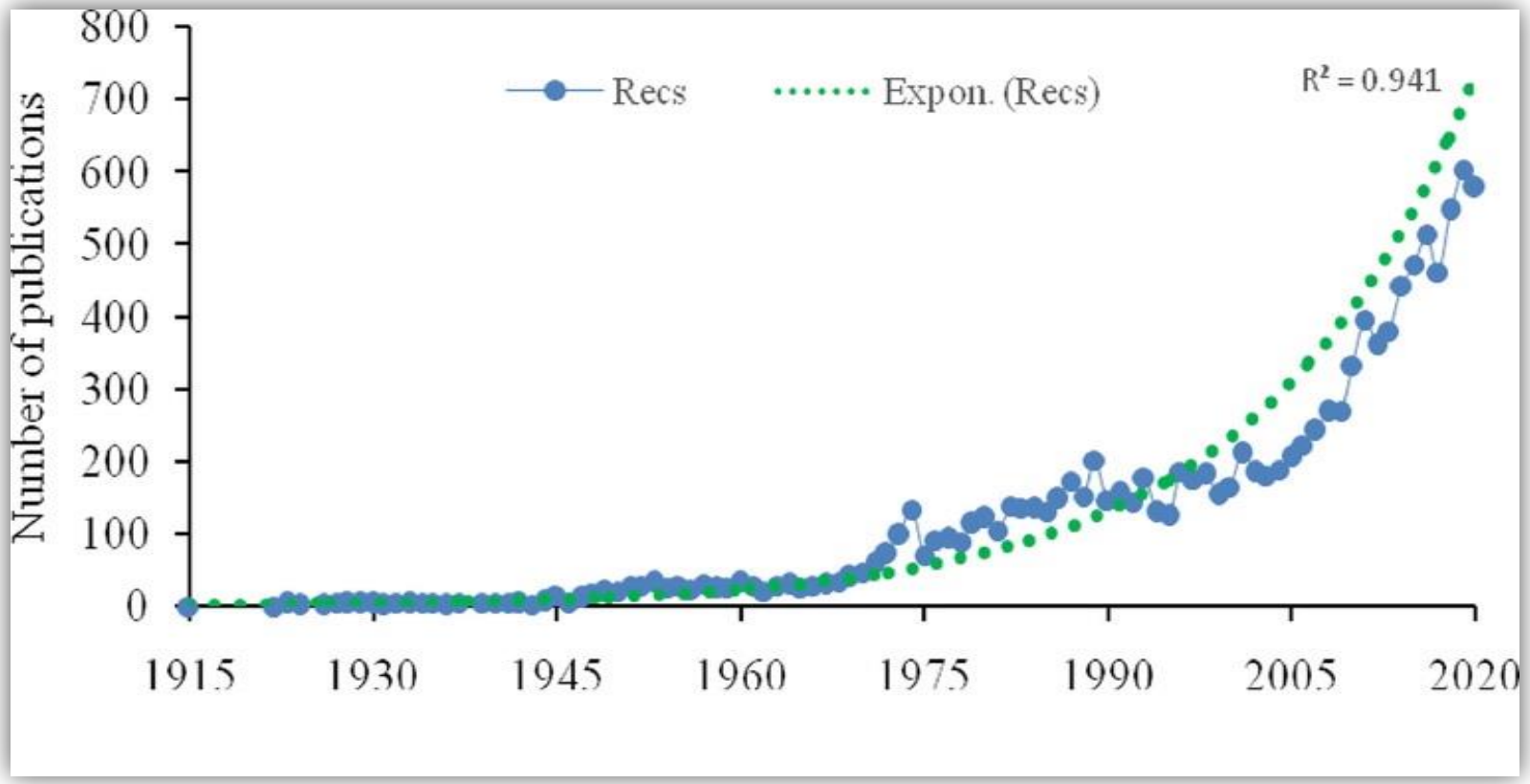


Table 1 | **Emerging treatment approaches for sickle cell disease**

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 therapeutical and supratherapeutical 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‡	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‡	Improves tissue oxygen levels	Hypothesized to prevent vaso-occlusive crises and leg ulcers	Limited data	284
Sevuparin (DF02)‡	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‡	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

Farmaci emergenti

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

HSCT - BMT

Strategia terapeutica con finalità curative della malattia, insieme alla terapia genica

Opzione terapeutica quasi universalmente disponibile in tutto il mondo

Strategia consolidata

INDICAZIONI ATTUALI

Table 79.1 Indications for HSCT in SCD patients

Age <16 years	
HLA identical sibling donor	
One or more of the following complications:	Stroke or central nervous system event lasting >24 h
	Sickle lung disease
	Sickle nephropathy
	Retinopathy
	Osteonecrosis
	Red-cell alloimmunization
	Acute chest syndrome
	Recurrent priapism
	Recurrent vaso-occlusive painful episodes
	Failure to benefit or unable or unwilling to continue supportive care therapy including hydroxyurea
	Impaired neuropsychological function with abnormal cerebral MRI and angiography
	Abnormal transcranial Doppler velocities

Recommendation 4. For patients with SCD with an indication for HSCT who lack an MSD, the ASH guideline panel *suggests* using transplants from alternative donors in the context of a clinical trial (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Kanter et al Blood Adv 2021

- Presenza di danno d'organo
- Disponibilità di un donatore HLA identico

Angelucci et al Haematologica 2014
Walters N Engl J Med 1996

SICUREZZA E EFFICACIA

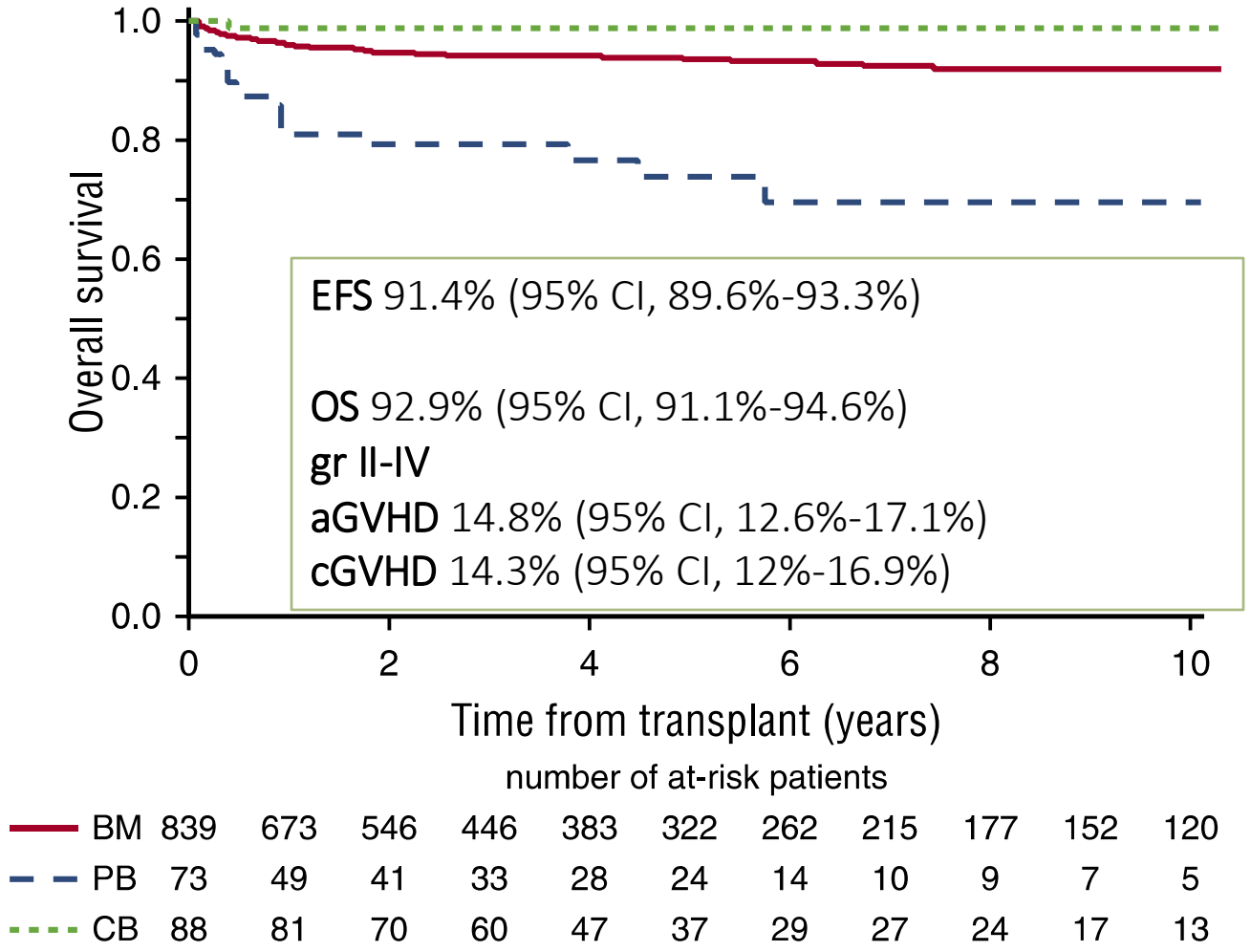
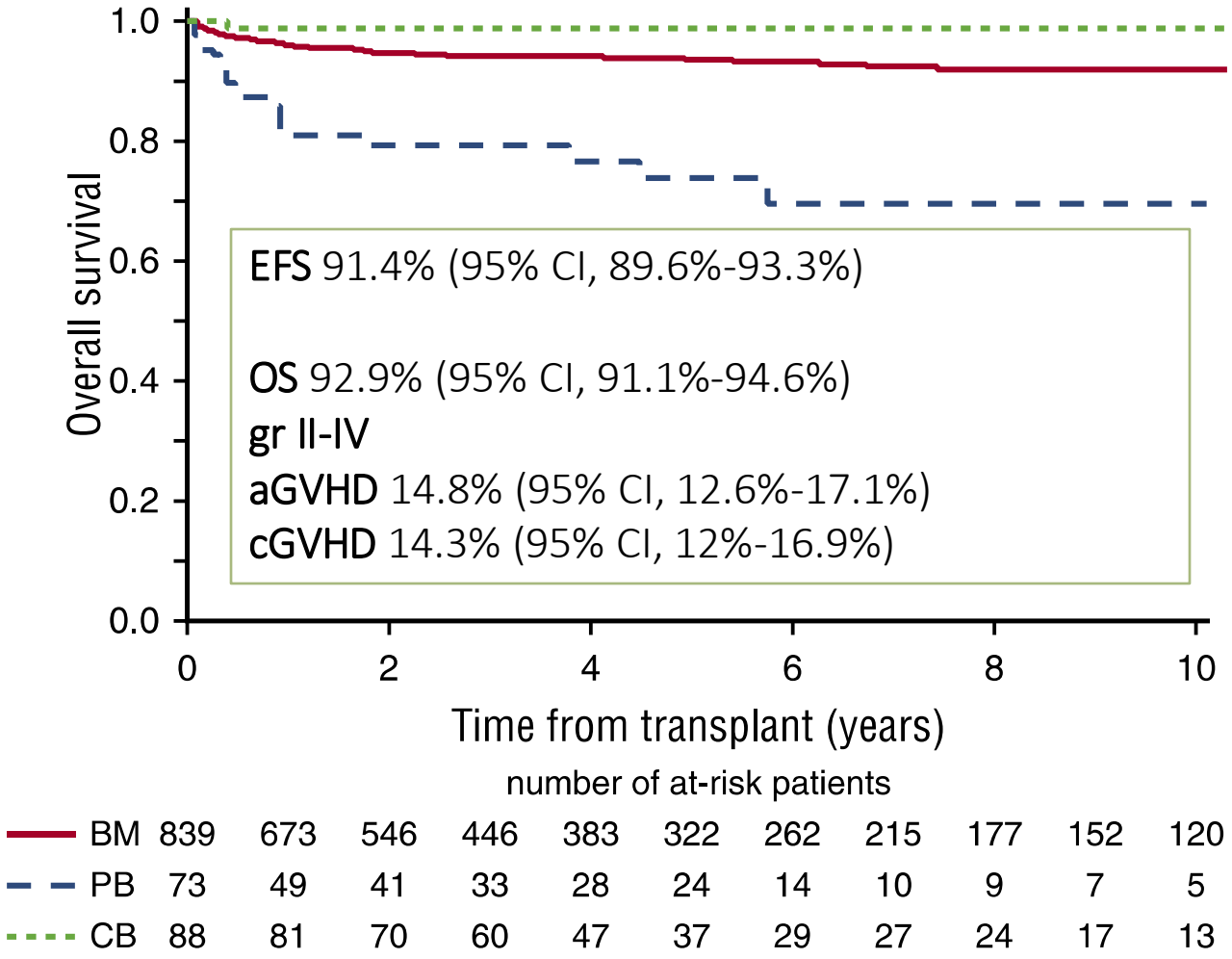


Table 1. Patients and transplant characteristics (n = 1000)

Variables	Total (n = 1000)
Follow-up, months, median (range)	54.5 (0.3-324.6)
Age, years, median (range)	9.4 (0.26-54.37)
Year of transplantation, median (range)	2007 (1986-2013)
Sex, n (%)	
Male	498 (49.8)
Female	502 (50.2)
Source of HSC, n (%)	
BM	839 (83.9)
PBSC	73 (7.3)
CB	88 (8.8)
GVHD prophylaxis, n (%)	
CsA	188 (19.9)
CsA+MTX	533 (56.5)
CsA+MMF	73 (7.7)
FK506±other	110 (11.7)
Other	39 (4.1)
In vivo TCD, n (%)	
None	173 (17.7)
ATG	692 (70.6)
OKT3	2 (0.2)
Campath	113 (11.5)
Conditioning, n (%)	
MAC	873 (87.4)
Bu+Cy	721 (82.6)
Bu+Flu±other	79 (9.0)
Flu±other	33 (3.8)
TBI±other	26 (3.0)
Other or missing	14 (1.6)
RIC	125 (12.5)
Bu+Cy	3 (2.4)
Bu+Flu±other	22 (17.6)
Flu±other	62 (49.6)
TBI±other	20 (16.0)
Other or missing	18 (14.4)

Gluckman et al Blood 2017

Sicurezza e efficacia



Fattori prognostici

- Età precoce
  - [HR EFS treat. Fail. 9%/year]
  - [HR OS treat. Fail. 10%/year]

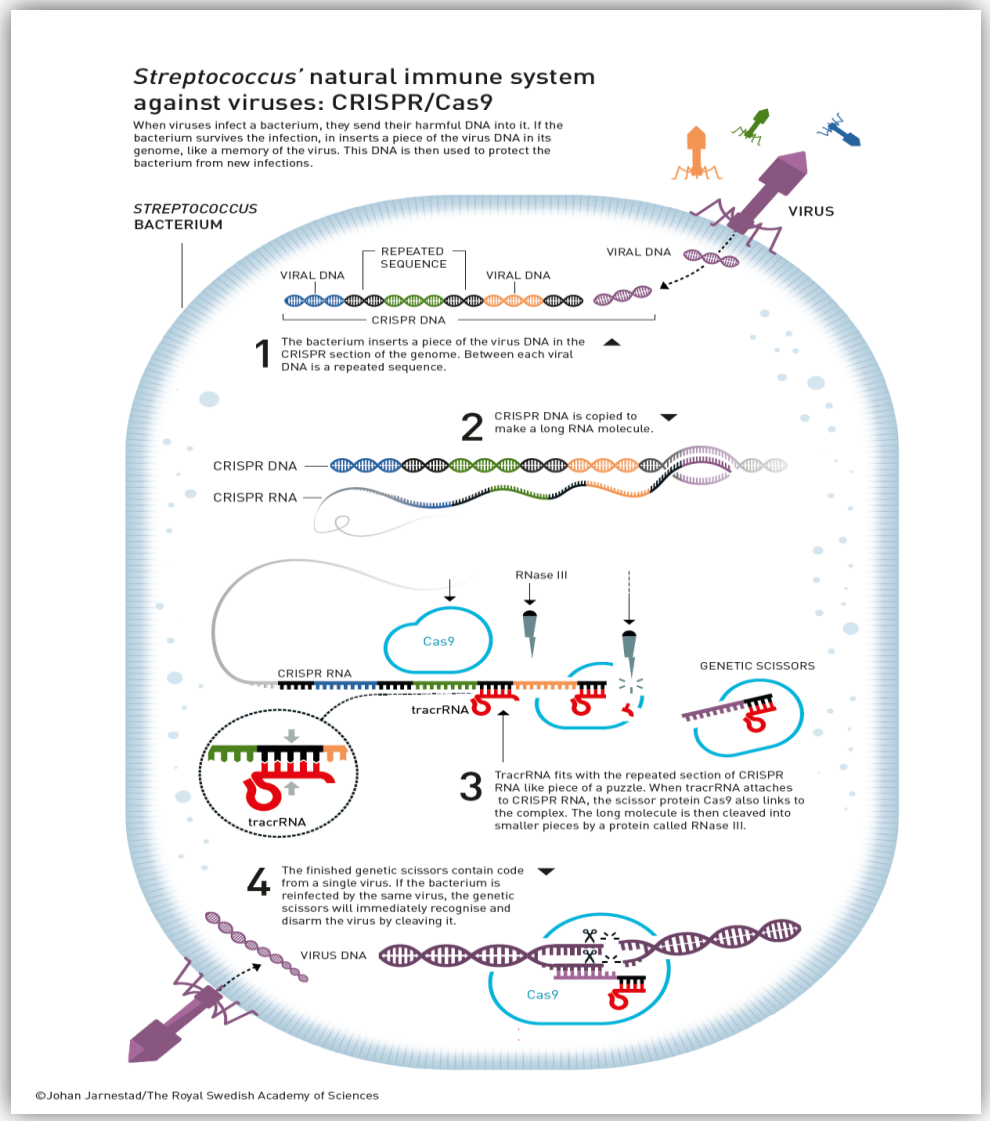
CB > BM > PB

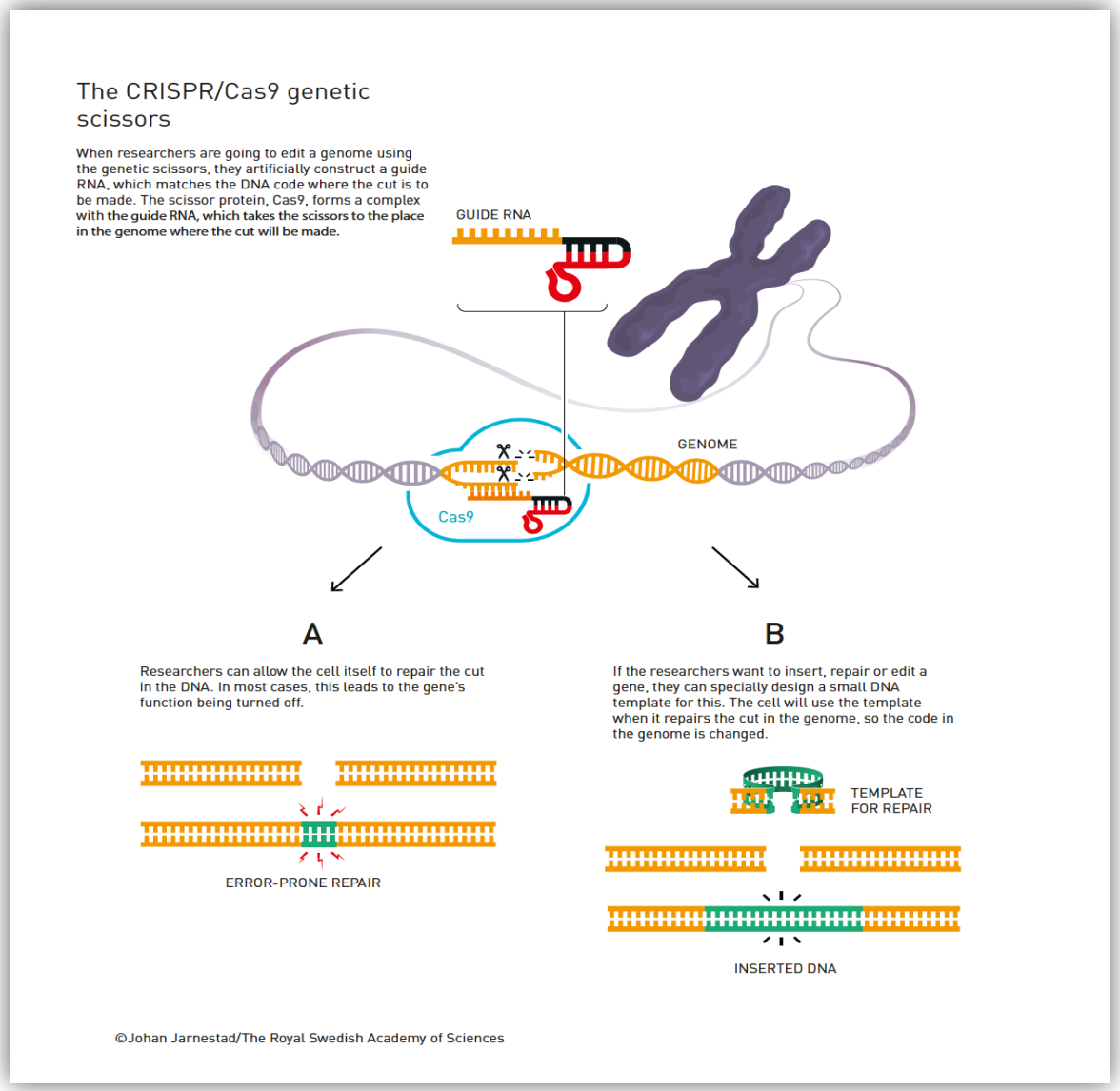
Recidiva: 10%.

Gluckman et al Blood 2017

Terapia genica
Gene editing- CRISPR Cas9

www.nobelprize.org





Protocollo Exa-Cell ® - - Vertex

HbF

- riduce morbidità e mortalità

BCL11A

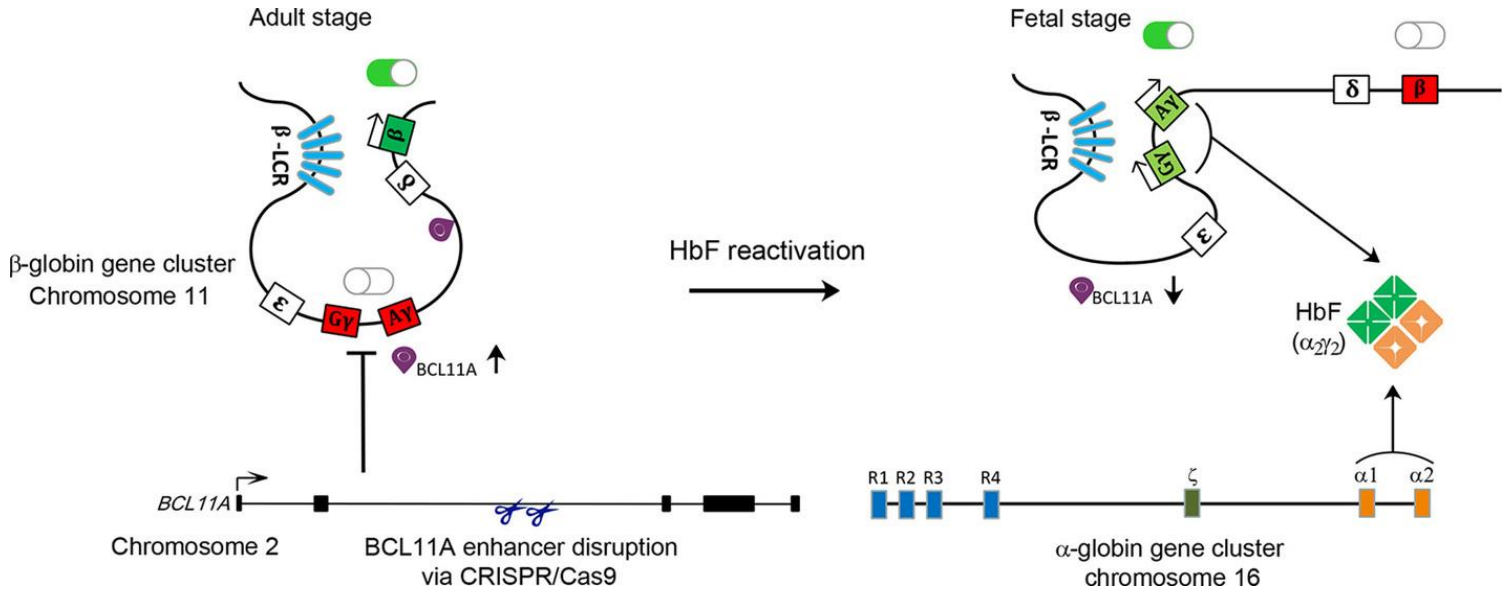
- sopprime HbF alla nascita

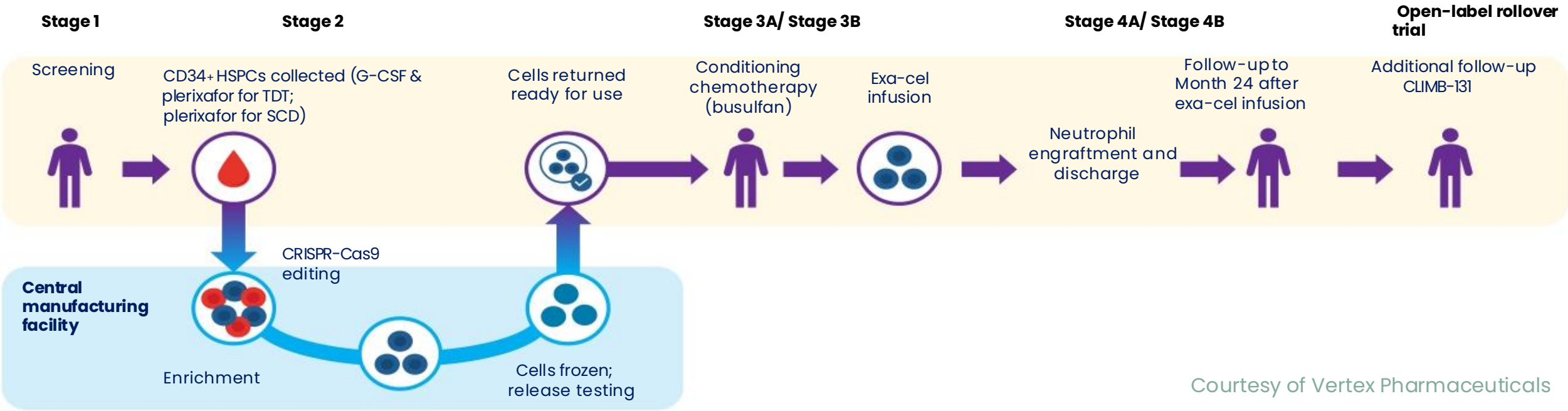
***Ex vivo* editing**

- di BCL11A per ridurne l'espressione

Aumento HbF

- Riduzione VOC e fabbisogno trasfusionale



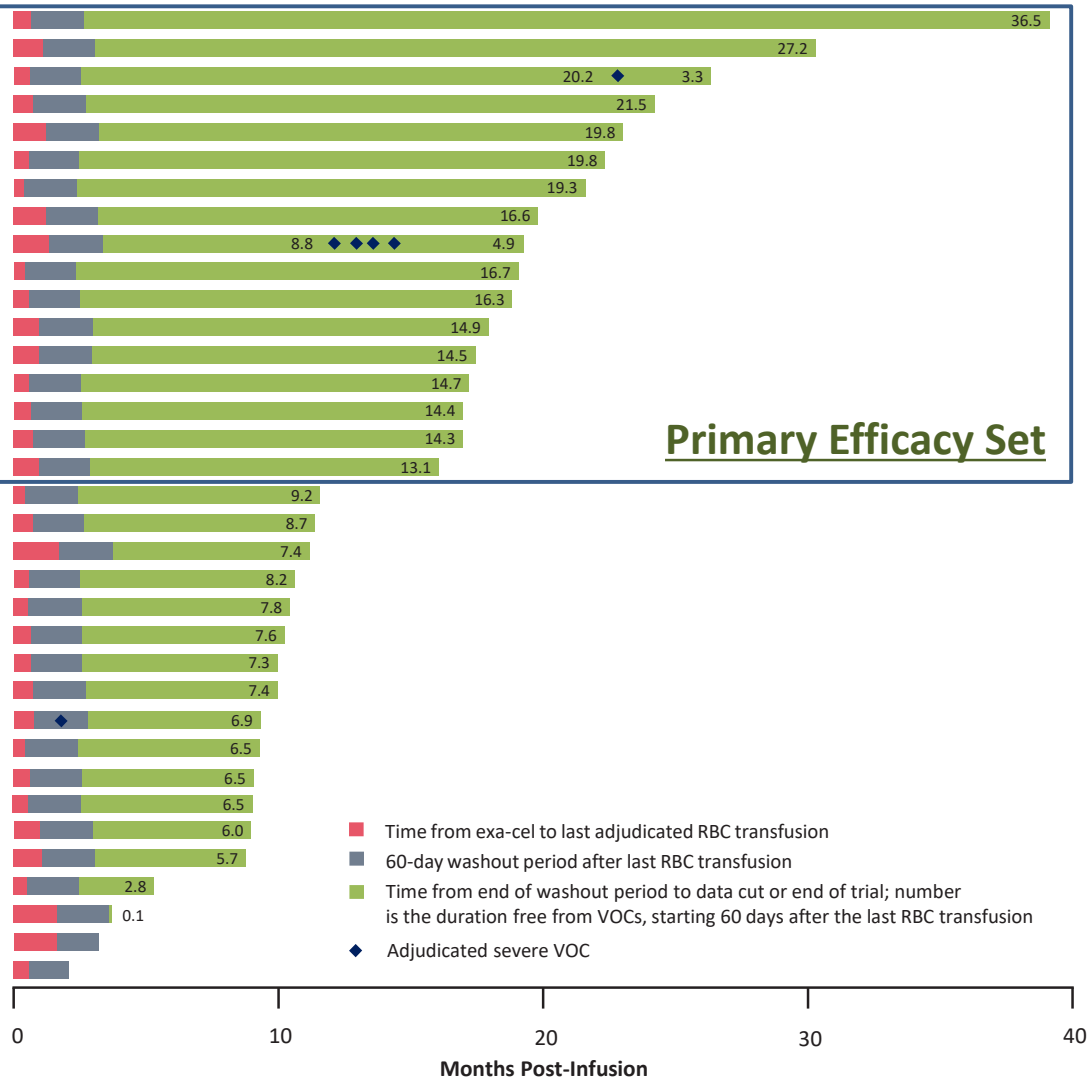


Courtesy of Vertex Pharmaceuticals

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

Full Analysis Set

Participant #	Total Follow-up	Historical Severe VOCs[c]
1[a]	39.1	7
2[a]	30.3	8.5
3[a]	26.3	4
4[a]	24.2	2.5
5[a]	23.0	5.5
6[a]	22.3	9.5
7[a]	21.6	4
8[a]	19.8	6
9[a]	19.3	3
10[a]	19.1	2
11[a]	18.8	2.5
12[a]	17.9	2.5
13[a]	17.4	4.5
14[a]	17.2	8.5
15[a]	17.0	4
16[a]	17.0	2.5
17[a]	16.0	2
18	11.6	2.5
19	11.4	2
20	11.1	3
21	10.7	2
22	10.4	2.5
23	10.2	5.5
24	10.0	2
25	10.0	2
26	9.3	4
27	9.3	2.5
28	9.0	3.5
29	9.0	4
30[b]	8.9	3
31	8.8	3.5
32	5.3	18.5
33	3.7	4
34	3.2	2
35	2.0	3.5



- **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.
[a]Participants evaluable for the primary endpoint; [b]Death from respiratory failure due to COVID-19 infection; [c]Pre-trial severe VOCs annualized over 2 years.

Courtesy of Vertex Pharmaceuticals

FDA NEWS RELEASE

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease

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For Immediate Release: December 08, 2023

A one-time transformational gene therapy with the potential to decrease or stop vaso-occlusive events (VOEs)

The efficacy of LYFGENIA was studied in 36 individuals. 32 individuals were evaluated for the number of vaso-occlusive events (VOEs) they experienced between 6-18 months after treatment.

3.100.000 $

lyfge
(lovotibeglog

did not experience any vaso-occlusive events (VOEs)
(28/32 individuals)

did not experience any severe vaso-occlusive events (sVOEs)
(30/32 individuals)

2.200.000 $

93.5% of people (29 out of 31 people) did not have a severe VOC for at least 12 months in a row after receiving CASGEVY

100% of people evaluated (30 out of 30 people) were not hospitalized for a severe VOC for 12 months in a row after

22.2 MONTHS ON AVERAGE‡

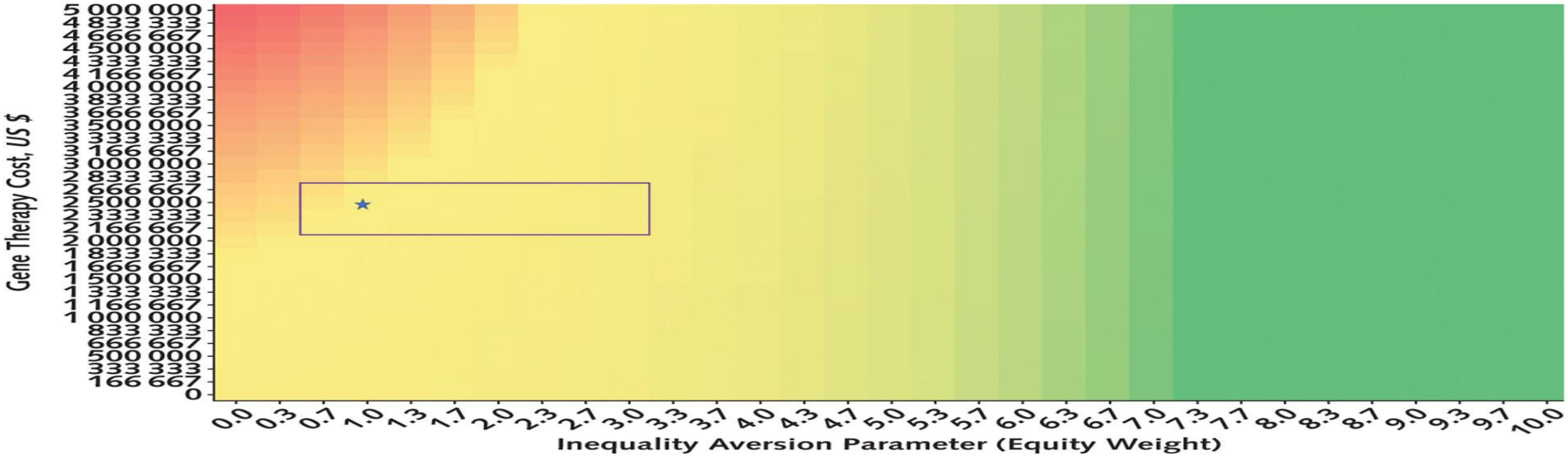
VOC for 12 months in a row:

So far, the average length of time without a severe VOC was 22.2 months (measured as a median‡ amount). One person experienced a severe VOC at month 22.8 and required hospitalization

casgevy™
(exagamglogene autotemcel)
suspension for IV infusion

‡This was measured as a median amount, which is the middle value of a group of numbers; half of the numbers are less than the median and half are higher.

		Non-elderly lifetime SCD-attributable costs (95% CI)		
Females	*Total medical costs*	$1,588,120 (1,262,183-1,914,057)	*Out-of-pocket costs*	$42,395 (34,756-50,033)
Males		$1,748,832 (1,420,634-2,077,031)		$45,091 (36,491-53,691)



Il dilemma

Cosa conta nella vita?

Qualità

- Patologia ad alta incidenza di complicanze
- Prospettive di vita ridotta
- Chi decide?

Valore

- Soddisfazioni
- Possibilità di cure definitive sempre più efficaci
- Quanto vale?