Revolutionary Advances in Hemophilia Treatment:
Scientific Innovations, Economic Challenges, and the Global Impact on Patient Care

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SFTH
SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE

CONGRÈS DE LA SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE

EN COLLABORATION ENTRE LYON ET GENÈVE

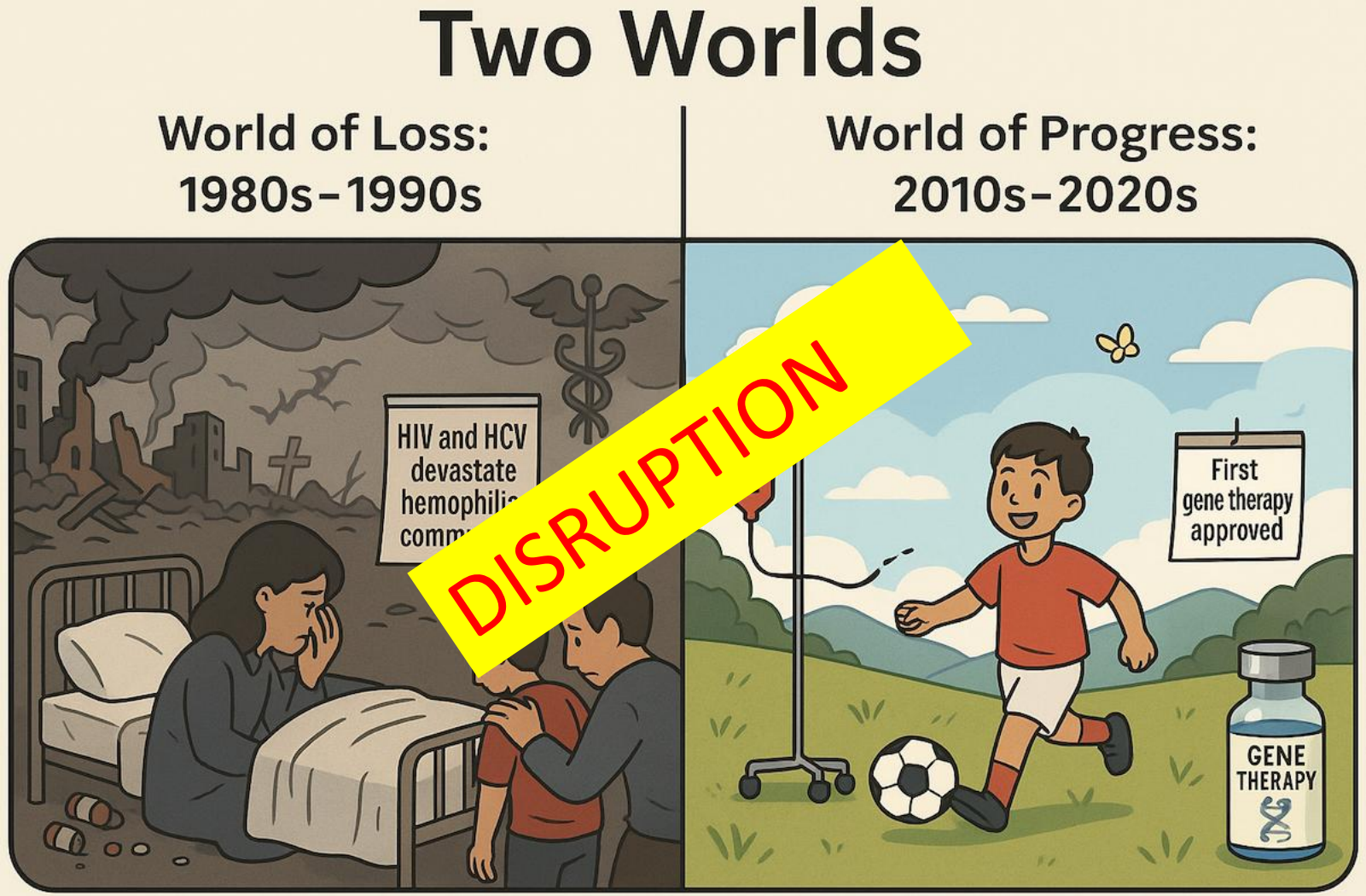
Disclosures

- Consultant: Inovio, Novo Nordisk, Roche, Sanofi, Sobi, Third Rock Ventures;
- Scientific Advisory Board: Be Bio, Frontera, Metagenomi, Typewriter, US National Bleeding Disorders Foundation Medical and Scientific Advisory Council (NBDF MASAC), ISTH Gene Therapy Working Group;
- Director: Voyager Therapeutics, World Federation of Hemophilia.

Fear. Stigma. Loss.
Injustice. Betrayal.

Hope. Healing. Normalcy
Hemophilia-free Mind

Bleak To Dynamic



Dichotomy 1982 vs 2025: Unprecedented therapeutic advances… enabled by continued technical advances in molecular and cellular engineering

1970s: HCV | 1982: HIV | 1996: HAART | 2014: EHLs | 2017: FVIII mimetic | 2022: Gene therapy

Dramatic Changes in Therapeutic Landscape: 2014-2025

Tools to prevent bleeding

- Plasma-derived clotting factors
- Recombinant clotting factors
- Bypassing activated clotting factors

- Genetically engineered clotting factors
- Chemically conjugated clotting factors
- FVIII mimetic bispecific monoclonal antibodies
  - SQ delivery
  - Oral delivery
- Rebalancing agents
  - Small inhibitory RNA to antithrombin
  - Mabs to Tissue Factor Pathway Inhibitor
  - Mab to Protein S
  - ~~Protein C inhibitor~~
  - siRNA to Z-dependent protease inhibitor

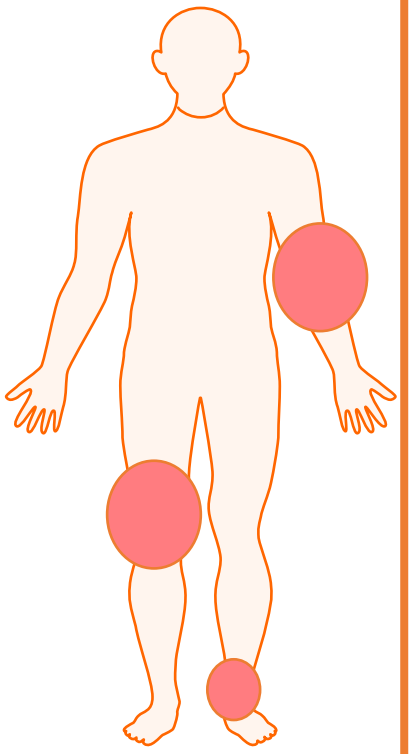
- Gene therapy
  - AAV delivered episomes
  - Lentivirus delivered gene insertion
  - AAV/CRISPR Cas LNP genome integration

Treatment goals

- **Zero bleeds**
- **Desired physical activity level**

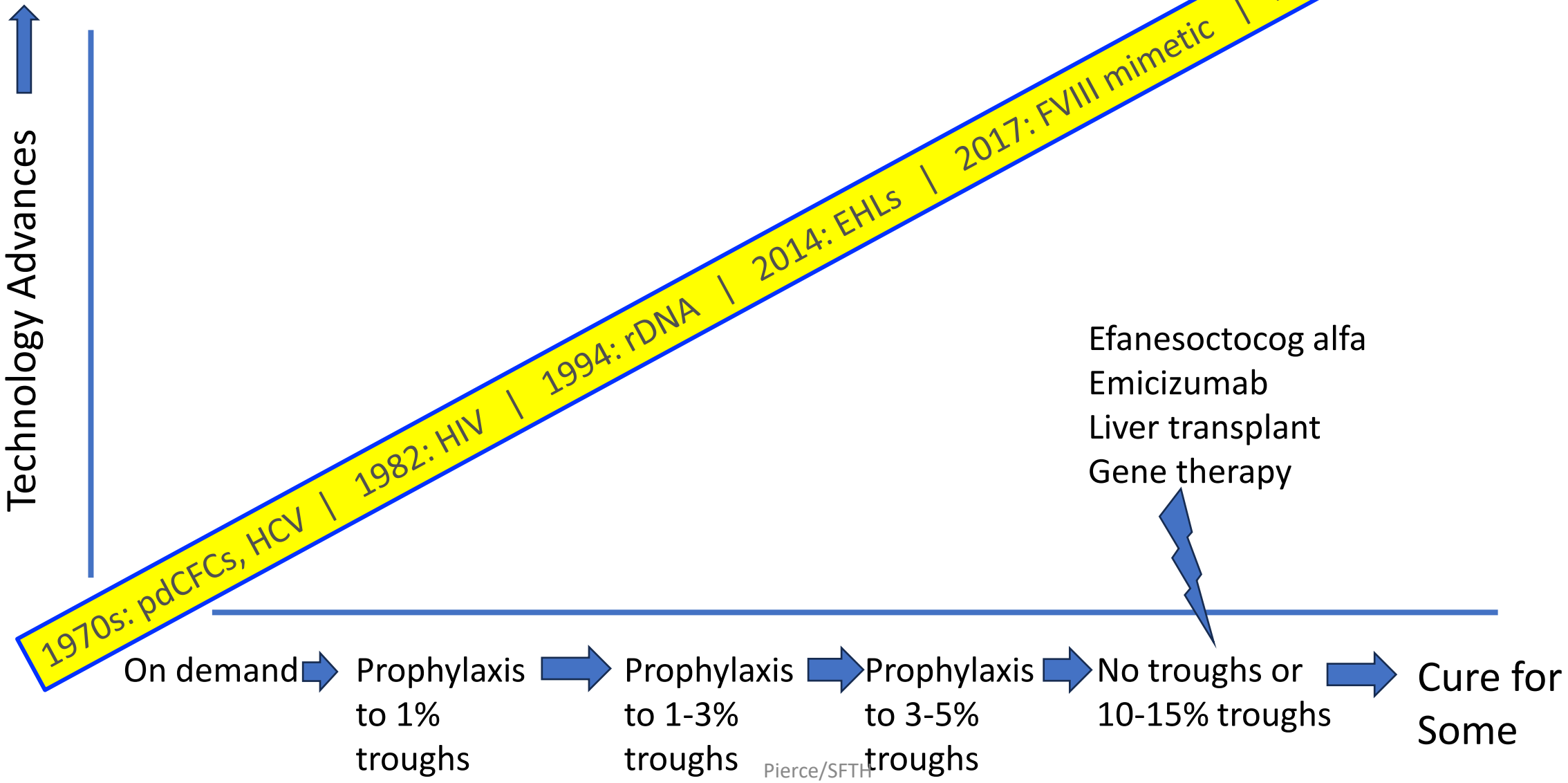
Hemophilia-free mind

Functional cure



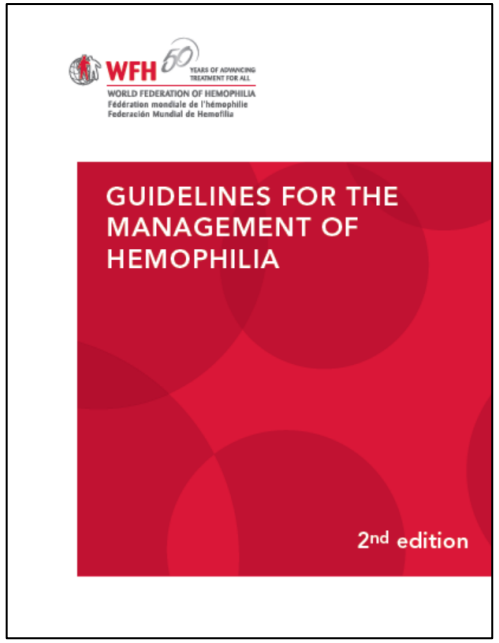
Hermans C, Pierce GF. Towards achieving a haemophilia-free mind. Haemophilia. 2023 Jul;29(4):951-953. doi: 10.1111/hae.14807.

Evolution and Revolution in Treatment and Management



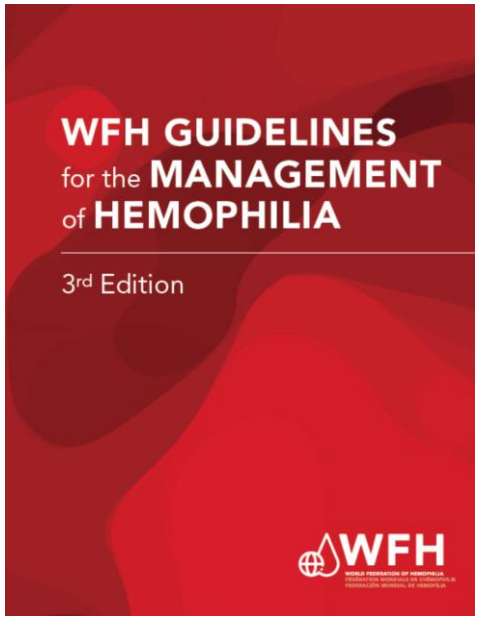
Treatment Goals Enabled by Evolving Technologies

2nd Edition 2012



1-3% troughs considered adequate

3rd Edition 2020



3-5% or higher troughs now preferred

Trough or steady state level needed to meet newer treatment goals?

Evolving goals based on technology advances

FVIII Activity Levels Associated with Zero Joint Bleeds

Factor levels of 15% or more are neede ve zero joint bleeds as demonstrated acros dels[1-6]

NOT ACHIEVABLE USING STANDARD HALF LIFE PRODUCTS

15%

2011

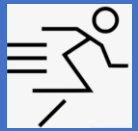
den Uijl I, et al. *Haemophilia* 2011[1]

Based on a multivariate model to estimate joint bleeds in people with non-severe hemophilia A

e J, et al. *od Adv* 2018[2]

sed on a regression model to predict joint bleeds in people with non-severe hemophilia A

35-40%



2016/2020

Chowdary P, et al. *Thromb Haemost 2020[3]*; Fischer K, et al. *Blood* 2016[4]

Based on PK models used to predict FVIII levels associated with zero joint bleeds in people with severe hemophilia A

Minimum Factor Levels to Prevent Joint Bleeding

	At least 1 joint bleed (n=100)	No joint bleeds (n=170)[2]	Mean difference (95% CI)	p
FVIII:C[1] mean (SD)	17.8 (10.8)	26.8 (11.6)	-9.0 (-11.7;-6.2)	<0.0001

- Lower mean FVIII levels were observed in patients with a history of at least one lifelong joint bleed compared with those with no previous joint bleeds
- Consequences of standard deviations
  - Patients will have individual minimal thresholds for bleeding
  - Most data are in mild patients. Patients with prior joint damage and target joints will require higher FVIII levels or a greater change in their ratio of pro- and anti-coagulants
    - Severe patients are phenotypically different from those with higher FVIII

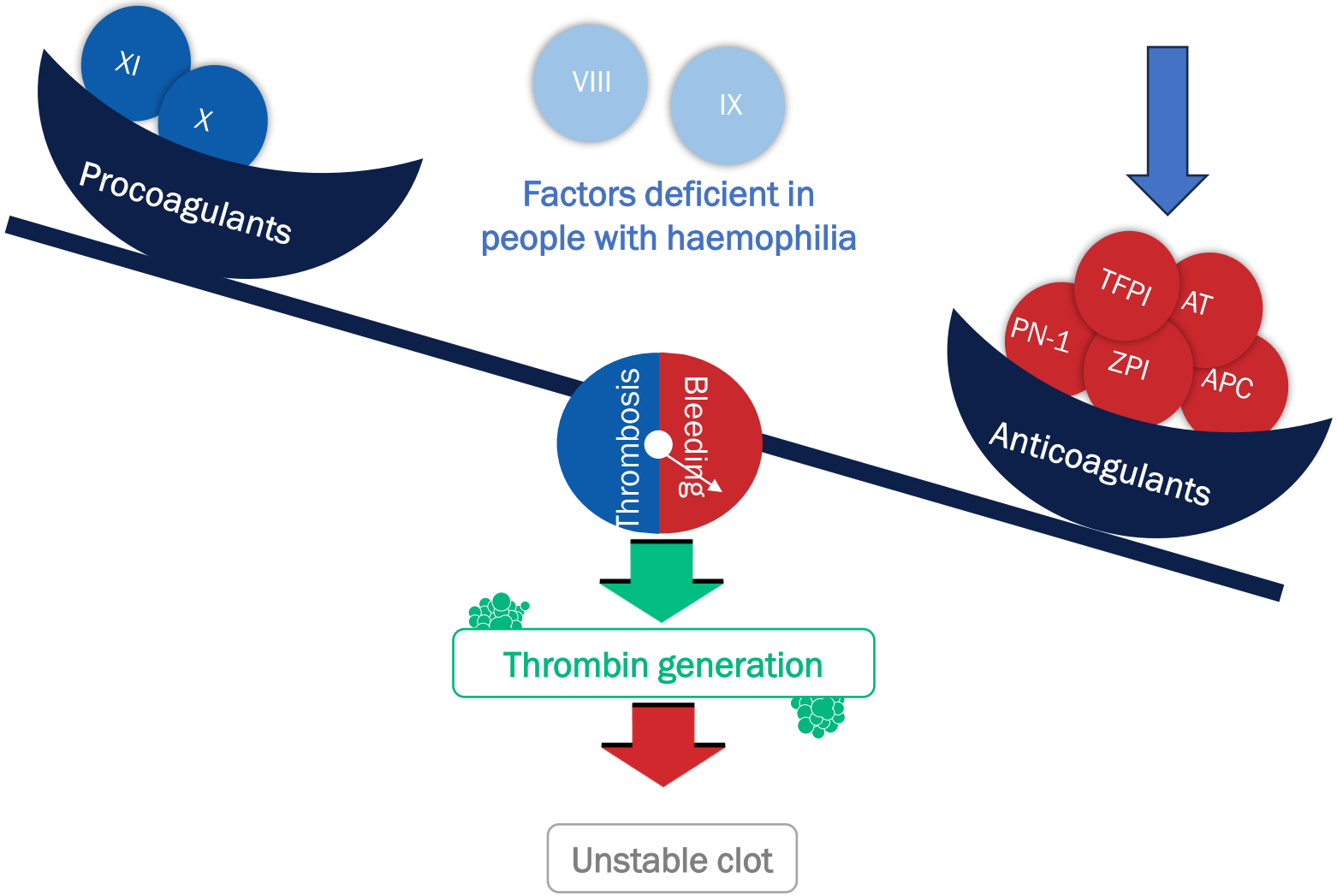
P Agosti, SM Siboni, S Scardo, A Torri, R Gualtierotti, F Peyvandi. Minimum factor VIII levels to prevent joint bleeding in mild hemophilia A. 2025. Blood Advances. https://ashpublications.org/bloodadvances/article-pdf/doi/10.1182/bloodadvances.2023011366/2085511/bloodadvances.2023011366.pdf

Thrombin Generation: Goal of Hemophilia Therapy

Haemostasis depends on **balanced coagulation** to generate **thrombin sufficient** to enable stable clot formation[1,2]

In haemophilia, lack of factor VIII or IX results in **insufficient thrombin generation** and **inability to form stable blood clots**[1,2]

Rebalancing agents aim to **correct thrombin deficiency** by **lowering anticoagulant levels**[2,3]



APC, activated protein C; AT, antithrombin; PN-1, protease nexin-1; TFPI, tissue-factor protein inhibitor; ZPI, Z-dependent protease inhibitor.

1. Willyard, C. Nature. 2014;515;S168–9; 2. Negrier C, et al. Blood Rev. 2019;38:100582; 3. Nogami K and Shima M. Blood. 2019;133:399–406.

Figure adapted from Aymonnier K, et al. Thromb Haemost 2021;121(03):261–269

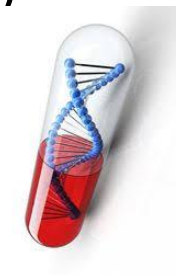
Comparison of Rebalancing Agents

Rebalancing Agent	Dosing Regimen	Annualized Bleeding Rate	Comments
Concizumab Anti-TFPI	SQ daily Weight based Concizumab level testing required	**2.1-6**, Explorer 7 and 8 trials	Thrombotic events led to new dosing regimen
Marstacimab Anti-TFPI	SQ weekly Flat dosing >12 years No lab monitoring	**2.3-5.1** Basis trial	No reported thrombotic events to date
Fitusiran siRNA to AT	SQ monthly Flat dosing based on AT level AT level testing required	**3.7** (median)	Adverse events led to new Phase 3 trial to test new dosing regimen to maintain AT levels 15-35%

Emicizumab, Efanesoctocog alfa, Mim8, valoctocogene roxaparvovec, etranocogene dezaparvovec ABR all <1

A Critical Juncture in Development of Hemophilia Therapeutics*

- **Goal: zero bleeds, hemophilia-free mind**
- **Status**
  - Many CFCs approved, no pending novel clinical trials for HemA/B
  - 3 rebalancing agents approved, one more in clinical trials (for VWD)
    - Long term safety and comparative real world efficacy needed
  - 1 FVIII mimetic on market, 3 more in clinical trials (including oral)
  - 2 gene therapies approved, 1 in clinical trials (lenti)
  - 2 gene editing clinical trials, more coming

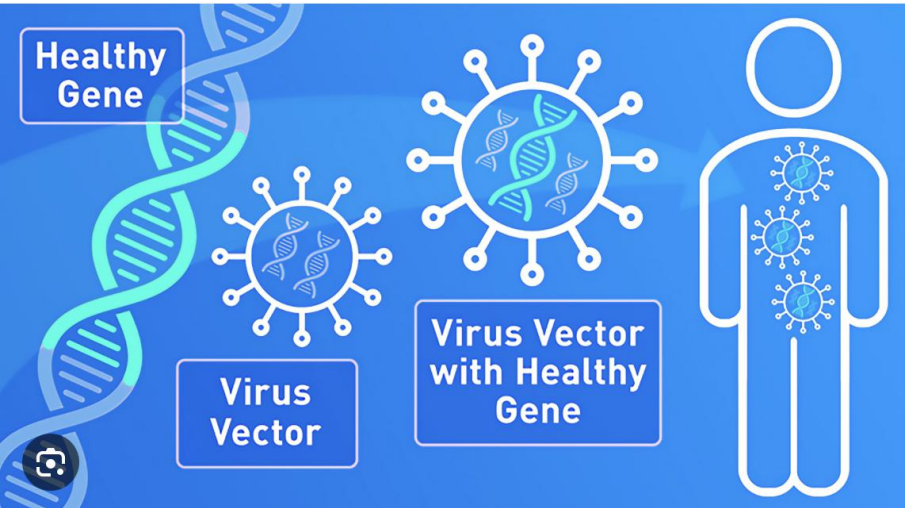


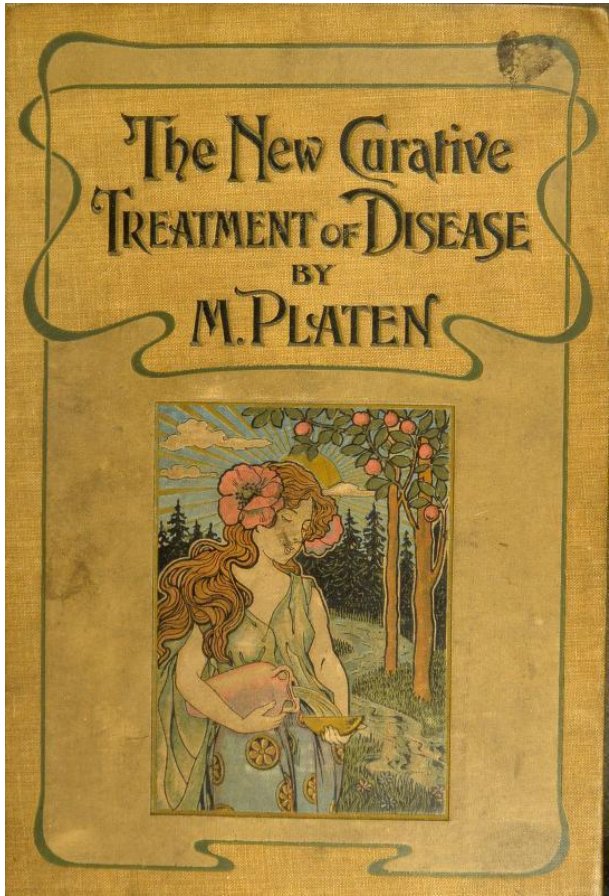
- **Next focus areas**
  - RBDs, VWD (+some above agents may be effective)
  - Next generation gene therapies including editing
  - Expanded access globally

* Not exhaustive list; not including China

The Roads Toward Curative Therapy

What Has Enabled Factor IX Curative Therapy in Many Treated Individuals?





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Printed in U.S.A.

Changing Residue 338 in Human Factor IX from Arginine to Alanine Causes an Increase in Catalytic Activity*

(Received for publication, December 22, 1997, and in revised form, March 5, 1998)

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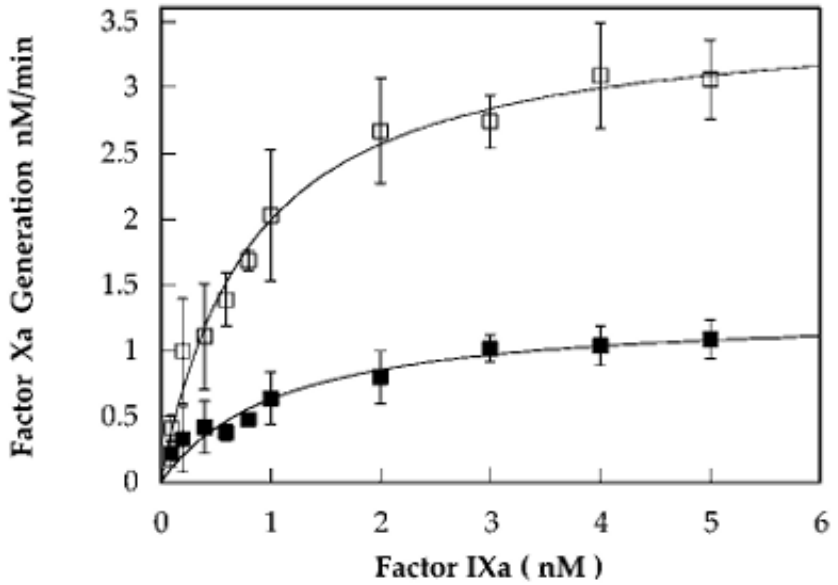
From the ‡Department of Biology, University of North Carolina, Chapel Hill, North Carolina 27599-3280, the §Division of Hematology-Oncology, Department of Medicine, Emory University, Atlanta, Georgia 30332, and the ¶Max Planck Institute of Biochemistry, D-82152 Martinsried, Germany

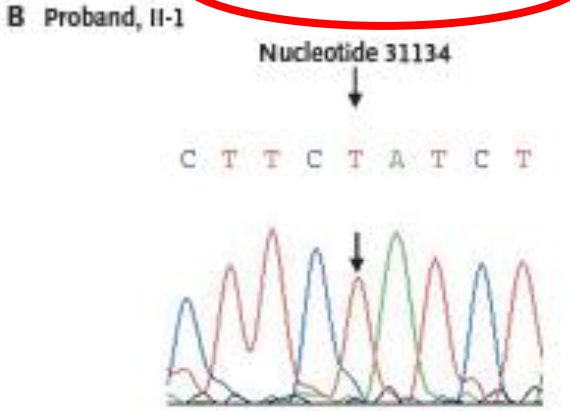


R338A
3x wt
FIX
activity

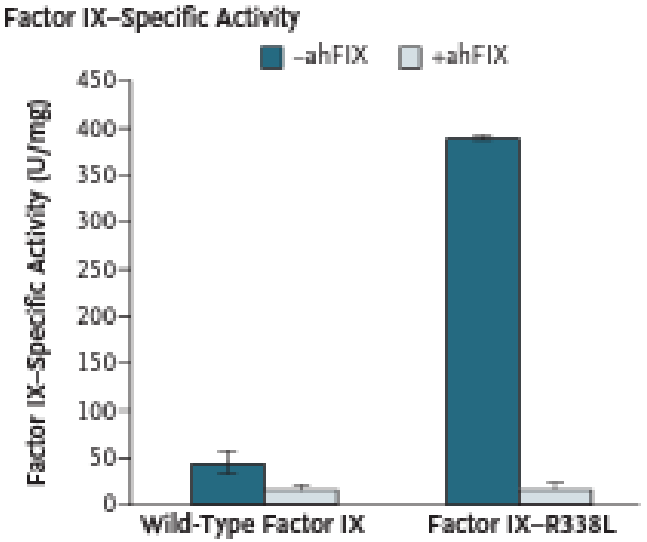
N ENGL J MED 361;17 NEJM.ORG OCTOBER 22, 2009

X-Linked Thrombophilia with a Mutant Factor IX (Factor IX Padua)

Paolo Simioni, M.D., Ph.D., Daniela Tormene, M.D., Ph.D., Giulio Tognin, M.D., Sabrina Gavasso, Ph.D., Cristiana Bulato, Ph.D., Nicholas P. Iacobelli, B.A., Jonathan D. Finn, Ph.D., Luca Spiezia, M.D., Ph.D., Claudia Radu, Ph.D., and Valder R. Arruda, M.D., Ph.D.



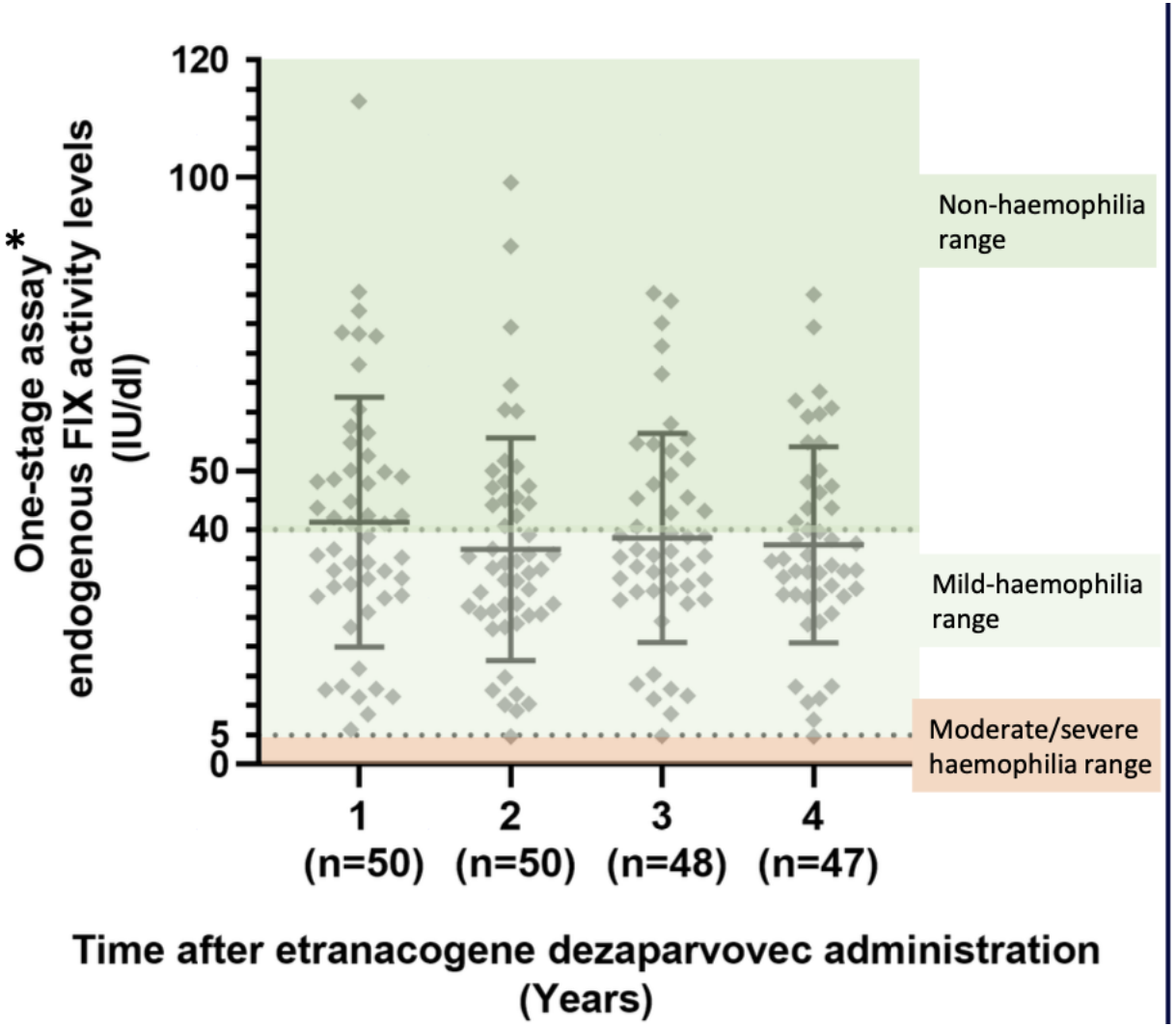
R338L
7-8x wt
FIX
activity



Increased specific activity is enabling

Pierce/SFTH

AAV5-FIX Phase 3 Results



The NEW ENGLAND JOURNAL of MEDICINE FEBRUARY 23, 2023 N ENGL J MED 388;8

Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B

S.W. Pipe, F.W.G. Leebeek, M. Recht, N.S. Key, G. Castaman, W. Miesbach, S. Lattimore, K. Peerlinck, P. Van der Valk, M. Coppens, P. Kampmann, K. Meijer, N. O'Connell, K.J. Pasi, D.P. Hart, R. Kazmi, J. Astermark, C.R.J.R. Hermans, R. Klamroth, R. Lemons, N. Visweshwar, A. von Drygalski, G. Young, S.E. Crary, M. Escobar, E. Gomez, R. Kruse-Jarres, D.V. Quon, E. Symington, M. Wang, A.P. Wheeler, R. Gut, Y.P. Liu, R.E. Dolmetsch, D.L. Cooper, Y. Li, B. Goldstein, and P.E. Monahan

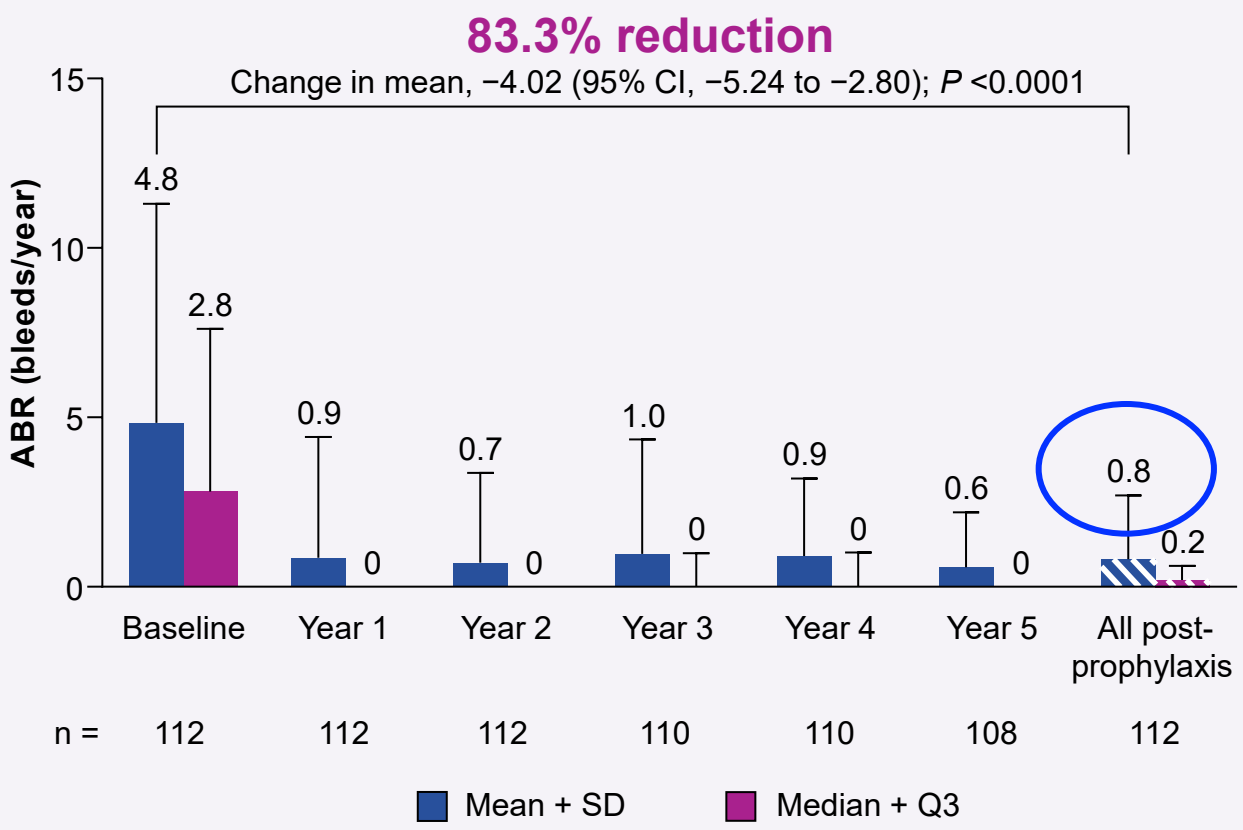
- Variability, some participants <10%
- High pre-existing anti-AAV5 inhibits
- Path to children slow
- One and done
- Some liver toxicity
- Can be considered curative for most
  - ABR 0.99; 67% zero bleeds after 2 years
- 1st generation HemB gene therapy

Coppens M, Pipe SW, Miesbach W, Astermark J, Recht M, van der Valk P, Ewenstein B, Pinachyan K, Galante N, Le Quellec S, Monahan PE, Leebeek FWG; HOPE-B Investigators. Etranacogene dezaparvovec gene therapy for haemophilia B (HOPE-B): 24-month post-hoc efficacy and safety data from a single-arm, multicentre, phase 3 trial. Lancet Haematol. 2024 Apr;11(4):e265-e275. doi: 10.1016/S2352-3026(24)00006-1.

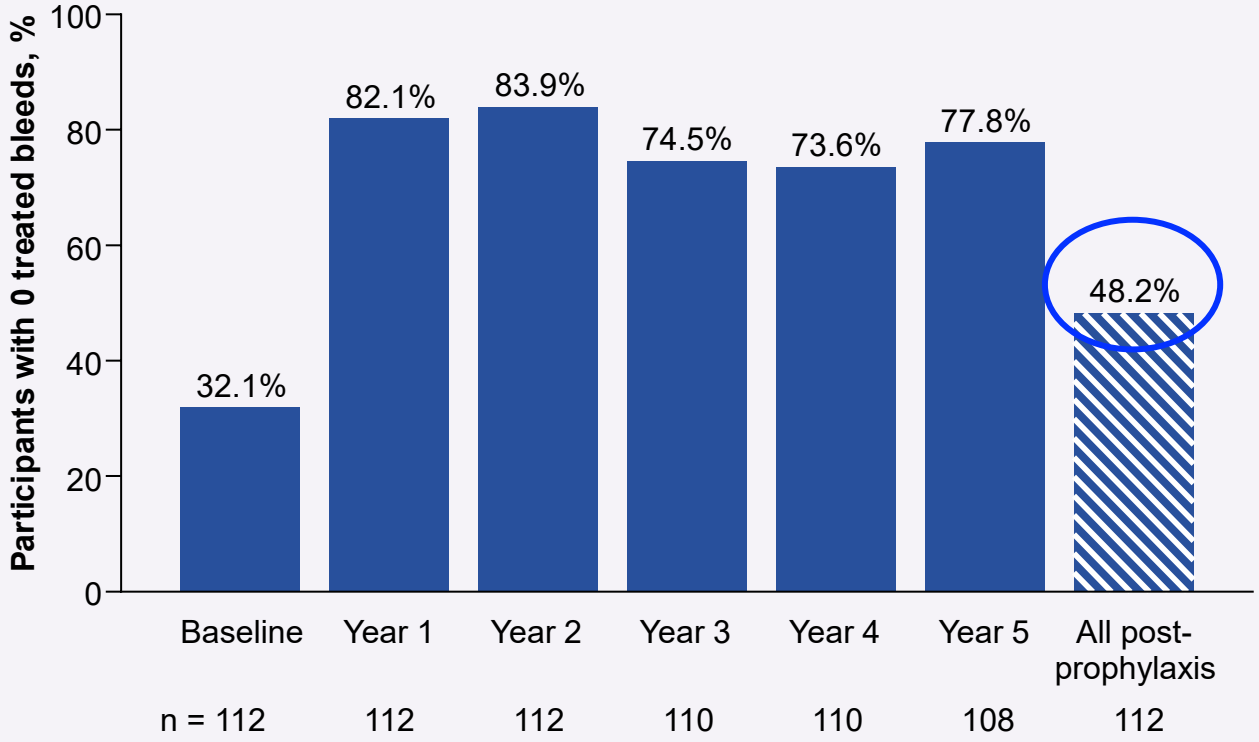
Valoctocogene Roxaparvovec: Hemostatic Efficacy Over 5 Years

Rollover population

ABR for treated bleeds decreased >80% from baseline during the post-prophylaxis period



In year 5, >75% of participants had no treated bleeds; overall 48% no treated bleeds



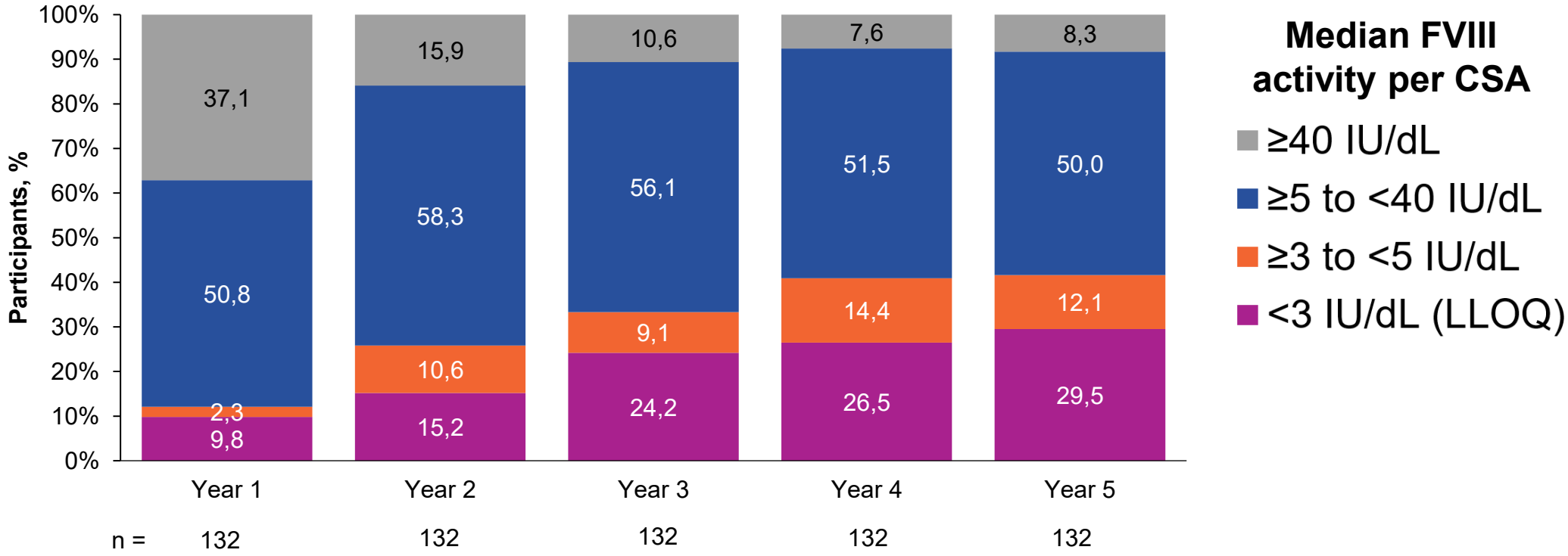
Missing data were not imputed.
ABR, annualized bleeding rate; CI, confidence interval; Q, quartile; SD, standard deviation.
Slide modified from BioMarin

Pierce/SFTH

(109/134) of participants remain off prophylaxis; 25 returned

Valoctocogene Roxaparvovec FVIII Activity (Chromogenic) Through Year 5 **mITT population**

58.3% remain in mild to normal range from 88% end of year 1
<3% patients: growing each year
>40% patients: decreasing each year



Because 2 participants did not reach year 4 follow-up, week 208 data are based on 130 participants. For participants who discontinued the study, missing FVIII values post-discontinuation were imputed as 0 IU/dL through the data cutoff date.
CSA, chromogenic substrate assay; FVIII, factor VIII; LLOQ, lower limit of quantification; mITT, modified intention-to-treat.
BioMarin data

Development Risks: Most New Drugs Fail

- Hemophilia used to be an exception. No longer
- All but **2** gene therapies have failed to commercialize since 1998
  - At least **15** others have failed during clinical testing.*
    - e.g., BAX335, BAX888, BAY2599023, FLT180a, fidanacogene elaparvovec, giroctocogene fiteloparvovec, dirloctogene samoparvovec, Spk-8016, AMT-060, AskBio009, Coagulin-B intra-muscular and intra-hepatic, Transkaryotic Therapies, Viagene, GenStar/Baxter*
  - Unrestrained Panglossian thinking
- Multiple protein therapeutics failed over 20 years
  - e.g., KG-Lip, 4 FVIIa variants, SerpinPC, 1 anti-TFPI, fitusiran first set clinical trials
- Cannot assume drugs going into Ph1 will emerge from Ph3

*Not including China, where BBN-H901 is approved for HemB and others for HemA/B have failed

Pierce GF, Fong S, Long BR, Kaczmarek R. Deciphering conundrums of adeno-associated virus liver-directed gene therapy: focus on hemophilia. J Thromb Haemost. 2024 May;22(5):1263-1289. doi: 10.1016/j.jtha.2023.12.005.

Molecular Therapy
Opinion

2022

Eliminating Panglossian thinking in development of AAV therapeutics

Radoslaw Kaczmarek,[1] Glenn F. Pierce,[2] Declan Noone,[3] Brian O'Mahony,[4] David Page,[5] and Mark W. Skinner[6]

https://doi.org/10.1016/j.ymthe.2021.10.025

Recognize manufacturing a semi-lifeform to interact with very complex lifeform

Recognize variables to creating in vivo biofactories are not understood

Recognize QC assays for cGMP production are reflection of insufficient knowledge base

Recognize success predicated on uncovering the biology of transduction, transcription and translation

Zhang, Herzog, Xiao. Subgenomic particles in rAAV vectors result from DNA lesion/break and non-homologous end joining of vector genomes. Mol Ther-Nuc Acids 2022; 29: 852-861 DOI: 10.1016/j.omtn.2022.08.027

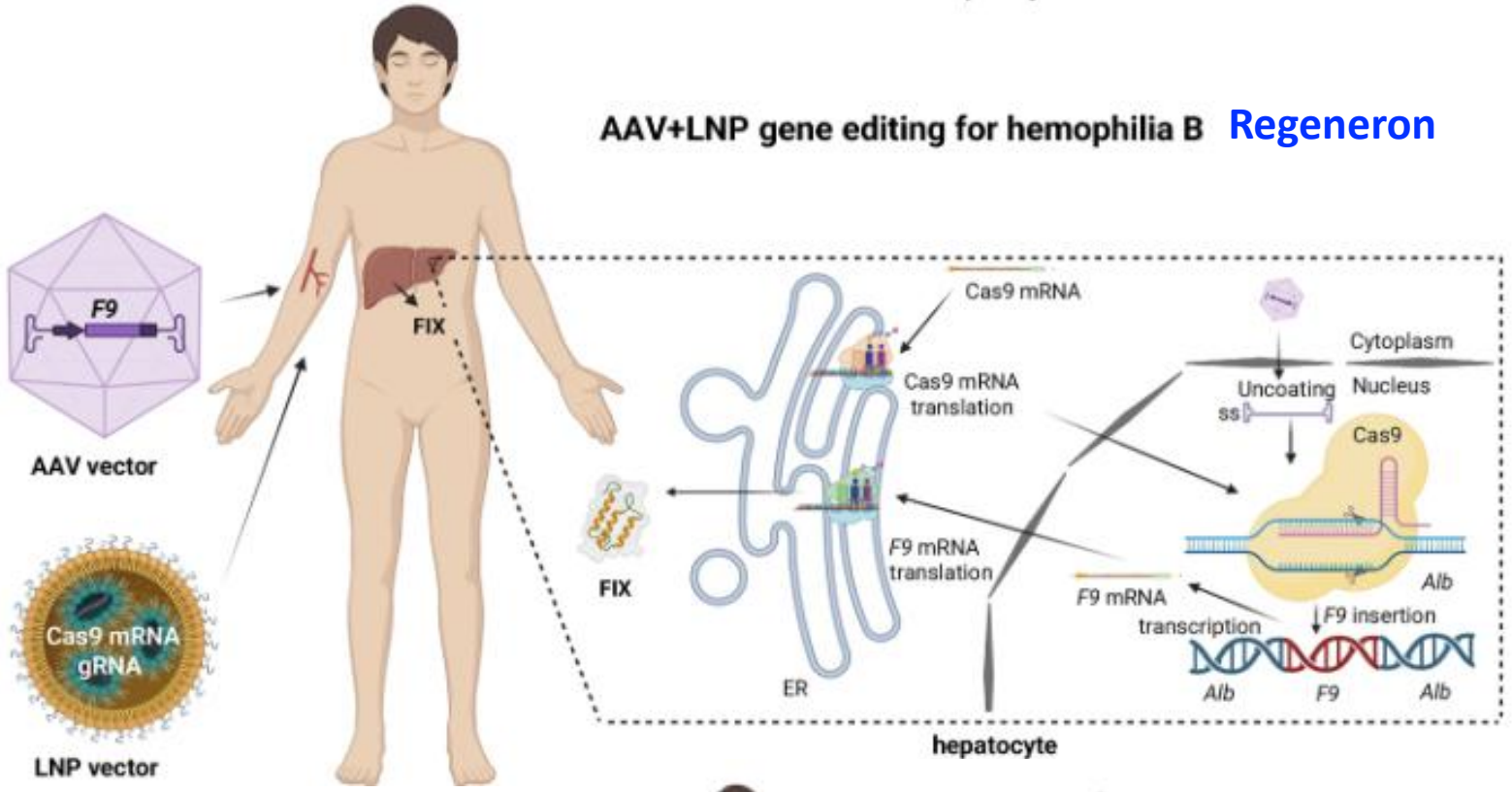
Status: Functional Cure of Hemophilia

- Improved gene therapy to increase therapeutic window, treat children
  - Gene editing, biobetter FVIII, non-AAV vector, and non-viral delivery may be enabling technologies
  - Once and done and durability (or repeat dosing) is required
- Ultra-long, Sustained Activity FVIII
  - Troughs above 10-15% consistently in all patients; IV=higher burden
- FVIII mimetics
  - Distinguish outcomes between 15%-45%-90% FVIII ”equivalency”
  - Monthly SQ dosing carries some, but diminished burden
- Oral FVIII mimetic
  - The Holy Grail, once daily pill, no clinical data yet
- Different GNI geographies offer different opportunities and risks
  - The 15% HIC pie can be divided only so much before there is not much left

Hermans C and GF Pierce. Bispecific antibodies mimicking factor VIII in hemophilia A: converting innovation to an essential medicine. Res Pract Thromb Haemost. 2023 May 10;7(4):100173. doi: 10.1016/j.rpth.2023.100173. Hermans C, Pierce GF. Ultra-Long factor VIII: a major step forward toward a hemophilia-free mind. J Thromb Haemost. 2024 Jul;22(7):1844-1846. doi: 10.1016/j.jtha.2024.04.010. Pierce GF, Skinner M, O'Mahony B, Rotellini D, Kaczmarek R. Why is the uptake of gene therapy in hemophilia less than expected? Res Pract Thromb Haemost. 2025 Jun 23;9(5):102948. doi: 10.1016/j.rpth.2025.102948.

On the Horizon

Phase 1/2 trials initiated in 2025



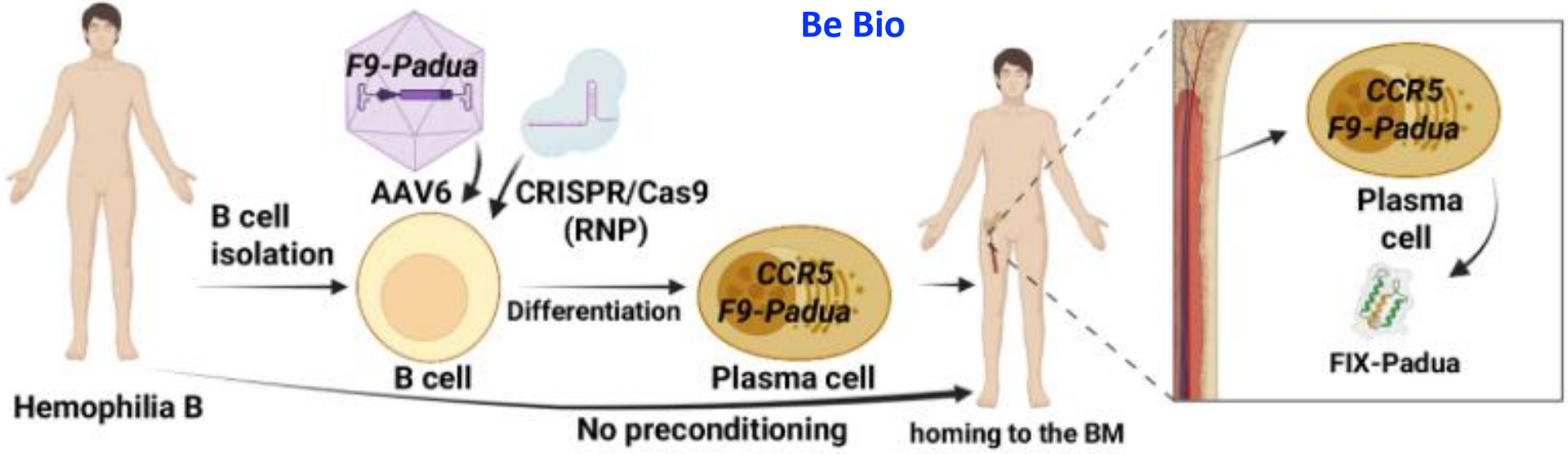
Pérez-Maroto J, Sepp-Lorenzino L, Castaño-Esteban D, Palacios D, Sot B. Advancements in Nonviral Gene Editing Strategies for Rare Diseases. Hum Gene Ther. 2025 Sep;36(17-18):1118-1137. doi: 10.1177/10430342251372056.

https://www.regeneron.com/science/technology/genetic-medicines

Metagenomi- same system for FVIII.

https://dbzipdrh8te83.cloudfront.net/MGX-ASH-December-2024.pdf

Be Bio



Trivedi N, Pitner RA, Rawlings DJ, James RG. Engineering B cells to treat and study human disease. Nat Biotechnol. 2025 Sep;43(9):1431-1444. doi: 10.1038/s41587-025-02757-y.

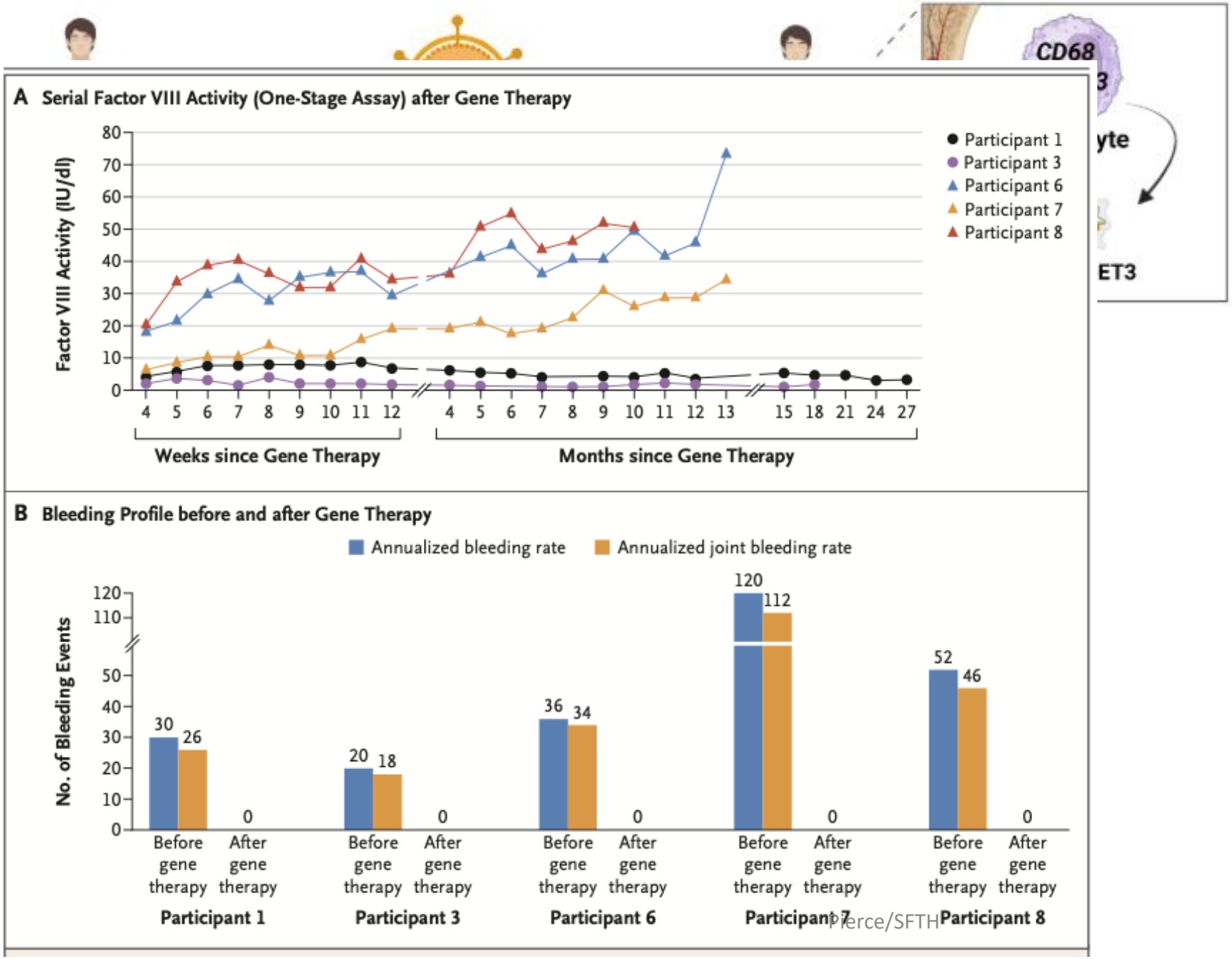
Cheng RY, Hung KL, Zhang T, Stoffers CM, Ott AR, Suchland ER, Camp ND, Khan IF, Singh S, Yang YJ, Rawlings DJ, James RG. Ex vivo engineered human plasma cells exhibit robust protein secretion and long-term engraftment in vivo. Nat Commun. 2022 Oct 16;13(1):6110. doi: 10.1038/s41467-022-33787-8.

https://be.bio/our-science/publications-presentations/

Herzog RW, Kaczmarek R, High KA. Gene therapy for hemophilia - from basic science to first approvals of "one-and-done" therapies. Mol Ther. 2025 May 7;33(5):2015-2034. doi: 10.1016/j.ymthe.2025.03.043.

On the Horizon

Ex vivo
F8-ET3: 9% porcine



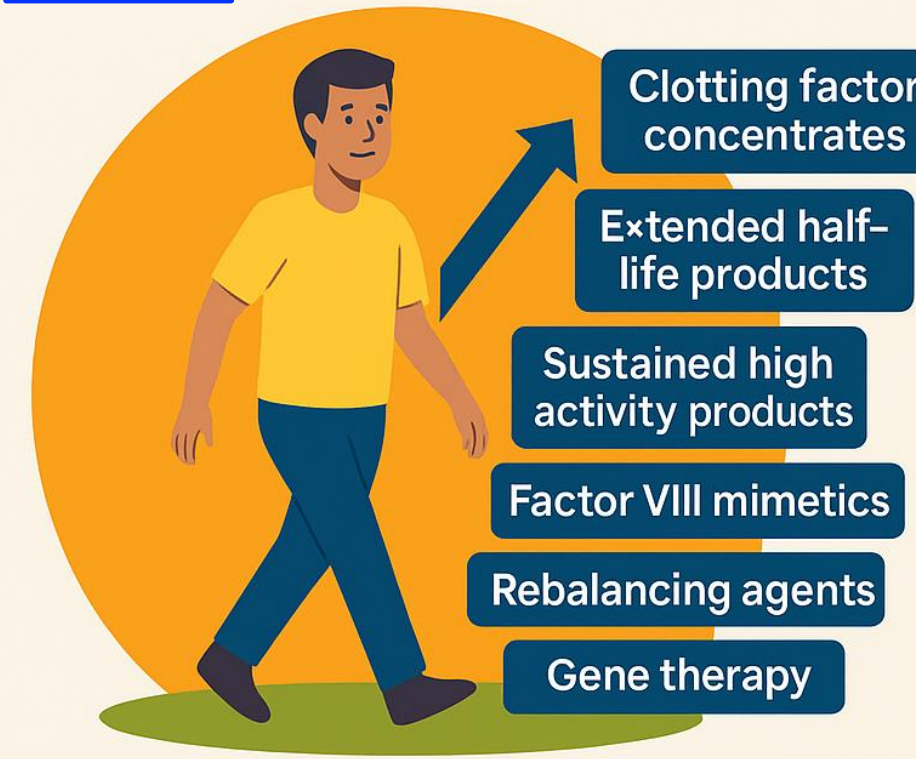
Srivastava A, Abraham A, Aboobacker F, Singh G, Geevar T, Kulkarni U, Selvarajan S, Korula A, Dave RG, Shankar M, Singh AS, Jeba A, Kumaar N, Benjamin C, Lakshmi KM, Srivastava VM, Shaji RV, Nair SC, Brown HC, Denning G, Lollar P, Doering CB, Spencer T. Lentiviral Gene Therapy with CD34+ Hematopoietic Cells for Hemophilia A. N Engl J Med. 2025 Jan 30;392(5):450-457. doi: 10.1056/NEJMoa2410597.

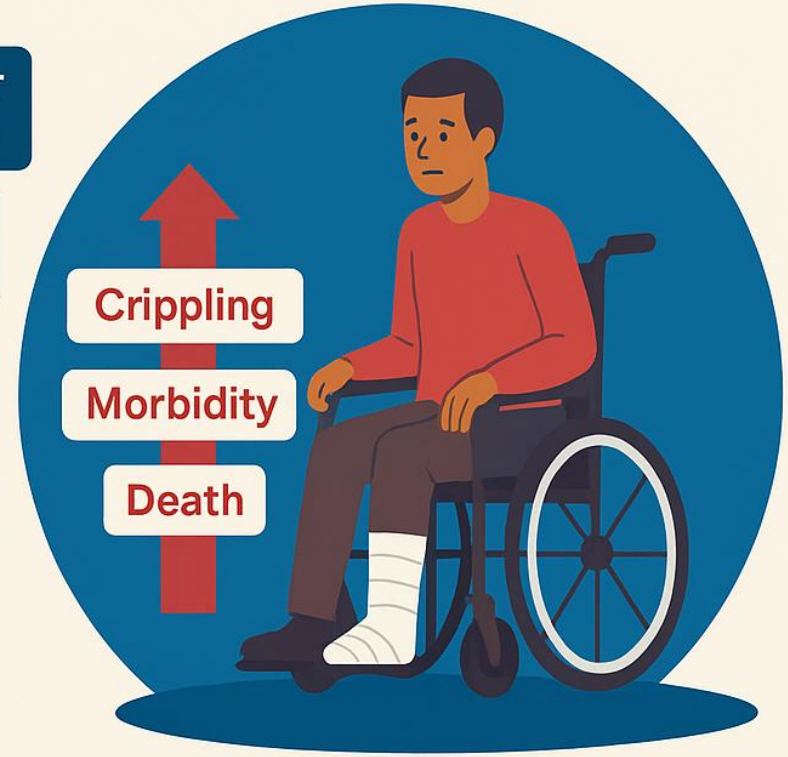
Herzog RW, Kaczmarek R, High KA. Gene therapy for hemophilia - From basic science to first approvals of "one-and-done" therapies. Mol Ther. 2025 May 7;33(5):2015-2034. doi: 10.1016/j.ymthe.2025.03.043.

15%

Two Worlds

85%



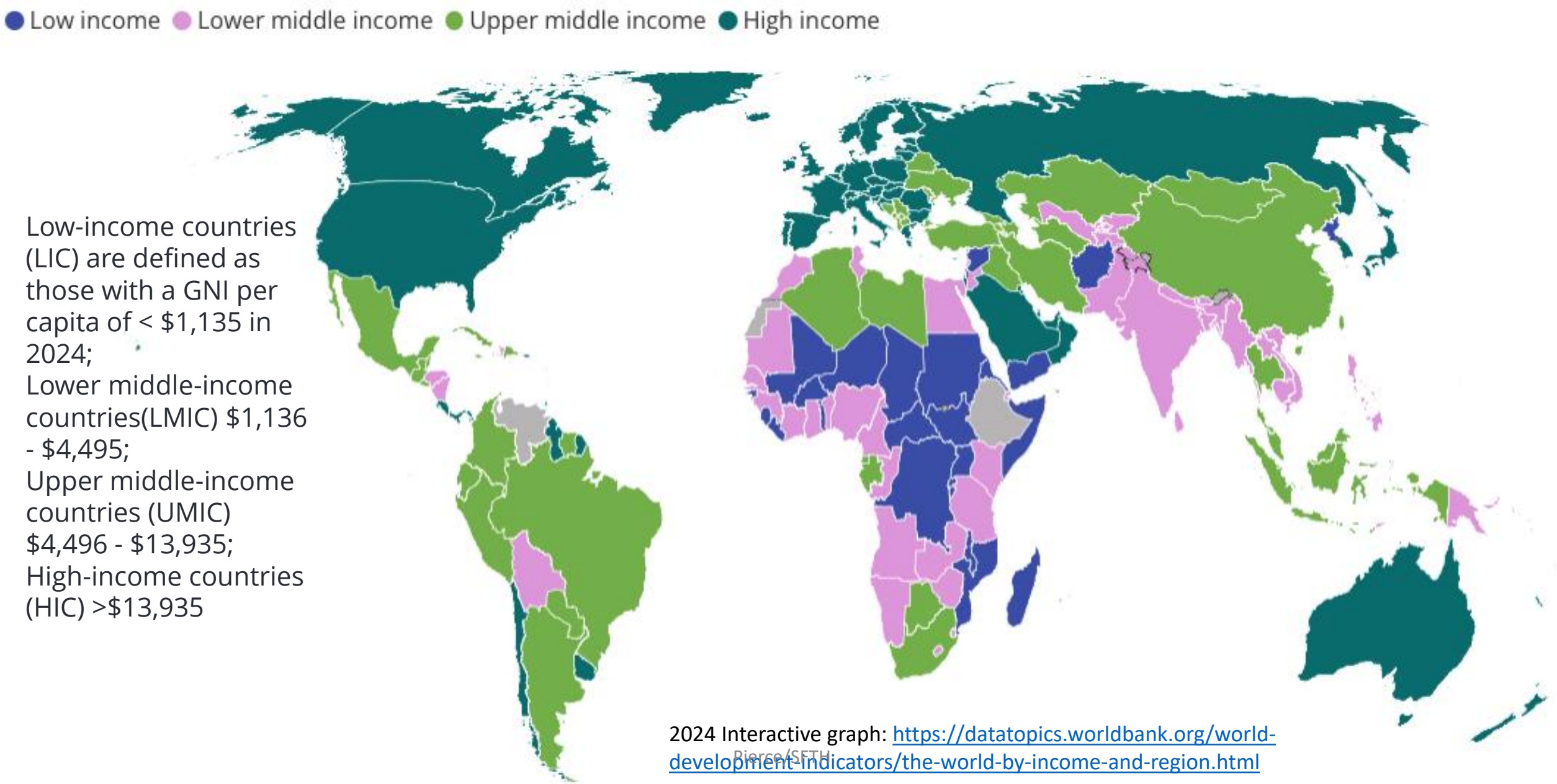


High-income countries
Hemophilia-free mind

Lower-income countries
Lower quality of life

Hermans C, Pierce GF. Therapeutic Innovations in Hemophilia: The Essential Role of a Positive Reinvestment Cycle. Blood Adv. 2025 Jul 1:bloodadvances.2025016497. doi: 10.1182/bloodadvances.2025016497.

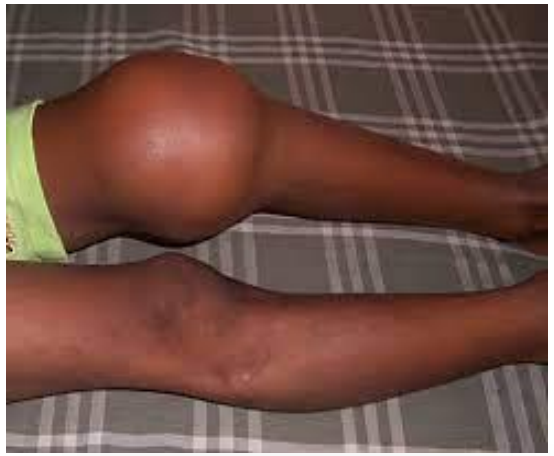
The World By Income

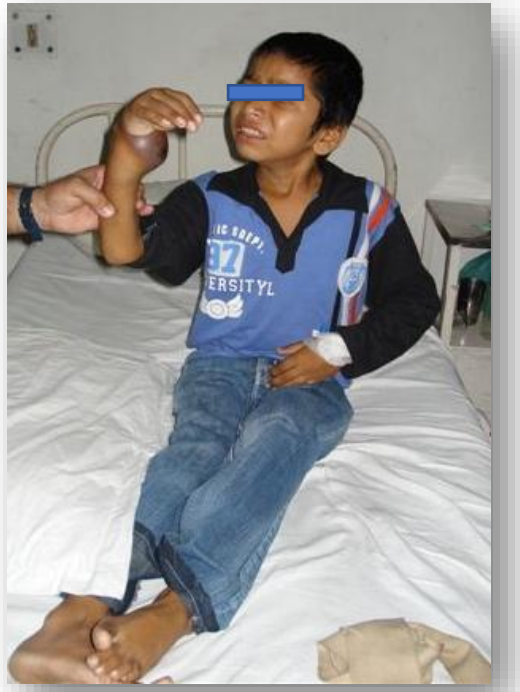


Low-income countries (LIC) are defined as those with a GNI per capita of < $1,135 in 2024;
Lower middle-income countries(LMIC) $1,136 - $4,495;
Upper middle-income countries (UMIC) $4,496 - $13,935;
High-income countries (HIC) >$13,935

2024 Interactive graph: https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html

The Human Face and the Reality of Uncertainty





- These two worlds have different Benefit-Risk for new therapies, including gene therapy

85%

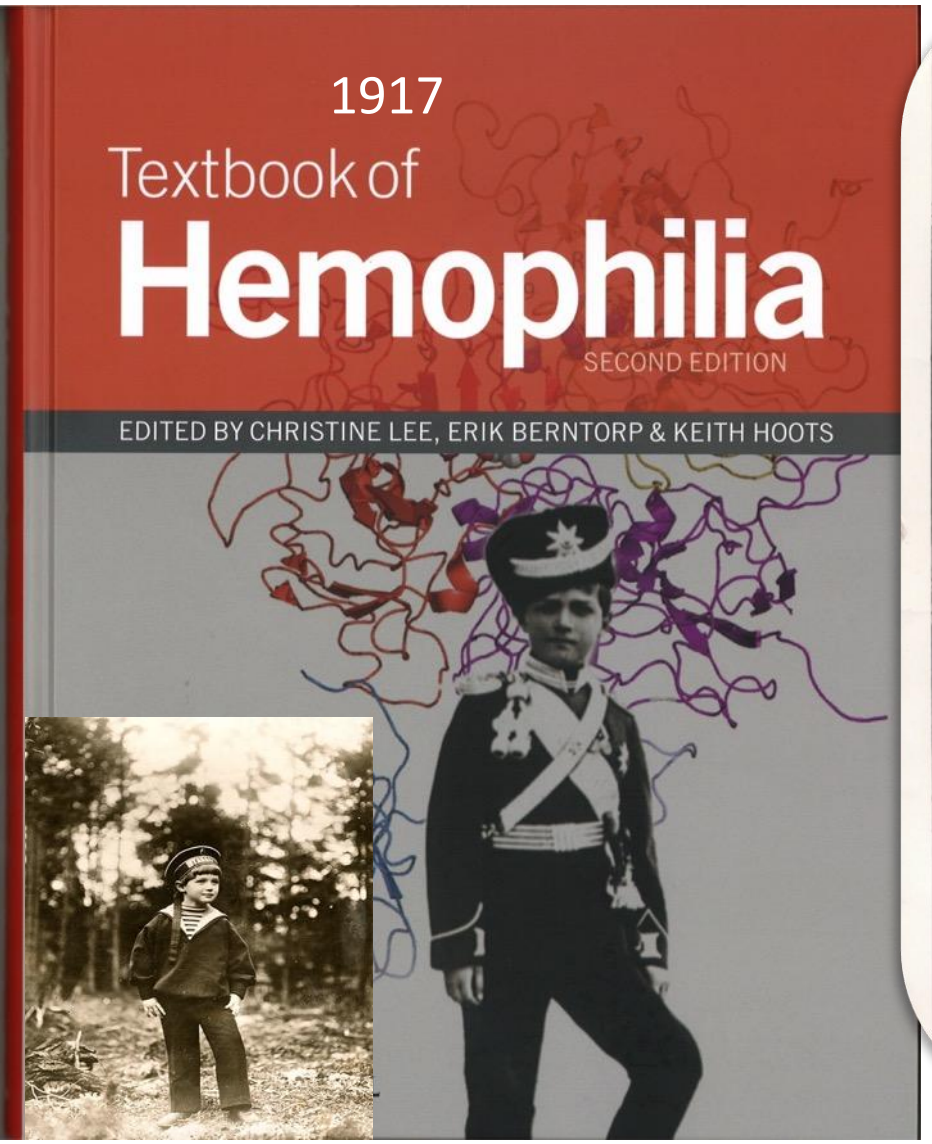
On-demand therapy… sometimes

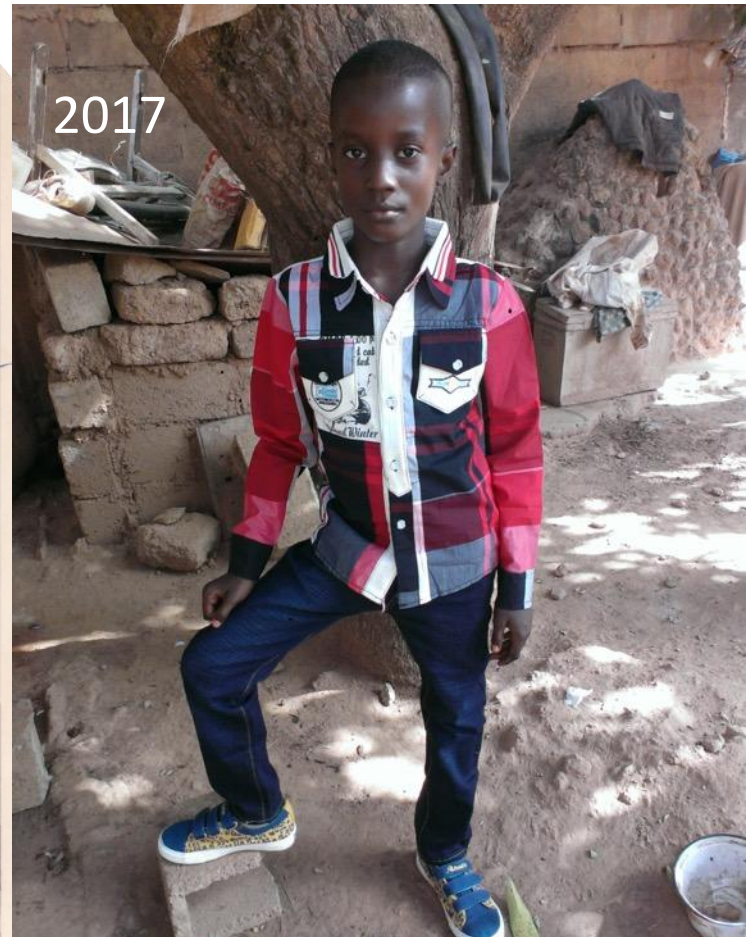
15%

EHL prophylaxis

Pierce/SFTH

Nothing Has Changed in 100 Years in Low Income Countries

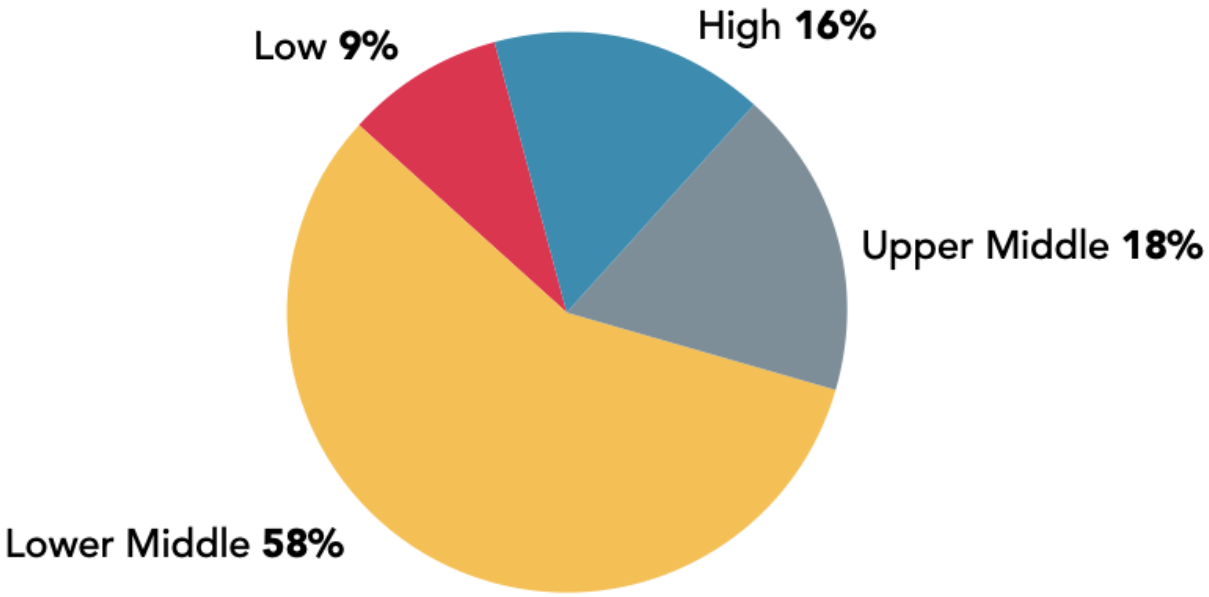




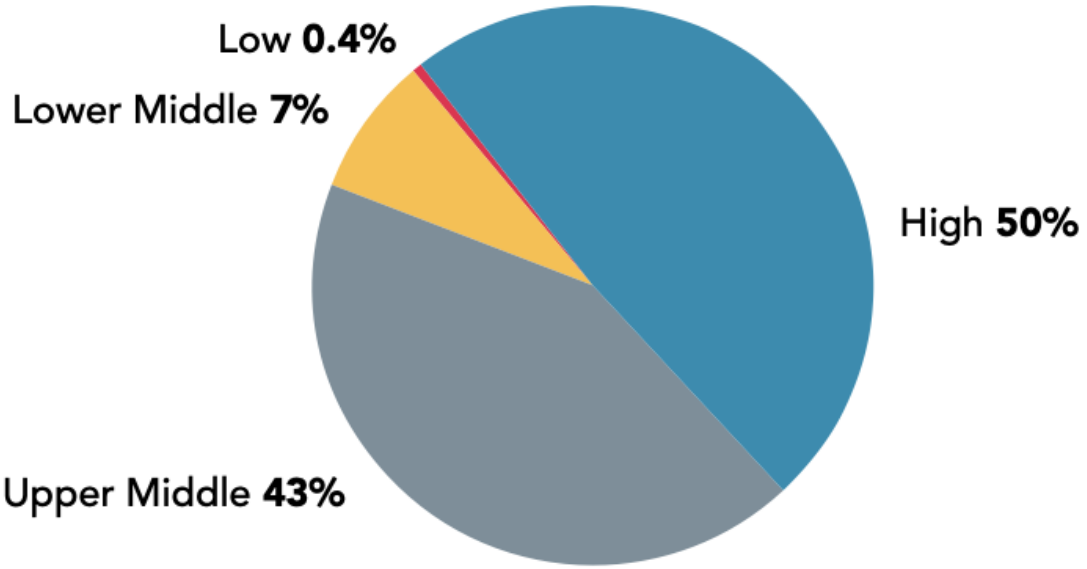
Or 100 years later…

Health Inequity in FVIII Numbers

Population by gross national income



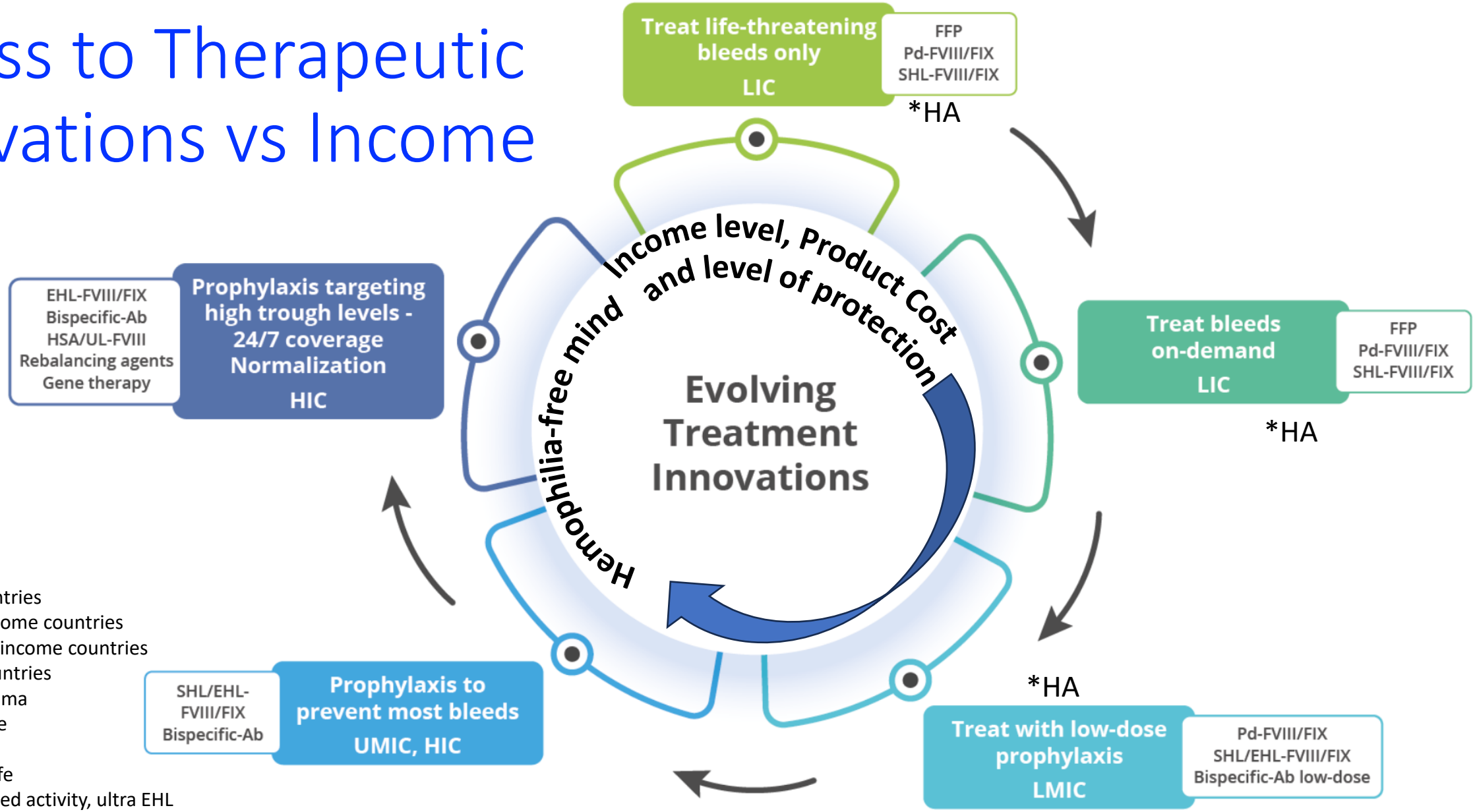
Total FVIII IU by gross national income



- HIC is 16% of population and uses 50% of product
- LIC is 9% of population and uses 0.4% of product
- LMIC is 58% of population and uses 7% of product

WFH Annual Global Survey 2023, https://www1.wfh.org/publications/files/pdf-2525.pdf

Access to Therapeutic Innovations vs Income



LIC, low income countries
LMIC, low middle income countries
UMIC, upper middle income countries
HIC, high income countries
FFP, fresh frozen plasma
SHL, standard half life
Pd, plasma-derived
EHL, extended half life
HSA/UL, high sustained activity, ultra EHL
HA, Humanitarian Aid

Modified from Hermans C, Pierce GF. Therapeutic Innovations in Hemophilia: The Essential Role of a Positive Reinvestment Cycle. Blood Adv. 2025 Jul 1:bloodadvances.2025016497. doi: 10.1182/bloodadvances.2025016497.

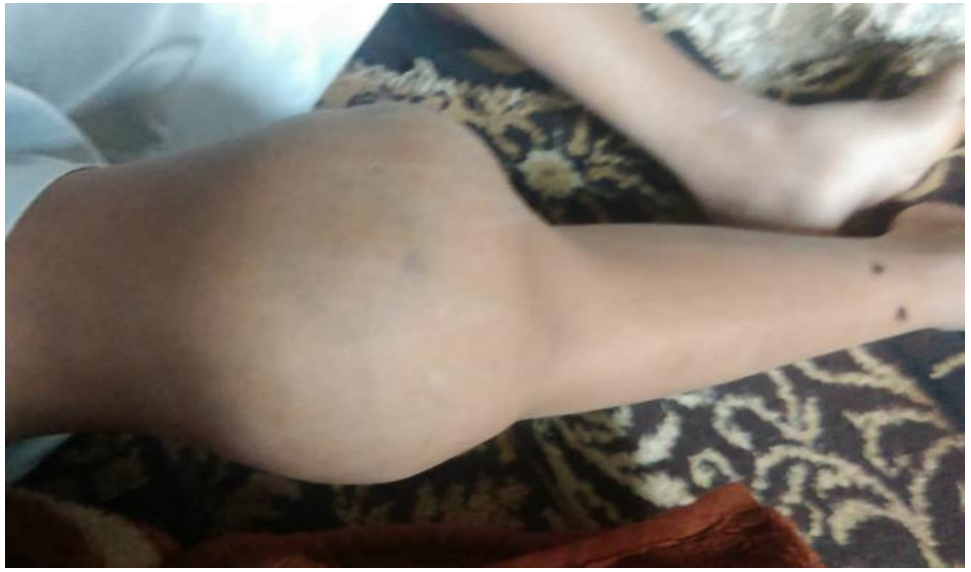
Towards Equity: the Humanitarian Aid Program

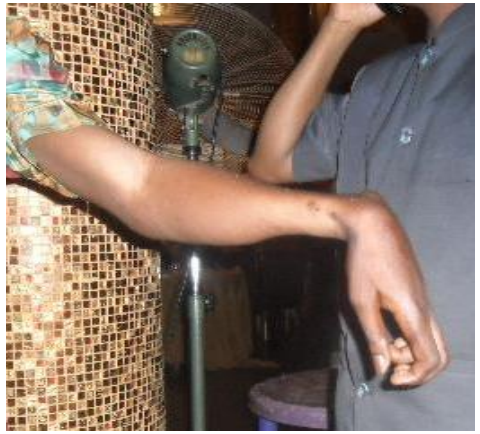
- A vital program that equally **treats and educates**
- **>350M** IU/year CFC, EHL, mimetic distributed to **>70** countries and **>30K** patients free, thanks to sponsors
  - (Sanofi-Sobi, Bayer, CSL, Chugai-Genentech-Roche, Grifols, Takeda, Hemophilia of Georgia)
  - Countless lives saved, hundreds of HCPs trained and patients taught how to treat hemophilia
  - All major pharmas except 2 are donating
  - Most treatment **not** at level of HICs; patients outside major cities difficult access
- A critical stopgap, but **not** the long term solution

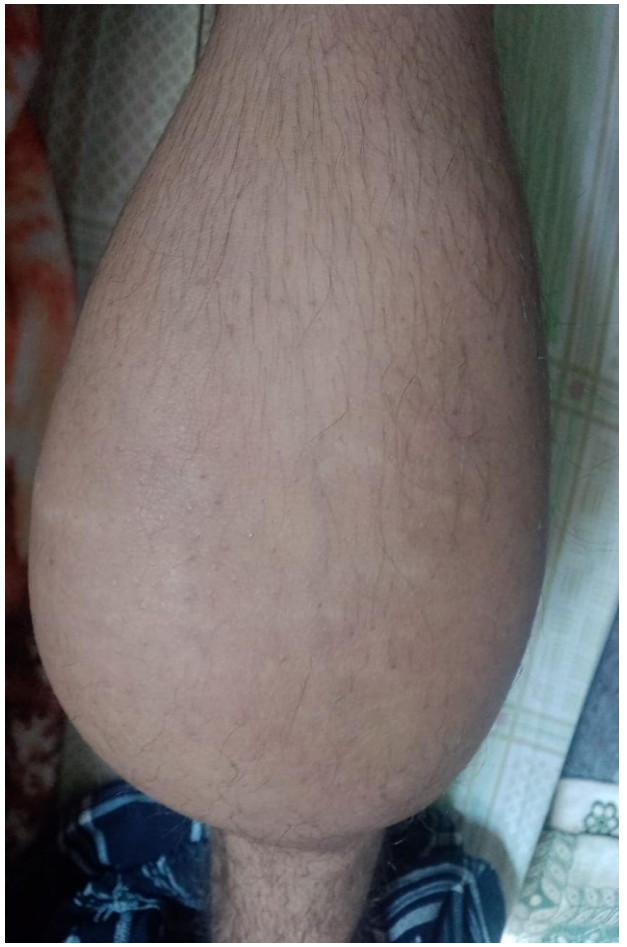
WFH HUMANITARIAN AID PROGRAM

Pierce GF, M Adediran, S Diop, AL Dunn, M El Ekiaby, R Kaczmarek, BA Konkle, SW Pipe, MW Skinner, LA Valentino, F Robinson, G Ampartzidis, J Martin, A Haffar. Achieving access to haemophilia care in low-income and lower-middle-income countries: expanded Humanitarian Aid Program after 5 Years. *Lancet Haematology*. 2022; 9:e689-e697. doi: 10.1016/S2352-3026(22)00209-5.

Cambodia, Yemen, Morocco, Nigeria







Pseudotumors, compartment syndromes (Volkmann’s contracture) still cause disability and death

Pune, India, 2018

Bali, 2017

Achieving access to haemophilia care in low-income and lower-middle-income countries:

Expanded Humanitarian Aid Program of the World Federation of Hemophilia after 5 years

Glenn F Pierce, Megan Adediran, Saliou Diop, Amy L Dunn, Magdy El Ekiaby, Radoslaw Kaczmarek, Barbara A Konkle, Steven W Pipe, Mark W Skinner, Leonard A Valentino, Fiona Robinson, Georgios Ampartzidis, Jayson Martin, Assad Haffar

Lancet Haematology 2022; 9: e689–97

As important as access is training and education

WFH HUMANITARIAN AID PROGRAM

The Unresolved Impasse to Growing Health Inequity

Innovation-driven evolution toward a Hemophilia-free mind

Exciting times for the 15%

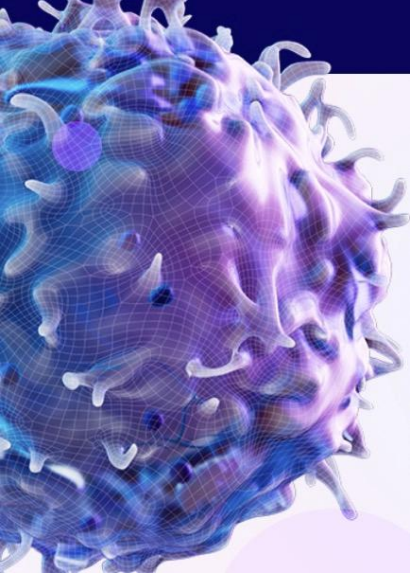
Shared, informed decision making

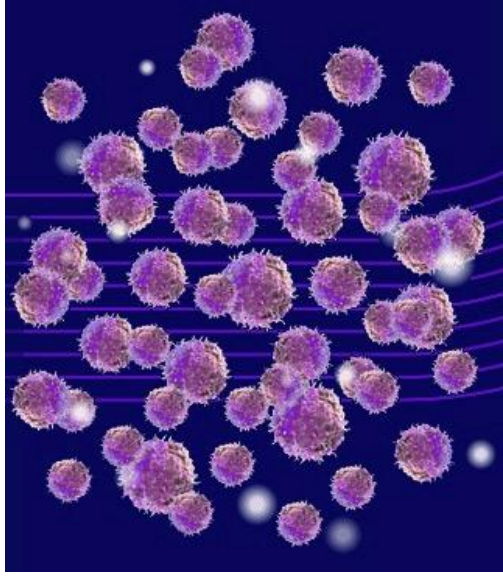
Priority pharma focus-HIC

85% are invisible

Change agents needed

Minimal focus LIC<LMIC<UMIC





Thank you

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