Personalized Medicine and Emerging Treatments

Glenn Pierce MD, PhD

VP Medical, World Federation of Hemophilia

25 August 2023
Pullman on the Park Melbourne

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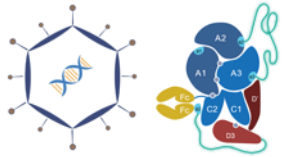
Treatment for Hemophilia Rapidly Advances

(for the 15%)

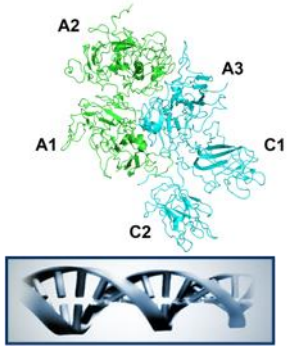


Gene therapy and an **ultra EHL FVIII**[4,5] approved for use. Additional nonfactor therapies under **clinical investigation**[6]

2022 and the future

EHL FVIII/FIX products and a **nonfactor FVIII mimetic therapy** introduced[3]

2000s to 2010s



Factor VIII /IX cloned and **recombinant FVIII/FIX products** introduced[2]

Prophylaxis standard of care

1980s to 1990s

Cryoprecipitate and fresh frozen plasma and later **lyophilized products** introduced[1,2]

1960s to 1970s

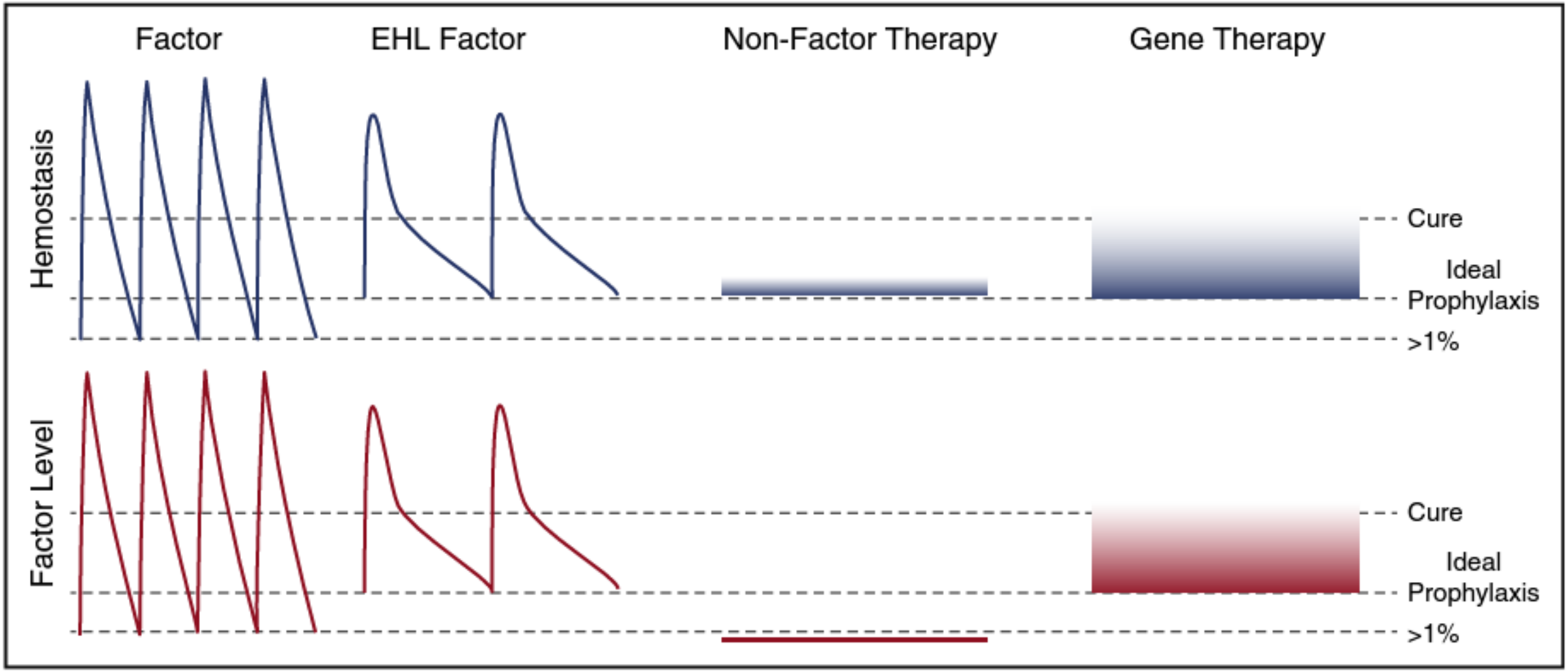
People with hemophilia A typically **did not reach adulthood**[1]

1940s

EHL, extended half-life; FVIII, factor VIII: FIX, factor IX.

1. Skinner MW, et al. *Haemophilia*. 2020;26(1):17-24. 2. Lusher JM. In: Kaushansky K, Berliner N, eds. *50 Years in Hematology: Research That Revolutionized Patient Care*. Washington, DC: American Society of Hematology; 2008:25-27. 3. Berntorp E, et al. *Blood Reviews*. 2021;50:100852. 4. Konkle A, et al. *N Engl J Med* 2020;383(11):1018-1027. 5. Keam SJ. *Drugs*. 2023;doi: https://doi.org/10.1007/s40265-023-01866-9. 6. Lenting PJ. *Blood Adv*. 2020;4:2111–2118.

Setting the Scene



Arruda VR et al, Blood, 2017

Characteristics of approved factor VIII and IX products with extended plasma half-life

Protein name and approval year	Brand name and manufacturer	Modification/technology	Plasma half-life (h)	Time longer half-life
Efmoroctocog alfa, rFVIII (2014)	Elocta/Eloctate, Sobi	Fc-fusion	19	1.5-1.7
Eftrenonacog al, rFIX (2014)	Alprolix, Sobi	Fc-fusion	82	4.3
Rurioctocog alfa pegol, rFVIII (2015)	Adynovi/Adynovate, Baxalta/Takeda	PEGylated (2 × 20 kDa)	14.3	1.3-1.5
Albutrepenanocog alfa, rFIX (2016)	Idelvion, CSL Behring	Albumin-fusion	101	5.3
Nanocog beta pegol, rFIX (2017)	Refixia, Novo Nordisk	GlycoPEGylated (40 kDa)	93	5.8
Damoctocog alfa pegol, rFVIII (2018)	Jivi, Bayer	PEGylated (60 kDa)	19	1.6
Turoctocog alfa pegol, rFVIII (2018)	Esperoct, Novo Nordisk	GlycoPEGylated (40 kDa)	18.4	1.6

Fc, fragment crystallizable; PEG, polyethylene glycol; rFVIII, recombinant factor VIII; rFIX, recombinant factor IX.

Mannucci PM. Hemophilia treatment innovation: 50 years of progress and more to come. J Thromb Haemost. 2023 Mar;21(3):403-412. doi: 10.1016/j.jtha.2022.12.029

Comparison of the main clinical characteristics of currently approved extended half-life FVIII vs FIX products

FVIII products	FIX products
1.5-1.7 fold increase	4-6 fold increase
Reduction of annual infusion number: 30%	**Reduction of annual infusion number: 60%**
Trough plasma levels: 2%-3%	**Trough plasma levels: 5%**
Patients with severe hemophilia A are transformed to a moderate phenotype	Patients with severe hemophilia B are transformed to a mild phenotype

Translates to: Treatment 2x/week Once every 1-2 weeks

Modified from Mannucci PM. Hemophilia treatment innovation: 50 years of progress and more to come. J Thromb Haemost. 2023 Mar;21(3):403-412. doi: 10.1016/j.jtha.2022.12.029

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2018 VOL. 379 NO. 9

Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors

J. Mahlangu, J. Oldenburg, I. Paz-Priel, C. Negrier, M. Niggli, M.E. Mancuso, C. Schmitt, V. Jiménez-Yuste, C. Kempton, C. Dhalluin, M.U. Callaghan, W. Bujan, M. Shima, J.I. Adamkewicz, E. Asikanius, G.G. Levy, and R. Kruse-Jarres

ABSTRACT

BACKGROUND

Emicizumab is a bispecific monoclonal antibody that bridges activated factor IX and factor X to replace the function of missing activated factor VIII, thereby restoring hemostasis. In a phase 3, multicenter trial, we investigated its use as prophylaxis in persons who have

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Mahlangu at the Faculty of Health Sci-

N Engl J Med 2018;379:811-22.
DOI: 10.1056/NEJMoa1803550

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A

Annette von Drygalski, M.D., Pharm.D., R.M.S.K., Pratima Chowdary, M.D., Roshni Kulkarni, M.D., Sophie Susen, M.D., Ph.D., Barbara A. Konkle, M.D., Johannes Oldenburg, M.D., Davide Matino, M.D., Robert Klamroth, M.D., Ph.D., Angela C. Weyand, M.D., Victor Jimenez-Yuste, M.D., Ph.D., Keiji Nogami, M.D., Stacey Poloskey, M.D., Bent Winding, M.D., Annemieke Willemze, M.D., Ph.D., and Karin Knobe, M.D., Ph.D., for the XTEND-1 Trial Group*

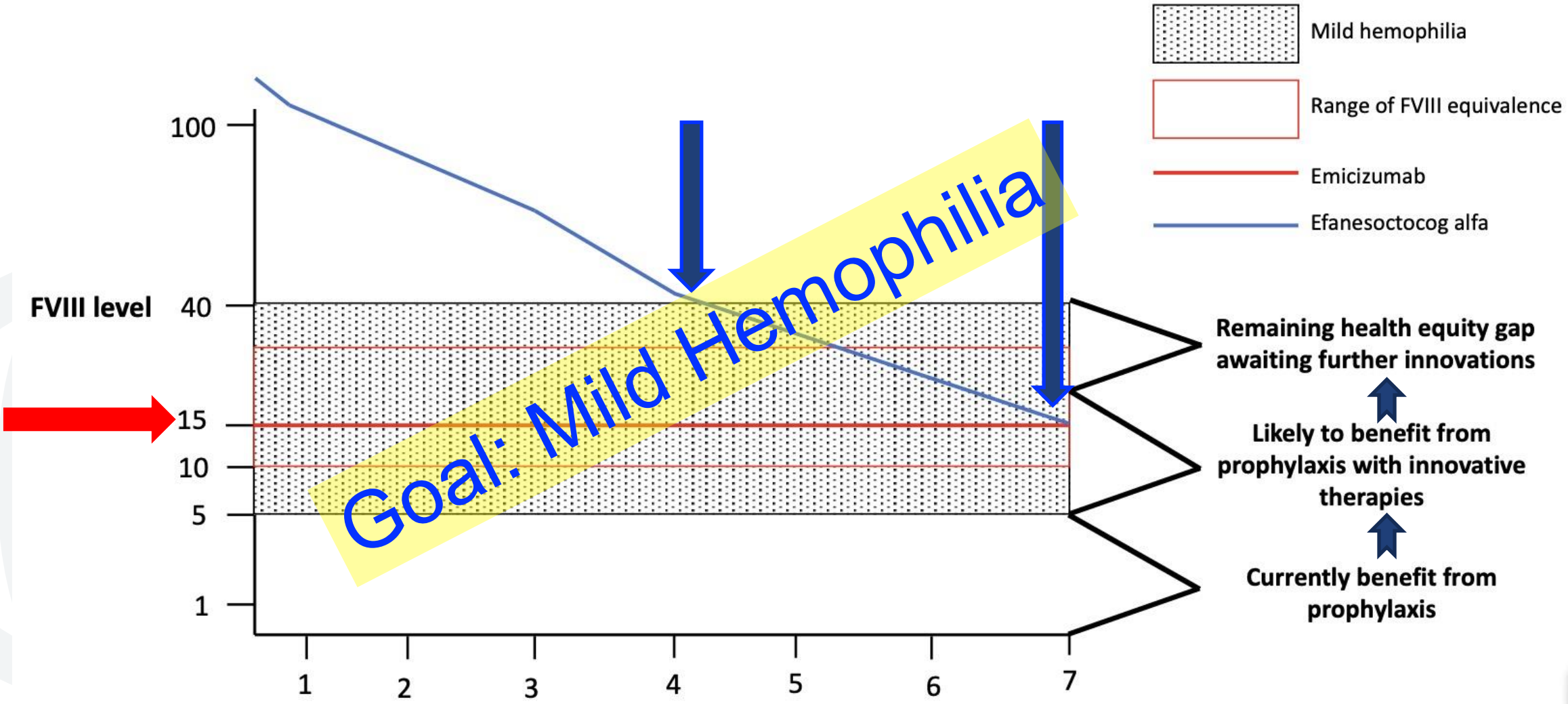
ABSTRACT

BACKGROUND

Efanesoctocog alfa provides high sustained factor VIII activity by overcoming the von Willebrand factor–imposed half-life ceiling. The efficacy, safety, and pharmacokinetics of efanesoctocog alfa for prophylaxis and treatment of bleeding epi-

N Engl J Med 2023;388:310-8.
DOI: 10.1056/NEJMoa2209226

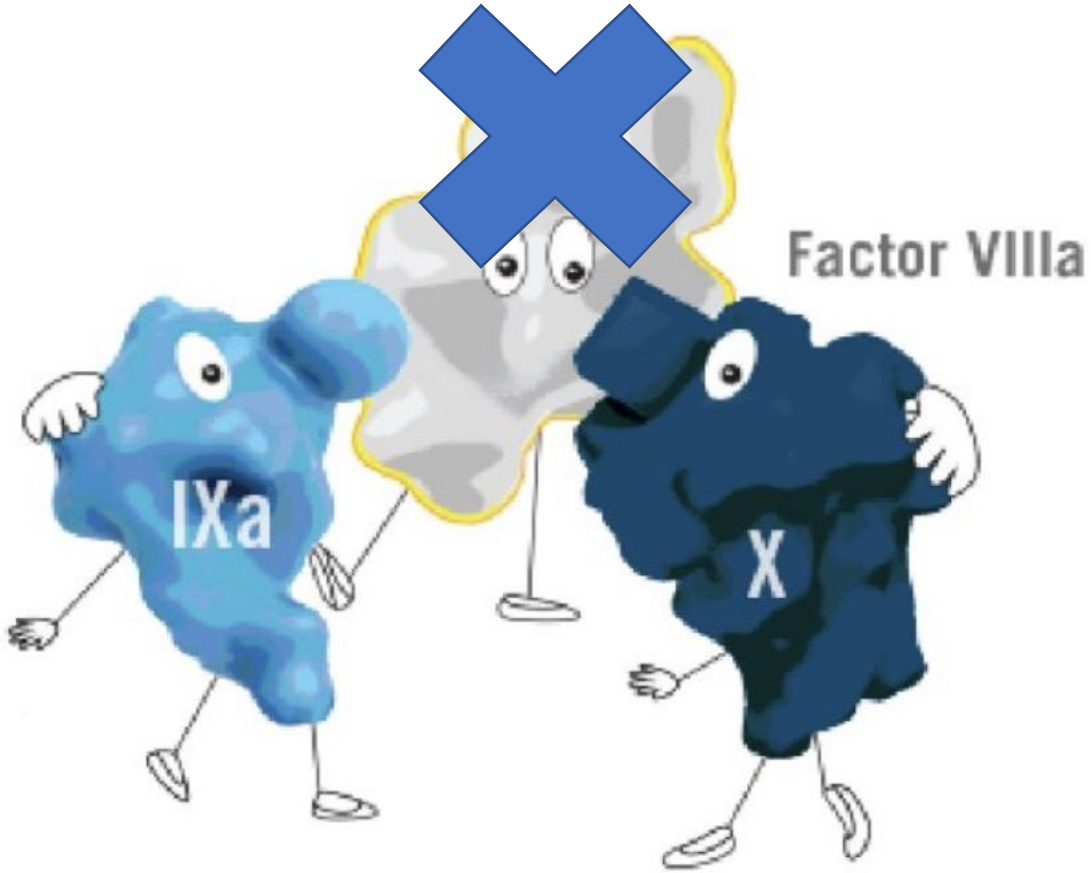
What Can Be Achieved in 2023?



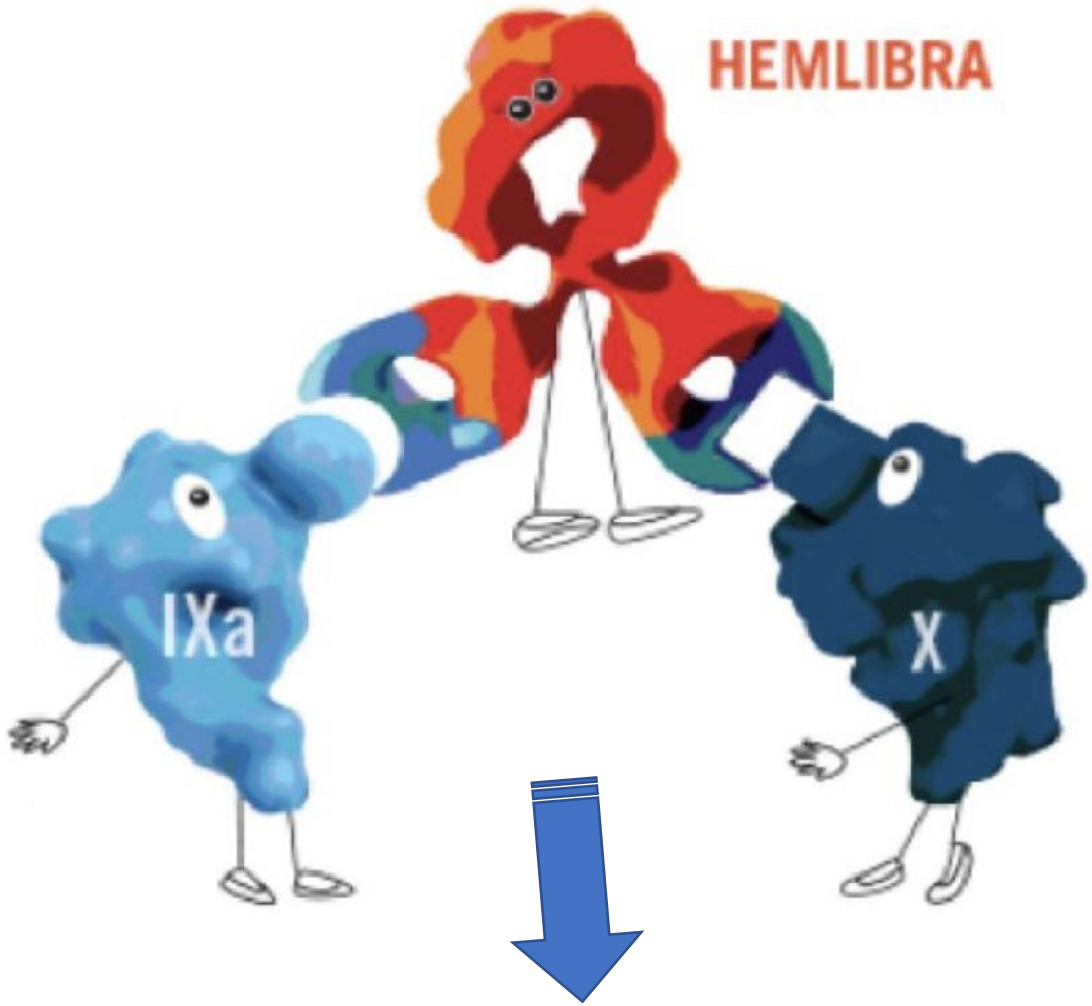
Weyand, Malec, Pipe 2023

WFH Treatment Guidelines, Hemophilia 2020

How FVIII and Emicizumab Work



Weak Clot Formation



“Normal” Coagulation ~15% FVIII equivalent

Annualized bleeding rates (ABR) and zero bleed rates with emicizumab dosing regimens in patients with severe hemophilia A with and without inhibitors in the context of the HAVEN pivotal studies

Study	Dosing regimen	ABR (median)	Zero bleed rates
HAVEN 1 Adults and adolescents with inhibitors	1×W prophylaxis (1.5 mg/kg) (n = 35) No prophylaxis (n = 18)	2.9 23.3	63% 6%
HAVEN 2 Children with inhibitors	1×W prophylaxis (1.5 mg/kg) (n = 68) E2W prophylaxis (3.0 mg/kg) (n = 10) E4W prophylaxis (6 mg/kg) (n = 10)	0.3 0.2 2.2	76.9% 90% 60%
HAVEN 3 Adults and adolescents without inhibitors	1×W prophylaxis (1.5 mg/kg) (n = 36) E2W prophylaxis (3.0 mg/kg) (n = 35) No prophylaxis (n = 18)	1.5 1.3 38.2	50% 40% 0
HAVEN 4 Adults and adolescents with or without inhibitors	E4W prophylaxis (6 mg/kg) (n = 41)	4.5	NR

1×W, once weekly; ABR, annualized bleeding rate; E2W, every 2 weeks; E4W, every 4 weeks; NR, not reported.

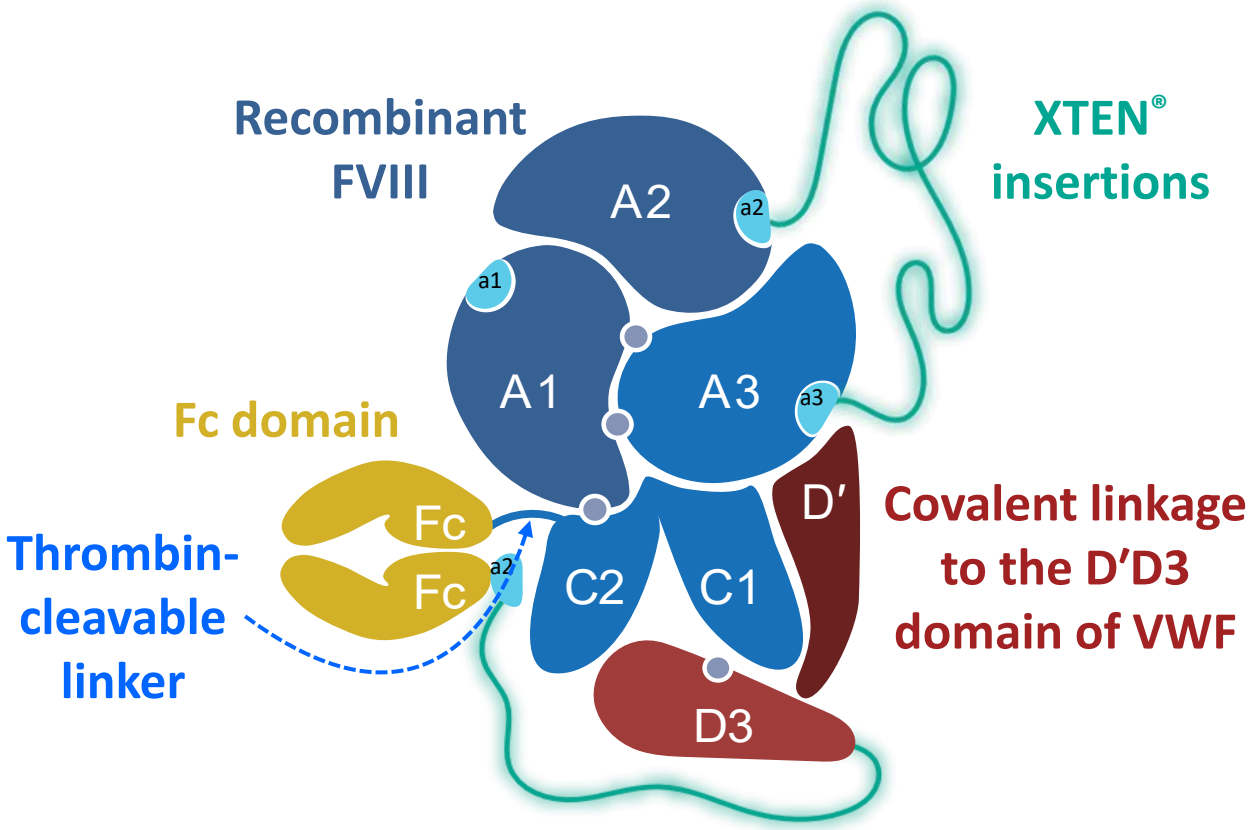
Mannucci PM. Hemophilia treatment innovation: 50 years of progress and more to come. J Thromb Haemost. 2023 Mar;21(3):403-412. doi: 10.1016/j.jtha.2022.12.029

Efanesoctocog Alfa: A New Class of FVIII Replacement Designed to Provide High Sustained FVIII Activity Levels

Efanesoctocog alfa is a novel fusion protein that **overcomes the VWF-imposed half-life ceiling**[1,2]

In a Phase 1 sequential PK study, efanesoctocog alfa had **a 3–4-fold longer half-life** than standard half-life and extended half-life rFVIII product comparators[3]

T1/2 =47 hours, weekly dosing trough average of 15% FVIII



a1, a2, and a3, acidic region 1, 2, and 3; FVIII, factor VIII; Fc, fragment crystallizable; PK, pharmacokinetic; rFVIII, recombinant factor VIII; VWF, von Willebrand factor.

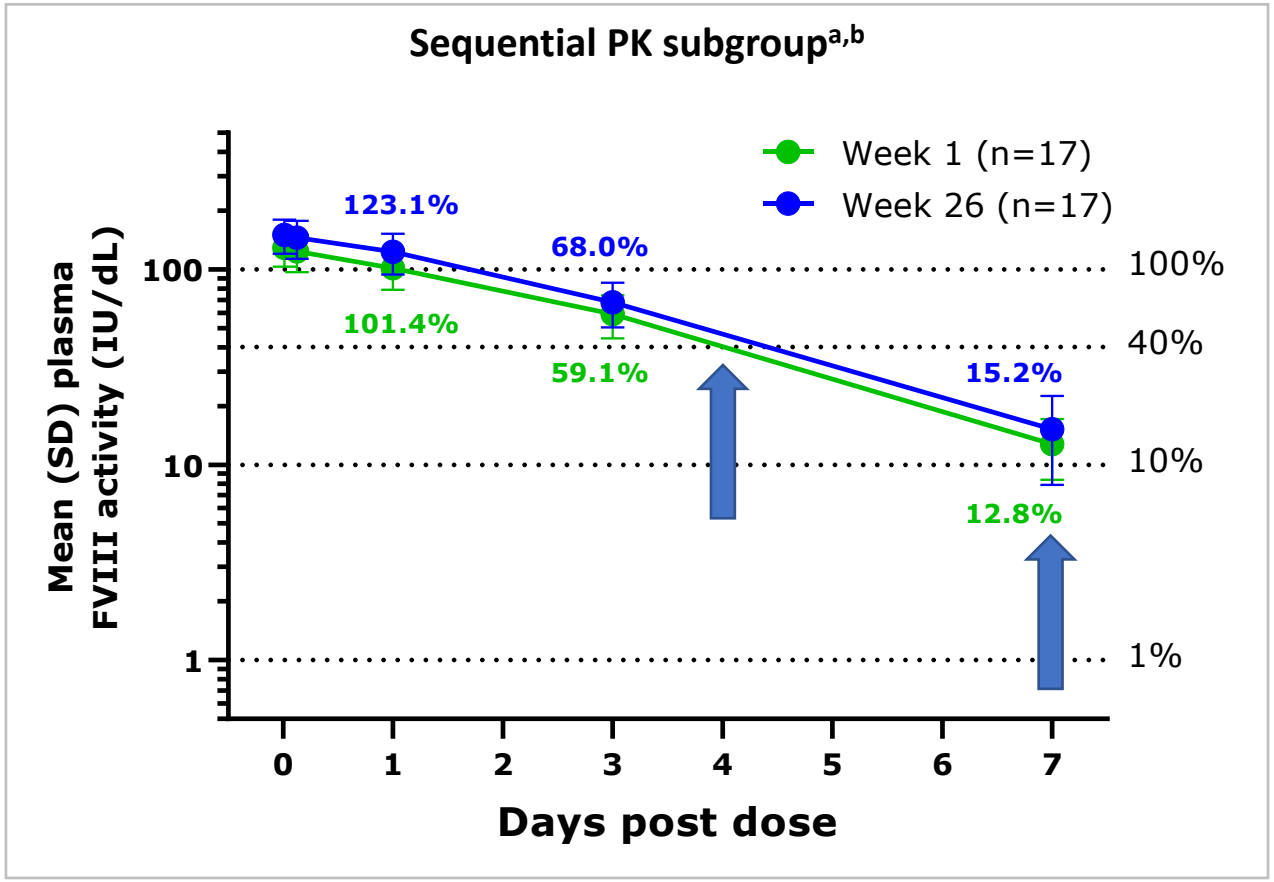
1. Chhabra ES, et al. *Blood.* 2020;135(17):1484-1496. 2. Konkle BA, et al. *N Engl J Med*. 2020;383(11):1018-1027. 3. Lissitchkov T, et al. Oral Presentation, WFH 2022. von Drygalski A, Chowdary P, Kulkarni R, Susen S, Konkle BA, Oldenburg J, Matino D, Klamroth R, Weyand AC, Jimenez-Yuste V, Nogami K, Poloskey S, Winding B, Willemze A, Knobe K; XTEND-1 Trial Group. Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A. N Engl J Med. 2023 Jan 26;388(4):310-318. doi: 10.1056/NEJMoa2209226.

Efanesoctocog Alfa Provides High Sustained FVIII Levels Throughout the Weekly Dosing Interval

Mean FVIII levels remained in the normal to near-normal range (>40 IU/dL) for ~4 days post dose, and at 15 IU/dL at Day 7

Geometric mean **half-life** (CI) at steady state was **47.0** (42.5–52.2) **hours**[a]

PK profile similar after the first dose and at Week 26



aPTT, activated partial thromboplastin time; CI, confidence interval; FVIII, factor VIII; PK, pharmacokinetics; SD, standard deviation.
[a]FVIII activity was measured with an aPTT-based one-stage clotting assay. [b]Samples were continued out to 14 days for the sequential pharmacokinetics group. The first 7 days are depicted to correspond to the once-weekly dosing regimen used for prophylaxis in XTEND-1.

von Drygalski A, Chowdary P, Kulkarni R, Susen S, Konkle BA, Oldenburg J, Matino D, Klamroth R, Weyand AC, Jimenez-Yuste V, Nogami K, Poloskey S, Winding B, Willemze A, Knobe K; XTEND-1 Trial Group. Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A. N Engl J Med. 2023 Jan 26;388(4):310-318. doi: 10.1056/NEJMoa2209226.

Conundrum, Continued

Proteins

Bispecific Mimetic MAbs

New Extended Half Life

Current Tx

Gene Therapy

Patients
Patient Advocates
Health care providers

Personal Preferences

Current Access and Availability

Access to Future Therapies

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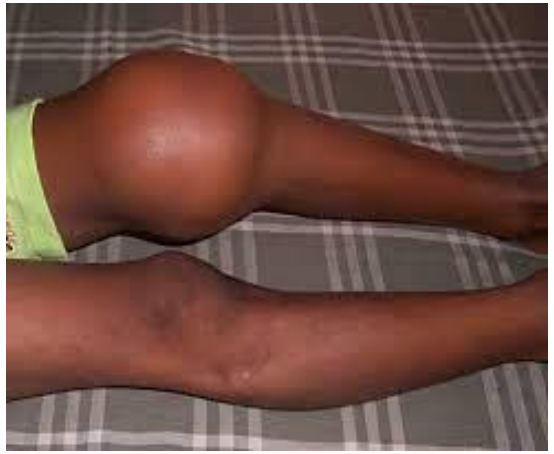
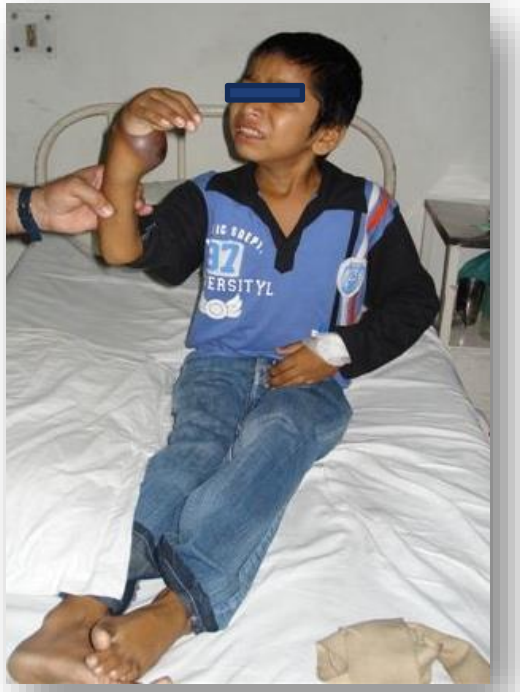
The Human Face and the Benefit-Risk Uncertainty



These two worlds have a very different Benefit-Risk consideration regarding the next frontier: gene therapy

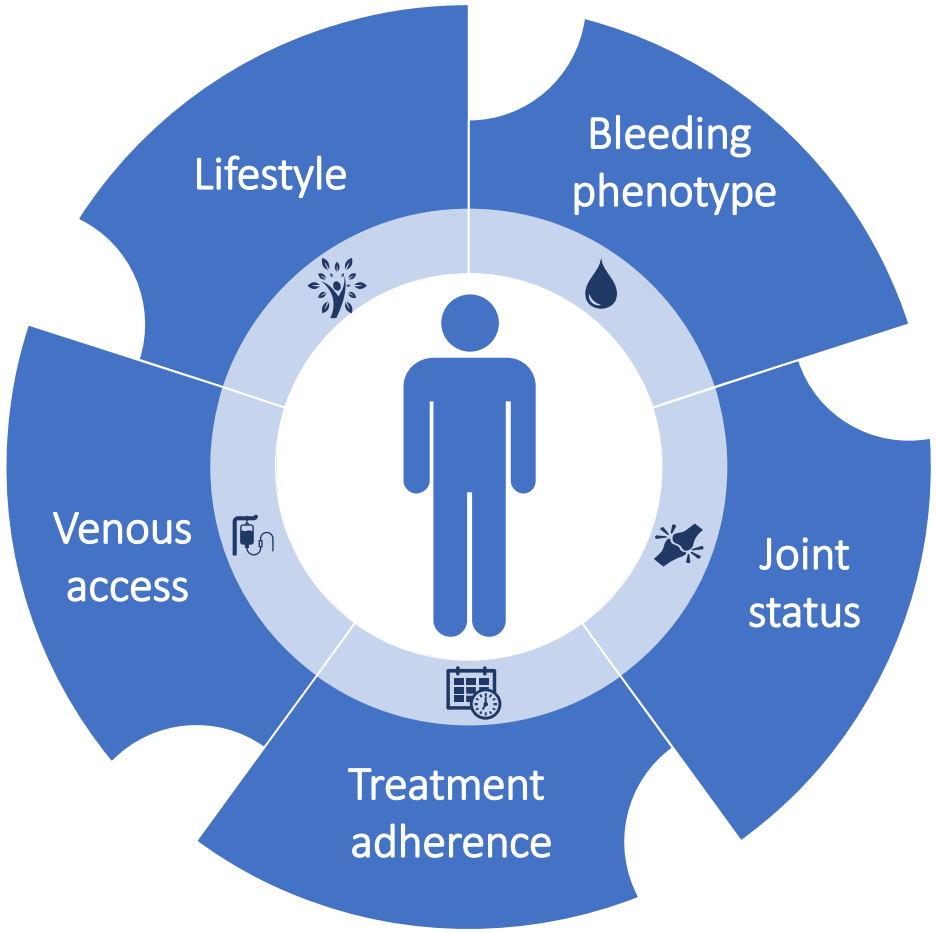


85%

15%

Patient-Oriented Algorithm for Personalized Treatment Choices

Five key objective variables:

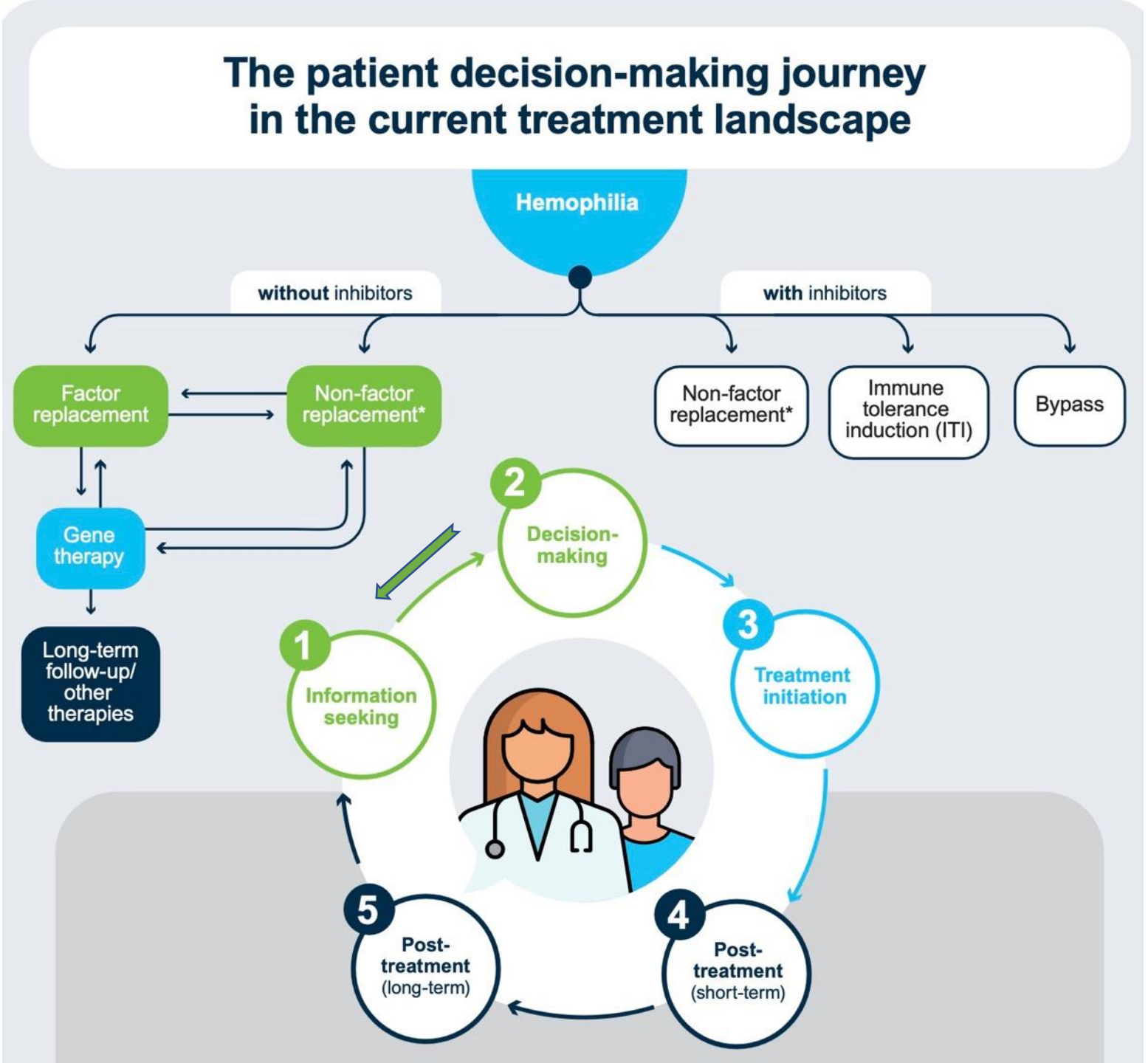


Gene therapy presents **unique considerations** in treatment decisions, including:

- Life-long treatment impact
- Benefit–risk profile difficult to quantify with current data
- Eligibility criteria
- Cost and reimbursement considerations

Hermans C., et al. Blood Rev 2022;52:100890

. Nossair F. and Thornburg C. D. Ther Adv Hematol 2018;9(8):239–4; 2



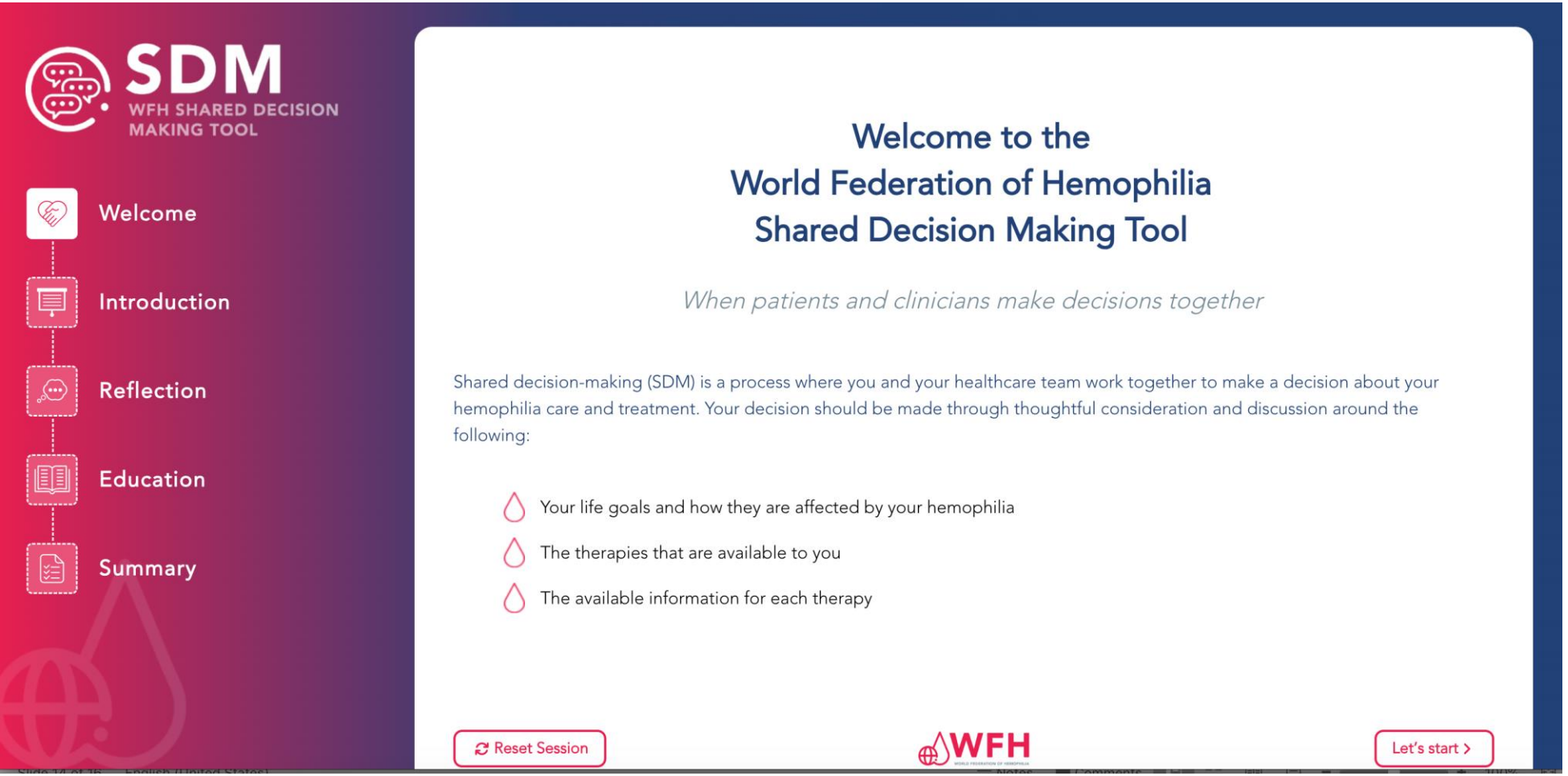
This journey should be done via a Shared Decision Making process

Wang M, Negrier C, Driessler F, Goodman C, Skinner MW. The Hemophilia Gene Therapy Patient Journey: Questions and Answers for Shared Decision-Making. Patient Prefer Adherence. 2022 Jun 9;16:1439-1447. doi: 10.2147/PPA.S355627.

WFH Shared Decision Making Tool

Now available SDM.WFH.org

Public Comment period: 1 Aug – 1 Nov 2023



SDM
WFH SHARED DECISION MAKING TOOL

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SDM
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1 **Welcome**
When patients and clinicians make decisions together

2 **Introduction**
Background information about SDM Tool

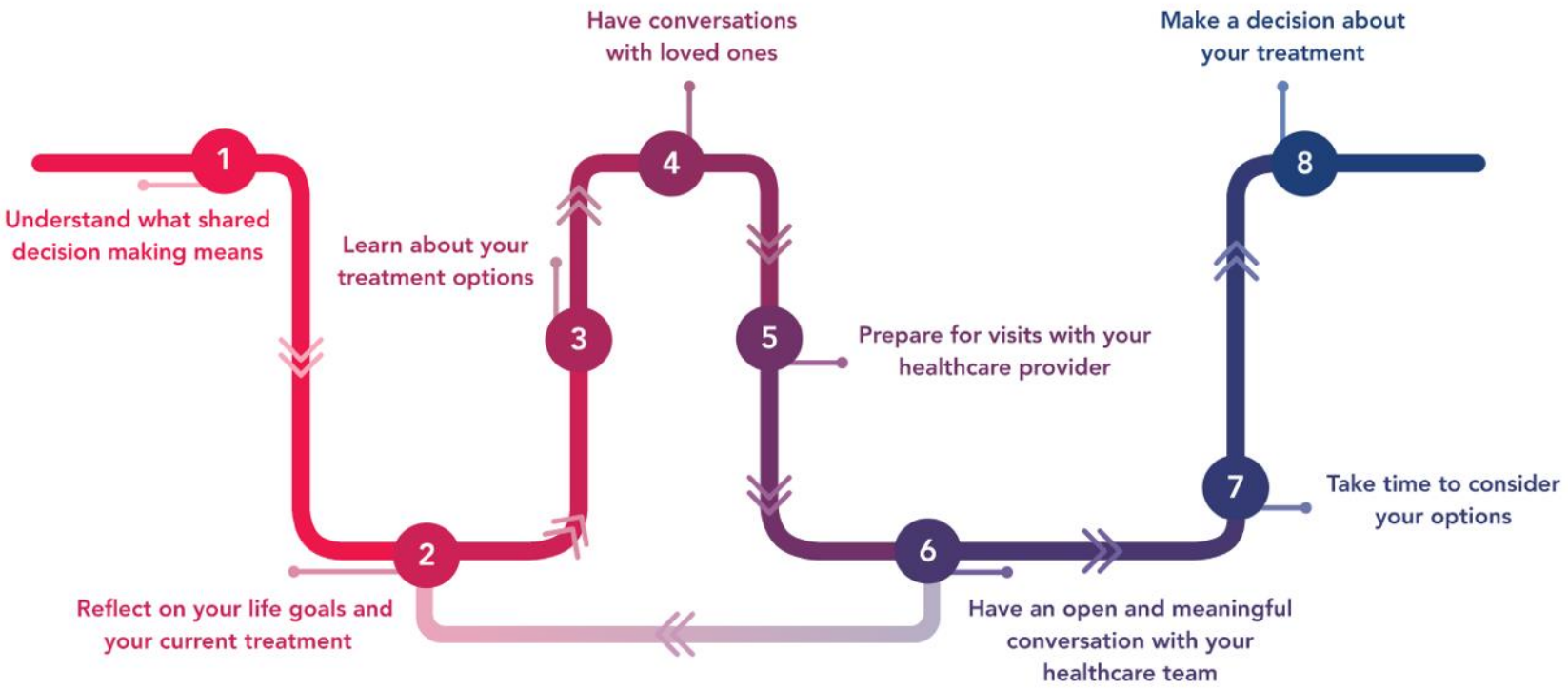
3 **Selection**
Select your type of Hemophilia

4 **SDM Content**
Landscape and new treatment choices

5 **Summary**
Bring it to your doctor

STEP-BY-STEP GUIDE IN MAKING A SHARED DECISION REGARDING YOUR TREATMENT

Note: you can move over the step numbers to display additional information



< Go back

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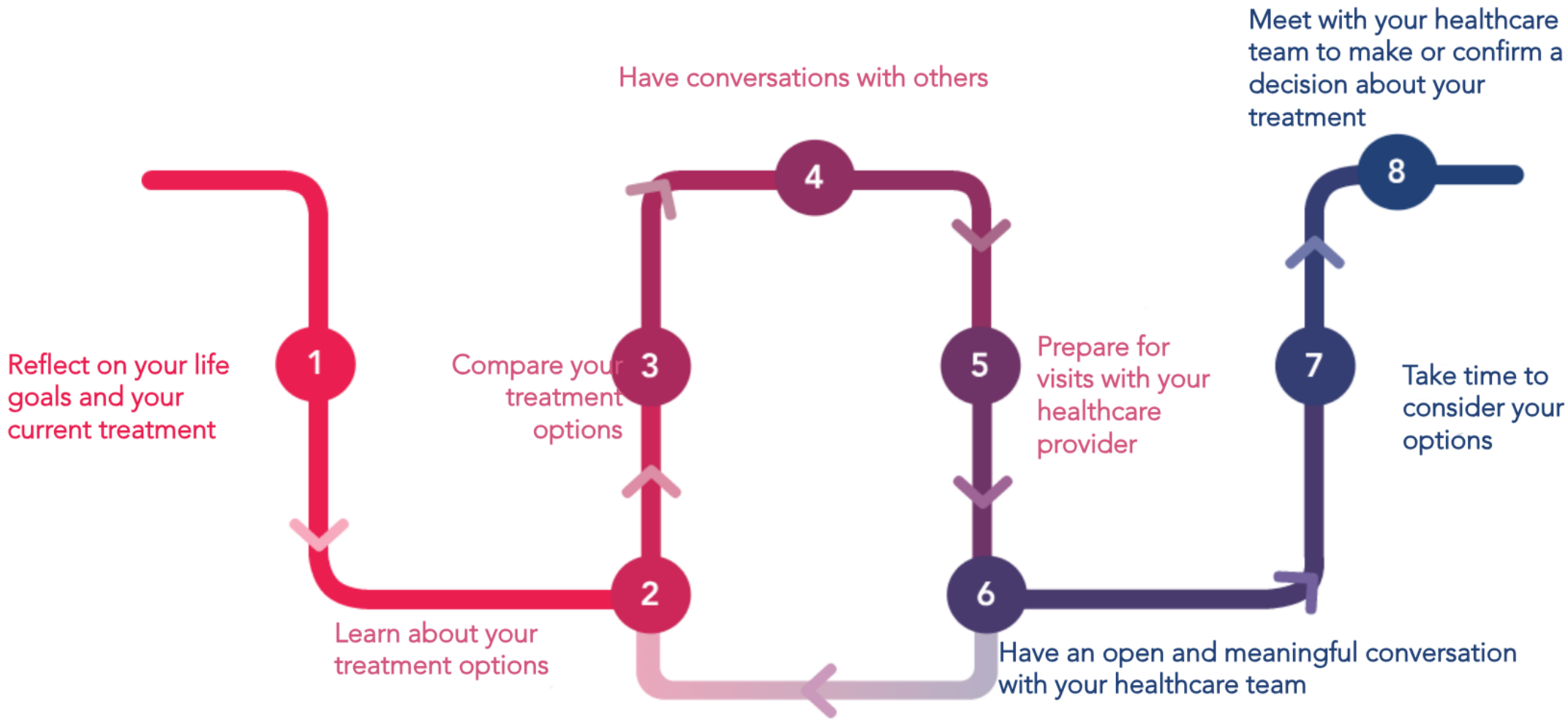
Continue >

SDM
WFH SHARED DECISION MAKING TOOL

A STEP-BY-STEP GUIDE FOR SHARED DECISION-MAKING

Note: you can move over the coloured text to display additional information

Click here to download the Step-By-Step Guide for the Healthcare Team



COMPARE KEY ATTRIBUTES OF THE MAIN TREATMENT CLASSES FOR HEMOPHILIA A

	Eligibility		Administration		Efficacy		Potential Safety Risks				Quality of Life
	Approval Status	Approved Population	Administration & Dosing Frequency	Yearly Follow-up Schedule	Treated Annual Bleed Rate	Factor Level	Hypers. Reactions	Inhibitors	Thromb. Events	Elevated Liver Enz.	Psychosocial Burden
SHL Factor Therapy	Multiple products that are widely approved	All Ages	2-4x/WEEK	1-2	0-2		✓	✓	–	–	
EHL Factor Therapy	Multiple products that are widely approved	All Ages	1-2x/WEEK	1-2	1-2		✓	✓	–	–	
Bispecific Antibody Therapy	1 product that is widely approved 1 product in phase 3	All Ages with and without inhibitors	1-4x/MONTH	1-2	<1.5		–	–	✓	–	
Hemostatic Rebalancing Therapy	1 product with limited approval 2 products in phase 3	Adults (12+) with inhibitors	24h 1x/MONTH	2	<1		✓	–	✓	–	
Gene Therapy	1 Product with limited approval	Adults with Hemophilia A		+	<1		✓	–	✓	✓	

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The technologies are complicated
The choices are complicated

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Unsolved Inequity in Bleeding Disorders Community

- Inequity
  - No treatment access
  - HemA/B vs VWD and RBD dx
  - Men vs women dx
  - Episodic vs prophylaxis access
  - Treatment for inhibitor access
  - Ortho access
  - Education and employment
  - QoL
  - Clinical trial access

- Some Solutions
  - Humanitarian aid program foundational for capacity building
  - Gene therapy - single most meaningful health equity change for LIC/LMIC/UMIC
  - Costs of manufacture minimal vis-a-vis proposed HIC charges (for once and done)
  - Vastly different risk/benefit profiles and decision making LIC/LMIC vs HIC

Will gene therapy help or harm the goal of health equity for lower socioeconomic groups?

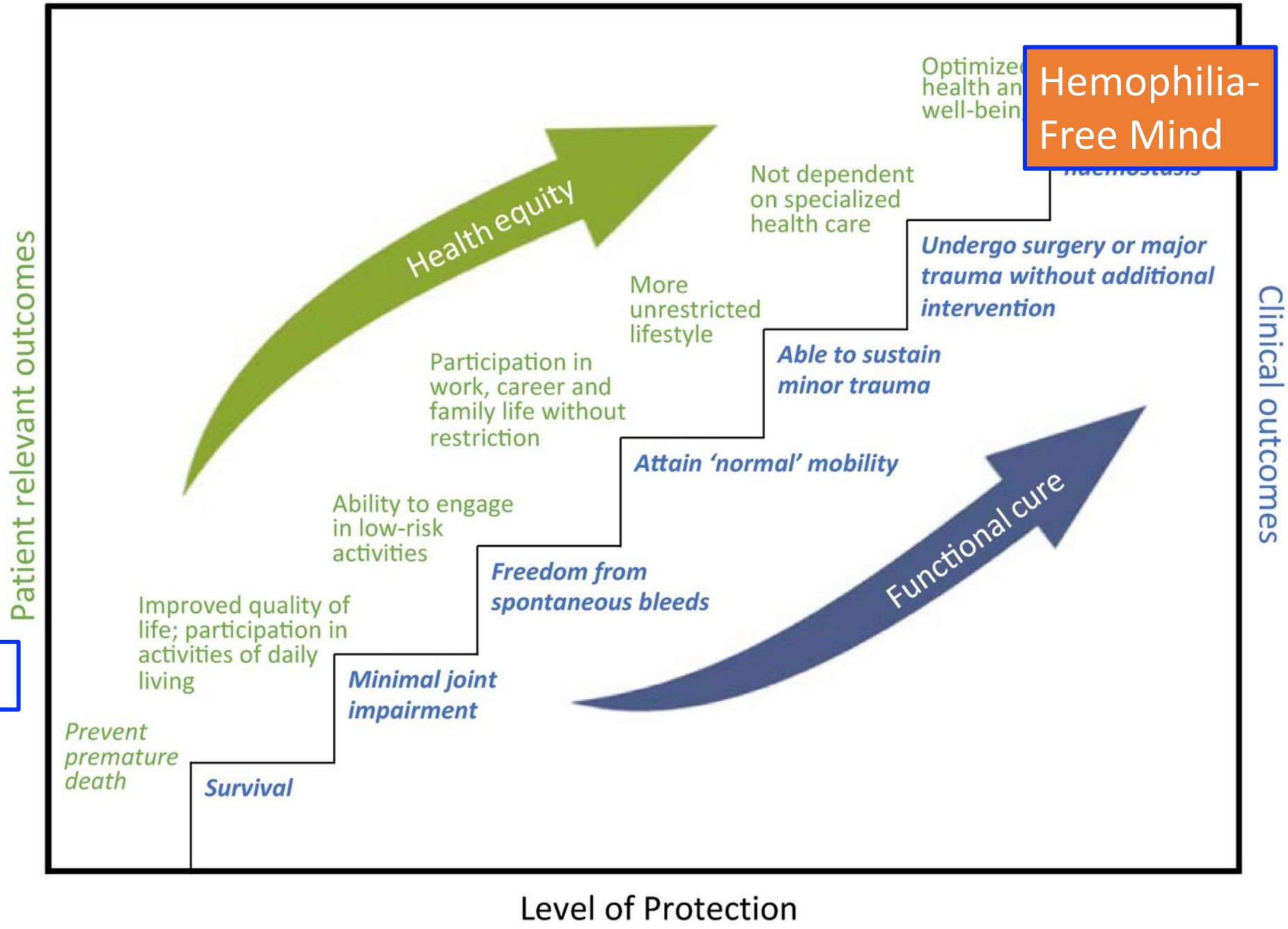
What's Next in Treatment?

- Proteins and RNA
  - Rebalancing agents- anti-TFPI antibodies (marstacimab, concizumab), SerpinPC, fitusiran (RNAi)
- Gene therapies
  - Next generation AAVs
  - Next generation non-viral gene therapies
  - Next generation gene editing
  - AAV-VWF?
  - AAV-RBD?

THE Goal

…"a 'functional cure' that achieves the goal of normal haemostasis would be transformative, eliminating any consideration of haemophilia in planning life, medical or emergency care."

= Hemophilia-free mind



MW. Skinner, D Nugent, P Wilton, B O'Mahony, G Dolan, J O'Hara, E Berntorp. Achieving the unimaginable: Health equity in haemophilia. Haemophilia 2019. 26:17-24, DOI: (10.1111/hae.13862). C Hermans, GF Pierce. Towards achieving a hemophilia-free mind. Haemophilia. 2023, in press.

THANK YOU!

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