Gene Therapy Today and Tomorrow

Glenn Pierce MD, PhD

VP Medical, World Federation of Hemophilia

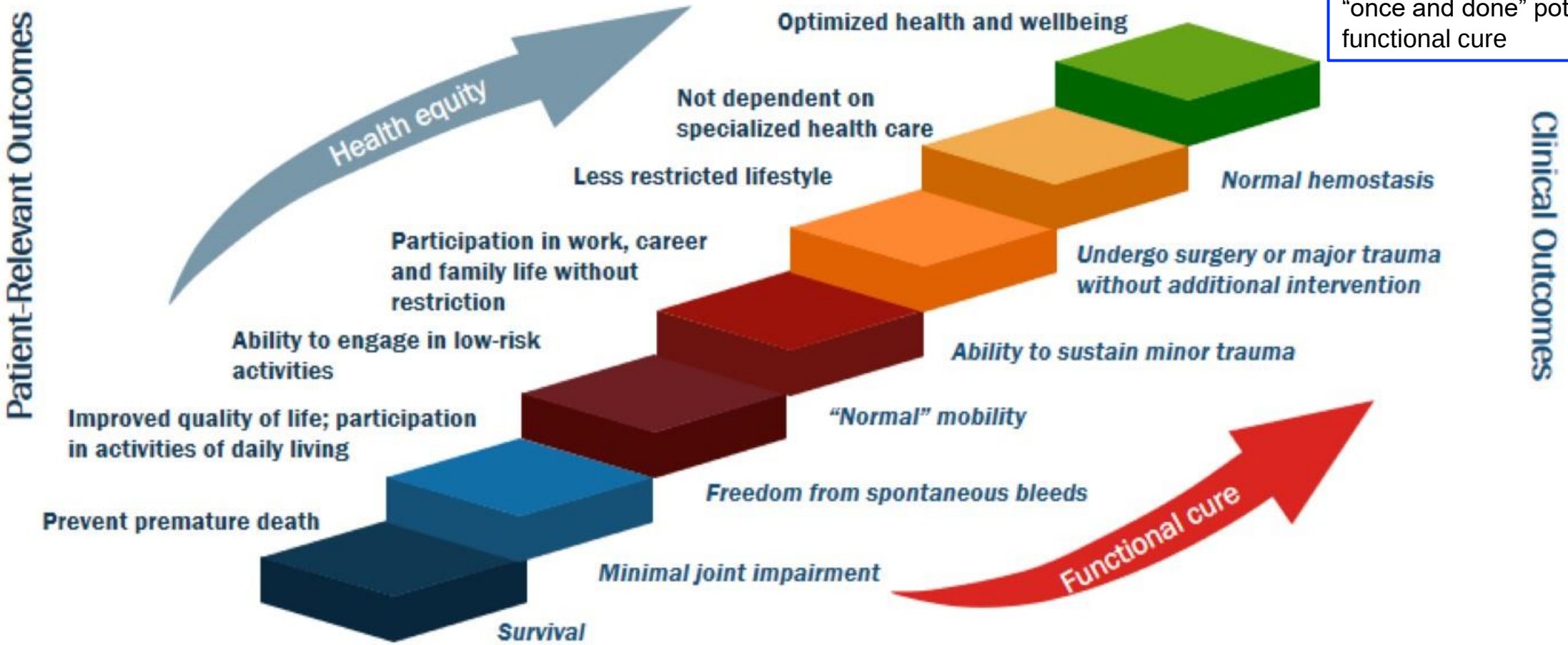
La Jolla, California, USA

Friday 25 August 2023
Pullman on the Park Melbourne

WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

The Goal of Hemophilia Management Should Be Health Equity

Gene therapy represents a “once and done” potential functional cure



Skinner MW, et al. Haemophilia 2020;26:17-24.

What Is Gene Therapy?

Factor IX (VIIII) gene (DNA) placed into a delivery vehicle (virus)
Virus enters cell, goes to nucleus
Factor IX gene makes Factor IX protein, secreted into circulation

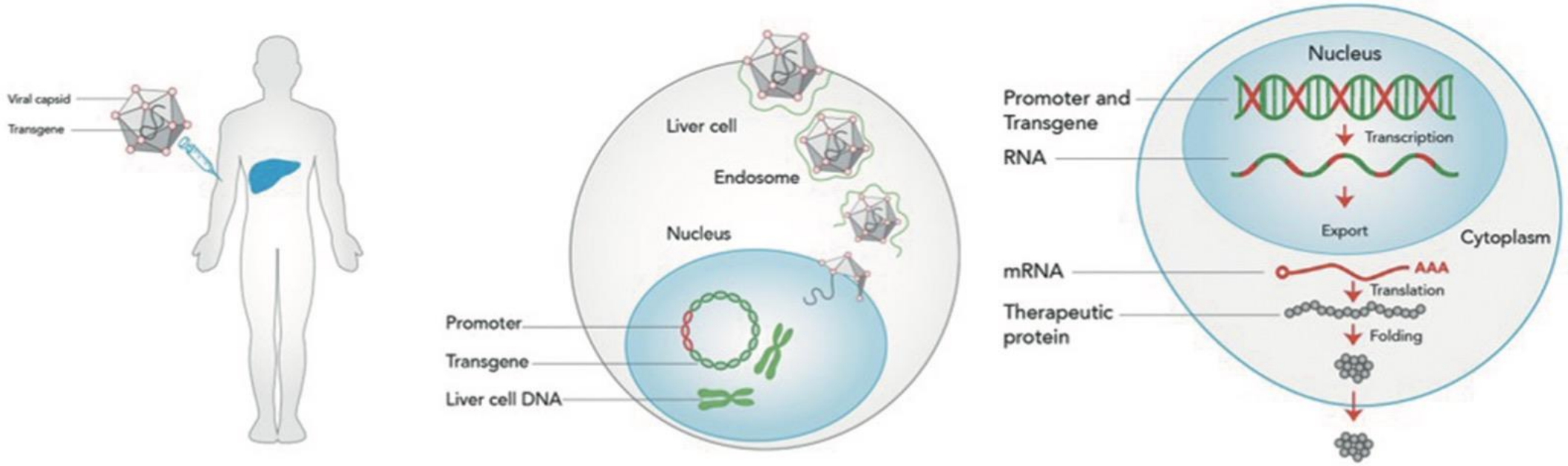
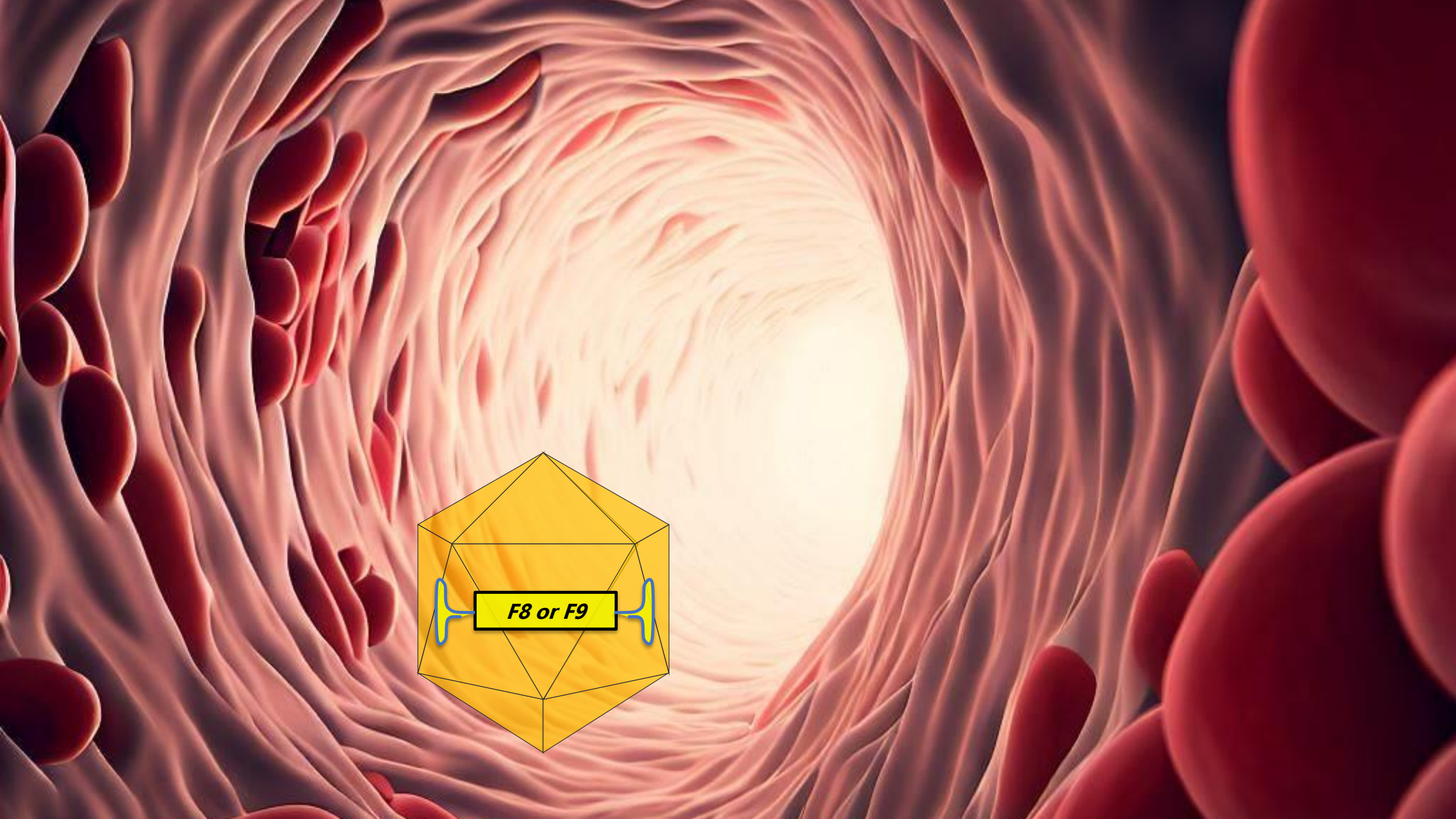


Figure 1. Targeted gene therapy schematic. The transgene of interest is packaged inside a recombinant viral vector and injected into the subject. The vector is taken up by many different cell types via endocytosis into organelles called endosomes. The vector escapes from the endosomes, attaches to the nuclear envelope, and injects its genomic payload into the nucleus. The vector genome contains a tissue-specific promoter such that it is only transcribed in the target cell type (e.g. hepatocytes). The host transcription machinery transcribes the transgene into mRNA, which is transported out of the nucleus and translated into the protein of interest.


F8 or F9

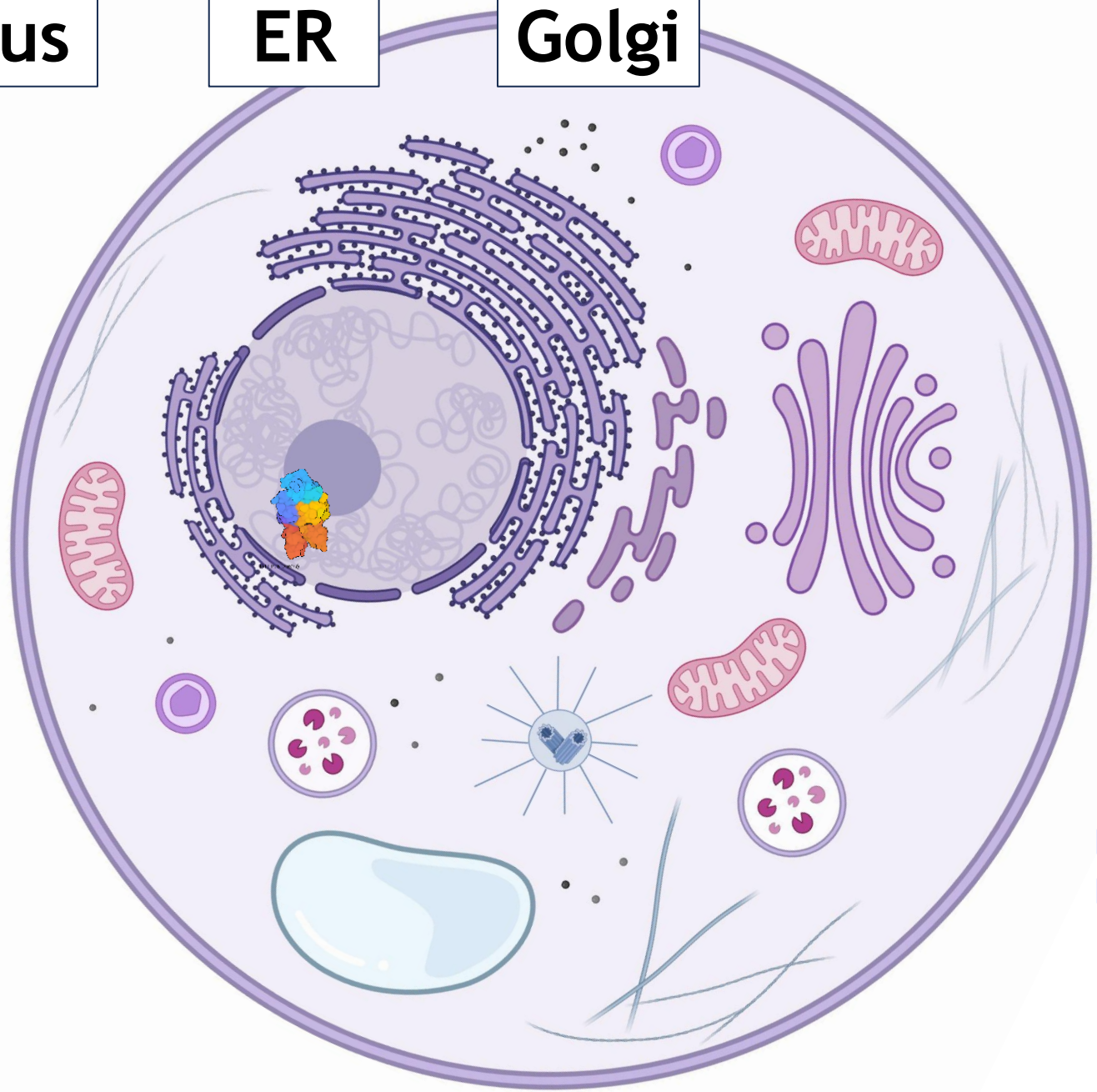
Nucleus

ER

Golgi

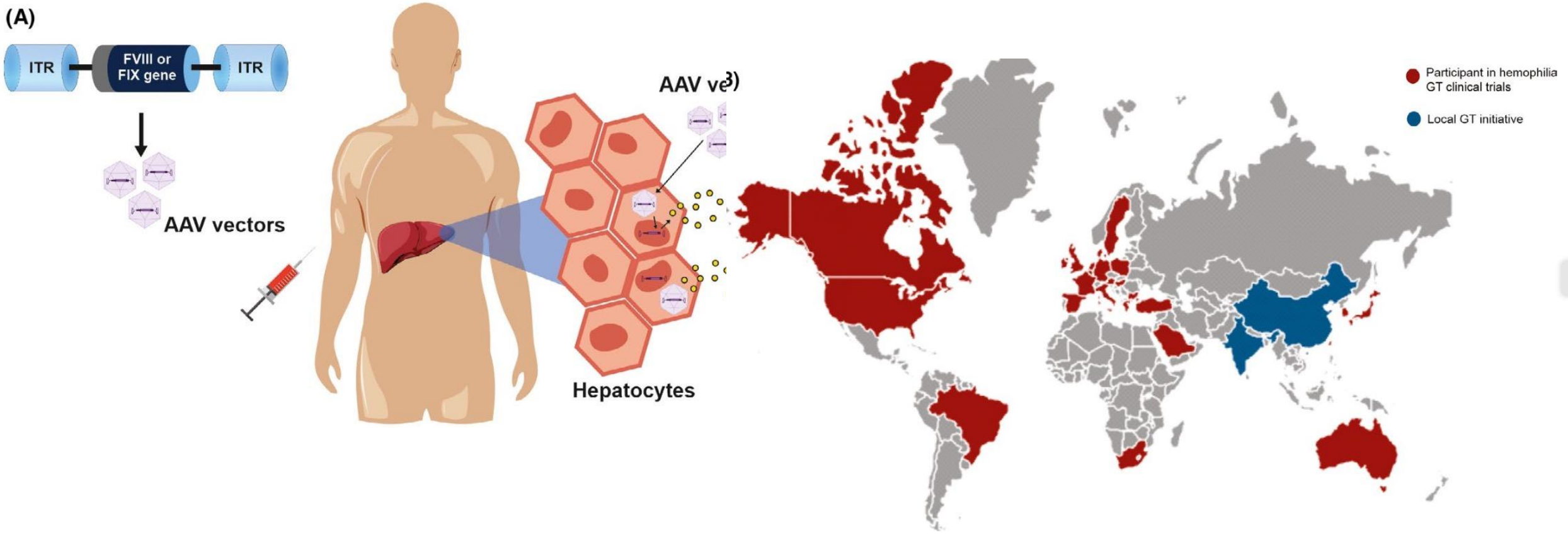
Circulation

Episomal
AAV genome
mRNA



FIX is secreted well
FVIII is not secreted well

Hemophilia Gene Therapy Clinical Trials



Adeno-associated virus(AAV) is the type of virus used as a delivery vehicle
Testing in people with hemophilia has occurred in many countries around the world

Two Approved in the US and Europe

Molecular Therapy
Editorial

First conditional marketing authorization approval in the European Union for hemophilia A gene therapy

Thierry VandenDriessche,[1,2] Steven W. Pipe,[3] Glenn F. Pierce,[4] and Radoslaw Kaczmarek[5]

Molecular Therapy
Editorial

First hemophilia B gene therapy approved: More than two decades in the making

Roland W. Herzog,[1] Thierry VandenDriessche,[2,3] and Margareth C. Ozelo[4]

Molecular Therapy
Commentary

Two gene therapies for hemophilia available: Now what?

Glenn F. Pierce[1] and Roland W. Herzog[2]

https://doi.org/10.1016/j.ymthe.2023.03.001

What does all this mean for the patient?
Efficacy and toxicity = benefit/risk
Is this the end of the beginning?

FVIII and FIX Phase 3 Results Are Different

N ENGL J MED 386;11 NEJM.ORG MARCH 17, 2022

Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A

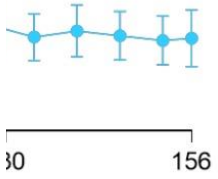
M.C. Ozelo, J. Mahlangu, K.J. Pasi, A. Giermasz, A.D. Leavitt, M. Laffan, E. Symington, D.V. Quon, J.-D. Wang, K. Peerlinck, S.W. Pipe, B. Madan, N.S. Key, G.F. Pierce, B. O'Mahony, R. Kaczmarek, J. Henshaw, A. Lawal, K. Jayaram, M. Huang, X. Yang, W.Y. Wong, and B. Kim, for the GENEr8-1 Trial Group*

Table 1. Extrapolated Factor VIII Activity.*

Time after Infusion	Factor VIII Level	
	Mean	Median (Range)
	IU per deciliter	
Wk 104	22.3±29.7	11.1 (BLQ–171)
Wk 156	16.9±25.0	8.9 (BLQ–156)
Wk 208	13.6±22.4	7.2 (BLQ–143)
Wk 260	11.8±21.0	5.7 (BLQ–131)

Mean (±SE) FVIII activity

End of Year 3 (N=17)
Mean 16.81
Median 9.30



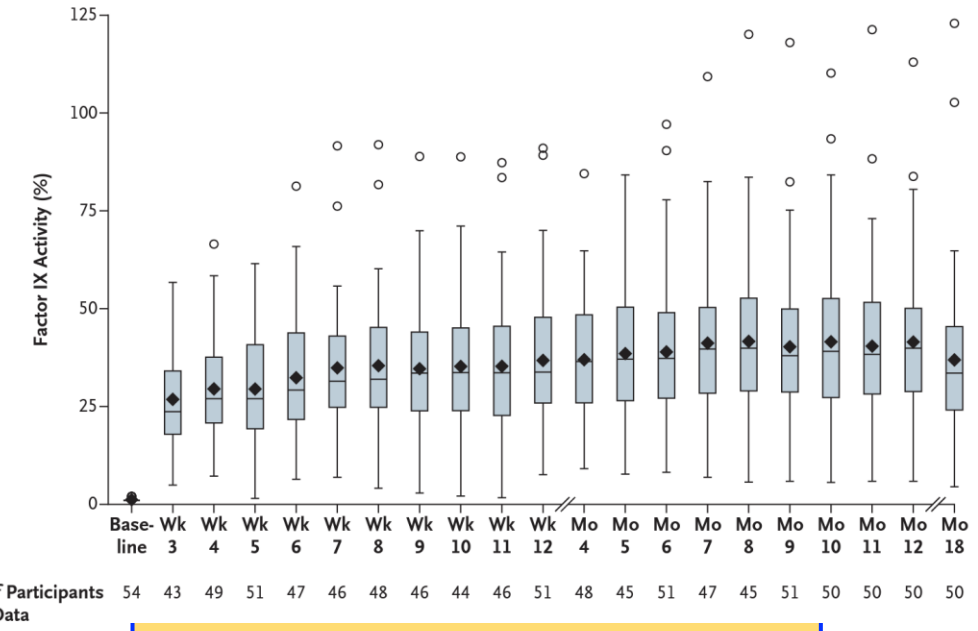
Highly variable therapeutic response
Year over year loss of FVIII through 6 years
No therapeutic index

T1/2 = 123 weeks (95% confidence interval, 84 to 232)

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

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



Variable responses
Projected to last at least 25 years

Mahlangu J. Two-year outcomes of valoctocogene roxaparvovec therapy for hemophilia A. N Engl J Med 2023;388:694-705., Pipe S et al. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia BN Engl J Med 2023; 388:706-718. DOI: 10.1056/NEJMoa2211644

J Shah et al (2023) Comprehensive analysis and prediction of long-term durability of factor IX activity following etranacogene dezaparvovec gene therapy in the treatment of hemophilia B, Curr Med Res Opin, 39:2, 227-237, DOI: 10.1080/03007995.2022.2133492

Gene Therapy Outcomes in 2023

- Once and Done? Maybe Yes HemB; Maybe Not HemA

Considerations	HemB	HemA
Ability to re-treat	No; may not be needed	No
Ability to boost a low result	No	No
Predictability of need for steroids, others	No, but short term	No, and some long term
Predictability of acute infusion reaction	No	No
Knowledge of the safety unknowns	No	No
Risk-benefit analysis favorable- HIC	Qualified yes	Many alternative therapies
Risk-benefit analysis favorable- LIC, LMIC	Yes	Possibly- ~7 year holiday
Works in children	No	No

Shared and informed decision making of the risk/benefit is essential - but only as good as the available data

How to Decide??

- The choices are now more technically complicated
- Use a **Shared Decision Making Tool** to Assess Near and Long Term Personal Goals
- Work with HTC personnel to assess benefits, risks of **ALL** available therapies and whether they contribute to your Quality of Life

What Patients Need to Know Before Gene Therapy

Expert Insights

The Basics	▪ How gene transfer works ▪ How treatment is administered ▪ Level of clinical follow-up required
Possible Benefits	▪ Level of expression that may be achieved ▪ Variability of results
Possible Risks	▪ Short term (liver toxicity, infusion reactions) ▪ Long term (thrombosis, malignancy, loss of expression)

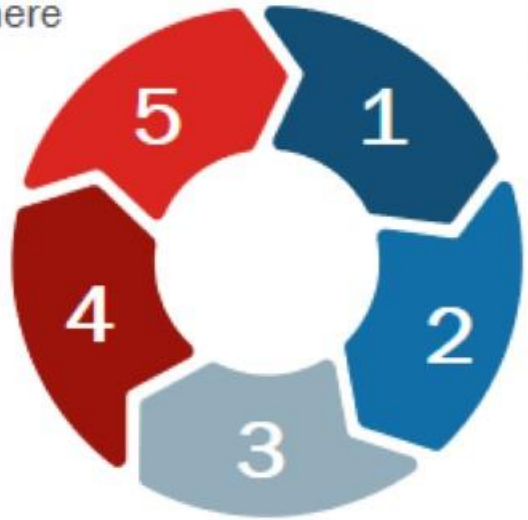
The Patient Journey
Shared Decision-Making

After Treatment (Long-Term)

What is known about long-term safety?
What are the treatment options if there is loss of factor expression?

Information Seeking

What is gene therapy?
How is it given?
Who is eligible?



After Treatment (Short-Term)

Can I exercise?
Can I take other medications?
What happens if bleeding occurs?
What happens if I require surgery?

Decision Making

Where will it be administered?
How likely is it to work?
What are the potential risks?
What do we not know?

Treatment Initiation

How do I prepare for treatment?
How will I know if it worked?
Can I drink alcohol?
Do I need to use barrier contraception?

Wang M, et al. Patient Preference Adherence. 2022;16:1439-1447.

Opportunities & Challenges of gene therapy
What we heard from patients made us begin to prepare

Patient anticipation & hope

- Gene therapy is uncharted but *promising*
- Clinical trials show that for many it can obviate regular infusion, decrease bleeding
- Potentially cost effective
- Newer technologies, e.g. CRISPR, Lentivirus

Patient level shared decision-making

- Why do I want gene therapy?
- What are my ambitions, goals, expectations?
- What is my optimal treatment? Alternatives?
- Do I understand the risks and benefits for myself, my family?
- How do I choose a gene therapy vector?
- Am I healthy enough for gene therapy?
- How do I make decisions?
  - Expert advice? Friends? Family? Internet? Shared decision-making? Do I know what I need to know?
- How do I deal with risk, uncertainty, failure?
  - Factor levels, duration, complications, newer therapy?

Wang M et al. Patient Prefer Adherence. 2022.

MASAC Document 277 - MASAC Recommendations on Hemophilia Treatment Center Preparedness for Delivering Gene Therapy for Hemophilia

- Key Elements for review (14):
- Potential ranges of efficacy and implications for participation in activities/invasive procedures
- Expected duration of response/lack of response and uncertainty for return to previous therapies
- Role of AAV antibodies positivity on outcomes
- Hepatitis and chronic liver disease history
- Expectations for the screening processes and day of infusion

•Required follow-up laboratory testing and clinic visits (short and long-term) and implications for non-adherence
•Restrictions on alcohol consumption
•Recommendations for barrier contraception and family planning
•Restrictions on concomitant medications
•Post-dose contact precautions
•Potential side effects and their management, including side effects related to immunosuppression
•Psychosocial impact
•Recommendations for social support
•Cost/insurance coverage/approvals needed

https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-277-masac-recommendations-on-hemophilia-treatment-center-preparedness-for-delivering-gene-therapy-for-hemophilia

Patient Monitoring

Pre-existing immunity and anti-AAV NAbs

Correlations between NAb titers and clinical outcomes (efficacy, safety)

Liver health/toxicity assessment

Screening, postinfusion, tumor surveillance, long-term liver health (alcohol intake, fatty liver, medications)

Centralized vs local laboratory data

Turnaround time for clinical decision-making

Bleed and factor infusion diaries

Adjudication of bleeding events

Monitoring requires clear communication between the patient, the dosing center, and the follow-up center

Pipe S. Presented at: WFH 2022; May 8-11, 2022; Montreal, Canada.

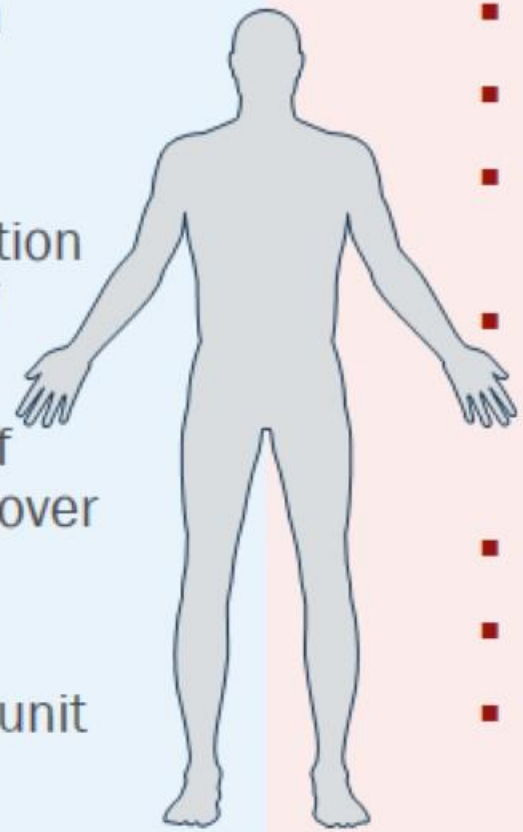
Managing Patient Expectations
Other Questions to Discuss With Patients

- What happens if the factor activity does not increase?
- What are the treatment options if there is loss of expression?
- Is it really a “cure” if continuous monitoring and care are still needed?

Who Is Eligible for Gene Therapy?
Typical Inclusion/Exclusion Criteria Used in Clinical Trials

Inclusion

- Men who are 18 years or older with established severe hemophilia
- FVIII ≤ 1 IU/dL, FIX < 2 IU/dL
- Treated/exposed to FVIII concentration or cryoprecipitate for a minimum of 150 exposure days
- On prophylaxis or certain number of defined bleeding episodes therapy over previous 12 months
- Results from a modified Nijmegen Bethesda assay of < 0.6 Bethesda unit



Exclusion

- Children under 18 years
- Women
- Detectable pre-existing immunity to the AAV capsid
- Significant liver dysfunction
  - Variably defined; imaging exclusion or cirrhosis/fibrosis
- Hepatitis B if surface antigen positive
- Hepatitis C if RNA positive
- HIV (not always an exclusion)

Pipe SW. Haemophilia. 2020;27(Suppl 3):114-121.

Who Is Eligible for Gene Therapy?
Other Considerations

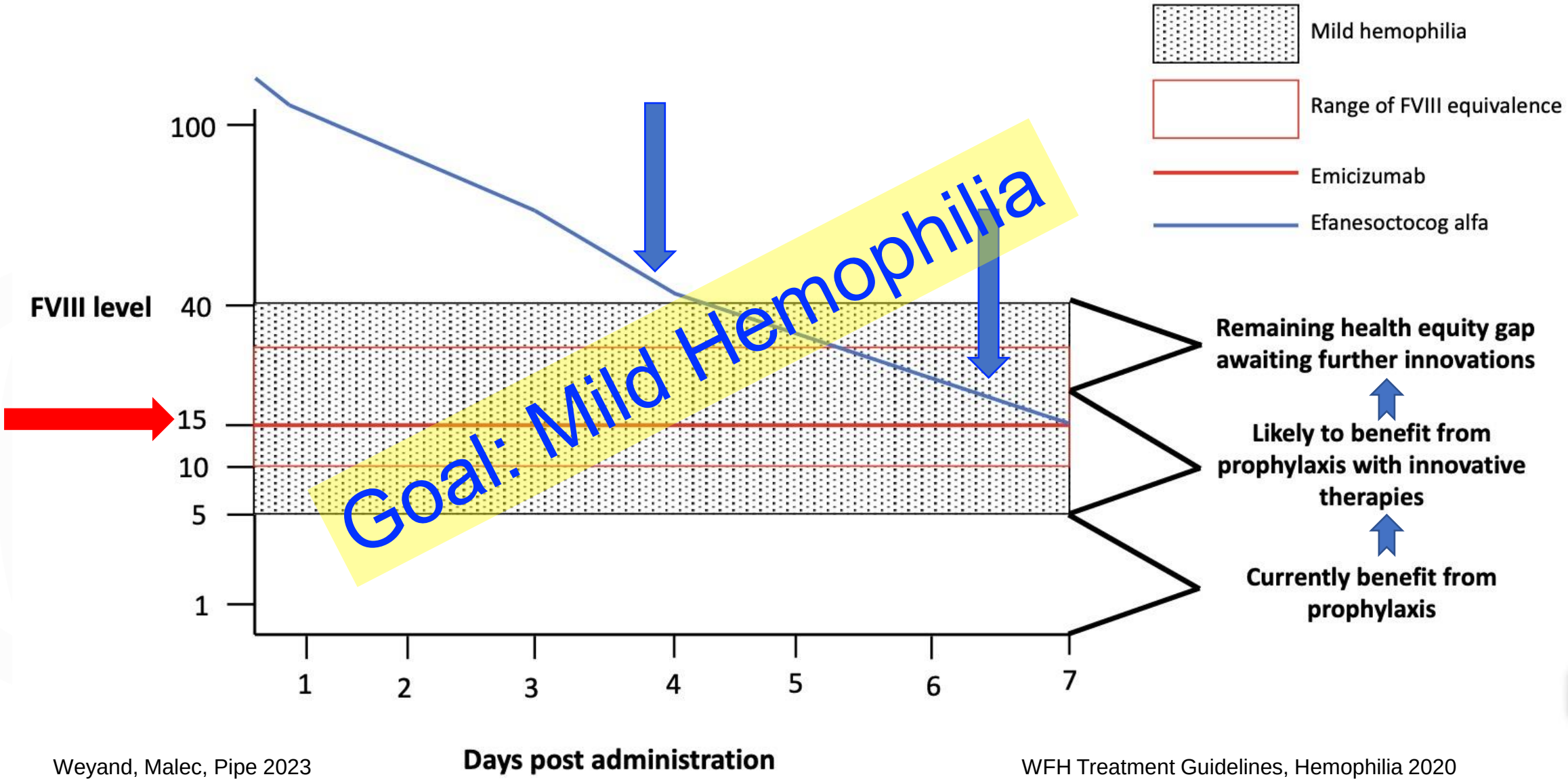
Good potential candidates may be...

- Young and active to elderly
- Seeking to be liberated from demands of prophylaxis
- Having problems taking current therapy
- In need of better protection than they are receiving from current therapy
- Experiencing increased bleeding due to severely damaged joints
- Experiencing increased bleeding due to anticoagulation

Poor potential candidates may have...

- Underlying liver disease
- History of presence of factor inhibitors
- Presence of anti-AAV NAbs (in most protocols)
- Contraindications to, or challenges with, the use of immunosuppressants (eg, upcoming surgical procedure, poor adherence to oral medications, prior reactions to corticosteroids)

What Can Be Achieved in 2023?



Weyand, Malec, Pipe 2023

WFH Treatment Guidelines, Hemophilia 2020

Decision Making: Phase 3 Gene Therapy Results in Context of Other Treatment Options?

- HemA

- EHL products IV q1w
- Emicizumab, SQ dosing q1-4w
- 2 FVIII mimetics in development[#]
- 4 Rebalancing agents in development*

- HemB

- EHL products IV q1-2w
- 4 Rebalancing agents in development*

[#]Mimate, 007

*fitusiran, concizumab, marstacimab, serpinPC

For AAV gene therapy, balance between chance to achieve “once and done” vs waiting and using a treatment that can achieve a mild FVIII/FIX range

Different Limitations Identified in Clinical Trials for HemA and HemB

Common for hemophilia A and B:

- liver toxicity (tolerability)
- reliability/predictability
- eligibility
- variability

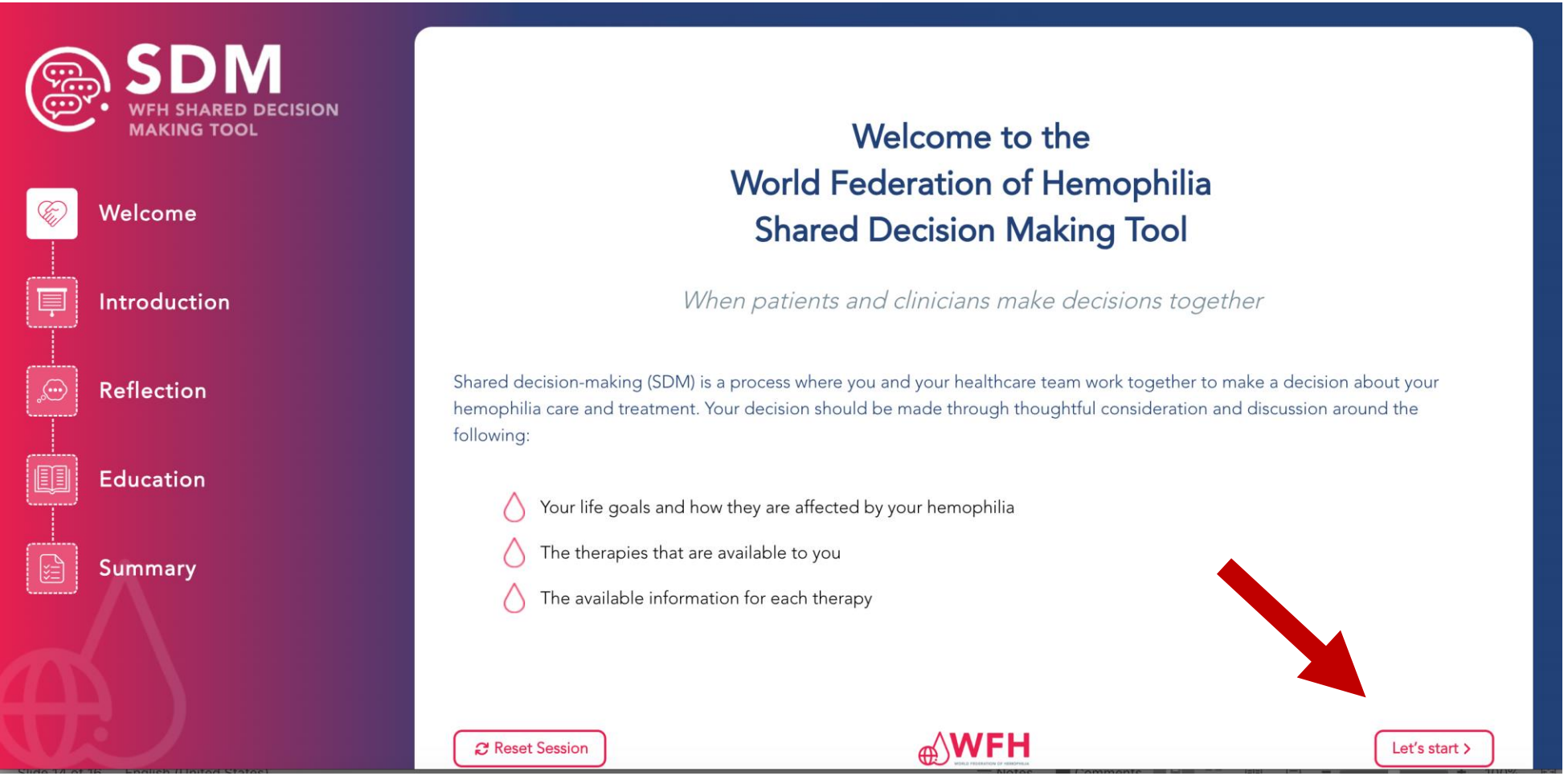
Additional for hemophilia A:

- durability
- liver toxicity (higher incidence=additional causes?)
- wider variability?

WFH Shared Decision Making Tool

Now available SDM.WFH.org

Public Comment period: 1 Aug – 1 Nov 2023



This allows the medical and psychosocial providers to know what the patient has learned, and the summary report gives everyone a common place to start the individual conversation

SDM
WFH SHARED DECISION MAKING TOOL

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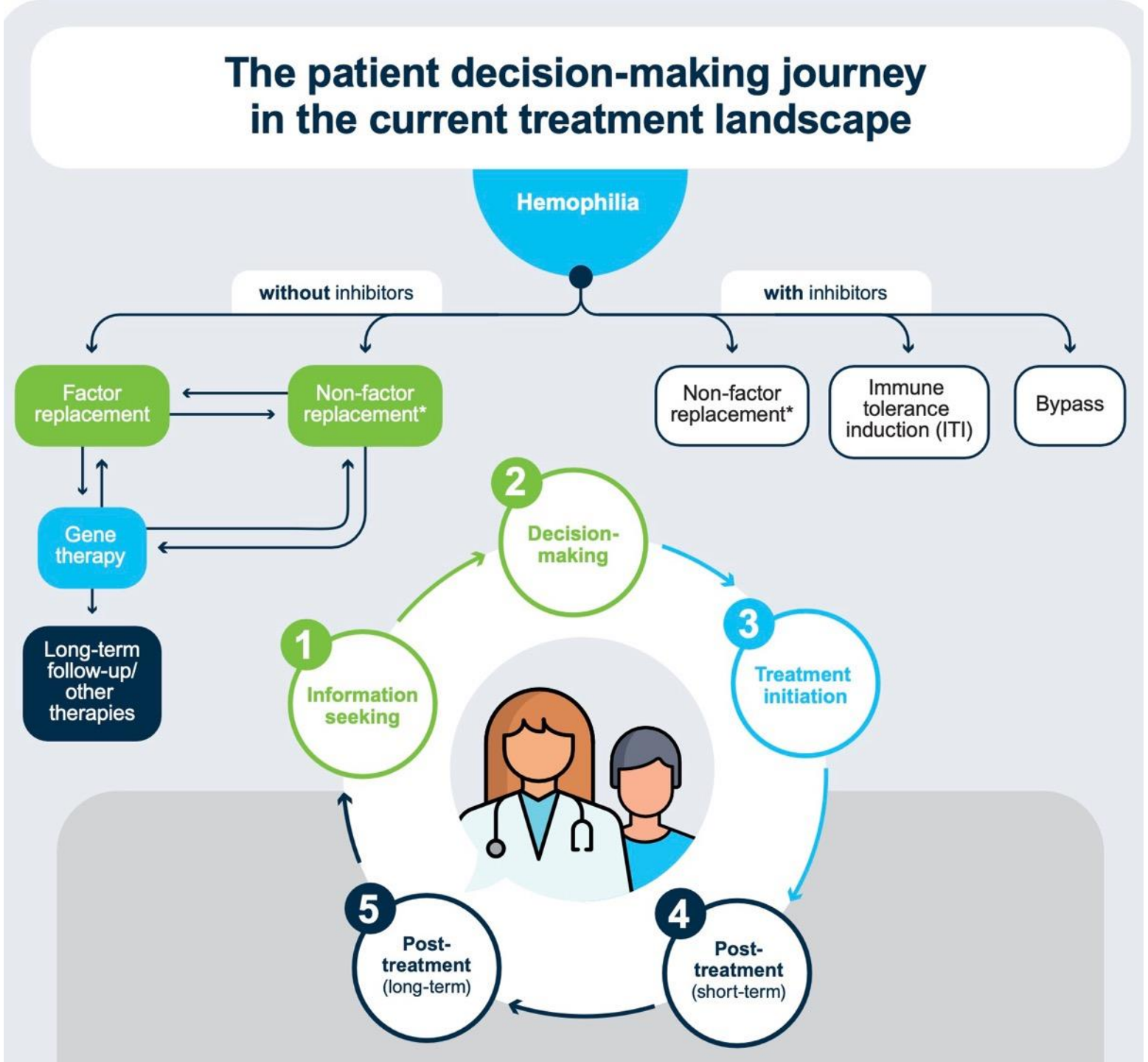


This journey should be done via a Shared Decision Making process

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.

Identifying Safety Signals in Rare Disease Populations

Gene therapy is an unprecedented and complex treatment for hemophilia

- Interaction between two complex life forms

Gene therapy recipients may be few at first, and will be scattered around the world:

- If data are not accumulated in ONE global registry, patterns of rare safety events will be difficult to identify
- Over time, long term safety, durability, variability

Patient safety is all of our responsibility

GTR
WFH GENE THERAPY REGISTRY

A Single International Registry Is Essential to Assess Long Term Benefit/Risk

The demonstrated potential for random integration merit a long-term follow-up, preferably lifelong

A consensus built core outcome data set to facilitate life-long monitoring of safety, efficacy, and durability outcomes was used to develop the WFH Gene Therapy Registry

GTR WFH GENE THERAPY REGISTRY

NOW LIVE

Published January 18, 2023

Haemophilia. 2021;27(Suppl. 3):126–131.

The critical need for postmarketing surveillance in gene therapy for haemophilia

Barbara A. Konkle[1] | Michael Recht[2,3] | Anneliese Hilger[4] | Peter Marks[5]

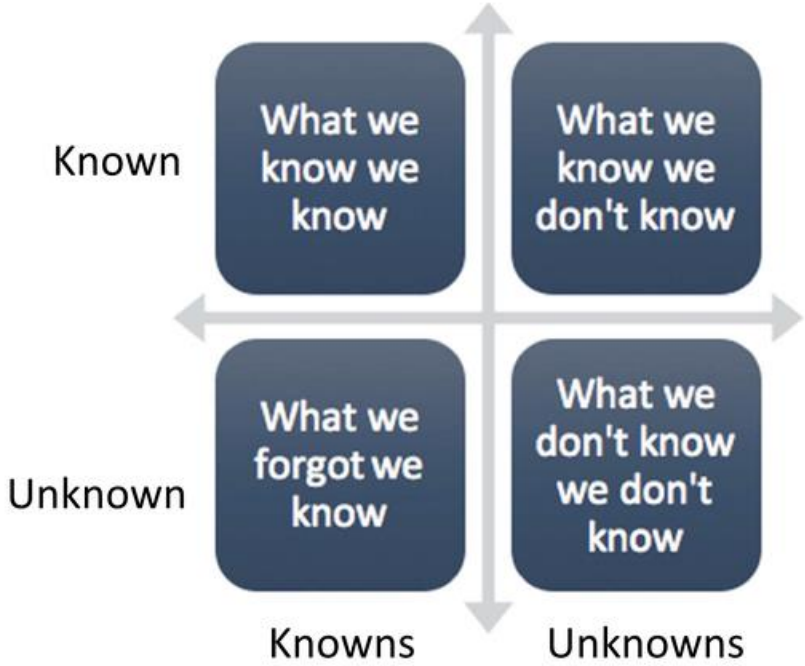
+Gene Therapy Industry Partners: BioMarin, CSL, Pfizer, Spark

Konkle B, Pierce G, Coffin D, Naccache M, Clark RC, George L, Iorio A, O'Mahony B, Pipe S, Skinner M, Watson C, Peyvandi F, Mahlangu J; ISTH subcommittee on Factor VIII, Factor IX, rare bleeding disorders. Core data set on safety, efficacy, and durability of hemophilia gene therapy for a global registry: Communication from the SSC of the ISTH. J Thromb Haemost. 2020 Nov;18(11):3074-3077. doi: 10.1111/jth.15023

Haemophilia. 2018;24(Suppl. 6):60–67.

Past, present and future of haemophilia gene therapy: From vectors and transgenes to known and unknown outcomes

G. F. Pierce[1,2] | A. Iorio[3]



Molecular Therapy Vol. 29 No 12 December 2021

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]

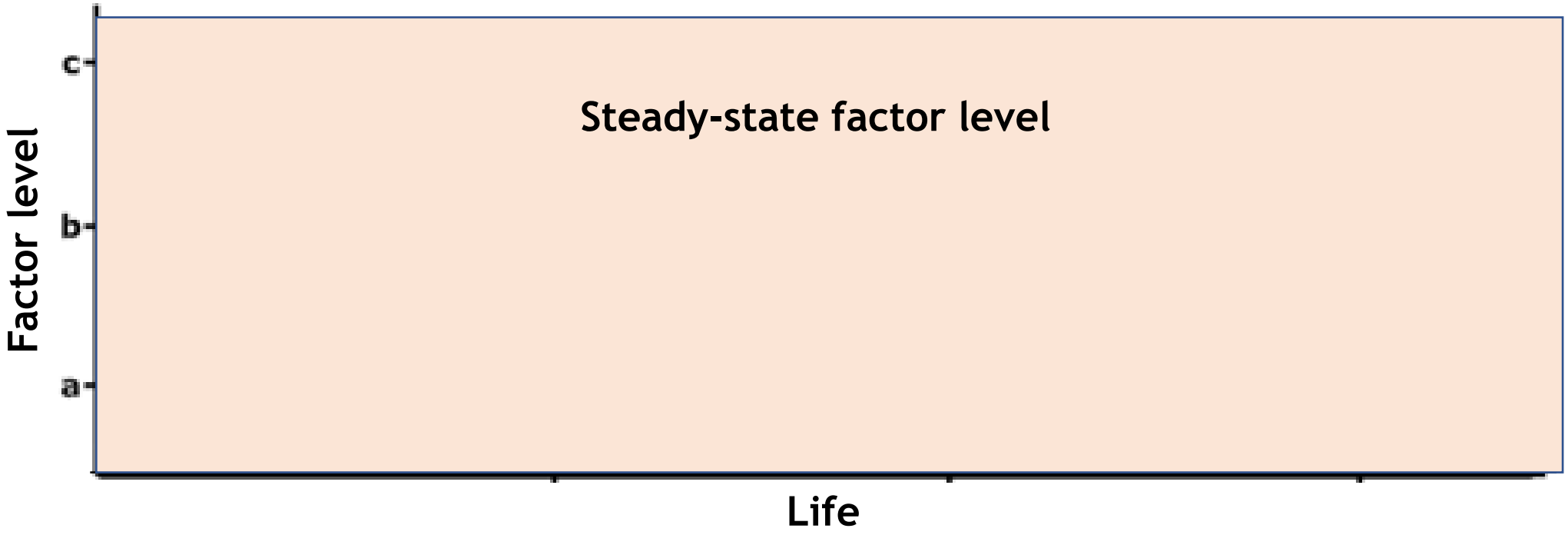
https://doi.org/10.1016/j.ymthe.2021.10.025

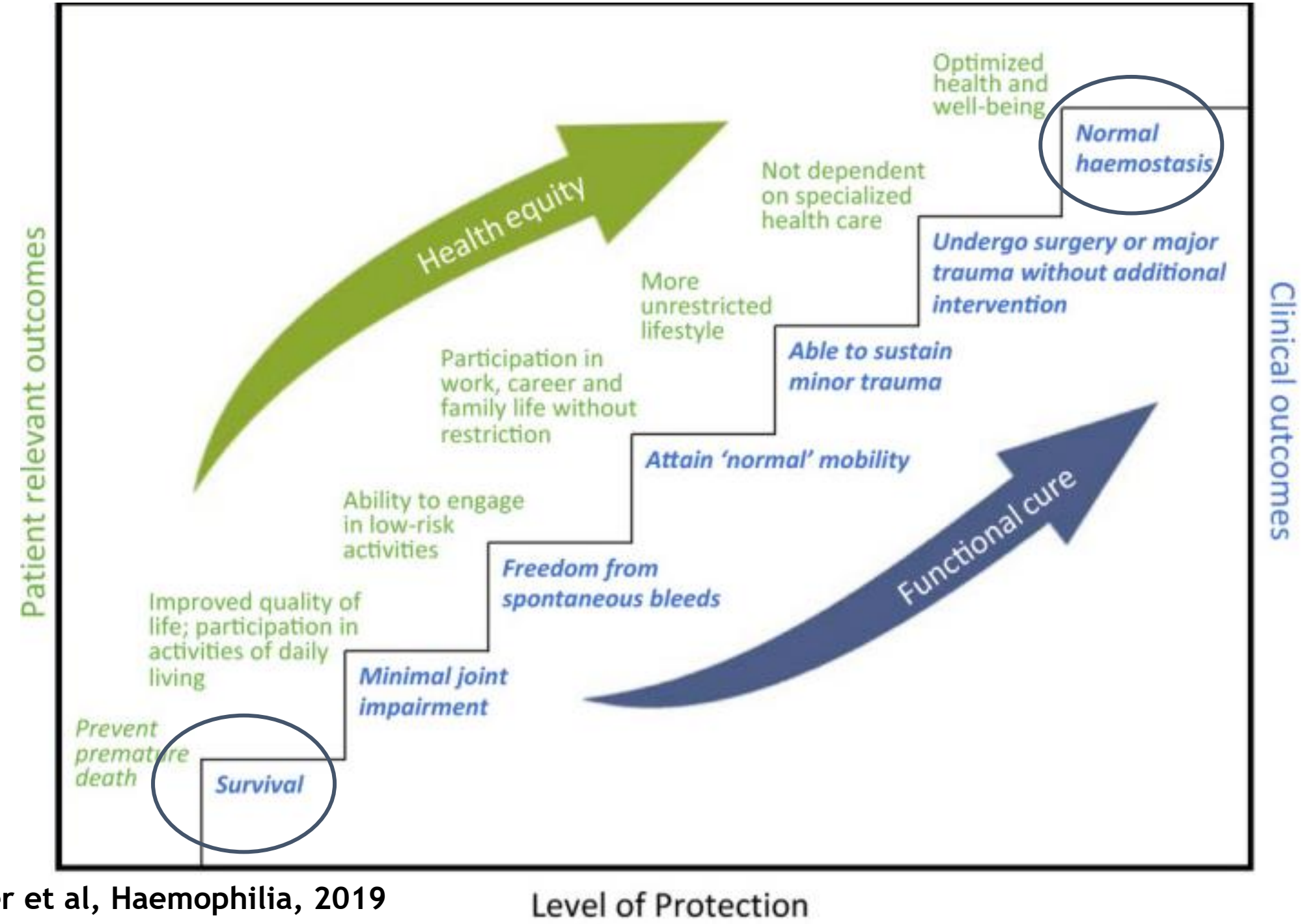
Haemophilia. 2020;00:1–3.

Gene therapy to cure haemophilia: Is robust scientific inquiry the missing factor?

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

Cures, not treatments





Skinner et al, Haemophilia, 2019

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THANK YOU!

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FEDERACIÓN MUNDIAL DE HEMOFILIA