

Gene Therapy 101 and Hemophilia 101

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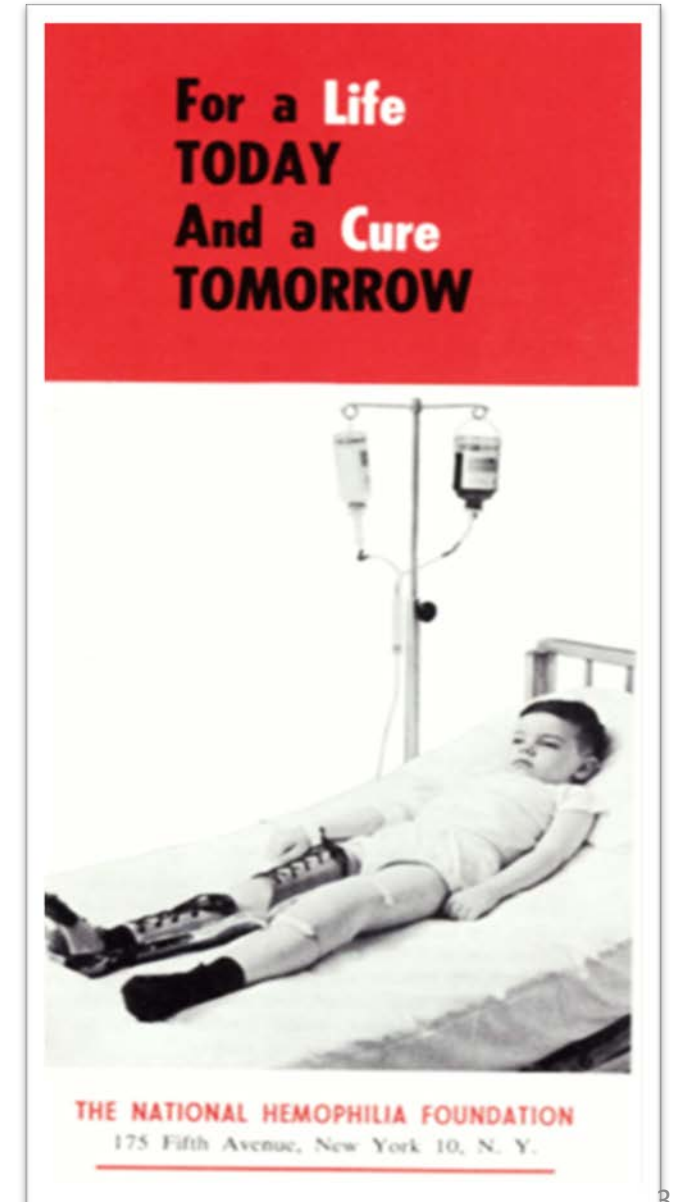
Former SVP, Hematology, Cell and Gene Therapies, Biogen

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What is Hemophilia?

- Incidence 1 in 10,000 (X-linked recessive)
 - ~50,000 PWH in Europe and North America
 - Equal opportunity disease
 - Predominantly male
- Well characterized genetically and clinically
 - Type: FVIII (Hemophilia A) 80-85%
 - Type: FIX (Hemophilia B) 15-20%
 - Severity: Severe 60%, Moderate 15%, Mild 25%
- Deficiency of clotting factor protein in blood
 - Blood does not clot properly
 - Severe patients (<1% clotting factor) at most risk

1940s-1960s



Queen Victoria's Secret

Hemophilia called “the Royal Disease” because Queen Victoria of England (1837-1901) was a carrier. Her 8th child, Leopold had hemophilia and died of a brain hemorrhage at the age of 31.

Two of Queen Victoria's daughters were carriers and passed the disease on to the Spanish, German and Russian Royal families.

Alexandra, the granddaughter of Queen Victoria was also a carrier. She married Nicholas, the Tsar of Russia and passed the disease on to her son Alexei.

And then...Rasputin and The Russian Revolution



What Does Hemophilia Look Like?

- Clinical manifestations
 - Internal bleeding into joints, soft tissues
 - Significant morbidity and mortality
 - ~20-30% PWH with severe hemophilia A develop neutralizing antibodies, greatly complicating treatment
- State of the art treatment
 - Prophylaxis (replace missing factor)
 - Many plasma-derived and recombinant products available
- Gene therapy promises a cure
 - Definition of “cure”?



Severe Hemophilia Treated 'On-demand'

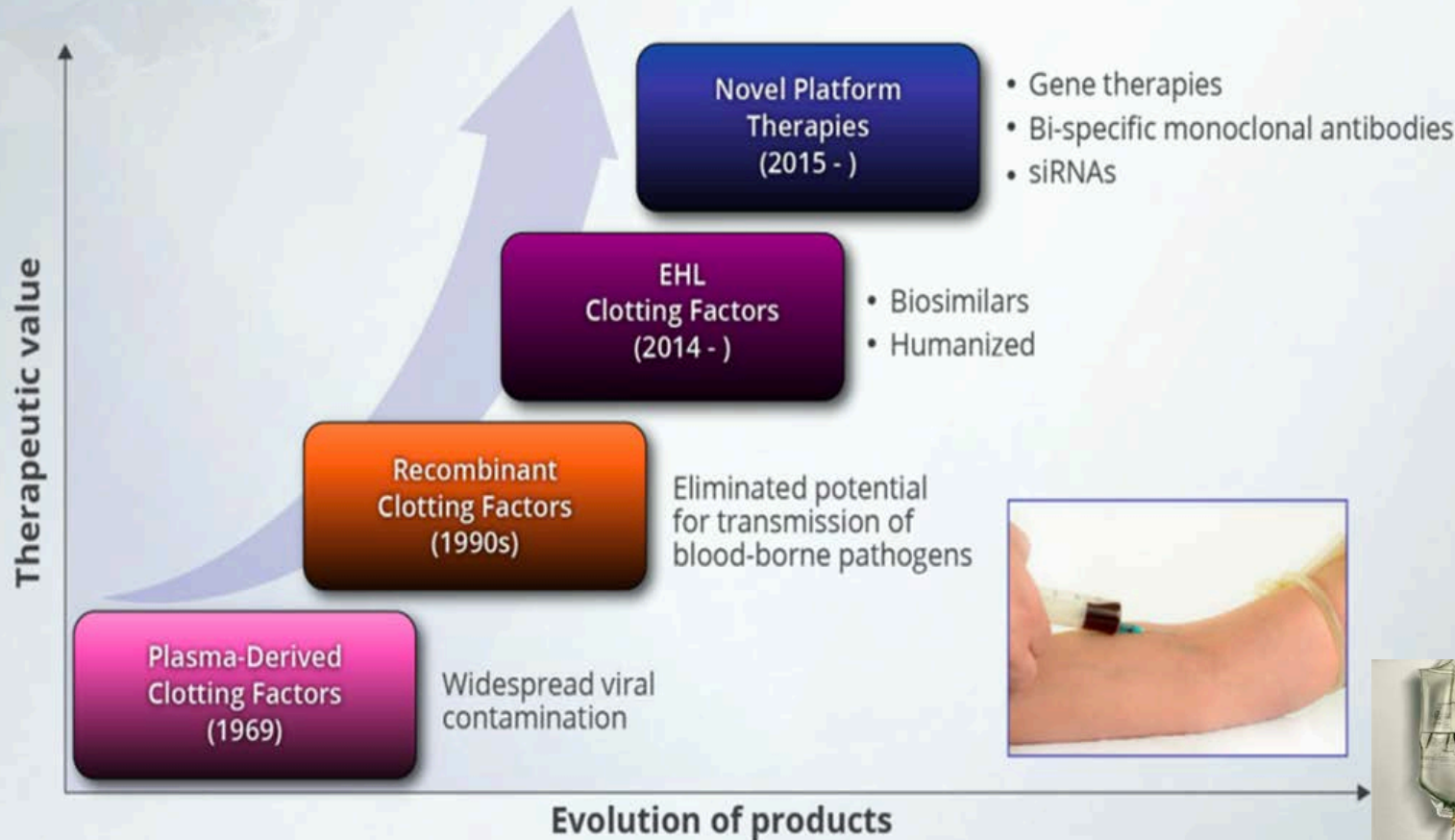


Patients are always at risk of bleeding- this is not the Standard of Care



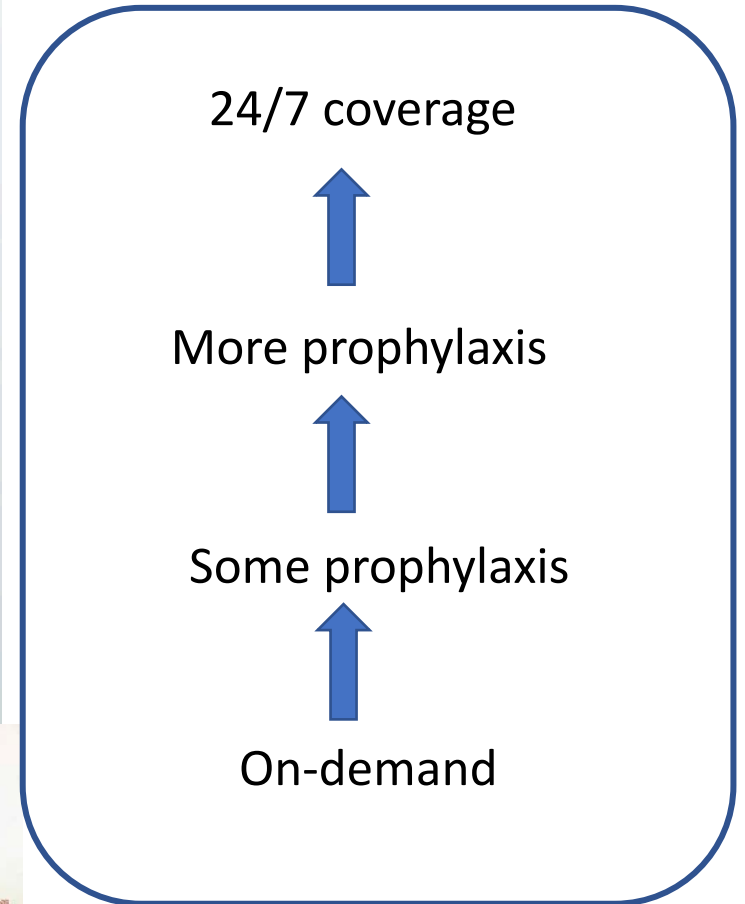
Role of Technology Advances in Evolving Hemophilia Care in Resource Rich Countries

Brief History of Hemophilia Treatments



THE SPREAD OF HCV AND HIV THROUGH THE BLOOD SUPPLY AND ITS LASTING IMPACT

Pierce



Complications and Solution (Prophylaxis)



Challenge of Treatment- Economics

TABLE 2 Median dose and infusion frequency for SHL and EHL clotting factor concentrates as of 31 December 2017 and the anticipated annual prophylaxis usage calculated from prescribed prophylaxis regimen

Factor concentrate type	Median prescribed dose (IU/kg)	Median prescribed annual infusions	Annual prophylaxis usage	Median WAC, product group ^a	Projected annual prophylaxis cost ^b
Standard FVIII	40	156 (thrice weekly)	6240 IU/kg	\$ 1.58	\$690 144
EHL FVIII	50	104 (twice weekly)	5200 IU/kg (↓17%)	\$ 2.07 (↑24%)	\$753 480
Standard FIX	67	104 (twice weekly)	6968 IU/kg	\$ 1.43	\$697 497
EHL FIX	75	52 (weekly)	3900 IU/kg (↓44%)	\$ 3.72 (↑62%)	\$1 015 560

^aEstimate median wholesale acquisition cost (WAC) for SHL and EHL factor concentrate groups based on Medi-Span Price Rx Basic August 2017.

^bBased on 70 kg individual.

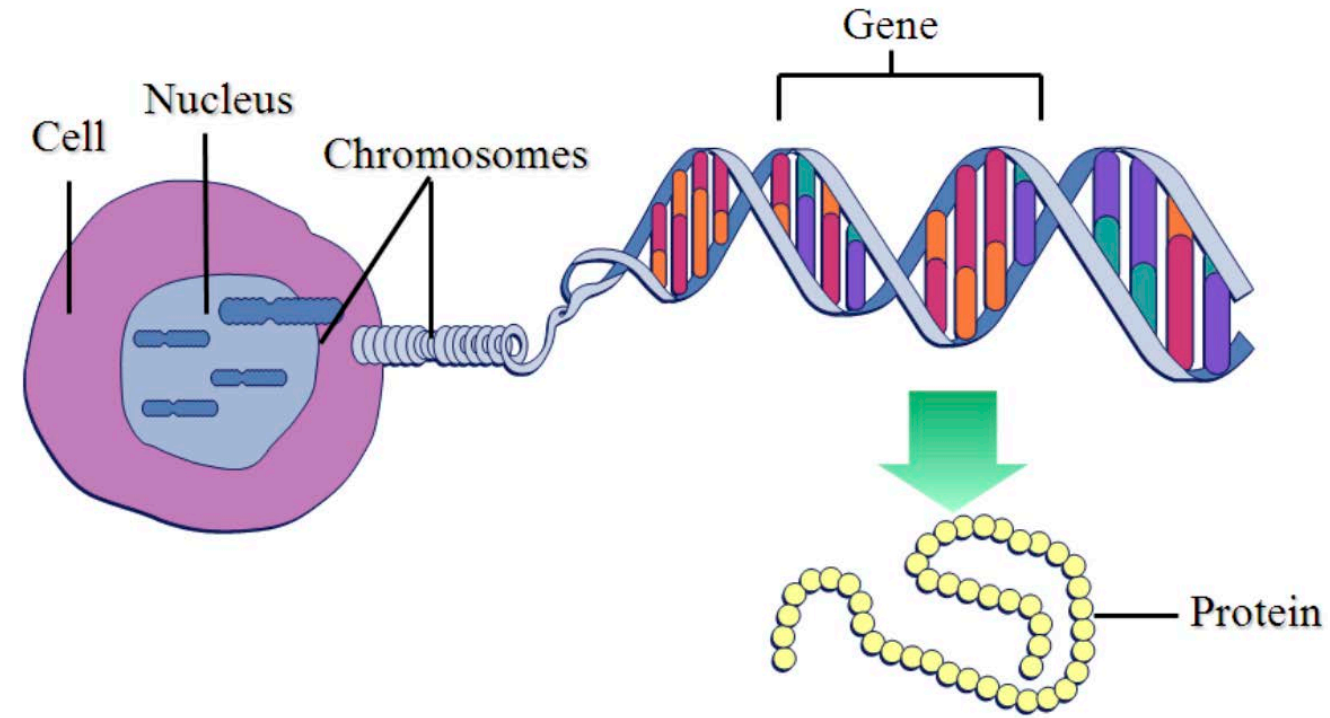
DOI: 10.1111/hae.13758 2019

Gene Therapy Landscape

Who, What, Why, When, How

What is a gene?

- Humans have about 20,000 genes
- They define who and what we are
- FVIII, FIX, VWF, FVII, FX, FXI, etc are all genes that can cause bleeding if they don't produce a protein that works

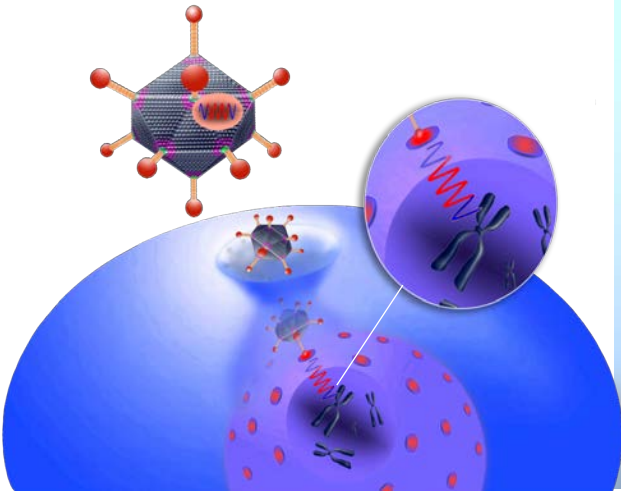


<http://igbiologyy.blogspot.com/2014/03/chromosomes-dna-genes-and-alleles.html>

The Continuum of "Gene Therapy" Technologies

- How might we achieve a cure for monogenic bleeding disorders?

Gene therapy



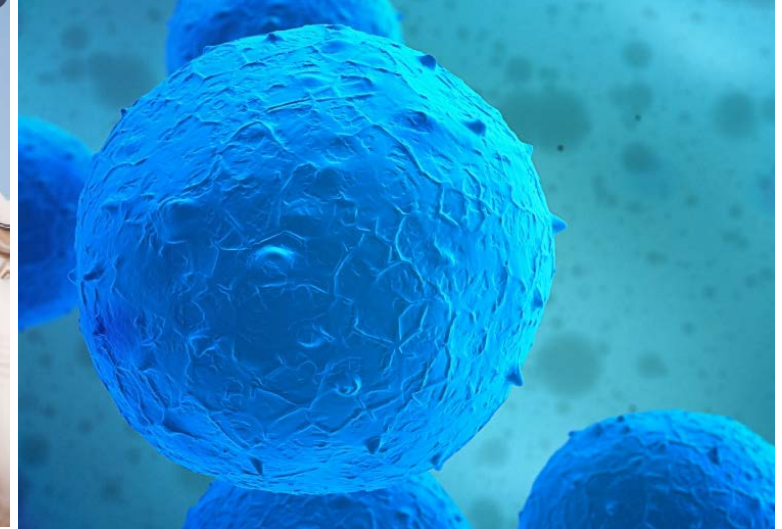
New gene transferred into cell nucleus, expressed; no removal of existing DNA sequence

Gene editing



Corrects faulty gene or inserts correct gene in its place

Cell therapy

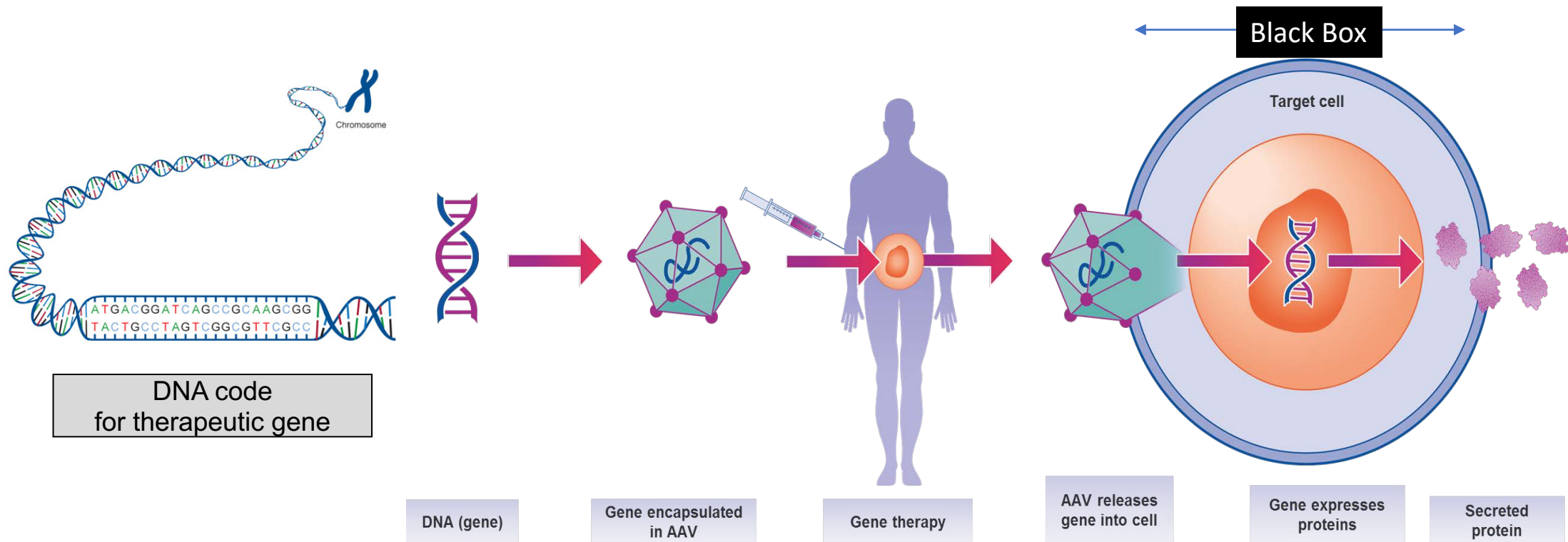


Cell therapy, which transplants whole cells. Cells may undergo gene therapy/ editing before delivery to recipient

Complexity

What Is Gene Therapy?

Adeno-associated Virus (AAV) Mediated Gene Therapy



Almost every genetic and acquired disease has been studied in animal models
>200 human trials using AAV – based gene therapy have been conducted in the past 30 years
ssDNA virus, 2 genes-rep and cap, 20nm, non-pathogenic upon human or animal infection



Image: National Human Genome Research Institute's Talking glossary
(<http://www.genome.gov/glossary/>) <http://www.abedia.com/wiley/vectors.php>

After 20 Years of Testing in Humans, Therapeutic Factor Levels Achieved

December 2017

Original Article

Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant

Lindsey A. George, M.D., Spencer K. Sullivan, M.D., Adam Giermasz, M.D., Ph.D., John E.J. Rasko, M.B., B.S., Ph.D., Benjamin J. Samelson-Jones, M.D., Ph.D., Jonathan Ducore, M.D., M.P.H., Adam Cuker, M.D., Lisa M. Sullivan, M.D., Suvankar Majumdar, M.D., Jerome Teitel, M.D., Daniel Hui, Ph.D., J. Fraser Wright, M.D., M.P.H., Alvin Y. Luk, Ph.D., Katie Wachtel, M.S., Angela Winters, M.D., Chen, M.D., Yun Liu, Ph.D., Valder R. Arruda, M.D., Ph.D., Johannes C.M. van de Tiefenbacher, Ph.D., Daniel Takefman, Ph.D., Marcus E. Carr, M.D., Ph.D., Olga Zelenaia, Ph.D., Daniel Takefman, Ph.D., and Katherine A. High, M.D. Couto, Ph.D., Xavier M. Anguela, Ph.D., and Katherine A. High, M.D.
N Engl J Med Volume 377(23):2215-2227 December 7, 2017

ORIGINAL ARTICLE

AAV5-Factor VIII Gene Transfer in Severe Hemophilia A

Savita Rangarajan, M.B., B.S., Liron Walsh, M.D., Will Lester, M.B., Ch.B., Ph.D., David Perry, M.D., Ph.D., Bella Madan, M.D., Michael Laffan, D.M., Hua Yu, Ph.D., Christian Vettermann, Ph.D., Glenn F. Pierce, M.D., Ph.D., Wing Y. Wong, M.D., and K. John Pasi, M.B., Ch.B., Ph.D.
N Engl J Med 2017; 377:2519-2530 | December 28, 2017 | DOI: 10.1056/NEJMoa1708483

The **NEW ENGLAND**
JOURNAL of **MEDICINE**

EDITORIAL

A Cure for Hemophilia within Reach

H. Marijke van den Berg, M.D., Ph.D.

N Engl J Med 2017; 377:2592-2593 | December 28, 2017 | DOI: 10.1056/NEJMe1713888

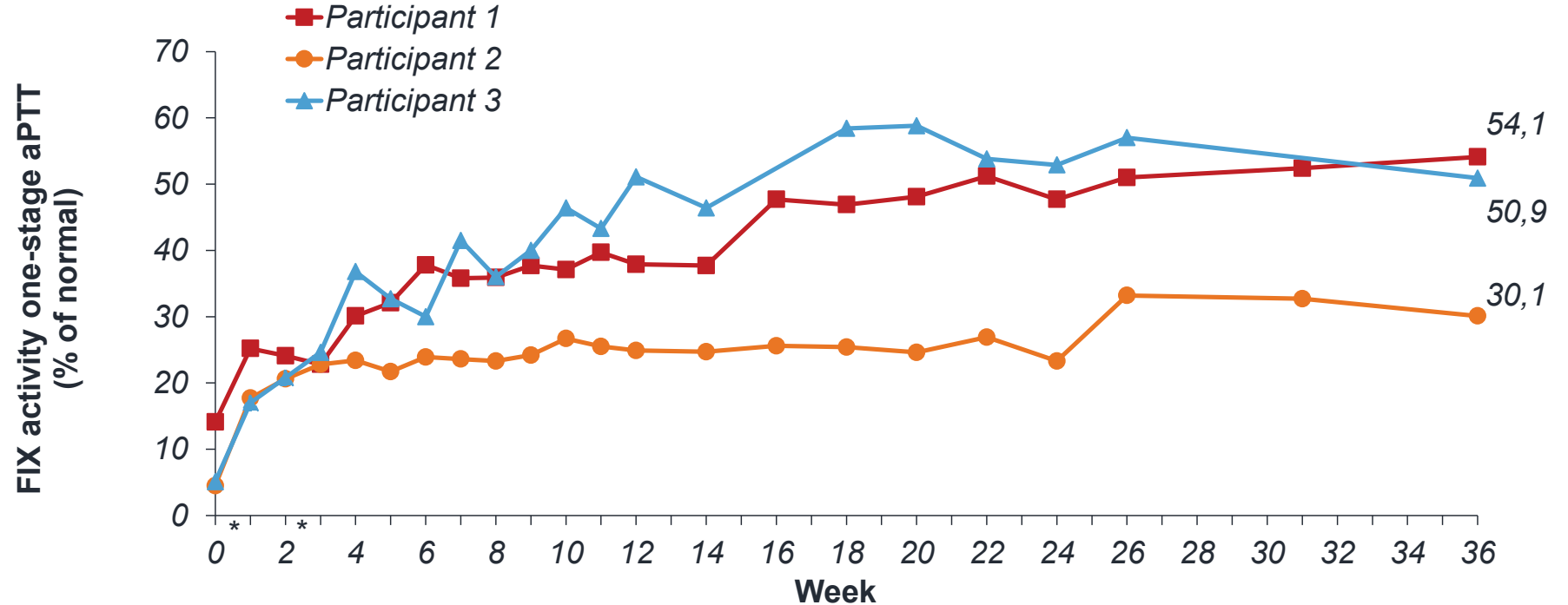
UniQure AAV5-FIX PADUA bridging study

- Effect of Padua (R338L) mutant on FIX levels at same 2E13/kg dose as Ph 1/2 (~7.5% FIX)

• Update: Phase 3 study completed enrollment 2019, N=55.

AMT-061 Efficacy: FIX activity at 36 weeks post-treatment

Mean FIX activity at 36 weeks: 45.0%

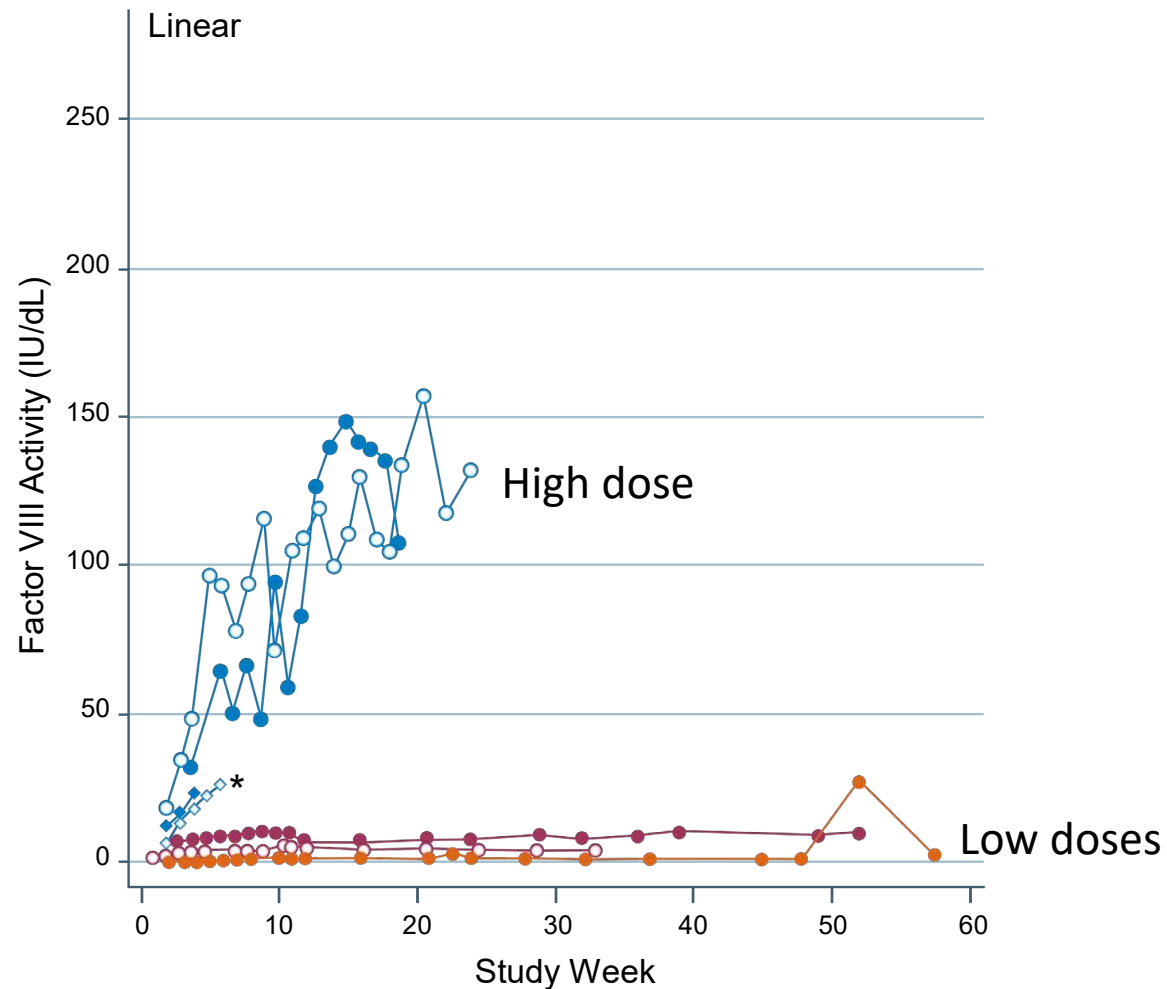


aPTT, activated partial thromboplastin time; FIX, Factor IX. No immunosuppression required. *May include activity from exogenous FIX replacement.

Sangamo Phase 1/2 study: AAV6-FVIII

Factor VIII Circulating Levels (Chromogenic Assay)

Clinicaltrials.gov, NCT03061201



Normal level 50-150%
Single infusion of AAV
Started Phase 3

* Subsequent to the data cut used for the ISTH presentation, Subject 9 attained normal levels

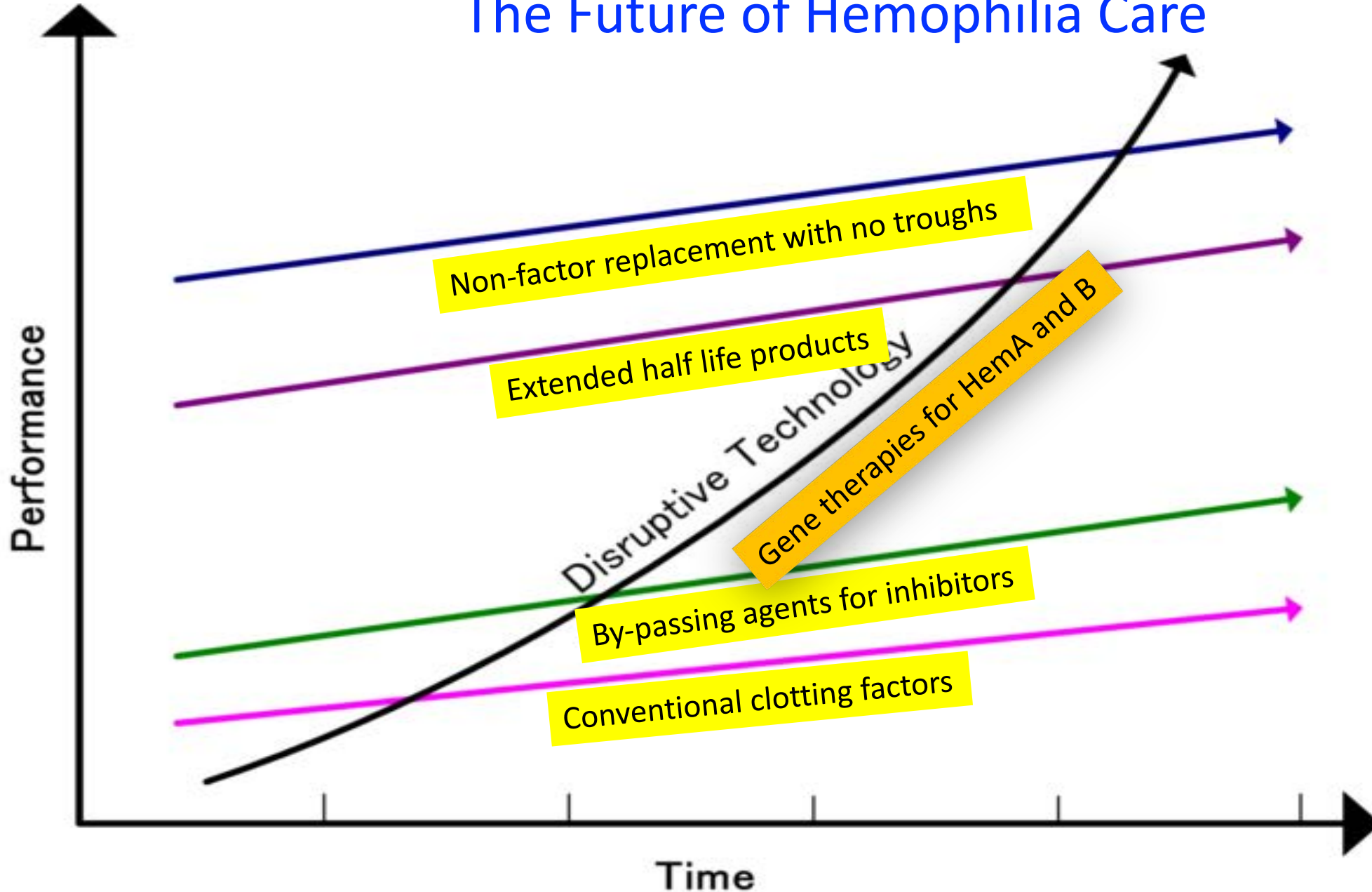
Phase 3 FIX Padua gene therapy Clinical trials

Drug (sponsor)	No. pts @ highest vg/kg	Mean steady state factor activity (% normal)	CS or OS assay	Prophy or Reactive steroids	Program status
AAV5-FIX, etranacogene dezaparvovec (AMT-061, uniQure)	3 @ 2E13	45% (30-54)	OS	None	Ph 3 fully enrolled
AAV-FIX SPK-9001 (Pfizer)	15 @5E11	30 (16-79)	OS	R	Ph3 Information blackout

Phase 3 FVIII gene therapy Clinical trials

Drug (sponsor)	No. pts @ highest vg/kg	Mean steady state factor activity (% normal)	CS or OS assay	Prophy or Reactive steroids	Program status
AAV5-FVIII Valoctocogene roxaparvovec (BMN-270, BioMarin)	7 @ 6E13	64% @ 1 yr 33% @ 3 yr	CS CS	P	Long term f/u
	16 @ 6E13 (interim)	36@23-26 wk	CS	R	Ph 3: 140 pts EMA, FDA filing on Interim analysis 4Q19
AAV6-FVIII (SB-525, Sangamo)	5 @ 3E13	Normal range	CS	R	Ph 3: Pfizer, run in
AAV LK03-FVIII (SPK-8011, Spark)	7 @ 2E12 Information blackout	Not reported	OS reported	R to P	Ph3? Loss of FVIII in 2/7 pts

The Future of Hemophilia Care



Foundational resource: eLEARNING.wfh.org



NEW eLEARNING
MODULE!

GENE THERAPY
FOR HEMOPHILIA



eLearning.wfh.org

Genes

Individuals have approximately 20,000 genes and inherit one copy of each gene from each parent. While most genes are the same in all people, a small number of genes have slight differences and this gives rise to different physical characteristics, such as hair and eye colour.

Some genes carry the instructions for making proteins. For example, the **F8 gene** carries the instructions to make **FVIII protein**, while the **F9 gene** carries the instructions to make **FIX protein**.

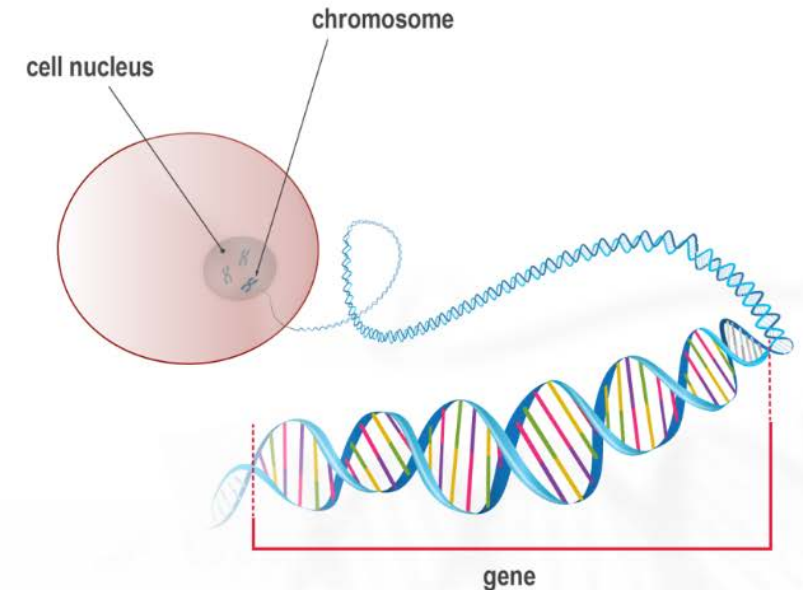


 How is a protein made from a gene?

 What is a genetic disease?

Select the "i" icons for further information on genes.

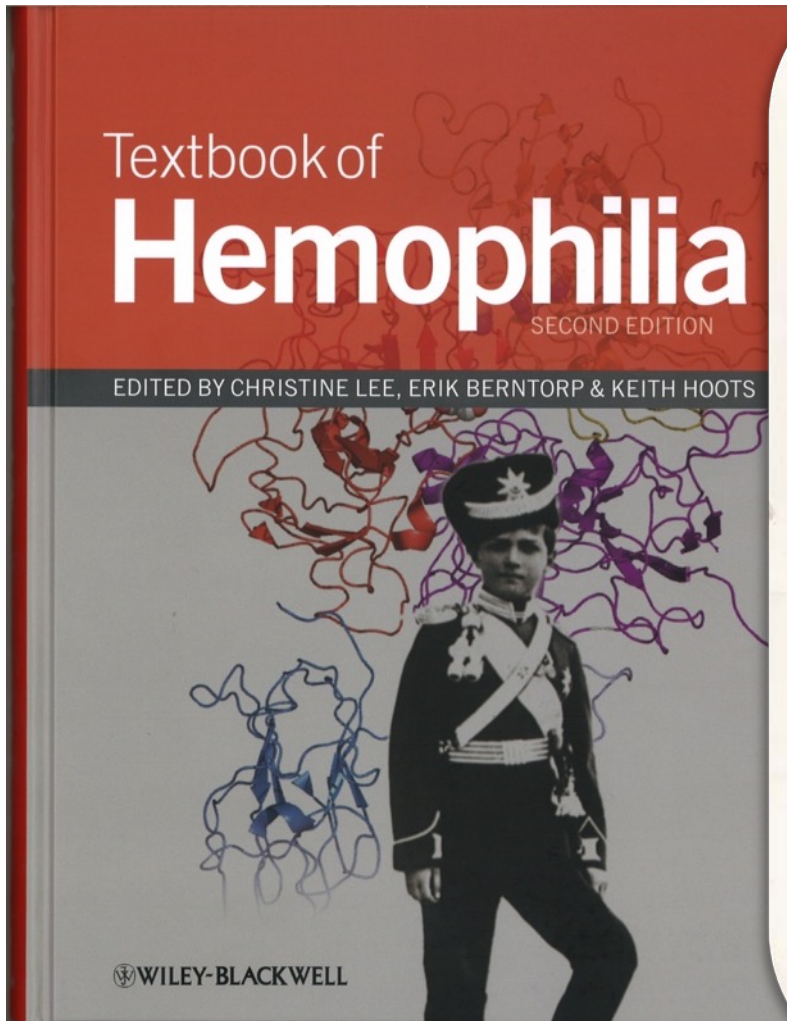
Select the Note icon for further information on gene naming conventions.



Genes are sections of DNA that carry instructions for making proteins. DNA is a long molecule that is packaged into **chromosomes**. Each chromosome contains many genes.

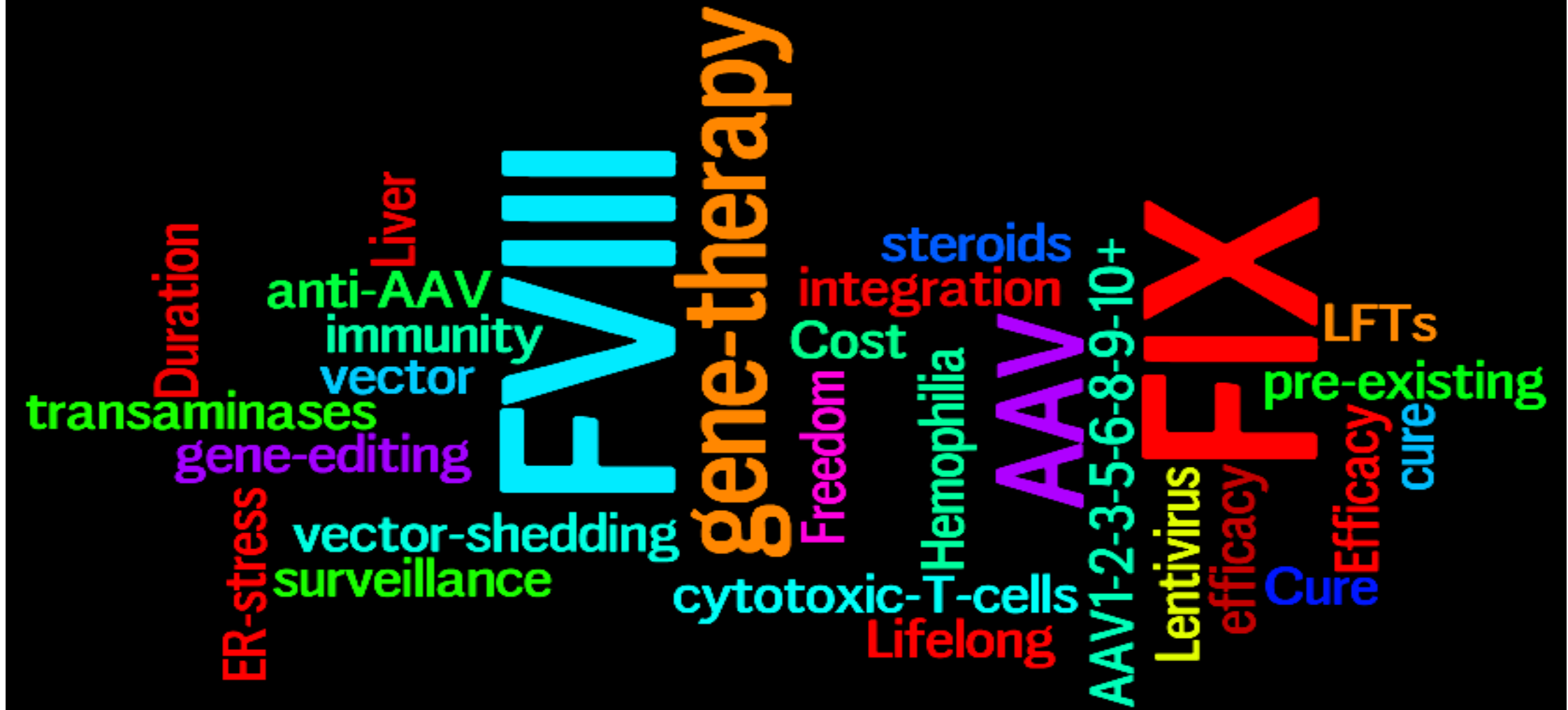


Fast Progress for Some, No Progress for Others



Or 100 years later...

70% of population has NO access to treatment



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THANK YOU