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ILLUSTRATED REVIEW

The Evolution of Hemophilia Therapeutics: An Illustrated Review

María G. Español[1,2] | Jessica N. Mistretta[1] | Michael D. Tarantino[1,3] | Jonathan C. Roberts[1,3]

[1]The Bleeding & Clotting Disorders Institute, Peoria, IL

[2]Department of Pediatrics, University of Illinois College of Medicine at Peoria, Peoria, IL

[3]Department of Pediatrics and Medicine, University of Illinois College of Medicine at Peoria, Peoria, IL

Correspondence
María G Español, MD, MHA., 427 W Northmoor Rd, Peoria, IL 61614, 309-692-5337.
Email: mespanol@ilbcdi.org

Abstract

Hemophilia is a rare genetic bleeding disorder historically associated with high morbidity and mortality. Some individuals with hemophilia suffer associated chronic joint disease, chronic pain, and other physical and mental health challenges. In the last 50 years, a better understanding of the pathophysiology of the disease has resulted in extraordinary therapeutic advances leading to enhanced quality of life and increased life expectancy.

We present an illustrated review of the evolution of hemophilia treatment from the development of non-factor therapies to gene therapy.

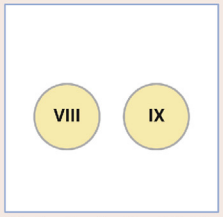
KEYWORDS
Hemophilia, treatment, illustrated review, bleeding disorder, gene therapy, hemophilia treatment

Essentials

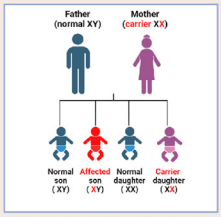
- Hemophilia is a bleeding disorder associated with high morbidity and mortality.
- Advances in hemophilia treatment have led to safer treatment options and a potential cure.
- Access to treatment and novel agents remains limited in low to middle-income countries.

HEMOPHILIA TREATMENT EVOLUTION

What is hemophilia and who is affected?



Bleeding disorder characterized by decreased or absent production of factor VIII (hemophilia A) and factor IX (hemophilia B).[1]



Inherited in a X-linked recessive manner.[1]

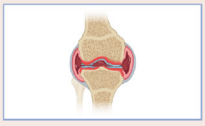
Affects most commonly males, but carrier females can have symptoms.[1]

SEVERITY

>5% but <40%	1%-5%	<1%
Mild.[1]	Moderate.[1]	Severe.[1]

CLINICAL MANIFESTATIONS

Severe and potentially life-threatening bleeding.[1]



Joint disease.[1]

Chronic pain.[1]

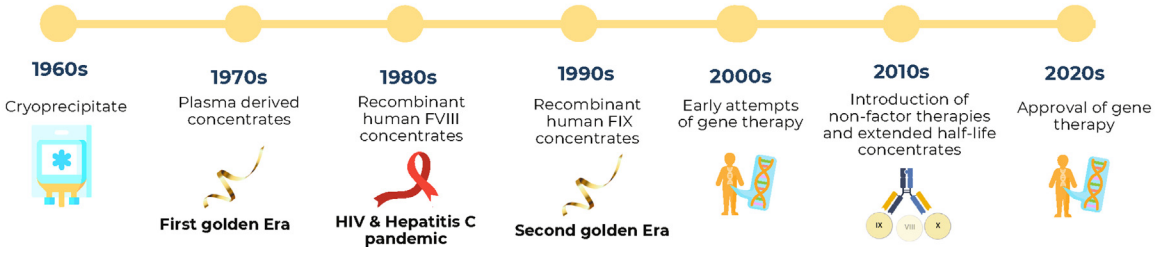
Mental health and physical challenges.[1]

HEMOPHILIA AROUND THE WORLD

20,000	17.1	3.8	818,928
New patients with hemophilia born worldwide every year.[2]	Number of males born with hemophilia A per 100,000 males born.[2]	Number of males born with hemophilia B per 100,000 males born.[2]	Males living with hemophilia in the world.[2]
?	1 in 5	8%	1,667
Prevalence of hemophilia in women around the world.[3-5]	Patients with mild hemophilia are female in the United States.[3-5]	Of women with hemophilia have severe disease.[3-5]	Women with hemophilia approximately seen in treatment centers in the United States.[3-5]

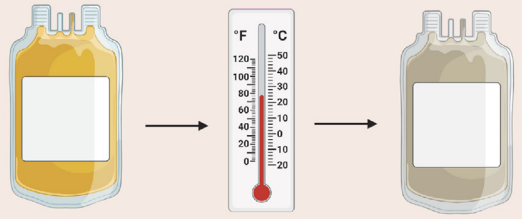
An Illustrated Review

This illustrated review will describe the evolution of hemophilia treatment from nonfactor therapies to the development of gene therapy.



CRYOPRECIPITATE, PLASMA-DERIVED CONCENTRATES, PATHOGEN INACTIVATION, AND REMOVAL METHODS.

In the 1960s, Dr. Judith Graham Pool and colleagues discovered and introduced the cryoprecipitate using a simple and low-cost technique adopted worldwide.[6-10]



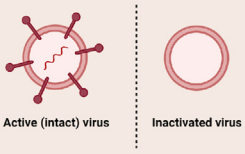
1 unit of fresh frozen plasma → **Slowly thaw at 1-6 °C** → **Cryoprecipitate**

- Rich in fibrinogen, FVIII, von Willebrand factor (VWF), and factor XIII.[6-10]
- Large amounts are needed for replacement therapy due to the low specific activity of FVIII.[6-10]
- Pooled product that does not undergo pathogen inactivation.[6-10]
- Associated with the transmission of bloodborne pathogens.[6-10]
- With time, Its use decreased due to production, transportation, and storage costs.[6-10]

The 70s were the first golden era in treating hemophilia by introducing plasma-derived concentrates. The use of unknown contaminated products with HIV and hepatitis C led to a pandemic and the development of donor screening techniques and pathogen attenuation methods.[8,10-12]

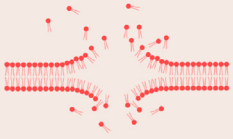
PATHOGEN INACTIVATION METHODS

Pasteurization



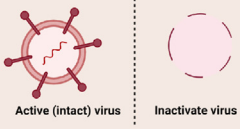
Inactivation of the lipid membrane using heat in an aqueous solution with a stabilizer to preserve the integrity of the factor.[13-14]

Solvent and detergent mixture (S/D)



Disruption of the lipid membrane using solvent and detergent mixtures with subsequent filtration to remove viruses.[13-14]

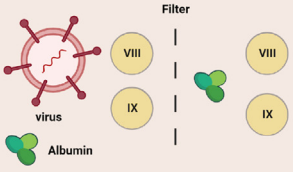
Dry and vapor heat treatment of lyophilized products



Utilization of heat to inactivate viruses that resist S/D treatment.[13-14]

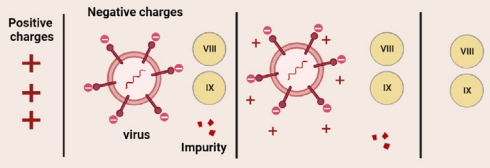
PATHOGEN REMOVAL METHODS

Virus filtration or nanofiltration



Viruses are removed from clotting concentrates using filters or membranes with pores smaller than the virus diameter.[13-14]

Chromatography



Viruses are removed using anion exchange.[13-14]

DEVELOPMENT OF RECOMBINANT FACTOR CONCENTRATES

In the 80s, the new generation of treatment started with the cloning first of FVIII and later with FIX and the production of recombinant human factor, which resulted in multiple generations of products and increased awareness of the development of inhibitors.[10]

FACTOR CONCENTRATE GENERATIONS

1 First generation

Contains animal and/or human plasma-derived proteins in the cell culture medium and in the final formulation vial.[10,14]

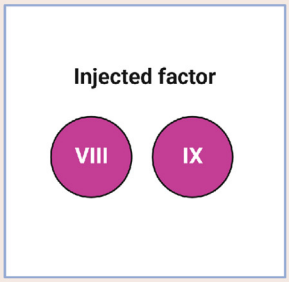
2 Second generation

Contains animal or human plasma-derived proteins in the culture medium but not in the final formulation vial.[10,14]

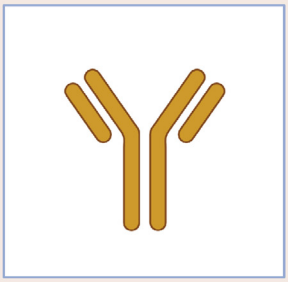
3 Third generation

Does not contain any animal or human plasma-derived proteins in the culture or medium or in the final formulation vial.[10,14]

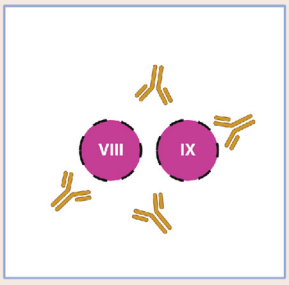
INHIBITORS



Patients with hemophilia received factor replacement therapy on-demand or prophylaxis.[15-21]



The use of factor concentrate triggers the development of IgG-neutralizing antibodies.[15-21]



IgG-neutralizing antibodies are proteins that decrease function (partially or entirely) and increase the clearance of infused factor.[15-21]

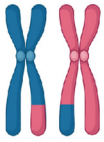
INCIDENCE AND RISK FACTORS FOR THE DEVELOPMENT OF INHIBITORS

25-32%

Lifetime risk of developing inhibitors in patients with severe hemophilia A.[15-21]

3-5%

Lifetime risk of developing inhibitors in patients with severe hemophilia B.[15-21]



Genetic risk factors.[15-21]

Environmental risk factors.[15-21]

Treatment-related risk factors.[15-21]

EXTENDED HALF-LIFE CONCENTRATES

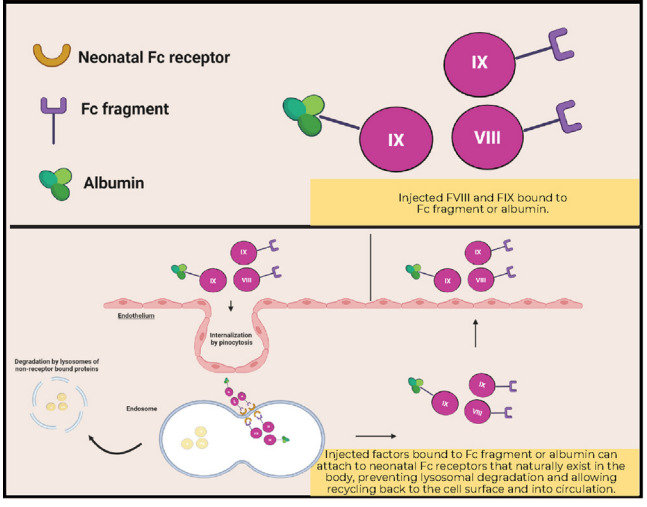
To decrease the treatment burden and improve treatment compliance and quality of life, extended half-life (EHL) concentrates were developed using different manufacturing methods.[22-30]

Using these methods, the half-life of FVIII and FIX can be increased by several fold:

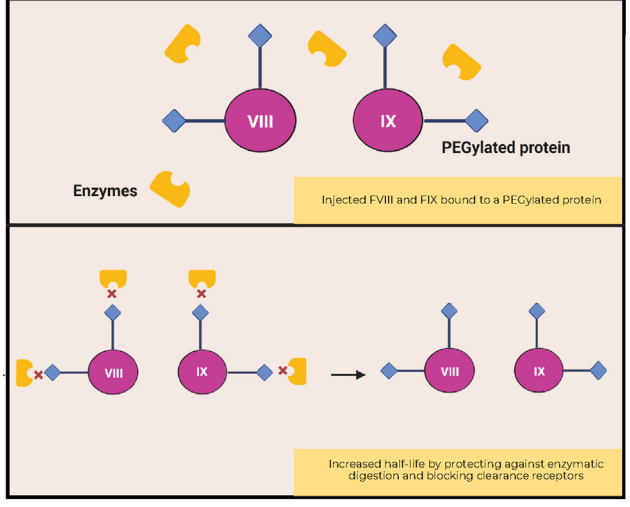
VIII — 1.5- to 1.7-fold

IX — 4- to 6-fold

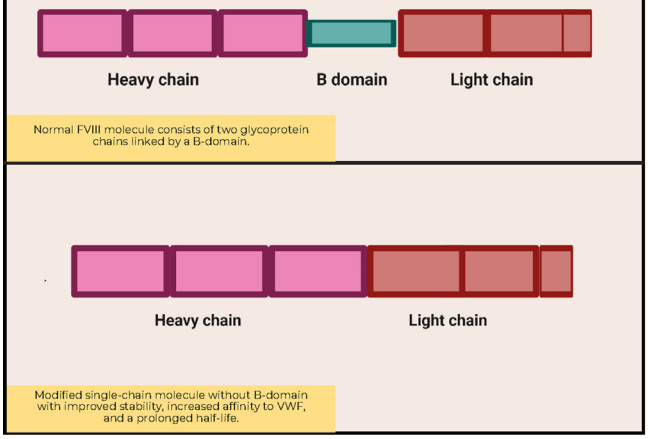
FUSION TO PROTEIN CONJUGATES



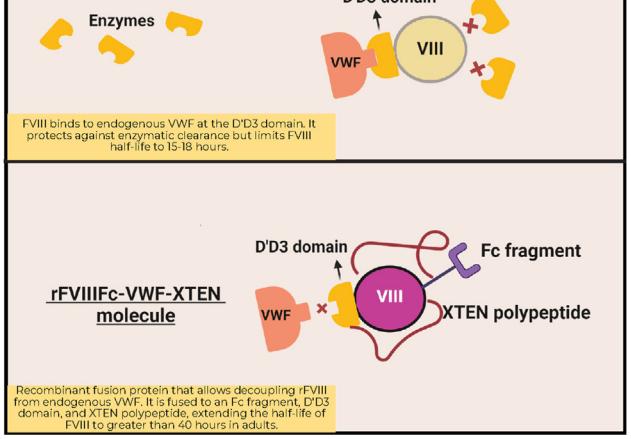
PROTEIN MODIFICATION:PEGYLATION



PROTEIN SEQUENCE MODIFICATION

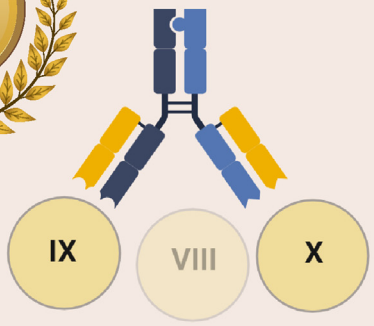


FUSION PROTEIN



NON-FACTOR THERAPIES: EMICIZUMAB

First bispecific monoclonal antibody approved for the treatment of patients with hemophilia A with and without inhibitors.[31-35]



- Mimics the action of FVIII by bridging FIX and FX to restore coagulation.[31-35]
- Partially corrects FVIII deficiency with the risk of breakthrough bleeding and bleeding in high-risk situations.[31-35]
- It is not inactivated by naturally occurring anticoagulants.[31-35]
- Given subcutaneously at infrequent intervals (weekly, biweekly, or monthly).[31-35]
- It is not neutralized by inhibitors and its use has been suggested in combination with ITI.[31-35]

Using emicizumab with bypassing agents like activated prothrombin complex concentrate (aPCC) has been associated with thrombosis. In the case of aPCC, cases of thrombotic microangiopathy have been reported when used at high doses (100 U/Kg/24 hours).[33]

If the use of bypassing agents is indicated, it is suggested that the recommended doses not be exceeded to decrease the risk of these events.[33]

MANAGEMENT OF BREAKTHROUGH BLEEDING ON EMICIZUMAB

With inhibitors[33]

rFVIIa or

aPCC or

Porcine FVIII (persistent bleeding not responding to aPCC)

VS

Without inhibitors[33]

FVIII concentrates (plasma-derived and recombinant)

Antifibrinolytics can be use in patient with and without inhibitors

FVIII TESTING ON EMICIZUMAB

Routine FVIII laboratory monitoring is not required in patients with and without inhibitors.[33-34]

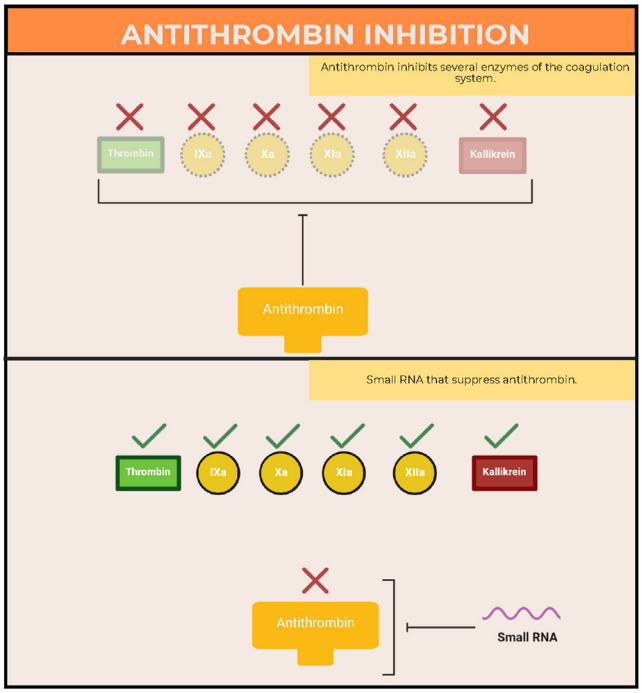
Indications for testing:
Surgery
Breakthrough bleeding
Suspected inhibitors

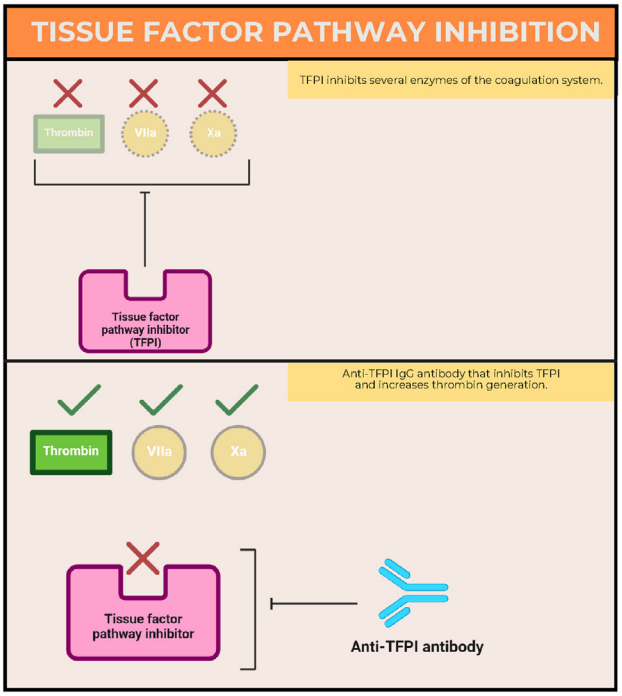
How to test?

FVIII level:
Bovine chromogenic assay.[33-34]
FVIII inhibitor:
Bovine chromogenic assay.[33-34]
Inhibitors to Emicizumab:
Measured using a modified one-stage clotting assay with emicizumab-specific calibrators.[33-34]

OTHER NON-FACTOR THERAPIES

Therapies are in development for patients with hemophilia with and without inhibitors. They affect different pathways inhibiting or enhancing coagulation; FVIII and FIX concentrates are still needed for breakthrough bleeding.[36-37]

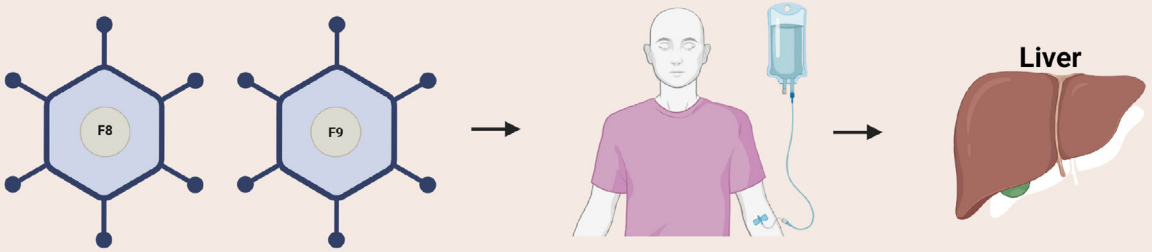




NON-FACTOR THERAPIES AT A GLANCE

	TYPE OF MOLECULE	HEMOPHILIA A	HEMOPHILIA B	USE IN PATIENT WITH INHIBITORS	REQUIRED PEAKS AND TROUGHS	ROUTE OF ADMINISTRATION	COMMERCIALLY AVAILABLE
Emicizumab	Antibody	Yes	No	Yes	No	Subcutaneous	Yes
Antithrombin inhibitors	RNA	Yes	Yes	Yes	No	Subcutaneous	No
Tissue factor pathway inhibitors	Antibody	Yes	Yes	Yes	No	Subcutaneous	Yes (Canada)

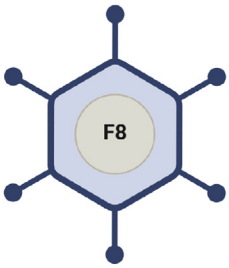
GENE THERAPY



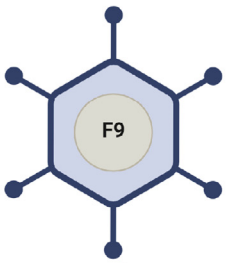
Adeno-associated virus (AAV) containing F8 or F9.[29,38-41]

F8 or F9 are delivered to the liver using an AAV as a vector and expressed in hepatocytes.[29,38-41]

Two gene therapy treatments are approved for adult patients with severe hemophilia A and B.[29,38-41]



Valoctocogene roxaparvovec-rvox



Etranacogene dezaparvovec

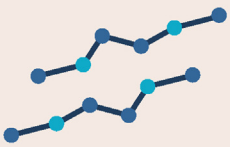
83%

Decrease in annual bleeding rate.[29,38-40]

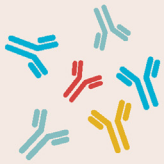
64%

Decrease in annual bleeding rate.[29,38-40]

LIMITATIONS OF GENE THERAPY



Variability in response.[39]



High prevalence of neutralizing antibodies to AAV.[39]

FVIII levels can decrease over time.[39]

Not approved in pediatric patients.[39]

USD$ 2 to 3 million per treatment.[39]

HEMOPHILIA AND GLOBAL ACCESS TO TREATMENT

Lack of access to treatment remains a barrier in low to middle-income countries.[41-46]

Financial constraints continue to be the primary cause of these disparities.[41-46]

TREATMENT AROUND THE WORLD

70% Of patients with hemophilia live in low-middle-income countries.[43]

15% Of patients in higher middle-income countries have insufficient but some access to therapy.[43]

15% Of the world population in high-income countries has access to advanced treatment for hemophilia.[43]

70% Of patients in low-middle-income countries have limited/no access to therapy.[43]

BARRIERS TO TREATMENT IN LOW AND LOW-MIDDLE-INCOME COUNTRIES

Limited healthcare infrastructure.[41-46]

Competing healthcare system and priorities.[41-46]

High costs of treatment.[41-46]

Lack of trained healthcare professionals due to human resource constraints.[41-46]

Lack of access to health insurance.[41-46]

INTERNATIONAL ORGANIZATIONS AND ACCESS TO TREATMENT

WFH
WORLD FEDERATION OF HEMOPHILIA

International organizations have helped patients in 112 countries, providing factor and nonfactor therapy and comprehensive care.[47,48]

>25,000 patients reached.[47,48]

CONCLUSIONS

Extraordinary advances have been made in the care of patients with hemophilia. A disease that once was associated with disabilities, high morbidity, and mortality today has a potential cure.

The evolution of hemophilia therapeutics has allowed these individuals to expand their horizons, setting personal goals never once thought attainable. Efforts continue to be made by international organizations to allow access to the standard of care and novel therapies to those living in low to middle income countries, to eventually realize a life without bleeds for the community worldwide.

DESIGN

The manuscript was designed and created using Canva and BioRender.

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AUTHOR CONTRIBUTIONS

All authors developed the concepts and images, wrote the manuscript, and approved the final content

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M.D.T. reports consulting fees from Pfizer, Sanofi, Sobi–Swedish Orphan Biovitrum, Takeda, Amgen Inc, Octapharma, Genentech, BioMarin, UCB Biosciences, Dova Pharmaceuticals, Novo Nordisk and honoraria from Sobi, Genentech, Amgen, Novartis, BioMarin, and Sanofi. J.C.R. reports grants from Takeda and GeneTech and consulting fees from CSL Behring, F. Hoffman-La Roche AG, Sanofi, HEMA Biologics, Novartis, Novo Nordisk, Pfizer, Takeda, and Genentech. M.G.E. reports participation on Sevenfact Advisory Board for HEMA biologics and honoraria from Octapharma.

ORCID

Jonathan C. Roberts https://orcid.org/0000-0002-9415-9543

X

Jonathan C. Roberts @JonRob08

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