Evolution of therapies in inherited bleeding disorders:

a remarkable journey from blood to gene therapy

Johnny Mahlangu

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Charlotte Maxeke Johannesburg Hospital and
Department of Molecular Medicine and Haematology
NHLS and University of the Witwatersrand, Johannesburg

Inaugural Lecture

April, 2017

Please meet Omran and Sipho

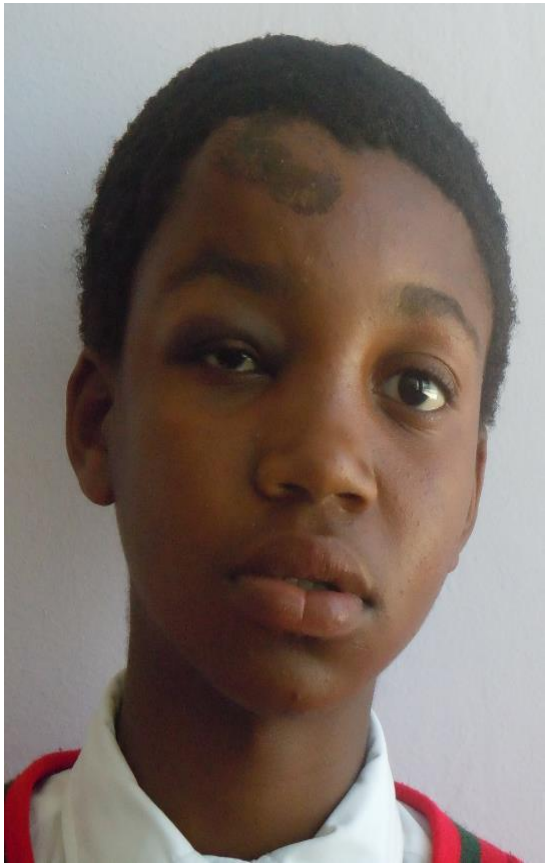
Omran Daqneesh

Similarities

- Injured brave boys
- Bleeding

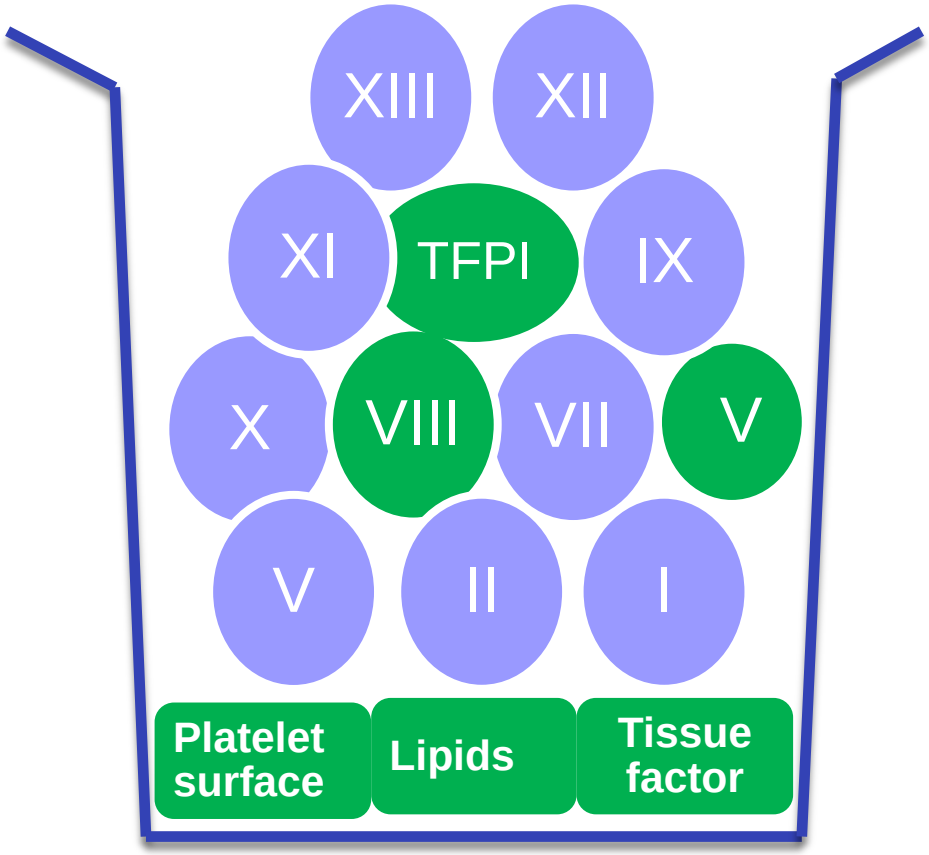
Differences

- External and internal bleeding
- Sipho will not stop bleeding whilst Omran will stop bleeding

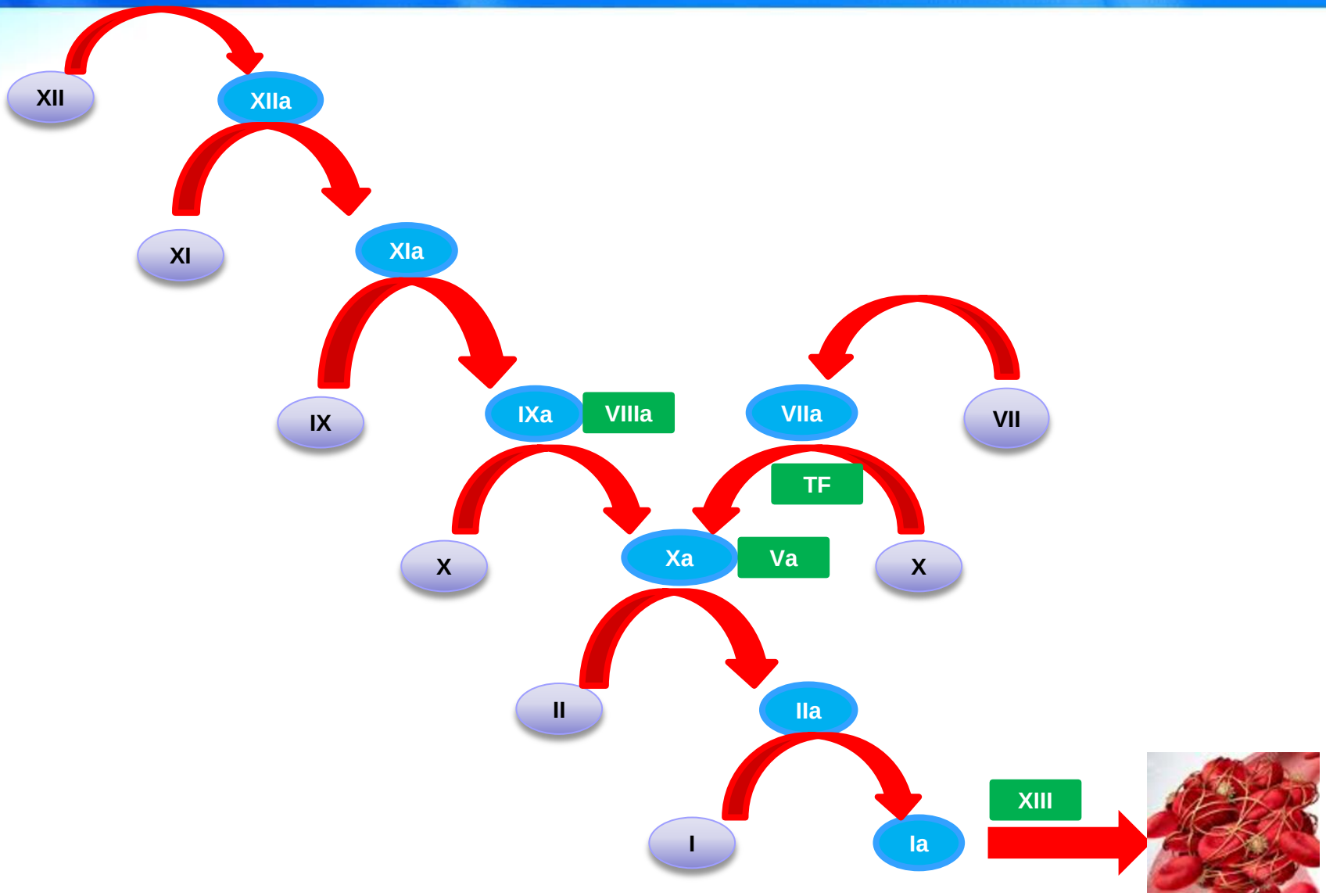


Sipho Sobayi

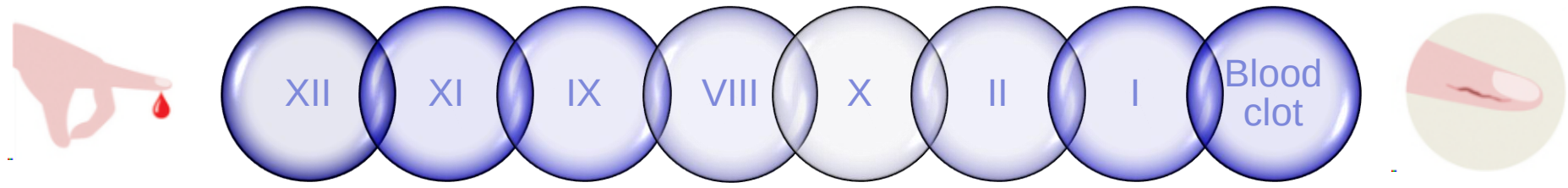
Omran has a full complement of coagulation proteins



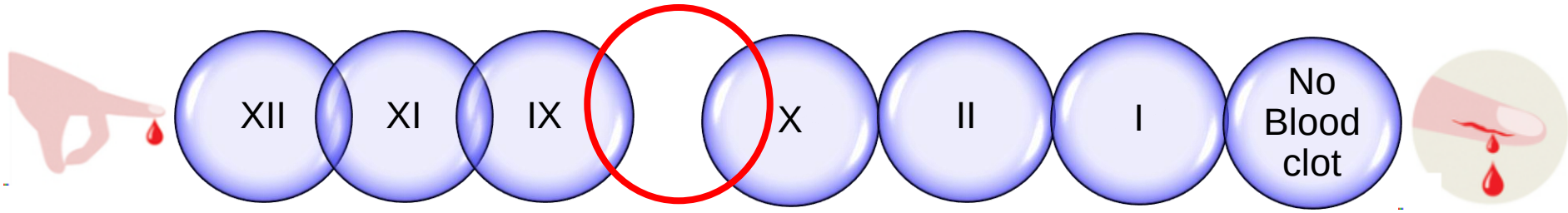
Coagulation cascade



Upon injury……

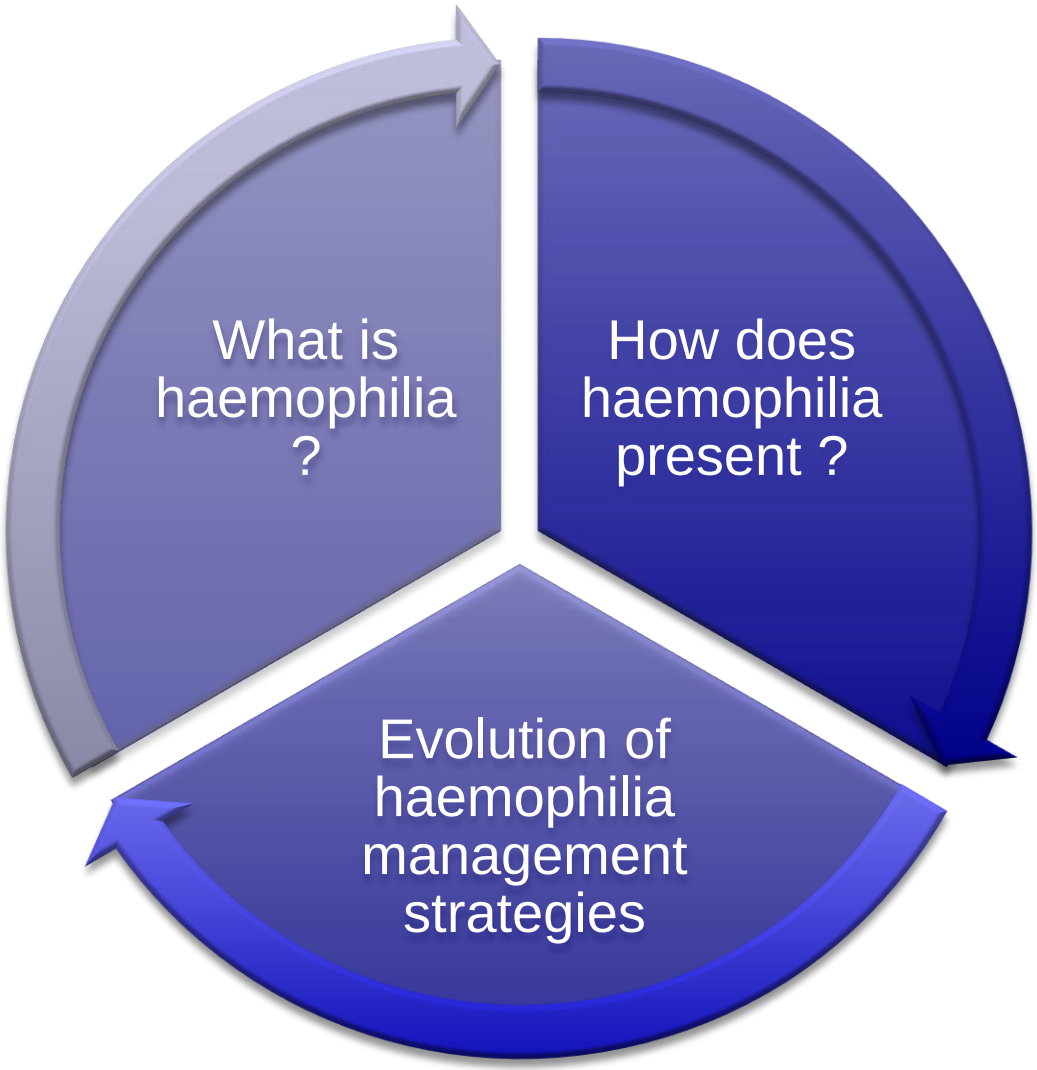


Omran has a normal haemostatic response



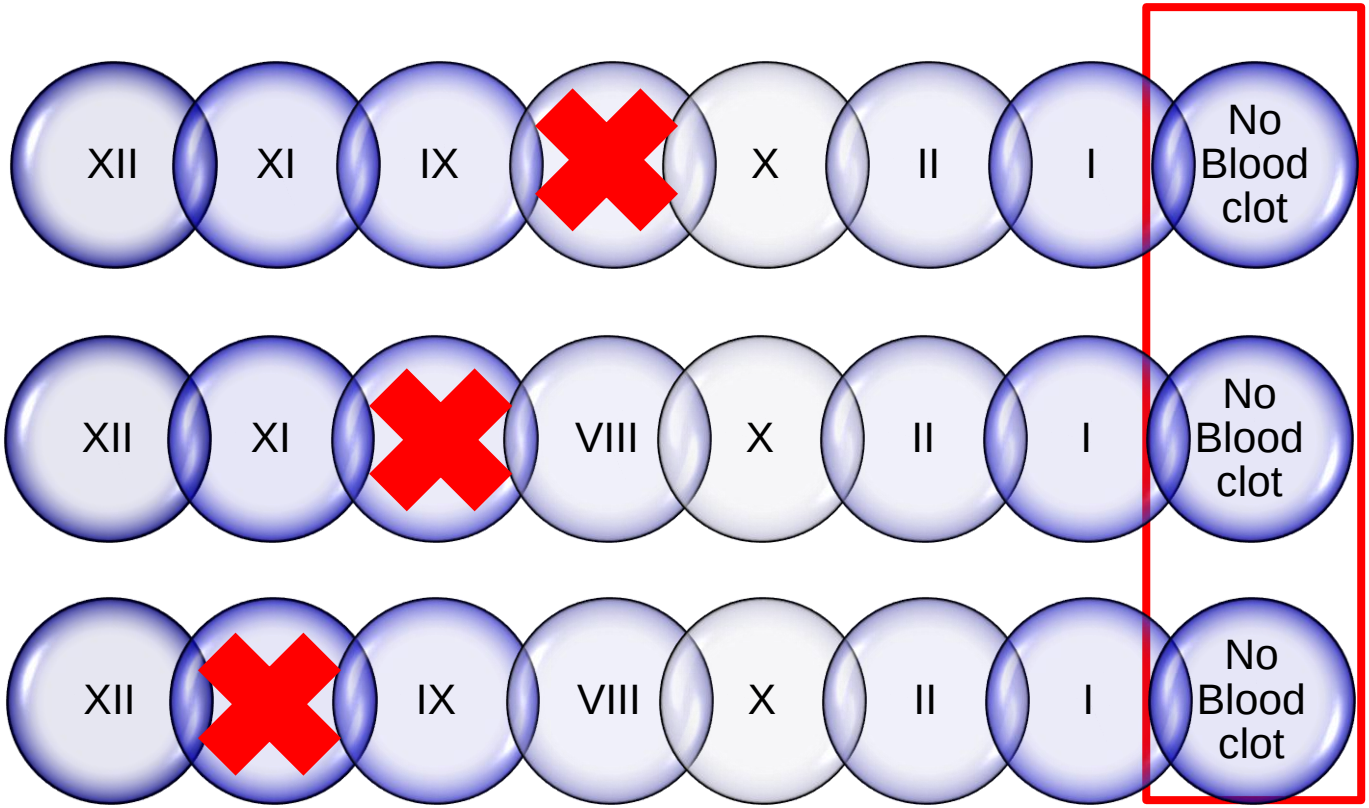
Sipho has an abnormal haemostatic response

Haemophilia


What is haemophilia ?
How does haemophilia present ?
Evolution of haemophilia management strategies

Haemophilia is deficiency of clotting factor

Haemophilia A



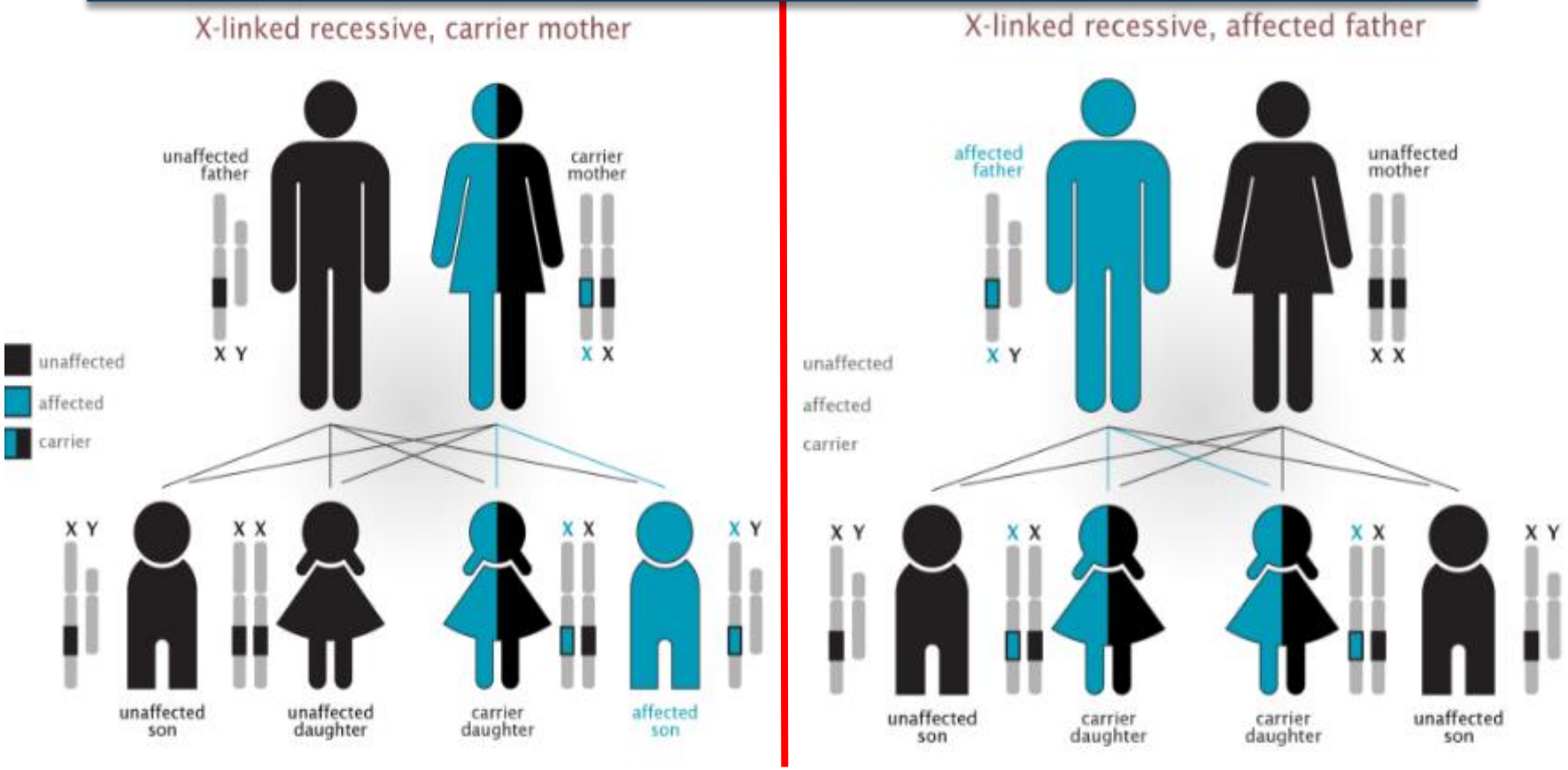
Haemophilia B

Haemophilia C

Inability to form a clot is inherited

Mode of inheritance is X-linked

Females are carriers and males are affected

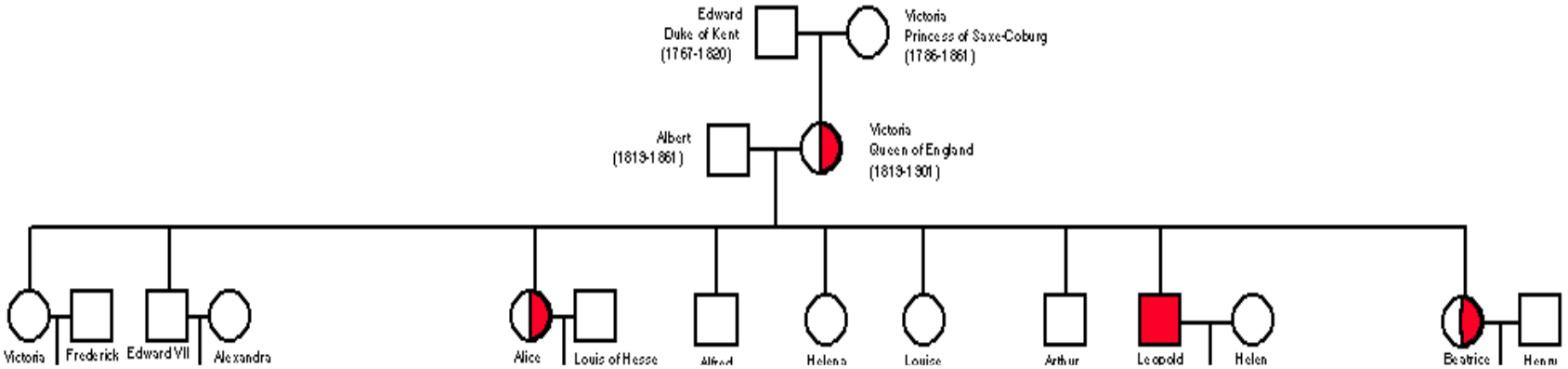


30% have no family history of haemophilia – spontaneous mutations

Haemophilia is a Royal disease

Queen Victoria(1813-1901)

Haemophilia in royal families



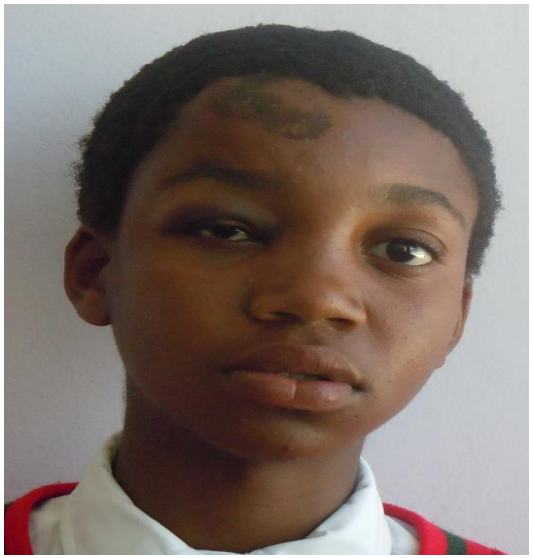
https://www.google.co.za/url?sa=i&rct=j&q=&

Haemophilia affects all races in all locations

The story of Omran and Sipho

Omran Daqneesh

Sipho Sobayi

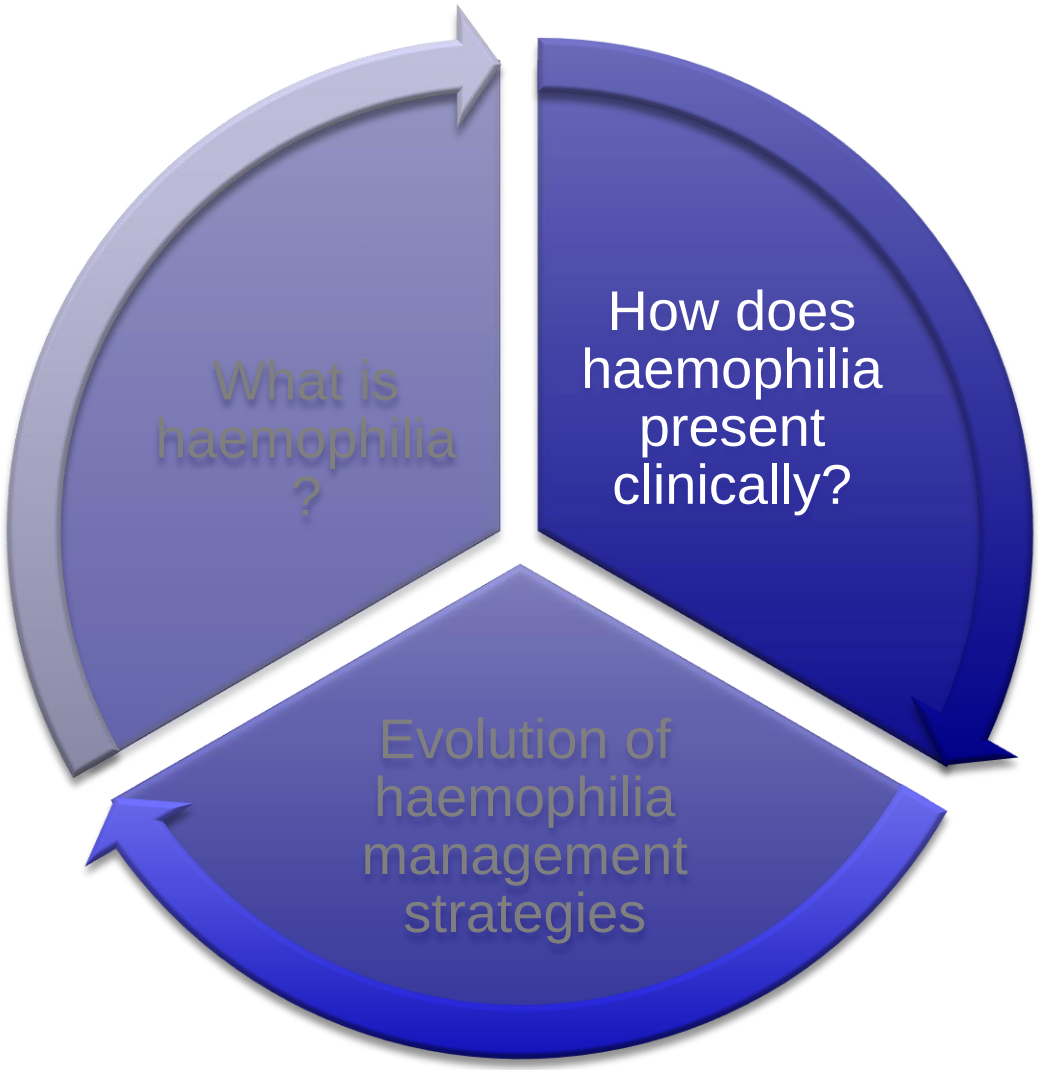


400 000 killed since the start of the Syrian civil war

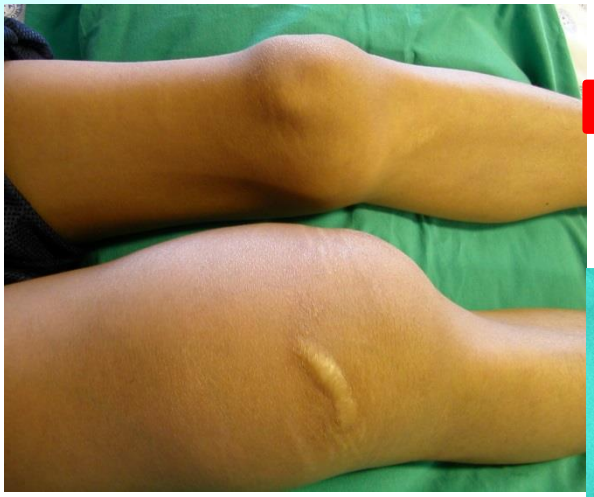
Sunday times, 14 August 2016

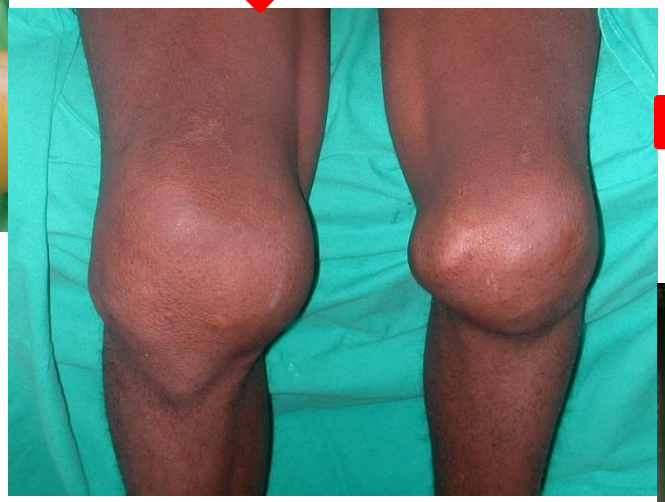
400 000 people with haemophilia in the world

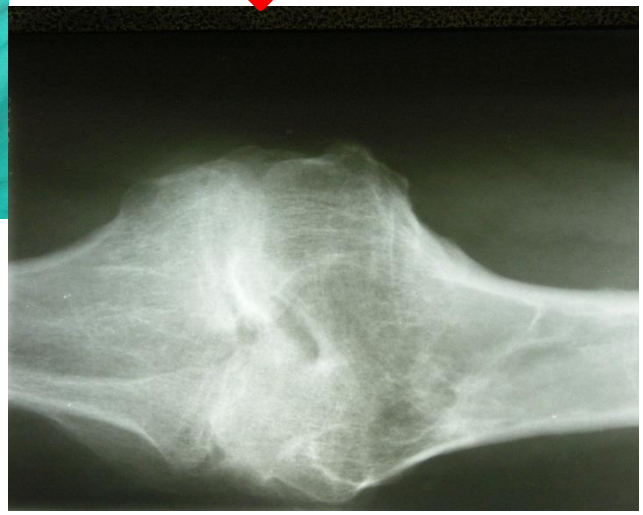
World Federation of Haemophilia Global Survey, 2016


What is haemophilia ?
How does haemophilia present clinically?
Evolution of haemophilia management strategies

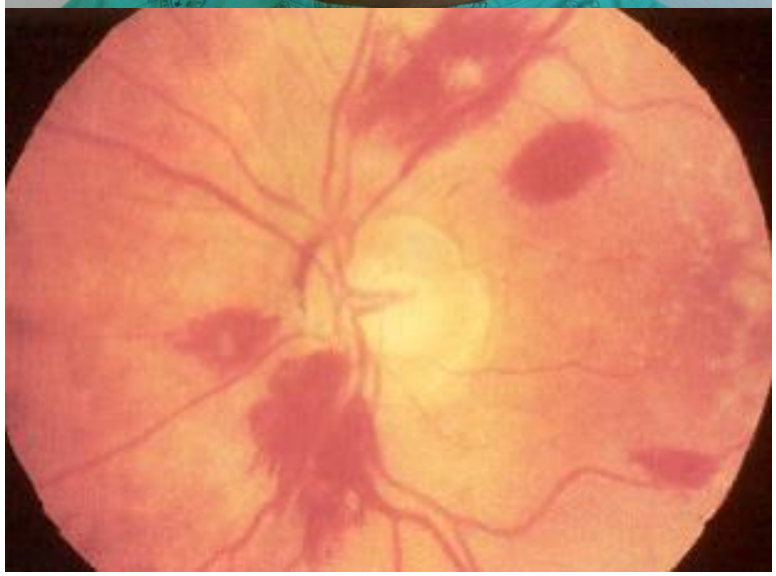
Joint bleeds are the hallmark of haemophilia

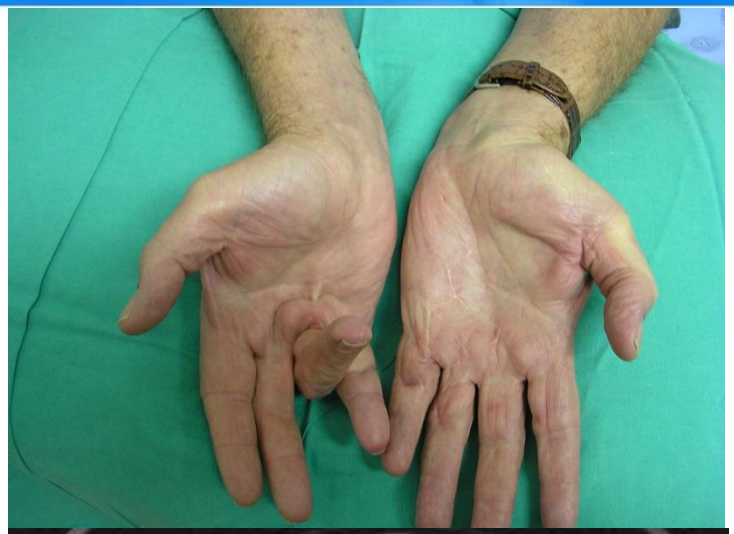


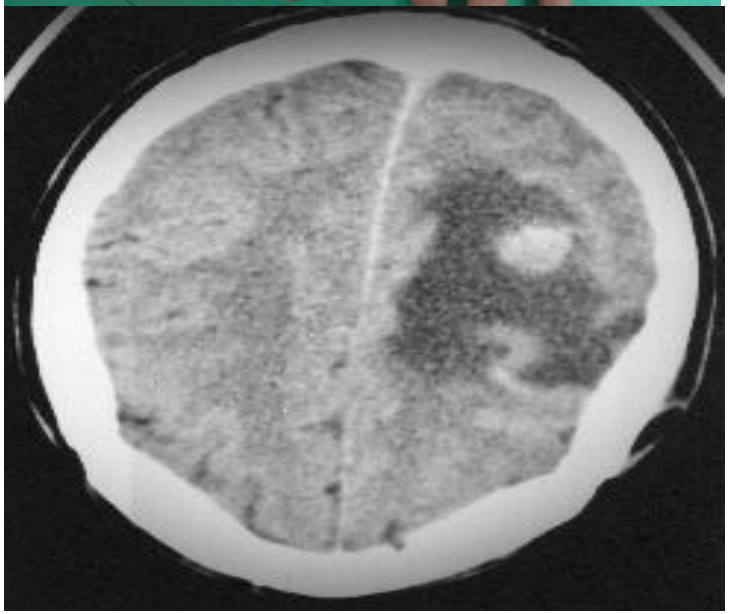




Bleeding can be anywhere….



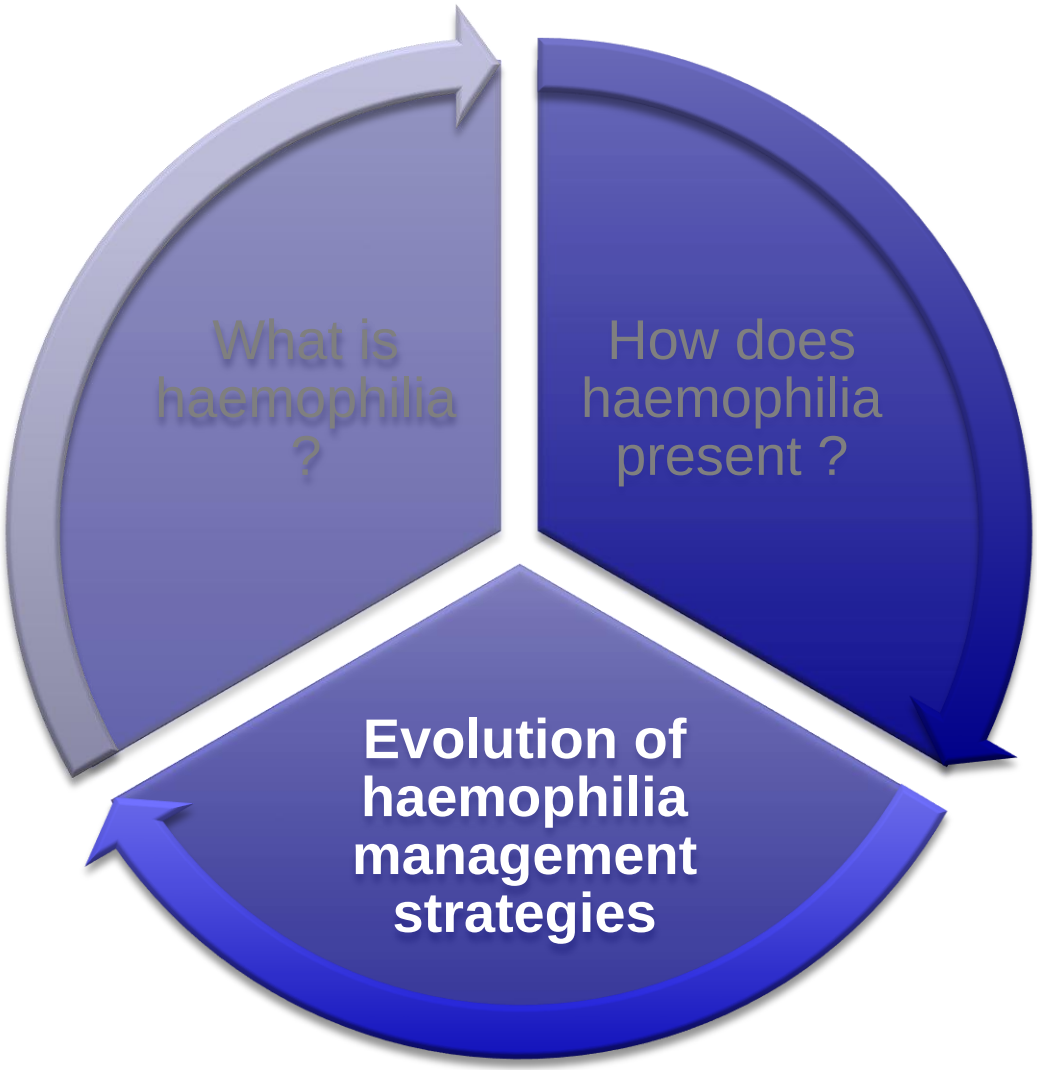




Can innovative protective measures work in haemophilia?

Factor level is the main determinant of bleeding phenotype

	Factor level	Bleeding Phenotype
Severe	< 1%	Bleed spontaneously without injury
Moderate	2-5 %	Bleed on minor haemostatic challenge/injury
Mild	5-50 %	Bleed on major haemostatic challenge/injury


What is haemophilia ?
How does haemophilia present ?
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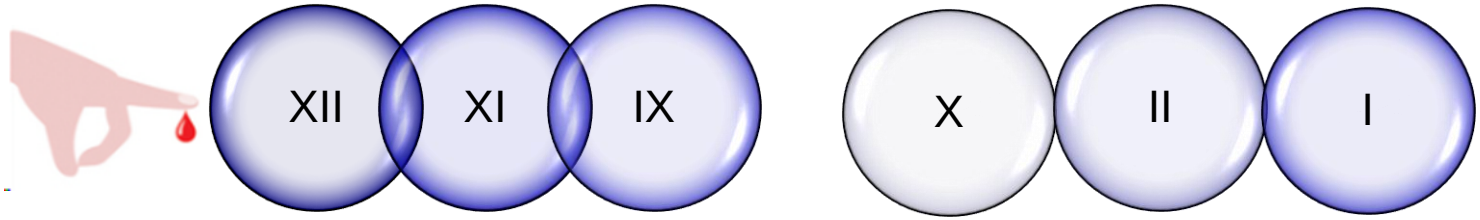
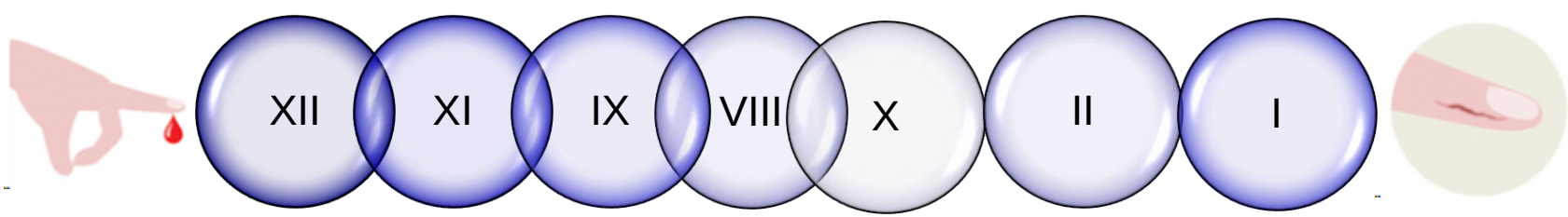
Standard of care is replacement of missing clotting factor



The source of replacement has been evolving

? replacement therapy

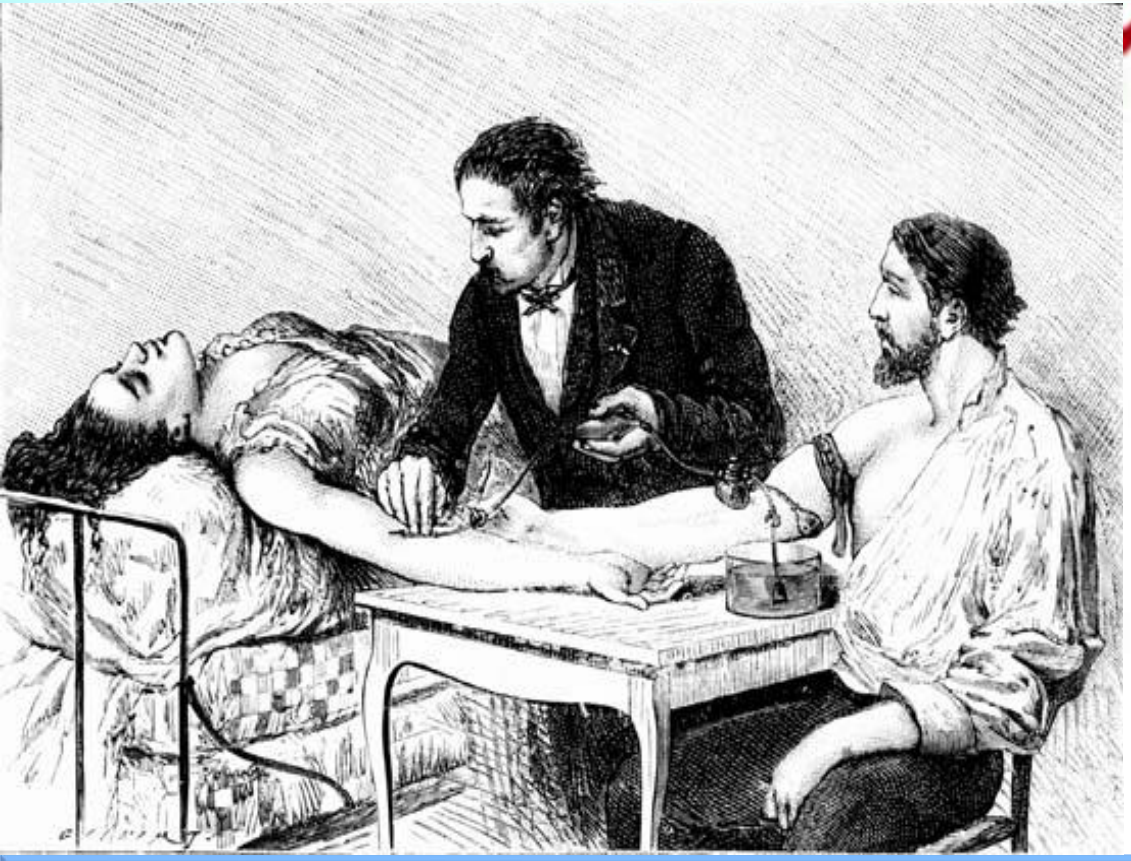


Evolution of haemophilia therapies

1944

- 1st use of whole blood

Whole blood replacement therapy 1944-Dr Alfredo Pavlosky



Challenges

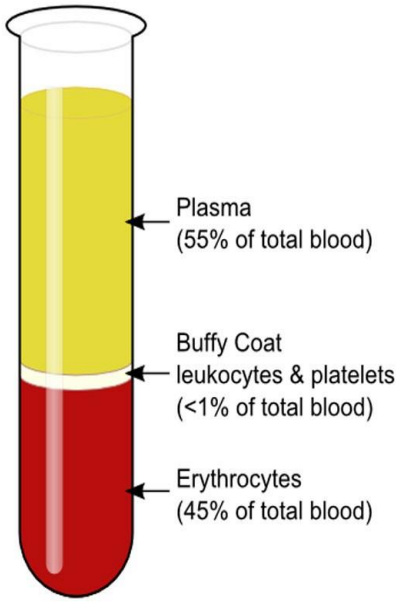
- Death due to incompatible transfusion reactions
- Did not work in all patients

Evolution of haemophilia therapies

1944
- 1st use of whole blood

1955
- 1st use of Fresh Frozen Plasma

Fresh Frozen Plasma
1955- Dr Kenneth Brink



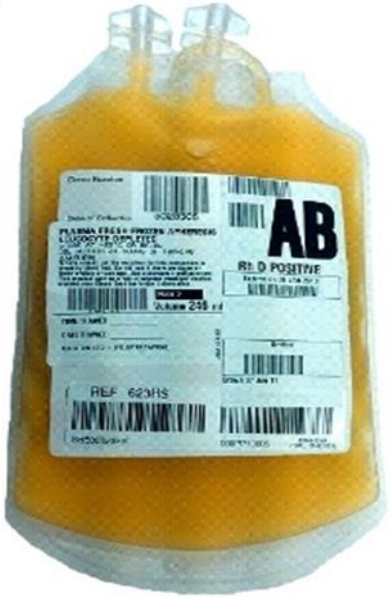
Challenges

- Non standardized factor levels
- Large volumes required - 15-25ml/kg body weight
- Handling logistics- must be kept frozen -20◦C

Evolution of haemophilia therapies

- **1944** • 1st use of whole blood
- **1955** • 1st use of Fresh Frozen Plasma
- **1964** • 1st use of Cryoprecipitate

Cryoprecipitate
1964- Dr Judith Pool



Challenges

- Emergence of transfusion transmitted infections
  - Hepatitis
  - Syphilis
  - HIV

Cryoprecipitate precipitated a crisis

The Sydney Morning Herald

Tuesday July 2, 2002 — First published 1831 No. 51,422 $1.20

Food chain
The talent that shaped Sydney dining
GOOD LIVING

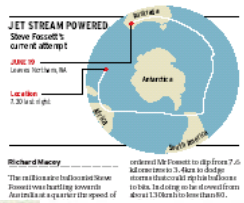
Mardi Gras
Why it's in meltdown
PAGE 4, OPINION PAGE 11

Hewitt stays hot
Through to quarter-finals
SPORT PAGE 36

Suspect blood: Red Cross faces scrutiny

Hepatitis C fears after suspect blood sent back into circulation

Up here, no-one can hear you scream along



Richard Macey

Murder charges brought in German HIV blood products case

Munich. Two officials of Haemoplas, a German blood products company, have been charged with murder for allegedly selling blood products not tested for HIV.

If convicted, Frank Giesbert, the director of the company — which is based in Osterode in the state (*Land*) of Niedersachsen — and Günter Eckert, the head of its blood product testing

Transfusions came from former president's home state


RELAXED: Bill Clinton plays golf in Prestwick before the banquet

Infected blood victims protest at Clinton visit

By **Matt Dickinson**

AIDS patients launched a protest yesterday outside a hotel where former US President Bill Clinton is due to speak.

Around 20 HIV-infected men and women from across the UK have gathered outside the Thistle Hotel in Glasgow.

The sufferers – all haemophiliacs – claim they contracted the disease from tainted blood taken from prisoners in Arkansas, the US state where Clinton was governor.

They said around 1,200 British people have since died, but the authorities involved have all refused to hold a public inquiry.

Andy Gunn, from Inverness, was among the protesters.

The 31-year-old musician said he was diagnosed with Aids and Hepatitis C 15 years ago after being given the blood between 1981 and 1986.

"I was one of 70 children infected with the blood taken to Yorkhill Children's Hospital in Glasgow," he said. "Only 17 of us are left.

"We are here to highlight the fact that thousands of people were infected by this tainted blood and the Government has done everything to cover it up. We want a public inquiry.

"We are not expecting to speak with Clinton, but we want him to be aware of what happened while he was governor."

Democrat Clinton was speaking at a £500-a-head banquet at the hotel, attended by 800 political and business leaders.

They included First Minister Jack McConnell and Sir Tom Hunter.

Public health minister Caroline Flint said compensation payments of up to £45,000 had been made available to those affected. She said a public inquiry would not provide "any real benefit" to those affected.


MEETING: Protesters, top, and McConnell with Clinton

■ JAPAN

Tainted blood death: AIDS chief arrested

Tokyo: Japanese prosecutors arrested the former head of a government AIDS task force yesterday in the first arrest linked to a scandal involving tainted blood products believed to have caused the deaths of about 400 hemophiliacs.

The arrest of Takeshi Abe, 80, came hours after prosecutors summoned him for questioning. He is the former head of the Health and Welfare Ministry's task force set up in 1983 to deal with AIDS.

The Tokyo District Public Prosecutors Office also


Takeshi Abe is taken for questioning by prosecutors.

India hit by contaminated blood scandal

A complaint that the Red Cross blood bank in Bombay supplied several hospitals with blood that was contaminated with HIV threatens to snowball into India's biggest blood scandal since the government made screening for HIV mandatory six years ago. A former Red Cross doctor has told government investigators that he has evidence that several hundred bottles of blood whose contamination status is unknown remain unaccounted for in the blood bank's records.

The controversy arose last month when

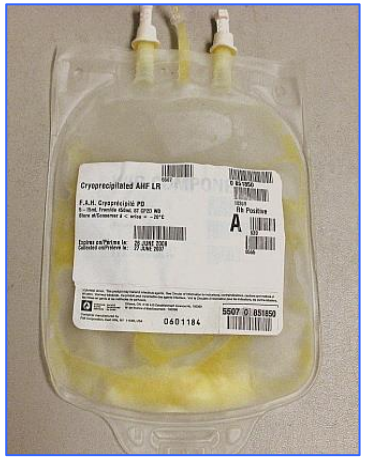
An urgent search for replacement product with golden triad properties

Evolution of haemophilia therapies

- **1944** • 1st use of whole blood
- **1955** • 1st use of Fresh Frozen Plasma
- **1964** • 1st use of Cryoprecipitate
- **1980** • 1st use of Plasma derived Clotting factor

Plasma derived clotting factor concentrate

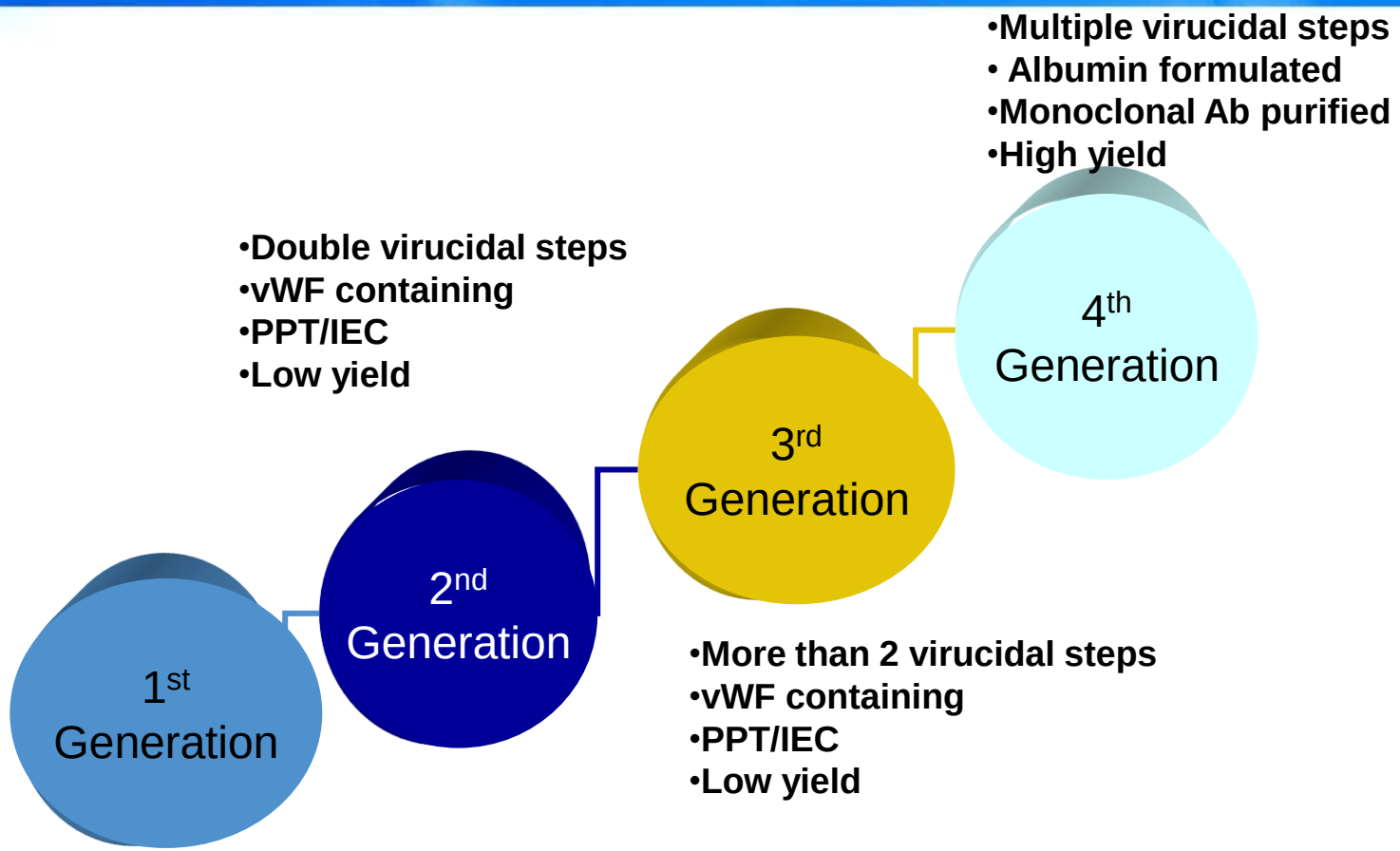
Cryoprecipitate → **Fractionation technology** → **pCFC**



Regulatory oversight/inspection
Good manufacturing practices
Clinical trial validation/verification

pCFC-plasma-derived clotting factor concentrate

Plasma derived Factor Concentrate



plasma derived clotting factor concentrates had challenges

- Only a limited number of blood donors worldwide
- Potential for transmission of known pathogens and viruses in the window period
- Potential for transmission of unknown human disease
- Limited shelf life of the plasma derived products

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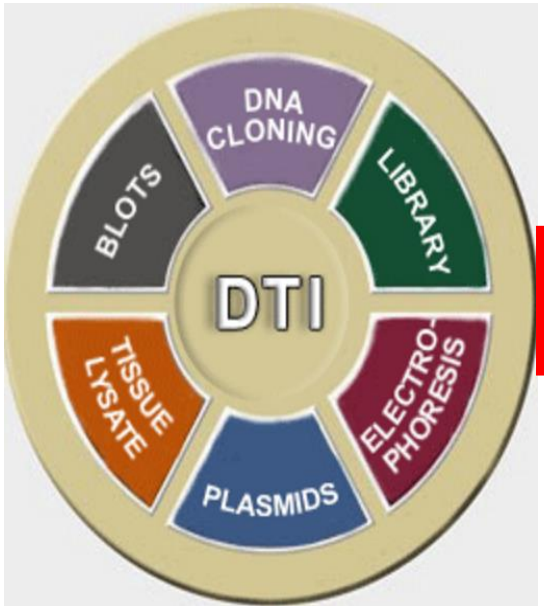
- **1990** • 1st use of recombinant Clotting factor

Recombinant clotting factor concentrate

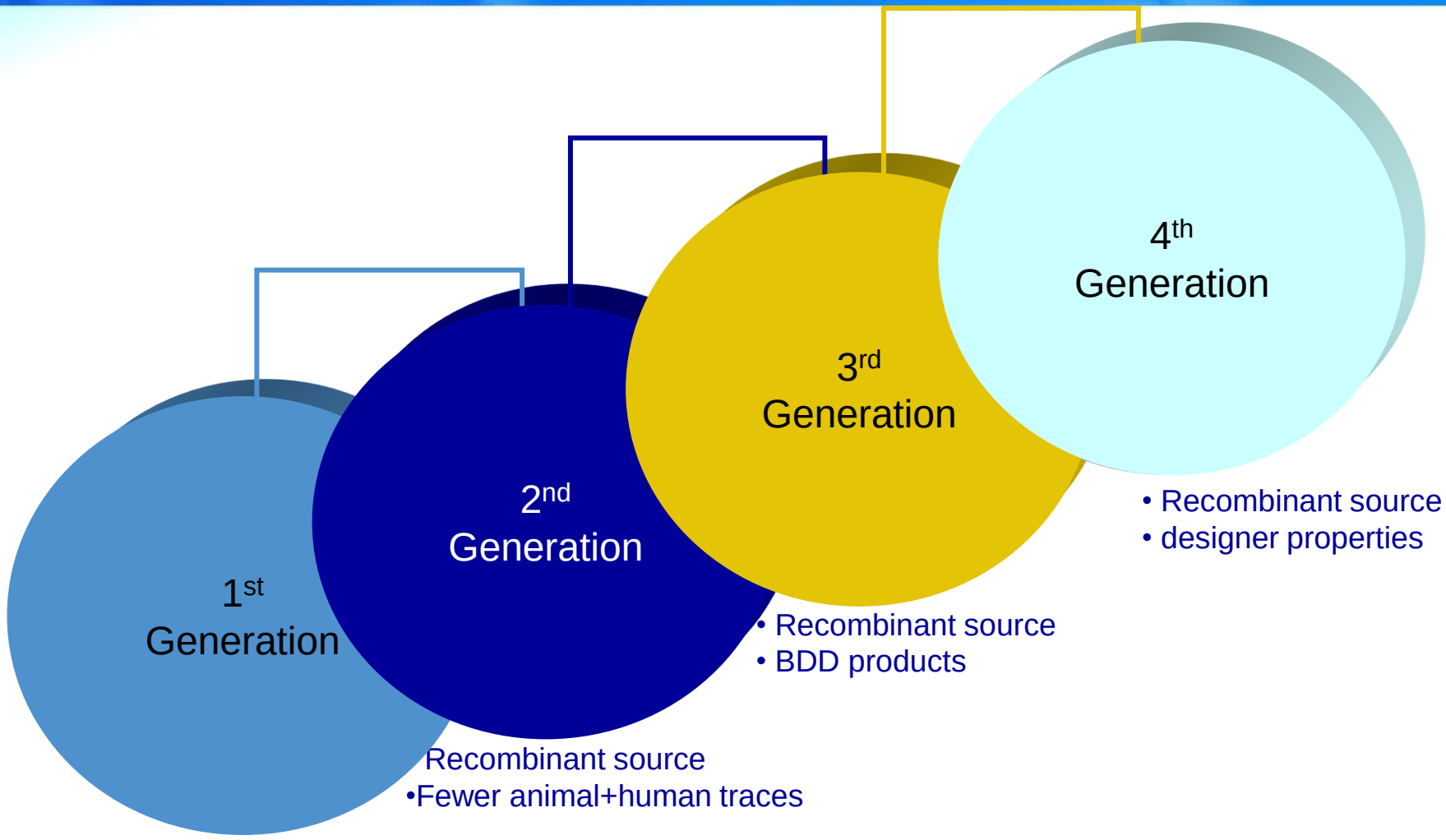
Clotting factor DNA

Recombinant DNA Technology

Recombinant clotting factor



Recombinant Factor Concentrate have evolved to eliminate human additives



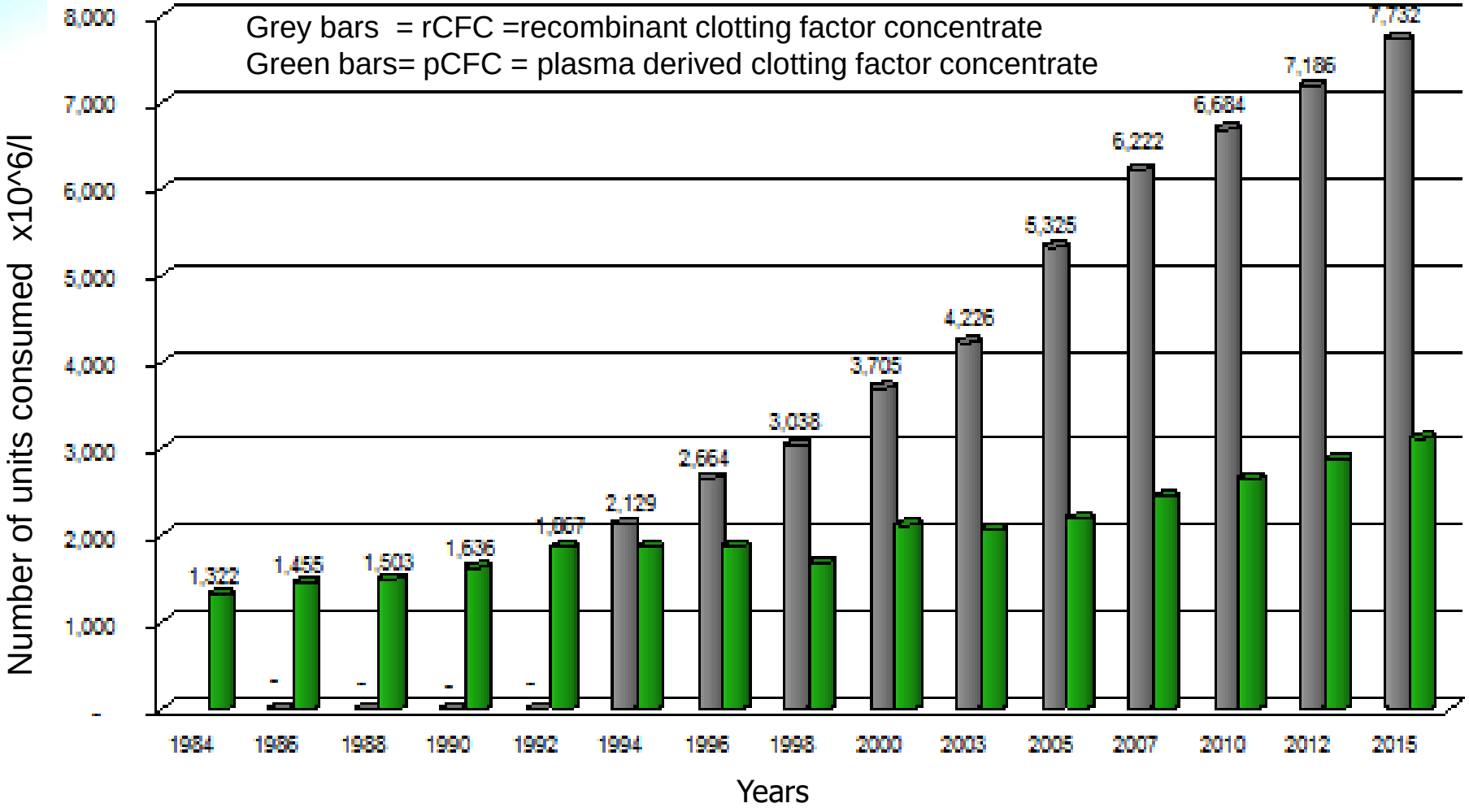
Traces = protein materials derived from the manufacturing process (nutrients, cell lines, monoclonal antibodies, etc.)

Advantages of rCFC

- No human derivatives
- Shelf life longer than that of blood products
- Unlimited quantities

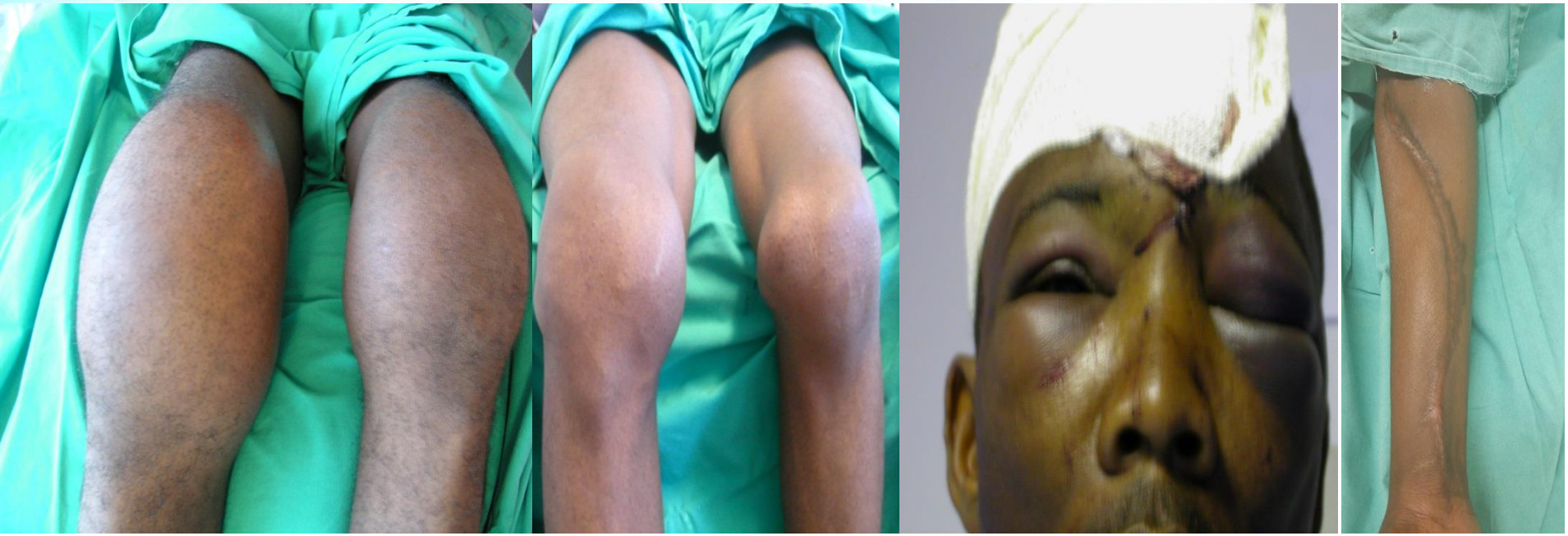
rCFC- recombinant clotting factor concentrate

Global consumption of CFC has increased



Global Clotting Factor Concentrate Consumption from http://marketingresearchbureau.com/list-of-reports/

Haemophilia complications persisted despite increased CFC consumption



	Factor level	Bleeding Phenotype
Severe	**< 1%**	**Bleed spontaneously without injury**

Factor level is the main determinant of bleeding phenotype

	Factor level	Bleeding Phenotype
Severe	**< 1%**	**Bleed spontaneously without injury**
Moderate	**2-5 %**	**Bleed on minor haemostatic challenge/injury**
Mild	**5-50 %**	**Bleed on major haemostatic challenge/injury**

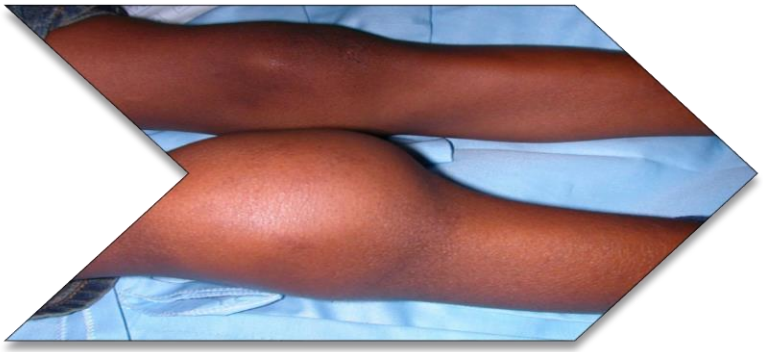
Paradigm shift in haemophilia care

Reactive approach

Proactive approach

On-demand treatment

Prophylactic prevention



Benefits of prophylaxis

Less clinical /radiological deterioration of joints
Fewer days lost from school/work

Aledort et al J Intern Med 1994 236(4): 391-399

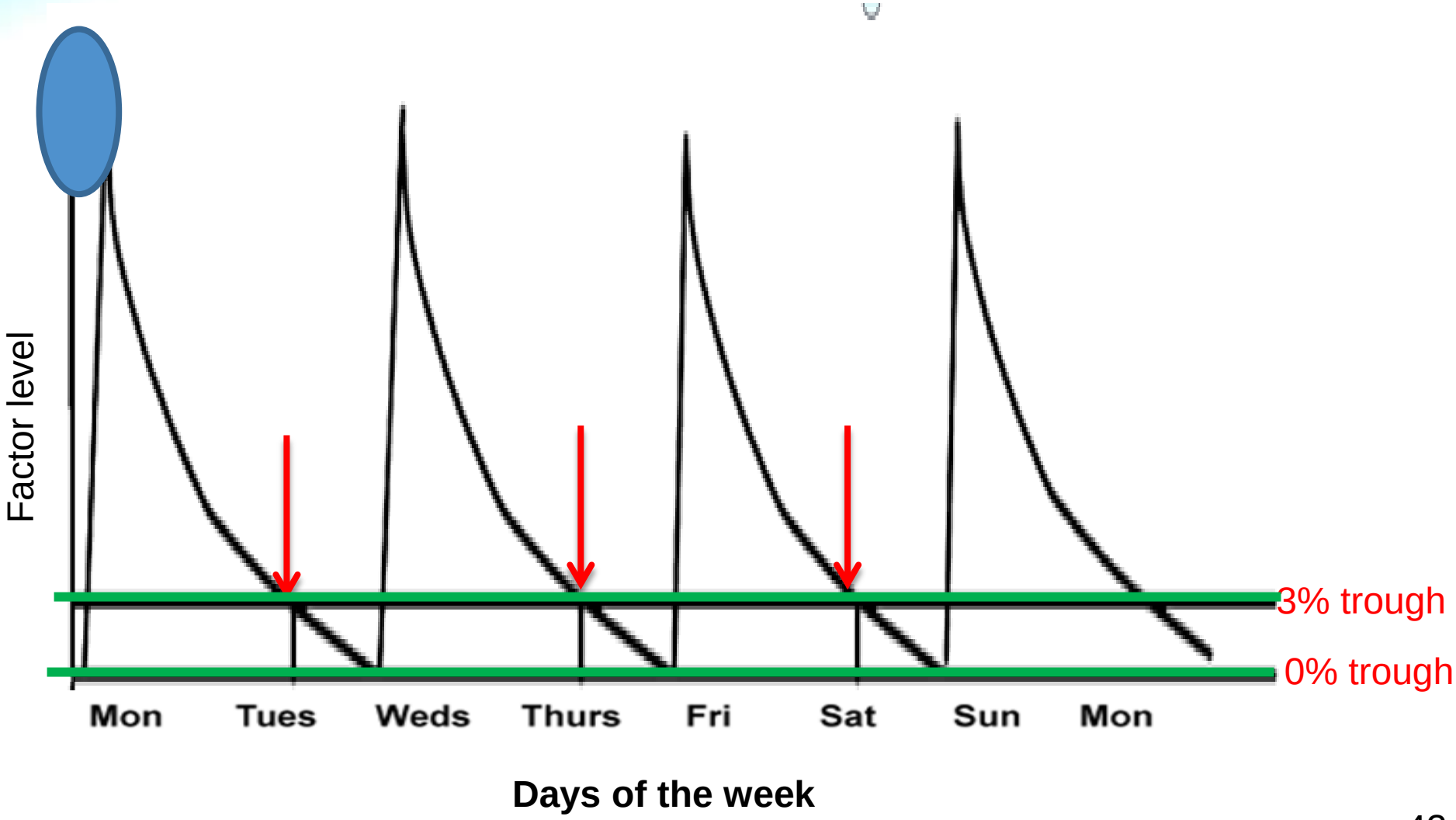
6 fold reduction in joint damage by MRI
7 fold reduction in number of bleeding episodes/pt/yr

Manco-Johnson et al N Engl J Med 2007;357:535-44

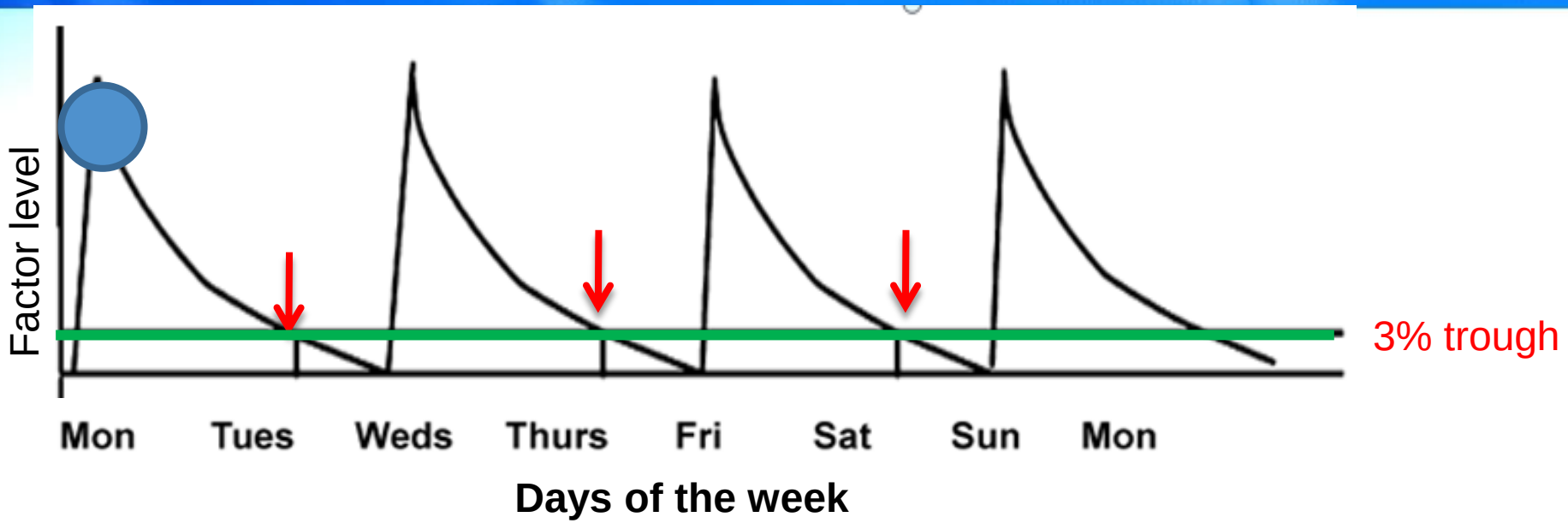
Increased physical activity
Preserved BMD in the prophylaxis group

Khawaji et al Haemophilia 2009, 15, 261–266

Prophylaxis converts severe to mild/moderate haemophilia

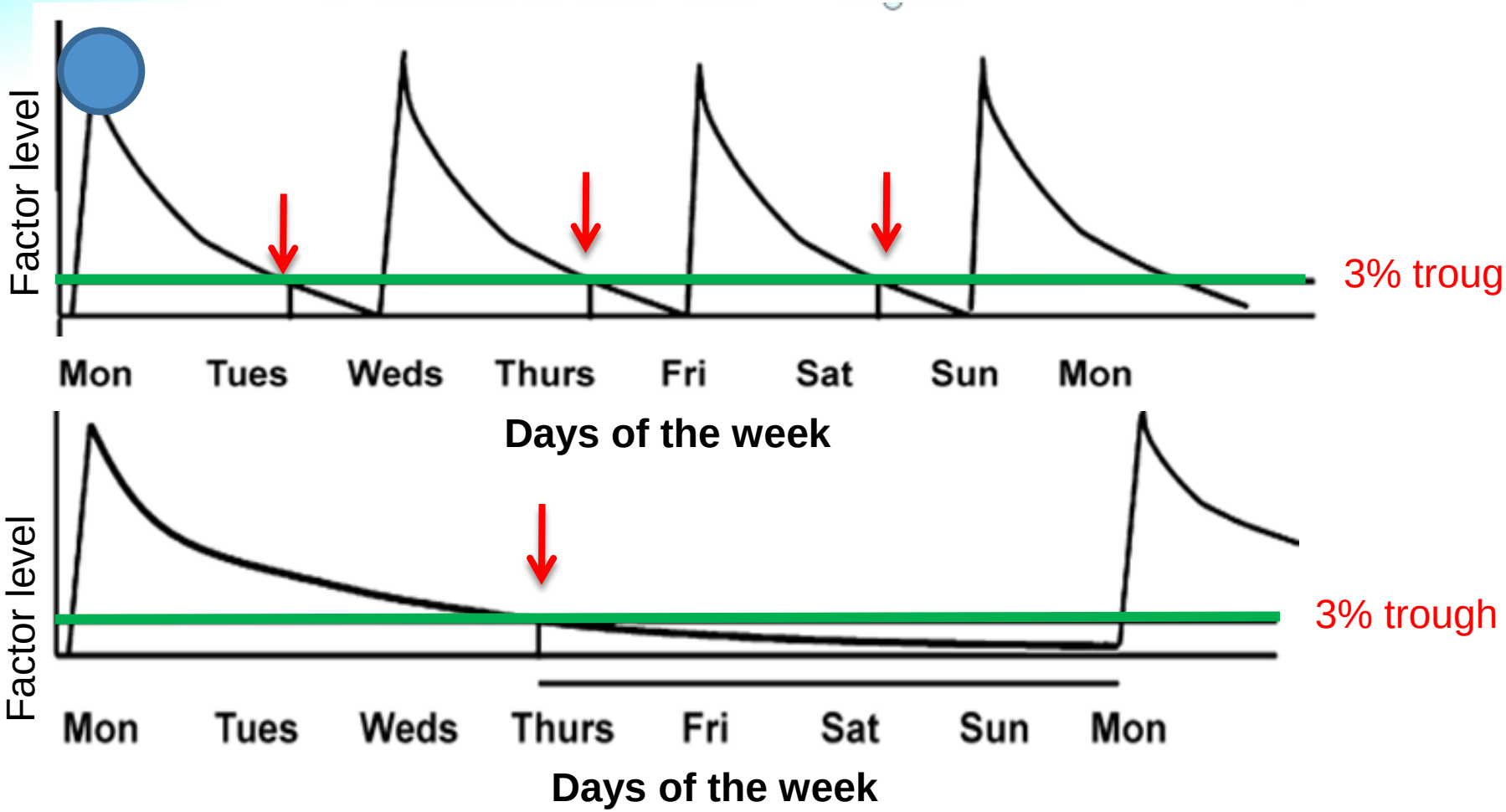


Prophylaxis challenge



- 3 x 52 = 156 injections per year
- 156 x 20 = 3120 injections 20 years of age

Reducing the frequency of injections



clotting factor concentrate with improved pharmacokinetic properties

Evolution of haemophilia therapies

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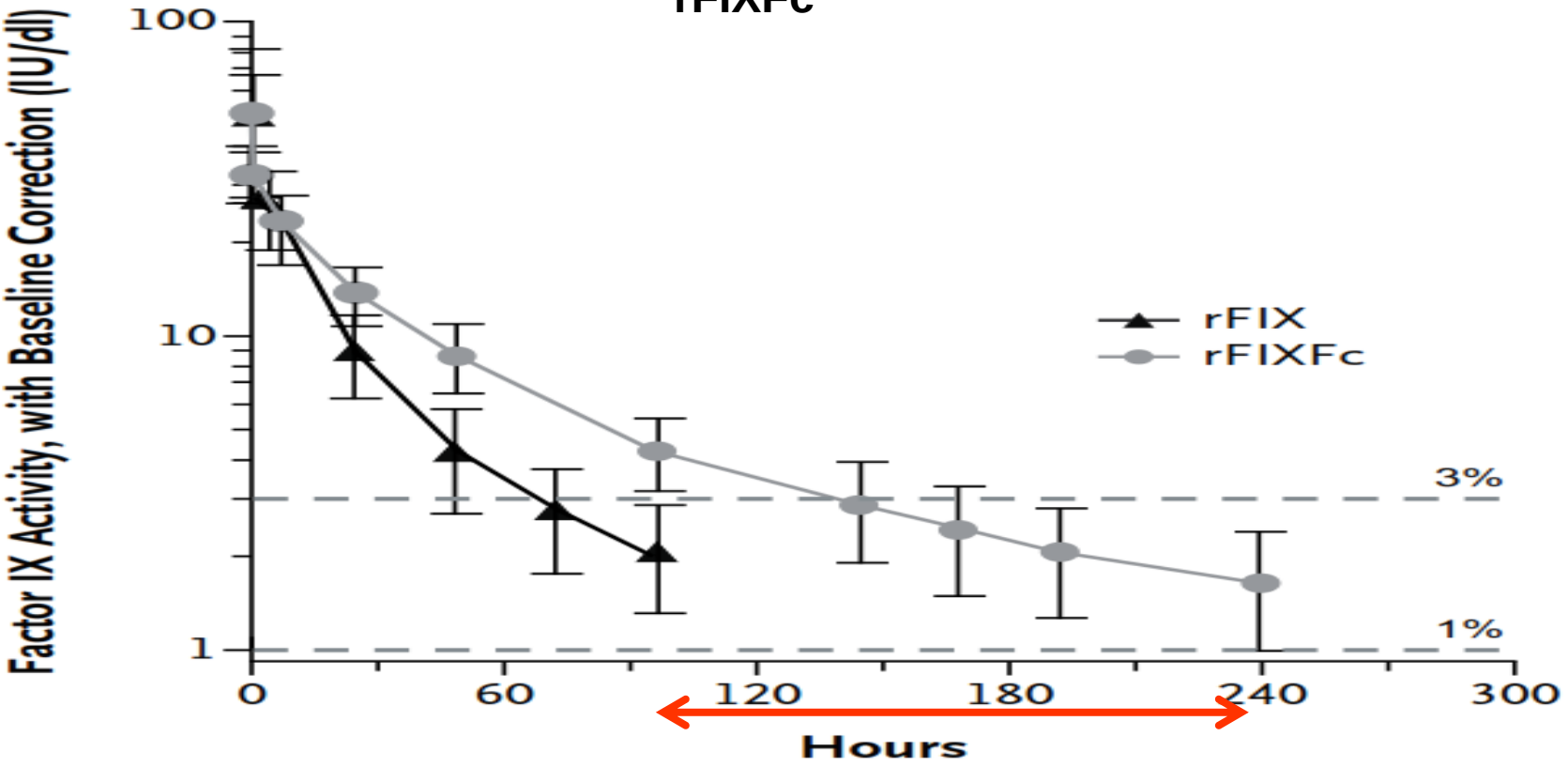
1964	• 1st use of Cryoprecipitate
1980	• 1st use of Plasma derived Clotting factor
1990	• 1st use of recombinant Clotting factor
1998	• 1st use of extended half life clotting factor

Innovations in half life extension technologies

Fusion technology	1.FC fusion	FVIII-FC	Mahlangu 2014
		FIX-FC	Powell 2013
	2. Albumin fusion	FVIII-FP	FVIII-FP
		FIX-FP	Santogostino 2016
		FVII-FP	Ongoing
	3. CTP fusion	FVII-CTP	Ongoing
	4 PSA fusion	BAX 826	Ongoing
PEGylation technology	1. Site directed	BAY 94 9027	Shah 2016
	2. Controlled	BAX 855	Konkle 2015
	3. GlycoPEGylation	N8-GP	Giangrande 2016
		N9-GP	Young 2016

rFIXFC was the first extended half-life CFC registered

rFIXFc[1]



1.Powell etal *N Engl J Med 2013;369:2313-23* ,

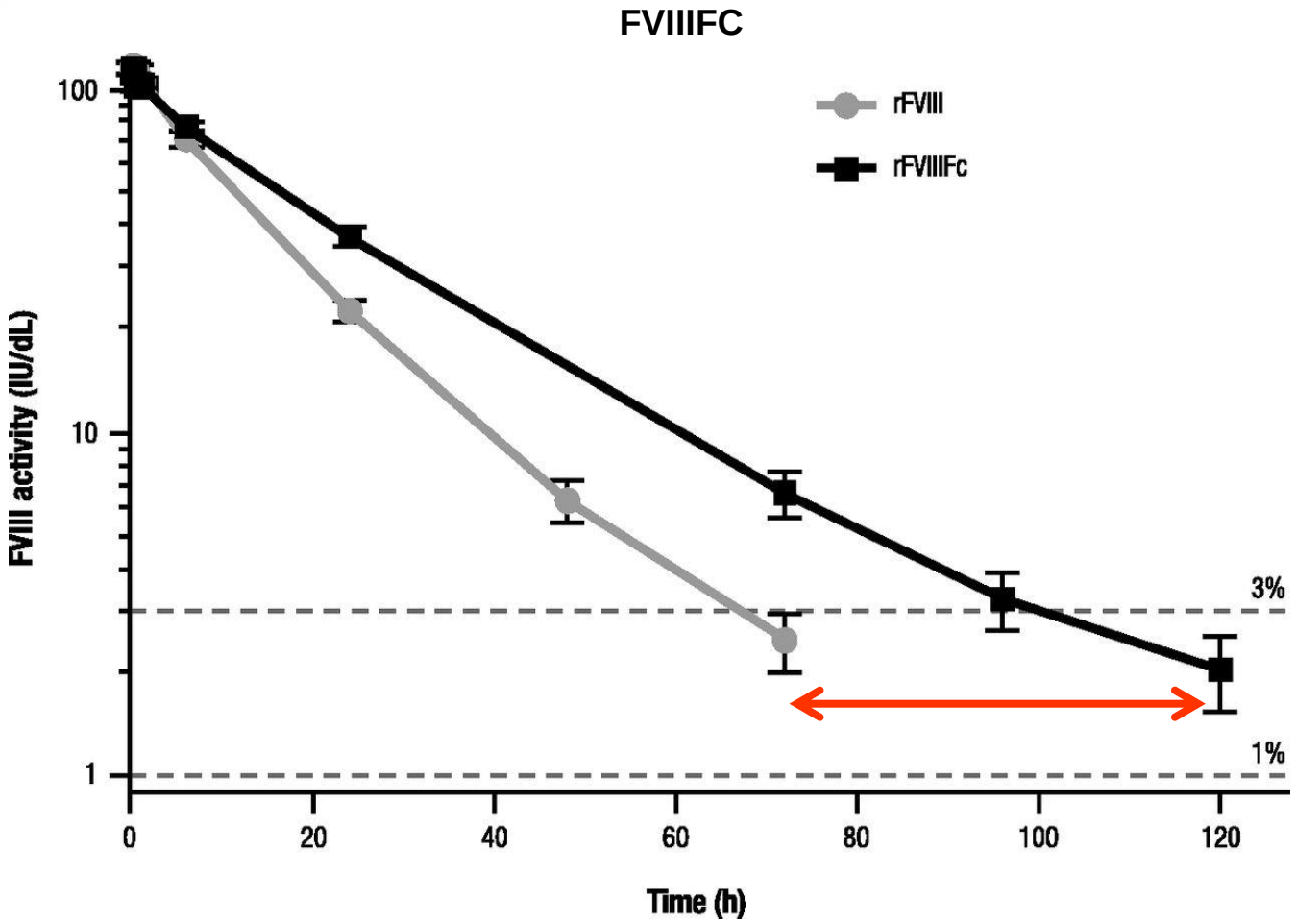
Half-life properties of the EHL-rFIX

	rFIXFc[1]	rFIX-FP[2]	N9-GP[3]
Number of patients	22	46	7
Mean half-life for EHL product	82.1	102	96.25
Mean half-life for SHL product	33.8	24.2	19.3
Ratio	2.4-fold	4.2 fold	4.8-fold

rFIX-recombinant FIX, EHL-rFIX- extended half-life recombinant Factor IX; rFIXFc- recombinant Factor IX Fc fusion protein; rFIXFP-recombinant Factor IX Albumin fusion protein

1.Powell etal N Engl J Med 2013;369:2313-23 ; 2.Santagostino etal Blood 2016;127(14):1761-1769 ; 3.Young etal Thomb Res 2016 ;141:69-76

rFVIIIFC was the first EHL CFC to be registered



Mahlangu *etal Blood* 2014; 123: 317-325

Half life properties of EHL rFVIII products

	BAX 855[1]	BAY94-9027[2]	rFVIIIFc[3]	N8-GP[4]
Number of patients, n	159	141	165	186
Half-life range, h	14.3-16.0	13.7-28.1	17.1-21.1	11.6-27.3
Mean half-life, h	14.3	18.7	19.0	19.0
Increase in half-life, ratio	1.4	1.4	1.5	1.6

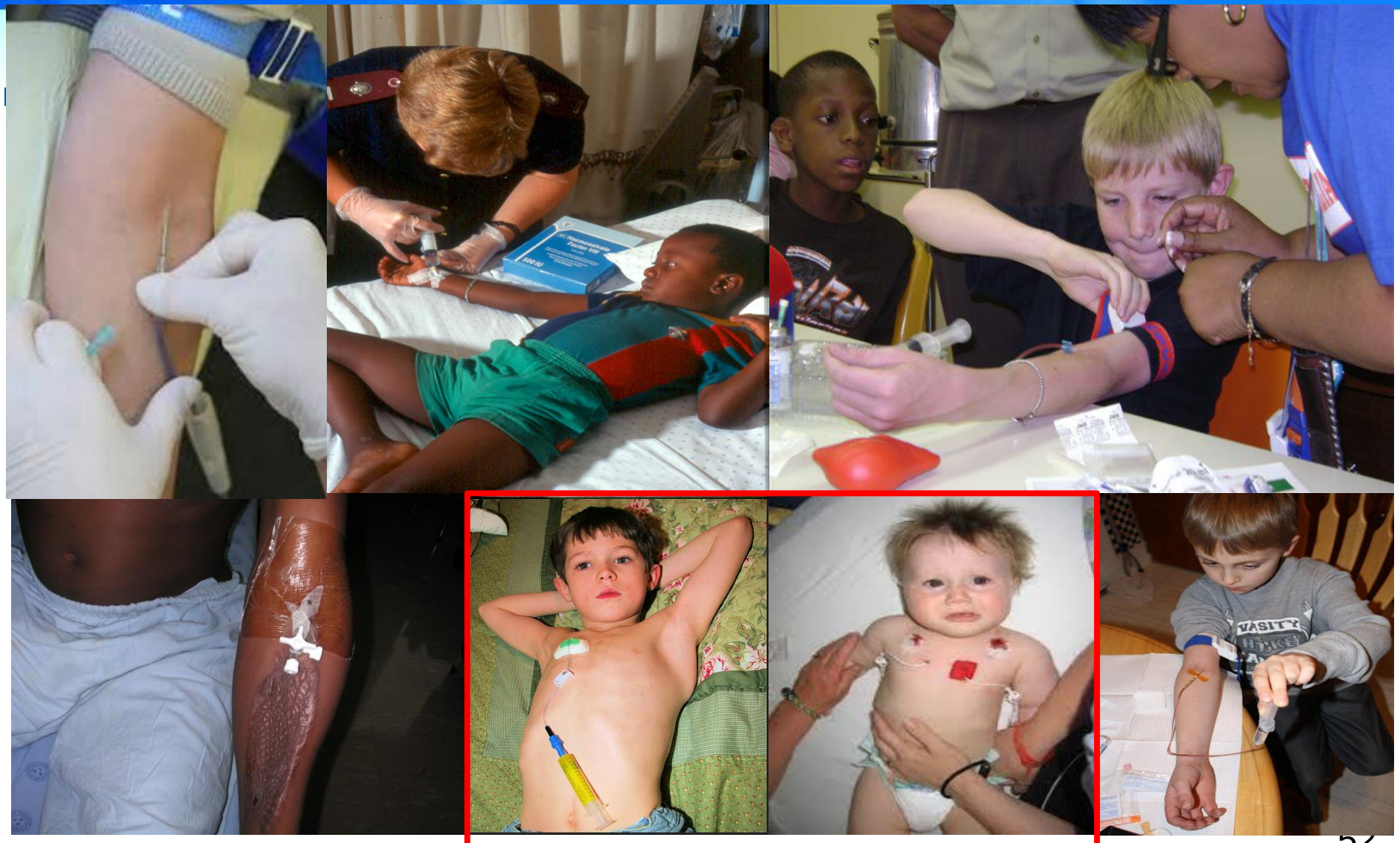
1. Konkle *etal Blood 2015; 126:1078-1085;* 2. Coyle *etlalJTH* 2014; 12: 488-496; 3. Mahlangu *etal Blood* 2014; 123: 317-325; 4.Lentz *etal Haemophilia* 2013; 19: 691-697

Challenges of replacement therapy

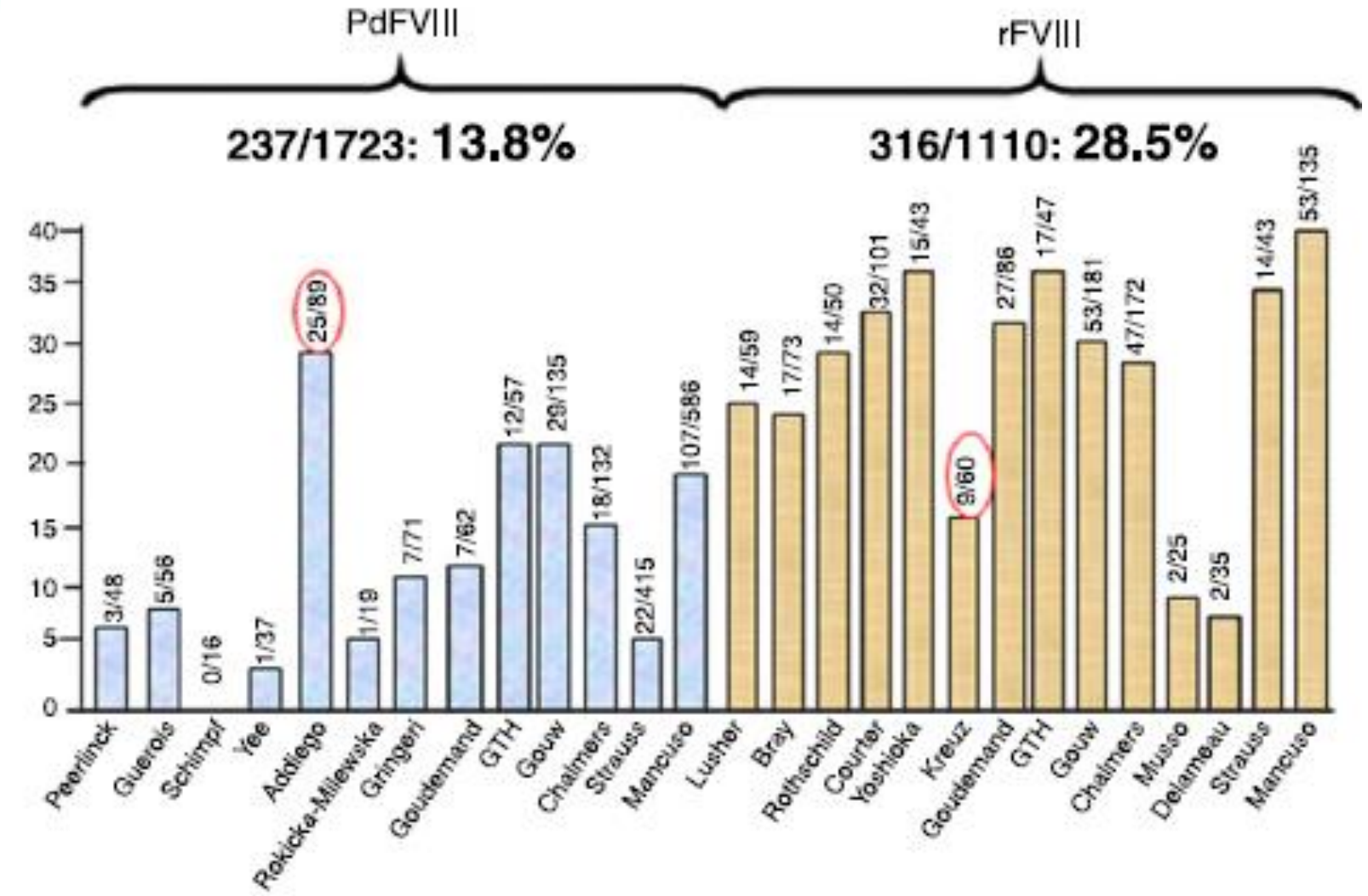
Need for intravenous infusion of replacement therapy

Development of neutralizing antibodies to replacement clotting factor

Intravenous infusion of clotting factor for life



Crude incidence of inhibitors in PTP



Manucci Haemophilia 2014; 20(Supp 6):2-16

ORIGINAL ARTICLE

Changes in the amino acid sequence of the recombinant human factor VIIa analog, vatreptacog alfa, are associated with clinical immunogenicity

J. N. MAHLANGU,* K. N. WELDINGH,† S. R. LENTZ,‡ S. KAICKER,§ F. A. KARIM,¶ T. MATSUSHITA,** M. RECHT,†† W. TOMCZAK,‡‡ J. WINDYGA,§§ S. EHRENFORTH,† and K. KNOBE,† FOR THE ADEPT™2 INVESTIGATORS[1]

**Haemophilia Comprehensive Care Centre, Faculty of Health Sciences, University of the Witwatersrand and National Health Laboratory Service, Johannesburg, South Africa; †Novo Nordisk A/S, Bagsværd, Denmark; ‡Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA; §Maimonides Medical Centre, New York, NY, USA; ¶Haemophilia Centre, National Blood Centre, Kuala Lumpur, Malaysia; **Department of Transfusion Medicine, Nagoya University Hospital, Nagoya, Japan; ††Hemophilia Center, Oregon Health and Science University, Portland, OR, USA; ‡‡Department of Hematooncology and Bone Marrow Transplantation, Medical University of Lublin, Lublin; and §§Department of Disorders of Haemostasis and Internal Medicine, Institute of Hematology and Transfusion Medicine, Warsaw, Poland*

To cite this article: Mahlangu JN, Weldingh KN, Lentz SR, Kaicker S, Karim FA, Matsushita T, Recht M, Tomczak W, Windyga J, Ehrenforth S, Knobe K, for the adept™2 Investigators. Changes in the amino acid sequence of the recombinant human factor VIIa analog, vatreptacog alfa, are associated with clinical immunogenicity. *J Thromb Haemost* 2015; **13**: 1989–98.

N Engl J Med 2016;374:2054-64.
DOI: 10.1056/NEJMoa1516437

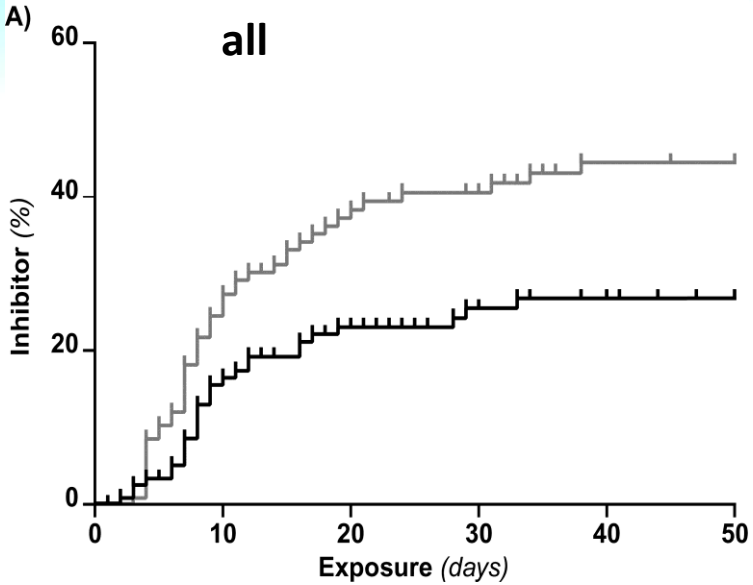
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A

F. Peyvandi, P.M. Mannucci, I. Garagiola, A. El-Beshlawy, M. Elalfy, V. Ramanan, P. Eshghi, S. Hanagavadi, R. Varadarajan, M. Karimi, M.V. Manglani, C. Ross, G. Young, T. Seth, S. Apte, D.M. Nayak, E. Santagostino, M.E. Mancuso, A.C. Sandoval Gonzalez, J.N. Mahlangu, S. Bonanad Boix, M. Cerqueira, N.P. Ewing, C. Male, T. Owaidah, V. Soto Arellano, N.L. Kobrinsky, S. Majumdar, R. Perez Garrido, A. Sachdeva, M. Simpson, M. Thomas, E. Zanon, B. Antmen, K. Kavakli, M.J. Manco-Johnson, M. Martinez, E. Marzouka, M.G. Mazzucconi, D. Neme, A. Palomo Bravo, R. Paredes Aguilera, A. Prezotti, K. Schmitt, B.M. Wicklund, B. Zulfikar, and F.R. Rosendaal

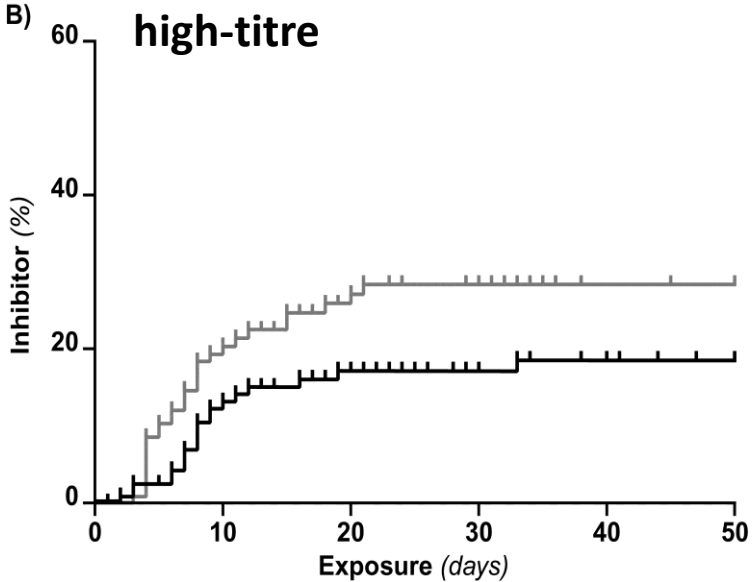
Inhibitor Risk per Treatment Arm



rFVIII: 44.5% (CI95 34.7-54.3)

pdFVIII: 26.8% (CI95 18.3-35.2)

HR 1.87 *(CI95 1.17-2.96)*



rFVIII: 28.4% (CI95 19.6-37.2)

pdFVIII: 18.6% (CI95 11.1-26.9)

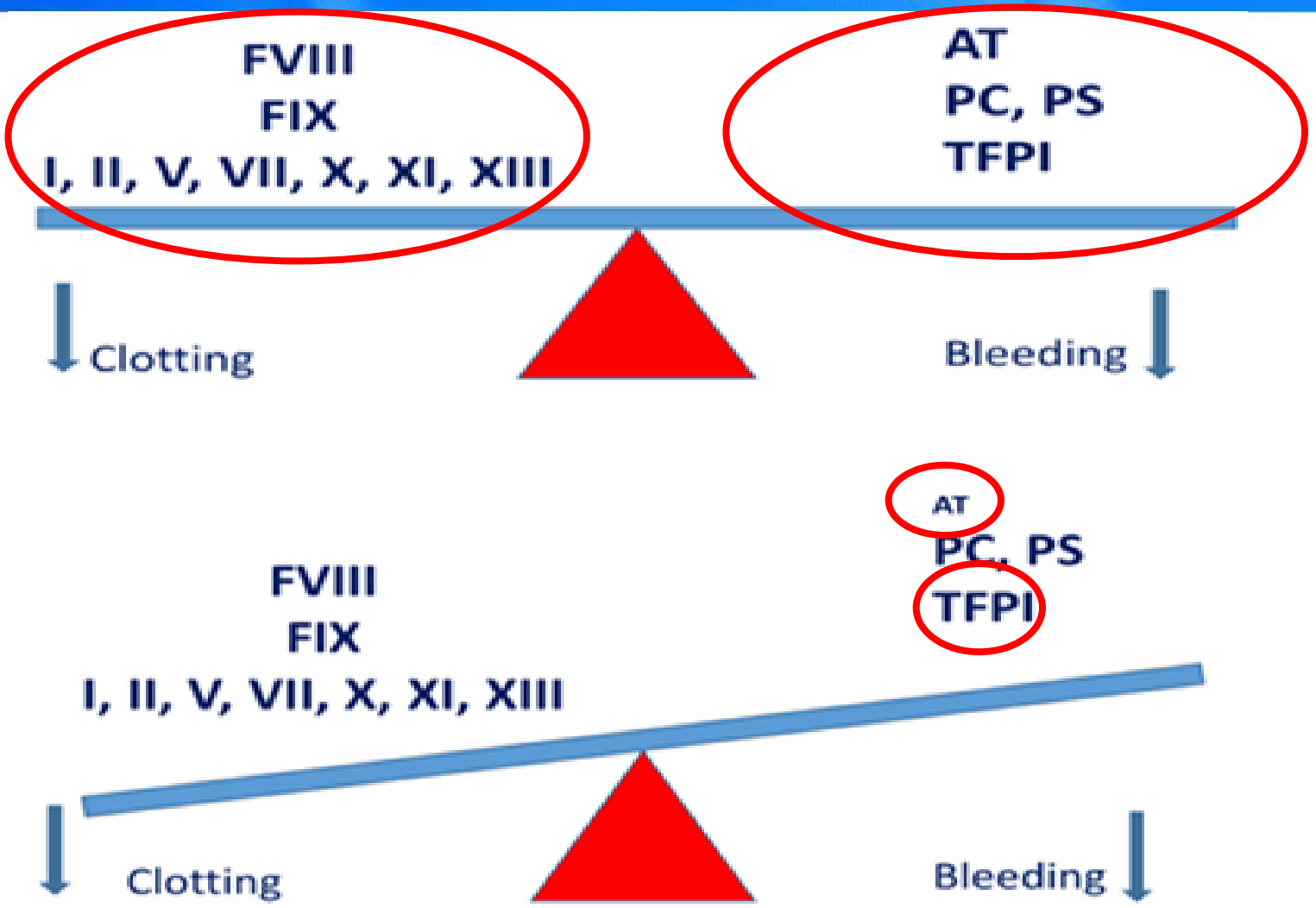
HR 1.69 *(CI95 0.96-2.98)*

Evolution of haemophilia therapies

- **1944** • 1st use of whole blood
- **1955** • 1st use of Fresh Frozen Plasma
- **1964** • 1st use of Cryoprecipitate
- **1980** • 1st use of Plasma derived Clotting factor
- **1990** • 1st use of recombinant Clotting factor
- **1998** • 1st use of extended half life clotting factor
- **2014** • 1st use of non-replacement therapy

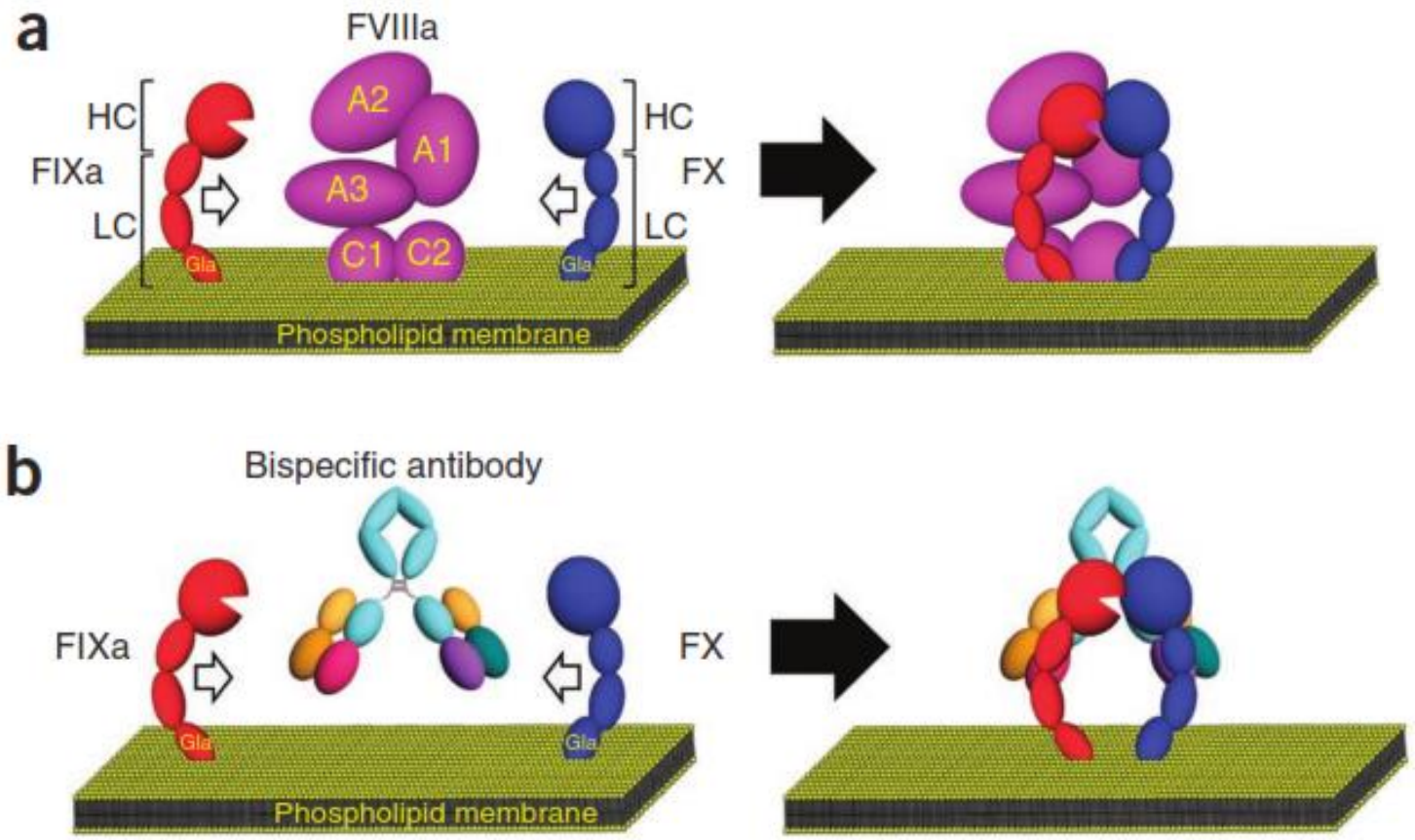
Non CFC replacement therapies		
	• Anti-TFPI (*concizumab*) • AT3 RNAi (*fitusiran*) • Anti IXa/X (*emicizumab*) • Gene therapy	• Chowdary 2015 • Pasi 2015 • Uchida 2016 • Nathwani 2014

Realignment of haemostatic balance



AT=antithrombin; PC-ptotein C; Protein S; TFPI-tissue factor pathway inhibitor

ACE910 Bispecific antibody



Kitazawa etal Nature Med 2012 ; 18(10): 1570-1574

Advantages of non-replacement therapies

- Subcutaneous administration
- Long biological half lives
- Lack of immunogenecity in phase 1 or 2 studies
- Manage haemophilia patients with and without inhibitors

Haemophilia is clearly manageable, is it curable ?

Evolution of haemophilia therapies

1944	• 1st use of whole blood
1955	• 1st use of Fresh Frozen Plasma
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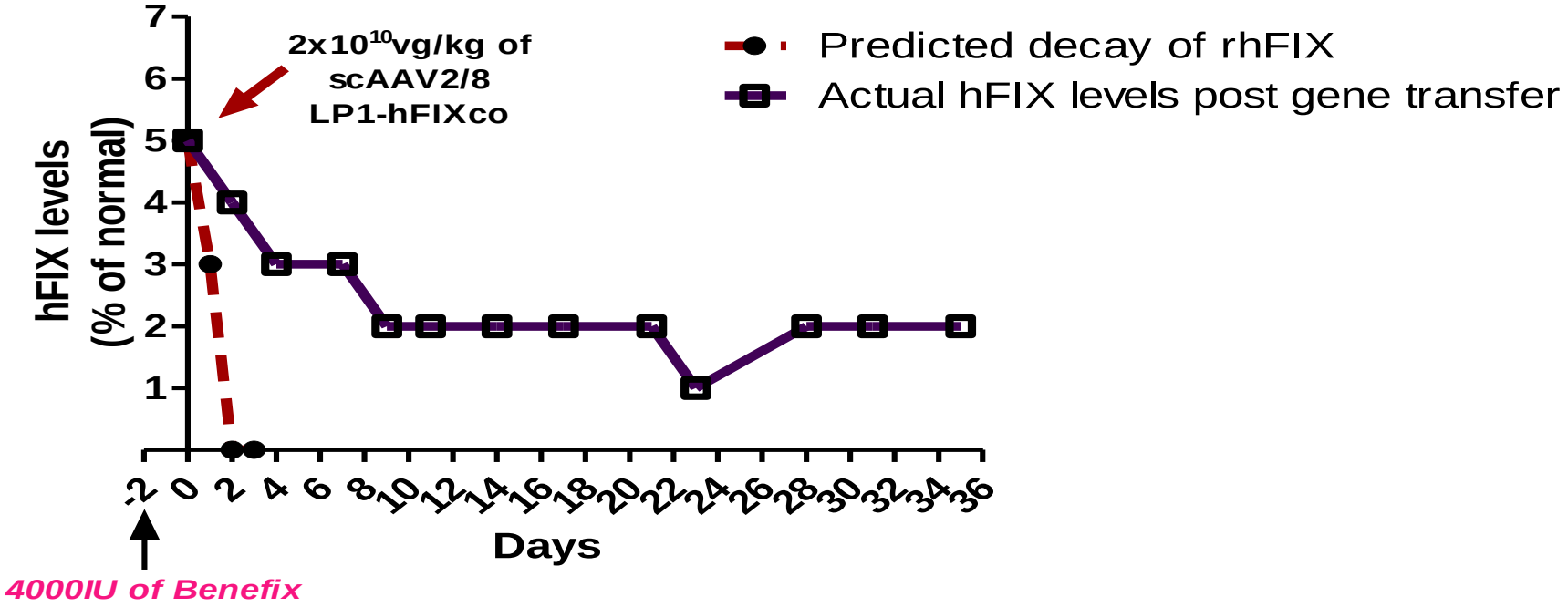
1990	• 1st use of recombinant Clotting factor
1998	• 1st use of extended half life clotting factor
2014	• 1st use of non-replacement therapy
2014	• 1st use Gene therapy

First successful FIX gene therapy in man)

- codon-optimized human factor IX (FIX) transgene (scAAV2/8-LP1-hFIXco)
- 6 patients, 2 in each of 3 dose escalations
- Durable FIX levels 1–6%
- 2/6 transient ALT elevation



Nathwani, et al. NEJM 2011;365;2357

The NEW ENGLAND JOURNAL of MEDICINE

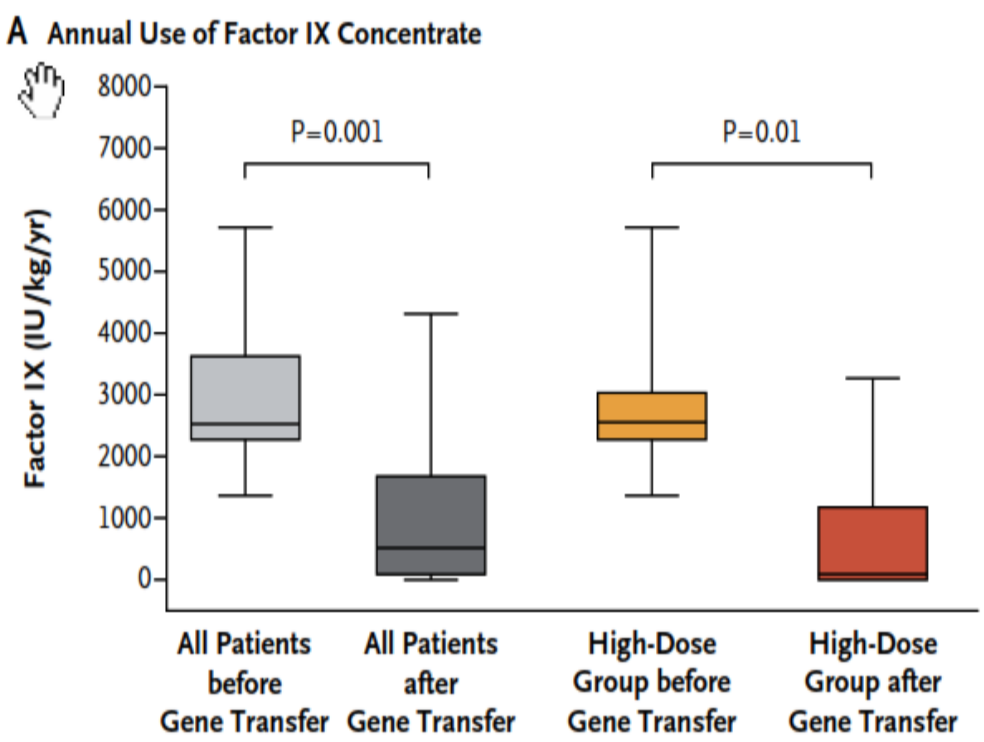
ORIGINAL ARTICLE

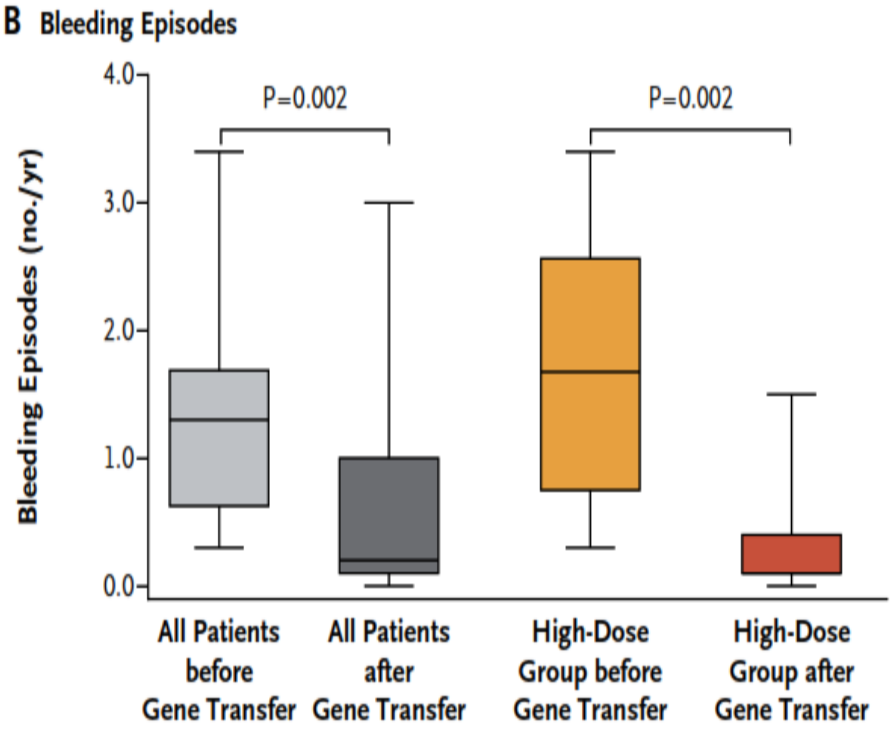
Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B

A.C. Nathwani, U.M. Reiss, E.G.D. Tuddenham, C. Rosales, P. Chowdary, J. McIntosh, M. Della Peruta, E. Lheriteau, N. Patel, D. Raj, A. Riddell, J. Pie, S. Rangarajan, D. Bevan, M. Recht, Y.-M. Shen, K.G. Halka, E. Basner-Tschakarjan, F. Mingozzi, K.A. High, J. Allay, M.A. Kay, C.Y.C. Ng, J. Zhou, M. Cancio, C.L. Morton, J.T. Gray, D. Srivastava, A.W. Nienhuis, and A.M. Davidoff

Nathwani *etal* N Engl J Med 2014;371:1994-2004

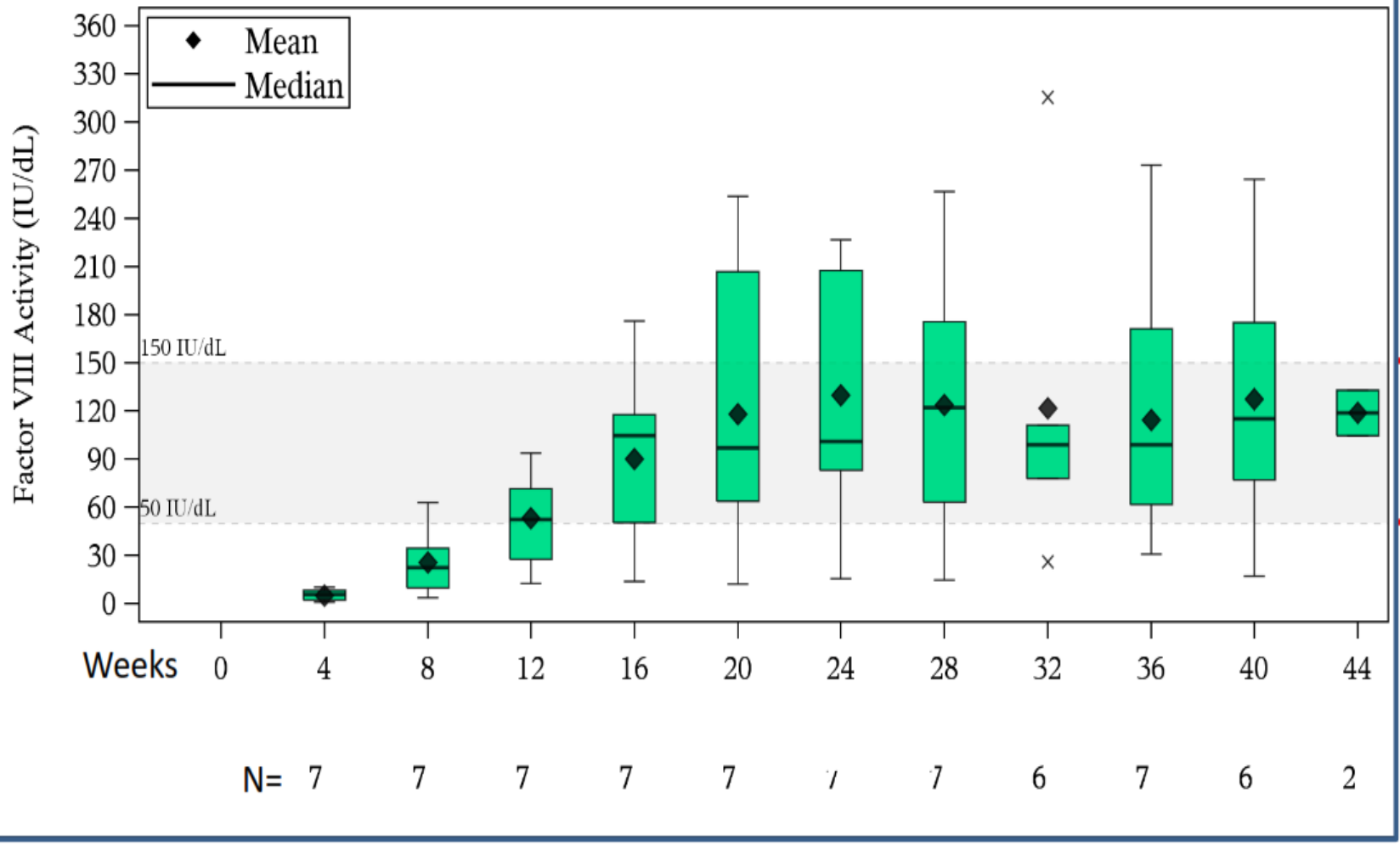
Impact of FIX gene therapy on factor consumption and bleeding rates



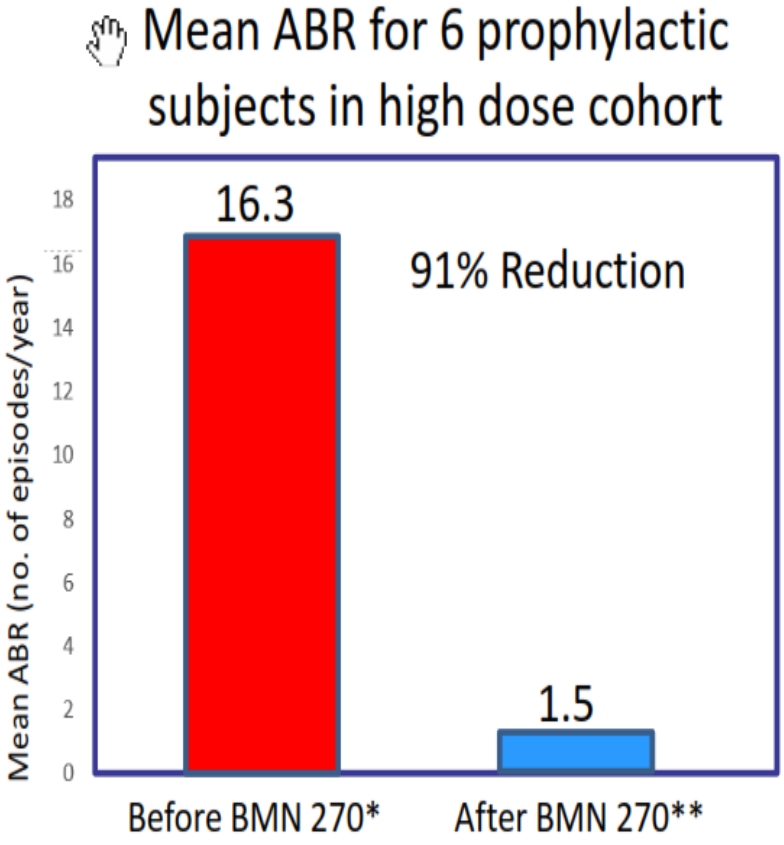


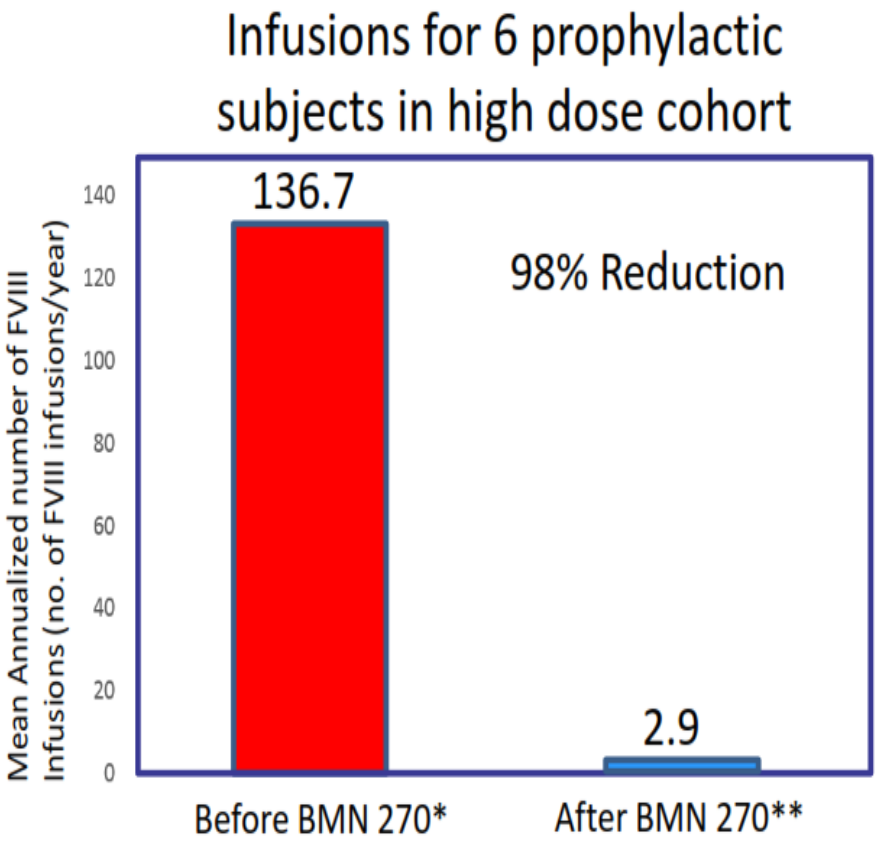
Nathwani *etal* N Engl J Med 2014;371:1994-2004

Factor VIII Gene therapy studies- Biomerin Phase 1 with AAV5



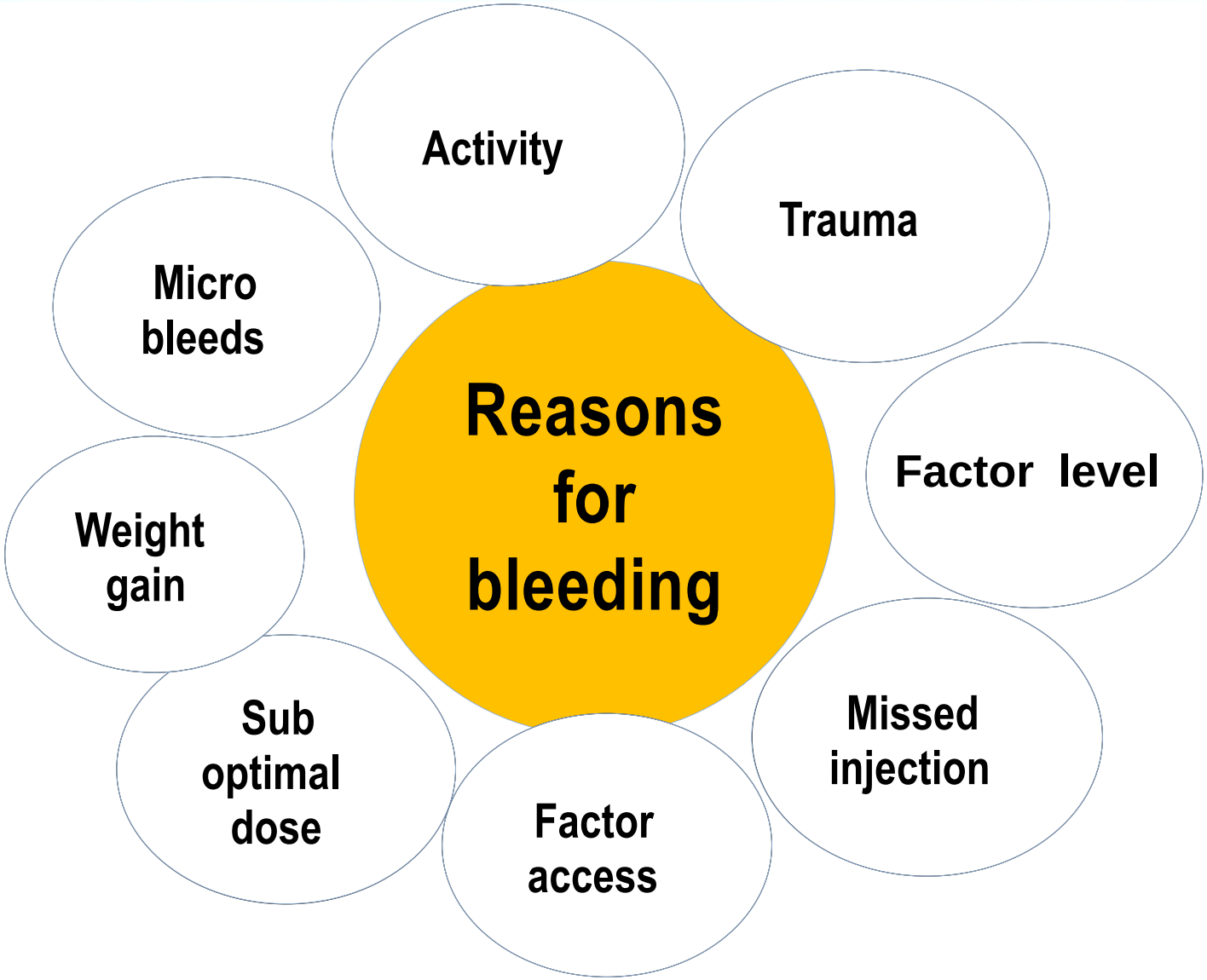
Impact of FVIII gene therapy on bleeding and infusion rates





ABR-annualized bleeding rates

There are many factors contributing to bleeding risk



Remarkable progress has been made

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1998	• 1st use of extended half life clotting factor
2014	• 1st use of non-replacement therapy
2014	• 1st use Gene therapy

With many challenges to overcome

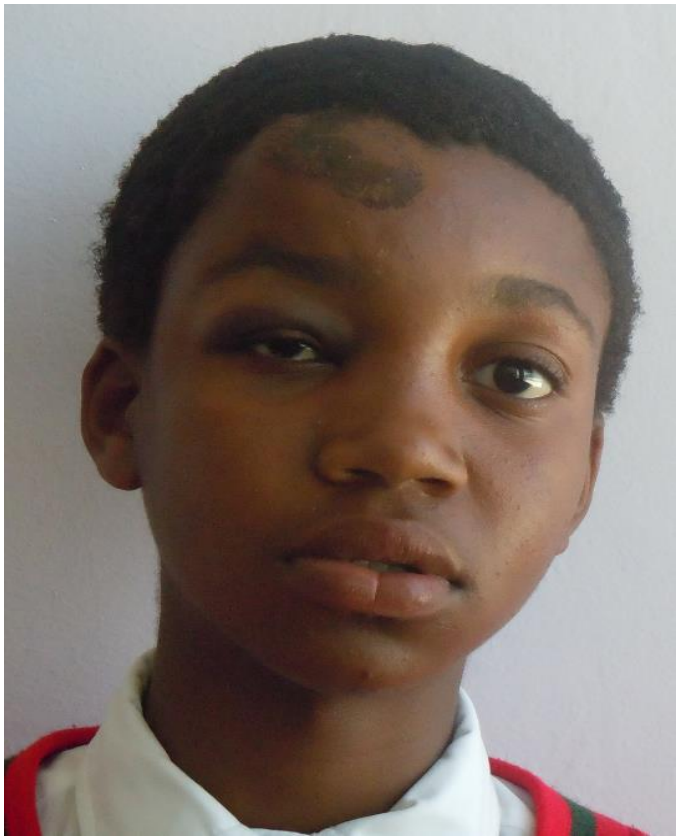
The USAF and USN announced today that the first ever C-17 carrier landing has been a total success... In other news, the USAF and USN have launched a study to determine the optimal method for getting a C-17 off of an aircraft carrier.

Despite these challenges, it is encouraging for all of us working in this space, that the goal of a **bleed free world** for people living with inherited bleeding disorders is now in sight

Back to Omran and Sipho

Omran Daqneesh

Sipho Sobayi

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Thank
You!