

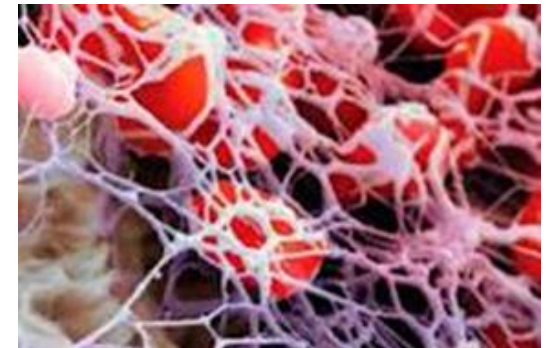


# Is That Your Final Answer?

## Bleeding Disorders 101



Eena Kapoor PT DPT  
Children's National Hospital





# Disclosures

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**Speaker's Bureau for Takeda, Bioverativ/Sanofi**

**NHF Physical Therapy Working Group**



# Learning Objectives

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- Participants will be able to compare and contrast the differing types of bleeding disorders
- Participants will be able to summarize objective measures that are essential for PT in HTC evaluation
- Participants will be able to compare and contrast different dosing options and how these effect PT
- Participant will consider various options for sports participation recommendations for persons with a bleeding disorder
- Participant will be able to summarize evidence based treatment guidelines for persons with a bleeding disorder

# Learning Outline

- Hemophilia
  - Pathology/Presentation
  - Genetics
  - Pharmaceutical Treatment Options
  - Physical Therapy Treatment Guidelines
  - Sports/Activity Recommendations
- VWD
- Rare Bleeding Disorders

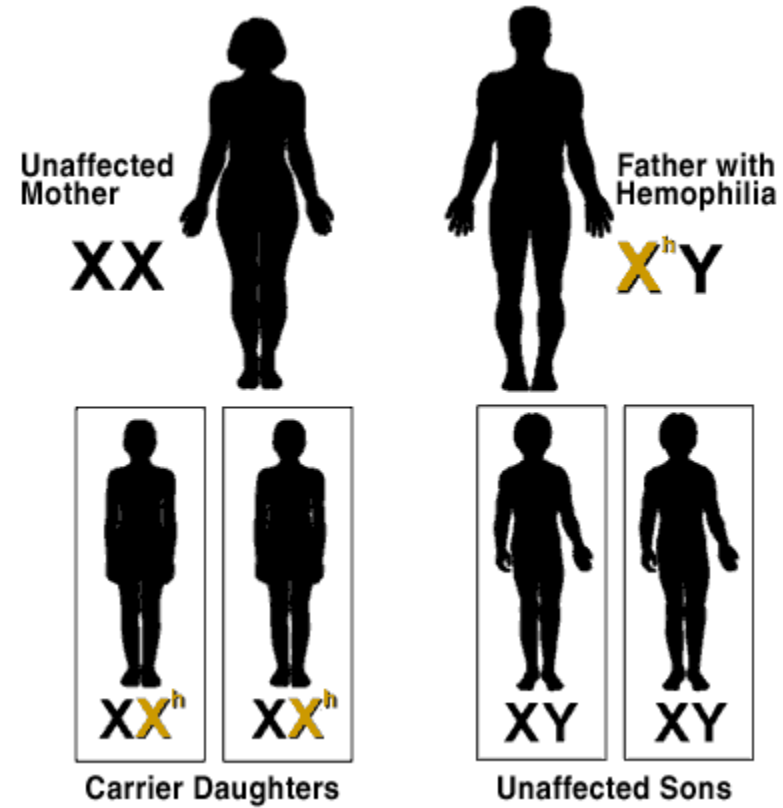
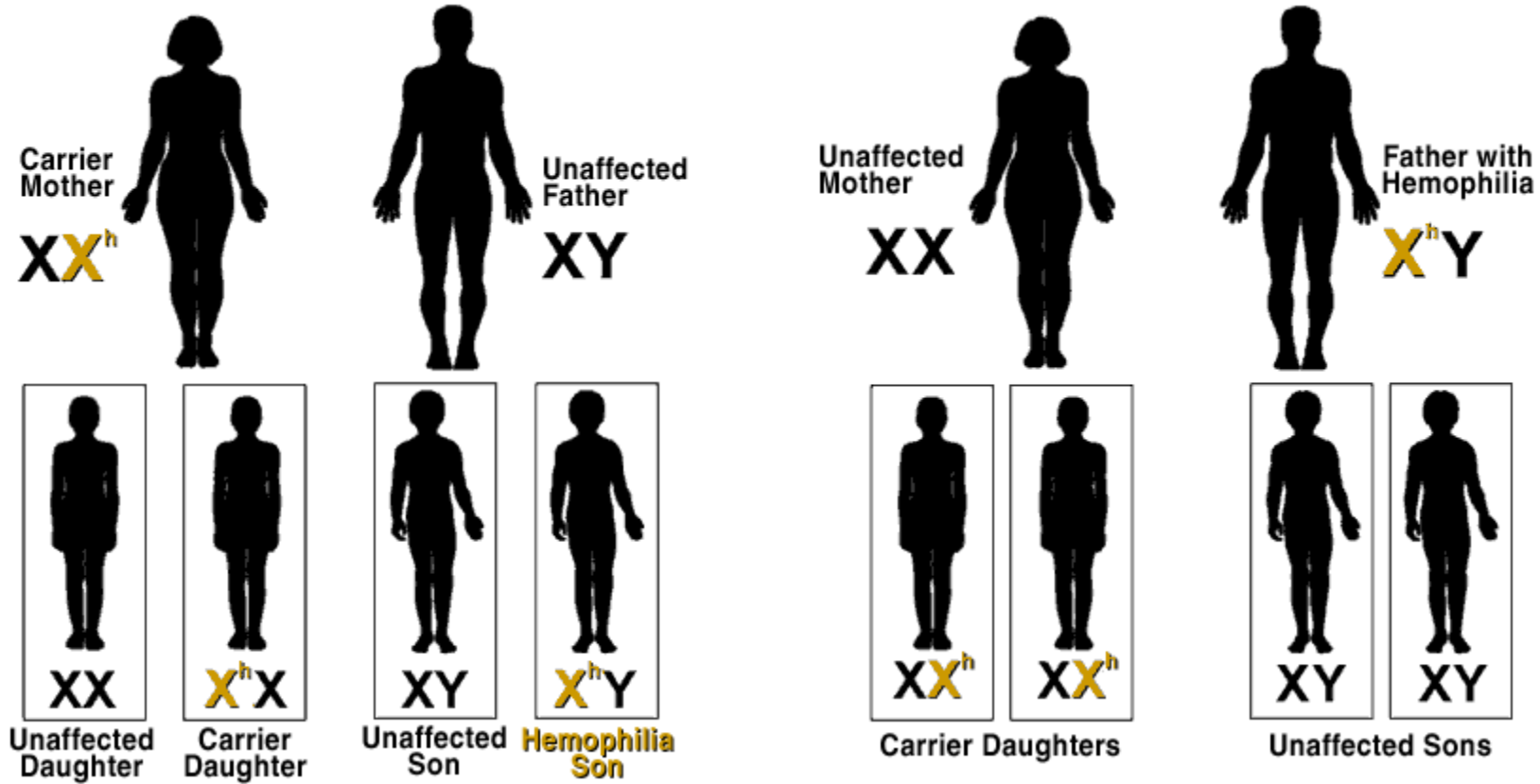


# What Is Hemophilia?

- Inheritance
- Clotting Cascade
- **Types**
  - Factor VIII deficiency
    - Hemophilia A
  - Factor IX deficiency
    - Hemophilia B
- Severity
- Presentation of Bleeds
- Treatment

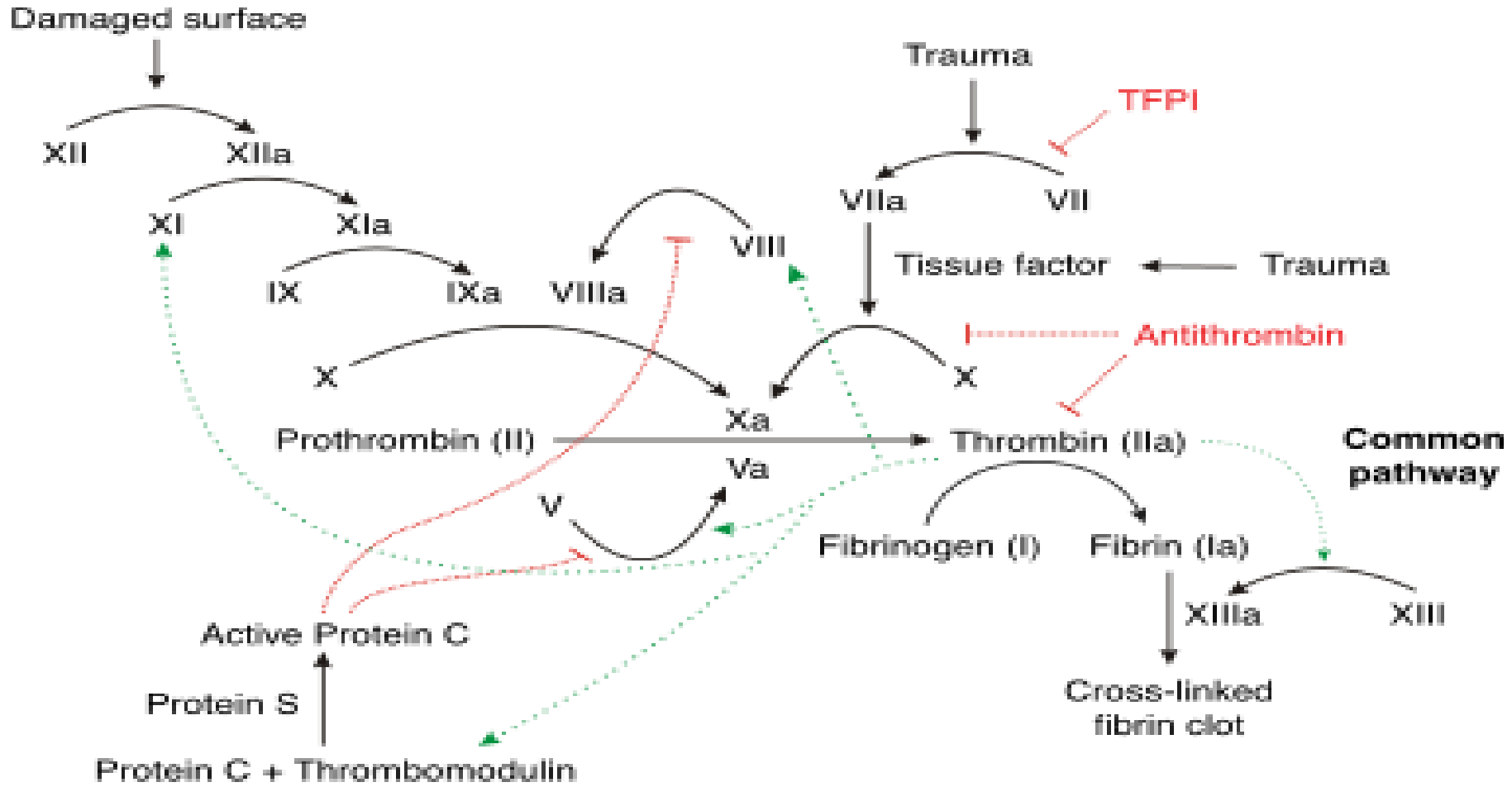


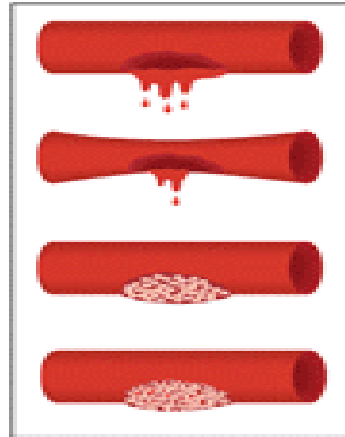
# Inheritance



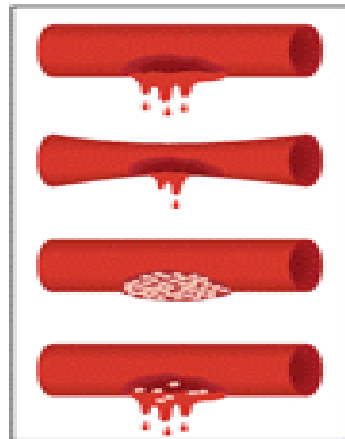
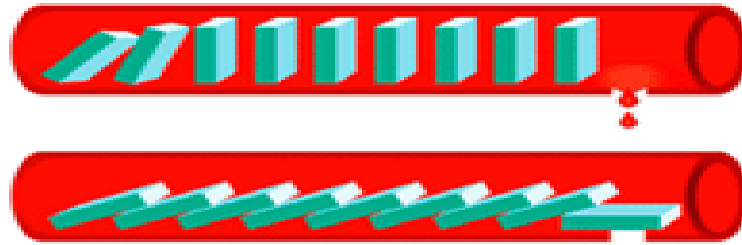
**Contact activation  
(intrinsic) pathway**

**Tissue factor  
(extrinsic) pathway**

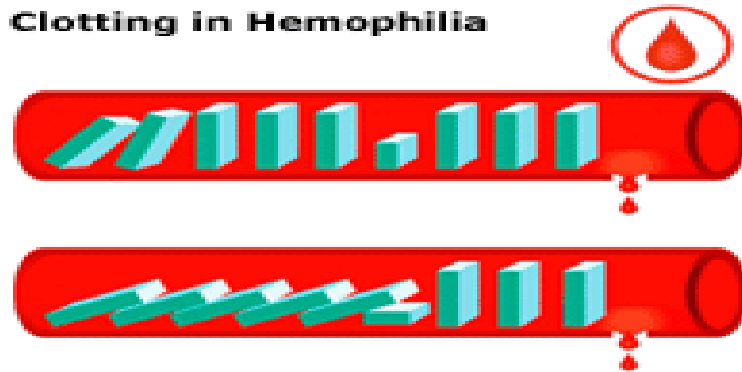




### Normal Clotting Process



### Clotting in Hemophilia







# Female Carriers

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- Most carriers should have normal factor levels but some may have mild Hph
- Why?

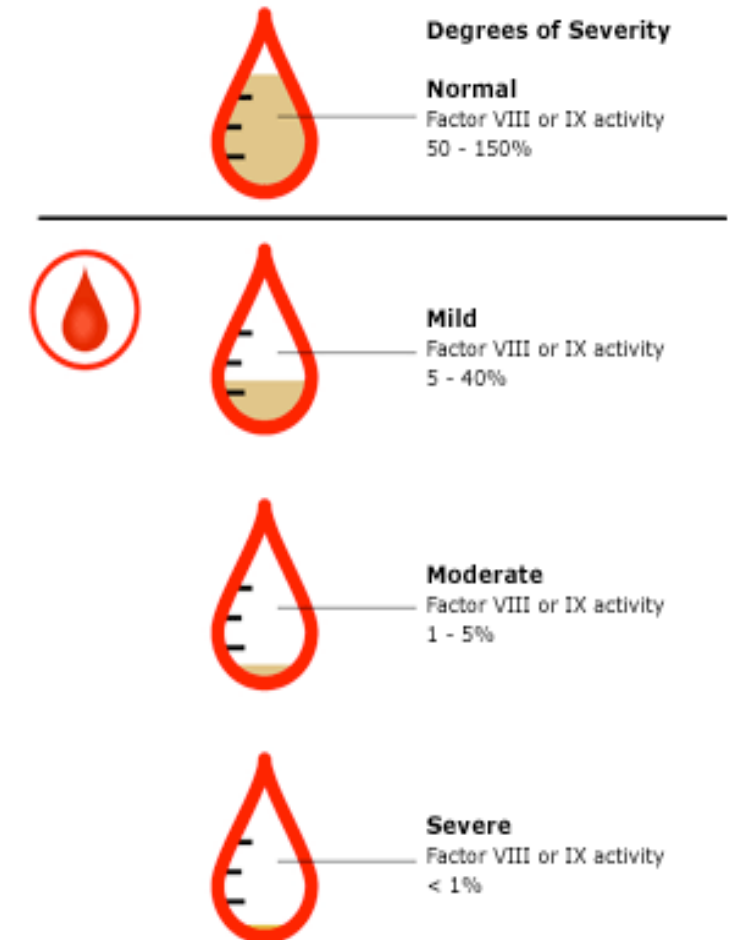


# Female Carriers

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- Up to 70% female carriers experience bleeding symptoms
  - Menstrual bleeding
  - Mucosal
  - Oral Surgery
  - **Muscle and Joint Bleeds!**
- FWH and Carriers
  - High risk of bleeding

SEVERITY	FACTOR LEVEL	BLEEDING SYMPTOMS
Normal	50 -150%	None
Mild	>5 - 40% (5-25% Campbell)	Prolonged bleeding with surgery, tooth extractions, major trauma Spontaneous bleed (no apparent injury) is rare
Moderate	1 - 5%	Prolonged bleeding with minor trauma or surgery Can have spontaneous bleeds
Severe	< 1%	Spontaneous bleeding into joints or muscles Frequent bleeding episodes 2 <sup>o</sup> trauma





# Bleeding Sites

Site of Bleeding	Approximate Frequency
Hemarthrosis (Joints) <ul style="list-style-type: none"><li>• More common into hinged joints: ankle, knees, and elbows</li></ul>	70-80%
Muscle	10-20%
Other Major Bleeds	5-10%
Central Nervous System (CNS)	<5%

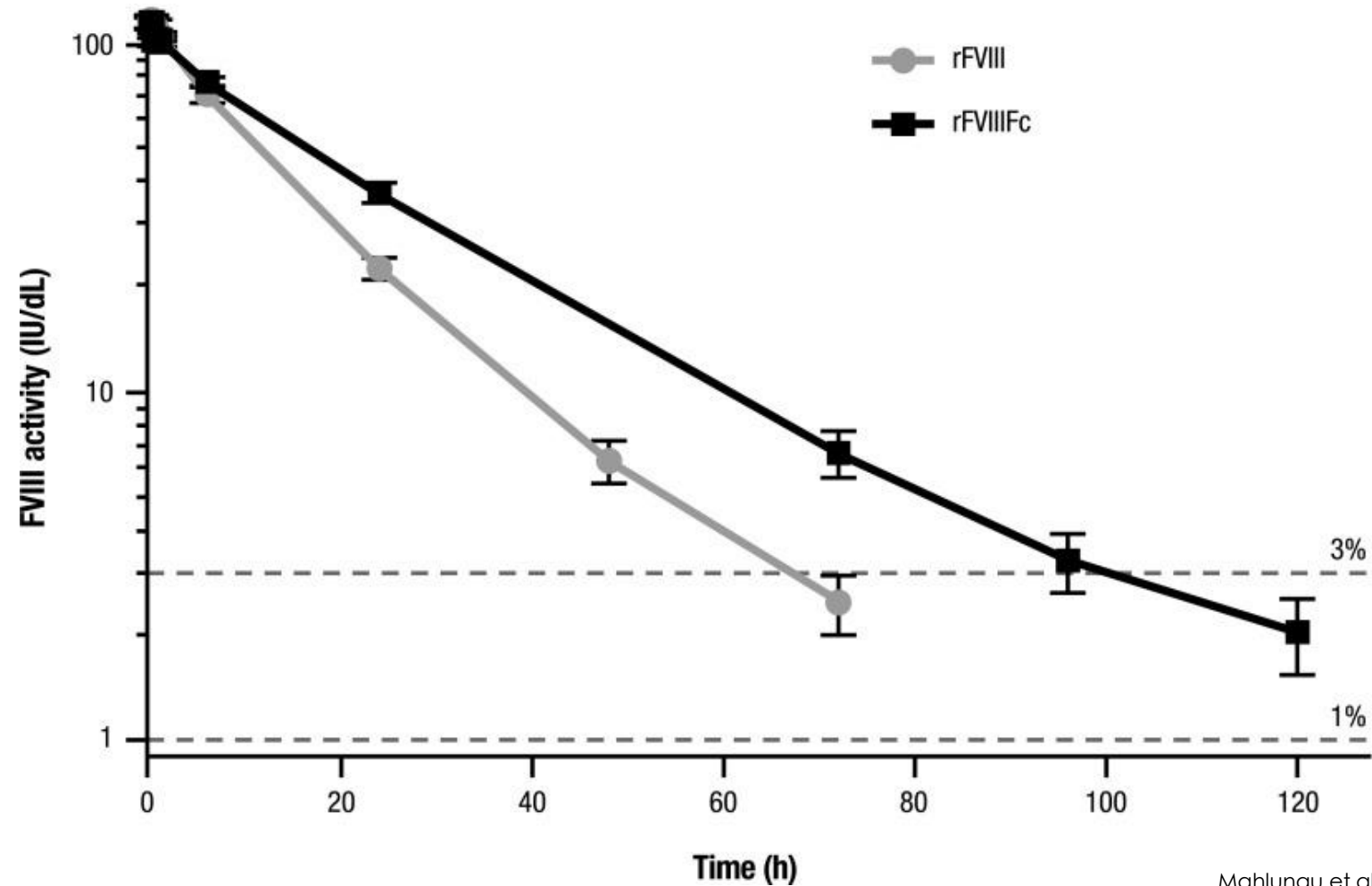
Any body part with a blood supply CAN bleed

# Pharmacological Treatment

- On Demand
- Factor Prophylaxis
  - Standard half life factor
  - Extended half life
- Non Factor Prophylaxis
  - Bispecific antibody



# Extended Half Life





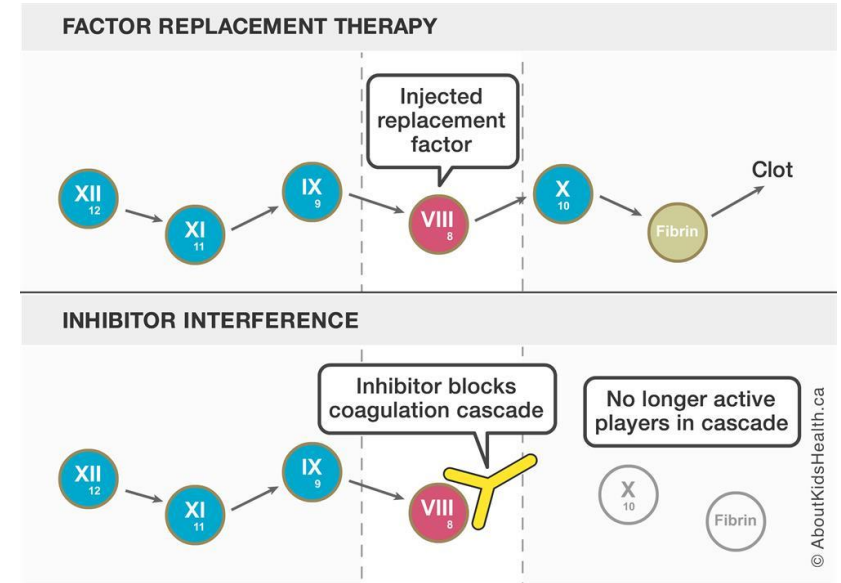
# Joint Outcomes Study

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- Prospective, randomized study
- Demonstrated benefit of prophylaxis (25units/kg every other day) over “aggressive” on-demand
  - 40units/kg at the time of joint bleed
  - 20units/kg at 24 and 72 hours later
  - continue every other day (max 4 weeks)

# Inhibitors

- Low titer
- High titer
- Treatment:
  - High-Dose Clotting Factor Concentrates
  - Bypassing Agents
  - Immune Tolerance Induction (ITI) Therapy
  - Products that mimic Factor VIII







# Emicizumab

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- **Indications**

- routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children of all ages, newborn and older, with hemophilia A

- **Administration**

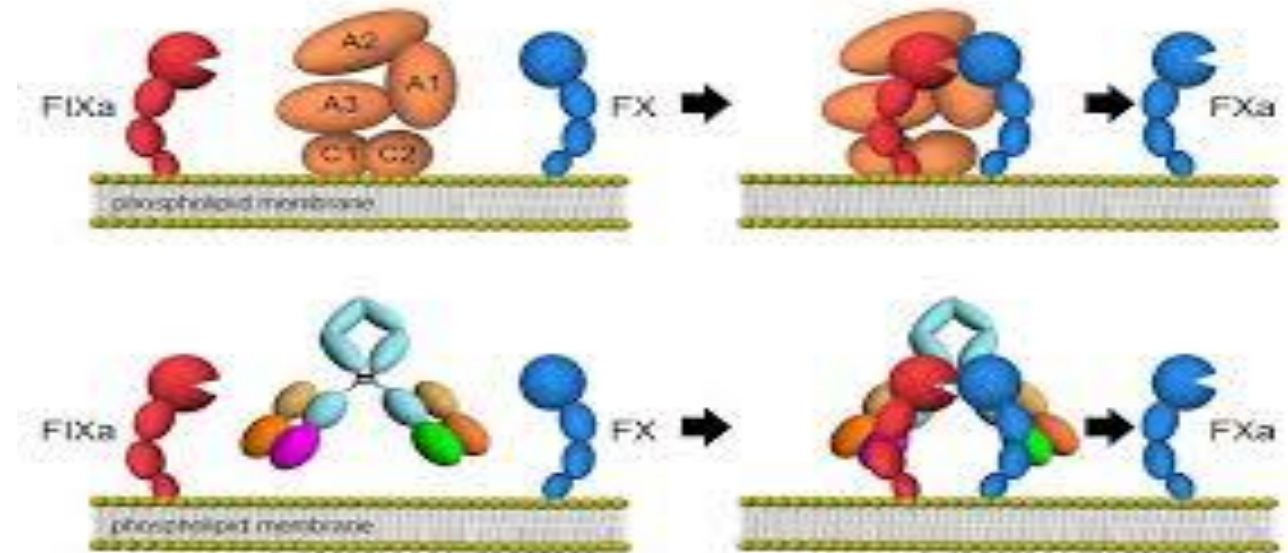
- subcutaneously at a loading dose of 3 mg/kg weekly for 4 doses, followed by one of three subsequent long-term dose regimens

- **Results**

- significant reduction in ABR at all doses for all age groups

# Emicizumab

- Replace FVIII with a bi-specific antibody which bridges FIXa and X to activate factor X in the absence of FVIII
- **Does not work for FIX deficiency**





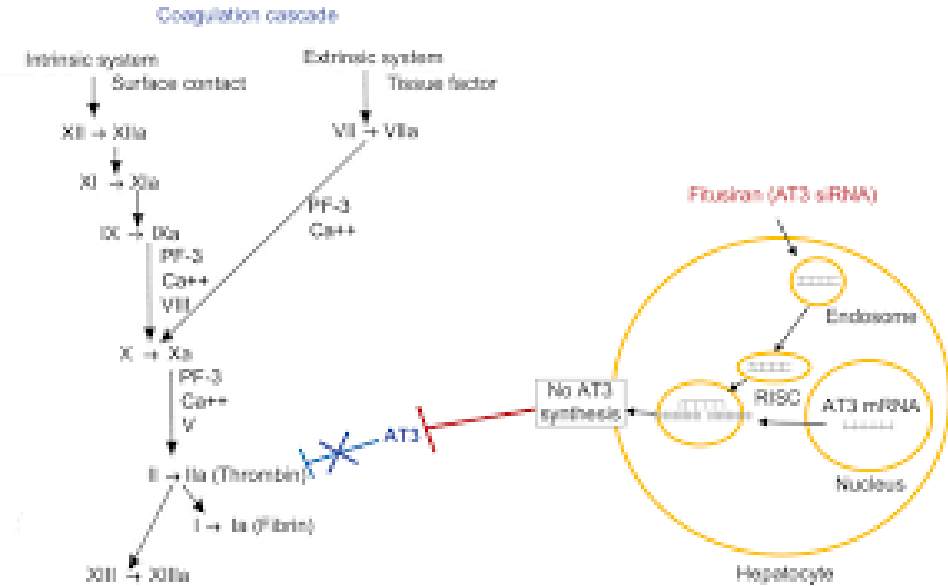
# Novel Treatment Approaches

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- Gene Therapy
- Fitusiran

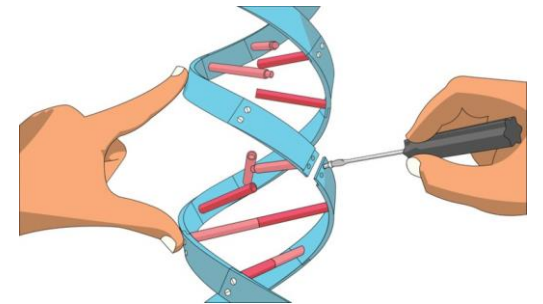
# Fitusiran

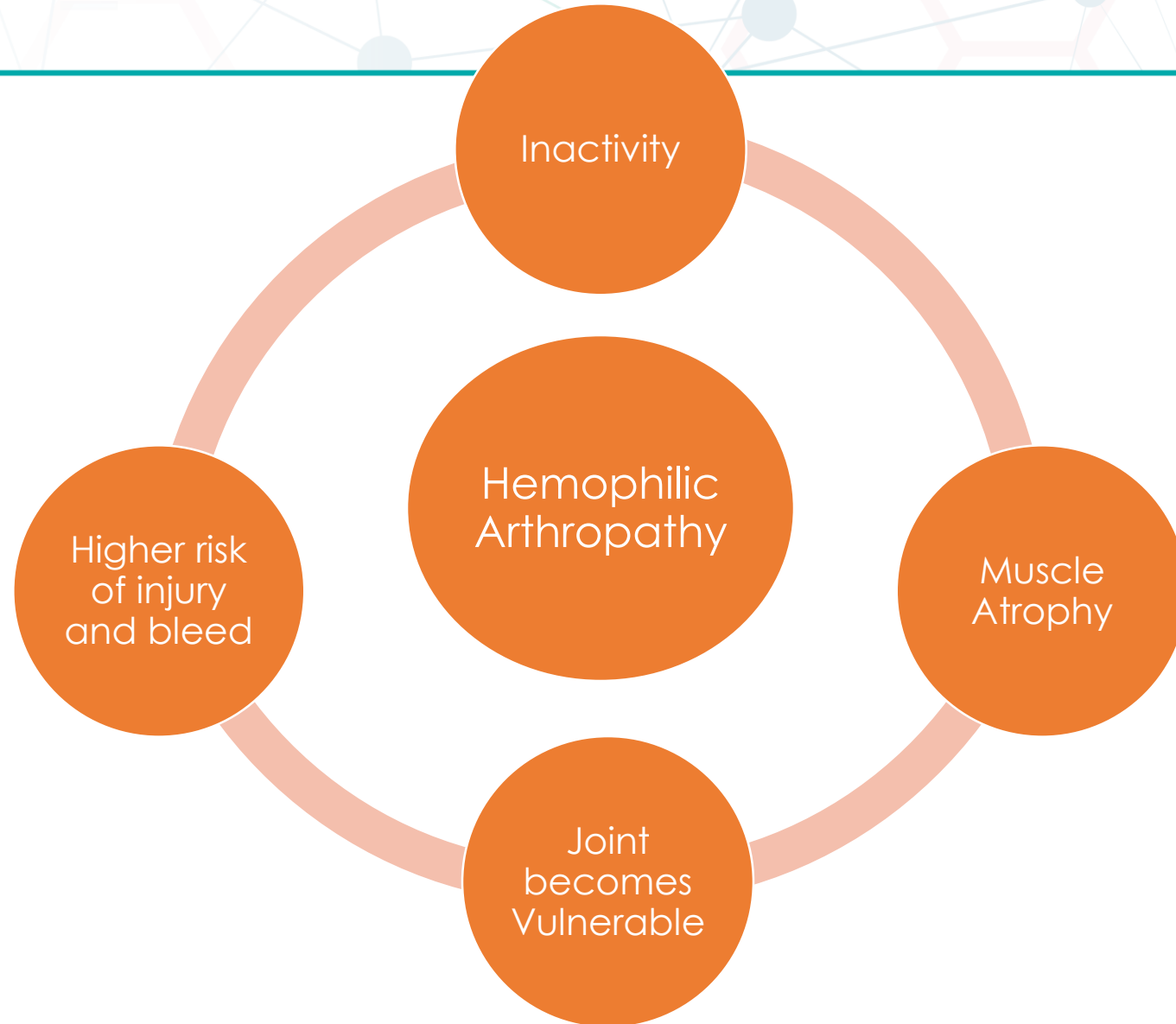
- RNA interference therapeutic
- Targets Antithrombin
- Improved thrombin generation
- Decreased annual bleeding rate
- Subcutaneous monthly administration



# Gene Therapy

- Utilize adeno-associated viral (AAV) vectors
- Recent clinical data
  - normalization of factor levels in some patients with improvements in bleed rate and quality of life
- Potential toxicity
  - early transient elevation in liver enzymes





# Joint Bleed



Healthy knee

The bleed starts to enter the joint.

The joint swells. It may become so large that it's called "cantaloupe knee."

# Presentation of Joint Bleed



Swelling of tissues  
in the knee may  
become permanent



Over time, this can  
lead to wearing away  
of the bone



Permanent damage  
results in a  
destroyed joint

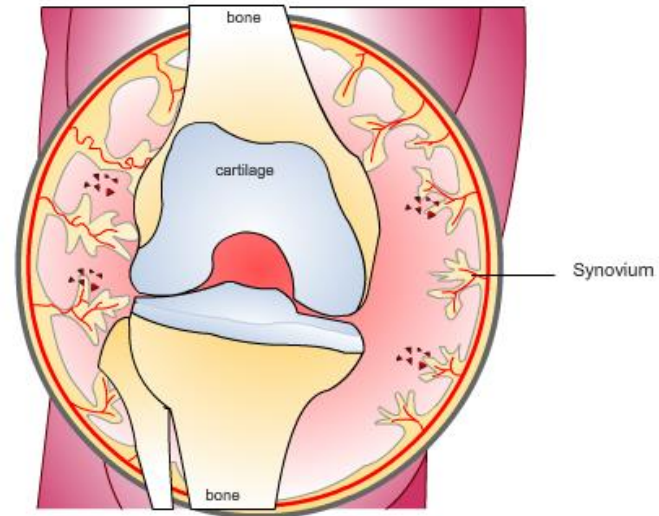




## Progression of Hemophilic Arthropathy

### Progression of Hemophilic Arthropathy

KNEE JOINT WITH RECURRENT BLEED



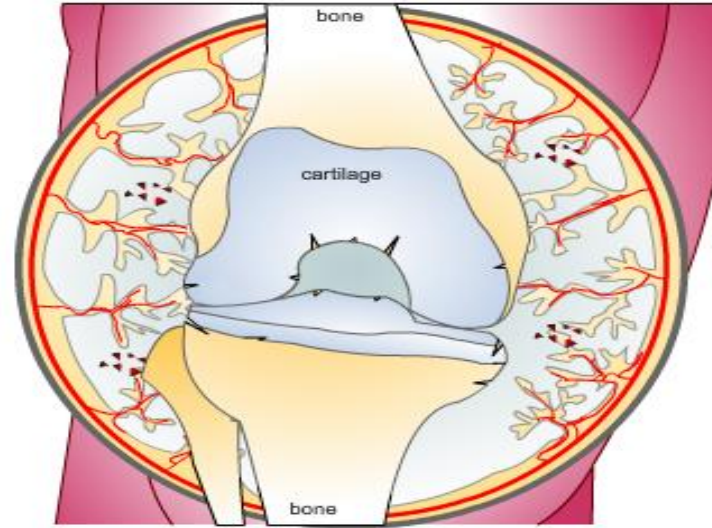
With recurrent bleeding the joint is swollen and boggy. The synovial lining shows villous hypertrophy (cauliflower like projections). These villi are very vascular, friable, tend to bleed easily and cause narrowing of joint space. Thus the cycle of bleeding continues. Bony changes also occur. Cellular responses play a role in not only synovial hyperplasia but also in the cartilage damage that follows. The flat synovial membrane grows into vascularized finger-like projections resulting in cauliflower (villous) like projections. Enzymes and cytokines are released that cause and propagate the inflammatory milieu within the joint. Iron from the blood further triggers proliferation and a vicious cycle of bleeding, hypertrophy, and re-bleeding develops. Inflammation is an integral part of the changes following a joint bleed. The effects of inflammatory cells, cytokines, and Reactive Oxygen Intermediate (ROI) on



## Progression of Hemophilic Arthropathy

KNEE JOINT WITH PAN ARTHRITIS

-  TNF $\alpha$
-  interferon gamma
-  IL-1
-  IL-6

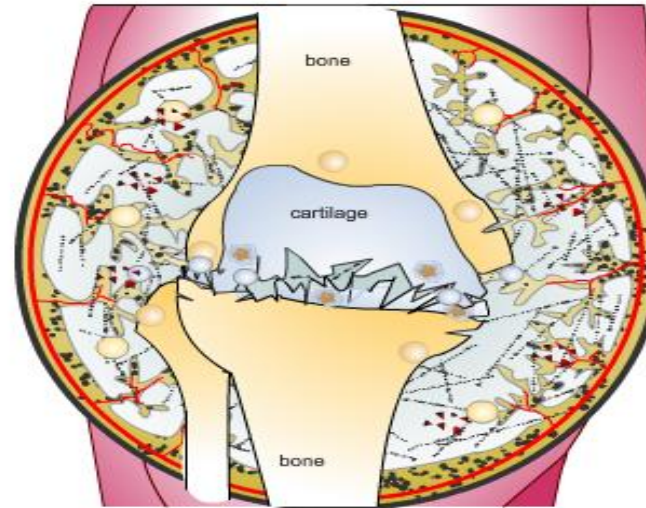


In the pan arthritis phase, there is extensive damage to the bone, cartilage, and synovium and this is accompanied by muscle wasting. There may be damage to the epiphyseal growth plates and osteoporosis. Highly vascularized granulation tissue develops, which is prone to bleeding. This is seen especially in the hemophilic joint where factor replacement may have been insufficient or fibrin formation inadequate (as may be the case in those with inhibitors to FVIII or FIX). Rebleeding exacerbates the vicious cycle described previously and bleeding begets more bleeding. The new blood vessels form with minimal stabilizing connective tissue. As the synovial fibroblasts proliferate within the synovial membrane, granulation tissue, collagen and other connective tissue components are produced leading to an increase in tensile strength of the repaired tissue. In the joint, this normal process of wound healing leads to the signs and symptoms of hemophilic arthropathy.



### Progression of Hemophilic Arthropathy

KNEE JOINT WITH FIBROSIS AND CONTRACTURES

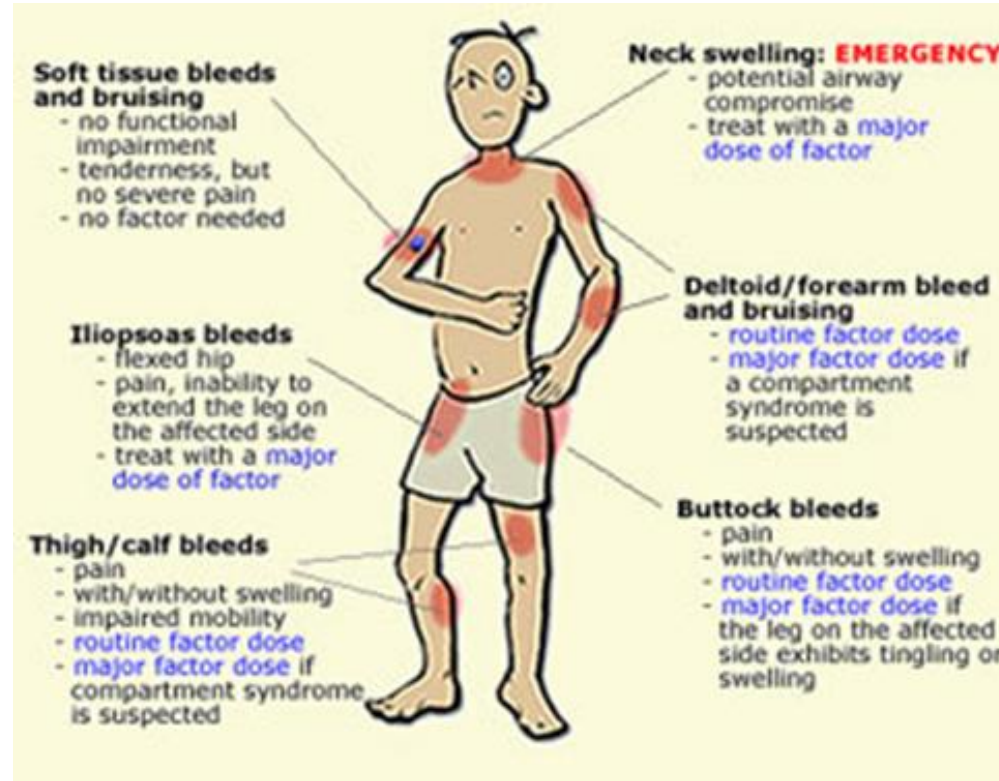


The end stage of repeated joint bleed is characterized by fibrous joint contracture and loss of joint space, as well as synovial destruction, and fibrous ankylosis. There may be osteophytic bone overgrowth; synovial effusion and thickening are not prominent.





# Muscle Bleeds



**Soft tissue bleeds and bruising**

- no functional impairment
- tenderness, but no severe pain
- no factor needed

**Neck swelling: EMERGENCY**

- potential airway compromise
- treat with a **major dose of factor**

**Iliopsoas bleeds**

- flexed hip
- pain, inability to extend the leg on the affected side
- treat with a **major dose of factor**

**Thigh/calf bleeds**

- pain
- with/without swelling
- impaired mobility
- **routine factor dose**
- **major factor dose** if compartment syndrome is suspected

**Deltoid/forearm bleed and bruising**

- **routine factor dose**
- **major factor dose** if a compartment syndrome is suspected

**Buttock bleeds**

- pain
- with/without swelling
- **routine factor dose**
- **major factor dose** if the leg on the affected side exhibits tingling or swelling

# Muscle Bleed

- Signs and Symptoms
  - Muscle guarding in shortened position
  - Swelling
  - Hematoma
  - Heat
  - Pain
  - Muscle inhibition



# Iliopsoas Bleed

- Potentially life threatening bleed
- Signs/Symptoms
  - Inability to extend hip
  - Pain in hip and/or groin region
  - Inability to stand erect or lie flat
  - Femoral nerve symptoms





# Iliopsoas Bleed: Acute Stage

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- Factor correction per medical team orders
- Bedrest
- TTWB for household mobility only
- Ankle pumps involved LE



# Orthopedic Surgery

- Synovectomy
  - Open or arthroscopic
- Radiosynoviorrhesis
- Arthrodesis
- Osteotomies
- Arthroplasty





# Objective Measures for Evaluation

- Range of Motion
- Strength
- Balance/Fall Assessment
- Posture
- Gait Analysis
- Functional Activities
- Joint Palpation
- Girth Measurements: note atrophy or edema
- Muscle flexibility
- Hemophilia Joint Health Score (HJHS)
- Leg Length
- Sensation
- Proprioception
- Special tests:
  - Orthopedic, Developmental, Neuromotor
- Other
  - MSKUS, orthotic evaluation, QOL measures

# Evaluation of Joint Health

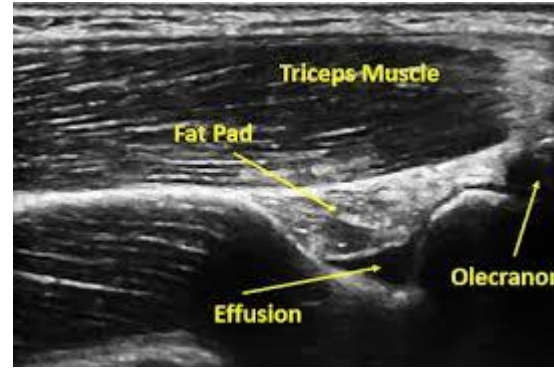
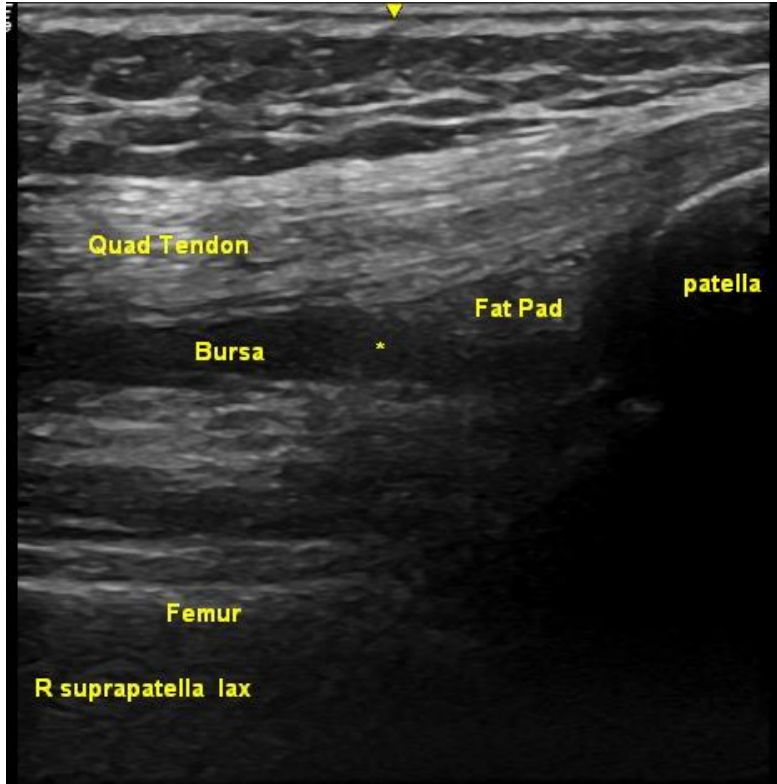
- Hemophilia Joint Health Score

- ROM
  - Loss of flexion/extension
- Swelling
  - Duration of swelling
- Joint pain
- Crepitus on motion
- Atrophy
- Strength



- International Prophylaxis Study Group website: [www.ipsg.ca](http://www.ipsg.ca)

# MSKUS: Musculoskeletal Ultrasound



Hemophilia & Thrombosis Treatment Center at UC San Diego Health

# What can PT Help With?

- Joint Preservation
  - PRICE
  - Alignment
  - Stretching
  - Strengthening
  - Bone Density
  - Proprioception
  - Sports Recommendations
  - **Education: Factor Correction**





# Chronic Pain

- MSK Joint Bleeds-hallmark of Hph
- Hemarthropathy
  - Chronic synovitis
  - Cartilage destruction
- PT Role
  - Activity modification
- Exercise Induced Analgesia

# Kinesiotaping





# Orthotics and Footwear

- Footwear



- Inserts



- AFO

- Orthopedic Shoes







# Sports Participation

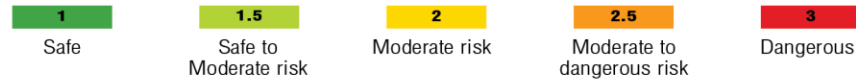
- Risk Minimization
- Protective Equipment
- Factor Prophylaxis
  - Timing





# Playing it Safe

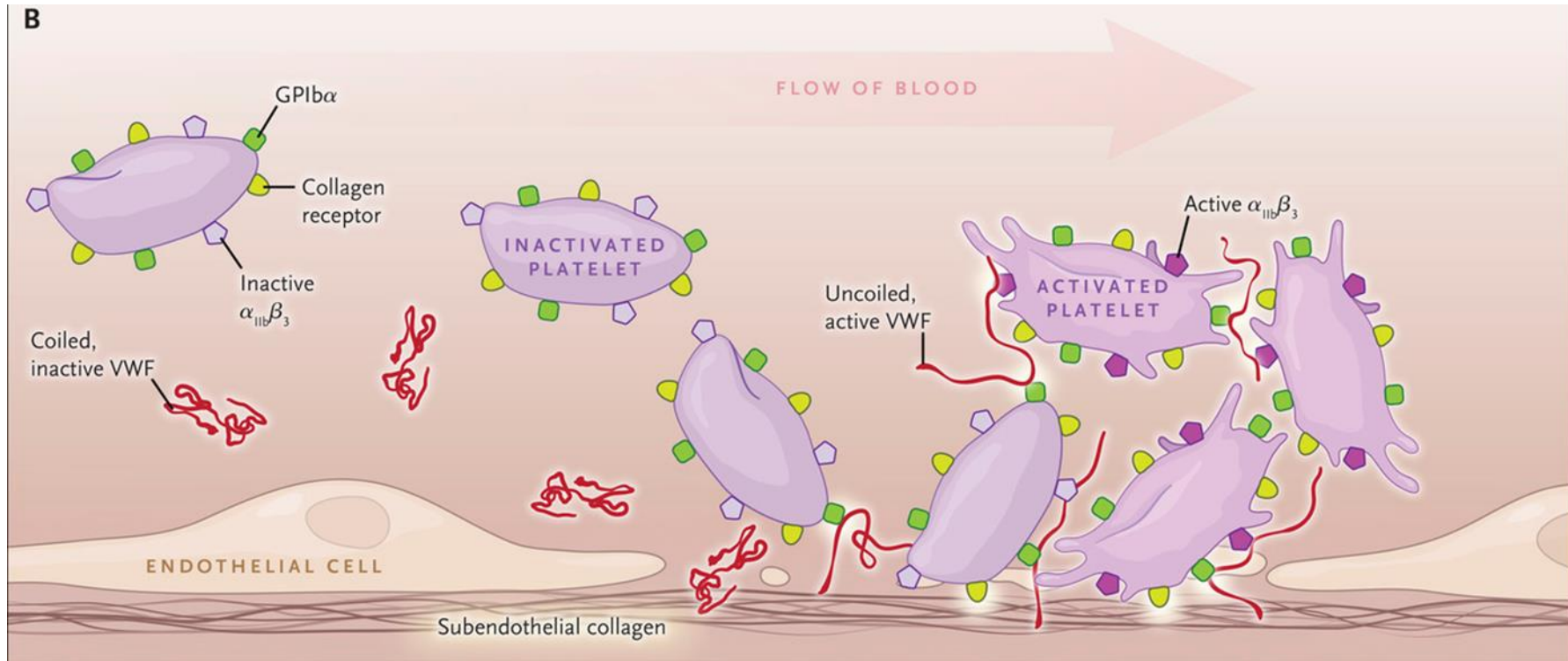
Activities have been divided into five ratings:



Activity	Category
Aerobics	2
Archery	1
Aquatics	1
Baseball	2.5
Basketball	2.5
Bicycling	1.5
BMX Racing	3
Bowling	2
Boxing	3
Canoeing	2.5
Cardiovascular Training Equipment	
Elliptical Machine	1
Rowing Machine	1.5
Ski machine	1.5
Stationary Bike	1
Stepper	2
Treadmill	1.5
Cheerleading	2.5
Circuit Training	1.5
Dance	2
Diving/Competitive	3
Diving/Recreational	2
Exercise Classes	
Body Sculpting	1.5
Cardio Kick-Boxing	2
Physioball	1.5
Spinning	1.5
Fishing	1
Football	3
Frisbee	1
Frisbee Golf	1.5
Ultimate Frisbee	2
Golf	1
Gymnastics	2.5
Hiking	1
Hockey (Field, Ice, Street)	3
Horseback Riding	2.5
Ice-Skating	2.5

Activity	Category
Inline Skating	2.5
Jet Skiing	2.5
Jumping Rope	2
Kayaking	2.5
Lacrosse	3
Martial Arts – Karate/ Kung Fu/Tae Kwon Do	2.5
Martial Arts/Tai Chi	1
Motorcycling/ Motor Cross Racing	3
Mountain Biking	2.5
Pilates	1.5
Power Lifting	3
Racquetball	2.5
River Rafting	2.5
Rock Climbing (Indoor/Challenge Course)	2
Rock Climbing (Natural Setting)	3
Rodeo	3
Roller-skating	2
Rowing/Crew	2
Rugby	3
Running and Jogging	2
Scooter (motorized)	3
Scooter (non-motorized)	2.5
Scuba Diving	2.5
Skateboarding	2.5
Skiing/Cross Country	2
Skiing/Downhill	2.5
Skiing/Telemark	2.5
Snorkeling	1
Snowboarding	2.5
Snowmobiling	3
Soccer	2.5
Softball	2.5
Surfing	2.5
Swimming	1
T-Ball	2
Tennis	2
Track and Field	2.5
Trampoline	3
Volleyball	2.5
Walking	1
Water-skiing	2.5
Weight Lifting/Resistance Training	1.5
Weight Lifting/Power Lifting	3
Wrestling	3
Yoga	2

# Von Willebrand's Disease





# Von Willebrand's Disease

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- Most common bleeding disorder
  - Mucocutaneous bleeding
    - nosebleeds
  - Bruising
  - Heavy menstrual bleeding
  - Post partum hemorrhage



# Von Willebrand's Disease

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- **Type 1**
  - Quantitative deficiency
  - Most common
  
- **Type 2**
  - Subtypes
    - Type 2A, 2B, 2M, type 2N
    - Qualitative deficiency
  
- **Type 3**
  - Quantitative deficiency
  - Joint and muscle bleeds
  
- **Acquired VWD**
  - development of antibodies to vWF

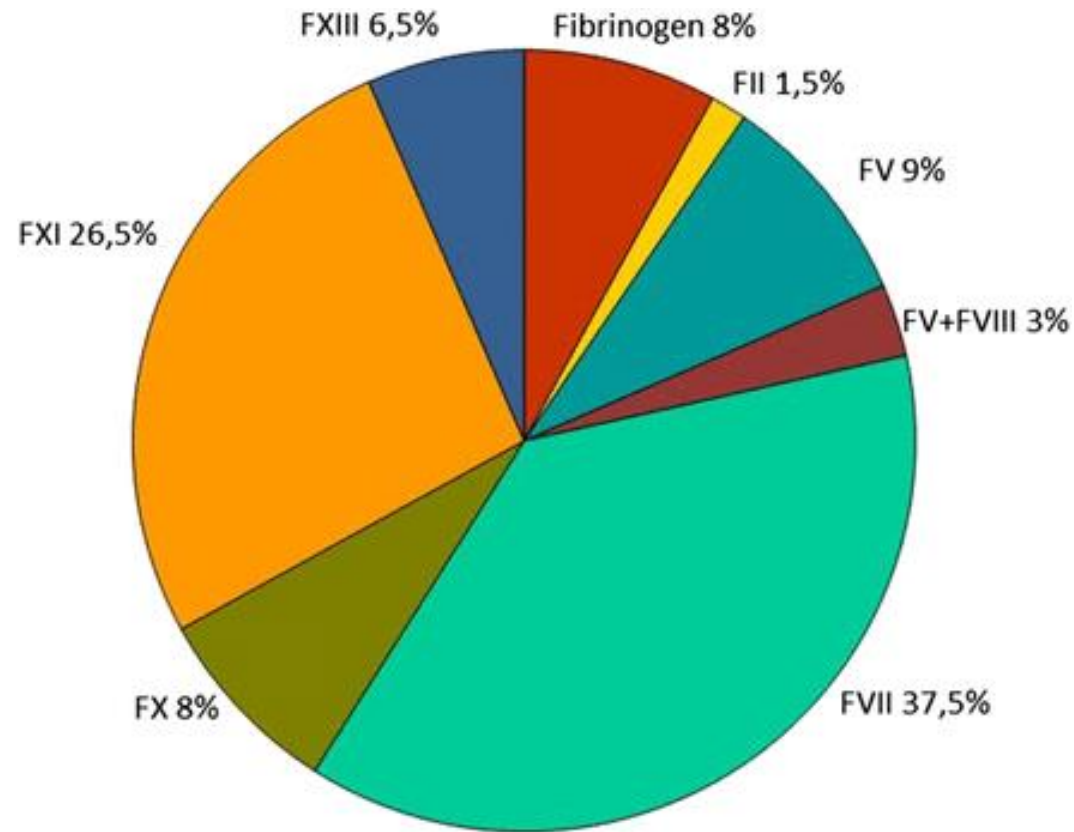


# vWD: Treatment

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- DDAVP
  - Desmopressin acetate
- Stimate
- Aminocaproic acid
- Tranexamic acid

# Rare Bleeding Disorders



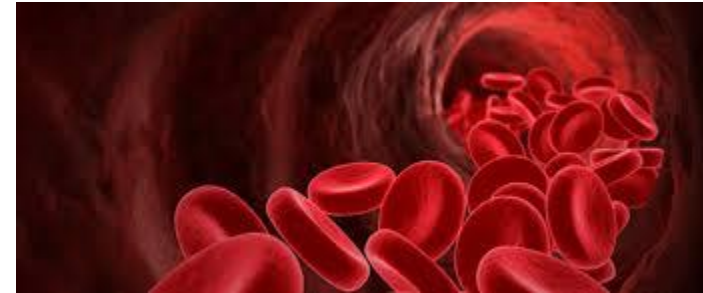
Worldwide distribution of RBDs derived from the WFH and EN-RBD



# Rare Bleeding Disorders

## **FVII deficiency**

- most common autosomal recessive coagulation disorder (1 in 500 000)
- Phenotypically variable
- Treatment: rFVIIa



## **FXI deficiency**

- estimated prevalence of severe FXI deficiency in most populations is ~1 in 1 million
- higher in Ashkenazi Jews where heterozygosity approaches 8%.
- Treatment: antifibrinolytic agents, FFP



# Resources

- Medical and Scientific Advisory Committee: [www.hemophilia.org](http://www.hemophilia.org)
  - Surgical Synovectomy
  - Joint Bleed
  - Muscle Bleed
  - Cryotherapy
  - Iliopsoas
  - Total Knee Replacement
  - Orthoses for Ankle Hemophilic Arthropathy (coming soon)
- Playing It Safe
- Partners in Bleeding Disorders Education: [www.Partnersprn.org](http://www.Partnersprn.org)
- NHF conference
- PT travel scholarship
- University of California San Diego Hemophilia and Thrombosis Treatment Center
  - <https://cme.ucsd.edu/httc/musks.html>
- HJHS Instructional Manual (IPSG)
  - <http://www.ipsg.ca>
- [www.wfh.org](http://www.wfh.org)
  - Educational modules
- Steps for Living:  
<https://stepsforliving.hemophilia.org/basics-of-bleeding-disorders/types-of-bleeding-disorders/hemophilia>
- Physical Therapy Working Group Website
  - [www.hemophilia.org](http://www.hemophilia.org)



# Take Home Message

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- Joint Preservation and Optimization
- Comprehensive Care Model
- Patient Education

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**Take a few minutes now to fill out the easy session evaluation:**

## **Rate this session**

- Meaningful?
- Learned new ideas/skills?
- Will implement new ideas/skills?

**How could this session be improved?**

**Comments?**

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**Friday: 12:00 noon @ NHF Booth**  
**Saturday: @ Awards Ceremony**