Bleeding Disorders 101

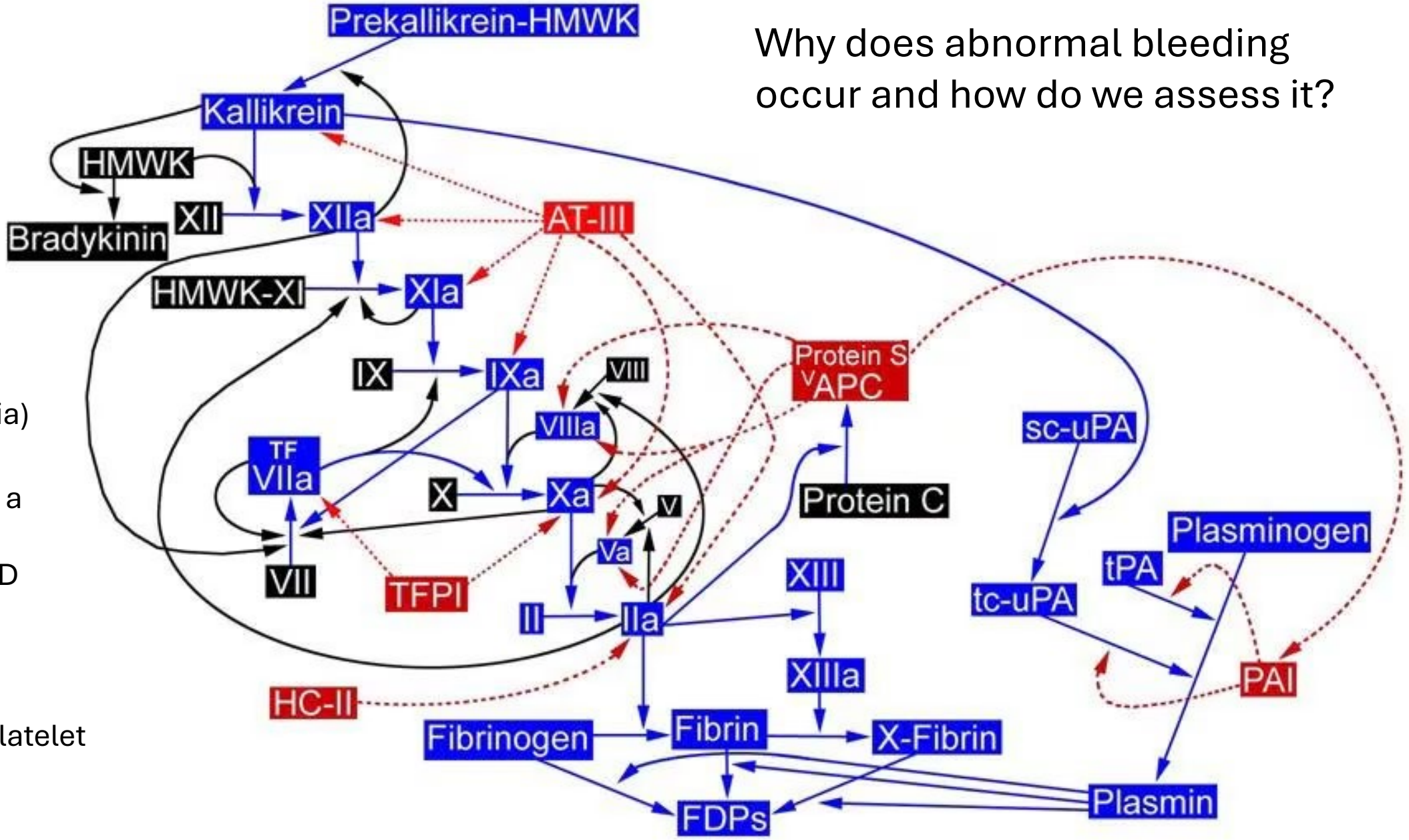
Nathan Hagstrom, MD, MHCM, FAAP
HTC Hematologist at Lehigh Valley Hospital
Physician-in-Chief at Lehigh Valley Reilly Children's Hospital
Regional Director of the Mid-Atlantic Region of HTCs
Professor of Pediatrics, USF Morsani College of Medicine

Why does abnormal bleeding occur and how do we assess it?

Deficiency of a component (e.g. hemophilia)

Dysfunction of a component (e.g. type 2 vWD

Excess of a component (e.g. Quebec platelet disorder

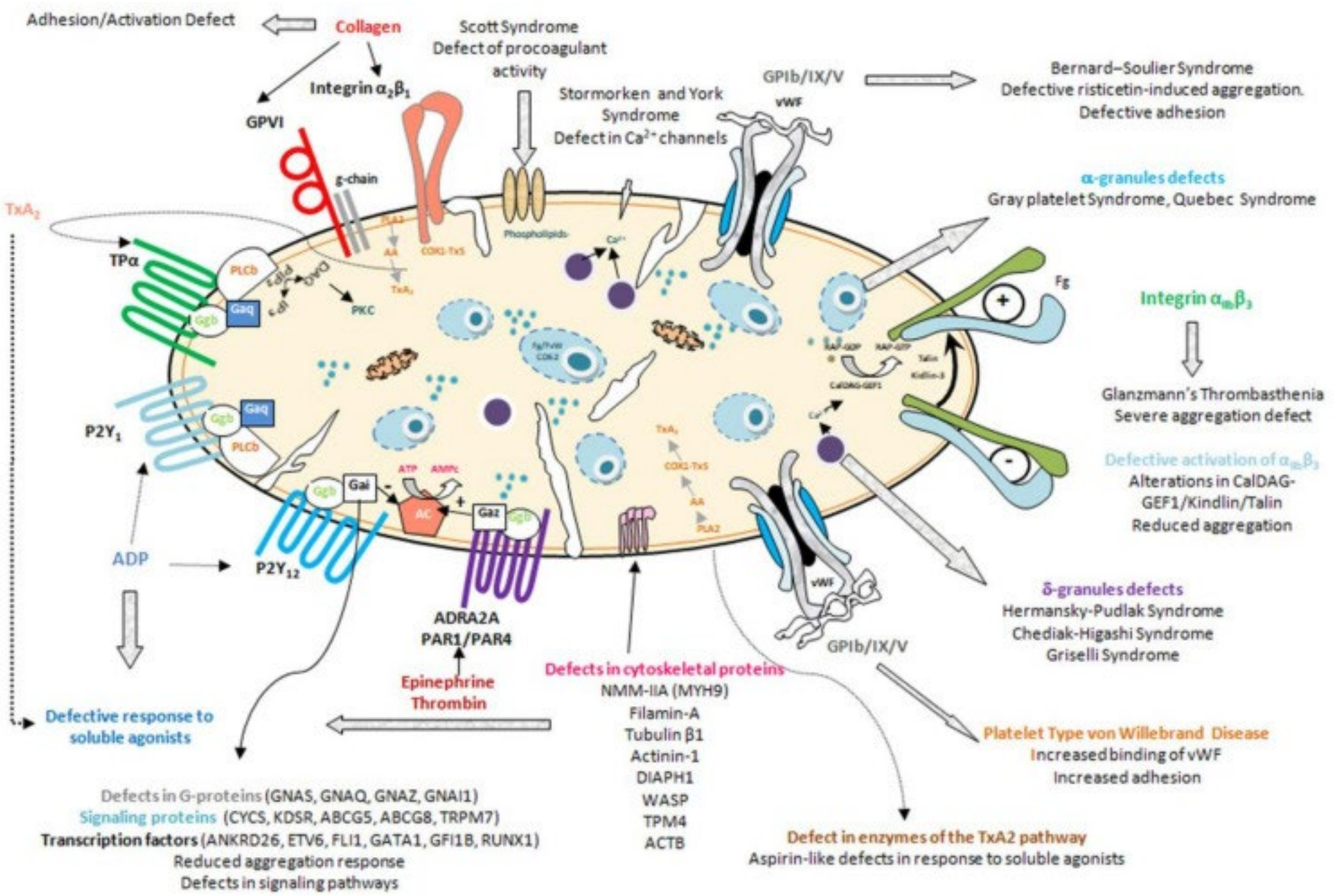


https://emedicine.medscape.com/article/779434-overview?form=fpf

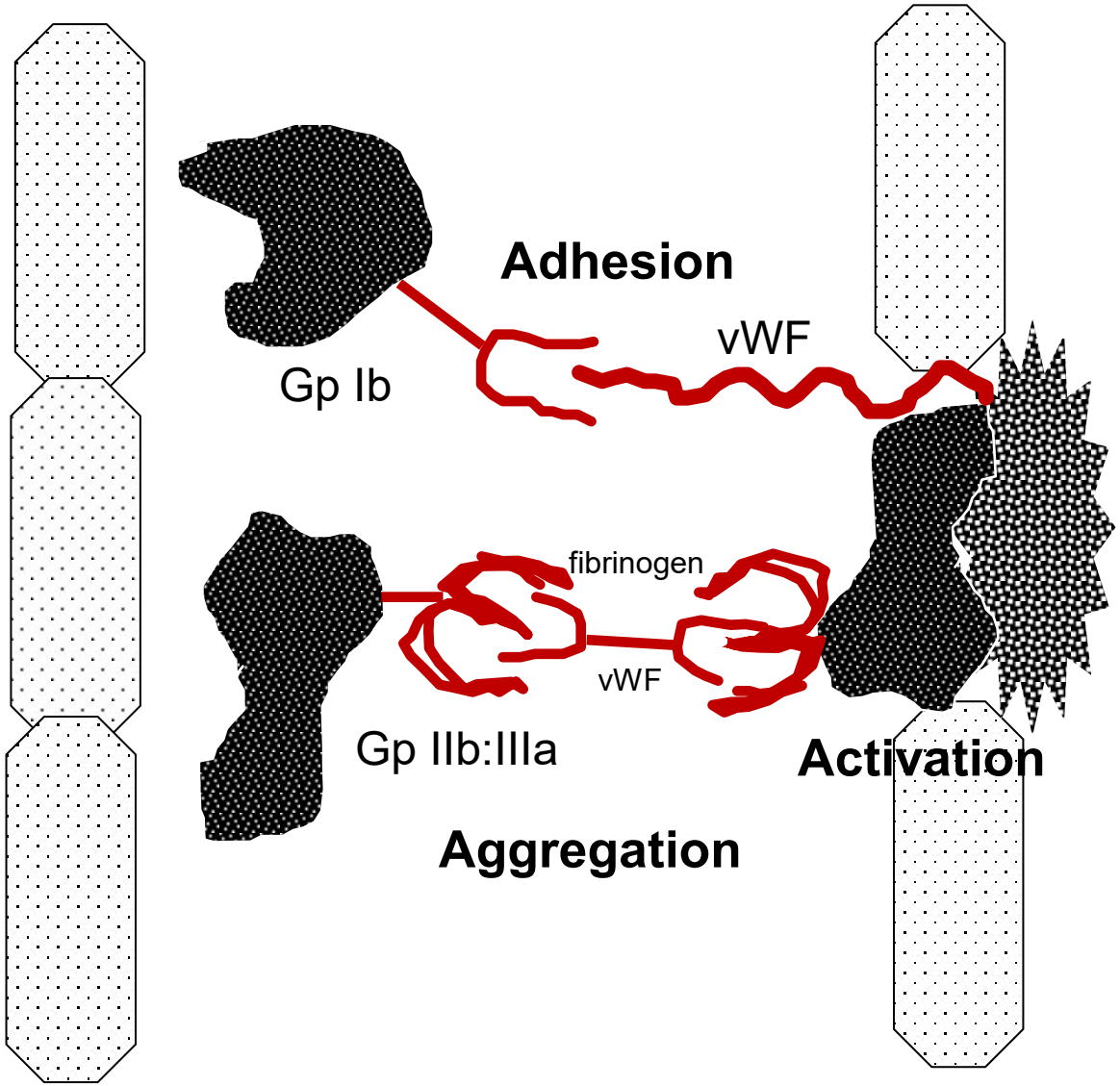
Decreased number of platelets (e.g. congenital amegakaryocytic thrombocytopenia, TAR)

Decreased components of the platelets (e.g. storage pool, dense granule def)

Dysfunctional components (e.g. platelet type vWD, Glanzmann)



The Platelet Plug



Platelet Disorders
Bernard-Soulier syndrome
Glanzmann's thrombasthenia
Storage pool disease
- Dense granule deficiency
- Hermansky-Pudlak syndrome
- Gray platelet syndrome

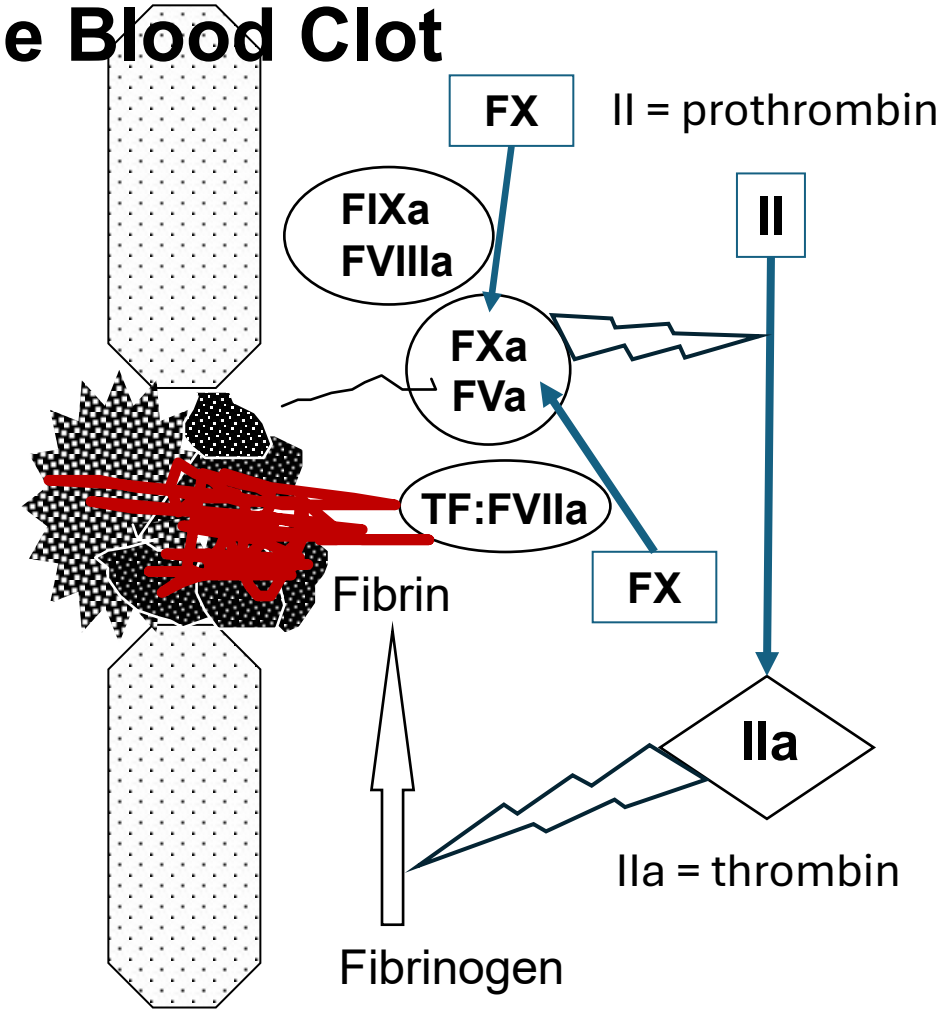
Signaling defects
RUNX1 deficiency

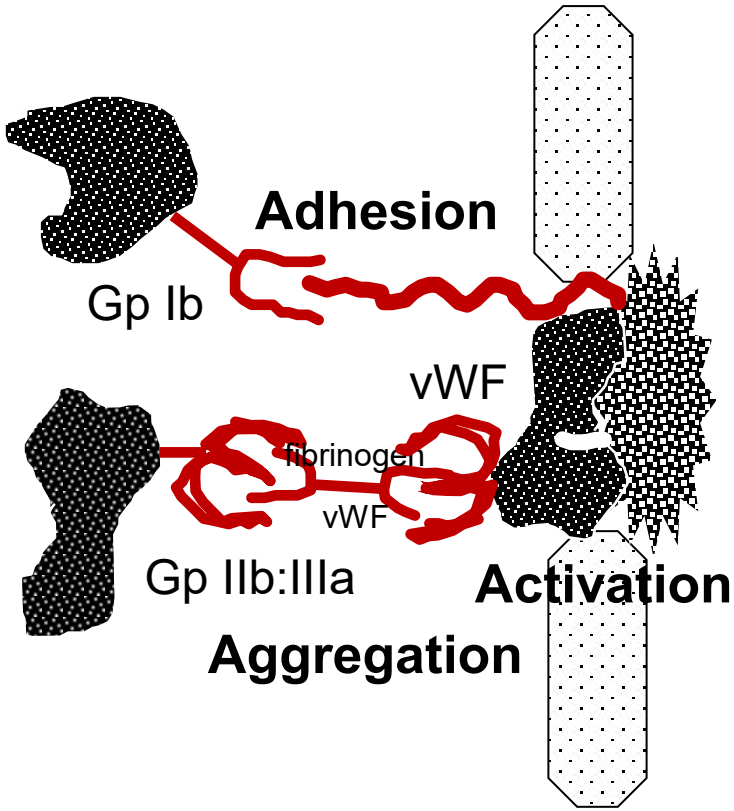
Primary Hemostasis Disorder
Von Willebrand Disease

The Blood Clot

<u>Disorders of Coagulation</u>
Hemophilia
Rare Factor Deficiencies

Von Willebrand Disease
[carrier protein for FVIII]





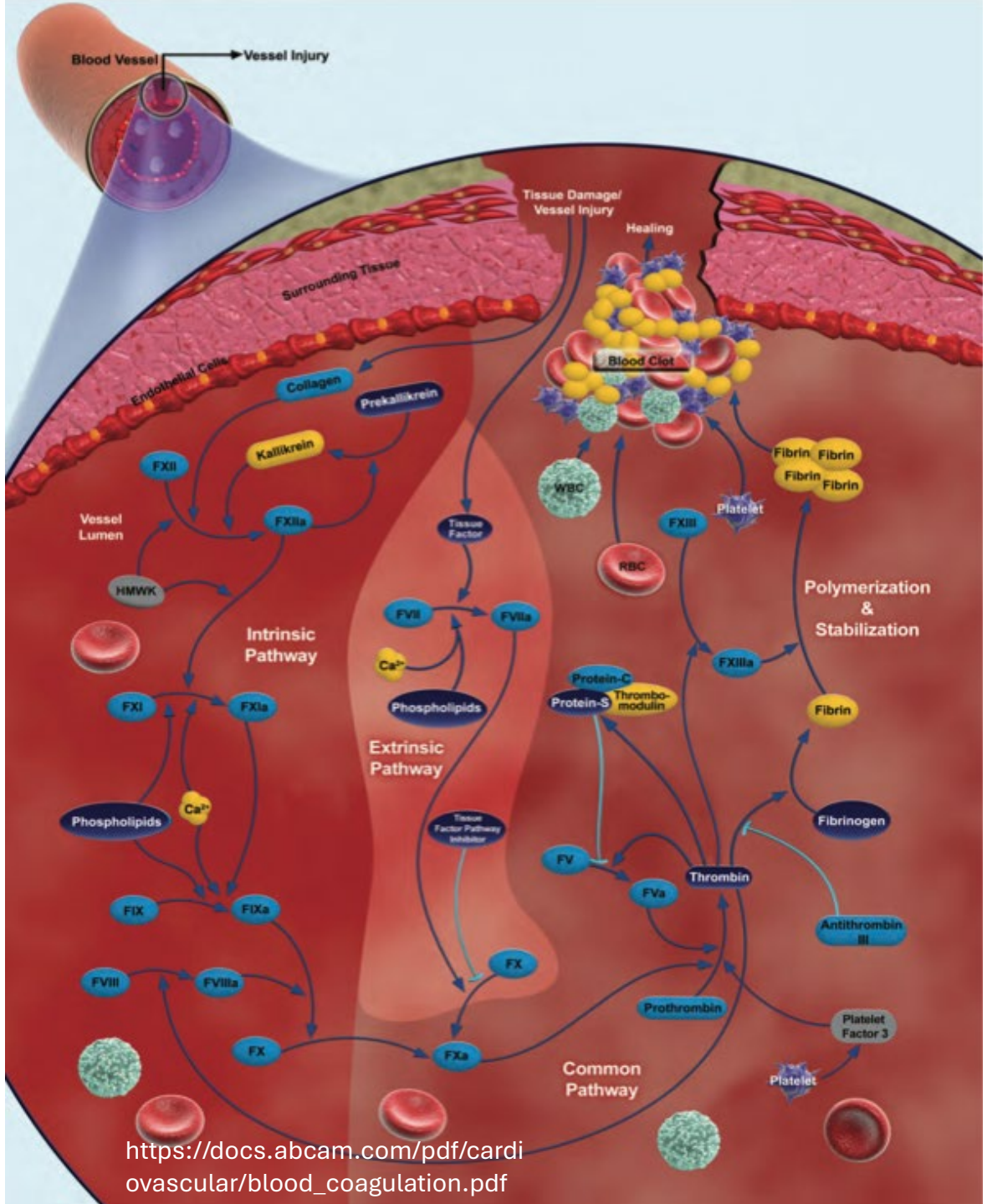
The Platelet Plug

Factor deficiencies causing bleeding:
Factor VIII deficiency
Factor IX deficiency
Factor XI deficiency
Factor VII deficiency
Factor X deficiency
Fibrinogen deficiency
Factor XIII deficiency
Factor V deficiency
Combined factor V and VIII deficiency
Combined deficiency of
the vitamin K–dependent clotting factors

Von Willebrand Factor deficiency

Other bleeding disorders:
PAI-1 deficiency
Alpha-2-antiplasmin deficiency
Hereditary Hemorrhagic Telangiectasia

Bleeding disorder of unknown cause (BDUC)



https://docs.abcam.com/pdf/cardiovascular/blood_coagulation.pdf

How do we assess for abnormal bleeding?

3 y/o girl with bruising

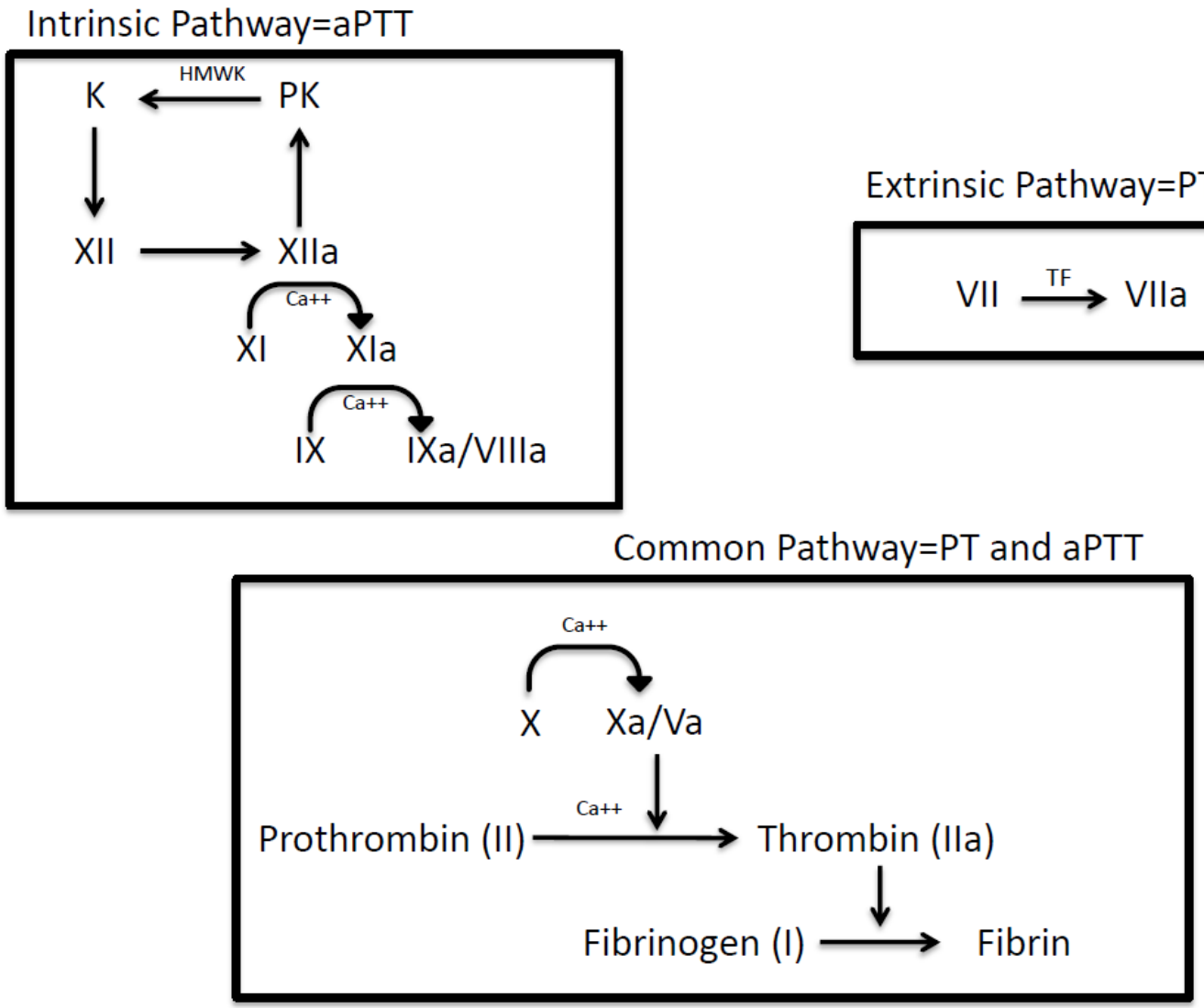
- Bruises are on the lower extremity as well as upper.
- Some bruises are flat and some are raised with associated hematoma.
- No h/o nosebleeds

Laboratory evaluation

- CBC, PT, PTT
- von Willebrand factor activity and antigen with a factor VIII activity
- +/- fibrinogen
- +/- factor IX
- +/- factor XI
- +/- platelet function analyzer (PFA-100)
- +/- platelet aggregation and secretion studies
- ? Bleeding time - no on really does this present day
- If Acquired consider:
  - Liver, kidney and thyroid function tests
- Rare factor deficiency causes of bleeding:
  - Factor XIII
  - Alpha-2-antiplasmin
  - PAI-1

Typically done when the first two are normal

Factor deficiencies and coagulation assays



aspho

Bleeding Assessment Tool

3 y/o girl with bruising

PEDIATRIC BLEEDING QUESTIONNAIRE

Biss TT, et al.
J Thromb Haemost
8:950, 2010
(Toronto Sick Kids)

Derived from the ISTH BAT
[Bleeding Assessment Score]

Symptom	–1	0	1	2	3	4
Epistaxis	–	no or trivial (≤5 per year)	>5 per year or >10 min duration	consultation only	packing, cauterization or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Cutaneous	–	no or trivial (≤1 cm)	>1 cm and no trauma	consultation only	–	–
Minor wounds	–	no or trivial (≤5 per year)	>5 per year or >5 min duration	consultation only or steri-strips	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Oral cavity	–	no	reported at least one	consultation only	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Gastrointestinal tract	–	no	identified cause	consultation or spontaneous	surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	–
Tooth extraction	no bleeding in at least 2 extractions	none done or no bleeding in 1	reported, no consultation	consultation only	resuturing, repacking or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Surgery	no bleeding in at least 2 surgeries	none done or no bleeding in 1	reported, no consultation	consultation only	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Menorrhagia	–	no	reported or consultation only	antifibrinolytics or contraceptive pill use	D&C or iron therapy	blood transfusion, replacement therapy, desmopressin or hysterectomy
Postpartum	no bleeding in at least 2 deliveries	no deliveries or no bleeding in 1 delivery	reported or consultation only	D&C, iron therapy or antifibrinolytics	blood transfusion, replacement therapy or desmopressin	–
Muscle hematoma	–	never	post-trauma, no therapy	spontaneous, no therapy	spontaneous or traumatic, requiring desmopressin or replacement therapy	spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	–	never	post-trauma, no therapy	spontaneous, no therapy	spontaneous or traumatic, requiring desmopressin or replacement therapy	spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system	–	never	–	–	subdural, any intervention	intracerebral, any intervention
Other: postcircumcision umbilical stump cephalohematoma macroscopic hematuria postvenipuncture conjunctival hemorrhage	–	no	reported	consultation only	surgical hemostasis, antifibrinolytics or iron therapy	blood transfusion, replacement therapy or desmopressin

3 y/o girl with bruising

Symptom	–1	0	1	2	3	4
Epistaxis	–	no or trivial (≤5 per year)	>5 per year or >10 min duration	consultation only	packing, cauterization or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Cutaneous	–	no or trivial (≤1 cm)	>1 cm and no trauma	consultation only ✓	–	–
Minor wounds	–	no or trivial (≤5 per year)	>5 per year or >5 min duration	consultation only or steri-strips	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Oral cavity	–	no	reported at least one	consultation only	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Gastrointestinal tract	–	no	identified cause	consultation or spontaneous	surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	–
Tooth extraction	no bleeding in at least 2 extractions	none done or no bleeding in 1	reported, no consultation	consultation only	resuturing, repacking or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Surgery	no bleeding in at least 2 surgeries	none done or no bleeding in 1	reported, no consultation ✓	consultation only	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin

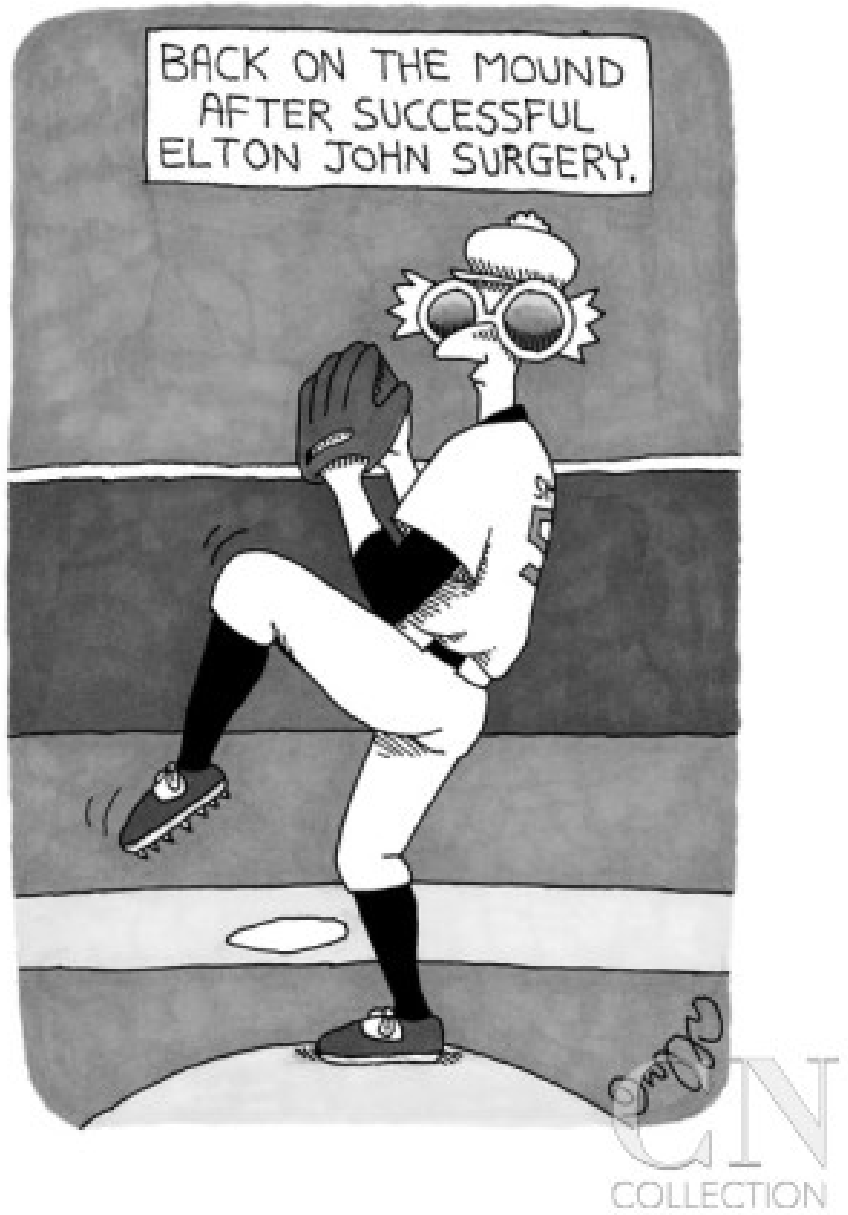
Score = 3
So far

	-1	0	1	2		
Menorrhagia	–	no	reported or consultation only	antifibrinolytics or contraceptive pill use	D&C or iron therapy	blood transfusion, replacement therapy, desmopressin or hysterectomy
Postpartum	no bleeding in at least 2 deliveries	no deliveries or no bleeding in 1 delivery	reported or consultation only	D&C, iron therapy or antifibrinolytics	blood transfusion, replacement therapy or desmopressin	–
Muscle hematoma	–	never	post-trauma, no therapy	spontaneous, no therapy	spontaneous or traumatic, requiring desmopressin or replacement therapy	spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	–	never	post-trauma, no therapy	spontaneous, no therapy	spontaneous or traumatic, requiring desmopressin or replacement therapy	spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system	–	never	–	–	subdural, any intervention	intracerebral, any intervention
Other: postcircumcision umbilical stump cephalohematoma macroscopic hematuria postvenipuncture conjunctival hemorrhage	–	no	reported ✓	consultation only	surgical hemostasis, antifibrinolytics or iron therapy	blood transfusion, replacement therapy or desmopressin

Score = 4

Surgeries with an increase risk of bleeding

- Dental extractions
- T+As
- Scoliosis surgery
- Head lacerations
- Craniofacial surgery
- Circumcisions
- GI surgery
- Orthopedic surgeries



Many children haven't had surgical challenges.

3 y/o girl with bruising has a bleeding score 2 without targeted questioning and 3 with surgery question and 4 with venipuncture question

Her lab test results:

Factor VIII = 30%
vWF antigen = 23%
vWF activity = <12%

Family history can be helpful:

- bleeding/bruising in 1st degree relative
- h/o hemophilia in other relatives

She had no known family history

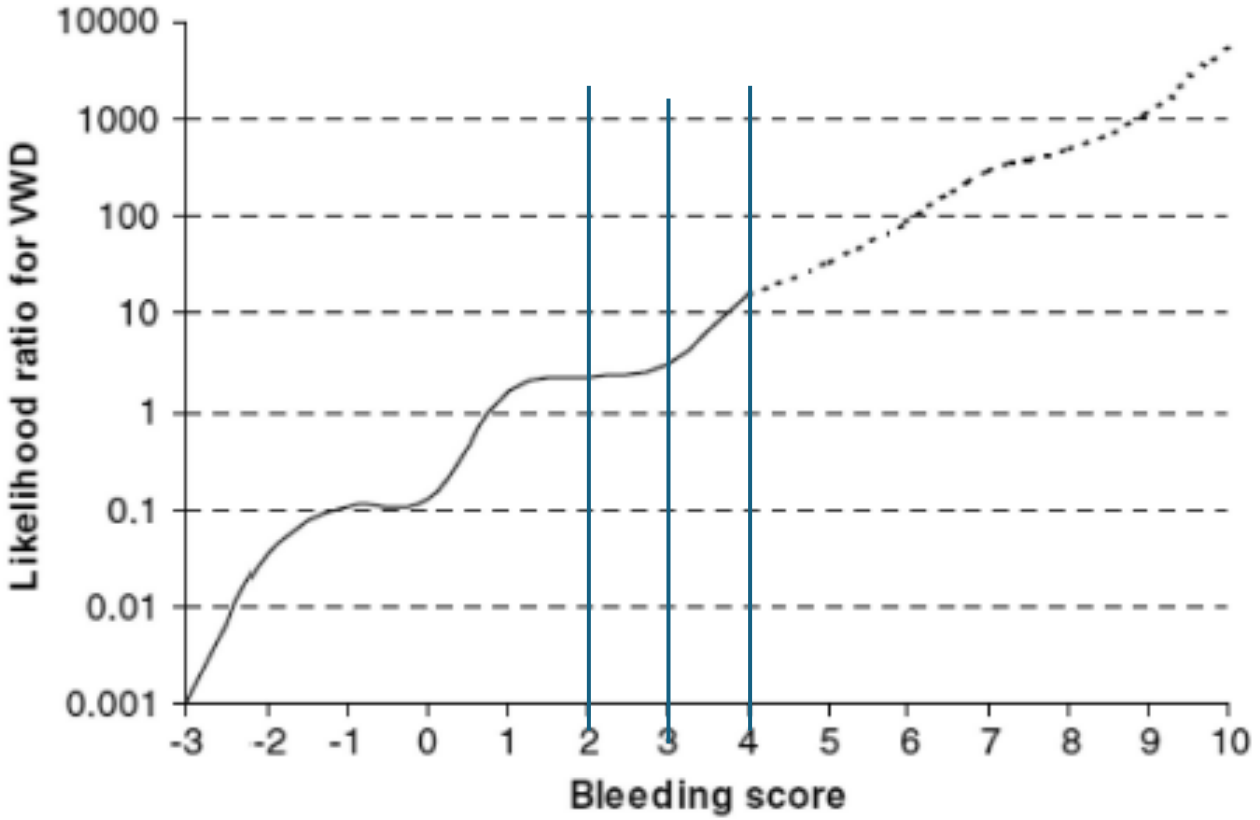


Figure 1. Likelihood ratios for VWD based on the Vicenza bleeding assessment tool (−1 version) and on data from the MCMDM-1 study. (Reprinted with permission from Tosetto et al.[15] Copyright 2007, Elsevier.)

O'Brien S. ASH Presentation 2018

3 y/o girl with bruising grows up

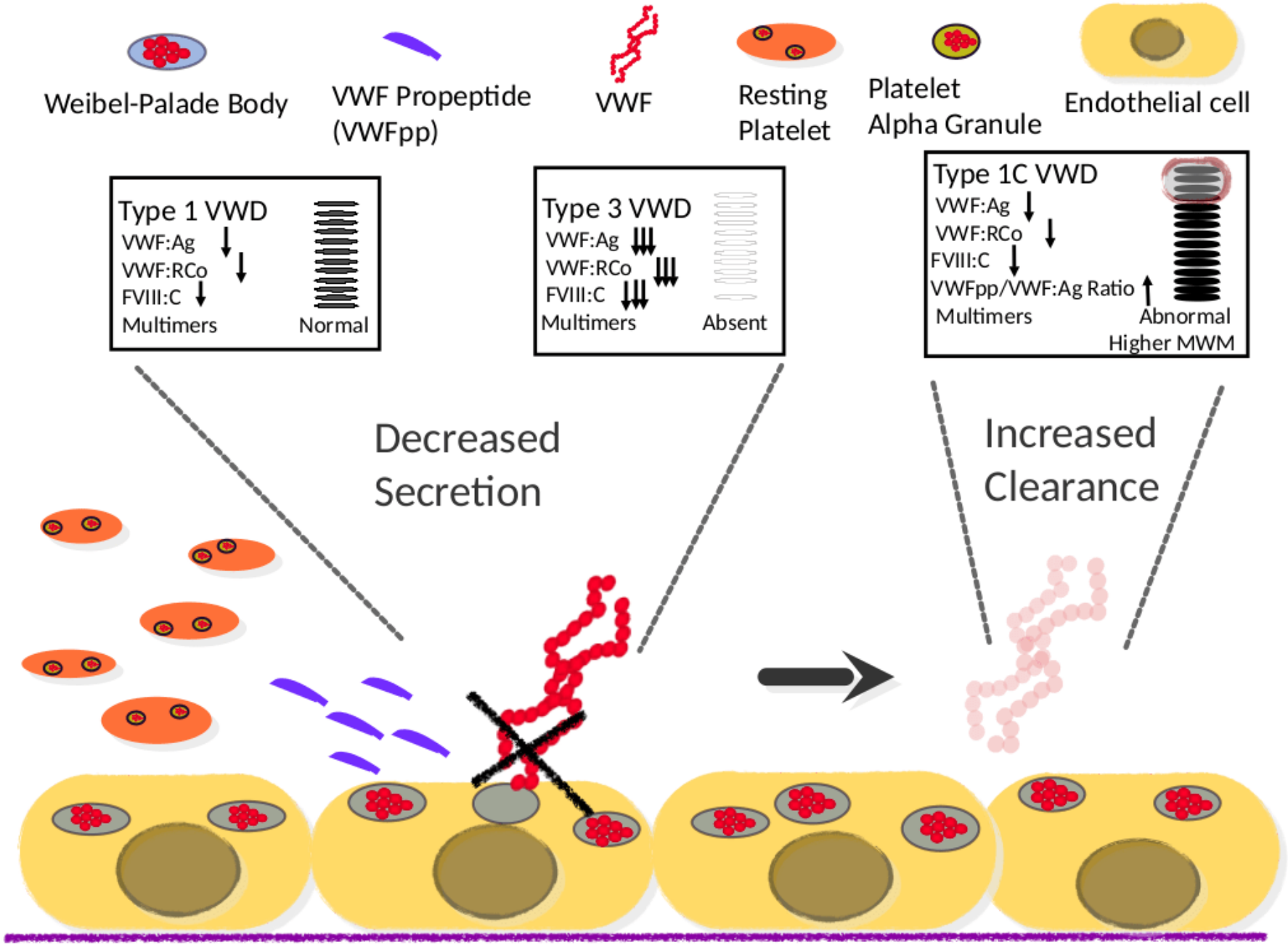
Symptom	–1	0	1	2	3	4
Epistaxis	–	no or trivial (≤5 per year)	>5 per year or >10 min duration	consultation only	packing, cauterization or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Cutaneous	–	no or trivial (≤1 cm)	>1 cm and no trauma	consultation only ✓	–	–
Minor wounds	–	no or trivial (≤5 per year)	>5 per year or ✓ >5 min duration	consultation only or steri-strips	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Oral cavity	–	no	reported at ✓ least one	consultation only	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin
Gastrointestinal tract	–	no	identified cause	consultation or spontaneous	surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	–
Tooth extraction	no bleeding in at least 2 extractions	none done or no bleeding in 1	reported, no consultation	consultation only	resuturing, repacking or antifibrinolytics ✓	blood transfusion, replacement therapy or desmopressin
Surgery	no bleeding in at least 2 surgeries	none done or no bleeding in 1	reported, no consultation	consultation only	surgical hemostasis or antifibrinolytics	blood transfusion, replacement therapy or desmopressin

	-1	0	1	2	3	
Menorrhagia	–	no	reported or consultation only	antifibrinolytics or contraceptive pill use ✓	D&C or iron therapy	blood transfusion, replacement therapy, desmopressin or hysterectomy
Postpartum	no bleeding in at least 2 deliveries	no deliveries or no bleeding in 1 delivery	reported or consultation only	D&C, iron therapy or antifibrinolytics	blood transfusion, replacement therapy or desmopressin	–
Muscle hematoma	–	never	post-trauma, no therapy	spontaneous, no therapy	spontaneous or traumatic, requiring desmopressin or replacement therapy	spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	–	never	post-trauma, no therapy	spontaneous, no therapy	spontaneous or traumatic, requiring desmopressin or replacement therapy	spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system	–	never	–	–	subdural, any intervention	intracerebral, any intervention
Other: postcircumcision umbilical stump cephalohematoma macroscopic hematuria postvenipuncture conjunctival hemorrhage	–	no	reported ✓	consultation only	surgical hemostasis, antifibrinolytics or iron therapy	blood transfusion, replacement therapy or desmopressin

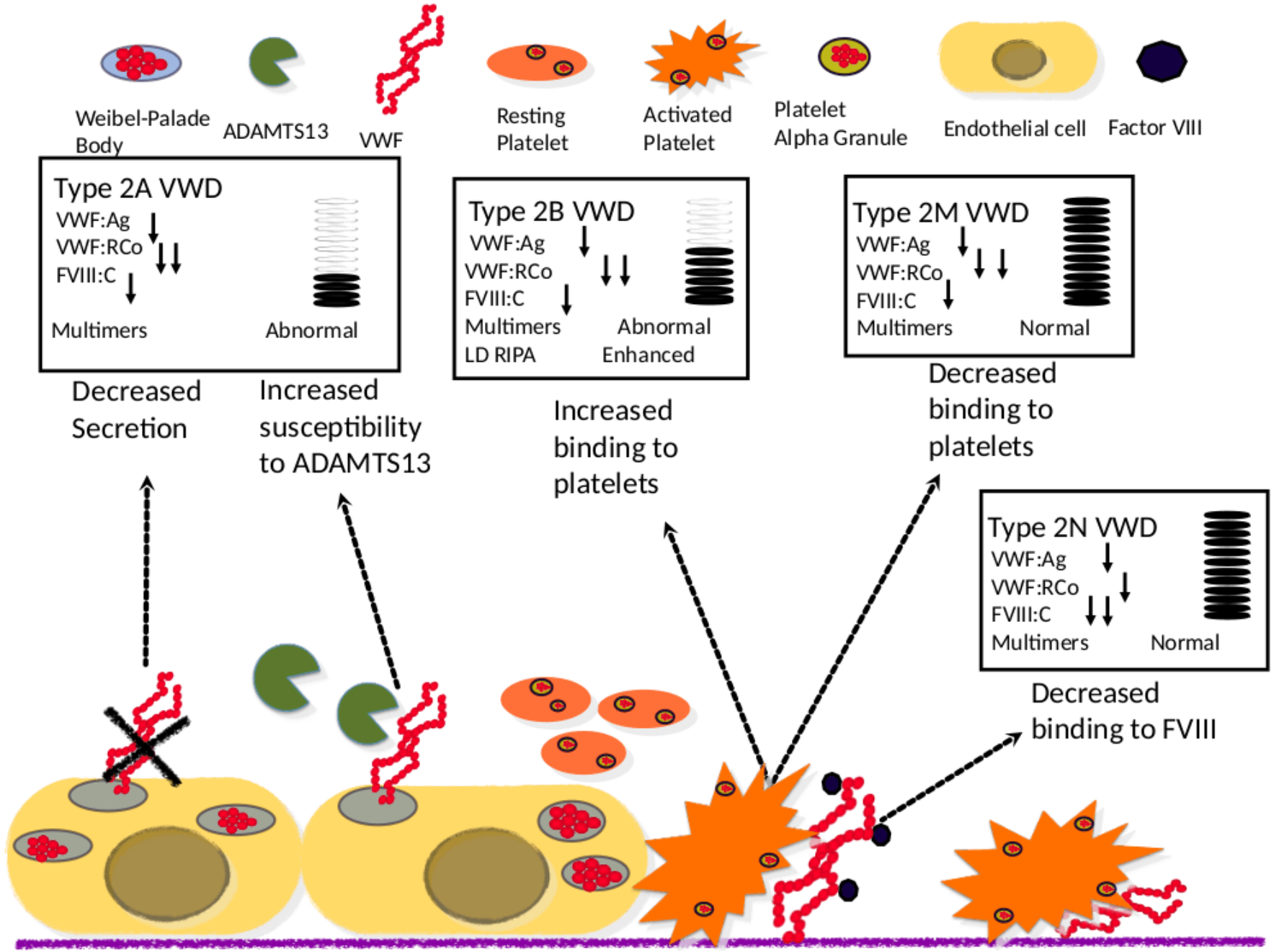
Score @ 15 yo is now 10

Differential Diagnosis for Abnormal Bleeding

- Von Willebrand disease
- Hemophilia and other factor deficiencies
- Factor XIII deficiency
- Hypofibrinogenemia
- PAI-1 deficiency
- Antiplasmin deficiency
- Platelet disorder – quantitative
- Platelet disorder – qualitative
- **Vascular disease:**
  - **Vasculitis**
  - **Scurvy**
  - **Hereditary hemorrhagic telangiectasia**
  - **Ehlers-Danlos**
- Non-accidental trauma

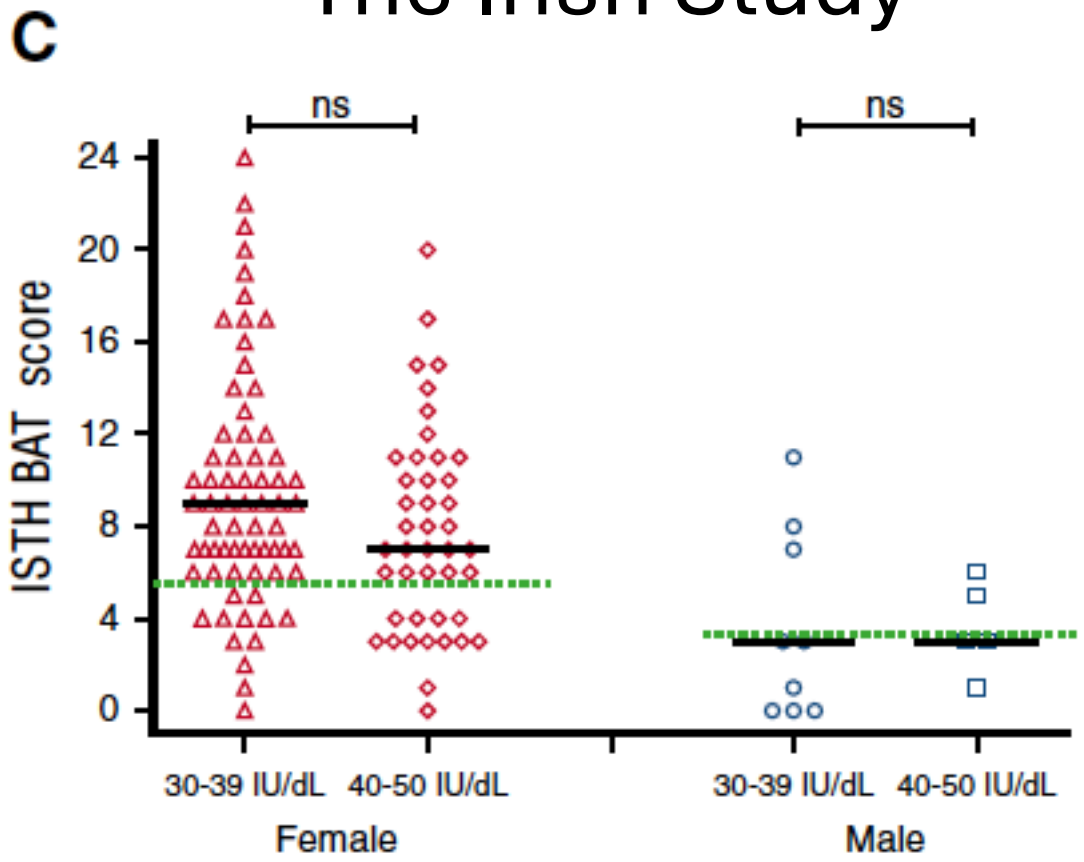


https://dipaolalab.wustl.edu/research/von-willebrand-disease/



https://dipaolalab.wustl.edu/research/von-willebrand-disease/

Low vWF levels versus true type 1 vWD
The Irish Study



Lavin M, et al. Blood 130(21):2344, 2017

https://stepsforliving.bleeding.org/basics-bleeding-disorders/bleeding-disorder-basics

Hemophilia

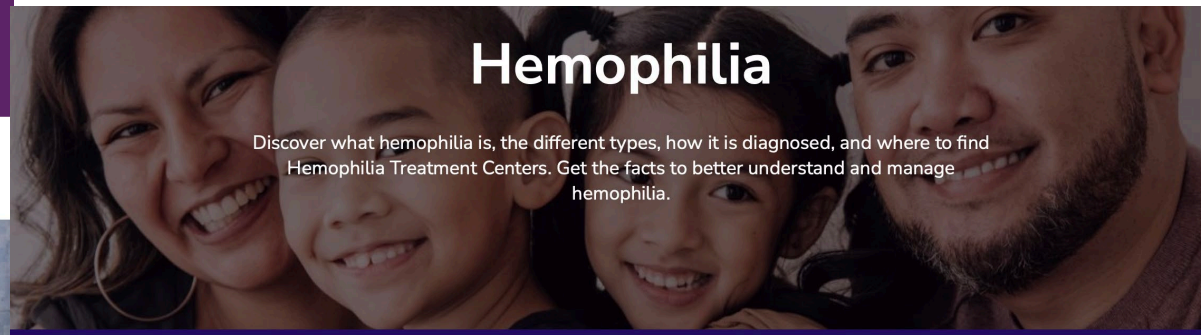
Discover what hemophilia is, the different types, how it is diagnosed, and where to find Hemophilia Treatment Centers. Get the facts to better understand and manage hemophilia.

Learn More

von Willebrand Disease

Learn about the symptoms, diagnosis, and management of von

https://stepsforliving.bleeding.org/basics-bleeding-disorders/bleeding-disorder-basics



Hemophilia

Discover what hemophilia is, the different types, how it is diagnosed, and where to find Hemophilia Treatment Centers. Get the facts to better understand and manage hemophilia.

I am a kid **I am an adult**

Bleeding disorders are a group of disorders that share the inability to form a proper blood clot, leading to continuous bleeding if not treated. When platelets and clotting proteins that are parts of a person's blood are missing or not working properly, then the person is unable to make a proper blood clot. The clotting proteins found in the blood are also known as clotting factors.

Hemophilia is the most well-known bleeding disorder and is caused when there is a lack or decrease of clotting factor VIII (8) or clotting factor IX (9). There are two main types of hemophilia. Hemophilia A happens if there is a problem with clotting factor VIII (8) and hemophilia B happens if there is a problem with clotting factor IX (9).

This section about hemophilia includes the following:

- **What is Hemophilia?**
- **Who Has Hemophilia?**
- **Diagnosing Hemophilia**

NATIONAL HEMOPHILIA FOUNDATION
www.hemophilia.org

Introduction to Bleeding Disorders

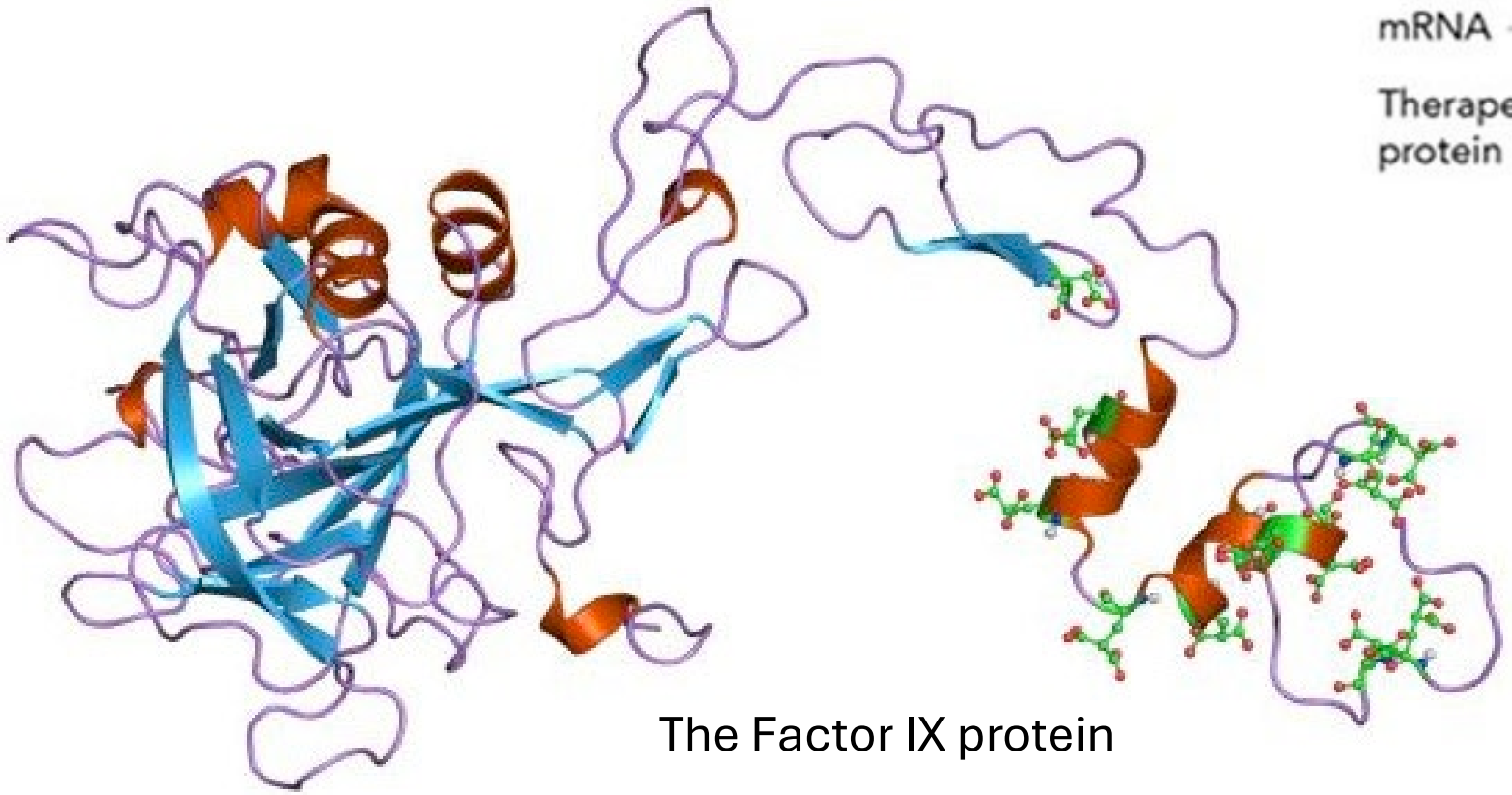
Regina B. Butler, RN

Bleeding disorders are relatively rare genetic disorders characterized by increased or prolonged bleeding due to abnormal coagulation (the ability of the blood to clot). The cause is a decrease in amount or function of one of the 11 proteins in the blood, called clotting factors, that work together to make the blood clot.

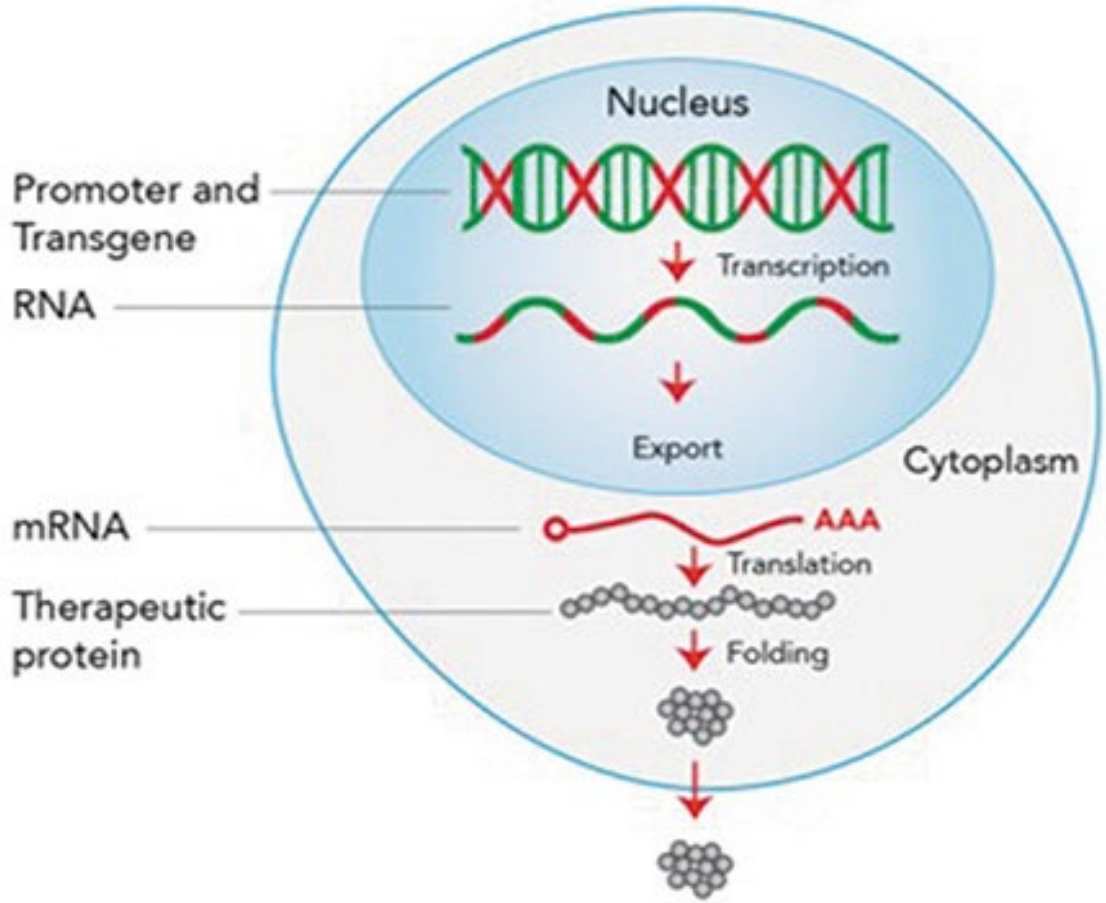
https://www.bleeding.org/sites/default/files/document/files/nurses-guide-chapter-1-introduction-to-bleeding-disorders.pdf

Bleeding Disorders and Genetics

DNA → RNA → Protein



The Factor IX protein



Pipe, S. W., Gonen-Yaacovi, G., & Segurado, O. G. (2022). Hemophilia A gene therapy: current and next-generation approaches. *Expert Opinion on Biological Therapy*, *22*(9), 1099–1115.

The genetics of hemophilia

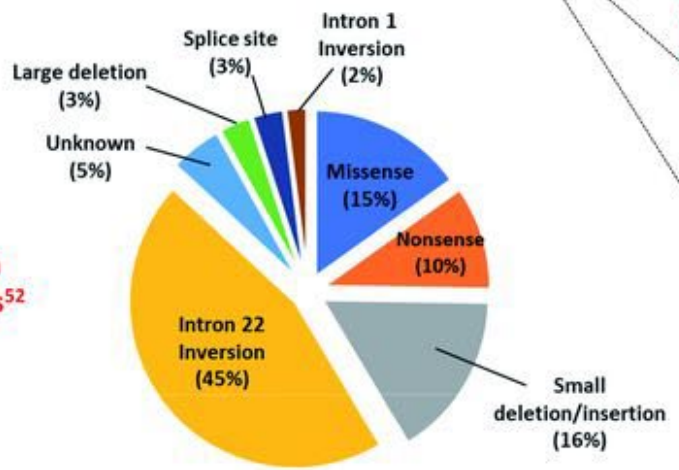
- Hemophilia A and B are both X-linked
- The factor VIII gene is at the telomere end (tail end) of the X chromosome (Xq28)
- The factor IX gene is more towards the center of the chromosome
- The factor VIII gene has 26 exons (it’s big)
- The factor IX gene has 8 with the last one coding 50% of the gene.

Hemophilia A

Prevalence: 1:5,000 males

Mode of inheritance: X-linked recessive

Clinical symptoms: Joint bleeding, muscle hematoma, soft tissue bleeding



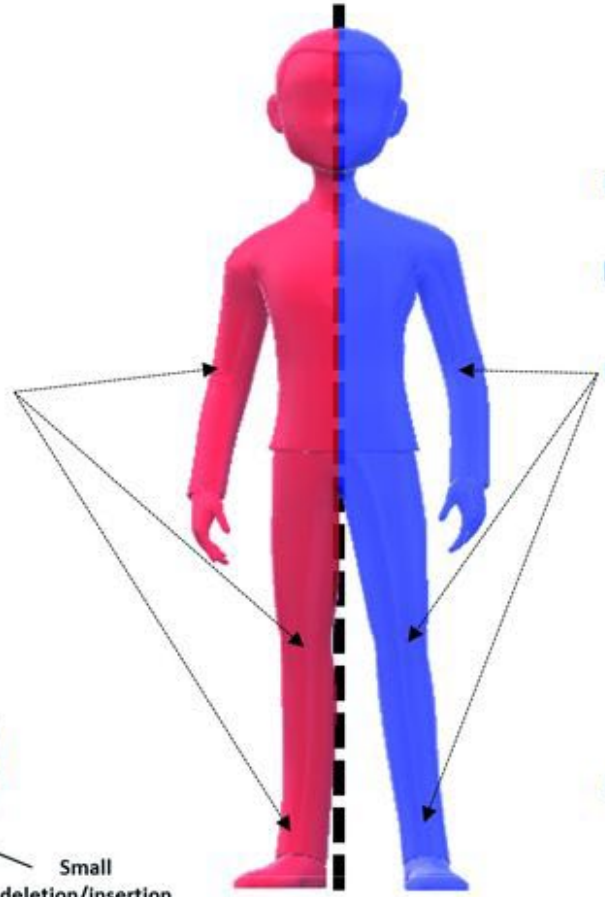
F8 gene defects reported in severe Hemophilia A patients[52]

Characteristics of missing clotting factor (FVIII):

Function: Co-factor

Molecular Weight: 280 kDa[53]

Normal concentration in plasma: 0.1-0.25 µg/mL

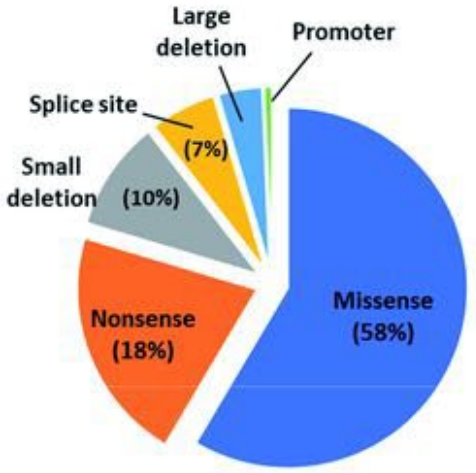


Hemophilia B

Prevalence 1:30,000 males

Mode of inheritance: X-linked recessive

Clinical symptoms: Joint bleeding, muscle hematoma, soft tissue bleeding



F9 gene defects reported in severe Hemophilia B patients[7]

Characteristics of missing clotting factor (FIX):

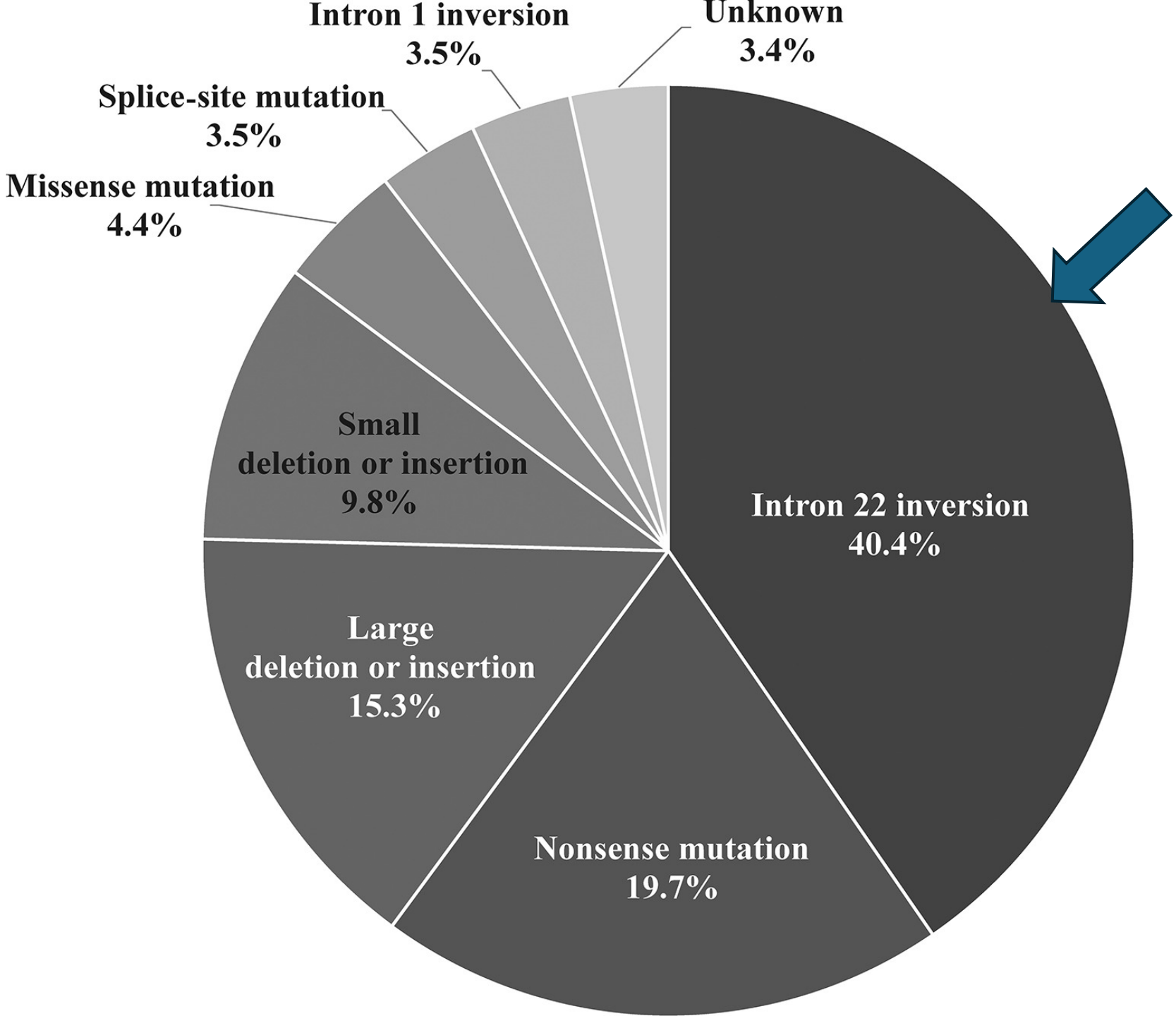
Function: Enzyme

Molecular Weight: 55 kDa[54]

Normal concentration in plasma: 3-5 µg/mL

Castaman G, Matino D. Hemophilia A and B: molecular and clinical similarities and differences. Haematologica. 2019 Sep;104(9):1702-1709. doi: 10.3324/haematol.2019.221093

HEMOPHILIA A
Genetic Mutations



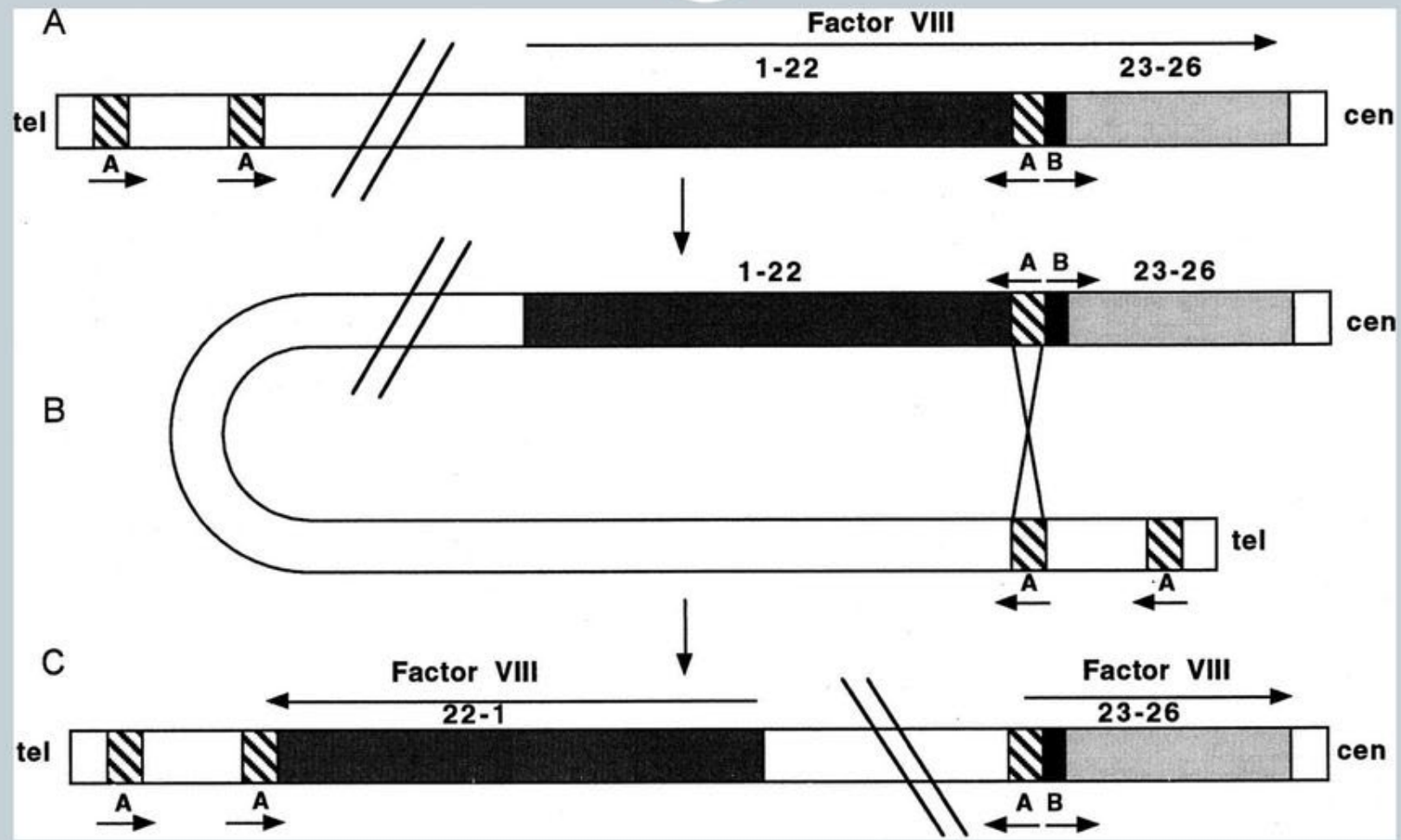
Sun J, Li Z, Huang K, Ai D, Li G, Xie X, Gu H, Liu G, Zhen Y, Chen Z, Wu R. *F8* gene mutation spectrum in severe hemophilia A with inhibitors: A large cohort data analysis from a single center in China. Res Pract Thromb Haemost. 2022 Jun 8;6(4):e12723. doi: 10.1002/rth2.12723. PMID: 35702590

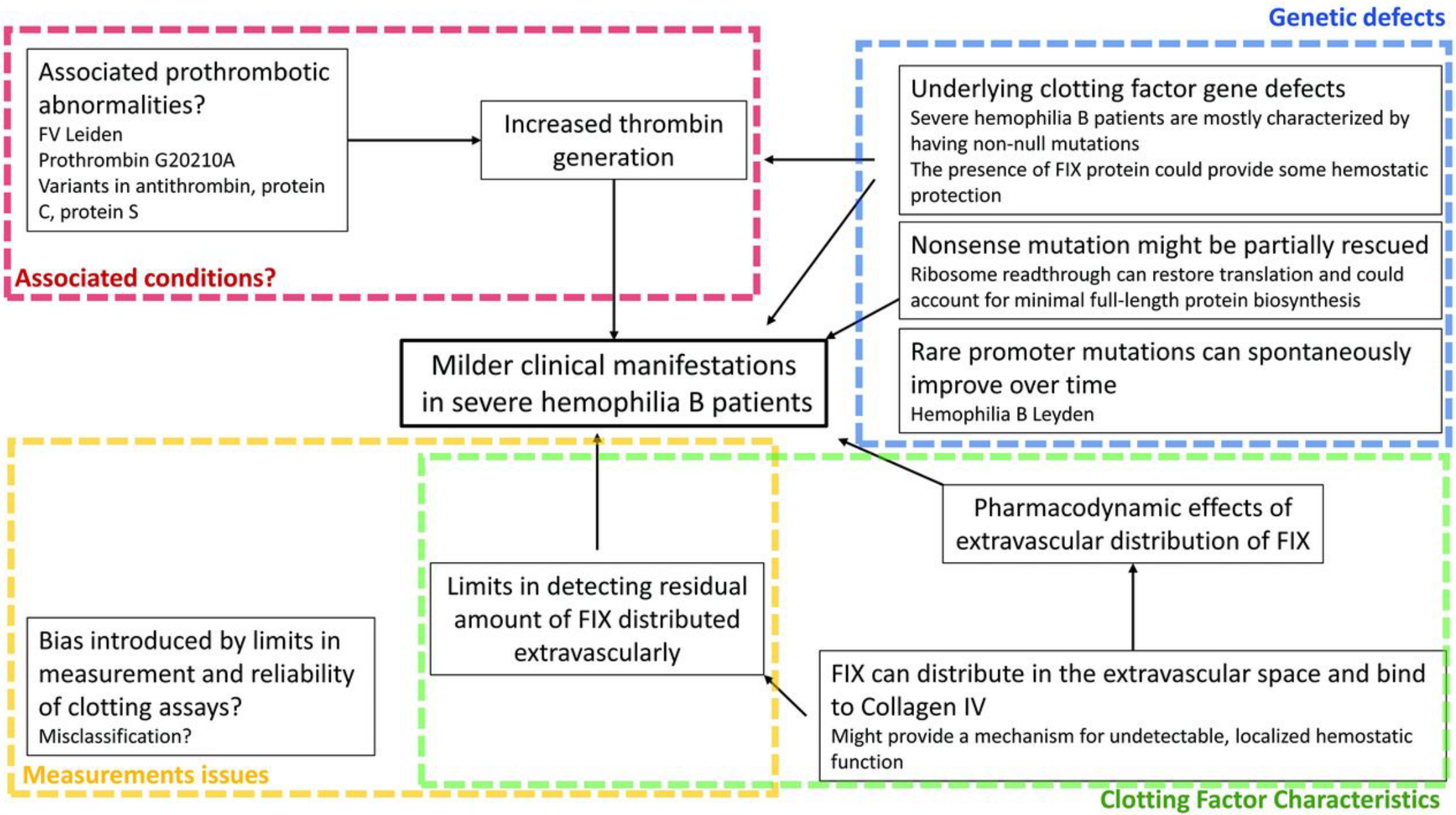
Hemophilia A and the intron 22 inversion

- The factor VIII gene has 2 notable introns – intron 1 and intron 22
- These introns have nucleotide sequences that are repeated outside of the factor VIII gene at the telomeric end (tail end) of the X chromosome
- The X chromosome can bend at the tail end and align the repeated (pseudo) introns with the actual introns
- This apparent homology can trigger crossing over during meiosis
- If the crossing over occurs it disrupts the normal gene

Inversion in intron 22 *F8*

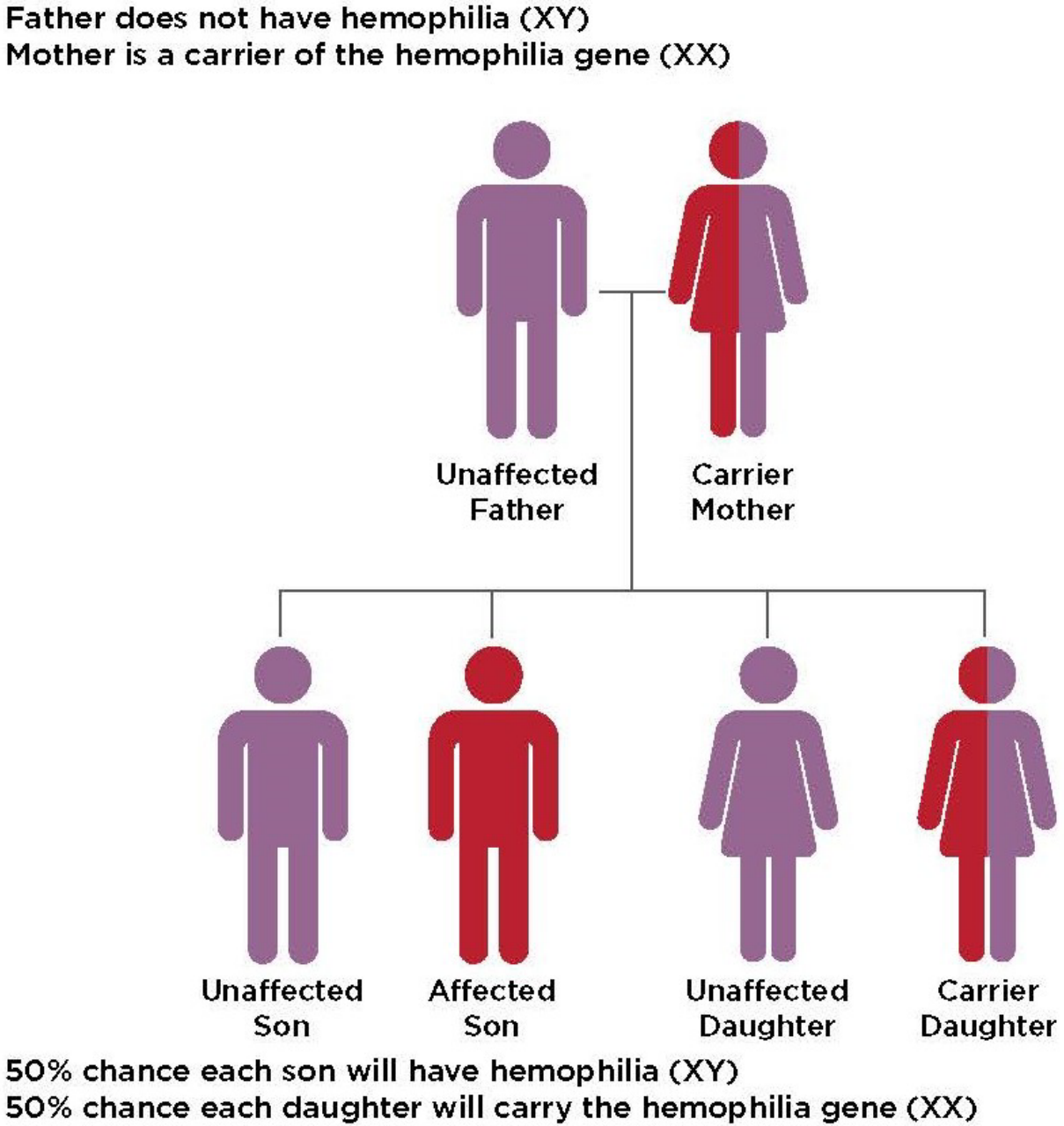
Courtesy of Tahnee Causey, MS, LCGC





Castaman G, Matino D. Hemophilia A and B: molecular and clinical similarities and differences. Haematologica. 2019 Sep;104(9):1702-1709. doi: 10.3324/haematol.2019.221093

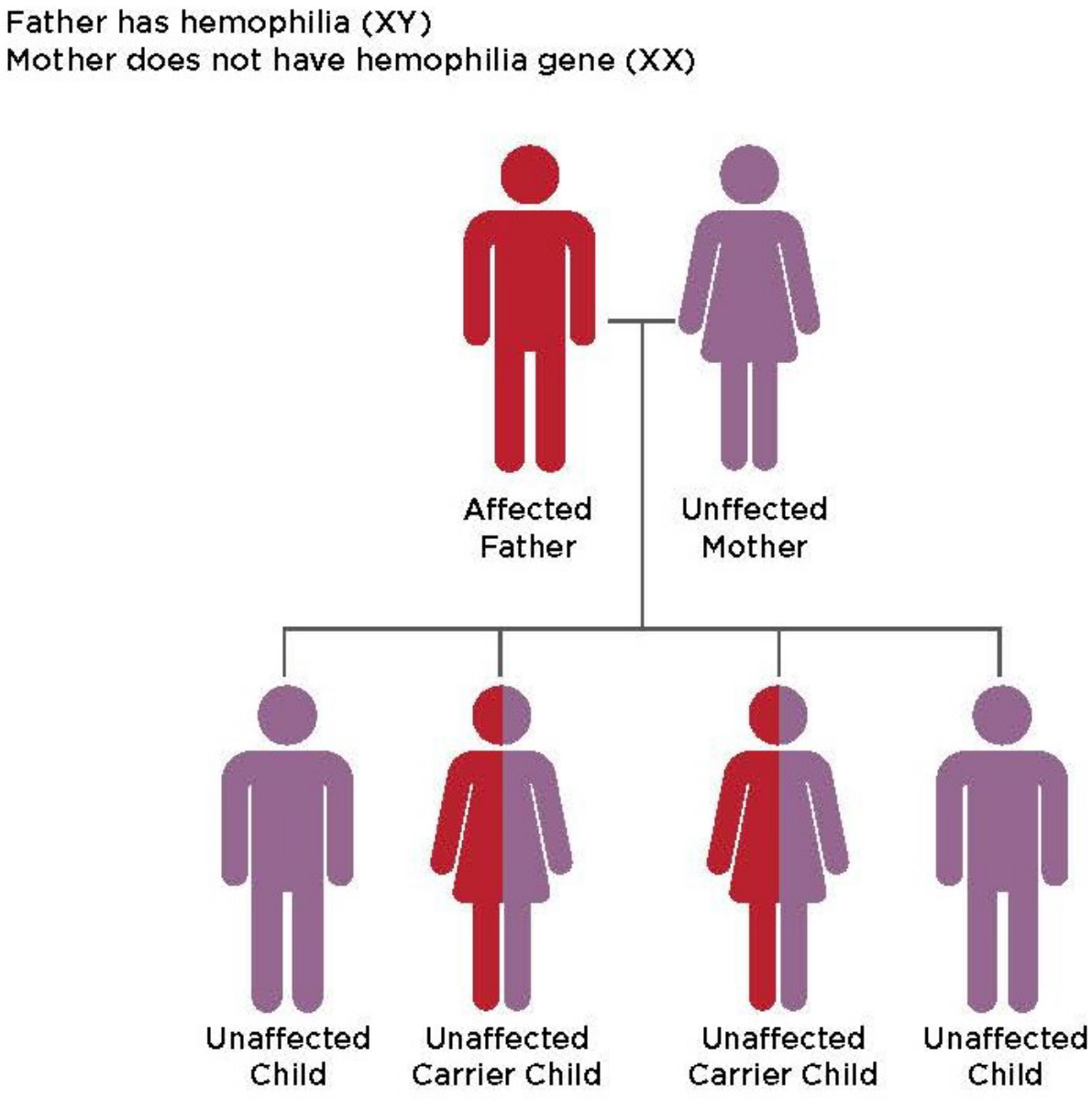
Conventional look at the inheritance of hemophilia – mother is a carrier



https://stepsforliving.bleeding.org/basics-bleeding-disorders/genetics-bleeding-disorders/how-does-person-get-bleeding-disorder

Figure 1c: X-Linked Inheritance Pattern

Conventional look at the inheritance of hemophilia – father is affected



https://stepsforliving.bleeding.org/basics-bleeding-disorders/genetics-bleeding-disorders/how-does-person-get-bleeding-disorder

Community Counts data on women and girls with hemophilia

•During the study period 1,667 women and girls received care in an HTC and met the study criteria for hemophilia (factor activity of 50% or less).

- Severe hemophilia was rare, occurring in only 51 women and girls.
- Moderate hemophilia was slightly more common, occurring in 79 women and girls.
- Mild hemophilia was the most common, occurring in 1,537 women and girls.

•92% of women and girls had mild hemophilia, compared to 30% of men and boys.

•Women and girls with hemophilia were older, more often White, and less often non-Hispanic than the men and boys with hemophilia.

•Women and girls with hemophilia had fewer HTC visits than men and boys with hemophilia. This difference in visits was seen within people who had all three severity levels – mild, moderate, and severe.

Mid-Atlantic and Mountain State Regions: Collaborative project to increase identification of girls and women with hemophilia

- Guidelines developed for HTCs
  - Identifying carriers
  - Determining status
    - Asymptomatic carrier
    - Symptomatic carrier
    - Hemophilia (activity level of 50% or less)
  - When to offer genetic testing
  - When to measure factor activity
    - Consideration for using the chromogenic method
- Identifying carriers has the benefit of earlier education and better follow-up

3 y/o girl with bruising

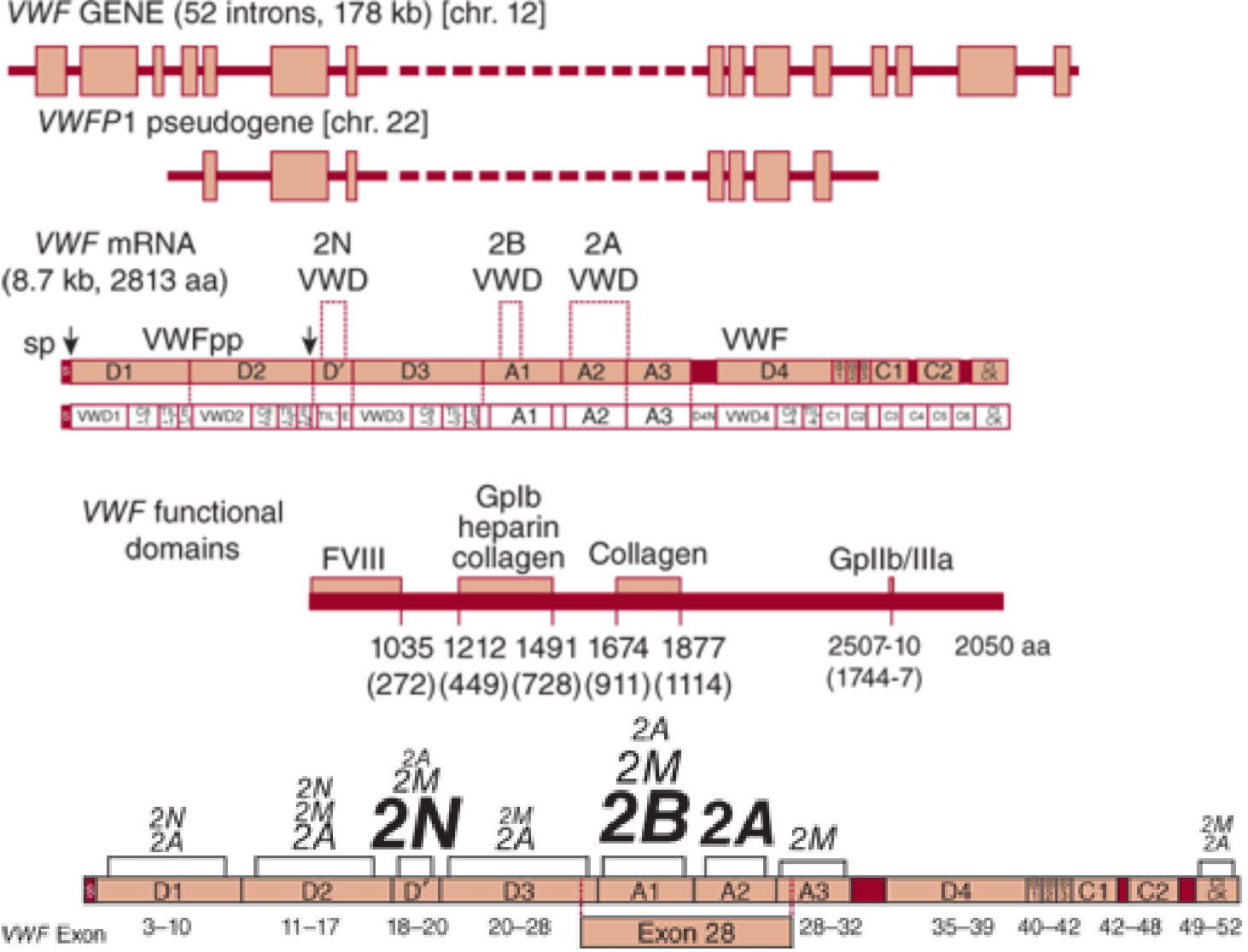
- Laboratory results:
  - CBC nl
  - PT/PTT normal
  - vWF Antigen 50%
  - vWF Activity 53%
  - Factor VIII 20%

- Diagnosis = Mild Hemophilia A
- Family history = a great uncle had a bleeding disorder, but not sure what it was

Genetics of von Willebrand Disease

- Type 3 – most severe form – is autosomal recessive
- Type 2 is autosomal dominant >80% of the time
- Type 1 is autosomal dominant with variable penetrance
  - Activity levels can vary and Bleeding symptoms can vary
  - There are multiple factors that impact the levels of active vWF

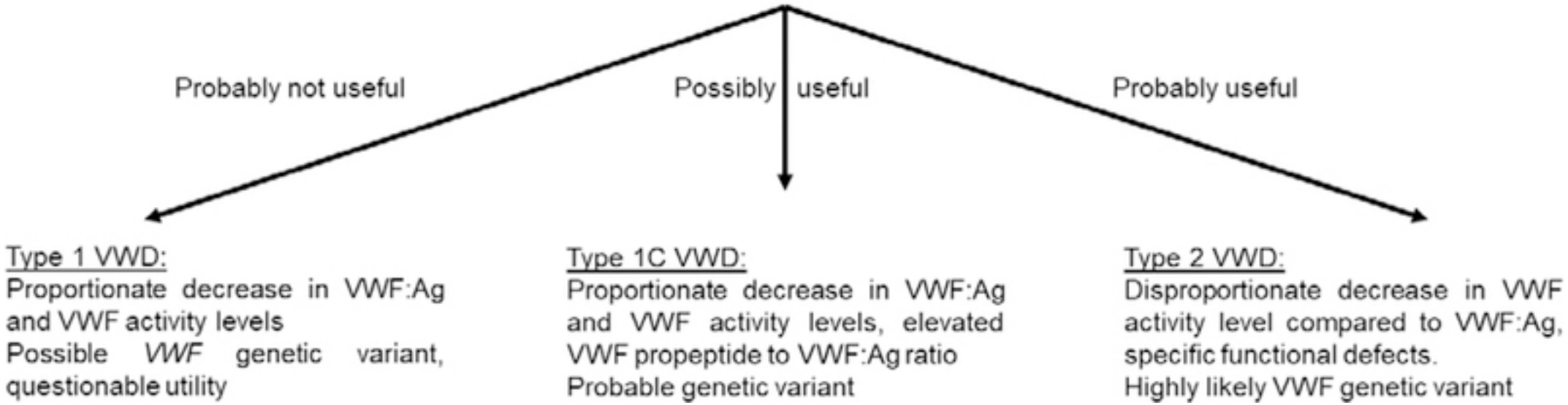
Modifier gene	**Putative function**
ABO	Clearance
CLEC4M	Clearance
STXBP5	Endothelial cell exocytosis
STAB2	Clearance, immunoregulation



- Many mutations across this large gene have been described
- ~90% of those with type 1 vWD and activity level of <30% have an identifiable mutation.
- ~60% of those with activity 30-50% had an identifiable mutation.

Source: K. Kaushansky, M.A. Lichtman, J.T. Prchal, M.M. Levi, O.W. Press, L.J. Burns, M. Caligiuri: Williams Hematology, 9th edition
www.accessmedicine.com

Utility of *VWF* gene sequencing



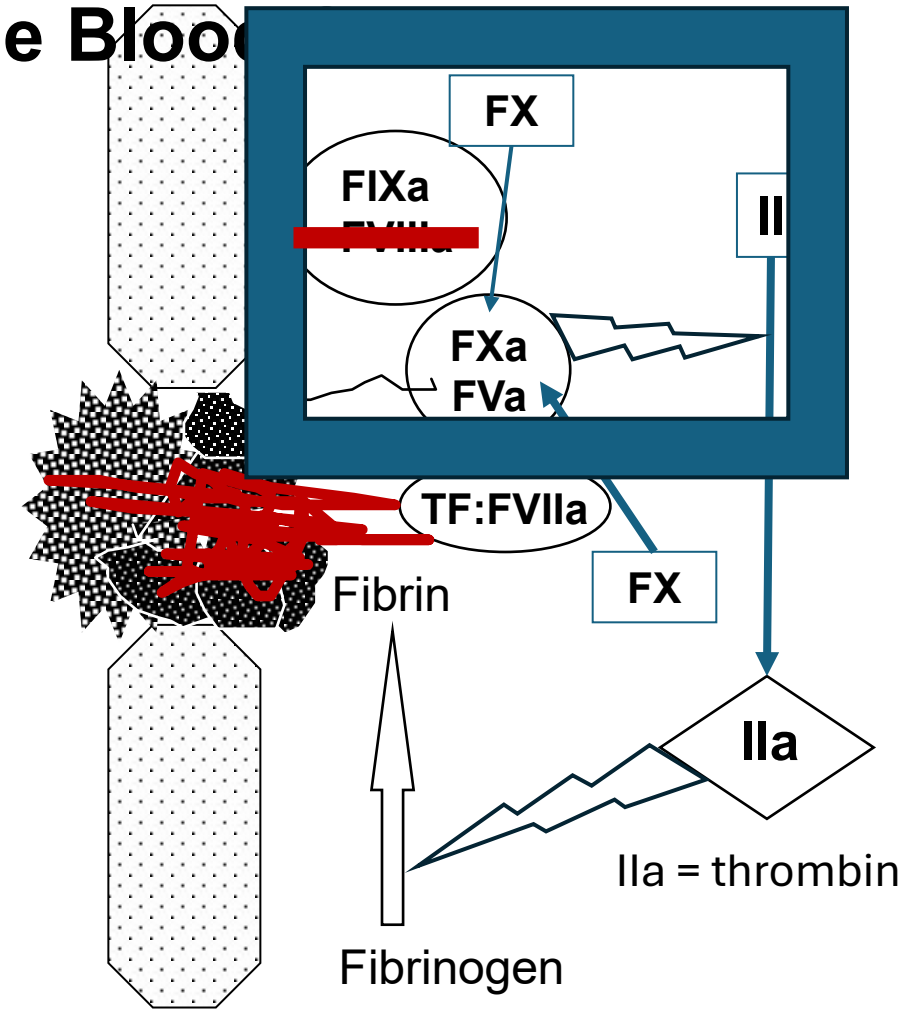
VWF p.D1472H variant

This variant has been associated with decreased VWF:RCo, and decreased VWF:RCo/VWF:Ag ratios across several studies, yielding levels that could result in a diagnosis of type 2M VWD. However, when you use other vWF activity assays, the levels are normal. Thus, there is no “disease”.

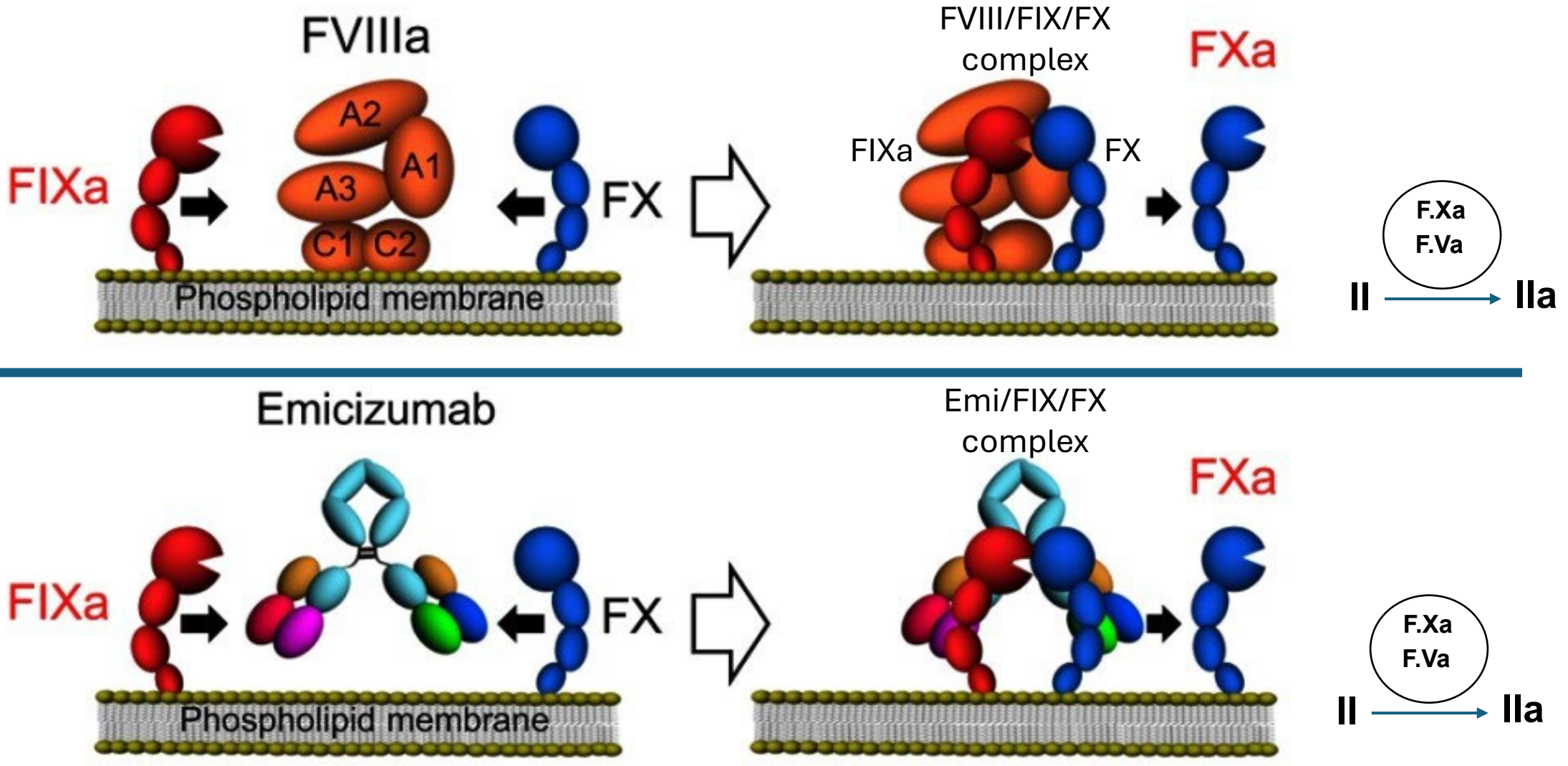
Some interesting biology about some of the new treatments

My purpose isn’t to promote any of these treatments or to provide any advice or education about their uses. My goal is to show you how some of these treatments work and how they relate to the biology of bleeding.

The Bloo

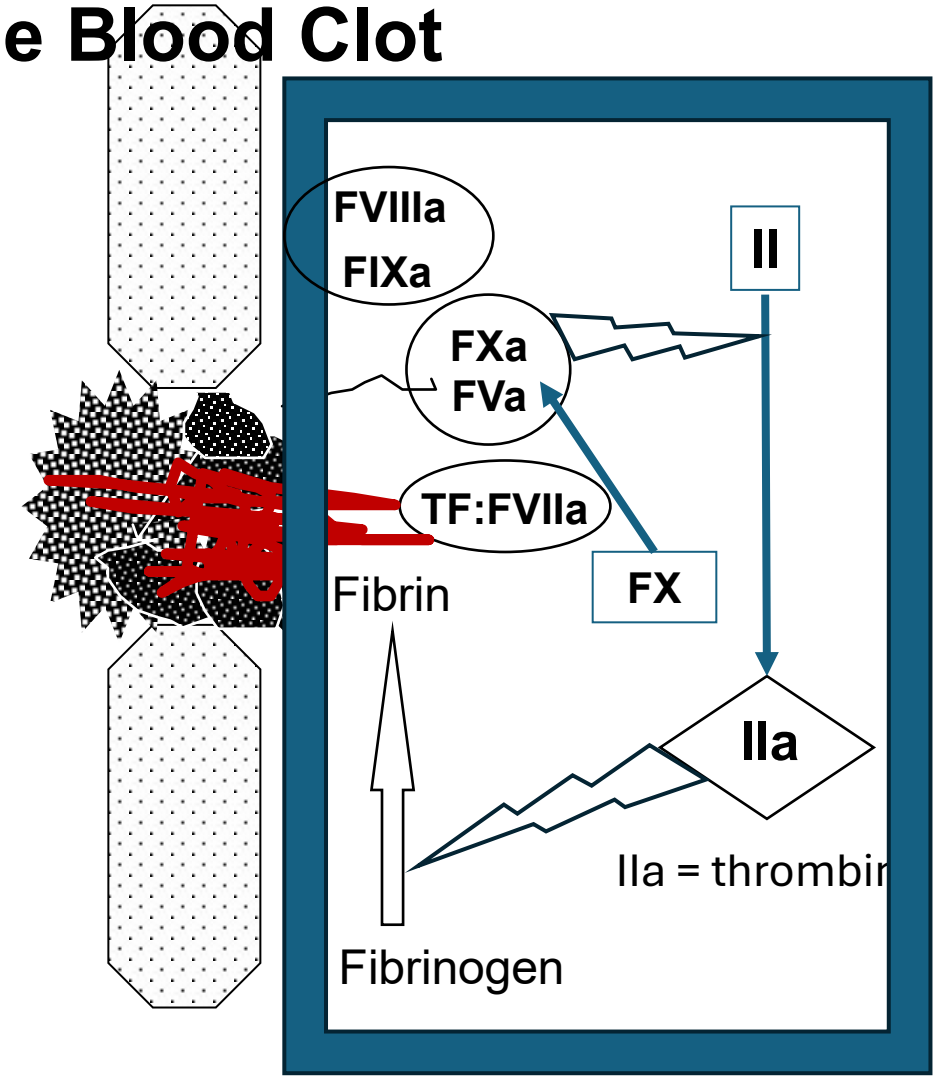

FX
FIXa
II
FXa
FVa
TF:FVIIa
FX
Fibrin
IIa
IIa = thrombin
Fibrinogen

Normal Conversion of FX to FXa

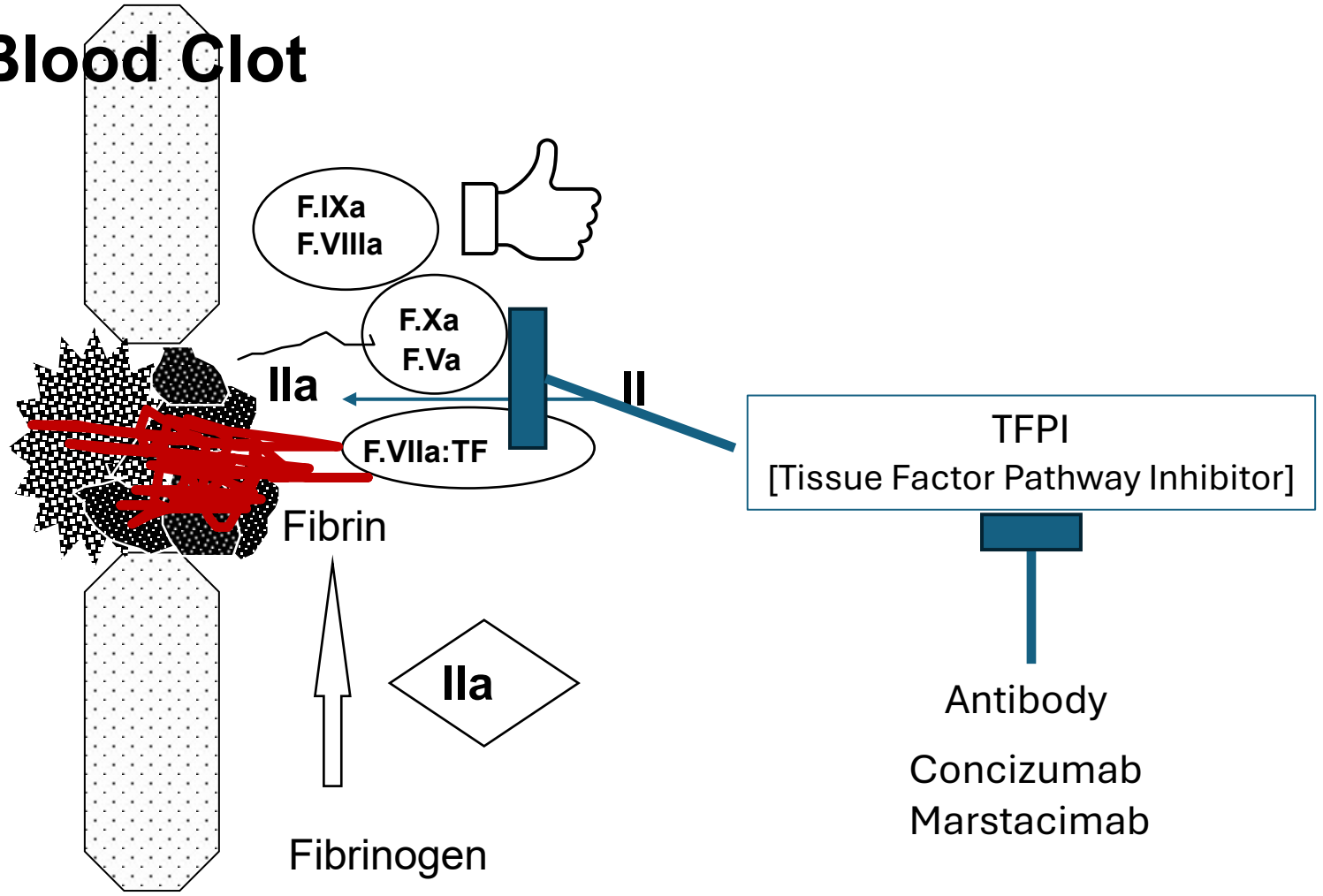


Yada, K., & Nogami, K. Spotlight on emicizumab in the management of hemophilia A: patient selection and special considerations. *Journal of Blood Medicine*, 2019.

The Blood Clot



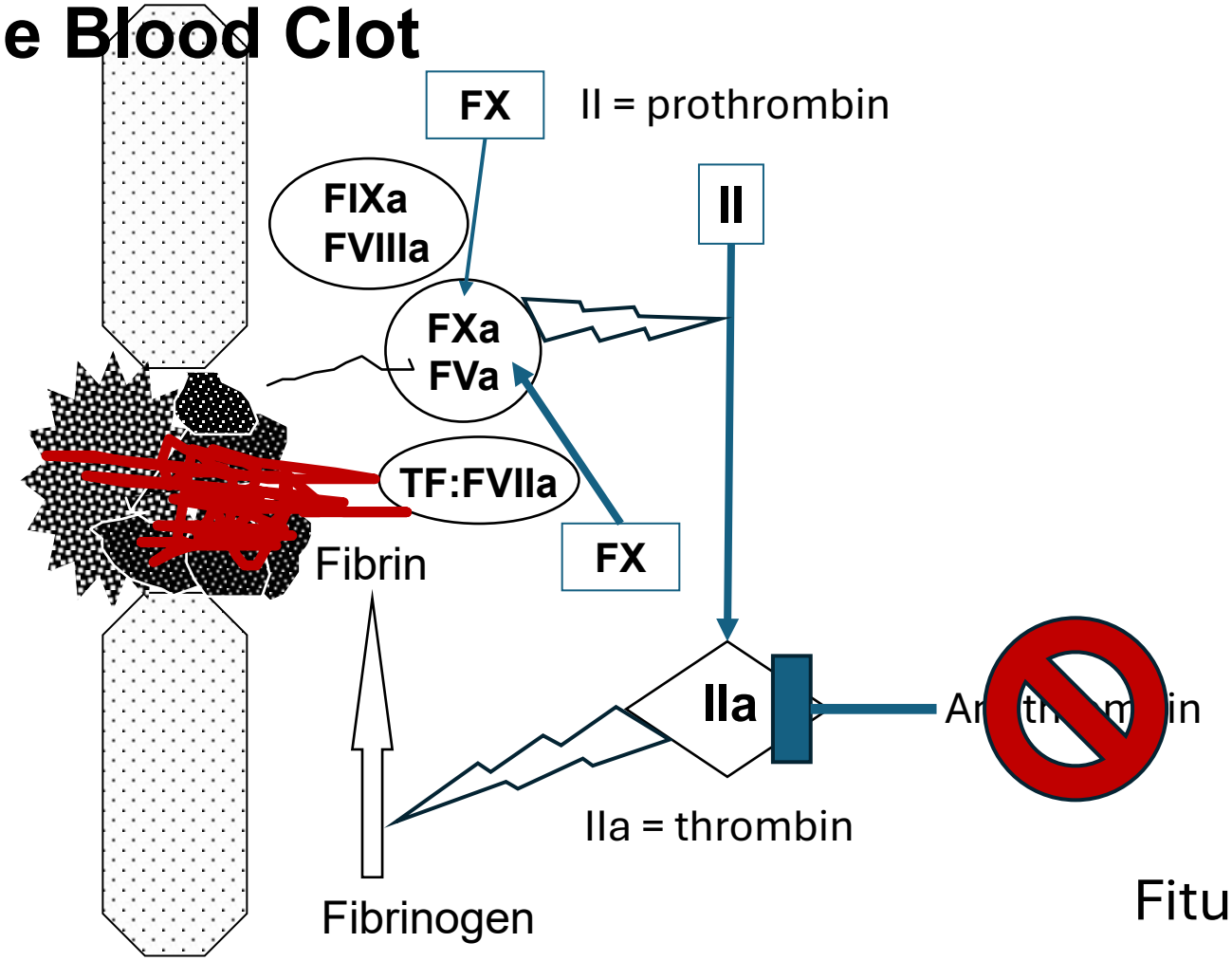
The Blood Clot



IIa = thrombin

II = prothrombin

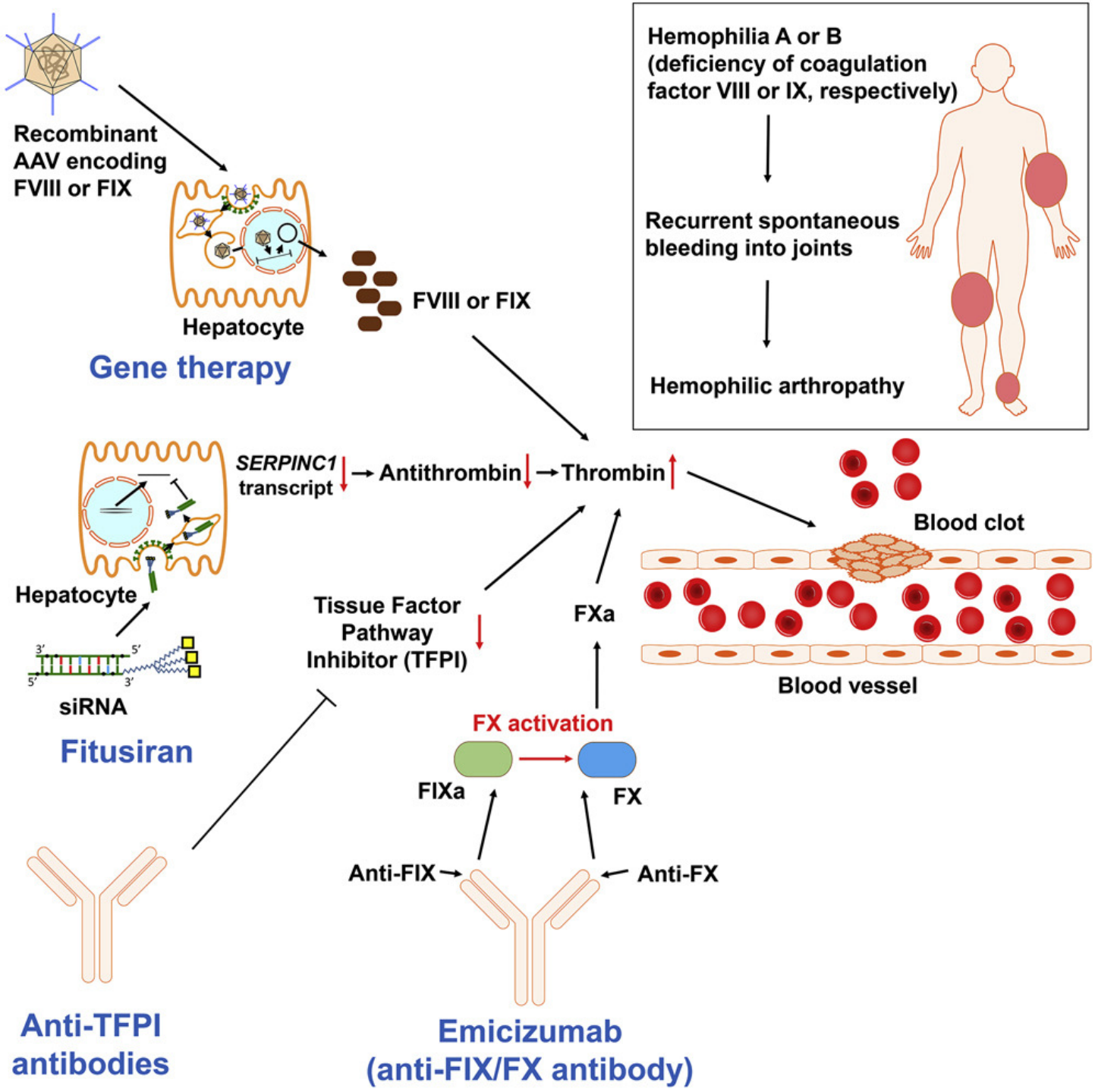
The Blood Clot



Fitusiran

siRNA

si = small interfering



Butterfield JSS, Hegec KM, Herzog RW, Kaczmarek R. A Molecular Revolution in the Treatment of Hemophilia. Molecular Therapy. Volume 28, Issue 4,2020.

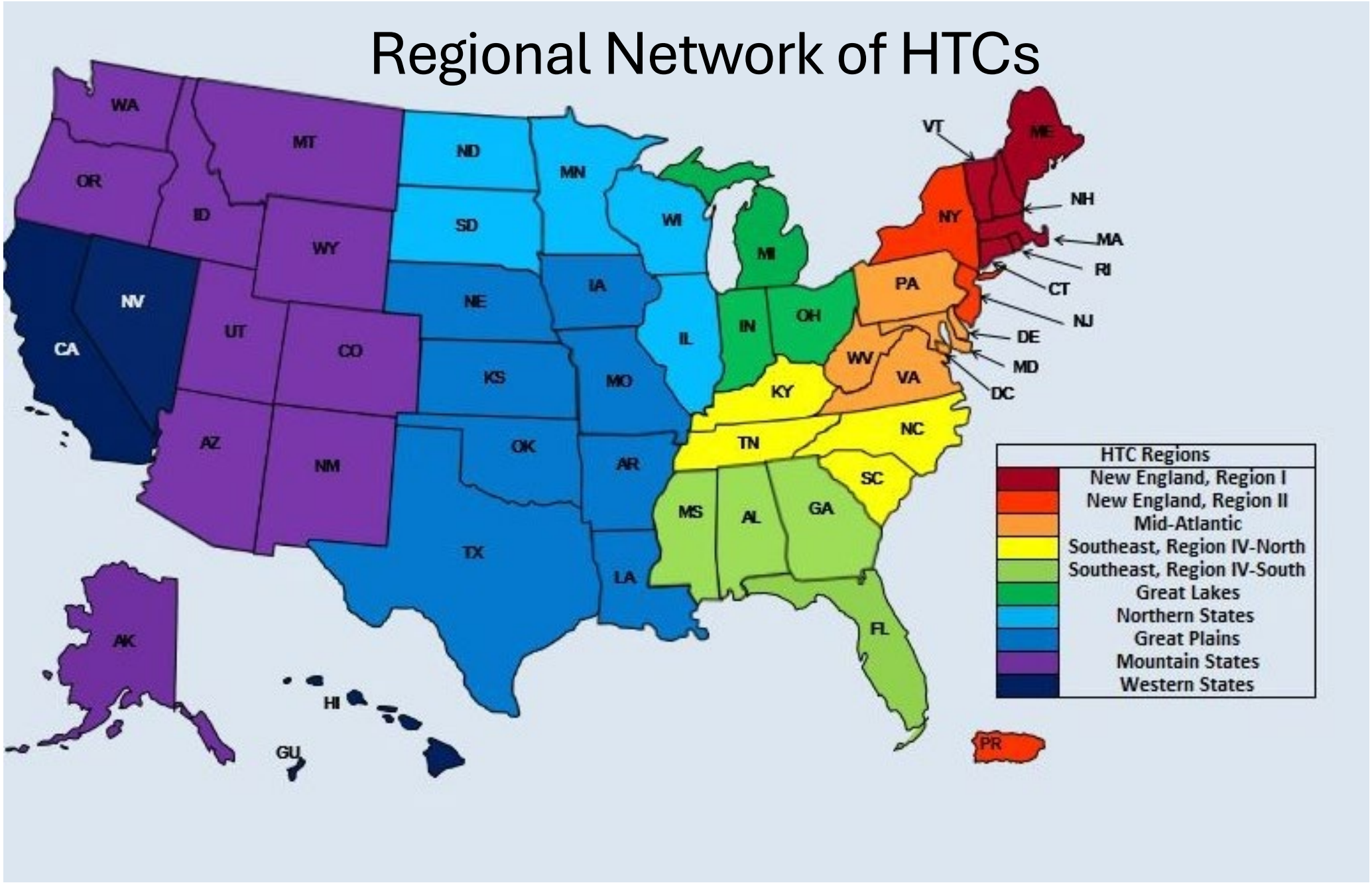
The Regional Network of HTCs

- The regional network of HTCs aims to improve the health of individuals with hemophilia and related bleeding disorders
- HTCs are organized into eight regions, with each region having a core center that administers and supports the HTCs within its area.
- HTCs provide a multidisciplinary team approach, including hematologists, nurses, social workers, and other specialists, to address the physical, psychological, and social needs of patients and their families.
- HTCs utilize the latest research findings to guide their treatment practices and ensure they are providing the most effective care possible.

The Regional Network of HTCs

- Regional networks focus on implementing quality improvement initiatives to enhance the overall quality of care provided to patients.
- The networks also provide expertise and resources to help HTCs build their capacity to deliver comprehensive care, including training and resource allocation.
- The regional networks facilitate communication and collaboration among HTCs, allowing them to share best practices, learn from each other, and work together to improve care for patients.
- The regional network aims to improve access to specialized care for individuals with hemophilia and related disorders, ensuring that they receive the necessary services and support.

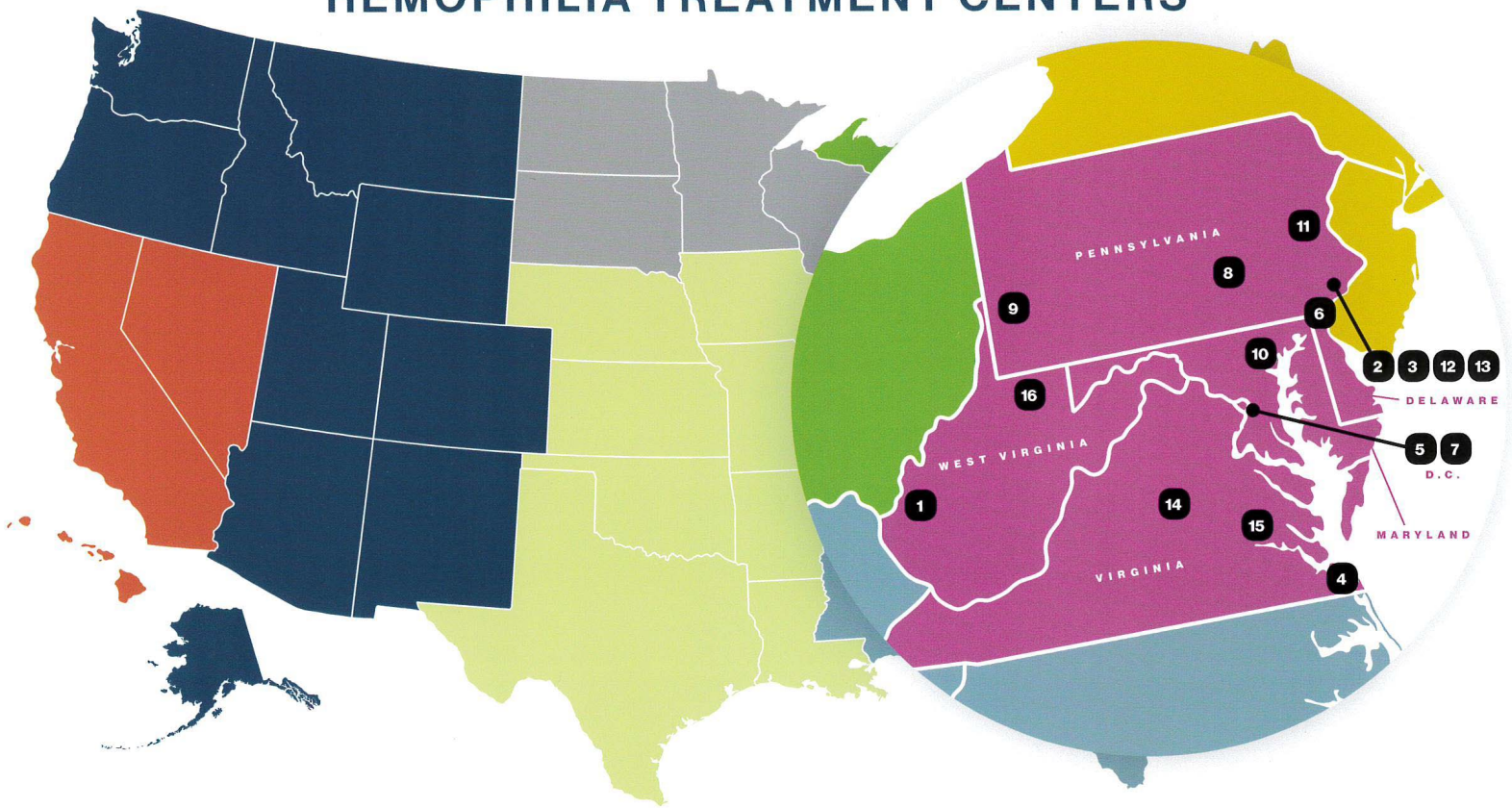
Regional Network of HTCs



Mid-Atlantic Region of HTCs

- Pennsylvania
  - Central Pa. – Hershey
  - Western Pa. – Pittsburgh
  - Lehigh Valley – ABE metro area
  - Philadelphia:
    - St Chris
    - CHOP
    - Penn
    - Jefferson
- Delaware
  - Christiana & Nemours
- District of Columbia
  - Georgetown
  - Children's National
- Maryland
  - Johns Hopkins
- Virginia
  - VCU
  - UVA
  - Children's of King Daughters
- West Virginia
  - CAMC
  - UWV

MID-ATLANTIC REGION III
HEMOPHILIA TREATMENT CENTERS



1 **Charleston Area Medical Center (CAMC)**
CHARLESTON, WV

2 **Cardeza Foundation Hemophilia Center (CFHC)**
PHILADELPHIA, PA

3 **The Children's Hospital of Philadelphia (CHOP)**
PHILADELPHIA, PA

4 **The Children's Hospital of The King's Daughters (CHKD)**
NORFOLK, VA

5 **Children's National Medical Center (CNMC)**
WASHINGTON, D.C.

6 **The Delaware Hemophilia Treatment Center (DE)**
WILMINGTON, DE

7 **Georgetown University Medical Center (GTU)**
WASHINGTON, D.C.

8 **Hemophilia Center of Central PA (HCCP)**
HERSHEY, PA

9 **Hemophilia Center of Western PA (HCWP)**
PITTSBURGH, PA

10 **John Hopkins Medical Center (JHU)**
BALTIMORE, MD

11 **Lehigh Valley Hospital (LVH)**
ALLENTOWN & BETHLEHEM, PA

12 **Penn Comprehensive Hemophilia Program (PCHP)**
PHILADELPHIA, PA

13 **St. Christopher's Hospital for Children (St. Chris)**
PHILADELPHIA, PA

14 **University of Virginia (UVA)**
CHARLOTTESVILLE, VA

15 **Virginia Commonwealth University (VCU)**
RICHMOND, VA

16 **West Virginia University (WVU)**
MORGANTOWN, WV

US HTC REGIONS

- New England
- MidAtlantic
- Southeast
- Great Lakes
- Northern States
- Great Plains
- Mountain States
- Western States

Research & Collaboration
Promote and conduct research and share new drug developments, therapies, insurance assistance, and other ideas to improve patients' lives.

Comprehensive Care
Assure access to comprehensive and coordinated care from physicians, nurses, physical therapists and social workers with expertise in bleeding and clotting disorders.

Education & Information
Develop educational programs and informational materials for patients, their families, and medical providers.

Best Practices
Assure adherence to accepted best practices for the care and treatment of persons with bleeding disorders.

Mentorship
Actively attract and develop the next generation of HTC professionals.

The Mid-Atlantic Region III HTCs
Core Center
Children's Hospital of Philadelphia
3501 Civic Center Blvd.
Division of Hematology
Philadelphia, PA 19104
267-426-5586