Inherited Bleeding Disorders:

Common Symptoms with not so rare diagnoses

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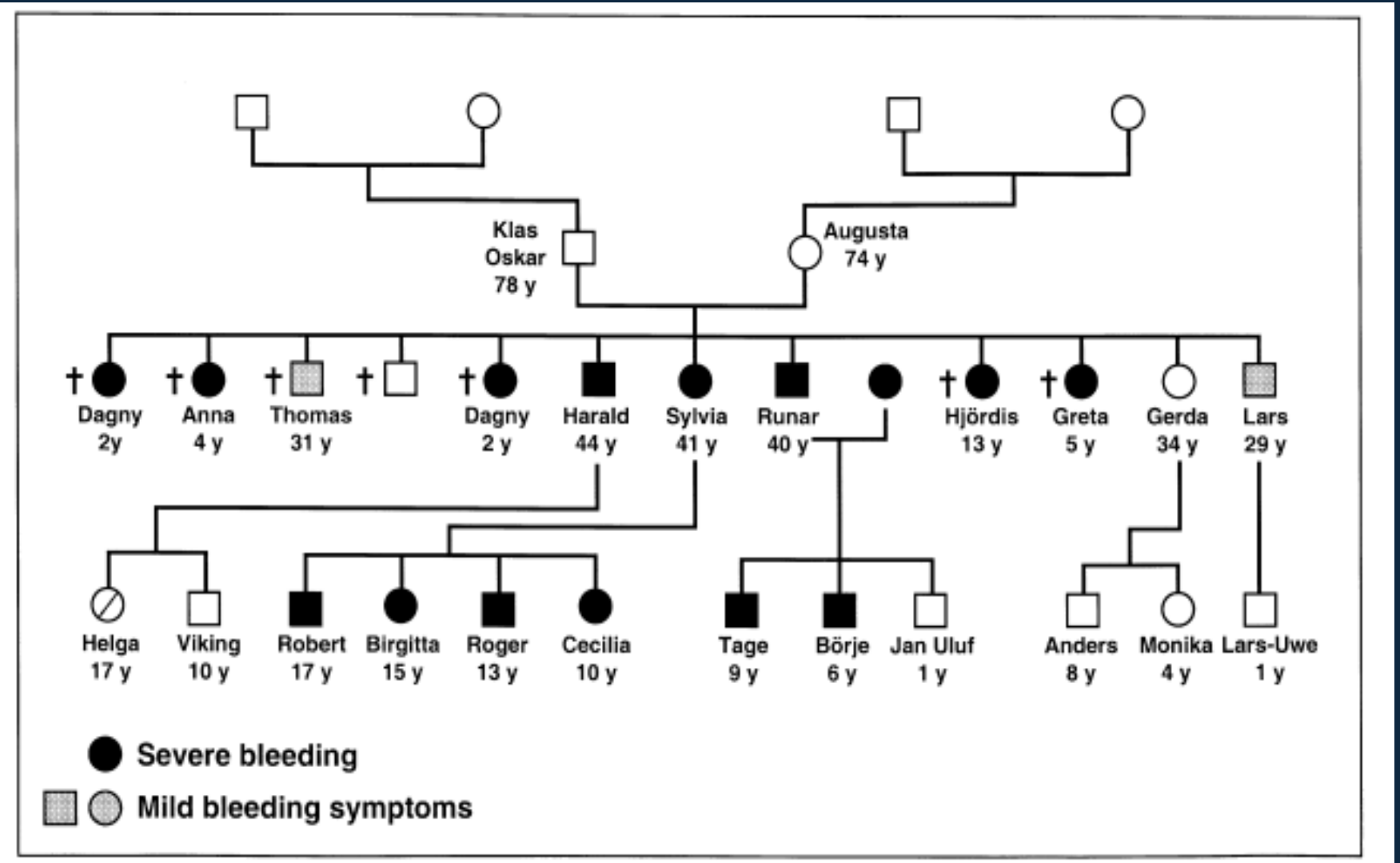
Disclosures

- Spark Therapeutics as a Principal Investigator in Gene Therapy in Hemophilia
- St Jude Children's Hospital as a Principal Investigator in Gene Therapy in Hemophilia
- CSL Behring as a Principal Investigator in Gene Therapy in Hemophilia

The story of von Willebrand Disease



Nilsson IM. Haemophilia. 2002.

Objectives

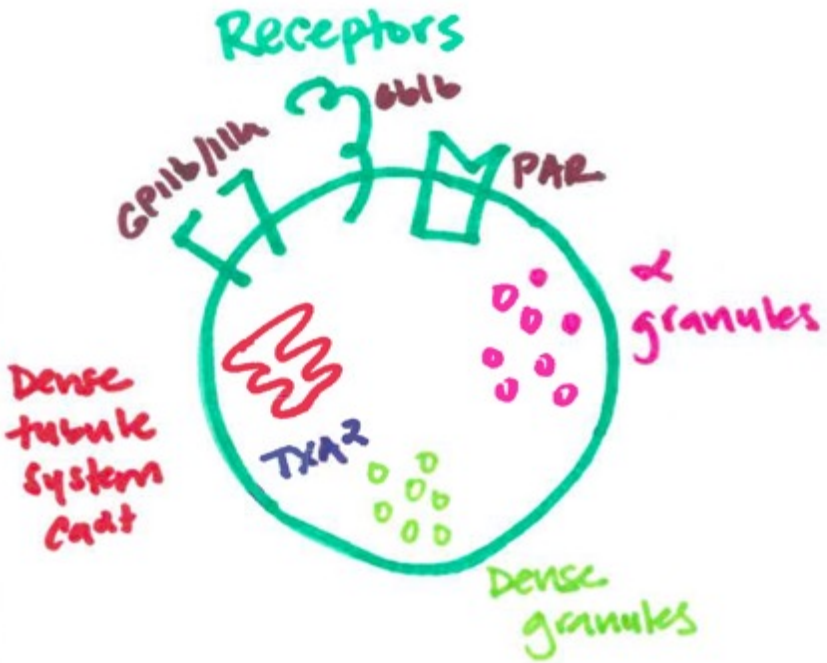
- Review normal hemostasis
- Describe where abnormalities in the hemostatic system can lead to bleeding symptoms
- List symptoms that might prompt a bleeding disorder evaluation
- Create a first-line bleeding disorder evaluation plan that can be implemented in the primary care setting
- Identify ways to connect with a hemophilia treatment center near you

Normal Hemostasis

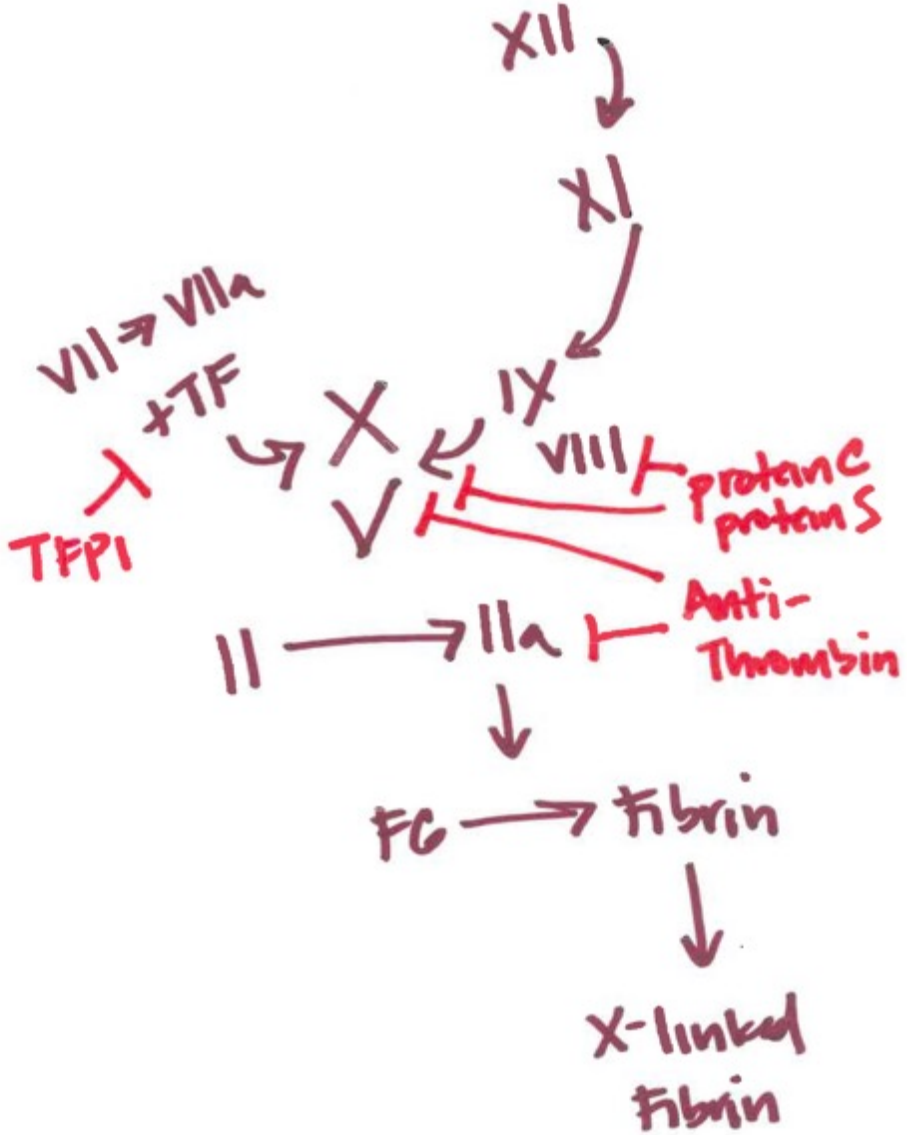
1. Injury → exposure of collagen and other proteins under endothelial cells
2. Response → coordinated and iterative, quickly inactivated

Hemostatic Actors	Job
Collagen and other ECM proteins	Something for platelets to stick to
Platelets	Stick down to injured area, send out signals, aggregate together
Von Willebrand Factor	Sticky protein for platelets, protect F8
Clotting proteins	Generate thrombin
Anti-coagulants like protein C & S, TFPI	Turn off the clotting system
Fibrinolytic proteins like Plasmin	Break down clots once they are formed
Anti-fibrinolytic proteins like TAFI	Inhibit clot breakdown

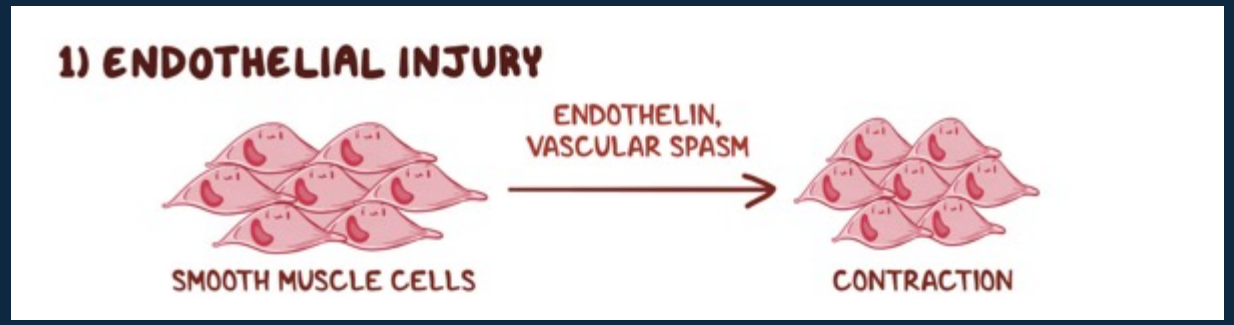
platelets

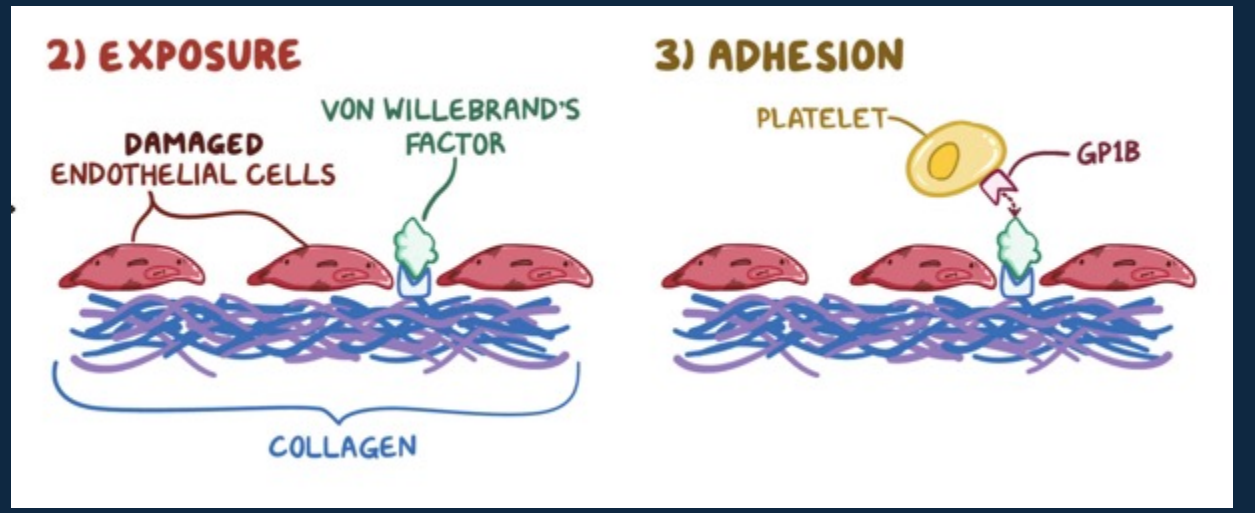


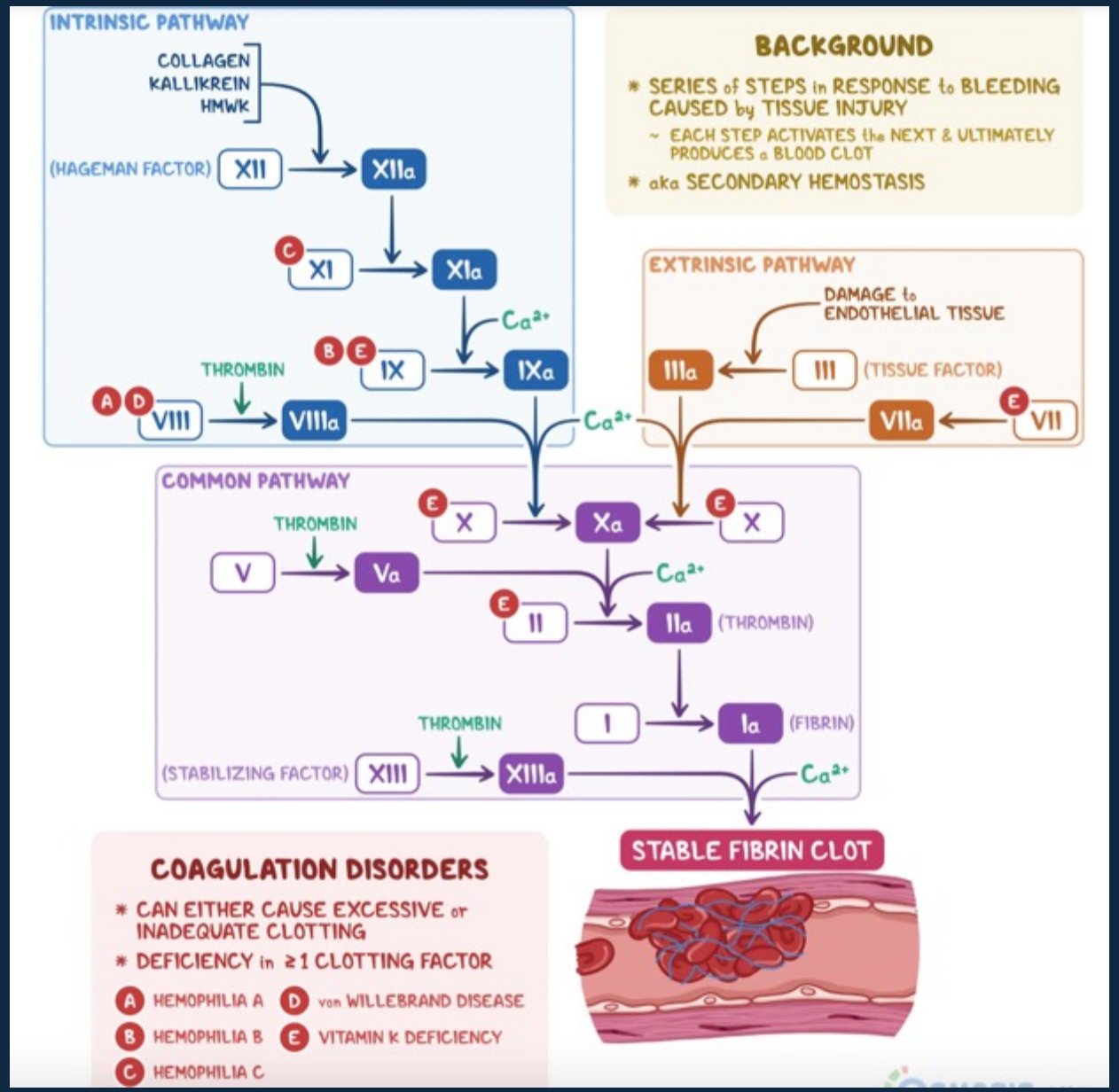
Clotting proteins



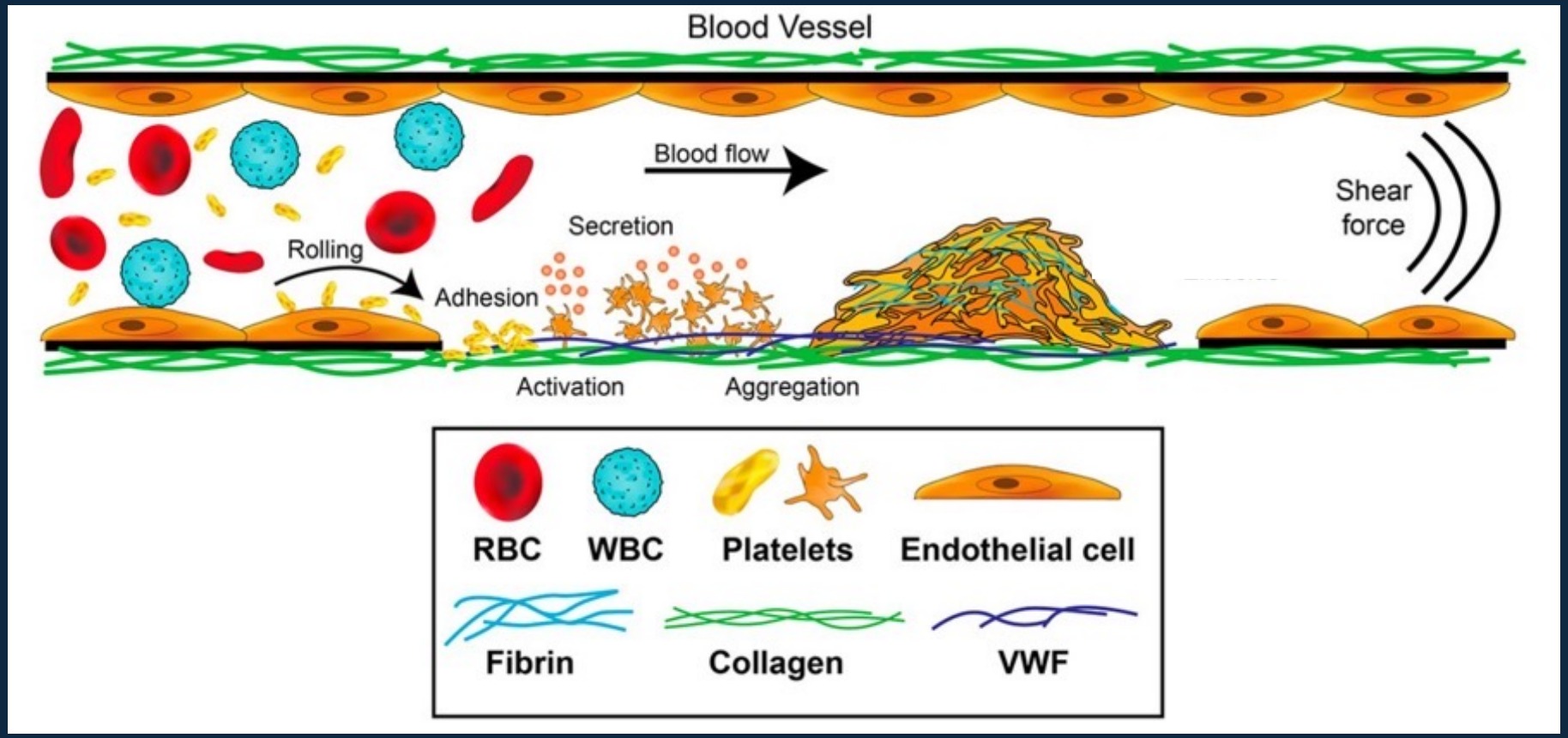
Hemostasis







www.osmosis.org/notes/Blood_Components_and_Function accessed 1/15/2024.



Injury → endothelial damage → exposure of extracellular matrix proteins → platelet adhesion → platelet activation → platelet aggregation

Simultaneously....

Factor VIIa + TF → Thrombin Burst → activation of the rest of the clotting factors → generation of fibrin → stable clot

And...

Immediate shut down of FVIIa and activation of the fibrinolytic proteins

Montague SJ, et al. Frontiers in Immunology. 2020.

Normal Hemostasis

- Difficult to account for:
  - Vasoconstriction
  - Interaction with subendothelial proteins
  - Interaction with red blood cells and white blood cells
  - Vascularity of a location
- Some things to keep in mind:
  - The system is iterative – and there is some compensation for deficiency/dysfunction
  - Mild deficiency/dysfunction may not rise to the level of clinical attention until met with “the” challenge
  - Our clinical assays of coagulation are trying to mimic a complicated process

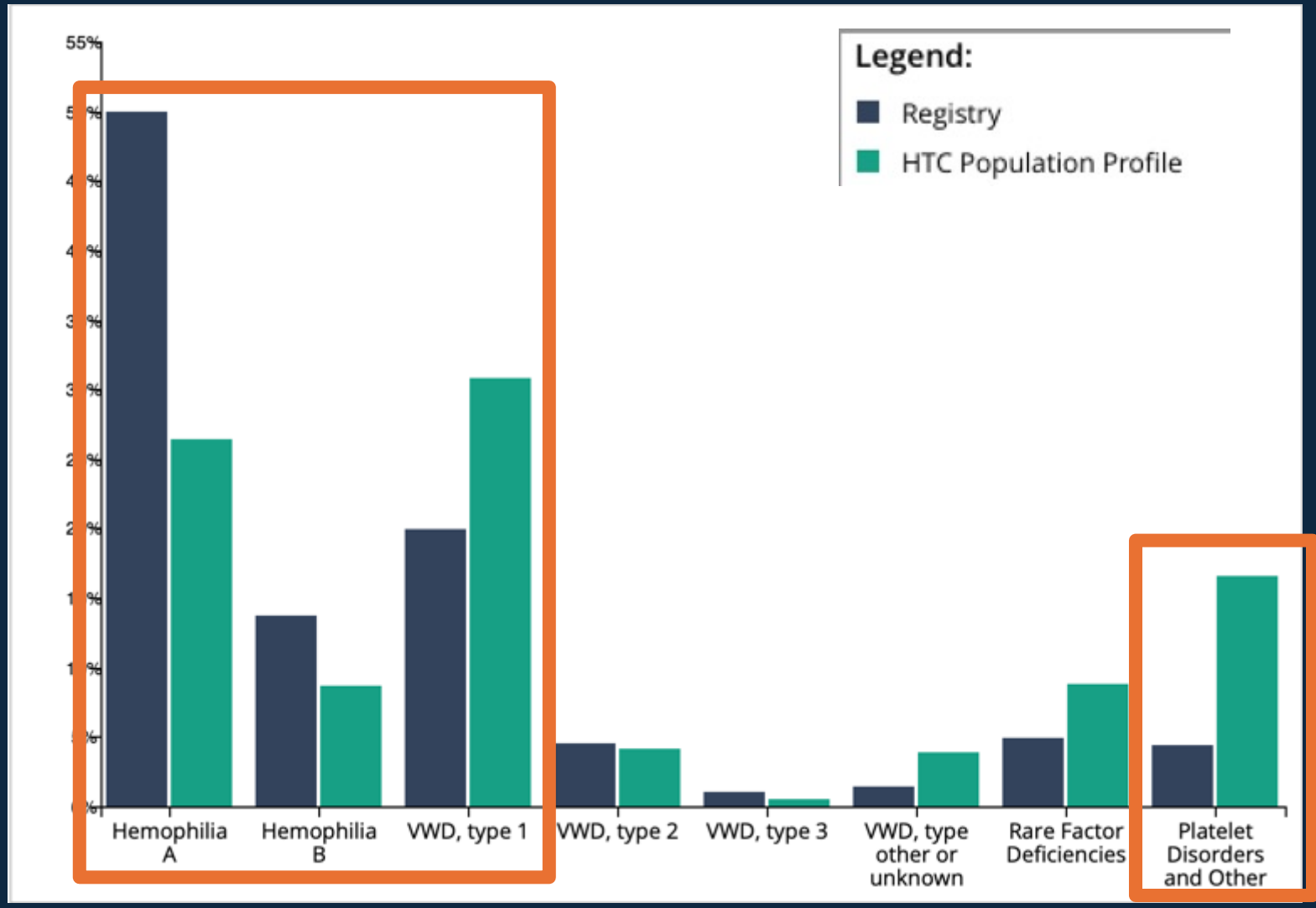
Abnormal Hemostasis-
Inherited Bleeding Disorders

- Primary Hemostasis: Platelets & Vessel Wall
  - Quantitative Platelet Disorders with Dysfunction
    - Bernard Soulier Syndrome
  - Qualitative Platelet Disorders
    - Glanzmann Thrombasthenia
  - Von Willebrand Disease
  - Collagen Disorders
    - Ehlers Danlos Syndrome spectrum of disorders
- Secondary Hemostasis: Clotting Factors
  - Hemophilia A
  - Hemophilia B
  - Other factor deficiencies
- Fibrinolysis: Fibrinolytic activators/inhibitors
  - Deficiency of proteins
    - PAI-1 deficiency

Inherited Bleeding Disorders

CDC Registry for Bleeding Disorders Surveillance in navy – includes 26,375 individuals

CDC Hemophilia Treatment Center Population Profile in green - includes 95,108 individuals



https://communitycountsdataviz.cdc.gov/ Primary Diagnosis, accessed 12/11/24

Inherited Bleeding Disorders

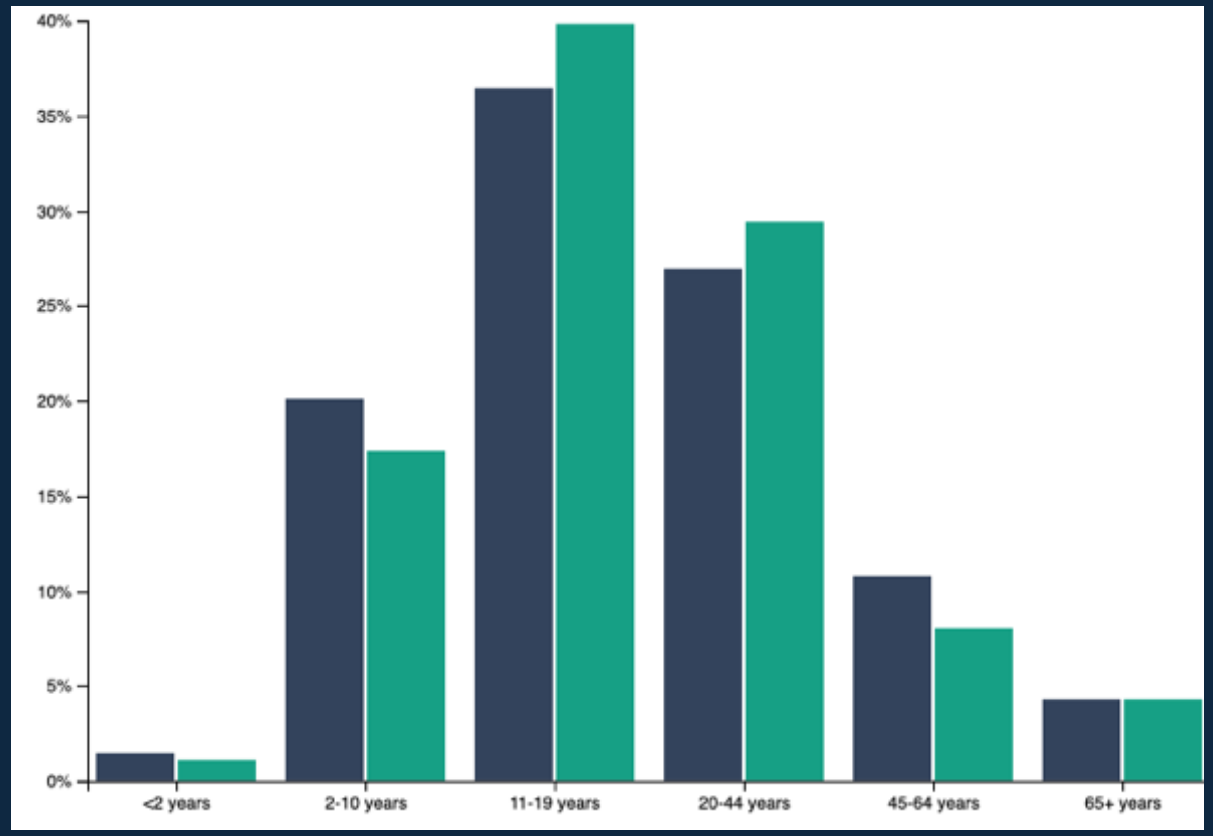
The most common bleeding disorder is von Willebrand Disease, with an overall prevalence of 1.3%

- VWD is due to deficiency or dysfunction of von Willebrand Factor
- There are 3 main types:
  - Type 1 VWD: mild to moderate deficiency of VWF (most common)
  - Type 2 VWD: variable dysfunction of VWF protein + deficiency
  - Type 3 VWD: severe deficiency of VWF (most rare)
- In most cases, it is inherited in an Autosomal Dominant fashion
- Clinical phenotype is widely variable

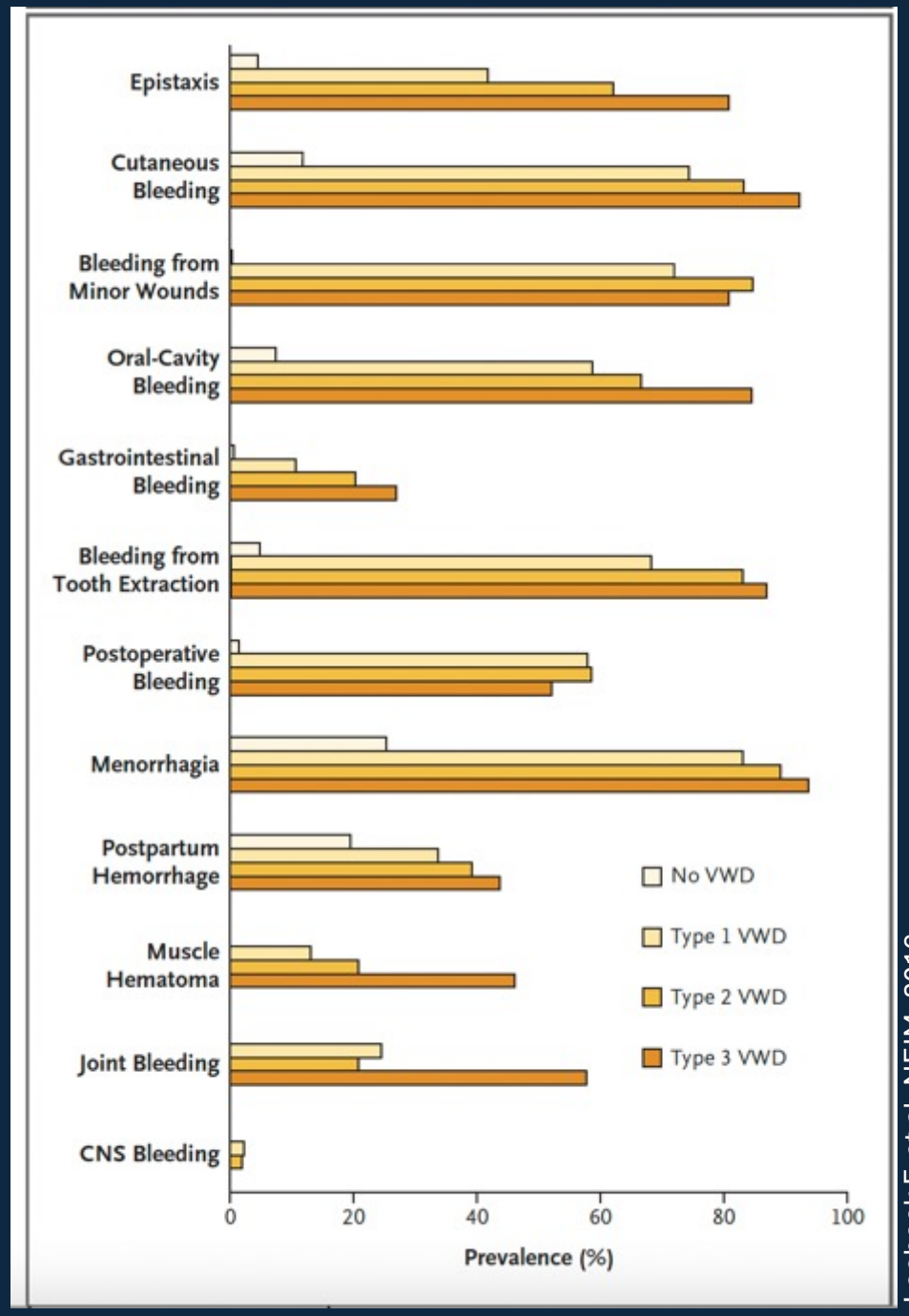
von Willebrand Disease

- Many pre-analytical variables can affect laboratory results
  - Delayed processing can result in falsely low levels
  - Physiologic stress can result in falsely normal/high levels
  - Rarely diagnose von Willebrand disease with a single set of lab values
- Entity called “low Von Willebrand Factor” which can be associated with bleeding in some people but not in others
- Diagnosis in adolescence or adulthood is not uncommon
  - Heavy menstrual bleeding may be the presenting symptom of VWD
  - As you ask more questions, a family history of bleeding may become clear but the bleeding has been normalized for generations

von Willebrand Disease



https://communitycountsdataviz.cdc.gov/ VWD by age, accessed 12/11/24



Leebeck F, et al. NEJM. 2016.

Inherited Bleeding Disorders

The most common clotting factor deficiencies are factor 8 and 9, hemophilia A and B

Factor VIII/IX level	Severity classification	Bleeding Phenotype
< 1%	Severe	Spontaneous bleeding into joints and muscles, bleeding with trauma/surgery, mucocutaneous bleeding
1-5%	Moderate	Bleeding with trauma/surgery, rare spontaneous bleeding, mucocutaneous bleeding
6-40%	Mild	Bleeding with trauma/surgery, mucocutaneous bleeding
>40% + gene + bleeding	Symptomatic carrier	Bleeding with trauma/surgery, mucocutaneous bleeding
>40% + gene, no symptoms	Carrier	none

van Galen KPM, et al. JTH. 2021.
Blanchette VS. JTH. 2014. 12: 1935-1939.

Hemophilia A & B

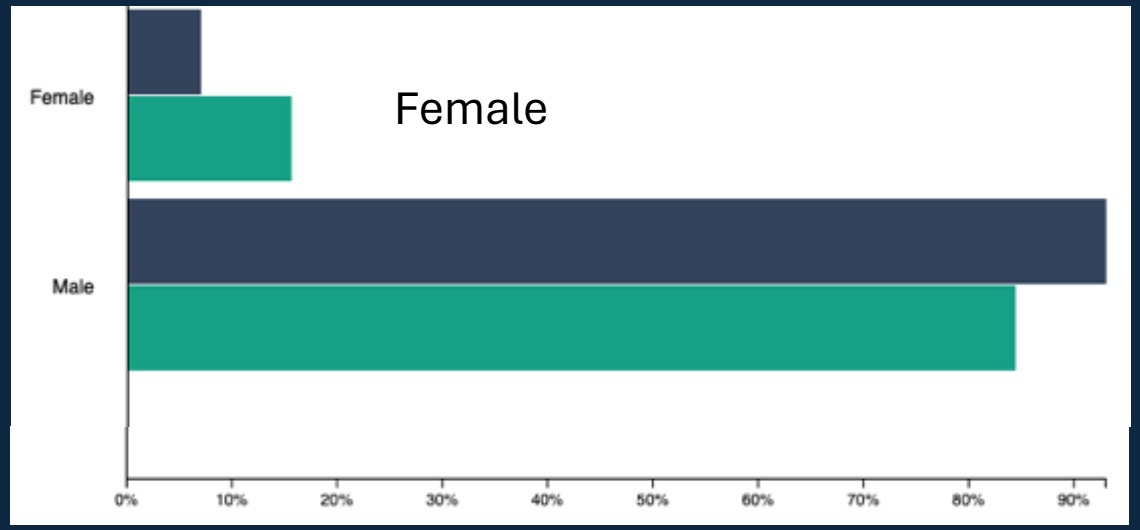
- Hemophilia is inherited in an X-linked recessive fashion
- In about a third of cases, hemophilia is due to a spontaneous factor variant and there is no family history
- Hemophilia B is more rare:
  - Affects ~1 in 19,000 male births
  - Prevalence: 3.7 cases per 100,000 US males
- Hemophilia A is still rare but not as rare:
  - Affects ~1 in 5,600 male births
  - Prevalence: 12 cases per 100,000 US males
- Note the lack of data on people with 2 X chromosomes

Soucie JM, et al. Haemophilia. 2020. 26:487-493

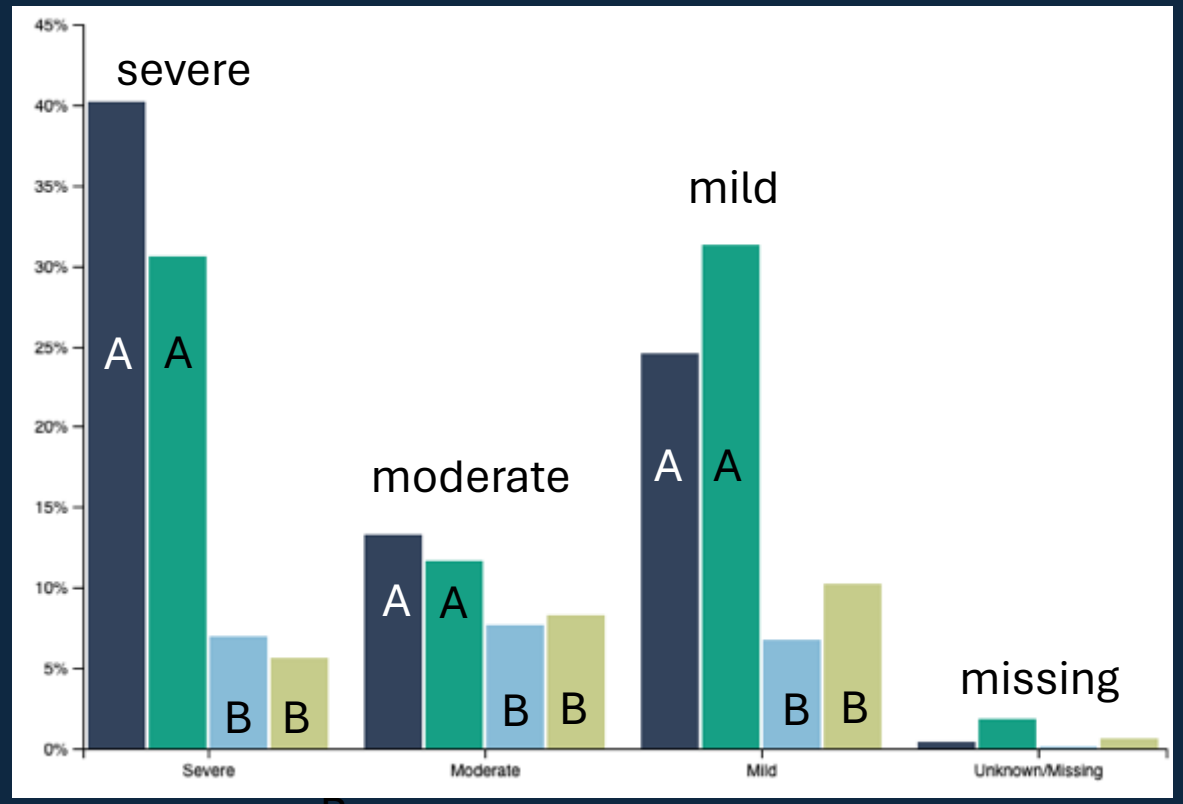
Hemophilia A & B

- Severe hemophilia is typically diagnosed soon after birth
- Mild hemophilia may not be diagnosed until adulthood
- Hemophilia will greatly prolong the PTT, and factor 8 and 9 assays are much more reliable than VWF assays
- We are working on increasing care for people with the potential to menstruate who have hemophilia or are at risk (eg: their dad has hemophilia or their son has hemophilia)

Hemophilia A & B



Female



B

https://communitycountsdataviz.cdc.gov/ Hemophilia by sex, Hemophilia severity, accessed 12/11/24

Inherited Bleeding Disorders

- Platelet disorders are a heterogenous group of bleeding disorders with heterogenous phenotypes
  - Severe bleeding: Glanzmann Thrombasthenia
  - Mild bleeding: Aspirin-like defect
- There are likely more platelet function disorders than we have named
- The inheritance pattern is variable depending on the disorder
  - Glanzmann Thrombasthenia is an autosomal recessive condition, with a prevalence of 1:1,000,000
  - MYH9 Disorders are autosomal dominant, with a prevalence of 1:20,000

Platelet Disorders

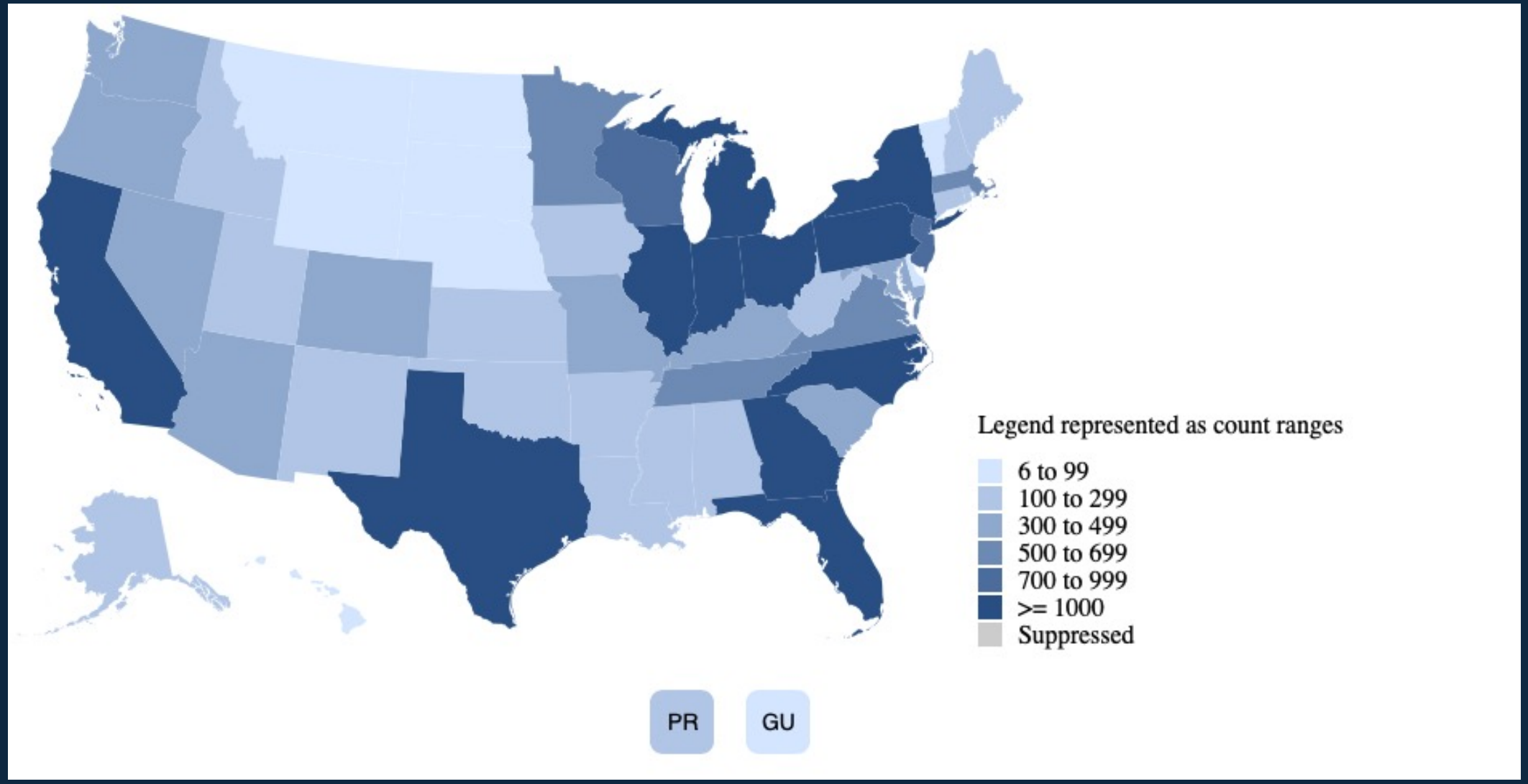
- Platelet disorders can be difficult to diagnose as the tests of platelet function are not widely available
  - For example, OHSU is the only place in the state of Oregon where you can get platelet aggregation testing
- Platelet Disorders sometimes are associated with other medical conditions, which may have a more clinically significant phenotype
  - MYH9 disorders are associated with renal dysfunction and hearing loss
  - Hermansky-Pudklak Syndrome is associated with oculocutaneous albinism, individuals are at risk for pulmonary fibrosis and IBD
  - Wiskott Aldrich Syndrome is associated with thrombocytopenia, eczema, and immune dysfunction

Inherited Bleeding Disorders

- Generally rare disorders (except von Willebrand Disease) with impactful symptoms that can affect generations
- Inheritance pattern is variable depending on diagnosis:
  - Can see increased prevalence in certain areas due to founder effect

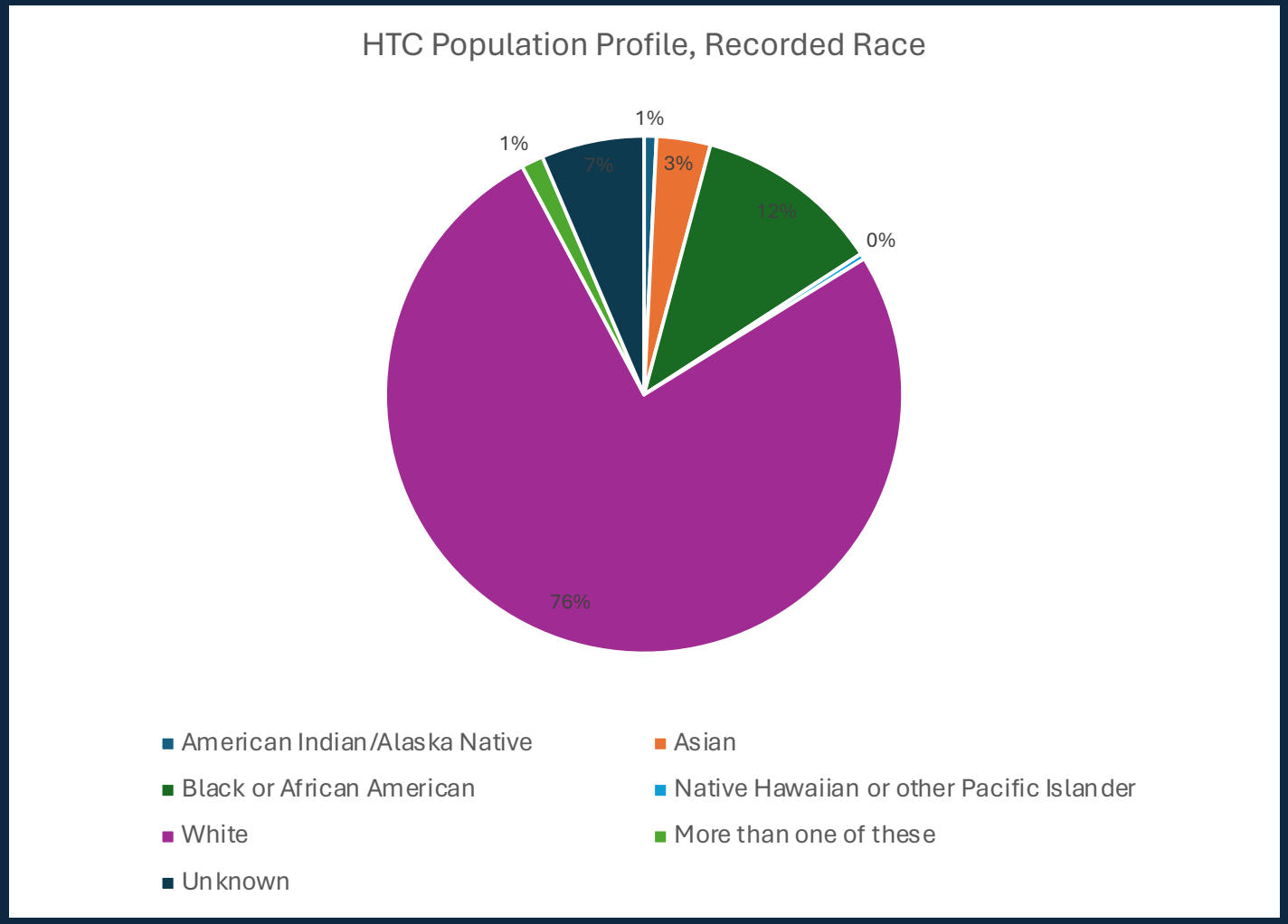
Bleeding Disorder	Inheritance Pattern
X-linked Recessive	Hemophilia A & B
Autosomal Dominant	Type 1 von Willebrand Disease MYH9 platelet disorders
Autosomal Recessive	Glanzmann Thrombasthenia Type 3 von Willebrand Disease Factor XIII Deficiency Factor XI Deficiency

Inherited Bleeding Disorders



https://communitycountsdataviz.cdc.gov/ Geographic Distribution, accessed 12/11/24

Inherited Bleeding Disorders



Race	Number	% of Total
American Indian/Alaska Native	338	0.77
Asian	1472	3.37
Black or African American	5116	11.70
Native Hawaiian or other Pacific Islander	157	0.36
White	33237	76.00
More than one of these	602	1.38
Unknown	2813	6.43

Inherited Bleeding Disorders

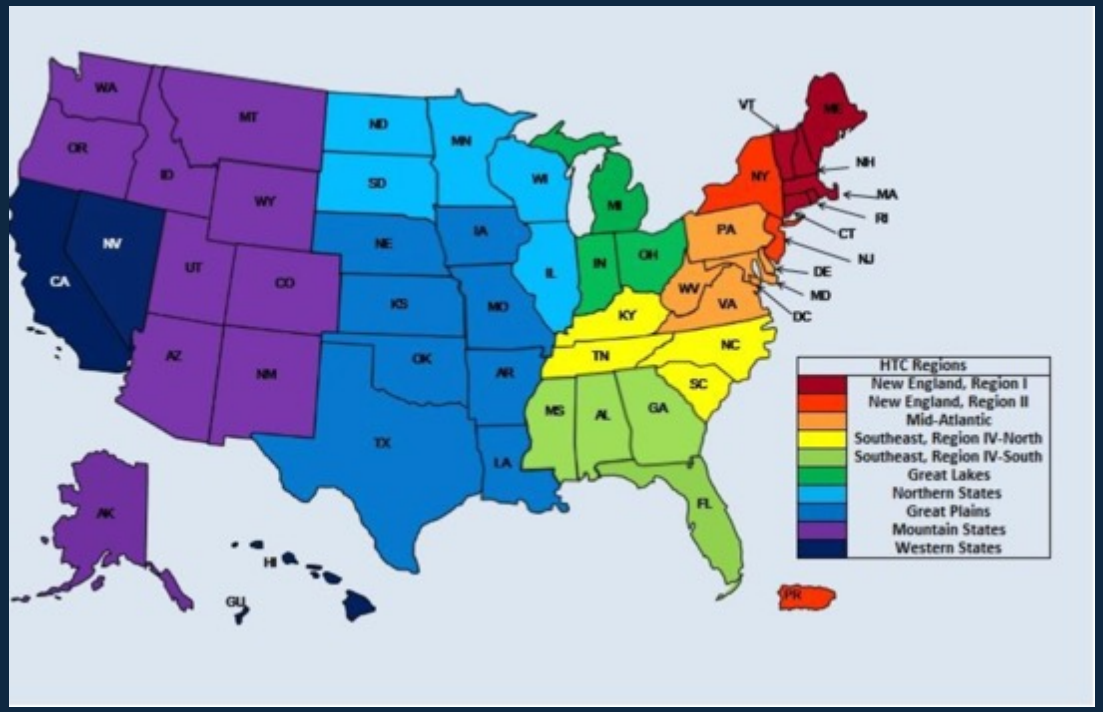
- Very limited published information regarding incidence/prevalence of bleeding disorders in individuals from Tribal and/or Indigenous Communities

Large Cohort of Symptomatic Female Carriers of Hemophilia in an Extended Native American Family

Becki Berkowitz, RN, CPON, Amber Federizo, RN, MSN, FNP-BC, Garrett E. Bergman, MD MBA, Paula J. Ulsh, RN, BSN

Large family from the Duck Valley Indian Reservation in Owhyhee, NV: A German man with Hemophilia A married 2 women of the Shoshone Tribe, and they had 14 children – after 4 generations, there are 162 descendants with the same hemophilia A gene mutation.

Inherited Bleeding Disorders



- Mountain States Hemostasis Network (purple)
  - Hemophilia and Thrombosis Center at University of Colorado – Aurora, CO
  - Ted R. Montoya Hemophilia Program at University of New Mexico – Albuquerque, NM
  - Arizona Hemophilia and Thrombosis Center at University of Arizona – Tucson, AZ
  - Arizona Hemophilia and Thrombosis Center at Phoenix Children's Hospital – Phoenix, AZ
  - Utah Center for Bleeding and Clotting Disorders at Primary Children's Hospital and University of Utah – Salt Lake City, UT
  - Seattle Children's Hospital – Seattle, WA
  - Washington Center for Bleeding Disorders – Seattle, WA
  - The Hemostasis & Thrombosis Center at Oregon Health & Science University – Portland, OR
  - St. Luke's Hemophilia Program – Boise, ID
  - Providence Sacred Heart Children's Hospital Hemophilia Center – Spokane, WA
  - Alaska Bleeding Disorder Clinics – Anchorage, AK

Inherited Bleeding Disorders - MSHN

- Across the MSHN region, there were 5200 active patients with bleeding disorders on the 2023 report
  - 123 patients had a reported race of American Indian or Alaska Native = 2.3%
    - In the 10 states, based on the 2020 US Census data, American Indian or Alaska Native race was reported for 1.3-15.2% of participants, with an average of 4.54%
  - For the MSHN 2023 data
    - 80% of the individuals with American Indian or Alaska Native recorded for race were under 35 years old
    - 80% of the individuals with White recorded for race were under 55 years old
    - Just over 50% of the individuals with American Indian or Alaska Native recorded for Race had a comprehensive clinic visit at the HTC
    - 66% of the individuals with White recorded for race had a comprehensive clinic visit at the HTC

Inherited Bleeding Disorder Symptoms

- Nosebleeds
  - Can be frequent and prolonged (20+ minutes)
  - Can interrupt school/work
- Oral bleeding
  - Recurrent gum bleeding can decrease desire to perform oral health
  - Minor dental procedures can become a life-threatening event
- Heavy menstrual bleeding & bleeding with pregnancy & childbirth
  - Can result in severe symptomatic anemia requiring transfusion
  - Often goes undetected and undertreated
  - Can be the first and only sign of a bleeding disorder

Inherited Bleeding Disorder Symptoms

- Muscle bleeding
  - Can inhibit function/movement
  - Can cause nerve injury, compartment syndrome, myositis ossificans (bone tissue forms inside a muscle), pseudotumor, infection
- Joint bleeding
  - Can inhibit function/movement
  - Can cause long-term joint damage/arthropathy that may require joint replacement
- Intracranial bleeding
  - rarely spontaneous – only in severe bleeding disorders
  - Trauma-induced – treat the bleeding disorder and then look for blood

Inherited Bleeding Disorder Symptoms

- Bleeding can also be related to trauma or surgery
  - Can be immediate or delayed
- Bleeding symptoms depend on bleeding challenges
  - Children may not have had a lot “opportunity” to bleed
- Bleeding symptoms overlap between inherited bleeding disorders, but some symptoms make us think one type or another

Bleeding Symptom	Characteristic Inherited Bleeding Disorder
Petechiae	Platelet Disorder
Hemarthroses	Hemophilia A or B
Prolonged bleeding from umbilical stump	Factor XIII deficiency
Mucocutaneous bleeding (nosebleeds, heavy periods, bruises, etc)	Von Willebrand Disease or Platelet Disorder

Assessing Bleeding Symptoms

- Bruising, nosebleeds, heavy periods are all really common symptoms
- In general, bleeding symptoms affecting life and work/school or resulting in iron deficiency warrant more attention – and consideration of an inherited bleeding disorder as a potential cause
  - But other things to consider include: nutritional deficiencies (eg: Vitamin C, iron deficiency, vitamin K deficiency), medication effect (eg: anticoagulants, NSAIDs, SSRIs), acquired bleeding disorders (eg: Immune Thrombocytopenia), non-accidental trauma

Assessing Bleeding Symptoms

- A standard approach to taking a bleeding history can help decide who needs further work up with laboratory assessment
- The International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT) is available on MD CALC
  - https://www.mdcalc.com/calc/10580/isth-scc-bleeding-assessment-tool

ISTH BAT Scores	
Group	Abnormal Score
Children	>/= 3
Adult Females	>/= 6
Adult Males	>/= 4

Epistaxis

No/trivial	0
>5 /year or >10 minutes	+1
Consultation only	+2
Packing, cauterization, or antifibrinolytic agents	+3
Blood transfusion, replacement therapy, or desmopressin	+4

Bruising

No/trivial	0
≥5 bruises (>1 cm) in exposed areas	+1
Consultation only	+2
Extensive	+3
Spontaneous hematoma requiring blood transfusion	+4

Assessing Bleeding Symptoms

- Laboratory assessments
  - PT and PTT will screen for clotting factor deficiencies
    - A prolongation of the PT or the PTT may indicate a factor deficiency
    - Can also indicate a lupus inhibitor/anticoagulant
    - Does not screen for factor XIII deficiency (but that is so rare)
    - Factor XII deficiency can prolong the PTT but does not cause bleeding
  - Von Willebrand testing:
    - Factor VIII Activity, VWF Antigen, VWF Activity
    - Be wary of falsely low or high levels
    - VWF Antigen & Activity levels >90% are pretty reliable at ruling OUT VWD
  - CBC and iron studies (ferritin at a minimum)
    - Screen for iron deficiency and anemia
    - Check for thrombocytopenia

Treatments for Inherited Bleeding Disorders

- Some general principles:
  - People with bleeding disorders don’t bleed faster – so first aid is always a great place to start!
  - The usual medications to treat heavy periods are what are recommended in bleeding disorders, too
  - Plan for potential bleeding: wear a medical alert, wear a helmet on a bike, create a hemostatic plan for dental work or surgeries
  - Mitigate other risk factors for bleeding: avoid NSAIDs, make a plan if an anticoagulant or antiplatelet is needed, eat a fruit or a vegetable
  - In many severe bleeding disorders, prophylactic therapies are utilized

Treatment for Inherited Bleeding Disorders

- Replace what's missing:
  - Intravenous administration of clotting factor concentrates
  - Blood products
- Release what's missing:
  - Desmopressin results in release of VWF from storage molecules in endothelial cells
- Augment Hemostasis:
  - Clotting factors like recombinant factor VII for platelet disorders
  - Newer therapies to replace factor function or inhibit inhibitors of factor function
- Prevent clot breakdown
  - Antifibrinolytics like Tranexamic Acid (TXA)

Treatment for Inherited Bleeding Disorders

Before Bleeding Happens	When Bleeding Happens
Stay active – keep muscles and joints strong	First Aid measures – pressure, RICE, local hemostatic agents
Dental hygiene and preventive care	Hemophilia: factor med +/- antifibrinolytic
Wear protective equipment for activities when indicated, wear a seat belt in the car	VWD: VWF concentrate or DDAVP +/- antifibrinolytic
Avoid contact sports/activities	Platelet Disorder: DDAVP or rFVII or platelet transfusion +/- antifibrinolytic
Take prophylactic medications as prescribed	Other meds used: other factor products depending on deficiency
Heavy periods: hormonal therapies, antifibrinolytic	Heavy periods: hormonal therapies, antifibrinolytic

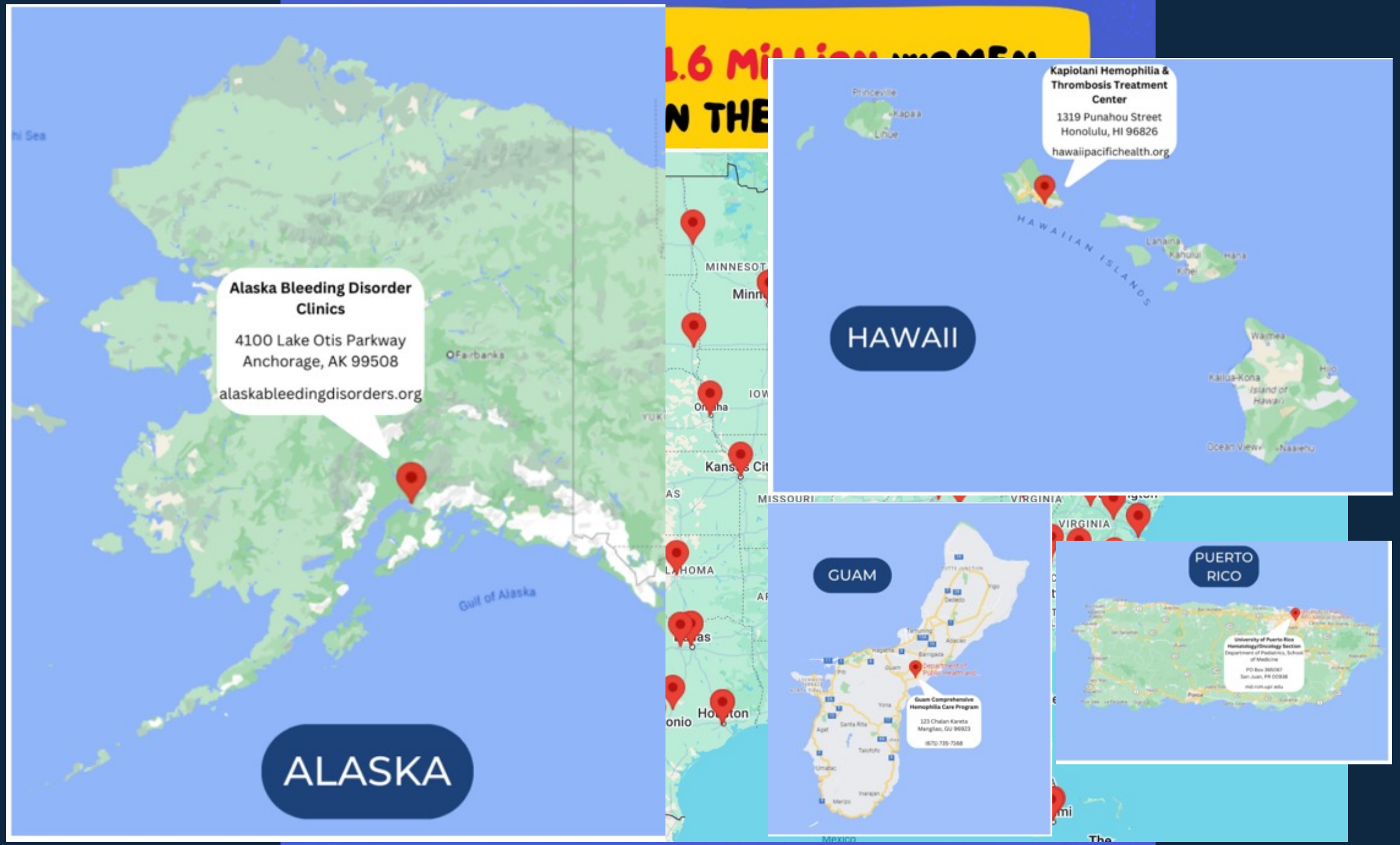
Treatment for Inherited Bleeding Disorders

Hemophilia Treatment Centers

- Specialized clinics for individuals with bleeding and clotting disorder
- Provide comprehensive care and coordination of care
- Services vary across HTCs but typically include
  - Hematologist
  - Nurse coordinator(s)
  - Social Work
  - Physical Therapists

Connect with resources

- Foundations for Women & Girls+ with Blood Disorders
  - www.fwgbd.org
  - Archived as well as live webinars
- National Bleeding Disorders Foundation
  - www.bleeding.org
  - Fast facts, bleeding disorder history, more specific information about bleeding disorders
- Hemophilia Federation of America
  - www.hemophiliafed.org
  - More patient facing education
- Let’s Talk Period
  - Letstalkperiod.ca
  - Self-bleeding assessment tool available


Alaska Bleeding Disorder Clinics
4100 Lake Otis Parkway
Anchorage, AK 99508
alaskableedingdisorders.org
ALASKA
Kapiolani Hemophilia & Thrombosis Treatment Center
1319 Punahou Street
Honolulu, HI 96826
hawaiipacifichealth.org
HAWAII
GUAM
PUERTO RICO

Summary

- Bleeding symptoms can be common, especially bruising, nosebleeds, and heavy menstrual bleeding
- Bleeding interfering with daily activities is a red flag and warrants further consideration
- For adult patients, completing an online self-Bleeding Assessment Tool can help identify those requiring further work up with labs
- Some labs to consider as first-line evaluation for bleeding problems include CBC, Ferritin, PT, PTT, VWF Activity, VWF Antigen, Factor VIII Activity
- Hemophilia Treatment Centers are here to help – interpret labs, see patients, connect patients and families to resources

Questions/Comments/Reflections

”Anemia”