Overview of Hemophilia A and B

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Overview of Hemophilia A and B

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01 Introduction to hemophilia

Disease description

Patient characteristics

Prevalence

Introduction to Hemophilia A and B

Disease description

- Hemophilia is characterized by excessive bleeding due to an impaired ability to form a blood clot. Bleeding can happen with or without a challenge to **hemostasis**, such as trauma or surgery.

Characteristics of hemophilia

- Caused by the deficiency of a functional **coagulation factor** (aka, **clotting factor**) in the blood.
  - Hemophilia A: factor VIII (FVIII) deficiency
  - Hemophilia B: factor IX (FIX) deficiency
- Disease severity correlates with the degree of coagulation factor deficiency.
- The factor deficiency is caused by a **mutation** in the gene encoding the deficient factor.
  - The genetic mutation is usually inherited, with two-thirds of affected patients having a family history of hemophilia. About one-third of cases have no family history and are thought to result from spontaneous genetic mutations.
- **Congenital** disorder generally affecting males.
- Hemophilia A is the most prevalent form.

FVIII

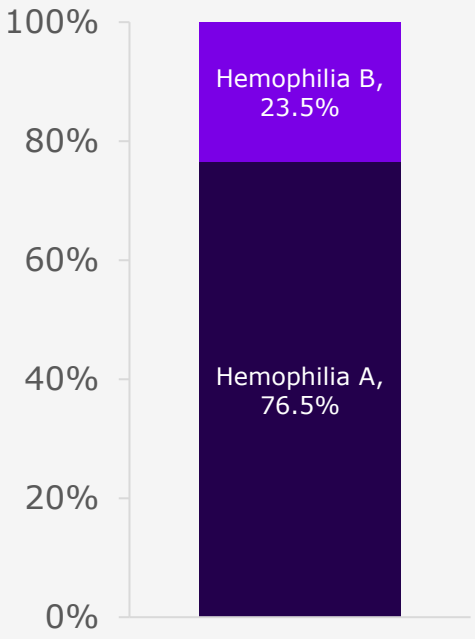
- Protein produced mainly in the liver.
- Circulates in inactive form in the blood, largely bound to another clotting protein, **von Willebrand factor (VWF)**, which protects it from breakdown and clearance, thus increasing the **half-life** of FVIII.
  - Half-life of VWF-bound FVIII: 12 hours
  - Half-life of free FVIII: 2 hours
- During **coagulation**, FVIII separates from VWF when activated by **thrombin**; it then acts as a **cofactor** with activated FIX.

FIX

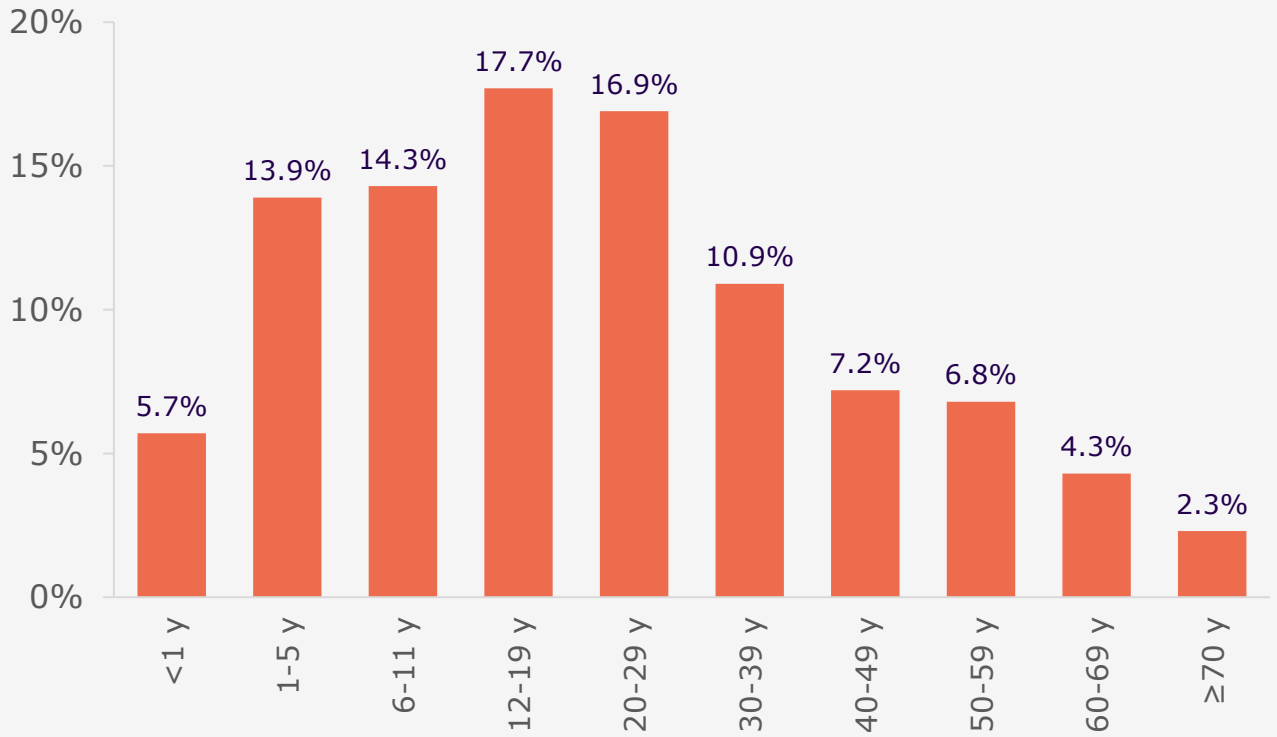
- Protein produced in the liver.
- Circulates in the blood in inactive form, with a half-life of 18-24 hours.
- During coagulation, activated FXI activates FIX, which then activates factor X (FX) in the presence of its cofactor FVIIIa.

Characteristics of Patients With Hemophilia

Proportion of patients with hemophilia type A or B



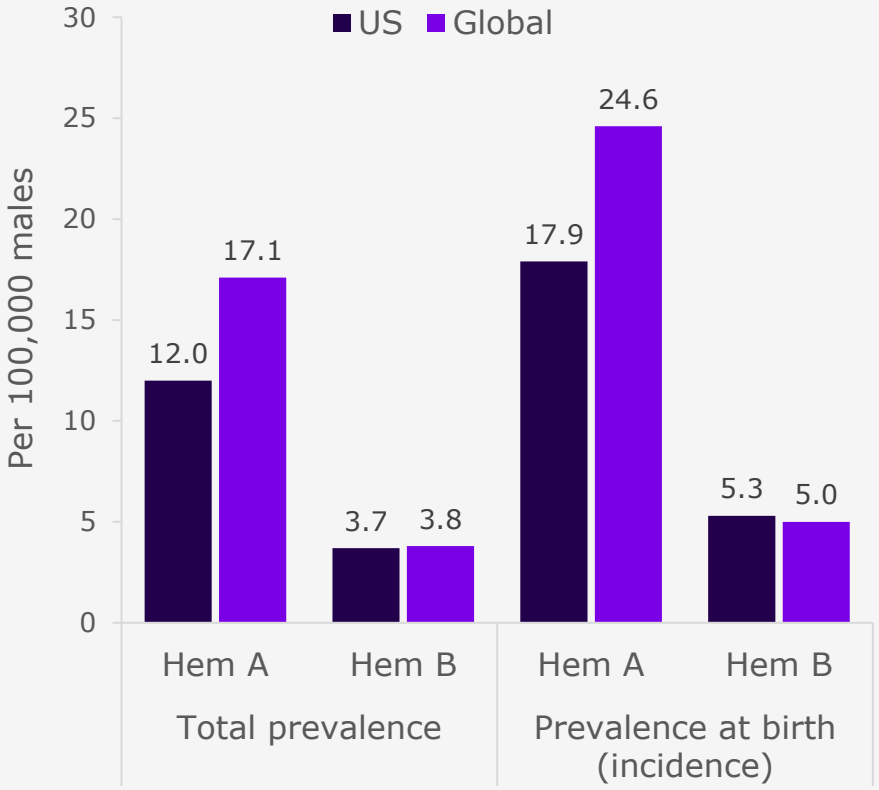
Age distribution among patients with hemophilia A or B



Data from 21,748 male patients with hemophilia receiving treatment from 139 hemophilia treatment centers (HTCs) in the United States between 2012 and 2018.

Prevalence of Hemophilia A and B

US and Global Estimates



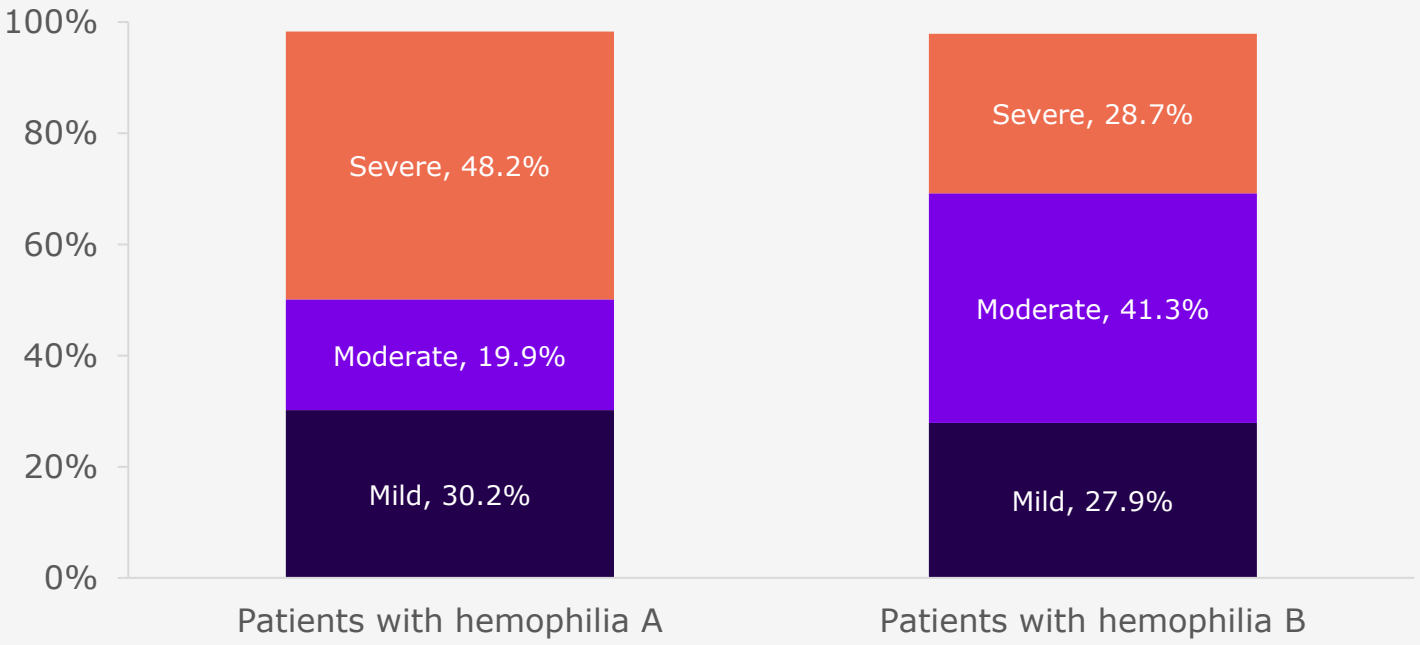
Estimated prevalence of males living with hemophilia

- US: ~30,000 to 33,000
- Globally: ~1,125,000

Global estimates of total prevalence are from patient registries in Australia, Canada, France, Italy, New Zealand, and the United Kingdom. Global estimates of prevalence at birth are from patient registries in Canada, France, and the United Kingdom.

Prevalence of Hemophilia by Severity

US Data



Data from 21,748 male patients with hemophilia receiving treatment from 139 HTCs in the United States between 2012 and 2018. Percentages do not total 100 because severity was unknown for a small proportion of patients.

The largest proportion of patients with hemophilia A have severe disease. In those with hemophilia B, the largest proportion have moderate disease.

02 Clinical manifestations of hemophilia

Bleeding

Complications

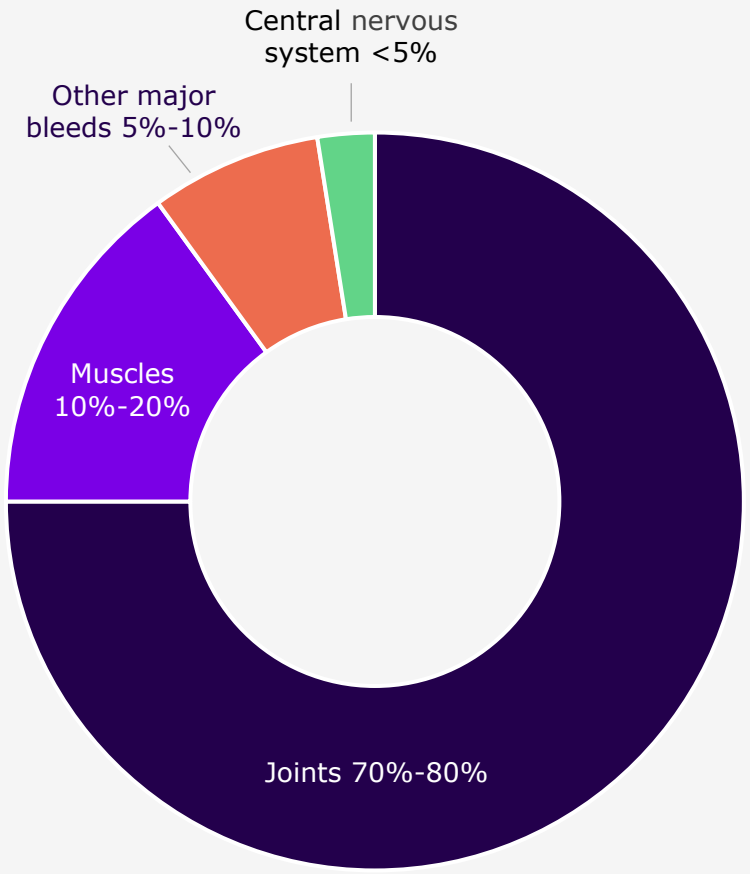
Burden

Clinical Manifestations

Bleeding

- Hemophilia is characterized by prolonged and excessive bleeding.
- The severity of bleeding correlates with the degree of coagulation factor deficiency.
- Mild hemophilia may not cause excessive bleeding unless an affected individual experiences an injury or undergoes surgery.
- Severe hemophilia is most commonly associated with **hemarthrosis** as well as bleeding into the muscles and internal organs, although bleeding can occur anywhere in the body.
- Common bleeds in newborns and children less than 2 years old with severe hemophilia include the following:
  - Intramuscular and soft tissue bleeds
  - Bleeding of the **mucous membranes** of the mouth and nose
  - **Extracranial** bleeds
  - Bleeding with medical procedures, such as **venipuncture** or neonatal heel prick, **central line** placement, and circumcision

Frequency of bleeding by site



Serious Bleeds

Serious bleeds most commonly occur in specific joints and muscles. The joints most often affected are the ankle, knee, and elbow, but bleeding into the the hip, shoulder, and wrist joints is not uncommon. In the muscles, the deep compartments are most affected, such as the **iliopsoas** in the pelvis, the **gastrocnemius** in the lower leg, and the forearm. Serious bleeds can also occur in the mucous membranes.

Bleeds that occur in the brain, gastrointestinal (GI) tract, or in the throat or neck (which can lead to airway obstruction) can be life-threatening and require immediate medical attention and treatment.

Complications of Bleeding in Hemophilia

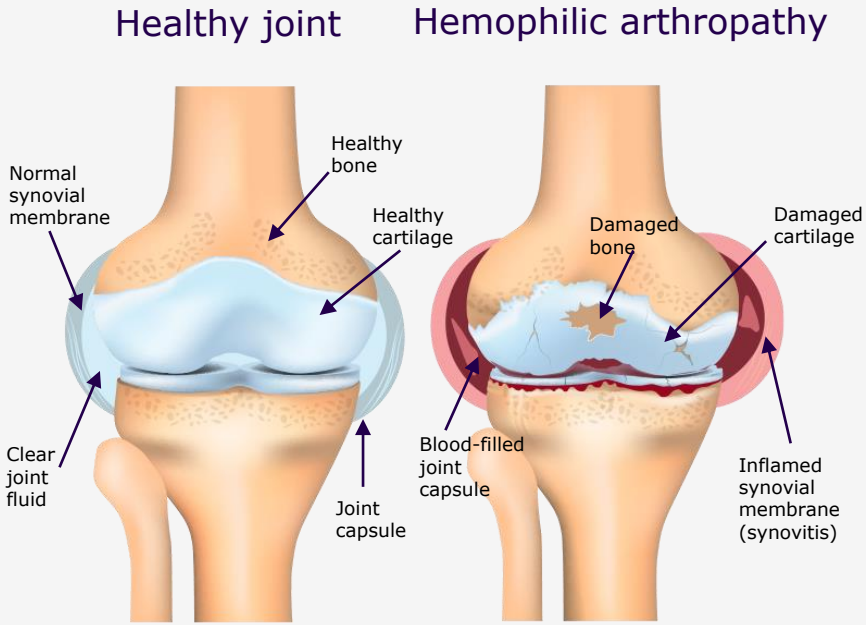
Joint Hemorrhage and Hemophilic Arthropathy

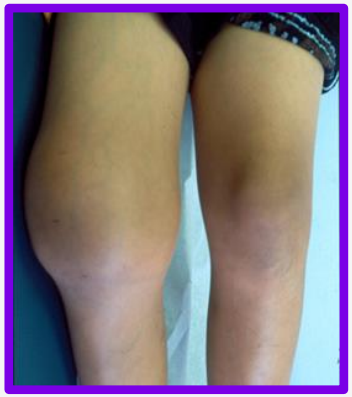
The acute bleeds that characterize hemophilia most often occur in the joints, usually the ankle, knee, or elbow. A target joint is defined by the World Federation of Hemophilia as a single joint in which 3 or more spontaneous bleeds have occurred within a consecutive 6-month period.

The accumulation of blood in a joint cavity causes **synovitis**. Recurrent joint bleeds lead to chronic synovitis and progressive joint damage as the chronically inflamed **synovial membrane** becomes enlarged and prone to further bleeds, ultimately resulting in irreversible damage to the cartilage and bone.

As **arthropathy** worsens, there can be progressive **fibrosis** of the synovium and joint capsule and the joint may become **ankylosed**. Thus, hemophilic arthropathy is both inflammatory and degenerative.

Chronic hemophilic arthropathy often manifests in young individuals, during the second decade of life, especially without preventative treatment. It is associated with substantial burden to patients, including chronic pain, disability, and the potential need for joint replacement.





An acute knee bleed in a patient with hemophilia

Image credit: National Hemophilia Foundation, Nurses Working Group. Image Slideshow. Accessed June 27, 2022. Available at: https://www.hemophilia.org/healthcare-professionals/allied-healthcare/nursing/nursing-resources

Complications of Bleeding in Hemophilia

Muscle Hemorrhage

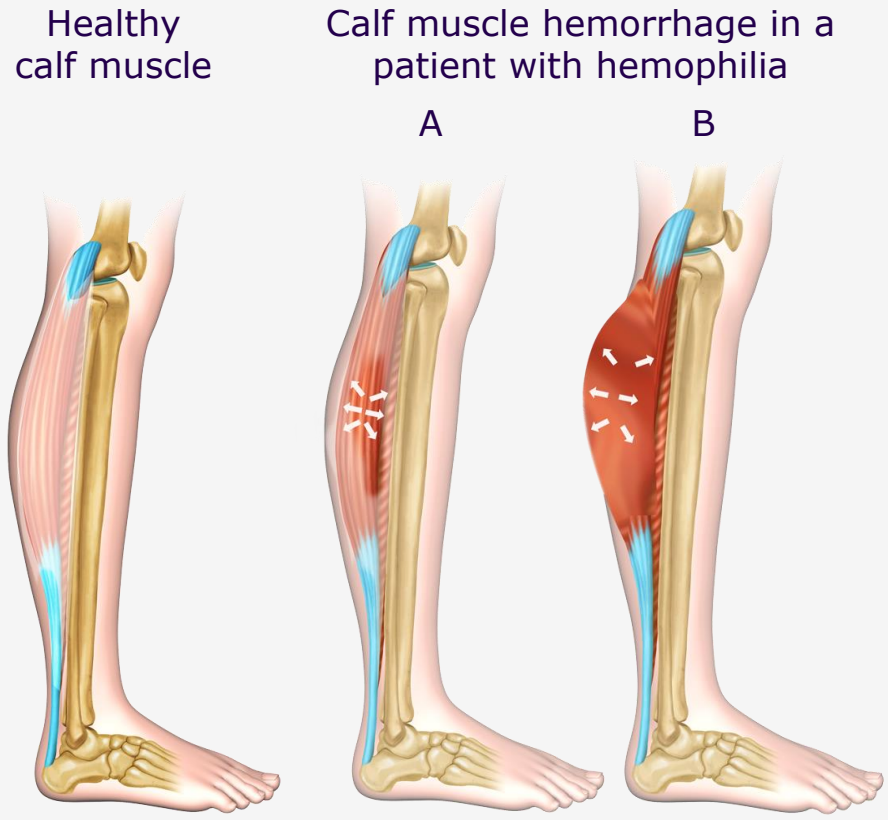
In patients with hemophilia, bleeds can occur in any muscle as a result of trauma, sudden stretching, or even spontaneously in patients with more severe disease.

Symptoms include pain (especially with muscle contraction or stretching), tension, tenderness to touch, swelling, and functional impairment.

Muscle bleeds are most problematic when they occur in the body's deep muscle compartments, such as in the iliopsoas, calf, or forearm. Bleeds in these locations can compromise associated nerves and blood vessels, and therefore require immediate medical attention to prevent permanent damage and loss of function.

Bleeding can also occur in more superficial muscles, including the biceps, hamstrings, quadriceps, and gluteal muscles.

Early identification and management are necessary to prevent rebleeding, permanent **muscle contracture**, and the formation of **pseudotumors**.

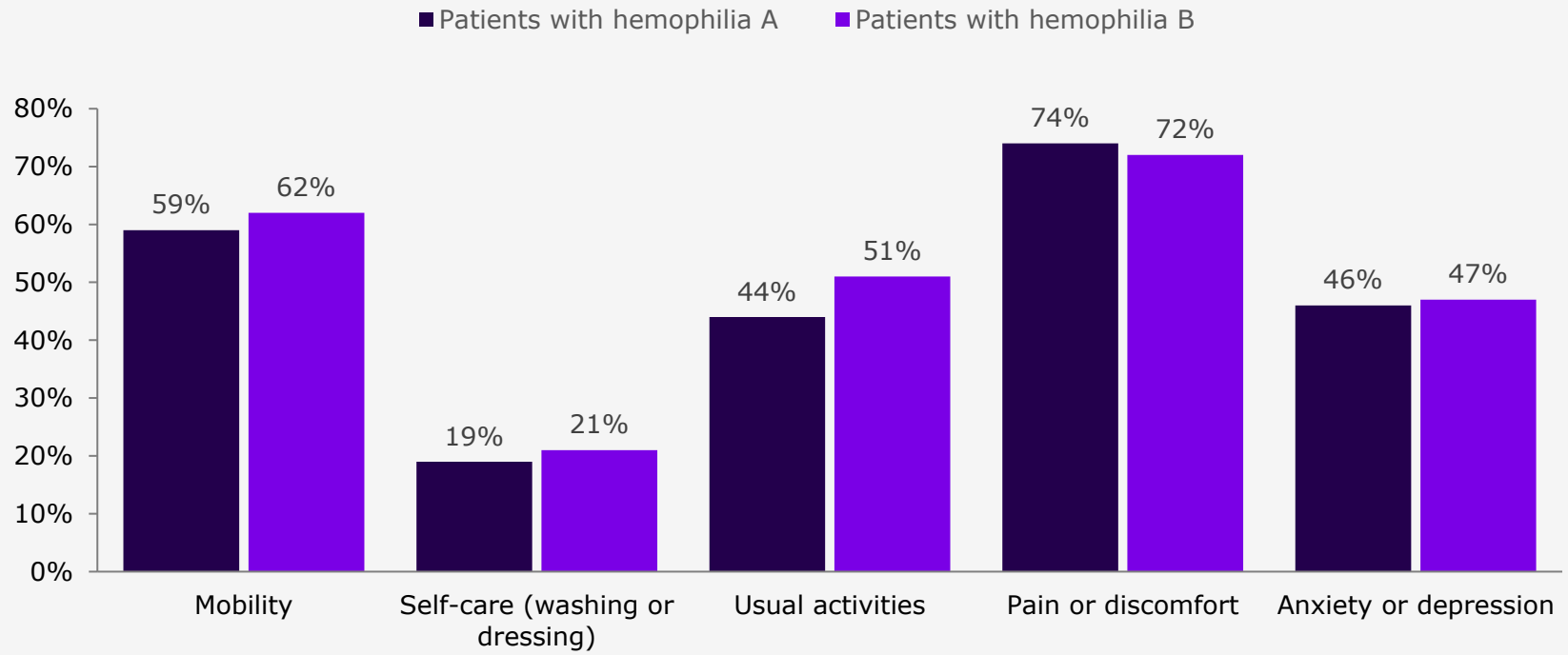


Panel A: Muscle bleeding forms a small **hematoma**. **Panel B**: Continued bleeding causes accumulation of a large amount of blood in the muscle, resulting in pain, swelling, and functional impairment

Burden of Hemophilia

Quality of Life

Number of patients with hemophilia reporting limitations (some impact or severe impact) in 5 quality-of-life measures



Hemophilia is associated with substantial quality-of-life burden

In a global study of 498 adult men with hemophilia A and 86 with hemophilia B from 10 countries, most participants reported limitations in mobility as well as pain that was either moderate or extreme in intensity. Nearly half of participants reported limitations in their usual daily activities and anxiety or depression.

03 Pathophysiology of hemophilia

Hemostasis

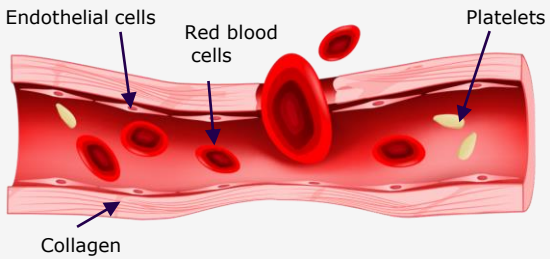
Pathophysiologic changes in hemophilia

Genetic basis and pattern of inheritance

Acquired hemophilia

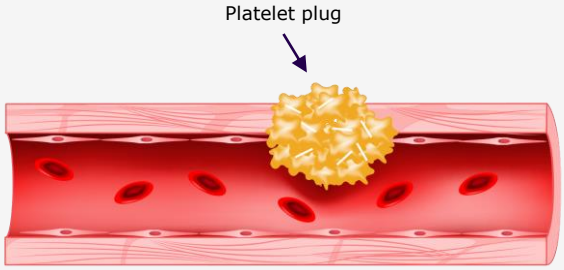
Hemostasis

Normal Response to Injury



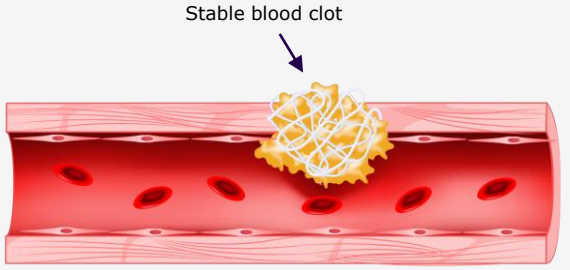
1 Vasoconstriction

Chemical **mediators** released from damaged **endothelial cells** as well as **platelets** cause tightening of the vessel in an attempt to stop blood loss.



2 Primary hemostasis

A weak platelet plug forms to help stop blood loss at the site of damage.



3 Secondary hemostasis

The platelet plug is stabilized by the protein **fibrin**, which has a thread-like structure that enmeshes the plug.

Secondary hemostasis is accomplished via the **coagulation cascade**, which generates the necessary fibrin. This step is inhibited in patients with hemophilia.

Simultaneous response

The processes of primary and secondary hemostasis are activated at the same time after an injury, and occur in tandem, with the common goal of forming a stable blood clot. These processes are discussed in more detail in the following sections.

Primary Hemostasis

Formation of a Platelet Plug

1 Platelet adhesion

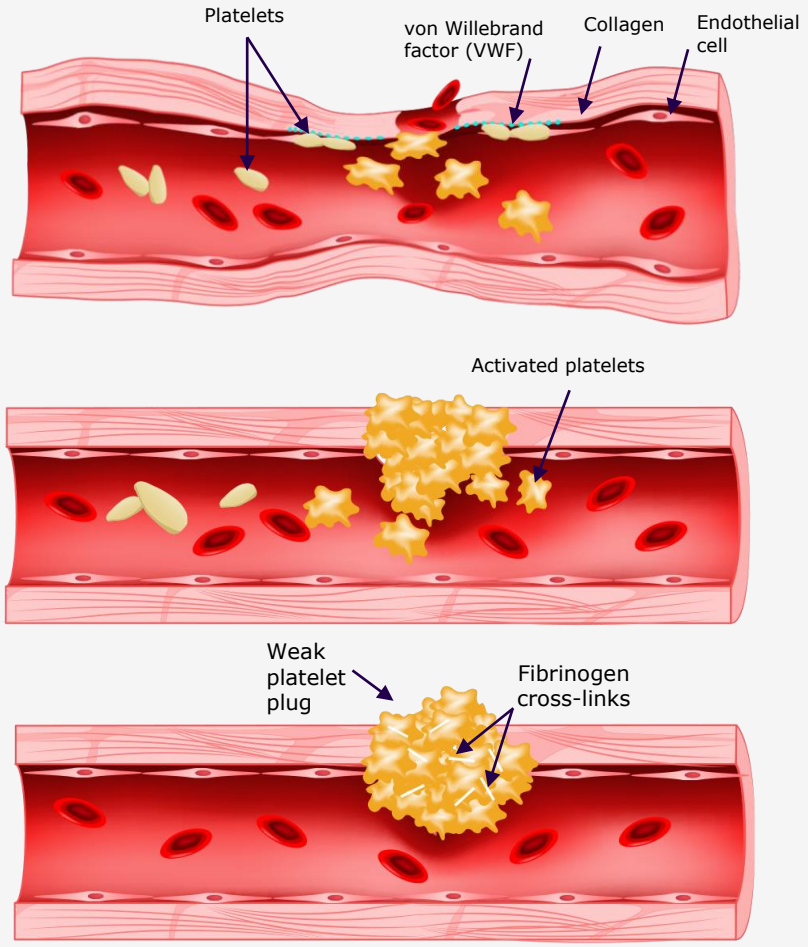
- The damaged endothelium exposes **collagen** and VWF below its surface.
- Inflammatory mediators cause platelets to attach to the exposed (subendothelial) VWF and collagen.

2 Platelet activation

- Thrombin activates VWF-bound platelets to secrete mediators for platelet aggregation.
- Platelets change in shape to a pseudopodal, or spiky, form that increases their surface area and promotes aggregation.

3 Platelet aggregation

- Activated, VWF-bound platelets adhere to fibrinogen in the blood. Fibrinogen is a plasma protein that is later converted to fibrin by the action of thrombin.
- The fibrinogen interconnects the platelets to form a weak plug.

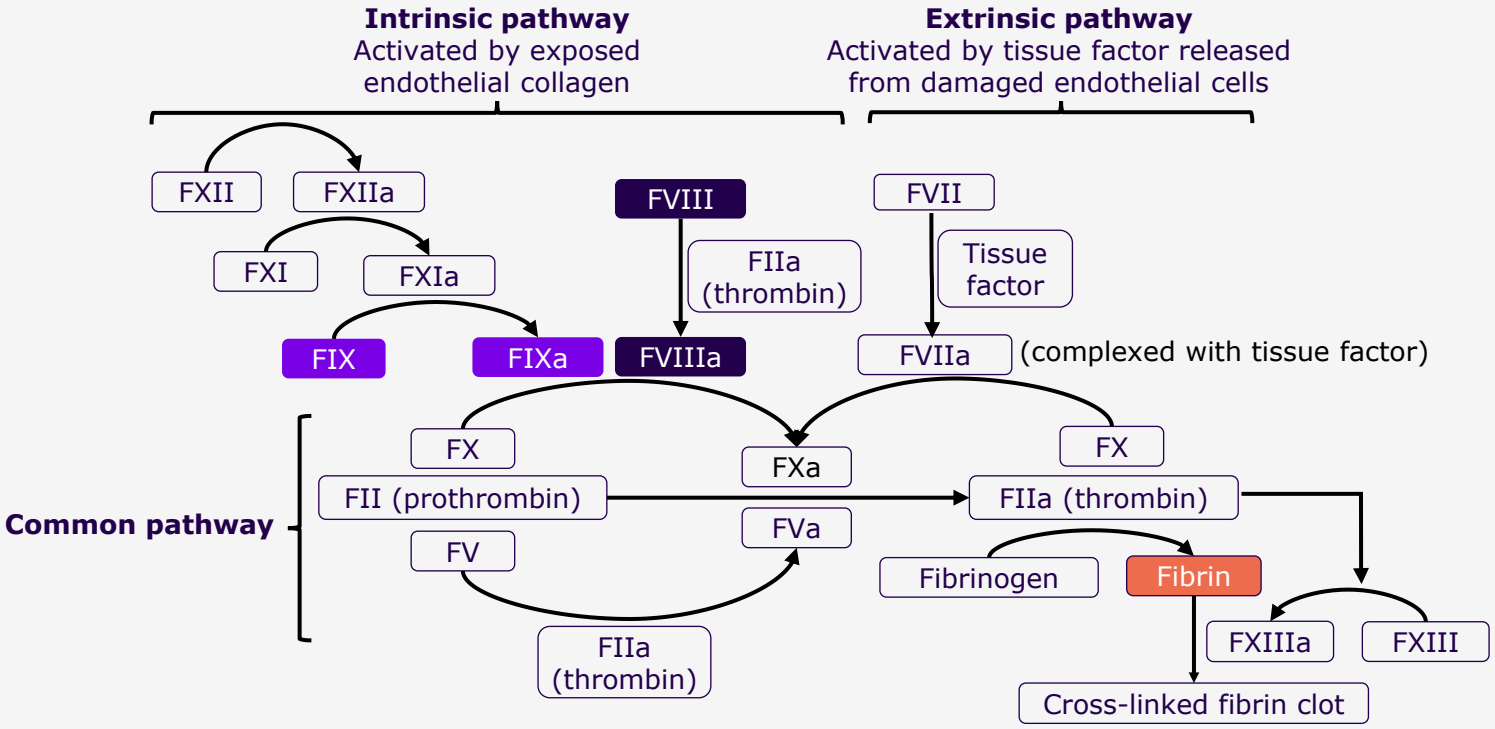


Secondary Hemostasis

Stabilization of the Platelet Plug With Fibrin

The coagulation cascade

Secondary hemostasis involves the activation of coagulation factors in a cascade to ultimately stabilize the weak platelet plug (formed in primary hemostasis) with fibrin mesh. It involves intrinsic and extrinsic pathways, which begin separately but meet to form the common pathway. The goal of the common pathway is to activate fibrinogen into fibrin, which forms strands that bind platelets together, thereby stabilizing the platelet plug. FVIII and FIX are both part of the intrinsic pathway.



The coagulation cascade. When thrombin, a key player in coagulation, is generated in the common pathway, it cleaves fibrinogen to fibrin and also reinforces the cascade by activating certain factors, including FV, FVIII, and FXIII. It also plays a role in platelet activation in primary hemostasis.

Arrows represent the activation of a clotting factor by the factor(s) directly above, below, or to the side of it. The "a" in a factor name indicates the activated form. The factors deficient in hemophilia A and B, FVIII and FIX, respectively, are highlighted, as is the goal of the cascade, fibrin.

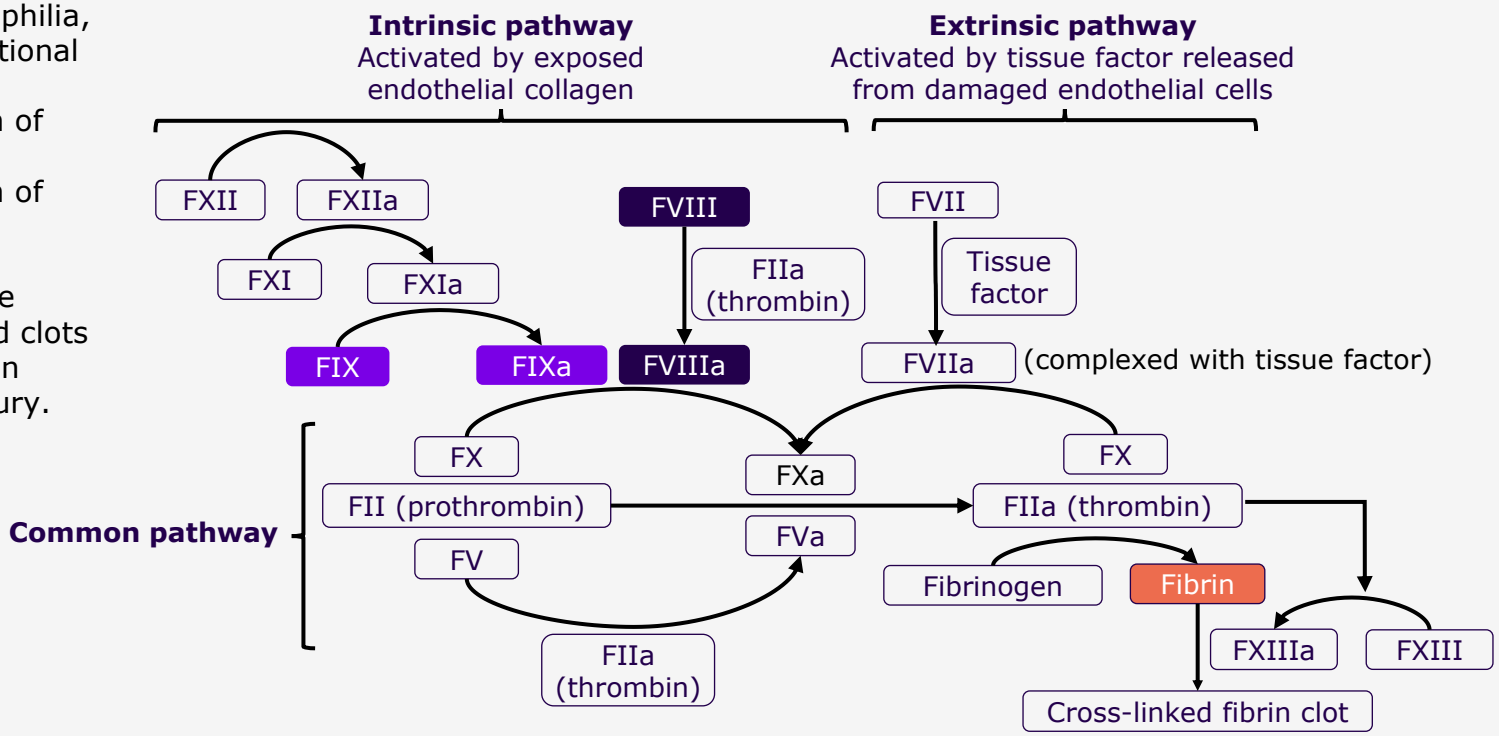
Pathophysiology of Hemophilia

Disruption of Secondary Hemostasis

The enzyme FIXa activates FX in the presence of cofactor FVIIIa.

In patients with hemophilia, the absent or dysfunctional FVIII or FIX results in insufficient generation of FXa, with consequent insufficient generation of thrombin and fibrin.

Ultimately, without the necessary fibrin, blood clots do not form properly in response to tissue injury.



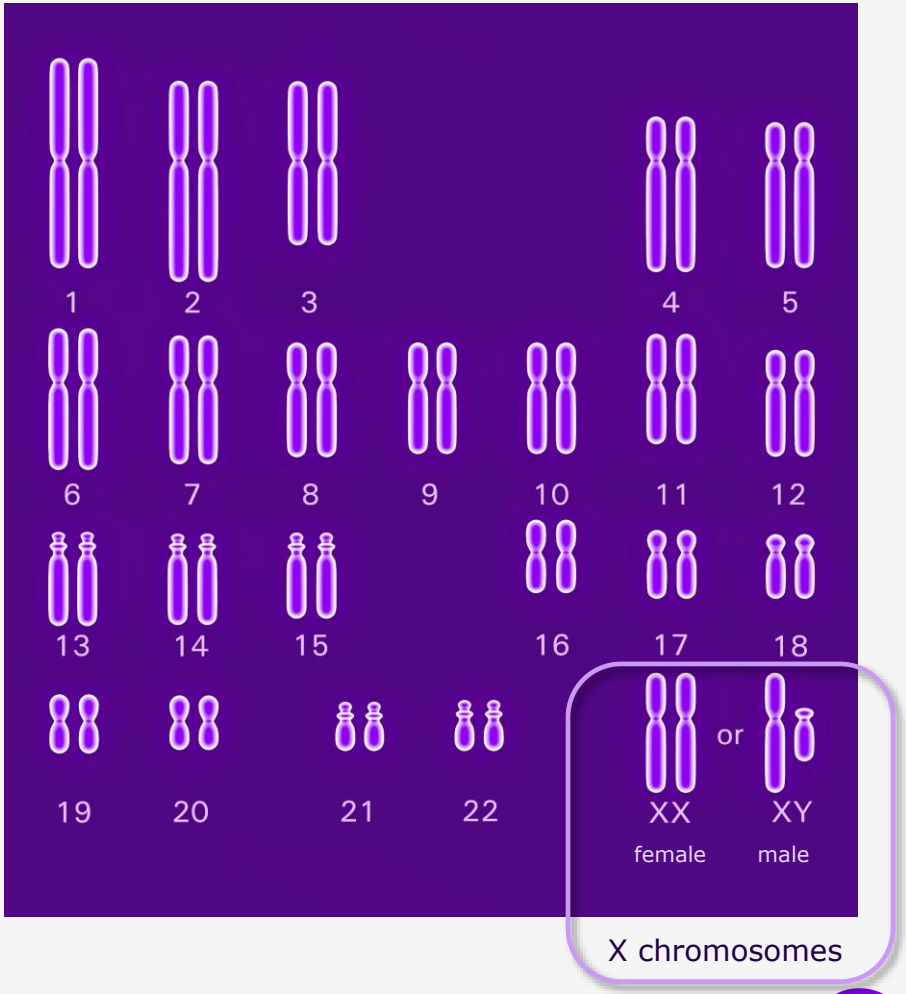
Genetic Basis of Hemophilia

An X-Chromosome–Linked Disorder

Role of genetic mutations

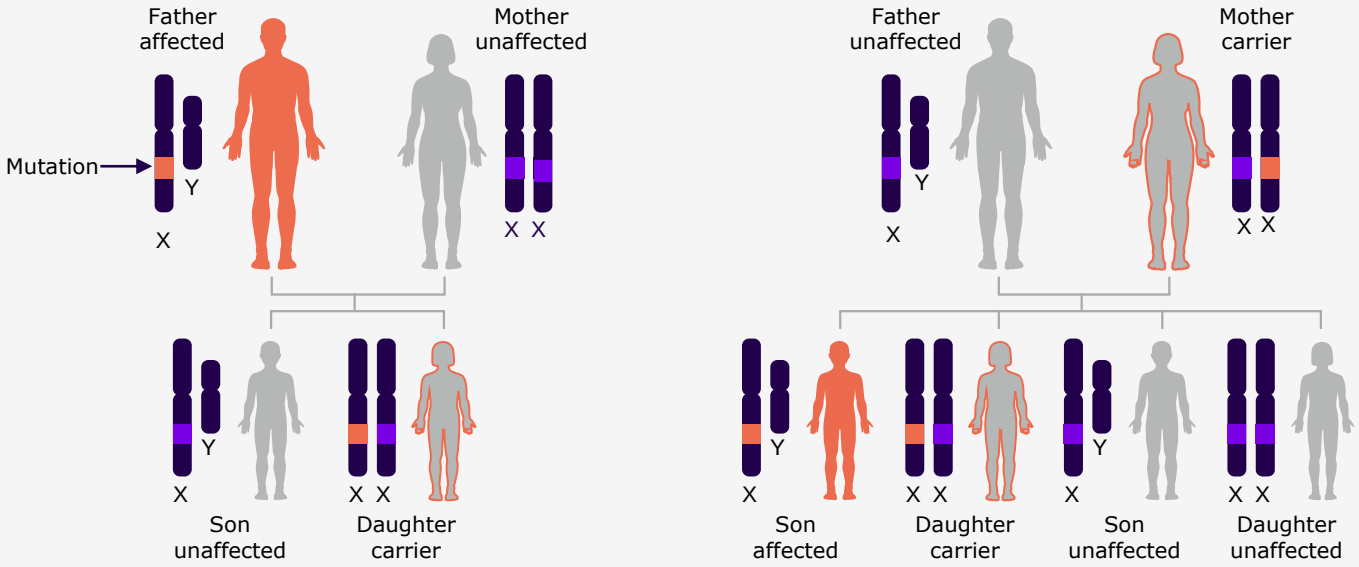
- The *F8* gene contains the genetic code needed to produce FVIII; mutations, or variants, in this gene cause hemophilia A.
- The *F9* gene contains the code needed to produce FIX; variants in this gene cause hemophilia B.
- Mutations result in missing or dysfunctional clotting factor. Some mutations can largely eliminate the activity of FVIII or FIX, thus resulting in severe hemophilia. Other mutations may reduce but not eliminate factor activity and are associated with milder forms of the disease. Thus, hemophilia A and B are **heterogenous** disorders, influenced by a breadth of possible mutations that result in differing factor activity levels and disease severities.
- Both *F8* and *F9* genes are located on the **X chromosome**; thus, hemophilia is an X-linked disorder.
- Males have only one X chromosome, whereas females have two. For this reason, a variant form of *F8* or *F9* generally results in hemophilia in males, but not in females.

Human chromosome pairs



Hereditary Pattern

X-Linked Recessive Inheritance



X-linked recessive pattern, explained

In X-linked **recessive** inheritance, males carrying a disease-causing mutation will be affected with the disease because they have only one X chromosome. Females carrying the mutation on one X chromosome, with a normal gene on the other, are generally unaffected (called carriers).

Affected fathers cannot pass the trait of hemophilia to their male children, but will produce daughters who are carriers of the variant on one of their X chromosomes. A male child with hemophilia is born from a mother who carries the *F8* or *F9* variant on one of her X chromosomes and then passes that affected chromosome to him. In rare cases, females can have both X chromosomes affected, or one affected and the other inactive, and may therefore show signs of hemophilia.

Acquired Hemophilia

A Rare, Non-Inherited Form of Hemophilia

An autoimmune disorder

Acquired hemophilia is a rare **autoimmune** disorder, with an incidence rate of 1.5 to 2 cases per million per year (rates from the UK and Canada, respectively). It is caused by the development of **immunoglobulin** G (IgG) **autoantibodies** against one of the clotting factors (these antibodies are called **inhibitors**). Thus, unlike the more common genetic, congenital form of hemophilia, individuals are not born with the acquired form.

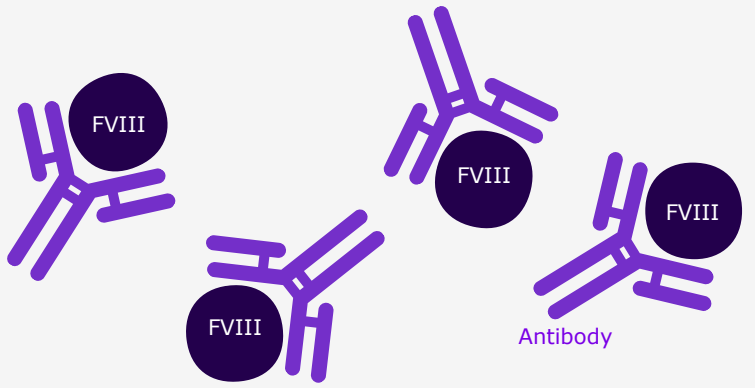
In the vast majority of affected patients, the inhibitors in acquired hemophilia are directed against factor VIII, rather than factor IX or other clotting factors.

Acquired hemophilia occurs with similar frequency in males and females, and incidence greatly increases with age, with a median age at onset of 75 to 78 years. Individuals may be predisposed by factors such as other autoimmune disorders, infections, pregnancy, cancer, and medications. The cause of acquired hemophilia is undetermined in about half of cases.

Affected individuals experience abnormal bleeding into muscles, skin, and soft tissue either spontaneously or in response to trauma or surgery. Bleeding severity varies but can be severe or life-threatening. Common bleeds include the following:

- Nose bleeds
- Bruising
- Hematomas
- **Hematuria**
- GI or **urogenital** bleeding

Unlike congenital hemophilia A and B, individuals with acquired hemophilia do not usually exhibit bleeding into the joints.



04 Diagnosis of hemophilia

Overview

Laboratory tests

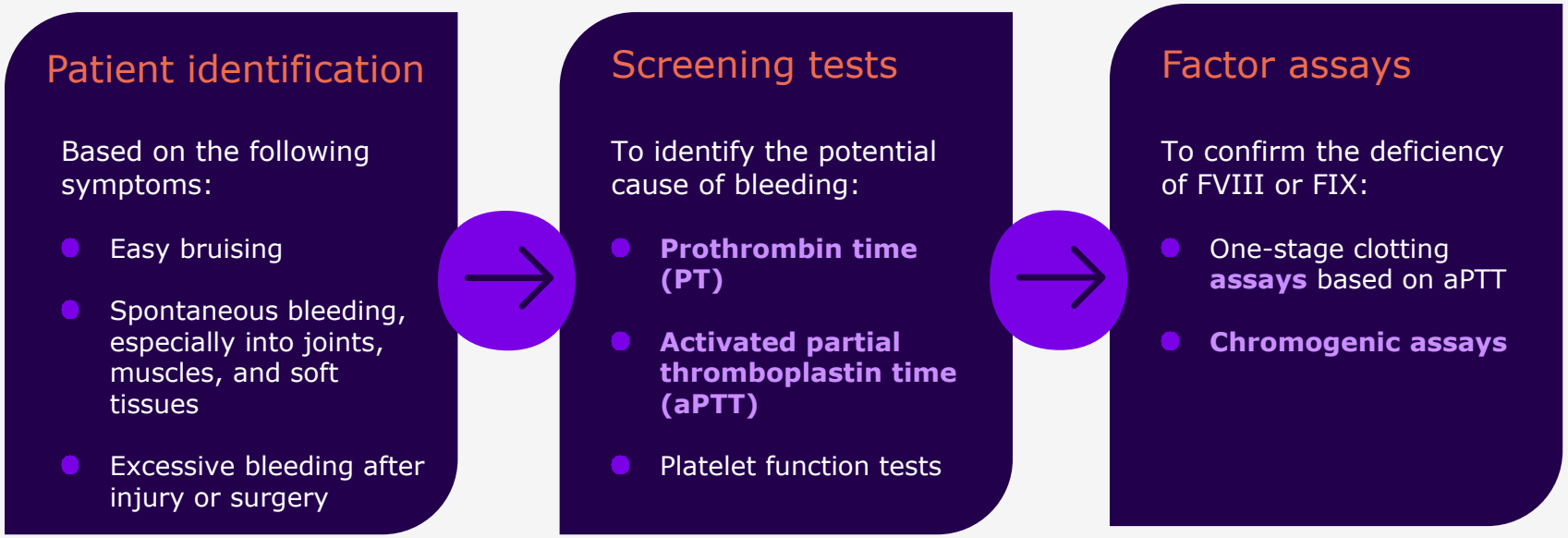
Hemophilia severity classification

Differential diagnosis

Genetic assessment

Diagnosis of Hemophilia

Overview



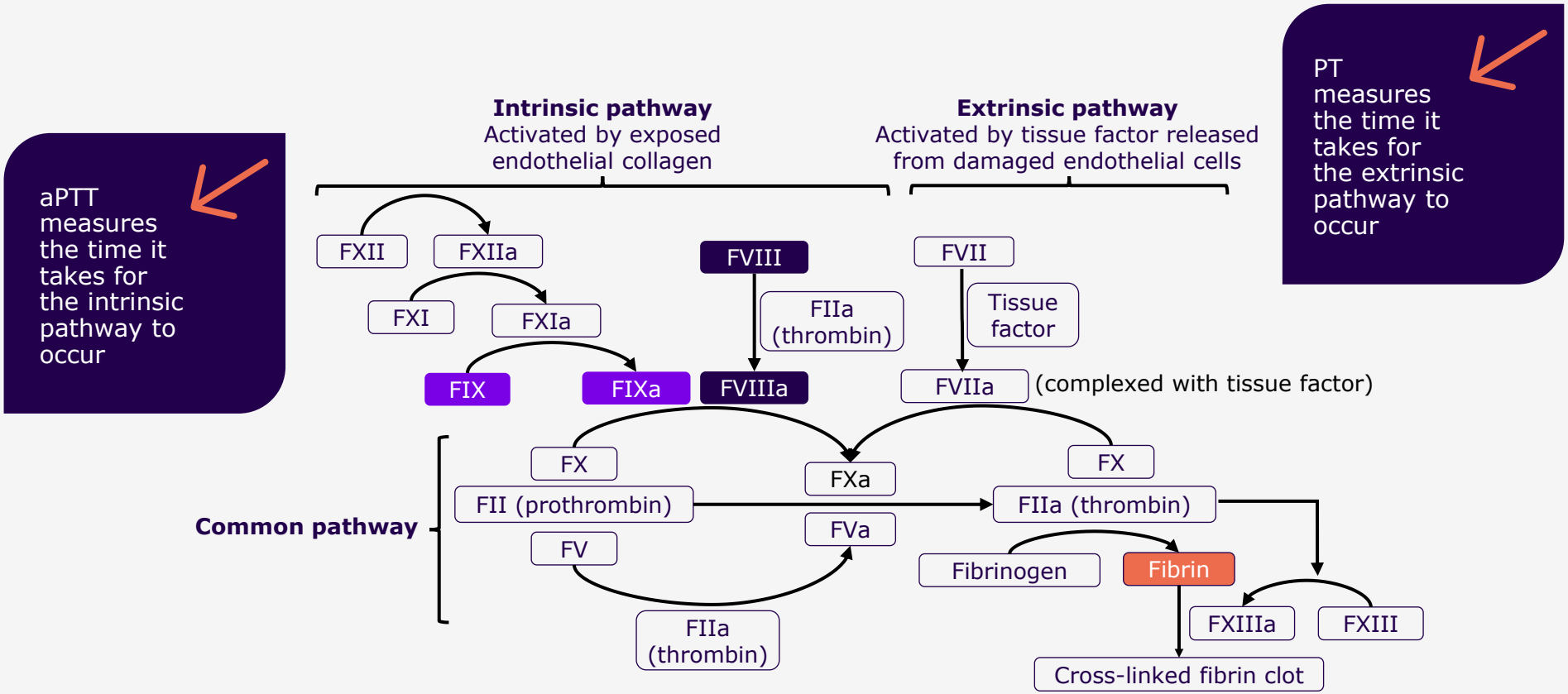
Patient identification—a stepped approach to diagnosis

Patients suspected of having hemophilia are identified based on symptoms of bleeding, including easy bruising, bleeding with no apparent cause, or excessive bleeding as a result of trauma or surgery. The bleeding history for these patients should be obtained, as well as any family history of abnormal bleeding to assess the potential of inherited disease. Once identified, screening tests are used to help determine the potential cause of bleeding. After other causes are ruled out and hemophilia is suspected, factor assays confirming reduced or missing FVIII or FIX activity are necessary for a definitive diagnosis of hemophilia.

Screening Tests

Evaluation of Intrinsic Versus Extrinsic Pathways

The prothrombin time (PT) is used to measure the time needed for clotting via the extrinsic pathway, whereas the activated partial thromboplastin time (aPTT) reflects the time needed for clotting via the intrinsic pathway. Thus, in patients with hemophilia, the PT is expected to be normal and the aPTT prolonged. However, a prolonged aPTT can also occur in other clotting disorders (eg, deficiencies of FXI or FXII). Thus, aPTT is not a definitive test for hemophilia.



Screening Tests

Interpretation

	Possible diagnosis			
	Normal	**Hemophilia (A or B)**	**von Willebrand disease**	**Platelet defect**
PT	Normal	Normal	Normal	Normal
aPTT	Normal	Prolonged	Normal or prolonged	Normal
Platelet count	Normal	Normal	Normal or reduced	Normal or reduced

aPTT, activated partial thromboplastin time; PT, prothrombin time.

Screening tests are suggestive, not definitive

The PT, aPTT, and platelet count are screening blood tests used in patients suspected of having a bleeding disorder. Patients with hemophilia A or B will generally have a prolonged aPTT but normal PT and platelet count. However, patients with mild hemophilia may have an aPTT within the reference (normal) range; thus, aPTT cannot rule out the disorder in patients for whom there is strong clinical suspicion of hemophilia (eg, suggestive symptoms, family history).

Another coagulation disorder, **von Willebrand disease (VWD)**, can present with findings similar to hemophilia on screening tests. Patients with VWD are deficient in VWF, the clotting protein that plays an important role in primary hemostasis. VWF also affects secondary hemostasis by acting as a carrier protein for FVIII in the circulation, protecting FVIII from degradation and thus prolonging its half-life, or active time in the body. When VWF is deficient, FVIII is more rapidly cleared from the body, causing a secondary deficiency of FVIII. More information on distinguishing hemophilia from VWD will be presented later, in the Differential Diagnosis section.

Platelet defects are associated with disorders of primary hemostasis.

Factor Assays

One-Stage and Chromogenic Assays

The one-stage clotting assay and the two-stage chromogenic factor activity assay (aka, chromogenic assay) measure FVIII and FIX activity levels. These assays are used for diagnosis and severity classification of hemophilia, monitoring of hemophilia therapy efficacy, potency labeling of factor replacement therapies, and detection of antibodies (inhibitors) to FVIII and FIX.

One-stage clotting assay

Based on the aPTT, this test reflects the functionality (time needed for clot formation) of the intrinsic and common pathways.

Specifically, it measures the ability of a patient's plasma sample to correct (shorten) the prolonged coagulation time (aPTT) of FVIII- or FIX-deficient reagent plasma.

- The most common assay used in labs
- Prone to variability in results based on the reagents used or the presence of interfering substances (anticoagulants or inhibitors)
- Requires serial dilutions and factor-deficient plasma
- Can measure FVIII, FIX, FXI, and FXII activity
- Guideline recommended for the diagnosis of both hemophilia A and B

Chromogenic assay

This two-stage assay measures the amount of functional clotting factor in a patient's plasma sample according to its ability to generate FXa.

Stage 1: A plasma sample is mixed with FX and other reagents, resulting in activation of the FX.
Stage 2: A chromogenic substrate added to the FXa produces a colored product—the color intensity of which reflects the amount of FXa generated, and thus, the amount of functional clotting factor in the sample.

- Less widely available, slower, and more technically complex and expensive than one-stage clotting assay, but less variability in results
- Does not require serial dilutions or factor-deficient plasma
- Can measure FVIII or FIX activity
- Guideline recommended for the diagnosis of hemophilia A only; current evidence is insufficient to support its use in diagnosis of hemophilia B

Hemophilia Severity Classification

Based on Degree of FVIII or FIX Deficiency

Diagnostic threshold for hemophilia

- Hemophilia is diagnosed in individuals with coagulation factor levels (FVIII or FIX) less than 40 IU/dL, or less than 40% of normal.

Patient classification	Coagulation factor level[a]	Bleeding manifestations
Healthy individuals	50–150 IU/dL (0.50–1.50 IU/mL) 50% to 150% of normal	No unusual bleeding
Mild hemophilia A or B	5–40 IU/dL (0.05–0.40 IU/mL) 5% to <40% of normal	Severe bleeding with major trauma or surgery; rare spontaneous bleeding
Moderate hemophilia A or B	1–5 IU/dL (0.01–0.05 IU/mL) 1% to 5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Severe hemophilia A or B	<1 IU/dL (<0.01 IU/mL) <1% of normal	Spontaneous bleeding into joints or muscles, often without an identifiable cause

[a]1 IU is equal to the concentration of coagulation factor in 1 mL of normal pooled plasma.

The term "near normal" can be used to describe values that fall between 40%-50%.

Differential Diagnosis

von Willebrand Disease

VWD and its subtypes

VWD is an inherited bleeding disorder that affects up to 1% of the population in the United States. VWD is caused either by abnormal (dysfunctional) VWF or an insufficient amount of normal VWF and is thus divided into subclasses depending on whether the VWF deficiency is qualitative or quantitative.

VWD subtype	VWF deficiency	Description
Type 1	Quantitative, partial absence	Patients have reduced levels of normal VWF (mildest and most common form of VWD)
Type 2	Qualitative	Patients have a normal amount of VWF, but it is dysfunctional
		2A reduced or absent high-molecular-weight VWF; results in decreased VWF binding to platelets
		2B VWF has increased affinity for platelets; can result in **thrombocytopenia**
		2M VWF has reduced binding to platelets or collagen
		2N VWF has reduced binding to FVIII, resulting in premature clearance of FVIII and low FVIII levels
Type 3	Quantitative, complete absence	Patients have virtually absent VWF and an associated FVIII deficiency (most severe and rarest form of VWD)

VWD, von Willebrand disease; VWF, von Willebrand factor.

Like hemophilia A, type 2N VWD (Normandy type) is characterized by normal VWF levels and low FVIII levels. Thus, hemophilia management guidelines recommend that all patients with reduced FVIII activity and a possible diagnosis of hemophilia A should have a full laboratory assessment to rule out VWD, with particular emphasis on distinguishing type 2N VWD from mild hemophilia A.

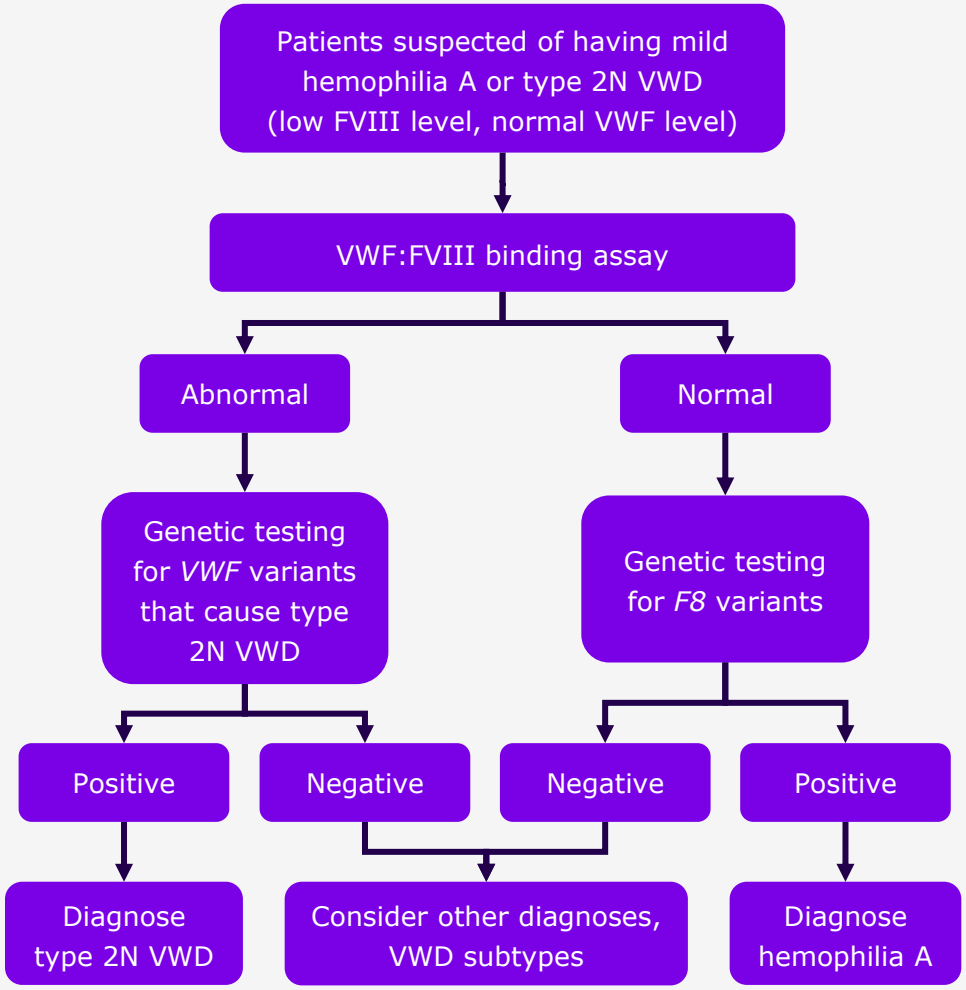
Differential Diagnosis

VWD Versus Hemophilia A—a Diagnostic Algorithm

There are two suggested laboratory tests used to differentiate hemophilia A from type 2N VWD:

- VWF:FVIII binding (VWF:FVIIIB) assay, which tests the capacity of a patient's VWF to bind FVIII. It is normal in patients with hemophilia A and abnormal in patients with type 2N VWD.
- Genetic testing, which involves analysis of the genes responsible for producing FVIII (*F8*) and VWF (*VWF*). Genetic variants in *F8* indicate hemophilia A, whereas variants in *VWF* indicate VWD.

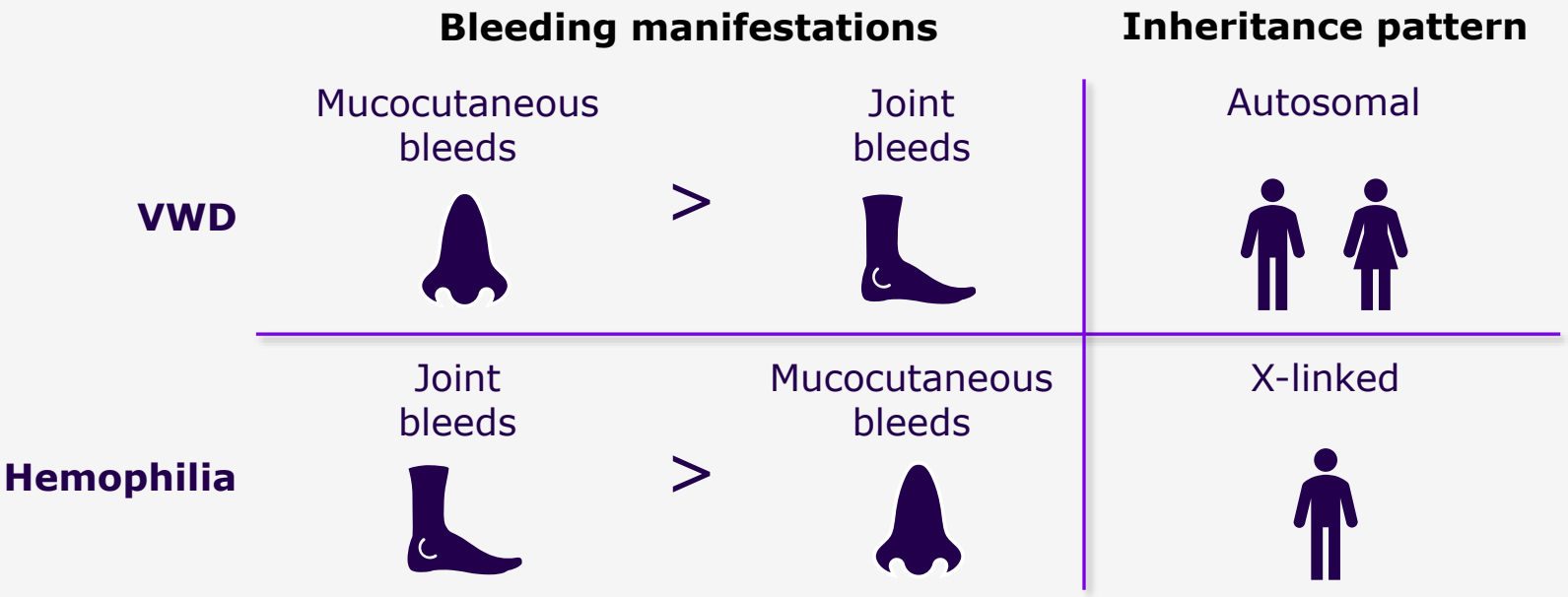
The two tests are considered complementary in the diagnostic evaluation of patients, and neither represents a preferred test. The flowchart to the right gives an example of testing use and interpretation.



VWD, von Willebrand disease; VWF, von Willebrand factor.

Differential Diagnosis

VWD versus Hemophilia A—Differences in Presentation



Differences in patient presentation

Unlike hemophilia, VWD is mainly characterized by excessive **mucocutaneous** bleeding (eg, nosebleeds, heavy menstrual bleeding and bleeding after childbirth, prolonged bleeding from the mouth [especially after dental work], GI bleeding, and easy bruising). However, similar to hemophilia, patients with VWD can demonstrate excessive bleeding after surgery, and **musculoskeletal** bleeding (eg, joint or muscle bleeds) can occur in more severe cases.

Because VWD is inherited in an **autosomal** pattern rather than X-linked, females can be affected.

Genetic Assessment

Identifying Causative Mutations

The role of genetic assessment

Genetic testing is used in patients with hemophilia to identify the underlying mutation in the *F8* gene (hemophilia A) or *F9* gene (hemophilia B). This testing is able to identify the causative variant in more than 95% of patients—approximately 2100 causative mutations in the *F8* gene and 1100 mutations in the *F9* gene have been identified to date.

Genetic assessment as standard care

Genetic assessment in patients with hemophilia has become part of the standard of care, and hemophilia management guidelines recommend that it be routinely offered to affected individuals and their at-risk female family members.

Genetic testing in patients with hemophilia has multiple purposes:

- Define disease biology
- Establish diagnosis in difficult cases
- Identify female carriers
- Provide prenatal diagnosis
- Determine the risk of inhibitor development

05 Summary

Hemophilia A and B

Hemophilia is a bleeding disorder resulting from the partial or complete lack of coagulation factor VIII (hemophilia A) or IX (hemophilia B). The deficiency is caused by a mutation in the associated gene that is found on the X chromosome (*F8* produces FVIII; *F9* produces FIX). Because hemophilia is an X-linked disorder, it generally only affects males. Hemophilia A is the most common form, affecting approximately 80% of patients with hemophilia.

Clinical manifestations

Hemophilia causes excessive, prolonged bleeding after injury or surgery, or sometimes for no obvious reason. Bleeding can happen anywhere in the body, but is most common in joints, which account for roughly three-fourths of bleeds. Recurrent joint bleeds ultimately lead to progressive damage of the associated cartilage and bone, known as chronic hemophilic arthropathy, a major burden for patients with hemophilia. Muscle bleeds are also common, resulting in pain, swelling, and functional impairment of the affected muscle.

Collectively, the bleeding manifestations of hemophilia impose substantial quality-of-life burdens, including chronic pain and impaired mobility, in affected patients.

Pathophysiology

Factors VIII and IX are central to the intrinsic pathway of secondary hemostasis. Without sufficient FVIII or FIX, a patient cannot generate the fibrin needed for adequate blood clot formation in response to a hemostatic challenge, or injury.

Diagnosis

For patients suspected of having hemophilia, a prolonged activated partial thromboplastin time (aPTT) is suggestive of the disorder, and a factor assay demonstrating FVIII or FIX activity of less than 40% of normal (<40 IU/dL) confirms the diagnosis. In patients for whom testing indicates hemophilia A, further laboratory analysis is needed to rule out type 2N von Willebrand disease.

The severity of hemophilia correlates with the degree of coagulation factor deficiency, with severe disease defined as a factor level below 1% of normal (<1 IU/dL).

In patients with hemophilia, genetic testing can be performed to identify the causative *F8* or *F9* mutation. Among other uses, this can serve to definitively establish the diagnosis in difficult cases and is considered part of the standard of care.

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07 Glossary

Glossary

Activated partial thromboplastin time (aPTT)	A test that measures the time needed for clotting via the intrinsic pathway; a prolonged time may indicate several disorders, including possible deficiencies in coagulation factors VIII, IX, XI, or XII.
Ankylosed	Stiffened, fixed in place.
Arthropathy	Joint disease.
Assay	Analysis of a substance to determine its parts and the relative amounts of each.
Autoantibody	An antibody that targets the body's own tissue (the targeted tissues are called self-antigens or autoantigens).
Autoimmune	Pertaining to an immune response against the body's own tissue (self-antigens or autoantigens).
Autosomal	Pertaining to autosomes, which are any chromosomes other than the sex (X and Y) chromosomes.
Central line	Also called a central venous catheter, a catheter that is passed through a peripheral or central vein to ultimately reach the right side of the heart or the vena cava, the large vein that empties into the right heart. A central line has several uses, including the infusion of certain types of concentrated solutions and medicines.
Chromogenic assay	A laboratory test that uses color change to identify the presence of a substance.
Clotting factor	Components of plasma involved in the process of forming a blood clot. Synonymous with coagulation factor.

Glossary

Coagulation	Formation of a blood clot.
Coagulation cascade	A series of successive steps beginning with the intrinsic or extrinsic pathways and progressing through the common pathway to the formation of a fibrin-stabilized blood clot. Each step involves activation of a proenzyme (an inactive precursor), which then catalyzes activation of the next proenzyme in the cascade. Also called the clotting cascade.
Coagulation factor	Any of various components of blood involved in the process of forming a blood clot. Synonymous with clotting factor.
Cofactor	A substance, such as a coenzyme, that must act in conjunction with another to perform a given function.
Collagen	Any of a group of related extracellular proteins that make up a major component of connective tissue.
Congenital	Present in an individual at birth.
Endothelial cells	Flat cells lining blood vessels; collectively, this layer of cells is known as the endothelium.
Extracranial	Outside of the cranium, which is the large round part of the skull enclosing the brain.
Fibrin	A filament-like protein formed from the action of thrombin on fibrinogen in the final stage of coagulation. Fibrin is deposited as interlacing filaments that enmesh blood cells and platelets to form a blood clot.

Glossary

Fibrosis	Repair of inflamed tissue by replacement with connective tissue; ultimately, the replacement of normal tissue with scar tissue.
Gastrocnemius	The large muscle of the calf.
Half-life	The time needed for the body to breakdown and clear half of the administered dose of a drug; an important consideration in determining proper drug dosage (amount and frequency of administration).
Hemarthrosis	Bleeding into a joint.
Hematoma	A swelling of blood outside of a blood vessel, resulting from a break in the vessel.
Hematuria	Blood in the urine.
Hemostasis	Arrest, or cessation, of bleeding.
Heterogenous	Varied, not uniform.
Iliopsoas	A deep muscle group that connects the spine to the legs through the pelvis; composed of the iliacus, psoas major, and psoas minor muscles.
Immunoglobulin (Ig)	Any of a group of related proteins that function as antibodies; divided into 5 classes based on structure and function (IgM, IgG, IgA, IgD, and IgE).

Glossary

Inhibitor	Immunoglobulin G (IgG) antibodies that develop either against exogenous clotting factor (in patients with congenital hemophilia) or endogenous clotting factor (in patients with acquired hemophilia). (Exogenous clotting factor is made outside of the body and administered/infused; endogenous clotting factor is produced naturally in the body). Inhibitors are a serious complication because they neutralize the activity of clotting factors, making bleed control difficult.
Mediator	A substance released from cells that causes a physiologic change or consequence.
Mucocutaneous	Pertaining to the mucous membranes and the skin.
Mucous membranes	Membrane that lines body passages or cavities that are in contact with the outside of the body, such as the digestive tract.
Muscle contracture	Static shortening of a muscle due to fibrosis or loss of motion of the adjacent joint.
Musculoskeletal	Pertaining to the bones of the skeleton as well as muscles.
Mutation	A permanent change in genetic material, usually in a single gene, that is transmissible.
Platelets	Round or oval-shaped disks found in the blood that are needed for blood clotting and hemostasis; they are fragments of megakaryocytes, which are large cells found in the bone marrow.
Prothrombin time (PT)	A test that measures the time needed for clotting via the extrinsic pathway; a prolonged time may indicate several disorders, including possible deficiencies in coagulation factors II, V, VII, or X.

Glossary

Pseudotumor	A serious complication of inadequately treated muscle or soft-tissue bleeds, these enlargements can create pressure on nearby nerves or blood vessels, with the potential to cause fractures, loss of limbs, or death.
Recessive	In genetics, a trait that is expressed only if it is present in the genes inherited from both parents.
Synovial membrane	Lining of the joint cavity. Also called the synovium.
Synovitis	Inflammation of the synovial membrane, which lines the joint cavity.
Thrombin	The activated form of prothrombin; among other functions, it converts fibrinogen to fibrin, which is essential for blood clot formation.
Thrombocytopenia	An abnormally low number of platelets in the circulating blood.
Urogenital	Pertaining to the genital and urinary body systems; also known as genitourinary.
Venipuncture	Puncture of a vein, usually to draw blood.
von Willebrand disease (VWD)	A congenital bleeding disorder characterized by deficiency in von Willebrand factor (VWF) caused by a genetic mutation in the gene encoding VWF. Affected patients have a prolonged bleeding time and common symptoms include nose bleeds, prolonged menstrual and postpartum bleeding, as well as increased bleeding after trauma or surgery.

Glossary

von Willebrand factor (VWF)	A protein that promotes platelet adherence to injured blood vessels during the formation of blood clots; deficiency results in von Willebrand disease (VWD).
X chromosome	One of the sex chromosomes; present in two copies in females and one copy in males.