

Hemophilia A

Factor VIII deficiency

Mechanism • Inheritance • Bleeding phenotype • Diagnosis

Pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain why factor VIII deficiency impairs secondary hemostasis.
- Connect X-linked inheritance and F8 mutations with clinical severity.
- Recognize hemarthrosis and deep-tissue bleeding patterns.
- Interpret the PT, PTT, and factor VIII-specific assay results.
- Relate replacement, bypass therapy, and inhibitors to mechanism.

Hemophilia A: Core definition

An inherited factor VIII defect that compromises the factor IXa–VIIIa complex and causes potentially life-threatening bleeding.

- Usually inherited in an X-linked recessive pattern.
- Residual functional factor VIII activity largely determines severity.

Where hemophilia A fits among bleeding disorders

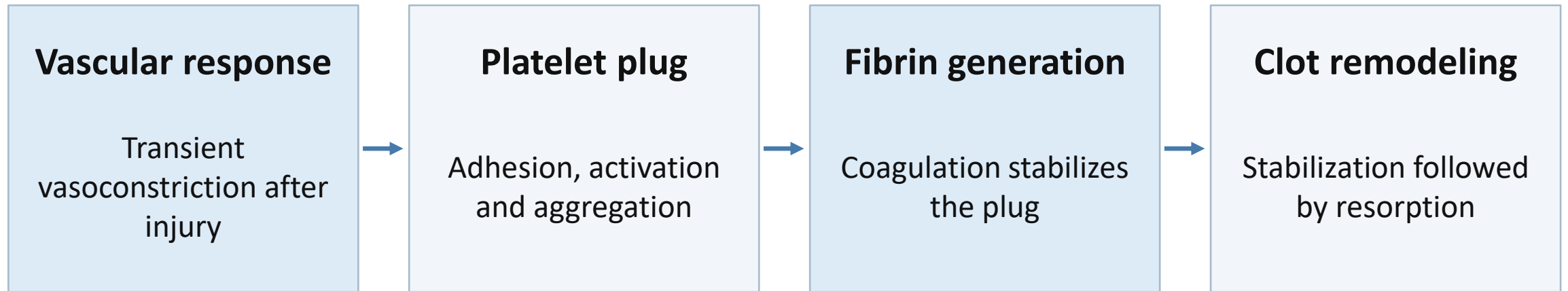
Defective primary hemostasis

- Platelet number or function is abnormal.
- Typical bleeding is mucocutaneous.
- Petechiae or small skin hemorrhages are characteristic.

Defective secondary hemostasis

- Coagulation factor activity is deficient.
- Bleeding commonly occurs in deep tissues and joints.
- Hemophilia A is a prototype of this pattern.

The phases of normal hemostasis

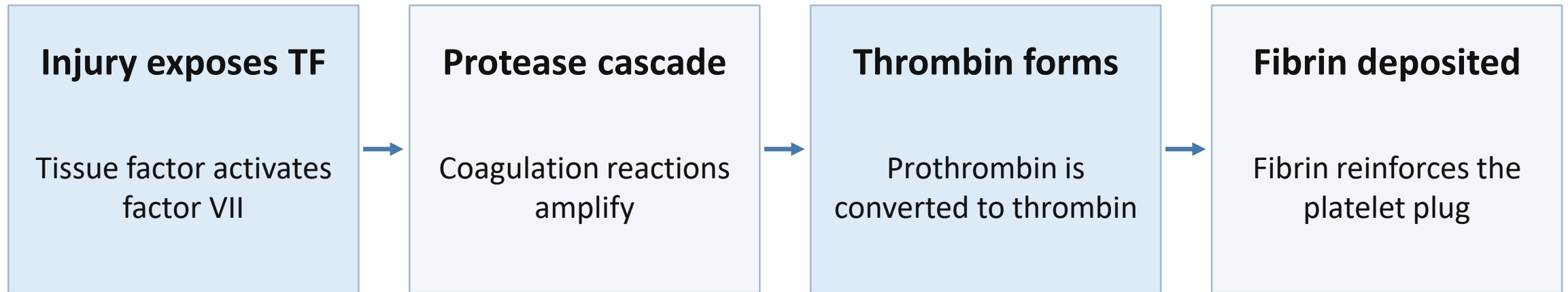


Factor VIII acts in the fibrin-generating, secondary-hemostasis phase.

Primary hemostasis: The initial platelet plug

- Endothelial disruption exposes subendothelial collagen and vWF.
- Platelet GpIb binds vWF to support initial adhesion.
- Platelet activation changes shape and recruits further platelets.
- GpIIb/IIIa and fibrinogen support platelet aggregation.

Secondary hemostasis: Stabilization by fibrin



An initially formed platelet plug is not sufficient for stable hemostasis.

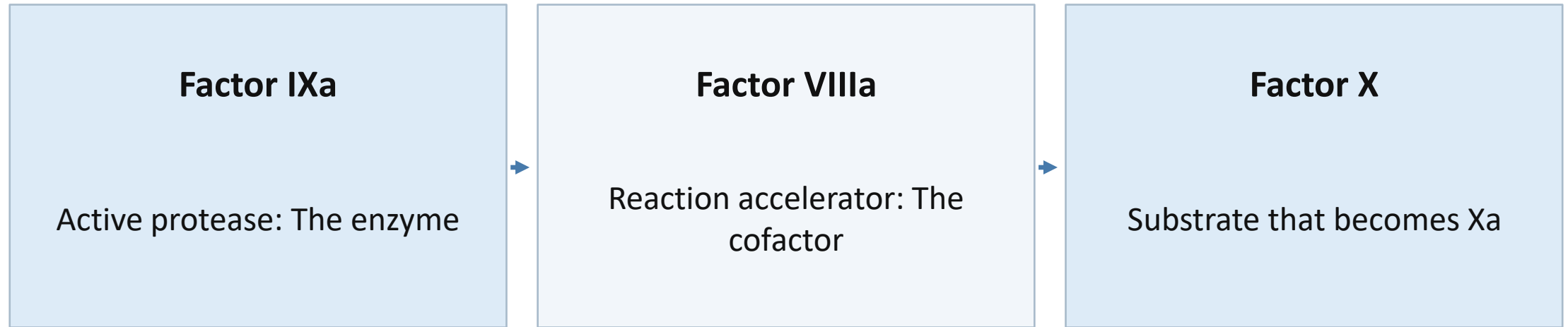
Two hemostatic defects; Two clinical signatures

Platelet / vWF defect	Small-vessel skin or mucosal bleeding; Petechiae, purpura, epistaxis.
Coagulation factor defect	Soft-tissue hematoma, hemarthrosis, or prolonged postsurgical bleeding.
Why this matters	A bleeding pattern provides an early clue to the defective hemostatic component.

The coagulation cascade is assembled on surfaces

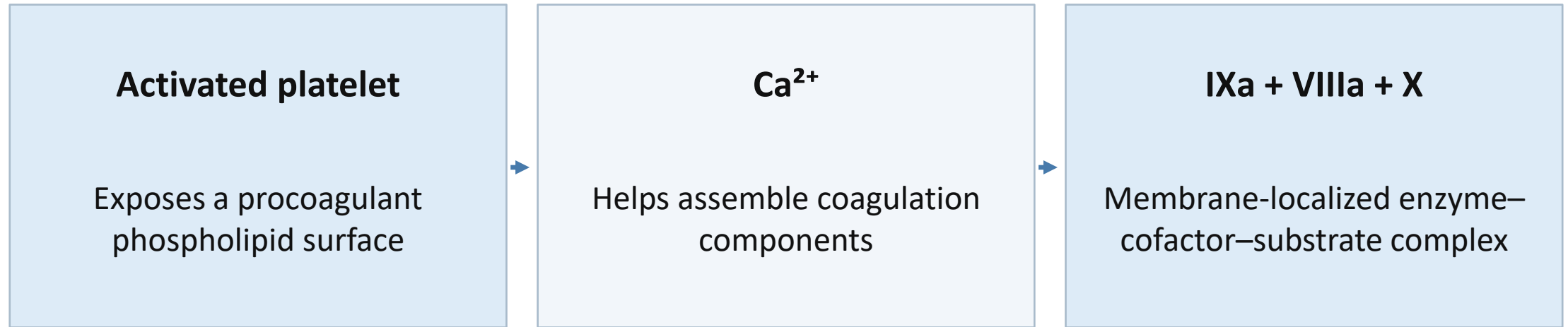
- Activated clotting factors are enzymes acting on substrate proteins.
- Nonenzymatic cofactors accelerate specific proteolytic reactions.
- Activated platelets provide negatively charged phospholipid surfaces.
- Calcium contributes to assembly of membrane-bound complexes.

Factor VIIIa is a cofactor—not the protease



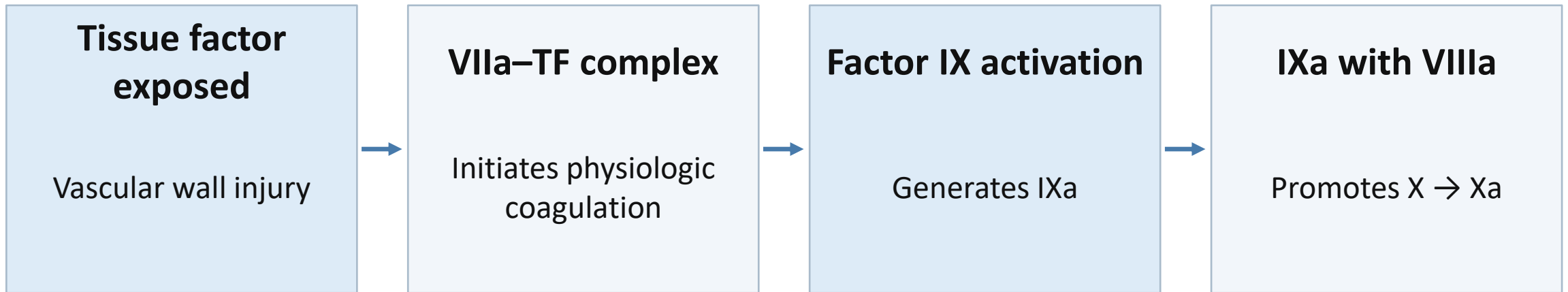
The assembled IXa–VIIIa complex promotes conversion of factor X to factor Xa.

Surface organization of the factor X-activating complex



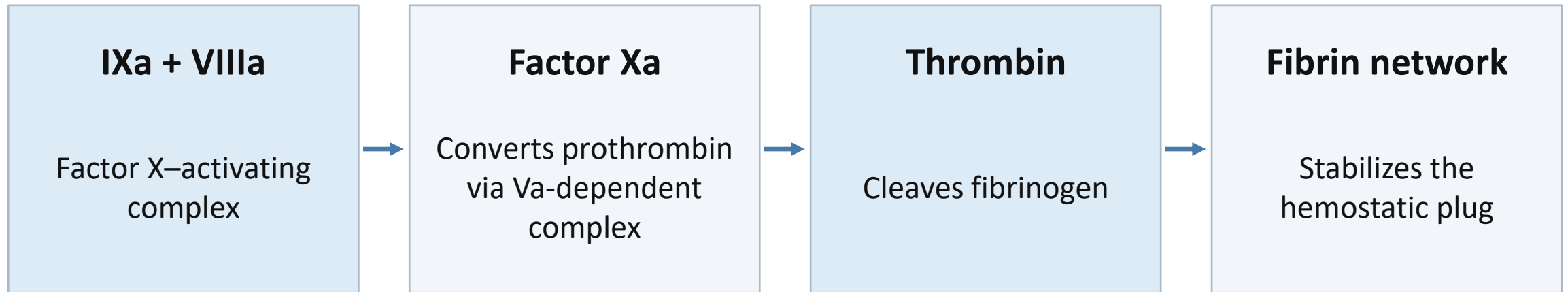
Correct assembly increases efficiency of factor X activation.

The major in-vivo route into factor IX activation



The in-vivo pathway is not identical to the isolated laboratory “intrinsic” pathway.

Downstream consequence of factor X activation



Deficient VIIIa reduces propagation of coagulation toward an effective fibrin clot.

Why factor VIII deficiency can cause major bleeding

The factor IXa–VIIIa complex is a principal activator of factor X during coagulation in vivo.

- A deficiency in a cofactor can be as consequential as loss of a protease.
- This explains why isolated factor VIII deficiency disrupts clot stabilization.

Laboratory cascade versus physiology

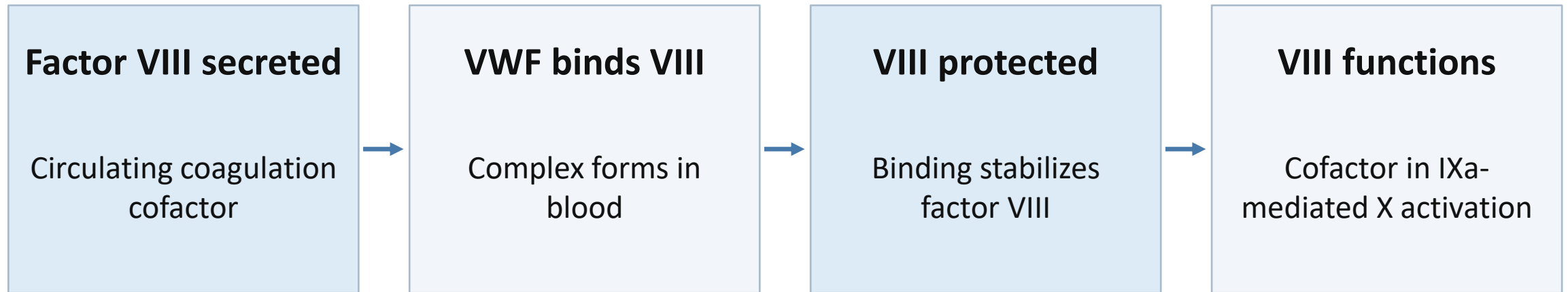
In laboratory assays

- PT measures the tissue-factor-initiated testing pathway.
- PTT interrogates the contact-activated testing pathway.
- These are functional plasma tests.

In living vessels

- Tissue factor is the major trigger.
- The IXa–VIIIa complex is central for factor X activation.
- Laboratory pathway labels are useful but incomplete models.

Factor VIII travels in plasma with vWF



VWF is a carrier and stabilizer of factor VIII, not its replacement in the coagulation reaction.

VWF binding prolongs factor VIII survival

A factor VIII half-life of approximately 2.4 hours without vWF stabilization versus 12 hours when bound to vWF.

- Loss of vWF may secondarily reduce circulating factor VIII.
- This helps explain how von Willebrand disease can affect both platelet function and PTT.

The vWF–factor VIII complex has two distinct roles

VWF: Platelet adhesion

- Subendothelial vWF can anchor platelets through GpIb.
- VWF connects injury-exposed matrix with platelets.
- Deficiency may cause mucocutaneous bleeding.

Factor VIII: Coagulation

- VIIIa supports IXa-driven factor X activation.
- Adequate factor VIII promotes fibrin formation.
- Deficiency produces a deep-tissue bleeding phenotype.

The defect in hemophilia A is specific

Factor VIII	Missing or dysfunctional cofactor for factor IXa.
Factor IX	Its role as protease is preserved if there is no independent deficiency.
VWF	Carrier protein is not the primary inherited lesion in hemophilia A.
Functional result	Inefficient X activation and inadequate secondary hemostasis.

Hemophilia A is caused by F8 gene mutations

Pathogenic alterations affecting the factor VIII gene reduce the amount or activity of functional factor VIII.

- The factor VIII gene lies on the X chromosome.
- Different mutations yield different residual factor VIII activities.

X-linked recessive inheritance

Pathogenic F8 allele

Located on the X chromosome



One X chromosome

Most males have no second F8 allele



Functional deficiency

A single pathogenic allele can produce disease

Hemophilia A mainly affects males, but symptomatic females also occur.

What a family history can reveal

- An affected male commonly has disease because his single F8 allele is pathogenic.
- Heterozygous females may transmit the altered X chromosome.
- Pedigree information supports—but does not establish—the diagnosis.
- A negative family history cannot exclude hemophilia A.

Carrier mother × unaffected father

Illustrative X-linked transmission: Maternal X^N / X^H and paternal X^N / Y

X^N / X^N Unaffected daughter	X^H / X^N Carrier daughter
X^N / Y Unaffected son	X^H / Y Affected son

Punnett square is a Mendelian educational inference, not patient-specific risk prediction.

Affected father × unaffected noncarrier mother

Illustrative X-linked transmission: Paternal X^H / Y and maternal X^N / X^N

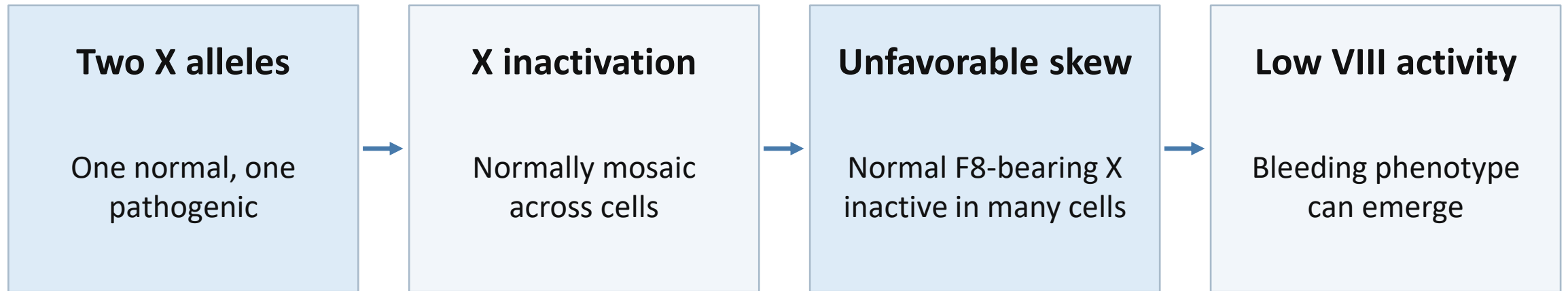
X^H / X^N Carrier daughter	X^H / X^N Carrier daughter
X^N / Y Unaffected son	X^N / Y Unaffected son

An affected father passes his X to daughters and his Y to sons.

How can a female have hemophilia A?

- Homozygosity for pathogenic F8 alleles can produce disease.
- Some heterozygous females experience excessive bleeding.
- Hemophilia A should not be considered categorically impossible in females.
- Clinical phenotype and factor VIII activity remain decisive.

Unfavorable lyonization in a heterozygous female



Skewed X inactivation is the explanation proposed by Robbins for some symptomatic carriers.

A negative family history is common enough to matter

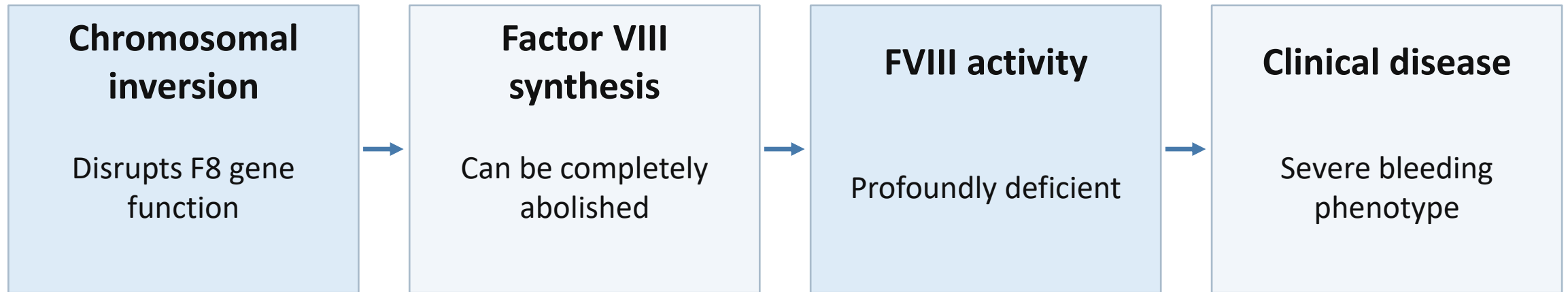
That approximately 30% of affected patients lack a family history and attributes their disorder to new mutations.

- Absence of affected relatives cannot rule out a congenital factor defect.
- Evaluation must rely on the phenotype and confirmatory factor VIII testing.

Allelic heterogeneity creates a severity spectrum

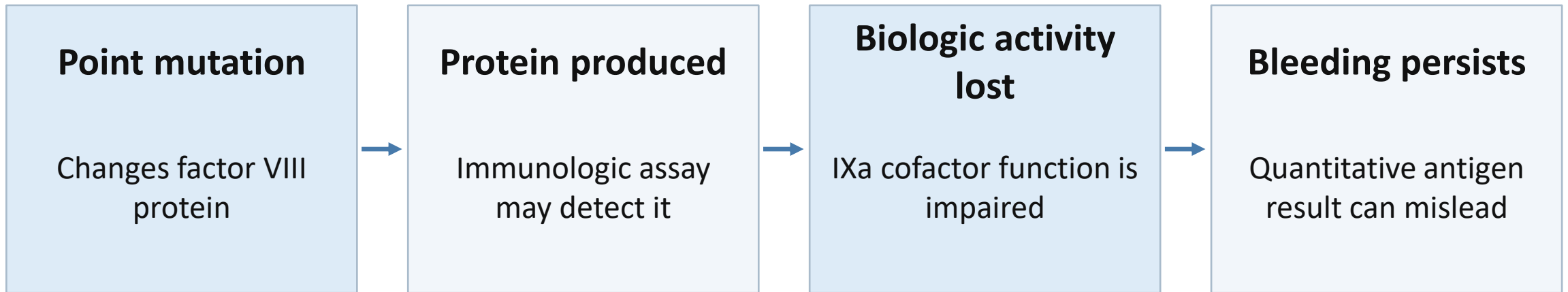
- Many different F8 mutations can cause hemophilia A.
- Some variants abolish production of factor VIII.
- Other mutations allow protein production but reduce its function.
- Variants preserving some active protein are associated with milder disease.

A severe mechanism: X-chromosomal inversion



The text associates its most severe deficiencies with inversions abolishing factor VIII synthesis.

A different mechanism: Nonfunctional factor VIII



The amount of protein detected does not always equal functional activity.

Antigen level is not equivalent to cofactor function

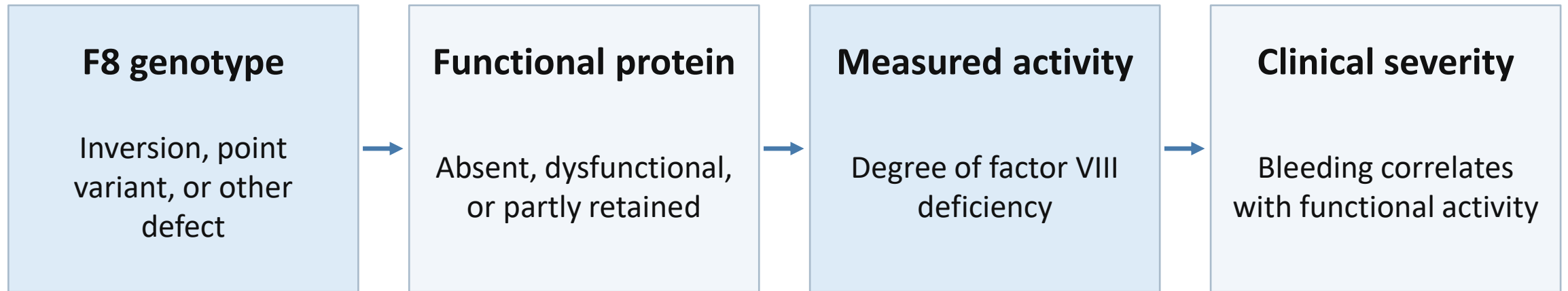
Immunologic measurement

- Detects the amount of factor VIII protein.
- A point-mutant protein may be present.
- Normal antigen does not guarantee normal hemostasis.

Functional activity assay

- Measures clotting activity attributable to factor VIII.
- Identifies functional cofactor deficiency.
- Needed to establish hemophilia A in the proper context.

Residual factor VIII activity determines phenotype



Severity cannot be inferred from gene status alone without functional information.

Robbins classification by factor VIII activity

Severe	< 1% of normal	Marked tendency to major bleeding
Moderately severe	2–5% of normal	Intermediate clinical severity
Mild	6–50% of normal	Bleeding may become evident with hemostatic challenge

The severity scale is a continuum

- Lower factor VIII activity generally predicts more severe bleeding.
- Not every patient has the same mutation or residual cofactor activity.
- Mild deficiency may remain clinically silent until a bleeding challenge.
- Activity measurement supplies a quantitative disease descriptor.

Severe hemophilia: Very low factor VIII activity

Severe disease is associated with factor VIII activity below 1% of normal in the supplied Robbins classification.

- Spontaneous deep-tissue and joint bleeding may occur.
- Trauma or surgery can precipitate major hemorrhage.

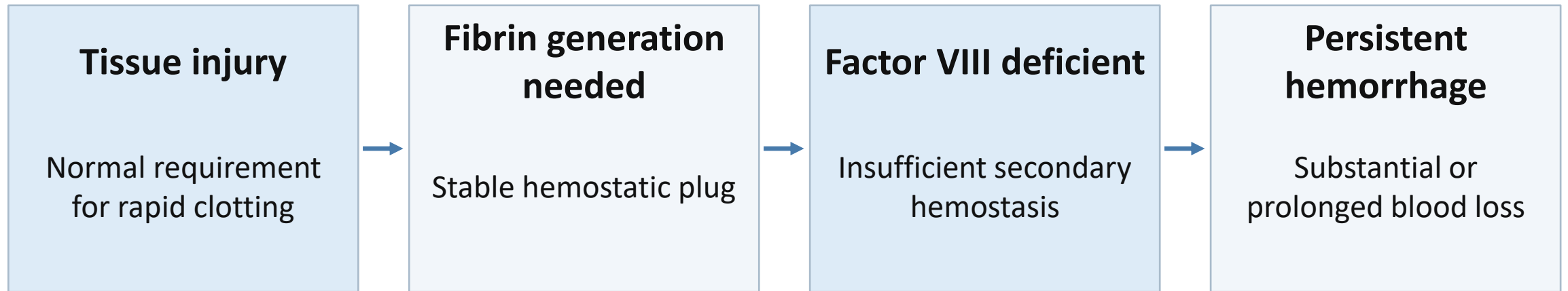
Intermediate factor VIII deficiency

- Robbins labels 2–5% activity as moderately severe disease.
- Bleeding severity lies between the severe and mild phenotypes.
- Clinical assessment must include previous spontaneous or injury-related bleeding.
- Measured activity connects the presentation to the mutation's functional effect.

Mild hemophilia A still carries procedural risk

- Robbins assigns 6–50% factor VIII activity to its mild category.
- Patients may not recognize their disorder without a major challenge.
- Dental work, trauma, or an operation can disclose an underlying deficiency.
- A mild baseline phenotype does not imply normal hemostatic reserve.

Trauma or surgery can expose a factor VIII defect



The source highlights massive hemorrhage after trauma or surgery.

A classic history: Prolonged bleeding after a procedure

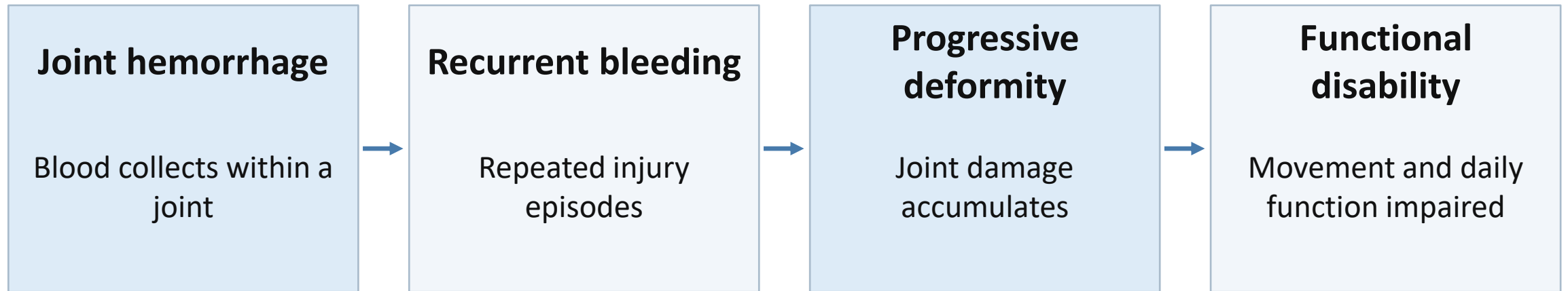
- Post-extraction or postsurgical bleeding suggests defective clot stabilization.
- Blood loss may continue despite initial platelet adhesion and aggregation.
- Repeated bleeding episodes support a significant coagulation factor defect.
- The anatomic pattern helps distinguish factor deficiency from platelet dysfunction.

Hemarthrosis is a defining clinical clue

Bleeding into a joint cavity is called hemarthrosis and is particularly characteristic of hemophilia.

- Joints experience repeated minor mechanical stress.
- Episodes may be described as spontaneous despite the absence of recognized trauma.

Repeated hemarthroses drive disability



Progressive disabling joint deformity as a complication.

Deep muscle and soft-tissue hemorrhage

- Secondary hemostatic defects predispose to deep soft-tissue bleeding.
- A hematoma represents localized extravasation and accumulation of blood.
- Muscle bleeding is an important part of the hemophilia phenotype.
- Large bleeds may follow an apparently minor injury.

Central nervous system bleeding is especially serious

The central nervous system is among the recognized sites of hemorrhage in severe coagulation-factor deficiencies.

- Clinical consequences depend strongly on the site of the bleeding.
- Neurologic bleeding represents a potentially fatal manifestation.

Why joints and muscles? An unresolved question

The precise explanation for preferential hemorrhage into joints, muscles, and the central nervous system remains uncertain.

- Common mechanical stress does not constitute a complete molecular explanation.
- Do not claim a proven tissue-specific mechanism that the source does not provide.

Bruising may be prominent, but interpret its pattern

- Hemophilia A may produce easy bruising and large posttraumatic ecchymoses.
- Deep hematomas are more suggestive than multiple pinpoint petechiae.
- Bleeding following a procedure deserves attention even without joint involvement.
- A characteristic phenotype guides, but cannot replace, laboratory testing.

Petechiae are characteristically absent

Unlike many platelet disorders, hemophilia A usually does not produce petechiae.

- Petechiae point toward small-vessel or primary hemostatic abnormalities.
- The negative finding helps localize a suspected bleeding defect.

Pattern recognition: Two patients who bleed

Patient with petechiae

- Numerous small skin or mucosal hemorrhages.
- Consider platelet number, platelet function, or vWF.
- Use the clinical context to select confirmatory tests.

Patient with hemarthrosis

- Deep joint bleeding following small stress or no clear trauma.
- Consider an intrinsic-pathway coagulation factor defect.
- Factor VIII and IX testing can distinguish common hemophilias.

Characteristic screening profile

Hemophilia A usually shows a prolonged PTT with a normal PT.

- This pattern points to a factor tested by the PTT assay.
- Factor VIII-specific testing is still required for diagnosis.

What does a prolonged PTT reflect?

- PTT assesses factors XII, XI, IX, VIII, X, V, II, and fibrinogen.
- Its initiation uses negatively charged surfaces, phospholipid, and calcium.
- Deficient factor VIII delays in-vitro fibrin clot formation.
- A prolonged PTT alone is not specific for hemophilia A.

Why is PT often normal?

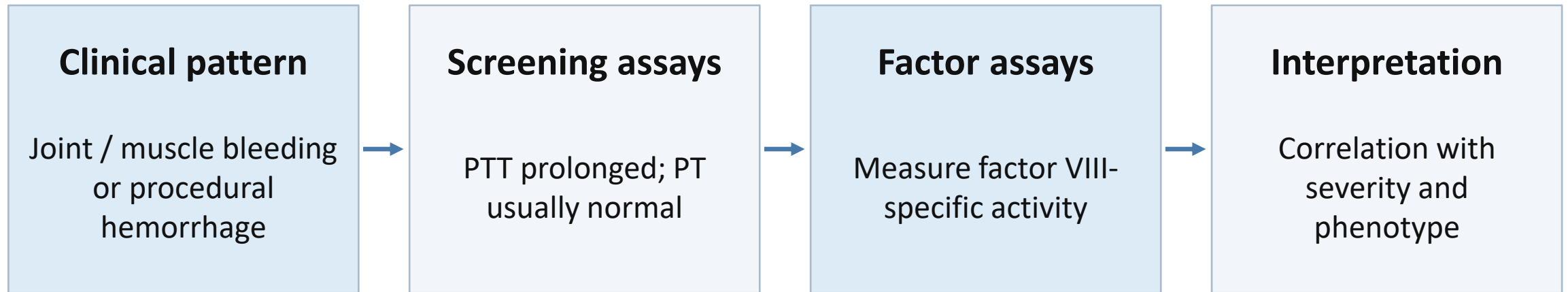
PT: Tested components

- Assesses factor VII and the common-pathway factors.
- Initiated with tissue factor in the laboratory.
- Factor VIII is not the defining component of PT.

PTT: Tested components

- Includes factor VIII and factor IX function.
- Hemophilia A selectively affects a PTT-dependent reaction.
- Normal PT plus prolonged PTT helps focus further investigation.

From bleeding history to confirmation



Screening narrows the possibilities; The factor VIII-specific assay establishes the defect.

A useful test hierarchy

PT and PTT	Show the pattern of abnormal coagulation; Do not specify the exact factor.
Factor VIII activity	Functional test required to diagnose and grade the deficiency.
Factor VIII antigen	Can be preserved despite loss of function in selected mutations.
Clinical correlation	Deep bleeding and inheritance reinforce the laboratory interpretation.

Hemophilia A and hemophilia B

Hemophilia A

- Deficiency of factor VIII cofactor.
- PT normal; PTT prolonged.
- Factor VIII activity assay identifies the defect.

Hemophilia B

- Deficiency of factor IX protease.
- Clinical phenotype can be indistinguishable.
- Factor IX-specific assay identifies the defect.

Hemophilia A versus von Willebrand disease

Hemophilia A

- Primary molecular lesion involves factor VIII.
- Dominant clinical clue: Deep-tissue and joint bleeding.
- Factor VIII cofactor activity deficient.

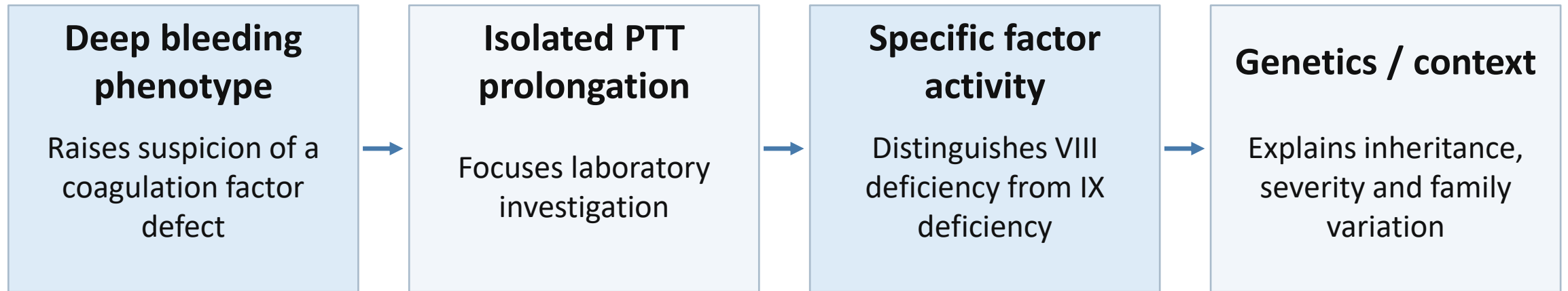
Von Willebrand disease

- Primary lesion involves vWF.
- Mucocutaneous bleeding often dominates.
- Factor VIII may fall because vWF normally stabilizes it.

Inherited versus acquired factor deficiencies

Hemophilia A	Typically one inherited clotting factor is affected: Factor VIII.
Severe liver disease	Multiple factor deficiencies may occur from impaired synthesis.
Vitamin K deficiency	Affects synthesis of II, VII, IX, X and protein C.
DIC	Multiple factors are consumed during systemic coagulation activation.

A disciplined diagnostic interpretation



Neither bleeding pattern nor PTT prolongation alone identifies factor VIII deficiency.

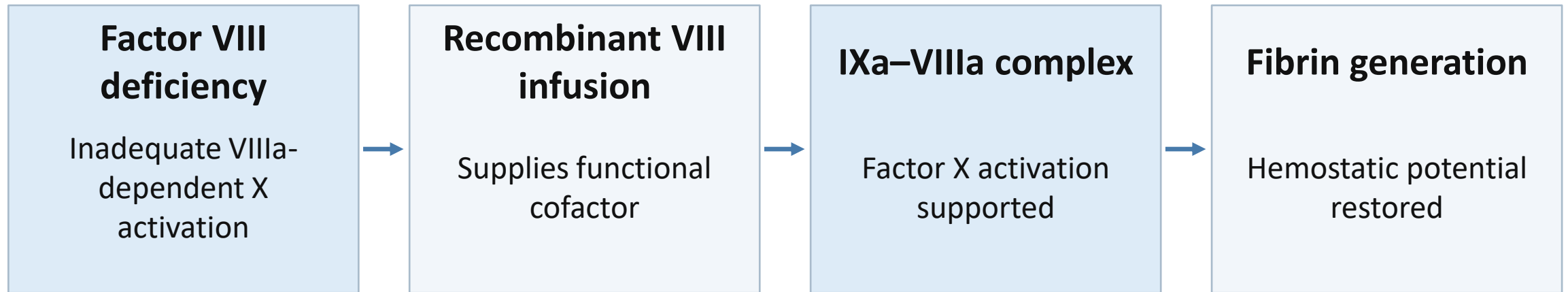
Pitfall: Normal antigen but deficient function

- Some severe F8 point mutations produce measurable factor VIII protein.
- An immunoassay may therefore appear reassuring.
- Functional cofactor activity can remain profoundly abnormal.
- Never equate normal antigen concentration with normal factor VIII activity.

Pitfall: No affected relatives

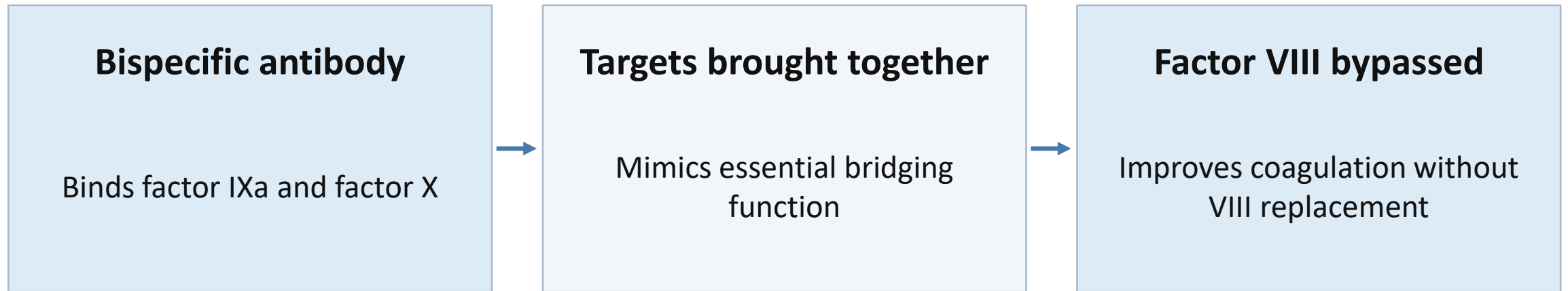
- About 30% of patients have no family history.
- A de novo pathogenic F8 variant can account for an apparently sporadic case.
- Carrier females may not have been recognized in a pedigree.
- The diagnosis rests on clinical and functional laboratory evidence.

Treatment principle: Replace the deficient cofactor



Recombinant factor VIII is a treatment approach.

Bispecific antibody: Functional bypass



The antibody strategy remains useful even when anti-VIII inhibitors are present.

Anti-factor VIII inhibitors complicate replacement

Inhibitory antibodies in about 15% of patients with severe hemophilia A treated with recombinant factor VIII.

- These antibodies bind factor VIII and inhibit its action.
- The risk creates a rationale for factor VIII-independent bypass therapy.

Two treatments act at different points

Recombinant factor VIII

- Directly supplies the deficient molecule.
- Requires functional activity of infused factor VIII.
- Inhibitory antibodies can prevent efficacy.

Bispecific antibody

- Brings clotting factors into functional proximity.
- Bypasses the requirement for factor VIII.
- Can remain active with anti-factor VIII antibodies.

A major limitation: Access and cost

The very high cost of both recombinant factor VIII and bispecific antibody therapy.

- These costs complicate treatment access in low-resource settings.
- Scientific efficacy and equitable availability are separate questions.

Case discussion: Recurrent swollen knee

A young male develops episodes of painful knee swelling after minor activity; The history includes prolonged bleeding after dental extraction.

Which part of hemostasis is most likely impaired?

- Recurrent hemarthrosis strongly suggests a secondary-hemostatic defect.
- Factor VIII deficiency is one leading candidate, but not the only one.
- PT, PTT, and factor-specific activity should clarify the diagnosis.

Case discussion: An isolated prolonged PTT

A patient has easy bruising and intramuscular hematomas. PT is normal and PTT is prolonged.

Why is a factor VIII assay necessary?

- The screening pattern suggests dysfunction in the PTT-tested factors.
- Hemophilia A and hemophilia B may look identical clinically.
- Functional factor VIII and IX assays distinguish the disorders.

Case discussion: Symptomatic female carrier

A heterozygous female from a family with hemophilia has excessive procedural bleeding and low functional factor VIII activity.

Can heterozygosity produce clinically significant hemophilia?

- Yes; Rare symptomatic heterozygous females.
- Unfavorable X inactivation provides one proposed mechanism.
- Measured factor VIII activity—not sex alone—determines clinical interpretation.

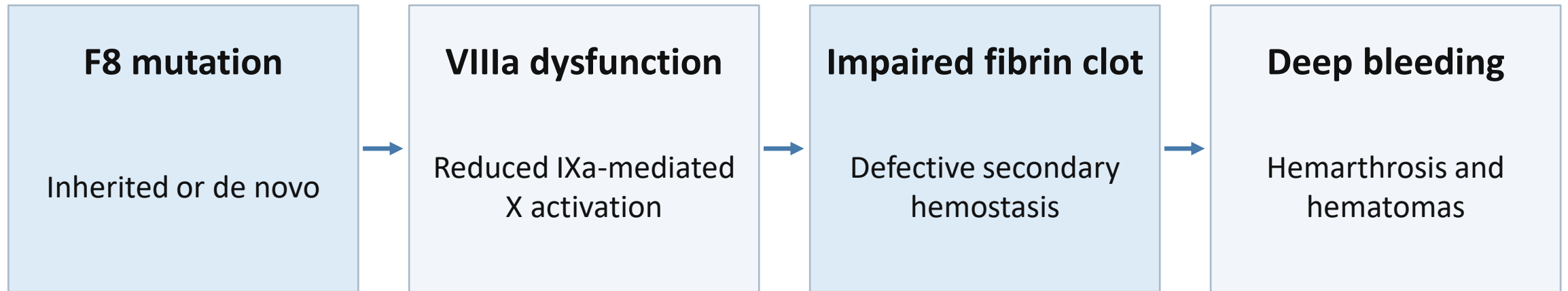
Case discussion: Antigen–activity discordance

An affected patient has severe bleeding, with factor VIII protein detectable by immunoassay but markedly deficient coagulation activity.

What molecular explanation fits this discrepancy?

- A dysfunctional factor VIII protein can be produced after a point mutation.
- Antigen detection and factor function measure different properties.
- Functional assay results best explain the bleeding phenotype.

Putting the disease together



Genotype → factor activity → coagulation failure → clinical phenotype.

Clinical–laboratory correlation

Mechanism	Functional factor VIII is missing or defective.
Typical phenotype	Hemarthrosis, muscle hemorrhage and excessive posttraumatic bleeding.
Laboratory pattern	Prolonged PTT, normal PT; Confirm with factor VIII activity.
Treatment rationale	Replace factor VIII or bypass its function; Consider inhibitory antibodies.

Five durable diagnostic lessons

- Factor VIII is a cofactor for IXa-mediated factor X activation.
- Residual activity largely explains clinical severity.
- Hemarthrosis and deep hematomas suggest factor deficiency.
- Normal PT plus prolonged PTT requires factor-specific confirmation.
- A negative family history or normal factor VIII antigen cannot exclude disease.

References and source boundary

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 14: Hemophilia A, pp. 607–608.
- Same textbook, Chapter 14: Coagulation-factor deficiencies and factor VIII–vWF complex, pp. 606–607.
- Same textbook, Chapter 4: Normal hemostasis, coagulation and bleeding phenotypes, pp. 103–110.
- FDA/DailyMed. Hemlibra (emicizumab) prescribing information (2025): bispecific binding to factor IXa and factor X.