Thromboembolic Risk Associated with Hereditary and Acquired Protein S Deficiencies

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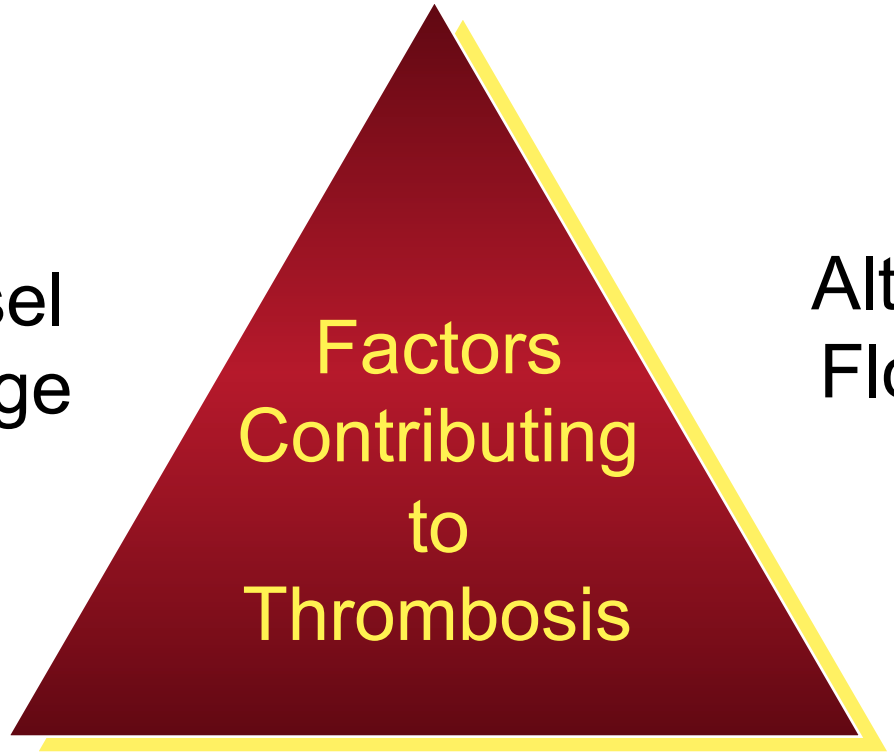
Outline

- Introduction
  - ✓ Pathophysiology of thrombosis
  - ✓ Epidemiology of venous thromboembolism
  - ✓ Role of protein S in regulating clot formation
- Protein S
  - ✓ Biology
  - ✓ Deficiency

Virchow's Triad (1850)



Blood Vessel Wall Damage

Altered Blood Flow (Stasis)

Altered Blood Composition (Hypercoagulability)

Different roles in arterial and venous thrombosis
Overlapping, but different, risk factors and causes

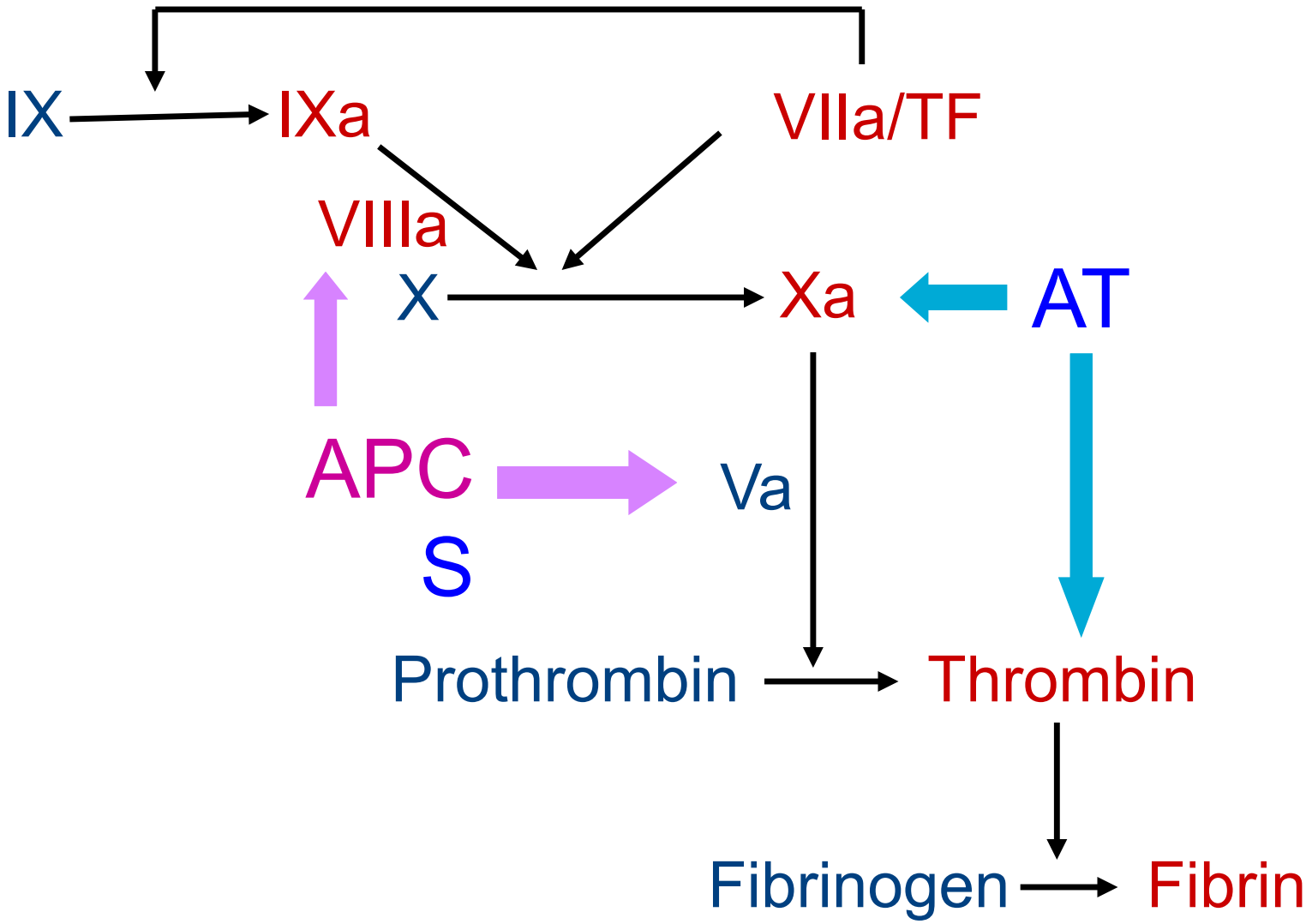
VTE in the United States

- ~350,000 – 600,000 new cases per year in US
- ~100,000 deaths per year

Condition	Annual Deaths
Coronary heart disease	568,000 (AHA, 2006 data)
Stroke	137,000 (AHA, 2006 data)
Pulmonary embolism	Up to 100,000
Breast cancer	39,000 (ACS, est 2010 data)
Traffic fatalities	37,000 (NHTSA, 2008 data)
AIDS	14,000 (CDC, 2007 data)

- Men > Women
- Incidence doubles with every 10 year increase in age (~1/1000/year in “middle age”)
- Hereditary thrombophilia is being looked for and diagnosed with increasing frequency

Location of Hereditary Thrombophilic Defects in the Coagulation Cascade



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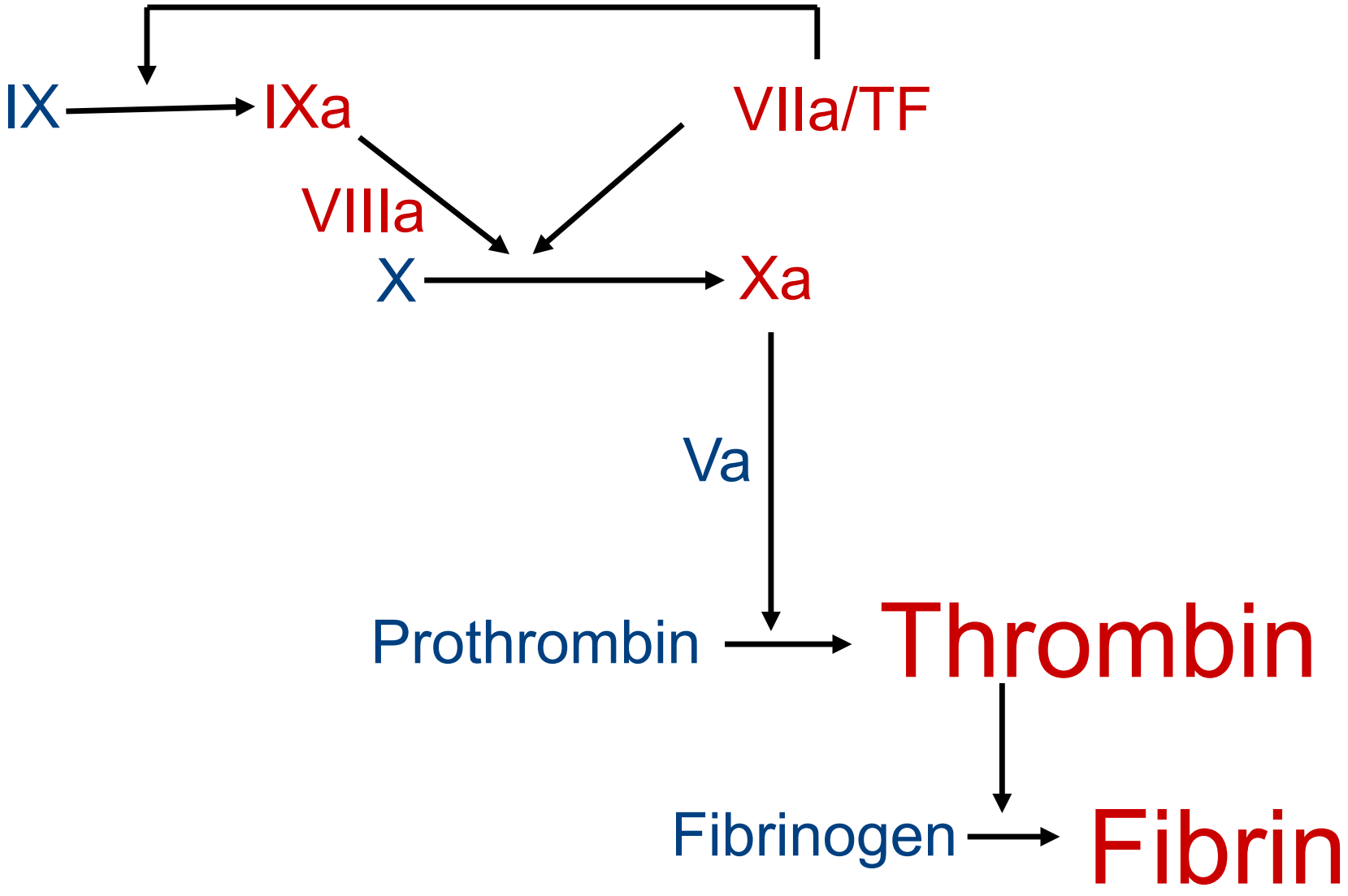
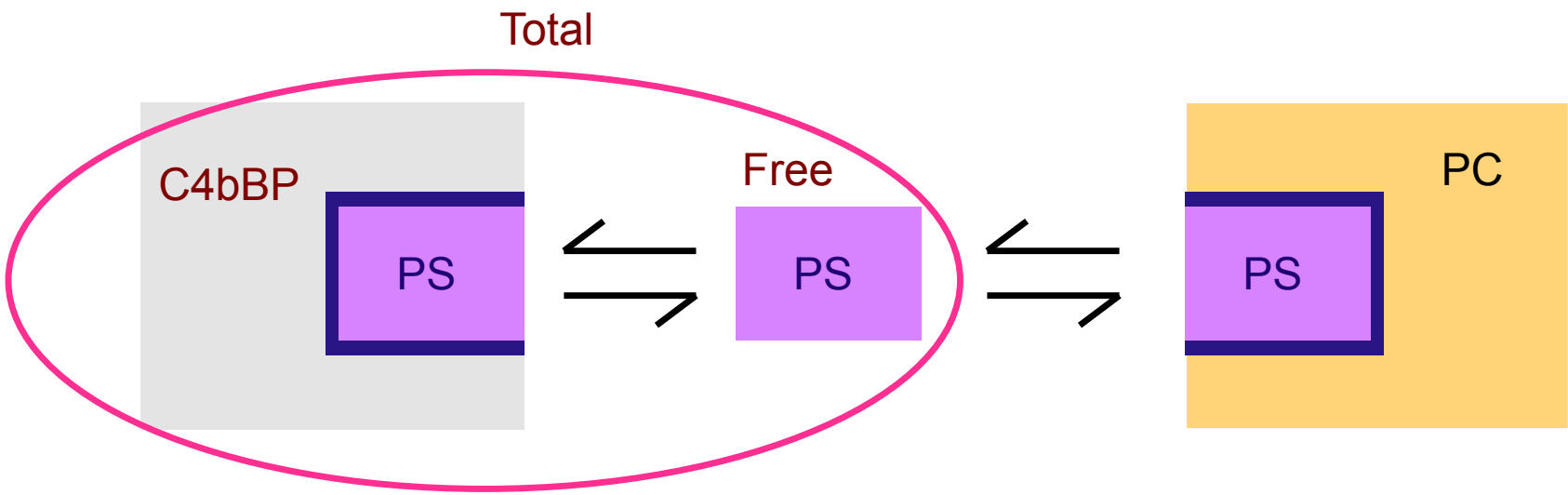


Protein S

- Vitamin K-dependent protein, synthesized predominantly by hepatocytes
  - ✓ Also other cells
  - ✓ Encoded by *PROS*1 gene, chromosome 3
- Primarily functions as nonenzymatic cofactor to APC
  - ✓ Enhances APC inactivation of factors Va and VIIIa
  - ✓ Enhances profibrinolytic effects of of APC
- APC independent anticoagulant functions
  - ✓ Inhibits tenase and prothrombinase complexes directly
  - ✓ Cofactor of tissue factor pathway inhibitor (TFPI) → regulates extrinsic pathway

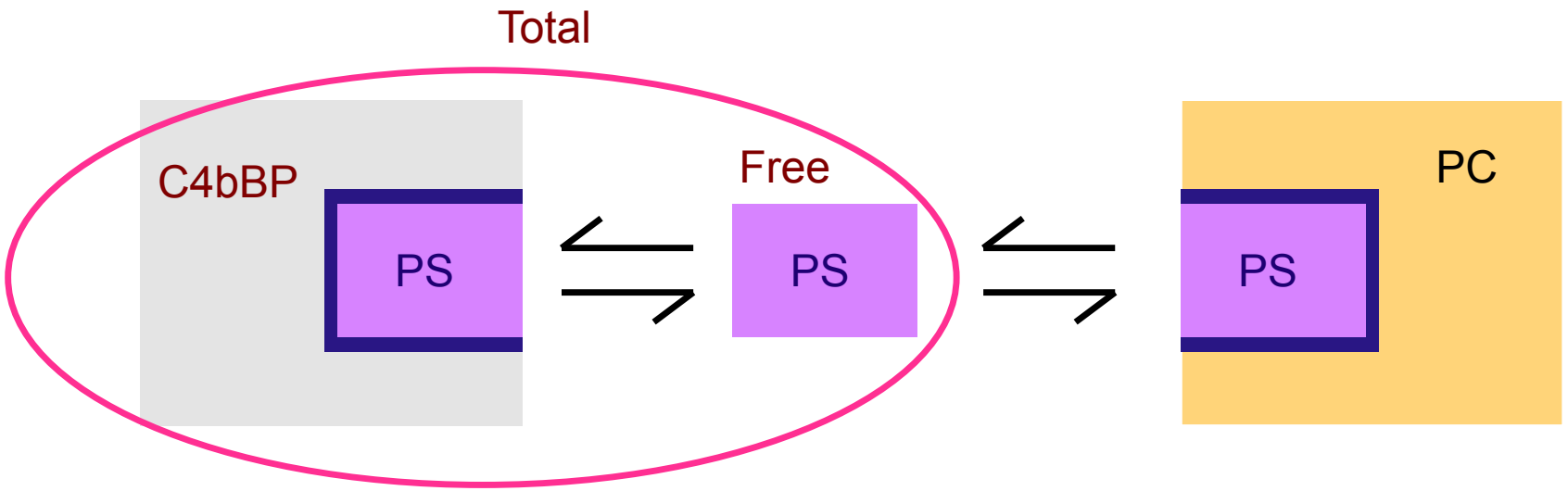
Circulating Forms of Protein S



~60% bound to C4bBP; ~40% Free

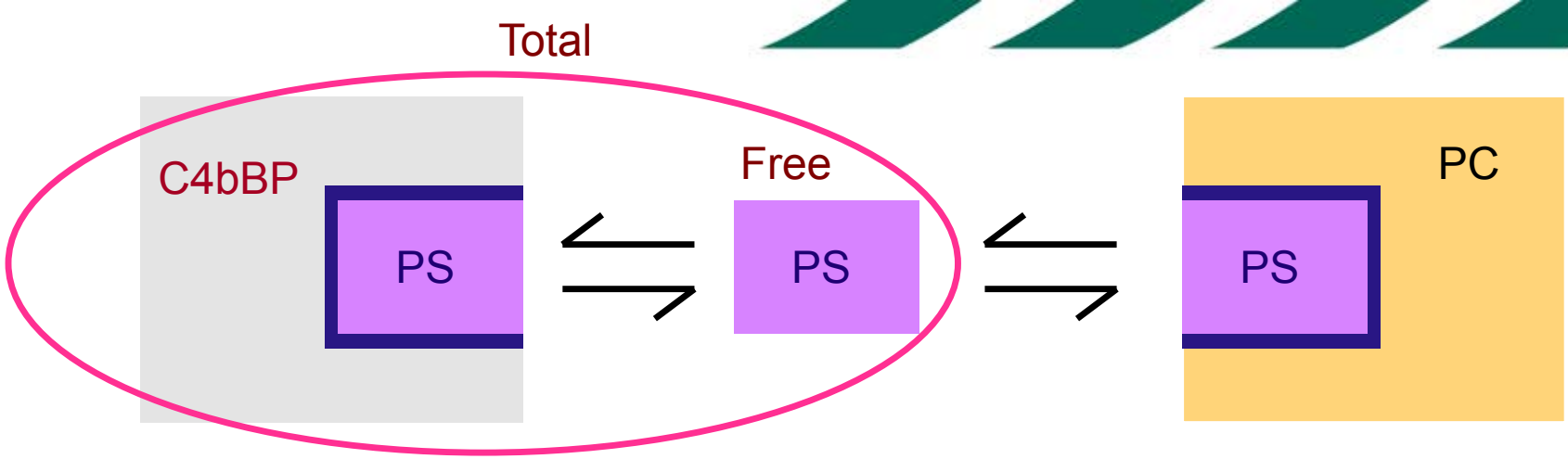
Laboratory Testing for Protein S

- Clot-based protein S functional assays
- Immunoassays for free and total antigen levels
- Reference ranges differ by laboratory but are generally ~60% at lower end to 140% at the higher end



Hereditary Protein S Deficiency

- Autosomal dominant mutations in *PROS*1 gene
  - ✓ Over 200 unique mutations described
  - ✓ Homozygous state usually lethal → neonatal purpura fulminans, DIC
  - ✓ Variable penetrance
- Rare in general Caucasian population – acquired more common
  - ✓ ~0.2%
  - ✓ ~2% of unselected patients with first VTE
  - ✓ ~8% of patients under age 70 with first VTE
- Women have lower levels than men
  - ✓ Increase with age
- Protein S activity levels ~20-55% in heterozygotes
- Increased risk of venous thrombosis
  - ✓ Relative risk 5-10-fold
  - ✓ Usually present before age 50

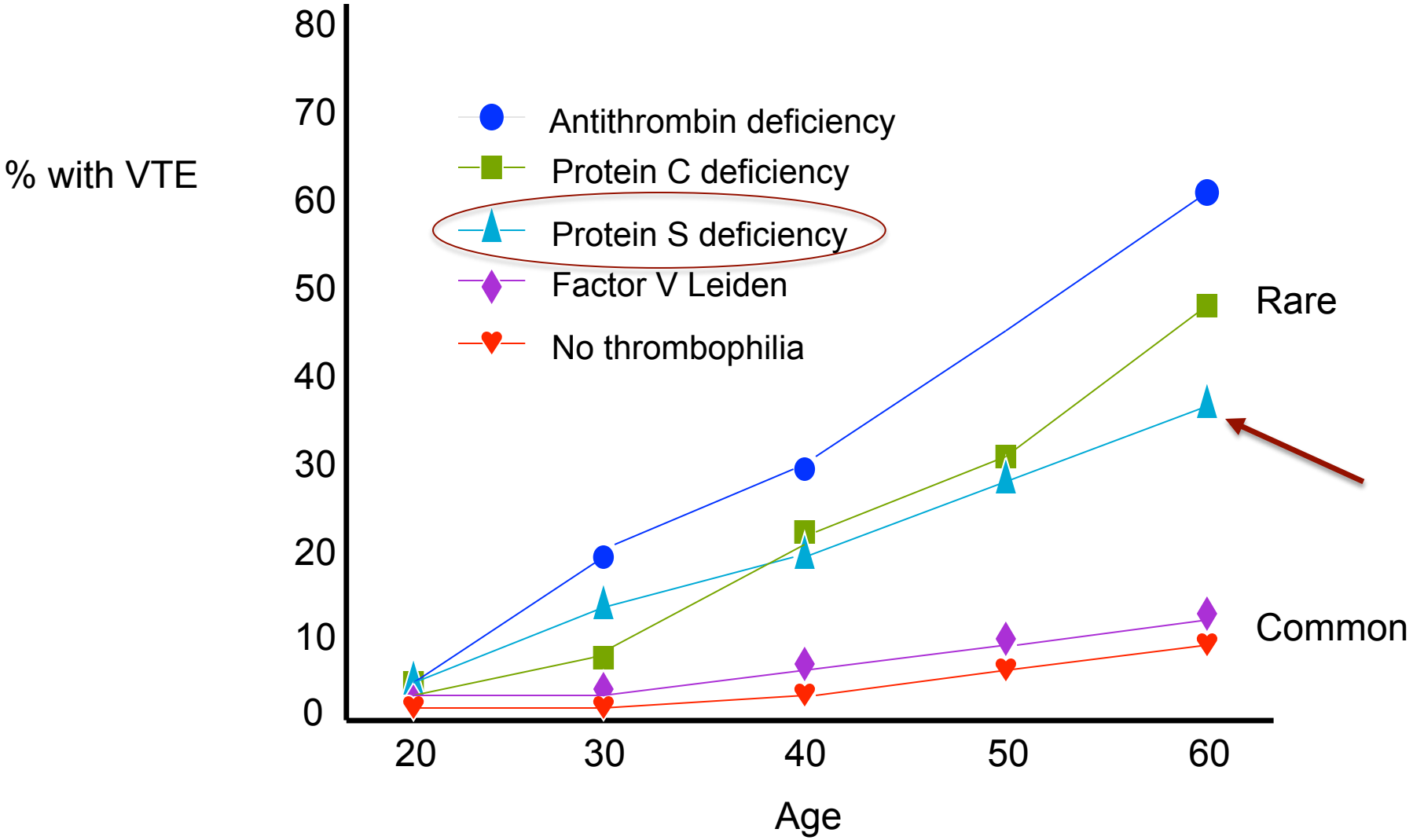


	Type I	Type II (IIb)	Type III (IIa)
Functional Activity	Low	Low	Low
Free Antigen	Low	Normal	Low
Total Antigen	Low	Normal	Normal
Acquired conditions	Consumption (acute clot, DIC, sepsis) Vitamin K deficiency Warfarin Liver disease HIV OCP, HRT Pregnancy		Increased C4bBP Acute phase reaction (sepsis etc) Chronic inflammatory state (SLE, RA, *etc*) Smoking Pregnancy

Prevalence of Major Hereditary Thrombophilia Subtypes

Thrombophilic Condition	General Population	First VTE	Familial VTE
Factor V Leiden (Heterozygote)	5%	20%	50%
Prothrombin Gene (Heterozygote)	2-3%	6%	18%
Antithrombin Deficiency	0.2%	1%	4 - 8%
Protein C Deficiency	0.2%	3%	6 - 8%
Protein S Deficiency	0.2% - 2%	1 - 2%	3 - 13%

Risk of First VTE with Hereditary Thrombophilia



Crowther and Kelton *Ann Intern Med* 2003;138:128-134.

Characteristics of Hereditary Protein S Deficiency-Associated Clotting

- Usually venous
- VTE at a young age
  - ✓ Often unprovoked but risk exacerbated by environmental factors
- Associated with increased risk for first VTE event but possibly not recurrence
- Increased risk for fetal loss
- Treatment
  - ✓ Not routinely for asymptomatic (aggressive thromboprophylaxis)
  - ✓ Anticoagulation for VTE, same as for normal protein S
- "Rule of 50"
  - ✓ 50% women/50% men/50% passed on to offspring (autosomal dominant inheritance)
  - ✓ 50% develop VTE by age 55
  - ✓ 50% unprovoked
  - ✓ Levels lower in women but increase by age 50
  - ✓ PROS1 mutation detected in 50% of protein S deficient

Case: 57 yo Woman with DVT and Family History of Fatal PE

First and only episode of VTE = calf DVT after starting HRT after a hysterectomy at age 43→ anticoagulation for 6 months

Healthy except for sarcoidosis

G5 P4, 1st trimester miscarriage

Family history: Father, recurrent phlebitis
Sister, fatal PE at age 16
Son, fatal PE at age 30
Daughter, age 21 VTE-free but wants to use OCP

Lab testing of the son:

Protein C antigen, 74% (normal)
Protein S total antigen, 79%
Factor V Leiden, PT G20210A tested but not reported

Lab testing of patient (Quest diagnostics) is normal.

Antithrombin activity, 108%
Protein C antigen, 132%
Protein S total antigen, 82%
Lupus anticoagulant, negative
Anticardiolipin antibodies, negative
Factor V Leiden, negative
PT G20210A, negative

Additional testing was done. What was it?

Patient

Protein C functional activity	191%
Protein S functional activity	43% (60 – 140%)

Daughter

Protein C functional activity	96%
Protein S functional activity	38% (60 – 140%)

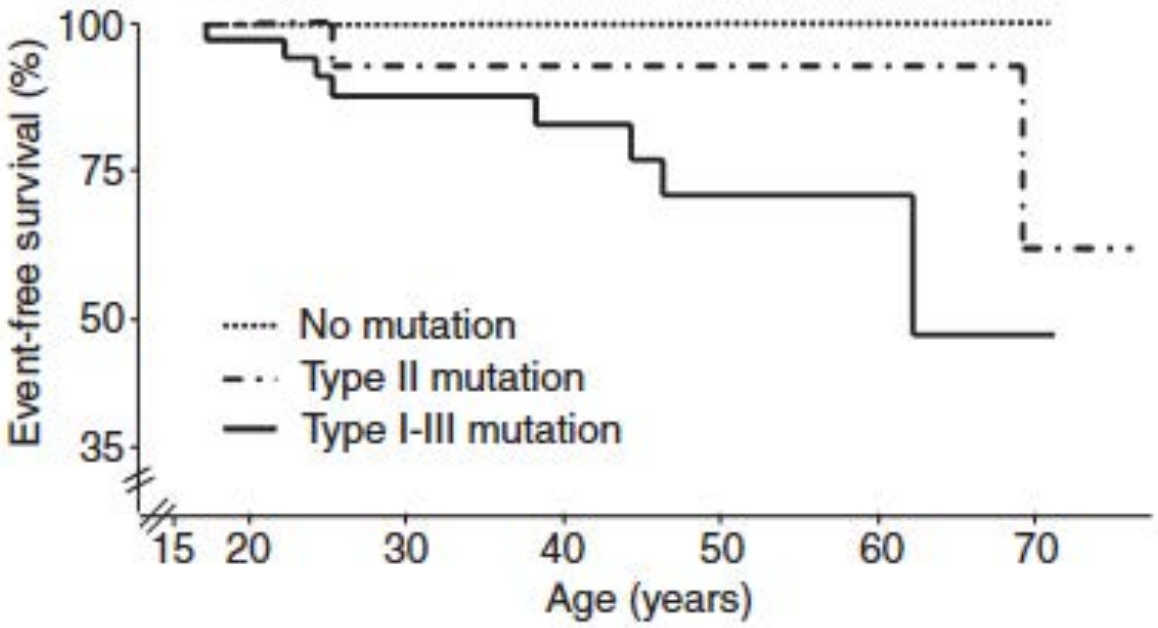
What is the diagnosis?

<u>Mother</u>

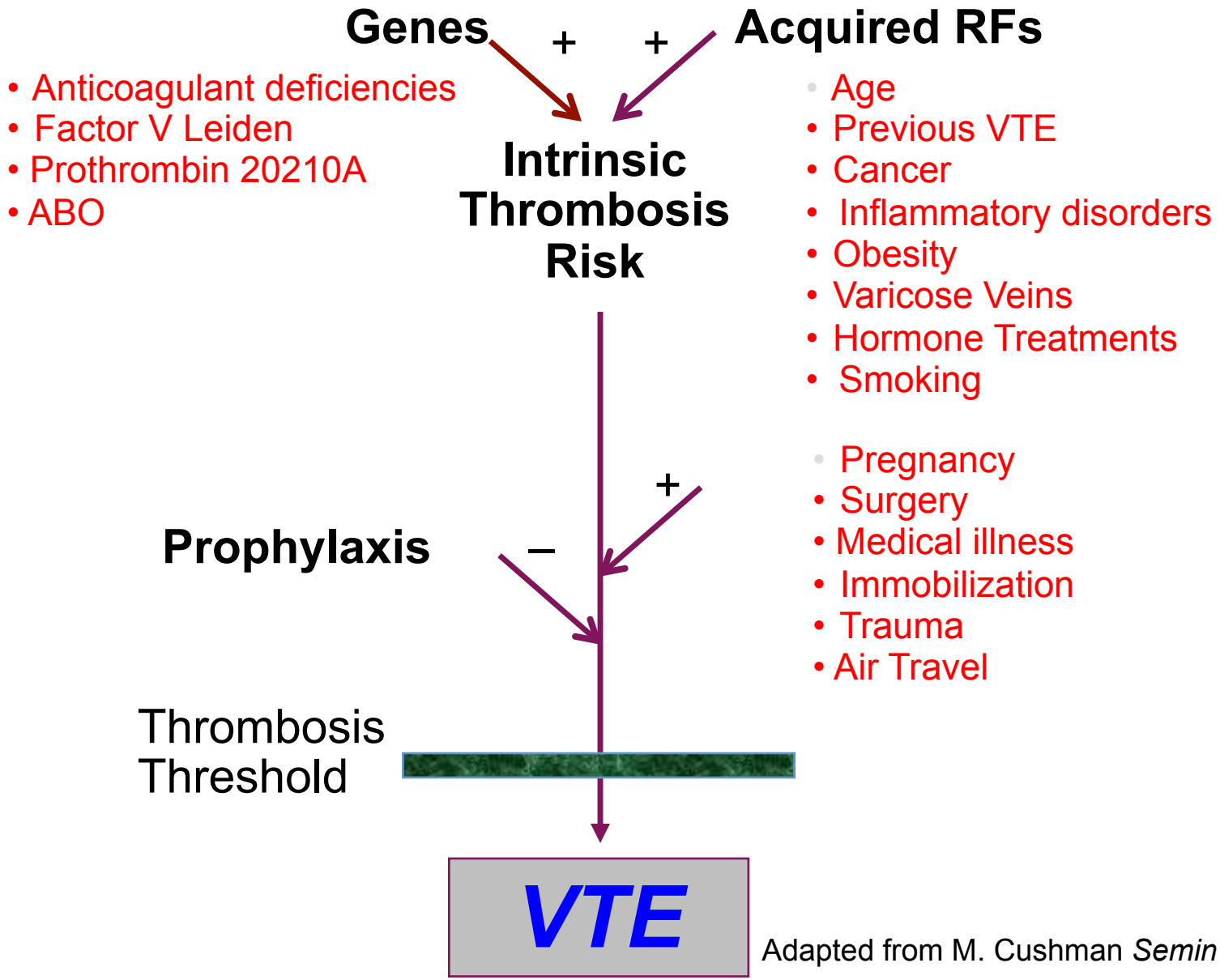
Protein C functional activity	191%
Protein S functional activity	43% (60 – 140%)
Protein S total antigen	82%
Protein S free antigen	67%

	Type I	Type II (IIb)	Type III (IIa)
Functional Activity	Low	Low	Low
Free Antigen	Low	Normal	Low
Total Antigen	Low	Normal	Normal

Risk of Thrombosis in Subtypes of Protein S Deficiency



VTE Risk Factor Model



Adapted from M. Cushman *Semin Hematol* 2007

Junior, drink your blood before it clots!