Bleeding Assessment and Approach to Coagulation Testing

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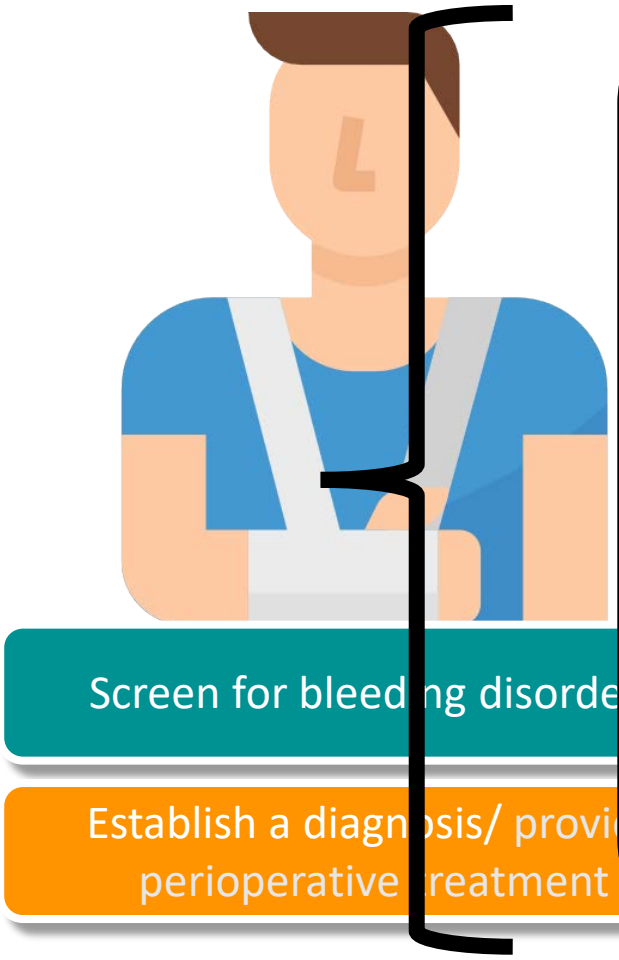
Disclosure

I have no conflicts of interest to declare with regards to the presentation of this topic

Learning Objectives



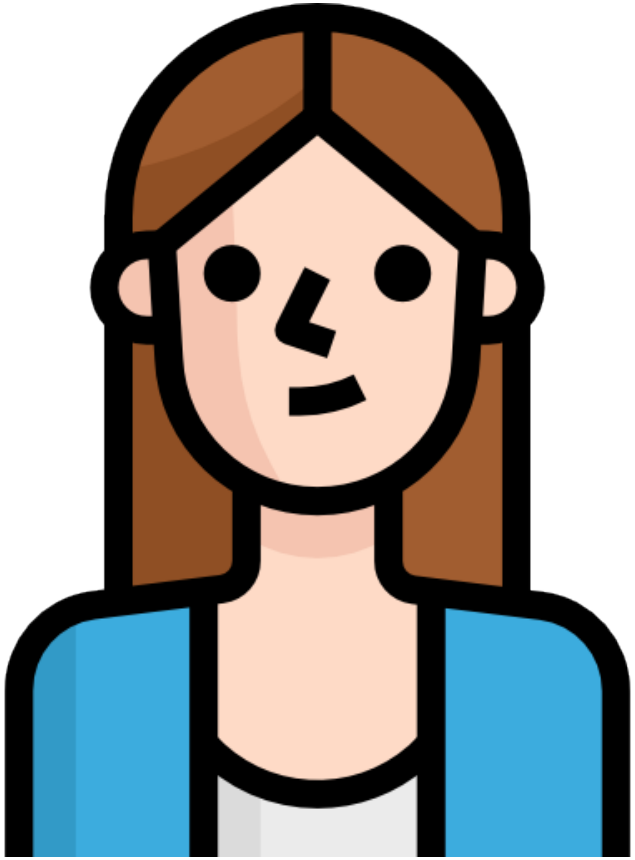
Use and Limitations of:

Bleeding History

Laboratory Investigations

- Primary Hemostasis (platelet plug)
  - Von Willebrand Disease (VWD)
  - Platelet Function
- Secondary Hemostasis (fibrin formation)
  - Global screens (PT/PTT)
  - Specialized tests

Why Bleeding Assessment Matters



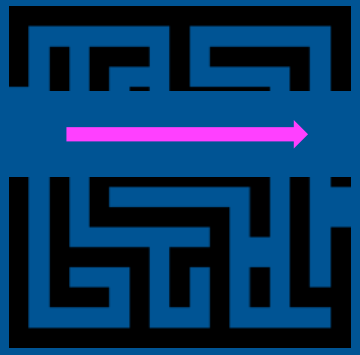
26 year old woman seen for preoperative assessment prior to tonsillectomy. PT/INR and PTT normal. Assessed by resident and approved for OR.

+++ bleeding. Requires 6 units pRBC, ICU admission and 2 return trips to the OR

On further review, history of heavy menstrual bleeding and severe post partum hemorrhage. Ultimately diagnosed with Von Willebrand Disease.

1. Bleeding disorders matter
2. Hemostasis is tricky…

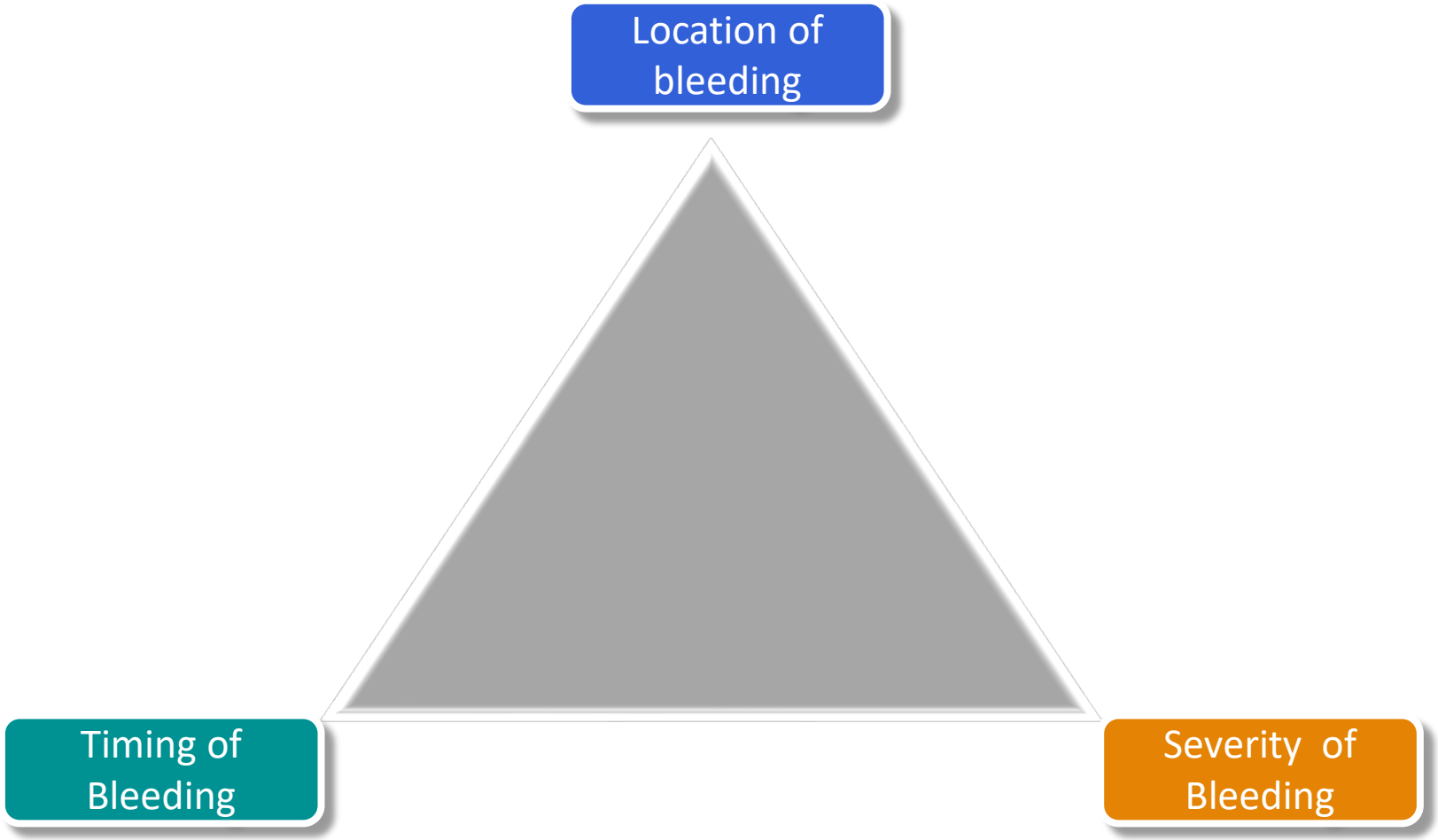
3. Bleeding History is the most important clinical part of hemostasis



BLD0195 Assess patients for surgical bleeding risk
BLD0196 Describe an approach to the bleeding patient

Bleeding History…

Bleeding History

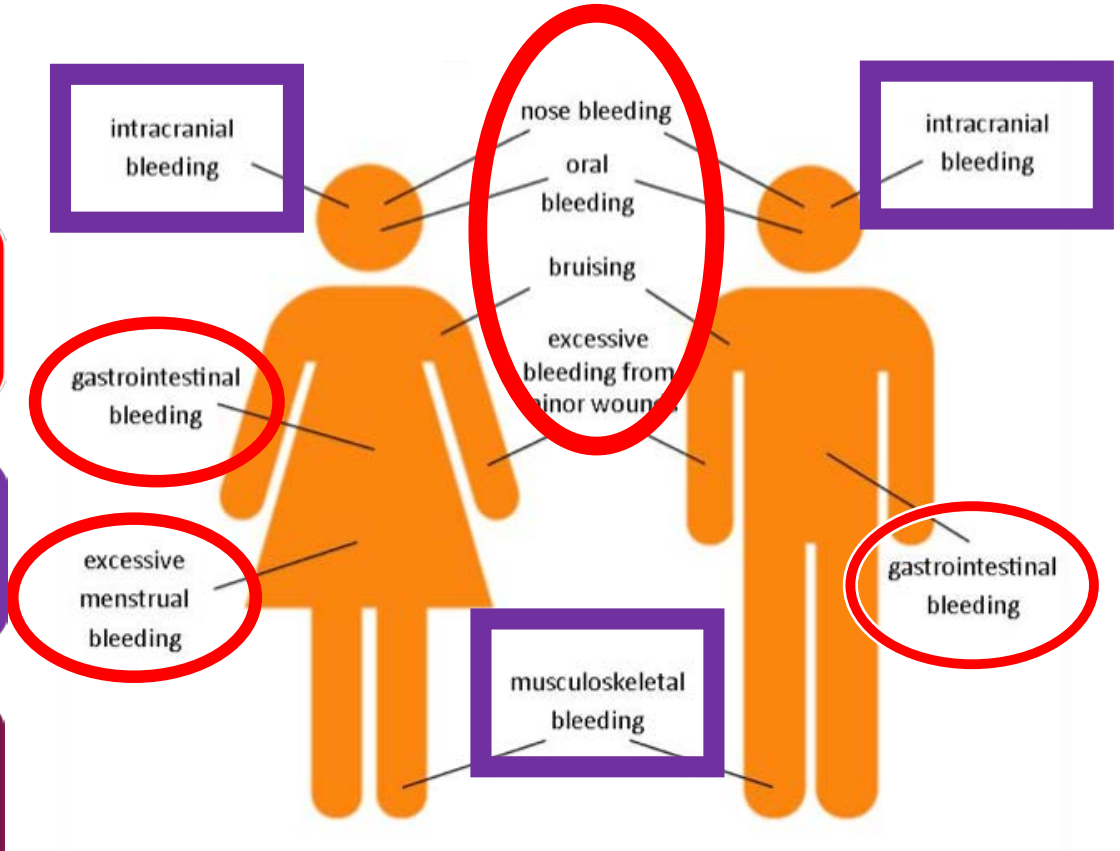


Location of Bleeding

Mucocutaneous Bleeding

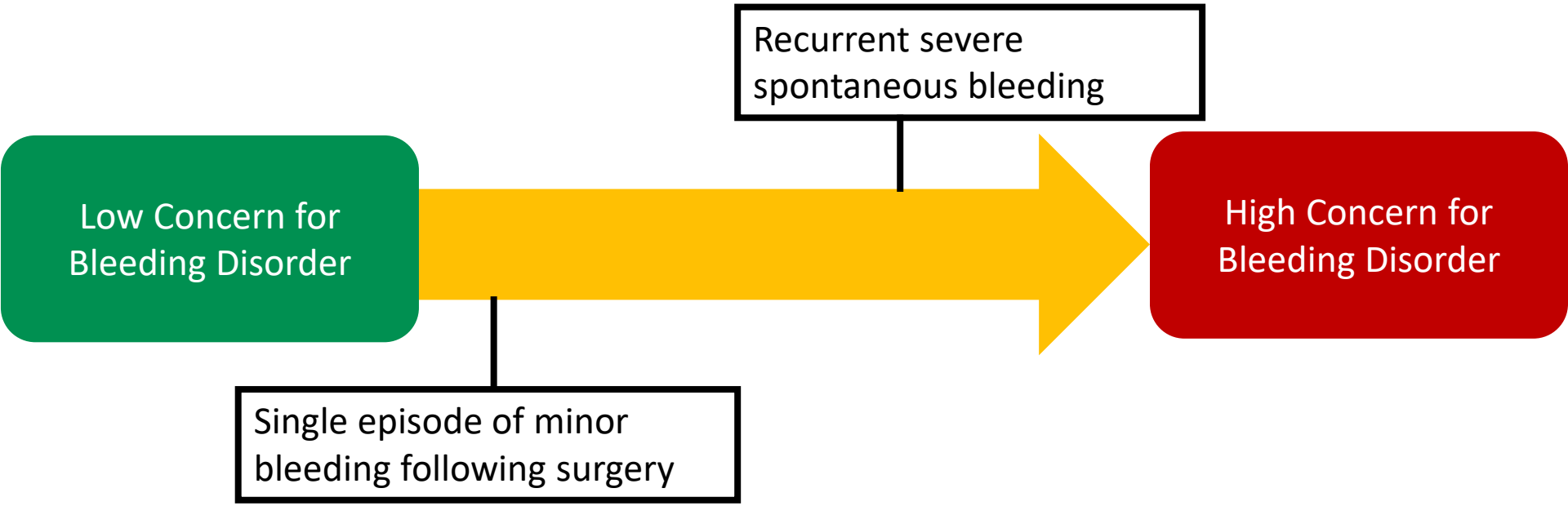
"Deep" Bleeding

"Delayed" Bleeding



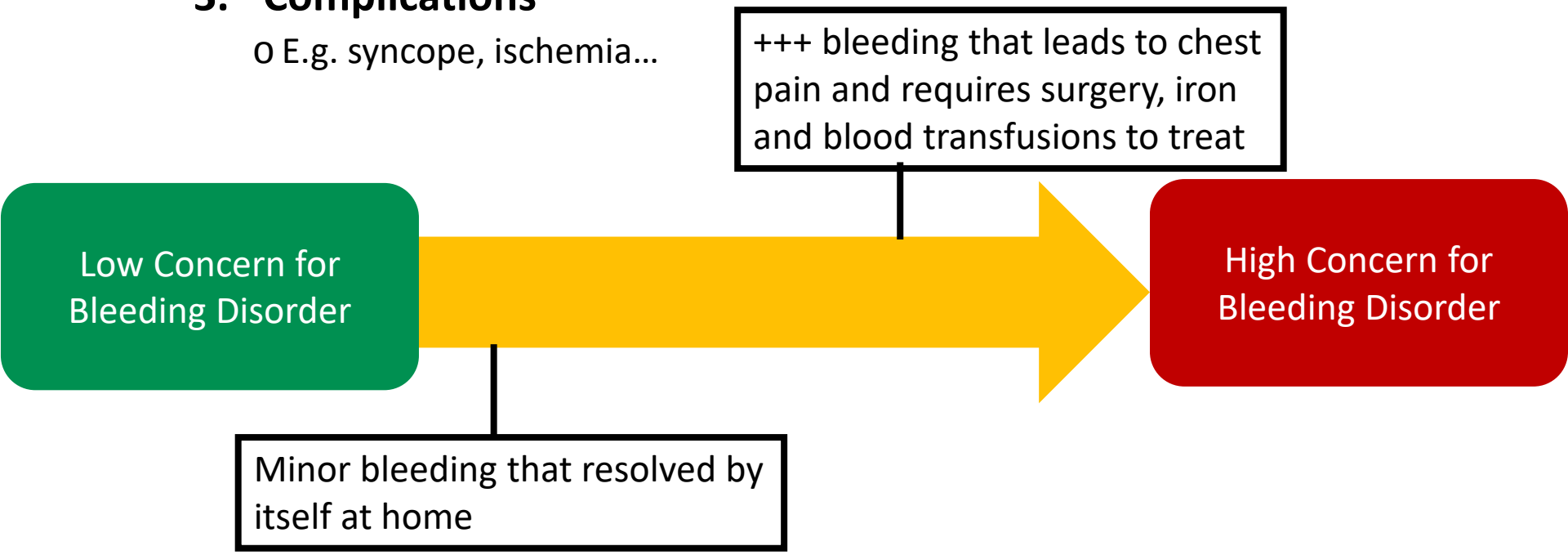
Timing of Bleeding

1. **Frequency and onset**
   - o Chronic vs. acute
   - o Duration
2. **Inciting factors**
   - o Spontaneous vs. traumatic



Severity of Bleeding

1. **Amount**
   - Be specific
2. **Treatment Required**
   - Iron infusions, blood transfusions, surgery
3. **Complications**
   - E.g. syncope, ischemia…



Bleeding Assessment Tool (BAT)

Condensed MCMDM-1 VWD Bleeding Questionnaire

	-1	0	1	2	3	4
Epistaxis	--	No or trivial (≤ 5 per year)	> 5 per year or more than 10'	Consultation only	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Cutaneous	--	No or trivial (≤ 1 cm)	> 1 cm and no trauma	Consultation only	--	--
Bleeding from minor wounds	--	No or trivial (≤ 5 per year)	> 5 per year or more than 5'	Consultation only	Surgical hemostasis	Blood transfusion or replacement therapy or desmopressin
Oral cavity	--	No	Referred, no consultation	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Gastrointestinal bleeding	--	No	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytic	--
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing or packing	Blood transfusion or replacement therapy or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1 surgery	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Menorrhagia	--	No	Consultation only	Antifibrinolytics, oral contraceptive pill use	Dilation & curettage, iron therapy, ablation	Blood transfusion or replacement therapy or desmopressin or hysterectomy
Postpartum hemorrhage	No bleeding in at least 2 deliveries	None done or no bleeding in 1 delivery	Consultation only	Dilation & curettage, iron therapy, antifibrinolytics	Blood transfusion or replacement therapy or desmopressin	Hysterectomy
Muscle hematomas	--	Never	Post trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	--	Never	Post trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system bleeding	--	Never	--	--	Subdural, any intervention	Intracerebral, any intervention

Bleeding history/ BAT's (bleeding assessment tools) most helpful as rule out tests

BAT score < 4 in an adult = unlikely to have bleeding disorder

But…. some limitations

- **Less sensitive if few bleeding challenges (young, male)**
- **Static**
- **Does not include family history**
- **Poorly captures new acquired bleeding disorders**
- **Scores influenced by available medical resources**
- **Only validated in certain settings**

bloody easy

Coagulation Simplified...

Second Edition

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QUICK REFERENCE

2012* Clinical Practice Guideline on the Evaluation and Management of von Willebrand Disease (VWD)

Presented by the American Society of Hematology, adapted from: The Diagnosis, Evaluation, and Management of von Willebrand Disease. National Heart, Lung, and Blood Institute, NIH Pub. No. 08-5832. December, 2007.

***This quick reference guide was revised in 2012.**

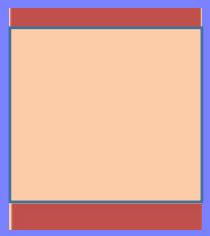
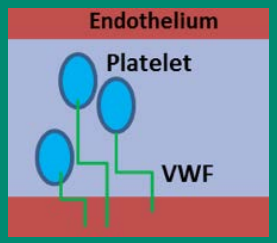
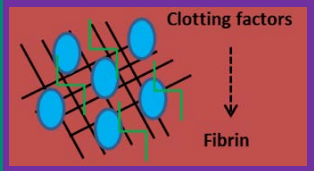
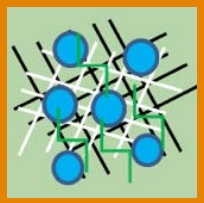
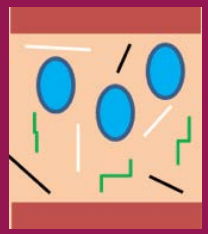
Take Home Point 1

The Bleeding History is the most important test of hemostasis

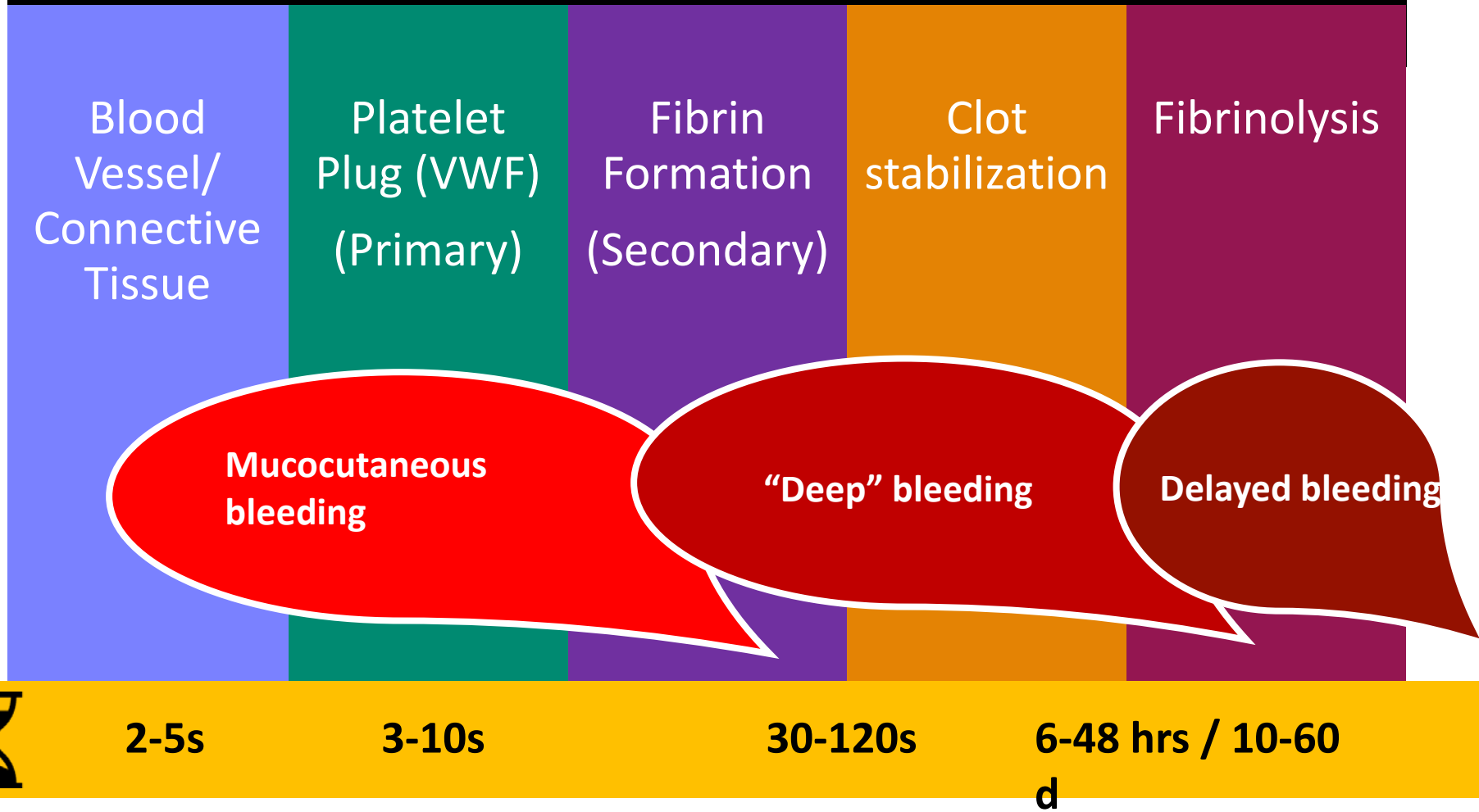
Effective rule out test but may miss:

- recently acquired bleeding disorder
- patients with few bleeding challenges

Problems with Hemostasis

Blood Vessel/ Connective Tissue	Platelet Plug (VWF) (Primary)	Fibrin Formation (Secondary)	Clot stabilization	Fibrinolysis
				
2-5s	3-10s	30-120s	6-48 hrs / 10-60 d	

Problems with Hemostasis



Laboratory Investigations Primary Hemostasis…

Primary Hemostasis Investigations

Hematologist

Low platelet counts

- CBC

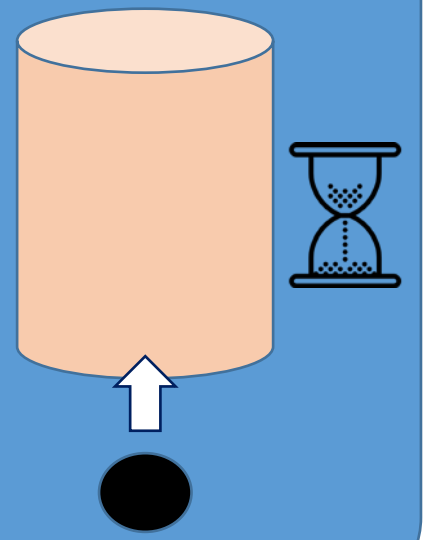
Dysfunctional platelets

- Drug history (ex. ASA)
- Platelet function tests
- Blood film

Measuring Platelet Function – Screening Tests

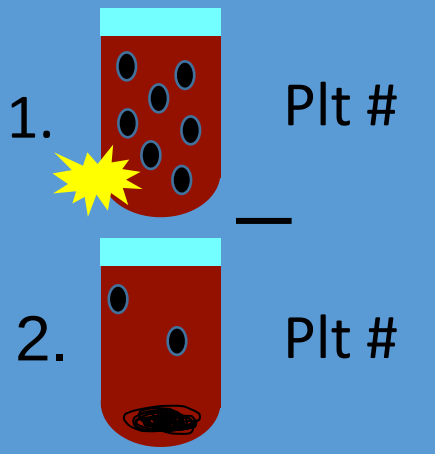
Platelet "stickiness"

Platelet function analyzer (PFA)



Platelet "inhibition"

PlateletWorks



Difference = inhibited platelets

Measuring Platelet Function – Confirmation

Platelet "reactiveness"

Platelet aggregometry

Platelet "appearance"

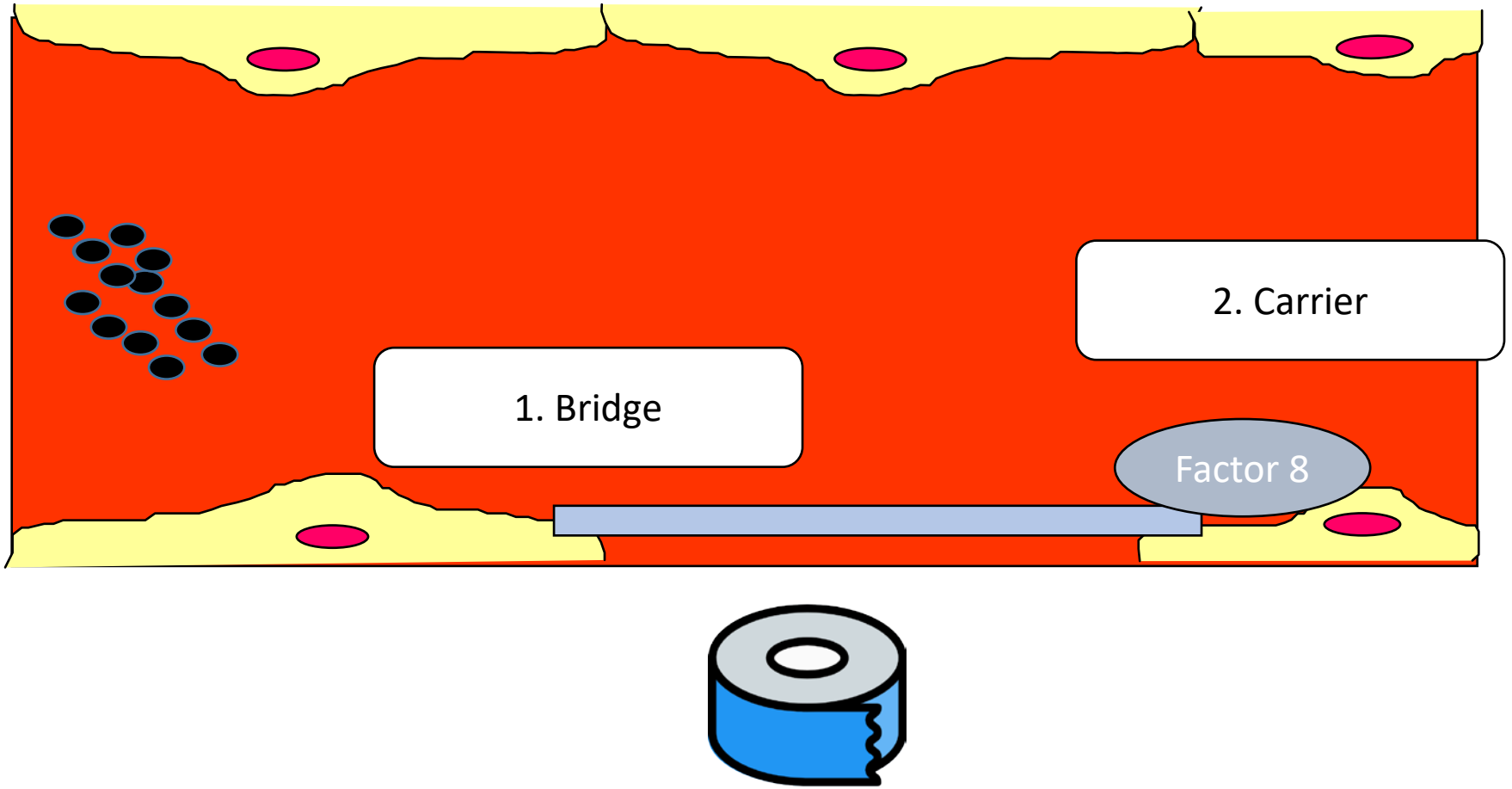
Electron microscopy

Primary Hemostasis Investigations

Hematologist

Low platelet counts	o CBC o Blood film	
Dysfunctional platelets	o Drug history (ex. ASA) o Blood film	o Platelet function tests o Blood film
Von Willebrand Disese		o VWF antigen o VWF ristocetin o Factor VIII

Von Willebrand Disease



Von Willebrand Disease Testing

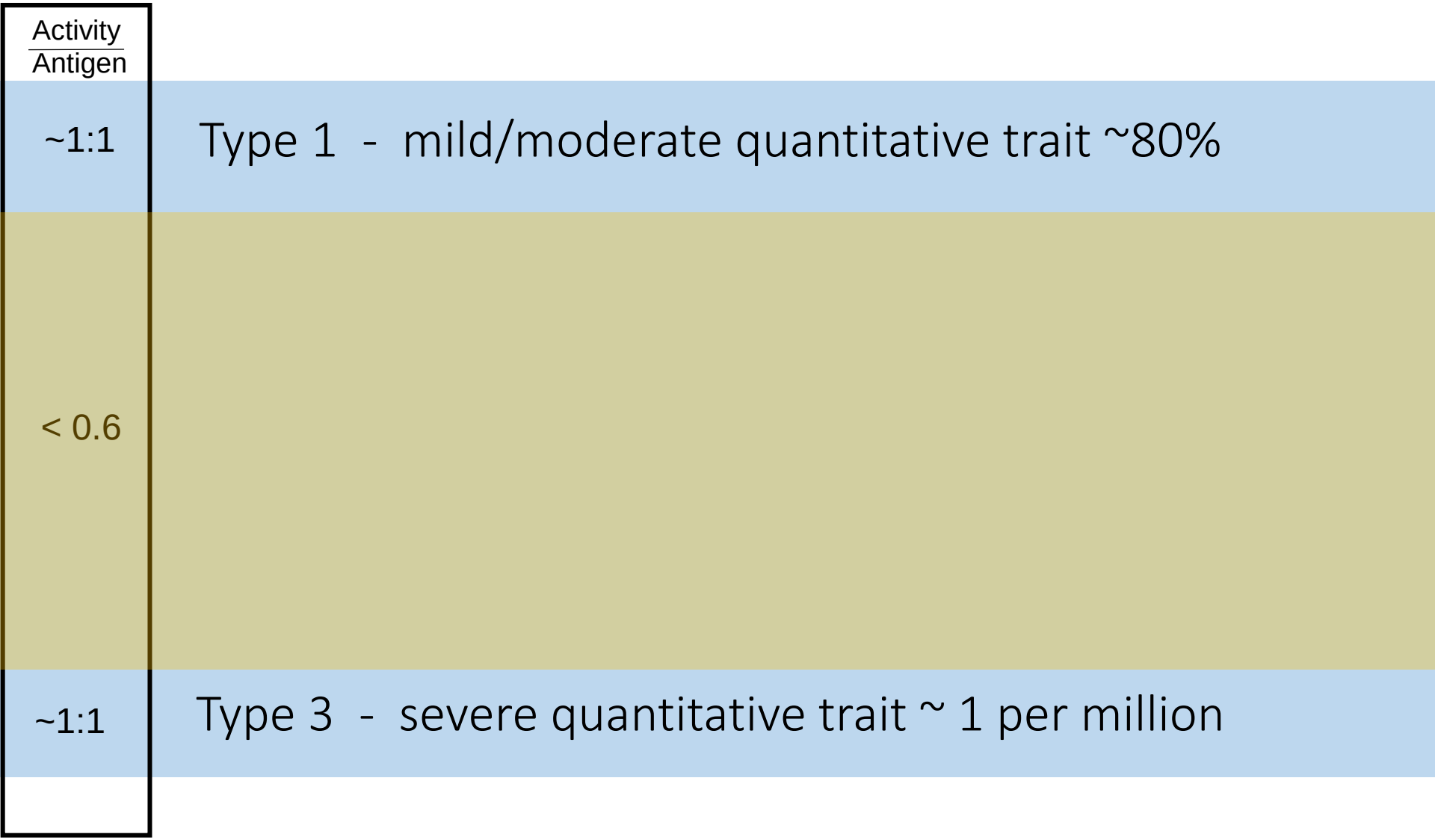
What to test (the basics):

Decreased level	Abnormal function
• VWF antigen level	• Ability to bind to platelets – VWF Activity (Ristocetin Cofactor Assay)
	• Ability to carry Factor 8 – Factor 8 level
• PFA 100/200	

Testing Caveats:

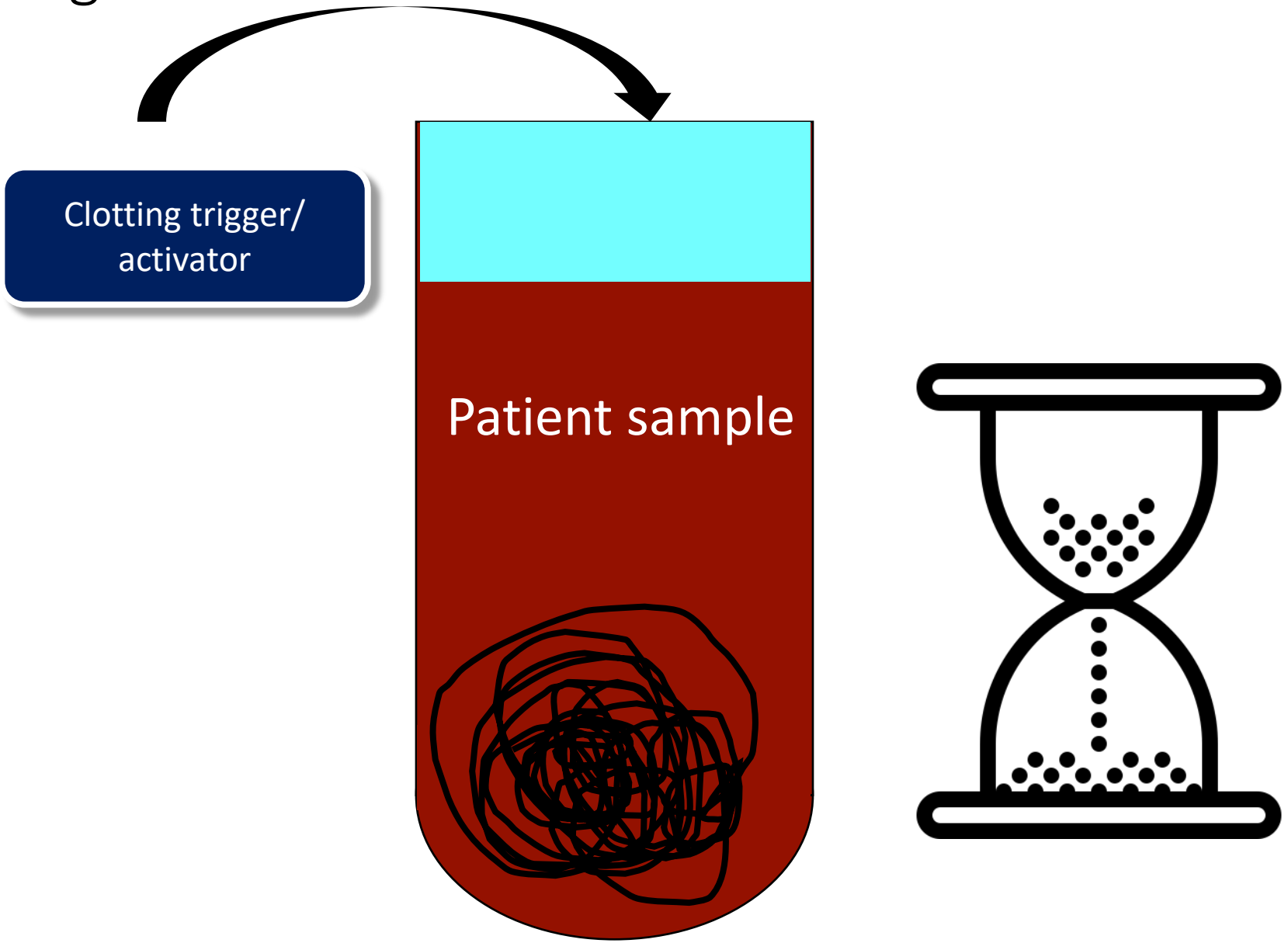
Elevated Values (false negative)	Decreased Values (false positive)
• High estrogen states (e.g. pregnancy) • Increased stress (e.g. postop) • Interference (e.g. rheumatoid factor)	• Group O blood • Outside lab

Von Willebrand Disease Classification



Laboratory Investigations Secondary Hemostasis…

Coagulation test basics

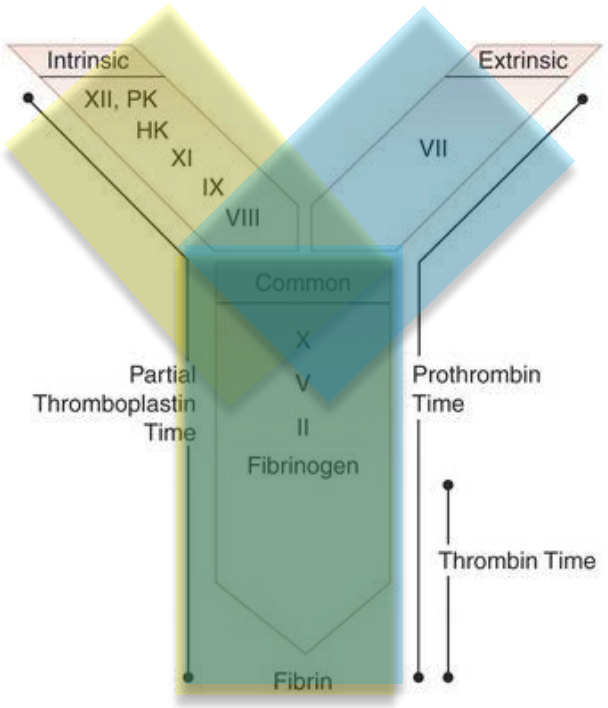


What does each test measure

PTT
(partial thromboplastin time)

Intrinsic
- Factor 12
- Factor 11
- Factor 9
- Factor 8

Common
- Factor 10
- Factor 5
- Prothrombin
- Fibrinogen

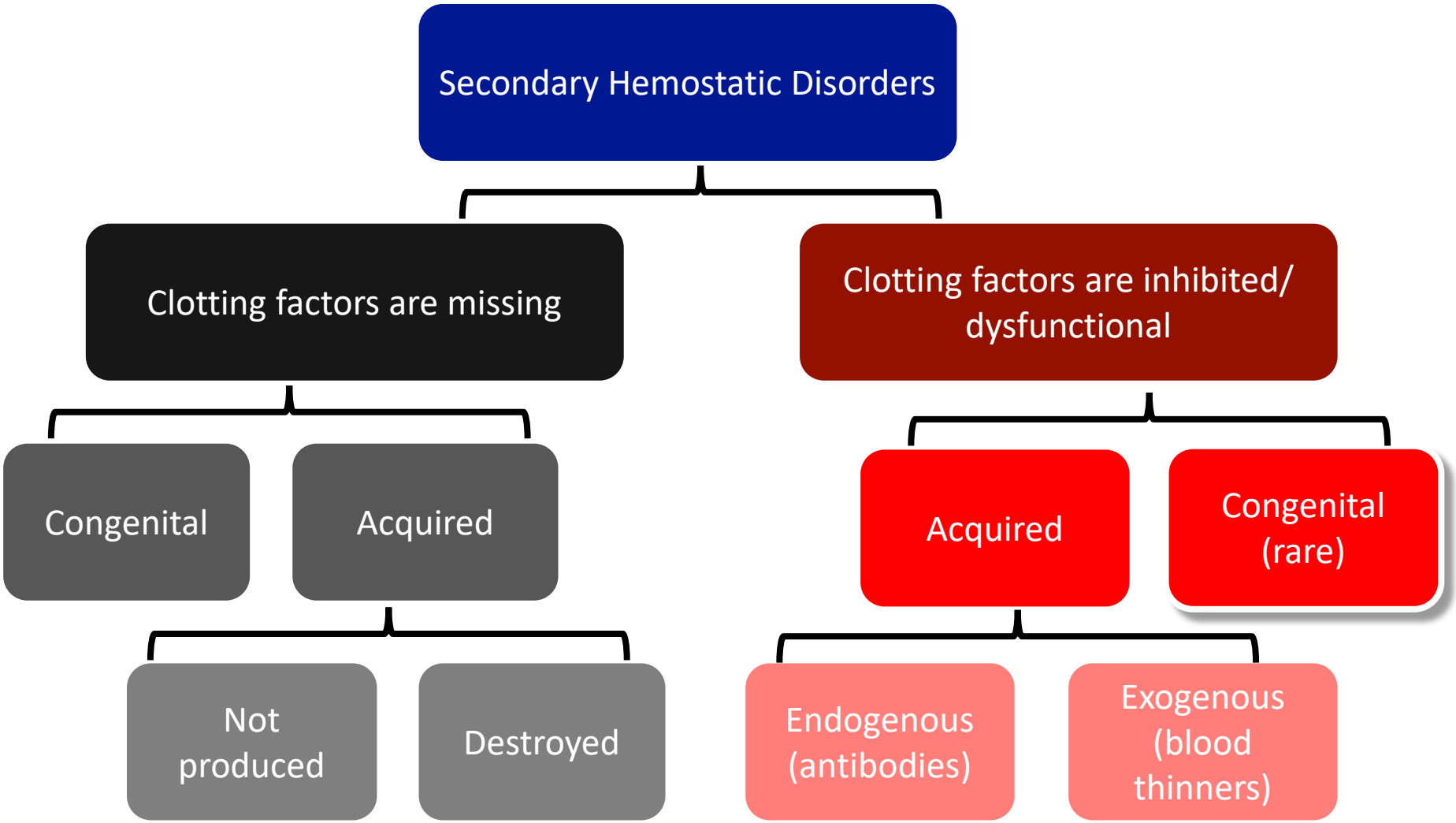


PT
(prothrombin time)

Extrinsic
- Factor 7

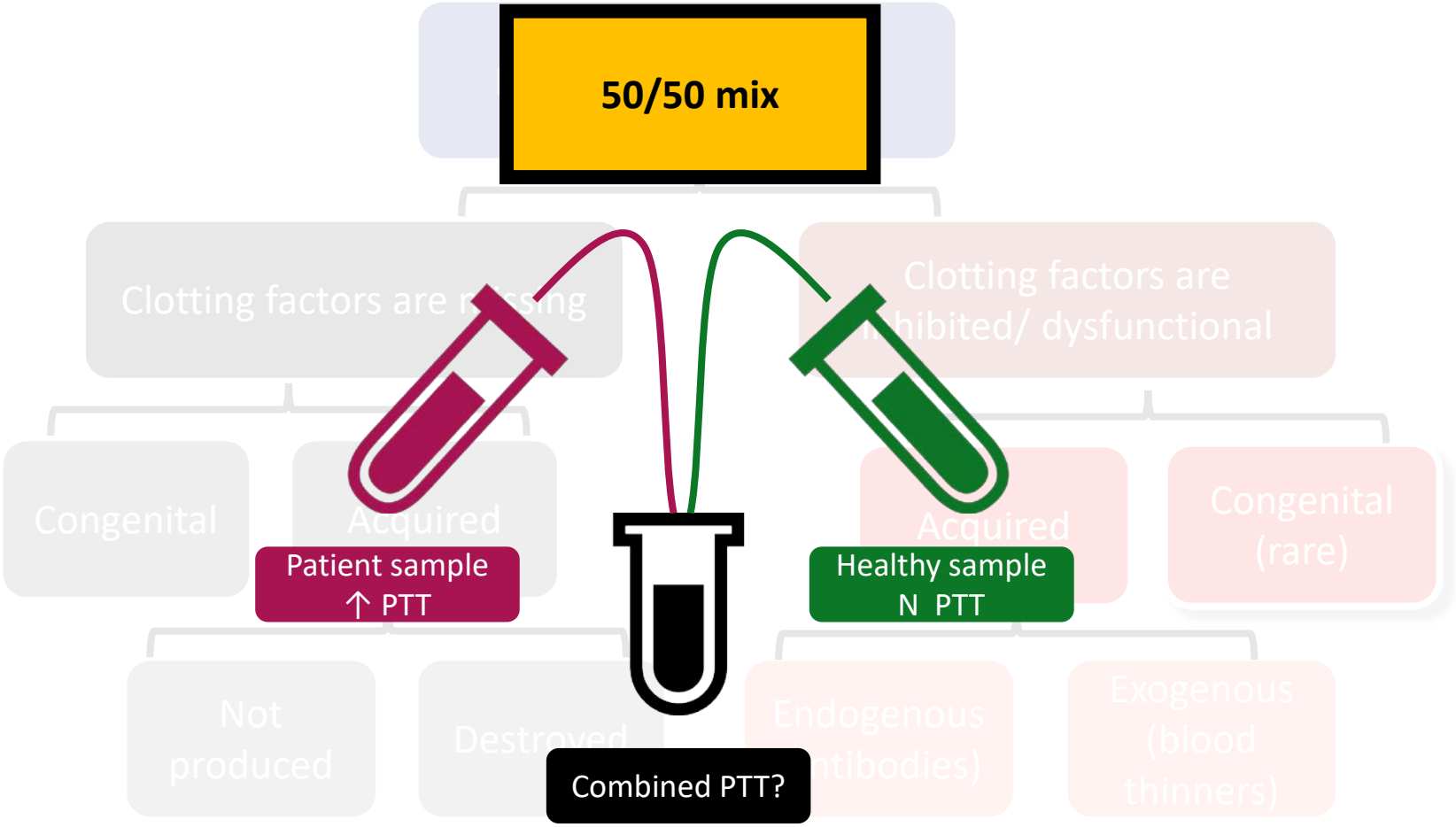
Common
- Factor 10
- Factor 5
- Prothrombin
- Fibrinogen

BLD0156 Describe drug targets and drug classes that can affect blood coagulation
BLD0165 Understand common coagulation tests used to assess hemostasis e.g., PT and PTT

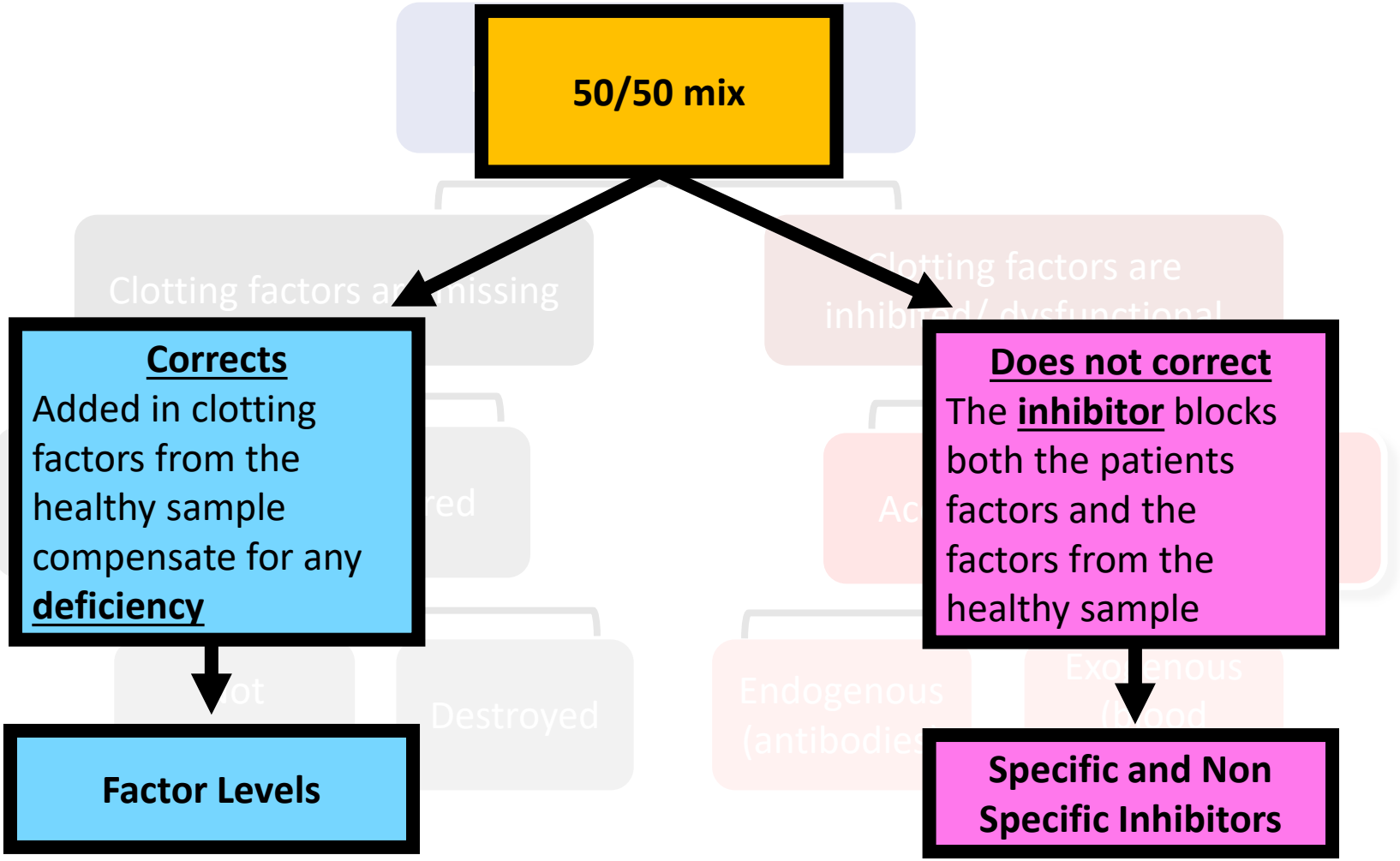


Not all of these cause bleeding!!!

Missing vs. Inhibited/ Dysfunctional



Missing vs. Inhibited/ Dysfunctional



Non Specific vs. Specific Inhibitors

Specific Inhibitors:

- Directed against single clotting factor
- Alloimmune (Hemophilia patients receiving factor replacement) vs. Autoimmune
- **Associated with bleeding**

Non –Specific Inhibitors (lupus anticoagulant):

- Anti-phospholipid antibodies
- **Associated with thrombosis**

INR/PT & PTT Limitations

- **PT**
  - Effective at determining the amount of warfarin that is present in steady state
- **PTT**
  - Historically designed to screen for inherited hemophilia pre-operatively in high risk patients
  - Subsequently validated to monitor unfractionated heparin therapy

These tests were never designed nor validated to screen for hemostatic defects in unselected patients!

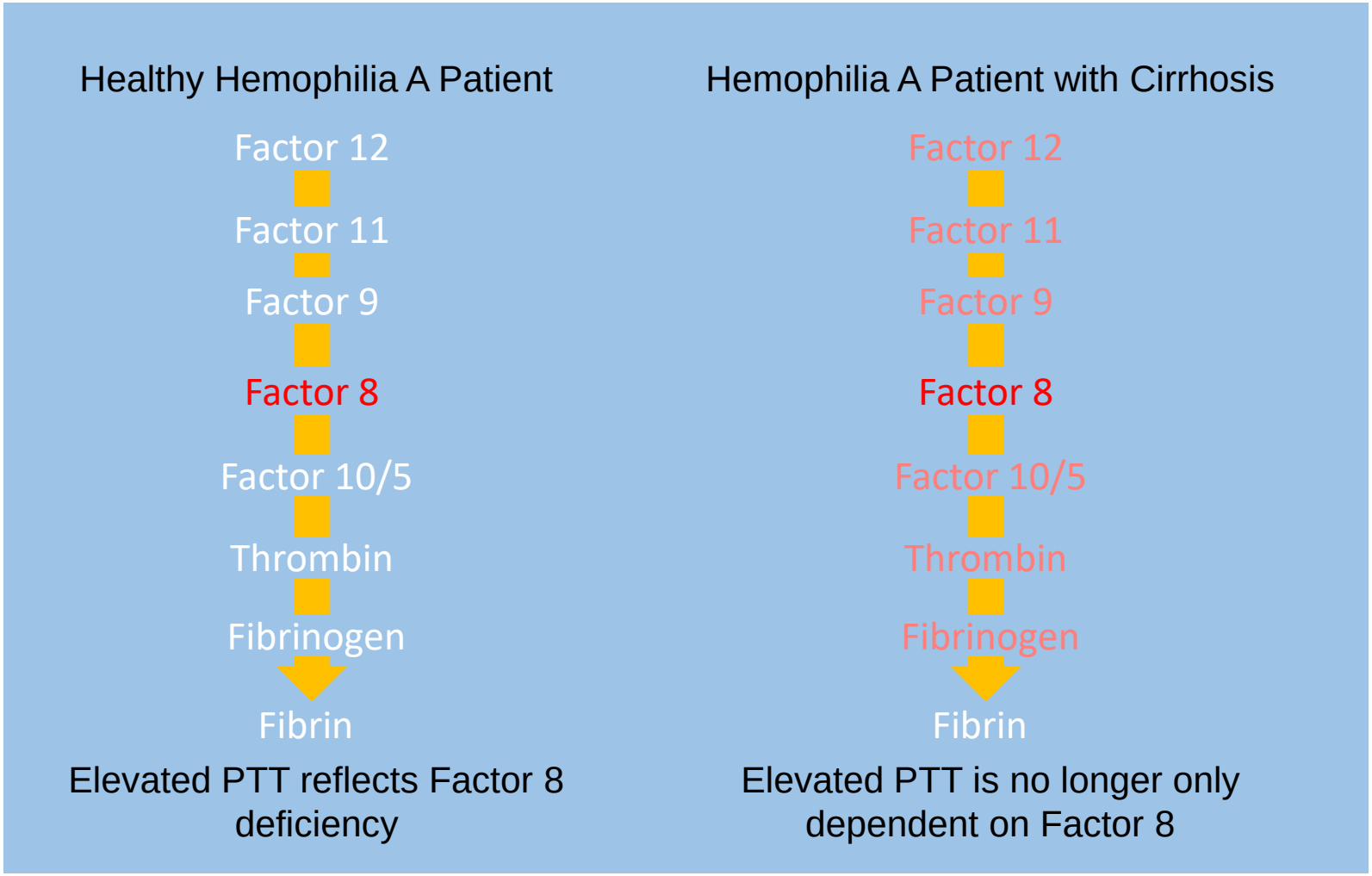
Chee Y et al. *BJH* 2008; Kitchens C. *JTH* 2005; Levy JH et al. *Clinics in laboratory medicine* 2014

INR/PT & PTT Pitfalls: 1) Variable Sensitivity

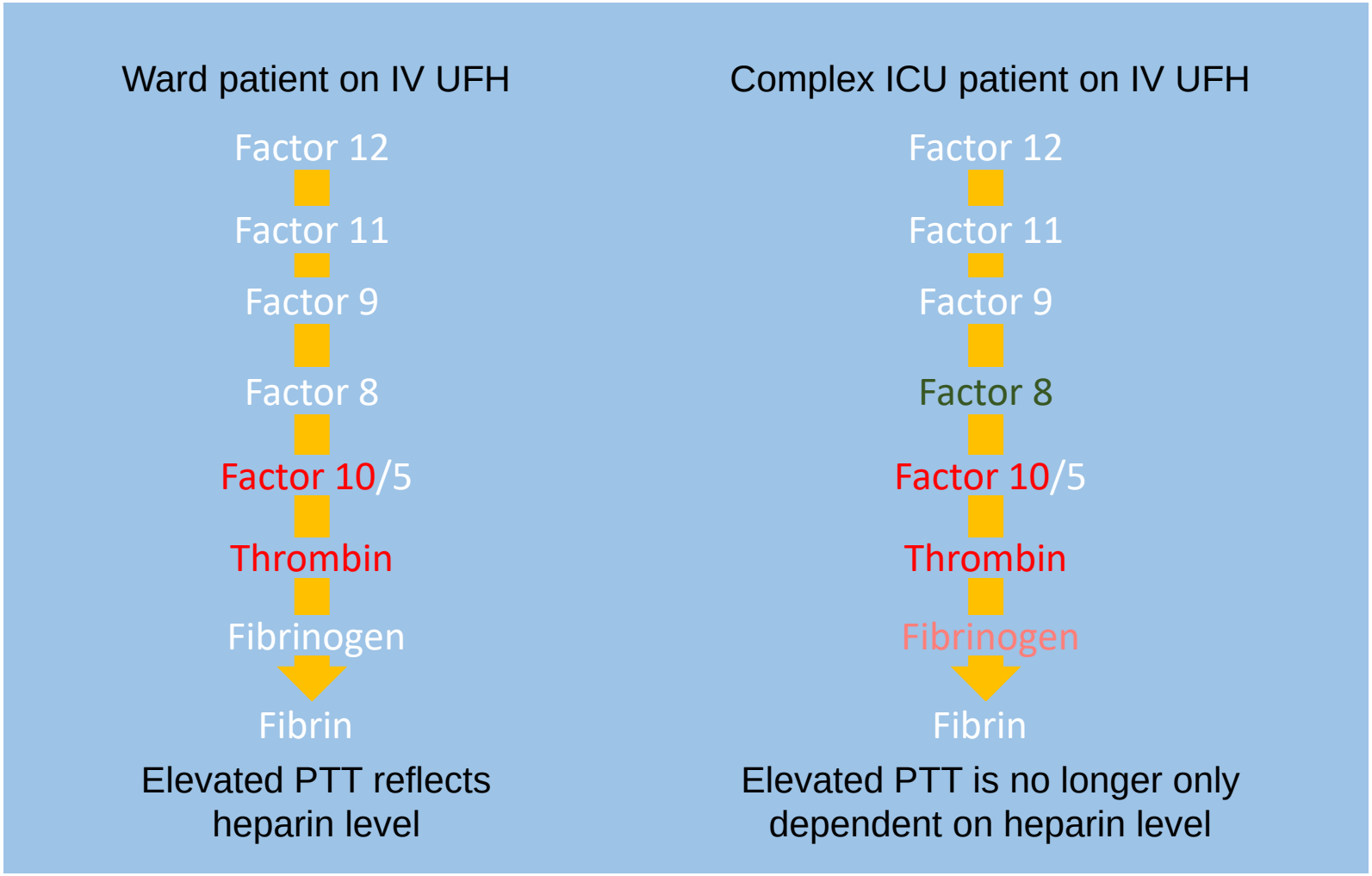
Drug Class	DOAC	Conventional Coagulation Testing		
		PT	APTT	TT
Direct Thrombin Inhibitor	Dabigatran	↑/↔	↑	↑
Factor Xa Inhibitor	Rivaroxaban	↑/↔	↑/↔	N/A
	Apixaban	↑/↔	↑/↔	N/A
	Edoxaban	↑/↔	↑/↔	N/A

Shih A and Crowther M. ASH Education Program 2016

INR/PT & PTT Pitfalls: 2) Clotting factors are connected



INR/PT & PTT Pitfalls: 2) Clotting factors are connected



Take Home Point 2

Abnormal coagulation tests ≠ bleeding risk

Normal coagulation tests ≠ no bleeding risk

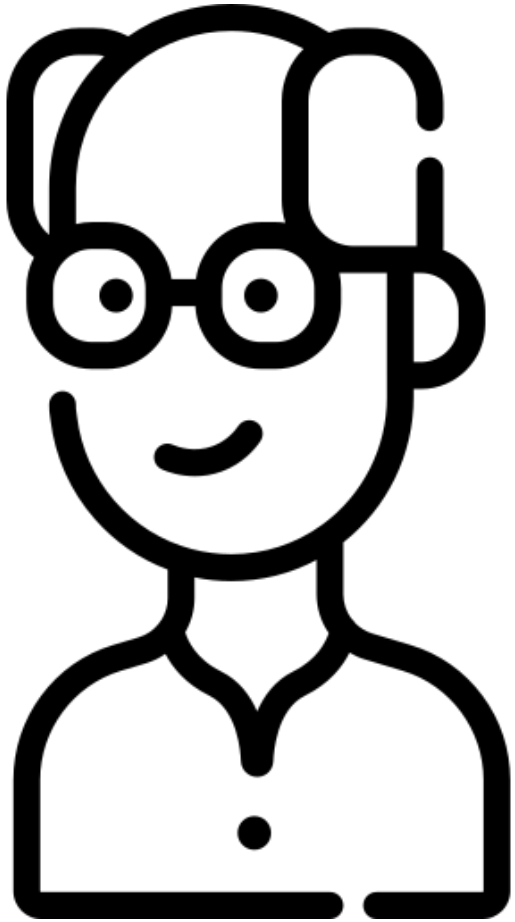
Putting it together: Assessing for bleeding risk

Case 1

72 year old male for cholecystectomy.

PMHx: HTN

Medications:
Amlodipine



Approach to Bleeding Assessment

1) Screen for bleeding risk

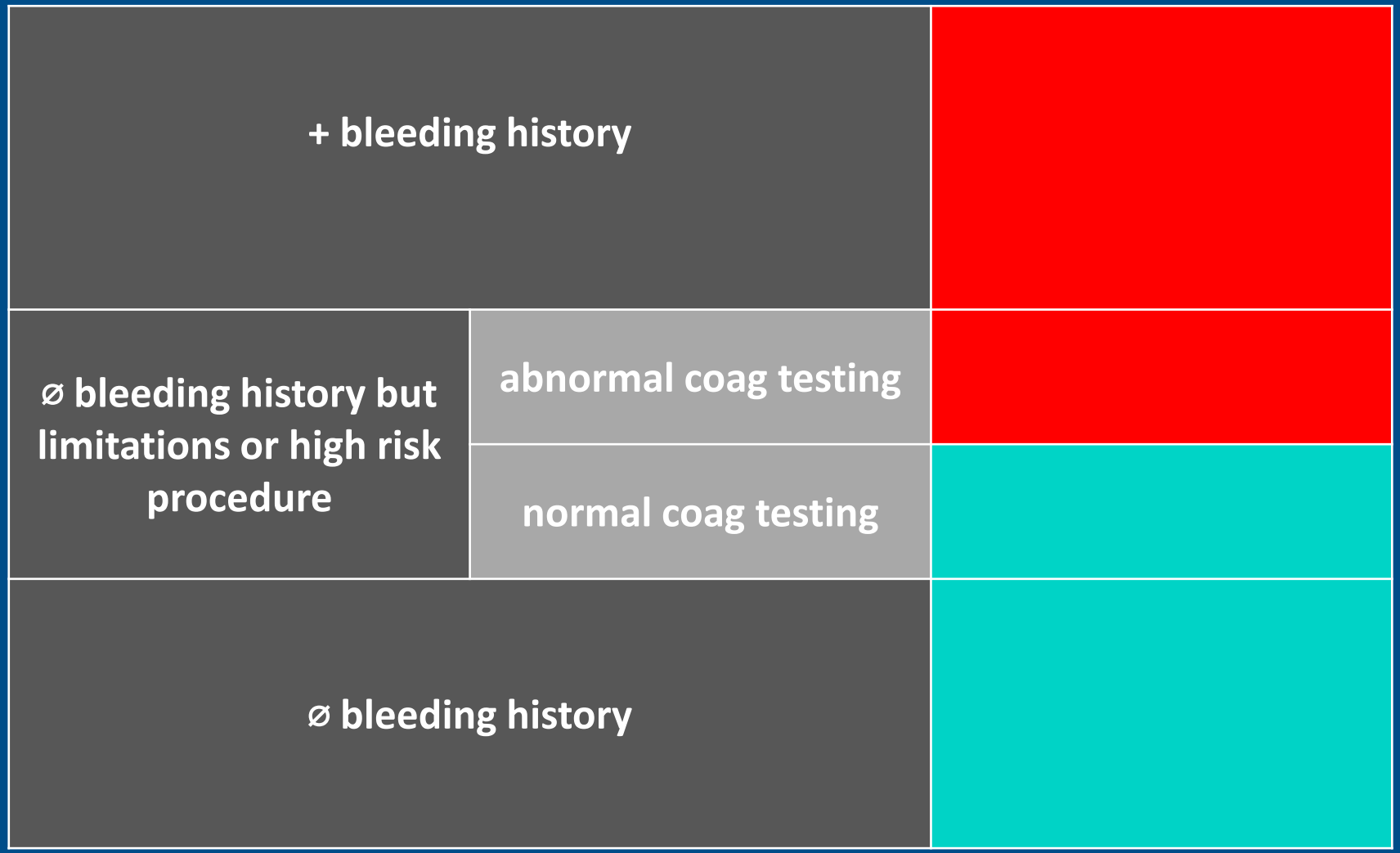
- Comprehensive bleeding history

*PTT & PT/INR for high risk surgeries or limited bleeding challenges

Bleeding Score = 7

1. History of epistaxis since childhood, requiring cauterization
2. Easy bruising
3. Bleeding following tooth extraction requiring packing

Decision for OR – General Rule



Approach to Bleeding Assessment

2) **Determine bleeding phenotype:**

- Clues from bleeding history
- Global hemostatic assays
  - CBC
  - PT/INR & PTT

- Predominately mucocutanous bleeding (? congenital)
- Hb 118, Plt 180, WBC 7.2
- INR 1.1, PTT 36 s

Mild factor deficiency vs. VWD vs. Platelet disorder

Approach to Bleeding Assessment

3) Confirm a Diagnosis :

- Involve Hematology
- Guided by global assays and clinical suspicion

1. PFA, platelet aggregation
2. VWD profile
3. Factor levels
4. Factor Inhibitors

- Abnormal PFA, no specific pattern with aggregation
- VWF antigen 0.62, VWF activity 0.65
- F8 0.81, F9 0.74, F11 0.88

Bleeding Disorder NYD

Take Home Points

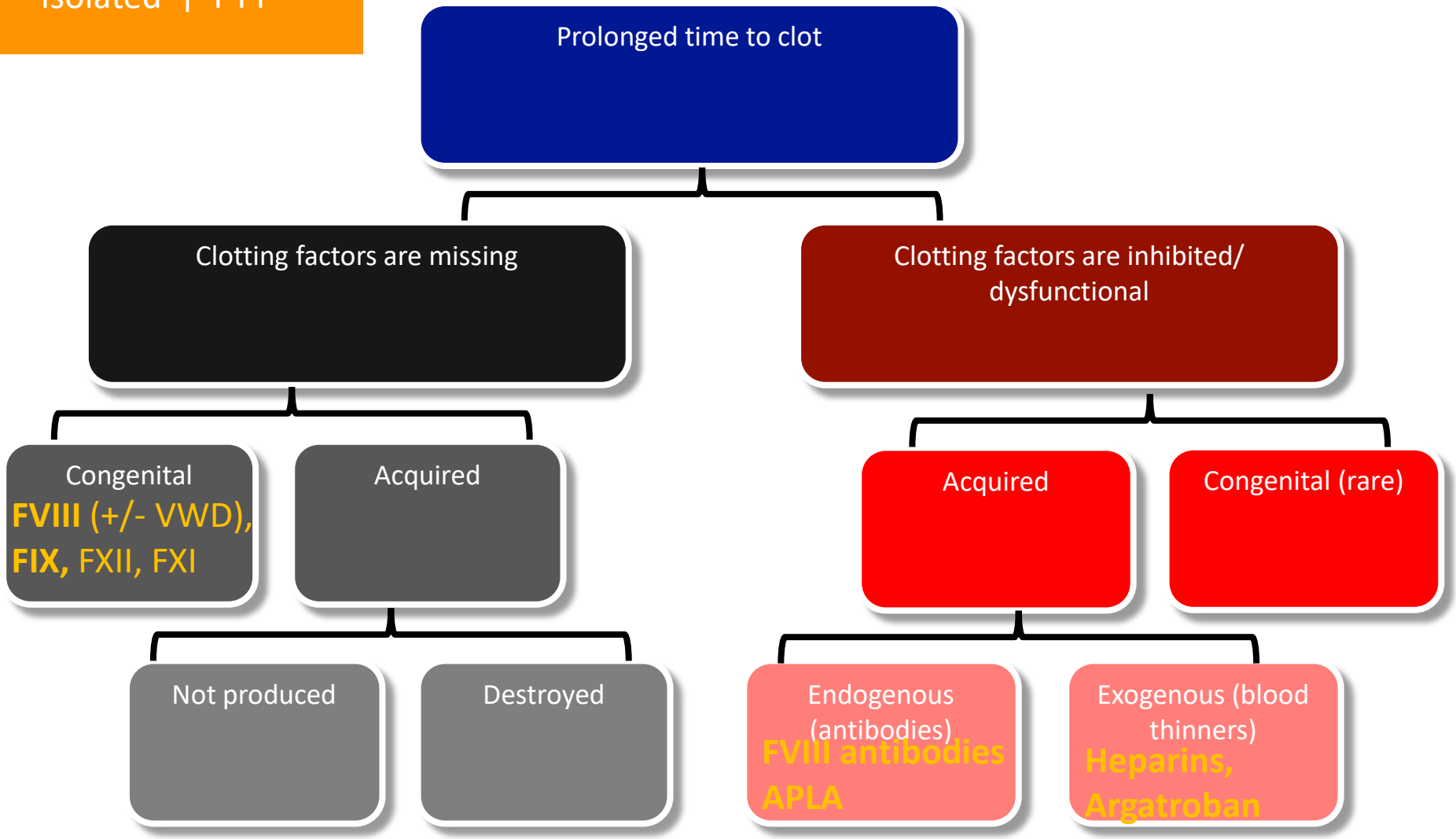
1) The Bleeding History is the most important test of hemostasis

2) Coagulation tests can help clarify risk of bleeding/ direct treatment in patients who have suspicious histories and physicals

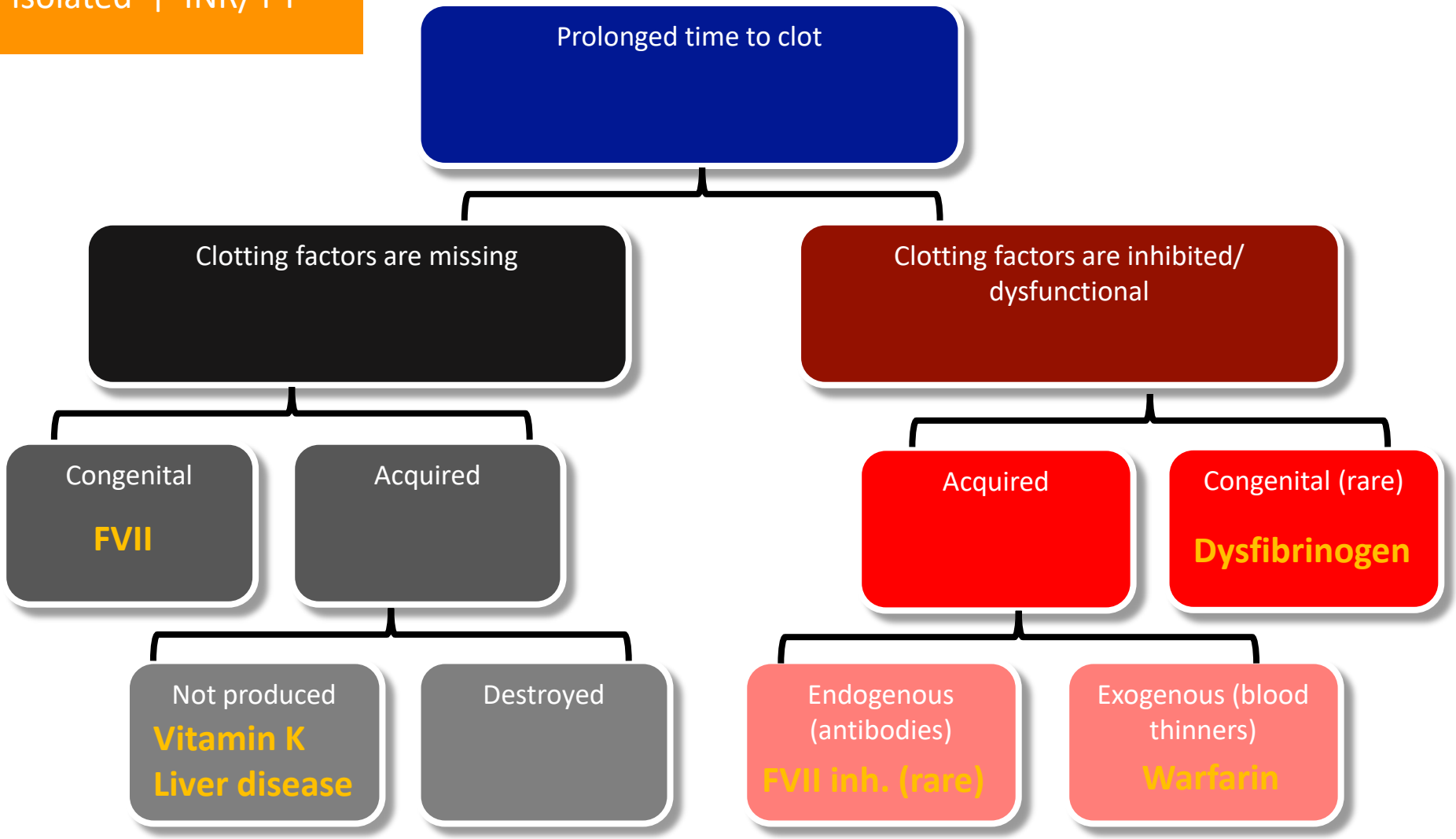
3) INR/PT and PTT have wide DDx and variable sensitivity/ specificity

Appendix

Isolated ↑ PTT



Isolated ↑ INR/ PT



Target: Outpatient Setting

MAKING THE BEST USE OF COAGULATION TESTS AND TOOLS

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BAT = Bleeding Assessment Tool
PT = Prothrombin Time
INR = International Normalized Ratio
aPTT = Activated Partial Thromboplastin Time

- Suspected bleeding disorder (e.g. recurrent epistaxis, excessive post-operative bleeding, menorrhagia, post partum hemorrhage)

CONSIDER BAT

(aPTT is rarely useful in the outpatient setting)

- Warfarin therapy
- Liver disease
- Risk factor for vitamin K deficiency (e.g. malnutrition, fat soluble vitamin malabsorption, cholestasis, prolonged antibiotics)

CONSIDER PT/INR

TOP 5 REASONS NOT TO ORDER PT/INR or aPTT

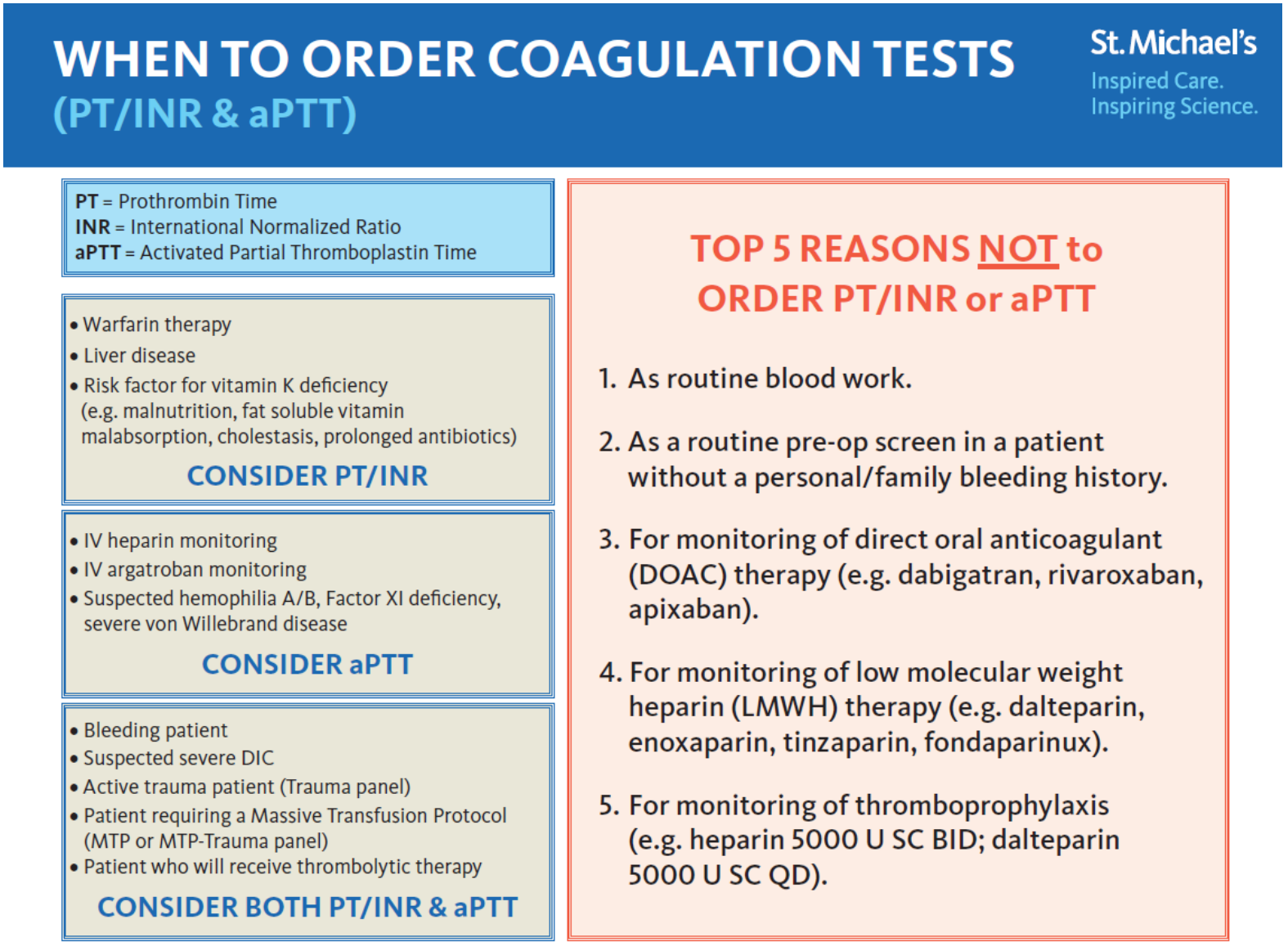
1. As routine blood work.
2. As a routine pre-op screen in a patient without a personal/family bleeding history.
3. For monitoring of direct oral anticoagulant (DOAC) therapy (e.g. dabigatran, rivaroxaban, apixaban).
4. For monitoring of low molecular weight heparin (LMWH) therapy (e.g. dalteparin, enoxaparin, tinzaparin, fondaparinux).
5. For monitoring of thromboprophylaxis (e.g. heparin 5000 U SC BID; dalteparin 5000 U SC QD).

MOST COMMON BLEEDING DISORDERS IN ORDER OF PREVALENCE:

1) Von Willebrand Disease
2) Platelet Function Disorders
3) Hemophilia A (FVIII) and B (FIX)
4) Factor XI Deficiency

Courtesy M. Sholzberg

Target: Inpatient Setting



WHEN TO ORDER COAGULATION TESTS
(PT/INR & aPTT)

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PT = Prothrombin Time
INR = International Normalized Ratio
aPTT = Activated Partial Thromboplastin Time

- Warfarin therapy
- Liver disease
- Risk factor for vitamin K deficiency (e.g. malnutrition, fat soluble vitamin malabsorption, cholestasis, prolonged antibiotics)

CONSIDER PT/INR

- IV heparin monitoring
- IV argatroban monitoring
- Suspected hemophilia A/B, Factor XI deficiency, severe von Willebrand disease

CONSIDER aPTT

- Bleeding patient
- Suspected severe DIC
- Active trauma patient (Trauma panel)
- Patient requiring a Massive Transfusion Protocol (MTP or MTP-Trauma panel)
- Patient who will receive thrombolytic therapy

CONSIDER BOTH PT/INR & aPTT

TOP 5 REASONS NOT to ORDER PT/INR or aPTT

1. As routine blood work.
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3. For monitoring of direct oral anticoagulant (DOAC) therapy (e.g. dabigatran, rivaroxaban, apixaban).
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Form No. XXXXX Dev. 02/2016

Courtesy of M. Sholzberg

HEMOSTASIS SIMPLIFIED

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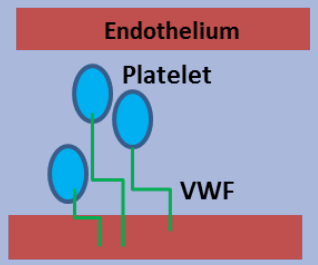
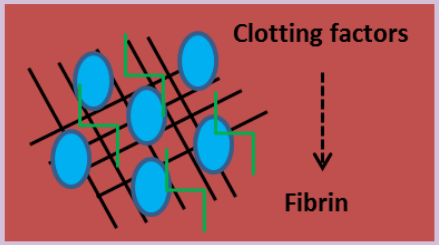
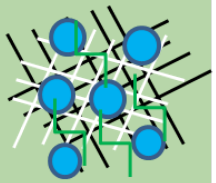
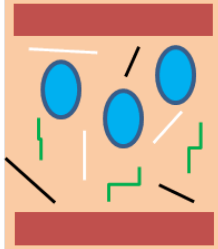
HEMOSTASIS PHYSIOLOGY	Primary hemostasis = formation of platelet plug	Secondary hemostasis = formation of fibrin rich clot	Clot stabilization = formation of strong clot	Fibrinolysis = clot breakdown
				
COMMON BLEEDING DISORDERS	• Von Willebrand Disease • Platelet Function Disorders	• Hemophilia A and B • FXI Deficiency		
ROUTINE TESTS	CBC • Assesses platelet count but not function	PT/INR and aPTT • **ONLY** test secondary hemostasis • Reagents are attuned to detect a single factor deficiency **ONLY** if it is < 30% of normal function • Do **NOT** assess primary hemostasis (VWD* and platelet disorders = the most common bleeding disorders)		
BLEEDING ASSESSMENT TOOL (BAT)	☑	☑	☑	☑

Slide courtesy M. Sholzberg

BLEEDING ASSESSMENT TOOL (BAT): HOW TO ADMINISTER AND INTERPRET

St. Michael's
Inspired Care.
Inspiring Science.

BACKGROUND

- BATs are good screening tests for bleeding disorders
- The Condensed MCMDM-1* BAT is the one used at St. Michael's hospital
- Validated for use in von Willebrand disease, platelet disorders, hemophilia carriers, and other mild bleeding disorders (sensitivity: 85-100%, NPV: 0.92-1.0)[1-5]

ADMINISTRATION

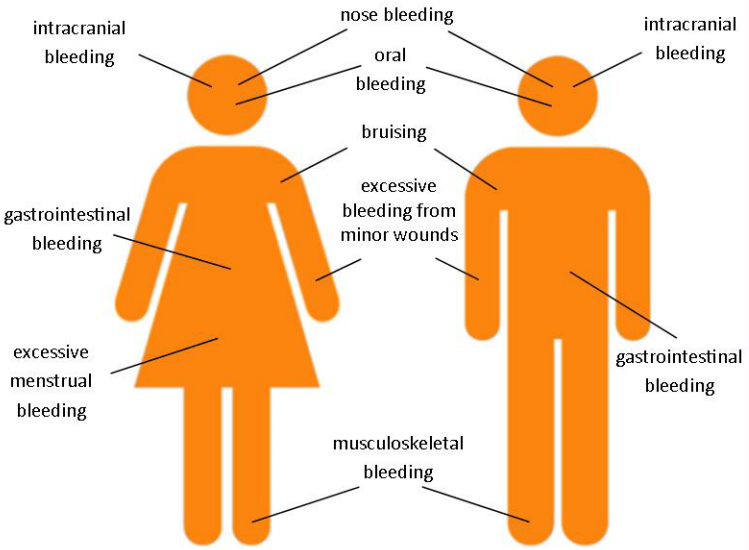
- Time to complete: 5-10 minutes
- Expert administered (MD, NP, or RN)

INTERPRETATION

- Negative BAT score (<4 for adults, <2 for children) AND negative family history of bleeding
  - ⇒ no additional hemostatic evaluation required
- Positive BAT score (≥4 for adults, ≥2 for children) AND/OR positive family history of excessive bleeding
  - ⇒ **Hematology referral suggested**

BLEEDING SYMPTOM CATEGORIES

1. Spontaneous Bleeding



2. Bleeding with Challenges

- Surgery
- Dental Extraction
- Childbirth

*MCMDM-1 = Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand disease

1. Bowman et al. (2008) 2. Tosetto et al. (2011) 3. Azzam et al. (2012) 4. Rydz and James (2012) 5. Paroskie et al. (2015)

Slide courtesy M. Sholzberg