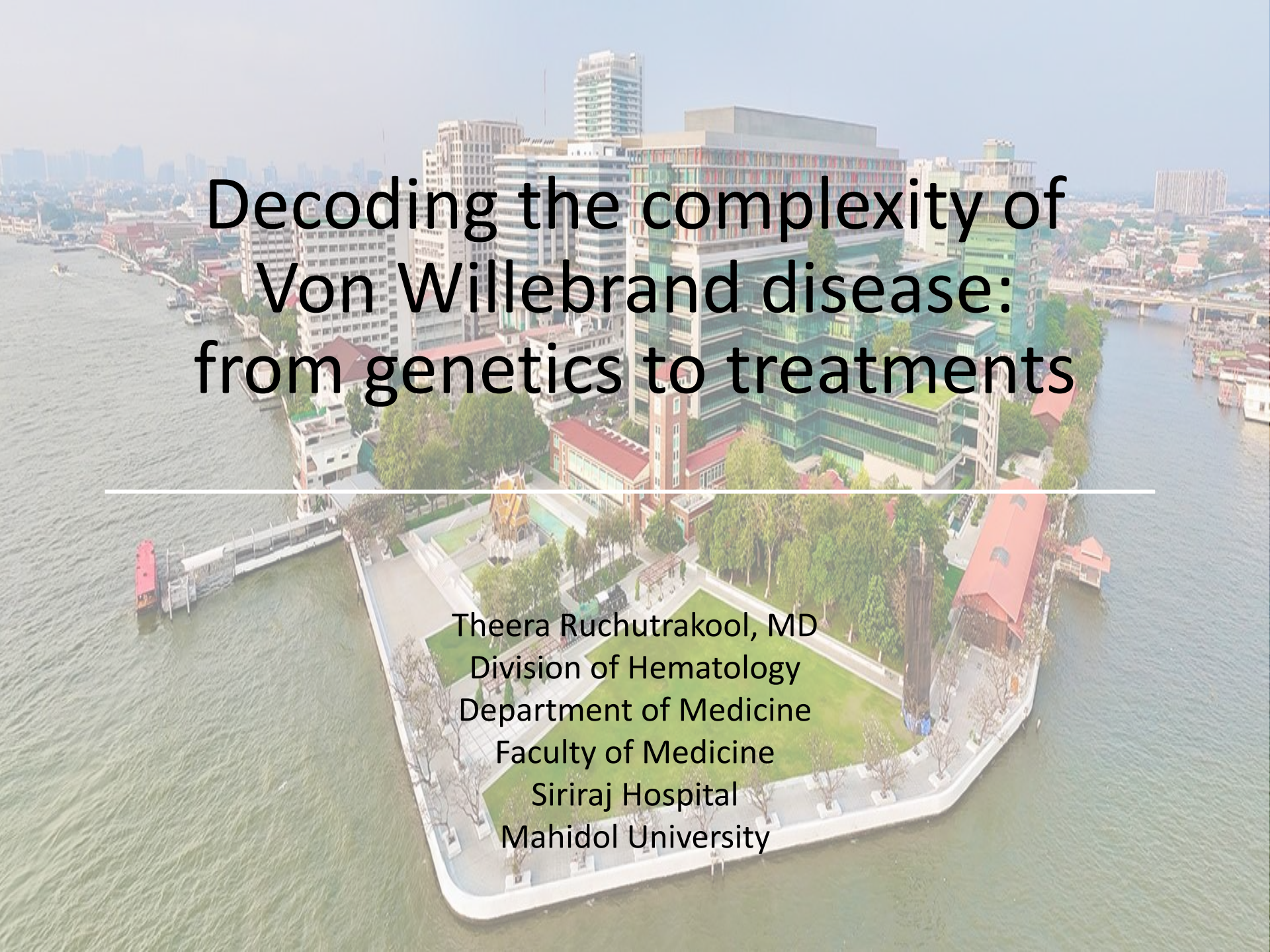


An aerial photograph of the Siriraj Hospital and Mahidol University campus, situated along a wide river. The main building is a large, modern structure with a colorful, multi-story facade. To the left, there's a smaller building with a red roof. The campus is surrounded by lush green trees and a paved walkway. A small boat is visible on the river in the foreground. The background shows a dense urban skyline with various high-rise buildings.

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Theera Ruchutrakool, MD
Division of Hematology
Department of Medicine
Faculty of Medicine
Siriraj Hospital
Mahidol University

Decoding the complexity of Von Willebrand disease: from genetics to treatments

A 52-year-old man presented with acute abdominal pain, prominently at right upper quadrant. Ultrasonography revealed acute cholecystitis and an urgent laparoscopic cholecystectomy was scheduled.

He had a history of right upper femur fracture 10 years ago from car accident. He underwent open reduction and internal fixation. Four months later, a large mass at right thigh was detected.

Preoperative coagulation times:

APTT 65 seconds (25-30 seconds)

PT 11 seconds (11-13 seconds)

FVIII:C 5 U/dL

VWF:Ag	12 U/dL
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VWF:GPIbM	14 U/dL
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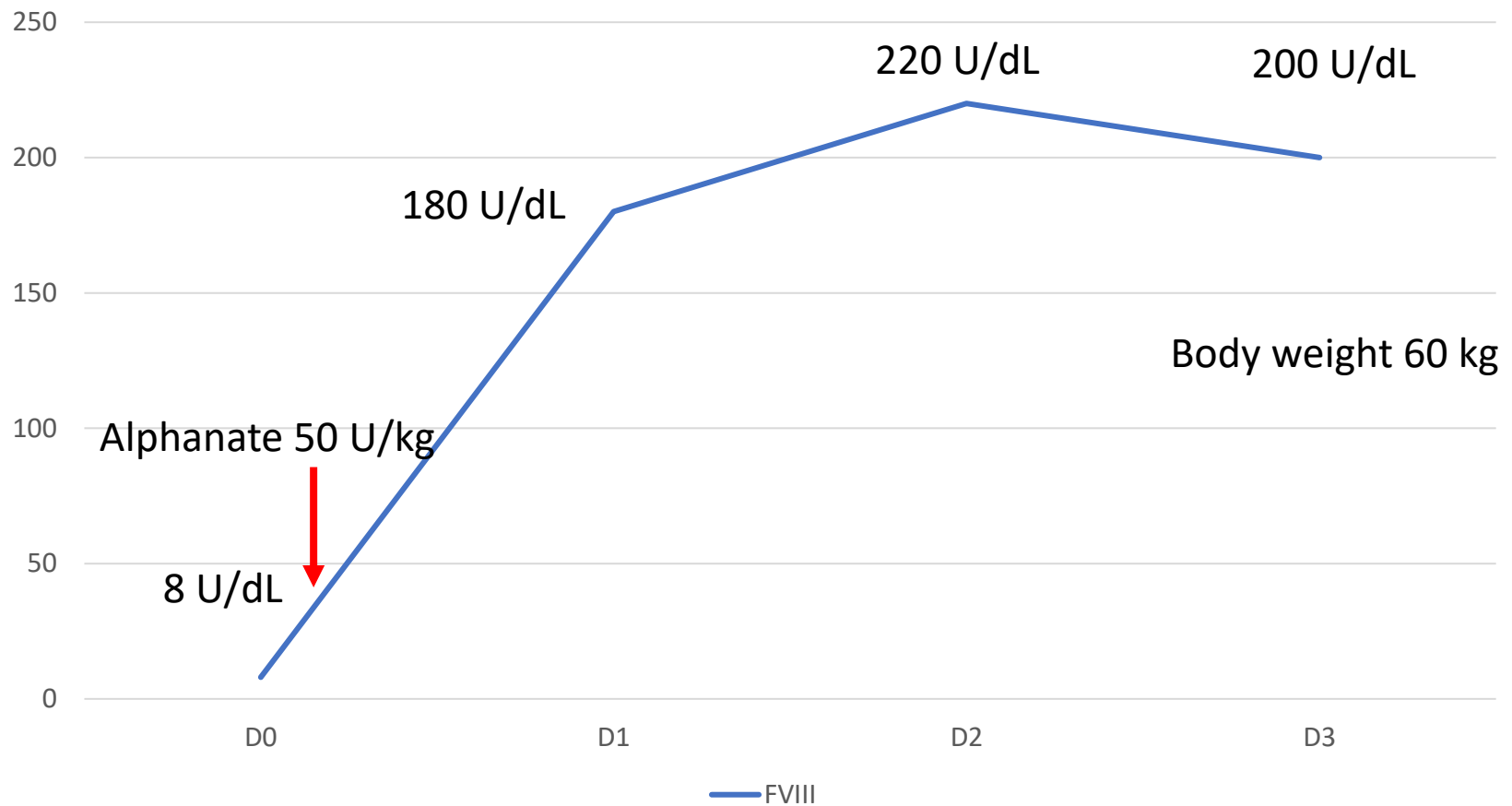
VWF:CB	18 U/dL
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FVIII:C/VWF:Ag	0.4
----------------	-----

VWF:GPIbM/VWF:Ag	1.1
------------------	-----

VWF:CB/VWF:Ag	1.5
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Decoding the complexity of Von Willebrand disease: from genetics to treatments



Decoding the complexity of Von Willebrand disease: from genetics to treatments

Outline

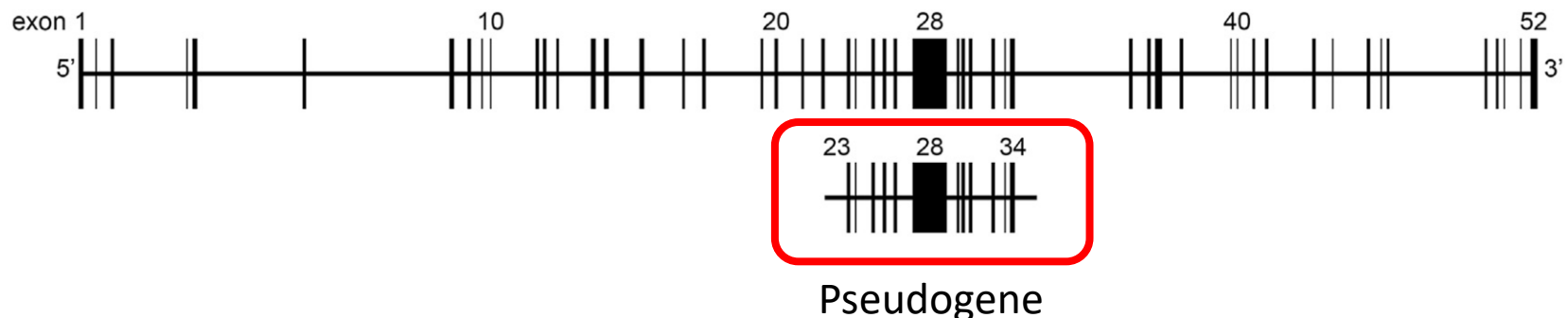
- Biology of Von Willebrand factor (VWF)
- Genotypes, phenotypes and classification
- Diagnosis
- Treatment

Decoding the complexity of Von Willebrand disease: from genetics to treatments

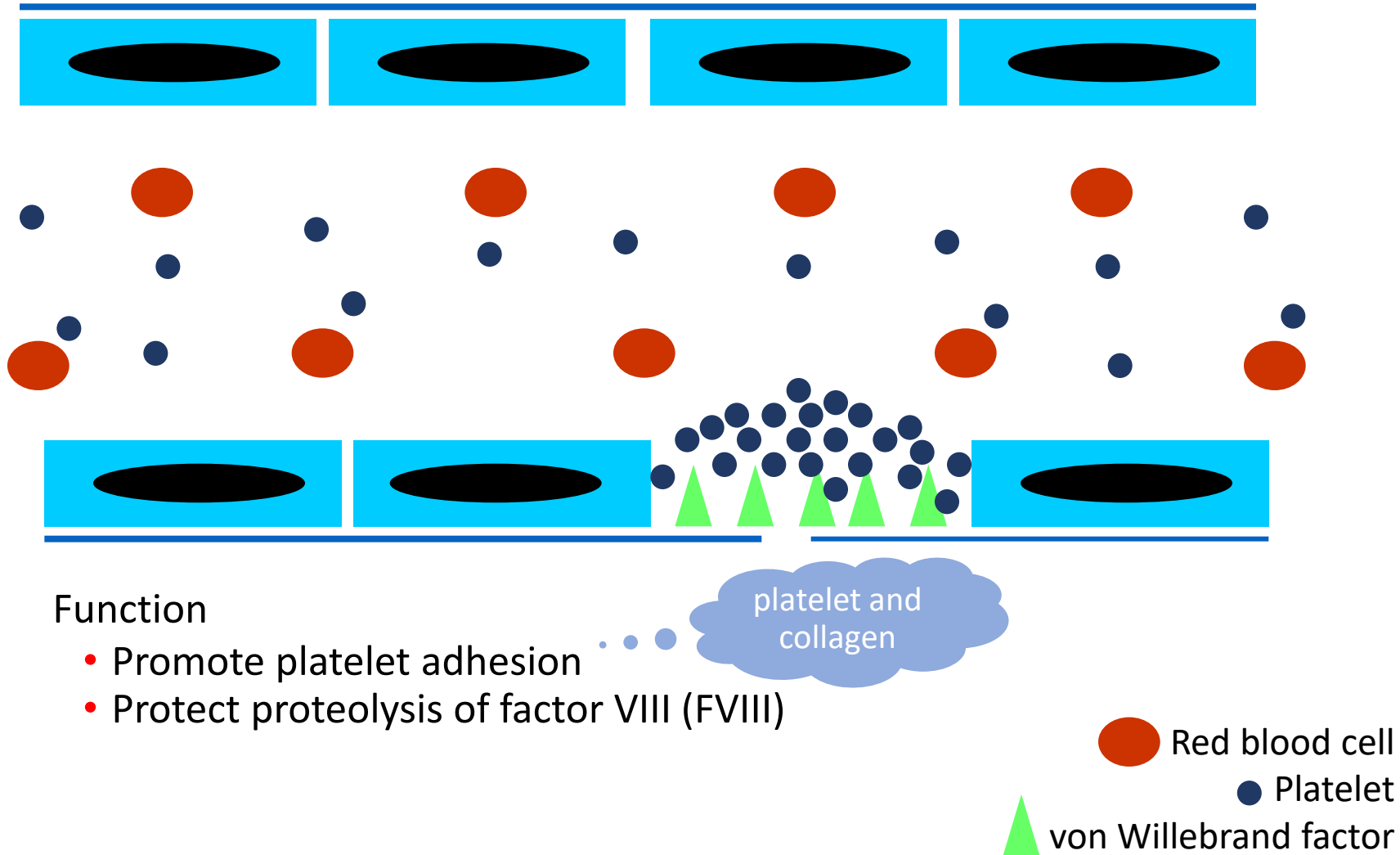
Biology of Von Willebrand factor (VWF)

Decoding the complexity of Von Willebrand disease: from genetics to treatments

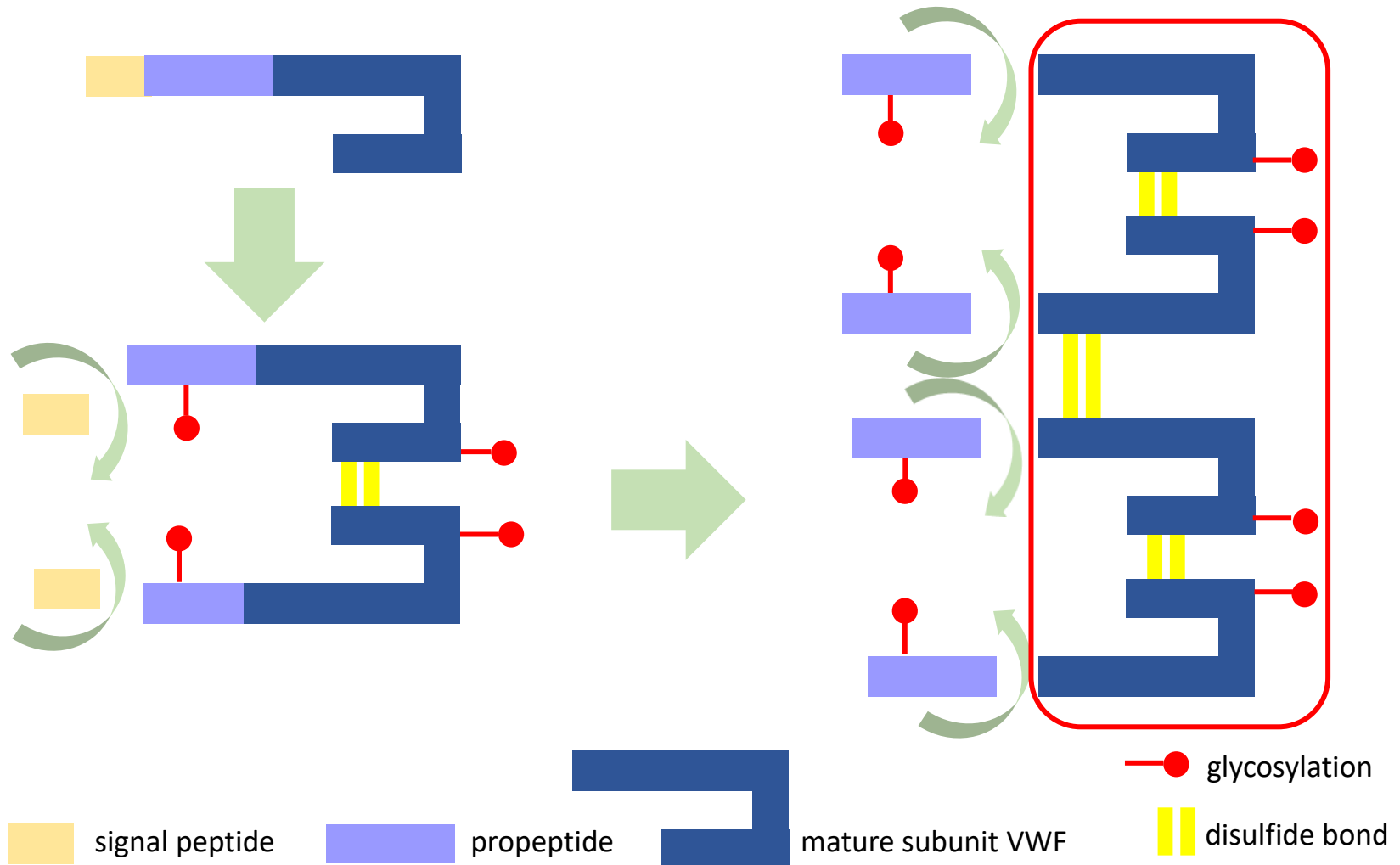
- The most common hereditary bleeding disorder.
- VWF gene, located on short arm of *chromosome 12* contains 180 kb (0.1% of chromosome 12).
- Composed of 52 exons (size range from 40 bp to 1.4 kb).
- Pseudogene at *chromosome 22*.



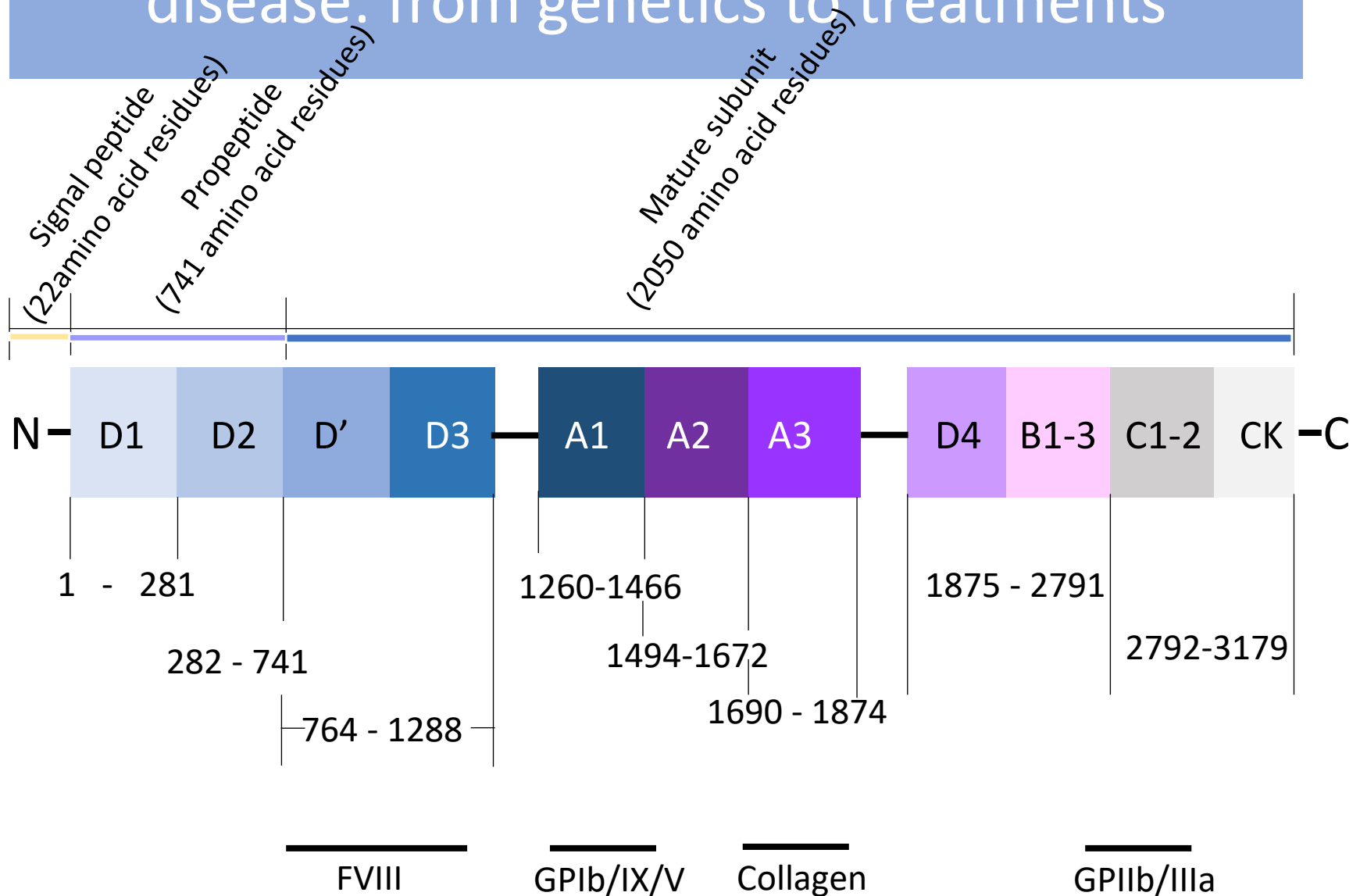
Decoding the complexity of Von Willebrand disease: from genetics to treatments



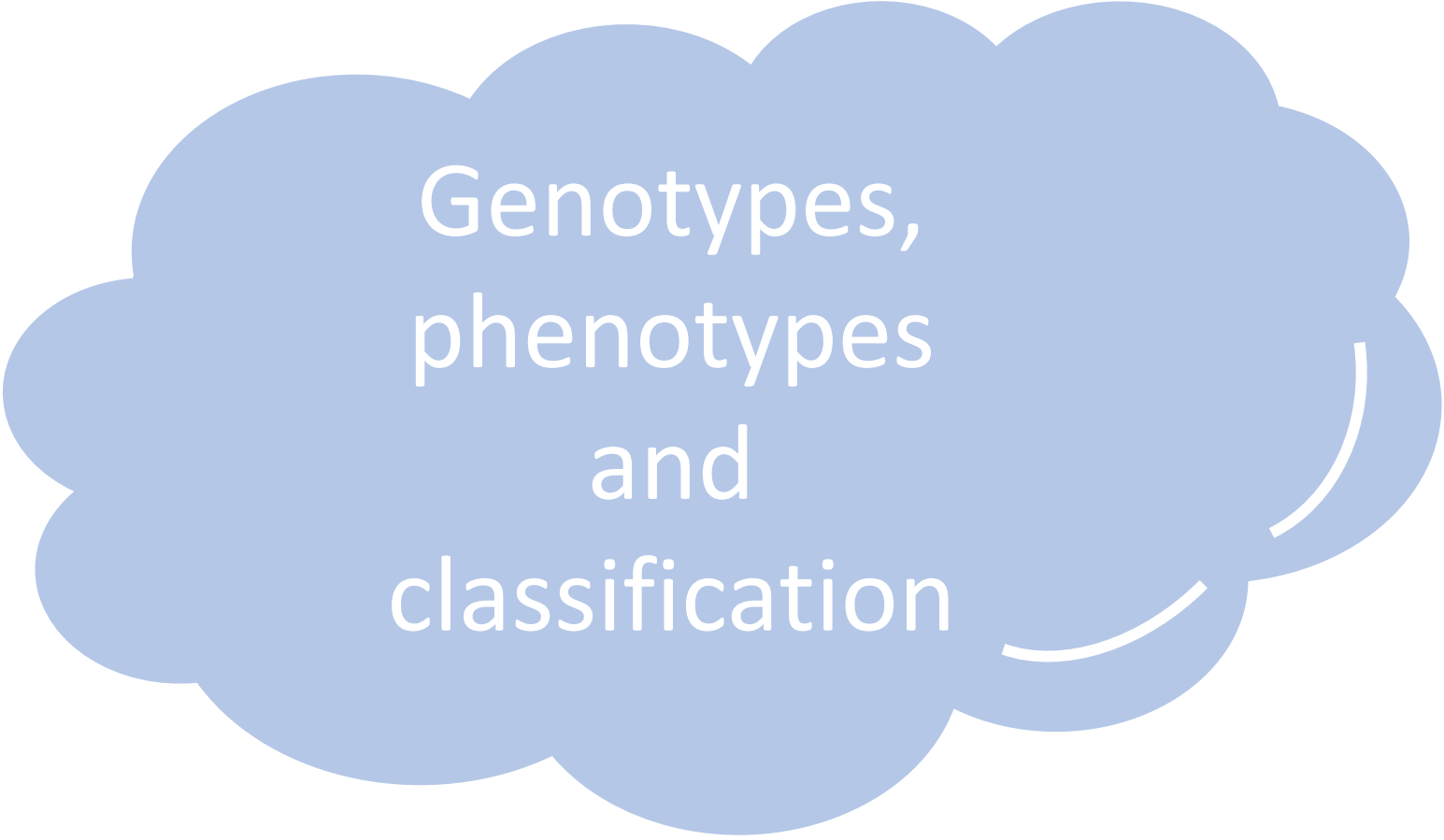
Decoding the complexity of Von Willebrand disease: from genetics to treatments



Decoding the complexity of Von Willebrand disease: from genetics to treatments



Decoding the complexity of Von Willebrand disease: from genetics to treatments

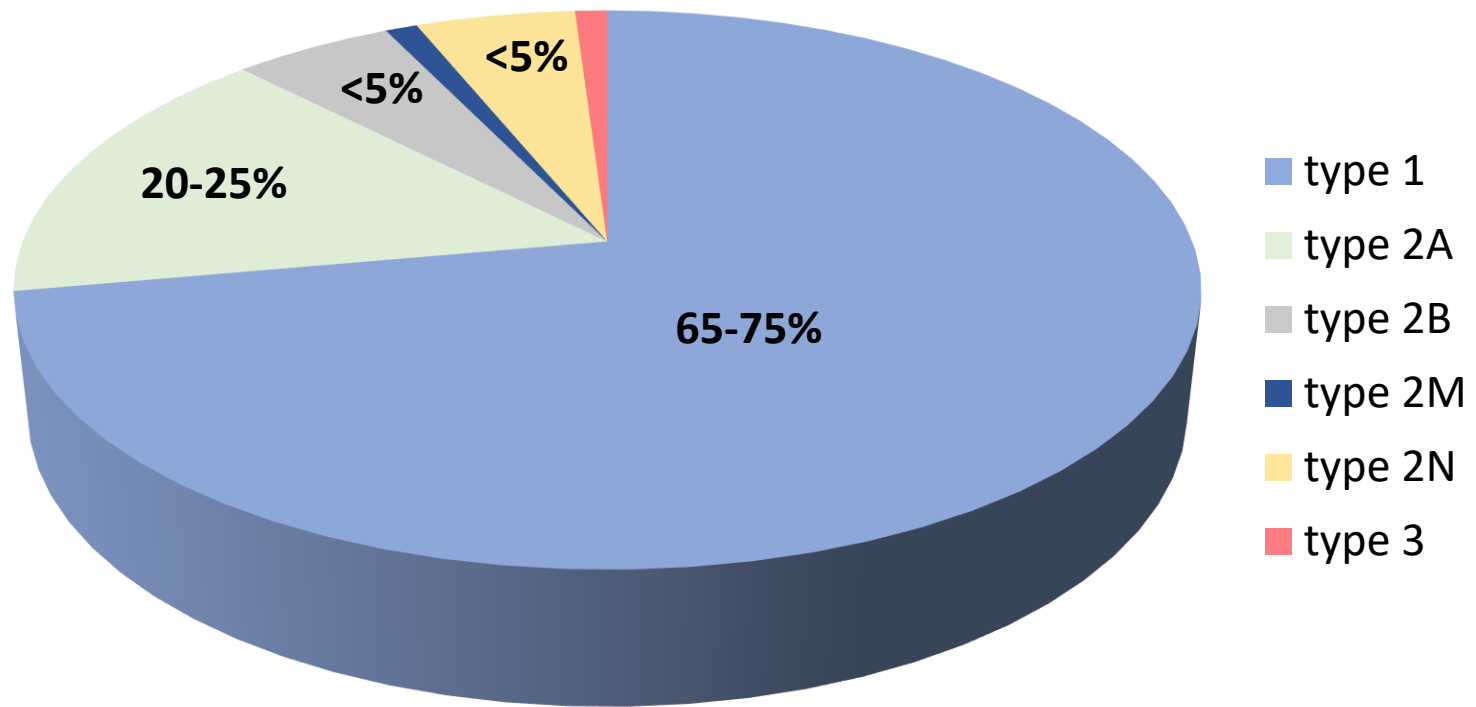


Genotypes,
phenotypes
and
classification

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Type	Defect	Genetic Transmission
1	Quantitative	AD with incomplete penetrance
2	Qualitative • 2A • 2B • 2M • 2N	AD, variability of expression, highly penetrance AD, variability of expression, highly penetrance AD AR, homozygous, compound heterozygous, FVIII binding mutation + null mutation
3	Combination	AR

Decoding the complexity of Von Willebrand disease: from genetics to treatments

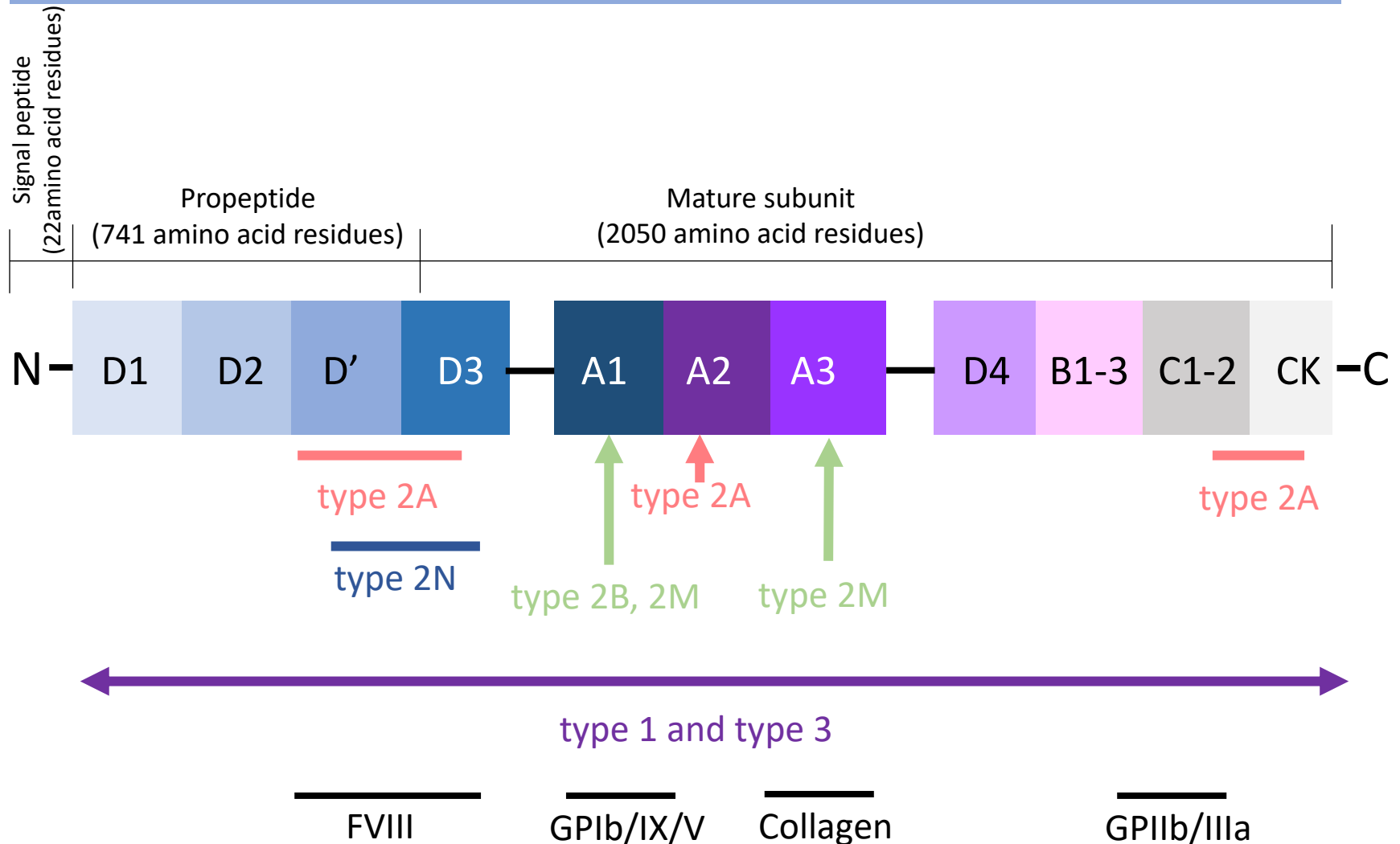


type 2M	rare
type 3	1-5:1,000,000

Robertson J, et al. Pediatr Clin North Am.2008;55:377-92.

Nichols WL, et al. Haemophilia.2008;14:171-232.

Decoding the complexity of Von Willebrand disease: from genetics to treatments



Decoding the complexity of Von Willebrand disease: from genetics to treatments

Type 2- point mutation-most common

- **2A** - missense mutation (exon **28-D'D3, A2 and C domain** influenced **assembly of multimer**, secretion and storage
 - missense mutation in **A2 domain** that **enhanced ADAMTS13 proteolysis**
- **2B** - missense mutation in **A1 domain** which is platelet GPIb/IX/V binding domain that **enhanced binding to GPIb**, and caused thrombocytopenia
- **2M** - missense mutation in **A1 domain** which is platelet GP Ib/IX/V binding domain **that decreased platelet binding affinity** and impaired collagen type VI binding
 - missense mutation in **A3 domain** will **impaired collagen type I and III binding (rare)**
- **2N** - missense mutation in **D'-D3 domain** which is factor VIII binding site that **caused low FVIII:C**

Decoding the complexity of Von Willebrand disease: from genetics to treatments



Diagnosis

Decoding the complexity of Von Willebrand disease: from genetics to treatments

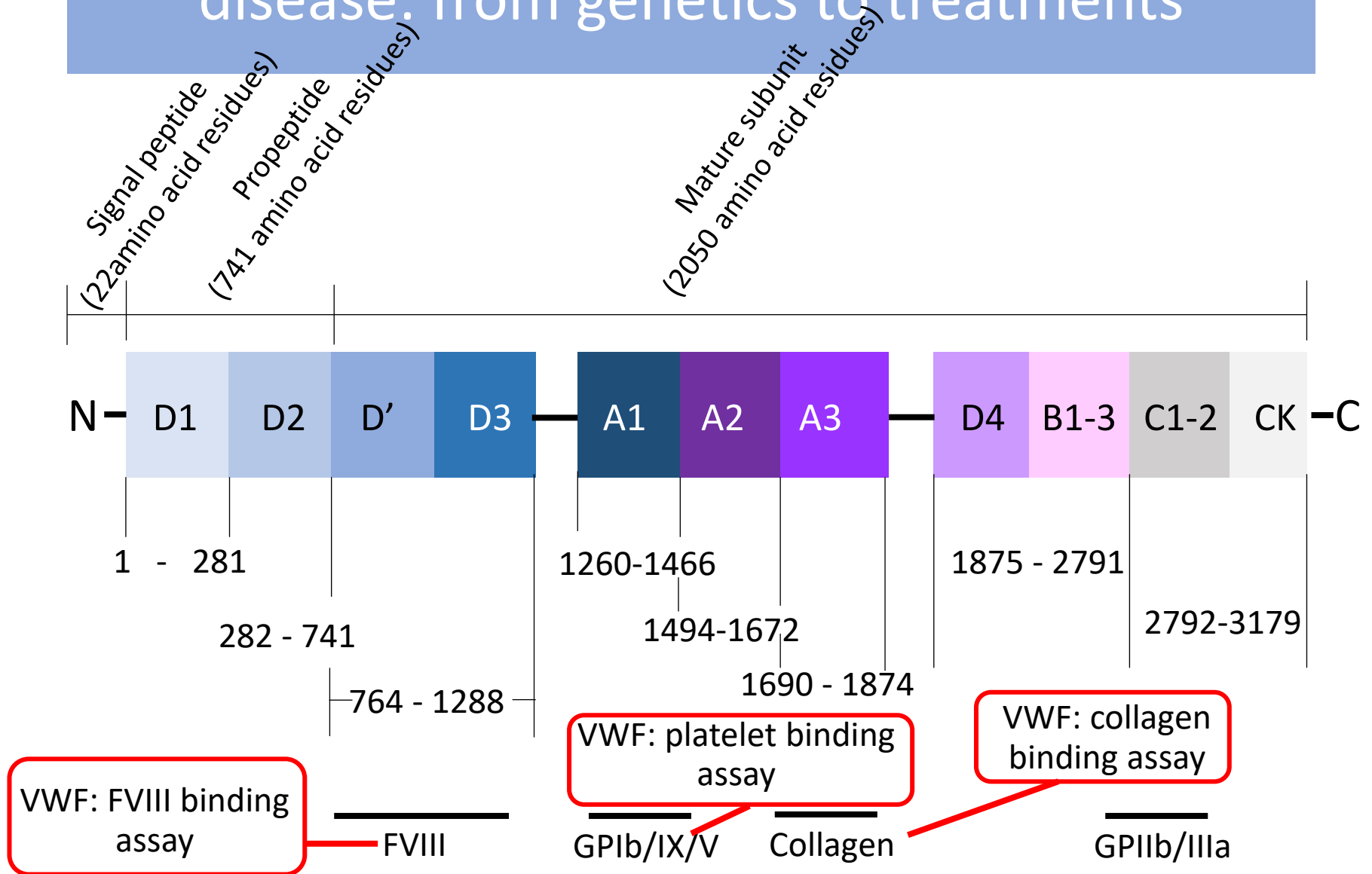
Diagnosis

- Clinical manifestation: bleeding score (BS)
- Laboratory:
 - CBC
 - APTT
 - VWF:Ag
 - VWF function:
 - Platelet binding: VWF:RCo, VWF:GPIbM, VWF:GPIbR
 - Collagen binding
 - FVIII binding
 - VWF:multimer
 - DDAVP trial

APTT: activated partial thromboplastin time; CBC: complete blood count;

DDAVP:1-Deamino-8-D-Arginine Vasopressin; PT: prothrombin time; VWF: Von Willebrand factor

Decoding the complexity of Von Willebrand disease: from genetics to treatments

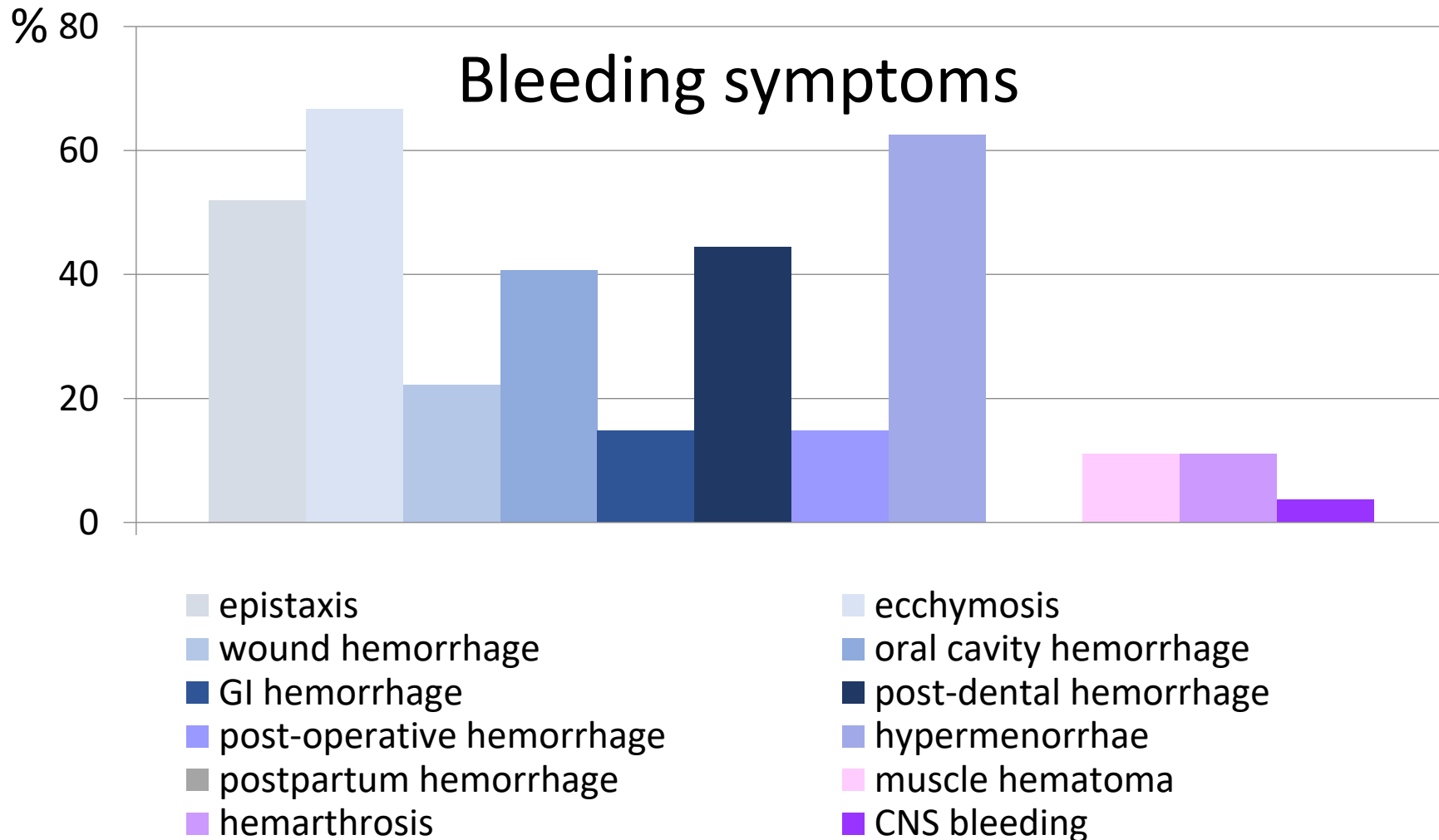


Decoding the complexity of Von Willebrand disease: from genetics to treatments

Clinical manifestation

- Age at presentation, sex, familial history
- Asymptomatic: prolonged bleeding after surgery
- Primary hemostatic defects
 - Mucosal bleeding, gastrointestinal bleeding (type 2A)
 - Ecchymosis
 - Hypermenorrhea
- Secondary hemostatic defects
 - Musculoskeletal bleeding
 - Hemarthrosis is rare (type 2N and type 3)

Decoding the complexity of Von Willebrand disease: from genetics to treatments



Decoding the complexity of Von Willebrand disease: from genetics to treatments

Bleeding questionnaire (BQ)	Score for individual bleeding symptom	Cut-off score	Remark
• Vicenza (2005)	0 - +3	≥3 males ≥5 females	first BQ, 40 minutes screening type 1 vWD (specificity 98% sensitivity 69%)
• MCMDM-1 (2006)	-1 - +4	> 3	adding negative score for increased sensitivity, 40 minutes
• Condensed MCMDM-1 (2008)	-1 - +4	≥ 4	5-10 minutes (specificity 81-98% sensitivity 25-100%) NPV 0.99 for type 1 and type 3 OC from normal control
• Pediatric BQ (2009)	-1 - +4	≥ 2 (boy and girl)	pediatric specific bleeding symptoms 20 minutes
• ISTH-BAT (2010)	0 - +4	≥ 4 males ≥ 6 females ≥ 3 children	remove -1 score, 20 minutes

Decoding the complexity of Von Willebrand disease: from genetics to treatments

CLINICAL GUIDELINES



ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease

Paula D. James,¹ Nathan T. Connell,² Barbara Ameer,^{3,4} Jorge Di Paola,⁵ Jeroen Eikenboom,⁶ Nicolas Giraud,⁷ Sandra Haberichter,⁸ Vicki Jacobs-Pratt,⁹ Barbara Konkle,^{10,11} Claire McLintock,¹² Simon McRae,¹³ Robert R. Montgomery,¹⁴ James S. O'Donnell,¹⁵ Nikole Scappe,¹⁶ Robert Sidonio Jr,¹⁷ Veronica H. Flood,^{14,18} Nedaa Husainat,¹⁹ Mohamad A. Kalot,¹⁹ and Reem A. Mustafa¹⁹

¹Department of Medicine, Queen's University, Kingston, ON, Canada; ²Brigham and Women's Hospital, Harvard Medical School, Boston, MA; ³Pharmacology Consulting, Princeton Junction, NJ; ⁴Rutgers-Robert Wood Johnson Medical School, New Brunswick, NJ; ⁵Department of Pediatrics, Washington University in St. Louis, St. Louis, MO; ⁶Division of Thrombosis and Hemostasis, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands; ⁷Marseille, France; ⁸Diagnostic Laboratories, Versiti Blood Research Institute, Milwaukee, WI; ⁹Auburn, ME; ¹⁰Bloodworks Northwest, Seattle, WA; ¹¹Division of Hematology, University of Washington, Seattle, WA; ¹²National Women's Health, Auckland City Hospital, Auckland, New Zealand; ¹³Northern Cancer Services, Launceston General Hospital, Launceston, TAS, Australia; ¹⁴Versiti Blood Research Institute, Milwaukee, WI; ¹⁵Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland; ¹⁶Coraspol, PA; ¹⁷Aflac Cancer and Blood Disorders, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; ¹⁸Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; and ¹⁹Outcomes and Implementation Research Unit, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Recommendation 1:

Suggested using BAT rather than unstandardized clinical assessment in VWD patients with low probability (at primary care setting).

Recommendation 2:

Suggested against using BAT in order to perform specific laboratory in VWD patients with intermediate probability (at hematology clinic).

Recommendation 3:

Suggested against using BAT in order to perform specific laboratory in VWD patients with high probability (first degree relatives of VWD patients).



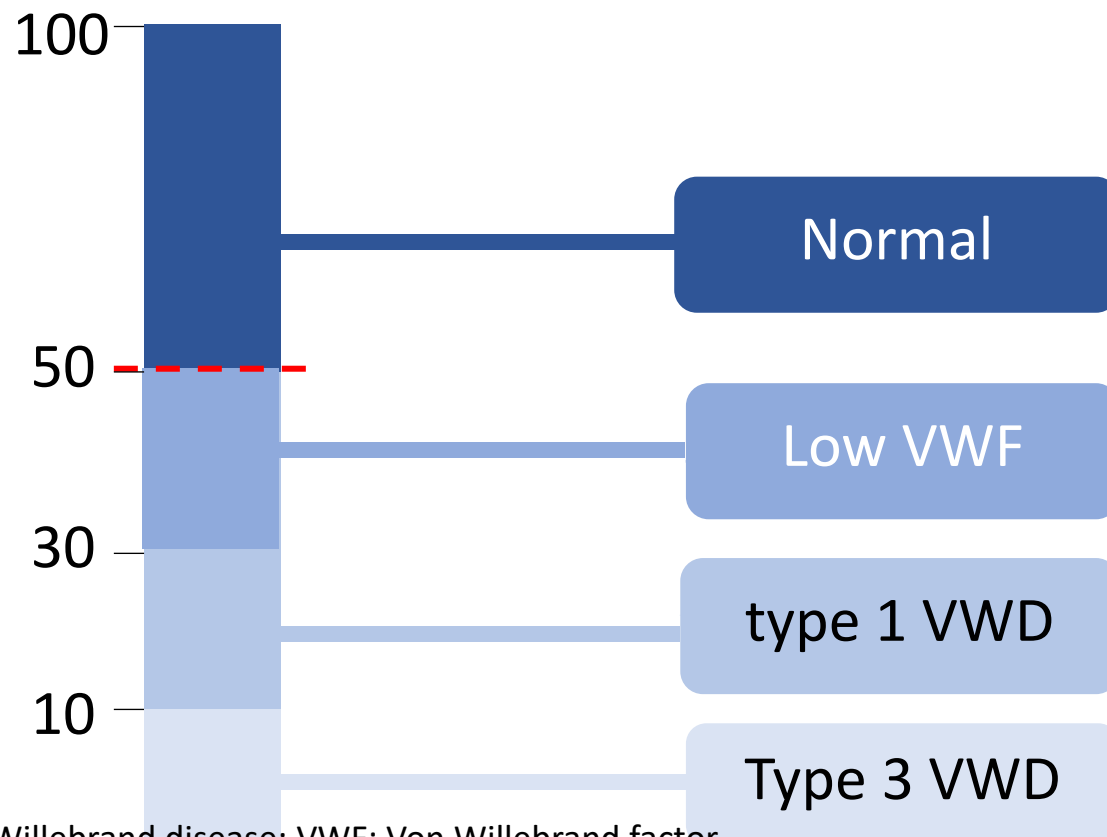
SCORE 7

	SCORE				
SYMPTOMS (up to the time of diagnosis)	0 ⁰	1 ⁰	2	3	4
Epistaxis	☐ No/trivial	☐ - > 5/year or - more than 10 minutes	☒ Consultation only*	☐ Packing or cauterization or antifibrinolytic	☐ Blood transfusion or replacement therapy (use of hemostatic blood components and rFVIIa) or desmopressin
Cutaneous	☐ No/trivial	☐ For bruises 5 or more (> 1cm) in exposed areas	☐ Consultation only*	☒ Extensive	☐ Spontaneous hematoma requiring blood transfusion
Bleeding from minor wounds	☒ No/trivial	☐ - > 5/year or - more than 10 minutes	☐ Consultation only*	☐ Surgical hemostasis	☐ Blood transfusion, replacement therapy, or desmopressin
Oral cavity	☐ No/trivial	☒ Present	☐ Consultation only*	☐ Surgical hemostasis or antifibrinolytic	☐ Blood transfusion, replacement therapy or desmopressin
GI bleeding	☒ No/trivial	☐ Present (not associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia)	☐ Consultation only*	☐ Surgical hemostasis, antifibrinolytic	☐ Blood transfusion, replacement therapy or desmopressin
Hematuria	☒ No/trivial	☐ Present (macroscopic)	☐ Consultation only*	☐ Surgical hemostasis, iron therapy	☐ Blood transfusion, replacement therapy or desmopressin
Tooth extraction	☒ No/trivial or none done	☐ Reported in ≤25% of all procedures, no intervention**	☐ Reported in ≥25% of all procedures, no intervention**	☐ Resuturing or packing	☐ Blood transfusion, replacement therapy or desmopressin
Surgery	☒ No/trivial or none done	☐ Reported in ≤25% of all procedures, no intervention**	☐ Reported in ≥25% of all procedures, no intervention**	☐ Surgical hemostasis or antifibrinolytic	☐ Blood transfusion, replacement therapy or desmopressin
Menorrhagia	☒ No/trivial	☐ Consultation only* or - Changing pads more frequently than every 2 hours or - Clot and flooding or - PBAC score>100#	☐ - Time off work/school > 2/year or - Requiring antifibrinolytics or hormonal or iron therapy	☐ - Requiring combined treatment with antifibrinolytics and hormonal therapy or - Present since menarche and > 12 months	☐ - Acute menorrhagia requiring hospital admission and emergency treatment or - Requiring blood transfusion, Replacement therapy, Desmopressin, or - Requiring dilatation & curettage or endometrial ablation or hysterectomy)
Post-partum hemorrhage	☒ No/trivial or no deliveries	☐ Consultation only* or - Use of syntocin or - Lochia > 6 weeks	☐ - Iron therapy or - Antifibrinolytics	☐ - Requiring blood transfusion, replacement therapy, desmopressin or - Requiring examination under anaesthesia and/or the use of uterine balloon/package to tamponade the uterus	☐ - Any procedure requiring critical care or surgical intervention (e.g. hysterectomy, internal iliac artery ligation, uterine artery embolization, uterine brace sutures)
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
CNS bleeding	☒ Never			☐ Subdural, any intervention	☐ Intracerebral, any intervention
Other bleedings [^]	☒ No/trivial	☐ Present	☐ Consultation only*	☐ Surgical hemostasis, antifibrinolytics	☐ Blood transfusion or replacement therapy or desmopressin

SCORE 7

Decoding the complexity of Von Willebrand disease: from genetics to treatments

VWF:Ag or VWF:function (U/dL)



VWD: Von Willebrand disease; VWF: Von Willebrand factor

Sadler JE. Blood.2003;101:2089-93.

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Factors that may interfere VWF level

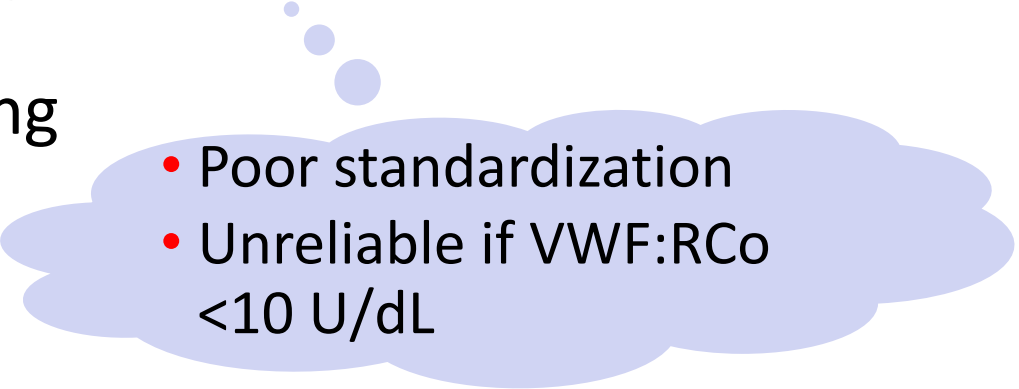
- Blood group: O vs non-O
- Inflammation (DDAVP trial should be performed when patient was normal, no bleeding symptoms)
- Age

Recommendation 5: suggested removing the diagnosis of previously confirmed VWD type 1 who now have normal VWF with increasing age.

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Diagnosis

- Clinical manifestation: bleeding score (BS)
- Laboratory:
 - CBC
 - APTT
 - VWF:Ag
 - VWF function:
 - Platelet binding: VWF:RCo, VWF:GPIbM, VWF:GPIbR
 - Collagen binding
 - FVIII binding
 - VWF:multimer
 - DDAVP trial

- 
- Poor standardization
 - Unreliable if VWF:RCo <10 U/dL

Decoding the complexity of Von Willebrand disease: from genetics to treatments

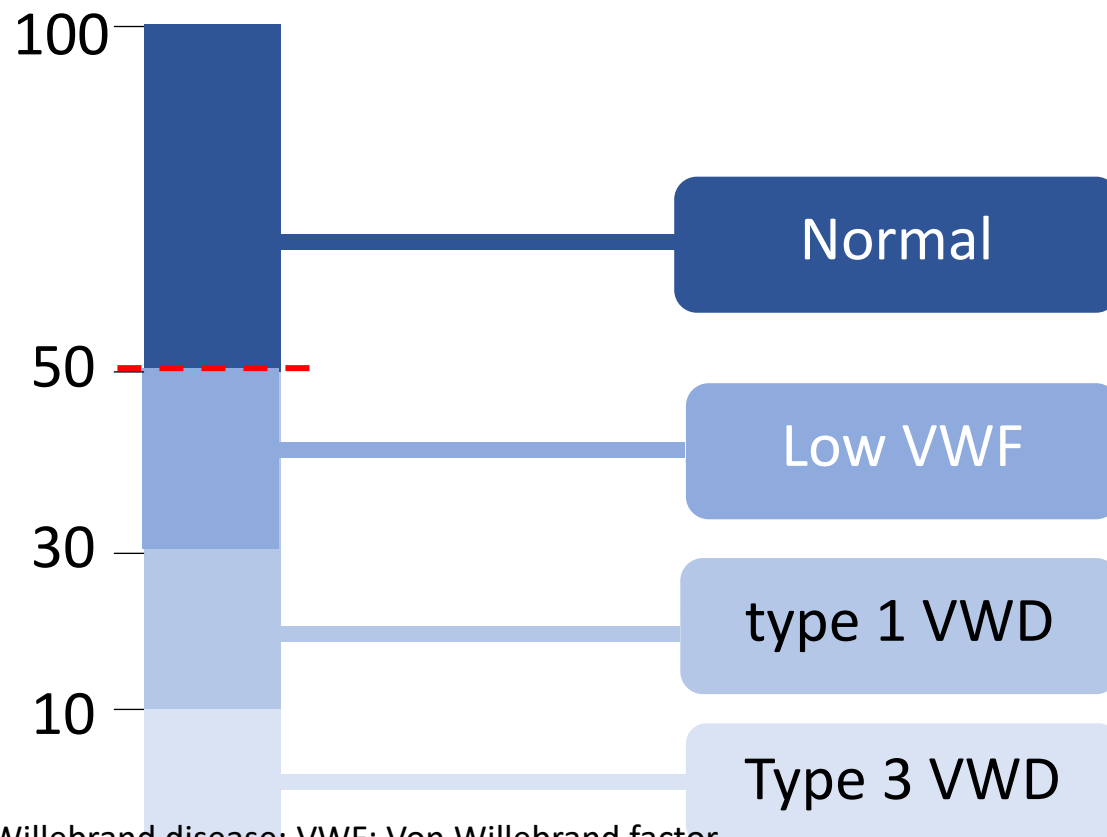
VWF:RCo

- Operator dependence
- Less accuracy if VWF:RCo <30 IU/dL
- Need ristocetin
- New platelet binding assay
 - Direct GPIb-binding assays: VWF:GPIbR, VWF:GPIbM)
 - VWF: GPIbM use mutant VWF (gain of function D235Y and M239V) instead, no need to add ristocetin

Recommendation 4: Suggested using newer platelet binding activity of VWF rather than using VWF:RCo in the diagnosis of VWD type 2

Decoding the complexity of Von Willebrand disease: from genetics to treatments

VWF:Ag or VWF:function (U/dL)



Recommendation 6: suggested the diagnosis of VWD type 1 if

- 1) VWF:Ag <30 U/dL regardless bleeding symptoms
- 2) VWF:Ag 30-50 U/dL with bleeding symptoms

Decoding the complexity of Von Willebrand disease: from genetics to treatments

VWF propeptide (VWFpp)

- For the detection of VWD type 1C or Vicenza
Propeptide:mature subunit 1:1 (normal person)
- Half life of propeptide VWF **2-3** hours
- Half life of mature subunit VWF **8-12** hours
- Elevated VWFpp found in increased clearance
- Decreased VWFpp found in decreased synthesis
- Diagnosis of type 1C if VWF:Ag
<30 U/dL and VWF pp/VWF:Ag
ratio ≥ 3

Recommendation 7:
suggest against using
ppVWF rather than
using DDAVP trial

Decoding the complexity of Von Willebrand disease: from genetics to treatments

DDAVP trial

- Blood for CBC, VWF:Ag, VWF:platelet-dependent activity, VWF:CB, FVIII:C at baseline, 1 and 4 hours.
- Changes in these variables would enhance the diagnosis of **type 2 VWD**.
- **Progressive thrombocytopenia** would suggest **type 2B VWD**.
- Decrease of VWF:Ag **>30%** of baseline could favor **type 1C VWD**.

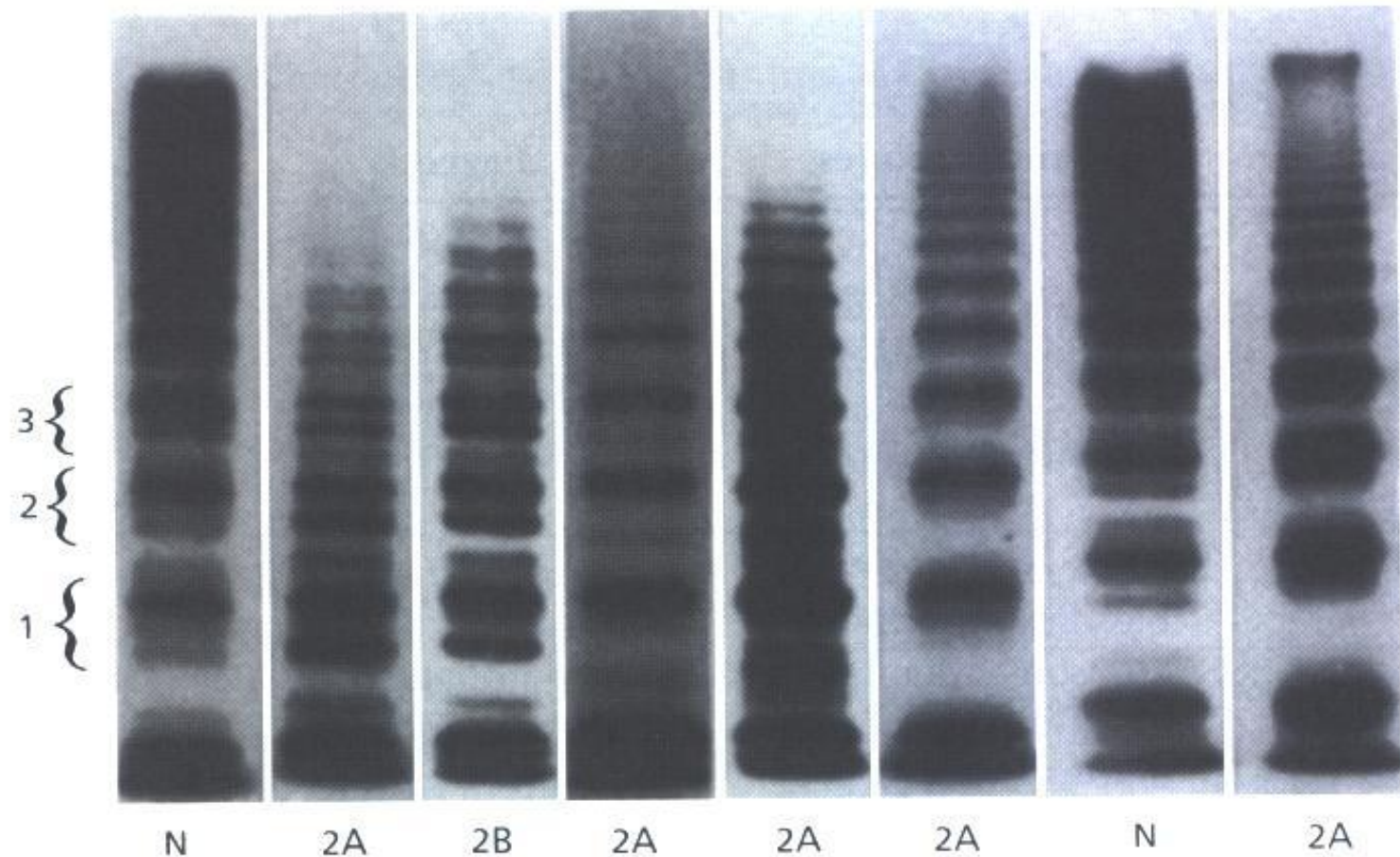
Decoding the complexity of Von Willebrand disease: from genetics to treatments

DDAVP trial

	Type 2B VWD	Type 1C VWD
	Platelet ($\times 10^9/\text{L}$)	VWF:Ag (U/dL)
• Baseline	90	25
• 1 hour	75	20
• 4 hours	60	15 (decreased >30% of baseline)

DDAVP: 1-Deamino-8-D-Arginine Vasopressin;
VWD: Von Willebrand disease; VWF: Von Willebrand factor

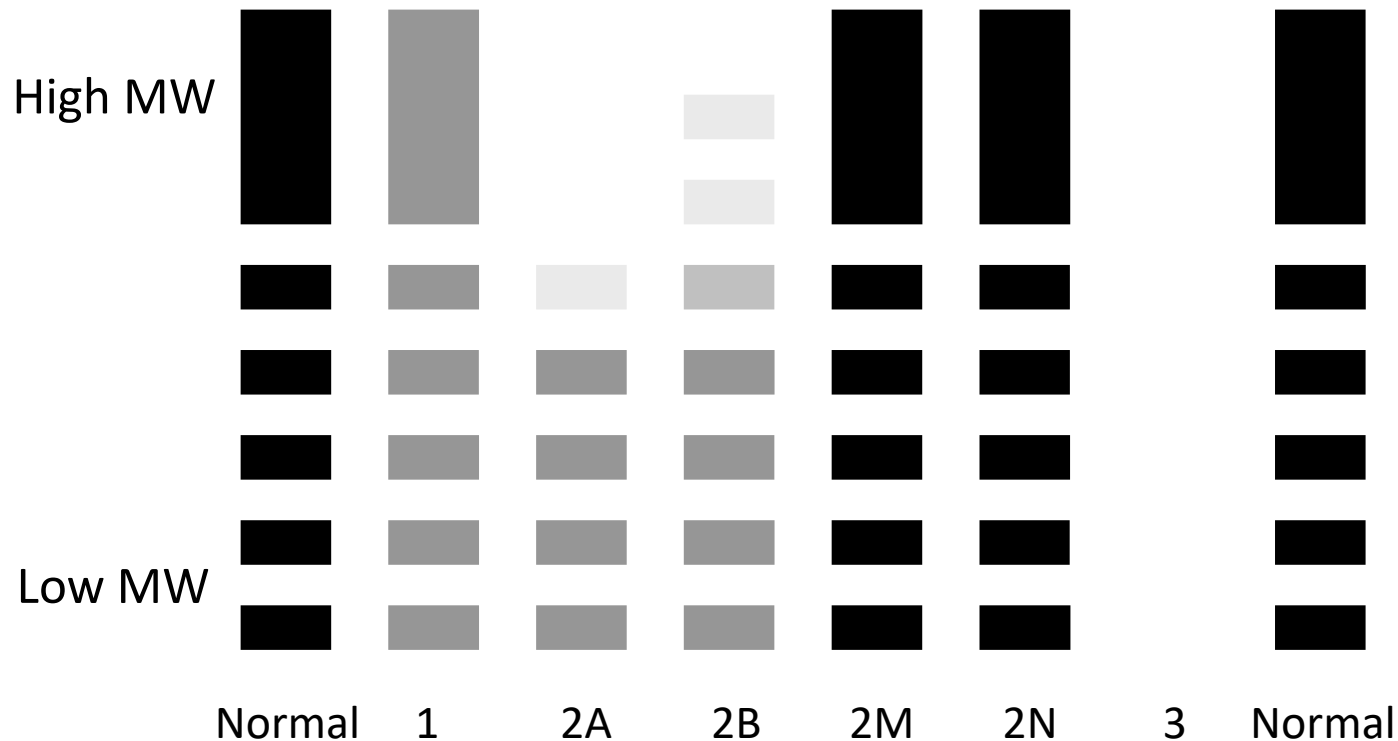
Decoding the complexity of Von Willebrand disease: from genetics to treatments



VWF multimer SDS-PAGE Analysis

VWF: Von Willebrand factor

Decoding the complexity of Von Willebrand disease: from genetics to treatments



Schematic Plasma VWF Multimers

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Recommendation 9:

- VWD type 2A, 2B or 2M needed VWF:multimer or ratio of VWF:CB/VWF:Ag.
- VWF:CB/VWF:Ag is a surrogate marker of VWF:multimer.
- Collagen type 1 and 3 (bind to A3 domain) is recommended.
- No standard cutoff level for the diagnosis (0.4-0.8).

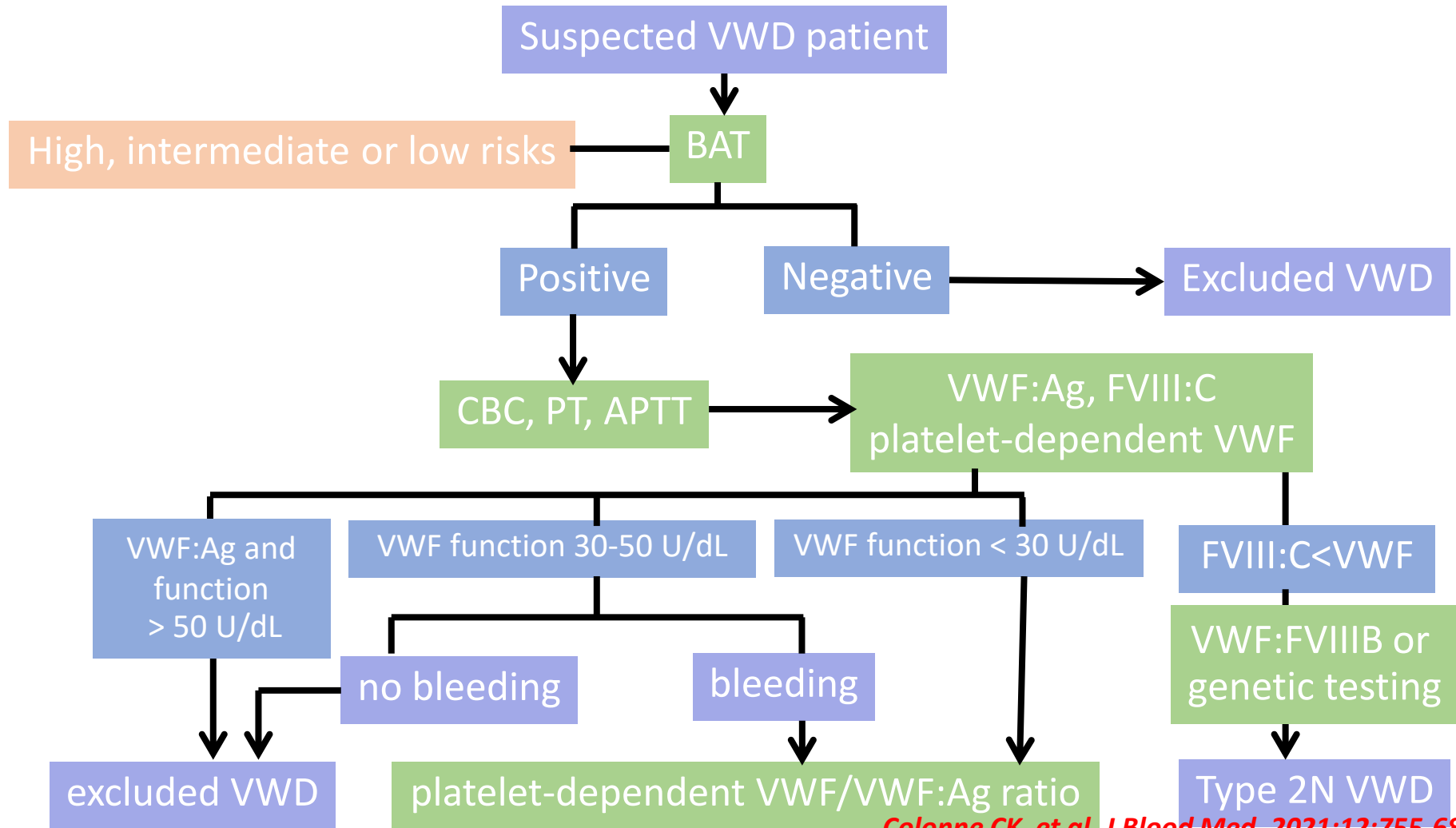
Recommendation 10:

- Suggested genetic testing over low dose RIPA in the diagnosis of VWD type 2B.
- Final concentration of ristocentin for standard RIPA and low dose RIPA are 0.6-1.2 VS 0.3 mg/mL, respectively.

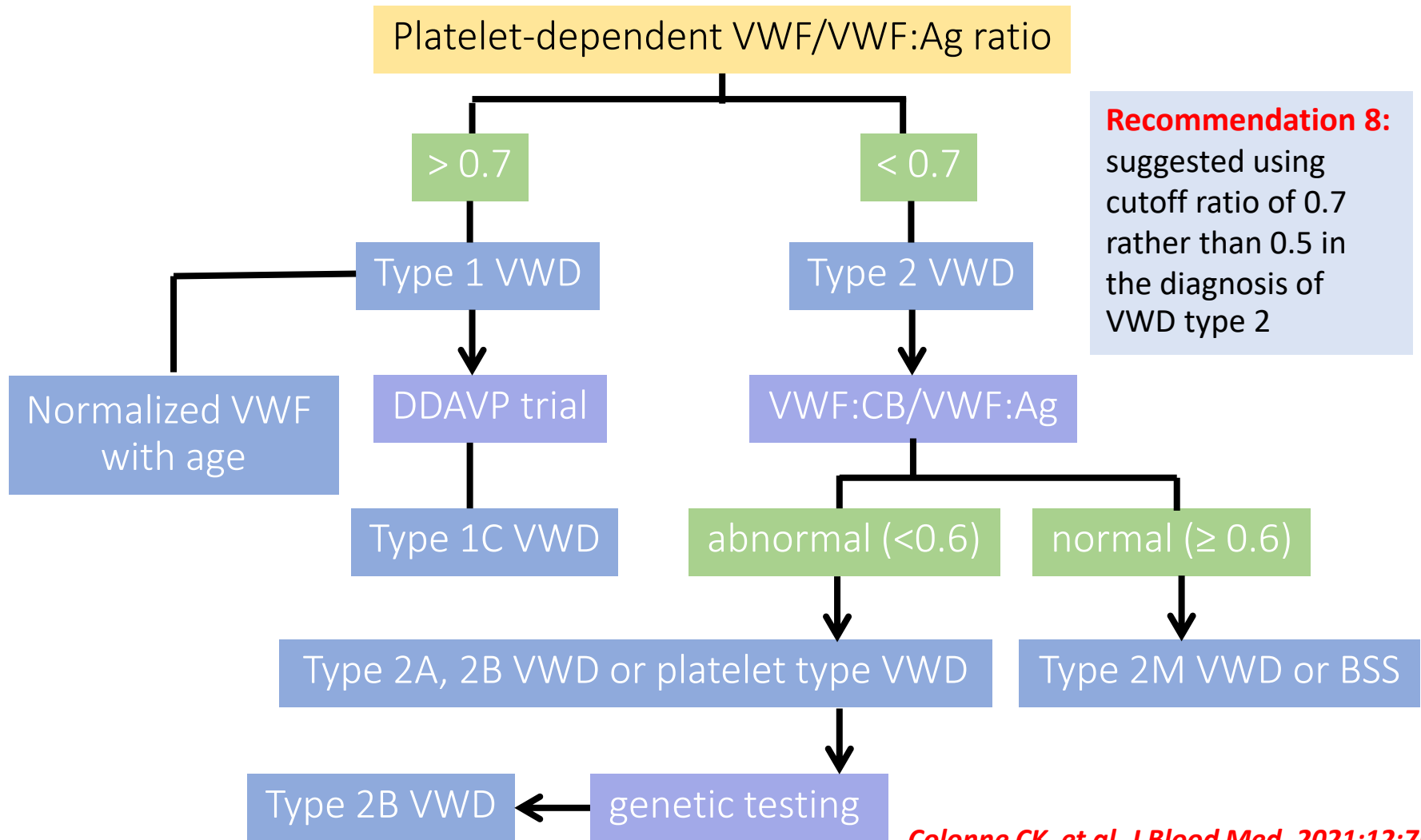
Decoding the complexity of Von Willebrand disease: from genetics to treatments

Type VWD	VWF: multimer		VWF:CB/VWF:Ag	
	sensitivity	specificity	sensitivity	specificity
• 2A	0.9 (0.90-0.99)	0.97 (0.94-0.99)	0.90 (0.78-0.96)	0.95 (0.89-0.98)
• 2B	0.9 (0.90-0.99)	0.97 (0.94-0.99)	0.90 (0.78-0.96)	0.95 (0.89-0.98)
• 2M	0.86 (0.73-0.98)	0.97 (0.94-0.99)	0.98 (0.96-1.00)	0.97 (0.94-0.99)

Decoding the complexity of Von Willebrand disease: from genetics to treatments



Decoding the complexity of Von Willebrand disease: from genetics to treatments



Decoding the complexity of Von Willebrand disease: from genetics to treatments

Genetic testing: NGS

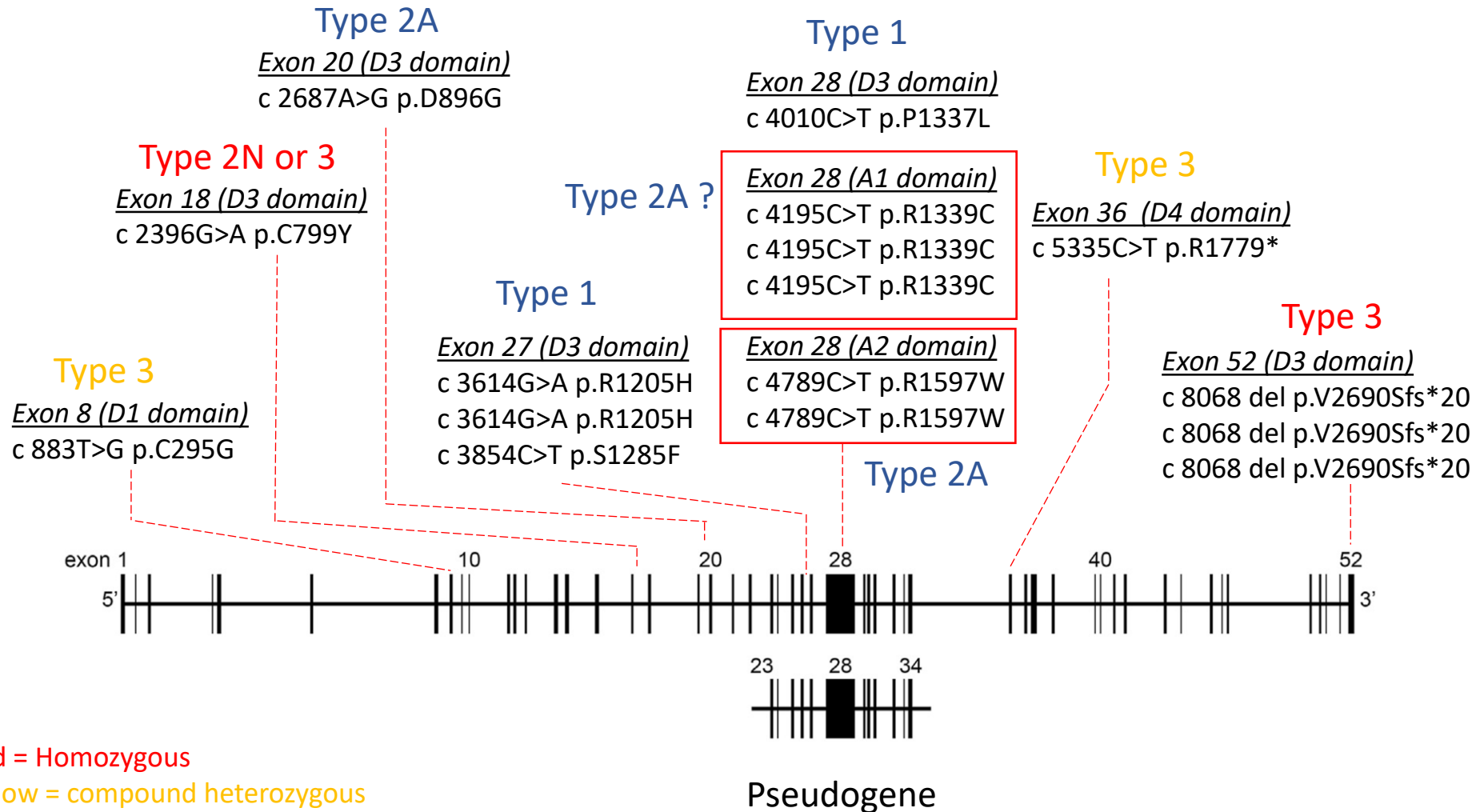
- Can identify single nucleotide variants (SNVs), small deletions, insertions/deletions and large copy number variants (CNVs).
- Different NGS platforms are available from various manufacturers.
- Large number of variants are classified as benign or of unknown significance.
- These features complicate the genetic analysis and interpretation of detected variants within individuals with reduced VWF.

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Genetic testing: NGS

- Care must be taken to ensure primer specificity to VWF in exons 23-34, where there is high homology with VWF pseudogene .
- Some NGS technologies may not be able to map sequence reads to specific areas of the gene, such as exon 26 in VWF.
- Such regions should therefore be analysed by Sanger sequencing.

Decoding the complexity of Von Willebrand disease: from genetics to treatments



Decoding the complexity of Von Willebrand disease: from genetics to treatments

LETTERS TO THE EDITOR

Haemophilia  WILEY | e149

Management of pregnancy complications in type 2N von Willebrand disease associated to a novel mutation

von Willebrand disease (VWD) is the most common of the inherited bleeding disorders and is caused by quantitative (types 1 and 3) and/or qualitative (type 2) defects in von Willebrand factor (VWF). In type 2N VWD (originally called “VWD Normandy”), the defective VWF has markedly decreased binding affinity for factor VIII (FVIII), resulting in loss of stability and a disproportionately low FVIII level relative to VWF antigen (VWF:Ag) levels.¹

to either the 2N mutation affecting VWF synthesis or, alternatively, the presence of a second quantitative mutation. She demonstrated only a partial response to DDAVP (Table 1). Sequencing of exons 17 to 28 of the VWF gene revealed homozygosity for a novel missense variant in exon 18 of the VWF gene, c.2396G>T (p.Cys799Phe), which is located in the D' domain of the VWF protein. No additional mutations were identified. Subsequent testing of her parents found both

Decoding the complexity of Von Willebrand disease: from genetics to treatments

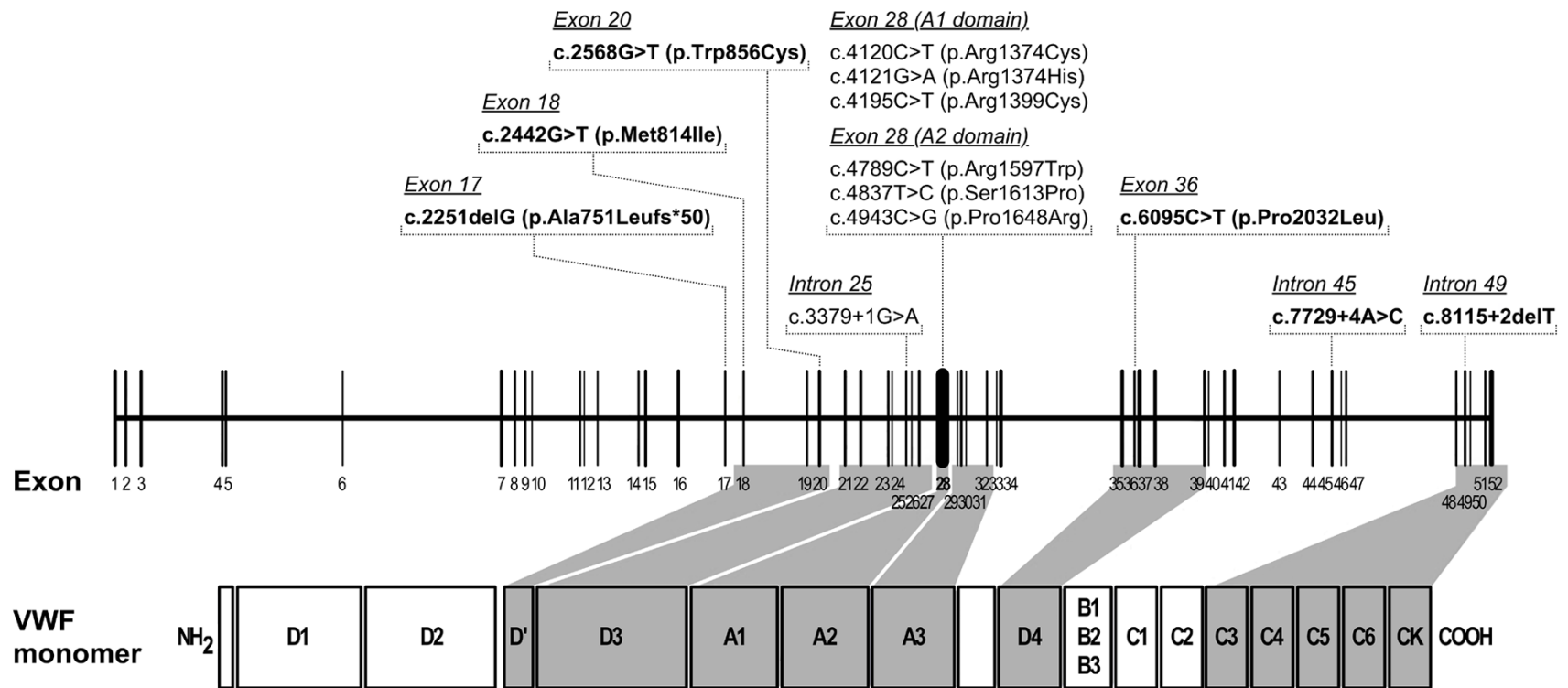


Figure 1 Summary of the sequence variations of the *VWF* gene identified in 15 Thai patients with type 2 and type 3 von Willebrand diseases. Novel mutations are indicated in bold types. VWF, von Willebrand factor.

Decoding the complexity of Von Willebrand disease: from genetics to treatments



Management

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Management of VWD: considering factors

- Type of VWD: 1, 2 or 3
- Available products
- Clinical situation:
 - Prophylaxis
 - Acute hemorrhage
 - Preoperative preparation
 - Pregnancy, delivery and puerperium

CLINICAL GUIDELINES



ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease

Nathan T. Connell,^{1*} Veronica H. Flood,^{2*} Romina Brignardello-Petersen,³ Rezan Abdul-Kadir,⁴ Alice Arapshian,⁵ Susie Couper,⁶ Jean M. Grow,⁷ Peter Kouides,⁸ Michael Laffan,⁹ Michelle Lavin,¹⁰ Frank W. G. Leebeek,¹¹ Sarah H. O'Brien,¹² Margareth C. Ozelo,¹³ Alberto Tosetto,¹⁴ Angela C. Weyand,¹⁵ Paula D. James,¹⁶ Mohamad A. Kalot,¹⁷ Nedaa Husainat,¹⁷ and Reem A. Mustafa¹⁷

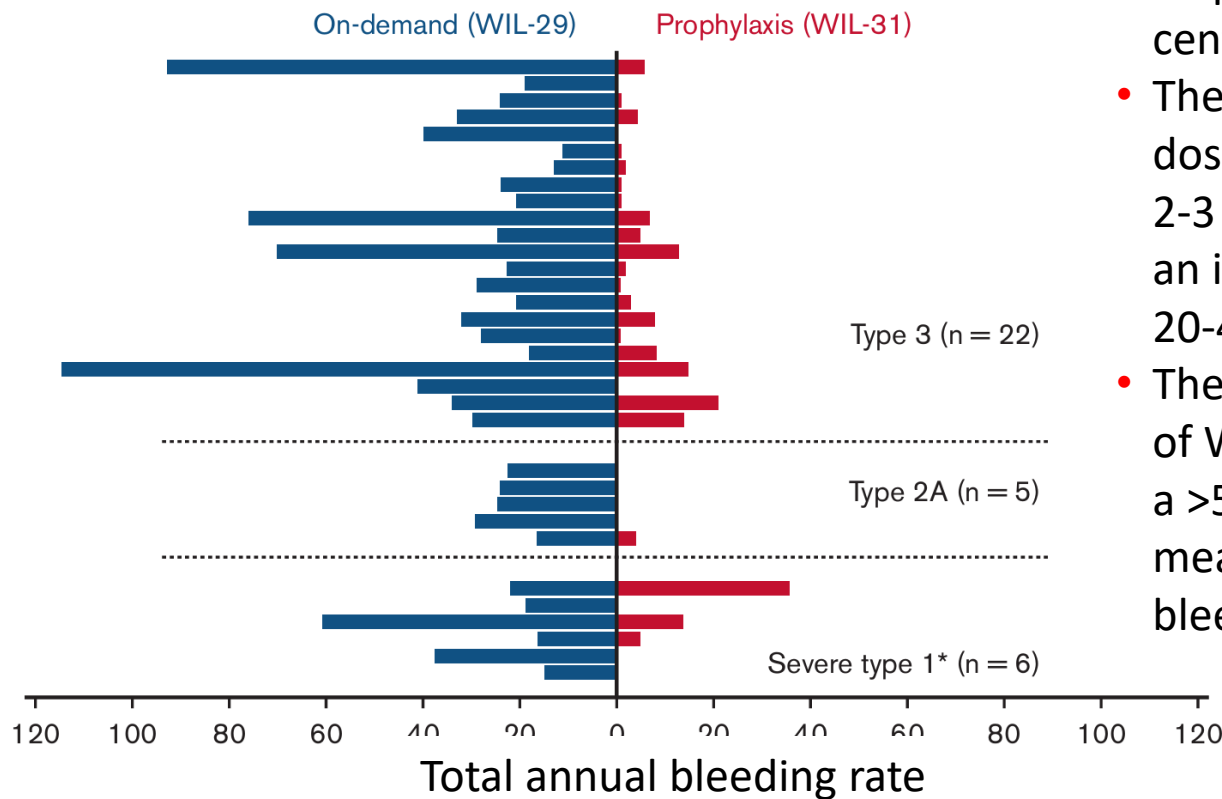
¹Hematology Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; ²Versiti Blood Research Institute, Medical College of Wisconsin, Milwaukee, WI; ³Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; ⁴Department of Obstetrics and Gynaecology and Katharine Dormand Haemophilia and Thrombosis Centre, Royal Free Foundation Hospital and Institute for Women's Health, University College London, London, United Kingdom; ⁵Middle Village, NY; ⁶Maylands, WA, Australia; ⁷Department of Strategic Communication, Marquette University, Milwaukee, WI; ⁸Mary M. Gooley Hemophilia Treatment Center, University of Rochester, Rochester, NY; ⁹Centre for Haematology, Imperial College London, London, United Kingdom; ¹⁰Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland and National Coagulation Centre, St James's Hospital, Dublin, Ireland; ¹¹Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands; ¹²Division of Hematology/Oncology, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH; ¹³Hemocentro UNICAMP, University of Campinas, Campinas, Brazil; ¹⁴Hemophilia and Thrombosis Center, Hematology Department, S. Bortolo Hospital, Vicenza, Italy; ¹⁵Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI; ¹⁶Department of Medicine, Queen's University, Kingston, ON, Canada; and ¹⁷Outcomes and Implementation Research Unit, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Recommendation 1:

VWD with severe bleeding should receive prophylaxis rather than no prophylaxis

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Management of VWD: prophylaxis



- 44 patients from 17 centers in 9 countries.
- The recommended dosing of Wilate was 2-3 times per week at an intravenous dose of 20-40 U/kg.
- The primary end point of WIL-31 was to show a >50% reduction in mean total annualized bleeding rate

WIL-29 (6-month, on-demand treatment with Wilate)

WIL-31 (Wilate prophylaxis for 12 months)

Sidonio RF Jr, et al. Blood Adv. 2024;8:1405-14.

Decoding the complexity of Von Willebrand disease: from genetics to treatments



ประกาศคณะกรรมการการแพทย์ตามพระราชบัญญัติประกันสังคม
เรื่อง หลักเกณฑ์และอัตราค่าบริการทางการแพทย์การให้ยาแฟคเตอร์ (Coagulation factor)
สำหรับผู้ป่วยกลุ่มโรคเลือดออกง่ายฮีโมฟีเลีย (Hemophilia) และผู้ป่วยกลุ่มโรคเลือดออกง่าย
วอนวิลเลแบรนด์ (von Willebrand)



ประกาศสำนักงานหลักประกันสุขภาพแห่งชาติ
เรื่อง การจ่ายค่าใช้จ่ายเพื่อบริการสาธารณสุข กรณีที่ต้องกำกับการใช้บริการอย่างใกล้ชิด
พ.ศ. ๒๕๖๖

ข้อ ๕ หลักเกณฑ์และอัตราในการจ่ายค่าบริการทางการแพทย์การให้ยาแฟคเตอร์
แก่ผู้ป่วยกลุ่มโรคเลือดออกง่ายฮีโมฟีเลีย (Hemophilia) และผู้ป่วยกลุ่มโรคเลือดออกง่ายวอนวิลเลแบรนด์
(von Willebrand) โดยสำนักงานจ่ายค่าบริการทางการแพทย์เพิ่มเติมรายการสำหรับการรักษาพยาบาล
เป็นค่ายาแฟคเตอร์ ดังนี้

(๑) กรณีการรักษาภาวะเลือดออกในระยะเริ่มต้น (Early Bleeding Treatment)

(ก) ผู้ประกันตนที่มีสิทธิได้รับยาแฟคเตอร์ ในระยะเลือดออกเริ่มต้น คือ ผู้ประกันตน
ที่ได้รับการอนุมัติและขึ้นทะเบียนเป็นผู้ป่วยกลุ่มโรคเลือดออกง่ายฮีโมฟีเลีย (Hemophilia) และผู้ป่วย
กลุ่มโรคเลือดออกง่ายวอนวิลเลแบรนด์ (von Willebrand) กับสำนักงาน

(ข) จ่ายค่าบริการทางการแพทย์ให้แก่สถานพยาบาลที่ขึ้นทะเบียนในการรักษา
ภาวะเลือดออกในระยะเริ่มต้น (Early Bleeding Treatment) สำหรับยาแฟคเตอร์ VIII และ ยาแฟคเตอร์ IX
ในผู้ป่วยกลุ่มโรคเลือดออกง่าย (Hemophilia) และผู้ป่วยกลุ่มโรคเลือดออกง่ายวอนวิลเลแบรนด์ (von Willebrand)
ตามปริมาณแฟคเตอร์ที่ใช้จริง ตามแนวทางการกำกับการใช้ยาแฟคเตอร์ (Factor VIII concentrate Factor IX
concentrate และ Factor IX complex) ตามประกาศคณะกรรมการพัฒนาระบบยาแห่งชาติเกี่ยวกับ
บัญชียาหลักแห่งชาติ ในอัตราเท่าที่จ่ายจริงไม่เกินราคากลางที่กำหนดในข้อ ๖ ของประกาศนี้

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Management of VWD: VWF increment

- Non-replacement therapy
 - Increased endogenous FVIII:C and VWF
 - DDAVP
 - Estrogen
 - Increased clot stability: antifibrinolysis
- Replacement therapy
 - Exogenous FVIII:C and VWF
 - Cryoprecipitate
 - Intermediate-purity FVIII concentrate
 - Exogenous VWF
 - VWF concentrate

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Management of VWD: DDAVP (1-Deamino-8-D-Arginine Vasopressin)

- Antidiuretic hormone derivative.
- First used in 1977.
- Increased FVIII and VWF release from endothelium.
- Document response of DDAVP at 1, 2, 4 hours prior to use (DDAVP trial).
- Three times higher than baseline and must be above hemostatic level.

Recommendation 2:
DAVP trial prior to
treatment with DDAVP

Note: not applicable to VWD whose DDAVP is not treatment of choice (type 2, 3 VWD or VWD underwent operation).

Connell NT, et al. Blood Adv. 2021 Jan 12;5:301-25.

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Management of VWD: DDAVP (1-Deamino-8-D-Arginine Vasopressin)

- Indications
 - Type 1 VWD (VWF 10-30 U/dL)
 - Type 2A VWD (some), 2N (some)
- Contraindications
 - Type 2B and type 3 VWD
 - Type 1C VWD with operation
 - Cardiovascular diseases
 - Age <2 years
 - Seizure disorders

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Management of VWD: DDAVP (1-Deamino-8-D-Arginine Vasopressin)

- Intravenous (single dose)
 - 4 µg/mL/vial
 - 0.3 µg/kg/dose
 - Intravenous infusion in 15-20 minutes
 - Time to peak 30-60 minutes
 - 3-5 times of baseline value
- Intranasal (single dose)
 - 300 µg/kg
 - Time to peak 90-120 minutes
 - Not available in Thailand

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Antifibrinolytic agents

Tranexamic acid

- orally 25 mg/kg/day tid
- intravenous 10 mg/kg/dose
- benefit in bleeding of high fibrinolytic activity organs e.g. oral cavity, urinary tract

Recommendation 5A:

tranexamic acid together with keeping VWF activity ≥ 50 U/dL by either DDAVP or VWF concentrate for minor operation

Recommendation 5B:

using only tranexamic acid for minor mucosal procedures in type 1 VWD with VWF activity >30 U/dL and mild bleeding phenomenon

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Estrogen

- Endometrial changes
- Increased endogenous FVIII and VWF
- Benefit in VWD with hypermenorrhea
- caution use of hormone in endometrial hyperplasia/cancer, polycystic ovary, high BMI, >35 years of age, DM, HT

Recommendation 6A:

One who do not wish to conceive:
hormonal therapy ± tranexamic acid rather than DDAVP for heavy period

Recommendation 6B:

One who wish to conceive:
suggested tranexamic acid rather than DDAVP for heavy period (who wish to conceive)

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Replacement Therapy

- 10-20% of VWD need replacement therapy.
- Sources of VWF
 - Cryoprecipitate
 - FVIII concentrate (VWF:RCo/VWF:Ag ratio >0.7)
 - Intermediate purity
 - High purity (monoclonal immunoaffinity chromatography or recombinant technology) not suitable for VWD.
- VWF concentrate (VWF:RCo/FVIII:C ratio >10 , Wilfactin[®]) in European countries.

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Factor concentrate	VWF:FVIII ratio
• Alphanate [®]	0.5:1
• Wilate [®]	1:1
• Humate-P [®]	2.4:1
• Wilfactin [®]	10:1

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Type of bleeding	Dose FVIII (U/kg)	Number of infusion	Target
■ Major surgery	50	OD or every 12 hours	Peak VWF:RCo >100 U/dL and trough >50 U/dL (5-10 days) avoid FVIII:C >150-200 U/dL
■ Minor surgery	30	OD or AD	Peak VWF:RCo >50 U/dL and trough >30 U/dL (1-5 days)
■ Dental extraction	20-30	single	Peak VWF:RCo >50 IU/dL
■ Delivery and puerperium	40	daily before delivery and postpartum period	Peak VWF:RCo >50 IU/dL (5-7 days)

Recommendation 4:

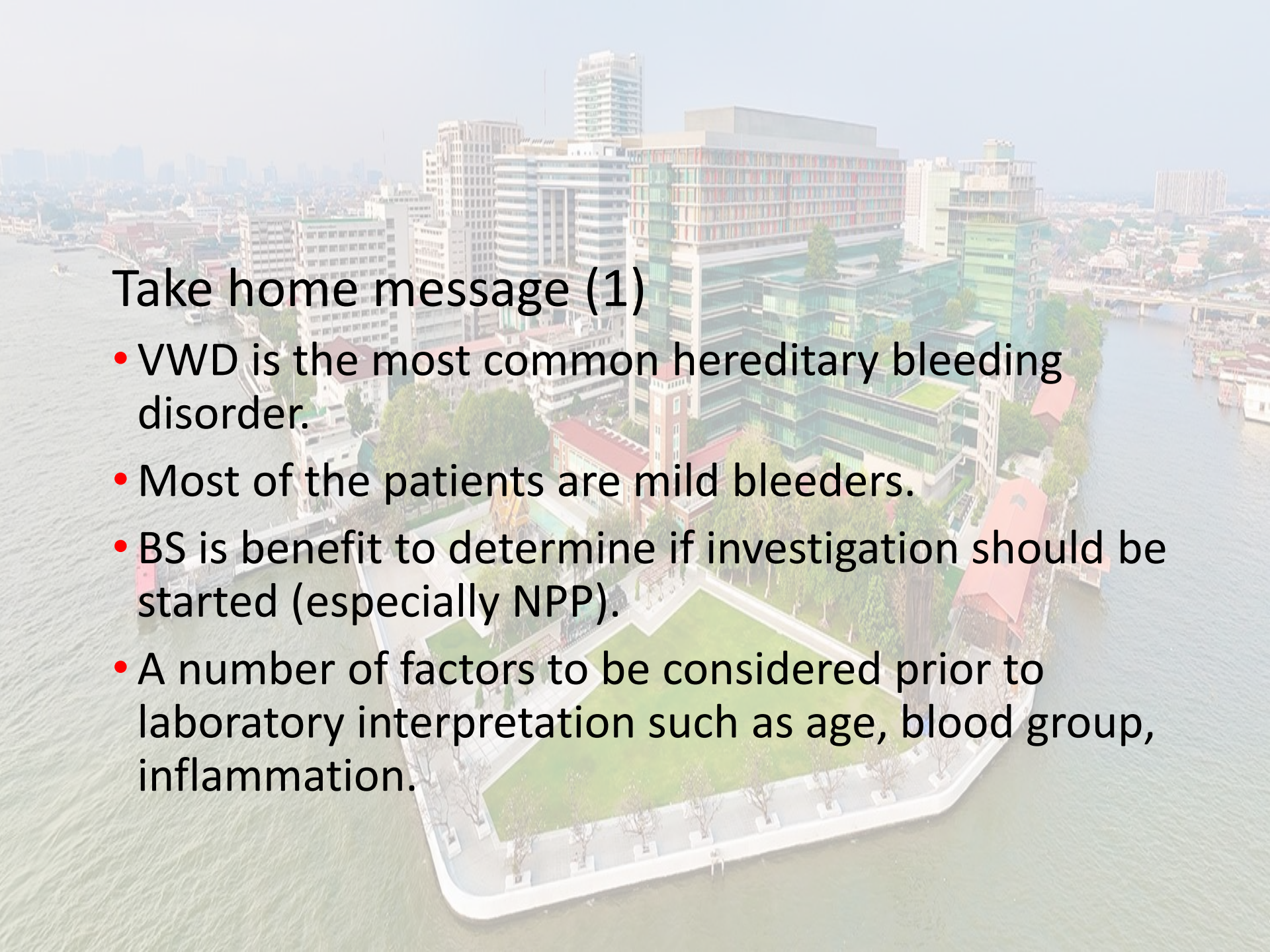
Suggested using both FVIII:C and VWF activity rather than only FVIII

Decoding the complexity of Von Willebrand disease: from genetics to treatments

VWD: Pregnancy, delivery and puerperium

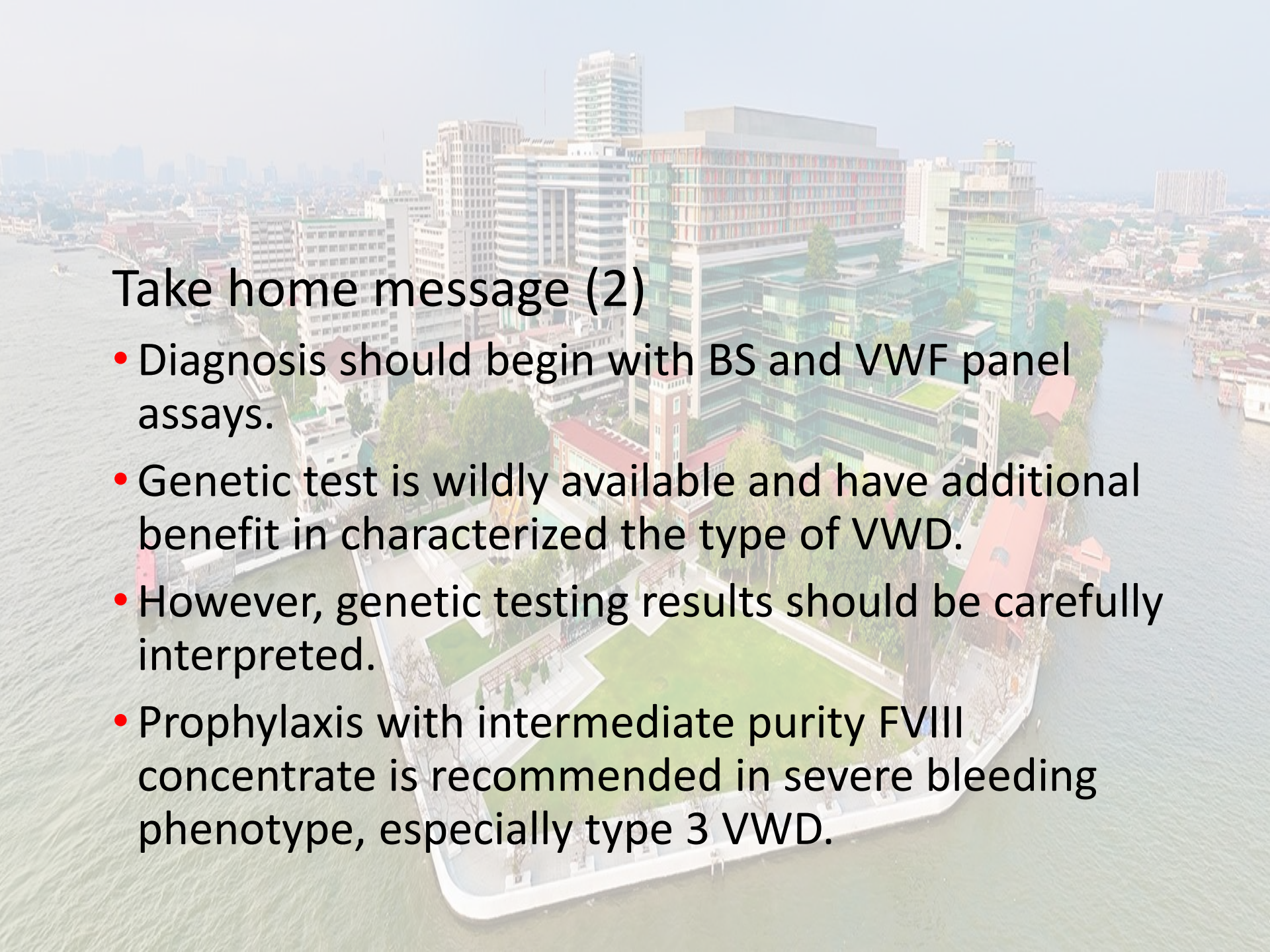
- Higher FVIII:C and VWF normally found during pregnancy (produced from placenta).
- Postpartum hemorrhage is **1.5-5.0 times** higher than normal women.
- Keep peak FVIII:C and VWF:RCo **>50 U/dL** during peripartum and postpartum period.
- Keep peak VWF:Rco **50-150 U/dL** if neuraxial anesthesia is needed.

Recommendation 8:
tranexamic acid 25 mg/kg/day tid during postpartum period and 10-14 days after delivery for type 1 VWD

An aerial photograph of a large, modern hospital complex. The main building is a multi-story structure with a colorful facade of red, yellow, and blue panels. It is surrounded by greenery, including a large central lawn and various trees. The hospital is situated near a body of water, with a city skyline visible in the background. The text 'Take home message (1)' is overlaid on the left side of the image.

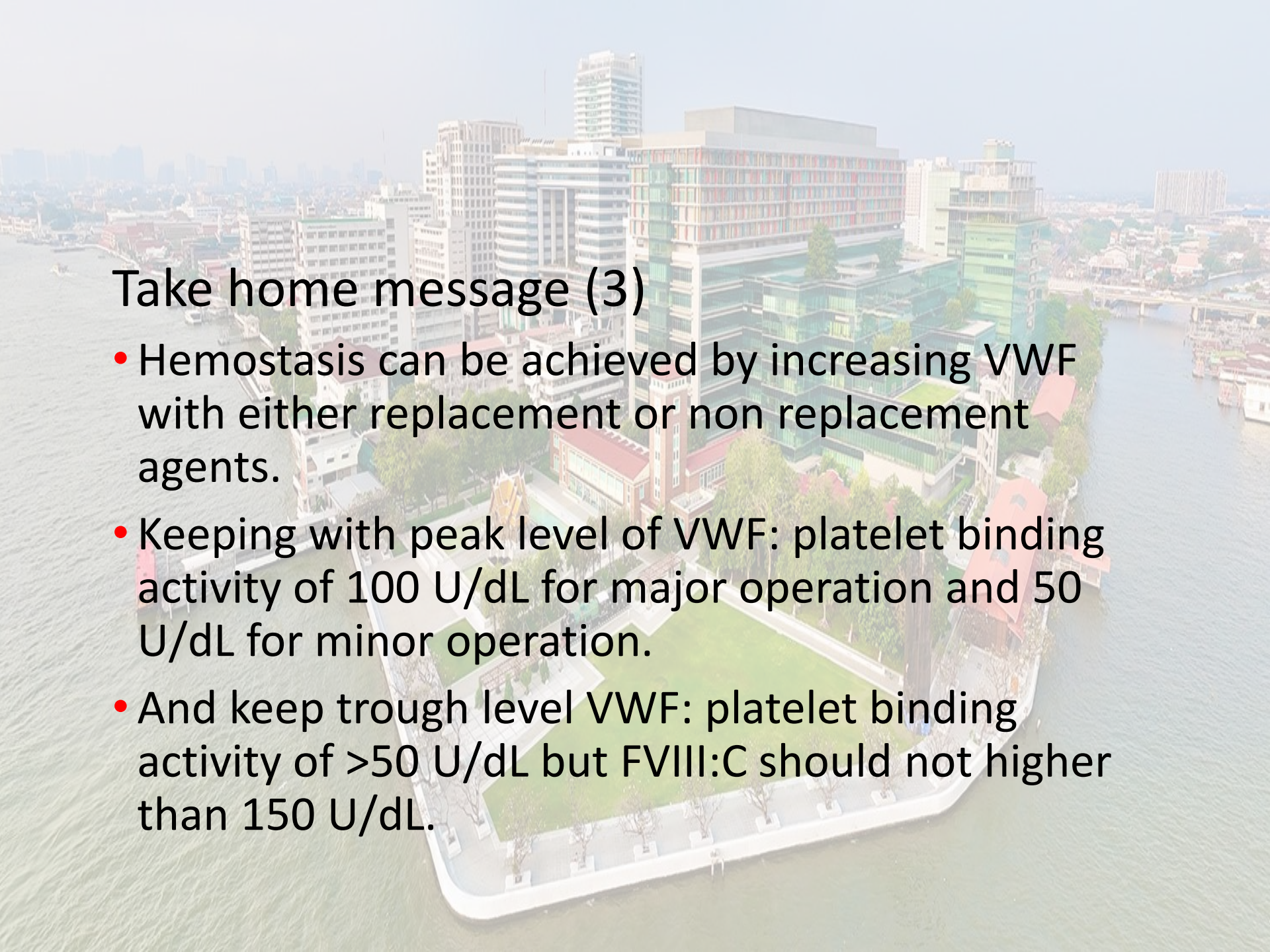
Take home message (1)

- VWD is the most common hereditary bleeding disorder.
- Most of the patients are mild bleeders.
- BS is benefit to determine if investigation should be started (especially NPP).
- A number of factors to be considered prior to laboratory interpretation such as age, blood group, inflammation.

An aerial photograph of a large, modern hospital complex. The hospital features several multi-story buildings with colorful facades in shades of blue, green, and red. A large, well-maintained green lawn is in the foreground, surrounded by a white fence. The hospital is situated near a body of water, with a city skyline visible in the background under a hazy sky.

Take home message (2)

- Diagnosis should begin with BS and VWF panel assays.
- Genetic test is widely available and have additional benefit in characterized the type of VWD.
- However, genetic testing results should be carefully interpreted.
- Prophylaxis with intermediate purity FVIII concentrate is recommended in severe bleeding phenotype, especially type 3 VWD.

An aerial photograph of a cityscape featuring a large, modern building complex with a prominent glass facade and a central tower. The complex is situated along a river, with other buildings and greenery visible in the background. The image is slightly faded to allow the text to be read clearly.

Take home message (3)

- Hemostasis can be achieved by increasing VWF with either replacement or non replacement agents.
- Keeping with peak level of VWF: platelet binding activity of 100 U/dL for major operation and 50 U/dL for minor operation.
- And keep trough level VWF: platelet binding activity of >50 U/dL but FVIII:C should not higher than 150 U/dL.

An aerial photograph of a city skyline along a river. In the foreground, a large, modern building with a colorful, multi-story facade is prominent. The building has a mix of green, blue, and red panels. To the left of the building, there is a large, open green space with a paved walkway and some trees. The river is visible on the left side of the image, and the city skyline continues in the background with various other buildings and structures.

Decoding the complexity of Von Willebrand disease: from genetics to treatments

Thank you