Hemostasis Update

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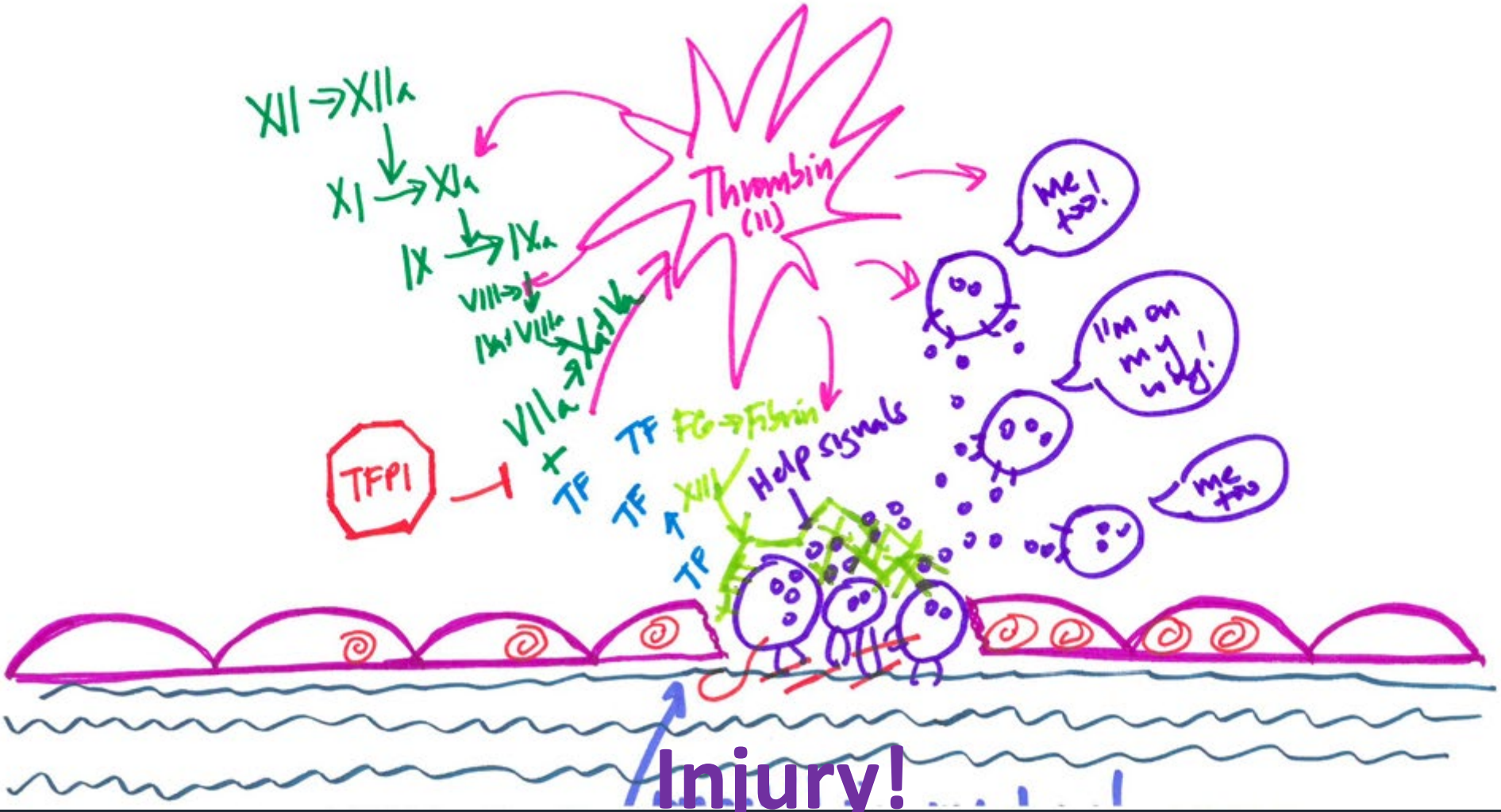
Disclosures

- I receive grant funding from the American Thrombosis & Hemostasis Network/Hemostasis & Thrombosis Research Society
- I will talk about some off-label use of medications

Objectives

- Describe the structure and services of The Hemophilia Center @ OHSU
- Review recently updated hemophilia nomenclature
- List treatment options for individuals with hemophilia
- Review recently updated VWD guidelines
- Identify and characterize bleeding disorders in people with the potential to menstruate


XII → XIIa
XI → XIa
IX → IXa
VIII → VIIIa
VIIa + TF
TFPI
Thrombin (II)
TF
TF
TF
TF
Fg → Fibrin
XIII
Help signals
me too!
I'm on my way!
me too
Injury!

Hemostasis - How it can not work...

- Collagen problems - ? platelet sticky problems? constriction?
- von willebrand protein - deficiency - mild-mod / absence
  - dysfunction - collagen binding
    - VIII Binding ↓
    - platelet binding ↑
    - platelet binding ↓
- platelets - granules
  - dense granule
  - gray platelet
  - Hermansky Pudlak
  - receptors
    - Bernard Soulier Syndrome
    - Glanzmann Thrombasthenia
  - Others
- Factor deficiency - VIII, IX, VII, X, XIII, VIII+V, V, II
- fibrinolysis - too much

Background on Bleeding Disorders

Symptoms:

- Nosebleeds
  - Can be frequent and prolonged (20+ minutes)
  - Can interrupt school/work
- Oral bleeding
  - Recurrent gum bleeding can decrease desire to perform oral health
  - Minor dental procedures can become a life-threatening event
- Heavy menstrual bleeding & bleeding with pregnancy & childbirth
  - Can result in severe symptomatic anemia requiring transfusion
  - Often goes undetected and undertreated
  - Can be the first and only sign of a bleeding disorder

Background on Bleeding Disorders

Symptoms Continued:

- Muscle bleeding
  - Can inhibit function/movement
  - Can cause nerve injury, compartment syndrome, myositis ossificans (bone tissue forms inside a muscle), pseudotumor, infection
- Joint bleeding
  - Can inhibit function/movement
  - Can cause long-term joint damage/arthropathy that may require joint replacement
- Intracranial bleeding
  - rarely spontaneous – higher risk in severe bleeding disorder, extremes of age
  - Trauma-induced – treat the bleeding disorder and then look for blood

Treatments

Before Bleeding Happens	While Bleeding is happening
Stay active – keep muscles and joints strong	First Aid measures – pressure, RICE
Brush your teeth & go to the dentist regularly	Hemophilia: factor med +/- Antifibrinolytic
Wear a helmet and a seat belt	VWD: DDAVP or VWF concentrate +/- Antifibrinolytic
Avoid contact sports	Platelet Disorder: DDAVP or rFVII or platelet transfusion +/- antifibrinolytic
Take prophylactic medicine as prescribed (factor, hormones, anti-fibrinolytic, etc)	Other meds used: other factor products (VII, XIII)
HMB: oral hormones, implants, IUD	HMB: estrogen + progesterone or progesterone only +/- antifibrinolytic

Factor medications are given intravenously. Because they are expensive, not all hospitals have factor on formulary. We encourage patients to keep at least one dose of their medicine on hand in case of emergency.

Hemophilia Treatment Center

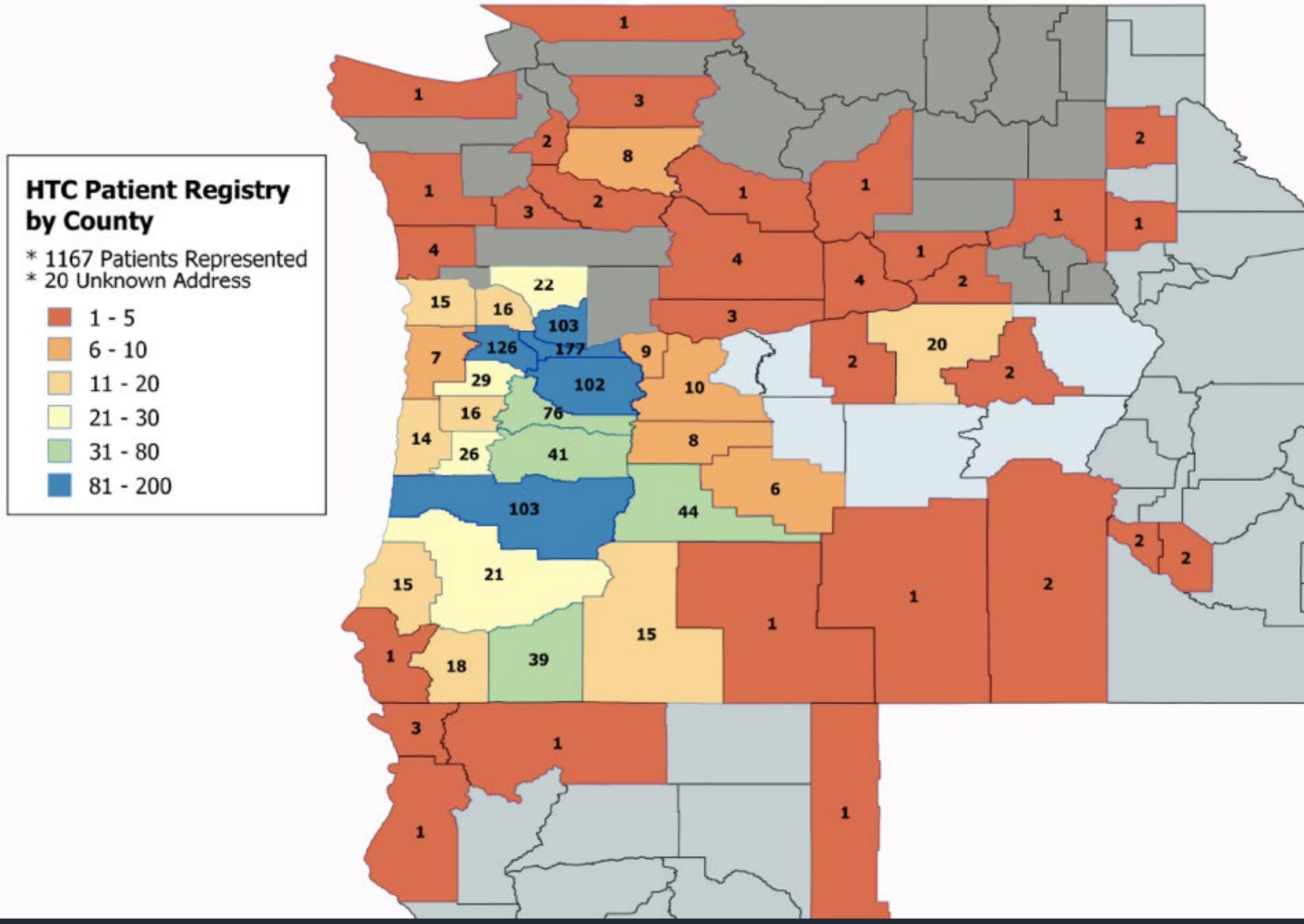
- A specialized health care center that brings together a team of doctors, nurses, and other health professionals experienced in treating patients with bleeding disorders.
- 1993-1995 CDC study of mortality of 2950 patients with hemophilia A and B: 236 people died (8%); people who received care at a HTC were 30% less likely to die than those who didn't.
- 1993-1966 CDC study of bleeding events requiring hospitalization in 2650 patients with hemophilia A and B found that people receiving care at an HTC were 50% less likely to experience a bleeding event requiring hospitalization.

Soucie JM, et al. Blood. 2000.

Soucie JM, et al. Haemophilia. 2001.

The Hemophilia Center @ OHSU

- An inter-disciplinary team caring for patients of ALL ages with bleeding and clotting disorders.
  - We are a life-span program
- Catchment area: Oregon, SW Washington, Northern California, sometimes Idaho, sometimes Alaska
  - We are the only HTC in the state of Oregon.
  - The next closest HTC is in Seattle or Spokane depending on where you are and how you drive.


HTC Patient Registry by County
* 1167 Patients Represented
* 20 Unknown Address
1 - 5
6 - 10
11 - 20
21 - 30
31 - 80
81 - 200
1
1
3
2
8
1
2
1
3
2
1
1
1
1
4
4
4
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22
15
16
103
3
126
177
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41
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103
44
2
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1

The Hemophilia Center @ OHSU

The Hemophilia Center @ OHSU

- Partners
  - Pediatric Dentistry Residency
  - Adult Pain Clinic
  - Center for Women's Health
  - Pediatric Hematology/Oncology and Adult Hematology
  - NICH
  - Interventional Radiology
  - LEND program
  - Molecular & Medical Genetics
  - Maternal Fetal Medicine
  - Hereditary Hemorrhagic Telangiectasia Center
- Clinics:
  - Comprehensive clinic
  - Acute/urgent visits
  - Spots, Dots, & Clots and Reproductive Hematology
  - Vascular Interventions Program

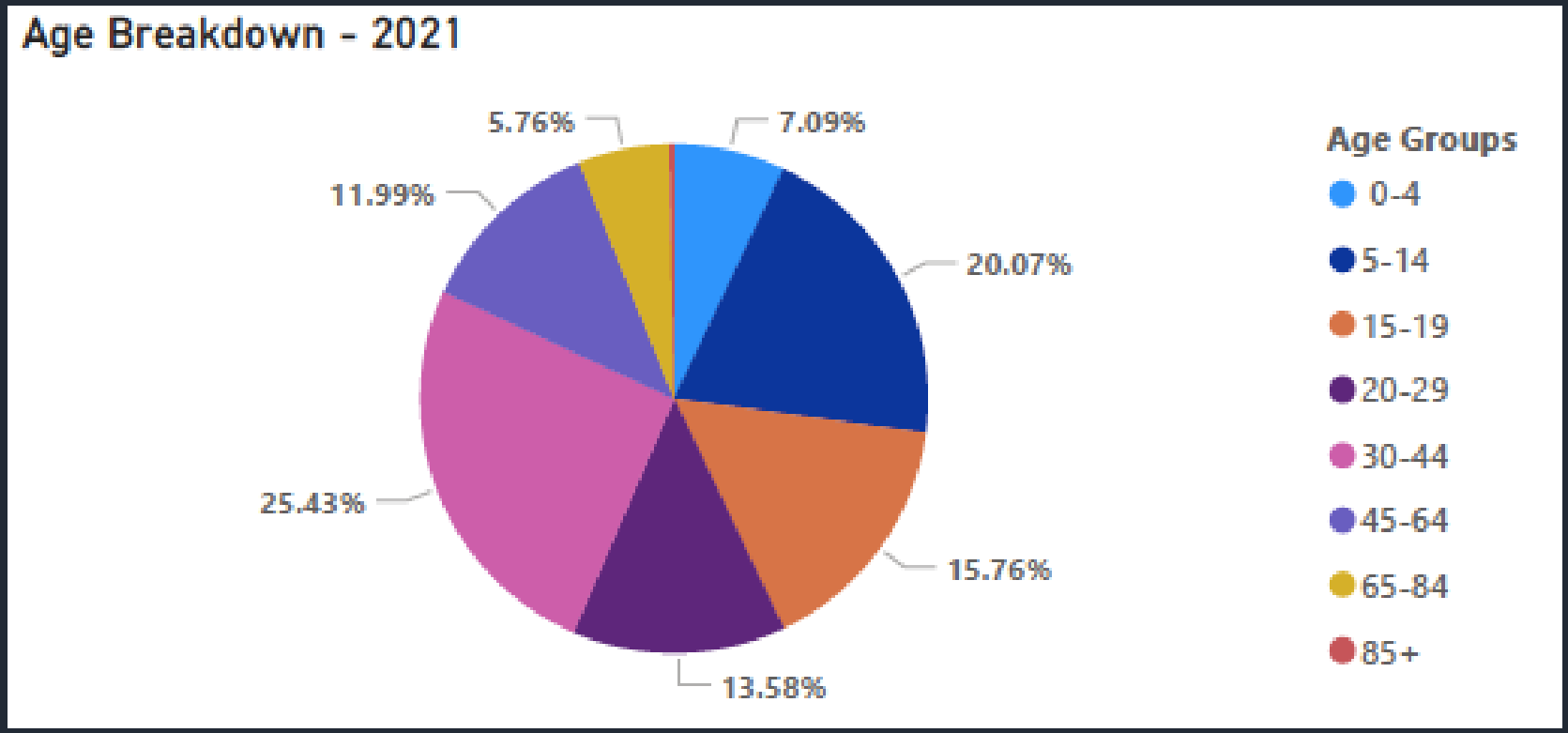
The Hemophilia Center @ OHSU

525 patients with diagnosed bleeding disorders seen January 2021-November 2021.

Diagnosis	# of patients seen
Hemophilia A	269
Hemophilia B	59
Von Willebrand Disease	146
Other factor deficiencies	34
Other bleeding disorders	37

**does not include new consults, uncertain diagnoses, thromboses

The Hemophilia Center @ OHSU



Hemophilia nomenclature

- Normal factor VIII levels are ~50-100%

Factor VIII level	Severity classification	Bleeding Phenotype
< 1%	Severe	Spontaneous bleeding into joints and muscles, bleeding with trauma/surgery, mucocutaneous bleeding
1-5%	Moderate	Bleeding with trauma/surgery, rare spontaneous bleeding, mucocutaneous bleeding
6-40%	Mild	Bleeding with trauma/surgery, mucocutaneous bleeding
>40% + gene + bleeding	Symptomatic carrier	Bleeding with trauma/surgery, mucocutaneous bleeding
>40% + gene, no symptoms	Carrier	none

van Galen KPM, et al. JTH. 2021.
Blanchette VS. JTH. 2014. 12: 1935-1939.

Factor VIII treatment in general

- Plasma-derived
  - Pooled human plasma
  - Contains VWF in addition to FVIII
- Recombinant
  - 3 cell lines: CHO, BHK, and HEK
  - Full length vs B-domain deleted
  - 1st (animal and/or human plasma-derived proteins in cell culture medium and final formulation) vs 2nd (animal and/or human plasma-derived proteins in cell culture medium) vs 3rd generation (no animal or human plasma-derived proteins) vs 4th generation (made in HEK cells)
  - Extended half-life (Fc, PEG)

https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-263-masac-recommendations-concerning-products-licensed-for-the-treatment-of-hemophilia-and-other-bleeding-disorders

Factor VIII treatment in general

- Inhibitor treatment
  - Treating bleeding: recombinant factor VIIa or FEIBA
  - Preventing bleeding: rFVIIa or FEIBA
  - Treating the inhibitor: immune tolerance induction
- Emicizumab
  - Bispecific antibody for activated factor IX and for factor X
  - Given subcutaneously to prevent bleeding
    - Weekly, q 2 weeks, q 4 weeks
  - For patients with and without inhibitors

Factor IX treatments in general

- Plasma derived
  - Pooled human plasma
- Recombinant
  - CHO lines
  - Extended half life with Fc, Alb, PEG fusion

Eloctate – Fc
Adynovate – PEG
Jivi – PEG
Novo8 – PEG

Table 2. Extended half-life factor VIII products.

Engineered protein	Year of first licensing	Manufacturer	Plasma half-life (hours)	Half-life prolongation*
Efmoroctocog alfa	2014	Biogen/Sobi	19	1.5-1.7
Rurioctocog alfa pegol	2015	Baxalta/Takeda	14.3	1.3-1.5
Danoctocog alfa pegol	2018	Bayer	19	1.6
Turoctocog alfa pegol	2019	Novo Nordisk	18.4	1.6

*Calculated from an average plasma half-life of standard coagulation FVIII of approximately 12 hours.

Alprolix – Fc
Idelvion – albumin
Rebinyn – PEG

Table 3. Extended half-life factor IX products.

Engineered protein	Year of first licensing	Manufacturer	Plasma half-life (hours)	Half-life prolongation*
Efrenonacog alfa	2014	Biogen/Sobi	82	4.3
Albutrepenonacog alfa	2016	CSL Behring	101	5.3
Nonacog beta pegol	2017	Novo Nordisk	93	4.9

*Calculated from an average plasma half-life of standard FIX products of approximately 19 hours.

Non-factor options on the horizon

- Concizumab: monoclonal antibody against TFPI
  - Daily subcutaneous injections
  - Trials complicated by thrombotic events
  - Open trial for patients with Hem A and Hem B with inhibitors
- Fitusiran: antisense oligonucleotide against anti-thrombin
  - Monthly subcutaneous injection
  - Trials also complicated by thrombotic events
  - Open trial for patients with Hem A and Hem B with inhibitors

Gene therapy

- Most gene therapy products use an AAV vector with hepatic tropism
- FVIII – B domain deleted
- FIX – Padua variant
- Challenges:
  - AAV antibodies
  - Liver toxicity
  - Sustained expression
  - Need for immune suppression
  - Integration into host genome?
- Anticipate FDA application for gene therapy in the next ? 6 months ?

Gene therapy

TABLE 3 Gene transfer and cellular therapy trials for hemophilia A and B

Product	Vector	Promotor-transgene	Clinical trial status	Trials identifier	Study population	Manufacturer
Hemophilia A						
AMT-180	AAV5	BDD-FVIII	Pre-clinical development	n/a	n/a	UniQure Biopharma
BAY259023	AAVhu37	BDD-FVIII	Phase I/II, recruiting	NCT03588299	Male, ≥18-years-old, FVIII activity <1%, PTPs ≥150 exposure days, excluding those with antibodies reactive with AAVhu37capsid	Bayer/Ultragenyx
GO-8	AAV2/8	HLP-FVIII-V3	Phase I, recruiting	NCT03001830	Male, ≥18-years-old, FVIII activity <1%, PTPs ≥50 exposure days, excluding those with large deletions (multiple exons) and nonsense mutations of the F8 gene and HIV	University College, London
Lenti-FVIII (Auto CD34 + PBSC)	Lentiviral vector Pleightlet (MUT6)	BDD-FVIII	Phase I, recruiting	NCT03818763	Male, ≥18-years-old, FVIII activity <1%, active high titer FVIII inhibitors (>5 BU), excluding those with known co-existing thrombophilia gene and HIV	Medical College Wisconsin
SB-525	AAV2/6	BDD-FVIII	Phase II, recruiting Phase III lead-in, recruiting Phase III, recruiting	NCT03061201 NCT03587116 NCT04370054	Male, ≥18-years-old, FVIII activity <1%, PTPs ≥150 exposure days Male, ≥18-64-years-old, FVIII activity ≤1%, PTPs ≥150 exposure days and on FVIII prophylaxis, excluding those with (SB-525 capsid) neutralizing antibodies Prior Hemophilia A participants of the lead-in study (NCT03587116)	Pfizer
SPK-8011	AAV-LK03	BDD-FVIII	Phase I/II, recruiting Long-term follow-up, enrolling Phase III lead-in, recruiting	NCT03003533 NCT03432520 NCT03876301	Male, ≥18-years-old, FVIII activity ≤2%, PTPs ≥150 exposure days, excluding those with anti-AAV-Spark 200 Previously dosed on a SPK-8011 study Male, ≥18-years-old, FVIII activity ≤2%, PTPs, excluding those with anti-AAV-Spark 200 neutralizing titers ≥1:1 and HIV	Spark Therapeutics
TAK-754	AAV8	BDD-FVIII	Phase I, active, not recruiting	NCT03370172	Male, ≥18-75-years-old, FVIII activity <1%, PTPs >150 exposure days, excluding those with AAV8 neutralizing titers ≥1:5 and HIV	Takeda
Valoctocogene Roxaparvovec (Roctavian, BMN270)	AAV5	BDD-FVIII	Phase I/II, active, not recruiting Phase III, active, not recruiting Phase III, not yet recruiting	NCT02576795 NCT03370913 NCT04323098	Male, ≥18-years-old, FVIII activity <1%, PTPs ≥150 exposure days, excluding those with detectable pre-existing antibodies to the AAV5 Capsid and HIV same population as above Addition of prophylactic steroids	BioMarin

Croteau SE, et al. AJH. 2020.

Gene therapy

TABLE 3 (Continued)

Product	Vector	Promotor-transgene	Clinical trial status	Trials identifier	Study population	Manufacturer
SIG-001	Encapsulated cell therapy	BDD-FVIII	Phase I, recruiting	NCT04541628	≥18-years-old, FVIII activity <1%, PTPs ≥150 exposure days	Sigilon Therapeutics
Hemophilia B						
SPK-9001	AAV-Spark 100	hFIXco R338L, Padua	Phase II, completed Phase III lead-in, recruiting Long-term follow-up, enrolling	NCT02484092 NCT03587116 NCT03307980	Male, ≥18-years-old, FIX activity ≤2%, PTPs ≥50 exposure days, excluding those with anti-AAV-Spark 100 neutralizing titers ≥defined titer Male, ≥18-64-years-old, FIX activity ≤2% and on FIX prophylaxis, excluding those with anti-AAV-Spark 100 neutralizing titers ≥1:1 Previously dosed on a SPK 9001 study	Pfizer
scAAV2/8-LP1-hFIXco	scAAV2/8	LP1-hFIXco	Phase I, active, not recruiting	NCT00979238	Male, ≥18-years-old, FIX activity <1%, PTPs ≥50 exposure days, excluding those with detectable antibodies reactive with AAV8	St. Jude Children's Research Hospital
FLT-180a	AAV-S3	hFIXco R338L, Padua	Phase I, recruiting Long-term follow-up, enrolling	NCT03369444 NCT03641703	Male, ≥18-years-old, FIX activity ≤2%, PTPs ≥150 exposure days, excluding those with AAV neutralizing antibodies and HIV Previously dosed on a FLT180a study	University College, London Freeline Therapeutics
TAK-748	AAV8	hFIXco R338L, Padua	Phase I/II, suspended	NCT04394286	Male, ≥18-75-years-old, FIX activity ≤2%, PTPs ≥50 exposure days, excluding those with anti-AAV8 neutralizing titers ≥1:5	Takeda
Etranacogene Dezaparvovec (AMT-061)	AAV5	LP1-hFIXco R338L, Padua	Phase II, active, not recruiting Phase III, HOPE-B, active, not recruiting	NCT03489291 NCT03569891	Male, ≥18-years-old, FIX activity ≤2%, PTPs >20 exposure days Male, ≥18-years-old, FIX activity ≤2%, PTPs ≥150 exposure days	UniQure Biopharma
SB-FIX	AAV2/6	ZNF mediated gene-editing three components of SB-FIX (ZFN1, ZFN2, and FIX cDNA Donor)	Phase I, active, not recruiting	NCT02695160	Male, ≥18-years-old, FIX activity <1%, excluding those with HIV	Sangamo Therapeutics

Croteau SE, et al. AJH. 2020.

2021 VWD guidelines

- ASH, ISTH, NHF, and WFH consensus guidelines on diagnosis and management of VWD
- A few highlights will be presented here – there are also one page summary documents available:
  - https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/von-willebrand-disease

James PD, et al. Blood Advances. 2021.
Connell NT, et al. Blood Advances. 2021.

VWD types – quick refresher

Table 1. Classification of VWD: major types and subtypes

Type	Characteristic
1	Quantitative decrease in VWF with preserved ratios between VWF/Ag, VWF/Act, and FVIII; normal multimer distribution
1C	Quantitative decrease in VWF with preserved ratios between VWF/Ag, VWF/Act, and FVIII; increased VWF/pp compared with VWF/Ag
2A	Decreased platelet-dependent VWF activity with loss of high-molecular-weight multimers
2M	Decreased platelet-dependent VWF activity with preserved multimer pattern
2N	Decreased binding of FVIII
2B	Increased binding to GPIbα, often leading to thrombocytopenia
3	Absence or near absence of VWF
Platelet-type VWD	Functional defect of platelet GPIbα, leading to excessive binding of platelets and VWF and subsequent thrombocytopenia and loss of high-molecular-weight multimers
Acquired von Willebrand syndrome	Decreased VWF and particularly loss of high-molecular-weight multimers as a result of either shearing from mechanical forces (eg, aortic stenosis resulting in Heyde syndrome), adsorption on tumors (eg, Waldenström macroglobulinemia or Wilms' tumors), or autoimmune inhibitor formation

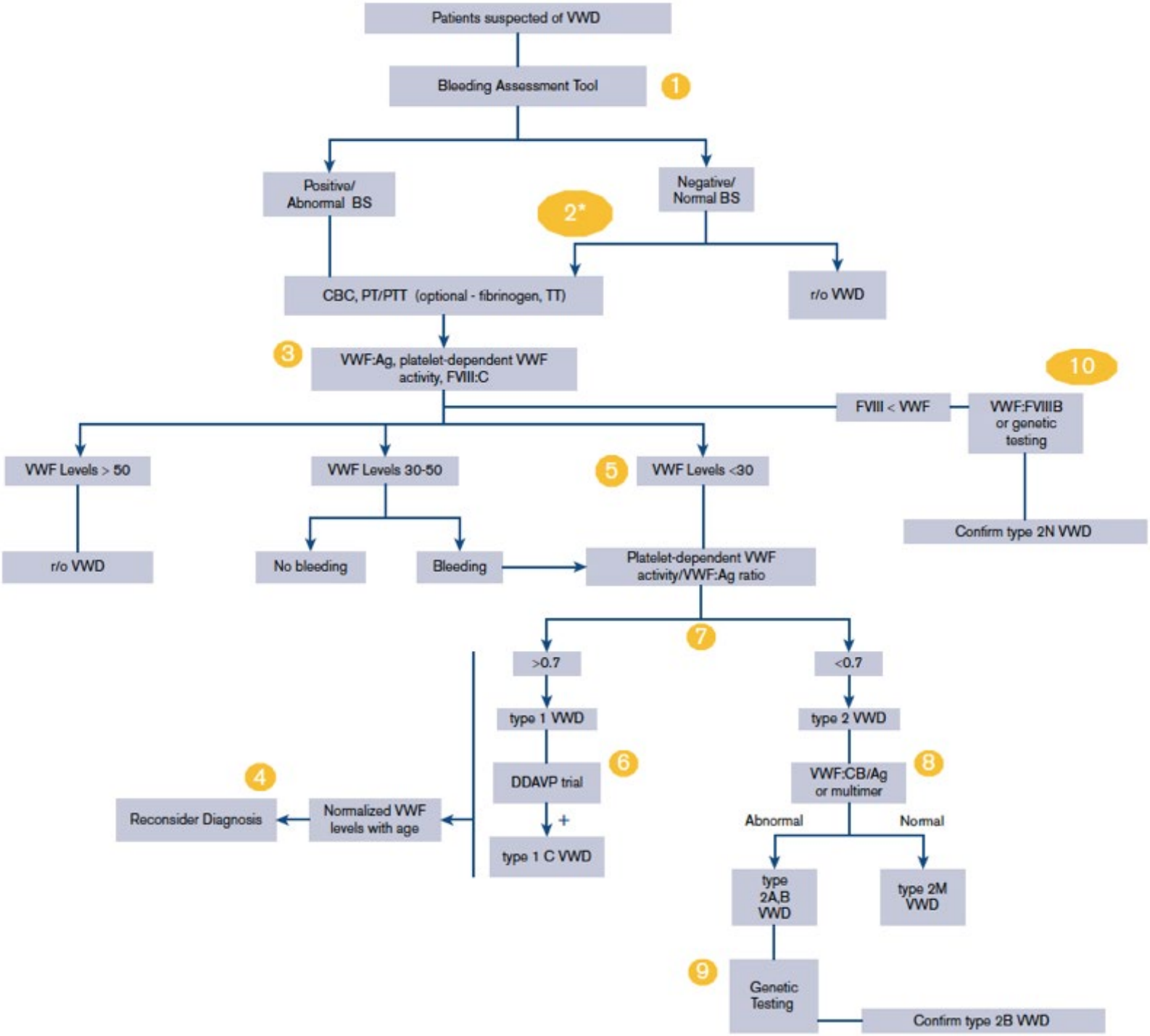
Act, activity; Ag, antigen; GPIbα, glycoprotein Ibα; pp, propeptide.

Connell NT, et al. Blood Advances. 2021.

2021 VWD guidelines on *diagnosis*

- Panel suggests using the newer assays of VWF activity that evaluate platelet binding (e.g. VWF:GPIbM, VWF:GPIbR) over the VWF:RCo assay
- Use a VWF level of <0.3 regardless of bleeding and <0.5 if + bleeding (ABO specific ranges are not needed)
- For people who have historical type 1 VWD but now have normal levels, reconsider the diagnosis but don't necessarily remove it
- For type 2B, use genetic testing over the RIPA test

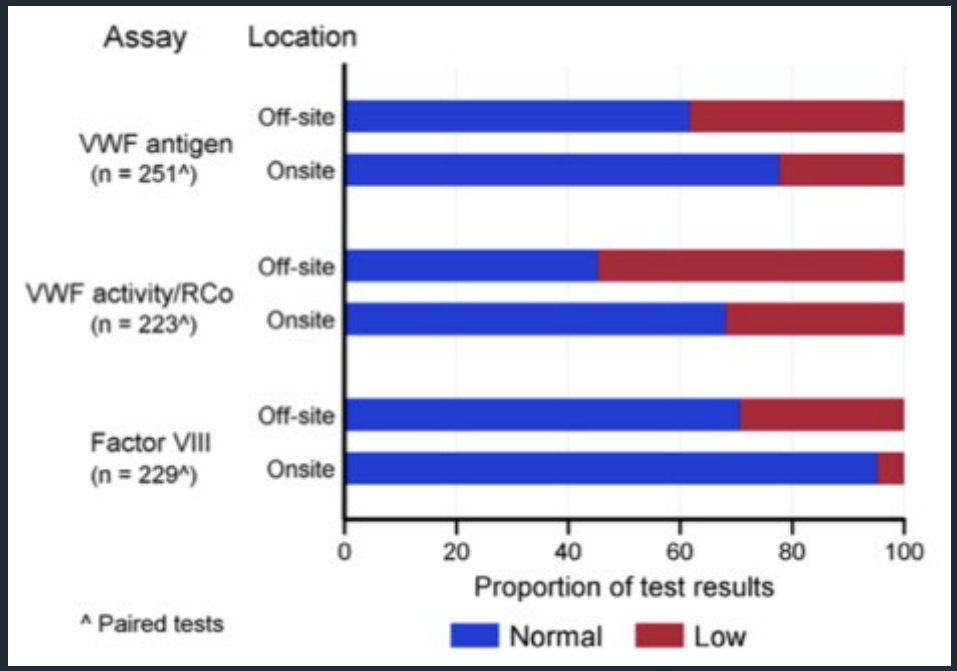
James PD, et al. Blood Advances. 2021.



James PD, et al. Blood Advances. 2021.

VWD diagnosis

- Multi-site study looking at “onsite” vs “off-site” VWD testing including 251 females
- <40% of people were ultimately diagnosed with VWD
- ~40% referred had normal hemostatic testing



Jaffray J, et al. AJH. 2020.

2021 VWD guidelines on *management*

- For patients with VWD and severe and frequent bleeds, long-term prophylaxis is suggested
- DDAVP challenges should be done for those who will likely respond (note Stimate is still not available) (could maybe skip it for adults if levels >0.30)
- DDAVP contraindications: active CV disease, seizure disorders, type 1C and surgery, type 2B, pre-eclampsia
- For surgeries: get FVIII and VWF levels >0.5 for at least 3 days

James PD, et al. Blood Advances. 2021.

2021 VWD guidelines on *management*

- For minor surgery, get levels over 0.5 AND use TXA
- Type 1 VWD with VWF >0.3 and mild bleeding phenotype, just give TXA for minor mucosal procedures
- Use TXA or oral hormonal pill for heavy menstrual bleeding rather than DDAVP
- For women with VWD and who are pregnant and need an epidural, get levels 0.5-1.5
- Give women TXA during post-partum period

Other VWD thoughts

- It’s important to consider the pre-test probability
- Combining your bleeding history with your labs is critical
- When the levels are not so low but the patient is really a bleeder, consider testing for platelet disorders
- Continuity of care is critical for patients with VWD – bleeding phenotype is an important factor in treatment considerations

The potential to menstruate + a bleeding disorder: fast facts

Up to 30% of w… int during their life

Or… for ever… truate you see

- 6 will report heavy menstrual bleeding at some point in their life
- Up to 1-2 may have an underlying bleeding disorder

30% c… HMB

15-30% of t… eding disorder

15% of 19,… ding disorder

30% of 19,2… ding disorder

Population of women 15-44 years by age: US, 2019

Females

	US (Percent)	US (Count)
15-19 yrs	16.0	10,308,963
20-29 yrs	34.9	22,672,834
30-39 yrs	34.1	21,929,275
40-44 yrs	15.0	10,014,484
Total	100.0	64,325,356

64,325,356 individuals with the potential to menstruate

Kadir RA, et al. Lancet 1998.
James P. Hematology 2020. Dilley A, et al. Obstet Gynecol 2001.
https://www.marchofdimes.org/Peristats/ViewSubtopic.aspx?reg=99&top=14&stop=125&lev=1&slev=1&obj=8

The potential to menstruate + a bleeding disorder: fast facts

- Up to 65% of adolescent patients with HMB have iron deficiency or iron deficiency anemia.
- Individuals with the potential to menstruate experience delays in bleeding disorder diagnosis (11.6 +/- 16.4 years vs 7.7 +/- 16.6 years for those without the potential to menstruate)
- In a review of 75 patients with von Willebrand Disease, 25% of women received a blood transfusion before being diagnosed with VWD
- Only 4 out of 10 women with HMB will seek care for their HMB.

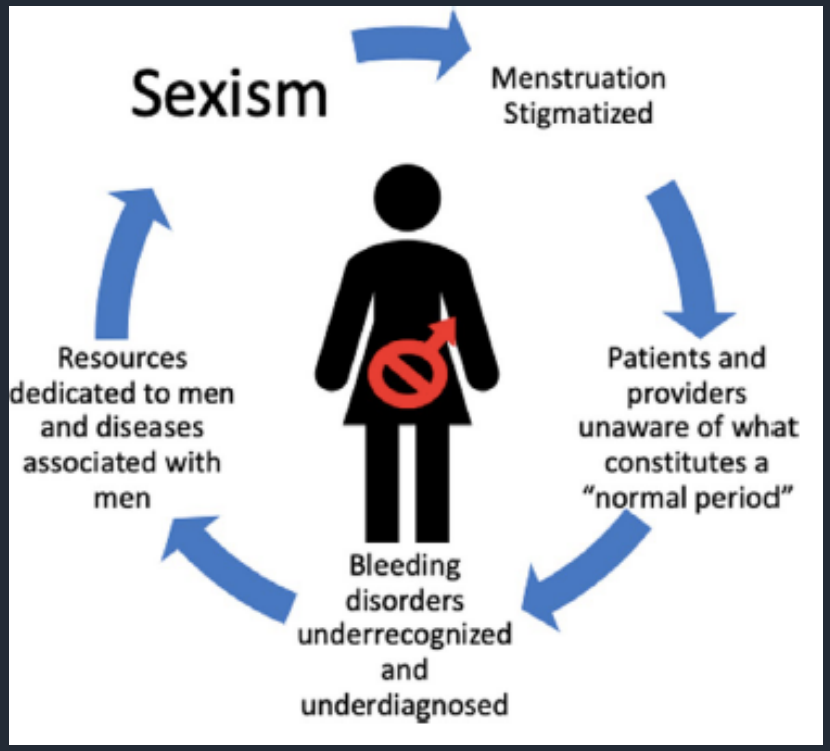
McLintock C. Haemophilia. 2018.

Kirtava A, et al. Haemophilia 2004.

Atiq F, et al. Eclinical Medicine. 2021.

Zia A, et al. Coagulation & Its Disorders. 2020.

Sexism in hematology



- In a 2017 survey of >10,000 men and women, 56% said they would rather be bullied than talk about periods.
- <10% of pediatricians and family medicine physicians document a full menstrual history during well adolescent visits.
- Individuals with XX chromosomes "should" make up 30% of the patients we see with hemophilia, but they make up only 3.5% of the population.
- VWD is at least 10x more common than Hemophilia A and B combined but there are at least 15,000 fewer publications in PubMed.

Weyand AC and James PD. RPTH. 2020.

Sexism in hematology

Differences between men and women with autosomal dominant blee… n

- "t… sex-sp… luded HI…
- Fo… years)

- "R… ter 1st tha… disorders bl… y of bl… raumatic bl… more of… nce these bl… se or to rule out an underlying bleeding disorder. "

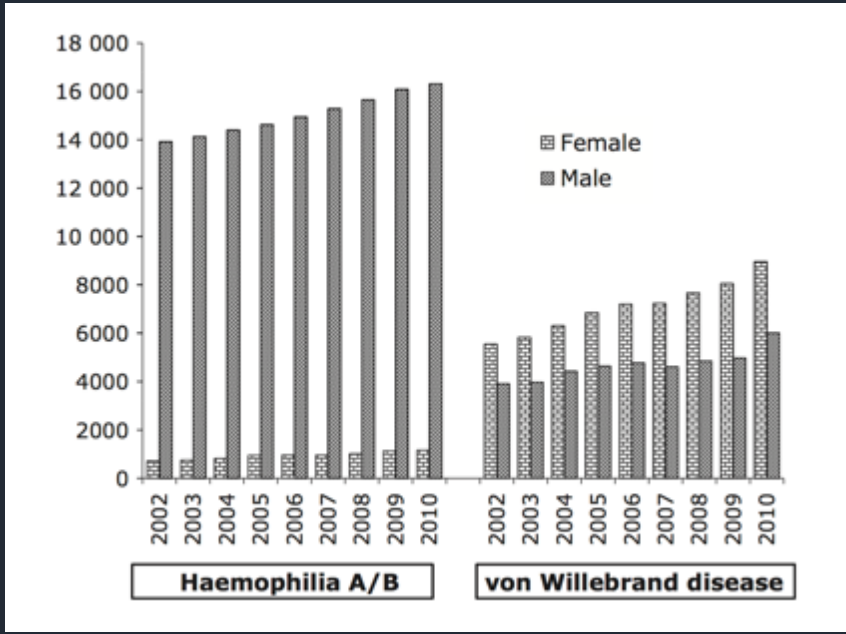
Table 1
Characteristics of the total study population.

	Men $n = 427$	Women $n = 665$	P-value
Age at inclusion, years	37.1 ± 21.8	41.2 ± 18.9	0.002
Age first bleeding, years	8.9 ± 13.6	10.6 ± 11.3	0.075
Age at diagnosis, years	16.6 ± 19.6	22.5 ± 18.4	<0.001
Diagnostic delay, years	7.7 ± 16.6	11.6 ± 16.4	0.002
Referred for bleeding, n (%)	145/396 (36.6%)	296/618 (47.9%)	0.002
BS	9.7 ± 6.9	11.6 ± 7.2	<0.001
Abnormal BS	341 (84.2%)	495 (80.6%)	0.145
BS without sex-specific bleeding	9.6 ± 6.9	8.8 ± 6.0	0.036
Bleeding requiring treatment in year prior to inclusion, n (%)	153/399 (38.3%)	215/623 (34.5%)	0.213

Data are presented as mean ±standard deviation unless otherwise specified. BS bleeding score. Abnormal BS is defined as ≥3 in children, ≥4 in males and ≥6 in females.

Atiq F. et al. EClinicalMedicine.2021.

There is hope!



- 1990: females comprised 13% of HTC patients
- 2010: females comprised 31% of HTC patients

- Map of clinics with heme/gyn focus across the US.
- The number of adult patients with the potential to menstruate and a diagnosed bleeding disorder seen at our center tripled when we dedicated staff to this population (2009: 43 patients. 2019: 141 patients).

https://www.fwgbd.org/clinics

Baker JR, et al. Haemophilia 2013.

What can you do?

- Include a menstrual history –for all your patients who could be having periods!
  - How often are you having bleeding? (more than once per month = too often)
  - How many days does it last? (more than 7 = too long)
  - Do you have to change your pad/tampon more often thane very 2 hours (yes = too heavy)
  - Do you have to wake up in the middle of the night to change products (yes = too heavy)
  - Do you have leaking/soaking of blood onto your clothes on a regular basis (yes = too heavy)

What can you do?

- When a patient tells you that their periods are heavy, believe them
- Not everyone with heavy periods needs a bleeding disorder work up but they may need an intervention to decrease iron deficiency and improve quality of life
- Counsel the patients that you take care of with bleeding disorders that their children may be at risk for heavy periods, depending on the disease
- Befriend a gynecologist to help make sure the patients get good therapy
- Or, connect them to our combined heme/gyn clinics at OHSU
- Identify and treat iron deficiency

Side note…

Iron deficiency: bleeding disorders

- From the Registry for Bleeding Disorders Surveillance (9173 males with hemophilia):

	Age Group									
	Less than 20		20–44 years		45–64 years		65+ years		All	
	n	%	n	%	n	%	n	%	n	%
Iron deficiency anemia	252	5.3%	133	4.6%	127	10.6%	42	12.0%	554	6.0%

- In 196 adolescents patients who presented with heavy periods, 43% of whom had a bleeding disorder, 119 (61%) were iron deficient

https://www.cdc.gov/ncbddd/hemophilia/communitycounts/registry-report-males/procedures.html
Zia A. Am J. Hematology. 2021.

Questions/Comments/Thoughts

”Anemia”