#### EVIDENZE NEL TRATTAMENTO DELLE PATOLOGIE TROMBOEMBOLICHE E DELLE PATOLOGIE EMORRAGICHE

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### Approccio diagnostico al paziente con diatesi emorragica

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#### Bleeding and bleeding disorders

- At least one bleeding symptom is reported by up to 40% of otherwise normal people (*low specificity*)
- The prevalence of inherited bleeding disorders ranges from 1:1,000 to 1:10,000 (*low prevalence*)

#### Bleeding and bleeding disorders



*P(IBD/Symptoms)=99/(99+39960)=0.2%* 

#### Consequences

- The *low specificity* of bleeding symptoms and the *low* prevalence of bleeding disorders makes the diagnosis difficult
  - Overlooking diagnosis: "Maybe you have a bleeding disorder, but you can consult a reference Center over the year"
  - Overtesting patients: "You need an hemostasis testing because you bled after hip surgery"

#### Bayes and bleeding disorders: the need for very informative results

Probability of disease = Prevalence × LRtest

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*Tests (or combination thereof) with a LR>10000 are needed!* 

### Likelihood: Probability of disease given a result



#### A quantitative approach to diagnosis: Bayes' theorem

Probability of disease = Prevalence × LRtest



# A specific test is more useful than a sensitive test for diagnosis

$$LR_{test} = \frac{Sensitivity}{100 - Specificity}$$

$$LR = \frac{100}{2.5} = 40$$

$$LR = \frac{70}{0.5} = 140$$

Bayes and bleeding disorders: is the lab sufficient to establish a diagnosis?

- Even with a very specific test, the LR of a lab test is usually well below 1000
- The lab can be *diagnostic* only for markedly abnormal findings

– e.g. FVIII:C<5 IU/dL

• You have to increase the pre-test probability by clinical evaluation!

### **Bleeding severity**

**Bleeding severity Clinical Presentation** 

• Trivial, non relevant Does never interfere with daily activities or require medical attention

 Minor (or Clinically relevant non Major)
Severe enough to interfere with the patients' everyday life, or to seek medical attention; may be treated at home

•	Major	May cause permanent damage to the patient or
	iviaj0i	threaten his/her life

### Minor (clinically relevant) bleeding

Symptom	Criteria
Epistaxis	Any nosebleed, especially occurring after puberty, that causes patient concern (e.g., interference or distress with daily or social activities)
Cutaneous bleeding	Bruises are considered significant when 5 or more (> 1cm) in exposed areas
Minor cutaneous wound	Any bleeding episode caused by superficial cuts (e.g., by shaving razor, knife, or scissors) or that requires frequent bandage changes
Tooth extraction	Any bleeding occurring after leaving the dentist's office and requiring a new, unscheduled visit or prolonged bleeding at the dentist's office causing a delay in the procedure or discharge
Menorrhagia	Any bleeding that interferes with daily activities such as work, housework, exercise or social activities during most menstrual periods

## Spontaneous major bleeding is always an alarming symptom

- Major bleeding occurs in ≈50% of patients with a severe clotting disorder not undergoing prophylaxis
- < 1 / 2,000 normal subjects has a major bleed every year</li>

$$LR = \frac{50\%}{1/2000} = 1000$$

• A bleeding disorder should be suspected in patients with major bleeding, particularly if at a young age and unprovoked

Manco-Johnson et al. Journal of Thrombosis and Haemostasis, 2013.

#### Minor bleeding is common

• Every «normal» adult person has a 5-8% annual probability of minor bleeding

Study	Participants	Bleeding rate (% pt-year)			
		Major	Minor		
Thrombosis Prevention Trial	1272 men (age 45-69 years)	0.05	5.3		
Women's Health Study	19942 women (mean age 54.6 years)	0.06	7.7		

 Could we estimate the expected «normal» probability of bleeding during lifetime?

#### Bleeding probabilities predicted at age 30 by a binomial model



Tosetto et al, JTH 2013

## Incidence of non-major bleeding in different bleeding disorders

Severity	Condition	Incidence (%pt/yr)
Mild Bleeding	ASA intake	6.5
Disorder	C1130F VWF mutation	7.5
	Use of VKA/DOAc	15-16.3
Severe Bleeding Disorder	Type 2M VWD	40
	Type 2A VWD	107

### Expected mean number of bleeds by age in different disorders



## Clinical criteria for «significant» bleeding history

- History of a major bleeding
- At least three clinically relevant bleeding symptoms: LR≈100
- A bleeding score >3 (5) in males (females): LR≈70-90
- Lower thresholds allowed in children?

Tosetto et al, JTH 2006 Rodeghiero et al, JTH 2005

# Likelihood ratios in type 1 VWD, data from the MCMDM-1VWD Study

	LN
VWF:Ag<20 IU/DI	261.02
VWF:Ag 20-40 IU/dL	78.03
VWF:Ag 40-60 IU/dL	2.67
Bleeding Score < 3	0.32
Bleeding Score 3 – 10	86.2
Bleeding Score > 10	>100

Tosetto et al, JTH 2006 Rodeghiero et al, JTH 2005

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#### Patient ID:

#### Prospective validation of a bleeding score Date of recruitment:

#### Sex: Date of birth:

Epistaxis		Ora	Oral cavity		Surgery		Muscle hematoma		
0	No or trivial (less than 5)	0	No	-1	No bleeding in at least 2 surgeries	0	Never		
1	> 5 or more than 10'	1	Reported at least one     CONSULTATION ONLY     Surgical hemostasis or Antifibrinolytics     Blood transfusion or Replacement therapy or Desmopressin		Not done or no bleeding in 1 surgery	1	Post-trauma no therapy		
2	CONSULTATION ONLY	2			Reported in <25% of all surgeries	2	Spontaneous no therapy		
3	Packing or Cauterization or Antifibrinolytics	3			intervention Surgical hemostasis or Antifibrinolytics	3	Spontaneous or traumatic requiring Desmopressin or Replacement therapy		
4	Blood transfusion or Replacement therapy or Desmopressin	4			Blood transfusion or Replacement therapy or Desmopressin	4	Spontaneous or traumatic requiring Surgical intervention or Blood transf		

Cutaneous		GI bleeding		Menorrhagia		Hemarthrosis	
0	No or trivial (<1 cm)		No	0	No	0	Never
Ľ		1	Associated with ulcer, portal	1	CONSULTATION ONLY	1	Post-trauma no therapy
1	>1 cm and no trauma	2	Spontaneous	2	Antifibrinolytics or pill use	2	Spontaneous no therapy
_	CONSULTATION ONLY	2	Surgical hemostasis or Blood	3	Curettage or Iron therapy	3	Spontaneous or traumatic requiring desmopressin or Replacement therapy
2		3	transfusion or Replacement therapy or Desmopressin or Antifibrinolytics	4	Blood transfusion or Replacement ther -apy or Desmopressin or Hysterectomy	4	Spontaneous or traumatic requiring surgical intervention or blood transfusion

Bleeding from minor wounds		Тос	Tooth extraction		Post-partum hemorrhage		CNS bleeding	
0	No or trivial (less than 5)	-1	No bleeding in at least 2 extractions	-1	No bleeding in at least 2 deliveries	0	Never	
1	> 5 or more than 5'	0	Not done or no bleeding in 1 extraction	0	No deliveries or no bleeding in 1 delivery	1		
2	CONSULTATION ONLY	1	Reported in <25% of all procedures	1	CONSULTATION ONLY			
3	Surgical hemostasis	2	Reported in >25% of all procedures, no intervention	2	Curettage or Iron therapy or Antifibrinolytics	2	•	
	Blood transfusion or Replacement therapy or Desmopressin	3	Resuturing or Packing	3	Blood transfusion or Replacement therapy or Desmopressin	3	Subdural, any intervention	
4		4	Blood transfusion or Replacement therapy or Desmopressin	4	Hysterectomy	4	Intracerebral, any intervention	

Total assigned score:

#### BATs for the diagnosis of MBD

	Sensitivity	Specificity	PPV	NPV
VWD				
Rodeghiero, 2005	64.2	99.1	41.1	99.6
Bidlingmaier, 2012	65.2	94.6	83.3	86.9
Any MBD				
Tosetto, 2011	41.1	81.0	34.6	84.5
Bidlingmaier, 2012	47.7	94.6	87.5	69.7

- High NPV, useful to *exclude* presence of MBD
- Sensitivity around 50 60% for the diagnosis of MBD
- Laboratory investigation always needed
  - in very young, asymptomatic patients
  - in patients with an abnormal bleeding score

#### BATs for the diagnosis of MBD



#### Conclusions

- The diagnosis of a bleeding disorder is a clear epitome of the need for a tight integration between laboratory and clinical data
- A laboratory diagnosis should be pursued only
  - In accurately selected patients, based on their bleeding history (e.g., BS > 3) or
  - In patients with a prolonged aPTT (especially if young)
- Clinical data will be even more important as NGS molecular information will become available in the next years (e.g., Thrombogenomics platform)