EQA for the diagnostic process – using case history and EQA samples

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CUTTING EDGE OF LABORATORY MEDICINE IN EUROPE
ANALYTICAL PERFORMANCE SPECIFICATIONS: MOVING FROM MODELS TO PRACTICAL RECOMMENDATIONS
The aim of this conference is to go through and discuss the three different models agreed by the Milan 2014 EFLM Strategic Conference to set APS for the medical laboratory and to give practical examples on how this can be done.

Clinical Utility of Analytical Performance Specifications?

What do we need from a clinical point of view?

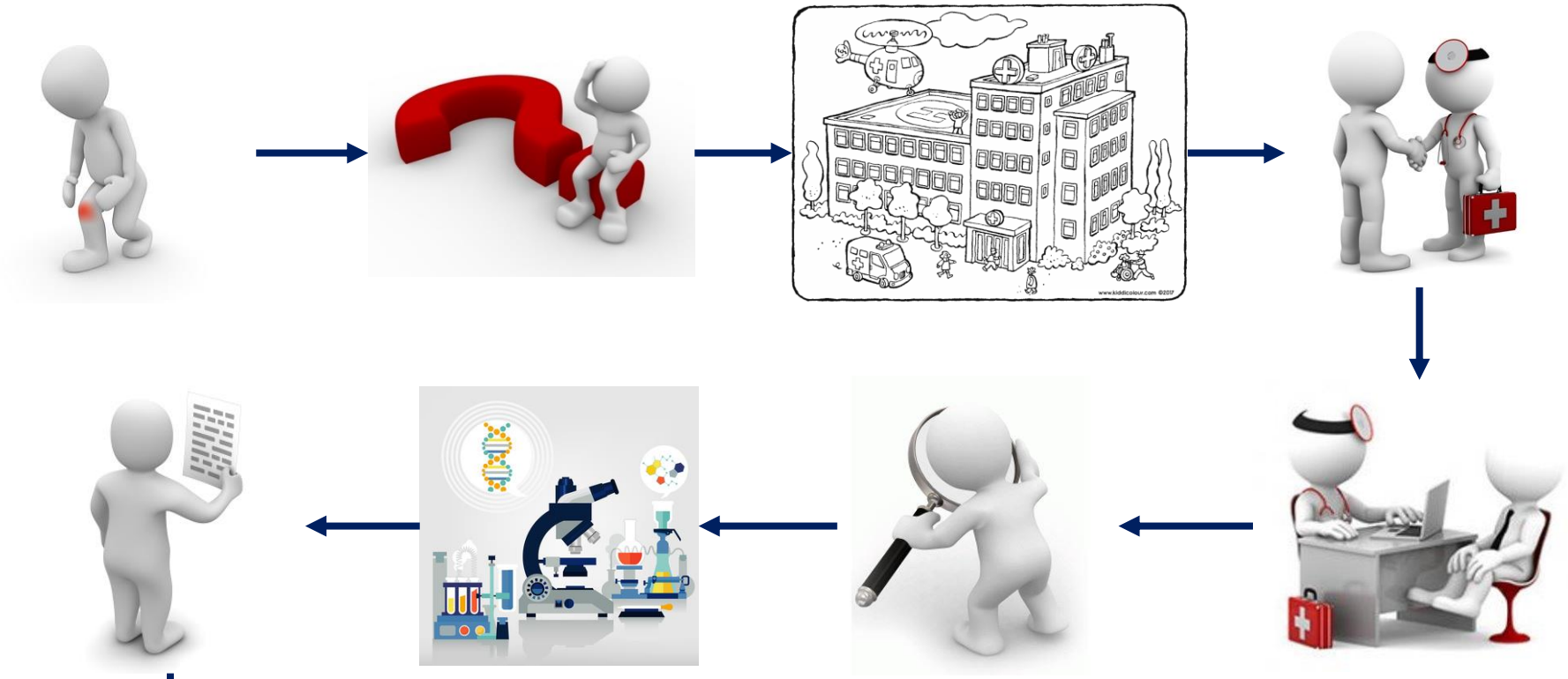
Do we understand the impact of measurment uncertainty on clinical decision making?

Analytical EQA		Diagnostic EQA
Focus on the analytical quality of a single analyte.		Integral approach to cover the entire diagnostic proces

Analytical EQA

Patient-centered EQA

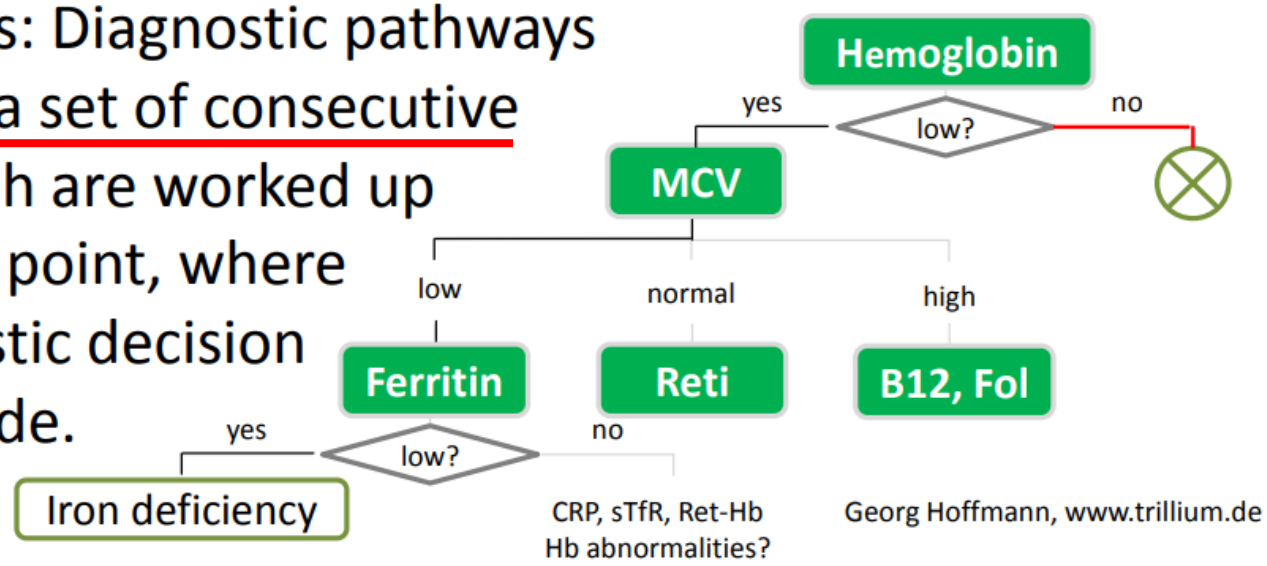
The story of the patient



How do we assure the laboratory delivers reliable results to the physician suitable for diagnosis or monitoring purposes?

The diagnosis is seldom based on the measurment of a single measurand!

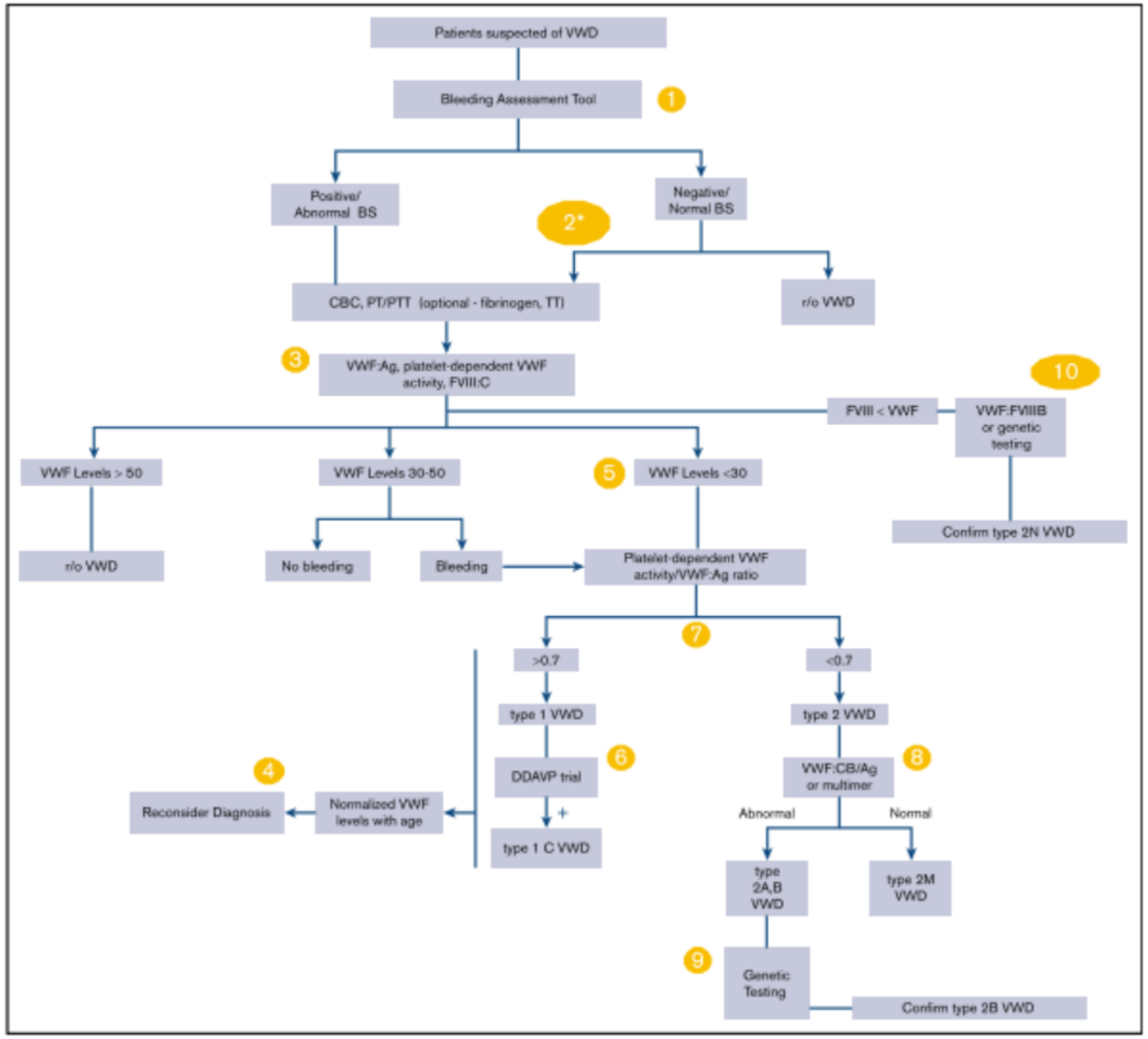
- Diagnostic pathways were originally designed to describe and standardize the diagnostic process from the initial medical question through to the findings.
- In practice, diagnostic pathways became a synonym for “smart test profiles”, based on decision tree algorithms.
- This means: Diagnostic pathways represent a set of consecutive tests, which are worked up just to the point, where an diagnostic decision can be made.



Von Willebrand Disease

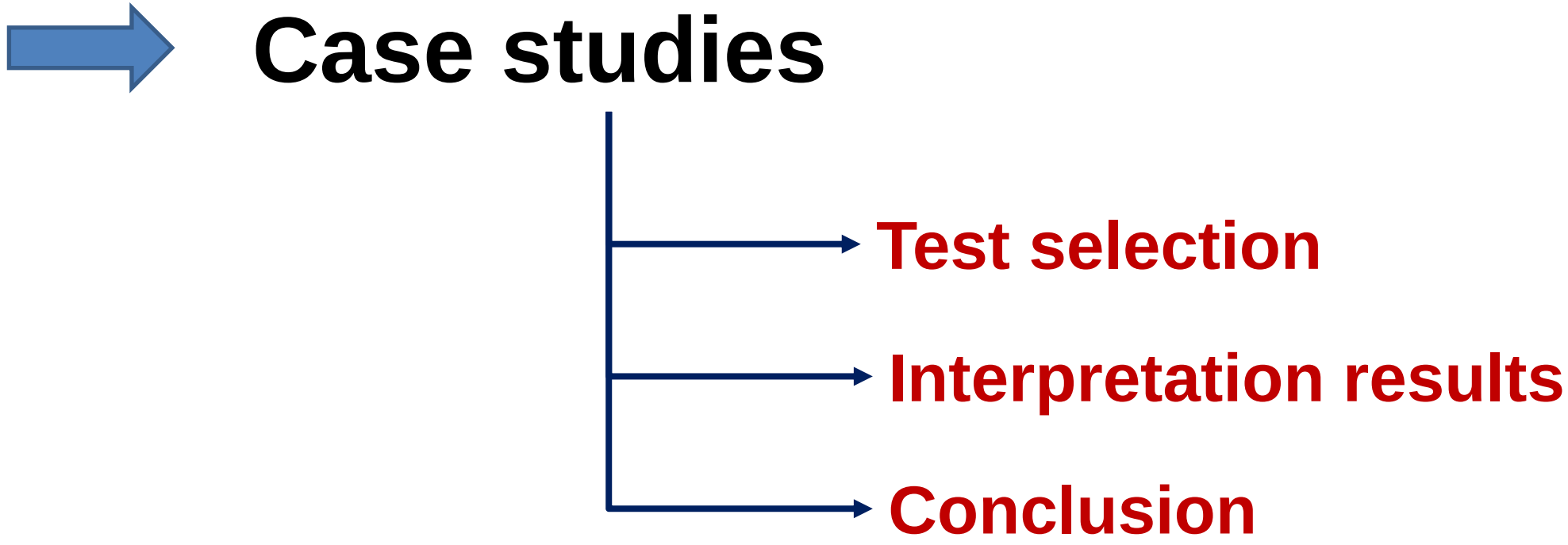
Most common bleeding disorder

Guideline-directed diagnostic pathway



James, P.D. *et al* Blood Adv 2021;5: 280 - 300

How can EQA play a role in assessment of quality assessment of diagnostic pathways?



Case Study strategy

- Case description
- Plasma sample
- First line Screening Tests
- Interpretation
- Reflective testing
- Intrepretation
- Diagnosis

CASE DESCRIPTION AND CASE STUDY REQUEST

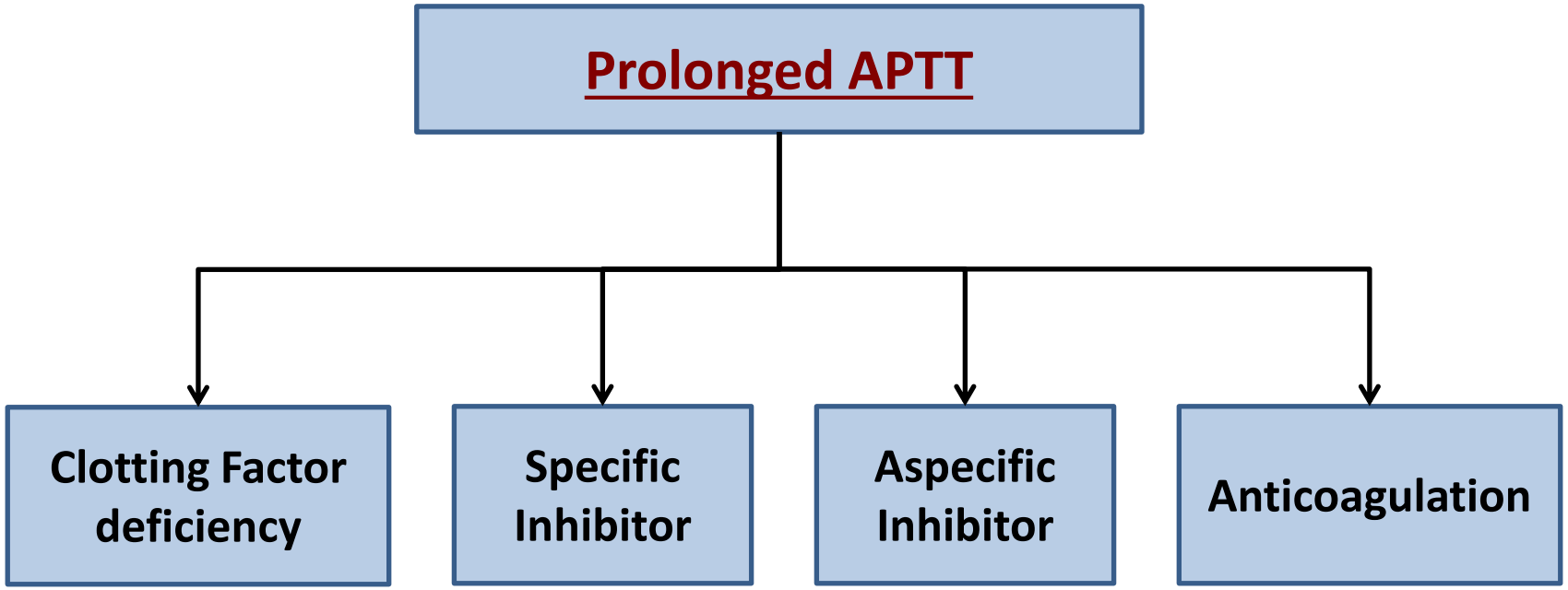
During a pregnancy, a 28 year old female presents a decrease in platelet count as low as 20 x 10^9/L. Previously she experienced severe vaginal bleedings.

Please, investigate the potential cause for these abnormalities by investigating the results of screening tests and any possible subsequent abnormal coagulation tests.
In case there is an abnormality, provide a possible diagnosis for the patient mentioned above.

Activated Partial Thromboplastin Time (APTT) (seconds)

The table below shows the classification of the test results for the APTT.

Reagent	N	Mean	Minimum	Maximum	Normal	Equivocal	Prolonged
All	61	-	-	-	0	0	61
I.L. HemosIL APTT-SP	2	54.7	54.0	55.4	0	0	2
I.L. HemosIL SynthASil	18	45.8	40.3	66.5	0	0	18
Siemens Actin FS	11	57.2	45.3	66.0	0	0	11
Siemens Actin FSL	2	46.5	46.0	47.0	0	0	2
Siemens Pathromtin SL	8	54.9	53.0	57.4	0	0	8
Stago Cephalin / Kaolin / CKPrest	6	51.1	49.3	56.5	0	0	6
Stago Cephascreen	1	49.5	-	-	0	0	1
Stago PTT automate / STA APTT	10	51.0	43.0	53.6	0	0	10
Tcoag Automated APTT	1	56.0	-	-	0	0	1
Tcoag TriniCLOT APTT HS	1	54.3	-	-	0	0	1
Tcoag TriniCLOT APTT S	1	51.2	-	-	0	0	1



Activated Partial Thromboplastin Time (APTT) (ratio *) without incubation

Reagent	N **	Median	Minimum	Maximum	Normal	Equivocal	Prolonged
All	12	1.23	1.03	1.89	16	2	2

RESULTS CLOTTING FACTORS

Because of the prolonged APTT and the normalisation in the mixing test a decreased level for at least one of the clotting factors VIII, IX, XI or XII could be possible. The table below shows the average results for these clotting factors. Results are given in IU/mL.

Clotting Factor	N	Median	Minimum	Maximum	Normal	Equivocal	Decreased
FVIII	56	0.18	`0.06	1.89	1	0	55
FIX	31	0.93	0.25	1.51	30	0	1
FXI	28	0.88	0.67	1.25	28	0	0
FXII	20	0.55	0.41	0.90	9	5	6

RESULTS VON WILEBRAND FACTOR

Most of the participants also investigated whether there was an abnormality in von Willebrand Factor causing a bleeding disorder. Below a summary of the reported results are given.

Clotting Factor	N	Median	Minimum	Maximum	Normal	Equivocal	Decreased
VWF antigen	55	0.40	0.21	0.46	3	2	51
VWF ristocetin cofactor activity	15 *	0.05	0.03	0.27	1	0	22
VWF activity	20 **	0.06	0.02	0.34	0	0	34
VWF collagen binding assay	10 ***	0.03	0.02	0.07	0	0	11

FINAL DIAGNOSIS

Type of diagnosis	Number
No diagnosis	3
Normal	0
Haemophilia A	1
Haemophilia B	0
von Willebrand Disease	53
Other factor deficiency	4
Unexplained bleeding disorder	2

Classification	Number *
Type 1	3
Type 2A	6
Type 2B	39
Type 2M	0
Type 2N	0
Type 3	0

Comments

The correct diagnosis is **Von Willebrand Disease type 2B.**
Eighty-four percent of the participants gave a **correct diagnosis** of von Willebrand Disease. Three participants did not indicate a diagnosis.
The majority (74%) of those participants who selected von Willebrand Disease classified a type 2B VWD

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FINAL COMMENTS

From the patient description it is clear that this female has a history of bleeding symptoms as well as a low platelet count.
A prolongation of the APTT was confirmed by all participants which was, in most of the cases, corrected in a mixing test. This may indicate a clotting factor deficiency. This is confirmed by the measurement of a low FVIII level. It should be realised that a low FVIII can also be caused by a von Willebrand Disease. Therefore, the measurement of VWF antigen and/or activity is very important in this type of patient sample. Indeed decreased levels of VWF antigen and activity were observed.
The low platelet-dependent VWF activity over VWF antigen ratio indicates a plasma of a VWD type 2 patient.
Furthermore, a low VWF:CBA ratio and the lack of high-molecular weight multimers indicate a plasma of a VWD type 2B patient.
The thrombocytopenia can be the result of the pregnancy but is also known for patient with a VWD type 2B or platelet-type VWD. Several participants indicated the possibility of the HELLP syndrome. However, this patient was not suffering from this syndrome.
The decreased levels of FV was a complicating factor in this patient sample and could be related to the sample collection and lyophilisation process.

Clinical Chemistry 57:11
1514–1523 (2011)

European Specialist Porphyria Laboratories: Diagnostic Strategies, Analytical Quality, Clinical Interpretation, and Reporting As Assessed by an External Quality Assurance Program

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Table 1. The 5 EPNET EQAS distributions: clinical case histories, diagnoses, and typical biochemical features (only the case histories accompanied the distribution of sample sets to participants).

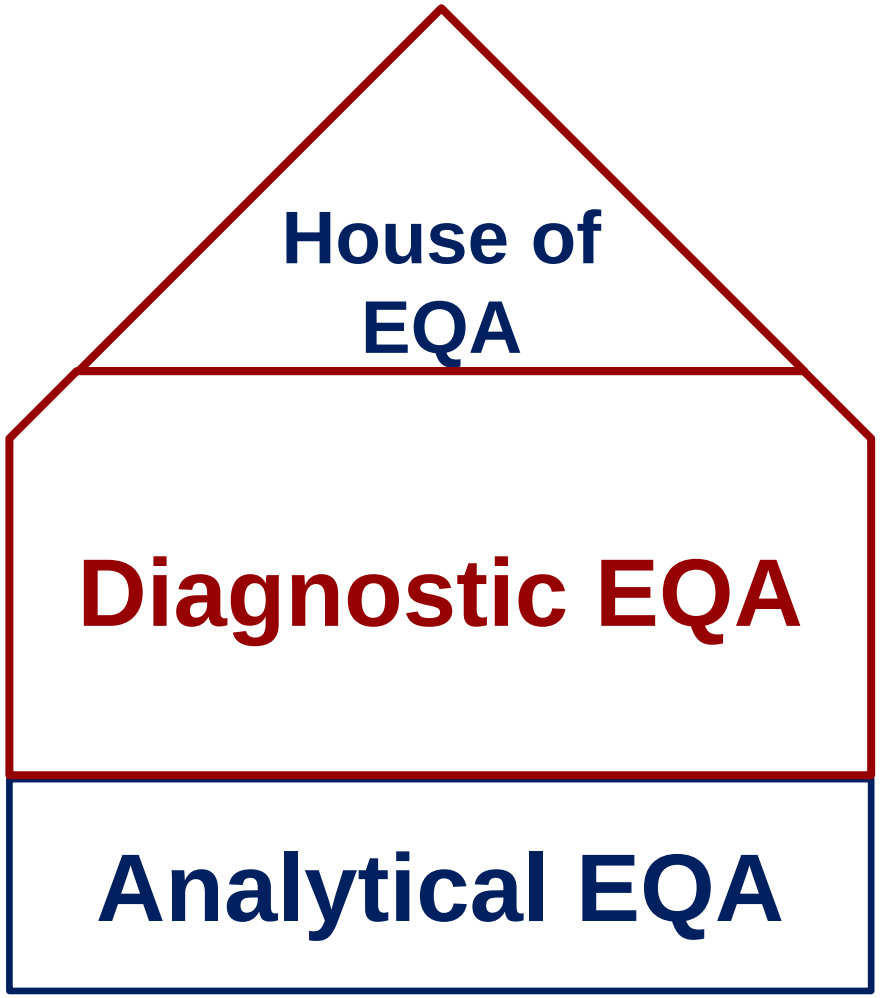
			Typical biochemical features in symptomatic patients [Deacon and Elder *(18)*]			
Distribution	Case history	Diagnosis	Urine	Plasma	Feces	Erythrocytes
A	Female born 12/23/1977 has had repeated attacks of abdominal pain and nausea since she was 14. She has been hospitalized once with "acute abdominal pain" with no surgical intervention, and was discharged after 3 days without further treatment. The samples were obtained 14 days after her last attack.	AIP	Increased PBG and ALA Increased total porphyrins Increased uroporphyrin	Fluorescence emission peak at 615–620 nm	Total porphyrins within reference interval or slightly increased	Protoporphyrin within reference interval

Table 2. Reporting details for the EPNET EQAS for specialist porphyria laboratories.

Preanalytical aspects: diagnostic strategies	Analytical aspects: laboratory analyses, with information on methodology, units, and reference limits		Postanalytical aspects: clinical interpretation and reporting
	Material	Analyte	
Selection of analyses based on clinical case history	Urine	ALA	The patient's diagnosis based on the clinical case history and all laboratory results
		PBG	Details on what would be reported to the requesting clinician
			Analytical results with or without interpretative comments
			Diagnosis
			Clinical information and advice for the physician and patient

CONCLUSIONS: Based on a case-based EQA scheme, variations were apparent in analytical and diagnostic performance between European specialist porphyria laboratories. Our findings reinforce the use of EQA schemes as an essential tool to assess both analytical and diagnostic processes and thereby to improve patient care in rare diseases.

Future Perspectives



Focus on diagnostic pathways, test selection, result interpretation and diagnosis

Performance assessment for single measurands.

DIAGNOSTIC EQA TOOLBOX

- Diagnostic Performance Specifications
- Assessment of the value of each measurand in the diagnostic process.
- Assessment of diagnostic strategies.
- ……

Thank you for your attention