Interactive session on the mutual communication between the physician and the laboratory

Michiel Coppens	What information does the doctor expect from the laboratory?
Steve Kitchen	What kind of services can a laboratory deliver to the physician?

What information does the doctor expect from the laboratory?

Michiel Coppens
Internist Thrombosis & Haemostasis
Amsterdam UMC Haemophilia Treatment Center
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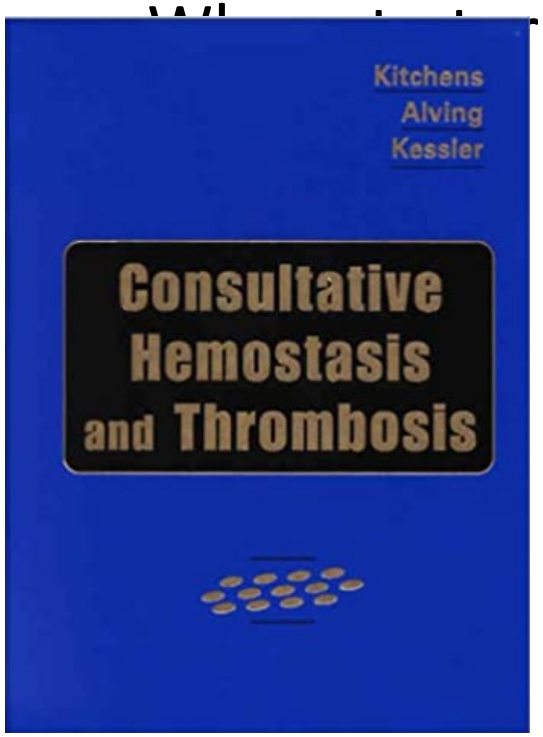
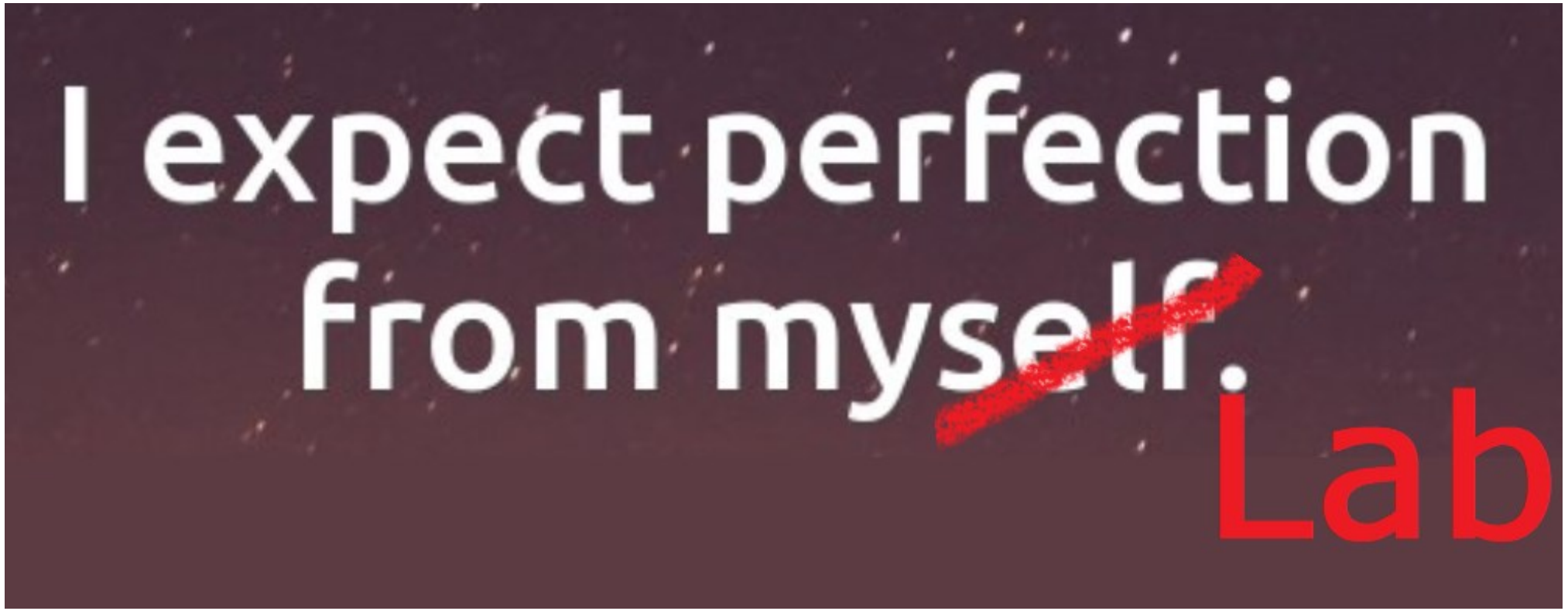
2004: more or less where it began

Felt I needed a head start



When you discuss assay discrepancies with Steve in the audience….


I expect perfection
from myself.
Lab

We will believe you…!!!

Lab-Clinic Interaction in Amsterdam

Mainly a clinician

EAHAD 2020 The Hague Promotional Film

Amsterdam UMC
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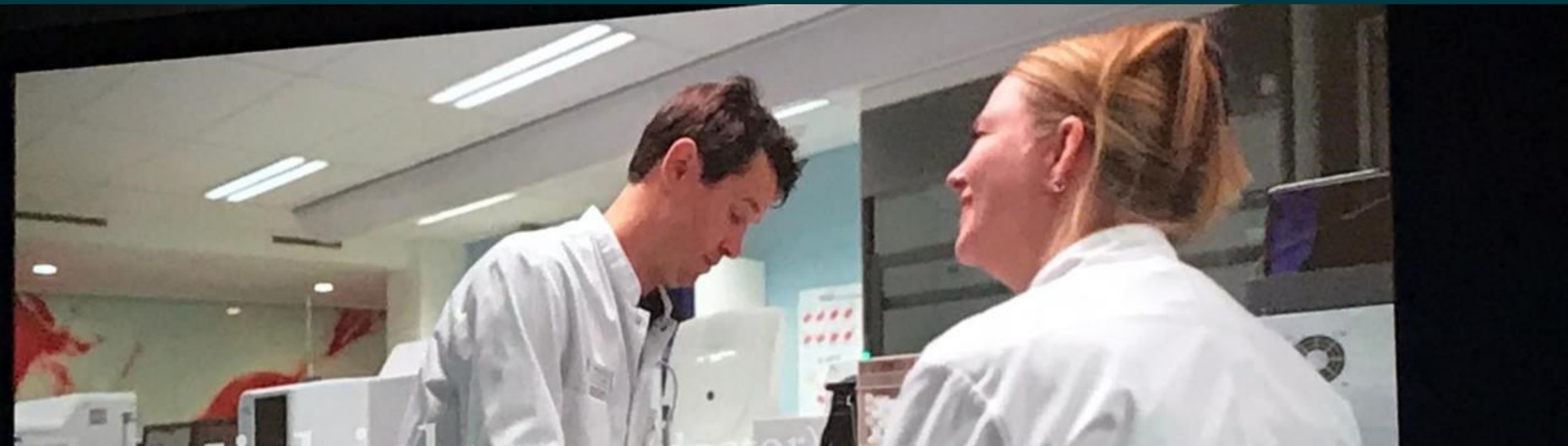
Cases illustrating the challenges of interpretation and communication:



Sep ’19

- Man, 79 years old
- Presentation with excessive hematomas and pr
- History myocardial infarction (- 14 yrs), 2 episod
  - R/ ASA, no anticoagulation

Factor VIII activity < 0.4%, anti-FVIII 28 BU

Acquired haemophilia A (AHA)

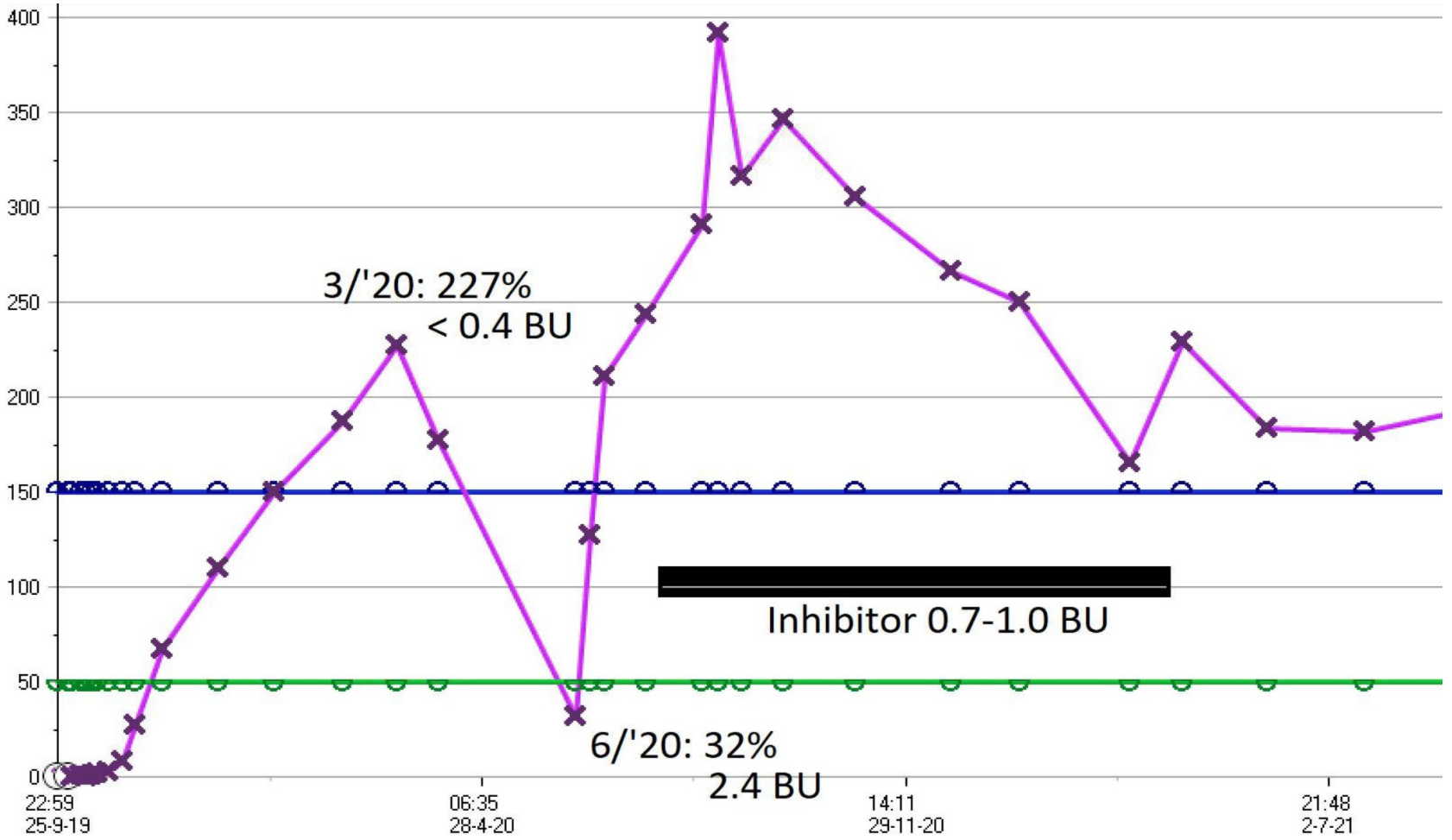
Bleed management

Activated PCC for 19 days

Immunosuppressive treatment

Prednisolon 1 mg/kg orally
Rituximab 375 mg/m^2, once weekly (4 wks)

FVIII over time



April ‘20

- Prednisolone 5 mg, further tapered to 2.5 mg

June ‘20

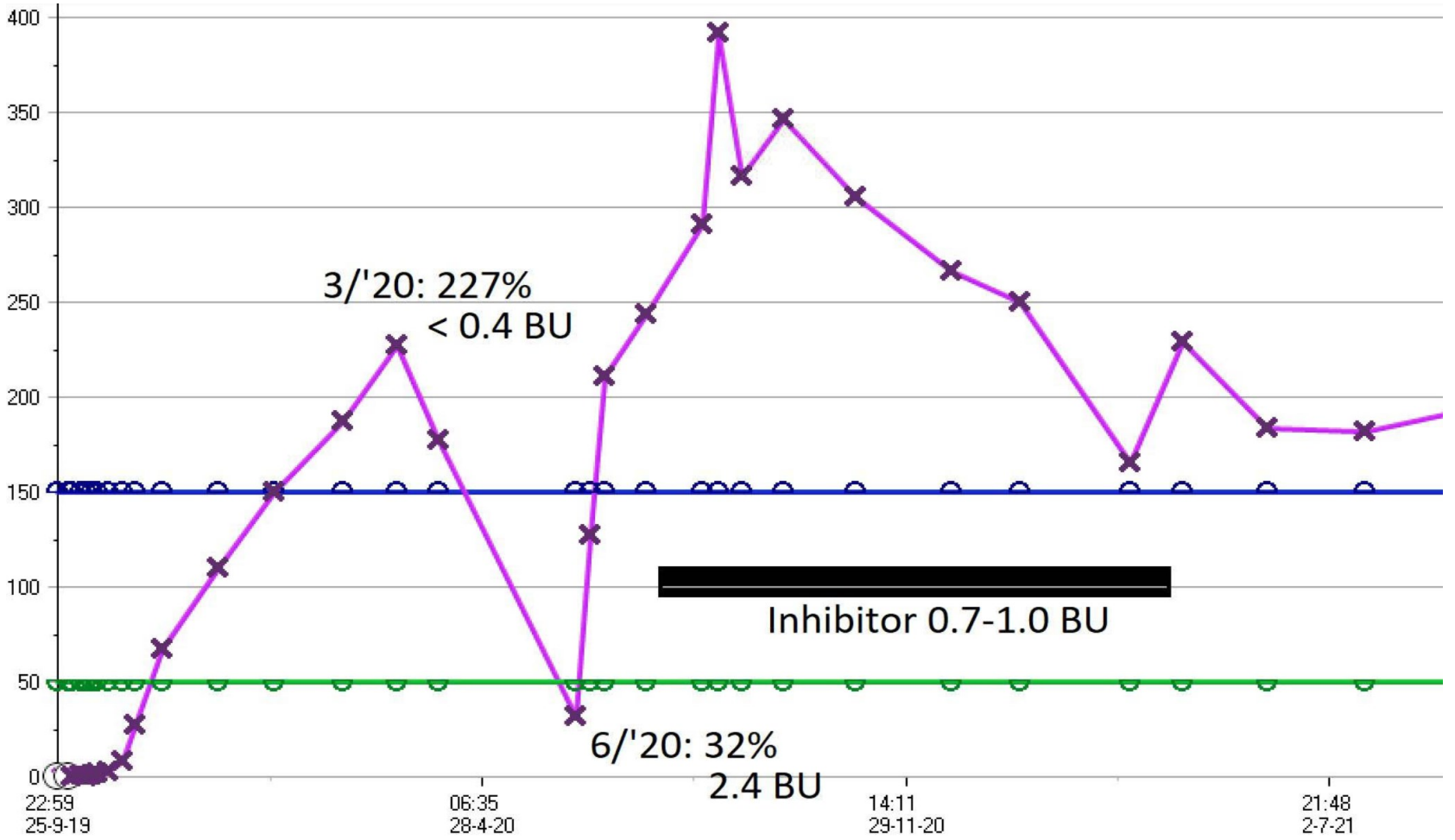
- Recurrence!
- Prednisolon to 30 mg
- Cyclofosfamide 3 mos

What we forgot to consider

May 2020

- Admitted for pneumonia in regional hospital
- Recurrence of atrial flutter
- Cardiologist calls and wants to start rivaroxaban 20 mg
    - We didn’t object

FVIII over time



Feb '21:

- Retested inhibitor after DOAC remove

  < 0.4 BU

- Retested all samples after June '21

  <0.4 BU

Lessons learned

- DOAC/Xa inhibitor can mimic Factor VIII inhibitor
    - Uses a one-stage assay

- Anticoagulation Rx now mandatory in lab order

<u>More recently</u>

- Lower chromogenic FVIII as well

Options at the lab end??

What kind of services can a laboratory deliver to the physician?

Steve Kitchen
Coagulation Laboratory
Sheffield Haemophilia and Thrombosis Centre
UK

What if the lab gets it wrong??

THE WALL STREET JOURNAL.

THE BUDGET SAFARI

OFF DUTY | W1

WHEN TO SUBTRACT A HOME ADDITION

MANSION | W9

DOW JONES | News Corp FRIDAY - SUNDAY, OCTOBER 21 - 23, 2016 - VOL. XXXIV NO. 186 WSJ.com EUROPE EDITION

THE PATIENTS HURT BY THERANOS

Questionable blood-test results caused alarm and prompted changes in treatment

The test is used to monitor effects of warfarin. Too much of the blood thinner can cause dangerous bleeding, while too little can lead to strokes.

It took Theranos nearly two months to warn a California man's doctor not to rely on the blood-coagulation test result he got Sept. 17, 2015.

In addition, 80% of the 834 quality-control checks that raised a red flag under Theranos's internal standards were more than three standard deviations from its average result, the inspection notes

Theranos stopped using the Siemens machine during the inspection and later told regulators it voided all coagulation tests run on the device from October 2014 to Sept. 17, 2015.

Ref: Wall Street Journal Oct 21 2016)

Partnership based on communication

Multi disciplinary team – individual cases

Medical and scientific leadership – setting policy

Automatic inclusion of Factor assays in an agreed/ Standardised Protocol

- To avoid delayed diagnosis of acquired haemophilia A.
- To avoid unnecessary delays in surgery.
- To avoid unprotected surgery in patients with previously undiagnosed bleeding disorders

Unexplained Isolated Prolonged APTT : Investigation in my lab

- Isolated – ie normal prothrombin time.
- Unexplained - ie not on anticoagulants, not a previously diagnosed factor deficiency etc
- Prolonged – any prolongation above reference range at all? How much prolongation warrants further investigation?

Unexplained isolated prolonged APTT?

- APTT with Lupus insensitive reagent (if initial reagent is lupus sensitive)
- Automatically add Thrombin time to exclude Heparin, Direct Thrombin Inhibitors (Dabigatran, Argatroban etc)
- No mixing study with normal plasma – correction of APTT in 1/3 or more of acquired haemophilia

How much APTT prolongation do we investigate in my centre under Isolated unexplained prolonged APTT protocol?

Proceed to Automatic assay of FVIII, FIX, FXI (& FXII) irrespective of time of day if :-

1. More than 10 seconds prolonged

or

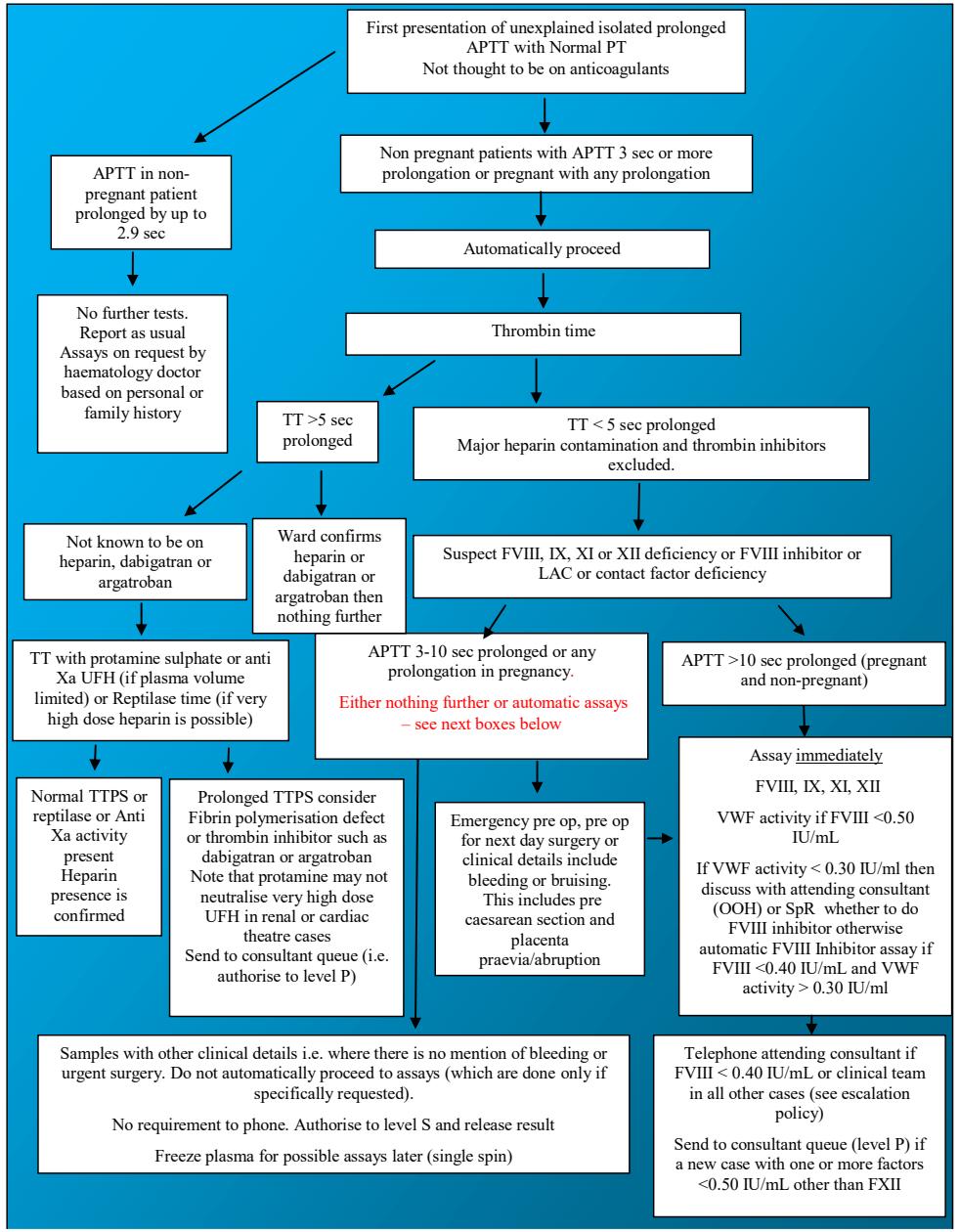
2. Between 3 and 10 seconds prolonged (non-pregnant) or any prolongation up to 10 sec (pregnant) either bleeding/bruising or before surgery

Why 10 seconds?

- Audit of acquired haemophilia A at presentation

- All had baseline APTT >10 seconds in our centre by our method

Sheffield Protocol



Unpublished Sheffield data

Audit of 5 months before and after revision of protocol
(50-55k APTTs in each period)

	Before	After
Number of cases having Factor assays	407	367
Number investigated for APTT >10 sec	36	49
Factor VIII	6 cases of Acquired HA	9 cases of Acquired HA

Advantages of Standardised Protocol

- Interval between occurrence of prolonged APTT and explanation reduced.
- Any previously unknown bleeding disorders diagnosed within 2 hours.
- Surgery or childbirth after likely diagnosis.
- Diagnosis of Acquired Haemophilia A within 6 hours of sample receipt.

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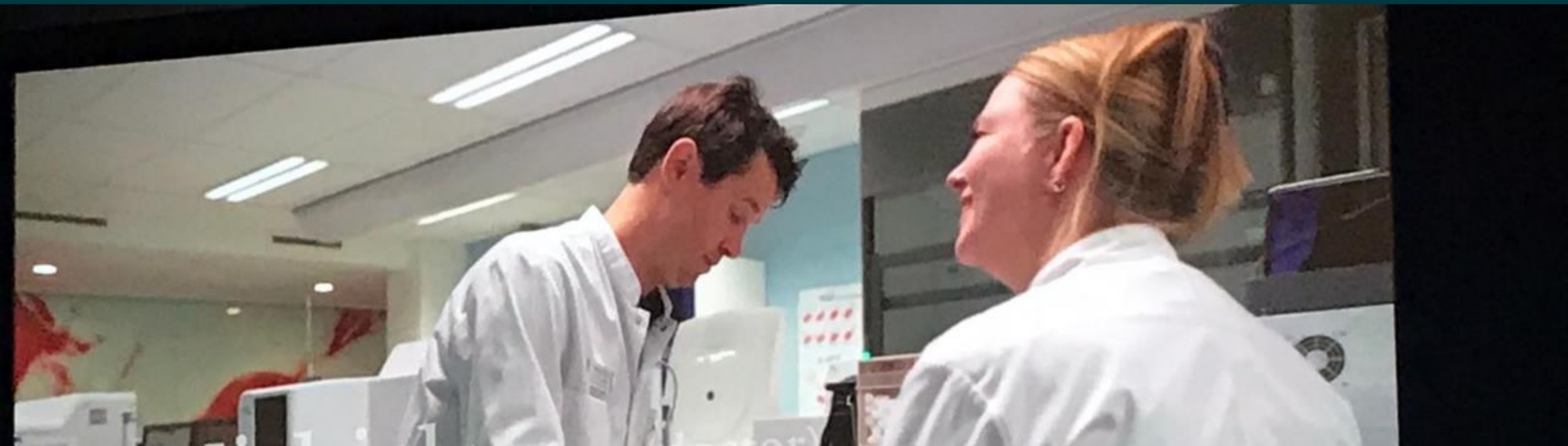
Challenges in the work-up of a suspected bleeding disorder



Woman, 25 years old

- Referred for suspected bleeding disorder:
  - Heavy bruising, as long as she can remember
  - Regular bleeding gum with brushing
  - Heavy menstrual bleeding from menarche (PE
  - No known familial bleeding disorders but mon
  - No pregnancies
  - No surgeries, tooth extractions
- ISTH Bleeding Assessment Tool (BAT) 6 points

In the Netherlands:

- Family physician: very limited work-up
- Can be referred to
  - General internist
  - Internist hematology
  - Tertiary haemophilia centre
- No strict guidelines on what should be tested
- Specialized test sent to centralized labs

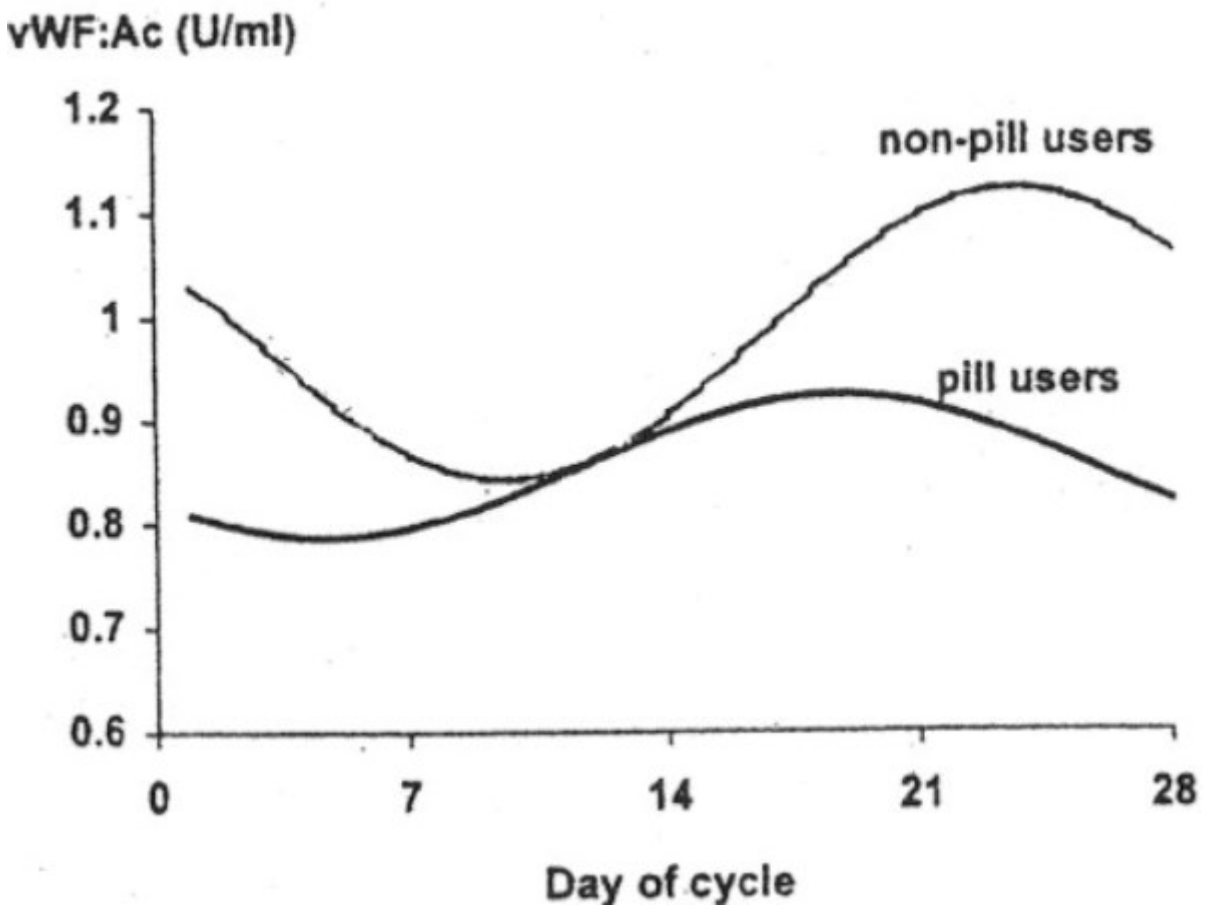
Lab assessment

- Normal blood/platelet count, incl MPV
- Normal PT / APTT
- PFA epinefrine & ADP normal
- VWF activity 59%; antigen 61%; FVIII 92% (ref: 50-150%)

How would you interpret for the clinician?

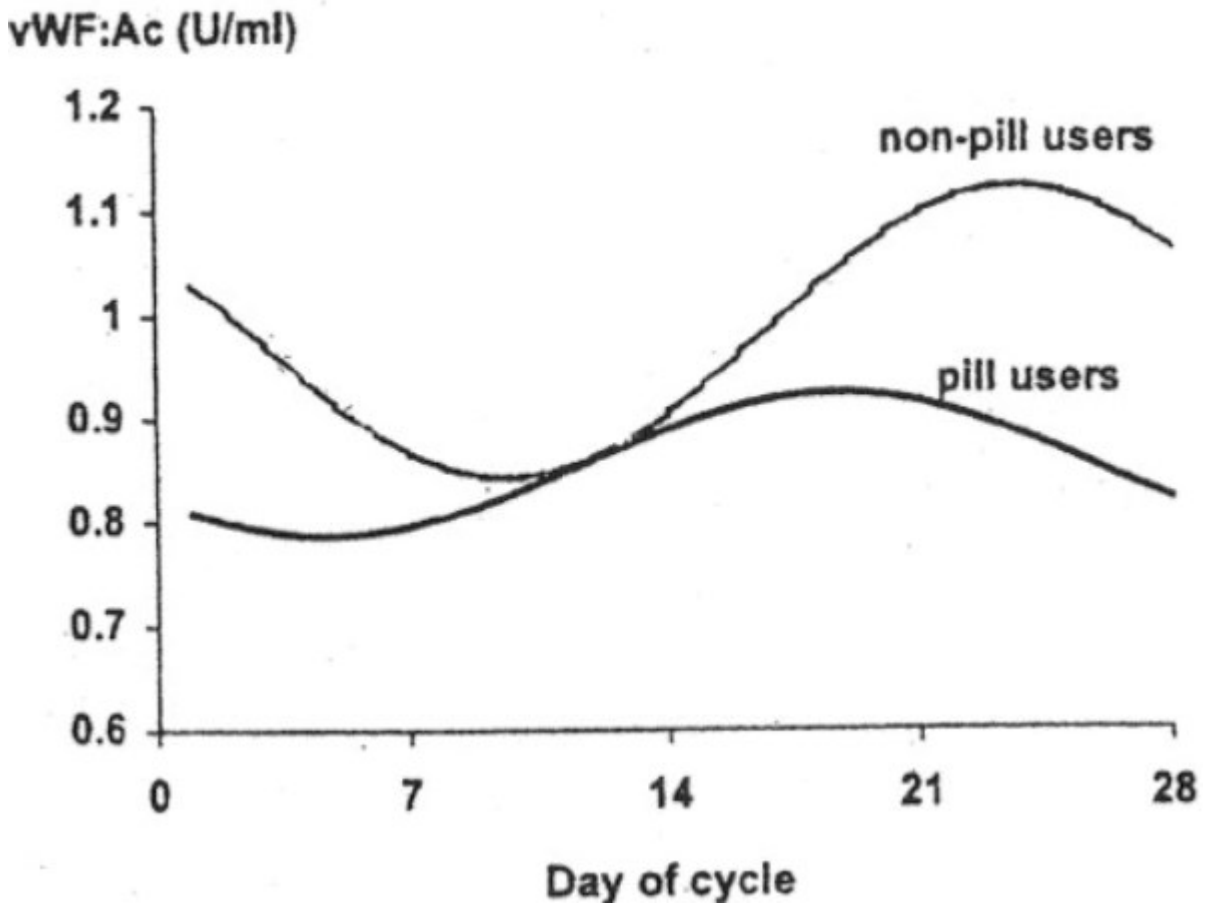
Remember this guy??

Cyclic variability of VWF



Christine Lee, Seminars in Hematology 2005

Cyclic variability of VWF



Retested around day 7 of cycle

VWF activity 40%, antigen 47%

Diagnosis “Low VWF”

Desmopressin/TXA now considered for interventions

Christine Lee, Seminars in Hematology 2005

Exception to the rule always apply

How do you convey them?

[Especially to my colleagues not working in Haemophilia Clinics?]

Woman, 25 years old

- *Referred for suspected bleeding disorder:*
  - *Heavy bruising, as long as she can remember*
  - *Regular bleeding gum with brushing*
  - *Heavy menstrual bleeding from menarche (PBAC score 210)*
  - *No known familial bleeding disorders but mom has more or less the same*
  - *No pregnancies*
  - *No surgeries, tooth extractions*
- *ISTH Bleeding Assessment Tool (BAT) 6 points*

Lab assessment

- Normal blood/platelet count, incl MPV
- Normal PT / APTT
- PFA epinefrine 153 s (N: < 165 s) & ADP 106 s (N: < 118 s)
- VWF activity 93%; antigen 97%; FVIII 108% (ref: 50-150%)

How would you interpret for the clinician?

Lab assessment

- Normal blood/platelet count, incl MPV
- Normal PT / APTT
- PFA epinefrine 210 s (N: < 165 s) & ADP 161 s (N: < 118 s)
- VWF activity 93%; antigen 97%; FVIII 108% (ref: 50-150%)

How would you interpret for the clinician?

Further lab assessment

- Platelet aggregation studies:
  - Irreversible/normal aggregation after stimulation with collagen, ristocetin, arachidonic acid
  - Reversible @ 1.0 um/L; normal/irreversible @ 2.0 um/L

How would you interpret for the clinician?

Clinical dilemma

Sensitivity/specificity PFA and aggregation studies

	EPI-CT (>165 sec)		ADP-CT (>110 sec)		Combined EPI + ADP CT		BT (>8 min)	
	Sens.	Spec.	Sens.	Spec.	Sens.	Spec.	Sens.	Spec.
All Congenital (%)	67	82	40	83	80	77	75	88
Nl Plt (n=9)	78	81	44	82	89	76	71	86
Low Plt (n=6)	50	79	33	82	67	74	80	85
All Acquired (%)	88	84	93	87	94	79	100	91
Nl Plt (n=2)	50	79	50	81	50	73	100	84
Low Plt (n=14)	93	84	100	87	100	79	100	90
All Cases (%)	77	89	66	90	87	84	88	98

*Nl = normal; Plt = platelet

Posan, Thromb Haemost 2003

ADP at higher conc present in up to 20% of normal population…

Consider genetic testing?

My take home points

- Clinic – Laboratory interaction important
- Anticoagulation can always interact
- Consult your lab in case of unexpected results
- Generally not against algorhythms
  - Help less experienced clinicians to use tests in sensible way
  - Remember that we tend to believe you at face value
  - **Where do we meet to discuss exceptions?**

Case

- 55 year old male. Nephrectomy infected pressure sores. Sepsis
- clotting screen performed
- PT 11.9 sec (Normal 9.5-11.5 Sec)
- APTT 50.7 sec (Normal 20.3- 27.5 sec)
- Fibrinogen 7.8 g/l (normal 2.0 -4.0 g/l)

Extra tests

- Thrombin time – 15.3 sec (normal 12.4 – 16.6)

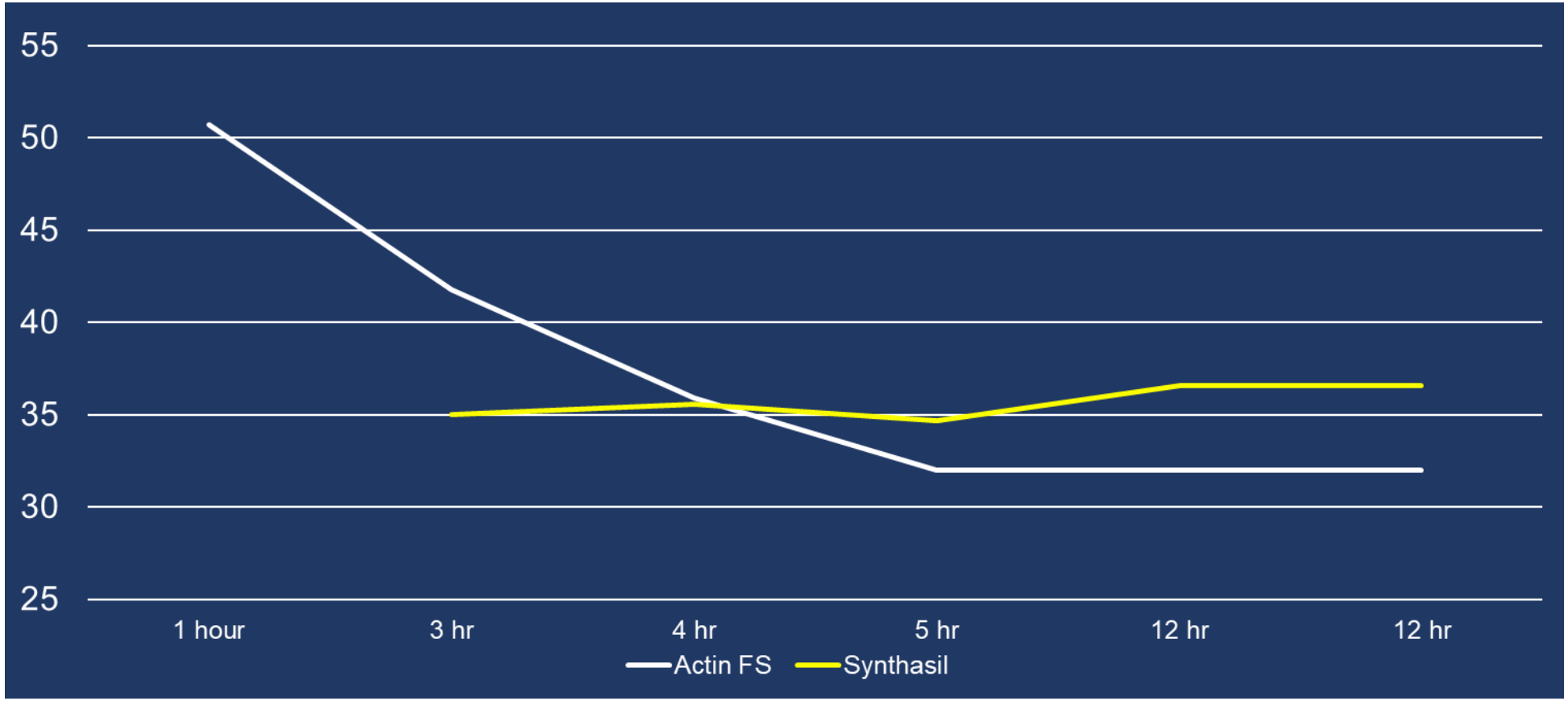
- No mix in my centre -
  - assays available 24/7
  - misleading results in non incubated mix in some acquired haemophilia
  - incubated mix wastes time

- No request for replacement sample – pre analytic checks exclude most artefacts so results on replacement usually match

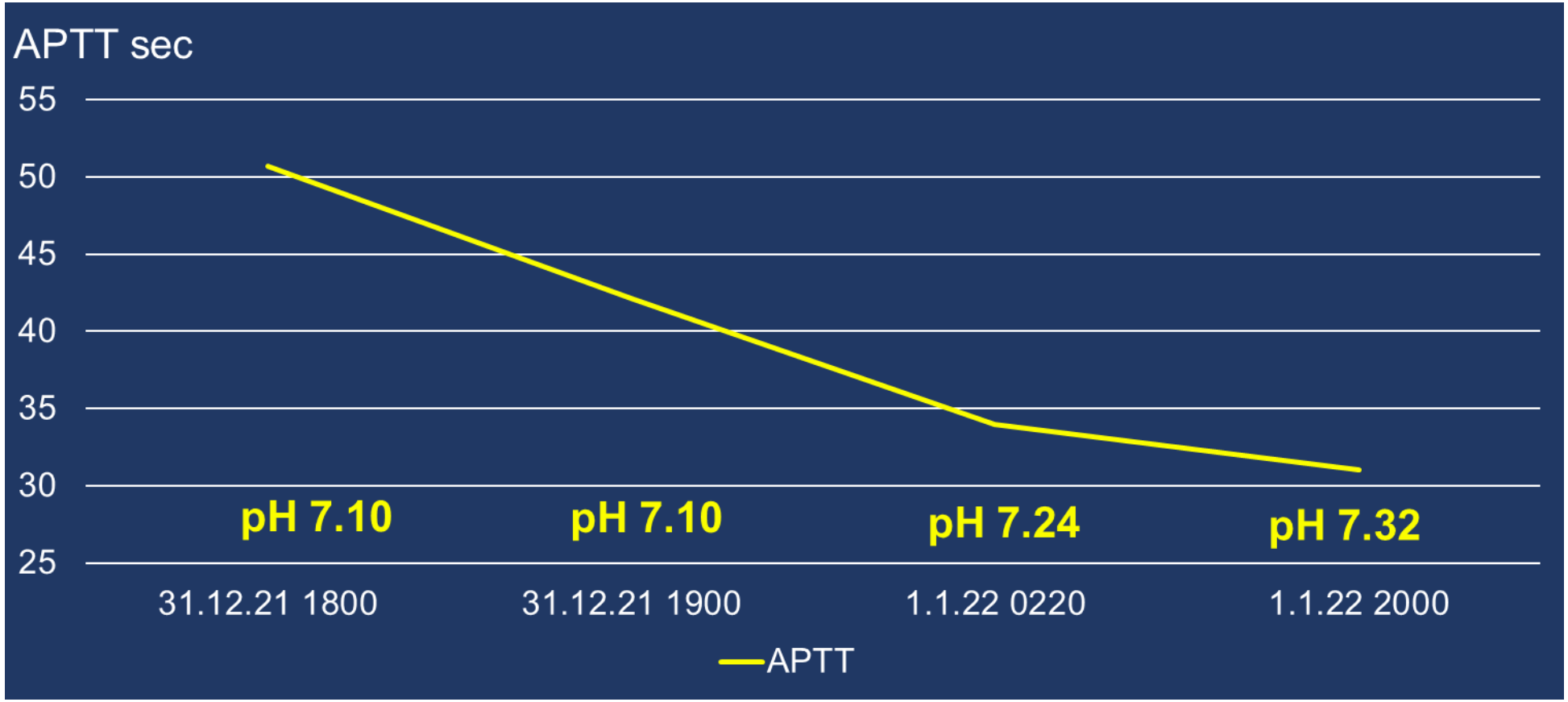
Factor assays and LAC

- FVIII 354 IU/dl (NR 62-199 IU/dl)
- FIX 215 IU/dl (NR 69-157)
- FXI 150 IU/dl (NR 67-169 IU/dl)
- FXII 120 IU/dl (NR 20-161 IU/dl)
- DRVVT – normal
- Previously normal APTT 2018 and 2019

APTT over time in separated plasma



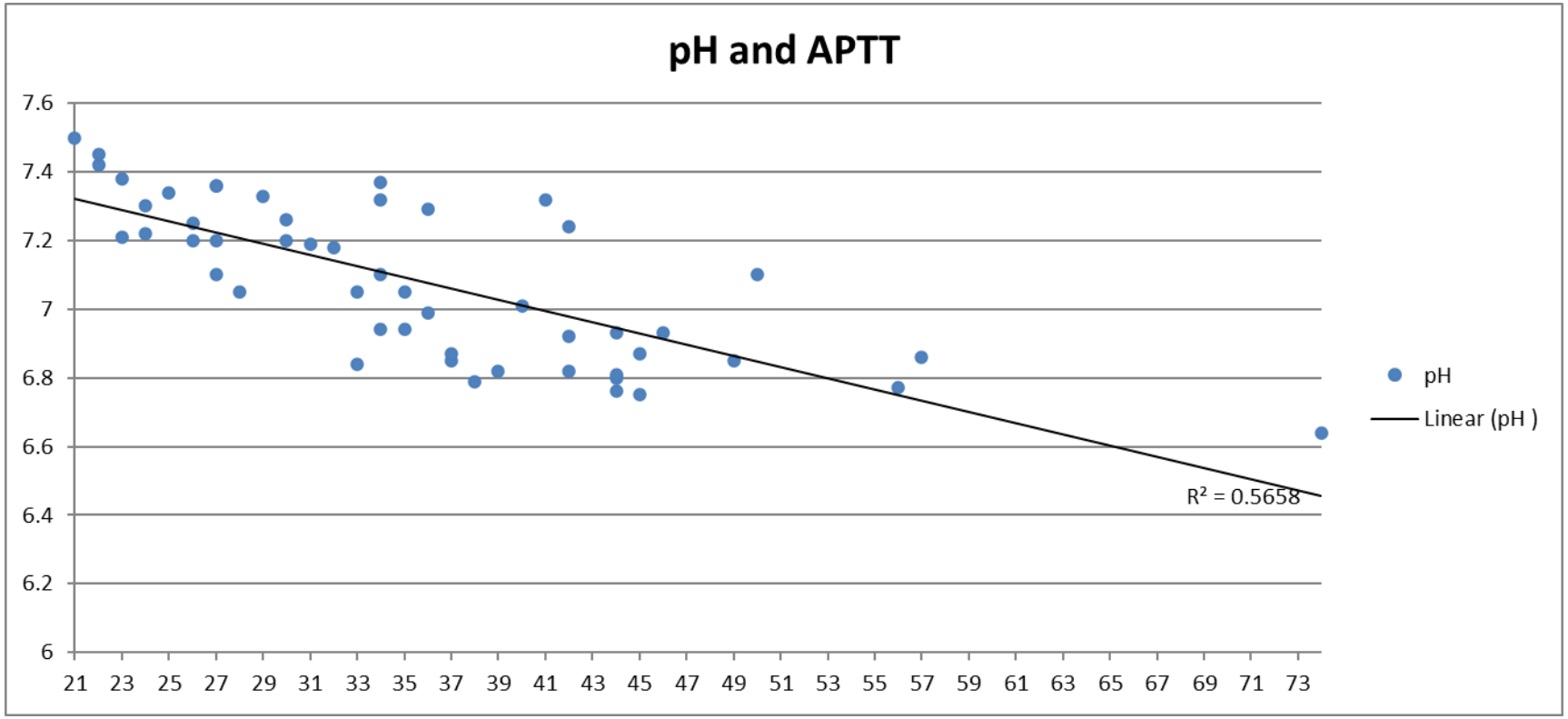
APTT and in vivo pH
(APTT NR 27.3 -27.5 sec)



Prolonged APTT with Actin FS in acidosis despite normal FVIII/IX/XI/XII

(7.35-7.45)	APTT (AFS) 20.3-27.5	APTT Synthasil 26-36.6 sec	pH (arterial) NR 7.35-7.45	clinical	Alternate APTT with AFS
9.8	43.5	27.2	6.98	DKA	19.3 (earlier)
9.8	44.5	32.8	6.80	DKA	26.9 (+12 hr)pH normal)
10.3	40.0	28.6		sepsis	23.8 (+15 hr) pH norm
11.4	39.5	32	6.88	Cardiac arrest	22.4 (earlier)

What else?


pH and APTT
7.6
7.4
7.2
7
6.8
6.6
6.4
6.2
6
21 23 25 27 29 31 33 35 37 39 41 43 45 47 49 51 53 55 57 59 61 63 65 67 69 71 73
R² = 0.5658
pH
Linear (pH)

Ph increases over 6 hrs in citrated plasma over cells or separated plasma but no impact on APTT with AFS or Synthasil