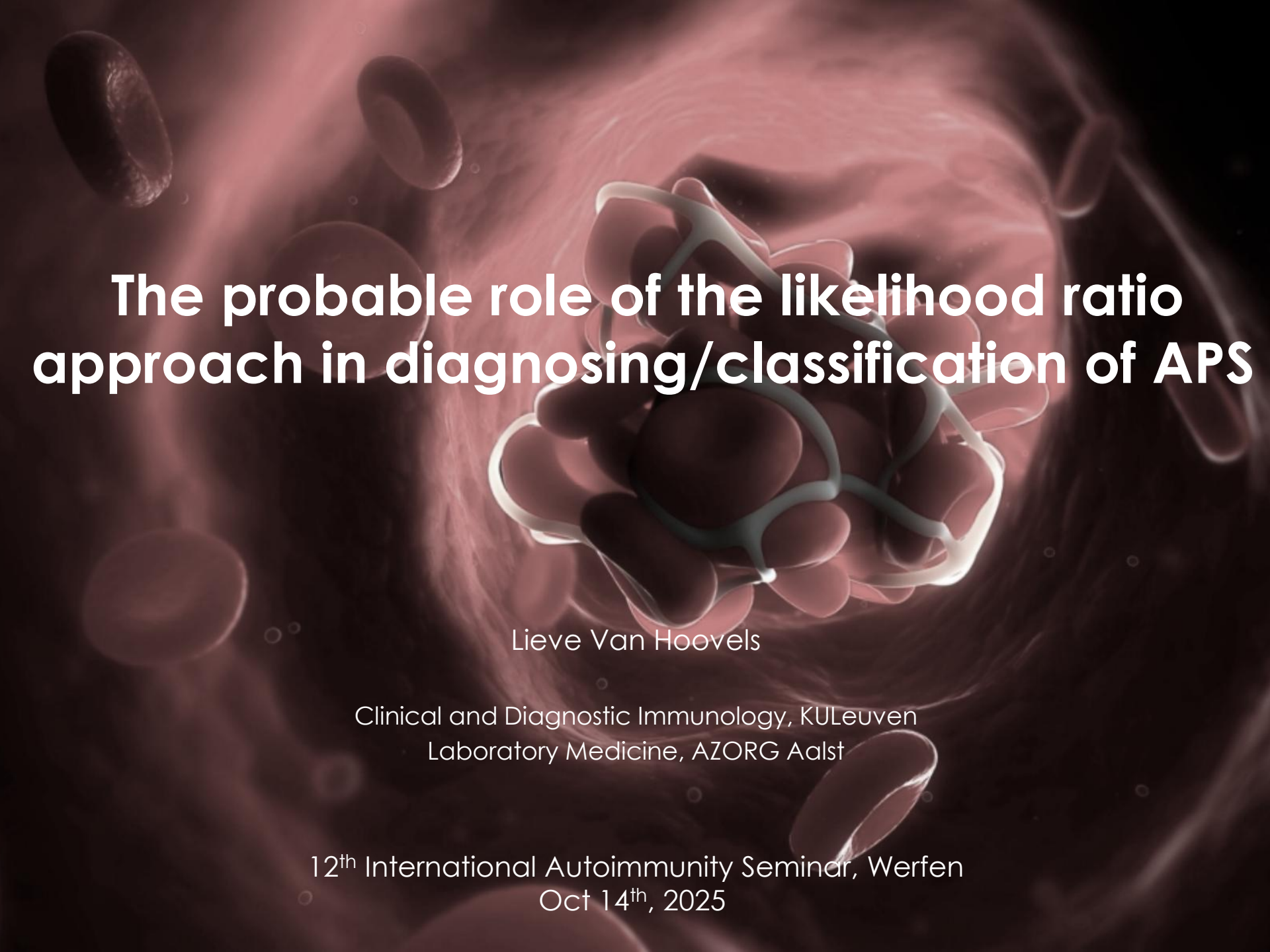


The background of the slide is a microscopic image showing several red blood cells (erythrocytes) in a reddish-pink hue. In the center-right, there is a prominent cluster of cells, possibly platelets or a small group of leukocytes, which are more densely packed and have a different texture than the surrounding red blood cells. The overall lighting is soft, with a slight vignette effect.

# The probable role of the likelihood ratio approach in diagnosing/classification of APS

Lieve Van Hoovels

Clinical and Diagnostic Immunology, KULeuven  
Laboratory Medicine, AZORG Aalst

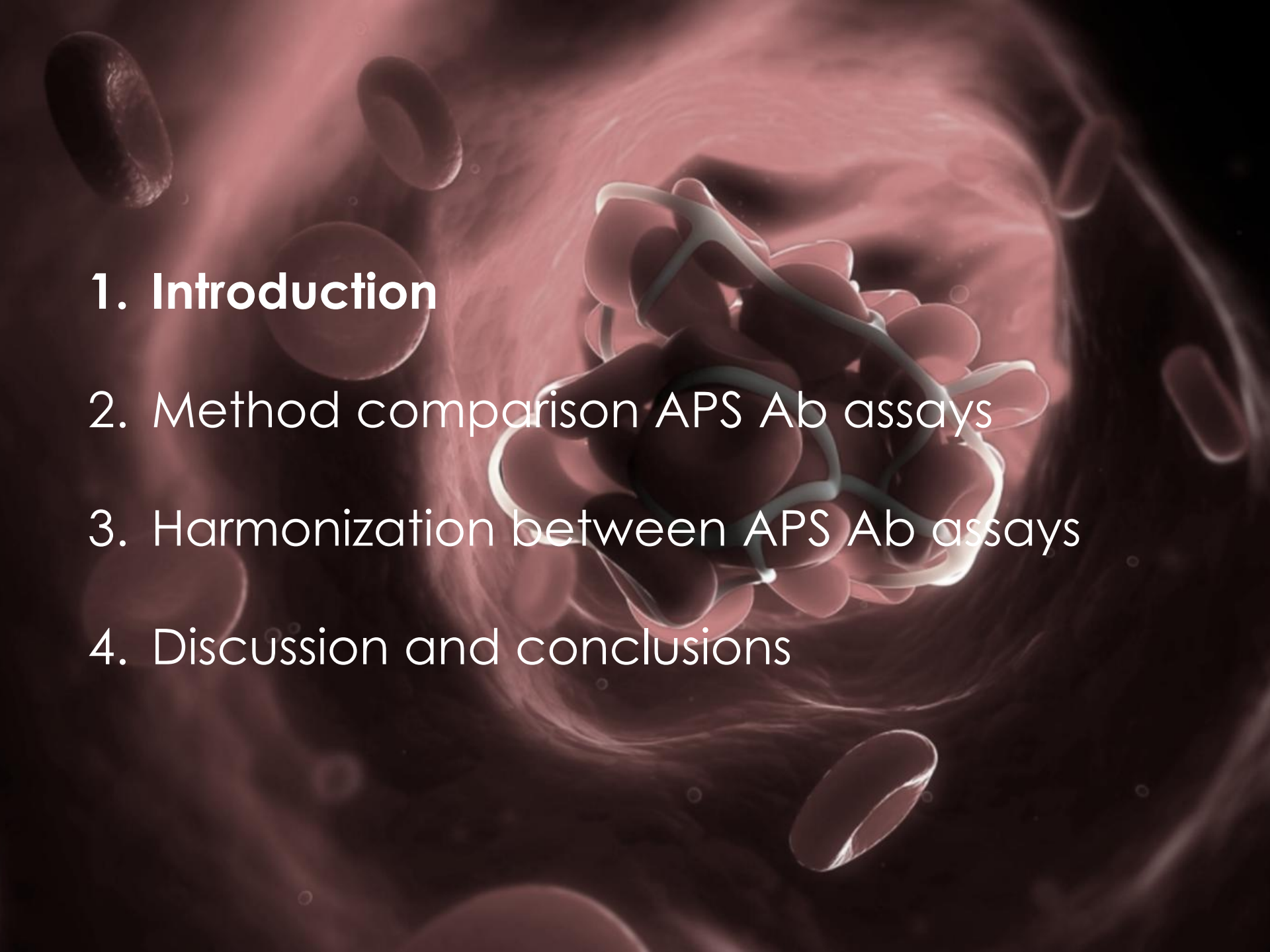
12<sup>th</sup> International Autoimmunity Seminar, Werfen  
Oct 14<sup>th</sup>, 2025

# Conflict of interest

---

Lecture fees: Thermo Fisher, Werfen

Consultant: Thermo Fisher, Werfen



# **1. Introduction**

2. Method comparison APS Ab assays

3. Harmonization between APS Ab assays

4. Discussion and conclusions

# 1.1 Antiphospholipid syndrome

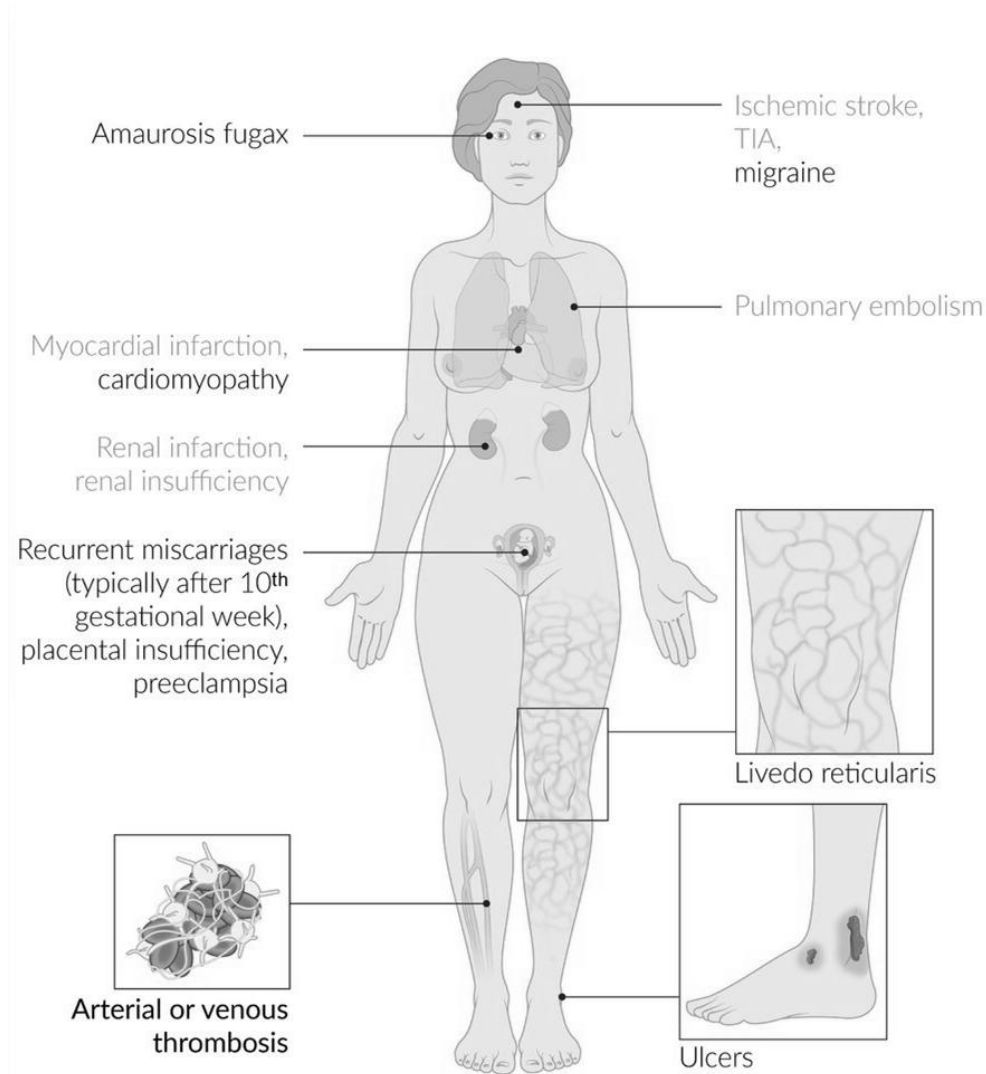
Systemic autoimmune disease defined by

## ✓ Clinical manifestations

- **Thrombotic** APS  
Catastrophic APS
- **Obstetric** APS
- Non-thrombotic manifestations
- 1<sup>ary</sup> versus 2<sup>ary</sup> APS (SLE)

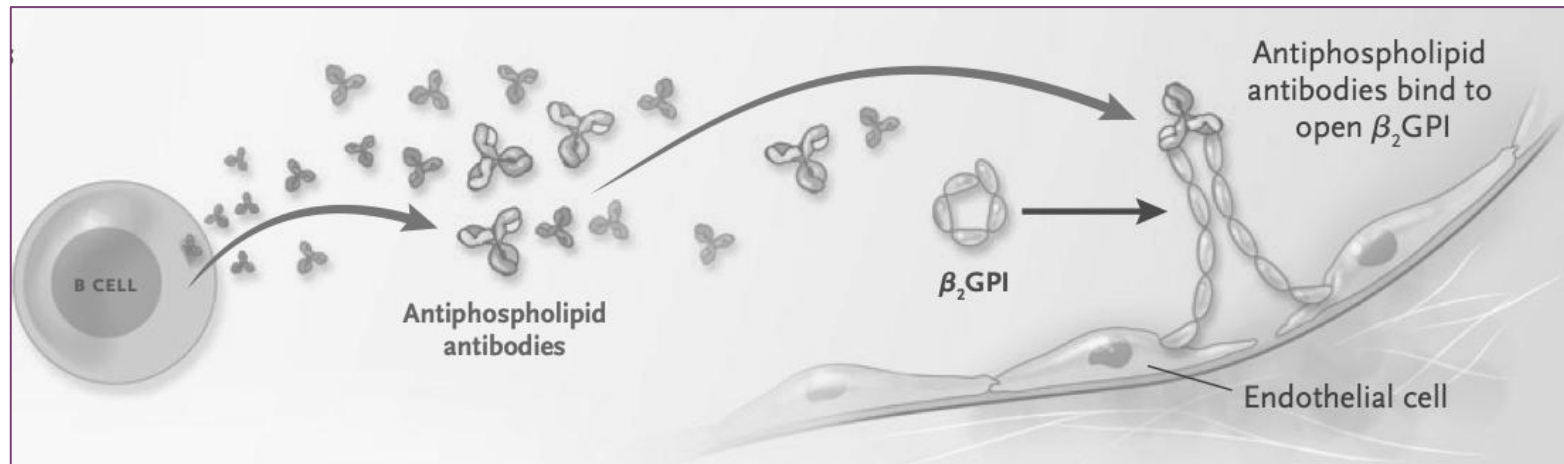
## ✓ Laboratory diagnosis

- Persistent aPL **antibodies**



# 1.1 Antiphospholipid syndrome

## Pathogenesis



Heterogeneous group of aPL Ab

**aCL IgG/M, a $\beta_2$ GPI IgG/M**

aCL IgA, a $\beta_2$ GPI IgA  
Anti-phosphatidyl/inositol  
Anti-phosphatidylserine  
Anti-phosphatidylethanolamine  
Anti-phosphatidic acid  
Anti-prothrombin  
Anti-phosphatidylserine-prothrombin  
Anti-vimentin/cardiophilin complex  
aPhL ELISA assay  
Annexin A5 resistance  
Anti-domain I of  $\beta_2$ GPI

Major target =  $\beta_2$ GPI

Closed, non-immunogenic  $\beta_2$ GPI



Open, immunogenic  $\beta_2$ GPI  
↑ avidity to phospholipid surfaces  
↑ ↑ avidity by binding of aPL Ab



+ inflammatory and endothelial cells  
+ coagulation  
interference with trophoblasts and decidual cells

# 1.2 Ab testing in APS

## Laboratory diagnosis of APS (ISTH-SCC LA/aPL)

### Persistent positivity of

Lupus anticoagulant (LA)

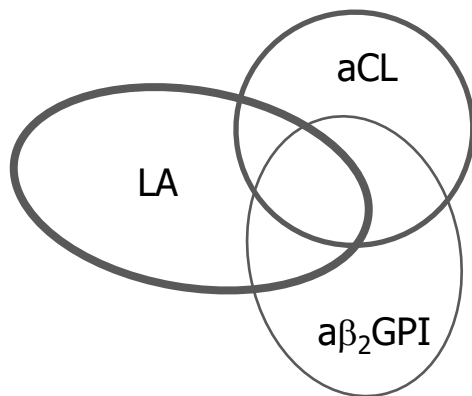
and/or

aCL IgG/IgM

and/or

a $\beta_2$ GPI IgG/IgM

### Pathogenicity of aPL

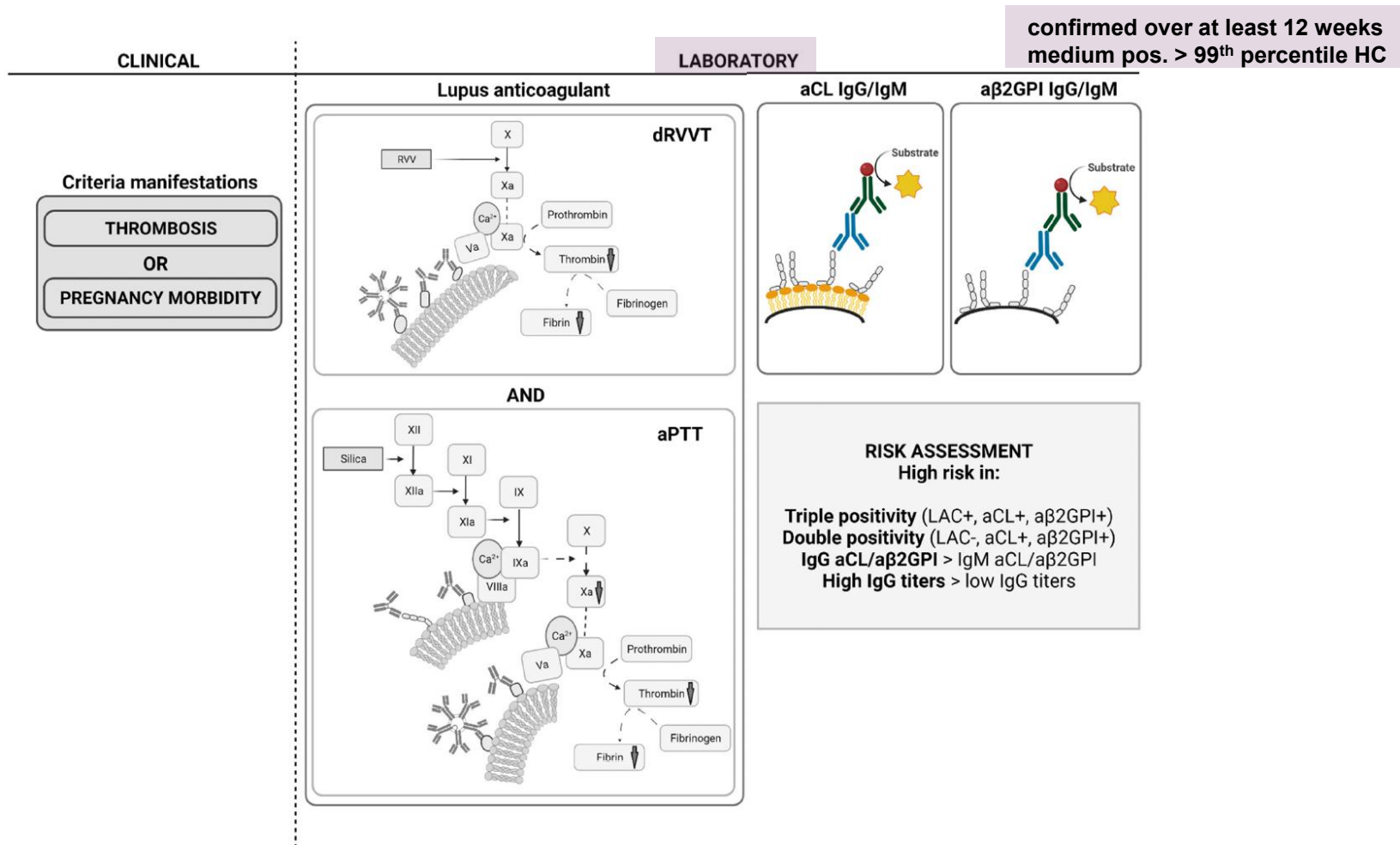


LA is a strong risk factor

|            | LA         | aCL        | a $\beta_2$ GPI | Diagnostic value |
|------------|------------|------------|-----------------|------------------|
| Single pos | Neg        | <b>Pos</b> | Neg             | +                |
| Single pos | Neg        | Neg        | <b>Pos</b>      | +                |
| Single pos | <b>Pos</b> | Neg        | Neg             | ++               |
| Double pos | Neg        | <b>Pos</b> | <b>Pos</b>      | +++              |
| Triple pos | <b>Pos</b> | <b>Pos</b> | <b>Pos</b>      | ++++             |

# 1.2 Ab testing in APS

## 2006 ACR/EULAR APS Classification Criteria



# 1.2 Ab testing in APS

## 2023 ACR/EULAR APS Classification Criteria

### Entry Criteria<sup>(a)</sup>

At least one documented<sup>(b)</sup> clinical criterion listed below (domains 1-6)

*plus*

A positive antiphospholipid antibody (aPL) test

(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti- $\beta_2$ -glycoprotein-I antibodies [IgG or IgM])  
within three years<sup>(b)</sup> of the clinical criterion

| Laboratory (aPL) domains and criteria <sup>(e)</sup>                                       | Weight                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>D7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LAC])</b> | <b>D8. aPL test by solid phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-<math>\beta_2</math>-glycoprotein-I antibody [a<math>\beta_2</math>GPI] ELISA [persistent])</b> |
| Positive LAC (single – one time)                                                           | 1                                                                                                                                                                                       |
| Positive LAC (persistent)                                                                  | 5                                                                                                                                                                                       |
|                                                                                            | Moderate or high positive (IgM) (aCL and/or a $\beta_2$ GPI) 1                                                                                                                          |
|                                                                                            | Moderate positive (IgG) (aCL and/or a $\beta_2$ GPI) 4                                                                                                                                  |
|                                                                                            | High positive (IgG) (aCL <u>or</u> a $\beta_2$ GPI) 5                                                                                                                                   |
|                                                                                            | High positive (IgG) (aCL <u>and</u> a $\beta_2$ GPI) 7                                                                                                                                  |



### TOTAL SCORE

Classify as Antiphospholipid Syndrome for research purposes if there are  
at least 3 points from clinical domains AND at least 3 points from laboratory domains

**99% specificity relative to 86% obtained with the revised Sapporo criteria**

# 1.2 Ab testing in APS

## 2023 ACR/EULAR APS Classification Criteria

### Domain 8 — aPL test by solid phase–based assay

Anticardiolipin antibody (aCL) and anti- $\beta_2$ -glycoprotein I antibody (anti- $\beta_2$ GPI) thresholds of moderate (40–79 units) and high ( $\geq 80$  units) should be determined based on standardised ELISA results, not based on other testing modalities such as new automated platforms with variations of the solid phase (eg, magnetic microparticles and microspheres) and various detection systems (eg, chemiluminescent immunoassay (CLIA), multiplex flow immunoassay (MFI), or flow cytometry).

Correlation of the numerical values between the moderate/high thresholds of ELISA and automated platforms varies substantially. For instance, based on the ISTH Scientific and Standardisation Committee (SSC) LA/aPL Subcommittee estimates from one study, an IgG aCL ELISA value of 40–79 units corresponds to a CLIA value of 200–400 units and MFI of 700–2000.<sup>33</sup> While these data may provide future guidance, there is currently no direct application and therefore, more validation studies are needed.

Recommendations to maintain homogeneity, consistency, and comparability of clinical research studies include the following: (a) results of analytical platforms should not be mixed; (b) pending additional studies and official guidance from the ISTH SSC LAC/aPL Subcommittee for semiquantitative comparisons on aCL/anti- $\beta_2$ GPI moderate/high thresholds of ELISA and automated platforms, we recommend delaying use of the automated platforms for APS classification; and (c) if no options exist beside the use of automated platform results for APS research, researchers should direct efforts to identifying and validating moderate/high thresholds of their platform, correlating it with aCL/anti- $\beta_2$ GPI ELISA moderate/high thresholds (these measures should be discussed in their methods, and supported by official guidance).

# 1.3 Diagnosis versus classification

605

## Classification Criteria for the Antiphospholipid Syndrome: Not the Same as Diagnostic Criteria for Antiphospholipid Syndrome

Emmanuel J. Favaloro, PhD, FFSc (RCPA)<sup>1,2,3</sup> Leonardo Pasalic, FRCPA, FRACP, PhD<sup>1,4</sup>  
Giuseppe Lippi, MD<sup>5</sup>

<sup>1</sup> Department of Haematology, Institute of Clinical Pathology and Medical Research (ICPMR), Sydney Centres for Thrombosis and Haemostasis, Westmead Hospital, Westmead, New South Wales, Australia

<sup>2</sup> School of Dentistry and Medical Sciences, Faculty of Science and Health, Charles Sturt University, Wagga Wagga, New South Wales, Australia

<sup>3</sup> School of Medical Sciences, Faculty of Medicine and Health, University of Sydney, Westmead Hospital, Westmead, New South Wales, Australia

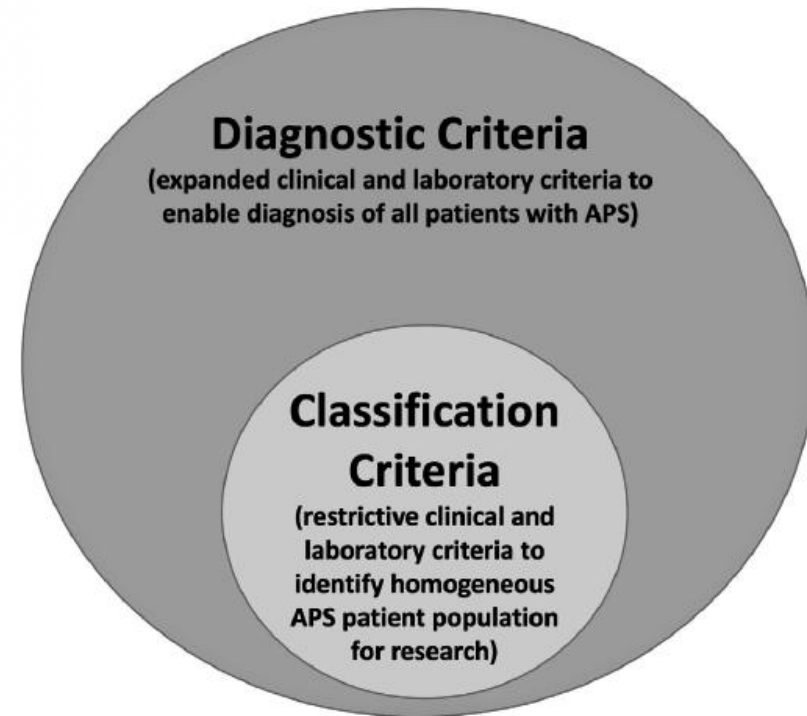
Address for correspondence Emmanuel J. Favaloro, PhD, FFSc (RCPA), Department of Haematology, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, New South Wales 2145, Australia  
(e-mail: emmanuel.favaloro@health.nsw.gov.au).

<sup>4</sup> Westmead Clinical School, University of Sydney, Westmead, New South Wales, Australia

<sup>5</sup> Section of Clinical Biochemistry, University of Verona, Verona, Italy

Semin Thromb Hemost 2024;50:605–608.

**In conclusion**, classification criteria can be used to diagnose APS, but clinicians should not restrict the diagnosis of APS to only the classification criteria



# 1.3 Diagnosis versus classification

## Summary of differences

| Classification criteria <sup>1-3</sup>                                                                                                                                                                                                                                                                                                                        | Diagnostic criteria                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical criteria restricted to certain clinical manifestations, with weightings applied in newest Classification criteria                                                                                                                                                                                                                                    | Broader set of clinical manifestations can be applied to diagnosis of APS                                                                                                                                                                                                                                                                                 |
| Laboratory criteria restricted to LA, aCL (IgG and IgM) and a $\beta$ 2GPI (IgG and IgM). LA positivity as per ISTH SSC guidance, <sup>11</sup> and persistence not mandated, but scoring higher. Solid phase aPL (aCL and a $\beta$ 2GPI) as measured by ELISA, with grading as moderate or high levels defined, respectively, as 40–79 and $\geq 80$ units. | Laboratory criteria can be broader, potentially using other subtypes for solid phase aPL (aCL, a $\beta$ 2GPI) such as IgA, and also more solid phase assays (e.g., aPS/PT and aDI). Additional methodologies to ELISA are available and indeed now dominating the test landscape. Potential use of 99 <sup>th</sup> percentiles to define cutoff values. |

\*aCL IgA, a $\beta$ 2GPI IgA  
Anti-phosphatidyl/inositol  
Anti-phosphatidylserine  
Anti-phosphatidylethanolamine  
Anti-phosphatidic acid  
Anti-prothrombin  
Anti-phosphatidylserine-prothrombin  
Anti-vimentin/cardiolipin complex  
aPhL ELISA assay  
Annexin A5 resistance  
Anti-domain I of  $\beta$ 2GPI

### Extra-criteria antibody specificities\*:

Restricted to specific case reports  
Only LA/aCL IgG/M, a $\beta$ 2GPI IgG/M

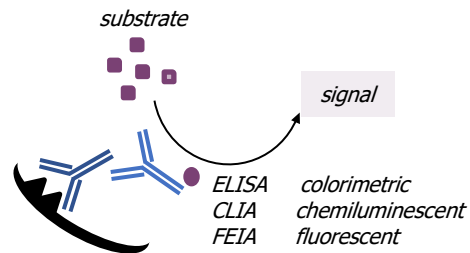
### Extra-criteria antibody methods\*:

Additional methodologies allowed

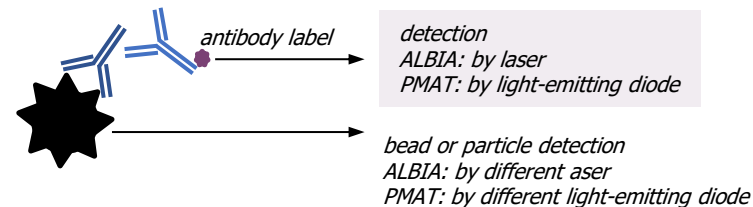
# 1.4 In-between assay variability

## Analytical confounders: assay technique

### Solid phase assays



### Multiplex assays



Modified from Bossuyt *et al.* Nat Rev Rheumatol 2020; 16: 715-26

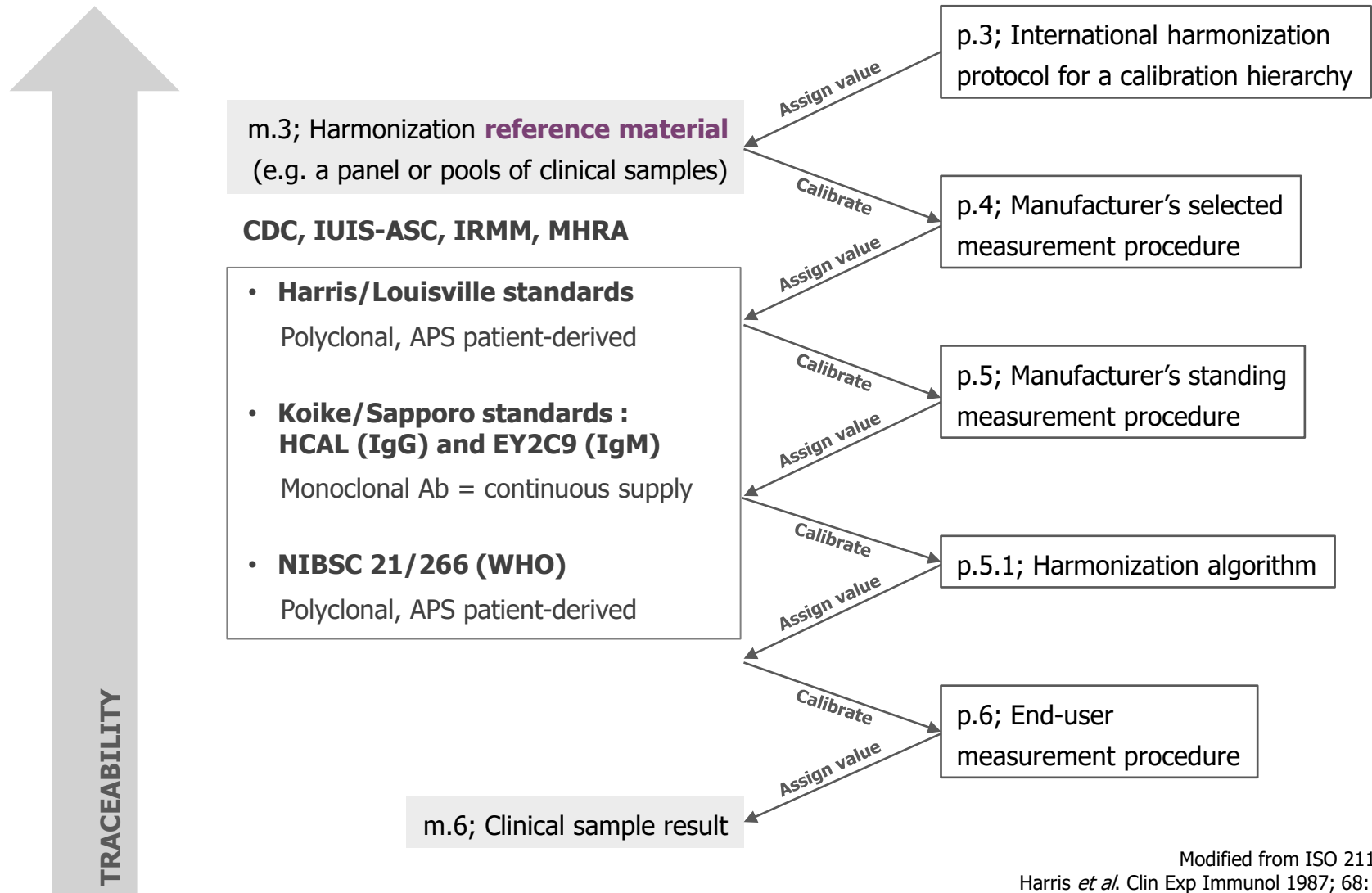
### Newer techniques:

- Apply consistent protocols: easier to use, less interoperator variation
- Faster TAT, random access,...

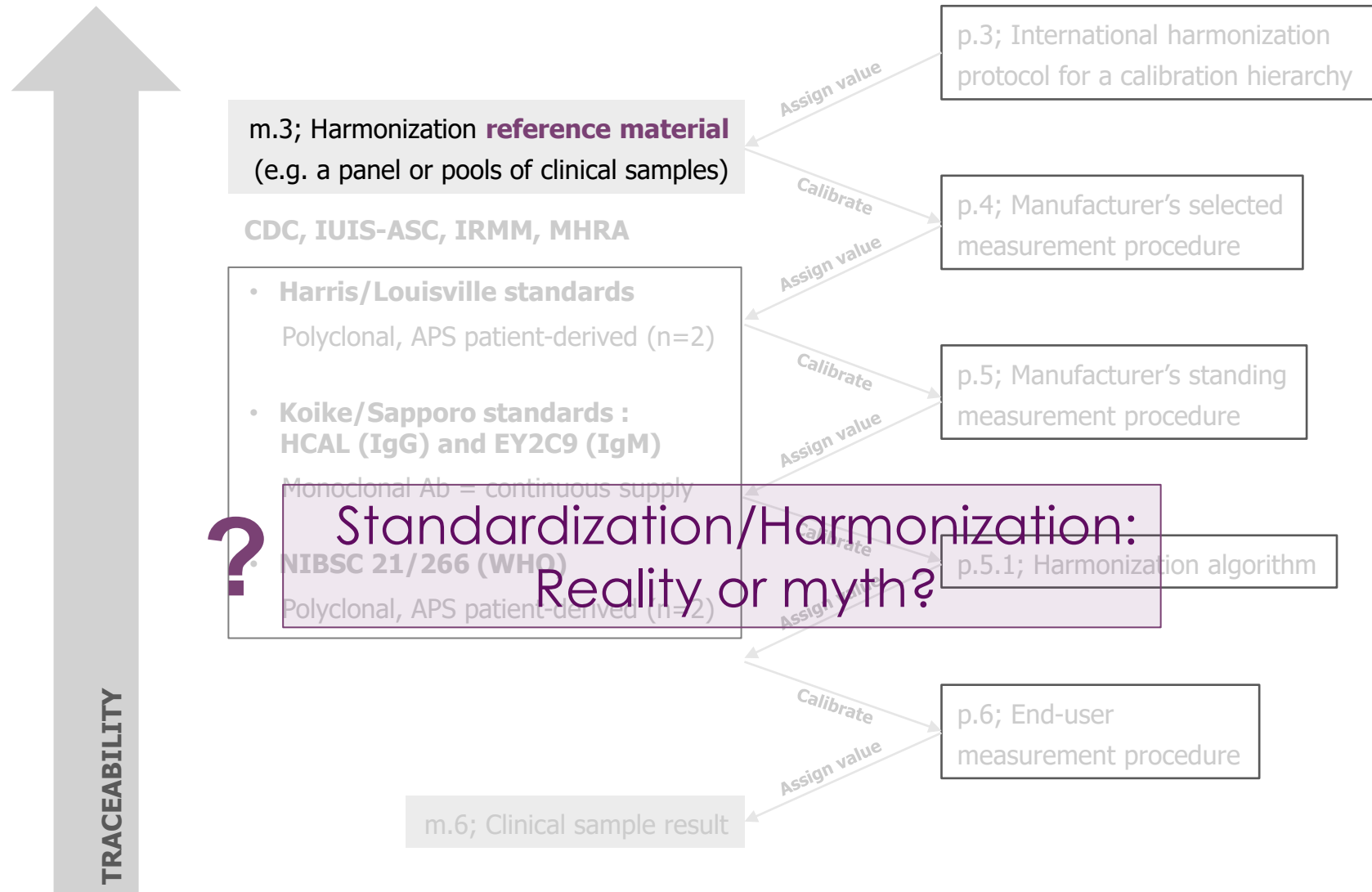
### aCL and a $\beta_2$ GPI assays can't be used interchangeably:

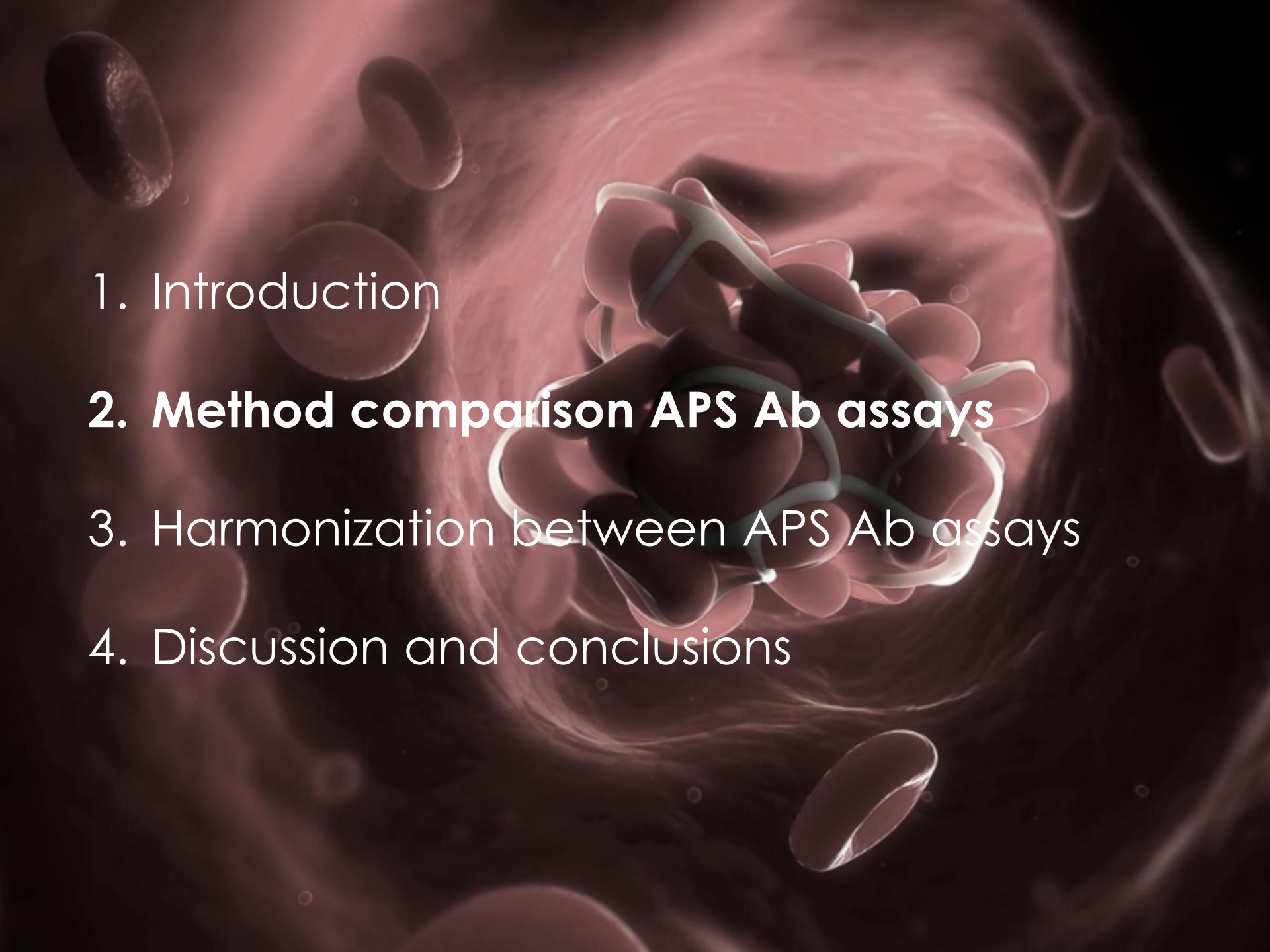
- Variation in Ag and Ab nature and source, calibrator traceability
- Variation in absolute values by assays

# 1.5 Standardization of autoantibody tests



# 1.5 Standardization of autoantibody tests



A 3D illustration of a blood vessel with red blood cells. In the center, there is a complex protein structure, possibly an antibody, rendered in white and light blue. The background is a dark, reddish-brown color with a swirling, vortex-like pattern.

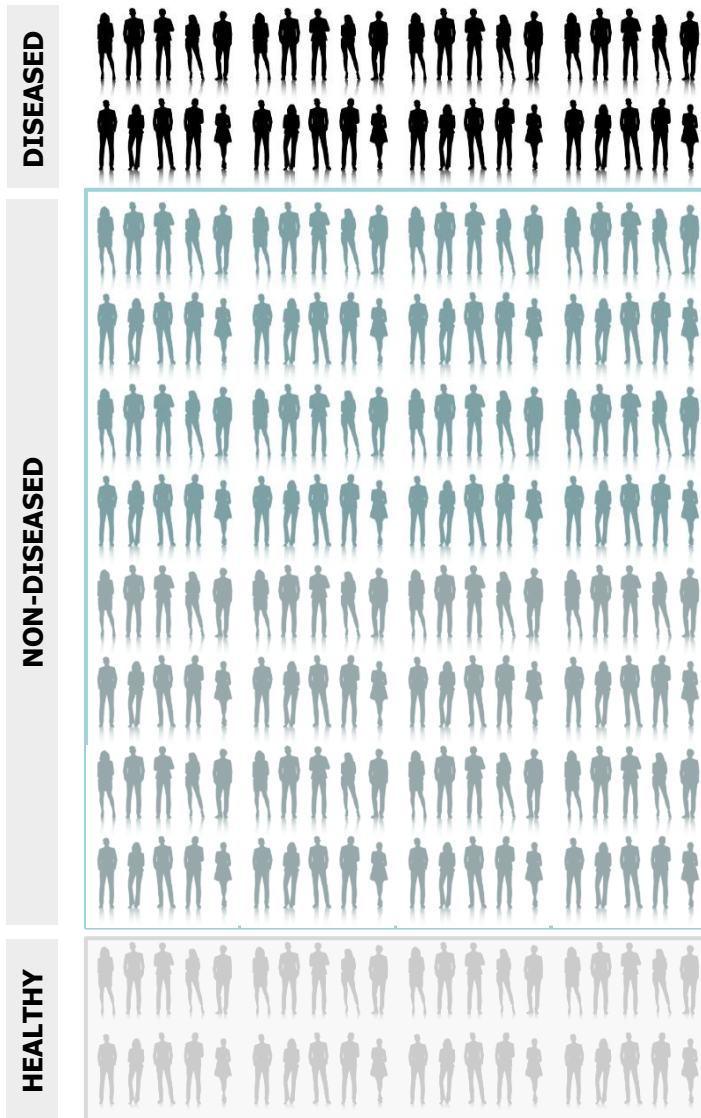
1. Introduction

**2. Method comparison APS Ab assays**

3. Harmonization between APS Ab assays

4. Discussion and conclusions

# 2.1 Study protocol: patient cohorts



## APS cohort (n=176)

Universita degli Studi di Brescia, Italy (Sylvia Piantoni/Angela Tincani); APS Ab home made ELISA; n=68

Center for Research of Immunopathology and Rare Diseases, San Giovanni Bosco Hospital, Turin, Italy (Savino Sciascia, ToTeam); APS Ab home made ELISA; n=108

F=73.9%; median age= 48 [19-81]

Clinical manifestations:

|                        |               |
|------------------------|---------------|
| Obstetric              | n= 30 (16.9%) |
| Thrombotic             | n=114 (64.8%) |
| Thrombotic + Obstetric | n= 32 (18.1%) |

## Non-APS cohort (n=433)

Consecutive (retrospective/prospective) disease related control cohort AZORG (Aalst) & ZAS (Antwerp) hospital Belgium

F=72.3%; median age= 51 [18-91] ( $p=0.013$ )

Clinical manifestations:

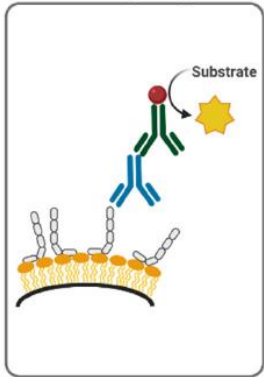
|                     |               |
|---------------------|---------------|
| Obstetric           | n= 75 (17.3%) |
| Thrombotic          | n=122 (28.2%) |
| Autoimmune          | n=233 (53.8%) |
| Autoimmune + Thromb | n= 3 (0.7%)   |

## (Presumably) Healthy controls (n=120)

F=66%; median age= 42 [21-65] ( $p=0.017$ )

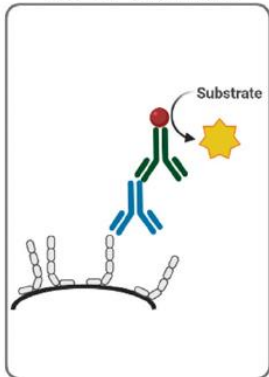
## 2.2 Study protocol: methods

aCL IgG/IgM



| Assay<br>(Manufacturer)                | Technique<br>(Instrument) | Antigen origin               | Antibody             | Units   | Traceability          |
|----------------------------------------|---------------------------|------------------------------|----------------------|---------|-----------------------|
| EliA™ ACA IgG/M<br>(Thermo Fisher)     | FEIA<br>(Phadia™ 250)     | ACA: bovine<br>β2GPI: bovine | Monoclonal;<br>Mouse | GPL/MPL | Harris                |
| QUANTA Flash® ACA<br>IgG/M (Werfen)    | CLIA<br>(BIO-FLASH®)      | ACA: bovine<br>β2GPI: human  | Monoclonal;<br>Mouse | CU      | HCAL/EY2C9            |
| Anti-Cardiolipin<br>IgG/IgM (Orgentec) | ELISA<br>(manual)         | ACA: bovine<br>β2GPI: human  | Polyclonal;<br>Goat  | GPL/MPL | Harris,<br>HCAL/EY2C9 |
| QUANTA Lite® ACA<br>IgG/M III (Werfen) | ELISA<br>(QUANTA-Lyser®2) | ACA: bovine<br>β2GPI: bovine | Monoclonal;<br>Goat  | GPL/MPL | HCAL/EY2C9            |

aβ2GPI IgG/IgM



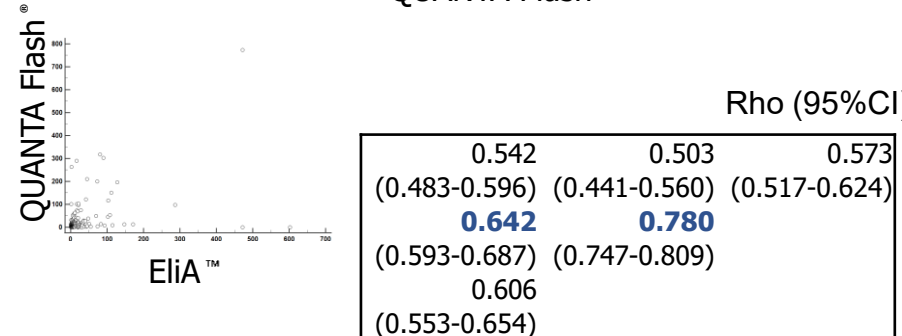
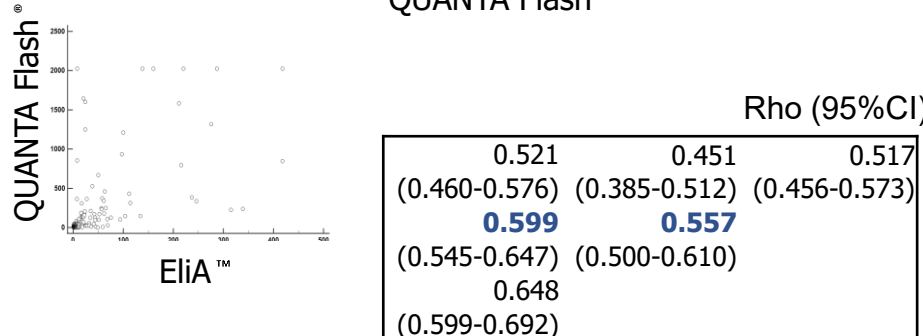
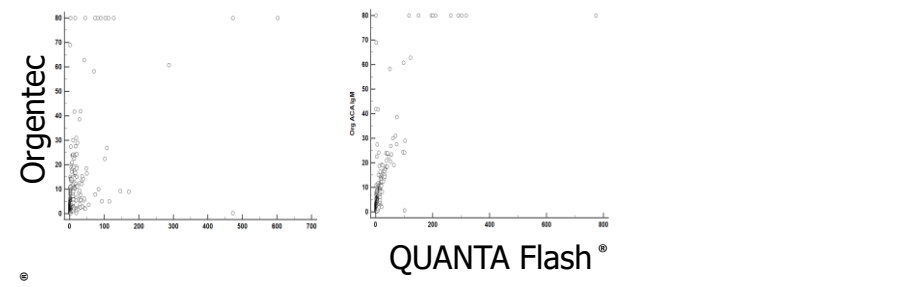
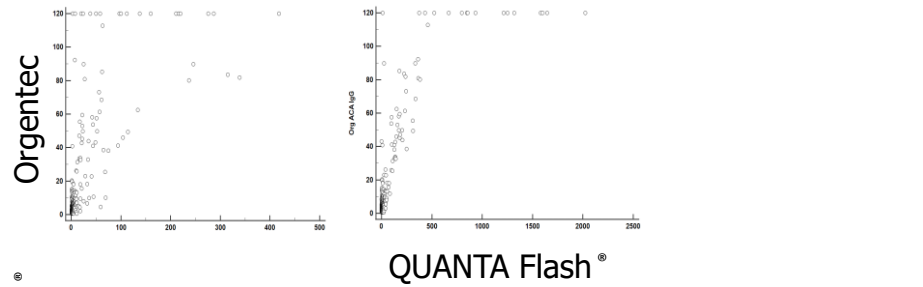
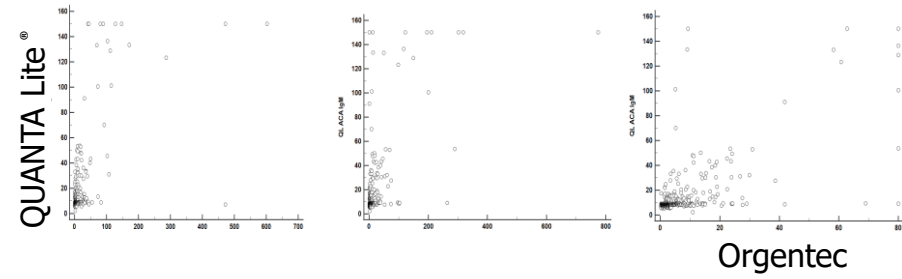
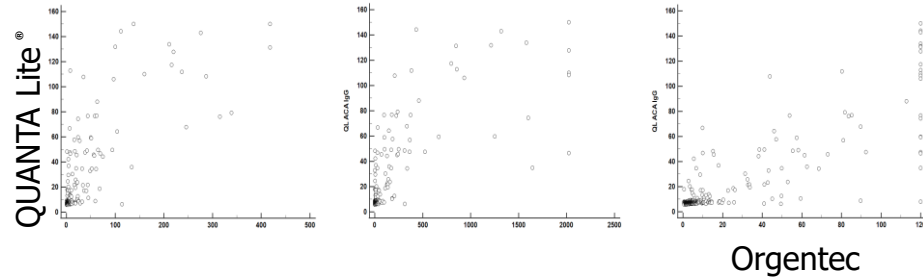
| Assay<br>(Manufacturer)                | Technique<br>(Instrument) | Antigen origin | Antibody             | Units   | Traceability          |
|----------------------------------------|---------------------------|----------------|----------------------|---------|-----------------------|
| EliA™ β2GPI IgG/M<br>(Thermo Fisher)   | FEIA<br>(Phadia™ 250)     | β2GPI: human   | Monoclonal;<br>Mouse | U/mL    | /                     |
| QUANTA Flash® β2<br>GPI IgG/M (Werfen) | CLIA<br>(BIO-FLASH®)      | β2GPI: human   | Monoclonal;<br>Mouse | CU      | HCAL/EY2C9            |
| β2GPI IgG/M<br>(Orgentec)              | ELISA<br>(manual)         | β2GPI: human   | Polyclonal;<br>Goat  | U/mL    | Harris,<br>HCAL/EY2C9 |
| QUANTA Lite® β2GPI<br>IgG/M (Werfen)   | ELISA<br>(QUANTA-Lyser®2) | β2GPI: bovine  | Monoclonal;<br>Goat  | SGU/SMU | /                     |

**Analytical validation/imprecision:** manufacturer iQC low/high; patient pool iQC low/high

## 2.3 Study results: spearman correlation

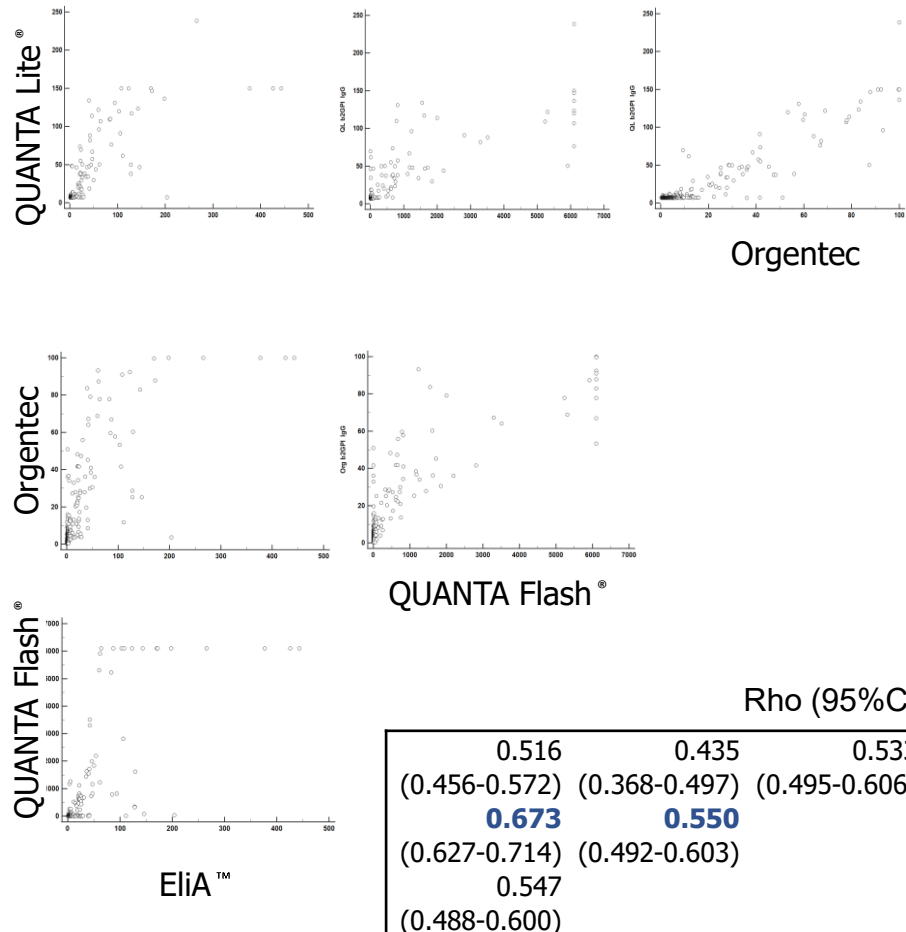
aCL IgG

aCL IgM

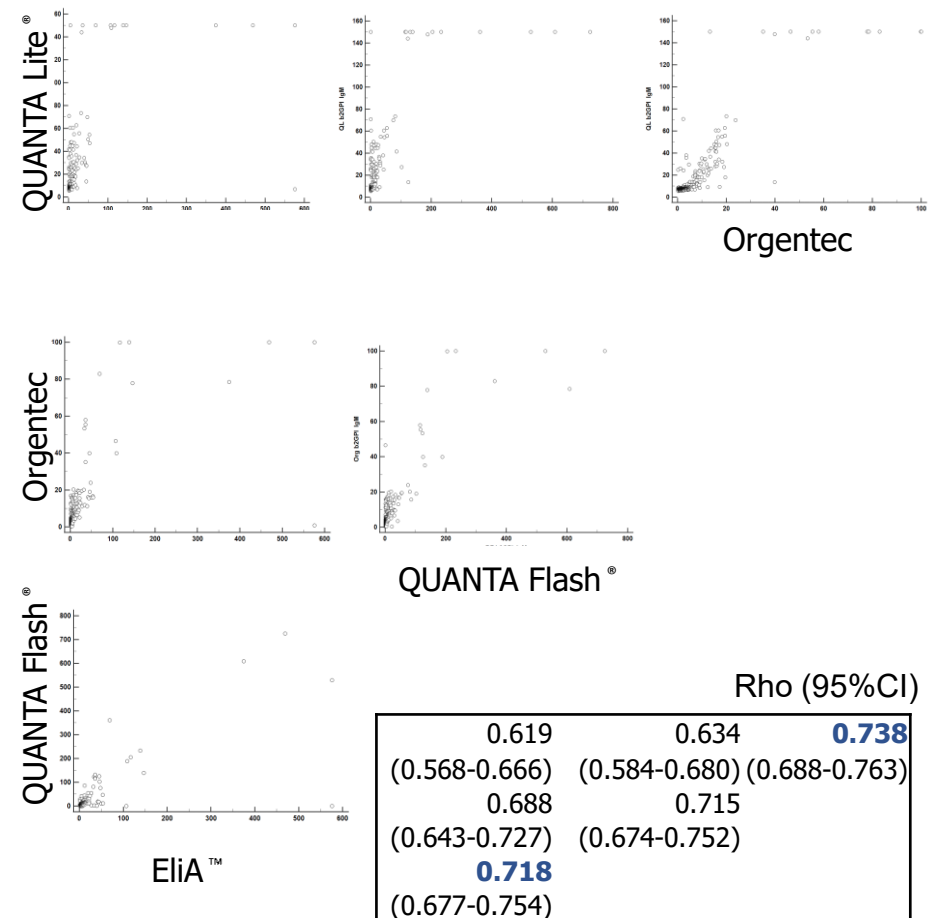


## 2.3 Study results: spearman correlation

a $\beta_2$ GPI IgG

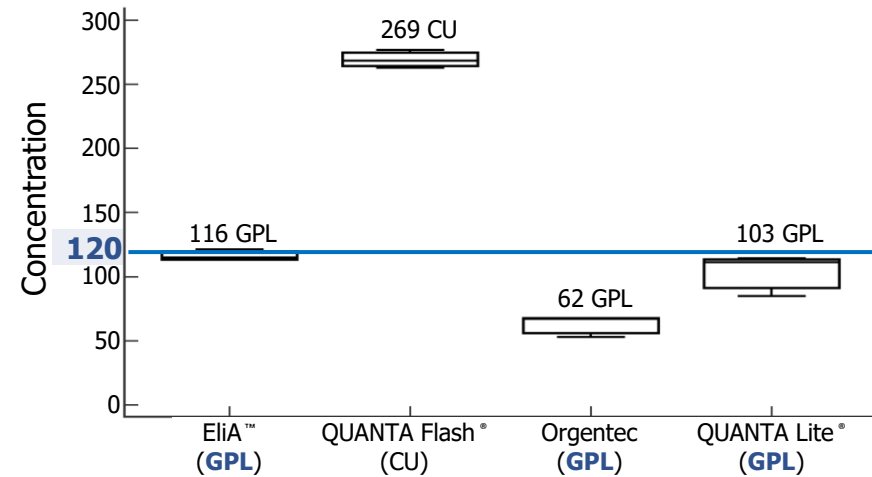


a $\beta_2$ GPI IgM

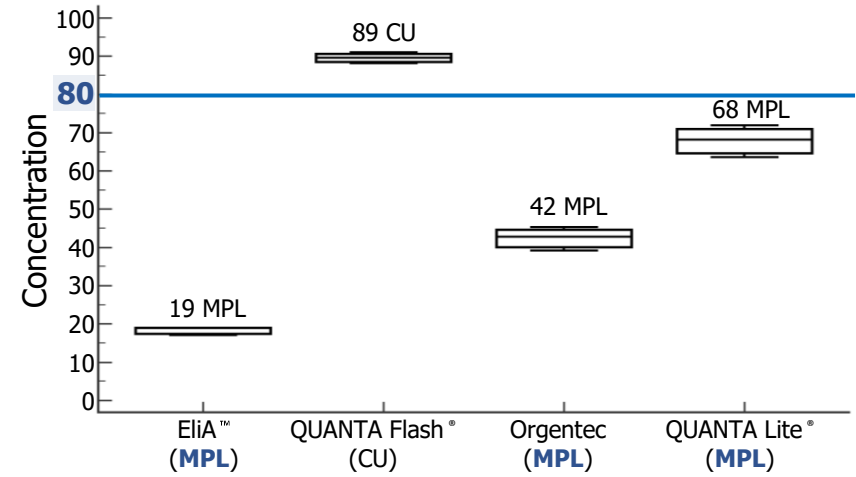


## 2.4 Study results: Harris/Louisville standards

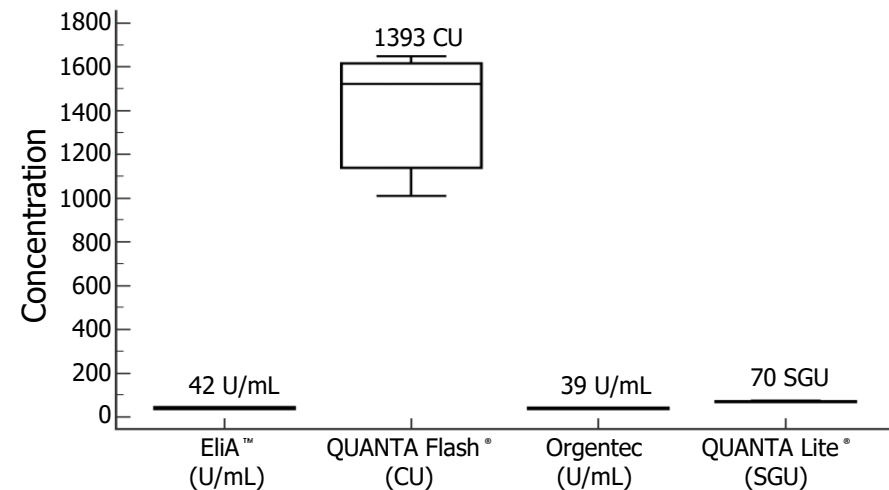
### aCL IgG



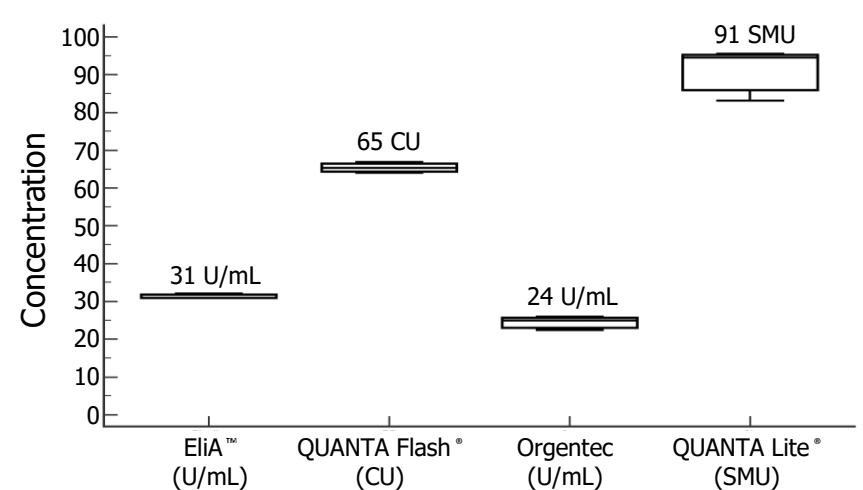
### aCL IgM



### aβ<sub>2</sub>GPI IgG



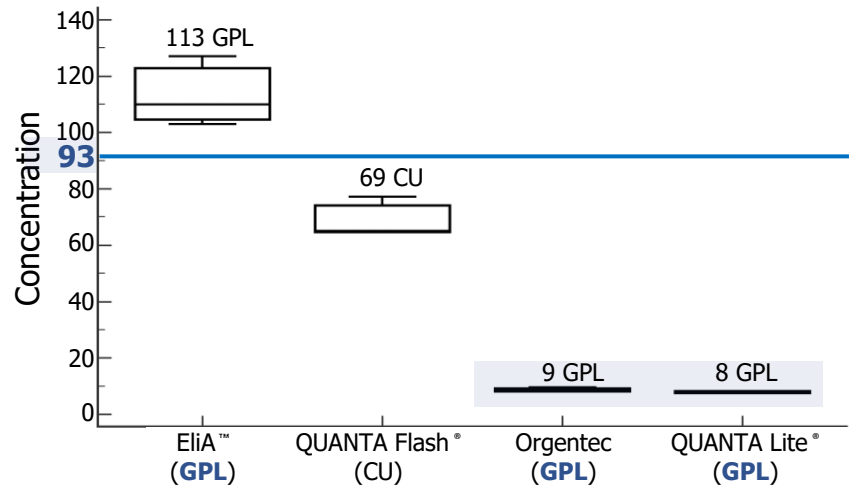
### aβ<sub>2</sub>GPI IgM



## 2.4 Study results: Sapporo standards

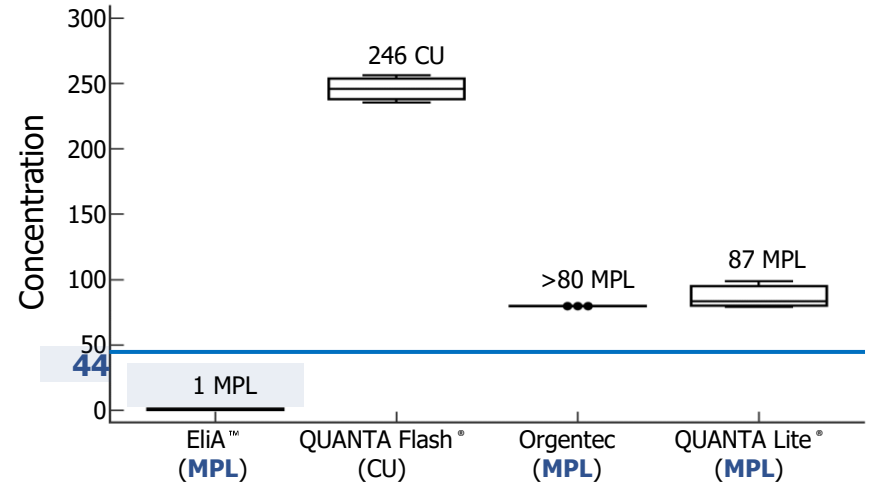
**HCAL**

**aCL IgG**

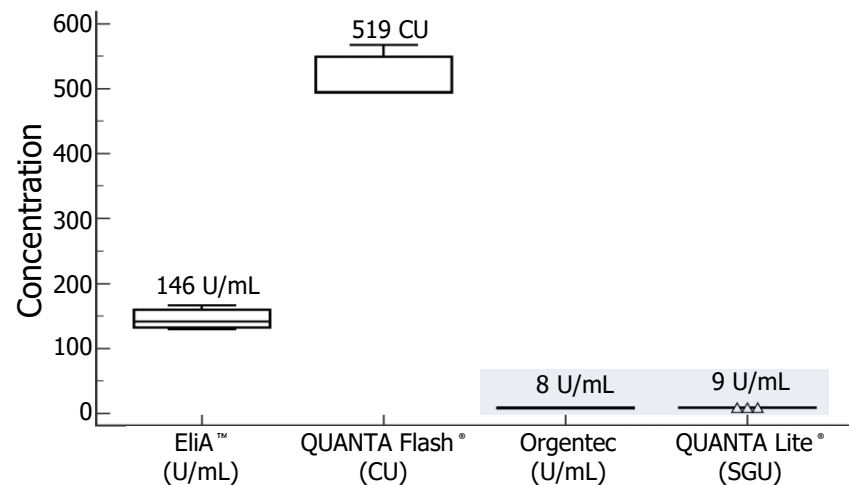


**EY2C9**

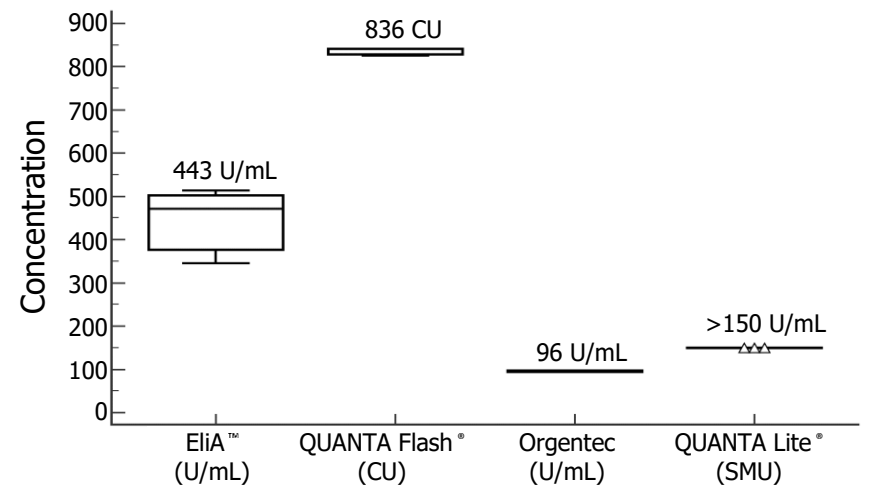
**aCL IgM**



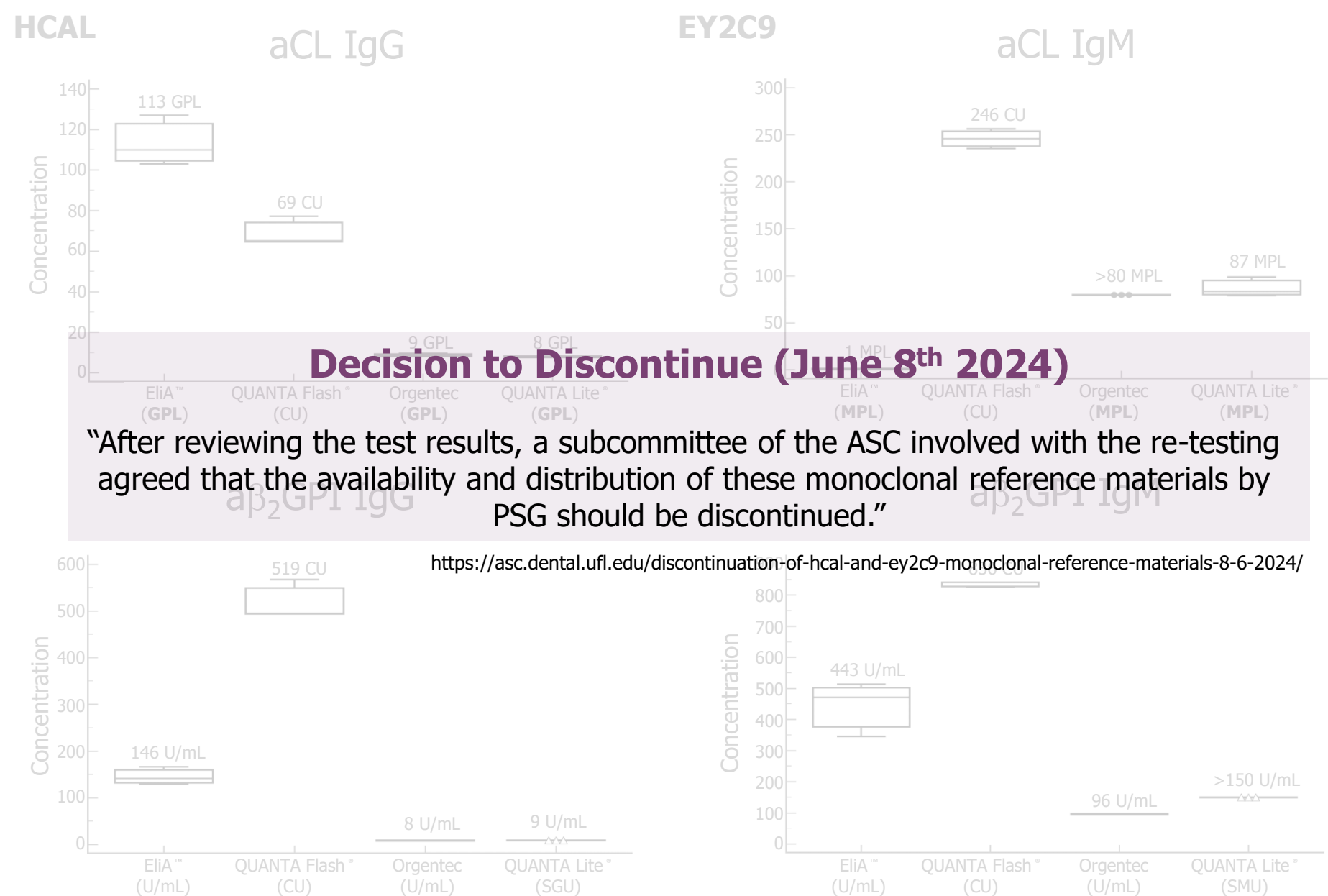
**aβ<sub>2</sub>GPI IgG**



**aβ<sub>2</sub>GPI IgM**



## 2.4 Study results: Sapporo standards



## 2.4 Study results: WHO $\alpha\beta_2$ GPI IgG

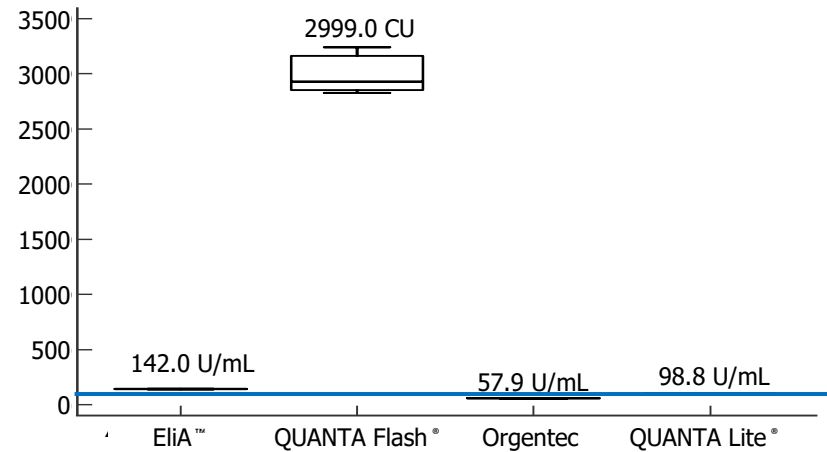
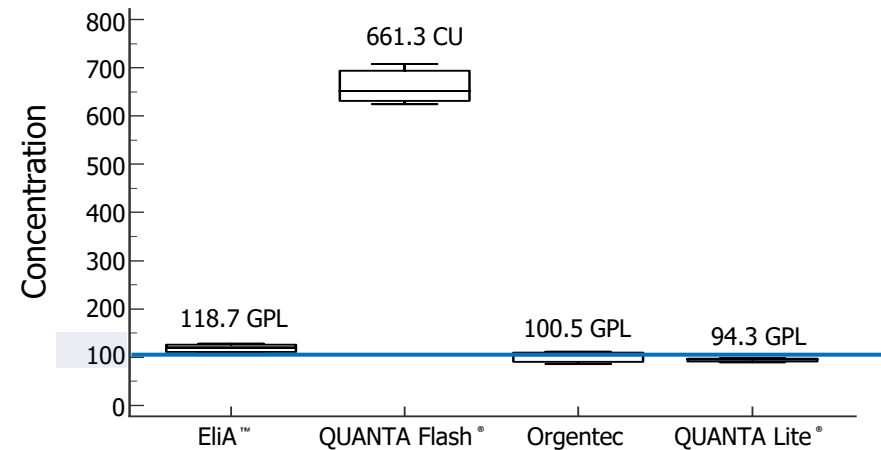
aCL IgG

a $\beta_2$ GPI IgG

- NIBSC 21/266**

|              | EliA™     | QUANTA Flash® | Orgentec  | QUANTA Lite® |  | EliA™      | QUANTA Flash® | Orgentec  | QUANTA Lite® |
|--------------|-----------|---------------|-----------|--------------|--|------------|---------------|-----------|--------------|
| <b>Mean:</b> | 234.7 GPL | 1263.3 CU     | > 120 GPL | 132.8 GPL    |  | 268.3 U/mL | >6100.0 CU    | 81.5 U/mL | > 150 U/mL   |

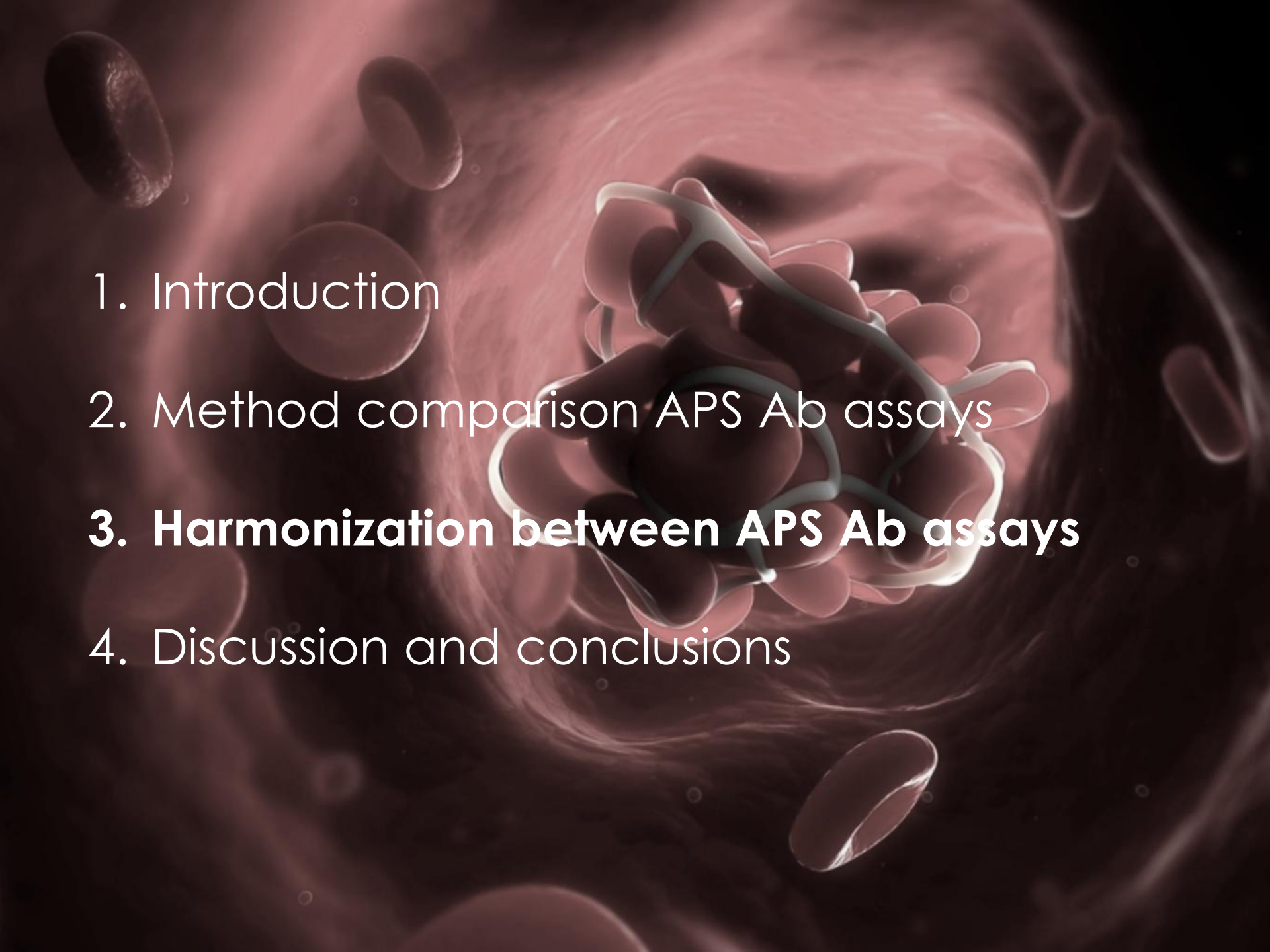
- 1/2 dilution NIBSC 21/266**



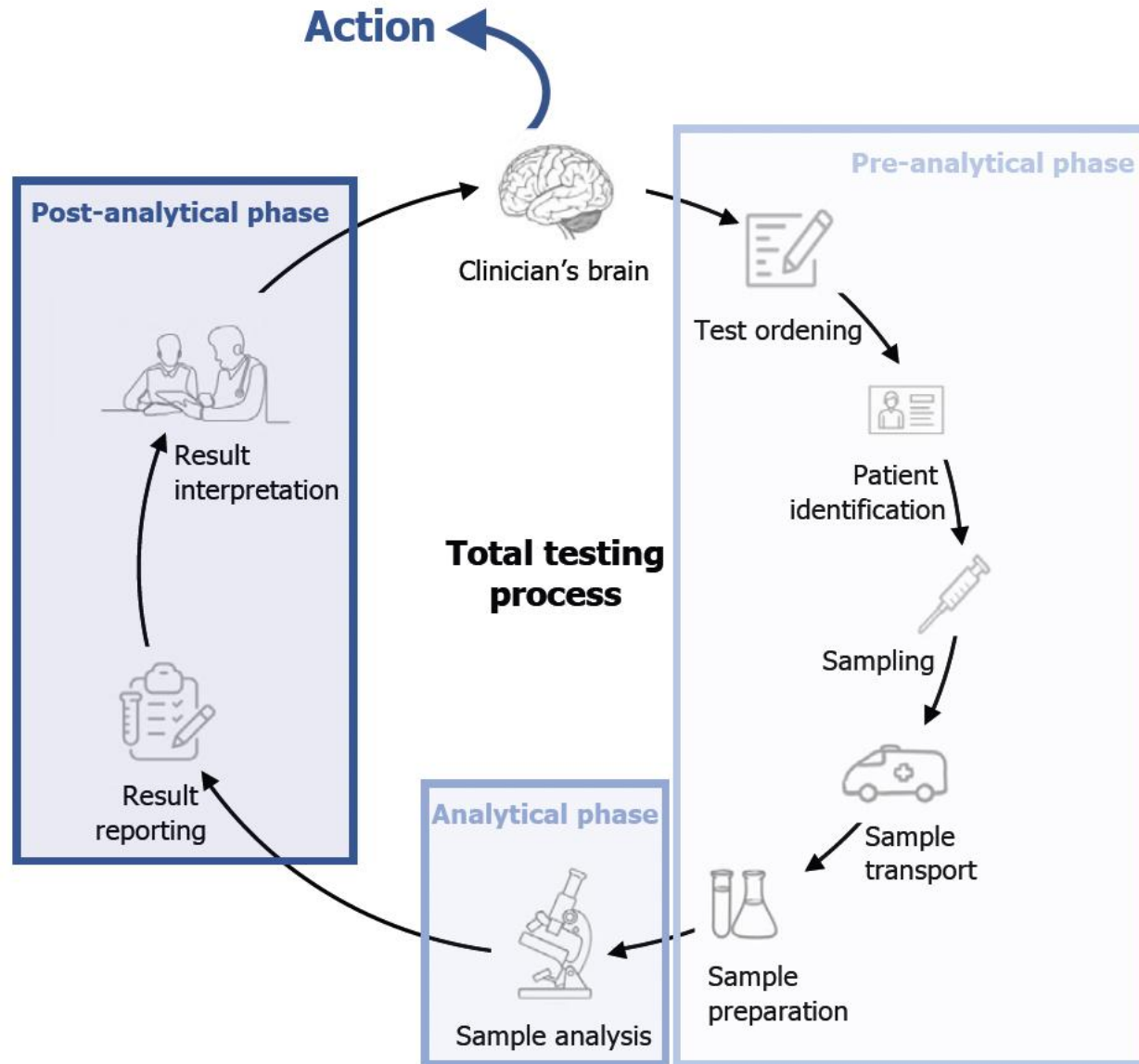
Standardization remains an unmet goal



**Harmonization**

- 
1. Introduction
  2. Method comparison APS Ab assays
  - 3. Harmonization between APS Ab assays**
  4. Discussion and conclusions

# 3.1 Harmonization in autoantibody testing



## 3.2 APS Ab-testing: pre-analytics

---

Gating strategy: 2023 ACR/EULAR APS classification criteria

**Entry Criteria<sup>(a)</sup>**

At least one documented<sup>(b)</sup> clinical criterion listed below (domains 1-6)

*plus*

A positive antiphospholipid antibody (aPL) test  
(a lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti- $\beta_2$ -glycoprotein-I antibodies [IgG or IgM])  
within three years<sup>(b)</sup> of the clinical criterion

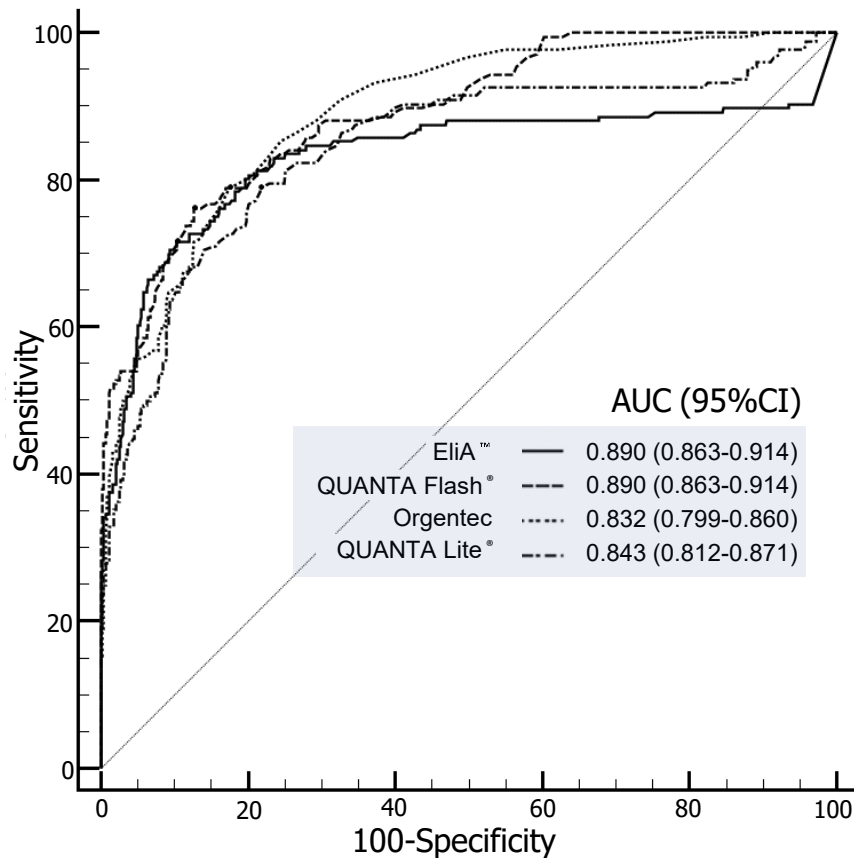


**If absent, do not attempt to classify as APS - If present, apply additive criteria**

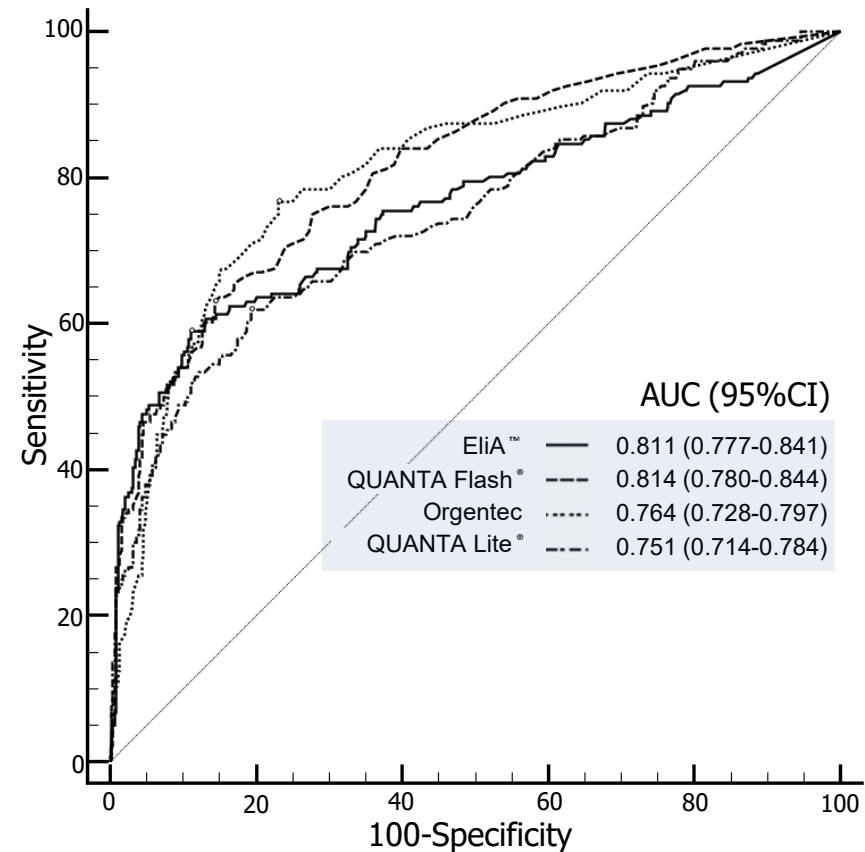
# 3.3 APS Ab-testing: analytics

## Diagnostic performance

aCL IgG



aCL IgM

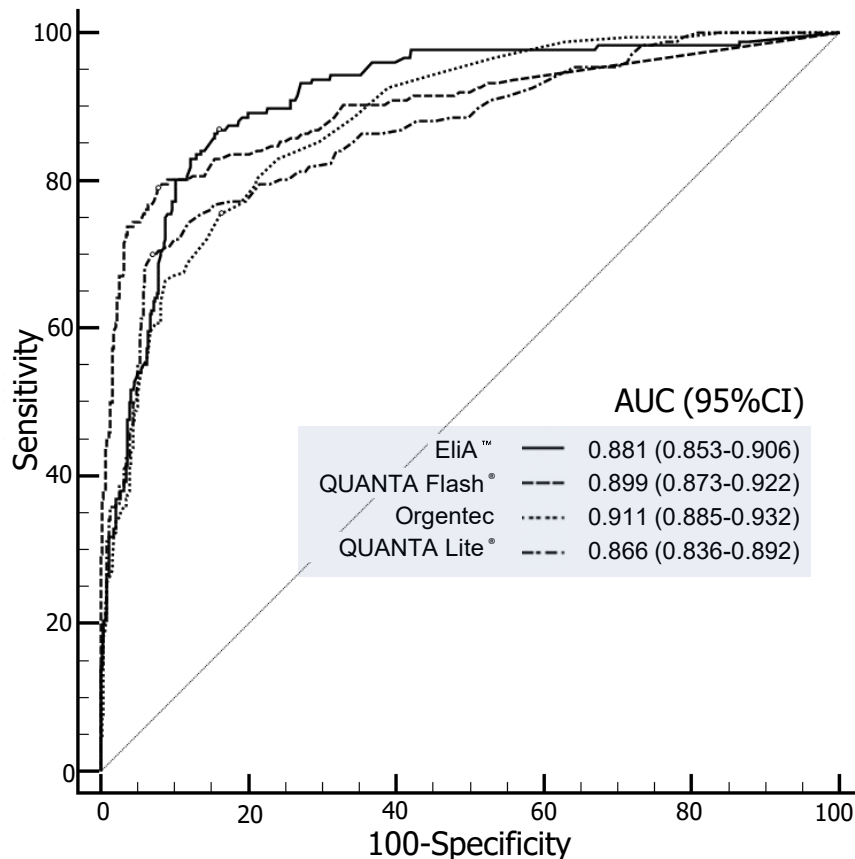


**Good agreement in diagnostic performance between ELISA/CLIA/FEIA (IgG>IgM)**  
**Diagnostic performance CLIA/FEIA > ELISA**

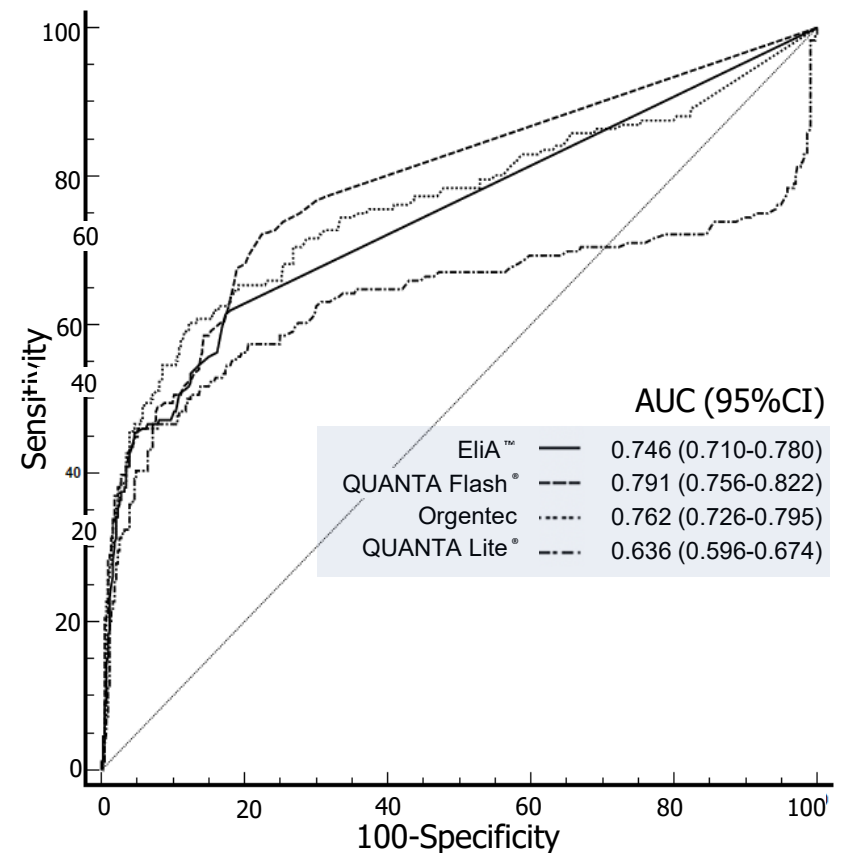
# 3.3 APS Ab-testing: analytics

## Diagnostic performance

$\alpha\beta_2$ GPI IgG



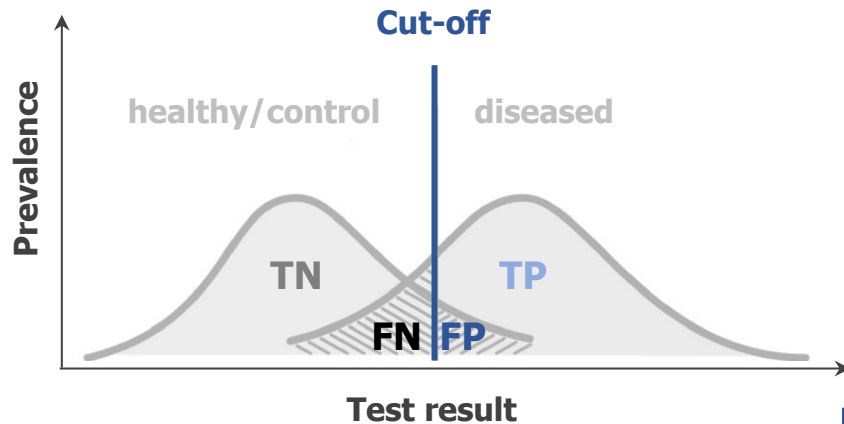
$\alpha\beta_2$ GPI IgM



**Diagnostic performance of  $\alpha\beta_2$  GPI IgG >  $\alpha\beta_2$  GPI IgM**  
**CLIA/FEIA/ELISA Org > ELISA QL**

## 3.4 APS Ab: post-analytics

### Manufacturer's cut-off

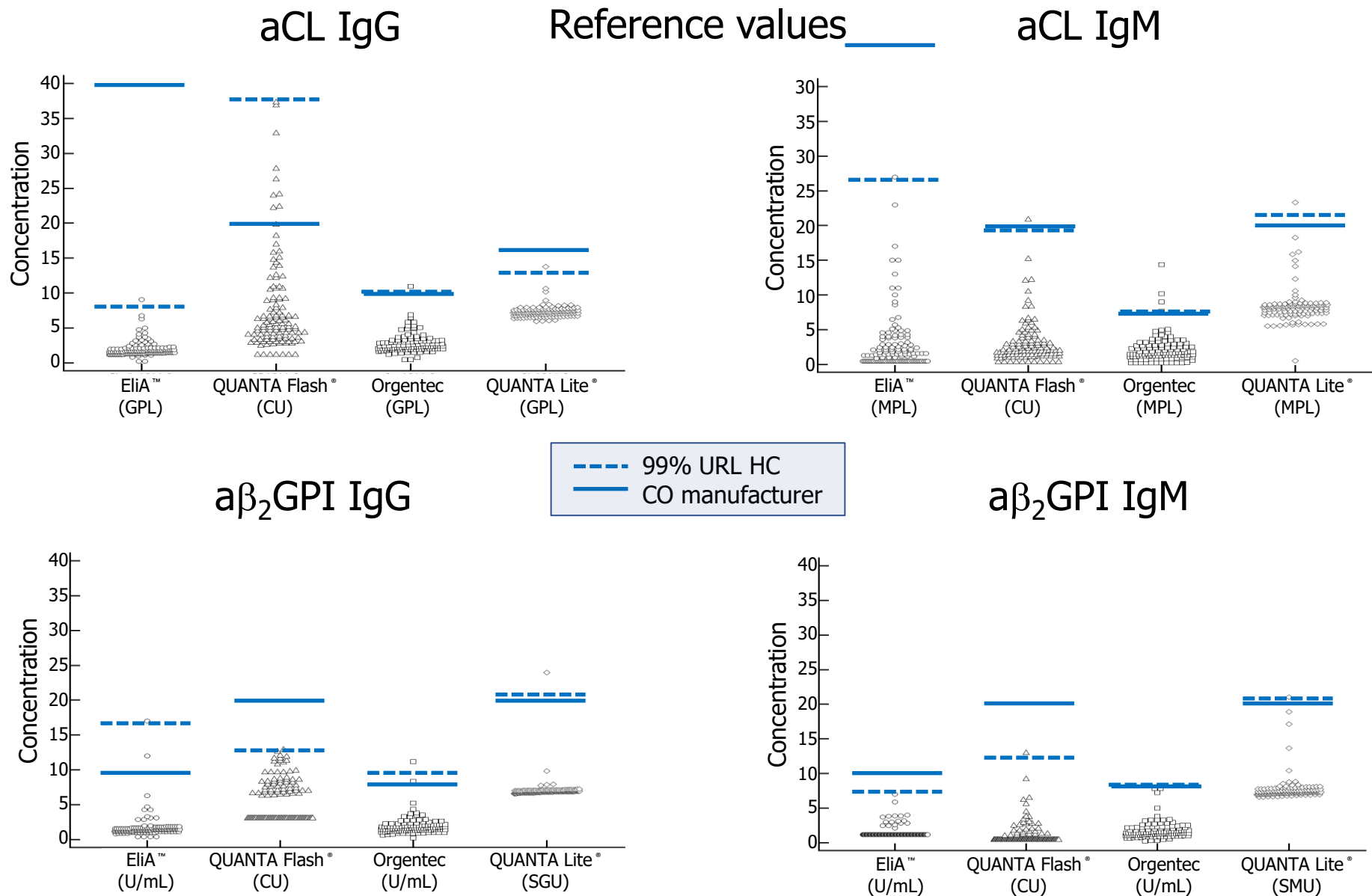


#### Dichotomous test result interpretation

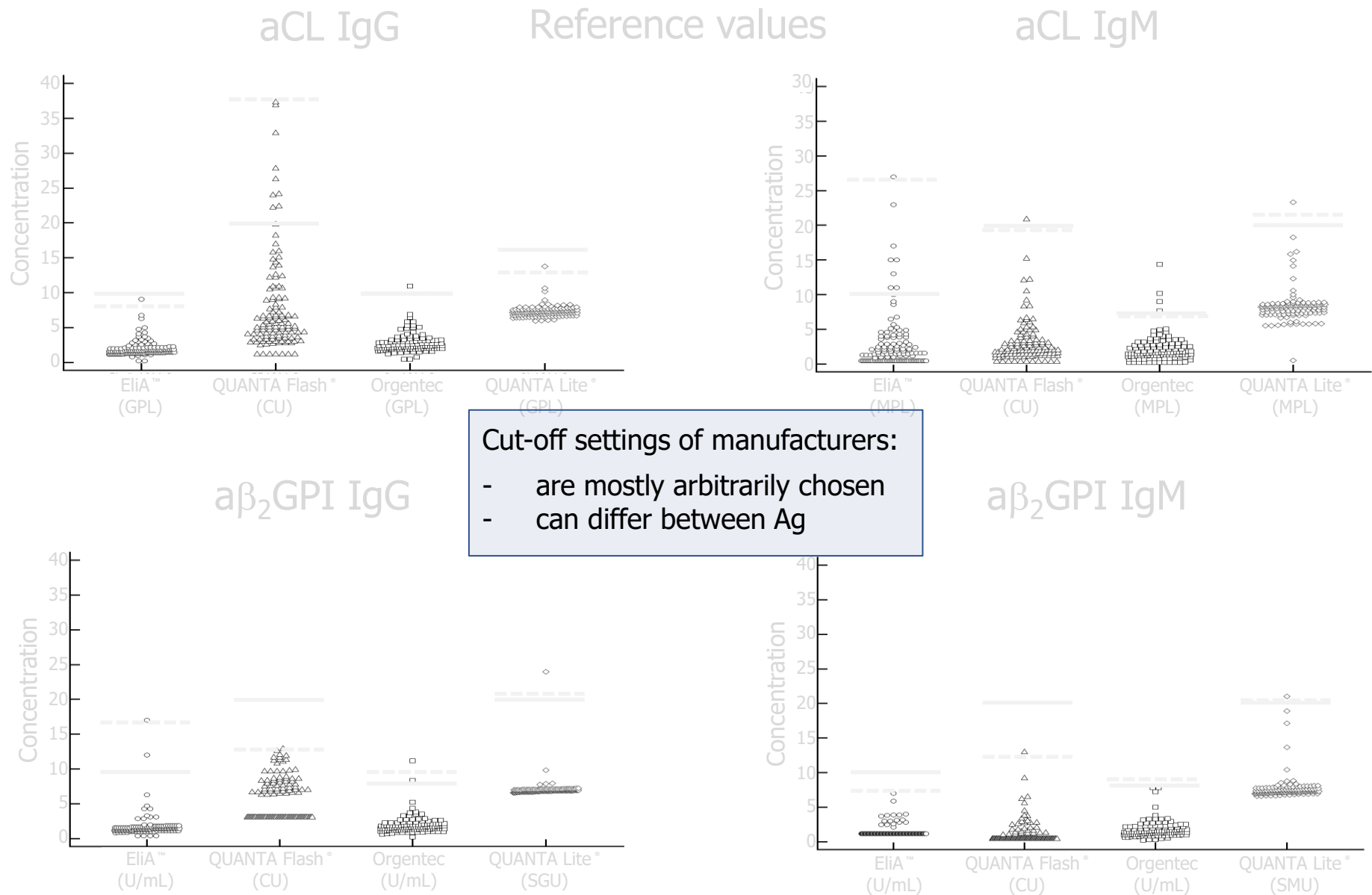
$$\text{Sensitivity} = \frac{\text{True positives (TP)}}{\text{True positives (TP)} + \text{False negatives (FN)}}$$

$$\text{Specificity} = \frac{\text{True negatives (TN)}}{\text{True negatives (TN)} + \text{False positives (FP)}}$$

# 3.4 APS Ab: post-analytics



## 3.4 APS Ab: post-analytics



# 3.4 APS Ab: post-analytics

## Manufacturer's cut-off

### aCL IgG

EliA™    QUANTA Flash®    Orgentec    QUANTA Lite®

| Cut-off         | > 40 GPL              | > 20 CU               | ≥ 10 GPL              | > 20 GPL              |
|-----------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Sensitivity (%) | 21.0<br>(15.3 – 27.8) | 54.0<br>(46.3 – 61.5) | 44.9<br>(37.4 – 52.6) | 31.3<br>(24.5 – 38.7) |
| Specificity (%) | 99.5<br>(98.3 – 99.9) | 97.3<br>(95.2 – 98.6) | 97.2<br>(95.2 – 98.6) | 98.9<br>(97.3 – 99.6) |
| LR+             | 45.5<br>(11.1-186.8)  | 19.5<br>(11.0-34.6)   | 16.2<br>(9.1-29.0)    | 24.6<br>(13.0-66.5)   |
| LR-             | 0.79<br>(0.74-0.86)   | 0.47<br>(0.40-0.56)   | 0.57<br>(0.50-0.65)   | 0.72<br>(0.63-0.77)   |

**CV% LR+ = 48.4%**

### aCL IgM

EliA™    QUANTA Flash®    Orgentec    QUANTA Lite®

| Cut-off         | > 40 MPL              | > 20 CU               | ≥ 7 MPL               | > 20 MPL              |
|-----------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Sensitivity (%) | 12.5<br>(8.0 – 18.3)  | 26.7<br>(20.3 – 33.9) | 47.7<br>(40.2 – 55.4) | 25.6<br>(19.3 – 32.7) |
| Specificity (%) | 98.6<br>(97.0 – 99.5) | 98.6<br>(97.0 – 99.5) | 94.9<br>(92.4 – 96.8) | 97.9<br>(96.1 – 99.0) |
| LR+             | 9.02<br>(3.72-21.9)   | 19.3<br>(8.4-44.3)    | 13.3<br>(7.38-24.1)   | 12.3<br>(6.15-24.6)   |
| LR-             | 0.89<br>(0.84-0.94)   | 0.74<br>(0.68-0.81)   | 0.65<br>(0.58-0.73)   | 0.76<br>(0.70-0.83)   |

**CV% LR+ = 31.8%**

### aβ<sub>2</sub>GPI IgG

EliA™    QUANTA Flash®    Orgentec    QUANTA Lite®

| Cut-off         | > 10 U/mL            | > 20 CU               | ≥ 8 U/mL              | ≥ 20 SGU              |
|-----------------|----------------------|-----------------------|-----------------------|-----------------------|
| Sensitivity (%) | 35.8<br>(28.7-43.4)  | 64.2<br>(56.6 – 71.3) | 43.8<br>(36.3-51.4)   | 20.5<br>(14.8 – 27.2) |
| Specificity (%) | 96.8<br>(94.6– 98.2) | 97.7<br>(95.8 – 98.9) | 96.3<br>(94.1 – 97.9) | 99.1<br>(97.7 – 99.7) |
| LR+             | 11.1<br>(6.37-19.2)  | 27.7<br>(14.9-51.7)   | 11.8<br>(7.12-19.7)   | 32.0<br>(11.7-87.1)   |
| LR-             | 0.66<br>(0.59-0.74)  | 0.37<br>(0.30-0.45)   | 0.58<br>(0.51-0.67)   | 0.71<br>(0.65-0.78)   |

**CV% LR+ = 52.2%**

### aβ<sub>2</sub>GPI IgM

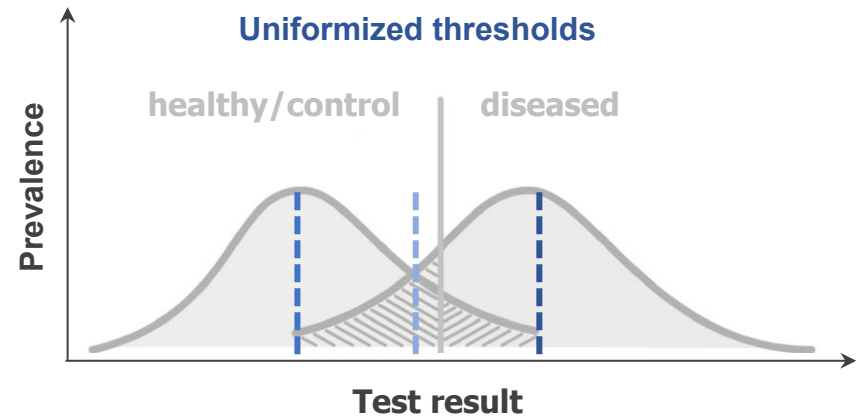
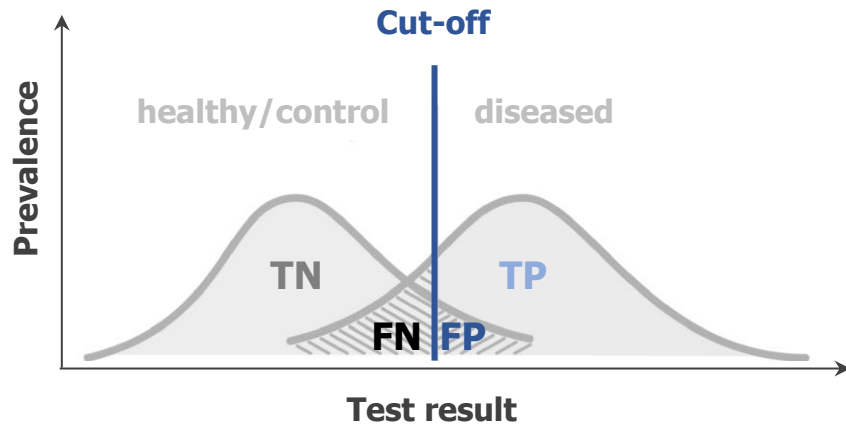
EliA™    QUANTA Flash®    Orgentec    QUANTA Lite®

| Cut-off         | > 10 U/mL             | > 20 CU               | ≥ 8 U/mL              | ≥ 20 SMU              |
|-----------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Sensitivity (%) | 28.4<br>(21.9 – 35.7) | 19.3<br>(13.8 – 25.9) | 35.8<br>(28.7 – 43.4) | 31.3<br>(24.5 – 38.7) |
| Specificity (%) | 98.4<br>(96.7 – 99.3) | 99.5<br>(98.3 – 99.9) | 97.7<br>(95.8 – 98.9) | 97.2<br>(95.2 – 98.6) |
| LR+             | 17.6<br>(8.1-38.0)    | 41.8<br>(10.2-172.2)  | 15.5<br>(8.14-29.5)   | 11.3<br>(6.19-20.5)   |
| LR-             | 0.73<br>(0.66-0.80)   | 0.80<br>(0.75-0.87)   | 0.66<br>(0.59-0.73)   | 0.71<br>(0.64-0.78)   |

**CV% LR+ = 63.9%**

## 3.4 APS Ab: post-analytics

### Specificity-based thresholds



# 3.4 APS Ab: post-analytics

Cut-off 97.5% specificity

## aCL IgG

EliA™    QUANTA Flash®    Orgentec    QUANTA Lite®

|                 |                       |                       |                       |                       |
|-----------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Cut-off         | > 7.3 GPL             | > 20.6 CU             | > 10.7 GPL            | > 10.9 GPL            |
| Sensitivity (%) | 47.7<br>(40.2 – 55.4) | 53.4<br>(45.8 – 60.9) | 43.8<br>(36.3 – 51.4) | 38.1<br>(30.9-45.7)   |
| Specificity (%) | 97.5<br>(95.5 – 98.7) | 97.5<br>(95.8 – 98.7) | 97.5<br>(95.5 – 98.7) | 97.5<br>(95.5 – 98.7) |
| LR+             | 18.8<br>(10.3-34.4)   | 21.0<br>(11.5-38.3)   | 17.0<br>(9.3-31.2)    | 15.0<br>(8.1-27.7)    |
| LR-             | 0.54<br>(0.47-0.62)   | 0.48<br>(0.41-0.56)   | 0.58<br>(0.51-0.66)   | 0.64<br>(0.57-0.71)   |

CV% LR+ = 14.3%

## aCL IgM

EliA™    QUANTA Flash®    Orgentec    QUANTA Lite®

|                 |                       |                       |                       |                       |
|-----------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Cut-off         | > 25.0 MPL            | > 15.4 CU             | > 10.2 MPL            | > 18.2 MPL            |
| Sensitivity (%) | 19.9<br>(13.8 – 25.9) | 34.7<br>(27.7 – 42.2) | 36.9<br>(29.8 – 44.5) | 26.7<br>(20.3 – 33.9) |
| Specificity (%) | 97.7<br>(95.8 – 98.9) | 97.9<br>(96.1 – 99.0) | 97.5<br>(95.5 – 98.7) | 97.5<br>(95.5 – 98.7) |
| LR+             | 8.4<br>(4.2-16.6)     | 13.6<br>(7.4-25.3)    | 14.5<br>(7.9-26.9)    | 10.5<br>(5.6-19.8)    |
| LR-             | 0.83<br>(0.77-0.89)   | 0.67<br>(0.60-0.75)   | 0.65<br>(0.58-0.73)   | 0.75<br>(0.69-0.82)   |

CV% LR+ = 24%

## aβ<sub>2</sub>GPI IgG

EliA™    QUANTA Flash®    Orgentec    QUANTA Lite®

|                 |                      |                       |                       |                       |
|-----------------|----------------------|-----------------------|-----------------------|-----------------------|
| Cut-off         | > 14.0 U/mL          | > 18.3 CU             | > 11.0 U/mL           | > 9.2 SGU             |
| Sensitivity (%) | 34.7<br>(27.1-41.6)  | 67.0<br>(59.6– 73.9)  | 36.9<br>(29.8 – 44.5) | 38.6<br>(31.4 – 46.3) |
| Specificity (%) | 97.7<br>(95.8– 98.9) | 97.5<br>(95.5 – 98.7) | 97.5<br>(95.5 – 98.7) | 97.5<br>(95.5 – 98.7) |
| LR+             | 14.8<br>(7.7-28.2)   | 26.3<br>(14.6-47.6)   | 14.5<br>(7.9-24.1)    | 15.2<br>(8.2-28.1)    |
| LR-             | 0.67<br>(0.61-0.75)  | 0.34<br>(0.27-0.42)   | 0.65<br>(0.58-0.73)   | 0.63<br>(0.56-0.71)   |

CV% LR+ = 32.4%

## aβ<sub>2</sub>GPI IgM

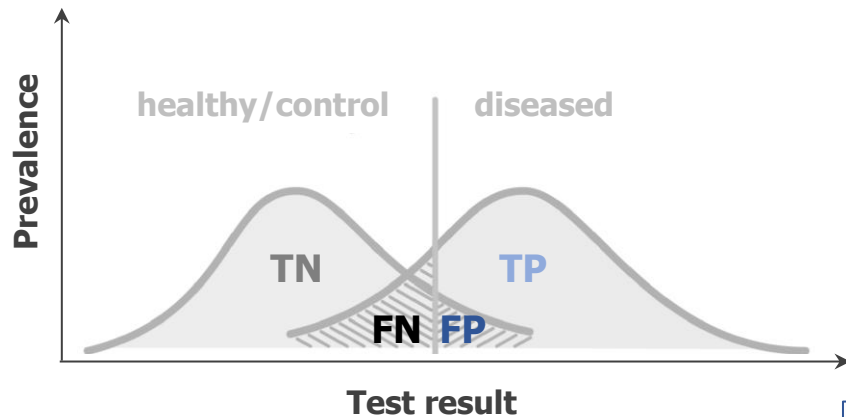
EliA™    QUANTA Flash®    Orgentec    QUANTA Lite®

|                 |                       |                       |                       |                       |
|-----------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Cut-off         | > 7.6 U/mL            | > 9.5 CU              | > 7.8 U/mL            | > 21.7 SMU            |
| Sensitivity (%) | 36.4<br>(29.3 – 43.9) | 38.6<br>(31.4 – 46.3) | 36.9<br>(29.3– 43.9)  | 31.3<br>(24.5 – 38.7) |
| Specificity (%) | 97.5<br>(95.5 – 98.7) | 97.5<br>(95.5 – 98.7) | 97.5<br>(95.5 – 98.7) | 97.5<br>(95.5 – 98.7) |
| LR+             | 14.3<br>(7.7-26.5)    | 15.2<br>(8.2-28.1)    | 14.3<br>(7.7-26.5)    | 12.3<br>(6.6-22.9)    |
| LR-             | 0.65<br>(0.58-0.73)   | 0.63<br>(0.56-0.71)   | 0.65<br>(0.58-0.73)   | 0.71<br>(0.64-0.78)   |

CV% LR+ = 8.7%

## 3.4 APS Ab: post-analytics

### Test result (interval)-specific LR



Likelihood ratio

$$\text{LR} + = \frac{\text{Sensitivity}}{\text{1 - Specificity}}$$

True positives (TP)

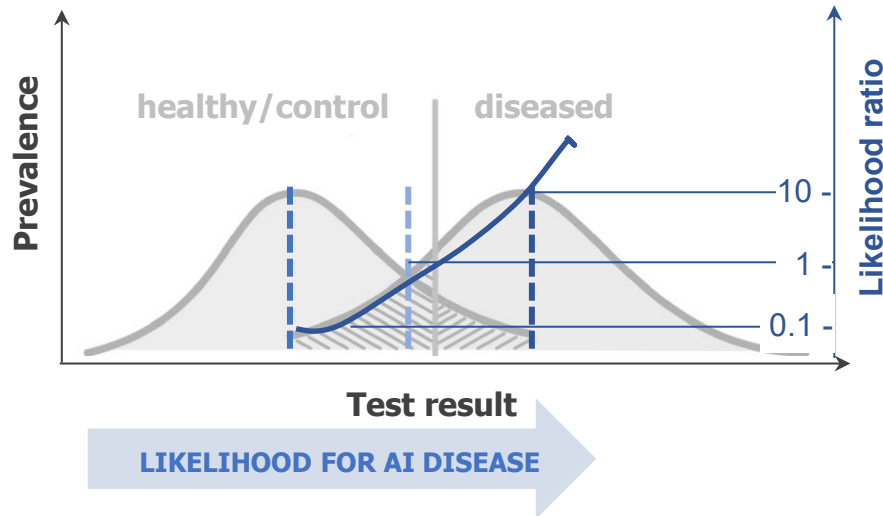
True positives (TP) + False negatives (FN)

False positives (FP)

False positives (FP) + True negatives (TN)

## 3.4 APS Ab: post-analytics

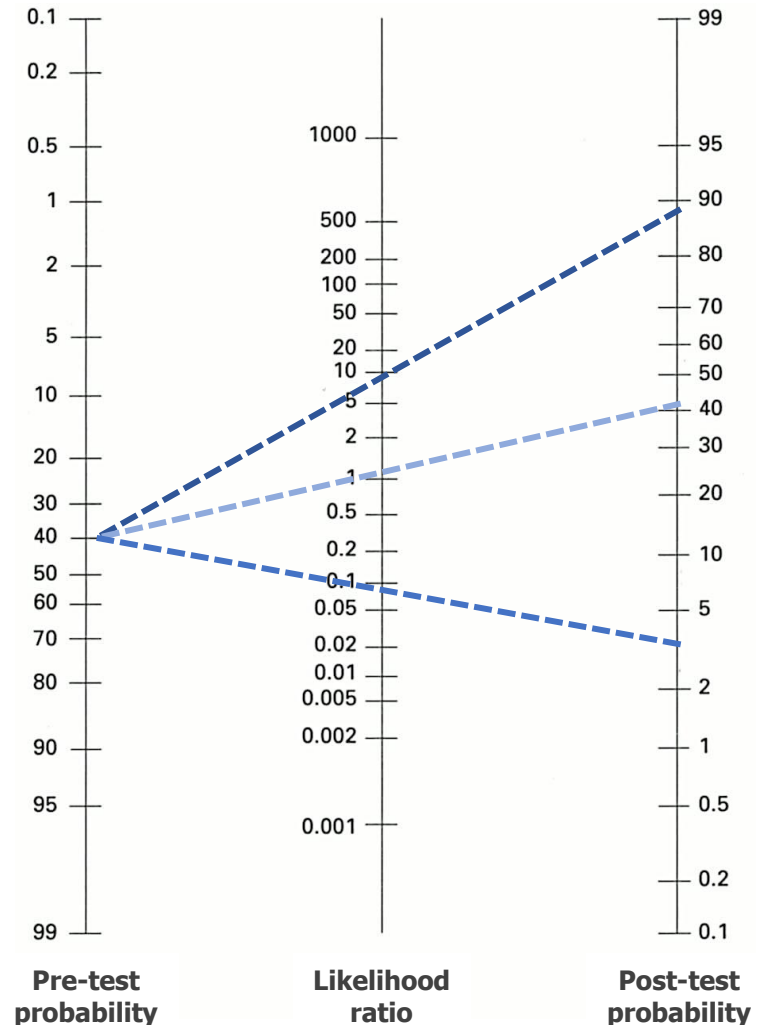
### Test result (interval)-specific LR



#### Continuous test result interpretation

- LR < 0.1** → test result is useful to exclude disease
- LR = 1** → test result hasn't clinical value
- LR > 10** → test result is useful to confirm disease

#### Clinical test result interpretation



# 3.4 APS Ab: post-analytics

## Test result-specific LR

### aCL IgG

|        | EliA | QUANTA Flash | Orgentec | QUANTA Lite |
|--------|------|--------------|----------|-------------|
| >90.0% | 7.0  | 7.2          | 7.1      | 6.6         |
| >92.5% | 8.2  | 8.8          | 9.4      | 6.9         |
| >95.0% | 11.5 | 11.6         | 12.1     | 10.0        |
| >97.5% | 18.8 | 21.0         | 17.2     | 15.0        |
| >99.0% | 40.0 | 51.7         | 37.5     | 30.8        |
| >99.5% | 54.1 | 96.0         | 73.8     | 59.1        |

### aCL IgM

|        | EliA | QUANTA Flash | Orgentec | QUANTA Lite |
|--------|------|--------------|----------|-------------|
| >90.0% | 5.7  | 5.4          | 5.6      | 4.9         |
| >92.5% | 6.4  | 6.8          | 6.8      | 6.1         |
| >95.0% | 7.0  | 10.1         | 9.8      | 7.9         |
| >97.5% | 8.4  | 13.6         | 14.5     | 10.5        |
| >99.0% | 11.1 | 28.9         | 25.8     | 24.6        |
| >99.5% | 20.9 | 13.5         | 11.1     | 29.5        |

LIKELIHOOD FOR APS

### a $\beta_2$ GPI IgG

|        | EliA | QUANATA Flash | Orgentec | QUANTA Lite |
|--------|------|---------------|----------|-------------|
| >90.0% | 6.8  | 8.4           | 7.8      | 7.3         |
| >92.5% | 8.2  | 10.3          | 8.7      | 9.5         |
| >95.0% | 10.1 | 15.3          | 11.0     | 10.9        |
| >97.5% | 14.8 | 26.3          | 14.5     | 15.2        |
| >99.0% | 27.7 | 48.5          | 28.9     | 33.8        |
| >99.5% | 39.4 | 82.2          | 44.3     | 43.1        |

### a $\beta_2$ GPI IgM

|        | EliA | QUANTA Flash | Orgentec | QUANTA Lite |
|--------|------|--------------|----------|-------------|
| >90.0% | 4.8  | 5.0          | 5.6      | 4.8         |
| >92.5% | 6.7  | 6.3          | 6.8      | 6.2         |
| >95.0% | 9.4  | 9.7          | 9.6      | 8.3         |
| >97.5% | 14.3 | 15.2         | 15.0     | 12.3        |
| >99.0% | 19.7 | 30.8         | 27.7     | 12.3        |
| >99.5% | 19.7 | 44.3         | 16.0     | 9.8         |

LIKELIHOOD FOR APS

# 3.4 APS Ab: post-analytics

## Test result-specific LR

aCL IgG

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|        |      |      |      |      |
|--------|------|------|------|------|
| >90.0% | 7.0  | 7.2  | 7.1  | 6.6  |
| >92.5% | 8.2  | 8.8  | 9.4  | 8.8  |
| >95.0% | 11.5 | 11.6 | 12.1 | 10.0 |
| >97.5% | 18.8 | 21.0 | 17.2 | 15.0 |
| >99.0% | 40.0 | 51.7 | 37.5 | 30.8 |
| >99.5% | 54.1 | 96.0 | 73.8 | 59.1 |

aCL IgM

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|        |      |      |      |      |
|--------|------|------|------|------|
| >90.0% | 5.7  | 5.4  | 5.6  | 4.9  |
| >92.5% | 6.4  | 6.8  | 6.8  | 6.1  |
| >95.0% | 7.0  | 10.1 | 9.8  | 7.9  |
| >97.5% | 8.4  | 13.6 | 14.5 | 10.5 |
| >99.0% | 11.1 | 28.9 | 25.8 | 24.6 |
| >99.5% | 20.9 | 13.5 | 11.1 | 29.5 |

**Using test result -specific LR**

**harmonizes inter-manufacturer**

**APS Ab test results interpretation**

a $\beta$ <sub>2</sub>GPI IgG

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|        |      |      |      |      |
|--------|------|------|------|------|
| >90.0% | 6.8  | 8.4  | 7.8  | 7.3  |
| >92.5% | 8.2  | 10.3 | 8.7  | 9.5  |
| >95.0% | 10.1 | 15.3 | 11.0 | 10.9 |
| >97.5% | 14.8 | 26.3 | 14.5 | 15.2 |
| >99.0% | 27.7 | 48.5 | 28.9 | 33.8 |
| >99.5% | 39.4 | 82.2 | 44.3 | 43.1 |

a $\beta$ <sub>2</sub>GPI IgM

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|        |      |      |      |      |
|--------|------|------|------|------|
| >90.0% | 4.8  | 5.0  | 5.6  | 4.8  |
| >92.5% | 6.7  | 6.3  | 6.8  | 6.2  |
| >95.0% | 9.4  | 9.7  | 9.6  | 8.3  |
| >97.5% | 14.3 | 15.2 | 15.0 | 12.3 |
| >99.0% | 19.7 | 30.8 | 27.7 | 12.3 |
| >99.5% | 19.7 | 44.3 | 16.0 | 9.8  |

LIKELIHOOD FOR APS

## 3.4 APS Ab: post-analytics

### Test result interval-specific LR

**Negative APS Ab** = < 97.5 % Specificity threshold\*  
**Medium-positive APS Ab** = [ 97.5-99.5 ] % Specificity threshold  
**High-positive APS Ab** = ≥ 99.5 % Specificity threshold

#### aCL IgG

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|              |      |      |      |      |
|--------------|------|------|------|------|
| < 97.5%      | 0.54 | 0.48 | 0.58 | 0.64 |
| [97.5-99.5%] | 10.9 | 4.4  | 4.6  | 5.2  |
| ≥ 99.5%      | 36.1 | 64.0 | 49.2 | 39.4 |

#### aCL IgM

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|              |      |      |      |      |
|--------------|------|------|------|------|
| < 97.5%      | 0.82 | 0.67 | 0.65 | 0.75 |
| [97.5-99.5%] | 4.9  | 13.4 | 15.3 | 6.3  |
| ≥ 99.5%      | 13.9 | 9.8  | 7.4  | 19.7 |

LIKELIHOOD FOR APS

#### aβ<sub>2</sub>GPI IgG

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|              |      |      |      |      |
|--------------|------|------|------|------|
| < 97.5%      | 0.67 | 0.34 | 0.65 | 0.63 |
| [97.5-99.5%] | 7.4  | 13.9 | 8.9  | 8.8  |
| ≥ 99.5%      | 27.9 | 54.9 | 29.5 | 29.5 |

#### aβ<sub>2</sub>GPI IgM

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|              |      |      |      |      |
|--------------|------|------|------|------|
| < 97.5%      | 0.66 | 0.63 | 0.65 | 0.70 |
| [97.5-99.5%] | 13.1 | 8.7  | 16.0 | 11.8 |
| ≥ 99.5%      | 13.1 | 29.5 | 10.7 | 9.8  |

\* Correlates with independently evaluated 99% ULN

# 3.4 APS Ab: post-analytics

Test result interval-specific LR

aCL IgG/M

a $\beta_2$ GPI IgG/M

combination

**Negative aCL IgG/M - a $\beta_2$ GPI IgG/M**

**Positive aCL IgG/M - a $\beta_2$ GPI IgG/M**

AND

aCL + a $\beta_2$ GPI IgG

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|         |      |       |      |      |
|---------|------|-------|------|------|
| < 97.5% | 0.52 | 0.32  | 0.58 | 0.57 |
| ≥ 97.5% | 35.1 | 73.00 | 20.0 | 66.4 |

aCL + a $\beta_2$ GPI IgM

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|         |      |      |      |      |
|---------|------|------|------|------|
| < 97.5% | 0.59 | 0.61 | 0.61 | 0.63 |
| ≥ 97.5% | 11.3 | 23.0 | 17.8 | 25.4 |

LIKELIHOOD FOR APS

aCL IgG/M + a $\beta_2$ GPI IgG

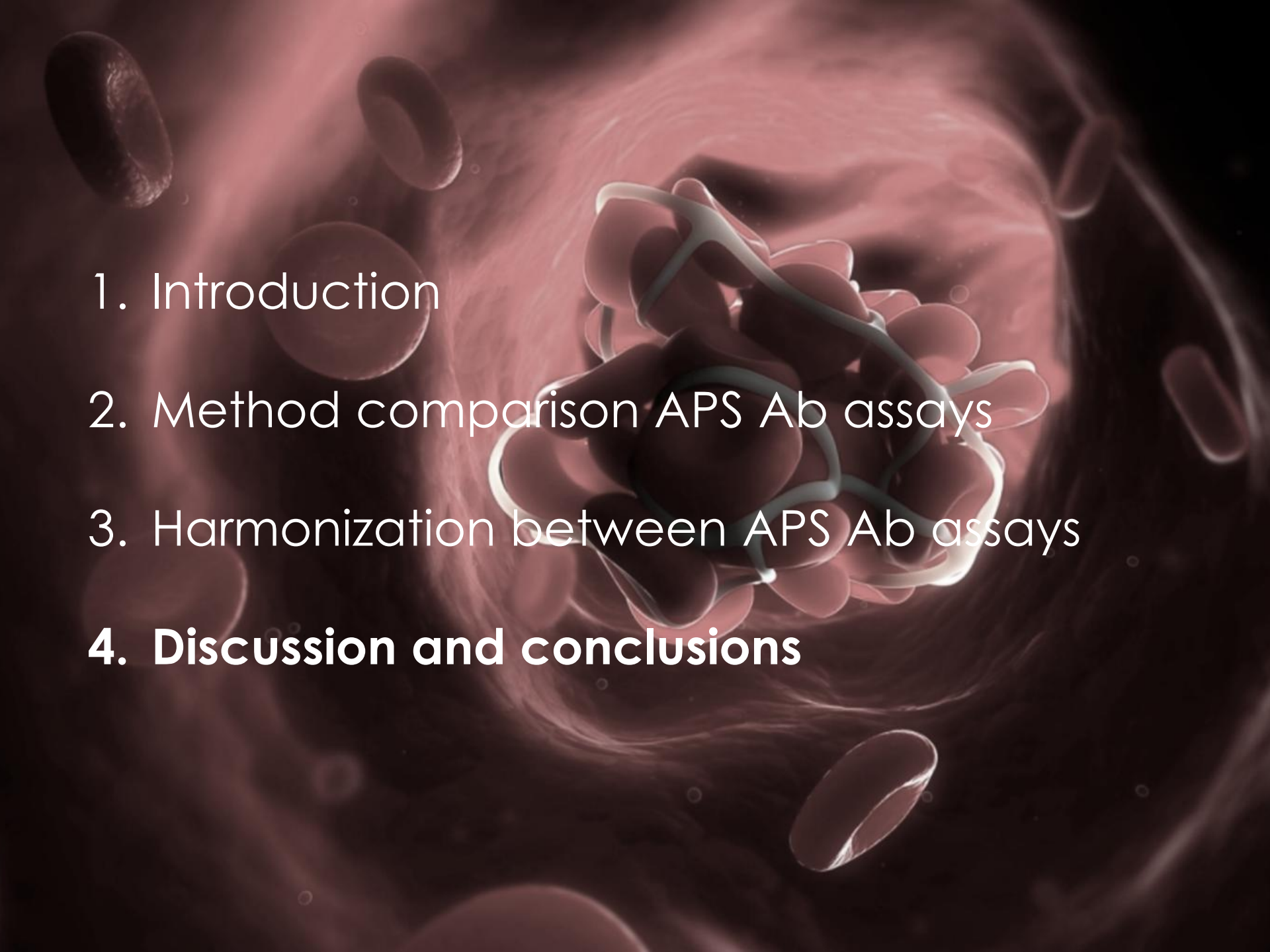
EliA    QUANTA Flash    Orgentec    QUANTA Lite

|         |      |      |      |      |
|---------|------|------|------|------|
| < 97.5% | 0.40 | 0.24 | 0.43 | 0.46 |
| ≥ 97.5% | 19.7 | 83.6 | 34.4 | 44.3 |

aCL IgG/M + a $\beta_2$ GPI IgG/M

EliA    QUANTA Flash    Orgentec    QUANTA Lite

|         |      |      |      |      |
|---------|------|------|------|------|
| < 97.5% | 0.28 | 0.22 | 0.41 | 0.37 |
| ≥ 97.5% | 12.3 | 78.7 | 25.8 | 24.6 |

- 
1. Introduction
  2. Method comparison APS Ab assays
  3. Harmonization between APS Ab assays
  - 4. Discussion and conclusions**

# 4.1 aPL test method

Immunologic Research  
<https://doi.org/10.1007/s12026-023-09443-8>

## CORRESPONDENCE



### Discouraging Non-ELISA antiphospholipid antibody assays in antiphospholipid syndrome classification may hinder clinical research

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#### No superiority of ELISA methods:

- analytically (> imprecision, low rho, lack of traceability)
- diagnostically (lower AUC versus CLIA/FEIA)

In line with ISTH APS diagnostic guidelines\* of 2018, alternative methods allow for accurate aPL Ab detection

\*Devreese *et al.* J Thromb Haemost 2018; 16: 809-13

> [Ann Rheum Dis.](#) 2024 Feb 15;83(3):e6. doi: 10.1136/ard-2023-225067.

### Correspondence on "ACR/EULAR antiphospholipid syndrome classification criteria"

Jan Damoiseaux<sup>1</sup>, Joyce van Beers<sup>2</sup>

> [Ann Rheum Dis.](#) 2024 Feb 15;83(3):e2. doi: 10.1136/ard-2023-225042.

### Correspondence on '2023 ACR/EULAR antiphospholipid syndrome classification criteria'

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> [Ann Rheum Dis.](#) 2024 Feb 15;83(3):e4. doi: 10.1136/ard-2023-225013.

### Correspondence on '2023 ACR/EULAR antiphospholipid syndrome classification criteria'

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## 4.2 Uniformized cut-off

Correlation of 99% URL HC with 97.5% Spec threshold

|                              |                    | Units | Cut-off | Median of HC | 99% URL in HC* | 97.5% specificity threshold in diseased controls |
|------------------------------|--------------------|-------|---------|--------------|----------------|--------------------------------------------------|
| <b>aCL IgG</b>               | EliA™              | GPL   | 10/40   | 1.7          | 8.6            | >7.7                                             |
|                              | QUANTA Flash®      | CU    | 20      | 5.6          | 37.3           | >20                                              |
|                              | Orgentec ELISA     | GPL   | 10      | 2.3          | 10.2           | >10.7                                            |
|                              | QUANTA lite® ELISA | GPL   | 15/20   | 7.2          | 13.2           | >10.9                                            |
| <b>aCL IgM</b>               | EliA™              | MPL   | 10/40   | 1.6          | 26.2           | >25                                              |
|                              | QUANTA Flash®      | CU    | 20      | 2.1          | 19.9           | >15.4                                            |
|                              | Orgentec ELISA     | MPL   | 7       | 1.6          | 7.8            | >10.2                                            |
|                              | QUANTA lite® ELISA | MPL   | 12.5/20 | 8.2          | 22.3           | >18.2                                            |
| <b>aβ<sub>2</sub>GPI IgG</b> | EliA™              | U/mL  | 7/10    | 1.4          | 16.0           | >14                                              |
|                              | QUANTA Flash®      | CU    | 20      | 6.4          | 12.9           | >18.3                                            |
|                              | Orgentec ELISA     | U/mL  | 5/8     | 1.6          | 10.6           | >11.9                                            |
|                              | QUANTA lite® ELISA | SGU   | 20      | 6.9          | 21.2           | >9.2                                             |
| <b>aβ<sub>2</sub>GPI IgM</b> | EliA™              | U/mL  | 7/10    | 1.2          | 6.8            | >7.6                                             |
|                              | QUANTA Flash®      | CU    | 20      | 0.6          | 12.3           | >9.5                                             |
|                              | Orgentec ELISA     | U/mL  | 5/8     | 1.4          | 7.8            | >7.8                                             |
|                              | QUANTA lite® ELISA | SMU   | 20      | 7.3          | 20.6           | >21.7                                            |

≠ 40 GPL/MPL ELISA's

\*Favaloro *et al.* Semin Thromb Hemost 2024; 50: 605-608

\*Devreese *et al.* J Thromb Haemost 2018; 16: 809-813

\*Miyakis *et al.* J Thromb Haemost 2006; 4: 295-306

## 4.2 Uniformized cut-off

### Variation in 99% URL in HC

| aPL type                     | aPL assay          | Units | Kaneshige <i>et al.</i> | Zigon <i>et al.</i> | Cabrera-Marante <i>et al.</i> | Van Hoovels <i>et al.</i> |
|------------------------------|--------------------|-------|-------------------------|---------------------|-------------------------------|---------------------------|
| <b>aCL IgG</b>               | EliA™              | GPL   | 34.9                    | nd                  | 18.5                          | 8.6                       |
|                              | QUANTA Flash®      | CU    | 24.9                    | 42.2                | <i>nd</i>                     | 37.3                      |
|                              | Orgentec ELISA     | GPL   | <i>nd</i>               | <i>nd</i>           | <i>nd</i>                     | 10.2                      |
|                              | QUANTA lite® ELISA | GPL   | 7.0                     | <i>nd</i>           | nd                            | 13.2                      |
| <b>aCL IgM</b>               | EliA™              | MPL   | 19.8                    | nd                  | 22.0                          | 26.2                      |
|                              | QUANTA Flash®      | CU    | 17.8                    | 45.6                | <i>nd</i>                     | 19.9                      |
|                              | Orgentec ELISA     | MPL   | <i>nd</i>               | <i>nd</i>           | <i>nd</i>                     | 7.8                       |
|                              | QUANTA lite® ELISA | MPL   | 20.4                    | <i>nd</i>           | <i>nd</i>                     | 22.3                      |
| <b>aβ<sub>2</sub>GPI IgG</b> | EliA™              | U/mL  | 3.0                     | nd                  | 11.0                          | 16.0                      |
|                              | QUANTA Flash®      | CU    | 14.4                    | 47.4                | <i>nd</i>                     | 12.9                      |
|                              | Orgentec ELISA     | U/mL  | <i>nd</i>               | <i>nd</i>           | <i>nd</i>                     | 10.6                      |
|                              | QUANTA lite® ELISA | SGU   | 2.6                     | <i>nd</i>           | <i>nd</i>                     | 21.2                      |
| <b>aβ<sub>2</sub>GPI IgM</b> | EliA™              | U/mL  | 5.0                     | nd                  | 11.0                          | 6.8                       |
|                              | QUANTA Flash®      | CU    | 8.8                     | 33.5                | <i>nd</i>                     | 12.3                      |
|                              | Orgentec ELISA     | U/mL  | <i>nd</i>               | <i>nd</i>           | <i>nd</i>                     | 7.8                       |
|                              | QUANTA lite® ELISA | SMU   | 18.0                    | <i>nd</i>           | <i>nd</i>                     | 20.6                      |

- Differences in statistical methods, demography
- Recommended: non-parametric 99% RI with outlier detection

## 4.2 Uniformized cut-off

### Variation in 97.5% Spec thresholds in DCG

| aPL type   | aPL assay          | Vandevelde <i>et al.</i> | Van Hoovels <i>et al.</i> |
|------------|--------------------|--------------------------|---------------------------|
| aCL IgG    | EliA™              | 21                       | >7.7                      |
|            | QUANTA Flash®      | 89                       | >20                       |
|            | Orgentec ELISA     | <i>nd</i>                | >10.7                     |
|            | QUANTA lite® ELISA | 32                       | >10.9                     |
| aCL IgM    | EliA™              | 33                       | >25                       |
|            | QUANTA Flash®      | 46                       | >15.4                     |
|            | Orgentec ELISA     | <i>nd</i>                | >10.2                     |
|            | QUANTA lite® ELISA | 42                       | >18.2                     |
| aβ2GPI IgG | EliA™              | 32                       | >14                       |
|            | QUANTA Flash®      | 300                      | >18.3                     |
|            | Orgentec ELISA     | <i>nd</i>                | >11.9                     |
|            | QUANTA lite® ELISA | 20                       | >9.2                      |
| aβ2GPI IgM | EliA™              | 22                       | >7.6                      |
|            | QUANTA Flash®      | 27                       | >9.5                      |
|            | Orgentec ELISA     | <i>nd</i>                | >7.8                      |
|            | QUANTA lite® ELISA | 41                       | >21.7                     |

Differences in DCG cohort selection  
Confirmation of cut-offs using 'real-life' controle cohorts is essential

## 4.3 Conclusions

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- **Lack of harmonization between APS Ab tests**

AI serology tests can't be used interchangeably

Not the assay technique (ELISA) determines the highest diagnostic performance ('gold standard?')

- **Lack of traceability**

Traceability to the same standards, does not allow for neither analytic nor diagnostic concordance among APS Ab tests

- **Definition of cut-off values**

Implementation of uniformized, objective thresholds (medium/high) for commercial APS Ab assays

More studies using representative study populations should confirm uniformized cut-off settings

- **aPL test panels**

Implementation of aPL analyses panels, to facilitate combined test result interpretation

- **Implementation of LR<sub>s</sub> on APS Ab test result reports**

Implementation of LR<sub>s</sub> on lab test results reports harmonizes clinical interpretation

Confirmation of cut-offs using 'real-life' controle cohorts is essential

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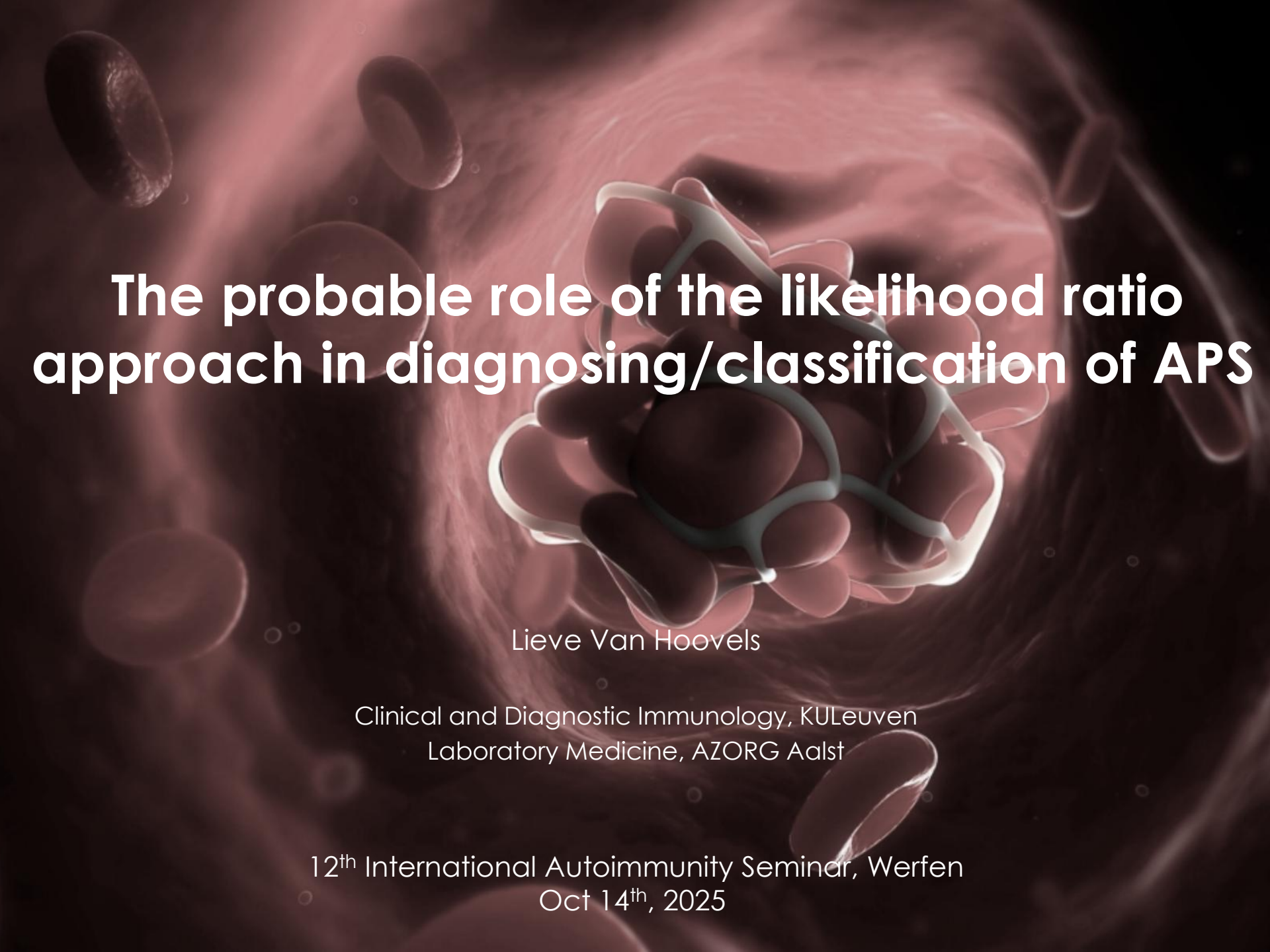
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Siska Blomme

Diagnostic manufacturers

The background of the slide is a microscopic image showing several red blood cells (erythrocytes) in a reddish-pink hue. In the center-right, there is a prominent cluster of cells, possibly platelets or a small group of leukocytes, which are more densely packed and have a darker, more complex appearance. The overall lighting is soft, with a slight vignette effect, making the central cluster stand out.

# The probable role of the likelihood ratio approach in diagnosing/classification of APS

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Oct 14<sup>th</sup>, 2025