Analytical Performance Specification (APS)

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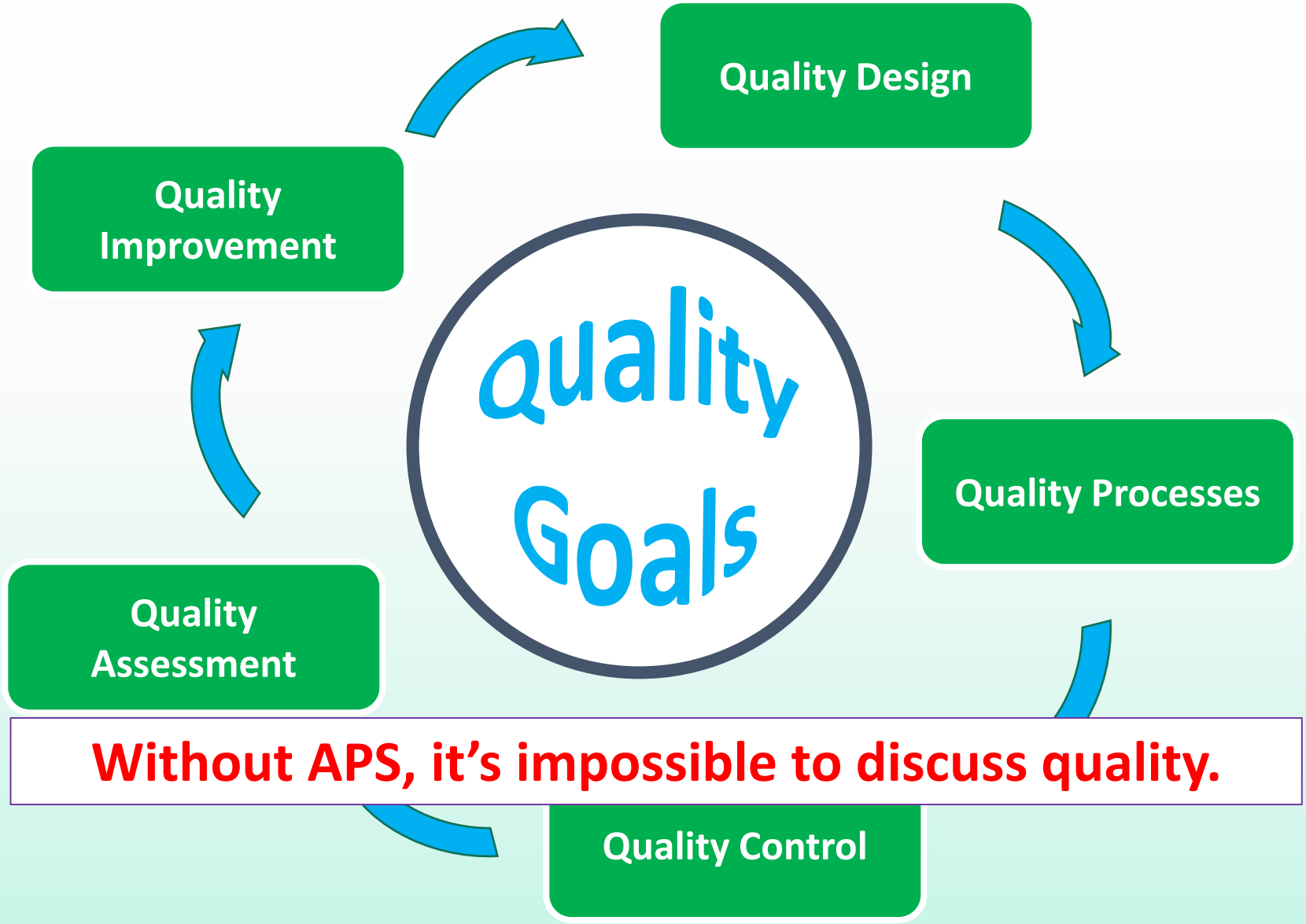
APS specify (in numerical terms) the quality required to deliver laboratory test information that would achieve the best possible health outcomes for patients.

Do more Good than Harm

Quality Lab Performance



Without APS, it's impossible to discuss quality.

APS are necessary for:

- Choosing/Evaluation of new assay methods
- Planning IQC
- EQA/PT
- Setting goal for manufacturers
- Improve weak methods

History

A history of more than 70 years

- **Tonks DB. (1963)**

A study of the accuracy and precision of clinical chemistry determinations in 170 Canadian laboratories. Clin Chem 1963;9:217–33.

The distribution of test results for a healthy population

¼ of RI; Allowable Deviation (TEa)

- **Barnett RN. (1968)**

Medical significance of laboratory results. Am J Clin Pathol 1968;50:671–6.

The medically important change in a test result;

Clinicians' opinion; Medically allowable Imprecision

- **Cotlove E, Harris EK, Williams GZ. (1970)**

Biological and analytic components of variation in long-term studies of serum constituents in normal subjects. III. Physiological and medical implications. Clin Chem 1970;16:1028–32.

The distribution of test results for a healthy individual

BV components; Medically allowable Bias

Aspen 1976 Conference:

"Three major approaches over past 30 years [before 1976]:

- *Medical significance criteria*
- *Relationships to the Normal Range or Biologic Variability*
- *Inter-laboratory testing criteria"*

Stockholm 1999 Hierarchy

IUPAC, the IFCC, WHO. Stockholm, Sweden. 25-56 April 1999

What?

1. Clinical outcome for specific clinical setting

2. Clinical decisions in general:

- Biological variation
- Clinicians' opinion

3. Professional recommendations:

Who?

- National/International
- Local groups/individuals

4. Performance goals:

- Regulatory bodies
- EQA

5. State of the art:

- EQA/PT
- Evaluation studies

Some inbuilt contradictions

Dependent on current analytical performance (Leve 5)

Aware of the state of the art

Can use level Outcome or BV

Example:

- (US) CAP uses Outcome goals
- (Netherland) SKML use of BV

Milan 2014 Models

1st EFLM Strategic Conference. Milan, Italy. 24–25 November 2014
Defining Analytical Performance Goals – 15 years after the Stockholm Conference

Model 1. Based on the effect of analytical performance on the clinical outcome

- 1a. Direct Studies
- 1b. Indirect studies

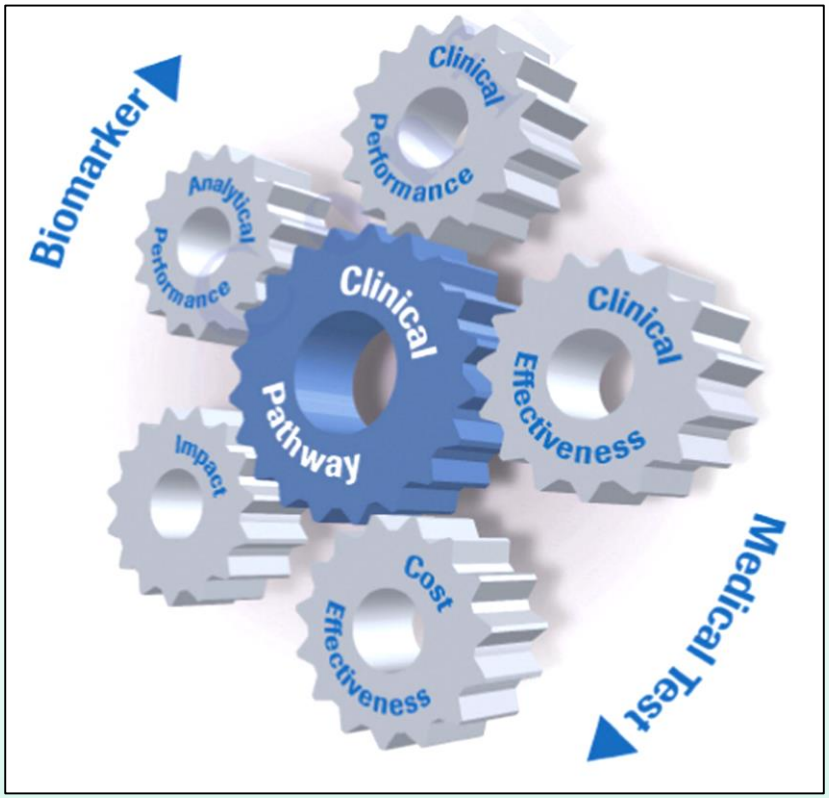
Model 2. Based on components of biological variation of the measurands

Model 3. Based on the highest level of analytical performance technically achievable; Stat of the art

➢ **Model 3 affects Models 1 & 2**

Model 1. Outcome-based APS

Testing guides the actions of clinicians and patients;
Testing-Management-Outcomes pathway



Setting analytical performance specifications based on outcome studies – is it possible?
A R Horvath et al. Clin Chem Lab Med 2015; 53(6): 841–848

Outcome-based APS

- Reflect clinical needs
- Tailored to the purpose, role and significance of measurand in a well defined clinical pathway
- Net health benefit at reasonable costs

Challenges

ELSEVIER

Journal of the American College of Cardiology

Volume 74, Issue 16, 22 October 2019, Pages 2044-2046

Original Investigation

Editorial Comment

It Will Take More Than Better Diagnostics to Improve the Care of Women With ACS *

Allan S. Jaffe MD, Sharonne N. Hayes MD

"…simply improving diagnostic accuracy cannot remedy … outcomes. Simply put, if one does not act on the data, no diagnostic test will ever have additional worth."

Model 1a. Direct approach (Empirical studies)

- Diagnostic double-blind RCT; the most appropriate design
  - Larger sample size than treatment RCTs
  - The smaller incremental benefits, the larger size
- More feasible for tests:
  - used in well defined and standardized decisions making,
  - with short-term health outcomes

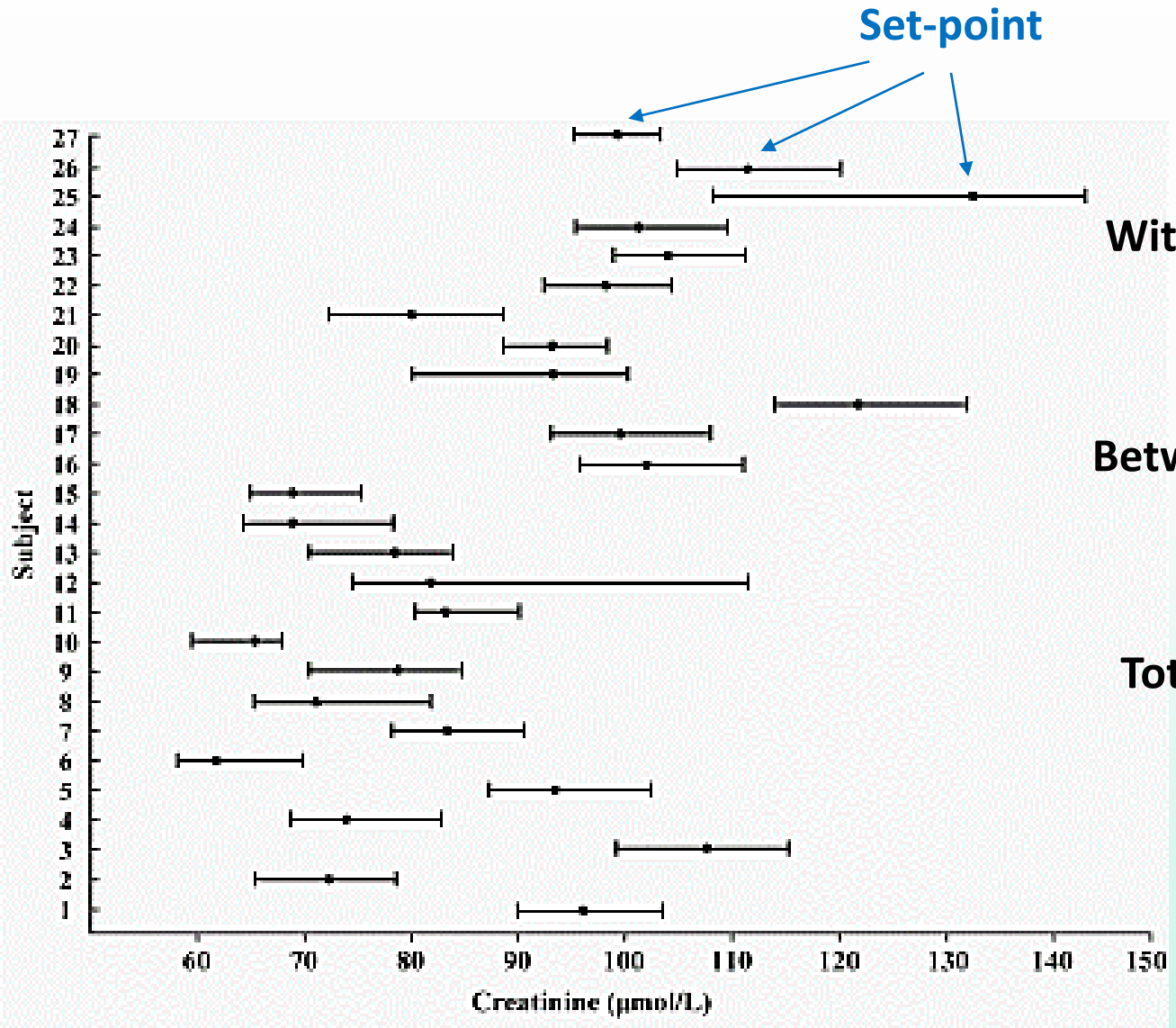
Model 1b. Indirect approach (Non-empirical)

- Investigating impact on clinical classifications/decisions; e.g. simulation or decision analysis
  - When diagnostic RCTs have already demonstrated the health outcomes
  - Commonly used to compare new vs. existing tests
  - Evidence usually from separate studies of the testing – management – outcomes pathway

Linked Evidence Approach

Model 2. BV-based APS

Reducing Analytic Noise compared to Biologic Variability



Within Subjects Variability, CVI

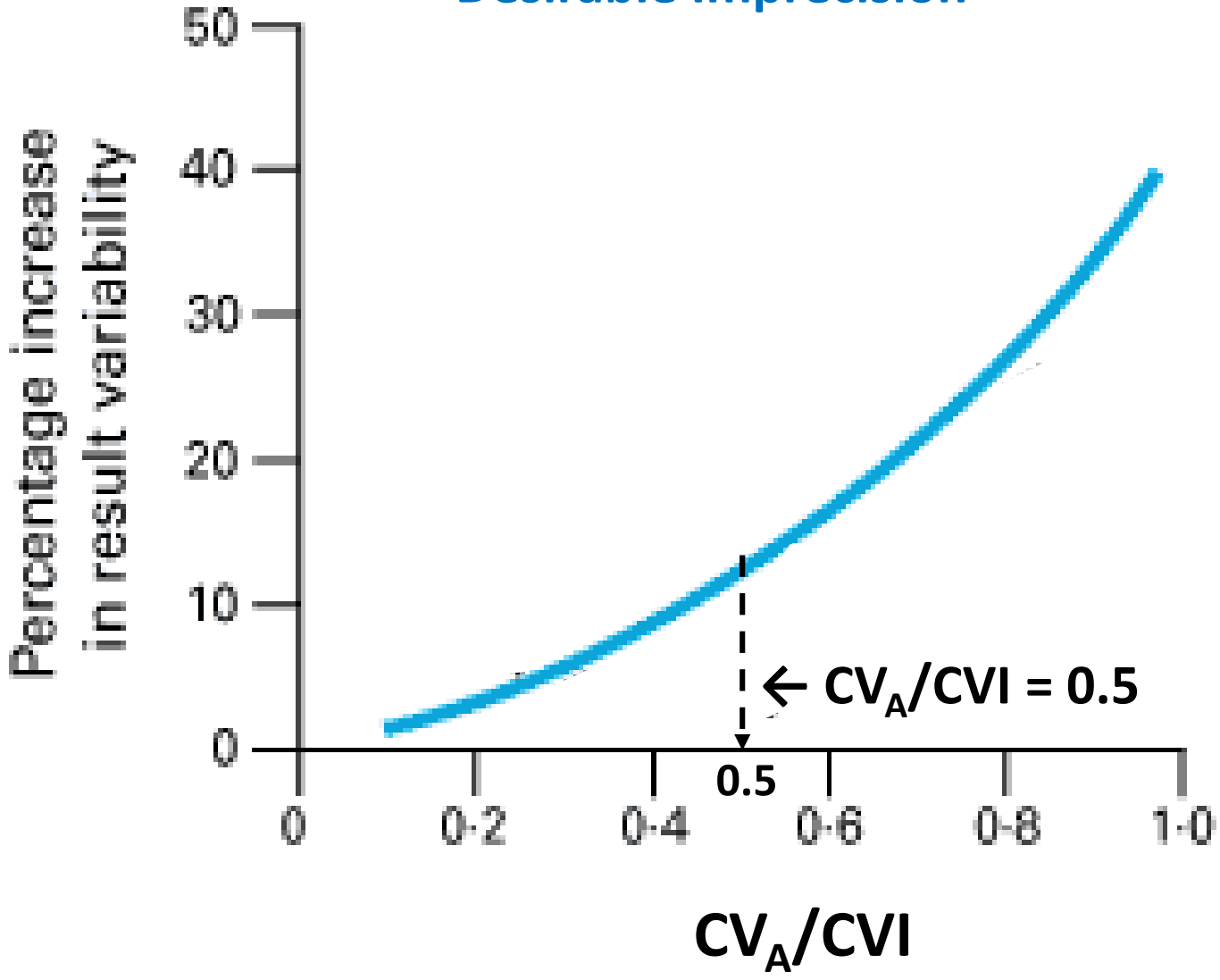
Between Subjects Variability, CVG

Total Biologic Variability

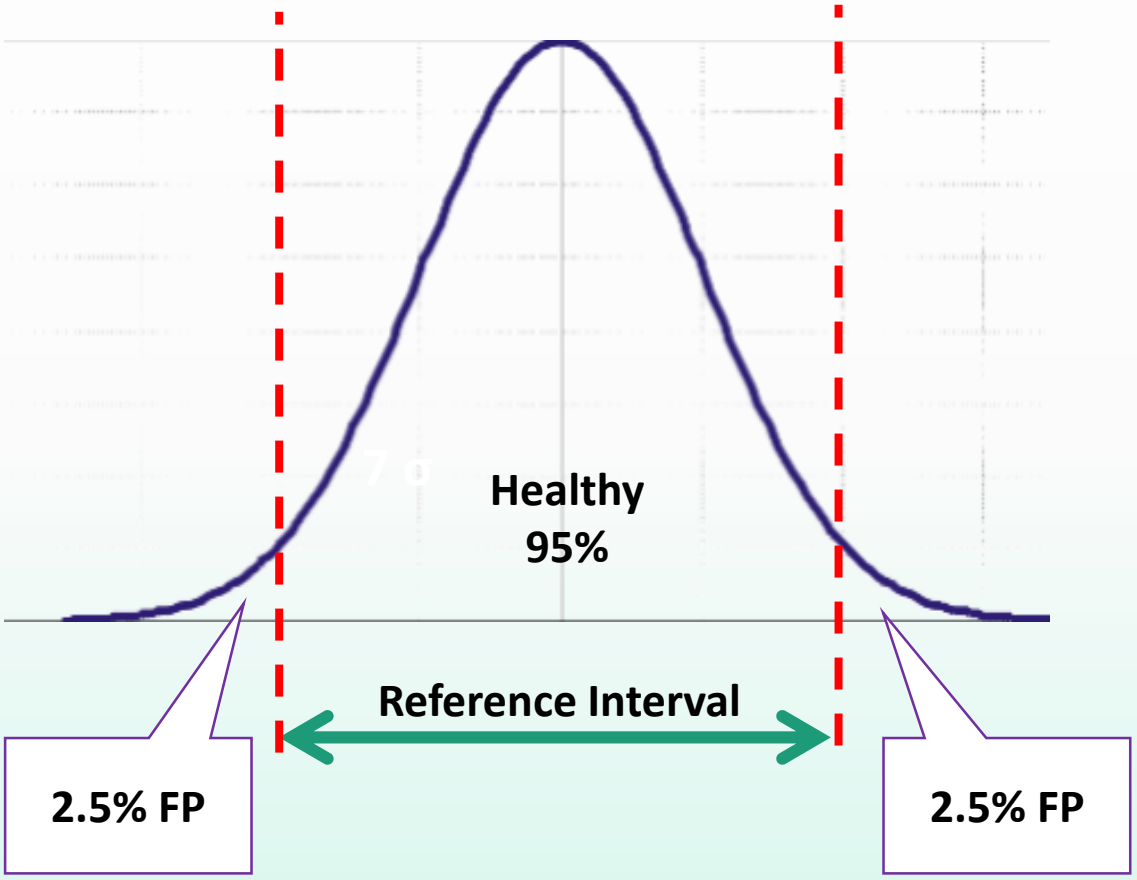
TotalBiCV

$(CvI^2 + CVG^2)^{0.5}$

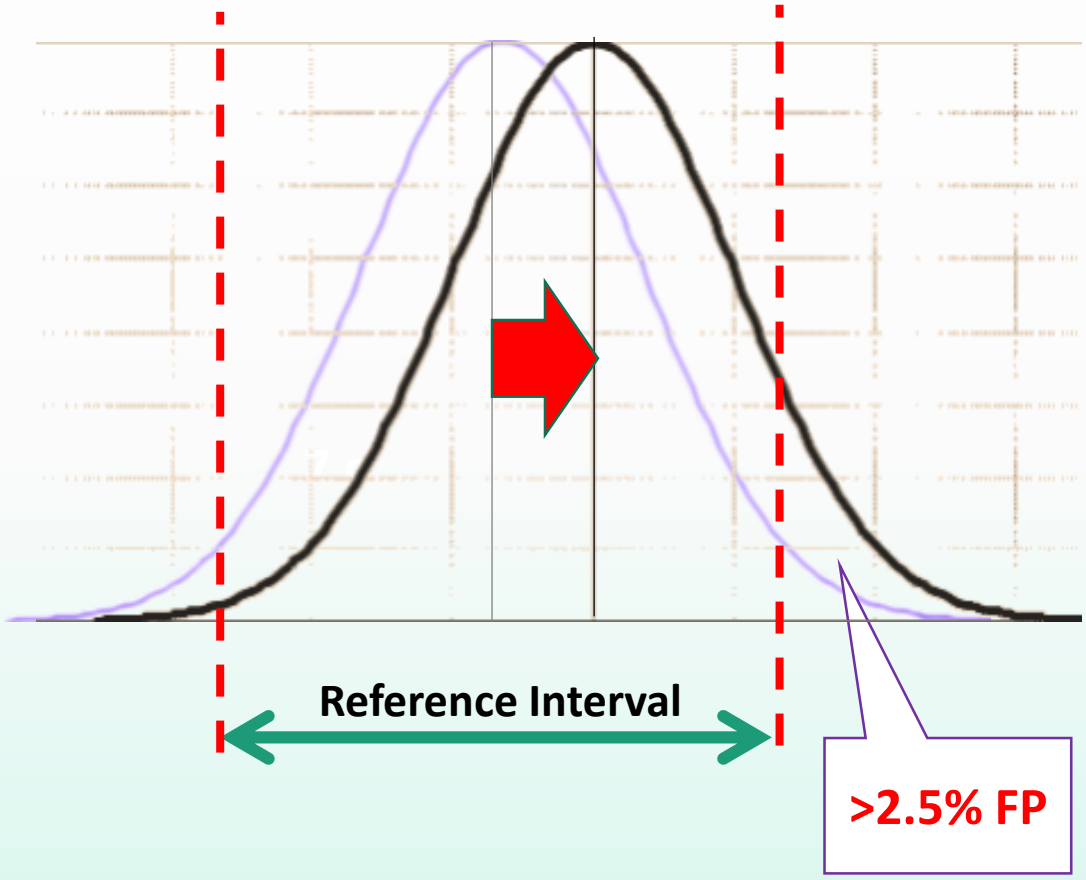
Desirable Imprecision



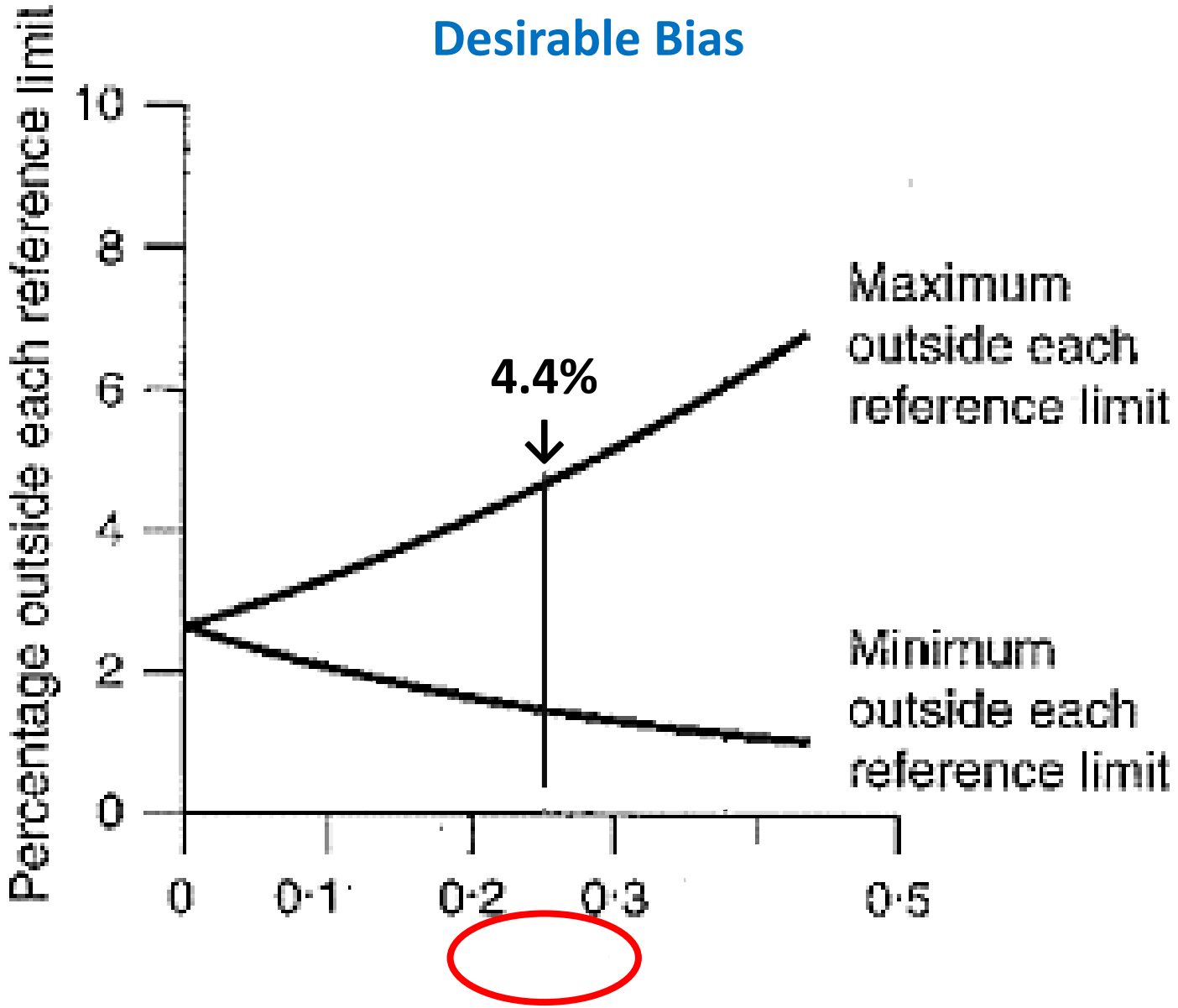
Desirable Bias



Desirable Bias



Desirable Bias



Bias/Total BiCV

$(CvI^2 + CVG^2)^{0.5}$

Desirable Biologic APS

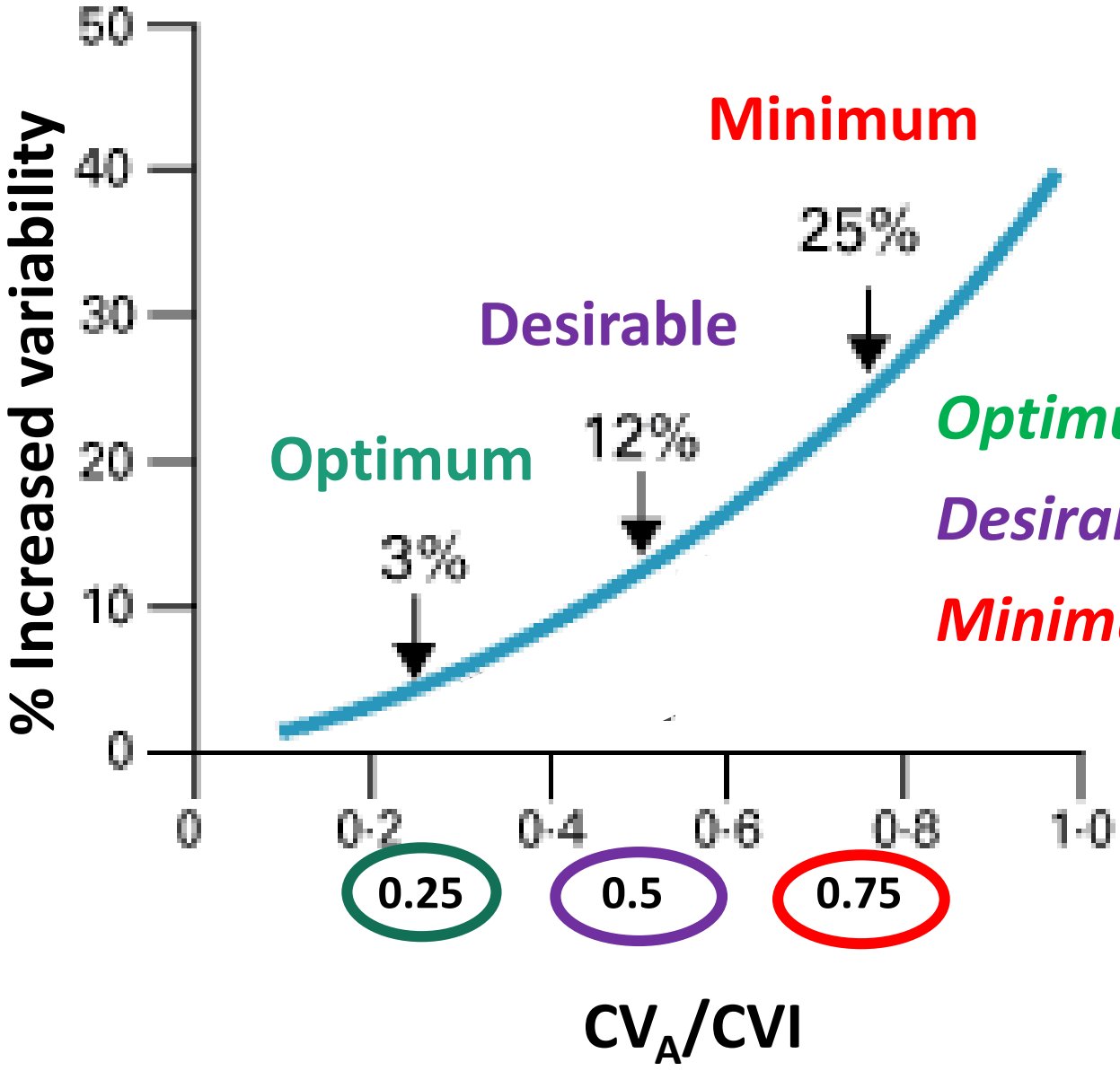
Allowable CV: $I\% = 0.5\ CVI$

Allowable Bias: $B\% = 0.25\ [CVI^2 + CVG^2]^{1/2}$

- Fraser GC, Petersen P:

For EQA: $TE_a = B\% + 1.65 \times I\%$

3 level Biologic APS; Fraser GC recommendation

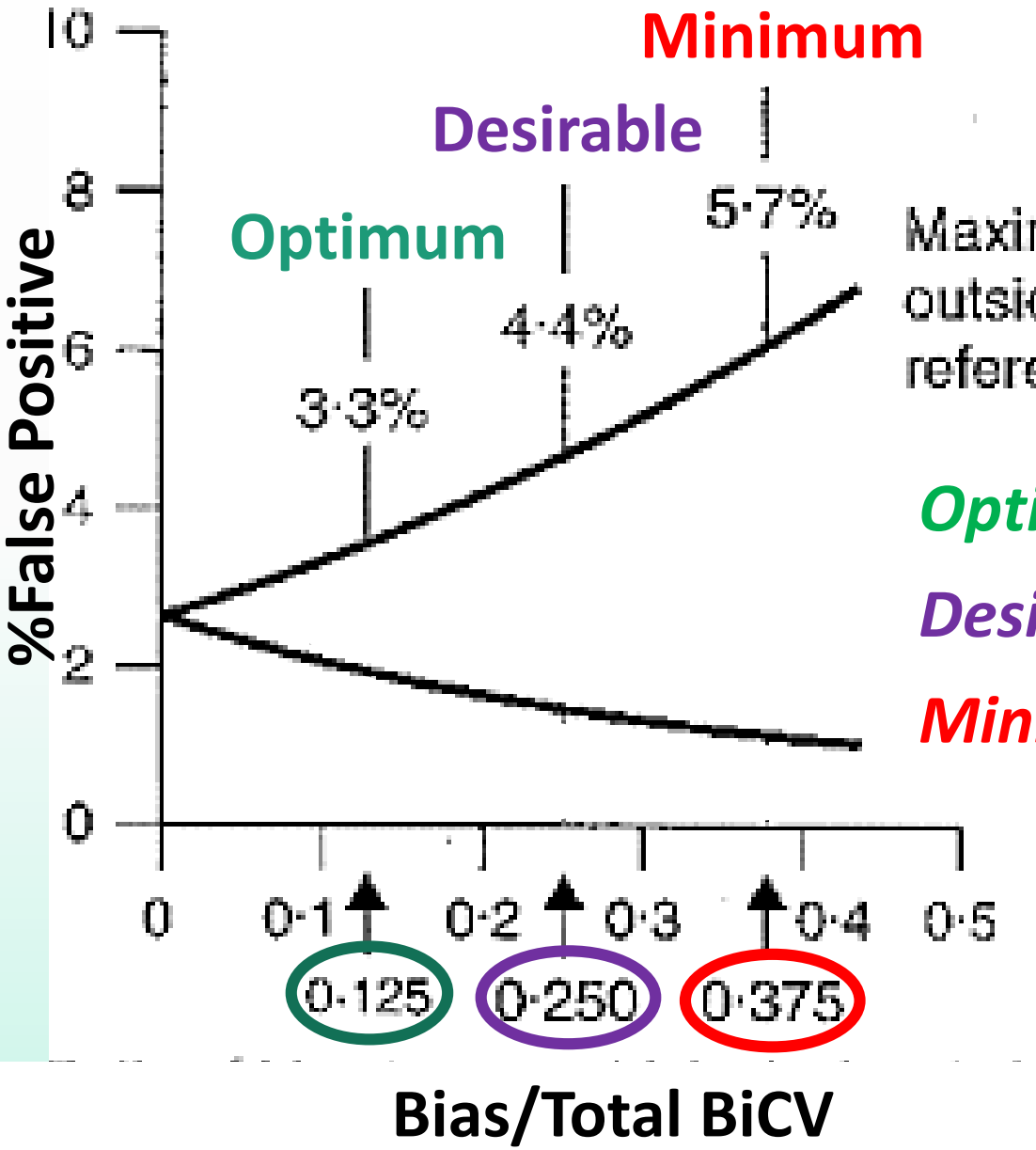


Optimum CV = 0.25 CVI

Desirable CV = 0.5 CVI

Minimum CV = 0.75 CVI

3 level Biologic APS; Fraser GC recommendation



Optimum B = 0.125 BiCVt

Desirable CV = 0.25 BiCVt

Minimum CV = 0.75 BiCVt

Model 3. State-of-the Art APS

- Highest level technically achievable
- Readily available; e.g. from EQA
- May not reflect clinical needs

Allocating analytes to Milan-2014 models

EFLM TFG-DM (2014-2016)

DE GRUYTER

Clin Chem Lab Med 2017; 55(2): 189–194

Opinion Paper

Ferruccio Ceriotti*, Pilar Fernandez-Calle, George G. Klee, Gunnar Nordin, Sverre Sandberg, Thomas Streichert, Joan-Lluis Vives-Corrons and Mauro Panteghini, on behalf of the EFLM Task and Finish Group on Allocation of laboratory tests to different models for performance specifications (TFG-DM)

Criteria for assigning laboratory measurands to models for analytical performance specifications defined in the 1st EFLM Strategic Conference

Allocating analytes to Milan-2014 models; EFLM TFG-DM

Model 1 appropriate for analytes:

- Have a central role in the decision-making of a specific disease/clinical situation
- Cutoff/decision limits are established for diagnosing/screening /monitoring
- Directly influence the management, consequently outcome
- Are Standardized/Harmonized measurands

Allocating analytes to Milan-2014 models; EFLM TFG-DM

Examples for Model 1:

- **HDL-c, LDL-c** – Central in definiation of cardiovascular risk, clearly defined thresholds, related treatment indications
- **Glucose, A1C** – Clearly defined thresholds
- **Albumin** – Measure of protein-energy nutritional status (KDIGO 2015); Quality indicator of dialysis centers (USA); Classify stage 1 MM (Int. Myel. WG); Calculation of dose and monitoring replacement therapy with human albumin
- **CRP** – Differentiate viral/bacterial infection; Establish severity of acute pancreatitis

Allocating analytes to Milan-2014 models; EFLM TFG-DM

Model 1; Examples (continued):

- **cTn** – CV<10% leads to misclassification of 1%
- **Hb** – Clearly defined thresholds for anemia, transfusion, and increased Hb
- **Platelets** – Thresholds for transfusion
- **Neutrophils** – <0.5x109/L indicative of high risk for infection
- **TSH** – Thresholds for diagnosis/treatment

Allocating analytes to Milan-2014 models; EFLM TFG-DM

Model 2 appropriate for analytes:

- Do not have a central role in the decision-making of a specific disease/clinical situation
- Have a steady state concentration
- Best achieved for measurands under strict homeostatic control

Allocating analytes to Milan-2014 models; EFLM TFG-DM

Examples for Model 2:

- **Electrolytes & Minerals** – Strictly controlled by hormones and other functions
- **Creatinine, Urea, Cystatin C** – Controlled by Kidney function
- **Urate** – Kidney compensates for endogenous production/dietary intake
- **Total Protein** – Long half-life and body water control
- **RBC count, HCT, MCV**
- **Hb** (for monitoring)
- **PT, PTT**

Allocating analytes to Milan-2014 models; EFLM TFG-DM

Model 3 appropriate for analytes:

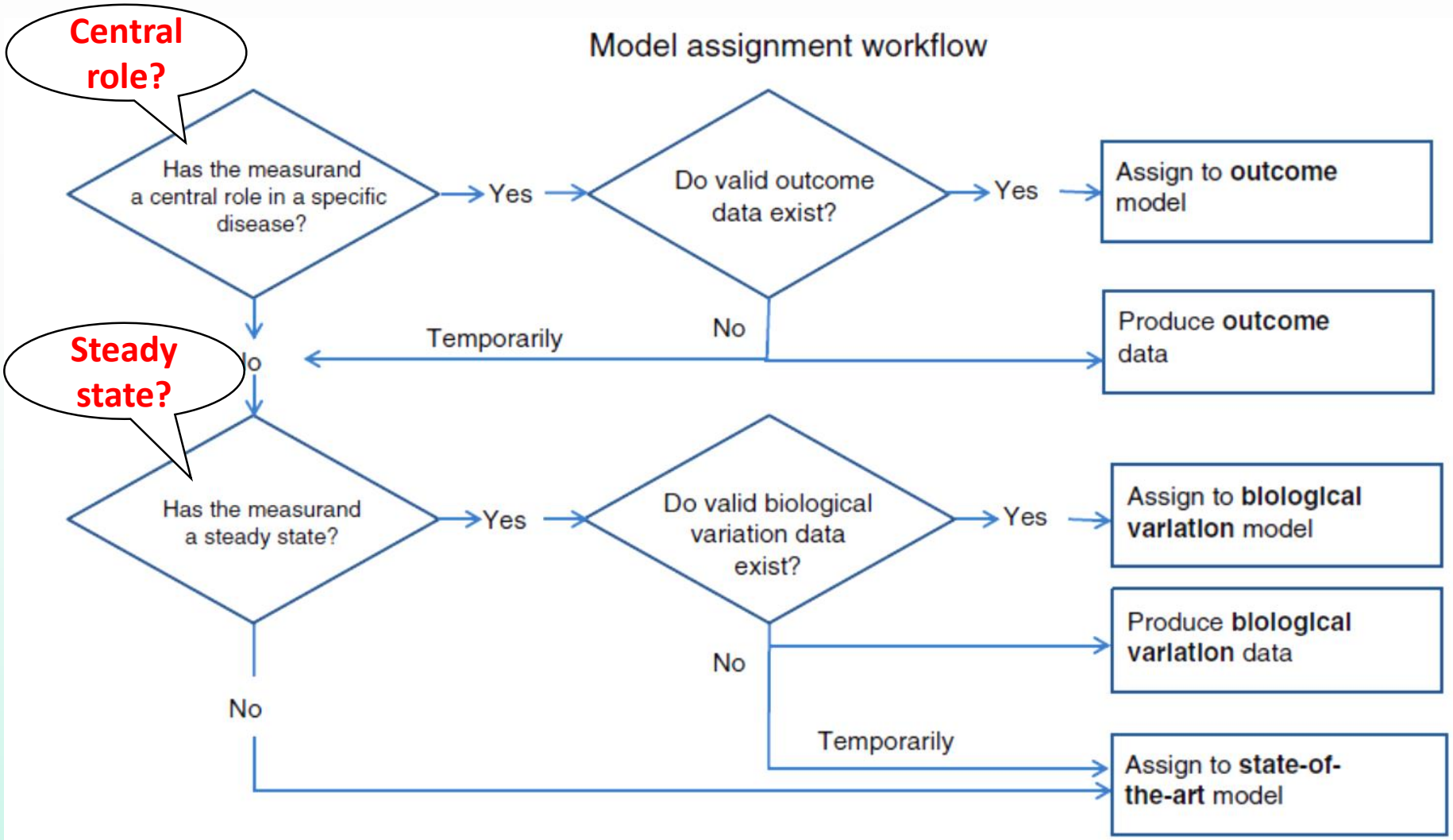
- Waiting for studies on Outcome/BV data; Temporary

- Models 1 & 2 are not applicable;

  Example:

  Many urinary measurands, e.g. Na, K, Ca, Mg, i-Ph, Cr, Urea, Urate

Allocating analytes to Milan-2014 models; EFLM TFG-DM



Need TEa?

- Addresses accuracy

Toward a Framework for Outcome-Based Analytical Performance Specifications: A Methodology Review of Indirect Methods for Evaluating the Impact of Measurement Uncertainty on Clinical Outcomes

June 2019 · Clinical Chemistry
DOI: 10.1373/clinchem.2018.300954

Alison F. Smith, Bethany Shinkins, Peter S. Hall, Claire T. Hulme, Mike P. Messenger

*"Common framework: The impact of discrepancy between **true** test value and **measured** test value"*

Need TEa?

- Addresses accuracy
- Necessary for IQC

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- Necessary for IQC
- Necessary for Sigma calculation

$$\mathbf{SM = \frac{TEa - |Bias|}{SD}}$$

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- A simple tool to allow rapid, standardized assessment of EQAP results

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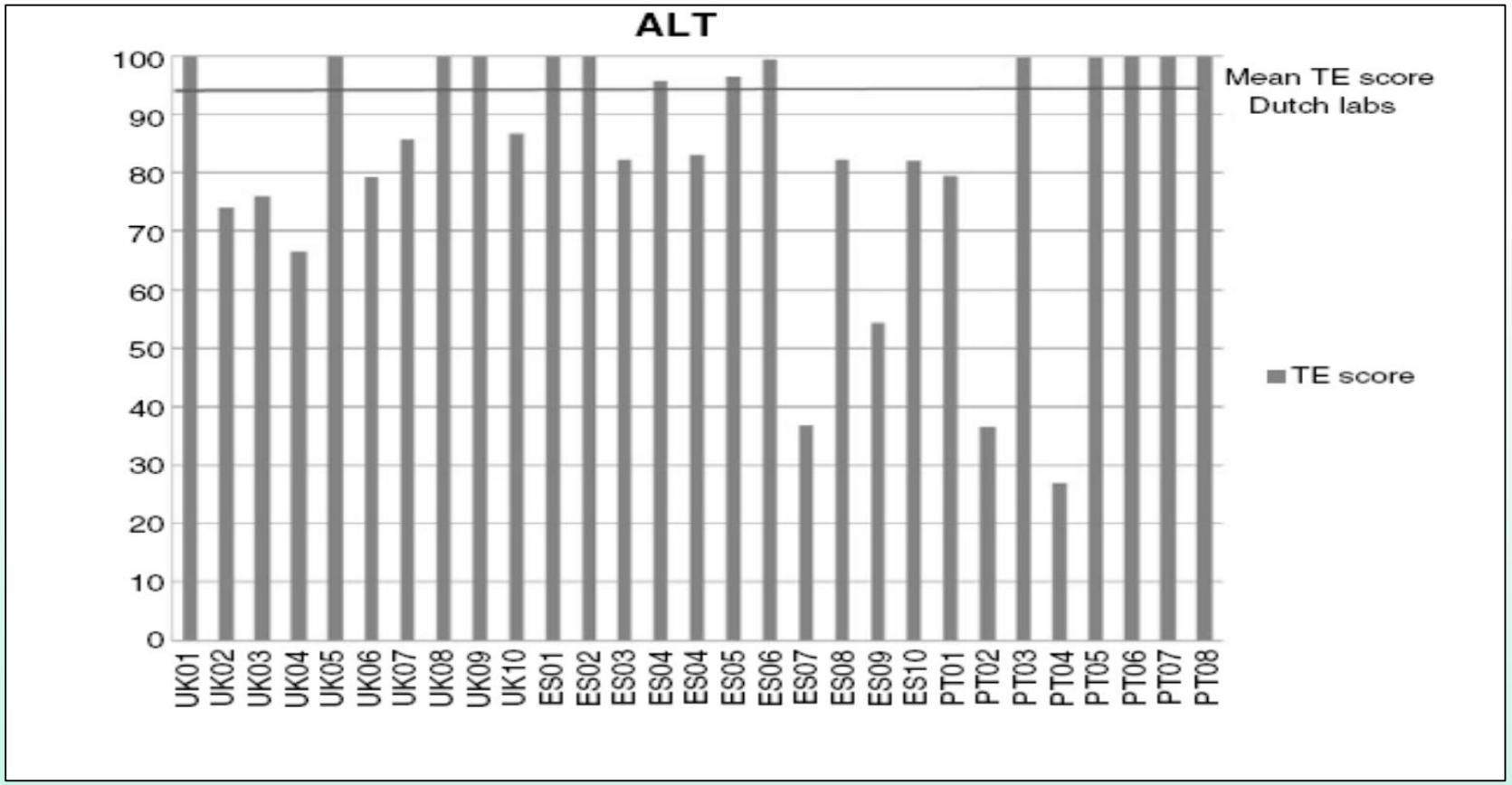
Need TEa?

Prof. J. Westgard: "Like or not, we need TE model."

- Addresses accuracy
- Necessary for IQC
- Necessary for Sigma calculation
- A simple tool to allow rapid, standardized assessment of EQAP results
- If TEa is met, a common RI can be shared

Communicating APS to other stakeholders

- Clinicians think the analytical quality is very good!
- Clinical guidelines take standardization for granted



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Laboratory experts must participate:

- In writing clinical guidelines
- Exchange information with diagnostic industry and the users of lab services


Thank you