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APFCB WEBINAR

MEASUREMENT UNCERTAINTY

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Melbourne Pathology.

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OUTLINE

1. What is MU?

2. How is MU estimated?

3. How can MU be reported?

4. What is the clinical value of MU?

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Sources

- References
  - VIM (Vocabulary) 1989 / ‘04
  - GUM (UM Guide) 1995 / ’04
- Standards
  - ISO 17025 (Lab Standards) 1999
  - ISO 15189 (Medical Labs) 2008

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ISO GUM 1995

(Guide to the expression of Uncertainty of Measurement)

- CIPM Comm Int des Pods et Mesures '77–'81
- BIPM Int Bur Weights and Measures
- IEC Int Electrochemical Comm
- IFCC International Federation of Clinical Chemistry
- ISO Int Org Standardisation
- IUPAC Int Union Pure Appl Chemistry
- IUPAP Int Union Pure Appl Physics
- OIML Int Org Legal Metrology

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What is MU?

"More decisive? How can I be more decisive?
- I live by the uncertainty principle!"

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The term 'uncertainty'

- the word uncertainty means doubt about the validity of a result.
- MU will also be used for quantitative measures of the concept.
  - GUM 2.2.1

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VIM (*International Vocabulary of Basic and General Terms in Metrology)*

- 2.11 (3.9)
  - measurement uncertainty
  - uncertainty of measurement
  - uncertainty
- parameter that characterizes the dispersion of the quantity values that are being attributed to a measurand, based on the information used

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Other terms:

- The *error* in a sample measurement
  - Result – True value.
  - This is not known because:

- The *true value* for the sample
  - This is not known

GUM 2.2.4

    - eg Na = 134 135 136 137 138 mmol/L

  - *The result is only an estimate of a true value and only complete when accompanied by a statement of uncertainty.*

GUM 3.2.1

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Types of Error

- Random error **GUM 3.2.2**
  - Cannot be eliminated, only reduced.
  - Unpredictable temporal and spatial variations
- Systematic error **GUM 3.2.3**
  - Cannot be eliminated, only reduced.
  - Can be quantified
    - If significant in size relative to required accuracy, a correction factor can be applied to compensate
    - Then it is assumed that systematic error is zero.
- *It is assumed that the result of a measurement has been corrected for all recognised significant systematic effects*

GUM 3.2.4

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LFT's Female DOB 30/1/1934

Date	29/01	28/04	14/05	02/07	Units	Range
S BILI	38	29	27	34	umol/L	(2-20)
S ALP	234	192	206	193	U/L	(30-120)
S GGT	93	83	87	74	U/L	(5-45)
S ALT	124	137	113	103	U/L	(5-40)
S AST	187	202	167	166	U/L	(5-40)

Some clinicians (and patients) believe that the results from laboratory assays have little of no uncertainty.

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Introduction to GUM

- When reporting the result of a measurement of a physical quantity, it is obligatory that some quantitative indication of the quality of the result be given so that those who use it can assess its reliability.

GUM 0.1

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ISO/IEC DIS 17025

- 5.4.7.2
  - apply procedures to estimate uncertainty or measurement

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How is MU estimated?

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ISO 17025 - 1999

- 5.4.6.2 Testing laboratories shall have and shall apply *procedures* for estimating uncertainty of measurement.

- *The degree of rigor* needed in an estimation of uncertainty of measurement depends on factors such as:
  - the requirements of the test method;
  - the requirements of the client;
  - the existence of narrow limits on which decisions on conformance to a specification are based.

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ISO 15189 – 2003(E)

- 5.6.2
  - The laboratory shall determine the uncertainty of results, where relevant and possible.

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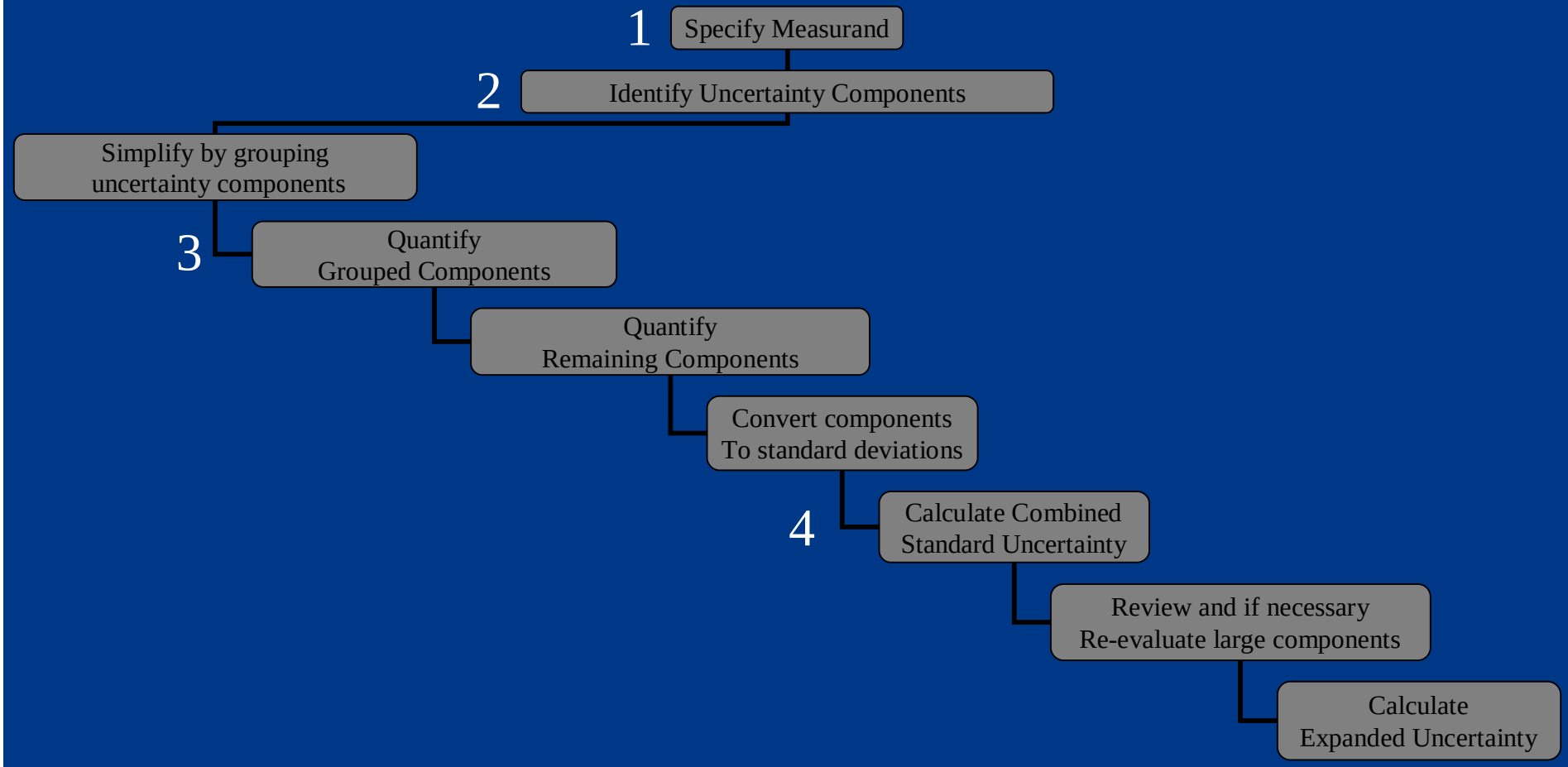
Eurachem / Citac Guide CG 4



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Estimating MU

1. Define the Measurand.

2. Identify all Sources of Uncertainty.

3. Quantify the Individual Uncertainties.

4. Calculate Combined Uncertainty

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Define the Measurand

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The measurand?

- This guide is primarily concerned with the expression of uncertainty in the measurement of a well defined physical quantity – *the measurand* – that can be characterised by an essentially unique value.

GUM 1.2

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The Measurand.

- The measurement should have one unique value:
  - Testosterone
    - Reference method (GCMS) value
  - ALT
    - Reference method (IFCC) value
  - PSA
    - No Reference method.
    - Multiple potential PSA method values.
    - Unique method specific PSA value
      - Measurand = 'PSA as measured by Abbott Architect Assay'
  - New Definition
    - The measurand is what is intended to be measured

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Identify all Sources of Uncertainty

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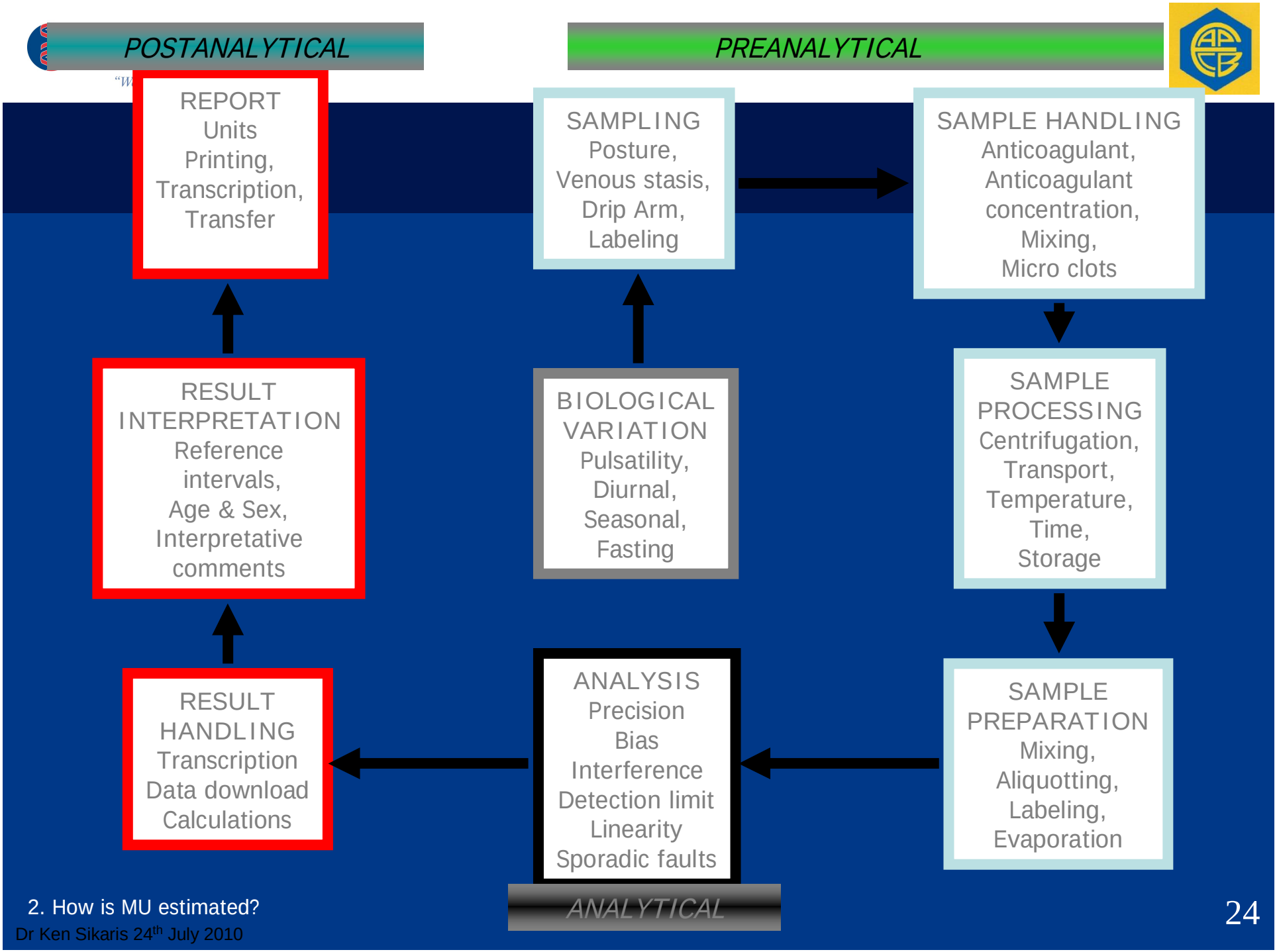
ISO 15189 – 2003(E)

- 5.6.2
- *Sources that contribute to uncertainty may include*
  - *sampling,*
  - *sample preparation,*
  - *sample portion selection,*
  - *condition of the sample*
  - *calibrators,*
  - *reference materials,*
  - *input quantities,*
  - *equipment used,*
  - *changes of operator,*
  - *environmental conditions*


POSTANALYTICAL
PREANALYTICAL
REPORT
Units
Printing,
Transcription,
Transfer
SAMPLING
Posture,
Venous stasis,
Drip Arm,
Labeling
SAMPLE HANDLING
Anticoagulant,
Anticoagulant
concentration,
Mixing,
Micro clots
RESULT
INTERPRETATION
Reference
intervals,
Age & Sex,
Interpretative
comments
BIOLOGICAL
VARIATION
Pulsatility,
Diurnal,
Seasonal,
Fasting
SAMPLE
PROCESSING
Centrifugation,
Transport,
Temperature,
Time,
Storage
RESULT
HANDLING
Transcription
Data download
Calculations
ANALYSIS
Precision
Bias
Interference
Detection limit
Linearity
Sporadic faults
SAMPLE
PREPARATION
Mixing,
Aliquotting,
Labeling,
Evaporation
ANALYTICAL

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General Approach ?

- Pre-analytical
  - Change laboratory habits and not to expand the uncertainty estimate.
- Post-analytical
  - Risk management procedures or failure rates and should be dealt with by general quality management policies.

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ISO 15189 – 2003(E)

- 5.8.3
  - Comments (e.g. quality or adequacy of primary sample which may have compromised the result..)
- 5.8.5
  - *The report shall indicate if the quality of the primary sample received was unsuitable for examination or could have compromised the result*

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GUM 3.4.7 - Blunders

- Blunders in recording or analysing data can introduce significant unknown errors in the result of a measurement.
- Large blunders can usually be identified by a proper review of data,
- Small ones could be masked by, or even appear as, random variations.
  - *Measures of uncertainty are not intended to account for such mistakes.*

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ISO/IEC DIS 17025

- 5.4.7.2
  - attempt to identify all the components of uncertainty
- 5.4.7.3
  - All uncertainty components which are of importance shall be taken into account
    - Components include reference materials, methods, equipment, environment, sample condition.

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Sources of Uncertainty

Inputs

- Calibration
  - Pipette imprecision
  - Standard curve confidence (S_{yx})
- Sample
  - Pipette imprecision
  - Evaporation
- Reagents
  - Lot to lot variation
  - Mixing
  - Water quality

Analysis

- Analyst
  - Novice/Experienced
- Environment
  - Temperature/Atm pressure
- Analyser
  - Maintenance/cleaning
- Product detector
  - Spectrophotometer
    - Calibration
  - Scintillation counter

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Quantify the individual uncertainties

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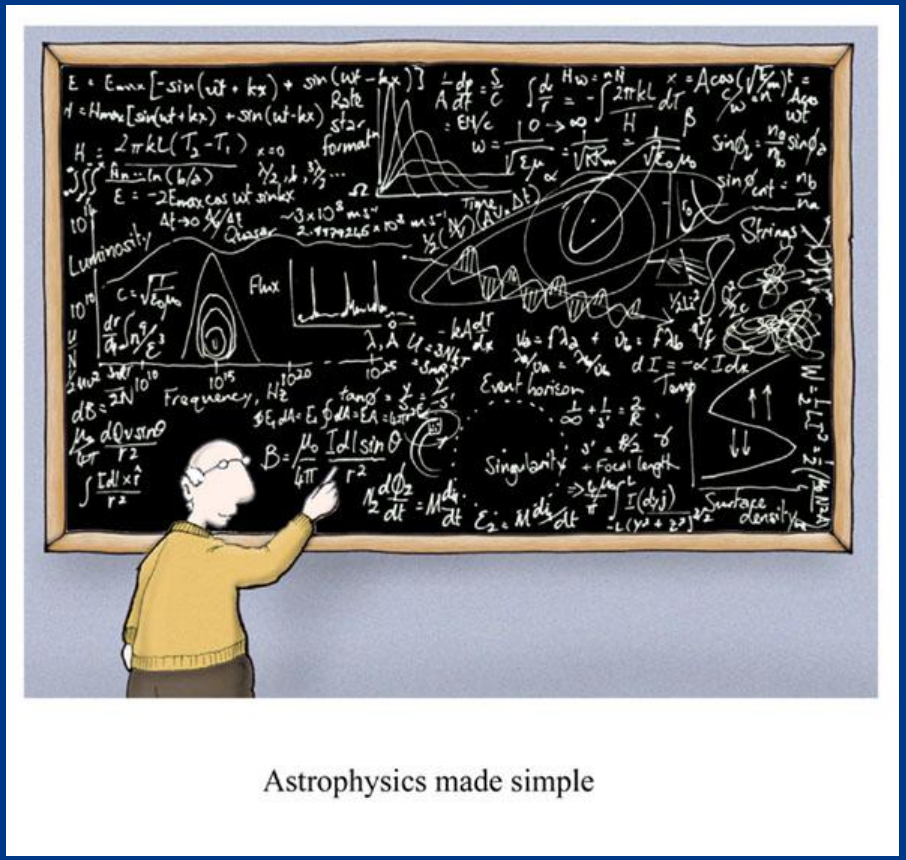
**** Warning ****



**** Statistical Exposure Ahead ****

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The mean

$$\bar{q} = \frac{1}{n} \sum_{k=1}^{n} q_k$$

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The variance

$$s^2(q_k) = \frac{1}{n-1} \sum_{k=1}^{n} (q_k - \bar{q})^2$$

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The standard deviation

$$s(q_k) = \sqrt{\frac{1}{n-1}\sum_{k=1}^{n}(q_k - \bar{q})^2}$$

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Two Categories of Uncertainty

- Category A.
  - Those which are evaluated by statistical methods
    - s_i^2 = Estimated variances

- Category B.
  - Those which are evaluated by other means –
    - u_i^2 Approximations of assumed variances

  - GUM 0.7

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Practical considerations

- If all of the quantities on which the result of a measurement a varied, its uncertainty can be evaluated by statistical means.

- However ***because this is rarely possible in practice due to limited time and resources***, the uncertainty of a measurement result is usually evaluated using a mathematical model of the measurement and the law of propagation of uncertainty.

GUM 3.4.1

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Type B evaluation

- Previously measured data.
- Experience with or general knowledge of the behavior and properties of relevant materials and instruments.
- Manufacturers specifications.
- Data provided in calibration and other certificates.
- Uncertainties assigned to reference data taken from handbooks.

GUM 4.3.1

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Type B & components

- In many cases little or no information is provided about the individual components from which the quoted uncertainty has been obtained.

- This is generally unimportant .. since all standard uncertainties are treated in the same way when the combined standard uncertainty is calculated.

GUM 4.3.3

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Which is better Category A or B?

- It should be recognised that a ***Type B evaluation of a standard uncertainty can be as reliable as a Type A evaluation***, especially in a measurement situation where a Type A evaluation is based on a comparatively small number of statistically independent observation.

GUM 4.3.2

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How many data points? GUM Table E1

n	Percent Increase in Uncertainty
2	76%
3	52%
4	42%
5	36%
10	24%
20	16%
30	13%
50	10%

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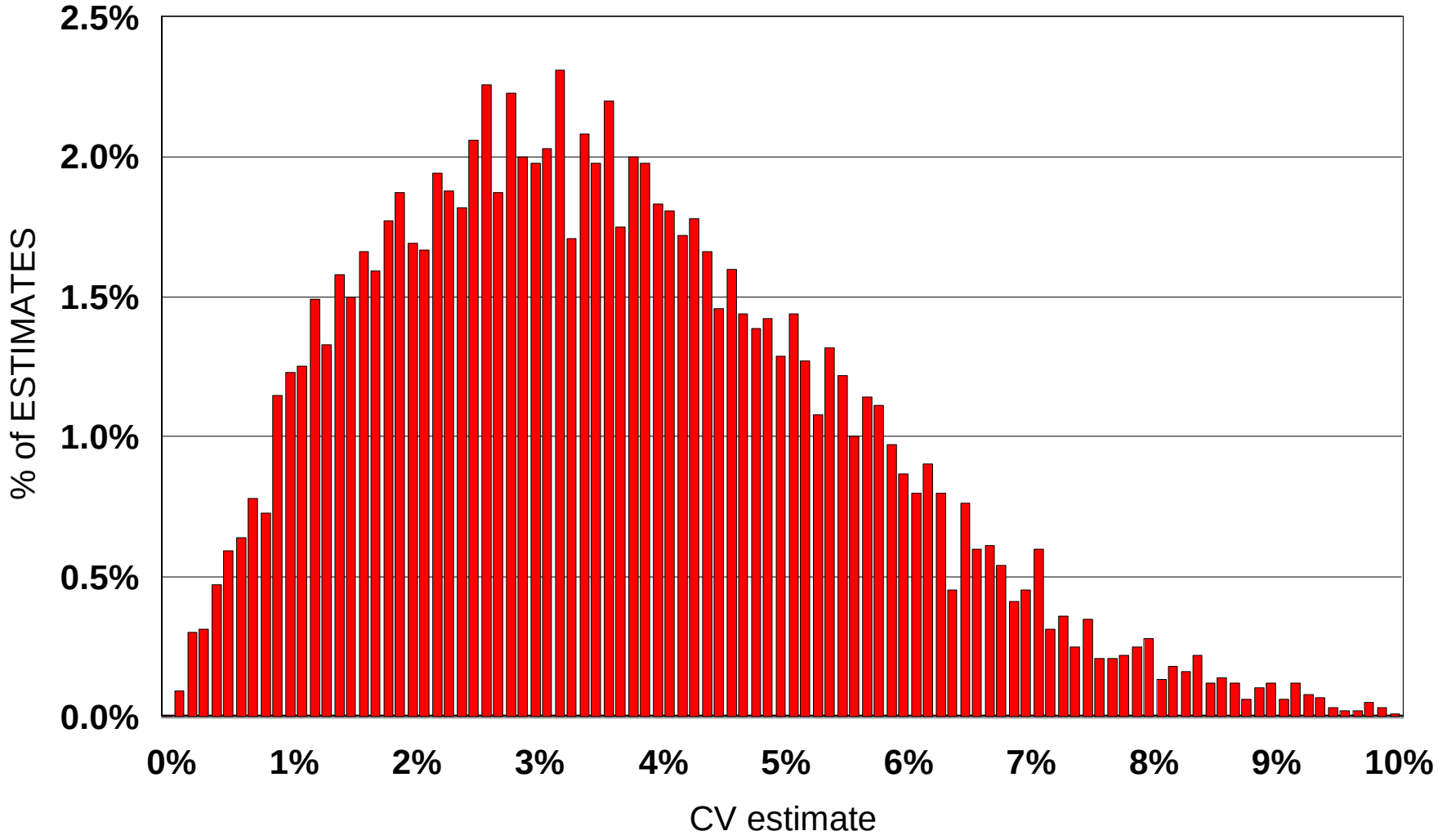
CV = 5% : Estimates using n=3



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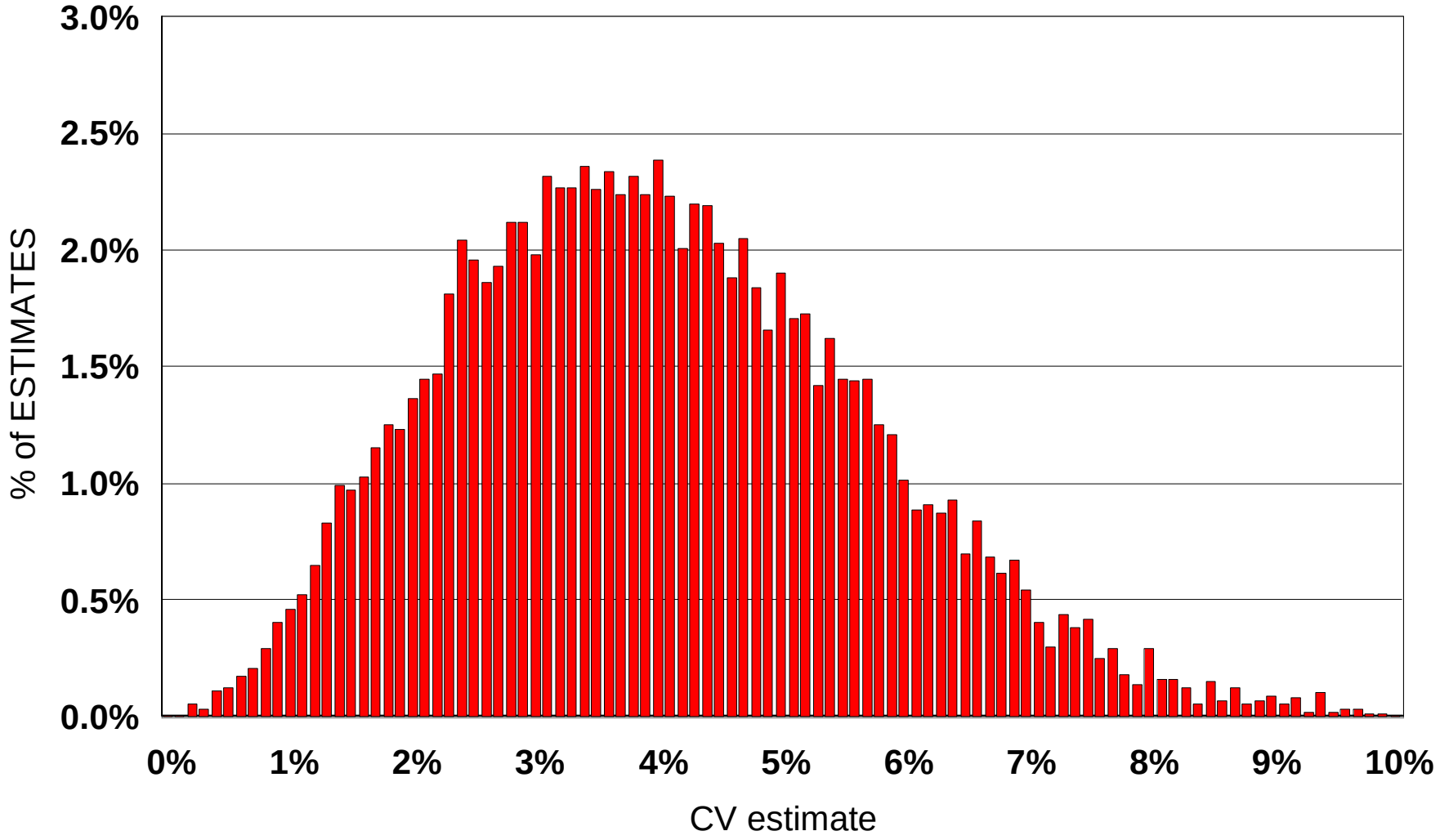
CV = 5% : Estimates using n=4



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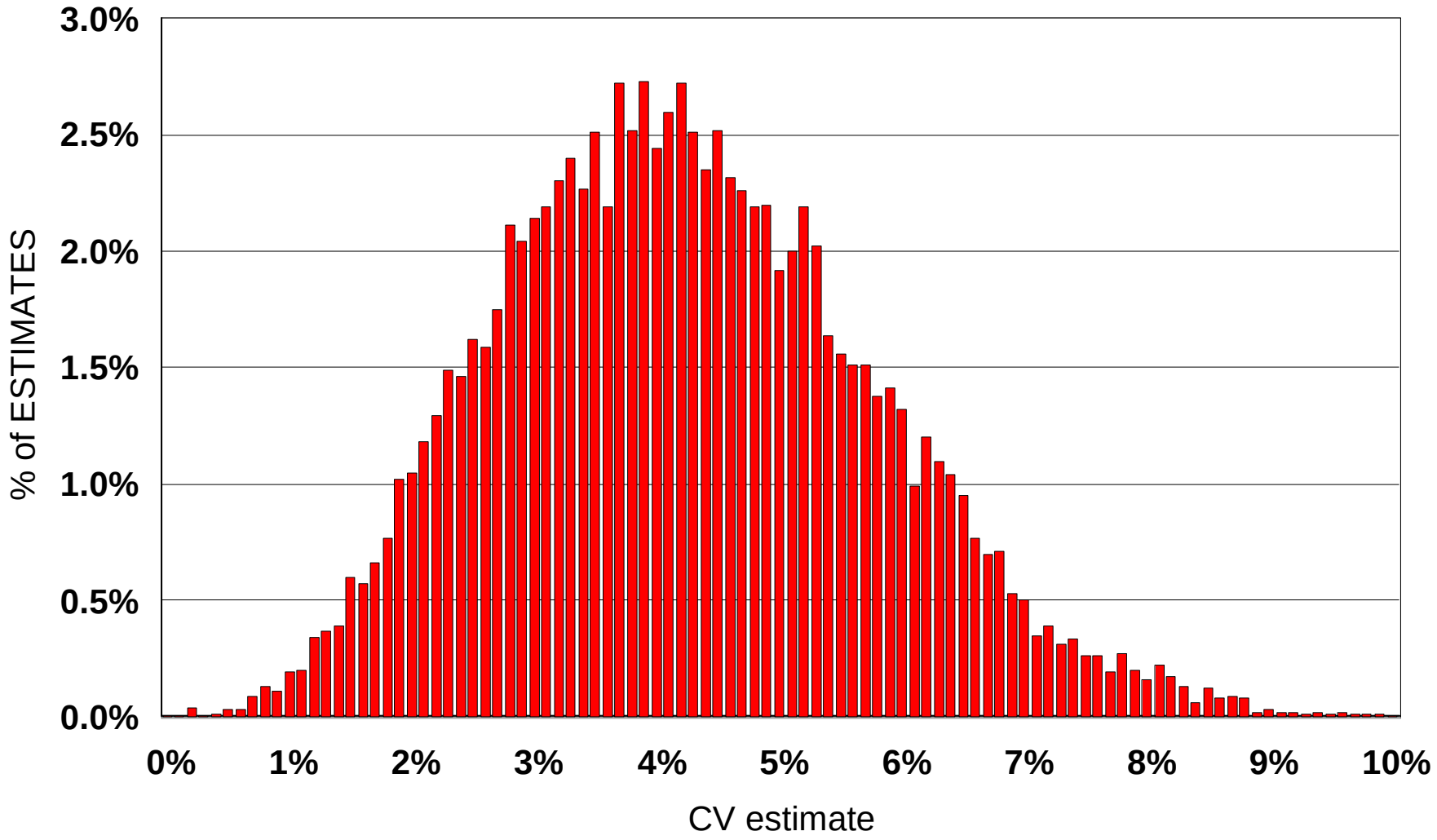
CV = 5% : Estimates using n=5



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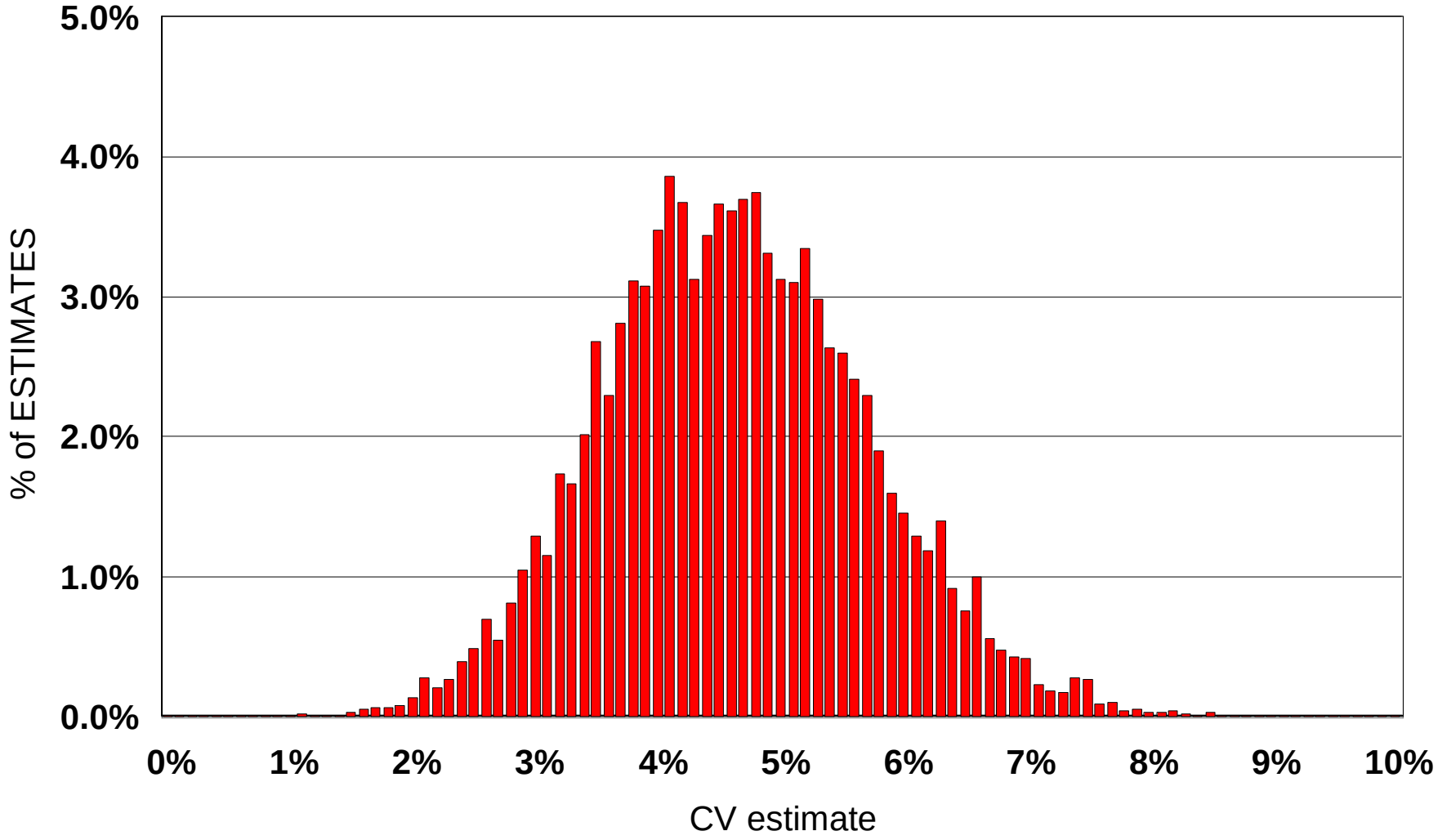
CV = 5% : Estimates using n=10



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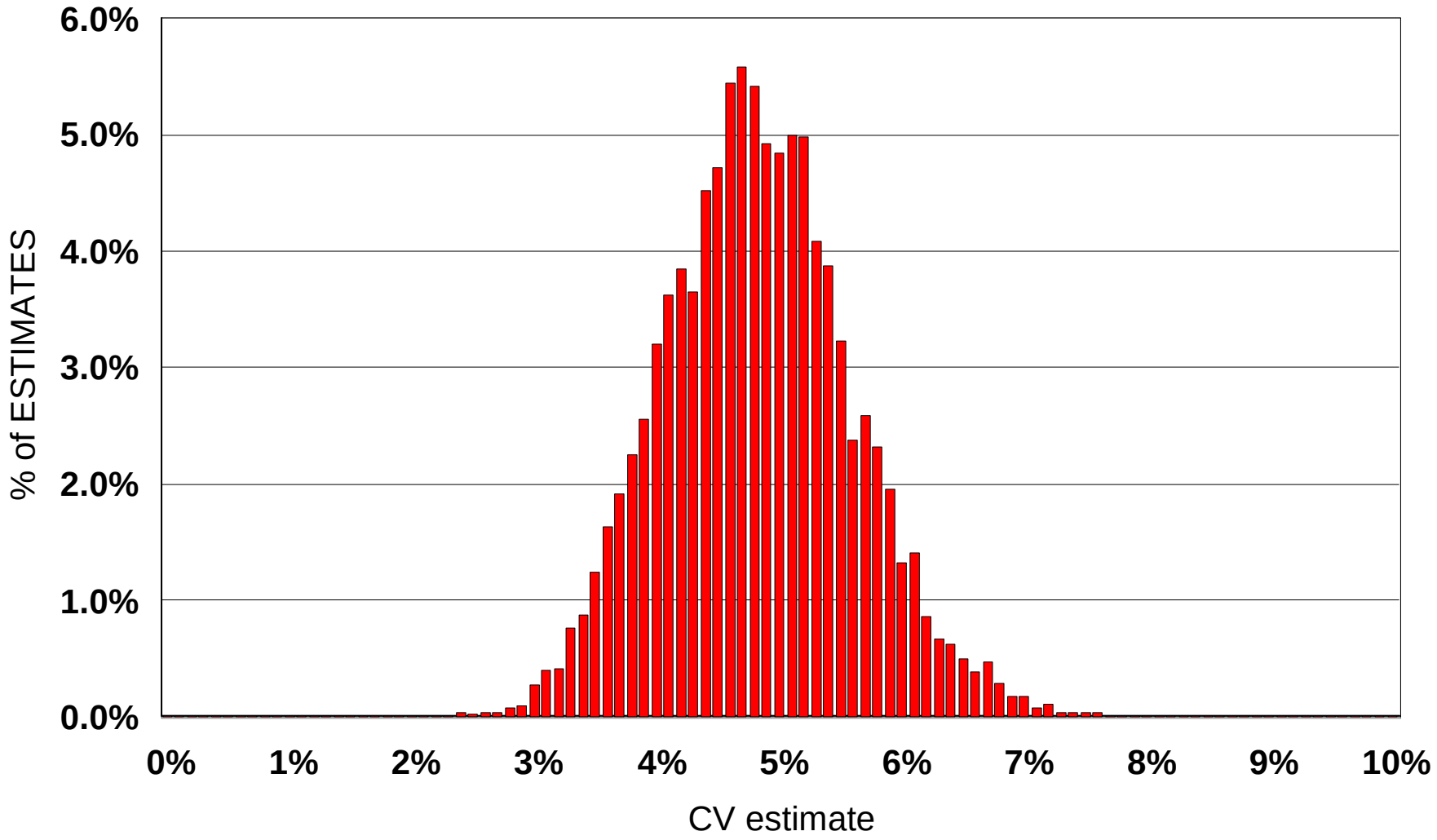
CV = 5% : Estimates using n=20



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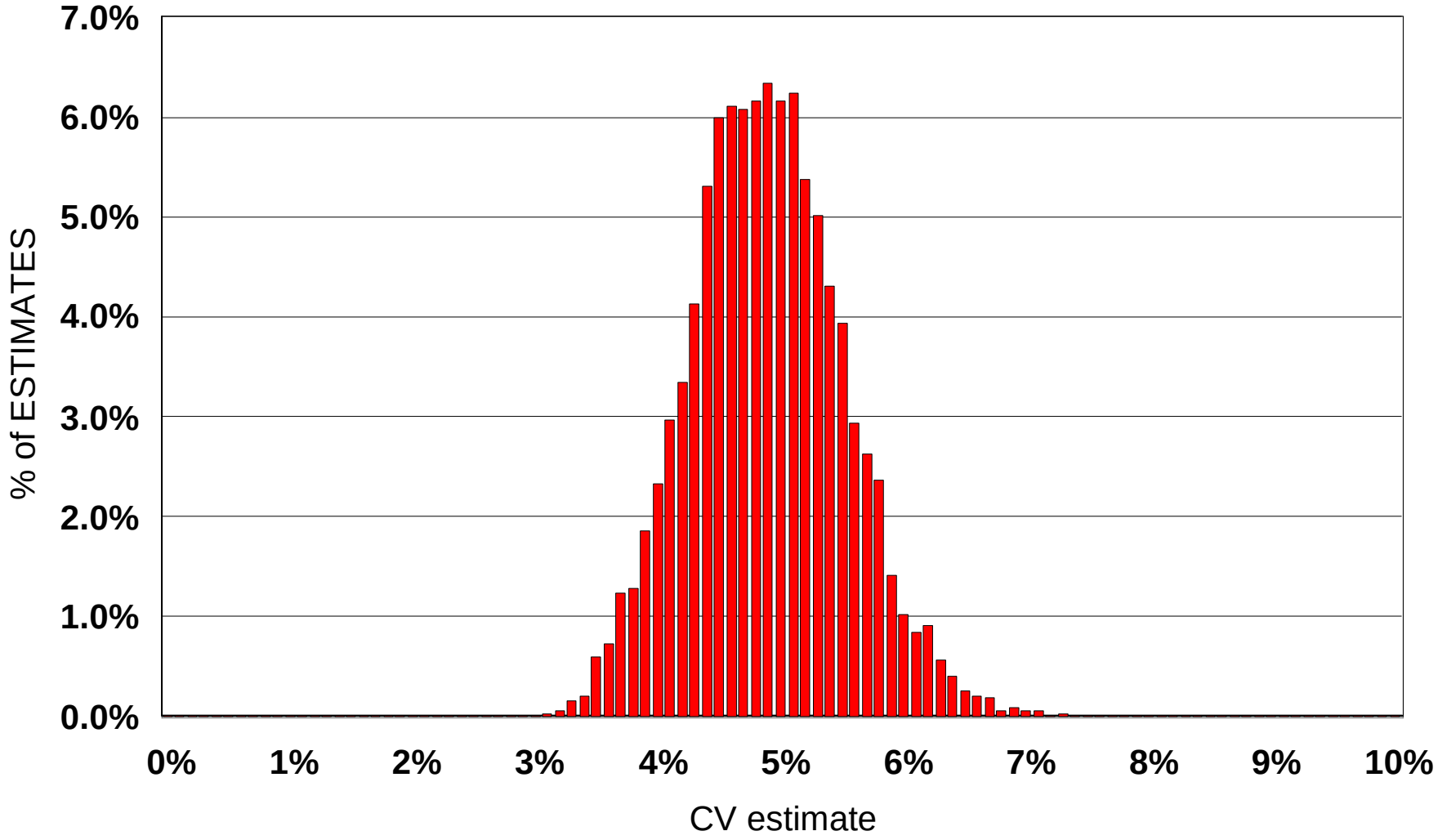
CV = 5% : Estimates using n=30



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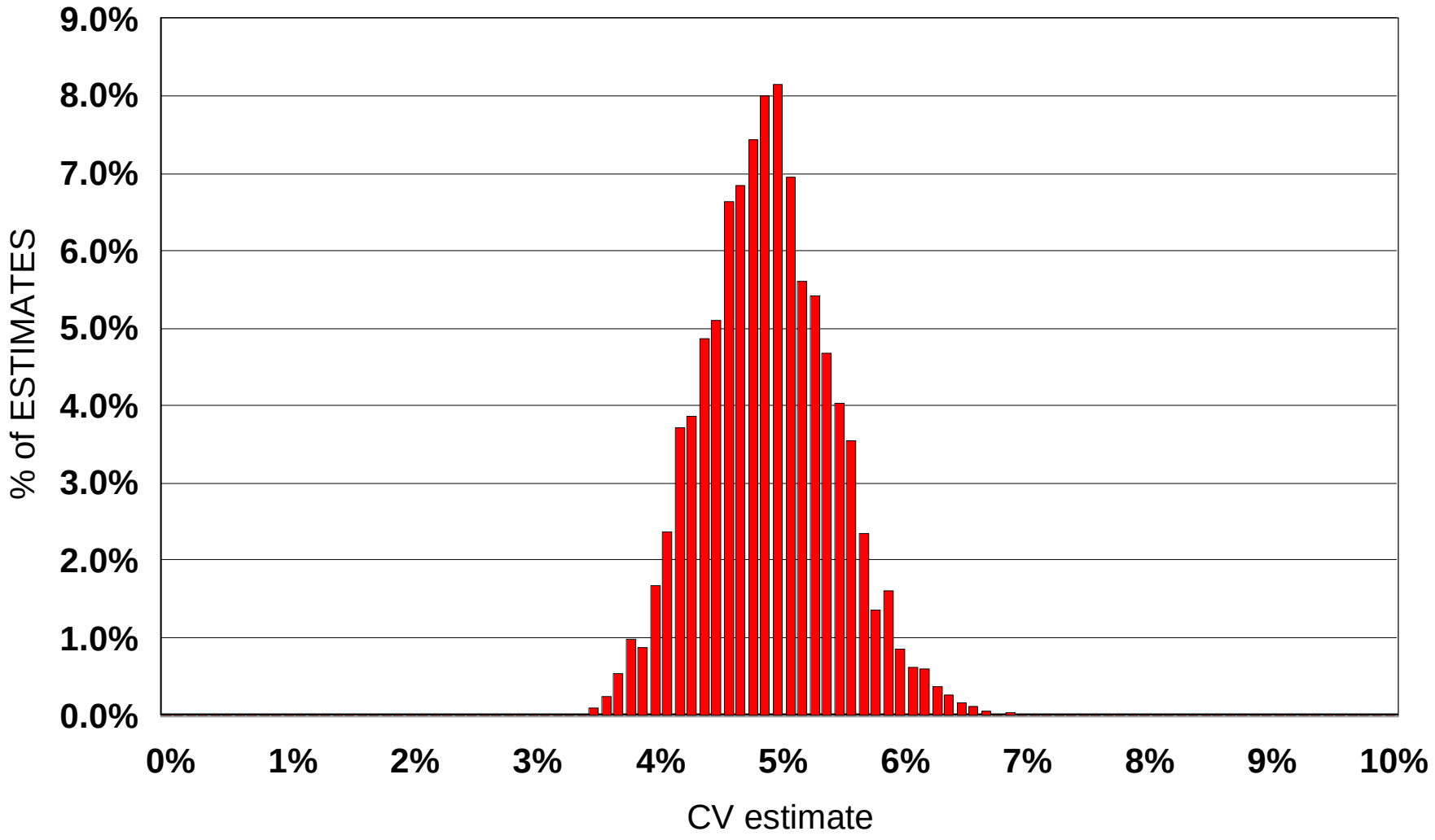
CV = 5% : Estimates using n=40



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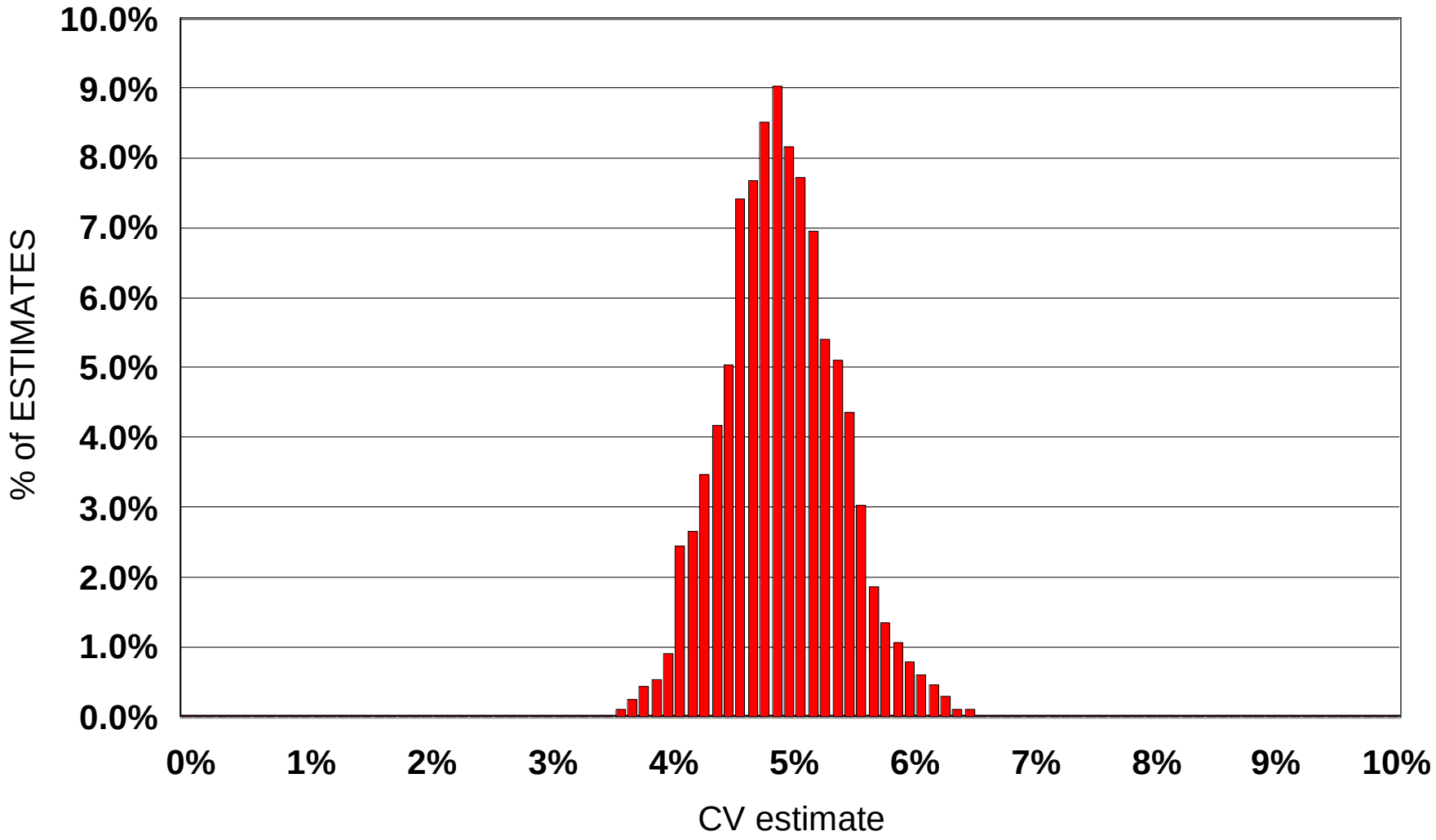
CV = 5% : Estimates using n=50



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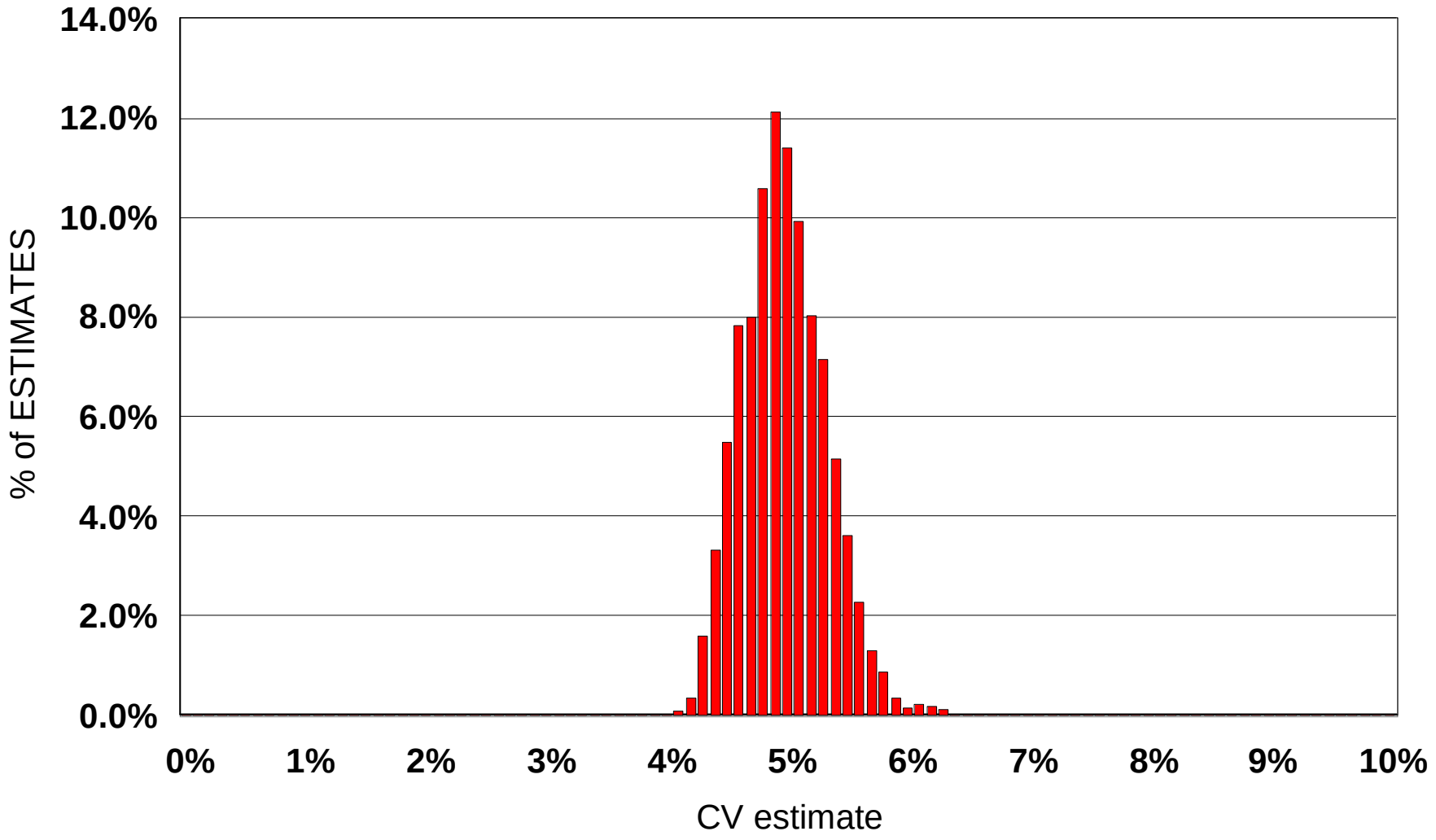
CV = 5% : Estimates using n=100



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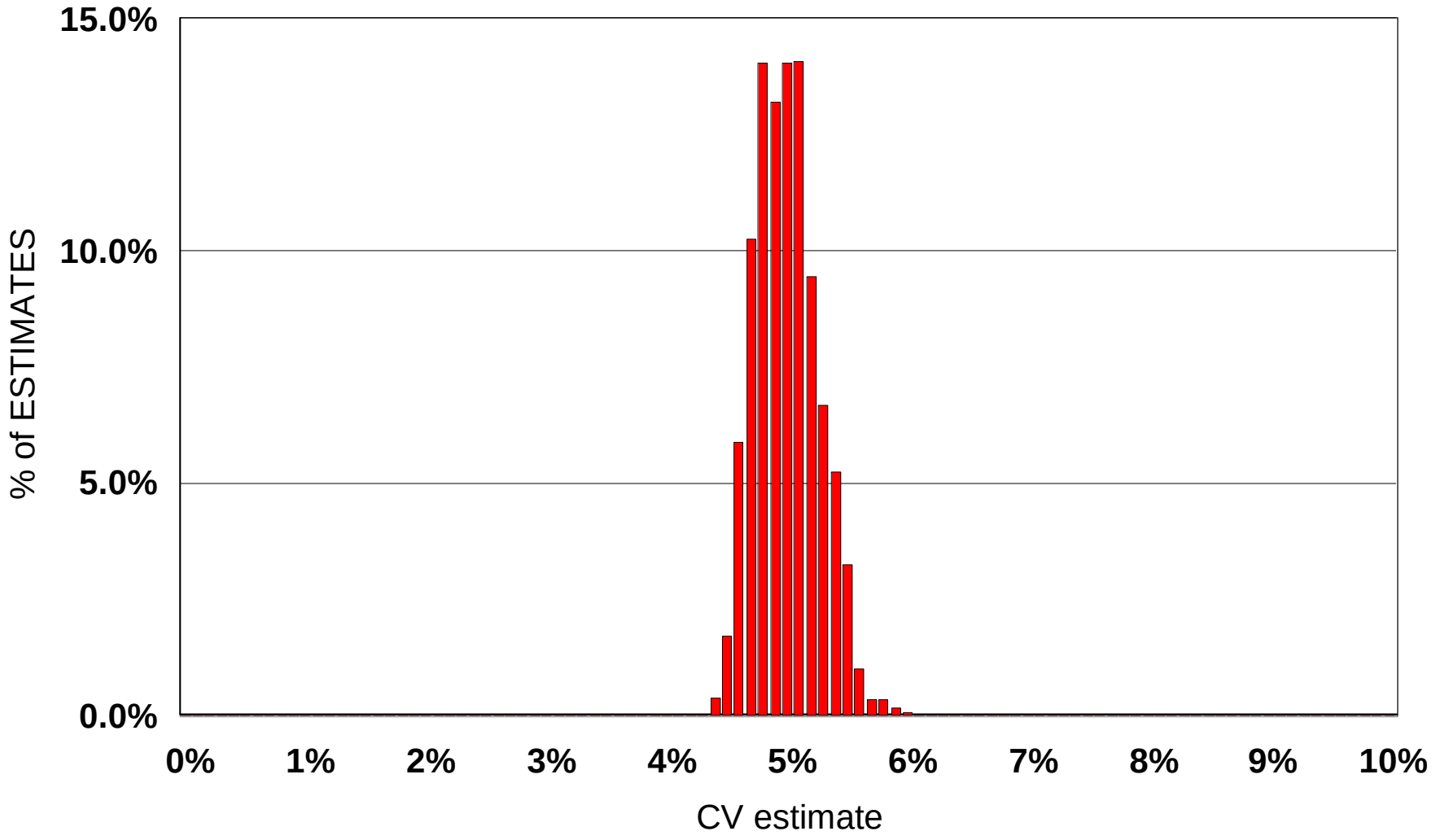
CV = 5% : Estimates using n=200



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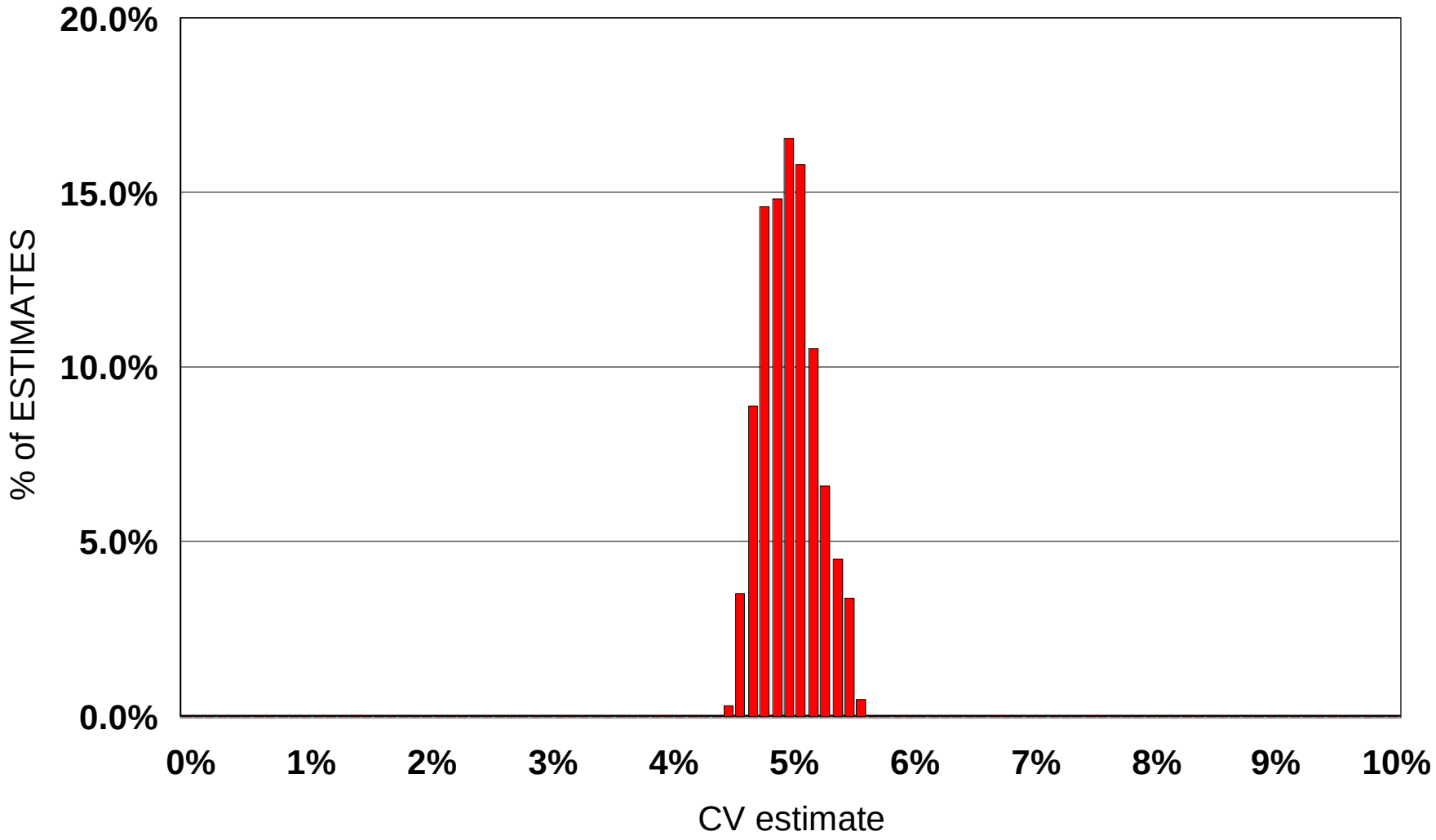
CV = 5% : Estimates using n=300



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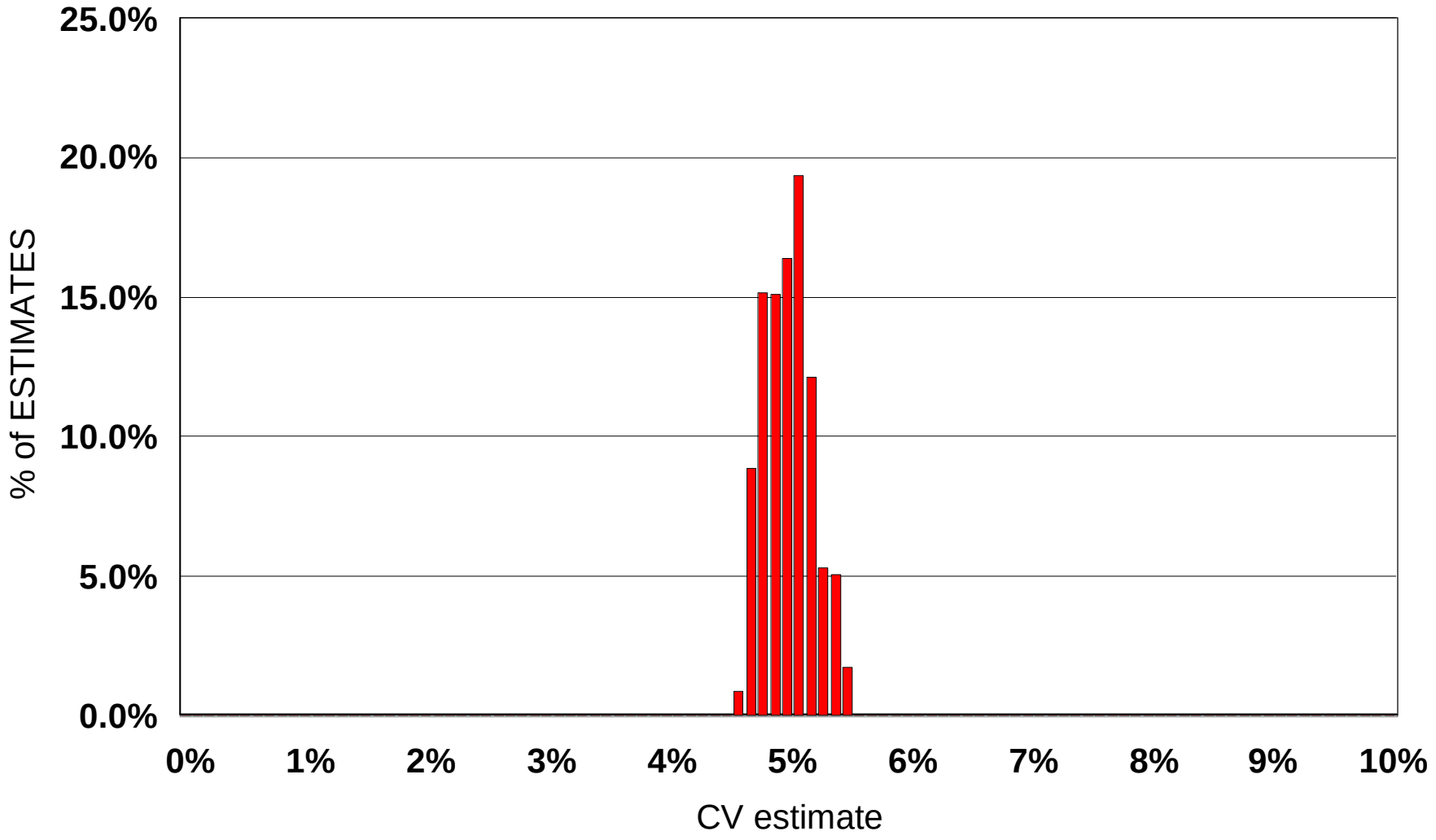
CV = 5% : Estimates using n=400



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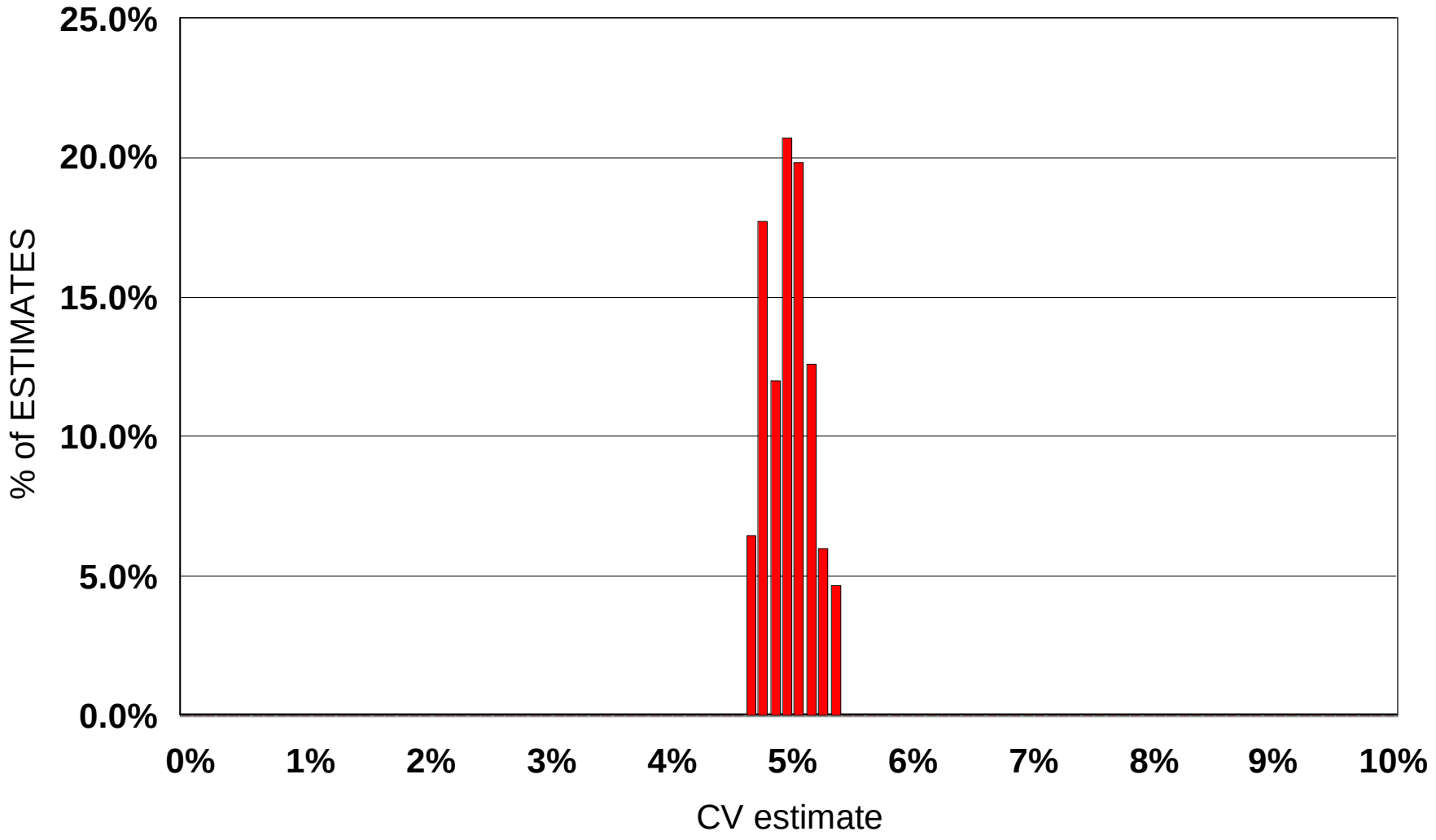
CV = 5% : Estimates using n=500



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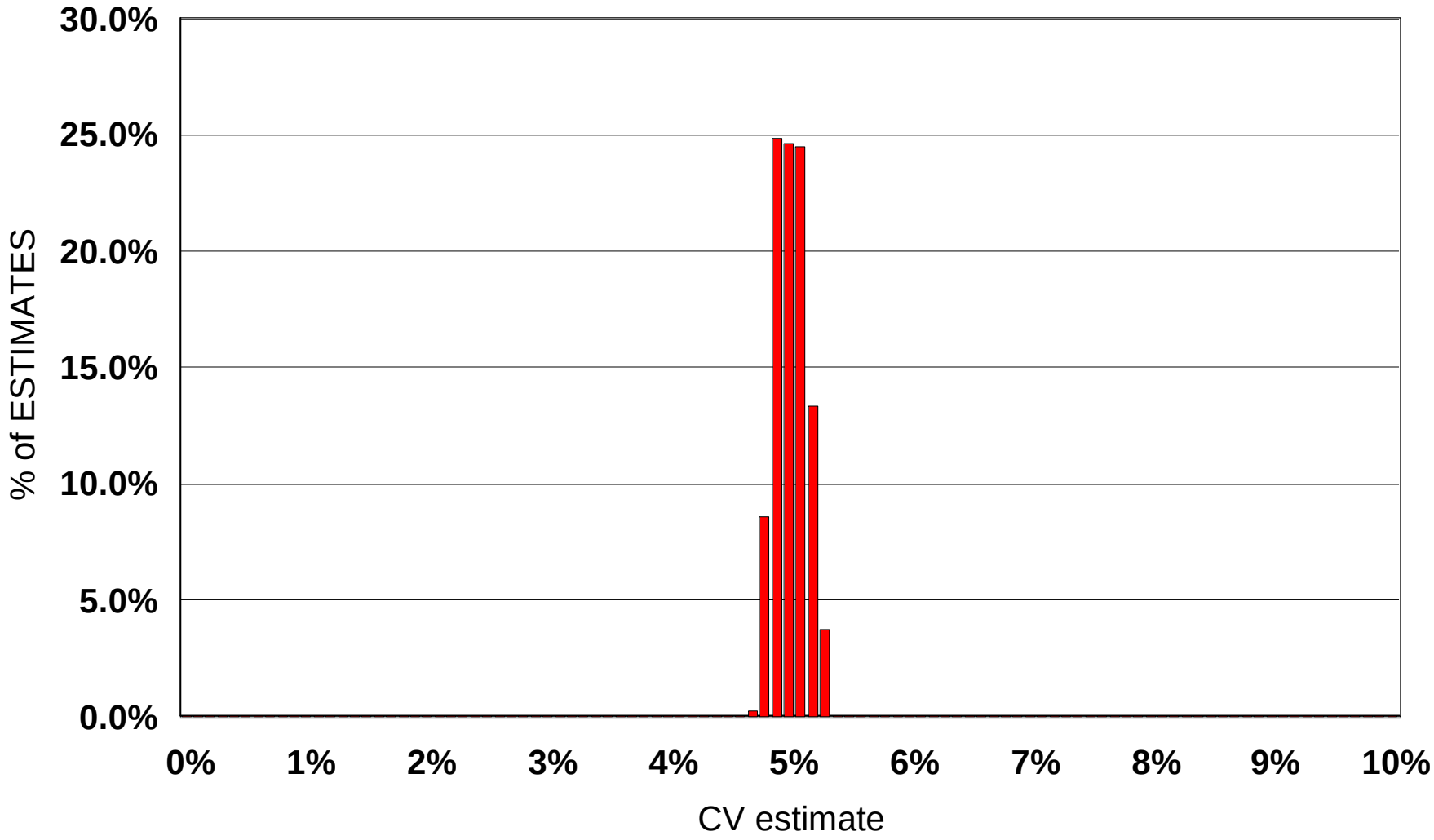
CV = 5% : Estimates using n=1000



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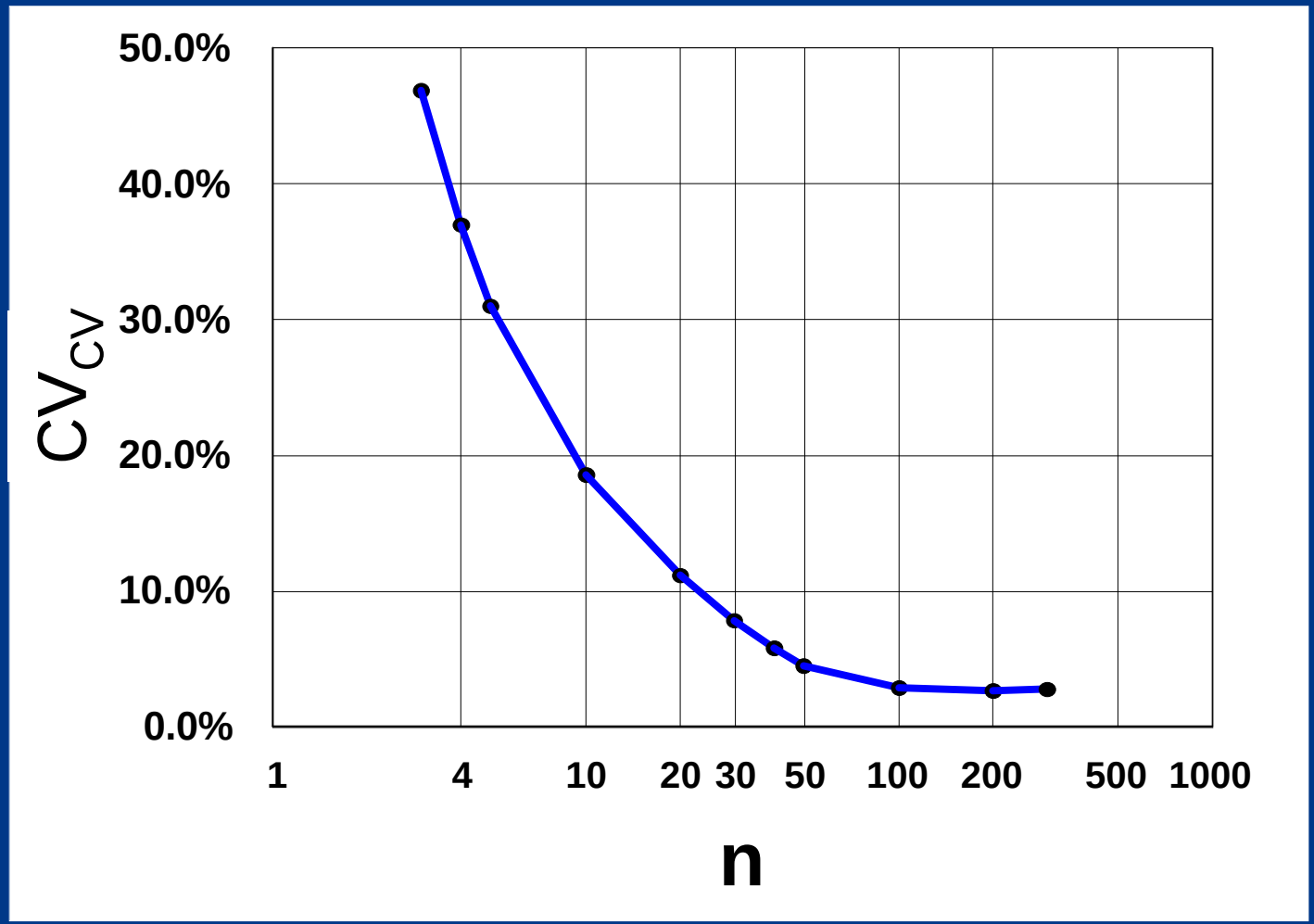
Uncertainty of Uncertainty



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IQC vs EQA

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GUM 3.4.2

- Because the mathematical model may be incomplete, all **relevant quantities should be varied to the fullest practical extent** so that the evaluation on uncertainty can be based as much as possible on observed data.

  – 'Good range of inputs.'

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GUM 3.4.2

- Whenever feasible the use of empirical models of measurement founded on **long term quantitative data**, and the use of check standards and control charts that can indicate if a measurement is under statistical control, should be part of the effort to obtain reliable evaluations of uncertainty.

  – 'Long period of evaluation.'

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External QA vs Internal QC

	External QA	Internal QC
Matrix	Not patients	Not patients
Concentration points	8	2 or 3
Analytical Range	Wider	Reference Interval
Measurements	<=16	Hundreds/Thousands*
Period	Months	Months – Years*
Bias	Estimated*	N/A
Outliers	Included	Excluded*

*Advantages

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Lab X (near QAP office)

ALBUMIN

	QA DATA	QC DATA
No. of Concentrations	8	2
Concentrations	24.9 – 51.6	25.8, 39.1
SD	0.65	0.55
CV%	1.7%	1.7%
Number of Results	16	613, 615

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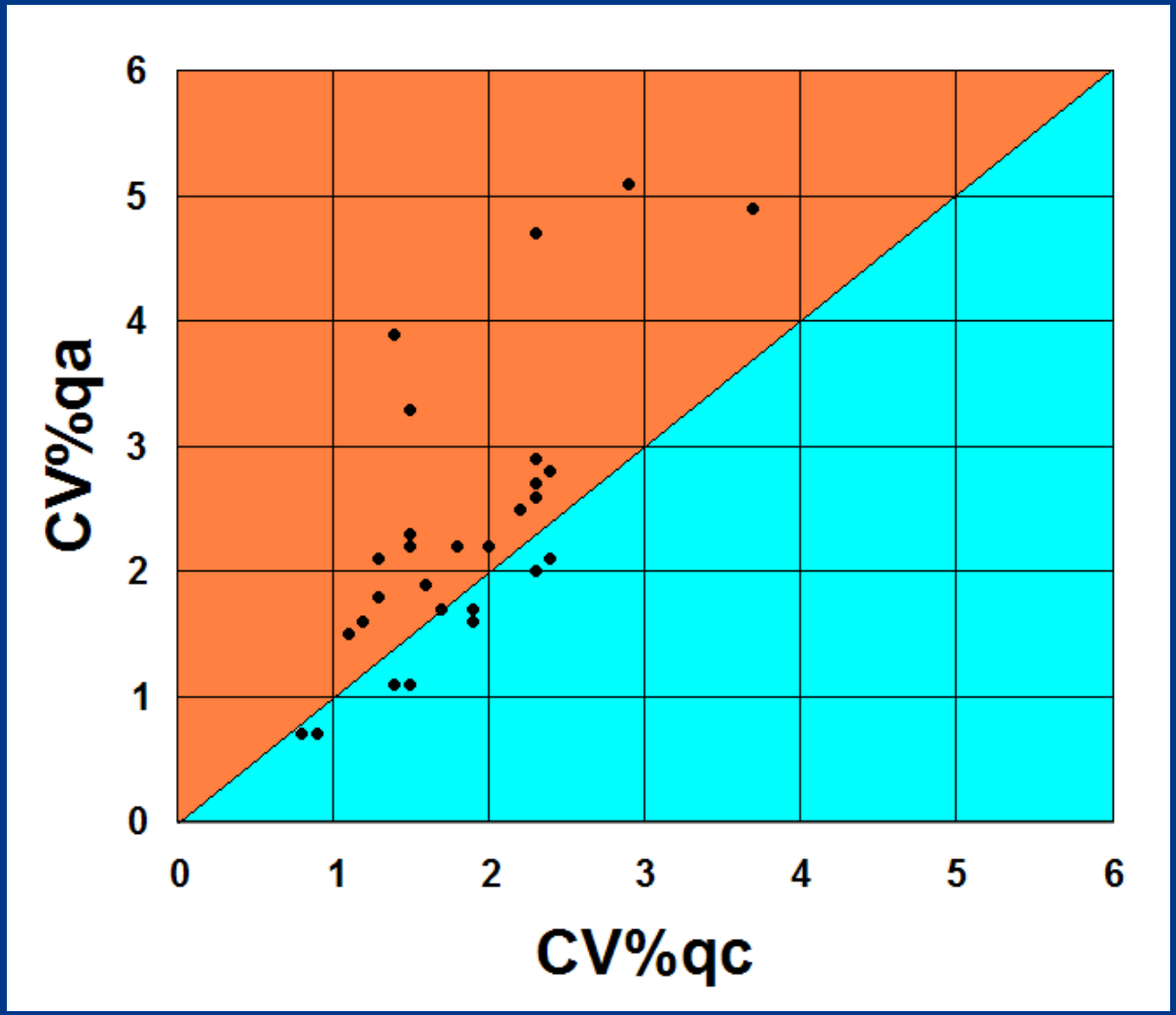
CV_{QC} vs CV_{QA}



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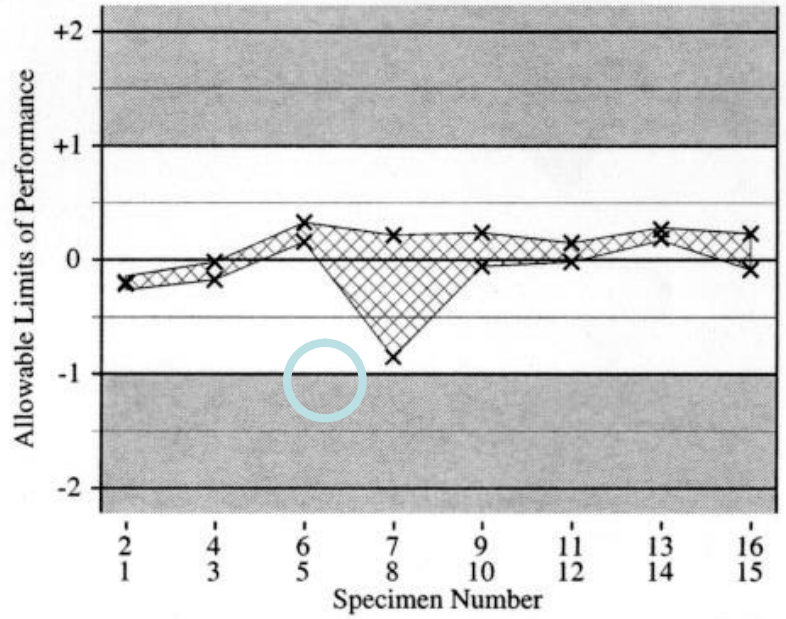
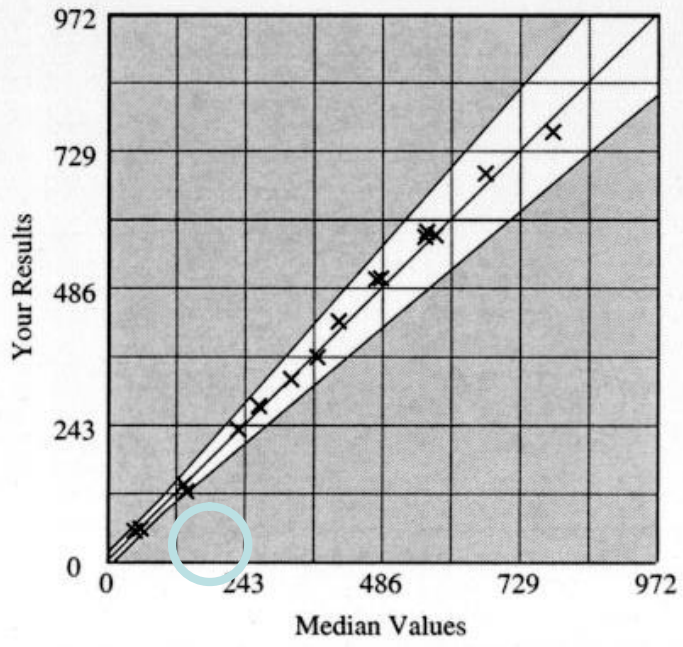
Creatine Kinase

	QA	QC
CV%	**3.3** (19th Percentile)	**1.5**
Range	**61 - 788**	**135, 451**





2. How is MU estimated?

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Calculate Combined Uncertainty

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Combined Uncertainty (u_c)

- Standard uncertainty
  - u (or s) : standard deviation

GUM 2.3.1

- Combined (standard) uncertainty
  - u_c : the 'sum' of the known standard deviations

GUM 2.3.4

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Combining Individual Uncertainties SD's

- For *sum* *(or difference)*
  - $V = X + Y$ $(V = X - Y)$
  - $SD_V^2 = SD_X^2 + SD_Y^2$
  - Use absolute SD (not CV)

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Sum or Difference

- Anion Gap
  - $AG = (Na + K) - (Cl + HCO_3)$
  - $SD_{AG}^2 = SD_{Na}^2 + SD_K^2 + SD_{Cl}^2 + SD_{HCO3}^2$

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Combining Individual Uncertainties CV%'s

- For product *(or quotient)*
  - V = X x Y *(V = X / Y)*
  - $CV\%_V^2 = CV\%_X^2 + CV\%_Y^2$
  - Use CV% (not absolute SD)

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Product or Quotient

- Creatinine Clearance
  - Clearance= $(U_{Cr} \times Vol) / (P_{Cr} \times Time)$
  - $CV_{Clearance}^2 = CV_{UCr}^2 + CV_{Vol}^2 + CV_{PCr}^2 + CV_{Time}^2$

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EDMA European Diagnostic Manufacturer Association

- $u_{result} = \sqrt{(u_{cal}^2 + u_{method}^2 + u_{sample}^2 + u_{other}^2)}$
- u_{cal}
  - Manufacturer
- u_{method}
  - Intralaboratory imprecision
  - Variation between operators, instruments, reagents, labs
    - (collaborative studies?)
- u_{sample}
  - Pre-analytical, Biological
- u_{other}
  - Interferences

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Analytical Components

- Minimum approach – short term
- $u_C(y) = \sqrt{(u_{Calibration}^2 + u_{Imprecision}^2 + u_{Instrument}^2 + u_{Reagent}^2)}$

Day to Day Lot to Lot
Run to Run

- Where long term imprecision includes the instrument and reagent contributions:

- Minimum approach – long term
- $u_C(y) = \sqrt{(u_{Calibration}^2 + u_{Imprecision}^2)}$

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Expanded Uncertainty (U)

- Expanded uncertainty
  - The confidence limits around a result

GUM 2.3.5

- Coverage factor
  - The number of SD's for the confidence limit
  - $U = u_c \times k$

GUM 2.3.6

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Coverage factor

- k=1.00 68.27% confidence
- k=1.64 90%
- k=1.96 95%
- k=2.00 95.45%
- k=2.58 99%
- k=3.00 99.73%

- One can assume that taking k=2 produces an interval having a confidence of 95% and taking n=3 produces an interval having a confidence interval of 99%.

GUM 6.3.3

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How can MU be reported?

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Introduction to GUM

0.1 - "When reporting the result of a measurement of a physical quantity, ***it is obligatory that some quantitative indication of the quality of the result be given so that those who use it can assess its reliability***."

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ISO 15189 – 2003(E)

- 5.8.3
  - uncertainty of measurement should be provided upon request;

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Reporting Conventions

- 1000 (30) mL
  - Defines the result and the (combined) standard uncertainty
- 1000 +/- 60 mL
  - Defines the result and the expanded uncertainty (k=2)
- 1000 +/- 60 mL at 95% confidence level.
  - Defines the expanded uncertainty at the specified confidence interval

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Other Reporting mechanisms

- Significant figures
- Commenting

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What is the clinical value of MU?

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Non-clinical uses of MU:

- QC & QA in production
- Law enforcement and regulations
- Basic and applied research
- Calibration to achieve traceability to national standards
- International reference standards and materials

  – GUM 1.1

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ISO/IEC DIS 17025

- 5.4.7.2
  - The laboratory shall use methods which meet the needs of the client

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ISO 15189 – 2003(E)

- 5.5.1
  - *The laboratory shall use examination procedures, …… which meet the needs of the users of laboratory services and are appropriate for the examinations.*

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Clinical Application Overview

A: Appropriateness for Use

- Analytical uncertainty & biological variability

B: Diagnosis

- Clinical Decision Limit (eg Gluc >6.9 mmol/L)
- Reference Interval

C: Monitoring

- Changes in result / clinical condition

D: Clinical Reporting of Uncertainty

- Confidence Limits
- Significant figures
- Commenting

E: Confidence in laboratory trouble shooting

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LFT's Female DOB 30/1/1934

Date	29/01	28/04	14/05	02/07	Units	Range
S BILI	38	29	27	34	umol/L	(2-20)
S ALP	234	192	206	193	U/L	(30-120)
S GGT	93	83	87	74	U/L	(5-45)
S ALT	124	137	113	103	U/L	(5-40)
S AST	187	202	167	166	U/L	(5-40)

Some clinicians (and patients) believe that the results from laboratory assays have little of no uncertainty.

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Sources of random variation

- *Biological* — *within-subject Biological Variation*
- *Pre-analytical* — *Preparation of subject*; *Sample collection*
- *Analytical* — *Imprecision*; *Changes in bias*

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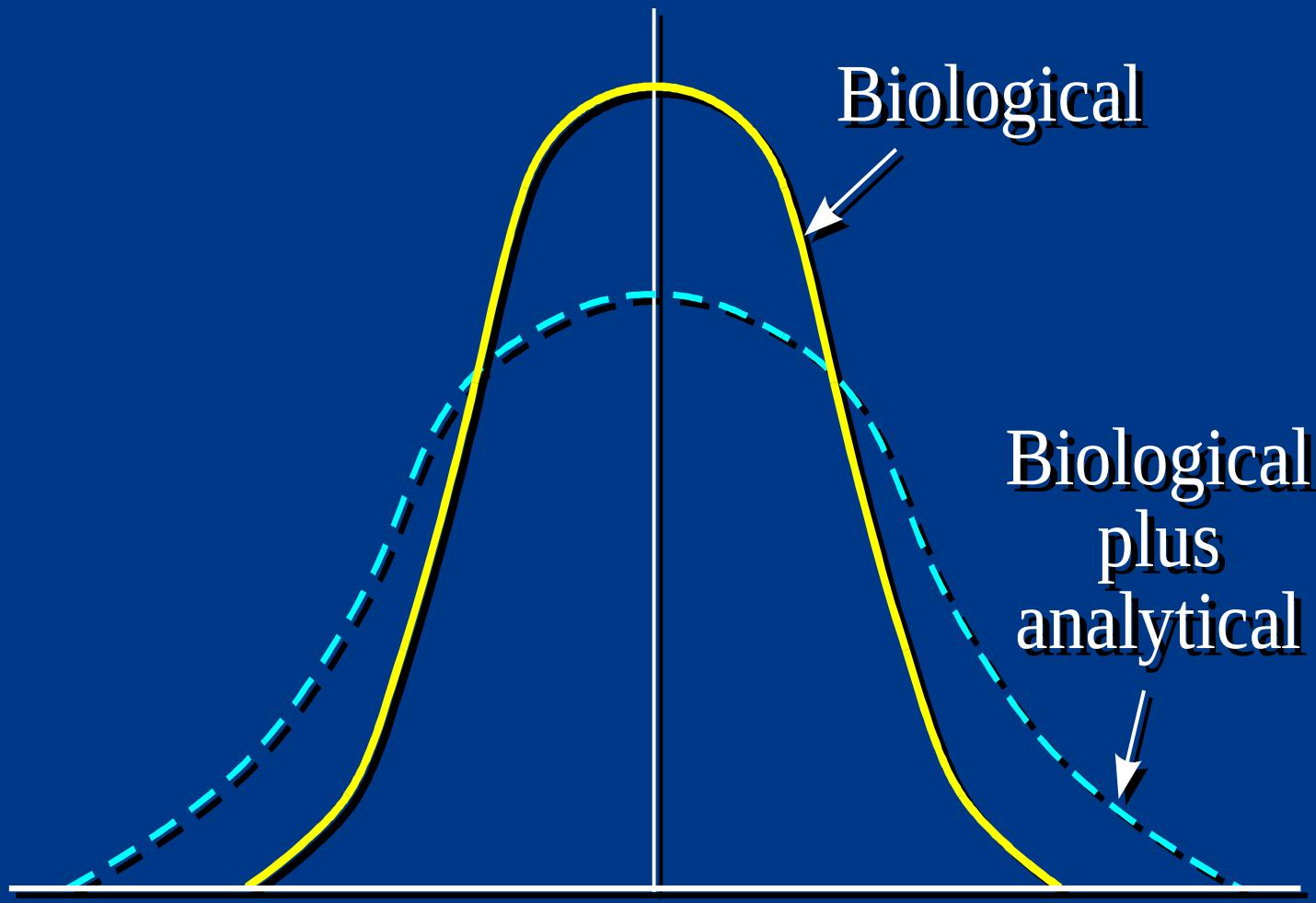
A single result represents a distribution



Slide courtesy of Callum G Fraser

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Data on biological variation

Over the years, many compilations

Ricos C, et al. Current databases on biologic variation: pros, cons and progress.

Scand J Clin Lab Invest 1999;59:491-500

2010 update at

http://www.westgard.com/biodatabase1.htm

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aacb testing for health

Ann Clin Biochem 2007; **44:** 343–352

Within-subject biological variation in disease: collated data and clinical consequences

Carmen Ricós[1,2], Natalia Iglesias[2], José-Vicente García-Lario[1,3], Margarita Simón[1,4], Fernando Cava[1,5], Amparo Hernández[1,6], Carmen Perich[1,7], Joanna Minchinela[1,8], Virtudes Alvarez[1,6], Maria-Vicenta Doménech[1,9], Carlos-Victor Jiménez[1,8], Carmen Biosca[10] and Raquel Tena[2]

Quantity	Matrix	CV_I (%) Healthy (median)	CV_I (%) Disease	n	d	s	Disease	Ref	Mean	Units
α-Fetoprotein	S	12	12	30	180	3	Colon neoplasm	10	2.86	μg/L
α-Fetoprotein	S		35	40	180	3–10	Hepatic disease, no cirrhosis	10	4.07	μg/L
α-Fetoprotein	S		38	85	180	3–10	Hepatocellular carcinoma	10	3.97	μg/L
α-Fetoprotein	S		40	45	180	3–8	Cirrhosis	10	3.83	μg/L
Alanine aminopeptidase	S	4.1	4.3	20	28	7	Chronic liver disease	29	1.39	μkat/L
ALT	S	24	11	20	28	7	Chronic liver disease	29	2.04	μkat/L
ALT	S		13	27	56	8	Type I- DM	27	0.52	μkat/L
ALT	S		25	9	2	11	Impaired renal function	23	0.21	μKat/L
Albumin	S	3.1	2.8	16	56	8	Type I- DM	27	44	g/L
Albumin	S		2.9	8	21	8	Chronic renal failure	28	41	g/L
Albumin	S		3.3	20	28	7	Chronic liver disease	29	39	g/L
Albumin	S		4.3	9	2	11	Impaired renal function	23	39.1	g/L
Albumin	S		6.7	20	4	19	Acute myocardial infarction	22	37.1	g/L
Albumin, first morning	U	36	42	47	21	3	Type I-DM	39	350	mg/L
Albumin, first morning	U		61	16	21–28	10	Diabetic subjects	33	14	mg/L
Albumin/creatinine ratio	U	NA	39	16	21–28	10	Diabetic subjects	33	1.25	mg/mmol
ALP	S	6.4	6.4	8	84	8	Chronic renal failure	28	3.21	μkat/L
ALP	S		6.6	20	28	7	Chronic liver disease	29	7.5	μkat/L
ALP	S		12.4	15	72	5	Paget disease	17	9.8	μkat/L
ALP bone isoform	S	6.2	4.9	15	72	5	Paget disease	17	136	μg/L
Amino-terminal proBNP	P	NA	8.6	37	1	6	Stable chronic heart failure	20	570	ng/L
Amino-terminal proBNP	P		20	37	5	5	Stable chronic heart failure	20	570	ng/L
Amino-terminal proBNP	P		35	37	42	15	Stable chronic heart failure	20	570	ng/L
Amylase	S	12	8.2	17	21	8	Chronic renal failure	28	110	U/L
Amylase	S		8.4	20	28	7	Chronic liver disease	29	8.7	U/L
Amylase	S		11.1	27	56	8	Type I- DM	27	4.58	U/L
Amylase (total) first morning	U	NA	35	47	21	3	Type I- DM	39	4.58	μkat/L
Amylase (pancreatic) first morning	U	NA	38	47	21	3	Type I- DM	39	2.90	μkat/L
Amylase	Saliva	NA	51	47	21	3	Type I- DM	39	1.60	μkat/L
Apo-A1	S	6.5	7.1	143	70	3	Lipid disorders	36	1.50	g/L
Apo-B	S	6.9	6.4	143	70	3	Lipid disorders	36	1.71	g/L
AST	S	12	10.6	20	28	7	Chronic liver disease	29	1.76	μkat/L
AST	S		12.3	37	56	8	Type I- DM	27	0.48	μkat/L
Bicarbonate	S	4.8	7.9	20	4	19.5	Acute myocardial infarction	22	19.5	mmol/L
BNP	P	NA	8.2	37	1	6	Stable chronic heart failure	20	135	ng/L

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BIOLOGICAL VARIATION DATABASE SPECIFICATIONS

Updated for 2010! Desirable Specifications for imprecision, inaccuracy, and total allowable error, calculated from data on within-subject and between-subject biologic variation. This database is updated and compiled by Dr. Carmen Ricos and colleagues. We are honored to be able to host this database.

Desirable Specifications for Total Error, Imprecision, and Bias, derived from intra- and inter-individual biologic variation

This most recent and extensive listing of biologic goals has been provided by Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minchinela J, Perich C, Simon M. "Current databases on biologic variation: pros, cons and progress." Scand J Clin Lab Invest 1999;59:491-500. ***This database was most recently updated in 2010: see what was updated here.***

Annex I, Part I: Within-subject and between-subject CV values of analytes and *Desirable Analytical Quality Specifications for imprecision, bias and total error*

11-Desoxycortisol through a-Fetoprotein
Albumin through CA 549 antigen
Calcium through Cystein
Dehydroepiandrosterone sulfate through Homocysteine
Immunoglobulin A through Lycopenene
Magnesium through Oxalate, output
pCO2 through Rheumatoid factor
SCC antigen through Zinc

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What's New

Lab Quality: Puzzle or Mystery?

Links to Latin America 2010

Pre-Analytical and Post-Analytical QC

QC Practices for Molecular Testing

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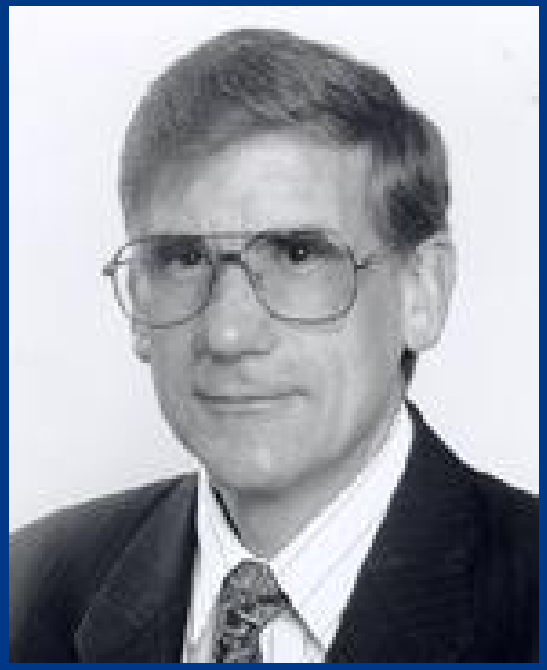
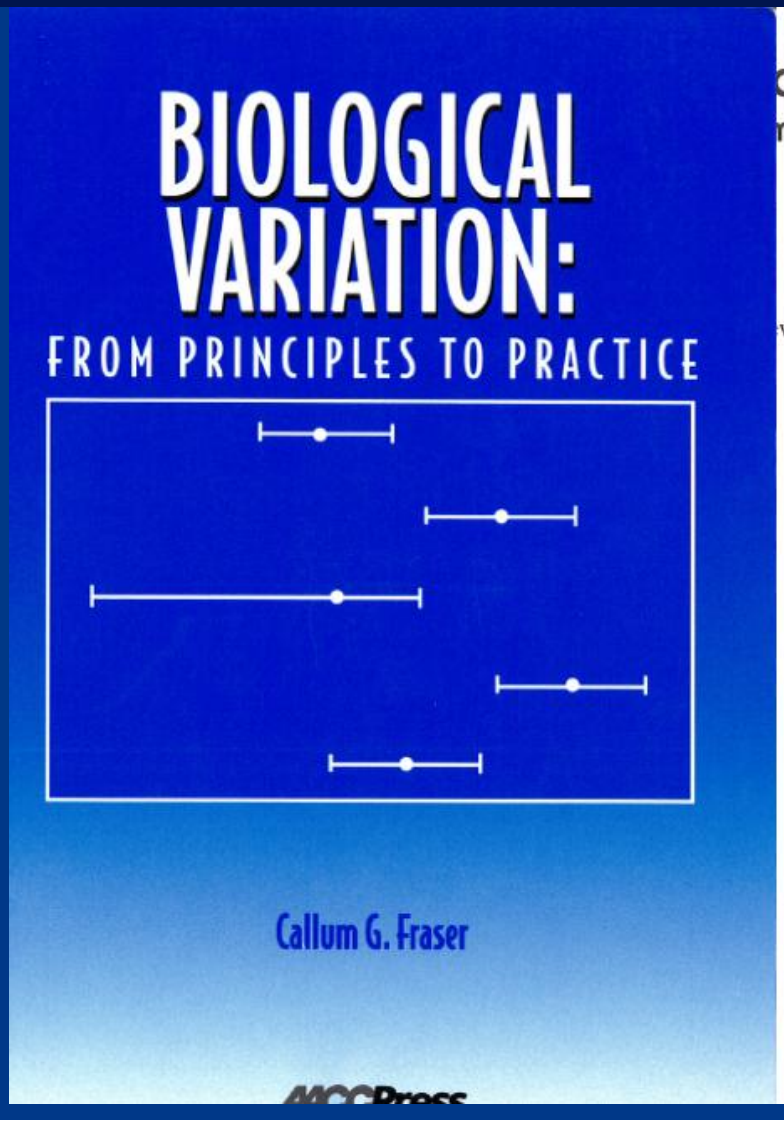
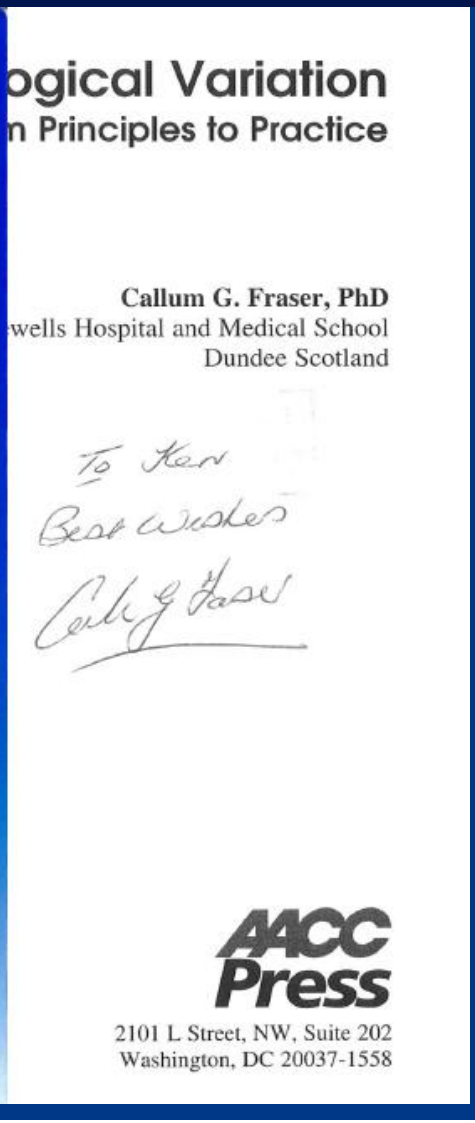
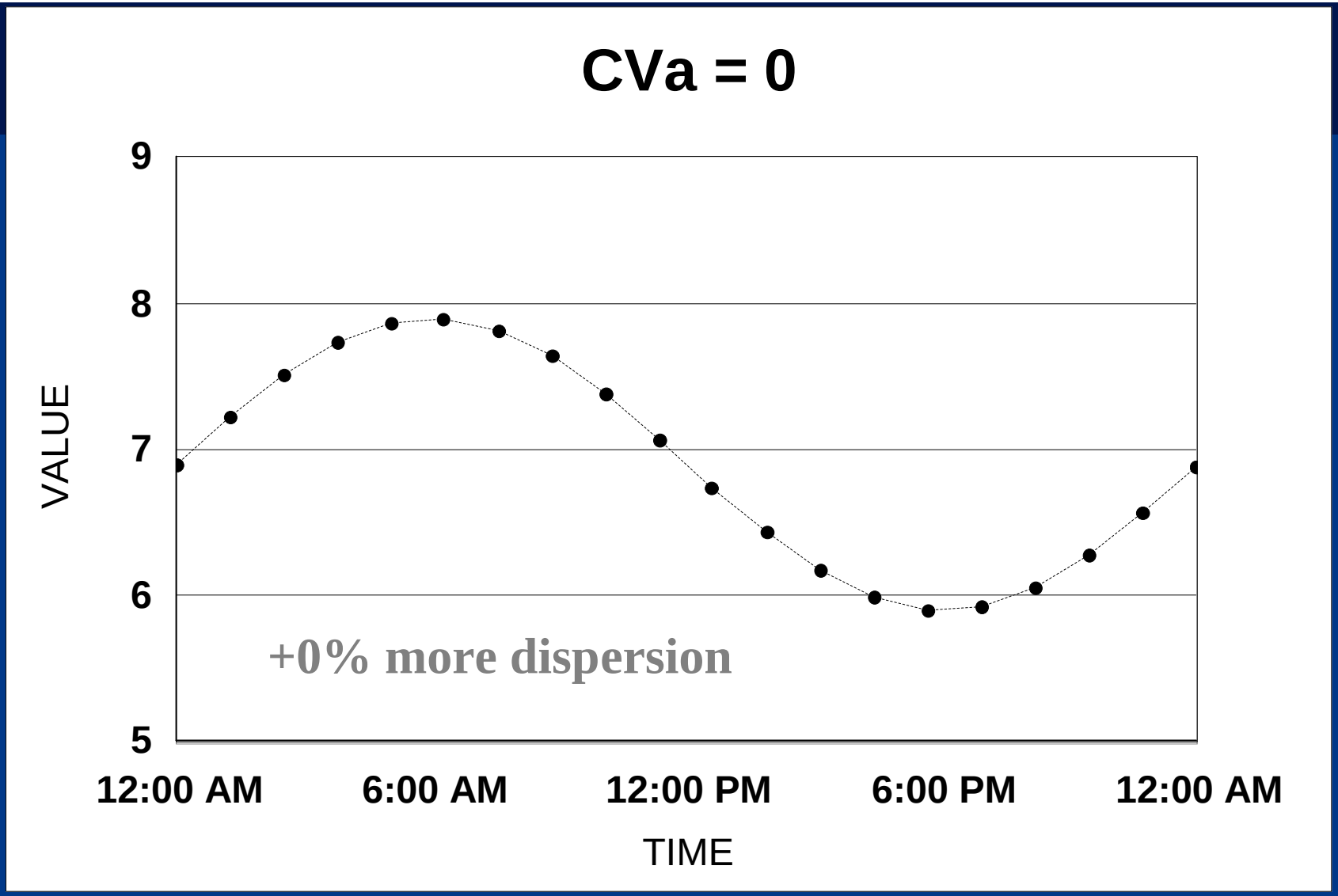
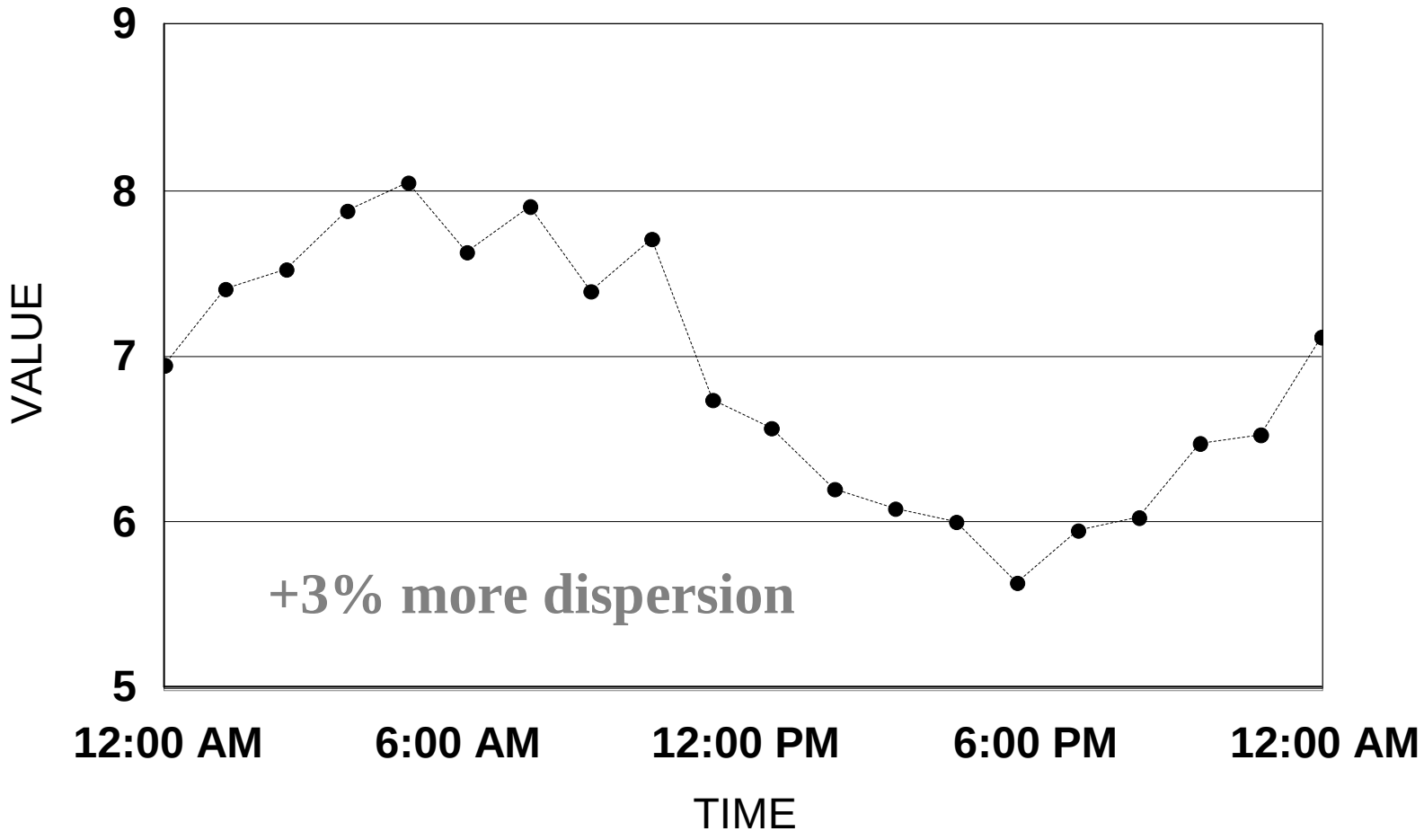







CVa = 0
9
8
7
6
5
VALUE
+0% more dispersion
12:00 AM
6:00 AM
12:00 PM
6:00 PM
12:00 AM
TIME

CVa = 0.25 CVb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7
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VALUE
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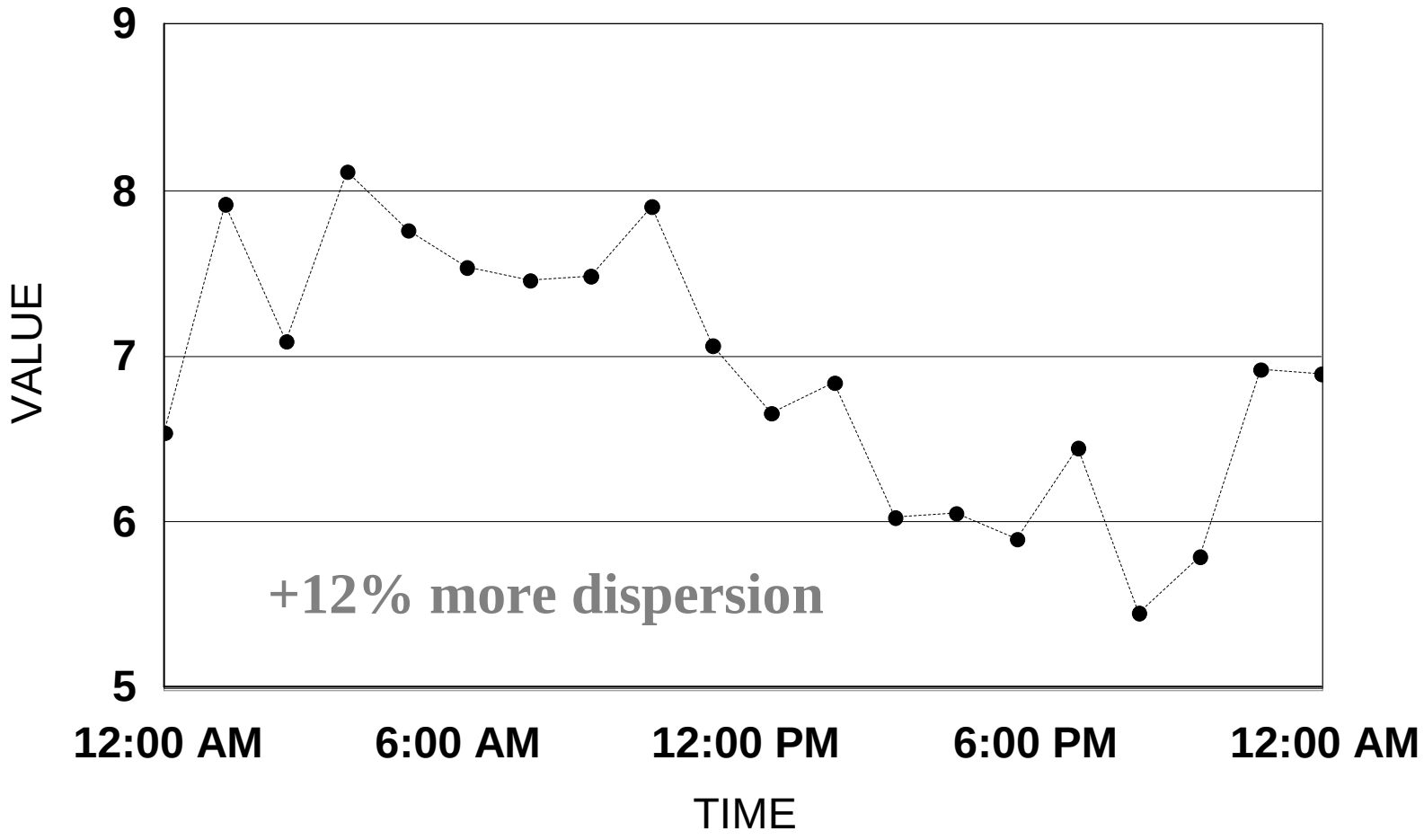
6:00 PM
12:00 AM
TIME

CVa = 0.5 CVb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VALUE
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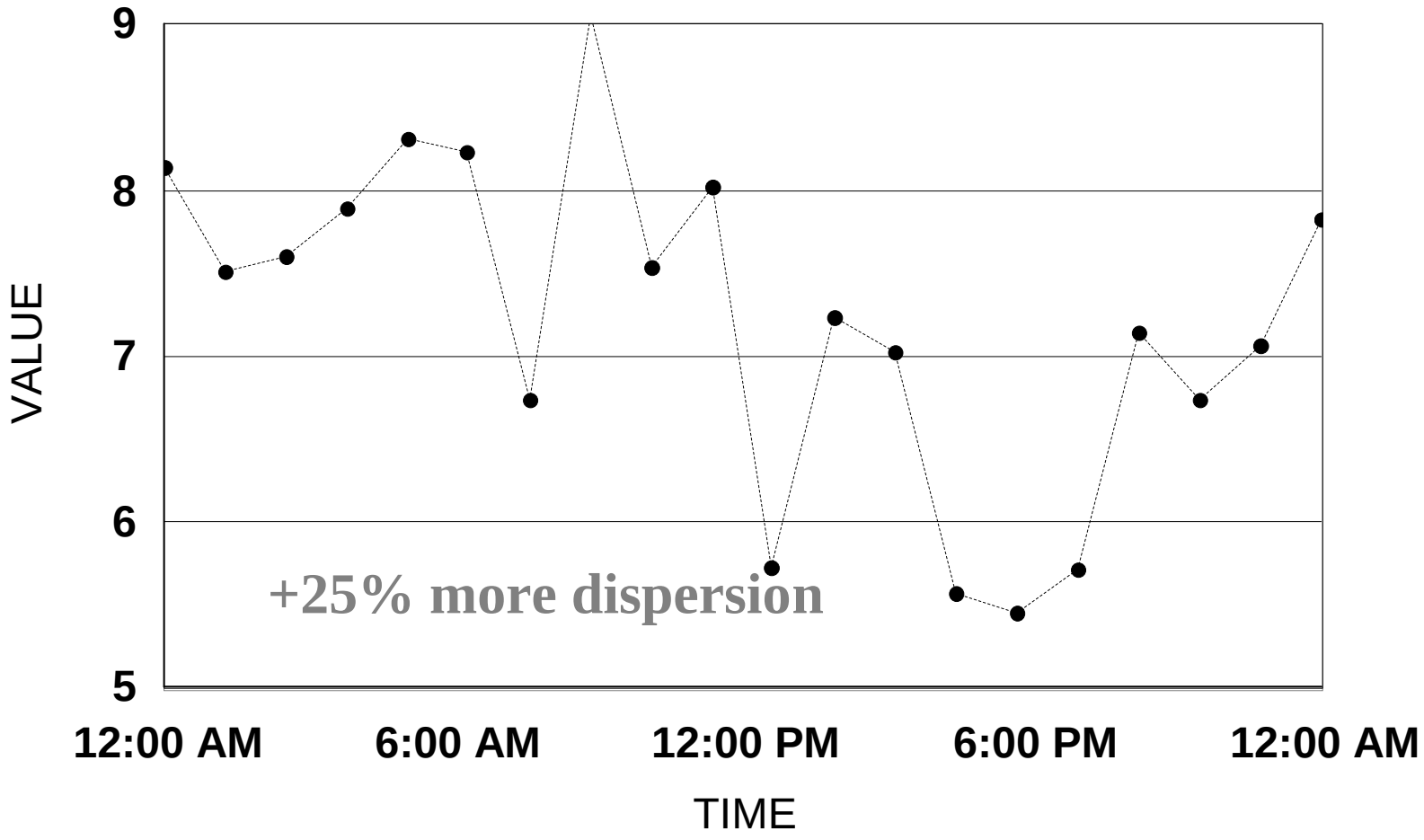
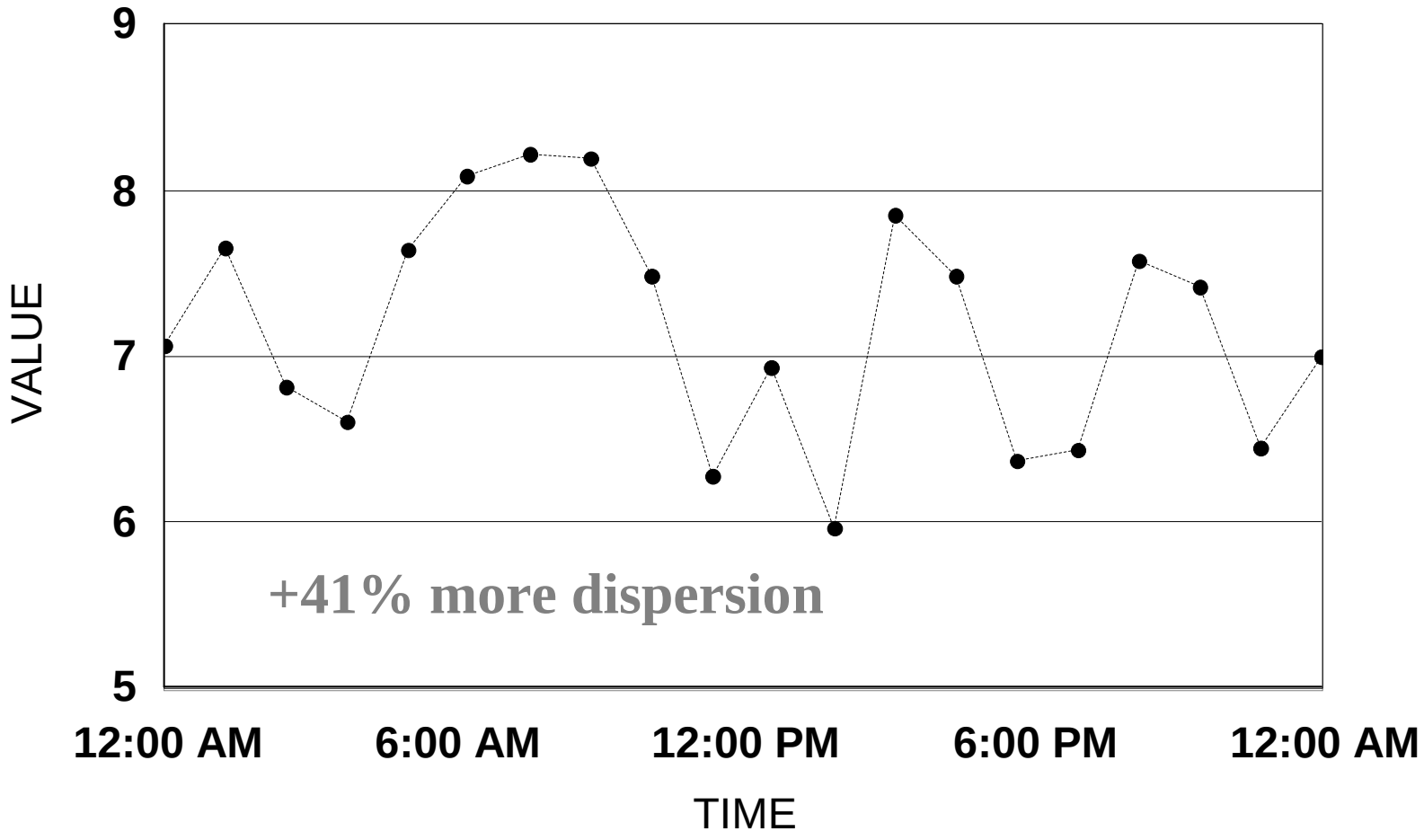
12:00 AM
TIME

CVa = 0.75 CVb



4. What is the clinical value of MU?

CVa = CVb


9
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7
6
5
VALUE
+41% more dispersion
12:00 AM
6:00 AM
12:00 PM
6:00 PM
12:00 AM
TIME

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Appropriate Imprecision

CV_A / CV_B

Minimum	0.25
Desirable	0.50
Optimum	0.75

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B: Diagnosis

- Diagnosis based on result can be made by
  - Reference Interval
    - eg 'hyponatraemia'
  - Diagnostic cutoff
    - eg 'diabetes'

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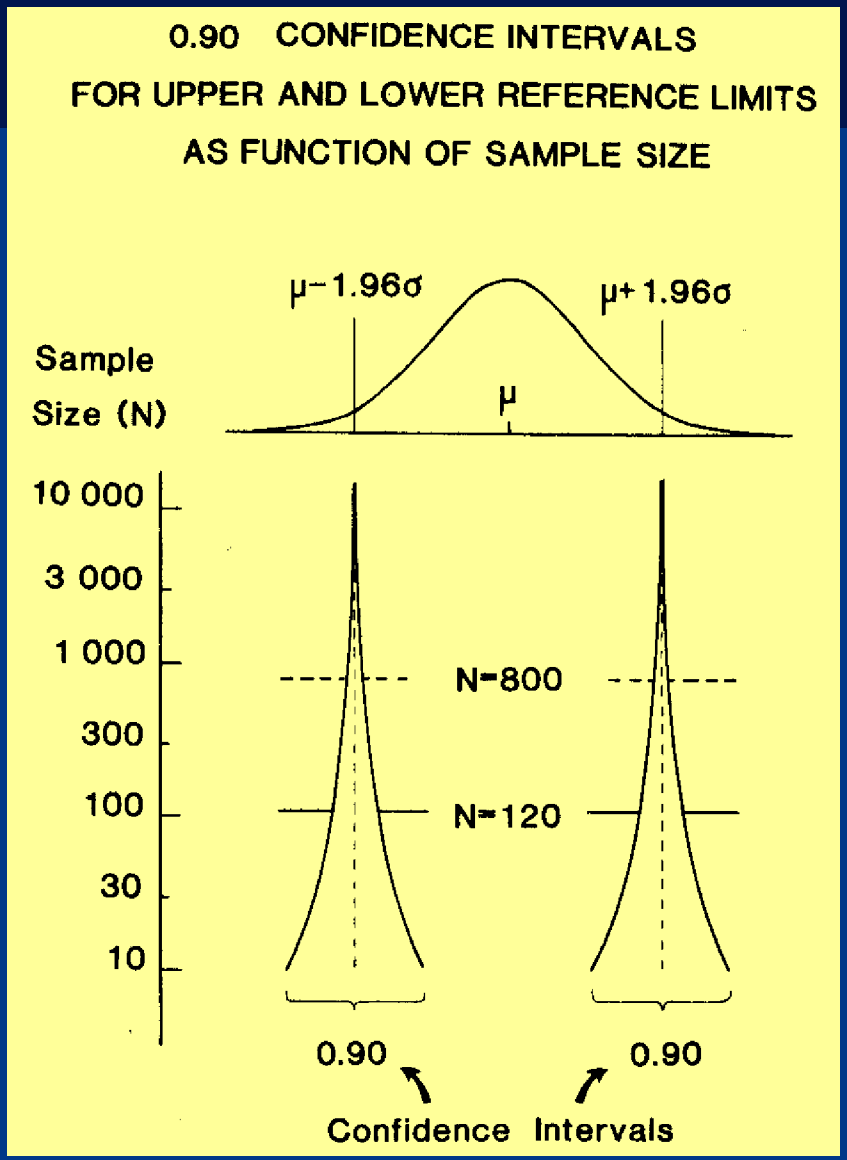
Reference Interval Confidence

Per Hyltoft Petersen et al,
Uppsala Med J 1993;98:241-256



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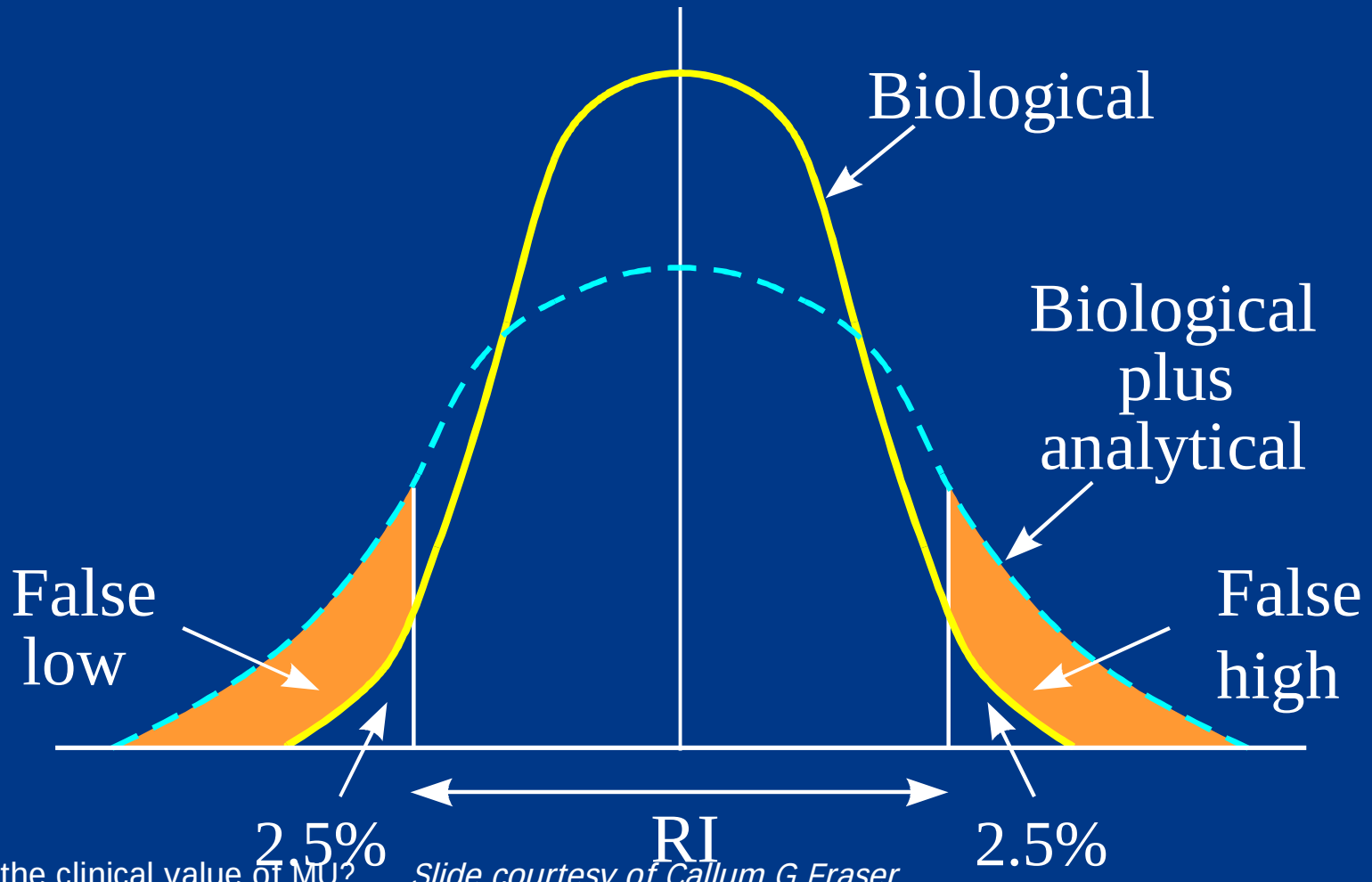
Analytical imprecision widens reference intervals



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Effect of imprecision on proportion outside reference limits

- *Inferior imprecision leads to more false positives – at both high and low values.*
- *Superior imprecision leads to more false negatives – at both high and low values.*

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Effect of Imprecision on Cutoff Diagnosis

- Cutoff is absolute.

– Cholesterol	>=	5.5	mmol/L
– Fasting Glucose	>=	7.0	mmol/L
– Opiates	>=	300	ug/L
– 9deltaTHC	>=	15	ug/L
– Pregnant hCG	>=	25	IU/L

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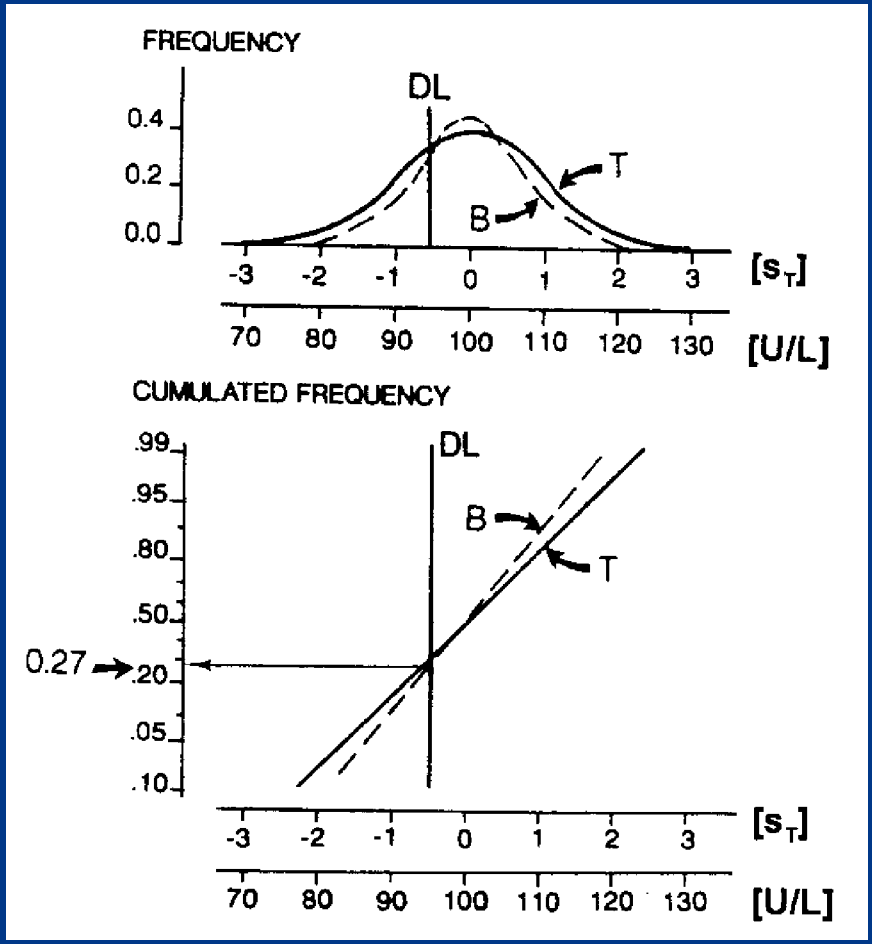
Effect of Analytical Imprecision on Cutoff Diagnosis



4. What is the clinical value of MU?

Per Hyltoft Petersen et al, Uppsala Med J 1993;98:221-240

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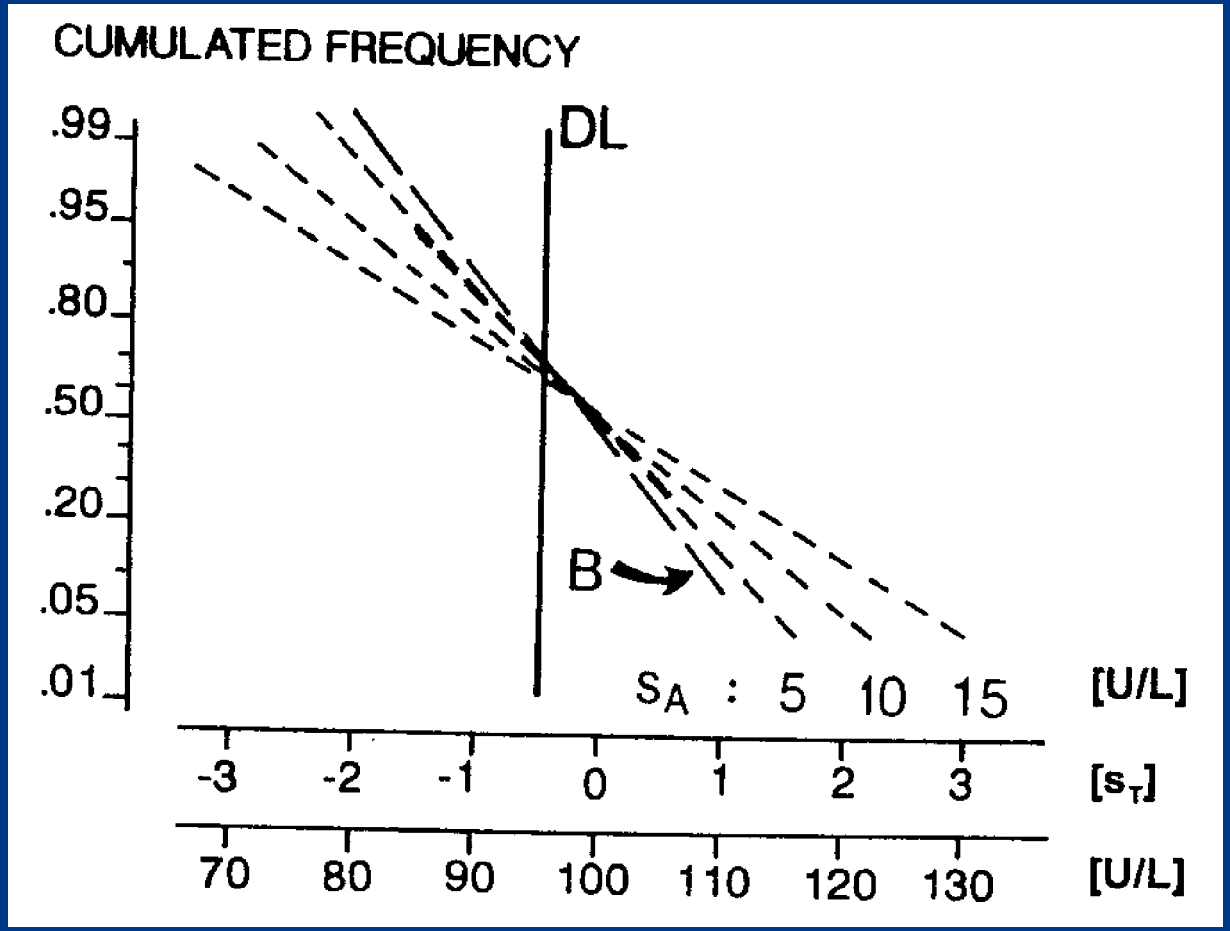
Effect of Analytical Imprecision on Cutoff Diagnosis



Per Hyltoft Petersen et al, Uppsala Med J 1993;98:221-240

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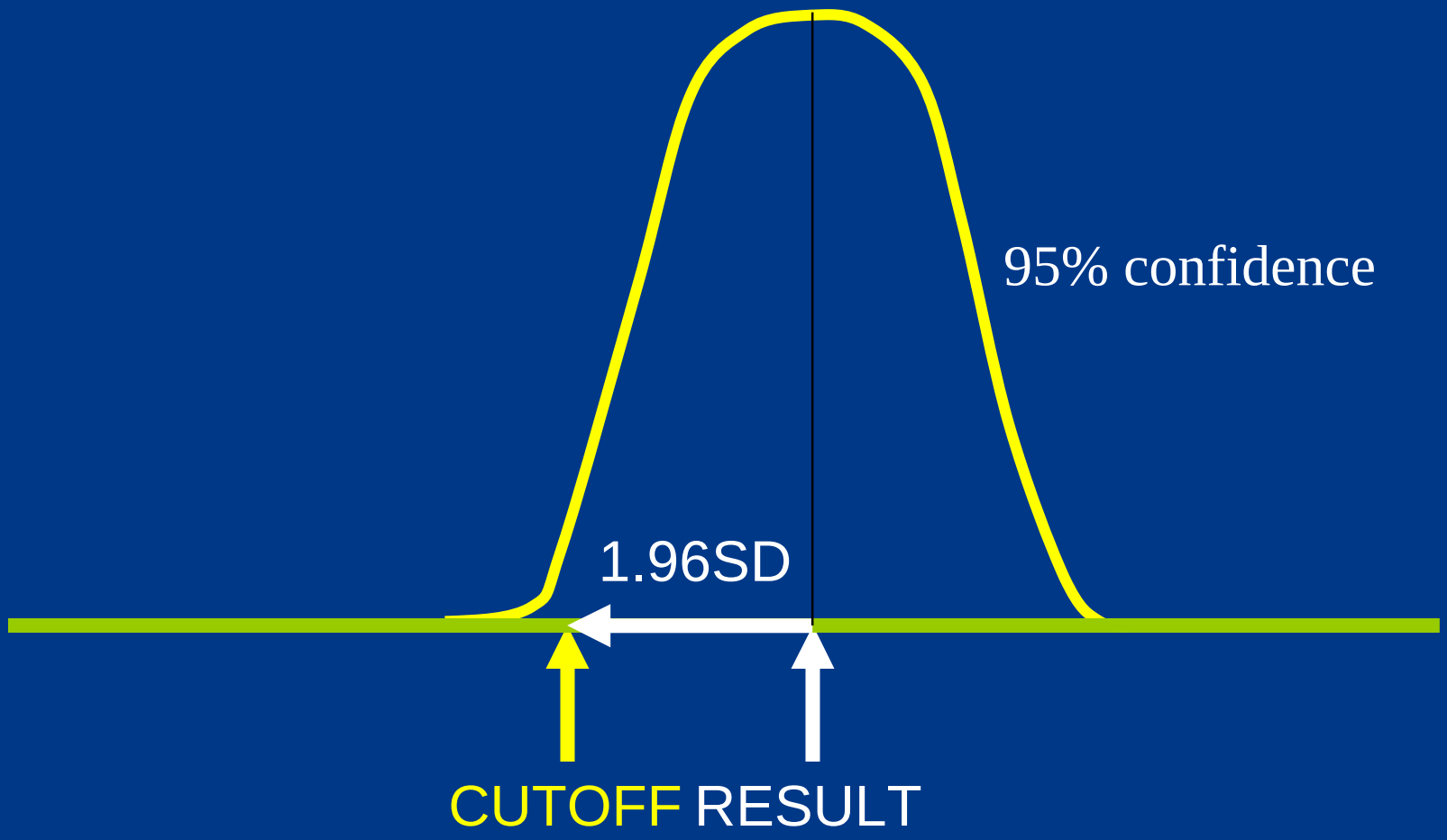
Analytical confidence above a cutoff:



4. What is the clinical value of MU?

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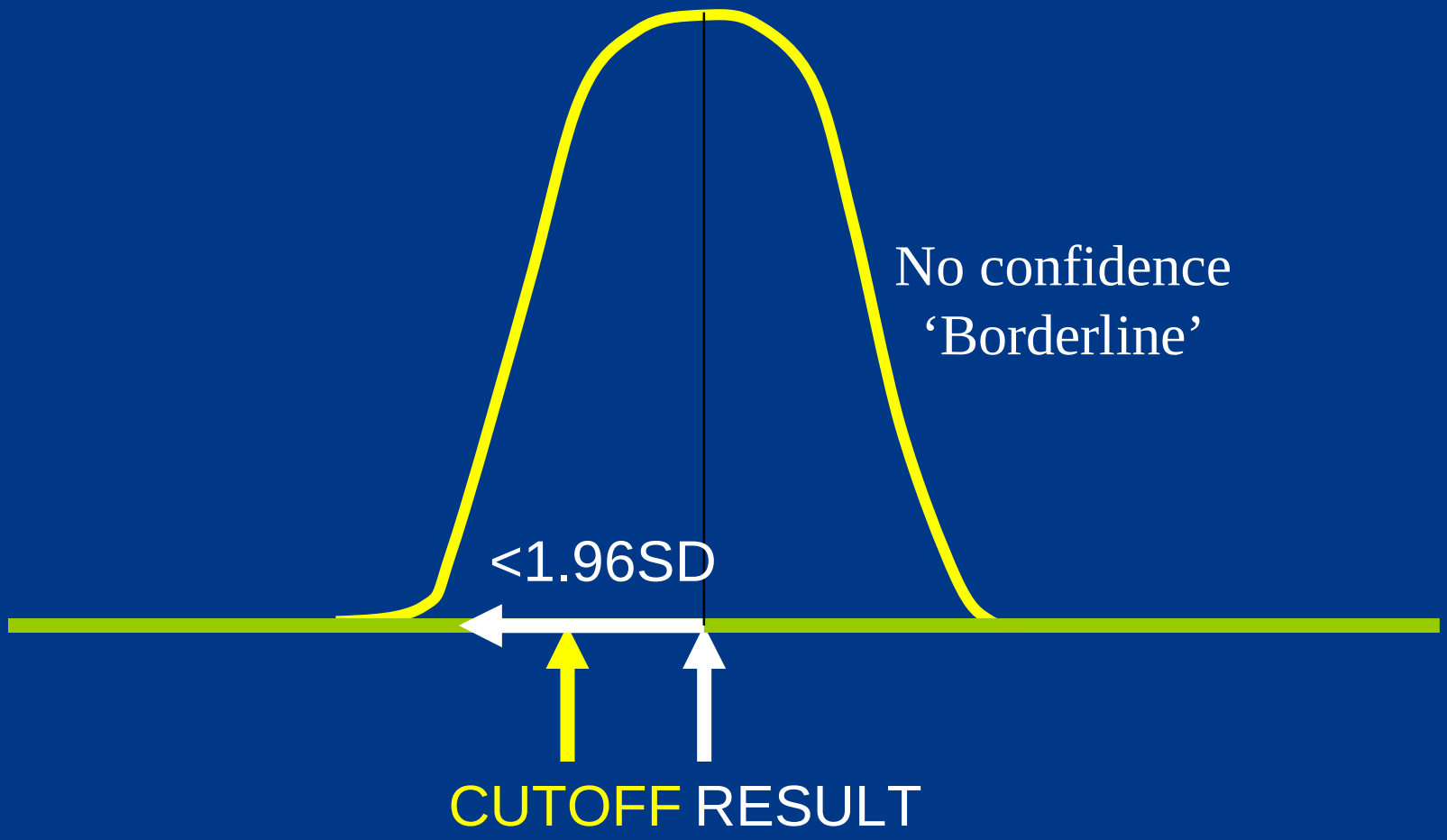
Analytical confidence above a cutoff:



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MONITORING

- Both Initial result and Final result have the same uncertainty
  - Same bias – cancels out
  - Same imprecision (assumed)

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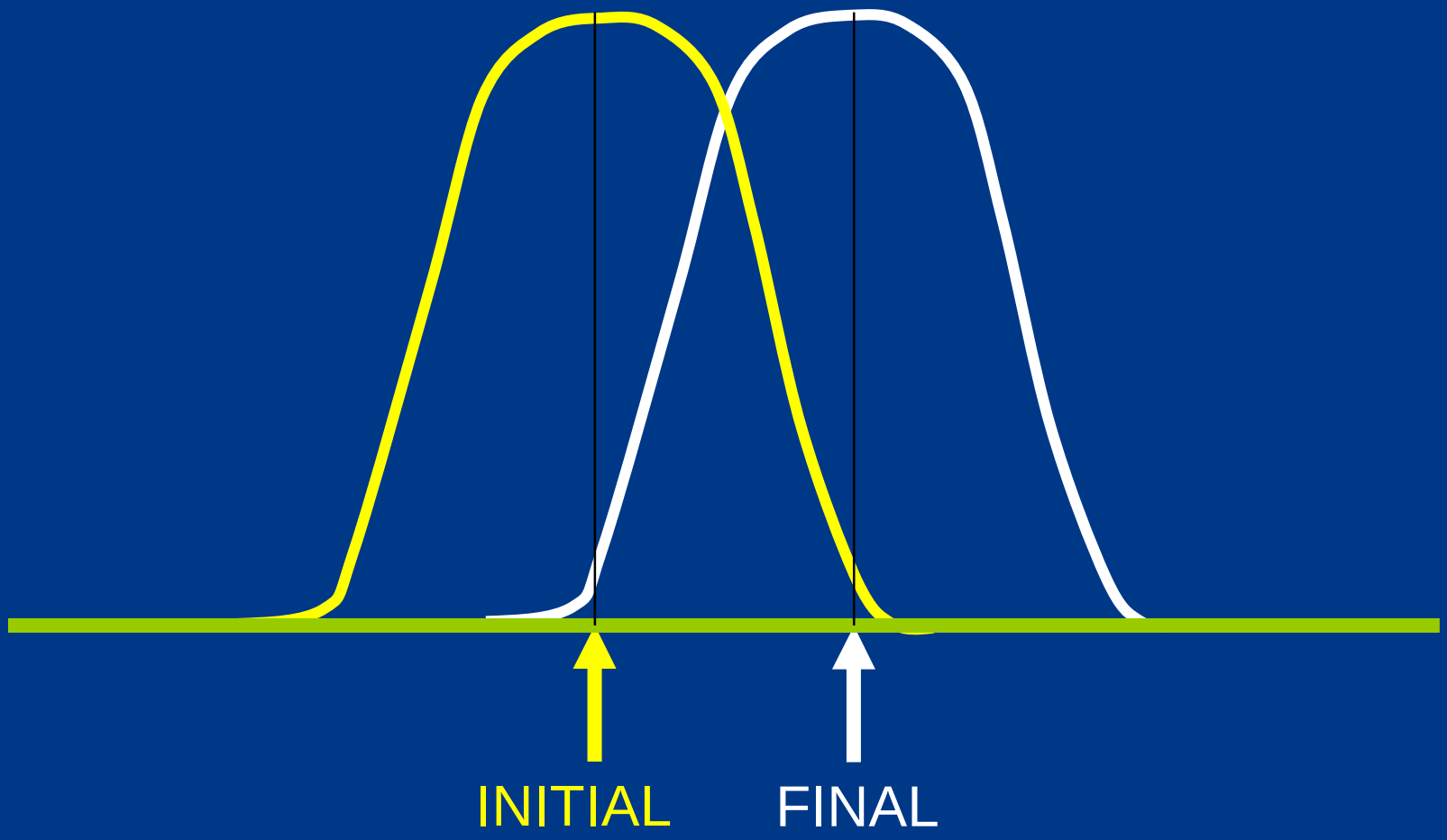
Analytical Confidence in a change:



4. What is the clinical value of MU?

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Analytical uncertainty of two results

- Total = variation of test$_1$ + variation of test$_2$
- $= z \times \sqrt{(CV_{A1}^2 + CV_{A2}^2)}$
- $= z \times \sqrt{(2 \times CV_A^2)}$
- $= z \times \sqrt{2} \times CV_A$
- $= 1.96 \times 1.414 \times CV_A = 2.77 * CV_A$

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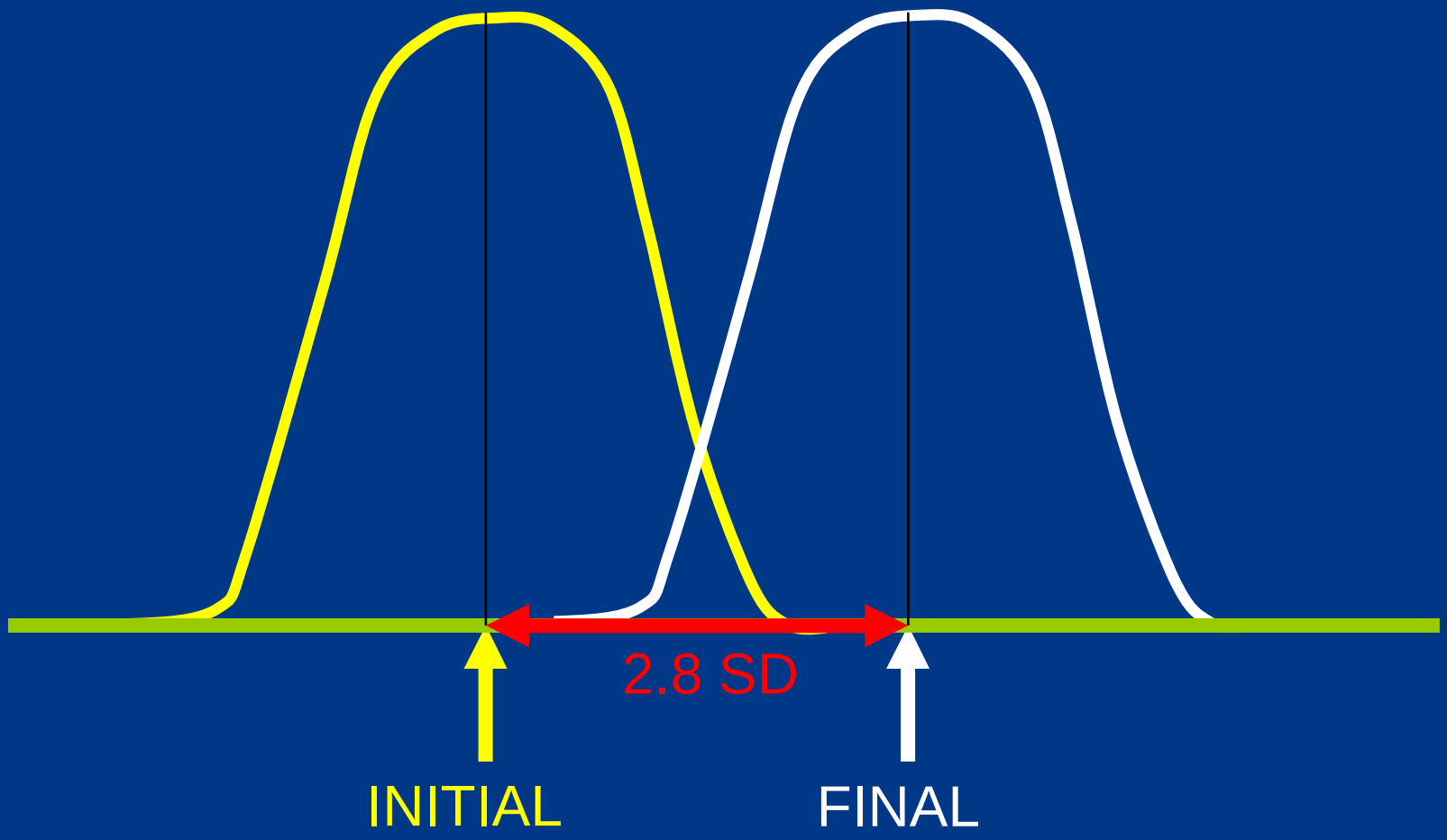
95% confidence in a analytical change:



4. What is the clinical value of MU?

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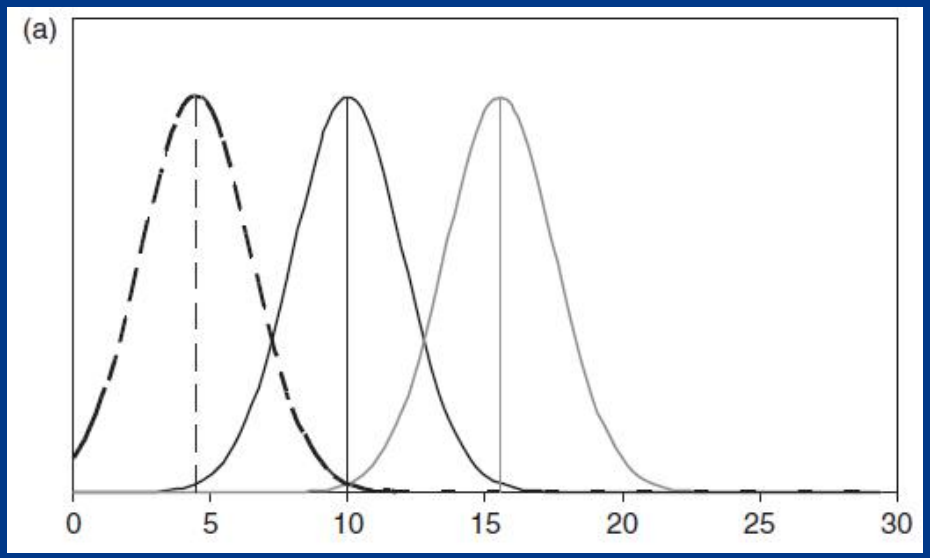
aacb testing for health

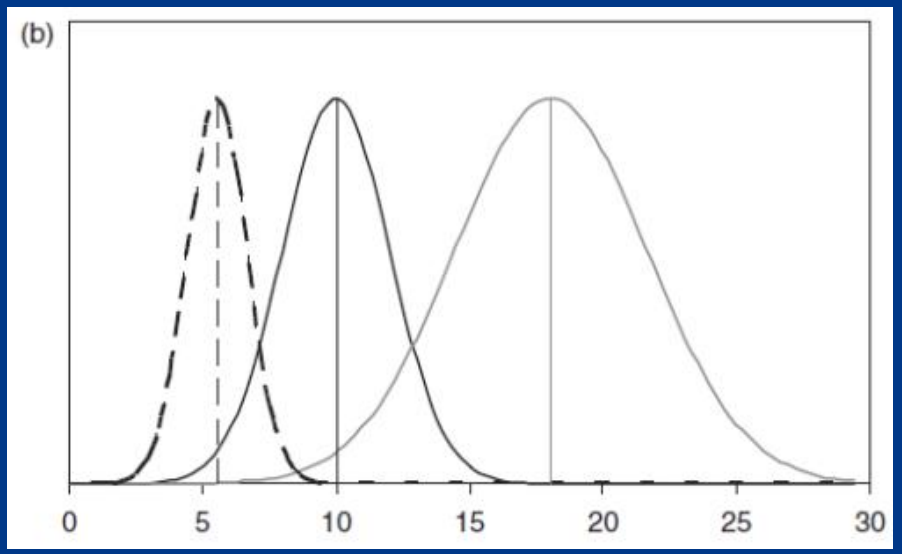
Ann Clin Biochem 2009; 46: 517–519.

Critical difference calculations revised: inclusion of variation in standard deviation with analyte concentration

Graham Ross Dallas Jones[1,2]



CD equally spaced at ±5.54 units.



CD decrease of −4.45 units and increase of 8.04 units

Figure 1 Graphical example of the current (a) and revised (b) calculations of critical difference (CD). A simulation of a test with a CV_{tot} of 20% and a first result of 10 units.

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Significant change

- Also referred to as
  - Reference change value
  - Critical difference
  - 'Delta check ?'
    - CLINICAL CHANGE

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Overall patient variability of two results

Total = variation of $test_1$ + variation of $test_2$

$$= z \times \sqrt{(CV_A^2 + CV_B^2)} + z \times \sqrt{(CV_A^2 + CV_B^2)}$$

$$= z \times \sqrt{(2 \times (CV_A^2 + CV_B^2))}$$

$$= \sqrt{2} \times z \times \sqrt{(CV_A^2 + CV_B^2)}$$

$$= 2.8 \times \sqrt{(CV_A^2 + CV_B^2)}$$

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LFT's Female DOB 30/1/1934

Date	29/01	28/04	14/05	02/07	Units	Range
S BILI	38*	29*	27*	34*	umol/L	(2-20)
S ALP	234*	192*	206*	193*	U/L	(30-120)
S GGT	93*	83*	87*	74*	U/L	(5-45)
S ALT	124*	137*	113*	103*	U/L	(5-40)
S AST	187*	202*	167*	166*	U/L	(5-40)

Are any of these results different to the previous?

4. What is the clinical value of MU?

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LFT's Female DOB 30/1/1934

Date	29/01	28/04	14/05	02/07	Units	Range	CD_A
S BILI	38	29	27	34	umol/L	(2-20)	4
S ALP	234	192	206	193	U/L	(30-120)	25
S GGT	93	83	87	74	U/L	(5-45)	8
S ALT	124	137	113	103	U/L	(5-40)	12
S AST	187	202	167	166	U/L	(5-40)	15

Are any of these results different to the previous?

4. What is the clinical value of MU?

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LFT's Female DOB 30/1/1934

Date	29/01	28/04	14/05	02/07	Units	Range	CD_A	CD_T
S BILI	38	*29*	27	*34*	umol/L	(2-20)	4	23
S ALP	234	*192*	206	193	U/L	(30-120)	25	44
S GGT	93	*83*	87	*74*	U/L	(5-45)	8	33
S ALT	124	*137*	*113*	103	U/L	(5-40)	12	81
S AST	187	202	*167*	166	U/L	(5-40)	15	61

Are any of these results different to the previous?

Some results are analytically different,

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LFT's Female DOB 30/1/1934

Date	29/01	28/04	14/05	02/07	Units	Range	CD_A	CD_T
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S AST	187	202	*167*	166	U/L	(5-40)	15	61

Are any of these results different to the previous?

Some results are analytically different,
But none are clinically different.

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aacb testing for health

824 CLINICAL CHEMISTRY, Vol. 36, No. 5, 1990

The Significance of Significant Figures

Robert C. W. Hawkins Roger N. Johnson

- Can we really distinguish the critical difference between two results?
- Biological difference in the patients results
  - $2.77 \times \sqrt{(SD_A^2 + SD_W^2)}$
- Analytical difference in the patients results
  - $2.77 \times SD_A$
    - < 1.9 then round to ones "126"
    - < 9.9 then round to fives "125"
    - < 19 then round to tens "130"
    - < 99 then round to fifties "150"
    - < 190 then round to hundreds "100"

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Ann Clin Biochem 2004; **41**: 385–390

Objective determination of appropriate reporting intervals

Tony Badrick[1], Susan R Wilson[2], Goce Dimeski[3] and Peter E Hickman[3]

- The majority of analytes are inappropriately reported when analytical precision alone is considered. The concept of uncertainty of measurement has not been adequately addressed.

Table 1. *Reporting intervals for general chemistry analytes*

Analyte	Analyser	Concentration or activity	Standard deviation (*s*)	Reporting interval* 95% confidence (2.77*s*)	50% confidence (0.954*s*)	Usual reporting interval	Meets RI_{50} criteria**	Recommended reporting interval**
Albumin	Hitachi Modular D	23 g/L	1.2	3.3	1.1	1 g/L	N	1 g/L
		42 g/L	1.3	3.6	1.2	1 g/L	N	1 g/L
ALP	Hitachi Modular D	35 U/L	1.2	3.3	1.1	1 U/L	N	1 U/L
		208 U/L	5.4	15	5.2	1 U/L	N	5 U/L
ALT	Hitachi Modular D	36 U/L	1.3	3.6	1.2	1 U/L	N	1 U/L
		195 U/L	4.1	11	3.9	1 U/L	N	5 U/L
AST	Hitachi Modular D	25 U/L	1.2	3.3	1.1	1 U/L	N	1 U/L
		217 U/L	3.2	8.9	3.1	1 U/L	N	5 U/L

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LFT's Female DOB 30/1/1934

Date	29/01	28/04	14/05	02/07	Units	Range
S BILI	38	*29*	27	*34*	umol/L	(2-20)
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S ALT	124	*137*	*113*	103	U/L	(5-40)
S AST	187	202	*167*	166	U/L	(5-40)

4. What is the clinical value of MU?

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LFT's Female DOB 30/1/1934

Date	29/01	28/04	14/05	02/07	Units	Range
S BILI	40	*30*	30	*35*	umol/L	(2-20)
S ALP	250	*200*	200	200	U/L	(30-120)
S GGT	95	*85*	90	*75*	U/L	(5-45)
S ALT	120	*140*	*110*	100	U/L	(5-40)
S AST	190	200	*170*	170	U/L	(5-40)

4. What is the clinical value of MU?

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Glucose Uncertainty & Variability

- Analytical Uncertainty
  - Glucose CV_A=2.4% (QAP)
- Biological variability
  - Fasting blood glucose CV_B= 7%
  - (2h post-load glucose CV_B=15%)
    - Scand J Clin Lab Invest. 2002;62(8):623-30.

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Commenting 1

- Fasting Glucose = 8.5 mmol/L
- Analytical uncertainty = 2.4%
  - Analytical confidence 8.5 +/- 0.4 mmol/L
- Biological variability = 7.0%
  - Biological confidence 8.5 +/- 1.2 mmol/L
- *"Diabetic Fasting Glucose."*

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Commenting 2

- Fasting Glucose = 7.5 mmol/L
- Analytical uncertainty = 2.4%
  - Analytical confidence 7.5 +/- 0.4 mmol/L
- Biological variability = 7.0%
  - Biological confidence 7.5 +/- 1.1 mmol/L
- *"Diabetic Fasting Glucose - Suggest repeat to confirm."*

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Commenting 3

- Fasting Glucose = 7.0 mmol/L
- Analytical uncertainty = 2.4%
  - Analytical confidence 7.0 +/- 0.3 mmol/L
- Biological variability = 7.0%
  - Biological confidence 7.0 +/- 1.0 mmol/L
- *"Borderline Fasting Glucose - Suggest repeat to confirm."*

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Change in HbA1c - 1

- 21/1/2004
- HbA1c 7.9
- "Fair diabetic control"

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Change in HbA1c - 2

	21/1/2004	30/4/2004
HbA1c	7.9	8.1

- "Bad diabetic control"

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Significant HbA1c changes

- HbA1c
  - CV_A=2.0%
  - CV_B=4.3%
- Analytical Difference = $2.77 * CV_A$
  - 8.0% +/- 0.4
- Critical Difference = $2.77 * \sqrt{(CV_A^2 + CV_B^2)}$
  - 8.0% +/- 1.0

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Change in HbA1c - 3

	21/1/2004	30/4/2004
HbA1c	7.9	8.1

- "No significant change in HbA1c, diabetic control is now bad."
- ??

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Change in HbA1c - 4

	21/1/2004	30/4/2004
HbA1c	7.9	8.1

- "Diabetic control remains borderline poor."

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Laboratory Confidence

- How does understanding components of analytical uncertainty contribute to clinical confidence.
  - Laboratory can solve QC failures faster.
  - Faster TAT to clinician.
  - Greater understanding of occasional analytical errors that are released
    - Prevented
    - Explained to clinician

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Summary (1)

- Clinical Biochemists have been aware of the degree of result dispersion and the contributory factors for decades.
- However, estimates of precision (CV%) and bias have had little clinical relevance.
- Laboratories are responsible for
  - Identifying their measurement uncertainty.
  - Ensuring doctors are aware of it.
  - Understanding its potential clinical impact.

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Summary (2)

- *Uncertainty is clinically important*
  - *Any single test result has an uncertainty.*
  - *Uncertainty must be kept within useful limits.*
  - *Diagnosis is made allowing for uncertainty.*
  - *Monitoring for significance changes is made by allowing for uncertainty.*
  - *Ability to gain and maintain clinicians confidence depends on our understanding of uncertainty.*


83°
130°
135°
120°
112°
145°
50°
58°
97°
83°
Angling

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aacb
testing for health

Dr Ken Sikaris 14th June 2009

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Precision Profile

- Use uncertainty profile that covers all the measuring concentration range

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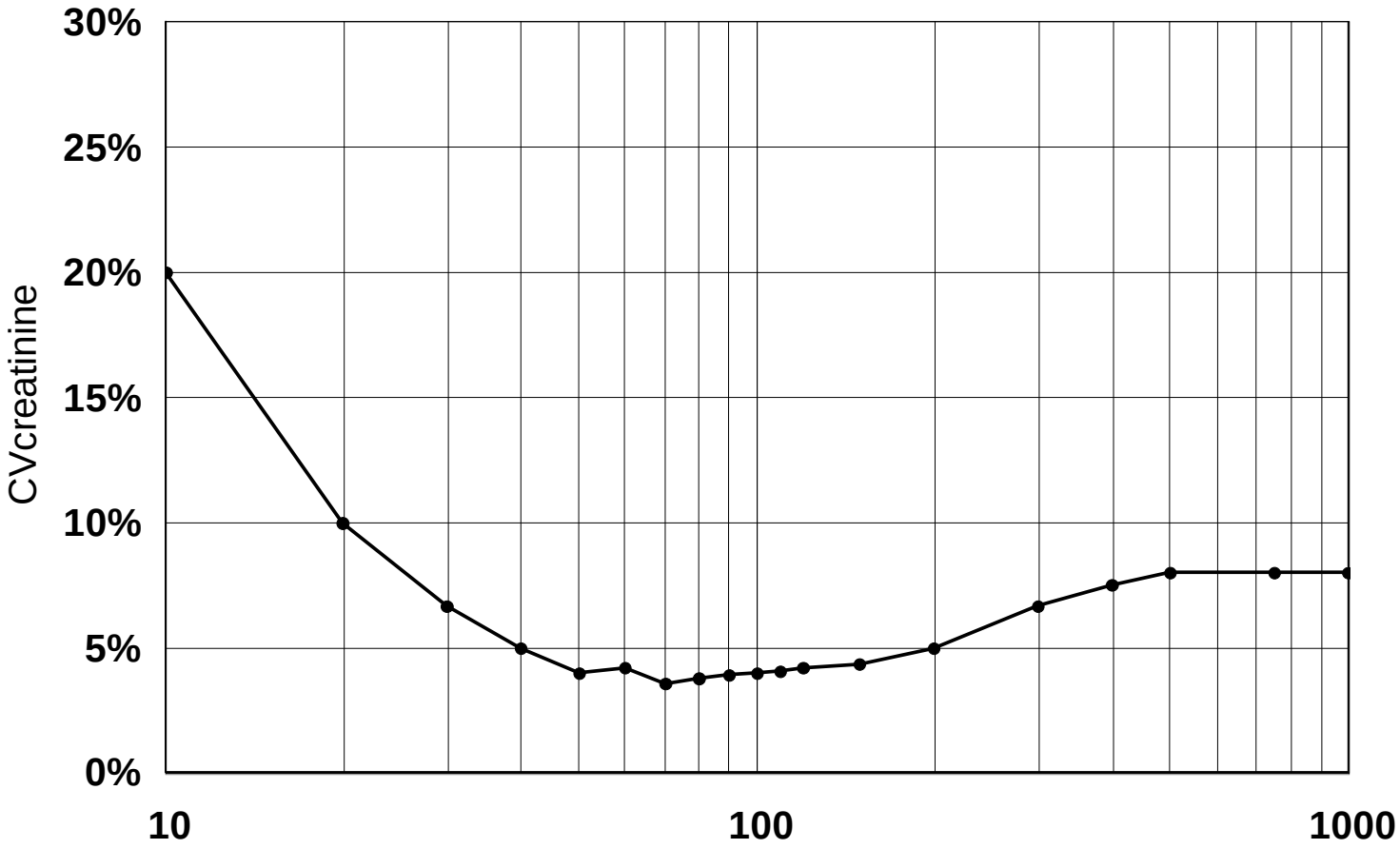
'Creatinine'



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CREATININE Critical Difference