APFCB WEBINAR

MEASUREMENT UNCERTAINTY

Friday 24th July 2010

Dr Ken Sikaris
MBBS BSc(Hons) FRCPA FAACB
Melbourne Pathology.
OUTLINE

1. What is MU?

2. How is MU estimated?

3. How can MU be reported?

4. What is the clinical value of MU?
### 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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1. What is MU?

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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

1. What is MU?
What is MU?
1. What is MU?

Dr Ken Sikaris 14th June 2009

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

---

1. What is MU?
Dr Ken Sikaris 24th July 2010
1. What is MU?

Dr Ken Sikaris 24th July 2010
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
  • 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 2.2.4

GUM 3.2.1

1. What is MU?
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Types of Error

- Random error
  - Cannot be eliminated, only reduced.
  - Unpredictable temporal and spatial variations

- Systematic error
  - 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*
<table>
<thead>
<tr>
<th>Date</th>
<th>29/01</th>
<th>28/04</th>
<th>14/05</th>
<th>02/07</th>
<th>Units</th>
<th>Range</th>
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<tbody>
<tr>
<td>S BILI</td>
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<td>umol/L</td>
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<tr>
<td>S AST</td>
<td>187</td>
<td>202</td>
<td>167</td>
<td>166</td>
<td>U/L</td>
<td>(5-40)</td>
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Some clinicians (and patients) believe that the results from laboratory assays have little of no uncertainty.

1. What is MU?
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
2. How is MU estimated?

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How is MU estimated?
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.
ISO 15189 – 2003(E)

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

2. How is MU estimated?
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2. How is MU estimated?
Dr Ken Sikaris 24th July 2010
Estimating MU

1. Define the Measurand.

2. Identify all Sources of Uncertainty.

3. Quantify the Individual Uncertainties.

4. Calculate Combined Uncertainty
Define the Measurand

2. How is MU estimated?
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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.
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
Identify all Sources of Uncertainty
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

2. How is MU estimated?
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2. How is MU estimated?
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.

2. How is MU estimated?
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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.

2. How is MU estimated?

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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.
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.

2. How is MU estimated?

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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
Quantify the individual uncertainties

2. How is MU estimated?
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2. How is MU estimated?
Dr Ken Sikaris 24th July 2010
The mean

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

2. How is MU estimated?
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The variance

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

2. How is MU estimated?

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The standard deviation

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

2. How is MU estimated?
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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
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
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.

2. How is MU estimated?
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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
## How many data points? GUM Table E1

<table>
<thead>
<tr>
<th>n</th>
<th>Percent Increase in Uncertainty</th>
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<tbody>
<tr>
<td>2</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td>52%</td>
</tr>
<tr>
<td>4</td>
<td>42%</td>
</tr>
<tr>
<td>5</td>
<td>36%</td>
</tr>
<tr>
<td>10</td>
<td>24%</td>
</tr>
<tr>
<td>20</td>
<td>16%</td>
</tr>
<tr>
<td>30</td>
<td>13%</td>
</tr>
<tr>
<td>50</td>
<td>10%</td>
</tr>
</tbody>
</table>

2. How is MU estimated?

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CV = 5% : Estimates using n=3
CV = 5% : Estimates using n=4
CV = 5% : Estimates using n=5
CV = 5% : Estimates using n=10

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CV = 5% : Estimates using n=20
CV = 5% : Estimates using n=30
CV = 5% : Estimates using n=40

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CV = 5% : Estimates using n=50
CV = 5% : Estimates using n=100
CV = 5% : Estimates using n=200

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CV = 5% : Estimates using n=300
CV = 5% : Estimates using n=400
CV = 5% : Estimates using n=500
CV = 5% : Estimates using n=1000
Uncertainty of Uncertainty

![Graph showing the relationship between CV and n]

- **CV**: Coefficient of Variation
- **n**: Sample size

The graph illustrates how the CV decreases as the sample size (n) increases, indicating a reduction in uncertainty with larger sample sizes.
2. How is MU estimated?

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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.’
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.’

2. How is MU estimated?
## External QA vs Internal QC

<table>
<thead>
<tr>
<th></th>
<th>External QA</th>
<th>Internal QC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Matrix</strong></td>
<td>Not patients</td>
<td>Not patients</td>
</tr>
<tr>
<td><strong>Concentration points</strong></td>
<td>8</td>
<td>2 or 3</td>
</tr>
<tr>
<td><strong>Analytical Range</strong></td>
<td>Wider</td>
<td>Reference Interval</td>
</tr>
<tr>
<td><strong>Measurements</strong></td>
<td>&lt;=16</td>
<td>Hundreds/Thousands*</td>
</tr>
<tr>
<td><strong>Period</strong></td>
<td>Months</td>
<td>Months – Years*</td>
</tr>
<tr>
<td><strong>Bias</strong></td>
<td>Estimated*</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Outliers</strong></td>
<td>Included</td>
<td>Excluded*</td>
</tr>
</tbody>
</table>

*Advantages

2. How is MU estimated?

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2. How is MU estimated?

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## Creatine Kinase

<table>
<thead>
<tr>
<th>QA</th>
<th>QC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV%</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>(19\textsuperscript{th} Percentile)</td>
</tr>
<tr>
<td>Range</td>
<td>61 - 788</td>
</tr>
<tr>
<td></td>
<td>135, 451</td>
</tr>
</tbody>
</table>

2. How is MU estimated?

Dr Ken Sikaris 24\textsuperscript{th} July 2010
2. How is MU estimated?
Dr Ken Sikaris 24th July 2010

Calculate Combined Uncertainty
Combined Uncertainty ($u_c$)

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

- **Combined (standard) uncertainty**
  - $u_c$ : the ‘sum’ of the known standard deviations

GUM 2.3.1

GUM 2.3.4
Combining Individual Uncertainties SD’s

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

2. How is MU estimated?
Sum or Difference

• Anion Gap

\[- AG = (Na + K) - (Cl + HCO_3^-) \]

\[- SD_{AG}^2 = SD_{Na}^2 + SD_{K}^2 + SD_{Cl}^2 + SD_{HCO_3}^2 \]

2. How is MU estimated?

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Combining Individual Uncertainties CV%’s

- For product (or quotient)
  - \( V = X \times Y \) \((V = X / Y)\)
  
  - \( CV_{V}^2 = CV_{X}^2 + CV_{Y}^2 \)

- Use CV% (not absolute SD)

2. How is MU estimated?
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Product or Quotient

- **Creatinine Clearance**
  
  - Clearance = \( \frac{U_{Cr} \times \text{Vol}}{P_{Cr} \times \text{Time}} \)
  
  - \( CV_{\text{Clearance}}^2 = CV_{U_{Cr}}^2 + CV_{\text{Vol}}^2 + CV_{P_{Cr}}^2 + CV_{\text{Time}}^2 \)
EDMA  European Diagnostic Manufacturer Association

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

2. How is MU estimated?

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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

- Minimum approach – long term

\[ u_C(y) = \sqrt{(u_{Calibration}^2 + u_{Imprecision}^2)} \]

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

2. How is MU estimated?
Expanded Uncertainty (U)

- Expanded uncertainty
  - The confidence limits around a result

- Coverage factor
  - The number of SD’s for the confidence limit
  - \( U = u_c \times k \)

GUM 2.3.5
GUM 2.3.6

2. How is MU estimated?
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## Coverage factor

<table>
<thead>
<tr>
<th>k</th>
<th>Coverage Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>68.27% confidence</td>
</tr>
<tr>
<td>1.64</td>
<td>90%</td>
</tr>
<tr>
<td>1.96</td>
<td>95%</td>
</tr>
<tr>
<td>2.00</td>
<td>95.45%</td>
</tr>
<tr>
<td>2.58</td>
<td>99%</td>
</tr>
<tr>
<td>3.00</td>
<td>99.73%</td>
</tr>
</tbody>
</table>

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

2. How is MU estimated?

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3. How can MU be reported?

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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.”
5.8.3

- uncertainty of measurement should be provided upon request;
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

3. How can MU be reported?
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Other Reporting mechanisms

- Significant figures
- Commenting

3. How can MU be reported?
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What is the clinical value of MU?
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

4. What is the clinical value of MU?
5.4.7.2

The laboratory shall use methods which meet the needs of the client
The laboratory shall use examination procedures, …… which meet the needs of the users of laboratory services and are appropriate for the examinations.
Clinical Application Overview

A: Appropriateness for Use
   – Analytical uncertainty & biological variability

B: Diagnosis
   – Clinical Decision Limit (e.g., 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

4. What is the clinical value of MU?
LFT’s Female DOB 30/1/1934

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<tr>
<th>Date</th>
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Some clinicians (and patients) believe that the results from laboratory assays have little of no uncertainty.

1. What is MU?

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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

4. What is the clinical value of MU?
A single result represents a distribution

4. What is the clinical value of MU? Slide courtesy of Callum G Fraser

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Data on biological variation

Over the years, many compilations


2010 update at
http://www.westgard.com/biodatabase1.htm
Within-subject biological variation in disease: collated data and clinical consequences

Carmen Ricós¹,², Natalia Iglesias², José-Vicente García-Lario¹,³, Margarita Simón¹,⁴, Fernando Cava¹,⁵, Amparo Hernández¹,⁶, Carmen Perich¹,⁷, Joanna Minchinela¹,⁸, Virtudes Alvarez¹,⁶, María-Vicenta Doménech¹,⁹, Carlos-Victor Jiménez¹,⁸, Carmen Biosca¹⁰ and Raquel Tena²

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Matrix</th>
<th>CV (%) Healthy (median)</th>
<th>n</th>
<th>d</th>
<th>s</th>
<th>Disease</th>
<th>Ref</th>
<th>Mean</th>
<th>Units</th>
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<tbody>
<tr>
<td>α1-Antitrypsin</td>
<td>S</td>
<td>12</td>
<td>12</td>
<td>30</td>
<td>180</td>
<td>Colon neoplasm</td>
<td>10</td>
<td>2.86</td>
<td>µg/L</td>
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<tr>
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<td>S</td>
<td>35</td>
<td>40</td>
<td>180</td>
<td>3-10</td>
<td>Hepatic disease, no cirrhosis</td>
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<td>4.07</td>
<td>µg/L</td>
</tr>
<tr>
<td>α1-Antitrypsin</td>
<td>S</td>
<td>38</td>
<td>85</td>
<td>180</td>
<td>3-10</td>
<td>Hepatocellular carcinoma</td>
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<td>3.97</td>
<td>µg/L</td>
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<tr>
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<td>40</td>
<td>45</td>
<td>180</td>
<td>3-6</td>
<td>Cirrhosis</td>
<td>10</td>
<td>3.83</td>
<td>µg/L</td>
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<tr>
<td>Alanine aminotransferase</td>
<td>S</td>
<td>4.1</td>
<td>4.3</td>
<td>20</td>
<td>28</td>
<td>7</td>
<td>Chronic liver disease</td>
<td>29</td>
<td>1.39</td>
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<tr>
<td>ALT</td>
<td>S</td>
<td>24</td>
<td>11</td>
<td>20</td>
<td>28</td>
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<td>Chronic liver disease</td>
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<td>56</td>
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<td>0.52</td>
<td>µkat/L</td>
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<tr>
<td>ALT</td>
<td>S</td>
<td>38</td>
<td>9</td>
<td>2</td>
<td>11</td>
<td>Impaired renal function</td>
<td>23</td>
<td>0.21</td>
<td>µkat/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>S</td>
<td>3.1</td>
<td>2.8</td>
<td>16</td>
<td>56</td>
<td>8</td>
<td>Type I DM</td>
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<td>4.4</td>
</tr>
<tr>
<td>Albumin</td>
<td>S</td>
<td>2.9</td>
<td>8</td>
<td>21</td>
<td>8</td>
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<td>20</td>
<td>135</td>
<td>ng/L</td>
</tr>
</tbody>
</table>
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, Minchinola J, Parich 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 Fibrinogen
- Albumin through CA 549 antigen
- Calcium through Cyslein
- Dehydroepiandrosterone sulfate through Homocysteine
- Immunoglobulin A through Lycopene
- Magnesium through Osteo, output
- pCO2 through Rheumatoid factor
- S02 antigen through Zinc
Callum Fraser
4. What is the clinical value of MU?
4. What is the clinical value of MU?

Dr Ken Sikaris 14th June 2009
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Dr Ken Sikaris 14th June 2009
4. What is the clinical value of MU?

Dr Ken Sikaris 14th June 2009
### Appropriate Imprecision

<table>
<thead>
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<td>Desirable</td>
<td>0.50</td>
</tr>
<tr>
<td>Optimum</td>
<td>0.75</td>
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</table>

4. What is the clinical value of MU?
B: Diagnosis

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

4. What is the clinical value of MU?
4. What is the clinical value of MU?

Analytical imprecision widens reference intervals

4. What is the clinical value of MU?

2.5% RI 2.5%

False low

Biological

Biological plus analytical

False high

Slide courtesy of Callum G Fraser
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.
Effect of Imprecision on Cutoff Diagnosis

- Cutoff is absolute.

- Cholesterol $\geq 5.5$ mmol/L
- Fasting Glucose $\geq 7.0$ mmol/L
- Opiates $\geq 300$ ug/L
- $9\Delta$THC $\geq 15$ ug/L
- Pregnant hCG $\geq 25$ IU/L

4. What is the clinical value of MU?
4. What is the clinical value of MU?

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

Dr Ken Sikaris 24th July 2010
Analytical confidence above a cutoff:

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
Analytical confidence above a cutoff:

No confidence
‘Borderline’

<1.96SD

CUTOFF RESULT

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
MONITORING

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

4. What is the clinical value of MU?
4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
Analytical uncertainty of two results

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

- = \( z \times \sqrt{(2 \times CV_A^2)} \)

- = \( z \times \sqrt{2} \times CV_A \)

- = \( 1.96 \times 1.414 \times CV_A = 2.77 \times CV_A \)

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
95% confidence in a analytical change:

4. What is the clinical value of MU?
Critical difference calculations revised: inclusion of variation in standard deviation with analyte concentration
Graham Ross Dallas Jones¹,²

**Figure 1** Graphical example of the current (a) and revised (b) calculations of critical difference (CD). A simulation of a test with a CV<sub>tot</sub> of 20% and a first result of 10 units.

CD equally spaced at ±5.54 units.

CD decrease of −4.45 units and increase of 8.04 units
Significant change

• Also referred to as

  – Reference change value
  – Critical difference
  – ‘Delta check ?’

• CLINICAL CHANGE

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
Overall patient variability of two results

Total = variation of test₁ + variation of test₂

\[ \begin{align*}
&= z \times \sqrt{(CV_A^2 + CV_B^2)} + z \times \sqrt{(CV_A^2 + CV_B^2)} \\
&= z \times \sqrt{2 \times (CV_A^2 + CV_B^2)} \\
&= \sqrt{2} \times z \times \sqrt{(CV_A^2 + CV_B^2)} \\
&= 2.8 \times \sqrt{(CV_A^2 + CV_B^2)}
\end{align*} \]

4. What is the clinical value of MU?

Dr Ken Sikaris 24\textsuperscript{th} July 2010
**LFT’s** Female DOB 30/1/1934

<table>
<thead>
<tr>
<th>Date</th>
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<th>14/05</th>
<th>02/07</th>
<th>Units</th>
<th>Range</th>
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</thead>
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<tr>
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<td>38*</td>
<td>29*</td>
<td>27*</td>
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<td>umol/L</td>
<td>(2-20)</td>
</tr>
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<td>S ALP</td>
<td>234*</td>
<td>192*</td>
<td>206*</td>
<td>193*</td>
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<td>(30-120)</td>
</tr>
<tr>
<td>S GGT</td>
<td>93*</td>
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<td>202*</td>
<td>167*</td>
<td>166*</td>
<td>U/L</td>
<td>(5-40)</td>
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Are any of these results different to the previous?

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
### LFT’s Female DOB 30/1/1934

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<td>137</td>
<td>113</td>
<td>103</td>
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<td>(5-40)</td>
<td>12</td>
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<td>166</td>
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<td>(5-40)</td>
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Are any of these results different to the previous?

4. What is the clinical value of MU?

Dr Ken Sikaris 24<sup>th</sup> July 2010
**LFT’s** Female DOB 30/1/1934

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Are any of these results different to the previous?

*Some results are analytically different,*

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
### LFT’s Female DOB 30/1/1934

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<td>(5-40)</td>
<td>15</td>
<td>61</td>
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</table>

Are any of these results different to the previous?

*Some results are analytically different,*

*But none are clinically different.*

4. What is the clinical value of MU?
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”
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**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Analyser</th>
<th>Concentration or activity</th>
<th>Standard deviation (s)</th>
<th>95% confidence (2.77s)</th>
<th>50% confidence (0.954s)</th>
<th>Usual reporting interval</th>
<th>Meets R\text{lab} criteria**</th>
<th>Recommended reporting interval**</th>
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<td>Hitachi Modular D</td>
<td>23 g/L</td>
<td>1.2</td>
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<td>1 g/L</td>
<td>N</td>
<td>1 g/L</td>
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<td>3.6</td>
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<td>5 U/L</td>
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<td>1.2</td>
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<td>1 U/L</td>
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**LFT’s**  Female DOB 30/1/1934

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<th>Date</th>
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<td>S ALP</td>
<td>234</td>
<td><strong>192</strong></td>
<td>206</td>
<td>193</td>
<td>U/L</td>
<td>(30-120)</td>
</tr>
<tr>
<td>S GGT</td>
<td>93</td>
<td><strong>83</strong></td>
<td>87</td>
<td><strong>74</strong></td>
<td>U/L</td>
<td>(5-45)</td>
</tr>
<tr>
<td>S ALT</td>
<td>124</td>
<td><strong>137</strong></td>
<td><strong>113</strong></td>
<td>103</td>
<td>U/L</td>
<td>(5-40)</td>
</tr>
<tr>
<td>S AST</td>
<td>187</td>
<td>202</td>
<td><strong>167</strong></td>
<td>166</td>
<td>U/L</td>
<td>(5-40)</td>
</tr>
</tbody>
</table>

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
# LFT’s Female DOB 30/1/1934

<table>
<thead>
<tr>
<th>Date</th>
<th>Units</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>29/01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28/04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14/05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>02/07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S BILI</td>
<td>40</td>
<td>30-35 umol/L (2-20)</td>
</tr>
<tr>
<td>S ALP</td>
<td>250</td>
<td>200-200 U/L (30-120)</td>
</tr>
<tr>
<td>S GGT</td>
<td>95</td>
<td>85-90 U/L (5-45)</td>
</tr>
<tr>
<td>S ALT</td>
<td>120</td>
<td>140-110 U/L (5-40)</td>
</tr>
<tr>
<td>S AST</td>
<td>190</td>
<td>200-170 U/L (5-40)</td>
</tr>
</tbody>
</table>

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
Glucose Uncertainty & Variability

- **Analytical Uncertainty**
  - Glucose $CV_A = 2.4\%$ (QAP)

- **Biological variability**
  - Fasting blood glucose $CV_B = 7\%$
  - (2h post-load glucose $CV_B = 15\%$)

4. What is the clinical value of MU?
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.”

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
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.**”

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
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.**”

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
Change in HbA1c - 1

- 21/1/2004
- HbA1c 7.9
- “Fair diabetic control”
# Change in HbA1c - 2

<table>
<thead>
<tr>
<th>Date</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/1/2004</td>
<td>7.9</td>
</tr>
<tr>
<td>30/4/2004</td>
<td>8.1</td>
</tr>
</tbody>
</table>

- “Bad diabetic control”

4. What is the clinical value of MU?
Significant HbA1c changes

- **HbA1c**
  - \( CV_A = 2.0\% \)
  - \( CV_B = 4.3\% \)

- **Analytical Difference** = \( 2.77 \times CV_A \)
  - 8.0\% +/- 0.4

- **Critical Difference** = \( 2.77 \times \sqrt{(CV_A^2 + CV_B^2)} \)
  - 8.0\% +/- 1.0

4. What is the clinical value of MU?

Dr Ken Sikaris 24\textsuperscript{th} July 2010
<table>
<thead>
<tr>
<th>Change in HbA1c - 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>21/1/2004</strong></td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
</tr>
</tbody>
</table>

- “No significant change in HbA1c, diabetic control is now bad.”

- ??

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
### Change in HbA1c - 4

<table>
<thead>
<tr>
<th>Date</th>
<th>HbA1c</th>
<th>21/1/2004</th>
<th>30/4/2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>7.9</td>
<td>8.1</td>
<td></td>
</tr>
</tbody>
</table>

“Diabetic control remains borderline poor.”

4. What is the clinical value of MU?

Dr Ken Sikaris 24th July 2010
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
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.
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.
Precision Profile

- Use uncertainty profile that covers all the measuring concentration range
'Creatinine'

![Creatinine Graph](image)

- **Creatinine Level** (umol/L)
- **CVcreatinine** (%)

Dr Ken Sikaris 24th July 2010
CREATININE Critical Difference

![Graph showing the relationship between Creatinine Level (umol/L) and Critical Difference. The graph displays a curve that increases sharply as Creatinine Level increases.]