量測不確定度應用篇
量測不確定度在臨床檢驗的範例

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課程內容

一. 了解實驗室與臨床需求內容
二. 制定量測不確定政策
三. 各類臨床實驗室量測不確定案例

需求面-符合實驗室與臨床的要求

Review

What information on measurement uncertainty should be communicated to clinicians, and how?

Clinical Biochemistry 57 (2018) 18–22

Mario Plebani*, Laura Sciacovelli, Daniela Bernardi, Ada Aita, Giorgia Antonelli, Andrea Padoan

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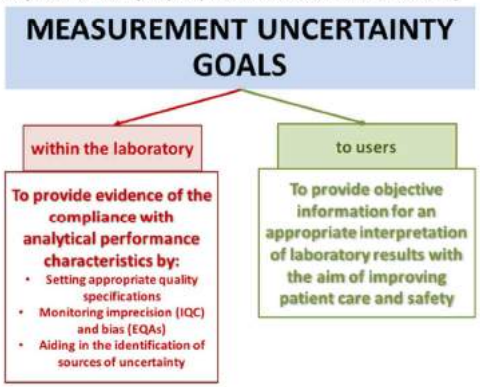

Fig. 1. Summary of the main goals of measurement uncertainty.

1. 結果值(含參考區間)
2. 總誤差(IQC+EQA)
3. RCV

結果值以及不確定度表示法

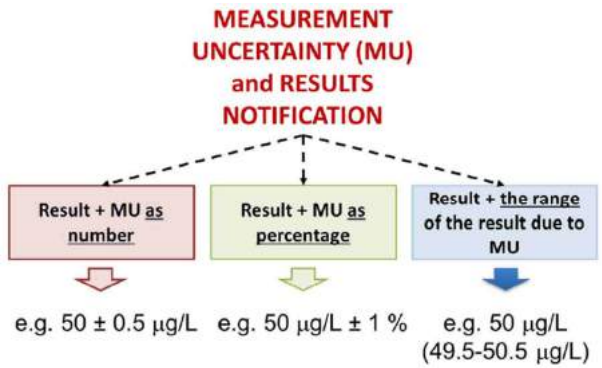

Fig. 4. Possible options to report measurement uncertainty in medical reports.

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Fig. 2. Example of reporting of Total Error (TE) in medical report.

Review

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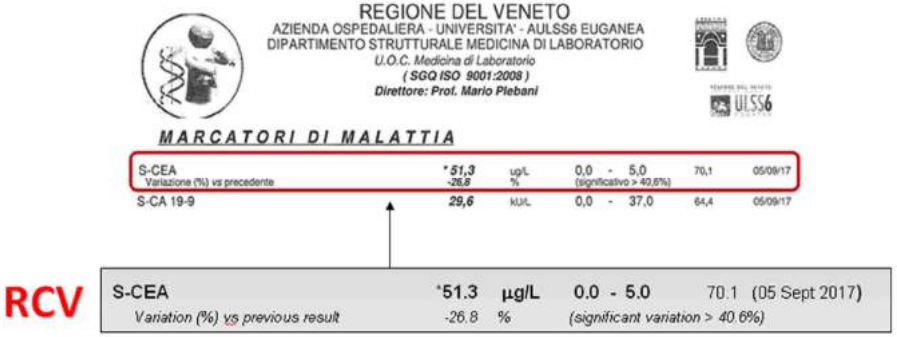
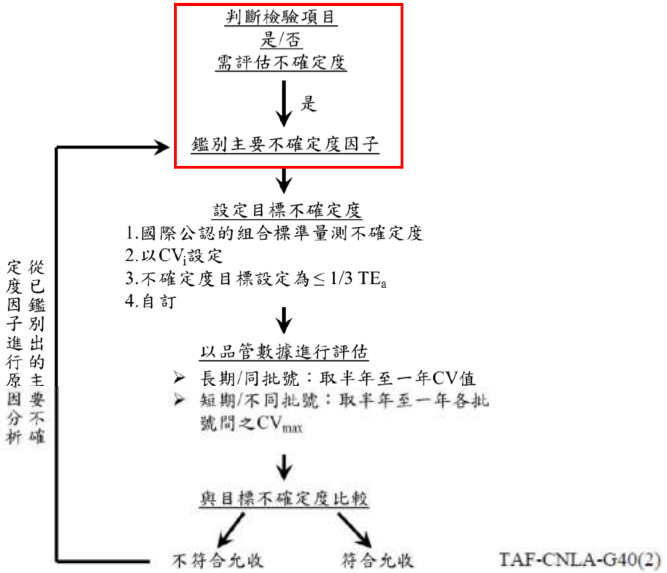


Fig. 3. Example of reporting of reference change value (RCV) in medical report. Significant variation (as %) indicates the RCV.

量測不確定度評估流程



量測不確定度實例-量測資訊

ANALYTE	hCG	Alkaline Phosphatase	Potassium	Albumin
MEASURAND	Serum/plasma intact βhCG, βhCG subunit concentration	Serum/plasma total alkaline phosphatase activity concentration	Serum/plasma /urine concentration (See separate entry for whole blood potassium)	Serum/plasma/urine concentration
MNEMONIC	βhCG	ALP	K	ALB
TEST PRINCIPLE	2 site sandwich microparticle immunoassay	PNPP/AMP	Valinomycin ion-selective electrode	Bromocresol purple dye-binding spectrophotometry
UNITS	IU/L	U/L	mmol/L	g/L
REFERENCE VALUES (Adults) see handbook for paediatric values	<5 IU/L - non-pregnant adult >25 IU/L - consistent with pregnancy	30-110 U/L - adult	Plasma: 3.2-4.3 mmol/L Serum: 3.5-5.0 mmol/L	In-patient: 31-44 g/L Out-patient: 33-46 g/L
TEST LIMITATIONS	For use in normal pregnancy only. Not to be used as a sole criterion for the diagnosis/management of trophoblastic or non-trophoblastic tumours.	None reported	Haemolysed specimens	Grossly haemolysed specimens
CLINICALLY SIGNIFICANT INTERFERENCES	Heterophilic antibodies; Murine antibodies used for imaging/therapy.	None reported	EDTA	None reported

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Table 1 Examples of measurand definition

Quantity intended to be measured	System	Kind-of-quantity	Measurement unit	Method
Sodium	Venous plasma	Amount of substance concentration	mmol/L	Flame photometry
Calcium ion	Arterial whole blood	Amount of substance concentration	mmol/L	Ion-selective electrode
Creatine kinase MB	Serum	Mass concentration	μg/L	two-site immunoassay
Creatine kinase MB	Serum	Activity concentration	mIU/L at 37°C	Immuno-inhibition
FMR1 gene	Genomic DNA	Number of CCG repeats in the FMR1 gene		Capillary electrophoresis
Chromosome 21	Cell	Number of FISH signals for chromosome 21 probe per cell		FISH
Haemoglobin	Venous whole blood	Mass concentration	g/L	Spectrophotometry
White cell count	Urine	Number concentration of white cells in urine	White cells per volume	Microscopy
Prolactin/ macroprolactin	Serum	Mass concentration	μg/L	two-site immunoassay
Rubella IgG	Serum	Rubella IgG + cross-reacting IgGs	Arbitrary units, IU/L	Immunoassay
Gentamicin	Serum	Trough mg/L–trough (8 hours post-dose)	mg/L	Immunoassay

Requirements for the Estimation of Measurement Uncertainty, 2007ed

量測不確定度實例-不確定度資訊

ANALYTE	hCG	Alkaline Phosphatase	Potassium	Albumin
CALIBRATOR TRACEABILITY	WHO 3rd IS 75/537 – calibrator values (IU/L): 0, 75, 250, 500, 1,000 Uncertainty data not provided by manufacturer	IFCC manual method, 1983 Calibrator value: 224 ± 5.03 U/L (95% confidence) Data from manufacturer	Gravimetry of analytical grade K salt. Low calibrator: 3.00 ± 0.02 mmol/L High calibrator: 7.00 ± 0.05 mmol/L (95% confidence) Data from manufacturer	470 Certified Reference Material (CRM), European Calibrator value: 38.2 ± 0.72 g/L (95% confidence) Data from manufacturer
ANALYTICAL BIAS	Mean 4.5% Cycle 21, QAP Endocrine.	N/A	N/A	N/A
UNCERTAINTY OF MEASUREMENT	Internal QC data for: 1/01/04 - 20/07/04 QC Mean 6.0 IU/L: SD: 0.47 IU/L CV: 8.2% 22.0 IU/L: SD: 1.2 IU/L CV: 5.4% 1754 IU/L: SD: 81 IU/L CV: 4.7%	Internal QC data for: 1/01/04 - 20/07/04 QC Mean 87 U/L: SD: 1.26 U/L CV: 1.45% 352 U/L: SD: 3.4 U/L CV: 0.97%	Internal QC data for : 1/01/04 - 20/07/04 QC Mean 4.2 mmol/L: SD: 0.04 mmol/L CV : 1.06% 6.2 mmol/L: SD: 0.05 mmol/L CV: 0.86%	Internal QC data for: 1/01/04 - 20/07/04 QC Mean 26.7 g/L: SD: 0.52 g/L CV: 1.95% 38.4 g/L: SD: 0.67 g/L CV: 1.75%

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標準品造成的不確定度

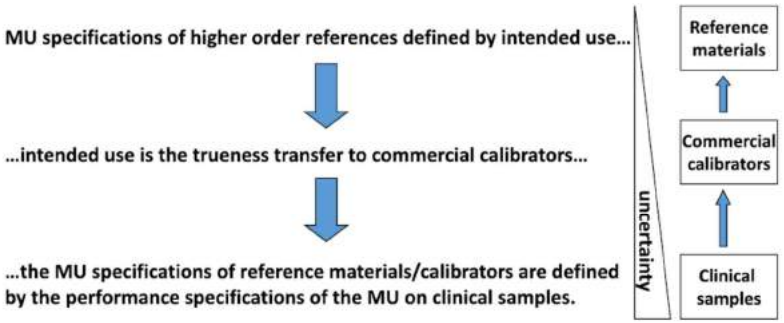

Fig. 3. Defining the suitability of the measurement uncertainty (MU) of higher order references by turning the approach upside down, focusing first on the established performance specifications for MU of clinical samples.

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The role of external quality assessment in the verification of in vitro medical diagnostics in the traceability era

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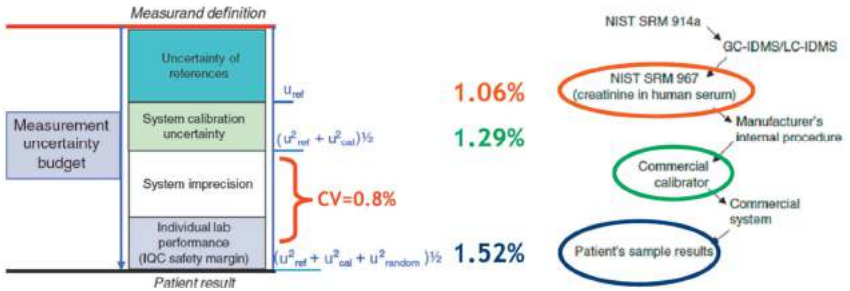
Abbott Architect c series
Creatinine enzymatic assay (code no. 8L24)
Multigent Clin Chem Calibrator (code no. 6K30)



量測不確定度實例-臨床適合度資訊

ANALYTE	hCG	Alkaline Phosphatase	Potassium	Albumin
ANALYTICAL GOAL	CV_A <5% at 25 IU/L Clinical requirement	CV_I = 6.4% (Westgard website) Desirable: < 0.5 CV_I = <3.2%	CV_I = 4.8% (Westgard website) Desirable: < 0.5 CV_I = <2.4%	CV_I = 3.1% (Westgard website) Desirable: < 0.5 CV_I = <1.6%
CV_A	5.4% at QC mean 22 U/L	1.45% at QC mean 87 U/L	1.06% at QC mean 4.2 mmol/L	1.75% at QC mean 38.4 g/L
FIT FOR PURPOSE	Borderline acceptable	Acceptable	Acceptable	Borderline unacceptable; assess relative QAP performance
REPORTABLE INTERVALS (Approximately 50% confidence – *see Reference 8*)	<20 IU/L: 1 U/L 20-100 IU/L: 2 U/L >1000 U/L: 100 U/L	< 300 U/L: 1 U/L > 300 U/L: 5 U/L	<10 mmol/L: 0.1 mmol/L	20-50 g/L: 1 g/L
ESTIMATION OF UNCERTAINTY OF MEASUREMENT FOR CLIENT INFORMATION	± 2 IU/L at 25 U/L ± 10% at >1,000 U/L	± 3 U/L for normal values ± 10 U/L at 500 U/L	± 0.1 mmol/L	± 1.5 g/L

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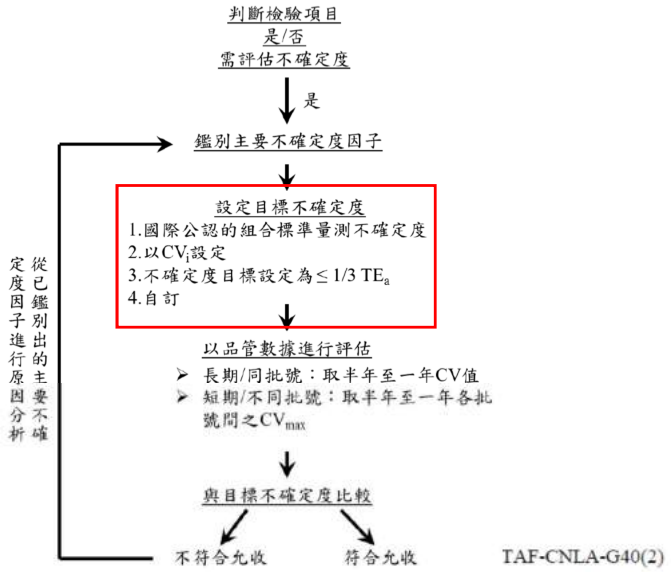
量測不確定度評估流程



設定品質目標(Quality goals)

- **品質的等級：**
  - 最低(minimum): conformance to requirements
  - 最高(maximum): demonstration of competency
- **品質目標：可容許總誤差**
  - Allowable total error (ATE，FDA)
  - Total error allowable (TEa，CLSI EP21)

TEa的制定

- 外部能力試驗
  - PT (proficiency testing)
  - EQA (external quality assessment)
- 實證醫學研究
- 專家、臨床醫師建議
- 生物變異性目標設定模式(Biological variability goal-setting models)

生物變異性目標設定模式 (1)

Quality goals in external quality assessment are best based on biology

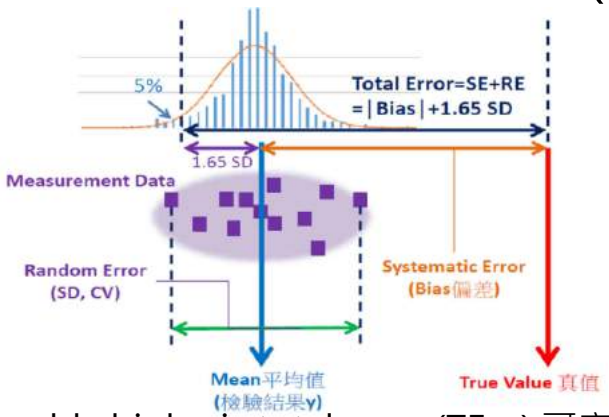
Scand J Clin Lab Invest 1993; 53 suppl. 212. Chapter I. Quality planning

C. G. FRASER & P. HYLTOFT PETERSEN

- 模式考慮以下因素：
  - CV_i: 個體內變異
  - CV_g: 個體間變異

- 定義分析目標：
  - Allowable analytical CV (CV_a) 可容許分析變異
    $= 0.5 \times CV_i$
  - Allowable analytical bias ($Bias_a$) 可容許分析偏差
    $= 0.25 \times \sqrt{CV_i^2 + CVg^2}$

生物變異性目標設定模式 (2)



- Allowable biologic total error (TEa_b) 可容許生物總誤差：
  $= Bias_a + 1.65 \times CV_a$
  $= 0.25 \times \sqrt{CV_i^2 + CVg^2} + 1.65 \times 0.5 \times CV_i$

生物內/間變異資料庫 (1)

Note on abbreviations:
CV_I = within-subject biologic variation
CV_G = between-subject biologic variation
I = desirable specification for imprecision
B = desirable specification for inaccuracy
TE = desirable specification for allowable total error

	Analyte	Number of Papers	Biological Variation		Desirable specification		
			CV_I	CVg	I(%)	B(%)	TE(%)
S-	11-Desoxycortisol	2	21.3	31.5	10.7	9.5	27.1
S-	17-Hydroxyprogesterone	2	19.6	50.4	9.8	13.5	29.7
U-	4-hydroxy-3-methoximandelate (VMA)	1	22.2	47.0	11.1	13.0	31.3
S-	5' Nucleotidase	2	23.2	19.9	11.6	7.6	26.8
U-	5'-Hydroxyindolacetate, concentration	1	20.3	33.2	10.2	9.7	26.5
S-	α1-Acid Glycoprotein	3	11.3	24.9	5.7	6.8	16.2
S-	α1-Antichymotrypsin	1	13.5	18.3	6.8	5.7	16.8
S-	α1-Antitrypsin	3	5.9	16.3	3.0	4.3	9.2
S-	α1-Globulins	2	11.4	22.6	5.7	6.3	15.7
U-	α1-Microglobulin, concentration, first morning	1	33.0	58.0	16.5	16.7	43.9
P-	α2-Antiplasmin	1	6.2	---	3.1	---	---
S-	α2-Globulins	2	10.3	12.7	5.2	4.1	12.6
S-	α2-Macroglobulin	4	3.4	18.7	1.7	4.75	7.56

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

生物內/間變異資料庫 (2)

Biological Variation Values

Desirable Analytical Quality Specifications for Imprecision, Bias and Total Error Upon Biological Variation

The following values are provided as a service to Bio-Rad Customers and are based upon desirable performance. The values are derived from Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minichela J, Perich C, Simon M. "Current databases on biologic variation: pros, cons and progress" Scand J Clin Lab Invest 1999;59:491-500. These values are updated/ modified with the most recent specifications made available in **2014**. ***(denotes updated values)**

S = serum; U = urine; P = plasma; B = blood
CV_w = within-subject biological variation; CV_b = between-subject biological variation; Imp = imprecision; TE_a = total allowable error

		BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
	ANALYTE	CV_w	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
S	11-Deoxycortisol	21.3	31.5	10.7	9.5	27.1	34.3
S	17-Hydroxyprogesterone	19.6	50.4	9.8	13.5	29.7	36.4
U	5-HIAA concentration, 24 h	20.3	33.2	10.2	9.7	26.5	33.4
S	5'Nucleotidase	23.2	19.9	11.6	7.6	26.8	34.7
S	α1-Acid glycoprotein	11.3	24.9	5.7	6.8	16.2	20.0
S	α1-Antitrypsin	5.9	16.3	3.0	4.3	9.2	11.2
S	α1-Globulin	11.4	22.6	5.7	6.3	15.7	19.6
S	α2-Globulins	10.3	12.7	5.2	4.1	12.6	16.1
U	α1-Microglobulin	33.0	58.0	16.5	16.7	43.9	55.1
S	α2-Macroglobulin	3.4	18.7	1.7	4.8	7.6	8.7
P	α-Aminobutyric Acid (AABA)	24.7	32.3	12.4	10.2	30.5	38.9
S	α-Amylase	8.7	28.3	4.4	7.4	14.6	17.5

http://www.qcnet.com/Portals/0/PDFs/BVValues1Final.pdf

能力試驗容許誤差

CLIA '88 PROFICIENCY TESTING LIMITS

ANALYTE	CLIA PROFICIENCY LIMIT
Alcohol, Blood	± 25%
Alanine Aminotransferase (ALT/SGPT)	± 20%
Albumin	± 10%
Alkaline Phosphatase	± 30%
Alpha-1 Antitrypsin	Target value ± 3 SD
Alpha-Fetoprotein (Tumor Marker) AFP	Target value ± 3 SD
Amylase	± 30%
Antinuclear Antibody	Target value ± 2 dilutions or positive/ negative
Antistreptolysin 0	Target value ± 2 dilutions or positive/ negative
Anti-Human Immunodeficiency Virus	Reactive or nonreactive
Aspartate Aminotrasnferase (AST/SGOT)	± 20%
Bilirubin, Total	Target value ± 20% or ± 0.4 mg/dl (greater)
Calcium, Total	Target value ± 1.0 mg/dl.
Carbamazepine	± 25%

TEa目標設定模式的等級

等級	$Bias_a$	CV_a
Minimal	$0.375 \times \sqrt{CV_i^2 + CVg^2}$	$1.65 \times 0.75 \times CV_i$
Desirable	$0.25 \times \sqrt{CV_i^2 + CVg^2}$	$1.65 \times 0.5 \times CV_i$
Optimum	$0.125 \times \sqrt{CV_i^2 + CVg^2}$	$1.65 \times 0.25 \times CV_i$

量測不確定度臨床生化實例(1)-HbA1c

受測量 Measurand	全血醣化血色素濃度 Concentration of HbA1c in Whole blood
單位 Unit	%
方法 Method	陽離子交換層析法 Cation –Exchange HPLC method
程序 Procedure	TOSOH HLC-723 G8 Variant Analysis Mode
目標不確定度 Target u	< 3%. From ADA: Diabetes Control and Complications trial (DCCT) – Level 1 Quality Goal (note: CVi=1.9%)
校正物追溯 Calibrator traceability	經由廠商取得其HbA1c校正物質，可追溯至NGSP認證證明(可追溯至DCCT醣化血色素標準)
校正物不確定度 u_{cal}	廠商校正物質追溯文件未能提供
偏移 Bias	有評估，以台灣醫事檢驗學會 TSLM Accuracy-based PT 結果評估。(note:亦可用 CRM 來評估)
報告位數 Reported value	HbA1c %小數一位
參考值 Reference values	4.0 % - 6.0 %
臨床決斷值 Clinical decision level	1.Pre-diabetes HbA1c 5.7%~6.4%. 2.Criteria for the diagnosis of DM HbA1c ≥6.5 %. 3.Target for treatment in diabetics <7%. 4.Change of therapy in diabetes >8%.

TAF-CNLA-G40(2)

量測不確定度臨床生化實例(1)-HbA1c

7.1.3 評估方式：

實驗室長期品管數據：

IQC:2013/1/2~2013/7/27	Level 1	Level 2
Lot No.	AB2010	AB2010
樣本數 *n*	213	213
平均值 Mean	4.97	9.89
標準差 Standard deviation	0.062	0.084

量測不確定度計算：

組合標準量測不確定度 u_c	0.062	0.084
相對組合標準不確定度 u_{rel}, CV %	1.2 %	0.8 %
目標不確定度 Target u < 3 %	< 3 %	< 3 %
判定水準 Fit for purpose	(1.2 % < 3 %) 符合允收目標	(0.8 % < 3 %) 符合允收目標

TAF-CNLA-G40(2)

量測不確定度臨床實例(1)-HbA1c

- 當HbA1c檢驗結果=6.3%
  - 接近QC Level 1 (mean = 4.97)
  - 擴充不確定度$U = k \times u = 2 \times 0.06\% = 0.12\% \fallingdotseq 0.1\%$
  - 報告格式：
    1. 6.3 ± 0.1%
    2. 6.3% (6.2~6.4%)

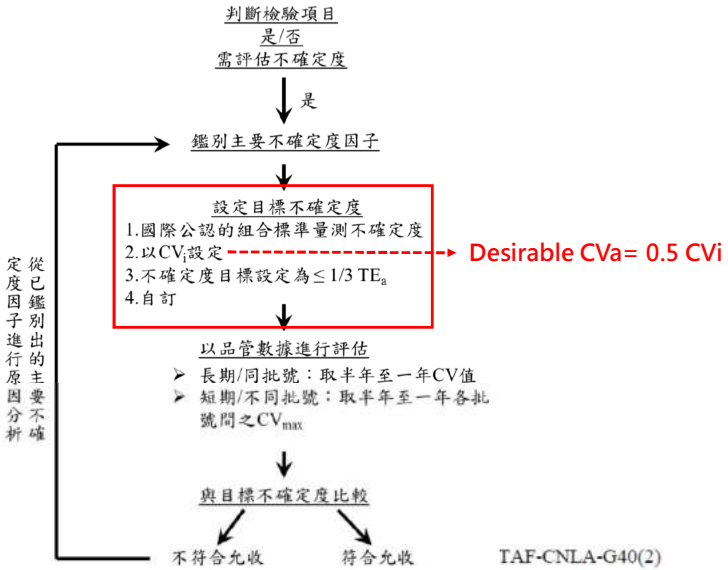
- 當HbA1c檢驗結果=8.3%
  - 接近QC Level 2 (mean = 9.89)
  - 擴充不確定度$U = k \times u = 2 \times 0.08\% = 0.16\% \fallingdotseq 0.2\%$
  - 報告：
    1. 8.3 ± 0.2%
    2. 8.3% (8.1~8.5%)

量測不確定度臨床實例(2)-PSA

受測量 Measurand	血清攝護腺特異性抗原濃度 Concentration of PSA in serum
單位 Unit	PSA, ng/mL
方法 Method	雙向免疫酵素分析法 Two-site enzyme-linked immunosorbent assay
程序 Procedure	PSA Test
目標不確定度 Target u	< 18.1 % From Westgard – Biological Variation Values Desirable Biological Variation Database specifications CV_i
校正物追溯 Calibrator traceability	Access Hybritech PSA Calibrators prEN ISO 17511
校正物不確定度 u_{rel}	廠商校正物質追溯文件未能提供
報告位數 Reported value	ng/mL 小數點下兩位
參考值 Reference values	< 4.0 ng/mL

TAF-CNLA-G40(2)

量測不確定度評估流程



量測不確定度臨床實例(2)-PSA

7.2.3 評估方式：

實驗室長期品管數據：

QC:2013/1/1~2013/6/30	Level 1	Level 2	Level 3
批號 Lot No.	QC 19951	QC 19952	QC 19953
樣本數 n	184	180	181
平均值 Mean	0.121	3.91	16.1
標準差 Standard deviation	0.0207	0.306	1.181

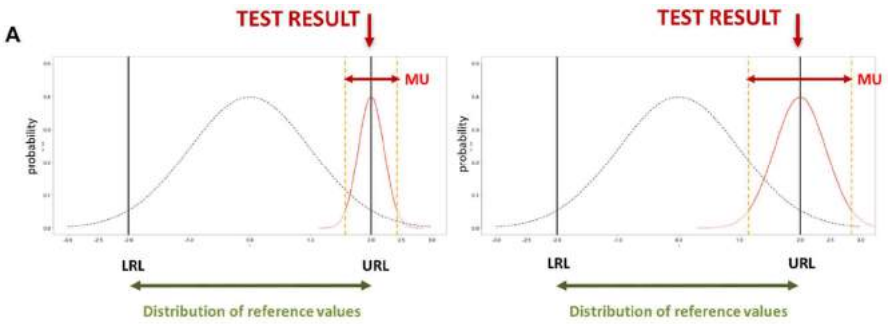
量測不確定度計算：

組合標準量測不確定度 u_c	0.02	0.31	1.18
相對組合標準不確定度 u_{rel}, CV %	17.10 %	7.83 %	7.34 %
目標不確定度 Target u: < 18.1 %	< 0.022	< 0.71	< 2.91
判定水準 Fit for purpose	(0.02 < 0.022) 符合允收目標	(0.31 < 0.71) 符合允收目標	(1.18 < 2.91) 符合允收目標

Target u =9.1%

TAF-CNLA-G40(2)

量測不確定度應用-
結果值落在參考區間邊界



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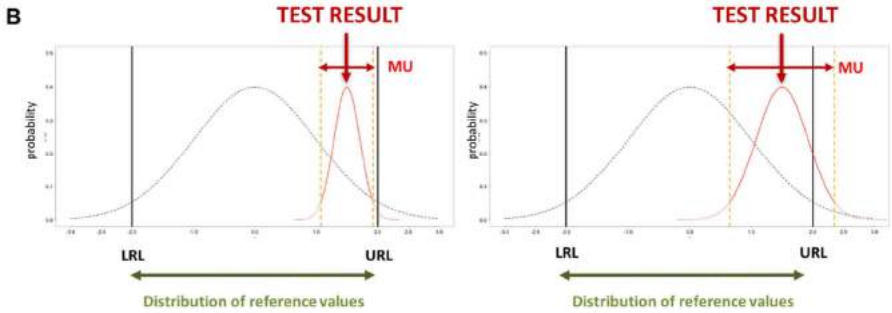
量測不確定度應用-
結果值落在參考區間內



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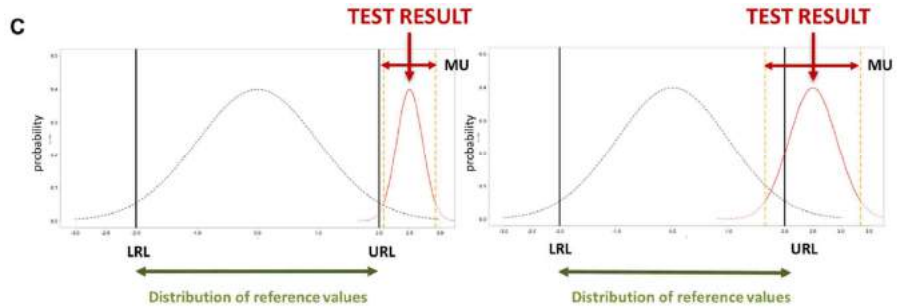
量測不確定度應用-
結果值落在參考區間外



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量測不確定度臨床實例(2)-PSA

- 當PSA檢驗結果=4.80 ng/mL，是否真的超過臨床決策值(>4.00 ng/mL)？
  - 接近QC Level 2 (mean = 3.91)
  - 擴充不確定度$U = k \times u = 2 \times 0.31 = 0.62$
  - 報告格式：
    1. 4.8 ± 0.62 ng/mL
    2. 4.8 ng/mL (4.18~5.42 ng/mL)
  - 因95%區間皆超過臨床決策值，建議做進一步病理檢查。

Reference Change Value (RCV)
參考變化值

- 應用時機：
  - 驗證同一檢體重新測試後差異是否顯著
  - 監控檢測數據是否產生顯著變化
- $CV_T^2 = CV_A^2 + CV_I^2 \rightarrow CV_T = \sqrt{CV_A^2 + CVI^2}$
- 95%區間，$k = 1.96 \rightarrow k \times CV_T$
- 兩次測試參考變化值(RCV)

$$= k \times \sqrt{CV_A^2 + CVI^2 + CV_A^2 + CVI^2}$$
$$= \sqrt{2} \times 1.96 \times \sqrt{CV_A^2 + CVI^2}$$
$$= 2.77 \times \sqrt{CV_A^2 + CVI^2}$$

(超過即有顯著差異，Delta check criteria)

RCV臨床案例應用

- 一男性病患一年前PSA檢測值為3.8 μg/L，本次檢查值為4.2 μg/L，請問PSA檢測數值是否真正上升？(已知u_{rel}=5%)

計算變化量：4.2 – 3.8 = 0.4 μg/L
計算變化率：0.4/3.8 × 100% = 10.5%

RCV臨床案例應用

計算變化量：4.2 – 3.8 = 0.4 μg/L
計算變化率：0.4/3.8 × 100% = 10.5%

- 同一個體，僅需考慮CV_A時，CV_I=0
- 此時，RCV = $2.77 \times \sqrt{CV_A^2 + CVI^2}$
  = 2.77 × 5% = 13.85% ≒ 13.9%
- 因 10.5% < 13.9%，無顯著上升。
  (至少需上升3.8 x 13.9% = 0.53 μg/L)

* 可用於短時間內監控或是同一檢體再次重測的狀況。

RCV臨床案例應用

計算變化量：4.2 – 3.8 = 0.4 μg/L
計算變化率：0.4/3.8 × 100% = 10.5%

- 同一個體，同時考慮CV_A、CV_I時 (CV_I =14%)
- 此時，RCV = $2.77 \times \sqrt{CV_A^2 + CVI^2}$
  $= 2.77 \times \sqrt{(5\%)^2 + (14\%)^2}$
  = 2.77 × 14.87% ≒ 41.2%
- 因 10.5% < 41.2%，無顯著上升。
  (至少需上升3.8 x 41.2% = 1.56 μg/L)

* 可用於長時間監控或是的狀況。

參考資料

- 醫學實驗室定量量測不確定度評估案例(TAF-CNLA-G40(2))
- Requirements for the Estimation of Measurement Uncertainty, National Pathology Accreditation Advisory Council. 2007ed
- Measurement Good Practice Guide No. 11 (Issue 2): A Beginner’ s Guide to Uncertainty of Measurement. National Physical Laboratory

參考資料

- Uncertainty of Measurement in Quantitative Medical Testing - A Laboratory Implementation Guide -, *Clin Biochem Rev* Vol 25 Suppl (ii) November 2004 I S1

課程結束，謝謝指教！