

# JCTLM Database – GAP analysis

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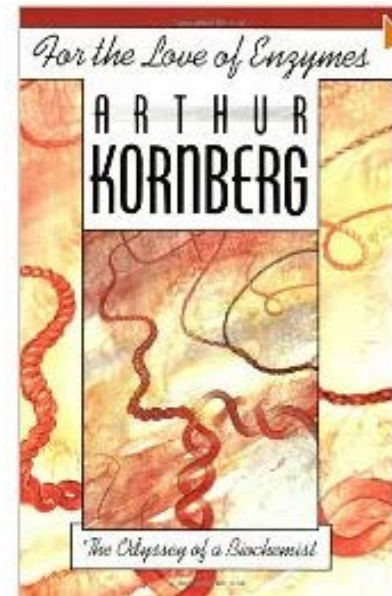
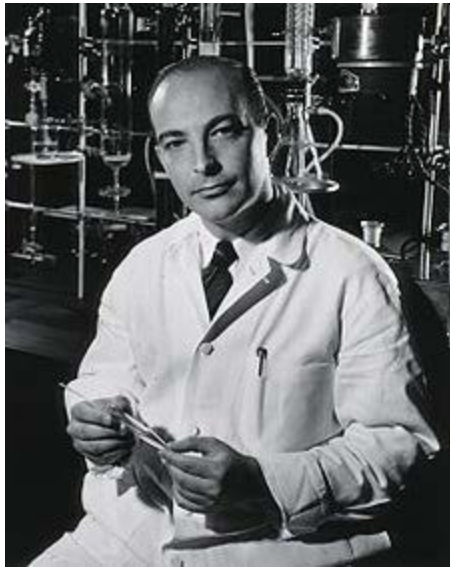
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# Arthur Kornberg

**Pathology test**

“I never met a dull enzyme”



Nobel Prize in Physiology or Medicine 1959  
"the mechanisms in the biological synthesis of DNA"

# DECLARATION OF COOPERATION BETWEEN THE CIPM, IFCC AND ILAC, FOR THE ESTABLISHMENT OF A JOINT COMMITTEE FOR TRACEABILITY IN LABORATORY MEDICINE (JCTLM)

JCTLM Mission Statement:

**identifying and prioritizing the measurands requiring international traceability** and comparability and thereby encouraging appropriate organizations to accept responsibility for the development of suitable reference methods and measurement procedures and certified reference materials;



# Gap Analysis

- Finding what is **not** in the database
- Possible targets for
  - Producers of materials
  - Developers of measurement procedures
  - Providers of reference measurement services

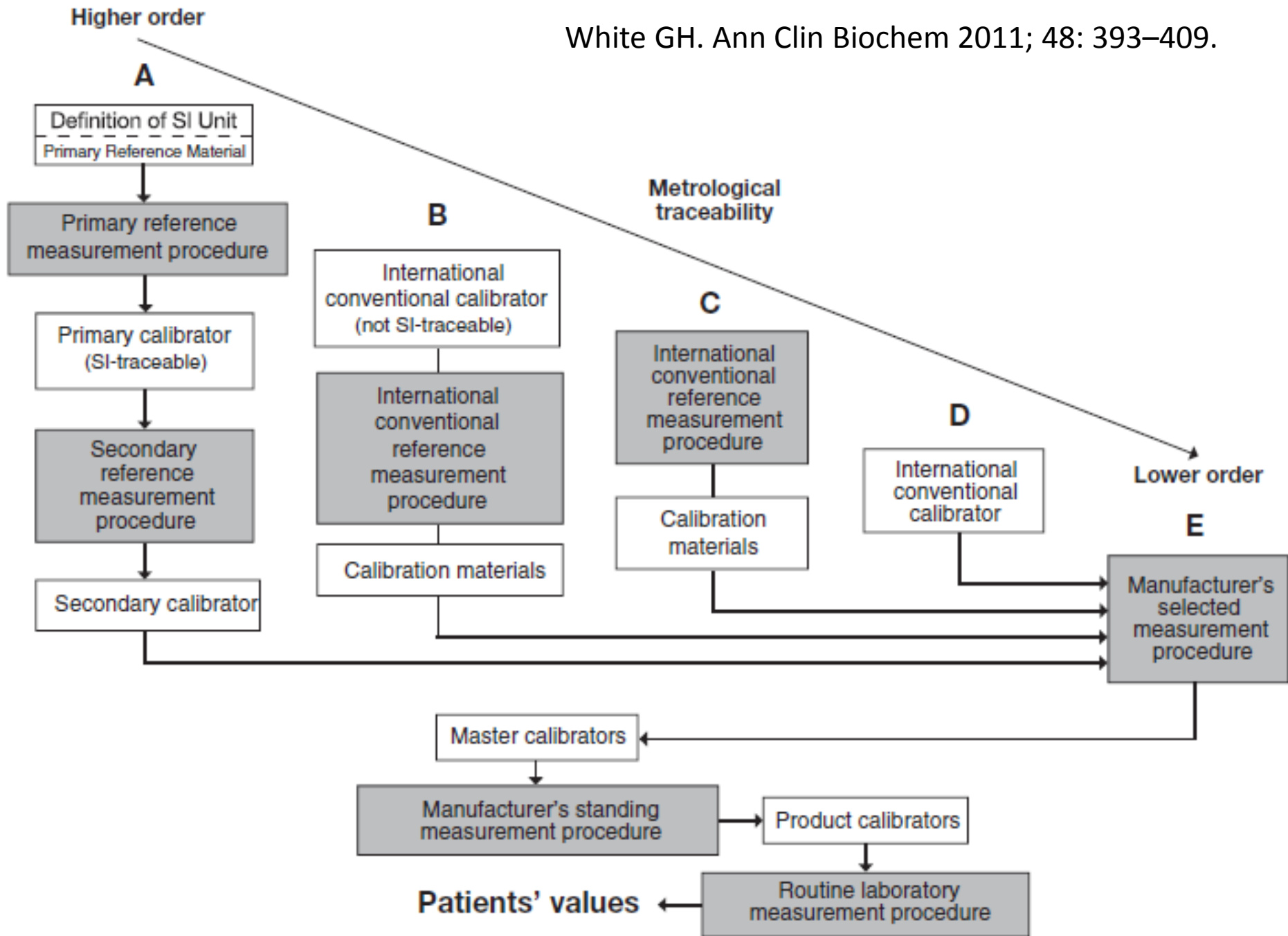
Review Team	Certified Reference Materials		Reference Measurement Procedures		Reference Measurement Services	
	Analytes	Entries	Analytes	Entries	Analytes	Entries
Blood cell counting			1	2		
Blood Gases						
Blood Groupings	3	3				
Coagulation Factors	1	2				
Drugs	24	31	7	13	3	3
Electrolytes	6	36	7	30	6	15
Enzymes	8	12	7	7	7	45
Metabolites & Substrates	41	86	15	46	9	38
Microbial serology						
Non-Electrolytes Metals	31	58	7	15		
Non-Peptide Hormones	11	23	12	30	10	21
Nucleic Acid	4	10				
Proteins	24	25	19	20	2	6
Vitamins & micronutrients	9	9	4	7	2	2
<b>Totals</b>	<b>162</b>	<b>295</b>	<b>79</b>	<b>170</b>	<b>39</b>	<b>130</b>

RM (pure) 97 analytes (170 materials)  
117 analytes (182 materials)



# GAPS

- 1. Tests without any JCTLM listings
- 2. Tests with incomplete JCTLM listings



# Gaps

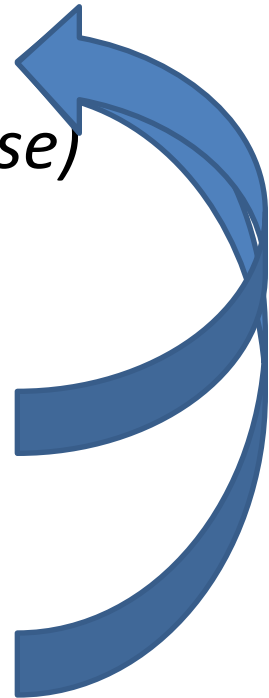
## **Prioritise measurands which are:**

- Frequently used (many patients)
- Widely used (many locations)
- Clinically important
- Currently poorly standardised  
(not otherwise achieved)
- Amenable to standardisation



# Data Used

- JCTLM Listed Measurands
  - Materials, Procedures, Services (*in the database*)
- Routine Laboratory (SydPath)
  - Numbers of tests requested (*frequently used*)
- EQA program (RCPAQAP)
  - Number of laboratories enrolled (*widely used*)



# Other Information

- WHO Reference Materials
- Harmonization.net
- Therapeutic Drugs
- Immunology
- IFCC C-NPU: Committee for Nomenclature, properties and Units

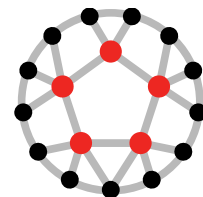
# Laboratory Data (*frequency*)

- Data from SydPath
  - Serving teaching hospital, private hospital, specialists and general practitioners
- Tests ranked according to request frequency
- Normalised to “1000” being most common request (full blood count)
- Highest ranking “missing” RMs, RMPs and RMSs listed



# EQA Data (*Widely used*)

- Data from RCPAQAP
  - Australian External Quality Assurance Program
- Tests ranked according to number of laboratories
- Normalised to “1000” being most common request (full blood count)
- Highest ranking “missing” RMs, RMPs and RMSs listed



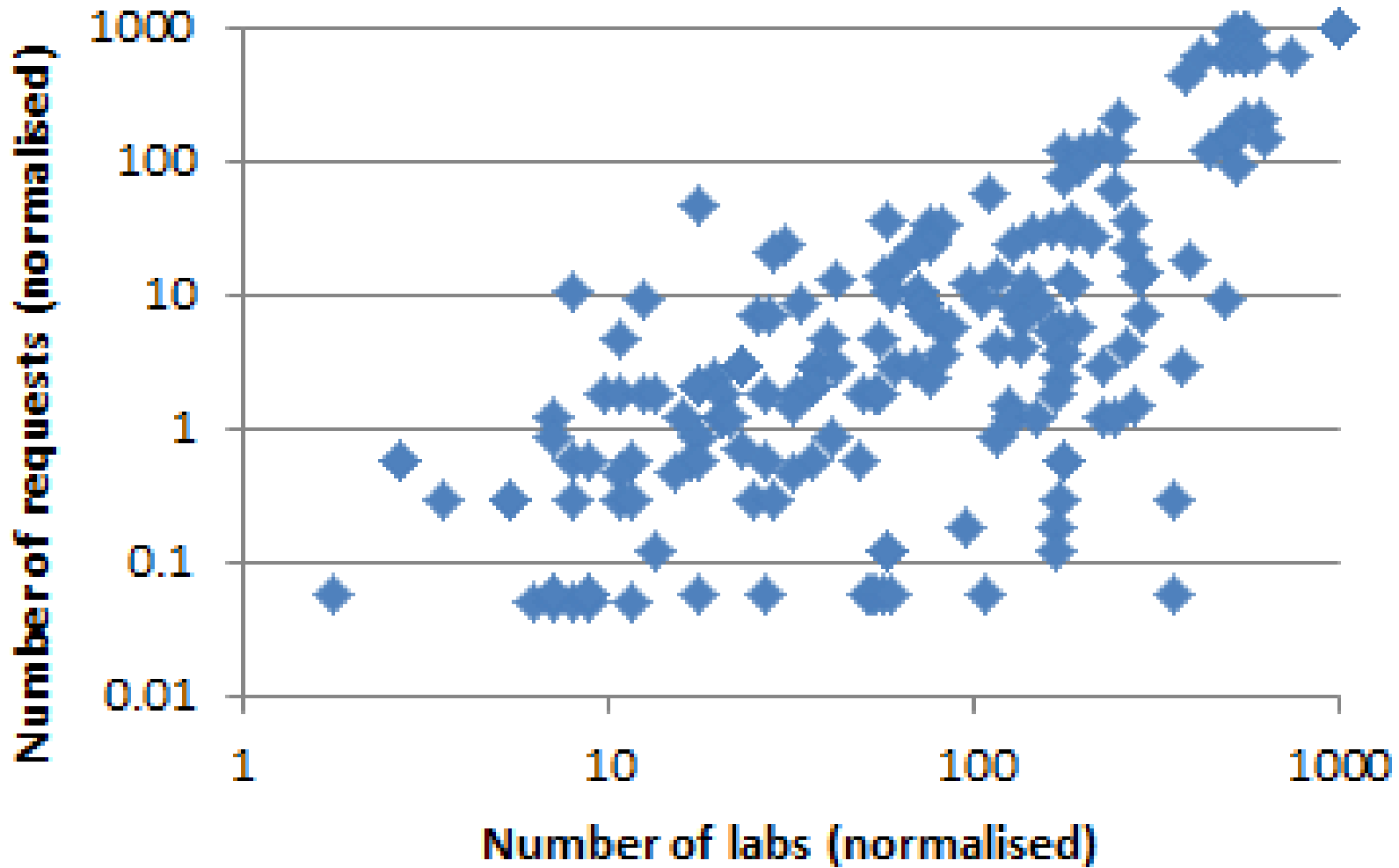
**RCPAQAP**  
RCPA Quality Assurance Programs

TEST LIST: List of routine pathology tests (based on RCPAQAP) with numbers of current JCTLM-listed RM, RMP and RMS													
Estimates of testing volume: normalised number of laboratories enrolled in RCPAQAP (max = 1000; column H); Normalised testing volume at SydPath (Max = 1000; column S).													
Count of entries:				216							2014 from SM:	64	
453	487	33	51	362	272	348	470	253		219	95	97	113
LIST ENTRY				RCPAQAP	RCPAQAP	RCPAQAP				JCTLM		Number of RM, RMP and RMS	
Entry Type	Entry Name	WHO	Harm.net(+HOG)	Speciality	RCPAQAP	TEST	SAMPLE	# Lab	#Labs(norm)	JCTLM TEST NAME	Pure	Pu	MATRIX
Routine Test	1,25diHydroxyVitaminD						serum		-				
Routine Test	17-Hydroxyprogesterone			Chemistry	Endocrine	17-Hydroxyprogesterone	serum	26	23.0	17-Hydroxyprogesterone			
	19-norandrosterone - urine						urine		-	19-norandrosterone (1 mass fraction)		1	
	25 HydroxyVitamin D2						serum	53	46.9	25-hydroxyvitamin D2			Human se
	25 HydroxyVitamin D3 Epimer						serum		-				Human se
Routine Test	3-Methoxytyramine			Chemistry	Plasma met	3-Methoxytyramine	plasma	13	11.5				
Routine Test	3-methoxytyramine - urine			Chemistry	Biogenic Am	3-methoxytyramine	urine	6	5.3				
Routine Test	5HIAA - urine			Chemistry	Biogenic Am	5HIAA	urine	30	26.5				
Routine Test	Acid phosphatase						serum		-	Acid phosphatase	Catalytic amc	1	
Routine Test	ACTH	3rd IS 1962, 59/016		Chemistry	Tumour Mar	ACTH	serum	42	37.2				
Routine Test	Adrenaline - urine			Chemistry	Biogenic Am	Adrenaline	urine	41	36.3				
Routine Test	Alanine						serum		-	alanine/L-alanine	in HCl	2	
Routine Test	Alanine Amino Transferase (ALT)		Active-IFCC/IRMM	Chemistry	Gen Ser Che	Alanine Amino Tr	serum	624	552.2	Alanine Amino Transf	Catalytic amc	1	1
Routine Test	Albumin			Chemistry	Gen Ser Che	Albumin	serum	629	556.6	Albumin			Human se
Routine Test	Albumin - CSF			Chemistry	CSF	Albumin (CSF)	CSF	30	26.5				
Routine Test	Albumin - urine		Active-IFCC/NKDEI	Chemistry	Gen Ser Che	Albumin	urine	184	162.8				
Routine Test	Aldosterone			Chemistry	Endocrine	Aldosterone	serum	28	24.8	Aldosterone			
Routine Test	Alkaline Phosphatase (ALP)		Active-IFCC/IRMM	Chemistry	Gen Ser Che	Alkaline Phosphat	serum	623	551.3	Alkaline Phosphatase	Catalytic amc	1	
Routine Test	Alpha 1 acid glycoprotein						serum		-	Alpha 1 acid glycoprotein			Human se
Routine Test	Alpha 1 antitrypsin			Immunology		Alpha-1-antitryps	serum	47	41.6	Alpha 1 antitrypsin			Human se
Routine Test	Alpha 1-antichymotrypsin						serum		-	a1-antichymotrypsin			
Routine Test	Alpha 2 macroglobulin						serum		-	Alpha 2 macroglobulin			Human se
Routine Test	Alpha subunit of hCG	1st IS 1974, 75/569					serum						
Routine Test	Alpha-fetoprotein		Feb14-Add	Chemistry	Endo / TMs	Alpha-fetoprotein	serum	118	104.4	Alphafoetoprotein	mass	1	
Routine Test	Alternaria alternata/tenuis	KU/L		Immunology		Alternaria alterna	serum		-				
Routine Test	Aluminium			Chemistry	Trace metal	Serum Aluminium	serum	13	11.5				
Routine Test	Aluminium - urine			Chemistry	Trace metal	Urine Aluminium	urine	6	5.3				
Routine Test	Amikacin			Chemistry	Gen Ser Che	Amikacin	serum	32	28.3				
Routine Test	Amiodarone			Chemistry	Special Drug	Amiodarone	serum	8	7.1				
Routine Test	Amitriptyline			Chemistry	Special Drug	Amitriptyline	serum	2	1.8				
Routine Test	Ammonia			Chemistry	Alc/Amm	Ammonia	serum	131	115.9				
Routine Test	Amphetamine - urine			Chemistry	Urine Drug S	Amphetamines sc	urine	82	72.6	Amphetamine	mass	1	
Routine Test	Amylase			Chemistry	Gen Ser Che	Amylase	serum	441	390.3	Alpha-Amylase	Catalytic amc	2	
Routine Test	Amylase - urine					Amylase - urine	Urine		-				
Routine Test	ANA pattern, ANA titre			Immunology		ANA pattern, ANA	serum	93	82.3				
Routine Test	ANCA			Immunology		ANCA	serum		-				
Routine Test	Androstenedione			Chemistry	Endocrine	Androstenedione	serum	18	15.9				
Routine Test	Angiotensin Converting Enzyme (ACE)			Chemistry	Endocrine	Angiotensin Conv	serum	29	25.7				
Routine Test	Anti-c antibodies						Plasma		-	Anti-c antibodies			defib pla
Routine Test	Anti-D antibodies						Plasma		-	Anti-D antibodies			Human pl
Routine Test	Antimony - urine						urine		-	Antimony			Urine

# Spreadsheet Summary

- Total number of items (measurands?): ~487
  - SydPath requested tests (245) #
  - RCPAQAP listed tests (348) #
  - JCTLM listed **# 450 laboratory tests**
    - RMs (pure 178 for 97 measurands)
    - RMs (matrix matched 188 for 116 measurands)
    - RMP (168 for 90 measurands)
    - RMS (109 for 43 measurands)
    - **TOTAL: 221 measurands #**
- Incomplete: serology, microbiology

# Number of Tests v No. of Labs



# LABORATORY REQUESTS - No JCTLM Listing

Listed: UEC,  
LFT, CPM

RANK	TEST
1	Basophils - blood
2	Eosinophils - blood
3	Haematocrit - blood
4	Mean Cell Volume - blood
5	Monocytes - blood
6	Red cell count - blood
7	Red cell Distribution Width (RDW) - blood
8	White cell count - blood
9	Bicarbonate
10	Calcium - ionised - blood
11	Lactate - blood
12	Oxygen partial pressure (pO2) - blood
13	pH - blood
14	Thyroid Stimulating Hormone (TSH)
15	APTT
16	ESR - blood
17	INR
18	Ferritin
19	Iron
20	Prothrombin Time

Full Blood  
Count

Blood Gas  
Analysis

Coagulation

Coagulation

Coagulation





## LABORATORY REQUESTS - No JCTLM Listing

RANK	TEST	
21	Vitamin B12	
22	Troponin T	
23	Human Chorionic Gonadotrophin (hCG)	
24	Human Chorionic Gonadotrophin (hCG) - urine	
25	ANA pattern, ANA titre	Immunology
26	Serum Protein Electrophoresis	
27	Albumin - urine	
28	Free T3 / Free Triiodothyronine	
29	Electrophoresis - serum	Immunology
30	Vancomycin	
31	Parathyroid Hormone	
32	Cyclosporin - blood	
33	Folate - red cell	
34	Thrombin Time	
35	ENA	Immunology
36	Rheumatoid factor	Immunology
37	dsDNA antibodies	Immunology
38	Reticulocyte count - blood	
39	ANCA	Immunology
40	MPO-ANCA	Immunology

# EQA Labs - No JCTLM Listing

RANK	TEST	
1	Haematocrit - blood	
2	Mean Cell Volume - blood	
3	Red cell count - blood	
4	White cell count - blood	
5	pCO2 - blood	BGA
6	Oxygen partial pressure (pO2) - blood	BGA
7	INR	Coagulation
8	APTT	Coagulation
9	Calcium - ionised - blood	BGA
10	Bicarbonate	
11	ESR - blood	
12	Lactate - blood	
13	pH - blood	BGA
14	Bilirubin-conjugated	
15	Carboxyhaemoglobin - blood	BGA
16	Methaemoglobin - blood	BGA
17	Lipase	
18	Paracetamol	
19	D-Dimer	Coagulation
20	Human Chorionic Gonadotrophin (hCG)	

Listed: UEC,  
LFT, CPM

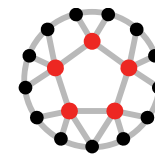


Full Blood  
Count



## EQA Labs - No JCTLM Listing

<b>RANK</b>	<b>TEST</b>
21	Thrombin Time
22	Gentamicin
23	Thyroid Stimulating Hormone (TSH)
24	Iron
25	Protein - Urine
26	Vancomycin
27	Vitamin B12
28	Luteinising Hormone (LH)
29	Follicle Stimulating Hormone (FSH)
30	Ferritin
31	Troponin T
32	Lactate
33	Protein - CSF
34	Phosphate - urine
35	Albumin - urine
36	Prolactin
37	Free T3 / Free Triiodothyronine
38	Osmolality - urine
39	Osmolality
40	Salicylate



# Clinical Need

- EQA assessment of between-laboratory variability
- If no problem: Low priority
- If significant problem: high priority

# Result Variability Assessment - EQA

External Quality Assessment / Proficiency Testing

- Commutable samples
- (Reference Method value assignment)

Other published studies



European Organisation For External Quality Assurance  
Providers in Laboratory Medicine

Piet Meijer (next speaker)

# Result Variability Assessment - EQA

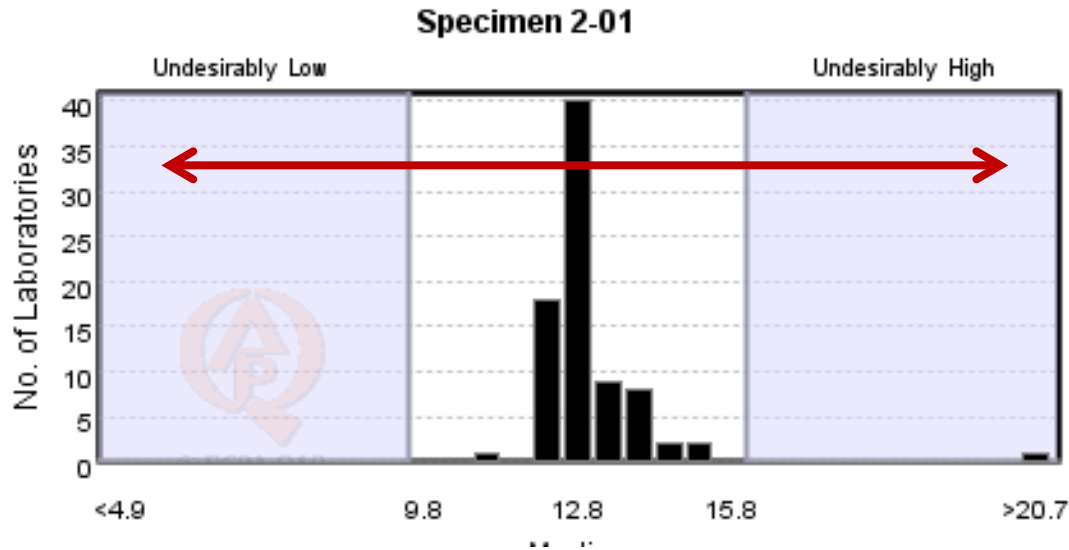
## External Quality Assessment / Proficiency Testing



- Liquid Serum Chemistry (commutable)
- 2 samples (1 male 1 female)
- Distributed same day
- Value assignment by median (*not RM, RMP*)
- >50 chemistry analytes, 7 calculated parameters (eg anion gap, serum globulins)

# Iron (commutable serum)

## Standard: Within-Subject; Optimal



### Allowable Performance

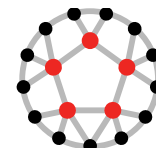
$\pm 3.0$  up to 25.0;

$\pm 12\%$  >25.0  $\mu\text{mol/L}$

### Biological Variation

$CV_i = 26.5$

$CV_g = 23.2$



# Iron (commutable serum)

Standard: Within-Subject; Optimal

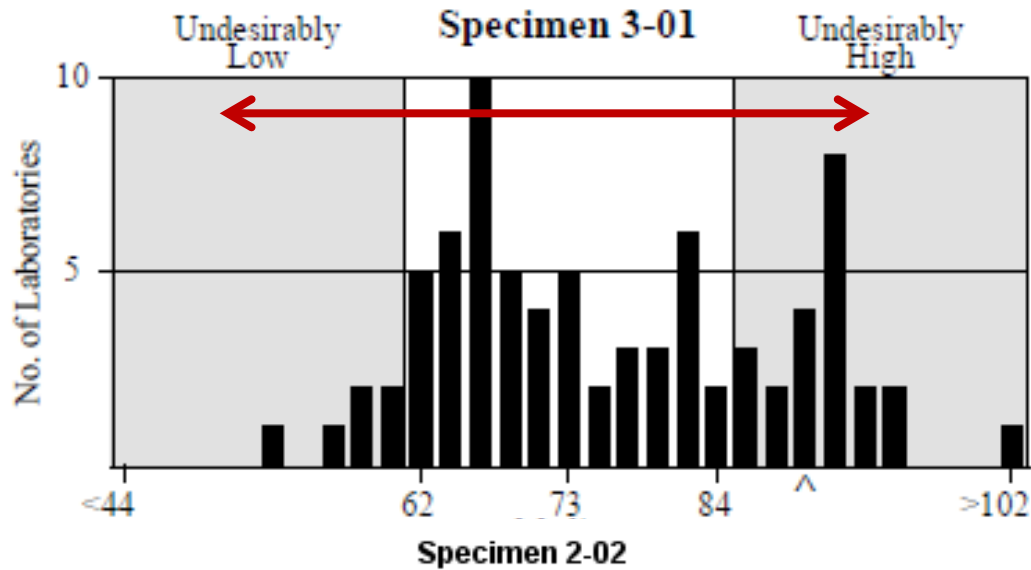
<b>M'Factorer</b>	<b>Instrument</b>	<b>Iron</b>	<b>Traceability</b>	<b>Ref Method</b>
Abbott	<b>Architect</b>		NIST SRM 3126	Gravimetric
Roche	<b>Modular</b>		NIST SRM 937	
Roche	<b>Integra</b>		NIST SRM 937	
Roche	<b>Cobas c</b>		NIST SRM 937	
Siemens	<b>Dimension RXL/EXL</b>		NIST SRM 937	
Siemens	<b>Dimension VISTA</b>		NIST SRM 937	
Siemens	<b>Advia</b>		NIST SRM 937	Candidate AACC Reference Method (Ferrozine)
Beckman Coulter	<b>DXc/Dxi</b>		SRM 937	
Beckman Coulter	<b>AU Platforms</b>		BC Master calibrator	

(SRM 937 not on JCTLM database)



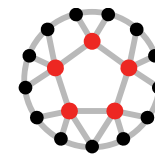
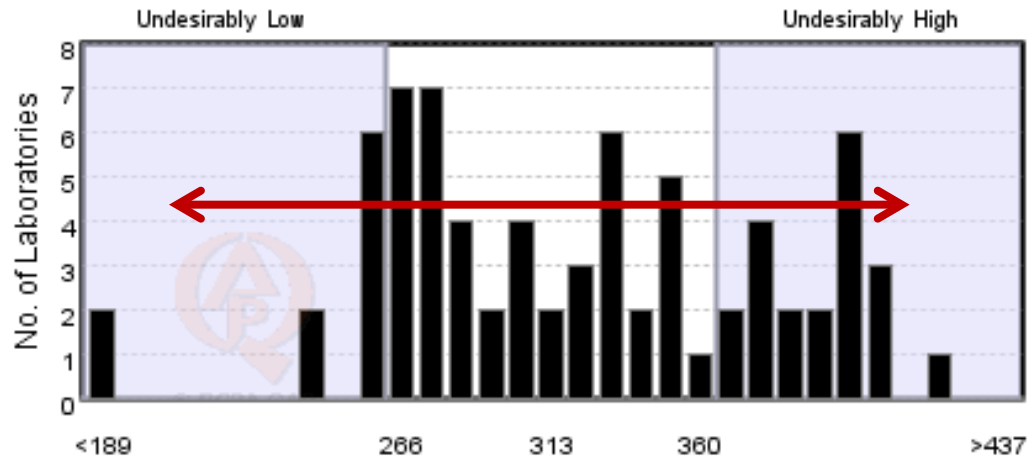
# Ferritin (commutable serum)

## Standard: Within-subject, desirable



Allowable Performance  
 $\pm 4$  up to 27;  $\pm 15\%$   $> 27$  ug/L

Biological Variation  
 $C_{vi} = 14.9\%$   
 $CV_g = 13.5\%$



**Table 2 | Predicted values obtained with each assay at current and historical KDOQI cutoffs<sup>a</sup>**

Assay	Ferritin (ng/ml)	Ferritin (ng/ml)	Ferritin (ng/ml)
Siemens Centaur	200	500	800
Beckman Access	178	439	700
Ortho Vitros Eci	172	439	706
Siemens Dimension RxL	212	486	759
Roche Elecsys 2010	194	548	902
Abbott Architect	224	632	1040

KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

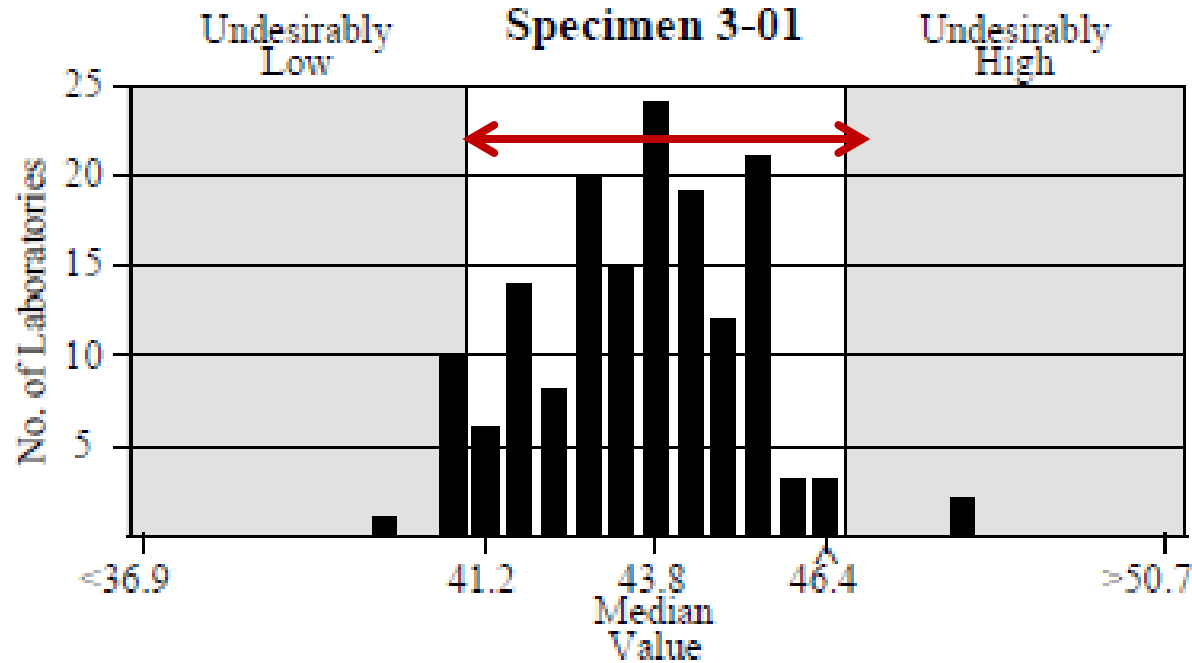
<sup>a</sup>Values shown are the predicted values from the Deming regression equations in Table 1, assuming values of 200, 500, and 800 were obtained using the Siemens Centaur method.

## Variability of ferritin measurements in chronic kidney disease; implications for iron management

Bradley A. Ford<sup>1</sup>, Daniel W. Coyne<sup>2</sup>, Charles S. Eby<sup>1,2</sup> and Mitchell G. Scott<sup>1</sup>

# Albumin (commutable serum)

## Standard: Total error; Desirable



### Allowable Performance

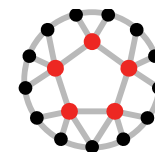
$\pm 2.0$  up to 33.0;

$\pm 6\%$  >33.0 g/L

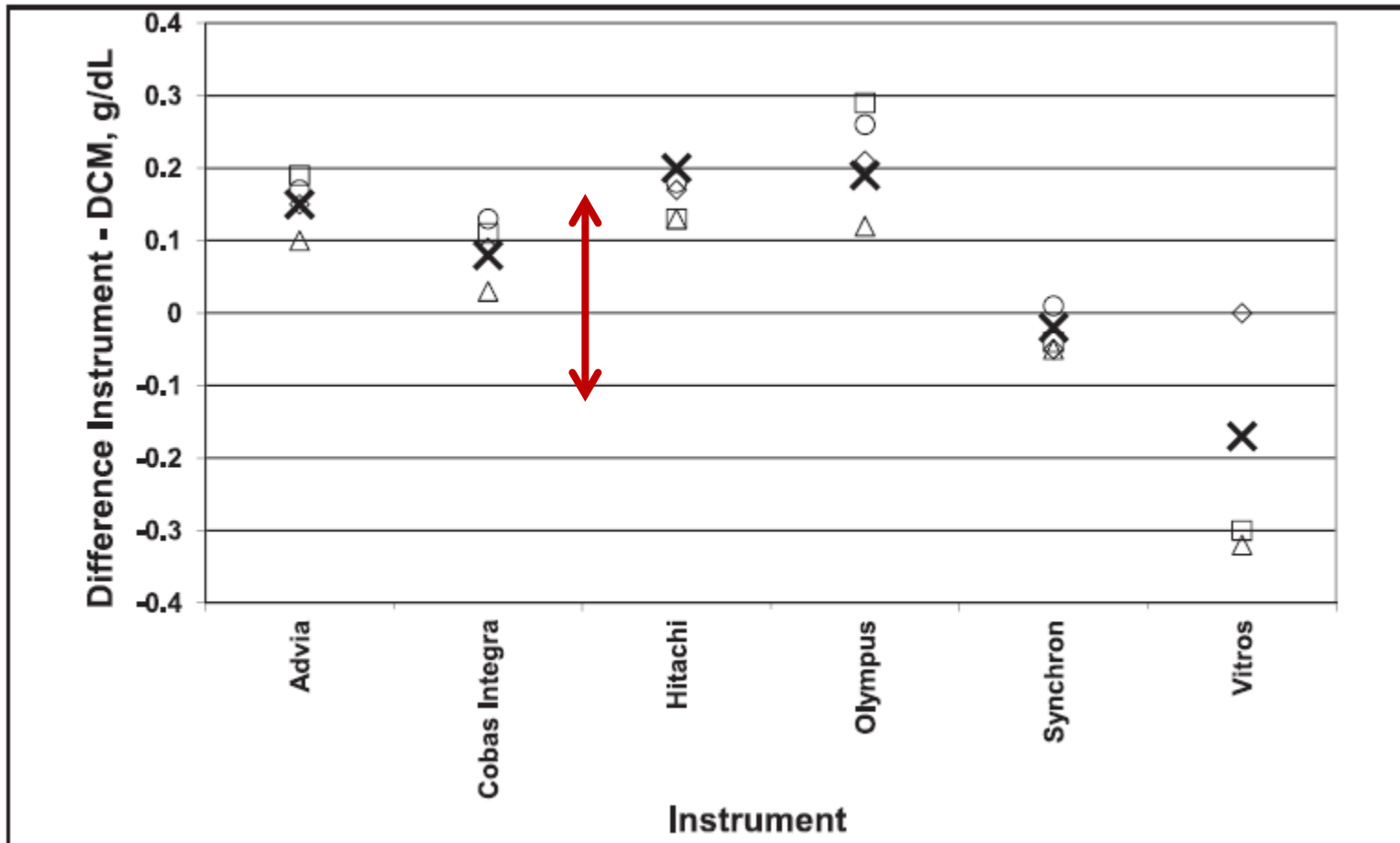
### Biological Variation

CV<sub>i</sub>=3.1%

CV<sub>g</sub>=4.2%



# Albumin (g/dL)



Lo S and Miller G. Arch Pathol Lab Med. 2013;137:912–920;

Cvi=3.1 CVg=4.2

## LABORATORY REQUESTS - No JCTLM Listing

RANK	TEST
1	Basophils - blood
2	Eosinophils - blood
3	Haematocrit - blood
4	Mean Cell Volume - blood
5	Monocytes - blood
6	Red cell count - blood
7	Red cell Distribution Width (RDW) - blood
8	White cell count - blood
9	Bicarbonate +/-
10	Calcium - ionised - blood
11	Lactate - blood
12	Oxygen partial pressure (pO2) - blood
13	pH - blood
14	Thyroid Stimulating Hormone (TSH) X
15	APTT
16	ESR - blood
17	INR
18	Ferritin X
19	Iron ✓
20	Prothrombin Time

## LABORATORY REQUESTS - No JCTLM Listing

RANK	TEST	
21	Vitamin B12	X
22	Troponin T	✓
23	Human Chorionic Gonadotrophin (hCG)	
24	Human Chorionic Gonadotrophin (hCG) - urine	
25	ANA pattern, ANA titre	
26	Serum Protein Electrophoresis	
27	Albumin - urine	
28	Free T3 / Free Triiodothyronine	✓
29	Electrophoresis - serum	
30	Vancomycin	
31	Parathyroid Hormone	X
32	Cyclosporin - blood	
33	Folate - red cell	X
34	Thrombin Time	
35	ENA	
36	Rheumatoid factor	
37	dsDNA antibodies	
38	Reticulocyte count - blood	
39	ANCA	
40	MPO-ANCA	

# Incomplete JCTLM Systems

- Not all JCTLM-listed measurands have
  - Pure RM
  - Matrix matched RM
  - RMP
  - RMS
- Gap analysis can identify

<b>JCTLM - Complete Reference Systems</b>				
<b>JCTLM TEST NAME</b>	<b>Pure</b>	<b>Matrix</b>	<b>RMP</b>	<b>RMS</b>
17 beta estradiol (RMP)	1	4	4	2
Calcium	3	5	7	2
Chloride	4	3	4	1
Cortisol	2	4	5	4
Creatinine	3	11	7	5
Digoxin	1	2	2	1
Glucose	1	4	5	5
Glycated Hb / HbA1c #	1	1	3	3
Lithium	2	4	3	2
Magnesium	4	4	5	2
Potassium	4	5	5	4
Progesterone	1	2	3	2
Sodium	4	5	5	4
Testosterone	1	2	4	3
Urea	3	2	3	3
Uric acid	3	3	4	3
Alanine Amino Transferase (ALT)	1		1	5
Alkaline Phosphatase (ALP)	1		1	3
Alpha-Amylase	2		1	3
Creatine Kinase (CK)	2		1	4
Aspartate Amino Transferase (AST)	1		1	5
Gamma glutamic acid (GGT)	2		1	5
Lactate Dehydrogenase (LDH)	2		1	5



## JCTLM - Incomplete Reference Systems

JCTLM TEST NAME	Pure	Matrix	RMP	RMS
Bilirubin	1		2	1
Creatinine - Urine	3		1	2
3,3',5-triiodothyronine (T3)	1		2	2
Glucose - Urine	1		1	1
Glucose - CSF	1		1	1
Theophylline	1		3	1
total thyroxine (TT4)	1		4	2
Triglycerides, triglyceride	1	2	2	
Urea	3		1	1
Uric acid	3		1	1
Total Cholesterol	1	1	8	7
Total glycerides		1	3	3
17-Hydroxyprogesterone			1	1
19-norandrosterone (norandrosterone)	1		1	
5-methyltetrahydrofolic acid		1	3	
Albumin		1	1	
Aldosterone			2	1
Alpha 1 acid glycoprotein		1	1	
Alpha 1 antitrypsin		1	1	
Alpha 2 macroglobulin		1	1	
Arsenic - Urine		1	1	

# Other Standardisation Efforts

- WHO
- Harmonization.net
- BIPM (CCQM)
- NIST
- CDC
- ....

## Biologicals

Biologicals

### WHO International biological reference

Vaccines

Biotherapeutics

Reference

Publications

About










**"To define an internationally agreed unit to allow comparison of biological measurements worldwide"**

Materials which serve as reference sources of defined biological activity expressed in an internationally agreed unit. These preparations are the basis of a uniform reporting system, helping physicians and scientists involved in patient care, regulatory authorities and manufacturing settings to communicate in a common language for designating the activity or potency of biological preparations used in prophylaxis or therapy, and ensuring the reliability of *in vitro* biological diagnostic procedures used for diagnosis of diseases and treatment monitoring.



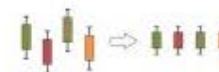
# WHO International Biological Reference Preparations

## Held and Distributed by the WHO International Laboratories for Biological Standards

PREPARATION	STANDARD	MATERIAL	HELD AT	CODE	WHO/BS DOCUMENT	
● A Disintegrin and Metalloprotease with Thrombospondin type 1 motifs 13 (ADAMTS13), plasma, Lyophilized., Function: 0.91 IU / ampoule Antigen: 0.92 IU / ampoule	1st International Standard, 2014	Blood products and related substances	NIBSC	12/252	2014.2246	
● Acellular pertussis vaccine for potency assay by modified mouse challenge test, Lyophilized, 34 IU / ampoule	1st International Standard, 2008	Vaccine	NIBSC	JNIH-3	08.2086	
● Activated coagulation factor XI, Lyophilized., 9.8 IU / ampoule	1st International Standard, 2014	Blood products and related substances	NIBSC	13/100	2014.2235	
● Actvin A, human, recombinant, Lyophilized, 5 units / ampoule.	1st Reference Reagent, 1998	Recombinant hormone	NIBSC	91/626	98.1882	
● Alpha-1-antitrypsin, (2006), plasma derived, Lyophilized, 243 nmol/ampoule, equivalent to 12.4 mg active inhibitor for plasma derived products.	1st International Standard, 2006	Purified plasma protein	NIBSC	05/162	06.2044	
● Alpha-1-antitrypsin, (2008), plasma derived, Lyophilized, 243 nmol/ampoule, use extended for recombinant products. Assigned values of 12.4 mg/ml for both total protein and antigen.	1st International Standard, 2008	Purified plasma protein	NIBSC	05/162	08.2092	
● Alphafoetoprotein, Lyophilized, 100,000 IU / ampoule.	1st International Standard, 1975	Human cord serum	NIBSC	AFP	75.1121	
● Amphotericin B, Lyophilized, 944 IU / mg. Approximately 100 mg of Amphotericin B.	2nd International Standard, 2007	Antibiotic	EDQM	ISA_29078	07.2073	
● Ancrod, Lyophilized, 55 IU/ampoule	1st International Reference Preparation, 1976	Enzyme	NIBSC	74/581	76.1130	
● Anthrax spore vaccine, Lyophilized spore suspension of Bacillus anthracis strain 34 F2., 1 IU / ampoule.	1st International Reference Preparation, 1978	Antigen	NIBSC	AxV2	78.1198	
● Anti-A and anti-B antibodies in intravenous immunoglobulin: Limit reference preparation, Lyophilized, Anti-A and anti-B titres in the 2-fold range 32-64 using direct haemagglutination of A1 and B red cells.	1st Reference Reagent, 2008	Human immunoglobulin	NIBSC	07/310	08.2091	
● Anti-A and anti-B antibodies in intravenous immunoglobulin: Positive control and negative control for haemagglutination tests, Lyophilized., The guide titres for anti-A and anti-B in the Positive Control preparation 07/306 are in the 2-fold ranges of 32-64 and 16-32, respectively. 07/308 is the Negative Control in the same assays.	1st Reference Reagent, 2008	Human immunoglobulin	NIBSC	07/306 & 07/308	08.2091	
● Anti-A blood grouping minimum potency reagent, Lyophilized, A 1 in 8 dilution defines the recommended minimum potency specification for anti-A blood grouping reagents.	1st International Standard, 2005	Monoclonal IgM (murine)	NIBSC	03/188	06.2053	
● Anti-B blood grouping minimum potency reagent, Lyophilized, A 1 in 4 dilution defines the recommended minimum potency specification for anti-B blood grouping reagents.	1st International Standard, 2005	Monoclonal IgM (murine)	NIBSC	03/164	05.2024	
● Anti-brucella abortus serum, bovine, Lyophilized, 1,000 IU / ampoule of agglutinating; 1,000 IU / ampoule of complement-fixing activity				BaDS	75.1124	

Approx 400 Materials

Entry Name	WHO	JCTLM TEST NAME
Apolipoprotein A1	1st IRR 1992	Apo A1
Haemoglobin A2 - blood	1st IRR 1993	
Haemoglobin F - blood	1st IRR 1993	
Apolipoprotein B	1st IRR 1993	
Glucagon	1st IS 1973 (porcine), (	
Insulin	1st IS 1974, 66/304	ASD
Renin	1st IS 1974, 68/356	
Alpha subunit of hCG	1st IS 1974, 75/569	
Vasopressin (ADH)	1st IS 1978, 77/501	
Growth Hormone	1st IS 1982, 80/505	
Beta-2-microglobulin	1st IS 1985	
C-Reactive Protein (CRP)	1st IS 1986	C-reactive protein
C-peptide	1st IS 1986, 84/510	C-peptide
Thyroxine binding globulin (TBG)	1st IS 1991; 88/636	
Inhibin A	1st IS 1994, 91/624	
Follicle Stimulating Hormone (FSH)	1st IS 1997, 92/510	
Inhibin B	1st IS 2000, 96/784	
Coagulation factor V	1st IS 2005	Coagulation factor V
Insulin-Like Growth Factor Binding Protein	1st IS 2008;02.254	
C1 esterase inhibitor	1st IS 2010	
Calcitonin	2nd IS 1991, 86/620	
Sex Hormone Binding Globulin (SHBG)	2nd IS 2010, 08/266	
Coagulation factor VII	2nd IS 2012	Coagulation factor VII



## CLINICAL LABORATORY TEST HARMONIZATION

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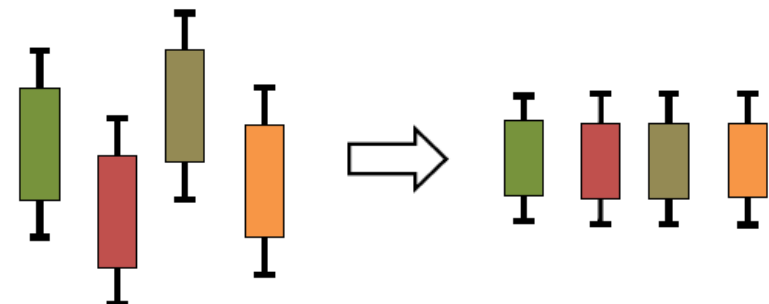
## **Measurand Checklist and Report to be completed by a Special Working Group (SWG)**

Section 1. Measurand

Section 2. Clinical Considerations (consider global and/or regional impact)

Section 3. Analytic Considerations (consider global and/or regional impact)

Section 4. Current status of harmonization







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## Quality Assessment and Standardization Committee

 [Report 2013](#)

### Committee Chairman

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 [CV](#)



[Sub-Committee for the Standardization of Autoantibodies in Rheumatic and Related Diseases](#)

[Sub-Committee on Leukocytes](#)  
[www.hcdm.org](http://www.hcdm.org)



# International Union of Immunological Sciences (IUIS)

Subcommittees on:

- Standardization of **Autoantibodies in Rheumatic Diseases**
- **Leukocytes**
- **Allergen Standardization**
- Standardization and quality assessment of **complement measurements**
- Standardization and Quality Assessment in Immunotherapy
- Standardization and Quality Assessment of **Immunological Diagnostics**
- **Organ-Specific Autoantibodies**



# Other Databases, data sources

- Analytes used in other industries
- Metals, blood gases (pH, pO<sub>2</sub>, pCO<sub>2</sub>), ammonia
- CCQM



What is the traceability of  
your blood gas analysers?  
(pH, pCO<sub>2</sub>, pO<sub>2</sub>)

Later that day...



## Traceability to Primary Standards

### Introduction

The Product Development Department at Nova Biomedical is responsible for establishing the traceability of the parameters measured by Nova analyzers. The traceability for pH,  $PCO_2$ ,  $PO_2$ ,  $cK^+$  and  $cCa^{++}$ ,  $cMg^{++}$ , and  $cCl^-$ , as well as the traceability for  $cHb$ , Saturation –  $SO_2 = 100$ , Saturation –  $SO_2 = 0\%$ ,  $F\text{COHb}$  – normal value,  $F\text{COHb}$  – 100%, Temperature, and Pressure are described herein.

All the reagents of Nova Biomedical Corporation (Nova) are traceable to NIST reference standards.

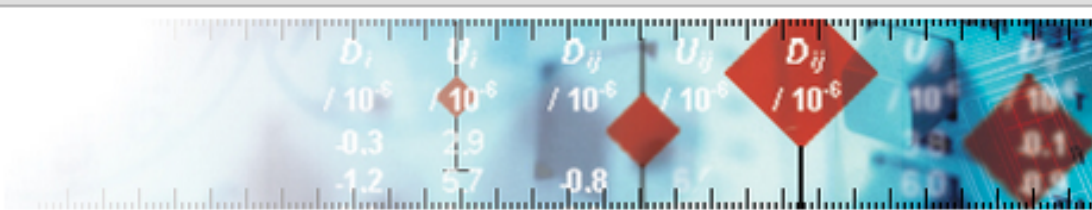
### Traceability

#### pH

The pH standards and reagents used for Nova's products are traceable to NIST primary pH reference material SRM 2186I and 2186II. Nova's standards and reagents are measured versus the NIST primary pH buffers using a pH glass electrode and a flowing 2MKCl Ag/AgCl reference electrode. The measurement is done at 37°C.

# Blood Gases

<b>pH</b>	Radiometer	Abbott	Nova	Siemens	Alere
	<b>ABL</b>	<b>I-STAT</b>	<b>pHOx</b>	<b>Rapidpoint</b>	<b>EPOC</b>
Materials	NIST SRM 186-I, 186-II, 185, 187, 191-2	NIST SRM 186-I, 186-II, 185, and 187	NIST SRM 2186I and 2186II	SRM186	NIST standards
Methods	Capillary type glass pH electrode with a saturate calomel reference electrode and a liquid junction saturated with KCL.		NIST primary pH buffers using a pH glass electrode and a flowing 2M KC1 Ag/AgCl reference electrode. The measurement is done at 37°C.	IFCC blood reference method	



## The BIPM key comparison database



### Refine your search

#### METROLOGY AREA

- [Mass](#) (93)
- [Amount of Substance](#) (38)
- [Ionizing Radiation](#) (13)
- [Thermometry](#) (12)
- [Electricity and Magnetism](#) (11)
- [Length](#) (1)
- [Photometry and Radiometry](#) (1)

#### TYPE

- [Key comparisons](#) (130)
- [Supplementary comparisons](#) (39)

#### STATUS

- [Approved for equivalence](#) (72)
- [Approved for provisional equivalence](#) (22)
- [Approved and published](#) (17)
- [Planned](#) (14)
- [In progress](#) (11)
- [Report in progress, Draft B](#) (9)
- [Report in progress, Draft A](#) (9)
- [Protocol complete](#) (8)
- [Ongoing, approved for](#)

### Result of the search

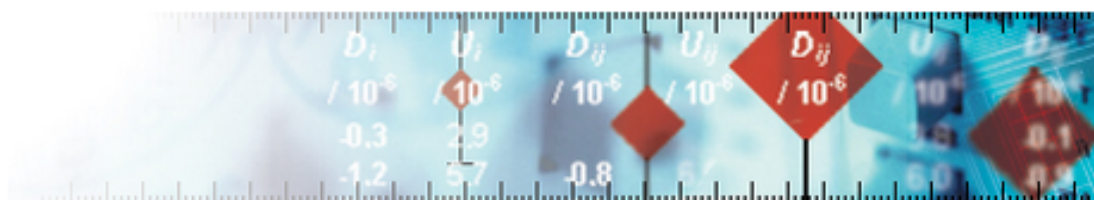
Your query 'pH' produced 169 results

1 2 3 [Next >>]

**pH**

[New search](#)

<b>CCQM- K9</b>	<b>pH measurement of phosphate buffer solutions 1999 - 2000</b>
Comparison type, Field	Key comparison in Amount of Substance, Electrochemistry
Parameter(s)	15 °C, 25 °C and 37 °C plus 7 other temperatures
Status	<b>Approved for equivalence, Results available</b>
<b>CCQM- K18</b>	<b>pH measurement of carbonate buffer solutions 2006</b>
Comparison type, Field	Key comparison in Amount of Substance, Electrochemistry
Parameter(s)	pH 10
Status	Temperature: 25 °C <b>Approved for equivalence, Results available</b>
<b>CCQM- K17</b>	<b>pH measurement of phthalate buffer solutions 2001</b>
Comparison type, Field	Key comparison in Amount of Substance, Electrochemistry
Parameter(s)	Temperature: 15 °C, 25 °C and 37 °C
Status	<b>Approved for equivalence, Results available</b>
<b>CCQM- K19</b>	<b>pH measurement of borate buffer solutions</b>



# The BIPM key comparison database



## Refine your search

### CMC AREA

- CMCs Chemistry (107)
- CMCs General Physics (1)

### PHYSICS

- Temperature (1)

### CHEMICAL MATERIAL

- cast iron (6)
- mono-elemental solution (4)
- iron ore (4)
- aluminium alloy (3)
- copper alloy (3)

### CHEMICAL ANALYTE

- iron (84)
- total iron as iron (III) oxide (5)
- chromium (3)
- manganese (3)
- molybdenum (2)

## Result of the search

Your query 'iron' produced 108 results

1 2 3 [Next >>]

# Iron

[New search](#)

### Argentina, INTI (Instituto Nacional de Tecnologia Industrial)

[Complete CMCs in Chemistry for Metals and metal alloys for Argentina \(.PDF file\)](#)

Matrix or material	Analyte or component	Dissemination range of measurement capability	
		Mass fraction in mg/kg	Relative expanded uncertainty ( $k = 2, 95\%$ ) in %
copper alloys	iron	500 to 2500	2 to 9

Mechanism(s) for measurement service delivery: Analytical service

Uncertainty convention 1.

Approved on 20 November 2014.

Internal NMI service identifier: INTI/INORGMET-1

### Canada, NRC (National Research Council)

[Complete CMCs in Chemistry for High purity chemicals for Canada \(.PDF file\)](#)

Matrix or material	Analyte or component	Dissemination range of measurement capability	
		Mass fraction in kg/kg	Absolute expanded uncertainty ( $k = 2, 95\%$ ) in kg/kg
high purity iron	iron	0.999 to 0.9999999	0.005 to 0.0000005

Mechanism(s) for measurement service delivery: Customer service; GD-MS-200; delivery only

# Nomenclature

- What tests are we talking about?
- Definition of the measurand
- Combining results in reports
  
- IFCC: C-NPU (Committee for Nomenclature Properties and Units)
- LOINC

JCTLM TEST NAME	NPU code	Short definition
17-Hydroxyprogesterone	NPU02460	P—17-Hydroxyprogesterone; subst.c. = ? nmol/L
a1-antichymotrypsin	NPU01270	P—Antichymotrypsin; subst.c. = ? µmol/L
Acid phosphatase	NPU01064	P—Acid phosphatase; cat.c.(37 °C; proc.) = ? µkat/L
Alanine Amino Transferase (ALT)	NPU19651	P—Alanine transaminase; cat.c.(IFCC 2002) = ? U/L
alanine/L-alanine	NPU01117	P—Alanine; subst.c. = ? µmol/L
Albumin	NPU19673	P—Albumin; mass c.(proc.) = ? g/L
Aldosterone	NPU01135	P—Aldosterone; subst.c. = ? pmol/L
Alkaline Phosphatase (ALP)	NPU27783	P—Alkaline phosphatase; cat.c.(37 °C; proc.) = ? U/L
Alpha 1 antitrypsin	NPU19692	P—alpha 1-Antitrypsin; mass c. = ? g/L
Alpha 2 macroglobulin	NPU27497	P—alpha-2-Macroglobulin; mass c. = ? g/L
Alpha-Amylase	NPU19652	P—Amylase; cat.c.(IFCC 2006) = ? U/L
Alphafoetoprotein	NPU19766	P—alpha-1-Fetoprotein; mass c. = ? µg/L
Antimony	NPU01274	U—Antimony; subst.c. = ? nmol/L
Antithrombin (3 levels)	NPU01277	P—Antithrombin; subst.c.(imm.; proc.) = ? µmol/L
Apo A1	NPU19695	P—Apolipoprotein A1; mass c. = ? g/L
Arsenic - Urine	NPU01308	U—Arsenic; subst.c. = ? nmol/L
Aspartate Amino Transferase (AST)	NPU19654	P—Aspartate transaminase; cat.c.(IFCC 2002) = ? U/L
Benzoylcegonine	NPU08994	U—Benzoylcegonine; arb.c.(proc.) = ?
Bilirubin	NPU01370	P—Bilirubins; subst.c. = ? µmol/L
Calcium	NPU01443	P—Calcium(II); subst.c. = ? mmol/L
Calcium	NPU04160	U—Calcium(II); subst.c. = ? mmol/L
Carbamazepine	NPU01457	P—Carbamazepine; subst.c. = ? µmol/L
Chloride	NPU01536	P—Chloride; subst.c. = ? mmol/L
Coagulation factor IX	NPU01637	P—Coagulation factor IX; rel.subst.c.(imm.; actual/norm; pro



Preferred term	Synonyms	Usage guidance	PUTS Unit	LOINC	System	Data combin
17-Hydroxyprogesterone	17OHP		nmol/L	14569-8	Ser/Plas	Red
Alanine aminotransferase	ALT	For assays with P-5'-P added to the reaction	U/L	1743-4	Ser/Plas	Green
Alanine aminotransferase	ALT	For assays without P-5'-P added to the reaction	U/L	1744-2	Ser/Plas	Green
Albumin		BCG method	g/L	61151-7	Ser/Plas	Green
Albumin		BCP method - preferred method	g/L	61152-5	Ser/Plas	Green
Albumin		Electrophoresis	g/L	2862-1	Ser/Plas	Red
Albumin concentration urine			mg/L	1754-1	Urine	Orange
Albumin creatinine ratio urine	ACR		mg/mmol	32294-1	Urine	Orange
Albumin excretion urine 24h			mg/24h	1755-8	Urine	Orange
Albumin excretion urine timed specimen			ug/min	49002-9	Urine	Orange
Alcohol		Reporting in mmol/L	mmol/L	15120-9	Bld	
Alcohol		Reporting in mg/dL	mg/dL	5643-2	Ser/Plas	
Alkaline phosphatase	ALP		U/L	6768-6	Ser/Plas	Green
Alpha-fetoprotein	AFP	For reporting in international units	kiU/L	19176-7	Ser/Plas	Red
Alpha-fetoprotein	AFP	For reporting mass concentration	ug/L	1834-1	Ser/Plas	Red
Alpha-fetoprotein MoM			MoM	20450-3	Ser/Plas	Red
Ammonia			umol/L	16362-6	Plas	Orange
Amylase			U/L	1798-8	Ser/Plas	Orange
Amylase fluid			U/L	1795-4	Body fld	Orange
Anion gap		Calculation including potassium	mmol/L	1863-0	Ser/Plas	Green
Anion gap		Calculation excluding potassium	mmol/L	10466-1	Ser/Plas	Green
Aspartate aminotransferase	AST		U/L	1920-8	Ser/Plas	Orange
Aspartate aminotransferase	AST	For assays with P-5'-P added to the reaction	U/L	30239-8	Ser/Plas	Orange
Bicarbonate	Total CO2		mmol/L	1963-8	Ser	Green
Bilirubin	Bili	"Total" not required	umol/L	14631-6	Ser/Plas	Orange
Bilirubin conjugated	Bili conj	Includes no delta bilirubin (eg dry chemistry instr	umol/L	29760-6	Ser/Plas	Green
Bilirubin conjugated	Bili conj	Includes delta bilirubin	umol/L	14629-0	Ser/Plas	Orange
Bilirubin unconjugated	Bili unconj		umol/L	14630-8	Ser/Plas	Orange
B-Natriuretic peptide	BNP		ng/L	30934-4	Ser/Plas	Red
B-Natriuretic peptide	BNP	For use with point of care analyzers	ng/L	42637-9	Bld	Red

165 Entries

Table 1 Australasian Harmonised Reference Intervals for Adults (AHRIA) \*

<b>Analyte</b>	<b>Male</b>	<b>Female</b>
Sodium	135 – 145 mmol/L	
Potassium **	3.5 – 5.2 mmol/L	
Chloride	95 – 110 mmol/L	
Bicarbonate	22 – 32 mmol/L	
Creatinine ***	60 – 110 µmol/L	45 – 90 µmol/L
Calcium	2.10 – 2.60 mmol/L	
Calcium (albumin adjusted)	2.10 – 2.60 mmol/L	
Phosphate ****	0.75 – 1.50 mmol/L	
Magnesium	0.70 – 1.10 mmol/L	
Lactate Dehydrogenase [L to P] (IFCC) *****	120 – 250 U/L	
Alkaline Phosphatase *****	30 – 110 U/L	
Total Protein	60 – 80 g/L	

# Haematology

- Session V (tomorrow – 9 am)

# Therapeutic Drugs



# JCTLM - listed materials Drugs

- NMIA-Australia (pure): heroin, MDA, MDMA, amphetamine, methamphetamine, morphine
- IRMM-Europe (pure): Tacrolimus, theophylline
- INMETRO-Brazil (pure): captopril, metronidazole, diclofenac
- LGC-UK (pure): Digoxin
- LGC-UK (serum): Digoxin
- NIST SRM 1599 (serum): carbamazepine, valproate
- NIST SRM 2381 (urine): codeine, morphine
- NIST SRM 960 (serum) ethosuximide
- NIST SRM 900 (serum): Phenobarbital, phenytoin, primidone
- NIST SRM 1511 (urine): benzoylcegonine, codeine, morphine, THC, phencyclidine



**51 Serum  
Drugs**



# Digoxin Assay Traceability

- Beckman Coulter – USP
- Roche Tina Quant – USP
- Roche Elecsys – USP
- Ortho Clinical Diagnostics – USP  
(gravimetric and RIA)
- Abbott Architect (2009) – not stated in IFU  
(compared with Multigent,  $y = 0.92x - 0.04$ )
- DRI – Microgenics – not stated
- Abbott AxSYM (2010) – not stated  
(compared with ACA, IMx, TDx)
- DRG ELISA (USA, 2010) – not stated

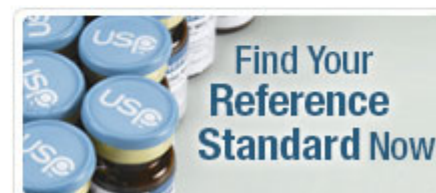
USP Reference Standards are highly-characterized physical specimens used in testing by pharmaceutical and related industries to help ensure the identity, strength, quality, and purity of medicines (drugs, biologics, and excipients), dietary supplements, and food ingredients. Our Reference Standard collection consists of more than 3,500 items ranging from drug substances, related impurities, residual solvents, biologics, excipients, botanicals, polymers, Near-IR and dissolution calibrators, photomicrographs, and melting point standards.

-2014)

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medicines (drugs, biologics, and excipients), dietary supplements, and food ingredients. Our Reference Standard collection consists of more than 3,500 items ranging from drug substances, related impurities, residual solvents, biologics, excipients, botanicals, polymers, Near-IR and dissolution calibrators, photomicrographs, and melting point standards.

USP Reference Standards are closely tied with the documentary standards published in the USP-NF, Food Chemicals Codex, and Dietary Supplements Compendium. Materials based directly on official monographs in the USP-NF—whose standards and procedures are enforceable by the U.S. Food and Drug Administration—are recognized for use in official standards in the United States, and their use is effective in demonstrating compliance with



## USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
<a href="#">1197018</a>	Diethyltoluamide Related Compound A (25 mg) (N,N-Diethyl-4-toluamide)	F004N0				[2728-05-4]	\$671
<a href="#">1197302</a>	Diflorasone Diacetate (200 mg)	H0G388	0.998 mg/mg (ai)		G (06/10) F-1 (03/00)	[33564-31-7]	\$215
<a href="#">1197506</a>	Diflunisal (200 mg)	G1F320	0.999 mg/mg (ai)		G (12/08)	[22494-42-4]	\$215
<a href="#">1198000</a>	Digitalis (3 g)	F				[8031-42-3]	\$215
<a href="#">1199002</a>	Digitoxin (200 mg)	N0I195	0.985 mg/mg (dr)		M (02/11)	[71-63-6]	\$215
<a href="#">1200000</a>	Digoxin (250 mg)	P0I054	0.985 mg/mg (ai)		O0B096 (04/12) N-1 (04/03)	[20830-75-5]	\$215
<a href="#">1200520</a>	Dihydroartemisinin (200 mg)	F0M339	0.988 mg/mg (ai)			[81496-81-3]	\$215
<a href="#">1200575</a>	Dihydroartemisinin Related Compound I (20 mg) ((3R,3aS,3a1R,6R,6aS,9S,10aS)-3,6,9-trimethyl-decahydro-2H-3a1,9-epoxyoxepino[4,3,2-ij]iso-chromen-2-one)	F009G0	1.00 mg/mg (ai)			n/f	\$671
<a href="#">1200600</a>	Dihydrocapsaicin (25 mg)	H1M408	0.997 mg/mg (ai)		H0F210 (02/15) G0C071 (09/07) F-1 (12/03) F (01/00)	[19408-84-5]	\$358
<a href="#">1200804</a>	Dihydrocodeine Bitartrate CII (200 mg)	J0K044	0.998 mg/mg (dr)		I0D205 (08/12)	[5965-13-9]	\$285

Approx 3,500 Materials



# JCTLM Methods (n=6)

Analyte	Reference measurement method/procedure	Applicable matrice(s)	Measurement principle/technique
acetaminophen	Roche method for quantification of acetaminophen in human	human EDTA plasma, human Li Heparin plasma, human serum (gel free tubes)	LC/MS/MS
phenobarbital	NIST method for antiepileptic drugs	human serum	ID-LC-MS/MS
phenytoin	NIST method for antiepileptic drugs	human serum	ID-LC-MS/MS
theophylline	INSTAND Reference Measurement Procedure for Theophylline	fresh, frozen or lyophilized serum or plasma	ID-GC/MS
topiramate	NIST method for antiepileptic drugs	human serum	ID-LC-MS/MS
vancomycin	Roche/Univ. Munich method for quantification of vancomycin in human serum by LC-MS/MS	fresh, or frozen human blood serum	LC-MS/MS

# Conclusions

- There are gaps in the JCTLM database
- Areas of need can be identified:
  - What is missing
  - How often it is used
  - How important is it clinically
  - How important *will it be* clinically (research)
  - What is technically possible
- Clear terminology / definition of the measurand needed
- Each test to be assessed separately