Harmonisation of Reference Ranges in Wales.

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WALES

Wales is a country in southwest Great Britain known for its rugged coastline, mountainous national parks, distinctive language and Celtic culture. Cardiff, the capital, is a refined coastal city with a nightlife scene and a medieval castle with ornate Gothic Revival interiors. Also to the south is Gower Peninsula, with beaches at Swansea and Rhossili bays offering surfing and other water sports.

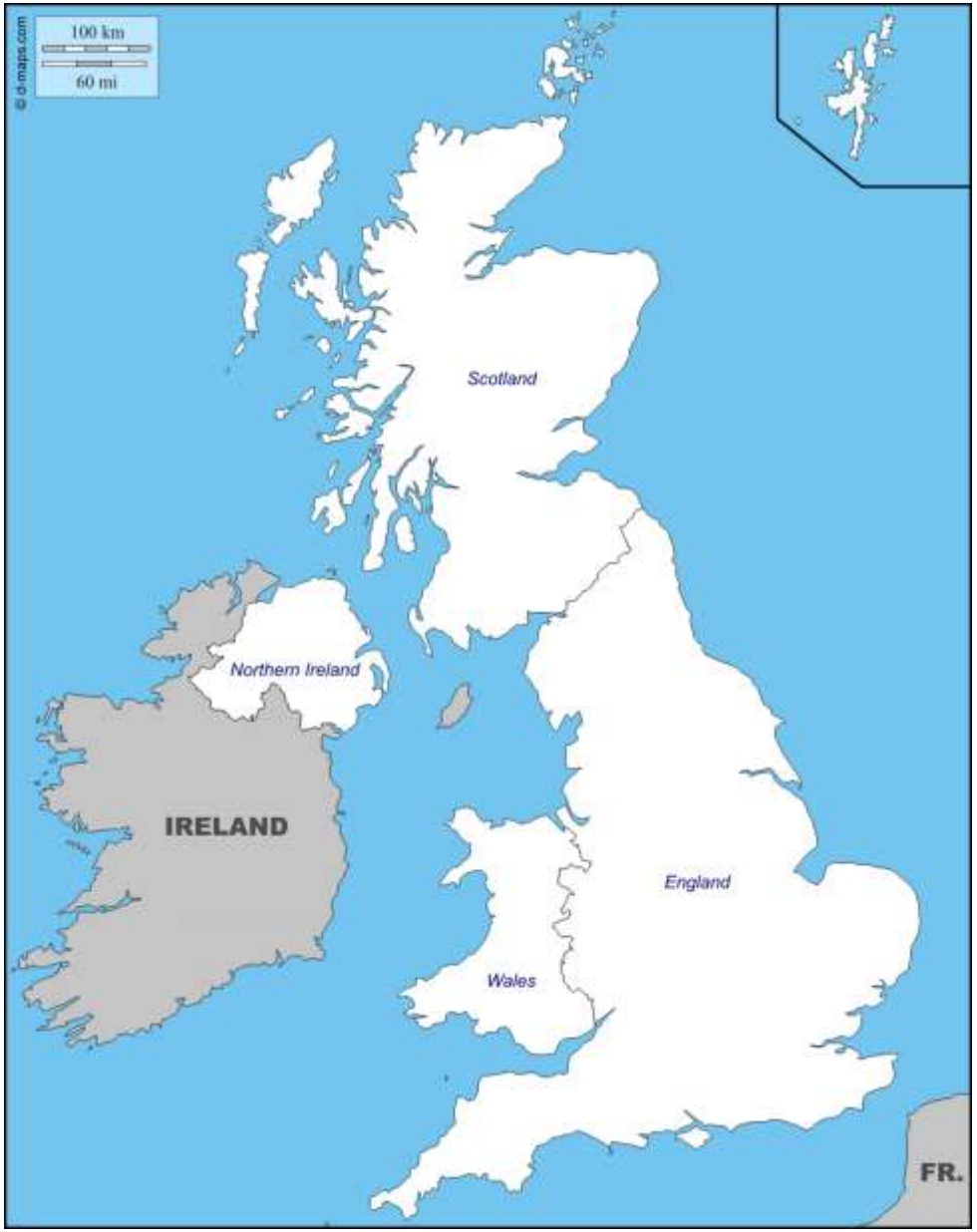
Capital: Cardiff

Currency: Pound sterling

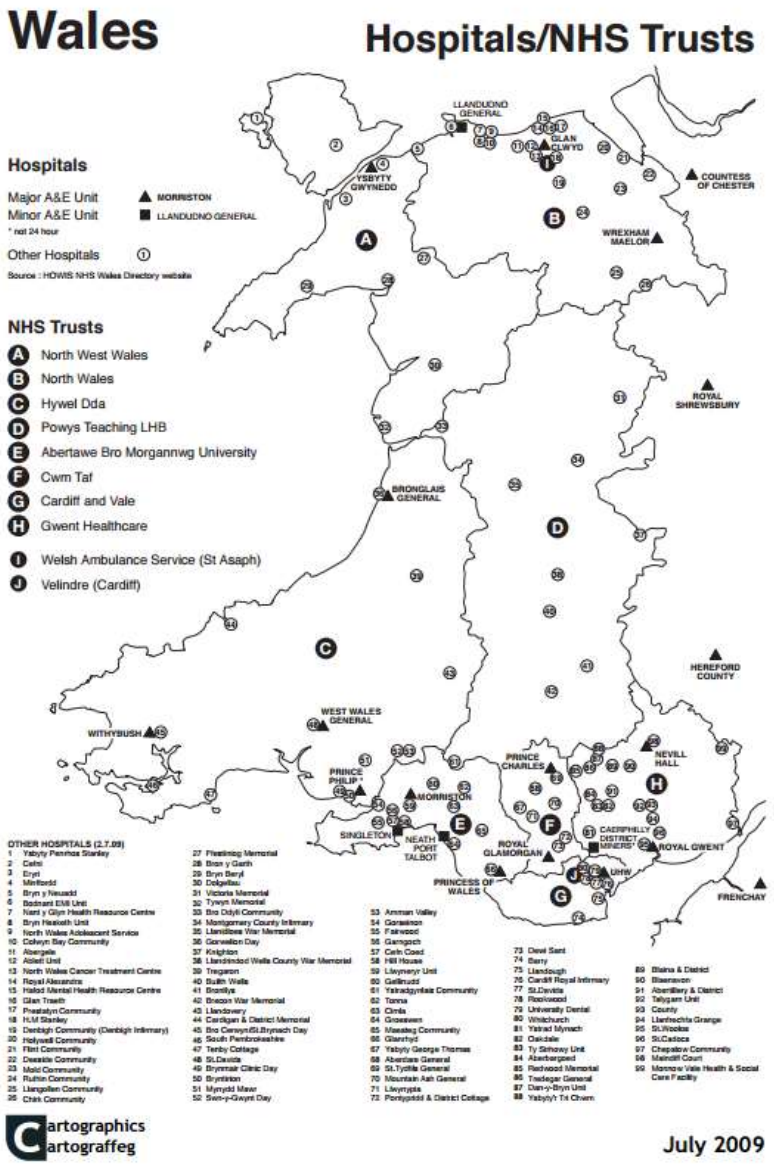
Population: 3,092,036 (2014)

National anthem: Hen Wlad Fy Nhadau

Official languages: Welsh, English



The driver to harmonise



On 1 October 2009, the biggest NHS reforms in a generation take place in Wales, with 22 Local Health Boards (LHBs) and seven NHS Trusts replaced with seven integrated Local Health Boards, responsible for all health care services. In addition, a new unified public health organisation, Public Health Wales NHS Trust, become fully operational.

As part of its Pathology modernisation plan in 2010, the Welsh Government agreed to fund a multi million pound initiative to provide a single Laboratory Information system (LIMS) across the country.

NHS Wales at that time had 18 Hospital Laboratories using 8 different IT systems and undertaking more than 21 million diagnostic tests each year with demand continuing to rise.

How will a new LIMS improve services?

The new LIMS was part of a networked national system linking Diagnostics with the Welsh Clinical Portal that would improve :

Reduce duplication

Improve Flexibility, portability and adaptability of service provision

Improve demand management and forward planning

Improve patient experience

Standardise the Service

Improve governance.

Integration of the single LIMS with patients' medical records would allow tests results to be shared and viewed, regardless of where the patient received care, or where the test was undertaken.

This provided a huge challenge to the Pathology Laboratories to agree on a standardised configuration of the LIMS prior to its implementation in 2012.

Clinical Biochemistry Standardisation Group

- Set up in Jan 2010 by Gethin Roberts
- To achieve this a Standardisation group was established with representation from each of the Health Boards with the aim to agree on : test/profile names, codes, units, reference and alert ranges, testing strategies, and minimum repeat requesting intervals.
- For Biochemistry this agreement was required for over 300 tests.

All Wales LIMS standardisation groups for Biochemistry and Toxicology disciplines

Lead: Gethin Roberts

Contributors:

Biochemistry	
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Toxicology	
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Work Programme

- Agreement on composition of test profiles
- Agreement on conventions for test/profile names, test/profile codes, units
- Agreement on reference ranges either Path Harmony, or based on analytical platforms
- Agreement on consensus for testing strategies e.g. thyroid, infertility, paraprotein investigations etc.
- Setting out proposals for minimum repeat requesting periods
- Examine other areas of the LIMS rule base which will impinge on biochemistry process to ensure that adequate flexibility is provided to allow safe and auditable provision of the service

How did we do it?

- Pragmatic approach : the group's remit
  - Look at existing data – Collecting and collating current information, what's similar what's different.
  - Look at evidence - Researching current guidance and other evidence as appropriate; EQA data, Professional bodies, Advice from Clinicians, All Wales Clinical Biochemistry Audit Group, NICE guidance, National Service Frameworks and Peer-reviewed journals.
  - Link with other initiatives such as Pathology Harmony and National Laboratory of Medicine Catalogue – chair of Wales Standardisation group part of Path Harmony UK.
  - Attending workshops, developing and refining recommendations.
  - Reviewing portfolios and obtaining feedback from colleagues.
  - Reporting back to their organisations.
  - Governance route via approval of SSAGCC (subcommittee of WSAC) which includes representation from WG.

Agree Composition of test profiles

The composition of profiles commonly requested across Wales (electrolytes, liver function tests, bone profile, thyroid profile and lipids) were approved by the SSAGCC for implementation in December 2008. These were set up as the default profiles on LIMS: e.g

UE profile for inpatients: **Urea, Sodium, Potassium, Creatinine**

LFT profile: **ALT, ALP, Bilirubin, Total Protein, Albumin, calc. Globulin**

Bone profile: **Calcium (total and adjusted), Phosphate, Albumin, Total Protein, ALP**

TFT profile: **TSH, freeT4**

Lipid profile : **Total Cholesterol, HDL-Chol, *calc. TC/HDL-C ratio,* Triglycerides, calc. LDL-Chol**

What's in a name?

Agreement on over 300 test names:

Based on NLMC Editorial Principles

Sample type required for the analysis is given in square brackets after name.
If no sample type given, [serum] is assumed
[blood] = whole blood

Result format - most results are numeric in nature; a minority will be reported by standard comment against a coded alphanumeric field.

Default units to be used for reporting - in line with IUPAC convention and NLMC editorial principles, concentrations are expressed per litre (with capital L) throughout; molar units are used wherever possible. Entirely different analytical methods may require a separate set with different units (e.g. TPMT, renin assays)

Number of significant figures/decimal places to express the result. For this element the Standardisation Group took the view that **reporting to an inappropriately high number of significant figures/decimal places was usually scientifically questionable**, potentially clinically misleading and a clinical risk due to higher likelihood of transcription errors. The view was therefore taken that the number of figures reported generally should be the minimum compatible with the precision of the analytical method and the required clinical discrimination for the test. The experience of the group was used to determine the balance between these (for example potassium need only be quoted to 1 d.p. although the precision of analysis is sufficient to allow 2 d.p.). *A necessary requirement identified by the group is to allow the reduction of the number of decimal points quoted with increasing magnitude of results.*

Field length for numeric results set to 6 places (including decimal point) this was considered adequate in the vast majority of cases.

Agree Reference ranges

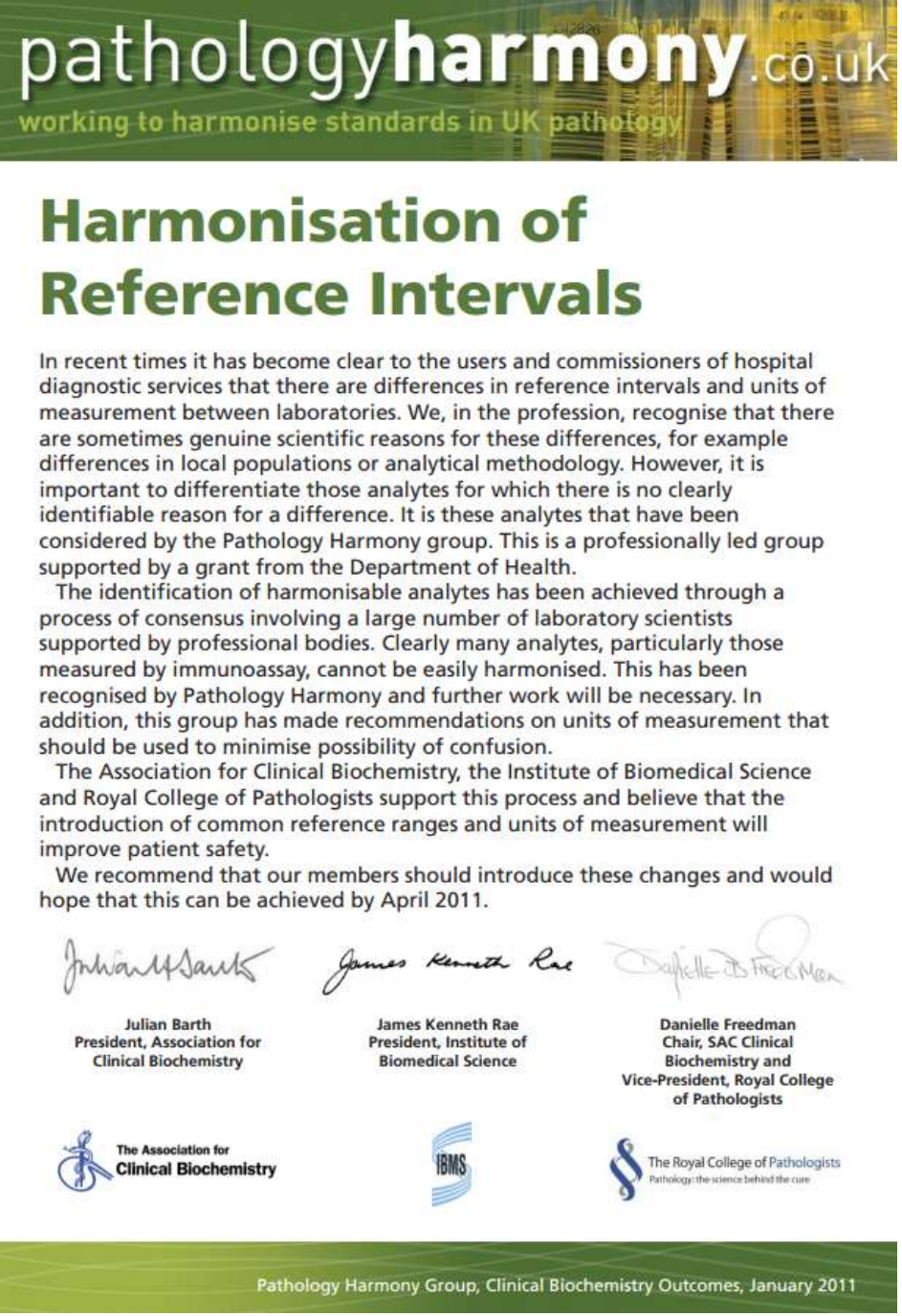
The aim was to minimise variation in reference ranges.

The All-Wales ranges agreed for Biochemistry for the LIMS are based either on Pathology Harmony ranges or by consensus following discussion at the Standardisation Group.

Methodology exactly the same as Pathology Harmony – gathering information on ranges used and basing a judgement of the most appropriate as a consensus weighted by any evidence from literature review.

UK Protein Reference Unit published ranges also used.

The remaining reference ranges are analytical platform or method specific; these have been derived from manufacturer's kit inserts, or, where these are unreliable, from literature based evidence.



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working to harmonise standards in UK pathology

Harmonisation of Reference Intervals

In recent times it has become clear to the users and commissioners of hospital diagnostic services that there are differences in reference intervals and units of measurement between laboratories. We, in the profession, recognise that there are sometimes genuine scientific reasons for these differences, for example differences in local populations or analytical methodology. However, it is important to differentiate those analytes for which there is no clearly identifiable reason for a difference. It is these analytes that have been considered by the Pathology Harmony group. This is a professionally led group supported by a grant from the Department of Health.

The identification of harmonisable analytes has been achieved through a process of consensus involving a large number of laboratory scientists supported by professional bodies. Clearly many analytes, particularly those measured by immunoassay, cannot be easily harmonised. This has been recognised by Pathology Harmony and further work will be necessary. In addition, this group has made recommendations on units of measurement that should be used to minimise possibility of confusion.

The Association for Clinical Biochemistry, the Institute of Biomedical Science and Royal College of Pathologists support this process and believe that the introduction of common reference ranges and units of measurement will improve patient safety.

We recommend that our members should introduce these changes and would hope that this can be achieved by April 2011.

Julian Barth
President, Association for Clinical Biochemistry

James Kenneth Rae
President, Institute of Biomedical Science

Danielle Freedman
Chair, SAC Clinical Biochemistry and Vice-President, Royal College of Pathologists

The Association for Clinical Biochemistry

IBMS

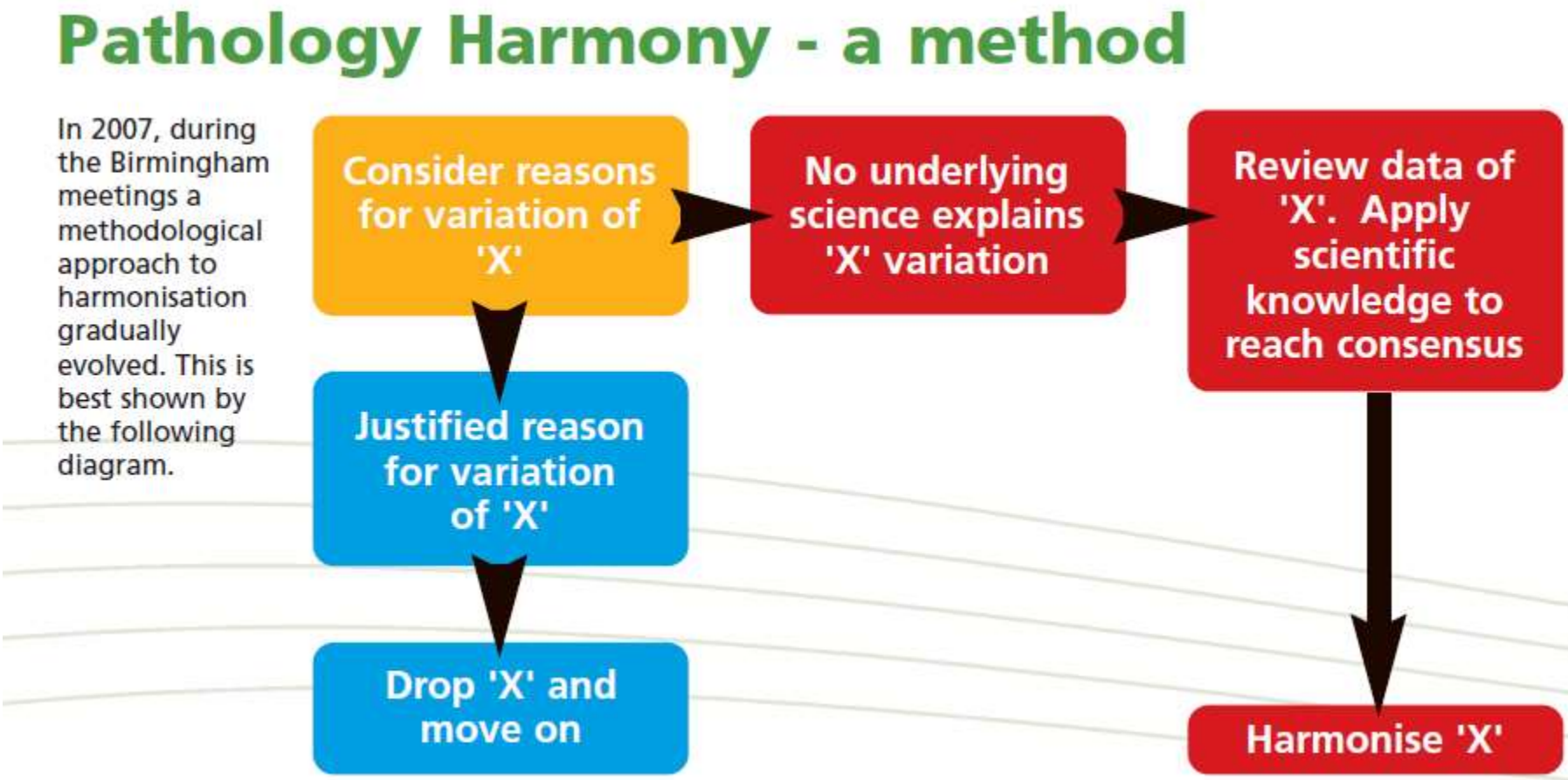
The Royal College of Pathologists
Pathology: the science behind the cure

Pathology Harmony Group, Clinical Biochemistry Outcomes, January 2011

This work began as part of the Department of Health's Pathology Action Learning Programme. It was initiated in West Midlands Clinical Biochemistry departments, but soon gained considerable momentum, growing to incorporate other work being done by colleagues in the North West Strategic Health Authority and in Wales. Several areas were identified where it was felt there was potential for harmonisation. Working groups were then formed to consider each area. The following were examined:

- Units of measurement
- Reference intervals
- Test name harmonisation
- Standardising procedure for phoning abnormal results to primary care
- Standardising advice on protocols for simple tests

How did they do it?



Berg J, Lane V. Annals of Clinical Biochemistry Volume 48 May 2011

Example of analyte harmonisation:

Serum sodium

Aim

To consider if serum sodium reference intervals can be harmonised.

Method - phase 1

Questionnaire to all laboratories asking for current reference intervals for serum sodium, including any sex, age or other variations.

Method - phase 2

Meet to review questionnaire results. Request further information and consider if variation has any basis either due to difference in equipment and reagents, population served or other technical, scientific or clinical reasons for observed variation.

Method - phase 3

Consideration of where variation has come from between laboratories, including assessment of original work undertaken on patient samples.

Results

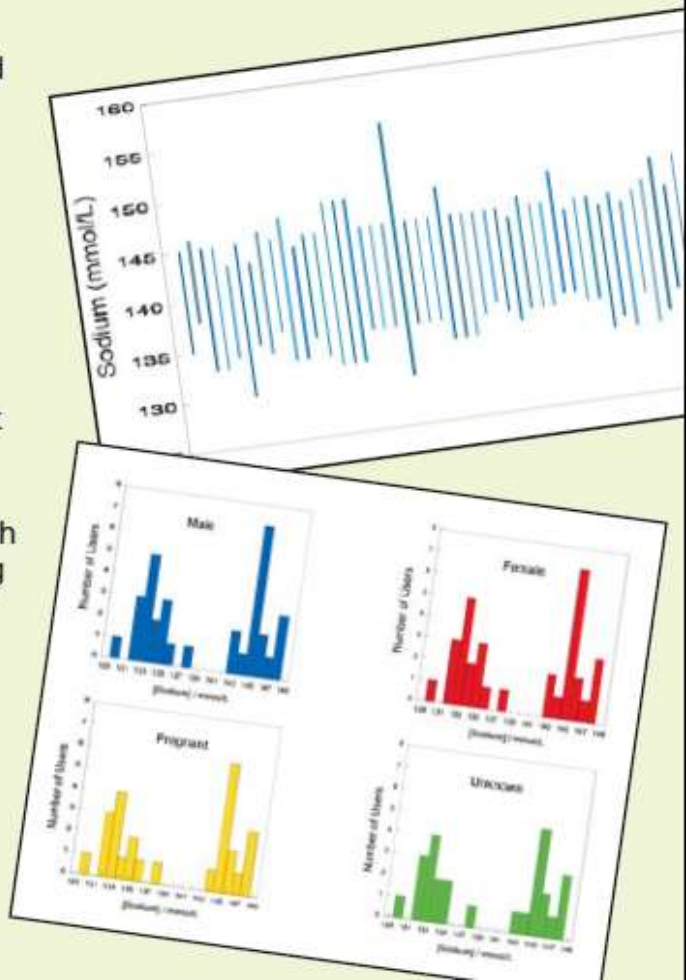
Variation in serum sodium in West Midland laboratories is shown in the figures. When the analytical platforms were reviewed it was found that the variation in reference intervals was not related to analytical platforms. Indeed, many laboratories used identical equipment and reagents but had small variations in the reference intervals they quoted for serum sodium. Population studies in no way explained variation.

Further work looking at variation between laboratories was brought back to the meeting and it was clear that the major reason for variation was simply historical, with no scientific foundation. Following this conclusion 'pragmatic science' was applied whereby the group considered the variations at the bottom and top end of the reference intervals and came to a consensus view on a sensible reference interval to propose.

Suggested referece interval: 133-146 mmol/L

Conclusion

The evidence was presented at the final action learning set and was unanimously approved.



Agreed Adult Clinical Biochemistry Reference Intervals

Test Name	Units	Range low	Range high	Comments
Sodium	mmol/L	133	146	
Potassium	mmol/L	3.5	5.3	
Urea	mmol/L	2.5	7.8	
Chloride	mmol/L	95	108	
Bicarbonate	mmol/L	22	29	
Phosphate	mmol/L	0.8	1.5	
Magnesium	mmol/L	0.7	1.0	
Albumin	g/L	35	50	
Total Protein	g/L	60	80	
Osmolality	mmol/kg	275	295	
Alkaline Phosphatase (ALP)	U/L	30	130	IFCC candidate method p-NPP using AMP buffer
Creatine Kinase (CK)	U/L	40 25	320 (M) 200 (F)	Ranges are for white Caucasian only; other ethnic groups may have higher values
Bilirubin (total)	µmol/L		<21	
Adjusted Calcium	mmol/L	2.2	2.6	Use adjustment equations normalised to mean calcium of 2.4 mmol/L
Urate	µmol/L	200 140	430(M) 360(F)	
Carbamazepine	mg/L	4	12	
Phenobarbitone	mg/L	10	40	
Phenytoin	mg/L	5	20	
Theophylline	mg/L	10	20	
Valproate	mg/L			No range should be quoted
Paracetamol	mg/L			
Salicylate	mg/L			
Methotrexate	µmol/L			
Lithium	mmol/L	0.4	1.0	Complies with NPSA guidance
Digoxin	µg/L	0.5	1.0	
Tacrolimus	µg/L			
25OH Vitamin D (including separately measured D2 & D3)	nmol/L			No ranges recommended
PTH	pmol/L			Method dependent
BNP/NTproBNP	ng/L			
Troponin I	ng/L			Method dependent
Troponin T	ng/L			
24 h Urine Calcium	mmol/24h	2.5	7.5	
24 h Urine Urate	mmol/24h	1.5	4.5	
24 h Urine Phosphate	mmol/24h	15	50	
24 h Urine Magnesium	mmol/24h	2.4	6.5	

What was the outcome?

Agreed Paediatric Clinical Biochemistry Reference Intervals

Test Name	Age	Units	Range low	Range high	Comments
Sodium	No age-related differences	mmol/L	133	146	
Plasma Potassium	Neonate	mmol/L	3.4	6.0	
	Infant	mmol/L	3.5	5.7	
	1-16 yrs	mmol/L	3.5	5.0	
Urea	Neonate	mmol/L	0.8	5.5	
	Infant	mmol/L	1.0	5.5	
	1-16 yrs	mmol/L	2.5	6.5	
Magnesium	Neonate	mmol/L	0.6	1.0	
	Infant - 16 yrs	mmol/L	0.7	1.0	
Plasma lactate	No age-related differences	mmol/L	0.6	2.5	Enzymatic method only
Bilirubin (total)	14 days - 16 yrs	µmol/L		<21	
Albumin	Neonate	g/L	30	45	
	Infant	g/L	30	45	
	1-16 yrs	g/L	30	50	
Calcium	Neonate	mmol/L	2.0	2.7	Actual not adjusted
	Infant - 16 yrs	mmol/L	2.2	2.7	
Phosphate	Neonate	mmol/L	1.3	2.6	
	Infant	mmol/L	1.3	2.4	
	1-16 yrs	mmol/L	0.9	1.8	
Alkaline Phosphatase (ALP)	Neonate	U/L	70	380	p-NPP using AMP buffer
	Infant - 16 yrs	U/L	60	425	
Ammonia	Sick or premature	µmol/L		<150	Follow metbio.net guidance
	Neonate	µmol/L		<100	
	Infant - 16 yrs	µmol/L		<50	
Plasma Bicarbonate	No age-related differences	mmol/L	19	28	

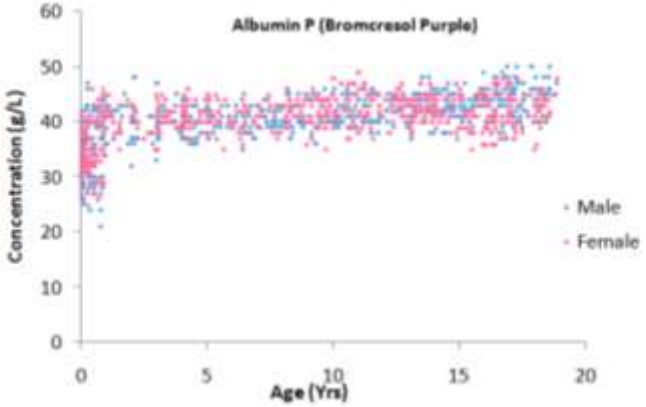
Definitions: Neonate <4 weeks; Infant 4 weeks – 1 year

What did we do in Wales?

- Pathology Harmony UK ranges and units were used for all adult ranges e.g. serum sodium, potassium, urea, chloride, bicarbonate, phosphate, magnesium, albumin, total protein, bilirubin, urate, osmolality, Carbamazepine , Phenobarbitone, Phenytoin Theophylline, Theophylline, and Lithium.
- For Alkaline Phosphatase, it was agreed that all Laboratories would use the IFCC method , for Creatine Kinase a common range for white Caucasians only was agreed, platform specific ranges were developed for the remaining enzymes.
- Platform specific reference ranges were developed for serum ACE, Calcium, Bilirubin conjugate, Lactate and the majority of the immunoassay methods.

What were the issues?

CALIPER



Albumin P (Bromcresol Purple) (g/L)

Published paper for the analyte on IFCC (Clinical Chemistry 2012) [illegible]

Female Reference Intervals					
Age	Lower Limit	Upper Limit	Samples	Lower CI	Higher CI
0 - 14 days	28	41	182	(26 - 29)	(40 - 42)
15 days - < 1 year	25	46	153	(21 - 27)	(44 - 47)
1 - < 8 years	35	45	298	(35 - 36)	(45 - 46)
8 - < 15 years	37	47	390	(37 - 38)	(46 - 47)
15 - < 19 years	35	49	119	(35 - 36)	(48 - 49)

Male Reference Intervals					
Age	Lower Limit	Upper Limit	Samples	Lower CI	Higher CI
0 - 14 days	28	41	182	(26 - 29)	(40 - 42)
15 days - < 1 year	25	46	153	(21 - 27)	(44 - 47)
1 - < 8 years	35	45	298	(35 - 36)	(45 - 46)
8 - < 15 years	37	47	390	(37 - 38)	(46 - 47)
15 - < 19 years	38	50	123	(37 - 39)	(48 - 50)

Pathology Harmony – Albumin g/L

Age	Lower limit	Upper limit
Neonate	30	45
Infant	30	45
1-16	30	50

Neonate and Infant ranges very different to CALIPER Study

Used CLSI C28 A3 Protocol. Inclusion criteria: healthy children (determined based on completed questionnaires) of all ages and both sexes (0-18 years of age).
Exclusion criteria: history of chronic illness or metabolic disease, acute illness within the past month, or prescribed medication over the past month. Demographic data collected include previous and current health status, diet, exercise status, ethnicity, BMI parameters and Tanner stage (where appropriate).

Paediatric Reference Range issues

Analyte	Comment
Albumin	Path Harmony and CALIPER differ significantly - Implement CALIPER ranges
ALP	Path Harmony and CALIPER differ significantly- Implement CALIPER ranges
AFP (kU/L)	
Urate	No paediatric ranges in place (Path Harmony for adults only). Implement CALIPER ranges
Urea	Little difference between the path harmony and CALIPER so use Path Harmony ranges
Triglycerides	No paediatric ranges in place (Path Harmony for adults only). Implement CALIPER ranges)
Total Protein	No paediatric ranges in place (Path Harmony for adults only). Implement CALIPER
Phosphate	Path Harmony and CALIPER differ significantly - Implement CALIPER ranges
Magnesium	Path Harmony and CALIPER differ significantly - Implement CALIPER ranges
Direct HDL-C	No paediatric ranges in place (Path Harmony for adults only). Implement CALIPER
Creatinine	Not appropriate to use enzymatic reference ranges on a non-enzymic method run on a different platform – specific CALIPER ranges.
Calcium	Little difference between the path harmony and CALIPER so use Path Harmony ranges

Where there was no consensus or data available – use laboratory derived data

e.g

- Adjusted calcium equations were derived for each platform to provide a normalised mean calcium of 2.4 mmol/l using laboratory data.

Weqas Questionnaire (April 08)

Please fax to: 02920 748336

Lab Code:

I would like to include Adjusted Calcuim - **Yes / No**
(Delete as appropriate)

If you need to add Adjusted Calcium to more than one section please list them below
……

Please enter your Adjusted Calcium Calculation

NHS WALES GIG CYMRU

Summary of current equations in use for adjustment of serum calcium. (2008 data courtesy of Keele NPBS & WEQAS)

	Albumin g/L (rounded)												
	35	36	37	38	39	40	41	42	43	44	45	46	47
Slope													
0.010	2					1							
0.011	2												
0.012		1											
0.013						1							1
0.015					1				1			1	
0.016				1		1							
0.017							1	2	6	1			
0.018	1					1	1	1	1			1	
0.02					1	58							
0.022						1		3					
0.025	1			1		7							
Totals	6	1	0	2	2	70	2	6	8	1	0	2	1

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Standardising adjusted calcium taken up by Pathology Harmony

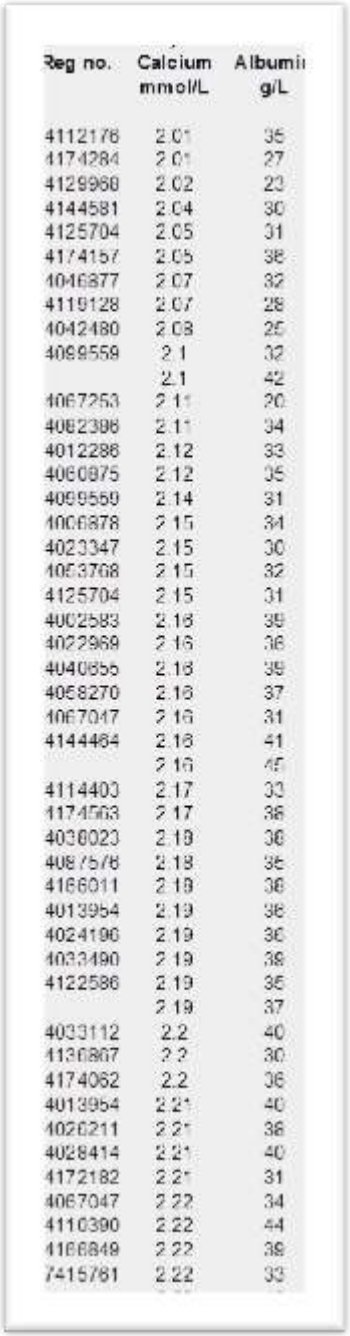
Many laboratories (58%) still use the traditional adjustment equation:

[Ca]adj= [Ca]tot+((40 –[Alb]) x 0.02)

- This assumes that the mean normal albumin is 40 g/L and that 0.02 mmol of calcium is bound to each gram of albumin, both not strictly true.
- This adjustment, whilst providing a reasonable correction for lower calcium and albumin values, tends to miss cases of hypercalcaemia, especially if a reference range the same as for total calcium is quoted (or assumed).
- Scientifically questionable to use a single regression equation when there are several distinctly different chemistries in use for measuring both serum calcium and albumin.
- Regression coefficient of calcium on albumin is dependent on analytical methods used

Proposal: that regression equations of calcium on albumin are generated from real laboratory data, and that the equations are normalised to a calcium value of 2.40 mmol/L.

Ashby JP, Wright DJ, Rinsler MG. Ann Clin Biochem 1986; 23: 533-537



Reg no.	Calcium mmol/L	Albumi g/L
4112176	2.01	35
4174284	2.01	27
4129960	2.02	23
4144581	2.04	30
4125704	2.05	31
4174157	2.05	38
4046877	2.07	32
4119128	2.07	28
4042480	2.08	25
4089559	2.1	32
	2.1	42
4067253	2.11	20
4082396	2.11	34
4012286	2.12	33
4060975	2.12	35
4089559	2.14	31
4006878	2.15	34
4023347	2.15	30
4053768	2.15	32
4125704	2.15	31
4002583	2.16	39
4022969	2.16	36
4040655	2.16	39
4058270	2.16	37
4067047	2.16	31
4144464	2.16	41
	2.16	45
4114403	2.17	33
4174563	2.17	36
4036023	2.18	30
4087578	2.18	35
4166011	2.19	30
4013954	2.19	36
4024196	2.19	30
4033490	2.19	38
4122586	2.19	35
	2.19	37
4033112	2.2	40
4136867	2.2	30
4174062	2.2	36
4013954	2.21	40
4020211	2.21	36
4028414	2.21	40
4172182	2.21	31
4067047	2.22	34
4110390	2.22	44
4166849	2.22	39
7415781	2.22	33

How do we calculate it?

Ideally 1000 values should be collected with at least 30 data points for each whole integer albumin concentration.

Exclusion Criteria:

Patients in whom there are other conditions that might affect calcium homeostasis.:

- Patients with renal impairment [creatinine > 200umol/L or urea >15mmol/L]
- Hypomagnesaemia [hypokalaemia as a surrogate marker i.e. K >3.5 and < 5.5mmol/L]
- Liver disease [ALT/ALP > upper reference limit]
- Total calcium concentration <2.0 and > 2.7 mmol/L

Hypo/hyperparathyroidism i.e. PTH outside the healthy population reference range

- Vitamin D deficiency
- Vitamin D toxicity
- Hypoadrenalism
- Patients on parenteral nutrition
- Patients with malignancy
- < 18 yrs.
- A pragmatic approach appropriate to local circumstances might be used based on the source of the test request e.g. excluding patients from nephrology, endocrinology, oncology, and haematology.

Barth JH et al Ann Clin Biochem 1996; 33: 55-58

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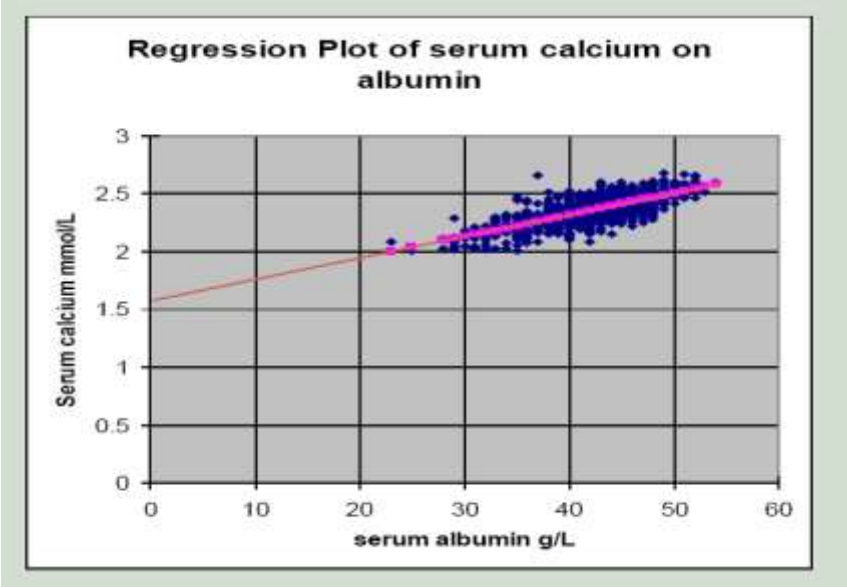


Y = m x + c

$[Ca]_{tot} = 0.0188[Alb] + 1.57$

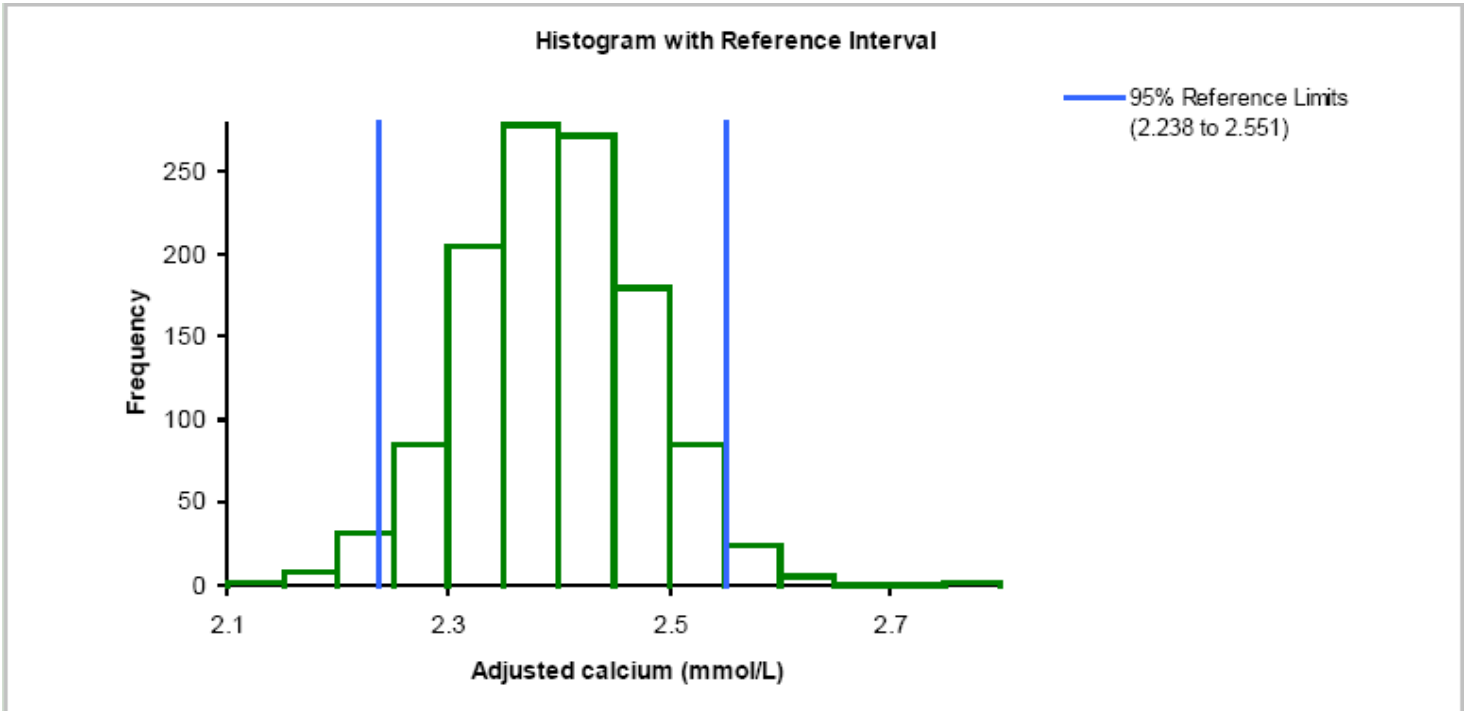
- A regression line was generated from the data using Microsoft Excel.
- The intercept is taken as the mean non-protein – bound calcium concn. of the population (1.57 mmol/l)
- The intercept is subtracted from 2.40 (mean ref range path harmony) to obtain normal protein - bound calcium (2.4 – 1.57 = 0.83 mmol/l).
- Ca is adjusted for alb by subtracting the product of the slope and the alb from measured Ca and adding the normal protein bound concentration.
- using the adjustment equation of:

$[Ca]_{adj} = [Ca]_{tot} – (slope[Alb]) + (mean [Ca]_{tot} – intercept [Ca]_{tot})$

$[Ca]_{adj} = [Ca]_{tot} – (0.0188[Alb]) + 0.83$

Which, rearranged gives:

$[Ca]_{adj} = [Ca]_{tot} + ((44.1 – [Alb]) \times 0.0188)$



Applying the formula to the collected data gave the distribution of adjusted calcium illustrated below with a mean of 2.40 and 95% reference limits of 2.24 –2.55 mmol/L

- Not necessary for every laboratory to generate adjustment equations.
- Master equations for analytical platforms or methods may be provided and used as appropriate.
- Using this normalised approach a reference range of **2.20 –2.60 mmol/L** may be universally applied to adjusted calcium results.

Albumin g/l (rounded) All Methods													
Slope	38	39	40	41	42	43	44	45	46	47	48	49	50
0.010													
0.011		1											
0.012			1										
0.013			3			1				2			
0.014		1					1	1					1
0.015													
0.016		1			1			1					1
0.017	1			1	3	1	1			1			
0.018				1	1	1							
0.019	1						14						
0.020			36	1									
0.021	2			1									
0.023													
0.024													
0.025			4										
Totals	4	3	44	4	5	3	16	2	0	3	0	0	2

BCP/ISE
BCP/AZE
BCP/NM-BAPTA
BCP/CPC

BCG/CPC
BCG/NM-BAPTA
BCG/AZE
VITROS
Conventional formula used across all methods

58% of laboratories are no longer using the Paynes formula.

Albumin g/l (rounded) BCG Methods													
Slope	38	39	40	41	42	43	44	45	46	47	48	49	50
0.010													
0.011													
0.012													
0.013						1				2			
0.014							1	1					1
0.015													
0.016								1					1
0.017					2	1	1			1			
0.018					1	1							
0.019							14						
0.020			22	1									
0.021	1												
0.023													
0.024													
0.025			3										
Totals	1	0	25	1	3	3	16	2	0	3	0	0	2

Albumin g/l (rounded) BCP methods													
Slope	38	39	40	41	42	43	44	45	46	47	48	49	50
0.010													
0.011		1											
0.012			1										
0.013			3										
0.014		1											
0.015													
0.016		1			1								
0.017	1			1	1								
0.018				1									
0.019	1												
0.020			14										
0.021	1			1									
0.023													
0.024													
0.025			1										
Totals	3	3	19	3	2	0	0	0	0	0	0	0	0

Other Developments

Establishing Standard comments

These were developed for all non-numeric sets.

2011 - they had been established for serum protein electrophoresis, Bence Jones' protein screening and immunofixation and monoclonal protein identification.

2011 - rule based reflex testing and agreed standard comments for thyroid function testing. (based on British Thyroid Foundation "UK guidelines for the use of thyroid function tests").

2011-2014 Expanded to include all other Endocrine tests, Lipids , HbA1c

Endocrine Comments in LIMS as of 21/4/15 – 63 Standardised Comments agreed

e.g. Parathyroid

PTH1	Increased PTH with hypercalcaemia consistent with primary hyperparathyroidism.	Increased PTH with hypercalcaemia consistent with primary hyperparathyroidism.
PTH2	Raised PTH and hypercalcaemia - suggest further tests.	Raised PTH and hypercalcaemia could be consistent with primary hyperparathyroidism or autosomal dominant hypercalcaemic hypocalcuria. Suggest sending PAIRED fasting serum sample and spot urine sample (second void of the day) for calculation of calcium excretion, to differentiate.
PTH3	Suppressed PTH. Consistent with a non-parathyoid cause of hypercalcaemia.	Suppressed PTH. Consistent with a non-parathyoid cause of hypercalcaemia.
PTH4	Consistent with hypoparathyroidism.	Consistent with hypoparathyroidism.
PTH5	Consistent with secondary hyperparathyroidism.	Consistent with secondary hyperparathyroidism.
PTH6	Consistent with tertiary hyperparathyroidism.	Consistent with tertiary hyperparathyroidism.
PTH7	PTH is not consistent with primary hyperparathyroidism.	PTH is not consistent with primary hyperparathyroidism.
PTH8	Minor elevations in serum PTH can occur due to vitamin D deficiency.	Suggest exclude other causes of hypercalcemia such as thiazide diuretics and immobilisation. Minor elevations in serum PTH can occur due to vitamin D deficiency.
PTH9	Serum PTH is inappropriate for the serum calcium concentration	Serum PTH is inappropriate for the serum calcium concentration. Possible primary hyperparathyroidism. Suggest repeat PTH and calcium in 2 months 'time.

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30 standardised comments agreed

TFT Comments April 2015

New code	Description	Comment
EU	Biochemically euthyroid.	Biochemically euthyroid.
HYPO1	Consistent with primary hypothyroidism. Consider levothyroxine treatment.	Consistent with primary hypothyroidism. Consider levothyroxine treatment.
HYPO2	TSH >10 mU/L with free T4 within reference range	TSH >10 mU/L with free T4 within reference range: consistent with actual/emerging primary hypothyroidism. Suggest repeat if new finding otherwise if symptomatic consider levothyroxine treatment.
HYPO3	Suggest send repeat sample for TFT in 3-6 months to exclude non-thyroidal illness	Suggest send repeat sample for TFT in 3-6 months to exclude non-thyroidal illness, subclinical hypothyroidism and drugs as a cause of the slightly increased TSH.
HYPO4		TSH increased on repeat. TPO antibodies added to stratify risk of progression to overt hypothyroidism.
HYPO5	No details with increased TSH	No clinical details. Increased TSH is consistent with hypothyroidism or poor compliance / inadequate dose of thyroxine.
ITU		Consistent with severe non-thyroidal illness or secondary hypothyroidism (hypopituitarism).
LTSH1	TSH below reference range, suggest repeat in 3 - 6 months	TSH below reference range. Assuming patient not on levothyroxine, suggest repeat in 3 - 6 months to exclude developing hyperthyroidism, non thyroidal illness or drug effects (e.g. beta-blockers and steroids can suppress TSH) as a cause.
LTSH2	Suppressed TSH, consistent with subclinical hyperthyroidism	Suppressed TSH. Assuming patient not on levothyroxine, consistent with subclinical hyperthyroidism. Suggest repeat in 2 months to exclude emerging overt hyperthyroidism.
NC	Unable to provide interpretation in the absence of relevant clinical information.	Unable to provide interpretation in the absence of relevant clinical information.
NTI1	Non thyroidal illness Auto comment on A&E	Screening of thyroid function is not generally indicated in the acutely ill due to frequent non-specific changes.
NTI2	Elevated FT4 may be secondary to non-thyroidal illness or medications.	Increased FreeT4 may be secondary to non-thyroidal illness or medications. TSH is in the euthyroid range.
NTI3	Suggest repeat thyroid function tests on recovery.	Suggest repeat thyroid function tests on recovery.
OV	Aim for a TSH within the reference range in primary hypothyroidism	If patient is on levothyroxine for the treatment of primary hypothyroidism, then consider reducing the dose, aiming for a TSH that is within the reference range.
PREG1R	Pregnant euthyroid women commonly have low free T4 in the second and third trimesters. (Roche method)	Pregnant euthyroid women commonly have decreased free T4 in the second and third trimesters. TSH within reference range.
PREG2	Suggest a slight increase in dose of levothyroxine	Suggest a slight increase in dose of levothyroxine to achieve a serum TSH in the range 0.4 - 2.0 mU/L which is appropriate for pregnancy.
PREG3	TSH often suppressed in first trimester of pregnancy	TSH often suppressed in first trimester of pregnancy

Examples of Auto Comments

Vitamin D autocomments	
	Total vitamin D <30 nmol/L is deficient. Please note this assay does NOT detect Alfacalcidol.
	Total vitamin D level 30-50 nmol/L may be inadequate in some people. Please note this assay does NOT detect Alfacalcidol.
	Total vitamin D level >50 nmol/L is sufficient in most individuals. Please note this assay does NOT detect Alfacalcidol.

GH autocomments	
GH1	Indicates adequate growth hormone reserve.

Progesterone autocomments	
	Progesterone <16 nmol/L: Ovulation unlikely to have occurred. If this is not a mid-luteal phase sample, suggest repeating approximately 7 days prior to expected menstruation.
	Progesterone 16-28 nmol/L: Ovulation may have occurred. If this is not a mid-luteal phase sample, suggest repeating approximately 7 days prior to expected menstruation.
	Progesterone > 28 nmol/L: Suggests ovulation has occurred.
For women aged > 48?? Suggested workflow	FSH alone is sufficient to assess menopausal status in women aged over 45 years

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LIMS Lipid Comments agreed by the Welsh Chemical Pathologists Jan 2015

Significant hypercholesterolaemia. Is there a family history of premature IHD or hypercholesterolaemia? Suggest exclude secondary causes and refer to a hospital clinic to assess for possible familial hypercholesterolaemia (FH).

If there is history of MI in a first degree relative < 60 (or second degree relative < 50 years), or a first or second degree relative with a total cholesterol > 7.5, consider Familial Hypercholesterolaemia (FH). Tendon xanthomas in the patient or a first or second degree relative would confirm FH. (LIP6)

Significant mixed hyperlipidaemia. Diabetes, alcohol and obesity are the commonest secondary causes.

Medication e.g. isotretinoin, anti-retroviral and anti psychotics may be a secondary factor for mixed hyperlipidaemia.

Mixed dyslipidaemia can be secondary to poorly controlled diabetes, excess alcohol, raised BMI or poor diet. Suggest lifestyle intervention in the first instance, with the addition of lipid lowering therapy if predicted cardiovascular risk is high.

Significantly elevated triglycerides are associated with a risk of pancreatitis. Suggested to make this an autocomment for TG>20mmol/L

Raised triglyceride. Suggest repeat as fasting sample.

Suggest check fasting glucose (or HbA1c), thyroid, renal and liver profile.

Suggest consider referral to a hospital lipid clinic.

Lipids may remain spuriously low for up to 3 months following acute illness.

Dynamic function testing

The forms an important aspect of the standardisation process which will allow equivalent standards of investigation whose results can be compared across Wales.

2011 Glucose tolerance test and Short Synacthen test only agreed.

2014 pituitary function tests, prolonged 72 hr fast, adrenocortical stimulation and suppression tests, GTT for acromegaly, petrosal sinus sampling with CRH, Synacthen test for CAH, water deprivation tests, domperidone test, GH-RH and arginine test of GH reserve.

Where are we now?

By April 2015 all laboratories in Wales were live on the new LIMS . Implemented for Blood Sciences, Immunology and Microbiology . Biochemistry standardisation group continue to review process.

Demand management – MRI agreed for a number of test. In July 2013 survey of current practice conducted to establish best practice. Number of MRIs being reviewed.

Guideline and best practice development ongoing – e.g. Renal Hyperkalaemia guideline, telephone limits, AKI algorithm implementation

Funding by WG for All Wales connectivity solution for POCT has been agreed. URS agreed.

Test names, comments, configuration in LIMS in process for POCT.