Standardisation of Laboratory Tests: Why It Is Needed

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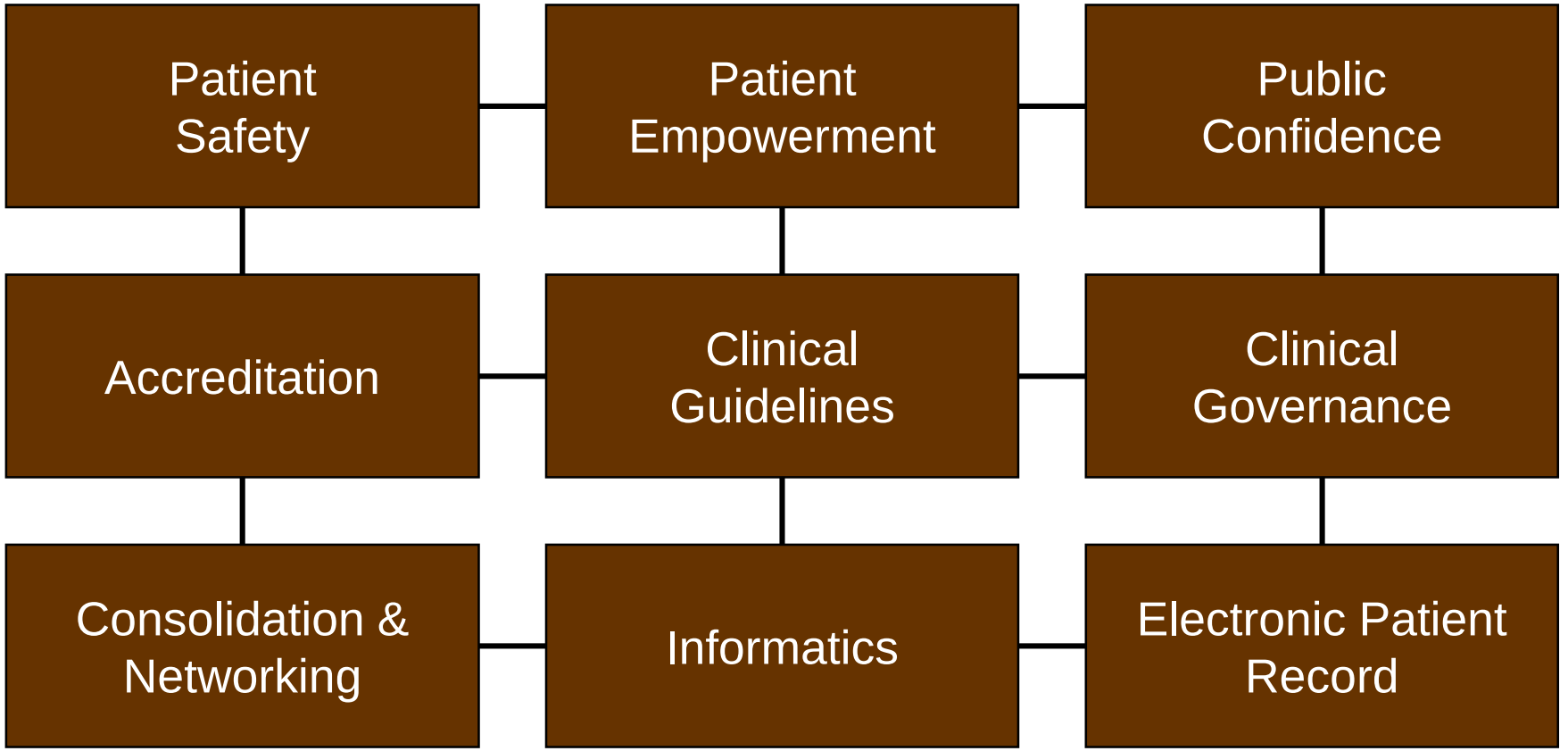
Outline of Talk

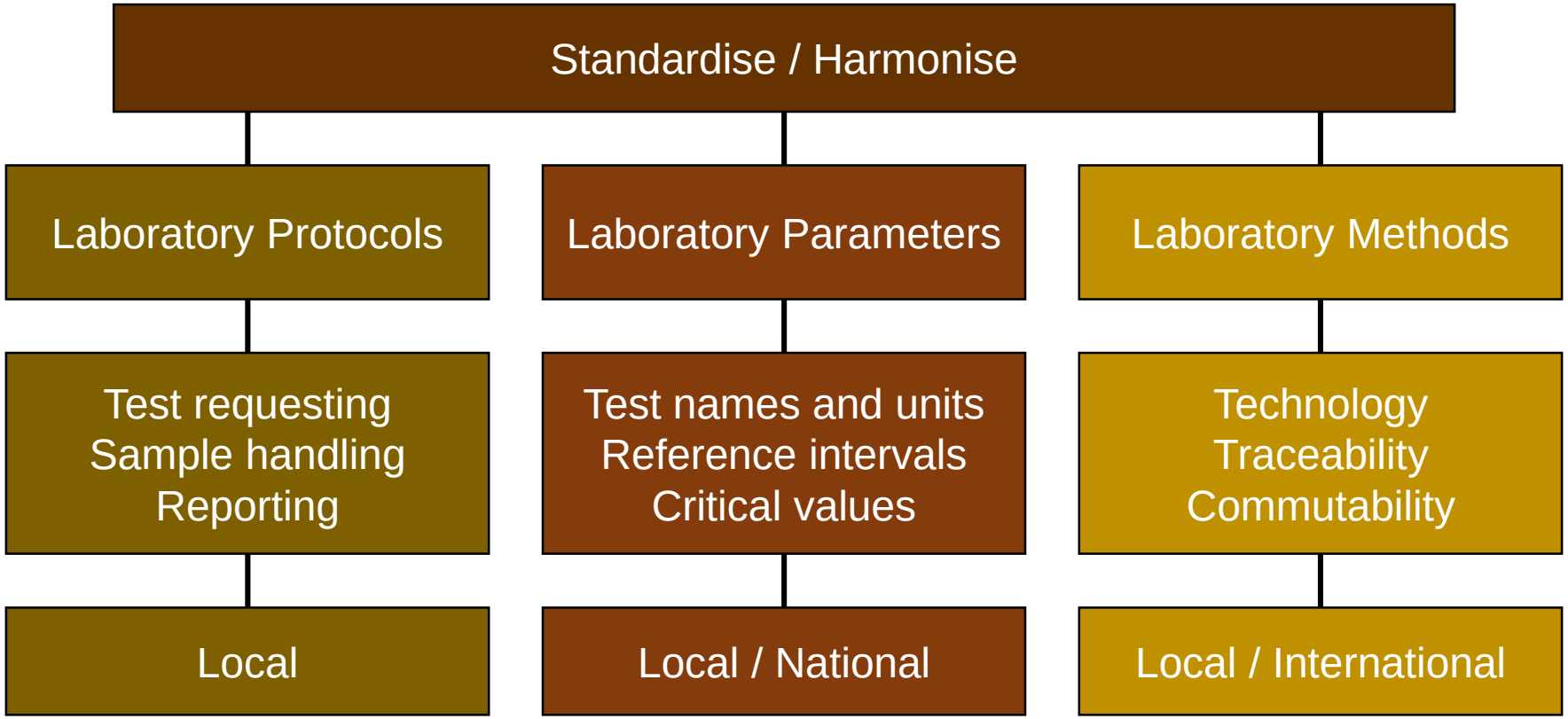
- The need for standardisation
- Analytes where standardisation has occurred – 2 examples
- Analytes where standardisation is needed – 2 examples
- Some challenging questions
- Key messages

Why Should We Standardise (Harmonise)?



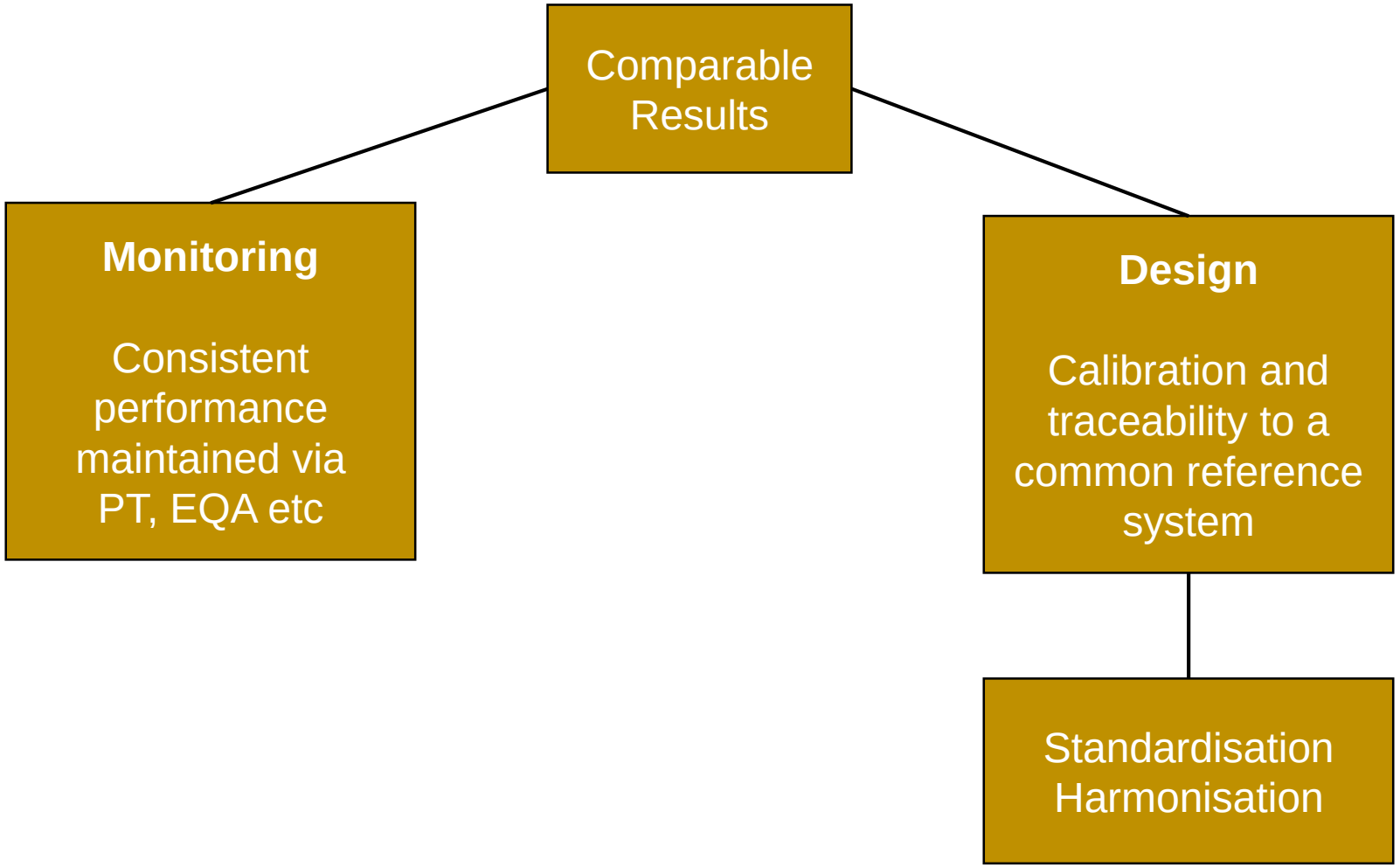
Adapted from Plebani, *Clin Chem Lab Med* 2013; **51**: 741-51

What Should We Standardise (Harmonise)?



Adapted from Plebani, *Clin Chem Lab Med* 2013; **51**: 741-51

Reducing Between Method Variability



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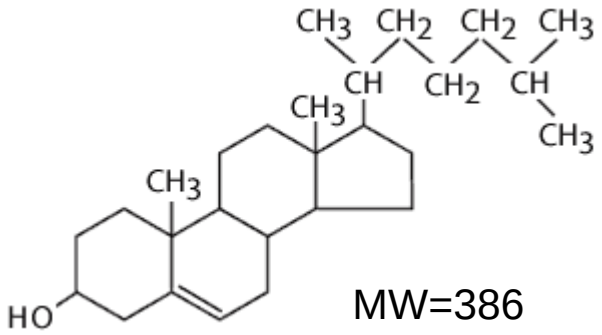
Cholesterol



MW=386

Measured in all clinical chemistry labs - both as total and HDL-cholesterol

High cholesterol associated with increased cardiovascular risk

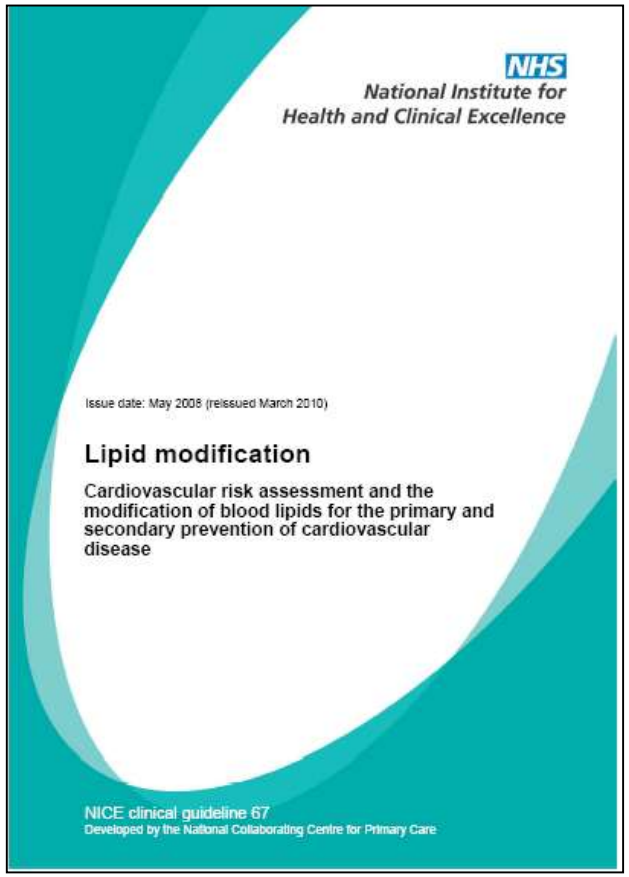
CDC standardisation program [Ref 1]
One of the first analytes standardized

One of the first analytes to have a reference laboratory network [Ref 2]

1. Myers GL, Cooper GR, Winn CL, Smith SJ. The CDC –National Heart, Lung and Blood Institute Lipid Standardization Program: An approach to accurate and precise lipid measurements. *Clin Lab Med* 1989; 9: 105-35
2. Myers GL, Kimberly MM, Waymack PP, Smith SJ, Cooper GR, Sampson EJ. A reference laboratory network for cholesterol: a model for standardization and improvement of clinical laboratory measurements. *Clin Chem* 2000; 46: 1762-1772

Cholesterol and Clinical Practice Guidelines

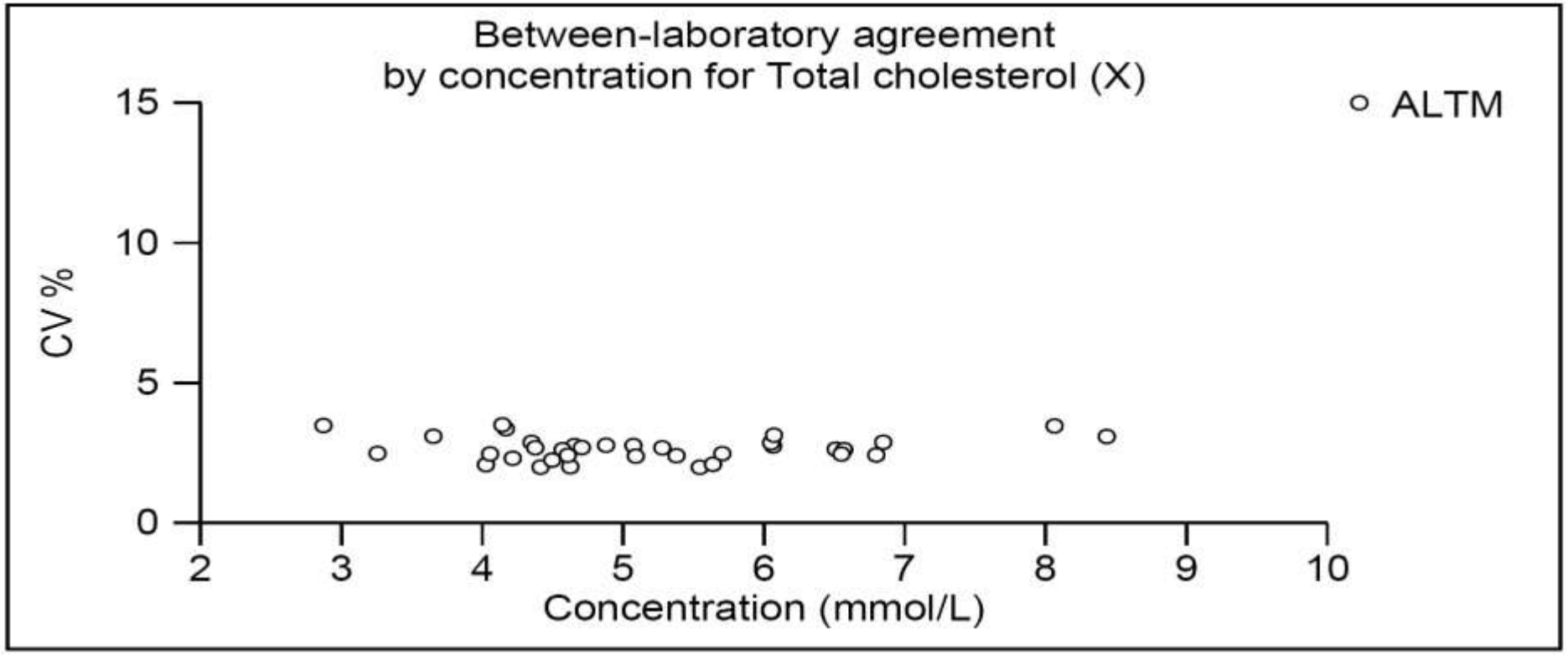
Many clinical practice guidelines exist for coronary heart disease that link management to target cholesterol levels



For example NICE Guideline on Lipid Modification

“In people taking statins for secondary prevention consider increasing to simvastatin 80mg or a drug of similar efficacy and acquisition cost if a total cholesterol of <4.0 mmol/L or an LDL cholesterol of < 2.0 mmol/L is not attained.”

Cholesterol: Current EQA Performance



- Distributions were single patient donations despatched on the day of collection
- No preservative was added
- CDC secondary reference method values obtained

UK NEQAS data – with permission

Cholesterol Methods: Fit for Purpose?

As a result of method standardisation the between method variability of cholesterol methods is at an acceptably low level

Age adjusted death rates from heart disease in the US fell by >50% between 1980 and 2006

Nearly one third of the reduction between 1980 and 2000 can be attributed to improved secondary prevention using statin drugs to lower serum cholesterol

Ford et al. Explaining the decrease in US deaths from coronary disease 1980-2000. *NEJM* 2007; 356 2388-98

Cholesterol standardisation has been shown to be cost effective

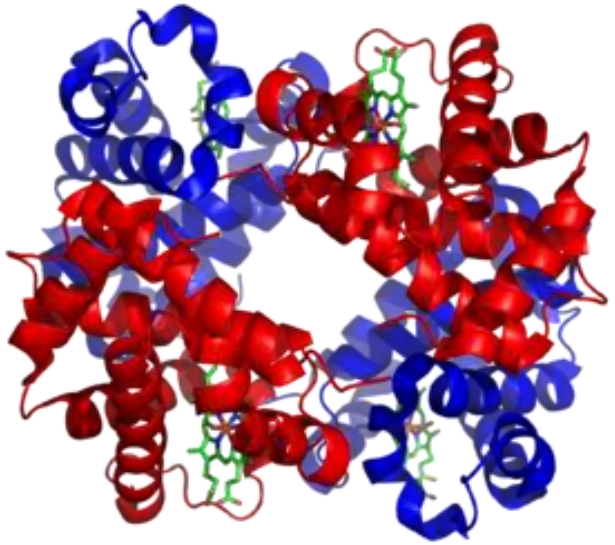
Cost of standardisation program $1.7M pa in 2007

Cholesterol-related benefits to health from standardisation of >$338M pa

Hoerger TJ, Wittenborn JS, Young W A cost-benefit analysis of lipid standardization in the United States. *Prev Chronic Dis* 2011; 8: A136

Standardisation improves clinical outcomes

Haemoglobin A_{1c} (HbA_{1c})



Established from major clinical trials as key analyte for long-term monitoring of diabetes

Method improvement following IFCC standardisation [Ref 1]

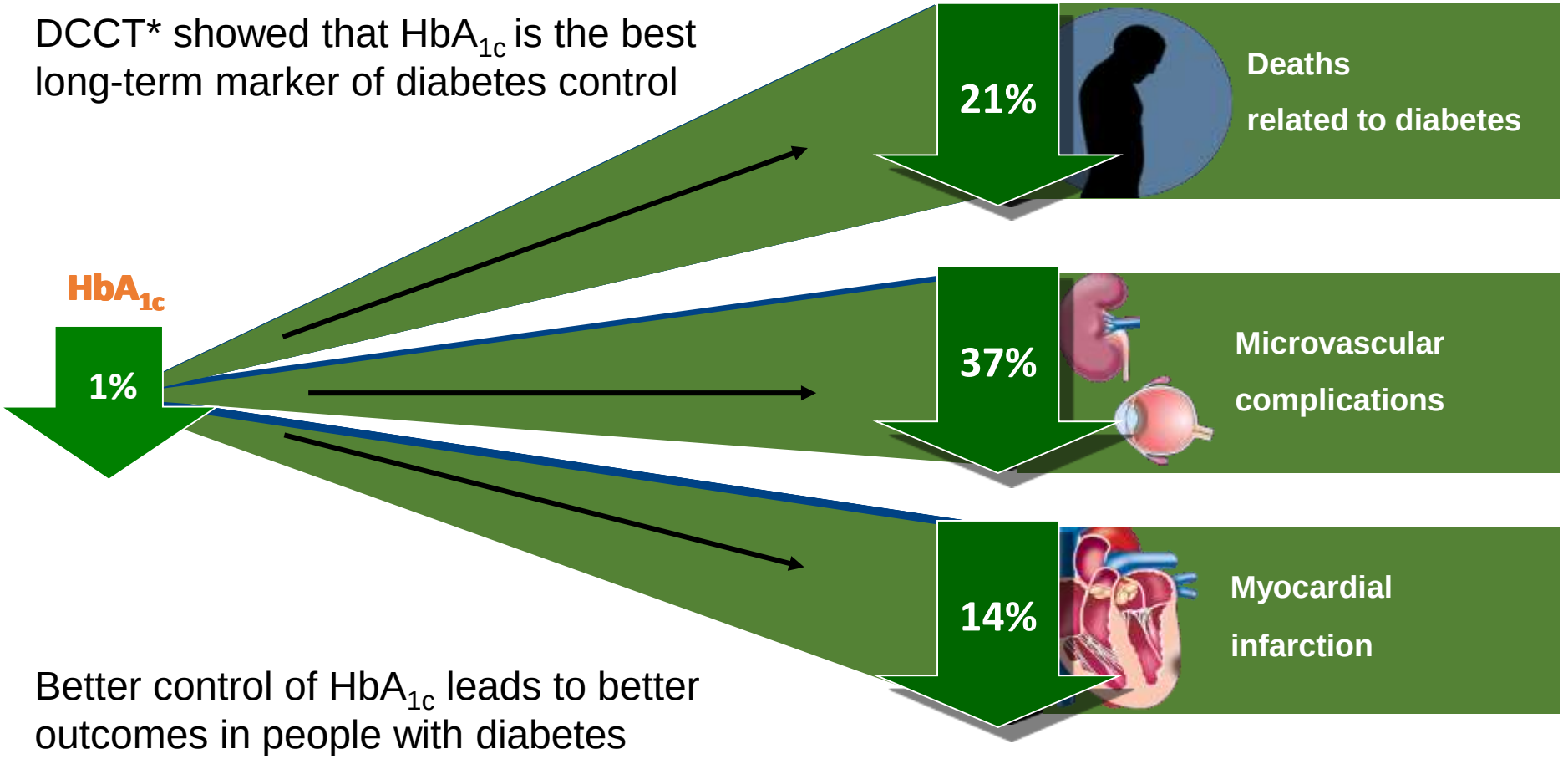
IFCC reference laboratory network established [Ref 2]

Many laboratory and POCT methods available

1. Hoelzel W *et al.* IFCC Reference System for Measurement of Hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan and Sweden: a method comparison study. *Clin Chem* 2004; 50: 166-174
2. IFCC network laboratories for HbA1c www.ifcchba1c.net

Why is HbA_{1c} So Important?

DCCT* showed that HbA_{1c} is the best long-term marker of diabetes control



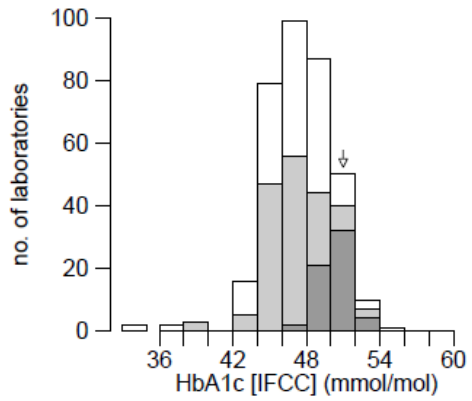
Better control of HbA_{1c} leads to better outcomes in people with diabetes

* DCCT = Diabetes Control and Complications Trial

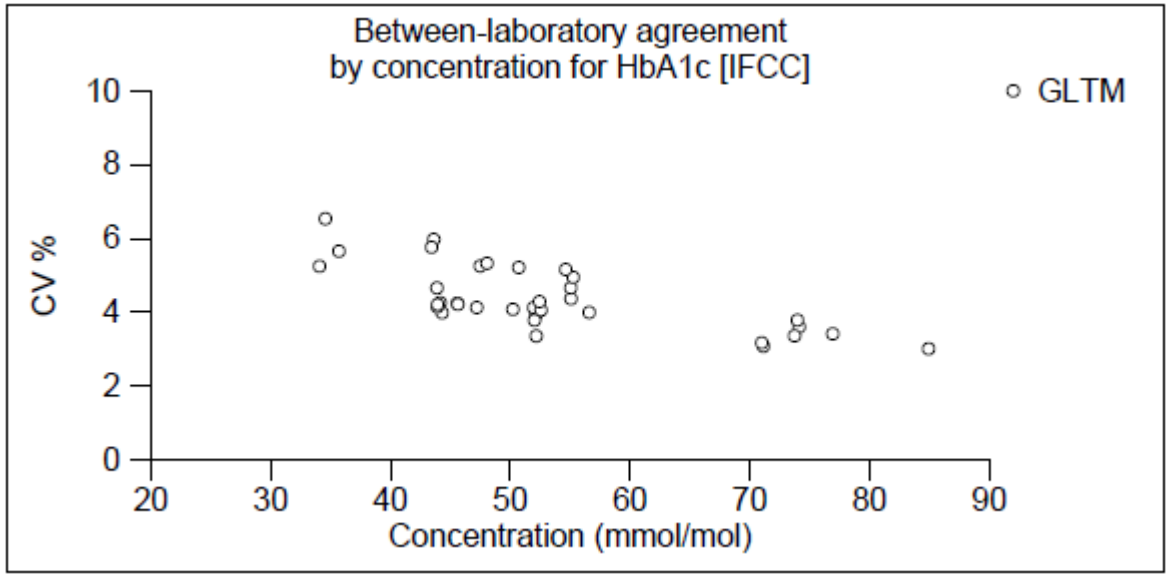
Stratton IM, *et al*. *BMJ* 2000; 321:405–412.

HbA1c: Typical Current EQA

Specimen : 370B	n	Mean	SD	CV(%)
All methods [ALTM]	349	48.1	2.5	5.2
Affinity chromatography	29	47.7	2.4	5.0
Menarini 9210 [2MN1]	15	48.7	1.3	2.7
Ion-exchange chromatography	202	48.3	2.6	5.3
Arkray HA 8160 [3BN3]	83	46.8	1.5	3.2
BioRad Variant (II)/Turbo [3BX4]	30	47.0	1.2	2.6
Tosoh G7 [3TO5]	14	51.1	1.1	2.2
Tosoh G8 [3TO8]	59	50.7	1.0	1.9
Immunoassay	104	47.7	2.5	5.2
Siemens DCA 2000 [6TE3]	17	48.7	2.3	4.6
Siemens DCA Vantage [6TE8]	81	47.5	2.4	5.0



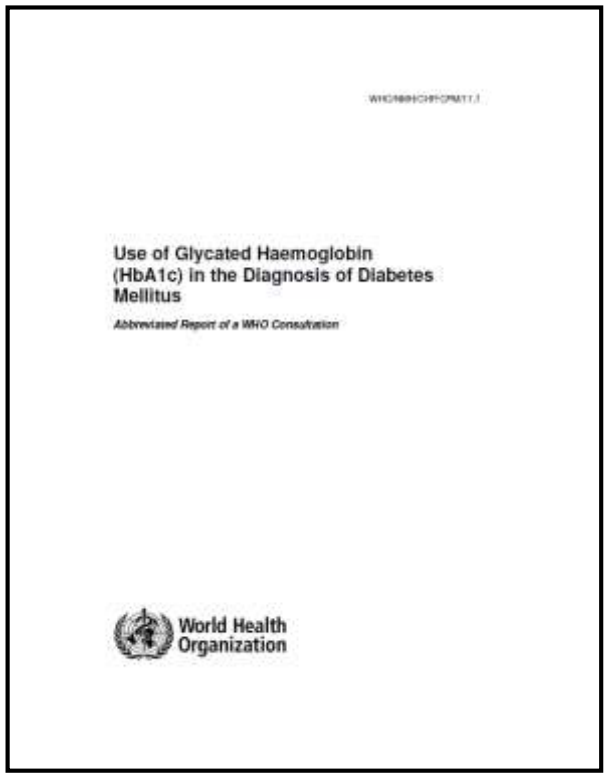
Your result	52
Target value (ALTM)	48.1
Your specimen:	
%bias	+8.2
transformed bias	+160
Accuracy Index	160
2ndary IFCC value	47.8
DCCT comp. value	6.52
ALTM (for information only)	48.07



UK NEQAS

HbA1c As A Diagnostic Test for Diabetes

Many clinical practice guidelines exist that link monitoring of diabetic control to target HbA1c levels. Recent guidelines are for HbA1c in diagnosis



WHO Guideline 2011

"HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to international values, and there are no conditions present which preclude its accurate measurement.
An HbA1c of 48mmol/mol (6.5%) is recommended as the cut point for diagnosing diabetes. A value of <48mmol/mol does not exclude diabetes diagnosed using glucose tests."

Investigation of 2 Models to Set and Evaluate Quality Targets for HbA1c: Biological Variation and Sigma-Metrics

Cas Weykamp, Garry John, Philippe Gillery, Emma English, Linong Ji, Erna Lenters-Westra, Randie R. Little, Gojka Roglic, David B. Sacks, Izumi Takei,

On behalf of the IFCC Task Force on Implementation of HbA1c Standardisation

Clin Chem 2015; **61**: 752-9

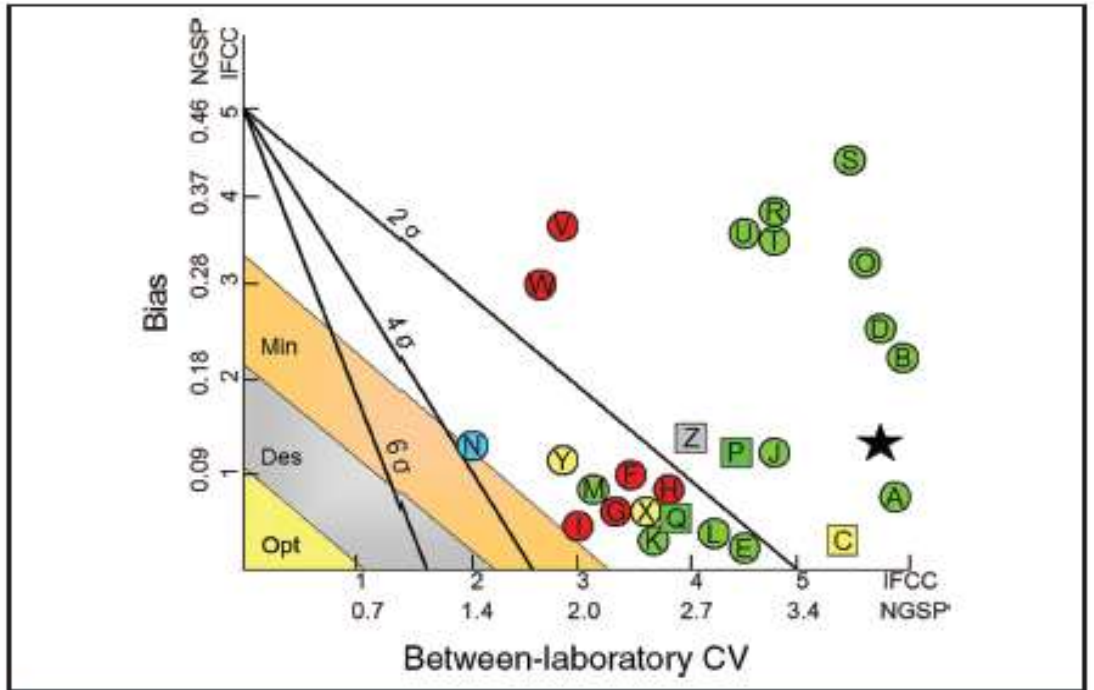


Fig. 2. Models applied to 26 manufacturer/instrument means in CAP 2014 GH2-A survey.
Mean within-manufacturer interlaboratory CV on the *x* axis; mean manufacturer absolute bias on the *y* axis. The black star represents the overall mean of all laboratories. The dots (laboratory instruments) and squares (POCT instruments) represent specific manufacturers with colors for analytical principles: green, immunoassays; red, ion-exchange HPLC; yellow, affinity HPLC; blue, capillary electrophoresis; gray, dry chemistry. Abbott Architect c System (A), Abbott Architect i System (B), Axis-Shield Afinion (C), Beckman AU systems (D), Beckman UniCel DxC Synchron (E), Bio-Rad D10 (F), Bio-Rad Variant II (G), Bio-Rad Variant II Turbo (H), Bio-Rad Variant Turbo 2.0 (I), Roche Cobas c311 (J), Roche Cobas c500 series (K), Roche Cobas Integra 400 (L), Roche Cobas Integra 800 (M), Sebia Capillarys 2 Flex Piercing (N), Siemens Advia Chemistry Systems (O), Siemens DCA 2000/2000+ (P), Siemens DCA Vantage (Q), Siemens Dimension Exl (R), Siemens Dimension RxL (S), Siemens Dimension Vista (T), Siemens Dimension Xpand (U), Tosoh G7 Auto HPLC (V), Tosoh G8 Auto HPLC (W), Trinity Biotech HPLC (X), Trinity Biotech Premier Hb9210 (Y), Ortho Clin Diag Vitros 5,1 FS, 4600, 5600 Chem System (Z). For more details, see online Supplemental Table 1. opt, Optimum; des, desirable; min, minimum.

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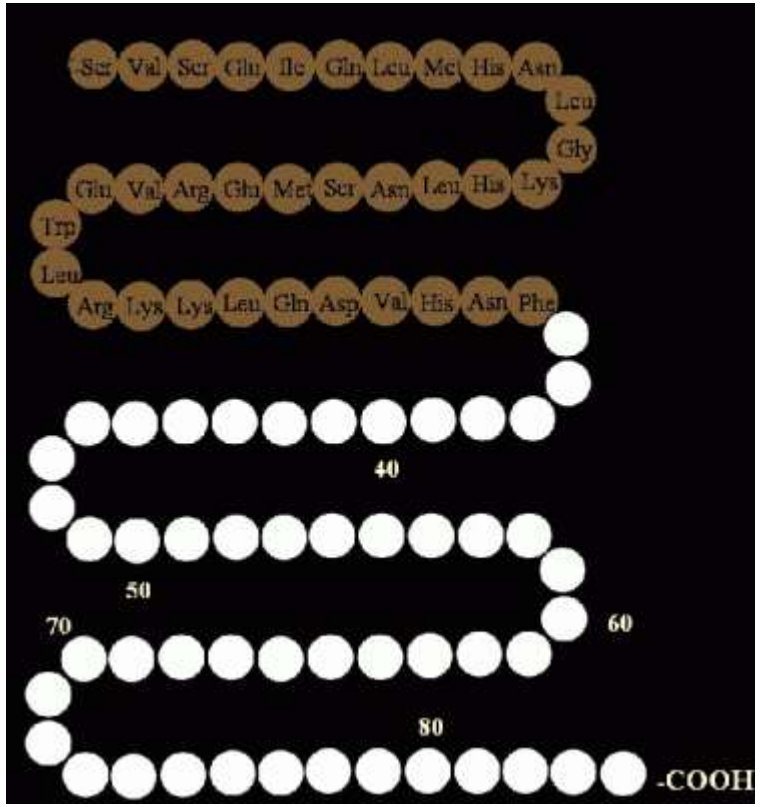
Parathyroid Hormone (PTH)



84 AA peptide MW = ~9500

Biological activity resides in N-terminal 34 amino acids.

Intact and N-terminal PTH have a short half life in plasma. C-terminal PTH fragments have a long half life and create assay interference issues, especially in renal patients

PTH is the key hormone in calcium homeostasis acting on bone, the kidney and the gut

PTH is a key biomarker in renal osteodystrophy

PTH and Clinical Practice Guidelines in CKD

1. Kidney Disease Outcomes Quality Initiative (K/DOQI) - 2003
PTH concentrations in dialysis patients should be maintained in the target range 150-300 ng/L (15.8-36.8 pmol/L)

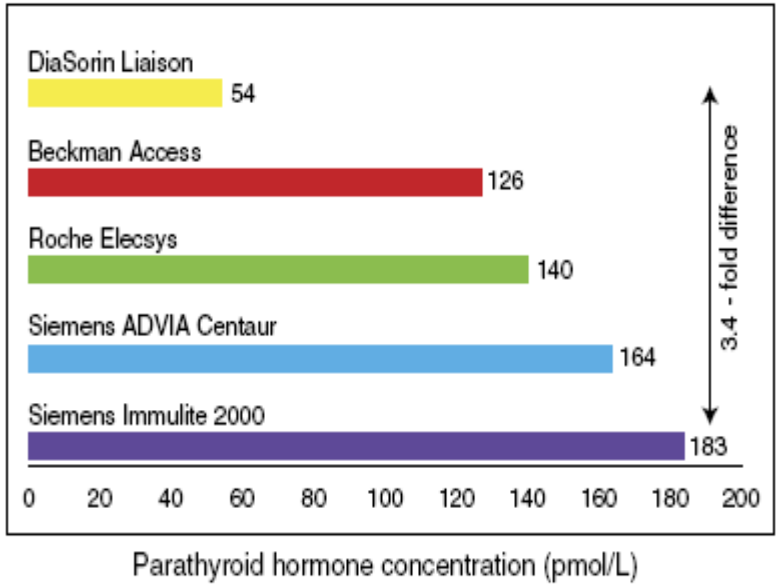
Superseded by

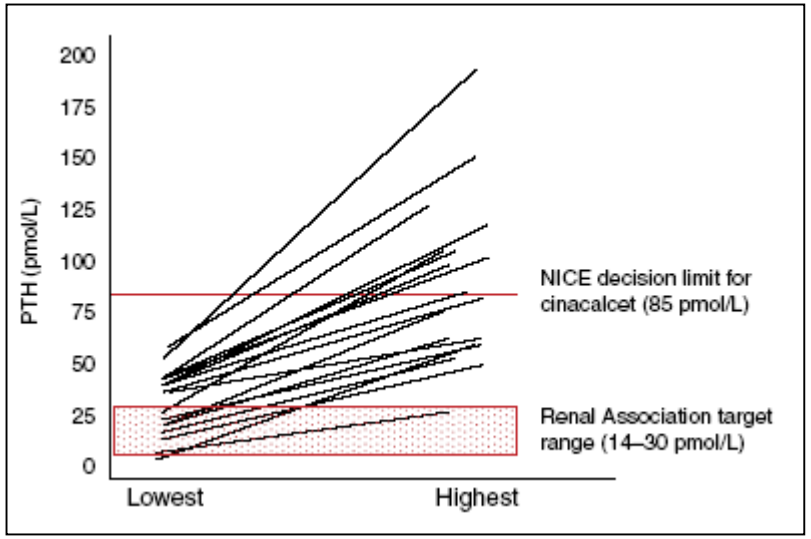
2. Kidney Disease Improving Global Outcomes (KDIGO) Initiative – 2009
Expressed target ranges as multiples of upper limit of normal (ULN) for each assay

3. The Renal Association
Always expressed target ranges as multiples of ULN
- 1995 recommended 2-4 times ULN
- 2011 changed to 2-9 times ULN depending on assay

4. National Institute for Health and Clinical Excellence (NICE)
Recommends use of cinacalcet in treating refractory secondary hyperparathyroidism only if PTH is >85pmol/L (>810 ng/L)

PTH: Between Method Variability





Almond A, Ellis AR, Walker SW
Current parathyroid hormone immunoassays do not adequately meet the needs of patients with chronic kidney disease
Ann Clin Biochem 2012; 49: 63–67

PTH Methods: Fit for Purpose?

Sturgeon CM, Sprague SM, Metcalfe W
Variation in parathyroid hormone immunoassay results—a critical governance issue in the management of chronic kidney disease
Nephrol Dial Transplant 2011; 26: 3440–3445

Short Term Recommendations

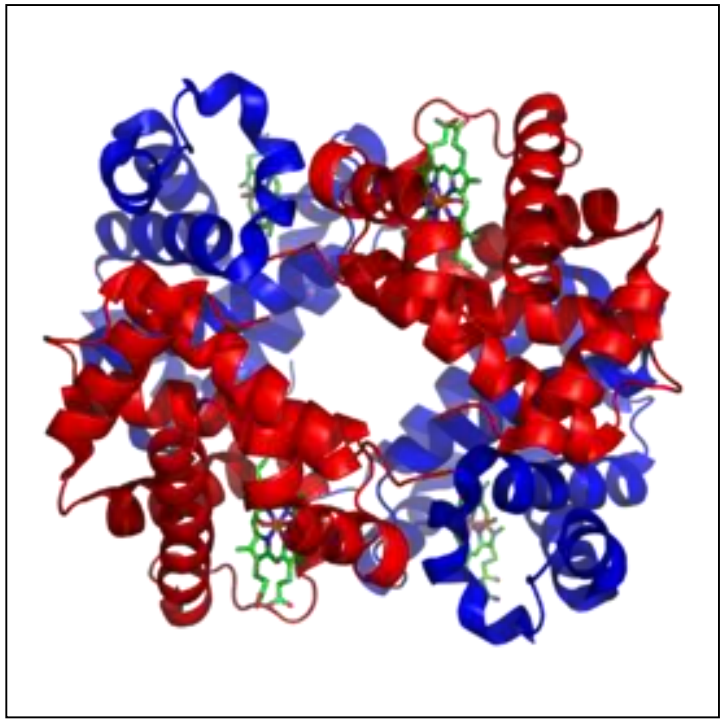
- Raise awareness amongst users
- Harmonise pre-analytical handling
- Advocate method specific action limits for PTH in renal patients

Longer Term Recommendation

- PTH method standardisation
- Now commenced as joint project between IFCC and CDC

Status of PTH methods is poor. Now improving as a result of changes to clinical practice guidelines and plans to manage the problem

Haemoglobin A2



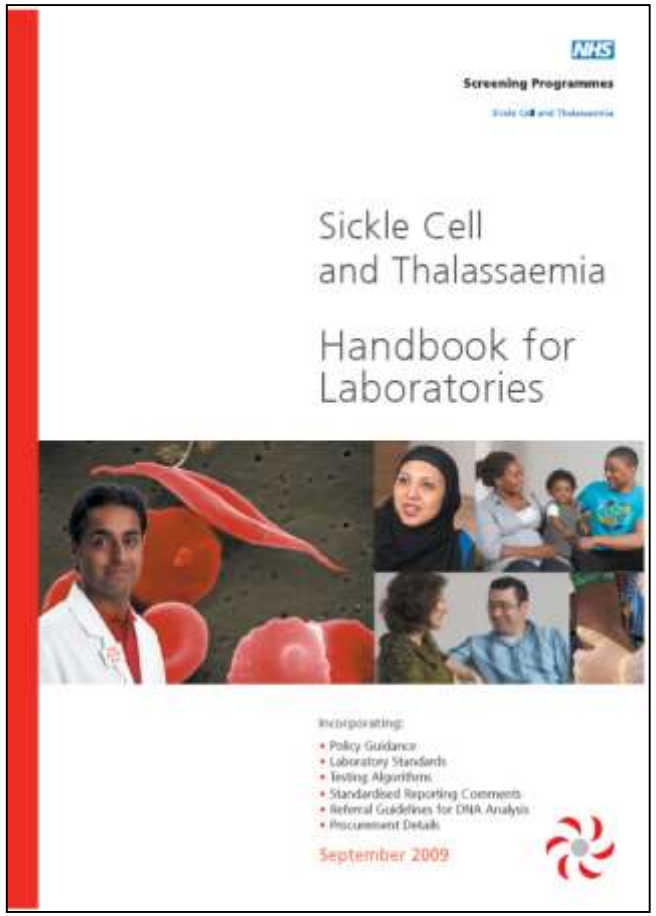
Haemoglobin A2 (HbA2) is a normal variant of haemoglobin A that consists of two alpha and two delta chains (α2δ2).

HbA2 exists in small amounts in all adult humans. Its biological importance is uncertain.

HbA2 concentration may be increased in beta thalassaemia or in people who are heterozygous to the beta thalassaemia gene.

HbA2 and Clinical Practice Guidelines

Many clinical practice guidelines exist for thalassaemia that link diagnosis to target HbA2 levels.



For example UK NHS sickle cell and thalassaemia screening programme:

“A national recommended cut-off for HbA2 of 3.5% has been set as the action point in the diagnosis of carriers of beta thalassaemia.”

Current HbA2 EQA Performance

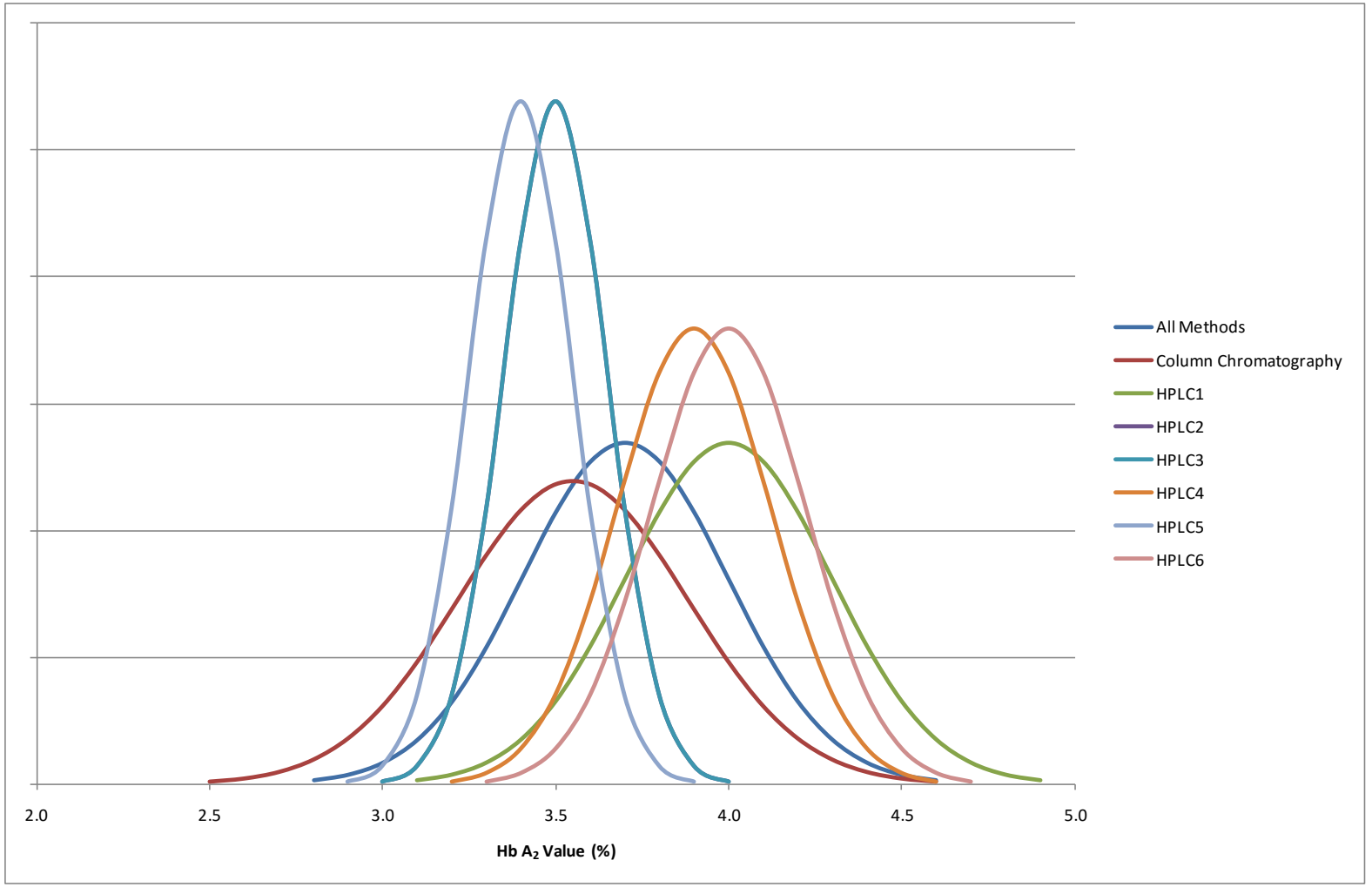


Figure from UK NEQAS with permission

HbA2 Methods: Fit for Purpose?

Between method variability of HbA2 methods at the clinically important cut-off is such that misclassification will occur

"A poor alignment of routine methods for HbA2 measurement was found. The need of a better standardisation of HbA2 measurement procedures was underlined."

Paleari R, Gulbis B, Cotton F, Mosca A Interlaboratory comparison of current high-performance methods for HbA2. *Int J Lab Haematol* 2012; **34**: 362-8

IFCC HbA2 Standardisation Project

Aim:

- Definition of an international reference system, including a reference measurement procedure and primary and secondary reference materials.

Collaborative Project with ICSH:

- Evaluation of secondary reference material for haemoglobin A2 (cooperation with IRMM).

Status of HbA2 assays is unsatisfactory. A collaborative project is underway to improve the situation

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How Many Analytes Are There in Laboratory Medicine?

- There is no definitive answer but the number on the database of tests carried out by laboratories across Finland is:

~4000

Paivi Laitinen HUSLAB, Helsinki, Finland, Sep 2015

How Many Methods Have Been Standardised?

There is no definitive list.

The best data is available from the database of: The Joint Committee for Traceability in Laboratory Medicine (JCTLM). In September 2015 the database contains:

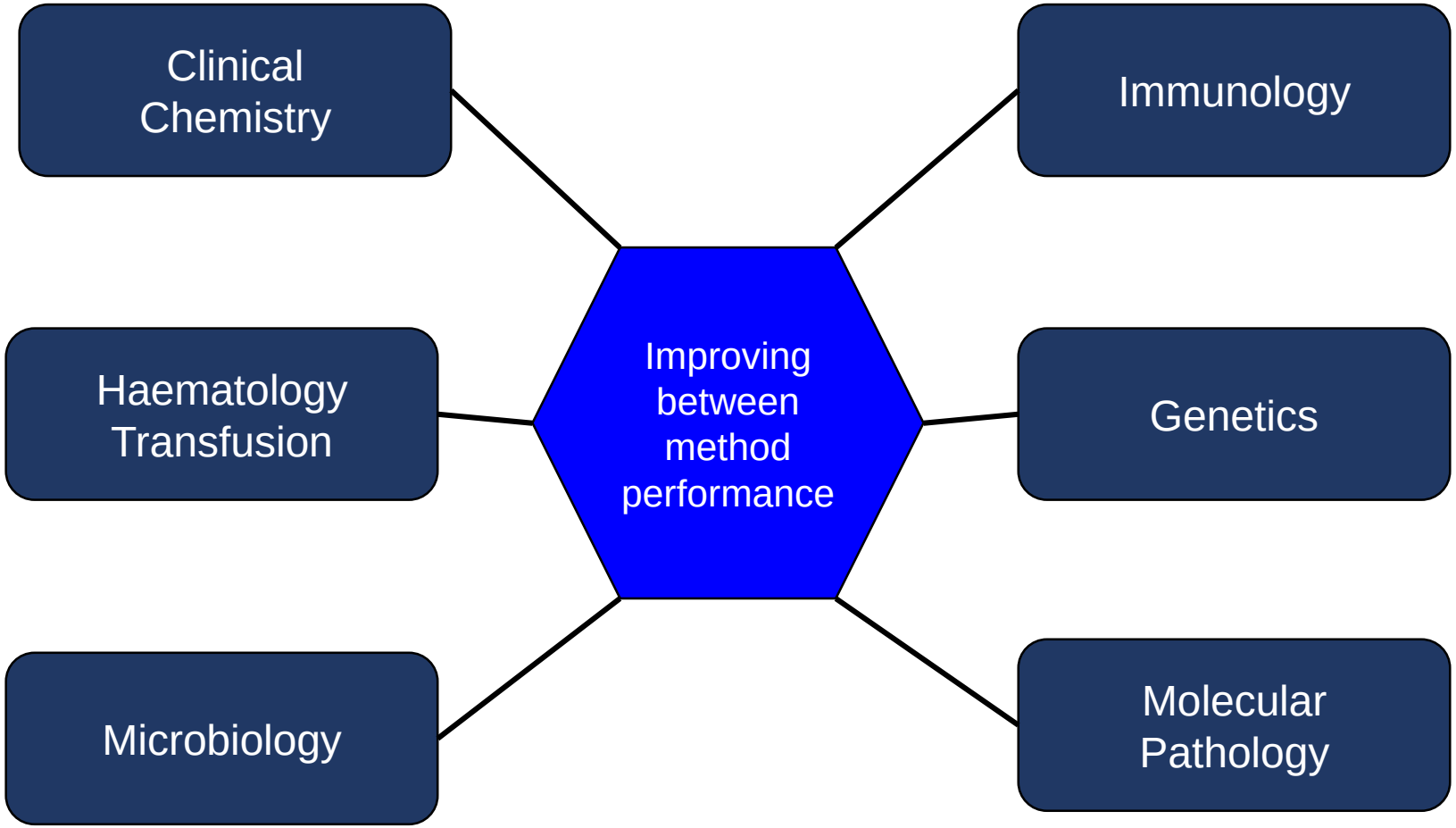
- **295** Certified Reference Materials
- **170** Reference Methods
- **130** Reference Measurement Services

JCTLM Database
Laboratory medicine and *in vitro* diagnostics

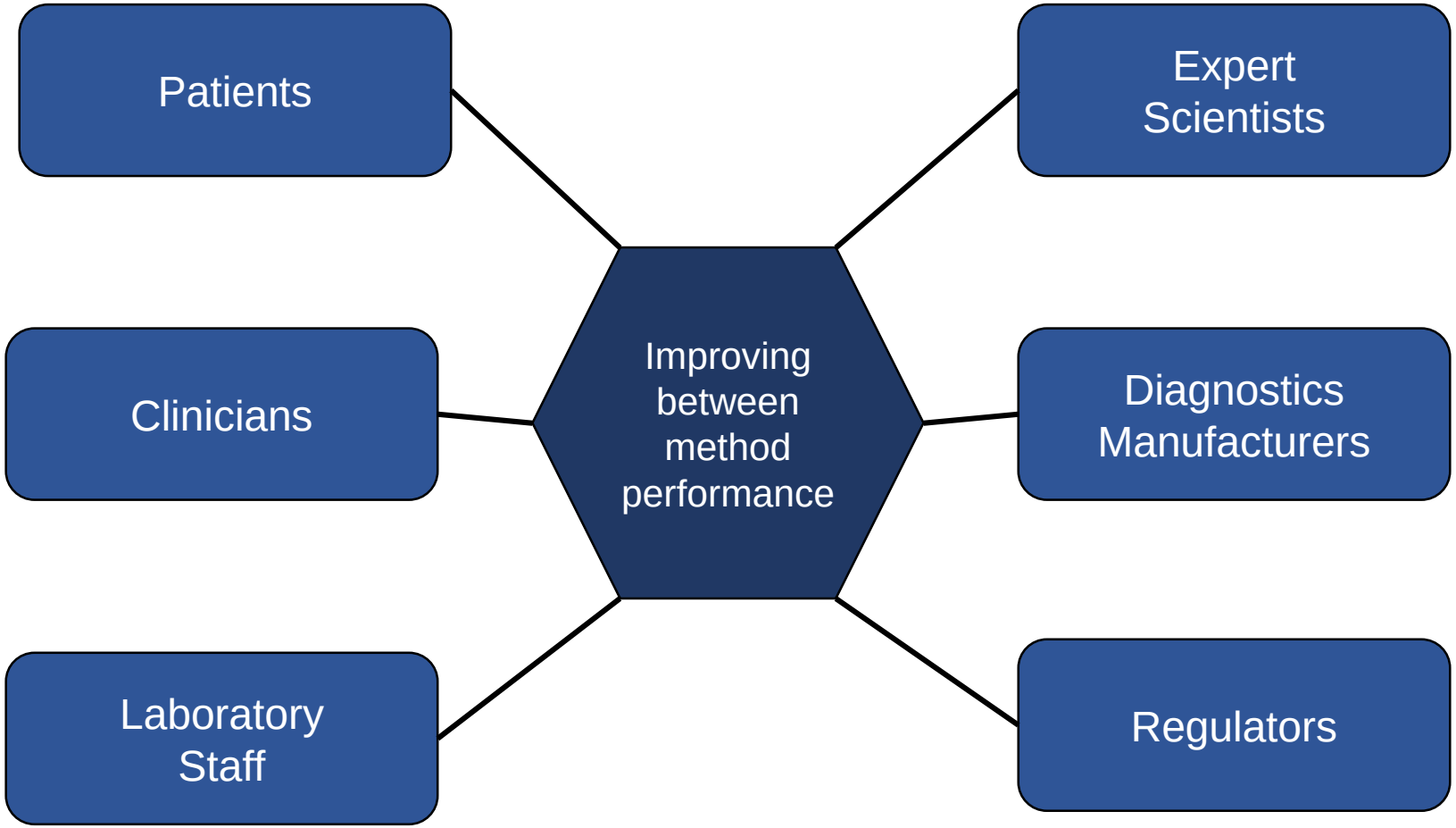
www.bipm.org/jctlm/

Robert Wielgosz, BIPM, Paris, France, Sep 2015

Where Do We Need To Standardise?



Who Are The Standardisation Stakeholders?



How Do We Standardise Laboratory Methods?

- The next two speakers in this session will tell you!!

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Key Messages

- As leaders in our profession we have responsibility to facilitate better patient outcomes
- One barrier to improved outcomes is excessive between method variability
- Only a small percentage of methods used in the clinical laboratory have been standardised or harmonised
- Where methods have been standardised or harmonised evidence of improved clinical outcomes is emerging
- As a profession we should:
  - Facilitate the standardisation or harmonisation of more methods
  - Work with clinical colleagues to demonstrate improved outcomes