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)?

- Patient Safety
- Patient Empowerment
- Public Confidence
- Accreditation
- Clinical Guidelines
- Clinical Governance
- Consolidation & Networking
- Informatics
- Electronic Patient Record

Adapted from Plebani, *Clin Chem Lab Med* 2013; 51: 741-51
What Should We Standardise (Harmonise)?

- Laboratory Protocols
  - Test requesting
  - Sample handling
  - Reporting
  - Local

- Laboratory Parameters
  - Test names and units
  - Reference intervals
  - Critical values
  - Local / National

- Laboratory Methods
  - Technology
  - Traceability
  - Commutability
  - Local / International

Adapted from Plebani, *Clin Chem Lab Med* 2013; 51: 741-51
Reducing Between Method Variability

Comparable Results

- Monitoring
  Consistent performance maintained via PT, EQA etc

- Design
  Calibration and traceability to a common reference system

Standardisation
Harmonisation
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Cholesterol

- 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]

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

Between-laboratory agreement by concentration for Total cholesterol (X)

CV %

Concentration (mmol/L)

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


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


Standardisation improves clinical outcomes
Haemoglobin A\textsubscript{1c} (HbA\textsubscript{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

2. IFCC network laboratories for HbA1c [www.ifcchba1c.net](http://www.ifcchba1c.net)
Why is HbA$_{1c}$ So Important?

DCCT* showed that HbA$_{1c}$ is the best long-term marker of diabetes control.

- 21% Deaths related to diabetes
- 37% Microvascular complications
- 14% Myocardial infarction

Better control of HbA$_{1c}$ leads to better outcomes in people with diabetes.

* DCCT = Diabetes Control and Complications Trial

HbA1c: Typical Current EQA

Specimen: 370B

<table>
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<tr>
<th>Method</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>CV(%)</th>
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<td>349</td>
<td>48.1</td>
<td>2.5</td>
<td>5.2</td>
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<td>2.4</td>
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</tbody>
</table>

Your result: 52
Target value (ALTM): 48.1

Your specimen:
% bias: +8.2
Accuracy Index: 160

2ndary IFCC value: 47.8
DCCT comp. value: 6.52
ALTM: 48.07

Between-laboratory agreement by concentration for HbA1c [IFCC]

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 Lengers-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
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Parathyroid Hormone (PTH)

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.

84 AA peptide MW = ~9500
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

   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)
Current parathyroid hormone immunoassays do not adequately meet the needs of patients with chronic kidney disease

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

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

**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
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

![Current HbA2 EQA Performance](image-url)
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.”


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

[www.bipm.org/jctlm/](http://www.bipm.org/jctlm/)

Robert Wielgosz, BIPM, Paris, France, Sep 2015
Where Do We Need To Standardise?

- Clinical Chemistry
- Immunology
- Haematology Transfusion
- Genetics
- Microbiology
- Molecular Pathology

Improving between method performance
Who Are The Standardisation Stakeholders?

- Patients
- Clinicians
- Laboratory Staff
- Expert Scientists
- Diagnostics Manufacturers
- Regulators

Improving between method performance
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