Harmonization of Methods in Laboratory Medicine: A Means to Improve Patient Safety

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Outline of Talk

- Introduction
- Standardization and Harmonization
- Why Standardize or Harmonize Methods?
- Traceability in Laboratory Medicine
- Status 2012:
  - Overall challenge
  - Clinical chemistry examples
- Meeting the Challenge
- Conclusions
Adding Value Cycle to Quality Laboratory Medicine Services Through the Application of ‘SCIENCE’

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Dictionary Definitions

• **Standardize**
  – “To cause to conform with a standard”
  – Everyday examples
    • Distance in kilometres
    • Weight in kilograms
    • Time in days, hours, minutes, seconds

• **Harmonize**
  – “To bring into agreement”
  – Everyday examples
    • Decisions reached by consensus

Standardization and Harmonization
Standardization v Harmonization

- Standardization is preferred to harmonization
  - Scientifically validated
  - Internationally transferable
- Harmonization – in the absence of a standard

- The distinction is not ‘black and white’
  - There are very few ‘absolute standards’
  - There is a hierarchy of ‘standards’
  - Confusion: standardization v harmonization
  - Apparent when considering laboratory methods

Laboratory Standardization / Harmonization
Laboratory Practices

These can be done at national or local level

Test Names
Reference Intervals
Action Limits
Standardize

Units of Measurement
Investigative Protocols
Core Results And POCT

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Between Method Variability: Does It Matter?

Thyroid specialists | Liaison | Patient organization

Reducing Between Method Variability

Comparative Results

Monitoring
Consistent performance maintained via PT, EQA etc

Design
Calibration and traceability to a common reference system

Standardization
Harmonization
Why Standardize / Harmonize Methods?

• Patient safety
  – Differences in practice can put patients at risk
• Clinical guidelines
  – Differences reduce the value of practice guidelines
• Public / patient confusion
  – Differences cause patients to lose confidence in labs
• Clinical governance
  – Differences leave labs vulnerable to challenge
• Electronic patient record
  – Differences prevent comparability of data

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What the Laboratory Sees

Material for calibration
Measurement procedure for value assignment
Define measurand and unit
Routine sample
End user’s routine measurement procedure
Result

Full Metrological Traceability

Material for calibration
Measurement procedure for value assignment
Define measurand and unit
Primary calibrator
Primary reference measurement procedure
Manufacturer’s working calibrator
Secondary reference measurement procedure
Manufacturer’s product calibrator
Manufacturer’s master measurement procedure
Routine sample
End user’s routine measurement procedure
Result

Adapted from EN ISO 17511
### Traceability Categories from ISO 17511

<table>
<thead>
<tr>
<th>Category</th>
<th>Reference measurement procedure</th>
<th>Primary (pure substance) reference material</th>
<th>Secondary (value assigned) reference material</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Possible</td>
<td>Electrolytes, glucose, cortisol</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Possible</td>
<td>Enzymes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Hemostatic factors</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Proteins, tumor markers, HIV</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Proteins, EBV, VZV</td>
</tr>
</tbody>
</table>

### Commutability: Same relationship for clinical samples and reference materials

![Commutability Graph](image)
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How Many Laboratory Methods Are There?

<table>
<thead>
<tr>
<th>Established Methods: UK EQA Scheme</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Chemistry</td>
<td>207</td>
</tr>
<tr>
<td>Drugs (TDM/DOA)</td>
<td>21</td>
</tr>
<tr>
<td>Genetics</td>
<td>30</td>
</tr>
<tr>
<td>Haematology</td>
<td>103</td>
</tr>
<tr>
<td>Histopathology</td>
<td>15</td>
</tr>
<tr>
<td>Immunology</td>
<td>134</td>
</tr>
<tr>
<td>Microbiology</td>
<td>68</td>
</tr>
<tr>
<td>Reproductive</td>
<td>6</td>
</tr>
<tr>
<td>Research Methods</td>
<td></td>
</tr>
<tr>
<td>New Methods</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>584</td>
</tr>
</tbody>
</table>
Standardized / Harmonized Methods

There is no definitive list.

The best data is available from the database of: The Joint Committee for Traceability in Laboratory Medicine (JCTLM). Formed 2002:

- 264 Reference Materials for ~130 measurands (analytes)
- 158 Reference Measurement Methods for ~80 health markers

So we still have a long way to go!

Picking the low-hanging fruit!

‘Molecular’ Microbiology
HCG TSH PSA Troponin I

glucose HbA1c AST ALT
cholesterol homocysteine
uric acid creatinine urea

Miller 2012
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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 standardization program [Ref 1]
One of the first analytes standardized

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

Cholesterol and Clinical Practice Guidelines

Many clinical practice guidelines exist for coronary heart disease that link management to target cholesterol levels. For example, the NICE Guideline on Lipid Modification states, "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

<table>
<thead>
<tr>
<th>Specimen: 131E</th>
<th>Mean</th>
<th>SD</th>
<th>CV(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All methods (ALT/IM)</td>
<td>126</td>
<td>5.28</td>
<td>0.14</td>
</tr>
<tr>
<td>Dry slide</td>
<td>7</td>
<td>5.44</td>
<td>0.18</td>
</tr>
<tr>
<td>CGD (HbA1c) [IU]</td>
<td>7</td>
<td>5.44</td>
<td>0.18</td>
</tr>
<tr>
<td>Cholesterol oxidase</td>
<td>119</td>
<td>5.27</td>
<td>0.14</td>
</tr>
<tr>
<td>Abbott reagents [ALT]</td>
<td>24</td>
<td>5.28</td>
<td>0.16</td>
</tr>
<tr>
<td>Beckman reagents [ALT]</td>
<td>9</td>
<td>5.18</td>
<td>0.16</td>
</tr>
<tr>
<td>Dade reagents [ALT]</td>
<td>3</td>
<td>5.34</td>
<td></td>
</tr>
<tr>
<td>Olympus reagents [CO]</td>
<td>17</td>
<td>5.36</td>
<td>0.13</td>
</tr>
<tr>
<td>Roche reagents [ALT]</td>
<td>45</td>
<td>5.29</td>
<td>0.13</td>
</tr>
<tr>
<td>Siemens (Bayer) reagents [ALT]</td>
<td>21</td>
<td>5.17</td>
<td>0.09</td>
</tr>
</tbody>
</table>

- The distribution was a single patient donation despatched on the day of collection
- No preservative was added
- CDC secondary reference method value obtained

UK NEQAS data – with permission.
Cholesterol: Current EQA Performance

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UK NEQAS data – with permission

Cholesterol Methods: Fit for Purpose?

As a result of method standardization 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 standardization has been shown to be cost effective
- Cost of standardization program $1.7M pa in 2007
- Cholesterol-related benefits to health from standardization of >$338M pa

Status of cholesterol methods = 'GOOD'
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

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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)
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

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**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
- Harmonize pre-analytical handling
- Advocate method specific action limits for PTH in renal patients

** Longer Term Recommendation**
- PTH method standardization
- Now commenced as joint project between IFCC and CDC

Status of PTH methods was ‘UGLY’. Now improving as a result of changes to clinical practice guidelines and plans to manage the problem
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Starting the Journey

Clinical Chemistry 57:8
1108-1117 (2011)

Special Report

Roadmap for Harmonization of Clinical Laboratory Measurement Procedures

W. Greg Miller,1 Gary L. Myers,2 Mary Lou Gantzler,3 Stephen E. Kahn,4 E. Raif Schönbüchner,5 Linda M. Thilenpoint,6 David M. Bunk,7 Robert H. Christenson,8 John H. Eckfeldt,9 Stanley F. Lo,10 C. Michi Nöbling,11 and Catharine M. Sturgeon12

Report from an AACC conference, October, 2010:
Improving Clinical Laboratory Testing through Harmonization: An International Forum
Model for the Future?

Identified Need to Improve Method Performance

International Steering Group

Either

Standardization

Method Specific Project Group

Or

Harmonization

Method Specific Project Group

Coordination

Improved Method Performance = Patient Safety

International Consortium for Harmonization of Clinical Laboratory Results

Currently under active discussion as part of:

Harmonization.net

www.harmonization.net
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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 standardized or harmonized
• Where methods have been standardized or harmonized evidence of improved clinical outcomes is emerging
• As a profession we should:
  – Facilitate the standardization or harmonization of more methods
  – Work with clinical colleagues to demonstrate improved outcomes
Why Standardization / Harmonization?

Patient Safety

Where to Standardize or Harmonize?

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

Improving between method performance
Standardization / Harmonization Challenge

- Chemical variability
  - Complex proteins
    - Infectious disease
  - Molecular methods
  - Simple peptides
  - Small molecules

- Biological variability
  - Complexity = Time and Money

Standardization / Harmonization Stakeholders

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

Improving between method performance
And Finally – Back to Free T4!

Before re-calibration

After re-calibration

Adapted from Thienpont et al. Clin Chem 2010; 56: 902-29

Acknowledgements

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  - Clinical Chemistry: Jane French, David Bullock
  - Protein Hormones: Cathie Sturgeon, Andy Ellis

- See www.ukneqas.org.uk
IFCC Visiting Lecturer Programme

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