



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

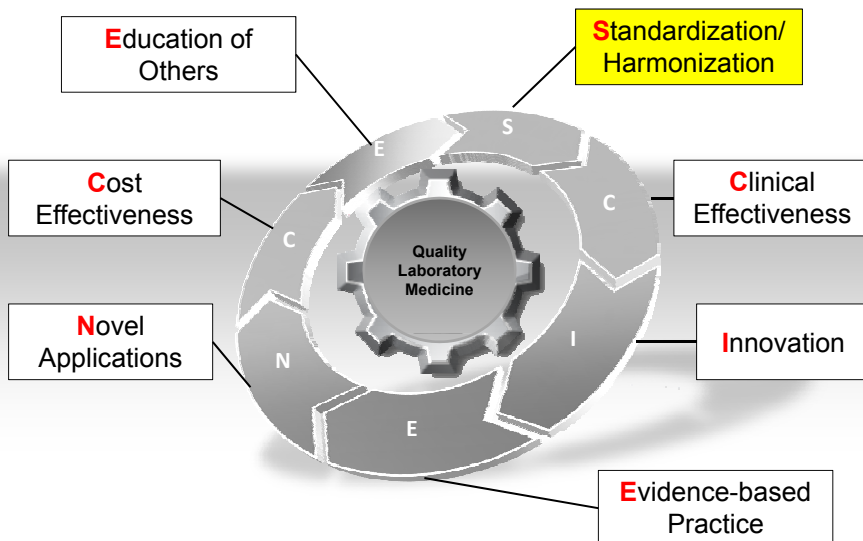
Graham Beastall

[gbeastall@googlemail.com](mailto:gbeastall@googlemail.com)

### 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'



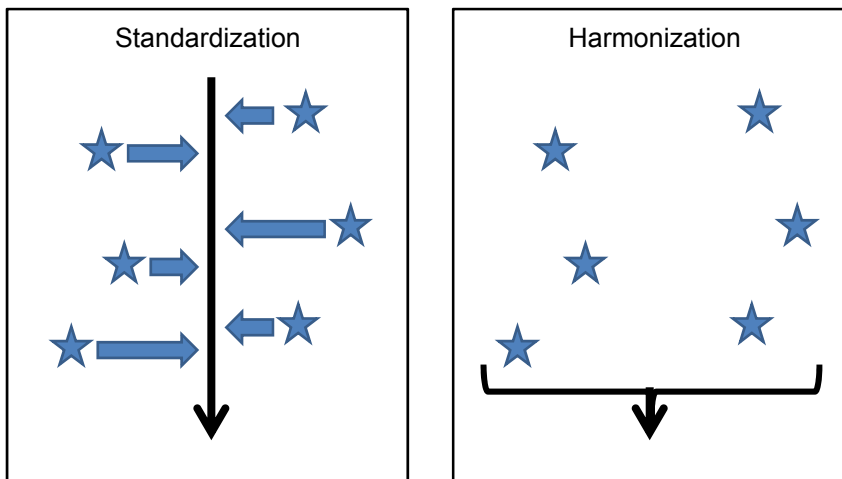
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## Dictionary Definitions

- **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

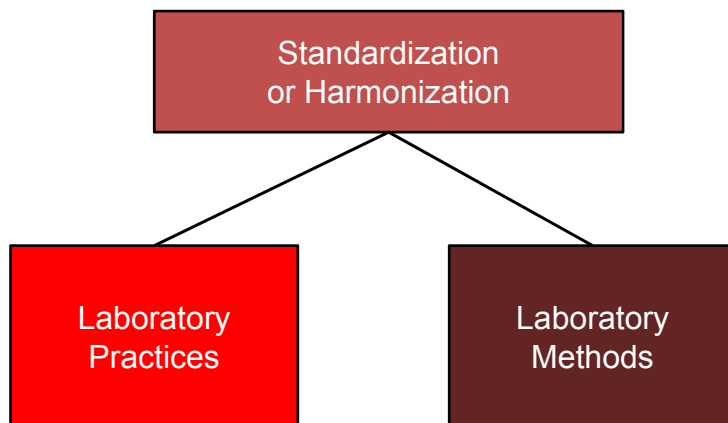
## Standardization and Harmonization



## Standardization v Harmonization

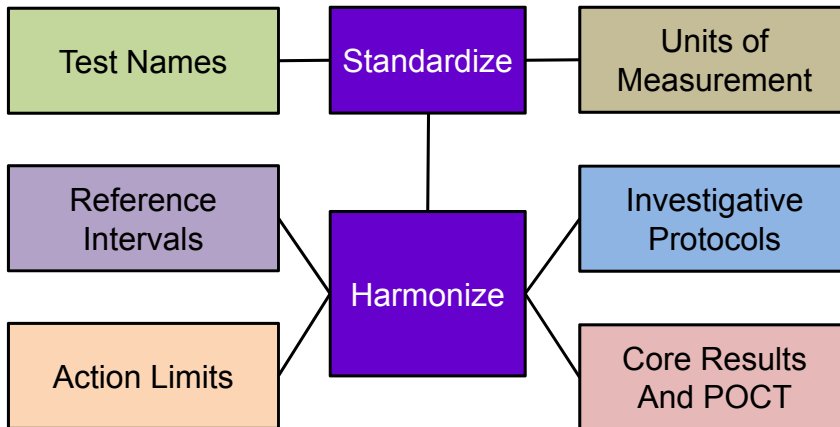
- Standardization is preferred to harmonization
  - Scientifically validated
  - Internationally transferable
- Harmonization – in the absence of a standard
- The distinction is not 'black and white'
  - There are very few 'absolute standards'
  - There is a hierarchy of 'standards'
  - Confusion: standardization v harmonization
  - Apparent when considering laboratory methods

## Laboratory Standardization / Harmonization



# Laboratory Practices

These can be done at national or local level



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## Between Method Variability: Does It Matter?

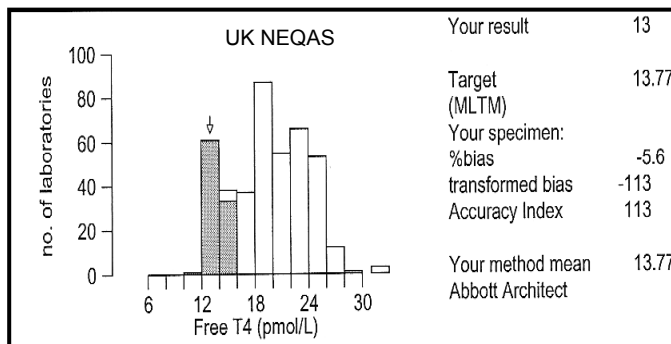


Thyroid specialists

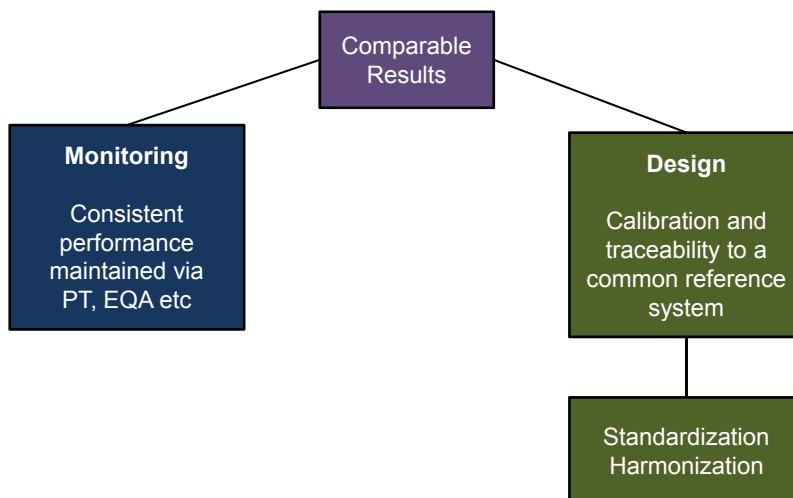
Liaison



Patient organization



## Reducing Between Method Variability



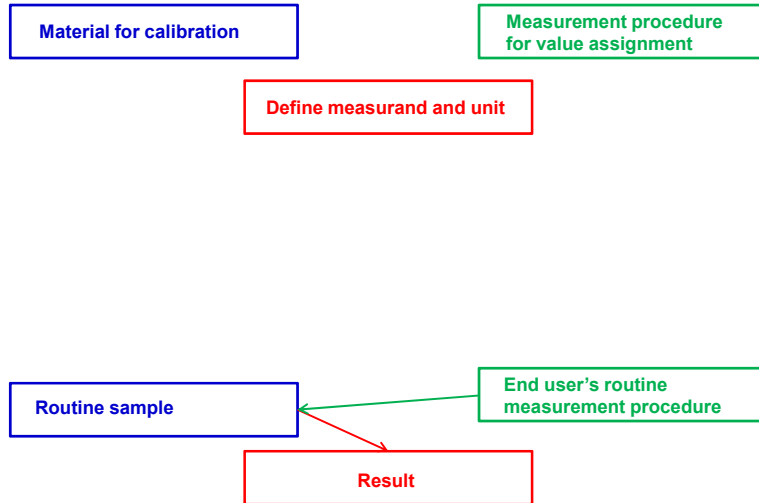
## Why Standardize / Harmonize Methods ?

- 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

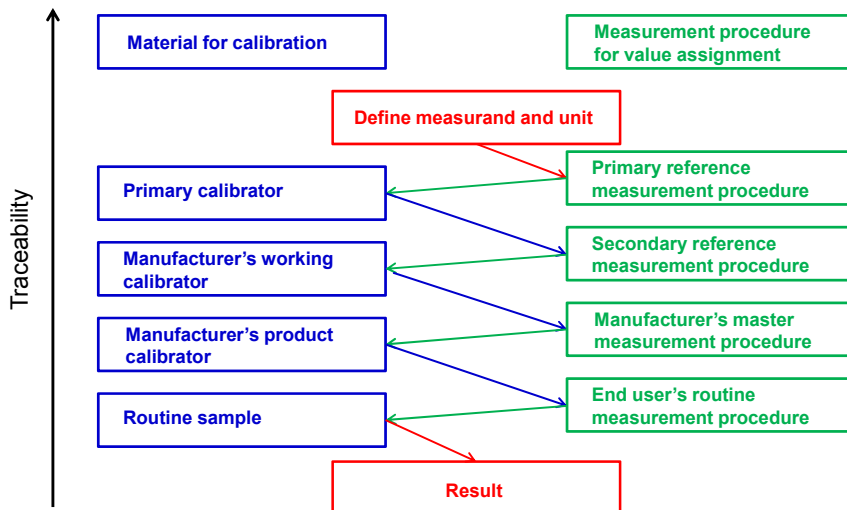
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# What the Laboratory Sees



# Full Metrological Traceability





## Traceability Categories from ISO 17511

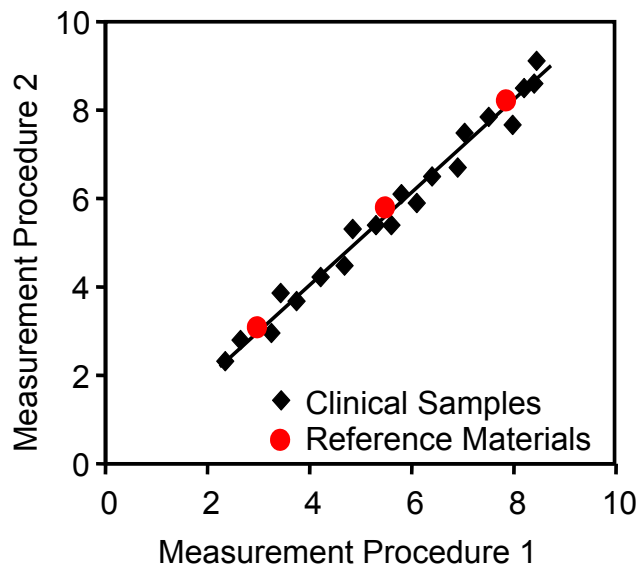
Standardization

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

Harmonization

Miller 2012

Commutability: Same relationship for clinical samples and reference materials

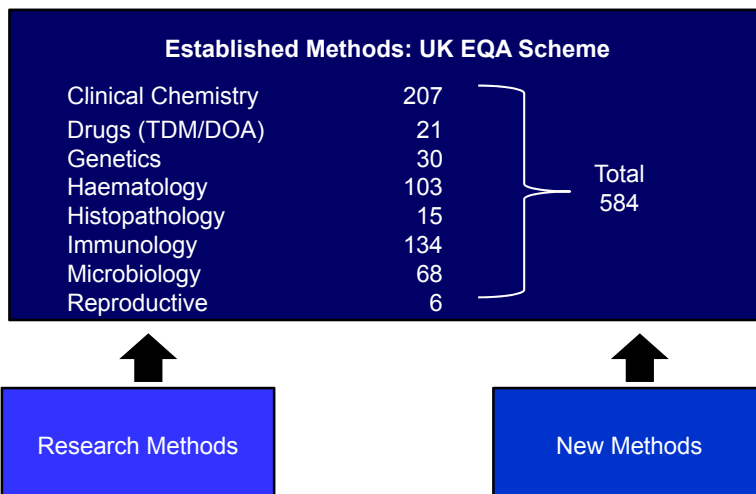


Miller 2012

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## How Many Laboratory Methods Are There?



## 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



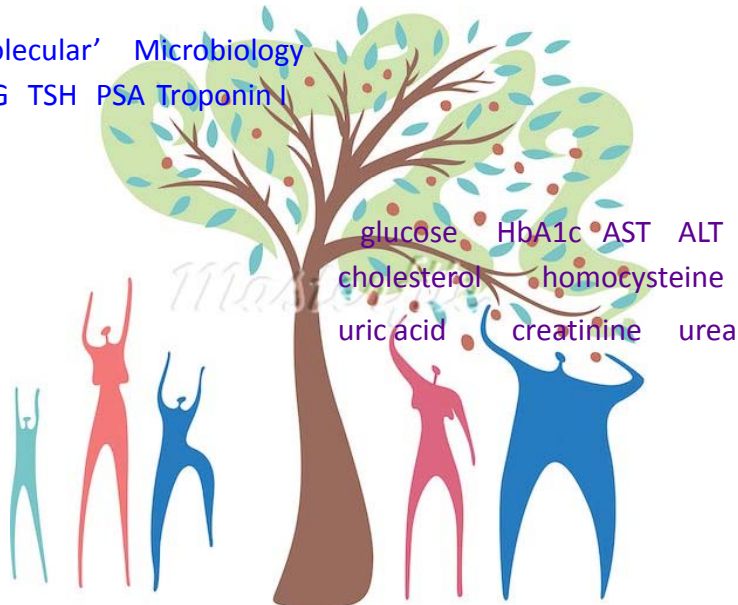
JCTLM Database  
Laboratory medicine and *in vitro* diagnostics

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

So we still have a long way to go!

## Picking the low-hanging fruit !

'Molecular' Microbiology  
HCG TSH PSA Troponin I

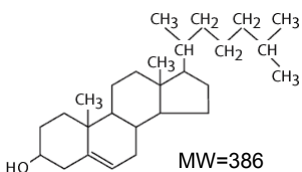


Miller 2012

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## Cholesterol



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

High cholesterol associated with  
increased cardiovascular risk

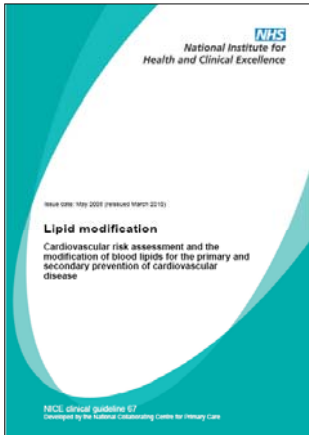
CDC standardization program [Ref 1]  
One of the first analytes standardized

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

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

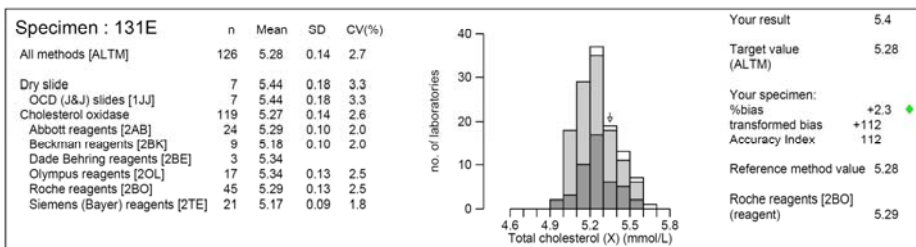
Many clinical practice guidelines exist for coronary heart disease that link management to target cholesterol levels



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.”

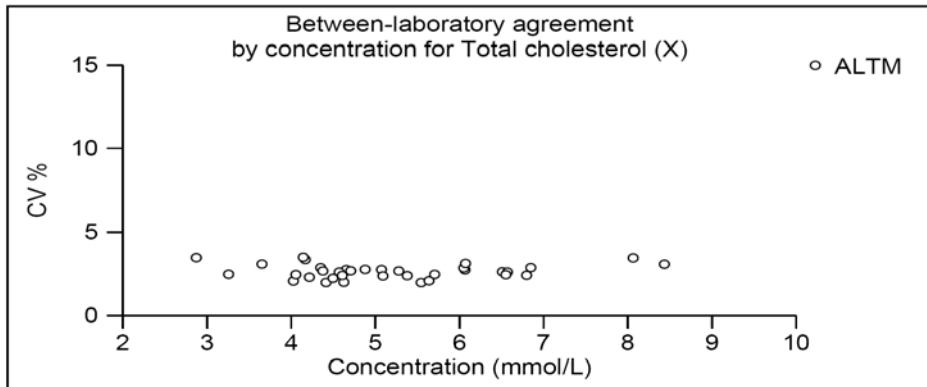
## Cholesterol: Current EQA Performance



- 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.

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## 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

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

Cholesterol standardization has been shown to be cost effective

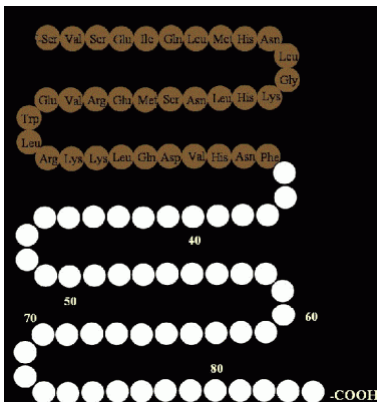
Cost of standardization program \$1.7M pa in 2007

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

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

Status of cholesterol methods = 'GOOD'

# 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

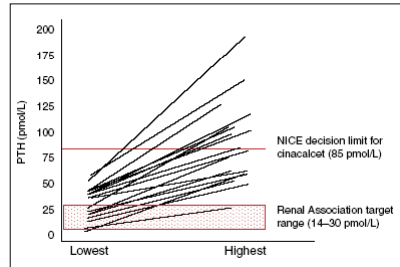
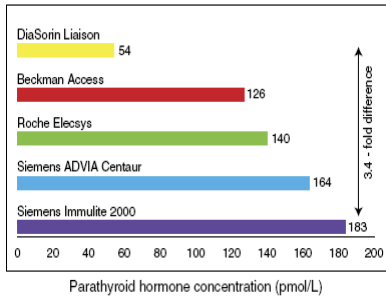
- 1995 recommended 2-4 times ULN

- 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
- 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

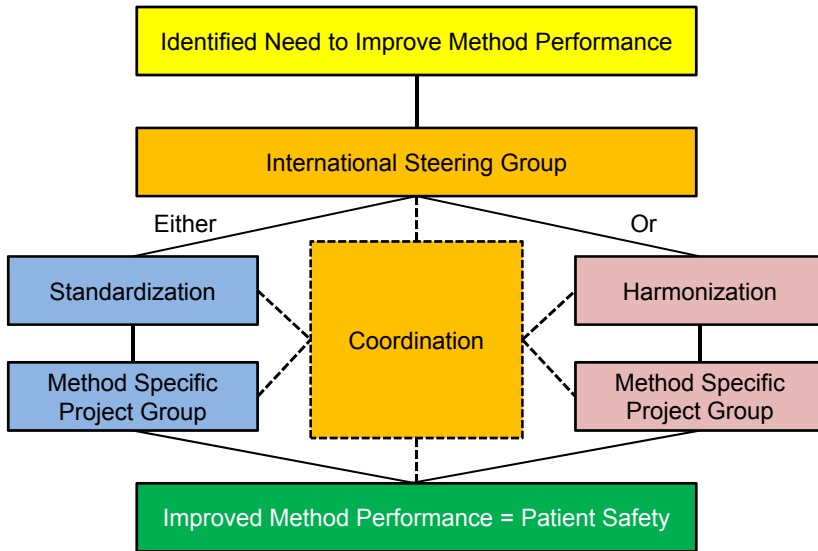
### Roadmap for Harmonization of Clinical Laboratory Measurement Procedures

W. Greg Miller,<sup>1\*</sup> Gary L. Myers,<sup>2</sup> Mary Lou Gantzer,<sup>3</sup> Stephen E. Kahn,<sup>4</sup> E. Ralf Schönbrunner,<sup>5</sup>  
Linda M. Thienpont,<sup>6</sup> David M. Bunk,<sup>7</sup> Robert H. Christenson,<sup>8</sup> John H. Eckfeldt,<sup>9</sup> Stanley F. Lo,<sup>10</sup>  
C. Micha Nübling,<sup>11</sup> and Catharine M. Sturgeon<sup>12</sup>

Report from an AACC conference, October, 2010:  
Improving Clinical Laboratory Testing through Harmonization: An International  
Forum

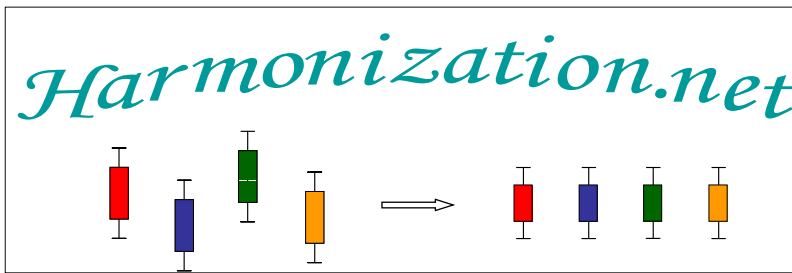
**AACC**

# Model for the Future?



## International Consortium for Harmonization of Clinical Laboratory Results

Currently under active discussion as part of:



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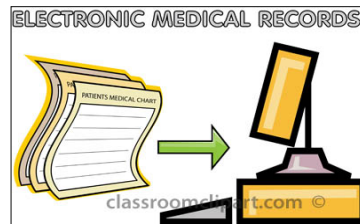
## Key Messages

- 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

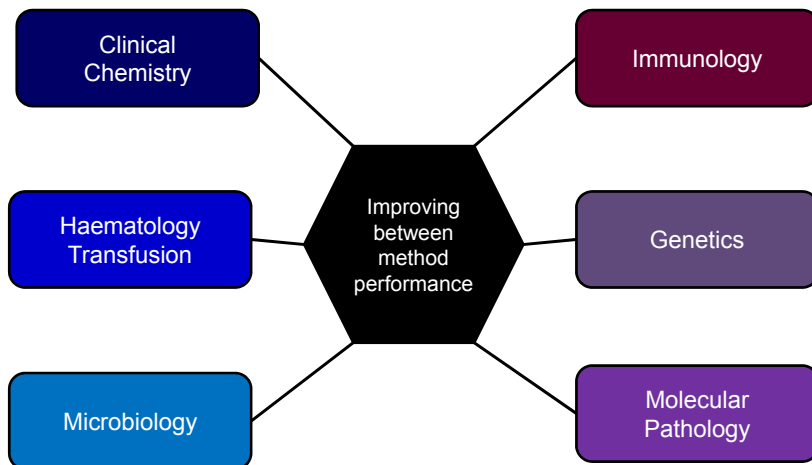
## Why Standardization / Harmonization?



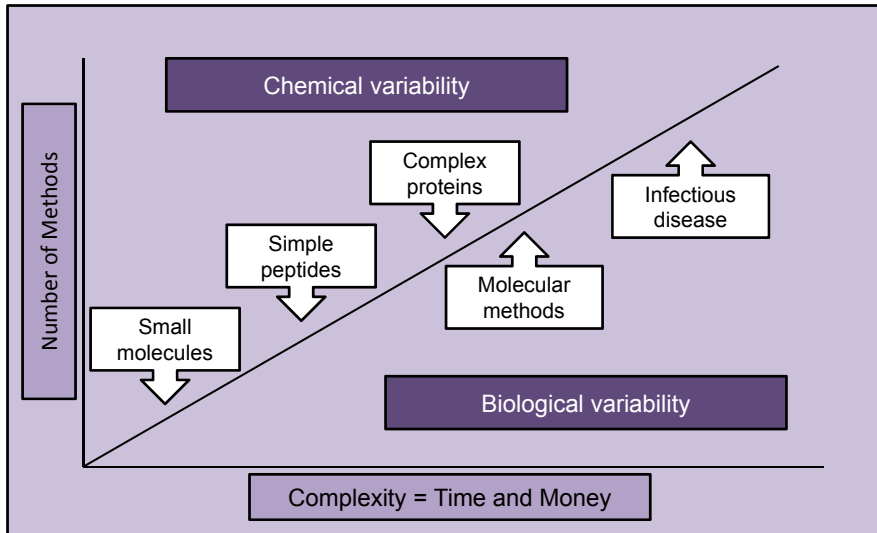
### Patient Safety



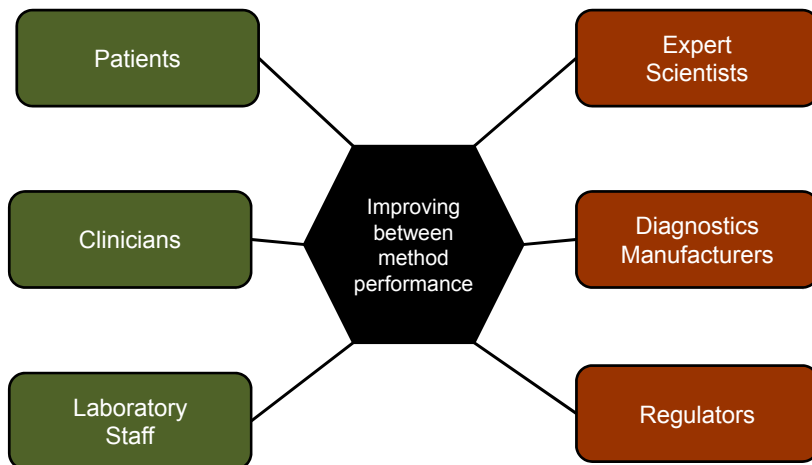
## Where to Standardize or Harmonize?



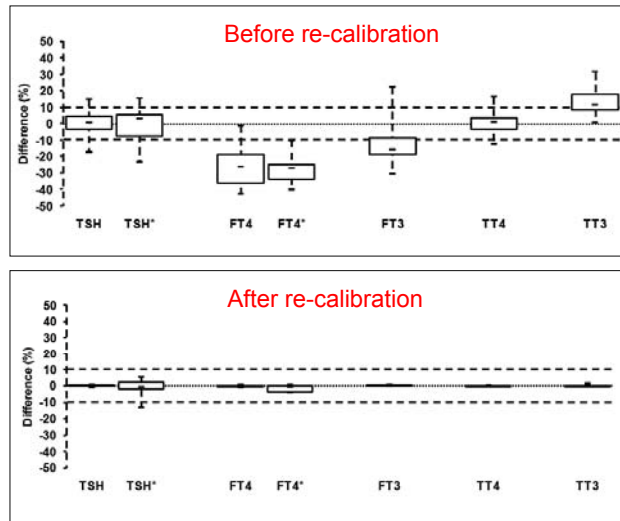
## Standardization / Harmonization Challenge



## Standardization / Harmonization Stakeholders



## And Finally – Back to Free T4!



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

## Acknowledgements

- Several colleagues from UK NEQAS provided data for use in this presentation:
  - Clinical Chemistry: Jane French, David Bullock
  - Protein Hormones: Cathie Sturgeon, Andy Ellis
- See [www.ukneqas.org.uk](http://www.ukneqas.org.uk)



# IFCC Visiting Lecturer Programme

IFCC gratefully acknowledges financial support  
from Abbott Diagnostics Division

