Why Traceability Matters to Patients?
(and you are all patients)

Graham Jones
Department of Chemical Pathology
St Vincent’s Hospital, Sydney
JCTLM Members and Stakeholders meeting, Paris 2017
Acknowledgements

Organisations are vital for advances
• Why traceability is important to the public
  (a talk-within-a-talk where we pretend you are not experts)

• What else is needed to benefit from traceable results?
  – Terminology
  – EQA
  – Reference Intervals
  – Knowing if a result is traceable
Why Traceability Matters to Patients?

Graham Jones
Department of Chemical Pathology
St Vincent’s Hospital, Sydney

Interested Members of the Public
Paris 2017
Why Metrological Traceability of Pathology Results Matters to Patients?

Graham Jones
Department of Chemical Pathology
St Vincent’s Hospital, Sydney

Interested Members of the Public
Paris 2017
Presentation Contents

• What is traceability?
• History of traceability
• Why is it important for laboratory medicine
• What we need to do
What is traceability?

• Traceability is how we get the right result

What is the right result?

• An accurate result
• The result we would get with the best method in the best lab

How does traceability work?

• Behind the scenes our results have been made to be the same as those from the best methods
• More later…
"The Kilo"
BIPM, Paris

Traceable results are comparable
“The Kilo”
BIPM, Paris

Same for Bathroom scales

Traceable results are comparable
“The Kilo”
BIPM, Paris

And for kitchen scales

Traceable results are comparable
Traceable Measurements

- Weight (mass)
- Length
- Time
- Temperature

We take it for granted that these measurements are comparable.
Bureau International de Poids et Mesures
(International Bureau of Weights and Measures)
(Pont de Sevres, Paris)
<table>
<thead>
<tr>
<th>Base quantity</th>
<th>SI base unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>length</td>
<td>metre</td>
</tr>
<tr>
<td>mass</td>
<td>kilogram</td>
</tr>
<tr>
<td>time, duration</td>
<td>second</td>
</tr>
<tr>
<td>electric current</td>
<td>ampere</td>
</tr>
<tr>
<td>thermodynamic temperature</td>
<td>kelvin</td>
</tr>
<tr>
<td>amount of substance</td>
<td>mole</td>
</tr>
<tr>
<td>luminous intensity</td>
<td>candela</td>
</tr>
</tbody>
</table>
For Users of Imperial Units

The ounce, pound, stone, ton, inch, foot, mile (etc), are all traceable to SI (using conversion factors)
• **Measurement** Traceability
• Trueness
• Bias
• Accuracy
• Comparability
• Equivalence
• “Getting the right answer”

• **Traceability makes results the same:** anywhere, any time
Our current scientific, manufacturing, trade and technological civilization is built on traceable measurements – The Systeme Internationale (SI)
Measurements in History

- Egyptian Engraving ~1600 BC

Balances used to measure by comparison
Black figure amphora. Men weighing merchandise, Taleides 560 - 530 BC
Mass – Ancient Greece

• Set of official weights, about 500 B.C.
• Found near the Tholos
• Inscribed with the name of the weight and a symbol.
• Also inscribed with the phrase *demosion Athenaion*, "public (property) of the Athenians."
Length (cubit)

Fourteen cubit rods range from 523.5 to 529.2 mm and are divided into seven palms, each palm is divided into four finger and the fingers are further subdivided.
• Clay public measure
• 4th century B.C.
• Inscribed *demosion*, indicating that it is official.
• Validating stamps are included.
Chia Measure: China 45 BC – AD 23

Combination of five volume measures.

2 he = 1 ho, 10 ho = 1 sheng, 10 sheng = 1 tou, 10 tou = 1 hu.

Inscription of 249 characters explains the origins, individual parts, and dimensions of the individual parts.
By about 500 BC, Athens had a central depository of official weights and measures, the Tholos, where merchants were required to test their measuring devices against official standards.

By about 1875 AD, The modern world had a central depository of official weights and measures, the BIPM, where measurement services were required to test their measuring devices against official standards.
What do you want from your lab?

An accurate Result!
(a traceable result)

what does this mean?
## Example:

Mr Bill Bloggs (DoB 1 Jul 1950)
Sample Collected: 21 Aug 2012, 10:00 am

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine:</td>
<td>125</td>
<td>umol/L</td>
</tr>
</tbody>
</table>
Interpreting laboratory results

Φ + θ/μ - βχπ
or λ ??
Interpreting laboratory results

Your results are interpreted by comparison with:

• A clinical decision point

• A reference interval (normal range)

• Your previous result

Creatinine: 110 125 umol/L

Professor Per-Hyltoft Peteresen, Sydney 2005
Interpreting laboratory results

Your results are *correctly interpreted* when your *lab result* is comparable to:

- A clinical decision point
  - *The method used in the paper*
- A reference interval (normal range)
  - *The method used in the study*
- Your previous result
  - *The method used for previous result*

<table>
<thead>
<tr>
<th>Date</th>
<th>Creatinine (umol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Aug</td>
<td>110</td>
</tr>
<tr>
<td>1-Aug</td>
<td>125</td>
</tr>
</tbody>
</table>

*Professor Per-Hyltoft Petersen, Sydney 2005*
Does it matter if results are different?
Applying Evidence

When comparing with a clinical decision point derived from the medical literature

- You want the best evidence
- Medical evidence comes from everywhere in the world
- (Freely available: INTERNET!)

- Labs around the world must be traceable to allow “Evidence-based medicine”
E-Health

• The Future is an **Electronic Medical Record**
• Patients want “all pathology results available”
• Different labs need to be comparable (or display and interpretation difficult)
• The public expects this!

➔ Labs must be **traceable to be IT Ready**
When patients travel...

- From GP to hospital
- From GP to specialist
- Use a different laboratory
- To a different city
- To a different country (holiday, work, migration)

- To manage your health, you need your pathology results from different labs need to be the same

*All labs must be traceable to allow you to move*
Financial effects?

• When results are not comparable
• Patients need to be tested again when:
  – Admitted to hospital
  – Visiting specialist
  – Changing location or laboratory

→ Traceable results avoid Waste
• Involves combining data from many sources
• Used to see patterns, plan services
• Requires comparable results

*Traceable results are needed for combining databases*
If the laboratories are different:

Results not comparable with other lab: (biased) ➔

• Wrong diagnosis
• Wrong management
• Incorrect monitoring

➔ Traceable results can avoid patient harm
Public expectations

• “you are scientists aren’t you”
• “why are the results different in different labs”
• Because commutable, historical, new method, blah, blah blah ....

*Traceable results are what the public expects*
Without comparable results..

Laboratory Medicine is:

*Not evidence-based*

*Not IT Ready*

*Not safe*

*Wasteful*

*Doesn’t serve patients needs*

You need traceable results!
Laboratory Measurements
Laboratory Measurements

• All numerical laboratory measurements are made by comparison

• Analyte concentration in the sample is compared with concentration in the assay calibrators.

• Calibrator values are assigned by traceability
The top of the traceability chain

- Material
- Method
- Laboratory
Joint Committee for Traceability in Laboratory Medicine (JCTLM)

- JCTLM - Joining of:
  - Metrology Community (BIPM)
  - Laboratory Medicine Community (IFCC)
  - Accreditation Community (ILAC)

- Aim to bring rigour and processes of metrology to laboratory medicine
Joint Committee for Traceability in Laboratory Medicine (JCTLM)

• **List of best:**
  – Reference Materials
  – Reference Methods
  – Reference laboratories

• **Promoting Traceability**
  – www.jctlm.org
The temple of lab standardization – Pillars

Braga et al., CCA 2014
The temple of lab standardization – Pillars

1. Reference methods
2. Reference materials
3. Reference labs
4. Quality manufacturers
5. Quality Laboratories
6. Common Units
7. Common Reference Intervals
8. External Quality Assurance
How are we going?

- Some tests fully traceable
- Some tests reasonable
- Some tests poor

“I give us a B”
What is needed?

- More reference materials/methods
- Assay improvement by companies
- Laboratories selecting good assays
- Regulatory support
- Units, reference intervals, EQA etc

“lets get an A+”
• Thank you
What else is needed to benefit from traceable results?

- Terminology
- EQA
- Reference Intervals / Decision Points
- Identifying Traceable Results
“Traceability” is a terrible term

- No one knows what it means
- It has other meanings (we mean metrological traceability)
- It is not descriptive of quality (all results are traceable)
JCTLM: Joint Committee for Trueness in Laboratory Medicine

JCCLLM: Joint Committee for Comparability in Laboratory Medicine

JCELM: Joint Committee for Equivalence in Laboratory Medicine

JCALM: Joint Committee for Accuracy in Laboratory Medicine

JCULM: Joint Committee for Unbiased Results in Laboratory Medicine
Terminology

Describing a result as “Traceable” does not help

Suggest develop new term, eg:

“Verified Traceable” result
- Claimed traceability to appropriate higher order references
- Uncertainty with specified limits
- Verified with EQA
The Role of External Quality Assurance

• Inherent in *traceability* is *uncertainty*. Inherent in *measurement traceability* is *measurement uncertainty*.

• Traceable results from different labs *will* vary:

• Differences due to:
  – Different reference materials/methods
  – Expected uncertainty in traceability chains
  – Unexpected uncertainty (e.g. non-commutability)

• Key questions:
  – Different by how much?
  – Is this difference important?
The Role of External Quality Assurance

• *Results* of EQA say how different

• EQA *Performance Specifications* say whether difference is important
Due Date: 10/07/2017

Magnesium (mmol/L)

How Different

How Good

Allowable Limits of Performance
±0.10 up to 1.25; ±8% >1.25 mmol/L
RCPAQAP – Commutable serum

Due Date: 10/07/2017

Alanine Amino Transferase (U/L)

Undesirably Low

Specimen 5-01

Undesirably High

How Different

How Good

No. of Laboratories

<12

20

15

10

5

< 12

Median Value

Allowable Limits of Performance

±5 up to 40; ±12% >40 U/L

RCPAQAP

RCPA Quality Assurance Programs
Consensus Statement

Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine
• Model 1 - Based on the effect of analytical performance on clinical outcomes

• Model 2 - Based on components of biological variation of the measurand

• Model 3 - Based on state of the art
Opinion Paper

Graham Ross Dallas Jones*

Analytical performance specifications for EQA schemes – need for harmonisation

Opinion Paper


Analytical performance specifications for external quality assessment – definitions and descriptions

To interpret EQA Analytical Performance Specifications, we need to describe:

1) EQA material and commutability;
2) Method used to assign the target value;
3) Data set to which APS are applied;
4) Analytical property being assessed (i.e. total error, bias, imprecision);
5) Rationale for the selection of the APS;
6) Milan model(s) used to set APS.

• The **comparator** is as important as the **result**

• **For results we:**
  – Validate methods
  – Control daily (or more) with QC
  – Check monthly (or more) with EQA
  – Troubleshoot problems in real time

• How good are our **comparators**?
Commentary

RCPAQAP First Combined Measurement and Reference Interval Survey

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¹SydPath, St Vincent’s Hospital, Sydney and ²RCPAQAP Chemical Pathology, Adelaide, Australia
*For correspondence: Dr Graham Jones, Graham.Jones@svha.org.au

Clin Biochem Rev 35 (4) 2014 243
Variation in Reference Intervals
• MORE than analytical differences

Were Differences in Reference Intervals due to assay bias
• No

Did differences in Intervals increase or decrease diagnostic accuracy
• Decrease
Between-lab CV of Upper Reference Limits

Between-lab CV of results

Sample CV
URL CV
National Survey of Adult and Pediatric Reference Intervals in Clinical Laboratories across Canada: A Report of the CSCC Working Group on Reference Interval Harmonization

Khosrow Adeli\textsuperscript{a,*}, Victoria Higgins\textsuperscript{a}, David Seccombe\textsuperscript{b}, Christine P. Collier\textsuperscript{c}, Cynthia Balion\textsuperscript{d}, George Cembrowski\textsuperscript{e}, Allison A. Venner\textsuperscript{f}, Julie Shaw\textsuperscript{g} on behalf of the CSCC Reference Interval Harmonization (hRI) Working Group

Clinical Biochemistry

Volume 50, Issues 16–17, November 2017, Pages 925-935
Serum Creatinine Reference Intervals

2 year old male

14 year old female

50 year old male
Table 2
Comparing variation and bias between reference sample results and reference intervals.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Instrument</th>
<th>$\text{CV}_{\text{BL}}$ (LRL)</th>
<th>%V (LRL)</th>
<th>%V (URL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT, U/L</td>
<td>All</td>
<td>24.6%</td>
<td>30.2%</td>
<td>30.2%</td>
</tr>
<tr>
<td></td>
<td>Abbott</td>
<td>7.5%</td>
<td>21.9%</td>
<td>30.2%</td>
</tr>
<tr>
<td></td>
<td>Beckman</td>
<td>15.0%</td>
<td>20.4%</td>
<td>30.2%</td>
</tr>
<tr>
<td></td>
<td>Ortho</td>
<td>5.3%</td>
<td>22.6%</td>
<td>30.2%</td>
</tr>
<tr>
<td></td>
<td>Roche</td>
<td>9.7%</td>
<td>6.4%</td>
<td>30.2%</td>
</tr>
<tr>
<td></td>
<td>Siemens</td>
<td>19.7%</td>
<td>36.8%</td>
<td>30.2%</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>All</td>
<td>6.6%</td>
<td>41.9%</td>
<td>30.2%</td>
</tr>
<tr>
<td></td>
<td>Abbott</td>
<td>3.8%</td>
<td>18.2%</td>
<td>52.3%</td>
</tr>
<tr>
<td></td>
<td>Beckman</td>
<td>5.2%</td>
<td>46.5%</td>
<td>35.7%</td>
</tr>
<tr>
<td></td>
<td>Ortho</td>
<td>2.1%</td>
<td>41.7%</td>
<td>43.2%</td>
</tr>
<tr>
<td></td>
<td>Roche</td>
<td>2.8%</td>
<td>23.1%</td>
<td>41.1%</td>
</tr>
<tr>
<td></td>
<td>Siemens</td>
<td>3.1%</td>
<td>41.1%</td>
<td>41.1%</td>
</tr>
</tbody>
</table>
Common Reference Intervals

- Australian Project
- 2013 – 2015 (ongoing)
  - 12 Common tests
  - Sodium, Potassium, Calcium …
Special Report

Harmonising Adult and Paediatric Reference Intervals in Australia and New Zealand: An Evidence-Based Approach for Establishing a First Panel of Chemistry Analytes

*Jillian R Tate,¹ Ken A Sikaris,² Graham RD Jones,³ Tina Yen,⁴ Gus Koerbin,⁵ Julie Ryan,⁶ Maxine Reed,⁷ Janice Gill,⁸ George Koumantakis,⁹ Peter Hickman,¹⁰ Peter Graham,¹¹ on behalf of the AACB Committee for Common Reference Intervals
<table>
<thead>
<tr>
<th>Analyte</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>2.15 – 2.55 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.75 – 1.50 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.7 – 1.1 mmol/L</td>
<td></td>
</tr>
<tr>
<td>LDH [L to P]IFCC</td>
<td>120 – 250 U/L</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>135 – 145 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5 – 5.2 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Chloride</td>
<td>95 – 110 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>22 – 32 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>60 – 110 umol/L</td>
<td>45 – 90 umol/L</td>
</tr>
<tr>
<td>ALP</td>
<td>30 – 110 U/L</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>&lt;40</td>
<td>&lt;35</td>
</tr>
<tr>
<td>ALT</td>
<td>&lt;40</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Total Protein</td>
<td>60 – 80 g/L</td>
<td></td>
</tr>
</tbody>
</table>
Uptake of recommended common reference intervals for chemical pathology in Australia

Graham RD Jones¹,² and Sabrina Koetsier³
Comparators:

- Benefits of traceability only delivered where comparators are also traceable
  - Reference intervals
  - Clinical decision points (guidelines)
  - Results from Other laboratories

- Improvements required
  - Using traceable methods for studies
  - Awareness of differences
  - Specialist involvement with guidelines
Using Traceable Results

• When interpreting (comparing) results – the user needs to know whether the patient results are comparable to the reference results

• This needs either:
  – All results (for a measurand) to be traceable
    • The ideal
    • Possible: Glucose, cholesterol HbA1c
  – Nomenclature / tools for identifying traceability
    • Test names eg AST (IFCC)
    • Coding (eg LOINC) for combining in displays (LOINC codes for traceable methods?)
Are My Results Traceable?

• Manufacturers
  – Better descriptions in IFU
  – Reference JCTLM where relevant (a “trusted brand”)

• Test Names for “Verified Traceable” results, eg:
  – AST (IFCC)
  – AST (JCTLM)
  – AST (non-traceable) (name by exclusion)

• Coding for IT Systems
  – eg LOINC code for “verified traceable” results
  – Only combine traceable results in databases
Traceability for the public

• Every civilisation and every craft has its tools for spreading measurement standards
• Traceability is the modern version
• It is vital we apply this to Laboratory Medicine
• There are many steps still to take …