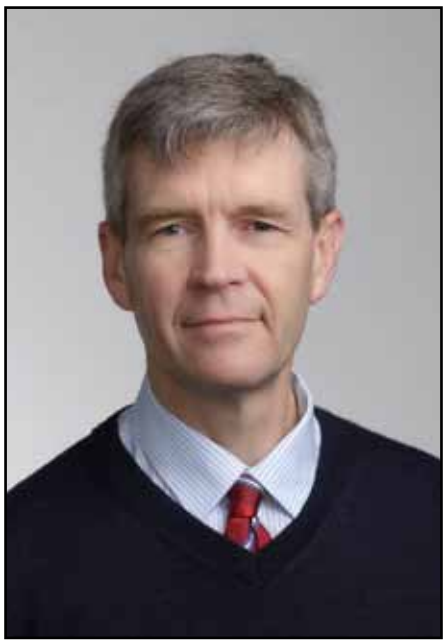
Dr Graham Jones

Chemical Pathology – Getting the Right Answer



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Introduction

The chemical pathology laboratory at SydPath tests samples on over 1,000 patients per day, performing any of over 100 different rests that are requested and releasing over four million individual test results each year. Each of these results is produced in a designed manner to allow correct interpretation to help the doctor make the correct decision for the best patient care. A particular aspect of these results is that they need to be comparable with other results to allow correct interpretation. The aim of this paper is to describe some of these "behind the scenes" activities that are part of high quality pathology.

Interpreting the "numbers" in pathology reports.

Whenever a doctor interprets a numerical pathology result, whether it is a serum sodium, a urine amino acid, or a whole blood lactate, it is done by comparison. The doctor may compare the result with a population reference interval, with a clinical decision point, or with a previous result from the same patient. A result without a comparison point is truly meaningless.

In making a comparison, it is vital that the test results and the results used to provide the comparison are "comparable". In this setting this means that the results and the comparator have no significant bias between the methods used to produce them, and are also not affected by assay imprecision (lack of reproducibility) or lack of analytical specificity (are not measuring the same thing).

The problem we are dealing with is local, national and also global – and solutions must be found at all levels. For example when a result is compared with a published clinical trial, an error may be made if the local results and the method using in the trial are not comparable. With modern internet library resources, we can, and do, access data from everywhere in the world, and thus we need comparable results everywhere in the world. On a local level, if a patient gets tests done at different laboratories, we can only make a valid assessment of any changes in the patient's results if the results between those laboratories are comparable. If we use a national or international guideline, we are only able to apply this correctly if the local result is comparable to those used to establish the guideline.

The process used to make all the different results comparable, is called "metrological traceability". In this paper I will briefly explain the processes, the importance for medicine and my small role in these activities.

Metrological traceability

When you last stepped on a set of bathroom scales, or weighed out the ingredients to cook a meal, the scales you used were part of the global system for measurement known as the "Systeme Internationale" or SI. Your local scales had been calibrated against a better set of scales when it was made, and those scales themselves were checked or calibrated against a better set of scales and so on.

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Table 1. Benefits of comparable (traceable) laboratory results

Application of evidence-based laboratory medicine
Clinical Guidelines
Patient safety
Patient results databases
Cost control
Common reference intervals

Each comparison and adjustment was made using a mass measured on both scales. For any weight measurement made anywhere in the world, these comparisons lead to one place – "the kilo", a platinum-iridium mass made in 1889 and housed in the International Bureau of Weights and Measures (BIPM) in Sevres in the south west of Paris **(Figure 1)**. This is the process of metrological traceability for mass measurements and covers all measurements from nanograms to tonnes. The BIPM is also responsible for other base measurements such as length (metre), time (second), temperature (Kelvin), current (ampere), luminosity (candela) and amount of substance (the mole). All the fundamental units other than for mass (the kilo) are concepts rather than physical items. For example the metre is the length of the path travelled by light in vacuum during a time interval of 1/299 792 458 of a second. With these building blocks, and processes for comparing results, all major measurements in the world are traceable to the SI system.

Traceability in Laboratory Medicine

All laboratory results are also traceable, although unfortunately they are not all traceable to the same standard. For example results for insulin, troponin or many autoantibodies are different in different laboratories. This is because manufacturers use different reference standards, or apply those standards in different ways. In these cases it is not usually possible to monitor a patient across different labs or use information in published papers without consideration of the method used. There are however now many tests which are well standardised globally. These tests include common electrolytes, glucose, lipids, creatinine and HbA1c. These tests are not aligned by accident, but are the product of scientific advances, international agreements and manufacturer uptake.

The Joint Committee for Traceability in Laboratory Medicine (JCTLM)

The JCTLM was founded in 2002 to improve the traceability of results in laboratory medicine. It was formed jointly by the BIPM, representing international metrology, the International Federation of Clinical Chemistry (IFCC) and the global body for accreditation (International Laboratory Accreditation Collaboration, ILAC). The JCTLM verifies the suitability of materials and methods to be recognised as international standards bringing the rigour of the SI system to laboratory medicine. The JCTLM publishes a freely available website of such reference materials and method (www.bipm.org/jctlm) and supports and promotes and educates about traceability in medicine (www.jctlm.org). In addition to the JCTLM there are international standards available for many tests from the World Health Organisation (WHO).

Benefits of traceability in laboratory medicine.

When results from different methods and different laboratories are comparable (traceable), a range of benefits follow. Looked at the other way, there are risks and costs from having assays which are not traceable. As noted above, international literature can only be applied where results are traceable, and valid clinical guidelines can only be written when the source data is comparable both within itself and with routine laboratories. In this way, *evidence-based medicine* can only be practiced when results are comparable. In the modern era there are many developments in the field of combined patient databases. Whether these are on a single doctors desktop, a local region or a whole country, *big data analytics*, i.e. combining results from different laboratories is only valid when results are comparable. The obvious sequelae from above is that if results which are not traceable are compared, erroneous clinical decisions can be made leading to patient harm. Thus comparable results are required for *patient safety*. As well as patient harm, the presence of differing assays can have important *financial costs*, with tests repeated unnecessarily and treatments given or withheld wrongly. Some of the benefits of traceable results are listed in the **Table 1**.

Australian activities to improve traceability and gain benefits.

The RCPAQAP, the external quality assurance (EQA) program of the Royal College of Pathologists of Australasia runs EQA programs for all Australian laboratories and many from overseas. The data from this program can demonstrate the closeness (or the scatter) of results from different laboratories.

A number of recent national guidelines which are based on laboratory tests have only been possible due to appropriate comparability of results from all laboratories in Australia. These include the use of HbA1c for diagnosis of diabetes mellitus and the routine reporting of eGFR for the diagnosis of chronic kidney disease. There has been both international projects to improve standardisation of HbA1c and creatinine assays, as well a local verification of assay quality in Australia through EQA.

Another recent activity is an ongoing project to harmonise reference intervals for common laboratory tests. In recent years work from the Australasian Association of Clinical Biochemists (AACB) and the RCPA has markedly reduced the unnecessary variation in reference intervals between laboratories for common electrolytes and some other tests. This work is only possible due to demonstrated comparability of assay results achieved through traceability.

In the area of risk reduction, the use of different units for reporting the same test is a potential point of failure and patient harm. This is particularly likely when results are given over the phone without the accompanying units. Recently most laboratories in NSW have aligned to reporting results for most therapeutic drug measurements in mass units (e.g. mg/L) rather than a variable use of mass and molar (e.g. umol/L) units. It is easy to see that a paracetamol of 100 mg/L (likely to be toxic), might be considered benign if it was thought to be 100 umol/L (15 mg/L). Standardisation of units is an ongoing activity to avoid risks to patients.

Conclusions

Pathology tests are a vital part of modern medicine, however they need to be used in a safe, evidence-based, cost-effective way. There is considerable activity behind the scenes to deliver comparable (traceable) results from different laboratories, reported in the same units with the same reference intervals. There is however a long way to go and until that time, clinicians need to be aware that not all results are the same.

Relevant Activities of the Author

Graham Jones
Executive member of the Joint Committee for Traceability in Laboratory Medicine (JCTLM) 2007 to present
Chair of RCPAQAP Chemical Pathology Advisory Committee 2005 to present
Chair of AACB common reference intervals meeting 2013 – 2018
Chair of working party on standard units for therapeutic drug measurements (2008-2012)
Co-chair Australian Creatinine consensus 2004 – 2012
RCPA representative on HbA1c for diagnosis working party 2010 - 2014
Recipient of the Barry Inglis medal from the National Measurement Institute of Australia for services to metrology – 2015

Figure 1. *"The Kilo" – held under three vacuum seals at the International Bureau of Weights and Measures in Paris, France*

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