Standardisation in clinical analysis for the benefit of patients

As the UK National Measurement Laboratory (NML), our role is to ensure confidence and quality in the chemical and bio-measurements measurements made in the UK. Our work has underpinned the standardisation of a crucial clinical biomarker for chronic kidney disease over the last 15 years, helping save the NHS £290m/year, and preventing over £1bn/year being spent globally on misdiagnosis.

Background

Chronic kidney disease (CKD) is a long-term condition often linked to age, high blood pressure or diabetes that affects between 7% and 10 % of the population. If is not detected early enough it can lead to an increased risk of heart attacks or, in extreme cases, even total kidney failure. In the UK over 1 % of the entire NHS budget (~£1.5bn) is spent on late-stage CKD treatments such as dialysis or kidney transplants, and in the USA these costs are over $99bn. Although early-stage CKD exhibits minimal symptoms it can be detected by monitoring levels of the biomarker creatinine in the blood in those patients most likely to be at risk. Ensuring correct early diagnosis through accurate and reliable creatinine measurements is crucial to reducing healthcare spend for an ageing society.

At the National Measurement Laboratory (NML), hosted at LGC, we have been working in the area of small molecule clinical characterisation for over 15 years to develop the underpinning measurement expertise needed to support accurate disease diagnosis and monitoring. This has included the validation of emerging clinical markers, improving the accuracy of those already used within the clinic or validating new technologies to enable time and cost savings within the NHS. Through UK government funding in our national role, we developed the reference method needed to underpin the standardisation of the crucial clinical biomarker creatinine.

The measurement improvement timeline

In 2002 an International Measurement Evaluation Programme study organised by the European Commission[1] assessed the standardisation of creatinine measurements across over 1000 reference, clinical and quality assurance laboratories around the world. The study demonstrated that the majority of measurements were 10 to 50 % higher than the true value. In a 2003 survey run by the College of American Pathologists (CAP), over 60 % of reference material producers were also shown to demonstrate significant routine biases (10 to 35 %) for creatinine measurements.

At this time, 1.5m people in the UK had been assessed as having CKD. Assuming a general false positive rate of 15 % (the lower end of the bias observed) in 60 % of cases, this indicates 135,000 people may have been incorrectly diagnosed, with almost 1,000 being mistakenly referred for renal failure. Beyond the avoidable patient distress misdiagnosis would have caused, these figures suggest that the NHS was spending at least £34m per year on unnecessary treatment due to lack of standardisation in this one area. Including potential unnecessary renal replacement therapy this figure could have been as high as £46m/year.

To address the need for creatinine standardisation, we developed a high accuracy, traceable method (isotope dilution mass spectrometry [IDMS]) for creatinine quantification that required minimal

[1] Van Nevel L et al. (2003) IMEP-17 Trace and Minor Constituents in Human Serum, JRC24446, European Commission, Joint Research Centre, Institute for Reference Materials and Measurements, Belgium.

sample preparation[2]. This method was validated against other national measurement institutes (CCQM) and as recognition of its status as a reference method, it was accepted for inclusion into the Joint Committee for Traceability in Laboratory Medicine (JCTLM) database in 2004.

To improve creatinine measurements, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), National Kidney Disease Education Program (NKDEP) and European Communities Confederation of Clinical Chemistry (EC4) launched a standardisation programme in 2006[3,4]. This required laboratories to use Reference Materials for their creatinine measurements and demonstrate traceability to JCTLM-listed IDMS methods, citing the NML method. In the UK the requirements for IDMS-traceable methods and RMs to improve standardisation were included in the NICE guidelines for creatinine measurements in 2008.[5]

To support these clinically-led requirements, a Reference Material (SRM967) was released by the US national measurement institute (NIST) in 2007, validated using our method. The uptake by the clinical community was encouraging, with over 150 units sold in the first year. A second batch (SRM967a) was released two years later using only our JCTLM-approved method for value-assignment. By 2011, all major creatinine assays suppliers were using this material for calibration.

A second study run by CAP in 2013, ten years after the first, showed the typical bias across reference material producers had reduced to <5 %, a significant improvement driven by the provision of traceable reference methods and Reference Materials.

Impact

Our reference method development allowed for the provision of the necessary reference materials to underpin the standardisation of creatinine. Standardisation has ensured that billions of pounds of healthcare funding have been effectively allocated. Since standardisation over 11m people in the at-risk group in the UK have been tested for CKD and correctly diagnosed. Prior to standardisation, almost 2m of these would have been given an incorrect positive diagnosis, resulting in significant patient distress and costing the NHS over £290m/year. In the USA, where 26m people have CKD, the cost of false positive diagnoses would have been over £1bn a year.

Recent regulatory drivers have further recognised the need for traceability and standardisation of clinical measurements. UKAS requires medical laboratories to be accredited to ISO 15189:2012 and the implementation of the in vitro diagnostics regulation by 2022 (Regulation (EU) 2017/746) requires diagnostic tests in a clinical setting to be traceable to higher order methods and materials.

Implementing standardisation in the clinic requires a significant amount of time, effort and the support of the relevant bodies (IFCC, EC, metrology institutes).

However, effectively leveraging this expertise can have a **dramatic impact on patient welfare and healthcare costs for the NHS**. Closer direct collaboration with the NHS through, for example, our successful Knowledge Transfer Partnership Programme, can reduce the temporal distance between measurement research and clinical implementation and significantly increase the impact of our underpinning work.

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[2] Stokes P, O'Connor G. Development of a liquid chromatography–mass spectrometry method for the high-accuracy determination of creatinine in serum. J Chrom B (2003) 794(1)125-36

[3] Myers GL et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem (2006) 52(1)5-18

[4] IFCC et al. The importance of metrological traceability on the validity of creatinine measurement as an index of renal function. Clin Chem Lab Med (2006) 44(10)1287-92

[5] NICE Guidelines CG182, Chronic kidney disease in adults: assessment and management