If we acknowledge our interpretations are critically important, how can we agree which interpretive comments are correct and which aren't? For quantitative results we can use statistics to test agreement, however for qualitative results we need some sort of gold standard. While the ultimate health standard is clinical outcome, it is difficult to ascertain if our interpretations have been truly beneficial, therefore we use the professional judgement of a group of experts to define the interpretations that are most appropriate. Ideally that reference expertise is both clinical and laboratory based, and we should aim to agree with the experts or at the very least be largely in agreement with them. Disagreement with the experts may similarly be an opportunity for quality improvement. Interpretations that cannot be supported by clinical outcome or expert opinion may undermine the quality and value of pathology testing.

OUTCOME-BASED ANALYTICAL PERFORMANCE SPECIFICATIONS – MISSION IMPOSSIBLE?

Andrea R. Horvath¹, Sarah J. Lord², Andrew St John³, on behalf of the Test Evaluation Working Group of the European Federation of Clinical Chemistry and Laboratory Medicine

¹SEALS Department of Clinical Chemistry, Prince of Wales Hospital and School of Medical Sciences, University of New South Wales, Screening and Test Evaluation Program, School of Public Health, University of Sydney, ²School of Medicine, University of Notre Dame, and ³ARC Consulting, Perth, WA, Australia

The 1999 Stockholm hierarchy for setting analytical performance specifications (APS) has recently been revised.¹ The top of the new hierarchy is based on a model that focuses on the link between testing and clinical outcomes.² This is based on the recognition that high quality analytical performance does not guarantee positive patient outcomes and poor analytical performance of a test that plays a very small part in a complex clinical pathway may not lead to unfavourable outcomes.

This talk reviews the need for outcome-based specifications, the most relevant types of outcomes to be considered, and the challenges and limitations of setting outcome-based APS. It will be highlighted how outcome-based APS should reflect the clinical needs of patients; be tailored to the purpose, role and significance of the test in a clinical pathway; and be defined at a level that achieves net benefit for patients at reasonable costs. The evidence-based methodology of direct (Model 1a) and indirect (Model 1b) outcome studies will be illustrated with examples on how outcome data can be translated to APS using the linked evidence and simulation or decision analytic techniques. Whilst it is acknowledged that direct evaluations of testing-related outcomes are difficult and may not be possible for all measurands, all other forms of setting APS are inferior to that standard, and can be regarded as approximations. Better definition of the relationship between the analytical performance of tests and health outcomes may contribute to the development of tests with improved clinical and cost-effectiveness.

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LIMIT OF DETECTION – A CONTRARIAN'S VIEW

Jacobus P.J. Ungerer

Department of Chemical Pathology, Pathology Queensland, Brisbane, Qld, Australia

Measurement of analytes close to zero poses unique challenges. This includes two important functions: to accurately detect the presence or absence of a substance, and to report minute amounts with appropriate accuracy. The approach to deal with this is based on statistical theory that has a long and murky history leading unfortunately to misconceptions, mystery and complexity. The inappropriate application of statistical parameters results in unexpected problems. In this presentation, I will highlight some of the tricky areas and will demonstrate how they may have far reaching implications. A fit-for-purpose approach will be presented that will provide a practical and logical solution.

WHY IS THERE CONCERN ABOUT ADOPTION OF THE NEW GDM CRITERIA?

N. Wah Cheung^{1,2}

¹Department of Diabetes and Endocrinology, Westmead and Nepean Hospitals, and ²University of Sydney, NSW, Australia

In 2010, the International Association of Diabetes in Pregnancy Study Groups (IADPSG) recommended the adoption of new criteria for the diagnosis of gestational diabetes. Using thresholds derived from the Hyperglycaemia Outcomes in Pregnancy (HAPO) Study, these criteria are based on more evidence than previous diagnostic criteria, and held the promise of international standardisation.

In the subsequent 5 years, the IADPSG criteria have generated considerable controversy. They been accepted by a number of organisations including the WHO, but do not have universal support in Australia, the USA, and the UK. Concerns about the criteria include the fact that the thresholds were determined by consensus, lack of evidence that treatment at these thresholds improves outcomes without causing harm, the increased number of women with GDM, questionable cost-effectiveness, the implications of lower treatment targets, and the extrapolation of these criteria for the diagnosis of early GDM.

Until these concerns are addressed, clinicians are faced with the dilemma of whether to adopt the IADPSG criteria for the sake of standardisation, without clear benefit.

URINE FREE CORTISOL MEASUREMENT: CLINICAL PERSPECTIVE

Ann McCormack^{1,2}

¹Department of Endocrinology, St Vincent's Hospital, and ²Hormones and Cancer Group, Garvan Institute of Medical Research, Sydney, NSW, Australia

Amongst even esteemed endocrinologists, making the diagnosis of Cushing's syndrome and determining the source of excess

cortisol production is a foreboding challenge. Yet, securing the diagnosis is important as untreated Cushing's syndrome carries a high mortality rate. Measurement of a 24 hour urine free cortisol (UFC) is one of the most widely used screening tests for Cushing's syndrome. However, its use in the clinical setting has many shortcomings. There is significant within-patient variability and falsely elevated levels can be seen with over-collection or increased urine volumes. Reported sensitivities up to 95% are only achieved over 2–3 separate collections, which is logistically difficult for the patient. Furthermore, mild cortisol excess can be missed, a problem particularly in patients with early recurrence of Cushing's disease. In the era of liquid chromatograph/tandem mass spectrometry (LCMS) this is even more of a concern. Often there are subtle excesses of cortisol metabolites in cases of Cushing's syndrome which are included in measurements using traditional radio or immunoassays, but not reported in pure free cortisol measurements in LCMS analyses. However, other testing methods are also fraught with problems, leaving the 24 hour UFC measurement still an important test in the diagnosis and management of Cushing's syndrome.

THE MYTHOLOGY OF VITAMIN D DEFICIENCY AND INSUFFICIENCY

Sonali Shah¹, Cherie Chiang¹, Ken Sikaris², Ego Seeman¹

¹Departments of Endocrinology and Medicine, Austin Health, University of Melbourne, and ²Melbourne Pathology, Melbourne, Vic, Australia

Vitamin D deficiency is defined as a serum 25-hydroxy-vitamin D (25(OH)D) of less than 30 nmol/L.¹ Vitamin D insufficiency is held to be present with values <75 nM.² The aim of this study was to examine the evidence supporting the use of these thresholds as surrogates of bone disease. If valid, then at a level of 25(OH)D below 30 nM, serum PTH and bone remodelling markers should be elevated, bone mineral density (BMD) reduced and microarchitecture deteriorated. Lesser degrees of these abnormalities should be present in persons with values of 25(OH)D between 30–75 nM.

We measured serum 25(OH)D, PTH, calcium and creatinine in 10,349 women and 3582 men (using blood samples obtained from Melbourne Pathology). We also critically reviewed the literature dealing with the pathogenesis and treatment of bone disease associated with vitamin D metabolism. Based on the literature, reduced serum 1,25 dihydroxy-vitamin D and calcium malabsorption was observed only at serum 25(OH)D levels below 10 nM.³ We and many other investigators report an inverse association between PTH and 25(OH)D but PTH remained within the reference range in over two-thirds (954/1416) of subjects with 25(OH)D ≤30 nM. There was no level 25(OH)D that distinguished persons with and without secondary hyperparathyroidism. PTH increased with age before and after adjusting for 25(OH)D and eGFR. The literature revealed little evidence of increased remodelling markers, reduced BMD or microarchitectural deterioration at 25(OH)D <30 nM but most

studies lacked subjects with 25(OH)D levels below 30 nM.^{4–6} Moreover, there was little evidence of hyperosteoridosis in post-mortem bone biopsy specimens from 675 deceased patients with serum 25(OH)D <30 nM (blood taken at death).⁷

The literature confirmed that administration of vitamin D increased serum 25(OH)D levels but there was little or no improvement in fractional calcium absorption.⁸ Suppression of serum PTH was achieved provided serum 25(OH)D was below 50 nM.⁹ Whether this is accompanied by reduced remodelling or slowing of bone loss is not known. In one metaanalysis (*n*=4082), fracture risk is reduced by ~8% when vitamin D is with calcium, but no benefit when administered alone.¹⁰

In summary, these null findings may be partly the result of issues in design and execution of the studies. Within these constraints, there is no serum 25(OH)D level that discriminates persons with and without calcium malabsorption, secondary hyperparathyroidism, deficits in BMD, microarchitectural decay, or evidence of osteomalacia. Nor is there robust replicated evidence of anti-fracture efficacy of vitamin D supplementation. In conclusion, the scientific basis underlying the choice of these thresholds of vitamin D deficiency and insufficiency, and indications for intervention, are poorly defined. Work is needed to identify surrogates that identify persons with bone disease with high sensitivity and specificity and demonstrate efficacy and safety of vitamin D treatment.

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