SYMPOSIUM 4 - Defining analytical performance requirements for laboratory tests to make them fit for clinical purpose

MAKING LABORATORY TESTS FIT FOR PURPOSE – REVIEW OF APPROACHES THAT CONNECT ANALYTICAL AND CLINICAL PERFORMANCE OF LABORATORY TESTS

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Analytical performance specifications (APS) based on outcomes (Milan Model 1) refer to how 'good' the analytical performance of a test needs to be to do more good than harm to the patient. To define how good analytically the test needs to be to meet medical needs, first we have to set the desirable clinical performance requirements for the measurand. These could be expressed as desirable clinical sensitivity, specificity or acceptable reclassification error rates that do not grossly influence the patient's management and thus their clinical outcome. This requires a risk-based approach and critical clinical thinking and understanding of the relevant patient population and setting, and how the test is used and acted upon in clinical practice.

In lack of appropriate and direct outcome studies (Model 1a), and because testing is indirectly linked to health outcomes through clinical decisions on patient management, simulation-based studies are mostly used to assess the impact of analytical performance on clinical decision making (Model 1b). There are several, mostly statistical approaches and tools published in the literature that use distributional or regression analysis, decision analytic models, error grid/contour plots, and cost-curve analysis. These studies usually describe the magnitude of reclassification due to analytical bias and imprecision, but they do not set a target for acceptable reclassification.

Thus, there is no consensus so far on how to derive Model 1b APS from such indirect approaches. The concepts of measurement uncertainty, clinically significant difference expressed by reference change values, clinician surveys and the linked evidence approach have been applied to these questions. This lecture will discuss some key definitions, concepts and considerations that should assist in finding the most appropriate methods for deriving Model 1b APS. We review the advantages and limitations of published methods and discuss the transferability of Model 1b APS to different settings.

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DEFINING CLINICALLY ACCEPTABLE ANALYTICAL PERFORMANCE SPECIFICATIONS – A PRACTICAL APPROACH

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Clinical laboratories need to assess whether their methods are fit for purpose in various scenarios, ranging from the introduction of a point-of-care assay to a new care pathway, verification of a method to the evaluation of errors caused by faulty reagent lots. Laboratories would benefit from practical tools to evaluate analytical performance across these different situations.

A clinical decision based on laboratory results consists of comparing the measured value to a decision limit, reference limit, or a previous measurement. These clinical decisions are inherently influenced by analytical, biological, and preanalytical variation. Building on this straightforward reasoning, we developed a model called Clinically Acceptable Analytical Performance Specifications (CAAPS), which utilizes clinically significant differences (CD) expressed as reference change values to determine limits of statistically significant change and to calculate allowable total diagnostic variation, CV(D): $CD = z*\sqrt{2}*CV(D)$. When biological and preanalytical variation are subtracted from the CV(D), we achieve a specification for the analytical variation that allows the detection of the CD. To compare this approach to other APS models, we used common clinical guidelines as a source for the clinically significant differences, but the CAAPS approach can be flexibly applied to varied clinical scenarios.

I will outline the CAAPS approach and show examples of its application in practice. CAAPS will be compared to other approaches in determining APS. CAAPS is geared towards setting minimum analytical performance requirements at the end-user level. Limitations of the CAAPS approach arise from the assumptions underpinning the model. Clinical decision limits are confounded by the state-of-the-art performance of current or historical methodology. The CAAPS model is also strongly influenced by the estimates of preanalytical and biological variations. CAAPS is a pragmatic tool for clinical laboratorians making judgments on analytical performance in today's clinical environment. Clinical decision limit-based reasoning is intuitive from the clinicians' perspective and can aid in taking measurement uncertainty from the laboratory bench to the bedside.

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IGF-1 AND IGF-1 SD-SCORE: CLINICAL PERFORMANCE SPECIFICATIONS GUIDING ANALYTICAL GOALS.

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The clinical utility of laboratory tests is directly related to the clinical performance specifications (CPS), defined by its clinical test role. To assess the clinical performance of a specific test, the analytical performance must be related to the predefined CPS for each intended use.
To aid clinical interpretation of IGF-1 results, SD-scores (SDS) are being calculated by LMS curve fitting of the reference data. In the Netherlands 5 different methods for IGF-1 measurement and at least 2 different SDS calculation algorithms are available. In theory these should all provide similar SDS, however in practice large differences are found. These practice variations contribute significantly to the measurement uncertainty (MU) of the SDS within the Netherlands. Earlier attempts to harmonize IGF-1 assays using a single harmonization sample have had limited effect (mainly around its consensus value)
We predefined the CPS of the IGF-1 test as MU < 0,5 SDS, as perceived by experienced academic (pediatric) endocrinologists. The effect of the measurement uncertainty of our IGF-1 assay on the corresponding SDS was calculated in two hypothetical cases, a GH deficient pediatric patient and an adult acromegalic patient. In both cases IGF-1 MU translated in maximal uncertainty of the corresponding SDS mostly within the defined 0,5 SDS. However, any extra variation contributed by between-lab method differences, both in immunoassay and in calculation of the SDS, will result in unacceptable MU of the SDS.
Further harmonization of IGF-1 tests and of the corresponding SDS calculation linked to a higher order reference method is needed to reduce between method variation. This will ultimately lead to a much-awaited reduction in test-variation between clinical centers.
It can be argued that the perceived CPS by clinicians is biased by the state of art MU of the currently available lab tests. Therefore, improving the analytical MU will ultimately lead to more stringent CPS, until analytical variation will no longer impact the total variation based on both analytical and biological variation.