How the routine reporting of laboratory measurement uncertainty might affect clinical decision making in acute and emergency medicine

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INTRODUCTION

Twentieth century medical practice placed an emphasis on history and examination skills, as expounded by William Osler. A clinical impression would be formed and laboratory tests would then confirm, refine or refute the diagnosis. This paradigm incorporates the concept of pretest probability — a Bayesian approach whereby the post-test probability of a disease is influenced by the sensitivity and specificity of the test and the pretest probability (ie, likelihood) of the disease.

In modern practice this order is often reversed; test results may be available before the patient is seen. The manner in which results are presented (based on the software used), for example, 'abnormal' results in red and 'normal' results in black, can lead to an undue binary distinction in the mind of the clinician. Compounding this, often a patient-centred reference range cannot be provided by the laboratory as relevant clinical information is missing. This may lead to misinterpretation of the result (postanalytical error). Inconclusive or abnormal results may lead to a cascade of further investigations to confirm or refute the initial tests.

The historic paradigm of estimating pretest probability, followed by laboratory tests to refine the likelihood of disease, frequently no longer applies. New approaches are needed to remind clinicians that if results are available before a consultation, they must not be taken in isolation but should be considered in relation to the clinical impression. One approach may be to provide a quantitative indication of the quality of a blood test result—the measurement uncertainty (MU). The MU is the value associated with the result of a measurement that

characterises the dispersion of the values that could reasonably (eg, with a given probability/confidence level) be attributed to the measurement.

Could routine provision of MU with a blood result reduce postanalytical error? Only time will tell with MU being made available for routine clinical use.

What is MU?

A repeated measurement on the same sample generally produces different values—even if measuring conditions are constant. Thus repeated measurements do not produce a single value—there is uncertainty as to the true value of the measured quantity. Biological variation (natural fluctuation of body fluid constituents around a homeostatic set point) also exists. For example, the biological variation of creatinine in healthy subjects is 4–5%.

A single blood sample could be measured for a range of indices. The term 'measurand' signifies 'the quantity intended to be measured'. The *'Guide to the Expression of Uncertainty in Measurement'* from the International Organization for Standardization states that "in general, the result of a measurement is only an approximation or estimate of the value of the measurand and thus is complete only when accompanied by a statement of the uncertainty of that estimate". In other words, without an indication of the result quality, measurement results cannot be meaningfully compared with a reference value. This could be problematic if the measurement result is relied upon to distinguish disease from no disease, such as a D-dimer >500 ng/mL to change the probability of a pulmonary embolus.

MU does not imply doubt about the validity of a measurement; on the contrary, it implies increased confidence of the result's validity. A result outside the range of uncertainty must, by definition, be considered certain. For example, at a reported creatinine concentration of 150 µmol/L (using the widely available Jaffe method) the SD is approximately 4 µmol/L. Although we cannot be sure the

creatinine concentration is precisely 150 µmol/L we can say, with 95% confidence that it is within 2 SD of this, that is, in the range 142–158 µmol/L. Hence, uncertainty assessment is required to decide if the result is adequate for its intended purpose and to ascertain if it is consistent with other similar or previous results. In this example, underappreciation of MU may lead to misclassification of estimated glomerular filtration rate (eGFR).

What causes MU?

MU is an inescapable part of laboratory practice and is not 'error'. Error is the difference between the measured value and the 'true' value whereas uncertainty is a quantification of doubt about the measurement result. Uncertainty is caused by the interplay of errors which create dispersion around the estimated value of the measurand; the smaller the dispersion, the smaller the uncertainty.

Sources for MU

The premeasurement phase includes specimen collection technique, sample transport, storage temperature/time or within-individual biological variation. The measurement phase is influenced by laboratory temperature, humidity and dust that may affect the sample stability, measuring systems (eg, balances), thermometer calibrations, reagents—including batch variation and calibrators. There is an ongoing debate as to how uncertainty should be determined and expressed for measurements of biological substances, with many theoretical and practical issues still needing to be resolved.

Expression of MU

The SD or coefficients of variation (CVs) of results achieved for the appropriate internal quality control are the most recognised. The CV may vary according to the concentration of the analyte, for example, troponin has increasing CVs as the concentration approaches zero—indeed, the concentration at which the CV is 10% has determined the lower limit of troponin reporting. Clinicians may not be aware that CVs can vary within and between assays—ranging from <1% to >20% depending on the analyte measured, its concentration and the analytical method used.

The 95% CI is calculated from the SD and gives a range over which the measurand is considered to sit. The interval may span a threshold with the reported value sitting above (or below) the diagnostic threshold. In this situation the clinician

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must draw upon their clinical impression, based upon history and examination, to interpret the result. A problem with this approach is it would require a step-change in clinician behaviour as in ordinary usage the term 'uncertainty' doesn't inspire confidence. However, if the laboratory use of the term is understood then clinicians may feel liberated and more in control of the clinical case. On the other hand, if a result spans a diagnostic threshold, a clinician might overinvestigate as they would be fearful of missing important diagnoses. Repeating the test may reduce the chance

of overinvestigation with invasive or expensive tests. However, the effect of reporting MU with results requiring urgent clinical assessment and treatment such as potassium >6.5 mmol/L or glucose <2.0 mmol/L will need to be considered.

Reporting of MU will not eliminate postanalytical (clinician) error but it may prove to be one small step to restoring the importance of clinical observation reported by Osler over 100 years ago.

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