Guest Editorial

# Evidence-Based Laboratory Medicine

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"Evidence-based medicine de-emphasises intuition, unsystematic clinical experience and pathophysiological rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research."[1]

The principles of evidence-based medicine have been established since the nineties, although it could be argued that its origins in medicine began in the eighteenth century in the new hospitals of Paris, where autopsies were used to try to identify linkages between symptoms and pathological abnormality.[2] These principles are (1) asking the question; (2) searching for evidence; (3) appraising the evidence; (4) applying the evidence; and (5) assessing the experience. Evidence-based laboratory medicine or EBLM is a separate branch of EBM which focuses on the evaluation and use of laboratory tests with an overall aim of improving patient outcomes,[3] and it is on this area, that this edition of the Clinical Biochemist Reviews will concentrate. It is worth noting that, despite the inherent reasonableness of EBM, the techniques of large scale meta-analysis are not uniformly supported and are criticised as being more a statistical approach rather than a scientific philosophy.[4]

Why should clinical chemists be interested? It is estimated that 70% of all health care decisions affecting diagnosis or treatment involve a pathology investigation. Decisions on an individual's diagnosis, treatment and subsequent therapeutic monitoring are often dependent on a range of pathology-based results. Yet many new laboratory tests enter clinical practice without evidence of improved patient outcomes.[5] There is a greater emphasis in all countries on the ever-increasing cost of health care and laboratories play a pivotal role in the efficient use of resources. Thus the laboratory of the future will be under greater financial and demand pressures, consequently there will be a need to ensure maximum utilisation of available resources.

Demand management will involve the following:[6]

- Reducing underutilisation of laboratory testing through greater adoption of guidelines and evidence-based medicine, to ensure patients receive appropriate and timely care,
- Managing over-utilisation through reducing inappropriate or unnecessary laboratory testing,
- Participating in improving chronic care management through proper use of clinical laboratory testing, leading to improved patient compliance and fewer episodic events,
- Eliminating those laboratory tests that offer little clinical value and those which are ineffective or obsolete.

To meet the challenge of these management imperatives, it will be essential to have highly trained staff who can critically evaluate current and potential tests, modify requester demand and manage the operations of a laboratory network as efficiently as possible. These are the objectives of EBLM. These management and consultation competencies need to be built into the future training processes for the pathologist, clinical scientist and laboratory manager.

The continuing proliferation of new tests and the expectation that laboratories will provide these to the clinical community, place pressure on a laboratory's ability to critically assess the literature. However technical articles about new tests are often focussed on analytical sensitivity and specificity rather than diagnostic accuracy and the benefit to a broad range of patients in different clinical situations. The astute laboratory must be able to put into context the usefulness of a test and its relative benefit over existing tests. There is also the very real concern that much of the research literature may not be reproducible so a critical appraisal of any paper is essential.[7]

It is not just in the critical evaluation of new tests that the principles of EBLM should be used, there are a number of other potential situations such as where there may be a new test which has not been described before, a different way of performing an existing test or a different application of an existing test, either using that test to diagnose or monitor a disease for which it is not currently used, or a different way

of providing that test. Alternatively 'new' diagnostic tests entering clinical practice could be considered as replacement, triage or add-on.[8] Examples of each of these situations are plentiful. New tests, particularly genetic tests, are described frequently. Adoption of a different testing modality before the test can be implemented may be involved.

Using an existing test in a new role is not as common. An example would be second trimester screening using β-hCG. This example also brings us to consider derived values, where existing tests may be aggregated or mathematically transformed. A change in technology may allow an existing test to be provided using this technology in a different setting. Examples include PoCT or improved sensitivity with Troponin assays.

Clinical chemists have used the concepts of quality assurance for decades and are well-versed in the broader ideas of quality improvement in terms of laboratory processes but many are unaware of the quality improvement tools used by clinicians.[9] These tools are clinical guidelines,[10] the equivalent of standard operating procedures, care maps similar conceptually to process maps,[11] and outcome measures,[11] which measure the performance of treatments as quality control measures the outcome of an assay system. These clinical improvement tools are not perfect and their value is dependent on the quality of the evidence that is used to implement them. These clinical improvement tools were developed using ever more sophisticated statistical and epidemiological techniques, which attempt to analyse multiple trials and treatments to objectively determine, for particular diseases and patient groups in particular situations, the best treatment to ensure the best outcome. Clinical chemists do not need to be able to use these tools but they should have the background skills to critically assess systematic reviews and meta-analysis data, and perhaps more basically, the ability to appraise a research paper should be in any scientist's skills-set. Indeed it is surprising that EBM has not has not become part of laboratory culture despite questions being raised about the appropriateness of much laboratory testing.[13,14] It would seem that the use of evidence-based arguments in laboratories would be an effective way to defend the key role laboratories play.

In this edition of the Clinical Biochemist Reviews, we will provide some tools that may be useful in critically appraising a research trial of a new treatment, or indeed of a new test, or the application of an old test in a new situation. But we should never lose sight of the primary reasons for evaluating the literature namely: (a) are the results of the study valid, (b) what are the results, and (c) will the results help in caring for a patient.[15,16] We will focus on the key components of EBLM which are the questions of determining efficacy of a diagnostic test and broadening the narrow view of analytical sensitivity and specificity, posing the appropriate question and finding the evidence. The application of the principles of EBM to diagnostic tests is covered in the articles of Florkowski[17] and of Doust and Glasziou.[18] Florkowski describes the evidence used to support the adoption of HbA1c as a screening test for diabetes. The emphasis in this article is differentiating the noise from the signal in the application of diagnostic tests. This is an area where we are just starting to understand the significance of measurement uncertainty, biological variation and reference change values.[19]

Diagnostic tests are used to confirm, exclude, classify or monitor disease to guide treatment. The value of a new test depends on whether the information it provides, ultimately leads to better patient outcome compared with an old test. When we consider a trial or test application, a number of possible inter-related measures of success or failure become apparent. If we are interested in using a new test, or a test in a new situation, then we will be interested in the analytical performance of that test and whether it is superior to another. But for a test to be useful, it must impact on clinical decisions and improve diagnosis. In addition, the expectation would be that there would be some longer term economic benefit of introducing the new test. Each of these different, but inter-related perspectives, on a new test/treatment, will require evidence to support a claim that using this test is better than existing tests. Each claim requires evidence and finding that evidence is a key principle of EBM.

The concept of a hierarchy of efficacy to produce a medical decision was first suggested by Fryback and Thornbury[20] in the context of medical imaging. We have a pyramid of evaluation phases of the efficacy of a new test/treatment. At each lower level, efficacy is logically necessary, but not sufficient to ensure efficacy at higher levels. This concept has been described and these inter-relations captured in a pyramidal form by Price.[21] The major phases of the evaluation are as follows:

1. Technical quality of the test
2. Diagnostic accuracy
3. Change in diagnostic thinking
4. Change in patient management
5. Change in patient outcomes
6. Societal costs and benefits

Often the evidence required for 3, 4, 5, and 6 is neglected. In this edition, St John and Price[22] have discussed the economic evidence supporting the use of PoCT in a number of situations including INR and CRP testing in community medicine,

and troponin in hospital practice. They describe different types of economic study and conclude that there needs to be more emphasis on value rather than cost, which requires disinvestment in some current tests.

Despite the obvious robustness of the EBM approach, many evidence-based decisions do not translate into changes in diagnostic test uptake. A recent example is the introduction of cystatin C as a marker of GFR. Cystatin C has many advantages over the traditional markers of GFR and yet it has not been adopted. There are various reasons for this and many of these can be related back to the hierarchy of efficacy described earlier. Chew et al[23] have summarised some of the reasons for the lack of uptake of cystatin C:

i. Clinicians do not like to replace familiar markers with new tests unless proven extensively to influence clinical decision making.
ii. Despite superior diagnostic accuracy, there is little evidence that cystatin C improves clinical decision making over the use of serum creatinine.
iii. The potential confounding effects of steroid therapy and thyroid disease and lack of data on other potential confounding variables such as malignancy.
iv. Different reference intervals have been published for different age groups and in addition, clinical decision points for cystatin C are not well-defined.
v. Lack of uniformity and standardisation of available commercial assay formats may be contributing to this limitation.
vi. Contradicting results in the literature, although the majority of studies showed superior or at least equal performance of cystatin C in comparison with serum creatinine in the detection of renal impairment.
vii. Turnaround time and cost of cystatin C measurements. For example, a nephelometric cystatin C measurement takes approximately eighteen minutes to complete and the cost per test is approximately twenty times more than a Jaffe creatinine measurement and three times the cost of an enzymatic creatinine measurement. At present, the convenience and low cost of serum creatinine assays have allowed this marker to remain widely used at the expense of accuracy.

Again this reinforces the importance of looking beyond the technical aspects of a potential new test to the broader issues of cost and the need to influence in diagnostic thinking.

Evidence-based laboratory medicine is attractive to laboratorians because of its inherent logic and well-defined process. Had it been in vogue one hundred years ago laboratory practice would be far different from today. The problems with the application of the principles still occur at the point where traditional behaviours must change and new tests or procedures adopted. Doust and Glasziou[36] challenge us to help clinicians by providing them with information about the imprecision of tests – both the analytic and the within-person variability. Monitoring treatment using diagnostic tests requires an understanding of the normal and unexpected variation of those tests in individuals. It is the responsibility of laboratories to understand this variation themselves as well as providing this information to clinicians in a user-friendly form.

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