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ANALYSIS

Time to harmonise common laboratory test profiles

The composition of routine laboratory test profiles varies between laboratories, causing confusion and unnecessary expense. **W S A Smellie** describes the Association for Clinical Biochemistry's draft proposals for unifying profiles and invites medical opinion

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Laboratories can help to limit costs and improve the quality of healthcare in many ways. Some, such as avoiding unnecessary testing and the further investigations and referrals that ensue, are difficult to achieve and measure. Others are more straightforward. One such candidate is the composition of routine laboratory profiles commonly known as urea and electrolytes (U&E), liver function tests (LFT), calcium/bone profiles (bone), and thyroid function tests (TFT). The tests included in these profiles vary between laboratories, often for historical reasons.[1] This variation has fallen over the past 15 years, at least among UK subscribers to the comparative national pathology benchmarking initiative,[2] but large differences remain. For example, there are 11 different profiles for liver function tests listed by the 49 laboratories subscribing to the initiative.

The ideal profile may not exist, but such differences can cause confusion and potentially affect patient safety. Removing tests that offer little incremental information would save money, avoid further investigation of clinically unimportant minor abnormalities, and remove confusion for doctors moving between hospitals using different laboratories.[3] It could also be an initial step towards problem based rather than panel based testing, which might be the ideal solution. We present proposals for rationalisation drawn up by a panel of members of the Association for Clinical Biochemistry. After consultation with members of the association's clinical practice section, the proposals were debated at its 2011 national scientific meeting, attended by about 100 people.

What is a test profile?

Current test profiles contain groups of measurements that reflect the function or state of an organ system. Not all the included tests, however, are specific to that system—alkaline phosphatase is commonly included in both liver and bone tests; nor are tests always organ oriented—a request for liver function tests on a patient with a non-specific illness may not only be to find liver disease. Some tests may be more useful in specific situations: routine blood bicarbonate measurements may be unnecessary in a fit hypertensive patient but are relevant in acutely ill patients. Defining a one size fits all profile is therefore difficult. We suggest that the routine profile should be the minimum set of tests required in everyday practice. These can be supplemented in specific situations.

How can we define standard profile content?

The evidence for the content of many laboratory profiles is necessarily limited, and their content probably has to be established by professional consensus. That should not prevent us trying to provide a rational and consistent process to determine what they should be. Although reducing the number of tests will produce only modest cash savings[3] (most tests cost around £0.07 each), the millions of tests performed each year make rationalisation important. Box 1 lists the criteria we used to determine whether a test should be included in a routine organ specific profile.

Profile proposals

Urea and electrolytes

This profile contains a variable selection of the tests shown in the table⇓. Sodium, potassium, and creatinine are core measurements of kidney function and seem to meet all our criteria. Bicarbonate could be removed from the core profile for non-acute illness because most decisions to adjust treatments such as diuretic therapy are based on other factors. Bicarbonate is, however, relevant in acute illness and advanced renal insufficiency.

Chloride measurement rarely adds more information than sodium, and very few clinical decisions are based on a chloride measurement. It costs nothing to measure, however, in many laboratories.

Although urea concentration often adds little to the information gained from measuring creatinine, it can provide information about the underlying reason for decreased renal function. It rises earlier and more than creatinine in common prerenal conditions

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Box 1 Questions to consider for core tests in a laboratory profile

- Is the test specific to the organ or system being investigated?
- If not specific, is there another reason for including it?
- Does an abnormal result add additional diagnostic or prognostic information to the other tests included?
- Does the added information provided by the test justify its cost?
- Is there a clinical intervention available that can influence outcome based on the test result?

such as hypovolaemia, notably that arising from diuretics and vasoactive drugs. In many routine situations, however (such as patients with a glomerular filtration rate >60 ml/min), urea is unlikely to add important information. It may, therefore, be possible to determine rules for when urea needs to be measured.

Although the estimated glomerular filtration rate costs nothing to calculate, it raises quality and potential safety concerns. The Renal Association and UK General Medical Services contract quality and outcomes framework recommend routine reporting of the estimated glomerular filtration rate using the modification of diet in renal disease (MDRD) equation.[4 5] However, the calculation is invalid in several situations (for example, extreme body morphology, acute changes in renal function, pregnancy, and in amputees[6]). Further thought is needed about whether this value should be calculated routinely or omitted in particular patient groups.

Liver function tests

Few of the liver function tests actually reflect liver function, although several reflect liver cell injury or enzyme induction. Alanine transaminase (ALT) is the most specific test of hepatocellular injury, although aspartate transaminase (AST) is also often included. Aspartate transaminase is not hepatospecific and adds little information except in specific situations (such as a marker of alcohol misuse). As a marker of alcohol misuse, it is mostly an opportunistic screening test and should be assessed as such on its own merits.

Bilirubin is a test of hepatic excretory function. It is not entirely hepatospecific and additional tests (for example, bilirubin conjugation) may be needed to discriminate between hepatic and extrahepatic causes (notably haemolysis).

Alkaline phosphatase, although not specific to liver, is the preferred enzyme marker of hepatic obstruction.[7] Gamma glutamyl transferase (γGT) can be added if the reason for raised alkaline phosphatase activity is not apparent.[8]

Although γ-glutamyl transferase is more specific to the liver, it is not clear whether isolated rises are diagnostically or prognostically relevant and whether any interventions have any clinical benefit. Like aspartate transaminase, it may be of value in specific situations such as monitoring abstinence from alcohol.

Lactate dehydrogenase (LDH) is not hepatospecific and provides little additional information to the other core tests. Its inclusion seems difficult to justify, and it is now rarely offered routinely.

Serum albumin concentration is a test of liver synthetic function, although it can be influenced by malnutrition, increased protein losses, and haemodilution. It helps determine potential underlying causes of oedema and is relevant both diagnostically and prognostically in liver disease.

Measurement of total protein has historically been included, mostly to allow total globulins to be calculated (total protein minus albumin concentrations). Globulins rise non-specifically in liver disease and systemic inflammation, and high globulins can also be an indicator of monoclonal gammopathy of unknown significance or myeloma. Its inclusion is more as an opportunistic screening test for monoclonal gammopathy, but no specific intervention exists other than watchful waiting. Further research is merited into whether this is a suitable screening test warranting inclusion in a routine profile.

Calcium/bone

Tests used to investigate calcium and bone metabolism vary depending on whether the presenting question is a disorder of calcium metabolism or bone disease, although there is some overlap.

Measurement of serum calcium and albumin—to allow an adjusted calcium value to be calculated—is appropriate because calcium alone does not reflect true serum calcium biological activity. Ionised calcium informs mostly in specific acute situations of acidosis or alkalosis and is not justified (nor often included) in a core profile.

Alkaline phosphatase informs the investigation of metabolic bone disease and also contributes to the investigation of hypocalcaemia and hypercalcaemia. Phosphate provides additional information in abnormalities of calcium metabolism, although this is usually supportive rather than diagnostic. Debate about these tests overwhelmingly supported offering two separate profiles, as shown in the table⇓.

Thyroid

The main question that arises with the thyroid profile is whether it should include both thyroid stimulating hormone (TSH) and thyroxine (usually free thyroxine (fT4)) or TSH alone. Thyroid hormone tests are among the more expensive routine tests (typical reagent cost about £0.25). However, both tests are needed to confirm hypothyroidism.[9] Although a normal TSH result effectively excludes primary hypothyroidism in the absence of acute illness (sick euthroid syndrome), it does not exclude hypothyroidism of hypothalamic or pituitary origin. TSH alone was also considered unsuitable for thyroid tests in some other situations (box 2). For this reason TSH alone should be routine only when the laboratory has sufficient clinical information to identify cases when thyroxine should also be measured. It can also be used in stable patients receiving thyroxine replacement therapy as a gauge to adequate replacement and in opportunistic screening for primary hypothyroidism in selected patient groups (such as those with type 1 diabetes, women at the menopause[9]).

Discussion

Harmonising profiles would not only save money but remove some of the confusion caused by laboratories using different profiles and reduce some of the additional investigations arising from incidental and clinically irrelevant minor abnormalities. A similar exercise has been ongoing to harmonise laboratory reference values.[10]

Several of the tests that are currently routinely done are required only in specific situations. One way of facilitating this would

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Box 2 When is thyroid stimulating hormone not sufficient to investigate thyroid function?

- New patients with symptoms or features suggestive of thyroid dysfunction (common use of the test)
- Confirming a diagnosis of primary hypothyroidism when TSH is raised
- Monitoring treatment of hypothyroidism and hyperthyroidism in the early months, or until patients are stabilised on T4
- Identifying erratic compliance in patients taking T4
- Diagnosing and monitoring thyroid dysfunction in pregnancy
- Diagnosis and monitoring treatment for central hypothyroidism
- Confirming a diagnosis of primary hyperthyroidism when TSH <0.1 U/L (T4 and tri-iodothyronine (T3) recommended) to identify severity or to exclude non-thyroidal illness
- Identifying patients with end organ thyroid hormone resistance or TSH secreting of pituitary origin
- Investigating children (<18 years)

be to move more towards diagnosis or condition based testing rather than organ based testing. This is now more feasible because tests are increasingly requested electronically. Information about diagnosis or condition would enable a laboratory to identify, for example, whether a patient required full liver function tests or just alanine transaminase to monitor potential drug hepatotoxicity. Users may also need to know more about when to add additional tests, as this is an important facilitator of rational testing.[11]

However these proposals are taken forward, it is important that the solution adopted is simple. Those who use laboratory tests need to be engaged in any process of change. Similarly, laboratories must also increase their efforts to engage with the test users to provide the help and knowledge to choose the right tests and add additional ones appropriately, whatever the core profiles contain. To harmonise profiles across laboratories, it is now essential to have the views of people who use these tests in routine practice. We welcome readers' thoughts through *BMJ* rapid responses.

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Table

Table 1| Proposed harmonised test content and some key remaining questions for common blood (usually serum) profiles

Profile	Potential content	Proposed
Kidney and electrolytes	Sodium Potassium Chloride Anion gap (now rarely reported) Urea Creatinine eGFR	Sodium Potassium Urea (could be omitted in specific situations) Creatinine eGFR for primary care Questionable: eGFR in inpatients and specific outpatient groups
Liver	Bilirubin Alanine transaminase Aspartate transaminase Alkaline phosphatase γ-glutamyl transferase Lactate dehydrogenase Albumin Total protein Calculated globulins	Bilirubin Alanine transaminase Alkaline phosphatase Albumin Questionable: total protein and calculated globulins
Calcium/bone profile	Calcium Albumin Adjusted calcium Phosphate Alkaline phosphatase	Two profiles: Calcium Calcium Albumin Adjusted calcium Bone Calcium Albumin Adjusted calcium Phosphate Alkaline phosphatase
Thyroid function tests	Thyroid stimulating hormone (TSH) Free thyroxine (T4) Free tri-iodothyronine (T3) Total T4 or T3 are occasionally offered as alternatives	TSH and free T4 (+/- fT3 depending on clinical situation) TSH alone can be used if laboratory has sufficient information to determine that fT4 is not needed

eGFR=estimated glomerular filtration rate.

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