



The Royal College of Pathologists

**Evaluating and introducing new diagnostic tests:
The need for a national strategy**

**Report from the short life working group on the
evaluation and introduction of new tests**

July 2006

Executive Summary

- New diagnostic laboratory tests are becoming available at an increasing rate, driven by rapid developments in molecular biology, proteomics and other developments in biological sciences.
- Evaluating the clinical relevance and utility of such tests is a difficult and incremental process. Historical approaches to such evaluation are becoming increasingly inadequate.
- Several organisations have an interest in evaluating new tests in specific small areas; but most areas of diagnostic practice, especially in relation to common diseases, are not covered.
- The identification of legitimate laboratory tests is essential for several national initiatives, notably the ‘unbundling’ of pathology in ‘Payment by results’ and the inclusion of pathology data in ‘Connecting for Health’.
- There is therefore a broad consensus that there is an increasing need for a single national body which provides authoritative, objective decisions on whether, and under what circumstances, new diagnostic tests should be made available for the investigation and management of NHS patients. This might be summarised as a ‘*NICE for diagnostics*’.
- **Our principal recommendation is that the Department of Health should establish a short-life working group, involving relevant stakeholders, to discuss how best to develop an authoritative mechanism for the evaluation of new laboratory investigations.**
- We suggest that the breadth of this task means that it would be best delivered by establishing a new body, but that (subject to some safeguards) it might be possible to expand the function of an existing body, such as NICE, to provide this service.
- Such a body would also identify when outdated tests can be withdrawn and when current tests should *not* be used.
- Once approved as cost-effective for specific circumstances, there should be an obligation on NHS commissioning processes to provide that test (much as NICE a decision on drug use results in an obligation to provide the drug when it is clinically indicated). However, questions of how an approved test should be *delivered* should be considered separately.
- A decision to approve a test should be accompanied by recommendations on how the test might most efficiently be provided, and what quality controls are needed, to assist commissioners. But unless there are clinical imperatives which require a specific mode of delivery these recommendations on delivery should be non-binding, to allow commissioners to select the most efficient mechanism under local circumstances.
- We have not at this stage assessed the financial impact of this proposal, but we note that there is considerable scope for financial savings in terms of improving diagnostic efficiency, better, more consistent decision-making, eliminating old tests, minimising unnecessary testing, reducing medicolegal liability and avoiding duplication of local evaluation processes. The arguments parallel those which justified the establishment of NICE.

Introducing new diagnostic tests - the nature of the problem

Introducing new tests into NHS diagnostic laboratory practice presents challenges which are relevant to all laboratory disciplines. The issues which must be addressed may be summarised as:

1. Is the scientific evidence for the validity of the new test sufficiently robust?
2. What is the relevant population group?
3. How large is the cost?
4. How large is the benefit?
5. Will it be possible to discontinue outmoded tests?
6. What are the risks (for patient care and in terms of litigation) of *not* introducing the test?
7. Is introducing the test cost-effective for that population group?
8. Can the necessary resources be found? (startup capital, running costs, skilled staff)
9. Who should provide the test? (e.g. reference laboratories or all laboratories)
10. How can ongoing quality assurance be provided?

These questions may also be relevant to decisions to alter the original range of application of an existing test. This has recently been highlighted by the substantial problems generated by HER2 testing. The decision to make Trastuzumab (Herceptin) available to all women with breast cancer suddenly made it essential to determine the HER2 status of all new breast cancer specimens. The initial test uses relatively simple immunohistochemical methods (cost estimated at £40 per test) with fluorescence in-situ hybridisation reserved for borderline cases; but nevertheless because breast cancer is a common disease the service was not prepared for this sudden increase in demand.

The history of the problem

Historically the introduction of new tests has been a piecemeal, evolutionary process with useful new assays being gradually disseminated throughout the NHS only after a prolonged period of evaluation in different centres. They would commonly be established in university laboratories, initially used by associated NHS departments, then as a referral service by other NHS laboratories, then (if justified by demand) implemented in local NHS laboratories. Decisions would be left to the clinicians responsible for individual patients, in consultation with relevant senior laboratory staff.

This unplanned approach to introducing new tests is becoming increasingly inappropriate because:

1. Developments in molecular biology are generating new methods of investigating disease at an increasing rate. These include a raft of new biomarkers for common diseases that will need proper evaluation.
2. There is increasing pressure to introduce new tests precipitously, without rigorous evaluation of their true utility, when related to emotive topics (such as cancer) or when there are possible medicolegal threats.
3. Many of these new investigations require substantial investment in equipment and staff skills, which cannot easily be accommodated within local NHS budgets.
4. It is difficult for staff to evaluate recently introduced tests objectively and consistently across the NHS; published evidence demonstrates that papers on the diagnostic accuracy of new tests are often

of poor quality¹ and to make a good decision is difficult² (www.consort-statement.org/Initiatives/newstard.htm).

5. To make a business case for such expenditure is complex, difficult and time-consuming. For every NHS laboratory to make the case independently represents wasteful duplication of effort. Local evaluation of the utility of such tests is often impractical and not a good use of resources.
6. The genetic nature of many new tests may introduce ethical issues with which laboratory staff are not familiar and which are better resolved at a national level.
7. Links between NHS and University departments have weakened with the recent decline in academic pathology. Many medical schools no longer have an identifiable department of pathology. Increased financial controls in NHS and universities makes it more difficult to justify informal transfer of time and expertise.
8. Local staff need authoritative advice on whether a new test can be regarded as sufficiently robust to allow reliance on its use without fear of allegations of negligence if a problem arises. Compliance with national decisions is perceived as providing a better legal defence than local opinion. There is a parallel medico-legal issue in timing the removal from the laboratory repertoire of existing tests which a new test has rendered obsolete. The absence of a national review process therefore tends to cause stagnation.
9. As part of Connecting for Health, there are plans to incorporate decision support systems into on-line ordering of laboratory investigations. This has the potential to improve patient safety, avoid unnecessary investigation, streamline investigation and cut costs; but the development of such an expert system presupposes the existence of an authoritative source of advice on which tests are appropriate under what circumstances. The advice will need to be constantly updated as new tests emerge.
10. The ‘unbundling’ of pathology costs within ‘**Payment by results**’ necessitates the identification of those tests which will be funded, as well as their cost. The most recently released data (Healthcare Resource Groups version 4) has lists of laboratory tests which are inaccurate or outdated in most specialties and almost non-existent in others. If ‘payment by results’ is to work within pathology, there has to be a mechanism for generating and maintaining these lists.
11. It is unacceptable to offer the benefit of a new test to patients in one part of the UK population but deny it to patients in another.

The current situation has many parallels to the uncoordinated introduction of new drugs and procedures into the NHS which preceded the development of the National Institute for healthcare and Clinical Excellence (NICE). If this analogy is accepted it follows that there is a need for a comparable system to provide authoritative assessments of how and when new tests should be introduced into the NHS.

What tests should be offered? Evaluating new tests

There are already some limited mechanisms in place to evaluate new tests.

- The National Institute for healthcare and Clinical Excellence (NICE) is focussed on treatment rather than diagnosis. It has so far commented on very few diagnostic tests, and only when they are linked to the provision or denial of a drug or other treatment. NICE has recognised that it does not adequately cover diagnostics and has suggested that it could establish a new work programme to cover diagnostics if Department of Health approval and appropriate funding were forthcoming. (NTRAC/OGKP report, 22nd November 2005; www.ntrac.org.uk/News/events/MDT-108/MDT-108.aspx).
- The Health Technology Assessment Programme (www.hta.nhsweb.nhs.uk/) regards the evaluation of new diagnostic tests as being within its remit, but in practice it has undertaken only a small number of in-depth reviews, mainly in relation to primary care and national policy issues such as screening for disease. There has therefore been little of relevance to laboratory medicine. It is not within the programme's remit to plan the provision of laboratory services.
- The Medicines and Healthcare products Regulatory Agency (MHRA - www.mhra.gov.uk/) is concerned with regulating *in vitro* diagnostic tests, but largely in relation to their compliance with regulations rather than addressing difficult questions of clinical validity and utility. For example, the MHRA is concerned to uphold CE marking on any new *in vitro* diagnostic test or equipment. But CE marking is only a declaration of compliance with European legislative requirements, not an evaluation of whether, how and when a test should be used.
- The NHS Purchasing and Supply Agency (PASA) www.pasa.doh.gov.uk/ has a key role in developing and improving the provision of comparative information on the purchasing and supply performance of the NHS. In the past this has involved evaluations of some new diagnostic assay but current activities do not include systematic evaluation of new diagnostic laboratory tests.
- The National Specialist Commissioning Advisory Group (NSCAG - www.advisorybodies.doh.gov.uk/nscag/index.htm) includes some very specialised laboratory services within its remit, but it only covers a small fraction of laboratory medicine and tends to concentrate on service provision rather than deciding what should be provided.
- The National Horizon Scanning Centre (NHSC) is located in the University of Birmingham, funded by the Department of Health. It concentrates on new drugs and treatments and has only occasionally taken an interest in laboratory investigations. Its choice of topics is mainly driven by commercial rather than academic developments.
- The National Genetics Reference Laboratories (Wessex and Manchester), set up under White Paper initiatives (www.ngrl.org.uk/Wessex/index.htm; www.ngrl.org.uk/Manchester/). This relates only to inherited disease.
- UKGTN (UK Genetic Testing Network) see: <http://ukgtn.org/index.html> . This relates only to inherited disease.
- MetBioNet (www.metbio.net/) . This relates only to metabolic disease.
- Specialist Assay Service – A consortium of reference laboratories providing rare tests - previously centrally funded - provides formal networking of providers of rare assays (predominantly in the field of protein analysis) and operates schemes for quality assurance of rare assays.

- The British In Vitro Diagnostics Association (www.bivda.co.uk/) provides advice, but is an industry body and cannot be regarded as an independent source.
- ‘Lab tests online’ is aimed at informing patients about established tests rather than professionals evaluating new tests.
- In the USA the Food and Drug Administration has established guidelines for the evaluation of new diagnostic tests (www.fda.gov). FDA approved tests currently concentrate on commercial test kits, mainly for microbial pathogens (see www.amp.org under ‘FDA-Cleared/Approved Molecular Diagnostic Tests’). There is also a scheme for approval of ‘analyte specific reagents’ (see www.aacc.org/govt/asr.htm). The remit of the FDA does not extend to the UK, but the model established may be informative.

It is clear from this list and from Annex A that in most areas of laboratory diagnostics there are no co-ordinated authoritative mechanisms to provide definitive evaluation of the clinical utility of concepts as they emerge from the scientific literature or from commercial sources. Even if the value of a new test is agreed by all, there is no national mechanism (other than market forces) to decide how best to provide that test to all NHS patients, unless the test is relevant to such a small group of patients that NSCAG becomes involved.

All mechanisms will have their critics, but it is essential that a clear and robust set of evaluation criteria is established for meta-analysis of the evidence base to provide confidence in the conclusions, and that the process involves critical review of the conclusions by individuals without a vested interest in promoting the new technology. This may involve adopting or adapting the work of initiatives such as STARD, the Cochrane review, HTA etc. This would all be best accomplished by a single forum, involving all stakeholders, lay and expert professional groups.

If the decisions of this group are to be effective it must be clear that once it has recommended that a specific diagnostic test should be made available (in defined circumstances) then a refusal to provide that test under the defined circumstances is not acceptable. This would closely parallel the present position of NICE recommendations on the provision of new drugs. However, it prompts the question of how such tests should be delivered.

Once approved, how should new tests be delivered?

We suggest that deciding *what* should be delivered and *how* it should be delivered are separate problems; but the solutions to each problem may need to be linked, to ensure an efficient outcome.

The best method to deliver a test will be highly dependent on the nature and complexity of the test, the number of tests to be performed and the cost of capital and recurrent resources. At one extreme might be a simple serological test for heart failure (e.g. Brain Natriuretic Peptide (BNP) assay) which, if relevant to all patients with heart failure, could efficiently be implemented in almost all NHS laboratories. At the other extreme might be a complex genetic test for a very rare inherited disorder, which could only be provided by one or two national centres. The optimum pattern of delivery may change over time, either with changing demand or due to technological developments.

A central system which decides how a test must be implemented and who should perform it is therefore likely to be rigid, unwieldy, and to produce systems which over time become inappropriate.

Market forces potentially provide a more flexible approach. However, if an authoritative decision is made that a test should be offered to a large numbers of patients, there has to be some co-ordinated planning on how best to deliver the test, or chaos would initially result and patients would suffer while a stable delivery system evolved.

The optimum system (in local laboratories or by national referral centres) will differ with each test. We therefore suggest that during the evaluation of a new test, recommendations on a delivery model should also be developed.

The outcome of the evaluation process would therefore be an authoritative decision on *what* tests must be available, to whom and under what circumstances; but the recommendations on *how* each test should be delivered would merely represent guidance, to be implemented or rejected in the light of local circumstances. Inclusion of these issues in the consultation process would give advance warning of likely outcome and demand, allowing laboratories and commissioning authorities to start to make necessary arrangements. Market forces, modified as necessary by the need for coordinated clinical advice and interpretation, could then be allowed to guide subsequent decisions on which laboratories offer which tests.

However, we are aware that in some locations there are demarcations between existing laboratories which may inhibit the implementation of the most efficient approach. Examples include the (fast-diminishing) distinction between clinical cytogeneticists and molecular geneticists, and between histopathology laboratories and genetics laboratories. Problems exist, but examples of excellent collaborative practice also exist. In cases where investigation of a specimen spans functions traditionally provided by different laboratories consideration will be needed on how best to ensure that appropriate collaboration takes place.

Any system of delivery must be subject to appropriate and compulsory quality assurance measures. Guidance on the development of appropriate quality assurance systems would have to be part of the planning process and would require liaison with independent EQA providers such as UK NEQAS and others.

Research

In general, we suggest that undertaking primary research into what tests should be offered should not be the remit of this agency, which should be restricted to collecting data and meta-analysis. However, there may be occasions when that process identifies specific questions which need to be answered by a defined research project. Such research projects may or may not be appealing to industrial sponsors or research grant-giving bodies. In that event we suggest that an agreement with the MRC or other grant-giving bodies should be established to facilitate competitive tendering for funding to undertake such research.

Conclusions

In respect of all laboratory specialties, we are led to agree with the conclusions of the OGKP / NTRAC report mentioned above, especially that:-

“There is a critical need for a reputable, independent agency to evaluate the evidence and approve the adoption of new molecular diagnostic tests within the NHS.”

It is clear that at present none of the bodies listed above fulfil the whole of this role, even in relation to molecular diagnostic tests; non-genetic tests are even less well served.

There is also a need for a mechanism to ‘horizon-scan’ for the next ‘big thing’ in diagnostic testing and to develop strategies to deal with evaluation in advance.

The Royal College of Pathologists has expertise in all aspects of laboratory medicine and expresses its enthusiasm, within its available resources, to assist in developing such a process. The College is certainly willing to assist in ‘horizon scanning’. However, acting alone, the RCPATH does not have the resources to produce a coherent solution to this problem. It is also important that a body which expects to influence NHS activity should be in close contact with wider NHS priorities and should not be perceived as a ‘pressure group’.

At this stage we are therefore suggesting a meeting of relevant stakeholders should be convened, to discuss how best to develop an authoritative mechanism for the evaluation and implementation of new laboratory investigations.

The alternative is to be forced to react in an unplanned manner to sudden adverse publicity and consequent public concern about the lack of availability of new tests.

A failure to provide promptly tests which can improve healthcare outcomes and which can predict and thus avoid adverse drug reactions could have serious medico-legal implications.

Without wishing to pre-empt the outcome of such a meeting, the Royal College of Pathologists suggests that:

- there should be a body established to evaluate new diagnostic tests
- that any interested person or organisation, including the RCPATH, should be free to ‘horizon scan’ and make recommendations to that body
- that the recommendations of that body as to *what* tests should be provided under specified circumstances should be authoritative and binding on NHS service providers
- that recommendations on *how* such tests are provided, and the quality assurance procedures needed, should be developed in parallel, but should represent no more than guidance to service providers. This should allow future adjustments to be made in the light of changing circumstances, clinical needs and market forces.

We suggest that none of the existing organisations with an interest in this area are ideally placed to take on this work, and that therefore a new body should be created which has structural parallels to NICE, which learns from the experience of NICE but which is devoted exclusively to diagnostic tests.

If it is decided that the task should be given to one of the bodies listed above we have concerns that it should not become subordinate to the existing functions and interests of that organisation. To that end, we suggest that it would be essential to set up a separate division within that organisation, with identified and protected funding, exclusively to cover diagnostic issues. Subject to that safeguard we suggest that, of the bodies listed above, expansion of the function of NICE is likely to be the preferable option.

References

- 1 Bachmann L M, Puhan M A, ter Riet G, Bossuyt P M. Sample sizes of studies on diagnostic accuracy: literature survey. *BMJ* 2006; **332**:1127-9.
- 2 Smidt N, Rutjes A W, van der Windt D A *et al.* Reproducibility of the STARD checklist: an instrument to assess the quality of reporting of diagnostic accuracy studies. *BMC Med Res Methodol* 2006; **6**:12.

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Annex A: Subject-specific summaries

Clinical Genetics

Progress has been greatly assisted by the 2004 White Paper on genetics and the additional funding for the long established network of laboratories at regional level. To some extent the problems considered in this paper are, for genetics, addressed by the Genetics Commissioning Advisory Group (GenCAG) and the United Kingdom Genetic Testing Network (UKGTN). However, the work of clinical geneticists has so far concentrated mainly on the investigation of diseases which are associated with defects in single genes and chromosome abnormalities. The number of such defects has increased considerably in recent years with almost 17,000 genetic diseases currently recorded in the Online Mendelian Inheritance in Man Database (<http://www.ncbi.nlm.nih.gov/Omim/mimstats.html>). However, the total number of patients remains small when compared with total NHS workload.

One can predict with reasonable confidence that we will soon see the emphasis shifting towards predicting disease susceptibility, rather than the presence or absence of an inherited disease. This will be associated with the development of much more complicated genetic investigations based on genome wide array-based technology, involving larger numbers of genes and novel mechanisms of assessment. We may anticipate that the efficacy of (or adverse reaction to) commonly used therapeutic agents, new or current, will be predicted by testing the patient's genome. This could rapidly create a demand which the service is not currently configured to supply. A failure to supply this service could result in therapy-associated deaths which could have been avoided if the test had been used, with consequent potential for adverse publicity and litigation.

The treatment of inherited metabolic disease could be regarded as a sub-specialty of clinical genetics, though its emphasis tends to be more on clinical management following the diagnostic application of relevant genetic tests. Problems in the organisation and funding of this sub-specialty have been highlighted in a recent report (available from the Public Health Genetics Unit, <http://www.phgu.org.uk/>)

Many novel tests in other branches of laboratory medicine share some, but not all, of the methods used in clinical genetics laboratories; but in practice there has been relatively little collaboration between pathology and clinical genetics departments, or even between the different sub-specialties of pathology. This may be partly (but not adequately) explained by differences in geographic location, historical differences in funding and the introduction of new techniques, differences in technical methods and differences in disease and specimen types. Increased collaboration has the scope to increase efficiency.

Histopathology / Cytopathology

The investigation of proteins in tissues using immunohistochemistry has been implemented over the last 20 years by the unplanned, incremental approach described above; but this is increasingly under strain as a wealth of new antibodies are introduced each year. The introduction of HER2 testing has demonstrated that we are not prepared even for the rapid national introduction of just one new antibody, if that test is needed for a common disease.

Modern methods of proteomics have not yet been introduced to routine practice, but this development can be predicted with reasonable confidence. Efficient implementation would almost certainly require that the service be based in a small number of referral centres.

Techniques of molecular genetics have been introduced for the investigation of a few rare tumours (e.g. soft tissue sarcomas, lymphomas), largely by referral of samples to academic centres. Expression arrays and array-cgh are beginning to have a significant impact on diagnostics in some rare tumours. But there is no co-ordinated approach to evaluate or implement such tests.

One can confidently predict that techniques of gene expression analysis, such as quantitative RT-PCR and gene expression profiling, will become increasingly relevant to the diagnosis and management of many common diseases.

The problem of introducing new tests in relation to cancer diagnosis and treatment was the subject of a meeting organised in November 2005 by the Oxford Genetic Knowledge Park (OGKP) and the National Translational Cancer Research Network (NTRAC). Representatives included NHS practitioners, researchers, NICE, the diagnostics industry and NHS management. Information from this meeting is available at <http://www.ntrac.org.uk/News/events/MDT-108/MDT-108.aspx>.

A report of this meeting has been passed to the Department of Health, but we note that its remit was limited to cancer and histopathology, whereas these problems are common to all diseases and all laboratory specialties.

Microbiology

The main trend in microbiology is towards direct detection of the genome of microbial pathogens rather than identification by culture and related conventional techniques. Where such methods are established they are quicker and more sensitive than conventional methods. In many cases they are also cheaper, especially where economies of scale can be achieved. Yet implementation of such methods is slow. For example, a recent survey reported that 80% of laboratories in the UK Clinical Virology Network still use viral culture rather than cheaper and more sensitive PCR methods to identify genital herpes infection (Sex Transm Infect 2005: 81:316-7), despite the presence of 14 peer reviewed papers indicating the benefits of PCR and an endorsement in the British Association for Sexual Health and HIV guideline (BASHH) a recent survey.

Haematology

Haematology is heavily reliant on new technology and will find molecular approaches important for its development. Haematology has been developing a number of DNA/RNA based technologies to add to current tests. The British Society for Haematology has a committee for Standards in Haematology. These Standards provide some guidelines for applicability and relevance. However, there is a need for coordination across the whole of pathology, including genetics. Current mechanisms for genetics, including the GenCAG committee, do not cover the requirements for haematology. There are numerous issues of applicability, relevance and quality.

Clinical Biochemistry

With new and emerging technologies such as tandem mass spectrometry there is and will continue to be a profusion of biomarkers, the most promising of which will require evaluation. Developments in technology make it feasible to test for individual or limited sets of markers simultaneously potentially offering very high sensitivity and specificity. There is currently no systematic and authoritative mechanism to evaluate these data and implement the results for patient benefit.

The detrimental effect of the lack of an authoritative system of evaluation is highlighted by the possibility of BNP testing for cardiac failure. This simple test costs approximately £12 and it is widely agreed that it could improve the lives of thousands of patients by facilitating early detection of heart failure. However, despite evidence of its benefit being available for several years its availability within the NHS remains limited and patchy.

Immunology

New tests in the immunological arena (covering Allergy, Immunodeficiency and Autoimmunity) are regularly developed as knowledge of the immunological basis of disease develops. These can include novel protein, functional and genetic tests for rare immunodeficiencies (at least 3 new genes having been identified in the last 5 year in the commonest cohort of immunodeficient patients) and new assays for investigation and management of common ailments, such as allergic disease, SLE , rheumatoid arthritis or vasculitis.

Histocompatibility testing for transplantation practice is nationally regulated and introduction of new assays is driven by the H&I community and which sufficiently small and well organised to network efficiently. However there is no national mechanism for overseeing the clinical utility and most efficient introduction of any new tests which might arise in the arena of transplantation.

Some existing services are nationally commissioned. For example the two National screening centres for X linked immunodeficiencies are NSCAG funded.

Various professional organisations (UKPIN/ESID) issue guidance on immunology and allergy practice, but few on laboratory testing.

Pressure to introduce new tests is often generated by organ-based groups which do not necessarily have insight into the performance characteristics of the tests they are requesting, and are not aware of the limitations of the use of such tests in screening programmes. Local expert evaluation is an important part of the role of the Immunologist - but would be made more consistent, efficient and effective by national standards for evaluation to ensure all decisions meet established evidence criteria.