

*In response to the Call for Evidence on Genomic Medicine from the House of Lords
Science and Technology Sub-Committee:*

Submission of evidence from the Specialty Advisory Committee on Histopathology of the Royal College of Pathologists

Background

1. *The Royal College of Pathologists (RCPATH) is a registered charity, bound by its Royal Charter to promote and maintain the standard of service in pathology (i.e. all of laboratory medicine, including genetics) for the benefit of patients and the general public. It is not a trades union and it does not discuss the terms and conditions of employment of its members.*
2. Histopathologists are concerned mainly with the diagnosis and evaluation of disease on the basis of the examination of diseased tissue samples, especially but not exclusively relating to cancer. We are well aware of the potential future impact of the detailed analysis of germline DNA on the diagnosis of inherited disease. We are also aware of the potential for the analysis of inherited genetic variations to provide detailed information on a person's susceptibility to many common illnesses, as varied as diabetes, vascular disease and cancer. These are extremely important areas. However, **our emphasis in this Submission of Evidence is on the optimal identification and classification of *established* disease processes, to facilitate better treatment and the provision of better prognostic information.**
3. Increasingly this involves aspects of genomic medicine other than the analysis of the inherited DNA sequence ('germline' DNA). These include testing for acquired DNA mutations in tumours; analysis of patterns of gene expression in diseased tissue ('transcriptomics'); and analysis of patterns of protein production in diseased tissue ('proteomics').
4. A separate response to this Call for Evidence is also being made by the Joint Committee on Medical Genetics. We support and endorse the views expressed in that submission, which has a greater emphasis on 'conventional' inherited diseases than does this one.
5. In the diagnosis of infection, the detection of the genome of a microbial pathogen can often produce faster, more sensitive and more specific tests than conventional microbiological approaches. This important area is not considered further in this Submission.
6. Diagnostic approaches based on the analysis of DNA (or RNA) are already an integral part of the management of patients with some relatively rare malignancies, notably haematological malignancies (leukaemia and lymphoma) and some sarcomas. For some new anti-cancer therapies it is already a requirement that information about genomic changes in the tumour must be available before the drug can be given. Data from one haematopathology laboratory (Prof. F. Cotter, Bart's & The London) indicate close to a threefold increase in the use of these techniques in the last two years. It is inevitable genomic analysis will soon be a standard requirement for many much more common tumours. Demand is set to increase exponentially.

Use of genomic information in a healthcare setting

7. As explained above, this submission is limited to the context of diagnostic services. In that context, in the future these techniques:

- will permit more accurate and biologically meaningful classification of disease, including the sub-classification of common conditions that were previously regarded as a single condition (for example, colon cancer), thereby providing explanations of previously unpredictable variations in response to treatment and in prognosis
 - will thereby guide more appropriate treatment and avoid ineffective treatment, and will identify some patients who do not need treatment
 - will be an absolute requirement before the administration of many new treatments, especially new anti-cancer drugs
 - will increasingly allow the prior prediction of severe adverse reactions to specific drugs, avoiding the current 'trial and error' approach to idiosyncratic drug reactions
 - will permit more accurate and earlier diagnosis using smaller and less invasive sampling methods (e.g. detection of mutated DNA in urine samples to detect bladder cancer, rather than cystoscopy and bladder biopsy)
 - will facilitate new population screening programmes to detect early disease
8. However, **all these developments will require investment if the benefits are to be achieved, and consequently a cost-benefit analysis is necessary before they are funded from the public purse.** Failure to do this properly will result either in the loss of potential health benefits to the population, or to resources being wasted.
9. The need for cost-benefit analyses apply to large healthcare organisations such as the NHS. But it also applies to individual members of the public, who may be persuaded to pay for directly-marketed 'genomic' investigations without fully understanding the risks and benefits. We are concerned about the risks to the general public posed by the unregulated direct commercial marketing of genomic investigations. 'Market forces' can only work if the purchaser is in a position to evaluate adequately the product which is being purchased, which we do not believe is the case here. This area has recently been explored by the Human Genetics Commission in their report 'More Genes Direct'(1) and, with our assistance, by the charity 'Sense About Science'(2). However, our current submission is limited to the provision of conventional (principally NHS) diagnostic services.

Research and scientific development

10. To assess the risks and benefits of a new diagnostic investigation is difficult. When a potential new avenue for disease investigation emerges from basic research, work is typically done to measure parameters such as diagnostic sensitivity and specificity (sometimes called 'clinical *validity*'). International standards for the reporting of test accuracy have been widely accepted(3).
11. Unfortunately there is rarely any evaluation of whether a clinically valid new test actually results in any patient benefit (i.e. 'clinical *utility*'). This is an important and complex question. There can be many reasons why a test with excellent clinical validity may ultimately produce no patient benefit, while conversely a relatively insensitive or poorly-specific test might help patient care considerably if it is relevant to a difficult clinical situation where no better test exists. An approach to such evaluations in the context of cancer diagnosis has been published(4) and is supported by the National Cancer Institute of the US National Institutes of Health, but has not been widely used.
12. **This lack of evidence on patient outcomes makes undertaking risk-benefit analysis very difficult**, resulting in reliance on 'expert opinion' or a failure to make any decision at all.
13. We believe that this lack of research on clinical utility is driven by several factors, including the organisational difficulty of conducting this type of research; its relative lack of 'prestige' amongst

the scientific community; and a traditional reluctance of the major grant-giving bodies to fund 'mundane' research into such practical matters, research which is not directed towards improving our understanding of the underlying disease processes. We also suspect that the distinction between clinical validity and clinical utility, explained above, is not widely understood.

14. The current ethical and regulatory framework for such patient-based research has largely evolved with therapeutic research on living patients in mind. The result is a system which is perhaps excessively cumbersome and bureaucratic for research which can involve little or no risk for patients, as the research materials are typically anonymised samples of surplus biological material linked to relevant clinical data.
15. Industry contributes very little to this type of research. We suspect this is partly because there is no regulatory requirement to undertake it, so companies find aggressive marketing to be more commercially effective than research; but it is also true that there are much lower profit margins in diagnostics than in pharmaceuticals, so the funds available for such research are quite limited.
16. **Consequently we recommend that incentives and funding should be established to encourage high quality research to evaluate whether and to what extent the many new genomic-based diagnostic approaches actually improve patient outcome.**

Policy Framework

17. We are concerned that the approach to evaluation and implementation of new diagnostic tests is fragmented, incomplete and ineffective. The introduction of new drugs for NHS use is overseen by a sophisticated regulatory system; there is no such framework for new diagnostic tests.
18. The MHRA is concerned to assess the safety of new 'in vitro diagnostic devices', but this is largely limited to ensuring compliance with EU regulations. It does not address clinical validity or utility as defined above. It has been suggested that this is analogous to insisting that a drug company ensures that a new drug is chemically pure and does not poison patients, without any requirement to demonstrate that it can actually produce any benefit for patients.
19. NICE and NHS QIS (Quality Improvement Scotland) have a responsibility to evaluate new diagnostic modalities in addition to their better-known role in relation to therapeutics, but in practice they have evaluated only a very small number of innovations in laboratory diagnostics.
20. The Department of Health (England) has identified several other organisations that have a responsibility in this area, including the National Horizon Scanning Centre, the Health Technology Assessment programme and the Centre for Evidence-Based Purchasing. However, we suggest that the existence of many bodies with overlapping responsibilities demonstrates that the work is not well coordinated. Furthermore, all these agencies are selective in the topics they will address, and many new innovations are not covered by the remit of any of them. In practice, evaluations from these bodies have had very little impact on laboratory practice in the UK, and we see no evidence to suggest that this situation will change in the near future.
21. **We therefore recommend the establishment of a new UK-wide body, or reorganisation of one of the existing bodies, to provide a single comprehensive function for horizon-scanning and evaluation of new laboratory investigations.** Such body should also advise on areas where research is needed to resolve the uncertainties explained above. It should work towards the development of an authoritative guide to the appropriate use of all laboratory investigations, in a way analogous to the service currently provided for drugs by the 'British National Formulary'.
22. This area was the subject of a recent conference of diagnostic specialists(5). The list of recommendations of that conference is attached as Appendix A. Very similar conclusions were

independently recently reached by the Science Council in an almost simultaneous report(6). We are not yet aware of any formal Government response to either of these reports.

Translation

23. In the absence of a national system of evaluation, discussed above, the implementation of new diagnostic techniques is left to local evaluation and decision-making.
24. In the NHS, the provision of laboratory diagnostics is usually based on a fixed annual budget, which may (or may not) be sensitive to major changes in demand, but which typically does not include efficient mechanisms for funding new developments.
25. Many of the new developments in genomics are dependent on investment in costly machines and extensive training. The rapid rate of progress in technology means that almost as soon as new equipment is acquired it is necessary to start planning for its next replacement. This is a difficult concept for many NHS managers to accept.
26. To deal with the data handling, storage and security, it will also be necessary for NHS IT schemes to invest in sufficient server capacity (as well as staff), PCs, equipment interfaces, and sufficiently sophisticated Laboratory Information Management Systems (LIMS).
27. Hence investment is an obvious requirement if the potential of genomic medicine is to be translated into improved diagnostic services for patients. But the availability of the necessary investment and facilities is being curtailed by the 'silo' structure of funding in the NHS, and by a historical under-resourcing of pathology services. These problems are clearly identified and analysed in Lord Carter's recent report on the provision of pathology services in England (7), but solutions to these problems have not yet been implemented.
28. Current Department of Health policy is to devolve decision-making to a local level as far as is possible. The arguments for this policy have been well presented and are understood. But in the present context of genome-based diagnostics, to fund any new development at local level demands that someone locally has the time and energy to draw up a well-argued business plan. This is difficult and time-consuming, for reasons given above.
29. To replicate such a time-consuming bidding and evaluation process in every hospital is an extremely inefficient use of staff time and will generate inequalities in provision across the UK (i.e. 'Postcode diagnostics')..
30. However, the more likely outcome is that local proposals to implement new developments are not made at all. This is because of the difficulty of the process and the lack of evidence of patient benefit explained above; because NHS staff rarely have the time to undertake this sort of work; and because the size of the investment needed is widely perceived as being unlikely to be available within the 'silo' budgets of an individual Trust.
31. The logical route to implementation is for local hospital units to co-operate and form collaborative networks, much as was recommended by Lord Carter (7).
32. Unfortunately, the Department of Health (England)'s current policy of 'contestability' and the establishment of independent Foundation Trusts have encouraged a climate of competition between NHS Trusts, making such collaboration difficult or impossible.
33. **We therefore suggest that the efficient implementation of new genomic-based diagnostic approaches will demand central direction and funding for the establishment of specialist laboratories to provide these services**, on a model similar to that of the current National Commissioning Group (formerly NSCAG). This nationwide approach has already been adopted in the comparatively small arena of 'conventional' inherited disease, as is explained in the separate Submission of Evidence by the Joint Committee on Medical Genetics; but this system is far too

small to address the issues raised by the involvement of genome-based diagnostics in much commoner diseases.

34. We suggest that if this model is adopted there will remain a need for local expertise in the requesting and interpretation of new investigations, but that the technical provision of the tests will be undertaken, as Lord Carter recommended, on a network basis.
35. An alternative would be to leave provision to the private sector. But the need for individual NHS units to evaluate what services should be purchased would remain; so most of the problems outlined above would not be resolved. In the absence of central guidance, commercial provision would raise the possibility of inappropriate local decisions being made on the basis of commercial pressure rather than on the basis of scientific evidence. The provision of individual investigations by a commercial organisation would presumably be limited to tests that are commercially attractive, thereby potentially disadvantaging patients with rare diseases.

Training and Education

36. In order to take advantage of future developments in Genomic and Molecular medicine it will be necessary to ensure that current medical practitioners as well as the next generation are educated in this subject. The RCPATH is exploring how genomic and molecular pathology might be brought into the curricula for trainee pathologists and Clinical Scientists. The intention is to have core level of understanding for all pathologists and more advanced training and curricula for specialists; but providing this training on such a large scale is proving difficult.
37. There is a need to train staff who specialise in medical bioinformatics, to support those staff carrying out testing and those staff receiving results.
38. There is also a need to improve training in molecular genetics in the undergraduate medical curriculum. That area is the responsibility of the General Medical Council.
39. In the UK a mere five individuals are qualified in the application of genomics to 'acquired' disease, in distinction to diseases that are conventionally regarded as 'inherited'. Only one of these is in NHS employment as a Genetic Pathologist (in Cardiff), the rest being employed in senior academic posts or in one case as a Clinical Geneticist. Of these five individuals, four are cancer geneticists.
40. There are nominally just two Genetic Pathology Specialist Registrar posts in the UK. In the absence of any consultant posts to absorb trainees the RCPATH has recently had to conclude that the specialty should be suspended in terms of training. This is surely a bizarre development, driven by the reality of short-term economics rather than any logical assessment of future need.

References

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4. McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. Reporting recommendations for tumor marker prognostic studies. J Clin Oncol 2005; 23 (36): 9067.
5. The evaluation of diagnostic laboratory tests and complex biomarkers. Summary of a Diagnostic Summit, 14 - 15 January 2008. Royal College of Pathologists and the PHG Foundation: 2008. At: <http://www.rcpath.org/resources/pdf/DiagnosticSummitFinalreport08.pdf>
6. Integration and Implementation of Diagnostic Technologies in Healthcare. A report from the Science Council's Science in Health Group. The Science Council: 2008. At: http://www.sciencecouncil.org/documents/diagnostics_execsummary.pdf
7. Report of the review of NHS pathology services in England (chaired by Lord Carter of Coles). Commissioned by the Department of Health, England: 2006. At: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4137606

Appendix A

Recommendations from the report of a Diagnostic Summit on “The evaluation of diagnostic tests and complex biomarkers”, hosted by the Royal College of Pathologists and the PHG Foundation, held in Cambridge on 14-15 January 2008.

The full text is available at: <http://www.rcpath.org/resources/pdf/DiagnosticSummitFinalreport08.pdf>

Recommendations

1. A new body should be established to ensure the evaluation of laboratory diagnostic tests and the creation of a database of new and existing laboratory tests.
2. This body might be established de novo along the lines of the UK Genetic Testing Network, or the responsibility could be placed with existing professional societies such as the Royal College of Pathologists, the Association of Clinical Biochemistry or the Academy of Royal Colleges.
3. A publically available database of existing and new diagnostic laboratory tests should be set up containing evidence, or explicitly the lack of it, for the validity and utility of clinical laboratory tests.
4. Where a test evaluation has already been carried out and published by an appropriate agency it should be linked to the database.
5. Where evidence is missing for existing tests, particularly evidence of clinical validity and utility, consideration should be given to funding the necessary studies.
6. Policy makers and all stakeholders should be encouraged to address issues around funding and gathering the necessary evidence for the clinical evaluation of new and complex biomarkers, and should consider the establishment of private-public partnerships to increase industry involvement.
7. An independent expert body should be responsible for the evaluation of the evidence for test performance and making recommendations about clinical use.
8. Commissioners and health care professionals should be encouraged to use only those tests where sufficient evidence of clinical performance exists.
9. Statutory regulators should be empowered to require that evidence (or lack of evidence) relating to test performance be placed in the public domain.
10. A more responsive and proportionate risk assessment during pre-market approval is needed to ensure patient safety.

Please note that very similar recommendations were developed almost simultaneously but quite independently by a working group of the Science Council.

A summary of the Science Council report, including its recommendations, is available at http://www.sciencecouncil.org/documents/diagnostics_execsummary.pdf