

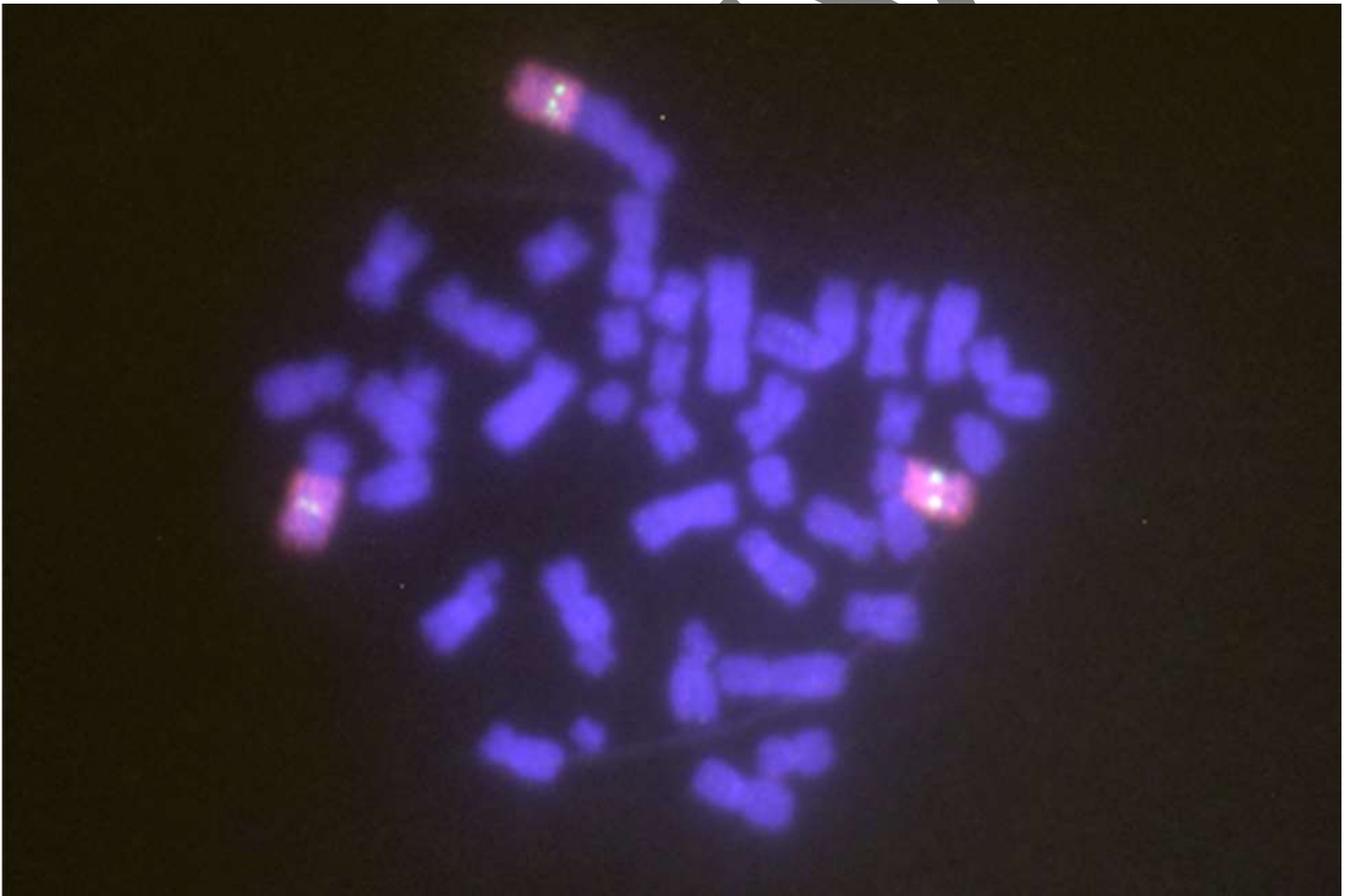


The Royal College of Pathologists
Pathology: the science behind the cure

**The future provision of molecular diagnostic services
for acquired disease in the UK**

October 2010

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Contents

| | |
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| Composition of the Committee | 2 |
| Summary of main findings and recommendations | 3 |
| Remit and definitions | 3 |
| Background..... | 4 |
| Current state of molecular diagnostics in the UK..... | 6 |
| Imminent developments in molecular testing..... | 10 |
| Research and biomarker discovery | 12 |
| Identifying the current issues | 12 |
| Overall recommendations | 13 |
| Recommended short-term changes | 18 |
| Concluding remarks | 20 |

Composition of the Committee

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Summary of main findings and recommendations

- Large numbers of new molecular tests are anticipated gradually to become available and this tendency will increase such that molecular tests are the norm; tests will be used for many purposes, such as predicting and assessing response to targeted treatments in cancer.
- Molecular diagnostic tests (outside the context of disease susceptibility) are currently provided patchily in the UK.
- Haematology and virology are leading the molecular diagnostics field.
- A single national body should approve molecular tests, educate the healthcare workforce and provide leadership; this has to be a dynamic and continuing process.
- Encouraging progress is being made to train the medical and scientific workforce to deal with these developments, but there are challenges in training sufficient, appropriately skilled scientists, particularly to undertake large-scale molecular testing of cancers and to report test results.
- NHS funds for molecular testing should be an explicit part of clinical budgets for patient care, rather than 'special' or 'separate'; this can lead to cost-recovery for molecular diagnostics from savings on targeted treatments.
- Molecular diagnostic testing should be undertaken in regional centres or larger laboratories.
- Explicit integration of molecular testing should be mandatory in all Trust business case development for new cancer and infection services.
- Greater local integration of clinical and pathology services within the NHS is required to provide for coordination of tests, access to equipment and sharing of expertise.
- Consideration should be given to establishing a new molecular oncology sub-department and to training some scientists in molecular genetics and basic histopathology.
- The trend towards outsourcing of NHS pathology must be considered, since molecular diagnostic testing is a prime candidate for this form of delivery.
- Regional molecular diagnostics facilities should be set up outside local hospital management, ideally based on partnership between the NHS, University and perhaps other parties.

Remit and definitions

The Committee was asked by the President of The Royal College of Pathologists to consider the future of molecular diagnostics in the United Kingdom, without any specific, pre-determined restrictions.

We have primarily defined 'molecular diagnostics' as DNA- or RNA-based tests used to classify disease, to predict outcome, to predict response to treatment or toxicity, to monitor disease burden, to identify pathogens or to perform any other similar function.

We have also considered protein analysis by Western blot or proteomic methods to be part of molecular diagnostics.

Owing to their relatively widespread current use and history, immunohistochemistry, immunocytochemistry and immunophenotyping by flow cytometry are considered separately. In-situ hybridisation techniques such as FISH (fluorescence in-situ hybridisation) and CISH (chromogenic in-situ hybridisation) have methodological and reporting similarities to immunohistochemistry, but are regarded as molecular diagnostic tests, because they are DNA-based.

Most molecular diagnostic tests considered herein involve acquired (somatic) changes or tests to detect pathogens. We have not, in general, specifically considered molecular tests that involve analysis of constitutional DNA (sometimes called 'germline' tests), since these are primarily used to predict disease susceptibility. On occasion, tests on constitutional DNA have been considered, for example where they are used to predict treatment toxicity. Germline testing and its delivery provide their own challenges, but can generally be delivered, we believe, alongside molecular diagnostics.

Background

Molecular biological knowledge about the underlying causes of cancer and other diseases has been increasing for over 30 years. We now face the prospect of molecular tests becoming widespread in disease management, a process that is partly driven by developments within the pharmaceutical industry of therapies that are targeted to specific molecules and to specific, disease-causing changes in those molecules. In addition, the development of new technologies promises to make tests easier to perform and/or less expensive. Although molecular diagnostics is still relatively limited in the UK, it is prudent at this time to plan for a large increase in its use. The provision of molecular tests is highly likely to involve individuals trained under the auspices of The Royal College of Pathologists.

Training for scientists working in pathology is currently undergoing a large reorganisation, principally under the Modernising Scientific Careers (MSC) programme. Other, smaller-scale changes are planned for the medical curricula in pathology. It is not our role to deconstruct programmes such as MSC. We note, however, that achieving the right skill mix in all pathological disciplines will be difficult. MSC is encouraging in that it intends to provide trainees with a broad basic knowledge and to allow flexibility in training and career paths. However, we are concerned that the training involved in MSC may be excessive in some situations: it must ensure on the one hand that highly-skilled scientists emerging from university do not have to undergo very extensive training before becoming registered and eligible to work as clinical scientists, yet the ability to deliver high-throughput, routine molecular analyses is not hampered by having too many trainees with unnecessary qualifications or skills.

For medical staff, there is an urgent need to address the decline of basic science content in the undergraduate curriculum. This has already begun to impact on the level of molecular knowledge of specialist registrars in haematology and histopathology. Lack of attention given to the advances in molecular medicine and the impact these will have on future clinical practice will create a barrier to change within the clinical community, if it is not reversed quickly. It will therefore be pivotal to include training modules in molecular diagnostics in specialist training curricula and college examinations.

Previous reports that have included delivery of molecular diagnostics

There have been several previous reports on pathology services in the UK and on genetic testing in the context of inherited disorders. There have been relatively few reports into molecular diagnostics. Two of the most relevant are the following:

- i) Carter Reports 1 and 2: These reports addressed the future of pathology delivery in the UK. They made several specific recommendations, including the development of pathology networks and the encouragement of 'stand-alone' providers. The Carter Committee, however, paid only limited attention to molecular diagnostics. Carter's recommendations included the formation of pathology networks and introduction of greater competition into

pathology, including private sector providers. Trials of these recommendations are in progress and these may become the norm, with profound consequences

- ii) House of Lords' Genomic Medicine Committee: This relatively recent report foresaw a great expansion of molecular testing, both in the germ line and for acquired disorders. It recommended that The National Institute for Health and Clinical Excellence (NICE) should approve molecular tests. The report generally supported some of Carter's recommendations, and also made its own recommendations regarding the need for regulation of direct-to-consumer tests.

Bodies involved in providing advice to and overseeing molecular tests and laboratories

There are multiple bodies with roles and interests in molecular testing. In addition, of course, governmental bodies, not least the Department of Health, have central roles. These bodies include the following:

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| RCPATH | The Royal College of Pathologists, oversees medical and scientific training and education |
| GenCAG | Genetics Commissioning Advisory Group, provides national overview of genetics in healthcare delivery |
| UKGTN | UK Genetic Testing Network, advises the NHS on testing for inherited disorders and is beginning to consider molecular diagnostics |
| GIG | Genetics Interest Group, alliance of charities with relevance to genetic testing |
| UK NEQAS | National External Quality Assurance Scheme, sets standards for molecular laboratories |
| QCMD | Quality Control in Molecular Diagnostics, sets standards in Europe, currently mainly for infectious diseases. |
| CPA | Clinical Pathology Accreditation (UK) Ltd, approves molecular laboratories that meet set standards |
| OSCHR | Office for Strategic Coordination of Health Research, part of the National Institute for Health Research, aims to improve translation of research into practice |
| NGEDC | National Genetics Education and Development Centre |
| NICE | National Institute for Health and Clinical Excellence, starting to consider companion diagnostic tests alongside approval of new therapies, and providing guidance such as <i>Improving Outcomes Guidance (IOG) on Management of Haematological Cancers, 2003</i> |
| NCAT | National Cancer Action Team, auditing implementation of NICE IOGs and performing peer reviews of cancer services |
| HTA | Human Tissue Authority, for blood nucleic acid testing (NAT) |
| MHRA | Medicines and Healthcare products Regulatory Agency, for blood NAT |
| HPA | Health Protection Agency, for example through the Regional Microbiology Network Molecular Diagnostics Forum |
| SAC on Safety of Blood, Tissues and Other Organs | |
| Clinical Molecular Genetics Society | |
| Association of Clinical Cytogeneticists | |
| JCMG | Joint Committee for Medical Genetics, which it aims to provide a single voice on medical genetics issues, with a focus on inherited rather than acquired disorders |
| GMC | General Medical Council, involved in postgraduate medical education and training. |

Current state of molecular diagnostics in the UK

Training programmes

Relevant training in molecular diagnostics is currently acquired patchily or on an *ad hoc* basis. Examples include:

- exposure to local initiatives in molecular diagnostics
- scientific training in clinical molecular genetics and/or cytogenetics
- academic experience, for example during a PhD or MD degree
- secondment/travel grants to visit laboratories where specific skill sets can be acquired
- a critical review of a molecular assay or a case report, as part of an FRCPATH portfolio.

Currently, clinical and scientific training programmes in pathology are distinct for some specialties and overlapping for others. At one extreme, histopathology training (apart from cytology) is essentially for medically qualified individuals and few scientists are in senior positions in this specialty. At the other extreme, molecular geneticists are almost all scientists and medically qualified individuals hold almost no senior posts. MSC aims to provide a broader range of experience for scientific pathologists. There are plans to introduce specific medical training in molecular diagnostics as part of higher specialist training for histopathology. However, the availability of appropriate trainers and/or training departments in the field may limit this. Similarly, whilst there are elements of molecular diagnostics in MSC, the fact that it does not exist as a discrete sub-specialty means that there may be a shortage of true specialists in the field, who, for example, have skills in both tumour morphology and molecular tests. As is the case for clinical training, the lack of appropriate trainers and/or training departments may constrain the ability of MSC in producing individuals with appropriate experience for molecular diagnostics.

As in many aspects of molecular diagnostics, haematology is a specialty that is leading the way and, we believe, providing an example for some other specialties to follow. In medical training for haematology, laboratory aspects are the first out of the four subject matters of the specialist curriculum and registrars are expected to acquire:

- an understanding of haematological laboratory practice
- the diagnostic techniques required in the practice of haematology
- some management skills required in the running of the haematology laboratory.

However, even here, no special consideration is given for evolution of traditional laboratory techniques away from 'traditional' techniques to DNA/RNA based methods. The haematology specialist training does not include a module on molecular diagnostics. There are difficulties in updating curricula to keep pace with a technology that is developing exceptionally rapidly.

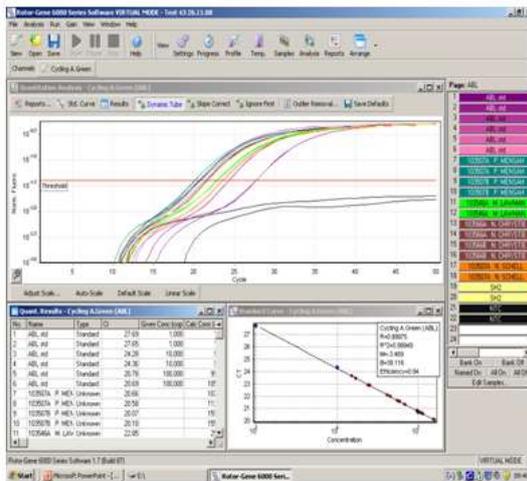
What tests are performed?

Without a full national survey, this cannot be a comprehensive list, but the most common tests and technologies are covered.

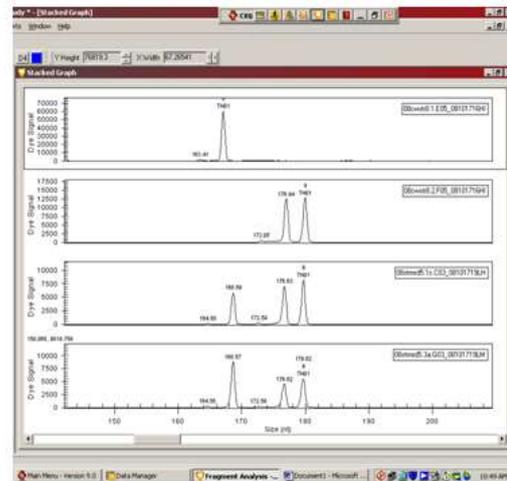
Haematology

Karyotyping and FISH (for translocations, aneusomies, etc), supplemented by diagnostic PCR (polymerase chain reaction) (for example, post-transplant), real-time reverse PCR for monitoring of minimal residual disease (MRD), sequencing for mutation detection and microarray-based copy number analysis. See figures below.

MRD monitoring by Real-time PCR



Post-transplant monitoring by T-cell specific STR chimerism analysis



Solid tumours

- FISH for HER2 (human epidermal growth factor receptor 2) to choose therapy in selected breast and gastric cancer cases
- Molecular testing for EGFR (epidermal growth factor receptor) and *KRAS* to choose therapy in lung and metastatic colorectal cancers
- Molecular testing for *BRAF* to choose therapy in melanoma
- *KIT* sequence testing in gastrointestinal stromal tumours (GISTs) as prediction of therapy response
- FISH for prognostic classification of neuroblastomas.

Microbiology and virology

Bacteriology/mycology is mostly still culture-based because of the need to do sensitivity testing, although some regional services have been introduced (for example, meningococcal PCR in Manchester). Chlamydia trachomatis is a major diagnostics service delivered in all regions using commercial molecular assays. There is also increasing commercial interest in the development of assays for microorganisms associated with hospital-acquired infection; cost, however is a significant barrier to their introduction and highlights a current lack of integration where cost reductions at ward level are balanced against incurred costs in the laboratory. Through necessity, virology has been a field-leader in essentially moving to molecular diagnostics, mostly real-time, for virus detection and load assessment. Mutational analysis is performed in cases such as HIV-resistance testing.

Where is current molecular diagnostic activity undertaken?

Service provision is currently patchy in terms of what tests are performed and who performs them. Activities are often decided locally and hence are subject to the influences of infrastructure availability, funding (core, NHS Biomedical Research Centres, academic research, commercial, etc.) and interests (clinical trials, etc.). Cytogenetic tests on cancers may be performed by cytogeneticists, haematologists or histopathologists. Haematologists undertake molecular tests in blood malignancies, and sequence-based molecular tests in the common cancers are increasingly being undertaken by molecular geneticists, although they may also be performed by other groups including the private sector. Virology laboratories have acquired the expertise and, following the response to the influenza pandemic, the equipment to deliver an increasing repertoire of high throughput tests and have become hubs for developing molecular testing for infectious diseases.

While setting up parallel hubs in bacteriology might seem desirable, it is probably unaffordable. The alignment of virology services within a microbiology setting or within a molecular hub is an obvious conundrum. In general, the management of outsourcing molecular based services to hub providers will create both difficulties and opportunities for the future that will need a reassessment of IT integration.

In addition to the NHS, there is a significant and increasing private sector presence in molecular diagnostics. This includes 'embedded' privatised laboratories and stand-alone laboratories. Pressure for increased private sector involvement is likely to grow. Whether this will also prove cost-effective is unclear.

The seed pool of knowledge underpinning molecular medicine, the rapid pace of technological developments and the advent of new pharmacological interventions will blur the edges of service and translational development for the immediate and foreseeable future. This means a much closer working relationship between university, industry and health service scientists and medical staff is very likely and should be factored into any workforce planning and skill-mix assumptions.

Approving and purchasing tests

There is currently no agreed list of useful molecular tests, although companion diagnostic tests are beginning to be approved by NICE. However, this approval is not mandatory and can be very slow, and it does not extend to tests outside this category. Not unrelated to this problem is the difficulty that NHS purchasers face in approving tests locally. Although some molecular diagnostic tests are performed as part of blanket funding for the management of particular disease types, only a few are funded specifically and many others are not funded at all. Consequently, the introduction of a new test is often 'unofficial'; it may save money, be funded from a budgetary surplus (that is, current under-spending), be funded from local sources or even be provided by a department running a deficit to pay for the test.

Increasingly, there will be a need to dovetail molecular diagnostics with clinical management and drug selection decisions in preparing business cases. Ideally, these should arise from transitional clinical trials to supply appropriate evidence base and validation data.

Ordering and reporting tests

In principle, any clinician can request a test. In practice, oncologists (especially medical), and their counterparts in haematology, comprise one of the groups are most likely to order a test. In haematology, decisions to order a molecular test are often made in the multidisciplinary team meeting (MDT), and tumour site-specific group (TSSG) guidelines on molecular testing might be available. Medical oncology and haematology are traditionally academically strong, and the awareness of tests is relatively good. However, there is undoubtedly a stronger desire from these clinicians for predictive marker tests than for tests to provide prognostic information or classify disease.

This situation contrasts with more traditional diagnostic tests, such as cancer morphology or immunohistochemistry, which are more likely to be undertaken for reasons of prognosis or classification. These types of test are most likely to be performed by histopathologists on their own initiative, as part of their diagnostic remit. Over time, molecular tests are increasingly likely to be added to the histopathologist's repertoire (as is already the case in haematology and virology). An important issue is how this will be performed in practice, given that histopathology is currently less centralised than most other pathological specialties.

On the one hand, the awareness of molecular tests among histopathologists is probably poorer than among oncologists and haematologists. On the other hand, there seems a reluctance by oncologists – undoubtedly often for good reason – to modulate the aggressiveness of solid tumour therapy in the face of prognostic assessment, in distinction to successful use of this strategy in haematological malignancies.

Whoever orders tests, in most cases, the precise nature of the molecular methods used are of little importance to the clinician and may be largely unknown by all but the laboratory. In virology, for example, molecular services are pivotal to and ordered by many general and specialist clinical services, for example post-transplant monitoring for infection, respiratory viral diagnosis and HIV mutational analysis. It will become increasingly important, nevertheless, that there exist doctors or scientists at the interface between the laboratory and clinic who can link the test result to the implications for patient management. These individuals will play critical roles in MDTs and in discussions with those who order and act on test results.

Unmet demand or over-supply?

Matching supply and demand in what are the early days of molecular diagnostics is inherently difficult, especially in the absence of statutory approval and recommendations. An interesting factor is the role of patient pressure. This is likely to be greatest for companion diagnostics, where effects are largest and issues are relatively simple ones of 'to treat or not to treat'. The positive and negative consequences of medical consumerism and patient pressure are well established; we remark only that patient pressure for available molecular diagnostics is likely to increase and, appropriately applied and modulated, this is welcome.

The supply of molecular diagnostics has often developed in academia and in clinical departments with a strong research and/or method development interests. The fact that there has been very little co-development of services or resource sharing has made this process somewhat inefficient. Funding decisions are often taken by commissioners with no molecular backgrounds. Molecular diagnostics, by its nature, is expensive and needs coordination. This scenario makes it attractive for new providers to enter the UK diagnostics market. Their costs might be less than existing laboratories, owing to greater availability of investment capital, newer technologies, higher throughput and lower overheads. In addition, they may employ staff with less formal training than those currently employed or envisaged under MSC. There is evidence, however, that owing to uncertainty over future demand, new providers will enter primarily to take over existing pathology services, and then only offer new molecular tests where there is expectation of profit.

International dimension

We believe that an international comparison would be of great benefit when planning UK services and warrants a more detailed investigation for the final report, although in all cases, the underlying constraint lies in the system of healthcare funding. In the Netherlands, for example, molecular assays are regarded as income-generating services, because of the cost recovery model, while in the UK they are often seen as loss leaders. This reflects the need to integrate clinical use and outcome with costs.

Increasingly, international-level testing is offered and performed although, for reasons of logistics and turnaround time, this is unlikely to be appropriate for specialist or non-urgent molecular tests. Nevertheless, it would be surprising if funders were not considering the supply of services such as routine tumour morphology outside the West and there are likely to be pressures for similar provision in molecular diagnostics.

The legalities of tendering linked to European Union directives are explicit and will be pivotal in bringing about the formation of core units. In reality, most molecular services will eventually require European tenders, perhaps within one to two years. Services may need to be set up on five-year cycles. For molecular services, each technology needs directing and steering by an appropriately trained scientist, with an appropriate training and background to integrate service needs with the chemistries and technologies available. Open competition for delivery of these services is at the core of legal procurement. Where this impacts on reagents for molecular diagnostics, then revalidation of tests becomes a very significant challenge – underpinning the need for staff and bio-archiving. Commercial validation of new assays is probably even more difficult for companies who will increasingly need access to ethically held BioArchives. There may be a need for a linked

national (and maybe international) archive to underpin molecular diagnostic services and Cancer Research UK are making plans, in collaboration with others, to develop such resources.

Is haematology the model for future developments in solid tumours?

Haematology is in the vanguard of molecular diagnostics. Reasons include:

- readily obtained and analysed high-quality samples
- relatively long-established, large-scale genetic changes with prognostic significance
- dual laboratory and clinical training of haematologists (the same individuals can order and run tests)
- scientists with diagnostic and molecular skills
- close links to longstanding, publicly-funded clinical trials.

NICE's *IOG Guidance on the Diagnosis and Management of Haematological Malignancies* and the National Cancer Team Audit states the following:

“Key features of the above guidance and audit can be summarized as follows:

- All haematological malignancy should be reviewed by specialists in the diagnosis of haematological malignancy, and who are integrated members of the MDT.
- There should be network/supra-network/agreed guidelines about which specialist tests should be carried out, when and where; as well as protocols about the choice and sequence of tests; these should be coordinated within the designated haemato-pathology service.
- Results of all tests should be brought together and given an overall integrated interpretation and diagnostic opinion by designated specialists in the diagnosis of haematological conditions and signed off in the form of an ‘integrated report’. This should incorporate the results of all the pathological diagnostic techniques used in that patients case (immunophenotyping, molecular genetics, cytogenetics and histological morphology).”

Aspects of this success could be extended into the setting of solid tumours, although there are evident constraints, such as the impracticality of extending dual accreditation to specialties such as histopathology.

Imminent developments in molecular testing

Technological drive

One factor cited in the reluctance to offer molecular diagnostic tests has been the problem of always playing catch-up in terms of technology. Despite this contention, in reality most current tests are relatively ‘low-tech’ and do not require exceptional capital investment. It is likely that technical advances will drive areas such as:

- higher throughput of samples
- ability to test multiple targets in one assay
- novel assays, for example based on serum and other fluids and perhaps involving RNA and protein.

What is less certain is how many of these methods will lead to clinically useful tests. It is difficult – and probably unnecessary – for the molecular diagnostics service to be just behind the forefront of technological development, or even to anticipate future developments in all but the very near term, owing to the uncertainty intrinsic to the development of new methods and tests. How useful, for example, is the NHS National Horizon Scanning Centre for such tests?

Scientific discovery

The pace of useful and reproducible biomarker discovery has been relatively rapid in historical terms, but there is no avalanche of tests. There may well be an increase in the discovery of biomarkers for specific targeted therapies, as more such agents are developed and attitudes continue to move towards patient selection rather than comprehensive use of such agents. Outside this category, technological development will probably cause a steady increase in biomarker discovery, but we expect that other factors – such as the need for large data sets and the currently limited research funding – will constrain this to a manageable pace from the perspective of service delivery.

Changes in careers

Clearly, there is a gradual long-term trend towards a greater component of molecular knowledge in training curricula. It is arguable whether this trend will, of its own accord, be sufficient to supply the expected requirement for molecular diagnostic expertise, but this is clearly the planned outcome for MSC and some of the changes in medical training (see above).

Local initiatives in service provision

Some local pathology divisions, such as Bart's and the London, Sheffield, Bristol and Belfast, have set up Institutes of Pathology, with partial integration of service provision across disciplines. These initiatives must be seen as examples for other centres to follow. Whether capital is available for other centres to follow suit is, however, unclear in the short term. In Belfast, for example, a virtual molecular pathology service has been formed, integrating medical genetics, virology, haematology, histopathology and histocompatibility and immunogenetics (H&I). Formal links with Queen's University Belfast have also been established. A four-hub model of (a) extraction, (b) archive – with local agreed funding (c) q-RT-PCR and (d) complex services (sequencing, fragment analysis, mass spectroscopy) is the working model and is over-seen by an operational group and a Molecular Board. The Board has representatives from all disciplines and takes strategic decisions.

Concentration/centralisation of service provision

Regionalisation of some pathology services already exists and is being formalised in cases such as the Leeds Haematological Malignancy Diagnostic Service. There are probably limits to this process if close links between pathologists and clinicians are valued, but this is a long-term trend that is likely to continue, probably more rapidly given the current financial situation. Regionalisation of specialist pathology services is implicit within the Carter Report and is strongly recommended by the NICE IOG on haematological malignancies.

Private providers

As noted above, partly derived from the Carter Report, there are considerable pressures from Government and the private sector itself for pathology to be outsourced or subjected to 'partnership' arrangements. Serco's involvement with the Guy's and St Thomas' NHS Foundation Trust is an example of the latter. It is difficult to see this trend being reversed, and indeed it may be extended, even to international outsourcing of tests. QIP initiatives are being picked up in the commercial world and there are clear funding initiatives aimed at industry to develop new and innovative platforms, such as KTP/i4i. A current comparison between the costs of tests, such as KRAS mutation screening, in the public and private sectors shows that current private providers do not necessarily provide better value for money, although neither public nor private sector currently has the benefits of economies of scale derived from high-throughput analysis.

Research and biomarker discovery

To date, the list of potential biomarkers for cancer and other diseases is very large, but few such markers are used in practice. The underlying reason is principally the difficulties in sorting wheat from chaff. Even powerful biomarkers, such as wildtype KRAS or for anti-EGFR therapy, have largely been chanced upon by accident.

In general, biomarker discovery has been typified by:

- erratic or opportunistic rather than systematic studies
- assessment of small numbers of markers, hence failure to identify primary associations
- technical problems in collecting and analysing samples such as urine and stool
- failure of replication of promising results
- failure of funding
- inability to collect sufficient samples to empower studies.

In the future, we believe that a distinction needs to be drawn between biomarkers for molecularly targeted therapies, and more general markers of early detection, disease burden, prognosis and response to non-targeted therapies.

For targeted therapies, the increasing move towards pharmaceutical industry-funded biomarker discovery alongside agent development and testing should be encouraged. A 'stick' rather than 'carrot' approach is most suitable here.

For other biomarkers, recent *in vitro* developments should be encouraged. Examples include synthetic lethal screens that have highlighted, for example, roles for PARP inhibitors in BRCA-mutant cancers. Additional funding needs to be provided – possibly by a consortium of Government, pharmaceutical industry and research charities through a body such as the Office for Strategic Coordination of Health Research – to provide a full, coordinated programme of prospective sample and data collection (for example, from clinical trials), to include blood, serum, tumour and other materials as appropriate. The proposals from Cancer Research UK are welcome in this regard. However, this activity should be linked to general biomarker discovery programmes based on these samples.

Identifying the current issues

1. Training programmes

- Training of medics and/or scientists in pathology must reflect the anticipated increase in molecular diagnostics
- Should this training be general, or restricted (apart from the basics) to a minority of those who plan to specialise in and supervise molecular work?
- What is the best balance between medics and scientists, especially in the light of cost issues?
- How can the existing expertise in molecular methods – mostly in NHS genetics laboratories – be best utilised?
- Should skills transferrable across pathological specialties be established using a 'cross-cutting' training programme?

2. Practical issues in undertaking tests

- Should regional centres of molecular pathology be established?
- Should local, integrated institutes of pathology be established?

- Who should report the results of tests?
- Who should interpret the results of tests?
- Who should decide on the change in management owing to tests?
- Is there a need for a changed laboratory approval?

Turn-around times, test volumes and cost will be key in establishing the appropriate model.

3. Regulation, funding, purchasing and ordering tests

- Should a 'Molecular NICE' (or even a 'Pathology NICE') be set up?
- How can the number of bodies approving and advising on tests be streamlined? Does The Royal College of Pathologists have a role in approving tests?
- Should funding for molecular diagnostics be ringfenced, or part of general clinical budgets for care of patients with a particular disease?
- Should tests be requested by oncologists, histopathologists or the MDT?

4. Private provision

- What factors should be considered when assessing private sector providers?
- How would histopathology departments interface with the private provider, or would pathology be transferred *en masse*?
- What training and accreditation is required by those running and working in private laboratories?
- What role does the Royal College have in approving private laboratories?

5. International comparison

- How is molecular pathology performed in other countries, in terms of scope and method of delivery?
- Is there a successful model system that could be adopted in the UK?

6. What are we trying to achieve?

- Appropriate tests (excellent evidence for efficacy, cost:benefit well-defined).
- Widespread accessibility of tests.
- Delivery within an appropriate budget.
- Consistency across UK.
- Equality across patients.
- Value for money (appropriately defined) with a suitable quality assurance and audit regime.
- High quality tests (rapid, accurate results).
- Happy, competent and appropriately skilled staff.
- Flexibility and investment for future demand.

Overall recommendations

The Committee considered various models. The following is proposed as that best able to achieve the stated aims.

1. Which tests should be available?

Ensure a powerful 'Molecular NICE'

There should be national decisions made rapidly (and reviewed regularly) on which tests are appropriate. All available research evidence and submissions from interested parties (see above) should be considered. Clear guidelines on what constitutes an appropriate test should be decided, to include both markers that change management (predictive, classifier or diagnostic) and those that indicate more generally (e.g. for prognosis). Ideally, 'Molecular NICE' should be the only national body that has quasi-legal power to decide on test availability. The bar must be set at an appropriate level for test performance. Given that some 'traditional' pathological tests are expensive and have poor predictive value, these should be considered alongside the new tests. It is highly desirable that where several alternative tests are available to provide the same result, reports are commissioned (repeatedly and rapidly) so that the best method or 'kit' can be provided on a national scale, with benefits of consistency and value for money. It must be decided whether non-approved tests should be outlawed or available to those outside the public sector. In principle, 'Molecular NICE' could form part of a broader 'Pathology NICE'. It should link to the National Laboratory Medicine Catalogue. The continuation of the technical and information explosion that has now begun will require a more rapid approach to test evaluation to underpin a 'Molecular NICE'. This will involve even closer partnerships between the NHS, academia and the commercial sector. The current Department of Health research governance framework will need to be more fit for purpose than currently constituted, and more collegiate in the broader sense in its functioning.

2. How should tests be funded in the NHS?

Make molecular testing an explicit, but intrinsic component of routine care budgets

Funding for approved tests must be made specifically available within clinical budgets to provide services for cancer, pathology, microbiology, haematology, etc. However, ringfenced funding for individual tests outside these budgets, which appears attractive, in reality may be bureaucratic, encourage cuts when budgets are limited and reduce local decision-making. In short, molecular diagnostics should be funded like other diagnostics and should not be the remit of specialist commissioners, in contrast to genetic tests for inherited conditions. This integrated commissioning will establish the necessary link between diagnostic and clinical budgets, allowing cost-recovery for diagnostics from ineffective or inappropriate drug prescribing and/or other clinical interventions. An example is the risk stratification of acute myeloid leukaemia patients according to NPM1/FLT-3 ITD mutation status (£56) that identifies a subgroup of patients who do not require bone marrow transplantation (£70,000) or the confirmation of PRV by JAK2 mutation analysis (£56), saving costly and imprecise and invasive diagnostic radiology (£1000). Overall, there should be co-development of molecular and clinical services, to share both the benefits and costs of these new services.

3. Who should request tests?

Continue the current system for requesting pathological tests, but promote education

Sample pathways should be redesigned to allow coordinated requesting of all diagnostic tests, including those of a molecular type. NICE IOG and NCAT have rightly recommended the establishment of a central specimen reception. Samples can then be analysed according to defined diagnostic algorithms as specified currently by TSSGs (and in future by 'Molecular NICE') and on the basis of the underlying histology or morphology. This prevents unnecessary requesting or duplication of requesting. In general, we believe that the pathologist testing the sample should be responsible for ordering tests. This does not mean that clinicians managing the patient cannot request tests from the pathologist after discussion in the MDT. Some molecular tests might be 'automatic', performed as standard for all patients, or at least a part of the management algorithms for routine patient care. In infectious diseases, for example, the bulk of tests will be of a simple high

throughput nature with a rapid turnaround, but will also include more complex protocols; it is most likely that both will be triggered by tailored test algorithms designed between the clinics and laboratory. As 'Molecular NICE' will have responsibility for approving tests, it should also have responsibility for educating the appropriate scientific, clinical, nursing and administrative staff about those tests. Local providers must increasingly develop and deliver these assays after careful discussion with the relevant clinical users to ensure widespread knowledge of what tests are available. Ordering systems can be designed around these discussions. User education is recognised in the recent Department of Health paper that called for the molecular education of the medical workforce as a whole.

4. Which organisations should undertake tests?

Concentrate molecular diagnostics, consider independence from local hospital management and encourage investment

Molecular diagnostics should be undertaken in regional centres (for example, one per NHS genetics region). This will raise issues of transport of samples and timely reporting of results, but it is simply impractical to equip all hospitals with staff and equipment to undertake molecular work. Centres also require a sufficiently high throughput of work to justify investment and provide economies of scale.

Performing tests within the NHS has advantages of consistency, continuity of care and collaborative approaches to patient management, at least in principle. There is also considerable molecular expertise within the NHS and associated university departments. However, investment by the NHS may be too limited in the short/medium term to allow molecular diagnostics to reach its full potential in the UK. In addition, regional laboratories would almost certainly benefit from being removed from local hospital/Trust management.

Performing tests outside the NHS continues to be encouraged as part of what appears to be a long-term plan to privatise UK pathology. However, the effects of privatisation/outsourcing, including cost implications, may take several years to become apparent. Some form of public-private partnerships for pathology may be attractive in the short term.

Given that molecular diagnostics is relatively new, it is very unclear as to whether the private sector will be more or less efficient than the public sector, and hence private sector profits (returns on investment) will be uncertain unless such laboratories are hyperfunded by the state.

Rules need to be established as to whether NHS, private or other groups can compete without restrictions for public, private, industrial and international business and offer any technically acceptable test irrespective of its clinical benefits. If this is allowed to be the case, it is possible that there will evolve a rather chaotic market, with multiple mergers, takeovers, start-ups and bankruptcies (as indeed is the case currently in the broader diagnostics sector). In time, it is likely that a few dominant providers will emerge, quite possibly based on those who are already successful in providing 'traditional' pathology services.

5. How should the NHS pathology service be organised to reflect molecular diagnostics?

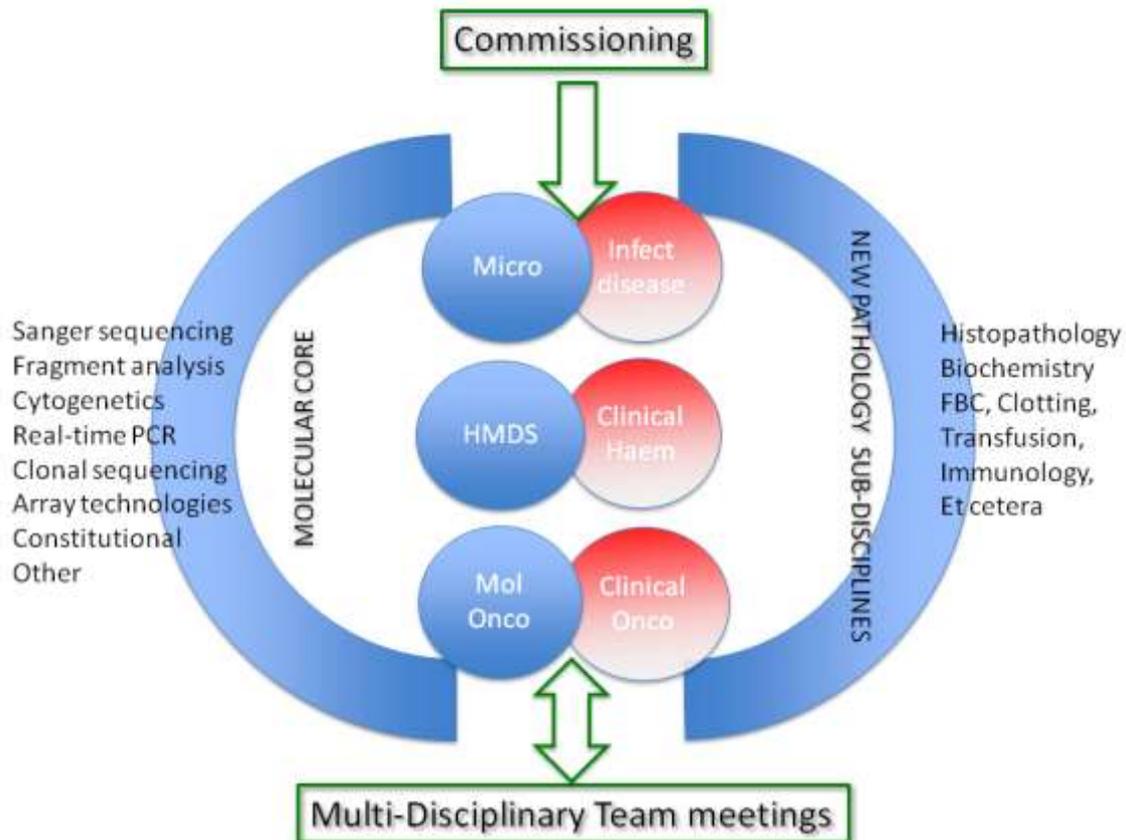
Integrate pathological disciplines for sharing of equipment and expertise, set up core equipment facility and establish a molecular oncology group

These recommendations do not necessarily apply to centres that are not undertaking molecular tests.

- Pathology departments should be located together on one site, so as to allow sharing of equipment, expertise and workforce, to enable coordination of tests on any sample, and to prevent unnecessary duplication of tests.

- In the longer term, pathology departments should be merged.
- Existing staff must be flexible in their areas of work and be willing to work across traditional pathological disciplines; ensure that new skills are acquired, especially in computing and bioinformatics.
- NHS cytogenetics/molecular genetics laboratories should gradually be rearranged such that one group concentrates on testing for Mendelian disorders and other staff are assigned to molecular diagnostics (of cancer). This process may happen naturally if pathology is co-located or merged.
- Groupings of staff are rendered less important by the reorganisation suggested above. Despite this, we suggest the following broad groups are suggested: molecular oncology; microbiology (bacteriology and virology); genetics (germline including pharmacogenetics). Molecular tests that do not fit within these categories would be assigned to one of them as most appropriate. For example, testing of haematological malignancies could be performed in molecular oncology. In addition, there would continue to be histopathology, haematology, biochemistry and the other smaller sub-specialties. (Other molecular tests – in the general sense – that may become available, such as those based on protein, might be performed by biochemistry or immunology as appropriate).
- A critical issue is what sort of person should run the molecular oncology group, which is expected to perform the majority of molecular diagnostics. Ideally, this individual would be medically qualified, with personal, 'hands-on' experience of molecular methods. Histopathology would be the most appropriate discipline. However, the group leader could also be a very senior scientist (e.g. equivalent of grades such as consultant medical practitioner or senior clinical scientist) from histopathology or molecular genetics who has personal experience of both 'traditional' diagnostics performing and supervising molecular tests.

Organisational model for molecular diagnostics

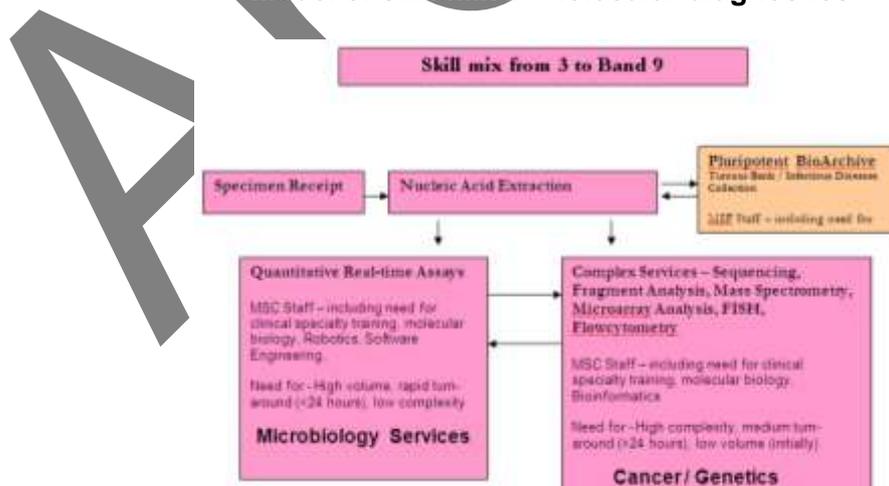


6. How should clinical and scientific training reflect the need for molecular diagnostics?

Provide core knowledge of molecular methods and tests for all, develop a new cadre of molecular diagnosticians, but provide an appropriate skill mix for available posts and roles

- There is no need to train the majority of medically qualified staff in molecular methods, but training should always include knowledge of the availability of tests, their basis and their utility. In many ways, such training should be no different in principle from that currently provided for tests such as immunohistochemistry.
- Higher specialist training in a molecular topic should always be available to clinical trainees in the pathological disciplines. Proper credit should be given for study for research degrees such that this route is not seen as a 'slow track'. Such training should be encouraged – as indeed it generally is already – in other relevant specialties such as oncology.
- There should be the option of fast-track registration to maintain highly specific skill sets learnt elsewhere.
- In its current form, MSC should allow some trainees in haematology, genetics (susceptibility), bacteriology and virology, and the other disciplines to acquire the dual experience required for them to undertake molecular diagnostic tests.
- Trainees in some scientific disciplines will not require more than basic molecular expertise and this should remain.
- MSC should ensure as far as possible matching of training to the skill-mix requirements of the laboratory; we acknowledge that there is a risk of producing over-qualified individuals for the available posts, for example as automation takes an increasing role in molecular testing.
- Public and private laboratories should have the same career structures and training programmes as public laboratories in order to be eligible for publicly funded tests; in either type of organisation, these structures not need be the same as those currently applicable.

Model of skill mix in molecular diagnostics



7. Who should regulate laboratories?

Build on current structure, but simplify to a single body

With the proviso that we urge simplicity wherever possible, we do not envisage major changes in the regulation of laboratories, except to ensure that public and private providers are treated

comparably. Regulation should treat molecular diagnostics in the same manner as other pathological tests. Molecular diagnostics should not be regarded as identical to genetic testing for germline mutations, which has different acceptability in terms of throughput, turnaround, validation and error rates.

8. How should molecular tests be reported?

Results to be reported by expert staff with knowledge of the molecular test and of its implications for patient management at the MDT meeting

Molecular test reports should be issued in the same way as reports for other pathological tests, by specialists with appropriate levels of competence. Wherever possible, some interpretation and implications of the results should be provided alongside the basic result. In general, molecular diagnostic tests should be presented alongside other tests and imaging results at the MDT meeting (or equivalent) and the data should be integrated. It is thus important that a member of the relevant molecular team attends the appropriate MDT meetings. It must be ensured that mechanisms exist so that results can be reported to clinicians from hospitals outside the test centre. Ultimately, the integration of molecular and broader clinical and pathological data – often from multiple sources – should remain the responsibility of the managing clinician.

Recommended short-term changes

The recommendations in the section above are measured and, we believe, achievable in the medium term. However, short-term changes can be made to assist in the development of molecular diagnostics in the UK.

1. Clarify commissioning of molecular tests as an integral part of clinical management

By linking diagnostics to drug budgets, the long-term running costs of integrated molecular diagnostics (estimated at £300,000 for 1.5 million catchment) should be guaranteed from savings on inappropriate prescribing. However, following the NICE IOG 2003, no provisions have been made for setting up molecular laboratories (costed for haematological malignancy diagnostics in 2003 at £230,000 for 1.5 million catchment).

2. Create molecular pathology/molecular diagnostics centres in the NHS

This is a central recommendation.

- The centres should be based regionally, for example at the sites of the Regional Genetics Laboratories (with some rationalisation, for example in Trent).
- They should comprise relevant parts of all the pathological disciplines and individuals at all levels of (including consultants, scientists and trainees with relevant experience).
- There should be some national coordination of their activities.
- They should hold and provide information on tests performed or planned locally.
- They should hold and provide information on tests performed or planned nationally.
- They should have some form of relatively small, dedicated budget.
- They should include staff with a remit to work flexibly across pathological disciplines.
- They should draw up protocols for sample preparation, analysis and reporting.
- They should serve and involve their local district general hospitals (for example, by MDT meetings).

- They should educate broadly and may well be involved in research activities and method development.
- They should be responsible for local equipment sharing.

3. Incorporate greater molecular training for selected medically-qualified pathologists and ensure molecular diagnostics training for scientists

Scientists and medics working in pathology should all have basic molecular knowledge as a result of general training. However, a cadre of individuals with deeper molecular expertise should be developed. Currently, medical training relies on individuals with particular interests and abilities and is therefore fragmented. We strongly support the molecular diagnostics module as a major option in higher specialist training for histopathologists. We regret that clinicians can no longer train in clinical cytogenetics and molecular genetics, but suggest that rather than reinstating this discipline, its content be updated into training in a new molecular diagnostics qualification for the FRCPath examination. Periods spent in research and in the clinical molecular genetics and cytogenetics laboratory would be encouraged and should count as fully as possible towards training and accreditation.

MSC has clearly given consideration to molecular diagnostics and we propose a formal qualification in this area. However, scientific training in molecular diagnostics is likely to suffer from a lack of training opportunities in the molecular oncology setting, because too few histopathology departments perform routine molecular tests and/or contain individuals with the time and expertise to be trainers.

In addition, the Royal College should consider carefully the skill mix of its scientific trainees, especially if much of pathology moves into the private sector. Training must be tailored to the available posts and raising expectations by over-training is as big a fault as under-training. There is, for example, currently an excess of highly trained individuals in NHS laboratory genetics. Fortunately, these individuals would be ideal for working with histopathology on molecular oncology tests. The College should ensure that some of these individuals can be trained in tumour biology, including morphology, so as to bridge the gap until the first trainees from the MSC programme come through.

4. Establish 'Molecular NICE'

The existing molecular diagnostic remit of NICE should be separated into an expanded committee or separate committee with remit in assessing all molecular diagnostics. This could form part of a new 'Pathology NICE'. Turnaround needs to be much more rapid than NICE, decisions should be reviewed as new data and methods accrue and there should be an educational role for this committee, especially in keeping pathologists, oncologists, etc. informed about test availability. One aspect of this proposal is the establishment of a national New Tests Forum. Coordination with NICE is essential (for example, drug approval and molecular test approval may be interlinked).

5. Establish trial pathology 'Trusts' with molecular diagnostic roles

There is a trend to outsourcing pathology services in the UK and concentrating provision in a smaller number of centres. This form of service provision can especially easily be applied to molecular diagnostics, which requires investment in technology and high throughput for efficiency. Indeed, most molecular tests are currently supplied on a regional basis within the NHS. Whilst some 'host' NHS hospitals have been very supportive of such molecular testing, others have regarded it as a 'Cinderella' activity and provided little investment. In principle, there is no reason for a regional service to come under the management of a local hospital, however large. We therefore propose setting up a small number of trial centres to undertake regional molecular diagnostics (where possible, including other services that come under the molecular pathology umbrella). This initiative is in line with the thrust of the Carter Report. It has recently been

suggested that outsourcing of pathology will become widespread in the near future, although whether this will lead to cost savings is extremely unclear, especially if staff pay and conditions are maintained. The structure of the pathology Trusts would be critical. A variety of models could deliver, depending on local strengths, but the ideal would capture local expertise in service provision, research and development activities and available investment (see Box).

Box: A new form of supra-regional pathology centre?

Ideally, the stakeholders in such an enterprise would include, as a minimum, the NHS at some level and the appropriate university departments. Whether or not private partners were involved may depend on the range of services offered.

In one model, NHS services would be provided at cost, and various non-profit-making business models and governance structures might be possible. This would not exclude the possibility that other work might be undertaken for profit, including testing on research contracts for the pharmaceutical industry or, perhaps, the private sector. Partnerships with the university would help to enable investment in new facilities and equipment, and also assist in bringing service and research activities closer together.

Such centres need not be restricted to molecular diagnostics, although this might be a catalyst for their creation. In fact, there is much in favour of including 'traditional' and other existing pathology services in the centre. The centre would benefit from being sited close to one of the main hospitals in the region. By trialling centres in selected regions – for example, where the existing service delivery is highly constrained or there exist partners who could bolster the NHS service – the arrangement will be given the best possible chance to improve services. The new centres may provide the best alternative to outright privatisation or outsourcing of NHS pathology in selected parts of the country, whilst maintaining important links with local clinicians.

Concluding remarks

In this report, we have attempted to formulate practical proposals, many of which could be implemented immediately. Some of our views represent more detailed expositions of those already expressed by, for example, Carter and the House of Lords. In general, we feel that our views go 'with the grain' of medical and scientific opinion within pathology. Most of our proposals are 'micro', and we have avoided options that we feel would be highly destabilising. However, some change will be necessary, for example in the blurring of demarcations between pathological disciplines. Our proposals are designed to cost relatively little, although a formal health economic assessment would be highly desirable. The development of molecular diagnostics need not, of itself, mean that the virtues of the NHS system – arguably well represented in the collaborative approach taken in areas such as Scotland – will be lost. However, this will require a formal policy decision, since there are multiple factors driving marketisation of molecular services. Although a fully deregulated market is unlikely to be appropriate for molecular diagnostics, it is already possible to see the beginnings of a heterogeneous supply of and demand for molecular tests in the UK. Whilst the outcome of this process is extremely difficult to predict, experience suggests that large organisations will come to dominate molecular test provision. Our proposals are designed to apply to the private and public sectors, but it is important that the most innovative and efficient NHS and university pathology departments are allowed to develop structures, staff and equipment to allow them to compete with private sector competition. To compete effectively with the private sector it will be essential for the NHS to operate on a collegiate rather than a departmental basis, which has not been the model to date, but it is here where cost containment is most likely to be achieved.