

MRC  
Molecular  
Pathology  
Review



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# 1. Summary

Molecular pathology is a discipline that seeks to describe and understand the origins and mechanisms of disease at the level of macromolecules (for example DNA, RNA and protein) largely using patient samples.

## Stratified Medicine

Individual diseases are defined based on a common set of signs and symptoms as well as diagnostic tests. However, these shared signs and symptoms can arise from a variety of disruptions to underlying mechanisms. For example, patients with type I and type II diabetes both present with high blood sugar levels over a prolonged period. However, this common presentation has different causes; Type 1 diabetes results from the body's failure to produce enough insulin and Type 2 diabetes from cells failing to respond properly to insulin. This means that not everyone who is classified with the same disease will necessarily experience the same rate of disease progression or respond equally well to the same drugs. By classifying and understanding the molecular differences between the different groups or strata of people with a shared condition we hope to more accurately diagnose them, better understand how their conditions will progress, and determine which treatments are most likely to be effective. The improved stratification of patients therefore has the potential to deliver significant health and economic benefits.

In recognition of the potential benefits offered by stratification, United Kingdom (UK) Government and charity funders including the Technology Strategy Board (TSB), the Medical Research Council (MRC), the National Institute for Health Research (NIHR), Cancer Research UK (CRUK) and Arthritis Research UK (ARUK) are collectively investing around £200m in the area, coordinated via the Stratified Medicine Innovation Platform (SMIP).

If the UK is to benefit from this substantial investment and capture the full potential of stratified medicine, it is critical to ensure that there are robust pathways and capabilities to develop and adopt the new diagnostic tests and therapeutic strategies that it will give rise to, as identified in the Academy of Medical Sciences (AMS) 2013 report on **Realising the potential of stratified medicine**.

## MRC review

While much consideration has been given to the challenges faced by those developing new therapies, less work has focused on the needs of diagnostics. This review has focused specifically on defining these needs and how they might be addressed, to better enable the potential benefits offered by stratification and molecular pathology to be captured. The review has been overseen by a steering group, chaired by Professor Sir Robert Lechler (Kings College London), with membership from the academic, clinical and industrial sectors (see Annex 1) and has drawn on primary and secondary publications, discussions with domain experts (see Annex 2), and a workshop held in November 2013 (see Annex 3).

This work has not considered the development and adoption of novel molecular imaging tools which are being considered in other initiatives, such as, in part, the **MRC Clinical Research Infrastructure Initiative**, being run by MRC in partnership with the Department of Health, the Wellcome Trust, CRUK, the British Heart Foundation, ARUK and the research councils. Also of relevance, but out of scope, is the cross-funder approach to increase coordination of tissue resources in the UK, with a joint call launched in March 2014.

The review has found that there are challenges to the delivery of improved diagnostics from molecular approaches across three domains:

- **Lack of a defined development path:** compared to therapeutics, the diagnostics development path is complex and poorly linked.
- **Fragmented landscape:** there is separation between the academic, pathology and industry sectors of the diagnostic development landscape.
- **Complexity of multi-platform signatures:** a growing proportion of diagnostic tests will be based upon the assessment of numerous markers drawn from many molecular classes (eg genetic, proteomic and metabolomic), the interpretation of which will require mathematical algorithms able to identify signatures characteristic of different disease strata.

To address these findings, the review sets out a vision that:

The UK will provide an optimal environment for the discovery, development and adoption of innovative molecular pathology tests, enhancing the benefits of stratified medicine for patients to deliver clinical, economic and research benefits.

In order to deliver this, the review steering group recommends that:

- **Path:** a clear map of the diagnostic development path should be produced, including the evidence needs of the regulatory, evaluation and commissioning organisations along the path. Consideration should also be given to whether these organisations provide appropriate coverage and support.
- **Proximity:** the research base, pathology services and industry have become separated, to the detriment of all. These parties should be brought back into closer proximity.
- **People:** the skills base of the UK should be enhanced, by developing future research leaders in pathology, and increasing capacity in data analysis and health economics.

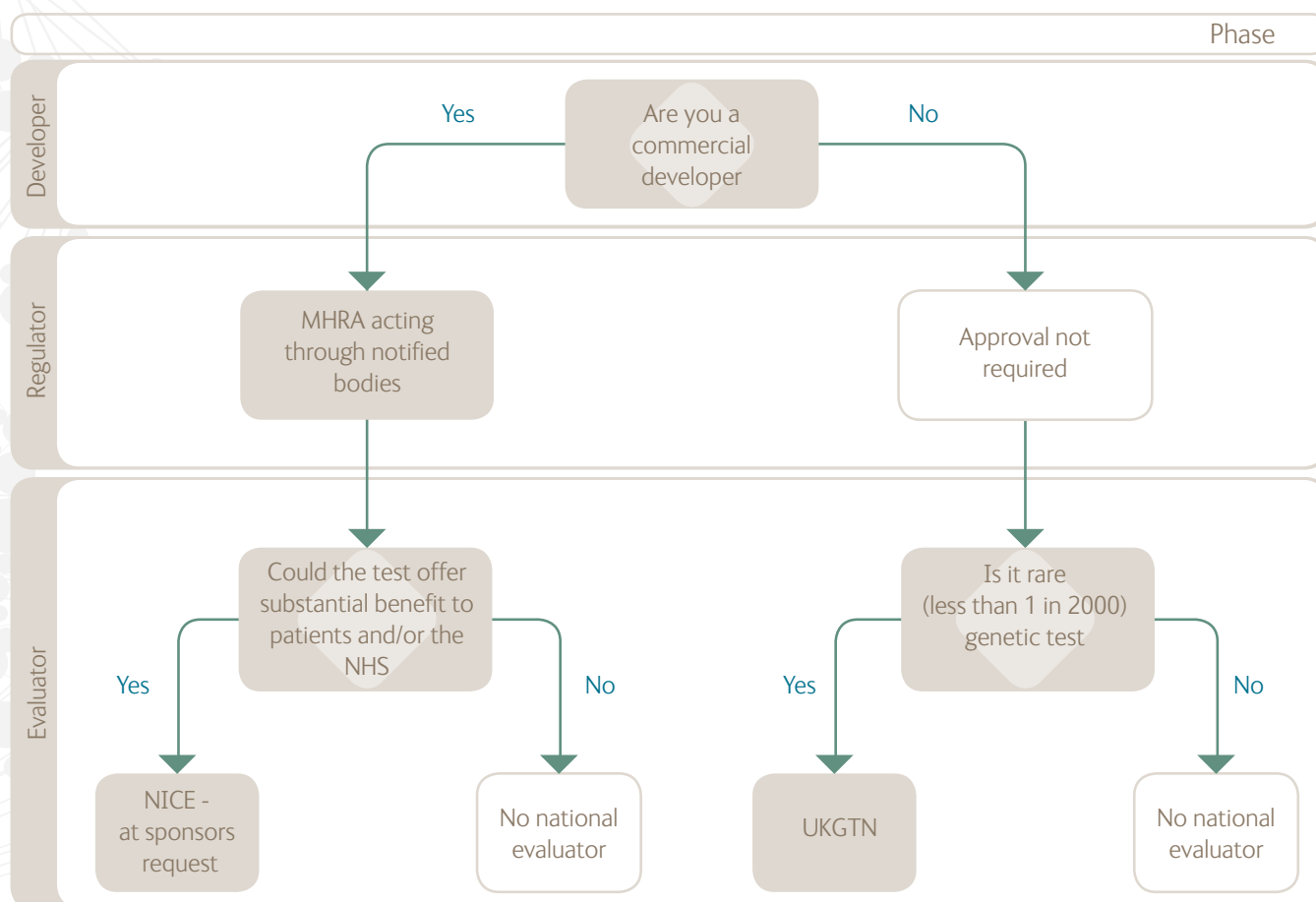
## 2. Findings

Advances in the description and understanding of molecular signatures relevant to disease diagnosis and progression offer the potential of significant healthcare benefits, through improved patient assessment and management, and the development of better targeted and effective therapeutic interventions. However, for the UK to capture this opportunity a number of hurdles must be overcome.

### 2.1 Lack of a defined development path

Compared to therapeutics, the diagnostics development path is complex and poorly linked.

The development path for new molecular pathology tests is complex, in part, because it tends to be driven by discovery and often suffers from restricted clinical 'pull' by defined clinical needs. Thus, molecules may be identified through discovery work, but their relevance for clinical care may not be well defined, leading to challenges in identifying the most appropriate route for development. In addition, the path to be traversed, including the various organisations – regulators, evaluators and purchasers – that need to be successfully engaged differs depending upon the nature of the developer and the test (see figure below). Greater complexity is added by the lack of clarity about the linkage between the relevant organisations and their evidence requirements, in part due to changing regulatory and NHS commissioning regimes.



## Regulation

New molecular pathology tests developed in-house by a health institution (in the UK this will be hospital) lab for use in the management of that institution's patients are exempt from European Union (EU) regulatory requirements. In contrast, commercially developed tests and those to be used for wider patient populations (beyond the initial institution) must gain regulatory approval, prior to being placed on the market.

The main regulatory route for diagnostics is through medical device approval (**EU Directive 98/79/EC** transposed into UK Law as **The Medical Devices Regulations 2002**) overseen by MHRA and with notified bodies providing CE marking.

In contrast to therapeutics, the regulatory approval of in vitro diagnostics (IVD) in the EU requires less evidence of clinical value. Neither clinical validity (the ability to accurately and reliably identify or predict the feature of interest) nor clinical utility (the likelihood that using the test to guide management will significantly improve health-related outcomes) have to be established for approval; most of the evidence being restricted to establishing analytical validity (the ability to accurately and reliably measure the biomarker of interest). Evidence of the latter is required for the test to be CE marked and placed on the market.

In the future, if the recommendations of a draft EU Medical Device IVD Regulation, which would repeal directive 98/79/EC (Procedure File **2012/0267(COD)**) are adopted, greater clinical evidence will be required to secure approval of new diagnostic tests, although the nature and extent of this evidence base is not, as yet, defined. This requirement, if introduced, has the potential to bring the research, clinical and industry sectors closer together, by making the field more clinically rather than metrologically driven. In addition, the lack of definition of the proposed clinical evidence provides an opportunity for the UK to shape the regulatory field as the new directive is implemented.

## Evaluation

While the lower clinical evidence requirement, compared to therapeutics, makes diagnostic market access for commercial developers easier, it results in a wider evidence gap between the process for regulatory approval and steps that the NHS and clinicians might deem appropriate for clinical evaluation – which would require evidence of both clinical validity and utility data. The challenge posed by this gap is compounded by the more limited budgets in the commercial sector available to diagnostic as compared to therapeutic developers. The potential regulatory requirement for increased evidence of clinical value could help narrow this evidence gap, although this will impose the financial burden of amassing the evidence required.

Even when an evidence base can be amassed, it is not always clear who has responsibility for its evaluation. In cases where the test is CE marked and has the potential to offer substantial benefit to patients and/or the NHS compared with current practice, the National Institute for Health and Care Excellence (NICE) Diagnostics Assessment Programme may review it. This occurs when it is requested to do so by the sponsor and where it is likely that the test will be adopted more consistently and more rapidly if NICE develops guidance on it. There is no national body to review commercially developed tests that do not meet the NICE criteria.

If the test is an in-house test developed for the genetic assessment of a rare (less than 1 in 2,000) disease, a request for national evaluation can be made to the UK Genetic Testing Network



(UKGTN), to provide reassurance to commissioners of the test's merits. There is no national body tasked with the evaluation of common genetic and non-genetic in-house developed tests. While NICE does evaluate in house developed tests, this is only as a comparator in the context of a review of an eligible commercially developed test.

Evaluation of tests for clinical use is likely to require the input of health economists, to assess whether the test is cost effective, given its potential clinical value. This analysis forms a critical part of the case to be made to downstream commissioners. This contrasts with the current regulatory position in which device assessment for CE marking relates solely to the accuracy of the test in meeting its stated parameters.

## Commissioning

The complexity of the evaluation landscape is intensified by the fact that the recommendations of the evaluation bodies, where they exist, are not mandatory upon the NHS. This contrasts with new therapeutics evaluated by NICE's Technology Appraisals programme, the recommendations of which the NHS is mandated to deliver upon. It should be noted however, that a lack of mandate was not viewed negatively by all contributors, as potential discrepancies between the speed of evaluation and of new tool development could result in the mandated use of out-of-date tests.

A further challenge for developers is that, in England, the NHS commissioning model is in flux, with commissioning of general hospital services having recently been passed to 211 local clinical commissioning groups (CCG), and commissioning of specialist hospital services and general practice being managed centrally by NHS England. The nature of what is being commissioned, individual tests, packages of service and/or pathways of care, was not yet clear to the review group, nor were the means by which commissioners will reach their decisions. Industry and patient groups have requested that the process and evidence base used in reaching commissioning decisions be clarified (**Stakeholder engagement report to inform the developing scope of the five-year strategy for specialised services 2014/15 – 2018/19**).

Given the critical importance of quality in diagnostic assessment spanning specimen identification, collection, transportation, processing, testing, analysis and reporting it will be important that commissioners support quality through their decision-making processes.

## Clinical pull

The slow uptake of innovations in the NHS is an acknowledged challenge (**Innovation Health and Wealth – Accelerating Adoption and Diffusion in the NHS**). For diagnostic developers, the absence of mandated adoption is a particularly pressing issue, due to their relatively restricted development budgets. Even when a positive NICE recommendation is achieved, the NHS's financial situation makes it challenging to introduce new tests that are not cost saving or cost neutral.

Much diagnostic development is driven by discovery push rather than clinical pull. Early engagement between the academic discovery and clinical communities could increase the likelihood of tests addressing true clinical needs, in turn increasing their likelihood of adoption. Such engagement could also help establish key clinical predictive criteria, which would help in the planning and powering of biomarker discovery and test development.

## 2.2 Fragmented landscape

There is separation between the academic, pathology and industry sectors of the diagnostic development landscape.

Optimal development of new molecular diagnostic tests that can pass into clinical use will occur in teams that bring together the complementary skills and assets of the research, clinical service and industry sectors.

Drivers, including cost pressures, the REF and the removal of pathology as a recognised subject in undergraduate medical school curricula, have led in many regions – perhaps inevitably – to the clinical speciality of Pathology becoming focused on service delivery over research. This has led to a distancing between pathology service work and the clinical research base, to the detriment of both. For example, the former lacks a line of sight to emerging opportunities, and the latter's effectiveness is hampered by a lack of access to assay and procedure development skills, and to data, tissue and information from clinical service.

The scale of the distancing of Pathology from the clinical research base is demonstrated, in part, by the erosion in the number of Pathology and infection/microbiology specialist medical clinical academics in UK medical schools from a total of c. 372 FTEs in 2000 to c. 138 in 2013, representing a 41 per cent reduction. The background reduction in total medical clinical academics over the same period was 12 per cent, as presented in **A Survey of Staffing Levels of Medical Clinical Academics in UK Medical Schools as at 31 July 2013**. This survey also identified an increasing age profile of clinical academic staff, reinforcing the need to enhance academic training programmes for effective succession planning, and noted that Pathology required particular attention, due to the small number of academic trainees in this speciality. These figures exemplify the challenge in ensuring that academic pathology remains an attractive career choice for young clinicians and ensuring an environment where clinical service can interdigitate with emerging science.

The separation between pathology services and the clinical research base is amplified by the lack of a significant industrial diagnostic R&D base in the UK, which might otherwise help bridge discovery through development to adoption. The industrial groups in the UK are mainly either SMEs with limited budgetary flexibility or the marketing arms of international diagnostic companies. In 2012 the medical technology industry in the UK, of which in vitro diagnostics is a significant part, was made up of 3,129 companies (with 71,144 employees), 99 per cent of which were SMEs and only 25 per cent of which conduct R&D (**Strength and Opportunity 2012: The landscape of the medical technology, medical biotechnology, industrial biotechnology and pharmaceutical sectors in the UK**). In contrast, the pharmaceutical industry had 387 companies (with 69,284 employees), 60 per cent of which conduct R&D. So although there are a broader range of medical technology companies, these are almost all SMEs with a relatively limited focus on R&D.



## 2.3 Complexity of multi-platform signatures

A growing proportion of diagnostic tests will be based upon the assessment of numerous markers drawn from many molecular classes (eg genetic, proteomic and metabolomic), the interpretation of which will require mathematical algorithms able to identify signatures characteristic of different disease strata.

### Disease areas

The disease areas in which stratification has had the greatest impact to date are infectious diseases and oncology. Researchers in the former area have utilised empirical and now genetic assessment of drug resistance to guide therapy selection for many years. In the latter area, the development of highly specific monoclonal antibody therapies, only active in the presence of the intended target, has led to the development of tests able to establish the presence or activity of the target and its associated signalling pathway, to better direct therapy choice. Examples of such tests including the HercepTest, a semi-quantitative immunohistochemical assay used to determine HER2 protein (c-erbB-2 oncoprotein) overexpression in breast cancer tissues, to predict likely response to Herceptin (trastuzumab), and the thescreen KRAS PCR genetic test, designed to detect mutations in the KRAS gene in colorectal cancer cells, which indicate that the patient is unlikely to benefit from treatment with Erbitux (cetuximab).

Looking beyond these traditional areas, commentators have proposed that coagulopathies, psychoses and autoimmune diseases are well placed for stratification (Davis et al., **The microeconomics of personalized medicine: today's challenge and tomorrow's promise**. *Nat Rev Drug Discov.* 8:279-86 (2009)). The latter two are the focus of five recently established MRC stratified medicine consortia, which are investigating the autoimmune diseases (rheumatoid arthritis/psoriasis (RA) and primary biliary cirrhosis) and schizophrenia, in partnership with industry. Additional MRC consortia are exploring opportunities in Hepatitis C, chronic obstructive pulmonary disease, and diabetes, while experts at a recent MRC workshop highlighted asthma, inflammatory bowel disease and pain as potential additional areas of opportunity.

### Technologies

As exemplified by the tests described above, current stratifying tests are mainly based on genetic or immunohistochemical analysis of individual biomarkers. Of the 19 companion diagnostic tests approved for use in therapy selection by the United States (US) Food and Drug Administration, 12 examine DNA changes using polymerase chain reaction, fluorescence in situ hybridization or chromogenic in situ hybridization; six measure changes in protein levels using immunohistochemistry; and one measures the level of iron non-invasively in blood using magnetic resonance imaging.

Newer tests are examining the expression levels of multiple biomarkers, the discovery and assessment of which requires technologies able to measure many biomarkers in parallel. The Oncotype DX test developed by Genomic Health, which was recently recommended for use by NICE for the prediction of response to adjuvant chemotherapy, assesses the level of expression of 21 genes by PCR. Crescendo Biosciences is developing a quantitative multiplexed

immunoassay test to measure 12 serum biomarkers for the stratification of RA. Further opportunities are to be found in the application of new technologies able to probe additional 'omes' relevant to disease, including the epigenome and the metabolome.

New technologies are also enhancing existing analyses. Digital pathology has the potential to enhance histological analysis by using image processing to extract additional information from specimens, aiding quantification and standardisation. Mass spectrometry imaging could also enrich histological analysis, by enabling the combined assessment of morphology and chemical composition.

## Data

To extract information from the large volumes of data produced by measuring multiple biomarkers across a range of 'omes' requires a means to capture and hold this data, and to then integrate it with relevant patient clinical information. Robust methodological and statistical approaches are then required to identify reproducible associations, which might provide both diagnostic and mechanistic insight. Managing and analysing this data will require an appropriate informatics infrastructure and an appropriately skilled workforce.

## 3. Recommendations of the steering group

**VISION:** The UK will provide an optimal environment for the discovery, development and adoption of innovative molecular pathology tests, enhancing the benefits of stratified medicine for patients to deliver clinical, economic and research benefits.

This vision requires an understanding of the requirements and drivers of academic research, commercial development and NHS adoption and the provision of support, capacity and infrastructure spanning discovery science, informatics and pathology laboratory capability. In addition, it will depend upon:

- a clear and proportionate regulatory and evaluation pathway
- vibrant partnership between the commercial, clinical and academic research sectors, closely aligned to the needs and delivery of clinical care
- an appropriately skilled and led workforce

The UK has contributed to the development of stratified molecular testing, including the development of the therascreen KRAS test described above, developed by DxS, prior to its acquisition by Qiagen. However, it is indicative of the current status of the field that the two more recent tests mentioned above, from Genomic Health and Crescendo Biosciences, were both developed in the US. This may reflect the larger US market opportunity, which is also a more rapid adopter of new technologies than the UK. A further advantage in the US may be better access to venture capital. An important requirement, given that it is estimated that Genomic Health spent c. \$100m to bring the Oncotype DX test to market. The economic opportunity of stratified testing is attested to by the current market capitalisation of Genomic Health (c. \$875m) and the price recently paid by Myriad Genetics to acquire Crescendo, the developer of the RA test referred to above (\$270m).

Unless the UK can attain a more leading role in molecular pathology, we are at risk of not capturing the full spectrum of health and economic benefits that stratified medicine can provide. The former will arise, in part, from earlier access to emergent tests and better alignment of these tests with UK needs, and the latter through company and job creation and improved efficiencies in healthcare delivery. In order for the UK to attain this role, it is recommended that:

### 3.1 Path

A clear map of the diagnostic development path should be produced, including the evidence needs of the regulatory, evaluation and commissioning organisations along the path. Consideration should also be given to whether these organisations provide appropriate coverage and support.

In recognition of the challenges posed by the complex diagnostic development path, organisations along the path to approval and adoption have established initiatives and programmes to aid developers. These include:

- MHRA and NICE joint advisory meetings to advise developers on their combined needs
- the NICE Implementation Collaborative to drive implementation of NICE guidance where there is slow or inconsistent uptake across the NHS
- NHS England:
  - Academic Health Science Networks (AHSN) to speed up adoption,
  - Innovation Connect team to assist innovators, and innovation scorecards, to increase transparency of adoption

While the establishment of these individual initiatives is to be applauded, there remains a need to produce a clear unified map setting out the critical path, milestones and required evidence for the discovery, development, regulatory approval, evaluation and commissioning of molecular pathology tests, drawing on the input of key stakeholders. This map might encompass a number of paths, depending upon the nature of the developer and the test.

The high-level holistic map could be complemented by more focused work developing guidance for developers on best practice in amassing required evidence. This latter work would also help to clarify methodological needs in the field.

Consideration should also be given as to whether the current bodies provide appropriate coverage and work synergistically together to ensure the quality, value and equity of access to newly developed molecular pathology tests. Evidence for this review indicated perceived gaps in:

- the evaluation of hospital-developed common genetic and non-genetic tests
- the alignment of NICE and other evaluator guidance and commissioning decisions
- the role of commissioning in ensuring quality and wide-scale adoption

Filling these gaps would need to be done in consultation with relevant stakeholders and in such a way that the challenges of development are reduced rather than increased. The current Department of Health-led review of the role of the UKGTN suggests that evolution in this area is possible.

## 3.2 Proximity

The research base, pathology services and industry have become separated, to the detriment of all. These parties should be brought back into closer proximity.

While this separation creates significant disadvantages to translation of research into clinical care, there are several reasons for its occurrence, which relate to different needs and constraints, as outlined above. In order to improve the flow of research to care and back again, it is recommended that the most realistic approach is an initial focus on key centres or 'nodes' to build linkages and then disseminate tests and opportunities across other UK centres. In order to re-engage the necessary contributors with the development and adoption of molecular pathology tests, it is recommended that these joint research/clinical service 'nodes' be developed in partnership with industry, to provide foci for innovation in molecular pathology tests, technologies and service delivery.

These nodes would provide centres for research and early adoption into clinical studies and care, through integration with local pathology service delivery. They should build on current strengths rather than seeking to replace pathology/genetic services; molecular pathology complementing existing services. Strong clinical leadership and linkages would aid the identification of patient groups in which to evaluate emergent tests and working in partnership with the local NHS would help to harness the "clinical pull" referred to earlier. In addition, industry partnerships would assist, where appropriate, the rapid and robust commercialisation of new tests and the establishment of appropriate quality control systems. Such nodes could also help ensure that the collated data from molecular pathology service delivery are made available to support future discovery programmes, in a virtuous circle.

The nodes will need to take account of a diagnostics future in which the means of generating data may, for reasons of cost and quality, become separated from the extraction of diagnostic value from the data through algorithmic signatures. This highlights the key difference between deriving 'data' and 'information' and creation of a test. This will require strengths in informatics, particularly analysis of large-scale datasets, statistical capabilities and access to multiple technology platforms, in order to link potential markers from various 'omic' approaches. The nodes would therefore also benefit from close partnering and embedding with the developers of novel technologies able to interrogate new, or better investigate established, biological/clinical features.

The nodes, which will be both research and service facing, will need to be clearly signposted to the wider community and should complement the industry-facing NIHR **Diagnostic Evidence Co-operatives** (DECs) (four centres funded at £1m each for four years) and the emergent Technology Strategy Board Precision Medicine Catapult (one centre funded at £50m over five years) and other research council and partner investments, including Genomics England's 100k Genomes Project. Together these investments should synergistically link the academic, clinical and industrial sectors.

The nodes are likely to be of a size intermediate between the DEC and Catapult models. Research council contributions could include linkage with existing and planned data initiatives and technology centres, and investment in support of technology development, proof of concept studies and training.

At their initiation, the nodes should be focused on the development of new tests but as they mature they should also assist in the local and regional adoption of these tests, working with host hospitals, academic health science centres, and AHSNs or equivalent organisations in devolved administrations. Having established local/regional adoption, the nodes might work together as a network to support diffusion. This support could, in part, be provided by the nodes acting together as a community evaluator of new tests, akin to the role of UKGTN in the assessment of rare genetic tests. For wide-scale diffusion it will be necessary to engage with and support both diagnostic and academic pathologists/geneticists.

Depending on the nature and volume of uptake of their newly developed tests, it may become appropriate for the nodes to pass test delivery to service centres able to operate at optimal volume levels to enable quality thresholds to be met robustly. This will need appropriate incentivisation, since nodes may be reluctant to pass over tests that they have helped establish and begun to generate income from. Although test delivery may become centralised, it will be critical for patient management that an ability to interpret test results is developed and retained locally.

While the review did not prioritise a need for investment in any individual technology within the nodes, the observed additional resolving power of cross-platform molecular signatures argues for the establishment of facilities with multiple technology capabilities. Such facilities would benefit from the creation of data sharing standards, akin to DICOM in radiology, to enable cross-platform data and health records to be linked and pooled. Such a shared data-pooling standard would support the development of an applications market for the identification of molecular signatures and for systems modelling of disease mechanisms.

### 3.3 People

The skills base of the UK should be enhanced, by developing future research leaders in pathology and increasing capacity in data analysis and health economics.

There is a generational gap in research pathologists with a number of the current leadership approaching retirement and a paucity of individuals in the following generation. There is a critical need to develop new research leaders in pathology able to drive forward the discovery and service-delivery agendas. At its heart, molecular pathology is the molecular understanding of disease, and as such touches on the interests of much of clinical research. This means leadership may emerge from disciplines other than Pathology.

The UK must support an appropriately skilled and motivated workforce if the full potential of this area is to be achieved. The proposed nodes should provide a supportive base for the training of the next generation of research leaders in molecular pathology; the success of which will also require consideration of supportive downstream career paths. A programme of training positions, available to pathologists and other related specialties, with guaranteed follow through clinical lectureships might provide a helpful start to this process.

Both the MRC and CRUK have supported pathology training programmes in the past. While these have been able to identify and attract strong candidates, their numbers, compared to related

fields, for instance pharmacology, were limited. This may reflect a different starting demographic, with pathology trainees, in general, being less attracted by research opportunities. In order to address this and to support wide-scale clinical uptake of molecular pathology approaches, there is a need for enhanced molecular pathology training at the undergraduate level in medical schools. There also need to be opportunities for the current generation of pathologists to up-skill, to better enable them to assess and interpret the new generation of molecular pathology test results. The nodes might play a role in both these requirements.

For the development of new tests, there is also a need for the further development of the UK's capacity in statistics, bioinformatics and health economics.

## 4. Conclusion

This review has identified the challenges that need to be met if the UK is to become an optimal molecular pathology environment. The changing regulatory and NHS commissioning regimes, complementary partner initiatives (including the formation of AHSNs, the NIHR DEC's, the TSB Precision Medicine Catapult and Genome England's 100k Genomes Project) along with the recommendations made here, provide a rich opportunity for the community to develop a synergistic and clearly signposted system supporting the discovery, development, adoption and diffusion of the next generation of molecular tests for patient and economic benefit.

## 5. Annexes

Annex 1 – Molecular Pathology Review Steering Group Membership

Annex 2 – Experts Consulted

Annex 3 – Molecular Pathology Workshop Agenda and Attendees



# Annex 1 – Molecular Pathology Review Steering Group Membership

## Professor Sir Robert Lechler, Kings College London - Chair

Professor Sir Robert Lechler qualified in Medicine in Manchester in 1975. Thereafter, he undertook four years of junior hospital doctor training in general medicine and nephrology before embarking on a PhD in transplantation immunology at the Royal Postgraduate Medical School. Following the PhD, he returned to full-time clinical work for two years and completed his scientific training at the National Institutes of Health in Bethesda, USA. He returned to the UK to a Senior Lecturer Post at the Royal Postgraduate Medical School in 1986 and became Head of the Department of Immunology in 1994. He became Dean of Hammersmith Campus at Imperial College Faculty of Medicine in 2001 and Head of the Division of Medicine in 2003. He moved to King's College London as Head of the School of Medicine at Guy's, King's College and St Thomas' Hospitals in September 2004 and was appointed Vice Principal (Health) at King's in October 2005. In 2009 Robert took on the role of Executive Director for King's Health Partners.

## Dr Ian Barnes, ex-National Clinical Director for Pathology, DH

Having trained in biochemistry at the University of Bath, and in clinical biochemistry in Bristol and London, he moved to Leeds General Infirmary in 1987 and was Head of Clinical Biochemistry and Immunology from 1991 to 1996 and Director of Pathology from 1996 to 1998. He has been a member of the Carter Review of Pathology Board and a former Chairman of the Association of Clinical Biochemists, the Federation of Healthcare Science and the Association of Clinical Scientists. Since 2001, Dr Barnes has been involved in the DH's Pathology Modernisation programme and in 2005 he was appointed as the first National Clinical Lead for Pathology. He was made National Clinical Director for Pathology in 2008 and stood down from this roll in March 2013.

## Professor Andrew Morris, Dean of Medicine at Dundee

Andrew Morris is the Professor of Medicine and Director of the Medical Research Institute at the University of Dundee. He leads a research team that uses informatics to study the epidemiological and molecular aetiological basis of diabetes and its complications. He also has a major interest in the use of informatics to support research quality improvement and inter-disciplinary patient care nationally. He leads the DARTS research study, has published over 200 original papers and has attracted over £20m in peer reviewed grant funding.

## Professor Simon Lovestone, Director of Research at the King's Health Partners Academic Health Sciences Centre

Simon Lovestone is Professor of Old Age Psychiatry at the Institute of Psychiatry, King's College London and Director of the NIHR Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Trust and the Institute of Psychiatry. He studied Microbiology at Sheffield University and then Medicine at Southampton University and has continued to practice both medicine and molecular science ever since. After working as a junior doctor in medicine and in health care of the elderly he trained in Psychiatry and then obtained a Wellcome trust fellowship to study the molecular relationship between plaques and tangles in Alzheimer's disease.

### Professor Chris Chamberlain, VP Experimental Medicine and Diagnostics, UCB

Chris Chamberlain was previously Medical Director for Personalised Healthcare at AstraZeneca and was Biomarker Expert at Roche Pharmaceuticals. He initially trained in Medicine at the University of Oxford & subsequently held lectureships within the Universities of London and Liverpool, whilst completing training as a specialist in Clinical Biochemistry. Prior to moving to Roche in 1999, Dr Chamberlain worked with both SmithKline Beecham as Associate Director of Human Genetics, and University College London as a Senior Lecturer in Medicine and the Genetics of Human Disease.

### Dr Tim Pitfield, Janssen Diagnostics and Chair of BIVDA Stratified Medicine Working Party

Tim is currently the Business Director at Janssen Diagnostics, a Johnson & Johnson company developing innovative new diagnostics in the Oncology setting. He has held various sales, marketing and management positions during his 20 years within in the diagnostics industry. He has extensive knowledge of the European diagnostics market and has considerable international experience through management of business opportunities across Africa, the Middle East and more recently the ASPAC region.

In 2005 Tim was presented with the opportunity to establish the Veridex Molecular Diagnostics business across Europe. He submitted the first Molecular Diagnostic product to be selected for an adoption project with the newly established NHS Technology Adoption Centre (NTAC) in 2007. Through this project he has developed considerable understanding of the complex hurdles preventing the adoption of new innovative diagnostics and has recognised the importance of linking product benefits and performance evidence to patient outcomes.

Tim was elected to the British In Vitro Diagnostics Association executive in 2011 where he Chairs the Stratified Medicine Working Party.

### Mr Miles Scott, CEO St George's NHS Trust

Miles was chief executive of Bradford Teaching Hospitals NHS Foundation Trust since August 2005. Before joining Bradford Teaching Hospitals Miles was chief executive of Harrogate and District NHS Foundation Trust for four years. He started his NHS career on the General Management Training Scheme in 1988 after graduating from Cambridge University with a degree in History. His career in the NHS has encompassed acute, community and mental health services, the King's Fund and Trent Regional Office.



## Professor Paul Stewart, Dean of the School of Medicine at Leeds

Trained in medicine at the University of Edinburgh, Paul held a number of positions in Edinburgh before joining the University of Birmingham in 1989. His career has been supported at the highest level by personal career awards from the Medical Research Council (MRC), Wellcome Trust Programme grants and, most recently, by a European Research Council Advanced Research Fellowship.

Paul is an Endocrinologist and has 270 original publications to his name that have generated in excess of 13,500 citations. His main research interest is in the field of steroid hormones and the role they play in hypertension, obesity/ metabolism and inflammation. On a national level, Paul is chair of the MRC Training and Careers Board, a MRC Strategy Board member, a trustee of the British Heart Foundation and Secretary-Treasurer of the International Society of Endocrinology.

## Annex 2 – Experts Consulted

Dr Kathryn Adcock (Wellcome Trust)  
Professor Tim Aitman (Imperial College London)  
Professor Jane Apperley (Imperial College London)  
Professor Denny Ausiello (Massachusetts General Hospital)  
Dr Tito Bacarese-Hamilton (LifeScan)  
Dr Jyoti Choudhary (Sanger)  
Mr Glyn Colebrooke (Philips Digital Pathology)  
Professor Terence Cook (Imperial College London)  
Professor Finbarr Cotter (Queen Mary University of London)  
Dr Nick Crabb (NICE)  
Professor Ian Cree (University of Warwick)  
Ms Jill Dhell (NIHR)  
Professor Mark Drayson (University of Birmingham)  
Dr Letizia Foroni (Imperial College London)"  
Professor Hani Gabra (Imperial College London)  
Professor Stephen Holgate (University of Southampton)  
Dr Zoë Holland (Cancer Research UK)  
Dr Tim Hubbard (King's College London)  
Dr Matthew Hurles (Sanger)  
Professor John Iafrate (Massachusetts General Hospital)  
Professor Paddy Johnston (Queen's University, Belfast)  
Mr Stephen Lee (MHRA)  
Dr Stephen Little (Premaithe Health)  
Dr Ultan McDermott (Sanger)  
Professor Sir Mike Stratton (Wellcome Trust Sanger Institute)  
Professor Shawn Murphy (Partners Healthcare, Boston)  
Professor Kikkeri Naresh (Imperial College London)  
Professor Adrian Newland (Barts and London NHS Trust)  
Professor Willem Ouwehand (University of Cambridge)  
Dr Aarno Palotie (Wellcome Trust Sanger Institute)  
Professor Sharon Peacock (University of Cambridge)  
Professor Stephen Pennington (University College Dublin)  
Professor Tim Peto (Oxford University)  
Dr Andrea Pithers (Genomic Health UK)  
Dr Archie Prentice (Royal College of Pathologists)  
Professor Philip Quirke (University of Leeds)  
Professor Manuel Salto-Tellez (Queen's University Belfast)  
Professor John Savill (MRC)  
Dr Emily Shaw (Cancer Research UK)  
Professor Stanley Shaw (Massachusetts General Hospital)  
Dr Rosalind Skinner (UK Genetic Testing Network)  
Professor Sir Steve O'Rahilly (University of Cambridge)  
Dr Aino Telaranta-Keerie (Trinity Biotech)  
Professor Karen Temple (University of Southampton)  
Professor Samuel Their (Massachusetts General Hospital)  
Dr Ian Tomlinson (University of Oxford)



Dr George Vassiliou (Wellcome Trust Sanger Institute)  
Dr Ian Walker (Cancer Research UK)  
Dr Madhuri Warren (Pathology Diagnostics Ltd)  
Professor David Waugh (Queen's University Belfast)  
Mr Paul Weinberger (Diasolve Ltd)  
Dr Lorenz Wernisch (MRC Biostatistics Unit)  
Dr Jo Whittaker (UK Genetic Testing Network)  
Professor Martin Wilkins (Imperial College London)  
Ms Doris-Ann Williams (BIVDA)  
Dr Penny Wilson (Technology Strategy Board)  
Professor Nick Wright (Barts Cancer Institute)

# Annex 3:

## Molecular Pathology Workshop Agenda

28th November 2013

Royal Institution, 21 Albemarle St, London W1S 4BS

10:00 Meeting Start

10:00 Meeting Opening – Professor Sir Robert Lechler (King's College London)

- Overview of Review and Meeting goals
- Definition of Molecular Pathology

10:05 Keynote – What molecular pathology can offer -  
Professor Stephen Holgate (University of Southampton)

10:20 Keynote –Molecular pathology, the commercial opportunity –  
Dr Stephen Little (Prematha Health)

10:35 Future Vision - Where is technology going

A vision for how medical science will lead to new approaches to molecular pathology over the next 10 to 20 years. This will be based on an understanding of how UK research can use molecular techniques to accelerate disease stratification for diagnosis and treatment and to elucidate disease mechanisms. It will also consider how to foster a creative interplay between disciplines and how to address barriers to this and to flow of innovation between academic research, commercial partners, Pathology laboratories and the NHS.

Chair: Professor Simon Lovestone (Kings College London); Speakers: Professor Stephen Pennington (University College Dublin) and Mr Glyn Colebrooke (Philips Digital Pathology)

- Areas of current and future scientific and clinical opportunity
- What will future tests look like (in house v kit based; central v point of care; physician v consumer directed)

11:30 Tea/Coffee Break

To clarify requirements to ensure that molecular pathology technologies that are discovered and applied to research are also implemented into clinical trials utility and clinical care and to ensure information also passes back from clinical service to research activity. This will encompass developments in genomics and genetics led by the Human Genome Strategy Group (HGSG) but also look at new and emerging areas (such as proteomics, metabolomics and digitisation) and how the experience of implementation of genetics into service can influence adoption of other new technologies. This will link to other relevant funding in stratified medicine and to initiatives such as the NIHR Diagnostics Evidence Cooperatives



11:45 Discovery to utility

Chair: Mr Tim Pitfield (Janssen Diagnostics); Speakers: Dr Nick Crabb (NICE); Dr George Vassiliou (Wellcome Trust Sanger Institute) and Dr Madhuri Warren (Pathology Diagnostics Ltd)

- Who needs to come together
- What do they need; and
- What are they aiming for

12:45 Lunch

13:15 Putting it into practice

Chair: Dr Ian Barnes (Leeds NHS Trust); Speakers Dr Jo Whittaker (UKTGN), Dr Tito Bacarese-Hamilton (Lifescan Scotland) and Dr Emily Shaw (Cancer Research UK)

- How should tests be recommended?
- Who commissions tests and drives adoption?
- How should they be delivered?

14:15 Coffee/Tea Break

14:30 UK Needs

To determine current strengths and weaknesses of the UK in this area compared to other countries; what does it have and what does it need?

Chair: Professor Sir Robert Lechler (Kings College London); Speakers: Professor Sir Steve O'Rahilly (University of Cambridge) and Ms Doris-Ann Williams (BIVDA)

- Infrastructure
- People
- Funding
- Route map

15:30 Coffee/Tea Break

15:45 Summation – Professor Sir Robert Lechler (King's College London)

16:00 Meeting Close



