Overcoming barriers to the uptake of molecular diagnostics

NCRI's CM-Path Molecular Diagnostics Forum, 26th January 2018

The CM-Path initiative is funded by ten of the NCRI Partner organisations:

Executive summary

CM-Path is a National Cancer Research Institute (NCRI) initiative, which aims to reinvigorate academic pathology in the UK. Over the past 15 years, the academic pathology workforce has experienced substantial attrition. In order to maintain innovation in pathology, this decline needs to be reversed.

To advance research in pathology, providing scope for wider and faster implementation of novel technology for patients' benefit, CM-Path recognises the value of collaborating with industry, regulators and others. To this end, the first CM-Path Molecular Diagnostics Forum took place on 26th January 2018 with the aim of identifying challenges, and their solutions, to the adoption of new molecular diagnostic tests within the National Health Service (NHS).

The key outcomes of the day were as follows:

1. A consensus process roadmap for the development and implementation of molecular diagnostic tests was agreed upon;
2. Eight key challenges to the implementation of molecular diagnostic tests were identified and possible solutions suggested for five of these;
3. The CM-Path Molecular Diagnostics Forum will meet on a regular basis to drive progress in this area – the next meeting will take place in autumn 2018 to discuss three of these challenges in greater detail (i. Culture, ii. Education/training, iii. Monitoring of uptake/response). We would also like to discuss the impact of the genomic commissioning on the roadmap;
4. A position paper will be published to summarise the outcome of the meeting, highlight the challenges identified and advertise the existence of the forum, with the aim of recruiting further members with knowledge and skills relevant to the field.

Introduction

Cellular and molecular pathology is the science of understanding disease at the level of cells, genes and molecular pathways. In this era of 'personalised' medicine, there is a rapidly escalating need for innovative molecular testing and application of a wide spectrum of technology to inform patient management and facilitate translational research. However, over the past 15 years, academic pathology in the UK has severely declined.

The new National Cancer Research Institute (NCRI) initiative in Cellular and Molecular Pathology (CM-Path) aims to achieve the changes needed to support academic cellular and molecular pathology in the UK and, by so doing, make the resulting benefits available to the wider community. The initiative is chaired by **Dr Karin Oien**, University of Glasgow. CM-Path contains four workstreams, each with an emphasis on a topic that the pathology community has identified as a key priority in the re-invigoration of pathology research in this country. Workstream 4, led by **Professor Clare Verrill**, focuses on 'Technology and Informatics', with an emphasis on the uptake of new technologies that can drive innovation in both molecular and digital pathology. **Professor Sarah Coupland** is the Molecular Diagnostics lead within this Workstream.

Members of Workstream 4 and representatives from industry held a joint workshop on 5th October 2016, with the aim of identifying challenges to the uptake of new technologies in molecular pathology and developing innovative solutions to these. The key challenges identified were:

1. Facilitating better communication between the pathology community and industry;
2. Difficulties for industry in accessing the human tissue samples needed to develop and validate their products;
3. Complexity of acquiring regulatory approval for such products;
4. Adoption of new technologies by the NHS including administrative and financial considerations;
5. Lack of capacity/skills amongst the pathology workforce and the need for further training of pathologists in molecular diagnostics.

Focusing on the need for "**better communication between the pathology community and industry**", a CM-Path Molecular Diagnostics Forum was established to promote interactions between pathologists, industry representatives and regulators in the hope that this would promote faster uptake of emerging technologies. To this end, the first CM-Path Molecular Diagnostics Forum took place on 26th January 2018 at the Royal Society of Medicine in London, with the aim of building a roadmap to facilitate the adoption of new tests into routine NHS practice.

Molecular diagnostics

Molecular diagnostics is a branch of laboratory medicine that applies molecular biology techniques to human tissue samples, in an attempt to decipher the genetic and molecular alterations that underlie the development of disease. The data that it generates can then be used to diagnose and classify disease, provide predictive (e.g. likelihood of responding to a particular drug) and prognostic information and to detect residual disease after therapy. However, whilst new molecular diagnostic technologies are continually being developed, for a number of reasons, their translation into the clinic can be a lengthy process, and the gap between test development and implementation is very large. During the CM-Path Molecular Diagnostics Forum, small group 'breakout' sessions were used to facilitate interaction between experts from a variety of different backgrounds with the ultimate aim of creating a process roadmap for the development and implementation of new molecular diagnostic tests.

1. Molecular diagnostics uptake: a process roadmap

Initially, delegates were grouped by sector: clinicians, academics, regulators and industry representatives. Each group was asked to identify the stages involved in taking a molecular diagnostic test from design to delivery. It became immediately clear that no single group was able to map the entire pathway, confirming the value of arranging this multidisciplinary meeting. It also became clear that what had initially been drafted as a linear process, was in fact a cycle of continuous test development and refinement and thus the "roadmap" became circular to reflect that. Ultimately, a final process roadmap was agreed by consensus between the groups (see Figure 1); it was felt that both health economics and education are key aspects that have central relevance to the entire process.

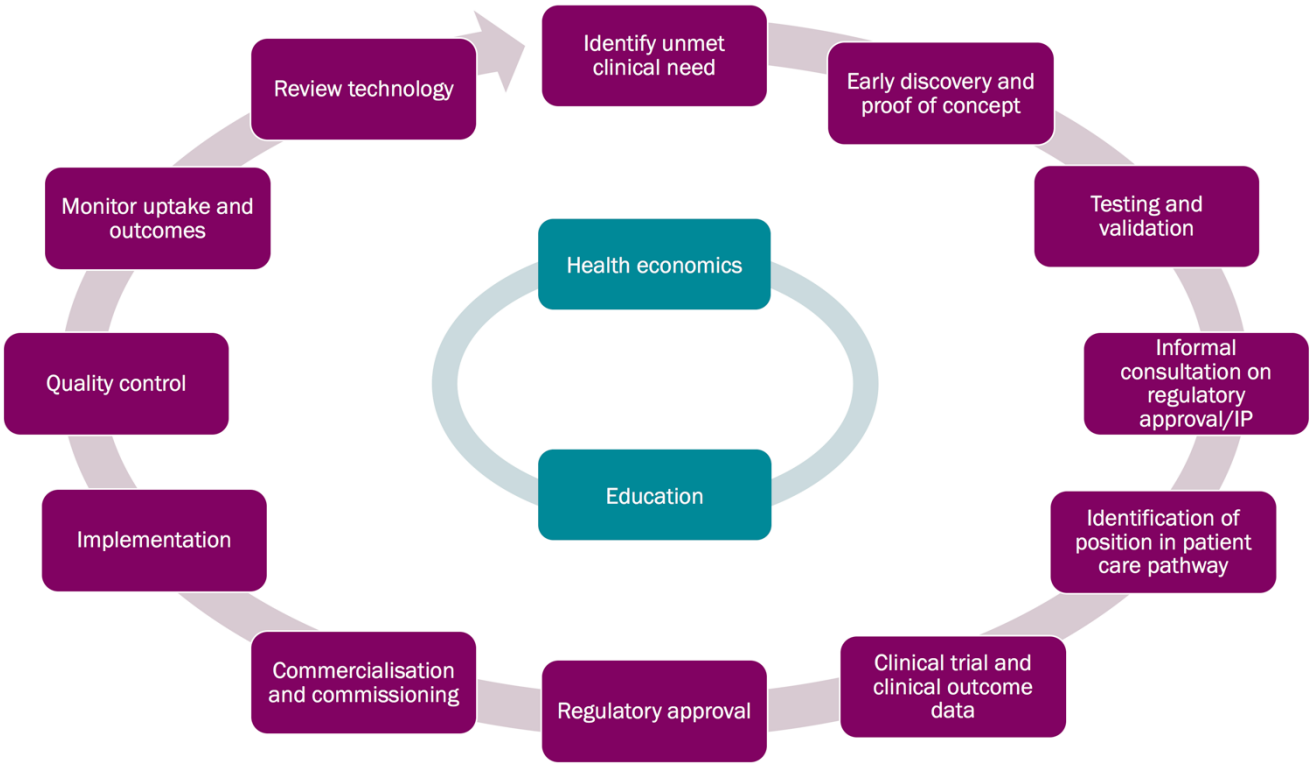

Figure 1 – Consensus process roadmap for the development and implementation of molecular diagnostic tests (Key: *IP = Intellectual Property*).

2. Challenges within the process roadmap that affect the uptake of molecular diagnostic technologies

Subsequently, the groups were mixed and asked to identify challenges affecting the efficient uptake of molecular diagnostic technologies. During this process, several key themes emerged, as outlined below.

1. Monitoring of uptake/response

Even with the direct monitoring of quality of testing offered through NEQAS the forum felt that data is lacking on the uptake of tests, their turnaround times, their impact in changing patient management and responses. Without these data, it is unclear which tests are being used in the clinic and there is a lack of evidence that tests are indeed improving cancer diagnosis and treatment. Furthermore, in some cases, multiple tests are being designed to assess the same biomarker, each with different sensitivities and specificities, and thus there is a lack of clarity as to the best choice of test.

2. Technical aspects of molecular diagnostic testing

In addition to a widespread lack of expertise in molecular diagnostics, there has been a reduction in the capacity of NHS diagnostic laboratories to undertake additional testing and a trend towards testing smaller tissue samples, often making testing more technically demanding. All of these factors need to be considered during the development of new diagnostic tests.

The NHS Information Technology (IT) infrastructure represents a significant challenge as this is currently not standardised across different Trusts. Significant software installation and validation will be required to provide new molecular diagnostic tests and must be accompanied by a robust IT infrastructure and accessible technical support. Currently, interpretation of many test results is still carried out manually. In the future, fully validated, automated quantification methods may be required to improve the accuracy and efficiency of testing.

3. Ethical issues

To develop a molecular diagnostic test, ethical approval and consenting procedures need to be in place to allow the correct validation studies to be carried out. This is a complicated process that involves approval from research ethics committees and can be a potential delay in the roadmap.

4. Regulatory issues

Laboratories and scientists undertaking validation studies for new molecular diagnostic tests must be accredited; however, it is often unclear what specific accreditation is required. Furthermore, molecular diagnostic tests themselves are subject to regulatory approval and may, for example, need to adhere to CE-IVD or ISO standards.

5. Communication

Lack of communication is a significant challenge across the roadmap. One of the biggest communication breakdowns can occur when a test has received regulatory approval and funding but clinicians remain unaware of its availability. This can significantly affect equity of access to new treatments, with patients receiving different tests depending upon the region of the country in which they are treated.

6. Funding

Financial issues play a key role in the development and implementation of diagnostic tests. Funding is required during the development phase to ensure that clinical validation can be undertaken. Once a test has been clinically validated and recommended by the National Institute for Health and Care Excellence (NICE), commissioning and availability of funding for its use within the NHS represent other major challenges.

7. Culture

Within the NHS, a cultural change needs to take place to ensure that its staff are willing and able to embrace emerging molecular diagnostic technologies. In particular, pathology laboratories should be actively seeking information on which tests are available locally and deciding whether or not they are suitable for integration into current diagnostic pathways.

8. Education/training

In general, there is a lack of training for pathologists and other clinicians on how to use and interpret molecular diagnostic tests. Whilst some schemes such as UK NEQAS (The United Kingdom National External Quality Assessment Service) do exist, these do not cover all available tests. It is essential that both trainee and consultant clinicians/pathologists have access to educational courses in molecular diagnostics and that the time and funding required to attend such courses is available to them. Improvements in the dissemination of molecular diagnostics knowledge and greater access to high quality training opportunities are required. Furthermore, patient education may also play a role, with well-informed patients being well placed to identify suitable tests for their disease and request these from their clinician.

3. Solutions that address key barriers within the roadmap

Subsequently, a group discussion took place where delegates were asked to pinpoint eight key challenges that could be taken forward by the group with the aim of identifying achievable solutions (see Figure 2). Finally, delegates were asked to select which challenges they would like to consider in greater detail, in order to create recommendations for further action by the CM-Path Molecular Diagnostics Forum. Five of the eight challenges were discussed during a breakout group session, as summarised below.

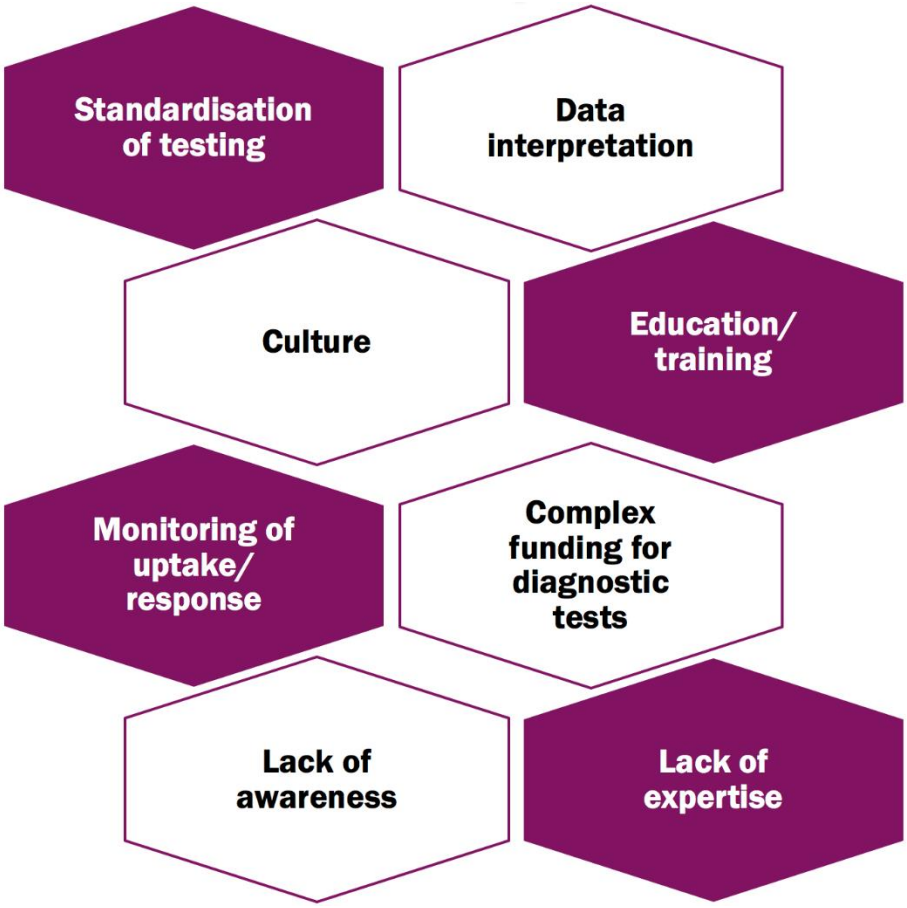

Figure 2 – Eight key challenges to the development and implementation of molecular diagnostic tests.

1. Standardisation of testing

Currently, there are many options for diagnostic tests that can be used in clinical practice. This results in variation in the tests used across different regions of the UK. The delegates recommended that UK NEQAS should advise on standard tests to ensure molecular diagnostic testing across the country is uniform, robust and informative. In order to ensure accuracy and consistency in how tests are performed and interpreted, it was recommended that standard operating procedures (SOPs) should be developed and that relevant staff should regularly participate in External Quality Assessment (EQA) exercises. In particular, tissue handling is a key component in accurate diagnostic testing. It would be useful to understand the extent of variation across the NHS in how tissue samples are collected and processed. Following this, guidance should be produced to ensure that

sample collection, fixation and processing is standardised; this should be educative and highlight the important effects of tissue handling on downstream analyses.

2. Data interpretation

Molecular diagnostic tests can generate a vast volume of data and a robust infrastructure is required to interpret these correctly. As outlined below in greater detail, staff performing and interpreting such tests will require further training to ensure accuracy of results. In particular, it will be vital to train both pathologists and other clinicians in data interpretation, to ensure that results are considered in the light of each case's overall clinico-pathological context. IT systems will have to be improved to process and store these data; these systems will have to be user friendly and compatible with existing software to ensure that results can be transferred between different departments/hospitals and added to traditional reports so that fully integrated reports containing morphological, immunohistochemical and molecular information can be provided to the treating clinician. In time, it is likely that emerging computational techniques, such as Artificial Intelligence, will assist in data interpretation to make the process more efficient. Furthermore, whilst creation of a centralised repository will facilitate data sharing for both clinical and research purposes, specific legal and ethical issues, including the requirement for informed consent, will have to be considered before this can be achieved.

3. Culture

To ensure that new molecular diagnostic tests are identified and implemented in a timely fashion, a change in culture amongst NHS clinicians, pathologists and laboratory staff is required. These individuals must embrace the opportunities that emerging technologies provide, rather than remaining attached to more tried and trusted methods. Delegates felt that, in particular, pathologists should be driving the innovation of molecular testing. This could be facilitated by the sharing of case studies detailing how new tests have previously been implemented successfully or the creation of a repository for details of molecular diagnostic tests that are currently in development or that have already received regulatory approval. This cultural change will likely require closer working with colleagues from other medical specialties (for example, oncology) and the earlier involvement of pathologists in all aspects of research. It was felt that the multidisciplinary team (MDT) meeting was an ideal opportunity to discuss issues relating to molecular diagnostics including interesting case studies, uptake of tests, turnaround times, missed opportunities for targeted drugs and sample processing/quality. Another way to change NHS culture would be to run a national workshop on the topic, involving both clinical and laboratory staff as well as NHS managers.

If they are empowered to demand their own molecular diagnostic tests, patients can also play a role in improving their own care and, thereby, drive change in the NHS. The NCRI Consumer Forum may be able to facilitate this change through education and mentoring of patients and by enhancing communication between patient representatives, pathologists and other clinicians.

4. Education/training

To create a workforce that is able to deliver high quality molecular diagnostic services, further education and training in the area is urgently needed. Undergraduates should be exposed to molecular pathology and encouraged to consider careers in academic and molecular pathology. Currently, only two weeks of the five-year Royal College of Pathologists postgraduate training programme is specifically dedicated to molecular pathology. Delegates recommended that molecular pathology should have a more prominent role in the postgraduate curriculum, but the exact nature of this training remains to be defined. In addition, it is also essential to upskill the senior pathology workforce through short courses that are compatible with their existing NHS commitments. It was

agreed that training should also be cross-discipline and cross-sector, to include clinicians, nurses, laboratory staff and industry. When deciding upon the exact form of training to provide, we should identify best practices from other countries as well as ensuring that adequate financial support is available to fund training events.

5. Monitoring of uptake/response

As previously discussed, there is currently no systematic monitoring of the nationwide uptake of molecular diagnostic tests. Therefore, there is a large gap in knowledge regarding current practice across the UK. The NHS England Innovation Scorecard is produced on a quarterly basis by the Health and Social Care Information Centre (HSCIC) with the aim of reducing variation in adoption of NICE Technology Appraisals. By doing so, it enables benchmarking and increases transparency to patients and the public. Whilst it does not currently report on molecular diagnostic tests, the delegates recommended that these should be included in future. Furthermore, the Royal College of Pathologists could ensure that NICE recommended molecular diagnostic tests are outlined in their guidelines and standards.

Finally, the imminent NHS genomic reconfiguration will bring about a new molecular diagnostics test directory and commissioning system, which may improve the availability of- and access to- diagnostic molecular tests for cancer (and rare diseases) in the future.

Appendix 1 – Summary of Presentations

Professor Graeme Black, University of Manchester

Despite the fact that precision medicine is at the heart of the UK NHS Strategy, rare disease diagnosis is still often delayed and inefficient. Furthermore, therapeutic intervention for rare disease is either unavailable or, when it is, there is significant inequality of access. Much of Professor Black's academic work has focused on rare ophthalmic diseases, such as congenital cataract and inherited retinal disorders, for which he has developed and delivered genomic diagnostic testing since 2012.

The first step in the pathway of developing this diagnostic testing was to define the need; this involved a multidisciplinary approach to measure patient need including medical support, psycho-social support and assistance with practical needs. The next phase of the pathway was to develop the genomic technology and then to translate this technology into clinical practice, which required it to be reliable and scalable. Further considerations needed to be taken for data protection, usage and sharing, and ensuring multidisciplinary reporting. Finally, work was carried out to measure the benefit of the test, which required care pathways to be carefully defined and evaluated.

The pathway for developing a molecular diagnostic test is complicated and lengthy; it requires one to adopt new skills and work with a broad range of research and clinical groups including health service research, improvement science and health economics. This also requires working across NHS organisations at all levels; crucially, ensuring financial and managerial 'buy-in' to ensure effective delivery of changes. Future considerations for diagnostic testing include the current inequality of commissioning of tests across the UK and a lack of workforce training, which will represent an ongoing barrier to implementing precision medicine as costs for genomic testing begin to decrease and become more affordable.

Dr Andy Feber, University College London

Dr Feber has developed UroMark, a molecular diagnostic test for the non-invasive detection of bladder cancer, which demonstrates significantly better sensitivity and specificity compared to the current standard of care dipstick test. In comparison with the traditional patient care pathway, the use of UroMark would allow a considerable cost saving benefit per patient.

The development of a diagnostic test takes a long time with multiple rounds of funding required. Initial steps in developing diagnostic tests are the identification of unmet clinical need, testing and validation. It's important to understand where the test would fit within the current or redesigned patient care pathway, not just within the UK but also other countries, especially Europe and the USA. The next phase of the pathway is focused on economics; does the new diagnostic test result in a cost saving? A test that is shown to be cost-effective will subsequently require regulatory approval and recommendation; it is therefore essential to become familiar with regulatory bodies including NICE and the U S Food and Drug Administration (FDA). A further consideration is Intellectual Property, which should not impact your ability to publish the work if interaction with a Technology Transfer Office is sought early. It is also essential to keep in mind what accreditations might be required, such as CE marking and ISO standards, as your diagnostic test will need to meet these regulatory standards before it is approved for clinical use. Finally, it is useful to identify

commercialisation options early; this could include partnering with other organisations or developing a spin-out company.

Becky Albrow, The National Institute for Health and Care Excellence (NICE)

The Centre for Health Technology Evaluation (CHTE) at NICE provides technology appraisals and guidance on diagnostics, medical technologies and interventional procedures. The diagnostics and medical technologies programmes were established in 2010, aiming to improve the timeliness and consistency of adoption of medical technologies and diagnostics with the potential to (i) improve patient outcomes, (ii) reduce costs and (iii) provide system benefits (e.g. facilitate service redesign).

The value of medical technologies and diagnostics varies depending on your perspective; NICE takes the perspective of the NHS and Personal Social Services (PSS). However, interpretation of clinical and cost-effectiveness can be a challenge for diagnostics due to many factors such as the complexity and variation in diagnostic and care pathways, real world implementation uncertainty and rapid product evolution. NICE have therefore taken the decision to defer to a Diagnostics Advisory Committee (DAC), an independent decision-making body that bases its recommendations on review of clinical and economic evidence.

NICE also has an adoption and impact programme that is responsible for identifying ways to overcome potential barriers to the implementation of technologies and develops web-based adoption support resources. Once NICE have made a recommendation, it can sometimes be difficult for the information to be circulated to the relevant clinical communities. Recently, the Royal College of Pathologists dataset for histopathological reporting of colorectal cancer highlights that NICE recommends to universally test all colorectal cancers for MMR status at the time of diagnosis, with the purpose of detecting Lynch syndrome. This has been helpful to ensure information is circulated appropriately. It should be noted that NICE cannot currently track the use of diagnostics within the NHS and, therefore, cannot evaluate the impact of recommendations that is has made.

Jane Coppard, Roche Diagnostics

Currently, in England, there is no direct mechanism for reimbursement for laboratory tests (tariff funding), meaning that tests have to be funded out of the main laboratory budget. Laboratories are mostly funded by their associated provider organisation (e.g. NHS Trusts) and, therefore, funding of diagnostic test depends on provider funding for the overall care pathway in which they are situated.

Analyses carried out by Cancer Research UK (CRUK) demonstrated that in 2014, 16000 melanoma, lung and bowel cancer patients missed out on an appropriate molecular test, which translated to 3500 patients missing out on a targeted treatment that might have been of clinical benefit [1]. In 2016, multiple organisations including CRUK, The British In Vitro Diagnostic Association (BIVDA) and The Association of the British Pharmaceutical Industry (ABPI) came together to achieve tariff funding for six molecular diagnostic tests for cancer [2].

Looking forward, the NHS genomic reconfiguration is likely to bring changes to the way that molecular diagnostic tests for cancer are commissioned. For industry, it's important to work closely with NHS England to ensure we keep abreast of these new developments. However, in the current landscape, it is also recommended that those developing molecular diagnostic tests initiate early conversations with the payor.

[1] https://www.cancerresearchuk.org/sites/default/files/policy_august2015_mdx_final.pdf
[2] https://www.abpi.org.uk/media/1606/commissioning_of_molecular_genetic_tests_for_cancer.pdf