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Stratified Medicine: Discovery to patient – Mind the gap

ABPI 2014 R&D Conference Report

The ABPI represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK.

Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. Our members supply 90 percent of all medicines used by the NHS, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases.

The ABPI is recognised by government as the industry body negotiating on behalf of the branded pharmaceutical industry, for statutory consultation requirements including the pricing scheme for medicines in the UK.

Preface

Stratified medicine, ensuring that the right patient gets the right medicine at the right time, is widely recognised to lie at the heart of future healthcare. Yet as our report published in November 2014 has summarised[1], although progress is being made, it is perhaps slower than many would have anticipated.

Medicine is moving beyond the era of mass production, to tailored treatments that better reflect an individual's specific set of circumstances. While industry is gearing up for this new era, other sectors in the healthcare landscape face significant challenges to their traditional ways of operating. If the undoubted benefits to patients and to UK plc are to be realised, all stakeholders will need to play their part.

It was therefore gratifying to see representatives from all key sectors – industry, academia, the NHS, Government, regulatory bodies, patient representatives, funding agencies and others – come together at the 2014 ABPI R&D Conference to discuss both opportunities and obstacles to progress. Only by working in partnership will the full benefits of this new era of medicine truly be realised.

This report is a summary of the conference.

1 *The stratification of disease for personalised medicines: Research-driven recommendations to strengthen a unified UK strategy through a stakeholder alliance*. Available at http://www.abpi.org.uk/our-work/library/medical-disease/Pages/100914.aspx

Executive summary

Stephen Whitehead,

Chief Executive, ABPI

Stratified medicine, getting the right medicine to the right patient at the right time, is widely recognised to be central to the future of healthcare. It is already a reality, particularly in fields such as oncology. Nevertheless, progress has not been as rapid as many had hoped.

The UK holds a world-leading position in stratified medicine, thanks to the excellence of its academic research base, strong industry presence, increasing collaboration between the two sectors, and supportive actions by Government and funders. Important underpinning work is being carried out to identify the molecular mechanisms of disease, while 'omics' and other technologies, as well as clinical data in electronic health records, are providing key tools to stratify patients.

Public sector funding bodies such as the Medical Research Council (MRC) and the National Institute for Health Research (NIHR) and charities such as Cancer Research UK (CRUK) have recognised the importance of stratified medicine. The MRC stratified medicine initiative is building additional bridges between industry and academia, and it is also addressing the important skills gap in molecular pathology. The NIHR has established an extensive infrastructure for experimental medicine studies, and recently launched Diagnostic Evaluation Cooperatives (DECs) will fill an important gap in the translational landscape.

Patient groups are strongly supportive and need to be involved in discussions about future developments, including those examining cost–benefit analyses and appropriate levels of regulation.

Nevertheless, despite much progress, take up of stratified medicine is patchy in the UK. Implementation is clearly a major issue: there is wide variation in its use across the UK, with no coordinated national strategy around funding of diagnostic tests.

New tools have been devised to support the development of local costed business plans for testing, but a national commissioning framework would also be beneficial to drive forward consistent practice and promote implementation.

Current difficulties with implementation may reflect the fact that diagnostics have not traditionally received as much attention as therapeutics, yet are pivotal to stratified medicine. A greater focus on diagnostics is needed, including joint evaluation of diagnostics and therapeutics. The evidence base is typically thin for diagnostics, and more work is needed on evaluation, ideally linking diagnostic use to outcomes.

Stratified medicine has profound implications for the way medicines are developed, regulated and implemented. Trial design is becoming more focused on likely responders, and adaptive trials are becoming more common. This will present a challenge to regulators, who will need to be more flexible about how evidence is generated to support market authorisation.

Similarly, adaptive pathways, with early approval followed by data capture during initial use, is likely to become more common. Such approaches emphasise the importance of electronic health records as a source of 'real world' evidence to support regulatory decision making.

Stratified medicine may also require more approaches to reimbursement. More flexible reimbursement models may be needed for both medicines and diagnostics, to reflect the fact that benefits are gained by a subset of patients, and that this subset may change as more accurate targeting is introduced. The value of medicines and diagnostics may also vary significantly between conditions.

Stratified medicine is a disruptive technology, but one that stands to benefit all parties, especially patients. Given its widespread ramifications, progress will only be made by all parties working together constructively and flexibly. Stratified medicine has begun to filter into everyday practice, but has yet to achieve its full potential. Concerted efforts are now needed to ensure it becomes a commonplace reality.

Introduction

Introducing the conference, **Stephen Whitehead** (ABPI) drew attention to both the opportunities offered by stratified medicine and the challenges it presented. The UK is well placed to be in the vanguard of implementation, accounting for 10% of global pharmaceutical R&D expenditure and developing one in five of the world's medicines. Yet it is a position that cannot be taken for granted, and 2013 saw the first ever drop in pharmaceutical R&D investment in the UK.

The industry is going through a period of profound change, with stratified medicine a major driver. It is forging new and stronger relationships with a range of partners, including biotech companies, diagnostics companies, the NHS, academia, informaticians and others. While industry is responding to the challenges, a key question is whether the UK policy framework is fit for the new world order. An end-to-end framework is required that embraces better detection of disease, more precise classification and targeted treatments.

In terms of the 'right medicine', stratified medicines are already a fact of life, particularly in cancer, some infectious diseases, and in targeted gene therapy for cystic fibrosis. Companies' medicines pipelines are packed with stratified medicines, and the new era of industry–academia collaboration will see more precisely targeted medicines developed.

Navigating such novel products through the regulatory system is challenging. There is a need to consider new mechanisms, such as smaller and adaptive trials, and early access to medicines initiatives, all of which call for a shift in regulatory mindset.

Similarly, identifying the 'right patients' is not straightforward. In particular, use of 'big data' to provide the basis for patient stratification is still technically challenging. The NHS is undoubtedly data-rich but extracting data in a usable form is in reality often difficult.

As for patients gaining access to medicines at the 'right time', adoption remains a major issue. Affordability will be a challenge when the proportion of national expenditure on health is low by global standards. Industry is playing its part through the pharmaceutical price regulation scheme, having agreed to underwrite growth in the NHS drugs bill for five years – a move that will see the equivalent of £4.5bn flowing back into the NHS, providing scope for the uptake of innovative new medicines.

Presenting the industry viewpoint, **Dr Neil Weir** (UCB) suggested that, despite its seeming drawbacks from a commercial perspective, industry had strongly embraced stratified medicine. The benefits to patients were overwhelming, and it offers opportunities for industry to change fundamentally the way it works.

The UK is in an ideal position to lead in stratified medicine. As well as a strong industrial sector, the UK has an exceptional academic research base and major research funders such as the MRC, NIHR, CRUK and others have bought into the concept of stratified medicine and welcomed the opportunity to forge closer ties with industry.

The upshot has been substantial focus on dissecting the molecular mechanism of disease, leading to the identification of new targets and the

development of appropriately targeted medicines. Large, interconnected data sets are being generated to stratify patient groups, and therapeutic and diagnostic development is increasingly proceeding hand in hand. New omics, imaging and other technologies are adding to the data pool, emphasising the need for skilled informaticians.

Although patient need is an important driver, stratified medicine also offers hope for more efficient medicine development. In theory, targeted medicines tested on selected patients are less likely to fail during costly phase III trials. Trial design is likely to change significantly, particularly with greater co-development of diagnostics. But it is also important to recognise the complexity of stratification – there will not always be simple 'yes/no' binary tests to guide choice of treatment.

Progress will depend on further strengthening of collaborations and partnerships. Disease understanding is being addressed by academia–industry partnerships, while product development is seeing pharmaceutical and diagnostic companies working much more closely.

Presenting the patient perspective, **Alastair Kent** (Genetic Alliance UK) noted that stratified medicine was a rare example where all groups benefit. It should lead to more efficient development of medicines and reduce patients' experience of adverse events. Even so, fragmentation of patient groups raises issues, particularly the fate of those with rare versions of disease.

The implications of stratified medicine are significant. The regulatory framework needs to adapt, to provide appropriate and proportionate regulation that protects individuals from harm but also encourages innovation. The era dominated by the large randomised controlled trial may be drawing to a close, with more innovative ways needed to evaluate safety, quality and efficacy.

Patients need to play a central role in discussions around future regulatory frameworks. Patients obviously have a vested interest in medicines development, and can provide an important perspective on risk–benefit analyses, as well as practical matters such as how trials are organised and how benefits are assessed. With appropriate support, patients should also have input into health technology assessments.

Patients may also benefit from early access schemes and compassionate use of medicines. Pricing and reimbursement will undoubtedly be thorny issues, and development of high-price medicines for growing numbers of small populations is unlikely to be sustainable in the long term, suggesting new financial models will be required.

Stratified medicine also has important implication for health services, with a greater focus on systems and patient pathways rather than conventional organ-based disciplines, and a need for new skills in areas such as informatics and diagnostics. Rare diseases may be in the vanguard of stratified medicine, mapping out new ways of working that will in time filter through into medicine more generally.

Research and regulation challenge

Stratified medicine is seeing ever closer collaboration between industry and academia. **Professor John Isaacs** (Newcastle) described two collaborative ventures – RA-MAP and an NIHR Translational Research Partnership (TRP) – to highlight factors underpinning successful cross-sector partnerships.

The five-year MRC/ABPI RA-MAP programme is focused on biomarker analysis in rheumatoid arthritis. It is undertaking extensive phenotyping of patients early in disease to identify factors associated with disease progression, with substudies examining factors such as remission.

The programme involves 10 academic groups and a similar number of industry partners, plus contractor organisations, presenting a great organisational challenge. Central to its success have been a dedicated programme manager with a good understanding of both sectors, open-mindedness, positive attitudes and a spirit of collaboration among participants from both sectors, a willingness to adapt procedures, and flexibility, particularly in resourcing. Hence, when it became apparent that patient recruitment was an issue, funds could be released to engage a contract research organisation. High levels of industry engagement have been critical, alongside a governance structure encouraging open communication and devolved decision making.

Challenges have included the inevitably complex but ultimately successful contract negotiations, managing and openly sharing the wealth of information generated, and interruptions caused by people moving or changing responsibility.

TRPs focus on early clinical development. They aim to support genuine partnerships between industry and leading groups in academia – nine in Professor Isaacs' Joint and Related Inflammatory Diseases TRP. The NIHR Office for Clinical Research Infrastructure (NOCRI) acts as a single point of contact and negotiates agreements based on standard templates to enhance industry access to world-class academic expertise and associated patient resources.

Some 20 or so studies have been completed or initiated at the Joint and Related Inflammatory Diseases TRP. Many of the same factors important to the RA-MAP initiative apply to the TRP, particularly the genuine spirit of collaboration and work towards shared goals, while NOCRI's involvement greatly facilitates entry for industrial partners by acting as a single point of access to the academic groups.

Addressing the question of skills, **Professor Sir John Savill** (MRC) drew attention to the MRC's considerable investment in stratified medicine, as well as the critical importance of molecular pathology. One of several investments in this emerging field, the MRC's Stratified Medicine Initiative has provided £60m funding for nine academia–industry partnerships, with new awards to be made shortly.

Given the importance of patient stratification, molecular pathology is another important part of the jigsaw. Unfortunately, academic pathology has been in decline, while many hospitals have outsourced sample processing, leading to an important loss of proximity between research, pathology services and clinical care. In addition, the translational pathway for diagnostics is complex and poorly connected. These and other issues were documented in a recent review of molecular pathology led by Professor Sir Robert Lechler[2].

The future is likely to see a growth of more sophisticated methods of analysis, leading to complex data sets that will be harder to interpret – highlighting the importance of developing a suitable skills base and technical infrastructure.

As one step towards this, the MRC has teamed up with the Engineering and Physical Sciences Research Council to establish molecular pathology 'nodes' – up to eight hubs that will support capacity development. Nodes will have an important interface with stratified medicine consortia, and feed into the Innovate UK's Precision Medicine Catapult and NIHR DECs.

The challenges that stratified medicine pose to the regulatory system were the focus of **Dr Tom Lillie** (Amgen). There is great potential to link genomic and clinical data, to identify candidate biomarkers. Breast cancer provided an example of where such factors had led to the fragmentation of a single disease into multiple subtypes. Importantly, subtypes are generally associated with multigene signatures, evidence that the 'one-test, one-drug' model is rapidly becoming outdated – a trend that will pose a real headache to regulators.

Use of electronic health records has enormous potential, though data linkage is challenging. Increasingly, data will need to be pooled on patient populations, potentially across national borders. Consent issues will be crucial to support such work. Variation in ethics committee decision making can hold back studies, while regulation relating to data privacy, although important, again has the potential to impede research. There may be merit in innovative solutions whereby patients are able to 'donate' their data or samples for research.

Industry has been based on competition, but in the new environment incentives may be needed to encourage collaboration not just in 'discovery' phases but during trials as well. Intellectual property incentives might be necessary to support therapy development for small populations or to encourage new uses for old drugs.

Electronic health records could play a greater role in trials. A Swedish cardiovascular study, for example, was run entirely through electronic health records, including recruitment, randomisation and data collection.

The interplay between diagnostic and treatment can complicate market authorisation, particularly when

2 MRC Molecular Pathology Review. http://www.mrc.ac.uk/documents/pdf/mrc-molecular-pathology-review/

biomarkers become available part-way through clinical development. Dialogue with regulatory authorities and a flexible approach will be important – as illustrated by a case in which the efficacy of a cancer drug was demonstrated by retrospective analysis as additional biomarkers became available.

Reimbursement policies may also need to adapt, with a need to examine therapies and diagnostics together. As targeting becomes 'cleaner', the value of therapeutics may change, calling for flexibility in pricing; similarly, the same therapeutic may have different values in different conditions.

Adaptive licensing is a further innovation posing new challenges. Again, electronic health records will be a valuable tool to support such an approach. It is likely to drive significant changes in trial design, and arguably also needs to be linked to adaptive pricing. There may also be increasing use of post-marketing commitments, such as validating the testing carried out to support use of targeted therapeutics – novel territory for companies.

Biomarker and diagnostic development are highly dynamic fields, and regulation differs markedly in the USA and UK. As biomarkers typically evolve more rapidly than therapeutics, tight linkage between the two may not be ideal – particularly as the 'one-test, one-drug' model is superseded. The use of large data sets will also pose issues for regulators, as these are generally held in academic settings.

Professor Mark Caulfield (Queen Mary, University of London and Genomics England) described one of the world's most ambitious initiatives in stratified medicine, the 100K Genomes Project.

Through large-scale whole genome sequencing allied to intensive clinical phenotyping, the 100K Genomes Project is pioneering the application of genomic technologies to characterise three classes of patients – those with rare inherited diseases, cancer, or a range of infectious diseases. It is being run as an 'NHS transformational programme', with a view to establishing systems that can be applied routinely within UK healthcare.

Rare diseases collectively affect some three million people in the UK. In more than half of all cases, no underlying cause is identified. Whole genome sequencing can increase discovery of disease-causing mutations by some 25%, improving patient management and providing new therapeutic leads. Sequencing is coordinated with extensive clinical phenotyping, and phenotyping strategies are being shared widely to promote standardisation. Genomics England is working with multiple partners, including with NIHR Rare Diseases Translational Research Collaboration, the NIHR Bioresource, and the Deciphering Developmental Disorders initiative, opening up access to affected families globally.

Cancer genome sequencing can help to identify the critical 'driver' mutations responsible for the development of cancer and provide a better understanding of cancer heterogeneity. The project has forged links with the International Cancer Genome Consortium, to pool resources, and with UK initiatives such as the CRUK Stratified Medicine Programme. Again, sequencing is complemented by extensive phenotyping, as well as linkage to risk factors and information held in cancer registries.

Work in infectious diseases focuses on susceptibility to Mycobacterium tuberculosis and viruses such as HIV and hepatitis C, as well as extreme responses to sepsis.

Genomics England is working closely with NHS England, which will ensure samples are collected from patients for analysis.

Through a partnership with Illumina, the project will have access to the latest sequencing technology, which will be housed in a new £27 million NHS Genome Sequencing Centre being built at the Wellcome Trust Genome Campus at Hinxton. A new data centre, funded by the MRC, will store and provide access to pseudonymised data. Up to 12 NHS Genomics Medicine Centres are to be established to enroll patients.

Education of healthcare professionals is a further priority, being taken forward in partnership with Health Education England. The project also plans to establish Clinical Interpretation Partnerships, combining clinicians and researchers, to lead on analysis of the data. An open innovation environment will be established, with industrial partners encouraged to contribute in pre-competitive consortia.

In discussion, delegates raised the importance of electronic health records and whether, following the issues with care.data, industry had a role to play alongside patients and the NHS in building public trust. As well as issues such as data privacy legislation, lack of public trust was seen as a potentially important obstacle to electronic health records research. Gaining the support of GPs was felt to be important, as their negative reaction to initial care.data plans provided a focal point for wider opposition. Some reservations were raised about an active role for industry at present but it was pointed out that without industrial partnership the full value of the programme in generating new diagnostics and treatments might be challenging to realise.

It was also noted that, for small patient populations, costs of treatment per patient were inevitably higher. Incentives have been established to promote work on rare diseases, but what will happen when 'common' diseases become fragmented? One important factor will be corresponding efficiencies in medicine development, as stratification will proceed hand-in-hand with a better understanding of diseases, enhancing target identification and underpinning

trials with selected patients, factors likely to reduce the risk of costly late-stage failure. Large-scale randomised controlled trials are likely to become less appropriate, with increasing scope for more flexible adaptive trials and innovations such as adaptive pathways and greater use of real world data.

Indeed, a key question is whether regulators are engaged with the changing landscape. It was felt that bodies such as the European Medicines Agency were aware of the implications of stratified medicine and engaging in constructive discussions with industry and patient groups. Adaptive licensing is being piloted. Nevertheless, regulators are in a difficult position, as society becomes increasingly risk-averse. More sophisticated risk–benefit analyses are needed, recognising that medicine development can never be risk-free, and eliminating all risk would end the development of new medicines.

A political perspective was provided by **George Freeman**, the UK's first Minister for Life Sciences. He stressed the UK Government's commitment to supporting the pharmaceutical sector and its appreciation of the importance of stratified medicine to the future of healthcare.

Mr Freeman suggested that the UK life sciences were in 'rude health', evidence that the Government's Life Sciences Strategy was working. Some £3.5 billion of new investment had been attracted since the strategy was announced, securing some 11,000 UK jobs. While he acknowledged that large companies faced major challenges, the overall picture was of a vibrant and world-leading sector.

The disruptive nature of stratified medicine has prompted the Government to launch an end-to-end review of innovative medicines and medical technology. This was, he suggested, a genuine consultation and he urged all parties to contribute, to help shape a landscape that accelerates the delivery of new medicines to patients.

Mr Freeman pointed to recent Government investments in stratified medicine, including Genomics England, Innovate UK's Precision Medicine Catapult and NIHR DECs. While acknowledging the NHS's significant financial pressures, he suggested that digitisation of health records would open up new opportunities. Furthermore, a commitment to the sector and policy stability provided a platform to build on the UK's leadership position.

The NHS response

The session opened with the launch of two ABPI reports on implementation of stratified medicine in the NHS.

Dr Louise Leong (AstraZeneca) launched the first report[3]. The motivation for the project was the industry's identification of adoption of stratified medicine in the NHS as a particular challenge. This 'baselining' project, run in collaboration with the Royal College of Pathologists, examined the current state of stratified medicine in the NHS, barriers to its implementation, and opportunities for wider and faster uptake for patients. Although focused on applications outside oncology, to be ready for the growing non-oncology portfolios and to complement the second cancer-specific project (see below), the project incorporated insight from the oncology field.

The project first involved a literature search to identify non-cancer medicines for which stratified approaches could be adopted (some 41 potentially targetable medicines were identified), and deep dive interviews of local health economies to explore current practices. To gauge future demand in the health service, a survey of ABPI member companies on their pipelines of stratified medicines likely to launch in the next three years was undertaken. This revealed that the number of new stratified medicines is set to grow substantially – particularly in cancer (including their companion diagnostic) – at a compounded annual growth rate of 27%. Finally, a nationwide stakeholder survey (with the majority of respondents based in the health service) found that stratified medicine was largely felt to provide benefits, but its full potential was not being realised. Implementation varied widely, but in most areas was felt to be incomplete. The most significant obstacles to uptake included availability of companion diagnostic tests, reimbursement and availability of funding.

To address these issues, the project made a number of recommendations. These included improved horizon scanning of stratified medicine pipelines to improve planning, a more coordinated and consistent approach to commissioning, and greater coordination among stakeholders prior to launch of diagnostics and therapeutics. The provision of services could be enhanced by taking a networked approach to encourage high-quality, cost-effective delivery, and improved management of the sample pathway. Decision-support tools would also help clinicians integrate stratified medicine into their clinical decision making.

A second collaborative project, summarised by **Ben Osborn** (Pfizer/ABPI POI), focused on cancer. The CMD-ImPACT project aimed to provide a clear picture of current practice and future challenges, examining the actual costs and benefits of stratified medicine in cancer, and developing practical tools to support implementation.

A wide-ranging consultation identified the lack of a national commissioning framework as the biggest single issue. Combined with considerable variation in how diagnostic tests are funded, the result is widespread heterogeneity in use of tests – a postcode lottery.

To support a more coherent approach, the project developed a business planning toolkit[4] to enable local pathology laboratories to quantify and cost their likely use of diagnostics. Potentially usable at a hospital or regional level, the toolkit enables a rational business case to be presented to managers and commissioners.

The project also conducted a detailed survey of some 30 sites across the UK to map out the current landscape of stratified medicine use in cancer, collecting data on key issues such as the current volume of tests, turnaround time and failure rates. A summary analysis is due to be published this year.

In practice, stratified medicine depends on the activities of pathologists working in the NHS, whose role was discussed by **Professor Ian Cree** (Warwick). Academic pathology has been under pressure in recent decades, shrinking to just one tenth of its former size. This has had considerable impact on translation. The importance of pathologists has belatedly been recognised and a number of initiatives have been launched to promote the discipline.

Despite its decline in universities, there remain 25,000 staff working in NHS diagnostic laboratories, accounting for £2.2 billion annual expenditure or 4% of the NHS budget. Some 900 million tests are carried out each year – including those supporting the use of targeted medicines.

The Royal College of Pathologists has established an interdisciplinary committee (chaired by Professor Cree) to promote molecular pathology. As well as the joint work with the ABPI with the ABPI it has also developed professional standards, provides training and education, and published guidance on molecular pathology in cancer.

Professor Cree pointed out that stratified medicine has to reflect the realities of pathology practice. Samples are likely to be small and repeat sampling from individual patients is rarely feasible. Technologies need to reflect such constraints, but next generation sequencing and other novel approaches can work with very small amounts of material. There is potential to carry out tests inhouse or to outsource to central facilities. While centralisation of specialist services may seem beneficial, performing analyses close to patients and their clinicians also has its advantages.

Professor Cree said that pathology laboratories have embraced new molecular technologies alongside their traditional work, and are well placed to implement a new era of stratified medicine. The sector's quality assurance systems are effective at maintaining standards. The biggest

3 *Stratified medicine in the NHS: An assessment of the current landscape and implementation challenges for non-cancer applications.* http://www.abpi.org.uk/our-work/library/medical-disease/Pages/121114.aspx
4 http://www.rcpath.org/cmd-impact/cmd-impact

issue is the availability of funding to support the use of tests. While local business planning tools are undoubtedly helpful, overcoming this obstacle fully may depend on a national commissioning framework (and perhaps the political will to avoid a postcode lottery).

With commissioning identified as a central issue in implementation, **Mr Malcolm Qualie** (NHS England) provided a commissioner's viewpoint on the challenges presented by stratified medicine.

The NHS faces major challenges, including financial constraints, rising expectations and an ageing population. Drug costs are a sizeable proportion of NHS expenditure and are rising rapidly, particularly in specialised areas of commissioning. Even so, there is plentiful evidence that drugs are not being used optimally, underpinning a major focus on patient-centred medicines optimisation.

Although some medicines are being used in a targeted way, stratified medicine presents several challenges to specialised commissioning. There is a lack of awareness of the full range of tests available and when they are likely to be used, considerable variation in current practice, and concerns about the quality of testing. Different mechanisms of funding of tests also raises difficulties – some are funded by industry, some by providers as part of routine care, and others require new funding.

How diagnostic services should be organised is not clear, while the practicalities of testing may introduce delays into treatment pathways, particularly if samples are shipped to external centres for analysis.

From a commissioner's point of view, it was helpful to have as much notice as possible when a test would be needed, how much it would be likely to cost, and how many tests would be needed. Diagnostics need to be supported by suitable commissioning tools and data flows, and industry and the NHS need to work together to develop such systems to support implementation and timely access to medicines.

Diagnostics play a critical role in stratification, and **Dr Tim Pitfield** (Janssen) provided a historical perspective on diagnostic development. He suggested that many of the issues faced today are not new. Novel approaches, initially automation and later emerging molecular technologies, have always been challenging to implement. However, advancing technologies and a greater awareness of the heterogeneity of disease mean the situation is increasingly complex. As in the past, though, successful and timely adoption remains the key issue today.

It is probably also true that the real value of diagnostics has not been fully appreciated. They are generally perceived as 'low-cost, low-value' items (despite their importance to clinical decision making).

There are ways in which adoption might be enhanced. Early partnering of therapeutic and diagnostic would be helpful, including joint trials from phase II onwards (ideally leading to joint approval of drug and companion diagnostic). Clear cases of the value of adoption need to be made to the NHS, perhaps by working with 'adoption stakeholder partners' (possibly Academic Health Science Networks or NIHR DECs). There is also a need for more support of diagnostic evaluations and for more rapid evaluation by bodies such as NICE.

In discussion, the likelihood of national commissioning was raised, but it remains unclear whether national frameworks will be introduced. Equity of access was thus likely to be an issue for the foreseeable future, with the possibility that some trusts would adopt testing routinely but others would not, exacerbating a postcode lottery.

It was also suggested that moving forward too rapidly could create problems, particularly if tests generate large amounts of hard-to-interpret data. A good evidence base was needed to support clinical implementation. It was suggested that the UK has a strong pathology infrastructure in place and well-established quality assurance mechanisms to ensure that tests are carried out routinely to a high standard. There was, however, a need for more outcome data to be linked to diagnostic use – a point picked up in the next session.

Valuing stratified medicine

Professor Adrian Towse (Office of Health Economics) brought a health economics perspective to the valuing of diagnostic tools. There are several ways in which diagnostics can generate value, for example by preventing adverse events, reducing time delays in the selection of treatments, increasing adherence to medication, enabling drugs to be targeted to specific small populations, and reducing uncertainties about value in risk-based decision making.

In terms of the processes that can be used to assess value, therapies and diagnostics can be reviewed together (as NICE is able to do, though some countries maintain separate programmes, raising issues for integration). If diagnostics are launched separately, or multiple diagnostics are available, separate diagnostic-specific mechanisms are required.

Crucially, assessment requires evidence, and generating the evidence can be challenging – not least because of the large costs of trials. If diagnostics are available during drug development, trial design can incorporate both. Alternatives include retrospective analysis of trial data or prospective studies, or newly commissioned trials. The evidence to date is that such work may often be publicly funded, emphasising the need for public investment to generate evidence to inform decision making.

Professor Towse pointed to a number of issues raised by evidence-based assessment. These include the need to align incentives, so that achieving greater value benefits both payers and manufacturers. This may require collecting evidence alongside the use of the test, price flexibility, allowing for price increases as additional evidence of value becomes available. Some form of additional intellectual property protection for diagnostics may be needed, to recognise the costs involved in generating evidence of clinical utility. These were among the recommendations made in a recent Academy of Medical Sciences report on stratified medicine[5].

Even after NICE approval, however, implementation remains a key issue. Professor Towse drew attention to the French model, where hospitals draw on a central body that provides tests at no charge. Financial justification comes from relatively simple calculations based on the sums saved in drug costs through use of a test and targeted treatment. Although highly effective at promoting use of tests, this model is not one that easily translates to the UK system.

The evaluation of diagnostics is part of the remit of NICE, whose processes were described by **Professor Adrian Newland** (Barts Health NHS Trust and NICE diagnostics committee).

Companion diagnostics can be evaluated through NICE technology appraisals, with drugs being recommended for use when a suitable diagnostic is available. However, these processes do not evaluate the diagnostics themselves, or consider implementation, and in some cases multiple diagnostics may exist. More specific evaluation and guidance on use is provided by the Medical Technologies Evaluation Programme and the Diagnostics Assessment Programme.

Evaluation of diagnostics presents multiple challenges. They rarely provide patient benefits directly, only influencing the use of therapies, there is generally little evidence available, and the speed of diagnostic development is often very fast. The challenge for NICE is to balance a desire for timely uptake with the need for rigorous evidence-based assessment.

The Medical Technology Evaluation Programme focuses on simple tests, and uses a straightforward cost consequences model, based on information submitted by manufacturers. The Diagnostics Assessment Programme uses more sophisticated approaches examining cost-effectiveness and clinical benefit. Ideally, this is based on impact on patient outcomes, but such evidence is rarely available. Cost-effectiveness calculations therefore require significant expert impact and sophisticated modelling, so the process is typically longer.

However, a NICE recommendation is not sufficient to guarantee reimbursement for a diagnostic. Take up is being impeded by unclear pathways of adoption, variation in reimbursement practices and NHS budgeting practice. While various approaches may be required to drive up uptake, there remains a need to generate evidence of cost effectiveness, where new initiatives such as NIHR DECs may have an important role, and for continuing discussions on the levels of evidence required for assessment of diagnostics.

As well as pre-approval evidence, data from the 'real world' after licensing can inform discussions of value, and more generally promote stratified medicine. **Dr Greg Rossi** (AstraZeneca) discussed key issues surrounding use of real world data, focusing on retrospective analysis of routinely collected clinical data and prospective non-interventional cohort studies.

Such data have been collected for other purposes, generally to support patient care. Critical questions include how accurate, complete and informative data are, while the complexity of the data landscape presents a major challenge. Data are typically stored in different formats in multiple repositories that may be difficult to integrate. Extraction, integration and analysis of such data, with patient approvals, is rarely straightforward.

Further complexity is introduced by the diversity of markers. Rather than the 'one-test, one-drug' model,

5 Academy of Medical Sciences. (2013) *Realising the potential of stratified medicines*. London: Academy of Medical Sciences.

patients are likely to be characterised by a range of markers (such as different mutations in cancer) each of which might inform decision making.

Adaptive pathways is enabling real world data to feed into the regulatory process. For medicines with breakthrough designation or subject to accelerated approval, evidence from use after initial licensing will be an important supplement to data from randomised trials. Patient access schemes also provide a framework through which more information can be gained on drug effects in actual patients.

Dr Rossi suggested that a more integrated patient-centred development cycle was needed, in which initial approvals following trials are followed by collection of real world evidence, identifying opportunities for improvement and informing the design of new trials. Greater use of real world evidence will depend on better systems infrastructure, and adoption of common standards to facilitate sharing and integration of data. This needs to take place within a well-established ethical and legal framework with, crucially, patient and public support.

With data predominantly in the research domain, this calls for extensive pre-competitive collaboration. Ideally, this approach has the scope to link use of diagnostics to clinical outcomes, supporting clinical practice and diagnostic evaluation.

In discussion, **Dr Paul Catchpole** (ABPI) suggested that current systems were imbalanced, focusing more on therapeutics than diagnostics. More emphasis needed to be placed on diagnostics (including more funding for diagnostic evaluation), with greater coordination of therapeutic and diagnostic evaluation. Regulators also needed to recognise the changing nature of the evidence base.

In discussion, the concept of value-based pricing was highlighted as an interesting model, but was it likely to become a reality? It was suggested that dialogue was needed, and that early access schemes might be a route by which it could be explored. The underwriting of the growth in the NHS medicines bill by industry included scope for value-based pricing. Clearly, value of medicines did vary over time, between indications, and when specific populations are identified that gain most of the benefits from a medicine. Currently, the only variation in medicine prices is in a downward direction, and there is considerable inertia in the system inhibiting other forms of price flexibility.

Conclusions

In his concluding statement, **Dr Neil Weir** (UCB) identified three key themes that had emerged in the meeting. The first was 'making it happen': stratified medicine offers a great opportunity, and is beginning to influence practice, and the major challenge now is to drive it forward so its full potential is realised. Electronic health records were a second important theme, with frequent mention of their potential to feed into biomarker identification and patient stratification, and to be linked to other biomarker data. Finally, Dr Weir stressed the fundamental importance of patients, whose data, samples and electronic health records facilitated the entire process.

Rounding up the event, **Dame Sally Davies**, the UK's Chief Medical Officer, elaborated on these themes. She highlighted the NHS and its cradle-to-grave care system as a unique opportunity for the UK. The NIHR has established a research platform integrated into this system, with close ties to the MRC not only driving forward translation but also ensuring that the UK maintains its reputation for scientific excellence.

Work with charity and industry partners can ensure full value is obtained from the platform established to support the development of stratified medicine. Alongside other NIHR structures, the new DECs will generate important evidence to support diagnostic evaluation and accelerate their uptake into the NHS. An important role could also be played by the Collaborations for Leadership in Applied Health Research and Care (CLAHRCs), as a test bed for innovative new technologies.

Electronic health records are a high priority. NIHR Biomedical Research Centres have been challenged to rationalise and enhance their record systems to promote research and collaboration. Finally, the NIHR has a strong commitment to engaging with patients and the public, who are the heart of all it does. Dame Sally drew attention to the remarkable commitment shown by patients eager to contribute to the 100K Genomes Project despite advanced disease – an almost entirely altruistic gesture to benefit the patients of the future.

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