



Health economics for stratified medicine

Summary of a workshop held on 5 October 2016 by the
Academy of Medical Sciences and the UK
Pharmacogenetics and Stratified Medicine Network

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The UK Pharmacogenetics and Stratified Medicine Network brings together the multidisciplinary groups of professionals that are needed to deliver stratified medicine to patients in the clinic. Through the Network groups of experts from academia, the healthcare sector, regulatory organisations and patient groups have the opportunity to highlight their expertise and form collaborations to analyse patient samples, and interpret their data to stratify patients into the subcategory of their disease, then identify novel drug target sites and develop new drugs and diagnostics to make stratified medicine a reality in the clinic. Our website (www.uk-pgx-stratmed.co.uk) provides a wealth of information for those working in the stratified medicine sector. For further information please contact network manager Christine McNamee cjmcn@liv.ac.uk

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences, or its Fellows.

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Executive summary

On 5 October 2016, the Academy of Medical Sciences and the Pharmacogenetics and Stratified Medicine Network held a FORUM workshop on ‘Health economics for stratified medicine’. The workshop aimed to explore the ‘value’ of stratified medicines and diagnostics and the evidence base underlying new approaches to economic evaluation.

The discussions at the meeting broadly focused on three main challenges: (a) consideration of new elements of value; (b) a new reimbursement model which reflects this value and the needs across different stakeholders; and (c) different standards of evidence. Key points of discussion from the workshop included:

- **Building a broader definition of value** for stratified medicines that incorporates aspects beyond direct health improvements such as reduced switching between treatments, patient ‘trust’ in clinical decisions and ability to work. There should be a drive to better accommodate different stakeholder needs and perceptions of value such as patient preferences.
- Establishing a robust model for **separating the value of a diagnostic and treatment**.
- **Acceptability of alternative forms of evidence** and methodologies used to generate such evidence as there are specific challenges in evidence collection for stratified medicines. It was agreed that there is an important role for academia in working with regulators and policy-makers to explore such methodologies. **Better alignment is needed on evidence requirements** from regulators, health technology assessment bodies, payers and other key stakeholders to drive patient access and provide clear signals for development programmes.
- **Limited evidence generation around diagnostics** which complicates assessment of these technologies. It was agreed that alternative forms of evidence should be accepted where required and in general, evidence generation on diagnostics must be better encouraged and incentivised to ensure that there is a robust evidence base underlying their use.
- Ensuring patient access through **driving uptake and adoption of stratified innovations in the NHS** and establishing flexible pricing and reimbursement models. These models must both reflect the value of an intervention, and the

potential evolution in value over time, as well as creating a mechanism by which innovations such as companion and complementary diagnostics, and combination products, can be appropriately evaluated.

- The overarching need for a **general culture change in the healthcare system**, particularly amongst commissioners and clinicians, moving from a short-term focus on cost-savings to a longer-term view of the benefits of moving towards a stratified approach.
- Achieving a **balance between value to individuals and populations** when assessing medicines, and the benefits of mechanisms such as shared decision-making in supporting choices at a personal level whilst enabling wider evaluation at a population level. It was agreed that to be feasibly incorporated into evaluation, personal utility and patient preferences must be considered at the population level, which will require societal evaluation similar to the quality-adjusted life year (QALY) measure.

Introduction

Stratified medicine offers a compelling opportunity to enhance patient care whilst delivering efficiencies across the healthcare system, enabling optimal treatment selection – the right treatment for the right patient at the right time – through a more targeted approach to therapy. However, as we move towards increasingly stratified, or ‘personalised’, approaches, there will be new challenges in the valuation and assessment of stratified medicines and diagnostics. The evidence generated for health economic models that are central to driving the development and adoption of such technologies in the healthcare system therefore needs to be considered in the light of these challenges.

In recent years, both the Academy of Medical Sciences and the UK Pharmacogenetics and Stratified Medicine Network have played an active role in reviewing and contributing towards the evidence base for stratified medicine.¹ The Academy’s 2013 report on ‘Realising the potential of stratified medicine’ recognised the challenges in health economic assessment of stratified medicines. It described the need for *‘a new definition of value’* for these innovations founded on *‘a strong evidence base for legitimacy’*, and so recommended improved flexibility in pricing for such technologies and a mechanism for distributing value between a drug and diagnostic.² In addition, two roundtables held recently by the Academy and NHS England on a stratified approach to diabetes and cardiovascular disease highlighted the need for strong economic evidence underlying adoption of stratified approaches in the NHS. The UK Pharmacogenetics and Stratified Medicine Network has hosted a number of UK and international events highlighting progress in research on stratified medicines and diagnostics, and the work of multidisciplinary research partnerships.³

On 5 October 2016, the Academy of Medical Sciences and the Pharmacogenetics and Stratified Medicine Network convened a workshop to discuss, in-depth, the challenges for the economic evaluation of stratified medicines, and possible ways forward. The workshop, chaired by Professor Sir Munir Pirmohamed FMedSci and Professor Stephen

¹ Academy of Medical Sciences (2007). *Optimizing stratified medicines R&D: addressing scientific and economic issues*. www.acmedsci.ac.uk/viewFile/publicationDownloads/120151486883.pdf

² Academy of Medical Sciences (2013). *Realising the potential of stratified medicine*. www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf

³ www.uk-pgx-stratmed.co.uk/

Holgate CBE FMedSci, brought together key stakeholders from across industry, the regulatory and health technology assessment sectors, academia, charities and policy, amongst others. Participants sought to identify the gaps in the health economics evidence base for stratified medicine and diagnostics, explore ways to address these gaps and discuss factors of importance when evaluating ‘personalised’ technologies in the context of possible alternative assessment models. This report provides a summary of the speakers’ presentations and the key themes from the discussion.

It should be noted that this document reflects the views expressed by participants at the meeting and does not necessarily represent the views of the Academy of Medical Sciences or the UK Pharmacogenetics and Stratified Medicine Network.

Key challenges in the health economics of stratified medicine

Over the course of the day, discussions broadly focused on three main challenges in health economics for stratified medicine. As described by Professor Adrian Towse, Director of the Office of Health Economics, these span: consideration of new elements of value; a reimbursement model which reflects this value and the needs of all stakeholders; and different standards of evidence.

New elements of value

Professor Towse outlined the need to understand the total value delivered by using a diagnostic to direct therapy compared with using a therapy without the diagnostic. The value of a diagnostic can be thought of in terms of health gain such as potentially avoiding adverse effects of treatment, reducing the switching of interventions or increasing the likelihood of positive response. It is also important to consider the indirect benefits of diagnostic tests, for example acceleration of treatment pathways, increased patient willingness to start treatment and improved adherence. These greater efficiencies in treatment could translate into productivity gains and potential cost savings within the health system. However, there are additional areas of value afforded by using a diagnostic which are less measurable. Diagnostics generate a value in ‘knowing’ about a condition, reducing patient uncertainty and offering hope or reassurance to a patient, especially where there are treatment options available upon stratification. Diagnostic innovations also have wider potential benefits for the research community and cost savings outside the health system (e.g. social care, employment). Professor Towse argued that these less tangible elements of value, beyond health gain, are not adequately captured in existing economic and policy decision-making frameworks, and that the relevant communities must be convinced of the merits of using such factors in evaluation. These elements of value must also be considered in the context of displacement of services, and therefore reflected in the threshold.

Paying for value

A proportionate share of treatment price, which reflects value, must be divided between the diagnostic and drug. In its report on ‘Realising the potential of stratified medicine’, the Academy made a number of recommendations relating to

reimbursement issues.⁴ The report highlights the importance of value-based pricing and in turn, value-based assessment of drugs and diagnostics evaluated by Health Technology Assessment (HTA) bodies, recommending:

- Flexibility in pricing to reflect both changes in value over time and varying relationships between drugs and diagnostics (e.g. companion tests comprising single biomarkers and platform tests of multiple biomarkers).
- Development of a model by HTA bodies which separates the value between a drug and a diagnostic where the medicine is considered the primary source of health gain in responders and the diagnostic is valued as benefits from reducing adverse reactions in non-responders (such as cost savings).

Expanding on these recommendations, Professor Towse identified two possible reimbursement approaches. The first option is a methodological approach, where a treatment option is assessed by the National Institute for Health and Care Excellence (NICE) and a price assigned to the drug and diagnostic. This requires methods to separately credit the value of a diagnostic and therapeutic. Alternatively, an institutional approach could be accepted, where the applicant themselves suggest a single price to NICE for the treatment option, having already decided how to divide the price between the producers of the diagnostic and drug. The reimbursement decision would operate in a 'black box' environment where agreement is established between producers without direct influence of the HTA body.

Standards of evidence

The Academy report on stratified medicine also recommends that HTA bodies, payers and regulators adopt a flexible approach to the generation of evidence on clinical utility for a diagnostic test. At present, there are very few examples of companion diagnostics used in stratified medicine where this could be done but Professor Towse suggested that this may be at a turning point.

He pointed out that prevailing evidence generation is seldom from diagnostic manufacturers.⁵ Where evidence on diagnostics has been generated such as clinical utility, this has originated from pharmaceutical companies' randomised control trials (RCTs) as part of therapy development, or public research bodies. The role of diagnostic manufacturers in this evidence process is less clear. Professor Towse explained that there are economic disincentives in the system for diagnostic manufacturers to produce evidence where stratification reduces market share, there is a lack of value-based pricing for diagnostics and a limited ability to protect intellectual property in diagnostics. The lack of competition in diagnostics can also stifle innovation and evidence generation. He emphasised the need to think innovatively about pricing solutions and the way that the healthcare system considers evidence, as well as the potential of real world evidence to overcome some of these challenges.⁶

⁴ Academy of Medical Sciences (2013). *Realising the potential of stratified medicine*. www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf

⁵ Garrison LP and Towse A (2014). *Personalized medicine: pricing and reimbursement as a potential barrier to Development and Adoption*, *Economics of*. Encyclopedia of Health Economics. 2, 484-490.

⁶ Academy of Medical Sciences & Association of the British Pharmaceutical Industry (2016). *Real world evidence*. www.acmedsci.ac.uk/more/events/real-world-evidence-workshop/

Building an evidence base for the evaluation of stratified medicine

Participants explored the key aspects to consider in the evaluation of stratified medicines from different stakeholder perspectives. Discussions focused on three areas essential to delivering a new assessment model: evidence requirements for evaluation of stratified medicines; incorporation of patient preferences; and assessment models that reflect a broader definition of value. The key themes from the discussions are outlined below.

Defining value

Companion vs. complementary diagnostics

Ms Carla Deakin provided an overview of the NICE assessment process for diagnostics.⁷ Companion diagnostics are typically assumed to be developed alongside a drug and so both the drug and diagnostic are considered as a package for HTA. NICE guidelines were updated in 2013 to include companion diagnostics in technology appraisals and so the cost of the diagnostic sits in the technology evaluation. However, she noted that in reality, companion diagnostics used in trials may not match those used in clinical practice and laboratories providing testing may instead develop alternative tests based on efficiency, skill base or available equipment. Therefore a complementary diagnostic may be employed for stratification which is not co-developed or approved alongside a drug. Ms Deakin highlighted that it is difficult to establish concordance between assessment of companion and complementary diagnostics. However, she also remarked that to date, NICE has not been approached to review many companion diagnostics applications.

⁷ Companion diagnostics are defined within the draft European In-Vitro Diagnostics Regulation (<http://data.consilium.europa.eu/doc/document/ST-10729-2016-INIT/en/pdf>) as a device ‘which is essential for the safe and effective use of a corresponding medicinal product to: identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; or identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product’. There is no formal definition of a complementary diagnostic within this legislation.

Decision analytic modelling is used to understand cost-effectiveness of companion diagnostics and NICE uses two assessment approaches for this:

- A ‘true’ authorised companion diagnostic which is co-developed alongside a drug, employed in clinical trials and used solely to support the treatment decision for the drug under evaluation is reviewed by a technology appraisal committee.
- Where tests are not true companion diagnostics and provide alternative diagnostic options in clinical practice, they undergo separate review via the diagnostics assessment programme (DAP). For example, different tests for epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutations have been reviewed by NICE through the DAP to identify those tests which support clinical and cost-effective use of specific drugs for non-small cell lung cancer.⁸

Challenges to developing companion diagnostics

Delegates recognised that companion and complementary diagnostics have different value ‘messages’ with advantages of using each. Companion diagnostics enable specificity for a certain disease process or safety issue, whilst complementary diagnostics afford a more general understanding of disease and may have multiple uses. It was suggested that more resource is required to create a companion diagnostic than a complementary diagnostic and there was concern that unless this is addressed, there will be little incentive to develop companion diagnostics. For example, in addition to the differing HTA processes outlined above, there is divergent regulatory assessment of companion and complementary diagnostics. Companion diagnostics deemed ‘essential’ by the test manufacturer may need assessment of the clinical performance study by a competent authority (MHRA) and then a review of the clinical evidence by a notified body and a medicines authority (e.g. European Medicines Agency), whilst complementary diagnostics may only require review through a notified body to receive the required CE mark. Promisingly, it was noted that previous lack of funding for companion diagnostics approved in NICE Technology Appraisals has been addressed by NHS England which now funds companion diagnostics approved alongside a drug.

Building a broader definition of value

Delegates noted the benefits of diagnostic tests beyond direct health improvements including the value of ‘knowing’ for a patient (through confirmation of a diagnosis). During her presentation, Ms Deakin described a recent study carried out by NICE to understand the wider value of diagnostics by examining indirect health outcomes, but this found that the diagnostic alone resulted in only small quality-adjusted life year (QALY) changes. However, the efficiency gains and budget implications as a result of using the diagnostic are important and should be captured. It was agreed that it is important to allow for different stakeholder perspectives of value and that currently, NICE often addresses the view of the health system and service users but there is also a need to incorporate the wider benefits for the patient. One delegate highlighted that ‘trust’ in the healthcare system is also not traditionally captured by the QALY metric. For example, treatment switching and adverse events may compromise patient trust in a clinician and more targeted treatment could mitigate some of this effect, although this is difficult to measure. A broader definition of value could be achieved through adoption of a value-based assessment model and there was consensus that a robust evidence-based approach is needed for any deviation from the current model. Delegates noted that the model is further complicated by inequity of QALY thresholds across different therapeutics and conditions. For example, NICE currently accommodates higher thresholds for end-of-life treatments and rare diseases.

Delegates felt that when tying diagnostics to a drug this may not adequately convey the inherent value of the diagnostic or the science behind the biomarker. However, it was also argued that value of stratification should not be based entirely on a biomarker where treatment outcomes and patient benefit should be considered more important than biomarker thresholds. Delegates cautioned that the move from single diagnostic tests to an array of different tests including biomarkers, genetics, proteomics and panel tests for multiple different diseases will further complicate assignment of value to the diagnostic element of the patient pathway. In addition, it was agreed that biomarkers are important throughout the drug development process, not simply restricted to identification of patients post-licensing but also for ensuring that developmental processes are more efficient and targeted such as expediting trial recruitment processes and avoiding non-responders.

⁸ NICE Guidance (2013). *EGFR -TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer*. <https://www.nice.org.uk/guidance/dg9/chapter/4-The-diagnostic-tests>

The overwhelming need for academia to work with HTA bodies and policy makers to devise better methodologies and broader assessment frameworks was described. Representatives from Scotland and Wales shared experiences of expanding HTA beyond consideration of clinical- and cost-effectiveness. For example, most personalised medicines undergoing HTA in Wales have been orphan medicines and so if they receive a ‘no’ following HTA, they are then further reviewed by the Clinician and Patient Involvement Group which considers wider holistic factors and social benefits informed by qualitative evidence.

Incorporating patient preferences

Mr Alastair Kent, Director of Genetic Alliance UK, acknowledged the ‘*unarguable*’ health and clinical benefits afforded by stratified medicine and the importance of HTA in supporting rational decision-making and economic savings for the healthcare system. However, he stressed that current decision-making models do not suitably consider aspects of significance to patients and although there is some clear overlap, important factors for the healthcare service are not coterminous with the needs or preferences of patients. Further to this, existing assessment frameworks may place undue emphasis on factors which can be measured (to enable scientific rigour) at the expense of factors which are difficult to quantify. Therefore he outlined the need for more nuanced assessment models that better incorporate factors important to end users. He asserted that a fit-for-purpose health economics framework will support innovation in a reliable, sustainable and equitable way for patients.

Overall, delegates recognised that the focus on science in medical innovation and financial constraints in healthcare have previously resulted in the evolution of assessment models without patient input. It was agreed that it is vital to ensure a patient-centric healthcare system with extensive patient involvement that fully addresses the breadth of healthcare needs in the UK.

Patient needs

During his presentation, Mr Kent noted that modelling assumes rational use of healthcare services when in reality, different pathways and compromises are chosen based on needs. For example, he argued for a more holistic approach to healthcare which incorporates the social context in which healthcare is provided such as consideration of childcare, time burdens, financial loss from non-employment and carer’s time. He noted that low cost interventions such as provision of care support would maximise the opportunity for patients to benefit from targeted therapies.

In addition, it is important to incorporate the symptoms of disease most important to the end user and Mr Kent underlined that the psychological impact of a disease is often overlooked in models. Health gain and indirect benefits from swifter access to treatment are clearly valuable for patients but as described earlier, the intrinsic value of ‘knowing’ from a confirmatory diagnosis is also important for a patient. This value of ‘knowing’ depends on multiple factors such as treatment options, family history and duration of symptoms, as well as any possible disadvantages of diagnosis such as a disease where there is no treatment available.

Personal utility and population preferences

Delegates noted that the concept of ‘personal utility’ encompasses the value of stratification to the individual as well as the wider population, and personal utility from a diagnostic test stems from patient empowerment amongst other factors. It was noted that current QALY measurements for cost-effectiveness do not adequately reflect this personal utility.

Participants felt that to be feasibly incorporated into evaluation processes, personal utility and patient preferences must be considered at the population level which will require societal evaluation similar to the QALY measure. Although there may be some factors where there is not a consensus, this would provide the most feasible method for representing user needs. The inevitable distribution of personal values requires a normative framework balanced against consideration of emotional factors.

Shared decision-making

Delegates pointed out that for an assessment model reflecting wider population preferences, there could be a level of autonomy at a patient level when implementing the framework. However, there was debate on how much weight individual choice should have against the wider societal valuation, for example when considering preferences for different interventions. It was highlighted that NICE Technology Assessment Programmes for stratified medicines use a guideline-based approach which allows for this autonomy. At the patient-clinician level, population and individual preferences can be used to inform patient choice in a shared-decision making framework. For example, NICE guidelines for anticoagulants recommend that decisions about whether to prescribe warfarin or a direct oral anti-coagulant are made jointly between the prescriber and patient, informed by NICE guidelines. It was proposed that for stratified medicine, where a biomarker correlates with efficacy/safety and a personalised medicine is available such that the drug will work and circumvent serious adverse effects for the patient, then the stratified medicine must be decided on by patients in an informed discussion with clinicians.

Patient involvement in research

Delegates argued that patient input must inform the development of medicines and diagnostics from the outset and patient advocacy groups will act as an important component of this input. Patients should be involved throughout research and development and it was proposed that researchers could carry out challenge-led research to address needs put forward by patients themselves. The NIHR-funded James Lind Alliance was referenced as a successful model for incorporating wider stakeholder views into research.⁹ In addition, there was discussion around the need to better use patient reported outcomes (PROs) in clinical trials to focus on measures important to patients rather than those chosen by developers or regulators. One delegate observed that the MHRA is currently carrying out a project on benefit-risk assessment which is taking into consideration PROs and how these can be more usefully included within regulatory frameworks. In general, it was argued that more sophisticated outcomes data are needed to support stratified medicines rather than the relatively crude measurements used such as mortality. The EQ-5D questionnaire used to measure health outcomes could be built upon to incorporate these data. Finally, the importance of patient data for informing research and assessment processes was emphasised by delegates. In Scotland, the 'GoSHARE' initiative enables this through obtaining patient permission to use data in research and the 'Wider SHARE' scheme records greater detail on patient illness and treatment to be used in research.¹⁰

Evidence requirements

Professor Katherine Payne, Professor of Health Economics at The University of Manchester, described two different vehicles for evidence collection that enable NICE to make an HTA decision:

- *Trial-based cost-effectiveness analysis* – using RCT patient-level data with robust internal validity. However, the RCT cost-effectiveness framework can sometimes suffer from limited generalisability and short follow-ups such that outcomes must be extrapolated to measure life-years and QALYs.
- *Decision analytic model-based cost-effectiveness analysis* – involves the collection of a range of data including RCTs, systematic reviews, observational studies and medical records. It has a key role in early economic evaluation and is recommended by NICE, with iteration of models as new evidence becomes available. Relevant diagnostic and care pathways are then mapped out as decision trees and data used to populate the model. Professor Payne noted that where expert judgment is relied upon, a robust qualitative and/or quantitative approach is needed. She described the distinction between expert opinion which is informed by qualitative methods to give a combined view of different pathways, and expert elicitation which is informed by quantitative methods that incorporate uncertainty.

Professor Payne outlined the wider challenges of carrying out trials for stratified medicines and she observed that alternative, reliable data sources to the 'gold standard' RCT are necessary. This will require the development of robust

⁹ www.jla.nihr.ac.uk/about-the-james-lind-alliance/

¹⁰ <http://www.goshare.org.uk/>

statistical methods for using observational data as well as standardised approaches to expert elicitation. In addition, delegates later explored the importance of establishing methods for managing uncertainty in evidence and outcomes, and the importance of proportionality and weighting of different elements when considering such uncertainty.

Case study: trial-based cost effectiveness analysis

Professor Payne described the TARGET study that used a pragmatic RCT to generate economic evidence on the stratification of patients prescribed azathioprine, based on prediction of side effects.¹¹ The study explored diagnostic tests for TPMT (thiopurine methyltransferase enzyme) which predicts individuals at risk of severe neutropaenia when taking azathioprine. Participants were split into three groups based on their experience when taking the drug: those at risk of adverse effects; those whose lives might be at risk; and those with no likely problems. Professor Payne demonstrated some of the challenges in evidence generation for these types of trials as the trial was underpowered due to the low number of patients experiencing neutropaenia and so the trial outcomes were changed to look at all adverse drug reactions.

Economic evaluations concluded that the TPMT test was cost-saving by reducing use of health service resources but resulted in some ‘loss’ of health status (due to a smaller QALY gain in the TPMT test group compared to standard clinical practice). This could be explained by low clinical adherence to the diagnostic recommendations, where clinicians did not start the appropriate full dosage of azathioprine on patients identified as not at risk of side effects. As such, the potential added value of using the TPMT test may have been diluted. Furthermore, the low number of patients with neutropaenia meant that the value of the TPMT test in preventing downstream costs and improving quality of life could not be adequately tested in the trial design. Moreover, Professor Payne noted that autoimmune diseases remit and relapse so these benefits can be difficult to record, demonstrating the difficulty of characterising uncertainty in economic modelling.

Challenges in evidence collection for adverse drug reactions

Professor Dyfrig Hughes, Co-Director of the Centre for Health Economics & Medicines Evaluation, Bangor University emphasised that adopting a stratified approach presents an opportunity to estimate the cost-effectiveness of reducing the incidence of adverse drug events (ADEs), of which adverse drug reactions (ADRs) have an annual projected cost of £466m for the NHS.^{12¹³} However, because ADRs can be rare, difficulties arise when conducting sufficiently large trials to generate acceptable evidence for evaluation. Moreover, the clinical effectiveness and cost of alternative courses of action for patients susceptible to adverse reactions must also be considered in economic evaluation. Professor Hughes noted further difficulties with this estimation caused by the broad range in cost of managing different ADEs where costs can vary across studies and indeed, across individual patients with the same event. For example, a recent study

¹¹ Thompson AJ, et al. (2014). *The cost-effectiveness of a pharmacogenetic test: a trial-based evaluation of TPMT genotyping for azathioprine*. Value in Health **17**, 22–23.

¹² For the purpose of this meeting, Professor Hughes described drug safety as encompassing all adverse drug events when undergoing treatment, and adverse drug reactions comprise a subset of these events.

¹³ Pirmohamed M, et al. (2004). *Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients*. BMJ, **329**(7456), 15–19.

showed that costs for patients admitted to hospital with ADEs ranged from €702 to €40,273.¹⁴

Professor Hughes noted that systematic reviews of economic evaluations of pharmacogenetic testing to prevent ADRs revealed only a handful of tests to be cost-effective.¹⁵ In many cases this was due to weak evidence of the association between a given pharmacogene and the ADR. However, in others, unfavourable cost-effectiveness resulted from very small QALY gains, which is related directly to the probability of the ADR. This is because prevention of very rare ADRs, even if potentially life-threatening, is unlikely to be cost-effective when the number needed to screen is high.

Considering this, he emphasised the importance of taking into account the wider benefits offered by some tests against the relative rarity of serious ADRs and potential for less effective alternative treatments. Key challenges around assessment of pharmacogenetics include difficulty in collecting evidence on rare events, requirements for large RCTs and challenges in defining all possible care pathways and treatment alternatives in a model. Professor Hughes also challenged the normative assumption that a QALY lost because of a condition should be valued equally to a QALY lost through medically-induced side effects, and asked whether a ‘value’ should be assigned to those pathways which circumvent ADRs.

Case study: assessing the cost-effectiveness of treating ADRs

Professor Hughes described an economic evaluation – through a decision analytic model-based framework – of patient screening in treatment of epilepsy with carbamazepine, where ADRs can range from mild rash and hypersensitivity syndrome to Stevens-Johnson Syndrome (SJS) with a high risk of mortality. On average, the milder ADRs occur in 5% of patients. Economic assessment of patient screening revealed that such an approach in European populations led to very small QALY gains (since the adverse effect was so rare amongst the population) when compared with current standard of care.¹⁶ However, the allele associated with SJS (*HLA-B*15:02*) is often found in some particular Asian populations such as Han Chinese. Therefore he emphasised that there is a strong argument for screening these populations, in particular, before starting treatment with carbamazepine. This recommendation has now been included in the Summary of Product Characteristics. By contrast, in Caucasian populations, the association is with another HLA allele (*HLA-A*31:01*). Interestingly, for the Summary of Product Characteristics it was found that there was insufficient data to support recommendation for screening for *HLA-A*31:01* before treatment with the drug, whereas health economic analysis concluded that routine testing for this allele in European populations would be cost-effective.

Evidence generation for diagnostics

A key issue reiterated throughout the workshop was the lack of evidence generated for diagnostics, particularly from diagnostic companies. Ms Deakin noted that rapid technological advancement in the sector makes gold-standard RCTs for diagnostics difficult, compounded by different challenges for the diagnostics industry around access and culture. Therefore NICE considers alternative evidence forms to RCTs for assessment of diagnostics. Delegates noted that the forthcoming new EU In-Vitro Diagnostic (IVD) Device Regulation will help to support better evidence generation – with

¹⁴ Batel Marques F, et al. (2016) *A systematic review of observational studies evaluating costs of adverse drug reactions*. Clinicoecon Outcomes Res. **8**, 413-426.

¹⁵ Plumpton CO, et al. (2016). *A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions*. Pharmacoeconomics **34**(8), 771-793.

¹⁶ Plumpton CO, et al. (2015). *Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy*. Epilepsia **56**(4), 556-563.

more evidence required for approval – and will ensure a change in expectations around clinical evidence on diagnostics. It was emphasised that the MHRA is supportive of co-development of diagnostics and drugs and is considering ways to streamline this evidence generation and evaluation process through differential analysis of diagnostics and drugs combined with payer evaluation.

Acceptability of different types of evidence

During his presentation, Mr Gavin Lewis noted that regulators have become increasingly agile and flexible when considering different types of evidence generation to support stratified medicines such as real world evidence, single arm studies and basket trials. He also noted that regulators have become more accepting of surrogate endpoints but argued that HTA bodies and commissioners have not shown such flexibility, illustrating the overarching need for greater integration of evidence requirements between regulators, HTA bodies and payers. He also noted that evidence standards not only vary across institutions but also at a global level in different countries. In general, Mr Lewis described increasing use of iterative product development plans where further phases of evidence gathering and data collection can enable licensing adaptations and population expansion throughout a product lifecycle. When using adaptive pathways, he recognised the importance of generating mature evidence post-approval if initial data only included short follow-ups, and the value of using methodologies to extrapolate from immature datasets. He emphasised that big data will help to further elucidate validity and greater accuracy to enable a variety of evidence sources to be used for better decision-making. However, delegates later described the difficulties with collecting sufficient evidence early on so that a clear signal-noise ratio can be used for ‘go’ or ‘no go’ decisions. Therefore assessment models at this stage need to match the pace of scientific advance.

During the discussions, delegates highlighted that real world data and observational trials, amongst other new forms of evidence, will be key for future assessment of stratified medicines and diagnostics. With stratified populations becoming increasingly restricted, it can be difficult to obtain sufficient patient numbers for the traditional RCT and so there is an opportunity for alternative evidence generation, for example using non-randomised real world studies. The Salford Lung Study between GSK and the University of Manchester was given as a successful exemplar of using data from routine clinical practice, although the significant infrastructure and costs of such a study were also noted.¹⁷ Some delegates suggested that further research is needed into methodologies used to analyse this data once it is generated as NICE may not have the expertise to analyse such data. It was agreed that there is a key role for academia in building these data analysis capabilities through working with key decision-makers.

Discussions also touched upon the importance of establishing reliable databases and registries for robust data collection, and ensuring quality and validity of databases and registries which may undergo less supervision is vital if they are to be used in assessment. It was emphasised that databases must collect the breadth of diagnostic data and should record all patients receiving a stratified medicine. For example, it was noted that cancer databases should be adapted to record all prognostic markers. However, delegates noted potential difficulties in accessing such data and public perceptions of access to data by public bodies compared with private companies.

Standardisation of tests

It was also argued that there is little standardisation of data and evidence generated on diagnostics and a need for quality assurance around their use. NHS laboratories vary in quality and ability to provide different tests and so it can be difficult to select the right test if a number of options are available, particularly as manufacturers often do not state requirements for a test to be conducted in a lab with a specific performance level. Therefore delegates agreed that there better accreditation of laboratories and skills is needed to ensure monitoring and standardisation of practice (although it was noted that most labs operate to the internationally recognised standard ISO15189). There was also discussion of potential benefits of limiting numbers of accredited labs available or having a few specialist centres of excellence for a specific diagnostic, to accumulate knowledge and improve quality of assessment.

¹⁷ Bakerly ND, et al. (2015). *The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in chronic obstructive pulmonary disease*. Respiratory Research **16**(101).

Patient access

Mr Lewis concluded that there are four key areas to improving patient access to stratified interventions:

1. Greater integration of clinical evidence requirements between regulators and payers when evaluating the benefits of stratified medicines.
2. Increased adoption of methods for evidence synthesis, disease modelling and management of uncertainty by HTA bodies.
3. Ability of healthcare systems to implement pricing flexibility to align price and value as evidence evolves and new indications emerge.
4. Investment in data sources to track medicine utilisation and outcomes, and implement patient access schemes.

There were different perspectives amongst delegates as to what patient access means in practice. It was noted that for industry, formularies, NICE and other stakeholders, their interpretation of this access was patients receiving a particular medicine. However, others interpreted patient access more broadly to encompass whether patients are aware of the availability of certain treatments. Ensuring awareness and general health literacy of the public was important for providing a 'pull' for stratified medicine into the healthcare system. However, careful consideration must be given to raising awareness to ensure a full understanding of the opportunity in this area, as delegates observed that the term 'stratified' can be associated with inequalities where one patient may receive a novel treatment and another with the same condition does not. There was discussion around greater 'socialising' of the NHS and stratified medicine, and the need to position stratified medicine as part of a wider holistic approach to healthcare.

Pricing and reimbursement models

The need for more flexible pricing and reimbursement models was explored alongside agility in medicines evaluation so that an evolution of evidence can be used to amend assessment and pricing decisions. Multiple indications of stratified medicines, alongside combination products, create a new challenge in economic assessment and pricing. Mr Lewis noted that the cost-effectiveness and 'value' profile of a medicine varies according to the condition it is used to treat but that such indication-based pricing is not possible in the current system. In addition, he noted that when pooling two or more licensed drugs in combination therapy, it may not be appropriate to combine the price of each drug cumulatively as there may be only incremental benefit provided through the combination. Therefore new pricing strategies need to be established to reflect the value of different uses and combinations of medicines, which it was proposed would better support patient access and provide incentives for development of stratified medicines.

Delegates also discussed outcomes-based pricing as a payment model with reimbursement based on those patients who respond to therapy. Even for targeted therapies, treatment outcomes can be variable and current economic thresholds do not allow for this variability. It was proposed that new pricing models could be facilitated by the Accelerated Access Review.¹⁸ These risk-sharing approaches could expedite patient access when there is uncertainty around outcomes or whilst decision-making is still underway. One delegate even proposed that individual patients may be interested in co-payment if a drug is not available on the NHS but others noted that this would be a challenging discussion for the NHS.

Uptake and adoption in clinical practice

The broad landscape of products (both medicines and diagnostics), combinations, and treatment plans available to clinicians is becoming increasingly complex and confusing. In addition, delegates argued that diagnostics that are already available are not being adopted in clinical practice. Therefore leadership and culture change are needed on the frontline to accelerate diffusion of stratified medicine, and it was recommended that clinical and patient champions, alongside exemplars of care, will help to drive this.¹⁹ NHS England's Personalised Medicine and Outcomes

¹⁸ The Accelerated Access Review was published following this meeting: Accelerated Access Review (2016). www.gov.uk/government/uploads/system/uploads/attachment_data/file/565072/AAR_final.pdf

¹⁹ Exemplar stratified care pathways in diabetes and cardiovascular disease were explored at two roundtables held by the Academy of Medical Sciences with NHS England: 1. Academy of Medical Sciences (2015). *Exemplar clinical pathways for a stratified approach to diabetes*. www.acmedsci.ac.uk/viewFile/57cf3c90098c.pdf 2. Academy of Medical Sciences (2016). *Exemplar clinical pathways for a stratified approach to cardiovascular disease*. www.acmedsci.ac.uk/viewFile/57cf5170e1de.pdf

Strategy should also help to drive culture change.²⁰

In addition, delegates stressed the need for broadcasting guidance on interventions and diagnostics from NICE and other technology assessment bodies to better inform clinicians, particularly where guidance may affect current practice. In addition, it was proposed that introducing educational resources for early stage clinicians and nurses is especially important to building a wider understanding of stratified medicine.

Commissioning and payers

Delegates felt that in order for stratified medicine to become embedded in the healthcare system, a culture change is needed in the commissioning and payer infrastructure. These stakeholders must be better engaged in the medicines development process to inform development through their understanding of local needs. It was also stressed that the long-term value of emerging technologies should be recognised, beyond short-term cost savings and even cost-effectiveness of different diagnostics and interventions. There was some feeling amongst delegates that commissioners may be highly sensitive to the cost of a diagnostic, which is a small part of the treatment pathway. If a test is expensive, it is therefore important to build an understanding of where it may have significant efficiency savings or improve outcomes downstream. Delegates suggested that sharing case examples of where stratified interventions have had such benefits would facilitate uptake and demonstrate value to commissioners.

²⁰ NHS England (2016). *Improving outcomes through personalised medicine*. www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf

Annex 1: Attendees list

Chairs and speakers

Professor Sir Munir Pirmohamed FMedSci (co-chair), David Weatherall Chair of Medicine, University of Liverpool

Professor Stephen Holgate FMedSci (co-chair), MRC Clinical Professor of Immunopharmacology, University of Southampton

Ms Carla Deakin, Associate Director - Diagnostics Assessment Programme & NICE Office for Market Access, National Institute for Health and Care Excellence

Professor Dyfrig Hughes, Co-Director, Centre for Health Economics & Medicines Evaluation, Bangor University

Mr Alastair Kent OBE, Director, Genetic Alliance UK

Mr Gavin Lewis, Global Head Oncology Market Access, AstraZeneca

Professor Katherine Payne, Professor of Health Economics, The University of Manchester

Professor Adrian Towse, Director, Office of Health Economics

Participants

Dr Sue Bailey, Disease Area Head, Oncology, Bristol-Myers Squibb

Professor Richard Barker OBE, Director, Centre for the Advancement of Sustainable Medical Innovation and Chair, Precision Medicine Catapult

Mr Patrick Batty, Scientific Assessor, Medicines and Healthcare Products Regulatory Agency

Dr Neeraj Bhala, Consultant Gastroenterologist, Queen Elizabeth Hospital Birmingham

Ms Ailsa Brown, Lead Health Economist, Scottish Medicines Consortium

Dr Fiona Carragher, Deputy Chief Scientific Officer, NHS England

Dr Paul Catchpole, Value and Access Director, Association of the British Pharmaceutical Industry

Mr Warren Cowell, UK Market Access Policy Lead, Janssen

Professor Neil Hawkins, Professor (Health Economics and Health Technology Assessment), University of Glasgow

Dr Kirsty Henderson, Policy Adviser, Cancer Research UK

Dr Christopher Hoyle, Director of Payer & HTA Policy, AstraZeneca

Dr Ed Hutchinson, Precision Medicine Strategy Lead, Scottish Enterprise

Ms Ruth Jamieson, Precision Medicine Catapult

Dr Andrea Jorgensen, Lecturer in Medical Statistics, University of Liverpool and co-lead, MRC HTMR Stratified Medicines Working Group

Mr Steve Lee, Biosciences Team Manager, Medicines and Healthcare Products Regulatory Agency

Dr Louise Leong, Director Science Relations, AstraZeneca

Dr Stuart Linton, Chairman, All Wales Medicine Strategy Group

Professor Andrea Manca, Professor of Health Economics, University of York

Ms Amanda Matse-Orere, Health Economics Manager, Roche

Professor Adrian Newland, Chair of the Diagnostics Advisory Committee, NICE and Clinical Professor, Queen Mary University of London

Mr Robert Pears, Consultant in Public Health, Hampshire County Council

Dr Jaime Peters, Senior Research Fellow, University of Exeter

Dr Krishna Prasad, Group Manager, Licensing Division, Medicines and Healthcare Products Regulatory Agency

Mr Juan Carlos Rejón-Parrilla, Senior Analyst - Science Policy and Research, National Institute for Health and Care Excellence

Dr Paul Robinson, Executive Director, Scientific Medical & Patient Perspective, Merck Sharp & Dohme

Dr Andrew Roddam, Vice President & Global Head Epidemiology, GlaxoSmithKline

Professor Philip Routledge OBE, Clinical Director & Chairman of the Board, All Wales Therapeutics & Toxicology Centre

Dr Gurdeep Sagoo, Health economist/epidemiologist, PHG Foundation

Ms Anum Shaikh, Health Economics Analyst, PHG Foundation

Mr Alexander Smith, Senior HTA Manager, Pfizer

Dr Andrew Sutton, Associate Professor in Decision Modelling, University of Leeds

Professor Anthony Wierzbicki, Consultant in Metabolic Medicine and Chemical Pathology, Guy's & St Thomas' Hospital

Dr Matthew Wintle, Independent consultant

Secretariat

Mr David Bennett, Policy Officer, Academy of Medical Sciences

Ms Liberty Dixon, Policy Officer, Academy of Medical Sciences

Ms Katharine Fox, Policy Intern, Academy of Medical Sciences

Dr Christine McNamee, Network Manager, Pharmacogenetics and Stratified Medicine Network

Ms Greta Mohan, Policy Intern, Academy of Medical Sciences

Dr Naho Yamazaki, Head of Policy, Academy of Medical Sciences

Annex 2: Agenda

09.45-09.50	Welcome Professor Sir Munir Pirmohamed FMedSci (co-chair), David Weatherall Chair of Medicine, University of Liverpool
09.50-10.10	Key issues in the health economics of stratified medicine Professor Adrian Towse, Director, Office of Health Economics
10.10-10.30	Modelling efficacy of stratified medicines Professor Katherine Payne, Professor of Health Economics, The University of Manchester
10.30-10.50	Health economics and drug safety Professor Dyfrig Hughes, Co-Director of the Centre for Health Economics & Medicines Evaluation, Bangor University
10.50-11.10	NICE evaluation of stratified medicines Dr Sarah Byron, Senior Technical Adviser, Observational Data Unit, National Institute for Health and Care Excellence
11.10-11.40	Tea and coffee
11.40-12.00	Health economics for stratified medicine - industry perspective Gavin Lewis, Global Head Oncology Market Access, AstraZeneca
12.00-12.20	Health economics for stratified medicine - patient perspective Alastair Kent OBE, Director, Genetic Alliance UK
12.20-12.50	Panel discussion Professor Stephen Holgate FMedSci (co-chair), MRC Clinical Professor of Immunopharmacology, University of Southampton
12.50-13.50	Lunch
Building an evidence base for the evaluation of stratified medicines	
13.50-14.00	Introduction to the workshop sessions Professor Sir Munir Pirmohamed FMedSci (co-chair), David Weatherall Chair of Medicine, University of Liverpool
14.00-15.30	Break-out sessions <ol style="list-style-type: none"> Health economics in stratified medicine – the evidence gaps and research priorities <i>Chair: Professor Katherine Payne, The University of Manchester</i> Assessing the health economics of stratified medicine from the healthcare perspective to facilitate uptake of innovation <i>Chair: Professor Dyfrig Hughes, Bangor University</i> Stratified medicine health economics: the perspective of the patient and public <i>Chair: Professor Stephen Holgate FMedSci, University of Southampton</i>
15.30-15.50	Tea and coffee
15.50-16.30	Feedback and conclusions Open discussion with the audience.
16.30	Close



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