The Academy of Medical Sciences

Stratified medicine stakeholder meeting

Meeting summary, 8 November 2013

Background

In July 2013, the Academy published its report '*Realising the potential of stratified medicine*'. This arose from a project that was undertaken to facilitate progress in stratified medicine research and development, and the implementation of these approaches in healthcare services, following on from the Academy's 2007 report, '*Optimizing stratified medicines R&D: addressing scientific and economic issues*'.

The report addressed barriers in clinical and research infrastructure, regulation and pricing and reimbursement. Overall the report concluded that: collection, analysis and use of biomedical and health data should be enhanced; changes to regulation and pricing systems are required as they currently do not provide adequate incentives for the development of stratified medicine products; influencing clinical practice will be critical for stratified medicine to be embedded in healthcare; and collaboration will be crucial to accelerate the development and adoption of stratified medicine.

On November 8 2013, the Academy hosted a follow-up meeting to discuss the implementation of the report's recommendations (Annex 1). Key stakeholders considered relevant plans, progress and opportunities for action, including the identification of short-term gains and long-term goals. The meeting was structured around key themes of the report's recommendations. Multiple attendees noted that the report was well received. It was stated that it was perceived as helpful – in particular to policymakers – in making clear recommendations that will enable the development and implementation of stratified medicine approaches. Many stakeholders are already taking forward some actions recommended in the report.

This meeting note provides a summary of these discussions, outlining activities that have occurred since publication of the report, and next steps that could be taken. The next steps suggested in this document are derived from the discussion amongst delegates, not the opinions of any individual.

Attendees are listed in Annex 2. The meeting was chaired by Professor Sir John Bell FRS HonFREng FMedSci, Chair of the Academy of Medical Sciences Stratified Medicines Oversight Group and Regius Professor of Medicine, University of Oxford.

Informatics

Professor Andrew Morris outlined the four key areas requiring development and coordination that were presented in the informatics chapter of the report: a collaborative research infrastructure to develop stratified medicine and clinical infrastructure to adopt it; capacity building, the education and training of professionals who will be contributing

to the delivery of stratified medicine; harmonisation of health and biomedical informatics; and engagement with patients and the public to guide the adoption of stratified medicine approaches.

This session focused on the informatics recommendations: the establishment of a virtual national network for informatics as an expert hub and the appointment of specialist informatics champions in the health service.

Recent developments

A consortium of 10 UK Government and charity funders, led by the MRC, established four E-Health Informatics Research Centres (eHIRCs), which opened in May 2013. These Centres aim to harness the wealth of UK electronic health records, such as those available through the Clinical Practice Research Datalink, to improve patient care and public health, tackling conditions such as diabetes and obesity, cardiovascular disease, cancer and child and maternal health.

The consortium also agreed to provide further funding to establish a formal collaborative eHIRC network called the Farr Institute, comprising University College London (Farr Institute @ London), University of Manchester (Farr Institute @ HeRC), Swansea University (Farr Institute @ CIPHER), and the University of Dundee (Farr Institute @ Scotland).[1] The Farr aims to provide physical and electronic infrastructure to:

- Support and accelerate collaborative work amongst the eHIRCs;
- Support partnership by co-locating NHS organisations, industry, and other UK academic centres;
- Facilitate collaboration, dataset sharing, and the adoption of common standards; and
- Develop new opportunities for large-scale future linkage and data analysis.

The network seeks to seed UK health informatics at scale in the UK, acting as a central hub of data, methodologies and experts that others can draw on.

Professor Iain Buchan, Director of the 'HeRC' eHIRC, presented examples of the Farr's work to date, indicating the future opportunities and challenges for its work. HeRC has been developing methods for analysing large datasets in both hypothesis- and data-driven ways. For example, in collaboration with Manchester University, machine learning approaches to allergic sensitisation data have identified novel asthma risk categories in children, which were not hypothesised at the start of the study.2

The eHIRCs have sought strong public engagement to steer the development of stratified medicine.[3] They have also expanded their collaboration with the NHS, academia and industry. For example, in response to needs identified by mental health services, HeRC has developed a smartphone app for service-users who have schizophrenia.[4] The app

---

[1] http://www.farrinstitute.org/

[2] Simpson A, *et al.* (2010). *Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study.* American journal of respiratory and critical care medicine **181(11)**, 1200-6

[3] See http://www.farrinstitute.org/centre/HeRC/65_Public-Engagement.html, http://www.farrinstitute.org/centre/CIPHER/36_Public-Engagement.html, http://www.farrinstitute.org/centre/Scotland/21_Public-Engagement.html, and http://www.farrinstitute.org/centre/London/12_Patient-And-Public-Engagement.html

[4] www.clintouch.com

employs the psychological theory of experience sampling to monitor mental health symptoms with the aim of improving adherence with medication and thereby reducing the risk of relapse. Professor Buchan noted that stratified medicine in the future may involve the identification not only of pathophysiological but also psychological disease subtypes, and will require more complex trials on single participants (n-of-1 trials) to optimise interventions.

Professor Buchan also raised the need for more systematic validation of clinical predictive algorithms. He spoke of the EuroScore model that aims to prospectively predict the risk of death from a cardiac surgical procedure, using a number of variables including age, existing pulmonary disease and previous cardiac surgery.[5] Using this example, he demonstrated how algorithms in current clinical practice drift in calibration between publications of the relevant models and their revisions, with significant implications for clinical decision-making and patient safety.[6]

Overall, 2014 is set to be a big year for the Farr Institute as they take the next steps forward toward method development, expansion of metadata dictionaries (currently standing at 34 cohorts), applying proportionate governance across eHIRCs, and forging key partnerships. They are already looking to commercialise the tools they are developing.

There are also relevant developments internationally. Earlier in 2013, researchers in Stanford developed methods for mining the free-text information captured in electronic clinical notes that would allow the earlier flagging of adverse events.[7]

Next steps forward

- *Maximising the use of existing data.* A mapping exercise should be undertaken in which all healthcare-related organisations should be encouraged to publicise any potentially relevant datasets they hold. This is particularly important for underused or inaccessible data. For example, ward round records represent a rich source of verbal and written information. Furthermore, data structuring could be developed, for example expanding the use of dictionaries in secondary care data.
- *Maximising the collection of richer longitudinal data.* The opportunities for longitudinal data gathering presented by mobile/ubiquitous technologies should be explored, as exemplified by the use of 'ClinTouch' in schizophrenia.[8]
- *Validating clinical predictive algorithms.* The revision of EU legislation regarding the approval and monitoring of medical devices and diagnostics may result in changes to the regulation of software, including the validation of clinical predictive algorithms. However, the systematic validation of such algorithms is not yet 'industrialised'.
- *Ensuring and facilitating collaborative use of data and novel data linkage.* For a stratified medicine data network to operate optimally for researchers, it will need to be used in a collaborative manner by appropriately trained individuals. For

[5] Roques F, *et al.* (2003). *The logistic EuroSCORE.* European heart journal **24(9)**, 881-2
[6] Hickey GL, *et al.* (2013). *Dynamic trends in cardiac surgery: why the logistic EuroSCORE is no longer suitable for contemporary cardiac surgery and implications for future risk models.* European journal of cardiothoracic surgery **43(6)**, 1146-52
[7] LePendu P, *et al.* (2013). *Pharmacovigilance using clinical notes*. Clinical pharmacology & therapeutics **93(6)**, 547–555
[8] www.clintouch.com

example, in a study in Salford, local public health staff contacted the researchers with deprivation data that was more accurate than that available from the Office for National Statistics (ONS). Approaches that connect users 'touching' the same data should be explored, such as those used by Google and Amazon.

- *Converging on a single set of data standards.* Harmonised data standards will be a prerequisite to allow data to be combined, yet their development and adoption will require significant negotiation: a strong leader is required.
- *Active participation by clinicians is critical and will require an incremental approach wherein the accruing benefits are made obvious to clinicians over time.* Demonstrating that informatics can deliver locally useful data and analysis will drive clinician take-up. Informatics systems should therefore be developed in a stepwise fashion that allows the incremental clinical benefit to be demonstrated at all stages.
- *European data protection legislation needs to provide an enabling environment.* There is significant potential for research to be impeded if proposed amendments to the emerging EU Data Protection Regulation are adopted.
- *Increasing the number of skilled informatics personnel in the UK healthcare system.* A drought of expertise is limiting the ability for data to be used and to flow effectively. For example, it was claimed that levels of undergraduate and postgraduate qualification in the NHS IT staff are low compared to the US healthcare system, which also contains Clinical Information Officers. Improving the situation will require consideration of leadership roles, recruitment and upskilling of the existing workforce, perhaps looking abroad to examples of training schemes.[9]
- *The informatics system should have a modular structure.* Designing a single large informatics system will take a significant amount of time and should be avoided. Instead, multiple smaller pieces of software should link together and sit alongside and on top of existing systems. This will facilitate a more responsive and innovative approach to the system's initial and ongoing development.

In summary the UK can be optimistic, because we already have considerable data resources. However, data linkage and curation need to be improved, and the workforce needs to be upskilled and provided with tools for collaborative working.

Regulation

The session focused on the regulation of the development and use of in-vitro diagnostic tests (IVDs), which are critical to decision making in stratified medicine approaches. Professor Richard Barker highlighted that the area continues to move quickly as acknowledged in the report: some single-use IVD tests are starting to be replaced by platforms, and multiple diagnostic tests continue to emerge for single biomarkers.

Professor Barker also outlined the report's recommendations, which aspired ultimately to contribute to the development of globally harmonised regulation that achieves appropriate oversight in a streamlined manner. Many of the recommendations were specifically aimed at influencing the new European Union in vitro diagnostic medical devices (EU IVD) Regulation: highlighting the need to increase co-ordination and

[9] For example, http://www.amia.org/clinical-informatics-board-review-course

collaboration between medicine and device regulators; supporting the adoption of a risk-based IVD classification system and the accreditation of laboratories performing diagnostic tests – whether scrutinised and approved as commercial products through the regulatory system (CE marked) or not ('in house' tests – IHTs). The report also recommended actions to support regulation, including the development of processes for ensuring robust quality assurance of all UK labs using IVDs, and the development of 'Good Genomic Practice' guidelines.

Recent developments

Mr Graeme Tunbridge, Head of EU Medical Devices Policy at the Medicines and Healthcare products Regulatory Agency (MHRA) updated the meeting on the development of the new European IVD Regulation. The following report recommendations are being adopted in the new Regulation:

- IVDs will be classified according to a risk-based approach.
- A specific IVD category of 'companion diagnostics' (CDx) has been defined. To reflect their critical role in clinical decision-making, products captured by this definition will be subject to greater evidenctiary requirements, and their regulatory approval will require the involvement of the European Medicines Agency or a national Competent Authority (e.g. the MHRA) alongside the Notified Body. The MHRA are starting to consider what joint approval of CDx should look like, including the potential to develop guidance for manufacturers.
- All laboratories undertaking IVD testing will need to be accredited to the ISO 15189 standard 'Medical laboratories — Particular requirements for quality and competence'. This standard is slightly more stringent than the current Clinical Pathology Accreditation (CPA) common in the UK, which is not mandated, resulting in some laboratories operating with little oversight.

Two core aspects of the report's recommendations are subject to ongoing negotiation:

- Clinical evidence requirements. The need for evidence to ascertain and compare the clinical utility of IVDs is strongly appreciated. There is a considerable debate to define appropriate evidentiary requirements, particularly pre-market and specifically the enhanced requirements for CDx, and what evidence ought to be publicly available. Evidentiary standards are likely to be articulated via the Common Technical Specifications standards for IVDs.
- The 'in house' exemption. The requirement for an exemption is acknowledged, such as when a new test needs to be developed quickly, or when the rarity of the disease has led to little commercial interest. However, closer scrutiny will be given to the use of the exemption – its use will need to be formally justified when a CE-marked equivalent exists.

Convergence toward the emerging EU system was felt to be likely in many parts of the world, due to Europe's history of being a leader in regulation.

Dr Rachel Butler, Chair of the UK National External Quality Assessment Service's (UK NEQAS) Special Advisory Group for Molecular Pathology, described the external quality assessment (EQA) system available to UK laboratories using IVDs. She explained the important role of accreditation and EQA, which considers the entire process from receiving a sample to reporting results. This includes sample receipt, the extraction of assayable material, assay performance, data interpretation and reporting of results:

regulation considers only the assay performance. EQA by UK NEQAS is only mandatory for laboratories with CPA. However it is not mandatory for laboratories to have CPA. Because of the importance of such comprehensive oversight, Dr Butler welcomed the emerging IVD Regulation's mandating that all laboratories performing diagnostic tests are accredited to ISO 15189. It was felt that there will be an increasing shift towards all tests being undertaken in consolidated specialist laboratories.

Dr Butler commented on UK NEQAS experience of genetic labs over the last 20 years. IHT use is widespread across the period. This is because IHTs can be developed in a fast and bespoke manner, are commonly easier to troubleshoot than CE marked tests, and also because CE-marked 'kits' have only started to become available recently. UK NEQAS have found virtually no poor performance of genetic IHTs as compared to CE marked tests over the last 20 years.

From looking at the whole process - considering the organisation, the personnel, the environment and assay quality - NEQAS find that a principal driver of overall quality, whether for CE marked tests or IHTs, is the quality of the laboratory personnel. Furthermore, they have observed that laboratories in which IHTs are developed and used tend to foster more highly skilled personnel: it was suggested that the process of developing and troubleshooting IHTs strengthens staff skills.

Next steps forward

- *Staying engaged with the development of the EU IVD Regulation.* Many of the report's recommendations are captured by the emerging EU IVD Regulation. The Academy will remain engaged with the MHRA throughout the remaining stages of the Regulation's development. The MHRA are keen to engage with key stakeholders as they seek to develop their guidance and advice on evidentiary requirements for companion diagnostics.
- *Supporting accreditation and EQA of laboratories.* There was strong support for the expansion of laboratory accreditation and EQA in the emerging regulation. There was a suggestion that before the Regulation comes into force (2018-19), payers insist that only laboratories with CPA and NEQAS are used for diagnostic testing.
- *Developing and implementing Good Genomic Practice*. A meeting will be held in the US early December.

Pricing and reimbursement

Professors Adrian Towse and Lou Garrison outlined the report's recommendations for developing a pricing and reimbursement system that would appropriately incentivise the development of stratified medicine products. Professor Garrison highlighted that these recommendations are of global relevance.

The recommendations called for: a flexible, value-based pricing system; the development of a model to separate the value between therapeutic drug and companion diagnostic; development of reasonable evidence requirements for companion diagnostics; and the consideration of Intellectual Property protection of companion diagnostics.

Recent developments

Professor Towse highlighted that the earlier update from the MHRA related to Recommendation 17 of the report, which stated that "To incentivise the generation of evidence about analytical and clinical performance and clinical utility successfully, consideration should be given to promotion of commercially approved diagnostic tests unless an 'in-house' test has evidence of equivalent or improved quality." The emerging IVD Regulation will expect CE-marked tests to be used by default (when they exist for a given biomarker) and require that a formal justification be provided for using an IHT instead.

The UK currently is currently hosting two activities particularly relevant to the recommendations:

- The National Institute for Health and Care Excellence (NICE) diagnostic assessment programme (DAP); and
- Discussions regarding value-based pricing.

Both of these will continue to develop over time.

The report called for a number of factors to be considered in the valuation of stratified medicine products. The principal factor is the minimisation of adverse events. However, further benefits arise from a patient's increased certainty as to whether or not they will benefit from a therapy. On an individual level, this is the patient's greater confidence in the outcome or their peace of mind, which can be termed as 'the value of knowing'. At a population level, the benefits are greater appropriate utilisation of medicines: the possible improvements in adherence to medication regimens, leading to better use of, and results from, a therapy; and generating a better expected benefit–risk balance for the stratified patients. It was noted that finding a single valuation model that is sufficiently flexible to adequately value products irrespective of their developmental pathway is a considerable challenge. The report stated that although the 2009 Pharmaceutical Price Regulation Scheme (PPRS) contained provisions for flexible pricing related to a value assessment, they were not used, for reasons that are unclear.

The meeting heard from Mr Danny Palnoch, Senior Economic Adviser at the Department of Health. He expressed the view that existing methods available using standard cost/effectiveness analysis can be used to assess the value of stratification in terms of harm avoided as a result of better targeting of treatments. Mr Palnoch presented the Heads of Agreement for the 2014 PPRS, which confirmed that the flexible pricing mechanism, introduced in the 2009 PPRS but yet to be used, would continue to be available on similar terms as an option for companies within the 2014 scheme: "Subject to any agreed amendments the rules on flexible pricing will apply as now with companies given flexibility to increase or decrease the original list price only when significant new evidence is generated that changes the value of an existing indication or where a major new indication is proposed whose value to NHS patients is significantly different from the original indication. This will only apply when medicines are subject to NICE appraisal and a review by NICE will be required to determine whether the proposed revised price provides value to the NHS."

This text is now part of the final 2014 PPRS, which acknowledges that this is "a novel approach with a number of practical challenges in implementation" and arranges for a

review of the initial proposals should there be no applications within the first two years of its operation.[10]

Next steps forward

- Monitoring the ongoing development of the NICE DAP.
- Contribute to any work by NICE to develop a broader value assessment for medicines.
- Utilising the 2014 PPRS to drive the development of a value based pricing system.

Developing the pricing and reimbursement system will be a longer-term stepwise process. As a first step, companies could identify potential candidate products for flexible pricing within the 2014 PPRS and generate evidence that could support an application.

Collaboration

Dr Penny Wilson, Innovation Platform Leader for Stratified Medicine at the Technology Strategy Board (TSB), updated the meeting on the activities and expansion of the Stratified Medicine Innovation Platform (SMIP). The SMIP comprises seven partner organisations, who together are investing around £200 million over five years (2011-2016). The partner organisations are the following: The Technology Strategy Board, Arthritis Research UK, Cancer Research UK, the Department of Health, the Medical Research Council, the National Institute for Health and Care Excellence, and the Scottish Government Health Directorate.

Recommendation 18 of the report called for the SMIP to expand, perhaps in a new form, to bring together a wider group of stakeholders and ensure a co-ordinated approach to facilitate the development and adoption of stratified medicine in the UK. The new body was asked to consider: developing frameworks for sharing risks and rewards of stratified medicine R&D; developing appropriate evidentiary and evaluatory standards for clinical utility; discovering the drivers of clinical adoption; and facilitating effective patient and public dialogue.

Recent developments

The TSB has undertaken a public dialogue exercise with Sciencewise-ERC (expert resource centre) funded by funded by the Department for Business, Innovation & Skills (BIS) which will publish in Spring 2014. The key aims were: to identify the social and ethical issues raised by stratified medicine; to discover how members of the public understand the term 'stratified'; to involve members of the public in a debate about the merits or otherwise of medicine becoming stratified; and to understand how people would feel about only being prescribed medicines if they have certain genetic characteristics.[11]

[10] Department of Health (2013). *The Pharmaceutical Price Regulation Scheme 2014.* https://www.gov.uk/government/publications/pharmaceutical-price-regulation-scheme-2014

[11] http://stratifiedmedicine.wordpress.com/

The TSB are forming a new Catapult centre 'Diagnostics for Stratified Medicine'. The draft aims of the Catapult are online, and the TSB would welcome any comments.[12] Dr Wilson outlined that the Catapult aims to:

- Provide access to samples, patients, instrumentation, specialised facilities and pathology services.
- Provide a forum to understand and discuss regulation.
- Maximise the opportunities afforded by big data.
- Support new business models to make opportunities commercially viable.
- Build a capability in health economics and reimbursement models.
- Build relationships with the clinical and academic communities.
- Maintain a knowledge of the stratified medicine landscape and a link to opportunities and markets in the UK and worldwide.
- Build public-private partnerships and precompetitive consortia to address challenges common to multiple sectors and organisations
- Link with other Catapults - in particular the Cell Therapy, High Value Manufacturing and Digital Economy Catapults.
- Provide a one-stop shop for industry to access the UK stratified medicine community.

Next steps forward

- *Expanding representation in the SMIP.* The TSB wishes to secure wider stakeholder representation on the SMIP. Three groups identified by delegates as needing representation on the group were: NHS England; organisations delivering care, e.g. the NHS Confederation; and the medical Royal Colleges. The SMIP will be liaising with the Office for Strategic Coordination of Health Research (OSCHR), as recommended in the report.
- *Widening the remit of the SMIP.* Dr Wilson would like the expanded platform to consider most of the issues and challenges laid out in the report, and intermittently keep tabs on implementation of the report's recommendations.
- *Informing the development of the TSB's Diagnostics for Stratified Medicine Catapult.* Key stakeholders should ensure to provide input to the development of the Catapult, through electronic comment and/or the nationwide workshops. The Catapult should seek to address the issue of producing diagnostic evidence. Diagnostics manufacturers don't have the money to run trials, meaning that the market undersupplies the evidence required by NICE. The Catapult should seek to liaise with the NIHR Diagnostic Evidence Co-operatives.

Summary of the meeting

The UK is uniquely placed to capitalise on the potential of stratified medicine, owing to its strong academic and industrial research base and highly capable agencies for health technology assessment and pharmaceutical regulation. The wealth of data within the NHS is a unique benefit, due to its quantity and ethnic diversity. Furthermore, it is predicted that the UK will soon have more genomic information than the rest of the world combined, due to the efforts of Genomics England.

[12] https://connect.innovateuk.org/web/diagnostics-for-stratified-medicine-catapult/overview

The next steps necessary for the implementation of the report's recommendations to facilitate the development and use of stratified medicine approaches in healthcare systems are:

- Building the necessary informatics infrastructure through: mapping existing data resources; converging data standards and linking data sources; exploring the possibilities offered by digital technologies for capturing longitudinal data; adopting a modular software architecture that sits on top of and around existing systems; developing tools to facilitate collaborative working and dataset manipulation; and continuously engaging clinicians by providing immediate incremental clinical benefit with each informatics development.
- Addressing the training, composition and culture of the workforce to enable the development of the informatics infrastructure and its effective use. This will require consideration of leadership roles, recruitment and upskilling of the existing workforce.
- Influencing further development of the emerging EU IVD Regulation: the Academy will remain engaged with the MHRA.
- Ensuring high quality diagnostic testing requires a focus on the laboratories as well as the tests. The expansion and maintenance of accreditation and external quality assessment schemes for diagnostic laboratories should be supported and facilitated.
- Industry should seek to use the provision in the 2014 PPRS as a first step towards an increasingly value based pricing and reimbursement system.
- The SMIP will expand in terms of its composition and remit to represent a wider range of stakeholders and consider the issues raised in the Academy's report, intermittently checking against implementation of the report's recommendations.

This document reflects the views of the attendees expressed at the meeting and does not necessarily represent the views of all participants or of the Academy of Medical Sciences. For further information, please contact Dr Naho Yamazaki, Head of Medical Science Policy (naho.yamazaki@acmedsci.ac.uk, (0)20 3176 2168).

The Academy of Medical Sciences

The Academy of Medical Sciences promotes advances in medical science and campaigns to ensure these are converted into healthcare benefits for society. Our Fellows are the UK's leading medical scientists from hospitals and general practice, academia, industry and the public service.

The Academy seeks to play a pivotal role in determining the future of medical science in the UK, and the benefits that society will enjoy in years to come. We champion the UK's strengths in medical science, promote careers and capacity building, encourage the implementation of new ideas and solutions – often through novel partnerships – and help to remove barriers to progress.

Academy of Medical Sciences
41 Portland Place
London, W1B 1QH
+44(0)20 3176 2150
info@acmedsci.ac.uk
www.acmedsci.ac.uk
Registered Charity No. 1070618
Registered Company No. 35202

Annex 1: Recommendations from the report

Informatics

Recommendation 1

We recommend that the UK E-Health Informatics Research Centres Network expands into a virtual national network by bringing together existing and new biomedical and health informatics centres and forms links with the European Bioinformatics Institute/Wellcome Trust Sanger Institute.

Our proposed virtual national network should form an informatics consortium with the Health and Social Care Information Centre, Clinical Practice Research Datalink, National Institute for Health Research and Public Health England and their counterparts in the devolved administrations to co-ordinate activities to enhance biomedical and health informatics systems that support stratified medicine research and development. This consortium should act as a focus for dataset standardisation in collaboration with the NHS (see recommendation 2), consistent approaches to development of research safe havens and sharing of data (see recommendation 3), capacity building (see recommendation 5), linkage with industry, high-quality stratified medicine studies, and support international endeavours that aim to enable responsible sharing of genomic and clinical data.

Recommendation 2

We recommend that our proposed informatics consortium (recommendation 1) leads in the development, publication and use of minimum core datasets for each key clinical disease and linkage of clinical and research information in collaboration with the NHS, building on the work already done by many clinical research networks. The aim should be to create an information commons of clinical disease definitions based on molecular pathology that can be integrated with medical records. The approach to defining data sharing agreements and standardised procedures adopted by the ENCODE (the Encyclopaedia of DNA Elements) project should be used as a model.

Recommendation 3

We recommend the Departments of Health in the UK and Department for Business, Innovation and Skills develop a consistent policy on governance for all research safe havens that supports data sharing for stratified medicine studies and harmonisation across biomedical and health informatics centres. This should draw on the work of our proposed informatics consortium (recommendation 1), the Farr Health Informatics Research Institute, the Administrative Data Taskforce and the Health Research Authority.

Recommendation 4

We recommend that operational NHS bodies, for example, hospital trusts and clinical commissioning groups, appoint experienced chief clinical information officers at board level to maximise the use of routinely collected clinical data to drive the development and implementation of stratified medicine across the healthcare system. This, which should also be a key aim of the Academic Health Science Networks, will result in improved patient care.

Recommendation 5
We recommend an immediate review of the existing provision of education and training of professionals who contribute to the delivery of stratified medicine; we also recommend an action plan be developed, which focuses on building the skills and knowledge of the current workforce and plans for the future. This work should be undertaken by NHS England, Health Education England and the devolved administrations, working with professional advisory structures such as the medical royal colleges and learned societies, the NHS and the educational sector, as well as our proposed informatics consortium (recommendation 1).

Recommendation 6
We recommend that a consortium of academia, the NHS, INVOLVE and industry work with medical research charities, patient organisations and specialist organisations such as Sciencewise to embed patient and public involvement in steering the development and implementation of stratified medicine. A first step is to consider the outcomes of the public dialogue led by the Technology Strategy Board to explore the concept of stratified medicine with members of the public.

Regulation

Recommendation 7
We welcome the proposal in the draft European *in vitro* diagnostic devices Regulation that requires consultation with the medicines competent authority or European Medicines Agency as a requirement for conformity assessment of companion diagnostics.

We recommend that the UK Medicines and Healthcare products Regulatory Agency advises the UK Government to endorse its inclusion and that the European Parliament and Council adopt this proposal in the final Regulation. The Regulation should ensure a two-way dialogue between the medicine and device regulators, rather than a unidirectional approach from the device regulators.
Explicit guidance on the role of each regulator and processes involved needs to be developed, with care taken to ensure that the new requirement does not lead to duplication of efforts or delay to patient access.

Recommendation 8
We recommend that regional and global pilots are used to develop a model to bring diagnostic and therapeutic scientific advice discussions together. This should be facilitated by a simple framework, developed for these discussions that include the following:

- Disease definition/specification and biomarker definition.
- Performance level required (diagnostic and therapeutic).
- Clinical utility data required.
- Labelling (what connection should be drawn between the diagnostic and the therapeutic and how much of this should be represented in the label).

The work should be taken forward by the European Medicines Agency, Food and Drug Administration and other major regulatory agencies with support from the International Conference on Harmonisation of Technical Requirements for Registration of

Pharmaceuticals for Human Use and the International Medical Device Regulators Forum, successor to the Global Harmonization Task Force.

The model should also inform the consistent application of whole genome sequencing, drawing on the global 'Good Genomic Practice' guidelines proposed in Recommendation 13.

Recommendation 9

We support the proposals in the new European *in vitro* diagnostic medical devices Regulation to move from a list-based to a risk-based classification system and to include companion diagnostics into a class that is subject to review by a Notified Body. We also welcome the proposal to introduce new requirements for clinical evidence for companion diagnostics. Explicit guidance should be developed outlining the acceptable levels of clinical evidence required, which enables the use of variety of methods for evidence generation including the use of well-conducted observational or retrospective analysis. We recommend that the UK Medicines and Healthcare products Regulatory Agency advises the UK Government to endorse their inclusion and the European Parliament and Council adopt these proposals in the final Regulation.

Recommendation 10

We recommend that efforts are made to ensure convergence across the regions for the risk-based classification of *in vitro* diagnostics. Ongoing international dialogue should be led by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and the International Medical Device Regulators Forum.

Recommendation 11

We welcome the proposal in the draft European *in vitro* diagnostic devices Regulation requiring health institutions developing and using 'in-house' tests to be accredited. We recommend that the
UK Medicines and Healthcare products Regulatory Agency advises the UK Government to endorse its inclusion and the European Parliament and Council adopt the proposal in the final Regulation.

Recommendation 12

We recommend that a programme be established to define the process and criteria for accrediting laboratories developing and performing 'in-house' diagnostic tests. This should involve the regulators such as the Medicine and Healthcare products Regulatory Agency, the pharmaceutical and diagnostic industry, hospital pathology laboratories and pathology academics. The exercise should be led by a European standards body – perhaps under the auspices of the International Organization for Standardization – with funding from Horizon 2020, the EU's new funding programme for research and innovation from 2014 to 2020.

Recommendation 13

We recommend the development of global 'Good Genomic Practice' guidelines to support development of regulation as and where appropriate. The guideline should cover the four key stages of: pre-analysis; sequencing; interpretation and clinical utility. The European Commission (using Horizon 2020 funding), the US Institute of Medicine and the US

National Institute of Health could lead in developing a roadmap to the production of Good Genomic Practice guidelines.

Pricing and reimbursement

Recommendation 14

To incentivise the development of stratified medicine products appropriately, we recommend that a pricing and reimbursement system is developed that (a) enables prices to be adjusted over time to reflect increases and decreases in value, and (b) can manage two diagnostic scenarios: companion tests of one biomarker and large platform tests of multiple biomarkers. This system should consider the impact on projected cost per quality adjusted life years gained, the cost offsets compared with existing practice, the value of greater certainty of response and the value of improved adherence and uptake in the population.

Recommendation 15

To incentivise stratification, at least in the short term, we recommend that health technology assessment bodies develop a model to separate the value between the drug and companion diagnostic. The medicine should be considered as the primary source of the health gain in responders. The diagnostic should be valued in terms of the cost savings and improvements in quality and length of life from reduced adverse drug reactions in non-responders, and in terms of increased certainty of response. Better patient adherence and greater overall appropriate use may also result, and this value could be divided similarly.

Recommendation 16

We recommend that health technology assessment bodies, payers and regulators adopt a flexible approach to the generation of clinical utility evidence required for diagnostic tests.

- A double randomisation model for the development of combination stratified medicine and diagnostic should not become a requirement.
- The delivery of a prototype diagnostic test for use in phase III development should not call for significant investment in advance of being in a position to recognise the efficacy or otherwise of the drug itself in phase II.
- Clinical utility of combination stratified medicine and diagnostic could be assessed in small randomised studies (if not built into phase III of drug development), which can lead to conditional reimbursement approval plus real-world data collection after launch.

Recommendation 17

We recommend that the problem of rewarding evidence generation for diagnostics used in combination with stratified medicines is addressed urgently. In determining the reward for a new stratifying diagnostic, pricing and reimbursement systems must consider the costs of evidence generation and not simply the costs of production. To incentivise the generation of evidence about analytical and clinical performance and clinical utility successfully, consideration should be given to promotion of commercially approved diagnostic tests unless an 'in-house' test has evidence of equivalent or improved quality.

Collaboration

Recommendation 18

We recommend that the Technology Strategy Board leads in the expansion of the UK Stratified Medicine Innovation Platform, perhaps in the form of public–private partnership, and which brings together the following stakeholders: academia; healthcare professionals and providers; pharmaceutical, devices, diagnostics and IT industries; research funders; regulators; health technology assessment bodies; and patient groups. The aim of this expanded Platform is to ensure a co-ordinated approach to facilitate the development and adoption of stratified medicine so that the UK benefits from the full potential of this approach to therapy. The Platform should provide regular reports to the Office for Strategic Co-ordination of Health Research.

Annex 2: Meeting delegates

Ms Georgina Apostoli	Policy Intern, Academy of Medical Sciences
Dr Sue Bailey	Disease Area Head, Oncology and Immunology, Bristol-Myers Squibb Pharmaceuticals
Professor Richard Barker	Director, Centre for the Advancement of Sustainable Medical Innovation
Dr Mark Beggs	Associate Director/Chief Operating Officer, Stratified Medicine Scotland Innovation Centre
Professor Sir John Bell FRS HonFREng FMedSci	Chair of the Academy of Medical Sciences Stratified Medicines Oversight Group and Regius Professor of Medicine, University of Oxford
Professor Iain Buchan	Professor of Public Health Informatics and Director of the Centre for Health Informatics, University of Manchester; Director of the Health e-Research Centre, Farr Institute
Dr Rachel Butler	Chair of the UK National External Quality Assessment Service's Special Advisory Group for Molecular Pathology
Mr Robert Butler	Economist of Medicines, Pharmacy and Industry Group, Department of Health
Dr Sandi Deans	Scheme Director, UK National External Quality Assessment Service for Molecular Genetics
Mr Simon Denegri	Chair, INVOLVE; National Institute of Health Research Director for Public Participation and Engagement in Research
Dr Janet Dixon	Sales Manager, Roche Molecular Systems
Professor Lou Garrison	Associate Director of Pharmaceutical Outcomes Research & Policy Program, University of Washington
Dr Alasdair Gaw	Lead Specialist in Stratified Medicine, Technology Strategy Board
Mr Nigel Gaymond	Executive Chairman, Personalised Healthcare Alliance
Dr David Griffiths-Johnson	Head of Innovation, Office for Life Sciences, Department for Business, Innovation & Skills

Professor Harry Hemingway	Professor of Epidemiology and Public Health, University College London
Professor Simon Hollingsworth	Executive Director of Stratified Medicine Studies, AstraZeneca
Dr Ian Hudson	Chief Executive, Medicines and Healthcare products Regulatory Agency
Dr Martin Johnston	Diagnostics for Stratified Medicine Project Manager, Technology Strategy Board
Dr Dorian Kennedy	Head of Immunisation Branch, Department of Health
Dr Hannah Kerr	Head of R&D Policy, GlaxoSmithKline
Ms Joan Kirkbride	Director of Operations, Health Research Authority
Dr Louise Leong	Head of Research and Development, Association of the British Pharmaceutical Industry
Dr Loic Lhuillier	Programme Manager, Stratified Medicine, Technology Strategy Board
Dr Thomas Lillie	Executive Medical Director of Regional Development, Amgen Ltd
Dr Richard Malham	Senior Policy Officer, Academy of Medical Sciences
Mr Adam Manhi	Life Science specialist, UK Trade and Investment
Ms Mirella Marlow	Director of Devices and Diagnostic Programmes, National Institute for Health and Care Excellence
Mr Jonathan Marron	Director of Strategy, Public Health England
Dr David Montgomery	Medical Director of Oncology UK, Pfizer
Professor Andrew Morris FRSE FMedSci	Dean and Professor of Medicine, University of Dundee
Dr Moditha Nawinne	Medical Advisor of Oncology, Pfizer
Mr Danny Palnoch	Senior Economic Adviser, Department of Health
Dr Marisa Papaluca Amati	Section Head of Scientific Support and Projects, European Medicines Agency
Dr John Parkinson	Director, Clinical Practice Research Datalink (CPRD)

Dr Jonathan Pearce	Translational Programme Manager, Medical Research Council
Mr Mark Samuels	Managing Director, National Institute of Health Research Office for Clinical Research Infrastructure
Professor Adrian Towse	Director, Office of Health Economics
Ms Alice Tuff-Lacey	Stratified Medicine Programme Manager, Cancer Research UK
Mr Graeme Tunbridge	Head of Medical Devices EU Policy, Medicines and Healthcare products Regulatory Agency
Dr Janet Valentine	Head of Public Health and Ageing, Medical Research Council
Professor Thomas Walley CBE FMedSci	Director, National Institute of Health Research Health Technology Assessment and Efficacy and Mechanism Evaluation Programmes; Professor of Clinical Pharmacology, University of Liverpool
Dr Martin Turner	Senior Policy Officer, The Association of Medical Research Charities
Professor John Whittaker	Vice President of Statistical Platforms and Technologies, GalaxoSmithKline; Professor of Genetic Epidemiology and Statistics, London School of Hygiene and Tropical Medicine
Dr Bridget Wilkins	Consultant Haematopathologist; member of the Interspecialty Committee on Molecular Pathology, Royal College of Pathologists
Professor John Williams	Director of Health Informatics Unit, Royal College of Physicians
Ms Doris-Ann Williams MBE	Chief Executive, British *In Vitro* Diagnostics Association
Dr Penny Wilson	Innovation Platform Leader for Stratified Medicine, Technology Strategy Board
Dr Naho Yamazaki	Head of Policy, Academy of Medical Sciences