The stratification of disease for personalised medicines

Research driven recommendations to strengthen a unified UK strategy through a stakeholder alliance

Vision paper, September 2014
Update to White Paper of April 2009
Foreword

This paper is a five year update and progress report on the original ABPI 2009 White Paper¹, which explored how public and private bodies engaged in biomedical research in the UK could work together to realise the significant benefits to the healthcare system and UK plc that will accrue by accelerating the development and adoption of stratified medicine. Patients will benefit from being prescribed those treatments which will most likely work for them and from access to new medicines. While the original paper was developed at the invitation of the Office for Strategic Co-ordination of Health Resource (OSCHR) and Innovate UK (formerly known as the Technology Strategy Board, TSB) in order to present prioritised recommendations for the UK, this paper represents the views of members of the ABPI R&D and medical communities in examining progress against key areas outlined in the 2009 paper.

This paper adopts a simple definition of stratified medicine, ie. “the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into stratified subpopulations that differ in their susceptibility to (or severity of) a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not”². It also involves the development, validation and use of companion diagnostics to achieve the best outcomes in the management of a patient’s disease or future prevention. Subsequent to the cross-UK dialogue catalysed by the 2009 paper, we have joined UK stakeholders in adopting the term ‘stratified medicine’ throughout this paper in place of ‘personalised medicine’, though perspectives from ongoing public engagement, such as through the Innovate UK/Sciencewise workstream, should also be taken into account.

Exploiting continuing scientific advances in genomics, molecular biology and medical technologies to detect and classify diseases more objectively lies at the heart of stratified medicine. While the report uses the word ‘stratification’ to describe this molecular sub-classification of disease and disease susceptibility using both biomarkers and a description of the phenotype, it is important to note that stratification more broadly is not limited to molecular technologies. Actual and future advances in these areas are leading to an increase in the efficiency and precision of drug use, dose selection and diagnostic discovery and development.

The ultimate vision for this endeavour is summarised in the following figure:

The ABPI believes that a focus on stratified medicine development, as part of an integrated stakeholder healthcare strategy in the service of patients, continues to represent a major opportunity for the UK to demonstrate world-class leadership.

² US President’s Council of Advisers on Science and Technology (PCAST)
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Executive summary

The call for action for an enabling environment for stratified medicine is driven by:

- Healthcare challenge: increased prevalence of common and chronic diseases, despite advances in medical technologies over the last 60 years.
- Development of more targeted treatments discovered through a deeper understanding of disease (cancer and rare diseases are the exemplars), which demonstrate improved productivity in the pharmaceutical industry after a challenging last decade.
- Potential benefits to patients, prescribers, payers, regulators, the biopharmaceutical and diagnostic industries, and to UK plc.

In 2009 R&D and medical representatives from ABPI biopharmaceutical companies discussed the priorities for disease areas and technological developments where co-operative public-private partnerships could accelerate progress. Two disease areas of immediate focus were recommended:

1. Oncology (patient selection and tracking response to treatment).
2. Inflammatory and autoimmune disease (particularly predictors of response in early treatment of rheumatoid arthritis and treatment choice for acute asthma).

In the medium to longer term we recommended priority activities to progress the underlying science for stratified medicine approaches to diabetes, chronic obstructive pulmonary disease, Alzheimer’s disease, chronic pain and the treatment of thrombosis. These recommendations were based upon:

- Clinical need
- Strong scientific foundation for therapeutic targets
- Multiple measures at different biological response levels
- Multiple targets and well established therapeutic pipelines
- Broad industry participation in relevant development programmes
- Need for patient stratification already recognised in clinical environment (with some tools already embedded clinically)

Progress made since 2009:

- Innovate UK has brokered a £200+ million UK alliance (the five year Stratified Medicine Innovation Platform) launched in October 2010.
- Activity from a range of stakeholders to aid stratified medicine advances, such as industry scientists, clinical academia, the curators of biobanks, data providers. For example, there has been government action on big data, electronic health records, the integration of general practice (GP) and hospital practice data within the Clinical Practice Research Datalink (CPRD). Recent initiatives such as Cancer Research UK’s stratified medicine programme and Genomics England’s 100K Genomes project may accelerate development in this field over the next three to five years, particularly in the National Health Service (NHS).
- MRC-ABPI immunology and inflammatory initiative created two academic-industry research consortia in chronic obstructive pulmonary disorder (COPD) and rheumatoid arthritis, and a third in diabetes, addressing the 2009 recommendations and providing a paradigm for open innovation. Together with a subsequent MRC call supporting further disease areas, a total of 30 academic and 41 industrial partners were brought together.
- Progress in oncology research has clearly been made, as evidenced in a growing pipeline, although significant hurdles still remain. Progress has also been made in supporting dementia research, with the announcement at the G8 dementia summit in December 2013 of a UK dementia platform, which will be formed in part of an MRC (Medical Research Council)/NIHR (National Institute for Health Research)/Industry consortium. Less progress has been seen in other disease areas.

3 In 2012, FDA- and EMA-approved medicines rose to record levels of 39 and 57 new entities respectively, reaching 27 and 81 respectively in 2013.
Immediate next steps:
➢ Barriers to implementation in addition to the scientific challenges, where further investment in translational medicine approaches are required, include technology and policy. For example, it is crucial that information technology and use of electronic patient records is addressed, as is linking biosamples, biological and clinical data to health records. On a policy level, patient privacy, data protection and consent need to be addressed (with patient engagement and involvement a crucial factor). Further policies are also required to evaluate and implement new stratified medicine technologies, along with the regulatory, reimbursement, intellectual property and economic environments.
➢ A new disease area recommendation includes infectious disease. The reduction of new medicines and classes in development for bacterial infections is a serious health concern, with solutions extending to new economic models.
➢ Ensuring the health service is configured to use stratified medicine including companion diagnostics, supported by appropriate commissioning tools and data flows, will make the treatments of the future a reality for patients.
➢ Given the potential benefit to healthcare, as well as the UK’s global standing in biomedical research, we firmly believe that a strategy for the development and deployment of stratified medicines should form a significant component of a future UK-based integrated healthcare system for patient service.

Background

The last 60 years has seen over 1,300 new medicines and vaccines discovered and developed by the pharmaceutical industry, approved for patient use by regulatory authorities around the world. These innovations have in turn helped shape modern medical practice and deliver exceptional value to patients, society and the economy. Together with other advances, especially in public health measures, they have led to much increased life expectancy throughout high income countries. Life expectancy in the developing world is also increasing due to a number of factors such as demographic changes and improved infectious disease control. Inevitably these developments are leading to an expanding elderly population and, therefore, increasing incidence of diseases associated with age. Thus the need for new medicines has not diminished and an aging population and typical polypharmacy increases the need for precision in selecting an intervention.

Healthcare systems and patients would benefit from a sustained rate of innovation and earlier access to new treatments, while industry seeks to contain the rapidly escalating costs of R&D to meet the increased complexity of the underlying science and regulatory requirements. Industry has begun to respond by adopting a stratified medicine approach, targeting the appropriate patient populations. This has been achieved due to an increased ability and commitment to link the genotype and phenotype criteria of the patient (including patient biospecimens, such as tumours). In addition, industry has also invested to discover and develop biomarkers that could predict a successful outcome for new medicines, as well as medicines that have already been launched. The impact of this change in strategy is already being seen, with recent analyses indicating that projects that have human genetic linkage to the target, to the disease indication or efficacy biomarkers, available at the start of clinical development have a more successful outcome.

However, to maintain momentum it is essential to continue to invest in the science, technology and policy related challenges to expedite advances in understanding the relationship of the target to the disease indication and the mechanism of action in the context of the right patient. In some disease areas this path will be longer than others.

The process for discovering, developing and registering a new drug is intrinsically long, risky and expensive. In addition, diseases with significant unmet medical need (eg. uncontrolled diabetes, Alzheimer’s disease and chronic pain) are extremely complex diseases, increasing the challenge. On average out of every 10,000 compounds synthesised in discovery laboratories, only one or two will successfully pass through all stages of the R&D process to become approved medicines.

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5 The pharmaceutical industry in figures, key data. EFPIA 2007
Compound attrition occurs throughout the R&D process and also in the post-marketing environment. Furthermore, not all medicines will be sufficiently successful to justify the costs of their development. The average R&D cost for a new approved medicine is now estimated to be upwards of £1billion\(^6\) taking into account the cost of the attrition of projects that fail. These costs continue to rise and despite significant technological advance and adoption of new approaches over the last decade, industry attrition rates remain stubbornly high. Further, recent EU regulation has increased post-approval requirements and resource.

The ABPI continues to believe that driving more rapid progress in the adoption of disease stratification and personalised medicine could make a significant contribution to improving the cost effectiveness and precision of the drug R&D process and fundamentally improve its competitiveness. Progress made in the last five years has been possible through the creation of a strong and coherent alliance between industry, the NHS, the funders of biomedical science and the medicines regulatory bodies (eg. as brokered through Innovate UK’s Stratified Medicine Innovation Platform and Ministerial Industry Strategy Group [MISG] forum). However, this progress has been evident mainly in oncology and the crucial aspect of reimbursement assessment is not as clearly developed. For the UK in particular, the development and execution of an integrated strategy across disease areas beyond oncology and integrating health technology assessments and reimbursement into these partnerships would enhance UK competitiveness and its position as a global leader in healthcare innovation. Failure to do so will inhibit further R&D growth in the UK and stymie the development of the small diagnostic sector.

The remainder of this paper presents a synthesis of 2014 views from the R&D community within ABPI member companies with respect to:

1. Describing the value drivers for stratified medicine to the different public and private stakeholders who need to be engaged.
2. Highlighting why the UK could be in a stronger position to lead an innovative and collaborative approach to this opportunity.
3. Recommending specific areas of short, medium and long-term impact where consortia could form to drive rapid progress.

The ABPI continues to believe that through the auspices of OSCHR and its supporting groups, Innovate UK, the third sector, the Office for Life Science, and through UK participation in the European Innovative Medicines Initiative (IMI), the UK has an exceptional opportunity to realise the benefit of stratified diseases and personalised medicines, for the benefit of all stakeholders, not least patients.

Potential benefits of stratified medicine to stakeholders

Patients
- Improved healthcare due to better matching of patient needs and therapeutic benefit
- Reduced likelihood of adverse events, and thus greater incentive to remain on therapy especially for pre-morbid conditions such as hypertension and hypercholesterolaemia\(^7\)
- More informed choice of therapy
- More rapid access to new and innovative medicines that work for patients
- Access to broader range of therapies supported by the NHS
- Greater personal involvement in treatment decisions and thus greater likelihood to adhere to treatment

Payers and healthcare providers
- More cost effective use of healthcare resources due to:
  1. improved response rates for the treatment of diseases
  2. avoidance of side effects and increased use of effective treatments
  3. avoidance of treatment for those who don’t need it, or won’t benefit from it

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• Improved and more specific diagnoses of diseases and their prognosis leading to more accurate forecasting on healthcare resource requirements.

**Regulatory authorities**
• Greater confidence for earlier/conditional approval and thus earlier access for patients
• Greater confidence in the interpretability of pharmacovigilance data

**Pharmaceutical industry**
• Safer, more effective medicines
• Focused discovery and development programmes based on more refined disease diagnosis
• Improved decision making and potentially lower attrition
• In the longer term, the ability to develop individual medicines with a greater value proposition with regulation and study design keeping pace (caveat: the costs of clinical trials are likely to go up in the near term with the additional cost of the development and validation of biomarkers required as diagnostics, and inability to pre-specify target populations accurately without a large number of patients)
• Earlier approval of new therapies with improved confidence in post-marketing pharmacovigilance systems
• More accurate targeting of the marketing of medicines
• Increased differentiation of new therapies from generic therapies leading to more valued products

**Diagnostics industry**
• Increased opportunity for cost effective diagnostics to partner with currently approved medicines and medicines in development, opening up new collaborative space with academia, patient groups, healthcare systems, pharmaceutical industry and government.

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**UK competitive position**

Stratified medicine has particular significance for the UK as it could offer an area where it could be uniquely competitive, show international leadership and create a more conducive environment for novel drug and diagnostic R&D. The UK environment has generally supported the considerations identified in 2009, and examples of progress include:

• **Electronic health records** are becoming more established in regions of the UK. This is a critical foundation stone for stratified medicine and will allow genomic and clinical data to be integrated into practice. This will be strengthened further with the implementation of a single portal to federated clinical information facilitating both clinical care and biomedical research. Two key bodies in this respect are the NHS Health and Social Care Information Centre (HSCIC), and the Clinical Practice Research Datalink (CPRD) hosted within the MHRA. Nonetheless there remains the urgent need to join up data systems for biological samples and clinical data.

• **Bioinformatics and health informatics investment** that has included creation of the Farr Institute of Health Informatics Research for research using electronic health records and the development of new methodologies and skills capabilities, MRC additional investment in bioinformatics and establishment of NIHR diagnostic evidence centres.

• **The 100K Genomes project** run by Genomics England Ltd is undertaking whole genome sequencing and linkage to clinical data to embed the necessary capabilities in the NHS, from informed consent to deployment of stratified medicine, to make routine genomic medicine a reality.

• The UK has significantly strengthened its academic clinician base over the last few years and the recent formation of recognised Academic Health Science Centres and Academic Health Science Networks provides a focus for disease science, patient resources and faster translation.

• The creation in recent years of a number of translational medicine centres (eg. the NIHR biomedical research units and centres, the Wellcome Trust/Department of Health clinical research facilities, the NIHR translational research partnerships and experimental medicine resource) will provide focus for research priorities and execution.

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• NIHR has implemented initiatives towards rapid approvals of clinical trials and focus on clinical trial performance. EHR should enhance this further, along with pharmacovigilance, and adaptive licensing approaches.
• **Joint MRC/ABPI stratified medicine initiatives** in COPD, rheumatoid arthritis and diabetes.

  • **IMI initiatives and investments**: ABPI members and UK academia are playing leading roles, eg. iPS cell bank from well characterised patients (EBiSC), U-Biopred investigating severe asthma, SUMMIT and DIRECT for diabetes, EMIF for obesity and Alzheimer's disease, QuIC-ConCePT for oncology, and eTRIKS building a translational research informatics and knowledge management programme.
  • The UK has been a leader in **evidence-based medicine** - eg. the Cochrane Collaboration - stratified medicine is a natural extension of this providing further molecular based decision making tools that can be incorporated into practice.
  • **NICE** now provides a single entity to conduct evaluation of clinical effectiveness and health technology assessment of prospectively developed stratified medicines and their companion diagnostics, though there remains a gap in the evaluation of new companion diagnostics for launched medicines.
  • **MHRA** regulates both medicines and devices including diagnostics.
  • The drive provided by **Innovate UK** to accelerate innovation and to catalyse multi-company, multi-academic and multi-government agency collaborations.

The UK Biobank sets the precedent for all patients to positively participate in the clinical research effort. There is a unique opportunity to broaden this example by linking samples to pseudo-anonymised NHS derived patient data proposed through CPRD. Sharing genomic data and samples between industry collaborators and between industry and academia to accelerate understanding of disease stratification, biomarker validation and drug response is now more commonplace. The UK (academia and industry) is now contributing significantly to the European wide Innovative Medicines Initiative that will also result in large-scale data sharing between academic and industry partners.

The profound benefit of building on current initiatives such as UK BioBank, various longitudinal cohorts, Genomics England’s 100K Genomes programme, CPRD and HSCIC, to create a fully integrated and linked UK health outcomes database where patient’s phenotypes are tracked over time cannot be underestimated. Technological advance is rapid and the era of having a full DNA sequence for each individual for less than £1,000 is already upon us. The availability of anonymised information from such a database would not only drive progress in personalised healthcare and enable more cost effective health management, but also distinguish the UK as a centre of choice for clinical research and outcome measurement. The parameters that should be derived that will inform drug discovery and delivery of right medicine to the right patient at the right time will be clear stratification of risk of disease, risk of rapid disease progression and then response to current intervention in terms of efficacy and adverse events. This can only be understood with detailed longitudinal clinical data. This may be data collected within NHS Electronic Health Records (EHR) and available through the HSCIC or CPRD.

**What are the technical and policy challenges to the implementation of personalised medicine?**

In 2009 R&D leaders recognised that industry needed to work in a different way. The development of new government strategies and the emergence of new clinical and scientific opportunities indicated a mandate for much closer working between the public and private health research sectors in order to ensure delivery of new ‘stratified’ medicinal products.

Here, we reflect on experience to 2014 on the eight policy areas outlined in our 2009 paper:

1. **Science and Technology**
   The key problems are the provision of high quality molecular sub-phenotyping data to stratify complex diseases and the slow speed of clinical validation of genomic-based molecular biomarkers.

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9 [http://www.mrc.ac.uk/Fundingopportunities/Calls/MRC-ABPI-Initiative/index.htm](http://www.mrc.ac.uk/Fundingopportunities/Calls/MRC-ABPI-Initiative/index.htm).
and diagnostics. Given its novel, high risk and high cost status, industry cannot plan and conduct this fundamental and translational work alone. Public/private partnerships will continue to be essential for progress to be made. These include:

- Development of a public/private sector ‘Stratified Medicine R&D roadmap’ for co-ordinating relevant discovery and translational research activities.
- Development of a process to identify and prioritise diseases that could benefit from the application of genomics-based technologies.
- Establishment of a capability to share standardised biospecimen repositories to support stratified medicine research.
- Establishment of a joint funding programme for biomarker standardisation and validation study design.
- Developments of large population cohorts for long term follow up of genetic and environmental health effects. Linkage of UK Biobank, CPRD, and 100K Genomes should progress.

Innovate UK have developed a roadmap for stratified medicine which should, therefore, be actively curated, disseminated and used\(^{10}\) to avoid piecemeal launches of the components essential for stratified medicine and slowing progress. Despite the lack of a clear process, disease area priorities have been and/or are being set, eg. MRC-ABPI immuno-inflammatory and diabetes consortia, MRC-NIHR dementia platform. Sharing of biospecimen repositories and funding programmes for biomarker standardisation study designs have also been slow to get off the ground, although discussions with UK Clinical Research Collaboration (UKCRC) partners have resulted in the recent launch of a call to fund such an activity. Biomarkers are being developed for individual projects within companies, IMI projects or the above MRC-ABPI and Innovate UK programmes, with trends moving towards multi-array platforms. Large population cohorts for long term follow up of genetic and environmental health effects are starting to emerge in the UK, but are currently very limited by access or gaps in data. UK Biobank is one example but unless there is transformative change in the immediate future, linking genetic and health data effectively to scale may take a few years. Technological hurdles have now been overcome to make this challenge a reality, but there is still work to be done on public engagement and engendering public confidence on privacy safeguards.

2. Regulation

The development of medicines that arise from the better stratification of disease will need to follow a slightly different regulatory paradigm from that which exists today. Reasons for this include:

1. The need for these medicines to be developed in conjunction with their specific diagnostic technology.
2. The fact that the data that would be provided to support registration could be anticipated to occur relatively earlier and with a smaller, restricted patient population.

Regulators and developers will, therefore, need to work together in order to:

- Agree the criteria for the early/conditional licensing of stratified medicinal products and their post-approval risk management, on the basis of an anticipated smaller pre-registration data set than suggested by the current regulatory paradigm.
- Establish guidelines that define regulatory standards for study design and sensitivity/specificity parameters for diagnostic products.
- Establish guidelines for the co-development of diagnostics and therapeutics.
- Develop an approach for the incorporation of the use of diagnostics in therapeutic products labelling.
- Adapt IVD (in vitro diagnostics) guidelines to accommodate emerging technologies for stratified medicine such as imaging and mobile devices.
- Ensure regular communication to articulate projections of the number and type of products in the development pipeline that are based on stratified medicine technologies.
- Ensure regular communication and discussion on anticipated emerging regulatory issues with these new technological developments.

\(^{10}\) Innovate UK roadmap: https://connect.innovateuk.org/documents/2843120/3724280/Stratified+Medicines+Roadmap.pdf/ fbb39848-282e-4619-a960-51e3a16ab893
Progress in this area has been made with, for example, early licensing of stratified medicinal products in the EU and US. Bespoke guidelines and strategies are being enacted in Europe due to the discrete nature of regulation of medicines and diagnostics, which are not always classified as devices. Revision of the EU IVD and devices regulation is in progress which is anticipated to enhance demonstration of clinical utility of companion diagnostics. In the meantime, guidance within Europe for the co-development of diagnostics and therapeutics is largely focused around pharmacogenomics and biomarker qualification. Additionally, the approach for labelling is dependent on the individual medicines and disease area, whilst communication is dependent on individual company strategy and so progress in establishing guidelines in these areas should still be tackled.

3. Reimbursement
Developers of either diagnostics or therapeutics that are suitable for incorporation into clinical practice will expect to be reimbursed at a rate commensurate with the investment to develop the technology and the value that it delivers. This will include the need for evaluation on the basis of the full value of the intervention. The need for flexible value based reimbursement must include a mechanism to increase prices if increased value is demonstrated. Developers and payers must, therefore, work closely together to establish a new paradigm for the evaluation and funding of these future innovations. This is critical to ensure that the development of stratified medicines becomes a major, established and sustainable focus for the pharmaceutical industry. In the UK, this was already possible in the 2009 and current (2014) Pharmaceutical Price Regulation Scheme (PPRS) agreed between government and the industry for the reimbursement of new innovative medicines.

By 2014, the majority of medicines that have been approved with stratification in mind, and often companion diagnostics, are new cancer treatments. Despite the increased precision of these medicines, reimbursement has sometimes not been easy to achieve from NICE in the UK. It may also be necessary to set up alternative evaluation systems for those medicines that are not selected for NICE appraisal so that they can be made available for use on the NHS. In cases of stratified medicine, where the use of a medicine is tightly linked to a companion diagnostic, reimbursement for that diagnostic or the medicine-diagnostic combination should be taken into account. Non-reimbursement of innovative medicines in the UK, which are reimbursed in the US and the EU, has a potential impact on clinical trial placement, if UK patient care and availability of the standard of care to enable comparator trials falls behind that of other high income countries.

4. Information Technology
Interoperable, standardised electronic health records and clinical decision support tools will be essential for the implementation of therapeutics and diagnostics for stratified medicine. Not only will they be critical to guide medical practice, but also to ensure ongoing research into the correlation between genomic markers and clinical outcomes. In the same way, interoperability would also be valuable to enable sharing of data within and between research consortia.

Some progress has been made in the last five years, but achieving the accuracy and quality of the EHRs to ensure excellent longitudinal data for interpretation remains a challenge. The large insurance based databases in the US, which require accurate ICD-9 codes, may be inferior in terms of stable patient long term longitudinal data, but are superior in terms of accuracy and ease of analysis. Complex algorithms are required to incorporate non-coded data from medical resources and combining these data with data from other coded datasets will maximise value. This will require collaboration between efforts to avoid duplication, specific expertise, as well as a huge need for additional data storage and infrastructure development that is secure, provides a user interface and can enable data linkage of diverse data sets that can be accessed to gain more insight and enable future analyses.

5. Intellectual Property (IP)
The assurance of a stable and robust IP environment will be essential for the bioscience sector to have confidence to commit the necessary high risk investments for the R&D of all novel products, including those to be derived from stratified medicine strategies. Overall the UK has robust protection of core IP for composition of matter for medicines and vaccines. However, IP based around diagnostic tests safeguarding their deployment, instead of substitution by in-house or unvalidated alternative testing provided locally, remains a challenge, as well as affecting good medical practice and the ability to conduct meaningful real world studies.

6. Privacy
A potential concern to patients is the potential for detailed genetic information to link to a specific individual and for that information to be used for non-medical/research purposes. Stakeholders should engage to better understand public hopes and concerns around access to medical information and to explain the safeguards in place to protect privacy in providing access for ethically approved medical research. This entails the establishment and maintenance of robust database security and controls on data use. This is not a requirement unique to stratified medicine, however, as it applies to the use and control of all confidential patient data.

The need for the establishment of capabilities to share standardised biospecimen repositories to support stratified medicine research was mentioned in the science and technology section above. However, as future research questions or technologies may not be known at the time the sample is collected, there will be a need to have an ethical informed consent process that allows for the testing of anonymous samples, eg. for markers not known or anticipated at the time of collection, with a means for ethical handling of incidental findings and associated privacy safeguards.

7. Physician and Patient Education
A clear roadmap of data security, privacy and utility needs to be developed in partnership, including the public, in order to facilitate the acquisition of 'safe data' to drive medical research for new and improved treatments. Medical progress in delivering the healthcare benefits of stratified medicine will be severely challenged without appropriate clinical advocacy and public confidence. We believe maximum transparency is needed from government and NHS, supported by academia, research charities, patient advocacy groups, the ABPI and BIVDA. We must clearly articulate the value of large datasets and their utility in developing new treatments and optimising current treatments. Having articulated the benefits, we should also be clear as to what is not permitted under ethical guidelines and sanctions for those who violate these restrictions.

8. Economics
In essence many of the key priority areas highlighted above (science and technology, regulatory, reimbursement, IP) will all contribute to an essential assessment of the medium to long-term economic viability of stratified medicine. This is of particular importance to research investors and to the pharmaceutical industry who shoulder the upfront development of new innovative medicines, and whose business model could not be sustained if stratified medicine did not deliver some risk alleviation, attrition reduction and promise of value driven return. As such there needs to be a significant dialogue between public and private sectors to ensure the identification and assessment of the economic factors that will incentivise the development and use of stratified medicine products both in the UK and around the world.

We have also worked with the Academy of Medical Sciences in 2012 to explore in detail specific areas of regulation, economics, clinical and research infrastructure.

12 http://www.dt-toolkit.ac.uk/routemaps/station.cfm?current_station_id=431
http://www.wellcome.ac.uk/About-us/Policy/Policy-and-position-statements/WTP052064.htm
13 Symposium report: http://www.acmedsci.ac.uk/viewFile/51e915f9f09f0fb.pdf
Disease area prioritisation: progress since 2009
Recommendations

The 2009 recommendations were the result of discussions between members of an expert group convened by the ABPI R&D and medical committees. They were made with reference to the current state of development of the science in each disease area and tried to take account of the progress of other international initiatives that had relevant ongoing collaborative work (eg. IMI, FDA Biomarkers Consortium etc). The recommendations were made at the highest level and anticipated that the next step would be a series of multi-partner workshops to define the opportunity in more detail and recommend clear plans. All areas were prioritised on a basis that they represented a high level of unmet medical need and that there was substantial existing R&D commitment in the biopharmaceutical community to develop new medicines and diagnostics, as well as academic strength.

Before reviewing specific progress, it is appropriate to summarise the current state of affairs in stratified medicine in R&D compounds and approved entities. An analysis of IMS data\textsuperscript{14}, using biomarker as a free text search term, indicates that oncology and immunological programmes represent the largest therapeutic area grouping. In approved product labels 121 FDA approved labels include pharmacogenomic information, compared with 39 in the EU (data extracted August 2013). There are several disease areas that need to be added to the recommendations in 2014. For example, there is an urgent need to preserve the current anti-bacterial armoury by rapid point of care diagnostics determining viral versus bacterial, gram negative versus gram positive and susceptibility and sensitivity testing (best available agent). Reinvestment in this field may be upon us, with new R&D investors attracted by pending regulatory simplification of clinical study design, and willingness of governments to explore and pilot new economic models.

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<th>2009 recommendation</th>
<th>Progress made by 2014</th>
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| **Short term (value realised by 2012)**                                           | 1. Oncology remains the most active therapeutic area representing 28% of all projects in the IMS database; clear progress has been made.  
2. Work is ongoing. Selection of patients with asthma based on eosinophilic characteristics has been shown to be successful. http://www.nejm.org.proxy1.athensams.net/doi/full/10.1056/NEJMoa1304048. MRC-ABPI programme ongoing in COPD, rheumatoid arthritis.                                                                                           |
| Improve activities which enable and embed stratified medicine in disease areas where science is available and where the use of current or imminent therapies could be improved, eg.                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
2. Inflammatory and autoimmune disease: rheumatoid arthritis and acute asthma, tools for identifying patients that will respond to new treatments.                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Biomarker toolbox development across these and other disease areas which will accelerate stratified medicine development in both industry and the NHS, eg. minimally invasive, molecularly specific and rapid response technology (such as imaging; innovative analytical techniques to replace pathology).                                                                 | Progress not evident although some centres have recently opened, eg. the MRC-NIHR National Phenome Centre (2012) that provides capability in targeted and exploratory high-throughput metabolic phenotyping and assay development.                                                                                                                                                                                                                             |

\textsuperscript{14} Office of Health Economics analysis of IMS data, IMS LifeCycle (2014), accessed February 2014
Infectious disease: Development of pathogen-specific diagnostics for bacterial infections, particularly for antimicrobial resistant pathogens, which would enable appropriate prescribing, and appropriate and enriched recruitment to clinical trials for new antibiotics. (Addition in 2014)

**Medium term (value realised between 2012-2019)**

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<td>Diabetes</td>
<td>Molecular tests for predicting those at risk and to signal earlier interventions; better stratification of disease for new therapies; larger responder/non-responder data collections.</td>
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<tr>
<td>Chronic Obstructive Pulmonary Disease (COPD)</td>
<td>Improved molecular stratification of the disease, larger collections with international collaboration. Responder/non-responder understanding for current therapies</td>
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<tr>
<td>Alzheimer’s disease</td>
<td>Improved and validated methods for early diagnosis; new approaches to risk modifications; stratification for initial treatment recommendation; methods for measuring response to treatment more rapidly and objectively.</td>
</tr>
<tr>
<td>Thrombosis/stroke</td>
<td>New tools to characterise clotting status quickly at a molecular level.</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>Improved phenotyping and molecular stratification of pain; larger collections with international collaboration.</td>
</tr>
</tbody>
</table>

**Long term (value realised beyond 2019)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>New understanding of non-responsiveness to develop new treatments. Improved molecular stratification of disease and development of related biomarkers.</td>
</tr>
<tr>
<td>Dementia and other neurodegenerative diseases</td>
<td>Further work on molecular stratification and validation of new biomarkers and measurement technologies. Better methods for determining pre-disposition and new approaches to prevention/delaying onset.</td>
</tr>
<tr>
<td>Cardiovascular and metabolic disease</td>
<td>New understanding of non-responsiveness and development of new treatments for sub-populations.</td>
</tr>
</tbody>
</table>

Innovate UK call in infectious disease. Cross-research council initiative for new therapeutics and diagnostics.

MRC-ABPI diabetes consortium and IMI DIRECT ongoing.

MRC-ABPI COPD consortium ongoing.

UK dementia platform announced December 2013 and IMI EMIF ongoing.

IMI Europain ongoing.
The disease areas listed above remain priority areas and continued progress should be pursued with vigour. There will be value in focusing on earlier diagnoses for some disease areas, such as Alzheimer’s disease, so that treatment can be efficacious before a disease is irreversible. Also important in the short term will be to improve upon translational models to ensure a quick transition between discovery and drug development. Increased ability to explore extreme phenotypes and responses to drugs will increase chances for stratification of disease for new therapies and moving disease areas, such as diabetes, into an arena where there will be value realised within the short term.

The generation/linkage of genotypic data to phenotypic/EHR data will increase our ability to study and understand human variability in populations and disease increases. In 2013, Genomics England Ltd (GeL) committed to sequence individuals with rare diseases, cancer and infectious disease and thus progress should be seen in these areas by 2017. It is essential to make further recommendations for disease areas for which genetic data is lacking and where this is unlikely to change over the next few years. For example, there is a lack of genetic data for complex chronic pain and whilst there is a recommendation to improve phenotyping and stratification of pain, timely stratified medicine approaches may be hindered without the ability to link genetic and phenotype data.

Areas are progressing where there are large scale genotype and phenotype efforts coming to fruition and the science is maturing to a stage where some function/mechanisms are being understood. A good example is schizophrenia. IMI work is helping understand responders and susceptibility [http://www.imi.europa.eu/content/newmeds](http://www.imi.europa.eu/content/newmeds).

### Recommended next steps for 2014 and beyond

We also recommend approaches that will enable the development of capabilities to facilitate stratified medicine:

**Data and governance:**
- Develop a clear stratified medicine roadmap authored by key interested parties to commend the sharing of biospecimens and health data for the benefit of patients.
- Develop quality protocols to ensure that longitudinal data is of better quality than, and at least of equivalent quality as other databases such as from US medical insurers.
- Establish a proportionate governance framework of clinical data storage, access and reuse.
- Address limitations of access to anonymised EHRs to allow hypotheses generated by either pharma or academia to be tested in a timely manner resulting in the advancement of, for example, use of therapies for patient sub-groups that would otherwise not be explored.

**Translational medicine approaches:**
- Invest in generating genetic data and setting standards for access to data as well as patient involvement and clinician advocacy.
- Invest in deep and frequent phenotyping of patients in critical diseases such as proposed within the UK dementia platform.
- Invest in biomedical and health informatics to allow better real-time patient segmentation.

**Regulation:**
- Ensure EU IVD regulation and classification is fit for purpose for UK industries and patients.
- Continued development of national regulatory framework to enable provision of stratified medicines.

**Value and access:**
- Establish a NICE and NHS commissioning framework to support value-based assessment and reimbursement of multiplex molecular testing platforms.

**Implementation and use in the health service:**
- Develop/invest in faster implementation of new diagnostics to move towards implementation within the NHS rather than rely on individual providers to implement diagnostics in practice.
• Harmonise diagnostic testing uptake across the UK so all patients benefit from innovative therapies.
• Incentivise adoption of novel diagnostic approaches to establish testing infrastructure prior to any therapy being available.
• Harmonise sample handling protocols of clinical samples across the UK to increase quality.

Societal engagement:
• Invest in health information about the benefits and challenges of stratified medicine, eg. workshops involving patients, physicians, industry and payers and promote patient participation and prioritise in the health policy agenda.

Summary

In 2009 we believed that stratified medicines, then a relatively new paradigm in the healthcare sector, offered potential significant benefits to patients, prescribers and healthcare payers. In the treatment of cancers and some rare diseases, it seems possible to remove the qualifier ‘potential’. In other therapeutic areas we have also seen steps towards more sophisticated ways of identifying patients who will benefit from specific interventions. Progress has perhaps been more slowly realised than hoped, but this is not atypical in medical research where cumulative small steps are eventually integrated into leaps forward. The progress that has been made has been achieved despite four years of economic recession and a fragile market place. In addition to the direct benefits to the healthcare community, further development of biomedical science and technology could provide a major foundation for improving both the UK’s future economic and industrial base and the wellbeing of its people. This area has begun to attract substantial public and private R&D investment and the NHS is developing a strong infrastructure to more rapidly assess and consistently implement beneficial innovations into practice. This infrastructure should not be a target for cost savings given ongoing public finance constraint, but should be seen as a future investment to attract inward investment and better value for patient care. Preserving these public/private investments has the potential to help maintain and grow both the large and small UK enterprises that in turn export these innovations globally.

Healthcare demand continues to rise driven by public expectation and extended life spans. The major challenge for government, regulators, healthcare providers and for industry is to find the best way to focus and exploit health improving innovations whilst ensuring that cost benefit is maximised for the UK citizen. Establishing technologies, processes and infrastructure in partnerships ensuring medical innovation is focused on those that would gain most benefit (and/or suffer fewer adverse reactions) presents a major opportunity for the UK. The NHS in particular contains so much unique and valuable data that could be converted into knowledge, to optimise current treatment deployment and provide new avenues for research into prevention and treatment of disease and maintenance of health. Progress has been made since 2009 but remains fragile in the face of economic and social headwinds. Hence, while progress has been good, it has been slower than hoped and further work is required to capture the benefits of stratification. A visionary stratified medicine roadmap with realistic goals shared by government, patients, payers and healthcare industries is necessary to solidify gains and accelerate progress.

Acknowledgements

The ABPI would like to thank the ABPI Stratified Medicine Working Group for updating this paper, with editing by Steve Felstead, Gemma Satterthwaite, Serena Scollen, and Louise Leong, and comments from other colleagues. The 2009 paper was developed by founder members of the group: Mark Edwards and John Stageman in conjunction with Paul Matthews, Duncan McHale, Aidan Power and members of their respective teams. Credit for figure on page one: Aidan Power.
