



The stratification of disease for personalised medicines

Research driven recommendations and the
rationale for a UK Stakeholder Alliance

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Foreword

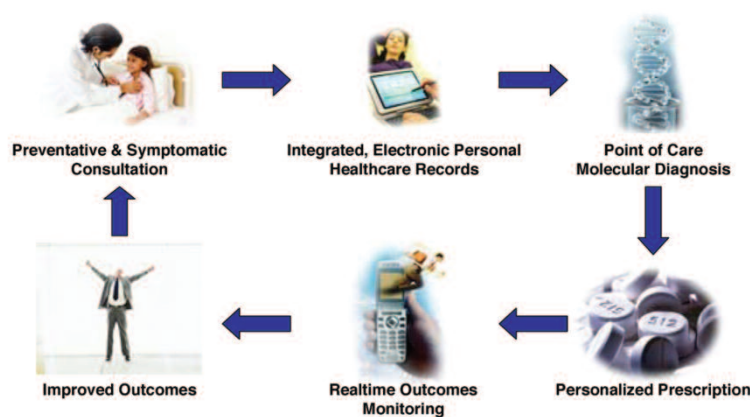
This paper explores how public and private bodies engaged in biomedical research in the UK could work together to realise the significant mutual benefits that will accrue by accelerating the development and adoption of personalised medicine. It represents the views of members of the ABPI R&D and Medical communities in response to a recent invitation from OSCHR and the TSB to present prioritised recommendations for the way forward. Industry believes that this paper is timely and that it sits very comfortably within the broader strategic perspective of its wider dialogue with Government concerning how the UK can preserve its position as an international location of choice for innovative drug and diagnostic research and clinical development.

Following a recent report by the US President's Council of Advisors on Science & Technology (PCAST) this paper adopts a simple definition of personalised medicine i.e. "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 subpopulations that differ in their susceptibility to 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". Critically, 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 their predisposition.

Exploiting recent scientific advances in genomics, molecular biology and medical technologies to detect and classify diseases more objectively lies right at the heart of personalised medicine. 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. Anticipated advances in this area will lead to an increase in the efficiency and precision of drug and diagnostic discovery and development, and in turn many aspects of future medical practice.

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

What it's all about: Integrated healthcare in the service of the patient



The senior R&D representatives at the ABPI believe that a focus on personalised medicine development, as part of an integrated stakeholder healthcare strategy in the service of patients, represents a golden opportunity for the UK to demonstrate world-class leadership.

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Executive summary

- Despite significant advances in medical technologies over the last 60 years, several common diseases are increasing significantly in prevalence and mortality driven by increases in life expectancy and population growth. Couple this to the rapidly escalating cost of modern healthcare and poor adherence of patients to chronic medicines, then there is clearly a need to target interventions more objectively and engage patients more effectively in therapy decisions.
- The pharmaceutical is facing the greatest productivity challenge in its history and must find new ways to prosecute its research and development, with a greater focus on partnership with other bioscience stakeholders.
- The development and execution of an integrated stakeholder strategy in personalised medicine could positively contribute to both problems and significantly enhance UK competitiveness and attractiveness for Drug and Diagnostic R&D.
- Personalised medicine is focussed on delivering the right medicine at the right dose to the right patient at the right time. It centres on research to classify individuals into subpopulations that differ in their susceptibility to 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. A critical success factor for its delivery will be a joined up approach involving all key stakeholder groups.
- The successful development of personalised medicines driven forward by an integrated UK strategy will provide a range of benefits to patients, prescribers, payers, regulators, the pharmaceutical and biotechnology industry, and to UK plc. We believe that the Technology Strategy Board is optimally placed to broker the shorter term and innovative technology aspects of this work.
- The development and implementation of an integrated strategy for personalised medicine cannot just focus on the science, which by itself will be a significant challenge; instead it needs to address the challenges presented across the full range of technology and policy-related areas, including;
 - How the science-driven opportunities and capabilities for the delivery of new diagnostic and therapeutic technologies will be evaluated and implemented
 - The regulatory, reimbursement, information technology, intellectual property and economic environments.
 - Patient privacy and education.
 - Electronic patient records and the objective measurement of benefit
- R&D and Medical representatives from the ABPI Pharmaceutical companies have discussed the priorities for disease areas and technological developments where co-operative public-private partnerships could accelerate progress.
- In the shorter term we recommend that two areas; Oncology (patient selection and tracking response to treatment) and Inflammatory & Autoimmune disease (particularly predictors of response in early treatment of Rheumatoid Arthritis and treatment choice for Acute Asthma). In addition a significant stimulus for biomarker development, validation and application is also required.
- In the medium to longer term we recommend priority activities to progress the underlying science for personalised medicine approaches to Diabetes, Chronic Obstructive Pulmonary Disease, Alzheimer's Disease, Chronic Pain and the treatment of Thrombosis.
- We firmly believe that a strategy for the development of personalised medicines should form a significant component of a future UK-based integrated healthcare system in the service of the patient.

Background

The last 60 years has seen over 1200 new medicines 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.

However, despite the huge and growing need for new and safer medicines, the industry is facing an enormous challenge to maintain its rate of innovation and flow of novel medicines to the market in light of rapidly escalating costs of R&D, the increasing complexity of the underlying science, the need to demonstrate greater safety and the understandable requirements from Governments and Payers to show value for money.

For example, although mortality rates are dropping, **cancer** and **circulatory diseases** account for approximately two thirds of all deaths in the UK. **Diabetes** is now the fifth leading cause of death globally and its prevalence in the UK adult population is increasing (*DoH "Health Profile of England", 2007*). The prevalence of **dementia** in the UK is forecast to rise by nearly 40% over the next 15 years (*Alzheimer's Society "Dementia UK – the Full Report", 2007*). Between 1965 and 1998 death rates in the US from **chronic obstructive pulmonary disease** (COPD) rose by over 160%. It is now the fourth leading cause of death in the developed world and its prevalence continues to grow (*GOLD workshop report 2001; www.goldcopd.com/*).

Additionally, it is known that patient adherence with medicines is often poor. It is estimated that only 50% of patients suffering from chronic diseases in developed countries follow treatment recommendations (*Adherence to long-term therapies: Evidence for action. WHO 2003*). Reasons for poor adherence are multiple but clearly include real or perceived lack of effect and real or perceived side effects. The consequences of poor adherence are also multiple and include the healthcare burden of continued ill-health and subsequent complications. There is also the direct economic impact of such enormous drug wastage.

The process for discovering, developing and registering a new drug is intrinsically long, risky and expensive. On average out of every 10,000 compounds synthesised in discovery laboratories, only one or two will successfully pass all through all stages of the R&D process to become approved medicines (*The pharmaceutical industry in figures, key data. EFPIA 2007*). Compound attrition occurs throughout the R&D process and also in the post-marketing environment. The average R&D cost for a new approved medicine is now estimated to be between \$0.8-1.3 billion 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.

R&D leaders in the ABPI believe that along with other key initiatives, 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 can only be made through the creation of a strong and coherent partnership between industry, the NHS, the funders of biomedical science and the Regulatory bodies. The result will be new medicines that offer enhanced patient outcomes (efficacy and safety), improved adherence, reduced wastage, and possess characteristics that will facilitate earlier uptake and adoption, through the clear "value proposition" they present to payers. In turn this would be anticipated to enhance industry's confidence to continue to invest in new areas of R&D. For the UK in particular, the development and execution of an integrated strategy in this area would enhance UK competitiveness and its position as a global leader in healthcare innovation.

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

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

The ABPI believes that through the auspices of OSCHR, its supporting groups and the Technology Strategy Board, and through its participation in the European Innovative Medicines Initiative, the UK has an exceptional opportunity to realise the benefit of stratified diseases and personalised medicines, for the benefit of all stakeholders

Potential benefits of personalised medicine to stakeholders

Patients

- Improved healthcare due to better matching of patients needs and therapeutic benefit
- Reduced likelihood adverse events
- More informed choice of therapy
- More rapid access to new and innovative medicines
- Access to broader range of therapies supported by NHS
- Greater personal involvement in treatment decision and thus more incentive to comply

Payers and healthcare providers

- More cost effective use of healthcare resources due to:
 - i. improved response rates for the treatment of diseases.
 - ii. avoidance of side effects and increased use of effective treatments
 - iii. avoidance of treatment for those who don't need it
- 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
- Greater confidence in the interpretability of pharmacovigilance data

Pharmaceutical industry

- Increased differentiation of new therapies from generic therapies leading to more valued products
- Focused discovery and development programs based on more refined disease diagnosis
- Improved decision-making and potentially lower attrition
- In the longer term, the ability to develop individual drugs more cost-effectively (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 drugs
- Safer, more effective drugs leading to improved perception of the societal value of the pharmaceutical and biopharmaceutical industry

UK competitive position

Personalised 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:

- Electronic health records are becoming more established in parts of the UK. This is a critical foundation stone for personalised medicine and will allow genomic and clinical data to be integrated into practice. This will be strengthened further with the implementation of Connecting for Health creating a single network of clinical information facilitating both clinical care and biomedical research.
- The UK has been a leader in evidence based medicine - e.g. the Cochrane Collaboration – personalised medicine is a natural extension of this providing further molecularly based decision making tools that can be incorporated into practice
- Recent changes to create the “Office for the Strategic Coordination of Health Research (OSCHR) and creation of DoH funded translational medicine centres will provide focus for research priorities and execution
- The drive provided by the Technology Strategy Board to accelerate innovation and to catalyse multi-company and multi-government agency collaborations
- NICE now provides a single entity to conduct evaluation of clinical effectiveness and health technology assessment
- MHRA regulates both drugs and diagnostic tests
- UK has significantly strengthened its academic clinician base over last 3 years and the recent formation of recognised Biomedical Research and Academic Health Science Centres provide focus for disease science, patient resources and faster translation

The Millennium BioBank has established the precedent for all patients to positively participate in the clinical research effort - there is a unique opportunity to broaden this example and to effectively link samples to anonymised NHS derived patient data. In turn this could set the model for sharing of genomic data and samples between industry collaborators and between industry and academe to accelerate understanding of disease stratification, biomarker validation and drug response. The UK (Academia and Industry) is also expected to contribute 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 ‘Connecting for Health’ and the Millennium BioBank 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 singularly distinguish the UK as a centre of choice for clinical research and outcome measurement.

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

Perhaps more so than ever before, the societal need for improved medicines, the industry need to work in a different way and the emergence of new clinical and scientific opportunities indicate a mandate for much closer working between the public and private health research sectors in order to ensure delivery of new “personalised” medical products. No single stakeholder group can do this alone.

However, it would be very wrong to imply that significant technical and policy-related challenges don't either already exist or will become apparent during the implementation of a personalised medicine strategy in the UK. We believe however, that all of these challenges are surmountable with a consistent all-party focus on common objectives and deliverables.

PCAST has suggested eight areas of policy challenge for consideration. These are adapted here;

Science and Technology

Here, 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 and diagnostics. Given its novel, high risk and high cost status, industry cannot plan and conduct this key fundamental and translational work alone, especially when considered in conjunction with the other productivity and environmental challenges it faces today.

Progress must be made through public/private partnerships. These may include the;

- Development of a public/private sector “Personalised Medicine R&D roadmap” for coordinating 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 PM research.
- Establishment of a joint funding programme for biomarker standardisation and validation study design.
- Development of a large population cohorts for long-term follow up of genetic and environmental health effects.

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 and 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 therefore will need to work together in order to;

- Agree the criteria for the early/conditional licensing of personalised medical 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.
- Ensure regular communication to articulate projections of the number and type of products in the development pipeline that are based on personalised medicine technologies.
- Ensure regular communication and discussion on anticipated emerging regulatory issues with these new technological developments.

Reimbursement

Here, 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. This will include the need for the procurement on the basis of value. The need for flexible value-based drug reimbursement must therefore 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 procurement of these future innovations. This is critical to ensure that the development of personalised medicines becomes a major, established and sustainable focus for the pharmaceutical industry.

Information Technology

Essential enablers for the development and widespread use of diagnostics and therapeutics for personalised medicine will be fully interoperable standardised electronic medical records and clinical decision support tools. As such, 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.

Intellectual Property

Despite recent examples of threats to the contrary, 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 personalised medicine strategies.

Privacy

Clearly, a major concern 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. There is therefore a need to establish and maintain robust database security and controls on data use. This is not a requirement unique to personalised medicine however, as it applies to the use and control of all confidential patient data. However, recent losses of datasets of similarly confidential types mandate the institution of technologies and procedures for the encryption, password protection, auditing and access coding of data, their use and control.

The need for the establishment of capabilities to share standardised biospecimen repositories to support PM research was mentioned in the science and technology section above. However, as the specific genetic test may not be known at the time the sample is collected, there will be a need to have an informed consent process that allows for the testing of anonymous samples for genetic markers not known or anticipated at the time of collection.

Physician and Patient Education

As personalised medicine is currently in its infancy, this is perhaps not an area of immediate urgency but is included here for completeness. However, as technologies emerge with their associated clinical decision tools, there will need to be a focus on the education of physicians and medical students on their use.

In parallel, patients, patient groups and the public will need to understand the potential benefits and limitations of personalised medicine from a practical and realistic perspective. Importantly this must include information and where necessary, reassurance with regard to the use of genomic data. It may therefore be appropriate to consider patient advocacy groups to join the teams who'll address the privacy issues above.

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 personalised medicine. This is of particular importance to the pharmaceutical industry who are already major risk-takers and research investors, and whose business model could not be sustained if personalised 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 personalised medicine products both in the UK and around the world.

Recommendations

These recommendations are the result of discussions between members of an expert group convened by the ABPI R&D and Medical Committees. They are made with reference to the current state of development of the science in each disease area and try to take account of the progress of other international initiatives that have relevant ongoing collaborative work (e.g. IMI, FDA Biomarkers Consortium etc). The recommendations are made at the highest level and anticipate that the next step will be a series of multi-partner workshops to define the opportunity in more detail and recommend clear forward 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 Pharmaceutical and Biotechnology community to develop new medicines and diagnostics.

Short-term (value realised within 3 years)

- Activities which enable and embed PM in disease areas where the science is available and where the use current or imminent therapies could be improved e.g.
 - Oncology: Major solid and haematological cancers. Tools for patient selection and for tracking the response to treatment
 - 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 PM development in both industry and the NHS e.g.
 - Minimally invasive, molecularly specific and rapid response technology (e.g. imaging; innovative analytical techniques to replace pathology)

Medium-term (value realised between 3 and 10 years)

- Diabetes: 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
- Chronic Obstructive Pulmonary Disease (COPD): Improved molecular stratification of the disease, larger collections with international collaboration. Responder / non-responder understanding for current therapies.
- Alzheimer's Disease: Improved and validated methods for early diagnosis; new approaches to risk modification; Stratification for initial treatment recommendation; methods for measuring response to treatment more rapidly and objectively
- Thrombosis / Stroke: New tools to characterise clotting status quickly at a molecular level

- Chronic pain: Improved phenotyping and molecular stratification of pain; larger collections with international collaboration.

Long-term (value realised beyond 10 years)

- Depression: New understanding of non-responsiveness to develop new treatments. Improved molecular stratification of disease and development of related biomarkers.
- Dementia and other neurodegenerative diseases: 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.
- Cardiovascular and metabolic disease: New understanding of non-responsiveness and development of new treatments for sub-populations.

Summary

Personalised medicines offer potential significant benefits to patients, prescribers and healthcare payers. 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 already attracts the largest 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 also has the potential to help maintain and grow both the large and small UK enterprises that 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 partnership that ensures that medical innovation is focused on those that would gain most benefit (and/or suffer fewer adverse reactions) presents a major opportunity for the UK.

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Association of the British
Pharmaceutical Industry
7th Floor, Southside,
105 Victoria Street,
London SW1E 6QT

t +44 (0)870 890 4333 abpi@abpi.org.uk

