

Realising the potential of stratified medicine



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Contents

| | |
|---|------------|
| Executive summary | 5 |
| 1 Introduction | 9 |
| 2 Stratified medicine: principles, promise and progress | 17 |
| 3 Informatics infrastructure, public engagement and capacity building in the healthcare system | 29 |
| 4 Regulation | 41 |
| 5 Pricing and reimbursement | 53 |
| 6 Conclusions | 65 |
| Annex I: Recommendations | 69 |
| Annex II: Symposium programme | 75 |
| Annex III: Symposium attendees | 77 |
| Annex IV: Memberships of oversight, preparatory and review groups | 81 |
| Annex V: Recent developments in stratified medicine | 85 |
| Annex VI: Glossary | 93 |
| Abbreviations and acronyms | 101 |

Executive summary

'Stratified medicine' is the grouping of patients based on risk of disease or response to therapy by using diagnostic tests or techniques. Patients and healthcare providers both benefit from more targeted and effective treatments, whereas industry benefits from the potential for more efficient therapeutic development as well as the market expansion for these new treatments. These benefits were outlined in the Academy of Medical Sciences' 2007 symposium report, '*Optimizing stratified medicines R&D: addressing scientific and economic issues*', which also identified several challenges for the development and adoption of stratified medicine.

The development of stratified medicine is being pursued globally as its benefits are increasingly recognised. The UK is uniquely placed to capitalise on its potential, owing to its strong academic and industrial research base, the wealth of data within the NHS, and highly capable agencies for health technology assessment and pharmaceutical regulation. These are bolstered by central strategic support from the Government's 2011 *Life Sciences Strategy* in developing and unifying relevant initiatives.

Despite rapid advances in research and technology that underpin the development and adoption of stratified – and ultimately personalised – approaches to medicine, progress has been slower than expected. The challenges identified by the Academy's symposium five years ago – in the areas of regulation, health economics and clinical and research infrastructure – have not been adequately addressed. To ensure these barriers do not persist for a further five years, in 2012 the Academy initiated work to identify the opportunities and ongoing challenges and to propose solutions for the development and use of stratified medicine products, namely targeted drugs and their associated diagnostic tests. These were discussed and refined at a symposium in October 2012 that brought together experts from the pharmaceutical and diagnostic industries, health economists, medicines regulators, health service providers,

clinical researchers, patient representatives and policy makers in the private and public sectors. A list of the recommendations made within this report is available at Annex I.

While acknowledging that many challenges to realising the potential of stratified medicine are globally relevant, this report focuses primarily on solutions for the UK and the European Union (EU). We recognise that some opportunities and challenges will evolve with advances in research and technology, such as the development of platforms for whole genome sequencing. Therefore, where possible, we focus on solutions that will address current challenges as well as set a direction for anticipated future challenges.

Increasing the pace of progress in stratified medicine requires multiple actions by many stakeholders

Stratified approaches to therapy are expected to become the standard for the management of a whole range of diseases, provided that there are the following:

- Continued research to understand the genetic and molecular bases of diseases.
- Development and use of increasingly sophisticated and powerful informatics technology.
- Improvement and standardisation of clinical data collection and linkage with genomic and other databases.
- Increased collection of tissues for biomarker research and evaluation, and its organisation in national and international biobanks.
- Greater efficiency and productivity in the development of therapeutics and diagnostics.
- The introduction of flexible and novel approaches for the regulatory assessments of innovative stratified medicine products.
- Improved flexibility in pricing for stratified medicine products – both for the diagnostic and for the associated therapy – to ensure cost-effectiveness for payers while encouraging innovation.

- Programmes and incentives to enable partnership across academia, industry, healthcare systems, regulatory/pricing authorities, research funders and patient groups.

Our 2012 symposium concluded that these factors will be necessary to optimise the benefits of stratified medicine for patients, healthcare systems and industry. Three key themes for progress, however, became apparent in our work: data, regulation and pricing, and the crucial role of healthcare practitioners. Addressing these will require collaboration among a broad range of stakeholders, including patients and the public, and consideration of the ethical and social dimensions of stratified medicine.

Data: developing its collection, analysis and use to create a linked biomedical and health informatics system

Progress towards stratified – and increasingly personalised – medicine relies fundamentally upon data, which is central to the following areas: research to understand the molecular basis of disease; development of targeted interventions; effective regulation, health technology assessment and valuation of stratified medicine products; and the stratification of treatment by physicians.

Large-scale datasets are essential to support all these functions. Work needs to be undertaken to harmonise and link databases and biobanks – nationally and internationally – to maximise the potential of collected data. To facilitate this, we recommend the development and agreement of standardised protocols for data collection in the UK by an expanded eHealth Informatics Research Centres Network, Health and Social Care Information Centre, Clinical Practice Research Datalink, National Institute for Health Research and Public Health England, with their devolved administration counterparts where appropriate.

This consortium will define what data should be collected and how they should be classified and inputted, building on existing best practice.

We call for an international effort to ensure that the data arising from whole genome sequencing are of consistently high quality for clinical use, by developing ‘Good Genomic Practice’ guidelines. These guidelines should cover multiple stages, from sample collection to data analysis, and be used to support development of regulation where appropriate.

To maximise the value of these databases we must increase the number and capabilities of bioinformaticians, drawing on experience in large dataset analysis from physics and engineering. At the UK level we address the need to guarantee privacy and protection of patients while enabling research by recommending that the Departments of Health across the UK and the Department for Business, Innovation & Skills lead the development of a consistent and proportionate governance framework for access to biomedical and health data for research.

Incentivising the development of stratified medicine products: changes to regulation and pricing

Regulation

Internationally, there are wide variations in the regulatory frameworks that underpin the development of stratified medicine products. We highlight the importance of improving co-ordination and co-operation between therapeutic and diagnostic regulators in the development of stratified medicine products, and recommend that global pilots are undertaken by the major regulatory agencies to develop and implement effective models for joint scientific advice. These discussions will need to address the required level and timing of clinical evidence for approval of stratified medicine products. The requirement should balance the need for robust proof of safety and evidence to support clinical value

with incentives for ongoing innovation. We call for both regulatory and health technology assessment bodies to take on board a wider variety of methods for evidence generation.

The current revision of EU diagnostics legislation presents an opportunity to address many of the issues raised in this report regarding the development of stratifying diagnostic tests. We support the proposed increase in clinical evidence requirements for companion diagnostics and the accreditation of laboratories that develop and use 'in house' tests. We also call for regulators and standards bodies to work with academia, industry and the health service to develop a standardised accreditation process.

Pricing

Pricing and reimbursement systems in healthcare do not currently reflect the specific benefits arising from the use of stratified medicine products, and thus remain a barrier to their development, especially for the diagnostic component. We therefore recommend the development of a pricing and reimbursement system that enables prices to be adjusted over time to reflect changes in value. Furthermore, we call for the establishment of a mechanism through which health technology assessment agencies can separate, and therefore reward, the value of stratification between the therapeutic and diagnostic components of the stratified medicine product.

Evidence of value will be required for such a flexible pricing and reimbursement system. However, weaker intellectual property protection for diagnostics compared with drugs diminishes the reward for evidence generation. Furthermore, there is a threat of competitor 'generic' in-house tests – which do not require regulatory approval – rapidly appearing to replace the use of more evidence-based commercial tests. These act as further disincentives for manufacturers to develop and generate evidence for innovative diagnostics. Amendments to the European diagnostic legislation will address some of these issues but – as highlighted before – ongoing discussion is required around the appropriate level of clinical evidence required and intellectual property protection for diagnostics.

Adoption by healthcare practitioners is crucial to realise the potential of stratified medicine and allow all stakeholders to access the benefits

The solutions outlined in this report would help to optimise the benefits of stratified medicine for patients, healthcare systems and industry. However, they will have little impact unless stratified approaches to medicine are adopted and translated into clinical practice by healthcare practitioners.

In addition to adopting this approach to therapy, healthcare practitioners could facilitate the development of stratified medicine through collecting and inputting consistently high-quality data using standardised disease classifications, and ensuring the use of only the best-evidenced diagnostic tests available.

We recommend that a review of the education and training of professionals that contribute to the delivery of stratified medicine is undertaken, led by NHS England, Health Education England and the devolved administrations, to ensure that professional education and development is used effectively as a vehicle to drive the necessary change. Changes to clinical guidelines and pathways may also be required to facilitate translation.

Need for collaboration

Collaboration will be fundamental for success. Academia, healthcare systems, industries, research funders, regulators, health technology assessment bodies and patient groups must come together to take forward these recommendations. We call for the expansion of the UK Stratified Medicine Innovation Platform to provide an overarching body that brings together all the key stakeholders. The expanded Platform should unify existing initiatives and co-ordinate future activities in this area to ensure that the barriers identified at the Academy's symposium five years ago are not again present in five years' time and the benefits of stratified medicine are fully realised. The Academy looks forward to working with stakeholders to ensure that the UK can capitalise on the potential of stratified medicine, and play a leading role in its global development.

1 Introduction

The increase of stratified approaches to medicine

Although patient treatment has always been personalised by clinicians based upon individual circumstance and medical history, advances in our understanding of the molecular basis of diseases are redefining how diseases are classified and present a powerful new dimension by which to tailor preventive measures or treatments to individuals further.^{1,2} These advances, resulting from progress in molecular biology and genomics, are revealing the presence of distinct sub-populations within particular clinical presentations. Classification (stratification) of patients into these sub-populations using diagnostic tests that identify the status of a particular biomarker (for example, the presence of a genetic mutation or protein), and tailoring the clinical approach accordingly, is referred to as stratified medicine. Although some aspects of this report are directly relevant to the stratification of preventive measures, this report mainly focuses on the stratification of treatment.

The clinical and economic benefits of stratification

The 2007 meeting of the Academy of Medical Sciences, '*Optimizing stratified medicines R&D: addressing scientific and economic issues*', concluded that stratification is desirable for patients, healthcare systems, and pharmaceutical and diagnostic companies.³ This is because a compelling case can be made based both on health economic and on clinical benefits. This report builds on the findings of the 2007 symposium, which confirmed the advantages of stratified medicine.

Stratification represents a more targeted approach to therapy, with the potential for greater efficacy of treatments and minimisation of their side effects. For example, stratification means that the 2–9% of patients who test positive for a particular genetic biomarker of hypersensitivity to Ziagen (abacavir, an HIV nucleoside reverse transcriptase inhibitor) are no longer prescribed this medication. Decreases both in ineffective prescriptions and in the requirement to treat illness arising from adverse drug reactions could be of great benefit to healthcare systems in limiting costs, which in the latter case have been estimated as potentially up to hundreds of billions of US dollars per year.⁴

The clinical benefits are evident in many of our case studies, summarised at the end of this chapter.⁵ For example, Xalkori (crizotinib) is a drug indicated for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive, which represents approximately 5% of such patients. This patient population has a 10% response to standard chemotherapy, yet 55% respond to the targeted therapeutic.⁶

There will be occasions where the cost of stratification exceeds the benefit, such that it is not a cost-effective strategy. This will depend on several factors, including the cost of testing the patient population, the proportion of 'responders' and the (saved) costs of treating non-responders, which will be larger the greater the health consequences of any adverse reaction. Therefore, as with any medical innovation, healthcare systems should prudently focus their adoption of stratification where it improves resource allocation.⁷

1 National Academy of Sciences (2011). *Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease*. http://www.ucsf.edu/sites/default/files/legacy_files/documents/new-taxonomy.pdf

2 Trusheim MR, Berndt ER & Douglas FL (2007). *Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers*. *Nature Reviews Drug Discovery* **6**, 287–293.

3 The Academy of Medical Sciences (2007). *Optimizing stratified medicines R&D: addressing scientific and economic issues*. <http://www.acmedsci.ac.uk/download.php?file=/images/project/AMSstrat.pdf>

4 Miller I, et al. (2011). *Market access challenges in the EU for high medical value diagnostic tests*. *Personalized Medicine* **8(2)**, 137–148.

5 <http://www.acmedsci.ac.uk/p47prid104.html>

6 Gerber DE & Minna JD (2010). *ALK inhibition for non-small cell lung cancer: from discovery to therapy in record time*. *Cancer Cell* **18(6)**, 548–551.

7 Danzon P & Towse A (2002). *The economics of gene therapy and of pharmacogenetics*. *Value in Health* **5(1)**, 5–13.

Drivers for stratified medicine

There are multiple drivers that make accelerating the development and adoption of stratified approaches to medicine both desirable and possible. There are 'pull' factors, in that the healthcare system needs to become increasingly effective and sustainable; in particular, with the current economic environment, reimbursement authorities are keenly focused on value. There are also 'push' factors, from recent advances in medical science and informatics, and the pharmaceutical industry requiring substantial improvements in research and development productivity to remain a viable sector in the long term. These factors could, if aligned, accelerate the momentum of stratified medicine and be transformative in the provision of care. They are explored in more detail below.

Effective and sustainable healthcare systems

Healthcare expenditure in developed nations has been increasing faster than gross domestic product (GDP) over the past 40 years, mainly because of increasing costs per capita.⁸ In the UK, the percentage of GDP spent on healthcare has doubled in the past 40 years, with most of the increase since 2000.⁹ Maintaining this trend will become increasingly unsustainable, particularly because of the increasing numbers of elderly citizens and prevalence of chronic disease. A stratified approach could result in better overall use of healthcare resources. As previously mentioned, decreasing ineffective prescriptions and treatment of adverse drug reactions in non-responders could be of considerable benefit to healthcare systems in limiting costs.^{10,11,12}

Furthermore, the approach could be applied for the re-purposing of inexpensive off-patent

medicines to new indications in defined patient sub-populations, or of withdrawn medicines should the sub-population(s) vulnerable to severe adverse drug reactions become identifiable. Re-purposing applications for off-patent agents are not always commercially attractive but may be incentivised through initiatives such as the Health Innovation Challenge Fund.¹³

Scientific and technological advances and the development of a new classification of disease

Owing to the increasing understanding of the molecular basis of disease, recent years have seen the number of stratified medicines expand from only a few, such as Herceptin (trastuzumab, a breast cancer treatment only suitable for those who overproduce the HER2 protein), Gleevec (imatinib, a specific inhibitor of a mutant kinase in chronic myeloid leukemia) and Ziagen (abacavir, an HIV inhibitor potentially fatal to carriers of a specific genetic variant), to a wider range of medicines, for instance addressing melanoma (Zelboraf, vemurafenib, which targets BRAF proteins in those with the V600E mutation) and cystic fibrosis (Kalydeco, ivacaftor, effective in sufferers of cystic fibrosis with the *G551D* mutation in the CFTR gene). Please see the summary of case studies in Table 1 at the end of this chapter.

These advances have relied on technological evolution such as the falling costs of whole genome sequencing, improved data storage capacity and processing capabilities, and the development of molecular imaging probes that enable non-invasive imaging of tissues. Work continues to translate these promising technologies into widespread clinical application, such as improving the half-lives of radioactive tracers used in imaging,

8 US National Bureau of Economic Research (2005). *Who's going broke? Comparing growth in healthcare costs in ten OECD countries.* <http://www.nber.org/papers/w11833>

9 Office of Health Economics (2012). *GDP and NHS expenditure, and per capita, UK, 1949/50 – 2010/11.* <http://www.ohe.org/page/health-statistics/access-the-data/expenditure/data.cfm>

10 Miller I, et al. (2011). *Market access challenges in the EU for high medical value diagnostic tests.* *Personalized Medicine* **8**(2), 137–148.

11 Lazarou J, Pomeranz BH & Corey PN (1998). *Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies.* *Journal of the American Medical Association* **279**(15), 1200–1205.

12 Miguel A, et al. (2012). *Frequency of adverse drug reactions in hospitalized patients: a systematic review and meta-analysis.* *Pharmacoepidemiology and Drug Safety* **21**(11), 1139–54.

13 <http://www.hicfund.org.uk/>

and developing a framework for clinically robust whole genome sequencing in the UK National Health Service (NHS).¹⁴ Likewise, the increasing understanding of the molecular basis of disease is set to continue. In the UK, this will be supported by recent investment in dedicated research projects and infrastructure (see Annex V), and will lead to a re-evaluation of traditional disease classification from one based on symptoms centred on organs and systems to one based on molecular pathways and associated physiological phenotypes. These developments will assist in the development of new drugs and could lead to more effective use of existing drugs. Developments in the understanding of the molecular basis of biological mechanisms are likely to impact upon fields beyond human health, such as the veterinary and agricultural sciences.

Challenges facing the pharmaceutical industry

The pharmaceutical industry is responsible for developing many of the key life-saving medicines in current use. However, development pipelines are now facing critical challenges. The increase in clinical development failure rates can sometimes be due to regulatory hurdles, but another major factor is drugs not demonstrating sufficient efficacy in later stage trials. This can be due to the trial design, which in some instances may mask significant responses in a certain subgroup. In the example of Vectibix (panitumumab, an epidermal growth factor receptor antagonist used in patients with colorectal cancer who do not have a mutation in the *KRAS* gene), post-approval analysis of the later stage study revealed an association between *KRAS* mutation status and treatment response.

The desirability of stratification in the development of new medicines is becoming more recognised. Stratification as a factor in drug response is now appreciated by bodies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).^{15,16} This is associated with a growing appreciation of the need to improve clinical trial productivity and to maximise the existing flexibility of regulatory processes to develop and approve innovative medicine for patients rapidly. Furthermore, new classes of therapeutics are by their nature increasingly targeted – for example, antibodies, small interfering RNAs and microRNAs – and therefore increasingly require a stratified approach.

Although stratification narrows the population of eligible patients and therefore decreases market size, it can also improve market share should the enhanced safety and efficacy of the drug establish it as a preferred treatment. Market size may also be further restored owing to the greater certainty of benefit encouraging underserved patients to enter the market, and diagnostic feedback improving long-term adherence.

Background to this report

The Academy's 2007 symposium discussed the state of the field and identified that the key non-scientific obstacles to widespread implementation of stratified approaches to medicine lay in the regulatory, pricing and healthcare systems:¹⁷

- In the challenge to define stratification prior to drug registration, because of the problems for simultaneous diagnostic-therapeutic development.
- In the weakness of incentives for diagnostic companies, because of the problems for intellectual property protection and cost of demonstrating clinical utility.

14 <http://www.number10.gov.uk/news/dna-tests-to-fight-cancer/>

15 Food and Drug Administration (2013). *Guidance for industry. Clinical pharmacogenomics: premarket evaluation in early-phase clinical studies and recommendations for labelling*. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf>

16 European Medicine Agency scientific guidance document on pharmacogenomics. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000411.jsp&mid=WC0b01ac058002958e

17 The Academy of Medical Sciences (2007). *Optimizing stratified medicines R&D: addressing scientific and economic issues*. <http://www.acmedsci.ac.uk/download.php?file=/images/project/AMSstrat.pdf>

- In the weakness of incentives for pharmaceutical companies because the current environment lacks pricing flexibility.
- More generally, because the infrastructure with which to assess clinical utility does not always exist.

Although there are increasing numbers of stratified medicines on the market and in development, the challenges identified in the Academy's 2007 report still remain. Progress in the identification and implementation of biomarker-driven diagnosis and treatment has been slower than hoped, and progress to facilitate the implementation of stratified approaches to medicine in healthcare services is also taking time. Existing models of operation, on the part of the pharmaceutical and diagnostic industries, health systems and health professionals, are not well set up for this future: stratified medicine will challenge all these participants. Sustaining and accelerating the pace of change will require ongoing progress in research, clinical development, regulation and reimbursement, clinical capacity building and public engagement. This report is the outcome of a project to address opportunities and challenges in these areas.

Project aims and conduct

The Academy appointed an oversight group to lead this project, chaired by Professor Sir John Bell FRS HonFREng FMedSci (see Annex IV for a list of oversight group members). The group developed a two-day symposium in October 2012 that was itself informed by four discussion papers, prepared by members of the oversight group and other experts (see Annex III). These papers generated potential solutions and pilot activities as the basis for consideration at the symposium. Eight case studies of stratified medicine products were developed that set out the drug and/or diagnostic development pathways used by industry and drew out the lessons learnt. These were used in the discussion papers and the symposium. A summary table of the case studies can be found at the end of this chapter. Both the discussion papers and the full case studies are available on the Academy's website.¹⁸

The objectives of the project, and the symposium, were to facilitate progress in stratified medicine research and development, and the implementation of these approaches in healthcare services by the following means:

- Considering the opportunities arising from the development and adoption of stratified approaches to medicine in healthcare.
- Considering regulatory and economic barriers to stratified medicine, and evaluating the research and clinical service infrastructure requirements.
- Focusing on identifying solutions to current barriers, including defining pilot activities to accelerate the implementation of stratified approaches to medicine.
- (Via the symposium) bringing together experts from the pharmaceutical and diagnostic industries, health economists, medicines regulators, health service providers, clinical researchers and policy makers in the private and public sectors.

This report draws on the discussions at the symposium, the four discussion papers, the case studies and the expertise of the oversight group. It tackles global issues, but because members of the preparatory groups and symposium attendees were mostly from the UK, does so largely from a UK and European perspective. We thank all those who contributed to this study.

The Academy is grateful for the support of Amgen, the Association of the British Pharmaceutical Industry (ABPI), GE Healthcare, the Medical Research Council (MRC), the Medicines and Healthcare products Regulatory Agency (MHRA), Roche and the Technology Strategy Board (TSB).

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This report was reviewed by a group appointed by the Academy's Council (Annex IV) and approved by the Academy's Council at its meeting in April 2013.

Report structure

Chapter 2 provides background information on stratified medicine, including the benefit to patients, the technologies used to stratify individuals and recent developments towards stratified approaches. In Chapter 3 we consider the informatics infrastructure, capacity building and public engagement requirements to implement stratified medicine. The regulatory changes that will be required to support the development of stratified medicines and their associated diagnostic tests are considered in Chapter 4. Changes to the pricing and reimbursement of drugs and diagnostics, necessary to incentivise the development of stratified medicine products, are considered in Chapter 5. The conclusions of the report are drawn together in Chapter 6. A full list of recommendations and a glossary are included as Annexes.

Table 1. Summary of case studies developed for this project

Cases were selected to capture a range of diagnostic development scenarios: before clinical development, during clinical development or after launch of the therapeutic. A more detailed rationale is given in the paper developed for the Academy of Medical Sciences symposium.¹⁹

| Disease area | Drug (Rx) and Companion diagnostic (CDx) | | US approval | | EU approval | |
|----------------------|--|--------------------------------------|--------------|---|--------------|---------------------|
| | Rx | CDx | Rx | CDx | Rx | CDx |
| Breast cancer | Herceptin (trastuzumab) Roche/Genentech | HercepTest Dako | Sep 1998 | Sep 1998 | Aug 2000 | Yes |
| | Herceptin targets the HER2 protein, present on cell surfaces. In some cancers, HER2 overproduction causes the uncontrollable cell growth driving the disease. HercepTest identifies if an individual's breast cancer involves HER2 overproduction: if so, they will respond to Herceptin. The HER2 marker was found during drug development. This was the first simultaneous approval of Rx and CDx. The product received subsequent approval for use in HER2-positive gastric cancer. | | | | | |
| HIV | Ziagen (abacavir) GSK/ViiV Healthcare | HLA-B*57:01 screening assay | Dec 1998 | N/A: unbranded test | Jul 1999 | N/A: unbranded test |
| | Action of HIV's reverse transcriptase enzyme is critical to the replication of the virus. Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir and abacavir-containing products. Extensive research established that patients who carry the HLA-B*5701 allele are at a high risk for experiencing a hypersensitivity reaction to abacavir. | | | | | |
| Breast cancer | N/A: Dx only | Oncotype DX Genomic Health | N/A: Dx only | Not FDA-approved: use supported by literature | N/A: Dx only | 2007 |
| | Developed through retrospective studies on tissue archives, Oncotype Dx is a diagnostic tool that predicts the likelihood of breast cancer recurrence and the benefit of chemotherapy in about 60% of breast cancer cases. The test is now included in major treatment guidelines for breast cancer in the US, and receives a value-based reimbursement, which is based on clinical data demonstrating the test's ability to restrict healthcare costs. | | | | | |

| Disease area | Drug (Rx) and Companion diagnostic (CDx) | | US approval | | EU approval | |
|---|--|--|---|---------------------|-------------|---------------------|
| | Rx | CDx | Rx | CDx | Rx | CDx |
| Colorectal cancer | Vectibix panitumumab) Amgen | EGFR pharmDx kit Dako therascreen®: KRAS RGQ PCR kit Qiagen | Sep 2006 | Sep 2006* | Sep 2007 | Yes |
| | | | | Jul 2012 | | Yes |
| Vectibix was designed to treat colorectal cancers overproducing a protein called EGFR. After going to market, it was found that EGFR overproduction does not indicate response to the Rx, and that individuals with this marker would not respond to therapy if they also carried a mutation in another protein, KRAS. KRAS is now established as a stratifying marker, and a marker for the safety of using Vectibix in combination with a certain type of chemotherapy. | | | | | | |
| Melanoma | Zelboraf (vemurafenib) Roche/Plexxikon | cobas® 4800 BRAF V600 Mutation Test Roche | Aug 2011 | Aug 2011 | Feb 2012 | Yes |
| | | | This drug was selected by Roche for development owing to knowledge of the biomarker: the drug showed effects in melanomas containing a particular mutation, V600E, in a protein called BRAF. The Rx and CDx were developed in parallel, and co-approved in one of the fastest FDA approvals in history (four months). Zelboraf was approved by NICE in November 2012. ²⁰ | | | |
| Non small cell lung cancer (NSCLC) | Xalkori (crizotinib) Pfizer | Vysis ALK Break Apart FISH probe kit Abbott Molecular Diagnostics | Aug 2011 | Aug 2011 | Jul 2012** | Sep 2011 |
| | | | A 2007 study linked a subset of NSCLC to the <i>ALK</i> fusion gene. This prompted a partnership between Rx and CDx manufacturers, and patient stratification using this CDx resulted in dramatic improvement in response rates. Approval was rapid both in the US and in the EU. | | | |
| Cystic fibrosis | Kalydeco (ivacaftor) Vertex/ Cystic Fibrosis Foundation Therapeutics Inc. | G551D mutation test | Jan 2012 | N/A: unbranded test | Jul 2012 | N/A: unbranded test |
| | | | One of the first treatments to target the underlying cause of cystic fibrosis, Kalydeco was developed based on gene and protein data from sufferers of the disease. The ability to test for specific cystic fibrosis mutations was critical both during development and for post-approval use, yet a specific brand of test is not specified on the label. | | | |
| Melanoma | BRAF/MEK inhibitor (dabrafenib and trametinib) GSK | BRAF™ mutation kit (v600E & K) bioMerieux | In development | | | |
| | | | This Rx-CDx combination is currently under development. The BRAF V600 mutations are present in approximately 50% of melanomas. Separately, the Rx showed positive results up to phase 3 trials. As a combination, they have shown promising results at phase 2, and are now at phase 3. GSK has been collaborating with bioMerieux to develop the CDx, which is being used to identify patients BRAF V600 status in the current phase 3 trials. | | | |

*Pre-market application review is ongoing

**Approval comprised a conditional marketing authorisation

2 Stratified medicine: principles, promise and progress

Overview

The precision of stratification has improved greatly in recent years, and patient treatment has changed significantly where stratified medicines have been introduced. This is due to advances in understanding the molecular basis of disease, aided notably by the advent of the genomic era, and the development of targeted therapies to address these new molecular targets. The introduction and improvement of key technologies and techniques has enabled these advances, by allowing the increasingly detailed investigation of the role of genes, proteins and metabolites in disease. These key technologies and techniques, which are set to advance further, include genomic, proteomic, metabolomic and digital pathology analyses on clinical samples, clinical imaging studies, and biomedical and health informatics.

Patient treatment is transformed by stratified medicine

In areas where stratified medicines have been introduced, patient treatment is being progressively transformed. This can be illustrated using the following examples of two highly prevalent diseases that have differed in the speed of progress in molecular understanding of the disease, and therefore the ability to introduce stratification: lung cancer and diabetes. Although stratification is outlined below using examples of non-communicable diseases, it is also relevant in infectious disease. As previously mentioned, the anti-retroviral Ziagen (abacavir) used by HIV sufferers can result in fatal hypersensitivity for a particular patient group.

Faster progress: NSCLC

Lung cancer is the most common cause of cancer death in the UK and worldwide.^{21,22} For many years, histological analysis of tumour tissue using microscopy has allowed classification of patients into two main groups: small cell (18% of tumours) and non-small-cell (NSCLC, 78% of tumours).²³ Median survival of untreated patients with NSCLC is four to five months, with only 10% of patients surviving a

year.²⁴ Most people are treated with surgery, chemotherapy or radiotherapy. Depending on how developed the cancer is, they can – at best – expect a 38% chance of living for more than five years.²⁵ A 2002 comparison of four platinum-based chemotherapy regimens for advanced NSCLC treatment showed median survival of 7.9 months, with 11% of patients surviving two years.²⁶ However, increased understanding of the molecular basis of NSCLC is improving the outlook for patients.

As seen in Figure 1, research has led to the identification of an increasing number of genes – oncogenes, which are usually genes involved in cell proliferation – whose mutation can drive NSCLC. Since the discovery of the first two NSCLC oncogenes, *KRAS* in 1987 and *EGFR* in 2004, many have been found – including *ALK*, *HER2*, *BRAF* and *MET*. The main contributing oncogene can vary between NSCLC tumours, including spatially and/or temporally within one individual. Although not all of these mutations are currently targeted at a molecular level by pharmaceuticals, some are, for example, the *EGFR* mutation responsible for the cancer in 10% of patients with NSCLC is targeted by both Gefitinib and Erlotinib.²⁷

21 <http://www.cancerresearchuk.org/cancer-info/cancerstats/types/lung/mortality/uk-lung-cancer-mortality-statistics>

22 Pao W & Girard N (2011). *New driver mutations in non-small-cell lung cancer*. *The Lancet Oncology* **12**(2), 175–180.

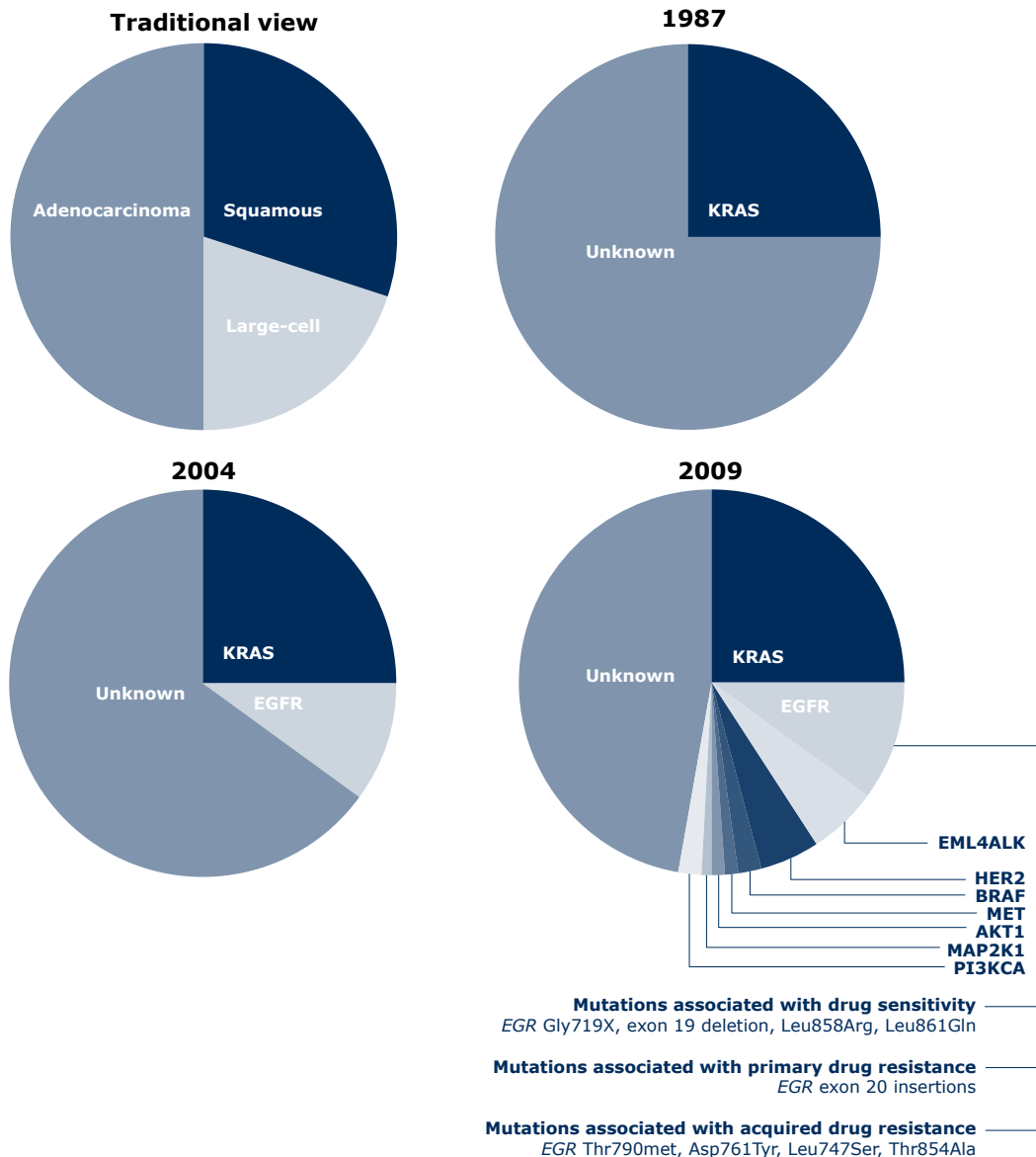
23 <http://www.cancerresearchuk.org/cancer-help/type/lung-cancer/about/types-of-lung-cancer>

24 Rapp E, et al. (1988). *Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer — report of a Canadian multicenter randomized trial*. *Journal of Clinical Oncology* **6**, 633–641.

25 <http://www.cancerresearchuk.org/cancer-help/type/lung-cancer/treatment/statistics-and-outlook-for-lung-cancer>

26 Schiller JH, et al. (2002). *Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer*. *New England Journal of Medicine* **346**(2), 92–98.

27 Pao W, et al. (2004). *EGF receptor gene mutations are common in lung cancers from 'never smokers' and are associated with sensitivity of tumors to gefitinib and erlotinib*. *Proceedings of the National Academy of Sciences of the USA* **101**(36), 13306–13311.

Figure 1: The molecular basis of NSCLC: developing understanding over time.²⁸

The *EML4-ALK* mutation can be used as an example of how molecular understanding accompanied by targeted medicines has transformed the treatment of patients with NSCLC. In 2007, research demonstrated that approximately 5% of NSCLC cases involve this mutation.²⁹ Within three years, targeted therapies were developed, and demonstrated dramatic efficacy.³⁰ Now patients with lung cancer can have biopsy tissue sent for genetic analysis to ascertain their suitability for this treatment, and receive an accurate, genetically

derived diagnosis in 7–10 days.³¹ These developments have transformed therapy for those 5% with NSCLC driven by the *EML4-ALK* mutation, meaning that by simply taking two capsules per day, the cancer shrinks or disappears for more than one in every two people treated, rather than for one in every ten as was the case with traditional chemotherapy.^{32,33} Although this dramatic response is not always sustained over time, it is highly beneficial to patients.

28 Pao W & Girard N (2011). *New driver mutations in non-small-cell lung cancer*. The Lancet Oncology **12**(2), 175–180.

29 Soda M, et al. (2007). *Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer*. Nature **448**, 561–566.

30 Kwak EL, et al. (2010). *Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer*. The New England Journal of Medicine **363**(18), 1693–1703.

31 <http://www.uslabs.net/resources/print/testPrint.php?hash=3533363&type=>

32 FDA label for Xalkori (28 February 2013) http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202570s003lbl.pdf

33 Gerber DE & Minna JD (2010). *ALK inhibition for non-small cell lung cancer: from discovery to therapy in record time*. Cancer Cell **18**(6), 548–551.

Similar advances are occurring throughout the field of cancer in other tumour types. As our molecular understanding of different tumour sub-populations develops, cancer patients may increasingly have molecular analysis and whole genome sequencing undertaken for their tumours, with the resulting data and analysis placed on their medical records and available to their clinician. A national informatics network will also allow diagnostic and treatment response data from multiple sufferers to be analysed by teams of researchers to develop further understanding of the genetic and molecular mechanisms underlying their disease. This will drive the redefinition of disease, better patient management, and increases and improvements in targeted medicines. We are already seeing profound implications for how we think of and treat disease: cancers are starting to be classified based on common molecular mechanisms revealed by modern analytical techniques, rather than where they occur in the body.³⁴

Slower progress: type 2 diabetes mellitus

Despite early stratification of diabetes into types 1 and 2 based on the status of a human leukocyte antigen biomarker, progress in stratification since then has been slower than for cancer. Currently, about 2.6 million people in the UK, 4% of the population, have type 2 diabetes mellitus.^{35,36} In type 2 diabetes mellitus, the body can produce insulin but it either does not produce enough, or does not respond to it correctly, termed insulin resistance. Sustained high blood sugar levels in diabetics commonly leads to the development

of complications including eye, kidney and cardiovascular disease, as well as nerve damage. In half of sufferers, there are already signs of these complications at the time of diagnosis. As the health of sufferers declines over time, personal and healthcare costs increase.

In about 5% of cases of type 2 diabetes mellitus, termed monogenic diabetes, a single genetic cause can be identified, and treatment can sometimes be stratified accordingly. For example, diabetes resulting from a mutation in the gene *HNF1A* can be treated using sulphonylurea compounds.³⁷ These improve patient treatment compared with use of insulin: they come as tablets, removing the need to inject the medication, and result in improved control of blood glucose.³⁸

Conversely, although environmental factors such as diet contribute to type 2 diabetes mellitus and surrogate markers of insulin resistance exist, knowledge of genetic factors and molecular mechanisms that result in individuals being predisposed to, or protected from, developing insulin resistance is just starting to develop.³⁹ As of 2011, 38 genes had been associated with type 2 diabetes mellitus by genome-wide association studies.⁴⁰ Most of these genes were linked to β -cell function, typically an indicator of type 1 diabetes, indicating either a more prominent role for β -cells in the molecular pathology of insulin resistance, or that the genetic factors of decreased insulin response remain to be discovered.

34 Gonzalez de Castro D & Stamp G (2011). *Molecular stratification of cancer*.

<http://www.jointcancerreport.org/discovery-development/molecular-stratification-of-cancer>

35 Cudworth AG & Woodrow JC (1976). *Genetic susceptibility in diabetes mellitus: analysis of the HLA association*. British Medical Journal **2(6040)**, 846–848.

36 Diabetes UK (2012) *Diabetes in the UK 2012: key statistics on diabetes*. <http://www.diabetes.org.uk/Documents/Reports/Diabetes-in-the-UK-2012.pdf>

37 Pearson ER (2008). *Recent advances in the genetics of diabetes*. Primary Care Diabetes **2(2)**, 67–72.

38 Shepherd M, et al. (2003). *No deterioration in glycaemic control in HNF-1alpha maturity-onset diabetes of the young following transfer from long-term insulin to sulphonylureas*. Diabetes Care **26(11)**, 3191–3192.

39 Singh B & Saxena A (2010). *Surrogate markers of insulin resistance: a review*. World Journal of Diabetes **1(2)**, 36–47.

40 Petrie JR, Pearson ER & Sutherland C (2011). *Implications of genome wide association studies for the understanding of type 2 diabetes pathophysiology*. Biochemical Pharmacology **81(4)**, 471–477.

Key technologies and techniques enabling stratified medicine

Genomic analysis

A new age of understanding the molecular basis of disease.

The first human genome sequence was published by the international Human Genome Project in 2000. This followed 13 years of work and a total investment of approximately US\$3 billion to research and develop the necessary DNA sequencing technologies and data handling infrastructure.⁴¹ The availability of this complete human DNA sequence heralded a new age of understanding disease: since 2000, genetic factors have been increasingly implicated in a range of diseases.⁴² Ongoing changes to the speed, precision and cost of sequencing continue to drive insights into the molecular basis of disease. Knowledge of variation in gene sequence or levels of gene expression is likely to become the most common factor used to stratify patients.

DNA and RNA microarrays

The cost of sequencing whole genomes has historically been prohibitively high. Therefore the increased genetic understanding of disease in recent years has been extensively supported by the use of DNA and RNA microarrays. These contain pieces of DNA or RNA (which is produced from a gene when it is active – ‘expressed’) from particular genes and measure the presence and abundance of matching DNA or RNA in a test sample. Microarrays can be useful to assess the presence of known disease-related genetic variants in a patient, or the expression levels of disease-related genes. For example, MammaPrint is a microarray-based diagnostic test that assesses the presence

of 70 different genetic variants in breast cancer tissue to predict the risk of metastasis (spread of the cancer).⁴³ However, microarray approaches are limited because they only assess the subset of genes represented on the microarray. Therefore, although RNA microarrays will remain useful for research into gene expression, DNA microarrays will probably soon be replaced by whole genome sequencing on the grounds of overall information obtained.⁴⁴

The rise of whole genome sequencing

Determining whole genome sequences provides an unprecedented opportunity to identify correlation between changes in genetic code and disease, owing to the increased accuracy and volume of genetic data available (both in terms of the number of individuals sequenced, and the amount of sequence per individual). The linking of these data to an individual’s medical record will allow research into associations between disease and genetic variations, leading to understanding of the molecular basis of disease and better personalisation of healthcare. Decreases in the cost of generating and storing the data now render whole genome sequencing feasible on a wider scale.

The development of faster ‘next generation’ sequencing – in which multiple fragments of the genome are sequenced simultaneously – has significantly decreased the cost of generating a whole genome sequence. The pace of progress in this technology means that within a few years it will be feasible to sequence whole genomes at scale for less than £1000 each.⁴⁵

41 http://www.ornl.gov/sci/techresources/Human_Genome/project/budget.shtml

42 Stranger BE, Stahl EA & Raj T (2011). *Progress and promise of genome-wide association studies for human complex trait genetics*. *Genetics* **187**(2), 367–383.

43 van't Veer LJ, et al. (2002). *Gene expression profiling predicts clinical outcome of breast cancer*. *Nature* **415**(6871), 530–536.

44 Cookson W, et al. (2009). *Mapping complex disease traits with global gene expression*. *Nature Reviews Genetics* **10**, 184–194.

45 For example, see DeFrancesco L (2012). *Life Technologies promises \$1,000 genome*. *Nature Biotechnology* **30**, 126.

The storage of whole genome sequences and their associated annotations will be a necessary requirement for their use in clinical practice. Progress in the compression of these datasets, whereby less than a gigabyte of space is required per individual, and the dramatic fall in costs of data storage, mean that an individual's whole genome data now costs less than US\$1 to store.^{46,47}

The digital storage of whole genome sequence data for many individuals (or their tumours, each of which may differ in the set of mutations in their genetic sequence) will transform research linking genetic variations and disease.

This is already evident from the work of Icelandic company deCODE genetics (now a subsidiary of Amgen).⁴⁸ This company has benefited from over half of the adult population of Iceland volunteering to have their genomes sequenced and the resulting information connected to their medical records held by Iceland's universal healthcare system. Using these data in conjunction with comprehensive genealogy information, deCODE's large-scale studies have revealed very rare genetic variants that strongly correlate with disease outcomes, for example, a mutation that protects against Alzheimer's disease.⁴⁹

The UK is capitalising on the decreasing costs of sequencing and data storage by being the first country to pilot the clinical use of whole genome sequencing at scale within its national healthcare system. The UK Government announced £100 million funding in December 2012 to pump prime the following: whole genome sequencing for up to 100,000 NHS patients with cancer or rare diseases; development of the associated data

infrastructure; training of genetic scientists and training of the NHS workforce in genomic medicine.⁵⁰ Furthermore, the UK Biobank is genotyping – that is, identifying the status of particular genetic markers – all 500,000 of its participants to enable research analysing the interplay of genetic and environmental factors in a range of diseases.⁵¹

The increasing focus on broadening the application of next-generation sequencing technology from research to the clinic presents a challenge: although current techniques for generating DNA and RNA sequences and the algorithms for piecing sequences together are accurate enough for research purposes, improvements are needed for use in clinical decision-making.⁵² Ongoing work on sequencing quality control will be essential to establish the necessary standards of accuracy and reproducibility to ensure appropriate data quality for clinical use.

Identifying genetic factors in disease

The association between a gene and a disease can be established using either statistical or biological approaches.

Statistical approaches identify correlations between the presence of genetic variants and the incidence of a particular disease.⁵³ Genome-wide association studies aim to link specific genetic variations with a particular disease.⁵⁴ They do so by analysing hundreds of thousands of genetic variations between the DNA sequences of carefully selected control individuals, and DNA sequences from individuals with the disease of interest. Genome-wide association studies have identified multiple genetic changes associated

46 Tembe W, Lowey J & Suh E (2010). *G-SQZ: compact encoding of genomic sequence and quality data*. *Bioinformatics* **26(17)**, 2192–2194.

47 <http://boingboing.net/2011/03/08/tracking-the-astound.html>

48 <http://www.decode.com/research/>

49 Jonsson T, et al. (2012). *A mutation in APP protects against Alzheimer's disease and age-related cognitive decline*. *Nature* **488(7409)**, 96–99.

50 <http://www.number10.gov.uk/news/dna-tests-to-fight-cancer/>

51 <http://www.ukbiobank.ac.uk/2013/03/genetics-study-targets-serious-disease/>

52 Bakker E (2006). *Is the DNA sequence the gold standard in genetic testing? Quality of molecular genetic tests assessed*. *Clinical Chemistry* **52(4)**, 557–558.

53 Womack JE, Jang HJ & Lee MO (2012). *Genomics of complex traits*. *Annals of the New York Academy of Sciences* **1271**, 33–36.

54 The Academy of Medical Sciences (2009). *Genome-wide association studies: understanding the genetics of common disease*. <http://www.acmedsci.ac.uk/download.php?file=/images/publication/GWASrepo.pdf>

with common polygenic diseases such as cancer, diabetes and coronary artery disease.^{55,56} The approach requires partial sequences from many individuals, and the computational power to perform the analysis, both of which have continually increased over the years. Within some families, diseases are inherited by certain individuals and not others: linkage studies compare genetic variations between DNA sequences of those family members with the disease, and those without, in order to identify the segment of DNA that contains the disease-relevant variation. Such studies were critical to identifying the specific genetic variants responsible for Huntington's disease and cystic fibrosis.^{57,58}

Biological approaches aim to establish a causative relationship between a genetic variant and a disease, beyond a statistical association. For example, a common variant in the *FTO* (fat mass and obesity associated) gene was statistically associated with predisposition to diabetes in humans through increased body mass index.⁵⁹ Studies in cells, and then mice, demonstrated that the protein produced by this gene is involved in DNA modification, is particularly active in the brain cells that regulate energy balance, and its activity is modified by feeding or fasting.⁶⁰

Ongoing challenges in understanding the genetic basis of disease.

There are challenges to realising the benefits presented by the substantial progress in generating sequences and storing the resulting data, such as the following:

- Standardisation of genome sequencing platforms should be promoted to avoid laboratory-to-laboratory variability

complicating the analysis of combined datasets.

- For research truly to benefit from the accumulation of whole genome sequence data, high levels of enrolment for sequencing are required, which will require that privacy and data protection concerns be addressed.
- Because of the complexity, capital expense of equipment and size of datasets, progress in molecular medicine is increasingly requiring collaboration between many academic groups, public institutions and industry, often across countries.
- Genomic information on its own, although useful, is only part of the story. Greater knowledge is gained when such genetic information is linked to clinical outcomes. Thus there remains a major hurdle to link genome databases to healthcare records, which need to be electronic for this to be done efficiently.
- Research is still required so that genetic variations are not only correlated to diseases, but causal links are established, if the underlying molecular mechanisms of disease are to be understood.
- Correlation of genetic variation and disease may sometimes not transcend ethnic groups. The Pharmacogenetics for Every Nation Initiative has been set up to address this issue.⁶¹
- The effect of epigenetic variations on drug response, pharmacoepigenomics, needs further research.⁶² Epigenetic variations are inheritable, affect gene expression levels and therefore phenotype, yet do not result from changes in the DNA sequence.

55 Hindorff LA, et al. (2009). *Potential etiologic and functional implications of genome-wide association loci for human diseases and traits*. Proceedings of the National Academy of Sciences of the USA **106(23)**, 9362–9367.

56 <http://www.genome.gov/gwastudies/>

57 Kerem BS, et al. (1989). *Identification of the cystic fibrosis gene: genetic analysis*. Science **245**, 1073–1080.

58 Gusella, JF, et al. (1983). *A polymorphic DNA marker genetically linked to Huntington's disease*. Nature **306**, 234–238.

59 Frayling TM, et al. (2007). *A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity*. Science **316(5826)**, 889–894.

60 Gerken T, et al. (2007) *The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase*. Science **318(5855)**, 1469–1472.

61 <http://www.pgeni.org/>

62 Ingelman-Sundberg M & Gomez A (2010). *The past, present and future of pharmacoepigenomics*. Pharmacogenomics **11(5)**, 625–627.

Proteomic and metabolomic analysis

Genomics is not the only route to understanding the molecular basis of disease, nor the sole source of factors used to stratify patients. It is also possible to assess the presence or status of protein variants or metabolites in clinical samples and their relation to disease states, referred to as proteomic and metabolomic analyses respectively. A range of existing technologies can be used to perform these analyses, such as microarrays containing antibodies that bind to the protein variant or metabolite in question.

Compared with genome sequencing, such analyses can provide a broader appreciation of the manifold molecular mechanisms involved in a disease. Proteomics and metabolomics are both actively developing fields with great promise for biomarker discovery.^{63,64} For example, proteomic and metabolomic diagnostics have been developed in ocular disease and colorectal cancer.^{65,66} A stratified medicine for allergic asthma based on a protein biomarker has been reported as under development by MedImmune: a therapeutic antibody that targets the IL-13 protein, a mediator of allergic asthma.⁶⁷ To identify asthmatic individuals with high IL-13 levels who may benefit from this treatment, bioMerieux have developed a diagnostic that tests the levels of periostin, a protein whose abundance in blood is influenced by the level of IL-13 through an unknown mechanism.⁶⁸ Once again, linking these datasets to genomic data and clinical outcomes provides the highest value, emphasising the central role of biomedical and health informatics for overall progress in stratified medicine.

Prominent current techniques for stratification: immunohistochemistry and quantitative polymerase chain reaction

Currently, stratification of cancer patients does not routinely use the aforementioned genomic, proteomic or metabolomic techniques: rather, it uses immunohistochemistry and polymerase chain reaction (PCR)-based techniques.

Traditional immunohistochemistry assays clinical samples for stratifying markers by using antibodies that bind to a specific molecule – commonly cell-surface proteins that are also the targets of stratified medicines – and appear with a distinctive colour under the microscope. For example, determining the status of the estrogen receptor biomarker in breast cancer patients is routinely performed using immunohistochemistry.⁶⁹ It has also been used to assess the status of PD-1 Ligand in directing antibody therapy for those suffering from a range of cancers, including advanced melanoma and colorectal cancer.⁷⁰ Immunohistochemistry is increasingly being used with digital microscopy and imaging analysis, known as digital pathology.⁷¹ Although immunohistochemistry is widely used in a clinical setting, it is not consistently performed with validated processes and diagnostic grade antibodies.

63 Blonder J, Issaq HJ & Veenstra TD (2011). *Proteomic biomarker discovery: it's more than just mass spectrometry*. Electrophoresis **32**(13), 1541–1548.

64 Monteiro MS, et al. (2013) *Metabolomics analysis for biomarker discovery: advances and challenges*. Current Medicinal Chemistry **20**(2), 257–71.

65 Izzotti A, Centofanti M & Saccà SC (2012). *Molecular diagnostics of ocular diseases: the application of antibody microarray*. Expert Review of Molecular Diagnostics **12**(6), 629–643.

66 Nishiumi S, et al. (2012). *A novel serum metabolomics-based diagnostic approach for colorectal cancer*. PLoS One **7**(7), e40459.

67 Wills-Karp M, et al. (1998). *Interleukin-13: central mediator of allergic asthma*. Science **282**(5397), 2258–2261. And May RD, et al. (2012). *Preclinical development of CAT-354, an IL-13 neutralizing antibody, for the treatment of severe uncontrolled asthma*. British Journal of Pharmacology **166**(1), 177–193.

68 Corren J, et al. (2011). *Lebrikizumab treatment in adults with asthma*. New England Journal of Medicine **365**, 1088–1098.

69 Gown AM (2008). *Current issues in ER and HER2 testing by IHC in breast cancer*. Modern Pathology **21**, S8–S15.

70 Topalian SL, et al. (2012). *Safety, activity, and immune correlates of anti-PD-1 antibody in cancer*. New England Journal of Medicine **366**, 2443–2454.

71 Siodkowska J & Garcia-Rojo M (2012). *Digital pathology in personalized cancer therapy*. Studies in Health Technology and Informatics **179**, 143–154.

Quantitative real-time polymerase chain reaction (qPCR) techniques are also commonly used. These monitor a selective DNA amplification process as it occurs, in which a signal is only produced if the particular DNA sequence(s) of interest is(are) present in the sample.

qPCR is commonly used diagnostically to test for the presence of key cancer mutations such as in *HER2*.⁷² However, like immunohistochemistry, qPCR is not always performed using standardised processes – including the performance of necessary control experiments – and diagnostic grade reagents.

Sample handling protocols greatly affect the analysis of DNA and other biomarkers

Identification of biomarkers – whether for research or diagnosis – requires the analysis of clinical samples. For these analyses to be accurate it is necessary that the *in vitro* samples analysed are representative of the *in vivo* environment.

Inadequate storage, handling and processing of clinical samples can lead to their degradation, resulting in aberrant or misleading test results. Improvement in methodologies for extracting quality samples for biomarker analysis, preferably from sources that can be obtained with minimum inconvenience to patients, is therefore essential. This will require the design and validation of protocols for sample collection, processing and handling, taking into account aspects such as the sample extraction processes, the containers used for storage and the use of stabilising agents.⁷³ Furthermore, samples should be stored in a ‘future-proof’ manner, meaning that steps are taken to ensure the samples can be used for the widest possible purposes over the longest period of time. Although extraction of DNA,

RNA, protein and metabolites from blood is relatively straightforward, even trivial changes to storage conditions can introduce small but significant changes to test results.⁷⁴ Obtaining these materials from tissue samples is more challenging due to issues such as degradation and heterogeneity of tissue, necessitating initiatives such as the UK STRATUM (Strategic Tissue Repository Alliance through Unified Methods) project, which is working to create the foundations of a UK tissue biobanking network for respiratory disease.⁷⁵

The challenge of developing well-validated sample handling protocols has been borne most sharply by biobanks.⁷⁶ These are research repositories of biological samples from large numbers of individuals and will be key to progress in stratified medicine. It is widely recognised, however, that the non-standard ways in which samples have been collected and stored impede research.

However, this issue extends beyond biobanks: high-quality protocols will be necessary in all institutions undertaking the collection and biomarker analysis of clinical samples, which will probably require changes to national guidelines, local policy and individual behaviour. This is considered in Chapter 3.

Improvement in biomedical and health informatics allows better tailoring of treatment

The research, development and implementation of stratified medicine will require data resources – a medical informatics system – that enable increasing amounts of molecular (from diagnostic analyses) and phenotypic (clinical) patient data to be collected, linked and accessed for research and clinical purposes. Developments and challenges in this area are considered in Chapter 3.

72 Barberis M, et al. (2008). *Quantitative PCR and HER2 testing in breast cancer: a technical and cost-effectiveness analysis*. American Journal of Clinical Pathology. **129(4)**, 563-70.

73 Elliott P & Peakman TC (2008). *The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine*. International Journal of Epidemiology **37(2)**, 234–244.

74 Peakman TC & Elliott P (2008). *The UK Biobank sample handling and storage validation studies*. International Journal of Epidemiology **37(1)**, i2–i6.

75 <http://www.ukcr.org/infrastructure/expmed/fundersvisionforhumantissuesresources/>

76 Peakman TC & Elliott P (2010). *Current standards for the storage of human samples in biobanks*. Genome Medicine **2(10)**, 72.

Clinical imaging enhanced by biomarkers

Unlike the previously described techniques, X-ray computed tomography (CAT), magnetic resonance imaging (MRI), positron-emission tomography (PET) and optical imaging do not require invasive procedures to obtain clinical samples. They visualise the interior of a patient's body by monitoring the interaction of electromagnetic radiation – such as radio waves, X-rays or gamma rays – with organs, tissues or molecules in the body. They allow the observation of the interior workings of the body without the need for surgery.

Although these techniques are well established, ongoing development of molecular probes has positioned them as a potential tool for patient stratification. These probes are novel chemicals that can be distinctly visualised using these techniques and only bind to specific molecular targets: their use allows specific disease-related molecules or molecular processes to be monitored in real time. Uses include the following:

- Cancer: 18-fluorodeoxyglucose (FDG) is a PET-active glucose analogue that disproportionately accumulates in tissues with a high metabolic rate, such as malignant tumours. In conjunction with PET imaging (FDG PET), it is now being used for diagnosis, defining the stage of the disease and assessment of treatment response in multiple forms of cancer.⁷⁷ Its utility in supporting treatment stratification, monitoring and prognosis for lymphomas has been established.⁷⁸ Imaging can also be used to measure the biological status of many tumour types through assessing markers of hypoxia, angiogenesis and apoptosis (programmed cell death).

- Neurological conditions: neuroscience has made key use of radioligands against neuroreceptors (e.g. dopamine, serotonin, opioid) in research of neurological diseases. Researchers are investigating the use of molecular imaging for stratifying patients with Alzheimer's disease (e.g. PET using carbon-11-labelled Pittsburgh compound).⁷⁹

Major challenges in translating these probes for clinical use remain, however, including the following: synthesis of tracers (which often have short half-lives) close to where they are required clinically; gaining regulatory approval for use (demonstrating both utility and safety); manufacturing under Good Manufacturing Practice; and cost in obtaining the equipment required. Fluorine-18 (18F) labelling is currently being used because of the tracer's longer half-life, which can help resolve the challenge of synthesising molecules close to use.⁸⁰ To overcome the challenge of regulatory approval there is interest in transforming older drugs into probes. For example, although 18F-DOPA (L-3,4-dihydroxyphenylalanine) PET/CT has been used to image Parkinson's disease since the early 1980s, it is now being used for other diseases, such as hyperinsulinemia.^{81,82}

Recent developments and initiatives in stratified medicine

The evolution of technologies and techniques described above, essential to increasing understanding of the molecular basis of disease and advancing stratified medicine, are set to develop further: increasing interest in stratified medicine since the Academy's 2007 meeting has led to a range of initiatives in the biosciences sector, as shown in Boxes 1 and 2.

77 Zhu A, Lee D & Shim H (2011). *Metabolic positron emission tomography imaging in cancer detection and therapy response*. *Seminars in Oncology* **38**(1), 55–69.

78 Baba S, et al. (2011). *Impact of FDG-PET/CT in the management of lymphoma*. *Annals of Nuclear Medicine* **25**(10), 701–716.

79 Quigley H, et al. (2011). *PET imaging of brain amyloid in dementia: a review*. *International Journal of Geriatric Psychiatry* **26**(10), 991–999.

80 Rischpler C, et al. (2012). *Advances in PET myocardial perfusion imaging: F-18 labeled tracers*. *Annals of Nuclear Medicine* **26** (1), 1–6.

81 Ismail D & Hussain K (2010). *Role of 18F-DOPA PET/CT imaging in congenital hyperinsulinism*.

Reviews in Endocrine & Metabolic Disorders **11**(3), 165–169.

82 Nanni C & Fanti S (2007). *18F-DOPA PET and PET/CT*. *The Journal of Nuclear Medicine* **48**(10), 1577–1579.

The UK has exceptional strategic support for stratified medicine: existing investments by the MRC and TSB were bolstered by £130 million investment announced in the Government's ongoing *Strategy for UK Life Sciences*, which was launched in December 2011.⁸³

This clear strategic prioritisation and funding for stratified medicine does not appear to be present in other countries, despite examples of relevant activities. For example, in the US:

- The National Institutes of Health (NIH) fund basic research relevant to stratified medicine, such as the Parkinson's Disease Biomarkers Program⁸⁴;
- The FDA, NIH and industry have come together to undertake a breast cancer trial to try to expand the use of investigational drugs⁸⁵;
- Strategic oversight was called for by the President's Council of Advisors on Science and Technology in 2008⁸⁶ and continues to be called for by the Personalized Medicine Coalition⁸⁷;
- A programme to identify genetic mutations in the tumours of cancer patients, based on a French national initiative, is now spreading rapidly in the major US medical centres⁸⁸; and
- The Institute of Medicine's workshops on 'Use of genomics data for drug discovery and development' and 'Refining Processes for the Co-Development of Genome-Based Therapeutics and Companion Diagnostic Tests'.^{89,90}

At the European level, organisations such as the European Personalised Medicine Association and the European Alliance for Personalised Medicine have been formed to help accelerate the development and adoption of personalised medicine.⁹¹ These organisations are working to bring together healthcare professionals and organisations, patients, industry, regulators, payers, insurers and governments, to consider issues including regulation, research and development, reimbursement, public awareness and training of healthcare professionals.

For the UK, there are several upcoming developments that will have relevance for the implementation of stratified approaches to medicine, notably the following:

- The UK Department of Health will implement a 'value based pricing' scheme for new pharmaceuticals in 2014.⁹² This will change the way pharmaceuticals are priced, potentially to allow for the recognition of the value added through stratification. If appropriately designed and implemented, this could provide incentives for innovation in stratified medicine. This is discussed further in Chapter 5.
- Changes to EU legislation about the approval and monitoring of in vitro diagnostic tests (IVDs).⁹³ These tests, which include companion diagnostics, provide the means to stratify patients. Therefore these changes will have significant impacts for stratified medicine. This is discussed further in Chapters 4 and 5.

83 <http://www.bis.gov.uk/assets/biscore/innovation/docs/s/11-1429-strategy-for-uk-life-sciences>

84 <http://pdbp.ninds.nih.gov/>

85 <http://www.ispy2.org/>

86 President's Council of Advisors on Science and Technology (2008). *Priorities for personalized medicine*.

http://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf

87 <http://www.personalizedmedicinedcoalition.org/>

88 http://ec.europa.eu/research/health/pdf/event06/13052011/fabien-calvo_en.pdf

89 Institute of Medicine (2012). *Genome-Based Therapeutics: Targeted Drug Discovery and Development – Workshop Summary*.

<http://www.iom.edu/Reports/2012/Genome-Based-Therapeutics-Targeted-Drug-Discovery-and-Development.aspx>

90 Institute of Medicine (2013). *Refining processes for the co-development of genome-based therapeutics and companion diagnostic tests: a workshop*. <http://www.iom.edu/Activities/Research/GenomicBasedResearch/2013-FEB-27.aspx>

91 <http://epemed.alwaysdata.net/index.php> and <http://euapm.eu/>

92 Department of Health (2011). A new value-based approach to the pricing of branded medicines – a consultation.

http://webarchive.nationalarchives.gov.uk/+www.dh.gov.uk/en/consultations/liveconsultations/dh_122760f

93 European Commission (2012). *Proposal for a regulation of the European Parliament and of the Council on in vitro diagnostic medical devices*. http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_541_en.pdf

- Changes to EU Data Protection legislation, which will impact significantly upon the generation and research use of electronic medical records.⁹⁴ The use of health data will be critical to research the molecular basis of disease, to monitor the benefits of stratification for improved patient management and to inform the pricing of stratified products: it is vital that changes in this legislation do not inhibit these developments. This is discussed further in Chapters 3 and 4.
- £100 million from the UK Government to pilot clinical whole genome sequencing in the NHS, as previously mentioned.⁹⁵

A summary of key recent activities (since 2007) and upcoming events, including but not limited to those referenced in this report, is attached in Annex V.

Box 1 Examples of UK bioscience initiatives since 2007 relevant to stratified medicine

The **MRC/ABPI** initiative to invest up to £17.5 million in **three disease-focused consortia** that will bring together key experts from industry and academia focusing on chronic obstructive pulmonary disorder (COPD), type 2 diabetes and rheumatoid arthritis.

The **MRC Stratified Medicine Initiative**, following the model established with the ABPI above, announced £10.6 million of funding in December 2012 for three consortia focusing on the following diseases: hepatitis C, rheumatoid arthritis and Gaucher's syndrome. All three bring together industry and academia in dynamic research platforms to stratify disease.

The **TSB's Stratified Medicine Innovation Platform**, with a detailed roadmap for making the UK the world leader in development and adoption of stratified medicine. This is mainly through funding projects to: foster collaboration; establish NHS pathways for stratified medicine; develop biomarkers for key diseases; and develop models for intellectual property, value and reimbursement that incentivise innovation.

The **MRC–National Institute for Health Research (NIHR) Phenome Centre**, which will provide the UK with a centre of excellence in targeted and exploratory high-throughput metabolic phenotyping, assay development and computational medicine.

The **Health Science Scotland – Stratified Medicine Scotland Innovation Centre** was announced in April 2013 after securing nearly £15 million from the Scottish Funding Council and private investors for the creation of an innovation hub providing world-leading facilities for stratified clinical trials and to foster the development of a new translational bioinformatics platform supporting the delivery of stratified medicine and care pathways.

94 European Commission (2012). *Proposal for a regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and the free movement of such data (General Data Protection Regulation)*. http://ec.europa.eu/justice/data-protection/document/review2012/com_2012_11_en.pdf

95 <http://www.number10.gov.uk/news/dna-tests-to-fight-cancer/>

Box 2 Cancer Research UK Stratified Medicine Programme⁹⁶***Aims of the programme***

The ultimate aim is to improve patient access to molecular diagnostics and targeted therapies through an improved molecular diagnostics infrastructure, and make high-quality molecular and clinical data from consenting patients available for research use. It also aims to establish a standardised and cost-effective molecular diagnostic service model which could be expanded throughout the NHS, through a collaborative approach involving the TSB and industrial partners AstraZeneca, Pfizer, Roche and Bristol-Myers Squibb.

Phase one

Finishing in July 2013, this phase has involved developing molecular analysis, informatics and consent frameworks. By September 2013, tumour genetic data for common and relevant mutations will have been captured from up to 9000 participants with one of six tumour types: breast, colorectal, lung, metastatic melanoma, ovary and prostate. These genetic data have been produced from standardised assays in externally quality-assured laboratories, and then linked to clinical data, which will be compiled for five years after diagnosis.

Work from this phase suggests that centralisation of diagnostic testing may be attractive to ensure quality and benefit from economies of scale. Patient consent has been granted for the prospective and retrospective testing of markers, and the research use of anonymised data by approved investigators.

Phase two

This forthcoming phase is expected to build on the infrastructure developed in phase one, but this time with a clear focus on lung cancer. It will also include mechanisms enabling researcher access to the accumulated clinical data, and an optimised route to place patients onto clinical trials.

In parallel, industry-led collaborations funded by the TSB have focused on the development of products that will support this type of structure:

A standardised and validated panel of genetic assays, to profile tumours for clinically relevant biomarkers, costing no more than £300.

An informatics system to capture, securely store, and retrieve tumour genetic data; and allow cross-referencing to clinical data (i.e. treatment and outcome).

3 Informatics infrastructure, public engagement and capacity building in the healthcare system

Overview

Its world-class research base and the NHS, as the single healthcare provider, place the UK in a unique position to seize the opportunities presented by stratified medicine. This is supported by an increasingly collaborative culture across academia, industry and the NHS. Many of the essential building blocks are already in place for the development and adoption of this approach to therapy. Furthermore, the UK has already made significant investment in research and clinical infrastructure (see Box 3), as well as in targeted initiatives for stratified medicine, as outlined in Chapter 2.

The current UK landscape, however, is fragmented and ongoing support is essential to: accelerate our understanding of the exact pathology of disease; improve the rate at which biomarkers are validated; and help develop and establish the clinical utility of diagnostics and therapies.

This chapter considers the following areas that require further advancement and co-ordination to facilitate stratified medicine research and development, and support the implementation of stratified approaches to therapy: informatics; capacity building, education and training; and public engagement to inform adoption.

Informatics

The development and adoption of stratified medicine will require the collection of, linkage between, and access to, increasing amounts of molecular (from diagnostic analyses) and phenotypic (clinical) patient data. A medical informatics system allowing this would enable improvements in the molecular understanding of disease by allowing observation of linkages between clinical presentation and biomarker status using large datasets. *In silico* approaches such as this would hugely speed up the progress of research, as projects could focus on analysis and not collation of data from disparate sources. Such an informatics system would also enable effective use and thus adoption of stratified approaches by clinicians, by allowing them to use these data to inform and improve their clinical decision-making.

The UK situation

In this regard, the UK is in a special position due to the comprehensive longitudinal health records held across the NHS and, given appropriate safeguards, public support for researcher access to health records.⁹⁷ Implementing digital health records containing increasing amounts of biomarker data as standard is increasingly feasible as the costs of data generation (e.g. whole genome sequencing) and data storage decrease. Alongside increases in the generation and storage of data, analytical approaches to large datasets have evolved. These ensure that research on large linked datasets is robust and useful – for example, avoiding spurious correlations between clinical and molecular data – by requiring careful experimental design and choice of statistical methodologies to account for, for example, potential biases in data arising from the way it was acquired or inputted.

97 British Heart Foundation (2012). *Clear and present data: how access to our medical records can help life-saving science.* http://www.bhf.org.uk/pdf/BHF_Clear_and_present_data_2012.pdf

Work currently being undertaken to move the UK in the direction of such an informatics system, addressing issues about linkage of, access to and consistent format and quality of the data involved, includes the following:

- The Clinical Practice Research Datalink (CPRD), launched in 2012 with £60 million funding, is an observational data and interventional research service. Operating across England, it will connect patient information from GPs and hospitals to other records, such as disease registries, and hold the resulting data in an anonymised form.⁹⁸
- The establishment of four E-Health Informatics Research Centres (eHIRCs), supported by a 10-funder consortium co-ordinated by the MRC, that opened in May 2013. These Centres aim to harness the wealth of UK electronic health records, such as those available through the CPRD, to improve patient care and public health, tackling conditions such as diabetes and obesity, cardiovascular disease, cancer and child and maternal health.⁹⁹ The consortium has also agreed to provide further funding to establish the eHIRCs Network, which aims to: incorporate and harness expertise in the wider UK research community; develop methods for integrating and analysing complex and heterogeneous datasets; share best practice and adopt standards; co-ordinate training and career development opportunities; provide an interface for the NHS, IT and pharmaceutical industries; and work closely with patients and the public on concerns and benefits of using health records and personal data in research.
- The MRC funded Farr Health Informatics Research Institute, which will build on the scientific programmes of the eHIRCs by developing new partnerships with academia, industry and the NHS and creating a digital infrastructure to enable safe sharing of health datasets across regional boundaries.
- The Health and Social Care Information Centre (HSCIC) has been established through the Health and Social Care Act 2012 to collect, store and disseminate national data from health and social care bodies. The HSCIC offers a data linkage service by combining and matching sets of data at an individual record level in a secure environment. The service is intended to support commissioners, local healthcare providers, researchers from academia and industry, and others.¹⁰⁰
- Cancer Research UK's Stratified Medicine Programme (see Box 2), as well as developing frameworks for pathology services and diagnostic funding, is also developing informatics and consent frameworks and mechanisms for research access to the accumulated clinical data.¹⁰¹
- Government support for broad progress in biomedical and health informatics was indicated by the Secretary of State for Health in January 2013.¹⁰²

98 <http://www.cprd.com/intro.asp>

99 <http://www.mrc.ac.uk/Fundingopportunities/Calls/E-healthCentresCall/MRC008159>

100 <http://www.hscic.gov.uk/home>

101 <http://www.cancerresearchuk.org/science/research/how-we-deliver-our-research/others/by-programme/stratified-medicine-programme/>

102 <https://www.gov.uk/government/news/jeremy-hunt-challenges-nhs-to-go-paperless-by-2018--2>

Box 3 Examples of UK research infrastructure***Research clusters and collaborations:***

Academic Health Science Centres

Academic Health Science Networks

Health Sciences Scotland

NIHR Biomedical Research Centres and Biomedical Research Units

NIHR Clinical Research Networks

National Institute for Social Care and Health Research (NISCHR) Welsh Academic Health Sciences Collaborations

NISCHR Biomedical Research Centres and Biomedical Research Units

MRC Stratified Medicine Consortia

Stratified Medicine Scotland Innovation Centre

High-impact strategic programmes and resources

Cancer Research UK Stratified Medicine Programme (see Box 2)

Cambridge Bioresource

Clinical Practice Research Datalink (CPRD), supported by NIHR and MHRA

Diagnostic Mutation database (National Genetics Reference Laboratory)

European Molecular Biology Laboratory – European Bioinformatics Institute

Generation Scotland

Human Gene Mutation Database (Cardiff University)

MRC co-ordinated eHealth Informatics Research Centres (eHIRCs) and Network

MRC Farr Health Informatics Institute

MRC birth and disease cohorts

MRC-NIHR Phenome Centre

NIHR BioResource

Stratified Medicine Innovation Platform (SMIP), led by TSB

Tissue Banks

- Breast Cancer Campaign Tissue Bank
- MRC UK DNA banking network, brain banks network and stem cell bank.
- Confederation of cancer biobanks established by the National Cancer Research Institute
- UK Biobank

Trust Case Control Consortium

Wellcome Trust Sanger Institute

The challenges to developing an informatics system fit for stratified medicine

Successful compilation and linking of data and tissue resources is critical to facilitate adoption and development of stratified medicine.

For instance, to determine whether a genetic variant has clinical significance – such as rare adverse reactions to a given drug – comparison needs to be made against genetic data from large cohorts in national or international databases.¹⁰³

Recent progress in the field of genetic and genomic research has generated a wealth of data and led to the development of numerous databases. There are now global initiatives to create 'raw' genome data deposits, including the European Bioinformatics Institute (EBI) in the UK and the National Centre for Biotechnology Information in the US.¹⁰⁴ These databases will be essential in managing and storing the large volume of data being produced and providing the basis for identifying disease-related genetic variation.

For these information sets to have medical value, however, they must be linked to phenotypic/clinical data so that the effect of genetic variation can be understood. Links to large annotated biobanks with high-quality, validated biological specimens will further enhance the utility of these resources.¹⁰⁵ Such a linked resource will enable investigation into whether a given genetic pattern can be clearly and repeatedly associated with a disease, increased susceptibility to it, or improved response to a therapy.

A recent report by the US National Academy of Sciences (NAS), *Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease*, for instance, calls for the creation of an international

infrastructure (Information Commons and Knowledge Network) to bring together molecular data, clinical data, environmental data and health outcomes to develop a more precise definition of the mechanism of human disease, or a 'new taxonomy of disease', and more broadly to modernise biomedical research and improve patient care.¹⁰⁶

Three key challenges exist:

- Standardised collection protocols and formats for data must be agreed, to ensure datasets can be meaningfully compared and/or combined.
- Methods must be developed to link multiple datasets, both nationally and internationally, to allow the necessary analyses to be undertaken.
- A proportionate governance framework must be established for data access, one that ensures that adequate patient privacy is maintained while research access is maximised.

Standardisation of collection and management processes of data and clinical samples

To build a biomarker–phenotype database that can serve the need of researchers and clinicians, it is imperative that there is an ongoing contribution of high-quality data from the community that uses the resource. Standardisation of collection and management processes will be essential both in facilitating access to and in sharing data as well as for quality control.

The ENCODE (ENCyclopaedia Of DNA Elements) project may provide a good template for such work.¹⁰⁷ The project, launched by the National Human Genome Research Institute with the aim of identifying all functional elements in the human genome sequence, is organised as an open consortium. Participants agree to abide by

103 Hattersley AT & McCarthy MI (2005). *What makes a good genetic association study?* The Lancet **366(9493)**, 1315–1323.

104 <http://www.insdc.org/>

105 <http://www.ukbiobank.ac.uk/>

106 National Academy of Sciences (2011). *Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease*. http://www.ucsf.edu/sites/default/files/legacy_files/documents/new-taxonomy.pdf

107 <http://www.genome.gov/10005107#4>

the criteria for participation and share results according to the ENCODE data release policy.

Standardisation of clinical data is another important element. Medical information should be recorded in the same way by all healthcare professionals. This will require the adoption of a classification system that allows accurate phenotypic diagnosis and recording. This classification system needs to redefine diseases in terms of known molecular/cellular (patho) physiology rather than 'signs and symptoms'. An improved definition of clinical diseases will help address the need to understand biomarker-phenotype relationships, which are at the core of stratified medicine. It is also important that researchers, as well as healthcare professionals, use the same disease classification system to annotate their databases.¹⁰⁸ The recently established Professional Records Standard Body in the UK could provide an important leadership in this area.¹⁰⁹

The need for standardisation of processes also applies for the development of any biobanks or tissue banks, to remove impediments to research use of these resources, as mentioned in Chapter 2. A further challenge is improving the processes of searching for samples and linking them to clinical records. Several efforts are currently underway in the UK to maximise the potential of existing bio-resources and tissue banks located in research and hospital pathology laboratories (see Box 3).

Integration of multiple data/sample resources

Efforts to promote sharing of data and samples through the standardisation of processes outlined above will be fruitless if the systems that store them cannot be connected.

The current reality, however, is that localised clinical and research databases are hard to

use at the national level, partly because of the proprietary nature of the applications used to store the data. It is vital that systems are designed in a way that allows integration of information regardless of who created them. This combination could include information on genomics, proteomics, metabolomics, clinical imaging, tissue histology, as well as clinical and social health records.

The development of interoperable systems has to be pursued at the global level to enable international data and sample sharing, such as the creation of information infrastructure proposed by the US NAS.¹¹⁰

Proportionate governance framework

The complexity of current arrangements for regulating the use of patient data has been identified as a significant barrier to health research.¹¹¹ Access to data and samples may also be restricted because the consent obtained prevents them from being used outside the original study for which they were collected. As noted already, however, these data and samples are crucial for the development of stratified medicine.

Patient data and samples must remain safe and secure but in a way that does not unnecessarily restrict effective sharing for research. Defining a proportionate governance framework that reduces burden and uncertainty and increases transparency is vital. This would involve setting standards, principles and best practices, with clearly defined responsibilities including data flows for data controllers and data stewards. Options for the provision of uniform high-quality advice and access in a single structure should be explored, as well as mechanisms for obtaining broad and enduring consent.

There is some work already in this area.

Provision of a single governance structure that

108 European Science Foundation (2012). *Personalised medicine for the European citizen: towards more precise medicine for the diagnosis, treatment and prevention of disease (iPM)*. http://www.esf.org/uploads/media/Personalised_Medicine.pdf

109 <http://www.theprsb.org.uk/>

110 National Academy of Sciences (2011). *Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease*. http://www.ucsf.edu/sites/default/files/legacy_files/documents/new-taxonomy.pdf

111 Academy of Medical Sciences (2011). *A new pathway for the regulation and governance of health research*. <http://www.acmedsci.ac.uk/download.php?file=/images/publication/newpathw.pdf>

will allow for consistent and robust decision-making was one of the recommendations of the Administrative Data Taskforce, which was formed by the Economic and Social Research Council (ESRC), the MRC and Wellcome Trust to examine the best procedures and mechanisms to make administrative data available for research safely.¹¹² The Health Research Authority, with its aim of creating a unified approval process and promoting proportionate standards for compliance and inspection within a consistent national system of research governance, offers an ideal structure for offering uniform advice on access to patient data and samples for health research.¹¹³

The importance of data sharing has already been highlighted. The UK ESRC believe that access to data from all research it funds is a 'right' of the research community.¹¹⁴ Accordingly, it mandates that all such data be placed in a publicly accessible archive. Social sciences have therefore pioneered research data openness, and this could serve as a model for the health research community.

There are also recommendations to move towards greater sharing of health data. The UK Human Genomics Strategy Group (HGSG), for instance, recommends that NHS England puts in place agreements that require data from tests performed by NHS-commissioned laboratories – either within the NHS or private sector – to be made available through nationally designed research databases within a framework that ensures patient confidentiality and data protection.¹¹⁵ The report from the Caldicott Review on information governance in health and social care discusses the practicalities of operating 'accredited safe havens' to access pseudonymised or key-coded data.¹¹⁶

Leadership in UK biomedical and health informatics

Establishing and linking the databases outlined above needs to be complemented with the development of informatics skills to interpret the stored data. The UK already has a strong bioinformatics research base in its universities, actively researching new technologies and methodologies for analysing, integrating and linking complex biological datasets from different sources. The new ELIXIR technical hub at the European Molecular Biology Laboratory – EBI, based at the Wellcome Trust Genome campus at Hinxton, will also act as a centre of excellence for bioinformatics across Europe providing training and co-ordinating bioinformatics services across several European centres.

There is a strong need for clearly identified individuals and organisations to act as champions and lead change in academic and NHS systems in the UK: to develop policies and procedures for best practice, as well as tools to tackle the ongoing challenges in relation to scale, format, annotation, storage, access, linkage and governance.

Both the House of Lords Science and Technology Committee report, *Genomics medicine*, and the HGSG report, *Building on our inheritance: genome technology in healthcare*, recommend the creation of a National Bioinformatics Institute to help translate information systems used for research into those that can be implemented in the clinical setting and facilitate the integration of healthcare and social databases (e.g. CPRD) with research databases (e.g. ELIXIR).^{117,118}

112 Administrative Data Taskforce (2012). *The UK Administrative Data Research Network: improving access for research and policy*. http://www.esrc.ac.uk/_images/ADT-Improving-Access-for-Research-and-Policy_tcm8-24462.pdf

113 <http://www.hra.nhs.uk/>

114 ESRC Research data policy (2010) http://www.esrc.ac.uk/_images/Research_Data_Policy_2010_tcm8-4595.pdf

115 Human Genomics Strategy Group (2012). *Building on our inheritance: genomic technology in healthcare*. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/134568/dh_132382.pdf.pdf

116 Department of Health (2013). *Information: to share or not to share? The information governance review*. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/192572/2900774_InfoGovernance_accv2.pdf

117 House of Lords Science and Technology Committee (2009). *Genomic Medicine*. <http://www.publications.parliament.uk/pa/ld200809/ldselect/ldscitech/107/107i.pdf>

118 Human Genomics Strategy Group (2012). *Building on our inheritance: genomic technology in healthcare*. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/134568/dh_132382.pdf.pdf

The eHIRCs Network, supported by a 10-funder consortium co-ordinated by the MRC, is scheduled to come into operation in mid 2013 and provides an opportunity for the development of such an Institute.

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 informatics 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 Encyclopedia 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.

Enhancing UK health information systems

The NHS is recognised as a special resource for developing stratified medicine as it provides a 'cradle to grave' record of each member of the UK population. It is also acknowledged, however, that the full potential of this resource is currently not being met.

For instance, a full longitudinal view of the patients for many chronic diseases is currently not available because data exist in silos across the UK healthcare system. The issue is compounded by data being stored in a range of databases and formats. Adoption of unique patient identifiers throughout the NHS would allow linkage of individuals' information across primary, secondary and tertiary care.

Another issue is inconsistency in routine data collection and the quality of these data across the UK. There needs to be an agreement on minimum core clinical datasets and, as noted above, standardisation in the way medical information is collected, recorded and stored. A sufficient level of data quality will need to be defined and enforced through robust quality assurance mechanisms.

Variability in the information system capability of hospitals is another factor that needs to be addressed. There is a need to develop the information technology infrastructure for improved data storage and handling capacity, and the rapid and secure transfer of data between different healthcare providers. Interoperability, both internally and externally, will be essential. Consideration should be given to centralised or distributed computing and networking solutions, for instance to ensure that data are accessible – with appropriate safeguards – to those involved in patient care, healthcare system decision-making and research. Improvement in infrastructure must also be accompanied by an enhanced informatics expertise within the NHS, which is discussed further below.

There is a need to harness the resources of industry in high-performance computing infrastructure and data analysis. The new Academic Health Science Networks are well placed to forge collaborative partnerships with industry to develop clinical and data infrastructure necessary for stratified medicine studies.¹¹⁹

Strong leadership and a clear vision across the NHS will be required to set up the necessary infrastructure, introduce standardised processes and support the adoption of these processes by instituting a change in clinical culture.

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.

Capacity building, education and training

The UK will need to invest in training and education to equip current and future researchers and clinicians with the understanding and skills required to develop and implement stratified medicine. Science and medical undergraduate and postgraduate courses will need to incorporate education in this field. There is also a need for training of the current workforce through suitable continuous professional development programmes. Furthermore, it is critical that jobs and career structures are created that will attract experts in this field to work in the UK in both the private and the public sectors.

Research expertise

There is a shortage of people across academia, industry and the healthcare system skilled in the breadth of fields necessary to design and perform the complex analyses required for stratified medicine research. These include the medical fields of translational medicine, genetics, genomics, proteomics, metabolomics, medical imaging, biomarkers, diagnostics and assay development, population science and public health. There is also requirement to source analytical expertise from non-medical fields such as physics and engineering, and from industrial partners. A further issue is the absence of career structure in enabling roles such as core technology development, technical support, data analysis and management, software engineering, statistics and informatics.

Clinical capacity

As highlighted in the Academy's response to the *Shape of training review of postgraduate medical education and training* (the Greenaway review), capitalising on the significant opportunities presented by developments in molecular pathology – to evolve clinical practice and improve patient care through stratified medicine – will require medical professionals to have a broad range of skills and scientific grounding in areas such as genetics, molecular biology and clinical informatics.¹²⁰

The concept of stratification will not only impact on therapeutic selection but also influence the healthcare approach to screening, early treatment and prevention. GP surgeries, mainstream clinical specialties and highly specialist units will all need to respond to this future.

The increase in the number of stratifying tests and a concomitant rise in the demand for them by clinicians, patients and their families will have implications for commissioning as well. There will be challenges around equity of access and management of cost. Where 'in-house tests' are involved there is also a need for an oversight of what is being developed and used, as well as quality assurance, which is discussed further in Chapter 4.

Understanding how the level of a biomarker identified through a stratifying test relates to an individual's risk of developing a disease or responding to a particular therapy may require the integration of data from multiple sources and involve complex analysis. Providing tools to clinicians and the public that offer clear interpretation of complex test results will therefore become increasingly important.

One of the outcomes of the Cancer Research UK Stratified Medicine Project (Box 2) is the need for further work to roll out standardised molecular pathology services across the NHS. It highlights the need for service reconfiguration to enable the systematic adoption of a stratified approach to therapy. Such a change will have to go hand in hand with a system-wide approach to information, understanding, education and implementation of stratified medicine.

Education and training for the professions involved in delivering stratified medicine – healthcare professionals along with healthcare managers, administrators and budget holders at all career stages – will be critical to embedding this clinical capacity. This has to be conducted in parallel with establishing appropriate infrastructure and career pathways to retain and recruit clinicians with high-level biological and analytical skills who can lead in the development and adoption of stratified medicine.

120 The Academy of Medical Sciences (2013). *Response to the shape of training review*. <http://www.acmedsci.ac.uk/download.php?file=/images/publication/FinalAMS.pdf>

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).

Public engagement and involvement

Patients and the public are exceptionally important stakeholders in making the adoption of stratified medicine become a reality in the delivery of healthcare, just as they have been in the adoption of new medical innovations in the past. To facilitate their involvement in the development of, and decision-making about, this approach to therapy, significant efforts must be made now and on an ongoing basis to build appropriate partnerships.

An important aspect of this is an open debate with patients and the public about the key issues raised by stratified medicine. Providing relevant and accurate information, and listening to their concerns, will be essential components of this.

More work is required: to identify the social and ethical issues raised by this approach to therapy; to discover and understand how publics interpret the word 'stratified'; to learn from publics about their views on the advantages and disadvantages of medicine becoming more stratified; and to understand how people would feel about not being prescribed medicines for certain genetic characteristics, particularly when there are no alternative treatments. The project exploring the concept of stratified medicine with members of the public – led by the TSB – will provide an important foundation in this area.¹²¹

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.

This consortium may need to consider how best to interact with patients and the public, in view of the increased sharing of personal information, communication and advocacy online, which may challenge the current models of engagement with these groups.^{122,123}

¹²¹ Sciencewise Expert Resource Centre (2012). *Developing stratified medicine*. <http://www.sciencewise-erc.org.uk/cms/developing-stratified-medicine>

¹²² <http://www.healthtalkonline.org/>

¹²³ <http://www.accesstomedicine.co.uk/>

Summary

Fast and efficient progress in the development and adoption of stratified medicine will require integration of the currently fragmented and incomplete landscape of key expertise and infrastructure.

Collection, storage and biomarker analysis of clinical samples are critical to generate accurate molecular data. These will need to be linked to accurate phenotype data captured from clinical practice. This linkage, which will enable both research into and clinical application of stratified medicine, will require comprehensive and robust biomedical and health informatics systems – a key rate-limiting step.

Standardised protocols for collecting and recording both types of data will be necessary to enable the comparison and combination of samples and datasets nationally and internationally, which is required to undertake the large-sample-size research that will advance the molecular understanding of disease.

The adoption of such protocols and use of medical informatics will depend upon the successful engagement with the public, patients and the clinical workforce.

4 Regulation

Overview

Adoption of a stratified approach to therapy relies on the development of effective tools for stratification and drugs tailored to the stratified groups. Stratifying diagnostics and therapeutics must both meet regulatory requirements before they can be marketed.

In an ideal situation, a new diagnostic is developed and analytically validated early in the development of a new stratified medicine. It is then studied in parallel with the medicine for clinical validation and determination of clinical utility, for example, Xalkori (crizotinib, for locally advanced or metastatic NSCLC).¹²⁴ In reality, there is little incentive for diagnostic manufacturers to co-develop a diagnostic when a drug begins its pre-clinical or clinical phase because of the different development timescales involved. On average it takes 9–12 years to develop a drug in contrast to 3–5 years for a diagnostic. This is compounded by the high risk that a drug may fail to meet the safety and efficacy requirements, making the associated diagnostic redundant. In addition, current regulatory and intellectual property systems do not facilitate or incentivise the generation of clinical evidence for stratifying diagnostics.

Co-development of a diagnostic and drug also necessitates that the biomarker has been identified before or early on in the drug development phase. This is clearly not always the case, and one or more biomarkers may be discovered or linked to a drug later on in its development, for example, the EGFR inhibitor Tarceva (erlotinib) used in lung cancer, or post-launch, for example, Vectibix (panitumumab, for metastatic colorectal cancer).^{125,126} Alternatively, a drug may be developed for an indication for which there is already a stratifying diagnostic and one or more other drugs on the market, for example, Tykerb (lapatinib, a tyrosine kinase inhibitor for use in HER2-positive breast cancer).¹²⁷ Furthermore, although the focus so far has been on bringing one diagnostic and one therapeutic to market, with improvements in technology it is increasingly possible to identify multiple biomarkers using a single panel test (such as a series of specific gene mutations) that leads to several treatment options, such as Oncotype Dx, challenging the idealised drug–diagnostic co-development model.¹²⁸ This will increasingly be the case with advances in next-generation sequencing technologies.

The regulatory framework must therefore take account of these different scenarios and make sure that – while ensuring appropriate safety of drugs and devices, and their efficacy and performance – it does not inadvertently introduce disincentives for the development of stratified medicines and diagnostics.

This chapter considers several regulatory challenges that currently exist under four broad areas:

- Co-ordination and collaboration between regulators;
- Classification and assessment of diagnostics that guide treatment decisions;

- Quality assurance of ‘in-house’ tests; and
- Future proofing regulation.

The challenges and possible solutions outlined here must be considered in the context of a very fast moving landscape. A rigid approach, for instance the strict co-development model

124 See Table 1 and <http://www.acmedsci.ac.uk/p47prid104.html>

125 Pao W, et al. (2004). *EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib*. Proceedings of the National Academy of Sciences **101(36)**, 13306–13311.

126 See Table 1 and <http://www.acmedsci.ac.uk/p47prid104.html>

127 Xia W, et al. (2002). *Anti-tumour activity of GW572016: a dual tyrosine kinase inhibitor blocks EGF activation of EGFR/erbB2 and downstream Erk1/2 and AKT pathways*. Oncogene **21(41)**, 6255–6263.

128 See Table 1 and <http://www.acmedsci.ac.uk/p47prid104.html>

currently pursued by the US FDA, will rapidly become at odds with the new models of diagnostics. Regulation must be able to adapt to the coming changes in a nimble fashion.

It should also be noted here that while this report was being developed, the European Commission finalised and published its proposals for the revision of regulation of medical devices, many of which echo the solutions that were put forward by the experts brought together for this current project.

Co-ordination and collaboration between regulators

Background

The regulatory frameworks that underpin the development of therapeutic and diagnostic products vary from region to region and, for diagnostics, sometimes country to country. The levels and types of evidence required are different, making global development of products more challenging.

In the US, for instance, application for diagnostic and therapeutic approval applications can be made simultaneously to the FDA (see Figure 2). The Centre for Devices and Radiological Health (CDRH) which reviews diagnostics and the Centre for Drug Evaluation and Research (CDER)/Centre for Biologics Evaluation and Research (CBER) for therapeutics review are co-located within the FDA.

The FDA has published draft guidance documents for the development of stratified medicine products.^{129,130} It promotes joint meetings between diagnostic and therapeutic manufacturers with the CDRH and CDER/CBER as early as possible. Co-development is recommended and the drug and its companion diagnostic are jointly approved by the FDA following appropriate labelling.

In contrast, in Europe, applications for drugs and diagnostics are made to different regulatory bodies (see Figure 3). For medicinal products, clinical trial

authorisation application must be approved by the competent authority of the Member State (e.g. the MHRA in the UK) before clinical development. After development, application for marketing authorisation is submitted either to the competent authority or – more frequently – to the Committee for Medicinal Products for Human Use (CHMP) at the EMA. The European Commission will grant a single authorisation that is valid in all EU countries, following recommendation by the EMA on the advice of the CHMP.

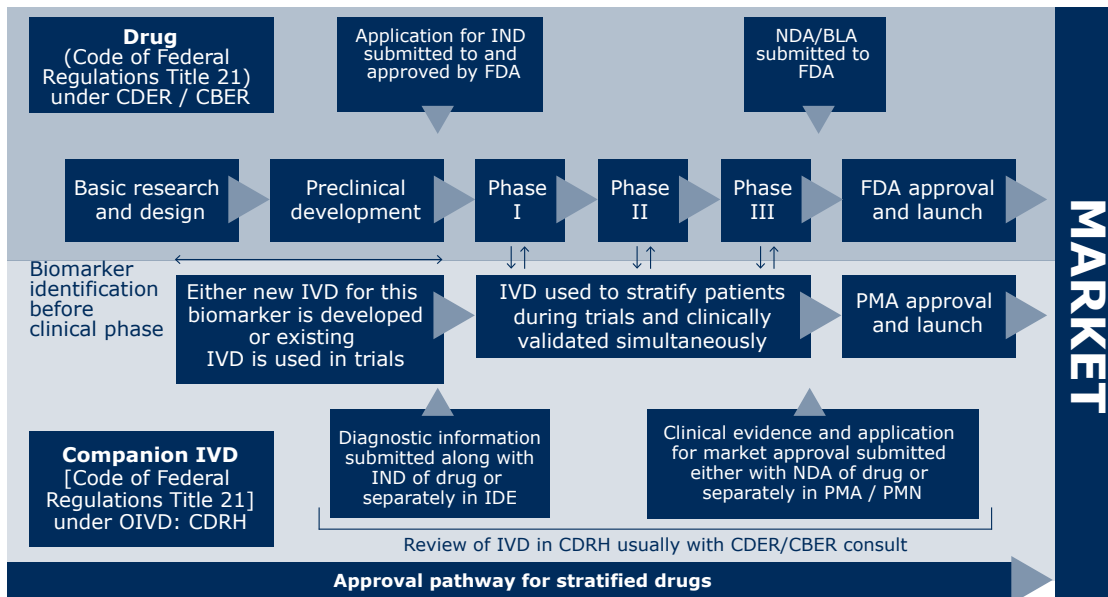
For devices, within which diagnostics are classified, application for clinical investigation must also be submitted to the relevant competent authority (e.g. the MHRA in the UK). The market approval process in Europe, however, is delegated by the competent authority to accredited notified bodies (e.g. the British Standards Institution in the UK). The level of pre-authorisation assessment required by the notified body before a manufacturer can affix a European Conformity (CE) marking to a new device for marketing throughout Europe depends on the category to which the device belongs, but the clinical evidence requirement is currently generally limited.

Although the integrated drug/diagnostics approval process in the US appears more adapted to stratified medicine products, in practice diagnostic companies prefer the lighter touch of the European arrangements, which enable faster market introduction. The model pursued by the FDA also does not take account of the many ways in which a diagnostic comes to market. A new diagnostic may be developed for an approved drug for stratification or for a new indication. In other cases, an existing diagnostic may be paired with a new or marketed drug after biomarker discovery and validation. The co-development model will be challenged further as we increasingly move towards multiple tests that can determine the expression and/or mutations of multiple genes and proteins, guiding treatment decisions to a suite of different therapies. The current European regulatory system, however, is also not conducive to the development of stratified medicine products, as discussed further in the subsequent section.

129 Food and Drug Administration (2005). *Drug-diagnostic co-development concept paper: draft—not for implementation*. <http://www.fda.gov/downloads/drugs/scienceresearch/researchareas/pharmacogenetics/ucm116689.pdf>

130 Food and Drug Administration (2011). *In vitro companion diagnostic devices: draft guidance*. <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>

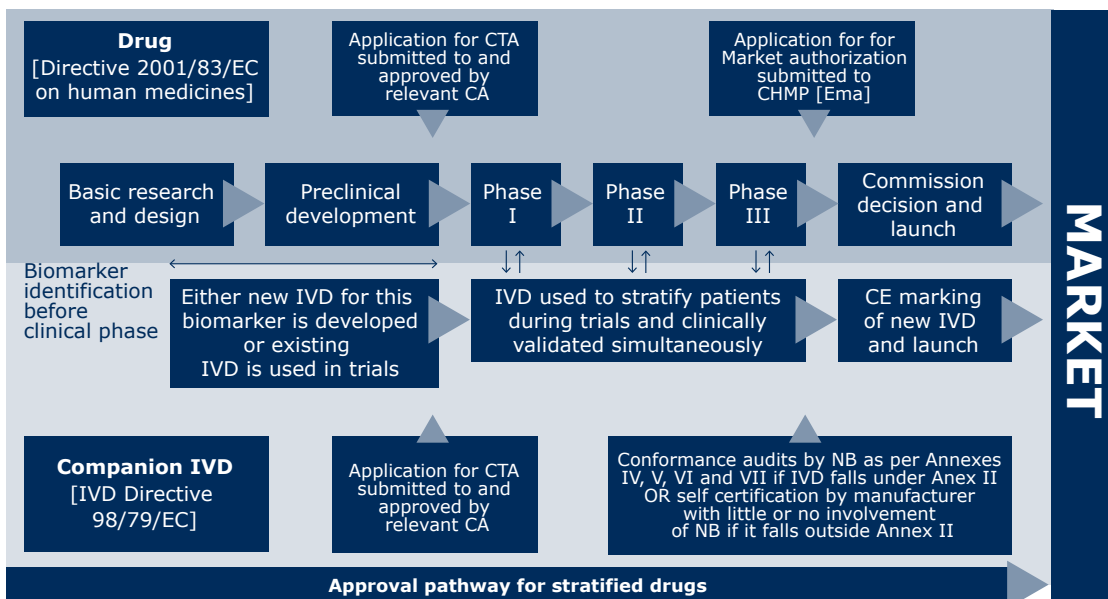
Figure 2: Representation of diagnostic and therapeutic development when biomarkers are developed before the clinical phase: US*



BLA: Biologic license application
CBER: Center for Biologics Evaluation and research
CDER: Center for Drug Evaluation and Research
CDRH: Center for Devices and Radiological Health
FDA: US Food and Drug Administration
IDE: Investigational device exemption
IND: Investigational new drug

IVD: *In vitro* diagnostics
NDA: New drug application
OIVD: Office of In Vitro Diagnostic Device Evaluation and Safety
PMA: Premarket approval
PMN: Premarket notification 510(k)

Figure 3: Representation of diagnostic and therapeutic development when biomarkers are developed before the clinical phase: EU*



CA: Competent authority
CE marking: European conformity marking
CHMP: Committee for Medicinal Products for Human Use

CTA: Clinical trial authorization
IVD: *In vitro* diagnostics
EMA: European Medicines Agency
NB: Notified bodies

* Based on a figure prepared by Kinapse Ltd

Need for improved regulatory co-ordination in Europe

The lack of any platform for aligning regulatory inputs for developing diagnostics and therapeutics at the EU level means that neither regulator sees the full picture of the regulatory requirements of stratified medicine products. Therapeutic and diagnostic development in Europe therefore often take place independently, with little early cross-fertilisation unless a pharmaceutical company identifies the need for a diagnostic and drives the co-ordinated development process with a diagnostic company. Collaboration may also develop because of the diagnostic company's need to access the trial data/clinical samples held by the pharmaceutical company to validate their diagnostic device.

The EMA has published reflection papers on co-developing therapeutics and diagnostics although it is not clear to what extent these documents are legally binding.^{131,132} The MHRA recently launched a web-based 'Innovation Office', from which advice and assistance on UK and EU regulatory requirements can be sought for innovations including drug-device combinations.¹³³ It should be noted, however, that their previous service to provide regulatory advice about joint diagnostic/therapeutic products received very little uptake. Given that at present there are separate regulatory pathways for therapeutics and diagnostics, this may not be surprising.

In September 2012, the European Commission published proposals for two new Regulations for medical devices and IVDs, which will replace the existing three Directives covering this area.¹³⁴ The proposed IVD Regulation contains a requirement for the notified body undertaking conformity assessment of companion

diagnostics to consult the relevant medicines competent authority of that Member State or the EMA.

A more co-ordinated guidance from the therapeutic and device regulators at an early stage is likely to ensure that appropriate development strategies are adopted at the outset. There needs to be clarity on the specifics of how this proposed consultation will work in practice, however, for instance around the grounds on which the EMA might object to an application. Without such clarity, there is potential for significant delays in approvals of diagnostics and associated therapeutics.

Any inflexible requirement by the regulators for co-submission of a companion diagnostic for approval of a stratified medicine is likely to act as a disincentive for manufacturers in this field. This is in part because, as outlined already, one diagnostic paired with one drug based on a known biomarker is only one of many models of the development of a stratified medicine product. Greater co-ordination between the medicine and diagnostic regulators should be introduced without the loss of flexibility in the current EU regulatory framework.

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

131 European Medicines Agency (2010). *Reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development: draft*. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC500094445.pdf

132 European Medicines Agency (2011). *Reflection paper on methodological issues with pharmacogenomic biomarkers in relation to clinical development and patient selection: draft*. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500108672.pdf

133 The Medicines and Healthcare products Regulatory Agency (2013). *MHRA launches an 'Innovation Office' to encourage the development of novel medical products and devices*. <http://www.mhra.gov.uk/home/groups/comms-po/documents/news/con249614.pdf>

134 European Commission (2012). *Proposal for a regulation of the European Parliament and of the Council on in vitro diagnostic medical devices*. http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_541_en.pdf

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.

Need for a joint scientific advice process

Development of a more comprehensive and standardised roadmap and guidance at the regional and global levels is likely to encourage more companies to develop stratified medicine products. This is best integrated into the scientific advice stage of dialogue between developers and regulators.

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.

There should also be an alignment in the scientific advice provided by the regulators and health technology assessment (HTA) bodies. In the UK, the NICE Scientific Advice Programme already provides parallel scientific advice alongside the MHRA and EMA.¹³⁵

Clinical evidence for diagnostic tests

As previously mentioned, differences in regulators' requirements for clinical evidence for diagnostics vary between regions. Clinical evidence consists of scientific validity, analytical performance and, where applicable, clinical performance. Scientific validity and clinical performance are also components of clinical utility (see Box 4).¹³⁶ The current FDA approach to diagnostics, which is generally more rigorous in terms of the clinical evidence required, is not economically viable for many diagnostic manufacturers owing to the cost involved in collecting evidence. In addition, the rate of change of technology in this field means that by the time the clinical investigation to generate the relevant data is completed, the diagnostic in question may already be outmoded.

In contrast, in Europe, manufacturers of diagnostics must satisfy essential safety and analytical performance requirements but they are not required to establish that the diagnostic has an impact on clinical outcomes to obtain a CE marking. Changes are proposed under the new European IVD Regulation, with new requirements on clinical evidence and clinical investigations. Details of what exactly will be required, however, remain unclear at present. It is recognised that lack of data on clinical utility impacts on adoption by clinicians. The information is also essential for HTA and pricing based on value, as discussed in Chapter 5. Furthermore, it is likely that not all biomarkers that determine treatment decisions will have

¹³⁵ http://review2011-2012.nice.org.uk/talking/Scientific_Advice_Programme/

¹³⁶ Global Harmonization Task Force (2012). *Clinical evidence for IVD medical devices – key definitions and concepts.* <http://www.fdanews.com/ext/files/12-12-ghhf-ivd-concepts.pdf>

a known mechanism of action (for example, the monitoring of periostin to guide the use of a therapeutic antibody that targets a protein

mediating allergic asthma in some patients), placing increased importance on the clinical utility evidence of tests.

Box 4 Definitions and concepts for diagnostic tests

The Global Harmonization Task Force provides the following definitions and explanations in Clinical evidence for IVD medical devices – key definitions and concepts.¹³⁷

Clinical evidence: clinical evidence for an IVD medical device is all the information that supports the scientific validity and performance of its use as intended by the manufacturer. Clinical evidence is a compilation of the scientific validity, analytical performance and, where applicable, clinical performance.

Analytical performance: the ability of an IVD medical device to detect or measure a particular analyte.

Clinical performance: the ability of an IVD medical device to yield results that are correlated with a particular clinical condition or physiological state in accordance with target population and intended user. (This term is sometimes referred to as **clinical validity**, which is used in this report.)

Scientific validity of an analyte: the association of an analyte to a clinical condition or physiological state.

Clinical utility: the usefulness of the results obtained from testing with the IVD medical device and the value of the information to the individual being tested and/or the broader population. Scientific validity and clinical performance are elements of clinical utility. Other elements may include acceptability, appropriateness, availability of treatments/interventions, and health economics.

At the same time, however, in the case of a diagnostic guiding the use of several drugs, it is unreasonable to expect separate clinical utility trials to be conducted on each treatment that is guided by the test. Additionally, the first diagnostic that comes onto market is often not the definitive version as companies often initially pursue development of 'simple' tests that could get through the regulatory processes faster. As is the case with most devices, the design of a diagnostic is also iterated throughout its life.¹³⁸ A rigid requirement for generation of clinical utility evidence at each

iteration is likely to have a negative impact on incremental improvement of the diagnostics.

A strict requirement for evidence generation using a double randomisation model (i.e. randomising patients first to test or not and then to stratified medicine or not, such as that proposed in Australia) is impractical and should be avoided.¹³⁹ In many cases, it may be preferable to define the performance of a test against technical criteria rather than seek upfront clinical utility evidence.

138 Food and Drug Administration (2011). *Draft guidance for industry, clinical investigators, and Food and Drug Administration staff – design considerations for pivotal clinical investigations for medical devices*. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265553.htm>

137 Global Harmonization Task Force (2008). *Principles of in vitro diagnostic (IVD) medical devices classification*. <http://www.imdrf.org/docs/ghtf/final/sg1/procedural-docs/ghtf-sg1-n045-2008-principles-ivd-medical-devices-classification-080219.pdf>

139 DHA (Department of Health and Ageing, Australia) (2012). *Co-dependent and hybrid technologies. Health technology assessment access point*. <http://www.health.gov.au/internet/hta/publishing.nsf/Content/co-1>, specifically [http://www.health.gov.au/internet/hta/publishing.nsf/Content/A66C37687EE064BDCA2577420081FB6A/\\$File/codependents.pdf](http://www.health.gov.au/internet/hta/publishing.nsf/Content/A66C37687EE064BDCA2577420081FB6A/$File/codependents.pdf)

Regulators should adopt a flexible approach to how clinical utility data are obtained which balances the need for high-quality evidence generation and driving innovation. The method used to obtain clinical evidence should be tailored to the type of diagnostic and its use and could include the following:

- Evolving clinical evidence submitted by defined healthcare providers under real-life settings.
- Small randomised control trials plus real-world data collection.
- Observational studies using biobanks.
- Post-hoc sub-group analysis using electronic health records over time, potentially with follow-up prospective studies.

Classification and assessment of diagnostics that guide treatment decisions

Background

Under the current European legislation, IVDs are classified as high risk only if the sample collection or its use, such as in invasive biopsy or blood testing, poses a high risk to the tester or the patient. Most companion diagnostics are classified as 'general IVDs' and therefore do not require assessment by a notified body before entering the market. The risk to patients receiving the wrong treatment due to incorrect diagnosis as a result of a poorly performed or inaccurate test is not recognised.

Proposed change to classification and assessment

The proposed new EU IVD Regulation replaces the existing list-based classification – composed in the mid-1990s and rarely updated – with a system based on risk. The proposal largely follows the approach developed by the Global Harmonization Task Force.¹⁴⁰

Under the proposal, IVDs will be divided into four classes of risk: A (lowest risk), B, C and D (highest risk). Tests providing information

about the predisposition to a medical condition or a disease (e.g. genetic tests) and those providing information to predict treatment response or reactions (e.g. companion diagnostics) are placed under class C.

This will mean that most stratifying tests will be subject to conformity assessment by a notified body and that manufacturers will no longer be able to self-certify. The change will bring EU legislation closer to that in the US and promote the safe and effective adoption of stratified medicine.

As noted in the previous section, the proposed new Regulation also contains new requirements for clinical evidence and clinical investigation. Although this is a positive step, as the need for quality clinical evidence is recognised, details on the type and level of evidence required remain unclear at present. It is important that detailed guidance for evidence generation is developed that enables the use of variety of methods, tailored to the type of diagnostic and its use, to minimise the potential for stifling innovation.

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.

¹⁴⁰ Global Harmonization Task Force (2008). *Principles of in vitro diagnostic (IVD) medical devices classification*. <http://www.imdrf.org/docs/ghtf/final/sg1/procedural-docs/ghtf-sg1-n045-2008-principles-ivd-medical-devices-classification-080219.pdf>

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.

Quality assurance of 'in-house' tests

Background

Some diagnostics are developed, evaluated, validated and used within a single laboratory or hospital. This is often because a commercial test is not available, for instance for rare diseases, but in other cases because the commercial test is deemed too expensive. Existing tests may also be customised to identify a subset of certain diseases. Under current legislation these 'in-house' tests (IHTs) are not required to follow quality assurance measures, raising two issues: safety concerns arising from variation in standards between sites and countries, and reduced incentives for manufacturers to develop diagnostics.

The following section explores the issue of variation in the standard of IHTs. The subject of IHTs compromising the commercial viability of first-to-market diagnostic tests – which may have gone through an extensive clinical development programme – and acting as a disincentive for manufacturers is explored further in Chapter 5.

One area where regulation (or professional codes) might assist in reducing this disincentive and ensuring patient safety, however, would be a requirement for laboratories to demonstrate that the quality of their IHTs matches that of any commercially available tests.

Accreditation of laboratories

With respect to safety concerns, accreditation of laboratories performing predictive and

prognostic diagnostic tests to defined criteria will facilitate standardisation and improve quality.

In the US, the Centers for Medicare & Medicaid Services regulates all laboratory testing (except research) performed on humans through the Clinical Laboratory Improvement Amendments (CLIA). Laboratories must be CLIA certified to receive funding from Medicare and Medicaid.

In Europe, each Member State has one recognised national accreditation body, which assesses laboratories against internationally agreed standards. In the UK, for instance, most laboratories are accredited by the Clinical Pathology Accreditation (UK) Ltd – recently acquired by UK Accreditation Service – which operates a voluntary accreditation scheme. There is, however, no pan-European requirement for laboratories to be regulated so the penetration of laboratory accreditation varies from country to country.

The proposed new EU IVD Regulation requires that while class A, B and C IVDs developed and used 'in-house' will be exempt from other provisions of the Regulations (except for the requirement for reporting of serious incidents and field safety corrective actions), an obligation is placed on health institutions developing and using them to be accredited according to the ISO 15189 standard.¹⁴¹ In contrast, 'in-house' IVDs falling under class D must comply with the Regulation, albeit with exemptions from some of the requirements such as provisions on traceability and registration.

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.

To ensure that accreditation facilitates standardisation and quality improvement across a wide network of laboratories and hospitals globally, current variation in the criteria and processes used must be addressed. For instance, some countries validate key tests with standard samples (e.g. France) whereas some accredit a person (e.g. the US).^{142,143} In the first instance, actions could be focused on accreditation of laboratories and/or their performance on specific tests based on pan-European standards. Quality assessment should consider the manufacture of IHTs, as well as all stages of the diagnostic process, including ways in which the tests are conducted, sample management and data analysis, storage and sharing.

Any work to introduce standardisation should take account of existing activities in this area, such as the review of quality assurance arrangements for NHS pathology services announced by the Department of Health in December 2012.¹⁴⁴ In addition, the UK HGSG made the following recommendations for NHS England in its report: collaborate with commissioners, the UK Genetic Testing Network and NICE to develop a robust process for the evaluation of clinical validity and utility of all genetic and genomic tests and markers; and set minimum national quality standards/assurance of each particular test, test centre and technology.¹⁴⁵

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.

Future shape of regulation

Background

The rapid pace of scientific discoveries and technological developments means that diagnostics platforms profiling multiple biomarkers that guide decision-making to several different treatments will increasingly become the norm.

In addition, next-generation sequencing technology will make sequencing an individual's (or their tumour's) entire genome to create a personal variant file an economically viable proposition. The whole genome could ultimately function as a set of biomarkers with sequencing of individual tumour genomes being used to inform treatment decisions based on *in silico* models.¹⁴⁶

Coupled with an improved understanding of the molecular pathway of disease, in the future prescribing could depend on matching the drug to the patient using their stored genetic profile, reducing the need for traditional companion diagnostics.

Regulators will need to be prepared for this future to ensure safe and effective uptake of the most advanced technology and therapies. In fact, manufacturers of sequencing platforms are already approaching regulators for clinical design advice, with some seeking FDA approval for their devices.

142 http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/11/WC500134977.pdf

143 <http://wwwn.cdc.gov/cia/regs/toc.aspx>

144 <https://www.gov.uk/government/news/pathology-quality-assurance-review-launched>

145 Human Genomics Strategy Group (2012). *Building on our inheritance: genomic technology in healthcare*.

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_132382.pdf

146 European Science Foundation (2012). *Personalised medicine for the European citizen: towards more precise medicine for the diagnosis, treatment and prevention of disease (iPM)*. http://www.esf.org/uploads/media/Personalised_Medicine.pdf

New models for generating clinical utility data

Increasingly, therapeutics will be launched based on small clinical trials with very restricted patient groups, and the FDA has recently issued guidance on enrichment strategies for clinical trials.¹⁴⁷ Linked to this is the need to develop models for continuous trials of multiple drugs with much smaller sample sizes, especially for rare diseases. Outcomes need to be defined, and appropriate statistical frameworks with which to assess them have to be developed. There should also be a shift in emphasis to use modelling as a valid testing method. In the extreme, it may be a trial of n-of-1 in the case of a clinician trying a series of drugs for a tumour based on the genome sequence of an individual patient or tumour.¹⁴⁸ The EMA's guidance on trials in small populations also includes a section on n-of-1 trials.¹⁴⁹

Discussions are also underway in both the US and Europe about adaptive approaches to licensing (or 'progressive patient access' arrangements).¹⁵⁰ This would involve a drug-specific development plan being agreed, which provides sufficient information on risk versus benefit to enable conditional approval for the earlier use of the drug in a defined group of patients and/or treatment settings. This would be followed by monitoring of 'real-world' efficacy and safety and may lead to further licence adaptation. In many cases, stratifying diagnostics will be pivotal to such plans. The programme of work of the MHRA's Expert Group on innovation in the regulation of healthcare includes discussion of this approach to licensing.¹⁵¹ The UK intends to launch pilots in this area, possibly under the auspices of the EMA, over the next year.

As highlighted earlier, there should also be further deliberation at the global level on the nature of evidence and the methods of collection required for assessing the clinical utility of diagnostics, which do not introduce undue disincentive for their development. In many cases, it may be preferable to define the performance of a test against technical criteria rather than seek upfront clinical utility evidence.

It will be important that information from these new, as well as existing, models of trials are captured and shared to build the global knowledge base. There is increasing recognition of the importance of greater transparency in clinical trial reporting for patient, social and scientific benefit. Discussions on practical steps to enable this are happening both in Europe and in the US and it will be essential that there is international co-ordination to develop uniform mechanisms and systems across the regions.^{152,153,154}

Whole genome sequencing

There is an urgent need to set global standards for whole genome sequencing, which should consider the following key stages (and challenges):

1. **Pre-analysis:** how to extract DNA (e.g. from a tumour where there are issues around heterogeneity and small sample size). This is discussed in more detail in Chapters 2 and 3.
2. **Sequencing:** the accuracy of whole genome sequencing is increasing rapidly but further work is required. This is also discussed in Chapters 2 and 3.

147 Food and Drug Administration (2012). *Enrichment strategies for clinical trials to support approval of human drugs and biological products: draft guidance*. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf>

148 Lillie EO, et al. (2011). *The n-of-1 clinical trial: the ultimate strategy for individualizing medicine?* *Personalized Medicine* **8(2)**, 161–173.

149 European Medicines Agency (2006) Guideline on clinical trials in small populations. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf

150 Eichler HG, et al. (2012) *Adaptive licensing: taking the next step in the evolution of drug approval*. *Clinical Pharmacology and Therapeutics* **91 (3)**, 426–437

151 <http://www.mhra.gov.uk/Committees/ExpertGrouponinnovationintheregulationofhealthcare/index.htm>

152 http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000556.jsp&mid=WC0b01ac0580614159

153 <http://www.abpi.org.uk/our-work/news/2013/Pages/190413.aspx>

154 Institute of Medicine (2013). *Sharing clinical research data - workshop summary*. <http://www.iom.edu/Reports/2013/Sharing-Clinical-Research-Data.aspx>

3. **Interpretation:** how to separate signal (informative biological differences) from noise (simple biological variation). This is a particular issue for common complex disease and cancer where individual tumours can display a high degree of genetic instability. There are statistical challenges around analysing the whole genome for responders compared with non-responders, and there may not be enough genomic data of sufficient quality to test the gene variant(s) for significance. This will be an evolving capability, and clinicians and scientists with a good understanding of disease will be essential. It is unlikely that all laboratories will have the required expertise in the future, which may lead to there being only a few accredited laboratories to conduct whole genome sequencing across the country.
4. **Clinical utility:** how should the results be used to best guide correct treatment decisions? Should laboratories simply report results or offer interpretation, in terms of probability of response to different treatment types (given the fast pace of development of the field and the likelihood that not all clinicians will be aware of the latest status)? In practice, therefore, will it inform patient management and lead to improved clinical outcomes?

There are already some frameworks for pre-analysis and sequencing stages but interpretation and clinical utility are areas that go beyond current regulatory guidance regimes. Other regulatory challenges include the following:

- How to regulate whole genome data. The sequencing device and informatics packages that decode it can be regulated but not the significance of the data themselves.

- How to manage new findings on gene–disease relationships that arise mid-trial.
- How to test the sophisticated algorithms that analyse whole sections of DNA to characterise disease. Regulators will need to develop in-house expertise
- Who oversees regulation if genome interpretation is to be used for public health, as opposed to individual treatments.

In the UK, the PHG Foundation has published reports covering several of these topics.¹⁵⁵ Furthermore, the Centre for the Advancement of Sustainable Medical Innovation has initiated discussions with key stakeholders on developing an appropriate framework to address the above issues.¹⁵⁶

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.

¹⁵⁵ For example, see PHG Foundation (2011). *Next steps in the sequence: the implications of whole genome sequencing for health in the UK.* <http://www.phgfoundation.org/reports/10364/>

¹⁵⁶ Barker RW, Brindley DA & Schuh A (2013). *Establish good genomic practice to guide medicine forward.* *Nature Medicine* **19(5)**, 530.

Summary

To ensure ongoing development and adoption of stratified medicine products, we have made recommendations aimed at addressing the following regulatory challenges:

- Current lack of co-ordination and collaboration between diagnostic and therapeutic regulators within Europe, and the need for a more comprehensive and standardised roadmap and guidance at the regional and global level.
- The need for clarification on the level of evidence that is acceptable for licensing a diagnostic, which balances the need for robust proof of clinical utility and inappropriate demands that will stifle innovation.
- The need for diagnostics that guide treatment decisions to be regulated based on a classification that takes account of risks to patients.
- Lack of requirements for IHTs to follow quality assurance measures, resulting in variation in standards between sites and countries.

Looking further ahead, the ability of regulators to adjust to the fast pace of scientific and technological development resulting in new and powerful diagnostics and therapies will be essential. This may require consideration of fundamental changes in the regulatory model, rather than an incremental progress of regulation based on current processes. Instead of viewing their role as simply ensuring the continuing safety, efficacy and quality of medicines and devices, regulators will also have to respond to new opportunities being presented by scientific innovation. Advances arising from the interaction of informatics, validated biomarkers and targeted interventions will be one of the most important aspects of this. The regulatory paradigm of the future may be quite different from that which we currently apply.

5 Pricing and reimbursement

Overview

In certain situations there may be a clear economic incentive for drug manufacturers to develop products that require healthcare providers to test and stratify the population into likely 'responders' and 'non-responders'. For example, in diseases where multiple drugs are available, stratification could differentiate the product from its competitors by representing improved efficacy in the responder population. However, there is often a double disincentive to manufacturers for developing a stratified medicine, compared with the development of a non-stratified medicine. Firstly, stratification commonly requires increased investment to develop a diagnostic test which, unlike an innovative drug, is not well protected by the patent system. Secondly, stratification may result in a smaller market size and consequently, other things being equal, decreased returns for the manufacturer, although this may be partly mitigated through greater uptake and adherence.

In the future, stratification is likely to be most commonly performed using broad diagnostic tests based on equipment 'platforms' (such as whole genome sequencing) that may direct the use of many stratified medicines, rather than the current paradigm of the 'companion diagnostic' based on single-use tests directing the use of a single medicine. This will diminish part of the double disincentive, in that a new diagnostic may not need to be developed. However, it raises new questions, such as how to calculate the value of a diagnostic that directs the use of multiple drugs, and how to incentivise diagnostic development effectively for business models based on platforms rather than single-use tests.

In this chapter we review the current pricing and reimbursement arrangements for stratified medicine products (drugs and companion diagnostics). These do not adequately reflect the benefits and costs of stratification. We recommend solutions to address the double disincentive to encourage both the development of stratified products and the stratification of existing medicines. We focus on solutions that address the current companion diagnostic scenario yet will be capable of evolving as the diagnostics landscape changes.

The current pricing and reimbursement systems for drugs

Evidence generation and the intellectual property system for drugs

The significant global research and development costs of bringing a new drug to market were recently estimated to average US\$1.5 billion.¹⁵⁷ The patent system grants manufacturers a time-limited monopoly in order to provide an opportunity to recover these costs, which include generating the evidence required by regulators for marketing authorisation and the evidence used by health technology assessors in

evaluating cost-effectiveness, i.e. benefit (health gain and related effects) for the money spent. When the patent expires on small-molecule compounds, 'generics' flourish and provide the proven innovation at much lower cost to the healthcare system.

Pricing and reimbursement of drugs for use in the UK NHS

In the UK, pricing of drugs for use in the NHS is currently undertaken within the framework of the Pharmaceutical Price Regulation Scheme (PPRS), which is a mechanism for controlling drug prices through limiting

¹⁵⁷ Office of Health Economics (2012). *The R&D cost of a new medicine*. <http://www.ohe.org/publications/article/the-rd-cost-of-a-new-medicine-124.cfm>

both price increases and the total profit of a pharmaceutical company based on the set of medicines they provide to the NHS. The terms of this scheme are renegotiated every five years, providing considerable stability and predictability for industry.¹⁵⁸

Although companies can flexibly price individual items at launch within their PPRS 'set', HTA by the National Institute for Health and Care Excellence (NICE) can indirectly influence pricing considerations. NICE calculates the cost-effectiveness of the drug, and, using a cost-effectiveness threshold, decides whether to *recommend the drug for use* within the NHS. This enables the company to understand the maximum price at which NICE would still recommend their drug for use. It involves NICE calculating a drug's 'value' as the ratio of changes to (a) costs in the healthcare system and (b) patient mortality and morbidity, measured in terms of quality-adjusted life years (QALYs).¹⁵⁹ Through this activity of NICE, the UK has implemented one of the most transparent and consistent systems in the world for rewarding 'value' in new medicines. Over time, NICE has made some adjustments to the system, for example, to consider end-of-life medicines.¹⁶⁰

However, payment levels for drugs are generally not flexible (other than to decrease) after the initial price is negotiated at launch. The 2009 PPRS contains provisions for flexible pricing, but this has not been used so far, for reasons that are unclear.¹⁶¹

The move towards value-based pricing for drugs

To provide the right incentives for pharmaceutical innovation, there have been calls for pricing and reimbursement systems around the world to move towards payments reflecting 'value'. The UK is in the process of designing a new pricing system for new medicines termed 'value-based pricing' (VBP), which will be implemented by the Department of Health from 2014, and within which NICE will be responsible for the full value assessment of medicines.^{162, 163}

Although the current approach is sometimes described as 'QALY-based', it also includes projected NHS cost savings due to both effectiveness-related reductions in medical resource use and changes in the profile of adverse drug reactions. It assesses these projected benefits and costs – including the proposed product price – compared with a 'threshold' that is meant to represent the opportunity cost to the NHS of investing in the new product. Although the QALY-based approach has been sufficiently robust that it will be the core element of VBP, efforts are underway to determine whether and how the current definition of 'value' used by NICE could be expanded to reflect other factors, such as the broader impact on society (for example, carers), the burden of illness (severity) and unmet medical need, and the degree of innovation.¹⁶⁵ Thus, at this stage, the term 'value' in the UK context is being re-defined.

158 Association of the British Pharmaceutical Industry (2009). *Understanding the 2009 PPRS – industry briefing*. <http://www.abpi.org.uk/our-work/library/industry/Documents/Understanding%20the%20pprs%202009%20final.pdf>

159 <http://www.nice.org.uk/newsroom/features/measuringeffectivenessandcosteffectivenessstheqaly.jsp>

160 National Institute for Health and Care Excellence (2009). *Appraising life-extending, end of life treatments*. <http://www.nice.org.uk/media/88A/F2/SupplementaryAdviceTACEoL.pdf>

161 Department of Health (2012). *The pharmaceutical price regulation scheme: eleventh report to parliament*. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/146828/dh_132793.pdf.pdf

162 Department of Health (2011). *A new value-based approach to the pricing of branded medicines – a consultation*. http://webarchive.nationalarchives.gov.uk/+www.dh.gov.uk/en/consultations/liveconsultations/dh_122760

163 HM Government (2013). *The Government's response to the Health Select Committee's Eighth Report of Session 2012-13 on the National Institute for Health and Care Excellence*. <http://www.official-documents.gov.uk/document/cm85/8568/8568.pdf>

164 Department of Health (2011). *A new value-based approach to the pricing of branded medicines – a consultation*. http://webarchive.nationalarchives.gov.uk/+www.dh.gov.uk/en/consultations/liveconsultations/dh_122760

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The term 'value' is ambiguous: it means different things to different people, both inside and outside economics. However, it is unavoidable because there is no adequate synonym. In economics, the term 'value' is broadly used to mean a market-oriented concept that asks, (a) what would, or even should, society be willing to pay to include a new product in the list of those available for use, and thereby reward innovators for their new medical products, and (b) what factors should be considered in defining the value created, and dividing it among the innovators?

Porter stated that 'value in healthcare is measured by the outcomes achieved... relative to costs', which was echoed in the Office of Fair Trading (OFT) report recommending VBP.¹⁶⁵ The OFT argued that health outcomes should primarily be measured by QALYs, and that value needed to be referenced against a value-for-money threshold that represents the opportunity cost to the NHS. This would, at least implicitly, reflect a 'willingness to pay' for value for the NHS.¹⁶⁶

The current pricing and reimbursement systems for diagnostics

Evidence generation and the intellectual property system for diagnostics

Diagnostic manufacturers are required to provide clinical evidence to support the marketing and labelling of a commercial diagnostic, including any claims made about the scientific validity and performance of the device. As discussed in Chapter 4, the clinical evidence required to obtain marketing authorisation varies from country to country. However, compared with drugs, both the standards and the amount of evidence required by diagnostic regulators are lower, and despite the potential relevance of the international patent system, the intellectual property protection is typically weaker in practice.¹⁶⁷ This is compounded in Europe: unlike the FDA, the EMA does not name a specific trademarked test in the product license when licensing a drug with a companion test (see Table 1).

The limited protection that the patent system provides for diagnostics substantially weakens, and can eliminate, the time-limited monopoly that effectively incentivises drug development by allowing recoupment of investment. This, therefore, undermines the incentive to invest in diagnostic development and the associated evidence generation. The disincentive is further heightened by the threat of nearly instantaneous, or at least fast-following, 'generic' tests. As outlined in Chapter 4, a regulatory exemption allows tests developed in a single health institution – IHTs – to be made available for use within that institution without being required to invest in the evidence generation required for an equivalent commercial test.¹⁶⁸

Pricing and reimbursement of diagnostics in the UK NHS

Payments for diagnostics are generally based on the perceived costs of production and thus do not reflect the cost of evidence generation or the value created.¹⁶⁹ Furthermore, diagnostic reimbursement within the UK NHS is not always included in the cost of care for outpatients, and is

165 Porter ME (2010). *What is value in health care?* New England Journal of Medicine **363**(26), 2477–2481.

166 Office of Fair Trading (2007). *The Pharmaceutical Price Regulation Scheme: an OFT market study*. http://www.oft.gov.uk/shared_oftr/reports/comp_policy/oft885.pdf

167 Human Genetics Commission (2010). *Intellectual property and DNA diagnostics: a report of a seminar on the impact of DNA patents on diagnostic innovation*. <http://www.institutoroche.es/web/pdf/2011/humangenteicscommision.pdf>

168 Medicines and Healthcare products Regulatory Agency (2011). *Directives bulletin 18 – the medical devices Regulations: implications on healthcare and other related establishments*. <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007499.pdf> and Torjesen I (2011). NHS laboratories are infringing DNA patents with cheap "home brew" tests, says Human Genetics Commission. *British Medical Journal* **343**, d5080.

169 Miller I, et al. (2011). *Market access challenges in the EU for high medical value diagnostic tests*. *Personalized Medicine* **8**(2), 137–148.

commonly spread across multiple siloed budgets. This means that a test developer may face high barriers to getting a test adopted by the NHS because of budget constraints, even when it has good evidence of cost-effectiveness.¹⁷⁰

The move towards valuation of diagnostics

The valuation of diagnostics through HTA is just starting to develop in the UK. NICE has introduced a Diagnostic Assessment Programme which will, in principle, use value as the basis for assessment, but it will only cover a few diagnostics, and rewarding the value of evidence generation is likely to remain an issue.¹⁷¹ Furthermore, the economic analysis of stratified medicine products may challenge conventional approaches to economic evaluation by potentially introducing new uncertainties, new roles for modelling, new issues in screening and in sensitivity analyses, new challenges to conformity with antidiscrimination legislation and ethical questions about inequality in HTA. However, since its inception, NICE has been at the forefront of monitoring and adopting potential methodological innovations in HTA, and may be well placed to take a lead in addressing these issues.

The benefits and costs of stratification

Currently, payments to drug manufacturers are based on projections of likely impacts on QALYs and costs, and diagnostic reimbursement tends to be based on costs. Therefore, it seems unlikely that either the full benefits or costs of stratification are fully reflected in the pricing and reimbursement systems for drugs and diagnostics in most EU healthcare systems. This is also likely to be true of the UK, although it arguably performs the most transparent accounting at product launch.

The benefits of stratification

Irrespective of the diagnostic technology

used to perform the stratification, stratified medicines provide health and economic benefits by focusing treatment on those with a higher probability of responding.¹⁷² Perhaps the most important and obvious advantage is the minimisation of adverse drug reactions in non-responders: as previously mentioned, it has been estimated that adverse drug reactions could affect thousands of people yearly in the US, with the resulting treatment costing potentially hundreds of billions of dollars.

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'.¹⁷³ 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.

Finally, the use of stratified medicine products can generate short-term cost savings through decreased prescriptions to non-responders, avoiding the associated production and distribution costs.

The costs of stratification

Although some tests are not linked to only one drug, such as HER2 tests or Oncotype Dx, delivering a stratified medicine usually involves providing a companion diagnostic for use alongside the medicine. This can occur either *ex post* (i.e. after the drug has been launched with a price) or *ex ante* (i.e. the drug and companion diagnostic that constitute the 'stratified medicine product' are launched together). The latter may arise from several scenarios, involving different levels of research and development investment. One scenario is the pre-clinical development of a stratifying diagnostic, which is then used

170 Miller I, et al. (2011). *Market access challenges in the EU for high medical value diagnostic tests*. *Personalized Medicine* **8**(2), 137–148.

171 National Institute for Health and Care Excellence (2011). *Diagnostics assessment programme manual*. <http://www.nice.org.uk/media/A0B/97/DAPManualFINAL.pdf>

172 Garau M, et al. (2012). *Can and should value based pricing be applied to molecular diagnostics?* <http://www.ohe.org/publications/article/value-based-pricing-and-molecular-diagnostics-117.cfm>

173 Garrison LP & Austin MJ (2007). *The economics of personalized medicine: a model of incentives for value creation and capture*. *Drug Information Journal* **41**, 501–509.

in trials to obtain a regulatory authorisation. Another possibility is that a failed broad phase 3 trial is 'salvaged' by discovery of a small responder sub-population defined by a particular biomarker, requiring the development of a diagnostic ahead of further phase 3 trials.

In the *ex post* case, the drug manufacturer may have reduced income unless the price is adjusted upwards, to reflect the improved outcome in the targeted population. In the scenario of a planned *ex ante* stratified medicine product (as opposed to the 'salvage' situation), it is conceivable that total research and development costs could be reduced if understanding of the molecular pathology is far enough advanced, although conducting parallel drug and diagnostic development could be more costly in total. In either case, the development of the diagnostic test needed to perform the stratification and its validation requires significant investment beyond the research and development for the drug alone.

Rewarding stratification: challenges and solutions

The expectation of smaller populations of patients for a drug and the required investment in developing a companion diagnostic can discourage the development of stratified medicines – the double disincentive mentioned above.

To counter the double disincentive, pricing and reimbursement systems must recognise and reward the value added through stratification, and incentivise the continual development of diagnostics with improved analytical and clinical performance, and clinical utility.

Four economic realities must underpin any policy changes intended to reduce the economic barriers to stratified medicine:

- Healthcare payers, both public (e.g. the NHS) and private, seek value for the money they collect and spend on behalf of those using their healthcare.
- Manufacturers of stratified drugs and their companion diagnostics need returns that justify their investment in developing the products and generating the evidence required to support the products' use.
- The value created by a stratified medicine product will be greater than can be achieved by either the drug or diagnostic alone. Consequently, given the synergy of the combination, the method of dividing the reimbursement for this value between the drug and diagnostic manufacturers would seem to be somewhat arbitrary or – at least – involve appealing to wider criteria.
- The fiscal constraints of the current environment add to the pressures on payers to obtain value for money and will affect their willingness to pay.

Summary of challenges and solutions

The following challenges and solutions to incentivising the development and adoption of stratified medicines and companion diagnostics were considered:

- Stratification is discouraged because it may result in a smaller population of eligible patients and decreased income for the drug manufacturer. To encourage stratification, the pricing and reimbursement system needs to be flexible to allow prices to go up or down after launch of the drug, depending on the actual value generated. A new and broader definition of value, which explicitly includes the full benefits of stratification, needs to be developed and adopted in the pricing and reimbursement systems for drugs and diagnostics.
- The development and continued improvement of a diagnostic test to perform stratification requires investment in generating evidence of analytical and clinical performance, and clinical utility. To incentivise this investment, generation of high-quality evidence needs to be rewarded through the pricing and reimbursement system.

Solutions

Flexible pricing based on value

We propose the introduction of a system of flexible pricing based on value both for drugs and for diagnostics to address three challenges. Firstly, that payment levels for new drugs are generally not flexible (other than to decrease) after the initial price is negotiated at launch, providing a disincentive to stratify, as this may narrow the patient population. Secondly, reimbursement for diagnostics is generally based on the process or cost of production, therefore not covering the costs of large-scale evidence generation. Thirdly, the benefits of stratification are not accurately rewarded in the current pricing and reimbursement systems for drugs and diagnostics.

A system of flexible pricing based on value should be applied both to drugs and to diagnostics and incorporate the benefits of stratification. This section considers firstly how to reward the added value of a stratified product, and secondly a possible approach for separating this value between the drug and the diagnostic.

As noted previously, the current provision for price flexibility in the 2009 PPRS has not been used, and it is not clear if the new VBP for branded medicines to be introduced from 2014 will provide the required flexibility. Our proposed approach would call for the prices of drugs to be able to go up post-launch (if evidence suggests greater benefits from the medicine either being targeted in a narrower group of patients or used in several different indications) or down (for indications or patient groups getting less benefit). This would be difficult to implement without accurate aggregate data on use by type of patient. However, improved data collection will make this more feasible. Additional challenges to implementing this approach are outlined on the next page.

It is notable that the European Commission is currently revising its Transparency Directive, and a current draft includes the provision that '*Member States shall ensure that an application to increase the price of the product can be submitted by the marketing authorisation holder at any point in time*'. This is in line with the pricing flexibility we propose and is welcomed.

The implementation of pricing flexibility could also be facilitated – in part – through using 'risk-sharing' schemes, a type of patient access scheme in the UK. Pricing flexibility would be introduced through a formula, or renegotiation-based mechanism, using clinical performance data collected post-launch. For example, in the US, the manufacturer of Oncotype Dx and the payer UnitedHealthcare agreed to a risk-sharing scheme, whereby they collected information on whether women actually forego chemotherapy when recommended to do so by the diagnostic. If not, the value of and payment for the test would be less as it is not leading to any change in healthcare provision.

A new definition of value

The complexity of defining value

In England, as previously mentioned, the current framework for assessing value that influences reimbursement decisions in the NHS is cost-effectiveness, or cost per QALY used by NICE. Although the QALY captures the basic health benefits of a longer and better life, it does not capture other beneficial health-related outcomes such as returning individuals to work, minimising future need for carer support, or whether the product addresses a rare disease, severe disease or unmet need.¹⁷⁴ Furthermore, existing HTA sub-group analyses will be useful in calculating health gain and cost-offsets in subgroups, but would also need to be supplemented with other measures including the value of knowing and

expansions to other sub-populations. Efforts are already underway to review the methods used by NICE ahead of the introduction of VBP for branded medicines in 2014. The drug and diagnostic evaluation programmes in the UK have 'rewarding innovation' as an aim: it must be ensured that this is realised in practice to recognise the value of stratification.¹⁷⁵

To support our proposed approach of flexible pricing based on value, a new definition of value – deciding what factors should be included – is necessary. This requires an understanding of the political and practical dimensions of implementing healthcare valuations, and how individuals' definitions of value are influenced by personal, cultural and political factors. It will also need a strong evidence base for legitimacy: this will require gathering evidence of what is valued by different communities – for example, patients and the public, clinicians and payers – and how they balance multiple factors when appreciating value. This will be greatly assisted by NICE's proactive engagement with patients for their input into its decisions: through corporate level representation, lay member representation in the advisory bodies and consultation with patient groups.¹⁷⁶

Additional challenges in determining value

Beyond developing a definition of value to support flexible pricing for stratified medicines and diagnostics, there are other issues that will need to be addressed over time, including the following:

- Estimations of value will rely on the accuracy of real world data, such as aggregate data on use, sourced from multiple locations and health practitioners. Therefore, consistent minimum standards for the capture and reporting of data need to be developed as discussed in detail in Chapter 3.
- Value estimates may change significantly, for example, should a more accurate diagnostic test be introduced. Capacity

to undertake repeat value appraisals will need to be developed for flexible drug and diagnostic reimbursement to incentivise development of improved stratified medicine products, requiring the provision of additional administrative resources at HTA bodies.

- This approach will need to reflect the value of a drug in multiple scenarios, for example, at different disease stages and for different diseases. For example, Herceptin (trastuzumab) would need to be valued at least three times, because it can be used in multiple HER2-positive cancers: metastatic and early-stage breast cancer, and gastric cancer. This will not only require increased administrative resources at HTA bodies (as above), but may also result in a novel scenario in which the same drug has different prices depending on the contexts in which it is prescribed. This will be difficult to implement in practice.
- The current model of one drug paired with one companion diagnostic is likely to change in the near future with platform diagnostics that will direct the use of multiple drugs for multiple indications. A system will need to be developed to evaluate the value of these platform diagnostics.

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.

175 Department of Health (2011). *A new value-based approach to the pricing of branded medicines – a consultation*. http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/consultations/liveconsultations/dh_122760

176 National Institute for Health and Care Excellence (2012). *Patient and Public Involvement Policy*. <http://www.nice.org.uk/media/F14/95/NICEPIPpolicy.pdf>

Value of therapeutics and diagnostics

The previous section called for a system of flexible pricing based on value to reflect and reward the benefits – the value – of stratified medicine products. This section considers a possible approach for separating this overall value between the two components necessary for the stratification: the drug and the diagnostic. A recent report on the economics of using value based pricing for molecular diagnostics provides further economic detail.¹⁷⁷

The qualitative division of value between therapeutic and diagnostic

The health gain will always directly arise from the action of the drug among responding patients. However, the potential value added in stratification by the diagnostic – as already noted – includes the following: the minimisation of adverse drug reactions in non-responders because they no longer use the medicine (the largest value contributor); and the increasing certainty of diagnosis and benefits from therapy, which may also potentially improve patient adherence and uptake. As demonstrated by the diverse case studies (Chapter 1 and online), in some scenarios there may be other values added by the diagnostic, for example, when the drug would have never come to market without the diagnostic.¹⁷⁸

The separate contributions towards value from therapeutic and diagnostic can be qualitatively defined as above. However, because they are usually developed by different companies and therefore require separate reimbursement, there often remains a requirement to separate their contributions quantitatively. In doing so, there should also be an aim to reward more accurate diagnostics and those with a stronger evidence base because of the delivery of greater certainty.

Quantitative separation of value between therapeutic and diagnostic

Two models for quantitative separation of value between drug and diagnostic can be considered: one conducted by the manufacturers and another by a HTA body.

Manufacturers negotiate separate values

Owing to the potential for significant changes in the diagnostic landscape that will greatly complicate the attribution of value and therefore reimbursement decisions, the simplest solution may be for HTA bodies and payers to require a specific companion diagnostic to be used to inform prescription of a given drug. In this model, a value-based price for the combination product is paid to the therapeutic company, who in turn pays the linked diagnostic company.

However, there are challenges with this model. Firstly, it does not remove or simplify the quantification of separate values for drug and diagnostic, but simply changes who performs the assessment. Secondly, as previously described in Chapter 4, diagnostics are not always developed in parallel with therapeutics, as this model would require. In addition, strict controls on the use of non-commercial IHTs would be required. Thirdly, insistence on a single diagnostic to be paired with a given drug could generate issues with respect to anti-trust legislation, as well as stifle innovation by acting as a disincentive for ongoing improvements of diagnostics. Fourthly, the co-development model may become increasingly redundant as we move towards 'panel' diagnostics that guide treatment decisions to a suite of different therapies.

177 Garau M, et al. (2012). *Can and should value based pricing be applied to molecular diagnostics?* <http://www.ohc.org/publications/article/value-based-pricing-and-molecular-diagnostics-117.cfm>

178 <http://www.acmedsci.ac.uk/p47prid104.html>

Health technology assessor calculates separate values

Another model that could be used is for a health technology assessor, such as NICE, to quantify the separate values of therapeutics and diagnostics. The calculation could attribute the QALY gain among responders to the drug, whereas the diagnostic could be valued according to adverse drug reactions avoided in non-responders and the increased certainty of diagnosis.

For drugs, the framework for calculating QALYs and cost-offsets – evaluated using data from phase III randomised controlled trials – and translating them into a pricing and reimbursement decision is well established.¹⁷⁹ Although Genomic Health was recently successful in using a cost-offset argument to establish a value-based price in the US for its diagnostic Oncotype Dx (see Table 1), there is currently no established framework in most countries for calculating the value added by stratification and separating it between the therapeutic and diagnostic. The ongoing development of NICE's assessment procedures, including the Diagnostic Assessment Programme, is an important exception to this.¹⁸⁰

Evidence and experiments would need to inform the development of this model. A framework for calculating value added by the diagnostic is feasible to develop using sufficiently detailed informatics and economic research. Robust data on adverse drug reactions, and the costs and outcomes of the alternative treatment provided to non-responders, would allow an estimation of the value of the adverse drug reactions avoided in non-responders. The increased diagnostic

certainty – a 'value of knowing' premium – could be estimated through economic research using 'contingent valuation' techniques, which estimate the monetary value of an effect.¹⁸¹ Improved adherence and greater appropriate utilisation could be estimated using epidemiologically based population-level models such as budget impact models that are commonly required by payers.¹⁸²

Accounting for the fast pace of diagnostic evolution

As noted before, the pace of change of diagnostic technology means that the current drug–diagnostic combination product scenario is likely to be less relevant in the long-term. This means that HTA bodies will need to ensure that sufficient flexibility is built into any value framework.

It will also require two paths for diagnostic approval: a drug-based HTA committee for *ex ante* drug-test combinations (e.g. the NICE Technology Appraisals Programme), and a diagnostic-only HTA committee for *ex post* development of new individual or 'panel' diagnostics or of new evidence for the value they can deliver when used to stratify patients (e.g. the NICE Diagnostics Assessment Programme).¹⁸³

Finally, any HTA system evaluating stratified medicine products based on value will need to ensure that 'double counting' of the value contribution of drugs and diagnostics is avoided.

179 <http://www.nice.org.uk/newsroom/features/measuringeffectivenessandcosteffectivenessstheqaly.jsp>

180 National Institute for Health and Care Excellence (2011). *Diagnostics assessment programme manual*. <http://www.nice.org.uk/media/A0B/97/DAPManualFINAL.pdf>

181 Neumann PJ, et al. (2012). *Willingness-to-pay for predictive tests with no immediate treatment implications: a survey of US residents*. *Health Economics* **21**(3), 238–251.

182 Trusheim MR, Berndt ER & Douglas FL (2007). *Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers*. *Nature Reviews Drug Discovery* **6**, 287–293.

183 Garau M, et al. (2012). *Can and should value based pricing be applied to molecular diagnostics?* <http://www.ohe.org/publications/article/value-based-pricing-and-molecular-diagnostics-117.cfm>

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.

The share of the added value that would be attributed to the drug innovator compared with the diagnostic innovator would depend on the specifics of each case. We might generally expect the price of the medicine to increase, to reward the value concentrated in the smaller population of responders (i.e. perhaps maintaining the same cost-effectiveness ratio for drug) after taking account of the costs of testing. This type of division would also separate the traditional overall cost-offset (i.e. against the price of the drug) between responders and non-responders.

Rewarding evidence generation for diagnostics

The cost of evidence generation is one half of the double disincentive to develop and improve stratified medicine products. The success of stratification – the value created by directing treatment to responders, and away from non-responders – depends upon the quality and clinical utility of the diagnostic test in combination with the stratified medicine, as demonstrated by evidence. Lack of evidence risks unnecessary harm to patients through inappropriate clinical decision-making based

on a faulty diagnosis. However, several factors act as a disincentive for the generation of robust evidence in diagnostic development: lack of effective intellectual property protection, competition from IHTs, and lack of requirements or rewards for evidence generation under the current regulatory and pricing and reimbursement systems.

Defending the data generated

As previously mentioned, although drugs can enjoy a period of exclusivity to incentivise their initial and ongoing development, this is generally not the case for diagnostics. Some examples of exclusivity exist, for example, through the test complexity (e.g. Monogram).¹⁸⁴ Incentivising evidence generation using intellectual property mechanisms warrants further consideration; the two main potential mechanisms are through the patent process and through the use of 'data exclusivity' provisions in the regulatory process. However, data exclusivity for first-in-class diagnostics may not be practicable to institute because of the weaknesses of current highly decentralised regulatory processes in the EU.

Competition from 'in house' tests

The weak patent system for diagnostics can result in the immediate availability of 'generic' IHTs, which reproduce the original innovation without allowing the innovator to recoup their investment. This is an issue for all commercial diagnostics, including those that have evolved from IHTs: in the UK this limits the capacity of the NHS to generate income from commercialising its own research and development.

As outlined in Chapter 4, although IHTs can play an important role where commercial tests are not available and unlikely to be developed, the current lack of regulatory oversight can raise serious safety concerns. Although significant inter-laboratory variability in their performance exists, there is no requirement for IHTs to provide evidence of analytical performance.^{185, 186}

184 Low AJ, McGovern RA & Harrigan PR (2009). *Trofile HIV co-receptor usage assay*. Expert opinion on medical diagnostics **3(2)**, 181–191.

185 Agency for Healthcare Research and Quality (2010). *Quality, regulation and clinical utility of laboratory-developed molecular tests*. <http://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id72TA.pdf>

186 Dowsett M, et al. (2007). *Standardization of HER2 testing: results of an international proficiency-testing ring study*. Modern Pathology **20(5)**, 584–91.

Furthermore, many such IHTs may be simply duplicating available commercial tests that have undergone regulatory oversight and are supported by evidence of at least analytical performance, if not clinical performance and utility.¹⁸⁷ Therefore, given that IHTs are used commonly by healthcare providers, partly owing to the reduced administrative (regulatory) burden, they can have a significant impact upon patient safety. The need for accreditation of laboratories developing and using IHTs is recommended in Chapter 4.

There may be merit in considering the mandatory use of (and therefore payment for) regulatory-approved diagnostics rather than IHTs, or linking reimbursement to evidence base. Diagnostic developers could find this to be an incentive to invest in the evidence generation required for innovative tests, knowing that their investment will not be undermined by the presence of 'generics': 'copycat' tests that lack evidence and were therefore cheaper to produce.

Flexible approach to evidence generation

As previously highlighted in Chapter 4, there needs to be a flexible approach to the generation of clinical utility data, which balances the need for high-quality evidence with incentivising innovation. The rapid pace at which technology changes for this sector means that a strict insistence on randomised control trials, for instance, may render a new diagnostic outmoded by the time pre-market evidence is generated. The costs associated with these studies are often also beyond the means of many diagnostic companies. Different approaches to evidence generation will need to be considered by HTA bodies and payers as well as regulators, including real-world data and observational studies. Establishment of a comprehensive, nationwide biomedical and health informatics system, as recommended in Chapter 3, could be an important source of evidence for HTA bodies for calculating value and cost-effectiveness.

It is also important that the pricing and reimbursement system takes account of the cost of evidence generation in appraising the value of the diagnostic.

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.

¹⁸⁷ Human Genetics Commission (2010). *Intellectual property and DNA diagnostics: a report of a seminar on the impact of DNA patents on diagnostic innovation*. <http://www.institutoroche.es/web/pdf/2011/humangenteicscommision.pdf>

Summary

Stratification creates value, from the minimisation of adverse drug reactions avoided in non-responders, to improved diagnostic certainty, which may improve patient adherence to medication regimes. However, stratification requires investment in diagnostic development and may involve loss of revenue for drug companies as they target narrower populations, especially if pricing systems are inflexible. Flexible pricing based on value – wherein prices can increase as well as decrease and the generation of evidence is rewarded – is needed to incentivise the development and continued improvement of stratified drugs and associated diagnostic tests. Such a system would require the development and adoption of a new definition of value that explicitly includes the benefits of stratification. To garner broad societal support, developing a new definition of value and process of valuation will require additional research with stakeholder involvement. Finally, improving the evidence base of stratified products needs to be incentivised, and the use of tests without performance evidence needs to be controlled, using a combined approach of regulation and clinical guidance.

6 Conclusions

Stratified medicine involves the classification (stratification) of patients with a particular disease into sub-groups based on knowledge of their risk of a disease, or how they will respond to a given therapy. As we have demonstrated in this report, widespread adoption of this approach to therapy is increasingly becoming a reality, with several stratified medicines already in use in the clinic – particularly in the field of cancer – and many more under development. This is set to continue as technology such as next-generation whole genome sequencing advances, our understanding of the molecular basis of diseases progresses and a new molecular taxonomy of disease develops.

The Academy of Medical Sciences 2007 symposium and report, '*Optimizing stratified medicines R&D: addressing scientific and economic issues*', showed that there are clear benefits for many stakeholders from a stratified approach to medicine¹⁸⁸. It called for an acceleration of progress in translation to make stratified medicine available for a wider range of conditions. Stratified patients benefit from being provided with more targeted and effective treatments. The increased certainty of the therapy's efficacy benefits stratified patients and healthcare providers. For the former, this may improve their adherence to the medicine. For the latter, stratification also enables more effective use of resources by cutting the expenditure associated both with prescribing medicines to those who will not respond and with treating their adverse drug reactions. Industry is another beneficiary. The use of molecular taxonomy in pharmaceutical development to identify likely responders could lead to fewer drug development failures and reduce development times and costs. Diagnostic manufacturers also clearly benefit from the increasingly central positioning of their products, which are necessary to stratify patients.

Despite these advantages, progress in the development and adoption of stratified medicine has been relatively slow and the barriers identified in the Academy's 2007 report largely remain. Existing systems – for research and clinical development, regulation, pricing and reimbursement, and healthcare – are still not set up to enable the effective widespread adoption of stratification, let alone realise and maximise the potential it offers.

These barriers, however, are not insurmountable if all the stakeholders collaborate to bring about change; where necessary developing new approaches, but sometimes linking together existing initiatives. The preceding chapters provide detailed actions to accelerate the development and adoption of stratified medicine but the following issues must be given priority. Flexibility must be at the heart of these actions as science is progressing rapidly and the landscape is changing almost on a daily basis.

Support for a data-driven approach from all stakeholders

High-quality data are fundamental for all dimensions of stratified medicine: research and development, regulation, payment and reimbursement and clinical decision-making. Development of appropriate infrastructure and working practices will be critical to generate and collect reliable data and ensure its secure storage, enable linkage of multiple data types (including genomic and phenotypic data, tissue and images) and support safe and secure data sharing under a proportionate governance framework. Comprehensive biomedical and health informatics systems should be developed that can be linked up across organisational and ultimately geographic boundaries.

188 The Academy of Medical Sciences (2007). *Optimizing stratified medicines R&D: addressing scientific and economic issues*. <http://www.acmedsci.ac.uk/download.php?file=/images/project/AMSstrat.pdf>

Changes to regulation and pricing and reimbursement systems

Current regulation and pricing and reimbursement systems do not provide adequate incentives for the development of stratified medicine products (drug and companion diagnostic), nor are they set up to appropriately assess the next generation of products that will arise from scientific and technological advances such as whole genome sequencing.

Both the regulatory and HTA bodies require high-quality evidence to ensure patient safety and the use of limited healthcare resources on products with appropriate clinical utility. There is a need, however, for greater flexibility and harmonisation by regulatory and HTA bodies globally in the level of evidence requested and the means by which this is generated. There should also be increased requirements on 'in house' diagnostic tests to provide appropriate clinical evidence to ensure their safety and performance, as well as improved accreditation of laboratories that perform these tests. In addition, new models for generating clinical evidence will become increasingly important, for instance to assess therapies targeted to very small cohorts of stratified patients, and diagnostic platforms that guide decision-making to several different treatments.

In the immediate term, to ensure ongoing development of stratified medicine products, prices should reflect (and, if necessary, be adjusted upwards post-launch to take account of) the value of stratification.

Adoption by healthcare practitioners

Even if we overcome the barriers above, development of stratified medicine products will have little impact unless they are adopted and translated into clinical practice by healthcare practitioners. Therefore influencing clinical practice will be critical for stratified medicine to become embedded in healthcare.

This is likely to require a system-wide approach to information dissemination, education and training, and implementation of stratified medicine.

Healthcare practitioner support for this approach to medicine will also be fundamental to progress the two priorities outlined above. Collection of data, which underpins stratified medicine, will in part be dependent on all healthcare practitioners using standardised disease classifications, and ensuring high-quality data capture and input. In addition, demand by practitioners for diagnostics with a high level of clinical performance and utility will address some of the concerns about the use of IHTs affecting patient safety and reduced incentives for the development of commercial tests.

Last, but by no means least, healthcare professionals must be at the heart of the patient and public dialogue that will be crucial to ensure that stratified medicine products are developed and implemented in a way that considers the needs and concerns of all these groups.

As noted before, there has to be a concerted effort by all stakeholders to bring about the required changes. We have recommended the establishment of several collaborative groups to address the challenges identified, for example, the need to develop an effective data infrastructure and global standards for the collection, analysis and use of genomic data, and to embed patient and public involvement in the development and adoption of stratified medicine. However, if the UK is to realise its strengths in stratified medicine and engage fully in European and global initiatives, we believe that there is the need for an overarching body that can champion and link the various activities.

We already have an established partnership that can form the basis of this, in the form of the UK Stratified Medicine Innovation Platform, which brings together seven organisations that have agreed to work together and combine

resources to help accelerate the rate of development and uptake of stratified medicine in the UK.¹⁸⁹ Further co-ordination can be provided through oversight by the Office for Strategic Co-ordination of Health Research, an independent office jointly funded by the Department of Health and the Department for Business, Innovation and Skills, with proportional contributions from the Scottish, Welsh and Northern Ireland administrations. This Office's mission is to facilitate more efficient translation of health research into health and economic benefits in the UK through better co-ordination of health research and more coherent funding arrangements to support translation.

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 a public-private partnership, and which bring 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.

Working, where appropriate, with collaborations already in existence as well as those recommended within this report, our proposed body should start by considering the following issues:

- How to share resources, systems, information and risks and rewards for the research and development of stratified medicine products—linking with the European Innovative Medicines Initiative and similar programmes.
- How to evaluate and demonstrate the clinical utility of stratified medicine products through a single, consistent and robust process with appropriate standards.
- How innovations in stratified medicine are used and adopted in a clinical setting, including the education and training of clinicians on the relevant technology and its impact on treatment choices.
- How best to facilitate effective patient and public dialogue on the value of stratified medicine and factors to be considered for widespread adoption to this approach to therapy.

The Academy looks forward to playing a part in this proposed body and helping to facilitate the implementation of our recommendations. We will follow up on the topic of stratified medicine by periodically bringing together the key stakeholders to discuss progress in this field and highlighting any new and ongoing challenges that need to be addressed.

Finally, although the focus of stratified medicine so far has largely been on providing more effective and targeted treatments, stratification is equally applicable for preventive measures based on the risk profile of individuals. In fact, this is an area that is increasingly likely to come under the spotlight as our ability to predict disease risks improves – based on a better understanding of how genomic, biological, environmental and lifestyle factors contribute to disease development – and as medicine continues to evolve towards ever more personalised approaches.

¹⁸⁹ <http://www.innovateuk.org/ourstrategy/innovationplatforms/stratified-medicine-.ashx>

Annex I: Recommendations

Informatics infrastructure, public engagement and capacity building in the healthcare system

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 Encyclopedia 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 II: Symposium programme

Job titles and affiliations are correct as at the time of the symposium (10–11 October 2012)

Day 1

Welcome and introduction

Professor Sir John Bell FRS HonFREng FMedSci

Where has the science taken us?

Pharmaceutical perspective

Professor Jonathan Knowles, Visiting Professor of Translational Medicine at the University of Oxford

Diagnostics perspective

Dr Iain Miller, Global Head of Personalized Healthcare Strategy and Partnerships at GE Healthcare

Current challenges, opportunities and solutions – presentations and discussion reviewing advance papers

The international regulatory environment

Dr Richard Barker OBE, Director of the Centre for the Advancement of Sustainable Medical Innovation

Pricing and reimbursement models: value for industry

Professor Adrian Towse, Director of the Office of Health Economics

Pricing and reimbursement models: value for health systems

Professor Lou Garrison, Associate Director of the Pharmaceutical Outcomes Research and Policy Program at the University of Washington (US)

Research and clinical infrastructure

Professor Andrew Morris FRSE FMedSci, Dean and Professor of Medicine at the University of Dundee and Chief Scientist for Scotland

Keynote speech

Professor Sir John Savill FRSE FMedSci, Chief Executive of the Medical Research Council

Day 2

Introduction and objective setting for breakout sessions

Professor Sir John Bell FRS HonFREng FMedSci

Breakout sessions

Facilitated breakout sessions – discussing solutions and pilot activities for:

- The international regulatory environment
- Pricing and reimbursement models – value for industry
- Pricing and reimbursement models – value for health systems
- Research and clinical infrastructure

Consolidation and closing remarks

Professor Sir John Bell FRS HonFREng FMedSci

Annex III: Symposium attendees

Job titles and affiliations are correct as at the time of the symposium (10–11 October 2012)

Dr Mark Bale Interim Director, Health Science and Bioethics, Department of Health

Dr Richard Barker OBE Director, Centre for the Advancement of Sustainable Medical Innovation

Dr J. Carl Barrett Vice President, Translational Sciences, Oncology Innovative Medicines Unit, AstraZeneca

Professor Sir John Bell FRS HonFREng FMedSci Chair of the Project's Oversight Group and Regius Professor of Medicine at the University of Oxford

Dr Graham Bell Lead Technologist in Stratified Medicine, Technology Strategy Board

Professor Sir Alasdair Breckenridge FRSE FMedSci Chair, Medicines and Healthcare products Regulatory Agency

Professor Chris Brightling MRC/ABPI Chronic Obstructive Pulmonary Disease consortium and Clinical Professor in Respiratory Medicine, University of Leicester

Dr Helen Campbell Portfolio Manager for Research Networks, Cancer Research and Clinical Research Facilities, NHS R&D National Cancer Programme

Professor Christopher Day FMedSci Pro-Vice-Chancellor of the Faculty of Medical Sciences and Professor of Liver Medicine, Newcastle University

Mr Simon Denegri Chair of INVOLVE and NIHR National Director for Public Participation and Engagement in Research

Mr Roland Diggelmann Chief Operating Officer, Roche Diagnostics

Dr Michael Doherty Global Head of Pharma Regulatory Affairs, Genentech

Professor Peter Donnelly FRS FMedSci Director, Wellcome Trust Centre for Human Genetics

Professor Lou Garrison Professor, Pharmaceutical Outcomes Research and Policy Program, University of Washington

Dr Alasdair Gaw Lead Specialist in Stratified Medicine, Technology Strategy Board

Dr Catherine Goddard Project Manager for the Kuwait-Scotland eHealth Innovation Network, University of Dundee

Dr Jeremy Haigh European Chief Operating Officer, Research & Development, Amgen Ltd

Dr Tim Hubbard Head of Informatics, Wellcome Trust Sanger Institute

Dr Ian Hudson Director of Licensing, Medicines and Healthcare products Regulatory Agency

Dr Alain Huriez Chair, The European Personalised Medicine Association

Professor Jonathan Knowles Professor of Translational Medicine at the Ecole Polytechnique Fédérale de Lausanne, Visiting Professor of Translation Medicine at the University of Oxford and Board Member at Cancer Research UK

Mr Kent Kost Head of Global Quality and Regulatory Affairs, Roche Diagnostics

Dr Mark Kroese Programme Director at the PHG Foundation, Public Health Adviser for the UK Genetic Testing Network, and member of the National Institute for Health and Care Excellence Diagnostics Committee

Dr Louise Leong Head of R&D, The Association of the British Pharmaceutical Industry

Dr Tom Lillie International Therapeutic Area Head for Oncology, Amgen Ltd

Dr Richard Malham Policy Officer, The Academy of Medical Sciences

Ms Mirella Marlow Programme Director for Devices and Diagnostics Systems, National Institute for Health and Care Excellence

Professor Joanne Martin Clinical Adviser to the NHS National Clinical Director for Pathology, Director of Academic Health Sciences and Professor of Histopathology at Barts and the London NHS Trust

Dr Nick Meadows Kinapse Life Sciences Consulting

Dr Iain Miller Global Head of Personalized Healthcare Strategy and Partnerships, GE Healthcare

Professor Andrew Morris FRSE FMedSci Dean and Professor of Medicine, University of Dundee and Chief Scientist for Scotland

Ms Candy Morris Senior Responsible Officer for Health Research Authority, Research Champion for the NHS, and Senior Consultant Strategic Projects for NHS South of England

Mr Alan Morrison Vice President, Regulatory Affairs, Amgen

Dr Helen Munn Executive Director, The Academy of Medical Sciences

Dr Marisa Papaluca Amati Section Head of Scientific Support and Projects,
European Medicines Agency

Dr Michele Pedrocchi Head of Global Business Development and Licensing, Roche Diagnostics

Professor Tim Peters Chair, Medical Research Council/National Institute for Health Research
Methodology Research Panel and Professor of Primary Care Health Services Research,
University of Bristol

Dr Duncan Purvis Stratified Medicines Technology Director, Integrated Medicines Ltd

Dr Rachel Quinn Director of Policy, The Academy of Medical Sciences

Professor Sir Michael Rawlins FMedSci Chair, National Institute for Health and Care Excellence

Professor Sir John Savill FRSE FMedSci Chief Executive, Medical Research Council

Dr Anna Schuh Head of Translational Molecular Diagnostics, Oxford Biomedical Research Centre

Professor Alan Silman FMedSci Medical Director, Arthritis Research UK

Dr Richard Smith CBE FMedSci Chief Executive, UnitedHealth Europe

Dr Stephen Spielberg Deputy Commissioner for Medical Products and Tobacco, US Food and Drug
Administration

Professor Sir John Tooke PMedSci President, Academy of Medical Sciences and Vice Provost
(Health), University College London

Professor Adrian Towse Director, Office of Health Economics

Dr Alice Tuff-Lacey Project Manager in Stratified Medicine, Cancer Research UK

Professor John Whittaker Vice President of Statistical Platforms and Technologies, GSK and
Professor of Genetic Epidemiology and Statistics, London School of Hygiene and Tropical Medicine

Ms Doris-Ann Williams OBE Chief Executive, British In-Vitro Diagnostics Association

Dr Penny Wilson Innovation Platform Leader for Stratified Medicine, Technology Strategy Board

Professor Sir Kent Woods FMedSci Chief Executive, Medicines and Healthcare products
Regulatory Agency

Dr Richard Wooster Vice President of the Cancer Metabolism Drug Performance Unit, GSK

Dr Naho Yamazaki Policy Manager, The Academy of Medical Sciences

Annex IV: Memberships of oversight, preparatory and review groups

Job titles and affiliations were correct at the time of the symposium (10–11 October 2012)

Oversight group

Professor Sir John Bell FRS HonFREng FMedSci (Chair) Regius Professor of Medicine, University of Oxford

Dr Richard Barker (Lead of preparatory group 1) Director, Centre for the Advancement of Sustainable Medical Innovation

Dr Graham Bell Lead Technologist in Stratified Medicine, Technology Strategy Board

Professor Lou Garrison (Lead of preparatory group 3 and member of preparatory group 2) Associate Director of the Pharmaceutical Outcomes Research and Policy Program, University of Washington

Dr Jeremy Haigh European Chief Operating Officer, Research & Development, Amgen Ltd

Dr Louise Leong Head of R&D, The Association of the British Pharmaceutical Industry

Dr Tom Lillie (Member of preparatory group 2) International Therapeutic Area Head for Oncology, Amgen Ltd

Dr Thomas Lönngrén (Member of preparatory group 1) Strategic Advisor, NDA Advisory Service Ltd

Dr Iain Miller (Member of preparatory group 2) Global Head of Personalized Healthcare Strategy and Partnerships, GE Healthcare

Professor Andrew Morris FRSE FMedSci (Lead of preparatory group 4) Professor and Dean of Medicine, University of Dundee and Chief Scientist for Scotland

Professor Adrian Towse (Lead of preparatory group 2) Director, Office of Health Economics

Dr Desmond Walsh Head of Infections and Immunity and Lead for Stratified Medicine, Medical Research Council

Members participating before the symposium

Mr Daniel O'Day Chief Operating Officer, Roche Pharmaceuticals

Sir Kent Woods FMedSci Chief Executive, Medicines and Healthcare products Regulatory Agency

Preparatory group 1: The international regulatory environment

Dr Richard Barker OBE (Lead) Director, Centre for the Advancement of Sustainable Medical Innovation

Dr Ian Hudson Director of Licensing, Medicines and Healthcare products Regulatory Agency

Mr Kent Kost Head of Global Quality and Regulatory Affairs, Roche Diagnostics

Dr Thomas Lönngren Strategic Advisor, NDA Advisory Service Ltd

Mr Alan Morrison Vice President, Regulatory Affairs, Amgen

Dr Marisa Papaluca Amati Section Head of Scientific Support and Projects, European Medicines Agency

Dr Stephen Spielberg Deputy Commissioner for Medical Products and Tobacco, US Food and Drug Administration

Preparatory group 2: Pricing and reimbursement models: value for industry

Professor Adrian Towse (Lead) Director, Office of Health Economics

Professor Chris Chamberlain Head of Companion Diagnostic Development in Personalised Healthcare and Biomarkers, AstraZeneca

Dr Tom Lillie Oncology International Therapeutic Head, Amgen Ltd

Dr Duncan McHale Vice President of Global Exploratory Development, UCB Pharma

Dr Iain Miller Global Head of Personalized Healthcare Strategy and Partnerships, GE Healthcare

Dr Michele Pedrocchi Head of Global Business Development and Licensing, Roche Diagnostics

Preparatory group 3: Pricing and reimbursement models: value for health systems

Professor Lou Garrison (Lead) Associate Director of the Pharmaceutical Outcomes Research and Policy Program, University of Washington

Professor Lon Cardon FMedSci Senior Vice President of Alternative Discovery and Development, GlaxoSmithKline

Sir Andrew Dillon Chief Executive, The National Institute for Health and Care Excellence

Professor Tim Peters Chair, Medical Research Council/National Institute for Health Research Methodology Research Panel and Professor of Primary Care Health Services Research, University of Bristol

Dr Richard Smith CBE FMedSci Chief Executive, UnitedHealth Europe

Preparatory group 4: Research and clinical infrastructure

Professor Andrew Morris FRSE FMedSci (Lead) Dean and Professor of Medicine, University of Dundee and Chief Scientist for Scotland

Dr Mark Bale Interim Director, Health Science and Bioethics Division, Department of Health

Dr J. Carl Barrett Vice President of Translational Sciences for Oncology Innovative Medicine, AstraZeneca

Dr Chris Corless Medical Director, Knight Diagnostic Laboratories and Cancer Pathology Share resource, Oregon Health & Science University.

Mr Simon Denegri Chair of INVOLVE and National Institute for Health Research Director for Public Participation and Engagement in Research

Professor Peter Donnelly FRS FMedSci Professor of Statistical Science and Director, Wellcome Trust Centre for Human Genetics

Dr Nic Dracopoli Vice President of Biomarkers Centocor R&D, Johnson & Johnson

Dr Alasdair Gaw Lead Specialist in Stratified Medicine, Technology Strategy Board

Dr Catharine Goddard Project Manager of Kuwait-Scotland eHealth Innovation Network (KSeHIN), University of Dundee

Dr Tim Hubbard Head of Informatics, Wellcome Trust Sanger Institute

Review Group

Job titles and affiliations were correct at the time of report review (March - April 2013)

Professor Susan Iversen CBE FMedSci (Chair) Emeritus Professor of Psychology, University of Oxford and Treasurer of the Academy of Medical Sciences

Professor Sir Alasdair Breckenridge CBE FRSE FMedSci *Formerly* Chair, Medicines and Healthcare products Regulatory Agency

Professor Anthony Culyer CBE FMedSci Professor of Economics, University of York and Ontario Chair in Health Policy and System Design at the University of Toronto

Professor Christopher Day FMedSci Pro-Vice-Chancellor of the Faculty of Medical Sciences and Professor of Liver Medicine, Newcastle University

This report was reviewed by an external panel appointed by the Council of the Academy of Medical Sciences. Reviewers were asked to consider whether the report met the terms of reference, and whether the evidence and arguments presented in the report were sound and supported the conclusions. Reviewers were not asked to endorse the report or its findings.

Secretariat

Dr Naho Yamazaki Policy Manager, Academy of Medical Sciences

Dr Richard Malham Policy Officer, Academy of Medical Sciences

Dr Rachel Quinn Director of Medical Science Policy, Academy of Medical Sciences

Annex V: Recent developments in stratified medicine

2009

1. The Association of the British Pharmaceutical Industry (ABPI): **The stratification of disease for personalised medicines**¹⁹⁰

The ABPI was invited to produce this White Paper by the Office for Strategic Co-ordination of Health Research and the Technology Strategy Board (TSB) to inform the TSB's focus in the life sciences. The benefits of the UK as a location for pioneering personalised medicine developments and the challenges facing this goal were broadly outlined, representing the views of ABPI R&D and medical community members. The challenges included 'the regulatory, reimbursement, information technology, intellectual property and economic environments', as well as patient privacy and education.

2. Fifth Forum of the Ministerial Industry Strategy Group, convened by the ABPI and the Medicines and Healthcare products Regulatory Agency (MHRA): **Personalised Medicine**¹⁹¹

'The Forum comprised representatives from patient groups, academia, the pharmaceutical industry, medicines regulators (representing UK, EU and US systems) and other Government officials concerned with medicines' pricing and reimbursement mechanisms and health technology assessments.' It recommended the following: that personalised medicine become a priority for regulatory bodies including the European Medicines Agency (EMA); that awareness/education campaigns be undertaken; that ethical implications of exclusion be considered; that incentives to develop diagnostics be developed; and that changes be made to regulation, licensing and health technology assessment (HTA).

3. House of Lords Science and Technology Committee: **Genomic Medicine**¹⁹²

The Committee sought to identify the state of progress in genomic medical research and how its translation into clinical practice could be facilitated. The report contains 54 recommendations, including the following: National Institute for Health Research (NIHR) to receive ring-fenced funding for a specific HTA programme for research into clinical utility and validity of genetic and genomic tests within the NHS; expand the remit of the National Institute for Health and Clinical (now Care) Excellence (NICE) to assess all genetic tests; Department of Health (DH) to commission NICE to provide clinician guidance for genetic testing; advocate EU reclassification of all genetic tests as 'medium risk' to ensure pre-market review of all tests; centralise all molecular pathology services in the NHS; Department for Business, Innovation & Skills (BIS) to address intellectual property issues associated with stratified medicine; DH to produce a national strategy to streamline medicine-diagnostic co-development; establish a new Institute of Biomedical Informatics to address data infrastructure issues; and introduce changes to the education of doctors and nurses.

¹⁹⁰ http://www.abpi.org.uk/_layouts/download.aspx?sourceurl=/our-work/library/medical-disease/Documents/The%20stratification%20of%20disease%20for%20personalised%20medicines.pdf

¹⁹¹ <http://www.mhra.gov.uk/home/groups/es-policy/documents/websitesources/con065593.pdf>

¹⁹² <http://www.publications.parliament.uk/pa/ld200809/ldselect/ldsctech/107/107i.pdf>

20104. PHG Foundation: **Public health in an era of genome-based and personalised medicine**¹⁹³

A meeting organised by the Foundation for Genomics and Population Health (PHG), detailed in this report, reached four conclusions. Firstly, that evidence needs to be collected to assess the utility and cost effectiveness of genomics approaches in public health; this will require training for clinicians. Secondly, that there should (at least initially) be a focus on disease areas that will result in a real impact on population health. Thirdly, that this effort should be international both to succeed and to ensure the benefits are available to the maximum amount of individuals. Finally, that care is needed to avoid overstating the potential of genomics to improve human health.

5. Medical Research Council (MRC)/ ABPI: **Initiatives to develop disease-focussed consortia**

The MRC and ABPI piloted three disease-focussed consortia in chronic obstructive pulmonary disease (COPD), rheumatoid arthritis and diabetes to bring together key experts from industry and academia to identify clinical and pre-clinical research priorities in areas such as biomarkers and disease stratification. Up to £17.5 million was allocated for investment across the consortia over five years, which represents a new working model for academic industry collaboration. The heart of each consortium is to develop deeper understanding of the patients, their phenotypes, disease strata and the mechanisms underpinning these strata.

6. The European Commission (EC) and European Federation of Pharmaceutical Industries and Associations (EFPIA): **Innovative Medicines Initiative (IMI)**¹⁹⁴

The IMI is a collaborative venture between the EC, European pharmaceutical companies, regulators, academia and patient organisations. Expert teams are pooling data and knowledge to tackle major challenges in pre-competitive drug research and development. The primary aims are to 'reinvigorate the European pharmaceutical industry and biopharmaceutical research, and to improve the health of patients' by finding solutions to some of the scientific challenges that hold up the search for new medicines. Project funding will total €2 billion over 10 years, provided jointly by the EC and EFPIA members. Two waves are underway with 23 projects in areas such as schizophrenia, rheumatoid arthritis, asthma, chronic pain, electronic health records, safety in qualifying biomarkers and standards for modelling and simulation tools. The third wave will include projects on autism, tuberculosis, diabetes and the safety of drugs and vaccines. A further focus is education and training.

7. Cancer Research UK (CRUK): **Stratified Medicine Programme** (ongoing)¹⁹⁵

CRUK is working with a number of industrial partners and the TSB to establish the foundations for a national stratified medicine programme for cancer. Phase 1, due to finish in July 2013, involves developing the pathology, informatics and consent frameworks. Work so far suggests that centralisation of diagnostic testing may be attractive to ensure quality and utilise economies of scale. Phase 2 is expected to include development of funding structures for diagnostics (currently paid for mostly by sponsors) and mechanisms for research access to the accumulated clinical data. See Box 2.

193 <http://www.phgfoundation.org/reports/6617/>

194 <http://www.imi.europa.eu/>

195 <http://science.cancerresearchuk.org/research/how-we-deliver-our-research/others/by-programme/stratified-medicine-programme/>

8. **Publication of proposals for the 8th EU Framework Programme for Research and Innovation (Horizon 2020)**¹⁹⁶

The EU's new programme for funding research and innovation will run from 2014 to 2020 with an €80 billion budget. Funding of stratified medicine research was mentioned in the proposals for the new framework.

2011

9. Committee on A Framework for Developing a New Taxonomy of Disease; National Research Council of the National Academies: **Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease**¹⁹⁷

The Committee derived from the American National Academies of Science was charged with exploring the need for and feasibility of 'a New Taxonomy of human disease based on molecular biology' and to develop a potential framework for creating one. The report outlines a long-term and intentionally broad framework for developing the infrastructure needed to collect and analyse sufficient data to boost and future-proof understanding of molecular pathology, and to exploit its use in healthcare. The Committee calls for a 'ground-up' approach accompanied by centralised strategic oversight.

10. TSB: **Stratified Medicine Innovation Platform** (ongoing)¹⁹⁸

The TSB published a strategic vision for making the UK the world leader in development and adoption of stratified medicine, and a detailed 'roadmap' to achieve this.¹⁹⁹ The innovation platform comprises seven partner organisations, who together are investing around £200 million over five years. This is mainly through funding projects to do the following: foster collaboration; establish NHS pathways for stratified medicine; develop biomarkers for key diseases; and develop models for intellectual property, value and reimbursement that incentivise innovation. The partner organisations are the following: TSB, Arthritis Research UK, CRUK, DH, MRC, NICE, and the Scottish Government Health Directorate.

11. MRC: **Stratified Medicine Initiative** (ongoing)²⁰⁰

Building on the MRC/ABPI initiative above (no. 5), the MRC is now funding £60 million over four years to develop UK-wide research consortia that are each focused on a specific disease area, in order to stratify that disease and develop a deeper understanding of the mechanisms underpinning the stratification. Initial priority was given to proposals that focus on diseases where an existing therapy exists as a driver for stratification. The consortia had to build upon existing scientific and clinical expertise as well as clinical research infrastructure, and have significant links with industrial partners. Each consortium had to provide a dynamic platform for research that will create future opportunities for further funding and collaboration. Shortlisted proposals included hepatitis C, asthma, rheumatoid arthritis and Gaucher's syndrome, while development workshops were funded in seven other disease areas to help build the consortia.

196 http://ec.europa.eu/research/horizon2020/pdf/proposals/proposal_for_a_regulation_of_the_european_parliament_and_of_the_council_establishing_horizon_2020_-_the_framework_programme_for_research_and_innovation_%282014-2020%29.pdf

197 http://www.ucsf.edu/sites/default/files/legacy_files/documents/new-taxonomy.pdf

198 <http://www.innovateuk.org/ourstrategy/innovationplatforms/stratified-medicine-.ashx>

199 https://connect.innovateuk.org/c/document_library/get_file?p_l_id=1720995&folderId=5719347&name=DLEF-53533.pdf

200 <http://www.mrc.ac.uk/Newspublications/News/MRC008547>

12. MRC/ABPI: **COPDMAP consortium**²⁰¹

Building on the MRC/ABPI initiative above (no. 5), COPDMAP brings together academia and industry at early stages of research and development to stratify their approach to the disease. The collaboration is undertaking biomarker, mechanism and target identification, as well as clinical trials.

13. PHG Foundation: **Next steps in the sequence: The implications of whole genome sequencing for health in the UK**²⁰²

The outcome of a year-long project, involving multiple stakeholders, to evaluate the implications of whole genome sequencing for health services. This followed a House of Lords Genomic Medicine inquiry above (no. 3), which identified the need for a strategy in the implementation of genomic technologies in the NHS. Recommendations include the following: implementation of next-generation sequencing in a clinically targeted manner; development of clinical bioinformatics expertise; development of clear, rational and transparent commissioning pathways; and development of clinical guidelines for healthcare professionals.

14. MRC: **E-Health Informatics Research Centres** (ongoing)²⁰³

A consortium of 10 UK Government and charity funders, led by the MRC, has invested £19 million to establish four E-Health Informatics Research Centres (eHIRCs) in London²⁰⁴, Manchester, Dundee and Swansea. The Centres opened in May 2012 and will harness the wealth of UK electronic health records, such as those available through the Clinical Practice Research Datalink (item 17) to improve patient care and public health. The four Centres will investigate a wide range of conditions that place a huge burden on the UK population, including diabetes and obesity, cardiovascular disease, cancer and child and maternal health. To strengthen this initiative, the funders have agreed to support an eHIRC Network, which will come into operation in mid 2013.

201215. Human Genomics Strategy Group: **Building on our inheritance: Genomic technology in healthcare**²⁰⁵

The Group was established in response to the House of Lords Genomic Medicine inquiry above (no. 3). This report makes recommendations for achieving the Group's strategic vision for the use of genomics in UK healthcare. These include the following: the development of a government strategy for genomics in healthcare; the development a centralised open data repository by DH, BIS and others; specific roles for NHS England in delivering genomic medicine; provision of high-quality training for action by DH and others; and development of socially acceptable consent mechanisms by the government.

201 <http://www.copdmap.org/>

202 <http://www.phgfoundation.org/pages/wholegenome.htm>

203 <http://www.mrc.ac.uk/Fundingopportunities/Calls/E-healthCentresCall/MRC008159>

204 <http://www.ucl.ac.uk/chapter>

205 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_132382.pdf

16. PHG Foundation: **Genomics in Medicine**²⁰⁶

This report summarises a 2011 Royal College of Physicians workshop, organised by the Joint Committee on Medical Genetics, which considered the practicalities of implementing genomic approaches in multiple clinical specialties. The UK Genetic Testing Network and NHS National Genetics Education and Development Centre were also involved in the workshop. Recommendations covered the following: the importance of training, both of clinicians and of commissioners; the requirement for multidisciplinary expert groups to sit formally within clinical commissioning groups; and the continuation of the UK Genetic Testing Network as the main testing network.

17. Roundtable on Translating Genomic-Based Research for Health Board on Health Sciences Policy; Institute of Medicine of the National Academies: **Genome-Based Therapeutics: Targeted Drug Discovery and Development – Workshop Summary**²⁰⁷

This is a report of a March 2012 workshop, whose purpose was to 'examine the general approaches being used to apply genomic-based research results to the discovery and development of new drugs, the successes achieved so far, and the challenges ahead.' The report does not contain any substantive recommendations, but provides a contemporary analysis of stratified drug development, including the current landscape, case studies, the role and impact of emerging technologies, the evolving paradigms for stratified drug development, and the critical need for collaborative strategies. It concludes with a comment that the key to development of stratified medicines is the scientific knowledge of molecular pathologies.

18. MHRA/NIHR: **Clinical Practice Research Datalink (CPRD)** (ongoing)²⁰⁸

A continually developing observational and interventional research service allowing researcher access to linked UK healthcare datasets. It is funded by the MHRA and the NIHR, and was launched in March 2012. It has incorporated, and builds upon, the General Practice Research Database.

19. UK Biobank: **UK BiLEVE (UK Biobank Lung Exome Variant Evaluation)** study²⁰⁹

A collaborative research study was launched in November 2012, which will use anonymous data from 50,000 UK Biobank participants to investigate the relationship between genetic variants and susceptibility to COPD.

20. MRC: **Stratified Medicine Initiative** (ongoing)²¹⁰

Building on the MRC initiative (no. 11), £10.6 million of funding was announced for three consortia in December 2012:

- Hepatitis C (STOP-HCV, led by the University of Oxford)
- Rheumatoid arthritis (MATURA, led by Queen Mary, University of London, and the University of Manchester)
- Gaucher's syndrome (GAUCHERITE, led by the University of Cambridge).

Other disease areas will soon be competing for funding.

206 <http://www.phgfoundation.org/reports/12093/>

207 <http://www.iom.edu/Reports/2012/Genome-Based-Therapeutics-Targeted-Drug-Discovery-and-Development.aspx>

208 <http://www.cprd.com/intro.asp>

209 <http://www.ukbiobank.ac.uk/wp-content/uploads/2012/11/Lung-disease-COPD-MRC.pdf>

210 <http://www.mrc.ac.uk/Newspublications/News/MRC008947>

21. Formation of the **European Alliance for Personalised Medicine**²¹¹

A coalition of professional and patient advocacy groups seeking to 'improve patient care by accelerating the development, delivery and uptake of personalised medicine and diagnostics.' The coalition makes the following recommendations: promote a regulatory environment that is conducive to early patient access; increase personalised medicine research and development; recognise novel approaches to reimbursement and public health assessment; and increase awareness and understanding of this approach.

22. European Science Foundation: **Personalised Medicine for the European citizen – towards more precise medicine for the diagnosis, treatment and prevention of disease**²¹²

Report of a foresight exercise that investigated 'issues affecting development and implementation of personalised medicine' in Europe. The ethical, legislative and regulatory challenges, as well as the organisational considerations, raised by developments in personalised medicine were considered by a wide range of stakeholders through a series of sequential workshops on technology, application to different disease areas, and issues shaping the future of personalised medicine. This report contains a substantial number of recommendations concerning the following: data handling; models and decision-making processes; interdisciplinary and translational research; and infrastructure and governance. Furthermore, the report outlines steps to be undertaken over the next 5, 10 and 20 years in medical adoption, analysis and information technology development, and integration.

23. HM Government: **NHS pilot of whole genome sequencing**²¹³

In December 2012, £100 million of government funding was announced for the following:

- Training a new generation of genetic scientists and the wider healthcare workforce in genomic medicine.
- Pump priming whole genome sequencing for up to 100,000 patients with cancer or rare diseases, including development of the associated NHS data infrastructure.

2013

24. Secretary of State for Health position on NHS data infrastructure²¹⁴

Jeremy Hunt outlines in a speech his desire to ensure that the NHS is 'paperless by 2018'.

25. Health Science Scotland: **Stratified Medicine Scotland Innovation Centre (SMS-IC)**

(ongoing)

The Scottish Funding Council and private investors have pledged nearly £15 million for the creation of a cross-sector innovation hub to be based at the new Glasgow South Hospital. By bringing together industry with academic researchers and clinicians, the centre will act as an accelerator for new developments in genomics, biomarker and companion diagnostics, and bioinformatics products. The project's primary objectives are to create a world-leading centre for stratified clinical trials, and develop a new translational bioinformatics platform that will enable the effective clinical delivery of stratified medicine and care pathways at the patient, clinician and health system level. The SMS-IC will invest in developing academic entrepreneurs

211 <http://euapm.eu/>

212 http://www.esf.org/uploads/media/Personalised_Medicine.pdf

213 <http://www.number10.gov.uk/news/dna-tests-to-fight-cancer/>

214 <https://www.gov.uk/government/news/jeremy-hunt-challenges-nhs-to-go-paperless-by-2018--2>

in stratified medicine and provide industry-led postgraduate courses in applied genomics and bioinformatics.

26. Formation of the **Professional Record Standards Body (PRSB)** (April 2013)

This new standards body was created to promote a UK-wide common standard for the structure and content of health and social care records. The PRSB will work with the NHS, the Health and Social Care Information Centre, and professional and patient organisations to establish national standards for the recording and retrieving of data, and support the implementation of these standards.

27. Implementation of 2011 **NHS reforms** (April 2013)

The new NHS structure detailed in the 2012 Health and Social Care Act came into force in April 2013, comprising a central NHS England, Public Health England, NHS Trust Development Authority, Health Education England and over two hundred Clinical Commissioning Groups.

28. **NIHR Diagnostic Evidence Co-operatives** (May 2013)²¹⁵

This £4 million funding was shared across four NHS organisations in London, Leeds, Newcastle and Oxford. These centres will promote research into medical tests for the diagnosis of a wide range of diseases and bring together experts and specialists from across the NHS and industry.

29. Development of **Academic Health Science Networks** (May 2013)²¹⁶

Organisations that will provide 'a more systematic delivery mechanism for diffusion and collaboration within the NHS by building strong cross boundary networks'. They will do this by aligning 'education, clinical research, informatics, training and education and healthcare delivery' and improving 'patient and population health outcomes by translating research into practice and developing and implementing integrated healthcare systems'. Fifteen Academic Health Science Networks have been designated and licensed, and are expected to become fully operational in October 2013.

30. **MRC-NIHR Phenome Centre** (June 2013)²¹⁷

MRC and NIHR have funded £10 million to two universities – Imperial and King's College London – to develop the Olympics testing laboratory into a national facility to study genetic and environmental factors in disease. It aims to be a centre of excellence in targeted and exploratory high-throughput metabolic phenotyping, assay development and computational medicine.

215 <https://www.gov.uk/government/news/four-million-pounds-of-funding-to-improve-diagnosis-of-diseases>

216 <http://www.england.nhs.uk/2013/05/23/acc-health-sci-ntwrk/>

217 <http://www1.imperial.ac.uk/phenomecentre/>

Forthcoming/current events of potential relevance31. MRC-funded **Farr Health Informatics Research Institute**

This will build on the scientific programmes of the eHIRCs, by developing new partnerships with the NHS, industry and academia and creating a digital infrastructure to enable safe sharing of health datasets across regional boundaries.

32. Leopoldina: **Personalised Medicine** (late 2013)²¹⁸

The German National Academy of Sciences Leopoldina, using a broad academic working group, is preparing a statement based on a November 2011 workshop. This will outline 'aspects of the field including the technological foundations, the applicability of personalisation strategies in clinical practice, the structural preconditions, the likely impact on compensation systems, as well as the many ethical, legal, and economic issues involved.'

33. Introduction of **Value-Based Pricing (VBP)** (January 2014)²¹⁹

DH consulted on a 'new value-based approach to the pricing of branded medicines' during 2011. VBP is scheduled to be implemented in 2014, replacing the Pharmaceutical Price Regulation Scheme. Although negotiations defining specifics of the approach are continuing between DH and industry, VBP could represent a more flexible reimbursement framework with scope to better stimulate innovation.

34. Developments in revision of the **EU Clinical Trials Directive (Regulation)**²²⁰

The EU published a proposed Regulation in July 2012 that is now passing through the EU legislative process.

35. Developments around the introduction of a **EU Data Protection Regulation**

The EU published a proposed Regulation in January 2012 that is now being considered by the Council of Ministers and Members of the European Parliament.

36. Developments around the **EU 'In Vitro Diagnostic Medical Devices' Directive (Regulation) (98/79/EC)**²²¹

The proposed Regulation was published on 26 September 2012. This will have EU-wide implications for the regulation and approval of in vitro diagnostics, including commercially developed and 'in house' tests.

²¹⁸ <http://www.leopoldina.org/en/policy-advice/working-groups/personalised-medicine/>

²¹⁹ http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/consultations/liveconsultations/dh_122760

²²⁰ <http://www.europarl.europa.eu/oeil/popups/ficheprocedure.do?reference=2012/0192%28COD%29&l=en>

²²¹ http://ec.europa.eu/health/medical-devices/documents/revision/index_en.htm, specifically http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_541_en.pdf

Annex VI: Glossary

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| Adverse drug reaction: | A noxious and unintended response (e.g. organ failure, insomnia, or hair loss) resulting from the use of a drug within the accepted therapeutic or diagnostic dosage range. When applied to instances in which dosage may not yet have been established (e.g. pre-approval, new indication) the term encompasses adverse responses resulting from any dose of the drug. |
| Analytical performance: | See Box 3. |
| Antibody: | Antibodies are a class of protein generated by the immune system that recognises a substance (i.e. an antigen) with high affinity and specificity. Antibodies are widely used tools in research and in diagnostics. More recently, they have been developed as therapeutic agents. |
| Antigen: | Substance whose presence stimulates the production of antibodies. |
| Biobank: | A repository of biological materials (e.g. blood, biopsy samples) for research use. 'UK Biobank' refers to an ongoing multi-stakeholder project which has collected and stored biological samples from a large cohort of volunteers whose health will be followed over the years to come. |
| Bioinformatics: | Multi-disciplinary approach concerned with the electronic storage, retrieval and interrogation of biological data such as genetic information. |
| Biomarker: | Biological feature that can be objectively measured and can be used to establish disease risk, disease presence and/or guide therapeutic decisions such as patient stratification. This might be, for example, the presence of a protein variant or a change in its level. |
| Biopsy: | Medical test involving the removal of a patient's cells or tissues for observation. |
| CE (Conformité Européenne) marking: | Mark that indicates a product's compliance with EU legislation. This marking is mandatory for the marketing of a product within the EU. For certain categories of medical devices, verification by a Notified Body is required before they can be sold within the EU with a CE mark. |

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| Chemotherapy: | Refers to treatment with chemical that kills rapidly dividing cells (e.g. platinum-based drugs such as cisplatin). This form of intervention is commonly administered in the treatment of cancer as the disease is characterised by rapid cell division. |
| Chronic disease: | Long-lasting medical condition that, in some instances, can persist over the remaining life of the affected individual (e.g. arthritis, diabetes, HIV/AIDS and cancer). Such conditions can require extensive patient management and care, and are major contributors to mortality. |
| Clinical evidence: | See Box 3. |
| Clinical performance/ clinical validity (<i>evidence</i>): | See Box 3. |
| Clinical utility (<i>evidence</i>): | See Box 3. |
| Data protection: | Refers to the protection of data pertaining to identifiable people, its collection, storage and dissemination. |
| Diagnostic: | Medical device intended for the detection of the presence or level of a biomarker which is informative for diagnosis, prognosis or treatment. Whereas targeted diagnostics monitor a particular marker (such as many companion diagnostics), panel diagnostics assay a range of potentially informative markers. |
| Digital pathology: | An image-based environment which allows the analysis, consultation and management of data acquired through the automated digitisation of microscopy glass slides. |
| DNA: | Deoxyribonucleic acid. A double-stranded molecule consisting of nucleic acids whose sequence directs the development and function of an organism through the production of ribonucleic acids (RNAs) and, through RNA intermediates, proteins. DNA can direct its own replication and serves as the repository of genetic information in living organisms. |
| Electronic health record: | A comprehensive register of digitised personal health information which can be securely accessed and shared across multiple healthcare environments, facilitating information transfer among healthcare practitioners. |

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| Epigenetic: | ('above' or 'over' genetics) Inheritable characteristic affecting gene expression which does not result from alterations of the underlying DNA sequence. Mechanisms of epigenetic control include the methylation of DNA and the modification of histones (structural proteins that package DNA). |
| Expression (<i>gene</i>): | Process by which a cell's genetic information is used to generate a gene product. This commonly refers to the production of proteins whose composition and structure is directed by a gene's DNA sequence via an RNA intermediate. Expression analysis measures not only the presence of, but also the quantity of, specific gene product(s). |
| First-in-class: | A product (in this case a drug or diagnostic) possessing a new and unique feature. For example, this can be a novel mechanism by which a drug treats a medical condition. |
| Genealogy: | The study of the familial lineages. |
| Genome sequencing: | Determination of the sequential order of nucleotide bases within a DNA sample. The older Sanger sequencing method is performed on amplified DNA fragments thus does not necessarily reflect sample heterogeneity; this bias does not apply to whole genome sequencing. |
| Generic drug/diagnostic test: | A product that is comparable to an existing branded one in content and indication, and relies on the regulatory approval given to the original product for market access. In the case of drugs, generics typically arise following the end of exclusivity granted by patent protection and can be produced by anyone. |
| Genetic variant/variation: | Refers to the genetic differences present in populations. Such differences arise from the presence of alternative forms of a gene or combinations thereof, or variation in the numbers of copies present; only a subset of genetic variation is relevant to disease states. |
| Gene: | A unit of heritable information. This refers to a stretch of DNA that encodes either a protein or an RNA strand that has a function within the organism. |
| Genome, genomic: | The totality of the hereditary information of an organism or cell, and the study thereof. In general, there is little variation in the genome of cells from the same organism; cancerous tissues are a relevant exception. |

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| Genotype: | The genetic makeup of an organism or cell, sometimes with respects to a particular gene. When used as a verb, it refers to the determination of the status of particular genetic markers. |
| Genome-wide association study: | Study in which the catalogue of genetic variants present in patient and control populations is compared to identify variants associated with the risk of a particular disease. |
| Half-life (radiation): | The time taken for a radioactive isotope to halve its radioactivity through decay. Each isotope has a different, but consistent, half-life. |
| Heterogeneity: | A lack of uniformity. In diagnostic samples, this refers to the presence of a feature in only a subset of the cells sampled. Tumour-derived samples can often be highly heterogeneous. |
| Immunohistochemistry: | Analytical technique in which a thinly sliced tissue sample is treated with a labelled antibody that binds to a marker, revealing its presence. |
| Indication: | Circumstance(s) in which the use of a particular medical intervention is deemed advisable or necessary by a regulatory body. |
| In-house test: | A test that has been manufactured by, and is destined for use within, a single health institution. Such tests are currently exempt from the requirements of EU medical devices Regulations, notably the need to provide evidence of analytical performance. |
| <i>In vitro</i>: | ('in glass') Said of processes using biological materials that have been isolated from their surroundings. |
| Kinase: | A class of catalytic protein. Kinases have important regulatory functions in cellular processes such as cell division, signalling, and metabolism. They act by rapidly and reversibly modifying other proteins. |
| Linkage study: | Study in which the genotypes of related individuals from families affected by an inherited disease are compared to identify genetic markers present in those who develop the disease, but not their healthy relatives. Markers identified through such studies are not necessarily the cause of the disease; they are merely associated with the physical segment of the genome linked to the inheritance of the disease state, and thus serve to narrow down the region of the genome in which the gene of interest may be present. |

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| Longitudinal: | Refers to data captured from an individual or population over an extended period. |
| Marker: | See Biomarker. |
| Metabolite: | A small molecule intermediate or product of metabolism; the ensemble of chemical processes necessary for life. |
| Metabolomic: | The systematic study of the metabolites present in a sample – this can be indicative of ongoing cellular processes potentially including disease states. |
| Microarray: | A platform used in the detection of variations in the levels of nucleic acid sequences (DNA or RNA) between samples, or of the presence of known sequence variants. As microarrays rely on probes for detection, only known variants can be monitored. |
| Molecular biology: | Branch of biology concerned with the underlying molecular basis of biological phenomena. |
| Molecule: | Level of organisation of matter consisting of two or more atoms. |
| Mutation: | Alteration to the DNA sequence of the genome: this can be a substitution, an insertion, a deletion, a rearrangement or a change in the number of copies. |
| Notified body: | Organisation nominated by a European Member State, and notified by the European Commission, to provide services for conformity assessments in support of European Conformity (CE) marking. In the UK, the Medicines and Healthcare Products Regulatory Agency is the competent authority tasked with designating notified bodies to carry out conformity assessments under the EU Medical Devices Directive. |
| Oncogene: | A gene that, under certain circumstances, can drive cancer formation. |
| Pathology: | The study and diagnosis of disease, in particular its causes, processes, development, and consequences. |

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| PCR/qPCR: | Polymerase chain reaction. A laboratory technique used to amplify DNA sequences selectively. Quantitative PCR (qPCR) refers to a variant of the method in which the amount of amplified sequence is monitored over successive amplification cycles: it is used to assess the abundance of a sequence of interest. |
| Personalised medicine: | A medical model in which medical care is customised to individual patients. The term encompasses and surpasses genomic, stratified and precision medicine, the latter term referring to the targeting of treatments to the specific elements driving the pathology in a patient at that particular point in time. |
| Phenotype: | The observable traits of an organism. The phenotype is influenced both by genetic and by environmental factors, and their interaction. |
| Polygenic disease: | Disease for which multiple genes can influence the pathology or risk factor. |
| Probes: | A molecular tool capable of detecting an analyte for which it has been demonstrated to possess both high sensitivity and selectivity. |
| Protein, proteomic: | Large molecule composed of one or more long chains of amino acids (polypeptides). Proteins are an essential part of living organisms, both as structural and as functional components of all body tissues. Proteomic refers to the large-scale study of the complement of proteins within a sample. |
| Quality-adjusted life years (QALYs): | A metric used in cost-utility analysis to assess the value of a particular intervention. The analysis takes into account the increase in longevity expected from a given treatment and the anticipated quality of life during these additional life-years. |
| Quality assurance: | Activities implemented with a view to ensuring that a service or product meets the desired level of quality, for example, ensuring that reagents used to carry out a diagnostic test meet purity standards. |
| Radioactive tracer: | A radiation-containing compound or molecule that can be used to monitor or visualise a biological process. |

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| Radiotherapy: | The use of ionizing radiation in medical treatment. This intervention results in localised and extensive DNA damage; it is typically applied in oncology. |
| Randomisation: | In the context of clinical trials, the process of randomly allocating trial participants to either the group receiving the treatment (or diagnostic) option under investigation or a control group. This process helps minimise the risk of allocation bias and the impact of confounding variables. |
| RNA: | Ribonucleic acid. Nucleic acid whose synthesis is templated by DNA. RNA has various functional roles, which include the following: protein production, gene regulation, catalysis, and that of structural component. Small interfering RNAs and microRNAs are part of a subclass of RNAs known to affect gene expression; there are efforts underway to develop these as therapeutic agents. |
| Scientific validity (evidence): | See Box 3. |
| Sequencing: | Determination of the sequential order of nucleotide bases within a sample. The older Sanger sequencing method is performed on amplified DNA fragments thus does not necessarily reflect sample heterogeneity; this bias does not apply to whole genome sequencing. |
| Small molecule compound: | A class of drugs and probes that is chemically synthesised and defined by its small size. |
| Stratified medicine: | A medical model that uses the grouping of patients according to disease risk or likely treatment response, as determined by diagnostic tests, to determine the course of care. Stratified medicine is a component of personalised medicine. |
| Symptom: | The manifestation of a clinical state or disease which is subjective and observable by the patient (e.g. nausea, pain or lethargy). This is in contrast to a sign which is a feature observed which can be objectively observed by a clinician (e.g. elevated blood pressure). Certain manifestations such as rashes can be considered to be a sign, a symptom or both. |
| Taxonomy: | The science of classification. Traditionally, the taxonomy of human diseases drew upon signs and symptoms, but biomedical advances have led to calls for this classification to reflect the underlying molecular basis of a patient's disease. |

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| Therapeutics: | Medicinal agent used in the treatment of disease or for improving well-being. This term encompasses biologically and chemically derived agents such as antibodies and small molecule compounds, respectively. |
| Tissues: | Level of cellular organisation consisting of cells of similar origin and, in some instances, non-cellular material. Organs comprise several types of tissue. |
| Tumour: | Lesion characterised by increased size or swelling. Although not synonymous, the term is often used to refer to a cancerous growth. |

Abbreviations and acronyms

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| ABPI | Association of the British Pharmaceutical Industry |
| BIS | Department for Business, Innovation & Skills |
| CAT | X-ray computed tomography |
| CBER | Centre for Biologics Evaluation and Research (FDA) |
| CDER | Centre for Drug Evaluation and Research (FDA) |
| CDRH | Centre for Devices and Radiological Health (FDA) |
| CE | Conformité Européenne (European conformity) |
| CLIA | Clinical Laboratory Improvement Amendments (US) |
| COPD | Chronic obstructive pulmonary disorder |
| CPRD | Clinical Practice Research Datalink |
| CRUK | Cancer Research UK |
| DH | Department of Health |
| DNA | Deoxyribonucleic acid |
| EBI | European Bioinformatics Institute |
| EMA | European Medicines Agency |
| ENCODE | Encyclopaedia of DNA Elements |
| ESRC | The Economic and Social Research Council |
| FDA | Food and Drug Administration (US) |
| GDP | Gross domestic product |
| HGSG | Human Genomics Strategy Group |
| HSCIC | Health and Social Care Information Centre |
| HTA | Health technology assessment |
| IHT | 'In-house' test |
| IVD | <i>In vitro</i> diagnostic |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MRC | Medical Research Council |
| MRI | Magnetic resonance imaging |
| NAS | National Academy of Sciences (US) |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NIH | National Institutes of Health (US) |
| NIHR | National Institute for Health Research |
| NSCLC | Non-small cell lung cancer |
| OFT | Office of Fair Trading |
| PET | Positron emission tomography |
| PCR (qPCR) | Polymerase chain reaction (quantitative) |
| PPRS | Pharmaceutical Price Regulation Scheme |
| QALY | Quality-adjusted life year |
| RNA | Ribonucleic acid |
| TSB | Technology Strategy Board |
| VBP | Value-based pricing |





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