

# STRATIFIED MEDICINES: THE FUTURE OF HEALTHCARE



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**Today if you are unlucky enough to develop an epileptic seizure you and your doctor will be left with a dilemma. You have a 1 in 3 chance of having another one. Is it worth treating you? The first line medicines were discovered over 20 years ago and have significant side-effects. On balance you will probably not be treated but if you do have a second seizure you will get one of the first-line medicines. You could spend the next 18 months trying different medicines and combinations until you get the one that works for you. That's two and a half years where your disease is not being treated and you could have more seizures.**

That is the reality today: but imagine a day when, after the first seizure, you get a blood test in the hospital and you are told that your risk of having another seizure is 90 per cent and that there is a medicine which will best treat you (say, levetiracetam) for which you need the normal dose. Yes you have epilepsy, but the uncertainty is removed and you can be sure you have the most likely treatment to work. Your risk of having a seizure and hurting yourself is as low as it can be, leading to greater quality of

life for you and minimum impact on the healthcare system.

Stratified medicines will allow us to do just that. Along with significant discoveries such as antibiotics, statins and HIV therapies, stratified medicines are set to transform healthcare in the next wave of pharmaceutical innovation. Alongside the next generation of innovative medicines will come diagnostic tests, which will much more accurately predict to whom the medicine should be given. This future is not far away, as we are already seeing the first wave of these stratified medicines come into the NHS – mainly to treat cancer, but therapies in other areas such as neuroscience are also being developed.

## PERSONALISED OR STRATIFIED MEDICINES

Stratified medicines enable us to target treatments specifically to patient subpopulations, identifying those with the greatest chance of benefit and the lowest risk of suffering adverse events. Called personalised medicine or personalised healthcare in the US, it is better known as stratified medicine in the UK, to avoid confusion with individualised healthcare. Many organisations here have adopted the definition by PCAST: it is 'not about creating medicines unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side-effects for those who will not'.<sup>1</sup>

It also involves the development and use of companion diagnostics to achieve the best outcomes in the management of a patient's disease.

Why the excitement? Current treatments can often only be designed to work across the board – in, say, between 30 and 60 per cent of patients on average. However as our insight into human biology in health and disease advances, we come to understand on the one hand, the heterogeneity of disease conditions, and on the other hand, heterogeneity amongst human population in response to medicine based on their physiological makeup, which can be defined at the pharmacological level. With this understanding comes the opportunity to use our medicines much more effectively, benefiting patients, the NHS and paving the way for further research.

Many pharmaceutical companies are embracing a stratified approach in medicine development, and we predict that analysts will see an increasing proportion of stratification emerging through the pipeline. This is made possible by the advancement of technology and the ability to build in predictive and stratifying biomarkers, as well as improved molecular understanding of disease pathways.

## RIGHT MEDICINE, RIGHT PATIENT, RIGHT TIME, RIGHT DOSE

Simply put, whether patients respond to a particular treatment,

may in part depend on the subtype of disease that they have (and therefore whether the target in the disease pathway that the medicine was designed to attack is relevant to the disease subtype); or their response to treatment, as in the example above; or their propensity to an adverse reaction. Therefore any that can target treatment more precisely would mean patients taking the right medicine at the right time that will give the best therapeutic benefit and avoid unnecessary side-effects.

## BIOMARKERS

The advent of stratified medicine is due to advances in science and technology, which is leading to an increase in the discovery of biomarkers – simply, biological measures of patient samples that can indicate disease progression, prognosis, or treatment response, for example. Some are physiological functions that can be detected by imaging scans. There are many types of biomarkers, and many ways in which they can be deployed in medicine development. Their central role in stratified medicine centres around predicting response to treatment. Biomarkers can also be developed into companion diagnostics for use with stratified medicines. Biomarker science is a highly complex area of research and for any promising avenue, thousands of possible biomarkers

Today if you develop Non-Small Cell Lung Cancer (NSCLC) you will have a choice of traditional chemotherapy with carboplatin/paclitaxel or newer therapies which are targeted against a protein called epidermal growth factor receptor (EGFR). The choice is vital as, when the new medicine works, it is significantly better than chemotherapy and has fewer side-effects. However get the choice wrong and the medicine may not help you at all. The decision is based on a change (mutation) in the gene for EGFR which switches the receptor to a permanently on state. The activating mutations are only present in 10-15 per cent of patients with NSCLC, but if they are you can now get a better safer medicine.

emerge. The challenge is to identify, qualify and validate the right ones that will prove useful. Hence, continued investment is vital to ensure that the science develops.

Researchers investigating biomarkers to establish specificity and relevance require access to tissue samples and well-phenotyped patient cohorts. Many tissue samples donated by patients sit in individual laboratory collections, and there would be value in creating a nationwide register, with the appropriate governance and consents, to enable researchers to know where to look for them. Continued investment in biomarker science is vital in order to drive the science base needed to enable stratified medicine.

## SMARTER WIRING-UP

Integrated health informatics offers rich potential for research in stratified medicine, with the right governance, anonymisation and controls. For example, better data linkages would enable researchers to establish associations between genotype and clinical phenotype. Talent in informatics and biostatistics in the UK must be built up to harness this potential. Government's recent commitment to link primary, secondary and tertiary electronic health records is encouraging in this regard. Access to biological databases (eg – omics, imaging information) would similarly be helpful. Further, a larger linking up of systems with pharmacies, such as has been done by a number of health systems in the US, would expedite use of stratified medicines in the real world.

The use of stratified medicines in the clinic is multidisciplinary, beyond a linear physician-patient relationship. Other experts in the healthcare chain are required to work with the clinician, such as experts in pathology and diagnostics. A good illustration of how this can work in practice has been demonstrated by INCa (Institut National du Cancer) in France, along with indicators of value derived for the health provider.<sup>2</sup>

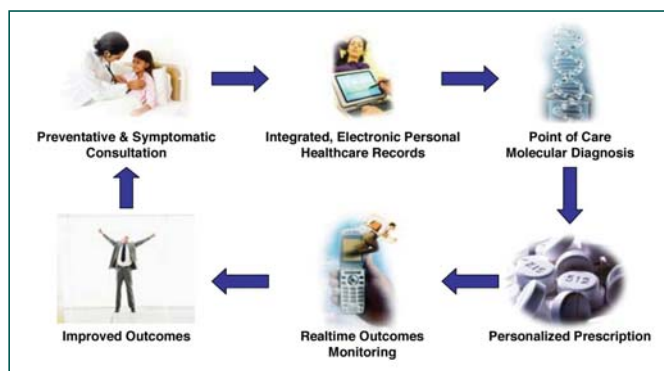


Figure 1 – What it's all about: Integrated healthcare in the service of the patient<sup>3</sup>

## PARTNERSHIPS

Improved understanding of biological pathways and biomarkers is crucial to enable stratification. The knowledge base underpinning this comes from scientific research in both academia and industry. Enhanced collaboration across sectors will be key to accelerating the development of stratified medicine. To this end, a number of multi-partner initiatives have been launched recently:

- The 5-year £50 million Stratified Medicine innovation platform coordinated by the Technology Strategy Board;
- MRC-ABPI research consortia in respiratory and inflammatory joint disease, and in diabetes;
- MRC £60 million 4-year research initiative in stratified medicine;
- Cancer Research UK Stratified Medicine initiative with AstraZeneca, Pfizer and TSB to lay foundations for standardised, high quality, cost-effective genetic testing of tumours.

## REGULATORY IMPLICATIONS

In line with stratified medicine, recruitment into clinical trials of the appropriate patient subpopulations most likely to respond to the treatment under investigation will involve enriched but smaller trial populations. While it is hoped that this would generate more efficient trials, it will nonetheless impact on trial design and statistical analysis. Regulatory (MHRA) data requirements for trial and licensing dossiers for more

traditionally designed drugs will need to be adjusted to be relevant to stratified medicine. Regulator engagement with new science and technology is therefore critical, to provide clear and appropriate guidance to trial developers. At EU level, we anticipate draft revision of the IVD (*in vitro* diagnostic) Directive. The commitment to an earlier access scheme announced by Government in December's *Strategy for UK Life Sciences* will be helpful.

Unsurprisingly, most experience thus far lies in retrospective qualification of companion biomarkers after the launch of a new medicine. This is a fast-moving field with multiple tests and it is here that medicine developers face burdensome hurdles to regulatory acceptance. Streamlined and harmonised regulatory requirements would help to benefit patients by removing the barriers to stratified medicines getting onto the market.

## THE FUTURE

It is clear that concerted action is needed across multiple policy areas for the UK to be an attractive location to develop and use stratified medicine. We are seeing new developmental models, with a range of alliances of pharmaceutical and diagnostic companies and academics across life science sectors to develop stratified medicines (eg the cancer drugs crizotinib, developed by Pfizer with a companion diagnostic co-developed by Abbott; and gefitinib developed by AstraZeneca and companion test developed by DxS).

In the UK, the development and implementation of an integrated stakeholder strategy in stratified medicine will bring benefits to patients, but also prescribers, payers, and regulators; it may also improve the efficiency and productivity of developing new treatments, and enhance UK competitiveness and attractiveness for drug and diagnostic research and development. On this front, we have intensively engaged on the development of an integrated stratified medicine approach over an extended period, working closely with a range of partners such as:

- The diagnostics sector
- Research funders
- Regulators
- Healthcare providers and policymakers
- Health informatics programmes
- Health economists

In summary, medicines can only be of use if they actually get to patients. With stratified medicines set to become a reality, we must ensure that we have the appropriate reimbursement frameworks in place. The cost of developing these medicines will reflect the additional complexity of stratification in combination with the development of companion diagnostics, and stratified medicines will be used by a smaller patient base. Future Health Technology Assessment (HTA) and reimbursement systems will need to be sensitised to this in order to value these developments appropriately and incentivise future research.

### Footnotes:

- 1 US President's Council of Advisors on Science & Technology (PCAST).
- 2 *Personalized medicine – a nationwide initiative for an equal access to cancer treatment in France.* [http://ec.europa.eu/research/health/pdf/event06/13052011/fabien-calvo\\_en.pdf](http://ec.europa.eu/research/health/pdf/event06/13052011/fabien-calvo_en.pdf)
- 3 *The stratification of disease for personalised medicines: Research driven recommendations and the rationale for a UK stakeholder alliance.* April 2009 <http://www.abpi.org.uk/industry-info/future/Documents/SDfPM%20final%202009-04-16%20.pdf>