Developing stratified medicines in the UK

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The UK holds a favourable position in the development of stratified medicines through strong scientific innovation, robust biotechnology and pharmaceutical industries and comparatively simple regulatory and reimbursement processes. Strong features such as its health technology agency and socialised healthcare system enable innovative medicines, including those requiring stratification for oncology and infectious disease, to be rapidly assessed for effectiveness and value to UK patients. However, our recent observations with a variety of UK healthcare stakeholders suggest that certain features require improvement if the favourable position in stratified medicines development, and consequential beneficial outcomes to patients, is to be sustained and indeed further enhanced to a position of pre-eminence. Key changes suggested are (a) to remove healthcare silos and enable multi-disciplinary teams to translate scientific and medical innovation into best practice; (b) to expand the UK skill base in certain disciplines including medical pathology, health economics and clinical informatics; and (c) to use successful pilot cases of stratified medicines to better educate stakeholders in a drive for a change in healthcare culture. Through this cultural change, the UK would offer healthcare based on prediction and prevention rather than symptom-based diagnosis and reactive treatment.

The contrasting assessments of targeted cancer therapies by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), particularly the

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requirements for predictive diagnostic testing, and the fact that the UK competent authority, the Medicines and Healthcare-related products Agency (MHRA), is most often used for EMA assessments, suggested to us that the UK may well be an excellent location to develop stratified medicines. Add to this that the UK healthcare is delivered predominantly by a single entity, the National Health Service (NHS), and that UK also piloted the use of health technology agencies, namely the National Institute for Health and Clinical Effectiveness (NICE), to assess the value of innovative medicines, then the UK seems to merit a pre-eminent position in producing new treatments that target the right patients, at the right time, at the right dose and at the right cost. To explore this hypothesis – that the UK is an excellent place to develop stratified medicines[♣] – we engaged key stakeholder groups, representing healthcare providers, healthcare regulators, the pharmaceutical & diagnostics industries, UK government and patients, to consider our proposition and to identify what additional factors would enhance the pre-eminence of the UK in this field.

From the Scientific / Technology perspective, stakeholders believe that the availability of suitable technology and engineering, while occasionally a problem, is not a key limiting factor. The bigger issue is one of translation, and not just vertically from the bench to the bedside, but also horizontally from academic clinical research into applied clinical research in pharmaceutical and diagnostic companies. The collection, annotation and accessibility of clinical data, while also securely managed were also viewed as important. To drive better translation and data integration, this stakeholder group viewed innovative, multi-disciplinary collaborations as essential vehicles to success. **The clinical/ medical perspective** also supported the development of better integrated and less siloed multi-disciplinary teams but also recognised that some key skills to contribute to such teams were limited. Clinical pathologists, molecular geneticists and informaticians seemed to be particularly under-represented in our healthcare systems. There was also a recognition that some stratified medicines would benefit from *in vivo* imaging modalities, and so the contribution of physical sciences, as well as medical

[♣] This was our working hypothesis but is intended to have a broader meaning than just developing pharmaceuticals, e.g., translating the research into routine patient benefits for positive health outcomes.

scientists, in disease areas such as chronic lung disease (asthma, COPD) and neurodegenerative disease (Alzheimer's, Parkinson's) should be encouraged by broadening of training and educational activities. Open innovation projects, such as the cancer genome sequencing initiative, remedy this for oncology, but COPD, infectious disease and CNS disorders should be considered too as areas of unmet need for stratified medicines. It was also recognised that stratified medicines should not be viewed merely as one therapeutic or one diagnostic test per therapy area, but rather a menu of medicines for a variety of sub-conditions guided by the objective use of testing to support clinician decision-making. Long-term benefits of appropriate stratified treatments could lead to additional benefits such as reducing the impact of co-morbidities. Investment to encourage such multidisciplinary approaches would serve as pilot cases to demonstrate the wider value of a stratified medicines strategy and to counter concerns over cost-of-goods around the diagnostic, the medicine or the combination. Core to this activity is access to appropriate prospective and retrospective clinical samples through co-ordinated clinical studies and/ or proactive tissue biobanking.

The regulatory/ reimbursement perspective also highlighted on the need to reduce silos, but with a particular focus on the budgetary aspects that then impact on the reimbursement of approvable stratified medicines. Budgetary silos pre-dominate in the NHS and could start to be removed through educational fora that facilitate more open communication; however, radical changes in structure and *modus operandi* between departments are also key. Open communication would also benefit government where the Department of Health would facilitate connectivity to other Departments, e.g., Work and Pensions, as well as agencies within its jurisdiction such as MHRA, NICE and the NHS. Indeed, the co-ordination of a number of agencies is essential if the regulation, pricing and reimbursement of stratified medicines and associated technologies are to be coherent. There were also a number of concerns around the budget planning process where a longer-term vision for improvements to patient healthcare through better targeting of medicines does not meet shorter-term targets of individual NHS departments. The need for evidence-generating health econometric studies was hindered in part by physical and temporal silos, but also in part by a skills gap in health economics and associated

informatics skills. The role of NICE in assessing the value of stratified medicines and companion diagnostics remains key and indeed a stronger link between evaluation and procurement would be a key driver in pricing and reimbursement of stratified medicines. **The socio-political perspective** on stratified medicine identified the need for a cultural change in the practice of healthcare in the UK and beyond, from reactive treatment-seeking for symptomatically-diagnosed illness to pro-active maintenance of good health or management of pre-symptomatic disease. To achieve this cultural change, a widespread programme of patient, physician and provider education and multi-disciplinary collaboration was essential and may represent *the* key near-term investment need. Such educational activities could also be supported by educational grants from industry, as well as from government agencies, and should focus on ensuring long-term change rather than short-term fixes alone. Delivering this broad educational agenda would serve to both remove silos and provide purpose for collaborative relationships. Piloting such educational activities would seem an appropriate position from which the UK can further consolidate its lead role in stratified medicine development.

The recommendations from our discussions with stakeholders on enhancing the UK position as an excellent place to develop stratified medicines are thus:

- Reduce silos through collaborative relationships across the healthcare industry
- Seek to fill skills gaps in key areas through targeted recruitment and/ or training
- Develop a co-ordinated multi-stakeholder education programme based on evidence from well-managed pilot cases
- Ensure that UK healthcare evolves into prediction and prevention through risk stratification and early treatment

The primary data supporting these recommendations and the analysis of this data in the form of a SWOT matrix can found in the Appendices.

Appendices

Appendix 1 – Primary Data Collected

Scientific/ technical forum
Key points:

- Why do projects aimed at stratification fail? Undoubtedly some fail because of cost-of-goods issues either around the diagnostic, the medicine or the combination.

- The thought was that projects fail because of engineering issues rather than from a "lack of good technology".

- Technology also needs to be built into clinical trials in order to provide more data about individual patients, the more information the better. Cancer genome sequencing (CRUK initiative) may remedy this.

- Which diseases will really benefit from stratification? COPD, infectious agents, neurodegenerative disorders and cancer (obviously!). Need to link academic R&D in biomarkers with pharma pipelines.

- Data management is important as much from a public relations perspective as from a technology development one (see comments in medical/clinical section).

- Non biological markers may exist in the future e.g., imaging, physical properties of cells etc, so physical sciences must be part of stratified medicines debate. **Silos need to be broken down**.

- Open innovation needs to include science, policy, insurers/payers, universities, regulators, clinicians globally as well as just UK.

- Patient benefit needs to be communicated and stratification needs to reflect this and not just commercial gain/cost savings.

Clinical / Medical Forum
Key points:

- The **physicians are becoming increasingly engaged** – previously, especially in oncology, they were of the view that "one size fits all." The last 5 years have seen a big change, mainly through the successful use of drugs such as herceptin.

- Still some people are **resisting** the move towards stratified medicine – mainly hospital managers, but some physicians as well, due to **the increased complexity**

that is not reimbursed. Payment By Results has introduced a distortion into the system which is to the detriment of adoption of the stratified approach.

- The **driver for the implementation of stratified medicines is mainly financial**, and who is going to pay? Any diagnostics must either save the NHS money, or be cost neutral.

- **Logistics**, (patient needing referral across different hospitals and departments), **infrastructure** (removal and storage of tissue) and **skills** (lack of clinical pathologists) are also **barriers**.

- Data management, which is a major issue, can be resolved without the need for a centralised database. This can be addressed via **federated databases**, where a database is developed collaboratively and then franchised to partners. This has been done for the International Cancer Genomes Project in Ontario.

- The **need for a multidisciplinary approach is clear**. There is increasing collaboration, but the key players who need to be working together "on the ground" include the physician, the technologist, the health economist, the clinical pathologist and the Primary Care Trust.

- A **fully resourced pilot is needed in the UK**, to fund studies and justify the case for significant investment, ideally where the stakeholders are already in close proximity to each other.

Regulatory / Reimbursement Forum
Key points

- What are the boundaries of stratified medicine – we did not attempt to define these but it was recognised that strat med does not have to be linked to a therapeutic

- The challenge of silos came through very strongly – silo budgets, especially in the NHS, silo governance (e.g. insufficient discussion between DH and Work and Pensions) and silo R&D activities. It was noted that there is little if any dialogue between the Rx and Dx/Medical Devices regulatory bodies/groups.

- How do we get high quality data that we can have confidence in?

- How do we get high quality samples for research etc?

- Do we need altered/improved bioinformatic capabilities to collate and analyse disparate data more appropriately? Who will fund the data mining?

- Data are imperative for health econometrics studies. How can we access data easily whilst maintaining the appropriate level of confidentiality and data security.

- We have a shortage of health economists and a shortage of data for them to model. High quality health econometrics studies are imperative.

- Medco is mining data to better understand opportunities – what cohorts benefit from what medicines .....

- The impact of improving an individual's health often goes further than improving the illness for which they are seeking treatment – it can delay the onset of co-morbidities. This important angle tends to be ignored in modelling.

- A question was raised as to whether pharma would be able to charge more for a "stratified medicine" to make up for any lost profit arising from being able to give the drug to just a percentage of people. Many felt this would not be justified or necessary but the question arose a few times.

- Will stratifying medicines mean that regulation will be more lengthy? If so will pharma be able to recoup its investment before the product comes off patent?

- What mechanisms can we put in place to begin to look at cost savings that may help to pay for strat med and other new and innovative technologies?

- Who is the customer, who pays, who saves?

- We aren't good at revisiting an individual's treatment regime especially for chronic diseases – can we have systems in place to help here? i.e. we should be more proactive in stratifying patients already on therapy and improving their quality of life.

- Can NICE/should NICE have more power where companion Dx are concerned? Will legislation (perhaps driven by the US) mean that pharma has no choice but to go down the strat med route.

- As with other disruptive technologies a need to link evaluation and procurement – should be discussed with NICE etc

- In theory the UK should be a great place to carry out strat medicine trials but how do we make it happen?

- Fear is often an inhibitor – with new healthcare paradigms healthcare providers are pushed out of their comfort zones.

- Are there lessons still to be learnt from Herceptin? It was offered for two years by BUPA before it entered the NHS.

Political / Societal Forum
Key points

- Captured in statements above

Appendix 2 – SWOT analyses

Key points:

Strengths	**Weaknesses**
People are starting to work together and recognise the value and need for a multidisciplinary approach and eliminate silos	There are "blocks" in the system (which is in itself very complex) – eg infrastructure, logistics, reimbursement etc.
A shift in business models within big pharma is leading to a higher efficacy rate within certain patient groups	Some resistance from physicians and hospital managers
Traditionally innovative academic base in UK	Lack of leadership in the past (although this is changing)
A socialised, free at the point of delivery healthcare system in the UK	A successful pilot does not necessarily lead to full implementation, especially if not properly resourced, with the stakeholders in close geographical proximity to each other
Science base	IT connectivity
Willingness of funders (RCs, charities, DH, TSB) and other bodies (OLS/LSD) to at least talk about the issues	Pathways for parallel development Rx and Dx interactions
Exemplars eg DxS	Value vs cost of development especially for Dx companies
NHS infrastructure	Access to drugs eg gold standard Rx
Strong large pharma and Dx (imaging)	Pathways for exploitation from academic through commercial product. Unrealistic expectations of academia in terms of technology licensing
Opportunities	**Threats**
There is an opportunity to engage an increasingly educated physician network and public in the UK	There is a limited health envelope, with finite resources (diagnostics must save money or be cost neutral)
Federated databases following a franchised model removes the need for a central database	Patients have variable disease pathways, and may make different choices about the management of their condition – some may opt not to use a stratified approach
As the costs of genomic sequencing come down, there is the potential to genetically profile patients on admission to the NHS	The process of stratification is currently slow and complex with two few clinical pathologists to support demand – this is likely to worsen in future, especially I service demand increases
Early predictive tests can help drive the disease management strategy	UK skills gap and cost cutting government
Partnering	Cost to NHS could increase unless the value of Stratification is demonstrated early

Focussed approach via disease are or theme	SM may not be equitable in application, some populations may benefit more than others. Patient education needed
Better or faster outcomes through collaborative approach	Failure of IT support
	International competition eg USA/NL
	Industry (Dx or Rx or both) needs a culture shift as does academia