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Sustaining development of stratified medicines in the UK healthcare system: a commentary

The UK healthcare system holds a favorable position in the development of stratified medicines through strong scientific innovation, robust biotechnology and pharmaceutical industries and comparatively simple regulatory and reimbursement processes. Organizations such as its robust health technology assessment agency, the NICE and its mature socialized healthcare system, the National Health Service, enable innovative medicines, including stratified treatments for cancer and infectious disease, to be rapidly assessed for their effectiveness and value to patients in the UK. However, our recent observations with a variety of UK healthcare stakeholders suggest that certain features need to be improved if the favorable position in stratified medicine development, and consequential beneficial outcome to patients, is to be sustained and indeed further enhanced to a position of pre-eminence. Key changes suggested are removing healthcare silos and enabling multidisciplinary teams to translate scientific and medical innovation into the best practice; expanding the UK skill base in certain disciplines including medical pathology, health economics and clinical informatics; and using successful pilot cases of stratified medicines to better educate stakeholders in a drive to change healthcare culture. Through this cultural change, the UK would offer healthcare based on prediction and prevention rather than symptom-based diagnosis and reactive treatment.

KEYWORDS: integrated translational science ■ multidisciplinary budgets ■ stakeholder education ■ stratified medicine

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Commentary & research methods

The contrasting assessments of targeted cancer therapies by the European Medicines Agency (EMA) and the US FDA, illustrated by differing initial requirements for predictive KRAS testing for cetuximab and panitumumab [1], and the fact that the UK competent authority, the Medicines and Healthcare products Regulatory Agency (MHRA), is most often used as a reference for EMA assessments, suggests that the UK may well be an excellent location to develop 'stratified medicines'. Stratified medicines are used with groups of patients with similar disease or response characteristics, and is a separate concept to personalized medicine in which the characteristics of individual patients are considered. Add to this the fact that the UK healthcare is delivered predominantly by a single entity, the National Health Service (NHS), and that the UK piloted the use of health technology assessment agencies, namely the 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, with 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 and diagnostics industries, UK government and patients, in a parallel workshop format to consider our proposition and to identify what additional factors would enhance the pre-eminence of the UK in this field. Note that our hypothesis is intended to have a broader meaning than just developing pharmaceuticals, for example, translating the research into routine patient benefits for positive health outcomes. The basis of our stakeholder selection is illustrated by the value net represented in FIGURE 1. The affiliations and panel assignments are indicated in FIGURE 2; the panels were integrated for an open forum discussion following parallel sessions.

Workshop panel summaries

The primary raw data from workshop panels is provided in the APPENDIX section (www.futuremedicine.com/doi/suppl/10.2217/pme.11.50) and is distilled in the following section to capture key points of discussion.

- The scientific/technology perspective panel believed that the availability of suitable technology and engineering, while occasionally a problem, is not a key limiting factor. In technology and engineering assessments, the panel

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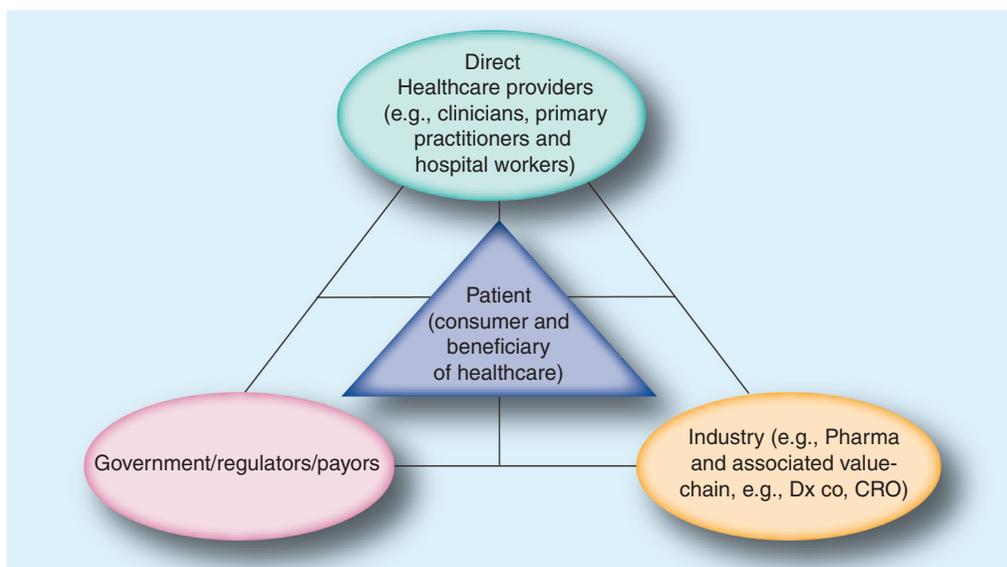


Figure 1. Healthcare stakeholders value net.
 CRO: Contract research organization; Dx: Medical diagnostic test.
 Reproduced with permission from [101].

considered various diagnostic formats (e.g., molecular, immunoassay and point-of-care) and supporting modules (e.g., sample/tissue preparation, microfluidics and detection). 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 securely managed were also viewed as important. To better drive translation and data integration, this stakeholder group viewed innovative, multi-disciplinary collaborations as essential vehicles to success.



Figure 2. Discussion fora and contributing organizations.
 †Horizon Discovery; Eagle Genomics; Illumina Cambridge Ltd; University of East Anglia; Business Link Advisory Service; Medical & Healthcare Regulatory Authority; Cambridge Enterprise Limited; Health Tech & Medicines KTN; Cambridge Enterprise; Sanger Institute; Philips; ONE NUCLEUS; Integrated Medicines; LAB21; Fulcrum Pharma; Bepak; Portsmouth Hospitals NHS Trust; Qiagen; Health Enterprise East; Thomson Reuters; Biolatris Ltd; Technology Strategy Board; Department of Health; BH Regulatory Consulting; EMA; ATPBio Ltd; Department Health; NWRDA; Pharmivation Ltd; British Consulate.

- The clinical/medical perspective panel also supported the development of better integrated and less siloed multidisciplinary teams; however, they also recognized that some key skills required 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 scientists, in disease areas such as chronic lung disease (e.g., asthma and chronic obstructive pulmonary disease) and neurodegenerative disease (e.g., Alzheimer's and Parkinson's) should be encouraged by broadening training and educational activities. Open innovation projects, such as the cancer genome sequencing initiative, remedy this for oncology; however, chronic obstructive pulmonary

disease, infectious disease and CNS disorders should also be considered as areas of unmet need for stratified medicines. It was also recognized 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 subconditions guided by the objective use of testing to support clinician decision-making. The long-term benefits of appropriate stratified treatments could lead to additional benefits such as reducing the impact of comorbidities. Investing in multidisciplinary approaches would provide pilot cases that could demonstrate the wider value of a stratified medicines strategy and to counter concerns about cost of goods of the diagnostic, the medicine or the combination. Core to this activity is access to appropriate prospective and retrospective clinical samples through coordinated clinical studies and/or proactive tissue biobanking.

Strengths

- People are starting to work together and recognize the value and need for a multidisciplinary approach and to eliminate silos
- A shift in business models within big pharmaceutical companies is leading to a higher efficacy rate within certain patient groups
- Traditionally innovative academic base in the UK
- A socialized, free at the point-of-delivery healthcare system in the UK
- Science base
- Willingness of funders (e.g., RCs, charities, DH and TSB) and other bodies (OLS/LSD) to at least talk about the issues
- Exemplars (e.g., DxS/Qiagen Ltd)
- NHS infrastructure
- Strong large pharmaceutical and Dx (imaging)

Opportunities

- There is an opportunity to engage an increasingly educated physician network and public in the UK
- Federated databases following a franchised model remove the need for a central database
- As the costs of genomic sequencing come down, there is the potential to genetically profile patients on admission to the NHS
- Early predictive tests can help drive the disease management strategy
- Partnering
- Focused approach via disease and/or theme
- Better or faster outcomes through collaborative approach

Weaknesses

- There are blocks in the system (which is in itself very complex, e.g., infrastructure, logistics and reimbursement amongst others)
- Some resistance from physicians and hospital managers
- Lack of leadership in the past (although this is changing)
- 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
- IT connectivity
- Pathways for parallel development of Rx and Dx interactions
- Value versus cost of development, especially for Dx companies
- Access to drugs (e.g., gold standard Rx)
- Pathways for exploitation from academia through to a commercial product. Unrealistic expectations of academia in terms of technology licensing

Threats

- There is a limited health envelope, with finite resources (diagnostics must save money or be cost neutral)
- 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
- The process of stratification is currently slow and complex with too few clinical pathologists to support demand – this is likely to worsen in the future, especially if service demand increases
- UK skills gap and cost-cutting government
- Cost to the NHS could increase unless the value of stratification is demonstrated early
- SM may not be equitable in application and some populations may benefit more than others. Patient education is needed
- Failure of IT support
- International competition (e.g., USA and The Netherlands)
- Industry (Dx or Rx or both) needs a culture shift as does academia

Figure 3. Strengths, Weaknesses, Opportunity, Threat (SWOT) analyses. DH: Department of Health; Dx: Medical diagnostic test; OLS: Office for Life Science; NHS: National Health Service; RCs: Research councils; Rx: Proprietary prescription medicines; SM: Stratified medicine; TSB: Technology Strategy Board.

- The regulatory/reimbursement perspective panel also highlighted 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 predominate in the NHS and could start to be removed through educational fora that facilitate more open communication; however, radical changes in the structure and *modus operandi* between departments are also key. Open communication, involving shared and readily accessible pertinent information, would also benefit the government where the Department of Health would facilitate connectivity to other departments, for example, work and pensions, as well as agencies within its jurisdiction such as the MHRA, NICE and NHS. Indeed, the coordination 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 regarding the budget-planning process in which 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 the pricing and reimbursement of stratified medicines.
- The sociopolitical perspective panels views 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 proactive maintenance of good health or management of presymptomatic disease. To achieve this cultural change, a widespread program of patient, physician and provider

education and multidisciplinary collaboration is essential and may represent the crucial 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 both to remove silos and provide a purpose for collaborative relationships. Piloting such educational activities appears to be an appropriate position from which the UK could further consolidate its lead role in stratified medicine development.

Conclusion & recommendations

Conclusions were captured through a strengths, weaknesses, opportunity, threat analysis, reproduced in FIGURE 3, which was constructed during an open discussion in the second phase of the workshop. The strengths, weaknesses, opportunity, threat analysis guided the open forum of stakeholders to then determine which of the various key points should be captured in a series of recommendations.

The consensus 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 coordinated multistakeholder education program based on evidence from well-managed pilot cases.

The enactment of these three key points should ensure that the UK healthcare evolves into a system that uses stratified medicines in such a way that prediction and prevention of disease, through risk stratification and early treatment, offers a more proactive and appropriate means of managing health, as opposed to the current system of treating illness. While

Executive summary

- To sustain leadership and gain pre-eminence in development and utilization of stratified medicines, UK healthcare stakeholders must consider:
 - Better integration of budgets and personnel to support multidisciplinary research;
 - Expanding the skill base in many disciplines associated with translational research, but particularly pathology, informatics and health economics;
 - Driving wider education of all stakeholders group in terms of the benefits to be gained by stratified medicines;
 - Publicising key demonstrator case studies to illustrate the benefits to be gained from integration, up-skilling and education;
 - Establishing a forward-looking implementation plan to support the above considerations.

much is made of targeted therapies for infectious disease and cancer, the broader implications for other disease areas have been broadly recognized [2].

Financial & competing interests disclosure

Edward Blair and Belinda Clarke are associates of a company that carries out consultancy work in the area of stratified medicine. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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