Stratified Medicine: a call for action

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Introduction

Stratified medicine is an innovative treatment concept based on the use of genetic or other molecular information to select the best therapeutic strategy in order to improve health outcomes, such as effectiveness and safety, for a targeted group of patients sharing similar biological characteristics.

The purpose of this paper is to give an overview of stratified medicine (also called personalised medicine or precision medicine), by describing what the anticipated benefits and major issues are and, ultimately, making recommendations to ensure a smooth transition towards this new paradigm. It is aimed to sensitise and to bring together all the stakeholders in the Belgian health care system in an effort to lay the foundation for and facilitate the implementation of this new form of medicine. The stakeholders in Belgium include specialists, general practitioners as well as other frontline health care professionals, regulators, patients, mutual insurance companies, the National Institute for Health and Disability Insurance (NIHDI), federal institutions like the Belgian Health Care Knowledge Centre (KCE), the Belgian Scientific Institute for Public Health (known as WIV-ISP) and the Federal Agency for Medicines and Health Products (FAMHP), BELAC (Belgian Accreditation Organization), the Superior Health Council (CSS), the VIB (a life sciences research institute), the Universities, the research community, the Belgian Cancer Center, diagnostics manufacturers, patient organisations, public health experts and pharmaceutical companies, to name a few.

Stratified medicine: the key concepts

The latest advances in science have resulted in major developments in molecular biology, leading to the emergence of a new approach to health care. Stratified medicine leverages these advances to create better diagnostic tools and targeted therapeutics. Put simply, the one-size-fits-all standardised or empirical approach is replaced by a group-specific disease management strategy based on the recognition that specific molecular aberrations responsible for the disease process (e.g. carcinogenesis) can be managed by specific drugs or approaches.

In the past, therapeutic strategies were mostly based on traditional diagnosis of disease and only rarely on biomarkers such as for example the oestrogen receptor (ER) in breast cancer. With the stratified approach, the efficacy of the treatment relies primarily on the successful correlation of differential patient response to a biological marker. The so-called bio-

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markers – defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses" – are the cornerstone of stratified medicine as they allow identifying a patient subpopulation likely to show a response to a specific treatment or to progress more rapidly or to be more sensitive to adverse events. These markers may be cellular, biochemical or genetic.

Anticipated benefits

The anticipated benefits of stratified medicine are numerous. Patients will receive more targeted treatments with the increased confidence that these will offer the best positive therapeutic effects. As for the clinicians, they will be able to prescribe tailored therapies avoiding poor efficacy or excessive toxicity, and ensuring better clinical outcomes. Stratified medicine also promises attractive health economics for the payers who will be able to optimise the allocation of resources in relation to the improvement in health outcomes. And, more generally, the whole health care system will benefit as this new approach will make available a lot more data on precise usage and outcomes, promoting further development in drug development and clinical practice.

1. Patient populations segmentation and care efficiency

Targeted diagnostics and therapeutics aim to offer "the right treatment for the right person at the right time", thus improving patient outcomes. This is undoubtedly the major benefit of stratified medicine. The much more precise segmentation of patient population is a tremendous and promising step forward as a specific patient population will only be matched with the therapy known to yield optimal results.

While stratified medicine offers higher chances of treatment success due to this targeted approach, it should be noted that, in some cases, the optimal available choice is no treatment – thus preventing patients who are predisposed to adverse drug reactions to receive a potentially harmful treatment and consequently avoiding needless cost to society. Sometimes, "this drug is not for everyone" means "… not everyone including you".

Some precision medicines are already on the market, mainly in the field of oncology which is undoubtedly at the forefront of stratified medicine. For instance, trastuzumab (Herceptin) is a breast cancer therapy only effective in tumours that reveal an overexpression of the human epidermal growth factor Receptor 2 (HER2) protein – an indicator of an aggressive form of cancer that is responsive to treatment by the drug. Another example of precision medicine is Imatinib mesylate (Gleevec), a tyrosine-kinase inhibitor (TKI) used to treat people with chronic myelogenous leukaemia (CML) and Gastrointestinal Stromal Tumours (GISTs). In these examples, a molecular test shows which patient will benefit most from therapy (a positive predictive biomarker). In other settings, a biomarker excludes patients from certain therapies as with K-ras mutation and absence of benefit from EGFR inhibitors (cetuximab, panitumumab) in colorectal cancers.

2. Predictive responsiveness

Currently, drugs are prescribed empirically based on studies regarding patient history, physical assessment and available diagnostic tests (laboratory or imaging), which are performed to confirm or exclude specific diagnoses. Stratified medicine complements this traditional practice in most cases by using biomarkers analysis to link a patient with a specific therapy. As a result, clinicians can prescribe with more confidence a treatment proved superior to patients with the appropriate genotype, while using standard therapy for those without the genotype. The best example is the outstanding tumour responses to EGFR TKIs (gefitinib, erlotinib) in non-small cell lung cancers harbouring activated EGFR mutations.

3. Transparent medical decisions

In today's empirical treatment approaches, drugs are prescribed on the basis of the corresponding indication for use. With stratified medicine, the treatment selection is becoming even clearer as it is based on evidence from, for example, biomarkers or molecular imaging, thus allowing for a more transparent prescription relying on the use of molecular screening and tools.

4. Cost-effectiveness

With the ageing population and the development of new innovative drugs, health care costs are rising dramatically. And there is a need to optimise the availability and the quality of health care provision at a reasonable cost. While the current system is not sustainable in the long run, stratified medicine offers the potential for better investment to payers, as it will

be easier to allocate resources in relation to a clear improvement in outcomes.

Although stratified medicine implies limiting the potential number of patients for a specific drug, stratified medicine would potentially benefit from higher adoption rates and longer treatment duration, due to their superior clinical performance. Also, a faster drug development cycle and the reduced number of patients in clinical trials might eventually optimise the costs of discovery, development and marketing. It is thus hoped that stratified "biomarkers driven" medicine can reduce the costs of developing new drugs. With the development of appropriate biomarkers, older active ingredients, that had been abandoned during earlier drug development, could be given a second therapeutic life, by using them only with those patients that benefit.

All in all, stratified medicine could help avoid many inefficiencies (e.g. failure of clinical trials, ineffective approaches, expensive treatments, hospitalisations due to adverse drug reactions), leading most probably to a more cost-effective and sustainable use of the health care budgets.

Challenges

Although stratified medicine is offering dramatic potential, the pathway toward achieving implementation of this "disruptive innovation" in clinical practice is a journey fraught with many pitfalls – including establishing the clinical validity of the associations between disease and a genetic/genomic variant (discovery), using novel clinical trial designs to validate the potential predictive biomarkers (validity), demonstrating the positive impact on public health (clinical utility and cost-effectiveness), and promoting the acceptance and uptake of stratified medicine in clinical care pathways (implementation).

The challenges also include supporting implementation research, promoting a better standardisation of data collection systems, creating a flexible regulatory framework, and ensuring adequate pricing and reimbursement of diagnostic tests and drugs.

1. Stakeholder awareness and expectations

Gene-drug interactions are complex, and responses may be variable. Patients may arrive with false expectations, ignoring that treatment access and efficacy depend on these complex interactions. With the stratified medicine approach, certain characteristics must be present for the selection of therapeutic options. In some cases, stratified medicine might not yield better results than conventional therapy. All depends on the predictive performance and the accuracy of the diagnostic test (as well as other genetic variables) that identifies the patient populations likely to benefit or not from targeted therapies. Indeed, if a test shows a negative result, but the test is not sufficiently accurate, it may be that treatment with the targeted drug is denied whereas the patient could have benefited from it. Even with tests showing a high sensitivity (the % with which the patients that can benefit from treatment are identified as such) and specificity (the % with which the patients who will not benefit from treatment will be identified as such), success is not guaranteed. If there is no biomarker or if its clinical validity is not sufficiently established, then there is no way to link a therapy to a patient subpopulation. In such cases, standard treatment based on empirical research might still be the best therapy option.

2. Research development pathway

Currently, there is a consensus that the timeline for drug development is too slow, from lengthy preclinical research to old-design clinical trials. Clinical research methodology should adapt to the new paradigm. A much more dynamic trial environment should urgently be negotiated together with the regulatory authorities.

There is a need for more flexible designs, where for instance biomarkers could be used to create relevant subgroups and where therapeutic response could be tested in these smaller enriched cohorts of patients. This narrowed focus, departing from that of the traditional clinical trial, would enhance clinical effectiveness. In fact, new innovative trials targeting on an enriched population of patients with a certain cancer, selected for the expression or lack of expression of a biomarker, have in principle smaller sample sizes than traditional trials in "all comers", because the benefit is larger and the statistical assumptions are different. Therefore the development of new agents in enriched populations can be faster and possibly cheaper and potentially lead to the better availability of new active agents. Moreover, it is anticipated that some previously failed medication could be recognised as safe and effective for patient subgroups with specific genetic markers.

Ultimately, the right balance should be found: regu-

latory frameworks should be improved to avoid hampering the drug development process, while offering strict protection for patients involved in research studies.

3. Reimbursement

Besides approval by the regulatory authorities, the reimbursement process is another challenge faced by stratified medicine. As a current rule, drugs and diagnostics are considered under separate appraisal and payment processes – putting drugs through a more stringent evaluation process.

In Belgium, diagnostic tests (Dx) and therapeutic drugs (Rx) are separately funded by the National Institute for Health and Disability Insurance (NIHDI) where decisions are currently made in two different commissions.

There should be a stable and smooth integrated reimbursement process including clear endpoints to decide which new tests/treatments should be covered by the health insurance. Close cooperation should be established between the FAMHP, NIHDI and the academic bodies in order to share information pro-actively for highly promising test/drug combinations fulfilling a potential unmet need. Ideally, health insurance decisions should then involve the combination of medication + biomarker test.

The specific methodological challenges to assess the cost-effectiveness (which is a key criterion in reimbursement decisions) of the test/drug combinations should also be recognised.

4. Training

It is crucial to efficiently integrate knowledge about stratified medicine in education and training curricula in order to educate the current and next generation of physicians, nurses and pharmacists on the complex issues raised by genomic and proteomic science.

At the same time, new training models are required. Instead of using traditional learning settings, education should take place in dedicated centres.

A constant exchange of information should be established with and between experts on a local and worldwide level. There should be networks around specific topics of expertise, and specific data could be obtained from clinicians working in a certain field together with academic laboratories and diagnostic and pharmaceutical companies.

5. Standardisation

A major hindrance to progress in the biomarker identification is the lack of standardisation in how specimens are collected, handled and stored. To obtain the sufficient sampling necessary for validation trials, the research community will have to adopt a uniform approach to biomarker discovery and validation.

Common standards should apply to the practice of tissue storage (biobanking). Local and international large-scale repositories will have to be established in order for researchers from all over the world to be able to access vital tissue and scientific data, as well as those stored in industry-managed biobanks. In this respect, the development of the Belgian tumour biobank system is a major achievement.

Also, clinical entities – including its subtypes – will need to be reclassified by molecular profiles whenever possible and the treatment approaches updated as our understanding of disease causation is rapidly evolving thanks to the expanding molecular data on health and disease.

Finally, and specifically for the cancer field, it is increasingly recognised that tumours are biologically heterogeneous within the same tumour location, between the primary tumour and the metastases, or can undergo changes in the course of the disease and treatment leading to a different expression of molecular markers. Obviously, this increases the complexity and the adequate interpretation of the prognostic and/or predictive value of biomarkers.

6. Patient recruitment

Conducting safety and efficacy trials also presents great recruitment challenges in stratified medicine. Identifying and recruiting appropriate patient cohorts with a targeted profile can be time-consuming. Moreover, the patient is often not aware of the possibility to enrol in clinical trials. The ongoing creation of a national clinical trial site that facilitates the access to such information could be a major help (e.g. cancertrial.be). Patient recruitment is also constrained by concerns around data handling and privacy. Consequently, patient consents are usually restrictive and do not allow use of information from the patients in any future national or international research projects. There is a need for a society-wide debate on privacy protection. These concerns should be addressed while creating a streamlined consent approval – valid internationally and for future use.

Recommendations

The following recommendations seek to show the areas which need to be advanced in order to accelerate the development and uptake of stratified medicine in Belgium.

1. Contribute at the national and European level to setting up a streamlined approval process to facilitate co-development of different drugs as well as drugs and companion diagnostics.
2. Organise regular information sessions between all the stakeholders in order to share, in an early stage, the latest evidence-based information with regard to personalised therapies.
3. Establish a well-tailored, synchronised reimbursement system for both drugs and diagnostic tests at the national level. In this respect, the two commissions with separate healthcare budgets should work together. It should also be stressed that in these decisions the cost-effectiveness and the budget impact for the full health care system must be considered.
4. Increase/promote the adoption of new cost-effective pharmacodiagnostic technologies/validated biomarkers quickly into hospitals. Explore the validation of comprehensive genomic screening methods for replacing individual gene testing.
5. Allow conditional (accompanied by specific requests with regard to further development and safety) and "reversible" drug approval for high impact agents at the international regulatory level, mainly based on early data when a companion diagnostic is available and high response rates (e.g. >50% antitumour activity in cancer) have been shown in the target population in early studies, without being outweighed by inacceptable safety issues, in a population in which available therapy has limited antitumour activity.
6. Develop an education system for all health care professionals who are potentially in contact with patients that are candidates for stratified medicine, in order to help increase awareness and generate realistic expectations. In addition, it is essential to organise common workshops of government personnel involved in regulatory and reimbursement issues and scientific bodies on clinical and pharmaco-economic aspects.
7. Promote data-sharing networks involving all the stakeholders at the national and international level and provide clear guidance for the collection, maintenance, and storage of such shared data.
8. Refining the legal framework for the design, management and usage of biobanks.
9. Develop a public awareness campaign on the benefits of participation to research, and design appropriate privacy regulations allowing broader informed participation.

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