Strategic Overview of Personalised Medicine

PEER REVIEWED

Personalised medicine is not yet fully implemented in healthcare developments, though the concept is several years old. The reasons might be scientific, technological, financial, regulatory, and ethical. The switch to personalised medicine cannot be achieved by merely considering one of those aspects isolated from the others, because they are all interleaved. It takes a global strategic analysis to determine how the healthcare industry should address this challenge. In this article, we outline recent trends in this regard. One observation relates to data science - or the lack of it - in current practice. So far, two players have been working together: the biopharma industry, responsible for R&D, production and commercialisation of the treatments on one hand, and the *in vitro* diagnostic (IVD) industry, responsible for biological measurements production on the other. The latter are supposed to address the issues of the former. Our point is that there is a missing link: players who can extract useful knowledge from the information contained within the huge amounts of data produced, be it clinical, -omics, imaging, etc. But data scientists are traditionally not massively present in the healthcare business. The integration of this complementary component into the current landscape is in itself a challenge, but full of opportunities.

1. Personalised Medicine – What and Why?

The model of blockbuster drugs aims at treating all patients with a given disease with the same treatment. This model has been the workhorse of the biopharmaceutical industry for decades. It allows for massive investments in R&D for long periods, which are amortised over a global market and over several years through protection by patents. This model is gradually exhausted, both conceptually and economically[1,2]. Conceptually, because the diseases that are difficult to handle nowadays are extremely heterogeneous, and therefore a single treatment is often ineffective - we speak of cancer when there are in fact many types of cancer, with very different specificities, while autoimmune diseases like lupus or arthritis may also have various forms. Economically, because investment in R&D and duration of treatment development are constantly increasing, while patent protection is limited to 20 years. Currently, a new drug development costs an average of 1.1 to 1.5 billion dollars according to estimates, and a clinical trial lasts about 13 years, leaving only seven years of patent coverage to recover this investment and realise the margin expected by investors. An extra protection of five years is possible in some cases (SPCs), but is not a sufficient extension. The ROI per Euro invested in R&D decreases, while at the same time the overall R&D budget increases exponentially. This is mainly due to failure to demonstrate sufficient efficacy of treatments in the final stages of validation. Medicine and healthcare then become progressively personalised and predictive by necessity, while putting the patient back at the heart of the business. New approaches are required, based on patient-tailored therapies[3]. There are in fact completely personalised medicine (a treatment per patient) and stratified medicine (a specific treatment for each subgroup of patients within the population with the disease)[4]. Here, we adopt "personalised medicine" broadly to mean both. If there is a clear need for personalised healthcare, how come there are not more such therapies available on the market? As we point out in this article, the causes are more due to a missing link in the value creation chain of the healthcare industry rather than to regulatory, political, economical or even ethical issues.

2. Ethical Issues

Ethical issues do not really restrain advances in personalised medicine, even if its emergence is controversial. For example, what will happen if we do not identify treatments for all subgroups of patients with same disease? If the cost of developing a treatment is unchanged, but the population that it targets is narrower, won't the price per dose explode? Conversely, must the community pay for the reimbursement of treatments when it can be known in advance they will be ineffective? Or for providing treatment to a patient if it can be predicted based on its profile that there will be harmful side-effects (not to mention the indirect costs of treatments to deal with these effects)? Finally, some concerns are also discussed in terms of respect of privacy, especially in relation to the recent availability of affordable complete genome sequencing solutions. At some point, the DNA is the identity of the patient, more than his passport. These privacy issues are generally answered by freedom of information, and advances in secured communications. The next section shows that regulatory authorities even make some of these questions obsolete before they are answered.

3. Market Access and Reimbursement

The Food and Drug Administration or the European Medicines Agency, although known for their strictness

and the high impact of their regulations, are not conservative regarding personalised medicine.

Recently, the FDA published many guidances (or drafts) that are consistent with rapid but intelligent deployment of personalised medicine strategies[5,6,7,8]. Interestingly enough, the recommendations in this area involve skills outside the traditional scope of the biopharmaceutical industry, including a focus on data analysis. Some recommendations namely advocate for the systematic collection, and if possible analysis, of DNA samples from all patients involved in any clinical study. We discuss data analysis later in this text. Personalised medicine requires different treatments for different patient profiles, which in turn requires the design of diagnostic kits for determining these profiles. Currently, the activities of drug development and diagnostic kits conception are provided by different actors (biopharma on one hand and the IVD industry on the other hand), with huge problems of collaboration, allocation of financial margins, intellectual property, even of drug-kit adequacy, etc.[9]. The FDA advocates in this area a closer collaboration for these activities, if not a merger: a personalised treatment and its companion diagnostic kit should be co-developed under the supervision of a single sponsor[10]. As these recommendations are getting implemented, the industry has no choice but to comply. Thus, regulatory authorities are rather guiding personalised medicine development than preventing it.

Aside from market access issues, new reimbursement strategies are also at stake. This question is generally not dealt with at a continental level, but more at a national level. It is thus not so easy to give a big picture. Just as an example, conditional reimbursement related to personalised medicine has been discussed by the Belgian parliament late in 2011[11]. Most of those new policies are not operational yet, but go in the right direction. Anyway, at present, most of the few examples of already available personalised treatments and diagnostic kits are not reimbursed, even if they get market access. Rather surprisingly, studies have shown that even without reimbursement, some of these quite expensive products can be commercial successes[12]. The same studies show that the two main factors for this success are i) the evidence of effectiveness of these therapies (patients are willing to pay more for a treatment whose efficacy is more likely), and ii) the views of professional associations.

4. Patients' Empowerment

After showing that neither ethical issues, nor market access and reimbursement are responsible for the lack of personalised medicine products on the market, let us consider the patient himself. Little has been said of patients so far, who are the beneficiaries of the entire healthcare industry. Could the patient be in disfavour of personalised medicine approaches? The patient is traditionally confident in his GP or the specialists he consults. However, with the advent of modern communication and information technology, many patients are keen to take control of their health. Today, even if the doctor is still the primary source of inside information taken by patients about a disease, 23% of patients look first on the internet, 25% go first to printed articles and books, and 43% of patients see medical websites each month[13]. Accordingly, we note the presence of actors recently offering B2C personalised medicine, such as 23andMe, Navigenics, and deCODEme. These online services offer to order a do-it-yourself DNA collection kit, which is then returned by mail. Hundreds of thousands of genetic traits are studied in a few days in an automated way, and the patient can then browse through his genetic peculiarities on the same web portal. These may be trivial in some cases (e.g., eye colour), but often have a prognostic value (x% higher than average risk of developing a disease) or include various information (the patient is genetically more of a long-distance runner than a sprinter, is lactose intolerant, etc.). These services are, in their current form, highly risky and questionable ethically, but this is beyond the scope of this work. The important point is that the patients want to participate in managing their health. Another evidence of that is the recent Genomera initiative, which enables any user to start a clinical study, in the web 2.0 spirit. Each user is free to participate or not, and to share his/her genomic data if available. Clearly, the patients, too, are enthusiastic about personalised medicine.

5. Diagnostics: Data Scientists at the Gate.

Could the bottleneck of personalised medicine be the complexity of biology itself? Molecular biology and imaging technology have made dramatic progresses to enable us gain a better picture of living entities. We now have a hard time ahead of us to analyse this big picture, and extract useful knowledge from it. The IVD industry's mission as a whole, as its name suggests, is to provide diagnostic

solutions. Based on a measurement of one or more biological parameters - whatever they are - these solutions are supposed to provide decisions (or at least decision support). Is the patient healthy or suffering from a given disease? And if he is, of which subtype, eventually? Among a given set of available treatments, which one will be more effective or safe?

In practice, there is some discrepancy between this strategic objective and the reality of the solutions provided. Indeed, in many cases, the solutions simply provide IVD measures, and increasingly in large numbers, but do not really provide decision support based on these data. There is therefore a relatively low adoption of these solutions by medical practitioners, unable to interpret the results. Referring physicians are also inundated with information about the latest developments in medicine. These advances are increasingly complex, and are occurring at increasing frequency. Many physicians have therefore neither the time nor in some cases the skills to keep pace with new discoveries. These IVD solutions are also sold to medical research centres and biopharmaceutical companies where they are already more useful, mainly for clinical research. However even in this latter case, they do not deliver their full potential if analysis capabilities are not available to deal with the data they generate, in conjunction with clinical observations on patients.

This chronic lack of data aggregators is pointed out by analysts[14], and is probably the main cause of the delay in personalised medicine successes. Real data scientists will not supersede biologists and medical doctors, but can help them make more of their tools.

There are numerous examples of clinical research where data is planned to be produced "just in case" and then left without proper analysis[8]. Data analysis is not about producing data. It is about generating knowledge from the information the data contain. A biomarker should not be named a biomarker just because a clustering analysis has shown that several subgroups of patients seem "similar". A biomarker should always be linked to a clinical outcome. But there comes a trickier issue: when many features are measured with respect to the number of samples available (as it typically is the case with modern IVD solutions), it is trivial to identify a biomarker that can perfectly split a cohort of patients into two groups. In fact, as soon as there are n-1 or more features that are measured on n patients, it is guaranteed that a perfect single biomarker can be found[15]. Is it good news? Not at all. But it explains why analysing microarray data (several tens of thousands gene expressions) produced on a few tens of patients led to diagnostic, prognostic, or response prediction biomarkers that subsequently proved useless on new patients. Special care has to be taken when dealing with high dimensional data on few samples. Traditional statistics books even recommend not to analyse data when at least 10 samples are not available for each measured feature. Where will we find 30 billion human beings to get sequenced if we are about to analyse next-generation sequencing data? So, many analyses that pretend to be predictive are in fact simply descriptive of the patient cohort at hand, but will prove very poor on new, unseen patients, which is however the aim of biomarker identification, on which personalised medicine is supposed to rely. Designing analysis protocols that avoid selection bias (validating biomarkers on the same patients used to identify them) or overfitting (a similar issue for predictive models) in itself requires expertise in data analysis. And the distinction between the question of identifying biomarkers and identifying a good predictive model on those biomarkers is frequently simply overlooked. Another limitation is that many of the approaches for identifying biomarkers that are used today are univariate, meaning that they consider the predictive (or descriptive) power of each candidate marker individually. It can be shown that several markers that are totally useless alone, once combined, can be very powerful at producing diagnostics.

And is there a scientific rationale for univariate diagnostic solutions anyway? But how to deal with every possible combination of several biomarkers within a set of a few thousands of potential ones, when it amounts to evaluating more combinations than particles in the universe? Again, smarter approaches are available, but require specific expertise in data mining or machine learning[16]. Those fields of research are related to statistics, applied mathematics/optimisation and computer science, and are complementary to the set of expertises that are traditionally found in the healthcare industry. They will help personalised medicine perform major advances in the coming years.

6. A Vision of Open, Innovative and Data-Driven Healthcare

Medicine and healthcare have become increasingly personalised and predictive, with the patients at the heart of their concerns. The model of blockbusters is exhausted, both economically and conceptually, and new approaches are required, based on more advanced diagnostics and treatments tailored according to patient characteristics. We outlined that most strategic aspects related to personalised medicine were good, but that the field required more attention to data analysis. The healthcare sector could then be seen as three axes working together on an open innovation mode.

The first component is the biopharmaceutical industry, responsible for making available new treatments. Until recently, biopharmaceutical companies ensured three facets of their business: R&D, production, and marketing. While they still perform the last two, they tend to increasingly outsource R&D. At present, it is not uncommon that the very concept of a new treatment, or a new technology platform, has emerged in a small entity (biopharmaceutical, hospital, CRO or research centre) and is simply then bought by a larger biopharmaceutical company. Beyond the simple relation of outsourcing, there is an increasing

tendency to co-development. This is the open innovation model[17]. Risks and investment are shared by a consortium of companies (and/or academic partners) and the benefits are equally distributed. While this trend is commendable and promising, it is not easy to implement, mainly due to partner size asymmetries, and requires heavy prior legal work. Nevertheless, the open innovation tendency is likely to increase in the future. The second component is the IVD industry, allowing a range of measurements of biomarkers (genomic, proteomic, imaging ...) growing larger, more efficient and more affordable. The third component is the data mining industry, responsible for analysing the massive streams of data produced by IVD devices for the biopharmaceutical industry, but also for hospitals, physicians or patients directly.

If applying real and fair open Innovation and incorporating data analysis solutions within the healthcare industry, all parties will benefit from personalised medicine. The biopharmaceutical industry will produce safer, more targeted and effective treatments, with reduced economic risk and development times. The IVD industry will meet its strategic objectives: producing real diagnostic tools, which are also useful to patients and doctors, rather than measurement devices. Patients will get better healthcare, with reduced, or at least more targeted, public health expenses.

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