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PERSONALISED MEDICINE: STATUS QUO AND CHALLENGES

PERSONALISED MEDICINES IN TWO PAGES

Personalised medicine is providing the right treatment, to the right patient at the right time by using modern biology's new methods and tools. Practically, this approach combines diagnostic and therapeutic tools to create predictable outcomes and tailor medical treatment to the individual characteristics of each patient.

Recent scientific developments have brought us closer to this concept, which stands for hope and excitement. On the other hand, personalised medicine is quite disruptive as it requires major changes in a many areas: in science, in research and development programmes of drugs, in diagnostic tools, in valuation and reimbursement and in health literacy.

Changes in science

Historically, patients diagnosed with the same disease are considered to suffer from the same underlying pathology. They are also expected to respond to the same treatments, although clinical experience proves otherwise. In the future, diseases will no longer be classified based on symptoms, but based on the underlying mechanisms.

Research of the last years has given us insights in signalling pathways: molecular mechanisms that determine a specific body function. Slight changes in these signalling pathways can cause disorders that lead to diseases. Evidence of such slight changes are measurements of presence or changes in specific biologic or chemical body substances. We call them biomarkers. Diagnostic tools to measure these 'biomarkers' can be developed to help clinical identification of the presence of a malfunction within a specific signalling pathway.

Over the last years, promising 'targeted' drugs have been developed: drugs that address an underlying molecular mechanism linked to the disease. Oncology is a front runner in this field, but lately biomarker candidates have also been discovered within rheumatoid arthritis and asthma.

Changes in drug research and development programmes

The cornerstone of personalised medicine are predictive biomarkers: biomarkers that can select a patient group with a higher chance for a favourable response to a medicine. In today's drug development programmes, the identification and qualification of biomarkers are integrated into the overall development of a treatment. It is assumed that biomarkers can increase the research and development productivity by increasing specific patient response rate to treatment, and therefore will reduce development timelines and costs as well as late stage attrition of the drug development pipeline.

To improve the development of targeted medicines, patients will have to be selected based on the presence or absence of specific biomarkers. In some situations, that may be a relatively small subset of the traditionally defined patient population. In other situations this may just as well lead to an extended patient group, if the same underlying mechanism appears in different diseases. At least the patients are better selected and response to treatment will be more consistent and predictable as well.

Changes in development of diagnostic tools

If a biomarker test is approved as an in-vitro diagnostic (an IVD), it can serve as a routine diagnostic test in clinics to select patients for a specific therapy. Ideally, drugs and companion diagnostics are developed together. Unfortunately, we are nowhere near that ideal situation.

Firstly, it is almost impossible to find clinically useful predictive biomarkers early on in a drug development programme, simply because they can only be established once the patients have responded differently to the drug, which is in the latest stage of a clinical trial.

Secondly, drugs and diagnostics are in many ways parallel universes: they have completely different development timelines, product lifecycles, return on investment, customers, regulations. Drugs require pre-market approval by regulators while IVDs are self-certified by the manufacturer. The IVD manufacturers currently compete with hospital laboratories, which can make their own diagnostic tests. However, the EU IVD regulation is under revision and requirements may be added on how to demonstrate clinical validity. This will probably increase safety, but also inevitably require greater efforts of IVD manufacturers, which can have a severe effect on innovation. The larger investments that are needed might restrict especially small innovative companies to discover biomarkers and develop routine diagnostic products.

Changes in valuation and reimbursement

Much of our experience with economic evaluations of medicines is based on medicines designed to treat the whole patient population. In the personalised medicine concept, a sub-group of responders is identified, or screened out. That raises the hope that economic evaluations will be more straightforward and positive. It also means that much of the efficiency gains of personalised medicines depends on test kits.

Studies on the cost-effectiveness of personalised medicines are still on the way but promising results are available. Personalised medicine could provide more value for money because of improved drug effectiveness and reduced toxicity, and it could also decrease the average research and development costs for new medicines.

But these efficiency gains may show only in the long run. There are still a few problems to be solved. Firstly, it is not easy to describe the costs of diagnostics. Secondly, the evaluation of cost-effectiveness is difficult. Thirdly, the regulatory pathway is fragmented.

Changes in health literacy

How do we integrate personalised medicine in the health practice in such a way that it maximizes health benefits and minimizes harm? This calls for empowered patients and carers, and investments in health literacy.

Personalised medicines provide more information about the health of individuals, on the efficacy of the drug and on the side effects. Patients will become more involved in making decisions about diagnostic tests and therapeutic options. All the implications should be discussed between doctor and patient. This asks for a serious investment in information and communication technology. Patients will want to search the internet, trying to find patients with the same patient's profile, based on biomarkers, or even find clinical trials that ask for patients with a specific profile. Personalised medicine also raises ethical questions, such as who will have access to the detailed patient information.

INTRODUCTION

Imagine your life partner or your child being severely ill. What would it be worth to you if a doctor could exactly predict to which medicine your beloved would respond? And what doses should be enough to kill the fiend with the least side effects?

This idealistic situation is not science fiction. But we still have a lot of work to do to reach this stage. We need tools to identify patient's profiles. Therefore we have to understand diseases better than we do now and we have to identify biomarkers: indicators on a molecular level that provide information on the physical state of a person. Biomarkers can be used diagnostically and predictively. Personalised medicine is about predicting response to therapy. Therefore we need to perform research on biomarkers and turn them into diagnostic and predictive tests.

So... why don't we? How can anyone be opposed to such an innovation?

These were the two questions the EuropaBio Personalised Medicine Taskforce tried to answer. We organised workshops and attended conferences in which many stakeholders participated.

We experienced that stakeholders have a lot of difficulties in embracing personalised medicine in practical terms. Adjustments to their way of working are often needed. Health organisations, companies and government institutions alike, will need to rethink, recalibrate and change their standard operating procedures to allow personalised medicine approaches to be adopted by the European healthcare system.

This white paper aims to give insights in the developments and challenges regarding personalised medicines. It provides guidelines for streamlining personalised medicine developments and routes to patients.

1 WHY WE ARE SO EXCITED: LATEST SCIENTIFIC DEVELOPMENTS

In this chapter we describe why scientific developments and recent treatment successes have made many of us so excited about personalised medicine. These successes show the effects of replacing traditional intuitive and empirical medicine by precision medicine.

Same symptoms: same disease

Patients diagnosed with the same disease may react very differently to the same treatment. This observation led the Canadian physiologist Sir William Osler (1849-1919)to the statement: "If it would not be about the variability among individuals medicine could well be a science and not an art". We are brought up with the idea that patients who have the same symptoms and whose course of disease follows similar patterns are likely to suffer from the same disease.

Scientific disciplines such as anatomy, developmental anatomy, physiology and biochemistry, helped us to get a better understanding of how a normal organism functions. Pathophysiology, micro and macro pathology and clinical chemistry helped to describe, classify and understand diseases.

However, few of these scientific advances led to a full understanding of the causes of diseases on a molecular, cellular or genetic basis. Today's medical text books still describe and define diseases on the basis of combinations of objective and subjective symptoms, macroscopic, microscopic, pathophysiological or biochemical findings, and the presence or absence of specific pathogenic organisms or substances. Most diseases are also classified according to the affected organ or organ system.

In consequence, patients diagnosed with the same disease are considered to suffer from the same underlying pathology. They are also expected to respond to the same treatments, although clinical experience tells us that this is only true in a limited number of situations. What is causing the symptoms on a molecular level, remains often unclear.

Effective therapies were educated guesses

We have to admit that our current knowledge of disease mechanisms unfortunately has not always resulted in the development of highly effective medicines yet. The effective therapies we have, were developed intuitively or empirically, or were even discovered by chance. Examples include antibiotics, alkaloids, calcium channel blockers, immunosuppressants and cytotoxic agents.

There are many examples of medicines, which were developed on the basis of wrong assumptions, and some examples of medicines, which proved to be effective in an unexpected condition. But there are also few examples of medicines, like oral contraceptives or modern targeted medicines in oncology and rheumatology, of which the development is based on an exact understanding of the relevant mechanisms.

Different symptoms: same underlying disease

In reality patients diagnosed with the same disease based on the same diagnostic criteria show very different courses of the disease, and respond very differently to the same treatment. In clinical practice, doctors have no other choice than to optimize the treatment by trial and error.

We now know that these patients are probably suffering from different diseases. In other words: the diseases have a different underlying pathology. While the scientific progress in basic scientific disciplines such as anatomy, physiology and biochemistry has been substantial over the last centuries, we still have a very limited understanding of the molecular processes in diseases. We know even less about the factors, which may determine whether a person has an increased risk of developing a particular disease. Is "type-2 diabetes" a single homogeneous disease, for instance?

New understanding of diseases

Over the last decades molecular research on sick and healthy cells gave new insights in cellular signalling pathways: mechanisms involving proteins and nuclear receptors, which are essential for the normal functioning of cells but under specific circumstances may lead to diseases. These discoveries have helped us to understand and classify diseases in a new way.

We have learned a lot from rare monogenetic disorders, which allow us to study the impact of specific genetic mutations on the clinical signs and symptoms of the disease.

This research allows us to gain insight in the underlying genetic alterations and the consequences of the presence and functioning of critical proteins. The answer to the question 'what causes diseases' is revealing itself little by little since we are able to decipher the genetic code of a person. There is growing evidence that specific genetic mutations involving specific signalling pathways play a significant role in disease development. The scientific discipline of epigenetics stresses the influence of life style and nutrition. Understanding the role of regulating RNA will lead to new ways of therapeutic treatments.

Phenotypically similar conditions classified as the same disease may originate from different genetic polymorphisms or mutations. Similarly, diseases affecting specific organs such as various types of cancers, or certain systemic inflammatory diseases may be triggered by a single common molecular mechanism.

Biochemical, genetic, genomic and other markers identifying such mechanisms can serve as biomarkers for specific disease mechanisms and diseases. Such biomarkers can be developed into diagnostics that are able to identify the specific mechanism involved in the disease affecting a specific patient. With our growing knowledge of such mechanisms we will be able to classify diseases based on the underlying mechanisms and pathways rather than on pathophysiology, pathology and phenomenology alone.

This new disease classification will finally support the development of medicines directly targeting specific disease mechanisms present in a patient.

Recent breakthroughs in biomarker research

Traditionally, oncology is the front runner in the field of personalised medicine. However, in the last decades there have been breakthroughs in other areas such as infectious diseases and haemostasis. Recently, a number of biomarker candidates have been discovered that link mode of action with disease pathophysiology within chronic inflammatory conditions including rheumatoid arthritis and asthma.

The clinical response rates to approved biologics for rheumatoid arthritis leave considerable space for improvement and predictability of the available treatments. Hence, there is currently a tremendous interest in identifying patient subsets that are more likely to benefit from a specific treatment.

Although the preliminary results of the targeted approach to treatment look promising, there are also some difficulties to be mentioned. Firstly, the identification of a disease mechanism does not necessarily mean that it can be addressed. Secondly, most cellular pathways are critical for healthy cells as well as diseased cells. Thirdly, cellular pathways consist of a sequence of reactions. If a specific molecular target is blocked or altered in this chain of events, bypass mechanisms may occur. These challenges require for their resolution further research.

Personalised medicine is science driven

Personalised medicine requires a fundamental change in our comprehension of diseases. Many traditional diagnoses may have to be revised. In the future we should be able to identify underlying molecular disease mechanisms more precisely, and in consequence make more effective treatment decisions. However, despite all this progress we may not succeed in identifying the underlying mechanisms for all diseases and biomarkers alone may not be sufficient to diagnose all diseases. It is inevitable that disease classifications and diagnoses will continue to require combinations of molecular and phenotypic classifications.

The right diagnosis will lead to the right treatment. Personalised medicine offers a more scientific approach to diagnosing and classifying diseases, and in consequence will lead to more effective treatment decisions for individual patients.

2 TRANSLATION OF PERSONALISED MEDICINE CONCEPTS

This chapter describes how the search for predictive biomarkers is likely to change drug development research. It may lead to a reduction of costs and an increase in productivity of research & development projects. Predictive biomarkers will change the way clinical trials are performed.

We need predictive biomarkers

Traditionally, biomarkers answer critical questions that arise during various stages of drug development – questions such as: Does the drug reach the target? Does it have the desired biological effect? Does it have an influence on other expected or unexpected targets? Does the drug affect characteristics that predict desired or undesired effects?

However, the concept of personalised medicine centres around *predictive*: biomarkers that can help select a patient population with a higher chance for a favourable response to a specific kind of medicine. In today's drug development programmes, the identification and qualification of biomarkers are integrated. If we are able to determine the biologically relevant dose, range and selection of the optimal target population by means of biomarkers, we are convinced that biomarkers will increase R&D productivity by reducing development timelines and will prevent costly late stage attrition.

Unfortunately, predictive biomarkers are often not applied until rather late in the clinical development programme, when clinical data show that an optimal benefit-risk profile is only achieved in a subpopulation of patients. In such situations, the attention is suddenly turned to other available research data that might explain the underlying biological nature of the research results. Over the last years we gathered examples of biomarkers, which have proven to predict clinical response better because they are linked to the mode of actions of the compounds in question. Examples include Her-2/neu (Trastuzumab/Lapatinib), KRAS (Cetuximab/Panitumomab), BRAF (Vemurafenib), and CCR5 (Maraviroc).

We lack model systems to predict drug response

In our opinion, it is crucial to identify and qualify biomarkers that predict clinical response. But we lack good model systems that predict drug response.

Generally a prerequisite to enter clinical development is that efficacy is established in animal models. Despite convincing data from animal models, the translation from animals to humans is not always successful.

Alternative models or an alternative technology are needed. This had been attempted with ex-vivo systems in areas such as rheumatoid arthritis and Crohn's disease. These assays have proven to be valuable for the evaluation of novel therapeutic targets.[1] The application of such assays seems promising, but it remains to be fully investigated.

A caveat of ex-vivo systems may be that the generated biomarker signal derives from a local tissue environment, which might be difficult to capture in peripheral blood samples. The oncology field has the best access to tissue biopsies. That is one of the reasons why oncology is a front runner in personalised medicine with several tissue based companion diagnostics. On the other hand, still very little is known about the drug resistance as encountered in the oncology field. This asks for biomarkers that elucidate more clearly what is going on in individual tumours.

[1] *Nic An Ultaigh S, Saber TP, McCormick J, Connolly M, Dellacasagrande J, Keogh B, McCormack W, Reilly M, O'Neill LA, McGuirk P, Fearon U, Veale DJ. Blockade of Toll-like receptor 2 prevents spontaneous cytokine release from rheumatoid arthritis ex vivo synovial explant cultures. Arthritis Res Ther. 2011 Feb 23;13(1):R33. PubMed PMID: 21345222*

New kind of trials

Studying targeted medicines in traditionally defined patient populations is quite problematic. For example, if we want to test a medicine like gefitinib, we do not need patients who are clinically diagnosed with non-small cell lung cancer, but patients with a specific EGFR mutation. If we were to test the medicine on a population which is not preselected for the presence of the mechanism in question, we might conclude that the medicine does not have an appropriate benefit-risk ratio. However, if tested on patients with the underlying mechanism we might come to the opposite conclusion. Gefitinib is therefore indicated for patients with tumours showing specific EGFR mutations, while it is irrelevant whether the tumour is located in the lungs.

In order to develop targeted medicines, patients will have to be selected based on presence or absence of specific biomarkers. In some situations, that may be a relatively small subset of the traditionally defined patient population. For instance: traditionally we would test a drug on patients with breast cancer. But now we would select patients with a similar disease pathway: e.g. Her-2 positive. Eventually, the patient population may be extended: it is to be expected that we can treat patients with malignant tumours in other organs with the same medicine, because the tumours are caused by the same molecular mechanisms (e.g. m-TOR mutations).

With this approach, patient populations participating in clinical trials can be smaller, or at least much more homogenous, and response to treatment will be more consistent and predictable as well.

Integrating biomarker research with target evaluation

We think continuous biomarker research, which ideally starts at least two to four years prior to first-in-man clinical trials, is needed. Before embarking on clinical trials, we should ideally have identified a broad panel of biomarker candidates that subsequently can be further qualified in appropriate in-vitro, ex-vivo, in-vivo, or in-silico model systems.

Bioanalytical assays for the selected candidates can then be established and validated prior to implementation in clinical trials. In order to be fully operational, this strategy requires competencies within three main areas: biomarker research, biomarker assay development and clinical biomarker implementation. These areas should collaborate to guarantee the quality of the biomarker data derived from clinical trials. This will strengthen the basis on which a personalised medicine programme can be evaluated.

Moreover, once embarked on clinical trials, it is advisable to continue the biomarker research activities in parallel with the clinical development programme. In this way it is possible to improve the biomarkers by applying data derived from early clinical trials to later stages of the programme.

This approach clinically validates pre-selected biomarker candidates but may also identify potential other and better biomarker candidates correlating with clinical outcomes.

Identifying biomarkers is a collaborative effort

It is difficult, time consuming and costly to identify and qualify biomarkers for other uses, such as predicting clinical outcomes. A biomarker needs sufficient evidence of broader clinical utility and validation in multiple independent studies, across different cohorts, ethnic groups and clinical subgroups. This is in line with recent guidance for biomarker qualification from the Food Drug Administration (FDA) and the European Medicines Agency (EMA).

Fortunately, multiple pre-competitive collaborative initiatives have been established globally. In recent years, large consortia have succeeded in the qualification and validation of various types of biomarkers. Examples of collaborative biomarker-consortia are the Biomarker Consortium (US) and Innovative Medicines Initiative (EU). They are supported by representatives from regulators, pharmaceutical industry, biotech industry and diagnostic industry, academia and governmental organisations.

3 FROM BIOMARKERS TO COMPANION DIAGNOSTICS

Once biomarker tests have been turned into diagnostic test kits, we would be able to routinely classify patients in clinics. But the development of those diagnostic test kits has to be co-ordinated between two entities - pharmaceutical companies and diagnostic manufacturers –with rather different regulation.

As we have seen in the previous chapters, biomarkers can play a critical role in classifying patients into subpopulations. A biomarker can be used as the basis for creating a routine diagnostic test for clinical use, after it has been approved as an in-vitro diagnostic (IVD) test: i.e. a certified product, reagent, application or other tool that analyses human material and helps to diagnose patients.

There is a tendency for regulators to require that drugs and companion diagnostics are developed in tandem.

A companion diagnostic test is essentially a biomarker test that enables better decision making on the use of a therapy. In other words: it is a diagnostic test that is specifically linked to a therapeutic drug. The goal here is to increase the safety and the efficacy of the drug.

Pharmaceutical and biotechnology companies are trying to change their tack now and are working hard on integrating the co-development concept but true co-development has been a rare phenomenon until now. There are two reasons for this. Firstly, clinically useful biomarkers are usually established late in the drug validation process. Secondly the worlds of drug development and diagnostics, although both part of health care, are parallel universes in many ways.

In the next paragraphs we will elaborate on these issues.

Clinically useful biomarkers found late in the drug validation process

It is quite difficult to find clinically useful predictive biomarkers early on in a drug development programme, simply because they can only be determined on the basis of the patients' responses to the drug. A number of biomarkers, such as KRAS and EGFR mutations, could only be established after a sufficient number of patients - well beyond the usual number for a Phase III trial - had elicited better understanding of differential drug response.

Maybe, in the future, if the method of clinical trials changes thanks to our new understanding of diseases and classifying patients (as we described in chapter 1 and 2), we might be able to find these biomarkers at an earlier stage. But as long as still 30% of the drugs fail during Phase III, diagnostic manufacturers will not be able to afford huge investments in the development of companion diagnostics.

Parallel universes

The worlds of drugs and diagnostics are parallel universes: in general they have different development timelines, product lifecycles, return on investment, customers, and regulations.

Drugs are valued and reimbursed as products, typically of high value. Diagnostics are valued and paid for as services, typically at a much lower value. Relatively few if any models exist for valuing a drug diagnostic combination. This issue will be discussed in the next chapter.

Drugs are protected by patents, but in the companion diagnostic arena, biomarkers are considered to be within the public domain and there is less emphasis on intellectual property. It is even debated whether biomarkers should be patented at all, because biomarkers are not invented but already exist in cells.

Moreover, drugs and diagnostics are regulated differently. It takes many years and a large amount of data from expensive clinical trials to get a drug approved. Under current rules, however in the current IVD Directive there is little mention of clinical evidence.

However, the EU IVD Directive, which regulates in-vitro diagnostics, is under revision. The current IVD classification does not take scientific and technological evolution into account which is expected to be changed towards a new risk-based approach.

A revised IVD Directive (which may even become a Regulation) will improve safety and efficacy, but will also raise difficulties. It is likely to state that an IVD assay must have the performance characteristics required for fulfilling a clinical purpose. Moreover, requirements may be added on how to demonstrate clinical validity, possibly proportionately with the risk level of the test.

The intention to increase safety will inevitably lead to higher costs and greater efforts for manufacturers. It will take IVD manufacturers years and unusually high investments to take an IVD past the regulators. Undoubtedly, Phase III trials would benefit from well validated biomarker tests. But it is almost impossible to comply with regulations that require a clinically validated diagnostic test, simply because clinical evidence will only be provided by a clinical trial itself, and this is unlikely to be required for many IVDs.

Another point is that more regulation can severely impact innovation. The larger investments that are needed might limit the ability of (especially small) innovative companies to discover and develop biomarkers.

The quality of diagnostic tests

In order to gain more insight into the consequences of stricter regulation, we must dive into the universe of diagnostic practice in the EU a little deeper, because there is another challenging reality.

In the diagnostic arena there are, basically, two types of tests in use: manufactured diagnostic products, which are regulated in the EU, and lab developed tests (LDT's), which are not regulated . Thus, in the EU, there is a broad range of methodologies, often driven by the individual laboratory's capabilities, access to diagnostic testing platforms, reimbursement and preferences of the individual team.

How this situation works in practice was pointed out by a multicenter study.[2] Various laboratories were asked to select patients with a positive EGFR biomarker or a KRAS biomarker. Some of the tests were in close agreement but, alarmingly, others were not. Due to the poor quality of so-called 'home brew tests' or inadequately validated tests in hospital laboratories, patients with a positive EGFR biomarker might be excluded from an effective therapy on false grounds.

The result of this industry dynamic is a lack of standardisation of testing and ultimately, inconsistent patient selection for therapy. Improper patient selections will lead to poor therapy outcomes, or worse, to adverse reactions to drugs.

This situation is not likely to change under a new EU IVD Regulation. IVD manufacturers may have to make greater efforts in the future, including financially, to get an IVD past the regulators. However, there is no legally enforced requirement to use the companion diagnostic test approved in the clinical trial.

So, for as long as regulatory bodies do not sanction laboratories that do not conduct tests in line with pharmaceutical clinical trials, the quality of the testing will not improve. Diagnostic partners cannot justify large investments in bringing products onto a market, in which there are no rules for laboratories to perform substitute testing. Regulation for testing laboratories will be a more effective first step towards increasing quality and safety than sharpening the rules for IVD manufacturers.

[2] *Whitehall V, Tran K, Umapathy A, et al. A multicenter blinded study to evaluate KRAS mutation testing methodologies in the clinical setting. J Mol Diagn. 2009;11:543–552.*

Discussion

The industry needs time to bring diagnostic and therapeutic research together. The regulation should leave room to develop companion diagnostics in various business models, instead of only requiring co-development. Let's not forget: many drugs have proven to be effective without companion diagnostic tests. We would not want to rule those out.

Regulation to increase safety is in itself a good thing, but it is also important to provide opportunities for small innovative enterprises to enter the market.

4 HEALTH ECONOMIC ASPECTS OF PERSONALISED MEDICINE

Personalised medicine has an impact on the healthcare budgets. Are the tools that healthcare economists and pricing and reimbursement authorities currently use suitable for analysing personalised medicine?

In short, the concept of personalised medicine revolves around the idea of the selection of patients who are likely to respond the medicine, so that the treatment will offer better outcomes. According to the recent Quintiles report "biopharma and managed care executives are optimistic that personalised medicine will improve efficacy, safety and public health".[3]

However, there is a widespread scepticism about the financial impact of personalised medicine. According to the same report 56% of managed care executives feel that personalised medicine will increase cost of prescription medicines. Consequently, pricing and reimbursement of personalised medicines need careful consideration and a balanced view on cost-effectiveness and incentives for innovation.

Another economic model is needed

Much of our experience with economic evaluations of medicines is based on medicines designed to treat the whole patient population. Evaluations of the economic value of a particular drug usually involve comparisons with treatment alternatives or palliative care. Such comparative effectiveness are typically assessed on the basis of data collected in randomised controlled trials across a broad population of patients.

There have been attempts to identify sub-sets of patients that benefit most noticeably from the medicine, i.e. patients over or under a certain age or patients judged to have a 'severe' form of a certain disease. But in many cases these evaluations were not supported by robust evidence, and the sub-groups were not well characterised nor were they statistically well-sampled in the clinical data.

Testing may be economically viable

In the personalised medicine concept, a sub-group of responders is selected or screened out, which raises the hope that economic evaluations will be more straightforward and positive. This is particularly true for the cheapest use of costly molecular targeted agents.[4] Biomarkers can improve the ability to identify responders and non-responders, and insure that the information is used to make better treatment choices. As a consequence, the respective drug gains a more favourable risk-benefit ratio, patients are expected to have better health outcomes and better quality of life and healthcare resources are likely to be used more efficiently.[5]

Much of the efficiency gains of personalised medicines depends on the testing – in other words, "testing before treating may be economically viable if the savings gained by avoiding ineffective treatment and adverse events are greater than the cost of testing."[6]

Studies on the cost-effectiveness of personalised medicines are still on the way but promising results are available. The introduction of a companion diagnostic strategy in advanced non-small cell lung cancer reduced overall treatment costs by more than € 800 compared to current treatment.[7] A cost-effectiveness analysis in the field of chronic myeloid leukaemia showed that the use of the FISH test reduced treatment costs by €12'500.[8] In addition, it increased the life quality.

Reduction of R&D costs

Personalised medicine may provide more value for money – not only because of improved drug effectiveness and reduced toxicity, but it may also decrease the average research and development costs for new medicines.

In fact, clinical trials are the most expensive part of R&D (nearly 50% of the investment). The costs of clinical trials seem to have risen by one third between 2005 and 2007 due to increasing regulatory and other requirements.[9] Biomarkers may enhance the efficacy of clinical trials of new drugs by investing more heavily in early research to identify key biomarkers, and in targeting relevant sub-groups of patients. Smaller (and maybe even shorter) clinical trials are likely to reduce development costs .[10]

This sounds promising, but since personalised medicine is in its early stages, efficiency gains may occur only in the long run.[11] Furthermore, companion diagnostics are likely to increase the additional costs and the complexity of the risky process of drug discovery and development. In oncology, where personalised medicine is currently progressing most rapidly, the late stage failure rate of new compounds has historically been higher than in any other area.

A well-known argument against personalised medicines is, that they will lead to smaller groups of eligible patients and therefore lead to higher unit prices in order to deliver competitive return on investment. Additional value, therefore, "needs to be captured in terms of premium pricing, faster adoption or longer effective patent life for a portfolio of targeted drugs, to offset the reduction in potential revenues from market stratification".[12] However, personalised medicines do not only diminish groups of eligible patients, they enlarge them as well (see chapter 2).

The following problems still have to be solved:

- The costs of diagnostics are not easy to describe
- The evaluation of cost-effectiveness is difficult
- The regulatory pathway is fragmented

3 *Quintiles (2011), The New Health Report. 2011. Exploring Perceptions of Value and Collaborative Relationships Among Biopharmaceutical Stakeholders, p. 18; see: www.quintiles.com/newhealthreport*

4 *Soria JC, Blay JY, Spano JP, Pivot X, Coscas Y, Khayat D (2011), Added value of molecular targeted agents in oncology; Annals of Oncology, p. 1-14*

5 *Sadée W, Zunyan D (2005), Pharmacogenetics/genomics and personalised medicine; in: Human Molecular Genetics, Vol. 14, Review Issue 2: 207-214; p. 207*

6 *Gaultney JG, Sanhueza E, Janssen JJ, Redekop WK, Uyl de Groot CA (2011), Application of cost-effectiveness analysis to demonstrate the potential value of companion diagnostics in chronic myeloid leukemia; Pharmacogenomics 12(3), 411-421*

7 *Zaim R, Gaultney JG, Redekop WK, Uyl-de Groot CA (2011), Potential benefits of introducing a companion diagnostic in advanced non-small cell lung cancer; ISPOR 14th Annual European Congress, Madrid*

8 *Gaultney JG, Sanhueza E, Janssen JJ, Redekop WK, Uyl de Groot CA (2011), Application of cost-effectiveness analysis to demonstrate the potential value of companion diagnostics in chronic myeloid leukemia; Pharmacogenomics 12(3), 411-421*

9 *See Rawlins M (2008), De testimonio: on the evidence for decisions about the use of therapeutic interventions; in: Lancet 372:2152-61, p. 2156; Collier R (2009), Rapidly rising clinical trial costs worry researchers; in: CMAJ 180(3):277-278*

10 *Deverka PA, Vernon J, McLeod HL (2010), Economic Opportunities and Challenges for Pharmacogenomics; in: Annual Revue of Pharmacology and Toxicology 50:423-37; p. 427.*

11 *Lewensohn D (2010), Towards Personalised Healthcare (Karolinska Institutet, in association with Science Business), p. 7f.*

12 *Deverka PA, Vernon J, McLeod HL (2010), Economic Opportunities and Challenges for Pharmacogenomics; in: Annual Revue of Pharmacology and Toxicology 50:423-37, p. 429*

Costs of diagnostics are not easy to describe

Implementing personalised medicines in healthcare is potentially a costly investment: it requires testing a whole patient population to identify groups of responding patients or to screen out patients likely to suffer adverse events or who need different dosing.

Some evaluations have attempted to tie the diagnostic to the use of a specific new medicine ("co-dependent technologies") and have in some cases passed the costs of diagnosis on to the medicines developer. But more and more multiple tests and multiple personalised medicines for particular diseases become available. For example, in colorectal cancer and non-small-cell lung cancer, a set of parallel tests are to be performed on a number of molecular biomarkers to decide between a range of personalised medicines. But more complex diagnostic and treatment pathways make it less easy to ascribe costs of diagnosis to the use of a particular medicine.

Evaluation of cost-effectiveness is difficult

To evaluate the cost-effectiveness of particular molecular diagnostic approaches is also problematic. Diagnostics are normally supported by analytical performance data and rarely by clinical or outcome data, but in order to perform a health technology assessment you need the latter. According to a systematic review, only eight studies evaluated the clinical validity, and none of the studies was a prospective evaluation of a test's clinical utility.[13]

In addition, personalised medicines may also require a different view on the clinical evidence available when a medicine is launched. In some examples, personalised medicines have been approved on the basis of a retrospective analysis of clinical data identifying the responsive sub-population. In other cases, personalised medicines have been launched under conditional approval mechanisms on the basis of phase 2 data alone (smaller studies, often without overall survival end points).

Regulatory pathway is fragmented

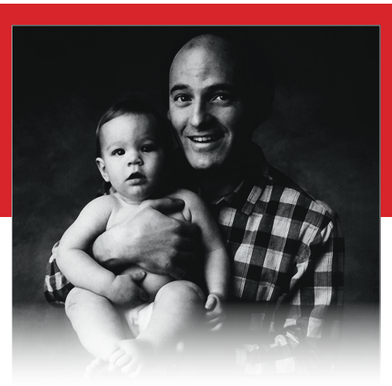
Eventually, market access of personalised medicines is highly dependent on the assessment process, in particular health technology assessment and pricing and reimbursement decisions. It is very costly to produce better evidence on the clinical utility of genomic tests for cancer prior to obtaining reimbursement. The current EU regulatory pathway for development and approval of drugs and companion diagnostics is fragmented. Ramsey et al. propose more creative funding strategies such as coverage with evidence development. However, "such an integrated model will require that test manufacturers, clinical trials groups and insurers modify their current ways of operating and paying for trials and treatment."[14]

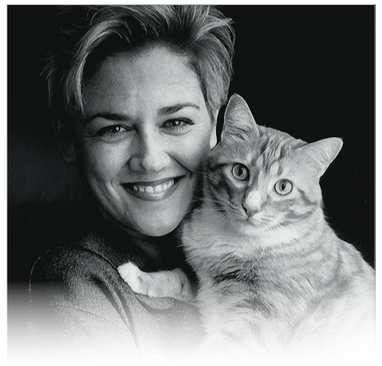
Discussion

Current health economic research shows that personalization of treatment, i.e. identifying responders and non-responders, has the potential to improve effectiveness and reduce costs. In addition, biomarker testing may lead to more successful R&D projects. However, the value of so-called tailor-made therapies depends to a large extent on the quality of the tailor. In other words, adaptations to both regulatory structures and market structures are necessary to encourage the development of personalised medicine.

13 *Ramsey SD, Veenstra D, Tunis SR, Garrison L, Crowley JJ, Bakerh LH (2011), How Comparative Effectiveness Research Can Help Advance 'Personalised Medine' In Cancer Treatment; Health Affairs, 30, no. 12:2259-2268*

14 *Ramsey SD, Veenstra D, Tunis SR, Garrison L, Crowley JJ, Bakerh LH (2011), How Comparative Effectiveness Research Can Help Advance 'Personalised Medicine' In Cancer Treatment; Health Affairs, 30, no. 12:2259-2268*





5 THE SOCIETAL PERSPECTIVE ON PERSONALISED MEDICINE

If personalised medicine is integrated in our healthcare system, the patient's world changes as well. This has an impact on the relationship between doctor and patient and it requires an investment in health literacy. It also has an impact on society as a whole.

This whitepaper argues that the concept of personalised medicine stands for great hope and excitement, as well as for questions and concerns. We have discussed the challenges in translation, development of routine companion diagnostics and pricing and reimbursing, but there is another challenge: how do we integrate personalised medicine into health practice in such a way, that it will maximize health benefits and minimize harm? This calls for empowered patients and carers, and thus investments in health literacy.

More information on people's health

Personalised medicine is about dealing with questions that relate to the individual person's body. What are the characteristics of this individual, such as age, gender, blood type, type of immune system or metabolism? To which diseases is the person susceptible? How is the individual's body likely to respond to diseases and medication?

The latest scientific developments have now reached a level at which molecular processes and genetic variations can supply better answers to these questions. In other words: personalised medicine can provide much more information about the health of an individual person. Are citizens ready for this? And are healthcare providers prepared to communicate accordingly?

More information on treatment options

It is important to realise that not all patients that will benefit from the personalised medicine concept are patients yet, or will ever be patients, in the traditional meaning of the word. Citizens and patients will be more and more asked to contribute to making treatment decisions.

Personalised prevention will become the key to personalised medicine. A test may, for example, reveal that someone is predisposed to develop a particular disease and thus enable that person to take preventive measures that may stop the disease from ever manifesting itself.

The comfort level with a treatment will increase when the patient can be assured that he or she does not belong to a category that is known to suffer from adverse reactions to that medicine, or to a category for which the medicine is not likely to work (in these cases, the doctor would have prescribed another medicine). Better knowledge, in advance, of the likely side effects of the medicine and their severity, makes it easier for the patient to plan for the treatment and to fit it into his or her daily life.

Impact on patient – doctor relationships

In order to get to know more about the individual's body and the way it may respond to diseases and medicines, it is often necessary to do some tests. This has several implications.

First of all, patients will become more involved in the decision-making process about their own treatment plan, beginning with a decision on a diagnostic test. A blood test is usually not regarded as inconvenient, but the results may not tell the whole story, while a biopsy, only obtainable under anaesthesia, will probably reveal the underlying problems, but could take several weeks to be analysed.

The patient and the doctor will have to discuss the options and consequences. What might happen if no treatment is administered, while waiting for the test results? What might happen if the medicine is prescribed without determining if it is suitable for the person in question?

Secondly, the patients will take part in the discussion about various therapeutic options. If any predictions can be made about the response to treatment, it will probably be expressed in a success rate. A patient's interpretation of 'chance' is a rather subjective. Some patients will think a 10% chance to respond well to the treatment is a fair chance, while others will not find it worth the discomfort or pain.

The patient will have to be supplied with information about the available personalised treatment options. Therefore, doctors will also have to know what is available and be capable of explaining things clearly to the patient. The doctor's expertise to analyse test results and put them in perspective, will also be crucial. As has been pointed out by experts, part of the responsibility to improve health literacy lies within the health systems.[15]

On the other hand, the patient will surely search the internet, looking for a 'patient like him or her', and participate in forums. Patients will be more empowered, better informed and more capable of making choices based on detailed information on their patient profile, in other words: they will be more 'health literate'. Moreover, it is to be expected that in the future patients will be able to find the results of clinical trials on the internet, with exact descriptions of the patient profiles based on biomarkers. Individual patients will be able to make a weighted and personal decision on their participation in clinical trials.

Finally, there is increasing availability of home tests which can be used to determine a person's biological disposition to a wide range of diseases including cancer. It is important to raise awareness about the fact that the presence of a biomarker for cancer does not necessarily mean that you will get cancer. If patients are concerned about the results of such tests, they should always consult a doctor.

Discussion

The future of medicine such as personalised medicine will be a major development but it raises also new questions. For instance ethical questions. While personalised medicine can identify patients who are likely to respond well to a particular medicine, it also offers the possibility to rule out patients for whom the medicine is not likely to be effective or suitable. What happens if there are no alternatives? Should the person still receive the only medicine available? Even if that medicine is likely to cause severe side effects or even adverse reactions? Moreover, would the medicine still be paid for by healthcare insurance companies?

Diagnostic tools are pivotal for the personalised medicine concept. Therefore biological samples are needed. What happens with the samples and related information that people provide? Who has access to it? Can individuals be identified? Who owns the data? Do employers or insurance companies have access to it? Would a predisposition to a disease influence a person's chances of employment or health insurance?

These and many more questions require an open dialogue between science, industry, policy and civil society.

15 *Kickbusch I and Maag D Health Literacy. In: Kris Heggenhougen and Stella Quah, editors International Encyclopedia of Public Health, Vol 3. San Diego: Academic Press; 2008. pp. 204-211.*