

For reprint orders, please contact: reprints@futuremedicine.com

Towards a framework for personalized healthcare: lessons learned from the field of rare diseases

A large percentage of medicines do not work for the patient populations they are intended to treat. Increased knowledge regarding genomics and the underlying biological mechanism of diseases should help us be able to stratify patients into groups of likely responders and nonresponders, and to identify those patients for whom a treatment might do more harm than good. This article sets out different policy perspectives for the healthcare systems, and draws in on 25 years of particular experience from the rare disease and orphan drug field, to illuminate the pathway forward in relation to key implementation aspects of personalized healthcare. In principle, we submit that targeting medicines to preidentified groups for whom we can predict a beneficial outcome is a good thing for everyone – first of all for the patients, but also for all the other stakeholders, including payers, treating physicians and industry – because it has the potential to create sustainable and functioning healthcare systems directed to better health and prevention of disease. Personalized healthcare over time could also lead to shorter drug-development times because of lower rates of failure in late-stage drug development. Using orphan medicines to treat well-diagnosed patients suffering from a life-threatening or seriously debilitating rare disease, is an attempt to work according to these principles. As there is much that needs to be done to turn the promise into reality, we need to identify the barriers and challenges to transform the potential opportunities into real-life benefits, and what needs to be done in order to overcome them. Learning from the field of rare diseases and orphan drugs may provide, perhaps unexpectedly, some of the answers to public policy questions related to future (personalized) healthcare, but of course not all aspects, are common between the two fields.

KEYWORDS: biomarkers ■ business models ■ diagnostic testing ■ education ■ ethics ■ incentives ■ multistakeholder collaboration ■ orphan drugs ■ patients outcomes ■ personalized healthcare ■ pharmacogenomics ■ rare diseases ■ registries ■ regulatory framework

Erik Tambuyzer

Genzyme Belgium NV/SA,
53 Ikaroslaan, Zaventem, Belgium
Tel.: +32 2714 1740
Fax: +32 2714 1747
erik.tambuyzer@genzyme.com

Some form of personalized healthcare has been practiced since the dawn of modern medicine. The concept of personalized healthcare today, however, is something very different, and its emergence is based on the development of the fields of life sciences and genomics. It is targeted at the genetic and biological make-up of the individual, or groups of individuals. This paradigm shift in science has created a much more comprehensive understanding of the biological mechanisms of disease, and the elucidation of the genome and of epigenome is still ongoing. In turn, this has led, and still leads, to a better understanding of a larger number of life-threatening or seriously debilitating rare diseases, for which treatments are being developed. Such treatments are called ‘orphan drugs’, as they had no ‘sponsoring parents’ in the past to develop them.

The new scientific findings provide an opportunity for stakeholders across the healthcare spectrum to move towards the development, use and reimbursement of targeted or

‘personalized’ therapies. Society in Europe, across stakeholders, seems to broadly embrace personalized healthcare across different stakeholders, as proven by a survey done in central Europe [101]. The new findings may be used, for example, to facilitate clinical translation and subsequent availability of beneficial drugs by stratifying patient populations during clinical trials, and by using input by the patients on quality of life, to guide clinical development of a product. This would increase the likelihood of showing benefit and, subsequently allows the physician to use patient-specific diagnostic information to guide the choice of therapy most likely to benefit that patient, if the right biomarker can be identified early in the development phase. The benefits of such a targeted approach are multiple but would have an impact on the entire healthcare framework, from patients to industry; and from academic researchers to payers. It has the potential to move us away from the current ‘trial-and-error’ paradigm of medicine – depending on

future
medicine part of fsg

the disease treated, between 20 and 75% of the medicines in use today do not seem to work properly for a broad set of patients [1,2]. The WHO estimates that, worldwide, half of all medicines are inappropriately prescribed, dispensed or sold, and that half of all patients fail to take their medicine properly [102]. Therefore, it is in society's best interest to dramatically change these numbers for the better.

There are already several examples of this approach to personalized medicine [103], but the concept is still in its early days, albeit with the potential to grow much larger. Today, approximately 10% of US FDA-approved drugs contain pharmacogenomic information [3]. The potential is also expressed by the Pharmacogenomics Working Party of the Committee for Human Medicinal Products at the European Medicines Agency (EMA) indicating in their draft guideline that the highest level of pharmacokinetic polymorphism is found in genes involved in drug metabolism [104]. Pharmacokinetics will indicate how the body 'digests' a specific drug after administration. This process can be affected by genetic factors causing differences in how the drug will perform, which are called polymorphisms. Much time is still needed to turn all that new knowledge into practical progress. Incentives and disincentives for reimbursement and data exclusivity also need to be addressed. Ethically, it is also important to ensure that the emergence of a more stratified approach to groups of patients does not prematurely deny beneficial treatment to an individual, because knowledge is still being added. A good but not yet perfect combination of a test with a therapy can indeed inspire health technology assessment agencies to advice to delay reimbursement while the proposed treatment solution could already benefit patients immediately. Such an attitude was initially seen from the National Institute for Clinical Excellence (NICE) in the UK, in the case of Herceptin[®], but has since been changed.

Of course, the practice of medicine will remain part science and part art. Hippocrates already recognized that 'it's far more important to know what person the disease has, than what disease the person has'. Personalized healthcare must continue to take some uncertainty of scientific results and the realities of human behavior into account, but the margins for uncertainty will be made smaller. Even if sequencing is 99.9999% accurate, a full genome sequence will contain 6000 errors [4].

As society looks to evolve its public policies around the emergence of personalized healthcare, it may be useful to examine the approaches used in the field of rare diseases. Learning from this field may provide answers to some of the policy questions as the field also features small(er) patient populations and rare diseases are frequently of genetic origin [105]. For that reason, we will discuss herein, from a policy perspective, some of these commonalities although not all answers will obviously come from this field.

This article is expanded from a presentation on 'Commonalities between Personalized medicine and Orphan Drugs' by Erik Tambuyzer that was presented at the annual European Forum for Good Clinical Practice (EFGCP) Conference, January 2010 [106], and a subsequent presentation by Wills Hughes-Wilson at a EuropaBio Workshop on 19 March 2010 [107]. Apart from a paper in social sciences [5], we could not find another paper in the literature regarding orphan drugs and personalized medicine, which is quite remarkable. In that paper, the conclusion is that there are many similarities in terms of registration and in social and economic impacts, and are regarded both positively and negatively at the same time.

Much lies between the emergence and the frequent application of personalized healthcare. In many ways, the current healthcare systems are indeed not designed to reward personalized approaches but to rather favor standardization of approaches to patient groups, and therefore, a shift towards personalized healthcare will require a major shift in healthcare systems, as well as in the business models of research-based pharmaceutical companies. This will also affect the other stakeholders.

While rare diseases and orphan drugs share some features with personalized medicine, they are also different in other aspects. Rare diseases may still not be economically interesting, are confronted with low awareness and expertise, and are very heterogeneous. By contrast, personalized healthcare is aimed at subgroups of mostly well-known large patient populations often already addressed by the healthcare systems and with well established infrastructures. We will mainly discuss the commonalities of both in this article.

What is personalized healthcare?

One of the issues with the concept of personalized healthcare is that it does not have a universally accepted working definition, which would be the first element to clarify the concept for broader use

in society. The lack of this makes communication and advances in the policy debate quite challenging. Often the concept of personalized healthcare is used negatively, owing to the glamorized picture painted for genetic tests for designer babies, partner traits for dating or marriage, and ancestry tests such as for ‘the daughters of Eve’, a test that determines from which of the so-called seven daughters of Eve (‘the first woman’) you might have descended from [108].

Current personalized healthcare is not solely oriented towards monogenic disorders but also paves the way in which new diagnostic and therapeutic approaches to common multifactorial conditions are emerging [4].

The US National Cancer Institute’s Translational Research Working Group defines translational research as ‘research that transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity and mortality’ [109]. Translational research is a combination of data from research in preclinical studies and in human trials with research to adopt best practices. Personalized healthcare is the concept that uses the results of such translational research combined with patients’ information, in the delivery of treatment and treatment protocols to stratified patient populations. From there, it may be further individualized by physicians and counselors using individual genetic information.

Therefore, we propose to define personalized healthcare as the use of modern biology’s new methods and tools that bring the right treatment for the right patient at the right dose and at the right time, in a sustainable way.

In the development of personalized healthcare applications, the major challenge will be the discovery and validation of biomarkers, especially for multifactorial, common diseases and to define patients and patient populations that can be ‘predicted’ to either react positively to a treatment, or to be susceptible to an unwanted adverse reaction or safety issue.

An important component of the delivery of personalized healthcare to patients will be the use of diagnostic tests to identify genetic or possibly other variations such as those involving environmental factors, diet, behavior or social circumstances [6]. Those diagnostic tests may be derived from biomarkers previously used in clinical trials, but not all biomarkers are expected to become diagnostic tests.

Diagnostic testing may be able to identify patients at a very early stage of disease or predict preventative measures, the latter not being

discussed further herein. Early detection offers the potential to preserve health and avoid irreversible damage, with the early institution of monitoring and treatment, and therefore, may contribute greatly to improved patient outcomes, but may also raise ethical questions such as the diagnosis of disease without potential to treat. Progressing in diagnostic, and even, preventative testing will require an examination of the current ethical, regulatory and reimbursement schemes associated with such testing and with the related therapy.

■ Is personalized really personal?

Personalized healthcare requires the development of products for targeted patient populations, a task primarily taken up by industry. These therapies will be further personalized in the practice of medicine by the physician, who will be using test information and other knowledge about the patient at his or her disposal, possibly coming up with an individual treatment plan for each patient, and adapting dosing, treatment regimens and so on, to that individual patient’s requirements. The outcome of personalized healthcare is, therefore, personal. The shared responsibility between therapy developer, treating physician and patient will necessarily lead to a higher degree of co-responsibility, because treatments need to be developed with individual patient outcomes in mind, and will not be standardized for very large patient groups as may be the case today with many treatments.

Personalized medicine should result in fewer adverse events [104], and thus should (at least over the long term) reduce healthcare costs [7]. The author expects that its application will increase the need of counseling, from diagnosis to treatment, because the finer details, and the implications of certain choices to be made, need to be conveyed to the patient. If done right, it may additionally result in better patient compliance/adherence to treatment because the treatment will work in almost all patients, which is a motivating factor for the treated patients. This in turn, can be expected to not only lead to a more cost-effective use of medicines but also to more consistent clinical outcomes. At the same time, the implementation will require a higher degree of education of treating physicians on an ongoing basis.

The above described process is already in use in treating rare diseases, where education is needed on an almost permanent basis, for treating physicians and for the patient. The author believes that this, in times of the internet patient, will enable physicians to regain a closer link with their patient, as counseling

will be individualized, and therefore, not possible by the patient him or herself by internet research alone.

What can personalized healthcare learn from the field of orphan drugs?

Orphan drug regulations have been approved in the USA in 1983, in Japan in 1993 and in 1999 by the EU. With more than 25 years of history in the USA [8], 17 years in Japan and 10 years in the EU [110], and some experience in other countries, there is much experience gathered that could inform the future development of personalized healthcare. The author believes that this is the case for the linkage, in the clinical practice, of diagnosis to therapy, for the use of registries to collect clinical data, for some aspects in the setup and running of clinical trials, for the need to educate the treating physicians, for the need for networks of excellence, for the more detailed collection and use of patient-centered quality-of-life data and other types of information coming directly from patients during drug development, for the closer relationship of developers and regulators with patient groups and finally for the need to optimally use scarce data to determine the clinical added value of a treatment.

Also, studying known monogenic disorders will improve our understanding of genetic and environmental modifiers of disease severity and provide an ideal for the discovery, evaluation and validation of novel bio-markers and -signatures for the prediction of severity that can be used for personalized therapies. Rapid and affordable testing for inherited disorders will reduce diagnostic delay, improve counseling and forge the modernization of genetic diagnostic services across Europe [111].

■ Rare diseases, orphan drugs & their regulations

Rare diseases, as defined in the EU by Regulation EC 141/2000 [112], are life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Community. This means fewer than 250,000 citizens out of approximately 500 million inhabitants in the 27 EU member states. Orphan medicinal products – orphan drugs – as defined in the same EU Regulation, are medicines for such rare diseases. They are called orphan because, without the provisional economic incentives, industry may be reluctant to invest in the development of a therapy because of the absence of a foreseeable return on investment.

There are an estimated 6000–8000 rare diseases that affect approximately 6% of the EU population, many of whom will not necessarily require treatment. Many of these patients are not yet diagnosed. Most rare diseases have a prevalence of less than 1/100,000, and therefore, may affect much fewer patients than the prevalence number defined by the EU regulation cutoff (for prevalence data, see Orphanet [113]). Some 70–80% of rare diseases are genetic in origin and most have no treatment available: the fewer patients affected, the less likely that a meaningful therapy already exists [TAMBUYZER E: RARE DISEASES, ORPHAN DRUGS AND THEIR REGULATIONS: ADDRESSING MISCONCEPTIONS. SUBMITTED MANUSCRIPT] [106,114]. In the case of one-third of orphan drugs in Europe, no alternative treatment to treat that disease (except supportive care) was available before the orphan drug was approved. In two-thirds of the cases, another treatment(s) was available but the approved orphan drug offers a ‘significant benefit to the patients treated’, as agreed upon by the regulatory approval body. This means that also from this perspective, while common diseases to be treated with personalized healthcare may have other treatment options, the situation for many rare diseases for which orphan drugs exist may not be dissimilar.

Since, in addition to a severe shortage of available therapies, patients with a rare disease confront low disease awareness, limited information is available and the knowledge about the disease is limited to few experts and expert centers with limited and late access to diagnostic testing. The challenge is therefore not only to develop therapies for these rare diseases but also to create a sustainable healthcare system capable of providing care, from diagnosis to treatment [TAMBUYZER E: RARE DISEASES, ORPHAN DRUGS AND THEIR REGULATIONS: ADDRESSING MISCONCEPTIONS. SUBMITTED MANUSCRIPT].

The field of rare diseases became a precursor of future developments in human healthcare [9,106,107], providing disease-modifying treatments and targeting smaller patient populations with high unmet medical needs. Once patients are diagnosed and their treatment decided, both the field of rare diseases and the field of personalized healthcare work with clearly identified patient groups, which may be small or even very small. Because the costs of developing orphan drugs and also of personalized medicines can be high, the economic rationale (on top of any safety concern) to provide such products only to patients who benefit, is important. This is only possible in practice through centers of excellence

for a specific disease or disease group, and only by treating patients using a confirmed diagnosis and treat according to treatment guidelines. Such links between diagnosis and therapy is highly important for orphan drugs and we believe is a commonality with personalized healthcare. The field of orphan drugs is expected to drive future healthcare developments such as the emerging collaboration of regulatory agencies and third-party payers on relative efficacy of drugs [10], which is also of high importance of the field of personalized healthcare. Examples of rare disease treatments are given in **Box 1 & Figure 1**.

■ Specificities of orphan drugs

The development of drugs for rare diseases faces difficult and complex challenges, related to the rarity of the diseases and their heterogeneous nature. Rarity does not eliminate the need during drug development to understand the disease being addressed, to testing potential solutions and selecting the best approach to move forward. In addition, the developed products also require a sustainable manufacturing process that can be scaled up. The cost of developing such a process can be substantial, certainly if the product is a biological. All of these costs are irrespective of the size of the patient population for which the product is developed. Subsequently, safety and efficacy testing in animal models (which may not be available), and confirming results in phased clinical trials are needed.

Disease rarity can have a significant impact on the clinical development pathway. Prior to development, very little may be known about that rare disease as no treatment may exist. Many physicians will not have heard of the disease, let alone had experience with patients affected. This causes 25% of the patients to receive a delayed diagnosis of between 5–30 years from the onset of clinical symptoms [115], and many different doctors consulted. On the one hand, this is very different for common diseases as we know about them today. However, those diseases become increasingly stratified into subsets and are classified differently, and many physicians are or will not be familiar with those subsets and new classification either.

Therefore developing a therapy for a rare disease faces amplified challenges: few patients may be available for study, the regulatory pathway may not be well-established, clinical end points may not be addressable over the short term and validated biological markers, which would allow for confirmation of clinical benefit in a reasonable period of time, may not exist. As

a consequence, the cost of developing a therapy for a rare disease is not necessarily less expensive than for other drugs. Similarly, the risks to obtain a positive result in drug development for a rare disease are higher, especially if no previous treatment yet exists [TAMBUYZER E: RARE DISEASES, ORPHAN DRUGS AND THEIR REGULATIONS: ADDRESSING MISCONCEPTIONS. SUBMITTED MANUSCRIPT].

Once clinical proof of principle has been established and because some rare diseases will affect small children, the manufacturer may be and often is under pressure from patients, physicians, and/or politicians to provide the therapy in development as compassionate-use material. This is also an aspect that we can learn from for personalized healthcare, when applied to severe diseases.

■ Registers & rare disease registries

Registers and registries are used to collect information about rare diseases and their treatments. They may also be important tools in the framework of personalized medicine in the future, and therefore, we define and describe such databases and discuss their use. A (patient) register is a database containing baseline information about patients with certain disorders, without any longitudinal follow-up. Such registers are setup, for example, at a national or regional basis by authorities to map rare diseases in their area and collect information on the prevalence of a rare disease. Italy is an example of a country using such an approach, but this may become a more common practice in the future. A (disease) registry is a specifically designed database to collect, mostly on a voluntary basis, observational clinical data from treating physicians, and is intended to explore and define the natural course and clinical characteristics of a disease, as well as to track and characterize response to treatment [116]. Such registries may be setup by either clinicians or researchers to collect data on a disease or on the use of a medicine for a specific disease, or by companies in conjunction with treating physicians when clinical trials for a treatment of a rare disease are started. They may also be required by the regulatory approval bodies as part of the approval process of the medicine, to continue to collect data about the treatment after approval. Rare disease registries are often setup on a global basis, instead of on a national or regional basis, because of the number of patients. Such registry is open to all physicians managing the disease and for all data of patients with the disease, whether they are treated or not.

Box 1. Examples of rare disease treatments and their analogy to personalized healthcare.**Enzyme replacement therapies for lysosomal storage disorders**

- Enzyme replacement therapies (ERTs) are used as treatment for very rare genetic disorders such as lysosomal storage disorders. We believe that they represent some good examples of personalized healthcare applications in practice, which are used in the medical practice outside the field of oncology. Some of the disorders which are treated, are life-threatening or seriously debilitating. They are very rare diseases as indicated in **FIGURE 1**, and relate to a genetic defect in the lysosomes, vesicles that are part of the human cell containing enzymes, which are each responsible for the elimination of a specific substrate used by the cell. If that does not happen, partially or totally, the cell will store these substrates and after a while this will make the cell malfunction. Each enzyme defect can cause a different lysosomal storage disorder, and each type can be very heterogeneous in its clinical manifestation.
- Before ERTs are used, the disease needs to be confirmed by a DNA test to ensure that the treatment will benefit the patient and will justify the cost of treatment.
- Clinical trials are setup with small patient groups and a registry is developed to follow-up the treatment longitudinally by registering patient data. Infrastructure, education, treatment guidelines and protocols had to be developed from scratch. Each disease can have subtypes in which the treatment may work better or worse. Examples of such already approved ERTs are: Cerezyme® for Gaucher disease, Fabrazyme® and Replagal® for Fabry disease, Myozyme® for Pompe disease, Elaprase® for Mucopolysaccharidosis-II (MPS-II [Hunter disease]), Aldurazyme® for MPS-I (Hurler-Scheie disease) and Naglazyme® for MPS VI.

Gene therapy applications

- Gene therapy is the correction of a genetic defect by providing a correct copy of the defected gene combined with a way to build this corrected copy into the cells expressing the gene. Gene therapy will need a confirmed diagnosis and strict clinical trials to show positive patient outcomes, and may also have to be controlled very tightly in terms of safety aspects, but it has the potential to dramatically change the life of the treated patients.
- Gene therapy will be another excellent example of personalized healthcare's commonalities with the rare disease field. No gene therapy-based medicines are approved yet, but it is believed that this will happen in the future, and very likely for rare diseases first. Successful clinical results have been shown recently in treating some Parkinson's disease patients [130]. An example of a gene therapy application for a rare disease that is moving forward in clinical trials is the correction of Leber Congenital Amaurosis Type 2, a form of hereditary blinding disorder belonging to the group of retinitis pigmentosa [131]. Theodor Karl Gustav von Leber described a form of inherited blindness in 1869, known as Leber's congenital amaurosis (LCA). In 1997, a related genetic defect in LCA2 was traced to gene *RPE65*, an enzyme required for photopigment generation. In 1998, the same blinding mutation was found in Briard dogs, and transgenic knockout mice were developed with the *RPE65* gene deleted resulting in visual impairment so an animal model is available. That made subsequent clinical trials possible and three independent clinical trials are now underway, of which two are in the US and one is in the UK.

Treatment of nonsense mutations

- Ataluren® [132] is an investigational (experimental) drug that is designed to enable the formation of a functioning protein in a patient with a genetic disorder due to a nonsense mutation. The complexity of the product and its delivery to patients is that it will only be possible to use for the treatment of genetic disorders that are caused by nonsense mutations, and not in patients who have other types of mutations. Nonsense mutations are single-point alterations in the genetic code that prematurely stop the translation process, thereby preventing production of a full-length, functional protein. This product is an excellent example of the promise that personalized healthcare holds to address significant unmet medical needs across different diseases, with the potential to make a major positive difference in the lives of patients and their families. It is being studied in several rare diseases, including Duchenne muscular dystrophy (DMD), a degenerative genetic muscular disorder, cystic fibrosis and hemophilia. Its use in medical practice will require gene sequencing to identify the patients that may benefit from the treatment. A case study by students at the Karolinska Institute, Stockholm, Sweden, as part of a study organized by Science/Business (Brussels, Belgium) notes the following:
 "Duchenne muscular dystrophy is a complex, inherited disorder – a perfect target for the potential of personalized medicine. The ailment affects one in 3500 males worldwide, making it the most common form of about 20 kinds of muscular dystrophy. Average life expectancy is less than 30 years. There is no cure – just inadequate treatment, with many side effects, by corticosteroids to slow or manage the disease progression. DMD sufferers cannot produce dystrophin, a protein that is an essential component of muscle. This is caused by a variety of genetic faults, which interrupt the production of the protein. Now, a number of potential treatments for DMD are in clinical development, targeting different ways of overriding the genetic faults to permit normal protein synthesis. Different treatments will be needed for different segments of the patient population, and patients will need to be genotyped to see which mutation they carry. Enter personalized medicine ... not just the treatment will be personalized; the delivery mechanism could end up having to be tailor-made, as well, depending on where the patient lives" [101].
- Gene sequencing brings us a step closer to personal genome sequencing, discussed in a recent article published in *The Lancet*. Genome sequencing comes with many practical challenges before it will enter the clinical practice [19,20], but holds enormous potential. In terms of costs, the goal of completely sequencing a human genome for US\$1000 is believed to be in sight [4].

While a company may provide the financing and IT backbone, patient and physician confidentiality for the registry is strictly maintained and the registry itself is often governed by an independent scientific or medical board of advisors.

The objectives of such disease registries are:

- To enhance the understanding of the variability, progression and natural history of the disease with the ultimate goal of better guiding and assessing therapeutic interventions;

- To assist the medical community with the development of recommendations for monitoring patients;
- To assist patients in learning about their disease and to report on patient outcomes to help optimize patient care;
- To evaluate the long-term effectiveness of the treatments, to report outcomes to the authorities;
- To provide clinical data for further product development for the disease.

The supranational or global nature of such registry will increase understanding (natural history, ethnicity and genetics) of and awareness about the rare disease and the therapy (timing, dosing and outcomes), facilitate physician patient monitoring and setup of therapeutic goals, support the development of diagnosis, disease-monitoring and disease-management guidelines, and analyze (long-term) treatment outcomes. It helps develop an international

community of treating specialists and stimulates physician and patient education and exchange of knowledge.

To be useful for health technology assessment, the data queried for, need to be incorporated in the registry design, which may often not (yet) be the case for registries setup for the follow-up of clinical trials or postapproval regulatory demands, and therefore, we may need adaptive registries in the future.

The challenges faced in developing registries and the methods for capturing patient data and outcomes may be important for personalized healthcare applications in real-life settings. Nevertheless, registries also have limitations: the data gathered are less controlled than in a clinical trial setting and related to all patients of which data are stored, and not to a specifically defined cohort of patients. These data may therefore also contain bias. Moreover, registries only contain data as defined at the time of the design of the registry, and therefore, may be limited in the responses that can be obtained from them.

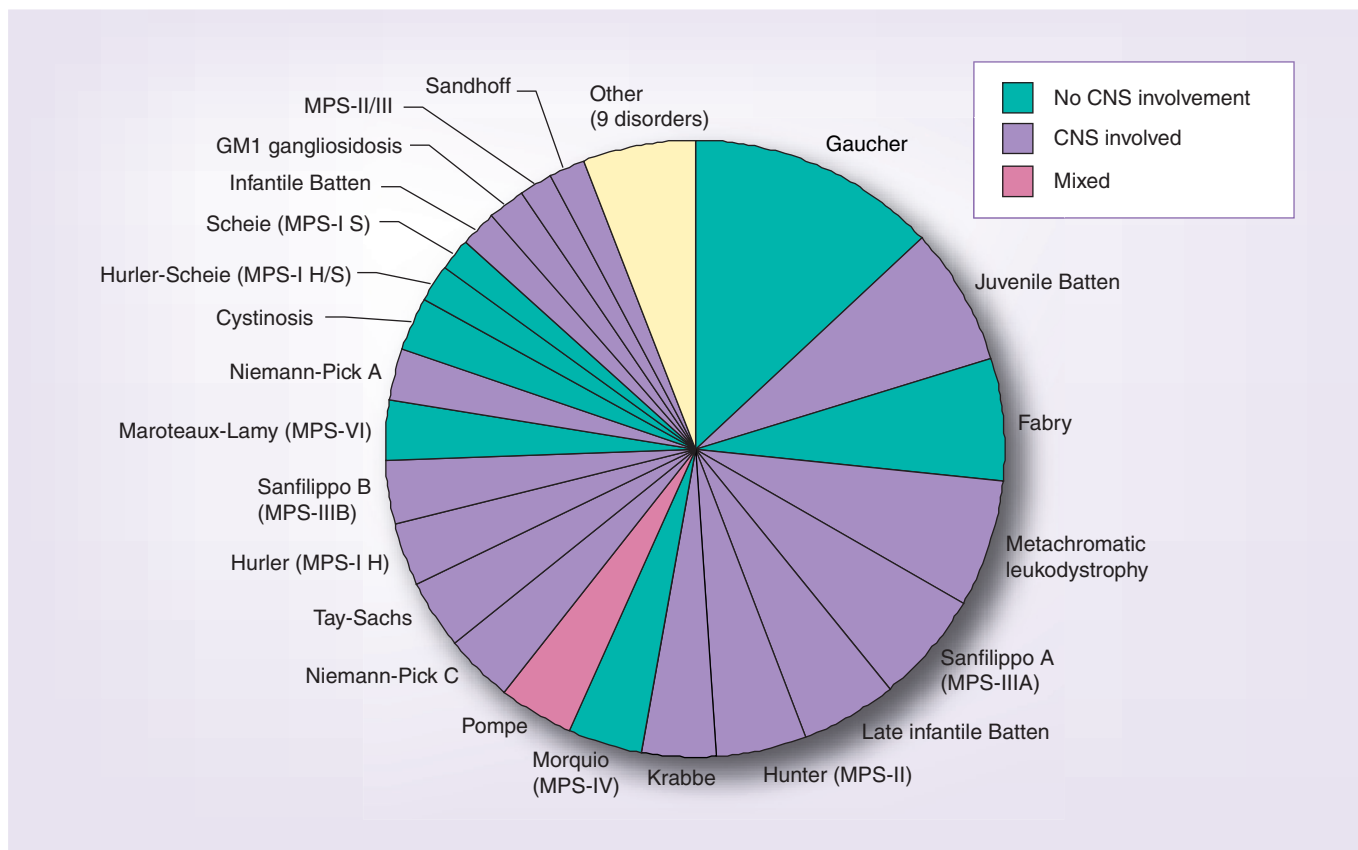


Figure 1. An overview of the relative frequency of lysosomal storage diseases. There are diseases caused by deficient enzymes in the liposomes. If they have involvement in the CNS, replacement enzymes are not able to pass through the blood–brain barrier because of their size. This means that such diseases are not targets for enzyme replacement therapies, and that another therapeutic approach is needed.

MPS: Mucopolysaccharidosis.
Data taken from [21].

■ Collaboration with patient groups

One of the characteristics of the field of rare diseases is the existence of well-organized, cross-border patient groups. Patient groups such as the National Organization for Rare Disorders (NORD) [117] and Genetic Alliance [118] are organized nationwide in the USA, with NORD as the driving force behind the US Orphan Drug Act approved in 1983. Rare Diseases Europe (EURORDIS), [119] and the European Genetic Alliance Network (EGAN) [120] are organized at a EU level. EURORDIS, which is strongly allied with NORD in the USA, was the driving patients' voice in the discussions about the European Orphan Medicinal Products Regulation. Those rare disease patient groups, and their members that are organized by disease but operate internationally, are not only involved in awareness building but also in the discussion of public policies as mentioned above, and operate more and more as the initiators of new policy initiatives. In addition, in the EU, they negotiated for representation in regulatory bodies such as the Committee for Orphan Medicinal Products, the Pediatrics Committee and the Committee for Advanced Therapies [121]. Patient groups also get involved in research about their disease and even fund company research for that purpose.

The unique setup and activity of rare disease patient groups has also led them to work very proactively with industry and act as a pulling force for information regarding the status of development projects. The collaboration and sharing of information between companies, patients and scientists have also led to productive mechanism of progress to discuss patient-relevant quality of life factors, communication pathways and novel forms of sharing information without breach of sensitive commercial confidentiality. The special ways of collaboration will also serve as a model for the way forward in personalized healthcare, both in terms of collaboration with industry as in terms of collaboration with regulators as both collaboration models are regarded as very positive in terms of productiveness and outcomes and is also the author's personal experience.

The impact of personalized healthcare on industry

Currently, industry is not only facing attrition, but also vastly increasing costs, driven by the increased demand for clinical data, stricter regulatory requirements and by evermore complex clinical trials. For this reason, public/private

partnerships such as the European Innovative Medicines Initiative (IMI; Brussels, Belgium) have been setup [122] to foster more biological and other knowledge development. At the same time, industry is facing downward pressure on prices because of patent expiry, and a more complex reimbursement and market access negotiation process based on clinical effectiveness, and soon comparative or relative effectiveness requirements. Moving into the development of personalized healthcare applications will require the full integration of genomics and genetics into a company's research and development programs and planning. The most adaptive companies have been doing this for more than a decade but for those that have not yet done so, several barriers remain. The first barrier is when a company cannot build the link between the integration of the genomics/genetics knowledge into its research and development, and a foreseeable and appropriate return on investment. Such investment will then be very vulnerable and may require careful, long-term research and development planning; getting over the 'valley of death' as this is being called [3]. This barrier is made higher by the lack of legal certainty for regulatory requirements of efficacy and safety for personalized medicine candidates, which are not (yet) harmonized internationally, and may decrease the will to invest in entering the field. The regulators are aware of this need and are working, both in the EU and in the USA, on filling these gaps. Those efforts entail the definition of what can be done in terms of co-regulating a 'companion' diagnostic test with a therapy, defining what will be required for biomarkers in clinical trials and in terms of data for the approval of a therapeutic and a diagnostic pair, or only a therapy, are producing guidelines on pharmacogenetics as referenced in the text [104]. Other aspects include the definition of clinical utility and validity for diagnostic tests.

Surely also the lack of availability of qualified/validated biomarkers to test the process is very important and for common diseases, there is a long way to go in order to map phenotypes with genotypes and determine the way forward from there.

Companies should also plan to deal with such increased regulatory requirements. Those with regulatory flexibility and expertise, and the willingness to confirm clinical utility via diagnostics will flourish. At the same time, harmonization of regulatory regimes at international level will be required, where appropriate, for industry to cope with more stringent regimes and control costs,

and not face another wave of increasing regulatory costs by nonharmonization, which would make innovative products even more costly to develop.

Furthermore, some of the questions of what is ‘ethically allowed’ in research and clinical trials, including about predictive genetic testing, are not yet fully answered in society: there is not yet ethical agreement on all aspects of what should be allowed and what would be socially unacceptable. Many issues that came up in genetics research or in the application of genetic testing in medical practice, such as the right of the individual patients – to know or not to know the result of a particular test for a severe disease – are amplified if used more broadly. In addition, personalized healthcare may also bring up some ethical issues related to gender or race.

Such barriers are amplified because of the volume of information gathered in the research and development phase, and by potential lack of a system to allow effective management and interrogation of all that information internally. Without rigorous processes, process issues may become ethical issues, for example, the lack of sufficient quality assurance in genetic testing would be an ethical issue. Key to this is the standardization of collection processes, quality of samples, full annotation (clinical, demographic and so on) of those biological samples and ready access by investigators in both the public and private sectors. The further development of personalized healthcare will also require a societal outreach component, which will need a collaborative effort with all involved stakeholders.

The growing interest of industry in the field of rare diseases is not only a consequence of the need for diversification after the research and development machine stalled. It is also because only 10–20% of rare diseases have some kind of treatment today [110], and those treatments can still be improved, thus the medical need remains high. However, even more important is that rare diseases as researched as models for more common diseases in a different field, such as oncology, neurology, autoimmune and infectious diseases, and provide a pathway to explore personalized medicine because of the many commonalities between the fields [110], or help identify molecularly distinct subtypes of some common diseases, which may lead to new therapeutic possibilities [3].

■ Changing business models in industry

Despite industry’s changing role, companies will need to change their view of a market that is moving towards personalized healthcare, even

if this is not always culturally easy [9,11,123]. Whether a company is owning or developing its own diagnostics business or not, is a company-specific choice. This may not dramatically influence its ability to be successful in personalized healthcare, as long as the understanding of the link with diagnostic testing is there. More importantly, companies will need to adapt from purely supplying a product to providing a full service to the patient, and to making sure that a full service is in place to guarantee the best possible patient outcomes. By contrast, personalized healthcare may have far-reaching and significant structural implications on the healthcare industry and on its business models, and have profound effects on healthcare systems overall. Some traditional pharmaceutical companies may encounter a great deal of trouble evolving their business model away from a core competency of selling drugs that only work for a portion of treated patients using broad-based sales and marketing teams, to a new approach targeting smaller populations. They may also face difficulties in including existing drugs in a personalized healthcare approach to optimize their value, rather than hoping that their sales will not falter and that regulatory bodies will not require new data to allow their further use. For all of this to materialize, it is clear that a company needs to be willing to plan for ‘the long view’, and not expect quick results but for a pharmaceutical company used to working on development timelines in the order of 12 years, this should not be an impossible requirement. A company should be prepared for sustained engagement with the patient groups, treating physicians as well as other stakeholders. The field of rare diseases and orphan drugs is a valuable and appropriate model for such engagement, and these elements are a prerequisite for sustained activity in the field.

Some believe that those companies that are slower to develop personalized targeted therapies risk losing substantial market share [12]. It is, however, in society’s best interest that companies that adapt can be sure of an appropriate return on investment. By giving much more predictable treatment outcomes, it is also expected that personalized healthcare will have a beneficial effect on the industry’s image, if the industry can stay away from hyping the concept and advocate true patient value.

At the same time, the premise that, in a future dominated by personalized healthcare, there will no longer be ‘blockbusters’, is wrong – if we follow the commonly used definition of blockbuster

as ‘a drug with more than (€ or \$) 1 billion in sales’. If the definition of a blockbuster is taken rather as ‘a drug for a large patient population’, then this premise may be more correct, but that definition is not the commonly used one for a blockbuster. We do, however, expect the nature of future blockbusters so-called ‘nichebusters’, to be different. Indeed, the value created by providing targeted therapies that address the real unmet medical need is enormous, so some of these products will still reach blockbuster status, while bringing great value to a relatively small patient group. Examples may be a disease-modifying treatment in a subset of Alzheimer’s patients or in life-threatening cancer indications.

Regarding the development of diagnostics, the most optimistic scenario is for those diagnostics that enhance drug use and appropriate delivery. In this case, the company that has developed and is selling the drug has an incentive to also provide the diagnostic test (e.g., the case of Roche’s Herceptin®). If a therapeutic product requires the testing of a candidate population, a pharmaceutical company will seek (a) partner(s) to develop biomarkers, which can hopefully be used as a diagnostic test for global use. Current healthcare systems leave diagnostic companies financially vulnerable, especially in a case where the company selling the therapy is not also providing the diagnostic test. Healthcare systems often reimburse testing activity and not the value brought by the test [11]. In the end, most probably, the majority of pharmaceutical companies will not develop and market tests with in-house resources, but will look for diagnostic companies to do so [13,124], this is an important consideration that needs to be solved. In fact, that is a very recognizable situation for the field of rare diseases.

Surely not all diseases and approaches will benefit from personalized healthcare? Some scientists, including Dr Malcolm Law of the Wolfson Institute of Preventive Medicine, UK, advocate that polypills, a combination of several medicines into one pill, may actually be a better solution, for example, in the cardiovascular field. This approach is going the other way compared with personalized healthcare [106]. Also vaccines will continue to be important preventative and therapeutic tools in the future. The current article is therefore not intended to criticize the research to discover and develop medicines to treat broad patient populations. Whatever works best in practice to treat a disease or a patient population should be pursued, and personalized healthcare adds another pathway to achieve that, but will not be the only one.

Role & value of diagnostic testing

Diagnostics and how to combine them with therapeutics in terms of regulatory approval, clinical use and reimbursement now are looked at in terms of healthcare systems that are setup to look at standard solutions, for large patient groups, and not for small patient groups. This is what the rare disease world has been confronted with, and is only slowly changing.

According to the WHO, much greater use of evidence-based diagnostic and treatment guidelines by health professionals is needed [102].

The use of diagnostics to predict individual response to treatment will also offer more safety and effectiveness [14]. The imperative use of diagnostic testing in personalized healthcare applications will require that the physicians are educated about rigorously using those diagnostic testing capabilities and about interpreting their results to explain them to the patients. If not, this would make personalized medicine fail. The introduction of the diagnostic test may be another layer of complexity but will improve patient outcomes, make them largely predictable and reduce liability for the physician. This may also be one of the reasons that personalized medicine will be put into practice in a hospital and specialized medicine setting and, only much later to primary care, if ever. This is another commonality with the field of rare diseases that is also hospital controlled and highly specialized.

Molecular genetic testing – looking for mutations in human genes – is used to identify single gene (Mendelian) disorders characterized by the absence of a critical protein or the presence of an abnormal protein. Examples include cystic fibrosis, muscular dystrophy, Gaucher’s disease and Huntington disease, although also subsets of common diseases may fall in this category in the future. Many common disorders have a genetic component, which may involve several genes, as well as interactions of these genes with the environment, diet and lifestyle. The quality of, especially genetic, testing has not always been guaranteed, but the extensive use of diagnostic tests in the process will start to put much more emphasis on the aspects of quality and quality control of such tests. Because treating physicians will heavily rely on reliable diagnostic results, more rules for quality control and quality assurance as well, and diagnostic testing laboratory accreditation, including for genetic testing, are being put in place. In Europe, the project EuroGentest was setup for this reason [125]. Patients should be confident that diagnostic tests reliably give correct results when used in making major medical decisions [3].

In addition to the need for technical quality, the use of diagnostic tests needs to be sufficiently validated by regulators in terms of their clinical utility and ultimately validity. Several guidelines are being developed and put in place (see for example [126]). Because genetic testing, especially DNA testing, has been based initially on small volumes of tests for relatively rare diseases on the one hand (cystic fibrosis, hemophilia and thalassemia) and for subgroups of more common diseases on the other hand (breast cancer and colon cancer) the timely provision of DNA-test results and models for international collaboration have come from the field of rare diseases. The work will benefit the field of personalized healthcare. But the further development will now also depend on a sustainable market for quality diagnostic tests. Why should medicines consistently be at higher than 80% profit margins and diagnostics at below 20% profit margins? [TAMBUYZER E:

RARE DISEASES, ORPHAN DRUGS AND THEIR REGULATIONS: ADDRESSING MISCONCEPTIONS. SUBMITTED MANUSCRIPT].

In order to develop diagnostics, fully consented tissue, serum and blood banks (biobanks) with anonymized clinical follow-up information are also needed; and this material is not often available. Therefore, the creation of biobanks is highly important and their coordination at multinational level such as by the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) [127] in Europe is applauded. Biobanks funding should be long-term and international harmonization of IT platforms a prerequisite in order to be fully useful.

For society as a whole, there is financial and societal benefit in getting a diagnosis right: in a study of autopsies in NY, USA, the findings were that 30% of people were being treated for diseases that they did not have [15]. So there is also a policy need to encourage better and more accurate diagnosis generally in order to better treat and lower costs, which is comparable to what happens in treating most rare diseases.

Healthcare system readiness

The current evolution also comes with challenges for the different players: healthcare systems currently may not be setup for the provision of the right patient with the right therapy at the right dose at the right time. Patients want better outcomes but are frightened by the complexity of the field. Also physicians are being overwhelmed by the volume of available data. They need additional tools to identify and track test/drug combinations, as well as more education on diagnostics

and genomics. They need more treatment guidelines and be organized in expert centers. Regulatory agencies are looking for the best way to include all the new information in a regulatory setting. Payers want evidence-based healthcare but are not yet getting all the answers yet.

Regulatory & regulatory policy issues

In order for personalized medicine to succeed, regulators and regulatory systems will need to adapt to the new knowledge, not to stifle innovation, be willing to take risk into account and to collaborate with patient groups, industry, experts and among themselves. Also in this context, the field of orphan drugs is a good example. FDA and EMA have a close collaboration for the evaluation and administration of orphan drugs [110]. The need to combine scarce data and expertise was recognized over the years, and this may also become the case for personalized healthcare. On top of the regulatory level, at the policy level a new system of regulatory data protection and exclusivity for new indications of existing medicines may increasingly become relevant and important for the field of personalized healthcare.

For a specific rare disease, as there are so many unknown ones, the regulatory pathway may not be well-established, clinical end points may not be addressable over the short term and validated biological markers, which would allow for confirmation of clinical benefit in a reasonable period of time, may not exist. This is what is being faced in personalized healthcare, in spite of existing other treatment options or not. But regulators face increased concerns about the safety of medicines, and need to remain up-to-date on new technologies [104]. For personalized healthcare, as for the development of new treatments in general, a shift towards ever-higher safety requirements for drugs in a risk-averse society [16] needs to be curbed, because a 'zero risk' expectation is a vicious circle. This does not mean that safety is not an important requirement, but that the answers will lie in new methods of collaboration to determine what safety is required in a specific application. Regulatory decisions cannot deny patients with life-threatening conditions access to drugs based on spurious safety signals [16]. This sounds very familiar to all those working in the field of orphan drugs. However, while personalized healthcare may address some safety concerns associated with the use of medicines, it is not a 'cure all' for risk.

Both the fields of orphan drugs and personalized healthcare need to prove that their products are not interchangeable with existing (cheaper) compounds already on the market [16]. In both cases, industry will also need to work with the physicians and patient groups on communication, as this communication not only includes the supply of a product, but also the link to a diagnostic test, counseling about the result of combining a test with a treatment, and the follow-up care. Before that, in both personalized healthcare and in rare disease applications, clinical trials need to be designed taking the small to very small patient population into account, and may be adaptive trials to collect as much information as possible. This is also happening in personalized medicine applications. [12,128]. In order to setup such clinical trials in optimal conditions, centers of reference, grouping experts in certain disease fields will greatly increase not only knowledge but also the effectiveness of setting up trials. This infrastructure need is exactly the same as in rare disease research.

In terms of stimulating personalized healthcare from a regulatory and policy perspective, our views about incentives how to do that are:

- To build the infrastructure as proposed by Hamburg and Collins [3], which would also stimulate work on saving failed drugs and encourage stratification work on existing drugs;
- To work on older or existing drugs while providing better regulatory data protection (a new system?) to protect the investment in additional therapeutic indications for existing medicines. Here, especially for products that are not or no longer patent protected, the market exclusivity provided by the Orphan Medicinal Products Regulation [112], may be a useful example on how such system may work, but it will not be the total solution, other elements will need to be added for patent-protected products;
- The work on biomarkers and epidemiology, as well as the work on biobanks needs to be stimulated by a different funding concept and with a longer term view. In that regard, the IMI [122] is a perfect example but only covers part of what is needed, especially on the biobanking aspect;
- The reimbursement situation for diagnostic testing, which relates to use in personalized healthcare, has to be based on value, not on technical acts, and this will require some work and suggestions from the EU level to make sure this is done in an harmonized way;
- Regulatory agencies should require pharmacogenetic data and diagnostic tests to be part of the submission package for regulatory approval where relevant.

One of the barriers for development of personalized healthcare is the lack of quality biomarkers, especially early in development, and their use to stratify patient populations. Their development and use may change throughout the development process of a therapy, but will need to stabilize at the latest in Phase III in order for regulators to evaluate their value in the process. This is being addressed by public–private partnerships such as the IMI [122] but also at national level by initiatives in several EU member states, including the Netherlands, UK and Belgium (Flanders region). But there is a lack of a single regulatory oversight for diagnostic testing and therapeutic regulatory pathways, allowing potentially conflicting pathways to market for a diagnostic test, either as a ‘regulated device’ or as a laboratory-developed test with an unclear conversion from a laboratory-developed test to a regulated device. There is also a substantial difference internationally on how this has been addressed so far, such as between the USA and Europe. Regulators also look at the use of diagnostics and the potential introduction of risks for patients or for therapeutics manufacturers, if prematurely used in clinical applications.

Biomarkers to facilitate drug development are already jointly qualified by the EMA and the FDA. The acceptance of surrogate end points that are not fully validated (including in the accelerated/conditional approval authorization pathways) is more likely in serious/life-threatening diseases with high unmet medical need and in rare disease populations.

■ Health technology assessment, payer & cost issues

The current environment is increasingly demanding more outcomes/evidence based end points, evidenced by the increasing use of Health Technology Assessment and relative/comparative effectiveness measures to understand the value of a product [10,17], be it a medicine or a device. Some regulatory agencies like the EMA take such trends already into account and build contacts with such bodies.

Because of the use of genomic biomarkers and the wealth of information they provide for the determination of the value of new drugs for use in reimbursement decisions needs translating into real-world solutions for human disease, regulators and payers are working together, now

that health technology assessments are a common feature in the healthcare landscape [10,17]. Payers face difficulties in following the rapid evolution of the diagnostics/genetics field but demand evidence-based medicine, so the evolution towards personalized healthcare should provide them with at least a part of the answer [18]. Making payment conditional on drug effectiveness [10], is facing challenges in the real-life situation as not all evidence is easily available and systems need time to adapt to collect additional data. Therefore, payers fund their own databases on patient outcomes, which they may not want to share with other stakeholders, but such sharing will become important even if there is a cost associated with it, and may even become an ethical requirement.

In demanding tests for evidence-based medicine, payers require providers to prove the relevance of such tests to the patient and the physician, and prove what they contribute in optimizing value for the patient and for society. In this context, more time needs to be spent in discussing and in recognizing the value of a diagnosis, and therefore, of diagnostic tests and testing. This includes a new look at how to improve reimbursement for such tests when combined with a therapy.

In the field of orphan drugs, the data regarding clinical value are also scarce and difficult to gather. Rather than having each country perform its own data gathering and analysis, even for very rare diseases, it is being proposed that clinical added value data are being collected at European level for common use by all countries. This is one of the recommendations of the High Level Pharmaceutical Forum [116]. This approach may also be useful for personalized medicine applications.

■ Ethical issues

Owing to the more intensive use of biological materials, the need for consented tissue, serum and blood materials from biobanks and more diagnostic testing, including genetic testing and the need for counseling, the broader use of personalized healthcare also brings a number of ethical issues to the forefront. Most issues are not purely ethical issues but a mixture of economic, emotional or cultural issues and these may be linked to each other.

The issue of what counseling is required before and after testing and by whom and who has access to genetic information is of high importance [19]. Such counseling will need to be optimally provided in order to ensure that the

patient understands the information supplied, but also to enable him/her to make a decision on whether he would like to receive certain types of information or rather not.

Additional issues include not only informed consent from patients, but also the anonymization of the data and the protection of the privacy of the patients. At the same time, the quality, appropriate validation and clinical utility of diagnostic testing will become even more important because important medical choices will depend on them. They will, therefore, become ethical issues, as medically relevant genetic testing will be considered an integral part of health services provision. Finding a level of regulation for genetic tests that both protects patients and innovation, as Hamburg and Collins put it [3]. Equal access to genetic testing will also have to be ensured, while preserving confidentiality and privacy. A multistakeholder approach may be the best way forward to discuss such complex issues. For example, the Strategic Analysis (STRATA) group in the EU, working on ethical, legal and social issues of genetic testing, recommended as early as 2004 that for rare, but serious diseases with an available treatment, EU Member States should introduce universal neonatal screening as a priority, when appropriate, along with a series of other recommendations [129].

High visibility of new developments and information to patients related to serious and life-threatening diseases needs to be in balance with the ethical issue of providing a timely and safe treatment for all patients in need. In other words, patients in need should be protected from 'hype', but at the same time, find a societally acceptable framework that gives them access to the benefits of increasing scientific knowledge. The decision not to use or to delay new technologies may impact the life of some: a responsible, informed and accountable healthcare system administration with long-term goals – not just looking at short-term budget goals – is an ethical requirement. A last element is that direct-to-consumer advertising of genetic tests that require genetic counseling is unethical, because it may subject a patient to an outcome that can be misinterpreted or can be an extremely shocking experience, and as such may have a detrimental effect on his/her health or mental state.

Corporate social responsibility will not only play a role in Europe or in the USA. As with orphan drugs, patients are not only living in the wealthy areas of the world, and these patients also deserve treatment. In personalized

healthcare, genome-based innovations will also be needed for less wealthy patients wherever they are located. The difference between the standard of care for patients receiving the latest therapies, and that for minority populations, for example, in cancer care [20], will be an enormous challenge to be overcome from an ethical point of view. Also for this complex discussion, the experiences from the field of orphan drugs and rare diseases may offer a good experience basis.

Finally, perhaps the most important issue that links the orphan drug field and personalized healthcare is the need for consensus building on how to move forward in complex, intellectually challenging situations. In such cases, as has been demonstrated in the field of rare diseases, the establishment of multistakeholder platforms is extremely helpful and ultimately time-saving. All stakeholders must work together to help reshape the healthcare system we need and make it sustainable [7,9].

Conclusion

Personalized healthcare is the direction taken by science and medicine. It is also what society would logically want because of its potential to improve patient outcomes, to reduce side effects, increase efficiencies in medicinal practice and create more predictability in the system overall. The 25 years experience gained in the orphan drug and rare disease field has many elements that could inform the personalized healthcare field. Much can be learned from orphan drugs and rare diseases to predict what future direction healthcare will take, including from the use of registries to collect real-life data, the use of expensive treatments for smaller patient populations under strict conditions of use, the role of industry, the need for centers of excellence and the collaboration with patient groups. This field is a 'societal laboratory'. However, personalized medicine will not be a 'cure-all' solution, and neither will all aspects be common with the field of rare diseases and orphan medicines. The commonalities lie mostly in that they both address unmet medical needs and combine diagnosis with therapy, that they both need a lot of communication and awareness-building, and that they both need the involvement of all stakeholders to optimize societal outcomes.

Therefore, policy makers should be willing to create incentives and pathways for industry and society to succeed and should look at the field of rare diseases for inspiration and solutions. One of the most important models to be

transferred from the field of rare diseases is the use of multistakeholder platforms to discuss the complex multifactorial issues associated with personalized healthcare.

Future perspective

The future of personalized healthcare is moving from science fiction to reality – the main things holding it up are various parts of and different elements within existing healthcare systems, which were designed for a very different business model. It is in society's best interest to go for better patient outcomes as promised by personalized healthcare, but current pressures on the various players are unsustainable, however.

Although for many applications, a major barrier is still the science, including the lack of biomarkers, in order to make the most of the possibilities opened up by already existing increased scientific knowledge, fundamental and almost revolutionary changes need to be made at all levels and for all stakeholders within the current healthcare systems. The tools for change are, arguably, already there: we could see a very different situation by the use of the molecular basis of disease, and the information provided by 'omics technologies (not only genetics but also those looking at other variable factors) to stratify patient groups into those likely to respond and those for whom treatment will have no, or a negative effect. This should not only improve treatment outcomes for patients, but should also better predictability for payers and in drug-development methodologies, including lower failure rates, and hopefully, increased patient compliance.

The 'traditional' concept of personalized medicine that has worked to date in the limited number of applications – a companion diagnostic for every treatment, or every drug developed together with a test – is unlikely to be the main business model as the concept gains more uptake, simply because it will be unworkable in practical terms for day-to-day clinical practice. There will be several different approaches, depending on the nature of the link between the genetic and other variable factors and the disease state in question, and each of these will require relying on collaboration with expert-center laboratories – similar to the 'Centers of Expertise' concept being developed for rare diseases. The partnership with the diagnostics sector will be well-developed, with accredited systems and laboratories performing essential functions in stratifying the patients pretreatment, and a guaranteed quality of testing results. Diagnostic

testing may enable to identify patients at a very early stage of their disease, which may enable early intervention, but this will also need to be handled ethically. This ethical framework is still

in development and scientific progress may run faster than what society can cope with in this respect. This should be taken into account and requires that counseling be given an appropriate

Executive summary

- The ongoing paradigm shift based on new scientific findings leads to a better understanding of the genetic and biological make-up of an individual.
- Society in Europe broadly embraces personalized healthcare across the stakeholders.
- There are already several examples of personalized healthcare practiced today but the concept is still in its early days.
- When society looks at public policies emerging for personalized healthcare, it is useful to examine the approaches used in the field of rare diseases and orphan drugs.

What is personalized healthcare?

- There is no uniform, simple definition of personalized healthcare for policy making.
- Main development challenges include the discovery and validation of biomarkers, main delivery challenges include the use of diagnostic tests.
- Aiming at improved patient outcomes, the physicians will individualize the treatment and personalized healthcare requires much involvement of all stakeholders throughout the process.
- About physician education, much can be learned from the field of rare diseases without which personalized healthcare will fail.

What can personalized healthcare learn from the field of orphan drugs?

- The link between diagnosis and therapy is a commonality between personalized healthcare and the use of many orphan medicines in practice.
- Centers of excellence by disease, being setup for rare diseases, allow the optimal use of scarce information for small patient groups. This will be a commonality between orphan medicines and personalized healthcare.
- Registries which are used for rare diseases may be an interesting tool for personalized healthcare to develop including in the regulatory process.
- Collaboration with patient groups, as in rare diseases, will further develop personalized healthcare: such collaboration is not limited to the development process, but extends to the regulatory and reimbursement approval process.

The impact of personalized healthcare on industry

- Industry is facing attrition, vastly increasing costs and downward pressure on prices of medicines: the integration of genetic and genomics does not come at an easy time. Personalized healthcare will require long-term thinking and a cultural shift in the industry, which some may not be able to make.
- There is a lack of regulatory certainty (e.g., co-regulation of a diagnostic test with a therapy) for personalized healthcare candidates.
- Industry will need to adapt to increased regulatory requirements, and regulators will need to harmonize regulatory regimes internationally.
- There is a growing interest from the pharmaceutical industry in rare diseases as models for common diseases because of the stratification into subtypes, and also because of the learning about the healthcare provision of tomorrow.
- Not all in healthcare will benefit from a personalized approach.

Role & value of diagnostic testing

- Physicians need to take diagnostic testing on board as part of the solution to improve patient outcomes.
- Personalized healthcare will be practiced in specialized medicine first. This is also true for the field of rare diseases, which is handled by specialized hospital centers.
- Stricter quality control and assurance of diagnostic testing will be of high importance because of the increased value of such test in the healthcare equation.
- The value that diagnostic testing brings to healthcare should be revisited and diagnostic tests should be more properly rewarded for that value: there is financial and societal benefit in getting a diagnosis right.

Healthcare system readiness

- New methods of collaboration between regulators and other stakeholders, as well as in-between regulators, can learn from the field of rare diseases.
- Communicating about benefits and the risks will become even more important.
- New incentives to stimulate personalized medicine should include new ways of data or intellectual property protection, long-term funding for and international harmonization of biobanks, and the better recognition of the value of diagnostic testing, and even more work on biomarkers will be needed, with even more public/private partnerships.
- Regulators, health technology assessment bodies and payers increasingly work together to derive the best value. The EU-level collection of clinical added value data for orphan drugs may provide a useful pilot study.
- Ethical issues may become more visible in the context of personalized healthcare, because applications become mainstream, and need to be addressed in society.
- Consensus building between stakeholders, as what has been happening for many years in the field of rare diseases, will help to make personalized healthcare sustainable for all.

place in the medicine of tomorrow. While this may increase costs over the short term, longer-term outcomes, with the avoidance of irreparable damage by early detection and of most adverse effects coming from the use of the wrong treatment, should be lower. The introduction of generic alternatives for major drugs of today may create space for such transition.

The collaboration of industry, regulators and health technology assessors/payers with participation of the patient groups will also better clarify what is to be expected in development and how data requirements can be kept at a reasonable level. The use of registries may help in this regard. The field of rare diseases is providing for real-life models and as more large companies are starting to study rare diseases as models for common diseases, the experience in the field of rare diseases and with orphan medicines will start to become more mainstream. This will also lead to the understanding of an increased level of co-responsibility by all involved stakeholders, so that a 'full service' for the patient results. This is only possible by taking the long view by all those involved. That long view has an important part reserved for education and communication, including the value and need for quality diagnostic testing. It will also include new incentives and public/private partnerships for things to move forward and put priority accents.

That priority accent will also mean that personalized healthcare will move forward first and foremost in specialized medicine hospital settings, a field that can also benefit the most from the experience with orphan drugs.

New players in the healthcare field will have become fully integrated partners and stakeholders in the healthcare systems. And, for the patient, more integrated approaches towards an overall successful healthcare outcome will mean better compliance and more efficient delivery of healthcare – and a move away from the 'try-it-and-see' or 'trial-and-error' treatment paradigm, which sees repeat physician visits at best and a visit to an emergency hospital department at worst.

Acknowledgements

The author would like to thank Alexandra (Wills) Hughes-Wilson from Genzyme, Brussels, Belgium, for discussions on the structure of the article and for helpful comments and suggestions about its content.

Financial & competing interests disclosure

The author is an employee of Genzyme. The author has 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.

Bibliography

Papers of special note have been highlighted as:

▪ of interest

▪▪ of considerable interest

- 1 Spear B, Heath-Chiozzi M, Huff J: Clinical application of pharmacogenetics. *Trends Mol. Med.* 7(5), 201–204 (2001).
- 2 Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR *et al.*: Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS ONE* 4(2), e4439 (2009).
- 3 Hamburg MA, Collins FS: The path to personalized medicine. *N. Engl. J. Med.* 363(4), 301–304 (2010).
- 4 Feero WG, Gutmacher AE, Collins FS: Genomic medicine, an updated primer. *N. Engl. J. Med.* 362(21), 2001–2011 (2010).
- 5 Boon W, Moors E: Exploring emerging technologies using metaphors – a study of orphan drugs and pharmacogenomics. *Soc. Sci. Med.* 66, 1915–1927 (2008).
- 6 Varmus H: Ten years on – the human genome and medicine. *N. Engl. J. Med.* 362(21), 2028–2029 (2010)
- 7 Davis JC, Furstenthal L, Desai AA *et al.*: The microeconomics of personalized medicine. *Nat. Rev. Drug Discov.* 8(4), 279–286 (2009).
- 8 Haffner ME: Adopting orphan drugs – two dozen years of treating rare diseases. *N. Engl. J. Med.* 354, 445–447 (2006).
- 9 Tambuyzer E: Targeted therapies: a sustainable business model? *Pharma. Focus Asia* 10, 26–29 (2009).
- 10 Eichler HG, Bloechl-Daum B, Abadie E, Barnett D, König F, Pearson S: Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. *Nat. Rev. Drug Discov.* 9, 277–291 (2010).
- 11 Quinn B: Personalised medicine: changing Business Models. *Pharma. Focus Asia* 10, 30–33 (2009).
- 12 The Pink Sheet. 71(008), 19 (2009).
- 13 Kubitzka L: The growth of personalized medicine will drive alliances between diagnostic and pharmaceutical industries. *Drug Discov. World* 17–24 (2009).
- 14 Blair E: Predictive tests and personalized medicine. *Drug Discov. World* 10(4), 27–31 (2009).
- 15 McDonald C, Hernandez M, Gofman Y, Suchecki S, Schreier W: The five most common misdiagnoses: a meta-analysis of autopsy and malpractice data. *Int. J. Fam. Pract.* 7, 2 (2009).

- **Based on autopsy data, an original paper showing the importance of a correct diagnosis, as many patients apparently were not treated for the disease they had.**
- 16 Eichler HG, Abadie E, Raine JM, Salmonson T: Safe drugs and the cost of good intentions. *N. Engl. J. Med.* 360(2), 1378–1380 (2009).
- 17 Schofield I: Burring the boundaries between regulatory approval and HTAs. *Scip News* 1b (2009).
- 18 Garber AM, Tunis SR: Does comparative-effectiveness research threaten personalized medicine? *N. Engl. J. Med.* 360(19), 1925–1927 (2009).
- 19 Samani NJ, Tomaszewski M, Schunkert H: Comment: the personal genome – the future of personalised medicine? *Lancet* 375, 12497–11498 (2010).
- **Interesting short perspective on the ethical issues and counseling in relating to personalized medicine.**
- 20 Borden EC, Raghavan D: Comments: personalizing medicine for cancer, the next decade. *Nat. Rev. Drug Discov.* 9, 343–344 (2010).
- 21 Meikle PJ, Hopwood JJ, Clague AE, Carey WF: Prevalence of lysosomal storage disorders. Batten data mapped from worldwide estimates. *JAMA* 281, 249–254 (1999).
- **Websites**
- 101 Science/Business Report and Survey on Health for All, Care for You, 22 April 2010 www.sciencebusiness.net/reports/healthforall/PM_survey_results.pdf
- **Recent and original report on a European survey regarding personalized healthcare and how various stakeholders look at it today.**
- 102 WHO: The World Medicines Situation: the rational use of medicines, 2004 <http://apps.who.int/medicinedocs/en/d/Js6160e/10.html>
- 103 The Case for Personalized Medicine, May 2009 www.PersonalizedMedicineCoalition.org/
- **Report from one of the most active groups worldwide on what personalized medicine will bring.**
- 104 European Medicines Agency www.ema.europa.eu/pdfs/human/pharmacogenetics/3764609endraft.pdf
- 105 Rare Diseases Europe www.eurordis.org/about-rare-diseases
- 106 The annual 2010 European Conference for Good Clinical Practice, about Aspects of Personalised Medicine for Society, Brussels, Belgium, 26–27 January 2010 www.efgcp.be/Conference_details.asp?id=235&L1=10&L2=2&TimeRef=2
- **Including the presentation on which this paper has been based.**
- 107 Hughes-Wilson W: Rare diseases and orphan drugs as a precursor to personalized medicine: analogies between the two fields www.europabio.org/Healthcare/events/Personalised-medicines-event-19-march-2010.htm
- 108 The Seven European Daughters of Eve <http://mctiernan.com/mtdna.htm>
- 109 National Cancer Institute www.cancer.gov/trwg/TRWG-definition-and-TR-continuum
- 110 European Medicine Agency conference: 10 years of orphan drug regulation in Europe, 3–4 May 2010 (including presentation by Erik Tambuyzer) www.ema.europa.eu/
- 111 Role of -omics in personalised medicine. Brussels, Belgium, 29–30 April 2010 http://ec.europa.eu/research/health/pdf/summary-report-omics-for-personalised-medicine-workshop_en.pdf
- **Recent report regarding the role of ‘omics in personalized medicine, by experts from all over Europe.**
- 112 EU Orphan Medicinal Products Regulation EC 141/2000 http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-1/reg_2000_141/reg_2000_141_en.pdf
- **From where it all started in Europe for rare diseases as a health priority: the EUs regulation on orphan medicinal products. Europe is now the world’s most active geographical area on rare diseases as a health priority.**
- 113 Orphanet report series www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf
- 114 Orphan drugs: rising to the challenge to ensure a better future for 30 million patients in Europe, EURORDIS statement www.eurordis.org/sites/default/files/publications/Statement_Future_of_Orphan_Drugs_14_October_09.pdf
- **Interesting analysis by EURORDIS, the EU patient group for rare diseases, about myths in the field of rare diseases.**
- 115 Rare Diseases Europe www.eurordis.org/sites/default/files/publications/Fact_Sheet_Eurordiscare2.pdf
- 116 Improving Access to Orphan Drugs for all affected EU citizens: EU-High Level Pharmaceutical Forum, 2 October 2008 http://ec.europa.eu/pharmaforum/pricing_en.htm
- **Set of policy recommendations originally drafted by a multistakeholder working group within the High Level Pharmaceutical Forum and accepted by the Forum.**
- 117 National Organization of Rare Diseases www.rarediseases.org/
- 118 Genetic Alliance www.geneticalliance.org/
- 119 Rare Diseases Europe www.eurordis.org
- 120 Patients Network for Medical Research and Health www.egan.eu/
- 121 European Medicines Agency: About Us www.ema.europa.eu/html/aboutus/emeaoverview.htm
- 122 The Innovative Medicines Initiative http://imi.europa.eu/index_en.html
- 123 Pharma 2020: Challenging Business Models, which path do you take? www.pwc.com/en_BE/be/pharma/pdf/Pharma-2020-Challenging-business-PwC-09.pdf
- 124 Diagnostics 2009: moving towards personalized medicine, PriceWaterhouseCoopers, 27 July 2009 www.pwc.com/us/en/healthcare/publications/diagnostics-2009-moving-towards-personalized-medicine.jhtml
- 125 Harmonizing genetic testing across Europe www.eurogentest.org/
- **Website of the European genetic testing programme, quality improvement and cross-border collaboration.**
- 126 American Association for Clinical Chemistry, Laboratory Medicine Practice Guidelines, Guidelines and Recommendations for Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice, edited by Roland Valdes, Jr, Deborah Payne and Mark W Linder www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/LAACP/Pages/default.aspx
- 127 Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) www.bbMRI.eu/
- 128 Kim Edward S, Herbst Roy S, Lee JJ *et al.* The BATTLE trial (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination): personalizing therapy for lung cancer. Presentation abstract AACR 2010, Washington, DC, USA, 21–27 April 2010

- www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=b21e246a-e09a-4c90-9c59-874f7139d921&cKey=381a62d2-5602-443c-83cc-f9a828f19e1b&mKey=%7b0591FA3B-AFEF-49D2-8E65-55F41EE8117E%7d
- 129 STRATA group: report on the ethical, legal and social aspects of genetic testing
http://ec.europa.eu/research/conferences/2004/genetic/pdf/report_en.pdf
- ■ **Good example of what a multistakeholder committee can achieve even in very complex areas such as ethical, legal and social issues of genetic testing.**
- 130 Gene therapy research on Parkinson disease
www.bloomberg.com/apps/news?pid=20601202&sid=aNohgZxH.NIU#
- 131 Leber congenital Amaurosis gene therapy (also published in March 2010 in Science Translational Medicine)
www.blindness.org/index.php?option=com_content&view=article&id=2062:new-study-paves-way-for-treating-second-eye-in-gene-therapy-clinical-trial&catid=65:retinitis-pigmentosa&Itemid=121
- 132 PTC Therapeutics
www.ptcbio.com/2.4_faqs.aspx