REVIEW ARTICLE

Personalized medicine: consequences for drug research and therapy

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Abstract: In drug research, a serious transformation has taken place. With increasing knowledge gained from molecular medicine, it became possible to refine and develop new therapies based on the molecular mechanisms of diseases. Medicine and drug development have seen a paradigm shift which can be characterized with the catchword "personalized medicine", also called "stratified medicine" or "precision medicine". Personalized medicine is based on defined tandems of therapeutic agents and diagnostic tests. With this addition to the regular medical examination of the patient, specific patient characteristics are determined. The results of such diagnostic tests are then decisive for the choice of therapy or control of the effectiveness of the chosen treatment. The benefit of personalized medicine for the patient is the higher probability of treatment success as well as improved effectiveness and reduced / avoided side effects. Health insurance systems and the public may have the advantage that the health funds can be used more efficiently on this basis. This new paradigm requires also a new debate on the remuneration in health care. In order to bring personalized therapies to patients as quickly as possible, all players in health care should work together to address the challenges associated with personalized medicine.

Keywords: personalized medicine, stratification of patient groups, tandems of therapeutic agents and diagnostic tests, patient care, cost efficiency

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Introduction

Drug research has changed fundamentally in recent decades. Thanks to a significantly better and more in-depth understanding of physiological and pathophysiological processes, molecular medicine has developed. This not only allowed a better understanding of disease processes but also provided knowledge regarding diagnostic and therapeutic measures on a molecular level.

As a result, the number of treatable diseases has increased significantly. The possibilities for differentiating between different indications and their sub-specialties have led to an armamentarium of new diagnostic and therapy options that was unthinkable 20 years ago. This applies both to the optimization of efficacy and the reduction/avoidance of undesirable side effects.

Thanks to the findings obtained and specialization, we can now work towards identifying the most suitable therapy for an individual patient — and in the correct dosage. Because the diagnostic and the therapeutic principle can be brought together on a molecular level — often through intervention on an identical

molecular target — we can now describe modern drug therapy as a step on the way to personalized medicine. In other words, medicine for various clearly identifiable patient subgroups based on highly specialized diagnoses as well as highly differentiated therapies both in quantitative and qualitative terms. Ideally, a specific diagnostic test to determine molecular characteristics should be carried out as part of regular patient examinations. The result of this test would then make it easier to decide on an appropriate therapy. The diagnosis and therapy should be so well matched that we can refer to a tandem comprising the therapeutic agent and diagnostic test.

In other cases, relevant parameters for metabolization or, more generally speaking, for the pharmacodynamics of the medicine are collected in order to adjust the dosage adequately. All these cases come under the heading of "personalized medicine", i.e., an optimized or differentiated therapy. For the research-based pharmaceutical and biotech industry and, in particular, for the doctor providing treatment, the challenges arising from this new understanding of personalized medicine are huge. Not surprisingly, this new paradigm also creates a need for a new debate regarding remuneration for health care services.

The article which follows will attempt to show what possibilities already exist today and what challenges — with a special focus on the German perspective — need to be addressed. The aim should be to make the idea of personalized medicine based on molecular findings a success — the success that patients need and the success we should be striving to achieve throughout the health care sector.

The Term "Personalized Medicine"

There are numerous definitions of personalized medicine, some of which are imprecise. These include "individualized medicine"[1], "stratified medicine"[2], "precision medicine"[3] and many others. In the present article, the term personalized medicine will be used.

The research-based pharmaceutical and biotech industry understands personalized medicine as defined tandems comprising a drug and a diagnostic test which lead to a differentiated therapy geared to individual patient groups rather than a diagnosis alone[4,5]. With the help of diagnostic tests, patients in need of therapy are subdivided into various patient groups: (i) patients for whom a specific medicine is an option, (ii) patients unlikely to benefit and (iii) patients who may experience serious side effects as a result of taking the medicine (e.g., because of a metabolic disorder). An alternative therapy must therefore be used for the last two patient groups (Figure 1). In light of this, the various therapy options are given a type of "suitability criterion".

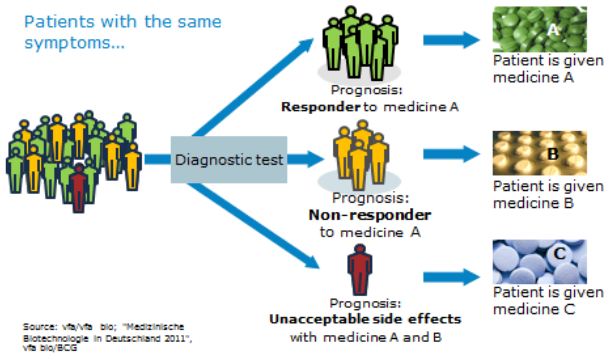

Figure 1. The principle of personalized medicine: On the whole, all patients exhibit the same or very similar symptoms. However, the diagnostic test shows that only some of the patients (the green ones here) would really benefit from taking medicine A. For certain patients (the yellow ones here), it becomes clear that they are non-responders to the medicine. These patients would not benefit from taking medicine A. The doctor therefore prescribes them medicine B. With the last group, there is a risk of unacceptable side effects. These patients too are then offered an alternative therapy option.

In order to identify this "suitability criterion" for the various therapy options, a diagnostic test (or possibly several tests) is carried out in addition to the regular medical examination of the patient to determine patient characteristics. These are then taken into account when choosing a therapy or checking progress. The test is designed to help choose a suitable therapy in each case and/or to determine the optimum dosage and possibly to check progress during therapy. A biomarker test can be used to check for the presence of specific gene alleles, gene expression patterns or biochemical parameters in blood or in other tissues and bodily fluids. The results of an examination using technical equipment can also make a contribution here.

The term "personalized medicine" therefore describes the targeted stratification of patient groups and is thus synonymous with "stratified medicine", another term used. The basic idea of keeping an eye on the patient and their particular needs when choosing a therapy is not what is new. After all, the knowledge and experience of the doctor providing treatment have always played a decisive role in diagnosing and treating illnesses. What is actually new about personalized

medicine is the fact that doctors are increasingly choosing therapeutic procedures using modern molecular diagnostic tools, taking into account the molecular basis/circumstances of the patient's or patient group's illness. This increases the efficacy of the treatment and unwanted side effects are either reduced (e.g., because the doctor knows a potential risk in advance and can include an additional therapy to treat the side effects before they show up) or avoided altogether (e.g., because of a metabolic disorder of the patient). The efficacy and tolerance of a medicine can also be predicted reliably for individual patients. Doctors can therefore make therapy decisions on an even broader, sounder basis.

Personalized medicine is thus a direct consequence of the achievements of modern biomedical research and, on the basis of these findings, the logical next step when diagnosing and treating illnesses. Thanks to progress in clarifying the genetic and biochemical causes of various illnesses, new molecular starting points are increasingly being identified. When applied to personalized medicine, these optimize the efficacy of medicines while reducing their side effects.

Consequences for Drug Development and Therapy

When work to develop personalized medicine began, looking for genetic or other markers for personalizing therapy was usually done later on. In some cases, it was not done until years after the therapy itself was introduced. Nowadays, this is an established step in many research and development programs. The clinical trials recorded in the international study register www.clinicaltrials.gov show that the use of biomarkers has increased significantly over the past 20 years — from approx. 4% before 1990 to 20% of all industry-sponsored trials in the years since 2005 (Figure 2A)[4]. An internal survey of vfa member companies also revealed that this figure in its trials could be as high as 40%[6]. This clear increase is confirmed by a further survey[7] (Figure 3) where the use of biomarkers for oncological trials rose from 19% in 2002 to 43% in 2013.

These figures show that research-based pharmaceutical and biotech companies are investing significantly in pharmacogenetics and other biomarker activities which provide an important basis for developing personalized medicine. Naturally, it is essential that informative, validated biomarkers with an appropriate level of sensitivity and specificity are available. Otherwise, the relevant medicine could be given to a patient for whom it is not suitable or patients could miss out on a suitable therapy. In contrast, the type of biomarker is of secondary importance. There is a broad range here — from clinical, genetic and biochemical biomarkers to results from imaging procedures.

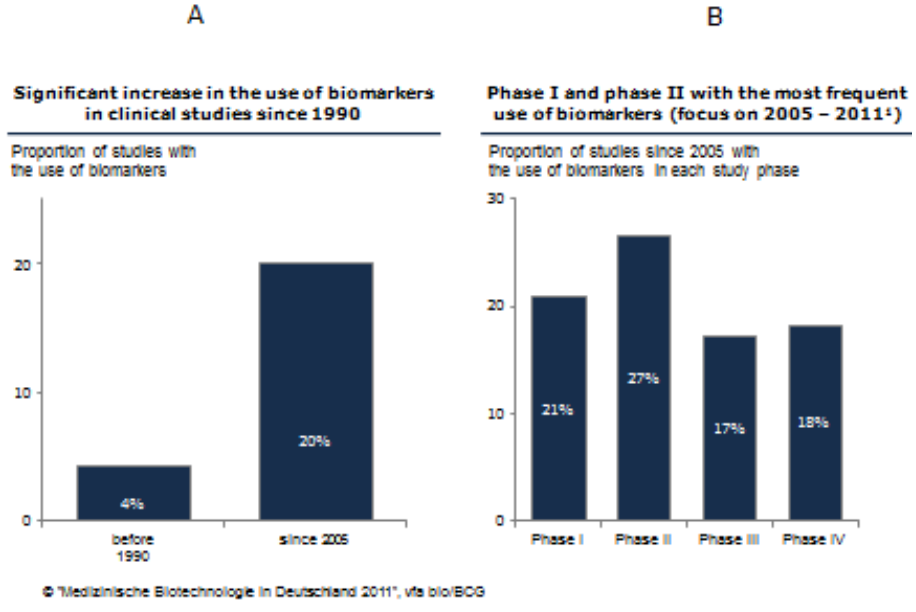

Figure 2. Significant increase in the use of biomarkers in clinical trials since 1990 — main focus on phase I and phase II trials; data basis: industry-sponsored active ingredient trials from http://www.clinicaltrials.gov (approx. 30,000 trials since ~1970); as at: February 2011; source: http://www.clinicaltrials.gov, BCG analysis[4]

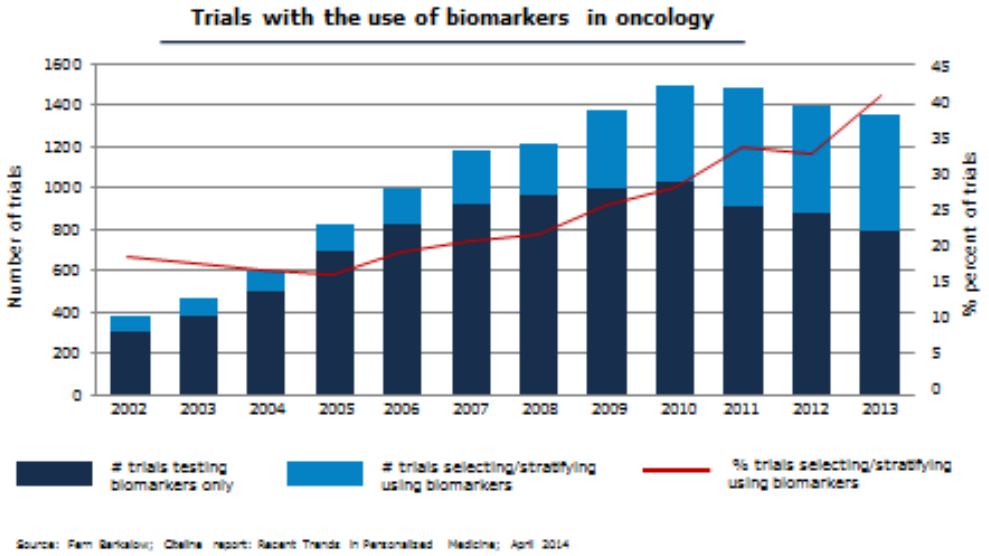

Figure 3. Significant increase in the use of biomarkers in clinical trials during the period from 2002 to 2013; data basis: evaluation in Citeline Trialtrove©; as at January 2014; source: Citeline Report[7]

When carrying out such clinical trials using this new therapy principle, there are however new challenges. These relate in particular to study planning and design, recruitment (many patients need to be "screened" before taking part in the trials) and carrying out such trials in general.

At the moment, biomarkers are most commonly used in the clinical phase II[4] (Figure 2B). In this phase, the efficacy of a medicine is checked with patients for the first time. In contrast, the use of biomarkers falls again in phases III and IV because this approach does not really benefit all medicines where personalization was originally researched. Indication-specific differences too are likely here.

All in all, these figures show that attempts are made to identify the patient groups who will benefit most from a therapeutic approach on the basis of pre-clinical findings early on in drug development.

Given the growing importance of diagnostics for personalized medicine, the research and development activities for new therapies which are already complex are set to become even more difficult and complex. Building up or acquiring diagnostic expertise for medicine development is therefore of particular relevance, whether it be in-house or via partnerships. One of the key problems is validating potential biomarkers. Better linking the results of basic research to clinical findings from well characterized patient cohorts is therefore important for the future. In Germany for example, work to establish a National Cohort (NAKO)[8] based on 200.000 people aged 20–69 years from all over the country began in 2014. This should hopefully provide new impetus for identifying and validating new markers.

In order to make progress here, the transfer of knowledge must be further improved and new forms of collaborations, partnerships and joint approaches between academia, pharmaceutical and biotech companies, diagnostic manufacturers, IT firms, service providers, approval authorities and HTA institutions need to be found.

Status Quo

As expected, oncology currently has the largest proportion of trials with biomarker checking — around 50%[4]. Biomarkers are used in more than one in three oncological trials (37%[4] and 43%[7]). Other important areas of use are cardiovascular and muscular diseases as well as immunology (Figure 4). Progress when it way for personalized medicine in other indication comes to molecular differentiation, in particular for oncological and immunological diseases, is paving the areas too. And personalized medicine is by no means a distant dream: in Germany, 48 drugs (Figure 5 and Table 1)[9] which may or should only be used in accordance with the described personalized medicine concept, i.e., following an appropriate pre-test, are currently approved.

Why is Personalized Medicine Important?

With the therapies previously available, it is known

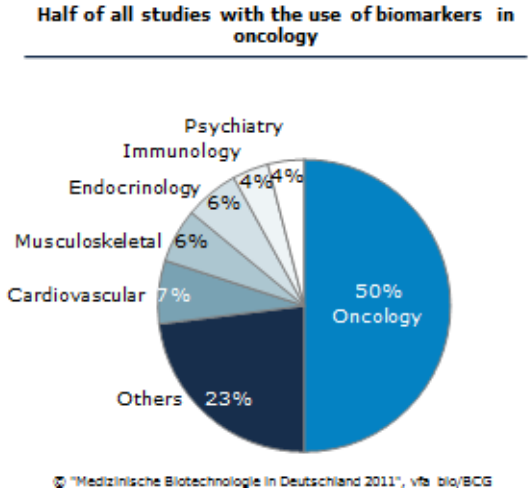

Figure 4. Oncology is a pioneer when it comes to the use of biomarkers; data basis: industry-sponsored active ingredient trials from http://www.clinicaltrials.gov (approx. 30,000 trials since ~1970 until February 2011); source: http://www.clinicaltrials.gov, BCG analysis[4]

that not every patient will respond or respond sufficiently to a medicine and could even experience side effects. In contrast, personalized medicine can give an indication of the correct dosage, tolerance and efficacy of a medicine by providing information about individual patient needs, e.g., specific enzymes required to dismount a drug's active ingredient. Personalized medicine methods fit into the range of diagnostic instruments available to doctors — from standard medical examinations and various diagnostic methods (e.g. laboratory tests, imaging) to an increasingly specific identification of diseases in light of the molecular circumstances behind the relevant patient's illness.

The doctor can increase the effectiveness of treatment thanks to the latest diagnostics and the subsequent use of new therapeutic procedures geared to the needs of the patient. Unwanted side effects can also be avoided or at least be reduced for the benefit of the patient.

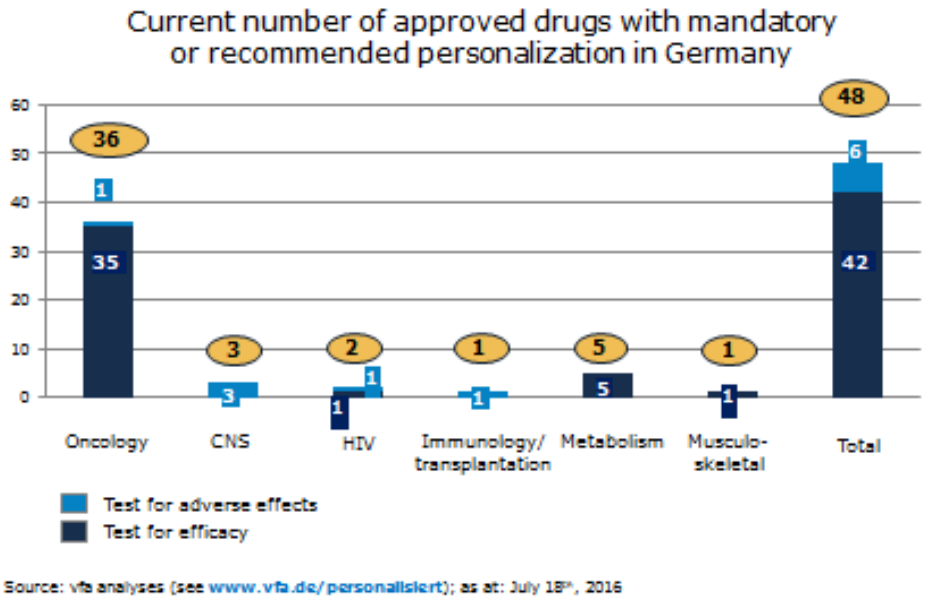

Figure 5. The number of active ingredients used in Germany with mandatory or recommended personalization in various areas of application — the majority of them are currently used in oncology[9].

Table 1. Explanation using Abacavir as an example: obligatory test for the presence of the HLA-B*5701 allele which increases the risk of possible serious side effects. In the event of a positive test result (approximately 5% of all patients), the drug will not be used. [Source: vfa research (see http://www.vfa.de/personalisiert.de)]

Active Ingredient	Indication	Test for....	Mandatory Test?
Abacavir	HIV	Side effects	Mandatory
Afatinib	Lung cancer	Efficacy	Mandatory
Anastrozol	Breast cancer	Efficacy	Mandatory
Arsentrioxid	Leukemia	Efficacy	Mandatory
Ataluren	Muscular diseases	Efficacy	Mandatory

(Continued)

Active Ingredient	Indication	Test for....	Mandatory Test?
Azathioprin	Transplants	Side effects	Recommended
Blinatumomab	ALL	Efficacy	Mandatory
Bosutinib	CML	Efficacy	Mandatory
Brentuximabvedotin	Lymphoma	Efficacy	Mandatory
Carbamazepin	Epilepsy	Side effects	Recommended
Ceritinib	Lung cancer	Efficacy	Mandatory
Cetuximab	Bowel cancer	Efficacy	Mandatory
Cobimetinib	Melanoma	Efficacy	Mandatory
Crizotinib	Lung cancer	Efficacy	Mandatory
Dabrafenib	Melanoma	Efficacy	Mandatory
Dasatinib	CML/ALL	Efficacy	Mandatory
Eliglustat	Gaucher's disease	Efficacy	Mandatory
Erlotinib	Lung cancer	Efficacy	Mandatory
Everolimus	Breast cancer	Efficacy	Mandatory
Exemestan	Breast cancer	Efficacy	Mandatory
Fulvestrant	Breast cancer	Efficacy	Mandatory
Gefitinib	Lung cancer	Efficacy	Mandatory
Ibrutinib	CLL	Efficacy	Mandatory
Imatinib	ALL/CLL	Efficacy	Mandatory
Ivacaftor	Cystic fibrosis	Efficacy	Mandatory
Lapatinib	Breast cancer	Efficacy	Mandatory
Letrozol	Breast cancer	Efficacy	Mandatory
Lomitapid	Hypercholesterolemia	Efficacy	Recommended
Lumacaftor/Ivacaftor	Cystic fibrosis	Efficacy	Mandatory
Maraviroc	HIV	Efficacy	Mandatory
Mercaptopurin	Leukemia	Side effects	Recommended
Migalastat	Fabry's disease	Efficacy	Mandatory
Natalizumab	Multiple sclerosis	Side effects	Recommended
Necitumumab	Non-small-cell lung cancer	Efficacy	Mandatory
Nilotinib	CML	Efficacy	Mandatory
Olaparib	Ovarian cancer	Efficacy	Mandatory
Osimertinib	Non-small-cell lung cancer	Efficacy	Mandatory
Oxcarbazepin	Epilepsy	Side effects	Recommended
Panitumumab	Bowel cancer	Efficacy	Mandatory
Pertuzumab	Breast cancer	Efficacy	Mandatory
Ponatinib	ALL	Efficacy	Mandatory
Tamoxifen	Breast cancer	Efficacy	Recommended
Toremifen	Breast cancer	Efficacy	Mandatory
Trametinib	Melanoma	Efficacy	Mandatory
Trastuzumab	Breast cancer	Efficacy	Mandatory
Trastuzumabemtansin	Breast cancer	Efficacy	Mandatory
Vandetanib	Thyroid cancer	Efficacy	Recommended
Vemurafenib	Skin cancer	Efficacy	Mandatory

Source: vfa research (see http://www.vfa.de/personalisiert.de); as at: July 18th, 2016

Thus, the patient will benefit from personalized medicine as the therapy is more likely to be effective and patients will more likely tolerate the drug administered. Ideally, ineffective treatments for patients not responding to treatment (non-responders) or therapies which need to be aborted prematurely owing to intolerances can be avoided. This is particularly important as many personalized drugs are currently used to treat serious and chronic illnesses.

What are the Challenges of Being Successful with Personalized Medicine?

The personalized medicines that are being developed or are already available show that there is a high level of inventiveness and innovation when it comes to academic activities in the field of biomedical science and in pharmaceutical and biotech companies. The scientific and technical requirements when developing this new branch of molecular medicine are very complex and resource-intensive.

Given the growing number of biomarkers and individual therapy options, the importance of personalized medicine is increasing. Therefore a challenge for the doctor is coming up too — keeping track of the ever more complex tests and therapy options. Owing to progress in research into the molecular causes of illnesses, the information base will grow continually. In light of this, ways must be found to cope with increasingly complex information. This is the case for example if a number of biomarkers to be tested and/or other diagnostic parameters need to be recorded for an illness at the same time.

In order to be able to compare patient profiles and the medication required quickly and reliably in spite of the increasing complexity of day-to-day medical work, quality-assured, high-performance and learning-capable Internet-based platforms are needed. With such platforms, a large number of therapies — even those with a complex biomarker background — could be personalized reliably and thus optimized in the future. These platforms must be stable, systematically updated and independently validated. Innovative IT platforms will play an important role in ensuring that personalized medicine becomes more widespread.

On the scientific side, efforts must be made to drive forward the identification and clinical validation of new biomarkers in order to be able to develop new personalized medicine approaches in the future too. The validation of biomarkers is essential when it comes to ensuring broad, reliable use of personalized medicine and requires significant use of resources on the part of research-based pharmaceutical and biotech companies.

There will also be further challenges affecting all areas. These include basic research (e.g., biomarker research, biobanks), clinical research (e.g., study planning/designs, screening a large number of patients in order to identify the few ones who are suitable for the chosen approach) and communicating with ethics commissions and patients until approval is given.

Specific Problems in Germany?

While the potential of personalized medicine is scientifically acknowledged, there are serious problems in Germany, in particular regarding remuneration for diagnostic tests which form the basis for the correct use of drugs with a recommended or prescribed test. At the moment, the tandem comprising diagnostic test and therapeutic agent still ends upon approval. The drug is approved as part of an official procedure and, when launched on the market, is initially paid for by the statutory health insurance system. Its additional benefit identified during the early benefit assessment must then be proven and a reimbursement price negotiated with the statutory health insurance system.

If a specific diagnostic test is required for a drug, the test must first be validated, a CE marking must be obtained and the test must be registered with the German Institute for Medical Documentation and Information (DIMDI). It will then be allowed on the market but will not be immediately reimbursable. An assessment procedure involving the joint self-administration of the statutory health insurance system and the medical profession then takes place. This laborious procedure can take up to six years. In the meantime, the drugs can already be used and the doctors (or their patients) are left to deal with the unanswered question as to whether or not the required diagnostic test will be reimbursed. And even after the test had reached this status, in many cases diagnostic tests are still challenged or will be replaced by new (and e.g., more reliable) approaches.

Those responsible for health care policy must therefore ensure suitable conditions for personalized medicine. The additional benefits of personalized drugs should therefore be acknowledged during the early benefits assessment — naturally on the basis of medical evidence and validated diagnostic tests. Steps must also be taken to ensure reasonable and immediate reimbursement of the costs of personalized drugs

and diagnostic tests.

In Germany, some progress is being made in this area. With the new doctors' fee schedule (EBM) guidelines which came into force on July 1st, 2016[10], a number of tests have been explicitly approved for reimbursement. 1st of July 2016 could have actually been a good day for personalized medicine. When the revised version of the EBM came into force, companion diagnostics (CDx) which indicate a response to lifesaving cancer drugs were for the first time given their own reimbursement code — and tumorigenesis examinations were even given a new chapter of their own (19.4). The Federal Association of Statutory Health Insurance Physicians (KBV) and the Central Association of Statutory Health Insurance Companies (GKV-Spitzenverband) who were responsible for the revision thus sent out a positive signal.

However, reimbursement by the health insurance system in Germany was explicitly ruled out for the liquid biopsy approach which is currently being promoted intensively on a scientific level. Two sentences in relatively simple legal language which precede the newly created Chapter 19.4 are causing concern for providers of molecular cancer therapies and the associated diagnostic tests: “The fee schedule items in Section 19.4 of the EBM may only be invoiced for in-vitro diagnostic tests for tumor genetic changes in neoplastically transformed tissues and organs. Analyses of free nucleic acids in plasma and gene expression analyses other than tests carried out under fee schedule item 19435 [blood cancer but not solid tumors] are not billable.” This means that contracted doctors can only invoice invasive tissue biopsy-based CDx tests. In contrast, liquid biopsy tests which are relatively inexpensive and patient friendly as they are non-invasive are excluded — even though they have already been approved for use on the market. This is detrimental to patients in Germany and will hinder the spread of personalized medicine.

However, there are still reasons to remain hopeful — the German Federal Government’s “Pharma Dialog” was concluded in April 2016[11]. It states that diagnostic procedures as part of personalized medicine “should be better reimbursed” in the future. A draft bill which may address the reimbursement problems is expected to be published in summer 2016.

The problem of reimbursement diagnostic procedures is not the only issue which needs to be addressed. Those who provide the medical service must also be compensated for the extra work involved in diagnosing an illness and explaining it to patients. A dedicated infrastructure for genetic data for example would be beneficial here. This would rule out possible multiple testing and could thus help to ensure cost-efficiency. A dedicated diagnostic infrastructure made up of regional diagnostic centers should be set up across the country. This already happened in France. It is not without reason that France is the European leader when it comes to carrying out such trials[7]. Research and the use of personalized therapy approaches as part of day-to-day therapy would benefit equally from this. After all, regional diagnostic centers of this type allow the proper validation of all diagnostic tests used and quality assurance, e.g., through standardization. This can also significantly reduce the risk of false positive or false negative test results — ensuring reliable results for the patient, the doctor providing treatment and research. Such centers can also feature virtual elements.

Furthermore, the full potential of personalized medicine can only be realized if the doctor has sufficient time and resources to carry out more complex analyses, to interpret them and to assess them. Ultimately, the patient should not have to deal with possibly complex information alone, for example if they find out that a new medicine is not an option for them owing to the molecular characteristics of their illness. Here too, doctors play a special explanatory and advisory role which must be supported and rewarded accordingly.

Acceptable legal conditions and a positive perception of the necessary genetic tests by politicians and the public are further requirements when it comes to the practical use of personalized medicine.

Conclusion

Many challenges still need to be addressed in order to establish personalized medicine as part of everyday medicine and to take advantage of the opportunities for patients[12]. Logically, everyone involved in the health care system should tackle the challenges posed by personalized medicine together. In future, more personalized therapies could be possible, allowing the best possible patient care including more efficient use of the available resources.

Conflict of Interest and Funding

Dr. Thorsten Ruppert and Dr. Sabine Sydow are employees of the Association of Research-Based Pharmaceutical Companies (vfa). Its member companies develop personalized medicines.

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