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AT THE GERMAN BUNDESTAG

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Individualised medicine and health care system

Summary

June 2008
Working report no. 126



SUMMARY

For some years now, the topic of individualized medicine has been discussed in futures studies and also in scientific literature as a significant development which could characterize health care in about twenty years' time. Against this background, in the current early phase in the research and health care policy discussion about the future option of individualized medicine, the objective of this futures report is to analyze

- > which development lines in the life sciences can contribute to an individualized medicine;
- > how the present status of science and technology and the possible future developments should be appraised;
- > which are the implications for technology development and the integration of these technologies in the future health care system, if they are to make a contribution to individualized medicine.

These implications will be discussed with particular emphasis on science and technology development, medical care, enterprises and health insurance companies. A systems perspective will be adopted.

DEFINITION AND TYPOLOGY OF INDIVIDUALIZED MEDICINE

Since there is currently no accepted standard definition of the term »individualized medicine«, it will be understood in this futures report to mean a possible future health care system which could develop out of the synergistic interaction of the three drivers »Medical and societal need«, »Scientific-technical developments in the life sciences« and »Patient orientation«. The medical and societal needs consist in this context in meeting the growing challenge of complex and often chronic diseases, such as cardio-vascular, metabolic, neurological illnesses and cancers which were only inadequately treatable up to now. Onset and course of these illnesses are determined by a complex, little understood interaction of many, not yet fully known factors (e.g. environmental influences, life-style, genetic disposition, socio-economic status). Approaches lie in the development of new or improved therapeutic, preventive and rehabilitative interventions, respectively in the introduction of new interventions with increased efficacy as well as in the avoidance of chronic diseases by means of preventive measures or in postponing the disease onset to a later age in life (»healthy ageing«). Ultimately, the quality of life should be increased while at the same time quality and



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cost targets in the health care system should be met and the strain on the social systems relieved.

A prerequisite for the development of prevention and treatment options for complex illnesses, which show an improved health outcome, is as comprehensive a knowledge as possible of all relevant disease factors and an understanding of their interaction. In this category belong environmental factors (e.g. nutrition, exposure to environmental pollutants, pathogens), life-style and socio-economic status, genes, physical and mental state as well as interventions (e.g. medication). In the case of individualized medicine it is hoped that genome and post-genome research, molecular medicine research and cell biology research in particular will provide a knowledge and technology basis on which improved possibilities for diagnosis, therapy and prevention can be developed.

Finally, in the past years the international and national health science and political discussion has tended increasingly to take more account of the patients: the up to now – compared with other actors in the health care system – weak position of the patients should be strengthened, so that they have greater influence on decisions and actions concerning their health. This aims at enhancing patients' autonomy and consumer sovereignty. At the societal level, this corresponds, on the one hand, with a growing health awareness on the part of citizens to assume responsibility for their own health, but on the other hand also with the increasing expectation of society that individuals should exercise this own responsibility via appropriate health-related behavior and financial contributions.

These three – initially independent – drivers are conjoined in individualized medicine, which offers the prospect of meeting quality and cost targets in the health care system by means of health care tailor-made to suit each individual. This made-to-measure care should be achieved on the one hand through advanced analytical and diagnostic possibilities to determine the individual state of health and risk of incurring disease. In this context, new biomarkers will be applied which were developed from genome and post-genome research and molecular medicine at the level of the genome, transcriptome, proteome, metabolome as well as morphology and cell biology, plus corresponding analytical methods, e.g. imaging techniques. On the other hand, individualized medicine consists of preventive or therapeutic interventions which are specifically adapted to individual situations.

In total, five different individualization concepts can be identified within individualized medicine («Typology of individualized medicine«):

- > biomarker-based stratification (group formation);
- > genome-based information about health-related characteristics;
- > identification of individual risks of incurring disease;
- > differential interventions; and
- > unique therapeutic measures.

»Unique therapeutic measures« represent therapeutic interventions tailor-made for individual patients (e.g. prostheses and implants individually manufactured by using »rapid prototyping« or cell therapies based on the patient's own cells), in which the »individualization« is based on the manufacturing process of single-unit production, that achieves its particular therapeutic quality in that it is only suitable or efficacious for the target patient, but not for other people in similar fashion.

In the other four concepts the »individualization« is primarily based on a division of the patient population into clinically relevant sub-groups beyond the present status quo (so-called stratification), e.g. in groups at increased risk of illness or in groups with a particularly good response to a specific therapy. The key assumption is that diagnoses, risk specifications and interventions can be better targeted, the more, respectively the more specific, the criteria can be applied to form groups. For this division, new and more specific biomarkers are used in individualized medicine, which were discovered especially in genome and post-genome research. This concept of biomarker-based individualized medicine suggests that this stratification into sub-populations leads to »groups« which consist only of single persons, however, for reasons of economy, practicality and usefulness this is not possible, so that a more suitable choice of phrase would be »stratified« medicine.

The two concepts »Determination of individual risks of incurring disease« and »Differential intervention offers« also contain a stratification with regard to the prevention, respectively the selection of appropriate interventions, whereby the former particularly appeals to the own responsibility of the patients for their health. In the concept »Genome-based information about health-related characteristics« genetic biomarkers are applied for the stratification. As the genetic make-up of each person is unique, individual and unmistakable, all genome-based procedures can be interpreted »per definition« as individualized medicine.

Each individualization concept is connected with specific issues and possible consequences. For the further discussion of individualized medicine it is impor-



tant to differentiate between these individualization concepts and not to mix them in an uncritical and unquestioned manner.

POTENTIALS OF INDIVIDUALIZED MEDICINE

The following expectations and potentials are linked to individualized medicine:

- > Increase the accuracy of disease diagnoses and prognoses, by additionally classifying illnesses on a molecular basis. This should – in particular in the case of diseases which are difficult to diagnose such as various types of cancer, certain neurological and psychological disorders – supplement the diagnosis which up to now was primarily oriented towards clinical symptoms. This is considered as a pre-requisite for developing more effective therapies.
- > Accurate early detection of persons at risk and early diagnosis of illnesses already in early, possibly pre-symptomatic stages, in order to be able to initiate timely preventive or therapeutic interventions. Through an early intervention before irreversible damage occurs it is hoped to influence the course of the illness favorably or even avoid diseases by means of preventive measures.
- > To a greater extent, accurate, knowledge-based estimates of the course of a disease and the chances for treatment and cures depending on therapy options (prognosis).
- > Targeted selection of those therapy options which are more likely to be effective for the respective patient or type of disorder than other therapy options. This can be, for instance in the context of regenerative medicine, transplants from the patient's own cell material or individually manufactured implants. At the level of drug interventions, it is intended to guide – by gene or metabolic profiles in terms of pharmacogenetics – the choice of drugs which address a molecular target structure which is actually present in the patient, or to optimally adapt the choice and dosage of medicines to the patient's ability to metabolize the drug. On the whole, this should increase the efficacy of medicinal interventions, reduce the incidence of adverse drug reactions, avoid unnecessary, non-effective interventions and also raise the patients' compliance with the therapy.
- > Better monitoring of the course of illnesses in order to be able to adapt the intervention faster and in a more focused way to the actual course of the disease.

For the pharmaceutical industry, an increase in efficiency in pharmaceutical research and development as well as the exploitation of new drugs, new drug targets new modes of drug action and new therapy principles are anticipated. At the same time, diagnostics and therapy can be offered as a package deal. For the medical device and diagnostics industry this development has the potential

to establish diagnostic tests and products on all stages of medical care provision and thus to greatly expand compared to the current status.

Via the medical-technical options offered to them, patients should be enabled by knowing about their personal current and future health situation to assume responsibility for their own health, e.g. by changing their life-style and adopting preventive measures: by using genotyping and multi-parameter diagnostics, individual risk profiles should be drawn up prior to the emergence of clinically detectable disease symptoms and thus probability prognoses about the individual's future health development could be made, which should result in a more accurate risk assessment than is presently possible based on the previously known risk factors.

STATUS AND PERSPECTIVES OF THE DEVELOPMENT OF THE KNOWLEDGE AND TECHNOLOGY BASIS FOR AN INDIVIDUALIZED MEDICINE

The process of creating the knowledge and technology basis for an individualized medicine up to its implementation in routine medical care comprises characteristic steps which imply a certain time sequence. These steps are:

- > Creation of the knowledge base through fundamental investigations of disease processes and therapy options, identification and characterization of biomarkers;
- > Creation of the technology base, e.g. by developing test, measurement and data interpretation procedures for the relevant biomarkers, developing prototype methods for manufacturing, drug delivery, diagnostic and therapeutic procedures;
- > Examination of the suitability for clinically relevant issues, e.g. by means of clinical trials and clinical validation;
- > Further development for and specific customization to the routine clinical use;
- > Approval;
- > Routine application in health care.

According to estimates by experts from the field of biomedical research, in the next twenty years it will be possible to elaborate the knowledge basis for individualized medicine. This basis comprises the development of a comprehensive understanding of the etiology and course of illnesses at the molecular level, the elucidation of gene-environment and gene-nutrition interactions, the clarification of cell and tissue development and differentiation processes, as well as working



out a comprehensive understanding of the determinants of health-promoting behavior or nutritional behavior.

At present the research activities and technology development are focused on the identification and characterization of new (molecular) biomarkers and the development of testing, measurement and data interpretation procedures for them. Most intensively researched and furthest advanced is the identification of genomic biomarkers for genes which are associated with complex diseases and the development of the necessary high-throughput technologies (DNA sequencing, DNA arrays [»gene chips«]). Not so far advanced and also technologically more challenging is the study of markers at the transcriptome, proteome and metabolome level, and the elucidation of their function and interaction. Currently the research is focused on single platforms or biomarkers, which is however not sufficient to achieve the goal of a comprehensive understanding of the disease at the molecular level. It is expected that the present platform- or biomarker-type-specific diverse knowledge stocks will be merged in the coming 10 to 15 years using systems biology to form integrative models which present an overall picture. To this end, software-based tools must be developed for the problem-oriented data mining and interpretation. It is expected that post-genome research will produce an overwhelming abundance of biomarkers in the next twenty years, which could be potentially beneficial for clinical application. However, the performance of the high-throughput technologies to identify potentially useful biomarkers also presents a challenge in the respect that only low-throughput methods are available for the characterization and resource-intensive validation which follows this identification. Therefore, the decision is extremely important, which of the numerous biomarkers are worth the considerable resources for the further development into clinically applicable tests. Thus systematic procedures and rational tools to support this decision-making process are urgently needed.

There is intensive interplay between technology platforms, which make certain measurements possible at all, the identification of molecular biomarkers, the growing knowledge about disease processes at molecular level and the exploration of possibilities in clinical application. For example, the development of high-throughput technologies to measure biomarkers in recent years has made it possible for the first time to complement hypothesis-driven research approaches (e.g. examination of candidate genes) by explorative approaches (e.g. genome-wide association studies). Simultaneously, the range of objects of investigation will be extended from model systems to populations and in future, e.g. with the development of high-performance sequencing methods for DNA, to individuals. For the future the challenge will be to exploit the synergies between these complementary approaches, by for instance using the results of explorative approaches to generate new

research hypotheses, which then in turn will be examined in hypothesis-driven approaches. Essential for qualitatively top-notch research and for obtaining sound results are the new and further development and wide-spread implementation of standards and quality criteria for relevant biomarker experiments, studies and statistical analyses, an all-embracing research infrastructure (e.g. databases and bio-banks operating on a long term basis [see TAB 2006 for associated issues]), as well as inter-institutional, interdisciplinary and international cooperation.

In order to arrive at a comprehensive understanding of the etiology and course of complex illnesses it is necessary to investigate the environmental factors in addition to the biomarker-based approaches, as they contribute to a greater extent than e.g. genetic factors to the onset of diseases. Therefore the previously established instruments for recording and measuring environmental factors must be qualitatively further developed, in order e.g. to be able to conduct continuous measurements in real time on individuals. These include e.g. miniaturized probes to monitor activities and body functions and telemetric transmission of the measurement data.

On the whole, in the next two decades a technology and knowledge basis which is utilizable in manifold ways will be created with the relevant technologies, biomarkers and findings. Currently, other uses outweigh individualized medicine: the first priority in basic research is at present to gain knowledge about the biological processes underlying complex diseases, to generate new hypotheses for further research, to extend the research approaches and to generate research resources for further work. In pharmaceutical R&D, researching pharmaceutical enterprises are focusing strategically on the utilization of this technology and knowledge basis to increase efficiency in clinical research and development, without however systematically seeking to transfer it into clinical applications. This also means that a comprehensive biomarker-based individualized medicine will not »automatically« develop out of this technology and knowledge basis. Rather, the potential of the knowledge and technology basis for individualized medicine could be exploited only imperfectly or with a time lag, unless more incentives are put in place or pharmaceutical companies set strategic priorities and allocate substantial resources.

Transfer of research results to clinical application

As the development of the knowledge and technology basis for individualized medicine is still in an early stage, there are as yet only few applications, products and services which are commercialized and utilized beyond clinical trials.



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The earliest applications of DNA-based technologies with additional medical benefits compared with the status quo can be expected for the genetic diagnosis of hereditary diseases and thus for diseases which are not customarily addressed in the context of individualized medicine. At present, with the »classical« molecular genetic tests approx. 800 diseases can be examined in a targeted manner in Germany. A parallel analysis of many hereditary factors in the sense of a »gene check« was until recently technically, financially and time-wise not feasible in clinical practice. This is beginning to change with the further development of DNA arrays: in the next five years, at least in the diagnosis of »classical« hereditary diseases, clinically validated »subject arrays« for specific diagnostic respectively analytical issues are expected in clinical application. In 2007, in approx. 10% of the chromosomal analyses conducted in health care, DNA arrays were utilized to detect deletions or duplications in defined chromosome regions and they could largely replace the conventional karyotype analysis in the next few years.

DNA arrays can also be used to analyse disease-associated genomic markers which are associated with complex illnesses. In research, such as in genome-wide association studies, high-density DNA arrays are utilized, which can test in parallel up to 1.8 m genetic markers (approx. 1 m single nucleotide polymorphisms (SNP) and ca. 800,000 markers for copy number variants), which are distributed across the entire genome. However, for most of the markers tested the functions are neither known, nor can they be suspected, so that the actual causes and genetic factors for the illness cannot be identified in this way. The results obtained with such analyses up to now thus represent primarily a research resource on the basis of which hypotheses, e.g. about the disease causes, can be generated and further analyses can be begun.

At the beginning of 2008 at least 27 firms offered SNP-based analyses for private persons on the internet, priced between US \$ 1,000 to US \$ 3,000 per analysis, for the purpose of specifying the individual risk of developing one or several complex diseases in later life. Thus for example the US firm Navigenics, Inc. offers private persons an SNP analysis in which the associations with 18 frequent illnesses are examined, for US \$ 2,500. Partly these offers also include working out recommendations for a health-oriented life-style, based on the individual disposition. Due to the lack of clinical validity and the predictive-probabilistic character of the analysis results, with insufficient relevance for clinical decision-making purposes, this offer is judged by clinicians to be premature. Firms with similar offers are for instance the in 2007 founded US firms 23andMe, Inc., Navigenics, Inc., Knome Inc., the Icelandic company deCODE genetics and the German enterprise LifeCode AG.

With regard to the total sequencing of individual genomes, the US firm Knome has assumed a leading position by offering this service to private persons at a price of US \$ 350,000. Otherwise the total sequencing of individual genomes is momentarily restricted to research projects.

Up to now, only few medicines respectively tests for an individualized medicine therapy have been approved, some of them have achieved very attractive turn-overs and can be classified in the new group of »niche-busters«, i.e. medicines directed towards small target markets with however high turnovers. The most important candidates for individualized therapeutic approaches from the perspective of the pharmaceutical industry are currently cancers, auto-immune diseases and disorders of the central nervous system. Commercialized products are found in various groups of the individualized therapeutic interventions:

- > Tests to support the decision about the type of treatment regimen to be applied. In this group, several genotyping tests and test systems to analyze transcription profiles are found. These are breast cancer tests based on transcription profiles *Oncotype DX*[®] (producer Genomic Health, Inc., USA), *MammaPrint* (Agendia BV, NL), the leukemia test *AmpliChip*[®] (Roche Diagnostics, CH) and tests for forms of cancer with an unknown primary tumor *CUPprint* (Agendia BV, NL) and tissue of origin test (Pathwork Diagnostics, Inc., USA). Further tests based on genotyping also assist in the decision on the kind of treatment regimen for AIDS, after heart transplants as well as for different types of cancer.
- > Certain drugs take effect in drug targets or in metabolic pathways which are only present in a sub-population of patients, so that this medicine is only effective with this patient sub-population. Whether a patient belongs to the sub-population which could benefit from this medicine will be determined by means of a suitable test method that indicates the presence of the drug target. In this category are the breast cancer medicine *Herceptin*[®] (Trastuzumab) and *Tamoxifen*, the leukemia medication *Glivec*[®] (Imatinib) and the AIDS medicine *Celsentri*[®] (Maraviroc).
- > Genetic factors play a role in the ability to metabolize certain drugs. Therefore, the individual genetic disposition contributes to which dosage of the drug is individually effective, respectively whether adverse drug reactions for this patient are to be expected. With an appropriate genetic or biochemical test the metabolic ability in each case will be identified and depending on the test result, the effective dosage will be decided or another drug will be chosen because of expected adverse drug reactions. In this group belong *AmpliChip*[®] *CYP450* which was approved in 2003 by the FDA, which analyzes the 30 different alleles of the gene *CYP2D6* and *CYP2C19* in parallel; *Verigene*[®] nucleic acid tests, which among inter alia support finding the correct dosage for the anti-



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coagulant Warfarin, a test to find the appropriate dosage for the colon cancer drug Camptosar® (Irinotecan), and the TPMT test to find the dosages of the leukemia drug Puri Nethol® (Mercaptopurin).

With the present low degree of commercialization and diffusion of individualized medicine, the clinical benefit for complex diseases will still be low in ten years. However, a growing number of new biomarker-based tests and examination procedures as well as individualized therapies will reach a development stage in the next few years, in which they find themselves on the application threshold in health care, so that from a scientific-technological viewpoint, individualization of the health care system seems possible within a time perspective of between 15 to 20 years.

Experiences with the clinical application of new medical procedures from the last decades, however, show that unintentional effects occur if the utilization is oriented rather towards what is technically feasible or scientifically or economically attractive than towards clinical benefit. This is frequently the case if the technology is available before the knowledge base to assess the new processes with regard to their validity and the conditions of their »meaningful« clinical application have been established. On the one hand, inadequate proof of the clinical validity and clinical utility can be a significant barrier to the broad application of a potentially beneficial procedure. On the other hand, investigation and treatment methods are sometimes applied more rapidly and widely in clinical practice than clinical evidence is established, or reference standards and guidelines are developed and validated.

Against this background, there is widespread consensus that the intended health-care effects of a biomarker-based individualized medicine will only occur, unintentional negative impacts will be avoided and thus also a biomarker-based individualized medicine can be integrated in the health care system on a larger scale and sustainably, i.e. beyond single niche, respectively short-term applications, if care is taken that no insufficiently validated methods of individualized medicine are introduced into the health care system.

From internationally recognized evaluation schemes for new test methods, as e.g. the ACCE model developed in the USA, it can be deduced that in particular data to assess analytical validity, clinical validity and clinical utility are required for the transfer to clinical use. However, the discussion is only beginning about which proofs for new testing methods must be provided in concrete terms, with which degree of reliability and by which actors in the health-care system, in order to

- > obtain market approval;
- > apply the tests and methods in health care outside the clinical studies, possibly step-by-step in target groups or institutional contexts to be specified;
- > obtain reimbursement of the incurred costs through health insurance firms, e.g. public statutory or private health insurers.

From the design of the respective requirements and their degree of liability depends essentially whether these tests improve clinical decision-making and can contribute to achieving health policy goals, to what extent and how rapidly these tests are introduced to clinical practice and whether it is economically attractive for the firms to develop and sell tests for individualized medicine. Provision of this information assumes a key role for the future development of individualized medicine. Against this background, measures are required which aim to

- > generate the knowledge base to evaluate analytical and clinical validity as well as clinical utility;
- > make available appropriate knowledge stocks for evaluation and decision-making processes;
- > disseminate the results of relevant evaluations to aid decision-making processes.

Particularly in the research promotion area, recently numerous promotional measures were implemented in Germany in the field of translational research, whose objective is the analytical and clinical validation of biomarker-based processes and which are intended to close a previous gap in the promotional landscape. In addition, other research sponsors, research institutions and enterprises actively involved in this field, as well as health insurance companies, are called upon to actively contribute towards gradually extending the as yet only rudimentary data and knowledge stocks available for the respective testing methods, in order to build up the necessary evidence in a multi-annual, non-linear, interdisciplinary multi-actor process, and to collaborate closely with decision-makers or coordinate decision-making processes. For implementing new procedures of individualized medicine in medical practice, it would be helpful to focus on a limited number of centers or multi-centered collaborations which have sufficient personal, infrastructural and financial resources to guarantee, on the one hand, the generation of the necessary databases for scientific assessment and the evidence-based further development of the new diagnostic and treatment methods to a stage in which they can be introduced in the health care system. On the other hand, they could ensure the coordinated cooperation of all disciplines required for the medical and possibly psycho-social care of the patients.



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New biomarker-based testing methods for individualized medicine must be approved according to the In-vitro Diagnostics (IVD) Directive or the Medical Devices Act. Only evidence of analytical validity must be provided to obtain this approval. As the EU Commission is presently revising the medical devices regulation, this is a favorable opportunity to plumb to what extent the proof of clinical validity as pre-condition for market approval should be required in the IVD Directive, at least for certain tests, in order to thus ensure that this data is made available for health care.

Introduction into the health care system

As how the transfer process from prototype applications in research to routine health care should be organized is still open, it is also very uncertain how a future health care system should be designed in which individualized medicine plays a greater role. From today's perspective, challenges and changes will lie in the following areas:

- > Medical staff;
- > Structures, processes and organizational forms of medical care delivery;
- > Cost reimbursement (health insurance companies, patients paying for themselves);
- > Patient demand and behavior;
- > More preventive orientation in health care.

With the increasing advent of individualized medicine in health care, a considerable need for education and further training arises for the health care professionals, in particular the medical personnel, as they will have to meet these new challenges:

- > Fundamental knowledge in genetics, molecular medicine and in the utilized test methods;
- > Identification of target groups for biomarker-based testing and diagnostic procedures;
- > Conduct of tests and evaluation of the measurements;
- > Interpretation of the test results with regard to the medical issues and choice of a suitable intervention;
- > Communication with patients.

In the mid term it will have to be clarified what the vocational training agenda entails and which educational objectives should be reached, what resources are required and which measures are to be implemented to attain these goals.

At the same time, the need to integrate data from multiple health and medical disciplines requires building new organizational structures and cooperation forms with service providers in the in-patient and out-patient sectors as well as across sectors.

It is currently open whether individualized medicine should be performed in future rather in a limited number of specialized institutions or on a broad basis in a variety of health care facilities. This will certainly be greatly influenced which requirements will have to be met with respect to the qualification of personnel, the equipment, the quality of the health services provided, and how binding these requirements will be. Whether the recently founded companies which have specialized in offering genome-based tests to doctors or directly to patients, will be able to firmly establish themselves in the market in the long term, cannot be judged yet.

Prevention

A core element of individualized medicine is the expectation that in the foreseeable future a personalized risk specification can be drawn up for each individual, based on the knowledge of predisposing genes, in order to place the persons involved in the position that with knowledge of their disease risk, they can assume responsibility for their own health and adopt preventive measures. The vision – mostly postulated by lobby groups supporting individualized medicine – goes even further, as here a significant driver for a radical renovation of the present health care system which is oriented to acute medical care into a prevention-oriented system is seen. Given the present status of science and technology, however, the chances of realization must be judged rather skeptically, and it is not foreseeable how individualized medicine could function as a main driver for a prevention-oriented health care system, even if it would surely benefit from it.

So far no test methods are available which in themselves would be suitable to identify persons at risk of developing common illnesses or even for screening the population; in individual cases they could improve the predictive power of existing risk scores if integrated into them. To what extent a risk specification would be possible in the future depends on the success of newly launched research approaches which aim to identify new risk genes, respectively gene combinations relevant for clinical decision-making.



Nevertheless, tests of this type of questionable clinical benefit are already on offer today, and preferably to health-conscious, well educated, prosperous people. For the purposes of consumer protection, it would be desirable to provide neutral, universally understandable information to counteract misconceptions about the possible benefits of these tests and to allow this group to make informed, autonomous decisions in full knowledge of the whole situation.

The extent to which the genetic susceptibility tests actually make an effective contribution to improving current prevention practice with a favorable cost-benefit ratio cannot be clearly answered in view of present knowledge, but is judged with skepticism. The stronger influence of non-genetic factors in the emergence of complex diseases was already mentioned. Empirical data on the cost-benefit ratio and on efficacy are not available and could also only be collected in large-scale, time- and resource-intensive studies. However, in prevention research there is a general need – not only with regard to individualized medicine – to evaluate the benefits of corresponding measures and to improve not only the efficacy, but also the cost effectiveness. At the same time, analysis of experiences from previous prevention programs for complex diseases and the case study diabetes shows that it is surely short-sighted to try to improve prevention by providing new valid susceptibility and early recognition screening alone. On the one hand, new tests are not always necessary. On the other hand, prevention goals can only be attained if the test procedures are embedded in a comprehensive prevention concept.

Patients

Individualized medicine particularly addresses aspects of patient autonomy and consumer sovereignty, if it promises to supply the patients with more and better information about their current and possible future state of health than available at present and to give them the greatest possible choices according to their own preferences. At the same time, the hoped for positive individual and collective health effects due to an individualized medicine can only be realized, if citizens are not only willing to have tests carried out to determine their own individual risk of disease, but are also in a position to translate the test result in – from a medical and health policy perspective – »meaningful« and appropriate health-related action.

For this, a high degree of health competence is required of the patients. For the foreseeable future, a high awareness to measures of individualized medicine, physical and cognitive pre-conditions to their demand and utilization are to be most probably found among health-conscious, well educated persons in

higher social and income groups, which consequently become a favorite target group for appropriate medical services. By contrast, less well educated persons and people from social disadvantaged backgrounds will with great probability have difficulties in acquiring the appropriate health competences and resources and to access individualized medicine, as long as they are not supported by target-group-specific measures.

In most publications about individualized medicine it is assumed in an unreflecting way that identified persons at risk will actually have recourse to effective preventive measures such as changing to a healthier life style, making use of close-meshed early recognition screening etc. This assumption has however not been empirically proved so far. From health, health care and prevention research, on the contrary, there are indications that the behavior outlined here is only one of numerous, at least equally plausible options of dealing with the tests and their results.

Up to now only few investigations of this issue have been conducted from a social science viewpoint. This is not unusual for new technologies and their possible utilization options, but is a frequently encountered research gap. For a research and technology area which aims at the »individualization« in the sense of customizing for a single person and his preferences, it is still remarkable that the actual target group has scarcely been questioned about their preferences up to now. Due to the complexity of the field investigated and different operationalization of the research issues, only isolated and partly inconsistent results are available from previous studies which do not allow clear statements.

Against this background, there is an urgent need to expand the social science investigation of possible future addressee and user behaviors and to conduct it already at an early stage of the research and development process of individualized medicine. The results should be used for the design of the technology and the framework conditions for its application, in order to achieve the health-related goals, taking into account the preferences and the behavior of the target group. For this a variety of research approaches will be needed in the course of the coming years. They range from investigating the reactions to a fictitious test result in hypothetical test scenarios over social-science monitoring within the framework of clinical studies for the validation of biomarker-based testing methods, up to relevant examinations in routine medical care.

Not least, patients are above all sick people, who expect or hope for support in coping with the illness – also from the medical staff, and also beyond the purely medical treatment. An individualized medicine presents options to overcome



illness which are result- and disease-process-oriented. Patients however often feel medicine to be »individual«, where in particular the emotional dimension and the question of how to continue living with the illness are addressed in the physician-patient relationship and options for action are put forward. Individualized medicine does not make direct contributions to this. Rather, in severe illnesses special mental burdens are associated with those individualized medicine methods which deliver predictive-probabilistic information, and difficult tasks must be solved to interpret these test results and transfer them into daily life. This indicates the necessity of integrating individualized medicine in contexts where the patients can receive assistance through »speaking medicine« and psycho-social support, if necessary.

Health economy

The companies which produce and market innovations in individualized medicine are pharmaceutical enterprises, medical devices and diagnostic companies as well as biotechnology firms. The activities of these enterprises co-determine at what speed, in which breadth and to which extent, with which products and services and for which indications and applications individualized medicine is driven forward. How these activities can be specifically designed depends largely on the type of enterprise as well as the framework and market conditions in the respective branch in which the companies operate. Each of these enterprise types covers only one part of the possible products, services and users of individualized medicine, in part only a certain phase in the innovation process. They must therefore collaborate synergistically in order to bring innovations in individualized medicine to application and market maturity. In order to exploit the emerging, economically rather attractive business models – from »niche-buster« via diagnostic-therapeutic package deals up to mainly value added for diagnostics – the challenge is to unite the previously very different business worlds and strategies for diagnostics and therapeutics into one coherent strategy.

The core business of researching pharmaceutical companies is to research, develop, produce and market pharmaceuticals. All the necessary competences and resources are usually present in the enterprises themselves, respectively are tapped by means of suitable cooperations, e.g. with biotech companies. In individualized medicine, besides medication to be administered preventively, diagnostic-medication package deals are of special interest to pharmaceutical firms, provided that overall higher turnovers and profits can be achieved than by marketing the drug alone. Currently, a handful of such products are approved, some of which have achieved »niche-buster« status. Until now only a few pharmaceutical companies have systematically explored the potential of biomarkers for



drug-diagnostics combinations, because for a parallel, integrated development of pharmaceuticals and related, clinically applicable diagnostics know-how is required which traditionally exists in diagnostic firms, but not in pharmaceutical companies. In single cases, this know-how was tapped through joint ventures or other cooperations with companies from the diagnostic industry, but it remains open whether such cooperations between pharmaceutical and diagnostic concerns will be entered into more frequently in the future.

Biotech companies are active in the individualized medicine field, above all in the research and development of new technologies, e.g. for drug screening and genome sequencing, identifying new biomarkers and drug candidates as well as new analytical and diagnostic methods. Although highly innovative, most firms lack the competences and resources to develop promising product candidates up to market maturity and market them on a broad basis. Therefore they usually forge strategic alliances with pharmaceutical concerns, to a lesser extent also with large medical device manufacturers or diagnostic firms. In addition, more than twenty firms are active worldwide that offer to identify individual genetic profiles, partly also their interpretation with regard to risk of disease. The acquisition of customers takes place via direct contact with patients or doctors on contract. A large variety of business models can be observed at present, whereby it cannot yet be judged whether this variety will be maintained or reduced to a few favored, possibly even new, business models.

Several large, research-intensive, internationally active medical device and diagnostic companies which develop and sell large devices for medical imaging (e.g. computer tomography and magnetic resonance tomography) or analysis platforms for lab tests, pursue within individualized medicine the strategy of making their appliances and procedures, already established in clinical analysis and diagnostics, more specific and more sensitive (in imaging techniques above all by molecular imaging), to penetrate all levels of medical service provision and to integrate the procedures in particular by appropriate software in the organization and work-flows of hospitals, laboratories and surgeries. As part of an individualized medicine, a significant expansion of the application possibilities for these large appliances and analysis platforms is hoped for. Although technologically well positioned, the market leaders in medical devices and diagnostics exhibit a relative dearth of innovative content (e.g. biomarkers, delivery systems, specific probes). For this reason they cooperate with small innovative molecular diagnostic firms, which thus gain access to the installed instrument base of the market-leading diagnostic companies. Moreover, the emergence of integrated diagnostic providers that offer lab and imaging diagnostics from a single source connected by tailor-made IT solutions is becoming apparent. This is based inter



alia on the idea that imaging techniques are usually too expensive to justify their use e.g. in preventive cancer screening tests for the general public. Therefore, inexpensive lab tests should identify those persons with an increased cancer risk who would then be tested with imaging techniques («door-opener function of the lab tests«).

For providing care in individualized medicine, besides the »traditional« health care providers in the German health system, the general practitioners in the out-patient sector and the university hospitals and clinics in the in-patient sector, specialized clinics come to mind. These specialty clinics, mostly privately owned and founded, have specialized in certain illnesses (e.g. cardio-vascular diseases) or specific client groups (e.g. affluent, health-conscious ones). These clinics have the most modern equipment and highly specialized personnel for the respective indication. Due to their advanced diagnosis and treatment methods, respectively their clients, who are particularly receptive to individualized medicine, they could be among the first providers of individualized medical techniques.

Health insurance

The implications of individualized medicine for the health insurance system are still limited, due to the early development stage and the low volume of services provided as yet. Because of the strong emphasis on identification of individual disease risk and own responsibility of the patients in individualized medicine, the question arises in particular how the individual risk of disease can or should be taken into account in determining the amount of monthly premiums and the benefits paid in the case of illness and nursing care.

In the current health insurance system, which consists of the public statutory health insurances based on the solidarity principle as well as the private health insurance companies based on the equivalence principle, this primarily applies to private health insurers. For them, the proper assignment of an applicant or insured person to a critical risk group is decisive, since the determination of increased risk rates, limitations and exclusions of insurance benefits or the refusal of insurance depends on this. Therefore, the methods of individualized medicine are principally of interest, which offer the prospect of better predicting the disease risk of a person who wishes to take out insurance cover.

If insurance companies can collect corresponding information within the framework of their right to gather information, then it is to be feared that persons with a high risk of disease to a greater extent than now

- > will only be able to buy health insurance at (for them) very unfavorable terms or possibly not at all;
- > will be confronted with high (financial) barriers in accessing the services of individualized medicine, from which they could especially benefit;
- > will be concentrated in the public statutory health system;
- > will no longer take tests in order not to have to inform the health insurance company about known risks resulting from them.

As in the statutory health insurance the premium amount and scope of treatment do not depend on the individual disease risks, the question arise, to what extent health care services in individualized medicine will become part of the catalog of benefits. This will essentially depend on how the criterion of necessity is interpreted and how strict the evidence requirements of the scientific data will be which are reviewed at such decisions. In addition, statutory health insurers must position themselves on what extent they judge the potential of individualized medicine to meet quality and cost targets in medical health care and through (limited) integration of individualized medicine in their catalog may achieve a competitive advantages among health insurers.

Broad utilization of biomarker-based predictive-probabilistic health information for granting or refusing insurance benefits, or demanding certain health-related forms of behavior would be a restriction of the individual's self-determination which would have to be balanced against the interests of community solidarity («Solidargemeinschaft»). It is to be legitimized under which conditions such a restriction appears justified, and also whether effective and ethically appropriate ways were chosen to influence the decisions of the individual. For this legitimation it must be clarified in detail whether the measure has been shown to be effective, the risk-benefit ratio is favorable and the cost-benefit ratio acceptable. These conditions are not yet fulfilled. Also, utilizing the least restrictive ways possible to influence the behavior of individuals (e.g. via information and advice, incentives instead of sanctions), which allow the individual greater room for subjective judgments, as well as transparent decision-making processes, are of paramount importance.



CONCLUSIONS, NEED FOR ACTION AND OPTIONS

Creation of the knowledge and technology basis for an individualized medicine

In order to further develop the knowledge and technology base in the direction of individualized medicine, three fields of action emerge:

- > Support for strategy planning: in view of the future development potentials of an individualized medicine, controversial estimates and uncertainties exist in actors in companies, politics, research institutions and the health care system. Support in strategic planning by means of systematic and long-term foresight of future developments, integrating all relevant stakeholders, based on the roadmap published in 2007 by the Gesundheitsforschungsrat (Health Research Council) for the federal government's health care research program could reduce these uncertainties.
- > Shaping research: future research challenges can only be met in multi- and interdisciplinary, also international cooperation, which must take place intra-institutionally and be strategically oriented. This requires a specific research infrastructure, e.g. comprehensive bio- and databases which must be set up and operated in the long term. In addition, the already initiated efforts to achieve quality standards and standardization should be further developed in the coming years and implemented in research practice. So far, only a limited spectrum of disease-associated variants in the human genome could be identified. In order to complement the still incomplete picture of disease-related genetic variants, the investigations should be extended also to other variants and those which occur with less frequency in populations. At present, research is focused primarily on single platforms or biomarker types. In the next 10 to 15 years, the challenge consists in integrating the present separate platform- respectively biomarker-type-specific knowledge stocks with the aid of system biology and to provide tools for problem-oriented data mining and interpretation. Furthermore, there is a need for systematic procedures and rational tools to contribute to selecting those biomarkers which are worth the considerable expenditure necessary for further development into clinically applicable tests and for utilization in medical treatment regimens.
- > Expansion of the research focus to include environmental and psycho-social factors: since the launching of large-scale genome research programs experts have been controversially discussing whether this prioritization can contribute to improved medical health care – for example, in the sense of an individualized medicine – in a manner appropriate to the resources invested. Whereas the gaining of insights in research directed towards genetic disease factors is not denied, with a view to achieving health targets it is pointed out that the influence

of genetic factors on the emergence of multi-factorial disorders – compared with environmental factors – is rather low, respectively via gene-environment interactions only an indirect one. Momentarily, research into genetic factors enjoys a higher status than environmental and psycho-social factors. Against this background, when setting future priorities in research programs it should be examined how an extension to exploring gene-environmental interactions, to strengthening the technical capacities to collect environmental factors and exposures as well as researching patient preferences and behaviors can be implemented in individualized medicine.

Transfer to clinical application

In the next 10 to 15 years the shaping of the transitional phase from research to application in routine health care will be of paramount importance for the future development of individualized medicine. In this development phase data for the evaluation of the analytical validity, clinical validity or clinical utility of the relevant applications will be required above all. To achieve this, in each case a non-linear, interdisciplinary multi-actor process lasting several years is needed, in order to gradually expand the presently only rudimentary data and knowledge stocks for each test method. Measures must be taken which are directed towards generating the knowledge base required to evaluate analytical and clinical validity as well as clinical benefits. This includes above all

- > a systematic foresight (horizon scanning) and prioritization of the tests and methods to be evaluated;
- > allocation of resources and building and extending capacity for necessary research work and evaluation processes;
- > making progress in developing methods and to continue the incipient discussion about which degree of evidence can be considered sufficient for which health-related decisions;
- > extending the spectrum of available instruments which are suitable, depending on the gradually increasing evidence, to make possible an extension of the also gradually expanding but still limited clinical applications; and
- > close integration of research with the decision-making processes, to ensure that research work is conceptually capable of providing answers to decision-relevant questions and that they are included in decision-making processes.

In the first instance, primarily research funding agencies, research institutes, Health Technology Assessment institutions, companies active in this area as well



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as health insurance companies and scientific and medical professional societies are called upon to take or participate in appropriate actions.

Recently in Germany numerous measures were implemented which, on the one hand, should generally strengthen translational research, i.e. the efficient and effective transfer of results of biomedical (basic) research to clinic application, on the other hand, however, should provide concrete resources for the analytical and clinical validation of new molecular biomarkers. In a medium-term perspective the extent to which they have made a major contribution to the challenges sketched above should be evaluated.

Translational research is very important, apart from individualized medicine, for transferring research results into clinical application and vice versa for feeding clinically relevant issues back to research. It is of great relevance for medical progress, the competitiveness of medical research and evidence-based patient care, market access for medical device and pharmaceutical firms and the attainment of quality and cost targets in the health care system. In the recent past, manifold organizational forms, models and instruments have been developed in translational research, which differ in their aims, participating actors and financing. With the goal of further developing and strengthening translational research, it could be planned to carry out a study which provides an overview of the various types and their suitability for certain objectives as well as analyzing their function in the translational research process.

Pre-requisite for marketing approval for new biomarker-based tests in the context of individualized medicine according to the In-vitro Diagnostics Directive (98/79/EC; IVD directive) respectively the Medical Devices Act is the proof of technical performance (analytical validity) by the manufacturer. A mandatory requirement that the manufacturer also has to supply proof of the clinical validity does not exist at present. As the EU Commission is currently revising the medical devices regulation, it should be explored at the European level to what extent the proof of clinical validity should be mandated in the IVD Directive as a pre-condition for marketing approval, at least for certain tests in higher risk categories, in order to ensure that this data necessary for health care is supplied. In the concrete design of the requirements a balance must be struck between protection of the patients and public health and simultaneously rapidly making new tests available in the health care system.

Furthermore, it should also be examined to what extent in national law an accreditation and a (specialist) doctor's reservation should be additionally introduced to guarantee a high quality in the conduct and interpretation of tests. Ap-

propriate provisions for genetic examinations and analyses are already planned in the draft Law on Genetic Diagnostics passed by the German cabinet in August 2008.

Patient preferences and behavior

Individualized medicine is a research and technology area in which to a great degree the circumstances and preferences of single persons are referred to for the »individualization« in the sense of customizing. It is therefore especially noteworthy that social science research on patients' preferences and their (possible) utilization behavior of individualized medicine is still very scanty. The need to explore the possible addressee and user behavior at an early stage in the research and development process of individualized medicine is urgent. The results are expected to indicate significant findings on how the technology and the framework conditions should be designed.

Ill people often feel that medical care is »individual«, in which living with the illness and the psycho-social dimension of the disease are discussed in the doctor-patient relationship and options for action are proposed. A biomarker-based individualized medicine, however, does not make any direct contributions to this. Possibly the psychological burdens can even be increased in the case of severe illnesses if the individualized medicine tests supply predictive-probabilistic information which is very difficult to transfer into appropriate action in daily life. Against this background, individualized medicine should be performed in situations in which the persons affected can be supported by »talking medicine« and psycho-social counseling.

Prevention

Future potentials for prevention are frequently postulated in the context of individualized medicine. They are essentially based on the assumption that in the foreseeable future a personalized test of disease risk will be carried out for each individual, based on the knowledge of predisposing genes or other predictive biomarkers, thus enabling the persons concerned to assume responsibility for their own health, knowing about their risk of disease and taking preventive measures. However, till now neither are appropriately valid testing methods available, nor is the assumption regarding patients' behavior empirically substantiated. Thus considerable research into patient behavior is needed.

Against this background, the chances of realizing the vision must be judged skeptically, which sees the biomarker-based identification of disease risks as a



main driver in a renovation of the current acute-medicine-oriented health care system into one oriented towards prevention.

In addition, from the possible integration of genetic factors in the identification of persons at risk for preventive measures it cannot readily be deduced that preventive behavior as the responsibility of the single individual must necessarily follow. Rather, the design of the subsequent intervention should be directed to the respective shares of the different risk factors and mechanisms which explain the occurrence of the disorder, and also take into account the degree to which an individual can influence them.

Information and education

Already some tests with questionable clinical benefits are on offer today, and preferably to health-conscious, well educated, prosperous persons. In individual cases and taking personal preferences into account, a benefit may exist. Individuals are thus faced with the personal choice for or against the application or use of such services. For this reason medical personnel and patients must have access to adequate information.

For the purposes of consumer protection it would be desirable to provide neutral, generally understandable and targeted information in order to avoid misleading people about the possible benefits of these tests and to allow informed, autonomous decision-making in full knowledge of the whole situation. Professional medical associations and neutral information providers for patients (e.g. the Federal Center for Health Education) should offer relevant information about specific applications of individualized medicine, already in the early phase of their market introduction. This currently applies for instance to genotyping, which promises to identify the individual risk of succumbing to disease for complex illnesses, and the collection and storage of umbilical cord blood.

It should be examined whether the competent authorities within the framework of existing regulations could to a greater extent check claims, product labels, product information and advertising material for biomarker-based tests for correctness, completeness and balanced presentation of the strengths and benefits, weaknesses and risks as well as knowledge gaps, in order to protect the user from false and misleading information.

Because of the partly complex and heterogeneous distribution paths for biomarker-based tests, the product information accompanying the test does not necessarily reach the physicians and patients. The option of an internet-based

register in which corresponding information must be deposited should be examined. Since this information is already largely included in the files which the applicant submits to the licensing authorities with his application for approval, such a register could possibly be located with these authorities. This would, however, require the medical devices legislation to be adapted, as these files are subject to confidentiality and even summaries or extracts thereof may not be published.

Genetic and predictive health information

Genome-based tests, genetic diagnostics and in particular predictive genetic tests occupy a prominent position in individualized medicine. In long-standing debates a consensus was reached that in principle regulation is needed for genetic testing and in August 2008 a draft for a Law on Genetic Diagnostics was passed by the German cabinet. From the analyses carried out in the framework of this study, no indications can be deduced which argue against concluding this advanced legislation project at this point in time because of questions related to the exceptional status of genetic information. In the mid term, however, new aspects can be perceived which will still require in-depth analysis and discussion.

In the draft bill for a Law on Genetic Diagnostics of August 2008 not only genetic analyses, but also analytical methods for gene products (RNA, proteins, metabolites) are covered in this regulation area, if they too determine genetic characteristics. It remains to be observed to what extent the differentiation foreseen in the draft between diagnostic investigations, on the one hand, and predictive-probabilistic examinations on the other hand will prove to be appropriate and feasible. The discussion about which differentiation criteria are to be applied should be continued, based on these experiences. Moreover, the comments of the National Ethical Council in particular on predictive health information triggered a perspective medical ethics and legal policy debate by the question, to what extent the discourse, till now focused on predictive genetic information, should be expanded to include predictive non-genetic health information. This debate which is still in its initial phase should be continued.

Currently, a very dynamic technology development is taking place in the procedures for DNA sequencing with the objective to sequence complete genomes of single organisms at a fraction of the previously required costs and time. These procedures hold great potentials for novel research approaches and research questions in the life sciences. This indicates, on the one hand, the need for statutory regulation of genetic examinations and analyses and of handling genetic samples and data for research purposes. At the same time, it is becoming ap-



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parent that ethical and legal principles which up to now guided dealings with genetic information may no longer be applicable in the previously practiced form. Therefore, a study should be considered in which the potentials of the new high-performance sequencing technologies as well as their ethical, legal and societal implications are analyzed.

Shifts in focus in the societal discourse

The emerging possibilities to identify individual disease risks by biomarker- and genome-based tests promised with individualized medicine are linked to a remarkable shift in focus in the debate. If up to now solidarity with and non-discrimination of ill persons and the rights of the individual to self-determination had high priority, increasingly role models of responsibility and civic responsibility are cited, in order remind people (more strongly) of their responsibility for third parties and solidarity with the community, whether in the context of donating body substances/ material and information for research purposes, participating in population-wide screening tests, influencing individual health care behavior, legitimizing co-payments for health-related services or the design of health insurance terms. How far this reminding persons of their duty may go, how it can be legitimized and which effective and ethically appropriate ways are to be chosen to influence the decisions of individuals, will repeatedly be a subject of health policy discussions in the years to come, also in the context of individualized medicine. This debate should be intensively continued.

The Office of Technology Assessment at the German Bundestag is an independent scientific institution created with the objective of advising the German Bundestag and its committees on matters relating to research and technology. Since 1990 TAB has been operated by the Institute for Technology Assessment and Systems Analysis (ITAS) of the Karlsruhe Institute for Technology (KIT), based on a contract with the German Bundestag



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AT THE GERMAN BUNDESTAG**

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