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Statement

Individualised Medicine

Prerequisites and Consequences

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Individualised Medicine

Prerequisites and Consequences

Preface

One of medicine's central goals has been and is to heal, relieve or even prevent patients' diseases. At the beginning of the 21st century, biomedical research and clinical medicine are undergoing a transformation, described by many as a paradigm shift. New approaches based on genome analyses and biomedical technologies are making it possible to analyse biological processes more precisely and more thoroughly than ever before. Associated with this is the goal of better understanding the causes of disease, providing accurate diagnoses, and last but not least, developing highly effective, precisely targeted therapies that have few side effects. For example, our understanding of why people who apparently have the same illness react differently to the same therapy is growing.

'Individualised Medicine' is an approach that adds another dimension to our understanding of illnesses. However, a number of ethical, legal and economic questions are associated with Individualised Medicine. For example, how can insights into molecular biological connections be implemented in medical practice in the future? How can sensitive personal data be adequately analysed and appropriately protected? And what general conditions must be met to be able to implement Individualised Medicine?

This Statement by the German National Academy of Sciences Leopoldina, acatech – the National Academy of Science and Engineering, and the Union of the German Academies of Sciences and Humanities, depicts current developments, challenges and framework conditions of Individualised Medicine. In order to reach specific conclusions, the statement addresses the complex area of Individualised Medicine with a focus on the genetic and pharmacological aspects of oncology, an area in which individualisation is most advanced. This restriction means that other closely associated topics, such as the perspectives of patients or healthcare, the area of medical technology or new developments with regard to other illnesses such as psychiatric ones, are not explored in this study and must be addressed separately at a later time.
We are very grateful to the members of the working group, who have over the last three years investigated this highly complex interdisciplinary topic in scientific symposia as well as numerous meetings and consultations, and would like to thank them sincerely for their great dedication and hard work.

Halle (Saale) and Berlin, December 2014

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Summary and Recommendations

For centuries, empirical approaches have determined the medical treatment of people with illnesses. Groundbreaking progress in the life sciences and in the development of medical technology procedures have led to a significantly improved understanding, grounded in the natural sciences, of the causes and development of illnesses. Decoding the human genome was a milestone on the path to being able to diagnose and treat, and ultimately prevent, illnesses by taking a particular patient's individual characteristics into account. There are several terms for this approach in medicine, such as Personalised or Individualised Medicine (which is used in this statement); other terms are Precision Medicine, Genomic Medicine and Stratified Medicine.

Individualised Medicine aims to improve the efficacy and quality of treatment by means of targeted prevention, systematic diagnostics and the use of tailored therapeutic procedures that are based on the needs of individual patients or patient groups. The goals of this approach include reducing adverse side effects and increasing the cost-effectiveness of healthcare over the long term.

Doctors have always taken the individual patient into consideration when determining what type of treatment to use; Individualised Medicine develops that practise further. Techniques (primarily molecular ones) for determining biological parameters or 'biomarkers' in a targeted way are increasingly being incorporated into the treatment process to precisely quantify and objectify patients' individual biological characteristics.

Although more and more people are now ageing in good health, overall the number of chronic illnesses, which often occur in combination (multimorbidity), and the resulting treatment costs, are increasing significantly. Many common chronic conditions, such as rheumatic illnesses, cardiovascular conditions, diabetes mellitus and dementia, are influenced by numerous genes and environmental factors. For these disorders as well, disease-associated genetic variants and other biomarkers are increasingly being identified. Categorising patients precisely into therapy-relevant subgroups (stratification) is much more difficult in these cases.

Modern high-throughput bioanalytical methods, or 'omics' technologies, now make it possible to record a person's entire genetic makeup (genome) and the programming of their genes (epigenome) as well as all their gene products, RNA (transcriptome) and proteins (proteome). It is, moreover, possible to determine the entire spectrum of metabolic products (metabolome) and to investigate the influence of the microorganisms that coexist with a human being (microbiome). Analysing the numerous data obtained from this and correlating that data with particular diseases or the effects of medical treatments is an enormous scientific challenge.

Genomic analyses are already being used to diagnose monogenic diseases, that is those caused by the mutation of single genes, as well as certain infectious diseases, for example immunodeficiency brought about by HIV. Tumour therapy is

also currently undergoing a fundamental transformation. Tumours are primarily the result of genetic changes in body cells. A deeper understanding of the molecular mechanisms of the genesis of numerous types of tumours has led to a new classification of tumours and makes it possible to develop molecular tumour diagnostics and targeted therapeutic agents based upon those diagnostic approaches. It is becoming evident that the use of these therapies is associated with fewer side effects than conventional treatment methods.

Medical progress is significantly increasing the amount of disease-relevant patient data and the number of treatment options that are available. Among the greatest associated challenges are standardising and securing these complex data and deriving reliable results and practical options from them. The latter must be transparent and comprehensible for patients, attending doctors and scientists working in medical research. Individualised Medicine thus requires the integration of new, particularly multi-layered organisational processes into existing healthcare structures.

This Statement analyses the potential of Individualised Medicine for further development and addresses challenges associated with its implementation. The topics are addressed as follows:

- Chapter 2 covers relevant research and the technologies that drive Individualised Medicine.
- Chapter 3 covers biomarkers as a basis for the classification of heterogeneous illnesses into subgroups defined in terms of molecular biology.
- Chapter 4 covers clinical studies on the development of individualised diagnostic tools and therapeutic agents for small defined patient groups.
- Chapter 5 covers predictive genetic diagnostics for the individual adaptation of preventive measures.
- Chapter 6 covers the clinical practice of individualised diagnostics and therapy of tumours, viral diseases and promising approaches to curing other conditions.
- Chapter 7 covers ethical-legal questions.
- Chapter 8 covers economic trends in the development of therapies and diagnostic tools for small patient groups, as well as potential cost effects.
- Chapter 9 covers structural framework conditions for Individualised Medicine.

The Statement comes to the following recommendations, which are divided into eight thematic areas:

Recommendation 1: Research and development

1.1 Our understanding of the generally complex causes of disease must continue to improve. Progress in medical research at the molecular level is leading to a more refined taxonomy of diseases and opening up the prospect of tailored preventive, diagnostic and therapeutic processes. There are already compelling examples of individualised therapeutic approaches in medical practice based on specific mutations, for example monogenic disorders and some types of tumours. Nevertheless, additional research efforts are needed to understand the complexity of these and other disorders. The influence that environmental factors, lifestyle, associated microbiomes and medications have on the gene expression activity of individual genomes must be analysed holistically; thus, the technologies necessary to do so should be developed further, and the resulting findings must be linked with the individual phenotype. In addition to research on causes, clinical translational research, preventive research and healthcare services research are indispensable for developing and establishing new individualised procedures.

1.2 The sensitivity and specificity of biomarkers for diagnosis and therapy must be improved. Biomarkers are objective biological parameters, such as proteins, sugars, lipids or nucleic acids, and can serve as indicators for biological processes in both healthy and ill individuals. The availability of suitable biomarkers is essential for the taxonomic classification of diseases, as well as assigning patients to preventive, diagnostic and therapy-relevant groups (stratification). Biomarker candidates must be reliably tested in clinical studies with regard to sensitivity, specificity and benefit. To date, only a small percentage of the numerous biomarker candidates described in the literature have been clinically tested and validated. Validating them requires numerous quality-assured biological samples and a large amount of personal clinical data – biobanks in particular can be used for this. The development and validation of biomarkers requires networked interdisciplinary collaboration among partners in research, university hospitals and industry.

1.3 Accompanying research in the areas of economics, ethics and law should be strengthened. The economic effects of implementing Individualised Medicine are the subject of particular controversy. Thus, accompanying socioeconomic investigation of the entire system is necessary for drawing reliable conclusions. In the area of ethics and law as well, Individualised Medicine is to some extent entering uncharted territory and needs to be supported by researchers. Key issues are the right not to be informed, management of patient-related databases with regard to data protection, potential undesirable developments and the possibility of misusing data, e.g. for commercial purposes. Restrictions on access to therapies based on economic considerations have far-reaching consequences for distributive justice, and dialogue about these problems should occur within society as a whole.

Recommendation 2:
Harmonisation and standardisation

2.1 Biobanks ought to be harmonised and standardised. Biobanks contain biological samples that are linked with data on patients or test persons whose phenotypes have been carefully documented. As such, biobanks are an important tool for identifying and validating biomarkers and should utilise standardised concepts concerning the removal and storage of tissue samples, body fluids, DNA, RNA and proteins, as well as the documentation of the associated medical data. Biobanks require sustainable funding; national networking and centralised coordination are also urgently needed.

2.2 Anamnesis and phenotypic data must be collected in a standardised way. Molecular genetic data are already being obtained using relatively uniform procedures. However, this is not true for anamnesis or for the recording of clinical characteristics (phenotyping). Here, recognised and consistent standards are largely lacking. However, exact phenotyping is especially necessary for Individualised Medicine, and can be achieved only in the context of a national initiative. A project to oversee the set-up of a medical metadatabase could serve as the foundation for this. Using a basic dataset, the metadatabase should uniformly define all the indication-related characteristics to be measured. Only then will the recorded characteristics be comparable and evaluable across studies.

Recommendation 3:
Adapted designs for clinical studies

Clinical studies should be adapted to new demands. Although conclusions are often drawn retrospectively in Individualised Medicine, prospective studies are indispensable for assessing the benefit of individualised approaches. Refining the

classification of diseases within Individualised Medicine makes it possible to conduct studies on better-defined and generally smaller patient groups (stratification). This requires novel concepts for efficient study design and study logistics, which also helps shorten the authorisation process. To be able to document the rare side effects of individualised therapies despite a decreased number of cases, following up on a new therapeutic process after it has been authorised is increasingly important. Efforts should be made to ensure international information exchange on the status of clinical studies; the publication of complete study data, including negative results, is necessary in this context.

Recommendation 4:
Building up infrastructure in hospitals

4.1 High-throughput bioanalytical procedures should be established at university hospitals. In the near future, sequencing techniques will make it possible to decode the individual human genome and test it for disease-relevant factors at reasonable time and cost. High-performance, high-throughput procedures for collecting genomic data are indispensable for Individualised Medicine, as are other technologies that can record molecular markers such as genomic expression (epigenome), RNA (transcriptome), proteins (proteome) and metabolic products (metabolome), all of which will become more significant in the future.

4.2 Expanding and networking IT infrastructure and bioinformatics are overdue. Processing the volume of data generated in the context of Individualised Medicine requires high-performance and well-networked information technology. Complex patient information should be uniformly linked in a digital patient record and made accessible without barriers to attending doctors. IT equipment and skills are just as much a part of a medical institution's infrastructure as its basic supply of electricity and water. Because of the different ways in which hospitals are funded in the different German federal states, however, there are still significant shortcomings that need to be remedied by means of targeted investments, even in some university hospitals. In addition to ongoing development of the necessary hardware, Individualised Medicine also relies on professional data analysis. There is a significant bottleneck here that can, if at all, only be addressed by educating and involving a sufficient number of specialised bioinformaticians.

Recommendation 5:
Protection of personal rights

5.1 Statutory data protection provisions must be observed. In order to make medical progress, clinical data should be bundled and made available to as many researchers as possible. Information that is collected in the context of patient care is subject to the obligation of medical confidentiality; the handling of genetic samples and data collected in the course of medical care is governed by the German Gene Diagnostics Act. Statutory data protection provisions also apply for personal data that are collected in the context of research projects. Patients may only release their data for scientific analysis via written consent. Dubious internet-based offers of genetic analysis using biological samples and accompanying phenotype information submitted by mail are a cause of concern. These include direct-to-consumer tests, the results of which are not currently subject to the necessary general quality control, and may also be misused because of commercial incentives. This can lead to a loss of trust and decreasing willingness on the part of patients to participate in scientific studies. Such developments can only be controlled by international consensus agreements.

5.2 The rights and duties of non-medical scientists must be regulated. Because of the cross-disciplinary expertise required in the context of Individualised Medicine, forming interdisciplinary teams of doctors, biologists, engineers and other natural scientists will be necessary. In this regard, non-medical scientists should be legally protected by being granted the right to refuse to testify. The code of conduct for non-medical scientists that was prepared by the EURAT project group in 2013 is supported in the present Statement. This code both protects scientists and contributes to the preservation of patient rights. Moreover, in the future clinical ethics committees will likely have to be increasingly involved in decision-making processes related to individualised healthcare.

Recommendation 6:
Framework conditions

6.1 Appealing framework conditions should be created for the development of companion diagnostics. The quality, reliability and timely availability of new diagnostic procedures are of decisive importance for the development of an individualised therapy. Jointly developing and authorising individualised therapeutic agents and companion diagnostics can thus significantly contribute to therapeutic success and to the avoidance of ineffective therapies; this strategy is already being used successfully in the treatment of various tumours. Insurers should develop harmonised authorisation processes and reimbursement modalities to promote the development and use of companion diagnostics.

6.2 Developing strategies for risk-adapted prevention should be supported. A better understanding of individual disease risks also creates new options for prevention. It is expected that health insurance funds and ultimately society as a whole will place special emphasis on disease prevention in the future. This approach is already apparent in the treatment of hereditary tumours and those caused by viruses. It is recommended that both early detection of treatable illnesses, tailored to individual risk, and investigating the efficacy of preventive steps be pursued further and with vigour. In addition, more consideration should be given to how people can be better motivated to take preventive measures, for example by means of bonus schemes. However, this must not lead to a violation of either patient autonomy or the right not to be informed.

6.3 University hospitals must have sufficient resources for clinical research and medical care based on that research. The progress and achievements of Individualised Medicine will be shaped in part by efficient translational medicine, that is the rapid transfer of research results into clinical practice. Structurally, this process can currently be implemented most efficiently, across its entire range of subject areas, at university hospitals. Translational medicine requires close interaction between scientifically designated groups and doctors working in healthcare, and our society would do well to make sufficient resources available for efficient university structures. Moreover, framework conditions need to be created that enable partners from academic research, industry and regulatory authorities to exchange information early on about specific requirements for the efficient translation of innovative and integrative medical approaches.

Recommendation 7:
Education and counselling

7.1 We must meet the increasing need for information and counselling. Patients and doctors must increasingly make diagnostic and therapeutic decisions together, based on information that is usually very complex. Herein lies

another major challenge for Individualised Medicine. In this context, it is important that doctors are able to convey the interdisciplinary aspects of treatment to the patient in a comprehensible way and that neutral, quality-assured and comprehensible information platforms are set up, to which both patients and doctors have access. The information service of the German Cancer Research Center can serve as an example here.

7.2 Basic and advanced training and continuing education must be adapted to the requirements of Individualised Medicine. New teaching concepts are necessary in order to purposefully incorporate Individualised Medicine into the basic and advanced training and continuing education of doctors. In particular, fundamentals in the areas of molecular biology and bioinformatics must be conveyed. Such measures will help increase the willingness to use innovative procedures on the one hand, and sharpen critical judgement on the other. This also implies the implementation of fundamental reform both within and outside of universities. In addition, natural scientists working as part of the team, as well as other healthcare workers, must be sufficiently familiarised with the relevant medical topics.

Recommendation 8:
Raising awareness in society and among decision-makers

Individualised Medicine requires structural adaptation and adequate funding in research and care. The parties involved in this study are aware that far-reaching structural adaptations in research and care are necessary to implement Individualised Medicine in patient care; this also requires significant funds. If the structural and material needs of Individualised Medicine are not met, the population will be denied opportunities for improved diagnostics, therapy and prevention of disease, and thus of important prerequisites for a longer, healthy life. This would very likely affect the less affluent segments of society the most. Society, especially individuals and institutions who bear responsibility for healthcare, should work together toward the implementation of Individualised Medicine.

1 Introduction

1.1 Starting situation

Promoting human health has always been medicine's most important concern, and for centuries, empirical approaches have determined patients' medical treatment. Groundbreaking findings in the life sciences and associated progress in the development of biochemical and molecular biological analytical techniques, as well as in medical technology processes, have led to a significantly improved understanding, grounded in the natural sciences, of the causes and development of illnesses. Decoding the human genome in 2001 was a milestone on the path to being able to diagnose and treat illnesses by taking numerous individual characteristics into account and classifying them in molecular terms.

As a result, medical progress can be recognised in roughly half of the approximately 8,000 monogenic diseases that are currently known: in this group of diseases arising from single mutations, the causes have been discovered. Explaining and diagnosing these conditions, which often occur during childhood and are usually very difficult to clinically differentiate between, represents a challenge for the genetic counselling of the affected families. Detecting the genetic causes that underlie these conditions has already enabled effective therapies for some of them.

Tumour diseases, which are a focus of this Statement, are the subject of intensive molecular biological investigation. Such diseases are predominantly the result of genetic changes in body cells (somatic mutations). The availability of tissue samples taken for diagnostic purposes makes molecular genetic analysis possible. Hopes are that the resulting genetic profile will give rise to a deeper understanding of the tumour process, and beyond this a precise categorisation of tumours into molecular subgroups (subtypes). Therapeutic decisions for many malignant tumours are already being made based not only on the morphological but also on additionally obtained molecular biological findings. Similar procedures also apply for the diagnosis and treatment of infectious diseases.

Many common chronic illnesses, which occur particularly at more advanced ages, are multi-factorial, that is they are caused by a large number of genes and environmental influences. These illnesses include, for example, rheumatic illnesses, cardiovascular disease, diabetes mellitus, obesity and neurodegenerative illnesses. Disease-associated genetic variants have also been found for these conditions. Precise assignment to particular forms of disease, however, is much harder, because the causes and the phenotype are determined by a complex interplay of genetic factors and individual environmental influences. Therefore, they are largely still the subject of ongoing research.

Older people make up an increasing percentage of the overall population, and although many of them age with good health, the number of chronic illnesses, which often occur in combination (multimorbidity), will also continue to rise (Nowossadeck, 2012). Currently, the most common causes of death in Germany are cardiovascular disease (about 40 percent), followed by tumour diseases (about

25 percent).[1] Worldwide, more than 382 million people – and the numbers are increasing significantly – already suffer from diabetes mellitus,[2] and at least 35 million are affected by Alzheimer-type dementia (Prince et al., 2013).

Thus far, the causes of these chronic illnesses could only be treated to a limited extent, and it is very difficult to clarify their primary causes because the factors that trigger them are complex and their course is currently poorly understood. It must therefore be assumed that the frequency of these illnesses and any associated complications will first continue to increase, incurring high and rising costs.

The progress that has been made to date in medical technology, along with increasing specialisation in the healthcare system, have significantly expanded therapeutic options and thus the number of potential healthcare claims and services. Most therapies that are available were developed through a cost-intensive process over many years. Moreover, assigning patients to therapeutic and prevention-relevant groups (stratification) has often not been very precise, meaning that many of the therapies that are standard today are effective only in some patients and may also be associated with serious side effects. Indeed, over five percent of hospital admissions in Western countries are associated with side effects of therapy (Kongkaew et al., 2008).

1.2 Individualised Medicine and its implementation

Numerous terms, such as Precision Medicine, Molecular Medicine, Genomic Medicine, Stratified Medicine or P4 Medicine, sometimes with varying definitions, are used to refer to Individualised or Personalised Medicine.[3] The terms are based on a strategic approach grounded in the natural sciences that takes individual biological characteristics of patients or patient groups, as well as influences of individual lifestyle and environment into account. The approach includes, as far as possible, all stages of care from prevention to diagnosis to therapy.

Goals of Individualised Medicine

Individualised Medicine aims to improve the efficacy and quality of treatment through targeted prevention, systematic diagnostics and tailored therapeutic procedures that are oriented to the needs of individual patients or patient groups; at the same time, Individualised Medicine aims to reduce side effects and increase the cost-effectiveness of treatment over the long term.

In the past, doctors also adapted diagnoses, prognoses and therapies to individual patients, based on their age, sex and anamnesis in conjunction with clinical findings, physiological parameters and laboratory data. This information was then used to make therapy decisions. Medicine's well-oiled machine is now being supplemented by the targeted methodical use of primarily molecular techniques. Biological parameters, especially molecular biomarkers, are increasingly included in the treatment process. It is expected that the use of these biomarkers will enable a progressively precise determination of individual biological characteristics, which can then be used as a basis for the appropriate diagnosis and therapy. With regard to the big picture, it will thus be possible to objectify medicine by precisely measuring and curing relevant changes in patients.

1 Cf. information from the Federal Statistical Office: www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Gesundheit/Todesursachen/Tabellen/SterbefaelleInsgesamt.html (last accessed: 16 September 2014).

2 Cf. information from the *International Diabetes Federation*: www.idf.org/diabetesatlas/introduction (last accessed: 16 September 2014).

3 Schleidgen et al. (2013) have developed the following definition of Personalised or Individualised Medicine based on an analysis of 683 definitions from the available scientific literature: "PM seeks to improve stratification and timing of health care by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics."

In the long term, the goal is also to develop a valid, more detailed breakdown of illnesses into taxonomic groups (molecular taxonomy) that will in turn form the starting point for the development of diagnostic tools and therapies specific to each group (target group specific diagnostics and therapeutic agents).

This development will likely significantly increase the volume of disease-relevant patient data that are available. One set of challenges for Individualised Medicine consists of standardising and securing these complex personal data and deriving results and practicable possibilities for action from them. The latter need to be transparent for the attending doctor, for scientists working in medical research and for the patient. Only in a multidisciplinary team can the new demands in Individualised Medicine be met; this will necessitate the development of both ethical standards for handling this information, and of special patient counselling structures.

It is difficult to predict the consequences of Individualised Medicine. There are also many challenges yet to be overcome (see Table 1), which means that the development process is likely to take many years. Individualised Medicine requires new organisational processes to be integrated into existing structures of the healthcare system, as well as careful monitoring with regard to ethical, legal and economic concerns. Moreover, it will be necessary to counteract undesirable developments in the commercialisation of patient-related information (e.g. in connection with direct-to-consumer tests).

Although the economic effects that Individualised Medicine will have on healthcare cannot be reliably foreseen, Individualised Medicine will likely increasingly become a part of healthcare despite the increased initial costs. In the end, supported by society as a whole, political resolve will need to contribute substantially to Individualised Medicine being realised.

Table 1. Challenges for Individualised Medicine.

Investigating the molecular causes of diseases, including complex ones that are still poorly understood.
Accelerating transfer of new results and procedures developed in basic research into clinical practice (translational medicine).
Further development and clinical establishment of high-throughput bioanalytical technologies, histological analytical techniques and high-resolution molecular imaging.
Compiling and analysing large amounts of patient-related data, and making these available for biomedical research, clinical studies and treatment of patients.
Identification, quality assurance and validation of biomarkers suitable for practical use.
Concerted development and authorisation of companion diagnostics and therapeutic agents, as well as comprehensive critical benefit assessment.
Adapting clinical studies to numerous but small patient groups.
Strengthening cooperation between public and private institutions to better coordinate research efforts across national borders.
Observing appropriate data protection guidelines and safeguarding patients' and test persons' privacy rights using ethical guidelines.
Coping with the growing need for patient counselling by developing new counselling structures.

1.3 Content and purposes of the Statement

The present Statement aims to present the development potential of Individualised Medicine and to provide an introduction to the relevant technologies. Starting from the current status of medicine, the Statement focuses on the example of molecular tumour diagnostics, and drug therapies based thereon, in order to illustrate this paradigmatically. It is already evident that Individualised Medicine will go far beyond genetic analyses.

This Statement also addresses the challenges associated with the implementation of Individualised Medicine, and underlines the need for accompanying research in the areas of economics, ethics and law. The study does not claim to provide a complete overview of the topics at hand. For example, it does not include a detailed discussion of progress in stem cell research that is relevant to regenerative medicine, of individualised fabrication and use of electronic implants and prostheses or of technical progress in precision radiation therapy and surgery.

The Statement supplements a number of reports that have already been published. For example, the Office of Technology Assessment at the German Bundestag published a comprehensive report (Hüsing et al., 2008) that addresses the state of affairs, further lines of development and implications of the relevant technologies, as well as their incorporation into the healthcare system. Coordinated by the Leopoldina, a statement on predictive genetic diagnostics was compiled that touches on some areas within Individualised Medicine (German National Academy of Sciences Leopoldina et al., 2010). In 2011, the European Commission held a European Perspectives in Personalized Medicine conference in Brussels, at which representatives from the realms of politics, academic and industry research, patient associations and clinics identified and prioritised the measures necessary to further develop Individualised Medicine. In the same year, the American National Research Council issued a report on the potential and opportunities for a new molecular biological taxonomy of diseases (National Research Council, 2011). The European Science Foundation published a subsequent report focusing on realistic timelines for the implementation of Individualised Medicine (European Science Foundation, 2012). This was followed by statements from the German Ethics Council (Deutscher Ethikrat, 2013), the Berlin-Brandenburg Academy of Sciences and Humanities (Berlin-Brandenburg Academy of Sciences and Humanities, 2013) and the EURAT project group[4] of the University of Heidelberg (Marsilius-Kolleg, 2013) on the ethical and legal aspects of sequencing the human genome. The reports of the British Academy of Medical Science (AMS, 2013), the US Food and Drug Administration (FDA, 2013) and the European Commission (European Commission, 2013) all focus on the insurance reimbursement and regulatory aspects in Individualised Medicine.

4 EURAT stands for Ethische und Rechtliche Aspekte der Totalsequenzierung (Ethical and Legal Aspects of Whole Genome Sequencing) of the human genome. See the table of abbreviations for additional abbreviations (Ch. 10.3).

2 Forerunners of Individualised Medicine

The first sequencing of a human genome in 2001 gave rise to expectations of soon being able to understand, cure, predict and even prevent numerous diseases by comparing the genomes of affected patients with those of 'normal individuals'. At the time, the rules of genetic determination that apply for monogenically inherited phenotypes or diseases were falsely generalised. In fact, however, frequently occurring diseases in particular result from disturbances within a very complex genetic arrangement.

The new precision of molecular analyses with which disease-associated changes can be detected could potentially lead to a profound transformation in our biological understanding of diseases. However, it is difficult to determine the correlation in individual patients between molecular and biochemical findings on the one hand, and the clinical expression of disease (clinical phenotype) on the other. In many cases, only statements of probability can be made in this regard. The problem becomes even greater when influences from the patient's family history, biography and psychosocial situation are also taken into account.

In this section, the technologies that are currently most instrumental in Individualised Medicine are presented in detail and illustrated with examples. Alongside the collection of genomic data, these include other analytical techniques such as epigenomics, transcriptomics, proteomics, metabolomics and advanced morphological and imaging methods. Bioinformatics, which must be used when compiling and interpreting large amounts of data, plays an important role.

2.1 Genome analysis using DNA sequencing

2.1.1 Variability in the human genome

The Human Genome Project established important prerequisites for systematically analysing the relationship between genotype and phenotype. Using the next-generation DNA sequencing that is available today, several hundred million DNA fragments can be sequenced at once per machine and per test run, meaning that these high-performance methods now make it possible to completely decode the genome of an individual in a few days, for a few thousand dollars.[5] For technical reasons, sequencing reactions involve errors that can only be minimised through multiple (redundant) sequencing, generally 30 times, of the same genome sequence. This is also referred to as 'depth of sequencing'. New deep-sequencing techniques enable very accurate sequencing in an experimental run. Some researchers even recommend 100-fold sequencing coverage for the reliable determination of a human genome (Ajay et al., 2011).

It is foreseeable that individuals could very soon have their genomes analysed affordably; it is estimated that a total of about 15 million alterations in individual genetic building blocks (single nucleotide polymorphisms, SNPs) occur naturally in all existing human genome sequences compared with a reference genome. These make up about 0.1 percent (3.5 million SNPs) of an individual ge-

5 Current cost calculations for genome sequencing can be found at www.genome.gov/sequencingcosts (last accessed: 16 September 2014).

nome. Sequencing techniques also enable the identification of small genetic variations (microdeletions and microduplications). Within each genome, there are also other genetic changes whose influence on the development of diseases and the effect of medications is currently poorly understood (see Table 2).

Knowledge of the personal (constitutional) genome has potential significance for the following areas:

- Predicting, i.e. foretelling, with a certain degree of probability, a phenotype (e.g. an illness) that has not yet manifested itself at the time of the test.
- Prevention, i.e. avoiding or delaying the occurrence of a disease.
- Diagnostics, i.e. classifying a disease and its stage.
- Therapy, i.e. delaying the progress of, or the relief, remission or cure of disease in a way that is specific and has as few side effects as possible.
- Prognosis, i.e. predicting the course of an existing disease.

Table 2. Average DNA sequence deviations of an individual human genome from the haploid reference genome (based on Meyer et al., 2013).

Approx. 3.5 million single nucleotide polymorphisms (SNPs).
Approx. 1 million microdeletions, microduplications and microinsertions.
Approx. 20,000 structural variations such as copy number variations (CNVs) and larger deletions or insertions.
Approx. 100 variants of protein-coding genes that have lost their function (loss of function).
9,000–11,000 variations in coding sequences that lead to altered protein sequences.
1–2 percent of the total sequence.

2.1.2 Genetic diagnostics

Genetic analysis can be used to diagnose diseases that are caused or partially caused by hereditary factors; the potential conclusions depend on the type of heredity. Monogenically inherited diseases (see Berlin-Brandenburg Academy of Sciences and Humanities, 2013 for a detailed discussion), which arise due to individual mutations and lead with a high degree of penetrance to a phenotype (see Ch. 5.4), are especially significant here. These must be differentiated from tumour diseases and multi-factorial diseases in which many genes, in combination with exogenic factors, contribute to the occurrence of the disease (see Ch. 5.6). In principle, the methodological approaches to recognising diseases that manifest themselves during the course of a person's life can also be used for predictive diagnostics (see Ch. 5).

2.1.3 DNA analysis in multifactorial diseases

In addition to DNA sequencing, specific DNA binding techniques (hybridisation) can be used to comprehensively analyse genetic samples for single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) in order to answer specific questions. DNA microarrays, also called gene chips, are used for this. These microarrays can detect several hundred thousand genetic variations at a time in a very small area. This method is used for research purposes with large patient and test person collectives in genome-wide association studies (GWAS). The goal in such a study is to identify, in the entire

genome, DNA variants associated with the disease based on statistical analyses. It is hoped that in this way the genetic component of a multifactorial disease can gradually be identified (see Ch. 5.6). Using GWAS, numerous associated gene variations have been found for a number of multifactorial diseases. The functional effects, however, still need to be clarified in additional investigations and must be understood for therapeutic use in Individualised Medicine.

A private-sector initiative is underway that plans to generalise this approach on a large scale. Each year, the genomes of up to 100,000 people from all age groups, including both healthy and sick individuals, are to be sequenced completely and correlated with the relevant person's medical and laboratory data (Brazil, 2014). Patients with tumour diseases will be studied in the first phase of the project, and later studies on those with heart disease, neurodegenerative conditions like Alzheimer's disease and Parkinson's disease, as well as microbiome analyses will be carried out (see Ch. 2.6). The hope is that researchers will find genetic patterns that correlate with the diseases.

2.1.4 Genome analysis in tumours

Tumour diseases arise from genetic, usually acquired, alterations (mutations) in individual cells. A tumour arises as a result of the cascade-like sequence and clustering of many mutations. An important task for research is to differentiate between mutations that are correlated with the disease process and relevant to a tumour and those mutations that are irrelevant. In some cases, this has already been done successfully. Chronic myeloid leukaemia (CML), for example, is usually the result of a DNA fragment translocation between chromosomes 9 and 22 that leads to the formation of a shortened chromosome 22 (Philadelphia Chromosome). The resulting *BCR-ABL* fusion gene can, as a tumour-causing oncogene, lead to uncontrolled reproduction of affected cells and thus to leukaemia (blood cancer).

Current research is seeking to comprehensively describe the genetic particularities of all known carcinomas (The Cancer Genome Atlas, Weinstein et al., 2013). One challenge, however, is the instability of tumour genomes and the resulting heterogeneity of phenotypically similar tumours or cell clones within a tumour. This makes clarifying molecular processes in tumour diseases more difficult. Using conventional techniques, the DNA of tens of thousands to millions of cells is tested. Progress in single-cell sequencing has made it possible to determine the DNA sequence of individual cells (Zong et al., 2012) and thus to ascertain the genetic differences within tissues when the cancer has spread (in metastases), or of tumour cells circulating in the blood or lymph.

The goal of the International Cancer Genome Consortium (ICGC), one of the world's biggest large-scale interdisciplinary biomedical projects seeking to clarify the causes of tumour diseases, is to make a decisive contribution to that area. The complete genome information of 50 different types of tumours is to be analysed by 2015. An important hope for sequencing is uncovering defects that can be directly or indirectly treated. However, the mutation pattern of every tumour is unique, and in addition to the genome sequence, other processes that are downstream of genetics also play a significant role in tumour formation (see Chapters 2.2 – 2.6). Nevertheless, the hope is to be able to find, for each type of tumour, a characteristic pattern in the mutations relevant to the genesis of that tumour; to date, more than 20 different tumour patterns have been extracted (Alexandrov et al., 2013).

Comprehensive knowledge of a tumour-specific mutation profile will be important for the therapy of numerous types

of tumours in the future. One possibility could be to synthesise specific tumour antigens (peptides) and use of them as individualised vaccines (Castle et al., 2012). Another possibility lies in the generation of tumour-binding antibodies that are coupled with chemotherapeutically active substances (Li et al., 2012) in order to specifically attack tumour cells (see Chapter 6.2.3).

2.2 Epigenetics

Epigenetics investigates molecular processes in the dynamic formation of the chromatin (the molecular complex of genomic DNA stored in the cell nucleus and the proteins that surround it) that form the basis for gene regulation. This 'gene programming' determines which gene products are formed when, where and to what extent. This can occur through enzymatic modifications of DNA-binding proteins (e.g. histones), ribonucleic acid (RNA) activity or by means of the methylation of DNA (the transfer of methyl groups onto cytosine, a building block of DNA). Epigenetic changes can occur in individual tissues or be present in all of an individual's cells. These changes can also lead to hereditary mechanisms that are not rooted in the genome sequence itself, and there are some early indications that these can cause severe illnesses (Heyn & Esteller, 2012; Mikeska et al., 2012; Rakyan et al., 2011). DNA methylation brings about the shut-down of a gene in a way that is comparable to a switch. The methylation pattern also determines the normal function of differentiated cells in tissues or organs, and can remain stable across many cell divisions.

Interestingly, tests on blood samples have shown that even monozygotic twins display differing epigenetic patterns at advanced ages (Fraga et al., 2005). This shows that the epigenome can change as a result of numerous non-hereditary influences to which people are subject in the course of their lives. The totality of these influences is also called the exposome. Differences in the exposome are one of the possible explanations for the fact that the same genotype can bring about different phenotypes. Third-generation DNA sequencing techniques like single-molecule real-time sequencing already permit us to determine complete methylation patterns in the human genome (Rivera & Ren, 2013; Ziller et al., 2013). In tumour research, the methylation patterns of numerous genes have been linked with tumour genesis (Ehrlich & Lacey, 2013) as well as with the efficacy of some medications (Meyer et al., 2013). Moreover, it is assumed that epigenetic patterns play a role in the development and hereditary transmission of obesity, for example (Guénard et al., 2013; Plagemann et al., 2009). It would therefore be very interesting to have systematic epigenome-wide association studies conducted, similar to the genome-wide association studies, on the correlation of disease-relevant phenotypes with epigenetic variations (Rakyan et al., 2011). Because epigenetic patterns are frequently tissue-specific, and the relevant organs are only accessible using invasive procedures, a large-scale investigation of this type can currently only be conducted within significant limitations.

2.3 Transcriptase analysis

The transcriptome depicts gene expression activity; that is, it reflects the dynamic activity of the genome, the switching on and off of genes in healthy or pathologically altered cells. The transcriptome also describes the totality of the ribonucleic acids (RNAs) that result in a time- and circumstance-dependant manner from DNA transcription. The coding mRNAs mediate between the genomic DNA and the protein biosynthesis of the cells, and provide insights into inactive and active areas of the genome. Many genes are not tran-

scribed equivalently into RNA and then into proteins; instead, the RNA is first processed further. This process involves the removal of certain areas called introns and the addition of other areas called exons. The exons are frequently put together in different tissue- and need-specific combinations; this is referred to as 'alternative splicing', which ensures that, depending on the need, products with different functions can result from one gene. Other non-coding RNAs (e.g. rRNA, tRNA, miRNA or lncRNA) are not transcribed into proteins, but they are involved in the regulation of gene expression or in catalytic processes. Non-coding areas of the genome and alternative splicing mechanisms have been linked with conditions like cystic fibrosis and Prader-Willi syndrome (Wang & Cooper, 2007) as well as with the efficacy of medications (Sadee et al., 2011).

As in the genome-wide association studies (see Chapter 2.1.3), RNA microarray technology is one method for analysing genome-wide gene expression. With this method, many thousands of RNA molecules are tested at the same time for differences in gene expression. Analysing these molecules requires knowledge of decoded genome sequences. For example, transcriptome analysis can be used to determine which genes are active under which conditions in which cell types. This possibility has already led to the development of tests based on gene expression. It is hoped that diagnosis, prognosis and therapy decisions for breast and intestinal tumours or leukaemia, as well as HIV and hepatitis C will thereby be facilitated (Rhodes & Chinnaiyan, 2005; Zadran et al., 2013). Because unknown RNA transcripts cannot be recorded using hybridisation methods, transcriptomes are increasingly determined using a method called RNA-seq. In this method, the RNA is first transcribed into cDNA and then sequenced and quantified (Ozsolak & Milos, 2011). About 80 percent of all characteristic-associated SNPs (see Ch. 2.1) are in non-coding DNA regions (Manolio, 2010). Therefore, transcriptome analysis will continue to be irreplaceable in the future for the clarification of genotype-phenotype associations and the determination of biomarker signatures (see Ch. 3).

2.4 Proteome analysis

Proteins, which are generated by the translation of mRNA, are the end products of coding genes; they also act as catalysts and provide structure for molecular biological processes and are largely responsible for organisms' appearance (phenotype). Taken together, proteins form the proteome, which like the transcriptome (see Ch. 2.3) is very dynamic, and the composition of which is, due to changing conditions (gene expression, environmental influences, metabolism, etc.), constantly undergoing transformation. Proteome profiles reflect physiological states or changes in cells and tissues. Specific profiles can arise from disease processes, drug treatment or other influences and thus are better able to represent biological status than genome and transcriptome analysis alone. For example, proteomics enables researchers to identify and clarify the faulty signal pathways in protein networks that often occur in tumour cells (Kolch & Pitt, 2010). There is great hope that it will be possible to correct altered signal processes using targeted interventions with drugs and to follow those corrections using proteome analysis.

Although proteome research has undergone rapid development in recent years with the sequencing of complete genomes, the ultimate goal of proteome research to comprehensively and accurately represent the world of proteins in humans has not yet been reached. Research in this area still focuses primarily on simple cellular systems. For human samples, which are significantly more complex, detect-

ing proteins that are often present only in very small quantities will require further development of mass spectrometry processes. Moreover, characterising the proteome presents a huge bioanalytical challenge because of the high degree of biochemical and structural heterogeneity of proteins. The approximately 23,000 human protein-coding genes are, depending on need, translated into possibly more than one million functionally distinct proteins in cells through alternative splicing (Ch. 2.3), processing and post-translational chemical modifications. In addition to their concentration, the cellular location of proteins also frequently determines their involvement in disease processes. In this context, molecular imaging (see Ch. 2.8) could contribute to a better understanding of functional cellular biology in particular.

Proteome detection techniques include antibody-based methods (such as immunohistochemistry, immunoprecipitation, ELISA, immunoblot) and further technological development of those methods aims to achieve higher throughput rates (e.g. tissue or protein arrays). Techniques that enable proteins to be identified after separation in two-dimensional gels are increasingly being replaced by liquid chromatography separation techniques. Along with the development of automated, highly sensitive mass spectrometry techniques, this now makes it possible to identify, quantify and even clarify post-translational modifications of proteins using a high-throughput procedure (Cox & Mann, 2011).

Testing body fluids is the most suitable way to investigate disease-specific proteome profiles in humans, and analysing urine proteins and their breakdown products is already very advanced (Albalat et al., 2013). Separating peptides using capillary electrophoresis and subsequent mass analysis (CE-MS) makes it possible to show peptide signatures in the urine. Work is being done to diagnose kidney conditions and malignant prostate alterations, for example, by comparing samples from affected patients and healthy test persons (Coon et al., 2008). Further, cerebrospinal fluid is being used in research on dementia to investigate the peptides associated with Alzheimer's disease. This opens up options for early diagnosis of this disease and for differentiating among various forms of dementia (Albert et al., 2011; Bateman et al., 2012; Jahn et al., 2011). The possibility of diagnosing the molecular causes of slowly progressing diseases early on and precisely could, it is hoped, be the first step toward development of a targeted therapy or of targeted preventive measures (Debré et al., 2012; Langbaum et al., 2013).

2.5 Metabolome analysis

Metabolites (metabolic products, e.g. sugars, amino acids, fats) are final or interim steps of intermediate metabolism. By measuring these products, far-reaching conclusions can be reached about an organism's reaction to nutrition, environmental influences, disease and therapies. For this reason, analysing metabolites has become an important component of medical diagnostics, for example, in lab tests on blood plasma and urine samples. These techniques are also used to analyse substances that are foreign to the body, such as medications, their breakdown products and environmental toxins, intoxicants and addictive drugs, as well as to gain indications of toxic effects. Recording toxic metabolites is preferentially based on NMR techniques (see below) because they require only small sample volumes, and the sample preparation process is relatively simple.

The totality of the metabolic products synthesised in body cells and taken in with food is called the metabolome. With approximately 6,500 low-molecular sub-

stances identified at present, the metabolome is smaller, numerically speaking, than the three billion DNA bases of the human genome and the number of proteins and protein aggregates, which are estimated to number over one million.

Using chromatographic separation techniques along with mass analysis, and based on magnetic resonance analysis (NMR analysis), it is possible to detect mere traces of metabolites as well as entire metabolite patterns (metabolic fingerprinting/profiling) in body fluids. In the context of research projects, metabolite patterns in particular are currently being used to identify biomarkers (see Ch. 3.1). For example, specific metabolite patterns have been identified that indicate increased risk for the expression of type II diabetes mellitus or are characteristic of a potential subgroup of the condition (Padberg et al., 2014; Wang et al., 2011).

Metabolic fingerprinting is, however, subject to limitations with regard to sensitivity and resolution. Like proteome profiles (see Ch. 2.4), metabolite patterns vary greatly depending, for example, on a test person's condition and on the treatment of the sample, the time of day the sample is taken and food intake.

By linking genome-wide association studies (see Ch. 2.1) with metabolome analyses, genetic influences on metabolic phenotypes can be identified in scientific studies (Suhre & Gieger, 2012). This provides insights into kidney conditions, gout, type II diabetes mellitus and into the efficacy of medications (Suhre et al., 2011). Metabolome analysis indicating a correlation with tumour genome data could, in the future, be used to obtain new information about tumour genesis (Meyer et al., 2013). Further, medications like cholesterol-lowering statins can also have a significant influence on metabolite patterns (Trupp et al., 2012). Early recognition of individual response to a drug therapy, before side effects become evident, is a very promising aspect of metabolome analysis (Kaddurah-Daouk & Weinshilboum, 2014; see also Ch. 6.1), and would enable rapid adjustment of the right combination of medications and/or of the dosage of a medication, thus helping to minimise side effects or speeding up the replacement of ineffective drugs (Chung & Griffiths, 2008). Metabolome analysis of blood plasma or urine samples has also made it possible to predict and follow the course of drug-induced liver damage in rats (Clayton et al., 2006). Specific metabolite patterns in urine samples from patients taken shortly after administering painkillers make it possible to predict liver-damaging effects long before typical clinical signs of liver toxicity occur (Winnike et al., 2010).

Because of the metabolome's high degree of molecular diversity, comprehensive metabolome analysis is relatively demanding in terms of the equipment required and is, like proteome analysis for diagnostic applications, still in the developmental phase.

2.6 Microbiome analysis

Many diseases are caused by pathogenic microorganisms such as *Escherichia coli*, *Mycobacterium tuberculosis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Certain strains of these bacterial species are among the much-feared multidrug-resistant hospital germs. Determining antibiotic resistance in bacterial infections, which has been practised for some time now, stratifies certain infectious diseases. In the future, rapid tests based on precise genetic analysis of the particular pathogen could significantly simplify the analysis of antibiotic resistance and thus the tailored treatment of bacterial infections. Making an appropriately large arsenal of suitable antibacterial substances available through further

research and development of antibiotics will be decisive here (Academy of Sciences and Humanities in Hamburg & German National Academy of Sciences Leopoldina, 2013).

The totality of the microorganisms that colonise humans is called the microbiome. It is estimated that there are ten times as many microbial cells, primarily bacteria, colonising each human being as there are cells in the human body (Turnbaugh et al., 2007). The significance of these largely non-harmful, and in many cases even beneficial or essential microbial colonisers was underestimated for a long time. To characterise the highly complex biotic communities of organisms in anatomical niches, for example in the intestinal and buccal flora, their metagenomes, that is the whole of the DNA or ribosomal RNA, is recorded using high-throughput sequencing (see Ch. 2.1). In this context, the American National Institute of Health launched the Human Microbiome Project (Turnbaugh et al., 2007) to sequence all the genomes of microorganisms that colonise humans. By 2012, more than 600 samples from 15 body regions of approximately 300 individuals had already been investigated (Cho & Blaser, 2012). The goal of this and other international projects is to decode human-microbiome interactions and to identify the correlations between metagenome patterns and pathological processes.

For example, associations have already been demonstrated between the composition of gastrointestinal flora and the development of obesity and chronic inflammatory bowel disease (Greenblum et al., 2012) as well as tumours, diabetes and atherosclerosis (Eloe-Fadrosh & Rasko, 2013). Microorganisms that colonise the skin and lungs have been linked with disorders of the immune system, which are also partly genetic, that result in the development of asthma and psoriasis (Cho & Blaser, 2012).

Important questions in microbiome research include the following:

- To what extent are microbiomes adapted to a person's genome and lifestyle (e.g. nutrition), and to what degree are they passed on to newborns by mothers?
- To what extent does the microbiome contribute to the genesis of disease?
- How do the microbiome and the administration of drugs influence one another?
- Can we influence individual microbiome patterns and thus the risk of disease by means of diet and pro- and antibiotics?

Classifying the millions of individual DNA sequences from metagenome analyses into taxonomic groups and subtypes of the microorganisms that are involved presents a particular challenge for microbiome research; to do this, bioinformatic methods are required. The problem is that there are still no reference genomes for many of the DNA sequences (Cho & Blaser, 2012). The definition of strains and subtypes plays an important role here, because even small genetic deviations can make the difference between commensal (non-harmful) and pathogenic organisms. For example, certain gene variations or additional genes can permit a pathogenic microorganism to attach to or penetrate into body cells and/or outsmart the individual human immune system.

Investigation into the significance of the microbiome for Individualised Medicine is still in the early stages, but there are a number of interesting starting points. For example, indicator organisms or organism communities may be useful in the future as biomarkers for the stratification of patients (Le Chatelier et al., 2013). Once the composition of health-promoting and health-damaging microbiomes is known, they could be influenced in a targeted way through diet, probiotic products

or specifically active antibiotics. Furthermore, patients could, particularly after treatment with broad-spectrum antibiotics, be recolonised with health-promoting microorganisms; this is already occurring in clinical practice. Individualised 'microbial cocktails' could also counter the concentration of germs that are multiresistant to antibiotics. Transferring intestinal flora, also called stool transplantation, has already been in therapeutic use for about 50 years against a particular clostridial infection, and many new applications for this technique are becoming evident (Borody & Khoruts, 2012).

2.7 Morphological and associated methods

Using bioanalytical high-throughput techniques (omics technologies), often in combination with traditional histomorphological techniques, increasingly promotes the identification and quantification of biomarkers. Various light microscopy techniques are standard procedure for the localisation of biomarkers (e.g. immune complexes, cell products, bacteria or nucleotide sequences) at the tissue and cell levels. Phenotyping using highly sensitive immunohistochemical and cytochemical techniques or in-situ hybridisation in particular is widely used in diagnostics and research. For sub-cellular localisation of single or small numbers of molecules, electron microscopy aided by functional methods must be applied. To use these techniques, cells or tissues are first removed for diagnostic purposes using cytological (cell smears, fine-needle puncture) and bioptical techniques or surgical procedures (sample excision or operations). These types of cell or tissue removal are often monitored using imaging techniques (Böcker et al., 2012) that are still undergoing intensive development and are enabling increasingly sensitive and specific biomarker detection.

Morphological techniques, often in combination with genotyping, are widely used in the diagnosis of many diseases. These techniques are especially important, for example, in oncological diagnostics and research, and are indispensable for typing tumours, determining the extent of tumours, recognising biomarkers and determining sensitivity to chemotherapeutic agents.

2.8 Imaging techniques

Imaging techniques help locate alterations caused by disease and determine the extent of those alterations within the body in order to follow the course of a disease or the success of a therapy (Leblond et al., 2010; Walter et al., 2010). Some techniques, such as ultrasound, computed tomography (CT) or magnet resonance imaging (MRI), tend to collect mainly structural, anatomical-morphological information. Other techniques, such as functional MRI (fMRI), positron emission tomography (PET) or single-photon emission computed tomography (SPECT), seek to provide detailed spatial and temporal representation of physiological and biochemical processes. To some extent, NMR-based imaging techniques in which metabolite biomarkers are determined *in vivo* already play a role in the diagnosis of conditions of the central nervous system and of certain tumour diseases (Öz et al., 2014). Improvements in spatial and temporal resolution, coupling of equipment modalities (e.g. PET/CT, SPECT/CT, PET/MRI), development of expert systems for automated image analysis and optimisation of image sequences are continuously increasing the performance of these techniques (Bailey et al., 2014; Engert et al., 2012; Vahrmeijer et al., 2013). This means that molecular imaging that permits the visualisation of particular molecules, such as receptors in living tissue, is beginning to be a possibility.

2.9 Biobanks

Individualised Medicine requires professionally managed biobanks of tissue, tumours, DNA/RNA samples and body fluids, as well as registries like electronic health/medicine records (EHRs or EMRs). While the latter are purely medical databases, biobanks are collections of biological materials in which annotated clinical data are filed in encrypted form in a digital database system. Biobanks were originally set up for research purposes in university facilities. While tumour tissue, for example, is quite often available at pathology institutes, samples of rarer diseases (orphan diseases) are significantly under-represented. There are particular demands on sample quality and on the associated clinical data for these diseases:

- The patient/test person informed consent form for use of samples (usually taken for diagnostic or therapeutic purposes) for research (Suh et al., 2013; see also Ch. 7.5).
- Adherence to legal provisions concerning data protection (e.g. using pseudonymisation).
- Standardised sample removal and storage.
- Knowledge of pre-analytical data (e.g. type and time of preservation).
- Exact histological characterisation of tissue prior to use (e.g. extraction of DNA, RNA or protein, percentage of necrosis, tumour tissue, normal tissue, etc.).
- Integration of clinical, biochemical and other data, especially with regard to the prospective consideration of the disease.

Within the scope of research projects, archived samples and data can be used to identify biomarkers. For example, with solid tumours, tissue sections from diseased organs should preferably be compared with appropriate control tissue. Differences in the distribution of individual proteins, in transcriptome or metabolome profiles or in patterns of individual genomic variants (SNPs, see Ch. 2.1) are correlated with pathophysiological and morphological changes. These archives thus frequently hold unrealised potential for recognising unknown disease relationships or testing hypotheses regarding disease genesis (Jensen et al., 2012). However, to formulate statements about the likelihood and possible molecular causes of a condition from genome-wide association studies (see Ch. 2.1), for one phenotype tens of thousands of samples are often needed to statistically assure the results. These samples can only be collected in national or international consortia involving academic institutions and possibly partners from industry and patient organisations (see also Ch. 9.3).

The sustainable funding of biobanks at university facilities often presents a big problem: Biobanks are interdisciplinary research facilities and must, after initial funding by third parties (e.g. the German Federal Ministry of Education and Research), continue to be supported by academic institutions. Moreover, handling fees must be charged to the users of samples from biobanks in order to guarantee the long-term existence of these facilities. Funds for this will therefore also be included in future research applications. Furthermore, fully developed biobanks of the future will have to collect and manage data on exogenic environmental influences (see Ch. 2.2) and imaging procedures (see Ch. 2.8), in addition to biological material and clinical data.

2.10 Data processing and bioinformatics

One important set of challenges for Individualised Medicine lies in applying bioinformatics in order to analyse the large amount of data being obtained with new technologies, relating that data to the associated clinical data, and conveying

the results of that analysis to doctors in such a way that they can be implemented in practice. To do this, the primary data need to be normalised, undergo quality control, and be validated and interpreted, and the results of the analysis need to be made accessible to users in an appropriate format. Information technologies for analysing and integrating data and for mathematical modelling and simulation are therefore becoming increasingly important.

2.10.1 Bioinformatics, information technology

Bioinformatics is the methodological basis for compiling as well as filtering, correlating and analysing patient data. The results of the analysis must then be reduced to a manageable amount and processed appropriately. This requires complex algorithms that meaningfully link information that is qualitatively very diverse (genome data, phenotypic data, clinical data, etc.) while taking into account known or hypothesised relationships and statistical requirements. The ambitious work of developing these algorithms represents a central bottleneck for Individualised Medicine's progress (Fernald et al., 2011).

Systems biology is frequently contrasted with bioinformatics. In other contexts, the two terms are used with a great deal of overlap and almost synonymously. However, systems biology involves far more than the analysis of biological data; it includes an important experimental field in which molecular data that relate to different cells (genome, transcriptome, proteome and/or metabolome, etc.) are recorded and considered in the context of the organism as a whole. These data are then analysed using bioinformatic methods. Based on hypotheses about the molecular relationships evidenced by the data, mathematical models of the structure and dynamics of the biological process being investigated (e.g. the development of a disease) are then developed.

Important bioinformatics tasks in Individualised Medicine are as follows:

- Processing and quality control of the large volumes of data generated by omics technologies and new techniques in medical technology.
- Interpreting molecular biological patterns with regard to functional effects and using them as the basis of differentiated disease diagnoses.
- Estimating the efficacy of therapies based on active substances.
- After utilising suitable software, preparing the findings for patient care purposes.

In Individualised Medicine, laboratory analysis of patient samples and subsequent evaluation using bioinformatics play an important role. One example is computer-supported HIV therapy (see Ch. 6.3); the strategy used here could in future be applied to tumour therapy as well (Bock & Lengauer, 2012). Ongoing developments in research on medical interrelationships are providing a growing arsenal of active substances to treat diseases. Taking all the available information about a patient into account once a diagnosis has been obtained, the goal is to select the best possible therapy from among the large number of potential active substances or combinations thereof. If enough data are available about disease courses with therapies based on different active substances, and/or if the causes and contexts of disease have been sufficiently investigated, then the often quite multi-layered therapy selection process can be carried out using appropriate assessment software.

With regard to multifactorial diseases, the genetic factors identified in genome-wide association studies have so far explained only a small percentage of increased risks of disease. To treat as well as to effectively prevent these conditions, which are usually common, com-

prehensive models for explaining and predicting them must be investigated and developed. In addition to biomarker signatures from omics data, the models must also consider environmental, nutritional, behavioural and lifestyle-related factors. Corresponding analyses primarily examine disorders of relevant biochemical reaction pathways (e.g. metabolic pathways and signalling pathways). Examples of such approaches include 'The Virtual Liver' (Holzhütter et al., 2012) and 'The Cardiac Physiome' (Bassingthwaighte et al., 2009).

Both an appropriate IT infrastructure and new bioinformatics and statistical approaches are needed to integrate such extensive information. Analysing the interaction networks is indeed highly complex, but it creates the possibility of increased precision in diagnostic, prognostic and preventive measures.

Despite the often very great complexity of the data, however, the goal should be to develop models that are feasible, have meaningful results, and are adapted to the constraints of healthcare structures. The wealth of options derived from the data must be reduced to an amount that is practical for use by the treating doctors and transferred into time-tested decision-making aids, such as guidelines and expert systems. The limits of the predictions must also be communicated clearly, for example in the form of comprehensible reliability data. In order to validate the decision-supporting software for clinical practice, the current concept of clinical studies must be developed further in a way that enables it to accommodate the more complex information-related aspect of therapy selection (see Ch. 4.4). The envisioned future of Individualised Medicine involves comprehensive bioinformatic computer models of individuals that result in a primarily preventive approach to healthcare (Hunter et al., 2013).

2.10.2 Standardisation of data collection and data integration

Standardising (harmonising) data collection and data processing is an important prerequisite of integrated methods for analysing heterogeneous data in Individualised Medicine. A lack of consistency in the data from different collection sites has a significant detrimental impact on the comparability and reproducibility of the results. Classifying (stratifying) test person and patient collectives with regard to risks of diseases still works better the higher the degree of quality-assured genotypic and phenotypic characterisation is of both the target and the comparison groups. As the size of these groups increases, the statistical significance of the results also increases.

Extensive records of patient molecular data in long-term investigations will be a key pillar in the understanding of diseases and their genesis, as well as the resulting effective treatment of patients. Ultimately, it will only be possible to understand particular chronic diseases like neurodegenerative diseases (Parkinson's, Alzheimer's), metabolic diseases (diabetes, atherosclerosis) and infections (HIV), through intensively observing patients over a long period of time; prospective studies on large collectives of well-characterised patients will be necessary to achieve this. In addition, the prospective investigation of healthy individuals, like that made possible by programmes such as the National Cohort[6] and the SHIP study[7] (see also Ch. 9.1), can also help generate important hypotheses. A great challenge with such long-term investigations is appropriately accommodating further developments in technology and methodology. To a certain extent, long-term studies epitomise the challenges in IT infrastructure faced

6 Further information at: www.nationale-kohorte.de (last accessed: 16 September 2014).

7 Further information at: www.medizin.uni-greifswald.de/cm/fv/ship.html (last accessed: 16 September 2014).

by Individualised Medicine, which include the following:

- Barrier-free networks for data transfer, data analysis and data storage;
- uniform terminologies and reference datasets;
- uniform testing and quality assurance protocols to standardise patient data;
- uniform archiving and documentation of samples in biobanks;
- international cooperation; and
- long-term guarantee of data protection.

In this context, the fact that healthcare is decentralised because of the federal structures in Germany is problematic. In the interest of research and patient care, there is an urgent need for uniform and barrier-free informatics for hospitals that allow for cross-regional exchange of information (see Ch. 9.5.3). The international *Elixir* project, launched in 2007, has since 2013 been a permanent institution co-financed by its member states. The project is seeking to create the prerequisites for a sustainable infrastructure for life sciences information and the translation of that information into medicine, environment, industry and society. This could represent an important step toward urgently needed uniformity in clinical data collection methods with regard to both medical research and patient care.

2.11 Conclusion

Insights gained using bioanalytical high-throughput techniques (omics technologies) have the potential to become the foundation for a far-reaching systems-biology understanding of human physiology and the generally very complex contexts of disease. This could lead to more precise description and classification in areas like the causes and courses of disease. Prospects would then open up for specific preventive, diagnostic and treatment techniques with a high degree of efficacy and as few side effects as possible.

Genome analyses are used in diagnosing monogenically inherited diseases and certain infectious diseases. Genome and transcriptome analyses play an important role in tumour research and, for some tumours, in diagnosis. Using findings from proteome, metabolome, microbiome and epigenome analyses and determining the extent to which they contribute to the association between genome and disease phenotype represent enormous scientific challenges. One further challenge for the Individualised Medicine treatment process lies in using bioinformatics to evaluate the large volume of data from analyses from omics, imaging and other technologies. To do this, the data must be validated, standardised, interpreted and integrated into a digital patient record in a way that is comprehensible to the doctor.

3 Biomarkers as a basis for developing new diagnostics and therapies

Biomarkers are characteristics that are objectively measured and evaluated as indicators for the description of normal and pathological biological processes (Atkinson et al., 2001). These markers also include reactions to preventive, therapeutic and other interventions relevant to health. In the field of medicine, biomarkers form the basis for developing decision-making rules, called classifiers, in order to divide patients into prevention- and therapy-relevant subgroups, that is, to stratify them. Although originally biomarkers were used primarily on the macro- and microscopic levels, for example blood pressure or morphological characteristics of tissues and cells, they are increasingly being recorded on the molecular level.

The great scientific and technological progress that has been made in the last 10 to 15 years, especially in omics technologies and imaging techniques (see Ch. 2.1 through Ch. 2.8), have enabled the discovery of numerous new biomarker candidates. These candidates have the potential to reflect structural or functional, static or dynamic parameters. A central challenge with regard to Individualised Medicine is to identify the biomarkers or biomarker sets that are suitable for clinical application and provide meaningful information.

3.1 Identifying biomarkers

The spectrum of potential biomarkers is broad, and includes, for example, clinical, morphological, biochemical, genomic, proteomic, microbiomic, pharmacogenetic and metabolomic parameters. Some biomarkers are directly associated with a disease process, while others reflect, for example, the effect of an intervention on the course of a disease ('surrogate biomarkers').

Biomarkers are mainly identified via two approaches:

- By means of a targeted hypothesis-grounded approach based on known pathophysiological mechanisms; or
- by means of a hypothesis-free approach, for example with a screening technique in which shared markers that are correlated with the disease can be discovered using a large number of measurements or samples from different patients.

Thus, for example, by means of the sequencing of 15 cancer cell lines an alteration in the BRAF protein was identified in up to 66 percent of melanoma patients (Davies et al., 2002; Flaherty et al., 2010). The altered protein now serves as a therapeutic target for treating the tumour with a specific inhibitor used only for the group of people in whom the underlying mutation has been detected (see Ch. 6.2). Many diseases, however, arise from alterations in complex molecular networks that may include genes, RNA molecules or proteins (Schadt, 2009). This complicates the identification of the disease-relevant biomarker sets, which are, accordingly, quite large. Biomarkers are usually identified in the context of academic, disease-oriented research programmes or industrial research projects, and are generally developed further by specialised companies. Often, the value that biomarkers have for clinical practice does not become evident until years after they are discovered.

Next-generation DNA sequencing in particular (see Ch. 2.1), in connection with international genome-wide association studies (see GWAS, Ch. 2.1.3), is of great significance for the development of genomic biomarkers and subsequent diagnostic procedures. Modern hybrid imaging techniques (see Ch. 2.8), together with radiopharmaceuticals, supplement pathophysiological information and enable spatial classification within the entire body or a section of the body. In addition, localisation at the cellular and sub-cellular levels is possible in tissue samples. Detection techniques at the RNA and protein levels are also becoming increasingly relevant for biomarker research. The so-called multiplex strategy, which is now usually based on chip technology (microarray) with parallel determination of numerous genomic or biochemical parameters, makes broad screening of potential biomarkers possible (Valentin et al., 2011). Thus, thousands of potentially disease-associated biomarkers have been described in over 150,000 publications (Poste, 2011). Only a few of these biomarkers, however, have been validated by independent studies (see Ch. 3.4).

3.2 Variability and use of biomarkers

Completely or partially recording the genotype is an important foundation of Individualised Medicine. Population studies are used to identify statistical correlations between genetic and phenotypic disease-related data (see GWAS, Ch. 2.1.3), meaning that gene variations or mutations can increasingly be used as biomarkers for the more precise classification, diagnosis and therapy of diseases. Often, apparently uniform but actually heterogeneous diseases are decoded, meaning that a more refined molecular taxonomy of illnesses can be created. This leads to molecularly defined subgroups (subtypes) of diseases previously considered to be homogeneous. Individualised diagnostics and therapies derived from this approach are illustrated in Chapter 6 using concrete examples from clinical practice.

Individual risks and courses of disease are often influenced by environmental factors and an individual's lifestyle, and thus by a high number of variables. Compared with genetic biomarkers, the systematic recording of dynamic biomarkers is much more complicated. Metabolic profiles (see Ch. 2.5) provide a particularly important example of this, as they can reflect both the genotype and the phenotype (Suhre & Gieger, 2012).

In the future, biomarkers could also make an important contribution to the planning and design of clinical studies for testing new therapies (see Ch. 4.2 and Ch. 4.4). Because the occurrence and expression of biomarkers can precede a patient's response to a therapy, they can serve as alternative endpoints for clinical studies and thereby significantly accelerate and simplify such studies (Atkinson et al., 2001). These so-called surrogate biomarkers (also known as surrogate endpoints) frequently refer to the effect of an intervention in molecular reaction pathways, and can help explain the empirical results of clinical studies. The biomarkers thus frequently make it possible to understand differences in clinical response, which are to some extent influenced by variables that cannot be controlled (e.g. a patient's individual drug metabolism).

Depending on the area in which they are used, biomarkers are divided into categories that may overlap with one another (see Table 3). In particular, identifying biomarkers that predict information about individually varying efficacies or genetically based toxic side effects of a therapeutic intervention is associated with the hope of Individualised Medicine prevent-

ing inappropriate treatments in the future (Poste, 2011). One goal is to use individualised drugs in tandem with a prior or concomitant biomarker test ('companion diagnostics'; McCormack et al., 2011; see also Ch. 6.1 and Ch. 9.6).

Table 3. Biomarker categories and their areas of application.

Biomarkers for predictive purposes serve to determine risks of disease before the disease becomes symptomatic, and make prevention possible (see Ch. 5). Well-known examples are mutations in the *BRCA1* or *BRCA2* gene, which result in a high probability (40–80 percent) of malignant breast or ovarian tumours (see Ch. 5.7.1).
Biomarkers for diagnostic purposes enable a precisely defined disease to be diagnosed as early as possible. One example is the detection of viral RNA four weeks after acute infection with the hepatitis C virus (HCV) in order to detect chronic HCV infection (see Ch. 6.3).
Biomarkers for prognostic purposes provide information about the expected course of a condition that is already symptomatic. An example is the concentration of *human epidermal growth factor receptor 2* (HER2) as an indicator of a particularly malignant type of breast cancer (see Ch. 3.3). HER2 also serves to predict therapeutic response.
Biomarkers for predicting therapeutic response provide information about the presumed efficacy and/or possible toxic side effects of a therapy (see Ch. 6.1). These include, for example, BRAF and HER2, which pre-therapeutically indicate the efficacy of the medications vemurafinib and Herceptin® for treating tumour diseases (see Ch. 6.2). These markers are often described as predictive, which is slightly misleading and not to be confused with predicting disease.

3.3 Prerequisite for a clinically suitable biomarker

As described in Chapter 3.2, biomarkers are used for predictive, diagnostic, prognostic and therapeutic purposes. Often, the results of a biomarker measurement only allow for quantitative statements (scores) or indices. Only a few candidates have so far met the strict criteria that biomarkers must fulfil to be suitable in clinical practice (see Ch. 3.4). Dancey et al. (2010) provide a good overview of the development and use of biomarkers in the context of clinical studies. In the simplest case, a biomarker only has a binary expression for predictive purposes; that is, the patient can be classified into either Group A or Group B. The measurement upon which this classification is based must have a high degree of specificity, meaning the percentage of correctly classified findings and the sensitivity, or analytical limit of detection, and must also be practical to carry out in the lab, as well as be easily reproducible.

A biomarker's positive predictive value, PPV, is decisive for its suitability. The PPV indicates the percentage of individuals with a positive test result in whom the characteristic or disease being sought is actually present. One example of this is mammography screening for breast cancer. If the expression of a biomarker (e.g. MRI findings) exceeds a certain threshold value based on the selected criteria, a breast biopsy must be performed to verify the findings. The obtained tissue is then tested using histological techniques to determine whether breast cancer is actually present. A low PPV means that many biopsies, which are burdensome to patients, must be performed.

Another example is the amplification (reproduction) of the *HER2* gene in cells of a type of breast cancer with a particularly malignant course (affects approx. 25 percent of these tumours). The genetic alteration leads to overproduction and dimerisation of the HER2 receptor, which supports the inadequately

controlled reproduction of the tumour cells. The increased 'gene dose' can be diagnosed using fluorescence in-situ hybridisation (FISH), and HER2 receptor overproduction can be detected immunohistochemically. Herceptin® is a medication that blocks the activity of the HER2 receptor, which causes the affected cell to be destroyed. The HER2 serves as both biomarker and target of molecular therapy (see Ch. 6.2), and has proven to be a suitable biomarker with a high PPV.

With a newly developed biomarker, evidence must be provided that it offers added value compared with previously used classifiers. This requires studies that compare the performance of the particular classifiers. This is often difficult, because there may, for example, be different methods of determining the particular molecular target structures, or because details of sample preparation and evaluation techniques may vary. For this reason, strictly standardising terminologies and techniques, as well as incorporating healthcare services research early on is paramount.

3.4 Validation, qualification and approval of biomarkers

Unreflective use of non-validated genomic biomarkers can lead to an exaggerated estimation of risk (over-diagnosis) and thereby to excessive therapy (Harris, 2011). The validation process is intended to make a 'promising' biomarker candidate into a 'reliable' biomarker, and to precisely define and document its specificity (percentage of correctly classified findings), sensitivity (analytical limit of detection) and clinical and economic benefit.

To date, only a small number – about 100 as of 2011 – of the many thousands of biomarker candidates for which an association with a disease has been postulated in the literature have been validated (Poste, 2011). This is due in part to the fact that many biomarker candidates were first discovered during research on cell lines cultivated in the lab, and testing has not yet been conducted to determine whether the results also carry over to the relevant cells in the human body (Poste, 2011). Academic research labs generally lack the logistical and financial resources, as well as the interdisciplinary expertise to make a robust correlation between biomarker and disease or response to therapy. Therefore, validation currently generally only occurs in the context of large clinical studies in defined programmes of pharmaceutical companies or large research consortia. In many incomplete biomarker studies, moreover, far too few samples are tested to be able to confirm relationships between biomarker sets – sometimes multiple sets – and pathophysiological alterations in a statistically valid manner (Ransohoff & Gourlay, 2010).

Removing and storing samples also frequently have a decisive influence on the expression of biomarkers, and many research labs still do not have sufficient access to quality-assured homogeneous and thoroughly documented samples (Poste, 2011). Uniform, (inter-) nationally networked biobanks (see Ch. 2.9) could counter this problem and thereby significantly increase the quality of the statistical results of future biomarker studies. Furthermore, support for biomarker research projects should in future be directed mainly toward large interdisciplinary research networks that bring together bioinformatics scientists, engineers, partners from industry and representatives from the healthcare field, as well as natural scientists and clinicians. International networks based on the example of the Cancer Genome Atlas initiative could, using yet-to-be-created internationally valid guidelines, significantly advance the exploration of clinically usable biomarkers.

Final assessment of biomarkers from the perspective of the regulatory authorities takes place during the qualification process. During this process, the results of validation as well as the biomarker's fitness for use are tested in a clearly defined context. The validation and qualification of surrogate biomarkers are also important basic prerequisites for developing and approving novel medications. Both the diagnostics industry and the pharmaceutical industry depend on close cooperation with academic facilities and consortia that have access to large biobanks. The development of biomarkers from discovery to qualification (see Figure 1) goes through stages comparable to those of pharmaceutical products before they are registered and approved by the regulatory authorities.

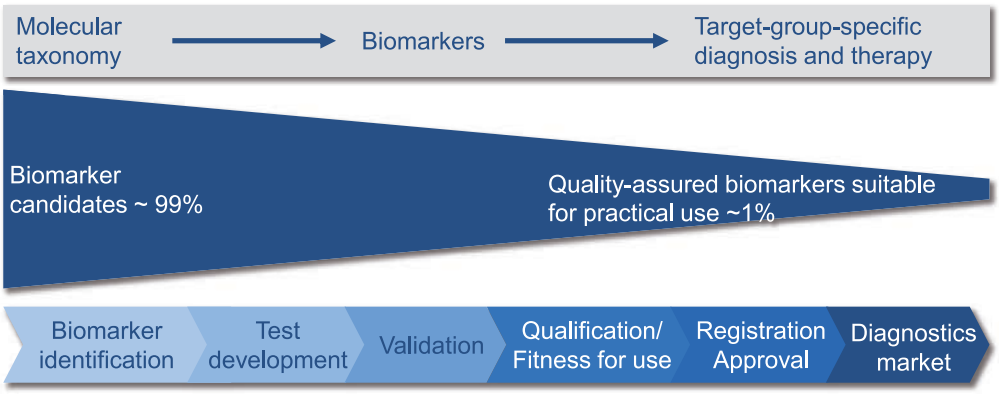

Figure 1. From biomarker screening to marketing approval. Biomarker candidates must, as in the development of new medications, undergo a time-consuming validation and qualification process, after which very few of them turn out to be suitable biomarkers for clinical practice.

3.5 Conclusion

As biological indicators, biomarkers form a central basis for stratifying heterogeneous disease presentations into subtypes with regard to molecular taxonomy. Biomarkers will thus be of decisive importance for the development of novel preventive, diagnostic and therapeutic strategies in Individualised Medicine. However, identifying disease-relevant biomarker sets, which are often very large, represents a challenge that should not be underestimated.

Of the thousands of biomarker candidates for which an association with a disease has been postulated in the literature, only a fraction has thus far been validated for clinical practice. One reason for this is the fact that academic research facilities generally lack the logistical and financial resources required for validation. Furthermore, many research labs do not yet have secured access to a high number of homogeneous, quality-assured samples; (inter-)nationally networked biobanks set up in accordance with standardised protocols would help counter this problem, but they also require long-term funding. Furthermore, support for biomarker research projects should in future be directed mainly toward large interdisciplinary research networks that bring together bioinformatics scientists, engineers, partners from industry and representatives from the healthcare field, as well as natural scientists and clinicians.

4 Clinical studies for the development of individualised diagnostics and therapeutic agents

In the context of Individualised Medicine, patients are being increasingly classified into therapy-relevant subgroups (stratified) using modern diagnostics. The goal here is to characterise the resulting patient groups precisely with regard to their response to a therapy in order to improve efficacy and reduce side effects. Assignment to the subgroups occurs via a general model-based decision-making rule (classifier) that suggests a clinical approach for a patient based on the data.

With regard to medical care, the design of the stratification must be as simple, economical and practicable as possible. When setting up decision-making rules for the formation of subgroups, ignoring secondary parameters, which unnecessarily complicate the classifier, presents a particular challenge. As a rule, ever more precisely defined patient classification results in a larger number of smaller patient populations. This significantly increases the logistical demands (e.g. availability of reference laboratories, low numbers of patients/test persons per study site, biobank logistics, ethics votes) on clinical studies on the one hand, while on the other hand the numbers of test persons or patients (number of cases) needed to prove an effect can decline if the group has a high degree of homogeneity. However, one problem is the fact that very rare side effects are not recorded, making it necessary to monitor therapies after marketing approval.

4.1 Procedure and benefit of clinical studies for assessment of new therapies; conventional approach

It can take a decade or longer to move a new therapeutic technique, for example a new active substance or combination of substances, from discovery to clinical practice. Drug candidates must be tested for safety, quality and efficacy in statutory pre-clinical and clinical studies before the authorities can issue approval.

The goal of pre-clinical studies is to assess the risk of possible reactions in humans to medical interventions; this occurs based on animal testing data. If the resulting risks are acceptable, the competent regulatory authorities and ethics committees can approve clinical studies in which the new therapy is tested on volunteers and patients. The clinical study testing that is prescribed by means of directives and guidelines is divided into several phases (see Figure 2). In the conventional approach, starting with Phase III, several thousand patients are compared with each other in at least two patient groups, of which the experimental group (verum group) receives the new, experimental therapy and the control group receives a standard treatment. The patients are assigned to the groups by chance (randomised) in order to avoid selection effects. In many cases, it is also necessary to blind the group assignments (therapy arms) for patients and the investigating doctor so that the participants do not know to which therapy group the particular patient belongs (double-blind study). This may involve both therapeutic arms using the same standard therapy as a foundation, but also administering the drug to

be tested to the experimental group and a placebo to the control group. The logistical and financial outlay for clinical studies is considerable, however, and often expectations are not fulfilled. Although only about 10 percent of all projects in clinical studies have to be ended prematurely due to unexpected side effects, most potential drugs ultimately fail because efficacy cannot be proven (Arrowsmith, 2011; Kubinyi, 2003). Targeted selection of patients and test volunteers with regard to the presence of molecular target structures, and thus presumably associated increases in efficacy, will make it possible to significantly reduce the duration, difficulty and economic risks of clinical studies in future.

4.2 Phase III studies with binary biomarker classifiers

Prospective randomised Phase III therapy studies to provide proof of efficacy and safety are a key requirement for evaluating and approving of new therapeutic procedures in healthcare. This applies equally for drugs, cellular therapeutic agents, medical devices and algorithmic therapeutic decision-making processes. Depending on the interim data situation regarding the efficacy of the new therapy, there are three different possible designs for Phase III studies with binary biomarkers (see Ch. 3.3; Freidlin & Korn, 2010):

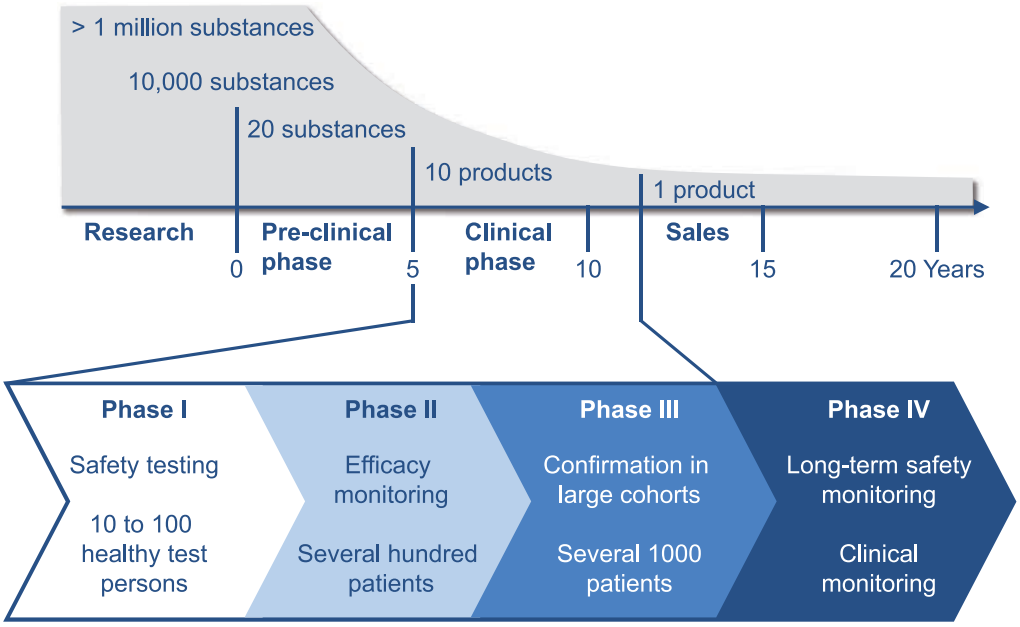

Figure 2. Procedure, scope and objectives of clinical studies. Phase I: Here, the safety and dosage of new medications are determined and unexpected side effects are discovered. Phase II: Here, the medication's efficacy and frequency of side effects are evaluated. Many projects fail in this phase. Phase III: Because of the high number of patients and lengthy follow-up period, long-term side effects are discovered and efficacy is studied with more statistical precision. Phase IV: After a drug is placed on the market, patient groups that have not previously been tested may show additional side effects. Targeted patient and test volunteer selection in Individualised Medicine and associated increases in efficacy could significantly reduce the complexity and duration of clinical studies.

1. Biomarker-stratified study design: In order to determine the differential effect of a defined molecular therapy in relation to the expression of a biomarker, all patients are randomised between the experimental therapy and the control therapy after that biomarker has been determined (positive or negative). Theoretically, this design delivers all the information about the differential effect of a targeted molecular therapy to patients with or without the relevant molecular target structure. However, in some cases this approach is not possible due to eth-

ical and scientific reasons, for example if the therapeutic agent cannot work because there is no target molecule or if an invasive procedure is required that would make a fictitious invasive procedure necessary in the control group.

2. Biomarker-enriched study design: If there is already convincing evidence that a therapy works only when there is positive expression of a biomarker, then only patients with positive expression of that biomarker are randomised between the therapy arms. Patients with negative expression likewise receive the control therapy. This approach determines only the therapeutic effect with positive expression of the biomarker (Novotna et al., 2011; Temple, 2010); that is positive effects in biomarker-negative patients are not recorded.

3. Biomarker strategy design: This design is used to compare complex, variable therapeutic strategies based on biomarkers with clearly defined standard therapies. For example, it is possible to make individualised therapeutic combinations using a defined decision-making algorithm, such as different medication dosages or combinations. In this case, the patients are randomised into a biomarker-dependent experimental group (individualised therapeutic strategy) and a biomarker-independent control group (non-individualised therapeutic strategy). This study design can evaluate complex individualised treatment strategies as a whole but cannot really evaluate the individual therapeutic components of an individualised strategy.

4.3 Combined Phase II/III study designs

Phase III studies are generally very difficult and time-consuming and often cost more than €50 million per study. Moreover, Phase III studies have relatively high rates of negative results (Adjei et al., 2009) and are therefore associated with significant financial risks for a company. Efforts are therefore underway to modify the upstream Phase II studies in order to dispense with options that are not very promising early on, and conversely, to have favourable results flow into Phase III studies promptly. There seems to be a consensus about this approach in the international debate (Freidlin & Korn, 2010; Freidlin et al., 2012; Seymour et al., 2010). The thinking is to already use, as a rule, a randomised design with experimental and control groups in Phase II. In order to maintain the exploratory character of these studies (i.e. selection of good candidates), requirements with regard to differences to be uncovered as well as statistical properties (error level, power) should be designed in such a way that feasible patient numbers lead to the establishment of efficacy. This applies especially for rare diseases, for example tumours in children, rare lymphomas, etc. The primary endpoints of these studies should nevertheless be as meaningful as possible – for example, in addition to determining success rates at a certain point in time, the early periods of time up until a defined therapy failure should also be considered (e.g. progression or recurrence of the disease). For all patients in these studies, relevant biomarkers should be determined and biological samples should be stored for any follow-up measurements.

Currently, combined Phase II/III designs are also being investigated in which a controlled transition between Phase II and Phase III would be possible under certain conditions. One basic idea is to include data obtained in Phase II in the analysis of data from Phase III studies, thereby saving time and money. Using the efficacies already observed in Phase II/III, for example with different medication dosages, planning for the number of cases for Phase III can be adjusted via so-called adaptive design. Further consider-

ations lead to the conclusion that the rate of random, previously firmly established patient distribution (e.g. 1:1) can be dynamically modified based on the course of the study. Simulation studies have shown that a Phase III study can be ended quite a bit earlier, for example for diseases with an unfavourable prognosis, when using a randomisation procedure called the Bayesian adaptive approach in which previous experience plays an important role (Trippa et al., 2012). Furthermore, it will in the future be standard practice to set up interim evaluations in Phase III studies based on biomarkers; these interim evaluations could then lead to premature discontinuation of the study if no benefit is seen. In many studies, this was not previously provided for, meaning they had to be carried out as planned until the end.

Many of the new study designs have not yet been sufficiently tested in practice, as the concepts often run up against scientific reservations (e.g. in the expert review process), regulatory barriers to approval and planning limitations due to uncertain budgets. New designs, like a study on breast cancer therapy (Barker et al., 2009), are currently being tested at the National Cancer Institute in the United States.

4.4 Special study designs

Sometimes there are several possible therapeutic intervention options for a patient group defined by a molecular biomarker. This may involve different drugs or merely differences in dosages. Selection designs have been suggested for Phase II studies in order to select the most suitable option for a comparison in Phase III from among multiple therapeutic options (Sargent & Goldberg, 2001; Simon et al., 1985; Thall et al., 1989). This involves randomising several competing experimental therapies against the control therapy. After a first interim analysis, all therapies below a certain minimum success rate are eliminated, and the study is continued with the remaining therapies. A second selection step is repeated with the remaining therapies, this time with an increased success threshold, and only therapies that pass this selection procedure are carried over into Phase III studies. In practice, the design may be difficult to implement, for example if innovative therapeutic agents from different companies are to be compared.

Problems sometimes occur with targeted therapies in the area of oncology, since as a rule numerous mutations may be present in individually differing combinations, even with very similar tumours. For some tumour identities, more than 10 molecular subgroups have already been identified (e.g. for lung tumours). For each of these subgroups, a different molecular target structure represents a potential therapeutic application point. Several of these structures can be present at the same time (e.g. multiple mutations); in principle, combination therapies against multiple target structures have to be assembled in this case. Separately assessing the effect of each individual therapy modality or each individual targeted therapy is a priority here. For this complex case, Vach & dePont Christensen (2006) have suggested a conceptually appealing 'multimarker-multitarget' study design that is intended to yield an optimum amount of information, but such a design has not yet taken hold in practice.

Increasingly, software of varying degrees of complexity is being used to interpret biomarker data for biomarker-based diagnosis. Such software can be based on the application of manually prepared expert rules or on mathematical-statistical data analysis (see also Ch. 6.3). Validation of this software must be appropriately incorporated into the study design. The fact that software is subject to a continuous development process and

cannot be seen as static must be taken into account here. For this reason, abbreviated validation scenarios for software updates should be facilitated. Clinical studies in general and certification processes in particular do not seem to be adequately prepared for this aspect.

The business model for targeted therapies has already triggered a large number of studies in the pharmaceutical industry to obtain approval for new drugs. Approval is initially being sought for specific applications (e.g. for molecular target structures of a defined tumour type or of pathogens). It is to be expected that after the approval of these substances new potential areas of use will be identified, especially in academic settings. These could involve, for example, broadening the scope of applications used in combination therapies or in other diseases with the same molecular target structure. The great progress that has been made in the area of systems biology also means that future involvement of systems biology models for the adaptation of clinical studies may be feasible. The increasing number of elderly, multi-morbid patients is leading, in geriatric medicine in particular, to an increased need for research that better addresses interactions involving multiple, often chronic diseases in study designs.[8]

4.5 Assessment of new biomarker-based endpoints

It is often argued, in connection with biomarker studies, that late endpoints (e.g. clinical progression after the end of therapy, survival time) delay the process of obtaining findings. For this reason, it is desirable to switch to earlier concomitant endpoints (surrogate biomarkers, see Ch. 3.2), for example early PET/CT imaging (see Ch. 2.8) in order to receive information about the therapeutic potential more quickly. In the area of oncology, however, there is a risk that successes will be assessed too optimistically, because a later relapse due to a cell population that is or has become resistant often follows an early response by a sensitive tumour clone.

On the other hand, analysing new therapies for oncological diseases with long average survival times also requires very long follow-up periods. Thus, in theory studies might not be able to demonstrate prolonged survival until many years after a new procedure has been placed on the market. This can, however, turn out to be problematic, since it is difficult to keep a sufficient number of patients in randomised clinical trials over such long periods of time. Against this backdrop, endpoints that refer exclusively to one point in time are often problematic for Phase II and Phase III studies. If it is nevertheless desirable to stick with them, their meaningfulness must be assessed in the context of endpoint studies designed especially for testing whether early successes lead to reliable predictions of successes at late endpoints.

4.6 Conclusion

In Individualised Medicine, all diagnostic and therapeutic options must be tested and validated in systematically planned prospective studies. It is to be expected that the need for clinical studies will grow because diseases that have until now been perceived as clinically uniform are increasingly being classified into molecularly defined subgroups. Separate studies have to be set up for each subgroup that also prove beneficial compared to previous standard therapies. Initially, this increases the amount of work required, but on the other hand, the number of patients required per study can decrease because gains in efficacy will probably be greater in groups defined, for example, via biomarker determination.

8 Headed by Leopoldina, the Evidence-Based Medicine for the Elderly working group is drawing up a statement on this topic.

Individualised Medicine requires innovative concepts for study design and study logistics, for information sharing, as well as interdisciplinary cooperation between academia and industry. Professional study groups that plan studies quickly, work with reference laboratories for biomarkers, set up standardised biobanks and involve experienced study coordination sites are of central importance for successful studies. In the future, these groups should include skills in the areas of molecular biology and bioinformatics, as well as biometrics. Internationally, there should be rapid information sharing on the status of Phase II and Phase III studies, which will require standardisation of study criteria and terminologies, as well as the publication of complete study data including negative results.

5 Predictive genetic diagnostics and their consequences

Genetic diagnostics already play a role in the Individualised Medicine approaches currently in use. The variability in an individual's constitutional, or inherited, genome is a result of the genetic variability of that person's parents' germ cells. This variability appears in all body cells and can make phenotypic predictions possible. This applies if certain mutations (alleles) have different functional effects that express themselves phenotypically. We speak of prediction when a phenotype that has not yet manifested at the time of genetic testing can be foretold with a certain degree of probability through genetic testing on a healthy person. Functional effects of mutations in body cells must be differentiated from predictive statements based on constitutional genetic variability. These somatic mutations, then, are found only in some body cells and characterise what is called a cell clone.

5.1 Diagnosis of monogenic diseases in the index case

Monogenic diseases are usually due to mutations that lead, with a high degree of penetrance (a genotype's probability of manifestation), to a phenotype that is qualitatively different from the average. We only know roughly how many of these mostly very rare diseases there are. Over 6,000 different monogenic diseases that are due to mutations in a certain gene are listed in the Weizmann Institute's online catalogue.[9] It is thought that about one person out of 200 will develop a monogenic disease over the course of their lifetime. The WHO, however, cites an estimate of as many as 10,000 monogenic diseases and indicates that about one percent of children are affected by such a disease at the time of birth. Among the reasons for the differing data about the total number of monogenic diseases are the reliability of clinical diagnosis, new mutations, late manifestation, unclear or lack of familial relationship, lowered penetrance, differing rates in various ethnic groups, and fluid boundaries between normal variability and disease. Currently, a conservative estimate of about 8,000 different monogenic diseases worldwide seems to be closest to the actual number; some of them are not yet attributable to a mutation in a known gene.

Depending on the function of the impaired gene product, or on the type of mutation, monogenic diseases may already manifest themselves at birth, or later in life. The person in a family who is first found to have a disease is called the index case. If relatives of the index case develop the same or similar symptoms, they are called secondary cases. Differentiating between index and secondary cases is important because symptoms are generally more pronounced in the former than in the latter. In the case of clear symptoms, the search for a mutation in a patient can target the relevant gene (e.g. Duchenne muscular dystrophy or Huntington's disease). In the case of variable symptoms, the search for a mutation serves to help confirm or reject the clinical hypothesis (e.g. cystic fibrosis). Sometimes clinical symptoms develop only over a prolonged period of time, meaning that it can be dif-

9 Cf. www.genecards.org/cgi-bin/listdiseasecards.pl?type=full (last accessed: 16 September 2014).

ficult to make the diagnosis in young patients. This applies in particular if findings in the family are normal and the disease results from a new mutation (e.g. myotonic dystrophy).

Genetic heterogeneity is a considerable diagnostic challenge with many monogenic inherited diseases. The clinical phenotype can arise from a mutation in one of many genes (e.g. in more than 40 gene locations in the case of pigmentary retinopathy). In this type of disease, all genes that currently come into question are sequenced using gene panels and tested for mutations; the individual subtype of the disorder can be determined simultaneously. The complete sequencing of the genome or the exome (see Ch. 5.5) is likely to become the preferred method in future.

5.2 Predictive genetic diagnostics

If a monogenic disease has been detected in an index case, healthy relatives who are potential carriers of the mutation can be tested for the causative mutation or for the original genotype. Because of very rapid developments in high-throughput sequencing (see Ch. 2.1), it will also be possible in the near future in Individualised Medicine to test individuals predictively for pathogenic mutations even if the genotype of an index case in the family is unknown because that person is deceased. This will be considered primarily when there are abnormal findings in the family, indicating that a relative has an increased risk and thus drawing attention to a group of genes.

However, the question of whether predictive genetic diagnostics are to be performed with regard to a treatable or preventable disease or with regard to an untreatable disease makes a big difference here (German National Academy of Sciences Leopoldina et al., 2010). Hereditary tumour syndromes (see Ch. 5.7), hereditary heart arrhythmias, the monogenic form of hypercholesterolaemia and a number of clotting disorders are among the currently treatable monogenic diseases. In these cases, it should be recommended that the predictively diagnosed persons receive a particular therapy or monitoring strategy (see Ch. 5.7). Predictive diagnosis of a disease that is currently untreatable, such as Huntington's disease, is associated with a situation from which there is no way out. Here, the benefit of the diagnosis lies at most in the knowledge that no other, possibly treatable, diseases are present. Individuals who are affected become the 'sick healthy' or the 'healthy sick' (see Ch. 7.6). Neurologists, human geneticists and self-help groups have, as a precautionary measure, established conditions that must be met, in addition to clinical and genetic counselling, prior to the use of predictive genetic diagnostics. These include, for example, a psychotherapeutic counselling session and a minimum interval of time between the decision to have the test and the actual lab analysis.

With treatable monogenic diseases that first manifest themselves at an advanced age in particular, there will in future be growing demand for predictive genetic tests that do not require findings from family members of the person being tested to be considered. For this purpose, more and more differentiated gene panels are being developed with which healthy adults can be predictively tested for whole groups of monogenic diseases.

If the offspring of a patient who has died wish to know whether they are at risk for that person's fatal disease even though the genetic cause is not known in the family (e.g. inherited tumour syndrome, neurodegenerative disease with development of dementia), the person at risk can be tested for mutations in multiple genes that can be involved in the occurrence of the disease. If no particular

gene can then be found to be definitively responsible for the disease, then it will at most be possible, taking the presentation of the disease in the deceased individual into consideration, to make statements of probability about the person at risk. If the particular disease is treatable, then the person at risk can be admitted into a screening program as a precautionary measure.

5.3 Predictive statements: taking penetrance and expressivity into account

Predictive detection of a mutation or a genotype in a healthy individual always requires interpretation by a competent doctor. Dominantly effective mutations can be completely penetrant, that is occur phenotypically in 100 percent of affected individuals (e.g. mutations in the *huntingtin* gene that lead to Huntington's disease), or they may have reduced penetrance; that is, they may lead to the disease only in a certain percentage of cases (e.g. mutations in the *BRCA1* or *BRCA2* gene that lead to hereditary breast and ovarian cancer). The degree or pattern of expression in carriers of a dominantly effective mutation can also vary greatly (e.g. mutations in the *NF1* gene that lead to type I neurofibromatosis).

While excluding a mutation or genotype that has been detected in a family generally means that the person at risk will not be affected, a disease may also not necessarily manifest itself even if the mutation or genotype has been detected. Among other things, epigenetic factors, which are to some extent not yet well understood, can also play a decisive role here (see Ch. 2.2). Conveying the probability of expression to a person at risk while taking penetrance and expressivity into account is the responsibility of genetic counselling before and after predictive diagnosis (see also Ch. 7.4).

5.4 Monogenic diseases: Heterozygote screening in sexual partners

For the several thousand known autosomal recessive diseases, cases of heterozygosity (having two different alleles) occur much more frequently (1:25 to 1:1000) than do cases of the corresponding homozygosity (having identical alleles). If both partners of a couple are heterozygous for a mutation in the same gene that leads to an autosomal recessive hereditary disease in the case of homozygosity, then according to Mendel's rules each of their children has a 25 percent risk of carrying two of these mutations (one from each of the parents) at the relevant gene location and thus to develop the disease. Systematic testing of healthy young people for heterozygosity for such mutations represents a special form of predictive genetic diagnosis. This is an option when a couple wishes to know their children's risk of disease before conceiving. If both partners are heterozygous, they have different options for preventing the birth of an affected child, for example by not having biological children or by using targeted prenatal diagnosis. The risk of the birth of a child with an X-chromosomal recessive disease can also be determined during heterozygote screening. With this type of heredity, generally only male children who have inherited the causative mutation from their mother are phenotypically affected. Because of the high number of possible genes, there is at least a one percent risk of both partners being heterozygous for a mutation in the same gene. This shows the far-reaching consequences of genetic diagnostics in the context of this Individualised Medicine approach.

5.5 Sequencing the entire genome or exome

The exome refers to the entire set of sections of the genome that code for proteins. Because of the practicability and falling costs

for exome and total genome sequencing, in the future these processes will probably be used more frequently in predictive genetic diagnostics. However, to do this, the variations that are relevant for answering medical questions must be identified from among the approximately 7 million individual exchanges (SNPs) and other DNA sequence variations in each individual genome (see Ch. 2.1). At the moment this is still difficult, but it can be assumed that the list of pathogenic mutations will become more and more complete in the future.

Exome and total genome sequencing can also result in unexpected additional findings associated with other risks of disease. The person being tested must be informed of this fact, and an agreement should be made prior to testing as to the type of mutations about which they wish to be informed and how they wish to be informed. The EURAT project group at the Marsilius Kolleg of the University of Heidelberg developed sample texts in 2013 for patient information sheets and consent forms in this area (Marsilius-Kolleg, 2013).

In this context, the German Gene Diagnostics Act (GenDG, *Gendiagnostikgesetz*) establishes that, in addition to briefing, genetic counselling must be offered to the person being tested prior to predictive genetic diagnostics (see Ch. 7.3). If the matter at hand is the testing of individual genes or the use of gene panels, that is, testing for the genetic disposition for a defined group of diseases, then specific genetic counselling can be practically implemented. However, only very general briefing can be provided prior to total genome sequencing.

5.6 Multifactorial characteristics and diseases

Like most 'normal' characteristics (e.g. height), common diseases (e.g. hypertension, type II diabetes mellitus, epilepsy, mental disorders) are the result of a whole pattern of genetic factors, usually in combination with exogenous influences. This means that variations in an often very high number of genes or genotypes generally influence the phenotype to unequal extents. Carriers of a higher number of relevant gene variations have a genetic disposition toward developing the disease. In this case, it is often exogenous factors (see Ch. 2.2), for example via a specific genotype-environment interaction, that determine whether this disposition will develop into a disease.

For most multifactorial diseases, a whole series of relevant genetic variations have already been identified, with each individual variation usually influencing the risk only slightly. Because the tests have usually been conducted using genome-wide tests with SNP arrays, functional implications can only be derived to a very limited extent from the individual associated SNPs. However, the associated SNPs exist in what is called linkage disequilibrium with functionally relevant genes. The associated chromosomal regions are being completely sequenced for a large number of patients in order to identify the gene variations that are responsible for the association. In future, in Individualised Medicine it will thus be possible to test the actual causative gene variations in a targeted manner.

Until now, the system used for multifactorial diseases has been based primarily on clinical symptoms. However, it must be assumed that the same genotypes are associated with different clinically defined multifactorial diseases. For example, it has been shown that sometimes a great deal of overlap exists in the association of alleles between different psychiatric diseases, such as between schizophrenia and the bipolar form of manic-depressive disorder and between unipolar depressive disorder and attention deficit hyperactivity disorder (ADHD; Lee et al., 2013). It is

not surprising that causative overlap has been found in particular for diseases of the brain, since the brain, more than any other organ, is characterised by functional redundancies, meaning that there are many possibilities for modification on the way from genotype to phenotype. The fact that different psychiatric disorders may have the same genetic cause also makes overlapping pathophysiologies likely.

First degree relatives (brother, sister, child) of a patient affected by a multifactorial disease have a statistically increased risk of developing the condition. If they ask about their risk of disease, for example for diabetes mellitus, hypertension, epilepsy or schizophrenia, it is currently only possible to tell them the statistical risks of developing the disorder. In the future, if there is knowledge of a sufficient number of gene variations or even causative mutations that contribute to the particular disease, first-degree relatives could be tested in a targeted way for the associated variations. The person being tested is generally interested in excluding a risk of the disease. However, this assumes that there is a genetic model that can be used to estimate the relationship between the profile of the variation and the manifestation of the disease. If there turns out to be a high risk of disease for the relative being tested, targeted preventive measures could be recommended to that person.

So far, risk prediction models based on polygenic information have not proven much more reliable than conventional models based on age, family history and body mass index (Khoury et al., 2013). It is, however, likely that in the future it will be possible, with the help of the growing volume of statistically valid data from genome-wide association studies (see Ch. 2.1) and a deeper understanding of pathophysiological relationships, to create comprehensive genetic profiles for multifactorial disease dispositions that will enable practicable predictive genetic diagnostics (Khoury et al., 2013). Because of the limited correlation between genotype and phenotype, however, for many affected individuals it will only be possible to a limited extent to declare, based on purely genetic data, just how pronounced symptoms will be. As explained in Ch. 2.10, intensive research work is required before the extensive data from omics analyses and other tests can be integrated into a meaningful individual profile (Chen et al., 2012).

5.7 Preventive measures as a consequence of predictive genetic diagnostics

In principle, knowing about genetically determined increased risks of disease opens up the possibility of preventing diseases through targeted intervention or at least of early diagnosis and treatment by means of screening tests. The possibilities for prevention, that is, reducing the risks of disease, have so far been limited to measures that can be taken against conditions with already known causes. These include, for example, avoiding carcinogens (smoking, asbestos), preventive medical check-ups for hereditary tumour syndromes and vaccinations against infectious diseases and tumours induced by viruses (e.g. HPV). In contrast, no preventive measures, or only insufficiently effective ones, are known for most common illnesses, which are generally multifactorial, because the constellation of causes has not yet been adequately identified. Here, Individualised Medicine could make targeted preventive measures possible, especially with comprehensive molecular analysis including individually specific influences from environmental factors. However, it is important to note that such measures are often difficult to establish because both their necessity and their success generally remain more or less invisible to patients and healthcare providers. A healthy person's knowledge about their own risks of disease can, on

the one hand, free that person from serious worries due to unsettling findings in the family. It can, however, also lead to a high level of emotional stress (Harris, 2011; see also Ch. 7.6).

5.7.1 Preventive medical check-ups for early detection of tumours

To detect common cancers like cervical, breast, colon and prostate cancer early on, in Germany it is recommended that individuals undergo regular preventive check-ups starting at age 50 at the latest. An analysis of US breast cancer monitoring data has called the value of regular breast cancer check-ups into question, as they may have resulted in an unexpectedly high number of false positive diagnoses (Bleyer & Welch, 2012). Similar debates have been going on for years regarding the use of prostate-specific antigen (PSA) as a biomarker for early detection of asymptomatic prostate carcinomas (Khoury et al., 2012).

Some gene defects result in mutations in certain tissues not being repaired adequately and further mutations occurring in increasing numbers. For example, a *BRCA1* mutation leads, in 80 percent and 40 percent of cases respectively, to breast or ovarian cancer during the lifetime of the affected woman (Walsh et al., 2006). Lynch syndrome, a hereditary disorder, leads in over 70 percent of cases to the formation of malignant tumours and is responsible for 2–3 percent of all cases of colon cancer (Steinke et al., 2013). For this most common form of hereditary colon cancer, a study has shown that annual monitoring of mutation carriers via colonoscopy and early surgical intervention can significantly reduce the frequency of advanced stages (Engel et al., 2010).

Within the realm of Individualised Medicine, therefore, there should in the future be an increased effort to identify the specific individuals who could benefit from these medical examinations. Environmental and lifestyle-related risk factors, as well as hereditary factors, should be taken into account whenever possible. For high-risk individuals especially, frequent early detection tests should already be recommended at younger ages. On the other hand, in the long term it should also be possible to identify groups of low-risk individuals that need fewer preventive medical check-ups. For example, newer overviews of the widely used breast cancer screening call for individualisation of this preventive measure (Pace & Keating, 2014). There are also concepts (Onega et al., 2014) and approaches to evaluation (Vilaprinyo et al., 2014) that could aid in the selection of optimal, individualised strategies.

5.7.2 Primary prevention of genetically caused conditions

In order to thwart the potentially fatal course of hereditary forms of breast, ovarian, colon or thyroid cancer, healthy carriers of the mutation sometimes opt for the surgical removal of mammary gland tissue, ovaries, thyroid or parts of the colon. This is not an easy decision because such radical preventive measures greatly restrict one's quality of life, and there is still a residual risk, which is not to be under-estimated, of tumour development even after tissue removal. For this reason, especially careful risk-benefit assessments by patients and advising doctors are necessary in this context.

Vaccinations have long been effective means of preventing infectious diseases; this applies as well for immunisation against human papillomavirus (HPV) to prevent cervical cancer (see Ch. 6.3). Currently, tumour-associated markers are being used for diagnosis and for monitoring the course of tumours. In the future, it may be possible to immunise individuals at increased risk of developing certain hereditary types of cancer (Umar et al., 2012). For example, tumour-associated antigens are already used in the clinical testing phase for the prevention of tumour

recurrences (see also Ch. 6.2.3). It is possible that the immune-stimulating activity of these substances can lead, for example, to prevention of genetically caused colon cancer (Kimura et al., 2013). First medications have also been approved that intervene in a targeted way in the final steps of molecular reaction pathways that would otherwise contribute to the development of cancer (Umar et al., 2012).

5.8 Conclusion

As the cost of genome sequencing decreases, such sequencing could in the future make it possible to test people predictively and comprehensively for a great number of pathogenic mutations. The inherited DNA sequence is just the primary blueprint of the genetic information. Epigenetic modifications, the nature of which differs in different tissues, can be produced in subsequent intracellular steps. This plays a role above all in tumours, and probably also in multifactorial diseases. In the latter, predictive genetic diagnosis does not allow for very reliable statements of probability because the disease-relevant genetic and exogenous factors still need to be identified. Making these interrelationships systematically usable for Individualised Medicine is a major scientific undertaking.

Interpreting the millions of DNA sequence variations in an individual genome represents a great challenge to the healthcare system with regard to medical questions and to the need for counselling for individuals undergoing testing. Determining risks of disease due to genetic dispositions could enable the individualised adaptation of screening strategies. If, for example, a person has a low risk, certain preventive medical check-ups are not needed as often. To date, prevention of common conditions that are influenced by genetics has, because of the complexity of such conditions, not been extensively researched. Initial preventive possibilities, for example protective vaccination against tumours, are emerging for hereditary tumour syndromes.

6 Individualised diagnostics and therapy

Conducting tests prior to making therapeutic decisions can make it possible to proceed in a targeted way with regard to medical treatment, particularly with regard to using drugs that intervene specifically in the disease process. This principle could apply for a number of indications and has already long been used with bacterial infections. Following initial successes in oncology, there is great hope that the principle of drug-based tumour therapy that accounts for a tumour's molecular particularities can be generalised (see Figure 3).

6.1 Pharmacogenomics and pharmacogenetics

When a medication is taken, the body interacts with the introduced substance at numerous levels. These include resorption, transport, metabolism, protein binding, interaction with a receptor, chemical modification and excretion of the substance. A patient's individual biological make-up can influence the response to a drug at any of these levels. In order to deal with this phenomenon, pharmacogenomics seeks to predict an active substance's efficacy or expected side effects before it is administered.

Pharmacogenomics and pharmacogenetics investigate the genotype's influences on the effects of a drug in an individual. Historically, pharmacogenetics has been based on phenotype and pharmacogenomics on variability at the DNA level. However, the two terms are often used synonymously. Modern pharmacogenomics research generally differentiates between candidate gene approaches, in which known degrading enzymes or receptor proteins are tested in a targeted way for genetic variations, and unbiased or hypothesis-free approaches. The latter type includes efforts to use genome-wide analyses to identify previously unknown factors that are responsible for variable drug effects.

For example, statins, which are intended to lower cholesterol levels, become effective only after uptake into the liver. Variants of the gene that codes for the corresponding transport protein can lead to decreased uptake of statins into the liver and thus to reduced efficacy (Canestaro et al., 2012). There are a number of examples in which variants of a gene lead to a pronounced change in metabolism and subsequent excretion of medications. Reduced metabolism of the active starting substance leads to intensified activity as a result of the accumulation of this substance. In these sometimes life-threatening situations the prescribed dose of the medication needs to be adapted. To date, however, there are only a few examples in which this individualised therapy has been established in clinical practice.

The drug Tamoxifen® is administered to women after breast cancer surgery to prevent recurrences and metastasis. Tamoxifen®, which is effective only in oestrogen-receptor-positive breast cancer, takes effect in the body only after enzymatic conversion. In approximately 10 percent of European women, the enzymatic step occurs to a greatly diminished extent due to a defect in the *CYP2D6* gene, making the medication less effective (Goetz et

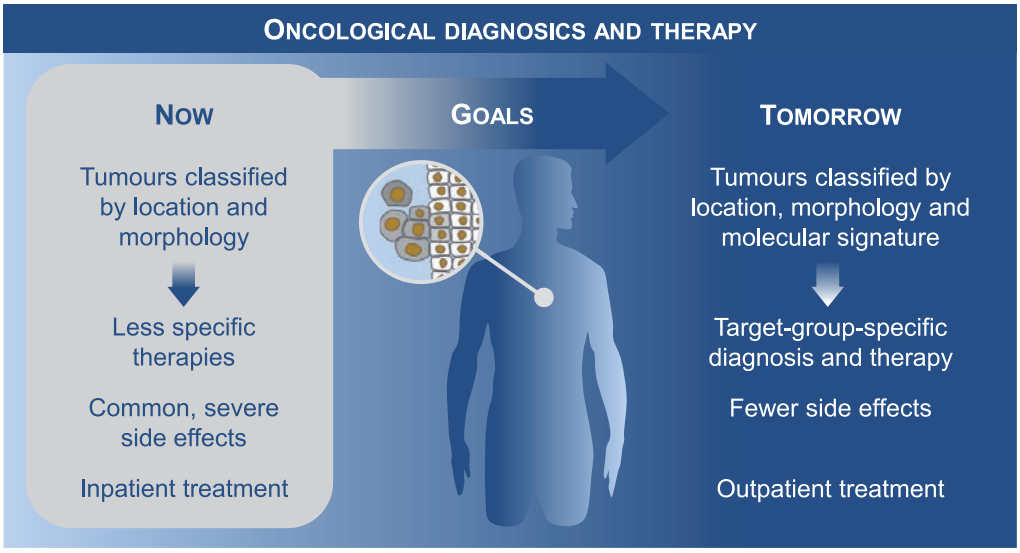

Figure 3. Individualised Medicine in oncology (further explanation in the text).

al., 2007). For molecular genetic diagnosis of the respective *CYP2D6* genotype, it has been shown that only DNA from germ cells, and not that of the tumour, should be used in order to avoid false interpretation of the findings (Brauch & Schwab, 2014).

Although diagnostic options have long been available for numerous other well-researched pharmacogenetic phenomena, there are still relatively few drugs that are prescribed only after concomitant molecular genetic testing (companion diagnostics). In Germany, 41 medications for which a gene test is required or at least recommended prior to use have been approved,[10] while the US Food and Drug Administration (FDA) already lists over 150 approved medications with pharmacogenetic implications in the instructions for use.[11] More than one-third of these medications are used in the area of oncology. Another one-third are drugs for the treatment of psychiatric or neurological disorders. For many of these medications, however, the pharmacogenetic factors that play a role have not yet been clearly demonstrated in scientific terms (Kitsios & Kent, 2012), or the consequences relating to practical use have not yet been adequately formulated for doctors and patients (Meyer et al., 2013). Determining the serum level of the medication taken or of its breakdown products in each particular case rather than determining pharmacogenetic status has the advantage that compliance to therapy and drug interactions are also recorded.

6.2 Individualised diagnostic and therapeutic concepts in oncology

The treatment of tumour diseases is currently undergoing a fundamental transformation. The work of the International Cancer Genome Consortium (see Ch. 2.1.4) has already led to the decoding of more than 10,000 cancer genomes. This involves analysing the patient's constitutional genome along with the tumour genome in each case. By the year 2025, it is expected that the number of decoded cancer genomes will reach 20 million.[12] As

10 Cf. information from the Research-Based Pharmaceutical Companies (vfa – *Verband der forschenden Pharma-Unternehmen*): www.vfa.de/download/individualisierte-medizin.pdf (last accessed: 16 September 2014).

11 Cf. www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm (last accessed: 16 September 2014).

12 Cf. www.phgfoundation.org/news/15442 (last accessed: 16 September 2014).

biomedical research rapidly deepens our understanding of pathogenesis, especially underlying genetic disorders in tumour cells, it will give rise to numerous new diagnostic and therapeutic tools.

6.2.1 Molecular biological concept of targeted tumour therapy

Genes that can be transformed via mutations into tumour-causing oncogenes are called proto-oncogenes. Most tumour cells contain numerous (50–30,000) mutations that lead to complex alterations (Alexandrov et al., 2013). Of these mutations, just a relatively small number generally act as what are called driver mutations. These mutations affect genes called tumour suppressor genes or are responsible for the transformation of proto-oncogenes into oncogenes, and thereby drive the malignant transformation of the affected cell (Greenman et al., 2006; Hanahan & Weinberg, 2011). This fact provides an important starting point for the targeted use of new vaccines and inhibitors to counter the protein products of oncogenes.

One important group of proto-oncogenes are the genes that code for tyrosine kinases. Tyrosine kinases enzymatically regulate coordinated cell division, cell migration and the life span of cells. Inadequately controlled cell reproduction is a key mechanism in the transformation of normal cells into malignant tumour cells when tyrosine kinases become 'deformed' as a result of genetic alterations. In recent years, the inhibition of tyrosine kinases with new tyrosine kinase inhibitors (TKIs) has become increasingly important in targeted tumour therapy (Kolch & Pitt, 2010).

6.2.2 Tyrosine kinase inhibitors (TKIs) in clinical use

The first clinically successful inhibition of such a tyrosine kinase was conducted using the antibody trastuzumab (Herceptin®) in breast tumours with *HER2* gene expression disorder (Slamon et al., 1989, 2001). Imatinib has been successfully used as the first targeted inhibitor to inhibit a different tyrosine kinase, ABL kinase, in chronic myeloid leukaemia (CML; see also Ch. 2.1). A follow-up study showed that about 90 percent of CML patients treated with imatinib remained recurrence-free for at least 5 years (Druker et al., 2006). Imatinib has an inhibitory effect on the c-KIT and PDGFRA proteins, as well as on ABL kinase. Mutations in the two associated genes play an important role in the genesis of gastrointestinal stromal tumours (GIST). Therapy with imatinib achieves a clinical response in up to 50 percent of cases in patients with inoperable GIST, and thus an additional survival time of 33 months on average, compared with a response rate of just five percent with conventional chemotherapy (Cohen et al., 2009; Heinrich et al., 2003).

Although CML and GIST are relatively rare, imatinib was the first medication to show the great potential of therapy with TKIs in the treatment of tumours. Introducing the TKIs erlotinib and gefitinib for treatment of the much more common non-small-cell bronchial carcinoma (malignant lung tumour) was likewise very successful (Shepherd et al., 2005). Mutations were found in the tyrosine kinase part of the epidermal growth factor receptor (EGFR) in approximately ten percent of all patients with bronchial carcinoma (in patients of Asian origin, the rate is as high as 30 percent; Sharma et al., 2007). The use of erlotinib or gefitinib in patients with *EGFR*-mutation-positive lung tumours leads to a response rate of 50–90 percent and to an increase in survival time of 27 months on average compared with conventional chemotherapy (Maemondo et al., 2010; Mok et al., 2009; Rosell et al., 2009; Tsao et al., 2005).

Malignant melanomas of the skin (black skin cancer) are also already being treated with targeted molecular ther-

apy. For this practice, sequence analysis of multiple genes (e.g. *KIT*, *BRAF* and *NRAS*) is necessary first. Therapies with imatinib and related TKIs are indicated in *c-KIT*-mutated, metastatic mucosal melanomas (Hodi et al., 2013; Lutzky et al., 2008). In *BRAF-V600E*-mutated and *BRAF-V600K*-mutated melanoma, the most effective treatment consists of therapy with the inhibitor vemurafenib (Chapman et al., 2011). Table 4 provides an overview of the use of targeted medications in oncology.

For reasons that are not entirely clear, even targeted tumour therapies often fail to work in all patients. The mutation rates, which are generally high, and the resulting genetic (clonal) heterogeneity of tumour cells represent a big problem, meaning that resistance often develops even in treatment with TKIs; recidivism (recurrence) of the tumour then occurs. Some of these mechanisms have been explained. For example, secondary mutations were found in the *BCR-ABL* gene in CML patients who developed resistance after several years of therapy with imatinib. Similar changes have also been described for the *EGFR* gene (Kobayashi et al., 2005). These mutations usually cause the particular TKI to lose its ability to bind. Spontaneous mutations in other proto-oncogenes (see Ch. 6.2.1) can, for example, also cancel out the therapeutic activity of gefitinib and erlotinib (Engelman et al., 2007; Sos et al., 2009). It is hoped that the development of new TKIs will cause the inhibitor to bind more selectively and hopefully irreversibly to the particular tyrosine kinase in order to reduce the potential for resistance formation. Examples of this are nilotinib and dasatinib, the second generation of BCR-ABL inhibitors (Kantarjian et al., 2010; Saglio et al., 2010) and afatinib, a promising new EGFR inhibitor (Lin et al., 2012).

Conventional chemotherapeutic agents are generally also effective on all regenerating tissue with rapidly dividing cells (e.g. bone marrow, epithelium of the gastrointestinal tract). This leads to the typical side effects such as nausea, vomiting, hair loss, mucosal damage and reduced formation of blood cells. TKIs do display a spectrum of side effects that is specific to the particular substance, but overall they are tolerated much better than less specific chemotherapy or radiation therapy (Hartmann et al., 2009).

6.2.3 Cancer immunotherapy

It has long been known that the immune system plays a decisive role in the elimination or inhibition of tumour cells, and it is assumed that this also occurs constantly in healthy individuals. There are also many indications of meaningful involvement by the immune system in the success of chemotherapy or radiation therapy in cancer patients (Galluzzi et al., 2012; Palucka & Banchereau, 2012). The identification of tumour antigens, that is tumour-specific molecular surface structures, is leading, via the analysis of tumour genomes, to the development of more new antigen-specific immunotherapies. As in targeted drug interventions, the immune system is guided to target the molecular structures of degenerated cancer cells in order to specifically eliminate these cells or inhibit their growth.

Immunisation-based approaches like tumour vaccination are still in the clinical development phase. In this form of active immunisation, the idea is to first synthesise tumour antigens based on a model of a patient's tumour-specific DNA sequences (see also Ch. 2.1) and then to inject them into the patient together with an immune-stimulating adjuvant. In animal tests, numerous antigens of a particular type of melanoma, for example, have been tested in this way for their potential to stimulate a specific immune response (Castle et al., 2012). The results open up new immunisation strategies that would allow patients to be immunised against

certain tumours using a suitable combination of relevant tumour antigens. However, this individualised approach is also associated with particularly major regulatory challenges (Britten et al., 2013).

In other techniques that are still being developed, tumour-reactive T-lymphocytes (white blood cells) are removed from a patient, enriched, reproduced and reinjected. This has led to encouraging results in a number of clinical studies, for example in the treatment of prostate and skin cancer (Palucka & Banchereau, 2012). In a similar strategy, dendritic cells are loaded, outside of the patient's body, with a combination of particular tumour antigens in order to stimulate a tumour-specific immune response after reinjection. One potentially promising example of this is sipuleucel-T, which was approved in the US in 2010, and is an immunotherapeutic agent against prostate cancer that leads to an increase in patient survival of four months compared with the patient group receiving placebo (Higano et al., 2010).

Several monoclonal antibodies have already been in clinical use since the late 1990s for passive immunisation against certain tumour diseases. Examples of this are rituximab, which is used in combination with chemotherapy in lymphoma and leukaemia patients (Coiffier et al., 2002; Hallek et al., 2010) and its approved successor product obinutuzumab (Goede et al., 2014). Trastuzumab, which is HER2-binding and is used in the treatment of breast cancer, may perhaps, in addition to its TKI effect, also stimulate an active immune response (see Ch. 6.2.2) (Taylor et al., 2007).

Table 4. Examples of medications used in oncological practice for which molecular diagnostics are required prior to administration.

Disease	Diagnostic gene	Target protein	Medication
Chronic myeloid leukaemia (CML, blood cancer)	*BCR-ABL*	ABL kinase	Imatinib, dasatinib, nilotinib
Colon carcinoma (Cancer of the large intestine)	*KRAS* exon 2-4, *NRAS* exon 2-4	EGFR	Cetuximab, panitumumab
Bronchial carcinoma (Lung cancer)	*EGFR* mutations	EGFR	Erlotinib, gefitinib
	EML-4ALK	ALK	Crizotinib
Promyelocytic leukaemia (Blood cancer)	*PML-RAR alpha*	Retinoic acid receptor alpha	All-trans retinoic acid
Melanoma (Skin cancer)	*c-KIT*	c-KIT	Imatinib
	BRAF V600E/K	BRAF	Vemurafenib
Mammary carcinoma (Breast cancer)	*HER2*	HER2	Trastuzumab (Herceptin®)
	erB1/erB2	EGFR/HER2	Lapatinib
Gastrointestinal stromal tumour (GIST)	*c-KIT* exon 11/9	activated c-KIT	Imatinib
	PDGFR alpha	PDGFR	Dasatinib

6.3 Individualised strategies for viral illnesses

Therapies for transmittable diseases like HIV infection are also individually adapted to patients in advance. More than two dozen substances with antiviral activity against HIV have already been developed; combining these leads to hundreds of possible therapeutic options. Approximately six percent of all patients cannot be treated with the active substance abacavir because of their HLA-B allele, as this could have life-threatening side effects (Martin et al., 2012). Moreover, hundreds of mutations that determine the complex resistance behaviour of the particular virus population are known for the viral genotype (approx. 10,000 bases). In the case of inadequate suppression of the reproduction of HI viruses as a result of sub-optimal medical therapy, resistant virus genotypes are selected, meaning that patients who have been undergoing therapy may collect numerous resistant variants of the virus, making additional therapeutic options hard to find. Therefore, computer-based expert systems are already widely used in clinical practice; such systems start with a viral genotype that has previously been determined via sequencing, and draw conclusions about resistance to the individual active substances. The strategically most promising therapeutic combination is then suggested.

In order to develop these bioinformatics systems, the relationships between viral genotype and resistance phenotype must first be ascertained using sufficiently large databases to link viral genotypes with therapy-dependent clinical courses. This is done either manually by expert groups or by computer using statistical analysis on large clinical/virological resistance databases. This strategy could theoretically also be used for cancer therapy in the future. This would, however, first require correspondingly large arsenals of active substances to be available, and the biomolecular foundations of the highly complex resistance behaviour of tumours to be better understood so that appropriate lab tests could be conducted in the context of a study (Bock & Lengauer, 2012).

Approximately 2.5 percent (between 0.5–48 percent, depending on the region) of the world's population suffers from chronic infection with the hepatitis C virus (HCV),[13] which often leads to cirrhosis of the liver with liver failure and liver cancer. So far, no effective vaccine has been developed. The activity of some direct antiviral medications depends, on the one hand, on the particular HCV genotype (Ghany et al., 2011; Poordad et al., 2011); on the other hand, several genome-wide association studies have demonstrated that the efficacy of the HCV medications peginterferon-alpha and ribavirin depends on a patient's individual IL28B genotype (Booth et al., 2012). Recently, however, a very effective medication was approved for treatment of the three most common HCV variants (genotypes 1, 2 and 3; Afdhal et al., 2014; Zeuzem et al., 2014).

Since the 1990s, human papillomaviruses (HPV) have been localised and typed using DNA analysis on cytological cervical smears produced in medical check-ups. Over 100 types of HPV are currently known. While low-risk types usually remain quiescent or cause benign tumours like warts, some high-risk types of the virus (especially HPV 16 and 18) are able to infect mucosal epithelial cells of the throat, nose and ear regions, as well as the cervix, and to transform those cells into malignant tumour cells by producing growth-stimulating and transforming proteins (E6 and E7). This is proven, among other evidence, by the fact that high-risk HPV genomes can be detected

13 Cf. information of the WHO: www.who.int/mediacentre/factsheets/fs164/en (last accessed: 16 September 2014).

in over 95 percent of cervical carcinomas that are tested (zur Hausen, 2009). For this reason, molecular virus diagnosis, to cite another example of already implemented Individualised Medicine, is now being used successfully as the foundation for individual prediction, primary prevention (protective vaccination) and secondary prevention (conisation) and therapy of cervical cancer.

6.4 Approaches to individualisation in other diseases

There has been notable progress, giving cause for hope, related to Individualised Medicine in oncology and virology. In numerous other diseases as well, first steps toward individualised approaches are already evident.

First approaches of biomarker-based medical techniques for cardiovascular disease include troponin-guided therapy of acute coronary syndromes and management of cardiac insufficiency therapy by monitoring *brain natriuretic peptide* and *N-terminal pro-brain natriuretic peptide* (Eschenhagen & Blankenberg, 2013; Völzke et al., 2013a). More widespread use will, however, require significantly improved understanding of the complex interrelationships between genome alterations and the clinical phenotype of cardiovascular diseases (Eschenhagen & Blankenberg, 2013; Völzke et al., 2013a). In the *SHIP* study (see Ch. 9.1), genetic and metabolic risk factors for developing high blood pressure were identified and a corresponding prediction model was created (Völzke et al., 2013b).

Many of the monogenically inherited diseases (see Ch. 5.1) that are currently known are metabolic disorders, and effective targeted treatments are only available for a few of them. Gaucher's disease, an autosomal-recessive disorder, is a rare fat metabolism disorder caused by a lack of the enzyme glucocerebrosidase. Depending on the disease subtype, the clinical symptoms can vary greatly, so that a selection must be made from among different therapy options such as enzyme replacement therapy (Weinreb et al., 2002) or substrate inhibition therapy (McEachern et al., 2007). Neonatal diabetes mellitus, which appears shortly after birth, has been attributed to various genetic defects that will probably require individualised therapeutic procedures (Greeley et al., 2010). A medication was recently approved for targeted therapy of a rare subtype of recessively inherited cystic fibrosis (mucoviscidosis; Antunovic et al., 2013; Davis et al., 2012).[14]

Similar progress may soon be achieved in the area of ophthalmology. For instance, Leber's congenital amaurosis (LCA) is triggered by a functional disorder of the retinal pigment epithelium that results in severe damage to vision, including blindness. In about 15 percent of affected individuals, there is a hereditary defect in the *RPE65* gene, and clinical studies have given rise to the hope that this and other monogenic forms of LCA can be treated using gene therapy (Sahel & Roska, 2013). Moreover, comparable progress is becoming evident in preclinical studies on gene therapy for a particular form of pigmentary retinopathy (Michalakis et al., 2014).

In the area of neurology, molecular biological analyses will hopefully open up options for early diagnosis and differentiation among different forms of dementia (Albert et al., 2011; Bateman et al., 2012; Jahn et al., 2011). The ability to diagnose the molecular causes of slowly progressing diseases like Alzheimer's early on and precisely is the first step toward developing a therapy or preventive measures (Debré et al., 2012; Langbaum et al., 2013).

14 In Phase III of the clinical study, participation by 213 patients was sufficient for approval of this substance (ivacaftor) by the US Food and Drug Administration (FDA, 2013). Ivacaftor is considered to be an exemplar of pharmacogenomics.

Numerous pathogenic mutations in the *dystrophin* gene are known for X-chromosome-linked recessively inherited Duchenne muscular dystrophy. There is therapeutic work being done on various strategies for targeted correction of the gene product (Andaloussi et al., 2012; Seto et al., 2012). It is already possible, in the case of certain mutations, to transform the severe early-onset form of the disease into a mild late-onset form by correcting the RNA splicing, and to thereby prolong patient life expectancy by several decades, on average (van Ommen & Aartsma-Rus, 2013). Interestingly, heterozygosity for mutations that cause Gaucher's syndrome is associated with a 30 percent risk of developing Parkinson's disease by the age of 80 (Böttcher et al., 2013). These and other insights into the role of certain gene variants in the expression of Parkinson's disease could open up new strategies for the development of targeted therapies (MacLeod et al., 2013; Zheng et al., 2010).

Using monoclonal antibodies that bind specifically to tumour necrosis factor (TNF) in therapy of rheumatoid arthritis, a common disease, has been constantly increasing since its initial approval in 1996. The side effects and costs of therapy are very high, and not all patients respond to it. The first biomarker candidates, such as certain antibodies, that could identify the patients that will respond to therapy with these medications were recently identified (Simsek, 2012). In other autoimmune disorders as well, such as scleroderma, there are promising initial efforts, and in particular a number of genetic biomarker candidates, for the development of targeted diagnostics and therapy (Assassi et al., 2013).

Genetic diagnosis also already plays a significant role in determining whether cochlear implants are indicated in cases of congenital deafness (Brown & Rehm, 2012; Yang et al., 2012; Żak, 2011). It is furthermore expected that imaging techniques, in conjunction with 3D printer technology and highly-developed materials, will in future significantly simplify and improve the manufacture of customised implants (Zopf et al., 2013).

6.5 Conclusion

An increasing number of validated genetic parameters makes it possible to predict the side effects of or therapeutic response to certain therapies. Because there are inadequate data from prospective clinical studies, only a few drugs are currently prescribed, and then only after a preliminary genetic test. This is due, among other factors, to the fact that drug activity, especially in multifactorial disorders, generally depends on a large number of genetic, phenotypic and exogenic factors, some of which are still inadequately understood. A fundamental transformation toward Individualised Medicine is taking place in oncology, and there is great hope that deeper understanding of the molecular mechanisms of tumour genesis will make it possible to develop additional effective and targeted medications. These medications are generally associated with fewer side effects than conventional, less specific treatments. Targeted substances like tyrosine kinase inhibitors are being further developed for the purpose of preventing drug resistance formation. Research on immunotherapeutic techniques like tumour vaccination and antibodies that bind to cancer cells should also be promoted.

In addition to the progress in oncology, there have been similar developments in the molecular diagnosis of transmittable diseases like HPV, HIV and hepatitis C. Taking the viral genotype and other patient parameters into account, precise prognoses and strategic therapeutic decisions can be made. The beginnings of targeted molecular therapies can already be seen in cardiology, rheumatology, neurology and the treatment of monogenically inherited metabolic disorders.

7 Ethical principles and general legal conditions

The complex interrelationships within, and consequences of, Individualised Medicine must be taken into account in ethics and in legislation. This process will be facilitated by the fact that Individualised Medicine is developing incrementally. Guiding principles could therefore be derived from concrete constellations. Human genetic data are being used more and more in medical practice. The German Gene Diagnostics Act (GenDG, *Gendiagnostikgesetz*) governs the handling of these data very closely. Furthermore, Statements by the Academy Group (German National Academy of Sciences Leopoldina et al., 2010), the German Ethics Council (Deutscher Ethikrat, 2013) and the EURAT project group (Marsilius-Kolleg, 2013) have drawn attention to important aspects that should be considered when predicting tendencies toward disease. To a certain extent, these play a guiding role for the practice of Individualised Medicine.

7.1 Basic issues in working with predictive information

Human genetic tests, whether DNA analyses, family histories or physical examinations, should, when they are used for prediction, all be evaluated in the same way with regard to ethics. Family history has long been an integral component of medical practice; this has not generally been considered a moral problem. It is therefore remarkable that direct DNA analyses are, by way of contrast, considered to be morally problematic. Often, public opinion attributes to 'genes' a much greater influence on human personality than can be scientifically proven. The broad use of genetic, and especially predictive, information in the healthcare system does, however, involve a number of morally significant prerequisites and consequences (Bartram et al., 2007; Thompson & Chadwick, 1999). These arise, on the one hand, from the methods used to acquire the information, and on the other hand from the need for additional counselling, as well as the behavioural requirements and the stress that can potentially result from knowing the results of certain tests. To the extent that non-genetic patient information can be used for predictive purposes, similar considerations apply for such information as well.

Borderline cases of patient autonomy with regard to informational self-determination are also among the ethically and legally relevant questions raised by Individualised Medicine (see Ch. 7.5). Until now, information associated with the medical treatment process has largely been protected by the medical confidentiality obligation. In the age of digital information technology, and because of the rapidly growing body of knowledge about human genetics – with which more and more personal medical data can be generated – the significance and sensitivity of this information takes on new dimensions. The following section discusses the extent to which problems can arise in individual cases in the practice of Individualised Medicine with regard to data protection and the right to information.

7.2 Opportunities and risks of predictive information

According to a still-widespread assumption, a person's conduct is determined in a causative way by their genome. This as-

sumption is called 'genetic determinism' and would, if it were applicable, have significant consequences: discussions about moralistic and legislative regulation of conduct would then be meaningless, since a being that is entirely or partially determined cannot be expected to behave sensibly (Gethmann & Thiele, 2008). Furthermore, knowledge of the determining genome would also open up the potential for manipulating certain types of conduct, such as consumer behaviour.

However, according to our current understanding a form of 'genetic probability' generally applies as long as an individual's cognitive functions are not impaired (e.g. by mental retardation or dementia); that is, it is assumed that our thinking and behaviour are largely guided by a number of mechanisms that are downstream from genetic influences. The interplay among genes, learning and environmental influences is so complex that it may never be possible to understand it, and certainly not in the foreseeable future. The idea that predictions can be made about a person's decision-making behaviour is therefore dubious (Turkheimer et al., 2014). Against this backdrop, the risks of passing on predictive information appear much less dramatic, since legitimate or illegitimate parties who acquire such knowledge will not automatically be capable of targeted manipulation. For this reason, the risks of acquiring this knowledge must be weighed against the great benefits that an affected individual may incur, for example by learning of health risks that can be influenced.

The risks and opportunities of increasingly incorporating genetic and other parameters for the purposes of Individualised Medicine cannot, however, be assessed for each particular individual; instead, binding regulations should be developed at the societal level. However, on the one hand the individual desires assurance that predictive information, including the right not to be informed (see Ch. 7.6), will be protected, while on the other hand collective interest requires the greatest possible amount of clinical data to be investigated for purposes of scientific and medical progress. The conflicts that arise from this situation can only be avoided if patients are comprehensively informed of the possible consequences of testing, and their predictive data are protected from unauthorised third parties.

One incentive for the misuse of predictive information is that commercialising such tests appears to be very profitable. Such information is especially likely to be utilised in the insurance system, in the employment market and when setting up biobanks (see Ch. 7.8). Numerous and sometimes dubious service providers are already offering so-called direct to consumer genetic testing over the internet based on the submission of samples. This is problematic, because the origin and removal of the samples that are sent in cannot be monitored, and the basis for the predictive information provided by the company is not subject to the necessary general quality control and is therefore not transparent. It has been shown that even reputable providers calculate very different relative risks for an individual (Imai et al., 2011). Above all, however, there is no guarantee of competent genetic and medical counselling for the customer. This is important, because DNA sequencing often results in false positive or false negative findings; there is also no guarantee of data protection. Dubious, internet-based offers of genetic analysis using consumer samples and accompanying phenotype information are therefore viewed with concern; the results of such tests could be misused for commercial interests. Such developments can only be controlled by means of adequate briefing of patients to strengthen their ability to take responsibility for themselves, and by international consensus agreements. The recommendations of the Leopoldina

(German National Academy of Sciences Leopoldina et al., 2010), the German Ethics Council (Deutscher Ethikrat, 2013) and the EASAC (Fears & ter Meulen, 2013) provide guidance for dealing with direct-to-consumer tests.

There are no simple solutions, such as a general prohibition or general permission, for the sharing of predictive information. Instead, the maxim should be to minimise possible risks to the affected parties through legal provisions on the one hand, and to maximise the utilisation of opportunities that arise on the other. This also applies to the legal regulation of data collection, data utilisation and data security for research purposes and for use in Individualised Medicine.

7.3 Collection and handling of predictive information

Long-term storage of information collected in a clinical context is indispensable for Individualised Medicine. One advantage of genome data in particular is that it only needs to be collected once and is then available for all further treatment processes, and for targeted diagnosis for family members in the case of a genetically based condition. For scientific purposes as well, it is very important that the collected data and the associated results are available for associated studies (see Ch. 2.1) and for the development and validation of new diagnostic tools and therapies (see Ch. 4) over the long term, and with as few barriers as possible. This data could be stored, for example in public research databases.

In the legal realm, genetic information is already treated differently from 'normal' medical data because it entails a fundamental risk of social, ethnic and eugenic discrimination and stigmatisation (McClellan et al., 2013). Moreover, genetic information is, within certain limits, immutable and remains with individuals throughout their entire life span. Furthermore, it could also be significant to genetically related individuals (third-party involvement), and often the scope of the information derived from it cannot be adequately assessed. In the future, similar considerations are likely to be raised with phenotypic and epigenetic information as well (see Ch. 2.2).

In Germany, the GenDG sets forth the legal requirements related to genetic testing for medical purposes, the handling of samples obtained in that context, and the resulting data. The GenDG entered into force on February 1, 2010, and should be considered a special provision for the area of application it covers. Already in 2010 the Academy Group adopted a critical position vis-à-vis the content of the GenDG with regard to predictive genetic diagnosis (German National Academy of Sciences Leopoldina et al., 2010). The Federal Data Protection Act (BDSG, *Bundesdatenschutzgesetz*) and the data protection laws of individual federal states apply along with the GenDG in cases where the GenDG does not contain any or contains only inconclusive provisions. A number of legal problems can also arise when determining the scope of the GenDG with regard to Individualised Medicine. For example, Section 3(1) of the GenDG defines the term 'genetic test' as a genetic analysis used to determine genetic characteristics for the purpose of the test, or an assessment of prenatal risks for the purpose of the test. It follows from Section 3(2) GenDG that genetic analysis is limited to testing methods involving laboratory techniques. Postnatal phenotype testing, for example, is therefore not covered by the GenDG.

Genetic analyses for research purposes are expressly not covered by the GenDG since in the eyes of the law this requires only regulation relating to research in general and not to research with genetic

data and samples in particular. One problem here is the question of exactly what the term 'research' means pursuant to the GenDG (cf. Sosnitza & Op den Camp, 2011); another is that in individual cases, differentiating between a genetic test for research purposes and one for medical purposes can be difficult. It is thus possible that research on samples may also lead to insights with important medical relevance to the donor; the consequences of such insights should be regulated in advance (see also Ch. 7.8.3). If the medically relevant results are to be shared with the affected individual, then corresponding application of the provisions of the GenDG makes sense, provided they can still be fulfilled retroactively. This applies in particular to the provisions on genetic counselling and on communicating test results (cf. Stockter, 2012; GenDG, Section 2, marginal note 32; Sections 7 et seq., marginal note 5).

7.4 Legal conflicts in tumour diagnostics

Pursuant to Section 3(4) GenDG, 'genetic characteristics' refer to genetic information of human origin that is inherited or acquired by the time of birth. It follows from this that the GenDG does not apply for tumour therapy if genetic testing is directed only at characteristics acquired after birth that are (also) responsible for the tumour disease. However, it can be difficult to know in advance, for example prior to diagnostic genetic testing, whether the mutation that is the cause (or among the causes) is one that was inherited or acquired before birth or one that was acquired after birth.

The GenDG also differentiates between predictive and diagnostic genetic tests (Section 3(6)-(8) GenDG), with different legal demands being placed on the collection of data in each case. Because predictive genetic tests involve both opportunities and risks (see Ch. 5), there are increased requirements for conducting such tests. These include, for example, the requirement for genetic counselling before and after testing (Section 10(2) GenDG) as well as the stipulation that the testing must be carried out by a qualified doctor (Section 7 GenDG). This differentiation becomes problematic when diagnostic findings are also meaningful with regard to prediction. Examples of this include hereditary mutations in cancer-causing genes (e.g. *BRCA1* or *BRCA2*; see Ch. 3.2 and Ch. 6.2), which are used in prognostic and pharmacogenetic testing of symptomatic tumour diseases and could also indicate high risks of developing additional tumour diseases. It is probable that in the future it will often be impossible to draw clear boundaries between diagnosis and prediction when comprehensive patient testing is conducted in the area of Individualised Medicine (Chen et al., 2012).

7.5 The right to informational self-determination

The basic right to informational self-determination is understood to be a further development of general personality rights arising from Art. 1(1) in conjunction with Art. 2(1) of the German Constitution (GG, *Grundgesetz*). This protects the individual's freedom to make decisions about the collection and use of their personal data (German Federal Constitutional Court [BVerfGE, *Bundesverfassungsgesricht*], 65, 1, 43); such personal data includes genetic information. The rights of defence and claims set forth in the German Constitution apply to such information if those rights are violated. For example, individuals can demand, in the context of rights of defence, that genetic information about them are not collected, stored or used without their consent. In the first and second sentence of Section 8(1), the GenDG accordingly stipulates that the affected individual must communicate their

consent to the collection and testing of genetic samples in writing and in advance to the competent medical professional. This includes both a decision about the scope of the genetic testing to be conducted and the extent to which the individual wishes to be informed of the test results and/or the extent to which the results are to be destroyed. On the other hand, affected individuals have the right to withdraw their consent at any time, effective *ex nunc*, in writing or verbally, to the responsible medical doctor and to thereby discontinue the genetic testing or analysis, which then requires the genetic testing results to be destroyed (fourth sentence of Section 12(1) in conjunction with the second sentence of Section 12(2) and the second sentence of Section 13(1) GenDG).

The prerequisite for effective, informed consent is that patients are thoroughly briefed by the doctor on the type, significance and scope of genetic testing (cf. also Section 9 para 1 sentence 1 GenDG). Because the spectrum of, and the extent of explanation required for, possible tests and therapies are increasing substantially within the realm of Individualised Medicine, the need for counselling and the requirements with regard to the content of briefing are also increasing to ensure that informed consent remains possible. This is making it ever more difficult to practically implement and adhere to the doctor's obligation to brief patients, for example when a general practitioner is considering a pharmacogenetic therapy. For example, according to Section 9(2)(1) GenDG, the affected individual must also be briefed about the results that can be obtained within the scope of the particular test's purpose, including the significance of the genetic characteristics to be investigated to an illness or health-related disorder. This can, especially when using DNA chip technology or exome sequencing (see Ch. 5.5), lead to substantial difficulties due to the large number of genetic characteristics to be investigated and potential additional findings or uncertainties associated with the results. Adequate briefing and counselling as the basis for an autonomous and self-determined decision would, because of the sheer volume of relevant information, likely overwhelm the affected individual. Further discussion of this problem and the possible solutions that have been developed are presented in the statements by the German Ethics Council (Deutscher Ethikrat, 2013), the EURAT project group (Marsilius-Kolleg, 2013) and the Berlin-Brandenburg Academy of Sciences and Humanities (Berlin-Brandenburg Academy of Sciences and Humanities, 2013).

7.6 The patient's right not to be informed

Knowledge about risks of disease can provide significant benefits and relief to the affected individual, but it can also involve stress and strain, with serious consequences (Eberbach, 2010, 2011; Kersten, 2011; Olberg, 2012; Woopen, 2011). One illuminating example of such stress is the prediction of an incurable monogenetic disease, since the underlying mutation will almost certainly lead to the onset of the disease. In this case, the patient is put in a situation of being a 'healthy sick' individual. Knowing about risks of disease and whether those risks are high or quite high can cause people great emotional stress. For this reason, each individual is granted the right not to be informed; this is called the right not to know. Implementing this right harbours significant conflicts within the practice of Individualised Medicine.

As mentioned in Chapter 7.3, a certain degree of genetic probability for the expression of a characteristic often allows for conclusions about genetically related individuals as well (discussed in detail in German National Academy of Sciences Leopoldina et al., 2010). Although the

right of affected individuals not to know should be protected as far as possible, in the case of a conflict, as a rule the directly affected individual's right to know takes priority. This applies in particular when patients are in an apparent emergency situation (e.g. in the case of hereditary breast cancer) and wish to prepare themselves as soon as possible for the risk of disease onset. In the case of pharmacogenetically-based intolerance of a medication (see Ch. 6.1), it would also be in the relatives' interests to learn of the risk and if applicable undergo testing themselves. The same applies for the predictive diagnosis of curable or preventable diseases. The GenDG stipulates in the fourth sentence of Section 10(3) that genetic counselling of affected individuals, at least in the case of a preventable or treatable condition, shall include a recommendation that they in turn recommend genetic counselling to genetic relatives. However, in the case of an untreatable disease, the right to confidentiality of the person undergoing testing and the genetic relative's right not to know take priority. Conflicts can arise for the treating doctor if the affected person refuses to recommend genetic counselling to the genetically related individual who could thereby be protected from health-related harm. If a doctor informs the genetically related individual him- or herself without the consent of the affected individual, that action could as a rule be justified based on a (justified) emergency situation pursuant to Section 34 German Criminal Code (StGB, *Strafgesetzbuch*). However, such an interpretation is contradicted by the definitive assessment of interests conducted by the legislative authority in the fourth sentence of Section 10(3) GenDG. Therefore, in the final analysis, the only option is to request that the legislative authority intervenes correctively in this regard (Heyers, 2009).

The relevance of genetic data for third parties can also lead to other conflicts, for example in relation to voluntarily sharing genetic data, such as with employers or insurers, because the rights of genetically related individuals could thereby also be compromised indirectly. One could consider stipulating that all affected parties must jointly provide consent (Wasserloos, 2005), but this would be both impractical and legally difficult to implement. In this regard, the GenDG currently only stipulates that insurance companies may not use these data to evaluate relatives. However, it is possible that in practice the data may nevertheless be taken into consideration.

Safeguarding the right not to know also runs into significant problems for the doctor-patient relationship in individual cases, because the doctor may need to assess a patient's capacity for stress in order to decide what predictive information he or she can in good conscience share with that patient. Usually only family doctors have the type of trust-based relationship with their patients that is necessary here, but they rarely have the specialised knowledge required to counsel patients about the numerous potential consequences of predictive genetic findings. It is also possible to imagine situations in which the doctor would experience a conflict between the right to know and the right not to know (Duttge, 2010), for example if patients must be briefed about the health risks of their medical treatment for informed consent purposes but have expressly stated that they do not wish to know about additional negative information about their health status that may come to light. In such a case, the doctor must respect the patient's wishes in accordance with the GenDG, but may then, by not initiating appropriate therapy, run counter to the doctor's general duty to provide medical care. It is questionable whether this is the optimal legal solution to the problem where the decision affects the patient's life.

7.7 Rights and duties of doctors and other non-medical professionals

Because of the sometimes serious consequences of genetic testing, the GenDG stipulates, in order to ensure that patients receive appropriate explanations from the doctor responsible for the testing, that for the most part only qualified doctors may perform such tests (Section 7(1) and (3) GenDG). It is to be expected that total genome sequencing and accompanying patient counselling will already be requested more often in the near future (see also Ch. 5.5). Increasingly, a division of labour and teamwork among the competent doctors and the centres in charge of sequencing and bioinformatic assessments will probably be necessary due to their different areas of expertise. For example, even if they are qualified pursuant to Section 7 GenDG, family doctors would, simply for reasons of time, become overwhelmed if required to provide extensive counselling. Molecular medical content and other areas of Individualised Medicine should be emphasised more in the relevant continuing education curricula for doctors seeking to become specialists. As computer-based analysis will play a big role in Individualised Medicine, this must also include knowledge of the principles of bioinformatic analyses. Non-medical professionals other than doctors will play an important role in this area in future. These professionals need to communicate continuously with doctors and be familiar with the counselling and decision-making process. In this context, the fact that predictive statements need not always be in the context of an illness should also be taken into account.

Individualised Medicine will, to a certain extent, go hand-in-hand with a shift in responsibility and decision-making power that will necessarily have ethically and legally relevant consequences. An example of this is the collection and assessment of genome data by sequencing site personnel for the purpose of guiding therapy. For this reason, non-medical scientists who are involved need legal protection. This includes the right to refuse to provide information in court that was shared with them during testing or treatment. In its statement, the EURAT project group suggests enlarging the group of individuals entitled to refuse to testify pursuant to Section 53 of the German Code of Criminal Procedure (StOP, *Strafprozessordnung*) (Marsilius-Kolleg, 2013). EURAT has also developed a code of conduct for scientists other than doctors that is based on the ethical guidelines for doctors and includes a self-commitment to prevent illegitimate sharing of data with third parties. These suggestions form a good procedural basis for future regulations and are exemplary, not just for genetic testing.

7.8 Special areas of activity

7.8.1 Clinical studies, approval, implementation

Stratification in the context of Individualised Medicine enables a reduction in the numbers of patients in clinical studies (see Ch. 4). This means that medications can be approved only for people with the particular molecular target structure on which the relevant medication was actually tested in the Phase III study (Kollek et al., 2004). If the pharmacogenetic relationship has been clearly proven empirically, then prescription of these medications should also be linked in a legally binding manner to a pharmacogenetic test to be performed beforehand. There always remains the possibility of off-label use, which is acceptable in principle and which a doctor can choose on an exceptional basis in an individual case within the scope of 'therapeutic freedom'. Independent use of targeted drugs could also be possible when new, unexpected indications arise (Sanseau et al., 2012). Moreover, follow-

ing up on a new therapeutic process after it has been approved (postmarketing surveillance) is especially important in order to reliably document rare side effects (Hennen & Sauter, 2005; Kollek et al., 2004).

7.8.2 Ethical implications of resource allocation

In the development of individualised therapies, the danger is sometimes that patients could be excluded from a treatment if they have only a low probability of therapeutic response based on pharmacogenetic tests. This would mean regulating access to possibly life-saving therapies based on statistical probabilities, for example the estimated prolongation of survival by a few weeks. On the other hand, this type of resource allocation is a prerequisite for positive economic effects (cost saving effects). Adequate ethical concepts (e.g. prioritisation guidelines) need to be developed in this context (McClellan et al., 2013).

Individualised procedures are not always targeted at curing a disease but can also be successful if they result in symptomatic relief and a delay in disease progression. This type of 'individualised chronification' trend can be seen in oncology and virology in particular. Good examples of this include the sequential therapies used in bronchial carcinoma or HIV, which are individually adapted whenever there is a recurrence. If the available arsenals of active substances continue to grow as expected, this strategy could in future also be used in the treatment of other conditions. Additional life years with the disease (years worth living) would thereby be made possible, but the time-consuming, expensive therapies could also become an untenable financial burden for the social safety net. Here as well, new ethical concepts are indispensable; patient organisations as well as health insurance funds and doctors and ethics committees should be included in the decision-making process. Patient organisations generally have a great deal of expertise, primary experience with the conditions and a great interest in the implementation of effective therapies.

7.8.3 Ethical considerations with regard to biobanks

Biobanks play a central role in progress in medical research and thus in Individualised Medicine (see Ch. 2.9). To protect the personal rights of the donor, both the sharing and the analysis of data should be regulated. Indeed, in Germany the provisions on research on human beings and the protection of personal data are in some regards significantly more restrictive than in the US (Langanke et al., 2011). The donor's right to informational self-determination should also be guaranteed within the scope of research projects. The GenDG does not cover analyses for research purposes (see Ch. 7.3). The general provisions of the German Federal Data Protection Act and the data protection laws of the individual federal states apply for the collection, storage and use of genetic data. One of the questions that arises in this regard is of practical significance, namely whether global consent (see also Deutscher Ethikrat, 2010) by the donor is possible or whether consent must be specific to particular research projects or research directions and limited to a definite period of time.

Biobanks are set up for the long term, meaning that often a sample donor may pass away or research objectives may change at some point; this lends support to the idea of unrestricted global consent. Furthermore, research projects are often international in scope, and information often needs to be shared rapidly without having to depend on inquiries to the donor. However, it is often unclear at the time of such consent what information will be later obtained from the sample. For this reason, a broadly worded declaration of consent should be requested. In

this context, the debate on the General Data Protection Regulation for the EU is viewed with great concern because this could result in a declaration of consent that is too narrow and thus counter-productive with regard to research.

In agreement with the German Ethics Council, the Academies are in favour of introducing a specific biobank secrecy clause according to which third parties (e.g. the government) would be prohibited from accessing the data and samples in biobanks (Deutscher Ethikrat, 2010). In many cases, completely anonymous data and samples will probably not be possible or desirable. Encoding must in individual cases allow for tracing samples back to donors so that they can revoke their consent at any time, upon request receive information about their genetic or physiological constitution or be contacted in the case of discoveries with serious medical relevance. Given these considerations, samples are generally given pseudonyms, and the relationship between the original name and the new one is retained securely in a depository so that matching samples and results is possible in an acute case. In this context, however, it should be mentioned that each genome is unique, and that it will in general probably be possible to trace published genetic data back to an individual with a certain amount of effort, especially if the genetic data are stored with other personal information (Gymrek et al., 2013).

7.8.4 Predictive tests in employment situations

Within the realm of Individualised Medicine, predictive tests could in future also lead to improvement in occupational health and safety, for example protection of individuals with allergies from exposure to allergens. Moreover, it is possible to imagine situations where an employee takes on a position with a particularly high level of responsibility (e.g. passenger airline pilots) where the employer is obliged to take extensive precautionary measures and faces potential indemnification claims, and therefore demands testing for certain risks. In addition, protection against employee deception is also a legitimate employer interest. Using genetic tests in employment situations therefore offers opportunities that could be in the interest of both parties. However, there are also justified concerns that genetic tests could lead to morally and legally unacceptable discrimination against and stigmatisation of employees. Employers have an interest in attracting employees who will perform at the highest levels possible, especially since terminations due to illness are difficult to implement. The GenDG establishes, in Section 19, that employers may not ask employees to undergo genetic tests or analyses either before or after they are taken on. The employer is also prohibited from accepting, using or requesting information from a previously performed genetic test or analysis. The same provision applies pursuant to Section 20(1) GenDG for genetic tests performed during employment-related screening tests. However, for occupational health and safety purposes, under certain circumstances an exception can be made for diagnostic genetic tests using gene product analysis (Section 20(2) GenDG).

If, in future, extensive information about phenotype and lifestyle are collected along with genetic data for Individualised Medicine purposes and incorporated into predictive statements, all of this information should be subject to the same level of protection as that which currently applies for genetic information. This would also counter the kind of 'genetic exceptionalism' upon which the GenDG is based.

7.8.5 Insurance system

Comprehensively determining risks of disease using Individualised Medicine is often thought to carry with it the danger that applicants with especially high risks could be required by private insur-

ance companies to pay higher premiums or even be classified as 'not insurable'. However, as set forth in Section 18 para 1 GenDG, insurers cannot require genetic tests or analyses to be performed before or after an insurance contract is concluded. Insurance providers are also fundamentally prohibited from accepting, using or requesting information from results or data from a previously performed genetic test or analysis. One exception to this principle, however, is provided for in relation to life, disability or long-term care insurance if an insurance sum of over €300,000 or an annual pension of over €30,000 is agreed upon (second sentence of Section 18(1) GenDG). The GenDG also makes it clear that the insured party must continue to inform the insurance provider of prior or current conditions upon request, regardless of how these already manifest conditions were diagnosed (cf. Section 18(2) GenDG).

7.9 Personal responsibility for health and obligations to take preventive measures

An increasing number of individualised preventive measures (see Ch. 5.7) within Individualised Medicine also bring up questions about the possibilities for and limits of patients' responsibility for their own health, and the extent to which incentives or sanctions may be used to exert an influence (Eberbach, 2010; Kersten, 2011). Early preventive measures in particular could reduce cost-intensive treatments and thereby contribute to decreasing the financial burden on the collective of insured individuals. In this regard, it would certainly be desirable for individuals to behave, in relation to their own health, with personal responsibility and simultaneously to the advantage of society. This leads to an increasing conflict between individual freedom and responsibility on the part of the collective of insured individuals. One the one hand, it seems ethically and legally problematic to oblige an individual to take preventive health measures, as this infringes upon that individual's authority to make decisions about what medical steps to take. Furthermore, an obligation to take preventive measures stands in contradiction to the right not to be informed (see Ch. 7.6). On the other hand, the social safety net cannot be expected to make up for every act of negligence by an individual.

This conflict has been previously discussed in the context of Section 52(1) Book Five of the German Social Code (SGB V, *Soziales Gesetzbuch V*; Eberbach, 2010), according to which insurance companies may, in the case of 'intentional acquisition of a disease', require an affected person to pay part of the cost of services and refuse to cover sick pay for the duration of the condition. If we interpret refusal to take preventive or predictive steps as 'intentional acquisition of a disease', then the person would be indirectly coerced, via the aforementioned cost-sharing or denial of sick pay, into carrying out the preventive measures. However, the fact that exercising the right not to know should as a rule not lead to disadvantaging the affected person (cf. Section 4(1) GenDG) speaks against this approach. At the same time, there are certainly already some questionable provisions involving penalties in the legal system that are applicable with regard to social insurance. For example, the first sentence of Section 62(1) SGB V stipulates that the copayment limit for insurees with chronic illnesses can be increased if those individuals do not regularly undergo appropriate tests for early detection of illnesses. With this in mind, it seems rather more acceptable for health insurance funds to increasingly use bonus systems or the option of premium reimbursements to motivate patients to take voluntary preventive measures in the future. A comparable approach is already being used with success for dental prostheses, for example.

7.10 Conclusion

Individualised Medicine has a number of ethical and legal implications, especially with regard to statistically estimated probabilities for the onset of a disease as well as for a therapeutic response and subsequently arising economic considerations. The German Gene Diagnostics Act (GenDG) governs the handling of predictive genetic information. Predictive statements can be made based on genetic tests or other methods, for example imaging procedures or epigenetic analyses. For this reason, regulations that are comparable to the GenDG will have to apply for careful handling of all patient data that allow for predictive statements. In the age of information technology, it would, for example, be relatively easy to obtain information about genetically related individuals from this data. Incorporating predictive information into medical practice is definitely a balancing act between using that information for therapy and prevention on the one hand, and maintaining anonymity in order to protect the privacy rights of third parties on the other. This set of issues needs to be discussed within society as a whole.

Predictive information can have advantages for affected individuals with regard to the prevention of disease and individually tailored therapies, but it can also be very burdensome and have serious consequences in the case of severe, untreatable diseases. For this reason, each individual is granted the right not to be informed, which can lead to conflicts in individual cases. As Individualised Medicine will in future ideally be oriented more toward individualised prevention of disease, consideration must be given to how healthy individuals can be motivated to take preventive steps without violating their autonomy and their right not to know.

As the spectrum and scope of explanation required for individualised diagnostics and therapies will increase significantly in the context of Individualised Medicine, the practical implementation of doctors being obliged to provide counselling and to educate patients will also become more difficult. Individualised Medicine will, to a certain extent, go hand-in-hand with a shift in responsibility, decision-making power and the use of available resources.

8 Economic aspects of Individualised Medicine

The growing need for care for older, often multimorbid patients, whose percentage of the total population is increasing as a result of the demographic change, is leading to an increasing financial burden on the healthcare system. Yet many of the therapies that are standard today are not demonstrating the desired therapeutic effect and/or have side effects of varying severity. With Individualised Medicine there are hopes, in addition to new opportunities for cures, of reducing or avoiding the aforementioned negative effects so that in the future the costs of therapy will be reduced or at least rise considerably less than in the past (Jakka & Rossbach, 2013). Whether or not these hopes are well-founded is the topic of current health policy debates. There are currently no authoritative figures upon which to base reliable macroeconomic analyses and prognoses regarding future cost developments. Critics imply that Individualised Medicine is just a marketing instrument to increase pharmaceutical industry profits. To be able to properly assess the potential of Individualised Medicine, prerequisites, processes, mutual dependencies and long-term consequences must be carefully evaluated by concomitant economic research. The following section sets out some important aspects that should be given particular attention in future economic analyses.

8.1 Development of therapies in the context of Individualised Medicine

Both the costs and the amount of work required for researching and developing new pharmaceuticals are high. Cost estimates vary depending on the period under consideration, underlying data and calculation technique (Morgan et al., 2011). For example, the average total costs per successfully introduced new active substance rose from US$161 million in the period from 1963 to 1975 to US$1.5 billion in the period from 1990 to 2003 (DiMasi & Grabowski, 2007). These costs currently stand at up to US$1.9 billion (Mestre-Ferrandiz et al., 2012). Reasons for the cost increases include research, development and approval costs, as well as the efficacy and safety evidence required by the regulatory authorities. In the area of research and development, the increasing incorporation of the new technologies discussed in Chapter 2 into preclinical and clinical development, as well as the continuing high failure rate of potential active substances due to a lack of efficacy contribute to the increase in costs. Whereas 30 years ago the costs of the clinical phase made up less than 50 percent of the total costs (Hansen & Chien, 1979), a more recent estimate puts the current percentage at around 70 percent (DiMasi & Grabowski, 2007; Paul et al., 2010).

Many of the most commonly used drug-based therapies are so-called 'blockbusters' with a high market volume and annual sales of more than €1 billion, but with very high development costs. The high prescription density of these rather unspecific therapies inevitably leads, because of patient individuality, to frequent therapy failure and high risks of side effects. Many pharmaceutical companies are increasingly attempting to move away

from developing and producing blockbusters, which until now has been the primary focus, to the 'niche buster' segment (Dolgin, 2010). These niche products include some of the targeted tumour therapies that are used only after the diagnostic stratification of patients and therefore on smaller patient groups. In future, cell-based therapies could increasingly fall into this category as well, although to date there are scarcely any comparative figures available for their development and production costs.

As niche busters are developed for specific characteristics of defined patient groups, their scope of application is limited, and this is also reflected in significantly higher prices. These are frequently drugs for rare disorders that affect no more than 1 out of 2,000 individuals in the EU, called orphan drugs. While sales in the billions of Euros have already been achieved with some niche busters (Dolgin, 2010), for others the annual sales are significantly under €50 million per year. To nevertheless promote the development of these medications for rare disorders, the European Union passed special legislation supporting the development of orphan drugs (EC Regulation no. 141/2000). Germany, in accordance with the EU classification criteria for orphan drugs, stipulated in Section 35a SGB V that proof of additional benefit (see Ch. 8.2) shall be considered to be a given with the EU drug approval for these products, as long as annual sales of the product do not exceed €50 million. Otherwise, the labour-intensive process of proving the additional benefit of a similar comparative therapy, if it exists, must be carried out.

With increasing stratification of patients and thus inevitably smaller, specific markets for drugs, it can be assumed that the pharmaceutical industry will increasingly fill the niche buster segment with individualised drugs and diagnostics (see also Pharmacogenomics in Ch. 6.1).

There are concerns that the special status of orphan drugs could lead to diseases being broken down into subgroups on purpose (orphanisation, or slicing) in order to then be able to take advantage of the financially attractive orphan drug status. The European Medicines Agency (see Ch. 9.6) is trying, through appropriate recommendations, to prevent this potential development (EMA/COMP/15893/2009). The increasing breakdown of diseases into molecular taxonomic subtypes will lead to many previously common diseases being classified into the category of orphan diseases. First examples of this are certain subtypes of skin (MART-1-positive malignant melanoma in HLA-A2-positive patients) and lung cancer (TERT-positive non-small-cell lung cancer in HLA-A2-positive patients).

According to estimates, linking the development of targeted therapies in oncology with genetic tests could reduce the costs of associated clinical studies by as much as two-thirds (Jakka & Rossbach, 2013). The individual development of therapies for increasingly better characterised, and therefore smaller patient groups requires innovative designs for the corresponding clinical studies that would otherwise be barely economically feasible (see also Ch. 4.3 and Ch. 4.4). It is conceivable that new drug development could be accelerated through progress in molecular disease taxonomy and that clinical studies will fail less often because of the identification of molecular target structures (Walker & Newell, 2009).

The structural changes in the pharmaceutical industry, including specialisation in individualised diagnostics and therapies, will not occur abruptly but will probably occur successively over a period of several years, giving companies the time to implement the necessary adaptive measures.

8.2 Evaluation of additional benefit and pricing of individualised therapies

In light of the constantly increasing number of available diagnostic and therapeutic procedures, thorough assessments of their benefit will in future be increasingly important for the appropriate and sustainable use of resources in the healthcare system. Only safety, quality and efficacy are tested in the approval procedure for new therapies (see Ch. 4.1). The prices of innovative individualised therapies are, because of their limited scope of application and the increased diagnostic work required, usually higher than those of the conventional standard therapy. Until a few years ago, manufacturers could still set prices in Germany themselves. In 2009, the statutory health insurance fund (SHI) (GKV, *Gesetzliche Krankenversicherung*,) found that expenditures increased by an average of 5.3 percent per patient, which corresponds to a total of €1.5 billion.[15] In order to contain this growth in expenditures, the Act on the Reform of the Market for Medicinal Products (AMNOG, *Arzneimittelmarkt-Neuordnungsgesetz*) entered into force in January 2011. The act obliges manufacturers to subject their new products to early benefit assessment by the Federal Joint Committee (G-BA, *Gemeinsamer Bundesausschuss*), which includes representatives from among doctors, hospitals and health insurance funds.

According to the Ordinance on the Benefit Assessment of Pharmaceuticals (*Verordnung über die Nutzenbewertung von Arzneimitteln*) pursuant to Section 35 SGB V, the benefit of a pharmaceutical is defined as the patient-relevant therapeutic effect, especially with regard to improving the patient's state of health, shortening disease duration, prolonging survival, reducing side effects or improving quality of life. A pharmaceutical that demonstrates additional benefit must exceed the benefit of the standard therapy. This must first be deduced and determined by the manufacturer from comparative clinical studies with customary therapies. If no additional benefit can be proven, the pharmaceutical is categorised either into a reference price group of comparable active substances, or a reimbursement amount is negotiated with the German National Association of Statutory Health Insurance Funds (*GKV-Spitzenverband*). If no agreement can be reached, then the arbitration office makes a decision. In this case, the G-BA, as a monitoring body, can additionally call for a cost-benefit assessment, which is usually prepared by the Institute for Quality and Efficiency in Healthcare (IQWiG, *Institut für Qualität und Wirtschaftlichkeit im Gesundheitssystem*). That assessment is intended to additionally determine what therapy costs will arise during use of the new medication and whether the prices of pharmaceuticals correspond to their benefit.

Such assessments will be very important both as possible 'brakes on cost' for new therapies without additional benefit and for the promotion of cost-intensive, effective individualised therapies and companion diagnostics. However, the question also arises whether the evaluation processes, which can be very time-consuming, are always suitable in this form (given the rapid developments in medicine and especially in oncology) or whether they also withhold new diagnostic procedures and new effective therapies from patients for an unnecessarily long period of time. The associated risks and potential benefit for patients must be carefully considered here.

Cost-effectiveness assesses the relationship between the costs and benefits of a medication, and is often represented

15 Cf. Information from the German Federal Health Ministry: www.bmg.bund.de/glossarbegriffe/a/das-gesetz-zur-neuordnung-des-arzneimittelmarktes-amnog.html (last accessed: 16 September 2014).

in costs per additional healthy life years (Russell, 2009). This is based on the ratio of additional costs to additional benefit. It is important to first select the right basis for comparison when calculating the additional costs. All direct and indirect costs, for example for development and production, marketing and sales, packaging and storage, as well as lost work time resulting from illness, must be included here. There are special methodological challenges involved in the economic evaluation of individualised approaches, for example with regard to assessing the consequences of false positive and false negative test results for care (Annemans et al., 2013).

8.3 Reimbursement by statutory health insurance funds (SHI) and private health insurance funds

After approving a new therapy for the SHI catalogue, the criteria for its use in healthcare are determined. These relate to the appropriate indication and to the question of which patients and above all which providers may use the new therapy. The process quality of the individualised healthcare services offered by providers (doctors in private practice and hospitals) should always be ensured via certification in accordance with the same principles as those used for conventional therapies. Use for a limited period of time by appropriate centres can certainly be permitted here.

The GKV and PKV positions on the assumption of costs can differ considerably. The GKV assumes costs only once an evidence-based decision-making basis has been established, whereas PKVs are much more willing to reimburse costs for innovative diagnostic and therapeutic approaches. For this reason, persons insured by PKVs receive a higher proportion of new medications, some of which are orphan drugs, than those insured by GKVs (Wild, 2012).

With regard to the use of individualised therapies, doctors are often uncertain about the reimbursement of costs, especially when diagnostic tests are required prior to using certain medications. Inpatient treatment is financed within the scope of the DRG (diagnosis-related group) accounting system.[16] However, often the DRGs are not adjusted quickly enough to increased costs that arise from new test procedures. In practice, this leads to a contradictory situation in which tests are not prescribed because of cost pressures, which means that an approved medication cannot be prescribed either.

Another problem is that individualised diagnostic tools that were first developed in retrospectively evaluated studies are usually not included and reimbursed in the GKVs' list of services because their benefit generally still needs to be proven in time-consuming prospective studies. However, this situation also varies by state and by insurance fund. For example, in some cases insurance covers a genetic test that can predict the likelihood that a certain type of breast cancer will recur; the test thus indirectly predicts the benefit of post-operative chemotherapy (Albain et al., 2010). Depending on the results and the validity of the test, patients may then be spared chemotherapy and the healthcare system spared the associated high treatment costs.

In addition to an increased need for differential diagnostics for more targeted patient selection, with individualised healthcare, insurers will also have to take into account a possible shift in care toward individualised disease prevention (see also Ch. 7.9).

16 Diagnosis related groups (DRGs) are the foundation of the service-oriented charging system that sets out flat rates at which general hospital services are remunerated. Since 2004, hospitals in Germany are required to charge for their services according to the DRGs.

8.4 Innovators in Individualised Medicine

Academic partners are increasingly involved in applied research for the development of pharmaceuticals and vaccines (Stevens et al., 2011), as well as many individualised procedures. Small and mid-sized enterprises (SMEs) are likewise important innovators in the area of Individualised Medicine. In recent years, an increasing number of SMEs have been founded that develop and market new diagnostic tests and testing equipment, or perform those tests based on DNA and RNA analyses and detection of proteins. For example, commercial biobank providers offer tissue samples and molecular pathological analytic techniques. Rapidly growing biotechnology companies are marketing molecular biological tests for rare hereditary diseases and are developing new diagnostic tools in collaboration with academic facilities and industrial partners. Ever more diverse diagnostic procedures are opening up additional business areas for both new and existing companies.

Research on indications for orphan drugs is made especially attractive since no evidence of additional benefit needs to be provided when developing medications for this niche indication, and companies benefit from a simplified and faster approval process (see Ch. 8.1) that reduces the development costs. While SMEs tend to develop and market products for niche indications by themselves, they seek collaborations with large pharmaceutical companies for larger, more cost-intensive indications. There is an increasing trend among established pharmaceutical firms to seek out new strategic areas of business by taking over or collaborating with SMEs and integrating them into their corporate portfolio.

8.5 Possible developments with regard to costs in individualised healthcare

Many critics of Individualised Medicine believe that it could lead to an explosion of costs in the healthcare system. The possible economic consequences of Individualised Medicine are highly complex and difficult to estimate (Hatz et al., 2014). However, this applies equally for many 'non-individualised' innovations in medicine (Bratan & Wydra, 2013) that will probably only become clear upon implementation and through long-term care and therapy optimisation studies.

Against a backdrop of increasing life expectancy for the population as a whole and the increased occurrence of chronic conditions, proponents of Individualised Medicine believe that numerous unnecessary treatments can be avoided, in particular through the increasing use of biomarkers to predict therapeutic response in patients (see Ch. 3.2). Instead of first trying out various ineffective medications, the idea is that in future patients will increasingly be able to receive the product that is effective for them right away. It is also hoped that increased use of targeted therapies with few side effects, for example in tumour therapy, will cause a shift away from cost-intensive inpatient treatments towards primarily outpatient care.

On the other hand, the costs of individualised therapies are often very high, amounting to as much as €100,000 per year or more, especially when they are based on the use of antibodies of cell-based therapeutic approaches (see Ch. 6.2.3). However, the prices of many of the new therapies are expected to fall substantially upon expiry of their corresponding patent rights. Patient stratification and the accompanying gains in efficacy can also reduce the development costs per therapy. There are several reasons for this: fewer patients in Phases II and III

of clinical development; a shorter study duration; a higher probability of success on the market; a lower failure rate; and the option of faster introduction onto the market due to shortened approval times (Blair et al., 2012).

When therapies work better, patient compliance with therapy usually increases as well. This could lead to increased demand for the pharmaceuticals, which would in turn increase the costs of health insurance funds. In addition to the actual treatment costs, however, secondary effects, such as productivity increases, travel costs, costs to the patient's family, etc., and even costs to society should also be considered.

The ongoing stratification of patients impacts costs in the area of diagnostics. The validation and qualification of new biomarkers are especially cost-intensive (see Ch. 3.4). Because treatment costs, for example for tumour treatment, already frequently amount to several tens or hundreds of thousands of Euros, associated biomarker tests generally make up only a small percentage of total treatment costs (e.g. *HER2* over-expression: €100–1000; combined test for *BRCA1* and *BRCA2*: €1000–1500; *BRAF-V600E*: approx. €100; MRI with contrast agent: €500–1000). While the potential savings on therapy easily justify the diagnostic expense in these situations, it can be very different in the case of screening tests that are required on a regular basis or of less cost-intensive therapies (Davis et al., 2009). The cost-effectiveness (see Ch. 8.2) of the tests also depends on the average percentage of patients in whom the relevant medication works (Blair et al., 2012). Although the costs of total genome sequencing are falling, the subsequent analysis requires additional specialised personnel, and the need for genetic counselling for patients will increase markedly (see Ch. 7.7). The costs of storage, analysis and management of the data from omics analyses have long since overtaken the costs of data collection (European Commission, 2013).

Many proponents of Individualised Medicine hope that fully developed prediction and prevention (see Ch. 5) will lead to a gradual transformation from the healthcare system's current, mainly reactive orientation to a preventive-proactive one (Hunter et al., 2013). According to the results of several studies in the US, however, preventive measures such as taking products to lower blood pressure or cholesterol levels, screening tests for early detection of tumours or preventive operations have so far only resulted in increasing healthcare costs (Russell, 2009). According to the principles of pharmacogenetics, however, tailored selection of preventive measures could markedly increase their cost-effectiveness (Russell, 2009). Procedures such as cancer screening tests are already being conducted much more frequently than before in individuals at high risk due to hereditary factors (see Ch. 5.7.1). In the future, low-risk individuals in whom certain types of monitoring can take place less frequently or be entirely dispensed with should also be identified in a targeted way. For example, new concepts (Onega et al., 2014) and approaches to evaluation (Vilaprinyo et al., 2014) have been developed for the broadly used breast cancer screening techniques to select optimal, individualised strategies.

Currently, there are not many reliable biomarkers of risk and preventive measures available for most common chronic diseases (see Ch. 5.7). However, it is very likely that additional studies in molecularly defined groups of individuals, in particular, will develop our understanding of the causes of diseases like cardiovascular conditions, diabetes or neurodegenerative disorders. It is also likely that the options for early individualised interventions will then increase, although it is not yet clear what impact this will have on healthcare costs.

8.6 Conclusion

There are hopes that individualised diagnostics and therapy will increase the chances of being cured. However, because of the smaller patient target groups, they are markedly more expensive than treatment methods that are not target group-specific. Nevertheless, there is a clear trend in the market toward the development of therapies and diagnostics for smaller, defined markets. In order to promote the development of therapies for rare diseases, exception-based regulations for benefit assessment and simplified reimbursement modalities are appropriate. Care should be taken, however, to ensure that the therapies with the greatest benefit for patients can become established over the long term and that ineffective therapies are avoided.

The growing need for care for older, often multimorbid patients in particular is leading to an increasing financial burden on the healthcare system. This trend could be countered by targeted use of individualised therapeutic interventions, reduction of side effects, shortened hospital stays and a partial shift of therapies into outpatient care. In the future, insurers will have to take into account an increased need for differential diagnostics in order to select patients in a more targeted fashion, as well as a possible shift in care toward individualised disease prevention. In sum, the long-term cost effects of Individualised Medicine within the healthcare system are ambiguous and highly complex. There are still no authoritative figures upon which to base reliable macroeconomic assessment. The impact of Individualised Medicine on costs will only become clearer after several years of its implementation in practice and with accompanying economic research, such as care and therapy optimisation studies.

9 Framework conditions for Individualised Medicine

Individualised Medicine is an interdisciplinary collaborative project with which available resources are used more efficiently than in the past and which requires the close collaboration of patients, medical providers, scientists, industry, insurers and governmental institutions (Mirnezami et al., 2012). Figure 4 summarises the complex framework conditions and key actors required to implement Individualised Medicine that are described in Chapter 9.

9.1 Research funding and structures in Germany

In Germany, the important federal actors in the funding of scientific projects related to Individualised Medicine are the Federal Education and Research Ministry (BMBF, *Bundesministerium für Bildung und Forschung*), the Federal Health Ministry (BMG, *Bundesministerium für Gesundheit*) and the German Research Foundation (DFG, *Deutsche Forschungsgemeinschaft*). The BMBF has initiated a number of funding measures since 1995 to help pave the way for Individualised Medicine. With its action plan titled 'Individualised Medicine: A New Path in Research and Healthcare', the BMBF has for the first time designated an entire line of funding to the topic of Individualised Medicine; €360 million has been made available until 2016 to fund projects along the entire innovation chain, from basic research to clinical testing. An initial goal is to accelerate the development of innovative procedures and products for biomarker-based stratification.[17] Another goal is to support collaboration among scientists, clinics and private enterprise. There has already been some experience with this in the context of the excellence initiative of clinical studies and leading-edge clusters. The support measures set out in the action plan also include dismantling hurdles between the individual phases of the innovation chain, the provision and validation of promising biomarkers in clinical studies, the development of systems biology, the preparation of plans for adapting clinical studies to Individualised Medicine and accompanying research on its ethical, legal and economic aspects. The content of the funding guidelines differentiates between diagnosis and therapy.

The German Epigenome Programme (DEEP, *Deutsches Epigenom Programm*), which is receiving funding in the amount of €20 million from 2012 to 2017, has the goal of preparing and biomedically analysing over 70 human and mouse reference epigenomes. The program's focus is on metabolic diseases and infections. The total amount of BMBF funding available through its framework programme Health Research (*Gesundheitsforschung*) is €5.5 billion from 2011 to 2014.[18] Another funding measure of the action plan is the research and funding concept called *e:Med*, which targets the system-oriented research of diseases by connecting life sciences and information sciences.[19] The goal of the GANI_MED

17 Cf. Information from the BMBF: www.bmbf.de/foerderungen/21804.php (last accessed: 16 September 2014).

18 Cf. Information from the BMBF: www.bmbf.de/de/gesundheitsforschung.php (last accessed: 16 September 2014).

19 See the BMBF action plan "Individualised Medicine: A New Path in Research and Healthcare" (available at: www.bmbf.de/pub/BMBF_Aktionsplan_IndiMed.pdf; last accessed: 16 September 2014).

project of the Greifswald University Hospital, funded with €14 million, is to create and test the prerequisites for integrating Individualised Medicine into clinical care. This involves, for example, ongoing systematic development of innovative analytic techniques that will provide insights into individual differences in the genesis and treatment of important diseases, as well as the targeted expansion of the necessary infrastructure (e.g. biobanks and bioinformatics). Furthermore, promising individualisation concepts are being tested for their suitability for the treatment of patients.

Among the goals of the BMBF-funded technology and methods platform for networked medical research (TMF, *Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V.*) are improving quality, organisation and collaboration in medical research, including quality assurance and quality management in clinical studies and biobanks. Further objectives include promoting the development of high-performance IT infrastructures and their integration within cross-institutional, networked structures.

The DFG has made topics related to Individualised Medicine a research priority[20] and supports them in almost all its funding avenues (graduate schools, special research areas, e.g. SFB 656 – *Molecular Cardiovascular Imaging*), clinical research groups (e.g. biological basis of individual tumour response for patients with rectal cancer), individual funding and large equipment initiatives (e.g. imaging mass spectroscopy, high-throughput sequencing). The DFG's support programme *Algorithms for Big Data* (SPP1736) and the BMBF's call for proposals *i:DSem* (*Integrative Data Semantics in Systems Medicine*) could contribute to the further development of big data management and thereby possibly also further develop the analysis of data collected in the context of Individualised Medicine.

In addition to the BMBF and the DFG, various federal states in Germany are also, on their own initiative, supporting state-specific steps with content related to Individualised Medicine as part of the federal government's cluster strategy. Support is being provided for different topics within the networks and clusters that have developed in the individual states.[21] For example, North Rhine-Westphalia is supporting Individualised Medicine research within the biotechnology and medical technology cluster that focuses on topics such as medical diagnostics, gene therapy and cardiovascular disease. In the state of Mecklenburg-Vorpommern, *BioCon Valley®* is creating networks to bring together the expertise of enterprises and academic institutions in the areas of medicine, medical technology and pharmacology. An interdisciplinary convention on Individualised Medicine (*PerMediCon*) was initiated in cooperation with Koelnmesse AG 2010 as part of the 'Biotechnology' cluster; this event is also meant to serve as a platform for dialogue and networking for all actors involved with Individualised Medicine. Moreover, the Bavarian Ministry of Economic Affairs and Media, Energy and Technology is supporting the *BayBIO* research and development project on biotechnology and gene technology.

The institutionally funded research facilities of the four large German research organisations and universities are also driving the development of Individualised Medicine. For example, the Helmholtz Association has set a goal of expanding its Individualised Medicine research field into a strategic interdisciplinary task for its individual centres within the con-

20 Information of the DFG (expert discussion on research funding on 21 October 2011, Berlin).

21 Further information at: www.clusterplattform.at/fileadmin/user_upload/clusterbibliothek/604_uberblick-netzwerk-und-clusteraktivitaten-der-bundeslander_in_deutschland_-_P5.pdf (last accessed: 16 September 2014).

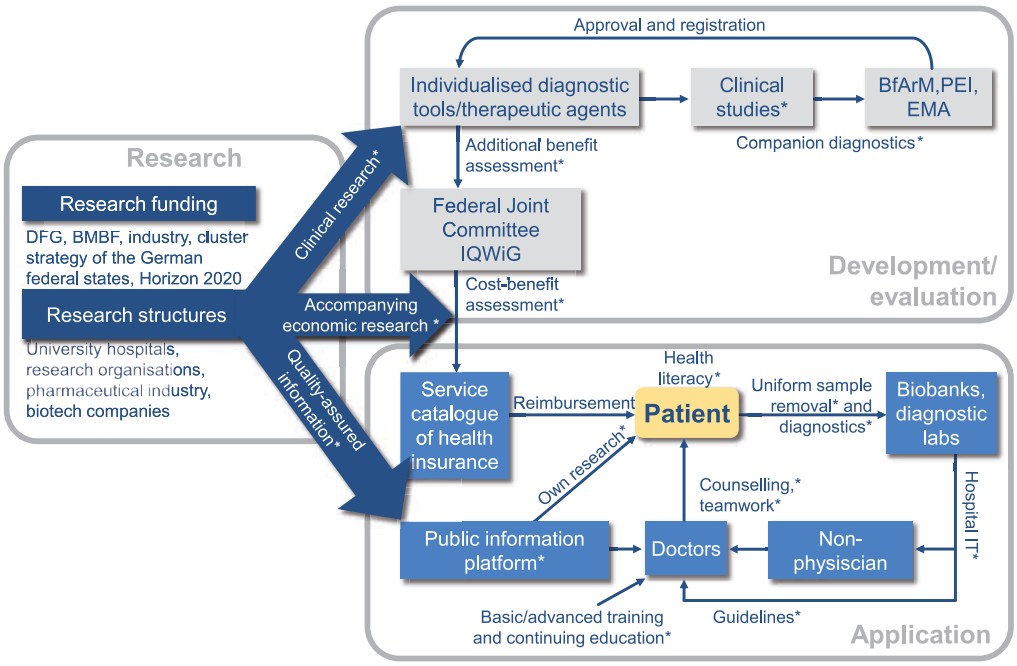

Figure 4. Framework conditions and key players in the implementation of Individualised Medicine. The areas marked with an asterisk will play a particularly important role in Individualised Medicine (further explanations in the text).

text of the Association's programme-oriented funding. Further, the Fraunhofer Future Foundation funds the *RIBOLUTION* research group, which consists of five Fraunhofer institutes in cooperation with several universities; this project has the goal of identifying disease-relevant, non-protein-coding RNAs (ncRNAs) by means of an automated, genome-wide screening programme and validating their potential as biomarkers for diagnostic use. Moreover, the Borstel Research Centre of the Leibniz Association seeks to contribute to new individualised therapeutic options for lung disease by setting up a new biobank. Lastly, basic research relevant to Individualised Medicine on the causes and mechanisms of depression, tumour disorders and diabetes mellitus is being pursued at the Max Planck Society's biology and medicine institutes.

Aspects of Individualised Medicine are among the cross-disciplinary topics that are being addressed by the German Health Research Centres (DZG, *Deutsche Zentren der Gesundheitsforschung*), which have been operating since 2009. The four most recently founded DZGs are distributed across 41 locations with over 100 universities, university hospitals and non-university research facilities, including several Helmholtz Association centres.[22] For example, at the German Centre for Lung Research (DZL, *Deutsches Zentrum für Lungenforschung*), new gene candidates are to be identified for targeted therapies using what is called deep phenotyping. Another example is the German Cancer Consortium (DKTK, *Deutsches Konsortium für Translationale Krebsforschung*), which is investigating topics like the molecular causes of disturbed signalling pathways in various types of cancer and the targeted therapy thereof.

The National Cohort (*Nationale Kohorte*) network serves as an interface between university-based and institutional research. The study, which started in 2014 and is scheduled to run for about 20 years, will investigate the influence of genetic factors, environment, social conditions and lifestyle on the genesis of common chronic conditions in 200,000

22 Cf. Information from the BMBF: www.bmbf.de/de/gesundheitszentren.php (last accessed: 16 September 2014).

volunteers aged 20 to 69. It is hoped that the expected findings will contribute to individualised disease prevention. Another population-based project is the *SHIP* study (*Study of Health in Pomerania*), initiated in 1997, in which comprehensive longitudinal data from several thousand test persons from the West Pomerania region are being collected in order to investigate the complex interrelationships between risk factors, subclinical abnormalities and manifest disorders. The research formats include interviews, lab tests, blood pressure measurements, dental, skin, cardiometabolic and ultrasound tests, whole-body MRIs, as well as the storage of samples and data in a biobank.

9.2 European funding programmes and structures

In the European Union, Individualised Medicine is also acknowledged to be an important development and is being funded at several levels. From 2007 to 2012, the EU Framework Programme for Research Cooperation (FP7), made an estimated €1 billion available for research projects to further develop Individualised Medicine (European Commission, 2013). Further, in 2011 the European Commission held a European Perspectives in Personalised Medicine Conference in Brussels, at which 450 representatives from the realms of politics, academic and industry research, patient associations and clinics identified and prioritised the measures necessary to further develop Individualised Medicine. Examples of project funding related to Individualised Medicine in the FP7 are the French R&D project *ADNA*, which was approved in 2008 and received €90 million, and the PHGEN I and II (Public Health Genomics European Network) project. In another project of the FP7, P-Medicine, 19 partners from nine EU countries are working together to obtain new knowledge on the topic of Individualised Medicine, and to overcome difficulties in clinical research.

The European Blueprint project launched in October 2011 is receiving funding of €30 million over five years. The project is dedicated exclusively to decoding the epigenomes of blood cells, and investigating how epigenomes develop in relation to disease, aging and changing environments and how they react to drug treatment.

The EU's new framework programme for research and innovation, Horizon 2020, is the follow-up programme of FP7. From 2014 to 2020, a research budget of around €80 billion is available, of which around €13 billion are earmarked for life sciences topics.[23] The interdisciplinary topic of Individualised Medicine extends into all four parts of the Horizon 2020 programme. Intentions are to make the application and administrative procedures for Horizon 2020 significantly simpler than they were for the predecessor programme (FP7).

In addition, a number of information and discussion platforms have been founded at the European level, and are designed to increase support for Individualised Medicine in Europe. These include the non-profit organisation European Personalised Medicine Association (EPEMED), which places a special focus on the development and use of diagnostic tools. Other platforms include the European Association for Predictive, Preventive & Personalised Medicine, which sees itself as the European coordinator in the area of Individualised Medicine, and the European Alliance for Personalised Medicine (EAPM), founded in 2012, which has patient representatives, health experts and organisations working to promote individualised patient care.

The Innovative Medicines Initiative (IMI), the largest European public-private initiative for the development of better

23 Cf. www.nks-lebenswissenschaften.de (last accessed: 16 September 2014).

and safer pharmaceuticals, has set itself the goal of paving the way for the establishment of Individualised Medicine and thereby accelerating Individualised Medicine's further development. The follow-up initiative IMI2 has a total budget of €3.3 billion, which is provided in approximately equal parts by the EU within the scope of Horizon 2020 and the European Federation of Pharmaceutical Industries & Associations (EFPIA).

9.3 Significance of clinical research for the development and evaluation of individualised therapeutic techniques: Translational medicine

The success of Individualised Medicine depends in part on how quickly research results can be transferred into clinical practice (translational medicine). Because of the geographic proximity of research and practice at university hospitals, structurally the entire range of topics involved in this process can, at the present time, be most efficiently implemented in that setting. Translational medicine requires close interactions between groups with a scientific track record and scientifically trained doctors working in healthcare. One of the most common problems in translational medicine is the lack of financial support from appropriate public and private funders, especially in the transitional phase between preclinical and clinical research. This represents a critical period in the development of new therapies, during which there are already promising results from *in vitro* or animal studies, but there is, because of the high level of financial risk, not yet any funding for first clinical studies that would provide definitive proof of efficacy. In order to be able to investigate innovative therapies, financial tools should be created to make it easier to bridge this critical phase. Funds for this could be acquired, for example, from foundations and national funding programmes. Translational efforts in biomarker research, like the international network Biobanking & Biomolecular Resources Research Infrastructure (BBMRI), also merit support. As part of the funding process, cooperation between pharmaceutical and academic research efforts should also be strengthened, with special attention paid to safeguarding the independence of the latter.

The ever-more-complex questions addressed by clinical research, especially in Individualised Medicine, place such high demands on the implementation of clinical trials that in future it may only be possible for large research organisations and industrial enterprises to fund such studies. As a result, research may soon be concentrated in a very small number of organisations. A concentration of clinical studies on just a few facilities and funders could lead to a disastrous knowledge bottleneck at a decisive point in translational medicine. In order to counter this trend, the bureaucratic requirements for conducting clinical research, which unintentionally further such a concentration, should be lessened.

Once therapies have been approved, wide-ranging and sometimes financial interests often determine how those treatments will be further evaluated. These considerations currently apply especially to the growing number of targeted, often very expensive therapeutic procedures in oncology (see also Ch. 6.2). In many cases, however, it remains unclear in the final analysis whether the newly approved medications really improve prognosis or quality of life, or whether the area of indication, that is the target patient group, should be defined more precisely and thereby be decreased in size. This also applies to orphan drugs, for which no proof of additional benefit is required due to their special status (see also Ch. 8.1). It is therefore urgent that a strategy be devel-

oped to evaluate new individualised diagnostics and therapies in close proximity to the sites of healthcare after they have been approved. Here, health insurance funds should also play a more active role, for example by introducing new imaging and omics technologies into routine clinical practice in registry studies.

9.4 New requirements for training and qualification of healthcare personnel

The willingness of doctors to use new diagnostic and therapeutic techniques will be of decisive importance for implementing Individualised Medicine in the healthcare system. For this reason, framework conditions need to be created in order to convey the necessary knowledge, especially in the area of genotype-phenotype correlation and associated molecular analytic techniques, to doctors and other healthcare personnel by means of training and further education, as well as regular ongoing professional education. This will, in part, require entirely new approaches to teaching. First, precise clarification will be needed regarding what specialised knowledge and skills (including psychosocial and communicative skills) are essential for understanding and using individualised procedures. At the same time, relevant reform of the licensing process is important, since Individualised Medicine is not yet officially included in any medical training curricula in European countries, and an increasing number of self-proclaimed Individualised Medicine experts have been springing up recently. Strengthening new, highly-specialised medical professional groups with expanded knowledge in the areas of molecular biology and bioinformatics is also recommended. The increasingly refined classification of disorders into molecular taxonomic groups will trigger new developments in the medical profession and its professional associations.

In Germany, the sustainable expansion of IT infrastructure and funding for training bioinformatics specialists has been neglected in recent years. To deal with the flood of information available, doctors need tools to simplify their treatment-related decision-making, for example evidence-based guidelines and IT-based decision-making aids that are continuously updated with new data. These will be increasingly important for Individualised Medicine in the future. As mentioned in Chapter 7.7, due to the need for interdisciplinary professional expertise there will very likely be an increasing division of labour among doctors, molecular biologists, bioinformatics scientists and engineers in the field of Individualised Medicine. The latter groups should also be trained in the fundamentals of human medicine.

9.5 Care structures for individualised healthcare

The provision of general medical care is ensured by means of outpatient (e.g. doctors in private practice, pharmacies, nursing care services) and inpatient (e.g. hospitals, rehabilitation clinics) care structures. The prerequisites and consequences for the healthcare system during the transition to a system based primarily on Individualised Medicine are matters of partially controversial debate that still require much clarification. These are discussed only peripherally within the scope of this study.

9.5.1 The role of the informed patient

Both the accessibility of institutions providing care and the health literacy of all parties involved play a decisive role for the acceptance and integration of Individualised Medicine into healthcare (Berkman et al., 2011). The multi-layered term ‘health literacy’ refers to the individual’s ability to make decisions that have a positive impact on health. Health literacy is

heavily dependent on the individual's level of education and is a decisive factor in questions relating to just, non-discriminatory access routes to Individualised Medicine (Berkman et al., 2011). Health literacy also influences an individual's personal responsibility for their health (see Ch. 7.9) and their sustained personal motivation to take preventive and therapeutic steps, as well as responsible behaviour with regard to the health of third parties (Nutbeam, 2000).

It can be assumed that the doctor-patient relationship will also undergo further transformation within the realm of Individualised Medicine. This relationship has long been characterised by a certain amount of paternalism, meaning that the doctors informed patients about facts that they considered relevant and decided on their own what treatment was most suitable for the patients. This has now developed into a relationship based more on the provision of information, or a partnership, in which patients and doctors make diagnostic and therapeutic decisions together based on information that is usually very complex. A self-determined decision by a competent, responsible patient (see also Ch. 7.5) is, however, only possible if that patient has access to high-quality, neutral information. This constitutes a serious challenge for Individualised Medicine, since doctors are already hard-pressed to master the specialised knowledge needed in order to thoroughly explain all relevant disease-related circumstances and therapeutic options and thereby provide patients with adequate counselling. Moreover, patients with tumour diseases in particular are already increasingly being treated by teams of professionals at large facilities. More value needs to be placed on ensuring that the doctor who is the patient's main contact person is able to convey the interdisciplinary aspects of treatment to the patient in a comprehensible way. Furthermore, patients are increasingly educating themselves via the numerous internet portals set up by various interest groups, and sharing their experiences with each other in support groups and social networks. It is therefore important that quality-assured, comprehensible information platforms are available that both patients and doctors can access freely in order to obtain additional information.[24] The information service of the German Cancer Research Center is a good example of this. For several years already, some health insurance funds have also been offering free patient counselling services from specialised doctors by phone.

9.5.2 Managing new complex clinical processes

Adapting organisational processes to the requirements of Individualised Medicine will also be necessary in the area of inpatient care. This includes, for example, coordinated collaboration among different specialised disciplines. Already in 2002, the German Federal Ministry of Health and Social Security (*Bundesministerium für Gesundheit und Soziale Sicherung*, now called *Bundesministerium für Gesundheit*) recommended structured treatment programmes (disease-management programmes) to improve the processes and quality of care for chronically ill patients (type II diabetes mellitus and breast cancer); these could be expanded by introducing individualised procedures into medical practice. In oncology, for example, patient treatment is increasingly being shifted to centres or networks that are jointly operated by hospitals and doctors in private practice. Given the enormous amounts of data that are generated in the context of individualised diagnostic and therapeutic processes, existing databases need to be expanded and new databases created. Access to such databases is subject to ethical and legal restrictions like those listed in Chapter 7.3.

24 This topic is addressed extensively in Nuffield Council on Bioethics (2010).

One important guiding element in the German healthcare system is the Law on Improvement of Care Structures in Statutory Health Insurance (GKV-VStG, *Gesetz zur Verbesserung der Versorgungsstrukturen in der gesetzlichen Krankenversicherung*), which entered into force in 2012 and is intended to ensure needs-based and comprehensive medical care. The system of interlocking outpatient and inpatient care structures and the creation of quick and effective access to medical innovations that this law seeks to gradually create could help accelerate the implementation of individualised processes into medical practice. Establishing efficient care structures for Individualised Medicine also depends largely on the willingness of the health insurance funds. Healthcare services research funded by the BMBF, BMG and GKV national associations plays a central role here. This branch of research investigates the efficacy, use and risks of new therapies in clinical practice and also incorporates economic aspects.

9.5.3 Standardisation of the processes of recording anamnesis and phenotype

The precise, reproducible and cost-effective collection of (family) anamnesis and patient characteristics (clinical phenotyping) poses a central problem for the implementation of Individualised Medicine into routine clinical practice. The latter can involve standard parameters like weight or blood pressure that are collected daily using simple technology or special analyses (e.g. tumour size using an MRI). Quality and reliability in the process of recording anamnesis and clinical parameters are important prerequisites for the entire individualised treatment process. However, even simple parameters are currently recorded in an imprecise manner and are useful primarily for purposes of orientation. For example, in order to measure blood pressure precisely, several consecutive measurements are necessary after a defined period of rest. For cost-related and organisational reasons, this process is currently very hard to implement comprehensively.

In order to deal with this problem, parameters recorded within the context of regular clinical operations can be subsequently tested for validity using appropriate statistical procedures. In this way, data from digital patient records can be used directly (Denny et al., 2013). Alternatively, high-quality clinical phenotypes can be recorded for selected patients and then used without further processing (Lieb et al., 2012). The standardisation of clinical phenotyping is problematic and has so far been achieved only to a limited degree. For example, quantitative findings from imaging procedures often depend on the technique used and are also associated with a large subjective component on the part of the evaluating doctor. Such findings therefore need to be confirmed by several specialised doctors. This problem can only be circumvented by certifying examiners and following up on the testing with ongoing quality controls using standardised test objects. Similar considerations apply when taking anamneses as well. Uniform, reliable recording is essential here. This information also makes up a significant part of the value of biological samples in biobanks (see Ch. 2.9).

Expanding hospital information technology equipment is also urgently needed so that complex patient information can be linked in a digital patient record uniformly and made accessible without barriers to the treating doctors. Developing the evaluation algorithms needed for this is still in the early stages (see Ch. 2.10.1). In international comparison, Germany is behind in the realm of hospital information technology, because IT solutions in hospitals are, if they exist at all, usually heterogeneous. Because of the different ways in which hospitals are funded in the various German federal

states, there are still significant shortcomings, even in some university hospitals, that can only be remedied by means of targeted investments. Quality control and standardisation of patient data should be pursued so that data can be shared between hospitals and doctors in private practice. This can help prevent unnecessary duplicate exams and medication errors, for example. However, the important question also arises of who will ultimately be legally and financially responsible for digital patient information in the field of Individualised Medicine. Ensuring data protection without generating significant barriers to medical research is also an important task.

9.6 Regulatory aspects

In Germany, the Paul Ehrlich Institute (PEI) is responsible for the approval and clearance of biomedical pharmaceuticals (e.g. vaccines, cell and gene therapeutic agents), the authorisation of clinical studies on the pharmaceuticals it oversees, and it also conducts its own research in these areas. The Federal Institute for Drugs and Medical Devices (BfArM, *Bundesinstitut für Arzneimittel und Medizinprodukte*) is responsible for the approval of all other pharmaceuticals, for recording and assessing the risks of medical devices, and for monitoring commerce in narcotics and basic materials. The top priority for both federal authorities is to increase pharmaceutical safety and thus ultimately patient safety.

Industry views the long processing times as a huge obstacle, especially for the authorisation of clinical research projects that fall, due to a lack of clear boundaries, into the regulatory purview of the x-ray and radiation protection ordinances, and thus the area of responsibility of the Federal Office of Radiation Protection (*Bundesamt für Strahlenschutz* – BfS; vfa & BPI, 2011). This is due primarily to the fact that there are no deadlines for the authorisation of studies by the BfS. This often causes significant delays at the beginning of clinical studies, meaning that Germany cannot participate in many international studies because of time lags. Increasingly, individualised approaches also fall into this category. It should be noted that patient safety can also be jeopardised by delays when new diagnostics and medications are approved only after a number of years, with patients suffering significant disadvantages in the meantime.

The European Medicines Agency (EMA) is responsible for granting Europe-wide authorisation to bring pharmaceuticals to market (centralised authorisation procedure). Approving all pharmaceuticals manufactured using biotechnological techniques as well as all medications for the treatment of HIV, tumours, diabetes, neurodegenerative disorders and rare disorders (orphan drugs) must occur via this centralised authorisation procedure. Applications for centralised authorisation of other pharmaceuticals that represent therapeutic, scientific or technical innovations can also be scientifically evaluated and authorised by the EMA.

Tandem development of new pharmaceuticals and their companion diagnostics often makes a great deal of sense in the context of Individualised Medicine, but the still widespread practice of separately handling drugs and medical devices for use in laboratory testing of samples that come from the body (in-vitro diagnostics) presents an obstacle to such tandem development. The EMA and the US FDA are both increasingly influencing the development and validation of biomarkers, and there is demand for simplified joint approval of diagnostic tools and corresponding therapeutic agents within a single process. This step is likely to be of decisive benefit to patients.

9.7 Conclusion

Individualised Medicine requires extensive structural adaptations in the realms of teaching, research and care, which will require substantial financing. Current German and EU-wide research programmes are already setting the course for Individualised Medicine. Structurally, the process of transferring research results into clinical practice can currently be implemented most efficiently, across its entire range of subject areas, at university hospitals. Research funding programmes should bear this fact in mind. Precise and uniform collection of information regarding anamnesis and clinical phenotype as well as well-developed, networked hospital information systems are among the structural prerequisites for Individualised Medicine. Corresponding teaching concepts, guidelines and information technology should be used to increase the willingness of all healthcare professionals to use new individualised techniques.

The quality, reliability and timely availability of new test procedures are of decisive importance for the development and application of individualised therapies. Joint development and approval of individualised therapeutic agents and companion diagnostics can make a significant contribution to therapeutic success and to the avoidance of ineffective therapies. Health insurance funds should develop harmonised approval processes and reimbursement modalities to promote companion diagnostics.

Independent of economic interests, evaluating individualised diagnostics and therapies after their approval is important to assess cost-benefit ratios under everyday conditions. In the long term, health insurance funds as well as patients will benefit from evidence for innovative techniques provided by independent studies. For this reason, patient organisations, policymakers, health insurance funds and doctors should work together to ensure that sufficient funds continue to be available for the independent production of such evidence through healthcare services research and therapy optimisation studies.

10 Appendix

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10.2 Glossary

Aetiology:
The cause of a disease or totality of causes of a disease.

Allele:
A differing or identical copy of a defined section of DNA. This may be a gene or a functionally irrelevant DNA sequence. Because the set of human chromosome is diploid, there are two alleles at every autosomal locus.

Amino acids:
A class of chemical compounds (amino carbonic acids) that are the building blocks of proteins.

Anamnesis (medical history):
Systematic questioning of patients about their entire disease-related history; intended to help reach a diagnosis.

Antigens:
Chemically characterised groupings (determinants) of a substance that the organism recognises as foreign and that are capable of triggering an immune response.

Antibodies (immunoglobulins):
Proteins that are formed by white blood cells (B-lymphocytes and plasma cells) as a reaction to an antigen. Antibodies are also used in diagnosis and research for the specific detection of components of tissues and body fluids (e.g. immunohistochemistry or immunocytochemistry).

Association:
In genetics, statistical linking of a genetic variant with a multifactorially-caused characteristic.

Atherosclerosis:
Slowly progressing pathological changes in blood vessels in which the vessel walls thicken, lose elasticity and the blood vessels become increasingly narrowed. This results in circulatory disorders (e.g. heart failure, arrhythmias or cardiac infarction).

Autosome:
Any of the 22 non-sex-determining chromosomes (see gonosomes).

Autosomal:
Heredity process in which the affected gene is on an autosome.

Biobank:
Organised collection of biological samples (e.g. body fluids or tissue samples) with associated data that is administered in databases for research, diagnostic and therapeutic purposes.

Biomarker:
Objective indicator (e.g. nucleotide sequence, protein or metabolite, morphological parameter) used to describe normal or disease-caused biological processes.

Carcinoma:
Malignant tumour arising from cells with an epithelial phenotype (e.g. skin or mucosal cells). Carcinomas make up the majority of all malignant tumours.

Cell-based therapy (cell therapy):
Therapeutic approach in which cells are introduced into the patient's body when treating a disease (e.g. immune cells or stem cells).

Classifier:
A general, model-based decision-making rule that suggests a clinical approach for a patient based on data (e.g. from measurement of a biomarker).

Codon:
Sequence of three nucleotides that contain the information for an amino acid or a translation signal (start/stop).

Cohort:
Systematically assembled group of healthy individuals or patients that are tested at regular intervals for the expression of a phenotype or disease, possibly depending on external influences.

Companion diagnostic:
Diagnostic test intended to show whether the planned therapy can lead to success in a specific situation. These therapy-accompanying tests are often developed together with a medication or for an existing therapy.

Constitutional genome:
See genome.

Diploidy:
Double set of chromosomes (23 pairs in humans), normal genetic state of body cells.

DNA (deoxyribonucleic acid):
The carrier of the genetic information of living organisms. The long chain molecules are organised in the form of double helices constructed of four different components (nucleotides) in a specific sequence. Every nucleotide contains, in addition to a phosphate and sugar remnant, one of four organic bases (adenine, thymine, guanine and cytosine).

Dominant:
Phenotypic expression of a (mutated) allele such that the phenotype is expressed in both homozygosity (having one allele) and heterozygosity (having two alleles; see recessive).

Enzyme:
Biomolecule, generally a protein, that can catalyse one or more biochemical reactions (i.e., accelerate their reaction speed). Enzymes play decisive roles in metabolic processes.

Epigenetics:
An area of science that investigates the mechanisms of the phenotypic implementation of cell properties that are not determined in the DNA sequence onto daughter cells.

Epigenome:
Overall programming of the genome. Guides the differential gene expression in different cell types. The epigenome is determined by the genetically established differentiation of stem cells as well as by environmental influences.

Evidence-based medicine:
Medicine based on empirical proof.

Exome:
Totality of expressed protein-coding gene sequences.

Exon:
Section of a eukaryotic gene that is present in the mature RNA after splicing and is transcribed into a protein or built into an RNA (see intron, splicing).

Exposome:
Totality of all non-genetic endogenous and exogenous influences to which an individual is exposed over the course of a lifetime.

Expression:
Type or degree of manifestation of a gene (see gene expression).

Gene:
Generally defined as the smallest unit of biological genetic information that codes for a gene product (RNA or protein). The human genome contains 21,000–23,000 protein-coding genes. They make up only about 1.5 percent of the total sequence.

Gene panel:
Systematic sequencing of all genes in which mutations could be responsible for a genetically heterogeneous disease (for example, pigmentary retinopathy).

Genetic code:
System for coding amino acids by means of a sequence of three nucleotides in each case (triplets).

Genetic marker:
Polymorphism for which the precise chromosomal position is known and the different alleles of which occur so often that they are suitable for population investigations.

Gene expression:
Process in which the information of a gene is translated into a product. The gene product can be an RNA or a protein.

Genome (genetic material):
Totality of an organism's inheritable information; generally present in all of that organism's cells (constitutional genome).

Genome-wide association study (GWAS):
Search process using large collectives of affected individuals and controls to identify DNA variants in the entire genome that can be associated with a multifactorially determined phenotype or a multifactorial disease based on statistical analyses.

Genotype:
Combination of two of the same or different alleles at one gene locus.

Gonosome:
X and Y sex chromosomes (see autosome).

Haploidy:
Single set of chromosomes (23 different chromosomes), normal genetic state of germ cells.

Heterozygosity:
Occurrence of two different alleles at one gene locus.

Histones:
Strongly basic proteins that are closely associated with the DNA in the cell nucleus and help package the genetic material. Histones often play a role in differential gene expression.

Homozygosity:
Identical alleles at one gene locus.

Hybridisation:
Molecular genetic technique in which labelled complementary individual strands of DNA or RNA (probes) are placed together using hydrogen bonds between complementary organic bases.

Indication:
Reason or circumstance for carrying out a specific medical measure that makes sense after weighing the potential benefit and risk to the patient, taking their overall situation into account.

In-situ hybridisation:
Molecular biological method for specific detection of a particular DNA or RNA in tissues or cells. A synthetically manufactured DNA or RNA is used as a specific probe (see hybridisation).

Intron (intervening sequence):
Section of a gene inserted between exons that contains no gene-product-coding information. This nucleotide sequence is transcribed but is cut out before translation of the gene.

In-vitro diagnostic tool:
A medical device for medical laboratory testing of samples from the body.

Licensing:
Qualification to practice the profession of medicine, granted by the state authority with jurisdiction upon request. The prerequisite is a successfully completed course of studies in medicine as per the regulation governing licensing for doctors, which is set forth in the form of a law.

Mendel's rules:
Rules for the inheritance of simply (i.e. monogenically) determined characteristics, named after their inventor Gregor Mendel.

Metabolism:
Totality of metabolic processes in the organism. The interim and final products of metabolism are called metabolites. They depend on uptake, enzymatic transformations or release to the environment by the organism.

Methylation:
Transfer of methyl groups. Usually in reference to methylation of the DNA building block cytosine or individual amino acids of histones in the context of epigenetic inactivation of a gene.

Microarray:
Technique for detecting an often very high number of genetic variants (DNA or RNA) using the principle of hybridisation.

Microbiome:
Totality of the microorganisms colonising a human being or one anatomical niche (oral cavity, skin, intestine, etc.).

Microdeletion:
Loss of a small piece in a chromosome.

Monogenic disorder:
Disorder caused by mutation of a single gene.

Morphology:
In biology, the science of the form and construction of humans, animals and plants.

Multifactorial disorder:
Phenotype brought about by the interaction of genetic factors and environmental influences.

Multimorbidity:
The simultaneous presence of several disorders in one individual.

Mutation:
Alteration of the DNA sequence in the genome of a cell or in all cells of an individual, either on the DNA level (e.g. base switching, insertion, deletion, rearrangement, changed number of copies) or on the chromosomal level (e.g. numerical chromosomal aberration such as free trisomy or structural chromosomal aberration such as translocation trisomy).

Next-generation DNA sequencing:
High-throughput technique in which thousands to millions of DNA fragments are decoded concomitantly.

Nucleotide:
DNA building block that contains, in addition to a phosphate and sugar remnant, one of four organic bases (adenine, thymine, guanine and cytosine; see DNA).

Omics technologies:
Bioanalytical high-throughput technique to determine the structure of DNA, RNA, proteins, carbohydrates, lipids, metabolic products or the identity of microorganisms.

Oncogene:
Mutated or deregulated allele of a normal gene (proto-oncogene) that induces tumour growth via its gene product (protein). Usually dominantly active (see proto-oncogene).

Orphan disease:
Rare, usually genetically caused disorder with a cumulative prevalence (frequency in the general population) of less than 1 per 2000 individuals.

Orphan drug:
Drug for a rare disorder.

Penetrance:
Percentage of carriers of a mutation (with dominant heredity) in which a mutation has a phenotypic effect.

Peptide:
Small protein or protein fragment consisting of fewer than 100 amino acids.

Phenotype:
Recognisable expression of a genotype in contrast to the expression of a different genotype.

Phenotyping:
1. Determination of the phenotype, for example for tumours in tissue that has been removed, using histological and/or immunocytochemical and molecular biological testing. 2. Determination of the phenotype of the whole individual using comprehensive medical testing.

Pharmacogenetics/pharmacogenomics:
Area of science that investigates the influence of genetic make-up on the effect of drugs.

Polymorphism:
Sequence variation. Position in the DNA sequence at which two or more alleles exist; usually used for variants that do not themselves have functional significance.

Prediction:
Prediction, after in-depth testing, of the occurrence of a phenotype (disorder) that is not yet apparent at the time of testing.

Prevention:
Preventive measures to avoid disease. Depending on the point in time, categorised as follows: Primary prevention (elimination/avoidance of risk factors), secondary prevention (earliest possible detection and treatment of preliminary stages of a disorder) and tertiary prevention (avoidance of subsequent disturbances from existing disorders).

Prognosis:
Estimation of future disease course after in-depth testing in the case of disease symptoms that are already present.

Protein:
Chain-shaped combination of amino acids.

Proto-oncogene:
Normal gene that can be transformed into a tumour-causing form by means of mutation (see oncogene).

Recessive:

Phenotypic expression of both (mutated) alleles of an autosomal gene locus; in other words, the phenotype is apparent in the case of homozygosity (see dominant). In the case of an X-chromosome-coded allele, the phenotype is apparent only in the male sex.

RNA (ribonucleic acid):

Macromolecule that is similar to DNA and originates from the transcription of DNA. Messenger RNAs (mRNAs) are translated into proteins in the cell. Other non-coding RNAs are involved in the regulation of gene expression or in catalytic processes.

Screening:

Systematic serial examination of all individuals of a particular age or sex for a phenotype, a disease or a risk of disease, for example genetic testing.

Sequencing:

Determination of the order of nucleic acids (DNA or RNA) in a sample.

SNP:

Single nucleotide polymorphism. Variation in a single base pair in a DNA strand.

Splicing:

Further processing of immature RNA in the cell nucleus. The mRNA, first formed in transcription, generally still contains introns and exons. The introns are removed and the adjacent exons are linked together into matured mRNA.

Stratification:

Assignment of healthy individuals or patients to defined (risk) groups as the basis for targeted prevention or medical intervention.

Target group-specific therapy:

An Individualised Medicine therapy that uses the stratification of patients based on shared biological characteristics.

Taxonomy:

Theory and practice of classification. In biology, a hierarchical categorisation of living organisms based on relationships.

Transcription:

Enzymatic synthesis of RNA using a DNA template by means of which the genetic information contained in the DNA strand is transcribed into a complementary base sequence.

Translation (in molecular biology):

Enzymatic synthesis of proteins using the genetic information contained in the mRNA template.

Translational medicine:

Transfer of scientific findings gained from basic research into clinical research and practice.

Tumour suppressor genes:

Genes that code for proteins which negatively control signal transfer into cells or the cell cycle and thus prevent, for example, excessive cell division as a cause of tumour formation.

Vaccines:

Biologically or synthetically manufactured antigens from proteins or killed or weakened pathogens. Used in immunisation to activate a specific immune response.

10.3 List of abbreviations

AMNOG	*Arzneimittelmarkt-Neuordnungsgesetz* (German Act on the Reform of the Market for Medicinal Products)
BMBF	*Bundesministerium für Bildung und Forschung* (German Federal Ministry of Education and Research)
BMG	*Bundesministerium für Gesundheit* (German Federal Ministry of Health)
CML	Chronic myeloid leukaemia
CNV	Copy number variation
CT	Computed tomography
DNA	Deoxyribonucleic acid
EASAC	European Academies Science Advisory Council
EURAT	*Ethische und Rechtliche Aspekte der Totalsequenzierung* (Ethical and Legal Aspects of Whole Genome Sequencing)
FDA	US Food and Drug Administration
fMRI	Functional magnetic resonance imaging
GenDG	*Gendiagnostikgesetz* (German Gene Diagnostics Act)
GIST	Gastrointestinal stromal tumour
GKV	*Gesetzlicher Krankenversicherer* (statutory health insurance provider) or *Gesetzliche Krankenversicherung* (statutory health insurance fund)
GWAS	Genome-wide association study
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
LCA	Leber's congenital amaurosis
MRI	Magnetic resonance imaging
NMR	Nuclear magnetic resonance
PET	Positron emission tomography
PKV	*Privater Krankenversicherer* (private health insurance provider) or *Private Krankenversicherung* (private health insurance fund)
PPV	Positive predictive value
RNA	Ribonucleic acid
SNP	Single nucleotide polymorphism
SPECT	Single photon emission computed tomography
TKI	Tyrosine kinase inhibitor
WHO	World Health Organisation

10.4 Methods

10.4.1 Participants of the working group

Spokespeople for the working group

Prof Bärbel Friedrich	Professor of Microbiology, Vice President of the German National Academy of Sciences Leopoldina
Prof Philipp U. Heitz	Department of Pathology, University of Zurich
Prof Heyo K. Kroemer	Chairman of Research and Teaching, Dean, University Medical Center Göttingen

Members of the working group

Prof Thomas Bieber	Clinic and Polyclinic for Dermatology, Universitätsklinikum Bonn
Prof Manfred Dietel	Institute of Pathology, Charité Universitätsmedizin Berlin
Prof Georg Ertl	Medical Clinic and Polyclinic I, University Hospital of Würzburg
Prof Carl Friedrich Gethmann	Research Centre “Shaping the future”, University of Siegen
Prof Michael Hallek	Clinic I for Internal Medicine, Universitätsklinikum Köln
Prof Michael Hecker	Institute for Microbiology, University of Greifswald
Prof Heinz Höfler	Institute of Pathology, Technische Universität München
Prof Jan C. Joerden	Chair of Criminal Law, especially International Criminal Law and Comparative Criminal Law, Philosophy of Law, European University Viadrina, Frankfurt (Oder)
Prof Klaus-Peter Koller	Faculty of Biosciences, Goethe University Frankfurt am Main
Prof Thomas Lengauer	Max Planck Institute for Informatics, Saarbrücken
Prof Markus Löffler	Institute for Medical Informatics, Statistics and Epidemiology, Leipzig University
Prof Martin J. Lohse	Institute for Pharmacology and Toxicology, Julius Maximilian University of Würzburg
Prof Peter Oberender	Faculty of Law, Business Administration and Economics, Chair of Microeconomics, University of Bayreuth
Prof Peter Propping	Institute for Human Genetics, University of Bonn
Prof Alfred Pühler	Center for Biotechnology, Bielefeld University
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Prof Jochen Taupitz	Chair of Civil Law, Civil Procedure, International Private Law and Comparative Law, University of Mannheim
Prof Hermann Wagner	Institute for Medical Microbiology, Immunology and Hygiene, Technische Universität München
Prof Hans-Peter Zenner	University Department of Otolaryngology, Head and Neck Surgery, Tübingen

Scientific consultants to the working group

Dr Johannes Fritsch	German National Academy of Sciences Leopoldina
Dr Kathrin Happe	German National Academy of Sciences Leopoldina
Dr Claudia Humbeck	German National Academy of Sciences Leopoldina

10.4.2 Reviewers

The present Statement was reviewed by the following eight independent scientists:

Prof Rudi Balling	Luxembourg Centre for Systems Biomedicine
Prof Boris Bastian	UCSF Cardiovascular Research Institute, San Francisco
Prof Michael Baumann	Faculty of Medicine Carl Gustav Carus, Clinic and Polyclinic of Radiotherapy and Radiooncology, Technische Universität Dresden
Prof Reiner Leidl	Chair of Health Economics and Health Care Management, Ludwig Maximilian University of Munich
Prof Reinhard Merkel	Institute for Criminological Research, Department of Criminal Law, Universität Hamburg
Prof Andreas Papassotiropoulos	Division of Molecular Neuroscience, University of Basel
Prof Jürgen Schölmerich	University Hospital Frankfurt
Prof Matthias Schwab	Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart

The Academies thank the reviewers for their many constructive remarks and suggestions for improvement. These as well as comments from the Presidium of the Leopoldina and the Standing Committee of the German National Academy of Sciences Leopoldina were taken into account in the final version.

10.4.3 Procedures

At the recommendation of the German National Academy of Sciences Leopoldina, the Standing Committee of the German National Academy of Sciences Leopoldina set up the working group on 18 June 2010. The working group then prepared the text of the Statement during eight meetings. An editorial group consisting of the spokespeople and other participants in the working group worked especially intensively on the text during 11 meetings. The results of three expert discussions, a two-day scientific workshop (see Ch. 10.4.5) as well as the results of a joint scientific conference of the Leopoldina and the Austrian Academy of Sciences in Vienna and a joint symposium by the Leopoldina and the Academy of Sciences and Literature, Mainz (*Akademie der Wissenschaften und Literatur Mainz*) were incorporated into the Statement. The Statement was approved on 4 September 2014 by the Standing Committee of the National Academy of Sciences Leopoldina.

10.4.4 Scientific events and expert discussions

As part of their working process, the working group held the following workshops and expert discussions:

- 21 October 2011: Expert discussion on research funding with representatives of the Helmholtz Association, the Ger-

man Federal Ministry of Education and Research, the German Research Association, the German national contact site for life sciences *(Nationale Kontaktstelle Lebenswissenschaften)*, and the Ministry of Innovation, Science and Research of the State of North Rhine-Westphalia, Berlin.
- 9–10 November 2011: International scientific status workshop on Personalised Medicine, Berlin.
- 1 March 2012: Expert discussion with representatives of the pharmaceuticals and diagnostics industry, Berlin.
- 6 June 2012: Expert discussion with patient groups, regulatory authorities, health insurance funds and health economics experts, Berlin.

In addition, the working group has incorporated valuable ideas from the following events:

- 12–14 January 2012: Scientific conference on Personalised Medicine, Vienna (joint event held by the German National Academy of Sciences Leopoldina and the Austrian Academy of Sciences).
- 26 March 2013: Personalised Medicine symposium, Mainz (joint event held by the German National Academy of Sciences Leopoldina with the Academy of Sciences and Literature, Mainz).

10.4.5 Agenda of the international scientific status workshop Personalised Medicine, 9-10 November 2011, Berlin

9 November 2011

13:00 – 14:00 | Arrival and snacks

14:00 – 14:30 | Welcome and introduction

Jörg Hacker, *President of the Leopoldina*
Bärbel Friedrich, *Coordinator of the Academy Group 'Personalised Medicine'*

14:30 – 16:00 | Keynote lectures – Part 1

Session chair: Bärbel Friedrich, Berlin

14:30 – 15:15

Next generation sequencing and -omics technologies as prerequisites towards an individualised medicine
Wolfgang Berger, *Institute of Medical Molecular Genetics, University of Zurich*

15:15 – 16:00

HIV-Therapy – spearheading personalised medicine
Thomas Lengauer, *Max Planck Institute for Informatics, Saarbrücken*

16:00 – 16:10 | Coffee break

16:10 – 18:10 | Keynote lectures – Part 2

Session chair: Bärbel Friedrich, Berlin

16:10 – 16:50

Oncology and internal medicine
Michael Hallek, *Clinic for Internal Medicine I, University Hospital Cologne*

16:50 – 17:30

Predictive molecular pathology: a prerequisite for personalised therapy in oncology
Manfred Dietel, *Institute of Pathology, Charité Berlin*

17:30 – 18:10

On the future of genetic risk assessment
Hans-Hilger Ropers, *Max Planck Institute for Molecular Genetics, Berlin*

18:10 – 18:30 | General discussion

Chair: Rudi Balling, Luxemburg

20:00 – 21:00 | Lecture

Incorporating gut microbiota analysis into personalised medicine – a microbiologist's perspective
Uri Gophna, *Department of Molecular Microbiology and Biotechnology, Tel Aviv University*

10. November 2011

09:00 – 10:20 | Session 1: 'Basics' (Coordination: T. Lengauer / H. Kroemer)

Session chair: Heyo K. Kroemer, Greifswald

09:00 – 09:20

Biobanking as a basis for personalised medicine
Peter Schirmacher, *Institute of Pathology, University Hospital Heidelberg*

09:20 – 09:40

From bioinformatics to hospital informatics: prerequisites for personalised medicine
Björn Bergh, *Center of Information Technology and Medical Engineering, University Hospital Heidelberg*

09:40 – 10:00

Personalised medicine and cohort studies
Karl-Heinz Jöckel, *Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen*

10:00 – 10:20

Study design – biometric considerations
Markus Löffler, *Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig*

10:20 – 10:40 | General discussion

Chair: Hans-Peter Zenner, Tübingen

10:40 – 11:00 | Coffee break

11:00 – 12:20 | Session 2: Diagnostics (Coordination: T. Schmitz-Rode / A. Pühler / M. Hecker)

Session chair: Michael Hecker, Greifswald

11:00 – 11:20

Proteomic concepts for a personalised medicine of the future – current state and perspectives
Marius Ueffing, *Institute for Ophthalmic Research, University of Tübingen and Department of Protein Science, Helmholtz Centre Munich*

11:20 – 11:40

Molecular cardio-vascular imaging
Otmar Schober, *Clinic for Nuclear Medicine, University Hospital Münster*

11:40 – 12:00

Personalisation strategies in image-guided therapies and medical device engineering
Thomas Schmitz-Rode, *Institute of Biomedical Engineering, RWTH Aachen*

12:00 – 12:20

Molecular imaging in oncology
Fabian Kiessling, *Department of Experimental Molecular Imaging, University Hospital Aachen*

12:20 – 13:00 | General discussion

Chair: Alfred Pühler, Bielefeld

13:00 – 14:00 | Lunch break

14:00 – 15:40 | Session 3: Therapy (Coordination: P. U. Heitz / H.-P. Zenner)

Session chair: Philipp U. Heitz, Zurich

14:00 – 14:20

Cardio-vascular diseases
Thomas Eschenhagen, *Institute of Experimental and Clinical Pharmacology and Toxicology, University Hospital Hamburg-Eppendorf*

14:20 – 14:40

PM outside oncology
Hans-Peter Zenner, *Otorhinolaryngology, University of Tübingen*

14:40 – 15:00

GANI_MED – The Greifswald Approach to individualised medicine
Heyo K. Kroemer, *Institute of Pharmacology, Ernst Moritz Arndt University Greifswald*

15:00 – 15:20

Pharmacogenomics and individualised drug therapy
Michel Eichelbaum, *Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart*

15:20 – 15:40

Restoring visual function – individualised therapy in the era of visionary genomics
Bernhard Weber, *Institute of Human Genetics, University of Regensburg*

15:40 – 16:10 | General discussion

Chair: Karl Sperling, Berlin

16:10 – 16:30 | Coffee break

16:30 – 17:30 | Session 4: Ethical, economic, and legal aspects (*in deutscher Sprache / in German*)
(Coordination: P. Oberender / R. Wolfrum / C. F. Gethmann)

Session chair: Florian Steger, Halle

16:30 – 16:50
Personalisierte Medizin – neues Paradigma mit alten ethischen Herausforderungen?
(Personalised Medicine -- new Paradigm with Old Ethical Challenges?)
Georg Marckmann, *Institute for Ethics, History and the Theory of Medicine, Ludwig Maximilians University Munich*

16:50 – 17:10

Standardisierung, Personalisierung, Skalierung – Zur Politischen Ökonomie künftiger Medizinversorgung
(Standardisation, personalisation, scaling – On the political economics of future medical care)
Hartmut Kliemt, *Frankfurt School of Finance & Management, Frankfurt/Main*

17:10 – 17:30

Rechtliche Aspekte der Personalisierten Medizin – ein Überblick
(Legal Aspects of Personalised Medicine -- an Overview)
Jan C. Joerden, *Chair of Criminal Law, European University Viadrina, Frankfurt/Oder*

17:30 – 18:00 | General discussion

Chair: Carl Friedrich Gethmann, Duisburg-Essen

Selected publications of the Monograph Series on Science-based Policy Advice

Academies call for consequences from the Ebola virus epidemic (2014)

Socialisation in early childhood. Biological, psychological, linguistic, sociological and economic perspectives (2014)

On designing communication between the scientific community, the public and the media. Recommendations in light of current developments (2014)

Clinical trials with medicinal products on humans. Ad hoc statement regarding the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (2014)

Animal experimentation in research. Statement on the Transposition of EU Directive 2010/63 into German Law (2012)

Preimplanation genetic diagnosis (PGD). The effects of limited approval in Germany (2011).

Predictive genetic diagnostics as an instrument of disease prevention (2010)

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