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Short version

Individualised Medicine

Prerequisites and Consequences

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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.

The 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.

Recommendations

1. Research and development

The understanding of complex causes of disease must improve. Progress in molecular medical research is leading to a more refined taxonomy of diseases and opening up the prospect of tailored preventive, diagnostic and therapeutic processes. There are compelling examples of individualised therapeutic approaches in medical practice based on specific mutations in the case of monogenic diseases and of some tumour types. 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.

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 sick individuals. The availability of suitable biomarkers is essential for the taxonomic classification of diseases, as well as for assigning patients to preventive, diagnostic and therapy-relevant groups (stratification). Biomarker candidates must be tested in clinical studies with regard to their sensitivity, specificity and benefit. To date, only a few 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. Networked interdisciplinary collaboration among partners in research, university hospitals and industry is needed to develop and validate biomarkers.

Accompanying research in the areas of economics, ethics and law should be strengthened. The economic consequences of implementing Individualised Medicine are the subject of controversy. Reliable conclusions can only be drawn through accompanying socioeconomic analysis of the entire system. Attentive support from the scientific community and dialogue within society as a whole are needed to solve new ethical and legal problems that arise with regard to Individualised Medicine. Key issues are the right not to be informed, the handling of patient-related data, undesirable developments and the possibility of misusing data, for example 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.

2. Harmonisation and standardisation

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.

Patient data collection must be standardised. Although molecular genetic data are obtained using relatively simple procedures, recognised and consistent standards are largely lacking for anamnesis and for the recording of clinical characteristics (phenotyping). However, exact phenotyping is indispensable for Individualised Medicine, and can be achieved by means of a national initiative to set up a medical metadatabase that would uniformly define indication-related characteristics. The characteristics that are recorded would then be comparable and evaluable across studies.

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 enables studies on precisely defined, usually smaller patient groups (stratification) and requires novel concepts for efficient study designs, with one of the goals being shortened authorisation processes for therapies. Despite a decreased number of cases, rare side effects of individualised therapies must be recorded. Following up on new therapeutic procedures after they are authorised is therefore 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.

4. Building up infrastructure in hospitals

High-throughput bioanalytical procedures should be established at university hospitals. In the near future, sequencing techniques will make it possible to decode individual human genomes and test them for disease-related relevance with a reasonable investment of time and money. High-performance, high-throughput procedures for collecting genomic data are indispensable for Individualised Medicine. The same applies for other technologies that record molecular markers like genomic expression (epigenome), RNA (transcriptome), proteins (proteome) or metabolic products (metabolome), all of which will become more significant in the future.

Expanding and networking IT infrastructure and bioinformatics are overdue. Processing the extensive data generated in Individualised Medicine requires high-performance and well-networked information technology. Complex, standardised patient information should be uniformly linked in digital patient record and made accessible without barriers to doctors. IT equipment and skills are part of the basic infrastructure of medical facilities. The differences in funding for hospitals in German federal states, however, have resulted in substantial discrepancies. There are still significant shortcomings that need to be remedied by means of targeted investments, even in some university hospitals. In addition to sustainable further development of hardware, Individualised Medicine depends on professional data analysis. The bottleneck that exists in this regard can be addressed only by means of targeted education and involvement of a sufficient number of specialised bioinformaticians.

5. Protection of personal rights

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 that are 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 processing via written consent. Dubious internet-based offers, for example direct-to-consumer tests, of genetic analysis using biological samples and accompanying phenotype information submitted by mail, are a cause of concern as the results are not subject to the necessary general quality control, and may 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.

Regulations are needed with regard to the rights and duties of non-medical scientists. It is absolutely essential to Individualised Medicine that interdisciplinary teams consisting of doctors, biologists, engineers and other natural scientists provide expertise across a wide range of fields. 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 is emphatically recommended. The code both protects scientists and contributes to the preservation of patient rights. Moreover, in the future clinical ethics committees should be increasingly involved in decision-making processes related to individualised healthcare.

6. Framework conditions

Appealing framework conditions should be created for the development of companion diagnostics. The quality, reliability and timely availability of new diagnostic procedures are decisive for the development of individualised therapies. 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.

Developing strategies for risk-adapted prevention should be supported. Improved understanding of individual risks of disease opens up new options for prevention. It is expected that health insurance funds and ultimately society as well 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. Early detection of treatable illnesses, tailored to individual risk, and investigating the efficacy of preventive steps should be vigorously pursued. In addition, consideration should be given to how people can be better motivated to take preventive measures, for example by means of bonus schemes. This must not, however, violate either patient autonomy or the right not to be informed.

University hospitals must have sufficient resources for clinical research and medical care based on that research. The progress and success of Individualised Medicine will be shaped in part by efficient translational medicine, that is, the rapid transfer of research results into clinical practice. This process can currently be carried out most efficiently at university hospitals and requires close interaction between scientifically designated groups and doctors working in healthcare. Therefore, sufficient resources should be made available to develop efficient university structures. Moreover, framework conditions need to be created to enable the sharing of information by partners from academic research, industry and regulatory authorities early on about specific requirements for the efficient translation of innovative medical approaches.

7. Education and counselling

Preparations must be made for the increasing need for information and counselling. Patients and doctors must increasingly make diagnostic and therapeutic decisions together, based information that is usually very complex. It is important here that doctors are able to convey interdisciplinary aspects of the treatment to patients in a comprehensible way. Quality-assured, comprehensible public information platforms are helpful for this. The information service of the German Cancer Research Center serves as an example here.

Basic and advanced training and continuing education must be adapted to the requirements of Individualised Medicine. Individualised Medicine cannot be implemented without new teaching concepts for basic and advanced training and continuing education of doctors. Basic knowledge in molecular biology and bioinformatics must be included in the curricula, which requires fundamental reform both within and outside of universities. Such training will also increase the willingness to use innovative procedures and the ability to make critical assessments. In addition, involved natural scientists and other healthcare professionals must be sufficiently familiarised with the relevant medical topics.

8. Raising awareness in society and among decision-makers

Individualised Medicine requires structural adaptations and adequate funding in research and care. Society, especially individuals and institutions who bear responsibility for healthcare, should work toward implementing Individualised Medicine within the healthcare system. Extensive structural adaptations in research and care, which will also require significant funding, will no doubt be necessary for this. Without these investments in the future, the population as a whole will be unlikely to be able to benefit from the improved diagnostics, therapy and prevention for a longer healthy life.

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