Advances in Predictive, Preventive and Personalised Medicine
Series Editor: Olga Golubnitschaja

Tobias Fischer
Martin Langanke
Paul Marschall
Susanne Michl *Editors*

Individualized Medicine

Ethical, Economical and Historical Perspectives

EPMA
European Association for Predictive Preventive & Personalised Medicine

Springer

Individualized Medicine

Advances in Predictive, Preventive and Personalised Medicine

Volume 7

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What this Book Series is About...

Current Healthcare: What Is Behind the Issue?

For many acute and chronic disorders, the current healthcare outcomes are considered as being inadequate: global figures cry for preventive measures and personalised treatments. In fact, severe chronic pathologies such as cardiovascular disorders, diabetes and cancer are treated after onset of the disease, frequently at near end-stages. Pessimistic prognosis considers pandemic scenario for type 2 diabetes mellitus, neurodegenerative disorders and some types of cancer over the next 10-20 years followed by the economic disaster of healthcare systems in a global scale.

Advanced Healthcare Tailored to the Person: What Is Beyond the Issue?

Advanced healthcare promotes the paradigm change from delayed interventional to predictive medicine tailored to the person, from reactive to preventive medicine and from disease to wellness. The innovative Predictive, Preventive and Personalised Medicine (PPPM) is emerging as the focal point of efforts in healthcare aimed at curbing the prevalence of both communicable and non-communicable diseases such as diabetes, cardiovascular diseases, chronic respiratory diseases, cancer and dental pathologies. The cost-effective management of diseases and the critical role of PPPM in modernisation of healthcare have been acknowledged as priorities by global and regional organisations and health-related institutions such as the Organisation of United Nations, the European Union and the National Institutes of Health.

Why Integrative Medical Approach by PPPM as the Medicine of the Future?

PPPM is the new integrative concept in healthcare sector that enables to predict individual predisposition before onset of the disease, to provide targeted preventive measures and create personalised treatment algorithms tailored to the person.

The expected outcomes are conducive to more effective population screening, prevention early in childhood, identification of persons at-risk, stratification of patients for the optimal therapy planning, prediction and reduction of adverse drug-drug or drug-disease interactions relying on emerging technologies, such as pharmacogenetics, pathology-specific molecular patters, sub/cellular imaging, disease modelling, individual patient profiles, etc. Integrative approach by PPPM is considered as the medicine of the future. Being at the forefront of the global efforts, the European Association for Predictive, Preventive and Personalised Medicine (EPMA, http://www.epmanet.eu/) promotes the integrative concept of PPPM among healthcare stakeholders, governmental institutions, educators, funding bodies, patient organisations and in the public domain.

Current Book Series, published by Springer in collaboration with EPMA, overview multidisciplinary aspects of advanced bio/medical approaches and innovative technologies. Integration of individual professional groups into the overall concept of PPPM is a particular advantage of this book series. Expert recommendations focus on the cost-effective management tailored to the person in health and disease. Innovative strategies are considered for standardisation of healthcare services. New guidelines are proposed for medical ethics, treatment of rare diseases, innovative approaches to early and predictive diagnostics, patient stratification and targeted prevention in healthy individuals, persons at-risk, individual patient groups, sub/populations, institutions, healthcare economy and marketing.

Prof. Dr. Olga Golubnitschaja

Book Series Editor

Dr. Golubnitschaja, Department of Radiology, Medical Faculty of the University in Bonn, Germany, has studied journalism, biotechnology and medicine and has been awarded fellowships for biomedical research in Paediatrics and Neurosciences (Medical Centres in Austria, Russia, UK, Germany, the Netherlands, and Switzerland). She is well-cited in the research fields of “gene hunting” and “subtractive hybridisation” applied to predictive prenatal and postnatal diagnostics published as

O. Labudova in years 1990-2000. Dr. Golubnitschaja is an expert in molecular diagnostics actively publishing in the fields of perinatal diagnostics, Down syndrome, diabetes mellitus, hyperhomocysteinemia, cardiovascular disease, neurodegenerative pathologies and cancer. She is the *cofounder* of the theory of multi-pathway organ-related blood fingerprinting with specific molecular patterns at epi/genomic, transcriptional and post/translational levels and author of fundamental works in *integrative medicine.* Dr. Golubnitschaja holds appointments, at the rank of Professor, at several European Universities and in International Programmes for Personalised Medicine and is author of more than 300 international publications in the field. Awards: National and International Fellowship of the Alexander von Humboldt-Foundation; Highest Prize in Medicine and Eiselsberg-Prize in Austria; She is *Secretary-General* of the "European Association for Predictive, Preventive and Personalised Medicine" (EPMA in Brussels, www.epmanet.eu), Editor-in-Chief of *The EPMA-Journal* (BioMed Central in London); Book Editor of *Predictive Diagnostics and Personalized Treatment: Dream or Reality,* Nova Science Publishers, New York 2009; Book Co-editor *Personalisierte Medizin,* Health Academy, Dresden 2010; Book Series Editor *Advances in Predictive, Preventive and Personalised Medicine,* Springer 2012; *European Representative* in the EDR-Network at the NIH/NCI, http://edrn.nci.nih.gov/; *Advisor and Evaluator* of projects dedicated to personalised medicine at the EU-Commission in Brussels, NIH/NCI, Washington, DC, USA, and Foundations and National Ministries of Health in several countries worldwide.

Preface

In 2012 the editors developed the idea of bringing together the research results from the disciplines of history, concept-based ethics, applied research ethics and health economics into one volume on "Individualized Medicine". These different disciplines constitute one project area as an integral part of the overall "Greifswald Approach to Individualized Medicine" (GANI_MED) research consortia. From their respective disciplinary affiliations, the editors and authors of the different sections hope to contribute to the ongoing debate on ethical, economical and societal implications of Individualized Medicine (IM) by focusing on the specific Greifswald approach. To address the challenges of this new approach in medicine, IM is first and foremost a research program capable of converging persons with different backgrounds and disciplines. This volume is also the result of intense interdisciplinary discussions and close cooperation with researchers from the clinic and information technology.

Our first thanks go therefore to all the Greifswalder researchers of any discipline and background for their readiness to cooperate and discuss these issues. Without this interdisciplinary exchange based on complimentary expertise, it would have been impossible to carry out some of the research projects, particularly to find together ethically adequate solutions to clinical and IT problems, to inform our conceptual understanding and to make economical analysis possible. Our special thanks go to Hans-Jörgen Grabe, the project leader and his assistants Claudia Richardt and Vivian Werner, who supported this publication from conception to completion.

We would like to express our special thanks to Olga Golubnitschaja, the competent and experienced series editor of the "Advances in Predictive, Preventive and Personalised Medicine" for admitting the contributions for publication. We thank Martijn Roelandse and Tanja Koppejan from Springer Biomedical, who have cleared up a number of editorial questions and provided us with useful help to go through the editing process.

An edited volume would be impossible to write without the help of many people who have proof-read, translated or commented upon manuscripts. First of all, James Wells has provided for editorial consistency by going through the whole volume. We are very thankful for all his stylistic improvements. Daniela Berner, Claudia

Gräfe, Stefan Kirschke and Sally Werner scrupulously read different parts of the volume and largely contributed to harmonize the manuscripts in form and style.

Last but not least, we are thankful to all the writers of this volume. The editors thank all who have contributed to the success of this project. Our thanks especially go out to them for their time, hard work and for their understanding for the gentle pressure which we sometimes had to put on them in order to keep to the tight time plan.

*

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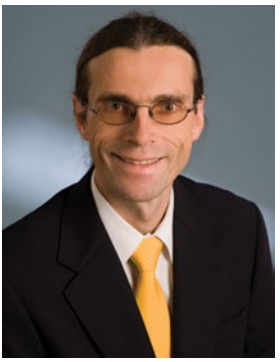

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Chapter 1
Introduction

Tobias Fischer, Martin Langanke, Paul Marschall and Susanne Michl

In October 2009 the University Medicine Greifswald launched the "Greifswald Approach to Individualized Medicine" (GANI_MED) to implement individualized diagnostic and therapeutic strategies in clinical settings. It was the first attempt to establish an Individualized Medicine (IM) program at a German university hospital. IM is a new approach in the context of prevention, tailored diagnostic and treatment of patients with regard to their individual characteristics. Since the completion of the human genome project in 2003, the approach of Individualized Medicine, along with other similar designations such as Personalized Medicine (PM) or Stratified Medicine (SM), has led to controversies about its clinical and economical potentials, as well as its societal implications and ethical requirements. History, applied research ethics, concept-based ethics and health-economics are integral parts of the GANI_MED consortium. In contrast to other comprehensive presentations of IM published so far, this anthology focuses on this research area. However, this volume includes some further contributions out of the GANI_MED context, contributing to an understanding of these works. In this book the research from these disciplines is

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presented. It draws attention to the fact that the implementation of individualized approaches into medical research and clinical practice is linked to changes in health care systems and societal values.

One of the core research fields of IM is pharmacogenetics. Its approach serves as an example of how to tailor individualized therapies for different patients or patient groups. Each person differs according to his or her individual heredity, health related behavior and metabolism. Furthermore, especially the elderly suffer from many diseases. To this day, drugs are prescribed according to the clinical picture of the disease without considering the individual make-up of different patients. As a result, medications with proven efficacy often induce (adverse) side-effects or fail to exert any effect in a subgroup of patients. Besides the impact on personal well-being, this approach leads to economic costs that could be saved by more targeted therapies. The advances of pharmacogenetic research since the late 1950s has provided deeper insights into the future potentials of individually tailored drug therapies.

This need for more tailored therapies must be understood in a broader sense, including a wider range of biomedical initiatives and application fields. It is the commitment of GANI_MED to test promising concepts of individualization for their applicability in this field. The GANI_MED consortium includes experts from various national and international academic institutions as well as industrial partners that help to lay the foundations for the implementation of individualized therapies into different clinical fields.

GANI_MED was designed as a clinical-epidemiological project. In contrast to other research projects, that invoke similar concepts, GANI_MED focuses on disease phenotypes outside of oncology, especially common diseases. GANI_MED is grounded in the understanding of the importance of biomarkers. These are molecular and non-molecular parameters that allow, individually or in combination, to predict courses of diseases and/or the response of therapies by using stratification techniques. GANI_MED aims at identifying adequate biomarker candidates with the help of association studies. Additionally, the translation of IM based approaches into clinical routine is an important objective of this research program.

Between the introduction (chap. 1) and the conclusion (chap. 16), there are six parts that present a collection of findings from research projects from different disciplines.

Critics have often called “Individualized Medicine” (or “Personalized Medicine”—the term more commonly used in English-speaking countries) a “misnomer” or a false and fraudulent labeling. Because the term includes a wide variety of meanings in medical and popular writings, there is substantial doubt, not only about the usefulness of the term in particular, but moreover about the potential of an individualized approach in general. Given the vagueness of the concept, a research consortium labeled as IM or PM needs to strive for terminological precision not only of IM or PM, but also related terms such as “research approach”, “health care practice”, “biomarker”, “prediction” and “stratification”. Within the GANI_MED joint project an interdisciplinary working group was established to develop a precise definition of IM and to demarcate it from other uses and designations. Chapter 2 is the result of the discussion led by experts from the field of ethics and theory of science (**Martin Langanke**, **Pia Erdmann**, **Tobias Fischer**, **Hein-**

rich Assel), medicine (**Wolfgang Lieb**, **Marcus Dörr**, **Heyo Kroemer**) and health economics (**Steffen Flessa**). In addition to this preliminary, conceptual and terminological part, in chapter 3, **Hans-J. Grabe** and **Henri Wallaschofski** outline what this understanding of IM means when applied to the almost 4000 patients recruited in nine cohorts at Greifswald University Hospital (heart failure cohort, cerebrovascular disease cohort, periodontal disease cohort, renal and renovascular disease cohort, metabolic syndrome risk cohort, fatty liver disease cohort, cohort of adverse medication effects, cohort of pulmonary diseases, cohort of sepsis). To integrate IM into clinical practice, a central data management structure has been implemented guaranteeing the standardization of protocols for the assessment of medical history, laboratory biomarkers, and the collection of various biosamples for biobanking.

The need for a precise definition of IM becomes apparent against the background of the fluid and contradictory ways in which the concept of "Personalized Medicine" has been used over the last 15 years. Drawing on the definition of IM in the context of the GANI_MED research consortia, Part II considers "Personalized Medicine"—the term used in the sample of writings analyzed in this part—as a societal phenomenon that involves different biomedical initiatives in and outside universities and research units. Since the late 1990s, the term "Personalized Medicine" has been coined to describe and enable collaborations between different stakeholders. As a rhetorical frame, it constitutes an imaginary framework of visions, expectations and claims for a better, more patient-centered and more efficient health care system. Instead of deciding whether "Personalized Medicine" is more "hype" or "hope", scholars from the social studies of technology and science emphasize that the expectations revolving around new technology are not only accessory parts of scientific inventions or innovation networks. On the contrary, they regard them as essential in shaping these technologies. In Part II on "Perspectives of Socio-Cultural and Historical Studies", **Susanne Michl** draws on this "sociology of expectation" by analyzing specific ways in which the individualized approach to medicine has been framed in current medical and popular writings since the invention of the term "Personalized Medicine" (chap. 4) as well as in past developments of the narrower field of pharmacogenetic research (chap. 5). The focus is on narratives connecting past performances, present states and the future promises. In a historical perspective, the author draws attention to alternative, partly forgotten, partly surviving, conceptual frameworks of research projects centered upon the concepts of "individuality" or "variability." Such observations are also relevant for our understanding of pharmacogenetics research since the late 1950s and the rediscovery of the work of Archibald Garrod at the beginning of the last century.

Part III outlines clinical examples to illustrate how integrated analysis of biomarkers leads to significant improvement of therapeutic outcomes for a subgroup of patients.

Marcus Dörr, **Uwe Völker** and **Stephan B. Felix** (chap. 6) deal with the hemodynamic effects of a novel treatment option (immunoadsorption with subsequent IgG substitution) for Dilated Cardiomyopathy (DCM), which is one of the most common causes of heart failure. The study demonstrates the potentials of

a biomarker-based research for DCM patients whose response to the therapy of immunoadsorption is predicted by the combination of two biomarkers (negative inotropic activity of antibodies in the blood and gene expression patterns derives from myocardial biopsies). Within the multi-disciplinary GANI_MED this clinical example led to an in-depth, health-economical analysis.

In chapter 7 of Part III **Henriette E. Meyer zu Schwabedissen** provides examples from pharmacogenetics, one of the major and most promising fields of IM. The part focuses on the underlying mechanisms of gene-drug associations, their clinical significance as well as the current status of clinical implementation. The first example, the association between CYP2D6 and tamoxifen in the treatment of ER-positive breast cancer, concerns a member of the protein family of cytochrome P450 enzymes that is historically one of the first findings paving the way to advances in pharmacogenetics in general. The contribution sheds light on the strengths, but also on the difficulties of pharmacogenetic findings and their successful clinical implementation. In addition to the optimization of treatment outcomes, genetic findings have contributed to the development of new drug therapies and their clinical approval, such as the development of CCR5 antagonists and inhibitors of the bcr-abl tyrosine kinase and the novel drug ivacaftor for patients with cystic fibrosis.

To assess the implementation of Individualized Medicine approaches into medical research and clinical practice requires more than an analysis of whether IM will live up to its clinical expectations. Since the late 1990s, IM has also raised ethical concerns. The following two parts deal with these ethical issues, including the conceptual layers of IM (Part IV) and applied research ethics (Part V).

The task of the philosophical project of GANI_MED is to produce a conceptual and critical reconstruction of the approach of IM. Adopting the reconstructive theory of science, **Konrad Ott** and **Tobias Fischer** (chap. 8) deal with constitutive momenta of IM (stratification, diagnosis, prediction, prevention and risk) and four different medical approaches (lifeworld, traditional-conventional medicine, human-ecological and "alternative" ways of healing, and the molecular-genetic approach). Over and above these conceptual issues, the contribution proposes an ethics of IM based on three pillars (informed consent, "cura sui" and solidarity). The authors argue that IM cannot be attributed to the molecular-genetic approach alone. Instead they opt for an understanding and framing of IM as an integrative health science in contemporary societies. Rather than deploring the vagueness of the term, Ott and Fischer emphasize the flexibility and the openness of the "epistemic grammar" of IM enabling the design of new scopes of medical practice.

In the second chapter of the part on concept-based issues (chap. 9), **Johann-Christian Põder** and **Heinrich Assel** address criticism according to which IM contributes to an extension of the concept of disease and a pathologization of life. In the near future, biomarker-based predictive medicine and the rapidly growing amount of health-related information might considerably increase the accuracy in predicting the onset of a disease leading to new personal and social patterns of identification (the "healthy ill persons"), decision-making and responsibility. To answer the question of whether IM will contribute to a pathologization of life, three

disease theories—the naturalistic theory by Christopher Boorse, the reconstructive theory by Peter Hucklenbroich and the "practical" theory by Dirk Lanzerath—are discussed. Against this background, the authors argue that medical terms and concepts should not only be elaborated from a medical (or political and economic) but also from a philosophical perspective as an ongoing task and challenge.

In addition to conceptual questions, Part V focuses on application-oriented ethical issues. One of the peculiarities of GANI_MED is that the ethical requirements and regulatory demands of clinical epidemiological research have been investigated within the collaborative project. To assure ethically appropriate ways of dealing with the recruitment of patient cohorts and the establishment of a biobank- and IT-infrastructure, bioethicists and clinical researchers have collaborated closely. This interdisciplinary cooperation between life sciences and the humanities has led to pragmatic, patient-centered solutions and procedural improvements that meet legal standards and establish new ethical standards that can serve as a model on how to integrate ethical research into clinical epidemiological settings for future research consortia.

In the first chapter of Part V **Martin Langanke, Jakob Fasold, Pia Erdmann, Roberto Lorbeer and Wenke Liedtke** present the informed consent process of the GANI_MED project including the consent documents and the response pattern of the patients participating (chap. 10). The challenge is that clinical epidemiological studies typically try to pursue several scientific goals at once. Data from different sources including those from third parties have to be collected to form a sample to generate hypotheses in the field of IM. The challenge then is that the complexity of epidemiological research designs has to be incorporated in the consent form in an easily comprehensible way. The ethicists of the GANI_MED joint project have designed a consent form for each cohort of patients and with several sections allowing the patient to consent or to refuse his or her full participation or to rule out certain aspects of the study. The analysis of the empirical data demonstrates that patients actually have seized this possibility to deselect and that the patients of different morbidity cohorts answer differently.

Once the patient has signed the informed consent documents, the next challenge is to store this information to guarantee that the contents of the agreements and the corresponding data can easily be connected, and made available. This next step of the management of informed consent—the processing of data items that belong to persons who have agreed to take part in medical research—requires both technical and ethico-legal considerations. In the following contribution (chap. 11) **Thomas Bahls**, **Wenke Liedtke**, **Lars Geidel** and **Martin Langanke** present a high-level architecture of an IT platform that guarantees quality and ethical validity of the informed consent documents and their automatic application during a data use and access process.

One of the distinctive features of the GANI_MED project is the integration of empirical-ethical studies. Whereas in research ethics, studies have focused on abstract ethical requirements, only few studies explore the actual expectations of participants before consenting and their stress during and after the examinations. Particularly the whole-body MRI examination leads to incidental findings consti-

tuting a challenge for both researchers and participants on how to handle them. **Pia Erdmann** takes up this issue by carrying out quantitative and qualitative surveys with participants of the "Study of Health in Pomerania" (SHIP) who underwent a whole-body MRI examination (chap. 12). The analysis of the questionnaires and interviews provide important insights into the subjective perception of health and the shifting risk-benefit evaluation as well as potential misjudgments of the conditions for participating. To conduct MRI examinations in an ethically appropriate way, researchers should avoid Diagnostic Misconception, as well as factors causing stress, by adjusting the mode of communication.

Part VI is devoted to different aspects of assessing IM from a health economic perspective. At first, **Steffen Flessa** and **Paul Marschall** examine in their contribution "Individualized Medicine: From Potential to Macro-Innovation" (chap. 13) the possibilities of IM to initiate a paradigm shift in the German health care provision. Economically the relevance of a novel idea or a new product can be captured by the concept of innovation and the associated penetration of society or a market. This can be linked to the question of whether IM has the potential to transform thinking and behavior within the health system. Different stages of innovation can be distinguished which express the adoption level within the system. Stakeholders and their attitude play a crucial role in the corresponding process. The authors analyze whether IM has the potential to change the relationship between doctors, patients and other agents, to alter the rules, institutions and regulations of the health care sector and even to influence societal values. In addition major barriers preventing the key stakeholders adopting this new approach to medicine must be considered. Flessa and Marschall firstly analyze these barriers and whether IM has the potential to become a macro-innovation, thus the most comprehensive level. Based on a characterization of the attributes of the current status of IM the authors study what has to be fulfilled so this approach can become the new standard solution for the health care system for allocating scarce resources.

In the medical section of this book **Marcus Dörr**, **Uwe Völker** and **Stephan B. Felix** (chap. 6) exemplify the use of biomarkers for the prediction of treatment response within the context of widespread diseases. **Paul Marschall**, **Timm Laslo**, **Wolfgang Hoffmann**, **Kerstin Weitmann** and **Steffen Flessa** address themselves to the same clinical example. In: "Assessing Individualized Medicine—the Example of Immunoadsorption" (chap. 14) they provide the corresponding picture from the economic perspective. Based on time studies and investigations of used resources at the University Medicine Greifswald they provide preliminary results for the costs of Immunoadsorption therapy with subsequent IgG (IA/IgG) substitution and the corresponding gene expression analysis. Under the current setting the latter can be regarded as diagnostics for deciding whether IA/IgG is appropriate. Currently, both parts of the IM tandem are not implemented in combination in clinical routine. The authors show that the reimbursement system has a critical role for providing incentives for health care providers to translate research into routine. For assessing whether a new therapy approach is useful, a full economic evaluation of costs and consequences is necessary. Marschall et al. also present some preliminary results of outcome evaluation based on disease-related quality of life.

Heart failure is currently one of the most cost-intensive diseases in Germany. It also represents one of the most common reasons for hospitalization. By now it is evident that due to demographic change prevalence and incidence of heart failure is enormously increasing. **Timm Laslo**, **Paul Marschall** and **Steffen Flessa** finally cover this issue in: "How individualized is medicine today? The case of heart failure in the G-DRG system" (chap. 15). Currently the remuneration of hospitals in the German DRG system (G-DRG) is carried out through the payment of a lump sum for each case of inpatient treatment. The system must be able to map complex cases. Based on a comprehensive data set from the University Medicine Greifswald the authors analyze how a pathway for clinical care is apparent for heart failure using the example of the base DRG F62. In this context the concept of cost homogeneity is of high relevance. In addition, criteria for the clinical course of symptoms of heart failure are determined by multivariate analysis. Furthermore, the authors discuss whether the G-DRG system is ready for the implementation of IM approaches into the clinical routine.

Finally in chapter 16 conclusions and recommendations based on the first 5 years of GANI_MED with respect to socio-cultural, ethical and health-economic issues are presented. Thereby we draw heavily on the experience of the studies pointed out in Parts I-VI.

Part I
Definition and Concept of Individualized Medicine

Chapter 2
The Meaning of "Individualized Medicine": A Terminological Adjustment of a Perplexing Term

Martin Langanke, Wolfgang Lieb, Pia Erdmann, Marcus Dörr, Tobias Fischer, Heyo K. Kroemer, Steffen Flessa and Heinrich Assel

Abstract This chapter introduces "Individualized Medicine" as a technical term. In order to do this the chapter first gives a precise, logical and conceptual analysis of relevant explanations and definitions from English and German speaking areas. It secondly presents a definition according to which the term "Individualized Medicine" should be used for describing research approaches and health care practices, when the

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biomarker-based prediction of (a) diseases and/or (b) the effectiveness of therapies by stratification is central. The relevant terms "research approach", "health care practice", "biomarker", "prediction" and "stratification" will be discussed in detail. Finally the term "Individualized Medicine" will be examined regarding its extension and be compared to "Personalized Medicine", which is also understood terminologically.

Keywords Definition · Aristotelian concept of definition · Individualized Medicine · Personalized Medicine · Medical research · Health care · Biomarker · Stratification

2.1 Background

"Individualized Medicine is fraudulent labeling and fiction." This provocative statement of Prof. Wolf-Dieter Ludwig, chairman of the Drug Commission of German Physicians, is quoted in an article from March 2011 which can be still found in the archive of the website of the Association of German Internists (Individualisierte Medizin: Etikettenschwindel 2011).

Such criticism of Individualized Medicine (IM), suggesting that the term is misleading, cannot be ignored by scientists who understand their research as a contribution to the establishment of IM. Moreover, such critical voices are not only part of the non-medical "accompanying discourse" about IM, but they come also—as shown by the initial quote—from researching physicians. The accusation made is serious and massively affects the integrity and academic respectability of any work in the field of IM. If this criticism is justified, IM would be only a label, which is, at best, useful for the acquisition of funding but it would not seriously describe a current branch of medicine.

To respond to this accusation is also in the interest of those research groups which are part of the joint project Greifswald Approach to Individualized Medicine (GANI_MED) of the Ernst-Moritz-Arndt-University Greifswald (Grabe et al. 2014; Langanke et al. 2011; Langanke et al. 2012a). There is a risk that their activities, which are within one of the most extensive projects concerning IM in Germany, will be discredited through the accusation of fraudulent labeling. In the light of this, this paper secures the result of the discussions within the interdisciplinary GANI_MED working group, which was established in order to do the terminological demands justice with regard to a refined "IM" term. Experts from the field of medicine, health economics, ethics and theory of sciences were part of this working group.

2.2 Preliminary Methodological Considerations

The spectrum of what is called IM today includes

a. medicine which is based on the use of unique therapeutic measures i.e. in the course of Tissue Engineering or cell therapy

b. pharmacogenetics and
c. other lines of research which aim at the improvement of the prediction of diseases and/or courses of diseases with the help of so-called biomarkers (Costigliola 2009; Hüsing et al. 2008; Kollek and Lemke 2008; Niederlag et al. 2010; Schleidgen et al. 2013).

If one reflects on possible introductory strategies for the term "IM", with regard to the differences concerning this term, one could at first consider the option to provide "IM" as a simple collective term and to list all the relevant trends which are understood as "IM".

The advantage of such a "collective term", created in an enumerative way, is that everything which praises itself as "IM" can be accepted as IM. However, this leads to the disadvantage of lacking a depth of focus. In particular, such an "IM" term leaves the question open of whether the different "IMs" match methodologically to one feature, or to a group of features, which is valid as a specific group characteristic in the sense that it is common for exactly all —"IMs", but not for comparable fields of action within medicine.

This disadvantage is particularly crucial in the present case: Within IM there are two different concepts of individualization circulating, as Hüsing et al. 2008 detected. These two concepts can methodologically not be reduced to a common concept. Whereas unique therapeutic measures are therapeutic interventions

> for the individual patient […] where the "individualization" is based on the manufacturing process of the custom-made item and the resulting product (Hüsing et al. 2008, p. 9).

"individualization" in the light of concepts like pharmocogenetics and/or biomarker-based IM means

> a division of the patient population into clinical relevant subgroups (so-called stratification) […] which goes beyond the status quo. Leading factors are the presumption that diagnostics, specification of risks and interventions can be more accurate if more criteria, including specific criteria, can be used for the group division (Hüsing et al. 2008, p. 9).

There are lines of research within IM which aim at the development of therapeutic options for only and exactly one individual patient, as well as lines of research which "just" aim at a *more* individual treatment of all patients who belong to a certain group. Therefore the validity of the definitions which eliminate these significant differences has to be questioned. This problem becomes greater if one assumes that methodologically the approach of stratification depends on statistic procedures. Hüsing et al. 2008 are able to bring both lines into coexistence because they introduce "IM" by using a typology of five individualization concepts. Behind them one can presume the same three "drivers" (Hüsing et al. 2008, p. 7).

The methodological problem mentioned above becomes quite clear wherever a definition of "IM", following the "Aristotelian" scheme of genus and specific differences, is aimed at, or at least used as heuristic orientation. According to the tradition of the Aristotelian philosophy of science, a term can be defined on the one hand by putting it under a generic term which includes all the phenomena which can be asked for, if they fall under the concept defined and on the other hand by

indicating certain characteristics (specific differences) which have only and exactly the phenomena which fall under the concept defined.

Not every term can be introduced by the scheme of genus and specific difference. (On the level of our everyday experience, colors like “green” or “red” are such a problem case and much debated because they are included in a generic term “color” but cannot be defined with regard to specific differences between the single colors. Thus—on the level of our everyday experience—colors can only be introduced by giving examples and counter examples.) However, the Aristotelian scheme embodies an ideal of definition theory.

If one takes up this ideal for “IM”, methodological decisions have to be made at two points specifically:

1. In order to introduce “IM” under the use of a relation between a generic and subsumable concept a decision has to be made with regard to the genus of “IM”. Thus, it has to be determined which phenomena of which kind are candidates for proving whether they are included in the term of “IM” or not.
2. Following the Aristotelian strategy of definition, one has to make criteria based decisions within the field, which can be outlined by listing a “collective term” such as “IM” in the broadest sense, in favor or to the disadvantage of some approaches. An “IM” term which is defined in the Aristotelian way cannot be as tolerant as a solely enumerative term.

2.3 The Question of Genus

It is characteristic for the German discussion that “Individualized Medicine” and “Personalized Medicine” are used equally. It is common that both terms appear next to each other in one article without any reflection on this alternative use (e.g. Fricke 2011). “Preventive Medicine” is another term which is commonly used to refer to, at least, certain approaches within the large field of medical lines of research and health care practices, which can be called “IM” by using the “IM” term of Hüsing et al. 2008.

This result needs a more specific classification in the frame of this paper by answering the question of whether the existence of different terms should be used for an objective difference as well. However, we do not want to artificially narrow down the discussion here. In the following, the question of genus will be raised with regard to firstly explanations which explicitly refer to the term “IM”, and secondly, by using relevant text passages which use the terms “Personalized Medicine” or “Predictive Medicine”. This “Babylonian language confusion” can be tolerated methodologically as long as the language use is only described but not standardized in the sense of a definition.

2.3.1 "IM" as Health Care

Hüsing et al. introduce their typology of "Individualized Medicine," saying that "Individualized Medicine" means "a possible future health care" (Hüsing et al. 2008, p. 7).

The indefinite article suggests that Hüsing et al. (2008) understand "IM" as a subsumable concept of "health care" or the way around "health care" as a genus or generic term for "IM". One could generally compare "IMs" to other forms of health care, according to this suggestion. If one follows the terminological suggestions which were established in the course of the three pillar model of health care, which were put up for discussion by Pfaff (2006) for the field of health care research, all *activities of health care institutions and personnel* are included in the term health care, which aim at

a. *the prevention or health promotion (preventive health care) and/or*
b. *measures for acute care in acute care clinics and family doctor or specialist practice (curative health care) and/or*
c. *a reintegration of the patient into society (rehabilitative health care)*

The use of the term "health care" in Hüsing et al. (2008) can be logically referred to the terminologically regulated discourse about "health care" in health care research according to Pfaff (2006): It should be clear that "IM", in the sense of Hüsing et al. (2008), is *not* a fourth pillar beside preventive, curative and rehabilitative health care and is therefore *no* fourth "health care type" *sensu* Pfaff (2006). It rather shows a possible manner of how health care can be designed on the one hand type-independent and on the other hand in all three fields. Moreover, it has to be noticed that the health care concept described by Pfaff (2006) covers the required logical possibility claimed by Hüsing et al. (2008), i.e. that several designs of health care, thus health care*s*, can be distinguished. Although every medical field has dependent on the indication a range of different methods, it can be indicated fairly precisely for a certain point in time t_1 and for a certain indication X which procedure in the context of the so-called conventional medicine is the standard way of health care. However, the decision concerning what a standard method is depends on the medical state of knowledge and temporal changes.

Generally, it is possible that within the three different health care types described by Pfaff (2006), procedures will be established as standard methods which are based on the use of unique therapeutic measures or the preventive use of biomarkers in the future. In the sense of Hüsing et al. (2008) this future health care could be characterized as "IM" and is to be separated from current health care, in which such procedures play only a subordinate role. From today's perspective one can say: "IM" will remain only a "possible future health care" until procedures like *Tissue Engineering* or biomarker-based prediction are used in the clinical practice significantly more often. If this is the case in the future, IM will have "become reality". By its constitutive embedding of "IM" in the genus "health care", the explanation by Hüsing et al. (2008) is one of the most sophisticated approaches of standardizing

the “IM” term in the German language area. With regard to its underlying genus decision, prominently published publications followed Hüsing et al. (2008) in the German language area (e.g. Niederlag et al. 2010).

In this chapter we cannot list all explications which understand “IM”, “Personalized Medicine” or “Predictive Medicine” as health care phenomenon. This is also due to many borderline cases which are linguistically so loose that competitive reading is possible which can be distinguished only with disproportionate hermeneutical effort.

2.3.2 “IM” Between Health Care and Research

The situation in the English language area is quite similar. One can find an existing range of explanations of the “IM” or “PM” term here also which linguistically and logically cannot reach the severity of a scientific definition. Only two examples shall be provided here:

The Council of Advisors on Science and Technology, which is advising the US president, discusses the term “Personalized Medicine” in its report “Priorities for Personalized Medicine”. Although the health care perspective is the main focus here under the keyword “tailoring of medical treatment”, a wording is used which is broadening, if not softening, regarding the genus problem:

> “Personalized medicine” refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment (President’s Council 2008).

When talking about the “tailoring of medical treatment” the cited explanation refers to a metaphoric expression at a logically crucial point. This is blurring with regard to the genus question in respect that one could ask if “tailoring” of medical treatment in view of individual characteristics of patients is understood as part of health care or if it is rather situated in the field of medical research.

Another explanation given by Costigliola et al. (2009) lies on the border between research and health. This explicative “border-crossing” is linguistically also caused by a figurative phrase. Costigliola et al. (2009) write in order to introduce the expression “Predictive Medicine”:

> Predictive Medicine is a new philosophy in healthcare and an attractive subject for currently initiated research activities aimed at a potential application of innovative biotechnologies in the prediction of human pathologies, a development of well-timed prevention and individual therapy-planning. The issue has several aspects which allow the expectations of great advantages for predictive diagnostics and personalized treatment as the medicine of future (Costigliola et al. 2009, p. 1).

According to this explanation, “Predictive” Medicine is not simply “a possible future health care”, as in Hüsing et al. (2008), but rather—much less clear—a “philosophy in health care”. “Philosophy” does not mean the academic subject, of course,