

Chapter 2

The Meaning of “Individualized Medicine”: A Terminological Adjustment of a Perplexing Term

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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 pharmacogenetics 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. 2008 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 *cares*, 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,

but rather—in a figurative sense—a “(basic) orientation”, “background concept”, “guiding principle”, “trend”, “development” (the authors use the expression “development” themselves for reasons of explanation), maybe “vision” also, in any case something abstract, which begins to shape and change health care on the level of terms, concepts and ideas.

The explanation by Costigliola et al. 2009 aims at or tolerates a certain openness of the term “Predictive Medicine” towards not solely health care aspects. However, it does not provide a suggestion which meets the *scientific* demands of a definition.

2.3.3 “IM” as *Medical Line of Research*

The two English explanations are examples of how figurative phrases can lead to the problem that “IM” or “PM” cannot be assigned to the genus of health care, as clearly as in Hüsing et al. 2008. However, there are also explanations which are really alternative to the understanding of “IM” (or “PM”) as new health care insofar as the term “IM” (or “PM”) is decidedly used for describing a phenomenon which is situated in the field of medical *research*.

One definition which develops this genus alternative with a demand of linguistic exactness is the following “working definition” suggested by Marckmann 2011.

Working definition: personalized (or individualized) medicine tries to identify individual (especially biological) factors which allow a better prediction of the risks of diseases and effects of therapies. [The] aim [of personalized or individualized medicine is]: a better prevention, diagnosis, prognosis and therapy tailored for the individual. (Marckmann 2011, additions within the quotation by the authors)

Although this definition does not have an “Aristotelian” structure externally, the special wording “tries to identify individual factors” shows that “PM”/“IM” is seen as a line of research which is characterized and united by a certain *τέλος*, i.e. the “individualization” of health care by identifying predictors. Thus, “PM”/“IM”—both expressions are used explicitly as synonyms by Marckmann 2011—fall under another genus than the “PM”/“IM” terms which have been discussed so far.

Accordingly, PM was qualified as a medical research approach in a no longer accessible article on the German website of the pharmaceutical company Merck-Serano, which is literally quoted and thereby partially conserved in Langanke et al. 2012b:

Personalized (stratified) medicine is a new and important approach of the modern medical research. In the course of this concept, medical solutions shall be found which are specifically tailored for the need and circumstances of individual patients or certain patient groups. (Langanke et al. 2012b, p. 302)

If “IM” or “PM” is included in the generic terms “medical line of research” or “medical research approach” as in the cited explanations, it has to be clarified what “line of research” or “research approach” means. This task is demanding in the view of theory of science. However, for our purposes it is sufficient to adjust both terms

in the following way: “Line of research” (in the following synonymous: “research approach”) means a system of scientific assumptions and procedures which are especially suitable for reaching a certain aim within a certain science or scientific branch. A line of research or a research approach does not have to have the form of a proper research program *sensu* Lakatos 1978. But it is crucial that representatives of the same research approach are like-minded when it comes to pursuing a certain scientific target in a certain way. This way is described by a certain spectrum of methods and the (theoretical and/or empirical) assumptions which support these methods.

If one accepts this explanation, further specification is needed: aims within sciences can be hierarchically graded, i.e. they can be more or less general or specific. The “primary” or “highest” aim in medicine, for instance, could be to heal or to reduce suffering. However, such a general aim is not suitable for constituting a line of research because it cannot be operationalized by using certain methods. Aims which constitute fertile and promising lines of research are defined on a lower level in that sense that they are formulated in the light of specific methods and in the knowledge about what these methods can do. In these operationalized aims working instructions regarding their pursuit are roughly “included”. Such a “well-formed” aim is, for instance, given when pharmacogenetics, as a medical line of research is aiming at a better prediction of the effects or side effects of pharmaceuticals through the systematic use of biological information about metabolizing dispositions of certain patient groups. This aim can be pursued with specific procedures.

2.4 Is Everything IM? The Question of Specific Difference

The leading aspect of evaluating the explanations and definitions in paragraph 2.3 was the genus problem. To which class of phenomena—we asked—belong IM/PM according to certain definitions? It was noticed that beside many loose and therefore not clear definitions, there are two scientifically valid suggestions: on the one hand, the IM and PM terms aim at activities which can be summarized under the generic term “health care”. On the other hand, the IM and PM terms open up a category under the generic term “medical line of research”.

If one asks, whether one of the two alternatives should be preferred or if a synthesis of both is desirable, it must be noticed, that by clarifying the genus questions, only half of the demands of the Aristotelian concept of definition will have been met. According to this concept a term is defined by providing specific characteristics. Then based on these specific characteristics a certain subgroup of phenomena can be distinguished from similar phenomena within the same genus. If applied to the IM or PM term, further investigation is needed with regard to how and by which means IM/PM can be distinguished from other health care or other medical lines of research.

2.4.1 *Individual or More Individual Medicine?*

Hüsing et al. 2008 distinguish five “concepts of individualization” within PM/IM which can be assigned to two strikingly different scientific and technological branches:

The first branch includes scientific and technological developments which aim at tailoring therapeutic and preventive intervention for the individual patient in the sense of unique measures. [...] The second [...] branch is based on the knowledge that dispositions for certain diseases determine the development of the disease and its course through a complex interaction of genes, environmental factors, lifestyle and social status as well as intervention [...]. The manifestation of these factors is different for every individual. With the help of sufficient biomarkers a better stratification of the patient population shall be achieved regarding the actual clinical problem which goes beyond the status quo. (Hüsing et al. 2008, p. 37)

If applied to the genus decision by Hüsing et al. 2008, this means that IM/PM is a possible future health care that

- a. is orientated at using therapeutic and preventive measures which are adjusted for the individual in a strict sense *and also*
- b. could be characterized by using medical means which address patient *collectives*, but in a more efficient way because the *means* are adapted more precisely to a certain subgroup of patients by making use of biomarker based stratification.

That this “and also” is “covering up” an important methodical difference on the level of the specific difference which was already mentioned in paragraph 2.2. Thus, it is sufficient here to emphasize that from our point of view the so-called “first strain” and the stratification concept of the “second strain” by Hüsing et al. 2008 are methodologically incommensurable approaches.

2.4.2 *Stratification—A New Paradigm Within Health Science?*

We have methodological concerns about combining the two approaches mentioned above, namely the specific patient approach and the concept of biomarker based stratification. If these concerns are met with approval, explanations such as the explanations of the US Council of Advisors on Science and Technology, which refer to one of these concepts of individualization become more plausible.

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)

If one chooses the stratification concept in order to understand the specific aspect of IM/PM, one has to face another problem, which cannot be ignored here: “Stratification”. In the German term “*Feinerstratifizierung*” one can see, by the use of the comparative form for the prefix, that stratification is not a *categorically*, but

only a *gradually* definable phenomenon: patient populations have for a long time already been stratified in the field of medicine. If IM/PM is now claiming that it uses the procedure of classification (or: taxonomical) division, which is the logical key principle of stratification of patient populations, in a more sophisticated, i.e. more precise way, it means indeed that within IM/PM nothing fundamentally new is done, rather a well-known instrument is being used in a refined way only. In the light of this it must be noted that wherever

- a. on the one hand, IM/PM stands for an approach, which is based on the stratification of externally uniformed patient populations with the help of biomarkers, and whereas
- b. on the other hand, this procedure is declared “new” or “innovative” or even—with regard to the very demanding discourse about the philosophy of science—a new medical “paradigm” (Kuhn 1970),

one has to be cautious. Certain medical fields have been using the underlying principle for a long time in the frame of their diagnostic and therapeutic routine. Thus, it is already in use as standard in the field of oncology where (1) endocrinological or genetic parameters are used for the molecular characterization of tumors and can therefore be used for a more individual and more effective coordination of therapy or (2) where certain medications are only prescribed when a genetic test was done beforehand which proved the patient’s genetic disposition of metabolism or that certain molecular structures (surface molecules), where certain therapeutics (e.g. monoclonal antibodies against these surface molecules) target, are expressed or over-expressed (Hasler-Strub 2009).

2.5 Individualized Medicine—Definition and Explanations

The explanation by Hüsing et al. 2008, which we have referred to several times, is suitable to show the semantic “irritations” which caused the authors of this chapter to work out a term of its own for GANI_MED.

- a. The “IM” term in Hüsing et al. 2008 is semantically narrowed on the genus level. This constriction occurs because the IM term is solely ascribed to the generic term of health care. Thus, a linguistic standardization is made for the term “IM” which is not suitable to define certain activities in the field of medical *research* as “IM”. For the authors of this chapter, this seems counter-intuitive. Moreover, this terminological decision leads to linguistic problems within the discourse about current scientific research projects regarding IM.
- b. On the other hand, the opinion of Hüsing et al. 2008 seems to be too tolerant when it comes to the question of specific difference. By combining the two methodologically incommensurable concepts of individualization, the term of “Individualized Medicine” is not provided in a way that it defines a methodologically joined and in this sense homogenous class of phenomena. It rather defines a heterogeneous field of different medical activities in a loose way.

Individualized Medicine

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