Nanoethics (2009) 3:243–255
DOI 10.1007/s11569-009-0078-7

ORIGINAL PAPER

Tensions and Opportunities in Convergence: Shifting Concepts of Disease in Emerging Molecular Medicine

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Received: 5 November 2009 / Accepted: 5 November 2009 / Published online: 21 November 2009

Abstract The convergence of biomedical sciences with nanotechnology as well as ICT has created a new wave of biomedical technologies, resulting in visions of a 'molecular medicine'. Since novel technologies tend to shift concepts of disease and health, this paper investigates how the emerging field of molecular medicine may shift the meaning of 'disease' as well as the boundary between health and disease. It gives a brief overview of the development towards and the often very speculative visions of molecular medicine. Subsequently three views of disease often used in the philosophy of medicine are briefly discussed: the ontological or neo-ontological, the physiological and the normative/holistic concepts of disease. Against this background two tendencies in the field of molecular medicine are highlighted: (1) the use of a cascade model of disease and (2) the notion of disease as a deviation from an individual pattern of functioning. It becomes clear that molecular medicine pulls conceptualizations of disease and health in several, partly opposed directions. However, the resulting tensions may also offer opportunities to steer the future of medicine in more desirable directions.

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Keywords Molecular medicine · Nanomedicine · Concept of disease · Concept of health · Technology · Reductionism · Personalized medicine

> '… deep molecular familiarity with the human body, along with simultaneous nanotechnological engineering advances, will set the stage for a shift from today's molecular scientific medicine in which fundamental discoveries are constantly being made to a molecular technologic medicine in which the molecular basis of life, by then well known, is manipulated to produce specific desired results.' ([13]: 162)

According to their proponents, converging technologies will bring about wonders. They are expected to bring many benefits to all kinds of domains, and medicine is no exception [34, 35]. It is said that the convergence of biomedical knowledge with nanotechnology and information and communication technologies (ICT) will 'revolutionize' medical science as well as health care practice. As the American nanomedicine pioneer Robert Freitas announces, such convergence may lead to a form of medicine that is thoroughly 'molecular'. It will use knowledge of molecular bodily functioning as well as nano-sized instruments ('molecular machines') to intervene in bodily processes at the molecular level.

Freitas' sketch of the future of medicine is highly speculative. His expectations reveal the impatience of

the techno-enthusiast. However, his claim that a 'molecular medicine' is emerging, based on the convergence of different technologies, is certainly grounded in current visions and techno-scientific developments. Both the United States and Europe have recently been developing visions, research agendas, roadmaps and funding opportunities for nanomedicine in which 'molecular medicine' is a guiding ideal [10, 11, 27].

Even though, or perhaps particularly because, the applications are as yet limited, the nature of the visions involved deserves philosophical attention. What exactly is envisioned for the future of medicine? Will it simply offer more effective tools to realize the widely shared goals of reducing disease/suffering and fostering health? Or will these goals themselves be transformed during the process? As pointed out in the introduction to this special issue, converging technologies tend to shift the meaning of many basic concepts we use to make sense of the world: they shift the 'symbolic order'. This paper elaborates this claim in relation to converging technologies in the medical domain. The central question is: Will current and future developments towards a molecular medicine shift the meaning of 'disease' and 'health', and if so, in which direction?

To investigate the conceptualization of disease and health in molecular medicine I will first present the visions, expectations of and ongoing developments in this domain. Subsequently, I will briefly discuss how technology in general constitutes 'disease' and present three ways of conceptualizing disease that are well known from the philosophy of medicine: the ontological or neo-ontological, the physiological and the normative/holistic concepts of disease. These different conceptualizations will then be used to analyse the way disease is conceptualized in the visions of molecular medicine. It will become clear that molecular medicine pulls the conceptualization of disease and health in several, partly opposed directions. I will conclude by discussing the resulting tensions and problems, as well as the opportunities these seem to offer for steering the future of medicine in more desirable directions.

Molecular Medicine: An Emerging Domain Enabled by Converging Technologies

What are we talking about when we speak of 'molecular medicine'? First, it should be noted that I use this term as the common denominator for a wide variety of technological, scientific and social developments and visions of the future of medical science and health care, all of which are enabled by converging technologies. Thus, molecular medicine in my view is more than a set of technological devices; it is a complex network of technological, scientific and social developments that mutually interact with each other. Moreover, these developments are driven by common visions of what the practice of medicine should be all about. However, by using one term, this paper inevitably makes these developments and visions seem more homogenous as well as more real than they actually are. It is important, therefore, to keep in mind that we are talking about an emerging set of visions and developments that seem to be moving in a similar direction, a large part of which is still speculative in nature.

Secondly, converging technologies in the medical domain are sometimes also denoted by the terms 'bionanotechnology' or 'nanomedicine'. Bionanotechnology refers to the convergence of life sciences and nanotechnology and thus includes non-medical applications (see for example [1]; [20]). It is too broad for the focus of this paper. Nanomedicine, on the contrary, seems to capture most of what I will denote here as molecular medicine. It is already a commonly known term, used in Europe and the United States to refer to 'the application of nanotechnology to health' ([10]: 6) or to 'medical intervention at the molecular scale for curing disease or repairing damaged tissues' [27]. Although 'nanomedicine' may be the more commonly used term, I prefer to use 'molecular medicine' for three reasons. To begin with, 'nanomedicine' neglects the important role of ICT in visions of medicine's future. Without the creation of huge databases, as well as methods for the analysis and communication of data, most applications of nanotechnology for medical purposes would not be realized at all. Like nanotechnology, ICT enables biomedical science and practice to develop in a specific direction. More importantly, however, by focusing on medical practice rather than technology, 'molecular medicine' allows us to conceive of the emerging developments and visions as including much more than a new set of devices. These devices require a specific social organization as well. Focusing on molecular medicine helps to envision how molecular tools articulate and reconfigure specific

forms of medical practice. Finally, 'molecular medicine' brings into very clear focus the central idea guiding these developments: disease and health are molecular processes and should be dealt with at that level (for a similar comparison of nanomedicine and molecular medicine see [25]: 174). In this respect molecular medicine differs from 'biomedical nanotechnologies' more broadly conceived, that use the characteristic properties of materials at the nanoscale for medical purposes [44].

That said, how is molecular medicine defined? Different definitions are circulating, but the recurring principle of all of them is to identify the molecular processes related to disease, as well as to design interventions in these processes that might counter or even prevent disease. As the journal Molecular Medicine states on its website:

> 'Molecular Medicine strives to understand normal body functioning and disease pathogenesis at the molecular level which may allow researchers and physician-scientists to use that knowledge in the design of specific molecular tools for disease diagnosis, treatment, prognosis, and prevention.'
>
> (source: http://www.molmed.org/about.html; accessed 2 September 2009)

Molecular medicine thus encompasses an approach in medical research as well as a vision of future medical practice. Scientific insight into bodily processes at the molecular level should lead to applications with medical purposes. As the National Institutes of Health put it, the first phase is concerned with 'understanding nature's rules of biological design that in turn will enable researchers to correct defects in unhealthy cells', whereas in a second phase 'the acquired fundamental knowledge and developed tools will be applied to understanding and treating disease.' [27].

Although its proponents promote molecular medicine as a novel and revolutionary enterprise, the idea that insight into molecular processes is crucial to understand and counter disease is actually much older. Physical chemist and Nobel Prize winner Linus Pauling is said to have coined the term 'molecular disease'. He is also credited with the idea of molecular medicine more generally. In 1949 he and his colleagues published a paper in Science entitled 'Sickle Cell Anemia, a Molecular Disease' that was commemorated in the same journal 50 years later, where it was described as "laying the groundwork for establishing the field of molecular medicine" ([29]: 543; [42]: 1488).

Pauling's idea only gained real driving power, however, when technologies that opened up these processes for human scrutiny became available. Since the 1990s, developments in nanotechnology have made it possible for biomedical scientists to observe human bodily functioning at the molecular level, for example, by novel imaging techniques or by lab-on-a-chip technology. In addition, the specific properties of nano-sized materials are exploited for monitoring and manipulating bodily processes. The investigation of the relationship between particular diseases and the occurrence of specific molecules ('biomarkers') was further enabled by the development of ICT, providing tools for the collection, storage and analysis of the huge amount of data necessary for this type of research. Biological functioning at the molecular level is conceived of as the continuous exchange of information. The molecular approach in medicine thus provides a clear example of the power that can emerge when biomedical science, nanotechnology and ICT converge.

Boosted by technological developments, molecular medicine began to institutionalize. In the 1990s several countries established research institutes focusing on this domain and an international journal was also founded (see www.molmed.org). The first textbook was published in 1998 [18], with an updated edition appearing in 2006 [37]. In the first decade of the new century, several Master's programmes and private companies explicitly focusing on molecular medicine emerged and the concept became visible in government and scientific funding programmes in several countries (for example in the Roadmap of the National Institutes of Health 2004; in the European Technology Platform's Nanotechnology for Health—Vision Paper and Basis for a Strategic Research Agenda 2005 and Strategic Agenda on Nanomedicine 2006; and in the Business Plan of the Dutch Centre for Translational Molecular Medicine [7].

As indicated above, molecular medicine is both a field of research and a vision of the future of medical practice. How then might this type of research change medical practice? From the current literature, seven different (often interlocking) aims can be derived:

1. Earlier and more reliable diagnosis
2. Improving prognosis and reducing over and undertreatment

3. Improving the effectiveness of drug therapy
4. Exploiting the regenerative capacity of the human body
5. Less invasive or burdensome medical technologies
6. Monitoring bodily functioning
7. Personalizing health care

In relation to all of these aims, there have been some successes, while many more applications are in development. Examples of existing technologies and those under investigation can be found in Table 1.

Taken separately, the aims summarized above are not very spectacular as most of them are familiar from earlier forms of medical research and practice. In the most far-reaching visions of molecular medicine, however, the functions of monitoring, early diagnostics, prevention and/or effective therapy are combined into an all encompassing system of medical care that is nonetheless claimed to be of little burden to the patients. Since the envisioned tools of molecular medicine are expected to be very small, they can be ubiquitous without the subjects involved noticing. In the guiding visions of molecular medicine, then, health care will extend both in time as well as in place.

Firstly, molecular medicine is envisaged to be active 24 h a day, 7 days a week, and from the cradle to the grave. It will enable the continuous monitoring and adjusting of the bodily functioning of individuals:

> 'Future applications of nanobiotechnology include development of in vivo sensors. Nano-sized devices are envisaged that could be ingested or injected into the body, where they could act as reporters of in vivo concentrations of key analytes. These devices would have a capability for sensing and transmitting data to an external data capture system. The constant vigilance of these devices would provide a real-time, 24/7 scrutiny of the state of a person's health.' ([12]: 172–173)

> 'Ultimately, it might be envisioned that when an infant is born, a blood sample will be collected for the purpose of determining the baby's genome. The information will then be used throughout that person's life to guide primary prevention strategies, make diagnoses on a molecular basis, and individualize drug therapy.' ([19]: 304–305)

Secondly, and closely related, both monitoring and intervention can take place anywhere. The miniaturization of medical instruments will allow them to travel beyond the walls of laboratories and hospitals to the everyday world of home and work:

> 'The integration of minimally invasive diagnostics with information technology for remote monitoring of the patient's condition may produce a radical shift of the point of care from the hospital or clinic to the home.' ([33], cited in [9]: 16–17)

Table 1 Goals and examples of current and future applications in molecular medicine

Goal	Example of an existing application	Examples of applications in development/envisioned
Earlier and more reliable diagnosis	Micro arrays for heart disease ([43]: 48)	Molecular machines detecting (and destroying) very first cancer cells [27]
Improving prognosis and reduction of over and undertreatment	DNA chips, micro arrays for breast cancer ([40]: 75–76)	DNA chips for leukaemia, mouth and throat cancer ([14]: 45)
Improving effectiveness of drug therapies	Polymeric nanocapsules for drug delivery ([10]: 10)	Drug delivery systems for brain disease, nanoplatforms, theranostics ([36]: 46–47)
Regeneration of bodily material	Twenty types of in vitro engineered tissue, including skin & cartilage ([24]: 3235)	Langerhans' islet regenerating therapy for diabetes ([10]: 10)
Minimizing invasiveness and burden of medical technology	Lab on a chip for monitoring lithium levels ([14]: 47)	Lab on a chip for colon cancer detection; wet sensors
Monitoring bodily functioning	Implantable chip measuring heart beat, temperature and blood sugar level ([9]: 16)	Implantable device for continuous measurement of blood markers ([12, 38]: 172–173; [10]: 10)
Personalizing health care	Treatment decisions based on biomarker tests specifying tumour subtypes ([40]: 75–76)	Molecular passport for life-long use ([19]: 304–305)

To conclude with one more citation from Freitas:

> 'Nanomedicine will involve designing and building a vast proliferation of incredibly efficacious molecular devices, including medical nanorobots, and then deploying these devices in patients to establish and maintain a continuous state of human healthiness.'([13]: 162)

Concepts of Disease and Health and the Role of Technology

In all the talk about molecular medicine, whether it is about a specific application or about grand visions, the developments are justified in terms of the value of health and the reduction of disease. These are widely shared goals with which it is difficult, though not impossible, to take issue. However, disease and health are also very elusive categories of our symbolic order. These concepts capture a rich set of meanings with regard to the phenomena of suffering and wellbeing. The boundary between the two is relevant to the distribution of many social roles and moral responsibilities, such as who may claim medical treatment, who is allowed to avoid specific duties and what is considered responsible behaviour.

Philosophers have spent much time and energy trying to capture the essence of these concepts and to determine the boundary between the two. These endeavours have been frustrated by the awareness that the meanings of 'disease' and 'health' tend to evolve in time. Several forms of behaviour or experiences that were characterized as diseases at times in the past, such as female hysteria and homosexuality, are not so today. In addition, individual cases have been either included or excluded from disease categories because explanatory models of disease have radically changed. This has raised the question of whether these changes in meaning are due to evolving phenomena, to changing knowledge and explanatory models, to technological developments, or whether they are just the result of the imprecise use of language.

This is not the place to address these questions in detail. I will align myself here with those philosophers who argue that the meaning of 'disease' is not something out there to be discovered with the appropriate objective methods (see for example [6, 26]). Our view of disease, as is our view of reality in general, is thoroughly mediated by the vocabularies and frameworks used with regard to the human body. These in turn are deeply influenced by the technologies that open up the body for investigation. Hofmann [15] has shown that technology provides the physiological, biochemical and biomolecular entities that are applied in defining disease. Moreover, it constitutes the signs, markers and end points of disease, influences explanatory models and establishes how we act towards disease. As he rightly argues, this amounts to the conclusion that 'disease' is invented technologically ([15]: 18).

Applied to current developments towards a molecular medicine, this means that the technologies enabled by the convergence of biomedical science with nanotechnology and ICT are predicated on, and at the same time reinforce, a particular way of looking at and dealing with disease. Due to technological and theoretical changes, the implied concept of disease may also evolve. Whether such changes can be discerned and if so, how they should be characterized, is the central question of this paper.

It may be helpful to distinguish and outline (be it very schematically) three concepts of disease often used in the philosophy of medicine as an initial framework with which to analyse and interpret the potential changes that molecular medicine might bring about. I will call them the ontological or neo-ontological, the physiological and the holistic concepts of disease [8]. As Hofmann shows in his extensive review of the positions and arguments in this field [16], the debate is much more complex and often confusing. It is not my aim to do justice to all the nuances, let alone to resolve the complexities. I will confine myself here to delineating three positions that I think may be helpful in analysing developments in molecular medicine.

The ontological conception of disease implies that 'disease' names entities in the world ([8]: 1076–77; [41]: 197). According to this view, a disease is an entity (an *ens morbi*) that can be identified and observed. Such an entity can be external (a virus or bacteria) or internal (a tumour or altered organ). It is there to be discovered and can be classified according to its natural kind. This view of disease is very old and still underlies many lay beliefs concerning disease as well as some medical-scientific views of disease.

In some cases, the 'disease' is equated with its presumed cause, for example, an altered cell or

aggregate of cells ([8]: 1076–77). This view was defended at the end of the nineteenth century in the mature work of Virchow, and was revived during the rise of genetics at the end of the twentieth century. In addition, the tendency to see a gene as the cause of the disease has sometimes led to the identification of gene and disease. At the very least a neo-ontological perspective is discernible in these cases [41].

However, the ontological view is not very prevalent in the philosophy of medicine. Its main weakness is that it has difficulty accommodating the many changes in our perception of and behaviour towards disease. This has led most philosophers and many medical professionals to opt for what is often called a physiological concept of disease. This view of disease focuses on abnormal bodily functioning, where disease is understood as a deviation from normal functioning ([8]: 1076; [41]: 197). Unlike the ontological view, it conceives of disease as a process in time, rather than as a stable bodily state. Moreover, it explicitly views disease in relation to other normal bodies, be it the same subject's body at an earlier time or the bodies of comparable subjects in a predefined population. A physiological concept of disease is thus comparative, but also nominalist and conventional: what disease is depends on what is considered normal. This also explains the constitutive role of science and technology in the definition of disease. Since science and technology constantly change our beliefs about what constitutes normal bodily functioning, the relevant points of reference may change over time.

The physiological view is clearly normative in a limited sense, since it refers to what is normal and what is not. However, opinions differ as to whether or not such a norm can be established in a value-neutral way ([16]: 223–24; [22]). An influential representative of the physiological view, Boorse, maintains that health and disease are neutral descriptions of a state of affairs [4]. According to Boorse, disease is an impairment or limitation of the functioning or abilities that are typical for one's species. When specifying the functions that are integral to being human, Boorse relies on an evolutionary perspective (in particular survival and reproduction), thus claiming to present a naturalistic justification of the norms which establish the boundary between disease and health [4, 5].

Others have argued, however, that the concepts of disease and health are inherently evaluative. Nordenfelt argues for a holistic view of disease, in which disease is an 'incapacity diminishing an individual's ability to reach her vital goals' [22, 28]. From this perspective, disease is linked to specific normative views on what it means to live a good life. These may be shared within a culture, but Nordenfelt explicitly leaves open the possibility that these goals vary between individuals. As a consequence, what is considered to be disease in case of one individual may not necessarily be so in case of others.

Concepts of Disease in Molecular Medicine

If molecular medicine is successful in its attempt to open up and intervene in processes of disease and health at the molecular level, it is only to be expected that specific diseases will be redefined and reconfigured by these developments. 'Disease' will be increasingly connected to the basic biological processes occurring in the body. This may lead to redefinitions, further distinctions of subtypes, as well as to extensions of specific disease labels. For example, at present, Alzheimer's Disease (AD) is considered to be a singular disease, provisionally identified by a combination of results on psychometric and biological tests, but definitively established only by pathological, post mortem proof of 'plaques' in the brain. However, the identification of molecular biomarkers for AD might very well lead to a specification of several subtypes of AD linked to these biomarkers and the disease pathways they suggest. Moreover, if a biomarker could be identified in asymptomatic individuals (or in cases of what is currently called Mild Cognitive Impairment), the label AD might be applied to a much larger group of individuals.

Considering the developments towards molecular medicine presented above, it can be argued that the redefinitions and reconfigurations they may cause are likely to take a specific direction. Molecular medicine stimulates a specific type of thinking about disease. I will highlight two tendencies in this way of thinking. The first is related to the search for molecular biomarkers which predominates in the emerging field of molecular medicine. This search seems to hinge on what I will call a cascade model of disease. The second tendency is linked to the guiding vision of personalizing health care, for which continuous

monitoring of bodily functioning is a crucial condition. Here, disease is conceived of as a 'deviation from an individual pattern of functioning'. I will discuss both tendencies successively.

Cascade Model of Disease

The thought that seems to provide impetus to most molecular medicine is that by opening up the molecular level of bodily functioning it will become possible to reconstruct the disease process itself. This ambition is both intellectual and practical in character. Molecular medicine, it is claimed, provides knowledge of and insight into the natural history of disease. As systems biologist Leroy Hood and colleagues (involved in the Roadmap Initiative of the National Institutes of Health) state: 'The dynamic progression of disease should … be reflected in temporal change(s) from the normal state to the various stages of disease-perturbed networks.' ([17]: 640). Such knowledge and insight would, subsequently, provide a truly scientific basis for timely medical intervention:

> 'Given enough measurements, one can presumably identify distinct patterns for each of the distinct types of a particular cancer, the various stages in the progression of each disease type, the partition of the disease into categories defined by critical therapeutic targets, and the measurement of how drugs alter the disease patterns. … In this scenario, molecular diagnostics will become an invaluable tool for molecular therapeutics. '([17]: 641)

No more trial and error, no more medicine as the art of healing: in the era of molecular medicine interventions will be based on knowledge of the most fundamental level of bodily functioning (for similar statements see the examples in [23]).

As is clear from Hood's work, but also from the research agendas of the National Institutes of Health and the European Technology Platform on Nanomedicine, molecular biomarkers are a focal point of concern in current developments advancing molecular medicine. Such biomarkers are thought to indicate specific stages in the process of bodily functioning. They can be changes in biochemical characteristics (for example DNA, RNA, protein, peptid) or anatomical characteristics (for several slightly different definitions of a biomarker see the [32]: 99–100; [10]: 3; [2]). Biomarkers are identified by molecular epidemiological research (often enabled by huge biobanks) which looks for relationships between specific molecular characteristics and the occurrence of disease.

Ideally, biomarkers may be used to reconstruct what is called the 'molecular pathway' or 'molecular network', the series of biochemical reactions in a cell, which in turn may be the starting point for the reconstruction of a 'disease pathway', that is, the chain of events leading to symptoms and complaints. Again, such a pathway is conceived of as a series of interconnected biochemical reactions, but now on the level of tissue, organs and the body as a whole, as well as within the cell. Both within the cell and the body at large, each reaction is thought to be dependent on one or more specific preceding reactions.

The implicit model of disease underlying this endeavour to reconstruct complete disease processes is that of a cascade: molecular changes in the cell lead to changes on the cellular level, transforming the functioning of tissues and organs, and meanwhile causing symptoms, signs and subjective experiences of non-wellbeing. In this way, in a series of steps quite small changes may lead to ever larger changes that in the end have very serious consequences for someone's health. Such a cascade model of disease conceives of disease as a process evolving in time as well as gradually extending in bodily space. It therefore strongly suggests the need for early intervention, as a freely flowing cascade is very difficult to stop.

The cascade model is not new to medicine. It has been the rationale behind many existing forms of preventive medicine for quite some time, in particular all forms of screening and attempts at early diagnosis. Its implicit use in the vision of molecular medicine is ambiguous, however. In some cases it seems to hint at a neo-ontological view of disease, but it can also be interpreted as reflecting a physiological view of disease. The neo-ontological interpretation is apparent when the search for biomarkers is equated with the search for the ultimate causes of disease. As in genetics, it is tempting to identify a disease with its presumed cause because this implicitly suggests that it is possible to eradicate it completely. Such a neo-ontological view is problematic because it reifies the disease process and views it as a specific state, thus neglecting the relevance of subsequent developments (that may or may not lead to experiences of suffering or disability).

The image of a cascade, however, may also accommodate a physiological view of disease. It points, after all, to the dynamic character of disease as a process extending in space and time. The physiological concept of disease is also visible in the way the meaning of biomarkers is established: by population research defining normal and abnormal functioning. Approaches in molecular medicine adhering to the physiological view are not guilty of reification and pay serious attention to disease dynamics. In practice, however, these dynamics are conceived of in a limited way: as a linear, automatic process and as reducible to bodily phenomena.

Viewing disease processes as automatic and linear neglects the possibility that they may be quite complex, with many interactions, feedback loops and several end points that may or may not have clinical significance [31, 39]. The direction of cause and effect is thought to move in one direction only, from molecules to cells to tissue to organs, whereas causal paths may also move in the other direction ([23]: 440–441). However, even if the complexity of bodily processes is acknowledged (which seems to be the ambition of systems biology approaches, for example), this way of modelling disease usually remains reductionist. The physiological variant of the cascade model still tends to reduce disease to a bodily defect, neglecting the role of the body in personal functioning and the relevance of the natural, social and cultural environment of individuals [21, 23].

Molecular medicine thus seems to hinge on a view of disease that is ambiguous as well as problematic in several respects. It might be argued that the problems observed above result from interpretations of the cascade metaphor that do not sufficiently acknowledge its richness. This would lead to a plea for more complex interpretations, which would make it apparent that a cascade is the result of the interaction, for example, between water and the environment. However, it remains to be seen how far the metaphor can be stretched. Moreover, the conception of disease as a cascade has two well-known effects that may, in any case, not be desirable.

For a start, the cascade model implies that disease can be asymptomatic, because it starts in a limited space and only extends later, with symptoms and complaints usually appearing at a relatively late stage. This means that individuals who do not experience any complaints may nonetheless be diagnosed as 'having a disease' The cascade model thus further severs the connection between subjectively experienced illness and objectively discernible disease. As a consequence, human beings must be considered incapable of monitoring their own health, as only the appropriate technology can reveal whether or not a body is diseased. This has led some to argue that such a view of disease reinforces paternalistic practices in medicine, since it reduces the role of the patient ([16]:227). This is true insofar as the appropriate technologies can only be applied by professionals. However, even if molecular medicine offered ample opportunity for self-monitoring, the potential gap between bodily experience and technologically mediated data should still be considered.

Closely related to this implication is a second effect that has already been pointed out: the cascade model of disease stimulates early diagnosis (or even the identification of groups at increased risk of disease) and early intervention (or prevention), since it suggests that the cascade can only be stopped if it is still in its early stages. If a full-blown disease has developed, it will be much more difficult to counter and drastic interventions may be required. As long as the disease models do not sufficiently acknowledge the complexity of disease processes, however, it seems probable that molecular diagnostics will not detect disease, but predict the future development of bodily processes. Only some of the individuals diagnosed with a specific biomarker will exhibit the expected disease process and end up with clinical symptoms and complaints. This means that biomarkers will function as predictors of increased risk. Whether they are more accurate than traditional risk estimates based on genetic, lifestyle or personal characteristics is a question that will have to be answered on a case-by-case basis.

In any case, the probabilistic character of biomarkers will give rise to the question of how to interpret the uncertainty involved when dealing with individuals. When is it justified to act on the basis of biomarker diagnosis rather than waiting to see how bodily processes develop? And who is to decide? Although these issues are already well known in the domain of predictive genetic diagnostics, no easy answers are available.

Disease as Deviation from an Individual Pattern

The second transformation in thinking about disease that molecular medicine may produce is not related to

the substance of what is being measured by molecular diagnostic tools, but to the procedures used in measurement. As indicated above, in the vision of a truly molecular medicine, both the timing and the location of medical activity change considerably. If the diagnostic tools become ever smaller and less invasive or burdensome, it becomes easier to increase the frequency of measurements. Moreover, the tools to be used may no longer be tied to a specific location, such as the hospital or the lab. Thus, the continuous and ubiquitous monitoring of bodily functioning seems to become a serious possibility. Let me quote systems biologist Leroy Hood once more, who believes that molecular changes in diseased tissue may be expressed in the pattern of proteins in the blood:

> 'New technologies will generate a hand held device that will be able to analyze a fraction of droplet of blood for 1,000 or more proteins and these will be a window into health and disease. This will be done twice a year. The information will be fed into a cell phone and then to a server, and then it will be analyzed and the patient and their physician will get an e-mail that says, "You are fine; do this again in six months." Or, "You should see your oncologist."' (Hood cited in [23], 436)

This vision is clearly inspired by the cascade model of disease, since it urges early diagnosis. However, the concept of disease here is definitely physiological. The outcomes of the biannual measurement of a set of biomarkers are to be compared to an existing set of data, defining the boundaries of what is to be considered 'normal', that is, healthy. Disease is seen here as a deviation from a pattern. But what pattern exactly? Whose functioning should guide the interpretation of results? Currently, normal values are usually defined on the basis of population means. In the era of molecular medicine, however, much more data about individual body functioning will be available, so that individual patterns may become much more important as a point of reference. This could result in a radical individualization of the boundary between health and disease. What is considered abnormal in one individual can be quite normal for another.

The ideal of personalized medicine that is often associated with the vision of and promises made on behalf of molecular medicine, ultimately implies a much more radical shift in thinking about health and disease than is usually acknowledged. Up to now 'personalized medicine' has most often been understood as a goal pertaining to the choice of therapy. The guiding thought then is that therapy should be tailored to the specific situation of the patient. In the era of molecular medicine this is usually interpreted in a reductionist way, meaning that therapy should be geared towards the biological characteristics of the disease. In practice, this goal is pursued by the identification of ever more subpopulations ([17]; for a similar argument in the context of nutrigenomics see [30]). Molecular biomarkers are thus an important tool for the improved stratification of patient groups. The hope is that these biomarkers will also provide clues for the development of therapies fitting those subpopulations, and thus reduce both under and overtreatment as everybody would receive the treatment to which they are expected to have the best response.

If the visions of molecular medicine were pursued to their radical end, however, personalization would mean much more than improved stratification. Personalization then becomes individualization: acknowledging the complexity of the individual case. If the ubiquitous and permanent monitoring of one's bodily functioning became possible, the resulting data might radically individualize both the definition of health and disease, as well as the boundary between the two. The physiological concept of disease might then be combined with or even give way to a holistic conception of disease, in which the goals and experiences of the subject would play a major role in the definition of health as well as disease. Personalization thus conceived is not just a means to realize the goal of medicine (restoring health or, more modestly, combating disease), rather it affects the goal itself [3].

One might wonder whether this radical implication departs too much from the scientific aspirations of modern medicine to be plausible, let alone desirable. It is true that medical practice exclusively based on knowledge of $n=1$ would have trouble in claiming to be 'scientific'. However, if one perceives the individual as situated at the potentially unique intersection of different stratifications, population research might still be relevant for the characterization of the individual case. An individual's bodily patterns would then be interpreted against the background of this population-

based knowledge. Such an endeavour implies a daunting task, both for medical science as well as the organization of health care.

Let me finish this section with four observations regarding what a radically individualized medical practice might entail. Firstly, it is ironic that the vision of molecular medicine as 'truly scientific' ultimately reminds us that we cannot do away with clinical judgment when it comes to dealing with individual cases. After all, a complex and daunting task of combining and weighing different types of evidence seems to await us. The more sophisticated and extensive the collection of data about bodily functioning becomes, the less easy it will be to draw conclusions about individuals. Any dream about the automation of medical judgment seems to evaporate when we realize that the interpretation of individual patterns still needs the input of the subject at hand.

Secondly, the radical individualization of medical diagnosis offers opportunities to reinforce the role of the subject (patient would not be the correct term here). As indicated above, the 'objective' data produced by the devices of molecular medicine must be connected to subjective experiences of the individual at hand to make any sense at all. Thus, it may not only become clear that individual bodies show a wide variety in functioning, but also that the relationship between bodily functioning and subjective wellbeing is less straightforward than is often supposed in medical science. However, if this is the case, it makes sense to leave ample room for subjective considerations about what does and what does not invalidate one's capacity to live a good life. Thus, establishing the boundary between health and disease becomes explicitly normative, or even holistic in Nordenfelt's sense.

Thirdly, increasing the role of the subject in medical practice is likely to make this practice more experimental. If an individual's situation is unique and cannot easily be compared with that of others, it is much more difficult to give guidance on when and how to intervene. Subjects will increasingly have to serve as their own guinea pigs through a lack of sufficiently representative preceding cases. This observation might be countered by arguing that such a lack of comparable cases has actually always hampered medical practice. The available evidence is much more crude than is usually acknowledged and does not suffice as a basis from which to advise individuals. Whether or not one is willing to grant this, it is clear that developments towards a molecular medicine not only urge us to reconsider the concepts of health and disease, but also the much used concepts of experimental research and regular care.

Finally, the development of a highly individualized medical practice will very likely raise complex issues with regard to the distribution of medical resources. What will be the conditions to qualify for medical care and who is to decide? If the definition of 'disease' is radically personalized, this presumably will have consequences for decision making about medical intervention as well. However, public resources for health care are limited, so choices will be necessary. As a result, the boundary between the medical domain and the domain of wellness may become fuzzier. Part of molecular medicine would then be developed for the market of the 'worried well'. One might even argue that it is much more important to ensure that all humans have access to basic health care and that molecular medicine is unjust if it deflects attention and funding from global public health needs. These are obviously important issues, which I cannot discuss in detail here, but which urgently call for attention[1].

Conclusion: Tensions and Opportunities in Molecular Medicine

The convergence of biomedical science with nanotechnology and ICT has led to an emerging molecular medicine. My analysis of the developments as well as the visions of the future circulating in this field shows that molecular medicine does indeed shift our symbolic order, at least as far as the concepts of health and disease are concerned. The direction of these shifts is, however, not unequivocally clear. Molecular medicine seems to pull our views on what health and disease are in different, partially contradictory directions. This may seem undesirable from a philosophical point of view if the focus is on conceptual clarity and coherence. However, it is not my aim here to propose a conceptually coherent

[1] This topic is actually dealt with in the draft Report from the Roundtable on Ethical and Social Aspects of Nanomedicine (Thorsten Kohl & Alfred Nordmann, rapporteurs, 2009), prepared in the context of the Nanomed Roundtable (http://www.nanomedroundtable.org/).

alternative. Nor do I have the time and space to systematically discuss the social and ethical impact of the shifts observed. I will briefly point to some undesirable effects of these shifts and conclude by pointing out how the existence of different views might precisely help to counter such effects.

As far as the cascade model of disease is concerned, I have shown that this model can be interpreted in a neo-ontological or in a physiological vein. The neo-ontological approach is often problematic because it leads to a reification of supposed disease causes. The developmental, dynamic character of bodily processes, as well as their interaction with the environment, is all too readily neglected. This effect may be partly countered by keeping in mind the potentially rich connotations of the cascade metaphor when interpreted in a physiological vein, because this view does acknowledge the dimension of time in disease.

However, as discussed above, the physiological understanding of disease in molecular medicine is often severely limited. It tends to work with a simple, linear model of disease causation and a biological-reductionist view of disease, in which the environment of the body receives very little attention. The first limitation might be countered by systems biology approaches within molecular medicine, which claim to leave the linear model behind and construct complex and elaborate network models of disease (for an example see [17]). However, Khushf [23]) notes that even within systems biology most attention is paid to the upward processes (from molecule to cell to tissue to organ, etc.). Interactions in the other direction, in particular with those levels in the systems hierarchy exceeding the individual, are rarely investigated. As Kushf argues, one might urge researchers in molecular medicine to take the implications of the systems metaphor more seriously.

The cascade model of disease, whether interpreted in a neo-ontological, physiological or systems biological way, generally supports an 'objectivist' approach to disease and health. Since disease is concealed within the body for a long time, with subjects only becoming aware of it quite late, devices and often professionals are necessary to determine whether someone is or is not diseased. Thus, a gap between subjective experience and objective measurement is created. Moreover, the proposed interventions are most often biochemical in nature. This model tends to reduce the role and influence of subjects and a large part of molecular medicine also displays this effect.

This undesirable effect might be countered, however, by molecular medicine's tendency towards more intense monitoring, implying that disease is as a deviation from individual patterns. If molecular medicine takes the ideal of personalization seriously and goes beyond stratification to individualization, this may offer novel opportunities for strengthening the subject's position in medical practice. Both subjective bodily experiences as well as individual views of the good life could become relevant considerations in future medical practice. If such developments are deemed desirable, it makes sense to reinforce those developments within molecular medicine that strengthen the role of subjective experience and individual views of the good life.

Of course, actively furthering the desirable development of molecular medicine is not easy. An elaborate sociological analysis of the forces that currently frame the emerging domain of molecular medicine would be needed to clarify whether and how attempts at steering the developments would be feasible. For the moment, let it suffice to say that the conceptual tensions within molecular medicine suggest that developments are not predetermined. On the contrary, I hope to have shown that we can take them as opportunities to steer the future of medicine in a more desirable direction.

Acknowledgements The research for this paper was partly funded by the Rathenau Institute as part of a project on the ethics of converging technologies. Thanks to Tsjalling Swierstra, Rinie van Est and Bart Walhout for stimulating discussions on this topic. My views on molecular medicine were sharpened at a relatively late stage of writing by the meeting of the Working Group on Ethics and Social Impact of the EU Roundtable on Nanomedicine, Geneva, September 18–19, 2009. Thanks to all participants for interesting contributions and discussions.

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