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SCIENTIFIC CONTRIBUTION

Molecular medicine and concepts of disease: the ethical value of a conceptual analysis of emerging biomedical technologies

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Abstract Although it is now generally acknowledged that new biomedical technologies often produce new definitions and sometimes even new concepts of disease, this observation is rarely used in research that anticipates potential ethical issues in emerging technologies. This article argues that it is useful to start with an analysis of implied concepts of disease when anticipating ethical issues of biomedical technologies. It shows, moreover, that it is possible to do so at an early stage, i.e. when a technology is only just emerging. The specific case analysed here is that of 'molecular medicine'. This group of emerging technologies combines a 'cascade model' of disease processes with a 'personal pattern' model of bodily functioning. Whereas the ethical implications of the first are partly familiar from earlier—albeit controversial—forms of preventive and predictive medicine, those of the second are quite novel and potentially far-reaching.

Keywords Concept of disease · Ethics · Emerging technology · Epistemology · Molecular medicine · Personalized medicine · Health technology assessment

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Introduction

It has often been observed in history and philosophy of medicine, as well as in philosophy of technology that new biomedical technologies frequently produce redefinitions or even new concepts of 'disease'. History of medicine shows that novel diagnostic as well as therapeutic technologies tend to reorganize the way we conceive specific diseases (see for examples: Reiser 1978; Davis 1981; Dillmann 1990; Pasveer 1992). Philosophers of medicine have argued that technology constitutes the concept of disease. Hofmann (2001b), for example, argues that technology provides the entities that are applied in defining disease, constitutes the signs, markers and end points of disease, influences explanatory models, and establishes how we act towards disease (see also Hoedemaekers and Have 1999; Horstman et al. 1999; Stempsey 2006a). This is in accord with insights from philosophy of technology in general, which state that new technologies often produce new ontologies, new roles and new responsibilities (Willems 1995; Vos and Willems 2000).

The technological constitution of disease (and by implication, of health) has raised extensive philosophical debates, for example on the descriptive or normative character of disease definitions, on their ontological or conventionalist character and on the relation between disease and illness (Schaffner 2000; Hofmann 2001a; Torres 2002; Engelhardt and Wildes 2003; Kushf 2006; Nordenfelt 2007; Tengland 2007). Testament to the ongoing debate in this field is a recent thematic issue of this journal (*Medicine, Health Care and Philosophy* 2007 no. 1).

It has been argued that such conceptual analysis of the use of 'disease' and 'health' is hardly linked to ethical analysis. Schramme, for example, suggests that conceptual analysis of 'health' is curiously lacking in biomedical

ethics, although health is generally considered a major constituent of a good life (Schramme 2007, p. 3). We might add that the lack of this type of analysis is even more remarkable in ethics of (emerging) biomedical technologies. Despite the steady increase in research in the area of ethical, legal and social aspects of new technologies, and notwithstanding the growing attention to ethics in (Health) Technology Assessment (Willems 1995; Grunwald 1999, 2000; Decker 2004; Oortwijn et al. 2004; Hofmann 2005; Lehoux and Williams-Jones 2007; Hofmann 2008), ethical analyses of novel biomedical technologies only rarely include analyses of the concept of disease and/or health implied by these new technologies.

As Hofmann (2008) and Stempsey (2006a, b) have shown, analysis of implied concepts of disease and/or health might be quite relevant to ethical debates on new and emerging technologies. Stempsey argues that emerging biomedical technologies continuously shift our norms of disease and health, thus bringing about new conceptions of health. In his view, such innovations "will inevitably challenge us and lead us into ethical challenges" (2006b, p. 241). In a different paper, he argues that genetic diagnostics presents ethical challenges because it relies on a neo-ontological concept of disease that is particularly problematic in a context of genetic reductionism (2006a). Hofmann, who has published both on the concept of disease (2001a, b) and on the role of ethics in Health Technology Assessment (Hofmann 2005, 2008), recently presented ten arguments why ethics should be integrated in HTA. The last argument is that "technology invents disease and its remedies. Accordingly, analytical perspectives that address this profound role of technology should be welcomed in the assessment of technology in a field so crucial to human beings as health care" (Hofmann 2008, p. 427). Neither Stempsey nor Hofmann, however, discusses how such an analysis could be performed, nor do they go into any detail regarding the additional value it might have to existing approaches in ethical technology assessment.

In this paper, I want to explore further the position that analysis of the concept of disease might be useful for ethics of biomedical technology, in particular for technologies just emerging. First, I will develop two arguments indicating why an analysis of implied concepts of disease and/or health may be useful for ethical agenda setting. Such an analysis may identify shifts in the goals of medical practice, even when a new technology is said to be just a more effective means towards a pre-established goal. In addition, such shifts enable the early anticipation of ethical issues associated with emerging technologies, since they are already discernable in the visions preceding and guiding the development of these technologies.

In the remainder of the article, I will illustrate this claim by analysing how the technologies emerging under the denominator of 'molecular medicine' change existing concepts of disease.[1] The field of molecular medicine is particularly interesting because although it is only just emerging, it appears to have the potential to radically transform medical practice. The goal of the case study is twofold: on the one hand it is meant as a first step in setting an agenda for ethical debate on molecular medicine; on the other hand it may serve to demonstrate the value and identify potential problems and weaknesses of the general approach. After reviewing both the current status of molecular medicine and its visions of the future, I will analyse the concepts of disease implicit in these developments and visions. This concept analysis will then be used to identify some of the ethical issues that might be involved. After summarizing the ethical agenda for molecular medicine thus produced, I will end with some general reflections on the usefulness of analysis of the 'disease' concept for anticipating ethical aspects of emerging technologies.

Concept analysis for ethical HTA

My claim, that an analysis of the concept(s) of disease implied by emerging biomedical technologies could be of great value when setting an agenda for ethical debate on these technologies, stems from two considerations:

1. An analysis of the concepts of health and disease envisioned in the development of emerging technologies enables debate about the desirability of (potential shifts in) the *goals* of medicine.
2. In addition, such an analysis can be performed *at an early stage* of technology development, thus maximizing the potential impact of ethical debate.

These arguments build on insights from philosophy of technology in general, as well as philosophy of biomedical technology. I will explain them briefly.

Technology and the goals of medicine

As Swierstra and Rip have shown in debates on new and emerging technologies, proponents often argue that this particular technology offers new, more effective or less burdensome ways to realize familiar, widely valued goals (Swierstra and Rip 2007, p. 9). This is certainly true for debates on biomedical technologies. New biomedical

[1] Although my general argument claims that technology may affect the conceptualization of both disease and health, for pragmatic reasons the case analysis will mainly focus on an analysis of the disease concept. Of course the two are interrelated and where the conceptualization of disease has consequences for or is dependent on a specific notion of health, I will note so.

technologies are usually presented as reducing disease and mortality and/or promoting health—widely shared values that are difficult to take issue with. Moreover, new biomedical technologies are often claimed to be more effective in realizing these goals, to have fewer side effects and/or to be less burdensome to the patient. New technology is thus put forward as a new or even 'revolutionary' instrument to realize traditional, widely shared goals. As Swierstra and Rip suggest, this way of arguing is particularly useful to ward off moral debate on new technologies. After all, if its goals are familiar and uncontroversial, a new technology can claim at least an initial moral legitimacy.

The question then is: are the goals really familiar and uncontroversial? Philosophers of technology urge us to be cautious here. Technological means are more than just neutral instruments; they act themselves (Ihde 1990; Verbeek 2005, pp. 43–45). While trying to realize familiar goals with different means, new technologies actually shift or reinterpret the goals—often in ways that are not immediately visible. Technology mediates both the way we experience the world and the way we act in it. This becomes clearer when we realize that technology is not just a material device: it is a socio-technical complex that consists of mutually dependent material and human elements. Much work needs to be done to make a material device effective; it presupposes a specific context of use. Moreover, in doing so, it redefines the relevant actors, their roles and responsibilities, and even the other material objects that are part of the technological practice. Thus we may end up with a world that is quite different from the one before the new technology was introduced.

Let me illustrate this with an example from the domain of biomedical technology, taken from Willems (1995, pp. 47–65). A spirometer, used to test lung function, is a large apparatus that requires an assistant to make sure the patient blows in the right way and to interpret results. Patients have to come to the lab to be tested, which is particularly problematic in the event of a sudden deterioration when instant testing is necessary. In addition, the characteristics of the spirometer impede its use in epidemiological research on large populations. These considerations led to the development of the peak flow meter (or actually to several different ones), i.e. small devices that can be used by general practitioners as well as patients themselves to measure lung function. One might thus assume that these peak flow meters are just better instruments to serve the same goal.

However, lung function measurement was actually transformed by the introduction of the peak flow meter. Creating its own parameter, 'peak expiratory flow' was installed as the definition of lung function together with the development of the device. In addition, the peak flow meter created new roles and responsibilities for patient and physician, who now had to produce and interpret test outcomes together. With the patient now able to monitor his/her own bodily functioning, information could be obtained that might even redefine the boundary between normal and abnormal on a highly individual level. In addition, self-management programmes were developed in which the roles of physician and patient and their relationship were again transformed.

The innovation of lung function measuring technology cannot thus be seen as a miniaturization of an existing instrument meant to attain an existing goal. In the process of miniaturization, new entities, roles, responsibilities and practices were produced. The former goal was transformed but also yielded many additional effects which would be wrong to denote as mere 'side effects'. The lesson to be drawn from this is that we should not accept claims at face value that a particular novel biomedical technology is just a neutral instrument for a predetermined or an accepted goal. Even when the goals guiding the development of a technology are familiar and acceptable, a technology may actually shift the meaning of 'disease' and/or 'health'. Moreover, it is possible to reorganize the world in such a way that these transformed concepts make sense.

It is thus advisable to ask which concept of disease and/or health is implied in any emerging biomedical technology. Subsequently, it should be asked how these concepts differ from existing ideas about disease and health and what the implications of such changes might be. This may result in an agenda for debate on the desirability of such changes.

Possibilities for early analysis and debate

An additional argument for the value of such a concept analysis for ethical agenda setting is that it may have more impact because it can be performed relatively early in the technology development process. It is widely acknowledged that ethical and social assessment of emerging technologies is important but that the timing of such an endeavour is problematic because of the so-called Collingridge dilemma (Collingridge 1980). If one assesses a new technology after it has been developed, opportunities for shaping it are limited. By then, the design of the technology has usually stabilized and the only decision left is to accept or reject the technology as a whole. Moreover, because of the time, energy and money spent in developing the technology, the pressure to accept it is often great. In theory, it is thus preferable to assess the potential impact of emerging technologies at an early stage, when there are more opportunities for steering. However, early steering poses difficulties as well since the object of assessment is still fluid and its effects are difficult to foresee.

One of the methods designed to deal with this dilemma is 'vision assessment' (Grin and Grunwald 2000). Instead of assessing novel technologies only after they emerge, Grin and Grunwald propose to assess the *visions* underlying and guiding technology development first. Such visions include images of the material devices to be designed, but also of the practices in which these devices would be put to use, and sometimes they even evoke images of the resulting society or culture. Since these visions usually precede technology development, assessing them early on enables public debate about future technologies, thus contributing to the democratization of technology development.

The concept analysis proposed here can be seen as part of such a vision assessment. Instead of waiting for a technology to emerge and then to start analysing the implied concept of disease and health, one could take the explicit visions of future technology as a starting point. As stated above, visions of future biomedical technologies usually include relatively specific claims regarding the reduction of disease, suffering and mortality, and/or the promotion of health; but they also contain images of future medical practice, of future patients (or healthy human beings, for that matter), and of society at large. Analysing the concepts of disease and/or health implied by these visions contributes to the early agenda setting for timely ethical debate on emerging technologies.

Molecular medicine: possibilities and promises

Since the proof of the pudding is in the eating, I will use the remainder of this article to put the approach outlined above into practice. The emerging field of molecular medicine will serve as a test case. Molecular medicine is a relatively new, internationally flourishing field of science and, to a lesser extent, of business. Whereas a journal and some research institutes were already established during the 1990s, most research institutes, master's programmes, funding opportunities and commercial start-ups were initiated only recently. The subject matter of the field is wide ranging, as are its ambitions. To quote some definitions used by the field itself:

> Considered the vanguard of the new millennium in which science truly complements the art of medicine, *Molecular Medicine* strives to understand the molecules key to normal body functioning and the pathogenesis of disease, and based on that knowledge, to design specific molecular tools for diagnosis, treatment and prevention. (from the website of the journal *Molecular Medicine*, http://www.molmed.org/about.html, accessed March 20, 2008)

> Molecular Medicine targets disease where it is caused: at the level of the gene or the gene product in the critical cell. It enables not only earlier and more precise detection of diseases and even predisposition, but also personalized treatments that are more effective, cause fewer side effects, and are more cost-effective due to stratification of specific patient risk and prediction of response to therapy. (CTMM Working Group 2006, p. 11)

Molecular medicine aims to diagnose and manipulate the molecular processes underlying disease and health. Central in all its activities is the knowledge of biological functioning of human beings at the most basic level. Both this type of knowledge and the possibilities to intervene in these processes have become available only by the convergence of biomedical science with nanotechnology and information and communication technologies. Whereas nanotechnology makes visible and enables manipulation of biological processes at the molecular level, Information and Communication Technology (ICT) helps to collect the information produced by nanotechnological instruments in huge databases, to analyse it and to recognize relevant patterns. Both nanotechnology and ICT thus create the conditions to gain fundamental biomedical knowledge and to use it in diagnosis and therapy.

Current literature on molecular medicine attributes five different, often interconnected, goals to molecular medicine.

1. *Diagnosing disease earlier and with greater reliability*: Molecular diagnostic devices are claimed to enable the detection of very low concentrations of biochemical substances indicating the start of disease processes. The company Nanosphere, for example, is developing a test that recognizes proteins produced by dying heart cells (TWA Netwerk 2006, p. 48). Nanoparticles with a specific coating bind to these proteins and subsequently to a micro-array with a similar coating, which makes them detectable by a digital camera. This test is thought to enable the detection of heart disease at a very early stage. Similar applications are being developed for different forms of cancer and other diseases (Health Council of the Netherlands 2006, p. 48; TWA Netwerk 2006, p. 51). The idea is not only that detection of low concentrations aids timely diagnosis but that it might also improve the reliability of diagnostic tests. In practice, however, this goal is not very easy to realize (Roszek et al. 2005, p. 54).

2. *Improving the reliability of prognosis and reducing over-/undertreatment*: Molecular devices may also contribute to tailoring treatments to the molecular characteristics of a patient's disease. Several DNA-chips using micro-array techniques have been developed that can differentiate between women with favourable and unfavourable

prognoses for breast cancer (Signaleringscommissie Kanker 2007, pp. 75–76). Only women with a bad prognosis are thus prescribed chemotherapy, whereas all women used to be treated this way, just to be on the safe side. Such prognostic DNA-chips may considerably reduce overtreatment. This is an advantage for the women involved, who are spared the awful side effects of chemotherapy, but also from an economic perspective. Similar DNA-chips are in the experimental stages of development, e.g. for leukaemia and cancer of the mouth and throat. Clinical applications are still rare, however (Health Council of the Netherlands 2006, p. 45).

3. *Improving the effectiveness of therapies*: Advancing and improving the reliability of diagnosis and prognosis may of course contribute to the effectiveness of therapies. However, molecular medicine may also improve the effectiveness of therapies more directly. Drugs for brain tumours that use nanoparticles in combination with directing molecules, for example, can pass through the blood–brain barrier. Such 'drug delivery systems' make drugs more effective and often reduce side effects because substances only do their work where they are needed (Health Council of the Netherlands 2006, p. 51). In addition, systems are being developed for 'nanoplatforms' with modules for different functions. This opens up the possibility of combining sensors for detection with the exact and timely release of active substances, thus combining diagnosis or monitoring with therapeutic functions (Roszek et al. 2005, pp. 46–47).

4. *Reducing the invasiveness or burden of diagnostic and therapeutic technologies*: It is characteristic of nanotechnology that it enables the miniaturization of medical instruments and devices for both diagnostics and therapy. As a result, these devices are becoming less invasive and can be transported more easily. In the case of diagnostics, for example, blood analysis may replace biopsies. The instruments needed to perform such an analysis are becoming so minute that they can also be used outside the lab or clinic. 'Labs on a chip' currently enable so-called 'point of care'-applications: lab analysis may be performed at a patient's bedside or at home, making results available much faster (Health Council of the Netherlands 2006, p. 47; TWA Netwerk 2006, pp. 48–49; European Group on Ethics 2007, p. 16). Medical instruments might also be so small that they can enter the body. So-called 'wet sensors' in the form of an ingestible chip measuring heart beat, temperature and blood sugar level are already available (European Group on Ethics 2007, p. 16). Such chips are combined with RFID labels, which can be 'read' at a distance without the carrier's noticing it. Future molecular medicine might well lead to forms of diagnostics and therapeutic intervention for which a patient hardly needs to interrupt his/her life.

5. *Monitoring health and personalized care*: Molecular diagnostics enables repeated monitoring of bodily functions, because it is neither very invasive nor burdensome. A lab on a chip is already available for patients using psychopharmaceutical drugs such as lithium. These patients can regularly monitor their blood lithium levels and dose their drug use accordingly (Health Council of the Netherlands 2006, p. 47). More futuristic promises suggest that if wet sensors were implanted in the body and measurement results were then sent to some huge, distant database (for example by using Radio Frequency IDentity (RFID) chips), information about an individual's functioning could be charted quite easily. Analysis of individual patterns and comparisons between individuals could hence construe a balanced image of someone's functioning, enabling timely and tailored interventions. A patient whose results deviate from his usual pattern might receive a message on his mobile phone urging him to consult his physician; one might even start monitoring important biomarkers in healthy people to improve early diagnostics (Schuurman et al. 2007).

The ultimate vision: monitoring health anywhere, anytime

An overview of the different goals and applications is given in Table 1. The distinction between the goals is often analytical, however. In the most radical visions of what molecular medicine might entail monitoring, early diagnostics, prevention and/or tailored therapy are combined in an all-encompassing system of vigilance, which is presented as hardly burdensome to its users. Such a system would extend the care for health over time as well as in space. Molecular medicine may be active 24 h a day, from the cradle to the grave:

> 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. (Fortina et al. 2005, pp. 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. (Johnson and Evans 2002, pp. 304–305)

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

Goal	Examples of existing applications	Examples of applications in development
Earlier and more reliable diagnosis	Micro arrays for heart disease	Micro arrays for different forms of cancer
More reliable prognosis and reduction of over-/undertreatment	DNA chips, micro arrays for breast cancer	DNA chips for leukaemia, mouth and throat cancer
Improving effectiveness of therapies	Drug delivery systems	Drug delivery systems for brain disease, nanoplatforms, theranostics
Minimizing invasiveness and burden of medical technology	Lab on a chip for monitoring lithium levels	Lab on a chip for colon cancer detection; wet sensors
Monitoring health and personalizing care	Ingestible pill monitoring body temperature	Wet sensor systems, including RFID technology and databases

Moreover, molecular medicine will transport the care for health: in the future, one may be the object of care anywhere.

> 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. (Rickerby 2006, cited in European Group on Ethics 2007, pp. 16–17)

This pervasiveness of health care is an outstanding example of what 'converging technologies' might do. First, the convergence between biomedical science and nanotechnology makes it possible to transport medical technology from the laboratory and the clinic to the public and the private spheres. ICT adds to this development by making the analysis and reporting of test results mobile. As a result, we can be monitored anywhere, anytime.

What's new?

Although molecular medicine is frequently labelled 'revolutionary' by its proponents, the aforementioned goals of molecular medicine are not so new after all. Most of them are related to improving diagnosis of disease (with respect to timing and reliability), prognosis (with respect to reliability) and treatment (reduction of over-/undertreatment, improving effectiveness, reducing side effects and burden). Only the last goal, monitoring health and personalizing care, is relatively young—although not completely novel. On the level of its explicit goals, molecular medicine thus hopes to make the activities usually undertaken to combat disease and restore health more effective. The value of 'health' and the undesirability of disease are taken for granted, just as in 'traditional' forms of medicine.

The more encompassing visions of the future enabled by molecular medicine slightly shift the focus of attention from fighting disease to maintaining health: they accentuate the *prediction, prevention and monitoring* of health risks. These goals have also been around for some time with prediction and prevention having been pursued on a large scale, even since the nineteenth century. Monitoring is hardly a goal in itself; it can be seen as a new means to make prediction and prevention more effective.

Does this mean then that molecular medicine is only building on widely shared goals? Not necessarily. As argued above, emerging biomedical technologies are often likely to shift or reinterpret the goals of medicine, even if they pretend to be just more effective means towards well known and widely accepted goals. An analysis of the concepts of disease implicit in these emerging technologies can indicate which shifts molecular medicine is likely to accomplish.

Shifting concepts of disease

It is not very bold to state that scientific and technological developments in molecular medicine will lead to redefinitions of diseases. The meaning of diseases in general will become more closely connected to the basic biological processes opened up by molecular medicine. If large-scale biobank research actually does identify 'biomarkers' related to the onset or development of specific diseases, these biomarkers will become part of the definitions used for specific diseases, either broadening or differentiating them. An individual receiving a positive result on a micro-array for heart disease *has* this heart disease, whereas until recently his General Practitioner would have sent him away with the reassurance that nothing was wrong (or more precisely: that nothing could be found). If research subsequently shows that the molecular processes in these a-symptomatic patients differ from those in symptomatic patients, a new disease differentiation may be born.

Reconfigurations like these will occur on the level of specific diseases and their definitions. However, such reconfigurations are likely to show a similar pattern since molecular medicine stimulates a specific way of thinking

about disease in general. I would like to draw attention to two general characteristics of the way molecular medicine conceptualizes disease: (1) the use of a 'cascade model' of disease, and (2) the use of what I will call a 'personal pattern model' of bodily functioning.

Disease as a cascade

As stated above, the ideal guiding most molecular diagnostics is that biomarkers reveal the very first stages of the disease process. These molecular changes are supposed to cause further changes, e.g. on the tissue level, then on the level of organs etc., and ultimately lead to symptoms and complaints. Ideally, molecular medicine would generate knowledge of and insight into the natural history of diseases. This knowledge would then enable us to intervene at the right time: neither too early nor too late. The specific concept of disease underpinning such claims is that of the 'cascade': one step leads to another, in a stream that with each subsequent step becomes more difficult to stop. The image of the cascade is essential for molecular medicine's claim that early diagnosis (and prevention or intervention) improves the chances of recovery or of staying healthy. The longer one waits, the more difficult it will be to turn the tide.

Approaching disease as a cascade, molecular medicine brings the disease *process* into focus and highlights the temporal development of diseases as well as the relations between cause and effect in each stage of this process. In doing so, molecular medicine's concept of disease goes beyond the simple ontological view of disease as an altered state (as present in, for example, traditional pathology) by investigating the process preceding and following the occurrence of such altered states. It also transcends the epidemiological reasoning underlying most predictive and preventive medicine to date by aiming to elucidate the actual process explaining the correlations between risk factors and disease.

It is doubtful, however, whether the cascade model of disease is fruitful in guiding medical research and practice. First, it is all too easily (though not necessarily) interpreted in a linear way, limiting the focus of research and neglecting the complexities and contingencies of disease. Disease processes may not evolve in a linear way: the processes may include feedback loops or complex interactions that are difficult or downright impossible to predict, and these interactions may have different end points without clinical relevance (Philippe and Mansi 1998). Moreover, there is an implicit tension in the cascade model that may prevent the realization of its promises. The cascade model inspires a search for biomarkers that enable early diagnosis, which, if found, will elongate the time span between (observed) cause and effect, thus increasing the chance of a surprising turn of events. For the moment the relation between known biomarkers and the clinical manifestation of the related disease is hardly ever automatic. Only a number of those individuals testing positive on a biomarker actually contracts the related disease later on and shows the predicted disease history (Chanock and Wacholder 2002). So, contrary to what the cascade model suggests, biomarkers do not, in effect, betray the onset of a disease; they predict it. Like traditional risk factors, they help medical professionals to estimate chances of specific events, but cannot offer certainty.

Personal patterns of bodily functioning

The second characteristic of the way molecular diagnostics conceptualizes disease does not result from the substance of what is being measured, but from the *way* this measurement is performed. As indicated above, molecular medicine may radically transform both the time and the location of medical activities: it seems to enable the permanent monitoring of bodily functioning in everyday life. Promises about implantable medical instruments and reading measured values from a distance are crucial here. If these promises do come true, the concept of disease may become based on deviations from personal patterns, reconstructed from collected evidence on individual functioning.

Most medical diagnostics, either in vitro or in vivo, is currently limited to measuring someone's bodily state at a specific moment in time. This is well recognized not only by physicians themselves but also in theoretical reflections on diagnostic work. As Bowker and Star state in their book on classification: "The body itself is constantly in motion and varies by individual, so ideal measurement is always a projection from a moving picture onto a timeless chart" (Bowker and Star 2000, p. 170). Repeating measurements or examinations might improve the reliability of diagnosis; repeating them regularly might help to form a picture of how a disease is developing. In practice, however, repeated measurements or examinations are difficult to realize. Often they are too burdensome for the patient, as well as too expensive.

Developments in molecular medicine might change this situation. If molecular diagnostics succeeds in developing small (or even 'wet') sensors that can register minor changes in protein levels or RNA activity, it will be easier to repeat measurements and to monitor individuals for longer stretches of time. Such intensive and relatively unobtrusive monitoring of individuals might lead to a radical change in the determination of 'normal' bodily functioning, and thus affect the boundary between health and disease. Until now normal values have been based on population research and indicate *mean* functioning of a group of individuals at a specific moment. Repeated measuring with implantable sensors might, in contrast, reveal

the *patterns* in the functioning of an *individual body*. The relevant field of comparison for isolated measurements would then not be the population but personal bodily history (Mol and Hendriks 1995). What is a deviant result for one individual may be quite normal for another. The predictive value of biomarkers would thus not be interpreted in the light of reference populations, but in comparison with the individual's former values. Close monitoring of an individual's functioning would moreover allow for tailoring the timing of an intervention to the individual case. Intensive monitoring of individuals might thus result in a highly personal boundary between health and disease.

Early diagnostics through monitoring: the lifelong health clinic

The two tendencies in molecular medicine set out above will probably not fully evolve together. Although they are interdependent, at least to some extent, the cascade model of disease will be reinforced especially if the search for biomarkers is successful, whereas personalization of the boundary between health and disease depends on the development of wet sensors and systems to transmit and analyse the information produced. More likely than not, these technologies will differ in their pace of development.

It is worthwhile, nevertheless, to speculate briefly how these tendencies may influence one another and how they might combine. First, the model of the cascade might be an important impetus to develop possibilities for the continuous monitoring of individuals. It fosters the idea that human beings are vulnerable to disease and that bodily processes can go wrong any moment. Moreover, it is linked to the idea that the ability of human subjects to experience and note changes in bodily functioning is limited, whereas medical technology can identify changes that an individual would not have been aware of. The results produced by such a technology have the additional advantage that they can be transported and compared with the results of others much more easily than people's personal reports on bodily experience. This seems to make diagnosis more 'objective', but it comes at a cost. As indicated above, diagnostic technology usually replaces the continuous, temporal character of personal experience with momentary images. This complicates the interpretation of test results; a complication that might be relieved if individuals were continuously monitored. The two tendencies might thus be combined in a practice of continuous monitoring of all individuals with the aim to diagnose disease from the onset. 'Lifelong health clinics' could organize permanent monitoring of a set of biomarkers in all citizens by means of wet sensors that are read at a distance. Data about bodily processes would be stored and charted in digital files. Ideally, the monitoring system itself would be able to note deviations from personal patterns and to send a message to the person involved. Depending on the character and seriousness of the observed deviation and the complexities involved in its interpretation, this person might receive some advice on lifestyle habits or be invited for a consultation with a medical professional. If drugs were prescribed, their effect could be monitored as well.

Ethical implications of shifting concepts of disease

On the basis of the analysis presented above, we can now conclude that the visions of molecular medicine on the one hand reinforce earlier shifts in the conceptualization of disease, and introduce new shifts on the other. This means that this group of technologies is not value neutral, offering new, more effective means to realize existing goals. It affects the goals themselves—in which case ethical reflection and debate on the desirability of such transformations is in order. As indicated earlier, we should question the desirability of the changed goals, but we should also look at the conditions that need to be met to make the technologies work since these may lead to additional, unintended effects.

If we combine these two types of ethical questions with the two tendencies in the conceptualization of disease in molecular medicine, a preliminary four-item agenda for ethical debate on molecular medicine can be compiled. The implied cascade model of disease raises (1) issues regarding the desirability of knowledge of future health risks and (2) issues regarding the uncertain status of this knowledge. These items are not completely new, but regain urgency in the context of molecular medicine. The personal pattern model of bodily functioning raises two additional, relatively novel and possibly more radical issues, regarding (3) the desirability of an increased role for the individual in health care and (4) the boundary between research and care in ubiquitous monitoring.

Desirability of knowledge about future health

As discussed above, the cascade model hinges on the presupposition that one's current bodily state, represented by the measurement of one or more biomarkers, enables predictions about one's future health. Accompanying this first presupposition is a second one that implies that personal bodily experience does not suffice as a diagnostic tool. Both presuppositions have already figured widely in all kinds of programmes for early diagnostics and preventive screening, e.g. for breast cancer or in predictive DNA diagnostics. Many of the ethical questions raised by the use of biomarkers for early diagnostics have been discussed in these earlier settings (see for example Horstman et al. 1999; Tijmstra 2004).

First, the desirability of knowledge about one's future health is questionable. Do we want to know what the future holds for us? This may depend on the possibilities to act on this knowledge. If effective preventive measures are available or if early diagnosis implies that therapy may be less drastic, predictive knowledge or early diagnosis seems helpful. Often there is a gap, though, between diagnostic or predictive possibilities and the therapeutic or preventive options. Moreover, the impact of the diagnostic technology itself may be quite far-reaching or pose more difficult questions than it can answer. Others argue that even if no therapy is available, early diagnosis may help to prepare for the unavoidable.

A common 'solution' to moral controversies like these is that each individual should decide for him-/herself whether or not to use these options for early diagnosis. People cannot be obliged to use it, but the technology should be available to all. Autonomy of citizens/patients is the central value here. This solution neglects, however, that the availability of such technologies invariably has cultural implications. In a society offering extensive possibilities for early diagnosis, a risk culture may evolve in which it is common practice to reduce health risks as much and as early as possible. The freedom to choose not to use these possibilities may be severely limited. In addition, the existence of such technologies forces people to explicitly choose an attitude or lifestyle that was implicit before; in a risk culture, for example, it will be more difficult to maintain a 'carpe diem' attitude.

This is related to another issue: choice comes with responsibilities. If services exist, people will have to explain why they do not use them. Is a person who refused the opportunity to use biomarker tests or to be permanently monitored responsible if he contracts a disease later on? And what about insurance companies and employers? Can they demand that you undergo such tests before accepting you as a client or employee? In view of such considerations, the desirability of knowing your future health risks is, to say the least, not completely self-evident.

Predictive value and uncertain results

The cascade model of disease suggests that knowledge of the future is desirable. In doing so, however, the model presupposes that the link between the beginning and the end of the cascade is strong and predictable. Past experiences in predictive medicine warn us not to take such presuppositions for granted. In the case of DNA diagnostics, for example, high expectations regarding the predictive value of DNA mutations were not met. As said before, genetic mutations usually do not automatically lead to disease; monogenetic diseases are the exception, not the rule (Chanock and Wacholder 2002; Pagon 2002; Lock 2005). As a result, DNA diagnosis for multifactorial diseases does not produce a clear message about one's future health. It results in risk statements, implying that even if one has a high risk, in the end one might belong to the minority that remains healthy.

Although molecular diagnostics is sometimes presented as identifying the first symptoms of (as contrasted with risk factors for) disease, history may repeat itself here. If disease processes do not fit the cascade model of disease presupposed in molecular diagnostics, the predictive value of biomarkers may be much lower than currently expected. Biomarker tests will thus be nothing more than new technologies to identify (new) risk groups. Whether or not they perform better than traditional risk factors can be decided on a case-by-case basis only.

Anticipating the possibility that emerging molecular diagnostic tests have low predictive value, we should prepare for the question how to deal with such uncertain test results. This is all the more important since molecular diagnostic tests might be offered directly to consumers, e.g. via internet companies. Who is best positioned to interpret the meaning of such test results: a medical professional, the client him-/herself, or representatives of the 'life-long health clinic'? Should tests with a very low predictive value be forbidden or should the information provided before testing satisfy specific criteria? In short, which distribution of roles and responsibilities is desirable when test results are ambiguous and unreliable? Again, the example of DNA diagnostics shows that the actual practice of testing and interpreting the test results may confront users with more moral complexities than the issue whether or not to have such a test (Boenink 2008).

The role of the individual

The conceptualization of disease as a deviation from one's personal pattern of individual bodily functioning assigns an important role to the individual in determining the boundary between health and disease. This role is motivated by both practical and moral reasons. Freitas, for example, explicitly states that what he calls 'nanomedicine' will personalize disease in two ways: disease is either the failure to maintain optimal bodily functioning (as dictated by one's personal bodily characteristics), or the failure to maintain one's desired functioning (as defined by personal preferences) (Freitas 2007, p. 167). He even announces that "the natural end result of nanomedicine is fully permissive medicine" (Freitas 2007, p. 169), suggesting that an autonomous choice to define oneself as healthy or ill should be respected.

However, putting the autonomous individual central stage, as Freitas does, both simplifies and forecloses ethical debate. In developing molecular medicine, the precise roles

and responsibilities in caring for one's health still need to be defined and distributed, and it is not a foregone conclusion that individual autonomy should always be decisive. What is more, the meaning of autonomy itself, as well as other concepts related to the value of the individual person, may be transformed by the emerging practices of molecular medicine, thus complicating moral decision making.

First, the actual role of individuals in monitoring is not fully determined by the material components of the technology. When using wet sensors, the subject him-/herself need not have an active part in the measuring process, besides having a sensor implanted. Both measuring and the feedback of results can be organized in very different ways. To whom, when and how are results communicated? How are 'results' defined anyway, and by whom? It is important to realize that monitoring systems can be designed in very different ways, with very different effects on the individual user, on medical professionals and society at large. The choices that need to be made when designing a monitoring system are, therefore, morally laden.

In addition, the question should be asked how the meaning of values related to the individual, like autonomy, bodily integrity and privacy, is affected by the emergence of complex monitoring systems. What does it mean to be autonomous when your 'health conscience' is at least partly outsourced to a technical system? Are wet sensors integral to one's body or external to it? Are the data transmitted by these sensors to the system private? Emerging technologies not only shift the conceptualization of disease but are also prone to shifting the meaning of moral values, which complicates the role of such values in deliberations regarding the desirability of these technologies. Anticipating such potential shifts in meaning before molecular medicine develops into a full-blown part of medical practice could at least prevent such moral change taking us by surprise later on.

Guarding the boundary between research and care

However, even if we accept that personalizing the definition of disease is desirable, the necessary practice may raise additional ethical issues regarding the boundary between research and care. Although the projected 'lifelong health clinic' is primarily envisioned as a form of care, it hinges on permanent and omnipresent examinations of both healthy and diseased subjects. This opens up the possibility for extensive comparative research. All individuals may benefit from such research since epidemiological knowledge will become more differentiated and more reliable. One could argue, then, as some have done in debates on biobanking (Chadwick 1997; Chadwick and Wilson 2004; Swierstra 2004) that all individuals have a civic obligation to participate in such research. It would, after all, contribute to their own as well as to the public good and it would hardly be burdensome for the individual. This seems to make it less urgent to maintain a strict boundary between research and care.

There are nevertheless considerations pulling in the other direction as well. If care is tailored to individual bodily functioning, it is actually also becoming ever more experimental. How to determine when intervention is necessary and which intervention would be best? If individual profiles proliferate, testing all novel interventions on subjects with an identical profile will become impractical. Knowledge based on reference populations will be less available, thus making interventions less evidence-based.

Of course, medical interventions like drugs are currently often (and also) applied to groups that were not included in the experimental design. Since most clinical trials still use young, male students, prescribing a new drug to anyone outside this group is in a way experimental. The personalization of care promised by molecular medicine thus clearly shows that medical interventions are often more experimental than acknowledged, because they are continuously transported to new domains. This raises the question whether the boundary between research and care should be moved in the other direction: should not all personalized care satisfy the strict criteria applied to experimental research with human subjects?

Conclusion and discussion

Although molecular medicine is only just emerging, an analysis of the concepts of disease implied by the visions in this field already enables us to anticipate some of its ethical implications. The 'cascade model' of disease and the 'personalized pattern model' of bodily processes implied by molecular medicine raise distinctive ethical issues. The cascade model in particular builds on conceptions of disease that have been around since the rise of preventive and predictive medicine. As a result, some of the ethical issues of predictive and preventive medicine resurface in molecular medicine. The personalized pattern model, on the other hand, diverges in important respects from existing models of disease and poses relatively new questions and problems.

The ethical issues listed above might be summarized in a preliminary 'ethical agenda for molecular medicine' that comprises at least the following four items:

1. the desirability of the predictive knowledge produced by molecular medicine;
2. the distribution of roles and responsibilities with regard to the interpretation of test results, in particular those with low predictive value;

3. the role of the individual in monitoring his/her own health and the shifting meaning of moral concepts such as autonomy, bodily integrity and privacy;
4. the boundary between research and care and the level of protection subjects should be guaranteed.

Of course, all these issues deserve more extensive analysis and debate. Some of them will have to be addressed by technology developers and medical professionals, whereas others should be the subject of public or even political debate. The analysis above is just a start.

Critics might claim that a similar ethical agenda could have been constructed without the preceding concept analysis. Since some of the items on the agenda are well known from earlier ethical debates, these might have been identified as well by reflecting on the analogies between molecular medicine and earlier biomedical technologies, or on a general set of ethical principles often at stake in medicine. The approach proposed here has several distinct advantages over these methods, however. It provides a *systematic and grounded basis* for ethical agenda setting *at an early stage* of technology development. Moreover, contrary to more traditional ways of ethical agenda setting, this approach *acknowledges the mutual interaction (and evolution) of technology and the goals of medicine*.

Thus, using molecular medicine as an example, I hope to have shown the usefulness of an analysis of concepts of disease implied in emerging biomedical technologies for ethical agenda setting on such technologies. Of course, one example does not definitively demonstrate the general value of the suggested approach. More research on different types of emerging technologies is needed. However, I do think that the preceding analysis illustrates how an analysis of implied concepts of disease can lay bare potential shifts in the goals of medical practice at an early stage. This in turn may serve as a starting point for ethical deliberation on the desirability of such shifts. Such debates are often hampered by the fact that it is hard to determine what a technology will be like when it is in an early stage of development. It is even harder to determine which implications it will have when it is introduced on a larger scale. By using the future visions put forward by technology developers themselves, it is possible to identify the concepts of disease guiding the technological developments. Even when the material devices and any ensuing practices are still uncertain and fluid, the underlying concept of disease is relatively clear and stable.

Identifying and analysing these concepts is thus a good starting point to anticipate the ethical issues an emerging technology may give rise to. It affords broader public and professional debate on technological and scientific development. Moreover, it enables the inclusion of ethical issues in the further design of technological devices and of the practices in which they will function. In this way, future technological practices may be acceptable to most of the parties involved and as a result will be relatively robust.

Let me finish here by pointing out two potential limitations of the approach to ethical agenda setting for emerging technologies outlined above. First, it is clear that the approach proposed here is liable to speculation. By taking the visions of technology developers as a starting point, the ethicist risks going along with unfounded, far-fetched claims on behalf of emerging technologies. As Nordmann has argued, this may result in a speculative ethics, deflecting scarce ethical resources from more pressing issues (Nordmann 2007).

This risk should not be neglected. When selecting and interpreting the technical and biomedical literature, a critical stance is needed to reject the claims missing scientific underpinning and to distinguish expectations and promises from downright science fiction. On the other hand, some speculation is inevitable if ethical debate is able to steer technology development. Analysing and debating the future visions of serious scientists and engineers helps to find a mean between realistic but late and ineffective ethical debate and completely speculative—and in the end also ineffective—early ethical reflection.

In addition to the risk of speculation, the outlined approach seems to point at another problem in ethics of emerging technologies. The approach starts from the observation that concepts of disease tend to shift when new biomedical technologies emerge. It explicitly uses these shifts to identify shifts in the goals of medicine. If these goals shift, however, it is no longer clear how to go about investigating the influence they have on disease. The analysis above has shown that this is also true for additional moral values playing a role in medicine, such as autonomy, bodily integrity or privacy.

Like the risk of speculation, this self-referential problem is inherent to all ethics of emerging technologies, even to all prospective ethics. Seen from an historical perspective, morality is not a stable, permanent phenomenon. The meaning and relative weight of moral values evolves over time and technological and scientific developments play an important part in triggering such evolution. Ethical analyses of emerging technologies should start, therefore, from the observation that both technology and morality are dynamic. Moreover, they mutually interact.

Hence we cannot proceed as if current meanings of disease and the related moral values are completely normative for the desirability of future developments. This is not to say, however, that anything goes. We cannot but judge future developments from our current standpoint but we can do everything that is possible to broaden our point of view. Imagining what the future might look like, in technical as well as moral respects, is one way to ensure

that we judge the desirability of emerging developments from such a broader point of view. It is in this respect that a conceptual and ethical analysis of emerging technologies is useful—even, or perhaps particularly, when both ontology and morality are in constant flux.

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