Application of genetic tests in clinical practice

Ethical and social aspects[1]

by

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1. Predictive Medicine

Genetic test have expanded the possibilities of diagnostics dramatically. It is to be expected that their relevancy will further increase in the future. Basically, there are three types of indications to be distinguished: Firstly, diagnostics of an already existing disease; secondly, diagnostics of a yet healthy person to establish the risk of a disease; and thirdly, genetic examination for research purposes.

Genetic tests to establish the risk of a disease on people in good health belong to the field of predictive medicine. This is to be understood as diagnostics either to establish the predisposition for a disease – especially the predisposition for the possible outbreak of a hereditary disease – or to determine the carrier-status. Furthermore, it has to be distinguished between the examination of a born and an unborn human. Besides postnatal tests of late-manifest diseases and family tree analysis there are various forms of prenatal diagnostics (PND) and preimplantation diagnostics (PID) which can be applied to in-vitro-fertilisation in order to test the in-vitro fertilized embryo for chromosome or gene aberrations.

If we talk here about genetic tests this doesn't only refer to molecular-genetic examination methods but also to other diagnostics which provide information about the genetic heritage of a human being. This includes methods on the phenotype level (e.g. ultrasound), on the biochemical level (e.g. triple-testing), on the chromosomal level (Amniocentesis), and on the DNA level.

The predictive appropriation of genetic tests raises a host of ethical questions.[2] Indeed, many hereditary diseases and chromosomal or genetic defects which are responsible for the development of diseases or disabilities can be diagnosed precisely. But in many cases there are aberrations from the norm whose relevancy for the individual is not clear-cut. The term *genetic disposition* refers to the difficulty to formulate clear criteria in distinguishing between disease and good health, normality and abnormality. The selective character of prenatal examination methods raises profound questions regarding the protection of life because of the

[1] Lecture given at the Bioethical Congress of the Italian evangelical Bioethic-Commission, 6th Oct 2006 in Torino.

[2] Cf. *U. Körtner*, Evangelische Sozialethik. Grundlagen und Themenfelder (UTB 2107), Göttingen 1999, S. 199-232 (chapter 8)

danger to distinguish between livable and unlivable life. On principle, any discrimination of people on grounds of their genetic heritage is unethical. The Human Rights Convention on Biomedicine by the Council of Europe (HRCB??) from 1997 states in article 11: "Any form of discrimination against a person on grounds of his or her genetic heritage is prohibited." In practice, the protection of people from this kind of discrimination (e.g. on the labour market or in the insurance industry) frequently raises questions such as data security and the protection of privacy. Another problem – which I will deal with in more detail later on – is the gap which opens up between diagnostics and therapy. Furthermore, conflicts can occur between the right of the individual *to know* and the right of others *to nescience*, e.g. in family tree analysis. And finally, the quality of genetic counselling has to be discussed from an ethical viewpoint.

The HRCB contains another set of basic regulations designed to provide protection of the human being in the field of genetic examination and genetic therapy. Thus, the article 12 reads: "Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling." According to article 13 of the HRCB germinal therapy is prohibited: "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants." Article 14 states a prohibition on principle to prenatally choose a specific sex. Medically assisted procreation must not be used for the purpose of choosing the future child's sex except where serious hereditary sex-related disease is to be avoided. For countries such as India where the birth of a girl is often undesired this prohibition is of high relevancy. But the problem of – from an ethical viewpoint – illegitimate choosing of a specific sex is already appearing in European countries, too: new blood tests which examine the blood of the pregnant woman allow to determine the sex of the unborn already within three months – a period where in most European countries abortion is legal.

2. Genetic counselling

Genetic counselling is to be understood as a process of communication dealing with human problems which are related to the occurrence or the risk of occurrence of a genetic disease within a family. For such counselling there are various indications such as an existing hereditary disease of the partner or an existing hereditary disease of a relative. Another reason

http://conventions.coe.int/treaty/en/treaties/html/164.htm

to call upon genetic counselling could be that there is already one child born with a hereditary disease or that there has been a series of unexplained miscarriages. Another indication can be that germ cells have been exposed to marring (mutagenic) forces or that a woman has been exposed to malformation enhancing factors (e.g. virus diseases, medication, chemicals) during pregnancy. Also pregnancy after the age of 35 is valid as an indication. Another reason for genetic counselling can be sonographic indications (ultrasound) which can be found during prenatal examinations. Finally, psychological reasons (e.g. anxieties of the pregnant woman) can turn out to be an indication for counselling and genetic analysis.

A fundamental problem for any genetic counselling is the deliberation between the possible benefit of an examination and the existing risks. This is valid not only for the invasive methods of prenatal diagnostics where the probability of a relevant finding has to be set in due proportion to the health risks for the unborn and the pregnant woman (damage or miscarriage). But also in genetically testing a born person there are risks which can even end up in suicide. One needs only to think of Chorea Huntington, the eventually fatal disease, accompanied by severe symptoms, whose outbreak can be very precisely predicted whilst there is no therapy available.

Generally, for every genetic counselling applies the principle of non-directivity. The counselling shall help the consulter to reach – on the basis of the information provided – a autonomous and in the long term acceptable decision. Any kind of paternalism or manipulation is to be avoided. But the generally accepted maxim that genetic counselling must be non-directive generates problems. As far as it tries to realize the principle of the autonomy of the patient it deserves approval. But the term non-directivity – stemming from psychotherapy[3] – cannot simply be applied to genetic counselling. In contrary to psychotherapy people are not looking for a new self-understanding or self-esteem but are rather seeking medical advice which means a *recommendation* on how to act whereas the decision of compliance to this recommendation is left to them.[4] Although the right of self-determination has to be respected unconditionally the counselling interview is ethically never neutral. Thus, the ethical implications of/for both the consulter and the advising genetics have to be made aware. Otherwise the danger could arise that the doctor – although increasing the knowledge and the frame of decision-making of the individual – would leave the individual completely on his own facing ethical dilemmas. The mere request for predictive diagnostics then substitutes ethics. Genetic counselling demands – besides medical expertise and the competence to interpret – both a high level at communicative skills and ethical competence.

[3] Cf. *C. Rogers*, Die nichtdirektive Beratung, München 1972.

[4] *S. Reiter-Theil*, Nichtdirektivität und Ethik in der genetischen Beratung, in: *E. Ratz* (Hg.), Zwischen Neutralität und Wertung. Zur Theorie und Praxis von Beratung in der Humangenetik, München 1995, S.83-91; *dies.*, Ethische Fragen in der genetischen Beratung. Was leisten Konzepte wie „Nichtdirektivität" und „ethische Neutralität" für die Problemlösung?, Conc 34, 1998, S.138-148.

Comprehensive consultation is necessary before and after gene analysis. The consultation before the actual examination has to clarify the personal side of the issue and the aim of the consultation. Besides anamnesis, extensive and comprehensible information about the diseases and disabilities in question as well as the existing or missing prophylactic or therapeutic possibilities are to be given. Furthermore, the relevancy of a positive medical finding has to be clarified in regards to the life and family planning. There has to be enough time for the consulter between the first consultation and the gene analysis in order to meet an autonomous decision. Moreover, the consulter must be able to terminate the process of examination and consultation at any time.

Ethical questions about genetic tests, PND and PID cannot be discussed here in detail. Thus, I have to restrict myself to a few basic considerations about the consequences of modern genetics on our understanding of disease and well-being, disabilities and suffering, of naturalness and creatureliness, of perfection and imperfection.

3. Medicalisation of life

Chances and dangers of genetics should neither be underestimated not exaggerated.[5] Both the prophets of the brave, new bio-world and their critics tend to overestimate the possibilities of genetic engineering. Considering it soberly it becomes quite clear that the ending of the human genome project has produced lost of "words" but little "meaning".[6] The idea of a human made to measure is doomed to fail on grounds of scientific-technical reasons in terms of the over-complexity of reciprocation of the human genes. The therapeutical object cannot be the society or even the whole of mankind but only real human individuals at present or in the probable predictable future.[7]

Strictly speaking, there might not be a single human being without a single gene imperfection even if this does not lead to a serious disease. Imperfection – which belongs to personhood – is apparent already in the microbiological area. Just as reputable scientists warn of gene reductionism since human beings are not defined and determined by the genome, genetics can make it clear that the line between disease and well-being, between disability and non-disability is somewhat blurred. If we would draw the line on grounds of genetics we would need to say that, eventually, everybody is disabled. Especially from the genetics

[5] Fundamentally on this issue see *U. Körtner*, Unverfügbarkeit des Lebens? Grundfragen der Bioethik und der medizinischen Ethik, Neukirchen-Vluyn [2]2004; *L. Honnefelder/P. Propping* (Hg.), Was wissen wir, wenn wir das mnehscliche Genom kennen?, Köln 2001; *W. Beer/P. Markus/K. Platzer* (Hg.), Was wissen wir vom Leben? Aktuellen Herausforderungen der Ethik durch die neuen Biowissenschaften, Schwalbach/Ts. 2003.

[6] *J. Reich*, Viel Text, wenig Sinn. Das entzifferte menschliche Genom bietet keinen Anlass für Stolz und Allmachtsfantasie, in: Die Zeit, Nr. 8, 15.2.2001, S. 31.

[7] *H. v. Schubert*, Geistig Behinderte als Forschungsobjekte? Die Bioethik-Konvention des Europarates, in: Zeitschrift für Evangelische Ethik 42, 1998, S. 140-146, hier S. 143.

viewpoint it is valid that *nobody is perfect*. But since cell division which our bodies run through during life is affected by mutations the idea of breeding the perfect human remains an illusion.

In the meantime research proceeds from genetics to genomics and proteomics. Genomics explores the actual functioning of genes in cells and cell bonds/collectives and the interplay between various genes in different settings. The causal-deterministic assumption that a gene always produces a certain protein is already outdated. Most of the genes of a cell are never read off. Conversely, various protein molecules can be produced by certain genes. Another step in development is proteomics. Proteom denotes the entirety of all protein molecules which are present in a cell at a certain time. Their interactions are even more complex than those of all genes, the so-called genome.

The British physicians, David Melzer and Ron Zimmern, warn quite rightly of the danger that humans might be put under medication and declared ill simply on grounds of genetic tests. "On a fundamental level, genetic science is forcing a reexamination of the concept of normality itself, by showing that everyone's genome is different and that we are all in some sense 'abnormal'."[8]

Disease and good health are not scientifically determinable phenomena but ultimately turn out to be social constructions which include a biologically describable issue without being identical with the issue. The step from genetics to genomics makes clear that the deterministic assumption that the genes determine our destiny and that there is a direct causal link between genetic aberrations and the outbreak of diseases and disabilities is – from a scientific viewpoint – plain wrong. Although there are countless studies positing a connection between gene variants and certain risks of diseases it turns out quite often that their results are not reproducible. Not even in cases of so-called monocausal diseases such as Chorea Huntington – whose outbreak can be predicted very precisely – exists linear determinism.

What's more, the lines between manifest chromosomal or genetic perturbances and genetic dispositions which might at some point lead to some form of disease are fluent. Significantly, predictive medicine has created a new category of human beings, the "un-patient". This means that basically there are no people in good health but only potentially or manifestly ill people.

In his book *The Disease Inventors* (*Die Krankheitserfinder*) medical journalist Jörg Blech warns of the way how healthy people are made to patients by an alliance of medicine and pharmaceutical industry.[9] Amongst other things he points out the dangers emerging from expanding genetic testing which today is already on offer on the internet. Also medical

[8] *D. Melzer/R. Zimmern*, Genetics and Medicalisation, British Medical Journal 324, 2002, S. 863-864, hier: S. 864.

[9] *J. Blech*, Die Krankheitserfinder. Wie wir zu Patienten gemacht werden, Frankfurt a.M. [7]2004.

professionals warn of the angst-ridden business tactics employed by some internet vendors.[10] The reliability and significance of certain tests which for example, allegedly, diagnose polymorphisms is highly disputed amongst experts. Not uncommonly, these test simply provide merely statistical statements on possible health risks which means statements of probability on which grounds one should not seriously jump conclusions regarding the actual course of life or preventive medical measures. Particularly with internet offers national rules and regulations which provide control over the reliability and quality of genetic tests can easily be eluded.[11] The European Group on ethics which has been appointed by the EU Commission has commented on these issues and pointed out the aforementioned problems.[12]

In order to curb the unscrupulous medicalisation and pathologisation of basically natural processes and diversities it is necessary to develop a concept of *non-diseases*. Richard Smith conducted a survey on this topic amongst British GPs and published the results in the BMJ. Smith defines non-diseases as "a human process or problem that some have defined as a medical condition but where people may have better outcomes if the problem or process was not defined in that way."[13] As examples for non-diseases Smith not only cites dacryocysts (tear sacs) or alopecia (loss of hair) but also aging and menopause. If one thinks of the booming anti-aging-medicine the discussion about non-diseases harbours quite some explosiveness.

4. Aporia(s) of modern medicine

Progress in the field of genetics and predictive medicine are basically welcome although medical genetics provides examples of aporias in which modern medicine as a whole gets. The fundamental aporia of medical progress exists in that in its battle against a destiny beyond human control it constantly generates new appearances of fateful destiny. New forms of heteronomy are the dialectic consequences of modern autonomy – also in the filed medicine. Philosopher Odo Marquard describes the period after the Age of Enlightenment as the Age of Feasibility. The way of modernity which was heavily influenced by scientific medicine leads "from fact to fate, from destiny to (doomed?) feasibility."[14] However, this process appears to be Janus-faced. The more the reality of life – and thus, also disease and

[10] *R. Leinmüller*, Gentests: Manchmal ein Geschäft mit der Angst, http://www.aerzteblatt.de/v4/archiv/pdf.asp?id=31826; *H. Berth/A. Dinkel/F. Balck*, Gentests für alle?, http://www.aerzteblatt.de/v4/archiv/pdf.asp?id=31170.

[11] Cf. section IV of the Austrian Bill on Genetic Engineering (§§ 64-79 GTG).

[12] *European Group on Ethics*, Statement „Advertising Genetic Testing via Internet", http://europa.eu.int/comm/european_group_ethics/docs/statgentest-en.pdf (Februar 2003).

[13] *R. Smith*, In search of „non-disease", British Medical Journal 342, 2002, S. 883-885, hier: S. 885.

[14] *O. Marquard*, Ende des Schicksals? Einige Bemerkungen über die Unvermeidlichkeit des Unverfügbaren, in: *ders.*, Abschied vom Prinzipiellen. Philosophische Studien, Stuttgart 1981, S. 67-90, hier S. 67.

well-being – is transferred into human meaningful action the more new contingencies are generated which haven't existed beforehand at all.

Just the development of medicine proves to be a blatant example. Intensive medicine, reproductive medicine and medical genetics have extended the scope for medical action enormously. At the same time they have produced utterly new forms of appearances of fate with which the concerned individual has to cope morally and psychologically. The more human beings want to control life the more uncontrollable the preconditions and consequences of their action become. "Thus: not only the unsuccessful but precisely the successful planning of action arranges itself– at least partially – around success. Therefore, in the age of the fate-destroying ambitions of human beings, the well-meant becomes not the Good; yet, the absolute regulating constitutes the non-regulable; the results compromise the intentions; and the absolute world improvement turns out badly into world confusion."[15]

The gap between already possible diagnostics and prognostics and the missing therapeutic approach is widening and is still one of the ethical problems of genome research and its clinical application. The application of predictive examination methods for instance in prenatal medicine can be of prophylactic use but is also conjuring up new conflicts of decisions. I will only mention the problem of embryopathic indication in abortion or the debate on PID which has been commented on by both the German Ethical Council and the Austrian Bioethics Commission in 2004.

Generally, contradictions regarding the protection of life before and after birth belong to the aporias of modern health systems. On the one hand our society and the current laws accept late abortions for embryopathic reasons; on the other hand everything possible will be done to save premature babies of the same stage of development. It is still valid that a human being is born and that this birth is the beginning of his or her existence as a legal person in the full meaning of this word. But birth as the clear line for the protection of life is to be relativised from the embryological-medical and ethical viewpoint. Although we cannot discuss the ethical questions involved in detail some contradictions should at least be mentioned.

It is out of question that genome research is opening new possibilities in the fields of diagnostics and therapy which are ethically acceptable. Even if sturdy economic interests should not be camouflaged and the chances of biomedicine should not be overestimated it seems to be somewhat problematic when the public discourse is primarily focusing on the possible dangers for instance under reference to the *Imperative of Responsibility* (*Prinzip Verantwortung*) by Hans Jonas in which he speaks of the "heuristics of fear".[16] Of course, he is right in criticising a melioristic perfectibility-utopia. But a voluntary collective self-

[15] O. Marquard, a.a.O. (Anm. 14), S. 81.

[16] *H. Jonas*, Das Prinzip Verantwortung. Versuch einer Ethik für die technologische Gesellschaft (stw 1085), Frankfurt a.M. 1984, S. 63f.70ff. Zur Kritik vgl. U. Körtner, a.a.O. (Anm. 2), S. 70f.90f.

restriction of human action might not have less problematic consequences than the unrestricted use of all technological possibilities. Not only action needs to justify itself ethically but also in-action, i.e. to refrain from doing things. The technological character of biomedicine as such doesn't offer a sufficient reason for ethically motivated critique. From an ethic of responsibility's point of view it has to be examined whether it might not be just the ethical duty to use the knowledge of biomedicine.

But all tendencies which might abet a eugenic mentality within society and an atmosphere of discrimination against disabled people need to be thwarted. For many multi-factorial diseases genome research will not be able to provide a miracle cure and even somatic gene therapy will probably be usable to a limited extent. Many diseases result from a complex interaction of the individual and the environment, the genetic disposition, individual life-style and social surroundings. Therefore, from an ethical point of view it would turn out problematic if the economic resources would be spent lopsidedly on gene research while other areas such as preventive medical measures, social medicine or care for long-term patients would be neglected.

5. The right to imperfection

At the core of all medical-ethical discussions stand basic questions of anthropology.[17] Behind the frequent but ostensible question whether medicine should be allowed to do what medicine actually *could* do lies the anthropological question: What is the human being? What is disease and good health? And wherein lies the *meaning* of disease, well-being, suffering and death for the person concerned?

Humane medicine is not only a technique, it is also an art. Medicine is neither pure science nor part of the humanities but a practical science. This basic understanding must be abandoned. But it has to be newly formulated and concretised under the terms of modern medical service. Otherwise there might be the danger that the already problematic idea of a right to good health – which has to be distinguished from the social human right of equal access to adequate health services! – could be inflated to the idea of the right to perfection. This is not only an issue in some utopian ideas of breeding human beings but already a factual consequence of already existing forms of predictive medicine.

How far reaching today's code of practice of prenatal diagnostics has changed our perception can be seen in rather spectacular court decisions. In one case a physician was sued for damages because his wrong prenatal diagnosis had led to the birth of a disabled child

[17] For the following cf. *U. Körtner*, „Lasset uns Menschen machen". Christliche Anthropologie im biotechnologischen Zeitalter, München 2005, S. 119ff.

which otherwise would have been aborted. In the decision the court said that the parents experienced material damage due to the costly care of the child. Although it has to be added that the expenses for the care were defined as damage and not the child itself this ruling is based on the assumption that the damage could have been avoided through abortion of the child. The right to have children turns into the right to have healthy children.

Another spectacular case caused a stir in France a few years ago. A severe disabled man sued not the physician but his parents for compensation because they did not let him die. The plaintiff won the case. We cannot go into details regarding the judicial implications of this ruling. Ethically it is important to note that one's own non-existence is to be preferred to a life in disability. If the assumed right to good health cannot be realised it becomes re-interpreted to the right to not being born at all. Since one's own birth cannot be reversed it is only a small step from the right to not being born at all to the right to euthanasia.

In view of the biomedical progress disabled or somehow imperfect life is felt as an unreasonable demand, be it for the person affected or for their environment. That life as such can be an unreasonable demand and that we as parents having given our children life in the first place expect something from them which in itself is an unreasonable demand is a basic fact. Thus, modern biomedicine forces us to (re)consider the term of reasonableness ethically.

The philosopher H. Jonas has annotated that "we, eventually, do not consult in anticipation of those coming after us what they *wish* to do (since this could be our own produce) but what they *should* do which is not made by us and stands above both of us. […] Thus, we have to rather not watch over the right of coming people – namely the right to happiness which is due to the unsteadiness of the meaning of happiness an awkward criterion anyway – but over their duty, namely their duty to true humanity: which is their *ability* to this duty".[18] Jonas speaks of a duty "which empowers [!] us well and truly one-sidedly not to give life to all of those coming after us as a gift (which would not go along well with imposition [!]) but rather as the demand of an unreasonable expectation [!] – the very existence that is capable of carrying the burden, which the duty is meant for. Whether they would wish to carry that burden – we would not ask them even if we could".[19]

It appears that such considerations regarding the expectations of life und its unreasonable demands are not self-explaining anymore. Unborn humans are being asked indeed hypothetically whether they would like to carry the burden to live a handicapped life. That the unsteadiness of the meaning of happiness is used here as a criterion and that one's own desires are projected onto unborn humans is accepted by society. If one, however, argues like this in the case of physical or mental disability why not also in view of the sex – which is already the

[18] H. Jonas, a.a.O. (Anm. 18), S. 89.
[19] H. Jonas, a.a.O. (Anm. 18), S. 90.

code of practice in India – or in view of colour of the skin, presumable intelligence or other features?

When the subjective right to happiness is declared as the measure of predictive medicine it amounts to the assertion of a right to perfection. But then we have to ask how humane a society still is if such a legal claim is accepted and enforceable. The humanity of man – thus my thesis – is linked to the right to imperfection. Indicating the humanity of a society is the question of how far it protects the right to imperfection. In the right to imperfection lies the positive meaning of what we called – subsequent to H. Jonas – the unreasonable demand and the reasonableness of life.

According to Christian belief the understanding has to be regained that human life is fragmentary and imperfect and that disabilities and suffering are part of a meaningful life.[20] The Christian view on human beings includes the difference of salvation and healing (Heil und Heilung) although the two are relating to each other.[21] This means that both medical action and medical research need to be released from all open or covert soteriological claims. At least according to theological belief salvation cannot be a sensible therapeutic aim neither in the meaning of some doubtful "wholeness" nor in the meaning of some utopia which employs medicine as a means to reach technical perfection of the human race. The art of healing must not be inflated/extended into an art of salvation.

Genome research and its application up to genomics and pharmacogenomics open up new possibilities for therapeutic approaches which are ethically welcome, indeed. But at the same time medical progress foster problematic tendencies which suggest coercion to perfection. Already from the genetic viewpoint the human being is an imperfect being. That he and she may stay that way is the right to be defended.

[20] *H. Luther*, Leben als Fragment, WzM 43, 1991, S. 262-273.
[21] *U. Körtner*, Dimensionen von Heil und Heilung, EthMed 8, 1996, S. 27-42.