Bioethical Issues in Genetic Screening and Patient Information

GENETİK TARAMA VE HASTA BİLGİLENDİRİLMESİNDE BİYOETİK SORUNLAR

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Summary

Recent progress in molecular genetics has dramatically improved clinical knowledge in pharmacogenetics, predictive and preventive medicine; this knowledge can be put to work in individualized drug prescription and in medical health risk prediction and prevention. A survey of the international bioethical and clinical literature will analyze a probable conflict between issues of privacy and informational property rights on one side and of medical benefits in prescribing efficacious drugs and in advising on preventive measures for individual genetic profiles on the other side. Special attention will be given (a) to cultural and bioethical traditions in accepting genetic screening, (b) to pharmacological and clinical genetic research and (c) to regulating culturally sensitive genetic research.

Key Words: Genetic screening, Informed consent, Cultural relativism

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Özet

Moleküler genetik alanında son dönemdeki gelişmeler, farmakogenetik ve koruyucu tıp alanındaki klinik bilgiyi dramatik biçimde ilerlemesini sağlamıştır. Bu bilgiler gerek ilaçların reçete edilmesinde, gerekse koruyucu tıp alanında kullanılabilir. Biyoetik ve klinik alanında yazılmış olan uluslararası literatürde yapılacak bir araştırma mahremiyet ve bilgiye dayalı mülkiyet hakkı ile etkili ilaç yazımındaki tıbbi çıkar ve genetik profile göre kişisel koruma tedbirlerinin önerilmesi arasındaki muhtemel çelişkiyi gösterecektir. Bu çalışmada, a) genetik taramanın kabul edilmesindeki kültürel ve biyoetik gelenekçilik, b) farmakolojik ve klinik genetik araştırma ve c) kültürel açıdan hassas olan genetik araştırmalara değinilecektir.

Anahtar Kelimeler: Genetik tarama, Aydınlatılmış onam, Kültürel göreçelik

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Towards an Ethics of Health Risk Factor Education

New knowledge in science and technology and new professional and personal applications of new knowledge require value assessment together with technology assessment. Breakthroughs in modern medicine did not come accidentally, they were sought after not for reasons of curiosity but for the sake of the 'patient's good' (aegroti salus) in the performance of humane ('ren") by skillful and honest physicians and health care workers. New knowledge in human genetics and pharmacogenetics will have a great impact on future predictive and preventive health care services, on individualized and more efficacious drug development and prescription, on lay health education on individualized health risk management and health protection and enhancement, on the interfaces of physical exercise, nutrition, medication, and prudent lifestyle management.

As scientific knowledge has changed rapidly, transfer of knowledge and a revised understanding of health and disease have to follow. Traditional concepts of health have become obsolete, so have the health policies based on outdated models of health. *Health* cannot simply be understood anymore as 'a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity', as the WHO defines, rather as a process of challenge and response, a process of balancing, which needs understanding, protection, and management by the individual person. Here is

a first thesis: *Health is not just a status; rather the balanced result of health-literate and risk-competent care of one's own physical, emotional, and social wellbeing and wellfeeling, achieved in competent understanding, modification and enhancement of individual genetic, social and environmental properties, with the support of health care professionals and through equal access health care services, including information, predictive and preventive medicine.*

The WHO definition of health seems to have outlived its usefulness and is in need of being replaced by a new concept of health and health care. The new situation suggests a re-evaluation and a re-prioritizing of traditional principles of care, confidentiality, beneficence, informed consent, and harm within physician's ethics. Long neglected patient's ethics and health care ethics of the lay has to become a prime topic for bioethics research, education and application in the clinical, primary care and public health care settings. Also, we will have to focus on *modified principles* such as duty to inform, duty to be told and to know, health education, health literacy, health care competence, informed request, informed contract, and the ethics of data availability. The new challenges to health care are challenges in health care education of health care experts and of individual citizens, their families and communities. New models of communication in trust and cooperation in trust between the experts and the lay need to be developed as, in the words of Ni Peimin, health care is 'not a matter of biology alone', but 'a never ending journey towards the highest perfection of human being' (1). Such a notion of caring for health was not only part of the Confucian tradition; there is a long tradition of dietetics, i.e. lay prudence in healthy lifestyle in European thought. Those concepts and maxims seem to have been lost in most modern systems of disease management and been replaced by an unfortunate repair mentality in health care matters.

Principles and maxims in bioethics have to be *balanced and weighted* for different scenarios and individual cases. Western reasoning, in part under the influence of legal requirements, has a tendency to adversariously stick to principles as to be as inflexible as possible, while the Thomist tradition of common sense - ' quanto magis ad particularia descenditur', the more we come to the individual case and the concrete situational challenge, the more absolute values have to loose their firmness and inflexibility, also been weighted against others - and the traditional Asian approach to balance maxims and requirements according to the situational circumstances seem to be of more promise in stewarding new challenges in health care (2). I call for an *ethics of situational flexibility in applying bioethics principles to different scenarios and individual cases taking the technical, cultural and ethical specifications into account, preferably in communication and cooperation with other moral agents and stakeholders.*

The so-called Georgetown mantra - autonomy, nonmaleficence, beneficence, justice - has shown a remarkable flexibility from its first introduction by the Belmont Report as principles for human research in a pluralistic society to the 7th edition of Beauchamp's and Childress' Principles of Bioethics, now called 'common morality'. Similarly, traditional Asian sets of virtues and principles such as those of Confucian scholar Yang Chuan - humane, compassion, cleverness, wisdom, sincerity, honesty-, the interactive sets of balancing I have proposed - self-determination versus compliance, quality of life versus length of life for the individual, professional responsibility versus respect for autonomy, nonmaleficence versus beneficence for the physician - allow for situational prioritizing, preferably in communication-in-trust and cooperation-in-trust among stakeholders, i.e. physicians and patients, but not excluding family and other by tradition or culture accepted moral agents or stakeholders (3).

Carrier Ethics and Family Health Care

New diagnostic knowledge in human genetics and pharmacogenetics make responsibility-sharing with citizens as future patients or actual patients possible. Based on Western and Eastern traditions of responsibility and self-determination within the individual's cultural environment, the obligation to

know about one's genetic heritage and its advantages and disadvantages, its risks and uncertainties is a precondition for living a self-determined, risk-competent educated life and for enjoying fullest possible individual quality of life. This would require a duty to inform, to educate, to counsel, and to support for the health care experts, a right to be told, and - in those cases, where others are not impacted negatively by individual self-determination a right to follow or to refuse to follow health care advise. There does not seem to be an obligation to tell, if diagnostic findings cannot result in advice or prescription; but one could make the argument that even in these cases of intervention futility citizens have the right to request information anyway, if they want to know (4). As a fourth thesis I can formulate: *There is a right to know and an obligation to tell, if health risks are present or predictable. There is, however, only a moral, not a legal obligation to follow health care advice; this obligation becomes more pressing if health care costs are shared solidarity.*

As genetic diagnosis provides potentially important information for family members in regard to health risk, health status, potentially helpful preventive measures and information essential for individual self-determination and quality of life decisions, each and every person diagnosed will need to consider her or his responsibilities towards family. In Western cultures, emphasis is put on privacy of patients or those diagnosed, while even during transitional periods of Asian professional and family cultures there is a high responsibility towards family, filial love, parental love, different forms of love within the wider family. As not only severe genetic disorders, a higher than average risk of hypertension, forms of cancer, metabolic disorders may run in families, information about these risk factors would be extremely important to carriers, so they seek frequent checkups and advice or might use preventive strategies to reduce impact or postpone onset. Interactive family health care ethics still have to be developed, able to adequately deal with issues of *family ethics*. Also, family relations will be influenced by new sources of - unfounded - guilt-feelings, shame, accusations, self-denials, maybe divorce, suicide, and the breakup of families and familial relations. The golden rule must be to not hide behind traditional attitudes towards secrecy and privacy, but to openly and aggressively inform, educate, teach and support dialogue and discourse in families and in society. It should be done, however, not against the grain of traditional familial forms of communication and cooperation or against the will of the diagnosed carrier, but in seeking her or his support and in making the best use of sometimes dormant principles of family responsibility and solidarity (5). This leads to my fifth thesis: *In complex issues of family ethics, privacy, disclosure, right not to know, and duty to know, diagnosed carriers would be the prime moral agents to make educated and responsible choices (a) to disclose, (b) to refuse disclosure of all or some information, and (c) to postpone hard choices in informing family members.* There will be hard cases, where information might be lifesaving to family members who might be carriers. WHO proposed guidelines on ethical issues in medical genetics suggest to rather violate the principle of confidentiality in favor of informing and consulting family members; but guidelines of national organizations differ from such a stern position (2). Additional, responsible parenthood in the future might include decisions whether or not (a) to have children at all, (b) to have prenatal testing and eventually elected abortion following positive testing, or (c) to do nothing and set trust into future breakthroughs in medical treatment of yet untreatable disorders (6).

Informational Property Rights and Data Profiling

Let us discuss the principle of *data availability* and the ethics of *individual health care cards*. Since the discovery of blood types, reliable diagnosis of blood types, typing and screening for blood types has become an essential part of emergency medicine and surgery and has saved directly or indirectly millions of lives. No one 100 years ago has made the point that privacy issues should prevent blood typing, nor does anyone today. It is well known that we do not differ only in types of blood but in many other individual properties, such

as in cytochrome P450 isoforms, controlling drug metabolism, causing non-efficacy, side-effects, even death, in some types of metabolizers. In hypertension treatment, calcium antagonists are metabolized by the 3A enzyme in the cytochrome P450 isoform system, while beta blockers are metabolized by 2D6, a switch from one to the other without proper drug metabolizing tests would be clinical and ethical malpractice; P450-2D6 enzymes metabolizing codeine for palliative care is absent in 7% of Caucasians, resulting in total non-efficacy in those individuals; P450-2C19 metabolizing diazepam (Valium) and other neuropharmaca is absent in 15% to 30% of Asians, who therefore would require much lower dosages than established in controlled clinical trials on Caucasians (7). When individual pharmacogenetic profiles for medication-typing scan be established the same way we easily can establish individual profiles in blood-typing, personalized drug delivery is possible and ethically required.

The fears that genotyping for drug metabolism will lead to discrimination are not convincing, they are theoretical, ethically unfounded. Blood typing did not lead to discrimination, even though some individuals have blood-types which are more rare, at least in certain populations, and therefore might have less access to blood replacement. Blood profiles and medication profiles do not describe disorders, i.e. an individual aberration from a generic image, rather they constitute different types, *variations*, none of which is the 'normal' one. We have a model of variation, not one of order and disorder. It would have been a crime against humanity and an unexcusable wrong towards all fellow humans who would have died and would die of their lives could not be saved by blood transfusion based on proper blood-typing. In drug metabolism as in every metabolic property the concept of normal versus disorder is wrong, as there is no normalcy, only differences in expression and action. Genotyping for drug compatibility causes no significant other ethical concerns than those associated with blood typing: clinical reliability of typing procedures, equal access to typing services, no (medication prescribing) intervention prior to typing (8).

The new scenario of metabolism typing has consequences for the traditional and accepted bioethical setup of vaccine development, clinical trials, prescription procedures, and nutrition advice. Therefore it should be considered unethical to not include genotyping into drug development and to establish efficacy, dosage, and side-effects for major types of metabolizers based on cytochrome P450 isoform properties and composition. This leads to my second thesis: *Individuals have a civil right to information about their individual proteonomic and enzymatic properties for metabolizing drugs and nutrition.* This informational right would best be served by providing inexpensive individual *Drug and Nutrition Cards* and access to information and education; also those drug-and-nutrition-chips need to become the golden standard in drug prescription based on metabolizer-type clinical research.

As individuals differ in more than our enzymes and protein metabolism, it would only be consequent to provide citizens with individual *Health Care Cards* containing information on individual genetic or acquired properties, abilities, disabilities and disorders such as risk of hypertension or diabetes. *Data availability* is the precondition for good diagnosis and prognosis, and subsequently for prevention and treatment. Personal data, including data on health and health care are the *informational property* of the individual. In other areas of life we share these informational properties with others for our own benefit convenience, such as with credit card providers, supermarkets, libraries, online-merchants, and insurers of various kind. Of course, we rightly worry about protection of private data; we have laws and regulations protecting private data which work most of the time; we accept these risks as we balance risk with benefit. Individual rights on individual health information should not be treated differently than other informational property rights. This leads to my third thesis: *Citizens are informational property owners of data concerning individual health status and health care. It is in their best interest to have Health Care Cards and to share information with professionals in a protected framework as*

data availability becomes as important as data protection. Health care professionals cannot provide quality service if denied access to information necessary for providing safe and efficacious service.

I feel that it would be extremely difficult to argue that those who do not share personal health status data with professionals can ever request those services or will get best possible service. If data are not stored and be made available, rather being generated every time anew, then costs will skyrocket without additional benefit and therefore those who do not entrust personal data to individual Health Care Cards should accept the higher costs of more expensive procedures. As far as the principle of solidarity is concerned, data availability is not only a prerequisite for good health care, it is also a potential factor to reduce costs.

Ethics of Genetic Research

Finally, reforms are necessary in clinical trials and human experimentation based on new challenges and opportunities particularly in genetic research, DNA-sampling and DNA-storing. It is my thesis that the traditional soft-paternalism principle of *informed consent* has to be replaced by the principle of *informed contract*, detailing for researchers and probandi or patients rights and obligations, liberating probandi and patients from their passive role of just consenting to a more adequate position of being a partner. In particular, issues of research in drug metabolism, DNA-sampling, and disease-specific research cannot be justified without taking into account the probable benefits to the patient or her or his families. Modern medical research will find quite a lot of information about pedigree and family members, which cannot be taken care of by the concept of individual consent only by those who participate in the research (9).

For genotyping in highly defined populations of patients suffering from certain subgroups of cancer or other diseases and receiving specific medication, it has been debated whether traditional models of informed consent would be enough for multipurpose long term DNA-banking. It probably means to *overburden the informed consent principle* in dealing efficiently with DNA-banking and the probable benefits to the patients and their families. Giving just informed consent to draw blood for unspecified research might not be in the interest of the patient, even though such a consent might benefit the research and other patients in the future. Informed consent forms rarely address issues of multipurpose screening and long term storage. It has been suggested that for genotyping only specific informed consent should be requested and that further use should be covered by new specific re-consent. On the other hand generic consent forms - in particular for prenatal and newborn screening - were proposed, but others criticized such an approach as lowering the standards of informed consent (10).

As the probability of benefits in cross-purpose genotyping and of future yet to be specified re-testing and new-testing is of great moral importance for the individual patient, patient groups and the progress of clinical research, one should work with a contract model, describing the obligation of the researchers to inform the patient on all or some of their findings and establish a contract spelling out the obligations towards the patient and her or his family: 'We ask you to sign a contract for genetic testing on information and properties which might or might not be associated with your disease and how they are associated with it; this might take along time and we might look for information we don't know yet. We make it our legal obligation to inform about any finding which might benefit your treatment and which might be beneficial to members of your family. Also, at any given time, you or your representative has the right to cancel this contract and to request that your biological properties be destroyed. If you want to share in possible financial gain associated with this particular research, we will provide you with a separate contract.'

Within the *contract*, patients or their legal representatives must be informed on standard data-protection. In order to solve complex issues of privacy and disclosure, the right not to know, and the duty to know, the contract must provide, that patients can make their own choices (a) for man-

dating disclosure of individual predictive, preventive, or therapeutic knowledge, (b) for refusal of all or some information, and (c) for postponing such a decision for later based on then existing individual circumstances or clinical results. The moral issues of informing and protecting family members similarly will have to be addressed within the contract by allowing the patient to choose among a number of procedures by which family members of various degree may or not be involved, informed, or invited. This leads my seventh and final thesis: *It is time to replace an outdated informed consent model totally or in part and replace it by a contract model in which stakeholders such as probands, researchers and sponsors delineate moral and legal contractual rights and obligations.* Some informed consent forms include features of informed contracts, but WHO and the European Forum for Good Clinical Practice have not yet addressed these issues or come up with proposals for reform (9).

Self-determination, Individual Values and Informed Consent

Modern medicine, recognizing the principle of autonomy and self-determination as a most basic human and civil right, allows for clinical research and medical treatment only, of the proband or patient has given free and informed consent based on individual concepts of risk, benefit, values, fear, and hopes. Global recognition of the informed-consent principle correlates to the vision of universal human rights, as expressed by the United Nations Declaration in 1948 and being a fruit of the processes of enlightment and emancipation since the European age of Reason. If immediate medical treatment is required in order to save life, the informed consent principle cannot be used as life and survival of patients is the higher principle, the highest order.Good as it looks in principle, there are quite a number of well-documented cases where the informed consent principle does not work or is used in an abusive and exploitative manner: [1] If people do not clearly understand risks and benefits associated with research and treatment, oral or written consent is void. [2] If people feel an 'obligation' to sign forms, such consent is not given freely. [3] If researchers cannot or do not adequately inform probands or physicians their patients, signed forms are a smoke-screen only to hide that true informed consent is not given; however the legal requirements seem to be satisfied.

In general, the informed-consent principle has been developed at a certain historic time under specific post-enlightment cultural conditions. It is a very useful tool to protect vulnerable persons from abuse; properly used it is the best tool available to protect human dignity and civil rights. However, even if no abuse is intended, there seem to be cultural obstacles associated with its rigid implementation under the maximal 'one size fits all'. Following I will discuss appropriations of the general principle which in certain cultural settings might be more adequate to protect vulnerable individuals and populations than the rigid application of classical legal forms developed for educated and risk-competent citizens. We see already *exemptions and modifications* form the general rule: [1] consent for minors is given by their ethical and/or legal representatives, mostly the parents. [2] competent adults may designate another person to give consent on their behalf, either immediately or under certain conditions in the future. [3] The consent required from psychiatric patients is related to their particular disease and situation at a given time; however, there are well developed treatment contracts signed by patients and their caretakers for possible future situations known to and experienced by the patient (11).

As we discussed, the informed consent principle does not work in genetic research and genetic testing, in particular in DNA sampling and storing. In genetic research and diagnosis it is *too restricted and short-sighted* in as far as information gained might also apply to blood-relatives, who might benefit or be harmed by information. Traditional consent forms do not and cannot handle those issues; therefore models of 'informed contracting' or 'participatory contracts' have been recommended at least for these situations.

The *classical model of informed consent*, as supported by WHO and mostly national legal sys-

tems, medical professional organizations and regulations and codes of conduct for clinical and genetic research, is based on the vision of the competent individual, making free and educated decisions for herself or himself, independently from prevailing attitudes, dependencies, trust-and-responsibility structures, surrounding family, community and culture. Only within these parameters does and will the model work. The bioethics literature on informed consent is full of publication evaluating how the model did not work, how it was manipulated or abused as a screen and alibi (12).

There are *standard deviations* in decision making for children, non-competent adults, psychiatric patients or the previously competent demented elderly.

Some cultures, even though they might be in transaction being more and more influenced by post-enlightment European cultures of individualistic ethics, still have a strong sense of family ethics and family decision making for the good of the individual family member, thus traditionally giving consent for the god of an individual family member as *family consent*. The classical European model is seen as an intrusion into a different trust-and-responsibility structure and, if used, only legally and without any cultural or ethical authority and validity. Family consent is not without risk. It might be the elder male or female head of the smaller or larger family accepting responsibility for his relatives, and been trusted by them to make those decisions, even far-reaching ones such as marriage, education, job training. Some individuals or branches of the family might not trust the proxy decision maker; elders might violate the trust they are endowed with. Those are the situations which have led to the rise of emancipation and enlightment in the Age of Reason. But there are still families and communities around for whom the model of an individual person making autonomous decisions by herself and for herself alone, is considered unethical, not supported by culture and values, actually decadent and perverse (13).

Moral or social communities quite often address ethical issues by *community consent*, even though individuals are subjects under risk. In Western civilization, religious orders and closely controlled religious groups obey and consent to decisions made by their superiors. The fact that different cultural and moral communities have different values, wishes, hopes, and fears, is well used when making proxy decisions in medicine for incompetent persons. Schools of communitarian ethics place great emphasis on supporting and respecting communal values. Ethics committees in pluralistic societies include *neighbourhood representatives* or representatives from religious or moral or social communities to which the incompetent persons belongs. If a village or province community widely and strongly shares religious, cultural and moral convictions, then most like individual preferences for participation in medical research or for medical treatment would be similar. Also, if this is a part of the specific culture, decisions would made by elders, wise men or women, elected or accepted otherwise. Researchers required to inform and educate and to gain consent, would be well advised to use the existing trust-and-responsibility structure for information and education and for contracting with the community and/or families and/or individuals. Benefits for the community, for the families, and the individuals should be spelled out in detail. In the case of DNA sampling contacts should be made some time before DNA is sampled, and definitely a long time afterwards information and health care education services should be contracted and provided. The larger and the more complex the community is, the more risky will be a communitarian approach and the more features have to be developed and supported to protect dissenting individuals and groups. There might be situations of communities in cultural transition or under indoctrinating and exploiting elders or oligarchic groups, where the communitarian approach to protect vulnerable individuals and families will not work and cannot work.

Given the diversity of individual and collective cultures in decision making, one size of consent does not fit all. It seems to be clear, that the classical model of informed consent has outlived its useful life as a general standard for all, for each and every personal, familial, communitarian, cultural or legal situation. Where the basic cultural

attitudes and legal preconditions are not in place to make the classical form of informed consent the preferred and most useful tool, it *cannot* be made a requirement that medical experts first of all change cultures and attitudes and then proceed with their medical work. It is also not acceptable that medical experts turn a blind eye on the missing of essential prerequisites for making informed consent work. Everyone has to work on implementing human rights and free decision making by competent and risk-literate adults; this task cannot be put on the physicians alone. Also, there might be true ethical situations where coherent *trust-and-responsibility structures* within families or communities are well developed, by cultural or religious tradition and in the history of ideas supported and proven to working well in quite a number of cases. In those situations it would be culturally and ethically insensitive and counterproductive to destroy a working network of trust, hope, responsibility, and reliability in order to replace it by a model developed under different cultural and historical conditions (14).

Research projects in the ethics of DNA sampling and storing, of clinical research, and of patient treatment are urgently needed for the benefit of those fellow-humans who for reasons of culture and attitudes do not fit the standard model for which the classical informed consent principle has been developed. Those research projects could work with narratives and structured interviews, also family meetings or town-hall-meetings.

An educated guess is, [1] that *models of contract* rather than one-sided still soft-paternalistic consent might work better in all situations. Another assumption is, that models other than the classical informed consent model would need [2] to have *'escape clauses'* or *'conscience clauses'* allowing each and every individual to decide for herself or himself on the basis of individual autonomy and self determination, if a trusted individual, a family, or a community has decided otherwise; greatest emphasis has to be laid on developed culturally sensitive tools and procedures for those who do want to make their own choices, even though values and attitudes in their community or family suggest otherwise.

Appendix I

Scenario Assessment for 'Informed Consent' or 'Informed Contract'

1. what are the benefits of this model?
2. what are the disadvantages?
3. can it be abused?
4. how can abuse be minimized or avoided?
5. evaluate different options within the chosen model
6. use real-life cases to prove your findings and options
7. what are the ethical implications of each model?
8. what are the legal implications of each model?

Appendix II

Scenario Development Procedure for Genetic Screening

1. Problem Identification

a. collect technical data
b. collect significant human data
c. identify ethical issues
d. evaluate technical, human, ethical issues

2.Develop Alternative Scenarios for Action

a. establish reasonable and workable scenarios
b. identify ethical principles and risks in each scenario
c. identify stakeholders and moral subjects
d. discuss ethical and technical cost-benefit assessments

3. Present a Set of Alternative Scenarios

a. discuss uncertainty in each scenario prognosis
b. include stakeholders in cost-benefit-risk assessments
c. present ethical cost-benefit-risk assessments
d. discuss differences in benefit-cost-risk balances

4. Formulate a Justification for Your Selection

a. specify your reasons for the selected course of action
b. clearly present the ethical basis for your action
c. understand ethical shortcomings of your justification
d. anticipate and discuss objections to your selection

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