

Current Topic

Ethical Issues in Genotyping for Pharmacogenetics and Genetic Disorders

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Abstract

New knowledge in human genetics and pharmacogenetics allows for new medical and ethical options, but also requires a review of traditional models of treatment and consulting. Pharmacogenetics will allow for individualised drug development and prescription; drug research and drug safety oversight has not yet responded to these new options. Genetic testing for disorders has an impact not just on carriers, but on their families as well; this requires the development of new models of family ethics and family responsibilities and solidarity, also of new models of communication-in-trust and cooperation-in-trust between the carrier and the consultant. Time has come to replace the soft-paternalistic model of informed consent by a true partnership model of informed contract between patient and physician and between geneticists and carriers.

Key words

Family ethics; Genotyping; Informed contract; Pharmacogenetics

We are witnessing a scientific, medical, cultural, and ethical revolution of gigantic dimension brought about by molecular genetics. Genetic knowledge and its application into the innerworkings of life forms, including human life and its exposure to inherent or environmental risk, is a new challenge in risks and benefits for humankind and human civilization and quite understandably creates controversies in ethical assessment.

On one side there are the foes of genetics pointing out that genotyping in human genetics will do more harm than good to the individual and to the moral and social fabric of mankind. They present five central arguments: (1) discrimination based on the individual's genetic setup will add to many other already existing forms of discrimination, (2) genetic information cannot be kept confidential and therefore will do more harm to the individual than good, (3) fellow humans with specific genetic setups will find it

harder, if not impossible, to gain access to certain jobs or being accepted by health insurance companies, (4) lifestyle regulation in the name of health risk management and cost reduction will be the logical consequence in predictive and preventive medicine, (5) a loss of solidarity towards those with known genetic disorders.

On the other side, there are five arguments by friends of human genetics: (1) individuals will be able to make more educated choices in life based on their genetic risk factors, (2) get guidance for making reproductive decisions giving them for the first time the opportunity for parental responsibility via preimplantation diagnosis and prenatal screening, (3) get more individualised medication with less side-effects based on their specific genetic setup for drug metabolism, (4) get a better understanding of their individual risk factors in the workplace and in the environment, thus protecting health and quality of life before acute or chronic illnesses occur, (5) improve health risk solidarity as each and everyone will have predictable risks in her or his genetic setup, some more severe than others.

As with all new forms of knowledge and technology, individuals, families, societies, professionals, organisations and governments, locally and globally, have to evaluate the risks and benefits associated with genotyping.¹⁻³ It will

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Received July 11, 2006

be a new world, but the blueprint of the story is the old one: *knowledge and technology can be used both ways*, for the good as well as for the bad. Old Chinese wisdom of Taoism said it this way: *'the sharper the weapons the people possess the greater confusion reigns in the realm' but at the same time, taboos and regulations are no remedy against villains: 'the more taboos and inhibitions there are in the world, the poorer the people become, ... the more articulate the laws and ordinances, the more robbers and thieves arise'*.⁴ We are truly venturing into a new world, one that must find (so far it has not done so) its own ethics, based on cultural and ethical traditions and a new understanding of health literacy, genetic literacy and responsibility. It is my thesis that new knowledge in genotyping will have to lead to an improved concept of autonomy and self-determination, empowering the individual to take better control over her or his health care and risk protection.

The revolution in genetic knowledge will also lead to a revolutionary modification of our concepts of health and disease, and of health care and its priorities. Health cannot simply be understood anymore as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity',⁵ rather as a process of challenge and response, a process of balancing, which needs understanding, protection, and management by the individual person. This is my **first thesis**: *Health is not just a status; rather health is the balanced result of health-literate and risk-competent care of one's own physical, emotional, and social well-being and well-feeling, 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 information including predictive and preventive services.* Health is not simply an objective and general criterion as expressed in the WHO definition of equality in physical, emotional, and social health, for which health care professionals provide proper services. On the contrary, individual health and individual health care cannot be separated from personal health literacy and health responsibility.

The new challenges posed by genotyping for drug metabolism and genetic heritage will also have to review and possibly modify some traditional principles in bioethics and might call for bringing other more suitable principles into the forefront. In particular, We will have to discuss traditional principles of confidentiality, beneficence, informed consent, and harm, and will have to introduce new principles of informed request, informed contract, duty to know, health literacy, health responsibility, pedigree

ethics. Also, issues of patenting and profit-sharing in genotyping will need further evaluation.

Improving Efficacy and Reducing Risk in Drug Metabolism

It is well known that certain drugs act differently in different people, some having severe side-effects, even causing death, others not efficacious. Efficacy and side-effects are controlled by the individual setup in drug metabolism by the specific cytochrome P450 isoforms. In hypertension treatment, calcium antagonists are metabolised by the 3A enzyme in the cytochrome P450 isoform system, while beta blockers are metabolised by 2D6. A switch from one to the other without proper drug metabolising tests would be clinical and ethical malpractice. P450-2D6 enzymes metabolising codeine for palliative care is absent in 7% of Caucasians, resulting in total non-efficacy in those individuals. P450-2C19 metabolising 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. The homepage of the Georgetown University Medical Center's Division of Clinical Pharmacology maintains a list of known properties of drug metabolised by the cytochrome P450 system (www.drug-interactions.com). If individual pharmaco-genetic profiles for medication-typing could be established as easily as we can establish individual profiles in blood-typing, personalised drug delivery would become available. Indeed, inexpensive, noninvasive, and accurate genotyping for drug metabolism directly or indirectly will soon be available and will produce a revolutionary improvement in drug development and individualised application.^{6,7}

The fears that genotyping for drug metabolism will lead to discrimination are not convincing and seem to be theoretical and 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 describe different types, none of which should be 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 if their lives could not be saved by blood transfusion based on proper

blood-typing. In drug metabolism as in every metabolic situation the concept of normal versus abnormal is wrong, as there is no normality, only differences in expression and action. Genotyping for drug compatibility is not doing anything more than typing for blood compatibility. It should only cause the same but no extra ethical concerns as those associated with blood typing, i.e. clinical reliability of typing procedures, equal access to typing services, no drug intervention prior to typing.

But the new scenario of medication typing would have consequences for the traditional and accepted bioethical setup of vaccine development and clinical trials. It is my **second thesis** that very soon it will become unethical not to include genotyping into drug development and not to establish efficacy, dosage, and side-effects for major types of metabolisers based on cytochrome P450 isoform properties and composition. It is well known that not only individuals and their families differ in regard to drug metabolism, but that entire populations have quite different genetic properties for all kinds of metabolism. Therefore it would not only be unscientific, but also unethical and inhumane to prescribe medication for people different in their metabolism properties from those who have been the subjects in successful clinical trials.

While normal differences between types of metabolisers cannot be called disorders, as we would not call one or the other of blood type a disorder, there are certain there are certain conditions which had been labeled as genetic disorders for which for over three decades, such as the typing of the major histocompatibility complex (MHC), the genetic property controlling what antigens are recognised by T-lymphocytes. The MHC also controls information about the susceptibility of infections and autoimmune diseases. This is done with antibodies using white blood cells, not by directly testing DNA. Therefore genetic testing of the MHC has escaped the critical eyes of those opposed to genotyping of any form. Also, it has not been reported that people carrying this kind of information on their donor cards had been discriminated against by employers or insurers for health or life.⁸

Enabling and Encouraging Carriers to Take Care of Their Genetic Properties

Some people have a defect in controlling antigens in their MHC, others have other capabilities or incapacities, abilities, inabilities or disabilities, talent or lack of talent. Some are more gifted than others. Some are more

challenged physically or mentally than others. As all of us have our specific set of ability, inability, and disability, a new form of solidarity might arise, a solidarity to help each other to overcome or live with incapacities and to cherish each other's capacities, to build on one's gifts and to learn to live with one's shortcomings, or (and this is my **third thesis**): *even if a new concept of health and health care, including solidarity in health care does not develop, for large health insurance providers the mix of insured requesting support for one or the other genetic setup might even out the balances paid to any one of them; but most of all, predictive and preventive literacy and responsibility will reduce the cost of acute intervention and improve the quality of life.*

Rapid discoveries of minute differences between individual person's genetic code, often only one letter or two, will not only lead to better prediction of individual risk to health and well-being, but will also provide new avenues of developing individually tailored recommendation for diet and lifestyle long before acute medical intervention and medication is required. Close to 100,000 single nucleotide polymorphisms (SNP's), molecular signposts expressing individual alterations from the human genome and determining individual capacities for health and susceptibility for disease, have been found and will make the understanding of health and disease even more a very individualised need and challenge.⁹ Not only will the interpretation of SNP's help in the development of new drugs for treating diseases, the strategy of drug development based on understanding SNP interaction and properties will in turn create drugs for balancing the individual genetic setup long before disease can develop. These developments hold great promise for the better understanding of predisposition for and fight against cancer, dementia, infections and heart disease.

We are close to prevention strategies, replacing old acute intervention strategies, for many genetically predetermined diseases. Phenylketonuria (PKU), a genetic disorder in milkfat metabolism, was brutally harmful for all newborn carriers, resulting in neurological disorders and impairment of development; but the disorder can be 'cured' by selective diet during the first weeks after birth without further medication or only minimal dietary restrictions or medical intervention in the more severe cases. Autosomal Dominant Polycystic Kidney Disease (ADPKD), a late-onset polycystic kidney disease which will require lifelong hemodialysis or kidney transplantation is caused by disorderly functioning of two proteins responsible in kidney maturation.^{10,11} It has been reported that specific diet in

transgenic polycystic kidney rats has caused the nondevelopment of cysts.¹² Recently, the Wall Street Journal (Oct 11, 1999) reported that scientists at Beth Israel Deaconess Medical Center in Boston, MA reversed signs of cystic fibrosis in mice by feeding them a fatty acid called docosahexaenoic acid (DHA), and that Genzyme Corp, having licensed rights to this technology, plans to start clinical testing in humans as early as next year. The journal Science (Oct 22, 1999) reported that the long searched for enzyme beta-secretase had been discovered by a research team of Amgen in Thousand Oaks, California. Successfully blocking this enzyme might prevent or slow down the process of this brutal disease.

These new pharmacological and dietary avenues are easier to apply both medically and ethically for severe genetic conditions such as Cystic Fibrosis, Chorea Huntington and ADPKD than widely debated therapeutic germline intervention. Germline therapy carries too many ethical and medical obstacles when compared to the new developments in molecular genetic diagnosis and therapy. If the disorderly function of an inherited protein on the enzymatic level is fully understood, it most likely can be neutralised or shut off by either medication or diet.

Even though CF and Huntington's disease are severe genetically determined diseases, the concept of 'disorder' versus 'healthy norm' will have to be revised. A better model would be to talk about severity of *impact* and probability of *redress* or *modification*. The ethical attitude towards individual genetic profiles and genetic predispositions therefore should be: *do ask and do tell*. Such an attitude of asking and telling would run against the grain of many traditional attitudes in medicine and genetic consultation, and also against the principle establishing a 'right not to know'. This is my **fourth thesis**: *It is the individual's obligation to ask and to gain general and individualised genetic knowledge for her or his control and improvement of health care and quality as well as length of life rather than to rely on the individual physician or the medical community to provide information, education, and consultation for implementing genetic knowledge on her or his diet and life style.*^{2,3,10}

Developing Challenges in Family Ethics

The transformation of medicine from priorities in acute care and intervention to long-term, nonacute predictive and preventive service and education will definitely have consequences for the transformation of parental and family

responsibilities and family relations, some of these new challenges might be very controversial and revolutionary at least in the beginning. Think about the case of Ms Han, who at the age of 60 was diagnosed as having endstage renal disease resulting from being a carrier of ADPKD. Now Mrs Han is faced with the crucial challenge to tell her daughters, one them pregnant in the first trimester, that they themselves and their children might have the same disease. Is Mrs Han morally required to trade her right to privacy against a moral obligation to inform her daughter and other members of her extended family about her own fate and encourage them to seek diagnosis for themselves and plan their lives accordingly based on the positive or negative outcome of genetic diagnosis? To know about one's carrier status of ADPKD is very beneficial in making lifestyle changes, such as strictest possible avoidance of development of hypertension, avoidance of sports such as certain forms of aerobics or stretching or riding. Hypertension control should be achieved either by calcium antagonists or beta blockers, depending on the individual patient's P450 metabolizing properties, not by shifts or fashions in medication preferences.

Also, responsible parenthood would require to make 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 by regarding a late onset disease as not severe enough to justify an abortion or hoping for progress in pharmacogenetics to treat genetic diseases such as ADPKD in two or three decades. Whatever Mrs Han, as a diagnosed carrier, decides will have far reaching effects on her immediate and extended family. Then, if she does not tell, should the physician do so against her will? Has he or she a moral or legal right or a strong moral obligation to let the potential carriers in Mrs Han's family know about the risk they might carry? And should the insurance companies or health care authorities pay for extended pre-symptomatic screening for this and other severe genetic diseases, at least for those disorders in the early stages of pregnancy? Which genetic aberrations are less 'severe' that they would not warrant physician's moral obligation to tell or insurance funds to pay?

Family relations will be influenced by new sources for (unfounded) guilt-feelings: shame, accusations, self-denials, also divorce, suicide, and the breakup of families and family relations. The golden rule for genEthics must be not to hide behind traditional attitudes towards secrecy and privacy, but to openly and aggressively inform, educate, teach and support dialogue and discourse in the family and in society. This 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^{4,13,14}

This leads to my **fifth thesis**: *In complex issues of privacy, disclosure, right not to know, and duty to know, individual patients should be legally empowered and morally supported in making individual choices (a) for mandating 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. This would include respecting the decision by some patients not to be informed about carrier status so that they can close their eyes before the challenge of deciding to inform or not to inform their family and relatives.* Moral issues of informing and protecting family members can be handled similarly by allowing (a) first the probands to choose for themselves among a number of procedures by which family members of various degree may or not be involved, informed, or invited, and then (b) secondly and based on the options chosen by the proband confront family members with genotyping matters. As the degree in which intimate and other internal relationships within families will change as a result of genotyping for carrier status is out of control of physicians and insurers, these decisions and the pros and cons associated with these decisions therefore should be left to the family. Only the support and encouragement of public education and discourse and the financial and institutional support of genetic screening, consulting, and educating services should be within the realm of political and social responsibility. The US based Polycystic Kidney Research Foundation provides a homepage (www.pkdcure.org), with literature for adults and children, dietary publications and chat rooms for carriers of ADPKD and their families. This is the kind of educational and interactive material which will allow carriers and their families to develop health literacy, self confidence, self responsibility and the quality of life within the parameters predetermined by genetic, social, environmental and other forces.^{3,11}

Request for New Interactive Counselling Models in Human Genetics

In genetic counselling, it has become the golden standard of modern bioethics to avoid paternalism and directive

counselling in favour of non-directive counselling. Given the severity of most renal genetic disorders and the importance of good symptomatic and pre-symptomatic patient-physician interaction in communication and cooperation, we feel that the controversy between directive and non-directive counselling should be replaced by new and more appropriate models of patient-physician interaction, an interactive counselling model of discourse and evaluation.

An interactive model of counselling respecting the patient's or client's self-determination, actually empowering autonomy, would require that the physician: (a) inform and educate the carrier, depending on the carrier's capacity to understand information and to make judgements and decisions; (b) assist and support the carrier to make medically important decisions such as compliance with routine check-ups, lifestyle modification, medication, and dietary regimen. Of course, there will be other very personal challenges and decisions related to the carrier status which do not belong to the realm of medical responsibility and involvement.

The new model of neither directive nor non-directive counselling has also been called 'interpretive ethics' (www.pkdcure.org).¹⁵ The interactive discourse-and-evaluation based dialogue model will work differently depending on the individual case and the carrier's or patient's quest for guidance or value statements by the consultant. Of course, the discourse model will have to make it clear, as is true of all models of non-directive counselling, that paternalism in decision making cannot be accepted and that carriers have to make final decisions and accept final responsibility for decisions made or not made. It will be a fine line, even in the absence of state-coerced eugenics, that professional genetic counsellors do not overstep their obligation to clearly and precisely state facts, issues and prospective problems and dilemmas, but at the same time refrain from providing biased information or assessment on the quality of life of carriers of genetic disabilities.¹⁶ There are and there will be patients who for various reasons are unable to accept responsibility or to follow a strict regimen. For those patients traditional forms of paternalism might still be appropriate, but there are limits to pressuring fellow humans into regimens they do not like and do not want.

Here is an interactive Action Guide for the discourse model, outlining challenges and responsibilities for both the carrier and the consulting health care expert:

Challenges for the Carrier:

- (1) Understand and accept your individual predispositions

for health and understand your individual genetic setup, which will allow you to define your very specific quality of life and goals in life, taking your genetic heritage into account.

- (2) Become health literate and define your individual challenge to happiness and health within the parameters of your genetic heritage and your challenges in the social and natural environment.
- (3) Live a happy life and protect your health and happiness by appropriate and prudent rules for diet, exercise and relaxation, work and love, social activities and self-determination.
- (4) Expect from the health care professional and the health care system individualised information on prediction, advice for prevention, guidance in health care and in acute care intervention, and a trust-based interactive professional and personal partnership in dealing with carrier status, chronic illness and suffering.
- (5) Understand that no health care professional can relieve you from being the prime caretaker of your health, happiness, and life.
- (6) Discuss your concept of health and disease, long term care plans, and advance care documents with health care professionals you trust and with family and friends.

Challenges for the Consultant:

- (1) You are responsible for your patient as a person, not just for her or his symptoms.
- (2) Inform and educate your patient about her or his individual predisposition for health and health risks and help the patient to understand individual challenges and opportunities.
- (3) Help the patient to find her or his individual way to respond to the technical details of dealing with the processes of degeneration and the possibilities of postponement of onset of more severe stages of their disorder.
- (4) Be a professional expert for your patient and do not discriminate against those patients who do not exercise their right to care for their own health in an appropriate manner.
- (5) You cannot expect any patient to become a medical expert; therefore you have to continuously and patiently educate your patient and keep yourself up-to-date with the best available options for prevention and treatment; you must stay in close contact with medical developments and the experts in your field.
- (6) Help your patient to find her or his own way to cope

with disorders, to develop long term care plans and to execute and review care directives in advance.

The Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services¹⁷ discuss sets of ethical principles to genetic services and in genetic counselling, also for genetic screening and testing. While the WHO recommendations base their proposals on the bioethical principles of respect for autonomy, beneficence, non-maleficence, and justice, I feel that, given good cultural and moral traditions in Chinese and European culture and history, appealing to virtues and attitudes, the establishment of virtue theory and the re-affirmation of dormant values and attitudes are the instruments of choice over ethical or legal principle for the initiation of public debate and of modifications in social and medical activities for the improvement of ethics and care in genetic services. Pellegrino discusses a set of seven virtues of physicians: fidelity, benevolence, effacement of self-interest, compassion, intellectual honesty, justice, and prudence,¹ but he grounds medical ethics, including the ethics of health care for genetic disorders, in physician's ethics alone or primarily, failing to recognise the interactive role of carriers and experts in caring for health. The ongoing academic debate between principle and virtue theory will be with us for a long time;¹ but the real controversy will arise when interactive ethics of lay people and expert in health care matters are developed further and obligations and rights of both sides are better delineated.

DNA-Banking, and the Ethics of Patenting and Ownership

Of special actual interest are the controversies of the ethics of DNA-banking for undisclosed or cross-purpose purposes, issues in the ethics of ownership of intellectual and biological properties and of patenting forms of life. Nationally and internationally legal and scientific experts as well as governments are dealing step by step with these issues for which there are no prior exemplary solutions. Of course, in breeding animals and plants breeder's privileges have been granted to the breeders allowing them to profit on their achievements, to guarantee the utility of the new varieties of life, and to take the liabilities, risks and benefits of market penetration and distribution.^{13,18} This is my **sixth thesis: Traditional breeder's privilege contracts and regulations as a good paradigm for developing frameworks of responsibility, liability and profit in developing and**

marketing genetically modified products.

Also, there are markets for profit in blood transfusion and organ transplant. Physicians, nurses, hospitals, and the Red Cross are part of the for profit market. Donors of organs or blood are not; but blood plasma donors get compensated financially when delivering the properties of certain rare blood plasma. This shows that in all cultures worldwide, we have a split market where some make money, while others for arguments of moral concern are supposedly not allowed to benefit from their contribution to the markets. Therefore their contributions are called donation or gift.^{13,18} Human organs and tissue are not for sale among individuals, but organisations sell and buy donated blood, heart valves, and other tissue. Money is made in the distribution, maintenance, explantation and implantation of human organs. The fact that owners of blood plasma are routinely included in the profit making business is the rare exemption. But then there are clear unethical stories of exploitation by the research and pharmacological establishments: John Moore, who had hairy cell leukaemia, was unethically treated by the researcher who lied to him while drawing his blood for, as the California Court put it, 'competitive, commercial, and scientific advantages'. Isolation, synthetization, immortalisation, and modification are technical procedures which always were considered to be a proprietary privilege of the individual, corporate or collective person, who together with quality control and efficiency guarantees market penetration of the product. Without effective protection of cultivated crops and animals there would not be an incentive to provide top quality products, the existence of which makes culture what it is: cultivated forms of life for the benefit of fellow humans in nutrition, medication, and production. If it were not be for the patents and the profits, we would not have the wealth of medication we have today. But, individually and collectively, we are still in the process of sorting out the arguments for and against the market approach.

Informed Request and Contract in DNA-Banking and Clinical Research

Of particular bioethical concern is the possibility of exploitation in the present race among drug companies and clinical researchers to collect DNA samples within highly defined populations of patients or entire defined populations in remote spots of the globe. In both scenarios, informed consent from patients and probands should be required and in most cases is given, but rarely is compensation discussed

and always patients and probands lose control over their property and the means and ends it is used for, in particular in multipurpose testing and banking for yet to be defined research. Both scenarios are quite uncomfortable ethically. Existing bioethical principles such as the 'informed consent', primarily developed for acute and precisely defined one-time medical intervention in diagnosis or therapy, do not seem to be adequate to the new situation of probable exploitation and abuse, and the exclusion from direct medical benefits and financial profits potentially made out of these adventures. Therefore, I suggest as my **seventh thesis**, *to replace the informed consent model with a model of informed request within a flexible contract model in which both parties, research and patient or proband, delineate their contractual rights and obligations.* Actually, some informed consent forms already look like informed contract forms.

The mapping of genetic properties of *genetically narrowly defined healthy populations* contributes to basic science and the differentiated understanding of the innerworkings of the human genome. Thus it is in the interest of mankind and progress in genetic knowledge, and probably will lead to better treatment. Also, it might directly and indirectly serve this particular population in describing prevailing traits in cytochrome P450 isoform-based drug metabolism. Whether or not members of a highly defined population want to contribute generously to scientific knowledge and medical progress, is an issue of their cultural and ethical attitudes and must be decided by them only. They might do it as a gift, or they might ask for reimbursement of costs associated, additional fees, and compensation for any risks associated with their gift or donation. They also might benefit collectively from information and description of their specific genetic properties in regard to medication, nutrition, lifestyle, and predisposition to or prevalence of certain disease.

These possible benefits should be dealt with in the *contract model*, spelling out precisely the obligation of the researcher to share results with donors for their personal health benefit or, if it turns out to be a contract with rights and obligations on both sides rather than a donation, to the contracting individuals and their families. *Rewards* to the contracting individuals and their families could be either monetary, nonmonetary, educative or medical, or a combination of all of them specifically spelled out in the contract.

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 overburdens 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.^{13,19,20} On the other hand generic consent forms – in particular for prenatal and newborn screening – were proposed, but others criticised such an approach as lowering the standards of informed consent.^{13,21} 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 ask for specific consent within 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 you 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 include terms that patients can make their own choices: (a) for mandating 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.

Instead of a Conclusion

Genotyping provides an entire set of new tools for mankind to better understand the human condition, to better care for health, and to fight against and to avoid sickness and disease. But as with all tools, new and old, genotyping can be used in a virtuous and in a vicious way. Public discourse and education and the appropriate protection of human and civil rights will be needed to steward and accompany the transition into a new millennium of health literacy and health care. Our charter into the new territories of self-understanding and self-destination, of better health care and improved quality of life for all will not be made easier if we hold on to old models of regulation and control by bureaucracies of various kind intending to protect the people from the dangers of progress, but in fact preventing progress to happen and preventing people from finding their own way to use and to enjoy the new properties of genetic knowledge for more liberty, more justice and for the pursuit of happiness. It might very well be that the scientific and cultural community of Hong Kong, because of 'its familiarity with Chinese and international culture and its material resources' will contribute to the development of 'a model for modern ethics with a Chinese face'.¹

The new challenges require a new action guide different from rules which were appropriate during periods of limited medical knowledge and lay ignorance. The new world of genotyping will also have to call more for lay ethics than physician's ethics in health care matters as carriers of sort will be given more and better information to take care of their health. This, then is **the eighth and final thesis**: *In the coming age of molecular genetic ethics, a new moral action guide is required to determine priorities for groups of moral subjects and for new priorities of ethical principles, among which health literacy, self-determination and self-understanding, the right and duty to know and to learn about one's own genetic properties and risk profiles, and genetic solidarity with other fellow humans will have to play more prominent roles.*

An Action Guide for moral agents involved has to address the different obligations and rights of health care stakeholders:

- (1) Educated and responsible people have a moral duty to learn about their genetic properties and how to make the most out of these properties; they also have a moral

duty to help fellow humans in taking care of their individual genetic properties, in particular to help members of their family.

- (2) Health care professionals are obligated not to suppress or withhold genetic information from patients; they have the duty to do their utmost to educate their patients and to guide and to accompany them in caring for their health.
- (3) Lay persons and health care professional should feel bound by an invisible contract of communication-in-trust and cooperation-in-trust, sharing responsibilities, rights, and obligations, also in the care of the less fortunate, less healthy, and less competent.
- (4) Governments, national and international institutions and organisations must provide legal, regulatory, and information networks for the protection of human and civil rights, for the development and improvement of health literacy, and for the protection against exploitation and discrimination; regulatory ethics in human genetics should be based on the ethics of information and education, also the promotion of predictive services and the protection of privacy.

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