Committee 2
Genetic Knowledge, Human Values
and Human Responbility

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GENETIC KNOWLEDGE AND HUMAN VALUE: A CLINICIAN'S VIEW

by

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INTRODUCTION: A MULTIGENERATIONAL FAMILY STORY

I met Mrs. Winter, 55, in 1981, when she became a dialysis patient in our dialysis unit. As a carrier of Autosomal Dominant Polycystic Kidney Disease (ADPKD), she had developed renal insuffiency. In 1977 large cysts in both kidneys and in the liver were confirmed by ultrasound diagnosis. After Mrs. Winter became a dialysis patient her four sons underwent ultrasound screening which showed, that all sons were presymptomatic carriers of ADPKD living healthy lives. These were the reactions of the sons after they learned about their carrier status: First of all the sons accused their mother for having as many as four children even though she knew, that this severe disease was running in the family. Mrs. Winter's father and his two brothers had also died in renal insuffiency caused by ADPKD. Albert, 32, married, and father of a 6-year old son, committed suicid when he developed first symptoms of pain and renal dysfunction three years later. Otto, 3o, married, sold a house, which was half completed, when he learned about the diagnosis. He did not want to make long term plans for his life and burden his family with a mortgage. Karl, 25, and his fiance dissolved their engagement because Karl did not want to have children, nore burden his fiance with his own genetic prediction. Paul, 21, the youngest, a student did not complete his studies and took a job in order to make money and enjoy life while it lasted.

The Winter family story demonstrates very clearly different ways of translating DNA prediction into real life situations. This is in short the clinical and ethical challenge of DNA testing for severe human hereditary disorders. We are not just

talking about genes and DNA, we talk about fellow humans, brothers and sisters, mothers, families with their hopes, fears, pain, satisfaction and enjoyment for life and suffering in life, discrimination and denial.

1. DNA-BASED PREDICTION OF SEVERE GENETIC DISORDERS

Molecular genetics has identified over 4oo factors for hereditary diseases, and every day new factors are described and identified. Two percent of newborns have genetic disorders of highest severity, which are lifethreatening, or reduce quality of life or span of life.

Severe genetic disorders occur among four groups of disorders: (BLUM, 1993): (1) HEMOGLOBINOPATHY: sickle cell anemia, beta-thalassemia; (2) ENZYMOPATHY a) Carbohydrate metabolism: galactosemia; b) Amino acid metabolism: phenylketonuria; c) Lipid metabolism: Gaucher's disease, Tay-Sachs disease; d) Mucopolysaccharid metabolism: Hunter syndrom, Hurler syndrom; (3) OTHER DISEASES IN METABOLISM: lack of alpha-trypsin, Lesch-Nyhan disease, Xeroderma pigmentosum, Duchenne's disease, Cystic Fibrosis; (4) ONCOLOGICAL and OTHER DISEASES: Retinoblastoma, Leukemia, Lymphoma, Huntington's chorea, Alzheimer's disease, Hemophilia A and B, Neurofibromatosis Recklinghausen, Friedreichsche Ataxie, ADPKD.

Not all hereditary diseases are of the severest form. Among the most severe Cystic Fibrosis (autosomal recessive), a multisystem disorder which is characterized by an abnormality in exocrine gland function. Nearly all patients develop chronic progressive disease of the respiratory system. Pulmonary disease

is the most common cause of death and morbidity. Multiple clinical feature include disturbences of gastrointestinal tract, reproductive system and skeletal system. Currently the median survival is about 2o years. The majority of Cystic Fibrosis patients are diagnosed in infancy or childhood. One of the most brutal disorder is the Huntington's Chorea, (autosomal dominant) characterized by a combination of involentary choreoathetotic movements and progressive dementia, usually beginning in midadult life. Younger patients, with onset of symptoms in the age group of 15-4o years suffer a more severe form of disorder than older patients with onset in the 5o s and 6o s. Lesch-Nyhan disease is an X-chromosomal-linked disorder of purin-metabolism. Affected patients have hyperuricemia and overproduction of uric acid with uric azid stones. In addition they have bizarre neurologic disorders, characterized by self-mutilation, hyperreflexia, choreoathetotis, spasticity and retardation of growth and mental function. The onset of symptoms begins at a young age between 15 and 3o years.

DNA factors inform about predictibility of disorders, not about severity, time of onset, severity of symptoms, span of life, quality of life and preventive options. Therefore genetic knowledge has to be translated into real life situations and predictions of families and individuals. Genetic risk factors alone do not predetermine the individual quality and the personal fate of human life. This is the clinical and ethical challenge to carriers, physicians, and society.

2. RISK AND RESPONSIBILITY OF PATIENTS WITH ADPKD

Individual, professional and societal challenges can be highlighted by ADPKD. This is a systemic disorder producing innumerable cysts of varying size in both kidneys, in liver, pancreas and ovar. There are also structural abnormalities in the gastrointestinal tract, e.g. colonic diverticulae, and in the cardio-vascular system, e.g. cardiac valvular abnormalities, thoracic aortic aneurysm, berry aneurysm of brain vessels. About 5-1o percent of all patients on dialysis treatment suffer from cystic kidney disease. The countries of the EEC spend roughly 4 billions Ecu each year on renal replacement therapy, dialysis and transplantation. The frequency of ADPKD is 1:1ooo, which is more frequent as Cystic Fibrosis and Huntington's Chorea. An estimated half a million people have the disease in United States. It is inherited as a autosomal-dominant trait with 1oo percent penetrance. Hence each child of a carrier has a 5o percent risk to become a carrier her/himself. No sex preference is noted.

2 .1. GENETICS AND PROGNOSIS

Careful studies of patterns of DNA fragments have revealed consistent differences in the structure of DNA in the short arm of human chromosom 16 in association with ADPKD (BREUNING, 1990) Recent observations (KIMBERLING, 1988) indicate, that at least two different defects can be responsible for a very similiar clinical picture, which cannot be distingueshed in a single patient. These PKD-2-carriers live into their 7th to 9th decades and often die of nonrenal causes. PKD-1 carriers have symptoms and signs of the disease in their 4th and 5th decade. It is the

usual experience that knowledge about the nature of ADPKD even in affected families, is poor.

Cysts are present in the kidneys from the 12th week of gestation. Very slowly these cysts grow in size and number, thereby destroying the functional tissue of the kidneys. End-stage renal failure usually occurs between the age 4o and 6o, but in fact varies considerably between patients, even between members of the same family. Autosomal dominant disorders are in general characterized by variability in age of onset and in phenotypic expression. Clinical age of onset is defined by the age at which symptoms appear or cysts can be found. The ages differ, depending upon the circumstances of inquiry (GABOW, 1993). Age of onset is also influenced by the technique used for screening.

The diagnosis of late stage ADPKD is easy: hypertension, abdominal pain, bilateral flank masses, hematuria or azotemia contribute to the typical clinical picture. Presymptomatic diagnosis can be done by ultrasonography, Computed-Tomography, or Magnetic Resonance Imaging. Since only about 6o percent of the patients will report a family history of this disease (GARDNER, 1989), presymptomatic even prenatal and preimplantation diagnosis can be done by methods of molecular genetics. DNA-based diagnosis is superior to ultrasound or x-ray based diagnosis as it can be done much,much earlier either by analyzing morula cells prior to implantation (HANDYSIDE, 1992) or by analyzing fetal cells collected from maternal peripheral blood by non-invasive methods (KÜRTEN, 1993, LO-Y MD, 1993) or by amniocentesis or chorion villis biopsy.

2.2. SYMPTOMS AND SIGNS

Pain, caused by expanding and large kidneys, is the most common clinical symptom of ADPKD in adults. Usually the pain is dull and constant, localized in the flank or lateral abdomen. Acute pain may arise from hemorrhage into a cyst or passage of a blood clot or stone. Sometimes inflammations, spreading to the renal bed from an infected cyst cause discomfort, usually in association with fever. Pain gradually increases over a patient's lifetime ultimately affecting more than 5o percent of the individuals.

Fifty percent of adult subjects with ADPKD experience hematuria at some time prior to diagnosis. Rupture of the cyst wall is blamed for the episodic hematuria in some patients. Episodes of gross hematuria can occur with strenous physical activity and may last from days to weeks.

Gastrointestinal complaints of nausea, vomiting, and diarrhea are less common than renal symptoms, but can pose significant problems for occasional patients.

Headaches, often severe and recurrent, are a common occurance unrelated to hypertension. Headaches may be caused by berry aneurysms of the brain vessels. They occur in 1o-4o percent affected persons and can rupture and cause sudden death.

Palpable hepatomegaly can be found in approximately one-half of individuals with ADPKD. They rarely cause symptoms or hepatic dysfunction or pain.

Hypertension is a common finding in otherwise healthy patients and occurs in approximately 6o percent of non-azotemic patients.

There are no typical changes in blood chemistry (anemia, serum-creatinin and urea levels) until the onset of renal insuffiency. (GRANTHAM, 1984)

We consider ADPKD to be a systemic disorder in which the phenotypic manifestation of the abnormal gene span an array of organ systems. Not every affected individual manifests all the possible aspects. Both, interfamilial and intrafamilial, variability occur in the extrarenal manifestation of ADPKD. Intrafamily variability is illustrated by differing manifestations and severities of structural defects despite similiar ages. Such intrafamilial variability may reflect the influence of the non-ADPKD allele, of other genes, or enviromental factors.

2.3. RISKS AND RESPONSIBILITIES OF PATIENTS

As the Winter family story shows clinical manifestation as well as presymptomatic knowledge about the ADPKD disorder translates into very different individual life stories. To be informed about ones own carrier status is important for good hypertension prevention and for avoidance of work related or sports related rupture of cysts; ways and responses in coping will be different individually.

Presymptomatic knowledge also seems to be important for making life plan decisions which take the specifics of the proberbility of dialysis treatment or kidney transplantation into account. Decisions include carrier planning, occupational, professional, and recreational activities, family planning, social and cultural interactions. Each individual will translate

her/his carrier status and symptoms into different parameters of individual life, its qualities, goals, and limitations. Knowledge is importent for preventive life style for example: most essential hypertension control. Some recreational activities are not recommended as they might cause haematuria, such as jogging, horseback riding, wrestling, soccer or heavy physical work. It is also important to know about ones carrier status when making reproductive choices.

This is an issue of self-determination for each carrier to have adaequate information, knowledge, and counselling in carrier planning, life style and family planning. My clinical experience is, that there is a duty to know about carrier status of ADPKD on behalf of the carrier and there is a responsibility for clinicians, geneticists, and families to consult with the carrier on medical and non-medical risks and decisions.

The challenges for ADPKD - patients include the medical control of symptoms but even more the challenge to redefine one's personal values and goals. These challenges can be summarized in 'Action Guide' for ADPKD - patients :

1. Accept your disease and redefine for yourself within its limitations the new parameters for your quality of life
2. Redefine your new roles within the family, among friends and peers. Be active, and find personal fulfillment and public recognition in achieveing new goals set by yourself.
3. Be responsible in your compliance with advices of the physician.
4. Exspect more than medical and technical intervention from your physician; exspect advice and understanding regarding the

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side effects of your disease and its treatment, exspect partnership and assistance in redefining your quality of life.
5. Define your concept of responsible parenthood in making reproductive choices.

3. RISKS AND RESPONSIBILITIES OF PARENTS

3.1. THE CASE OF ANITA M.

The ethical parameters of responsible parenthood of carriers of severe genetic diseases are well illustrated in the case of Anita M. Anita had been diagnosed as a carrier of ADPKD at the age of 16 when she was a subject in a research project which studied the family history of patients with this disease. Five years later she is 21-years old and pregnant. Her mother, 45, divorced, is a RDT-patient, her grandmother has just died due to liver complications after being in dialysis treatment for 14 years. Anita requests prenatal testing which now can be done by genetic screening. She expresses an obligation not to give birth to a baby with definite diagnosis and prognosis of ADPKD, as this means dialysis dependency in later years, and the certainty of decreased quality of life, such as renal complications, pain, and hypertension allowing only for limited quality of life and a way of suffering and dying she just had witnessed in her grandmothers last years. The test identifies the fetus positively as a carrier. Anita schedules a counselling session prior to setting a date for selective abortion, but she misses this appointment, never calls back, and probably had moved somewhere else and had given birth to her child.

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3.2. VALUES AT CONFLICT

In Anita's case there are at least four different values at conflict: first of all respect for life, secondly self-determination, further more responsible parenthood, and family planning.

As in most cases of reproductive ethics Anita faces a special challenge in balancing the respect for unborn life and responsible parenthood. This is a different situation than normal conflicts between right to choose (selfdetermination of the mother) and right to live (respecting potential interest of the fetus). Anita's fetus carriers a severe genetic disorder which forecasts, if nothing else happens, uncomfortable and quality of life reducing dialysis treatment or transplantation plus all other associated burdens and symptoms of ADPKD. (KIELSTEIN, 1993)

Aborting the fetus might be an ethical option of responsible parenthood and indeed, it was the predetermined choice of Anita. The fact that she did not have the abortion might be caused a) by emotional stress, b) actual situational ethical uncertainty, c) by exspecting to become a mother and having a baby, no matter what the carrier status is, d) avoiding making any decisions, further more it could have been f) by setting trust in progress of ADPKD treatment for the next 3o years, until to the onset of her fetus's symptoms. (KIELSTEIN/SASS, 1992).

3.3. MEDICAL MORAL SCENARIO FOR RESPONSIBLE PARENTHOOD

I see at least 8 scenarios of decisionmaking in reproductive

ethics for severe genetic disorders in cases similiar to Anitas' situation:

1.) GIVE BIRTH: Giving birth and establishing a family by having children is a very normal individual and cultural goal in a womans life. An ADPKD carrier most likely will be 'healthy' and happy for a long period of life and might even die of other causes a long time before the onset of severe symptoms. The offspring might have a family of his own and over the next few decades progress in medicine might develop new methods of prevention, healing, or treatment of kidney cysts. On the other hand the mother knowingly gives life to a carrier of a very severe genetic disorder. Can she responsibly do that being aware of many future risks and uncertainties including expensive and uncomfortable dialysis treatment or transplantion ? Also accusations of unresponsibly parenthood' may come from the offspring, the spouse, the family at large, the society and the insurance companies.

2.) ABORTION: Anita could have chosen abortion as her prefered means of contraception because she did not want to give birth to a child having the same disease as her mother, grandmother and herself. But other family planning methods would be of higher moral acceptance such as sterilization, the use of contraceptives, or selective abortion after prenatal diagnosis only.

3.) ABORTION AFTER PRENATAL DIAGNOSIS: would value the principle of responsible parenthood higher than the principle of respect for life or giving birth in general. If parents have responsibilities for the children than there is a prime parental duty to not harm the unborn by an unhealthy life style, such as smoking

cigarettes or drinking alcohol excessively and consequently there might be a duty not to give birth to a child 'harmed' by ones own severe genetic disorder.

4.) PREIMPLANTATION DIAGNOSIS: Carriers of severe hereditary diseases might for medical, ethical, and emotional reasons prefere preimplantation diagnosis over elective abortion. Preimplantation diagnosis has been reported to be successfull in Cystic Fibrosis (HANDYSIDE, 1992) and might become the ethical instrument of first choice in responsible parenthood decisions.

5.) NOT HAVING CHILDREN might be a choice for those who, for religious or ethical reasons, do not accept diagnosis or selection of unborn human life.

6.) NOT GETTING MARRRIED or having no heterosexual partners most likely will be based on other than reproductive decisions but will have the side effect that carriers will not implant their own severe disorder into other (new) people. In the modern world the carrier status also could be used as an excuse for a responsibility-free singles life style.

7.) ADOPTION of a non carrier would allow for having a child of one's own who would not be a carrier but family planning by adoption would come within the well known parameters of ethical and emotional 'pros and cons' of adoption.

8.) To give birth to a carrier and let the carrier be adopted by others would be a worst case scenario for responsible parenthood.

There are never uniform medical or ethical cases. Each case will be different medically and ethically, so will the family situation and the enframing culture. I recommend that we avoid

the inflexible legal or medical standards for handling reproductive choices of ADPKD carriers or any other carriers of severe genetic disorders. Rather I feel non-directive counselling would be the best ethical approach of clinicians and geneticists. In my opinion severe genetic disorders are part of the family history heritage and should be dealt with, within the family and not by governmental or medical authorities. In order to assist the patient in making responsible decisions for her/himself and for reproductive choices a four step approach in medical and ethical counselling can be used. This four step method helps the carrier, presymptomatic or symptomatic, to make decisions for her/himself or in family planning.

The first step identifies the problem by a) collecting DNA-based data and b) human data and c) identifying value elements. In a second step the consultant a) establishes the medical prognosis for different future scenarios, b) identifies the ethical principles and problems for each scenarios, and c) discusses medical, ethical and personal issues with in each scenario with the patient. A third step addresses risks and risk management by a) dicussing medical and moral uncertainties, b) identifying moral agents, and c) assisting the patient to define 'the best solution.' In a final step the consultant assists the patient in reviewing the patients decision by a) asking her/him to clearly specify her/his reasoning, b) to address uncertainties and risks associated with the patients reasoning, and c) to defend her/ his decision.

3.4. IDENTIFYING RISK TAKERS AND MORAL AGENTS

Moral agents for making decisions, exclusively or jointly, could be governed by law, insurance companies or health care systems, religious or societal groups, consulting professional (clinician and/or geneticists, ehticist, or team) families, spouses, women. In this and the following scenarios my personal choice would be to make the woman the prime moral agent for reproductive choice and responsible parenthood. She is the nucleus, as she carries the future person in her, it is a part of her body, and none has access to it.

Following responsibilities are in the wider circles of spousal responsibility, thereafter family, physician (primarily clinicians rather than geneticists) and ethicists have consulting but no deciding authority (non-directive counselling !). I see some reasons for moral input on behalf of the payment system (however that is organized), but very minimal rights of the state to intervene in very private family matters. There might be a difference between post-enlightment European individualism and traditional Confucian and Asian thinking in the framework of family network and solidarity, which I hope we will address in detail in our discussions on the multicenturallity and crossculturallity of moral decisionmaking in reproductive ethics.

4. CONCLUSIONS

Let me conclude with questions rather than answers. Answers are not easy in modern pluralistic societies based on individual self-determination; they are even more complicated in the global multicultural world. Predictive medicine presents new scenarios for the physician-patient-interaction and will change priorities

among traditional principles, maximes, and models of medical ethics.

Progress in DNA testing and in predictive medicine is more a challenge to the ethics of law persons than to the medical profession. Acute crisis-style intervention, step by step, will have to be replaced by non-acute predictive or preventive discourse. New methods of assessing technical and ethical risks and probabilities will have to be developed in order to translate the certainty and hereditary facts into uncertainty of prognosis and health risks, quality of life parameters, health literacy and self determination of the citizen/patient, and the design of prevention and therapy. The clinical and ethical challenges of DNA based predictive medicine can be summarized around five questions:

(1) Who is the prime moral agent?

Progress in genetic knowledge will make the carrier of genetic disorders the prime moral agent for prevention, treatment, and acceptance of individual health risk and diasbilities. the health care establishment has to provide predictive information and consultation and treatment services. Society are responsible to allocate health care resources, health care services, the protection of individual data.

(2) Is there a duty to know or a right not to know ?

Carriers of health risks should have the right to full information, consultation and service in regard to their individual disorders. There is a duty to know about genetic health risks if such a knowledge can be made instrumental in postponing, reducing, avoiding or preventing the acute outbreak

of diseases or disorders. There is no obligation to know about the disorders which cannot be prevented, postponed or reduced by having such information nore can be established obligation to live a healthy lifestyle.

(3) How will predictive medicine influence future medicine?

Predictive medicine will change the health care establishment by emphazing prediction and prevention over acute care and will have to change traditional paternalistic relations between physician and patient. The medical establishment has an obligation in developing new forms of partnership in physician/patient interaction.

(4) How will the predictive medicine influence the future medical ethics?

Predictive medicine as a challenge to everyone, the healthy, the sick, and the ill, the lay, and the experts.

New forms of health literacy and health responsibility of the educated citizen have to be developed.

(5) How will the 'global village' deal with moral issues?

There will be individual and cultural different responses towards the challenges of genetic knowledge. Family and parents will have to redefine the concept of responsible parenthood. Individual and cultures will have to realize hat everyone is a carrier of one or the other disorder, gift or burden and have to develop a new dimension of understanding of responsible brotherhood, responsible sisterhood, responsible parenthood, and responsible 'love of your neighbour' and a new understanding of the precious gift of human individuality and family destiny, challenge, and opportunity.

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