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10 May, 2005

Associate Professor Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
20 Biopolis Way, #08-01 Centros
Singapore 138668

Dear Prof Terry Kaan:

Refer to your letter dated on 4 April 2005 to Professor Jackie Ying, Executive Director of Institute of Bioengineering and Nanotechnology, requesting for feedback on the consultation paper from your committee, I am forwarding you our two cents worth as follows.

Dedicated to improving the health and quality of life, Institute of Bioengineering and Nanotechnology (IBN) focuses its research activities on the following 6 areas:

- Nanobiotechnology
- Delivery of Drugs, Proteins, and Genes
- Tissues Engineering
- Artificial Organs and Implants
- Medical Devices
- Biological and Biomedical Imaging

There are two aspects of our on-going studies that are related to your discussion on Genetic Testing and Genetics Research, namely the development of gene delivery vectors/systems and medical devices for genetic diagnosis.

Gene Therapy:
The current version of the recommendations has mainly focused on clinical genetic testing, which is indeed the most commonly used gene technology in hospitals currently. In terms of gene manipulation, we note and concur with the recommendation 13 on germline genetic modification, the clinical practice of which should not be allowed at this time. However, in view of the importance of somatic genetic modification, e.g. gene therapy, a new medical approach widely tested right now, we would appreciate hearing the views from the Bioethics Advisory Committee on what will be your recommendations and whether there is anything that is not allowed.

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Since the first clinical trial gene therapy started in 1990, many such human clinical trials are on-going right now all over the world. In USA, gene therapy is subject to greater oversight than virtually all other therapeutic technologies. The NIH guidelines require federally funded institutions and their collaborators to submit detailed information about proposed and ongoing clinical trials of gene therapy products. Much of this information must be disclosed to the public. Singapore has conducted several early-phase gene therapy studies and will for sure have more years down the road. Your recommendations would be crucial in protecting patients without impeding the development of gene therapy products.

Some of the comments from USA are copied blow for your information:

"The field of gene therapy continues to focus on patients with severe and life-threatening diseases who usually have few treatment options or who have failed all available therapies. Thousands of patients have now received somatic cell (nonreproductive cell) gene therapies targeted at life-threatening genetic diseases, cancer and AIDS. We therefore recommend that the first candidates for gene therapy should be patients:

- in whom the disorder is life threatening or causes serious handicap;
- for whom treatment is at present unavailable or is unsatisfactory but for whom treatment may be beneficial.

Judgments on the ethics of gene therapy in man will initially apply to individual cases and will require assessment of factors such as safety, efficacy, alternative treatments and prognosis - in other words, the balance of risk and benefit for the patient.

In the near future, treatment by gene therapy might be justified in cases of invariably fatal or life threatening diseases for which no alternative treatment is available."

Related to somatic genetic manipulation, stem cells have been tested for transplantation into human bodies. These stem cells could be genetically modified before the transplantation. While the related issues have probably been addressed in the sets of recommendations for stem cells application, the genetic manipulation part may need to be emphasized in your recommendations on Genetic Testing and Genetic Research.

Genetic Testing

Regarding genetic tests, we would suggest the consideration of using the term of "genetic analysis" instead of "testing" in some sentences. For example, page4

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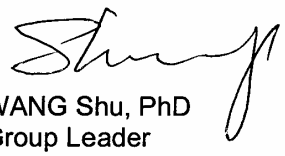
2.3(g) "Genetic testing for research" would be better illustrated by "Genetic analysis for research".

On page 5, 2.4(a) "genetic tests are commonly accomplished by direct testing, where tests are performed on the DNA or RNA specific for a gene". This statement is true for most of traditional genetic tests. These days, many new "genome"-based tests have been developed, for example DNA microarrays for SNPs and STRs, which would have nothing to do with genes but those non-coding sequences of human genome, meaning genetic tests could be simply based upon DNA sequence analysis. This point should probably be clarified either in 2.4(a) or 2.4 (c) linkage testing.

Also, in line with the definition on "gene technology" provided by the NMEC, we suggest using "Ethical, legal and social issues in genetic analysis and manipulation" as the title of your recommendations.

Sincerely yours,



WANG Shu, PhD
Group Leader
Institute of Bioengineering and Nanotechnology

cc: Prof Jackie Y. Ying, Executive Director
Noreena AbuBakar, Director, Administration

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16 May 2005

Associate Professor Terry Kaan
Chairman, Human Genetics Subcommittee
BIOETHICS ADVISORY COMMITTEE
20 Biopolis Way
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Singapore 138668

Dear Professor Kaan

REQUEST FOR FEEDBACK ON CONSULTATION PAPER "ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND GENETICS RESEARCH"

Thank you for inviting my comments on the above consultation paper.

I agree with all the recommendations set forth.

Yours sincerely

A/Prof Wong Kim Eng
Chairman, Medical Board
IMH/WH

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20 May 2005

Associate Professor Terry Kaan
Chairman
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20 Biopolis Way
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Singapore 138668

Dear Terry

REQUEST FOR FEEDBACK ON CONSULTATION PAPER

I refer to your Request for Feedback on Consultation Paper entitled " Ethical. Legal and Social Issues in Genetic Testing and Genetic Research". I am pleased to inform you that the feedback from our clinicians have been very favourable and agree with the 24 recommendations.

In addition, the following pointers were raised for your consideration:

1. That the results of the Genetics should not be kept in the patients casenotes as it concerns very sensitive information, as shown by the degree of discussion necessary for the implementation of such tests.

2. That Item 8) "advertising.... to the public" should be prohibited rather than being strongly discouraged, as advertisment by manufacturing companies primarily serves to increase demand for their products, and in this case for a test of highly sensitive nature.

For your perusal.

Dr Tay Eng Hseon
Chairman Medical Board

Our Ref: LS/12/05/CSY/sha Your Ref:

18 May 2005

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Associate Professor Terry Kan
Chairman, Human Genetics Sub-Committee
Bioethics Advisory Committee
20 Biopolis Way #08-01
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Dear Sir,

Re: Request for Feedback on Consultation Paper

I refer to your letter of 4 April 2005 together with enclosures.

I am pleased to enclose the comments of the Law Society's Ad-Hoc Committee on Bioethics on the consultation paper on 'Ethical, Legal and Social Issues in Genetic Testing and Genetic Research'.

If you require any information or clarification, please call me at 65300215 or email me at <yasho@lawsoc.org.sg>.

Yours faithfully

Yasho Dhoraisingam (Ms)
Chief Executive Officer

Enc./

c.c. Ad Hoc Committee on Bioethics
c.c. Council

THE BIOETHICS ADVISORY COMMITTEE'S CONSULTATION PAPER ON ETHICAL, LEGAL AND SOCIAL ISSUES IN GENETIC TESTING AND GENETICS RESEARCH

Ad hoc Committee Members:

Chairman : Christopher Chong,
Messrs Rodyk & Davidson

Members : Kuah Boon Theng,
Legal Clinic LLC

Audrey Chiang
Messrs KhattarWong

Mak Wei Munn
Messrs Allen & Gledhill

We have been appointed by the Law Society of Singapore to provide our comments on theConsultation Paper by the Bioethics Advisory Committee ("BAC")on Genetic Testing and Genetic Research.

All members of this ad-hoc committee are involved in advising and representing individuals and organisations in the health care industry as part of their legal work.

This Committee has necessarily limited their comments to the legal aspects of the Consultation Paper based on the current law in Singapore. Although we have no doubt that due consideration is being given to the legislative amendments that would be necessary to regulate Genetic Testing and Genetic Research, we have also included some comments on what we view to be lacunae within the current legislative framework that should be addressed.

This Committee agrees, in general, with the recommendations of the BAC, save for comments on the following points. For convenience, we have addressed issues in the order in which they appear as recommendations in the Consultation Paper.

1. **The Role of Institutional Review Boards/ Ethics Committees**

1.1 Presently, most hospitals have Institutional Review Boards (IRBs) and Ethics Committees that approve all applications for clinical trials. Part of the approval process includes the vetting of the patient information sheets and consent forms. The IRBs review the information sheets and consent forms to ensure that sufficient information is provided to the patient in order for the patient to have sufficient

information in arriving at a decision to participate in the clinical trial. The consent form is also vetted to ensure that the patient's rights are protected. At present, it is sometimes the case that samples that are taken in the course of a specific clinical trial may be retained for purposes of genetic testing, whether presently contemplated or even for purposes to be determined in the future. There may be a variation in the amount of information being conveyed to the research subject regarding the implications of genetic testing. It is suggested that there be a requirement for all research involving Genetic Testing, whether as the main objective of the research or incidental to a clinical trial, to be subject to approval of the relevant IRBs, who can then ensure that appropriate information to the subject and suitable arrangements for genetic counselling is provided.

2. **Recommendation 3 & Paragraph 3.9**

2.1 Although the right of the individual to withdraw his consent in participating in the research study is recognised, it is not clear what the individual's rights are following the withdrawal of his participation in Genetic Testing in respect of:-

(a) the genetic material already taken from him; and

(b) the information/ results derived from such material.

2.2 We would suggest that there be a mechanism for the individual to withdraw from the test and at the time his consent is taken, information setting out how the individual can withdraw.

2.3 Further, information should also be provided at the outset to the individual, stating whether the individual can insist on the destruction of all material and test or research results upon his withdrawal from the research, and if not, assurances as to anonymization of the information derived from the genetic material and whether the information can be traced to the individual.

3. **Paragraph 3.11**

3.1 Paragraph 3.11 allows the healthcare professional to decide to postpone disclosure of a test result if the individual is not in a suitable condition to receive such information. This is a well recognised doctrine of therapeutic privilege.

3.2 However, we are concerned that it is suggested that the decision to disclose would depend on whether the condition can be medically treated or alleviated. It is also unclear from the Report whether this is intended to allow the doctor to merely postpone the disclosure of the information, or not to disclose the information at all on

grounds of therapeutic privilege. The disclosure (or non-disclosure) of test results is known to be based on a variety of factors and specifically referring to whether the condition is capable of being treated/alleviated would appear to give greater weight to that factor, which in our view, is unwarranted. This is because the process of pre-test genetic counselling should already have warned the individual of the possibility that the results may reveal a condition that cannot be treated or alleviated, and if the individual has consented to undergoing the genetic testing on that basis, we should feel that the results should not be withheld from him or her.

3.3 Furthermore, to say that the healthcare professional need not disclose test results based on present knowledge of treatment options puts the onus on healthcare professionals to subsequently review these cases. In the event treatment becomes available in the future the healthcare professional may bear the burden of tracking individuals who were previously tested, for purposes of recalling them for consultation.

4. **Consent**

4.1. It must be remembered that unlike consent for medical treatment, consent for clinical trials, genetic testing and research are different as there is seldom a direct benefit to the individual or any benefit that may be derived is questionable.

4.2 As such, greater must be taken to ensure that individuals are fully aware of all relevant information and are able to consent to participate in the proposed research.

5. **Genetic Testing on Children- Paragraphs 3.16 and 3.17**

5.1 Paragraphs 3.16 and 3.17 recognise that mature adolescents may be capable of making informed decisions on undergoing or refusing Genetic Testing. Paragraph 3.17 states that for mature children or adolescents, their decision to undergo or refuse Genetic Testing should be "respected".

5.2 It is not clear if the decision of a mature child or adolescent can override that of a parent. This could give rise to practical difficulties if the position is not made absolutely clear.

5.3 There are 3 possible approaches. Firstly, obtaining consent for medical treatment is like a key- the door can be unlocked by anyone with a key, in which case, for a person below the age of 21, as long as either parent or the child gives consent, the other cannot override that consent.

5.4 The 2nd approach is to respect the sanctity of the body. Once a child is mature enough to make decisions regarding his own health, then his decisions alone should be the determining factor *unless* he is then deemed insufficiently mature.

5.5 The 3rd approach is that until the child reaches the age of majority, his wishes can be considered but ultimately, the parents decide. This does not appear to accord with the consultation paper and we assume that this is not the basis for consent to be obtained.

5.6 A position should be taken on whether the analogy of a key and a lock is to apply or the 2nd viewpoint is to be preferred by the Advisory Committee.

6. **Recommendation 5**

6.1 For Carrier and Predictive Testing, the recommendation appears to be against the idea of testing for young children. Carrier and Predictive Testing can be carried out where a mature child consents, or in exceptional circumstances for a young child, where the parents *and* the physician consent.

6.2 Some members of this committee are of the view that allowing for exceptional circumstances for young children may create more problems. Based on the example given, carrying out a test to address a parent's difficulty of not knowing the genetic status of the child exposes the child to even greater risk where the test results are "unfavourable". We would like the Advisory Committee to consider if testing for such reasons alone should be allowed and whether it would be better for a consistent approach to be taken instead of allowing exceptions. Where there are reasons to make exceptions, we feel that any decision should be taken together with the relevant IRB (if it involves clinical research) or Ethics Committee.

7. **Persons of Unsound Mind- Paragraph 3.18**

7.1 There are unaddressed issues in relation to mentally incompetent adults as the identity of a person legally authorised to consent may not be easily understood nor can that person be easily identified.

7.2 We recognise that in cases of "idiots, mentally disordered persons and persons of unsound mind", the Court has the power to appoint a Committee of Persons under the Mental Disorders & Treatment Act. This power also extends to persons who are comatose or suffering from other serious neurological deficit but not brain dead.

7.3 Leaving it to the researcher or healthcare professional to obtain consent to carry out genetic testing or research on a mentally incompetent adult from a Committee of Persons may not be workable in practice.

7.4 Firstly, in reality, a Committee of Persons is seldom appointed for mentally incompetent persons as relatives are seldom advised of the procedure nor are the relatives keen to apply to Court due to the costs involved. In practice, where a mentally incompetent patient requires medical treatment, treatment is still provided if it can be certified that the treatment is in that patient's interest.

If there is no Committee of Persons, no consent can be obtained, unless the researchers undertake this process of getting a legal guardian appointed for the purposes of obtaining consent.

7.5 Further, the medical professional/ researcher will seldom be able to obtain the consent of a responsible Committee of Persons, unless the medical professional/ researcher can show that the Genetic Testing will benefit that individual. This is because the duty of the Committee of Persons is to act in the best interest of the individual. If the Committee of Persons were to consent to the extracting genetic material from that individual for tests when the individual derives no benefit, this may be construed to be a breach of their fiduciary duty to the individual.

7.6 Currently, the Medical (Therapy, Education and Research) Act (Cap 175) sets out a framework whereby the relatives of a deceased can consent to the deceased's body being given to an appropriate institution for purposes under this Act and the Act sets out clearly who can consent and the order of priorities among the relatives who can give such consent. The problem is that the Act only addresses cases where the donee is dead.

7.7 Our suggestion is that the provisions in the Medical (Therapy, Education and Research) Act be extended to cover such cases. To protect the patient, it should be expressly provided that the patient can withdraw from the test/research should he recover his mental competence.

8. **Cadaveric Tissue**

8.1 The added benefit in extending the use of the Medical (Therapy, Education and Research) Act is that it would then deal with the use of cadavers for genetic testing and research, an issue which has not been dealt with in this Consultation Paper.

9. **Confidential Information- Recommendation 7 & Paragraph 3.24**

9.1 Given the starting premise that genetic information is to be treated like other medical information, the physician or researcher would be under a strict duty of confidentiality and the information can only be disclosed in certain well defined circumstances- usually involving the consent or implied consent of the patient.

9.2 Paragraph 3.24 appears to recognise the defence of public policy in allowing disclosure of confidential information. However, at present, there are no decisions by the Singapore courts on the ambit and the applicability of public policy as a defence to the disclosure of confidential information.

9.3 It is only the Infectious Diseases Act that mandates the disclosure of certain information by the physician for specific diseases. We suggest that genetic information be subject to the same requirements and where necessary, public disclosure for specific conditions be statutorily mandated.

10. **Pre-Natal Genetic Diagnosis- Recommendation 14**

10.1 It must be remembered that under the Termination of Pregnancy Act, a pregnancy can only be terminated within 24 weeks of gestation. Any guidelines or legislation in relation to foetal tests should be consistent with this timeline to allow for termination of the pregnancy.

11. **Recommendation 15**

11.1 Although the use of PND for gender selection or selection of other traits for non-medical purposes will be prohibited, care must be taken to ensure that creative means of subverting these prohibitions do not surface. As such, the ambit of serious genetic diseases that require PND must be clearly and expressly defined. As an example, we note that colour blindness may be considered a sex-linked disorder. To suggest that PND be conducted for such a condition and possibly allow an otherwise normal foetus to be aborted would surely not be the intended position of the Advisory Committee.

11.2 Even where the PND does relate to a serious disease or condition, often the results may only confirm that the foetus has a slightly higher chance of developing the disease as compared to a normal individual. We have a concern whether parents should be allowed to undergo tests and decide to abort on the basis of a slim chance of a disease occurring. This is especially acute in the case of late onset diseases.

11.3 Therefore, in considering whether genetic tests should be offered to parents as part of PND, the following considerations should be noted:-

(a) the accuracy rate of the test;

(b) likelihood of the condition manifesting itself;

(c) when the condition is likely to manifest (i.e. how late in life);

(d) whether the condition is treatable.

If it is felt that the option of these PND genetic tests should be offered to the parents, they should be advised of the matters in (a) to (d) above.

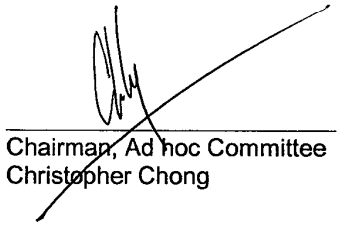
11.4 Accordingly, the severity of the condition, the accuracy of the available tests and the availability or likely availability of treatment of the disease are important considerations to be included in the Recommendation.

12. **Paragraph 6.43**

12.1 Reference is made to the statement "These routine newborn and prenatal programmes have become socially acceptable in Singapore and hence informed consent is not explicitly taken".

12.2 Our view is that, for all screening procedures, informed consent must be expressly obtained. The statement highlighted above may not or should not reflect current medical practice.

Dated this 11th day of May 2005



Chairman, Ad hoc Committee
Christopher Chong