

HUMAN TISSUE RESEARCH

A REPORT BY THE
BIOETHICS ADVISORY COMMITTEE
SINGAPORE

November 2002

FOREWORD

In June 2002, the BAC published its first report, *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive Cloning and Therapeutic Cloning* (the Stem Cell Report). The report was the culmination of a painstaking and lengthy process of research, and of consultation with religious, medical, professional and civic groups undertaken by the Human Stem Cell Research (HSR) Subcommittee of the BAC, chaired by Senior District Judge Mr Richard Magnus. The Government's acceptance of the BAC's recommendations in the Stem Cell Report was announced by Deputy Prime Minister Dr Tony Tan on 17 July 2002.

In parallel with the work of the HSR Subcommittee on stem cell research and cloning, the BAC's Human Genetics Subcommittee (HGS) has been carrying out a similar process of research and consultation on ethical, legal and social issues arising out of human tissue banking and human tissue research. The HGS was formed by the BAC to consider and address ethical, legal and social issues arising from research on human biology and its applications, other than those involving human stem cell and cloning.

As with the HSR Subcommittee's Report, a thorough public consultation process was conducted to obtain input and views from all sectors of the community on the issues involved. This Report on *Human Tissue Research* is the product of this process of research and consultation, which began in February 2001.

The BAC records its sincere thanks to the expert writers who submitted papers to the BAC, as well as to the parties in the consultation process who so kindly took the time to consider and give thoughtful feedback during the consultation process. As with the Stem Cell Report, we are pleased to append to this Report a complete record of all the written representations received by the HGS.

Finally, I would like to thank my fellow Committee members, especially the Chairman of the HGS, Associate Professor Terry Kaan, as well as the members of his Subcommittee, for the hard work which they put into the project, and for ensuring that this Report is one that is a considered, fair and sensitive response to the often difficult issues raised, and which takes into account the diversity of views presented.

Professor Lim Pin
Chairman
Bioethics Advisory Committee
November 2002

THE BIOETHICS ADVISORY COMMITTEE

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About the Bioethics Advisory Committee

The Bioethics Advisory Committee ("the BAC") was appointed by the Singapore Cabinet in December 2000. The BAC was directed to "examine the legal, ethical and social issues arising from research on human biology and behaviour and its applications" and to "develop and recommend policies ... on legal, ethical and social issues, with the aim to protect the rights and welfare of individuals, while allowing the Life Sciences to develop and realise their full potential for the benefit of mankind".

The BAC reports to the Ministerial Committee for Life Sciences. For further information about the BAC and its work, please visit <http://www.bioethics-singapore.org>

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The BAC welcomes views, comments, suggestions and other feedback on the issues raised in this and other consultation papers, or on any bioethical issue within its remit. All feedback should be addressed to:

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EXECUTIVE SUMMARY

- i. In December 2000, the Bioethics Advisory Committee (the “**BAC**”) was appointed by the Cabinet to examine the potential ethical, legal and social issues arising from research in the biomedical sciences in Singapore, and to recommend policies to the Life Sciences Ministerial Committee.
- ii. Three Sub-Committees were constituted by the BAC: one of these Sub-Committees is the Human Genetics Sub-Committee (the “**HGS**”), which was constituted in February 2001 and given the task of examining ethical, legal and social issues arising specifically from human genetics research in Singapore.
- iii. A Consultation Paper on Human Tissue Research was prepared by the HGS for the BAC after extensive research, careful deliberation and consultation with experts towards the end of February 2002. With a view to seeking a broad and representative spectrum of views, the Consultation Paper was used by the BAC as the focus of a consultation process in which views and input were sought from a total of 66 religious, civic, professional, scientific, medical and health care organisations, as well as from members of the public.
- iv. This Report on Human Tissue Research (the “**Report**”) is the culmination of that process of research, consultation and deliberation on issues affecting the conduct and governance of human tissue research and human tissue banking in Singapore.
- v. The Report is organised as follows:
 - **Part I: Introduction**
Part I covers Sections 1, 2 and 3 of the Report. **Section 1** describes the consultation process that culminated in this Report. **Section 2** sets out definitions: we use the term “human tissue” to refer to all

kinds of human biological materials derived from living or dead persons. Blood banking for therapeutic purposes is excluded from the purview of this Report, as this is already statutorily regulated in a comprehensive way. Likewise, cadaveric donations made under and governed by the Medical (Therapy, Research and Education) Act are also excluded. This Report and the recommendations which we make here are not intended to supplant the more specific recommendations which we made in relation to the treatment of human embryos, cord blood, gametes and stem cells in our earlier Report of June 2002 entitled “Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning” (the “**HSR Report**”), and therefore do not apply to such tissues. **Section 3** sets out the main objectives of this Report, and our general approach to the formulation of applicable principles.

- **Part II: Human Tissue Research**

In Part II, we examine the role and promise of human tissue research in the advancement of genetic and medical knowledge (**Section 4**), and the current state of practice of human tissue banking in Singapore (**Section 5**). We suggest that all forms of tissue banking which permit research access be statutorily regulated through licensing by a statutory authority. We exclude collections of tissues taken for purely therapeutic or diagnostic purposes from the purview of this Report, so long as these tissues are retained only as part of the record of patients, and for which no research access is intended. The licensing authority could be the same statutory authority which we previously recommended to be set up for the regulation and supervision of human stem cell research in Singapore. We recommend that as a general rule, collections of tissues intended for research use should be held by institutions only, as opposed to private individuals.

- **Part III: Law & Practice**

In Part III, we survey the state of the current law (**Section 6**), and identify some issues which we think need to be addressed for the future. We conclude that a full consensus has yet to emerge internationally on many of the most critical issues in relation to human tissue banking. The most difficult problems in this regard are the issues of property, control and ownership rights to tissue samples. We suggest a continuing professional and public dialogue on the ethical and social considerations which should inform the shape of the law in this area. This dialogue should be undertaken with a view towards ensuring the harmonisation of our laws with accepted international best practice and consensus on relevant legal

doctrines and principles such as are being developed in the leading jurisdictions around the world.

- **Part IV: Specific Issues**

In Part IV (comprising Sections 8 to 11), we address specific issues, and advance our recommendations:

- **Section 8** deals with the issue of consent to donation. We take the view that research tissue bankers and those taking tissue for research have an obligation to ensure that valid and appropriate consent is obtained, and that such consent should be informed and free. Sufficient information should be given to prospective donors to enable them to exercise a real choice. Gifts of human tissue should be made as outright gifts, in the sense that the donor should renounce any property rights to the tissue. But donors should be entitled to choose between making a general gift (which may be used for any research purpose), or a restricted gift (which may be used only for research purposes specified by the donor). Where a primary purpose or objective of the taking of the tissue is research, the consent form for the donation of the sample for research should be separate from the consent form for the taking of the tissue for therapeutic or diagnostic purposes. In such cases, consent for therapy or diagnosis should be taken separately by the attending medical practitioners (for therapy or diagnosis) and by the researchers (for research).
- **Section 9** covers the issue of consent in relation to legacy tissue collections. We take the view that it is consistent with good stewardship to allow reasonable and respectful research use of such legacy tissue collections for the greater public good.
- **Section 10** deals with the obligation of researchers and tissue bankers alike to respect and protect the privacy of donors, and the confidentiality of personal information. The use of arrangements such as anonymised data arrangements which protect the confidentiality and privacy of the donors is an alternative in situations where consent or re-consent is impossible, difficult or socially unacceptable to obtain.
- **Section 11** deals with approaches to governance. Given the current pace of developments in the genetic and genomic sciences, we recommend against hard-coding specific rules in legislative form for the regulation of research and commercial

activity, as overly-specific rules run a risk of rapid obsolescence. Instead, we recommend a more flexible and responsive legislative regime in which a statutory authority is constituted to supervise and regulate research tissue banking. The principal point of supervisory control could be through the licensing of accredited institutions, rather than through the direct regulation of individual researchers and tissue collections by the statutory authority. The emphasis should be on institutional responsibility and good internal self-governance, and on the promotion of adherence to the spirit rather than to the letter of the law. This proposed statutory authority could be the same statutory authority which we recommended be constituted for the regulation of human stem cell research.

- **Part V: Recommendations**

In this Part, we set out our recommendations. The body of ethics and law in the field of human tissue and research is still in a state of flux and rapid evolution in leading jurisdictions around the world, as some of the most fundamental issues are just only now beginning to be grappled with and debated. Our recommendations represent our considered responses to some of these challenges, and are our contribution towards providing a foundation for the sound development of a body of ethical guidance and professional best practices in a field where global debate continues on many fundamental issues. We recommend that:

- **Recommendation 1:**

We recommend the adoption of the following ethical principles:

- **1A. Primacy of the Welfare of the Donor.** That the health, welfare and safety of the donor shall be the paramount consideration in the taking of any tissue.
- **1B. Informed Consent.** No tissue should be taken, or be accepted, unless the full, free and informed consent of the donor has been obtained. Patients should be informed when material left over following diagnosis or treatment might be used for research, and their consent sought and obtained. Special attention should be paid to the legal and ethical resolution of consent issues in relation to legacy tissue collections. In specific situations, it may be ethically acceptable to proceed in the absence of clear consent provided that sufficient precautions are taken for the protection of the privacy of the patient and the patient's family (for example, through appropriately

designed anonymisation procedures for legacy tissue collections).

- **1C. Respect for the Human Body.** The human body and its remains should be treated with respect. Researchers and tissue bankers need to be sensitive to religious and cultural perspectives and traditions, especially when whole cadavers or gross organ parts are concerned. Especially where these are concerned, donors or their families should be consulted in advance of the donation as to their wishes for the appropriate disposal or return of surplus tissues when these are no longer required.
 - **1D. Donations to be Outright Gifts.** Gifts of tissues should be accepted only on the basis that the donor renounces any property rights or claims to the tissue that they choose to donate. Donors should be informed of this principle, and if they do not agree, then their donation should not be accepted.
 - **1E. Ethical Review of Research Proposals and Access Requests.** All research using human tissue samples should be approved by appropriately constituted research ethics committees or institutional review boards.
 - **1F. Confidentiality.** Researchers and all those involved in research tissue banking have an obligation to protect the confidentiality of the personal information and the privacy of donors. This obligation extends to the confidentiality of the personal information given by donors about individuals who are not themselves donors (such as information given about family members in providing details of the medical history of the donors' family members).
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- **Recommendation 2:**
Subject to our views as set out in Section 5, we recommend that research tissue banking should be conducted only by or through institutions such as may be approved by the appropriate authorities to do so, and not by private individuals.
 - **Recommendation 3:**
We recommend that there should be statutory regulation and supervision of research tissue banking, and that a statutory authority should be given supervisory and licensing jurisdiction for this purpose. We further recommend that all institutions that conduct research tissue banking should have in place

transparent and appropriate systems and standards for the proper ethical, legal and operational governance of research tissue banking. This proposed statutory authority could be the same statutory authority which we recommended be constituted for the regulation of human stem cell research.

- **Recommendation 4:**

Given the background of a rapidly shifting and evolving consensus and opinion in the leading scientific jurisdictions, we recommend that a continuing professional and public dialogue be initiated towards:

- Settling the principles which should guide the conduct of research tissue banking, against the background of evolving consensus on these principles in the leading scientific jurisdictions, and
 - Achieving an early resolution of the legal and ethical questions in relation to the ownership and custody rights to donated human tissue.
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HUMAN TISSUE RESEARCH

A REPORT

I. INTRODUCTION

1. About this Report and the Consultation Process

- 1.1. At the end of February 2002, a Consultation Paper entitled “Consultation Paper on Human Tissue Research (the “**Consultation Paper**”) was prepared and submitted by the **Human Genetics Sub-Committee** of the **Bioethics Advisory Committee, Singapore** (the “**BAC**”) to the BAC. The members of the Human Genetics Sub-Committee are set out in **Appendix A**.
- 1.2. In its work on the Consultation Paper, the Human Genetics Sub-Committee (the “**HGS**”) had the benefit of valuable expert advice and background information presented by eminent experts and professional bodies in a series of Position Papers commissioned by the BAC. Copies of the commissioned Position Papers relevant to the Consultation Paper and this Report are set out in **Appendix B**. The BAC records its appreciation to the Chapter of Pathologists of the Academy of Medicine; Professor Edison Liu of the Genome Institute of Singapore; and Associate Professor Kon Oi Lian of the National Cancer Centre for these Position Papers.

- 1.3. With a view to seeking a broad and representative spectrum of opinion, the Consultation Paper was sent by us (the BAC) to a total of 66 religious, civic, professional, scientific, medical and health care organisations on 27 February 2002 with a request for feedback and suggestions. A copy of the Consultation Paper is set out in **Appendix C**. In addition, a press conference was held on 4 March 2002, and public participation was invited in the feedback process. The release of the Consultation Paper and our invitation to the public was widely reported upon in the media. This consultation exercise was carried out in an effort to inform, test and shape the recommendations which we propose for adoption in this Report.
- 1.4. A total of 37 parties to date have responded to our request for feedback on our Consultation Paper. Of these, 33 parties responded with comments and suggestions, while the remaining 4 parties replied to say that they had no comments. The full text of all the written responses received by us are set out in **Appendix D**.
- 1.5. In general, respondents were supportive of the principles proposed in our Consultation Paper. This Report is a revision of our Consultation Paper, after carefully considering and debating at length the responses that we have received to date.
- 1.6. As indicated in our Consultation Paper, our primary objective has been to recommend a basic framework for the ethical and legal regulation of human tissue research in Singapore. We believe that the recommendations set out at the end of this Report meet this objective, and provide a firm foundation for the proper and ethical governance of human tissue research in Singapore, both for the present and for the future. We are reinforced in our views by the comments expressed by the majority of our respondents, and by the fact that the core principles are consonant with those held to be applicable in the leading scientific jurisdictions.
- 1.7. Human tissue research is a broad field of inquiry. This Report is not intended as an exhaustive survey. Instead, we focus on a few specific issues arising out of the practice of human tissue banking which we think require resolution as a matter of priority. Other issues (some of which are also identified in this Report) may be addressed at a later time in separate working consultation papers and reports.
- 1.8. We have made recommendations on issues where we think such recommendations may be reasonably and confidently advanced. As to the other issues, we have simply identified some issues which we think merit further discussion and consideration. As in our Consultation Paper, we have not made any specific recommendation for those issues and we

continue to invite views, comments, suggestions and other feedback on these other issues.

2. Definitions

2.1. In this Report, we use the term “**human tissue**” to refer to all kinds of human biological materials derived from living or cadaveric donors, including solid body tissues, organs, foetuses, blood and other body fluids and their derivatives, cord blood, embryos, gametes (sperm or eggs) or any part or derivative thereof.

2.2. However, we exclude the following from this review:

- a. Blood banking for therapeutic purposes, as this is already well-regulated in Singapore (but blood and blood derivatives collections which are used for research are covered by this review);
- b. Donations of cadavers, organs and cadaveric tissue made under and governed by the Medical (Therapy, Education and Research) Act; and
- c. Human stem cell research, reproductive and therapeutic cloning. These recommendations are not intended to supplant the more specific recommendations which we have made in relation to the treatment of human embryos, cord blood, gametes and stem cells in our separate Report of June 2002 entitled “Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning” (the “**HSR Report**”). Where common ground is covered in this Report and the HSR Report, it should be understood that the more particular and specific recommendations which we made in the HSR Report in relation to human embryonic stem cell research and on human cloning, should control: the particular recommendations made in the HSR Report are to be taken as being in addition to the general recommendations set out in this Report.

2.3. In practice, human tissue banking is carried out in the following main settings:

- a. Human tissue which is taken for the purposes of clinical diagnosis or treatment, but which could be used subsequently for research. Blood, urine and other biological fluids are commonly taken for the purposes of clinical diagnosis or monitoring of patients’ medical conditions, or less frequently, for treatment. Upon completion of the clinical testing procedures, excess blood or urine are often kept in the clinical laboratory as part of the patients’ medical records. However, such collections of excess blood, urine or other biological fluids could also be used in research

studies. In the same way, tissue may be removed from a patient for pathological diagnosis in the form of a biopsy or surgical excision. Tissue may also be removed from a patient as part of his or her treatment, for example, when a cancer is resected from the big intestine. Such tissue is processed and examined histologically by the pathologist as part of the clinical care of the patient. Excess tissue which is stored as frozen tissue or in the form of paraffin blocks is retained by the institution as part of the patient's medical records in case the tissue needs to be reviewed in the future for patient care purposes (see also paragraphs 5.1 to 5.6 below). However, such collections of tissue can also be used in research studies;

- b. Small or limited collections of blood or tissue may be taken or stored with the patients' consent for specific research projects conducted by individual doctors or research teams. In such cases, the collection is only made for the limited purposes of specific research projects. On the completion or termination of the research projects, these collections may remain in the care of the individual researchers or teams of researchers, or they may be merged through accession to the larger research tissue banks of institutions as discussed in (c) below. We discuss these small or *ad hoc* collections for specific research projects in paragraphs 5.15, 5.16, 5.19 and 5.20 below, and make the recommendation that, where appropriate and where the prior patient consent allows the researcher to do so, they should be consolidated into larger institutional tissue banks upon the completion or termination of the research project (see paragraph 5.22 below); and
- c. Research tissue banks are collections of human tissue which are assembled specifically for the purpose of research. Such research tissue banks differ from that in (b) immediately above, in that the scale of collection is generally much larger, and in that donations may be sought for a much wider range of research applications. In many cases, the tissue donated to such research tissue banks are donated for research in general, without any restriction on the research uses to which they may be applied. Such research tissue banks need not be physically centralised (see paragraph 5.21 below). Tissue in such research tissue banks may also be made up at least in part of tissue originally collected as in (a) and (b) above, but which are subsequently consolidated into larger institutional research tissue banks upon exhaustion of their original purpose or use. We further elaborate on such research tissue banks in paragraphs 5.7 to 5.15 below.

3. The Objectives of this Report

- 3.1. In recent years, much public attention has been focused on developments in the new life sciences, and on genetic and genomic research in particular. These new life sciences offer enormous promise of potential benefits.

- 3.2. In many of the current thrusts of the new life sciences, researchers are entering completely new grounds which raise many novel legal, ethical and social issues. Consequently, the body of community ethics is being asked to offer ethical direction and guidance for the ethical conduct of research in entirely new situations for which there are no readily available precedents. In many areas too, the state of the law sometimes lags far behind the realities of the current and future state of technology, so that practitioners and researchers in the new life sciences are forced to act in the absence of clear legal guidance.
- 3.3. We believe that, in this respect, the development of sound ethical principles which are acceptable to and supported by the community at large will assist in the formulation of the law in areas and for situations where this is eventually felt to be necessary. Such a body of sound ethical principles will also serve as the common understanding on which ethical research work may be carried out.
- 3.4. The majority of scientists and researchers are responsible and are aware of potential ethical concerns in the work that they do, and in that which they may propose to carry out. Most wish to do what is ethically right. Indeed, some may be inhibited from participating in some areas of research (which may in fact be entirely acceptable to the community, and be in the public interest) by the lack of clear ethical direction or agreement on a given point, or by uncertainty generated by controversy in related areas.
- 3.5. Accordingly, **the principal objectives of this Report** are:
- a. To review current issues affecting the conduct of human tissue banking and human tissue research in Singapore;
 - b. To recommend a national framework for the proper governance of research tissue banking activities in Singapore; and
 - c. To recommend a body of appropriate ethical principles and guidelines for the ethical conduct of research tissue banking and human tissue research in Singapore.
- 3.6. Where there is broad agreement in leading jurisdictions on applicable principles, we have in general tended towards recommending the adoption of these principles. It is only recently that various developed jurisdictions have embarked upon the task of the formulation of guidelines and rules for the governance of the new life sciences, and to examine the ethical issues involved. In some areas, an international consensus is beginning to emerge. But in many other areas, the future shape of the body of ethics is still being debated. We hope that the recommendations advanced in this

Report will help fill some of the more obvious gaps. We also hope that the public and the professional debate generated by the release of the Consultation Paper and this Report will help advance that process.

II. HUMAN TISSUE RESEARCH

4. The Role and Promise of Human Tissue Research

- 4.1. Research involving the use of human tissue, or the use of information derived from such human tissue, is a fundamental cornerstone of modern medical research and knowledge. Many of the advances in the life sciences which have contributed so much to our health, physical well-being and long life expectancy are founded on knowledge gleaned in one way or another from human tissue research. For instance, vital epidemiological information about the pattern and incidence of occurrence of various forms of diseases such as cancers has been (and continues to be) gained from human tissue research, and through the analysis of such information, important discoveries about the prevention, control and treatment of such diseases have been made for the benefit of humankind.
- 4.2. Although tissue banking in some form or another has been practised for well over a century, it is only in the last decade that tissue banking has come into the public limelight because of the rapid advances in research technology and knowledge in the fields of human genetics and genomics. We use the term “**tissue banking**” to refer to a structured and organised resource collection of tissue, put together by one or more individuals for the purposes of facilitating biomedical or genetic research, or for public health and epidemiological purposes, or any combination of these. In the genomics era, research on well-characterised collections of tissues linked with good clinical information, will enormously improve our basic understanding of disease and holds great promise for the discovery of new screening, diagnostic and therapeutic approaches which would benefit mankind.
- 4.3. However, such research has to take place within a framework which safeguards the public’s and patients’ interests. In particular, there is a need to ensure that:
 - a. Tissue is only obtained and collected with the full, free and informed consent of the patient or donor;
 - b. The taking of tissue does not compromise the patient’s clinical care in any way;
 - c. Where whole organs or whole limbs or substantial parts of either are banked, that these be treated with respect for and sensitivity to religious and cultural perspectives and traditions; and

- d. Tissues in tissue banks are used in ethically appropriate ways, and in accordance with the purposes authorised by the consent.
- 4.4. In this Report, we attempt to canvass some of the issues which we think need to be eventually addressed for the establishment of a sound ethical, legal and social foundation for the proper conduct of human tissue banking and research in Singapore for now and for the future.

5. Human Tissue Banking In Singapore

- 5.1. **Tissue Collection for Therapeutic or Diagnostic Purposes.** In the past, human tissue banks in Singapore have been built up largely as an incidental by-product of diagnostic procedures. Most commonly, human tissue samples would be removed during surgery or other medical procedures and processed for pathological examination and investigation. For example, suspected tumours would be preserved or fixed in the form of paraffin blocks to facilitate further pathological investigation. These tissue collections largely comprise tissue slides, paraffin blocks and tissue preserved with wet preservation techniques. These techniques render the cellular material non-viable. Some large collections, mostly institutional, have been assembled in this way.
- 5.2. Pathologists in Singapore have traditionally taken (and continue to take) the view that this retention is on the basis that these tissue samples form part of the medical records of donors, and that they (and the institutional host for the collection) are “stewards and guardians” or custodians of these tissue samples on behalf of the donors.
- 5.3. Human tissue is collected not only from living donors, but also from the dead. Cadaveric tissue samples are also collected in the course of coronial or consensual autopsies for the purposes of diagnostic procedures.
- 5.4. On completion of the pathological investigations, these tissue samples (from living and cadaveric donors alike) are generally archived and added to the human tissue collection. The Chapter of Pathologists of the Academy of Medicine, Singapore, states that this is done “in accordance with current good clinical practice guidelines, [so that] the case files (in this case [the] slides and blocks) can be reviewed and perhaps sent for expert opinion. The tissue is kept against the chance that there may be a medico-legal challenge regarding the diagnosis or [in the case of living donors] the possibility that new prognostic and therapeutic markers may be developed, and used during the patient’s lifetime”.

- 5.5. Where tissue is collected only for therapeutic or diagnostic purposes (or both), and not for research, the primary objective of the taking of the tissue is the benefit of the patient in the context of the relationship between a physician and patient. In this kind of relationship, the well-established ethical and legal principles and rules governing this professional relationship controls: comprehensive and adequate ethical, professional and legal (both statutory and at common law) controls already exist for the proper governance of this professional relationship, and it is unnecessary for us to add to these in our Report.
- 5.6. Accordingly, the recommendations set out in this Report are not intended to apply to collections of tissues taken only for therapeutic or diagnostic purposes, and kept only as part of the medical records of patients and not applied towards research purposes (we refer to this kind of tissue collections as “**therapeutic/diagnostic tissue collections**” in this Report).
- 5.7. **Research Tissue Banks.** However, the status of tissue collections is not always so clear-cut. It is common practice for patients to be asked for their consent to allowing the tissue taken from them for the primary purpose of therapy or diagnosis to be made available for research use after the primary purpose of therapy or diagnosis has been exhausted or satisfied. Consequently, the distinction between therapeutic/diagnostic tissue collections and research tissue collections or research tissue banks becomes blurred, because collections of tissue originally taken for the purpose of therapy or diagnosis eventually effectively become “incidental” tissue banks for research purposes after their original therapeutic or diagnostic purposes are exhausted or satisfied.
- 5.8. We take the view that if a tissue collection or a tissue bank is made available for research or study (such study being other than for the direct interest and benefit of the donor), then such a tissue collection or tissue bank must be regarded as a **research tissue bank**, regardless of the fact that the tissue may have been originally taken for therapy or diagnosis, or both.
- 5.9. The main reason for making this distinction between therapeutic/diagnostic tissue collections and research tissue banks is set out at paragraph 5.5 above. In sum, where therapy and diagnosis are the only purposes, the ultimate objectives of both the taking physician and the patient are *ad idem*: the taking of the tissue is aimed at directly benefiting the donor. This is not the case when tissue is taken for research purposes. Research is not aimed at the immediate and direct benefit of the donor, although indirect benefit may accrue to the donor through breakthroughs or advances in medical knowledge or technology as where insights are gained through research involving the use of the donor’s tissue. In the

case of the taking of tissue for purely therapeutic or diagnostic reasons, the interests of the taking physician and of the donor patient are in accord: the direct benefit of the patient. In the case of tissue taken for research, this is not the case: researchers necessarily have their own research objectives, and these research objectives are seldom completely coincident with that of direct benefit to the donor individual. For this reason, consent to the taking of tissue for therapy or diagnosis is not consent to the use of the tissue taken for research purposes.

- 5.10. We are also conscious of the fact that while tissue which is taken purely for therapy or diagnosis is always (and indeed is required by law to be so) taken by registered medical practitioners in the context of the comprehensively regulated ethical, professional and legal relationship between a physician and his patient, there is no guarantee of a similar relationship with its attendant safeguards between a researcher and a donor. Arguably, donors are not covered by this physician-patient relationship even when the research is carried out by registered medical practitioners, because the research is being carried out by the registered medical practitioners in their capacity as researchers, and not in their capacity as physicians to their patient. The ethical, professional and legal safeguards that apply in the physician-patient relationship may have no or limited application in the researcher-donor relationship. That being the case, clear ethical rules and guidelines are required for the ethical conduct of human tissue banking as it relates to research tissue banks, and human tissue research.
- 5.11. Accordingly, the recommendations set out in this Report are intended to apply to all **research tissue banks**, and to all engaged in the conduct or operation of research tissue banks, regardless of whether therapy or diagnosis was one of the objectives, or was the sole original objective, of the taking of the tissue.
- 5.12. In recent years, however, research tissue banking in Singapore has moved beyond the merely incidental towards **purpose-assembled research banks**. In this kind of tissue bank, human tissue is collected purely or primarily for the purpose of research, and not merely as an incidental benefit of diagnostic procedures. These purpose-assembled research banks fall squarely within our definition of research tissue banks.
- 5.13. There has also been a parallel trend towards the establishment of collections of human tissue in which the biological material remains viable or potentially viable, at least in some respects, at the cellular level. For instance, human tissue samples may be flash-frozen and stored in liquid nitrogen or deep freezers. Likewise, cell lines may be propagated on culture media. This greatly increases the value of the samples for many

lines of research, as they can be applied towards a wide range of biological investigations for which fixed materials are not suitable.

- 5.14. We take the view that such purpose-assembled research banks are to be encouraged, provided that all appropriate ethical and legal considerations and concerns are appropriately met and addressed, as they promote and enhance research, which offers the promise of immense benefit in the future for humankind.
- 5.15. A significant proportion of current holdings in research tissue banks (as defined by us above) consist of tissues taken originally and primarily for therapeutic or diagnostic purposes. For the purposes of this Report, however, they fall within our definition of research tissue banks notwithstanding the fact that they consist of collections of tissues taken originally and primarily for therapeutic or diagnostic purposes, by reason of their being made accessible or available for research use. The largest collections of these kind of incidental research tissue banks are generally held by hospitals, teaching centres and large health institutions, although some much smaller “private” collections have apparently been built up by individual doctors or groups of doctors in the course of their research into specific medical conditions.
- 5.16. Our view is that human tissue collections by private individuals should not be encouraged. We therefore propose that, in general, research tissue banks should only be held by institutions (for example, by a hospital, a university or a research institution). Such institutions may be of a public (e.g. a teaching hospital) or private (e.g. a private hospital or a private commercial research venture) character.
- 5.17. We also take the view that all research tissue banks should be subject to statutory supervision for proper operation, governance and adherence to good practices, compliance with the law, and conduct according to appropriate ethical and professional standards. Given the rapidly evolving state of human tissue research, as well as of the attendant body of ethics both in Singapore and internationally, we think it is best to adopt an approach emphasising professional self-regulation by accredited institutions. This would provide the most flexible and responsive management model in a field which is only in its earliest stage of development in Singapore, and for which field many of the most fundamental issues remain to be settled and agreed upon internationally.
- 5.18. We therefore suggest that the best and most flexible way of administering such statutory supervision would be to give a statutory authority licensing jurisdiction over all research tissue banks, and that only institutions be licensed to maintain research tissue banks. Through its power to license,

the statutory authority can impose conditions for the issue of licences (such as adherence to and implementation of the principles set out in Recommendation 1 of this Report, and the minimum content suggested by us for the Standard Operating Procedures of research tissue banks in Recommendation 3 of this Report). Such an approach would place the emphasis on institutional responsibility and good internal self-governance, and promote adherence to the spirit of principles rather than to the mere letter of the law.

- 5.19. We make clear however, that we do not object to the collection of tissue for specific research projects or programs, whether by individuals, or by groups of individuals, provided that the individuals collecting such tissue are employees of or are otherwise directly accountable to an appropriately licensed supervising institution. We appreciate that many research programs which may yield useful and important data and knowledge are assembled by individual researchers or groups of individual researchers in this way. For example, individual researchers or research groups within an university or a medical institution may wish to collect tissue for particular research projects. In such an arrangement, the individual researchers need not be licensed directly by the proposed statutory authority, but may conduct their research under the supervision of a licensed supervising institution and upon such terms as may be stipulated under the general licence granted by the statutory authority to the supervising institution.
- 5.20. In exceptional cases, if for any reason collections have to be made by private individuals who are not affiliated or directly accountable to any institution (for example, a collection of a specific kind of tissue made by a medical specialist in private practice for the purpose of clinical research in the context of the specialist's own clinical specialty), application should be made by such private individuals to the statutory authority, which may then issue a restricted licence upon such terms as it may deem appropriate. We think that such terms should in particular include an undertaking that the collection, management and use of the tissue collection should only be assembled in collaboration with a licensed supervising institution.
- 5.21. Institutional human tissue holdings need not be physically centralised. It would be sufficient, for example, for an institution to have in place a current database of all human tissue holdings within that institution. Such a database could be part of the institution's database of research projects, with information fields such as the research area, disease, human tissue collected, where they are stored within the institution, and the units and persons responsible for these human tissues. The database should extend to the tracking of any subdivisions or extracts taken from samples held.

- 5.22. Consolidation of smaller human tissue collections in larger institutional holdings confers many benefits. A larger institution has more resources for the proper maintenance and stewardship of the human tissue samples under its charge. Continuity and preservation of the human tissue samples are also assured, and there is a greater likelihood of their being available to a wider pool of researchers. By itself, the size of holdings is also an important benefit of consolidation: a large-scale collection is more useful (particularly for population studies) than a small and limited collection.
- 5.23. We make it clear that in recommending that only institutions be licensed to maintain research tissue banks, we take no position on the issue of ownership, custody and property rights to the tissue in the collection. These are primarily legal questions which remain to be resolved in a definitive way by legislation or the common law. In Recommendation 4 of this Report, we make the recommendation for a continuing professional and public dialogue be initiated towards achieving an early resolution of the legal and ethical questions in relation to ownership, custody and property rights to donated tissues.
- 5.24. We also recognise that the development of the body of ethics governing research tissue banks and human tissue research is but in its infancy, and that agreement on many of the most fundamental issues have yet to be reached either in Singapore, or domestically within the leading jurisdictions of the world, or internationally. We therefore emphasise that the recommendations contained in this Report should be taken as a contribution towards the development of a mature body of ethics governing human tissue research in Singapore, and not as a definitive end statement of all applicable principles.

III. LAW & PRACTICE

6. Current Law

- 6.1. There is currently little in the way of law (either common law or statutory law) governing some of the most fundamental questions in relationship to tissue banking in Singapore.
- 6.2. In respect of donations of cadaveric tissue, Parliament has provided a statutory mechanism for donation in the form of the Medical (Therapy, Education & Research) Act. This enables people to state in advance their intention to donate their bodies, organs or tissues for research or for transplantation after their death. It also enables the family of a deceased person to donate the body, organs or tissues for research or for transplantation.
- 6.3. In relation to gifts by *living* donors, there is currently very little guidance in the way of either statutory law or common law, outside of some provisions in the Human Organ Transplant Act.
- 6.4. Currently, the only express statutory provision for the governance and regulation of tissue banking is to be found in the Private Hospitals and Medical Clinics Regulations 1993. These Regulations provide that where a “private hospital” proposes to perform certain specified specialised procedures or services, prior approval of the Director of Medical Services must be obtained at least 30 days in advance. “Tissue banking” and “sperm banking” are included in the list of specialised procedures or services which require such approval.
- 6.5. Trade in human organs or blood is prohibited in Singapore. Under Part IV of the Human Organ Transplant Act 1987, it is a criminal offence, punishable with a fine or a term of imprisonment, or both, for persons to enter into a contract or arrangement for valuable consideration for the sale or supply of any human organ or blood. Likewise, the Act also makes clear that it is a criminal offence to issue any advertisement relating to the buying or selling in Singapore of any human organ or blood. The Act does provide exemptions for the *bona fide* reimbursement of expenses incurred by donors, Government-approved schemes for granting medical or other privileges to organ or blood donors and their families, and for production and sale of products derived from human organs or blood as may be specially sanctioned by the Minister under the provisions of the Act. But the general rule is clear, and we endorse and repeat the principle that all trade in human organs and blood is, and should continue to be, prohibited in Singapore. Our interpretation of the current provisions is accordingly

that the sale or the proposed sale for profit of human tissue samples is prohibited in Singapore by the Human Organ Transplant Act 1987.

- 6.6. At the present time, there does not appear to be any uniform approach to the governance and regulation of tissue banking internationally. The Draft Discussion Document entitled *Data Storage and DNA Banking for Biomedical Research: Informed Consent, Confidentiality, Quality Issues, Ownership, Return of Benefits: A Professional Perspective* issued by the Public and Professional Policy Committee of the European Society of Human Genetics as part of the EUROGAPP Project 1999-2000 offers an illuminating survey of the gamut of existing opinions, legislation, guidelines and other policy statements applied in or issued by EC institutions, 18 European countries, the United States, and international organisations. Except in the case of the United States, and possibly France, the majority of the jurisdictions surveyed are notable more for the absence of specific agreed national guidelines or legislation than for the presence of such guidelines or legislation in relation to storage of data derived from human tissue research and DNA banking.
- 6.7. For the present time, we must conclude that a full consensus has yet to emerge on many of the most critical issues in relation to human tissue banking. The most difficult problems in this regard are the issues of property, control and ownership rights to tissue samples.
- 6.8. We think, however, that it is desirable that a review be undertaken of the law governing this area, and a professional and public dialogue initiated to discuss the ethical and social considerations which should inform the shape of the law in this area.
- 6.9. Legal review has recently acquired a new urgency in light of moves by other countries to clarify their own laws on human tissue banking with the current interest worldwide in the new life sciences. Increasingly, the harmonisation of laws and rules in this field is likely to emerge as an important consideration in shaping the laws and rules in each jurisdiction.
- 6.10. In a world where large-scale collaborative research projects tend to transcend national borders, there is an increasing likelihood that many countries may demand proof of each other that there is approximate equivalence in the degree of ethical and legal protection or regulation before they will allow the cross-frontier transfer of research data, or allow cross-border research collaboration which involves access to their national tissue collections or data.
- 6.11. For example, Singapore researchers may be asked to demonstrate that their protocols for the safeguarding of the confidentiality of data meet the

standards of the jurisdictions in which their proposed collaborators are based. Failure to achieve such standards locally may well mean that Singapore researchers may be excluded from opportunities for collaboration with researchers in those jurisdictions (which include most developed countries).

I V . S P E C I F I C I S S U E S

7. In this part, we address and set out our views on specific issues arising out of the practice of research tissue banking and human tissue research.

8. Consent Generally

- 8.1. Full, free and informed consent is the cornerstone of the legal and ethical legitimacy and validity of a gift of human tissue intended for research.
- 8.2. Operators of research tissue banks have an obligation to ensure that valid and appropriate consent to the donation of the gift is obtained.
- 8.3. Consent should be informed and free. Sufficient information on choices and potential consequences, and the unfettered voluntary exercise of free will are the minimum required of an ethically valid consent given by a person of sound mind, full age and capacity. We recognise that there is still some continuing debate as to what constitutes acceptable consent from a legal viewpoint. But we believe that this is an issue that can be readily resolved with appropriate and ethically-informed legal advice and forward planning in advance of the actual taking of human tissues. In this respect, we urge against approaches which place the emphasis on mere technical or formal legal compliance. Those who take tissue must make an honest and common-sense assessment for themselves as to the state of mind of the donor, the sufficiency of the information given to the donor, and the understanding of the donor of that information given to him or her, and finally, the reality of the donor's consent.
- 8.4. We accept that there are circumstances in which it would be impracticable or impossible to insist on consent being obtained. Such a situation may arise, for example, if there is no clear person from whom valid consent can be obtained, and where the donor himself or herself is already deceased, or is legally incompetent to give the requisite consent. Nonetheless, it may be possible in some circumstances for consent to be lawfully given on behalf of the incompetent donor by a legal proxy of the donor. It is beyond the remit of this Report to identify who may stand as valid legal proxies for incompetent donors at law. In any event, the extent and scope of a given legal proxy's lawful authority to give consent may well depend on the particular circumstances, and on the putative proxy's legal relationship with the donor. Where valid consent cannot be given directly by the donor for reasons such as incompetence or incapacity (for instance, if the donor is legally a minor), especial attention should be paid to the ethical and legal validity of any consent taken from the identified legal

proxy for the donor. In such situations, we recommend that, always acting within the limits of the law, the standard protocols and forms to be used in the taking of consent given on behalf of incompetent donors by their legal proxies should be reviewed and settled by the institution's ethics board or institutional review board, acting with the advice of the institution's legal advisors. The same ethics boards and legal advisors may also be consulted for a review of consent formalities in research projects for which it is anticipated that a significant proportion of the donors are or are likely to be legally incompetent.

- 8.5. We are keenly aware that there is an inherent conflict between presenting information to potential donors in a clear and simple way, and between disclosing all the possible kinds of research procedures which may be carried out on the donated human tissue sample, as well as of the benefits which may be derived from it. Inevitably, there must be some compromise between clarity and detail in the drafting of consent forms. We believe that this conflict may be greatly reduced if the consent forms make clear that the intention of the donor is to make an outright gift, with the donor agreeing to renounce all rights whatsoever to and in connection with the gift of the human tissue sample. Framing the request and the consent in this way also properly directs the minds of the donor and the recipient towards the issue of rights in the donated tissue: obviously, both the donor and recipient should be in agreement on this point. We therefore suggest that if a donor is unwilling to make an outright donation, then that proposed donation ought to be declined.
- 8.6. Even in the situation that we suggest, where the donor makes a gift on the basis that it is to be an outright gift, we note that the use of a tissue sample must be governed by the terms of the consent under which the gift was made. Although a donor may make an outright gift of his or her tissue in the sense he or she renounces any property rights to or in connection with the tissue, it is entirely open to the donor to stipulate or define the kind of research uses to which the tissue may be applied. Researchers have a legal and ethical obligation to honour such stipulations. Only research of the kind to which the consent relates (or covers) should be carried out on a given tissue sample.
- 8.7. If it is likely that donated tissue samples will in the future be made available for commercial research with consequent financial benefit or gain to third parties, we suggest that this possibility be made clear to donors at the very outset even if the arrangement is to be that the donors completely renounce their rights to any share of these gains or benefits. In this respect, we note the governing common law principle that informs the letter of the law of both the Human Organ Transplant Act, and of the Medical (Treatment, Education and Research) Act: no person may enter

into a contract for the sale of his body, or any part thereof, including organs, tissue or blood. No person is under any compulsion to give. Nor is any person under an obligation to accept a gift. Again, we emphasise our view that where there is uncertainty as to whether a given potential gift is absolutely unconditional, it would be ethically prudent for a researcher or research tissue banker to decline that gift.

- 8.8. We think that it is unethical to take consent from a donor who may be under the impression (even if such an impression is completely without foundation) that the best efforts made for his or her therapeutic or diagnostic benefit might depend on or be affected by the giving or refusal of consent to the donation. For this reason, where a primary purpose or objective of the taking of the tissue is research, it is important that the consent form for the donation of human tissue samples for research should not form part of the consent form for the taking of the tissue for therapeutic or diagnostic purposes. A physician's objective in taking tissue for therapeutic or diagnostic purposes (or both) from his or her patient is for the welfare and benefit of his or her patient. This objective is an intrinsic and inalienable part of his legal, ethical and professional duty to his or her patient. This objective is quite different from that of a researcher who takes tissue from a donor for the purpose of research. Those who take tissue have an obligation to ensure that prospective donors fully understand and appreciate this fundamental difference in the nature of the objective and purpose between the two kinds of taking, as well as the different uses to which the tissue may be applied. For the avoidance of any conflict of interest (or potential for, or appearance thereof), when tissue is to be taken from a patient with research as one of the primary objectives in addition to therapy or diagnosis, we recommend that separate people should be responsible for the taking of consent for the separate purposes of therapy (or diagnosis, or both), and of research. This means that if research is one of the primary purposes of the proposed taking of the tissue (in addition to therapy or diagnosis), the consent for the taking of the tissue for the objectives of therapy or diagnosis should be undertaken by the donating patient's attending physicians. Then, and separately, consent for the taking of the same tissue and for its use should be the responsibility of the researcher or research team seeking the gift and the use of the tissue in research.
- 8.9. We note, however, that in a large proportion of cases, patients who have tissue removed for therapeutic or diagnostic reasons (or both) are willing to give their informed consent (after being given full information and disclosure) for the archiving or accession of their tissue samples to a research tissue bank for future research after the objectives of therapy or diagnosis are exhausted or satisfied. In these kinds of situation, the primary purpose for the taking of the tissue is clearly therapy or diagnosis.

The purpose of research is only incidental in such cases to the primary purpose of therapy or diagnosis. In such cases, where research is not the primary or immediate objective of the taking, we think that it is permissible for the attending physician who takes consent for the taking of the tissue for therapeutic or diagnostic purposes to also take consent for the use of the tissue, after the therapeutic or diagnostic purposes are exhausted or satisfied, for research purposes.

- 8.10. Blood, urine and other biological fluids which are collected non-invasively without surgery for the purposes of clinical diagnosis may be useful for research purposes. Given the large number of samples routinely taken of blood, urine and other biological fluids for the purposes of clinical diagnosis, we think it would be impractical to require doctors to ask for consent for possible future research use in every case. Exceptionally, we think that the rights of patients in such circumstances can be adequately protected by controls such as requiring appropriate institutional ethics committee or institutional review board approval for applications for research use, and by requiring that such research use do not compromise the confidentiality of the personal information of individual donors (this could be done, for example, through appropriate anonymisation procedures). If the blood, urine or other biological fluids is taken with research as the primary purpose, our observations and recommendations in this Section otherwise apply.
- 8.11. Donors should be free to decide whether their gift should be a general one (in that the gift may be applied towards any research use or purpose), or for a specific (and specified) limited research use or purpose only. Where the intention of the donor is that the gift should be for an unrestricted general research use or purpose, one way of simplifying the procurement of consent may be to have a system in which consent is completely delinked from any particular research purpose. In this system, the donor makes an outright gift of tissue to a specified research tissue bank. The terms of the consent should make it clear that the gift is not to be linked to or be conditional upon any particular research use or purpose. It should also be made clear to the donor that research applications are reviewed and approved by an independent ethics review committee or body. This arrangement may obviate any subsequent argument that the consent given by the donor did not cover the specific research use to which the tissue was subsequently applied.
- 8.12. Such an arrangement would also go a long way to solving the issue of whether "reconsent" is required when tissues originally acquired for a specific research purpose is subsequently sought for use in another, and there is doubt as to whether the original consent covers the subsequent use.

- 8.13. It is beyond our remit for us to suggest how the requirements of valid consent may be formally met. We cannot prescribe the particulars of how consent should be obtained, and we take the view that it is the responsibility of institutions to work out their own consent procedures and consent forms with their legal advisors, and to train their staff accordingly.
- 8.14. In taking the consent, especial attention is necessary to ensure that donors fully understand what is proposed to be taken, particularly if gross human tissue samples (e.g. entire organs or blocks of organs, or of limbs, as opposed to tissue slides or small tissue blocks) are involved. Gross human tissue samples may be viewed in a very different light from small human tissue samples by the public. The issue of respectful and appropriate methods of disposal for such gross human tissue samples may have to be considered by the custodians of such samples when they are no longer needed and de-accessed from the bank or collection. Researchers and institutions having responsibility for the custody, use and disposal of such tissues should at all times be sensitive to social, cultural and religious sentiments relating to the treatment, use and disposal of such tissues.
- 8.15. We also think that researchers and tissue bankers should bear in mind that consent to the taking, and consent to particular uses are two quite separate things. Consent given for the taking of tissue for a specific purpose does not necessarily authorise the use of the tissue for a different purpose.
- 8.16. Similarly, human tissue taken originally under statutory authority (for example, a post-mortem examination carried out on the authority of the State Coroner) for a statutory purpose, should not be used for other purposes once the statutory purpose has been exhausted, unless consent has been obtained for uses not covered by the statutory authority.
- 8.17. At law, a failure to take consent for taking of tissue may not only amount to a civil wrong (a tort), but in some circumstances may also amount to a criminal offence. The current law is less clear in relation to very small samples taken without any invasive methods (for example, by the interception of material intended for disposal). In this regard, we note with interest the recent recommendation made by the UK Human Genetics Commission that “consideration be given to the creation of a criminal offence of the non-consensual or deceitful obtaining and/or analysis of personal genetic information for non-medical purposes”¹.

¹ UK Human Genetics Commission, Inside Information: Balancing interests in the use of personal genetic information May 2002.

9. Consent and Legacy Tissue Collections

- 9.1. A special difficulty faced by tissue banks in Singapore and in the rest of the world is posed by the existence of large collections of tissue samples accumulated over many years for which no specific or adequate consent for research investigations has been obtained. In the vast majority of the cases, the original donors can no longer be reliably traced for consent to research, or such tracing may no longer be practicable or socially acceptable (for instance, in the case of very old collections in which there is a strong likelihood that many of the donors may have since died, especially if the sample tissues were originally taken for diagnostic purposes in relation to conditions such as cancer). We refer to these collections as legacy tissue collections.
- 9.2. These legacy tissue collections, by virtue of their sheer size and range of coverage, are often very valuable to academic and commercial researchers alike.
- 9.3. While some have advocated the extreme view that no research use should be made of these legacy tissue collections, we take the view that it is not in the wider public interest to suggest a blanket ban on access to these collections by researchers. We take the view that it is unreasonable to expect those who have assembled such collections in good faith for the advancement of medical knowledge to have divined the importance now placed on consent.
- 9.4. We take the practical approach that tissue collected in good faith at a time when there was a lack of any clear ethical, professional or legal guidelines governing the collection of such tissues is not something to be condemned: it is not the fault of medicine that the law and bioethics often lags very far behind the reality of medical practice and technology. In the absence of guidance from the law, or from an established canon of bioethics, medical workers and researchers can only act in good faith according to the best professional practices of the day.
- 9.5. On this basis, we take the view that it is consistent with good stewardship to allow reasonable and respectful research use of such legacy tissue collections for the greater public good.
- 9.6. It is one of the recommendations advanced by us in this Report that steps should be taken to formulate a national ethical policy governing research access to such legacy tissue collections. There may be a possibility that legislative intervention may be necessary to cure the defect stemming from problems with the lack of consent. Otherwise, the scientific value of these legacy collections may be severely impaired by the need to maintain

separate access guidelines for legacy tissues and those tissues for which appropriate and adequate consent has been obtained.

10. Confidentiality

- 10.1. Confidentiality lies at the heart of the physician-patient relationship. A common theme of the position papers and representations submitted to us is the acceptance, as a fundamental controlling principle, of the donor's right to privacy and confidence.
- 10.2. In relation to genetic information derived from human tissue, the obligation of confidentiality is one which is universally recognised. Article 7 of the 1997 UNESCO *Universal Declaration on the Human Genome and Human Rights* requires that "[g]enetic data associated with an identifiable person and stored or processed for the purposes of research or any other purpose must be held confidential in the conditions set by law". The World Health Organisation has proposed that "[g]enetic data should be treated as confidential at all times. Genetic data should only be used to advantage and empower an individual or family, and for better treatment or prevention of disease. Data relevant to health care should be collected and kept by medical geneticists in secure confidential files"².
- 10.3. We agree that researchers and research tissue bankers alike have an obligation to protect the confidence and privacy of donors.
- 10.4. We further note that the general obligation of confidence is one which is protected by the general common law principles applicable in Singapore. In certain specific circumstances, some aspects of the obligation of confidence may be mandatory under statute.
- 10.5. Confidentiality and consent are closely interlinked and interwoven issues. The common ground between them is that both spring from the obligation to protect and respect the dignity and autonomy of patients and donors. In this respect we note that the UK Medical Research Council has examined confidentiality issues in medical research at length in their report on *Personal Information in Medical Research* (October 2000).
- 10.6. The MRC took as their first governing principle that:
 "Personal information of any sort which is provided for health care, or obtained in medical research, must be regarded as confidential. Wherever possible people should know how information about them is used, and

² World Health Organisation, Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services 15-16 December 1997 (WHO/HGNG/GL/ETH/98.1).

have a say in how it may be used. Research should therefore be designed to allow scope for consent, and normally researchers must ensure that they have each person's explicit consent to obtain, hold and use personal information. In most clinical research, this is practicable."

- 10.7. In our view, however, the requirements of consent and confidentiality should not be applied inflexibly and blindly to all circumstances. If the central common purpose of the general obligations of consent and of confidentiality is the protection of and respect for the dignity and autonomy of patients and donors, then there may be special circumstances in which specific departures from the general rule of these two obligations may be permissible, so long as the central common purpose of the obligations is preserved.
- 10.8. For example, strict adherence to the principle of privacy and confidentiality may be difficult to square completely with other equally compelling objectives. In other cases, it may be difficult or impossible to recontact the donor or the donor's family for consent (or re-consent) to further research, or it may be socially unacceptable to do so (for example, if there is a strong likelihood that the donor may be dead). We think that in these and in other situations where consent or re-consent may be impossible or difficult to obtain, it is permissible for researchers to consider the use of anonymised data arrangements or data-escrow arrangements as may be approved by appropriately-constituted ethics boards or institutional review boards.
- 10.9. In these and other similar arrangements, the object is to preserve the confidentiality and privacy of the donors. The central common purpose of the general consent and confidentiality requirement is not compromised. We recommend the use of such arrangements where practicable, and where the scientific objectives of the proposed research will not be compromised.

11. Approaches to Governance

- 11.1. Given the current pace of developments in the genetic and genomic sciences, we do not think that it is appropriate to resort to hard-coding specific rules in legislative form for the regulation of research and commercial activity in the genetic and genomic sciences. Overly-specific rules run a risk of rapid obsolescence, and of abuse by those minded to be seen to comply only with the letter but not the spirit of the law.
- 11.2. In general, we recommend legislative intervention only in situations where it is clear that effective professional self-regulation and a fair balance of

rights and interests between individuals and the public in encouraging research cannot be achieved without legislative teeth.

- 11.3. We think however that there is a role for carefully targeted legislative assistance in the form of enabling legislation (as in our suggestion in relation to the statutory remedying of consent for research access to legacy tissue collections), and in empowering appropriate Government agencies to exercise a supervisory jurisdiction as gatekeepers over certain kinds of activities in relation to research tissue banking.
- 11.4. In the context of the genetic and genomic sciences, we note that one particularly obvious gateway is the research tissue bank itself. Researchers, whether they be commercial or academic researchers, and whether they be currently regulated under the various medical Acts or by the Ministry of Health, require access to collections of physical tissues for their work. This being the case, we suggest that appropriate legislation for the control and supervision of this gateway, through the appropriate Government agency being given an approval and supervisory jurisdiction over the establishment and conduct of research tissue banking, would be a flexible and efficient means of basic control over the genetic and genomic sciences in Singapore. An important advantage of such a regime would be that non-medical researchers (who are not subject to the current provisions of the Private Hospitals and Medical Clinics Act) and medical researchers alike would be subject to the same set of such operational and ethical guidelines as may be imposed by the appropriate authorities, and thereby operate on a level playing field.
- 11.5. In the HSR Report, we recommended (in Recommendation 8 of the HSR Report) that a statutory authority be set up to license, control and monitor all human stem cell research conducted in Singapore. If such a statutory authority is to be eventually established for the regulation of human stem cell research, it may be appropriate for this statutory authority to be given the supervisory and licensing jurisdiction over research tissue banks in Singapore as well. Such a statutory authority should be given sufficient powers of direction, enforcement and supervision, so as to enable it to effectively give ethical and legal direction for the conduct of research tissue banking in Singapore, to ensure compliance with such direction, and such other relevant rules, standards and codes of conduct, to establish and maintain proper operational governance, as well as to protect the interests and rights of patients, donors and their families.
- 11.6. As explained in Section 5, our preference and recommendation is for a system which emphasises institutional responsibility and good internal self-governance, and the promotion of adherence to the spirit rather than to the letter of the law. We think this can be best achieved through the

licensing of responsible institutions with proven and acceptable systems of self-regulation rather than through the direct regulation of individual researchers and tissue collections by the statutory authority.

V. RECOMMENDATIONS

12. In this Part, we set out our current recommendations arising out of the matters discussed above. We emphasise that these recommendations should be viewed as our considered responses to the challenge of the development of a sound body of ethical guidance and professional best practices in the current circumstances. Research tissue banking is a rapidly evolving field in Singapore, and we expect that over time, new issues and new questions in the social, ethical and legal spheres will arise and require resolution. On many issues, such as the issue of legal property in the body, there is still a lack of international consensus and an absence of clear law both locally, as well as internationally. We also emphasise that not all the issues raised in this Report can find an immediate solution in either ethics or the law, let alone both, and that some of them can only be resolved after further professional and public debate and dialogue, and with a better understanding of the issues involved, as well as the needs and concerns of the relevant participants.

13. WE RECOMMEND THAT:

Recommendation 1: Governing Ethical Principles

13.1. As a starting point for this dialogue, we recommend the adoption of the following principles in the conduct of research tissue banking¹:

1A. Primacy of the Welfare of the Donor

13.1.1. The health, welfare and safety of the donor shall be the paramount consideration in the taking of any tissue.

Where tissue is being taken primarily for a therapeutic or diagnostic purpose, research considerations should not be allowed to compromise or prejudice in any way the primary purpose of the taking. Where a tissue sample has been taken primarily for the purposes of diagnostic procedures, no further sub-sample should be taken from the main sample for the purposes of research until the diagnostic procedures are satisfied, or unless the diagnosing pathologist certifies that the taking of the sub-sample will not compromise the main diagnostic purpose of the taking of the main tissue sample. Where the taking of the tissue is primarily for the purpose of research, such taking and research should only be

¹ A number of these principles are adapted from the Report of the UK Medical Research Council entitled Human Tissue and Biological Samples for Use in Research: Operational and Ethical Guidelines (January 2001).

proceeded with if the potential benefits of the taking outweighs the potential risks to the patient. All living donations involve some degree of risk to the donor, although in the vast majority of cases, this risk will be negligible.

1B. Informed Consent

- 13.1.2. No tissue shall be taken, or shall be accepted, unless the full, free and informed consent of the donor has been obtained. Our remarks in the section on Consent above applies, as well as the exceptions noted thereto.
- 13.1.3. Clinicians and researchers should not assume that tissues left over following diagnosis or treatment (described as surplus to clinical requirements) may be used for research. Patients may be under the expectation that any waste tissue will be disposed of appropriately, and may object to the use of such tissue for research, or to their inclusion in a research tissue bank. The appropriate consent as outlined in the section on Consent above should be sought, and obtained.
- 13.1.4. Special attention should be paid to the legal and ethical resolution of consent issues in relation to legacy tissue collections. Where such resolution cannot be satisfactorily achieved, we recommend separate regimens of access for the legacy and non-legacy portions of a research tissue bank holding both kinds of tissue. We take the view that it is consistent with good stewardship to allow reasonable and respectful research use of such legacy tissue collections for the greater public good, and recommend accordingly. We repeat our comments in relation to legacy tissue collections in the section on Consent and Legacy Tissue Collections above.
- 13.1.5. We recognise, however, that there are arguments that in specific situations it may be ethically acceptable to proceed without consent provided that sufficient precautions are taken for the protection of the privacy of the patient and the patient's family. For instance, this may be achieved through appropriately designed anonymisation procedures or data escrow arrangements as may be approved by the institution's ethics committee or review board. We also recognise that it may be impractical to apply the principle of informed consent in its full force to legacy tissue collections, or to research tissue banks in which the legacy tissue material cannot be reliably separated. In these cases, a national ethical policy may have to be worked out as suggested in paragraph 9.6 above.

- 13.1.6. Research tissue banks should develop and have in place electronic database systems that will enable the consent status and consent conditions (if any) of every human tissue sample to be tracked.

1C. Respect for the Human Body

- 13.1.7. Ethics, the law, and the cultural and religious traditions of our society are all in agreement with the principle that the human body and its remains are to be treated with respect. Researchers and tissue bankers need to be sensitive to religious and cultural perspectives and traditions, and should in particular be aware that whole cadavers, limbs or gross organ parts are viewed in very different light from small tissue samples by lay persons. Researchers and research tissue bankers should always ensure that donors and the families of donors fully understand the extent of the intended gift. For example, the term “tissue” should not be used without further elaboration and explanation if in fact it is intended that limbs, organs or substantial parts of organs or limbs are to be taken. Especially in the case of gross tissue samples, donors or their families should be consulted in advance of the donation as to their wishes for the appropriate disposal or return of surplus tissues when these are no longer required.

1D. Donations to be Gifts

- 13.1.8. Donations of tissue samples for use in research should be accepted only if they are given as outright gifts. Gifts of tissues should be accepted only on the basis that the donors renounce any claim to property or rights in tissue that they choose to donate. Donors should be informed of this principle, and if they do not agree, their donation should not be accepted. As a corollary of this principle, it should be made clear to donors that they should not expect any personal or direct benefit from the donation of tissue, including information of any medical condition or predisposition or likelihood of such discovered in the course of research on the sample, unless this has been agreed upon in advance of the donation of the tissue. Likewise, researchers and research tissue bankers should not be under any obligation to disclose such information to the donors, unless they have agreed to do so in advance of the donation. If a donor is not prepared to make the donation on the basis of an outright gift, then we recommend that the donation be declined.
- 13.1.9. Although donations are to be in the nature of outright gifts, the use of such tissue (except legacy tissue) must remain governed by the terms of the consent to the donation: researchers should ensure that the proposed use of a given sample of human tissue is covered

by the terms of the consent. Donors should be free to choose between making a general gift (which may be used for any research purpose) or a restricted gift (which may be used only for research purposes specified by the donor). Where the intention is for a general gift, it may be appropriate to ask for consent to be given for any and all research purposes as may be approved by a properly-constituted ethics committee or institutional review board in accordance with any rules, standards or codes as the relevant authority may lay down. To this end, effort must be made in good faith to give the donor or the donor's family a fair picture of the principal uses which the tissue is likely to be put to, with the caveat that new uses not within current contemplation or practice may and are indeed likely to arise in the future. In certain cases, it may be that re-contacting a donor (or the family of a deceased donor) for re-consent may itself be an impractical or insensitive exercise: in such cases, the ethical review board of the relevant institution should give guidance to researchers as to whether such recontact and re-consent may be dispensed with on a case-by-case basis.

- 13.1.10. Donors should not be paid any financial incentives for the donation, although they may be given reasonable reimbursement of any expenses incurred in the donation of the sample.

1E. Ethical Review of Research Proposals and Access Requests

- 13.1.11. All research using human tissue samples should be approved by an appropriately constituted research ethics committee or institutional review board. Especial attention must be paid to the independence and integrity of such committees or review boards, and any conflict of interest (whether real or potentially real, or even the semblance of a conflict of interest, even if such semblance is in fact unfounded) should be scrupulously avoided. The appointment, and constitution of such ethics committees or review boards should be as transparent as is practicable.

1F. Confidentiality

- 13.1.12. Researchers and all those involved in the conduct of research tissue banking have an obligation to protect the confidentiality of the personal information of donors, as well as the privacy of donors. Consent must be obtained from the donor (or from his or her family, if deceased) for the release of any personal information to researchers or to any third party.
- 13.1.13. Researchers and all those involved in the conduct of research tissue banking also have an obligation to protect the confidentiality of personal information given to them by donors about other

individuals who are not themselves donors, as well as the privacy of such individuals. Scientifically valuable information is often given by donors of tissue samples which may relate to individuals other than the donor himself or herself. Commonly, a donor may be asked to provide details of the medical history of family members. Researchers should recognise that such information and such individuals should be accorded the same respect and protection as accorded to the donor.

Recommendation 2: Institutional Research Tissue Banking

- 13.2. Subject to our views as set out in Section 5 above, we recommend that research tissue banking should be conducted only by institutions such as may be approved or licensed by the proposed statutory authority to do so, and not by private individuals or groups of private individuals.

Recommendation 3: Operational Aspects of Research Tissue Banking

- 13.3. We recommend that all research tissue banks should be licensed by a statutory authority, which should be conferred the appropriate supervisory jurisdiction. No research tissue banking should be carried out without the licence of the statutory authority. The statutory authority should be given sufficient powers of direction, enforcement and supervision, so as to enable it to effectively supervise and give ethical and legal direction for the conduct of research tissue banking in Singapore.
- 13.4. Institutions that conduct research tissue banking should have in place transparent and appropriate systems and standards for the proper ethical, legal and operational governance of research tissue banking.
- 13.5. Such systems and standards might include, but need not necessarily be limited to:
- 13.5.1. The formulation of clear and transparent written ethical guidelines and policies for the operation of research tissue bank and the governance of their research tissue banking activities;
 - 13.5.2. The formulation of clear written Standard Operating Procedures for the day-to-day operations of the research tissue bank, with especial attention being paid to ensure the integrity and biological safety of the tissue holdings;
 - 13.5.3. The establishment of an appropriately constituted research ethics committee or institutional review board to oversee requests for

research access to or the use of human tissues, on clear, objective and transparent criteria;

- 13.5.4. The provision of a proper system for periodic and impartial census and audit, and a proper inventory system for their tissue holdings and for research accesses to the holdings;
- 13.5.5. The working out of simple and clear procedures and proper documentation of the required consent process in consultation with their legal advisors;
- 13.5.6. The establishment of clear and written policies for the sharing of research tissue bank resources with other tissue bankers and researchers;
- 13.5.7. The establishment of written procedures and policies for the culling and appropriate disposal of unneeded human tissue samples from the bank;
- 13.5.8. The establishment of legally and ethically adequate and acceptable systems to protect and safeguard the confidentiality of personal information of donors, and the privacy of such donors and of any other individuals (not being donors themselves) whose identity or personal particulars to which such information may relate; and
- 13.5.9. The establishment of a system for the periodic reporting of activities to those who have overall responsibility of the larger institution to which the research tissue bank belongs.

Recommendation 4: Initiating An Ethical Dialogue

13.6. Given the background of a rapidly shifting and evolving body of ethics, legal rules and opinion governing human tissue research and banking in the leading scientific jurisdictions, we recommend that a continuing professional and public dialogue be initiated towards:

- Settling the principles which should guide the conduct of tissue banking, against the background of evolving consensus on these principles in the leading scientific jurisdictions, and
- Achieving an early resolution of the legal and ethical questions in relation to the ownership, custody and property rights to donated human tissue.

- 13.7. This dialogue should be undertaken with a view towards ensuring the harmonisation of our laws with accepted international best practice and consensus on relevant legal doctrines and principles such as are being developed in the leading jurisdictions around the world.
- 13.8. While we expect that most of the input in the dialogue will come from professionals in the life sciences, we also recommend that the views of the public be sought. This Report is issued by us as part of that process.
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APPENDICES

Appendix A : Human Genetics Sub-Committee

Appendix B : Position Papers

Appendix C : BAC *Human Tissue Research* Consultation Paper

Appendix D : BAC *Human Tissue Research* Consultation Documents

- Distribution List, 27 February 2002
- Written Submissions received by the BAC

Human Genetics Subcommittee

Chairman

Associate Professor Terry Kaan Sheung-Hung
Faculty of Law
National University of Singapore

Members

Mr Jeffrey Chan Wah Teck
Principal Senior State Counsel (Civil)
Attorney-General's Chambers

Dr Samuel Chong
Department of Paediatrics
National University of Singapore

Dr Ong Toon Hui
Director
Elderly Development Division
Ministry of Community Development and Sports

Professor Yap Hui Kim
Vice-Dean, Research, Faculty of Medicine
National University of Singapore

APPENDIX B

POSITION PAPERS

- Human Tissue for Biomedical Research
Chapter of Pathologists, Academy of Medicine, Singapore
- Testing of DNA and Tissue in Human Research
Dr Edison Liu, Executive Director, Genome Institute of Singapore
- Tissue Banking for Biomedical Research
Dr Kon Oi Lian, Director, Division of Medical Services, National Cancer Centre

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Human Tissue for Biomedical Research

1 Introduction

- 1.1 The global demand for use of human tissue in research is growing rapidly and this trend is reflected clearly in Singapore where current demand far outstrips availability. Ethical and legal issues however have yet to be fully addressed.
- 1.2 At the request of the Human Genetics Subcommittee, National Bioethics Advisory Committee, 'tissue' will refer to small tissue samples; however, the Chapter feels that ethical issues raised in this paper would also apply to all other types of human tissue, including samples of subcellular structures like DNA to cells, tissue samples (including bone, muscle, connective tissue and skin), blood, gametes, embryos, fetal tissue, placenta, body fluids and waste (including hair and nail clippings); as well as whole organs.

2 Sources

- 2.1 Human tissue for research may be obtained from living volunteers/ research subjects, who donate their tissue for a specific project.
- 2.2 Provision for anatomical gifts is covered under the Medical (Therapy, Education and Research) Act where it is stated that persons over the age of 18 may donate all or part of their body (the gift to take effect upon death) for any of the specific purposes and donees stated. (Approved institutions as notified by the Minister, or specified individual for therapy or transplant.)
- 2.3 Tissue samples (including blood and blood products, and body fluids) left over from diagnostic or therapeutic sampling may also be harvested or archived for research purposes. Currently this category forms the largest group of archived and banked tissue.
- 2.4 Noncoronial autopsies may also provide a source of tissue for research. This issue has been addressed in the Chapter's Interim Guidelines : Autopsy Practice in Singapore. A copy of this is appended for your information.
- 2.5 Human embryos, eggs and sperm are banked in Singapore. Ethical and legal considerations for this group are not covered in this paper as they are considerably more complex.

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3 Consent

- 3.1 The Chapter is of the opinion that the patient should be informed, and where possible, consent should be taken if any tissue sample is to be used for purposes other than what it was originally removed for.
- 3.2 Validity of consent is well covered in law, and the principles behind recognition of persons authorised to give consent for treatment and operation should apply to donation of 'surplus' therapeutic or diagnostic tissue for research. In the case of tissue removed in an emergency procedure where the patient is not conscious, consent for/lack of objection to donation of tissue for research could be obtained from relatives or family members. In absence of these, the advice of the hospital's ethics review board and tissue review board should be obtained.
- 3.3 For healthy living volunteers, the Chapter feels that the legal age of consent for donation of tissue should follow what is specified in MTERA for donation of body parts; which is persons over the age of 18. Tissue from the mentally incompetent/incapacitated or from those below this age group should preferably not be taken, especially if harvesting of tissue requires any form of surgery or anaesthesia. In exceptional cases, if tissue harvest is contemplated, researchers should ensure that the procedure does not carry any adverse on the donor. Consent must also be obtained from the legal guardians, and approval of the ethics review board of the hospital or institution involved in the study documented.
- 3.4 Where donated tissue, or tissue removed prospectively from volunteers is concerned, the consent is for a particular, specified approved project. In these cases, the question would be whether the initial consent extends beyond the original project. It has been common practice to store collections of tissue (including blood, blood products and body fluids) on completion of the project, with a view to using these for future yet to be specified projects. The principal investigator may also 'share' samples with other researchers. The Chapter recommends that these issues be addressed in the original protocol and that patient consent for, or objection to, archival of specimens and further research (on completion of the original project) be documented. Any further research project (assuming consent is given), should be treated as a new proposal and be submitted for approval by the relevant authorities. (of Section 7, Archived Tissue)
- 3.5 In the case of tissue removed for therapeutic or diagnostic purposes, the consent is usually for the surgical procedure with removal of tissue, for diagnostic or therapeutic purposes. Presently, the use of this tissue for research and other scientific purposes, though widespread, is not formally addressed.

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- 3.6 The Royal College of Pathologists, UK, has recently issued transitional guidelines for handling of 'surplus' tissue arising from surgical procedures. Here the College recommends that 'generic' consent be taken from patients for use of surplus tissue for laboratory quality control and research work and that any research programme utilising this tissue would require the approval of an institutional ethics/ review board. The Chapter fully endorses this view.
- 3.7 The Chapter recommends that 'consent for operation' forms should include an option whereby the patient is able to indicate lack of objection to, or donation of, 'left over' or 'surplus' tissue for medical research. For instance, a consent form may include the following sentences:
'I understand that tissue is necessarily removed and will be submitted for analysis and diagnosis. I consent/do not consent to the donation of this tissue for research, teaching and other scientific purposes.'
- 4 Repositories and Storage
- 4.1 **Storage :** Human tissue may be stored as fresh tissue without fixative, frozen tissue or processed tissue for instance as paraffin blocks or slides. This also applies to blood and blood products, and other tissue or cell samples.
- 4.2 **Repositories:** Tissue holdings exist in many hospitals, institutional and research laboratories in Singapore. The diagnostic laboratories hold tissue samples which have been used for diagnostic purposes and may hold donated or surplus tissue. Research laboratories may hold donated tissue, or surplus archived tissue.
- 4.3 **Diagnostic Pathology Departments :** All institutions and hospitals in Singapore with service laboratories hold tissue blocks and slides, and archived samples of body fluids, blood and blood products. A few may hold wet tissue. Generally these departmental holdings are probably the largest tissue archives in Singapore.
- 4.4 **Diagnostic Departments :** archive diagnostic tissue samples in accordance with current good clinical practice guidelines, the case files (in this case slides and blocks) can be reviewed and perhaps sent for expert opinion. The tissue is kept against the chance that there may be a medico-legal challenge regarding the diagnosis or the possibility that new prognostic and therapeutic markers may be developed, and used during the patient's lifetime. One such example is the use of Herceptin which requires evaluation of a erb B2 expression on the tumour cells. All service departments have standard procedures regarding documentation, minimum retention times, conditions of storage and use of tissue as well as cyclical laboratory audits.

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- 4.5 **Research Departments** : Tissue, blood and blood product holdings in non diagnostic departments are not as well regulated, and is very much dependant on the individual researcher or principal investigator. Because of this dependence, these holdings/research banks are the source of some concern as guidelines for documentation, conditions of storage, identification of biohazards, verification and use of the tissue held are not clearly given nor audited by any professional body.
- 4.6 **Research Collections** : The fate of collections kept by individual researchers under specific grants are influenced by mundane matters such as resignation or prolonged leave of the researcher/principal investigator or lack of funding of the research programme.
- 5 Tissue Banks**
- 5.1 The concept of establishing tissue banks to encourage biomedical research is currently very much in vogue. The Chapter however is concerned at the haste in which such banks are being set up without proper audit and due accreditation of processes. A census of tissue banks/collections in Singapore, and details of their holdings is highly recommended. These should be made known to the hospital or host institution where these holdings reside.
- 5.2 All tissue banks must be properly audited and accredited. There should be a quality programme, on a national level, to ensure "good tissue practices". The Chapter would recommend and support the formation of an ad hoc committee involving regulators, professional bodies and the biomedical industry with a view to register, inspect and accredit tissue banks in Singapore.
- 5.3 All tissue collected need quality assurance control, verification of tissue type and screening for biological hazards. For this, a pathologist has to be involved. The Chapter strongly urges that all tissue banks must have a named accredited specialist pathologist in a supervisory and legally accountable role.
- 5.4 In the case of tissue collected purely for specific research projects, a finite end point and retention time for these specimens must be stated in the research protocol and the disposal of such tissue should be addressed, cf Section 3.4
- 5.5 **Collection of surplus tissue** should take place after examination of the tissue by the reporting pathologist. This is because the legal responsibility of reporting margins, adequacy and extent of resection falls on the pathologist. This is also an important tissue audit issue as the question of unnecessary surgery and excessive harvesting of tissue may arise, especially if the

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surgeon/clinician performing the biopsy are involved in a study that utilises this tissue. Collection of fresh tissue can be facilitated if prior arrangements are made with the reporting pathologist.

- 5.6 If there is chance that these samples are to be archived after completion of the project and possibly used for subsequent projects, this intention must be stated at the time that tissue was harvested. Documentation should include conditions of storage and disposal, presence or absence of linkage to patient identity, and ethics committee approval for other future research projects. cf Section 3.4.
- 5.7 **Central banking** has been mooted in several countries, but issues regarding intellectual ownership, patient consent and ultimate fate of harvested/stored tissue have arisen. This is well addressed in Livolsi's paper. Under the present circumstances, the Chapter does not support the idea of central banking. As all service departments are required to keep good documentation of the extent and type of holdings within their premises, the Chapter suggests that each individual institution be responsible for their own service holdings, but perhaps subscribe to some central data network where availability and location of tissue holdings are listed.
- 5.8 The tissue bank should also be able to audit end users of the human tissue samples supplied.
- 6 Custodianship**
- 6.1 The Chapter is of the opinion that the legal owner of the tissue is the tissue donor himself/ herself.
- 6.2 **Diagnostic Service Departments** : act as stewards or guardians of the tissue on the patient's behalf. Tissue archives in these departments are part of the hospital's medical records. The Chapter's guidelines for ethical laboratory practice states in paragraph 6.5 that as stewards of the patient's tissue, 'the laboratory providing the primary diagnostic analysis is responsible for the maintenance and integrity of archival tissue', and that while researchers should not be prevented from using this tissue, the pathologist must ensure patient confidentiality and also that there is sufficient tissue left over for diagnostic review and for the possibility of subsequent prognostic work up.
- 6.3 The responsibility for upkeep, maintenance, use and audit of research collections should be the responsibility of the institution/hospital/research organisation where the original research collection was approved, or to which the tissue was donated. The institution should have proper documentation of tissue collections under its custody. Although the principal investigator may have immediate daily responsibility for the tissue, the host institution should be the formal custodian.

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- 6.4 **Tissue collections** should not be allowed to be transferred between institutions or researchers without approval of the ethics and institutional boards. Collections of human tissue samples should not be regarded as the 'personal property' of any one individual investigator or team.
- 6.5 For **diagnostic tissue**, the service department has the right to refuse release of this tissue for research projects that have not been approved by the proper ethics/institutional review board, and which have not sufficiently met all the criteria as defined by that particular laboratory.
- 6.6 If **paraffin blocks** are removed from the service record files, there should be some arrangement for these to be traceable at all times, and for these to be returned to the original laboratory when the study is completed. The intellectual property and work of the pathologist/department in identifying the diagnostic tissue for these projects should be addressed satisfactorily in the study protocol.
- 6.7 '**Surplus Tissue**' : Custodianship of material left over from therapeutic or diagnostic procedures rightly lies with the laboratory where the initial diagnosis was made. The Chapter would emphasise that it is only after the pathologist has examined the tissue and the diagnosis made, that the remaining tissue can be considered 'surplus'. In principle, the Chapter feels that this tissue is best managed by the pathology department as this is the very nature of that department's functions. However this is an issue for each individual institution to resolve.

7 Research on Archived Tissue

- 7.1 The Chapter has received several submissions on the definition of 'research' and whether all research projects require ethics committee approval.
- 7.2 The **Royal College of Pathologists UK**, state that as long as the research proposal requires the performance of new or additional testing, this requires the approval of the ethics review board. However, if the 'research' proposal merely reviews and compares old slides and data on files, and has no adverse consequences to the patient, then the project can proceed with a minimum requirement that the review board is informed. The Chapter endorses these recommendations.
- 7.3 For **genetic research**, the Chapter supports the recommendations of the Medical Research Council, UK and the Advisory Committee on Genetic Testing - specifically regarding the necessity of consent for tests and that genetic testing should not be added onto an existing study without consent.

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8 Patient Confidentiality

- 8.1 Tissue banks providing samples to researchers should ensure patient confidentiality. Samples should be nonidentifiable/non linked/ anonymised where possible. In all these cases, however, the original tissue bank should have a comprehensive documentation and a good tissue tracking system.
- 8.2 Reference is made to the Chapter's Guidelines on Ethics of Laboratory Practice where patient confidentiality is addressed. Researchers do not have automatic right of access to patient records. This must be approved by Ethics Review Boards.
- 8.3 Researchers should consider if donors' of tissue samples/research participants wish to be informed of the results of the research project. This should be addressed in the research protocol. This is of particular importance in the case of genetic testing.
- 8.4 If, in the course of the project, a particular individual result reveals a finding of clinical and therapeutic importance, good clinical practice norms would require that there is a clear duty of care to inform the research participant via the clinician responsible for his or her care.

9 Financial Consideration

- 9.1 Donation of human tissue must be free. There should be no financial payment of the donor.
- 9.2 There should be no commercial exploitation of human tissue. The rights of the tissue donor with respect to potential patents and financial profit should be clearly addressed in the study protocol. Customarily, the tissue donor renounces these rights as the proportion of an individual tissue donor's contribution in a study may be impossible to quantify. This aspect however needs be explained and consent documented from the outset, especially if the purpose of the tissue collection is to establish a commercially viable product.
- 9.3 The laboratory providing the tissue banking service should be allowed to recover the costs of the service.

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Appendix

Submissions were invited from HOD, Pathology in various restructured and private hospitals, and from the Chairman Chapter of Surgeons, Academy of Medicine Singapore.

Replies received as of 15th October are appended.

1. Dr Raymond Lin, KKH.
2. Prof Chong Siew Meng, NUS.
3. Dr Roger Qualfe, Parkway Laboratories.
4. Dr Ivy Sng, Singapore General Hospital.
5. Dr Christopher Goh, Chairman, Chapter of Surgeons, Academy of Medicine, Singapore.
6. Interim Guidelines – Autopsy Practice.
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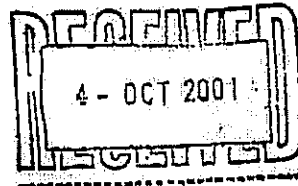
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**KK WOMEN'S
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HOSPITAL**

02 October, 2001



Dr Angela Chong
Chairperson
Chapter of Pathologists, Academy of Medicine
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Dear Dr Chong

Tissue banking

Thank you for your invitation to comment on the use of human tissue for research in relation to the position paper being prepared by the Human Genetics Subcommittee.

In the context of foetal tissue, it may be difficult to draw a distinction between tissue, organs and body parts. I should expect the same principles apply to all three categories. Use of tissue for genetic research should follow the principles set out in the Good Clinical Practice guidelines governing research.

In principle, all research, genetic or otherwise, should be conducted only with the consent of the patient, particularly if the research project has been planned.

For tissues which are archived or stored for diagnostic purposes, but for which future unplanned research might pertain, it would be advisable to include an appropriate clause in the consent form that the residual or archived tissue might be used for research.

Notwithstanding the above consent if obtained, the use of such tissue for research should still be rigorously evaluated by an ethics committee to safeguard the interests of the patient.

In the context of genetic research, a specific consent where applicable is preferred to a general consent for "any genetic research".

Particular care has to be exercised where the objective of the genetic research is not relevant to the reason for which the tissue was obtained. For example, piece of breast tissue being investigated for possible breast cancer oncogenes is different from being investigated for schizophrenia genes.

In all cases, safeguarding the patient's anonymity and privacy is paramount.

Where genetic research results in the propagation of a cell line or in a patentable product derived from the genetic information of a particular individual, explicit consent of the patient or next-of-kin should be sought, or the issue should be brought to a high-level authoritative body for decision. In order for such consent to be obtained, traceability is required. Traceability will then need to be reconciled with the requirement for anonymity.

I have come across a research protocol where the consent is for such-and-such (specific purpose) and "further possible genetic research". This type of proposal and consent should be discouraged.

From the title I presume that the paper will address tissue banking for the express purpose of genetic research. In this case, two important mechanisms must be put in place: policies, rights and consent for tissue banking; consent for research as indicated above.

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I will concentrate only on an aspect which I feel has been insufficiently highlighted. This is the issue of informed consent for. It seems clear that informed consent is necessary when human tissues, or products thereof, are to be commercially exploited. There are several subtleties here though.

- 1) Commercial exploitation requires research and the patient would therefore have to consent to having his tissues researched upon. Insufficient attention, however, has been devoted to examining exactly what constitutes research. Applying a blanket rule that consent is required for 'research' without specifying exactly what constitutes research is likely to cause a complete halt to many research activities currently carried out in pathology departments. Traditionally, pathologists have analysed suitably anonymised tissues in different ways – histopathology deals essentially with morphological analysis while chemical pathologists are obviously involved in biochemical analysis. Does a patient need to consent to these, or other traditional forms, of research, that do not involve molecular genetic analysis? It would seem to me that the area of greatest public concern is genomic analysis and consent should certainly be required for that. Where, however, does one draw the line – would investigation of up- and down-regulation of genes in disease processes e.g. inflammatory conditions, constitute genomic analysis? In any case, it would be difficult to explain to patients that there are different forms of research.
- 2) If consent is not given, can a pathologist then study the features of the patient's disease in the diagnostic tissue sections or samples that have been subjected to genetic (or any other) analysis and publish those results as part of a suitably anonymised series? If one follows the letter of the law, it would appear that this is not possible.
- 3) How is consent to be obtained? A suggestion has been that the consent that a patient gives at time of biopsy be modified to include a statement that the patient does not object to having his tissues researched upon. This consent is kept in the patient's file and not made known to pathology departments. How are pathologists to know whether or not the patient has given consent for appropriate research (whatever that means)? It would be almost impossible for pathologists to keep track of individual consents and would greatly hamper retrospective analysis of tissues.
- 4) To complicate matters, no consent seems to be required for the drawing of blood or the collection of samples of other natural fluids for analysis.

A/Prof Chong Siew Ming
Chief
Department of Pathology
National University Hospital

Shanita

From: "Roger Quaife" <Roger.Quaife@gleneagles.com.sg>
To: <main@academyofmedicine.edu.sg>
Cc: "George Pusavat" <George.Pusavat@gleneagles.com.sg>
Sent: Tuesday, October 09, 2001 11:44 AM
Attach: main1.html; index_gn.html; Nuffield Council Recommendations.htm
Subject: Human Tissue research

Dear Shanita,

Thankyou for asking for my opinion on this subject. I would tend to follow the recommendations of the Nuffield Council and have attached these for your information. In addition, the Clinical Molecular Genetics Society of the UK and the American based Association for Molecular Pathology have views that you may find appropriate. I hope this is of some help. Best Wishes - Roger Quaife.

(See attached file: main1.html)(See attached file: index_gn.html)

(See attached file: Nuffield Council Recommendations.htm)

10/22/01



Singapore General Hospital

Department of Pathology: Tel: 3214930/4931 Fax: 2276562

18 October 2001

Dr Angela Chong
Chairperson
Chapter of Pathologists 2001-2002
Academy of Medicine
142 Nell Road
Singapore 088871

Dear Angela,

Re: Tissue Banking

I apologise for the delay in replying to your request for comments on the above subject. Thank you for sending me your preliminary submission on "Human Tissue for Biomedical Research" which I just received. I enclose my comments on the next sheet. Please keep me informed on the position paper.

With regards.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Ivy Sing'.

Dr Ivy Sing
Head, Histopathology

SI/jn

TISSUE BANKING

1. The Role of the Pathologist

The primary task of the anatomical pathologist when given a surgical biopsy or operative tissue specimen is to ensure that all diagnostic specimens have adequate pathologic examination for the purpose of providing a diagnosis and information that might be required for further patient management. Tissue requirements for pathologic diagnosis, gross and microscopic examination as well as surgical margins and extent of the lesion are of prime importance. These requirements must be met with before the harvesting of tissue for the Tissue Bank. This is to safeguard the patients' interest first and fulfill standard requirements of reporting for oncologic management in grading, staging and prognostic indicators.

2. Tissue Harvesting for Research

Harvesting of tissue for the additional requirement of research should be done by the pathologist or by personnel under direct supervision of a pathologist. Removal of part of an operative specimen before pathologic examination may compromise the diagnosis by affecting surgical margins or by the removal of portions of tissue required for diagnosis. Because pathologists are trained to identify and to separate diseased tissues from intermixed tissues grossly and microscopically, a pathologist must be involved in the quality control examination of tissues obtained for research. All institutional surgical pathologists should be supportive of this effort as in return, a tissue resource or repository will also benefit pathologists who wish to participate in research.

3. Tissue Banking at the Singapore General Hospital – Historical Status

Historically, the Department of Pathology has been the repository for human tissue obtained for diagnosis at the Singapore General Hospital. Tissue selected for diagnosis is stored as embedded tissue in paraffin blocks and the archival tissue is stored at the Department of Pathology at SGH, NUH Department of Pathology and specially leased storage areas. Storage has been for perpetually (about fifty years). Remnant human tissue not used for diagnostic purposes are stored, discarded or both. Pathologists may use the tissue for their own research. Up to now it is presumed that signed consent given by the patient for the surgical procedure to procure tissue for diagnostic purposes has implied within the consent the right to use the tissue whether in paraffin embedded blocks or remnant "wet-fixed tissue" for medical research. The extent of patient informed consent required remains an area of uncertainty and it is hoped the Human Genetics Subcommittee may in time address the issue.

Fresh tissue removed from operative specimens was not taken until storage facilities were available in the nineteen nineties with the availability of special deep freezers (liquid nitrogen or -70°C freezer). The Department of Colorectal Surgery embarked on a research programme whereby tissue from colorectal cancers and other lesions were removed for storage.

In 1998, the Singapore Cancer Centre (now National Cancer Centre) set up a Tissue Bank and embarked on a programme to harvest tissue for research. A Tissue Banking Committee was set up under a Director and comprised members from various medical and surgical disciplines as well as research scientists from the Cancer Centre. Principles and Procedures guiding the workings of the NCC Tissue Repository were set up. I represented the Department of Pathology, SGH on the Committee.

It is necessary in my opinion as a pathologist and echoing the sentiments expressed in the earlier portion of this submission that certain ground rules regarding tissue harvesting for research be stated. They are in Enclosure I. These instructions were formulated after discussion with all the staff pathologists in SGH and the Head of the Department of Pathology.

4. Workings of the Tissue Bank – SGH. Current Status

There are no major problems with respect to conditions of use of the tissue. The details regarding standard procedures, ownership, etc may better be sought for through the Human Genetics Subcommittee seeking further information from the relevant authorities. Problems have arisen when tissue was harvested by non-pathologists, at times surgeons, without the knowledge of the pathologist. This has resulted in the compromise of diagnosis when certain information could not be obtained from the specimen which is cut-up before it reaches the pathologist. In an attempt to assist in providing the full pathological report, I requested that a list of harvested tissue from patients be sent to the Department on a regular basis in order that I might track the tissue for re-assembling should there be difficulty in orientating the specimen or even where the pathology is "missing". The pathologists in the Department are not in favour of having tissue removed prior to pathological gross assessment. There is no disagreement in obtaining tissue for research but there should be no compromise in accurate reporting of specimens. For medicolegal reasons, should the specimen be received with parts removed prior to examination, this should be indicated on the report issued to the surgeon (and patient).

I append a submission, Enclosure II by Dr Kent Mancer, Senior Consultant Pathologist who has had experience in this matter and has worked in various institutions in Canada and U.S.A.

5. Conclusion

My main address has been regarding the workings of tissue procurement from patients for research. I hope the Human Genetics Subcommittee will look into aspects of :

- Maintaining patients' rights with regard to how tissue is used -- looking into the Donation Declaration and informed consent.
- Commercialization of genetic research in a market-driven economy.
- Should the standard consent or permission form contain a clause giving additional consent for the retention of tissue for the purpose of teaching or research.

Submitted by :

Dr Ivy Sng, FRCPA, AM
Head, Histopathology Section
Department of Pathology
Singapore General Hospital

18 October 2001



ACADEMY OF MEDICINE, SINGAPORE

PATRON: PRESIDENT OF REPUBLIC OF SINGAPORE

20th October 2001

Dr Angela Chong
Chairperson
Chapter of Pathologist
Academy of Medicine Singapore

Dear Angela

Ethical Issues on Tissue Banking

Thank you for Inviting us to give our views on tissue banking. The issues related to tissue banking will certainly have an impact on surgeons because we are probably the main source of specimen collection for tissue banking. It is therefore timely that such issues be discussed and a consensus be arrived at.

It is our view that tissues collected for banking should remain the property of the institution and not to the individual. However, to encourage greater participation in tissue banking, some institutions have agreed that tissues collected for banking can only be used for research by the individuals who were responsible for its collection and this is over a stipulated period of time (eg. 2 years). We have no objections to such practices as the tissues are still under the jurisdiction of the institutions concerned.

The other issue for discussion is the method of tissue collection. Our stand on this is that the care and welfare of the patient is paramount and cannot be compromised. We would therefore recommend that all specimens should be sent intact to the pathologist before tissues are taken for banking. This is done to prevent the possibility of sending portions of the specimen which are essential for diagnosis for banking and leaving non-diagnostic specimens for the pathologist.

Another issue which we would like to highlight is that tissues sent for banking should be traceable to the patient from whom it was taken. This is necessary as there may be occasions when new information about the patient is discovered subsequent to tissue collection which may have an impact on those handling the tissues (eg. HIV positive status).

On the other hand, incidental findings of genetic defects or aberrations may be discovered during the course of research work on the banked tissues. We would like to recommend that under such circumstances, the researcher should not be obligated to act on these findings as the work is purely research in nature and should not have any direct clinical bearing on the patient.

We hope that we have been able to contribute in some way to your request. Thank you once again for giving us the opportunity to share our views on these important issues.

Yours sincerely,

Dr Christopher Goh
Chairman
Chapter of Surgeons

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ACADEMY OF MEDICINE, SINGAPORE

PATRON: PRESIDENT OF REPUBLIC OF SINGAPORE

15 October 2001

Dear Chapter Members

INTERIM GUIDELINES FOR AUTOPSY PRACTICE

Enclosed please find a copy of the Interim Guidelines for Autopsy Practice.

These have been drawn up by a subcommittee of the Chapter and are intended to serve merely as guidelines and are not meant to enforce any particular mode of practice or philosophy.

The Chapter would very much appreciate feedback regarding the Interim guidelines.

The final position paper will be prepared after a reply from the Director of Medical Services regarding two specific issues raised.

Dr Angela Chong

Chairperson

Chapter of Pathologists 2001 – 2002

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Chapter of Pathologists, Academy of Medicine, Singapore
15/10/2001

INTERIM GUIDELINES

POST MORTEM AND RETENTION OF ORGANS AND TISSUES IN SINGAPORE

I. Introduction

1. Issues regarding retention of organs and tissues following autopsy have recently been the subject of much concern for practicing pathologists. The legality and the ethics of such retentions were questioned extensively in the United Kingdom during inquiries involving the Bristol Royal Infirmary and the Royal Liverpool Children's (Alder Hey Children's Hospital) Inquiry.
2. Between 1999 and 2001, the Royal College of Pathologists, United Kingdom and the Royal Australasian College of Pathologists have reviewed their practice procedures regarding retention of tissue following post-mortems. In view of this, the Chapter of Pathologists thought it prudent to review the practice in Singapore and to recommend practice guidelines for pathologists involved in non-coronial post mortems.
3. The medical community has the responsibility of keeping faith with patients who consult them. They should not break this trust. Similarly with pathologists, this trust extends to the handling and reporting of tissue samples or organs, whether these tissues or organs be from surgical procedures or autopsies.
4. To address this issue, the Chapter set up a subcommittee comprising two members from the main Chapter Committee, both practising histopathologists, and 3 pathologists from other practices with autopsy services. The members of the subcommittee thus formed are :

Dr Angela Chong, Chairperson, Chapter of Pathologists
Dr Inese Busmanis, Committee Member, Chapter of Pathologists
Dr Chong Siew Meng, National University of Singapore
Dr Paul Chul, Health Sciences Authority
Dr Sim Chee Seng, Changi General Hospital, SingHealth

II. Role of Autopsy

1. The importance of an autopsy or post-mortem examination cannot be denied. Since the early development of medical science, autopsy has revealed much in the way of disease processes and is a much undervalued means of investigation. It is also an audit of clinical practice.
2. Reference is made to the Royal College of Pathologists report on Autopsy and Audit, c 1991, where it is stated that "In a study of 100 intensive care deaths, 10% of autopsies revealed findings, which if detected before death would have led to a change of management".
3. Autopsies in Singapore fall under two categories - coronial and non-coronial. The coronial autopsies are required by law and come under the Criminal Procedure Code. Non-coronial autopsies are performed on request and serve to investigate or confirm the nature and extent of disease leading to death of the patient.

III. Current Practice

1. Non-coronial autopsies : In Singapore these are performed by hospital or private pathologists and include adult, pediatric and perinatal deaths.

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2. Number : The actual number of non-coronial autopsies is small. The large majority of non-coronial post-mortems are perinatal post-mortems, a practice which is directly influenced by the social and cultural practices of Singapore's ethnic Chinese population where the remains of stillbirths and perinatal deaths are traditionally not claimed.
3. Authorisation : Authorisation or consent is usually obtained from the next of kin. This duty usually falls to the requesting physician. Where the body is unclaimed, the law (under Medical Therapy, Education and Research Act) provides for the mechanism to allow post-mortem examinations to be carried out without consent from next of kin.
4. Extent of Examination : A post-mortem examination entails external and internal examination of the body. An internal examination entails removal of organs from the body cavity for examination and includes histologic assessment of relevant tissue samples suspected of showing disease. This provides a better understanding of the disease process or the underlying abnormality. Organs and tissues not retained are returned into the body cavity before release of the body for burial or cremation.
5. Tissue Samples : Diagnostic tissue samples are first taken as wet tissue (tissue which is placed in a fixative such as formalin), processed into wax blocks and sectioned for microscopic examination. Excess wet tissue is subsequently disposed of in accordance with the laboratory's usual procedures, through licensed biological waste contractors.
6. Archival tissue : Whole organs or parts of organs which contain specific diagnostic or unusual changes related to disease, other pathologic conditions or developmental malformations, may be retained and archived for use as examples in teaching or research.
7. Report : Following post-mortem, the pathologist will issue a report of his findings to the attending and/or requesting physician. The physician may wish to release a copy of this report to the next of kin or other physicians involved in the management of the deceased.
8. Cause of Death Certificate : Presently the attending pathologist will issue the Cause of Death Certificate after performing the post-mortem (*cf. Section XI para 3*). In the case of a limited post-mortem, if the cause of death cannot be determined within the limits imposed on the pathologist, the attending physician should issue the certificate.
9. Medicolegal cases : In cases where the attending pathologist feels that there could be a medicolegal issue, the pathologist should inform the Forensic services. (Duty Pathologist, Centre for Forensic Medicine through the duty officer, Police Radio tel : 2256879)

IV. Extent of Post-mortems (Full vs Limited)

1. Questions are occasionally raised as to the extent of post-mortems. It is preferable that any post-mortem that is conducted should be a full post-mortem. This entails external and internal examination of the body and its organs including brain.
2. The extent of tissue sampling, and its importance should be clearly stated and explained. This information is standard and could be made available in a handbook. This would obviate exhaustive lists appearing on the consent/authorisation form.

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3. A limited post-mortem is sometimes requested whereby only a specific organ or a few specified organ systems are examined. The benefits of the full examination should be explained to the relatives before consideration of a limited post-mortem as this may prove inconclusive. This point has to be made clear to both requesting clinician and next of kin.
4. For limited post-mortems, the committee advises that there be clear written indication of which systems are to be examined and what methodology is to be employed. The pathologist should ensure that the post-mortem examination stays within the specified limits.
5. If in the course of the post-mortem it becomes apparent that additional tissue, parts of organs, or whole organs not previously specified need be retained for further diagnostic work up, the relatives or family members should be notified prior to release of the body for burial. There is no legal basis for mandatory retention in a non-coronial procedure.
6. The committee strongly advises against usage of general terms such as 'partial post-mortem' without further clarification.

V. Retention of Organs and Tissues

1. Retention of organs and tissues is a contentious issue. There is great educational value in retained tissue samples and organs. In the past, retention without consent was the accepted 'traditional' practice but the increasing demand for transparency in professional procedures warrant a change in this practice.
2. In the March 2000 issue of Guidelines for Retention of Tissues and Organs at Post-Mortem Examination, the Royal College of Pathologists, United Kingdom states clearly that retention of tissue *must be defensible, open and justifiable in law* and that this practice should be *professionally regulated to high ethical standards*. The committee subscribes to this view.
3. Small samples of tissue taken for histologic diagnosis are part of the patient's records. The committee is of the opinion that these tissues, which are stored as wax blocks and slides should be handled in the same manner as surgical diagnostic tissue and remain the property of the pathology department. Retention of the blocks and slides would then fall under the guidelines and procedures set in place for surgical accessions.
4. Whole organs may be removed for diagnostic purposes. This may be because of special fixation requirements, as in the case of the brain and spinal cord or other reasons. In these cases, there should be documentation that there is no objection from the family, and that they understand that these organs will not be available for burial with the body.
5. For bodies which are not claimed for more than 24 hours after death, provision is given in MTERA for the DMS (Director of Medical Services) to authorise in writing, the use of the body or any specified part for the purposes of medical or dental education, research therapy or transplantation. The department involved is advised to obtain this documentation as part of its standard operating procedures.
6. If retention of tissue or organs is sought for purposes of research rather than diagnosis or education, the committee for this research programme should have prior clearance from a properly constituted Ethics Committee within that institution. For research protocols, the committee advises that the duration of retention of human material be specified.

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VI. Archival Specimens

1. Collections of archived tissue and organs exist in Singapore. These may come from autopsy or from surgical resections and are used for teaching and education of medical and dental students. They are also occasionally requested by various authorities for display at public health exhibitions.
2. The committee feels that such collections should be under the care of a public institution, be it a hospital or a university. These specimens should never be considered, or be allowed to form part of an individual's personal collection.
3. Administrative boards and the senior officers of these institutions should be aware that these collections exist within their domain and that the maintenance of these collections fall within their responsibility. There should be written guidelines addressing purpose and use of the collection, conditions of storage, display and ultimate disposal of the collection or individual specimens within that collection. A responsible and trained senior person should also be named as curator of this collection.
4. Archived organs are rightly used for education and teaching of students of medicine and related disciplines. However noble the intention, the committee feels that public display of the organs should be discouraged. Graphic representation could serve the public health education purposes equally well.
5. A census of current holdings is recommended. This would then form a baseline indication of where these specimens are currently housed and in what numbers. This census should include minimum data such as numbers and types of specimens. If possible, diagnosis (i.e. reason for retention) and year of collection should be included.
6. Future additions to these holdings should be carefully documented and open for audit if and when required.

VII. Period of Retention

1. Archived museum specimens are often kept in perpetuity. Should there be a change in status, these should be disposed of in the proper manner according to the guidelines of that institution.

The committee recommends those conditions of storage and disposal be made known to the family at the point of collection.
2. The issue of diagnostic samples stored as waxed blocks and glass slides has been addressed in *Section V paragraph 3*. The committee recommends that these be governed by the same guidelines and procedures as applies to surgical tissue.
3. In the case of wet tissue, the committee recommends that these be retained for a period of 3 months from the date of issuance of the post-mortem report. Reports should be available not more than 3 months from the date of post-mortem examination. This gives allowance for prolonged fixation and investigation techniques.
4. Wet tissue thus retained should be disposed of in the appropriate manner according to the department's written guidelines. The mode of disposal should be made clear to the estate of the deceased.
5. There may be occasion when relatives/estate of the deceased request for tissue or organs to be returned to them for delayed burial. The committee recommends

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that where possible, the wishes of the bereaved family should be accommodated. The tissue should preferably be delivered to a licensed undertaker of the family's choice as the lay public should not be expected to handle wet tissue or organs in its original form.

6. The committee considered obtaining an opinion from the main religious groups regarding delayed burial of body parts, but in view of the diversity of groups, this was not done. The committee advises that this is an issue that should be discussed on a case by case basis, at the time of consent and the agreed outcome documented for future reference.

VIII. **Authorisation for Post-mortem**

Consent for Post-mortem

1. In Singapore, according to the Medical (Therapy, Education and Research) Act, post-mortems can be authorised in the following manner :
 - a) Any person over the age of 18 may authorise a post-mortem examination of his body, either in writing or orally in the presence of two witnesses for the purpose of establishing or confirming the cause of death or of investigating the existence of abnormal conditions. This authority is effective upon the death of that person.
 - b) The next of kin, in absence of actual notice of contrary indications by the deceased person or the opposition by another member of the same class or prior class as specified in the Schedule, may authorise a post-mortem examination of the deceased person.
 - c) In the case of bodies unclaimed for more than 24 hours after death, the Director of Medical Services may authorise in writing the post-mortem examination of the body for the purpose of establishing or confirming the cause of death or of investigation the existence of abnormal conditions.
2. The person who obtains consent for post-mortem examination should be fully versed with the purposes of the examination and procedures. The committee fully endorses the recommendation of the Royal College of Pathologists, UK (RCPATH) that this person be a senior and properly trained doctor, preferably "the consultant who knew the relatives best during the patient's last illness".
3. The pathologist should not be involved in the taking of consent or authorisation for a post-mortem as issues regarding conflict of interest may arise.
4. The committee recommends that each hospital should designate a professionally trained person to communicate with the family. This person may be medically qualified or be a member of the nursing or allied health profession. The responsibility of adequacy of training and competence lies with the hospital concerned.
5. The committee is cognizant of the sample authorisation/consent form from the College of American Pathologists, which includes the statement "I understand that it is standard procedure in this hospital to remove certain organs and tissues and retain them for education, research and potential future therapies". (attached appendix).
6. The committee is of the opinion that post-mortem consent forms in Singapore should include a similar statement in particular regarding retention of tissue samples for diagnostic, educational and research purposes. The actual details could be addressed in an accompanying information booklet.

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7. In the case of whole organs retained for archival purposes, the committee feels that specific consent for archival purposes should be obtained. In non-coronial post-mortems, there is no medicolegal basis for retention, other than for diagnostic purposes, thus there should be distinction between the status of retained diagnostic tissue and retained archival organs.
8. Authorisation forms should be written in a language easily understood by lay public. The post-mortem procedures, the subsequent examination and retention of tissue should match the expectations and perceptions of what the relatives or family of the deceased have agreed to. A copy of the consent and what was agreed upon could be given to the family for retention and future reference.

IX. Certificate of Cause of Death (CCOD)

1. The law requires a medical practitioner to sign and deliver a death certificate within 12 hours of the death due to natural causes of any patient he has attended to.
2. In the case of a non-coronial post-mortem, pathologists have been mindful of a circular from Dr Kwa Soon Bee (*Circular Prof No 14/75, ORGH 20:05, Standing Order on Death Certification, Coroner's Cases and Authorisation for Use of Unclaimed Bodies*) stating that "when an autopsy is performed with the consent of the relatives, the pathologist will issue the death certificate". (Appendix 3)
3. The law requires deaths where the cause of death is not known to be made Coroner's cases. The committee understands from Dr Paul Chui that the corollary would be that non-coronial post-mortems should be performed only when the cause of death is known. As such it may be argued that the attending clinician should issue the CCOD prior to the post-mortem.
4. In light of this, the Chapter has written to the Director of Medical Services for clarification regarding the current status of the standing orders from Dr Kwa. Pending this, the Chapter advises members to confer closely with their clinical colleagues prior to performance of the post-mortem.
5. In this context, the committee encourages pathologists to include a cause of death statement in the autopsy report. The College of American Pathologists have stated in their Practice Guidelines for Autopsy Practice that it is preferable that certification be completed after a cause of death is determined at autopsy. However the college also recommends that the autopsy report address whether the autopsy findings are consistent with the cause of death as stated on the death certificate.
6. If there is a significant difference between actual and expected findings, the pathologist should recommend that the CCOD be amended.
7. Where the post-mortem discovers a cause of death which is unnatural, the physician should make the case a Coroner's case. The Centre for Forensic Medicine, Health Sciences Authority may be contacted for further advice.

X. Post-mortem Examination of Stillbirths and Fetuses

1. Registration of stillbirths is required by law and these should be managed procedurally in the same manner as a neonatal death. It is useful to note that guidelines regarding the gestational age of stillbirths vary. In Singapore it is taken as 28 weeks (fetal weight approximately 1000g). Australia recommends 24 weeks (fetal weight approximately 600g) while some others recommend 20 weeks gestation as the cut off point.

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2. The committee understands that at present, there is no legal provision for examination of fetuses and abortuses and no guidelines as to what should be considered autopsy and what should be considered as biopsy.
3. In these circumstances, provided legal guidelines regarding definition of still births and neonatal deaths are followed, the committee recommends that the actual demarcation between autopsy and biopsy for births of lower gestational age, should be resolved individually in each hospital's working procedures. These should be clearly documented.
4. The main difference in the practice of pathology regarding what is submitted as a biopsy and what is submitted as a request for post-mortem seems to lie in issues regarding consent and recommended formats of examination.
5. Generally, formats governing procedures in non-coronial autopsy, in particular regarding consent and mode of examination are more regulated and detailed. In addition, many perinatal autopsies are performed in specialised units with specific interests in pediatric pathology and in presence of the attending pediatrician.
6. In the case of biopsy specimens, consent is usually related to the fact that the surgical procedure is performed for diagnostic and/or therapeutic purposes. In the case of abortuses and fetuses the pathologist currently assumes that consent for examination is implied. Furthermore reporting parameters in surgical pathology regarding examination of abortuses and fetuses may not be as well defined as in autopsy pathology.
7. The Royal College of Pathologists' guidelines recommends that "for the examination of fetuses delivered dead, written parental agreement must be obtained regardless of gestational age". The committee supports this view, and would encourage all hospitals to incorporate into the authorisation for termination of pregnancy, a simple line to allow examination of the resulting abortus and placenta.
8. Retention of tissue in the case of surgical biopsies are well set out in all laboratories.
9. Retention of tissue and organs in pediatric and neonatal post-mortems should follow the same principles as set out for other post mortems. If there is a possibility that whole organs are to be retained for diagnostic purposes (and not be available for burial with the body), these organs should be specified and made known to the parents.
10. Again, a simple booklet with relevant information would help in disseminating information. This booklet would have to contain information relevant to pediatric post-mortems.
11. Similarly if fetal tissue is required specifically for research, approval from the relevant Ethics Committee should be obtained. Parental consent should be obtained and this consent for fetal tissue research should be obtained separately from authorisation for termination of pregnancy, as these are two unrelated issues.
12. Tissue or organ collections from pediatric and neonatal post-mortems should be governed by the same guidelines as for any other archival organs (*cf. section VI*). These collections should belong to institutions, not individuals and should have proper documentation.
13. The issue peculiar to Singapore is the examination of fetuses and stillbirths, which are not claimed. In these cases, the traditional view is that the MTERA guidelines (requiring written permission from DMS before any procedure is commenced on

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unclaimed bodies applies). The Chapter has written in to the DMS for clarification on this issue.

14. Although examination of unclaimed bodies are provided for by law, the committee is of the opinion that parents should still be entitled to know if examination of the fetus or stillborn child will take place, if organs are to be removed, and the purpose of removal. This should be explained to the parents and an opt out clause in the notification of no claim is suggested. Again a trained staff member or counselor and an information booklet would be of use in these situations.

XI. Recommendations

1. It must be restated that retention of tissue must be defensible, open and justifiable in law and that this practice should be *professionally* regulated to high ethical standards.
2. A census of all archival tissue collection in Singapore should be conducted. The details of this census should be made known to heads of departments and senior administration of institutions where these collections reside.
3. An information booklet regarding practice of post-mortem and its purpose should be readily available.
4. Consent should be documented for archival retention of whole organs.
5. A list of licensed undertakers should be made available to pathology departments so that retained tissue can be released to them for disposal, should relatives opt for delayed burial.

XII. Outstanding Issues

1. Clarification from Director is pending regarding issuance of Cause of Death Certificate and the status of unclaimed bodies under MTERA. The letter written by the Chapter is appended for information of members.

Chapter of Pathologists, Academy of Medicine, Singapore
15/10/2001

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**Chapter of Pathologists, Academy of Medicine, Singapore
15/10/2001**

Appendix

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2. Letter to Director of Medical Services.
3. Letter to Dr Pwee Keng Ho.
4. Sample Consent, College of American Pathologists.
5. Comments from Dr Norman Walford.

GUIDELINES: ETHICS OF LABORATORY PRACTICE

Prepared by
Working Committee
Chapter of Pathologists 1999 - 2000
Academy of Medicine, Singapore

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1 INTRODUCTION

- 1.1 Pathology is a clinical service which carries out investigations on specimens from patients as an aid to the diagnosis, management and treatment of disease. Departments of Pathology also provide specialist interpretation of the tests and advice.
- 1.2 In Singapore, pathologists are medical specialists recognised and named on the register of specialists kept by the Singapore Medical Council and are governed by the ethical code of the Singapore Medical Council.
- 1.3 The practice of pathology is continually changing. Currently the four traditional branches of pathology - anatomical pathology, microbiology, haematology, and chemical pathology have been joined by an increasing number of subspecialties such as immunology, genetics and molecular pathology. This list and the work undertaken, will continue to expand.
- 1.4 Modern technology has provided improved laboratory information systems and electronic communication. Technical advancements and new methodology have resulted in new ways to investigate, archive and preserve human samples, be it tissue, body fluids and cells or blood and blood products. Pathologists now find themselves gatekeepers of a plethora of information and archival specimens, the value and potential implications of which are not properly understood or specifically addressed in law.
- 1.5 It is the purpose of this paper to highlight possible problems that may arise and suggest guidelines for ethical laboratory practice. Matters pertaining to issues arising from postmortem (both coronial and noncoronial) examinations will be addressed in a separate paper.
- 1.6 From time to time the Licensing and Accreditation Branch, Ministry of Health (previously known as the Medical Audit Accreditation Unit) has also sought the opinion of the Chapter. The Chapter has responded to the best of its ability and the correspondence is appended for reference.

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Chapter of Pathologists, Academy of Medicine, Singapore

GUIDELINES : ETHICS OF LABORATORY PRACTICE

2 RESPONSIBILITY

- 2.1. As a member of the medical profession, the pathologist has professional obligations to his patients, to the profession and to society. This is set out in the Ethical Code of the Singapore Medical Council. (Published 1995)
- 2.2. As a medical laboratory professional, the pathologist has a duty to ensure that tests performed in the laboratory are of a high professional standard, and that the requirements of regulatory authorities and professional organisations are complied with in the laboratory.

3. SPECIMEN ACCESSION and CONSENT

- 3.1 The pathologist should be aware that no medical action or investigation, can proceed without the patient's consent.
- 3.2 The medical laboratory usually receives 'sent in' specimens (tissue, blood, body fluids) with a request for examination. In these cases, the laboratory is entitled to assume that the requesting physician has obtained the requisite consent.
- 3.3 For this reason, the Chapter recommends that pathology laboratories only accept requests/ specimens from registered medical practitioners of good standing. (Ref Appendix I)
- 3.4. Consent is usually inferred when a patient willingly presents himself to the laboratory for a specific test procedure. However the pathologist in charge of the laboratory should ensure that the patient understands the test procedure and the implications of the test.
- 3.5. There may be occasion where a laboratory may decide to process a request from a member of the general public. Should this occur, the laboratory must have medically qualified personnel on site. The import of abnormal tests should be explained and the patient advised to consult, or be given the opportunity to be referred to a qualified, registered physician for further management. (Ref Appendix II)

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4. LABORATORY RECORDS

- 4.1 Laboratory records are part of a patient's medical records and should be treated with the same degree of confidentiality. Unauthorised disclosure of information obtained from patients in confidence or in the course of attending to a patient is a breach of the doctor's professional duty of confidence. However, disclosure may be required by law, or in interests of public safety.
- 4.2 Pathology tests carried out in the medical laboratory are requested by physicians in the course of investigation or treatment and are generally considered a consultation between an attending clinician and the laboratory physician. The pathologist / laboratory on completion of the test usually reports or transmits the results of the tests through the requesting physician.
- 4.3 The Chapter is of the opinion that if a patient is transferred to another institution, or changes his/her primary physician, copies of the laboratory results should ideally be furnished by the original/referring physician as part of the patient's case records. The laboratory is generally not party to the transfer and has no way of corroborating this information.
- 4.4 The laboratory may be presented with requests for test results from other physicians or other hospitals (which were not originally indicated on the request or accession form). The laboratory, in these cases assumes that the patient has been referred for further management and releases results in good faith. In these cases, the Chapter suggests that such requests be accompanied by a simple statement stating that the patient is now under the care of that particular physician and that the patient consents to releasing of results.
- 4.5 All other requests for release of information, especially to third parties e.g. insurance agencies, should be accompanied by written documentation of the patient's consent.

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- 4.6 In the case of genome and DNA testing, similar principles of privacy, confidentiality and security apply. Sampling of DNA for analysis should remain a medical act and be part of medically recognised practice. Results of these tests should be revealed only to the patient and the attending physician. Parents and family members may not have the automatic right of access.
- 4.7 The Chapter strongly recommends that all laboratories should have written guidelines regarding release of information. The laboratory has a right, and duty to first satisfy itself as to the identity of the person requesting information. The laboratory has a right to refuse release of information.
- 4.8 The pathologist/laboratory should also take reasonable precautions to ensure that the method of release of information is secure and reliable. There should be safeguards regarding accidental release of information, including electronic information.

5. DATA REGISTRIES

- 5.1 Disclosure of medical records to data registries e.g. cancer registries, tissue registries, are often asked for. While this is an important resource for epidemiological research, laboratories should be cognizant that there may be legal and ethical issues as regards collection, storage and use of such information.
- 5.2 Release of information regarding infectious diseases, for instance HIV are governed by acts of law and statutory obligations will have to be complied with.
- 5.3 The French National Consultative Ethics Committee advises that laboratories should disclose information only to accredited organisations which have:
- i) guarantees of confidentiality
 - ii) an accountable person in charge
 - iii) policies whereby researchers given access to the information are restricted from contacting patients.
- 5.4 Except where notification is governed by law, the best policy would be to obtain consent from the patient for inclusion into a registry. This is to avoid potential disputes arising between patients and laboratories regarding disclosure of confidential medical records. Laboratories may be held responsible for unauthorised disclosure.

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- 5.5 Pathologists may not have direct communication with the patient. To avoid misunderstanding, the French National Ethics Committee suggests that release of confidential medical information to accredited organisations or registries be made by the attending physician, after first obtaining consent from the patient. Although individual practices may differ, the Chapter would like to bring this arrangement to the attention of its members.
- 5.6 The Chapter suggests that all requests for disclosure of patient data records for research projects be covered by express permission from the ethics committee of their respective institution or hospital.
- 5.7 The ethical principles surrounding keeping and using of medical registers also apply to DNA banks. An individual's genome is part of his bodily person and should be treated with similar respect.

6. HUMAN TISSUE

- 6.1 The pathology laboratory receives specimens e.g. tissue, blood, blood products, body fluids, for analysis and testing. All tissue removed in the course of investigation or therapy should be submitted to the pathologist /pathology laboratory for analysis as diagnosis is of primary importance.
- 6.2 Residual tissue/ blood/ fluids from therapeutic or investigational procedures which are no longer required for diagnostic purposes have traditionally been regarded as 'abandoned goods' and have been used as a source of research / teaching material or as material for clinical controls. This includes excess fluids e.g. plasma from a clinical blood test which may be used in a clinical laboratory to ensure quality of instrument analysis. As these are anonymised and not linked to patients, specific consent is not sought. This is the current accepted practice but as illustrated in the recent revision of guidelines by the RCPATH and as a direct outcome of inquiries such as in Bristol, the legal and ethical rules governing this area is rapidly changing and may need to be reviewed from time to time to ensure conformity with public expectation. Please refer to para.7.3.

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- 6.3 The Royal College of Pathologists and the Nuffield Council on Bioethics have recommended that standard consent forms include the possibility that tissue removed in the course of treatment be stored or used for medical research or education. This would in effect cover the concerns raised in paragraph 6.2. The patient, their legal guardians or other legally authorised persons have a right to refuse this request.
- 6.4 In the case of archived diagnostic material e.g. paraffin tissue blocks, the pathologist has substantially transformed specimens from their original state. The Royal College of Pathologists in 1999 stated that 'The durable material thus produced can be considered the property of the entity which produced them.' Even within this framework, the pathologist or hospital acts as the custodian or steward.
- 6.5 The laboratory providing the primary diagnostic analysis is responsible for the maintenance and integrity of the archival tissue and are hence stewards of the patient's tissue. While researchers should not be prevented from using this tissue, the pathologist must ensure that there are sufficient safeguards regarding patient confidentiality, and also that sufficient tissue is left for diagnostic review or for subsequent prognostication.
- 6.6 Tissue removed expressly for research should have approval from national/institutional ethics boards and must have documentation of informed consent. The interim report from the Bristol Inquiry includes a recommendation that unless tissue removed is to be used only for that one single project, that consent for continued storage and future use also be obtained.
- 6.7 The Chapter joins other pathology associations in recommending that each laboratory should have guidelines regarding provision of tissue (archival or residual) for research, and strongly advises that all projects have been approved by relevant authorities. The laboratory should have the right to refuse release of tissue should any of the above criteria not be fulfilled.
- 6.8 The laboratory must also have guidelines and records regarding proper disposal of excess or discarded tissue.

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7. TISSUE BANKS

- 7.1 Pathologists involved in tissue banking should ensure that the bank has been approved by the Ministry of Health, Singapore. Hospitals, clinics and other entities covered by the Private Hospitals and Medical Clinics Act are required to secure written permission from the Director of Medical Services in advance of starting tissue or sperm banking.
- 7.2 Laboratories should be aware of problems associated with commercial use of human tissue. Laboratories involved in tissue banking should also ensure that the bank has guidelines to prevent misuse and mishandling of tissue and that tissue samples are anonymised.
- 7.3 Generally tissue taken for tissue banking is tissue which has been removed in the course of therapeutic or investigational procedures but is no longer required for diagnostic purposes. The medical community has an ethical obligation to inform patients of how it intends to use this tissue. An informed consent is recommended.

8. CONCLUSION

The World Health Organisation and the Council of Europe states that 'when in the course of intervention, any part of the human body is removed, it may be stored and used for a purpose other than that for which it was removed only if this is done in conformity with appropriate information and consent'. The Chapter endorses this view.

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GUIDELINES : ETHICS OF LABORATORY PRACTICE

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Position Paper on the Testing of DNA and Tissue in Human Research.

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Executive Summary

Singapore wishes to establish the ethical and legal parameters on tissue and DNA research to guide its biomedical research initiative. A critical element in formalizing the trust in tissue-based research is the role of the Institutional Review Board (IRB), and the transparency of the regulatory system. In this position paper, I have proposed a number of solutions that may assist Singapore achieve its goals in the biomedical sciences and propel this country as a leader in the arena of the ethical and social issues of tissue and DNA based research.

1. The Common Pact:

The study of human tissues should be viewed as necessary for citizen health, but the research community must also commit to the notion that their research must have as its goal to improve human health and not simply to satisfy theoretical curiosity.

2. The distinguishing boundaries:

Without this exercise, rules could be promulgated that are either too broad to be interpretable, or too narrow to be useful. In tissue and DNA research, several boundaries define the need for different regulations:

- Therapeutic vs. observational uses of research tissues
- Whole organs vs. tissue fragments
- Germline DNA vs. Somatic DNA
- The study of genes with high penetrance phenotypes vs. those with low attributable risk
- The impact of the test results: community vs. individual risks

3. The regulatory issues:

IRB review for tissue and DNA research is essential for ethical conduct of research. Informed consent, which is the act of informing the subject of the experiment and asking their consent in participating in the study, is deemed appropriate when research may have adverse outcomes to the subjects. There are mechanisms (establishment of a formal data escrow system, case-based precedents that help guide local IRBs in their decision-making and formalizing the concept of a central or national IRB for the conduct of national studies) that will allow for quality research to be conducted with waivers for informed consent and without the need for anonymization, which limits the utility of clinical material.

I propose that clear guidelines be developed for the use of previously consented patient materials by defining the requirements for reconsent. Inherent in this proposal is my belief that reconsent is unnecessary in many situations as the data escrow systems can be an alternative to provide the confidentiality necessary to permit the issuance of a waiver for reconsents.

I propose that research on somatic changes, or involving genes associated with limited hereditary phenotypes be exempt from obtaining re-consent. Those that specifically target germline mutations with obvious and adverse phenotypes should obtain informed consent/re-consent. The local IRBs *with national guidance* are suited to make these distinctions.

There is no specific right to ownership of tissues for the patient once the tissue has been separated from the body and after permission has been given through a clear informed consent process. The institutions funding and collecting the tissues are the owners and has ethical responsibilities with this ownership.

4. Proposals for the governance of Singapore's tissue and DNA research:

I propose the following platforms for confidentiality: *data escrow and honest broker/agent*. The data escrow structure is that an impartial third party, that is not the researcher, keeps the tissue/DNA "identifier key". I believe that Singapore is uniquely suited to initiate one of the first public domain data escrow platforms and become a world leader in this technology. I believe that the data escrow system coupled with key mediators whom I call honest brokers (akin to data safety and monitoring board members), can establish a coded link between a tissue block repository to disease registry tracking data.

Singapore is highly compact and has a history of social consensus and hence I propose the establishment of a *National IRB* specifically formed to review proposals of comprehensive national scale (many sites) and those employing the linked disease registries, which are national resources. The decisions of this national IRB would be accepted as the overriding decision throughout the country.

A major concern is the forced disclosure of this information by insurance companies, employers, or the government. The key issue is the protection of individuals from loss of job, and loss of medical/health insurance because of genetic tests either performed for clinical care, or in the course of research. I believe that there are several legislative options for Singapore that can balance the protection of citizen privacy: laws to protect insurability and certificates of confidentiality.

Lastly, I propose to further clarify the requirements for informed consent and re-consent with the following extended guidelines:

- The informed consent and re-consent are required when therapeutic interventions, physically accessing new tissues for research, or new information gathering requiring direct patient contact are considered.
- Informed consent and re-consent are required if the research on archived samples seeks to test germline mutations in highly penetrant phenotypes, and to link these results to clinical data and patient identifiers.
- Informed consent and re-consent/IRB review are not required when samples are anonymized.
- Informed consent and re-consent can be waived: (a) If the patient will not be re-contacted and if the test does not involve interrogation of germline DNA mutations associated with highly penetrant phenotypes. (b) If the linkage between the patient identifier and the test outcome can be sufficiently obscured by electronic means and the use of Data Escrow agents. This guideline specifically permits the use of coded information without informed consent or re-consents since the primary investigator will not have access to unique identifiers of each patient. It is therefore important for the Singapore BAC to clearly define the acceptable parameters for such a Data Escrow interface.

Consent, confidentiality, and IRB oversight are the cornerstones of ethical regulation in tissue and DNA research. My major criticisms of the recent US system governing tissue and DNA research have been that the regulations do not recognize the differences between the varying forms of tissue/DNA based research and that there have been no definitive structural mechanisms within the IRB system that seeks to resolve overarching conflicts and controversies. Singapore, through the current BAC process, has the opportunity to establish a regulatory framework that not only protects research subjects, but also facilitates scientific discovery.

Introduction

The use and the study of human tissues have been the hallmark of medical research since the days of Hippocrates. Dissection of human cadavers for anatomical education was followed by post-mortem examinations as a major tool for the medical observational science. The discipline of histopathology, now considered standard of medical care, was, in fact, an experimental science that led to the 1906 Nobel prizes of Ramon y Cajal and Golgi. Thus, the extension into molecular and genetic technologies for the study of human tissues is in line with a long and tested history of medical research.

Along with this history of advances have also been controversies when research and social customs/religious standards clash. The center of this controversy has been the issue of respect for human remains, which is often interpreted as respect for cultural customs. Dissection of cadavers has been either prohibited or severely limited, and anti-vivisection laws enacted in response to the perceived disrespect during the scientific analysis on human remains. More recently, these issue resurfaced, first with the reaction of families in Ireland upon disclosure that the remains of infants were used for educational purposes, and second with the desire of native Americans to re-inter the skeletal remains of ancestors that have been put on display as archeological finds.

Currently, the issues have been further complicated by the ability of DNA studies to divine the future risk of an individual and his or her relatives to disease. Thus, access to one person's tissue could be interpreted as knowledge of the medical destiny of an entire family. Balancing these concerns, however, is the power of genetic technologies to deliver precise diagnostics, and in identifying the constitutional predisposition to disease. This knowledge will lead to tailored preventative and therapeutic interventions that inevitably will improve a nation's health.

Singapore wishes to establish the ethical and legal parameters on tissue and DNA research to guide its biomedical research initiative. The discussion herein is commissioned by the BAC subcommittee on Human Genetic Testing and will be restricted to comments on the analysis of human tissues including DNA in clinical translational and epidemiological research. I will not be touching on the harvesting of human tissues for the purpose of therapeutics. Because of time constraints, I will not be able to detail the history of the controversies surrounding this topic with significant documentation. Though I hope to be informative in my discussion, I will concentrate on my observations from the perspective of a translational and population scientist, and as a former government official with the National Institutes of Health (USA) involved in governing tissue and DNA based research. From these observations of the critical problems, I will propose a number of solutions that may assist Singapore achieve its goals in the biomedical sciences and propel this country as a leader in the arena of the ethical and social issues of tissue and DNA based research. Much of the supporting information has been provided by my long-time colleague, Lynn Dressler from the University of North Carolina at Chapel Hill through her thesis work in the ethics of tissue and DNA research. This information

is seen in various attachments to this document. I have also appended in Attachment VI comments on this proposal by colleagues in the field so that the BAC can see other opinions as well.

1. The Common Pact

The fundamental ethics for human tissue research are embodied in the Belmont principles: respect for persons, beneficence, and justice. It is also appropriate to extend this discussion for clinical/epidemiological research on human tissues to include three more basic premises:

- 1.1 Clinical and epidemiological research is essential for public health
- 1.2 Clinical and epidemiological research must be done for the public good
- 1.3 Clinical and epidemiological research must be performed in an ethical fashion conforming to the cultural consensus of the population.

The study of human tissues should be viewed as necessary for citizen health, but the research community must also commit to the notion that their research must have as its goal to improve human health and not simply to satisfy theoretical curiosity. This pact between the scientific community and society is the necessary balance that will ensure that only science with impact will be conducted and for society to be reassured that only the best and the most ethical science will be permitted. It is this inherent trust between investigator and the constituent population that builds the permissive environment for tissue-based research. These fundamentals will be important in framing the downstream discussion and the resultant regulations. A critical element in formalizing this trust is the role of the Institutional Review Board (IRB), and the transparency of the regulatory system. A well constituted, and well-funded IRB can provide the imprimatur of community consensus needed in the ethical validation of the research.

This is an unusual time in the history of biomedical sciences. Technology has dramatically accelerated the rate of discovery such that leads pertinent to treating and curing human disease emerge more quickly than the capacity to validate them. The limiting factor is now access to highly annotated tissues from well-structured studies. An important issue to resolve is the reuse of tissues collected from historical studies. The maturity of these investigations allows for linkage to disease and to clinical outcomes without waiting for events to occur which often takes years to decades. Current regulations in the US are unclear about the reuse of these tissue banks. Resolution and clarity will greatly facilitate scientific investigations.

2. Defining the Problem: What are the distinguishing boundaries?

In constructing regulations, it is important to identify the problems these rules are created to solve and the conceptual boundaries they govern. Without this exercise, rules could be promulgated that are either too broad to be interpretable, or too narrow to be useful. In tissue and DNA research, several boundaries define the need for different regulations:

- Therapeutic vs. observational uses of research tissues
- Whole organs vs. tissue fragments
- Germline DNA vs. Somatic DNA
- The study of genes with high penetrance phenotypes vs. those with low attributable risk
- The impact of the test results: community vs. individual risks

2.1 Therapeutic vs. observational uses of research tissue

The collection of tissues for processing to derive therapeutic agents requires a significant level of sophistication to following Good Laboratory Practice (GLP) guidelines. Thus, there is unanimity that such tissues (lymphocytes, organs, etc.) should be procured with informed consent and with IRB review. There is also consensus that tissues obtained for the purpose of

research require IRB approval (e.g., buccal swabs, blood samples). The controversy, however, lies in the analysis of unconsented tissues, primarily tissue blocks or archived tumors, obtained during the course of standard care. Previously, pathologists might perform a study on paraffin-preserved tissues for marker validation without IRB approval and without informed consent. Over the years, the emerging standard in the US is for informed consent to be obtained for these samples unless the tissue blocks are anonymized prior to study. It is implicit that IRB review is needed prior to use of these tissues. Though IRB review is considered reasonable, the need for informed consent is thought to be problematic by many in the scientific field since the cost and time needed to conduct this research becomes prohibitive (impracticable) despite the significant value of this information. Resolution for this problem of consent and re-consent will greatly facilitate clinical and epidemiological research.

2.2 Whole organs vs. tissue fragments

Perception of respect is important in the use of tissues for research. Thus research on tissue fragments has different cultural connotations from research on whole organs, or on whole fetuses. Whole organs and organisms (entire cadavers and fetuses) are thought by many cultures to be spiritually closer to the intact human. However, the focus of this paper is on tissue fragments and important points to be resolved are whether IRB approval is necessary for some forms of tissue research and when informed consent is required. We believe that when dealing with whole organs, entire cadavers, or whole fetuses, IRB approval and informed consent should be required. In this manner community standards will be weighed against scientific importance in a transparent manner.

A separate category of tissue work involves the use of tissues and organs/cadavers for educational purposes. It is my position that educational uses should be governed by the same regulatory standards but with provisions for institutional/departmental approvals. For example, it is unnecessary to require a proposal to be tendered for every course in pathology or histopathology each semester. Instead, consideration should be given for yearly "bundled" approvals for the use of cadavers for anatomy courses, or for tissues in a group of histopathology courses. In all cases strict confidentiality by preventing patient disclosure is required.

2.3 Germline vs. Somatic DNA

Not all DNA research is the same and therefore DNA research should not be regulated in a monolithic manner. The greatest distinction is between the analysis of DNA from germline as compared to DNA from somatic sources. Germline mutations are the genetic defects that are passed on from generation to generation. Somatic mutations are, however, lesions that exist only in the end organ (such as liver), which may then give rise to a cancer. These somatic mutations are restricted to the local tissue and cannot be passed on to other generations. Germline DNA analysis, such as from normal tissues for the purpose of studying heritable conditions has the potential impact not only on predicting the future health of the subject but also the condition of his/her relatives. Mutations in BRCA1 associated with susceptibility to breast and ovarian cancer are examples of germline aberrations with such impact. Somatic DNA/tissue analysis from tumor specimens examines the genetic changes in the tumor that occur during the conversion to cancer. Amplification of HER-2/neu in breast cancers is an example of somatic genetic alteration affecting the behaviour of the tumor but is not inherited. This information does not have heritable implications and therefore is limited to the patient and her condition.

The College of American Pathologists (CAP) grappled with this question of whether genetic information is different from other medical information and determined three characteristics that have been proposed to account for that difference: power, predictiveness, and implications for individuals other than the patient (Grizzle et al. Arch Pathol Lab Med. 123:296-300. 1999, see Attachment I). A qualitative difference between genetic and non-

genetic data is that genetic data may provide information about more than just the individual from whom the data are derived. The CAP group cited that "potential differences in the extent of harm that may result from the misuse of different kinds of medical information and thus there is a need for an operative definition of genetic information." They suggest that genetic tests should be defined as tests that provide information used for diagnosing an inherited disorder acknowledging the difference between somatic changes and germline mutations.

It is our position that whereas germline DNA research requires IRB approval and informed consent in all cases, somatic DNA/tissue research should be performed with IRB approval but may be conducted with a waiver of informed consent even when linked to patient information.

2.4 Study of high penetrance genes vs. those with low or no attributable risk

In the study of germline DNA, the ability of the analysis in predicting future risk of disease in the subject is highly variable. In the case of Huntington's disease, the identification of a germline mutation provides near certainty that the disease will manifest, and that there is risk to family members. By contrast, the information from sequencing for single nucleotide polymorphism (SNP) discovery has no immediate predictive value and therefore no risk to the patient and his family members. In all cases involving germline DNA analysis, the general principle remains that IRB approval and informed consent should be obtained unless the samples are anonymized. When studying gene mutations with definitive risk of disease, provisions should be made for GLP certified genetic testing and counseling. When the research is to define the risk associated with a mutation, and the genetic tests used have not been "hardened" to GLP quality, clinical testing can be made available to subjects after the results of the study have been announced in the aggregate. These approaches are now becoming standard operating procedures.

One controversy, however, is whether such a stringent approach is necessary for all germline genetic research. For example, functional polymorphisms of drug metabolism genes have little to no significance in normal human biology except when an individual is challenged with specific drugs. The metabolism may be altered depending on the genetic configuration of the individual, but the medical consequences are limited. In this situation, the germline analysis has less implication for health and for social issues such as insurability than that of a highly penetrant phenotype such as in BRCA1 or Huntington's disease gene mutations. Therefore the requirements for the conduct of studies involving BRCA1 gene mutations and those of drug metabolism genes may be different and still be ethical.

The second controversy is in the need for re-consent for studies not included in the original informed consent. The issue is whether new research can be performed on tissues for questions not originally consented. For example, germline DNA is obtained from a case control study of SNP associations with lung cancer. The original informed consent specifically explains this study goal. Three years later, a putative gene for lung cancer has been identified but the association needs to be validated. The DNA from this case control study is ideal to perform the validation study. Should all patients in the SNP study be contacted and re-consented for approval to test the new lung cancer gene? Currently, re-consent is often (but not uniformly) required by local IRBs, but there are no definitive guidelines for when the requirement for re-consent can be waived. The importance of resolving this re-consent issue is that cohort and case control studies are difficult and costly to mount. If a new study were required for all new markers, the cost would make this research impracticable. Re-consent is similarly impracticable if each new marker required recontacting the patients for consent.

We believe that there should be creative and ethical alternatives to requiring re-consent in many retesting situations. For example, the establishment of data escrow structures may permit the delinking of clinical data to patient identifiers to preserve confidentiality.

2.5 *The impact of the test results: community vs. individual risks*

Some in the U.S. have advocated the principle of community consent. The basis is that if a germline mutation is focal to a specific ethnic population, then research on individuals, even if informed consent was obtained, may adversely affect the ethnic population in terms of discrimination. Thus, if a study is directed at ethnic groups, then some form of group consent may be needed. We believe this is a dangerous concept because it violates the right of the individual subject to define the communities to which he/she belongs. Moreover, questions such as what constitutes a community and who speaks for the community will always remain unclear. While U.S. regulations require that IRB members represent the diversity of the community be sensitive to local factors including cultural backgrounds and community attitudes, there is no regulation requiring group or community consent. We therefore recommend that the concept of community consent be rejected.

3. *Defining the Problem: What are the regulatory issues?*

Major issues relating to DNA and tissue based research involve informed consent, the need for IRB approval, and confidentiality. The critical questions that need to be addressed are:

- When is IRB approval required?
- When is informed consent necessary? What is the definition of practicable?
- Can research be performed on tissues for questions not originally consented?
- What should the guidelines be for tissues collected in the course of standard medical care?
- Should subjects be given a portion of profits from the research? Should the investigator be allowed to benefit from this access to critical tissues?
- In registries where consent is implicit and part of public health, how linked can the data be?

With any solution, several factors must be considered: rules must be clear and simple in principle; rules must be communicated to the research and clinical community; and there should be set times to reevaluate and even reconstruct the rules so that regulations governing human research remain dynamic and responsive to both scientific and social needs.

3.1 *When is IRB approval required?*

IRB review is the fundamental community check on human investigation. However, the operational activity of the IRB can either improve or hinder research. A bureaucracy that is not guided by principles, not dynamically changing, and that is risk adverse will hinder progress. Thus, it is important for Singapore to establish a system that, from the beginning, embraces best practices. We believe that IRB review for tissue and DNA research is essential for ethical conduct of research. Such a review can be by the complete IRB panel or through a single designated official in cases when a waiver of consent is acceptable. We also believe that there should be different forms of review tailored to the impact of the research on patient confidentiality, patient risk, and the advancement of science. We believe that it is unreasonable to ask that each IRB arrive at local standards for every case especially in a country that is compact and whose systems are central and integrated. The recent experience in the field of research ethics in western countries, especially in the U.S., can help frame the discussion for Singapore (see Attachment II definition of a human subject). However, there are problems and constraints of the U.S. system engendered by its diverse cultural society, its focus on individual rights, and its legalistic/litigious approaches that Singapore can rationally bypass. It is our goal to recommend regulations involving tissue and DNA research that will place Singapore in the forefront of the interface between science, public health, and ethics. Thus, we believe that IRB review (even to obtain a waiver of informed consent) should be obtained for all forms of tissue and DNA research, but that the rules need to be clear, and the procedures tailored to optimize public good.

3.2 *When is informed consent necessary? What is the definition of practicable?*

Informed consent is the process of informing the subject of the experiment (risks, benefits, alternatives) and asking their voluntary consent to participate in the study. Informed consent is deemed appropriate when research may have adverse outcomes to the subjects. In therapeutic investigations where an intervention is given, there is an absolute requirement for informed consent. This is because all therapeutic interventions have potential adverse outcomes. In observational studies, such as epidemiological and clinical investigations looking at linking a biomarker to the incidence or severity of disease, the impact of the results may be far-reaching, such as those involved in germline mutations in highly penetrant disease genes, or have minimal impact, such as associations with low attributable risk. Again, in all cases, whenever an intervention is needed to obtain tissues for research purposes alone (such as blood), informed consent is necessary.

However, the controversy resides in two situations: first, when research is performed on tissues obtained through standard clinical care, and second, when experiments are performed on DNA or tissues which were not covered in the original informed consent document. In large clinical and epidemiological studies, rigid adherence to obtaining informed consent in the use of archived samples may make important studies so costly as to render the research impracticable. Much of the controversy has been in the definition of impracticable, and the threshold for providing a waiver of informed consent. This has been compounded by the diversity of opinions of local IRBs in the requirements for informed consent and re-consent, and the unwillingness of the US federal government to providing strong guidelines in this arena.

The Office for Protection from Research Risks (OPRR) (or OHRP – Office for Human Protection changed in the year 2000) in the U.S. federal government opines that a waiver of consent can be obtained if the IRB finds: “1) the research involves no more than minimal risk; 2) the waiver or alteration will not adversely affect the rights of the subject; 3) the research could not practicably be carried out without the waiver or alteration, and 4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.” (from OPRR, 1993 referring to 45 CFR 46). The 1993 guidelines do stress the IRB carefully consider if the study truly qualifies as minimal risk. However, there are no guidelines as to what constitutes minimal risk or what is considered impracticable. The absence of guidelines and a formal mechanism to vet consensus on these definitions has been a major problem.

The National Bioethics Advisory Commission (NBAC) of the United States grappled with this question of waiver of consent in their 2001 report (<http://bioethics.gov/pubs.html>). Implicit is that IRB oversight (either by the entire committee or by the IRB official) is needed: “When a study is of minimal risk, informed consent is no longer needed by a subject as a form of self protection against harms. However, it is still appropriate to seek consent to show respect for the subject unless it is impracticable to do so. Thus when important research poses little or no risk to subjects whose consent would be difficult or impossible to obtain, it is appropriate to waive the consent requirement.”

NBAC recommends that IRBs should operate on the same presumption that research on coded samples is of minimal risk to human subjects if:

- a) the study adequately protects the confidentiality of the personally identifiable information obtained in the course of research
- b) the study does not involve the inappropriate release of information to third parties and
- c) the study design incorporates an appropriate plan for whether and how to reveal findings to the sources or their physicians should the findings merit such disclosure (i.e., disclosure guidelines).

In determining whether a waiver of consent would adversely affect subject's rights and welfare, NBAC recommends that IRBs consider:

- a) whether the waiver would violate any state or federal statute or customary practice regarding entitlement to privacy or confidentiality
- b) whether the study will examine traits, commonly considered to have political, cultural, or economic significance to study subjects (such as inherited traits research to affect employment, health insurance, social stigmatization)
- c) whether the study's results might adversely affect the welfare of the subject's community.

NBAC suggests that coded samples be treated the same way as identified tissues, which means that those studies with coded samples still require IRB review, but may not require informed consent (waiver of consent) if the research does not present more than minimal risk to the subject.

Current U.S. federal regulations indicate that whenever appropriate the subjects of waived consent will be provided with additional pertinent information after participation (45 CFR46.116(d)(4)). In general, NBAC felt this fourth consideration of waiver of consent is not relevant to research using human subjects and may be harmful if it forced investigators to recontact individuals who may not have been aware that their tissue was used in research.

We believe that there are mechanisms that will allow for quality research to be conducted with waivers for informed consent and without the need for anonymization, which limits the utility of clinical material. The mechanisms that will be discussed include:

- a) The establishment of a formal data escrow system
- b) Case-based precedents that help guide local IRBs in their decision making and in developing national consensus
- c) Formalizing the concept of a central or national IRB for the conduct of national studies.

3.3 *Can research be performed on tissues for questions not originally consented?*

A major piece in the informed consent discussion has been the issue of re-consent. Recently, many epidemiological or clinical studies have assembled tissue and DNA samples for its primary analysis. As the clinical data matures, possible associations with patient outcome render the collected tissues highly effective in answering medically relevant questions. This is especially true when new putative markers of disease are uncovered and the validity of the associations can be tested on these archived tissues. For example, breast cancer samples have been collected for a study on HER-2 amplification and prognosis. Three years later, a putative gene for drug resistance has been identified and a polymorphism in this gene is associated with greater resistance to adjuvant chemotherapy but this association needs to be validated. The DNA from the tumor blocks from this clinical study is ideal to perform the validation study. Will it be necessary to contact the patients and obtain informed consent for every new marker tested on the original samples?

In the past, these archived tissues were considered the property of the investigators and therefore the concept of obtaining consent for the testing of new and emerging markers was considered unnecessary. However, the specter of germline DNA testing with its downstream implications for insurability and family health raised the level of concern, but the regulatory standards remain unclear. We propose that clear guidelines be developed for the use of previously consented patient materials by defining the requirements for re-consent. Inherent in this proposal is our belief that re-consent is unnecessary in many situations. We also believe that data escrow systems can be an alternative to provide the confidentiality necessary to permit the issuance of a waiver for re-consent even in linked situations. Lastly, we suggest that laws be promulgated that will protect the family histories and genetic test results obtained in research situations from being used to deny insurability or in criminal proceedings. This

means that no other governmental or private agency can access the tissues and the research data unless permission is given. Such laws will be necessary to ensure the public that the government supports population-based research as a tool to achieve public health.

3.4 *What should the guidelines be for tissues collected in the course of standard medical care?*

Over the years, it has become implicit that IRB approval (either reviewed by the committee or by a responsible official) is needed prior to use of tissues even in those collected during the course of standard clinical care. Most commonly, a waiver of informed consent permitted the investigator to explore association studies without the onus of seeking and recontacting the individuals. The emerging standard in some US IRBs, however, is for informed consent to be obtained for these samples unless the tissue blocks are anonymized prior to study. Cited for this shift has been the fear that germline information can be obtained that might disclose knowledge of hereditary conditions. Many scientific groups have resisted this move to require informed consent on archived clinical material arguing that the risk to the patient is small, the benefits to society great, and the cost and time needed to access this consent is prohibitive (impracticable). Indeed, the collective information in standard pathology tissue archives will support the development of many markers of human disease at remarkably low cost and with short timelines.

We believe that the problems have been in the confusion between germline and somatic research, and the notion of penetrance/attribution risk (see above). If a clear and acceptable demarcation can be made between disclosure risk and the need for informed consent/reconsent, these problems can be resolved. Thus, we propose that research on somatic changes, or involving genes associated with limited hereditary phenotypes be exempt from obtaining reconsent. Those that specifically target germline mutations with obvious and adverse phenotypes should obtain informed consent/reconsent. The local IRBs *with national guidance* are suited to make these distinctions. Alternatives to obtaining informed consent would be to anonymize the tissue and its associated clinical data. To limit the ability to identify specific patients in a population by "triangulation" of clinical parameters, the use of data escrow agents may be needed. These conditions can be decided by an informed IRB.

The level of clinical information collected for such studies has also been scrutinized. Review of medical records has been the preferred analytical approach. Such research requires IRB approval, but informed consent/ reconsent should be waived once the investigator can provide assurances to the IRB of provisions for patient confidentiality. The need for informed consent comes when recontact is needed for accession of more clinical data. We propose that patient recontact be a demarcating principle for the need for consent/reconsent.

Central to the regulations governing points 3.3-3.4 is the definition and concept of patient confidentiality. Again, the problem in implementing the regulations has been the conflict between the theoretical vs. operational definitions. Some ethicists claim that any exposure of information even in protected archives can be considered a potential breach of confidentiality and require informed consent/reconsent. The College of American Pathologists (CAP) outlined important operational recommendations (Grizzle et al. Arch Pathol Lab Med. 123:296-300. 1999): CAP contends that "confidentiality means that information will not be disseminated freely" implying a fiduciary duty not to disclose the information to others without the person's consent, actual or implied, or otherwise in his or her interest." They recommend that pathology departments develop written procedures concerning privacy and confidentiality protections, including procedures for releasing information for research. Like OPRR (now OHRP), they recommend that data be coded and stored physically separate from clinical or personally identifying information. Security policy and procedures should be written out. They consider, however, once these safeguards are firmly in place that provisions for waivers of

consent could be given.

Similar to NBAC, the CAP paper suggests that “when information about the specimen sources is withheld from researchers and any link is provided only through *IRB approved confidentiality procedures*, the risk to research subjects from unauthorized breach of confidentiality is minimal.” Again, this puts burden of responsibility on the IRBs to have criteria for approval of mechanisms of security and appropriate processes of unlinking data. Unfortunately, there has been no governmental leadership on this topic and the ensuing ambiguity has caused problems.

One important concept brought forward by the CAP paper is that research data should not be considered genetic information. “It is important to realize that information developed in the course of research generally is not valid patient information for use in genetic counseling. Therefore research data should not be considered genetic information as that information is used in statutory information.” This is a significant point in the discussion of what needs to be disclosed to patients/subjects of their individual data after research is completed.

3.5 Should subjects be given a portion of profits from discoveries? Should the investigator be allowed to benefit from this access to critical tissues?

The central issue of this question is who owns these tissues. We believe that there is no specific right to ownership of tissues once the tissue has been separated from the body and after permission has been given through a clear informed consent process. This has been the principle governing organ and blood donations and functions well. Patients may demand, and researchers may decide to share the downstream profits from this tissue access, but it should not be a requirement for any tissue accession programme. Since no individual investigator actually privately supports his/her own tissue collections, it also means that the investigator is not the owner. Instead, the institutions funding and collecting the tissues are the owners, holding ethical responsibilities with this ownership.

The direct sale of clinical material to a commercial entity is a larger societal issue. Patients will support biomedical research, but should not be expected to support the sale of their tissues without some remuneration (as a one-time payment) or prior consent where they waive remuneration. Waiver of remuneration is commonly done in organ donation and can be a model for tissue accession for research. In this model, a society determines that the donation of organs for transplantation is sufficiently important for the public good that all organ donations are managed publicly and funded by non-profit/governmental sources. The donors ask for no remuneration, the recipients do not pay for the organ, but the doctors and the hospital performing the transplantation receive compensation for their services. The same conceptual paradigm can be applied for tissue-based research. The donation of tissue for research is for the public good (both for public health and public prosperity) and those individuals and institutions working on this tissue may benefit from this research because the ultimate outcome is better medical products for patients, and more economic activity for the country. This model works if there the Common Pact as described in section 1 is accepted. The perception should be that this research is not solely for academic gain, but for the public good. This also requires that governmental or non-profit agencies be involved in assuring that the best science is done, and that specific ethical guidelines are followed.

Recently, in the US, there have been voices suggesting that patient donors should be provided royalties from the use of their tissues. The assignment of downstream intellectual property (IP) rights and licensing agreements to the tissue donor is impracticable and unenforceable. Even more dangerously, such a system may encourage individuals to “sell” their tissues to the highest bidder, thus establishing an untenable ethical situation. Therefore, such allowances should not be entertained.

3.6 In disease registries where consent is implicit and part of a public health programme, how linked can the data be and how should it be used in research?

The governance of national disease registries deserves special attention, because of the mandatory nature of the information collection and the ubiquity of the coverage. The information from these registries is vital in monitoring the public health of a country and for public policy. In addition, disease registry data is often the foundation of impact epidemiological research. This has been borne out by the fact that much of the best public health research is performed in those countries with advanced and enforced disease registries and accompanying infrastructure: the US, Scandinavia, China.

Singapore is quickly developing a world-class disease registry system that can be used for public good through biomedical research. The development of effective and ethical but streamlined approval processes for national registry research will make Singapore a unique international center for population studies. One concern voiced frequently related to the IRB approval process for disease registry research is the number of IRB approvals that are necessary to initiate a study. The original intent of local IRB control is that local sensibilities may be better voiced in this format. For epidemiological studies with limited sites, and for countries with large geographical space and cultural diversity, this local overview is important. For Singapore, with its compactness and history of centralization, epidemiological studies using this national resource studying questions of broad national importance may not require the same local scrutiny. Streamlined approval processes for such comprehensive studies serve to advance public health knowledge in a manner unique in the world.

We therefore propose the establishment of a National IRB specifically formed to review proposals of comprehensive national scale especially using the linked disease registries. This national IRB may initially reside in the BAC and evolve as needs arise. The composition and intention of this National IRB is to have the expertise to review the social and health implications of such global public health research and to ensure that patient confidentiality is secure. The decision of this National IRB will be accepted by all other IRBs if there is no comment after a one month study period. If, within the month of receipt of the National IRB decision, the local IRB finds an aspect objectionable, it can opt-out of the national study. We propose that this system be given two years trial, at the end of which, a more formal system can be enacted.

4. Proposals for the governance of Singapore's tissue and DNA research

4.1 Principles:

We propose that the governance of tissue and DNA research in Singapore be driven primarily by principle and not solely by process. For this reason, the acceptance of the Common Pact in a form outlined in section one is important. This pact declares that tissue and DNA research is essential for public health and implicitly states that the regulatory system should facilitate this research but always in an ethically rigorous manner. It begins with the individual centric focus of western thought and adds the communal good as part of the equation.

Some of the recommendations below extend outside the boundaries of operational doctrines espoused by some thought leaders in the U.S. concerning DNA repositories and research. A summary of these current concepts is noted in Attachments II and III, which is excerpted from notes by Dr. Lynn Dressler (University of North Carolina, Chapel Hill). Attachment IV has the draft recommendations from European Society of Human Genetics (ESHG).

4.2 Platforms for confidentiality: Constructing a dynamic regulatory organization to advance the common good

Data Escrow: The concept of data escrow arises from the desire to separate the investigator from the primary source of patient information so as to limit the potential for inadvertent

disclosure of confidential information. This is especially useful in situations where research tests are proposed that are beyond what was originally consented. The structure is that an impartial third party that is not the researcher keeps the tissue/DNA "identifier key." Investigators can access clinical data and link it with their molecular findings only by coded means through this third party. Access is determined by a predefined governance process. This set-up is especially important in research situations where rich clinical information is linked to a well-structured tissue or DNA repositories. For example, when a new molecular test is employed that was not available or even conceived during the writing of the original informed consent document. To avoid the intrusion and the cost of recontact and recontact, new tests can be validated in this coded/limited access approach still maintaining patient confidentiality. This is especially important in cohort studies where survival and disease outcomes are part of longitudinal follow-up of patients. The ability to test associations of clinical outcome with emerging candidate markers is of great importance and can only be practicably done if recontact/reconsent of patients for each new marker is waived. A major genomics company, Genomics Collaborative Incorporated (GCI) uses this structure as its fundamental principle in organizing their tissue and data collections (see outline in Attachment V). Their third party agent is:

Recall Information Management
2109 Bering Drive
San Jose CA. 95131
Tel 408 453 2753
Fax 408 441 6826

With advanced computer security, such data escrow systems can provide reasonable assurance for a high level of security. The key requirements for an Data Escrow Agent is that he/she has no stake in the research, there is a clear and transparent governance system in place, the computer systems are sufficiently advanced, and there are provisions for the data should the support company falter. As concerns for personal data security grow, there will be a market niche for data escrow platforms not only in the health care sector, but also in financial information as well. We believe that Singapore is uniquely suited to initiate one of the first public domain data escrow platforms and become a world leader in this technology.

Honest broker/honest agent: Consent, confidentiality, and IRB oversight are the cornerstones of ethical regulation in tissue and DNA research. IRB has jurisdiction over research regardless of whether informed consent is required. However, there are situations where archived data or tissues of great scientific value are available for research but consent was not obtained at the time. There are a large number of paraffin tissue banks coming from standard pathology laboratories that potentially represent a rich substrate for validation and discovery. The unique potential for this resource in Singapore is the ability to link with survival and disease registry databases that would augment the scientific value of these tissues. Here, reconsent would render the advantage null because of the cost of recontact and the perceived intrusion by individuals/family members during this recontact process. The dynamic tension is between the primary researcher and the regulatory IRB and surrounds the question of whether patient confidentiality can be maintained. We believe that the data escrow system coupled with key mediators whom I call honest brokers (akin to data safety and monitoring board members), can establish a coded link between a tissue block repository to disease registry tracking data. This code can be held by the data escrow agent, the tissue held by the investigative unit/repository, and the survival/registry data residing at the Ministry of Health (MOH) sites. The linkage takes place at the data escrow agency so that neither the MOH nor the investigator has all the data/identifiers. This process is overseen by the honest broker.

4.3 National IRBs

The rationale and proposed operation of a National IRB is described in section 3.6. We propose the establishment of a national IRB specifically formed to review proposals of

comprehensive national scale (many sites) and those employing the linked disease registries, which are national resources. The purpose is to reduce the time and expense of reviewing a national population based study by all participating local IRBs. This is justifiable in the Singaporean situation since the country is highly compact and has a history of social consensus thus making it likely that a single national IRB would discharge their duties appropriately. The specific use of disease registry data in a linked fashion to tissues and other databases should trigger the use of this national IRB. The decision of this National IRB will be accepted by all other IRBs if there is no comment after a one month study period. If, within the month of receipt of the National IRB decision, the local IRB finds the study objectionable, it can opt-out of the national study, but it cannot amend. This National IRB should be restricted to reviewing those studies of comprehensive national scale and using MOH or other governmental databases. It probably should not be used as an appeals court for the decisions of the lower IRBs.

4.4 Legislative solutions

The crux of the confidentiality problem is the potential loss of rights and of personal assets if genetic information is disclosed. A major concern is the forced disclosure of this information by insurance companies, employers, or the government. The key issue is the protection of individuals from loss of job, and loss of medical/health insurance because of genetic tests either performed for clinical care or in the course of research. In the US, laws protecting genetic "rights" of an individual are usually rather porous (with "loop holes") and selective (directed against only one or a small number of diseases) rather than comprehensive. For example, some states in the US have laws specifically preventing the discrimination based on sickle cell diagnosis but not any other genetic diagnosis. In the absence of legislative relief from the possible loss of job or insurability, laws have been established that limit access to genetic information. We believe that there are several legislative options for Singapore that can balance the protection of citizen privacy, with that of the need to advance public health. We propose several that do not require a change in the medical care funding system:

- a) *Laws to protect insurability:* Several laws have been passed in the U.S. and additional ones are being considered that progressively attempt to protect the insurability of individuals with genetically transmitted disease. A discussion of these laws and proposed legislation is beyond the scope of this document, however, most of these laws have sufficient exceptions that render them less effective. Singapore is in the position to decide its legislative approach to genetic insurability. A key principle should be that individuals cannot be denied the right to medical care simply because of his/her genetic history. This can be accomplished by prohibiting insurance companies from denying insurability for those testing positive for a genetic disease, or for those with family histories of genetic disorders. Companies should not raise the premiums for those genetically at risk as an indirect means to drive these high-risk individuals out. Without some form of protection, the use of genetic testing to best determine at risk populations will not be socially feasible.
- b) *Remedies for breach of Confidentiality:* Plaintiff may obtain an injunction to stop publication or prevent further publication of the confidential information. It is however, important to rigorously define confidentiality such as the assignment of identifying variables so that the person can be easily selected from a crowd. With repeated breaches of confidentiality, the investigator may have his/her rights as an investigator revoked and their ability to write for research grants removed.

Certificates of confidentiality: Even if no laws can be passed that will protect the insurability of individuals, there should be at least some form of legal protection for participants in genetic research. In the United States, research institutes may request from the Department of Health and Human Services, a Certificate of Confidentiality. Such a certificate protects the institution from being forced to release socially sensitive information obtained during the course of biomedical research even when subpoenaed. Originally established to protect against

enforced disclosure of personal drug and alcohol history, the use of Certificates of Confidentiality have been expanded to include AIDs research and genetic research. This adds an element of security to the research participant that his/her personal information cannot be extracted without their permission. We recommend that Singapore adopt, as a minimum, such a legal mechanism to protect against enforced disclosure of research information.

The operational implementation of such a certificate system is as follows: A research center applies to the central IRB governing body for a certificate of confidentiality. In this application, the purpose, a short description of the project and of the methods to ensure confidentiality are provided. The IRB approved protocols are appended.

4.5 Clarity of purpose/Know what we are governing

My major criticisms of the recent U.S. system governing tissue and DNA research have been that the regulations do not recognize the differences between the varying forms of tissue/DNA based research and that there have been no definitive structural mechanisms within the IRB system that seeks to resolve overarching conflicts and controversies. Such differences include: somatic vs. germline DNA investigations, and studies involving highly penetrant genetic states vs. those with low attributable risk. As these research regulations became more confusing for IRBs and researchers, conflicts arose between these communities. The central regulatory bureaucracies adopted a stance of non-interference referring to the importance of local IRB control. Local IRBs were given no guidance as they struggled with interpreting the complexities of the new science and ambiguous laws. Into this leadership void came the special interest groups both outside and within the government thereby politicizing the issues. Thus, understanding and acknowledging the differences in research domains (i.e., somatic vs. germline) is an important first step in formulating solutions.

4.6 Clarity of Purpose/Black and white and then the gray: informed consent and re consent

Central to the current tissue research controversies has been when informed consent/reconsent is required. The NBAC (U.S.) has promulgated central guidelines that are very reasonable:

“NBAC proposed process for research using human biological materials incorporates these categories to determine if the research is subject to human subjects regulation and IRB review. If the samples are publicly available, unidentified, the subject is deceased or the process of unlinking the samples is sound, the samples may be legally used without informed consent or IRB review (although a designated IRB person must help to make this decision). If the samples are **coded or identified** the research is subject to human subjects regulation and IRB review (see Chart 1, Appendix D of NBAC Volume I, p 106). It is then determined whether the research is eligible for expedited review and if informed consent is needed, both of which are based whether or not the research is minimal risk. If minimal risk the research is eligible for expedited review. If waiving the informed consent will not adversely affect the subjects’ rights and welfare, then no informed consent is required.”

We believe the operational problem in the U.S. following the NBAC report will be in regulating the use of coded samples, a debate that have already been politicized by earlier processes. We propose to further clarify with the following extended guidelines:

4.6.1 The informed consent and re consent are required when therapeutic interventions, physically accessing new tissues for research, or new information gathering requiring direct patient contact are considered.

4.6.2 Informed consent and re consent are required if the research on archived samples seeks to test germline mutations in highly penetrant phenotypes, and to link these results to clinical data and patient identifiers.

4.6.3 Informed consent and re-consent/IRB review are not required when samples are anonymized.

4.6.4 Informed consent and re-consent can be waived:

4.6.4.1 If the patient will not be recontacted and if the test does not involve interrogation of germline DNA mutations associated with highly penetrant phenotypes.

4.6.4.2 If the linkage between the patient identifier and the test outcome can be sufficiently obscured by electronic means and the use of Data Escrow agents. This guideline specifically permits the use of coded information without informed consent or re-consent since the primary investigator will not have access to unique identifiers of each patient. It is therefore important for the Singapore BAC to clearly define the acceptable parameters for such a Data Escrow interface.

4.7 *Continuous learning and forums for conflict resolution*

The various IRBs function as a democratic forum for citizenry to inject their ethical sensibilities into the research activities of a country. As such, they form an invaluable forum for public participation and feedback. However, as local forums, they cannot be expected to work in isolation promulgating decisions on topics of extraordinary complexity. We therefore recommend that formal mechanisms be developed:

4.7.1 Whereby the local IRBs can be linked to the activities of the BAC and that a continuous dialog can emerge between the national and the local bodies empowered to oversee research ethics;

4.7.2 Whereby the local IRBs can meet with other IRBs, perhaps yearly, to learn of new scientific methods, to discuss issues of concern to them, and to dialog with the scientific and regulatory communities;

4.7.3 Whereby the IRBs can learn of decisions by other IRBs concerning research touching on interesting or sensitive ethical or operational issues. A central body such as the BAC may use this as a mechanism to keep in touch with the pulse of the country, and as a means to test consensus in the community. To this end, we believe that such decisions can develop into a body of "case law" to guide, but not to dictate, the thinking of other local IRBs. In this process, interesting and potentially controversial studies and their IRB deliberations can be shared with all Singaporean IRBs followed by an open discussion/comment period. Such "case studies" should be disseminated to IRBs and to institutional researchers on a regular basis and can be used as reference in future decisions.

ATTACHMENT I

{From Grizzle et al. Arch Pathol Lab Med. 123:296-300. 1999.}

In March of 1996, the CAP produced a white paper which was endorsed by 17 pathology related organizations and approved as the official policy of the CAP (draft form not published). In 1999, the authors of the consensus statement revised portions that were being misinterpreted.

Is Genetic Information different than other medical information?

Similar to other groups they grappled with the question is genetic information different than other medical information and determined three characteristics have been proposed to account for that difference: "power, predictiveness and implications for individuals other than the patient. Gostin indicated a qualitative difference in that genomic data unlike other health information are inherently linked to one person. Clayton and Reilly indicated that genetic data may provide information about more than just the individual from whom the data are derived. The CAP group cited that "potential differences in the extent of harm that may result from the misuse of different kinds of medical information and thus there is a need for an operative definition of genetic information . "Information used for diagnosing or treating an inherited disorder or for genetic counseling." "Genetic tests should be defined as tests that provide information used for diagnosing an inherited disorder."

Confidentiality:

Like, NBAC, they maintain that genetic information be "subject to the same standards of privacy, confidentiality and security as nongenetic medical information." The definition of genetic information focuses on validated medical information, "important enough clinically to warrant counseling patients and their families members as to risks or future disease." They maintain that the "same confidentiality considerations should apply to patient information obtained during the course of research and investigation, even though the information is not part of the medical record. (similar to call for privacy guidelines from elsi, 1999).

CAP contends that "confidentiality means that information will not be disseminate freely" implying a fiduciary duty not to disclose the information to others without the person's consent, actual or implied, or otherwise in his or her interest." They recommend that pathology departments develop written procedures concerning privacy and confidentiality protections, including procedures for releasing information for research. Like OPRR, they recommend coding of data and that research data be stored physically separate from clinical or personally identifying information. Security policy and procedures should be written out.

Research data is not genetic information:

One of the concepts that they brought forward is that research data should not be considered genetic information. "It is important to realize that information developed in the course of research generally is not valid patient information for use in genetic counseling. Therefore research data should not be considered genetic information as that information is used in statutory information. Similar to MacKay's principles of what constitutes information (1984) that is cited in the OPRR Genetic research guidelines (1993).

Misuse:operational challenge is one of security:

"There is no disagreement with the fact that confidential information has been and will continue to be at risk for inappropriate disclosure. The operational challenge is, thus, one of security." "Security is the notion of unlikelihood of undesired disclosure or leakage of

confidential information, intentional or not." They recommend that "organizations and individuals must operate under rules of conduct and use physical systems that reasonably protect this information from inappropriate disclosure." (same principle as NBAC with sound system for unlinking; some of this is addressed with HIPAA regulations"

They contend that samples collected under the stewardship of pathologists (during the course of the clinical care of the patient) are a vital part of the medical record. "The laboratory that provides the primary diagnostic analysis of specimens is responsible for the maintenance and integrity of this part of the medical record". They also assert that is the pathologist's duty and responsibility "to provide appropriate material for research studies that have received IRB review."

"Breach of confidentiality is major risk research subjects encounter when it is possible to link a specimen to a source." Similar to NBAC they suggest that "when information about the specimen sources is withheld from researchers and any link is provided only through *IRB approved confidentiality procedures*, the risk to research subjects from unauthorized breach of confidentiality is minimal." (Again this puts burden of responsibility on IRB to have criteria for approval of mechanisms of security. It may be that HIPAA requirement laid this foundation for "appropriate process of unlinking" (NBAC).)

Recommendations:

Existing, anonymized specimens, should be, for research purposes, treated as anonymous specimens that were never linked to a source as defined by 45 CFR 46. (therefore using the 45 CFR 46 criteria that the specimen cannot be linked and that the specimen is publicly available, it meets to criteria for exemption from IRB review and informed consent). (here anonymized is defined as " where linkages have been removed irreversibly, rendering the specimen equivalent to an anonymous specimen-it this what NBAC refers to as unlinked? How do you remove linkages irreversibly??)

Where the specimens or data are identifiable or linked (where the specimen is coded for research purposes but can be linked to the sources through a code) researchers must agree to prohibitions restricting them from contacting both the patients who were sources of specimens used for research and their families. The prohibition of patient contact does not preclude obtaining information from tumor registries.

Requests for contact of subjects or families must be made through the appropriate IRB. If the IRB approves contact, the IRB should determine the method of contact.

Before releasing specimens to researchers, stewards of specimens should ensure that the researchers have IRB approved research proposals and they have signed nondisclosure statements or have obtained written exemptions from the IRB.

Publications and presentations must not permit the identification of individual sources of research specimens without specific consent of the patient.

In the case of identifiable specimens, it must not be possible, without the patient's specific consent and IRB approval, either for research results to become part of the medical record or for the patient's to be aware of research performed on their specimen. Information developed in the course of research generally is not regarded as valid for the clinical care of the patient, and therefore research results should not become part of the medical record and physicians should not base their care of patients on the results of

research. (but what if this is part of a clinical research trial, where patients are treated based on result of a test -test should be a valid test done in a diagnostic lab).

Penalties: Abuse in research (breach of confidentiality) is best dealt with via sanctions against the offending individuals and institutions.

Ownership:

"If a patient gives his or her tissue specifically for research, it is unclear whether the tissue becomes the property of those to whom it was given." However, they go on to indicate that since the specimen was substantially "transformed from its original state", through the process of fixation and embedding in a wax block, "the durable goods thus produced, can fairly be claimed the property of the entity that produced them."

The pathologist "holds the tissue in trust, primarily for the patient but also for society at large."
Consent:

Posit that the consent doctrine criteria described in 45 CFR 46 were intended for application to therapeutic interventions and that "applying this same consent doctrine to research with human tissues, the interests of patients are fundamentally different from those in which therapeutic intervention is at issue" (Yes, but it still boils down to risk and harm and benefit).

Harm in disclosure:

"A single research study does not establish irrefutable scientific fact, and the results of a single investigation have no applicability to an individual patient." "Disclosure of a single research project's results to a patient is at best not beneficial and at worst could be misleading or even harmful."

Future use/current consent doctrine not useful for non therapy research.:

"To give a description of each and every research protocol that might be performed in the (sometimes distant) future on a patient's tissue is an unreasonable burden for the patient and the researcher." The current consent doctrine is not well suited to research that does not involve therapy. Recommend the use of simple consent forms.

Again they maintain that this is use of excess tissue, which is not necessary for the integrity of the medical record and that consent for such donations [of tissue] "should be regarded as sufficient for the protection of patient's rights."

Forms to be worded so patients can agree or disagree to consent for tissue donation. In response to the statement that some genetic research involves greater risk than other medical information--"However the rules of privacy, confidentiality and security should equally apply to all patient information. Genetic information, like other research information, would be adequately protected if the recommendations of this document were followed."

Addressing risk as part of informed consent process:

Risk is primarily social (stigmatization, loss of insurance, etc) and should be addressed through social mechanisms-law, regulations or code. "It is unrealistic to ask patients to foresee all

adverse societal consequences [or investigators for that matter] of research as part of the informed consent process. "Such potential risks should be balanced by the health benefit that will accrue to the population by the research. "

Living vs dead:

Similar to NBAC does not feel that regulations should apply to only living persons, because genetic information can provide info to family members still living. However the CAP group contends that " if safeguards are in place to prevent unauthorized disclosure of medical information, " the risk is minimized.

CAP suggests that if tissue is collected specifically for research (not left over) then informed consent is required.

Prospective vs retrospective sample use:

"In prospective studies the research study or protocol was designed and approved prior to the collection of the sample. In retrospective studies, materials are used that have been stored and were originally obtained for diagnostic and therapeutic purposes or obtained for use in a previous research study."

Simple consent:

"In both prospective and retrospective studies, residual specimens can be made free of identifiers (anonymized or anonymous) or can be made free of direct identifiers (i.e., linkable or coded). We recommend that the appropriate regulatory agency modify the current federal regulations so that simple consent for research should be sufficient for the use of all samples that are anonymous or anonymized"

(here we assume, simple consent means the surgical consent?)

Waiver of consent:

"Provided that the written non-disclosure confidentiality, and security policies have been approved by the IRB, we recommend that the appropriate regulatory agencies should provide guidance to IRB's to permit broader latitude to waive consent for research on identifiable (linkable or coded) samples. Such a waiver should be granted on a case-by case basis, including assessment, nondisclosure and security policies that adequately protect patients and sample donors from inappropriate disclosure of protected information."

Note:

The white paper and subsequent revision/clarification has been formally endorsed by 17 different associations including: Academy of Clinical Laboratory Physicians and Scientists; American Association of Cancer Research, American Association of Neuropathologists, Inc., American College of Veterinary Pathologists, American Registry of Pathology, American Society of Investigative Pathology, American Society of Clinical Pathologists, American Society of Cytopathology, Arthur Purdy Stout Society of Surgical Pathologists, Association for Molecular Pathology, Association of Directors of Anatomic and Surgical Pathology, Association of Pathology Chairs, College of American Pathologists, Society for Hematopathology, Society of Toxicologic Pathologists, United States and Canadian Academy of Pathology, Universities Associated for Research and Education in Pathology.

ATTACHMENT II

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According to NBAC and modifying from OPRR, the research must first be defined as human subjects research. NBAC does not feel that anonymous samples which represent minimal risk should be considered human subjects and therefore are not regulated by 45CFR46, however most feel IRB review is warranted to ensure sound science. Also if individual is deceased AND the research will not adversely affect any family or community, the research is not considered human subjects by NBAC and OPRR.

Definition of a Human Subject:

In order to decide if human subjects regulations and IRB review applies to the research, the definition of a human subject is required. NBAC indicates (Chart 1, p106) that if the human samples are coded or identified then the research is subject to the Common Rule and IRB review. According to NBAC recommendations, samples that can legally be used without informed consent or IRB review include the following kinds of samples:

- samples that are publicly available¹
- samples that are unidentified (anonymous)
- samples from deceased subjects²
- identifiable samples, where the process of unlinking the samples is sound³

Well known sources of publicly available information include telephone books and land title records. It is not clear what kinds of biologic materials might be considered publicly available. OPRR's definition, "unrestricted access on demand (ie unrestricted availability subject to only limited quantities and/or related cost)", is still unclear and provides little guidance.

Although, both NBAC and OPRR (now OHRP) have indicated that a deceased individual is no longer considered a human subject, NBAC further clarifies that if the research would adversely impact the deceased individual's family or community, then the research needs to be considered regulated by the Common Rule and subject to review by an IRB to determine level of risk. For example, this might well relate to certain types of genetic research such as studying a specific mutation in the BRCA1 gene believed to be more common in Ashkenazi Jewish women.

How one determines that the process is sound is currently up to the IRB's to decide. There are certain models that may be helpful to promote as examples.

OPRR GUIDELINES (45CFR 46):**What is a human subject?**

As defined by OPRR (Chart 2, p107), the definition of a human subject must meet the following criteria: "Is there an intervention or an interaction with a living person that would not be occurring or would be occurring in some other fashion but for this research? " If the answer to the questions is yes then human subjects are involved and the Common Rule applies for informed consent and IRB review unless the criteria for exemptions are met. If the answer to the question is no, but the answer to the following question is yes, Will identifiable private data or information be obtained for this research in a form "associable" with the living individual, then human subjects are involved and one must follow the Common Rule or meet exemptions. If however, the answer to both of these questions is no, then the Common rule does not apply and the research is not considered human subjects research.

ATTACHMENT III

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Guidelines for DNA Banking:

Testing of DNA began in the early 1960's, with newborn screening for phenylketonuria (PKU). However, at that time, few laboratories were actually involved in the process of banking. "DNA based presymptomatic, predictive, and identity testing has spawned new practices: DNA banking (the long-term storage of cells, transformed cell lines or extracted DNA for subsequent retrieval and analysis) and DNA data banking (the indefinite storage of information derived from DNA analysis, such as linkage profiles of persons at risk for Huntington's disease)." [Philip Reilly, AJHG, 1992]. Today, academic centers, private and commercial organizations, bank DNA for medical as well as research purposes. In addition, several other resources constitute "virtual" banks of DNA, including Guthrie cards, (dried blood spots from newborn screening from which DNA can be extracted) and surgical pathology blocks (tissue specimens obtained at the time of surgery, preserved in fixative and embedded in wax blocks for long term storage).

Currently, however, the largest banks of DNA are associated with forensics and the military, for the purpose of identification of individuals. In 1996, 40 states had statutes to establish state forensic DNA banks, 32 of which had already begun to collect samples, totaling nearly 400,000 samples [Jean McEwen]. The Department of Defense had already collected 1.5 million samples at that time, with the expectation that the bank would be complete by 2001, containing 3 million samples. A federal law passed in 1994, the DNA Identification Act, helped to fund forensic DNA analysis activities [DNA Identification Act of 1994, Pub. L. No.103-322, 108 Stat. 1796S21304 (1994)] and a computer network, CODIS, (Combined DNA Identification System) was authorized by the Federal Bureau of Investigations to enable exchange of forensic DNA information between the data banks in the different states [42 U.S.C.S 14312 (1994)]. This law provides some privacy protections as well as criminal fines for violating these protections. Specifically, the law "requires crime labs, as a condition of participating in the CODIS network, to limit disclosure of stored individually identified DNA samples and data to criminal justice agencies, for law enforcement identification purposes" [DNA identification act]. Thus there is an infrastructure in place for DNA banking. It includes not only collection of specimens or DNA (DNA bank), but the storage of data derived from the analysis of the DNA (DNA databanks) and the opportunity to share this data electronically. However, except in the forensic context, most DNA banks and DNA databanks established for medical, research, or commercial purposes are largely unregulated.

There have been, however, several groups in the United States and elsewhere who have suggested guidelines for establishing and maintaining DNA banks. Most of these guidelines focus on banks of samples rather than banks of data and include ethical as well as practical recommendations. The following parameters are common to most all guidelines: 1. Samples should be coded with an identification number to protect the identity of the DNA source; 2. The bank must provide provisions to allow an individual to remove their DNA or have their DNA destroyed should they decide at some time in the future not to continue to be a participant in the bank; 3. The bank should indicate to the DNA source how long the DNA will be stored and 4. The bank should have a plan for the future of the bank, in the event that the laboratory or company currently responsible for the bank is no longer funded or in operation.

Most all guidelines address the concept of informed consent or waiver of such, but the criteria for requiring consent or waiver are not uniform. Most all guidelines include some aspect of access to samples, however there are major differences from group to group, especially for

the use of specimens for future, yet unspecified genetic research. Some guidelines indicate that for each intended use or study, recontact of the individual for consent is a requirement, unless the DNA is completely anonymous; other guidelines indicate that the general nature of the future research must be indicated in the informed consent, eg. that future research includes only cancer -related studies or will not include studies of social behavior or intelligence.

ASHG: Points to Consider

In 1987, recognizing the medical importance of DNA analysis information, the American Society of Human Genetics Ad Hoc Committee on DNA technology published their official "DNA Banking and Analysis Statement" [ASHG statement]. Their "Points to Consider" guidelines were geared toward "banking for the preservation of DNA needed for analysis at a future time." The ASHG indicated that differences existed between DNA analysis for clinical purposes versus other clinical genetic tests at that time, specifically, 1. "The long term stability of DNA may permit questions to be answered later that were not envisioned at the time of its procurement; 2. Since DNA analyses commonly involved linkage analysis, a concept that is unfamiliar to laypersons and to many health care professional, there is significant risk of misinterpretation of results by recipients and 3. The rapid advance of DNA diagnostic capabilities places special responsibility on the providers of these services to keep current." These concepts still apply today.

Although these guidelines were referring to the clinical context, they are still relevant in the research setting.

There are 11 points to consider in this document including appropriate submission of samples, ownership of DNA, banking policies to inform the depositor, disclosure of results, transfer of data, accuracy of test result, quality assurance practices for the lab and competence of the director, secondary use of samples and the role of the ASHG in this process:

Submission of samples to the bank or diagnostic laboratory:

The recommendation is that DNA banks or diagnostic laboratories accept samples and requests for analysis only from health care professionals and not from individuals or families "without the mediation of health care professionals." This guideline places responsibility on the health care provider to provide appropriate quality control and quality assurance, including determining the nature of the genetic information that is needed by the family and if DNA analysis is likely to provide this information; interpretation of results and counseling individual/families regarding significance, accuracy, "attendant risks, such as identification of non-paternity". The health care provider would also facilitate sample collection from the individual and other family members as needed. A genetic evaluation should precede banking of any DNA. The health care individual assuming this responsibility would need to be knowledgeable about human genetics and the nature of these tests. This last point may seem obvious, however, even today, DNA analysis is requested and results interpreted by health care professionals who may not be competent to do so.

Ownership of the DNA in a bank:

"The banked DNA is the property of the depositor, unless otherwise indicated." The depositor is not considered a "donor", which implies gift.

Written bank policies to avoid misunderstandings between the depositor and the DNA bank:

A written document should be used to inform the depositor of the bank's policy prior to the individual submitting a sample . It is recommended that the document contain the following information: "services provided, duration of storage, disposition of the DNA at the end of the agreed upon time of storage or upon death of the depositor, conditions

under which the DNA can be used for purposes not requested by the depositor, eg. research, a discussion of risks associated with banking, such as loss of samples; an agreed upon method of maintaining contact between the depositor and the bank.

Release of DNA analysis results:

Results of DNA testing should be released " to the appropriate health care professional, who has the responsibility of informing the patient or family of the results and their meaning". This allows only those individuals (of the family) who want the results to get the results. The guidelines indicate that the "results of the tests should be subject to the traditional principles of medical confidentiality and should be released to third parties only with the express consent of the individual ". ("Express consent" is not further defined as written or verbal).

Transfer of DNA to a third party:

The laboratory must obtain "express consent" before transferring DNA to a third party. However they do include the caveat that "unless immortalized cell lines have been established, patient DNA is exhaustible, and the patients needs should take priority". Here the concern was not so much a legal/ethical issue but a practical issue.

Accuracy of the reported result:

At the time of these guidelines, most DNA testing results were given as DNA linkage results. The ASHG recommended that these results be reported in terms of probability of a disease carrier state" (to the health care professional who submitted the sample). The DNA analysis laboratory is responsible for error "due to improper laboratory technique or due to improper estimate of disease likelihood." The lab is also responsible for requesting another sample if " the DNA sample is lost or found to be unsuitable" for analysis. The health care professional is responsible for an error "due to an incorrect statement of genetic relationship of family members.

Secondary use of the sample.

The deposited DNA can only be used for purposes unrelated to the original request of the depositor with the express consent of the depositor. The depositor's desires should be determined at the time the sample is collected. (Process for "express consent" is not defined).

Minimal standards for quality assurance.

Several practical aspects for running a DNA bank are indicated: a DNA bank should occupy separate space from other DNA work, have secure, alarm-equipped facilities. A lab should have a written manual of procedures and training of personnel in meticulous technique. Samples should be coded "so that a minimal number of individuals have access identity of the depositor. Written records should be maintained to track the receipt, disposition and storage of each sample. They also recommend dividing each sample and storing in two physical separate places. Control samples should be analyzed before deposit to ensure integrity of sample, and at periodic intervals of storage (to determine that RLFP patterns are not affected by storage).

Competence of Laboratory Director/Certification of Directors.

ASHG recommends and endorses a certification program for directors of DNA banks and DNA analysis laboratories, which involves "analyzing test samples and providing appropriate risk assessments based on the test results."

The ASHG role in "ensuring that banks meet patients" was to publish these recommendations, support the certification program mentioned in point 9 above. "advocate

accessibility of testing to all who would benefit", take a lead in education of health professionals and address ethical and social policy issues. Since the publication of these points to consider the ASHG has published a statement on Informed Consent for Genetic Research (1996) based on level of anonymity and study design (retrospective versus prospective).

Robert Weir, DNA Banking and Informed Consent:

Specific recommendations for informed consent for DNA banking in the research context were published eight years later in 1995, in the journal, **IRB, A review of Human subjects research**. These recommendations were based on the results of an ELSI project conducted at the University of Iowa. Bioethicist Robert Weir and associate Jay Horton evaluated 79 consent forms from 50 investigators in 25 states that responded to a letter sent to 155 randomly selected genetics investigators who were members of the American Society of Human Genetic (ASHG). The 24 consent forms that related to DNA banking were used in their study. Seven categories of content was used in the evaluation of the consent forms and form the basis of the subsequent guidelines, including : confidentiality and privacy, control and ownership of biologic materials, withdrawal from the research study, length of storage, future access to genetic information, future third party access, and secondary use. Their contention was that all seven categories should be addressed in a consent form relating to DNA banking and yet they did not find any one form addressing all these areas.

Confidentiality and Privacy.

"Stored biologic materials (tissues, DNA samples, cell lines) and derivative genetic information need to be kept confidential: authorized access to the materials and information is limited to and by the investigators and lab personnel anticipated in the agreement with the sample source; and private: unauthorized access to the materials and information by persons without a professional need to have access is limited by physical and computer security measures."

Control and Ownership of the banked biologic materials.

The consent document should address the investigator's plan for banking, including the possibility of a creating a cell line and address related issues of control, ownership and possible financial profit (eg. the transformed cell lines may be patented and become reasonably profitable). Their suggestion is that "the consent document interpret research participants and investigators as being **sequential owners** of the original tissue sample or cell line and that the research participants be promised a percentage, perhaps 10-25% of any profits resulting from future use of the cell lines." They also offer an alternate process, whereby the investigator would re consent the sample source if a cell line turned out to be commercially valuable. " A disclosure statement along these lines, is, we think, mandatory in consent documents for DNA banking when the source of the tissue sample is likely to remain identifiable and/or when the investigators who secure the tissue sample decide to transform it into a cell line." They further indicate, however, that, if the sample source is anonymous or "truly anonymized" ("so that no subsequent identification of or link to the sample source is possible) and that the investigators do not anticipate any commercial possibilities, the disclosure statement can be omitted from the consent. Nineteen of the 23 documents evaluated did not mention the issue of ownership.

Withdrawal from the research study.

Consent documents frequently address a participants subsequent decision to withdraw from the study. The authors point out thought that "**in genetic studies that involve future**

research on stored material , the issue of withdrawal concerns not only the withdrawal of a participant from a study, but also the decision regarding his or her **continued contribution to** (eg tissue, blood, DNA, cell line) **or personal identification with** an ongoing research project using banked samples."

They recommend that the withdrawal from a study using DNA banking can take two forms: "1. The possibility of participants subsequently requesting that their stored biologic materials be destroyed and/or 2. The possibility of participants subsequently requesting the anonymization of the DNA samples.

Length of storage.

The consent document should indicate how long the investigators plan to store the DNA, rather than suggesting that the materials will be stored for an indefinite period of time, eg. an arbitrary number of years or the period funded for the research. "Either way, investigators would convey a sense of certitude, structure, scientific goal and control to potential research participants, rather than a sense of unplanned, unstructured guesswork about future research." The authors state further, however, "the necessary indefiniteness of research time on immortalized cell lines is different from the time-limited research that is possible with stored tissue samples."

Future (participant) access to genetic information:

The authors first address a research participants "right to know" or "right not to know" personally relevant information gained from the study . "The expectation is grounded in personal autonomy, the right of self-determination and more specifically the right to be informed, at the completion of the research project regarding any information that has been learned that would be of clinical relevance to them or that would be relevant to major decisions they face concerning procreation or appropriate health care." The authors recommend that language in the informed consent indicate that potential research participants have a choice to make-to have access or not to information gained from the study that has "clinical relevance to them." If the participant chooses to be informed, consent documents should indicate the policy of such disclosure: "1. Interim results and/or incidental findings (eg false paternity) to research participants.

Future third party access:

In their study, 20 or 23 documents made no reference to third party access to banked biologic materials or personal genetic information. The authors include family members, employers, insurance companies, government agencies in this category. Although they make no definitive recommendation, the authors suggest that research participants might be interested in restricting this type of access without written consent from the individual participant or their legal representative.

Secondary use of genetic information:

Secondary use was defined by the authors as : " 1. Use of tissue samples or cells lines secured for one genetic study by the principal investigator but for another scientific study with another scientific purpose; or 2. Use of the tissue sample or cell lines by other investigators in the PI's laboratory for different scientific purposes than the original study; or 3. Use of the tissue samples or cell lines by other investigators outside the PI's laboratory but for the same research c purpose; or 4. Use of the tissue samples or cell lines by other investigators outside the PI's laboratory for different scientific purposes."

Because of “the frequent practice of secondary use and the limited awareness of the practice by persons outside the biomedical field”, the authors recommend that “consent forms for genetic research should adequately inform potential research participants about secondary use.” The authors suggest three ways this can be accomplished “by assuring potential research participants that there will be no secondary scientific use of their stored biologic material; by giving them the option of consenting now to future secondary use of their DNA sample , or by promising them that they will be recontacted for consent if the investigators subsequently decide to make secondary use of the stored sample, especially if the purpose is different than the original research study. ”

Another publication from the United Kingdom shows a sharp contrast to the recommendations of the US organizations. For example, for service (or clinical) work, consent, either verbal or written was not obtained prior to blood collection or DNA banking, although the purposes of the investigation were explained to participants. For research purposes, verbal consent was recommended and “ in some circumstances, written consent.”[Yates et al , 1989]. Most the research activities at that time were focused on single gene disorders such as Huntington’s chorea, cystic fibrosis, neurofibromatosis, Duchenne/Beck muscular dystrophy and haemophilia. It is important to note, however, that these guidelines, which were published in 1989, focused on practical aspects of quality assurance, ensuring that each specimen could be correctly identified and tracked to the appropriate family. Yates and colleagues specifically indicated that “medicolegal [or ethical issues] were not being considered.” Other issues brought up in this article were the possibility of a national registry of data, to ensure a centralized monitoring of information and banked DNA for future use by the family.

The most striking example of a national repository is that which has been developed in Iceland.

Discussion of George Annas article-privacy rules for DNA databanks Protecting coded Future Diaries:

George Annas has likened DNA databanks to “an individual’s probabilistic *future diary*”, arguing that genetic information is different from medical information, because the information contained in the DNA is “*more sensitive, written in a code that has only been partially broken and contains information about an individual’s parents, siblings and children.*”(Annas, JAMA, 1993). He further argues that “ current rules for protecting the privacy of medical information cannot protect either genetic information or identifiable DNA samples stored in DNA databanks ”and that the decoding of the human genome “will lead us to alter radically our view of privacy.” Although he suggested that optimally we should have a moratorium on DNA banking until reasonable rules are developed, and that either uniform state laws or federal legislation should be developed, he conceded that these possibilities are unlikely. He therefore recommended voluntary agreement on DNA banking rules and recommended overall that a “DNA databank licensing board be established to license all DNA databanks in the US with uniform rules. Specific recommendations for consideration included the following four areas:

- No DNA databank should be created or begin to store DNA unless three criteria are met:
- a) public notice that a DNA bank is being established and the reason for the bank;
- b) a privacy impact statement prepared and filed with a designated public agency that is responsible for developing and enforcing privacy guidelines for a DNA bank; and
- c) burden of proof should be on the DNA bank to establish that storage of DNA molecules is

necessary to achieve an important medical or society goal.

No collection of DNA for storage is permitted without written authorization and agreement that: a) sets for the purpose of the storage; b) sets forth all uses, including any and all commercial uses; c) guarantees the individual: i) continued access to the samples and all records about the sample; ii) the right to correct incorrect information; iii) the absolute right to order the destruction of the sample or its return should the DNA bank significantly change its identity or cease operation.

DNA samples can only be used for the purposes for which they were collected, and linkages to other computerized information systems are prohibited. Specifically: a. no waivers or boilerplate statements, b. no access to DNA information by any third party without written authorization; no access by third part to any identifiable information; d. strict security measures, including criminal penalties for misuse or unauthorized use of DNA information.

Mechanisms developed to notify and counsel those whose DNA samples are in storage when new information is that can have significant impact on their health is obtainable from their stored DNA.

**ATTACHMENT IV
Data Storage & DNA banking for Biomedical Research from the Public & Professional
Policy Committee of the European Society of Human Genetics (ESHG)**

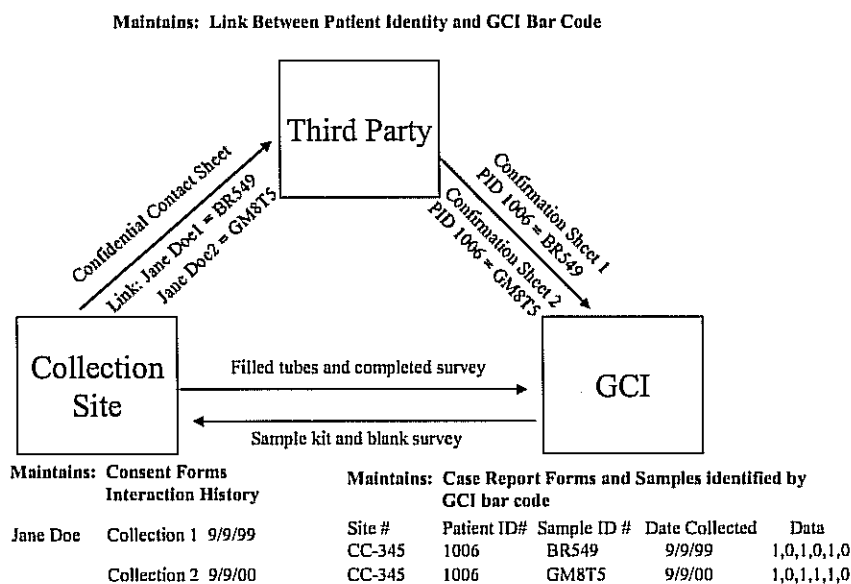
Please refer to:

<http://www.eshg.org/Banking%20background%20consult.pdf>

ATTACHMENT V
Genomics Collaborative, Inc. Third Party System

In this plan, the third party will serve as an escrow agent and will be responsible for maintaining the link between the GCI bar code and the patient identity. Neither GCI nor any other party is allowed access to this link. GCI can request (for itself or on the part of the FDA or a customer) additional information about a specific donor or may request duplicate information from a specific donor to validate GCI's data collection process through the Third Party.

Longitudinal Collection Methodology



The interactions between the collection sites, Third Party, and GCI are illustrated below.

Initial Collection

GCI sends out kits and case report forms to participating sites

Physician identifies patients, completes consent, confidential contact sheet, case report form and blood collection

Physician retains a copy of the consent form and records name and date of collection for the individual who has donated, retaining this information in his/her office (not in the donor's medical record).

Physician sends completed case report form and sample kit, identified by GCI bar codes, to GCI

Physician sends the confidential contact sheet connecting the GCI bar code number and patient name to Third Party.

Re-Contacting Patients

In the event that GCI requires additional data and/or samples from specific donors:

GCI would supply a list of sample ID numbers requiring follow-up to Third Party and supply new case report forms to the collection sites that originally collected the samples.

Third Party will contact collection sites indicating patients require followed up

Physician will send completed case report forms (with an additional sample, if required) to GCI using a new sample ID number

Physician sends link between new sample ID number and patient name to Third Party

Third Party will send the link between new sample ID number and the previous sample ID number to GCI

GCI links new case report forms to existing case report forms.

**Commissioned Paper for the Human Genetics
Subcommittee of the Bioethics Advisory Committee**

Tissue Banking for Biomedical Research

**Kon Oi Lian
National Cancer Centre
11 Hospital Drive
Singapore 169610**

31 October 2001

Commissioned Paper for the Human Genetics Subcommittee
of the Bioethics Advisory Committee
on Tissue Banking for Biomedical Research
Kon Oi Lian
Page 2 of 22

This document outlines procedures currently practised in Singapore for collecting and storing human biological materials* (HBM), surveys the range of biomedical research that use such materials and raises problematic areas encountered in tissue banking.

Preamble

Tissue banking as a means of providing material for medical research is not a new activity. The first known repository was initiated in 1847 by the eminent German pathologist Rudolf Virchow, who eventually amassed more than 23,000 human tissue specimens. Concurrent with the development of pathology (especially histopathology) as a specialised discipline essential for the diagnosis and prognosis of a large number of human diseases (principally cancer, inflammatory and degenerative conditions), pathology departments in hospitals and academic medical institutions have come to house large and near-permanent collections of preserved human tissues. Tissue specimens held in such archives, while originally obtained in the context of medical treatment (i.e. for clinical service), are increasingly recognised as invaluable research resources.

Tissue banking as an adjunct to biomedical research was not, until recently, a prominent activity of mainstream medicine but its backwater status has changed radically as human genetic and genomic research have gathered pace. With initial annotations of the draft human genome sequence at hand, it now appears highly probable that the complete but encrypted set of instructions that specify *Homo sapiens* may soon be comprehensible. Genome mapping and sequencing have also spawned technological advances that, for the first time, enable global surveys of genomes, transcripts and proteins as well as large-scale genotyping of individuals (e.g. by single nucleotide polymorphisms). The convergence of genome information with new techniques for high capacity molecular characterization is expected to yield a cornucopia of discoveries. New insights into human health and disease are clearly of keen interest to both academe and industry. These developments have consequently

* The terms 'tissue' and 'tissues' are used interchangeably with 'human biological materials' in this document since solid tissues are the predominant form of collection in tissue banks.

transformed tissue repositories from esoteric academic resources to invaluable materials with clear commercial value for genetic and genomic research. The emergence of commercial entities in recent years that procure and supply human tissues for the biotechnology and pharmaceutical industries is telling evidence, if any was needed, that human tissues have become coveted commodities.

Against the backdrop of recent accelerated landmark achievements in human genome research, a mood of confidence has predictably become pervasive in biomedical research today. Few, if any, research and technological goals in the field are now regarded as completely unattainable. This exhilarating wave of triumphalism is, however, accompanied by an undertow of disquiet that genetics and genomics possess unprecedented power over individual human health and happiness. Resurgent awareness of potential uses and abuses of medical, especially genetic, research has rightly served to focus attention on operational, bioethical and legal aspects of tissue banking – particularly as they pertain to the protection of human research subjects - and of the need to devise principled policies to govern academic-commercial collaborations.

Tissue Holdings in Singapore

Human biological materials used in research may take the form of solid tissues, body fluids (mainly blood and derivatives thereof) or cells. Such materials are harvested in different contexts, for a range of purposes, and are stored and used in variable ways.

Some HBM collections are initiated for the sole intention of providing material for research only. These tend to be collections of fresh frozen tissues (less commonly of cells or blood components) accumulated by particular investigators for specific research projects. Such project-based collections comprise the majority of tissue holdings in Singapore. They are often limited in scope (both in quantity and type of tissue stored) and generally not available to multiple users for other research projects i.e. they are closed ‘private’ collections.

Multi-user tissue repositories differ from the foregoing in the antecedent intention to develop core research resources that serve, through formal application and oversight procedures, to provide HBM to investigators who may or may not have contributed to the actual process of tissue acquisition i.e. these operate as open 'public' collections, usually with long-term funding. Repositories of this type are uncommon in Singapore although clearly advantageous in accelerating disease-oriented research.

Less well recognised as *de facto* tissue banks are HBM collections, particularly those extant for a decade or longer, that did not originate from planned research efforts but whose continued existence in the genomic era makes them highly tempting to investigators. These are principally large archives of formalin-fixed human tissues stored as paraffin blocks in pathology departments, blood (or blood-derived) samples in blood banks, clinical chemistry and haematology laboratories and other more specialised collections e.g. gamete, cord blood and embryo banks. HBM stored in these locations are nearly always by-products from the provision of a range of clinical services during the course of standard health care i.e. they arose from medical services rather than from primary biomedical research.

Population-based studies such as population genetics, disease registries, clinical genetic services, neonatal and adult disease screening programs may all come to possess large collections of HBM (usually blood) linked to demographic and medical information. Such collections may also function as 'accidental' tissue banks for *post hoc* research objectives. This constitutes secondary use of human tissues. Furthermore, HBM such as lymphocytes obtained from identifiable subjects, families or other groups may be immortalized, thereby generating an unlimited supply of source material that obviates the need to return to the same subjects for more biological material. This has been a technically helpful expedient especially in clinical genetic services and in research on multi-generational families or siblings aimed at the identification of disease-causing genes or the transmission of familial mutations.

Recognising the value of genotypes in the identification of individuals, some countries have developed HBM collections of defence (e.g. military) personnel and of

penal populations. It is a reasonable prediction that such practices are likely to be more widely adopted by many more countries in the near future.

Tissue Banking Procedures in Singapore

A representative overview of tissue banking procedures in Singapore requires a reliable survey of its practitioners. Such information is not available to the author of this document. Nevertheless, tissue banking may be considered broadly as comprising a suite of interlinked processes, some of which are outlined below.

Bioethics procedures

- (a) Obtaining and documenting comprehension and consent of subjects to provide tissue(s), as well as any conditions that may accompany such decisions (e.g. the ability to specify type of research, duration of storage, provision for re-contact and to be informed of results of tissue analysis, family's status regarding disclosure of genetic data, profit sharing, posthumous use), and the benefits and risks of providing tissue for research
- (b) Clarifying 'ownership' of banked tissues and the nature of such tissues e.g. as waste products, outright donations or conditional gifts
- (c) Balancing the relative rights and responsibilities *vis-à-vis* human subjects whose tissues are banked, medical and research personnel who 'add value', the institution that performs tissue banking, governmental and other funding agencies (including commercial backers).
- (d) Rational and consistent application of policies on retaining and using or disposing of tissues harvested without prior documented consent and on the practice of obtaining retrospective consent
- (e) Establishing safeguards against inadvertent and improper disclosure of identifying and/or confidential information when data derived from tissue-based research are deemed to require correlative medical and/or personal data for enhanced interpretation

Operational aspects

- (f) Harvesting tissues that are surplus to clinical care without compromise to the tissue donor
- (g) Storage of harvested tissues in conditions that are optimal for research
- (h) Developing an inventory system for tracking and retrieval of banked specimens
- (i) Implementing safeguards against physical loss or significant deterioration of tissues and/or associated records
- (j) Quality verification of banked tissues
 - histopathological diagnosis
 - pathogen status
 - integrity of biological macromolecules e.g. nucleic acids and proteins
- (k) Training repository personnel to high standards of safe laboratory practice, awareness of biosafety, meticulous inventory keeping, databasing and appropriate conduct regarding privacy and confidentiality.
- (l) Supporting the tissue bank with a database, having carefully considered:
 - mechanisms to prevent identification of donors to researchers
 - policies and practices that disallow direct access of researchers to donors, donor relatives and their medical/other records
 - defined categories of information to be extracted from the donor's medical/other records for the tissue bank database
 - security measures for controlled access to the tissue bank database
 - policies on sharing tissue bank resources (e.g. tissues, databases, processed experimental data) with academic (not-for-profit) institutions, commercial entities, foreign countries and governmental agencies.
- (m) Consider post-harvest processing for scarce tissues
- (n) Develop safe and acceptable disposal process(es) for culling tissues from the bank

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Allocation of HBM resources for research

- (o) Define policies and procedures to evaluate and render decisions on requests from investigators to withdraw tissues from the bank
- (p) Ensure compliance with conditions for use of banked materials (e.g. acknowledgement of source, indemnification against injury, non-warrantability, presumptions of safe laboratory practice, authorship/collaboration rights, transfer of materials to third parties, commercial use or otherwise)
- (q) Establish priority of allocation, if necessary, when tissues are limiting

A general impression of tissue banks in Singapore is that few, if any, operate to the foregoing undemanding standards. A Manual of Standard Operating Procedures of the National Cancer Centre's Tissue Repository is appended as an example of how tissue banking is practised in one institution in Singapore. It details the policies and operational practices of this multi-user resource that was established to facilitate cancer research.

The Case for Informed Choice of Human Subjects

Possibly the most egregious feature of current tissue banking practice in Singapore is common neglect of the informed consent process - not from ignorance but rather from the desire not to inconvenience investigators or impede the pace of research.

Obtaining the consent of human subjects has not always been considered as important as it is today. More stringent standards of conduct have evolved mainly as a consequence of major innovations in genetic and genomic analysis coupled with a perception that genetic information has unique properties not shared by other forms of biological information. In essence, genetic information

- (i) reveals an individual's past and present
- (ii) possibly predicts a person's future
- (iii) is informative of families
- (iv) may be informative of ethnic groups

- (v) is obtainable without consent
- (vi) may be accessible indefinitely
- (vii) has potential commercial value.

These far-reaching implications of engaging in genetic/genomic analysis of human subjects call for substantially higher levels of bioethics sensitivity than is currently prevalent in Singapore. The foundational reasons for operating, whenever feasible, within the bounds of informed choice freely given by competent subjects are:

- (i) respect for individual autonomy, rights and privacy
- (ii) protection of research subjects against exploitation and abuse
- (iii) protection against discrimination
- (iv) protection against stigmatization
- (v) fostering trust and
- (vi) winning public support for biomedical research

By virtue of its personal, familial and societal nature, genetic information is justifiably regarded as being more susceptible to misuse.

Research Involving Human Biological Materials

Although research using human tissues antedates the genome era, recent advances have greatly increased its demand. Research for which HBM is essential may be considered in three partially overlapping domains. (Certain uses have matured into standard methods employed in clinical care.)

Human genetics Diagnosis of genetic diseases through mutation analysis, prenatal diagnosis (including embryos obtained by *in vitro* fertilisation), carrier detection, reproductive counseling, risk assessment (e.g. of cancer, Alzheimer's disease), predicting responses to pharmacological agents (pharmacogenetics) and discovery of disease-causing genes (e.g. by positional analysis) cannot be performed without recourse to human tissues.

Global molecular analyses Techniques for simultaneous analysis of large numbers (typically thousands) of macromolecules e.g. genomic DNA, messenger RNA, proteins and metabolites on relatively small, compact and high density or high throughput physical platforms are increasingly characteristic of technology employed in biomedical research. This feature distinguishes the newly emergent ‘-omic’ disciplines from their precursors e.g. ‘genomics’ and ‘transcriptomics’ from genetics, ‘proteomics’ from protein chemistry and ‘metabolomics’ from classical metabolic studies. Global surveys (or profiling) of cells and tissues are likely to be more effective and efficient at identifying biological networks and circuits than traditional gene-by-gene or protein-by-protein approaches.

A few examples will suffice to illustrate how tissue-based global surveys are poised to expand, deepen and transform current knowledge of human biology. Correct classification of diseases and accurate diagnosis are the foundation of treatment. While disease taxonomy has long relied principally on tissue and cellular morphology, certain clinical observations point persistently to biological heterogeneity within apparently homogeneous categories. Resolution of this conundrum is emerging from the capacity to generate transcript profiles (‘molecular signatures or portraits’) of tissues taken from subjects bearing the same clinical and histopathological diagnosis. That molecular signatures constitute a biologically relevant and robust basis for refining disease taxonomy has already been demonstrated for several human cancers in the past two years – and will undoubtedly be extended to many more disease states. This in turn is likely to lead to new diagnostic methods having superior precision and sensitivity. Refining taxonomy *per se* would not, in itself, be of general interest were it not for the fact that more precise diagnosis has also been shown, for certain diseases, to predict response to treatment and survival to a degree that current taxonomy does not.

Another application of high throughput analytical techniques is the study of genetic and genomic variations (polymorphisms) among individuals of similar ethnicity and between ethnic groups. Intense efforts, particularly by the

pharmaceutical industry, to map and investigate genetic polymorphisms for possible correlations with phenotypes of interest is premised on the likelihood that some will prove to be predictive of future events e.g. response to environmental and exogenous influences including drugs and disease occurrence, in addition to forming, at least in part, the substrate for behavioural traits and cognitive functions e.g. learning and social skills.

Molecular profiling of tissues under defined conditions is also thought to be a powerful approach to mining the genome for new drug targets against which entirely novel therapeutic agents could be developed. This prospect is especially alluring when the number of current drug targets (fewer than 500 gene products) is far below even the tentative gene content of the human genome (estimated by both major genome groups to be approximately 30,000).

Large-scale genotyping and molecular karyotyping are other variants of the same technological principles that are being applied to dissecting the genetic contributors of complex diseases (e.g. obesity, diabetes, hypertension, asthma, neuropsychiatric disorders and many others) and to delineate detailed pathways of disease causation.

Cell and tissue engineering Although most banked tissues are unviable when withdrawn for use, specialty banks exist for long-term storage of viable cells and embryos. Such banked resources and freshly harvested tissues are used in research aimed at regenerating differentiated cells (with or without additional genetic modifications) having therapeutically desirable properties e.g. neurons, blood-forming cells, insulin-secreting cells, skin, cartilage, that would be useful in cell-based treatment of a wide range of human disorders.

Problems and Issues

Notwithstanding its relatively long history, contemporary tissue banking poses questions and problems that are troubling, contentious, potentially litigious and probably insoluble by imposing universal standards of policy and practice. What

follows is an outline of some of the more pressing dilemmas that the writer has encountered in Singapore.

(a) Informed consent

The most serious and common flaw is the wilful or unintended failure to even consider the need to obtain consent from human subjects before their tissues are banked. The omission is usually justified on the grounds that patients will be 'confused' if consent is sought and/or that obtaining consent is intolerably cumbersome and obstructs research. In certain collections, human subjects are not even informed that their cells will be immortalized, with all the implications thereof. Harvesting tissues from children, mentally impaired (incompetent) and posthumous sources requires special consideration. Tissue archives that pathology departments retain for many years may raise problems when used for research. Such tissue blocks were nearly always obtained during the course of standard medical care (i.e. they accrued as an integral part of clinical service rather than research), yet often come to be recognised as highly valuable resources for (retrospective) research. The possibility that it might be proper to seek consent before using paraffin-embedded tissues for research seldom surfaces among investigators (perhaps because it is suppressed and ignored), nor is much effort given to devising ethically and socially acceptable alternatives if consent has not been obtained for research use. Similar considerations apply also to research use of blood specimens or blood derivatives that remain from clinical chemistry and blood banking services, or from population studies.

(b) Overreliance on quasi-legal procedures

Informed consent policies that are developed after extensive review of the recent bioethics literature are likely to be excessively reliant on legal procedures for a veneer of propriety. When tissue banks act under compulsion to adopt informed consent practice without a corresponding understanding of

and commitment to the true purpose of the informed consent process, human subjects remain equally unprotected against exploitation. There is a pressing need for investigators to act on the clear understanding that one of several key elements that should underpin informed choice is information of appropriate quantity and complexity that could be comprehended by subjects from whom tissues are sought. Merely procuring a subject's signature on a consent document unaccompanied by the subject's comprehension of what is being done violates the purpose of seeking informed consent – although it might simulate rectitude. Assessment of how much information should be presented for subjects to sufficiently comprehend what is being asked of them, and thus to enable consent to be freely given or withheld must be firmly emplaced within the cultural, socioeconomic, religious and educational context of particular societies. Too little or too much information militates against understanding. Thus, the manner in which informed consent is obtained may well change with time in societies whose levels of literacy and social development are evolving. An unhelpful opinion especially prevalent among the *literati* holds that policies and practices espoused by North American bioethicists should *de facto* become the 'gold standard' to which tissue banks in all countries must operate or be found wanting. Such an unthinking embrace of standards that even North American tissue banks do not uniformly adopt or practise reflects an unhealthy preoccupation with external appearances of propriety rather than a sincere purpose of protecting human subjects and building public trust in biomedical research.

(c) *Disposition of unconsented tissues and the practice of retrospective consent*

Careful consideration should be given to deal with the ethical, legal and social impasse when scientifically persuasive reasons are advanced for secondary and retrospective use of HBM collections unconsented for research e.g. tissue blocks in pathology departments, stored blood samples, embryos and progenitor cells. A related question is the propriety (feasibility aside) of seeking retrospective consent.

(d) Status of banked tissues

It may be helpful for each tissue bank to clarify what it regards to be the status of banked tissues, as this may modulate the approach to informed consent. Surplus tissues that are harvested for research may be considered waste products in which the subject of origin has no interest and perhaps no rights (e.g. placentas). Banked tissues may be considered instead to be outright donations from subjects who, in consenting to donate, also renounce their interests and rights in such materials. An intermediate position regards banked tissues as conditional gifts for which donors may specify terms of use. It would appear that all three designations could be justified and implemented. However, tissue banks rarely articulate the category in which they operate, although widespread neglect of the informed consent process suggests that most have seized the implicit prerogative of treating surplus tissues as waste.

(e) Ensuring uncompromised medical care

Tissues that are banked for research must be surplus to the requirements for making accurate and complete diagnoses. Overzealous harvesting, especially of cancerous tissues, puts the patient at clear risk of incomplete or even wrong diagnosis, leading to sub-optimal treatment or worse, to no treatment if excessive tissue had been removed for research. For example, advanced cancer may be diagnosed wrongly as early cancer, or the diagnosis of cancer may be missed entirely if the cancerous portion of a tissue specimen had been completely removed for research, leaving behind only normal tissue for diagnostic evaluation. There is an urgent need for tissue banks to operate under guidelines to ensure that patients' interests are not made subservient to research.

(f) Quality of banking

Tissue banks have a clear responsibility to operate competently to preserve the physical integrity of stored tissues for biomedical research, if such tissues are not considered waste products but rather donations or gifts from individuals who freely chose to contribute to biomedical research. The corollary of this

position is that soliciting tissue donations without the operational competence to properly store tissues is unethical.

(g) Assessing research requests

An axiom that remains cogent is that 'bad science is bad ethics'. Tissue banking is not limited to establishing and maintaining competence of physical operations but should function in tandem with impartial and scientifically credible procedures that evaluate the merit of research projects for which tissues are requested.

(h) Secondary use

HBM that was originally obtained for a specified research purpose may sometimes be useful for other types of research. Whether such secondary use requires fresh consent from the subjects whose tissues/blood are diverted to other research projects is a contentious and unresolved problem.

(i) Ownership

Tissue banks need clear and consistent policies on ownership. Competing claims to partial or complete ownership of HBM emanate from several sources i.e. subjects whose tissues are collected, clinicians who perform tissue harvesting, institutions that provide physical and other support, sources that finance tissue banks, investigators and others who add value to the tissue collection. The question of ownership applies not only to the physical forms of HBM but equally to derivatives - whether in the form of data, discoveries or biological products.

(j) Confidentiality and privacy

It is generally agreed that permanently and completely unidentifiable HBM is of limited research value. Such material could be used in prevalence studies but little else. HBM released to investigators should not bear any information that could identify the subject from which it was obtained but could be linked, with appropriate safeguards, to clinical (though not personal) information about the subject that may be relevant to the research objective(s) and that would enhance interpretation of research data.

Tissue banking operations therefore frequently encompass databases of varying depth and quality to provide regulated access to linked information of correlative value. Biomedical communities that are new to tissue banking are often uninformed of the need to protect the confidentiality and privacy of medical and personal information. Moreover, little consideration is given to how access to medical records could be allowed, if at all, to individuals outside the clinical care team. At an even more rudimentary level, HBM may not always be provided in coded manner to investigators. The assignment of a unique National Registration Identification (NRIC) number to each Singapore citizen and permanent resident and its ubiquitous use makes this single identifier a key that could turn many locks in national and institutional databases.

(k) A dichotomy of standards

While the power of genetic information has rapidly come to be appreciated by societies at large, it is also narrowly perceived that only analyses involving nucleic acids (i.e. DNA and RNA) yield genetic information. The fact that superficially 'non-genetic' analyses e.g. of proteins, hormones, metabolites, and even radiologic imaging may, in certain situations, be equally informative as genotyping appears to have escaped many. This may explain the invidious tendency to handle what is wrongly perceived to be 'non-genetic' medical information with much less care and attention to bioethics concerns than overtly 'genetic' information. This common and unacknowledged dichotomy of standards is not only irrational but, given the relatively large corpus of medical information not derived from DNA and/or RNA analysis, continues to place numerous human subjects at risk of breached confidentiality and privacy.

(l) Disclosure of data and re-contact

Tissue banks differ significantly in their policies on whether results from tissue or blood analysis, especially if considered to have potential medical implications, are disclosed to the subject and/or relatives. Some offer subjects

the choice of receiving information about analysis of their tissues/blood. Other operations do not disclose such information on the grounds that observations gleaned in a research project are of uncertain clinical significance until reproduced and rigorously validated by other investigators. A related issue arises when re-testing is judged to be in the subject's interest for clinical management. In such instances, re-testing should optimally be performed in a facility accredited for provision of clinical laboratory service.

(m) Commercial access to tissues and data; sharing profits and benefits

Keen and aggressive commercial interest in human tissues, medical information and data derived therefrom is a development whose ramifications are as inescapable as they will be enduring. The large financial investments required to develop new pharmaceutical agents, diagnostic tests, novel treatments and devices for clinical use compel collaboration of not-for-profit research institutions with the biotechnology and pharmaceutical industries. This economic reality of medical progress urges reflection on how research integrity and just treatment of human subjects can be upheld when conjoined with overtly commercial interests. The manner in which profits and/or benefits reach individuals and communities should garner public support by winning society's trust. Points to consider in this regard are informing patients in advance of possible commercial interest in and exploitation of research performed on HBM, whether profits will be shared with patients, and how material and non-material benefits of applied research might reach the community.

Recommended Policies

1. Increase awareness and practice of bioethical tissue banking

Prevailing awareness of bioethics among biomedical researchers in Singapore is disturbingly low and not consonant with Singapore's aspiration to excel in medical care and research. Clinical and other investigators need to become far more knowledgeable about bioethics of the genome era, to be aware of clearly

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proscribed actions and controversial issues.

2. Encourage basic standards for all tissue banks

All tissue collections in Singapore should be urged to function to basic standards of bioethics and operational competence. Departments and institutions that possess service collections of tissues, blood and other HBM should use (or allow the use) of such materials for retrospective research only with rigorous ethics oversight and approval.

3. Mandate involvement of pathologists in tissue banking

Tissue harvesting, particularly of surgically excised and biopsied samples, should always be performed under the guidance of trained surgical pathologists. This optimizes harvesting of surplus tissues for research while ensuring that complete and correct diagnosis is not compromised. Operating in an adversarial relationship between tissue bankers and pathologists is liable to undermine the reputation of tissue banking and expose clinicians to medico-legal risks.

4. Tissue audits

Regular audits of tissues that were also harvested for banking could be performed to ascertain the frequency, if at all, of compromised tissue evaluation and diagnosis by inappropriate harvesting.

5. Develop institutional standards of basic tissue banking procedures

Academic and medical centres that engage in tissue banking could be encouraged to accelerate development of acceptable standards by providing their faculty/staff with standard institutional procedures that meet basic standards of tissue banking. The availability of such 'template' operational procedures could be modified for specific purposes but would nonetheless be time-saving for individual efforts.

6. Train tissue bankers

There is a dearth of structured training for personnel at all levels who are employed to bank tissues for research. That tissue banking is still a relatively

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small activity makes formal training courses even rarer. Nonetheless, some effort should be made to identify training courses in better developed countries or to consider initiating some form of regional training.

7. Develop appropriate informed consent

Deliberately collecting tissues from human subjects without their prior informed consent would be regarded, by current standards, to be akin to rogue behaviour. There is a pressing need in Singapore to develop contextually appropriate processes for research subjects to make informed choices without adopting *en masse* practices espoused in more litigious and literate societies that are likely to seriously impede research (and all the societal benefits that derive therefrom), while not concurrently affording real protection to research subjects in Singapore. In this regard, North American hegemony in the bioethics literature badly needs to be balanced by bioethics models from other cultures and societies. The establishment of an Asian Centre for Bioethics could well be valuable in bringing other views to bear on this growing field.

8. Records and audit of informed consent

Tissue banks could be encouraged to retain documentation of the informed consent of all research subjects and to perform periodic audits to ascertain compliance with and quality of the informed consent process as practised in their host institution.

9. Resolving the dilemma of unconsented HBM

Notwithstanding the problems presented by retrospective use of HBM that were collected when bioethics standards were far less stringent, it may still be possible to develop acceptable mechanisms and safeguards to enable release of these valuable resources for research. A multidisciplinary coalition, including lay representation, could be entrusted to examine the issues and propose recommendations.

10. Security of medical and other information

More carefully regulated access to medical records and clinical databases is needed. It is at present neither difficult nor unusual for individuals outside the

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clinical care team to obtain such records and information. Chart reviews have been assigned to individuals who may not be fully cognizant of the need to maintain confidentiality.

Conclusion: Achieving Balance

The landscape of biomedical research has changed irrevocably and the genomic sciences have thrown up new issues in bioethics that cannot be ignored. The way forward is neither through overprotection of research subjects nor overprotection of research interests, whether academic or commercial. Asian biomedical research centres need to develop confidence to work out the dilemmas presented by the genomic sciences in their own cultures, and to develop codes of conduct that uphold the protection of individuals while not denying society the benefits of research.

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38. National Bioethics Advisory Commission (USA) Publications and Reports
<http://bioethics.georgetown.edu/nbac/pubs.html>
39. National Reference Center for Bioethics Literature, Georgetown University (USA)
<http://www.georgetown.edu/research/nrcbl/>
40. University of Montreal, Canada
GenConnect is a compendium of more than 300 governmental and non-governmental organizations formulating policies
<http://www.humgen.umontreal.ca/en/>

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<http://www.nuffieldfoundation.org/bioethics/publication/pub0000000308.html>
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CONSULTATION PAPER

HUMAN TISSUE RESEARCH

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SINGAPORE

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About the Bioethics Advisory Committee

The Bioethics Advisory Committee ("the BAC") was appointed by the Singapore Cabinet in December 2000. The BAC was directed to "examine the legal, ethical and social issues arising from research on human biology and behaviour and its applications" and to "develop and recommend policies ... on legal, ethical and social issues, with the aim to protect the rights and welfare of individuals, while allowing the Life Sciences to develop and realise their full potential for the benefit of mankind".

The BAC reports to the Ministerial Committee for Life Sciences. For further information about the BAC and its work, please visit <http://www.bioethics-singapore.org>

Contacting the Bioethics Advisory Committee

The BAC welcomes views, comments, suggestions and other feedback on the issues raised in this and other consultation papers, or on any bioethical issue within its remit. All feedback should be addressed to:

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I. INTRODUCTION

1. About this Paper and the consultation process

- 1.1. This Consultation Paper on Human Tissue Research (the “**Paper**”) is issued by the Bioethics Advisory Committee, Singapore (BAC) as part of its efforts to obtain professional and public feedback on the issues outlined in this Paper. The feedback and suggestions received by the BAC will help inform and shape the recommendations which the BAC will be making to the Government.
- 1.2. Human Tissue Research is a broad field of inquiry. This Paper is not intended as an exhaustive survey. Instead, we propose to focus on a few specific issues arising out of the practice of human tissue banking which we think require resolution as a matter of priority. Other issues (some of which are also identified in this Paper) may be addressed at a later time in separate consultation papers.
- 1.3. We have made preliminary recommendations on issues where we think such recommendations may be reasonably and confidently advanced. We invite views, comments, suggestions and other feedback on the preliminary recommendations outlined in this Paper, and on such other issues as we may have identified in this Paper.
- 1.4. The recommendations in this Paper are intended primarily as a springboard for discussion, and do not necessarily represent the final recommendations which the BAC may make to the Government.

2. Definitions

- 2.1. In this Paper, we use the term “**human tissue**” to refer to all kinds of human biological materials derived from living or cadaveric donors, including solid body tissues, organs, fetuses, blood and other body fluids and their derivatives, cord blood, embryos, gametes (sperm or eggs) or any part or derivative thereof.
- 2.2. As blood banking is already well-regulated in Singapore, we exclude **blood banking for therapeutic purposes** from the ambit of this review, and do not include it in our definition of “**tissue banking**”. However, we do include in our definition research involving studies of blood collections (whether the original samples were collected for therapeutic or research objectives, or a

combination of both) or the use of such blood samples or their derivatives for purposes other than direct therapeutic ones such as transfusions.

- 2.3. The recommendations set out in this Paper are intended to apply generally to all human tissue as defined above, with the caveat that account should be taken of specific recommendations which the BAC may have made or may make in relation to human embryos, cord blood, gametes and stem cells in its separate report and recommendations on **human embryonic stem cells and human cloning**.

3. Formulating Principles

- 3.1. In recent years, much public attention has been focused on developments in the new life sciences, and on genetic and genomic research in particular. These new life sciences offer enormous promise of potential benefits.
- 3.2. In many of the current thrusts of the new life sciences, researchers are entering completely new grounds which raise many novel legal, ethical and social issues. Consequently, the body of community ethics is being asked to offer ethical direction and guidance for the ethical conduct of research in entirely novel situations for which there are no readily available precedents. In many areas too, the state of the law sometimes lags far behind the realities of the current and future state of technology, so that practitioners and researchers in the new life sciences must act in the absence of clear legal guidance.
- 3.3. We believe that, in this respect, the development of sound ethical principles which are acceptable to and supported by the community at large will assist in the formulation of the law in areas and for situations where this is eventually felt to be necessary. Such a body of sound ethical principles will also serve as the common understanding on which ethical research work may be carried out.
- 3.4. We take the view that the vast majority of scientists and researchers are responsible and are acutely aware of potential ethical concerns in the work that they do, and in that which they may propose to carry out. Most wish to do what is ethically right. Indeed, many may be inhibited from participating in some areas of research (which may in fact be entirely acceptable to the community, and in the public interest) by the lack of clear ethical direction or agreement on a given point, or by uncertainty generated by controversy in related areas.
- 3.5. Where there is broad agreement in leading jurisdictions on applicable principles, we have in general tended towards recommending the adoption of

these principles. It is only recently that various developed jurisdictions have embarked upon the task of the formulation of guidelines and rules for the governance of the new life sciences, and to examine the ethical issues involved. In some areas, an international consensus is beginning to emerge. But in many other areas, the future shape of the body of ethics is still being debated. It is hoped that the feedback received by the BAC on this Paper will help advance that process. For these reasons, too, the recommendations which we make at the end of this Paper are advanced as Interim Recommendations, pending the emergence of a clearer body of consensus and direction internationally in the areas under discussion.

I I . H U M A N T I S S U E R E S E A R C H

4. The Role and Promise of Human Tissue Research

- 4.1. Research involving the use of human tissue, or the use of information derived from such human tissue, is a fundamental cornerstone of modern medical research and knowledge. Many of the advances in the life sciences which have contributed so much to our health, physical well-being and long life expectancy are founded on knowledge gleaned in one way or another from human tissue research. For instance, vital epidemiological information about the pattern and incidence of occurrence of various forms of diseases such as cancers has been (and continues to be) gained from human tissue research, and through the analysis of such information, important discoveries about the prevention, control and treatment of such diseases have been made for the benefit of humankind.
- 4.2. In the future, human tissue research is likely to assume a more important role as new uses for the information derived from such research are discovered. Most notably, almost all forms of genetic and genomic research use human tissue, directly or indirectly, as the starting point of their investigations.
- 4.3. Although tissue banking in some form or another has been practised for well over a century, it is only in the last decade that tissue banking has come into the public limelight with the recent surge of interest in the new life sciences, and in particular, in the fields of human genetics and genomic research.
- 4.4. In the past, human tissue collection and banking has arisen largely as an incidental adjunct to the collection of human tissues primarily for diagnostic procedures and pathological examination. These collected tissues were put to research purposes after their primary purpose was exhausted. Through this process, however, a great deal of extremely valuable information was gained

for the advancement of medical science and public benefit. With the rise of the new life sciences, and in particular in the context of recent advances in the fields of human genetics and genomic research, tissue banks and collections have assumed a new importance.

- 4.5. At the heart of the matter is the fact that research involving the study of human tissue samples, or of the information gleaned from such research, or both, lies at the very foundation of nearly all lines of genetic and genomic research and enterprise.
- 4.6. Even given the likelihood of at least some dead ends and over-optimistic media hype in the emerging fields of human genetics and genomic research, there is a general consensus that many of the answers and solutions to some of the most intractable medical and public health problems are likely to emerge from genetic and genomic research and enterprise in the near future. Apart from providing therapeutic advances, the genetic and genomic sciences now offer exciting new prospects in the field of preventive medicine, especially through advances in genetic screening.
- 4.7. In this Paper, we attempt to canvass some of the issues which we think need to be eventually addressed for the establishment of a sound ethical, legal and social foundation for the proper conduct of human tissue banking and research in Singapore for now and for the future.

5. Human Tissue Banking In Singapore

- 5.1. In the past, human tissue banks in Singapore have been built up largely as an incidental by-product of diagnostic procedures. Most commonly, human tissue samples would be removed during surgery or other medical procedures and processed for pathological examination and investigation. For example, suspected tumours would be preserved or fixed in the form of paraffin blocks to facilitate further pathological investigation. These tissue collections largely comprise tissue slides, paraffin blocks and tissue preserved with wet preservation techniques. These techniques generally render the cellular material non-viable. Some large collections, mostly institutional, have been assembled in this way.
- 5.2. Pathologists in Singapore have traditionally taken (and continue to take) the view that this retention is on the basis that these tissue samples forms part of the medical records of the donor, and that they (and the institutional host for the collection) are “stewards and guardians” or custodians of these tissue samples on behalf of the donors.

- 5.3. Human tissues are collected not only from living donors, but also from the dead. Cadaveric tissue samples are also collected in the course of coronial or consensual autopsies for the purposes of diagnostic procedures.
- 5.4. On completion of the pathological investigations, these tissue samples (from living and cadaveric donors alike) are generally archived and added to the human tissue collection. The Chapter of Pathologists of the Academy of Medicine, Singapore, states that this is done “in accordance with current good clinical practice guidelines, [so that] the case files (in this case [the] slides and blocks) can be reviewed and perhaps sent for expert opinion. The tissue is kept against the chance that there may be a medico-legal challenge regarding the diagnosis or [in the case of living donors] the possibility that new prognostic and therapeutic markers may be developed, and used during the patient’s lifetime”.
- 5.5. The largest collections of these kind of **“incidental” tissue banks** are generally held by hospitals, teaching centres and large health institutions, although some much smaller “private” collections held by individuals or groups of individuals apparently do exist. These “private” collectors may be specialist physicians or medical researchers with research interests in specific medical conditions. In some of these cases, these private human tissue collections have been accumulated on the principle that the referring physician has the right to the possession or at least the return of the human tissue sample.
- 5.6. Currently, there are no clear guidelines as to whether referring or sending physicians have a right to demand the return of these tissue samples.
- 5.7. In general, our view is that human tissue collections by private individuals should not be encouraged, and that, as far as possible, tissue banks should be held by institutions (for example, by a hospital, a university or a research institution). Such institutions may be of a public (e.g. a teaching hospital) or private (e.g. a private hospital, or a private commercial research venture) character. If non-institutional collections have to be made for any reason (for example, collections of a specific kind of tissue pursuant to a specific research project), such collections should only be assembled on the understanding that the human tissues collected will eventually be consolidated with the larger collections of institutions. Institutional human tissue holdings need not be physically centralised. It would be sufficient, for example, for an institution to have in place a current database of all human tissue holdings within that institution. Such a database could be part of the institution’s database of research projects, with information fields such as the research area, disease, human tissue collected, where they are stored within the institution, and the units and persons responsible for these human tissues.

- 5.8. Consolidation of smaller human tissue collections in larger institutional holdings confers many benefits. A larger institution has more resources for the proper maintenance and stewardship of the human tissue samples under its charge. Continuity and preservation of the human tissue samples are also assured, and there is a greater likelihood of their being available to a wider pool of researchers. By itself, the size of holdings is also an important benefit of consolidation: a large-scale collection is more useful (particularly for population studies) than a small and limited collection.
- 5.9. In recent years, however, tissue banking in Singapore has moved beyond the merely incidental towards **purpose-assembled research banks**. In this kind of tissue bank, human tissue is collected purely or primarily for the purpose of research, and not merely as an incidental benefit of diagnostic procedures.
- 5.10. There has also been a parallel trend towards the establishment of collections of human tissue in which the biological material remains viable or potentially viable, at least in some respects, at the cellular level. For instance, human tissue samples may be flash-frozen, and/or living cell lines may be propagated on culture media. This greatly increases the value of the samples for many lines of research.
- 5.11. We take the view that such purposed-assembled research banks are to be encouraged, provided that all appropriate ethical and legal considerations and concerns are appropriately met and addressed, as they promote and enhance research, which offers the promise of immense benefit in the future for humankind.

III. LAW & PRACTICE

6. Current Law

- 6.1. There is currently little in the way of law (either common law or statutory law) governing some of the most fundamental questions in relationship to tissue banking in Singapore.
- 6.2. In respect of donations of cadaveric tissue, Parliament has provided a statutory mechanism for donation in the form of the Medical (Therapy, Education & Research) Act. This enables people to state in advance their intention to donate their bodies, organs or tissues for research or for transplantation after their death. It also enables the family of a deceased

- person to donate the body, organs or tissues for research or for transplantation.
- 6.3. In relation to gifts by *living* donors, there is currently very little guidance in the way of either the statutory law or common law, outside of some provisions in the Human Organ Transplant Act.
 - 6.4. Currently, the only express statutory provision for the governance and regulation of tissue banking is to be found in the Private Hospitals and Medical Clinics Regulations 1993. These Regulations provide that where a “private hospital” (no mentioned is made of individuals, or of private clinics or research laboratories) proposes to perform certain specified specialised procedures or services, prior approval of the Director of Medical Services must be obtained at least 30 days in advance. “Tissue banking” and “sperm banking” are included in the list of specialised procedures or services which require such approval. Tissue banking is not defined in the Regulations, or in the parent Act, or indeed in any other statute. Neither the Regulations nor the parent Act spell out any guidelines for the proper conduct of tissue banking.
 - 6.5. At the present time, there does not appear to be any uniform approach to the governance and regulation of tissue banking internationally. The Draft Discussion Document entitled *Data Storage and DNA Banking for Biomedical Research: Informed Consent, Confidentiality, Quality Issues, Ownership, Return of Benefits: A Professional Perspective* issued by the Public and Professional Policy Committee of the European Society of Human Genetics as part of the EUROGAPP Project 1999-2000 offers an illuminating survey of the gamut of existing opinions, legislation, guidelines and other policy statements applied in or issued by EC institutions, 18 European countries, the United States, and international organisations. Except in the case of the United States, and possibly France, the majority of the jurisdictions surveyed are notable more for the absence of specific agreed national guidelines or legislation than by the presence of such in relation to storage of data derived from human tissue research and DNA banking.
 - 6.6. For the present time, the BAC concludes that a full consensus on many issues has yet to emerge on many of the most critical issues in relation to human tissue banking. The most intractable problems in this regard are the issues of property, control and ownership rights to tissue samples.
 - 6.7. We think, however, that it is desirable that a review be undertaken of the law governing this area, and a professional and public dialogue initiated to discuss the ethical and social considerations which should inform the shape of the law in this area.

6.8. Legal review has recently acquired a new urgency in light of moves by other countries to clarify their own laws on human tissue banking with the new interest worldwide in the new life sciences. Increasingly, the harmonisation of laws and rules in this field is likely to emerge as an important consideration in shaping the laws and rules in each jurisdiction. In a world where large-scale collaborative research projects tend to transcend national borders, there is an increasing likelihood that many countries may demand proof of each other that there is approximate equivalence in the degree of ethical and legal protection or regulation before they will allow the cross-frontier transfer of research data, or allow cross-border research collaboration which involves access to their national tissue collections or data. For example, Singapore researchers may be asked to demonstrate that their protocols for the safeguarding of the confidentiality of data meet the standards of the jurisdictions in which their proposed collaborators are based. Failure to achieve such standards locally may well mean that Singapore researchers may be excluded from opportunities for collaboration with researchers in those jurisdictions (which include most developed countries).

IV . S P E C I F I C I S S U E S

7. In this section, we address and set out our views on specific issues arising out of the practice of human tissue banking and human tissue research.

8. Consent Generally

8.1. Full, free and informed consent is the cornerstone of the legal and ethical legitimacy and validity of a gift of human tissue intended for research.

8.2. We take the view that, where it is practical to do so, tissue bankers have an obligation to obtain consent to the donation of the gift.

8.3. We recognise that there is still some continuing debate as to what constitutes acceptable consent from a legal viewpoint, but we believe that this is an issue that can be readily resolved with appropriate and ethically-informed legal advice and forward planning in advance of the actual taking of human tissues.

8.4. We are keenly aware that there is an inherent conflict between presenting information to potential donors in a clear and simple way; and between disclosing all the possible kinds of research procedures which may be carried out on the donated human tissue sample, as well as of the benefits which may

be derived from it. Inevitably, there must be some compromise between clarity and detail in the drafting of consent forms. We believe that this conflict may be greatly reduced if the consent forms make clear that the gift is to be an absolute one, with the donor renouncing all rights whatsoever to and in connection with the gift of the human tissue sample.

- 8.5. If there is any possibility that donated tissue samples may in the future be made available for commercial research with consequent financial benefit or gain to third parties, then this possibility must be made clear to donors at the very outset even if the arrangement is to be that the donors completely renounce their rights to any share of these gains or benefits.
- 8.6. Consent should be informed and free. It would be unethical to take consent from a donor who may be under the impression (even if such an impression is completely without foundation) that the best efforts made for his or her therapeutic or diagnostic benefit might depend on or be affected by the giving or refusal of consent to the donation.
- 8.7. For this reason, we think it is important that the consent form for the donation of human tissue samples for research should not form part of the consent form for the taking of the tissue for therapeutic or diagnostic purposes. We recommend that, where possible, the person responsible for explaining the nature of the donation and the taking of the consent for the donation should not be the person who receives the consent for the taking of the tissue for therapeutic or diagnostic purposes.
- 8.8. Another way of simplifying consent is to have a system in which consent is completely delinked from the research purpose. In this system, the donor makes an absolute gift of tissue to a specified tissue bank. But it is made clear to the donor that the consent to the gift is not to be linked to or conditional upon any particular approved research use or purpose. It is also made clear to the donor that research applications are handled and approved by an independent ethics review committee or body. This arrangement may obviate any subsequent argument that the consent given by the donor did not cover the specific research use to which the tissue was subsequently applied.
- 8.9. Such an arrangement would also go a long way to solving the issue of whether "reconsent" is required when tissues originally acquired for a specific research purpose is subsequently sought for use in another, and there is doubt as to whether the original consent covers the subsequent use.
- 8.10. We accept that there are circumstances in which it would be impracticable or impossible to insist on consent being obtained. Such a situation may arise, for example, if there is no clear person from whom valid consent can be obtained, and where the donor himself or herself is already

deceased, or is legally incompetent to give the requisite consent. In such situations, we recommend that, acting within the limits of the law, the decision for the taking of the human tissue from such a person should be referred to an appropriately constituted ethics board or institutional review board.

8.11. In taking the consent, especial attention is necessary to ensure that donors fully understand what is proposed to be taken, particularly if gross human tissue samples (e.g. entire organs or blocks of organs, or of limbs, as opposed to tissue slides or small tissue blocks) are involved. Gross human tissue samples may be viewed in a very different light from small human tissue samples by the public. The issue of respectful and appropriate methods of disposal for such gross human tissue samples may have to be considered by the custodians of such samples when they are no longer needed and de-accessed from the bank or collection. Researchers and institutions having responsibility for the custody, use and disposal of such tissues should at all times be sensitive to social, cultural and religious sentiments relating to the treatment, use and disposal of such tissues.

8.12. We also think that researchers and tissue bankers should bear in mind that consent to the taking, and consent to particular uses are two quite separate things. Consent given for the taking of tissue for a specific purpose does not necessarily authorise the use of the tissue for a different purpose.

8.13. Similarly, it should not be assumed that human tissue taken without consent, even though under statutory authority (for example, a post-mortem examination carried out on the authority of the State Coroner), may be used for other purposes once the statutory purpose has been exhausted.

9. Consent and Legacy Tissue Collections

9.1. A special difficulty faced by tissue banks in Singapore and in the rest of the world is posed by the existence of large collections of tissue samples accumulated over many years for which no specific or adequate consent for research investigations have been obtained. In the vast majority of the cases, the original donors can no longer be reliably traced for consent to research, or such tracing may no longer be practicable or socially acceptable (for instance, in the case of very old collections in which there is a strong likelihood that many of the donors may have since died, especially if the sample tissues were originally taken for the diagnostic purposes in relation to conditions such as cancer). We refer to these collections as legacy tissue collections.

- 9.2. These legacy tissue collections, by virtue of their sheer size and range of coverage, are often very valuable to academic and commercial researchers alike.
- 9.3. While some have advocated the extreme view that no research use should be made of these legacy tissue collections, we take the view that it is not in the wider public interest to suggest a blanket ban on access to these collections by researchers. We take the view that it is unreasonable to expect those who have assembled such collections in good faith for the advancement of medical knowledge to have divined the importance now placed on consent.
- 9.4. We take the practical approach that tissue collected in good faith at a time when there was a lack of any clear ethical, professional or legal guidelines governing the collection of such tissues is not something to be condemned: it is not the fault of medicine that the law and bioethics often lags very far behind the reality of medical practice and technology. In the absence of guidance from the law, or from an established canon of bioethics, medical workers and researchers can only act in good faith according to the best professional practices of the day.
- 9.5. On this basis, we take the view that it is consistent with good stewardship to allow reasonable and respectful research use of such legacy tissue collections for the greater public good.
- 9.6. It is one of the interim recommendations advanced by us in this Paper that steps should be taken to formulate a national ethical policy governing research access to such legacy tissue collections. The formulation of such a policy should be led by a national-level body. There may be a possibility that legislative intervention may be necessary to cure the defect stemming from problem with the lack of consent. Otherwise, the scientific value of these legacy collections may be severely impaired by the need to maintain separate access guidelines for legacy tissues and tissues for which appropriate and adequate consent has been obtained.

10. Confidentiality

- 10.1. Confidentiality lies at the heart of the physician-patient relationship. A common theme of the position papers submitted to us is the acceptance, as a fundamental controlling principle, of the donor's right to privacy and confidence.
- 10.2. In relation to genetic information derived from human tissue, the obligation of confidentiality is one which is universally recognised. Article 7 of the 1997 UNESCO *Universal Declaration on the Human Genome and*

Human Rights requires that “[g]enetic data associated with an identifiable person and stored or process for the purposes of research or any other purpose must be held confidential in the conditions set by law”. The World Health Organisation has proposed that “[g]enetic data should be treated as confidential at all times. Genetic data should only be used to advantage and empower an individual or family, and for better treatment or prevention of disease. Data relevant to health care should be collected and kept by medical geneticists in secure confidential files”¹.

- 10.3. We agree that the researchers and tissue bankers alike have an obligation to protect the confidence and privacy of donors.
- 10.4. We further note that the general obligation of confidence is one which is protected by the general common law principles applicable in Singapore. In certain specific circumstances, some aspects of the obligation of confidence may be mandatory under statute.
- 10.5. Confidentiality and consent are closely interlinked and interwoven issues. The common ground between them is that both spring from the obligation to protect and respect the dignity and autonomy of patients and donors. In this respect we note that the UK Medical Research Council has examined confidentiality issues in medical research at length in their report on *Personal Information in Medical Research* (October 2000).
- 10.6. The MRC took as their first governing principle that:
“Personal information of any sort which is provided for health care, or obtained in medical research, must be regarded as confidential. Wherever possible people should know how information about them is used, and have a say in how it may be used. Research should therefore be designed to allow scope for consent, and normally researchers must ensure that they have each person’s explicit consent to obtain, hold and use personal information. In most clinical research, this is practicable.”
- 10.7. In our view, however, the requirements of consent and confidentiality should not be applied inflexibly and blindly to all circumstances. If the central common purpose of the general obligations of consent and of confidentiality is the protection of and respect for the dignity and autonomy of patients and donors, then there may be special circumstances in which specific departures from the general rules of these two obligations may be permissible, so long as the central common purpose of the obligations is preserved.

¹ World Health Organisation, Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services 15-16 December 1997 (WHO/HGNG/GL/ETH/98.1).

10.8. For example, strict adherence to the principle of privacy and confidentiality may be difficult to square completely with other equally compelling objectives. In other cases, it may be difficult or impossible to recontact the donor or the donor's family for consent (or re-consent) to further research, or it may be socially unacceptable to do so (for example, if there is a strong likelihood that the donor may be dead). We think that in these and in other situations where consent or re-consent may be impossible or difficult to obtain, it is permissible for researchers to consider the use of anonymised data arrangements or data-escrow arrangements as may be approved by appropriately-constituted ethics board or institutional review boards.

10.9. In these and other similar arrangements, the object is to preserve the confidentiality and privacy of the donors. The central common purpose of the general consent and confidentiality requirement is not compromised. We recommend the use of such arrangements where practicable, and where the scientific objectives of the proposed research will not be compromised.

11. Approaches to Governance

11.1. Given the current pace of developments in the genetic and genomic sciences, we do not think that it is appropriate to resort to hard-coding specific rules in legislative form for the regulation of research and commercial activity in the genetic and genomic sciences. Overly-specific rules run a risk of rapid obsolescence, and of abuse by those minded to be seen to comply only with the letter but not the spirit of the law.

11.2. In general, we recommend legislative intervention only in situations where it is clear that effective professional self-regulation and a fair balance of rights and interests between individuals and the public in encouraging research cannot be achieved without legislative teeth.

11.3. We think however that there is a role for carefully targeted legislative assistance in the form of enabling legislation (as in our suggestion in relation to the statutory remedying of consent for research access to legacy tissue collections), and in empowering appropriate Government agencies to exercise a supervisory jurisdiction as gatekeepers over certain kinds of activities in relation to human tissue banking.

11.4. In the context of the genetic and genomic sciences, we note that one particularly obvious gateway is the tissue bank itself; researchers, whether they be commercial or academic researchers, and whether they be currently regulated under the various medical Acts or by the Ministry of Health, require access to collections of physical tissues for their work. This being the case, we suggest that appropriate legislation for the control and supervision of this

gateway, through the appropriate Government agency being given an approval and supervisory jurisdiction over the establishment and conduct of tissue banking, would be a flexible and efficient mean of basic control over the genetic and genomic sciences in Singapore.

- 11.5. We especially think that, for example, the jurisdiction of the Director of Medical Services under the Private Hospitals and Medical Clinics Act could be extended to all individuals or bodies (and not just healthcare establishments, hospitals, medical clinics and clinical laboratories) minded to engage in the conduct of tissue banking. Such a supervisory jurisdiction would place non-medical researchers (who are not subject to the provisions of the Act) and medical researchers alike on a level playing field and subject them to the same set of such operational and ethical guidelines as may be imposed by the appropriate authorities.
- 11.6. Alternatively, if a statutory agency is eventually established for the regulation of stem cell research (as has been suggested by the BAC), it may be appropriate for such a statutory agency to be given regulatory jurisdiction over human tissue banking in Singapore as well. Such a statutory agency should be given sufficient powers of direction, enforcement and supervision, so as to enable it to effectively give ethical and legal direction for the conduct of all forms of tissue banking carried out in Singapore, to ensure compliance with such direction, and such other relevant rules, standards and codes of conduct, to establish and maintain proper operational governance, as well to protect the interests and rights of patients, donors and their families.
- 11.7. We take the view that it is desirable to have consistent and transparent rules and standards which should have common application to all forms of tissue banking in Singapore, whether carried by the private or public sector, and whether such tissue banking is carried out primarily or incidentally for the purposes of research, and whether such research is for a commercial end or for a non-profit end.
- 11.8. In the interest of promoting accountability and transparency, we think that a national-level committee or consultative body comprising experts from relevant industrial, academic, research and professional sectors of the life sciences, together with appropriate representation from the public, could assist in formulating a sensitive and flexible approach to regulation.
- 11.9. To take this proposal further, such a national committee could assume the role of a national ethics review board which would be responsible for the formulation of national policy relating to the regulation, conduct and governance of tissue banking in Singapore. For this purpose, it could be constituted to advise the proposed statutory agency accordingly.

- 11.10. A further role that such a national committee might assume could be the oversight of the decisions of institutional review boards or institutional ethics committees on applications by researchers for access to human tissues. The national committee could review these decisions to ensure that common standards are applied nationally by such institutional review boards or institutional ethics committees. By the same token, the institutional review boards or institutional ethics committees could be given representation either on the national committee itself, or a standing professional standards forum of the national committee.
- 11.11. Such a national committee or consultative body could also help formulate other non-legislative informal aspects of regulation, such as the specific rules or codes of conduct and operational codes by which human tissue banks in Singapore may agree to be bound.

V. INTERIM RECOMMENDATIONS

12. In this section, we set out our preliminary recommendations arising out of the matters discussed above. We emphasise that these are only interim recommendations: human tissue banking is a rapidly evolving field in Singapore, and we expect that over time, new issues and new questions in the social, ethical and legal spheres will arise and require resolution. We also emphasise that not all the issues raised in this Paper can find a ready solution in either ethics or the law, let alone both, and that some of them can only be resolved after further professional and public debate and dialogue, and with a better understanding of the issues involved, as well as the needs and concerns of the relevant participants.

13. **WE RECOMMEND THAT:**

Recommended Ethical Principles

- 13.1. As a starting point for this dialogue, we recommend the adoption of the following principles²:

² A number of these principles are adapted from the Report of the UK Medical Research Council entitled Human Tissue and Biological Samples for Use in Research: Operational and Ethical Guidelines (January 2001).

Primacy of the Welfare of the Donor.

13.1.1.1. The health, welfare and safety of the donor shall be the paramount consideration in the taking of any tissue. Where tissue is being taken primarily for a therapeutic or diagnostic purpose, the secondary purpose of taking tissue for research, or the way in which the tissue is taken for research, should not be allowed to compromise or prejudice in any way the primary purpose of the taking. Where a tissue sample has been taken primarily for the purposes of diagnostic procedures, no further sub-sample should be taken from the main sample for the purposes of research until the diagnostic procedures are satisfied, or unless the diagnosing pathologist certifies that the taking of the sub-sample will not compromise the main diagnostic purpose of the taking of the main tissue sample. Where the taking of the tissue is primarily for the purpose of research, such taking and research should only be proceeded with if the potential benefits of the taking outweighs the potential risks to the patient. All living donations involve some degree of risk to the donor, although in the vast majority of cases, this risk will be negligible.

Informed Consent

13.1.1.2. No tissue shall be taken, or shall be accepted, unless the full, free and informed consent of the donor has been obtained. Our remarks in the section on Consent above applies, as well as the exceptions noted thereto.

13.1.1.3. We also recommend that patients should be informed when material left over following diagnosis or treatment (described as surplus to clinical requirements), might be used for research. Patients may be under the expectation that any waste tissue will be disposed of appropriately, and may object to the use of such tissues for research.

13.1.1.4. Special attention should be paid to the legal and ethical resolution of consent issues in relation to legacy tissue collections. Where such resolution cannot be satisfactorily achieved, we recommend separate regimens of access for the legacy and non-legacy portions of a tissue bank holding both kinds of tissue. We repeat our comments in relation to legacy tissue collections in the section on Consent and Legacy Tissue Collections above.

13.1.1.5. We recognise, however, that there are arguments that in specific situations it may be ethically acceptable to proceed without consent provided that sufficient precautions are taken for the protection of the privacy of the patient and the patient's family. For

instance, this may be achieved through appropriately constructed anonymization procedures or data escrow arrangements. We also recognise that it may be impractical to apply the principle of informed consent in its full force to legacy tissue collections, or to tissue banks in which the legacy material cannot be reliably separated. In these cases, a national ethical policy may have to be worked out as suggested in paragraph 9.6 above.

- 13.1.1.6. Tissue banks should develop and have in place electronic database systems that will enable the consent status and consent conditions (if any) of every human tissue sample.

Respect for the Human Body

- 13.1.1.7. Ethics, the law, and the cultural and religious traditions of our society are all in agreement with the principle that the human body and its remains are to be treated with respect. Researchers and tissue bankers need to be sensitive to religious and cultural perspectives and traditions, and should in particular be aware that whole cadavers or gross organ parts are viewed in very different light from small tissue samples by lay persons. Researchers and tissue bankers should always ensure that donors and the families of donors fully understand the extent of the intended gift. For example, the term “tissue” should not be used without further elaboration and explanation if it is intended that organs or substantial parts of organs are intended to be taken. Especially in the case of gross tissue samples, donors or their families should be consulted in advance of the donation as to their wishes for the appropriate disposal or return of surplus tissues when these are no longer required.

Donations to be Gifts

- 13.1.1.8. Donations of tissue samples for use in research should be treated as outright gifts. Donors should not be paid any financial incentives for the donation, although they may be given reasonable reimbursement of any expenses incurred in the donation of the sample. As a corollary of this principle, donors should not expect any personal or direct benefit from the donation of tissue, including information of any medical condition or predisposition or likelihood of such discovered in the course of research on the sample. Likewise, researchers and tissue bankers should not be under any obligation to disclose such information to the donors, unless they have agreed to do so in advance of the donation. Where appropriate and possible, it may be desirable to ask for consent to be given for any and all research purposes as may be approved by a properly-constituted ethics committee or institutional review board in

accordance with any rules, standards or codes as the relevant authority may lay down. To this end, an effort must be made in good faith to give the donor or the donor's family a fair picture of the principle uses which the tissue is likely to be put to, with the caveat that new uses not within current contemplation or practise may and are indeed likely to arise in the future.

Ethical Review of Research Proposals and Access Requests

- 13.1.1.9. All research using human tissue samples should be approved by an appropriately constituted research ethics committee or institutional review board. Especial attention must be paid to the independence and integrity of such committees or review boards, and any conflict of interest (whether real or potentially real, or even the semblance of a conflict of interest, even if such semblance is in fact unfounded) should be scrupulously avoided. The appointment, and constitution of such ethics committees or review boards should be as transparent as is practicable.
- 13.1.1.10. A national-level committee or consultative body comprising experts from relevant industrial, academic, research and professional sectors of the life sciences, together with appropriate representation for the public, should be formed to assist in formulating a sensitive and flexible approach to regulation.
- 13.1.1.11. This national-level committee could take the form of the national ethics body suggested by us in paragraphs 11.8 to 11.11 above. Such a national ethics body would also serve the function of fostering common standards and approaches among individual institutional review boards or ethics committees in Singapore.

Confidentiality

- 13.1.1.12. Researchers and all those involved in the conduct of tissue banking have an obligation to protect the confidentiality of the personal information of donors entrusted to them, as well as the privacy of donors. Consent must be obtained from the donor (or from his family, if deceased) for the release of any personal information to researchers or to any third party.
- 13.1.1.13. Researchers and all those involved in the conduct of tissue banking also have an obligation to protect the confidentiality of personal information given to them by donors of other individuals who are not themselves donors, as well as the privacy of such individuals. Scientifically valuable information is often given by donors of tissue samples which may relate to individuals other than the donor himself or herself. Commonly, a donor may be asked to

provide details of the medical history of family members. Researchers should recognise that such information and such individuals should be accorded the same respect and protection as accorded to the donor.

Institutional Tissue Banking

- 13.2. Subject to our views as set out in paragraphs 5.5 to 5.8 above, tissue banking should be conducted only by institutions such as may be approved by the appropriate authorities to do so, and not by private individuals or groups of private individuals.

Ethical Governance of Operational Aspects of Tissue Banking

- 13.3. There should be statutory regulation and supervision of all forms of tissue banking, and a statutory authority should be constituted for this purpose. No tissue banking should be carried out without the licence of the statutory authority. The statutory authority should be given sufficient powers of direction, enforcement and supervision, so as to enable it to effectively give ethical and legal direction for the conduct of all forms of tissue banking carried out in Singapore, to ensure compliance with such direction, and such other rules, standards and codes of conduct, to establish and maintain proper operational governance, as well as to protect the interests and rights of patients, donors and their families.
- 13.4. Institutions that conduct tissue banking should have in place transparent and appropriate systems and standards for the proper ethical, legal and operational governance of tissue banking.
- 13.5. Such systems and standards might include, but need necessarily be limited to:
- 13.5.1. The formulation of clear and transparent written ethical guidelines and policies for the operation of tissue bank and the governance of their tissue banking activities;
 - 13.5.2. The formulation of clear written Standard Operating Procedures for the day-to-day operations of the tissue bank, with especial attention being paid to ensure the integrity and biological safety of the tissue holdings;
 - 13.5.3. The establishment of an appropriately constituted research ethics committee or institutional review board to oversee requests for research access to or the use of human tissues, on clear, objective and transparent criteria;

- 13.5.4. The provision of a proper system for periodic and impartial census and audit, and a proper inventory system for their tissue holdings and for research accesses to the holdings;
- 13.5.5. In consultation with their legal advisors, the working out of simple and clear procedures and proper documentation of the required consent process;
- 13.5.6. The establishment of clear and written policies for the sharing of tissue bank resources with other tissue bankers and researchers;
- 13.5.7. The establishment of written procedures and policies for the culling and appropriate disposal of unneeded human tissue samples from the bank;
- 13.5.8. The establishment of legally and ethically adequate and acceptable systems to protect and safeguard the confidentiality of personal information of donors, and the privacy of such donors and of any other individuals (not being donors themselves) whose identity or personal particulars to which such information may relate; and
- 13.5.9. The establishment of a system for the periodic reporting of activities to those who have overall responsibility of the larger institution to which the tissue bank belongs.

Initiating An Ethical Dialogue

- 13.6 A professional and public dialogue be initiated to settle the principles which should guide the conduct of tissue banking. While we expect that most of the input in the dialogue will come from professionals in the life sciences, we also recommend that the views of the public be sought. This Paper is issued by the BAC as part of that process.

Resolution of Legal and Ethical Issues in Relation to Ownership and Custody

- 13.7 Finally, we recommend that a dialogue be initiated with a view to achieve an early resolution of the legal and ethical questions in relationship to the ownership and custody rights to donated human tissue.
-

**HUMAN TISSUE RESEARCH CONSULTATION PAPER (27 Feb 2002)
DISTRIBUTION LIST**

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31	Bishop John Tan	President	National Council of Churches of Singapore
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33	Prof Lim Yean Leng	Director	National Heart Centre

#	Name	Designation	Organisation
34	Dr Yee Woon Chee	Deputy Director (Research)	National Neuroscience Institute
35	Mr Lim Boon Heng	Secretary General	National Trade Union Congress
36	Prof Chan Soh Ha	Director	NUMI, NUS
37	Prof John Wong	Chairman, Medical Board	National University Hospital
38	Prof John Wong	Director	Office of Life Sciences
39	Prof James P. Tam	Dean	School of Biological Sciences, NTU
40	Mr Bhajan Singh	Chairman	Sikh Advisory Board
41	Dr Chew Tuan Chiong	Honorary Secretary	Singapore Association for the Advancement of Science
42	Venerable Shi Ming Yi	Secretary General	Singapore Buddhist Federation
43	Mr Tan Geok Tian	Chairman	Singapore Cancer Society
44	Venerable Seck Fatt Kuan	President	Singapore Chinese Buddhist Association
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46	Dr Lewis Lee	President	Singapore Dental Association
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48	Mr Gerard Ee	Chairman	Singapore Hospice Council
49	A/Prof Shirley Lim Siew Lee	President	Singapore Institute of Biology
50	Dr Ang Chong Lye	Director	Singapore National Eye Centre
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62	Mr Joseph Benjamin	Honorary Secretary	The Jewish Welfare Board, Singapore
63	Mr Palakrishnan SC	President	The Law Society of Singapore
64	Ms Susie Kong	President	The Singapore Nurses Association
65	Mr William Hui	Secretariat Manager	The Spiritual Assembly of the Baha'is of Singapore Ltd.
66	Mr R. M. Ghadiali	President	Zoroastrian Association of Singapore

APPENDIX D**WRITTEN SUBMISSIONS TO HUMAN TISSUE REPORT CONSULTATION
PAPER**

1. Academy of Medicine
2. Alexandra Hospital
3. Ang Mo Kio Community Hospital
4. Biomedical Engineering Society
5. Changi General Hospital
6. Faculty of Medicine, National University of Singapore
7. Genome Institute of Singapore
8. Graduates' Christian Fellowship
9. Health Promotion Board
10. Institute of Mental Health/Woodbridge Hospital
11. Institute of Molecular and Cell Biology
12. KK Women's and Children's Hospital
13. Law Reform Committee, Singapore Academy of Law
14. Life Insurance Association
15. Majlis Ugama Islam Singapura
16. National Cancer Centre
17. National Council of Churches of Singapore
18. National Neuroscience Institute
19. National Skin Centre
20. National University Hospital
21. Office of Life Sciences, National University of Singapore
22. East Shore Hospital
23. Gleneagles Hospital
24. Mount Elizabeth Hospital
25. Singapore Association for the Advancement of Science
26. Singapore Cancer Society
27. Singapore General Hospital
28. Singapore Medical Association
29. Singapore Medical Council
30. Singapore National Academy of Science
31. Singapore National Eye Centre
32. Singapore Nursing Board
33. Tan Tock Seng Hospital
34. The Catholic Medical Guild of Singapore
35. The Jewish Welfare Board
36. The Law Society of Singapore
37. Zoroastrian Association of Singapore



ACADEMY OF MEDICINE, SINGAPORE

PATRON: PRESIDENT OF REPUBLIC OF SINGAPORE

25 March 2002

(By fax : 65-8379190)

A/Prof Terry Kaan
 Chairman
 Human Genetics Subcommittee
 Bioethics Advisory Committee
 250 North Bridge Road
 #15-01/02
 Raffles City Tower
 Singapore 179101



Dear Sir,

Re : Human Genetics Subcommittee Consultation Paper: Human Tissue Research

1. Thank you for asking the Chapter of Pathologists, Academy of Medicine Singapore to comment on the Consultation Paper on Human Tissue Research. We wish to state that we are in full support of the Bioethics Advisory Committee's (BAC) philosophy and principles as outlined in this paper and highly commend the suggestions framed within the Interim Guidelines. There are however a few areas that the Chapter would like to emphasize.
2. The Chapter strongly endorses the Bioethics Advisory Committee's stand on subsampling of tissue as outlined in paragraph 13.1.1.1. For this category where the sample of tissue is necessarily removed for the medical care of the patient, the duty of care is always, first and foremost to the patient. Hence the Chapter fully agrees that there should be no subsampling prior to analysis and examination of this tissue. This is especially so when fresh tissue is cryopreserved and banked for research. Without the reporting pathologist's input, tissue taken as 'non tumour' tissue may contain small foci of primary tumours or may be marginal tissue required for prognostication.
3. The term 'human tissue banking' is broad and fairly non specific in as much as it could be used to mean several very different entities. The Chapter is of the opinion that while there are issues in common, for instance of consent, confidentiality, governance and respect for the welfare of the donor, a distinction should be made between tissue banks assembled specifically for immediate patient therapy – as in skin grafts and bone grafts, versus research tissue banking, where tissue is assembled to facilitate medical education and medical research, both in the halls of academia as well as in the fields of industry. We believe that the comments regarding use of tissue archives in the BAC's paper refer to research tissue banking.

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Branch Office : MD5 Level 3, National University of Singapore, 12 Medical Drive, Singapore 117598
 Tel: (65) 7771233 Fax: (65) 7779633 E-mail: training@academyofmedicine.edu.sg

4. The Chapter applauds the council's view on good stewardship of tissue, as stated in paragraph 9.5. The Chapter fully agrees and has stated in its own position paper on Ethical Laboratory Practice, that researchers should not be refused access to archival (stored) tissue. However, the Chapter would like to point out that pathology departments holding diagnostic tissue, that is samples on which diagnosis were based, have a duty to ensure that there is sufficient tissue remaining for possibility of satisfying diagnostic or medicolegal challenges and for future prognostic or therapeutic tests.

Patients may seek treatment in other countries or institutions, and often this is accompanied by a request that diagnostic tissue be submitted for revaluation by their diagnostic team. Therapeutic agents may arise some years after the primary diagnosis of a tumour. Two examples of newly developed cancer therapies are Herceptin for Breast Carcinoma and Glivec (STI571/Imatinib) with respect to Intestinal Stromal Tumours. The guidelines concerning effective use of these agents recommend that positive expression of specific tissue markers are sought prior to initiation of treatment. Had all tissue been released for research on completion or issuance of the report, there would have been no archival tissue left to submit for revaluation or on which to perform such tests. It is for these reasons that the Chapter, in line with other Colleges of Pathology advocate that where possible, the laboratory should keep sufficient diagnostic tissue to meet potential challenges.

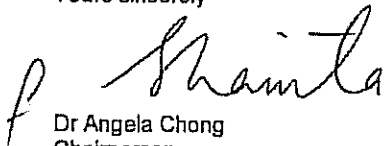
5. The establishment of a research tissue bank using 'surplus' tissue is important in the development of medical and biological research. The Chapter fully appreciates the fact that issues of conflict of interest are circumvented by the BAC's suggestion in paragraph 8.7, for separating the process of consent for donation of 'surplus' tissue (with respect to form and person obtaining consent) from that of the therapeutic or diagnostic procedure. The Chapter hopes that should these recommendations be upheld, that the agencies involved in tissue procurement will use professional trained (and accredited) personnel, as this is a time when the patient and family are most vulnerable. The Chapter suggests that information regarding the functions of research banking and the ultimate use of this donated 'surplus' tissue be made easily available to patients and members of the general public.
6. We would also like to draw attention to the fact that this separation of tissue for research versus tissue for medical diagnosis should and must extend to procedures pertaining to small biopsies where patients may be asked to donate tissue obtained by a second sampling, for medical research after the (taking of the) initial diagnostic sample. In this instance, this second sampling should not be regarded as 'surplus' to the first sample, as the primary purpose of this sample is research and not primarily for diagnosis. The purpose of this second pass or 'bite' should be clearly distinguished from the diagnostic sample.

7. In matters of **governance**, the Chapter supports the BAC in its recommendation for a national level committee comprising experts from relevant fields to oversee tissue banking in Singapore (Paragraph 11.8). The Chapter would like to underscore the importance of including medical research scientists and pathologists in institutional and national committees that involve research on human tissue. Tissue that is altruistically donated to the community should be put to optimum use, with the strictest of quality controls (inclusive of biohazard issues) and audit. Pathologists would have the training and expertise to advise on this.

8. We wish to state that the Chapter's views are made in line with **best professional practices** and with the welfare of the patient first and foremost. The duty of the doctor is firstly to his patient, and then to investigate and study disease. We as pathologists hold these values dearly. We hope our comments have been of use to your committee. Please feel free to contact us should you require any further clarification or information.

Thank you.

Yours sincerely



Dr Angela Chong
Chairperson
Chapter of Pathologists 2001 - 2002



ACADEMY OF MEDICINE, SINGAPORE

PATRON: PRESIDENT OF REPUBLIC OF SINGAPORE

2 April 2002

Assoc Prof Terry Kaan
Chairman
Human Genetics Subcommittee, BAC
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101

Dear Assoc Prof Kaan

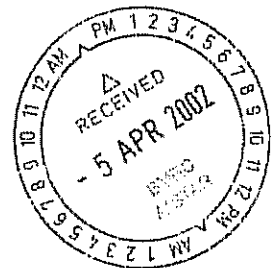
Consultation Paper on Human Tissue Research

Your letter dated 27 February 2002 to the Master requesting for feedback regarding the consultation paper on Human Tissue Research is referred. The Academy of Medicine has no further comments to add.

Yours sincerely

A handwritten signature in black ink, appearing to be 'Ms Monica Wong'.

Ms Monica Wong
Executive Director



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Tel: (65) 2238968 Fax: (65) 2255155 E-mail: main@academyofmedicine.edu.sg

Branch Office: MD5 Level 3, National University of Singapore, 12 Medical Drive, Singapore 117598
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A/Prof. Rajasoorya
MBBS, MMed, FAMS, FRCP (E),FACE
Chairman Medical Board
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18 March 2002

A/Professor Terry Kaan
Chairman
Human Genetics Subcommittee, BAC
Bioethics Advisory Committee
250 North Bridge Road
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Singapore 179101

Dear Prof Kaan

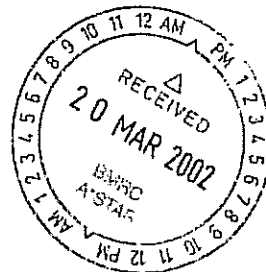
**CONSULTATION PAPER ON HUMAN TISSUE RESEARCH
EXTENSION OF DEADLINE FOR SUBMISSION OF FEEDBACK**

Thank you for your letter of 11 March 2002. I have circulated this paper to some senior clinicians in my hospital and attached is a summary of our comments.

Yours sincerely

A handwritten signature in black ink, appearing to read "C Rajasoorya", is written over a vertical line.

Clinical A/Prof C Rajasoorya
Chairman Medical Board





A/Prof. Rajasooriya
 MBBS, MMed, FAMS, FRCP (E), FACE
 Chairman Medical Board
 Senior Consultant and Head
 Dept of Medicine
 378 Alexandra Road
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SUMMARY OF COMMENTS ON HUMAN TISSUE RESEARCH

The Human Genetics Subcommittee should be commended for coming up with this Consultation Paper. It is an important initiative and I agree that we need to set up guidelines and processes for governance in this area.

A re-consent is advisable, preferably after the tissue diagnosis is made known to patient, specifically whether the tissue concerned is to be donated for research, or dispose of after a certain time frame. Since the diagnosis is already known and a treatment plan in place, it would not matter if the person who obtains this second consent is the same or different from the one who obtains consent for the procedure. This "re-consent" should be 'general' and not linked to a specific research project and 8.8 can follow.

Item 8.5

How are you going to settle the dispute if a donor later discovers that his tissues contain the genetic code that confers immunity to an incurable disease like AIDS and that code led to the manufacture of an antibody or vaccine that cures AIDS. The company can practically make millions or billions of dollars and this donor who is now in debt, wants some share of the fortune. May be better to decide on the quantum of compensation and make it into a law so that the company must pay whether the donor signs his tissue away for free or not. This will avoid costing disputes.

How are you going to police institutional staff from "selling" tissues to private companies for making a product that can be an economical success?

The genetic code on which the product is made must be traceable to the donor identity and this must be kept in the institution. Suppose the company refuses to reveal where the genetic code – how are you going to find out if it came from an institution and whether it was released to the company for R and D.

The current pace of development in genetic and genomic science is indeed very rapid. Hence the 'makers' of the rules and regulations must be nimble enough to not just respond to the changes but also have the foresight of impending change. It is difficult, but we do need "specific rules" (11.1) as the stakes are very high.

1 April 2002

A/Prof Terry Kaan
Chairman
Human Genetics Subcommittee, BAC
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101

Dear Assoc Pro Terry Kaan

**CONSULTATION PAPER ON HUMAN TISSUE RESEARCH
EXTENTION OF DEADLINE FOR SUBMISSION OF FEEDBACK**

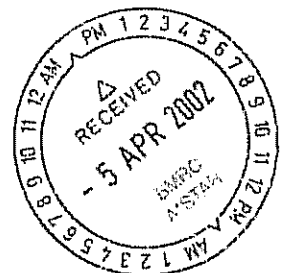
I refer to your letter to Mr Bertie Cheng, Chairman Board of Directors, Ang Mo Kio Community Hospital dated 11 March 2002

There is no feedback from Ang Mo Kio Community Hospital. Human Tissue Research is not done in our Community Hospital.

Thank you.



DR LAU HONG CHOON
Hospital Administrator





Biomedical Engineering Society (Singapore)

c/o Orthopaedic Diagnostic Centre, National University Hospital
Lower Kent Ridge Road
Singapore 119074

Tel: 772 4424 Fax: 774 4082

March 28, 2002

Assoc Prof Terry Kaan
Chairman, Human Genetics Sub-Committee
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101

Dear Prof Kaan,

Request for feedback regarding human tissue research in Singapore

Thank you for sending the above-mentioned to our Society for our perusal and feedback.

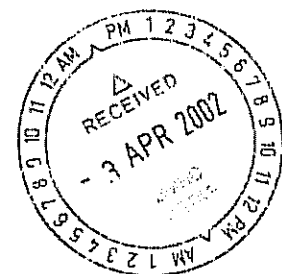
Our Executive Committee met on the 27th March 2002 to review the document. We found the document to be balanced, on one hand ensuring that patients and donors' safety and rights are well protected, and on the other hand enabling human tissue research to progress without undue hindrance and having safe guards to minimize abuse. We found the Interim Recommendations to be adequate.

While the patients and donors' safety and rights are adequately address in the document, the committee felt that related issues such as the quality of staff and facilities involved in human tissue banking are just as important with regards to "Respect for the Human Body" and protection and safety of staff involved in such activities. It is not certain whether these related issues fall under the purview of BAC's, nevertheless they need to be addressed.

Thank you.

Yours sincerely,

Assoc Prof James Goh,
Vice-President





CHANGI GENERAL HOSPITAL

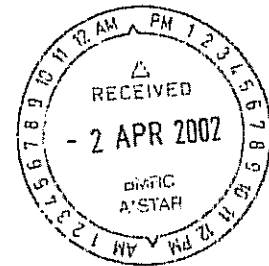
DEPARTMENT OF RADIOLOGY

Dr Khoo Teng Kew
 MBBS, DMRD, FRCR
 Senior Consultant & Chief

1 April 2002

Assoc. Prof Terry Kaan
 Chairman
 Human Genetics Subcommittee
 Bioethics Advisory Committee
 250 North Bridge Road
 #15-01/02 Raffles City Tower
 Singapore 179101

Dear A/Prof Kaan



REQUEST FOR FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN SINGAPORE

Thank you for the opportunity to give some feedback on the consultation paper on human tissue research.

I have taken the liberty to circulate to members of Medical Ethics Committee, Changi General Hospital, the consultant paper.

A/Prof Stella R Quah from the Department of Sociology, NUS brought up two relevant points:

1 **Paragraph 8 – Item 8.2:**

Tissue bankers have the obligation to obtain consent to the donation of the gift. This obligation should not be qualified “where it is practical to do so” because such a qualification invalidates this principle. In situations where the tissue bankers find it impossible to obtain consent, they should be required to present their case for discussion and approval by the respective appropriately constituted research ethics committee or institutional review board (described in item 13.1.1.9).

2 **Recommended Ethical Principles – Informed Consent – Item 13.1.1.5**

“in specific situations it may be ethically acceptable to proceed without consent ...”

This item should apply ONLY to the legacy tissue collection given the difficulty of tracing donors who donated tissue several decades ago.

Page 2

Mr William Toh, another member of the MEC contributed the following comments:

1 **Consent**

The consent form should try to list down possible uses/research of the tissue donated, in case some intentions are objectionable(ie. cloning).

2 **Confidentiality**

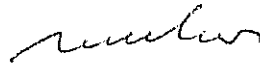
Tissues should be coded and such codes is only breakable by legal authorities (eg. court of law) for reasons of such magnitude the court deem justifiable.

3 **Ownership**

There should be a clause that restricts sale or transfer of ownership.

How about safeguards against theft and sabotage.?

Yours sincerely



DR KHOO TENG KEW
Chairman
Medical Ethics Committee

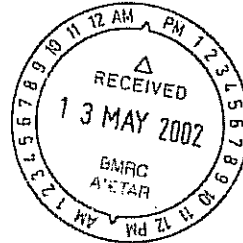
Cc: Chairman, Medical Board(CGH)
Hon. Secretary, Medical Ethics Committee(CGH)

Faculty of Medicine
Dean's Office



13 May 2002

Assoc Prof Tery Kaan,
Chairman, Human Genetics Sub-Committee,
Bioethics Advisory Committee,
250 North Bridge Road,
#15-01/02 Raffles City Tower
Singapore 179101



Dear Prof Kaan,

Request for feedback regarding human tissue research in Singapore

Thank you for sending the above-mentioned to our Faculty for feedback and perusal.

Attached are our comments on the BAC HGS Tissue Research Consultation Paper.

Thank you.

Yours sincerely

Prof Lee Eng Hin
Dean

Comments to BAC HGS Tissue Research Consultation Paper

Para 5.7

In the first sentence, "...tissue banks should be held by institutions...", although some examples are given, there is otherwise no definition of "institution". Is there a need to define it? Does a biotech company that does research come under the definition of "institution"? Can an "institution" be purely profit-driven, or must it be solely non-profit or not-for-profit?

With regard to the Faculty of Medicine, NUS, it is important to note that most tissue samples are collected as part of investigator-initiated research projects approved by a Research and Ethics Committee. These samples are not housed in any centralized tissue bank but are located in the various research laboratories within the Faculty premises. There are no centralized facilities for tissue storage, and no funds to establish and maintain such a facility, within the Faculty. Also the majority of projects are non-overlapping, except for certain projects studying common diseases such as cancer, heart disease, and diabetes.

We thus support a position that there is no need and no benefit from centralizing the storage of research tissues used in the majority of research projects conducted in the Faculty of Medicine. We do however agree with the need for tissue banks for certain tissues involving disorders which may be of interest to multiple research groups, as this will simplify access to them. In fact, there already exists a tissue bank at the National University Hospital for the storage of tumors and other cancer tissues.

Para 8.7

We feel a clear distinction must be made between the use of tissue leftover from clinical testing for purposes of laboratory QC/QA and test development/validation, and use of tissues in research. Test QC/QA and development/validation are absolute necessities in all clinical diagnostic labs; unfortunately, without actual patient samples these cannot be accomplished satisfactorily and the validity of all tests become suspect. It is the standard practice of clinical laboratories worldwide to retain samples that have tested "positive" as "positive control" samples for subsequent testing of other patient samples (not all samples that are tested will be positive for the tested disease). So long as confidentiality of patient identity is maintained (which is not an issue in clinical laboratories), and all leftover samples are used within the laboratory, clinical laboratories must be allowed to utilize leftover patient samples for clinical purposes (as positive controls for test QC/QA, development, and validation).

With regard to research use of leftover material, many diagnostic laboratories in the United States provide consent forms which include a section on consent for use of leftover tissue for research. The question of whether patients are under the impression that they might or might not get the best care has never arisen, because the tissues are taken by referring physicians who use the forms provided by the referral laboratory. There is also no question as to different standards of care from the same laboratory, as all tests are fee-for-service. The physicians also do not have a vested interest in whether or not patients consent to use of samples for research.

We agree that the situation in Singapore hospitals may be different, with laboratories and physicians working under the same institution. However, simply separating the consent for tissue donation for research from the consent for testing, and requiring different people to take consent for testing and for research, will not allay patient fears. They only serve to give the impression to others that consent for research use of leftover tissue is freely given, but create more paperwork and manpower requirements, thus substantially raising the "cost" of

research and medicine. This is because the "different" people taking consent for testing and research use will still be construed by patients as being part of the same team.

It is more important to ensure that when consent to use leftover tissue for research is requested, that patients are fully informed of their absolute right to refuse, and assured that their decision will not impact their disease management.

Central to the fears of patients in donating leftover tissues for research is the issue of confidentiality, as these samples will be studied in a research setting. We are in favor of following the practice in the United States of allowing samples leftover from testing to be used for research purposes after samples are completely anonymized, with no possibility of patient identification and recontact.

Paras 8.8 and 8.9

We strongly support the idea of delinking tissue donation from research purpose, but would like to see this option made available to all tissue donations, not only in the context of centralized tissue banks but also for investigator-initiated research projects.

The rationale is that delinking of tissues with research purpose will make tissue collections much more useful to other researchers, who may need the samples to look at other diseases. Re-consent is a major obstacle to the use of stored tissue that is hampering new research in the United States. Since all human research requires approval by Research and Ethics Committees under a standard set of guidelines, the question of improper use of tissues will not arise.

Para 9.6

With regard to legacy tissues from which no consents were originally sought, we suggest that the best strategy to ensure patient confidentiality while not "wasting" precious research resources is to anonymize these samples by removal of all patient identifiers to ensure that there is no possibility of patient identification and recontact.

Para 10.8

We wish to draw attention to another common situation, that of samples leftover from clinical tests for which either no research consent had been obtained, or consent was given only for a specific research project. Recontact of such patients for consent to perform a new research project may be difficult, especially for samples tested a long time ago and for referral laboratories which had no initial direct contact with patients. Such samples should be allowed to be used for research after proper and complete anonymization procedures.

Para 13.1.1.3

As we have stated in our comments to Para 8.7 above, our position is that a clear distinction must be made for samples leftover following diagnosis or treatment that are used within the clinical laboratory for QC/QA and test development and validation purposes. The confidentiality of patient identity is maintained as these samples are utilized within the clinical laboratory. It is critical that clinical and diagnostic laboratories continue to have access to test-positive patient samples for diagnostic or therapeutic purposes, and these samples should not be subject to the same informed consent requirements pertaining to research, if such laboratories are to function properly.

For the category of samples leftover following diagnosis or treatment that are used for research purposes, we recommend the continued use of clinical test consent forms which include a section on informed consent for research. The informed consent should clearly indicate the nature of research, or should clearly state that the samples are not linked to any specific research. The patients should be assured that their decision to decline donation will not impact their disease management in any way. We feel that in the Singapore context, proper counseling of patients is more important than mechanisms construed to give the impression of impartiality, such as separate consent forms for research and different people for taking clinical and research consents.

Finally, for clinical test samples for which no consents for research were obtained, such leftover samples should be allowed for research purposes provided proper anonymization of samples has been performed. Of course, proper informed consent is the preferred method for research uses, because it would allow re-contact of patients should the need arise, such as to obtain more epidemiological and/or family history information. However, sample anonymization provides a reasonable alternative to utilize rare and/or interesting samples for research purposes that do not require re-contact of patients, family history information, or any information that could identify the patients.

Paras 13.1.1.4 and 13.1.1.5

We similarly feel that with regards to legacy tissues and non-legacy portions of tissue banks, sample anonymization be provided as an option of last resort so that precious and rare samples can be used for research instead of being consigned for destruction.

Comments from Faculty of Medicine, NUS.

Assoc Professor Terry Kaan
Chairman, Human Genetics Subcommittee,
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101

March 13, 2002

Re: Human Genetics Subcommittee Consultation Paper: Human Tissue Research

Dear Prof Kaan;

I want to congratulate your subcommittee on a remarkable draft of a new framework for human tissue research. I think, when implemented, it will propel Singapore to becoming a paradigm of ethical human research. My comments are more in terms of style, seeking clarification, and only occasionally addressing the substance of the document.

Specific Comments:

Section 8.7: The recommendation is for a decoupling of the consent for research on tissues and that for therapeutic consent. There is a growing movement for a tissue "consent" to be incorporated into standard admission or surgical consent forms. This is to obtain patient consent for the use of excess tissues procured during the conduct of standard-of-care procedures. The Subcommittee's comment in section 8.7 may be interpreted as a blanket prohibition against this. Is this your intent? If so, I would ask you to reconsider. I think that the incorporation of consent (with an opt out capacity) for use of excess material into the standard hospital surgical consent would not only validate the use of excess tissues for research, but can be used as a tool for educating/or engaging patients in the biomedical research enterprise.

Section 8.8/8.9: It is implied that delinking the consent for accession to that of a specific research process might solve the problem of reconsent. Though I am in agreement with this approach, but unless better described in this document and clearly structured, such an important operational concept might be rejected. I would urge an expansion of this section to provide a more extensive explanation.

Section 8.12: The comment "Consent given for the taking of tissue for a specific purpose does not necessarily authorize the use of the tissue for a different purpose..." appears contradictory to Section 8.8/8.9.

Section 10.8: The concept of data escrow has been raised, however, data escrow means many things to many people. I suggest that more space be devoted to define the concept better.

Section 13.1.1.3: This section states that patients should be informed when material left over following standard medical procedures are used for research. Here again, I would like to raise the possibility of a clause in the standard surgical or pathology consent forms for such a tissue accession procedures. Please refer to my comments on Section 8.7

General Comments/Overview:

I think the concepts that you have proposed are all correct and important. Several issues are of vital importance and would benefit from a presentation of clear models:

Legacy tissues: I recommend that in addition to the national forum/body that would decide on the management of these tissues, that you provide some models for how this problem can be resolved. For example one could recommend defining a clear set of guidelines (like the obtaining of a waiver of consent through an IRB), the activation of the national IRB board to adjudicate these difficult legacy cases until a sufficient experience in "case law" has been achieved, and the activation of a data escrow system.

Data Escrow systems: It seems apparent that the establishment of a robust data escrow system is an essential solution to many of the ethical dilemmas we anticipate. For this reason, I recommend that the subcommittee be more forceful in describing the elements of a successful Data Escrow system. This can be used as a framework for development.

National IRB: I laud the strong recommendation in your document for the establishment of a national IRB. I would also recommend that the final subcommittee report include concrete models for how such a national body would look like.

Health care providers: Throughout the document, there were clear discussions of actions that would be deemed unethical and should be prohibited. However, there was no discussion as to the punishment that would follow some of these high level breaches of research ethics. I think there should be consideration of whether criminal penalties should be placed on the more egregious infractions. In addition, there should be a game plan in the final document on how the medical community will be educated in the details of the new regulations. This is key to the successful implementation of the new guidelines.

Prioritization of actions: I strongly suggest that the final report should include a prioritization of necessary actions for establishing the new regulatory framework

in Singapore. For example, establishing the national IRB/consensus body and the guidelines for a Data Escrow system should be considered first. These structures will be important in guiding the building of the other bodies.

Thanks for letting me participate in this important event. I would be happy to help in the implementation of the final recommendations.

With Best Regards,

Edison Liu, M.D.
Executive Director, Genome Institute of Singapore
Professor, National University of Singapore

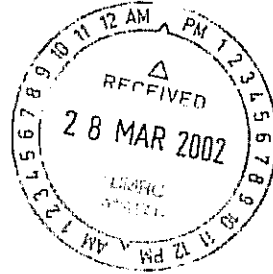


GRADUATES' CHRISTIAN
FELLOWSHIP

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Telephone 63144 910 Fax 63144 739

28 March 2002

Assoc Prof Terry Kaan
Chairman
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101



Dear Prof Kaan

The Graduates' Christian Fellowship [GCF] would like to thank the bioethics advisory committee [BAC] for its consultation paper. We also acknowledge the sedulousness with which the BAC has presented the issues and regulations pertaining to the subject and its generally judicious and sensitive recommendations. Nevertheless we would like to provide the following brief feedback from a Christian point of view as represented by the GCF.

The Christian view of the human body:

In contradistinction to the secular, humanistic and naturalistic view that man is solely the result of a random, purposeless and evolutionary process taking millions of years, and thus is a highly sophisticated and complex molecular, computerized, biological robot imbued with an incredibly complex maze of neuron circuits which in principle could be replicated in the future with the rapid advance in artificial intelligence research and advances in nanotechnology, Christians affirm that man is created in the 'image' of God. Thus a human being comprises both a physical body limited to the four dimensional spacetime continuum and a soul which is not constrained by this physical space time continuum and continues to exist after the physical death of the body. However, we also hold that a human being is a psychosomatic being who cannot express himself or herself in any other way except bodily as opposed to the traditional form of Cartesian dualism where the human body is perceived simply as a physical instrument to communicate what the 'soul' within it thinks. In the light of this, violation of human dignity occurs when the human body is not treated with due respect. The GCF therefore supports the BAC's emphasis on the importance of the principle that 'the human body and its remains are to be treated with respect and that researchers and tissue bankers need to be sensitive to religious and cultural perspectives and traditions'.

SECTIONAL GROUPS & MINISTRIES

Christian Conciliation & Arbitration Ministry
Christian Medical & Dental Fellowship
Fellowship of Christian Care Professionals
New Graduates' Ministry

Lawyers' Christian Fellowship
Teachers' Christian Fellowship
Technical Interest Group

Areas of concern:

The GCF is of the view that human tissue research does present some ethical concerns with respect to the definition of human tissue. The BAC document states that human tissue refers to 'all kinds of human biological materials derived from living or cadaveric donors, including solid tissues, organs, fetuses, blood and other body fluids and their derivatives, cord blood, embryos, gametes or any part of derivative thereof.' From the Christian viewpoint, we view with concern the inclusion of fetuses and embryos in this definition. The GCF contends that the fetus and embryo constitute at the very least potential human beings and at a certain stage of development, become full human beings although the point of transition is unknown and has been and still is being debated and we are of the opinion that we will never know this with certainty.

In the light of the above, we are of the view that it is ethically acceptable to use fetuses and embryos that have perished because of spontaneous miscarriages for research. With regard to excess embryos created for IVF, we would not encourage the use of such embryos for research unless there are strong mitigating factors.

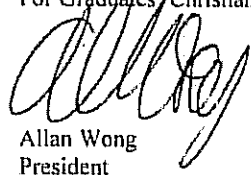
We are also of the view that it is unethical to abort the embryo and especially the fetus for research purposes. As for the creation of a human embryo in the laboratory for research, opinion is divided whether it is acceptable although the majority would probably be against it.

We agree that it is unethical to use gametes for research if they have been obtained through commercial transaction and to create hybrid individuals through the mixing of human and animal gametes.

As for the use of gametes for reproduction, we are unable to provide any firm recommendation at this stage.

We trust that our brief response maybe of assistance in your future deliberations.

Yours Truly
For Graduates' Christian Fellowship



Allan Wong
President

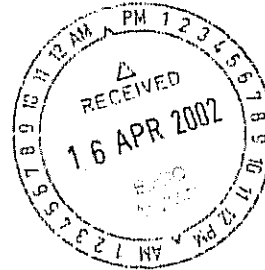
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11 April 2002



Assoc Prof Terry Kaan
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Bioethics Advisory Committee
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Health Promotion Board
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Dear *Prof Kaan*

CONSULTATION PAPER ON HUMAN TISSUE RESEARCH

Please refer to your letter of 27 Feb 2002.

2 The views of the Health Promotion Board's Ethics Committee were sought on the consultation paper "Human Tissue Research". The consolidated views of the members are stated below:

(a) Para 8.4

Members expressed concern about the right of donors to retract their consent should they object to any unstated purpose for tissue donated. Members are unanimous in that donors should still have a right over their tissues and should be free to withdraw their consent at any time rather than the tissues be considered as 'absolute gifts'.

(b) Para 8.10

Members are also concerned about cases where consent might be difficult to obtain eg incompetent or deceased. Members proposed that these tissues should either be considered as 'out of bounds' or clear guidelines must be given for these 'specific situations' as to the instances where consent can be referred to the designated Ethics Committee or institutional review board.

(c) Para 9.4

Some members were uncomfortable that it be assumed that legacy tissues were harvested in good faith and therefore can be utilised for research purposes without adequate consent. Another member is of the opinion that actions carried out prior to guidelines being set should not be penalised but wonders if future legislation would apply to legacy tissues as well and if so, at what length researchers would have to go to try and gain consent.

(d) Para 13.1.1.5

A member felt uncomfortable that the provision for proceeding without consent is not spelt out specifically. "In specific situations" can be opened to many interpretations. The scenarios should be specified (eg, deceased and next of kin not available).

(e) Para 13.1.1.8

Some members wondered whether free/discounted medical care/surgical fees/operation costs related to the removal of the tissue (either as a research or part of a diagnostic/therapeutic procedure) would be considered as the 'reimbursements' or would it be construed as 'payment' for the tissues obtained. Clear financial benefit/gain are objected.

(f) Section III

A member of the Committee commented that the revocation of an "irrevocable" donation is a major issue to be considered. The general thrust of the law, & attitude among the public, at present, is to protect the rights of individuals. To give researchers more teeth, statute must re-define rights of individuals & the needs of society. It will also be difficult for various ethics committees to bring about this shift in legal thinking, or to change attitudes.

It was opined that the paper must be discussed publicly and the public educated as to the facts before final decisions are made.

Yours sincerely


DR LAM SIAN LIAN
CHIEF EXECUTIVE OFFICER
HEALTH PROMOTION BOARD



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9 Mar 2002

A/Prof Terry Kaan
Chairman
Human Genetics Subcommittee, BAC



HUMAN TISSUE RESEARCH IN SINGAPORE

I am responding on the behalf of Professor Kua Ee Heok, CEO of the Institute of Mental Health, to your request for feedback regarding your consultation paper which you and your subcommittee has prepared.

I am grateful for this opportunity to raise certain concerns on this very important topic.

A suggestion of 'simplifying' the consent process involved in tissue banking is to delink it from research. It is also further suggested that it would be made clear to the donor that research applications are handled and approved by another independent body. Would the donor be told that although the tissue taken is primarily for diagnostic or therapeutic purpose(s), the leftover tissue could be used subsequently for research albeit after approval from a relevant body? Does this mean that the informed consent of the donor (if still available) does not need to be obtained for subsequent research projects as ownership has now flowed to this body? If this is the case, then the individual is in effect being asked to sign a waiver of consent.

Your committee has rightly pointed out that consent process for tissue donation has two components. The first is the consent to obtain the tissue and the second is consent for the specific use(s) of this tissue. An individual may consent to have his or her tissue taken for a diagnostic purpose and may even give a broad

consent for the leftover tissue to be used for some future research. However, if one wants to be faithful to the spirit of informed consent where the emphasis is on *informed*, and if the donor does not know what sort of research is being done on his or her leftover tissue, it would therefore not be informed.

A tissue bank is a powerful and valuable resource for research material for present and future studies. It is the latter that is more problematic when it comes to obtaining consent because of the difficulties that your committee has highlighted. A solution is to ensure that data is "anonymised" and where the donor cannot be identified. In this case, a broad consent would have to be taken with the explicit understanding that the donor cannot be identified. In which case, new consent would then did not to be taken for research protocols that are not known at the time of tissue collection. While ethically this is acceptable, it would limit the utility of the tissue bank and precludes combinatorial analysis.

Another problem that may arise is when a research subject wants to withdraw from a project and exercise his or her right to have the donated tissue destroyed – would the delinking of data make this impossible or is the donation absolute in that the donor has no further right to it? On the other hand, one could also argue that medical data of patients which are produced in the process of health care have been traditionally used for health care planning for the collective good of society. The cross-matching of medical records and tissue data (e.g. DNA) could potentially enable studies which may lead to significant advances in our knowledge of illnesses as well as economic gains – one of the driving force of Singapore's massive investment in the life sciences. At the micro level, there may also be benefits to the donors (provided there are measures to prevent discrimination) in that individuals at risk for a illness may be identified.

It is a difficult task that your subcommittee has undertaken and it is unlikely that all the subsequent recommendations would win universal approval. But there must be a commitment that whatever recommendations made and regulations

implemented, these would be reviewed and revised to make them relevant to advances in science and changes in our societal needs and values.

Yours sincerely



A/Prof Chong Siow Ann

Chairman

Research and Ethics Committee

Institute of Mental Health & Woodbridge Hospital

Copy to : Professor Kua Ee Heok



INSTITUTE OF MOLECULAR AND CELL BIOLOGY
 An Institute Affiliated to
THE NATIONAL UNIVERSITY
of SINGAPORE

28 March 2002

Assoc Prof Terry Kann
 Chairman, Human Genetics Subcommittee
 Bioethics Advisory Committee (BAC)
 250 North Bridge Road
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 Singapore 179101

Dear A/Prof Kann

REQUEST FOR FEEDBACK CONCERNING CONSULTATION PAPER ON HUMAN TISSUE RESEARCH IN SINGAPORE

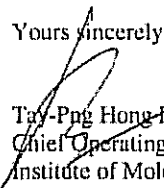
Thank you for your letter dated 27 February 2002 to Prof Hong Wanjin.

As per request, feedbacks from the Institute of Molecular and Cell Biology are as follows:

Feedbacks	
1.	Tissue banking: consider general access to all tissue banks for all Singapore researchers based on scientific merit of the proposed projects.
2.	There should be only one "Human Tissue" Organization to cover everything from Genomic research, IVS, Blood, Pathological samples ... etc.
3.	Points 8.5 and 8.7 are hard to define. With the advance in technology, any disease and non-disease human tissues are fundamental to development of diagnostics kits for commercialization.
4.	It is best if a "law" could be passed for the government to own those legacy of tissue collection.

Thank you.

Yours sincerely


 Tay-Png Hong-Lan (Mrs)
 Chief Operating Officer
 Institute of Molecular and Cell Biology

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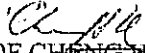
**KK WOMEN'S
AND CHILDREN'S
HOSPITAL**

18 March 2002

Assoc Prof Terry Kaan
Chairman, Human Genetics Subcommittee
Bioethics Advisory Committee
250 North Bridge Road
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Singapore 179101

FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN SINGAPORE

With reference to your letter of 27 February, a committee was convened to review the Consultation Paper on Human Tissue Research. We are forwarding the comments of the said committee (please see enclosure), which also represents our stand on the matter.


A/PROF CHENG HENG KOCK
Chairman, Medical Board



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9 March 2002

FEEDBACK ON CONSULTATION PAPER "HUMAN TISSUE RESEARCH"

Preamble

Having been tasked by Chairman, Medical Board to prepare a feedback report on the Consultation Paper "Human Tissue Research" submitted by the Bioethics Advisory Committee, the following members met on 9 March 2002 to discuss the relevant issues:

Dr Carolyn Tan Eng Looi
Chairman, Division of Paediatric Surgery (designate)

A/Prof Yeo Seow Heong
Chairman, Division of Obstetrics & Gynaecology (designate)

Dr Ivy Ng Siew Lian
Head, Paediatric Medicine
Chairman, KKH Research Committee

Dr Chew Sung Hock
Senior Consultant, Histopathology

General Comments

All members felt that the Paper was very well deliberated and covered the relevant issues in today's context of biomedical research. It addresses the legitimate concerns of the donors and also shows a pragmatic approach to opportunities for the advancement of medical science.

Specific Issues Raised

Consent:

1. Format of the consent:
A standard format for consent for obtaining tissues for research would be preferable.
2. The tissue sample as an outright donation, the donor renouncing all rights:
This benefits the researchers, and the donor has no direct benefit. Therefore an advocate for the patient would be important and may be represented by the Institutional Review Board (IRB). Strong representation from the lay public within the IRB's would therefore be important. The issue of rights to the tissue should be handled cautiously and sensitively, and donors should be helped to understand that losing their rights to the tissue would be one result when the tissue is anonymised. Public feedback and discussion on this issue would be crucial.
3. IRB approval for collection and use of human tissue samples for research:

The consent form should state

- that the donated tissue will only be used for research vetted and approved by the IRB
- that the patient's treatment will not be affected in any way by his/her decision on the donation of the tissue
- the tissue will be treated with respect

4. Person to take the consent:

It was felt that the principal clinician and the research team should not take the consent, as they have vested interests. The principal clinician could, however, bring the research project to the attention of the donor, and provide some explanation of its aims.

An option to consider is to appoint a full-time staff member who is not directly participating in research projects and who is under the authority of the IRB to obtain the consent. It would be best if this individual had a nursing or paramedical background.

5. If consent is denied:

When the tissue is obtained as part of the treatment, eg an operation, this tissue sample should be made part of a medical archive and not part of a tissue bank. The work processes must allow for clear distinction between tissues that are available for research purposes and tissues that are kept only as part of the patient records.

6. Donors changing their consent decisions:

An issue to be considered is whether consent for donating one's tissue to research is binding indefinitely.

7. Education:

Public education about the use of human tissues in research would be helpful to engage the lay public and to answer their concerns. The beneficiaries of such research will be our generations to come.

Legacy Tissue Collections:

1. Consent:

It is reasonable not to retrospectively trace all donors for consent, as this will be very difficult and in some cases, impossible.

2. Database:

It would be necessary for current legacy collections to be entered into databases in a nationally standardised format. If there is any doubt about the adequacy of the consent previously taken, based on the principles now set out by the Bioethics Advisory Committee, it would be better to regard that consent had not been obtained. The databases could be managed by those who currently hold responsibility for the tissue collections, but the data must at all times be available for audit and access by the IRB.

3. Pathology specimens:

All current specimens stored by Pathology Departments, including Pathology Museums maintained for academic purposes, should be categorised as legacy tissue collections, and entered into databases. Subsequent to the formalisation and regulation of all tissue collections,

Pathology Departments will need a system for identifying which tissues are available for research and which are not.

Confidentiality:

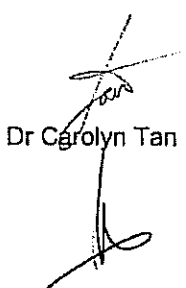
1. Unexpected findings of genetic diseases:
In the course of using tissue samples for research, the researchers may unexpectedly identify genetic diseases in the samples. The ethical dilemma presented to the research team as to whether the donors should be informed needs to be addressed.
2. Researchers blinded to donor identities:
As far as is practical, researchers using human tissues should not have direct access to identities of the donors, and perhaps a section should be included in research protocols using human tissues as to the proposed anonymisation methodology to maintain donor confidentiality.

Governance:


1. Institutional Review Boards meeting international standards:
As there are existing international guidelines regarding IRB's, it would be timely to ensure that all institutions participating in research involving human tissues set up IRB's meeting international standards. IRB's should have jurisdiction over all human tissue collections in their respective institutions.
2. Private tissue collections:
Private tissue banks should be subject to the same rules and regulations as public tissue banks, and be governed by IRB's either within the private institution or at the Ministry of Health.
3. National Regulatory Agency:
Members agreed that such an agency would be necessary. The relationship between the IRB's and the proposed agency, and their respective levels of jurisdiction will need to be clearly worked out.

Interim Recommendations of the Bioethics Advisory Committee

All members opined that the recommendations are logical and reasonable. However, members hoped that the points raised in the previous section would be considered.



Dr Carolyn Tan Eng Looi



A/Prof Yeo Seow Heong



Dr Ivy Ng Swee Lian



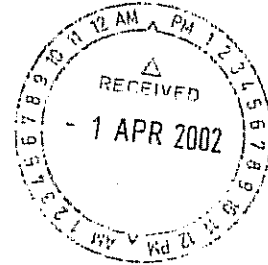
Dr Chew Sung Hock



S I N G A P O R E A C A D E M Y O F L A W

1 April, 2002

ASSOC PROFESSOR TERRY KAAN
CHAIRMAN
HUMAN GENETICS SUBCOMMITTEE
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179 101



Dear Assoc Prof Kaan

Feedback Regarding Human Tissue Research in Singapore

Thank you for your letter dated 27 February 2002. We set out below our members' views on the interim recommendations advanced by the Human Genetics Subcommittee (HGS) in the consultation paper on "Human Tissue Research".

2 The Committee is of the view that there are two issues that must be treated discretely in any determination of policy regarding human tissue banking. First, the **tissue banking industry**. The role of regulators here would be to ensure oversight of tissue banking, guiding co-operation with other government or research agencies, tabling an established cycle of tissue bank inspections, mandating registration of tissue banks and developing assurances with regard to quality control (including bringing practices in line with international convention).

3 Next, there is **informed consent by the donor**. The role of a national-level body here would differ in the sense that it is not regulating a commercial industry. It would manage the process of obtaining consent and donations, including elements such as the timing of the request for donation, mode of request, staff training and supervision in handling such queries, the provision of written materials for the donor or donor's next-of-kin and the review of standards for obtaining consent. While the Committee was in agreement with the general principles raised by HGS, we did not immediately agree with the consolidation of these two discrete aspects of human tissue banking. As such, we would not encourage the establishment of one body that would manage both the industry and ensure informed consent of the donor.

4 Establishing Distinctions at the start ~ paragraphs 2.1 & 2.3: Definitions

4.1 Members were unequivocal in their insistence of separate treatment for (a) research materials relating to human embryonic stem cells and human cloning; and, (b) the other human biological materials generally described in paragraph 2.1. Perhaps this was appreciated by the BAC in its decision to establish two separate

subcommittees for Human Stem Cell Research (HSR) and HGS respectively. Human biological materials described in (a) and (b) should be dealt with in separate frameworks. At the very least, the present sweeping caveat in paragraph 2.3 cannot stand without a clear and distinct explanation of areas where the BAC may have differing recommendations in relation to human stem cell research materials. The BAC should indicate where the caveat would apply.

4.2 Flowing from this distinction, our members would welcome separate statements by the BAC on stem cell research and other tissue research, regarding (1) existing ethical rules that apply (for example, from present medical professional practice); (2) possible scenarios where the researchers have exploited ethical rules – in those cases, what were the ethical rules; and, (3) what future rules would be needed to arrest these possible scenarios. It is these ethical issues which we hope will be raised in the continuing process of consultation.

5 Consent ~ paragraph 8 generally; paragraphs 13.1.1.1 to 13.1.1.6

5.1 Even though paragraph 13.1.1.2 spelt out the overriding principle of consent, paragraph 13.1.1.3 should nevertheless be clarified to state that full, free and informed consent of the patient must be obtained before a donor's tissue can be used for research. There is also an issue as to the scope of the consent required and the extent to which it must correlate to the exact type of research to be undertaken. Reasonable explanation of what the research entails should be given and the donor should be offered an opportunity to ask questions.

5.2 A distinction is made at paragraph 8.12 between consent to the taking and consent to the particular use of tissue. We seek the BAC's confirmation on the consent procedures required in the taking and use of tissue alluded to in paragraphs 8.7 and 8.8 and invite HGS to put in place a recommended procedure to reflect this position.

5.3 In respect of 'informed consent', our members would welcome a definition. They were of the view that the principles mentioned, for example, at paragraph 13.1.1.1 merely informed the doctor or governing body of relevant considerations in evaluating consent; however, further definition could be given to assist the donor in being assured he or she has sufficient information to give consent.

5.4 Following some discussion, members agreed that consent may be waived in the following instances:

- (a) where it is required for purposes of police criminal investigation;
- (b) where it is required for public health and safety reasons; and
- (c) where there is an emergency that threatens the life and health of a person.

Naturally, the same 'national-level body' would be responsible for evaluating the reasons in each case that may arise in (b).

6 Legacy Tissue Collections ~ paragraphs 9.6; 13.1.1.5

6.1 While we agree that there should not be a blanket ban on access to these collections, this cannot mean a blanket referral to a 'national-level body'. The Committee considered that it would be appropriate for the framework of consent to tie in with existing regimes such as the Human Organ Transplant Act. Consistent with provisions in this statute, the question of consent should be referred to the donor's relatives. If the donor's next-of-kin refuses consent, there is no consent.

6.2 Where there is evidence that credible attempts to contact the donor's next-of-kin have been unsuccessful, perhaps the 'national-level body' can consent. However, it is recommended that the BAC explore existing 'national-level bodies' to determine whether there may be an overlap of functions and to employ existing resources in drawing up a framework.

6.3 Our Committee would recommend that this approach be legislated in respect of such collections as suggested at paragraph 9.6.

Persons with Mental Disorders

6.4 This approach may be extended to Singaporean donors who are not possessed of consistent complete decision-making capacity. We are aware that a somewhat different framework was recommended by the U.S. NBAC in its December 1998 report. Their recommendation identified several categories of consent – from 'assent' by a person incapable of independent decision making for whose donation will be applied to minimal risk research studies, to surrogate decision-making in three main forms. Applying this analysis locally, we would recommend the approach suggested above in relation to legacy collections. This corresponds to the U.S. NBAC's third category of consent described as 'Projection of personal relationships'. In this case, the donor appoints a proxy to make decisions regarding his or her biological materials in specific situations. We look forward to a separate analysis of informed consent for donors with mental disorders.

7 Donations to be Gifts

7.1 While in agreement with the underlying principle, members of the LRC felt strongly that the present phraseology used in paragraph 13.1.1.8 should be avoided. The discussion of financial incentives in the same breath as reasonable reimbursement of expenses incurred should be separated. They serve entirely different functions where 'financial incentives' possess a commercial character that cannot be ascribed to the act of reasonable reimbursement.

7.2 To this end, it is recommended that paragraph 13.1.1.8 should be rephrased to place emphasis on the principle that donors must not be induced by any financial incentives or benefit for the donation. BAC should also address the issue of whether trading in stem cells should be allowed. The Committee was of the view that the tissue bank should expressly be prohibited from sale or export of tissue for profit. To give flesh to its views, the BAC could give its recommendations should a situation such as the Moore case (USA) arise in Singapore. The BAC may also wish to comment on its position with reference to that of Iceland's Biobanks Act.

7.3 Finally we would welcome a detailed outline of the type of opportunities (cross-border collaborations alluded to in paragraph 6.8) which has hastened the BAC's production of this paper. The Committee would urge BAC to look into regulating potential markets that bloom from the tissue banking industry. For example, the E.U. Group on Ethics in Science and New Technologies met in November 2001 to discuss the ethical aspects of patenting inventions involving human stem cells.

8 Governance ~ paragraphs 11.6 and 11.7; 13.1.1.9 to 13.1.1.11

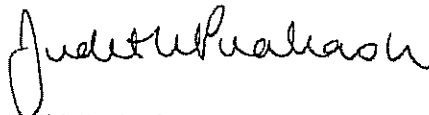
8.1 Paragraph 13.1.1.9 did not address the fundamental question of what type of research should be permitted. Furthermore, our members were concerned that the process of approval may not be transparent. There appears to be a lack of policy guidance regarding various scenarios. There is also no mention of how the research ethics committee or institutional review board would be constituted and what its composition would be. While our own research into the matter suggests the BAC may be considering adoption of the U.S. system of IRB review etc, we would ask the BAC to go further, for example, by identifying research protocols and the need for a mechanism to review these protocols.

8.2 Moving from the statutory agency to the board or committee, there is an absence of discussion on whose interests the respective body's members would represent. There is some reference in paragraph 13.1.1.10 to 'appropriate representation for the public' but no suggestion is given as to how this will be determined and achieved. In setting out the board's objectives, we hope the BAC will bear in mind our discrete treatment of banking and donor consent raised at our paragraphs 2 and 3 above.

Conclusion

We appreciate having been given the opportunity to comment on the consultation paper. Thank you.

Yours sincerely



Judith Prakash
Chairman
Law Reform Committee



30 Cecil Street #23-04A
Prudential Tower
Singapore 049712
Tel: 6438 8900
Fax: 6438 6989
Email: lia@lia.org.sg
Website: www.lia.org.sg

28 March 2002

BY POST ONLY

Assoc Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
250 North Bridge Road #15-01/02
Raffles City Tower
Singapore 179101

Dear Assoc Prof Kaan

CONSULTATION PAPER ON HUMAN TISSUE RESEARCH IN SINGAPORE

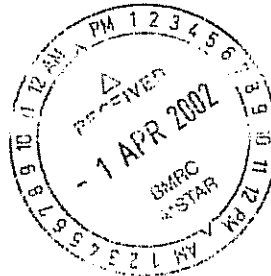
Our members, i.e. life insurance companies, generally have no comments to make, save for one.

The latter is enclosed.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Pauline Lim', written over a horizontal line.

PAULINE LIM
Executive Secretary



Copy: Tan Beng Lee, President

Request for feedback regarding human tissue research in Singapore

The current practice in the life insurance industry is that requests are usually made for medical reports from clinics and hospitals when potential policyholders declare a particular condition which they have when making a proposal to be insured. The authorization by the individual is usually recognized by the hospital or clinic.

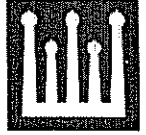
The industry should have no problem with all of the interim recommendations except for 13.1.1.2 to 13.1.1.6 under Informed Consent and 13.1.1.12 to 13.1.1.13 under Confidentiality. As an insurance life company the concern is our ability to verify the risks involved in insuring a particular individual who have declared a particular condition.

Hence the industry would like explicit clauses to be included which allows an individual to authorize the use of information and reports to be made available to insurers based on his consent. This is not clear from the interim recommendations.

While one can understand the paranoia involved especially since the technology holds the promise of more accurate diagnosis of an individual's medical health, its value to the life insurance industry is its availability. While underwriting rules may have to be revised to accommodate this change, the information must be made available to the insurer once the individual has given his consent.

Date: 13 March 2002

مجلس اڪرام اسلام سڃاڻپورا
Majlis Ugama Islam Singapura
(Islamic Religious Council of Singapore)



Islamic Centre of Singapore, 273 Braddell Road, Singapore 579702. Website: <http://www.muis.gov.sg> Telephone: 2568188 Fax: 2537572

MUI/OOM/31/2

10 Apr 2002

DID: 63591473

FAX:62519197

Assoc Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101

Dear Sir

REQUEST FOR FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN SINGAPORE

I refer to your letter dated 26 Mar on the above matter.

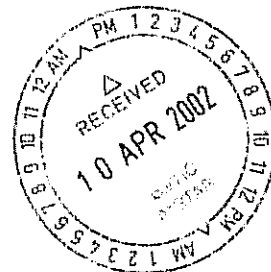
2 Thank you for giving us the opportunity to provide our feedback on the consultation paper for the Human Tissue Research.

3 Our initial feedback is enclosed. Please take note that the feedback is not a Fatwa (Ruling) issued by the Legal (Fatwa) Committee.

4 Thank you.

Yours sincerely,

Syed Ahmad Syed Mohamed
Assistant Mufti
For Secretary
Majlis Ugama Islam Singapura



FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN SINGAPORE

1. Definitions

1.1 There is no definition of “donor” in the paper.

2. Current Law

2.1 We agree to the proposal as stated in *article 6.2* that the donor should be given the opportunity to state in advance their intention to donate their bodies, organs or tissues for research or for transplantation after their death. We would like to suggest that the donor is also required to obtain the consent of two waris (next-of-kin). This is also in accordance with HOTA for kidney transplantation. The two next-of-kin are also regarded as witnesses to the donation of their bodies, organs or tissues for research or for transplantation after their death.

2.2 The witnesses and their relationship to the donor should be in accordance with the Muslim hierarchy of next-of-kin as indicated below:-

1. Father
2. Paternal grandfather
3. Son
4. Grandson
5. Full brother
6. Half brother (same father different mother)
7. Full brother's son
8. Half brother's son
9. Full paternal uncle
10. Half paternal uncle (same grandfather different grandmother)
11. Full paternal uncle's son
12. Half paternal uncle's son
13. MUIS (for those who do not have relatives as above).

3 Consent Generally

3.1 We agree that the tissue bankers have an obligation to obtain consent to the donation of the gift from the donor as stated in *article 8.2*. They are also required to obtain consent from two waris (next-of-kin) of the donor as stated in **para 2.1**.

3.2 The next-of-kin must comply to the following conditions:-

1. Reach puberty
2. Sane
3. Able and capable to make decision
4. Willing

3.3 In the circumstances when a re-consent is required for specific research purposes not stated in the consent form, after the death of the donor, as stated in *article 8.10*, the consent should be sought from the next-of-kins based on the Muslim hierarchy (refer to **para 2.2**).

When there is no clear person from whom valid consent can be obtained, and where the donor himself / herself is already deceased, or is legally incompetent to give the requisite consent, we recommend that the matter be referred to the religious authority for advice and consent.

In the case of Muslim deceased without any next-of-kins, Muis can act on behalf of the deceased in giving the consent for the tissue donation. This is due to the fact that Muis is the highest religious authority responsible for Muslim affairs in Singapore. The above should be stated clearly in the consent form.

3.4 We agree to the *article 8.11* which stated that the researchers and institutions having the responsibility for the custody, use and disposal of such tissues should at all times be sensitive to social, cultural and religious sentiments relating to the treatment, use and disposal of such tissues.

There should be proper guidelines with regard to the disposal of such tissue samples when they are no longer needed and deaccessed from the bank or collection.

For Muslims' gross human tissue samples that involve entire organs or blocks of organs, the organs should be buried appropriately. For any such samples, which involve parts of human body or of limbs, the parts should be cleansed and buried according to Islamic teachings. The limbs should be buried at a Muslim cemetery. It is also acceptable as stated in *article 13.1.1.7* that "*donors, or their families should be consulted in advance of the donation as to their wishes for the appropriate disposal or return of surplus tissues when these are no longer required.*" This is also the current practice in hospitals when Muslim parents are consulted on the disposal of placenta after delivery.

Conclusion

The researchers and the institutions involved in the Human Tissue research should be clearly informed on the ethical conducts in handling the human tissue especially with regard to the consent and confidentiality procedures. They also should be sensitive during any occurrences that involve religious sentiments to seek the advice and consent of appointed / relevant religious authority upon agreement by the donor in the consent form. Any involved party in these research activities should sign a declaration form.

8th April 2002

Our Ref : BAC1-tk-020408



To : Assoc Professor Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
250, North Bridge Road,
#15-01/02 Raffles City Tower,
Singapore 179101

Dear A/Prof Kaan,

RE: FEEDBACK ON THE CONSULTATION PAPER ON HUMAN TISSUE RESEARCH,

Thank you for inviting our views on the issues outlined in the consultation paper & the interim recommendations advanced by the Human Genetics Subcommittee.

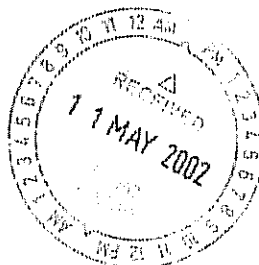
We enclose the comments from the Chairman, National Cancer Centre Ethics Committee (see enclosed) for your perusal.

Thank you.

Yours Sincerely,

A handwritten signature in black ink, appearing to read 'Audrey-Anne Oei', written over a horizontal line.

Ms Audrey-Anne Oei
Research Manager,
National Cancer Centre Singapore



cc. Prof Soo Khee Chee
Dr Vijay Sethi

CEO, National Cancer Centre
Chairman, NCC Ethics Committee

Encl. Comments from the Chairman, National Cancer Centre Ethics Committee

COMMENTS FROM THE CHAIRMAN, NATIONAL CANCER CENTRE ETHICS COMMITTEE:

1. **Section 3.3**
We agree that the ethics that are applied should reflect the ethical stand of the community at large. In this respect we think that some degree of "public education" on ethical issues should be recommended by the committee. Exactly which bodies should do it can be decided later. The reason for asking for this is that a large number of doctors in Singapore still hold very paternal views and feel that the man-in-the-street is unable to understand the issues involved.

2. **Section 3.4**
Our own impression (from attending local courses on medical ethics) is that many persons involved in medical research are not actively thinking "ethics" especially when the ethical problems that may arise can delay or prevent their study. Therefore, the statement 'that the vast majority of scientists and researchers ... are acutely aware of the potential ethical concerns' is not something that we agree with. As with point 1 above, we suggest that the committee recommend education on ethics for doctors as well.

3. **Section 5.7**
Databases should also concern themselves with the eventual or final outcome of the tissues to prevent unauthorised use of the tissue when it leaves the tissue banks. Many studies by drug firms tend to leave this aspect vague and this may allow use of the tissues, at a later date, for other unrelated studies for which they have not taken specific consent.

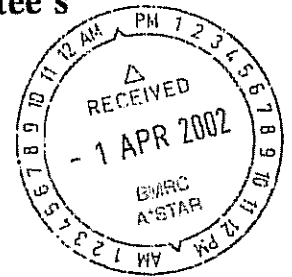
4. **Section 8**
Arising from our observations (see 2 above) we feel that as far as possible, in a study or research setting, consent should always be obtained. As for the question of "reconsent" this can be a difficult issue, especially in cancer research where a large number of donors may not live for long.

On the whole we think section 8 provides a good basis for consent, (especially 8.10) where an ethics committee has a final say.

5. **Section 11. 9 &10**
Most if not all members of such committees use their "common sense" and as they are usually experienced persons they bring a depth of understanding to the discussions that are not "common." Our own observation as members of an ethics committee is that some form of special training in ethics can be useful. In addition the ethics people often need to draw on other resources to make their decisions. In this respect such committees will benefit from having their own administrative support.

**Feedback on the Bioethics Advisory Committee's
Consultation Paper on
*Human Tissue Research***

Presented by the National Council of Churches Singapore



Introduction

The National Council of Churches Singapore (NCCS) wishes to thank the Bioethics Advisory Committee (BAC) for presenting a consultation paper entitled 'Human Tissue Research' for discussion and feedback. The NCCS also wishes to acknowledge the industry and thoroughness with which the BAC has presented the issues and regulations pertaining to human tissue research, and its generally sensitive and sound recommendations. The issues surrounding human tissue research must be studied in the larger context of research involving humans. What follows is a Christian response to the consultation paper, especially in relation to some ethical issues pertaining to the use of foetal or embryonic tissues.

Theological and Ethical Perspectives

A Theology of the Body

We begin our response by presenting, albeit only in outline form, what might be called a *theology of the body*. This is not a new theology, although its import is sometimes obscured in the history of Christian theology by cultural factors. The Christian Tradition holds that a human being, created in the image of God, is a psychosomatic being, comprising *both* body and spirit. The dualism that prevailed in certain periods in the history of Christian theology is not reflective of the fundamental theological anthropology of the Church. Because a human being is a psychosomatic unity, the lived body cannot be seen simply as a material instrument, used to communicate what the 'real person' living within it thinks. This form of Cartesian dualism is inimical to the Christian Tradition. Put differently, a human person does not possess a body. Rather, from the moment of conception, a person is an embodied being, and therefore cannot express himself or herself in any other way except bodily. Against the Cartesian body-soul dualism, we must assert that our bodies are fundamental to our essential humanity and constitute our identity. The doctrine of the incarnation affirms the importance of the body, for in the mystery of the incarnation the Son of God became body in order to bring healing and restoration to our bodily nature. The doctrine of the resurrection of the dead, so integral to Christian eschatology, also affirms this unitary view of a human being.

Human Dignity

This theology of embodiment implies that transgressing against the body is a violation of human dignity. The NCCS therefore supports the BAC's emphasis on the

importance of the principle that the ‘human body and its remains are to be treated with respect’ and its insistence that ‘researchers and tissue bankers need to be sensitive to religious and cultural perspectives and traditions’ (13.1.1.7). Respect for human dignity will produce an ethic of research involving human subjects that embrace two important principles: (1) the selection and achievement of morally acceptable ends, and (2) a morally acceptable means to those ends. It is unacceptable to treat a person solely as a means (i.e., as a mere object) to an end, for by doing so, not only will the intrinsic dignity of the person concerned be violated, but all of humanity will be impoverished. The theology of embodiment here articulated, which sees a human being as a unitary being, cannot but produce an ethic which aims to respect human dignity by protecting the multiple and interdependent interests of the person – bodily, psychological, spiritual, cultural. It cannot allow medical research to violate this principle, regardless of the promise of such research.

Areas of Concern: Research Involving Embryos, Foetuses and Human Gametes

Human tissue research does present some ethical concerns to the Church. These concerns have to do with the definition of human tissue. According to the BAC document, *human tissue* refer to ‘all kinds of human biological materials derived from living or cadaveric donors, including solid tissues, organs foetuses, blood and other body fluids and their derivatives, cord blood, embryos, gametes or any part of derivative thereof’ (2.1).

The inclusion of foetuses and embryos in this definition must be challenged from the Christian perspective. The NCCS maintains that the foetus and embryo are human beings, and to describe them as human tissue is to mislead.

Foetuses and Embryos

Therefore concerning the use of tissue from human foetus or embryo for research, the NCCS reiterates its position that human life begins at conception, and that the embryo from its earliest life is a human being deserving of the protection and respect that is accorded to all human beings. On the basis of this, the following guidelines obtain.

- a. It is unethical to abort the embryo or foetus for the purpose of research. This remains true even for countries in which abortion is legal, e.g., Singapore.
- b. It is ethically unacceptable to create a human embryo for research purposes. The NCCS maintains its position that therapeutic cloning for the purpose of research cannot be countenanced by the Christian church.
- c. It is ethically unacceptable for embryos which are created for reproductive purposes, and which are no longer needed for such purposes, to be used for research. This refers to excess embryos created for IVF.
- d. However, it is ethically acceptable to use foetuses and embryos that have perished because of spontaneous miscarriages for research, so long as these miscarriages are not caused intentionally.

The foetus should not be subjected to dissection procedures if a heartbeat is still apparent, or when there are other obvious signs of life. In circumstances where tissue is obtained from a deceased foetus, the following guidelines should be followed.

- a. Research involving foetal tissue taken in such circumstances should nonetheless be guided by respect for the woman's dignity. The same guidelines for free and informed consent should apply here.
- b. Research procedures should not be conducted in the immediate area in which clinical procedures are being carried out.
- c. Those concerned with research should not be involved in the management of either the mother or the foetus.

Human Gametes

Not enough is said in the BAC document on obtaining human gametes for research, although it is assumed that the general principles outlined in the paper obtain in this case as well. Here are some more guidelines for consideration.

- a. It is ethically unacceptable to use gametes for reproduction, even between tissues.
- b. In addition to free and informed consent, one must add that full disclosure of the purpose of the proposed research must be made to the donor.
- c. It must also be said that it is unacceptable to obtain gametes from cadavers, and from those from foetuses or individuals unable to consent for themselves.
- d. It is not ethical to use gametes for research if they have been obtained through commercial transaction, including transaction for service. The commercialisation of human reproduction must be prohibited morally because it transgresses the basic principle of respect for human dignity.
- e. It is unethical to create hybrid individuals by means of mixing human and animal gametes, or by transferring somatic and germ cell nuclei between cells of humans and other species. This violates the basic norm of human dignity.

Comments on the Recommendations Presented by the BAC

Primacy of the welfare of the donor (13.1.1.1)

The NCCS applauds the BAC for emphasising the primacy of the welfare of the donor, and for insisting that the health of the donor is paramount (13.1.1.1). Perhaps a clause on the respect for persons who are vulnerable, that is, those who have a diminished capacity or competence for making decisions on their own should be added. This would include children and institutionalised persons who require special protection against abuse, exploitation and discrimination. Special regulations should be established to protect the interest of such persons.

Informed Consent (13.1.1.2 – 13.1.1.6)

The BAC's insistence that 'no tissue shall be taken, or shall be accepted, unless the full, free, and informed consent of the donor has been obtained' must be affirmed. The BAC document states that consent should be obtained 'when it is practical to do so' (8.2). The NCCS, however, recommends that that consent should be obtained 'at all times' unless it is impossible to do so. The issue of voluntariness is important here.

It must be stressed that free and informed consent must be given *voluntarily*, and not as the result of manipulation and undue influence or coercion. Undue influence may take the form of inducement or deprivation. It must also be stressed here that consent may be withdrawn at any time.

Ethical Review of Research Proposals and Access Requests (13.1.1.9 – 13.1.1.11)

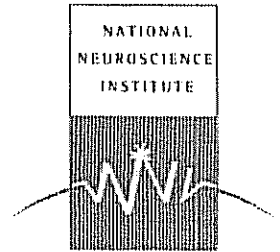
While it is important that a national-level consultative committee be formed for providing ethical and other guidelines to govern human tissue research, such a committee must not only comprise professionals from relevant sectors but also representatives from the religions. This is to ensure that such committees will not be concerned only with scientific and pragmatic considerations, but will take into account the views of the various religious traditions. Input from the religious bodies will introduce important perspectives that is concerned with the good of society and that are not governed by scientific or economic ambition. The NCCS affirms the BAC's conviction that the community's views should guide the ethical framework for tissue banking and research (3.2, 3.3, 3.4). But the NCCS would like to add that the community should be adequately represented and should contribute in defining vague terms such as 'appropriate' (5.11) and 'reasonable and respectful research' (9.5).

Confidentiality (13.1.1.12 – 13.1.1.13)

The issue of privacy and confidentiality is also paramount, and the BAC document has delineated some strict guidelines to ensure that personal information of donors is protected. But in reality confidentiality is difficult to protect. There are several categories of human biological materials. The first is *unidentified specimens* for which identifiable personal information is not collected, and therefore not available in the repository. *Identified specimens* are linked to personal information in such a manner that the person from whom the material is obtained can be identified by name, patient number, etc. In research environments, samples can be similarly termed as 'unidentified' and 'identified'. Over and above these categories, there are also 'anonymised' samples, i.e., samples that lack identifiers or codes that can link a particular sample to a particular specimen or individual human being. But how anonymous are 'anonymised' samples? Merely stripping a sample of some of its identifying detail may not necessarily ensure anonymity. What circumstances would make it difficult to render a sample anonymous? And what policies can be created to ensure true anonymity? This is an issue that the BAC document must address more fully.

8th May, 2002.

A/Prof Terry Kaan,
Chairman,
Human Genetics Subcommittee,
Bioethics Advisory Committee.



11 Jalan Tan Tock Seng
Singapore 308433
Tel : (65) 357 7153
Fax: (65) 256 4755

Dear A/Prof Kaan,

Re : Feedback regarding Human Tissue Research in Singapore

I had earlier spoken to you in relation to the consultation paper on human tissue research in Singapore. I regret it has taken so long to put those opinions on paper.

In general, I am in agreement with the proposals for the process of taking informed consent (IV-8, V-13). However, there is one comment on item 8.7. Contrary to the concerns expressed, there are renowned institutes in the US where the request for consent to donate tissue samples for research is on the same consent form for the surgical therapeutic or diagnostic procedure to remove the tissue (see enclosed example from Sloan Kettering Memorial). Although the use of the same consent form may predispose to an impression that "the best efforts made for his or her therapeutic or diagnostic benefit might depend on or be affected by the giving or refusal of consent to the donation" (sic 8.6), whether or not this impression results ultimately depends on the honesty, integrity and communication skills of the person taking the consent. Note that the use of a separate consent form does not necessarily prevent the risk of an inappropriate impression. Perhaps the Committee may wish to revisit this point.

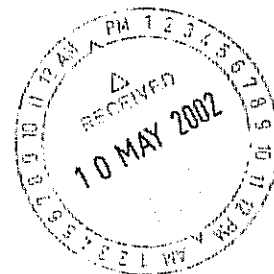
My other concerns are with the use of legacy tissue collections (IV-9, V-13.1.1.5), specifically with recommendation to ensure confidentiality by using anonymisation arrangements or data-escrow arrangements. This is impractical, if not impossible, when the research requires the correlation of tissue findings with clinical information. I note that the Committee did recognise the impracticality of some of their recommendations for legacy tissue. I wish to reinforce this point.

Thank you,
With kind regards,

Yours sincerely,

A handwritten signature in black ink, appearing to read "Yee Woon Chee". The signature is written in a cursive style and is positioned above the typed name.

Yee Woon Chee,
Deputy Director (Research)
National Neuroscience Institute.



CONFIDENTIAL PATIENT INFORMATION - HANDLE ACCORDING TO HOSPITAL POLICY

Memorial Hospital for Cancer and Allied Diseases



Patient Consent Form For Diagnostic and Therapeutic Procedures



Patient Identification

I hereby give consent for the performance of the following procedure(s): _____

by or under the direction of _____ M.D.

The undersigned physician has fully explained to me why I need the proposed treatment, the risks involved, potential problems, the chances for success and the problems I may experience as I recover. We have also discussed alternatives to treatment and the risks and consequences of no treatment. If assistance of Anesthesia Service is required, I understand I will have an opportunity to discuss the anesthesia options, risks and possible complications with an anesthesiologist prior to my procedure.

If my doctor finds something he/she does not expect, I consent to have additional or different procedures the doctor thinks are in my best interest. I know the procedure has risks. I also know there is a chance that I might have a reaction or outcome that is not expected. I know that I will be given transfusions of blood or blood products if I need them and the risks associated with transfusions have been fully explained to me.

The hospital has my permission to use tissues and/or organs removed during the procedure for diagnosis and after that, in any way that advances medical science. I know the tissues and/or organs will be disposed of according to hospital practice.

As long as my identity is disguised, the hospital may publish or televise photographs and/or videotapes taken during the procedure if it is for the purpose of advancing medical education.

For females only: I do not think I am pregnant now, and if I am, I understand that there is a possible risk to the fetus (unborn child).

I have had the chance to ask questions and I am satisfied that they have been answered. By my signature below, I confirm that I have read and understand the information in this form, and that all blank spaces have been completed prior to my signing. I acknowledge that no guarantees or assurances have been made to me concerning the results intended from this treatment.

*Signature of Patient/Agent/Relative or Guardian

Witness (Optional)

(Print Name)

Date

Time

Relationship, (if signed by person other than patient)

Print Name of Interpreter (if consent discussion is translated on behalf of a patient)

Signature of Interpreter attesting to having translated the full and complete content of the discussion to the best of his/her ability.

***THE SIGNATURE OF THE PATIENT MUST BE OBTAINED UNLESS THE PATIENT IS AN UNEMANCIPATED MINOR UNDER THE AGE OF 10, OR OTHERWISE INCOMPETENT TO GIVE CONSENT.**

PHYSICIAN CERTIFICATION

I hereby certify that the patient/agent/relative/of guardian has stated in my presence that he/she has received an explanation of the nature, purpose, benefits, reasonably foreseeable risks of, and alternatives to the use of interventional contrast media, has had all of his/her questions answered, and has given his/her consent.

Date

Time

(Physician Signature)

(Print Name)



**NATIONAL
SKIN
CENTRE**

An Affiliated Teaching Hospital for
National University of Singapore

15 May 2002

**A/Prof Terry Kaan
Chairman
Human Genetics Subcommittee, BAC
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101**

Dear A/Prof Kaan

**REQUEST FOR FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN
SINGAPORE**

Please be informed that we do not have any comments to make regarding your
consultation paper.

Thank you.

With kind regards,

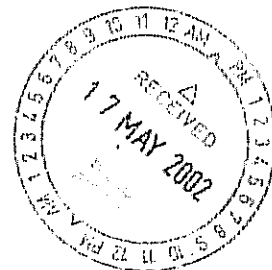
Yours sincerely

**Dr Goh Chee Leok
Clinical Professor
Director / Senior Consultant Dermatologist**

DID: 3508401

Internet email: nsc@pacific.net.sg

1 Munday Road
Singapore 308206
Tel: 253 4466 Fax: 253 0226
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University
Hospital**

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Singapore 119074
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<http://www.nuh.com.sg>

17 April 2002

Professor Lim Pin
Chairman, Bioethics Advisory Committee
250 North Bridge Road
#15-01/02
Raffles City Tower
SINGAPORE 179101

Dear Prof Lim

HUMAN TISSUE CONSULTATION PAPER BY BIOETHICS ADVISORY COMMITTEE

The members of the NUH Research & Ethics Committee (REC) met on 2 April 2002 and deliberated carefully on the abovementioned paper.

In summary:

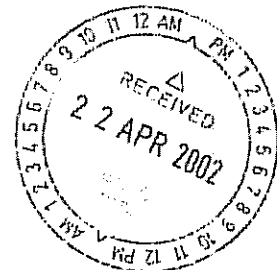
1. The NUH REC gladly accepts all the points put forward as the paper conforms to the Singapore law and principals as well as existing regulations of overseas countries. The paper is clearer and well defined compared to those from many developed countries. This paper will be helpful in advancing the Singapore biomedical life sciences.
2. There is one main reservation with regards to "Item 2 : Definitions". The committee feels that foetuses, gametes (sperms or eggs) and embryos should be categorized separately rather than as a broad category such as "human tissue". Inclusion into this broad categorization may infringe on many religious, moral and social beliefs especially in this multi-racial, cross-cultural country such as Singapore. Our view is that fetuses, gametes and embryos should be treated as a separate category.
3. REC will also like to see a clearer definition of "tissue bank" and "blood bank". What quantity of tissue / blood samples have to be collected in order to be constituted as a "bank" and at what stage would the "banks" be considered as "licensed"?

Thank you.

Yours sincerely

*Assoc. Professor K O Lee
Chairman, Research and Ethics Committee
National University Hospital
C/o Medical Affairs Department*

Cc: CEO, NUH
CMB, NUH
VCMB (Research), NUH
NUH REC



Office of Life Sciences



28 April 2002

John E L Wong
Professor of Clinical Oncology
Director, Office of Life Sciences

Assoc Prof Terry Kaan / Dr Sylvia Lim
Chairman
Human Genetics Subcommittee, BAC
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101



Dear Terry

CONSULTATION PAPER ON HUMAN TISSUE RESEARCH

Thank you for the opportunity to provide feedback on the consultation paper.

This is an excellent paper. My only comment pertains primarily to Item 8.7, under Section IV : Specific Issues. It would not be practical for 2 separate people to take consent.

Thank you.

With kindest regards

John Wong



PARKWAY GROUP HEALTHCARE PTE LTD

28 March 2002

A/Prof Terry Kaan
Chairman
Human Genetics Sub-committee
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101

Dear Sir

CONSULTATION PAPER ON HUMAN TISSUE RESEARCH

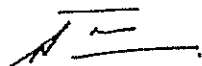
Thank you for sharing the paper on Human Tissue Research.

Overall we feel that the paper covers most areas of concern and that the interim recommendations proposed are sound and can form the basis for the legal and ethical framework to be built upon.

We will continue to discuss these issues at our hospital Medical Advisory and Independent Review Board levels and hope to be able to maintain a dialogue with your committee on these issues.

With kind regards

Yours sincerely


Dr S Thanasekaran
PGH Medical Affairs

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Fax: 475 1832

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80 Marine Parade Road
#12-01/02
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E-Mail : tsinnath@gleneagles.com.sg

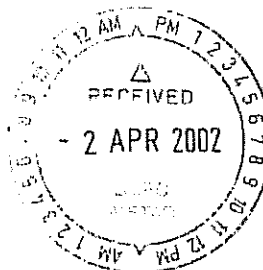
FAX: 64705 605

GROUP HOSPITALS

- East Shore Hospital,
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- Gleneagles Hospital,
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- Mount Elizabeth Hospital,
Singapore
- Gleneagles Medical Centre,
Penang
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- Gleneagles Hospital,
Cebu
- Gleneagles Coleman,
Brisbane
- The Heart Hospital,
London

GROUP SERVICES

- General Practitioner (GP)
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- Laboratories
- Managed Care
- Pharmacy
- Renal Dialysis



Singapore Association for the Advancement of Science

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15 Science Centre Road
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Tel : (65) 425 2500
Fax: (65) 565 9533

18 April 2002

A/Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101



By fax 68379190

Dear Prof Kaan

CONSULTATION PAPER ON HUMAN TISSUE RESEARCH IN SINGAPORE

Thank you for your letter of 27 Feb, inviting our Association to provide feedback on the consultation paper prepared by your Subcommittee in relation to human tissue research in Singapore.

We recognize that it is a difficult issue and whilst the study appears balanced, some feedback have been received from our members. These are summarized hereunder :

Para 8.4 and 8.5

It may not be fair to the donor if the gift is to be of an absolute one which requires the renouncing of entire rights so that all possible kinds of research procedures may be carried out on the donated human tissue sample. This also includes renouncing of all rights to possible future financial gains or benefits.

Para 13.1.1.1

Details need to be given as to what criteria are used to decide whether the potential benefits of tissue-taking outweighs the potential risks to the patient. For instance, in major breakthroughs in research, the financial rewards and prestige from the researcher's viewpoint would obviously seem to outweigh the risks to the patient. However, from the latter's viewpoint, the risks incurred are of greater significance than the researcher's reward. Are we willing to sacrifice the life of a single person for the benefit of others.

Para 13.1.1.2

The Committee should further define what they mean by 'informed consent' – for example, what is the nature of the Information required and how much of it are they

willing to disclose to the potential tissue donor. There should be a standardization of the quality and quantity of information given to the patient. Information should include not only the purpose of the tissue-taking but also the risks involved; the nature, location and quantity of tissue taken; how invasive the surgery would be, and so on.

General

The highly intellectual and well drafted consultation paper also exposes one thing. The subject, combining complex legal and scientific issues, is too "cheem" for the layman (Singapore word for esoteric).

The "fair picture" that is to be presented to the layperson donor could be elusive, if not impossible. The confidentiality promise will ^{be} hard to enact, both in reality and in perception.

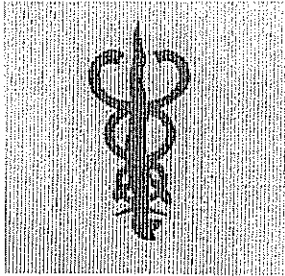
We need a campaign of public education, to take the meaningful dialogue beyond the legal and scientific experts. An exhibition, and a series of simple talks will go a long way to bring the subject into the consciousness of the general public. While their grasp of the technical issues will not be comprehensive, their collective moral views ought to really matter.

With best wishes.

Yours sincerely



Dr Chew Tuan Chiong
Hon Secretary



SINGAPORE CANCER SOCIETY

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Email: cancers@pacific.net.sg Website: <http://cancer.org.sg>

16th May 2002

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Prof John Wong

Assoc Prof Terry Kaan
Chairman
Human Genetics Subcommittee
Bioethics Advisory Committee
250 North Bridge Road
15-01/02 Raffles City Tower
Singapore 179101

Dear Assoc Prof Kaan,

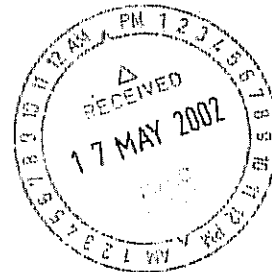
RE: Consultation Paper on Human Tissue Research

Thank you for your letter and the consultation paper on Human Tissue Research. We would like to inform you that we have no feedback on the consultation paper.

Thank you.

Sincerely

Dr Khin Khin Win
Medical Administrator





Singapore General Hospital
A Tradition of Caring & Excellence

11 March 2002

A/Prof Terry Kaan
Chairman, Human Genetics Subcommittee
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101

Dear A/Prof Kaan,

REQUEST FOR FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN SINGAPORE

Thank you for your letter dated 27 February 2002.

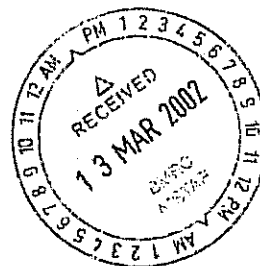
I am pleased to enclose SGH Ethics Committee's feedback on the HGS consultation paper for your attention.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Woo Keng Thye'.

Prof Woo Keng Thye
Acting Chairman
Medical Board

enc





Singapore General Hospital

MEMORANDUM

To : Ag CMB
From : Dr Aw Swee Eng, Chairman, Ethics Committee
Date : 8 March 2002

REQUEST FOR FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN SINGAPORE

The members of the Ethics Committee are in general agreement with the well-crafted document. It is open-ended enough to accommodate any changes that will crop up when there is a better understanding of the issues.

I am not clear about the implications of 11.5. It is here suggested that "the jurisdiction of the DMS under the Private Hospitals and Medical Clinics Act be extended to all individuals and bodies (and not just healthcare establishments, hospitals, medical clinics and clinical laboratories) minded to engage in the conduct of tissue banking."

Although the reason is to place both non-medical researchers (who are not subject to the provisions of the Act) and medical researchers alike on a level playing field, the net is too wide. The difficulty will come in the direction, enforcement and supervision of such individuals or bodies in regard to the ethical and operational guidelines that the appropriate authorities may impose on them.

Moreover 11.5 contradicts the spirit of the guidelines laid down in 5.5 - 5.8 with reference to the subject of tissue banking. In particular, 5.8 states:

"Consolidation of smaller human tissues in larger institutional holdings confers many benefits. A larger institution has more resources for the proper maintenance and stewardship of human tissue samples under its charge."

The section on Informed Consent is acceptable. The details on anonymisation and data escrow arrangements need to be fleshed out.

There are some minor amendments:

- 13.1.1.6 The words "to be accessed" should be added to the end of the sentence.
- 13.1.1.8 "principle" should be "principal" and "practise" should be "practice".

Thank you.

A handwritten signature in black ink, appearing to read 'ASW'.

Dr Aw Swee Eng
Chairman, Ethics Committee

2 College Road Level 2
Alumni Medical Centre
Singapore 169850



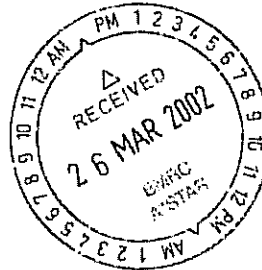
SINGAPORE
MEDICAL
ASSOCIATION

Tel: 223 1264 Fax: 224 7827
Email: sma@sma.org.sg
Website: www.sma.org.sg

Our Ref: SMA/148HTR/2002

22 March 2002

Prof Lim Pin
Chairman
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101



By Mail & Fax: 68379190

Dear Prof Lim

**REQUEST FOR FEEDBACK REGARDING
HUMAN STEM CELL RESEARCH IN SINGAPORE**

Thank you for the letter of 27 February from Prof Terry Kaan inviting the SMA to provide feedback on the Consultation Paper on Human Tissue Research.

While we are considering your HGS Consultation Paper, we are already encountering the commercial overture of human tissue collection and banking. Some of our O&G colleagues have been approached by commercial enterprises with offers of compensation for collection of cord blood.

We would like to request the inclusion of the "ethics of compensation for collection of cord blood" in your HGS paper. We look forward to receive an interim statement from the BAC which we may circulate to our doctors and to commercial companies which are making such enquiries.

The SMA stand is that such transactions should be forbidden until the BAC has considered the matter and come up with a statement.

Yours sincerely

A/PROF GOH LEE GAN
Chairman
SMA Ethics Committee

cc: A/Prof Terry Kaan, Chairman - Human Genetics SubCommittee, BAC
Dr Lee Suan Yew, President, Singapore Medical Council
Prof Tan Chorh Chuan, DMS, MOH

2 College Road Level 2
Alumni Medical Centre
Singapore 169850



SINGAPORE
MEDICAL
ASSOCIATION

Tel: 223 1264 Fax: 224 7827
Email: sma@sma.org.sg
Website: www.sma.org.sg

Our Ref: SMA/148HTR/2002

28 March 2002

A/Prof Terry Kaan
Chairman, Human Genetics Subcommittee
Bioethics Advisory Committee
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101

Dear Prof Kaan

**REQUEST FOR FEEDBACK REGARDING
HUMAN TISSUE RESEARCH IN SINGAPORE**

Thank you for your letter of 27 February and the enclosure. We are grateful for the opportunity accorded to us to review the HGS Consultation Paper.

We have found the HGS Consultation Paper to be a well-thought-out paper which encompasses the various aspects that require consideration. We have no further suggestions to add with regard to the content of the paper.

As submitted by A/Prof Goh LG, Chairman - SMA Ethics Committee, on 22 March, we would however like to request for the inclusion of the BAC's stand on "ethics of compensation for collection of cord blood". We look forward to receiving the interim statement of BAC on this issue for circulation to the medical profession and commercial companies that make enquiries. Our view is that such transactions should be forbidden prior to the receipt of the BAC statement.

One of our members has taken the liberty to edit the layout of your recommendations, and the draft of this editing is attached as an annex for your consideration.

Yours sincerely

PROF. LOW CHENG HOCK
President
for 42nd SMA Council

Enc:



REQUEST FOR FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN SINGAPORE

The following minor changes are tabled for consideration from syntax point of view.

1. para 2.1 (on page 3) - to delete the words "kinds of"

"2.1. In this Paper, we use the term **"human tissue"** to refer to all human biological materials derived from living or cadaveric donors, including solid body tissues, organs, foetuses, blood and other body fluids and their derivative thereof.
2. para 2.2. (on page 4) – to change the word "ones" to "uses"

"2.2 As blood banking is already well-regulated in Singapore, we exclude **bloodbanking for therapeutic purposes** from the ambit of this review, and do not include it in our definition of **"tissue banking"**. However, we do include in our definition research involving studies of blood collections (whether the original samples were collected for therapeutic or research objectives, or a combination of both) or the use of such blood samples or their derivatives for purposes other than direct therapeutic uses such as transfusions.
3. Para 8. (on page 10) - **Consent Generally to amend to read "Informed Consent"**

8.1. Full, free and informed consent is the cornerstone of the legal and ethical legitimacy and validity of a gift of human tissue intended for research.
4. Para 13. (on page 17) we suggest to amend by deleting the words " and to replace with

"13. We recommend the Adoption of 8 Ethical Principles ⁽²⁾ as a starting point for this dialogue:
5. **Primacy of the Welfare of the Donor.** (page 18) - we suggest to amend as "13.1 Respect the Primacy of the Welfare of the Donor".
6. para "13.1.1.1" to be amended to read as "13.1.1"

"13.1.1 The health, welfare and safety of the donor shall be the paramount consideration in the taking of any tissue.....
7. **"Informed Consent"** to number the para as "13.2"
8. "13.1.1.2" to renumber as "13.2.1"

13.2.1 No tissue shall be taken, or shall be accepted, unless the full, free and informed consent of the donor has been obtained...

- "13.1.1.3" to renumber as "13.2.2"
 "13.1.1.4" to renumber as "13.2.3"
 "13.1.1.5" to renumber as "13.2.4"
 "13.1.1.6" to renumber as "13.2.5"
9. "Respect for the Human Body" to number as "para 13.3"
 10. Paragraph 13.1.1.7 to renumber as "13.3.1"
 11. To start new paragraph and number as "13.3.2" at "Researchers and tissue bankers should always ensure that donors and the families of donors fully understand the extent of the intended gift."
 12. "Donations to be Gifts" to be numbered as para "13.4"
 "13.1.1.8" to renumber as "13.4.1".
 13. Amendment to the paragraph as follows:
 "13.4.1 Research tissue samples for use in research as outright gifts. Donors should not be paid any financial incentives for the donation,of such discovered in the course of research on the sample.
 14. To start new paragraph and number as "13.4.2" at
 "Likewise, researchers and tissue bankers should not be under any obligation to disclose such information to the donors, unless they have agreed to do so in advance of the donation."
 15. "Ethical Review of Research Proposals and Access Requests" to renumber and be amended to read as "13.5 Set up Ethical Review Bodies".
 16. Paragraph "13.1.1.9" to be renumbered as "13.5.1"
 17. To start new paragraph 13.5.2 at "The appointment, and constitution of such ethics committees or review boards should be as transparent as is practicable."
 "13.1.1.10" to renumber as "13.5.3"
 "13.1.1.11" to renumber as "13.5.4"
 18. "Confidentiality" to number as "13.6" and to amend as "Respect Confidentiality of donors and relations"
 19. "13.1.1.12" to renumber as "13.6.1"
 20. "13.1.1.13" to renumber as "13.6.2"

21. **"Institutional Tissue Banking"** to number as **"13.7"** and to amend as **"Limit Tissue Banking to Institution"**
22. **"13.2"** to number as **"13.7.1"**
23. **"Ethical Governance of Operational Aspects of Tissue Banking"** to number as **"13.8"** and to amend as **"Set up Statutory Authority for Tissue Banking Governance"**
24. **"13.3"** to renumber as **"13.8.1"**
"13.4." to renumber as **"13.8.2"**
"13.5" to renumber as **"13.8.3"**.
"13.5.1." to renumber as **"13.8.3.1"**
"13.5.2." to renumber as **"13.8.3.2"**
"13.5.3. " to renumber as **"13.8.3.3"**
"13.5.4." to renumber as **"13.8.3.4"**
"13.5.5." to renumber as **"13.8.3.5"**
"13.5.6." to renumber as **"13.8.3.6"**
"13.5.7." to renumber as **"13.8.3.7"**
"13.5.8." to renumber as **"13.8.3.8"**
"13.5.9." to renumber as **"13.8.3.9"**
25. **"Initiating An Ethical Dialogue"** to number as **"14"** and to amend as **"Invitation of the Professions and the Public to an Ethical Dialogue"**
26. To delete the numbering **"13.6"** but to keep the whole paragraph intact
27. **"Resolution of Legal and Ethical Issues in Relation to Ownership and Custody"** to number as **"15"** and to amend as **"Resolution of Ownership and Custody Rights to Donated Human Tissues"**
28. To delete the numbering **"13.7"** but to keep the whole paragraph intact.



SINGAPORE MEDICAL COUNCIL

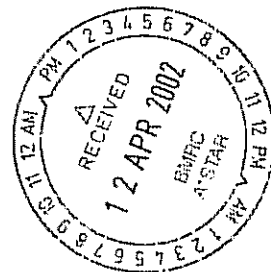
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Our Ref: SMC 14.2 Vol. 6
Your Ref:

Tel: 6392 3070
Fax: 6221 0558

9 April 2002

A/Prof Terry Kaan
Chairman
Human Genetics Subcommittee, BAC
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101



Dear A/Prof Kaan

REQUEST FOR FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN SINGAPORE

I refer to your letter dated 27 Feb 2002.

2. The Medical Council's comments on the issues outlined in the BAC's Consultation Paper are at Annex.
3. Please let me know should you require further clarification.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Lee Suan Yew'.

DR LEE SUAN YEW
PRESIDENT
SINGAPORE MEDICAL COUNCIL

Annex

SINGAPORE MEDICAL COUNCIL'S FEEDBACK ON BAC'S CONSULTATION PAPER ON HUMAN TISSUE RESEARCH

Paragraph 5 – Human Tissue Banking in Singapore

- (a) Clear guidelines must be set as to what type(s) of "institutions" can have tissue banks. Preferably these should be not-for-profit institutions.
- (b) Centralisation of tissue banks is important for certain tissues that will benefit multiple groups doing research in the same area(s). However, smaller research groups with specific needs for certain tissues must not be prevented from collecting tissues if done in the proper manner. Where the storage of tissues is liberalised, it should be within the guidelines of legislature and professional ethics.
- (c) Confidentiality of the donor must be protected at all times - anonymisation of the tissues is important to protect the donor.
- (d) Legacy tissues collected in good faith at a time when there was a lack of any clear ethical, professional or legal guidelines governing the collection of such tissues should not be discarded as they are a valuable source of material. Anonymisation of the donors of the tissues should be done and the tissues can then be used for research purposes.
- (e) Agree that purpose-assembled research banks may be encouraged provided that all appropriate ethical and legal considerations and concerns are appropriately met and addressed.

Paragraph 8 – Consent Generally

- (f) When taking consent for tissues for research purposes, proper counselling must be done so that the patient knows that refusal to donate tissues for research will not affect his treatment in any way.
- (g) Consent for specimen collection for diagnostic or therapeutic purposes should be totally de-linked from consent for use of same specimen for research i.e., both consents should not be requested together. The consents should be so separated by time and place that a patient could not possibly feel any pressure to provide the latter consent, believing (albeit incorrectly) that diagnosis and therapy for an illness could somehow be linked to consent for research. For example, the latter consent could only be obtained after a patient has successfully completed treatment for an episode of illness. If the patient dies, then the family should be asked for a

second consent later. Careful and compassionate explanation/ counseling would be in the best interest of both the patient and researcher.

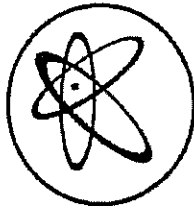
- (h) The concept of 'absolute gift' is attractive, but it does not address the right of a donor to object to some uses of his tissue. For example, a donor may object to the use of his tissue for reproductive or therapeutic cloning or for transplantation into another person. While it is an easy option to ask for blanket consent, patients' concerns may not be satisfactorily addressed.
- (i) Concerning the issue of 're-consent', it may be helpful to have a concept of 'statute of limitations'. For example, after a certain reasonable time, no further consent should be required for further use of a tissue sample for new purposes that were unknown at the time of original consent.

Paragraph 9 – Consent and Legacy Tissue Collections

- (j) A concept of 'statute of limitations' may also be helpful in the case of legacy tissue collections.
- (k) Good stewardship includes the presence of an institutional review board. Where there is such an arrangement, there need not be another layer of bureaucratic control.

Paragraph 13.1.1.8 – Donations to be Gifts

- (l) Where the origin of a specimen is known, it could be unethical to withhold from a patient the knowledge of any information gleaned from the specimen that revealed a medical condition or predisposition or likelihood of disease, especially if intervention could change the likelihood or course of that disease. This needs to be addressed.



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PATRON

Dr Toh Chin Chye

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4 April 2002

A/Prof Terry Kaan
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Human Genetics Subcommittee
Bioethics Advisory Committee
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Fax: 68379190

Dear Prof Kaan

**CONSULTATION PAPER ON HUMAN TISSUE RESEARCH
IN SINGAPORE**

Thank you for your letter of 27 Feb, inviting our Academy to provide feedback on the consultation paper prepared by your Subcommittee on human tissue research in Singapore.

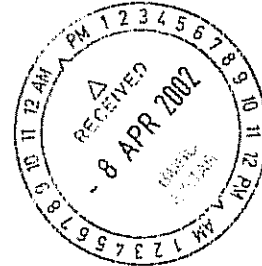
Our Academy recognizes that it is a difficult issue to comment on. Whilst the study appears balanced to some members of our constituent societies, others have given some inputs, with a view towards contributing to the fine-tuning of certain aspects of the consultation paper. These are summarized below:

Para 8.4 and 8.5

It may not be fair to the donor if the gift is to be of an absolute one which requires the renouncing of entire rights so that all possible kinds of research procedures may be carried out on the donated human tissue sample. This also includes those relating to the renouncing of all rights to possible future financial gains or benefits.

Para 13.1.1.1

Details need to be provided as to what criteria are used to decide whether the potential benefits of tissue-taking outweigh the potential risks to the patient. For instance, in major breakthroughs in research, the financial rewards and prestige from the researcher's viewpoint



would obviously seem to outweigh the risks to the patient. However, from the latter's viewpoint, the risks incurred are of greater significance than the researcher's reward. Are we willing to sacrifice the life of a single person for the benefit of others?

Para 13.1.1.2

The Committee should further define what they mean by 'informed consent'-- for example, what is the nature of the information required and how much of it are they willing to disclose to the potential tissue donor. There should be a standardization of the quality and quantity of information given to the patient. Information should relate to not only the purpose of tissue-taking but also the risks involved; the nature, location and quantity of tissue taken; how invasive the surgery would be, and so on.

Generally speaking, the recommendations of the Committee should apply not only to tissues taken within Singapore but also to tissues taken from sources outside Singapore for use (research or diagnostic) within the republic.

With best wishes.

Yours sincerely



Professor Leo Tan Wee Hin
President



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3 April 2002

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Total No. of Pages: 3
(including this page)

Dear Terry,

**CONSULTATION PAPER ON HUMAN TISSUE RESEARCH
EXTENSION OF DEADLINE FOR SUBMISSION OF FEEDBACK**

I refer to the abovementioned matter.

Please find attached the comments from our Ethics Committee for your attention.

Please do not hesitate to contact me at Tel: 6 3228323 should you require any classifications.

Thank you.

Yours sincerely

DR ANG CHONG LYE
Director



FAXED & post
DATE: 03/4/02

Branches & Affiliated Centres

- Chong General Hospital (Clinic G & G) • KK Women's and Children's Hospital (Clinic F) • Mount Alvernia Hospital (Medical Centre Block B)
- National University Hospital (E) & Clinic • Singapore General Hospital (L Clinic) • SNEC Eye Associates, Mount Elizabeth Hospital

A member of SingHealth

REQUEST FOR FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN SINGAPORE

As in all medical ethical issues, we are concerned for the patient --- his safety, and his rights.

Item

- 4.4 If the tissue collection is done primarily for research, then the risk (if any) of the collection or harvesting should be explained to the patient / subject, and informed consent taken. E.g. in the eye, removal of an early pterygium for research purposes, should be explained to the patient as risky, as it can cause a recurrence which is worse than the primary condition. See Items 5.9 and 13.1.1.1
- 2.2 A safety limit should be specified for Blood collection, which should not exceed, say, 50 ml. per subject at any one time. Otherwise the subject will need to have his Hb level checked.
- 2.1 We should separate human tissues derived from the living and those derived from the dead. In the case of cadaveric donors, safety is no more a concern ; they are governed by the Medical (Therapy, Education & Research) Act, and the Human Organ Transplant Act. See Items 6.2 & 6.3. We should also separate embryonic stem cell research and cloning, as stated in Item 2.3, which depend very much on whether you think an embryo is a person having all the rights of a person, but cannot give consent.
- 4.2 We should separate genetic (and genomic) research which is governed by the "Ethical Guidelines for Gene Technology" published in February 2001 by the National Medical Ethics Committee.
- 8.4 This is important, as in the case of cancer patients who die before the research is over. In order to avoid claims from heirs, it is best to anonymise the tissue. Anonymisation will also prevent breach of confidentiality, and use by health and insurance companies.
- 8.8 It is important that, as stated here, the research applications are approved by an Independent Ethics Review Committee, which ensures the scientific and ethical validity of the research work. See Item 13.1.1.9.

12...

- 2 -

- 8.10 This would also apply to taking of tissues (e.g. blood) for research work on Emergency Cases, where consent may be difficult to obtain.
- 8.11 Will researchers be allowed to distribute tissues to other centres in other countries when requested for ?
- 13.1.1.10 The social, religious and political issues, implications and reactions have not been dealt with, and must be sought for, especially with regard to embryonic tissues. Whether one believes the embryo is a person or not depends very much on religious belief. Also, the cultural belief that one must go to Heaven with an intact body has always been an obstacle in eye donation.
- 13.6



SINGAPORE NURSING BOARD

13 Mar 2002

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Singapore 179101

Dear Prof Kaan

REQUEST FOR FEEDBACK REGARDING HUMAN TISSUE RESEARCH IN SINGAPORE

Thank you for inviting the Singapore Nursing Board to provide feedback regarding human tissue research in Singapore.

We agree with the interim recommendations in para 13.

We would like to commend the Human Genetics Subcommittee for the comprehensive coverage of the potential ethical, legal and social issues related to human tissue research.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Ang Beng Choo'.

ANG BENG CHOO
REGISTRAR





Tan Tock Seng
HOSPITAL

Our Ref TTS/MED

27 March 2002

A/Prof Terry Kaan
Chairman, Human Genetics Subcommittee
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Dear A/Prof Kaan

CONSULTATION PAPER ON HUMAN TISSUE RESEARCH

I refer to your letters of 27 February 2002 and 11 March 2002.

I have sought the views of the relevant personnel and am attaching their comments / feedback for your consideration:

- Dr Angela Chong Pek Yoon
Senior Consultant
Dept of Pathology & Laboratory Medicine
- Dr Richard Bellamy
Registrar
Dept of Infectious Diseases
- Ms Cynthia Chan
Manager, Legal Services

Thanks for seeking our views on your consultation paper. We hope our feedback is useful to your Committee.

Yours sincerely

Clin Prof Chee Yam Cheng
Chairman, Medical Board

Kfn: Y: bioethics

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Feedback from Dr Angela Chong, Senior Consultant, Dept of Pathology & Laboratory Medicine, TTSH, on the Consultation Paper "Human Tissue Research" by The Bioethics Advisory Committee

1. Agree with the Interim Guidelines.
2. Subsampling - No subsampling until diagnostic procedure has been completed or until therapeutic procedure has been confirmed that is after the pathologist has examined the tissue. Completion does not occur at the end of the surgical/ invasive procedure.
3. Tissue archives. Pathology archives currently store diagnostic tissue. This should NOT be given out to researchers without the consent of the hospital concerned - as these patients may still require their tissue for prognostic markers, therapeutic markers or for diagnostic or medicolegal challenge. As we have heard recently, we need to have some record. To have no record is not a valid excuse.
4. The border between 'legacy' tissue and current diagnostic tissue is not drawn. The hospital should retain the right to determine where to draw this line - with guidance from national oversight committees.

2: Tissue-path

Feedback from Ms Cynthia Chan, Manager, Legal Services, TTSH on the Consultation Paper "Human Tissue Research" by The Bioethics Advisory Committee

I agree that there is a dearth of legal precedents in this area of law, which is fast developing and has shot to prominence as a result of the surge of interest in the new life sciences such as human genetics and genomic research as well as recent events in Britain and New Zealand.

I have gone through the Consultation Paper on Human Tissue Research ("the Paper") prepared by the BioEthics Advisory Committee of Singapore ("BAC") in great detail and my comments are as follows:-

- 1) I agree that human tissue collections should be managed by a national databank and not by private individuals. All non-institutional legacy tissue collections build up over the years in hospitals, universities or research institutions should eventually be amalgamated with the larger collections of institutions.
- 2) I also agree that purpose-assembled research banks should be encouraged, provided that all appropriate ethical and legal considerations and concerns are appropriately met and addressed, in order to promote and enhance research for the benefit of mankind.
- 3) In view of the lack of any uniform approach to the governance of regulation of tissue banking internationally, the lack of any clear definition of "tissue banking" in the Private Hospitals & Medical Clinics Act ("the Act") or the Regulations under the Act or in any other statute and the dearth of any guidelines for the proper conduct of tissue banking, it would be prudent for us in Singapore to proceed cautiously on the various issues of property, control and ownership rights to tissue samples.
- 4) It is imperative that changes to the above be implemented as soon as possible to avoid blocking essential work. I wholeheartedly agree that a review has to be undertaken of the law governing this area by the Attorney-General's Chambers ("AGC") and that a professional and public dialogue should be initiated to discuss the ethical and social considerations which should shape the law in this area.
- 5) I fully agree that there is a need to procure the full, free and informed consent of the patients to the taking of their tissue samples, which should be separate from the normal Consent Form which the parties sign when they undergo an operation/procedure for therapeutic or diagnostic purposes. I am also in favour of the recommendation that wherever possible, the person responsible for explaining the nature of the donation and the taking of the consent for the donation should not be the person who receives the consent for the taking of the tissue for therapeutic or diagnostic purposes.
- 6) I am cognisant of the fact that there may be situations where consent may be given generally and not for a specific purpose, or where it would be impracticable or impossible to insist on consent being obtained. I agree that in the latter situations, an appropriately constituted Ethics Committee or institutional review board should be looking into the decision for the taking of human tissue from such persons within the limits permitted by law.

- 7) In view of the multi-racial society that we have in Singapore, we should be mindful of social, cultural and religious sentiments in relation to the custody, use and disposal of tissues and take extra care with the same.
- 8) I support the recommendation that steps should be taken to formulate a national ethical policy governing reasonable access to such legacy tissue collections, to be led by a national-level body. I feel that in this aspect, the National Medical Research Council ("NMRC") would be the most appropriate body to undertake this role (which would mean an expansion of its current role), rather than have a separate body constituted for this purpose.
- 9) I agree that in cases where it may be difficult or impossible to re-contact the donor or the donor's family for consent (or re-consent), for example, in the case of legacy tissue collections for the purposes of further research on the tissues or where it may be socially unacceptable to do so, for example, where there is a strong possibility that the donor is dead or otherwise uncontactable, it is permissible for researchers to consider the use of anonymised data arrangements or data-escrow arrangements as may be approved by appropriately-constituted Ethics Committees or institutional review boards.
- 10) The BAC has recommended legislative intervention only in situations where it is clear that effective professional self-regulation and a fair balance of rights and interests between individuals and the public in encouraging research cannot be achieved without legislative teeth. I agree that this should be the case and it would not be the first time that this approach has been taken. In the case of the Electronic Transactions Act, the intention of the government is to allow the individual organisations freedom to embrace and adopt Internet-advanced technology as long as it is done in a responsible manner, being mindful that overly-specific rules would run the risk of rapid obsolescence as stated in paragraph 11.1 of the Paper. It is submitted that the same applies to the rapidly developing field of life sciences.
- 11) I agree that the jurisdiction of the Director of Medical Services could be extended to all individuals or bodies inclined to engage in tissue banking activities, so as to subject both medical and non-medical researchers to the same set of operational and ethical guidelines as may be imposed by the appropriate authorities. I am of the view that it may not be necessary to establish a statutory agency for the regulation of stem cell as that would create an additional superfluous layer of bureaucracy and may possibly lead to greater confusion on the ground.
- 12) While it is desirable to have consistent and transparent rules and standards which ought to apply to all forms of tissue banking in Singapore, whether carried out by the private or public sector, whether carried out primarily or incidentally for the purposes of research and whether such research is for a commercial end or for a non-profit end, I am not agreeable to the recommendation that a national-level committee or consultative body be appointed. This national committee already exists in the form of the NMRC, whose role can be extended to formulate a national party relating to the regulation, conduct and governance of tissue banking in Singapore. If need be, the members of the NMRC can be expanded to include experts from the relevant industrial, academic, research and professional sectors of the life sciences.

- 13) NMRC already has some supervisory powers over the decisions of institutional review boards or institutional Ethics Committees. I am of the view that the applications by researchers for access to human tissues can be dealt with in a manner similar to current applications for all other types of research work. There may be a need to fine-tune the available procedures to suit the particular aspects of tissue banking.
- 14) I also agree that tissue banks should develop and have in place electronic data systems that will enable the consent status and consent conditions (if only) of every human tissue sample to be accurately recorded and to facilitate ease of access by researchers, for the greater good of mankind.
- 15) It is imperative that researchers and all those involved in the conduct of tissue banking understand and adhere to the obligation of confidentiality of the personal information of donors entrusted to them, as well as the privacy of the donors. Appropriate consent must be obtained before the release of any such personal information to researchers or to any third party.
- 16) I wholeheartedly agree that there should be statutory regulation and supervision of all forms of tissue banking and that it should not be carried out without licence. The governmental authority (whether it be the Director of Medical Services or a separately established statutory authority) should be given sufficient powers of direction, enforcement and supervision, so as to enable it to effectively give ethical and legal direction for the conduct of all forms of tissue banking carried out in Singapore. This authority should also be tasked with ensuring compliance with such direction and such other rules, standards and codes of conduct so as to establish and maintain proper operational governance and protect the interests and rights of patients, donors and their respective families.
- 17) It is of utmost importance that institutions which conduct tissue banking have in place transparent and appropriate systems and standards for the proper ethical, legal and operational governance of tissue banking as stated in paragraphs 13.4 and 13.5 of the Paper.
- 18) Finally, I agree that a professional and public dialogue should be initiated as soon as possible to settle the principles governing tissue banking, so as to achieve an early resolution of the legal and ethical questions in respect of the ownership and custody rights to donated human tissue.

Feedback from Dr Richard Bellamy, Registrar, Dept of Infectious Diseases, TTSH, on the Consultation Paper "Human Tissue Research" by The Bioethics Advisory Committee

Generally I think that this document is well written and considers most of the important relevant ethical issues. The document has not paid much attention to the effect which ethical guidelines may place on the practical aspects of tissue banking and on the impact this may have on research. This may be deliberate and may also be because the UK MRC guidelines did not explore this issue fully. However I believe it is important to consider these issues because the culture of institutions and the rights of individual researchers are very different here. Institutions here may read this consultation paper and then institute directives to comply with them without considering all of the potential future practical implications. There are several specific issues which I feel should be addressed.

Individual or Institutional ownership?

The consultation paper disapproves of individual ownership of tissue banks and states that these should be held by institutions. This does not recognise that most research tissue samples held within institutions are informally regarded as the property of the individual who has collected them. An institution may decide to end all individual rights to ownership on the basis of this paper. What potential problems could this cause? If you were to spend several years collecting a large number of samples for your own research you may feel it is wrong for the institution to decide what can be done with them. You would probably be in the best position to determine their value and to what use they should be put. If another individual in the same institution wants to use them for a purpose which you feel is a waste of the sample, should the institution be empowered to allow this without your approval? What if the samples have a high commercial value? Should the institution be allowed to sell them for profit without your agreement? This may be the end of your research!

Do not take this to imply that I feel that individual ownership is right either. This is something I strongly disagree with. In the past it has meant that scientists have been able to collect samples for one purpose and then do anything they want with them without any ethical regulation. Clearly this is not right. Also it has meant that individuals moving between institutions have nearly always taken their research collections with them. Whether this is right or not is a matter of debate.

My own opinion is that joint ownership agreements are needed between individuals and institutions. The consultation paper should discuss the ethical issues arising from this but not specify the nature of such agreements. These details could be decided at institutional level.

Can samples be sent abroad?

Tissue samples may be sent abroad for research which cannot be done in Singapore. It is not clear who should have the authority to agree to this. I do not think that the individual should have. Perhaps it could be the institution or perhaps the National Ethics review board. This is an important issue as research may be carried out which would not be allowed in Singapore.

Should samples be sold to commercial interests?

In the consultation paper it states that the consent form should state that "the gift is an absolute one, the donor renouncing all rights". I do not think that it is acceptable to use such terms as patients should have some rights and these should be protected by the institutional regulations. More appropriate wording would be "the sample may be used for any research purpose which is felt to be appropriate by the institution and which is approved by its ethics committee". This then places responsibility on the institution to ensure that the samples are used appropriately and ethically. This is particularly relevant to the issue of commercial interests using the samples. I believe it is acceptable for such groups to use the tissue samples under the regulation of the host institution. Each project would then need individual ethical approval. However I do not believe it is acceptable for the host institution to give/ sell the samples to a commercial interest and give up its control on what the samples are used for. If this is a possibility then this should be expressly stated on the consent form as many patients could be unhappy with this.

A formal approach to medical ethics

The consultation paper does not formally discuss the four principles of medical ethics, beneficence, non-maleficence, respect for autonomy and justice (Beauchamps and Childress). As a result of this the document has largely ignored two of the principles, non-maleficence and justice. Regarding the first of these it must be recognised that research can have potentially negative effects on the individuals who have donated the samples. For example if I had a collection of blood samples from cancer patients and I looked for mutations which might be associated with familial cancer and found some positive samples what should I then do? If I contact the individuals concerned I may cause unnecessary anxiety or problems with insurance etc. The patient may be cured of the first cancer but may be at increased risk of other cancers. Alternatively other relatives may be at risk etc. If I do not contact the patient he may die from an undiagnosed and curable cancer. This is just one example and the consultation paper should include some discussion of these issues. With regard to justice the paper should consider the uses samples are put to and the potential for others to benefit in the future. This is particularly important for commercial interests but also applies to patents and institutions etc. For example if I use some samples and make a great scientific breakthrough which has some financial worth I may sell the patent rights and become rich without considering if the patent will obstruct future research, drug development, vaccine development etc. My benefit and/or my institution's interests may conflict with those of patients and/or the scientific community. These issues should be discussed as they are common problems.

On the whole I think that the discussion paper has struck a good balance between the rights of individuals and the needs of research. Attempts at clarifying the ethical and legal issues are to be welcomed.

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ASSOCIATE PROF TERRY KAN
BIOETHICS ADVISORY COMMITTEE
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30th March 2002

Dear Sirs

CONSULTATION PAPER ON HUMAN TISSUE RESEARCH

We write in response to the BAC's request for feedback on the consultation paper entitled "Human Tissue Research".

First of all, we would like to thank you for your interest in our views on a matter as important as this. We understand that members of the BAC have devoted significant time and effort in coming up with such a paper, guided by a voice of conscience which you hold so true and dear.

Before we proceed further, we would like to state a few principles on which our response is made:

1. We defend, promote and accord absolute respect to every human being from the moment of conception to the point of natural death, including his primary and fundamental right to life, and his dignity as a person. (1)

2. The evaluation of the morality of abortion is to be applied also to forms of intervention on human embryos which inevitably involve the killing of those embryos.

This moral condemnation also regards procedures that exploit living human embryos and fetuses, either to be used as "biological material" or as providers of organs or tissue for transplants in the treatment of certain diseases. The killing of innocent human creatures, even if carried out to help others, constitutes an absolutely unacceptable act. (2)

God alone is the Lord of life from its beginning to its end: No one can under any circumstance claim for himself the right directly to destroy an innocent human being." (3)

3. To use human embryos or fetuses as the object or instrumentation of experimentation constitutes a crime against their dignity as human beings having a right to the same respect that is due to the child already born and to every human person. (4)



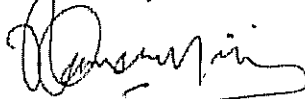
4. No end believed to be good, such as the use of stem cells for the preparation of other differentiated cells to be used in what look to be promising therapeutic procedures, can justify an intervention that will harm or destroy the embryo. A good end does not make right an action which in itself is wrong.

Having read the consultation paper on human tissue research, we have come to the conclusion that we have no choice but to disagree with it for the following reasons:

1. The consultation paper skirts the issue concerning what sort of ethical guidelines or regulations will be imposed on embryonic stem cell research. Instead the consultation paper deals with so many general principles and leave the specifics to statutory bodies to be set up. Various interest groups will not have an idea what will be the final ethical guidelines and regulations until they are enacted and published. By which time, it would be very embarrassing to put those published guidelines and regulations into reverse gear if we should be able to point out to something debatable or unethical.
2. At para. 8, "Full free and informed consent is the cornerstone of the legal and ethical legitimacy" in the gift of human tissue. This is not correct since an embryo is a human being from the moment of conception and has an independent right to life. An embryo certainly cannot give consent. Further, it is doubted if researchers will ever be so full and frank when obtaining consent to ask "Ma'am, can we have your consent to kill your baby embryo and use his cells for the purpose of our scientific research?" A parent's consent is certainly needed in many cases, but when such consent involves the killing of an offspring, and not given for the promotion of his interests, it cannot be considered valid.
3. In 2.1, it was stated that the term "human tissue" refers to all kinds of human biological materials derived from living or cadaveric donors, including ...foetuses.....embryos, gametes or any part of derivative thereof. Since the rest of the paper refers to the above as well, we cannot but voice our unequivocal objection to it for the same reasons as stated in our earlier points.

We hope our feedback is of use to you. We thank you for your interest in our opinions, and trust that you will look into them with due consideration.

Yours faithfully



REV FR JAMES YEO
CO CHAIRMAN
ARCHDIOCESAN BIOETHICS COMMITTEE
ARCHDIOCESE OF SINGAPORE



DR JOHN HUI
MASTER
THE CATHOLIC MEDICAL GUILD OF SINGAPORE

References:

1. Donum Vitae
(Instruction on Respect for human life in its origin and on the dignity of procreation), Introduction
2. Evangelium Vitae (The Gospel of Life), 63
3. Donum Vitae Introduction, 5
4. Donum Vitae 1, 4

cc Msgr Nicholas Chia, Archbishop of the Catholic Archdiocese of Singapore



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15 March 2002

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Chairman
Human Genetics Sub Committee
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250 North Bridge Road
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Singapore 179101



Dear Assoc. Prof. Kaan

**REQUEST FOR FEEDBACK REGARDING HUMAN
TISSUE RESEARCH IN SINGAPORE**

We thank you for your letter of 27 February 2002.

Enclosed please find our feedback which we hope is of use to you.

Thank you.

Yours sincerely

Joseph Benjamin
Honorary Secretary

Enc: 3 pages

Organ Donation

by Rabbi Shraga Simmons

The Jewish position on organ donation is as complex as the issue of life and death, because it derives directly from the Jewish perspective on the sanctity of life and the role that our physical existence plays in the advancement of our spiritual selves.

On the one hand, we have a sacred obligation to preserve human life (*pikuah nefesh*). This is an overriding principle in Jewish law -- so important that almost any other law can be broken for this reason. For example, we can break Shabbat to drive an injured person to the hospital.

On the other hand, Jewish law prohibits desecration of a dead body (*nivul hamet*). A dead person's body, since it once housed the holy soul, is to be treated with the utmost respect. Every part of the body must be buried -- which is why you see the heart-wrenching images of religious Jews dutifully going around after a terrorist bombing, scraping up pieces of flesh and blood for burial.

How do we resolve these two principles?

TO SAVE A LIFE

Organ donation is permitted in the case when an organ is needed for a specific, immediate transplant.

In such a case, it is a great mitzvah for a Jew to donate organs to save another person's life.

Organ donation is not necessarily limited to dead people: Someone who can afford to spare a kidney, for example, may donate one to someone in need.

Yet in consideration of the prohibition against desecrating the body, it is forbidden to simply donate to an "organ bank," where there is no specific, immediate recipient.

Furthermore, it is also forbidden to donate for general medical research or for students to dismember in medical school.

CAUTION NEEDED

Even when there is a specific, immediate transplant, there is need for caution, because oftentimes in order to obtain organs as fresh as possible, a doctor will remove the organ before the patient is actually "dead" according to Jewish law.

The doctor is therefore effectively killing the patient, which is, of course, forbidden.

The bottom line is that each case is different. A myriad of considerations in *halacha* must be reviewed. So before going ahead with any procedure, consult with a rabbi well-versed in Talmud and Jewish law. It is clearly not as simple as blankly signing an organ donation card.

Sources:

Rabbi Yechezkel Landau - Noda BeYehudah II, Yoreh Deah 210
Rabbi Moshe Feinstein - Igrot Moshe, Yoreh Deah II, 174
Dayan Weiss - Minchat Yitzchak V, 7
Rabbi Eliezer Waldenberg - Tzitz Eliezer X, 25

Further information:

Institute for Jewish Medical Ethics in San Francisco (800-258-4427)
"Judaism and Healing" by Rabbi J. David Bleich (Ktav Publishing 1981)

QUESTION : Organs from a Cadaver: the Status of the Deceased and of his Family

Is a person obliged, or even allowed, to consent during his lifetime to the donation of organs after his death?
 Is a person obliged, or even allowed, to sign a form of consent and to carry a donor's card?

Reply

A person has possession and ownership of his body while he is still alive, but his rights are limited by certain bans determined by the Torah, namely, deliberate suicide, self-inflicted injury, endangering oneself, and the like. A person is not forbidden to donate an organ from his body to save someone else's life, or to donate blood to cure even a patient whose life is not at risk, as he is doing this for an important reason where the ban on self-injury does not apply. It appears that a person has the same right to give permission to donate from his body even after his death for the purpose of rescue. If he has clearly expressed his wish to do so, no member of the family has any right to object to it. If there is good reason to suppose that were he asked he would agree, that is sufficient. On the other hand, if he expressed his clear objection to it, his wish must be respected. One who asks advice on whether or not to grant permission for his organs to be used posthumously for saving life should be encouraged, in that it is a *mitsva* (a worthy deed) which, although he is not duty-bound to perform after death, will stand to his credit on the Day of Judgment. However, one who asks advice should not be advised to sign an authorization or to carry a donor's card since this is meaningless except in the case of sudden death such as in an accident. It is not desirable for a person to express the possibility of such an occurrence, which he prays and hopes will never happen to him. The rabbis have already warned against this in their dictum "A person should never open his mouth to Satan."

QUESTION 4: Consent of Donor's Family

What is the status of the family of a deceased person in respect to consenting or refusing to donate organs?

Reply

Whenever someone suffers shame, disgrace or humiliation, this affects his family who in turn suffer hurt, upset, and humiliation. In particular, they feel humiliated by the humiliation of the dead. At the same time it is the duty of close relatives to deal with his burial. Consequently, when it comes to taking organs or parts of the body from a corpse for a transplant to save a Jew's life, the family does have a status. They have status as interested parties and may prevent the use of the organs of the deceased if he had expressed clear opposition to this during his lifetime. However, where the deceased had agreed to donating an organ or where there is good reason to suppose that were he asked he would have agreed, their opposition may be disregarded, since the saving of life is of such great importance. Likewise, if the wish of the deceased is unknown, the family is obliged to give their consent. This duty overrides the duty imposed on them to bury the dead, as far as the relevant organs are concerned, but they should bury the remainder of the body in a suitably dignified manner.

Our Ref: LS/66/02/CSY/sha

Your Ref:

28 March 2002

Assoc Prof Terry Kaan
 Chairman, Human Genetics Sub-Committee
 Bioethics Advisory Committee
 250 North Bridge Road #15-01/02
 Raffles City Tower
 Singapore 179101

Dear *Prof Kaan*

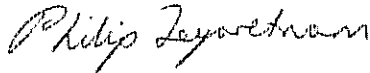
Feedback Regarding Human Tissue Research in Singapore

I refer to your letter of 27 February 2002 enclosing a consultation paper entitled "Human Tissue Research".

On behalf of the President, Mr Palakrishnan, SC, I am pleased to enclose for your attention the Law Society's feedback on your consultation paper. Council had referred the matter to our Intellectual Property Committee and the enclosed feedback is confined to legal issues only.

Thank you for inviting us to give our views and feedback on the matter.

Yours sincerely

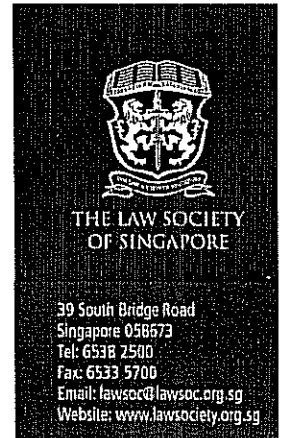


Philip Jeyaretnam
 Vice-President
 for President

Enc./

c.c. Council

c.c. Intellectual Property Committee

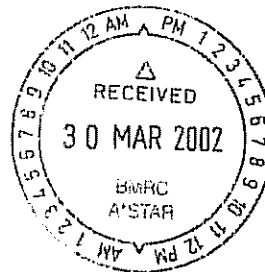


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HUMAN TISSUE BANKING AND RESEARCH IN SINGAPORE

INTRODUCTION

We are invited to present our views and suggestions on the issues and interim recommendations outlined in the consultation paper prepared by the Human Genetics Subcommittee (HGS) in relation to the above topic ("the Consultation Paper").

In doing so, we will proceed on the basis that human tissue research and banking will play an important role in the discovery of modern medical research and knowledge and to that extent the practice should be encouraged and continued. The scope of this analysis will be to comment on specific guidelines as to the implementation as well as the use of information derived from such research, while balancing the interests of the individual and respect for the human body. In addition, we also offer some recommendations for the kind consideration of the Bioethics Advisory Committee.

COMMENTS

Consent Generally

Paragraphs 8.1. & 8.2.

Construing the taking of human tissue for research as the donation of a gift presupposes a right of ownership in the human tissue. As a matter of principle the obligation to obtain consent cannot thus be qualified. To allow human tissue to be taken without consent in certain circumstances such as for example that contemplated in 8.10. would be inconsistent with the principle of ownership unless permitted by legislation.

Taking without obtaining consent should be justified on the basis that there are no claimants rather than the impracticality of obtaining such consent.

Paragraphs 8.4.

Consent forms may state that the gift is an absolute one but a donor should not be denied the right or opportunity to qualify the use to which his gift should be put to if he so wishes. Moreover, a donor should also be given the right to withdraw at anytime from any potential research applications including the destruction of their sample. The unavailability of such options and leaving a donor with only the choice of giving all or nothing could discourage donations and deprive the research community of badly needed material.

Paragraphs 8.7.

It is important that there should be no perception of undue influence or coercion when consent is sought for a donation. To this end, there should be present a third party, if the person

responsible for explaining the nature of the donation and taking of the consent for the donation is the same person.

Paragraphs 8.12.

We suggest that there should be different consent forms for two separate purposes. The form and substance of the consent forms should be prescribed by legislation. This would allow consent to be given with more certainty.

Paragraphs 8.10.

Where a donor is deceased, the person who is legally entitled to the body of the deceased may provide the consent. However, there are situations where there may be differing claims for a deceased's body for example, siblings to the body of a deceased parent. It has yet to be established whose priority in terms of the personal relationship between a deceased and the claimants takes precedence. The general position is that a "consent" order of court will have to be sought by either claimants. Where there is no unanimity between claimants or order of court, it is suggested that the donation should not be taken.

Consent and Legacy Tissue Collections

Paragraph 9

Whilst we share the view that reasonable and respectful research of legacy tissue collections based on good faith and best professional practices of the day should be permitted, we do advocate that an ethics committee or similar body should be tasked to oversee the use thereof. Further, We recommend that the composition of the proposed research ethics committee or institutional review board be drawn from a wide section of society. Members of the committee should not comprise primarily members of the medical profession. There is concern that their motivations may not encompass the concerns of lay persons.

Confidentiality

Paragraph 10

It should be a condition for the use of anonymised data or other like arrangement that have been made to obtain consent or re-consent and such efforts have proven to be futile.

The concept of maintaining confidentiality in human tissue research should be closely protected by enactment of legislation to that effect. By way of example in New South Wales, Australia, there exists a statutory obligation to preserve confidentiality. This obligation is to safeguard against malpractices by overzealous medical researchers and similar members of the industry. Any breach of confidentiality should be made a breach of statutory duty. Protection of both tissue and donor would be the objective for imposing such an obligation.

Approaches to Governance

Paragraph 11

The enactment of legislation would be preferred in areas such as consent for use of existing tissues use of legacy tissues and where consent is difficult or impossible to obtain. Legislation could spell out the preconditions such as the need to make due inquiries through inter alia public advertisements and taking reasonable care where consent cannot be obtained from a donor or his next of kin. A legislative framework given structure to regulations and guidelines. If there is no legislation enacted, ministry guidelines will be subject to the common law which as yet unsettled in this area.

That said, it is recognised that there are areas where guidelines, as opposed to legislation is desirable. Guidelines are more autonomous, allow greater flexibility and are easier to amend when the need arises.

It is feasible to have a system whereby broad legislation and ministry guidelines co-exist. The legislation would be complemented by the ministry guidelines thereby accomplishing the objectives of having both structure and flexibility.

RECOMMENDATIONS

Consent

Informed consent to the taking of all tissue is desirable, whether from the living or from relatives of the dead, and to the extent that there is lacunae in the existing law in relation to the same, steps should be taken to address them.

Recommendations

1. Where there are gaps identified in paragraph 6 of the Consultation Paper in relation to the requirement of consent, these should *be studied and considered whether there is any need for legislative measures. Not all consent needs to be regulated.*
2. If feasible, the recommendation is for an *omnibus code of conduct* for the securing of all kinds of consent in relation to the receipt of tissue samples, subject to exceptions where necessary for selected purposes.

Collection And Ownership Issues

Only approved tissue banks

Given the potential difficulties faced with monitoring the collection and granting of access to tissue samples, we agree with the recommendation that only tissue banks that are institutions (and not individuals) that have been approved by a central regulatory body be allowed to collect store and grant access to tissue samples.

If this central regulatory has a directory listing of tissue stored at each tissue bank, it would give an idea of the types of tissue stored, and facilitate the quick retrieval of tissue for purpose-based research.

Create Sui Generis Property Right

On the basis that tissue donated constitutes a gift, and that donors or their relatives retain no rights of ownership over such donated tissue, it is nonetheless worthwhile considering creating a sui generis property right in the donated tissue in favour of tissue banks not unlike creating the sui generis database right under European Community law¹.

There is existing law that provides some guidance on this topic² although it was implied in a case that in the interests of scientific progress there should not be property in human tissue in favour of the donor.³

The creation of such a property right would entitle the tissue bank to deal with the tissue sample in its own discretion. This would add certainty and legal standing to any terms and conditions they would impose on researchers seeking access to tissue samples. To counteract any instance of abuse of this right, provision might be made for compulsory licences to researchers. There is also the issue of commercial exploitation of any research, which is covered below. Two examples of tissue banks that we could possibly emulate in conjunction with this proposal are set out below:

- The International Institute for the Advancement of Medicine in Pennsylvania ("IIAM") was established in 1986 as a non-profit research tissue bank. It facilitates the distribution of non-transplantable human organs and tissue for biomedical research, education and development.

It uses a legal agreement, the "Biological Materials Transfer Agreement" ("BMTA") that sets out the responsibilities of the IIAM and the applicant regarding the use of tissue for research. They recognise that the BMTA may be difficult to enforce, but is helpful in order to ensure compliance with legal and ethical requirements, and gives an element of control over the use of the tissue.

- The UK Human Tissue Bank ("UK HTB") is a non-profit organisation based at DeMonfort University in Leicester, UK⁴, and collects processes and distributes non-transplantable human tissue for research purposes to scientists. They claim to adhere to all UK laws governing the donation and use of human tissues for biomedical research purposes.

It is interesting to note that not all the jurisdictions have decided on the ownership point yet.

¹ Directive 96/9/EC on the legal protection of databases

² See for example *R v. Kelly* [1999] 2 WLR 384 CA, *Williams v. Williams* (1882) 20 Ch. D 659 and *Dobson v. North Tyneside HA* [1997] 1 WLR 596

³ *Moore v. Regents of the University of California* 51 Cal 3d 120

⁴ Please see www.ukhtb.org/welcome.html

Right of Access and the Exclusive Right to Exploit

The crucial role of tissue banks would be grant access of tissue to researchers. There must be some consideration as to how these banks are funded, and whether to charge a fee for granting such access. There is also the consideration of whether to allow the researchers or the tissue bank the exclusive right to commercially exploit the results or findings of any research done on such tissue. A property right in such tissue may go some way towards resolving this issue.

Recommendations

3. Only approved tissue banks should be allowed to collect, store and grant access to tissue. The approval should come from a central regulatory body with a central database listing of all tissue samples held by each tissue bank.
4. Create a sui generis property right in the donated tissue in favour of the tissue bank that allows them to licence, grant rights or enforce if necessary.
5. Consider the funding aspects of each tissue bank, and whether it is feasible to allow tissue banks to charge for access to tissue.
6. Consider also whether, bearing in mind the funding aspects, and the basic principles behind the setting up of tissue banks, it is desirable to allow amonopoly over the right to commercially exploit the results of any research done on such donated tissue, and if so, whether the external researchers, the tissue bank or anyone else should hold that right.

CONFIDENTIALITY

The basic concept for the requirement of confidentiality is accepted. The issue would be to set out clearly what, if any, are the exceptional circumstances that would warrant a departure from the usual requirement of confidentiality.

Recommendation

7. The suggestion is to consider whether as a matter of policy, it is correct to provide for exceptions to confidentiality in circumstances of competing interests, and if so, such as the identification of a possible criminal, inheritance claims, or whether it would be in the public interest to do so.

CONCLUSION: A HARMONISED APPROACH

We agree it is preferable to develop and reform the current laws in consultation with comparable organisations in other jurisdictions. All our underlying concepts and procedural rules should operate under basic principles that are universally accepted and in line with international standards.

This not only facilitates cross-border research collaboration and mutual exchange of tissue, but also gives an element of certainty to our industry of tissue banking and research, giving others confidence in our system.

Furthermore, to avoid over-regulating the industry, which may have the adverse effect of stifling or inhibiting research activity, there should be a balance between self-regulation and legislation.

Recommendations

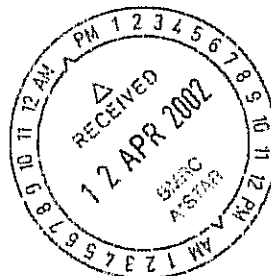
8. The operational procedures, rules and regulations governing tissue banking and research should be developed in line with international standards and in consultation with relevant overseas bodies.
9. A co-regulation model could be adopted under which the industry self-regulates in conjunction with enforcement measures by the authorities in selected areas such as enforcement agencies and approval bodies (please see below). The intention being that guidelines would only be necessary to stop abuses and not for the conduct of the research.
10. The law should establish a basic framework in co-existence with code(s) of conduct, thereafter refined by legal precedent and improvements.

Prepared by
Law Society IP Committee
27 March 2002

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30 March 2002

Assoc. Prof. Terry Kaan
Chairman
Human Genetics Subcommittee, BAC
BIOETHICS ADVISORY COMMITTEE
250 North Bridge Road
#15-01/02 Raffles City Tower
Singapore 179101



Dear Assoc. Prof. Kaan,

FEEDBACK ON HUMAN TISSUE RESEARCH IN SINGAPORE

We refer to your letter of 27 February 2002. Below are the following comments from the Zoroastrian committee point of view:

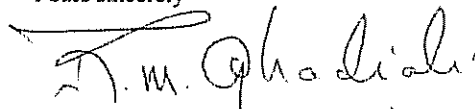
1. The bioethics committee has indeed made a very good and comprehensive study of the problems of use and donation of organ or tissue for research purposes. They have dealt with all aspects like consent, legal issues, confidentiality etc. and there is nothing really to add to that.
2. As to its impact from the point of view of our Zoroastrian beliefs and teaching, there is nothing in the scriptures that could refer to organ or tissue donation for research. However, in our religion any part of the dead body or any tissue or organ removed from the body is considered as "NASO". However, Zoroastrian have donated their eyes, organs, and body parts after death for use for others and there has never been any objection raised from the point of view of subsequent funeral ceremonies and rituals by our priests.

In fact, donating organs and tissues for the good of humanity has been considered noble from the point of view of Zoroastrian teachings.

3. Individuals may have objections about use of human tissues or organs for "cloning" of human beings or for example use of frozen sperms of a deceased husband for in vitro fertilization of the wife's ovum (egg). Such objections could be on personal level but not from religious point of view.

Hope these comments will be of some use to you.

Yours sincerely


R. M. GHADIALI