Bioethics Advisory Committee
20 YEARS OF BIOETHICS Singapore

Bioethics Advisory Committee
Singapore

The Future of Bioethics in Singapore

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Table of Contents

Foreword

Prior to the nineties, investment in Research and Development (R&D) did not enjoy priority in Singapore. It was only in the year 2000 that the government recognised the potential value of Biomedical Science Research to Singapore's future development. With the birth of the Biomedical Science (BMS) initiative, biomedical science emerged to become one of the nation's key economy drivers.

In order for Singapore to start off on the right footing, the Bioethics Advisory Committee (BAC) was established in December 2000 by the Singapore Government to address the potential ethical, social and legal issues arising from biomedical science research in Singapore, as well as make policies and recommendations to the Life Sciences Ministerial Committee. The BAC's recommendations and guidelines will ensure that research conducted in Singapore will be accepted, respected and recognised both locally and internationally. BAC's central approach has been to safeguard the privilege and welfare of people while allowing biomedical sciences to progress and realise their potential for the benefit of mankind. Good practices identified in overseas institutions were adapted to Singapore's needs. They were selected, integrated and synthesised into our system.

Since its establishment, the BAC had comprehensively investigated numerous issues, covering from stem cell research to cloning and human biomedical research. Recommendations made set the foundations for bioethics in Singapore's research scene. In her early days, the BAC was confronted with many challenges, especially the lack of common understanding on bioethics issues among people given the multi-racial and religious demographics of Singapore. The lack of consensus due to differences in religious teaching was intensified as the general public then was not sufficiently informed on the issues relating to research and bioethics. The BAC tackled this issue by creating a common understanding that regardless of religion, research conducted must be for the benefit of mankind. This consensus was achieved through a series of consultation sessions, the gathering of feedback through paper and web with both the community and organisations with medical, scientific, religious, ethical and legal interest to address the related issues. Different viewpoints were taken into account and reconciled to overcome any roadblocks encountered.

Notably, some of the major debatable issues that BAC resolved include issues on cloning, both reproductive and therapeutic, the use of embryonic stem cells (ESC) and the establishment of Institutional Review Boards (IRBs). With consultations and expert engagements, BAC permitted the conduct of therapeutic cloning with proper regulations and disallowed reproductive cloning. BAC's recommendations for ESC research provided guidelines on the sources and usage of ESC. The IRBs were established with the aim of evaluating and scrutinising research as only with IRB's approval, can the research proceed. IRBs' functions include to ensure that research proposals have been evaluated to have scientific merit and possess the provisions for the consent process to ensure that consent, proper and valid to the proposed research, is achieved.

Moving forward, biomedical research is critical to developing cures for disease as well as methods to alleviate patients' suffering. With Singapore established as a renowned scientific hub, having a strong foothold in R&D can boost Singapore's economy by attracting investments and creating employment opportunities. The attraction of scientific talents will further support Singapore's standing as the region's scientific research centre. Singapore's international reputation in the field of bioethics has been elevated through the strategic links which BAC built with overseas counterparts and her active involvement in the UNESCO Bioethics Programme under the chairmanship of Chief District Judge (Ret.) Richard Magnus. As such, bioethics will continue to play a crucial role to ensure that science develops in sync with the values of its society.

Apart from tracing the growth and honouring the development accomplished by BAC, this book offers a prospective look into how bioethics and BAC's work may transform in the future together with the authors' perspective on several contentious issues. Most authors have personal experience with the works of BAC and their chapters will present an extensive narrative of how different areas of their expertise intertwine with bioethical works.

Chapter 1 by Ho takes the readers on a brief journey through the development of BAC for the past 20 years, highlighting the role of BAC in the Human Biomedical Research Act and the wider health research governance framework in Singapore. With the up and rising use of big data and Artificial Intelligence in biomedical research, it brings along the potential issues of ethical, social and legal challenges. This chapter will open up on the possible roles in which BAC can assume pertaining to address these challenges.

Chapter 2 by Greenfield of the Nuffield Council of Bioethics ventures into the new challenges arising from biomedical research where he emphasises on the significance of bioethics and offers his insights on some of the recent controversies in the field of reproductive medicine.

Chapter 3 by Ng explores the future of biomedical sciences in Singapore. The Biomedical Sciences (BMS) initiative was launched in June 2000 to establish BMS as the 4th pillar of Singapore's economy. In addition to the BMS initiative, his review of this topic includes a comprehensive account of Singapore's several other projects and endeavours, which have successfully placed Singapore in the forefront of the BMS field. He also acknowledges the importance of ethics developing alongside the sciences to safeguard the integrity of Research & Development in Singapore.

Chapter 4 by Yi is an interesting venture into public health ethics. The core of public health ethics lies in the moral and ethical justification of policies and measures that serve to promote public health. Yi offers insight into several theories and ethical principles which are essential to provide grounds for the justification of public health actions. His views are highly relevant in our COVID-19-stricken world today.

Chapter 5 by Joseph explores the historical developments and the legislation surrounding medical ethics, potential challenges in the clinical field in which Singapore will eventually need to address, bringing in topics such as ageing and end-of-life issues. As he currently chairs the National Medical Ethics Committee (NMEC), his views on this topic will be pertinent.

Chapter 6 by Reis and Tan delves into the significance of National Bioethics Committees (NBCs). They explored how NBCs tackled emergent techniques and developments in the biomedical sciences, and provided a detailed coverage of events and activities supported by NBCs.

Chapter 7 by Magnus and Lim provides an insightful perspective with regard to the importance of Singapore's participation in global and regional forums. They also share their personal experiences at the UNESCO IBC, IGBC and other regional forums as the representatives of Singapore.

Chapter 8 by Voo brings readers closer to the younger generation where he offers his perspective on the importance of bioethics education, as well as how bioethics can serve as a tool for dealing with certain challenges that the younger generation may encounter in the future.

Chapter 9 by Nazirudin presents how the bioethics landscape is like in a multi-racial and religious country like Singapore. As the Mufti of the Republic of Singapore, he will share the perspective of one of the religious groups on the importance of having conversations on bioethics in Singapore, given our diverse demographics.

Chapter 10 by Lim offers readers a glimpse of the legal landscape of bioethics in Singapore. As a Senior State Counsel at the Attorney-General's Chamber, he offers his valuable insights on the seminal cases in Singapore dealing with research or clinical ethics that have affected common law in Singapore.

Chapter 11 by Kon highlights the possible privacy issues arising from genetic testing and introduces the concept of genetic exceptionalism. She gives an insight into the initiatives and penalties imposed to prevent privacy leaks and reviews how privacy is regarded in the age of data.

Chapter 12 by Chan sheds light on a rising topic in bioethics, Mitochondrial Replacement Therapy (MRT). As a valuable member of the MRT review team, he gives a brief introduction followed by his insights on the acceptability, potential issues and reasons for revisiting the topic after BAC's disapproval to the use of this technology back in 2005.

Chapter 13 by Cole ventures into public engagement and bioethics in Singapore. This chapter surrounds the importance of public engagement, what has been done by BAC and what BAC can do in the future.

In the final chapter, Magnus brings readers through BAC's journey over the past 20 years. He also shares his vision of the BAC to advance the biomedical sciences in Singapore, while ensuring that the welfare of the people is not compromised.

20 years may seem long, but our journey ahead is much longer. Bioethics is an ever-evolving field, evolving in tandem to the development of new science technologies. While the foundations for bioethics have been set, there is still a need to uphold bioethics standards in Singapore. The bioethics landscape now is unlike what it was back then, but our purpose remains, to guide research with proper recommendations for the benefit of humanity. Singapore will not shy away from addressing new issues nor revisit past recommendations to stay updated and be ready for what the future of bioethics may hold for us.

Lim Pin & Stella Tan

Acknowledgements

The year 2020 marks the 20th Anniversary of the Bioethics Advisory Committee (BAC)'s establishment. This publication serves to celebrate BAC's achievements and work accomplished over the past 20 years. Our main objective for this publication is to educate and raise awareness of bioethical issues in Singapore, as well as internationally. This is extremely important given the ethical conundrums and uncertain nature of biomedical research. To find an ethically acceptable threshold for every intervention, we need to encourage public discussion and international sharing of ideas.

This book includes the contributions from established experts and researchers in ethics, law, philosophy, and the biomedical and social sciences, all of whom have played a part in the institutionalisation of bioethics in Singapore. Though the authors are closely associated with the BAC, all opinions and views expressed in this book are personal to the authors, and do not necessarily represent the views of the BAC or any other organisation.

This publication took an immense amount of work and could not have been possible without the contributions from various supportive people. Firstly, I would like to extend my deepest appreciation to the authors for their invaluable perspectives and insight in the respective bioethical issues, and their efforts in meeting tight deadlines. Thank you for giving this publication life and fulfilling our vision for this publication. I would also like to thank the BAC Chair, Chief District Judge (Ret.) Richard Magnus; and the BAC Secretariat, comprising Dr Lee Wei Liang, Dr Tiong Wei Wei, Dr Durkeshwari Anbalagan-Raj, Mr Louis Peter Hor, Mr Nicholas Wong, Ms Toh Si Min, Ms Germaine Goh, Ms Syafiqah Abdullah and Mr Teo Guoy Siang, for planning and coordinating the project, from its conception to publication, thus putting us in good stead since the very beginning. I am grateful to A/Prof Stella Tan and her editorial team, consisting of Ms Grace Cheng, Ms Karyn Lim, Mr Chin Kok Hee, Ms Chen Mei Jun, Mr Ng Wei Bo and Ms Tan Shi Yun for their comprehensive editorial work and proofreading of the manuscripts. Your suggestions and comments have helped us refine and enhance our ideas; the publication indeed is richer with your contributions. We are also appreciative of past and present members of the BAC, as well as many other individuals (some of whose names may not be enumerated), who have supported this project in one way or another through the sharing of their ideas and expertise. Finally, I would like to acknowledge with gratitude the love and support from our families.

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Richard MAGNUS, LL.M., is a retired Chief District Judge and the current Chairman of the BAC (since 2011). He was previously elected as the Vice-Chair of UNESCO's International Bioethics Committee, the only advisory body of the United Nations system engaging in ethical issues related to life sciences and its applications in order to ensure respect for human dignity and freedom.

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Stella TAN Wei Ling also acts as the managing editor of this publication. Her editorial team consists of **CHEN Mei Jun**, **Grace CHENG**, **CHIN Kok Hee**, **Karyn LIM**, **NG Wei Bo** and **TAN Shi Yun**. Over the past year, they have tirelessly read and edited the manuscripts, and provided suggestions to refine our ideas throughout the creative process.

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1

Human Biomedical Research in the Age of 'Big Data' Analytics and Artificial Intelligence

Calvin WL Ho*

INTRODUCTION

The Bioethics Advisory Committee (BAC) was established in 2000 by the Singapore government as an expert body to provide her with advice on the ethical, legal and social implications of emergent technologies in human biomedical research. Its accomplishments in the first decade since its founding are most evident in the establishment of a research governance framework comprising ethical principles and guidelines, as well as institutional and policy recommendations. These accomplishments in advancing the nation's Biomedical Sciences Initiative have been documented in an edited monograph,[1] and were celebrated in 2010 at the 8th Global Summit of National Bioethics Committees and the 10th World Congress of Bioethics, hosted by the BAC in Singapore.

The second decade of the BAC has been one of consolidation and systematisation, which culminated in the issuance of an updated and comprehensive set of ethical guidelines in 2015. These guidelines constitute the normative bedrock of the Human Biomedical Research Act (HBRA),[2] which was enacted shortly after. In the following section, we consider the crucial role that the BAC has had in the establishment of a statutory framework on human

* JSD, LLM, MSc, Advocate & Solicitor (Singapore); Associate Professor, Faculty of Law, and Director (Law), Centre for Medical Ethics and Law, The University of Hong Kong. I have had the privilege of serving in the Secretariat of the Bioethics Advisory Committee (BAC) from 2001 to 2011. The late Associate Professor John M Elliott (1945 – 2019) was a member of the Secretariat (2005 – 2012), having also served as a member of the BAC before that. It has been my great fortune to have worked with Dr Elliott, and my hope is that this chapter also speaks to his contribution to the continuous flowering of the BAC's efforts and initiatives.

[1] John M Elliott, Calvin WL Ho and Sylvia SN Lim, *Bioethics in Singapore: The Ethical Microcosm*. Singapore: World Scientific, 2010.

[2] Human Biomedical Research Act 2015 (No. 29 of 2015). Available at: https://sso.agc.gov.sg/Act/HBRA2015. This statute will be further discussed in the second section of this chapter.

biomedical research from the publication of its first set of recommendations in June 2002. An understanding of this role also illustrates what may arguably be an adaptive and hence uniquely Singaporean approach to the governance of human biomedical research as a normatively complex and demanding social (and national) enterprise. As we shall see, the regulatory regime is itself a sophisticated one that comprises statutes that are organically enmeshed within a supporting ethico-regulatory system. The discussion in this section also highlights the dynamic relationship that the BAC has had with the Ministry of Health (MOH).[3] While the MOH remains primarily responsible for the governance of clinical care and certain innovative medical technologies that apply to reproductive medicine, it has in recent years assumed responsibility for the governance of human biomedical research. In collaboration with the MOH, the BAC has been adopting a melting pot of international standards, professional and local requirements and expectations – all of which have been crucial resources in the construction and continuous calibration of a regulatory regime that effectively balances scientific innovation and progress with individual and societal needs and concerns.

The past decade has also witnessed rapid advances in Information and Communications Technologies (ICT). A large amount of data has become available in different forms, and degrees of accuracy and reliability in what has become known as the "Big Data" phenomenon.[4] This phenomenon has contributed to the development of new data analytics and the use of sophisticated technologies like Artificial Intelligence (AI) to combine, process and analyse large amounts of data aggregated from multiple sources. Such technologies aid the diagnosis and monitoring of health conditions, make predictions, and support optimal decision-making based on these predictions.[5] If appropriately applied, these technologies could advance research goals, as well as better enable health systems to address important challenges that include the growing prevalence of chronic diseases that require long-term management and care, and escalating healthcare costs. Thereafter, in the next section, we consider these developments in the context of the recently promulgated National AI Strategy and its implications on human biomedical research in Singapore. This is followed by the final section of the chapter, which considers the important role that the BAC could assume in addressing challenges that will arise in the rapid digitalisation of human biomedical research and healthcare.

[3] For the purposes of this chapter, all reference to the MOH includes statutory bodies that operate under its purview, such as the Singapore Medical Council established under the *Medical Registration Act*, Cap 174, 2014 Rev Ed.

[4] Kelleher JD. Tierney B. *Data Science*. Cambridge MA: MIT Press; 2018.

[5] Sejnowshi TJ. *The Deep Learning Revolution*. Cambridge MA: MIT Press; 2018.

SHAPING THE REGULATORY LANDSCAPE IN SINGAPORE

Until 2000, formal research ethics review was confined to either within highly institutionalised and defined fields of practice, such as clinical trials, or on a 'when necessary' basis, by an *ad hoc* Institutional Review Board (IRB) or similar body within academic and healthcare institutions.[6] From 2002 onwards, an institutional framework on biomedical research ethics was put in place as a matter of national policy mainly through the efforts of the BAC, in collaboration with the MOH. The BAC's recommendations relate primarily to the biomedical research community, whereas the MOH was primarily concerned with research conducted within healthcare premises or by healthcare professionals. This dual approach is due in part to historical factors, particularly since the medical profession and healthcare establishments have traditionally been closely regulated,[7] unlike researchers and research institutions (except on matters of biosafety). In spite of these differences, a governance framework has emerged incrementally and through ever closer connections between the biomedical research and medical communities.

In 2004, the BAC built on the guidelines of the MOH's National Medical Ethics Committee[8] and enlarged their application to all human biomedical research conducted in Singapore. Its report on research involving human subjects essentially formalised the requirement for all human biomedical research in Singapore, including research involving human tissue or medical information, to be subject to ethics review by IRBs.[9] The guidelines promulgated in the report add to the existing system of regulations for pharmaceutical trials and human biomedical research conducted by hospitals, private clinics and other healthcare establishments under the supervision of the MOH. They also set out the constitution, accreditation and operation of IRBs, as well as their roles and responsibilities, in addition to those in place for research institutions and individual researchers. In the main, the BAC regards high standards of ethical governance for the protection of life, health, privacy and dignity of human

[6] Calvin WL Ho and Sylvia SN Lim, "The Coming of Bioethics to Singapore", In: John M Elliott, Calvin WL Ho and Sylvia SN Lim (eds.), *Bioethics in Singapore: The Ethical Microcosm*. Singapore: World Scientific, 2010, pp. 1-29.

[7] *Private Hospitals and Medical Clinics Act*, Cap 248, 1999 Rev Ed; and *Medical Registration Act*, Cap 174, 2004 Rev Ed.

[8] National Medical Ethics Committee, *Ethical Guidelines on Research Involving Human Subjects.* Singapore: Ministry of Health, August 1997.

[9] Bioethics Advisory Committee, *Research Involving Human Subjects: Guidelines for IRBs.* Singapore: Bioethics Advisory Committee, November 2004.

subjects in biomedical research as vital to the progress of biomedical sciences in Singapore. The fundamental responsibility of an IRB is set out as conducting ethics review with the "primary objectives of the protection and assurance of the safety, health, dignity, welfare and well-being of human research subjects".[10] Although the guidelines of the BAC do not have any direct regulatory authority, they have been accepted by the MOH,[11] and by the Agency for Science Technology and Research (A*STAR) – the principal public funder of biomedical research in Singapore. Consequently, the medical profession and biomedical researchers funded by A*STAR are required to observe these guidelines. In 2007, the MOH issued supplementary guidelines on the day-to-day workings of an IRB, for which the BAC has set out the operating principles. These include guidelines on the composition of an IRB, a more elaborate discussion on the informed consent process, meeting requirements and requirements relating to documentation.[12]

The HBRA, enacted by Parliament on 18 August 2015, establishes a legislative framework for human biomedical research that is in many ways an amalgamation of critical features of a prototype legislation that was proposed by the MOH in 2003,[13] and the BAC-MOH ethico-regulatory framework centred around IRBs. The explanatory statement sets out the goals of the HBRA as regulating the conduct of human biomedical research, regulating tissue banks and their associated activities, prohibiting certain types of human biomedical research, and prohibiting the commercial trading of human tissue. However, it is interesting to note that most of the legislative provisions are concerned with the first two goals. Essentially, all human biomedical research that falls within the scope of the HBRA must be approved (unless exempted) by an appropriate IRB before it can be carried out. Whether a research intervention or activity falls within the scope of the legislation is determined in accordance with an inclusion-exclusion criterion prescribed by it. This inclusion-exclusion criterion is not intended to displace the ethics framework, but must be interpreted within it as the legislative intent is to confer on certain ethical provisions legal authority.

While the HBRA does not significantly modify the existing ethics review infrastructure, this re-articulation of regulatory oversight in the legislation is

[10] *Ibid*. p. 41. para 5.20.

[11] Ministry of Health, *Directive 1A/2006: BAC Recommendations for Biomedical Research,* 18 January 2006.

[12] Ministry of Health, *Operational Guidelines for Institutional Review Boards*. Singapore: Ministry of Health (Biomedical Research Regulation Division), December 2007, pp. 8-9, paragraphs 7.10.5, 7.12, Section 10.

[13] *The Regulation of Biomedical Research Bill*, 2003. Public consultation was conducted on this document, but it was never presented in Parliament.

necessary to redraw a regulatory space, so that it could apply uniformly to all human biomedical researchers and research institutions. The legislation also defines what is recognised as a research institution. As the term suggests, such an entity must be composed of at least two or more persons, and have management and control over human biomedical research that is conducted in Singapore. In order to be legally recognised, the research institution is required to notify the MOH and submit a declaration of compliance before it commences operation. Once recognised as such, it is under legal obligation to appoint an IRB to review all research under its supervision and control, and to report any serious adverse events as defined in the legislation. Within what is described as a system of self-accountability, research institutions play a central role. The legislation further requires a close relationship between a research institution, and its appointed IRB, primarily because the research institute assumes responsibility for the research that has been reviewed by its IRB. The legal responsibilities of an IRB are essentially similar to its role within the ethical framework; its primary responsibility is to ensure the protection of the safety, dignity and welfare of human research participants.

In 2015, the BAC consolidated the ethical principles, recommendations and guidelines that were discussed and presented in all its reports published prior to that year.[14] Five ethical principles have been identified as foundational to the ethics governance of human biomedical research in Singapore. These principles are: respect for persons, solidarity, justice, proportionality and sustainability. In addition, the BAC highlights the principle of beneficence and research integrity as important considerations that should be accounted for when appropriate to the context.[15] It is based on this ethics premise that the substantive responsibilities of research institutions, IRBs and researchers have been set out by the BAC. Procedurally, these responsibilities have been taken up in regulation and are hence enforceable under the HBRA.[16] Having considered the BAC's role in shaping the ethics review infrastructure, we now consider its contributions which are more specific to research involving human tissue, pluripotent stem cells, personal information and genomics.

[14] Bioethics Advisory Committee, *Ethics Guidelines for Human Biomedical Research*. Singapore: Bioethics Advisory Committee, 2015.

[15] As the BAC explains, the principle of beneficence is not considered to be distinct from the principle of respect for persons for many research endeavours, and is hence not set apart as a standalone principle. *Ibid*. Section 2.13, p. 18.

[16] *Human Biomedical Research Regulation 2017*. Available at: https://sso.agc.gov.sg/SL/HBRA2015-S621-2017?DocDate=20171030

Human Tissue

As noted above, another important component of the HBRA is concerned with regulating the collection and use of human tissue in research, and these provisions are set out within Part 6 of the legislation, duly entitled: "Regulation of human tissues activities and tissue banking". The definition of 'human tissue' is broad in scope[17] and encapsulates any human biological material except those specified in the First Schedule of the legislation. Excluded materials are essentially those that have limited scientific value (such as hair shaft, nail plate and naturally excreted bodily fluids and waste products) or materials that have been substantially manipulated (further defined through a list of exclusions in the First Schedule) and rendered non-individually identifiable.

On the normative front, human tissue research and tissue banking in Singapore have been largely shaped by ethical recommendations set out by the BAC more than a decade prior to the enactment of the HBRA. While legislative provisions are generally consistent with pre-existing normative expectations, the HBRA addressed at least two concerns that were highlighted by the BAC. Specifically on information to be provided before taking appropriate consent, the legislation[18] emphasises the need to clearly explain the purpose for which the tissue is to be used. Crucially, the legislation empowers an IRB to waive the requirement of appropriate consent in certain statutorily defined situations. Where human biomedical research involving human biological material (or health information) is concerned, this requirement may be waived where the IRB is satisfied that (Fifth Schedule Part 2, HBRA): the individually-identifiable human biological material may not practically be carried out unless there is a waiver; the use of such material involves no more than minimal risk to the research subject or donor; the waiver will not adversely affect the rights and welfare of the research subject or donor; and the research would reasonably be considered to contribute to the greater public good. This statutory provision is important in addressing a long-standing legal lacuna that was first highlighted by the BAC in 2002.[19]

Prohibited and Restricted Research

Ethically contentious types of research such as those that involve human embryonic stem cells and human-animal combinations (HACs) are listed on the Third and Fourth Schedules. Under the Third Schedule, the types of prohibited

[17] *Ibid*. Section 2.
[18] *Ibid*. Section 12(2).
[19] Bioethics Advisory Committee, *Human Tissue Research*. Singapore: Bioethics Advisory Committee 2002, paragraph 9.6.

human biomedical research give effect to the recommendations of the BAC, and are listed as those that involve:[20]

(1) Development of cytoplasmic hybrid embryos or HAC embryos created *in vitro* beyond 14 days or the appearance of the primitive streak, whichever is earlier;

(2) Implantation of any HAC embryo into the uterus of an animal or a human;

(3) Introduction of human stem cells (including induced pluripotent stem cells (iPSCs)) or human neural cells into the brain of living great apes whether prenatal or postnatal; and

(4) Breeding of animals that have had any kind of pluripotent stem cells (including iPSCs) introduced into them.

In contrast, restricted research may only be conducted after requirements set out in the BRA are satisfied. These requirements include notifying MOH, IRB review, appropriate consent having been obtained from the research subject, and/or conduct of the research only by certain specified persons, at certain specified premises and in the specified manner.[21] These types of research are listed on the Fourth Schedule. It is unclear if any substantive review will take place for the purposes of approval by MOH. In its earlier reports, the BAC has recommended that a single national body be established to review and monitor all stem cell research involving human pluripotent stem cells or HACs conducted in Singapore. Such a recommendation could also apply to gene-editing technologies that could substantially and permanently alter the genetic composition of a person. This national body that the BAC has proposed is likely to be similar to the national entity that has been recommended by the Academy of Medical Sciences in the United Kingdom,[22] or akin to a dedicated review process proposed by the International Society for Stem Cell Research.[23] It is still unclear if such a separate and dedicated entity, or a triaging body, will be established and the level of additional review that may be conducted.

[20] *Human Biomedical Research Act 2015*.

[21] *Human Biomedical Research Act 2015*, Section 31.

[22] Academy of Medical Sciences, *Animals Containing Human Material*. London: Academy of Medical Sciences, 2011.

[23] International Society for Stem Cell Research, Guide*lines for Stem Cell Research and Clinical Translation*, 2016. Available at: http://www.isscr.org/docs/default-source/all-isscr-guidelines/guidelines-2016/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=4

These categories of prohibited and restricted research have been earlier on identified by the BAC, and they broadly correspond with its topical deliberations on human pluripotent stem cell research (which includes human embryonic stem cells), research involving reproductive cells (human oocytes in particular) and HACs, as well as certain types of reproductive technologies. Not all of these provisions are encapsulated in the HBRA or regulations prescribed under its authority. As these ethical provisions are to be applied by IRBs, a research protocol must give effect to them in order to secure the requisite IRB approval.

Human Pluripotent Stem Cells, Human Oocytes, Embryos and Human-Animal Combinations

The first set of recommendations published by the BAC is on human stem cell research, reproductive and therapeutic cloning.[24] These recommendations include proposals for stringent regulation of human embryonic stem cell research in Singapore and the legal prohibition of reproductive cloning, which was taken up by the legislature with the enactment of the *Human Cloning and Other Prohibited Practices Act* in 2004. As with other major scientific jurisdictions, the legislation imposes a 14-day limit so that research involving a human embryo is allowed up to that point in development. Embryology is relied upon as justification for this standard as public consultation showed that there was no consensus among the main religious groups in Singapore as to when 'personhood' could be said to begin.[25] On this basis, one could perhaps conclude that at least in ethical policy, human life begins from 14 days of embryonic development, or when the 'primitive streak' becomes evident.

Following the publication of these recommendations, scientific developments in relation to cloning and iPSC technology necessitated the continuous review of Singapore's ethical policies on stem cell and cloning technology. A review of the recommendations published in 2002 was formally undertaken in 2007, focusing on ethical, legal and social issues arising from the procurement and use of human eggs for biomedical research, and on research involving HACs. Apart from scientific developments, review of these areas was considered to be necessary following the scandal from the unethical procurement of human eggs in South Korea; and more importantly, from revisions to ethical policies and guidelines in the United States, Australia, Canada and a number

[24] Bioethics Advisory Committee, *Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning*. Singapore: Bioethics Advisory Committee, 2002.
[25] Calvin WL Ho, Benjamin Capps and Teck Chuan Voo, Stem Cell Science and its Public: The Case of Singapore, *East Asian Science, Technology and Society: An International Journal* 4 (2010): 7-29.

of European countries such as Britain and Denmark. Recommendations relating to the donation of human eggs for biomedical research were published by the BAC at the end of 2008,[26] after public feedback was received on various issues presented in a consultation paper between 7 November 2007 to 7 January 2008, and at a public forum on 11 November 2007. Another consultation paper was distributed for public discussion and comment on research involving HACs between 8 January and 10 March 2008. In September 2010, the BAC published a set of recommendations that permit the creation and use of cytoplasmic hybrid embryos and animal chimeras in research on a strictly regulated basis.[27]

For human oocytes and embryos that are obtained in Singapore, additional requirements relating to appropriate consent-taking have been set out in the regulation on restricted research. Essentially, these requirements are directed at ensuring that only surplus oocytes or embryos are used, that the donors of oocyte and embryo for research are acting voluntarily (and free of undue influence), and that they are clearly aware that the donation is distinct from artificial reproduction treatment or other therapeutic treatment.[28] In order to secure IRB's approval for research involving surplus oocytes and embryos, the IRB must ensure that regulatory requirements are satisfied.[29] Where MOH approval is concerned, it is unclear if substantive review will be undertaken. It seems that MOH could subject the research protocol to scientific review although the regulatory provision suggests that this is discretionary, and the review could also encompass ethical issues and concerns at the wider societal level.[30]

Where HACs are concerned and for the purposes of this chapter, it need only be noted that the creation and use of cytoplasmic hybrid embryos and animal chimeras in research are permitted in Singapore but only on a strictly regulated basis. In its consolidated guidelines published in June 2015, the BAC indicates that the main "ethical hazard lies in the possibility of inadvertently creating an animal with human characteristics, especially, but not exclusively, mental attributes".[31] In ethics review, it sets out six relevant factors that should be considered together: proportion or ratio of human to animal cells in the animal's

[26] Bioethics Advisory Committee, *Donation of Human Eggs for Research*. Singapore: Bioethics Advisory Committee, 2008.
[27] Bioethics Advisory Committee, *Human-Animal Combinations in Stem Cell Research*. Singapore: Bioethics Advisory Committee, 2010.
[28] *Human Biomedical Research (Restricted Research) Regulations 2017*, S 622/2017, Sections 11 and 12.
[29] *Ibid*. Section 14.
[30] *Ibid.* Section 15.
[31] Bioethics Advisory Committee, *Ethical Guidelines for Human Biomedical Research*. Singapore: Bioethics Advisory Committee, 2015, at 56, paragraph 7.22.

brain, age of the animal, recipient species, brain size of the animal involved, state of integration of human neural cells, and presence of pathologies in the host animal.[32] The BAC further indicates that research using established pluripotent stem cell lines and confined to cell culture, or research that involves routine and standard research practice with laboratory animals should be exempted from IRB review.[33] Other ethical requirements set out by the BAC do not differ from international best practices, although it maintains in its provision that no clinical or research personnel with a conscientious objection to human pluripotent stem cell or HAC research should be under a duty to conduct or assist in such studies. It further requires that no one should be put at a disadvantage only because of his or her objection.[34]

Personal Information and Genomics

Ethical governance of genetic research was formulated at two different junctures: at the point where genetic information is derived through various means of testing, and in the management and use of the information itself.[35] The report on genetic testing and genetic research serves to operationalise several internationally recognised ethical principles in the local context.[36] These ethical principles relate to the voluntary and informed basis of genetic testing, special care and responsibility when vulnerable persons are tested, and ethical conduct of human genetic research, among others. Specific ethical considerations have also been set out by the BAC in relation to five types of genetic testing, many of which can have profound influence over reproductive choices and reproduction. Preimplantation genetic diagnosis and preimplantation tissue typing are reproductive technologies that can be ethically practised in Singapore, but on a regulated basis. As for prenatal genetic diagnosis, the BAC states that it should be limited to serious medical disorders, and must not be applied for the selection of desired traits or gender. The recommendations in this report and those in the report on egg donation, taken with a set of Directives of the MOH on assisted

[32] *Ibid*. p. 57. These considerations have been drawn from Mark Greene, *et al*. Moral Issues of Human-Non-Human Primate Neural Grafting, *Science* (2005) 309: 385-386.
[33] *Ibid*. p. 57, para 7.24.
[34] *Ibid*. p. 59, para 7.31.
[35] Bioethics Advisory Committee, *Personal Information in Biomedical Research*. Singapore: Bioethics Advisory Committee, 2007. The BAC's recommendations in this report were mainly concerned with the use of individually identifiable medical information, genetic information or demographic information in research. Some of these recommendations overlap with provisions in the Personal Data Protection Act, which was enacted in 2012.
[36] Bioethics Advisory Committee, *Genetic Testing and Genetic Research*. Singapore: Bioethics Advisory Committee, 2005.

reproduction, constitute the governance framework for reproductive technologies in Singapore.[37]

Due to safety concerns arising from germline genetic modification, the BAC did not think it should be clinically applied.[38] More recently, it observed that any intervention that alters the germline of an individual leading to a change in the genetic makeup of that individual's descendants raises serious ethical and moral concerns. It was further observed that there is insufficient knowledge of the potential long-term consequences of such interventions, as they are still in the experimental stage, and that many countries, such as Australia, Canada, and Finland, have laws that prohibit germline modification.[39] However, the BAC appears to be receptive to certain types of genetic germline modification technologies, such as assisted reproductive techniques to prevent the transmission of mitochondrial diseases, provided that these techniques are shown to be sufficiently safe and effective.[40] These techniques include ooplasmic transfer, pronuclear transfer and maternal spindle transfer; these techniques were the focus of a public consultation that was conducted by the BAC in 2018.[41]

'BIG DATA' ANALYTICS AND ARTIFICIAL INTELLIGENCE

The preceding section makes clear the profound accomplishments of the BAC in realising the Biomedical Sciences Initiative that was launched in 2000 through the establishment of a regulatory governance system that applies uniformly to all human biomedical research conducted in Singapore. As we have considered, this system comprises a socially and historically adapted blend of ethical and regulatory requirements. These requirements dynamically calibrate the balance between the need to safeguard the welfare of research participants with the goal of enabling scientific progress in a responsible manner determined by internationally accepted normative standards. In 2019, the Singapore government announced the National AI Strategy under which five national projects will be

[37] Ministry of Health, *Licensing Terms and Conditions for Assisted Reproduction Centres*, 2011. Regulation of reproductive technologies is primarily achieved through the licensing of assisted reproduction centres (or ARCs) in Singapore.

[38] Bioethics Advisory Committee, *Genetic Testing and Genetic Research*. Singapore: Bioethics Advisory Committee, 2005, paragraphs 4.51 and 4.52, and Recommendation 12, at 37 and 38.

[39] Bioethics Advisory Committee, *Ethical Guidelines for Human Biomedical Research*. Singapore: Bioethics Advisory Committee, 2015, paragraph 6.4, at 49-50.

[40] *Ibid*. p. 50. para 6.5.

[41] Bioethics Advisory Committee, *Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology: A Consultation Paper*. Singapore: Bioethics Advisory Committee, 2018.

initiated to deploy AI in addressing certain challenges and delivering impactful social and economic benefits to the people.[42] Healthcare is one of these projects, which will seek to apply AI to analyse clinical and genomic data, medical images and health-related behaviours to assess the risk profile of patients. This allows for the provision of care and management of relatively prevalent chronic conditions in Singapore, like diabetes, hypertension and high blood cholesterol. The implementation of the strategy is intended to be human-centric, and articulated in terms of three characteristics: (1) AI should be designed, developed and applied in ways that best serve human needs, rather than to develop the technology for its own sake; (2) risks and governance issues that arise from the use of AI should be addressed proactively; and (3) the population and workforce should be prepared to accept and adopt the technology.[43] To this effect, A*STAR has been indicated as having established a human-centric AI Research and Development programme to develop and train AI software and AI-based technologies to be human-compatible.[44]

As a first step, the National AI Strategy indicates that the Singapore Eye LEsioN Analyser (SELENA+), an AI-based clinical decision support system (CDSS), will be deployed to detect 3 major eye conditions: diabetic eye disease; glaucoma and age-related macular degeneration.[45] This AI software is stated as being capable of analysing retinal photographs as accurately as, and faster than, eye care professionals, and could thereby increase productivity by allowing these professionals to spend more time with patients who have complex conditions. Where a CDSS like SELENA+ is capable of adapting to new conditions through 'unsupervised' learning, its risk profile can significantly deviate from the version that secured regulatory approval– which may raise ethical concerns, particularly those relating to patient safety and effectiveness. In 2018, a similar AI-based CDSS was granted regulatory approval from the US Food & Drug Administration. However, the clinical study that supported the approval was conducted under highly controlled conditions where a relatively small group of carefully selected patients was recruited to test a diagnostic system along with

[42] Smart Nation Singapore, *National Artificial Intelligence Strategy: Advancing our Smart Nation Journey*. Singapore: Smart Nation Singapore, 2019.
[43] *Ibid*. p. 18.
[44] *Ibid*. p. 19. An advisory committee has been established for the ethical use of AI and data by the Inforcomm Media Development Authority (IMDA), although their remit is much wider than that of an ethical advisory body like the BAC, and likely to be also less specialised. See: IMDA, 'The composition of Singapore's Advisory Council on the Ethical Use of AI and Data (Advisory Council) was announced by the Minister for Communications and Information Mr S Iswaran at AI Singapore's first anniversary', 30 August 2018; available at: https://www.imda.gov.sg/news-and-events/Media-Room/Media-Releases/2018/composition-of-the-advisory-council-on-the-ethical-use-of-ai-and-data
[45] *Ibid*. p. 31.

narrow usage criteria at primary care clinics until it was autodidactic.[46] Hence, since the autodidactic functionality was locked, regulatory approval was only based on the CDSS functioning like a standard medical diagnostic device, which in turn greatly contained the variability of the range of outputs.[47]

The point here is not to comment in any way on the reliability of the autodidactic capability of SELENA+, but simply to highlight that developers of such CDSS are expected to have an appropriate level of control to manage changes during the lifecycle of their AI-based products. Modifications are expected to be made throughout the lifecycle of the product, including its maintenance phase.[48] Software maintenance may relate to post-marketing modifications that are adaptive (modification performed to keep the software product usable in a changed or changing environment); perfective (modification to detect and correct latent faults in the software product before they are manifested as failures); corrective (reactive modification of a software product performed to correct discovered problems); or preventive (modification of a software product to detect and correct latent faults in the software product before they become operational faults).[49] When a developer makes changes to the CDSS that consequently alters the core functions that it was designed to perform, its risk categorisation will need to be re-evaluated. Change is inevitable since failures that arise may be due to errors, ambiguities, oversights or misinterpretation of the specification that the software is intended to satisfy, problems in writing code, inadequate testing, incorrect or unexpected usage of the software or other unforeseen problems. A software change management process to ensure that the modified AI-based product remains safe and of acceptable quality and performance will need to include considerations relating to the socio-technical environment, the technology and system environment as well as information security.

More generally, digital tools (which may or may not be AI-based) are increasingly being used in healthcare and health-related research. Applications identified in the National AI Strategy as part of the national projects are those that help to generate personalised risk scores for individuals with chronic diseases,

[46] M. D. Abràmoff, P. T. Lavin, M. Birch, N. Shah, J. C. Folk, *Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices*, 1 Digital Medicine 39 (2018).

[47] P. A. Keane, E. J. Topol, *With an eye to AI and autonomous diagnosis*, 1 Digital Medicine 40 (2018).

[48] International Medical Device Regulators Forum, *Software as a Medical Device (SaMD): Key Definitions. IMDRF/SaMD WG/N10FINAL:2013*; available at: http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf

[49] International Organization of Standards, ISO/IEC 14764:2006 Software Engineering – Software Life Cycle Processes – Maintenance (2nd ed., 2006).

and empower these individuals to better manage their conditions.[50] Digital tools that may be deployed include mobile sensing devices equipped with sensors to track mobility and fluctuations in a range of biomarkers of these individuals to meet therapeutic and/or research goals. For instance, such digital tools are being applied elsewhere to study mental health problems,[51] some of which involve children and young persons.[52] Major research funders like the National Institutes of Health in the United States have provided support for the use of these digital tools, which are broadly categorised as mobile imaging, pervasive sensing, social media and location tracking (MISST) tools.[53] While there is still relatively limited guidance on ethical study design, digital tools applied in such research are nevertheless subject to research ethics review and must comply with regulatory requirements on personal data collection and use. Recent contributions to the digital health and bioethics literature have identified ethical concerns that could arise from methodological limitations that make it difficult to draw definitive conclusions from the research,[54] along with additional ethical and regulatory considerations that should be taken up in research ethics review when digital tools and social media platforms are applied to locate, track and communicate with research participants.[55] Where digital tools like mobile sensing devices are used on vulnerable populations, there is arguably an ethical imperative to collaborate with particular groups and communities who are part of the research in its design and implementation stage.[56] To this effect, online platforms have been developed to enable stakeholders in the digital health ecosystem to collectively shape research

[50] Smart Nation Singapore, *National Artificial Intelligence Strategy: Advancing our Smart Nation Journey*. Singapore: Smart Nation Singapore, 2019, pp 30-31.

[51] Iorian Ferreri, Alexis Bourla, Charles-Siegfried Peretti, Tomoyuki Segawa, Nemat Jaafari, and Stephane Mouchabac. 'How New Technologies Can Improve Prediction, Assessment, and Intervention in Obsessive-Compulsive Disorder (e-OCD): Review' (2019) 6(12) *JMIR Mental Health* e11643. See also: Melanie Lovatt and John Holmes, 'Digital phenotyping and sociological perspectives in a Brave New World' (2017) 112 *Addiction* 1286.

[52] Candice L. Odgers and Michaeline R. Jensen, 'Annual Research Review: Adolescent mental health in the digital age: facts, fears, and future directions' (2020) 61(3) *Journal of Child Psychology and Psychiatry* 336.

[53] Sarah Dunseath, Nadir Weibel, Cinnamon S Bloss, and Camille Nebeker, 'NIH support of mobile, imaging, pervasive sensing, social media and location tracking (MISST) research: laying the foundation to examine research ethics in the digital age' (2018) 1 *Digital Medicine* 20171.

[54] Chris Hollis, Caroline J. Falconer, Jennifer L. Martin, Craig Whittington, Sarah Stockton, Cris Glazebrook, and E. Bethan Davies, 'Annual Research Review: Digital health interventions for children and young people with mental health problems – a systematic and meta-review' (2017) 58(4) *Journal of Child Psychology and Psychiatry* 474.

[55] Ananya Bhatia-Lin, Alexandra Boon-Dooley, Michelle K. Roberts, Caroline PRonai, Dylan Fisher, Lea Parker, Allison Engstrom, Leah Ingraham, and Doyanne Darnell, 'Ethical and Regulatory Considerations for Using Social Media Platforms to Locate and Track Research Participants' (2019) 19(6) *American Journal of Bioethics* 47. See also: Samuel D. Lustgarten, and Jon D. Elhai. Technology use in mental health practice and research: Legal and ethical risks (2018) 25 *Clinical Psychology Science and Practice* e12234.

[56] Samantha Breslin, Martine Shareck, and Daniel Fuller, 'Research ethics for mobile sensing device use by vulnerable populations (2019) 232 Social Science & Medicine 50.

practices.[57] The National AI Strategy, like the Biomedical Sciences Initiative, does not speak to these issues, but the implicit understanding is that a similarly enabling, responsive and trustworthy regulatory infrastructure is in place.

At this point, I make three observations on these developments as may be relevant to the BAC. First, the high-connectivity of AI-based CDSS and digital tools challenges the conventional assumption that the research context is distinct from the healthcare and public health contexts. As noted above, continuous monitoring, evaluation and adaptation are essential to the development of an AI-based CDSS, and in this sense, research concerns are not limited to pre-marketing stages of product development. In the foreseeable future, the relationship between the oversight responsibilities of IRBs and those of hospital ethics committees will need to be carefully considered as the boundary between research and clinical care is blurred (which is arguably a phenomenon that we already see in the governance of reproductive technologies like pre-implantation genetic diagnosis). Second, risk and governance issues are likely to be more pervasive as the pool of interested stakeholders is expected to widen and diversify. For instance, AI device developers may assume active research roles along with certain users, unlike conventional research where the roles and responsibilities of researchers could be neatly set apart from those of research subjects. Third, the trend in regulatory governance of AI devices is increasingly participatory, anticipatory and responsive,[58] and where stakeholders (which includes developers and regulators) actively and collaboratively engage with one another through dynamic processes throughout the lifecycle of the product. The current IRB-based ethico-regulatory regime and device-based regulatory regime may be too disjointed and static to support the high degree of participation and responsiveness that are needed in the development and deployment of AI technology in a truly "human-centric" healthcare.

However, there have been important (albeit relatively distinct) advancements in the ethical and regulatory governance of AI and digital tools in healthcare. On the ethics front, a framework for Big Data in health and research (hereafter, BDF) has been published by a Singapore-based expert group convened and supported by the Centre for Biomedical Ethics (CBmE) of the National University of

[57] John Torous and Camille Nebeker, 'Navigating Ethics in the Digital Age: Introducing Connected and Open Research Ethics (CORE), a Tool for Researchers and Institutional Review Boards' (2017) 19(2) *JMIR* e38.

[58] Calvin Ho, Derek Soon, Karel Caals, Jeevesh Kapur, *Governance of automated image analysis and artificial intelligence analytics in healthcare*, 74 *Clinical Radiology* 329, 330.

Singapore.[59] In essence, the BDF seeks to present a reflective, principle-based, processual and participatory approach that could be applied in practical decision-making on ethical issues that arise from the use of big data in a variety of health and research contexts. Broadly speaking, there are three main components of the BDF; these being a list of values considered to be central to a number of big data contexts, a systematic deliberative decision-making process, and three rule-like 'considerations' that operate as a value- and decision-framing mechanism.[60] While the BDF is intended for a wide range of professional audiences that include policymakers, ethics committees, data access committees and data controllers, and on matters that pertain to the national project on healthcare under the National AI Strategy (notably cross-sectoral sharing of data projects that use and link biomedical data beyond the health sector,[61] and on AI-assisted decision-making in healthcare),[62] there is no direct connection between the BDF and the National AI Strategy. There is also no clear connection between the BDF or the National AI Strategy with regulatory developments on AI governance spearheaded by the International Medical Devices Regulators Forum, of which the Health Sciences Authority is a member.[63] One useful initiative that the BAC may consider moving forward could well be in bridging these various initiatives as relevant to healthcare.

There will always be occasions for genuine and reasonable disagreement over the use of these digital tools and data which, for some, will fail to strike an appropriate balance between the protection of the (privacy) interests of participants and the promotion of social value in research. The BDF highlights the need for mechanisms to gauge participants' expectations as to their concerns and interests (such as privacy) and, as to what counts as research that is of social value that should be factored into decision-making processes. In addition, mechanisms are required to allow participants to voice their concerns about what might be

[59] Vicki Xafis, G Owen Schaefer, Markus K Labude, Iain Brassington, Angela Ballantyne, Hannah Yeefen Lim, Wendy Lipworth, Tamra Lysaght, Cameron Stewart, Shirley Sun, Graeme Laurie, and E Shyong Tai, 'An Ethics Framework for Big Data in Health and Research' (2019) 11 *Asian Bioethics Review* 227.

[60] Graeme Laurie and E Shyong Tai (on behalf of the SHAPES Working Group), 'Delivering a Practical Framework for Ethical Decision-Making Involving Big Data in Health and Research' (2019) 11 *Asian Bioethics Review* 223.

[61] Graeme Laurie, 'Cross-Sectoral Big Data: The Application of an Ethics Framework for Big Data in Health and Research' (2019) 11 *Asian Bioethics Review* 372.

[62] Tamra Lysaght, Hannah Yeefen Lim, Vicki Xafis, and Kee Yuan Ngiam, 'AI-assisted decision-making in healthcare: The application of an ethics framework for big data in health and research' (2019) 11 *Asian Bioethics Review* 299.

[63] Calvin WL Ho, 'Deepening the Normative Evaluation of Machine Learning Healthcare Application by Complementing Ethical Considerations with Regulatory Governance', *American Journal of Bioethics* (2020) forthcoming.

happening to their data and to their privacy; to exercise certain rights (such as the right to withdraw at any time and for any reasons without consequence); and to remain engaged in big data research as a social enterprise if they so wish. A crucial role that the BAC could have in the application of AI and big data in healthcare and health research may be in the development of a governance approach that enables constructive engagement among all stakeholders. In this more fluid but responsive set-up, researchers should not be only concerned with form filling, IRBs should not be only concerned with compliance, and data controllers and data privacy regulators should not be only concerned with prescribing rules.

THE NEXT DECADE

In the first decade since its establishment, we have considered how the BAC has had an instrumental role in establishing an ethico-regulatory governance framework for human biomedical research in Singapore. The second decade witnessed the consolidation of important aspects of this framework into a statutory regime, but also one which remains very much an integral part of the normative foundations that the BAC has laid. These developments were considered in the second section of the chapter, which also illustrates an arguably Singaporean-styled approach to addressing complex normative challenges that have arisen from advances in biomedical science and technologies. In the third section, we have considered a number of challenges that could be anticipated with the increasing digitalisation of human biomedical research and healthcare, particularly as the implementation of the National AI Strategy gains speed.

In the next decade, the BAC could conceivably have a continuingly crucial, but qualitatively different role to play in sustaining the delicate balance of promoting innovation on one hand and securing individual and social values on the other. If one could consider the latter as pertaining to public trust, it may well be necessary for the BAC to assume a more active role in engaging with key stakeholders – notably software developers, researchers, and a wide and diverse range of software users. As the distinction between the clinical and research contexts become rapidly eroded by the digitalisation phenomenon, the remit of the BAC may well have to be broadened beyond research, as conventionally defined. For instance, concerns with encouraging the development of representative training datasets, adoption of a common interoperable software framework for research and clinical purposes, and the establishment of standards for benchmarking, assessing and/or implementation of AI and big data applications are unlikely to be adequately addressed through top-down

prescription of rules. Fundamental to all these initiatives is the need to develop and sustain a responsive governance framework that is responsive, in the sense of promoting and supporting collaborative engagement among all stakeholders. Such a framework will require close integration of ethical commitments, legal requirements and good practices, in some ways similar to the one that the BAC has had a key role in establishing for human biomedical research in the first two decades since 2000. This framework, along with its supporting institutions, must be trustworthy and must engender trust in order to be viable.

2

Scientific and Ethical Challenges in Biomedical Research and Innovation: Heritable Interventions in Humans

Andy Greenfield

INTRODUCTION

Bioethics is playing an increasingly significant role in the 21st century. Emerging biotechnologies promise to transform practices in medicine and agriculture, but because of this, they are routinely controversial. Are they safe and do they work? Who stands to benefit or suffer from their introduction? How should their use be governed? Do they threaten to transgress any strongly held ethical commitments or disrupt social norms? Such questions are commonplace. Bioethics, as a discipline, intends to help answer these questions. Behind all such developments in medicine are usually many years of fundamental pre-clinical research, the fruits of which are occasionally translated into clinical research and practice. What responsibilities do scientists and clinicians have in performing such research? What freedoms are they entitled to? With a focus on heritable interventions, I will discuss some familiar examples of research and clinical practice in the areas of reproductive medicine and assisted reproductive technologies (ARTs) and highlight the ethical issues they raise, as a way of exploring such questions of responsibility, freedom and social acceptability. I will then discuss how bioethics, as a distinct expertise, might be equipped to deal with the challenges such technologies pose.

BIOETHICS: ITS EVOLUTION AND CONTINUED SIGNIFICANCE

What is bioethics? There are a number of ways of trying to answer this question. One involves the presumption that it 'does what it says on the tin', namely, that it considers ethical questions arising in the biosciences and medical sciences. The way forward seems straightforward: the subject of ethics, as

taught in many philosophy departments throughout the world, should be central to our understanding of bioethics. Ethics has a distinctive profile. It deals with questions of value, such as goodness, fairness and dignity. Using such concepts, it attempts to provide arguments that support normative statements, such as 'x should be permitted' etc., and even considers whether such statements can be straightforwardly true, and if so, how. Bioethics would then consist simply of adapting these familiar practices of ethics to address specific questions that arise in the areas, broadly conceived, of biology and medicine.

Another way of answering the question is to look at writings that purport to be examples of bioethics, which can be found in academic journals, and consider their character. Now, a wide variety of activities is likely to be observed. It is not surprising that bioethics, as practiced, is often concerned with matters of power and its exercise, since as a discipline, its emergence is associated with developments in biomedical science in the 1960s and 1970s, including organ transplantation, assisted conception and the rise of recombinant DNA and the biotechnology industry.[1] For example, whose interests are, and have been, served by a particular policy and what was the role of these interested parties in delivering such policy? How does the type of language used in justifying such a policy consequently influence the likely response to it? Should the decision to introduce a novel technology be arrived at democratically, or should it rely on the testimonies of experts? It is not that these questions no longer concern matters of value, because they clearly do; rather, answering them appears to require knowledge of several other disciplines taught in Universities, such as politics, sociology, economics, history and psychology. Bioethics is evolving, and as with biological evolution, this has resulted in a profusion of branches, in the form of sub-disciplines, each with a distinct focus, lexicon, and style. This makes it harder to understand the actual form of contribution that bioethics is making. Is it attempting, in traditional fashion, to offer objective reasons for making certain decisions, based on argumentation? Or is it a form of activism, a rallying cry for social justice, a tool for applying political pressure? Can it be all of these?

Whatever bioethics now is, it is undoubtedly influential. There are numerous bioethics advisory groups, and associated bioethicists, who can offer to advise anybody considering 'making a move' in the spaces surveyed by bioethics: biological and medical research, clinical practice, public policy and governance. Whatever the main objectives of such bioethics bodies or individuals are, there

[1] Kuhse, H. and P. Singer (1998). What is bioethics? A Historical Introduction. *A Companion to Bioethics*. H. K. P. Singer, Blackwell: 3-11.

is one significant contribution that they can and should make, which is to offer clarity. That is, if somebody wishes to argue, for example, that a certain area of novel clinical practice is merited, the bioethicist should be able to examine the argument, in terms of its structure, the language and concepts it employs, its scope and significance. The bioethicist can subsequently advise on whether the argument is sound or valid, the responses it is likely to elicit and suggest ways through the thicket of securing support for its conclusions, potentially by improving it. This suggests that bioethics can at least offer techniques for thinking about certain topics in a productive fashion, regardless of whether or not it can furnish us with the correct answer to the question: should we do this? This alone is an important contribution.

SOME CONTROVERSIAL TOPICS AND WAYS TO THINK ABOUT THEM

I will now consider some topics in reproductive medicine, both in pre-clinical research and its translation into clinical practice, which have been, and will continue to be, controversial. I will also evaluate responses to various claims made about their ethical acceptability.

I. Human Embryo Research

Experimentation on human preimplantation embryos is lawful in several jurisdictions, including the United Kingdom (UK). There, it is regulated by the Human Fertilisation & Embryology Authority (HFEA), the statutory body formed by the enactment of the Human Fertilisation and Embryology (HFE) Act in 1990.[2] The Act specifies certain activities that can be performed with embryos – most commonly keeping, storing and using them. These support various permitted research purposes, such as 'increasing knowledge about the causes of miscarriage' or, perhaps something that should emerge from any well-designed research project, 'increasing knowledge about the development of embryos'. Each research licence applicant must justify their use of human embryos – as opposed to animal embryos, for example – and the estimated numbers to be used. Applications are assessed by the HFEA's Licence Committee. Such pre-clinical research aims to improve our understanding of human developmental biology with a view to positively impacting, for example, the success rates of ARTs, the development of novel therapies for infertility and recurrent miscarriage, and regenerative medicine.

[2] Human Fertilisation and Embryology Authority (2018). Code of Practice. 9th edition.

Of course, the fact that there is impeccable surveillance of human embryo research will not assuage those who are fundamentally opposed to it, because they believe, for example, that such research results in the destruction of something that is entitled to the same sorts of protections that the law routinely affords humans at other stages of development. They may, at the same time, endorse some of the 'protections' afforded to the embryo by such regulation. One of these, limiting the period of culture of human embryos to 14 days or the appearance of the primitive streak, was identified in the 1984 report of the 'Warnock Committee', the intellectual basis of the HFE Act.[3] Of course, if it is the destruction of the embryo that one finds objectionable, no matter at which point of development, then this protection might be viewed as entirely inadequate. Nevertheless, the so-called '14-day rule' reflects the special status of the embryo conferred by the HFE Act in one sense, because it stops development before the stage at which the embryo could conceivably be considered sentient and thus capable of suffering. This formulation suggests a utilitarian element to the rule, with minimisation of suffering as a morally significant outcome. In Germany, by contrast, human embryo research is unlawful due to the country's Embryo Protection Act, reflecting a commitment to the protection of inherent human dignity and the right to life.[4] Exploring the basis of these divergent judgments on the ethical acceptability of human embryo research would require a careful examination of their philosophical, religious, historical and cultural origins.

The possibility of revising the 14-day rule, which is widely accepted internationally, has been a topic of much discussion in recent years.[5 6 7 8 9 10] This debate, of course, is taking place primarily in the ethical space of reasoning that finds human embryo research acceptable: the question here is whether there are good scientific reasons to allow cultures of human embryos to proceed, at least in certain experimental circumstances, beyond 14 days - perhaps to 21 or 28 days?

[3] UK Department of Health & Social Security (1984). "Report of the Committee of Inquiry into Human Fertilisation and Embryology." Chairman: Dame Mary Warnock London, UK: Her Majesty's Stationery Office.

[4] Flos, P. (2017). "Human dignity in a comparative perspective: embryo protection regimes in Italy and Germany." Law, Innovation and Technology 9: 45-77.

[5] Hyun, I., A. Wilkerson and J. Johnston (2016). "Embryology policy: Revisit the 14-day rule." Nature 533 (7602): 169-171.

[6] Nuffield Council on Bioethics (2017). "Human Embryo Culture." London, UK: Nuffield Council on Bioethics.

[7] Hurlbut, J. B., I. Hyun, A. D. Levine, R. Lovell-Badge, J. E. Lunshof et al. (2017). "Revisiting the Warnock rule." Nat Biotechnol 35 (11): 1029-1042.

[8] Appleby, J. B. and A. L. Bredenoord (2018). "Should the 14-day rule for embryo research become the 28-day rule?" EMBO Mol Med 10 (9).

[9] Chan, S. (2018). "How and Why to Replace the 14-Day Rule." Curr Stem Cell Rep 4 (3): 228-234.

[10] Williams, K. and M. H. Johnson (2020). "Adapting the 14-day rule for embryo research to encompass evolving technologies." Reprod Biomed Soc Online 10: 1-9.

Such reasons do exist and include the possibilities of permitting: i) extended study of the peri-/post-implantation period to shed light on the physiology of implantation, to improve success rates of in vitro fertilisation (IVF) and better understand the causes of miscarriage; ii) examination of the emergence and development of distinct embryonic cell lineages, notably primordial germ cells, with a few to improving techniques aimed at developing gametes from stem cells in vitro and regenerative medicine more broadly; iii) more prolonged, and thus informative, safety and efficacy assessments of novel ARTs, such as mitochondrial replacement and heritable (used here synonymously with 'inheritable') genome editing. Of course, these possibilities presuppose that scientists will develop methodologies that permit such prolonged culture; such techniques, whilst imperfect, are emerging.[11] [12] [13]

The 14-day rule was never intended to demarcate a clear moral boundary – there are no obvious differences between the moral status of a 13-day and 15-day human embryo, just 48 hours of further human development. It is true that the expected appearance of the primitive streak at around 15 days suggests that the embryo is now an 'individual', but this only allows one to conclude that prior to this stage the embryo was 'at-least-one-individual', which does not self-evidently warrant the attribution of reduced moral status. None of this is meant to imply that significant moral status, and an attendant claim to enhanced protection, does not emerge at some point in the developmental process. Gradualists are likely to believe that such status grows in significance over time. Nevertheless, those arguing for an extension believe that prior to, for example, 28 days, the absence of the possibility of suffering, due to the lack of any relevant neural structures, indicates that no significant threshold in moral status has yet been reached. From this perspective, the point is that the line in question (even if re-drawn to 28 days) is best viewed as a regulatory one. Even though somewhat arbitrary, it provides clear and unequivocal guidance on when an experiment must be terminated and clarity is always useful for regulators. This brings me to why regulation is so important.

Lawful research on human embryos, such as under the provisions of the HFE Act of the UK, is often seen as emerging from a kind of compromise, or settlement. The Act permits a social good – research on human embryos that

[11] Deglincerti, A., G. F. Croft, L. N. Pietila, M. Zernicka-Goetz, E. D. Siggia et al. (2016). "Self-organization of the in vitro attached human embryo." Nature 533 (7602): 251-254.
[12] Shahbazi, M. N., A. Jedrusik, S. Vuoristo, G. Recher, A. Hupalowska et al. (2016). "Self-organization of the human embryo in the absence of maternal tissues." Nat Cell Biol 18 (6): 700-708.
[13] Xiang, L., Y. Yin, Y. Zheng, Y. Ma, Y. Li et al. (2020). "A developmental landscape of 3D-cultured human pre-gastrulation embryos." Nature 577 (7791): 537-542.

promises to yield valuable knowledge and benefits to medicine – but only within an oversight structure that demands justification for the experimentation from those clearly equipped to perform it and with a time limit on it. To the extent that this is a settlement, it is a political one: it aims to establish public trust in the regulated use of human embryos by scientists. It is not a case of 'anything goes' when it comes to human embryo research. Any attempt to revise the 14-day rule would, therefore, require re-visiting the settlement and the labyrinthine argumentation that preceded it, with an attendant risk that trust may be threatened, or lost. Such a risk exists no matter how cogent the arguments are for an extension to the time-limit.

Attitudes towards the ethical acceptability of human embryo research partly reflect our understanding of what an embryo is. Is it just a ball of cells? Or an embryonic (potential) person? Or something between these two? Such understanding is being challenged by the development of embryo-like entities that are not the product of fertilisation of an egg by a sperm, but rather are formed by the culture and manipulation of stem cells in vitro.[14] In the mouse, an individual stem cell, known as an expanded potential stem cell, can give rise to an embryonic structure, a blastoid, with cellular and molecular properties similar to a normal blastocyst (3.5-day old mouse embryo). Such mouse blastoids can be implanted into a uterus and give rise to distinct tissues of all three embryonic germ layers.[15] Work using human pluripotent stem cells to generate embryo-like entities has also been reported.[16] [17] [18] Embryo-like entities can be useful for fundamental research in human developmental biology,[19] and may be cultured to allow developmental events to be studied that would currently fall into the post-14-day period in an embryo produced in the standard way.[20] Here, the question is: should such entities inherit the legal protections that are currently afforded to bona fide human embryos? The better the model, the more 'like' the embryo-like entity is, the more pressing this question will become. Attitudes are likely to depend partly on

[14] Aach, J., J. Lunshof, E. Iyer and G. M. Church (2017). "Addressing the ethical issues raised by synthetic human entities with embryo-like features." eLife 6: e20674

[15] Li, R., C. Zhong, Y. Yu, H. Liu, M. Sakurai et al. (2019). "Generation of Blastocyst-like Structures from Mouse Embryonic and Adult Cell Cultures." Cell 179 (3): 687-702 e618.

[16] Warmflash, A., B. Sorre, F. Etoc, E. D. Siggia and A. H. Brivanlou (2014). "A method to recapitulate early embryonic spatial patterning in human embryonic stem cells." Nat Methods 11 (8): 847-854.

[17] Shao, Y., K. Taniguchi, R. F. Townshend, T. Miki, D. L. Gumucio et al. (2017). "A pluripotent stem cell-based model for post-implantation human amniotic sac development." Nat Commun 8 (1): 208.

[18] Rivron, N. C., J. Frias-Aldeguer, E. J. Vrij, J. C. Boisset, J. Korving et al. (2018). "Blastocyst-like structures generated solely from stem cells." Nature 557 (7703): 106-111.

[19] Hyun, I., M. Munsie, M. F. Pera, N. C. Rivron and J. Rossant (2020). "Toward Guidelines for Research on Human Embryo Models Formed from Stem Cells." Stem Cell Reports 14 (2): 169-174.

[20] Moris, N., K. Anlas, S. C. van den Brink, A. Alemany, J. Schroder et al. (2020). "An in vitro model of early anteroposterior organization during human development." Nature 582 (7812): 410-415.

whether such a human embryo-like entity, if used to establish a pregnancy, could ever yield a healthy newborn. Notwithstanding the impermissibility of such an action, and its implausibility given current technologies and ethical norms, if evidence suggested that such entities could be successfully used as a form of human reproduction, it would be difficult to see how the law could offer them less protection than a 'standard' embryo. But the evidence at the moment suggests that we are some way from this scenario.

Of course, culture models that do not attempt to sustain the development of an entire embryo, with related potential for development, should not raise similar ethical concerns;[21] the only exception would be experiments aimed at generating sophisticated neural networks from embryo-like entities, if such were possible, since this might, in the eyes of some, raise the possibility of suffering. It should also be noted, finally, that the standard timings of events during human embryonic development are likely to be disrupted by both the generation of embryo-like entities in different ways, and by the inactivation or alteration of certain genes by genome editing (see Section (III)). The incorporation of the observation of such events, such as primitive streak formation, into a revised rule, would not be straightforward if it aims to capture experimentation beyond the analysis of the standard embryo. This may be why the clear avoidance of the possibility of suffering may be central to any new limit, requiring the identification of events that are reliably associated with relevant neural differentiation and development. Matters of public trust will, again, inform and shape the trajectory of regulatory policy in this area.

II. Mitochondrial Replacement Techniques (MRT)

One area in which pre-clinical research on human embryos has played a central role is the development of mitochondrial replacement techniques (MRT), also known as mitochondrial donation.[22] [23] These techniques aim to prevent or limit the transmission of mitochondrial diseases, caused by mutations in mitochondrial DNA (mtDNA), from mother to offspring. This is achieved either by transfer of the maternal chromosomes on the spindle of the metaphase II-arrested (MII) oocyte to a donor oocyte from which the maternal chromosomes have been removed; or the transfer of the female and male pronuclei, formed

[21] Hyun, I., M. Munsie, M. F. Pera, N. C. Rivron and J. Rossant (2020). "Toward Guidelines for Research on Human Embryo Models Formed from Stem Cells." Stem Cell Reports 14 (2): 169-174.
[22] Greenfield, A., P. Braude, F. Flinter, R. Lovell-Badge, C. Ogilvie et al. (2017). "Assisted reproductive technologies to prevent human mitochondrial disease transmission." Nat Biotechnol 35 (11): 1059-1068.
[23] Herbert, M. and D. Turnbull (2018). "Progress in mitochondrial replacement therapies." Nat Rev Mol Cell Biol 19 (2): 71-72.

shortly after fertilisation of the prospective mother's oocyte, into a fertilised donor oocyte from which the pronuclei have been removed. Donor oocytes are selected to be free of pathogenic mtDNA mutations.

Since the 1980s, MRT methodologies have been employed in research settings, involving model organisms such as the mouse. Considerable amounts of data indicate that they can yield embryos of comparable developmental potential to controls, if performed by appropriately skilled embryologists under optimal conditions. Nevertheless, given that MRT represent a first-in-human alteration of germline cells (oocytes or zygotes) with heritable consequences, concerns about the safety of this intervention have been expressed. The UK HFEA convened four separate scientific reviews of the safety and efficacy of MRT over several years, as part of the translational pathway to clinical implementation and governance of MRT.[24] Two concerns were at the centre of these reviews: i) that embryos generated by MRT should have low levels of mother's pathogenic mtDNA and that this should remain so throughout development; and ii) that the new combination of maternal and paternal nuclear genomes generated by MRT should function alongside the donor's mtDNA, without any impairment. Furthermore, a principle familiar to medical ethics discourse, based on harm-benefit analyses and the role played by uncertainty, required that MRT should only be offered when no other existing (tried and tested) intervention is available. As a consequence of these concerns and the principle, HFEA regulation of MRT in the UK includes the requirements that firstly, *only* women with consistently high levels of pathogenic mtDNA in their germline (possibly indicated by family history) should be offered access to MRT, since the use of preimplantation genetic diagnosis (PGD) - an existing method for determining whether embryos with acceptably low levels of pathogenic mtDNA are available for transfer - would be most unlikely to be successful in these circumstances. Also, women who undergo MRT treatment should be offered prenatal testing to allow assessment of pathogenic mtDNA levels in the foetus. Furthermore, consideration should be given to matching the mtDNA haplotypes of the prospective mother and donor, given the possibility of mito-nuclear functional mismatch. Finally, MRT should not be used as a speculative treatment for infertility. The net effect of the scientific reviews was, therefore, a cautious adoption of MRT in the UK clinic, with the incorporation of various mitigations against potential harms, as a 'risk reduction strategy'. Further research was also recommended. Such an outcome was not something that could simply be inferred from the scientific data – it was the product of a

[24] Greenfield, A. (2016). "Scientific Review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update." Report to the Human Fertilisation and Embryology Authority (HFEA)

combination of scientific, clinical, social and ethical considerations.[25] This is a useful reminder that scientific assessments of safety and efficacy, based on pre-clinical data, cannot deliver certainty of clinical outcome in advance of clinical use, and will usually operate alongside other *evaluative* frameworks in delivering recommendations to policymakers and regulators.

The fact that a novel intervention such as MRT is viewed by experts as sufficiently safe for limited clinical application should not imply that its use is thereby ethically justified. Other morally relevant considerations exist in addition to safety and efficacy. But it seems that expressions of concern about safety and efficacy often operate as placeholders for fundamental *ethical* objections. In the case of MRT, these are related to concerns about social need and justice, naturalness, identity, and whether one germline intervention might lead to other such interventions, including heritable human genome editing (see Section (III)).

It has been pointed out by opponents that the use of an egg donor in conventional IVF would also prevent mitochondrial disease transmission. But in this case, the mother would not be genetically related to the child born. But should the desire for genetic relatedness be considered so significant that it warrants the development of potentially harmful treatments, especially given that this is time-consuming and requires the use of scarce public resources that would benefit so few? Proponents respond by pointing out that the rarity of a harmful phenomenon should not undermine the ethical acceptability of its treatment or prevention, and that valuing 'genetic relatedness', or family resemblance, in practice, has been an important aspect of human reproduction for millennia, including assisted reproduction more recently.[26] [27] [28] [29] Opponents have expressed concern about the birth of a child with 'three parents'. What impact would this have on the psychological well-being of that individual?[30] Would they share any family resemblances with the mtDNA donor?[31] Would it be fair to withhold the identity of their mtDNA donor from them? Proponents responded by questioning

[25] Lewens, T. (2019a). "The division of advisory labour: the case of 'mitochondrial donation'." European Journal for Philosophy of Science 9 (10)

[26] Hendriks, S., K. Peeraer, H. Bos, S. Repping and E. A. F. Dancet (2017). "The importance of genetic parenthood for infertile men and women." Hum Reprod 32 (10): 2076-2087.

[27] Greenfield, A. (2018). "Carry on Editing." British Medical Bulletin 127 (1): 23-31.

[28] Hendriks, S., M. van Wely, T. M. D'Hooghe, A. Meissner, F. Mol et al. (2019). "The relative importance of genetic parenthood." Reprod Biomed Online 39 (1): 103-110.

[29] Segers, S., G. Pennings and H. Mertes (2019). "Getting what you desire: the normative significance of genetic relatedness in parent-child relationships." Med Health Care Philos 22 (3): 487-495.

[30] Scully, J. L. (2017). "A Mitochondrial Story: Mitochondrial Replacement, Identity and Narrative." Bioethics 31 (1): 37-45.

[31] Greenfield, A. (2020). "Use of Mitochondrial Donation." in Controversies in Assisted Reproduction, eds. Rizk & Khalaf., CRC Press: 116 - 127.

whether the mtDNA donor should be viewed as a parent at all. 'Three-person' IVF might be a better description since there are three gamete providers. And studies on families created using other innovative ARTs such as PGD and IVF by gamete donor, suggest that individuals (and their parents) can adjust to the unusual circumstances surrounding their birth.[32] [33]

Some have expressed opposition to the very idea of heritable interventions, of which MRT is an example. To some, it is an affront to human dignity to be born as a result of a plan, a plan to constrain or direct the characteristics of a human being. Such an act suggests that the child in question is not loved unconditionally, but only insofar as they meet certain criteria, established in advance by parents. Such parental desires, if left unchecked, will lead to the commodification of children and the control of heritable traits beyond disease prevention, or so they argue. This brings me to the topic of heritable human genome editing.

III. Heritable Human Genome Editing (HHGE)

A profusion of narratives can be found on the topic of heritable human genome editing (HHGE) i.e. genome editing of embryos, gametes or gamete precursor cells to establish a pregnancy and influence a heritable (usually disease) trait of the child born as a consequence. But many of these can be lumped into larger metanarratives. Two dominant examples are as follows: i) to use genome editing to control human inheritance is wrong, because it would be an infringement of fundamental human rights, an affront to human dignity and is socially unjust; ii) we should embrace genome editing's potential contribution to ART, since it aims to deliver no more than existing (lawful) ARTs, such as genetic testing of embryos, and reflects the noblest of human traditions – the use of our intellects to reduce the burden of human existence. The opinions expressed in i) are familiar given the above discussion of objections to MRT. I will discuss these ideas first, before moving onto the positive thoughts expressed in ii). Before doing so, I make it clear that I will not discuss the safety and efficacy of HHGE, despite the importance of these. My focus will be on whether we should use a safe and efficacious HHGE since we should clearly *not* use an unsafe or ineffective treatment. At the time of writing, the most efficient genome editing methodology, i.e. some variant of the CRISPR/Cas9 methodology, is not sufficiently precise to

[32] Golombok, S., R. Cook, A. Bish and C. Murray (1995). "Families created by the new reproductive technologies: quality of parenting and social and emotional development of the children." Child Dev 66 (2): 285-298.

[33] Imrie, S., V. Jadva, S. Fishel and S. Golombok (2019). "Families Created by Egg Donation: Parent-Child Relationship Quality in Infancy." Child Dev 90 (4): 1333-1349.

justify its clinical use in a human embryo or gamete i.e. to establish a pregnancy.[34] More pre-clinical research, a good deal of which will require human embryos, is needed to identify appropriate methodologies, if these exist. Small-scale clinical trials might then follow, but a number of scientific, clinical and societal conditions would need to be met first. Alternative approaches, such as the use of gametes derived from genome-edited stem cells, may be developed. But *in vitro*-derived gametogenesis would obviate the requirement for genome editing in most cases where the aim is to prevent the inheritance of a monogenic disease, and the consequences of its use in society are likely to be just as disruptive, if not more so than those arising from the use of HHGE.[35]

Article 24 of UNESCO's Universal Declaration on the Human Genome and Human Rights states that interventions in the human germline "could be contrary to human dignity".[36] In 2019, the German Ethics Advisory Council (Deutscher Ethikrat) published its ethical analysis of HHGE, suggesting that human dignity "stands for that value which is resistant to any trade-offs... man is regarded as 'an end in himself'".[37] This places human dignity within a familiar Kantian framework, one which opposes the types of 'trade-off' associated with utilitarianism, which allows potential harms to be 'offset' by potential benefits when evaluating the ethical acceptability of an act. In the context of HHGE, a central question is whether future persons are instrumentalised by this controlled intervention i.e. assigned a devalued status as a 'commodity', which would violate their dignity. Would children become mere projects of their parents' imaginations? I will leave aside whether this is a blatant example of unwarranted genetic exceptionalism, given that many parents intentionally, without obviously offending against ordre public or morality, control the destiny of their children from birth through non-genetic means, by imposing educational regimes etc.[38] I will instead focus on another problem here, which is that, in the context of intervening in the germline to prevent the transmission of a serious monogenic disease such as cystic fibrosis, another intervention already exists and is lawful in many jurisdictions: PGD, also known as preimplantation genetic testing for

[34] National Academy of Medicine, National Academy of Sciences and the Royal Society (2020). "Heritable Human Genome Editing" Washington, DC: The National Academies Press. https://doi.org/10.17226/25665.

[35] Bredenoord, A. L. and I. Hyun (2017). "Ethics of stem cell-derived gametes made in a dish: fertility for everyone?" EMBO Mol Med 9 (4): 396-398.

[36] UNESCO (1997). "Universal Declaration on the Human Genome and Human Rights." Article 24. Available at: https://unesdoc.unesco.org/ark:/48223/pf0000110220.page=47

[37] Deutscher Ethikrat (2019). "Intervening in the Human Germline." English translation of Executive Summary and Recommendations.

[38] Lewens, T. (2019b). "Blurring the germline: Genome editing and transgenerational epigenetic inheritance." Bioethics 34: 7-15

monogenic diseases, PGT-M. PGD involves the genetic testing of embryos to permit selection of those that lack a disease-causing genotype prior to establishing a pregnancy, and its availability is often cited as a reason for the use of HHGE not being required, or at least not compelling. Of course, this is a way of noting that one reason that PGD and HHGE are often compared is because both are germline interventions, as both involve the creation of embryos from germ cells and their subsequent manipulation in vitro, to influence inheritance. If HHGE is an affront to human dignity or some related ethical norm, isn't PGD too? Hardly any discussions of the ethical acceptability of HHGE in the context of monogenic diseases go on to draw conclusions about the ethical acceptability of PGD or note that it is itself a germline intervention. Wouldn't the conclusion that HHGE is unethical require us to revise our attitude, at least as a society, to PGD? And why are so few inclined to draw this conclusion? Perhaps it is because PGD is not considered especially problematic by many people in many countries. Perhaps HHGE is simply the focus of moral opprobrium because it is new?

It is difficult to envisage a clear ethical difference between the acceptability of PGD and safe HHGE, at least in these envisaged circumstances, given that the shared aim of both would be to prevent life-shortening and debilitating monogenic diseases. HHGE has the potential to allow more sophisticated and complex interventions in the human genome, but it is unclear why this potentiality should reflect on the ethical acceptability of more modest (and currently more realistic) uses of its powers. Any ethical difference is likely to trade on the difference between selection between alternatives versus altering DNA, as a means to avoid the disease, and has, therefore, a metaphysical whiff to it. For example, is selection from existing options more natural? Why is this a difference that would matter to somebody being offered counselling in a future IVF clinic, if both techniques are safe and effective, or if HHGE is likely to be more effective? Can any IVF technique be considered 'natural'? And besides, doesn't the purview of 'natural' include all sorts of undesirables, such as cancer and other bodily insults caused by aging? Finally, since life-shortening diseases and their associated suffering are themselves an all-too-common affront to human dignity, it would be ironic if their prevention by HHGE were to be considered a violation of dignity in future humans.

The other common element in objections to the use of HHGE is the attendance to issues of social justice. Will there be equitable access to HHGE? How are the needs of those who wish to have genetically-related children free of a disease to be compared to routine clinical needs of those suffering from existing

diseases, given the finite resources for healthcare provision? And what impacts will the normalisation of HHGE have on those living with genetic disease? If the numbers of these decrease, will they still receive the aid and care they need? Will they (or their parents) be stigmatised and face discrimination? The latter questions, whilst very important, are to some extent empirical, requiring some degree of estimation or prediction. It is worth noting here, however, that the increased use of PGD over the last two decades has not coincided with any obvious increase in stigmatisation of those living with disability – rather, disability awareness is rising in many countries.

The Nuffield Council on Bioethics (NCOB), in its 2018 report on the ethics of HHGE, concluded that HHGE could be ethically acceptable in some circumstances;[39] but, importantly, NCOB recommended that a condition of just use of HHGE be that it "should not increase disadvantage, discrimination or division in society". One important question that arises immediately from this principle, aimed at informing policy, is how it is to be decided whether a particular use of HHGE – on the assumption that there is no such thing as deciding on the merits of HHGE in general – is likely to increase disadvantage, discrimination or division in society. Who decides? And based on which criteria? The answer will likely depend, at least to some extent, on whether a respondent considers themself to be a potential beneficiary of HHGE, or whether they fear a negative impact on their quality of life or that of loved ones. These responses are not themselves self-evidently ethical, given their focus on self-interest or prudence. But they are important, nevertheless. However, there will be those who respond to this evaluative question with certain of their own general ethical commitments in mind, some of which we have encountered, such as human dignity, the welfare of the future child, social justice and solidarity. They may also express concern about creeping parental responsibilisation i.e. "a problematic expansion of the understanding of parental responsibility".[40] But to the extent that we live in societies characterised by ethical and political diversity, there is unlikely to be a single overarching ethical commitment that drives such responses. And now we can see that answering such a question in the public sphere will require societal conversations and negotiations that use all of the same fundamental ethical concepts and values that were required to arrive at the original recommendation. There has been a deferral of the pressing nature of the question of whether a society should accept a given use of HHGE in certain circumstances, but not an answer.

[39] Nuffield Council on Bioethics (2018). "Genome Editing and Human Reproduction: Social and Ethical issues." London, UK: Nuffield Council on Bioethics.

[40] Bredenoord, A. L. and I. Hyun (2017). "Ethics of stem cell-derived gametes made in a dish: fertility for everyone?" EMBO Mol Med 9 (4): 396-398.

There are other fundamental ethical or evaluative goods that are more often invoked in favour of the prospective use of a safe and effective HHGE, such as our duties to assist those in need, to use science (the scientific method generated by our intellects) to reduce the burden of human existence,[41] to prevent suffering, including by intervening in human reproduction.[42] Here, using the language of 'rights', we see a focus on positive rights, rather than negative. Advocates of technologies such as HHGE are often also advocates of the freedom to perform scientific research, and consider science a human achievement to celebrate, even when it generates knowledge that has no immediate or obvious use. We cannot predict which pieces of knowledge will turn out to be useful, so, the argument goes, it is undesirable or dangerous to yoke scientific research objectives too closely to perceived human needs. We may even discover inconvenient truths; but that risk simply comes along with trusting the scientific method, rather than individual scientists. However, in terms of public policy, it will always be the case that more than science is required to decide when innovation is acceptable and how it is to be regulated. Is such innovation in the public interest? Again, when such questions arise, we inevitably revisit the ethical discussions had above, in public spaces but also, perhaps, around the regulator's committee table.

BROADER BIOETHICAL THEMES AND THE FUTURE

We have seen that there appear to be no generic answers to questions such as: should we permit the use of MRT? Or HHGE? Public policy in such matters is usually a matter of codifying ethical principles, with a view to providing clarity, whilst acknowledging practicalities; but particular circumstances may be decisive when considering acceptability. "Case-by-case" evaluations, sensitive to individual circumstances, are likely to be the order of the day, at least initially, as is the case with the use of MRT in the UK. This raises the question, as we have seen, of how certain general ethical principles are to be employed in a particular case. So, I will finish with some comments on the role of bioethics, moving forward.

Argumentation is still important in evaluating applications of new technologies, despite a diversity of voices. Indeed, voices alone are not enough. A diversity of arguments is required, incorporating the lived experience of individuals. This means that it is still possible to evaluate arguments and even

[41] Harris, J. (2016). "Germline Modification and the Burden of Human Existence." Camb Q Health Ethics 25 (1): 6-18.
[42] Savulescu, J. (2001). "Procreative beneficence: why we should select the best children." Bioethics 15 (5-6): 413-426.

decide that some are unsound or invalid. Arguments that survive such a cull might have persuasive force, and may even change minds. Holding out for this possibility means a logical distinction can be made between the quality of an argument and its popularity; it also allows us to resist the temptation to see diversity as inevitably leading to disagreement and stalemate.

Bioethicists are experts at analysing how arguments and their constituent premises, involving potential benefits, harms and opportunities, are commonly expressed (framed) in a way that embeds certain broader values or commitments concerning what matters, and thereby exclude alternatives. Such framing may be intentional and crude – as in a tabloid newspaper headline – or more subtle and unconscious – emerging from the uncritical use of certain value-laden beliefs or assumptions. But the role of the bioethicist is surely to examine the broadest possible framings – consistent with being able to survey them at all - those which are immune, or at least more immune, to a straightforward critique that they are too narrow, selective and misleading. Within these broadest framings, arguments that are often not seen together can be considered side-by-side, and new arguments will arise as a consequence. Bioethics should not be reduced to relatively simple critiques of narrow framings, nor wedded to the idea that arguments can only ever express factional interests of a balkanised public. Indeed, the roles that the interests of individuals or groups play in ethics and morality is problematic. As the philosopher, Thomas Nagel, has written: "The basis of morality is a belief that good and harm to particular people is good or bad not just from their point of view, but from a more general point of view, which every thinking person can understand".[43]

These comments about framing suggest, nonetheless, that languages – the choice of words and other rhetorical devices - are important, since it is hearts and minds that must be won to effect change or resist it. We are all familiar with those tropes that often dominate discussions of genetics and genetic technologies. If, as a society, we are to innovate with public consent, we need an ordinary language that does justice to the key complexities of science and ethics in this area – and this is a major challenge. For example, there is no widespread understanding of the nature of genomes, nor the nature of valid arguments, in most societies. Bioethicists should help to build a language for public dialogues, partly by resisting the use of technical jargon of academic journals, through which they communicate and argue with each other. Instead, they should consider relating to real-world contexts more regularly, in which the topics discussed in this

[43] Nagel, T. (1987). What Does it All Mean?, Oxford University Press, p. 67.

commentary actually come into view, for most people. The communication that such language allows is likely a condition of trust developing between those who wish to innovate, those who spend careers critiquing such innovation and those who have an interest in such innovations but are not necessarily aware that they do.

Earlier, we considered whether changing the 14-day human embryo culture limit might be warranted. We saw that even if the best arguments suggest that it is, the consequences of making them and advocating change can be unpredictable. The significance of arguments is grasped in a particular social context and there may be consequences of public debate that do not tally with the conclusions of an argument. In this vein, bioethicist Sarah Chan has claimed that HHGE might "exacerbate social division and marginalisation not only via the use of technology itself but also by the ethical, political and public discourse surrounding it: the hope, hype and imaginaries attached to the future of genome editing. As bioethicists, we must be conscious of how the arguments we advance, as well as when and how we choose to do so, affect this discourse."[44]

CONCLUSION

This commentary has surveyed certain pressing debates involving biomedical research and innovation, especially those involving the human germline and interventions that attempt to direct human reproduction. This topic has not just fascinated scientists and bioethicists: our literature is replete with imagined futures in which science and technology have had major impacts on the nature of society and its cultural norms. But balance is required here too. We also need such literary futures to explore positive outcomes for innovation using genetic technologies, not just dystopian visions. As I have suggested, future research using human embryos and technologies such as genome editing is vital in producing knowledge that will drive innovation in assisted reproduction, but a focus on science alone will not be sufficient to build societal consensus on the acceptability of these interventions. Bioethics will also be needed to consider what the 'science and technology' means for us, and to act as a guide along possible future paths.

[44] Sarah, Chan. (2019). Commentary on 'Moral reasons to edit the human genome': this is not the moral imperative we are looking for. Journal of Medical Ethics 45(8): 528-529

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3

Future of the Biomedical Sciences in Singapore

Ng Huck Hui

CURRENT STATE OF BIOMEDICAL SCIENCES IN SINGAPORE

The emergence of the biotechnology industry in Singapore started with the establishment of a production plant in Singapore by the leading British pharmaceutical company, GlaxoSmithKline. To remain competitive among other rising countries, Singapore's economy was diversified from production into other fields and was steered towards Research and Development (R&D) as a means to launch Singapore up the value chain.[1] In tandem with her vision of becoming a renowned scientific hub, Singapore launched the Biomedical Sciences (BMS) initiative in June 2000 to establish BMS as the 4th pillar of the economy.[2] This initiative focused on developing a comprehensive spectrum of capabilities ranging from the nurture and recruitment of top scientists to the assembly of state-of-the-art facilities for research in BMS. We have several organisations involved to push the initiative forward. These include the Agency for Science, Technology and Research (A*STAR)'s Biomedical Research Council (BMRC), Ministry of Health's National Medical Research Council (NMRC), Singapore's Economic Development Board (EDB)'s Biomedical Sciences Group (BMSG) and Bio*One Capital. BMRC is responsible for overseeing research institutes that conduct strategic biomedical research in bio-pharmaceutical, bio-manufacturing, food and consumer care, and development of strategic initiatives leading to economic and societal impact. NMRC oversees the development and advancement of medical research. BMSG is involved in industrial development while Bio*One Capital focuses on strategic investment in companies to bring economic benefits to the country.[3]

[1] Agency for Science, Technology and Research, and JTC Corporation. The Biopolis Story: Commemorating Ten Years of Excellence. A*Star and JTC Corporation, Singapore, 2013, p. 5.

[2] Yeoh K-C. Singapore's biomedical sciences landscape. J Commer Biotechnol. 2008. doi:10.1057/jcb.2007.35

[3] Beh, Swan Gin. "Singapore–The Biopolis of Asia." Asia-Pacific Biotech News 9.18 (2005): 952-954.

The BMS initiative can be divided into different phases. In the first phase (2000-2005), Singapore invested to develop basic research capabilities and infrastructure to attract R&D laboratories and talents.[4] In 2003, the Biopolis was set-up as the central facility for biomedical research for both the private and public sectors. This R&D hub was built with the aim to transform Singapore into a global biomedical science cluster to advance human health through R&D, production and healthcare delivery. The Biopolis housed various cutting-edge research facilities and biomedical sciences research institutes such as the Institute of Molecular and Cell Biology (IMCB) and the Genome Institute of Singapore (GIS).[5] Another notable infrastructure was the Tuas Biomedical Park built for manufacturing activities in the biomedical sciences sector and it housed some of the world's renowned pharmaceutical companies like Merck and Novartis.[6]

In the second phase of the BMS initiative (2006-2010), the country's translational and clinical research capabilities were enhanced to improve healthcare delivery and human health. Bio*One Capital brought in several biologics manufacturers such as Lonza to set up production operations in Singapore. The dedicated plans and infrastructure built in place showed the government's commitment towards the BMS sector and this gave external investors and companies the confidence to set up plants and production lines in Singapore.[7]

Besides the BMS initiative, the Cabinet implemented the Research, Innovation and Enterprise (RIE) 2015 plan to further establish Singapore as a global R&D scientific research centre. Through competitive funding, efforts and resources were channelled to support the best research projects. There was greater emphasis on the development of products and services which had the potential to generate greater economic and healthcare benefits for the country. Multi-disciplinary science received greater public investment as well.[8] In the RIE2020 plan, Singapore will continue to grow our R&D capabilities and encourage innovations to fulfil the needs of the country. These careful long-term plans exhibit the foresight and commitment of our leaders to transform our city-state using R&D for the betterment of our people.[9]

[4] Sheo, S. Rai. "Overview of the BMS Industry." Asia-Pacific Biotech News 10.08 (2006): 404-406.
[5] Agency for Science, Technology and Research, and JTC Corporation. The Biopolis Story: Commemorating Ten Years of Excellence. A*Star and JTC Corporation, Singapore, 2013, p. 22
[6] Lim, Lisa PL, and Michael J. Gregory. "Singapore's biomedical science sector development strategy: Is it sustainable?." Journal of Commercial Biotechnology 10.4 (2004): 352-362.
[7] Wong, Niki, and Yap, M. "The future of biomanufacturing in Singapore." Biotechnology Journal: Healthcare Nutrition Technology 2.11 (2007): 1327-1329.
[8] Ministry of Trade and Industry, Innovation and Enterprise (RIE) 2015, November 2011, p. 4
[9] Ministry of Trade and Industry, Innovation and Enterprise 2020 Plan: Winning the Future through Science and Technology, January 2016.

The importance of BMS research in Singapore is evident especially so during times of disease outbreak, apart from the economic benefits it brought for Singapore. The 2003 Severe Acute Respiratory Syndrome (SARS) outbreak was considered the most difficult challenge faced by the Singapore's public health system then, as the city-state was caught by surprise when this invisible virus attacked.[10] Fortunately, researchers from both the public and private sectors, GIS from A*STAR and Roche Diagnostics, raced against time to develop the SARS detection kit to help address the outbreak situation in Singapore.[11] Time and funds invested in the BMS sector raised the country's readiness towards a disease outbreak as they improved our research capabilities, along with increased training for healthcare personnel to deal with an infectious disease outbreak and specialised infrastructures.[12]Adopting best practices and international standards, the National Centre for Infectious Disease (NCID) was also built to house clinical services, public health research and community engagement to enhance infectious disease management of the nation.[13]

Disease outbreaks can bring about economic and health safety crises. While Singapore can import diagnostic and treatment solutions, it is crucial for Singapore to develop core capabilities that she needs during times of epidemic or pandemic crises. Singapore's foresight to focus on BMS allowed us to develop diagnostic tools to surveil, monitor and control the COVID-19 situation. One of which includes the Fortitude Kit 2.0 which was deployed in the front line globally to detect COVID-19 infections. Used in over 20 countries in their fight against the virus, the high-accuracy test kit utilises a real-time RT-PCR process and was developed by A*STAR's Experimental Drug Development Centre (EDDC), Bioinformatics Institute and the Tan Tock Seng Hospital (TTSH), with support from Diagnostics Development Hub (DxD).[14] Another notable diagnostic tool is the cPass™, developed by Duke-NUS Medical School (Duke-NUS) and DxD at A*STAR. cPass™ is a rapid serological test to detect neutralising antibodies without the use of live biological materials. It is deployed for use in situations

[10] Ooi GL, Phua KH. SARS in Singapore - Challenges of a global health threat to local institutions. Nat Hazards. 2009. doi:10.1007/s11069-007-9194-2

[11] Agency for Science, Technology and Research, and JTC Corporation. The Biopolis Story: Commemorating Ten Years of Excellence. A*Star and JTC Corporation, Singapore, 2013, pp. 26-27.

[12] Chan MC, Yeo S, Chong YL, Lee YM. "Stepping forward: urologists' efforts during the COVID-19 outbreak in Singapore." European Urology (2020).

[13] "About NCID." National Centre for Infectious Diseases, Singapore, www.ncid.sg/About-NCID/Pages/default.aspx.

[14] "From Singapore to the World: Where Fortitude Kit 2.0 Has Been Deployed." A*STAR HQ Corporate Website, www.a-star.edu.sg/News-and-Events/a-star-news/news/covid-19/from-singapore-to-the-world-where-fortitude-kit-2.0-has-been-deployed-globally.

like contact tracing and assessing herd immunity.[15] The ability of Singapore to create these test kits is paramount in solving the supply chain problem, exhibiting readiness and the intrinsic ability of Singapore to perform R&D in troubled times. In other words, R&D carried out during peace time drove the rapid development of novel solutions in times of crisis. Singapore now demonstrates her efficient coping mechanism through active screening, extensive contact tracing and early isolation of cases to minimise the spread of disease.

POTENTIAL OF BMS TO DEVELOP AND IMPROVE HEALTHCARE

Apart from artificial intelligence and big data which have been covered in Chapter 2 by Dr Calvin Ho, there are other ways where BMS in Singapore can develop and improve healthcare. Under the current RIE2020 plan, there is an emphasis on research that aims to enhance health services delivery to improve health outcomes. Research efforts have been steered towards five therapeutic areas of focus identified by the Ministry of Health (MOH), namely, cancer; cardiovascular diseases; diabetes mellitus and other metabolic or endocrine conditions; infectious diseases; neurological and sense disorders.[16]

BMS had improved healthcare services in both local and global contexts where discoveries in laboratories have been translated into disease treatment, management and prevention. The patient's genetic, proteomic and environmental information are acquired using technology to assess the patient's suitability for treatment by identifying possible adverse effects and toxicity of drugs to the patient.[17] Genomic medicine (GM) has gained popularity among the health services landscape in Singapore with more hospitals adopting the use of GM in recent years. The era of modern genomics in Singapore started in 2001 when GIS began to utilise contemporary genomic science to study the genetics of human diseases. After which, we have various initiatives such as Personalised OMIC Lattice for Advanced Research and Improving Stratification (POLARIS), Surveillance and Pharmacogenomics Initiative for Adverse Drug Reactions (SAPhIRE) and SingHealth Duke-NUS Institute of Precision Medicine (PRISM) on-board to drive the adoption of PM in Singapore. POLARIS aimed to improve

[15] "One-Hour Antibody Test Tracks Neutralising Antibodies of COVID-19." A*STAR HQ Corporate Website, www.a-star.edu.sg/News-and-Events/a-star-news/news/press-releases/one-hour-antibody-test-tracks-neutralising-antibodies-of-covid-19.

[16] Ministry of Trade and Industry, Innovation and Enterprise 2020 Plan: Winning the Future through Science and Technology, January 2016.

[17] Vogenberg, F. Randy, Carol Isaacson Barash, and Michael Pursel. "Personalized medicine: part 1: evolution and development into theranostics." Pharmacy and Therapeutics 35.10 (2010): 560.

patient outcomes through collaboration with the various healthcare institutions. Under SAPhIRE, genomic science contributed to the discovery of biomarkers which are predictive of specific adverse drug reactions (ADR) for surveillance. PRISM seeks to encourage the use of GM, with emphasis on diseases pertinent to Asian populations.[18]

Medical Technology (MedTech) is another rising sector in the healthcare landscape which encompasses technologies that diagnose, treat and improve human health. Apart from economic contributions, the growth in MedTech will support our healthcare system and address unmet healthcare needs.[19] Singapore is one of the global manufacturing bases for MedTech companies, producing 60% of the world's microarrays and a third of the world's thermal cyclers and mass spectrometers,[20] making MedTech a key sector within the BMS industry which will further boost our economy. Housing more than 50 regional headquarters of the world's leading MedTech firms, nurturing the MedTech sector will allow us to expand our manufacturing, engineering and research capabilities in BMS.[21] As the interface between biomedical sciences and engineering, MedTech translates clinical research into the development of MedTech products which eventually benefit consumers and patients. This can be illustrated with the development of the GASTROClear diagnostic kit by a local-based biotech company, MiRXES. The Singapore Gastric Cancer Consortium and DxD, together with researchers and clinicians from the National University Hospital (NUH) and TTSH, created the world's first microRNA-based blood test for early detection of gastric cancer. The test comprises several selected miRNA biomarkers associated with gastric cancer and was approved for use in conjunction with gastroscopy during clinical use. MiRXES also took the lead in mass-production of Fortitude diagnostic kits to control the COVID-19 outbreak to meet both local and global demand.[22] We can see how the extensive collaboration between different stakeholders in the relevant fields brings research to deployment.

From screening to diagnosis, there is a trend towards non-invasive imaging to reduce the patient's risk of procedural complications which could result in adverse health outcomes. Non-invasive medical imaging technologies such as

[18] Chong, Huey Yi, Pascale A. Allotey, and Nathorn Chaiyakunapruk. "Current landscape of personalized medicine adoption and implementation in Southeast Asia." BMC medical genomics 11.1 (2018): 94.

[19] "Medical Technology." A*STAR HQ Corporate Website, www.a-star.edu.sg/Collaborate/industry-sectors/medical-technology.

[20] Edb.gov.sg, www.edb.gov.sg/en/our-industries/medical-technology.html.

[21] *Ibid*.

[22] "Practical Use of MicroRNA and RNA for Early Disease Detection." Mirxes, 16 May 2020, mirxes.com/for-physicians/.

ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) remain popular among the clinical field with their ability to provide high-resolution images of tissues and organs. The use of contrast dyes, hybrid imaging and molecular probes could push the potential of current imaging techniques to greater heights.[23] In Singapore, the National Heart Centre introduced Cardiovascular Magnetic Resonance (CMR) to assess the heart's structure and function non-invasively.[24] CMR utilises a strong magnetic field and radiofrequency pulses to produce high-resolution images of the cardiovascular system within a reasonable time frame. This method omits the use of ionising radiation and possesses low test risk to the patient. It is a known challenge to assess the right ventricle due to its complex shape and the ability of CMR to provide complete coverage of the heart without geometric assumption makes it an ideal benchmark to evaluate the right ventricle. The superior resolution and the ability to isolate the right ventricle from surrounding tissues surpassed conventional echocardiography. Moreover, CMR is highly accurate and reproducible, making it crucial for serial assessment in patients to monitor disease progression and response to treatment.[25]

HOW WILL BIOMEDICAL SCIENCES CONTINUE TO DEVELOP?

The R&D field in Singapore can be considered to be in the youthful stage as compared to countries with a long research history such as the United States of America and the United Kingdom. This is why Singapore must constantly improve our system to develop new technologies to boost our advancements. Innovation has proven to bring both economic and health impacts on the society and region. As science continues to progress, R&D in Singapore will shift towards promising areas of investment and healthcare.

Singapore is starting to look into the diversification of her research portfolio as she moves beyond traditional biomedical research. Singapore now ventures into research that studies the developmental origins of health and diseases. This gave rise to the local "Growing Up in Singapore Towards Healthy Outcomes" GUSTO study, a collaborative cohort study between KK Women's and Children's Hospital,

[23] Barsanti C. Diagnostic and prognostic utility of non-invasive imaging in diabetes management. World J Diabetes. Published online 2015. doi:10.4239/wjd.v6.i6.792

[24] Cardiovascular Magnetic Resonance: Improving Cardiac Visualisation and Assessment." SingHealth. Available at: www.singhealth.com.sg/news/medical-news/cardiovascular-magnetic-resonance-improving-cardiac-visualisation-and-assessment.

[25] Tan, R. S., and K. K. W. Chen. "Coronary artery disease: comprehensive evaluation by cardiovascular magnetic resonance imaging." ANNALS-ACADEMY OF MEDICINE SINGAPORE 33.4 (2004): 437-443.

National University of Singapore, National University Health System and Singapore Institute for Clinical Sciences, A*STAR, which investigates mothers and children cohort in Asia with over 100 investigators involved.[26] The aim of the study is to assess how different factors operating during early development affect metabolic pathways and body compositions. Somatic growth and metabolic health were assessed in relation to neurocognitive and emotional development. Molecular and epigenetic analyses were conducted to identify possible allergic disorders and other potential influences.[27] The influence of various conditions during pregnancy and early childhood on the health and development of both mother and child were assessed. Longitudinal observations were conducted to track the diet, emotions and development of the family members.

The eating habits of children were found to influence susceptibility to non-communicable diseases such as obesity.[28] Conditions during pregnancy can bring about pregnancy complications that affect both mother and child. Mothers who suffer from Gestational Diabetes Mellitus (GDM) during pregnancy have an increased risk of post-natal type 2 diabetes and the child would have an increased risk of developing metabolic conditions in the future.[29] These findings unveiled another dimension of biomedical research and serve as means to inform clinical studies aimed at neurodevelopment in children, children's capacity to perform in school and to reduce the rates of non-communicable diseases in children. Results from the studies form the foundation for interventions that aim to improve mothers' health and diet due to their prospective influence on the health of the child. The GUSTO study had pushed for authorities such as the United Nations to focus on the developmental dimension to prevent and control non-communicable diseases in people.[30] It is paramount for us to gather data and seek improvement in current policies or to formulate policies to assist and benefit future generations. There is maturity in how biomedical sciences in Singapore is evolving to impact the lives of our residents.

[26] Agency for Science, Technology and Research, and JTC Corporation. The Biopolis Story: Commemorating Ten Years of Excellence. A*Star and JTC Corporation, Singapore, 2013, p. 28.

[27] Soh, Shu-E, Mya Thway Tint, Gluckman, P., Godfrey, K., Rifkin-Graboi, A. et al. "Cohort profile: Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study." International journal of epidemiology 43.5 (2014): 1401-1409.

[28] Fogel, A., Goh, AT., Fries, L., Sadananthan, S., Velan, S. et al. "Faster eating rates are associated with higher energy intakes during an ad libitum meal, higher BMI and greater adiposity among 4·5-year-old children: Results from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort." British Journal of Nutrition 117.7 (2017): 1042-1051.

[29] De Seymour, Jamie., Chia, A., Colega, M., Jones, B., McKenzie, E. et al. "Maternal dietary patterns and gestational diabetes mellitus in a multi-ethnic Asian cohort: the GUSTO study." Nutrients 8.9 (2016): 574.

[30] Agency for Science, Technology and Research, and JTC Corporation. The Biopolis Story: Commemorating Ten Years of Excellence. A*Star and JTC Corporation, Singapore, 2013, p. 28.

Moving forward, the future of BMS research lies in the people we have. Considering the small population of the country, it is necessary for us to devise a comprehensive approach to develop and draw in experts from around the world to complement our local talent pool. Two of our comprehensive public universities, the National University of Singapore (NUS) and Nanyang Technological University (NTU), were transformed into first-rate, research-intensive institutions that consistently climb the world rankings amid the progressively competitive academic landscape.[31] Having a top-notch higher education system is a means for us to attract and train both local and overseas academic talents. Passion fuels the continual drive to discover. Prospectively, we need to instill the passion for science in the society and our younger generation to develop our local pool. Efforts can be seen through community engagement in educational institutions such as the Science Centre Singapore to showcase how science has benefited society. Besides stimulating young minds through improved science education in schools, we need to open up more opportunities for progression in the research fields for the growth of the research talent pool. Scholarships and scientific training have been offered to support promising individuals in their pursuit of science.

While the society embraces new dimensions of research, we need to understand the deployment process of new technology. Everything starts with the knowledge and discoveries in the laboratories. These spark the downstream process towards the creation of products such as test kits or treatment methods which will ultimately benefit the public and subsequently mankind. This process will require an entire ecosystem involving different players and stakeholders. To move downstream from researchers in research institutes, we need engineers and entrepreneurs to manufacture and distribute the product for public access to the new technology. This explains the trend towards multi-disciplinary specialisation such as science together with business or engineering, so as to push future scientific initiatives forward. The close-knit collaboration between the different disciplines is essential as they cross-fertilise each other and balance the portfolio.

IMPORTANCE OF ETHICS DEVELOPING ALONGSIDE WITH SCIENCES

As science continues to advance, bioethics and guidelines will play their role to ensure the legitimacy of research. Ethics is the fabric which safeguards research conducted in Singapore, ensuring that public investment is accounted

[31] Poh, L. C. "From research to innovation to enterprise: The case of Singapore." Cornell University, INSEAD, and WIPO, The Global Innovation Index (2016): 133-139.

for and utilised in a purposeful manner to uphold the international R&D standard in Singapore. The importance of ethics is more than just restraining research practices, it guides research towards curing diseases and alleviating the suffering of mankind.[32] Ethical guidelines serve as a protection against unethical practices or adverse incidents which will mislead the field in the wrong direction and jeopardise Singapore's reputation in research.

Ethics needs to develop alongside science. Although scientific advancements bestow mankind the ability to surpass the innate capabilities of humanity, they also raise new ethical, social and legal concerns. My thoughts on the importance of ethics developing alongside science resonate well with Professor Lee Eng Hin's and Associate Professor John Elliot's views shared a decade ago. Professor Lee highlighted that ethical direction and consistency are critical to support the legitimacy and commitment of public resources to research which involves uncertainty for the betterment of the people.[33] Professor Patrick Tan gave his insight into the need for constant updates, suggesting the need for guidelines to be revisited and revised in order to reflect the current perspectives and values of society.[34] While science and ethics continue to evolve in tandem, the fundamental principle behind the establishment of ethical guidelines remains, which is to allow for science to continue to develop and for mankind to benefit. Back then, Associate Professor Elliot accurately highlighted "that consistency of principle is maintained with a potentially very different set of actions"[35] and this holds true even after a decade and will continue to be relevant in the future.

The stand and approach adopted by the Bioethics Advisory Committee over the past 20 years have been commendable. Considering the multi-racial and religious demographics of Singapore, the committee has to reconcile different and sometimes opposing views and values on topics. With proper public education on the topic, together with consultation sessions and papers to gather their feedback and perspectives, more have realised the importance of bioethics and its role to shape the research direction in Singapore.

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[32] Michael, Elliott John, Lim Sylvia SN, and Ho Calvin Wai-loon, eds. Bioethics in Singapore: the ethical microcosm. World Scientific, 2010, pp. 4-5.

[33] Michael, Elliott John, Lim Sylvia SN, and Ho Calvin Wai-loon, eds. Bioethics in Singapore: the ethical microcosm. World Scientific, 2010, p. 5.

[34] Michael, Elliott John, Lim Sylvia SN, and Ho Calvin Wai-loon, eds. Bioethics in Singapore: the ethical microcosm. World Scientific, 2010, p. 4.

[35] Michael, Elliott John, Lim Sylvia SN, and Ho Calvin Wai-loon, eds. *Bioethics in Singapore: the ethical microcosm*. World Scientific, 2010, p. 236.

CONCLUSION

Singapore is a global R&D hub, spearheading biomedical research and healthcare services. With the valuable potential of biomedical sciences to advance healthcare services and Singapore's economy, there is a positive outlook for disease treatment. R&D displayed its importance where it not only creates investment for the country, it also ensures that the country is able to respond under crisis. While we celebrate the advances in research, technology and healthcare services, we need to account for the ethical concerns which arise to allow consistency between the advancements and the values of society to receive international acceptance. BMS has advanced tremendously over the past two decades and it holds tremendous potential in the future and time to come. Singapore has just started on this scientific journey and the end is yet to be near.

4

Public Health Ethics: Ethics for Just Society and Health

Huso Yi

DEFINITION AND HISTORY

Public health ethics is a body of knowledge that defines, defends, and recommends the moral principles and practices applied in public health policy, research and practices. It focuses on ethical issues, challenges, and considerations in the implementation of policies concerning the health of the public rather than individuals.[1] [2] Public health ethics has its own history and evolution distinctive from biomedical ethics – the latter was developed in response to unethical medical experiments, clinical trials of human subjects without proper informed consent, and medical treatments which pose ethical dilemmas (e.g. withdrawing or withholding treatment and refusal of offering or receiving treatment). [3] [4] [5] [6] In particular, the recent advances of biomedical technology have made a significant impact on biomedical ethics by reconfiguring fundamental questions about human being, medicalisation, well-being, disability, suffering, enhancement, conception, and death.[7] [8]

Since the mid-20th century, the world has experienced changes in demographics (e.g. ageing population with multiple chronic conditions), poverty, food security, biosecurity, migration, forced displacement, outbreaks of emergent infectious diseases, pandemics, and increasing nature- and human-made disasters due to climate change and political conflicts. All these global changes require the critical re-examination of the traditional boundary of individual autonomy-

[1] Mastroianni A, Kahn JP, Kass NE. The oxford handbook of public health ethics. Oxford: Oxford University Press, 2019.
[2] Bayer R, Bruce J, Gostin LO, Jennings B, et al, eds. Public health ethics: theory, policy, and practice. New York, NY: Oxford University Press, 2006.
[3] Mastroianni A, Kahn JP, Kass NE. The oxford handbook of public health ethics.
[4] Bayer R, Bruce J, Gostin LO, Jennings B, et al, eds. Public health ethics: theory, policy, and practice.
[5] Gostin LO, ed. Public health law and ethics. Berkeley: University of California Press, 2010.
[6] Beauchamp T, Childress J. Principles of biomedical ethics, 7th Edition. New York: Oxford University Press, 2013.
[7] Campbell AV. The body in bioethics. New York, NY: Routledge-Cavendish, 2009.
[8] Parker M. Ethical problems and genetics practice. Cambridge: Cambridge University Press, 2012.

based biomedical ethics and its implications (e.g. informed consent), which are often found to be conflicting or even contrasting with the public 'good'.[9] [10] Public health has also been influenced by social-cultural movements around the world for human rights and social justice, such as feminism, civil rights, sexual rights, disability rights, one health, and global justice.[11] [12] [13]

Public health ethics has been developed to encompass a broad range of societal responses to public health problems and health equity caused by inequalities of resources, welfare, and capabilities.[14] It aims to understand the roles and responsibilities of individuals, communities, private industries, and public institutions for the health of the public.[15] Thus, there are values at stake in the decision-making process of public health measures, including individual liberty, privacy, security, diversity, equity, proportionality, solidarity, and fairness.[16] Our pluralistic society inevitably raises a key moral question – what is 'just' public health? Public health ethics needs to answer to it.

THEORETICAL FOUNDATIONS

Theories and principles are necessary as a ground for the justification of public health actions. Public health ethics are often centred on utilitarian accounts of 'the greatest good for the greatest number'.[17] Utilitarianism appears to best represent the goal of public health as it holds that policies and actions are morally justified if they best promote the health of the public as a whole. The theory justifies undermining individual liberty to maximise the public good.[18] In response to public health urgencies, such as an infectious disease outbreak, restriction of individual liberty to protect the public can be justified. Precautionary measures of isolation, quarantine and lockdown during the outbreak are necessary to protect the larger population. Such restrictive measures do not go against liberalism in terms of the 'harm principle', which holds that interventions, involving coercion,

[9] Mastroianni A, Kahn JP, Kass NE. The oxford handbook of public health ethics..
[10] Peckham S, Hann A. Public health ethics and practice. Bristol: Policy Press, 2009.
[11] Mastroianni A, Kahn JP, Kass NE. The oxford handbook of public health ethics.
[12] Mann JM, Gruskin S, Grodin MA, Annas GJ. Health and human rights. New York: Routledge, 1999.
[13] Benatar S, Brock G, eds. Global health and global health ethics. Cambridge: Cambridge University Press, 2011.
[14] Eyal N, Hurst SA, Horheim OF, Wilker D. Inequalities in health: concepts, measures, and ethics. Oxford: Oxford University Press, 2013.
[15] Gostin LO, ed. Public health law and ethics. Berkeley: University of California Press, 2010.
[16] Anand S, Peter F, Sen A. Public health, ethics, and equity. Oxford: Oxford University Press, 2004.
[17] Mill JS. Utilitarianism, 1861. R Crisp, ed. Oxford: Oxford University Press, 1988.
[18] Gostin LO, ed. Public health law and ethics. Berkeley: University of California Press, 2010.

or otherwise putting constraints on individuals' freedom, can be justified only if these are necessary to prevent harm to others.[19] [20]

Public health policy is designed to benefit everyone, even those who do not contribute. The policy will be undermined if many people choose not to comply. This may be a reason to implement some form of coercion. Even John Stuart Mill, a liberalism philosopher, acknowledges that coercion is permissible to ascertain that people do "their fair share" in the protection for all.[21] There is a moral basis for coercive measures that aim to prevent harms to others in public health ethics. Importantly, the harm principle provides not only a justification for setting constraints to liberty but also a valid reason for coercion.

This stance of public health justifies paternalism – which is considered to be wrong in clinical ethics – and precautionary measures in a public health crisis.[22] As such, the government plays an essential role in the application of public health ethics. In other words, it has moral obligations to protect citizens from preventable diseases by mandating policies and behaviours that can restrict individual liberty.[23] For example, during the course of infectious disease control, public health actions, such as surveillance, extensive contact-tracing, quarantine, isolation, confinement, travel ban, and lockdown, could create a tension with the values of individual liberty and prioritisation (e.g. resource reallocation). Legal implications such as the criminalisation of risk behaviours and/or noncompliance, must be accompanied with appropriate justification.[24]

Although moral conflicts between public good and individual liberty are often focused on public health actions, they should not be seen as the fundamental problem of public health ethics. Presenting the conflict as the central problem may pose a risk that any public health programmes that interfere with individual liberty, even a paternalistic policy with voluntary participation (e.g. childhood vaccination), is assumed to be *prima facie* wrong, and morally problematic.[25] Emphasis on the conflicts may lead to the overlooking of various values at stake in public health, such as equity, privacy, solidarity, transparency, social justice and overall well-being. The utilitarian approach in public health does not exclude any disadvantaged groups in a population. Rather, it acknowledges health disparity

[19] *Ibid*.
[20] Nuffield Council on Bioethics. 2007. Public health: ethical issues. London: Nuffield Council.
[21] Mill JS. On liberty. London: Longman, Roberts & Green, 1859.
[22] Gostin LO, ed. Public health law and ethics. Berkeley: University of California Press, 2010.
[23] *Ibid*.
[24] *Ibid*.
[25] Nuffield Council on Bioethics. 2007. Public health: ethical issues. London: Nuffield Council.

and attempts to address egalitarian concerns. Some forms of consequentialism explicitly seek to promote the values of equality besides utility.[26] These values raise a wide range of practical moral problems, which are central to public health ethics – what disadvantages and inequalities are unjust and on what grounds.[27]

There is an egalitarian concern in public health.[28] With distributive justice, public health ethics develops normative accounts of the role of the government in promoting public health, beyond preventing harm to others.[29] It includes the state obligations to protect groups who are particularly vulnerable to health-related adversities. Initially, theories of justice in health focused on equal access to healthcare in response to fundamental human rights to health (not rights of health). However, there has been accumulating empirical evidence that social-economic conditions have more impact on health status than equal access to healthcare.[30]

The magnitude and pervasiveness of health inequalities emphasise the importance of promoting just distributions of wealth, healthcare resources, and access to education.[31] The relationships between income and health are complex (not necessarily causal, as not all poor people have poor health), but it is reasonable to assume that any health inequalities caused by unjust societal and structural factors are themselves unjust.[32] If we accept the poor health status of disadvantaged populations to be unjust, there are strong reasons for public health to promote the health of populations which are disadvantaged, and therefore at-risk for poor health.[33] This requires prioritisation of resources for targeted health needs and possibly even coercive interventions.

Egalitarian accounts also focus on equality of welfare. In a just society, everyone is ensured a sufficient level of well-being, which includes a sufficient level of health. In this aspect, social justice is a basic moral foundation for public health. However, the definition of a "sufficient" level of health is highly contested and an ongoing debate in public health ethics.[34] Another egalitarian

[26] Anand S, Peter F, Sen A. Public health, ethics, and equity. Oxford: Oxford University Press, 2004.
[27] Venkatapuram S. Health justice. Cambridge: Polity Press, 2011.
[28] Eyal N, Hurst SA, Horheim OF, Wilker D. Inequalities in health: concepts, measures, and ethics. Oxford: Oxford University Press, 2013.
[29] Rawls J. A theory of justice. Cambridge, MA: Harvard University Press, 1971.
[30] Daniels N, Kennedy B, Kawachi I. Is inequality bad for our health? Boston: Beacon Press, 2000.
[31] Rawls J. A theory of justice. Cambridge, MA: Harvard University Press, 1971.
[32] Venkatapuram S. Health justice. Cambridge: Polity Press, 2011.
[33] Eyal N, Hurst SA, Horheim OF, Wilker D. Inequalities in health: concepts, measures, and ethics. Oxford: Oxford University Press, 2013.
[34] Fourie C, Rid A. eds. What is enough?: sufficiency, justice and health. Oxford: Oxford University Press, 2016.

account of equality of capabilities was developed by Amartya Sen, centred on human development and focused on the notion of human flourishing and health.[35] Thus, the moral imperative of public health policies should address the equality of capabilities rather than equality of resources and/or welfare.[36] Equality of capabilities emphasises respect and self-determination, which is coherent with the central tenets of the theory of human rights.[37] While the state promotes the capabilities of individuals, they have the responsibilities toward one another to contribute to this common good. This embodies communal solidarity by emphasising a substantial role for the community in all of our lives. In this manner, public health represents a common good – health of the public as social justice.

PRINCIPLES

Public health ethics, compared to biomedical ethics, has different principles as public health policies and practices are directed to populations, communities, and broader social-environmental context rather than individuals. Public health actions are preventive in nature with the primary goal to reduce the risks associated with diseases – 'better to prevent than to cure'.[38] Increasing life expectancy and quality of life are not only results from better treatment of patients, but also made possible by the improvement of living conditions (e.g. housing, sewerage systems, food security, and urban infrastructure). Public health considers social, political, and cultural contexts and recognises the existence of competing values and perspectives.[39] [40] Thus, direct application of medical ethics principles – autonomy, beneficence, non-maleficence, and justice – would be problematic. Several principles have been proposed. It is important to note that these principles should not be regarded as definitive but rather heuristic.

Efficiency. It is evident that public health (and healthcare) systems lack resources – as there are more health needs than resources available to deal with them. Using scarce health resources efficiently, locally and globally is a moral duty.[41] Efficiency in resource use will produce more health benefits for a greater number of people. The principle of efficiency demands evidence-based policy, often based on cost-benefit analysis. However, the concepts of 'cost' and 'benefits'

[35] Sen A. Development as freedom. New York: Anchor Books, 1999.
[36] Venkatapuram S. Health justice. Cambridge: Polity Press, 2011.
[37] Sen A. Human rights and capabilities. Journal of Human Development, 2005;6(2): 151–166.
[38] Borysiewicz LK. Prevention is better than cure. Lancet. 2010;375(9713):513-523
[39] Mastroianni A, Kahn JP, Kass NE. The oxford handbook of public health ethics.
[40] Gostin LO, ed. Public health law and ethics. Berkeley: University of California Press, 2010.
[41] Benatar S, Brock G, eds. Global health and global health ethics. Cambridge: Cambridge University Press, 2011.

are complex matters. They are value-dependent, and the boundary of costs for health is not clear due to the underlying social causes of health. 'Cost' efficiency should not be solely used to justify any or little action in public health.[42] Thus, the principle of efficiency has moral applicability, which needs to be disentangled from other considerations of economic efficiency.

Solidarity. The public in public health is a collective agency to achieve its goal. Individuals in a society influence the health of others; therefore, they have shared responsibilities towards the common good and health of the belonged community and society.[43] In practice, public health interventions are naturally joint enterprises, set up and carried out by societal institutions. While it is inevitable for the government to play a central role, public health programmes require proactive public participation to be successful.[44] They have to comply with hygiene recommendations, get vaccinations, choose healthy meals, etc. Even small changes in behaviour across the population may have large effects on preventing morbidity and mortality. This principle of solidarity is one of the most contested concepts in terms of which goals should and can be considered as a common good in public health, how individual members of society should and can contribute to the common good, and to what extent solidarity provides sufficient basis to justify particular public health measures (e.g. lockdown or movement restriction during the infectious disease outbreak).[45]

Transparency. This principle refers to procedural justice, where decisions are made. Transparency is the foundation of solidarity. First, when a decision regarding a public health action needs to be made, all the stakeholders should be involved with equal input of deliberations. In particular, if the action requires strong restrictions or potential harms, the engagement of the public community is essential. Second, the procedure of decision-making should be as clear and accountable as possible. Third, the decision-making should not be influenced by political interference and any coercive manners by stakeholders.

Reciprocity. Once public health action is warranted, there is an obligation on social entities such as public health institutions to assist the individual (or community) in the discharge of their duties.[46] Complying with public health

[42] Eyal N, Hurst SA, Horheim OF, Wilker D. Inequalities in health: concepts, measures, and ethics. Oxford: Oxford University Press, 2013.

[43] Nuffield Council on Bioethics. 2007. Public health: ethical issues. London: Nuffield Council.

[44] Gostin LO, ed. Public health law and ethics. Berkeley: University of California Press, 2010.

[45] Anand S, Peter F, Sen A. Public health, ethics, and equity. Oxford: Oxford University Press, 2004.

[46] Nuffield Council on Bioethics. 2007. Public health: ethical issues. London: Nuffield Council.

restrictive measures may impose burdens on individuals in many aspects. The principle of reciprocity holds that the government should be prepared to compensate individuals for their 'sacrifices' in complying with restrictions.

Proportionality (Least Restrictive Means). The principle of proportionality refers to striking the balance between under- and over- regulation. The degree of infringement and restrictions on individual rights, liberty or autonomy, should be proportional to the degree of expected benefits from public health interventions.[47] This principle has become one of the most influential public health ethics policy against public health threats. For example, mass quarantine as a form of confinement, lockdown or mandatory vaccination to control the spread of infectious disease are only justified by the public health benefits from their enforcement, and other methods with less restrictive measures are not known to be effective.[48] More coercive measures should be employed only when less coercive measures have failed to (or are not found to) bring about the expected outcomes. In practice, the justification of proportionality should be able to resolve potential and actual conflicts between individual liberty and public health goal.[49] Balancing individual/private and public interests raises central questions of public health ethics in terms of individual roles and responsibilities in public health and the government's accountability. Voluntary action through education precedes prohibition or criminalisation. If restrictions are made, they should be legitimate and non-discriminatory.[50]

Social Justice. The human being should have equal moral worth. The principle demands equal access to healthcare, as well as a fair distribution of quality health resources and health outcomes. Health equity is thus, a matter of fairness and justice.[51] Social justice is also the principle that covers normative aspects often discussed in solidarity and reciprocity. Public health also takes distributive justice into consideration, and it develops an account of the role of the state and public health agencies that go beyond prevention, but also includes obligations to protect populations and communities that are especially vulnerable to disease due to their disadvantaged status. Health inequalities caused by unjust social causes are themselves unjust.[52] Thus, social justice is a moral foundation for public health, and actualisation of social justice should be part of public health policies and practices.

[47] *Ibid*.
[48] Peckham S, Hann A. Public health ethics and practice. Bristol: Policy Press, 2009.
[49] Gostin LO, ed. Public health law and ethics. Berkeley: University of California Press, 2010.
[50] *Ibid*.
[51] Anand S, Peter F, Sen A. Public health, ethics, and equity. Oxford: Oxford University Press, 2004.
[52] Daniels N. Just health: meeting health needs fairly. Cambridge: Cambridge University Press, 2008.

For example, amidst the COVID-19 pandemic across the world, there has been global calls to not neglect vulnerable segments of society, such as migrant and refugee populations.[53] In Singapore's context, more must be done to reduce the health inequity in migrant workers.[54] Excluding migrant workers from the healthcare infrastructure would ultimately cause them to be more susceptible to COVID-19. The impact of public health crises would be distinct and will hit disadvantaged groups the hardest. The exclusion would go against one of the goals in the UN 2030 Agenda for Sustainable Development – "Leave no one behind".[55]

CONCLUSION

Public health professionals increasingly face difficulty making the 'right' decision in the design and implementation of health policies and practices as our society becomes more diverse and pluralistic with increasing health risks of emergent infectious and non-communicable diseases. Widening social-economic inequality has caused health disparity and inequity and its consequent unfairness more than ever before. Public health is a moral imperative to protect humanity. Public health ethics is a reflective and engaging task of normative inquiry of health as public good and human rights.

[53] The Lancet. (2020). COVID-19 will not leave behind refugees and migrants. The Lancet, 395(10230), 1090. https://doi.org/10.1016/S0140-6736(20)30758-3

[54] Yi H, Ng ST, Farwin A, Low PTA, Chang CM, Lim J. Health equity considerations in COVID-19: geospatial network analysis of the COVID-19 outbreak in the migrant population in Singapore. Journal of Travel Medicine. 2020: 159.

[55] Orcutt M, Spiegel P, Kumar B, Abubakar I, Clark J, Horton R. Lancet Migration: global collaboration to advance migration health. Lancet 2020; 395: 317–19.

5

The Status of Medical Ethics in Singapore

Roy Joseph

INTRODUCTION

Medical ethics is about the "shoulds", "oughts" and "musts" of life, as well as the moral principles by which decisions are made by physicians. In turn, medical ethics shapes the principles and practice of medicine. From a practical perspective, ethical medical practice respects all 4 of the following principles – Respect for Autonomy, Beneficence, Non-maleficence and Justice.[1] Current and past pandemics have highlighted additional ethical values and principles like Common Good (Utility/Efficiency), Equity, Solidarity, Reciprocity, Accountability, Transparency and Good Governance that are applied during public health crises.[2] [3] Medical ethics is thus described more comprehensively as, "the analytical activity in which the concepts, assumptions, beliefs, attitudes, emotions, reasons and arguments underlying medico-moral decision making are examined critically".[4] It follows that it is not an exact science.

The importance of medical ethics and its central position in Western medical practice is the continuing and central importance of the principles in the Hippocratic Oath (500-300 B.C.). The core principles in the Hippocratic Oath have been articulated and expanded upon by the medical profession e.g. Percival's Medical Ethics (1803) from the Royal Infirmary of Manchester, the American Medical Association Code of Medical Ethics (1847), the World Medical Association's dual Declarations – Geneva (1948) and Helsinki (1964), American College of Physicians Ethics manual (1984) and the British General Medical Council's Good Medical Practice (1995). Most countries now have their own versions of medical practice codes and guidelines.

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[1] Beauchamp TL and Childress JF. Principles of Biomedical Ethics, New York, Oxford University Press, 2019 (8th edition).

[2] Esther ST Ng, Paul Ananth Tambyah. The ethics of responding to a novel pandemic. Annals Acad Med Singapore. 2011; 40:30-5.

[3] WHO guidelines on ethical issues in public health surveillance. Geneva: World Health Organization; 2017 Licence: CC BY-NC-SA 3.0 IGO.

[4] Gillon R. Philosophical Medical Ethics, London, Wiley 1997.

THE THREE PILLARS

Singapore has placed a similar emphasis on medical ethics. Education, Regulation and Health Policy are the three pillars on which a commitment to ethical medical practice is grounded and developed as evident from its historical development. The steady strengthening and evolution of each of these pillars are indicators of a healthy status of medical ethics.

Education – Medical Students

In Singapore, doctors receive education in medical ethics as part of their undergraduate and postgraduate curricula, their professional working environment, continuing professional development activities, and finally, life-long self-directed learning. This education facilitates regular effective application, reflection, and internalisation, thus equipping doctors to conduct themselves in a manner that is professional and ethical.

The first medical school in Singapore began in 1905 through a societal initiative. It used to be called the Straits and Federated Malay States Government Medical School.[5] [6] It has since undergone numerous but significant name changes: These being in 1921 – King Edward VII College of Medicine, in 1949 – Faculty of Medicine, University of Malaya, in 1962 – Faculty of Medicine, University of Singapore and in 2005 – Yong Loo Lin School of Medicine, National University of Singapore.

The 1960s brought the onset of nationhood and rapid development of health services. This was accompanied by complex ethical issues created by the very same developments. The associated strains on doctors and the system inevitably led to a distinct increase in the number of complaints and disciplinary proceedings against doctors. Passive mentoring alone was no longer an adequate form of preparation of the medical student for the ever-changing practice. There was a pressing need for a firm theoretical grounding in the understanding and application of medical ethics.

Until the mid-1970s, the undergraduate medical curriculum did not include a section on medical ethics. Ethical learning took place through the 'Hidden Curriculum', namely the day to day interaction with clinician teachers and the

[5] Yahya Cohen. Association, Profession, Adaptation. SMJ, 1971; 12: 121-126.
[6] Lee YK. The founding of the medical school in Singapore (part 1). SMJ, 1980;21:544- 555.

observation of their conduct. Many generations of medical students accomplished the aspiration of ethical medical practice through this method of learning. This was possible because they accepted ethical medical practice as a philosophy for their life. The late Dr. Chen Su Lan, from the first batch of medical students, is a well-known example. The current doctors who teach and model medical ethics in Singapore are the products of this "first-generation" medical curriculum. The adequacy or otherwise of this curriculum could be revealed by studying the ethical practices of senior medical practitioners in Singapore.

Through editorials and speeches, doctors in practice began to describe new ethical issues and advocated for the addition of medical ethics to the existing undergraduate curriculum.[7] [8] [9] In the seventies, the Faculty of Medicine responded by introducing ethics and professionalism through a series of lectures in the final year of the curricula.[10]

From this beginning, the exposure increased in 1995.[11] There were 2 Core lectures on Ethics during the Year 3 Medicine posting. In Year 4, formal teaching of Ethics was undertaken in the departments of Community and Family Medicine, Obstetrics & Gynaecology and Pathology (Forensic Medicine). Topics included ethical and legal aspects of medical practice, genetic diseases, genetic manipulation, abortion, assisted pregnancy, surrogacy, obstetric litigation, medical examination, medical errors, professional negligence, and professional secrecy.

In 2000, the next phase of curriculum review yielded the Physician Development Programme, which blurred the traditional divide between the Pre-Clinical and the Clinical Years through early exposure to patients in Year 1. This showed Medicine as a whole, including the nature of the Doctor-Patient relationship, the inter-professional skills needed in addition to the application of the Basic Sciences.[12]

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[7] Gwee AL. The changing state of medical ethics. Editorial. SMJ Vol, No 1 Mar 1960.

[8] Gwee AL. New Problems in Ethics. Editorial. SMJ Vol2, No 2, June 1961.

[9] Lim Siew Meng. Medical Ethics and the Singapore Medical Association. In Medical Ethics in Singapore, Ed Tan Joo Liang, Singapore Medical Association, 1969.

[10] Wong Heck Seng. Address by the president to final year medical students. The Publication of the College of General Practitioners, Vol 1, No 2, Nov 73 pg 32-34.

[11] Revised Medical Curriculum Core Content. Faculty of Medicine, NUS, Singapore, 1995. NUS. [LG 399 NUSFM].

[12] Ref New Medical Undergraduate Curriculum for Year 1 – Handbook for Students. NUS 2000 [LG 399 NUSFM.N].

Duke-NUS Medical School (Duke-NUS)

Duke-NUS is the first US-style graduate-entry medical school in Singapore. It was established in 2005 through a partnership between Duke University and the National University of Singapore, under the Biomedical Sciences Initiative launched in the year 2000. Duke-NUS students and graduates are to adhere to the Duke-NUS Honour Code. The Duke-NUS Honour Code outlines "the standards of intellectual honesty, integrity, responsibility and professionalism expected from students of Duke-NUS".[13] It is meant to "ensure the highest conduct and behavior of Duke-NUS students and graduates and to ensure the safety of patients".[14]

In 2006, the NUS Centre for Biomedical Ethics (CBmE) at the Yong Loo Lin School of Medicine was established under the leadership of the inaugural Chen Su Lan Centennial Professor of Ethics, Professor Alastair Campbell. Soon after, in 2008, a substantially revised undergraduate curriculum in Health ethics, Law and Professionalism was introduced. Designed as a longitudinal tract that spans across all 5 years to enable spiralled and continual learning, the curriculum was structured to facilitate reflective practice and integrated learning, and to support medical students' professional identity formation. Core elements of the Health ethics, Law and Professionalism curriculum include knowledge of ethical, professional, and legal foundations of clinicians' duties to patients, families, interprofessional colleagues, and other stakeholders.[15]

The curriculum which has served the students well, is now being conceptually refined through a closer alignment with competencies being developed in conjunction with the Ministry of Health (MOH). Other key areas of refinement include integrating academic learning with the clinical learning of the science of medicine and establishing more opportunities for the individual student to practise ethical reasoning.

In addition, the Lee Kong Chian School of Medicine (LKCMedicine) was established in 2013, through a partnership between Nanyang Technological University, Singapore and Imperial College London. LKCMedicine has developed the Good Research Practice framework. Good Research Practice outlines the school's commitment to "research excellence, and in particular, to

[13] Duke-NUS Honour Code, Duke-NUS Medical School. Available at https://www.duke-nus.edu.sg/docs/default-source/default-document-library/duke-nus-honour-code.pdf?sfvrsn=e5f5b7ed_4

[14] *Ibid.*

[15] Chin JJ, Voo TC, Karim SA, Chan YH, Campbell AV. Evaluating the effects of an integrated medical ethics curriculum on first-year students. Ann Acad Med Singapore. 2011;40 :4-18.

the highest standards of ethics and integrity in all its clinical and non-clinical research endeavours".[16]

Education - Post-graduate and Professional

Until the 1950s, the majority of publicly reported ethical issues arose from the 4A's – Alcoholism, Adultery, Addictions and Advertisements.[17] It was becoming obvious that doctors in practice also needed continuing education and guidance to maintain an ethical practice in the face of new clinical situations e.g. reproductive rights, futility of interventions, the introduction of technology in medical interventions, and the commercialisation of medical practice.

The Academy of Medicine Singapore

The Academy of Medicine Singapore was formed in 1957, as the outcome of steady medical progress in medical education as well as a stimulus to further professional endeavours.[18] It was patterned on the Royal Colleges in Britain and Australia, its first Master was Professor of Medicine, Sir Gordon Arthur Ransome and it serves as the corporate body for all medical specialists. At the same time, a Committee of Post-graduate Medical Education was formed and charged with the maintenance of the highest standards of professional and ethical practice through teaching, instructing, and training those who wish to learn and specialise. This led to the establishment of the School of Post Graduate Medical Studies in 1969 and in 1970, the institution of higher professional medical examinations leading to the degree of Master of Medicine (MMed) in Internal Medicine, Paediatric, Surgery and Obstetrics and Gynaecology. To establish high and stringent standards of specialist practice, the Academy established the Roll of Specialists in 1980.

Ethical medical practice requires sound medical judgment. In the next phase of improving medical judgments, postgraduate examinations in Anaesthesiology, Diagnostic Radiology, Emergency Medicine, Family Medicine, Occupational Medicine, Ophthalmology, Otolaryngology, Psychiatric Medicine and Public Health were established. This was followed in 1991 by the establishment of a Joint Committee for Advanced Specialist Training with representations from the Academy, the Division of Graduate Medical Studies and the MOH with

[16] James, B. Good Research Practice, Lee Kong Chian School of Medicine. Available at: http://www.lkcmedicine.ntu.edu.sg/Research/Pages/Good-Research-Practice.aspx

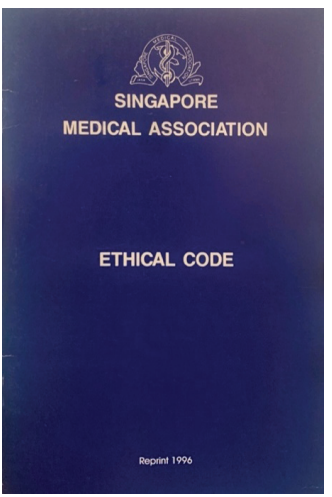
[17] Gwee Ah Leng. Ethical Problems encountered in Singapore and Malaysia. In Medical Ethics in Singapore 1969. Ed Tan Joo Leng. Singapore Medical Association, 1969.

[18] Chin Hin Chew and Pin Lim. Academy of Medicine Singapore – The first twenty-five years. Ann Acad Med Singapore 2007; 36:457-476.

the objectives of including the provision of 'Advanced Specialist' training, certification and accreditation of training posts. The Academy was given the responsibility for the training and certification in 23 sub-specialities through 'Exit Certification'. Since 1997, the training was coordinated and regulated through 35 Specialist Training Committees appointed by the Specialist Accreditation Board. The School's name was changed to the Division of Graduate Medical Studies in 2002. To ensure that all Registered Medical Practitioners (RMPs) maintain the currency of their knowledge, Continuing Medical Education was made mandatory from 2003. This was developed in 2007 into the Maintenance of Certification programme introduced by the Singapore Medical Council as an additional tier in maintaining practitioners' competency.[19] The Academy continues to specifically promote and support ethical and professional medical practice through its Colleges, Chapters, the Annual scientific meetings and through its Journal, the Annals of the Academy of Medicine, Singapore.

The Singapore Medical Association

At around the same time that the Academy was established, the Singapore Medical Association (SMA) was formed in September 1959 and initiated a multi-pronged strategy to build medical ethics as a capacity in its members.[20]

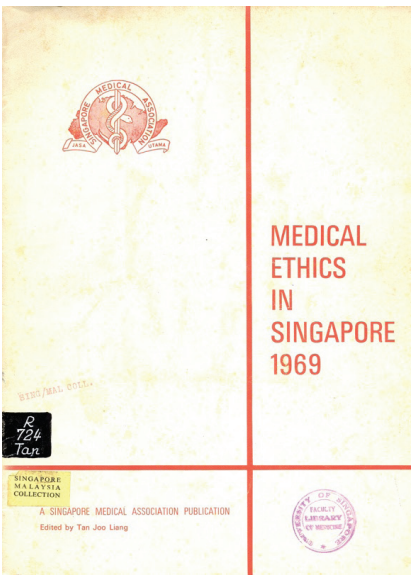


The first was the SMA Ethical Code, published in 1963. Accessible records and personal communications with senior doctors indicate that this code is the first locally published guide to ethical medical practice. A copy of this historical document appears to be unavailable. The reprint published in 1996 is available.

The second prong in the initiative was establishing an in-house advisory ethics committee to meet in a formative manner, the needs of its members. Its first Chairman was the late Dr. Lee Yong Kiat.

[19] Raj M Nambiar, Yam-Cheng Chee. Academy of Medicine, Singapore- The next twenty-five years 1982-2007. Ann Acad Med Singapore 2007:36:477-492.
[20] Gwee Ah Leng. Quo Vadis SMA? The growing SMA and realities. SMA Newsletter 1985; 16:68-69.

The third prong was the convening of an annual ethics forum. On March 28th, 1969, doctors in Singapore and the public had the opportunity to attend what would have been the first public forum on Medical Ethics.[21] During the forum, all 4 speakers (Dr. Arthur Lim, immediate Past President of the SMA, Dr. Yeoh Ghim Seng President of the Singapore Medical Council, Dr. Gwee Ah Leng, Chairman of the Ethics Committee and Mr. David Marshall, barrister) referred to the 1963 SMA Code.



The fourth prong was the publication of the "Singapore Medical Journal" which included papers in ethics and professionalism submitted by its members. These papers supplement the clinical knowledge of physicians, and thus aim to enrich medical practice and clinical research in Singapore and worldwide.

The need for this professional support and education was acknowledged as a continuous process, requiring the investment of dedicated personnel and other resources. The SMA in 2000 established the Centre for Medical Ethics and Professionalism (CMEP). The CMEP objectives were to develop resources, standards, and research along with the provision of educational, health law, mediation and conflict resolution programmes for doctors and other healthcare professionals and to develop standards for ethical medical practice and their applications. Another important objective was to promote community (public) awareness of current medical and ethical issues in healthcare. Its inaugural director was Professor T Thirumoorthy.[22] From 2006, its 2 and 1/2-day course on Medical Ethics, Professionalism and Law has become a mandatory learning activity for Advanced Specialty Trainees.

[21] Medical Ethics in Singapore, Ed Tan Joo Liang, Singapore Medical Association, 1969.
[22] Loy Ming Shi. Celebrating 15 years of SMA CMEP. SMA News. 2015; June:18-19.

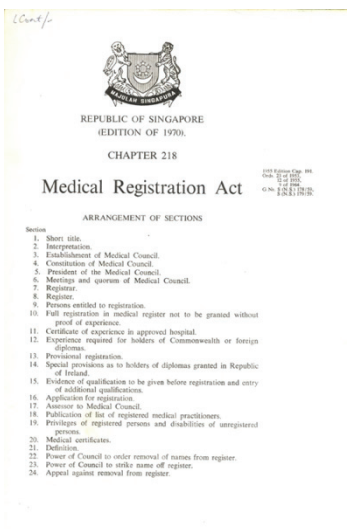
The Centre for Biomedical Ethics

The third organisation in Singapore that is building capacity among Health Professionals is the NUS CBmE.[23]

It works to develop understanding, capacity for good judgement, and sound ethical practice in the context of healthcare provision, biomedical science, and health-related policy. CBmE is responsible for the development and implementation of the Health ethics, Law and Professionalism curriculum. CBmE also has 2 initiatives with the first being CENTRES (Clinical Ethics Network + Research Ethics Support), a networking and training platform to enhance the capabilities of the nation's Clinical, Transplant and Research Ethics Committees. The second is SHAPES **(**Science, Health and Policy-relevant Ethics in Singapore). SHAPES focuses on bioethical research, promoting sound practices, providing support and ethics expertise to policymakers and engaging in ethics-related research. CBmE is also a WHO Collaborating Centre and supports the WHO's works in health ethics, law, and policy. The CBmE, through its journal, the 'Asian Bioethics Review', provides a forum to express and exchange original ideas on all aspects of bioethics, especially those relevant to the region. In 2014 and 2017, CBmE published the first and second volumes respectively of its online case book on medical ethics.[24]

Regulation of Medical Practice

The Medical Registration Act



REPUBLIC OF SINGAPORE
(EDITION OF 1970).

CHAPTER 218

Medical Registration Act

ARRANGEMENT OF SECTIONS

Section
1. Short title.
2. Interpretation.
3. Establishment of Medical Council.
4. Constitution of Medical Council.
5. President of the Medical Council.
6. Meetings and quorum of Medical Council.
7. Registrar.
8. Register.
9. Persons entitled to registration.
10. Full registration in medical register not to be granted without proof of experience.
11. Certificate of experience in approved hospital.
12. Experience required for holders of Commonwealth or foreign diplomas.
13. Provisional registration.
14. Special provisions as to holders of diplomas granted in Republic of Ireland.
15. Evidence of qualification to be given before registration and entry of additional qualifications.
16. Application for registration.
17. Assessor to Medical Council.
18. Publication of list of registered medical practitioners.
19. Privileges of registered persons and disabilities of unregistered persons.
20. Medical certificates.
21. Definition.
22. Power of Council to order removal of names from register.
23. Power of Council to strike name off register.
24. Appeal against removal from register.

For the few doctors who have difficulty committing to upholding medical ethics and regulation, remediation and discipline become necessary. Under the Medical Registration Ordinance 1905, the Medical Council of the Straits Settlements was established concurrently with the commencement of the Medical School. The purpose was to legalise the status of medical practitioners through establishing a Register of medical

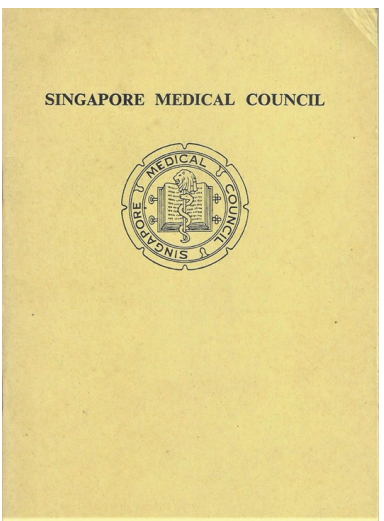
[23] Centre for Biomedical Ethics, Yong Loo Lin school of Medicine. Available at: https://medicine.nus.edu.sg/cbme/.

[24] Chin, Jacqueline, Nancy Berlinger, Michael C. Dunn, Michael K. Gusmano (eds.), A Singapore Bioethics Casebook, 2 vols (Singapore: National University of Singapore, 2017). Available at: http://www.bioethicscasebook.sg.

practitioners, to prevent unqualified persons posing as doctors and to deal with gross professional misconduct. There were then 219 RMPs.[25] From the beginning, the legislature required the profession to self-regulate. With the disbandment of the Straits Settlements in 1946, the name changed to the Medical Council of Singapore, before eventually being known as the Singapore Medical Council (SMC) in 1953.

In 1970, the ordinance was replaced by the Medical Registration (Amendment) Act (MRA). The duty of the Medical Council became the protection of the public, by enabling them to distinguish between qualified and unqualified practitioners, to take disciplinary action against medical practitioners for professional misconduct or for conviction of a heinous offence, and to uphold the reputation and standing of the profession. The SMC then had a Penal Committee of 3 persons to inquire into disciplinary matters.

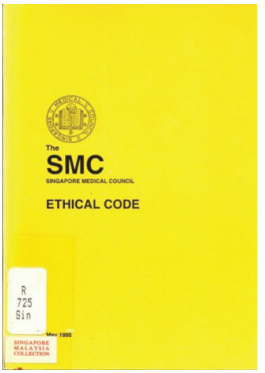
Doctors were expected to be competent and honourable in the discharge of their responsibilities and in relation to their patients. The code of what was honourable and good moral conduct had as its basis the doctor's character, conscience, and upbringing. The level of conduct for which the profession is held in high esteem stems from the precepts and traditions of the past.



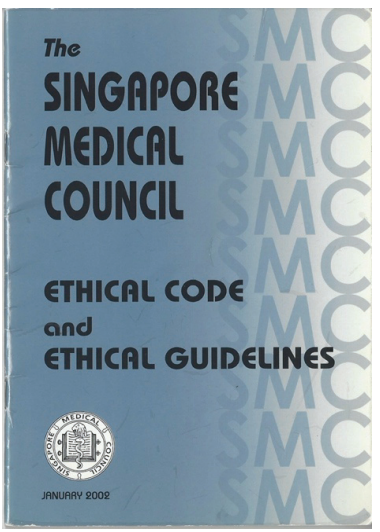
Sometime between 1979 and 1982, the SMC published a guide to its functions and operating rules "primarily for the information of doctors who have recently qualified and registered in Singapore". This publication listed the types of offence or misconduct which may become the subject of disciplinary action. These included (i) disregard of personal responsibilities to patients, (ii) abuse of the relationship between doctor and patients, (iii) abuse of a doctor's knowledge, skill or privileges, (iv) offences indicating tendencies dangerous to patients, (v) offences discreditable to the doctor and his profession, (vi) improper attempts to profit at the expense of professional colleagues, abuse of financial opportunities and (vii) abortion.[26]

[25] The origins of medical registration in Singapore, Lee YK, Part 1, SMJ, 1983; 24: 314-322.
[26] A Guide on the Singapore Medical Council circa 1982.

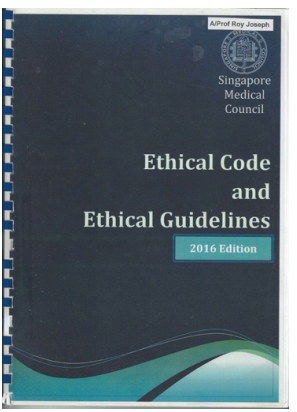
Ethical Code and Guidelines



The SMC in May 1995 published its Ethical Code, which was based on the preceding 7 behaviours described in the earlier Guide and the detailed explanations on them.[27] The Ethical Code represented the fundamental tenets of conduct and behaviour expected of doctors practicing in Singapore. This Ethical Code served the profession well for some time.



In 2002, a new set of Ethical Code and Ethical Guidelines were developed to keep pace with the major developments that had occurred in medical care and the systemic changes.[28] The Ethical Guidelines elaborated on the application of the Code and were intended as a guide to all practitioners as to what the SMC regards as the minimum standards required of all practitioners in the discharge of their professional duties and responsibilities in the context of practice in Singapore. As serious disregard or persistent failure to meet these standards could harm patients or bring disrepute to the profession, disciplinary action could be a consequence. The new guidelines proved to be useful for fifteen years, longer than the first which served for seven years. Rapid changes in practice and commercialisation of medicine resulted in ethical and professional issues arising from the proliferation of advertising, aesthetic medicine, complementary and alternative medicine, telemedicine, managed care, and international patients. This was coupled with a generation of more well-informed patients.



The latest revision was in 2016 and had grown from a 26-page booklet into a 64-page book in

[27] Singapore Medical Council Ethical Code. (1995)
[28] Singapore Medical Council Ethical Code and Guidelines. (2002)

response to the call for greater specificity and granularity.[29] The President of the SMC in the Foreword to the Code and Guidelines exhorted medical professionals to *"understand medical ethics, train in ethical analysis and decision making, develop knowledge, skills and attitudes needed to deal with ethical conflicts and to consult with colleagues, Ethics Committees and other experts when ethical conflicts arise"*. As the Guidelines had substantial additions and revisions, it was accompanied by an educational resource, the SMC Handbook on Medical Ethics.

Disciplinary Proceedings

The MRA has undergone major amendments in 1997, 2002, 2010 and 2014, aimed at enabling the Council to better fulfil its duties. Today the SMC has 27 members, comprising the Director of Medical Services, 2 RMPs appointed by the Minister from each of the three medical schools, 12 RMPs elected by fully RMPs and 8 RMPs appointed by the Minister. The appointees and the elected members hold office for 3-year terms. The Council functions to keep and maintain registers of RMPs and Specialists, approve or reject applications for registration, issue practising certificates, make recommendations on the courses of instruction and examination leading to the Singapore degree, make recommendations for the training and education of RMPs, determine and regulate the conduct and ethics of RMPs as well as the standards of practice and the competence of RMP's within the medical profession, and other administrative and necessary services.

To respond to complaints about doctors, the SMC has appointed a Complaints Panel comprising RMPs and laypersons. For each complaint, a Complaints Committee (CC), comprising 2 RMP members and 1 layperson from the Panel is appointed. The CC is authorised to inquire and investigate the complaint. On completion of its deliberation, the CC has the power to make an array of orders, including to dismiss the complaint, or issue to the RMP a letter of advice or a letter of warning. It can also issue orders to the RMP e.g. to seek treatment, undertake and complete specified learning or report on the fitness status of his physical or mental condition. The RMP can also be ordered to seek advice on the management of his practice. The CC, by agreement with the RMP, may also remove the name of the RMP from the Register, suspend the registration for a period not exceeding 3 years or change the Registration to one of Conditional Registration. The CC may also refer the matter for mediation or make any other order as it thinks fit. If the CC determines that a formal inquiry is required, it shall order that an inquiry be held by a Health Committee (HC) or a

[29] Singapore Medical Council Ethical Code and Guidelines. (2016)

Disciplinary Tribunal (DT). The SMC, the RMP or the Complainant if aggrieved by the decision of the CC, may appeal to the Minister.[30]

Details of the composition, proceedings, findings, orders of the DT or the HC are found in Divisions 5 and 6 respectively of the MRA. Appeals against the orders of the DT and the HC may be made to the High Court and the Minister of Health, respectively.

The DT functions in a quasi-judicial manner, listening to the arguments and supporting evidence presented by the respective counsels for the SMC and the RMP and subsequently determining if the charges have been proved beyond a reasonable doubt. Charges may be one or more of the following – conviction of an offence involving fraud or dishonesty, conviction of an offence implying a defect in character which makes the RMP unfit for his profession, improper conduct which in the opinion of the DT brings disrepute to the profession, professional misconduct and finally failure to provide professional services of a reasonably expected quality. These are detailed in Section 53 of the MRA.

The conviction of a RMP by the DT provokes intense media attention and public scrutiny, often followed by calls to improve the selection of medical students, improve teaching and training, and additional increased efforts in accountability and mentoring. At a systemic level, the rising absolute number of complaints against doctors is cited as justification for the basis of this opinion.

The Annual Reports published by the SMC provide detailed descriptions of the work done by the Council across its various responsibilities. The annual rate of complaints per 1000 doctors in 1978, 1988, 1998, 2008 and 2018 were 9.7, 6.5, 10.7, 16.2 and 14.0 respectively.[31] More recently, in the 5-year period between 2014 to 2018, there were 833 complaints.[32] This is an average of 166 complaints per year. Of the 752 complaints that were considered, 445 were dismissed and 8 were sent for mediation. Letters of advice and warning were sent to 170 and 60 RMP's, respectively. During this period, 98 RMPs were referred to DTs. These also include those originating in complaints before 2014.

An analysis of the 80 DT outcomes during this period reveals that over this 5-year period, a total of 18, 25 and 6 RMP's respectively were disciplined with

[30] The Statutes of the Republic of Singapore, Medical Registration Act (Chapter 174), Divisions 2 and 4, 2014.
[31] Singapore Medical Council Annual reports 1980,1988,1998, 2008 and 2018.
[32] Singapore Medical Council Annual Reports, 2014 to 2018.

a censure/fine, suspension or erasure from the Register. Another 15 were either withdrawn or acquitted. The outcomes of the remaining 16 were pending appeals. The annual rates did not show any progressive increase. This is despite medical care becoming more complex and unpredictable and a greater proportion of the sick being the aged.

Health Policy

Ministry of Health

The Government, through the MOH, has always maintained close communications with the medical profession to better understand issues pertaining to the delivery of medical care. When necessary, the MOH, through cooperation and collaboration with the medical profession, has established policies that are implemented through legislation, regulations, directives and guidelines to maintain the health of the society, improve the quality of medical care and ensure ethical and professional conduct of doctors. The process usually begins with the formation of an 'Advisory Committee' of professionals who will study the proposed initiative and offer recommendations. Where the recommendations raise the possibility of Ethical and/or Professional issues, further advice will be obtained from the National Medical Ethics Committee (NMEC).

The National Medical Ethics Committee

The formation of a NMEC was first announced during the parliamentary debate on the White Paper titled "Affordable Health Care" on 11 November 1993 by the former Minister of Health, Mr. Yeo Cheow Tong. The NMEC was set up in January 1994 by the MOH to (a) advise the Ministry on specific clinical ethical issues of interest and potential clinical ethical issues which may occur in Singapore based on the trends in other developed countries; (b) identify the prevailing ethical issues relating to public health, medical practice and research in Singapore; (c) develop ethical codes of conduct for doctors practising in Singapore; and (d) form sub-committees to deal with special issues as and when necessary.[33]

Its members are from diverse backgrounds and appointed on 2 year-terms. Its first Chairman was Dr. Chew Chin Hin. One of the first recommendations from the NMEC was for the setting up of 'Hospital Ethics Committees'. The

[33] National Medical Ethics Committee – A review of Activities, 1994-1997.

subsequent establishment of Hospital Ethics Committees has been a major milestone in guiding clinicians to resolve ethical issues. More recently, it has become a policy that every hospital has an Ethics Committee. To manage the unique issues that arise during solid organ transplantation from live donors, specialised Transplant Ethics Committees have been established through statutes.

Since then, the NMEC has issued ethical guidelines on human organ and tissue transplantation (1996), termination of pregnancy for mothers with foetuses with lethal malformations (1996), medical treatment of high-risk infants (1997), research involving human subjects (1997), practice of psychiatry (1997), gene technology (2001), handling of communications in advanced care planning (2010), clinical decision-making in collaboration with patients (2012) and end-of-life decision-making (2017).

In addition, in response to requests from the MOH, the NMEC has provided its views on ethical issues associated with advertisements related to medicines, aesthetic medicine, bone marrow donors, conjoined twins separation, financial issues in medical practice, human reproduction, organ donation, psychosurgery, public funds for high-cost treatments, research subject welfare, status of children bill, surgery for 'Jehovah's Witnesses' and, treatment of infectious diseases. These views and guidelines have been used in the informing of policies.

Most recently, the NMEC and the Bioethics Advisory Committee have begun to collaborate in the approach to the study of ethical issues arising in the rapidly evolving liminal space shared by translational research and medicine. It aims to develop frameworks that will guide Clinicians, Hospital Ethics Committees, Researchers, Institutional Review Boards, Funding Agencies, Hospitals and to collaborate and cooperate in advancing effectively and efficiently while upholding the welfare of the research subject, the patient and the common good.

Regulation, Directives and Laws for Regulating Medical Practice

1. The most recent development is the Healthcare Services Act (HCSA), introduced and passed in Parliament on 6 Jan 2020 and its regulations to be implemented in 3 phases. It will eventually replace the current Private Hospitals and Medical Clinics Act (PHMCA) when PHMCA is repealed. The HCSA is a service-based licensing regime that aims to provide regulatory clarity, strengthen governance and accountability of licensees and at the same time, introduce new and enhanced safeguards

for patient safety, welfare and ensure continuity of care. The new Bill will also allow a more flexible and modular services-based licensing regime that caters to the licensing of different healthcare services, while enabling the development of new and innovative services, centred around patient needs.

2. The gazetting of "Proton Beam Therapy" (PBT) as a specialised service under the Second and Third Schedules of the Private Hospitals and Medical Clinics (PHMC) Regulations (2017) is an example where Regulations have been used to rapidly introduce a socially important medical service that is extremely expensive and equally capable of being misused.

3. Changing social norms have resulted in a severe disruption of the natural reproduction rate of the population and there is a desperate reaching out for Assisted Reproduction services, another expensive and resource-intensive service with relatively low yields that may not be the best solution for the population. Hence, as a policy, Licensing terms and conditions were introduced in 2011 for practices offering this service.

4. Widespread uncertainty among RMP's were addressed through a 2016 Directive on consent taking practices for procedures performed by all RMPs.

5. Areas in clinical practice where legislation and policies have been used to ensure a zero-tolerance approach for unethical or unprofessional medical practice are listed in Appendix A.

Ethics Capability Committees

Aware that a significant proportion of the current healthcare personnel may not have had a sufficient grounding in medical ethics to address current and future ethical and professional issues, the MOH in 2014 established the National Ethics Capability Committee (NECC) to develop a competency framework and training roadmap in clinical ethics for all healthcare professionals from graduation to retirement. Two courses have been rolled out since 2016. The first is the Core Ethics Programme in Healthcare Ethics, Law and Professionalism, a foundational-level course for healthcare professionals. The second is the NECC Educators' Course

in Healthcare Ethics, Law and Professionalism, a train-the-trainer programme, designed to equip learners with skills in ethical analysis and case facilitation. With the development and approval of the framework and roadmap by the Director of Medical Services and their subsequent implementation, the initiative has since 2019, been continued by the Health Ethics Capability Committee (HECC) to oversee the implementation of the Training Roadmap and periodically review the competency framework for healthcare professionals. In addition, the HECC has been tasked to review the competency needs and training programmes for the specialised ethics committees (Hospital/Clinical Ethics Committee, Transplant Ethics Committee, Institutional Review Boards and other Ethics Committees or bodies that may be set up arising from MOH requirements).

SUMMARY AND CONCLUSION

The current status of undergraduate, postgraduate and professional medical education and training, the regulation of medical practitioners and medical practice, the policies, legislations and regulations that govern medical practice provides a strong basis for concluding that medical ethics in Singapore is thriving. A plethora of bodies function in tandem to develop medical ethics and ensure ethical medical practice under the direction of MOH. The numerous doctors and other healthcare personnel involved all serve in a voluntary capacity.

The COVID-19 pandemic has resulted in a comprehensive, intensive and ongoing demonstration of the ethics and professionalism that the Singapore healthcare profession practices and adheres to even in the most trying of situations while exposing themselves to grave personal risks. The spontaneous, exuberant and vivid responses to the profession from the media, society and individuals during the recent months and in particular, the 2020 National Day celebrations, are a strong affirmation of their trust, and the valued and appreciated current status of medical ethics. The ultimate aim of medical ethics is to enable the best interests of an individual patient and that of the common good of society to be achieved. Hence, the perspective of the individuals and society would be an important validation of the status of medical ethics. The time is opportune to conduct an empirical study at the national level to determine in more objective terms the level of trust of the society in the profession and to identify areas that can be worked on.

In every profession, unethical conduct will be present in a minority. Prompt and appropriate disciplining of unethical conduct in the healthcare profession

sends a strong signal to society that the profession does not tolerate unethical practices. Nevertheless, the speed and ease with which news of such misconduct is disseminated can result in fear and unwarranted generalisation of the conduct of the healthcare profession as a whole, which may lead to a gradual erosion of trust in the profession. There is a need to actively counter this erosion, especially because numerous challenges to both patients and physicians are inevitable.

Public engagement and education in medical ethics, which so far have been on the backburner, will achieve the goal of empowering society and individuals to engage the healthcare profession and communicate their values, goals and preferences and to collaborate in decision making. An incidental but important goal will be to reassure society and the individual patient of the commitment of the profession to act in their best interest whether in times of crises or peace. Health professionals will also need education and training in engaging and collaborating with the public in this space. In this respect, the critical role of seniors as role models and mentors to juniors must be encouraged and insisted upon by leaders. The dual and parallel development of both parties is a sure way to foster and preserve ethical medical practice in the years to come.

Appendix A

Laws in Singapore that relate to Medical Practice

The COVID (Temporary Measures) Act (2020)

Mental Health (Care and Treatment Act) (2012)

Mental Capacity Act (2008)

Health Products Act (2008)

Human Cloning and Other Prohibited Practices Act (2005)

Health Science Authority Act (2001, Revised 2002)

Traditional Chinese Medicine Practitioners Act (2001)

Advanced Medical Directives Act (1996, Revised 1997)

Human Organ Transplantation Act (1987, Revised 2012)

The Human Biomedical Research Act (1987, Revised 2015)

Private Hospitals and Medical Clinics Act (1980, Revised 1999)

Medicines Act and the Medicines (Advertisements and Sale) Act (1975, Revised 1987)

Infectious Diseases Act (1976, Revised 2003)

Termination of Pregnancy Act (1974, Revised 1987)

Voluntary Sterilization Act (1974, Revised 2013)

Medical (Therapy, Education and Research) Act (1972, Revised 2014)

The Poisons Act (1938, Revised 1999).

6

The Growing Importance of National Bioethics Committees

Andreas Reis and Stella Tan
Assisted by Chin Kok Hee

INTRODUCTION

The 21st century is widely considered as the age of novel technologies, such as digital health and biotechnology. Landmark achievements in the field of biology include the development of genetics since the 1990s, the successful cloning of Dolly the sheep in 1996, the completion of the Human Genome Project in 2003, the generation of induced Pluripotent Stem Cells (iPSCs) in 2006, and the discovery of the clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 gene-editing technology in 2012 by Emmanuelle Charpentier and Jennifer A. Doudna, who have been awarded with the Nobel Prize in Chemistry 2020.[1] The rapid advancement in biological discoveries has been translated into cutting-edge innovations, technologies, and treatments. However, with the advent of new technologies and treatment methods, ethical, legal, and social issues inevitably arise. Numerous governments across the globe have realised the need to address such bioethical issues as they have to make hard choices on complex and often challenging questions. Consequently, in the past two decades, we have witnessed the establishment of more and more national ethics advisory bodies, also known as bioethics committees or councils, which have proven to be critical in contending with various bioethical issues that have materialised.[2] The deliberations, consultations, views, and guidance provided by these committees have been instrumental for governments that aim to craft policies and legislation targeted at achieving a balance between advancing science and managing the possible risks which may arise from unethical research and practices.[2] In the following section, we shall accentuate the importance of national bioethics committees (NBCs) and the general functions they perform in their countries.

[1] Press release: The Nobel Prize in Chemistry 2020. NobelPrize.org. Nobel Media AB 2020. Sat. 10 Oct 2020. <https://www.nobelprize.org/prizes/chemistry/2020/press-release/>

[2] Elgharieb, M. E. (2015). Committees: National Bioethics Committees. In H. ten Have (Ed.), Encyclopaedia of Global Bioethics (pp. 1–8). Springer International Publishing. https://doi.org/10.1007/978-3-319-05544-2_103-1

In the next chapter, we will highlight the significance of NBCs in addressing new and upcoming advancements in the field of biomedical sciences. Thirdly, we will share various activities and events that have been supported by NBCs, both on a regional and global level. To conclude, we shall discuss the future outlook of NBCs and the importance of capacity building in Low-and-Middle-Income Countries (LMIC), especially in countries without a NBC.

SIGNIFICANCE AND FUNCTION OF NBCs

While research ethics committees had been widely established following the Declaration of Helsinki, it was not until the 1980s that the first NBCs saw the light of day. After the research summit "*Assises de la recherche*" in France, French President François Mitterrand decreed the establishment of the first NBC in the World, the National Consultative Ethics Committee on Health and Life Sciences (*Comité Consultatif National d'Ethique pour les Sciences de la Vie et de la Santé*, CCNE)in 1983.[3] Its objective was to identify contentious issues arising from advances in life sciences and to promote society's deliberation on such issues.

In 2005, The Universal Declaration on Bioethics and Human Rights was adopted by the United Nations Educational, Scientific and Cultural Organisation (UNESCO). Article 19 of the Declaration supports the establishment of independent, multidisciplinary, and pluralist ethics committees.[4] In its guide '*Establishing Bioethics Committees'* UNESCO defines a NBC as "a committee that systematically and continually addresses the ethical dimensions of (a) the health sciences, (b) the life sciences, and (c) innovative health policies."[5] Each NBC usually consists of a group of multi-disciplinary experts which will deliberate and resolve bioethical issues and challenges.[6] NBCs examine the individual and societal norms, morals and values before assessing if a particular research, treatment, or public health programme is desirable or permissible.

The main purposes of NBCs were also well-defined in the same UNESCO's guide. NBCs are to confer advice to government organs on bioethical and moral

[3] Décret n° 83-132 du 23 février 1983 portant création d'un Comité consultatif national d'éthique pour les sciences de la vie et de la santé (JO du 25 février 1983). https://www.ccne-ethique.fr/fr/pages/1983-creation-du-ccne-par-decret-presidentiel-decret-ndeg-83-132#.UTjlcNYzB8E

[4] UNESCO. *Universal Declaration on Bioethics and Human Rights*; 2006. Available at: https://unesdoc.unesco.org/ark:/48223/pf0000146180.locale=en

[5] UNESCO, *Establishing bioethics committees*. Guide no. 1. Paris, 2005. Available at: https://unesdoc.unesco.org/ark:/48223/pf0000139309.locale=en

[6] *Ibid.*

issues cropping up from advancements in life sciences, healthcare, biomedical sciences, and biotechnology. Secondly, NBCs should issue advice on bioethical issues which will impact how policies are crafted. and. When policy-makers draft legislation in response to progress in life sciences and biotechnology, recommendations from NBCs will be taken into serious consideration in many countries. Lastly, NBCs will also strive to increase public awareness of bioethical issues promote public engagement, for example through citizen's participation in consultation and townhall sessions, or through traditional and new media, such as television, radio and social media.[7]

The mandates and roles performed by the NBC in each country may differ widely between different countries, but the importance of NBCs for policy-making is often significant. One particular example in the United Kingdom (UK) is the Nuffield Council on Bioethics, which pinpoints and addresses ethical questions raised by new developments in biological and medical research, as well as in public health. It subsequently scrutinises and describes these questions at hand in order to facilitate public comprehension and debate and publishes reports and discussion papers on different bioethical topics. Besides engaging the stakeholders on bioethical issues, it has a dedicated education subgroup which aims to promote deliberation of bioethics topics among students. The Council's recommendations have also been accepted by the European Court of Human Rights to prohibit the keeping of genomic data and samples of innocent individuals in the UK's National DNA Database.[8] In India, the Central Ethics Committee on Human Research (CECHR) assesses and offers opinions on relevant and contentious issues arising from biomedical research and presents it to the relevant government bodies. The Indian Council for Medical Research (ICMR) developed a core bioethics curriculum, which the Medical Council of India, responsible for medical education, has administered to both undergraduate and postgraduate medical students, life science students, institutional ethics committee members, researchers, and faculty members.[9] It is clear that while NBCs across the globe have different responsibilities and mandates, they all strive to ensure that the advancement of human knowledge and welfare is achieved in line with ethical norms.

Some National Ethics Committees do not have a broad mandate of providing advice on ethical issues arising in new technologies or health policies. Rather,

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7 *Ibid.*

8 UNESCO, *National Bioethics Committees in action*; 2010. Available at: https://unesdoc.unesco.org/ark:/48223/pf0000189548.locale=en

9 *Ibid*, p33.

they provide national ethics oversight to research with human subjects, by either formulating related policies, overseeing local research ethics committees, or by reviewing individual research projects. One particular example of the crucial function of National Research Ethics Committees is the role that some of the West African committees played during the 2014-2016 Ebola epidemic. The most hard-hit countries, Liberia, Guinea, and Sierra Leone, in 2014 and 2015 saw a very rapid increase in important research projects in relation to Ebola. The national research ethics committees often had to face extremely difficult ethical challenges, under extreme time pressure to process the proposals quickly. They rose to the challenge, adapted special emergency procedures, and were able to facilitate ethical research during these emergency times. As evidenced by the current COVID-19 pandemic, more work is needed in order to streamline processes for review during emergency situations.[10]

HOW THE NBCs TACKLE NEW AND EMERGING DEVELOPMENTS IN BIOMEDICAL SCIENCES

Two recent cases exemplify important ways in which NBCs play a decisive role in advising policy-makers and guiding science in the area of new developments in biomedical research.

Germ-line editing refers to the use of any related biological techniques, such as CRISPR/Cas9 technology, to intentionally edit a sequence of DNA which may code for a functional protein in a living cell. This living cell can be a human embryo, sperm, egg or a primordial germ cell, which are the precursors of human sperm and eggs. If there are no further interferences, the edited genome could likely be passed on to the child's future generations. This technique is also known as Heritable Human Genome Editing (HHGE). The academia was shocked after biophysicist He Jiankui announced the birth of two twin girls, Lulu and Nana, who had their genomes edited through CRISPR/Cas9 technology. Formally presenting his study at the Second International Summit on Human Genome Editing at the University of Hong Kong on 25 November 2018, he had aspired to assist individuals with fertility problems, in particular, Human Immunodeficiency Virus (HIV)-positive fathers and HIV-negative mothers.[11] Using the CRISPR/Cas9 system, He edited the DNA of the embryo, which

[10] Saxena et al (2019): Ethics preparedness: facilitating ethics review during outbreaks - recommendations from an expert panel. BMC Med Ethics, . 2019 May 6;20(1):29. doi: 10.1186/s12910-019-0366-x.

[11] Greely, H. T. (2019). CRISPR'd babies: Human germline genome editing in the 'He Jiankui affair'*. Journal of Law and the Biosciences, 6(1), 111–183. https://doi.org/10.1093/jlb/lsz010

codes for a gene *CCR5*, a chemokine receptor involved in coordinating immune responses in a healthy human body. The protein CCR5 facilitates the entry of HIV into cells, which is the first step of the HIV infection. An edited version of the CCR5 would mean that the child born from the edited embryo is thus immune to HIV. His experiment had thus contravened international and national ethical norms. For example, Article 24 of the UNESCO's *Universal Declaration on the Human Genome and Human Rights* states that germ-line interventions could be contrary to human dignity.[12] Such modifications would mean that the individual is merely a 'commodity', which violates their dignity. The Oviedo Convention, which is binding international law for signatory countries, equally includes a prohibition of germ-line interventions.[13] In response to his experiments, the CCNE, German Ethics Council (*Deutscher Ethikrat*) and the Nuffield Council on Bioethics jointly issued a statement, raising four main points: Firstly, as there is no international authority that is able to enforce universal measures, any form of HHGE should be under the administration of the government and any violations should be subjected to penalty. Secondly, there should be no clinical use of HHGE unless it has been deemed as being ethically acceptable after deliberation by all relevant societal groups. Thirdly, there should be no attempt of HHGE until research has dispelled doubt about the risks of clinical use to a satisfactory level. Lastly, before conducting clinical trials or applications of HHGE are allowed, procedures must be present to assess, observe, and review the risks of adverse effects for individuals, groups, and society in totality.[14] This is just one example of NBCs across the globe responding promptly to advancements in biomedical sciences and providing a clear direction for science and policy-makers.

Preimplantation genetic testing (PGT) has been conducted since 1990 and consists of two procedures, preimplantation genetic testing for Monogenic/Single-Gene Disorders (PGT-M) and preimplantation genetic testing for aneuploidies (PGT-A). PGT-M is employed before the embryo is implanted in the mother's uterus to scan for genetic mutations which may give rise to serious and debilitating diseases. PGT-A is utilised to scan the embryos for chromosomal aberrations, to ensure that the embryo contains all 23 pairs of chromosomes. These genetic mutations are possessed by the prospective parents and some wish to prevent the

[12] UNESCO, *Universal Declaration on the Human Genome and Human Rights*, 1997 Article 24. Available at: https://unesdoc.unesco.org/ark:/48223/pf0000110220.page=47

[13] Council of Europe, *Convention on Human Rights and Biomedicine*, 1997 Article 13. Available at: https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98

[14] Nuffield Council on Bioethics, *Joint Statement on the Ethics of Heritable Human Genome Editing*, 2020 Available at: https://www.nuffieldbioethics.org/news/joint-statement-on-the-ethics-of-heritable-human-genome-editing

passing of these diseases to their offspring. PGT raises a host of ethical issues, which have been addressed both by international and national bodies, and are reflected in laws and regulations in many countries. At the international level, UNESCO's International Bioethics Committee (IBC) released a report on PGT already in 2003. The committee acknowledged the ethical concerns from PGT, which included the special status of human embryos, picking, and destroying of embryos, as well as the possible health repercussions for women.[15] On a national level, the legislation on PGT varies across the world. In Europe, PGT is permitted in Spain, France, Norway, Sweden, Denmark, Portugal, and UK. It is prohibited in Ireland, Austria, Switzerland, Italy, and Luxemburg.[16] In Asia, PGT is allowed in Singapore, Malaysia, and Australia. When Australia's five-year moratorium on the use of PGT for Non-Medical Sex Selection (NMSS) was due in 2010, the NBC, National Health and Medical Research Council (NHMRC), thus conducted a review of the issue.[17] Upon the announcement of the review, it sparked a huge public debate on NMSS. Couples who wished to have a baby of a specific gender had to travel to other countries where NMSS was permitted, such as Thailand. The controversy was ignited even further after it was revealed that a couple had recently aborted twin boys which were conceived through IVF and wished to have a girl through PGT.[18] The NHMRC guidelines were reviewed twice in 2007 and 2017, with a public consultation held in 2015. NHMRC acknowledges that there are alternate verdicts for the appropriateness of NMSS; it holds the view that the "Australian society needs to be ready, both socially and politically, for there to be a change in its [NMSS] availability."[19] A study conducted in 2018 revealed that 67% of Australian adults surveyed "disapproved" or "strongly disapproved" the use of PGT for gender selection, with those who strongly disapproved increasing from 31% in 2007 to 40% in 2016.[20]

These examples illustrate first the importance of having competent bodies

[15] UNESCO IBC, *Report of the IBC on Pre-implantation Genetic Diagnosis and Germ-line Intervention*, 2003 Available at: http://www.unesco.org/shs/ibc/en/reportfinalpgd_en.pdf

[16] Duguet, A.-M., & Boyer-Beviere, B. (2017). Preimplantation Genetic Diagnosis: The Situation in France and in Other European Countries. European Journal of Health Law, 24(2), 160–174. https://doi.org/10.1163/15718093-12420347

[17] Australia considers lifting ban on sex selection, BioNews, 15 March 2010, Available at: https://www.bionews.org.uk/page_92226

[18] Whittaker, A. (2015). Media debates and 'ethical publicity' on social sex selection through preimplantation genetic diagnosis (PGD) technology in Australia. Culture, Health & Sexuality, 17(8), 962–976. https://doi.org/10.1080/13691058.2015.1018947

[19] National Health and Medical Research Council. *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research*. 2017. https://www.nhmrc.gov.au/guidelines-publications/e79.

[20] Kippen, R., Gray, E., & Evans, A. (2018). High and growing disapproval of sex-selection technology in Australia. Reproductive Health, 15. https://doi.org/10.1186/s12978-018-0577-5

at the national levels to analyse and advise on ethical issues raised by new technologies. Second, they speak to the importance of public engagement and ensuring that local norms and contexts are taken into account in formulating recommendations at the national level. Lastly, they also show that many ethical quandaries in today's world cannot be solved by national laws and regulations alone; rather, an international consensus needs to be reached and implemented.

NETWORKING ACTIVITIES OF NBCs

I. The Global Summit

In November 1996, by the joint invitation of the US National Bioethics Advisory Committee and the CCNE, the NBCs of 18 countries around the world and observers from six international bodies attended the first Global Summit of NBCs in San Francisco, California, USA. It was held in conjunction with the 3rd World Congress of the International Association of Bioethics (IAB).[21] The Global Summits of NBCs have since taken place every two years.

They provide a platform for national bioethics representatives to exchange experiences on ethical issues arising from health and public health practices. They are a forum for dialogue and the various committees discuss a plethora of notable ethical issues that every country around the world has a stake in.[22] Through the exchange of opinions and discussions on bioethical issues, the summit aims to achieve consensus building and common understanding between nations. In addition, the summit supports nations with developing national bioethics infrastructure and regulations. Not only have they served as a platform for the debate of bioethical issues, they have concentrated on ethical issues that no country can tackle on its own, but can only be resolved through global actions. The Summits offer an exceptional occasion for NBCs across the world to pinpoint bioethical issues of global significance, analyse the latest evidence and strive towards a consensus on these issues. 13 Global Summits have been held biennially thus far, with rotation through the different WHO regions. The Permanent Secretariat has been served by the Global Health Ethics Unit at WHO since 2002. The latest Summit was jointly organised by the Portuguese

[21] Bouesseau, M.-C., Reis, A., & Ho, W. C. (2011). Global Summit of National Ethics Committees: An essential tool for international dialogue and consensus-building. Indian Journal of Medical Ethics. https://doi.org/10.20529/IJME.2011.062

[22] Manuel Hugo Ruiz de Chávez Guerrero, Raúl Jiménez Piña *10th Global Summit of National Ethics/ Bioethics Committees: Finding Paths Through the World* Comisión Nacional de Bioética/Secretaría de Salud, 2015.

National Council of Ethics for the Life Sciences (*Conselho Nacional de Ética para as Ciências da Vida*) and the WHO, in collaboration with UNESCO. It was held virtually from 9th September to 11th September 2020 due to the COVID-19 pandemic.

The Bioethics Advisory Committee Singapore (BAC) has and will continue to play a significant role in the local and global bioethics landscape. BAC had previously hosted the 8th Global Summit in July 2010 which was attended by delegates from 33 different countries, as well as the WHO, the Council of Europe and the European Commission.[23] Subsequently after the 8th Global Summit, BAC hosted the 10th World Congress of the IAB. Both sessions were a valuable platform for NBCs around the world to discuss and establish global consensuses on common international bioethical issues.

II. Regional Summits

In addition to the global summits, regional summits have also been held in different continents around the world. At the 11th Global Summit held in Berlin on March 2016, delegates suggested organising regional summits between the Global Summits, which have been held bi-yearly, to deliberate on bioethical issues that are of particular concern to the particular regions. For example, the inaugural Regional Bioethics Summit for the Eastern Mediterranean/Arab States was held in Muscat, Oman on April 2017. The main objectives of the Regional Summit were to cultivate the progression of NBCs in the region as well as to achieve efficient procedures of regional association and alliance to tackle issues arising from biomedical research.[24] During the Regional Summit, topics of interest from the previous and upcoming Global Summits were discussed and participants had the opportunity to share their experiences and debate on current bioethical issues. The second Regional Bioethics Summit for the Eastern Mediterranean/Arab States was held in Cairo, Egypt, in December 2019, and another one is planned for end of 2021 (COVID-19 permitting).

The South-East Asia Region, together with the Western Pacific Region, held the first Asia-Pacific Regional Meeting for National Ethics/Bioethics Committees (AP-NEC) in Seoul, Korea, in October 2017. It aimed to promote the critical role

[23] Bioethics Advisory Committee Singapore, Global Health Ethics Team, World Health Organization, Ministry of Health, Singapore. Brief Report on the Eighth Global Summit of National Bioethics Advisory Bodies. Singapore. 2010 July 26-7.

[24] Summary report on the Eastern Mediterranean/Arab States regional summit of national ethics and bioethics committees. Cairo: WHO Regional Office for the Eastern Mediterranean; 2017. Licence: CC BY-NC-SA 3.0 IGO.

of health ethics in the 2030 Agenda for Sustainable Development, to enhance national capabilities in promoting bioethics through NBCs and to cooperate regionally to tackle common bioethical issues. The second AP-NEC was held in Wellington, New Zealand in October 2019. Its theme was "reducing inequities through solutions-orientated bioethics.". Health inequities issues arising from three different settings were investigated – climate change, emerging technologies and indigenous populations. Health ethics was divided into three branches – public health ethics, clinical care ethics and health research ethics.[25]

In the European Region, the European Commission has been organizing the NEC Forum, an independent informal network of representatives of the National Ethics Councils for the exchange of information, experience and best practices on issues of common interest in the field of ethics and science. That forum meets once or twice a year and brings together the NBCs from the 27 members of the EU, under the leadership of the country that assures the EU presidency in the respective semester.

In the Region of the Americas, the Bioethics Network for Latin America and the Caribbean (*REDBIOÉTICA*) has been formed with assistance from UNESCO. Its founding coincided with an international meeting on the Human Genome Project and was galvanised by the first and second World Congress of the IAB held in Tokyo and Brazil.[26] The biannual International Congress of the *REDBIOÉTICA* is a significant event in the South American region which revolves around the ethics of science and technology. Experts and academia from Latin America and the Caribbean attend the Congress and deliberate on numerous bioethical issues.

In Africa, the inaugural Regional Conference of National Ethics and Bioethics Committee was held between 12-14 February 2020 in Mombasa, Kenya. It was hosted by the Kenyan National Commission for Science Technology and Innovation, under the auspices of UNESCO. Held in anticipation of the Global Summit 2020 in Portugal, its aims were to discuss and agree on a common regional position on the ethical dimensions of climate change; to bring to the forefront

[25] WHO ROWP. *Meeting Summary Second Asia-Pacific Regional Meeting for National Ethics/ Bioethics Committees*, 2019 Available at: https://iris.wpro.who.int/bitstream/handle/10665.1/14477/RS-2019-GE-39-NEZ-eng.pdf

[26] Garrafa, V. (2009). Redbioética – A UNESCO Initiative for Latin America and the Caribbean. Conference presented in the Open Session of the Sixteen Session of the IBC - International Bioethics Committee of UNESCO. México City.

the ethical dimensions of climate change and enhance better understanding of related issues; to create awareness among the public on climate change, through the collaboration with media entities; and to identify policy recommendations that address ethical aspects of climate change.[27]

III. Capacity-building of NBCs

Several international organizations, notably UNESCO, WHO, the European Commission and the Council of Europe, have been supporting countries to establish or strengthen NBCs.

Article 19 of UNESCO's Universal Declaration on Bioethics and Human Rights promotes the establishment of independent, multidisciplinary, and pluralistic bioethics committees. Article 22 states that countries should advocate for the establishment of bioethics committees.[28] These committees can engage the public and society routinely to exchange views on bioethical issues. In countries with poor or incomplete regulations on bioethics, the establishment of bioethics committees could thus be able to encourage the progression of bioethics. However, not every state in the world has a NBC. Therefore, UNESCO has introduced the Assisting Bioethics Committees (ABC) programme to aid member states in establishing bioethics committees.[29] At this point of time, the ABC programme has so far assisted 19 Member States to establish NBCs in their respective countries.[30]

The ABC programme is executed in three stages. The first stage is the exploration phase. If a country wishes to establish a NBC, UNESCO arranges an exploratory mission which consists of a group of experts. These experts are proficient with the workings within their respective NBCs in their country.[31] The

[27] UNESCO. African Regional Conference of National Ethics and Bioethics Committees; 2020. Available at: https://en.unesco.org/events/african-regional-conference-national-ethics-and-bioethics-committees

[28] UNESCO. *Universal Declaration on Bioethics and Human Rights*; 2006. Available at: https://unesdoc.unesco.org/ark:/48223/pf0000146180.locale=en

[29] Ten Have, H., Dikenou, C., & Feinholz, D. (2011). Assisting Countries in Establishing National Bioethics Committees: UNESCO's Assisting Bioethics Committees Project. *Cambridge Quarterly of Healthcare Ethics*, *20*(3), 380–388. https://doi.org/10.1017/S0963180111000065

[30] UNESCO. Assisting Bioethics Committees (ABC), n.d. Available at: https://en.unesco.org/themes/ethics-science-and-technology/assisting-bioethics-committees#:~:text=In%20this%20context%2C%20UNESCO%20has,to%20reinforce%20its%20bioethics%20infrastructure.&text=The%20ABC%20programme%20is%20a,ethics%20of%20science%20and%20technology.

[31] Ten Have, H., Dikenou, C., & Feinholz, D. (2011). Assisting Countries in Establishing National Bioethics Committees: UNESCO's Assisting Bioethics Committees Project. *Cambridge Quarterly of Healthcare Ethics*, *20*(3), 380–388. https://doi.org/10.1017/S0963180111000065

mission holds talks with the interested stakeholders in the host country and briefs them on the necessary infrastructure and functional matters in order to expedite the establishment of a *de facto* NBC. In the second stage, the ABC programme assists the new committee to become a functional organisation.[32] In the final stage, a formal accord is signed between UNESCO and the host country. The Memorandum of Understanding lays down the technical support which will be provided by UNESCO. The support includes training courses, provision of documentation, internships for the secretariat, networking, and partnerships, and co-organizing public events.[33] Over the years, UNESCO has also published guidebooks that are readily available online. The topics range from the constitution of NBCs, recommended procedure, and policies NBCs should adopt as well as the approach to public policy and public engagement.

WHO, through its six Regional Offices, around 140 Country Offices, and Global Network of WHO Collaborating Centres for Bioethics, has also been providing assistance to NBCs, in particular in LMICs. The Global and Regional Summits (see previous section), co-organised by WHO, have greatly contributed to mutual exchange and learning and to strengthen newly-established NBCs. As discussed above, the European Commission and Council of Europe organises bi-annual regional meetings to promote cooperation and facilitate information exchange among NBCs in Europe.

CONCLUSION

From the inauguration of the world's first NBC in France in 1983, the number of countries with NBCs worldwide has increased to over 100 as of March 2021.[34] NBCs have proven to be critical in advising officials and stakeholders on ethical issues arising in biomedical research and public health. However, much remains to be done. A collaborative effort between international organizations such as UNESCO, WHO, the European Commission and the Council of Europe, is needed in order to support bioethics capacity building in countries where NBCs do not exist as yet, and strengthening nascent NBCs. Twinning arrangements with countries with well-established NBCs can prove beneficial for transferring knowledge and best practices. By establishing a NBC, these states will be empowered to provide their policy-makers with authoritative ethical advice, and also have the opportunity to participate in Regional and Global Summits

[32] *Ibid*, p384
[33] *Ibid*, p385
[34] Koehler J et al. (2021). A survey of national ethics and bioethics committees. Bulletin of the World Health Organization 2021;99:138-147. https://dx.doi.org/10.2471/BLT.19.243907

for Ethics/Bioethics Committees to bring their respective national concerns to international attention.

As bioethics is an ever-changing subject, the BAC consistently deliberates on past and upcoming bioethical issues, in order to craft new recommendations or review current recommendations. For example, in view of the latest scientific advancements and international deliberations on genetic germline modifications, the BAC has decided to reconsider its stand on mitochondrial genome replacement technology, one technique of genetic germline modification. I am certain that the BAC will continue to address impending bioethical issues and support events and activities by NBCs.

7

Singapore's involvement in UNESCO IBC, IGBC, and other regional forums

Charles Lim Aeng Cheng and Richard Magnus

INTERNATIONAL BIOETHICS COMMITTEE (IBC) AND INTER-GOVERNMENTAL BIOETHICS COMMITTEE (IGBC)

The key bodies of the UNESCO Bioethics Programme are the IBC and IGBC.

The IBC was established in 1993 by Dr Federico Mayor Zaragoza, Director-General of UNESCO at that time. The IBC has been important in developing declarations in the field of bioethics. To date, IBC has produced three international instruments that have been adopted by the UNESCO General Conference (GC):

(1) Universal Declaration on the Human Genome and Human Rights (1997);

(2) International Declaration on Human Genetic Data (2003); and

(3) Universal Declaration on Bioethics and Human Rights (2005).

The IGBC was subsequently created in 1998, under Article 11 of the Statutes of the IBC, with the mandate to "examine the advice and recommendations of the IBC". It comprises 36 Member States that are elected by the UNESCO GC, taking into account cultural diversity and geographical representation. The elected Member States serve four-year terms with around half of the seats up for election at each GC session. The IGBC further elects from among its members a Chair, four Vice-Chairs and a Rapporteur, to form the IGBC Bureau. Bureau elections are held after each IGBC election, i.e. Bureau members effectively serve two-year terms each time.

Although the IGBC is required to meet "at least once every two years", it has been meeting annually on a regular basis. For better coordination between the IBC and the IGBC, a joint meeting is held in alternate years. Examining the work of the IBC, the IGBC informs the IBC of its opinions, and submits these opinions along with proposals for follow-up of the IBC's work to the Director-General for transmission to Member States, the Executive Board (EB) and the GC. As the IBC comprises independent experts appointed by the Director-General of UNESCO rather than the governments of Member States, this mechanism allows the IBC to take into account the inputs and concerns of governments.

The main "deliverables" of the UNESCO Bioethics Programme are the periodic IBC reports on the issues that it has reviewed. Besides the IBC reports, the UNESCO Bioethics Programme seeks to define and promote a common ethical standard-setting framework for Member States to formulate and implement policies in the field of bioethics.

Since Singapore's participation in the UNESCO Bioethics Programme, the IBC has issued reports on: the Principle of Respect for Human Vulnerability and Personal Integrity (2013), Traditional Medicine Systems and their Ethical Implications (2013), the Principle of Non-Discrimination and Non-Stigmatization (2014), Updating the Reflection on Human Genome and Human Rights (2015), the Principle of Sharing of Benefits (2015), the Bioethical Response to the Situation of Refugees (2017), Big Data and Health (2017), the Principle of Individual Responsibility as Related to Health (2019), and Assisted Reproduction Technologies and Parenthood (2019).

Our participation in the many deliberations and debates that ensued in the process of developing these reports had allowed us to broaden our understanding of these issues with international perspectives which the BAC could then draw from when developing our own recommendations for Singapore.

SINGAPORE'S INVOLVEMENT IN THE UNESCO BIOETHICS PROGRAMME

Chief District Judge (Ret.) Richard Magnus was the first Singaporean appointed onto the IBC for the 2012–2015 term. He was re-appointed onto the IBC for a second four-year term 2016–2019. During his tenure on the IBC, he was also elected as Vice-Chair of the IBC for two consecutive two-year terms for 2016–2017 and 2018–2019.

Our initial involvements in the UNESCO Bioethics Programme through the IBC led us to recognise the value of Singapore and the BAC's participation at such international platforms. As part of our intent to remain connected with our international counterparts, the BAC, with support from the Ministry of Health, submitted Singapore's candidature for the UNESCO IGBC for the 2014–2017 term.

Singapore was first elected to the IGBC for a four-year term from 2014 to 2017, and was re-elected for a second four-year term from 2018 to 2021. Singapore's representative to the IGBC is BAC Member Mr Charles Lim Aeng Cheng, Principal Senior State Counsel in the Attorney-General's Chambers. He was elected as the IGBC Rapporteur for two consecutive two-year terms for 2016–2017 and 2018–2019.

Our representation through the UNESCO IBC and IGBC has enabled Singapore and the BAC to take part in international discussions with global bioethics community on a wide range of bioethical issues.

NOTABLE ISSUES DISCUSSED AT REGIONAL FORUMS

Pandemics: Ebola and Covid-19

Given the Covid-19 pandemic in 2020, an interesting incident on pandemics is worth recounting. At the Singapore Delegation's very first session in 2014, the French Delegation surprised many delegates with a proposal for a draft statement on the Ebola epidemic for adoption by the Member States, as part of the joint session's "Sharing of Benefits" theme. At the initiative of the French Delegation, this session deliberated a statement expressing solidarity with ongoing global efforts to counter the Ebola virus epidemic in West Africa.[1] No prior notice was given of this proposal. Neither was it on the agenda. Some delegates opined that it was not necessary for the statement to be adopted as only countries with weak health systems were likely to be affected and adopting such statement might loosen the ethics requirements to conduct research during such outbreaks. An ad-hoc working group was shortly set-up to modify the draft which was adopted unanimously on the next day. The Singapore Delegation had no reason to object to the statement. Six years later on 6 April 2020, the IBC and World Commission

[1] Twenty-first session of the International Bioethics Committee of UNESCO (IBC) & Joint Session of the IBC and the Intergovernmental Bioethics Committee (IGBC) Final Report (2015). Available at: https://wayback.archive-it.org/10611/20181208181204/http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/international-bioethics-committee/ibc-sessions/twenty-first-and-joint-session-paris-2014/

on the Ethics of Scientific Knowledge and Technology (COMEST) published a joint statement to address the ethical issues relating to the ongoing COVID-19 situation — "Covid-19: Ethical Considerations from A Global Perspective".

In their joint statement, the IBC and COMEST highlighted several critical ethical issues from a global perspective, and appealed to governments to take action on these concerns. We aim to highlight some of the ethical issues which were raised during the IBC session. Firstly, the IBC and COMEST take the stance that health and social policies at national and international levels should be scientifically grounded, guided by global ethical considerations and made in consideration of uncertainties that prevail during a global pandemic. An international effort is recommended to establish a set of standardised criteria for data collection about the COVID-19 spread and its impact. It is essential for an interdisciplinary dialogue between law, political, ethical and scientific authorities in a global pandemic characterised by many unknowns. In the event of a global pandemic that places stress on healthcare systems, the IBC and COMEST emphasise the importance of the micro- and macro- allocation of healthcare resources and a robust public health system. The allocation of resources is only ethically justified when they hinge on the fundamental principles of justice, beneficence, and equity. Clinical procedures need to be open, transparent and should respect human dignity. The IBC and COMEST also reaffirm our shared responsibility of vulnerable persons, which include the elderly, people subject to poverty, discrimination, disability, incarceration, as well as refugees and stateless persons (see Report of the IBC on the Bioethical Response to the Situation of Refugees (2017)).[2] Measures like social distancing and quarantine could heavily impact vulnerable persons financially and psychologically, and hence additional care and institutive actions should be taken to provide them with the extra support they require. In addition, as outlined in its report on the Principle of Individual Responsibility as related to Health (2019)[3], the IBC highlights that our right to health can be assured only by our duty to health on both individual and collective levels. There are responsibilities of governments across the world to safeguard public health and safety; responsibilities of the public to abide by safe distancing and self-isolation rules in protection of the wider community; responsibilities of healthcare workers to administer medical care to patients. Moreover, the urgency to find a vaccine or cure for COVID-19 should not take precedence over the regulatory protocols that govern research practices. Research still needs to be conducted responsibly and comply with ethical principles, while being subject

[2] Available at: https://unesdoc.unesco.org/ark:/48223/pf0000248721
[3] Available at: https://unesdoc.unesco.org/ark:/48223/pf0000367824

to scrutiny by competent ethics committees. The aforementioned are some of the ethical considerations highlighted in a joint statement by IBC and COMEST in 2020. This statement serves as an appeal to governments across the world to contemplate these issues, and thus make prudent political decisions and work on ethically acceptable solutions that can effectively guide us out of this challenging pandemic.

Science & Technology and Sustainable Development

It can be argued that science and technology may be counterproductive to sustainable development. For instance, the use of machines, which are the products of science & technology, drive fuel consumption and instigate climate change which threatens sustainable development. Therefore, in pursuance of sustainable development with the aid of science and technology, we need to integrate ethics as a guiding light. This guiding light functions to direct us to the moral principles which are necessary when managing novel technological developments. The consideration of ethics allows us to maximise the benefits and minimise the adverse consequences associated with technology. This is critical in ensuring sustainability in the future development of neurotechnology, big data, robotics, genomics and energy science.

To facilitate discussion in ethical, legal and political implementations of science and technology in the context of sustainable development, the 26th Session of the IBC was held in conjunction with Thailand's Conference on the Ethics of Science & Technology and Sustainable Development in 2019. The themes of the Thailand Conference included the use of genomic technologies, artificial intelligence, robotics, big data, climate change and fostering the culture of research integrity.

The conclusion of the Conference was marked by declaration of the Bangkok Statement on the Ethics of Science and Technology and Sustainable Development, which encouraged countries to recognise and give more attention to ethical issues of science and technology in the context of sustainable development. The Bangkok Statement spurred countries to develop common best practice guidelines for new and impactful technologies to ensure the ethical practice and integrity of researchers. At the same time, it hoped to galvanise members of the younger generation to be more engaged in ethical issues in the realm of science and technology.

During the Conference, the BAC (represented by BAC Chair, Chief District Judge (Ret.) Richard Magnus) participated in a panel session to discuss how ASEAN countries should work together to foster greater regional collaborations in the area of the Ethics of Science and Technology and Sustainable Development. Acknowledging that ASEAN collaborations for bioethics were paramount as there were few regional platforms on bioethics within Asia, we expressed our hopes that the Bangkok Statement would set in motion future collaborations between the ASEAN Member States (AMS).[4] Dr Kanchana Wanichkorn from Thailand, Vice-President at the Office of National Higher Education Science Research and Innovation Policy Council, was the moderator of the panel discussion. She suggested that within the AMS, Thailand and Singapore could initiate and spearhead a regional network to develop novel ideas and exchange information on new technologies.

The Bangkok Statement served as one of the reference documents that inaugurated the partnership for ethics in science & technology and sustainable development on a regional level. As part of ASEAN, Singapore seeks to contribute positively to the ASEAN community. Singapore recognises the importance of regionalisation and aims to enhance synergy in science & technology among the AMS by means of research & development (R&D) cooperation, engaging in cross-ASEAN technopreneurships that integrate ideas, knowledge, sociocultural diversity, highly skilled labour, and capital utilisation across ASEAN.

"SOFT LAW" AND INTERNATIONAL NORMS

As a global intellectual forum to review and reflect on a wide range of bioethics-related issues, the IBC's reports have the potential to shape the ethical norms and acceptable standards in biomedical sciences and research. The IGBC plays an important role in moderating and injecting different perspectives from the governments and institutions. While the reports are not legally-binding instruments, they are nonetheless issued under the auspices of an established UN agency. UNESCO is the only international organisation at the UN level that issues instruments on bioethics. In the absence of any other binding international instrument or agreement, opinions and recommendations in these reports could gain traction in the international arena. There is a possibility that some of the instruments may over time gain the status of 'soft law' or even international norms.

[4] Conference on the Ethics of Science & Technology and Sustainable Development. First Edition. (2020). National Committee on Ethics of Science & Technology, Thailand.

PROTECTING SINGAPORE'S INTERESTS

The Singapore Delegation's engagement in IGBC seeks to protect Singapore's interests by seeking consistency between these reports and Singapore's policies and positions on bioethics and health issues. The Singapore Delegation was also mindful that Singapore does not become an 'outlier' in the global community in the area of bioethics. As an illustration in 2017, the IGBC discussed the IBC's Draft Report on Big Data and Health. The Singapore Delegation submitted a written intervention with the objective of ensuring that the IBC report will not inhibit domestic thrusts in relation to Precision Medicine and the use of big data in biomedical research. Anonymisation is one of the tools employed by Singapore researchers to facilitate the use of personal data in human biomedical research. Singapore's interventions sought to clarify and qualify the IBC report's criticism of anonymisation to pre-empt any future inhibition of biomedical research using big data. Some IBC members felt that anonymisation will not be able to provide sufficient protection for privacy in the context of big data. However, they also acknowledged that many countries still relied on anonymisation in their regulatory framework, and the IBC would need to reflect this reality. Subsequently, most of Singapore's comments were carried in the "Conclusions of the 10th IGBC Session".

Apart from seeking to align our interests in biomedical research, the Singapore Delegation also sought to present Singapore's successful public healthcare strategies. In the 2018 IGBC discussions on the Draft IBC Report on the Principle of Individual Responsibility as Related to Health, the Singapore Delegation sought to clarify that the draft report should not adversely view public health policies that seek to promote good health by reducing unhealthy behaviours, especially behaviours which have an impact on the health of others in the vicinity or community, e.g. smoking. The Singapore intervention successfully urged the IBC to re-evaluate their assessment of health promotion measures such as taxation and nudging vis-à-vis their real-world efficacy. We highlighted scenarios where coercive and prohibitive public health measures were necessary to prevent harm to others.

AN "EYE-OPENER"

Singapore's participation in IGBC has also been an "eye-opener" in that it exposed us first-hand to international trends in bioethics such as the European Union's position on genetic research (germline modification) and the developments

in leading Asian biomedical research countries such as China, Japan and South Korea. We were able to network with other delegations on the side-lines as well as with members of the UNESCO Secretariat, some of whom have been invited to participate in BAC's programmes in Singapore. While the European delegations are well-organised and coordinated with their own EU Bioethics Committee, the Asian delegations were not as well organised. Singapore has tried to be a catalyst for greater collaboration and coordination amongst Asian members.

We were also kept abreast of important developments in other UNESCO committees, in particular the COMEST. One memorable and topical illustration was the presentation in 2016 on COMEST's Preliminary Draft Report on Robotics Ethics by Dr Luka Omladic, the coordinator of the Working Group which drafted the report. This wide-ranging report discussed issues from Robots in society to Robots as moral machines. It went beyond current uses (such as use in surgery) to analysing future uses of robotics such as in elderly care, education, as child companions, and the human-robot relationship. Of particular relevance to BAC would be the ethical implications of the use of Robots and AI in healthcare and biomedical research.

CONCLUSION

Given the marked revolution and advances in biomedical sciences, the ethical, social and legal issues with regard to this field are of increasing significance. The realm of bioethics is complex and multidisciplinary and therefore requires professional views and public feedback. The regional forums serve as a valuable platform for discussion and reflection regarding ethical issues, and promote mutual support and cooperation on ethical and bioethical issues of international importance. They also aim to ensure mutual understanding between scientific experts and governmental representatives. Furthermore, the importance of regional and international forums is especially paramount in the age of rapid globalisation. It is pivotal to acknowledge that each country's resolution on bioethical issues will have reciprocal effects on the affairs of other countries. Through mutual dialogue and deliberation, a general consensus can be reached such that it bolsters the movement towards adoption of the proposed Declarations. In this way, we can collectively advance science while ensuring ethical principles and values are observed to promote the common good of humanity.

The BAC remains committed to participate in regional and international forums and conferences. We aim to provide valuable insights and constructive feedback at these forums, and work closely with experts and relevant stakeholders from across the globe. This will allow us to develop partnerships and engage in bioethical issues in an informed, responsible and productive manner.

8

Bioethics for Future Generations

Voo Teck Chuan

INTRODUCTION

As an academic field, bioethics originates from the need to deal with increasingly complex ethical issues in medical practices and research, and those raised by new biomedical technologies. It now includes public health ethics, global health ethics, and the ethics of One Health (which seeks to optimise the health of human beings, animals and our shared environments which are interconnected) as subfields. Bioethicists have also embraced new methods in addition to philosophical arguments; conceptual, jurisprudential or policy analysis; and the bearing of religious and cultural perspectives to problematise and address ethical issues. 'Empirical' bioethics, which blends social scientific analysis with ethical analysis to draw normative conclusions, is now an accepted mode of research and inquiry, with standards promulgated to ensure academic rigour and that such work remains recognisably bioethical.[1] Bioethics is at its heart a normative enterprise: to make a case for how we ought to act, live or be, based on moral understandings, values and reasons.

Bioethics also appears to have increasingly real-world influence and impact at national and international levels. For example, unlike the response to the 2002-2003 SARS epidemic, the global research and innovation response to the COVID-19 pandemic coordinated by the World Health Organization (WHO) and Global Research Collaboration for Infectious Disease Preparedness and Response (GLOPID-R) included an ethics working group alongside scientific groups. An international team comprising of public health practitioners, clinicians, members of ethics committees and academics in their respective countries, the WHO Working Group on Ethics and COVID-19 "develops advice on key ethical questions that Member States need to address", and "advises WHO's technical units regarding ethical aspects of their COVID-related work".[2] Such a group illustrates the interdisciplinary and practical nature of bioethics work.

[1] Ives J, Dunn M, Molewijk B, et al. Standards of Practice in Empirical Bioethics Research: Towards A Consensus. BMC Med Ethics 2018;19:68. doi:10.1186/s12910-018-0304-3.

[2] World Health Organization 2020. Ethics and COVID-19. Available at: https://www.who.int/teams/research-for-health/covid-19 (accessed 29 September 2020).

The above development suggests that bioethics is a burgeoning "assemblage of knowledge, experts, and techniques"[3] for addressing ethical issues as they relate to the lives of human beings and other living things, through its core activities of scholarly inquiry, contribution to ethics guidance and policymaking, and participation in ethics committees or groups to provide ethics review or advice.[4] What might bioethics mean for future generations, and how might bioethics be used as a tool for dealing with the challenges they may encounter in the future? I examine these questions with respect to two groups: medical students as future doctors, and future academic bioethicists, based respectively on my experiences as a healthcare ethics teacher and an academic bioethicist trained in philosophy and medical jurisprudence.

BIOETHICS EDUCATION AND FUTURE DOCTORS

An interesting thing I have observed, having worked in bioethics for more than a decade, is that medical practitioners may differ from bioethicists in their perception on what ethics is. For example, doctors may regard treatment advice or recommendation as purely a clinical activity, as it is based on scientific evidence and clinical knowledge i.e. their experience on how particular treatment and care options may play out for patients. Ethicists may however claim that this involves ethics because treatment recommendation involves an assessment of benefits and harms, which are values of moral significance. Moreover, a doctor should seek to understand a patient's perspective on the benefits, risks and harms *that matter to that patient*, especially when the decision is not a minor one (e.g. surgery).

It seems to me that both interpretations of ethics are not wrong. It is not uncommon for medical practitioners to have the perception that ethics comes into play only when values conflict. So when a doctor recommends some treatment options, he or she would typically not see it as an activity involving ethics, even if his or her recommendation is (implicitly) based on benefit and harm assessment. What the ethicist is trying to do, on the other hand, is to make values explicit and in doing so, makes it clear that values require valuing, which may differ from patient to patient. As such, the ethicist seeks to imbue in the doctor a sensitivity to the possibility of a tension in values with the patient because of the differences in valuing and value priorities. But the doctor might not know this, as an ethicist may go on to suggest, unless he or she engages the patient through appropriate

[3] Reubi D. The Will to Modernize: A Genealogy of Biomedical Research Ethics in Singapore. International Political Sociology; 2010;4:142–158.

[4] McMillan J. The Methods of Bioethics: An Essay in Meta-Bioethics. Oxford University Press, 2018.

informational disclosure, and, through an inquiry into the patient's considerations and concerns, 'activates' the patient to participate in the decision-making process. In this way, the ethicist hopes to impress on the doctor the ethical import of an approach to care – shared decision-making – that is centred on the patient as a person. Doctors ought to form a partnership with patients in healthcare decisions to fulfil their role as a healer.

The discussion here reflects what goes on in medical ethics education at the National University of Singapore (NUS), Yong Loo Lin School of Medicine (YLLSoM), under the 5-year longitudinal curriculum Health ethics, Law and Professionalism (HeLP) track implemented by the Centre for Biomedical Ethics (CBmE). Much like other bioethical activities, the key role of a bioethicist in medical ethics education is to make plain the morally salient features of a practical issue at hand—to medical students in this case, and give normative reasons for what ought to be done, by appealing to relevant values and associated ethical principles, concepts, frameworks and approaches to care. Medical ethics education prepares medical students to respond to potential value conflicts and ethical dilemmas in healthcare as future doctors. When ethical issues or dilemmas occur, doctors should be able to recognise them and respond appropriately, and, importantly, give ethical reasons to justify their actions if asked, so that the pros and cons of their actions and of alternatives may be discussed. Medical ethics education is successfully delivered when medical students gain competencies in ethical sensitivity, reasoning, and justification, and see them as part and parcel of medical professionalism.

Higgs, a general practitioner and a medical ethicist from the United Kingdom (UK), reminds us, however, that while 'one of the "most important contributions medical ethics has made in medical care has been to focus on the idea of arguments: that we should be explicit about our reasons for doing things", good medical care may hinge on 'ordinary talk'.[5] What he means by ordinary talk is simply modes of communication to connect with people in everyday life, such as greeting others. Ordinary talk is not just about polite behaviour or good manners. Higgs uses the case of a patient with undiagnosed severe abdominal pain to demonstrate the potential 'transformative' effects of ordinary talk on medical care. After almost a fortnight of unsuccessful investigation, a senior doctor sat down with the patient, introduced himself and with the question "When

[5] Higgs R. In That (Hard) Case: Could Ordinary Talk in Clinical Care Have an Extraordinary Moral Importance? In: Voo Teck Chuan, Richard Huxtable and Nicola Peart (eds.) Healthcare Ethics, Law and Professionalism: Essays On the Works of Alastair V. Campbell. London: Routledge, 2019: 88–103.

did the pain begin?", and got the patient to recall that it started when her husband forcibly took her son back to their country of origin. The pain was linked to the anxiety and distress caused by this event; treatment should therefore go beyond the physical.

Aside from its possible benefits for medical care and outcomes, ordinary talk matters to patients in subtle ways: their perception of feeling respected, being acknowledged as equals, whether the doctor is 'there' for them and so forth. Higgs writes:

> *To someone who has never experienced receiving or working in healthcare, this seems a bizarre idea: what is the big deal about introducing oneself? Yet to an experienced patient, it may seem revolutionary and is part of the instruction given to neophytes learning about communication skills in medicine and nursing. With the advent of uniform scrubs, the situation has become worse: it is often obscure why different people wear different clothing or colours. Even as a relative sitting by, I was at a loss when a colleague asked, 'Well, who has she been seen by?" Name may mean less than expertise or position, but the anxiety of a conscious patient may increase as it is clear that something is about to be done. If the patient has been in hospital for more than a short time, the space round the bed has become home: would any of us accept people barging into one's home without asking, or saying who they were or why they were there?*[6]

I discuss Higgs's views extensively because it reminds me of the dissatisfaction sometimes expressed by clinical educators with medical ethics education provided by non-clinical, academic bioethicists like myself in the context of Singapore. A bioethicist may feel that he or she has done his job in teaching by transmitting tools for analysing and resolving ethical dilemmas to medical students. Clinical educators, on the other hand, may feel that medical ethics education should pay more attention to the cultivation of values such as compassion, empathy, integrity, humility and respect for others (which goes beyond respecting the decisional autonomy of someone else). These values, which some regard as internal to medicine, are vital to *prevent* behaviours that undermine a relationship of care and trust with patients, such as showing up late for patient appointments, dressing sloppily relative to what patients may expect from a healthcare professional, being rude to a junior colleague in the presence

[6] *Ibid*.

of patients etc. Staring at the computer screen and firing off questions with nary a look at the patient may seem efficient from a doctor's perspective in terms of 'communication' and information gathering but, as Higgs[7] writes, it may "kill a developing relationship stone dead."

Individuals are usually selected for medical training in good part because of their desire and aspiration to serve humanity by saving lives or helping patients live better, as exemplified by the compassionate care of some doctor(s) they might have encountered. If well-designed and administered, medical school admission processes would be able to exclude those who have little potential for achieving these ideals and values. Selected students would likely, therefore, have already understood, appreciated and even exhibited these values to some degree. Conceptual analysis of what these values mean, and abstract reasoning about how they can positively impact medical care are likely to be highly limited in terms of helping students translate their tendencies towards these values into regular habits of thought and action—as part of their professional identity.

Medical ethics education, as a subset of professional bioethics work, also needs to be interdisciplinary, and embrace pedagogical methods that impact most on students' conduct as medical trainees and as future practitioners. One such approach is to work with clinicians to provide regular mentorship to students, and help students reflect on what they see, hear, feel and experience in the wards or in patients' homes through the method of narrative ethics.[8]

Baldwin[9] writes that narrative ethics requires "sophistication because of the nuances of voice, of characterisation, and of narration that storytelling involves".[10] It requires "reflexivity, seeing oneself as participating in the story, having an effect on, and being affected by the story".[11] Importantly, narrative ethics requires a "commitment to openness to the story of the other, to collaboration and dialogue in the construction of both backward- and forward-looking narratives, and to the desires, values, hopes, and expectations of the person whose story it

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[7] *Ibid*.

[8] NUS Medicine has a Longitudinal Patient Experience (LPE) program, which provides pre-clinical students opportunities for appreciation of patient care through a one-year longitudinal follow-up of patients living in the community with chronic illnesses. LPE seeks to "inculcate the familiar and yet often overlooked values of empathy, patience, [and] kindness…" See website https://medicine.nus.edu.sg/newsletters/issue-14/my-story/longitudinal-patient-experience-programme/

[9] Baldwin C. Narrative Ethics. In: ten Have H. (ed.) Encyclopaedia of Global Bioethics. Cham, Switzerland: Springer, 2015. https://doi.org/10.1007/978-3-319-05544-2_302-1

[10] *Ibid.* p.8

[11] *Ibid*.

is".[12] This 'person' may be the patient or other characters, including students themselves. The essence of narrative ethics is to use stories to understand how we arrive at where we are, and what we expect of ourselves in the future, so as to understand and care for others, and ourselves. Narrative ethics may help improve ethical deliberation, or illuminate common but positive professional behaviours appreciated by patients and colleagues. By interrogating the mundane, medical ethics may become a tool for practicing ethics through ordinary talk and actions.

BIOETHICS SCHOLARSHIP AND FUTURE ACADEMIC BIOETHICISTS

Academic bioethics has been described as "the scholarly activities of individuals, usually trained in an academic discipline that deals with ethics, such as theology, moral philosophy, or law, and usually working within institutions dedicated to teaching and research".[13] To understand the meaning of bioethics scholarly activities to future academic bioethicists, as described above, we need to understand what motivates or incentivises them to do the work they do.

Obviously, like other academics, academic bioethicists' scholarly activities are motivated by personal interests, prevailing societal issues, institutional factors etc. What they research and write on and where they publish would, to some extent, be incentivised by metrics used to measure academic success: number of publications, journal impact factor, authorship roles and positions, citation count, grant income and so forth. An increasing number of academic bioethicists are turning to empirical bioethics. It is speculative but plausible that this is because of the ease to compete for grants or justify a higher grant amount when one is collecting data, as opposed to a research project that uses only a conceptual or policy analysis approach. This is not to say that empirical bioethics is not motivated by good scholarly reasons, which I discuss below.

I have written elsewhere with public health colleagues about the risks of an over focus on quantitative academic metrics to assess research output and its value in the context of public health, such as incentivising academics pursuing limited faculty positions to work in niche areas "to demonstrate novelty and differentiate their work from that of peers" and publish in prestigious journals to boost those

[12] *Ibid*.

[13] Institute of Medicine (US) Committee on the Social and Ethical Impacts of Developments in Biomedicine. Systematic Approaches to Bioethics. In: Bulger RE, Meyer Bobby E, Fineberg HV (eds.). Society's Choices: Social and Ethical Decision Making in Biomedicine. Washington (DC): National Academies Press (US), 1995: 67–86. Available from: https://www.ncbi.nlm.nih.gov/books/NBK231968/.

metrics but which may only translate to little societal value or impact.[14] In the context of bioethics, chasing novelty and metrics heightens certain risks to one's scholarly work and academic credibility because of the particular normative nature of 'good' bioethics.

A common enough joke among bioethicists is that if you want to be published in a top bioethics journal or attract citations, write something morally controversial. Controversial moral arguments may attract citations but also other things, which happened in the case of two philosophically trained, then-junior academic bioethicists, Giubilini and Minerva, who published a paper titled 'After-birth Abortion: Why Should the Baby Live?' in *The Journal of Medical Ethics* in 2013 (first online in early 2012). The paper argues for the moral permissibility of killing a new-born – which they coined as 'after-birth abortion' – in all contexts where abortion is morally permissible, on the basis that like a foetus, a new-born is only a potential person that do not possess a set of necessary properties for a right to life. The authors included disabled and healthy new-borns within their argument. They received a lot of academic criticisms on their argument, in addition to abuse and death threats from the public, and suffered setbacks to their academic careers.[15] They[16] defended themselves by saying that they had merely extended the logic of previous arguments, published *much earlier* (some in the 1970s) by other philosophers/bioethicists, and one of them highlighted social media and the erosion of respect for academic freedom (including by other academics) as reasons for the difference in treatment between them and other philosophers.[17]

But another plausible reason, in my view, for why their paper attracted higher than usual academic criticisms of a non-collegial kind[18] is that bioethics by then has become associated with practical normativity. As McMillan[19] writes,

[14] Tam C, Offeddu V, Voo TC, Sundaram N. Public Health Needs an Injection of Genuine Impact. Times Higher Education, 13 Dec 2018. Available at: https://www.timeshighereducation.com/opinion/public-health-needs-injection-genuine-impact.

[15] Described in Minerva F. What I've Learnt About Controversy. London School of Economics and Political Science Higher Education Blog, 23 August 2019. Available at: https://blogs.lse.ac.uk/highereducation/2019/08/23/what-ive-learnt-about-controversy/.

[16] Giubilini A, Minerva F. After-birth Abortion: Why Should the Baby Live? Journal of Medical Ethics 2013;39(5):261-3. doi: 10.1136/medethics-2011-100411.

[17] Described in Minerva F. What I've Learnt About Controversy. London School of Economics and Political Science Higher Education Blog, 23 August 2019.

[18] See for example, Benagiano G, Landeweerd L, Brosens I. "After Birth" Abortion: A Biomedical and Conceptual Nonsense. The Journal of Maternal-Fetal and Neonatal Medicine 2013; 26:1053-9. doi: 10.3109/14767058.2013.779661.

[19] McMillan J. The Methods of Bioethics: An Essay in Meta-Bioethics. Oxford University Press, 2018.

'good' bioethics aims to be practically normative, in the sense that it helps us find a way forward with pressing moral issues. According to McMillan, to achieve this aim, bioethics requires 'empirical' engagement, i.e. it needs to engage with the experiences, issues, concerns and (difficult) moral choices of patients, clinicians, researchers, policy-makers etc. Empirical bioethics enhances such engagement by, for example, collecting and analysing the experiences of those implementing a policy or those affected by it. McMillan argues that philosophical arguments or thought experiments, including those on morally polarizing issues like abortion, can be empirically engaged if they address actual pressing ethical questions faced by decision-makers, and practically normative if they open up new ways of thinking of these questions, by for example challenging the assumptions of our moral positions.

McMillan's account of good bioethics, which I think is right, helps us identify just why Giubilini and Minerva's argument is problematic from a bioethics scholarship perspective: it seems to lack any serious empirical engagement. They sought to defuse the backlash by declaring that "we are philosophers, and we deal with concepts" and that "we did not recommend or suggest anything in the paper about what people should do (or about what policies should allow)".[20] There are portions of the text that seem to suggest otherwise.[21] My intention is not to add to or revive the criticisms of the two authors, but to use it as a case study to understand when one has gone off-track from good bioethics. Framing one's bioethical arguments, whether controversial or not, as a purely academic and philosophical exercise to defend their advancement suggests that one has not aimed at good bioethics.

To be clear, I am not suggesting here that current academics metrics related to research adopted by many universities do not measure research productivity and impact in any way. Nor am I making a special pleading for bioethics research to be exempted from such metrics, or that future academic bioethicists or the early career ones should adopt a more conservative approach to what they publish. The argument here is for a more balanced and pertinent approach to assessing bioethics scholarly work, given its practical normativity.

[20] Described in Minerva F. What I've Learnt About Controversy. London School of Economics and Political Science Higher Education Blog, 23 August 2019.

[21] For example, they wrote: "… we do not claim that after-birth abortions are good alternatives to abortion. Abortions at an early stage are the best option, for both psychological and physical reasons. However, if a disease has not been detected during the pregnancy, if something went wrong during the delivery, or if economical, social or psychological circumstances change such that taking care of the offspring becomes an unbearable burden on someone, then people should be given the chance of not being forced to do something they cannot afford" (p. 263).

For some bioethicists, practical normativity means social advocacy. For instance, in *The Future of Bioethics*, Brody[22] argues that bioethics should seek to address power disparities in society and advocate for the interests of the voiceless, "especially when we can find ways to assist them to speak for themselves".[23] This means that bioethicists should engage in practical, scholarly activities such as community dialogue and engagement to enable the public to play a greater role in bioethical deliberations, and confront international and global ethical issues driven by unequal relationships and power beyond local medical ethics issues. Community engagement is now a common method used in bioethical research, as there is an increasing understanding that the standard bioethical toolbox of respect for autonomy and associated mechanisms of informed consent do not do all or most of the important normative work in determining the ethical acceptability of practices and policies, since they almost always impact on disempowered or vulnerable people whose voices need to be heard to understand how best their interests might be safeguarded beyond consent or voluntary agreement.

Others pursue scholarship in public health and global health ethical issues as these areas of inquiry, which emphasise collective- or social justice-oriented values such as solidarity, reciprocity and equity, are better modes for bioethics as advocacy. As Dawson[24] writes, "Public health ethics, along with public health policy and practice, is necessarily engaged in political and social activity. Such an approach is an appropriate model for bioethics as a whole".[25] For others, bioethics means acting on one's normative conclusions in a sustained and committed way, i.e. activism which may be defined as a spectrum of activities to campaign for change to rectify ongoing wrongs or wrongdoings.[26] The risks and cost of bioethics as activism, such as loss of academic objectivity (perceived or actual), have been discussed.[27]

My point here is that there is growing recognition that bioethics scholars should aim to have a real-world ethical impact in their research, which is enhanced by engagement with experience through ethics committee work, policy writing and contributions, engagement and dialogue with relevant stakeholders for the

[22] Brody H. The Future of Bioethics. New York, Oxford University Press, 2009.
[23] *Ibid.* p.217.
[24] Dawson, a. (2010), The Future of Bioethics: Three Dogmas and A Cup of Hemlock. Bioethics, 24: 218-225. doi:10.1111/j.1467-8519.2010.01814.x
[25] *Ibid.* p.224
[26] Draper H, Moorlock G, Rogers W, Scully JL. Bioethics and activism. Bioethics 2019;33(8):853–856. doi: 10.1111/bioe.12680.
[27] See the special issue 'Bioethics and Activism' in Bioethics (volume 33, Issue 8) published in October 2019.

research topic, and of course interdisciplinary collaboration with scientists, practitioners, humanities and social science scholars etc.

Besides peer-reviewed publication in well-regarded international journals, bioethicists could deliver real-world societal value by, for example, writing a commissioned report to scope key ethical issues and considerations to support policy-work; or, publishing original work in a local medical publication on an issue close to local practitioners' hearts. For bioethicists from high-income settings with resources like internet access and well-stocked libraries, they may find it important to apply for research funding on projects led by colleagues from a low-and middle-income setting to study under-prioritized but pressing ethical issues in low-and-middle-income countries (LMIC) settings, and publish resultant articles or even their study protocol in open access, funded-based and peer-reviewed platforms[28] to enable LMIC scholars to build upon the ideas. As educators often say, assessment drives learning. It is also a truth that research evaluation systems drive productivity in scholarship. Socially impactful bioethics scholarship comes in many forms, which should be recognized and valued by academic institutions to motivate bioethicists to aim for and achieve practical normativity.

CONCLUSION

Professor Alastair Vincent Campbell, who founded NUS CBmE, is a former member of the Bioethics Advisory Committee and is fond of nautical metaphor and imageries. He[29] describes the potential misuse of bioethics committees by governments to "sanction what, on economic and political grounds, they intend to do anyway" as 'blessing the battleship'.[30] On medical ethics, he[31] argues that it should engage with the "social-political context [such as the globalization and the force of free-market ideology] within which medicine seeks to preserve and promote human values"[32] and not just the conduct of medical practitioners. Critiquing only the latter would be akin to "merely rearranging the deck chairs on board the *Titanic* even as the vessel sinks".[33] As his mentee, I shall continue his

[28] An example of such a platform is Wellcome Open Research.
[29] Campbell AV. Public Policy and the Future of Bioethics in Asia, Asian Bioethics Review 2008; inaugural edition: 24–30.
[30] *Ibid.* pp. 24-25
[31] Campbell AV. An Accidental Ethicist. Reflections On My Career in Medical Ethics. In: Voo Teck Chuan, Richard Huxtable and Nicola Peart (eds.) Healthcare Ethics, Law and Professionalism: Essays On the Works of Alastair V. Campbell. London: Routledge, 2019: 11–19.
[32] *Ibid.* p. 18
[33] Campbell AV. Public Policy and the Future of Bioethics in Asia, Asian Bioethics Review 2008; inaugural edition: 24–30.

tradition. Simply put, bioethics, be it in education, research or service, should sail in the well-charted waters of interdisciplinarity and practice-based and -oriented approaches to arrive at ports of academic, moral and societal significance.

9

Inclusive Bioethics for the Future in Multi-religious Singapore

Nazirudin Mohd Nasir

INTRODUCTION

The fabric of industrialised societies in advanced economies continues to evolve in many ways under the twin influences of modernity and globalisation. In Singapore, while state governance and public institutions remain staunchly secular, faith communities continue to be a significant part of society with many Singaporeans identifying strongly with a religion.[1] Unlike secularism that is commonly found in the West such as the French *laïcite*', faith communities here are free to hold on to their beliefs and practices both in private and public so long as the common good is not compromised and religion is not politicised as a tool for governance. This middle path but delicate state of affairs require all segments of society to play their role judiciously. Every community, even as it seeks to advance its own interests, should place the collective good of society above all else. There are many examples that speak to this principle in the context of Singapore. In this chapter, I wish to highlight the role of the Bioethics Advisory Committee (BAC) over the last twenty years since its founding that has facilitated and encouraged the inclusion of diverse voices, including faith-based ones, on bioethics. I argue that this inclusive approach is important in a culturally and religiously plural state. When such inclusivity is pursued, the benefits to society are innumerable. However, this approach is neither intuitive nor sustainable without further efforts by both the state and society in a world that is becoming increasingly exclusivist and polarised.

RELIGION AND SCIENCE

Religion and science, as with faith and reason, have had a long and fractious relationship, in large part because of different ontological and epistemological views of the world. From the trial of Galileo by the Roman Catholic Inquisition in

[1] Mathews, M. (2019). Religion in Singapore: The Private and Public Spheres. IPS Working Paper Series.

the early seventeenth century to Darwin's theory of evolution by natural selection in the nineteenth century, religion and science had been seen as independent authorities on truth. There are also the resultant problems of scepticism and distrust – one views the other as less objective, less moral, or even less honest about its aims and objectives. Faith in the most traditional sense places people on an entirely different plane from the rationality of science. Each speaks as a victor triumphant over the other and dialogue becomes inconsequential. Barbour calls this relationship a 'conflict', which harks back to the time of Galileo and Darwin.[2] Yet, if we go back even further, in the earliest days of the interaction between faith and reason, such an adversarial view of affairs is misleading, or at least incomplete. Not all people of faith dismissed science and rational thought or see either as incompatible with religion. Luminaries in medieval thought - the Muslim philosopher and jurist Averroes (Ibn Rushd) in *The Decisive Treatise on the Harmony between Religion and Philosophy*, his contemporary the Jewish philosopher Moses Maimonides in *The Guide to the Perplexed*, and the Christian theologian Thomas Aquinas in *Summa Contra Gentiles* - addressed questions of conflict or reconciliation. For these thinkers, the human intellect or reason has an important place alongside faith, and to varying extents, both can be harmonised.

The thriving spirit of discovery, not only in the scientific sense but also in cultural, religious and civilisational expressions, manifested by travellers such as Christopher Columbus and scientists such as Copernicus and Galileo, opened up new philosophical frontiers and challenged age-old frameworks and worldviews, much of which were grounded in conventional religious beliefs and theology. It is true that some still view that the 'religious' and the 'scientific' are two distinct and irreconcilable worldviews. For example, the Draper-White thesis arose from two late nineteenth-century publications that spoke of conflict – 'religion' supposedly draws its legitimacy from faith, myths, emotions and metaphysics, while 'science' is empirical, objective, rational, and normative. However, others have argued against this conflictual stance, inspired by the luminaries of harmonisation from the middle ages. In reality, this relationship was much more complex than imagined – there was conflict, but there was also dialogue, accommodation, compromise, and understanding.[3] Today, others have argued that religion is not irrational, whilst science is also not bereft of metaphysical concerns.[4] Using Barbour's taxonomy, dialogue and integration are certainly feasible outcomes.

[2] Barbour, I. (2000) When Science Meets Religion. San Francisco: Harper.

[3] Lindberg, D. C. (2002). Medieval Science and Religion, in Gary B. Fergnren (Ed.) Science and Religion (pp. 57-72). Baltimore and London: The Johns Hopkins University Press.

[4] Biggar, N. (2015) Why religion deserves a place in secular medicine. Journal of Medical Ethics, 41 (3), 229-233.

We could go further and argue for the complementarity of both as we seek to overcome complex current and future challenges.

THE 'RELIGIOUS' AND THE 'SECULAR'?

Even after we accept the premise that religion can get along well with science and its philosophical presuppositions, other questions remain on the place of religion and religious voices in an increasingly diverse public sphere. In matters of public policy, how should this diversity be addressed? More specifically, what role does religion play, if any, in shaping public opinion and policies within a secular context? Are both dialogue and integration still possible and should it be encouraged? For a start, we need to revisit the ways we understand 'religion' and avoid getting trapped in a reductionist worldview. There is little doubt that religion and its diverse traditions are usually understood with reference to religious texts, cultures, rituals and institutions. In the simplest terms, there is no 'Buddhism' without the Buddha, no 'Hinduism' without the Vedas, no 'Islam' without the Qur'an, no 'Christianity' without the Bible etc. Religious institutions and sacred spaces too, such as temples, monasteries, priesthood, play fundamental roles in religious expression and life. But the more restrictive our view of the meanings and roles of religion is, the more we misconceive that the spiritual and social spaces of faith communities exist in and of themselves, apart from other facets of society. Yet, we also know that religions are deep hermeneutical movements – there is constant interpretation, negotiation, adjustment, and accommodation to the world. In many cases, faith communities are important actors and agents of social change itself.

The history of religions itself is precisely a history of social transformations. In ancient times and antiquity, religious movements were born in response to human pain or suffering, oppression, social depravity and inequalities. In the ancient East, the young Siddhartha Gautama witnessed suffering and meditated until his eventual enlightenment and the emergence of the figure of Buddha. Biblical prophets in the Old Testament, and Jesus in the New Testament, assailed against despots and unjust rulers, seeking to achieve kindness and compassion to self and others. In the modern period, the German sociologist Weber discussed social transformation in the context of Protestant Europe.[5] A common feature of religions that permits this sort of interactivity with society is the emphasis on ethics, especially social ethics.

[5] Weber, M. (1905). The Protestant Ethic and the Spirit of Capitalism.

As faith communities navigate the world around them, they will almost certainly interact, sometimes very fiercely so, with other forces and spaces. Today, the 'secular' is dominant as a social and mental force and space, where religious principles and teachings prima facie do not hold sway over public governance and policies. In the modern period, the booming scientific enterprise driven by a relentless pursuit of economic growth led some to imagine a world soon without religion. The world entered what the philosopher Charles Taylor termed 'a secular age'.[6] But Taylor and others pointed out an important observation that challenged this 'secularisation theory' – many faith communities remained strong even as their societies modernised.[7] Such communities have either learnt to co-exist with material progress no matter how tenuous or threatening the relationship, or privileged religious practices and lifestyle over material concerns. No doubt faith's once persuasive power in the public realm have weakened, but its appeal to large swathes of the population continued and takes new forms.[8]

In their response to the onslaught of scientific advancement and secularisation, some communities have been able to accommodate change so well as to result in a sort of cultural infusion and enmeshment that challenges the notion of a bifurcated world – the 'religious' and the 'secular'. Such neat delineations and boundaries that we may still hold on to are not reflective of a new social reality that we live in. Singapore is a good example in this regard. Even within spaces which have largely been traditionally defined as 'religious', 'secular' spaces co-exist. Whether in the physical or mental sense, faith communities give due consideration to 'secular' needs and interests and adapt to these even as they remain committed to their faiths.

In our recent experiences in dealing with the COVID-19 pandemic, faith communities have had to make fundamental adjustments to their practices in the interest of public safety and to save lives. But we need to remember that religions are, in essence, about community life – social contact and collective presence are defining features of many faith communities. 'Social distancing' is therefore anathema to religious life.[9] While some may argue that there was not much choice in this matter, the reactions of faith communities and their leaders to such adjustments denote a significant degree of acceptance of scientific insights, such as how the virus is transmitted and what safety measures are necessary to

[6] Taylor, C. (2007) *A Secular Age*. Harvard: Harvard University Press

[7] Joas 2009 'Does modernisation lead to secularisation?' in W. Gräb & L. Charbonnier (eds.), Secularization theories, religious identity and practical theology, Lit Verlag, Münster.

[8] Casanova, J. (1994) Public religions in the modern world, University of Chicago Press, Chicago.

[9] Akyol, M. (2020, April 8). Thou Shalt Practice Social Distancing. Foreign Policy. https://foreignpolicy.com/2020/04/08/thou-shalt-practice-social-distancing/

prevent it. Their acceptance that their faith is not compromised as they adapt to the unprecedented circumstances is premised on their *belief* in science-based facts in the same way they adhere to religious tenets and teachings. On a global scale, there have been examples of faith communities rejecting science and medical guidance, on the basis that religion (in some cases, theologies) opposes such insights. 'God is greater than the virus', some have declared. We are fortunate that we do not see similar attitudes here in Singapore. On a whole, faith communities here have been more receptive to scientific advice and opt to live under the guidance of both scientific insights and religious teachings. Like Averroes, Aquinas or Maimonides, we have found ways to reconcile. This highly sophisticated intertwining of our mental frameworks can, over time, lead to a model of co-existence between the 'religious' and the 'secular' that could reshape traditional bifurcated models.

BAC AND INCLUSIVE CONSULTATION

The ways in which faith communities have responded to COVID-19 are not the only examples of how religion interacts with science in Singapore, nor are they unprecedented. As noted above, although Singapore is governed in a secular fashion, its society is largely religious.[2] This fact alone gives rise to innovative ways for the state to address the religious needs and interests of society, which includes engaging faith communities on issues of public interest. In this regard, the BAC has done well to adopt an inclusive bioethical discourse in Singapore. In considering the role of religion, the BAC holds the view that:

> *... in a multi-racial, multi-religious and pluralistic society like Singapore, public policy has to be based on a considered weighting and balancing of the spectrum of views held by various sectors.*[10]

It has consistently engaged faith communities and considered religious views when deliberating major bioethical quandaries.

The BAC was formed in 2000, soon after Singapore embarked on the Biomedical Sciences Initiative as part of its economic restructuring. It consults widely with the aim to advise the government on the regulation of human biomedical research. It is thus important to ensure that the recommendations which BAC put forth to the government include responses from a wide spectrum

[10] Bioethics Advisory Committee (2002) Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning.

of the Singapore society. To this end, the BAC actively seeks views by inviting religious groups to respond to its consultation papers. In the first published report by the Committee on human stem cell research in 2002, it sets out clearly the consultative approach and process that take into account Singapore's social and religious diversity:

> *With the relevant scientific, ethical, social and legal issues in mind, the BAC embarked on an extensive consultative process, to further understand all aspects of the subject matter, and more importantly, to understand the concerns and sentiments of local interest groups and the general public. The consultation process enabled the BAC to obtain very comprehensive information, especially on theological, social and cultural sensitivities, for the purposes of its deliberations.*

The report further adds that 'social norms, theological perspectives, and philosophical persuasions shape the answers given by each society.' In one of its conclusions, the 2002 report states that "the recommendations strike a proper balance between allowing research with tremendous potential therapeutic benefits to mankind to proceed while affording a measure of respect and level of protection to human embryos which takes into consideration the diversity of views on the status of the human embryo."[11] This principle is also reiterated in a more recent report on guidelines for Human Biomedical Research published in 2015. Throughout the report, the BAC explicitly acknowledges differences in views attributable to religious positions (such as on elective abortions and the beginning of human life). The BAC had also dedicated greater academic discussion to the issue of genetic privacy through a publication in 2013, in which specific chapters dealt with Confucian and Muslim ethics alongside legal and western philosophical approaches.[12] In the 2015 report titled Ethics Guidelines for Human Biomedical Research, the Committee made clear the need to respect religious and cultural diversity on the autonomous aspect of human beings, as well as on the use of human tissue.[13] All these clearly demonstrate the adherence by the Committee to a comprehensive and inclusive approach in considering ethical views.

To date, nine consultation papers ranging from human stem cell research in 2001 to the most recent mitochondrial genome replacement technology in

[11] Bioethics Advisory Committee (2002) Ethical, Legal and Social Issues in Human Stem Cell Research, Reproduction and Therapeutic Cloning.

[12] Kaan, T. S. & Ho, C. W. (2013). *Genetic Privacy*. London: Imperial College Press.

[13] Bioethics Advisory Committee (2015) Ethics Guidelines for Human Biomedical Research.

2018 have been issued, and most religious groups and their representatives have offered views on each, either through written submissions or by attending dialogue sessions organised by the Committee. I have been personally involved in many of these consultations as a representative of the Muslim community. I have also had the honour of being a member of the BAC, which has helped me consider a wider range of scientific, legal, and ethical thought, as well as to put the views of my community in perspective. This process has been immensely beneficial, and is, in my view, more important than the outcome. The engagement has been direct, transparent, and inclusive. I would go so far as to argue that it serves as a good model for citizen-engagement in other public policy matters, which has become increasingly important with a changing demography.

REFLECTIONS ON THE FUTURE

Biomedical technologies and advancements in the last few decades had raised numerous ethical concerns, much of which had to do with long-term impact on humanity. Today, scientific industries are part of the larger and much more dominant capitalist culture which operate autonomously from other non-scientific considerations, including religious ones. Big pharmaceuticals are intensely developing new and innovative treatments that could improve human lives but also radically alter its trajectory or could even cause moral hazards. The COVID-19 pandemic and the quest for a vaccine is the most recent example in a long list of biomedical issues that will have wide-ranging impact and consequences on the ways we lead our lives.

At the time of writing, some countries, including Singapore, have embarked on community immunisation programmes in the hope of returning life to pre-COVID-19 conditions as soon as possible. While there is great urgency for such works – because the longer the pandemic lasts, the worse its health and economic impact – the ethical considerations both in developing as well as implementing vaccination are equally important. In Australia, prominent Catholic figures have spoken in defence of the rights of its followers to refuse a vaccine on religious and moral grounds,[14] while many others remain concerned over the safety of the vaccines especially over the long term. The vast field of biomedical ethics has therefore become all the more critical in ensuring a carefully-developed and thought-through scientific and medical progress for the future. As I have argued elsewhere, as long as such advancements and technologies affect humanity,

[14] The Archbishop of Sydney expressed concerns about vaccines developed from the cell lines of electively aborted foetuses.

bioethical discussions should include all voices regardless of creed, race or social status.[15]

Considering that the realm of public morality concerns the fundamental question of how we ought to live as a collective unit, religious communities would recognise and accept that this is not their exclusive prerogative. However, some theistic ideas and reasoning, i.e. those that deal with notions surrounding the idea of God, scripture and the sacred, can appear exclusive even as they speak on anthropocentric concerns such as human suffering, and can deepen some fault-lines with science. These include (1) science plays God; (2) pain and suffering are part of God's plan and should be accepted; (3) divine-based moral ethics are superior to scientific ones. While it is true that such theistic reasoning has been commonly espoused in faith circles, we also need to recognise that faith, traditions, and religious thought are diverse because internal hermeneutics and other socio-political factors can influence one's moral worldview. There are strands of thought and practice within faith communities that offer greater hope of partnership with science in the pursuit of sustainable and morally acceptable futures.

In this regard, many emerging areas of studies such as thick anthropology, cognitive science, evolutionary biology, and cultural anthropology, help us better understand the multifaceted universe and sources of moral thought. Even for those who speak from a faith perspective, his or her moral view is most likely an outcome of a combination of factors. From the lens of cognitive psychology, Pascal Boyer argues that religious codes are not necessarily the origin of moral thought, and even religious people's ideas on morality are constrained by intuitions which they share with everyone else.[16] In the case of Islam, other studies have shown that Muslim communities living in more secular societies, such as in Southern and Eastern Europe, disagree if one must believe in God in order to be a moral person.[17] This raises doubts on the approach to typologise moral thought into the religious and the non-religious. Add to this the question of where should we situate the moral views of hyphenated identities in our societies today – those of a religious humanist, a secular Muslim or a secular Jew, as examples. Would it therefore be of much benefit to demarcate their moral views and classify them as religious or otherwise?

[15] Nasir, N. M. (2013) Individual Right vs. Public Interest, in Kaan, T. S. & Ho, C. W. (2013) *Genetic Privacy* (London: Imperial College Press)
[16] Boyer, P. (2001) Religion Explained.
[17] Pew Research Centre. (2013). The World's Muslims: Religion, Politics and Society.

To continue to insist on such classifications may inadvertently divide our society further in a new and plural social reality. We have also seen new possibilities in the complementarity and overlaps of ethical thought, such as between eastern and western philosophies as well as religiously and non-religiously derived. Perhaps, the challenge then is not so much relating to the substance of moral thought as to adapting our moral language. Some contemporary philosophers such as John Rawls and Habermas have begun to envision this possibility through the means of public reason. The latter, once a staunch critic of the role of religion in the public sphere because of his earlier thought on secularism, is of the opinion that increasing religious and cultural pluralism calls for greater consideration of religion in the public sphere. But how could this be balanced with the principle of keeping the public sphere neutral and for all parties to speak without prejudice to other viewpoints? One way is to adopt a common and non-religious language and mode of discussion, i.e. to move away from faith-based claims. The question arises if this is at all possible. In contemporary Catholic thought, the idea of public theology is one such response, where more rational discussions in the public sphere should be encouraged.[18] De Gruchy explains this further that "good public theological praxis requires the development of a language that is accessible to people outside the Christian tradition."[19]

In my view, the BAC provides a good example of how to approach the plurality of moral language. It has shown the ability to consider reasoning couched in religious contexts, but engages with such views by taking into account other possible interpretations of the same reasoning. In its most recent report,[20] it discusses the notion of science 'playing God'.

> *The expression 'playing God' is often heard in connection with research or practice at the boundaries of medicine, and the exact meaning to be attributed to it may depend on the speaker. Religious critics may mean by it that interference with the process of creating and destroying life is interference with divine prerogative. In its secular form, this criticism can imply that we may suffer from scientific or ethical hubris, a pride in power that blinds us to limitations or unforeseen risks. Such concerns should not be lightly dismissed, but they are not without answers. Whatever we do will affect future*

[18] Kim (2007) 'Editorial', *International Journal of Public Theology* 1, 1,'4.
[19] De Gruchy (2007) 'Public theology as Christian witness: exploring the genre', International Journal of Public Theology 1, 26, 41.
[20] Bioethics Advisory Committee (2002) Ethical, Legal and Social Issues in Human Stem Cell Research, Reproduction and Therapeutic Cloning.

generations. It is thus also 'playing God' if we prohibit research that might help patients.

This approach permits a richer conversation and a more inclusive discourse. Yes, there is a risk that we end up 'secularising' moral thought and excluding religious views once again. As such, we should open up public discourse not at the expense of any particular mode of moral thought. Rather, we should anticipate differing viewpoints and even disagreement, and move away from the unhelpful assumption that differences are a product of a clash between religious and non-religious worldviews.

CONCLUSION

We live in a world beset with unprecedented and existentialist crises. Science can and will help humanity overcome some of these challenges. In doing so, science itself can become a 'religious' experience; its mission is to improve our human condition. If this bears resemblance to religiosity, then perhaps that speaks to the artificiality of the boundaries between science and religion. Likewise, religion too can be scientific when it engages in the quest of rationality. The crises we face will force both sides to adapt and reconcile so that humanity survives and our lives improve. When this happens, the boundaries between them will dissipate even further.

When we are no longer limited by oppositional categories such as the religious or the secular, we will worry less about when to speak and focus more on the pertinent matters at hand, for the betterment of our common humanity. Noting that the interest and aims of both scientific research and religions in securing and enhancing the common good and improve human condition coalesce, it is possible to imagine, and becomes imperative to forge, a more inclusive public sphere. The BAC has done well in this regard for the last twenty years. I am optimistic of its contribution in shaping an inclusive bioethical discourse in an increasingly diverse world for the future.

10

Bioethics and the Legal Landscape

Charles Lim Aeng Cheng

JUDICIAL RECOGNITION OF BAC

This chapter's approach is to explain how the work of the Bioethics Advisory Committee (BAC) has influenced the development of biomedical laws in Singapore — both legislation and the common law. The Singapore Court of 3 Judges[1] in 2013 in the landmark decision on the ethics of innovative treatment and biomedical research in *Pang Ah San v Singapore Medical Council* ("*Pang Ah San*")[2] described the BAC as —

> *the Bioethics Advisory Committee…, which was appointed by the Singapore Cabinet*[3] *in December 2000 to examine the legal, ethical and social issues arising from research on human biology and behaviour and its application, and to develop and recommend policies on legal, ethical and social issues with the aim of protecting the rights and welfare of individuals, while allowing the life sciences to develop and realise their full potential for the benefit of the wider community.*

MEANING OF BIOMEDICAL RESEARCH AT COMMON LAW

In determining the meaning of "biomedical research", the *de facto* Court of Appeal in *Pang Ah San* cited with approval the BAC's definitions of direct and indirect "human biomedical research" in its Report, "Research Involving Human Subjects Guidelines for IRBs (November 2004)".[4] The Court also highlighted the Ministry of Health's directive to all doctors in January 2006 that the BAC Guidelines would be used as *the standard for ethical conduct in research* in the

[1] The High Court of 3 Judges has been referred to by the Court of Appeal itself as a *de facto* Court of Appeal and often comprises a coram similar to the Court of Appeal which is the apex court in Singapore.

[2] Pang Ah San v Singapore Medical Council [2013] SGHC 266 at [32]

[3] The Chair and members of the BAC are no longer appointed by the Cabinet but instead by the Minister for Health.

[4] [2013] SGHC 266 at [33] and [34].

evaluations and deliberations of the Singapore Medical Council.[5] In *Pang Ah San*, V K Rajah JA (as he then was) explained at [64] the significance of the distinction between research and therapy. Therapy is excluded from the regulatory regime which provides for prospective review applicable to research, as recognised by the BAC Guidelines. The objective of this distinction is to identify an activity where there is a deviation between serving the best interests of the patient and the interests in developing "generalisable knowledge".

ROLE OF INSTITUTIONAL REVIEW BOARDS

The role of Institutional Review Boards were explained in detail in Chapter 2. The importance of the role played by IRBs in the ethical governance of research was also recognised in *Pang Ah San.* The Court recognised that IRBs acted as an "ethics review gateway" for all human biomedical research. The Court cited paragraphs 4.4 and 5.6 of the BAC Guidelines for IRBs 2004 that IRBs assure the "safety, health, dignity, welfare and well-being of human research subjects and to safeguard against research practices and objectives that are not ethically acceptable to society at that point in time". The BAC Guidelines for IRBs recommended that all human biomedical research be reviewed and approved by a properly constituted IRB before it is allowed to proceed. Some research, however, could qualify for Exempted Review or Expedited Review. Research institutions should establish and maintain effective IRBs. These roles and duties of IRBs were institutionalised with the enactment of Part 4 of the Human Biomedical Research Act 2015 (HBRA). Part 4 of the HBRA and the Human Biomedical Research Regulations 2017 are consistent with many of these recommendations.

Interestingly, the Court made an *obiter* observation on the potential liability of IRBs for the unintended consequences arising from research, which to date has not been tested in the courts. The Court stated that IRBs "should not be held legally responsible for any unintended consequences arising from the employment of innovative treatment". It is the researcher or physician who should be wholly responsible. Paragraphs 6.5 to 6.6 of the BAC Guidelines were cited by the Court in support of this observation.

THE STAGE IS SET

The Court's recognition of the BAC and the role of the BAC's reports and guidelines in *Pang Ah San* set the stage for this review of the BAC's influence

[5] See Ministry of Health, Governance Framework for Human Biomedical Research (December 2007) ("Governance Framework for Human Biomedical Research") at footnote 2

on the development of Singapore's biomedical legal landscape. The Court recognised that the BAC Guidelines are "*the standard for ethical conduct in research*". As we shall see later, the recommendations in the BAC's reports have directly influenced Singapore's policymakers and the legislature in the formulation of biomedical legislation. It is not possible to cover in detail all the BAC recommendations that have been translated into legislation. This chapter therefore endeavours to cover the more significant recommendations.

FIRST BAC REPORT ON STEM CELLS ETC.

The BAC's first report issued on 21 June 2002 focused on the Ethical, Legal and Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning.[6] The BAC recognised that it was crucial to set up a comprehensive legislative and regulatory framework to control human stem cell research. It proposed the establishment of a regulatory body to license, control and monitor human stem cell research in Singapore. In 2002, there was only a diffused system of oversight by IRBs or ethics committees and a patchwork of legislation and guidelines such as the Medicines (Clinical Trials) Regulations which applied only to pharmaceutical trials.

Dolly the sheep became a scientific sensation when her birth was announced in 1997. Her relatively early death in February 2003 fuelled the debate on the ethics of cloning research and the long-term health of clones. The BAC took the view that the creation of a human being by any cell nuclear replacement techniques or any other method should be prohibited as the public policy reasons against this were and still are overwhelming. The Singapore legislature responded in 2004 by banning human reproductive cloning through the enactment of the Human Cloning and Other Prohibited Practices Act 2004 (2004 Act). This Act also prohibits the import and export of any human embryo clone into and out of Singapore and the commercial trading of human eggs, sperm and embryos. These were also recommendations in the BAC Report. In addition, the BAC Report recommended the prohibition of the development of a live human embryo for research purposes beyond 14 days. The BAC reasoned that the primitive streak appears with the onset of cell differentiation and organ formation including the nervous system (recommendation 2) on day 14. Section 7 of the Act implemented this recommendation by prohibiting the development of human embryos outside

[6] See Knoppers, Kirby and Isasi, Genetics and Stem Cell Research: Models of International Policy-making, chapter in Bioethics in Singapore, the Ethical Microcosm, World Scientific, 2010 Editors Elliott, Ho and Lim

of the body of a woman for a period of more than 14 days. The policy framework established by the BAC was previously reinforced by the "Directives for Private Healthcare Institutions providing Assisted Reproduction Services" issued by the Ministry of Health.[7] This framework was placed on a firmer footing and superseded in respect of research in November 2017 by the Human Biomedical Research (Restricted Research) Regulations 2017. Recommendation 7 prohibiting the implantation of a human embryo clone into a womb or any treatment of such a human embryo for development into a viable infant was implemented by Section 13 of the 2004 Act. Under Section 31 of the HBRA, certain types of sensitive research such as those involving human embryos are regulated as "restricted research" and subject to case-by-case approval by the Director of Medical Services. Even after approval, they are subject to additional requirements. Section 30 of the HBRA also prohibits ethically unacceptable research such as research into certain types of human-animal research, human-animal embryos, or human embryos beyond 14-days, on pain of criminal sanctions.

EARLY ATTEMPTS AT COMPREHENSIVE BIOMEDICAL RESEARCH LEGISLATION

As mentioned above, the BAC's first report in June 2002 recognised that it was crucial to set up a comprehensive legislative and regulatory framework to control human stem cell research. It proposed the establishment of a regulatory body to license, control and monitor human stem cell research in Singapore. There was an early attempt at crafting this comprehensive framework in the form of the public consultation on the draft regulation of Biomedical Research Bill issued on 10 November 2003 by the Ministry of Health. The proposed draft Bill was not however introduced in Parliament. The Ministry explained on its website that after carefully considering the feedback received, it decided "to adopt a step-by-step approach to regulating biomedical research activities". As a first step, it proposed to enact the Human Cloning and Other Prohibited Practices Act to prohibit human reproductive cloning, as this was the issue associated with the greatest ethical concerns at that time. One perspective of the HBRA made with the benefit of hindsight is that this early and highly prescriptive regulatory legislation might have impeded biomedical research in unintended ways in the period between 2002 and 2015 when the HBRA was enacted. For example,

[7] These Directives then established the regulatory framework for all research involving human embryos and oocytes. Regulation 4 of the Private Hospitals and Medical Clinics Regulations (Cap 248, R1) mandates compliance with the Directives. Cited in Knoppers, Kirby and Isasi, Genetics and Stem Cell Research: Models of International Policy-making in Bioethics in Singapore, the Ethical Microcosm, World Scientific, 2010 Editors Elliott, Ho and Lim.

subsequent scientific advancements might render the statutory definitions of some technical terms obsolete or the regulatory net might have been cast unduly wide and caught unintended activities (e.g.anonymous online surveys with no other interaction with research subjects). Even after its enactment in 2015, this "step-by-step approach" was adopted in bringing the HBRA into force incrementally in phases culminating with the implementation of the human tissue framework only on 1 November 2019.

PROTECTION OF PERSONAL INFORMATION IN RESEARCH

The BAC in its May 2007 report, "Personal Information in Biomedical Research", recommended the establishment of a comprehensive statutory framework relating to the use and protection of personal information in biomedical research. Recommendations were also made for the early de-identification of personal information used for research and for adequate measures to be taken by researchers to prevent inadvertent identification and safeguard the confidentiality and privacy rights of individuals if their personal information was identified (recommendations 2 and 3). The Report also recommended that irreversibly de-identified personal information need not be subject to privacy and confidentiality requirements (recommendation 4) and the issue of proportionality to the sensitivity of the information or the research in adopting privacy and confidentiality safeguards (recommendations 5 and 6). With the exception of the recommendation relating to the national diseases' registry, the recommendations in the Report have by and large been implemented in the HBRA.

Individually-identifiable information and the HBRA

The ambit of the HBRA turns largely upon the definition of "human biomedical research" in Section 3. With certain exceptions, the definition is limited to research involving *individually-identifiable* human biological material or individually-identifiable health information. The exceptions are research subjecting an individual to intervention and what is known as "restricted research" involving human gametes or embryos and human-animal combinations. The requirement for appropriate consent to be obtained for the use of an individual's biological material or individually-identifiable health information is an important pillar of the HBRA (Section 25). Every person who has obtained individually-identifiable information or human biological material for the purposes of human biomedical research must take all reasonable steps and safeguards as may be

necessary, including rendering information or material non-identifiable, to protect such information or material (Section 27). Section 28 further prohibits the re-identification of anonymised information or biological material without consent or a court order. Persons such as IRB members, research institution staff and ministry officials are also prohibited from disclosing any individually-identifiable information of any research subject which has come to their knowledge in the course of discharging their functions or duties under the HBRA (Section 29). Recipients of such information are also held accountable.

National Disease Registries

The 2007 Report also recommended the clarification of the legal basis for the disclosure of medical information to national disease registries by physicians. Mechanisms should be established, enabling national registries and healthcare institutions to facilitate the use of personal information held or controlled by them for biomedical research that can significantly advance the public good, while safeguarding privacy (recommendation 7). This recommendation was implemented with the enactment of the National Registry of Diseases Act in 2007 to establish the National Registry of Diseases and impose mandatory obligations[8] on healthcare institutions to submit relevant epidemiological data to the National Registry of Diseases for public policy and planning purposes.[9] Of ethical importance is the fact that the patient's consent for the disclosure is not required but the *quid pro quo* are the safeguards imposed on the registry as custodian of the confidentiality of such patient information. In moving the National Registry of Diseases Bill on 27 November 2007, the then Health Minister Khaw Boon Wan explained that the Act drew upon the recommendations of the BAC in its 2007 report after an extensive public consultation. The Minister cited the BAC's conclusion that it is "ethically proper for medical information to be disclosed by physicians to national disease registries without patients' consent, provided that adequate privacy and other ethical safeguards are in place and patients are appropriately informed".[10] Identifiable patient information may be disclosed under the Act for the purposes of national public health programmes. Such disclosure will need the approval of the Director of Medical Services (DMS).

[8] The Act (Section 6) imposes on the manager of a healthcare institution the duty to notify the Registrar of cases in which a person has been diagnosed with or undergoing treatment for a reportable disease at the healthcare institution. The Act (Section 7) empowers the Registrar or an authorised Registry officer to collect prescribed additional information from the manager of a healthcare institution who has made such a notification.

[9] The long title of the Act explains it as "to provide for the compilation of information on the incidence of certain diseases for use as a basis for the direction of programmes for disease prevention and control".

[10] BAC Report, Personal Information in Biomedical Research, May 2007 at para 20, p. 4.

In deciding whether to give his approval, the DMS will, amongst other things, consider the aims and objectives of the proposed programme, and whether it has any public health benefits to Singapore. He must be satisfied that the programme cannot be carried out using anonymised data. Furthermore, the DMS must be convinced that adequate measures will be put in place to protect the individually-identifiable information from unauthorised disclosure.

HUMAN TISSUE FRAMEWORK

On 12 November 2002, the BAC issued its second report titled "Human Tissue Research" which set out guidelines for human tissue banking, and for biomedical research which involves the use of human tissue samples. The BAC explained that "our primary objective has been to recommend a basic framework for the ethical and legal regulation of human tissue research in Singapore", and that the new guidelines should meet the objective of providing "a firm foundation for the proper and ethical governance of human tissue research in Singapore".[11] The BAC's recommendations included: i) building on the system of institutional self-regulation by tissue banks and suggested a safeguard in the form of a statutory licensing system for research tissue banks; ii) the adoption, in the conduct of research tissue banking, of the principles of the primacy of the welfare of the donor, the requirement for informed consent, the obligation of confidentiality, and respect for the human body. Other guidelines and recommendations dealt with the basis on which donations of human tissue are to be made, procedures for the ethical review of research proposals and access requests, and operational aspects of tissue banking.

These recommendations were implemented with the enactment of the HBRA in 2015. The legislative framework for the regulation of human tissue activities and tissue banking is found in Part 6 of the HBRA. Part 6 and the Human Biomedical Research (Tissue Banking) Regulations 2019 comprised the last phase of the HBRA to come into force (1 November 2019). The framework for the regulation of human biomedical research had entered into force earlier on 1 November 2017. The duties of tissue banks are set out in Sections 34 to 36 of the HBRA. In accordance with the self-regulatory approach advocated by the BAC, tissue banks need not apply for a licence, but they must notify the DMS of their existence and their particulars. They must comply with the statutory requirements and duties including detailed requirements in the Regulations listed in the HBRA.

[11] BAC Press Release, 12 Nov 2002, "Release of second report by the Bioethics Advisory Committee on Human Tissue Research in Singapore" at [3] at www/bioethics-singapore.gov.sg/publications.

The tissue banks will then have to make regular declarations of compliance with these duties and requirements. The above ethical principles of welfare, informed consent, confidentiality and respect for the human body recommended by the BAC are implemented in Sections 37 to 39 of the HBRA. Restrictions relating to appropriate consent for activities relating to human tissue are set out in Section 37. Section 38 prohibits compelling a person to donate human tissue and the personal information of a tissue donor is protected under Section 39.

HUMAN-ANIMAL COMBINATIONS

The phrase "human-animal combinations" refers to any kind of living organism in which there is some mixing of human and animal materials. A cytoplasmic hybrid is created by injecting the nucleus (genetic material) of a somatic cell from a human body into an enucleated animal egg. This technique allows disease-specific or patient-specific stem cells to be derived in order to study nuclear reprogramming and understand genetic diseases. Animal chimeras are produced by injecting human stem cells into animals at various stages of development. Such chimeras are needed in research to study stem cell biology, as well as to find new and more effective ways to treat diseases. In response to increasing ethical debates internationally, the BAC issued the Report on Human-Animal Combinations in Stem Cell Research on 22 September 2010. Richard Magnus, then Chairman of the Human Embryo and Chimera Working Group, explained in the press release that "ethics review will ensure that research involving human-animal combinations is permitted only where there is strong scientific merit, potential medical benefit and in the absence of a satisfactory alternative way of pursuing the same research. In addition, those who have a conscientious objection to such research should not be under a duty to conduct or assist in the research." The Report also recommended that a single national body should be established to review and monitor all stem cell research involving human pluripotent stem cells or human-animal combinations conducted in Singapore (recommendation 1). Cytoplasmic hybrid embryos should not be allowed to develop beyond 14 days or the appearance of the primitive streak, whichever is earlier, nor be implanted into any human or animal uterus (recommendation 2). Animals into which human embryonic stem cells, induced pluripotent stem cells, or any other kind of pluripotent stem cells have been introduced should not be allowed to breed (recommendation 4). An important recommendation (recommendation 3) was the need to avoid the creation of entities in which human sentience or consciousness might be expected to occur.

HUMAN-ANIMAL COMBINATIONS AND THE HBRA

These recommendations have been implemented in the HBRA through the dual concepts of "*prohibited research*" (Section 30) and "*restricted research*" (Section 31). *Prohibited research* is ethically unacceptable and completely disallowed. Research into certain types of human-animal research, human-animal embryos, or human embryos[12] beyond 14-days are considered serious offences, punishable with fine and imprisonment. These prohibitions are consistent with the BAC's recommendations 2 and 3. *Restricted research* involves sensitive research including those involving human-animal combination embryos, the introduction of neural cells in animals, and human stem cells.[13] Such restricted research must comply with the additional requirements prescribed in the Human Biomedical Research (Restricted Research) Regulations 2017. Even if the human-animal combination research falls within the definition, it will only be permitted if it receives case-by-case approval from the DMS. This is consistent with the BAC's recommendation 1. The BAC's recommendation 3 on avoiding human sentience or consciousness is partially implemented through regulation 6 of the 2017 Regulations that empowers the DMS to impose conditions relating to the occurrence or likelihood of human sentience or human consciousness in human-animal combination research.

FUTURE CONSIDERATIONS

As mentioned at the start of this chapter, it is not possible to cover every recommendation made by the BAC. Some BAC projects such as the Ethical, Legal and Social Issues in Neuroscience Research (2013 Consultation Paper) and the Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology (2018 Consultation Paper) are still at the Consultation Paper stage and their reports have not been issued. It is therefore understandable that these projects have not yet been implemented. One recommendation in particular does not appear to have been implemented by legislation. This is found in the BAC Report on the "Donation of Human Eggs for Research, November 2008". No doubt the recommendations in this Report relating to the informed consent of egg donors for research and the welfare of the donor are covered by provisions in the HBRA and guidelines. But the main recommendation that

[12] The types of research are specified in the Third Schedule. The list follows broadly the BAC recommendations. Of interest is the prohibition against the introduction of human neural cells into the brain of living great apes whether prenatal or postnatal.

[13] The types of research are specified in the Fourth Schedule. The list follows broadly the BAC recommendations.

donors should be reimbursed for expenses incurred and compensated for the loss of time and earnings as a result of the procedures required to obtain the eggs has not been legislated. Such reimbursements are arguably still prohibited by Section 13 of the 2004 Act which prohibits the giving of valuable consideration for the supply of any human egg. The only exception is "reasonable expenses" which is narrowly defined. It is arguably anomalous that this definition is narrower than the payment of reimbursements for costs and expenses incurred by a living organ donor permitted under Section 14 of the Human Organ Transplant Act (Chapter 131A). On the other hand, it is also acknowledged that such an amendment to the 2004 Act might attract disproportionate controversy despite being a BAC recommendation as it is conceivably susceptible to misunderstanding by advocates of women's rights.

CONCLUSION

This chapter has traced in roughly chronological order the significant recommendations of the BAC and how they have contributed to the development of the biomedical legal landscape in Singapore — both case law and legislation. Thankfully, a researcher or tissue banker today need not trawl through all the 7 reports. In June 2015, on the occasion of BAC's 15th Anniversary, the BAC consolidated and updated its past recommendations into a single accessible volume simply called the "Ethics Guidelines for Human Biomedical Research". On its 20th anniversary, the BAC can reflect with pride on the fulfilment of the recommendation in its very first report in 2002 for a comprehensive legislative framework and guidelines for human stem cell research. As we have seen, the BAC recommendations have shaped both the form and substance of the biomedical laws in Singapore. The bulk of its recommendations have been taken seriously by policymakers and implemented by the legislature. With advances in cutting-edge medical technology such as the use of artificial intelligence, leveraging on genetic data, in medical research and healthcare, the BAC will continue to shape the biomedical laws of Singapore in the next 20 years.

11

Genetic Testing, the Data Universe and Privacy

Kon Oi Lian

INTRODUCTION

Genetic testing today is not what it used to be. The modern era of genetic testing for human disorders began in the late 1950s when cytogenetic techniques diagnosed Down syndrome by the presence of trisomy 21.[1] Tests for an increasing number of single-gene disorders using different cytogenetic and genetic methods rapidly followed.[2] Since the 1990s, several converging trends have radically expanded the breadth and depth of genetic testing. The Human Genome Project greatly accelerated technical advances in DNA sequencing and computational biology, such that automated, high-throughput, accurate and increasingly inexpensive DNA sequencing technologies and sequence interpretation have become key enablers of expansive genotyping at ultra-fine single-base resolution.[3] These technical innovations have reduced the current cost of sequencing a human genome by about a thousand-fold compared to what it had cost to sequence the first human genome (Fig 1).[4]

[1] Lejeune K, Gauthier M and Turpin R. Les chromosomes humains en culture de tissus [The human chromosomes in tissue culture]. *Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences* **248**, 602-603 (1959).

[2] Beaudet AL, Scriver CR, Sly WS and Valle D. Genetics, biochemistry, and molecular bases of variant human phenotypes, in *The Metabolic & Molecular Bases of Inherited Disease,* eds. Scriver CR, Beaudet AL, Sly WS and Valle D. McGraw Hill, 2001, Volume 1, pp. 3-45.

[3] International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. *Nature* **431,** 931-945 (2004).

[4] Wetterstrand KA. DNA sequencing costs: Data from the NHGRI genome sequencing program (GSP). Available at: www.genome.gov/sequencingcostsdata. Accessed 4 June 2020.

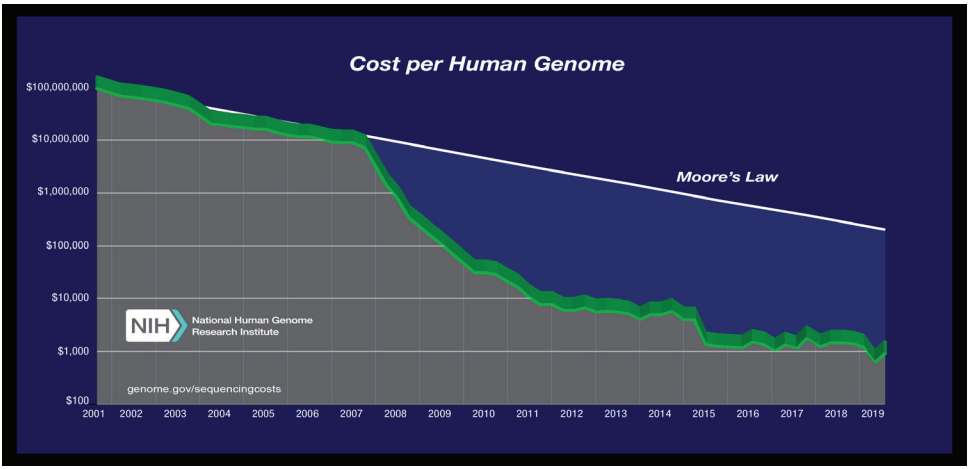

Fig. 1. Sequencing costs per human genome in US dollars from 2001-2019. Note the logarithmic scale on the vertical axis. The rate of decline deviated sharply from the hypothetical Moore's Law in 2008 when next-generation sequencing techniques were adopted widely. The graph is obtained from the NHGRI genome sequencing program.

Another development that has altered the landscape of genetic testing is the realisation, arising from the Human Genome Project and subsequent genomic research, of the multi-layered complexity of genomes. Current genome science is only a foretaste of a deep trove of structural and functional genomic information, especially of the genome's extensive dark matter previously dismissed as junk DNA.[5] These technological advances have transformed two distinct applications of genetic testing, namely clinical genetic services and research genetics. The former are integral to the clinical care of individuals who present with medical indications for genetic testing. Clinical genetic services are now standard of care and codified by professional guidelines in Singapore and other countries.[6] [7] [8] What follows is limited to genetic testing performed for biomedical research as this is a focus area of the Bioethics Advisory Committee.

[5] Collins FS, Green ED, Guttmacher AE and Guyer MS. A vision for the future of genomics research. *Nature* **422,** 835-847 (2003).

[6] Standards for the provision of clinical genetic/genomic testing services. Standards for the provision of clinical laboratory genetic/genomic testing services. Ministry of Health, Singapore. 28 June 2018. Available at: https://www.moh.gov.sg/licensing-and-regulation/regulations-guidelines-and-circulars/details/code-of-practice-on-the-standards-for-the-provision-of-clinical-genetic-genomic-testing-services-and-clinical-laboratory-genetic-genomic-testing-services

[7] Santani A, Simen BB, BriggsM, Lebo M, Merker JD, et al. Designing and implementing NGS tests for inherited disorders: a practical framework with step-by-step guidance for clinical laboratories. *J Mol Diagn* **21,** 369-374 (2019).

[8] Hume S, Nelson TN, Speevak M, McCready E, Agatep R, et al. CCMG practice guideline: laboratory guidelines for next-generation sequencing. *J Med Genet* **56,** 792-800 (2019).

The arrival of the genomic era, with wide dissemination of DNA sequencing technologies, has extended the range of genetic tests from conventional targeted sequencing of genes responsible for monogenic diseases to genome-scale techniques such as short tandem repeats, genome-wide association studies of single nucleotide variants, whole exome sequencing, whole genome sequencing, molecular cytogenetics, functional studies of structural genomic variants and the epigenome. DNA data are the output from all these different techniques. Given the expanded scope of genetic testing, this article uses genetic testing, genotyping and DNA testing interchangeably; DNA data refers to both gene-based and genomic data.

AGGREGATION, SHARING AND GLOBALISATION OF DNA DATA

Extracting new biomedical insights and making discoveries from genomic data which could be applied in healthcare require aggregating and analysing DNA data of thousands, and even millions, of individual research subjects in large datasets. Many are released in public databases, increasingly warehoused in cloud environments. The open science ethos enables other investigators to access these DNA datasets as a means of making the best use of research resources. Indeed, research funders commonly make data sharing a condition of support.

DNA datasets generated from research conducted in universities and public institutions increasingly co-exist in an ecosystem with other types of data, such as electronic medical records, biobank data, socioeconomic data, personal information disclosed in social media platforms, forensic records, genealogical and lifestyle databases.[9] Parallel datasets generated by commercial direct-to-consumer DNA genotyping services almost certainly hold the lion's share of all global DNA data.[10]

Traditional identifiers of research participants are redacted in academic DNA databases. Nonetheless, it has been clear for some time that re-identification of individuals or groups is both a potential and actual risk when such data co-exist in

[9] de Montjoye YA, Radaelli L, Singh VK and Pentland AS. Identity and privacy. Unique in the shopping mall: on the reidentifiability of credit card metadata. *Science* **347,** 536-539 (2015).
[10] Regalado A. More than 26 million people have taken an at-home ancestry test. *MIT Technology Review* (2019). www.technologyreview.com/s/612880.

ecosystems of overlapping datasets.[11] [12] [13] [14] There are degrees of re-identification – from complete re-identification, when identified genetic information is matched to an anonymous dataset, to various forms of partial re-identification, such as disclosure of anonymous paternity, phenotype/genotype inference or membership of a social/ethnic group. Breaches of privacy have thus become a well-recognised risk associated with the public release of individual DNA data, even when de-identified and aggregated with many thousands of other individuals.

SENSITIVITY OF GENETIC INFORMATION

Concerns about genetic privacy centre on perceptions of the nature of DNA data. Although there is a dearth of well-conducted studies of public perception of genetic information especially in Asia, there are sufficient reports from Western countries to show that a clear majority, among research participants and the public in general, view genetic information as distinct and unique from other types of information.[15] [16] [17] [18] Reasons for holding this view of genetic exceptionalism are rooted in perceived characteristics of the genome, namely its immutability, uniqueness as a personal identifier, its information content disclosing past and present health, probabilistic prediction of future health, links to genetic relatives and ancestry. Over and above these attributes, the genome - "my DNA" - is for many a deep cultural signifier of the very core of personhood. Wariness about the loss of genetic privacy is also, in some societies, haunted by the lingering shadow of historical abuse and genetic discrimination.

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[11] Homer N, Szelinger S, Redman M, Duggan D, Tembe W, et al. Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP genotyping microarrays. *PLoS Genet* **4(8),** e1000167 (2008).

[12] Gitschier J. Inferential genotyping of Y chromosomes in Latter-Day Saints founders and comparison to Utah samples in the HapMap project. *Am J Hum Genet* **84,** 251-258 (2009).

[13] Gymrek M, McGuire AL, Golan D, Halperin E and Erlich Y. Identifying personal genomes by surname inference. *Science* **339,** 321-324 (2013).

[14] Cai R, Hao Z, Winslett M, Xiao X, Yang Y, et al. Deterministic identification of specific individuals from GWAS results. *Bioinformatics* **31,** 1701-1707 (2015).

[15] Trinidad SB, Fullerton SM, Bares JM, Jarvik GP, Larson EB and Burke W. Genomic research and wide data sharing: views of prospective participants. *Genet Med* **12,** 486-495 (2010).

[16] McGuire AL, Oliver JM, Slashinski MJ, Graves JL,Wang T, et al. To share or not to share: a randomised trial of consent for data sharing in genome research. *Genet Med* **13,** 948-945 (2011).

[17] Goodman D, Johnson CO, Bowen D, Smith M, Wenzel L and Edwards K. De-identified genomic data sharing: the research participant perspective. *J Commun Genet* **8,** 173-181 (2017).

[18] Clayton EW, Halverson CM, Sathe NA and Malin BA. A systematic literature review of individuals' perspectives on privacy and genetic information in the United States. *PLoS One* **13:** e0204417 (2018).

Genetic exceptionalism is roundly disavowed by most, but not all, in academia.[19] [20] Critics maintain that genetic information is no different in sensitivity compared to other types of medical information (such as radiological information or mental health history), or even to other types of personal information (such as financial status or marital history). There have been concerns that since genetic information can be predictive of future health, it is potentially stigmatising and could inflict emotional harm. However, such concerns are equally true of some non-genetic information. As such, genetic information is regarded by anti-exceptionalists as a subset of all personal and health-related information, and should therefore receive the same – not special or exceptional – privacy protections. Moreover, allowing notions of genetic exceptionalism to influence policies and legislation wrongly gives credence to misapprehensions of genetic reductionism and determinism. Negative consequences of according special status and regulatory protection to genetic information will likely impede biomedical genomic research to the detriment of the common good without affording meaningful additional protection to research participants.

Releasing de-identified data in public databases is an irreversible decision even when research participants have the option of withdrawing their data because there is no way of knowing who has already obtained the data. Privacy once lost cannot be recovered.

> *And our DNA is not like our credit cards: we simply cannot get a new number. As long as someone has our identifiable DNA sample, he or she will be able to learn things about us we may not know, may not want to know, and certainly don't want others to know.*[21]

GENETIC EXCEPTIONALISM REDUX

Regarding genetic and non-genetic data as either strictly binary or non-binary categories has become an apparent intractable barrier in public policy discourse which hinders the overarching goal of biomedical research to maximise genome science for the common good. At least two theoretical models have been proposed as potential approaches to negotiate the impasse. The proponents acknowledge the public's perception of the unique power of genomic information,

[19] Murray TH. Genetic exceptionalism and " future diaries": is genetic information different from other medical information? In *Genetic Secrecy; Protecting Privacy and Confidentiality in the Genetic Era,* ed. Rothstein MA. Yale University Press, 1997, pp. 60-73.

[20] Roche PA and Annas GJ. Protecting genetic privacy. *Nat Rev Genet* **2,** 392-396 (2001).

[21] Roche PA and Annas GJ. DNA testing, banking and genetic privacy. *New Engl J Med* **355,** 545-546 (2006).

even if considered ill-informed by scholars, and urge accommodation of privacy concerns.

Sulmasy used the metaphor of nakedness to illustrate the thesis that not all sensitive information is equally sensitive and that genomic information is qualitatively distinct in important respects from other types of information.[22] On this account, it would be a mistake to completely deny special status to all genomic information. The naked genome is analogous to the naked body insofar as a person whose genomic information is "seen" by another is exposed both physically and informationally. It is further asserted that abuse or misuse of genomic information in itself constitutes harm, regardless of other consequences. In the "special but not exceptional" view of genomic information, policies designed specifically to protect genomic privacy "only make explicit what should be true of all aspects of patient privacy". Such policies may be special but are not exceptional - and hence, disavowal of anti-exceptionalism is avoided. A further nuance to note is that the range of privacy concerns may require different levels of protection. For example, a closed door suffices for a private conversation, but a closed door and thick curtains are needed when doctors examine patients. In sum, Sulmasy maintains that safeguards tailored to protect genomic privacy are acceptable, and indeed necessary, provided they are "reasonable and fair".

In their view, Garrison and co-authors maintain that policies and practices directed explicitly at genetic tests and information should not be rejected out of hand.[23] Genetic tests have a "fundamental duality" insofar as they are similar to non-genetic tests in some respects, yet distinctive in others. In discerning their distinctiveness, the circumstances in which genomic tests and information are discussed is most important. This approach, which they term genomic contextualism, may help to unblock intransigent positions in policy debates. They go further in characterising anti-genetic exceptionalism as a "rhetorical oversimplification that has outlived its usefulness." To this charge, Murray offers a post-hoc explanation of the original rationale which framed the case against genetic exceptionalism in the 1900s, namely that it was intended to promote understanding (and dispel misunderstandings) of genetic science and its societal ramifications.[24]

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[22] Sulmasy DP. Naked bodies, naked genomes: the special (but not exceptional) nature of genomic information. *Genet Med* **17,** 331-336 (2015).

[23] Garrison NA, Brothers KB, Goldenberg AJ and Lynch JA. Genomic contextualism: shifting the rhetoric of genetic exceptionalism. *Am J Bioeth* **19,** 51-63 (2019).

[24] Murray TH. Is genetic exceptionalism past its sell-by date? On genomic diaries, context, and content. *Am J Bioeth* **19,** 13-15 (2019).

PRIVACY AND ITS BREACHES

There is no universal definition of privacy among legal scholars, philosophers and bioethicists, in part because different cultures hold varying values of privacy, define its boundaries differently and experience different consequences of privacy loss.[25] Privacy concerns are heterogeneous even within communities, and have known associations with educational attainment, socioeconomic status and cultural background, among others. Different types of privacy are recognised, namely physical, informational, spatial, associational and intellectual privacy. Genomic privacy is mainly physical and informational. Thus, a working definition could be "a state of limited access to an individual or information about an individual".[26] Privacy may also be understood as that which disrupts social norms.[27] What is considered private thus depends on the actual context in which such disruptions may or may not occur.

Privacy concerns have come to the fore in the genomic era. Genome-scale data are inherently uniquely identifiable even when stripped of conventional identifiers, thus putting research participants at some risk of re-identification. Knowledge of certain risk genotypes that reveal current disorders or impute future ill health may disadvantage individuals in education, employment, insurance and marriage.

Surveys have shown that half or more of the public and participants in genome research are concerned about privacy, and a significant proportion regard privacy as very important.[28] [29] [30] [31] [32] Given its importance to research participants, privacy attacks that have re-identified individuals endanger trust in the research enterprise and could undermine the trustworthiness of scientists. Moreover, as the public release of DNA data is effectively irrevocable, research participants

[25] Solove DJ. Conceptualizing privacy. *Calif Law Rev* **90,** 1088-1155 (2002).

[26] Clayton EW, Evans BJ, Hazel JW and Rothstein MA. The law of genetic privacy: applications, implications, and limitations. *J Law Biosci* **6,** 1-36 (2019).

[27] Solove DJ. Conceptualizing privacy. Calif Law Rev 90, 1088-1155 (2002).

[28] Trinidad SB, Fullerton SM, Bares JM, Jarvik GP, Larson EB and Burke W. Genomic research and wide data sharing: views of prospective participants. *Genet Med* **12**, 486-495 (2010).

[29] Clayton EW, Halverson CM, Sathe NA and Malin BA. A systematic literature review of individuals' perspectives on privacy and genetic information in the United States. *PLoS One* **13**: e0204417 (2018).

[30] Kaufman DJ, Murphy-Bollinger J, Scott J and Hudson KL. Public opinion about the importance of privacy in biobank research. *Am J Hum Genet* **85,** 643-654 (2009).

[31] Sanderson SC, Brothers KB, Mercaldo ND, Clayton EW, Antommaria AHM, et al. Public attitudes toward consent and data sharing in biobank research: a large multi-site experimental survey in the US. *Am J Hum Genet* **100,** 414-427 (2017).

[32] Oliver JM, Slashinski MJ, Wang T, Kelly P A, Hilsenbeck SG and McGuire AL. Balancing the risks and benefits of genomic data sharing: genome research participants' perspectives. *Publ Health Genom* **15,** 106-114 (2012).

have no meaningful recourse to recall or control the use of their data.

Privacy hacking requires a combination of sophisticated statistical algorithms and genomic knowledge. Erlich and Narayanan listed thirteen different privacy breaching techniques of very low to high technical complexity which could be used for identity tracing, attribute or phenotype disclosure and genotype imputation.[33] Seven of the techniques have been used in actual privacy attacks. Since then, new re-identification techniques have been reported.[34] [35] Preliminary evidence even suggests that facial recognition of individuals is feasible from a profile of their autosomal single-nucleotide polymorphisms.[36] As current privacy breaching techniques are beyond the competence of casual hackers, the real risk of re-identification at present is low. However, as recent trends show that such methods are becoming more powerful and easier to use, the risk of re-identification can be expected to increase.

MITIGATION MEASURES

Measures to mitigate the loss of privacy fall into four categories: a) technical and computational solutions; b) governance frameworks; c) sanctions and penalties; and d) ethics awareness and tools.

Technical and computational solutions are an active area of development. Current methods to protect data or data servers include data suppression, k-anonymisation and its variants, differential privacy, open personal data stores, blockchain technology, homomorphic encryption, secure multiparty computation, cryptographic hardware and data safe havens.[37] [38] [39] These evolving solutions impose significant demands on computational overheads and time, and are currently not sufficiently practical for implementation beyond simulated

[33] Erlich Y and Narayanan A. Routes for breaching and protecting genetic privacy. *Nat Rev Genet* **15,** 409-421 (2014).
[34] Lippert C, Sabatini R, Maher MC, Kang EY, Lee S, et al. Identification of individuals by trait prediction using whole-genome sequencing data. *Proc Natl Acad Sci USA* **114,** 10166-10171 (2017).
[35] Erlich Y, Shor T, Pe'er I and Carmi S. Identity inference of genomic data using long-range familial searches. *Science* **362,** 690-694 (2018).
[36] Sero D, Zaidi A, Li J, White JD, Zarzar TBG, et al. Facial recognition from DNA using face-to-DNA classifiers. *Nat Commun* **10,** art. no. 2557 (2019).
[37] Erlich Y and Narayanan A. Routes for breaching and protecting genetic privacy. Nat Rev Genet 15, 409-421 (2014).
[38] Azencott CA. Machine learning and genomics: precision medicine versus patient privacy. *Philos Trans A Math Phys Eng Sci* **376,** 20170350 (2018).
[39] de Montjoye YA, Shmueli E, Wang SS and Pentland AS. openPDS: protecting the privacy of metadata through SafeAnswers. *PLoS One* **9,** e98790 (2014).

experimental environments.[40] Data stewards need to constantly keep abreast of new threats to cybersecurity, the occurrence of actual privacy breaches and advances in privacy-enhancing measures to appropriately update safeguards.

Governance to protect the interests and privacy of research participants should adapt to the increasingly common practice of genomic datasets shared among multi-institutional and multi-national research consortia. Developing governance to achieve the optimal balance between protecting research participants while advancing research for the common good (often viewed as opposing goals) is arguably the most challenging task in managing genomic data. Governance encompasses several problematic processes which are best entrusted to panels of multidisciplinary experts. Although a detailed account is beyond the scope of this article, governance frameworks are, at a minimum, responsible for the following: properly informed consent, establishing competent research ethics committees or institutional review boards, ensuring quasi-identifiers are stripped from genomic data, evaluating data for open or controlled access, setting criteria that qualify investigators to access controlled data, implementing data access agreements, monitoring compliance with terms of data access, establishing channels for confidential reporting of data misuse, and delegating enforcement authority. The interested reader is directed to exemplars of governance practice for data security and privacy.[41] [42] [43]

DISCIPLINE FOR DATA ABUSE

Disciplinary processes, sanctions and penalties for data misuse are relatively neglected aspects of governance. This hiatus arises when institutional review boards have no meaningful role beyond approving research projects, are not charged with oversight of actual research practice, and when an independent audit of data use is effectively non-existent. An audit is especially challenging at the supra-national level when datasets are shared across national borders. Bundling DNA data with health-related information is increasingly common in genome-scale biomedical research, precision medicine and direct-to-consumer genotyping services which have varying policies on the ownership of DNA data.[44]

[40] Tang H, Jiang X, Wang X, Wang S, Sofia H, et al. Protecting genomic data analytics in the cloud: state of the art and opportunities. *BMC Medical Genomics* **9,** 63 (2016).

[41] Kaye J. The tension between data sharing and the protection of privacy in genomics research. *Annu Rev Genomics Hum Genet* **13,** 415-431 (2012).

[42] Milius D, Dove ES, Chalmers D, Dyke SOM, Kato K, et al. The International Cancer Genome Consortium's evolving data-protection policies. *Nat Biotechnol* **32,** 519-523 (2014).

[43] Global Alliance for Genomics and Health: Data privacy and security policy. Version POL 001/v. 2.0; August 2019. https://www.ga4gh.org/genomic-data-toolkit/regulatory-ethics-toolkit/

[44] Laestadius LI, Rich JR and Auer PL. All your data (effectively) belong to us: data practices among direct-to-consumer genetic testing firms. *Genet Med* **19,** 513-520 (2017).

[45] [46] Proactive development of appropriate disciplinary policies will minimize the risk of being badly wrong-footed by hasty reactions when malfeasance is discovered.

Where privacy is protected by laws on use of personal data, researchers are likely to have only a vague understanding of their responsibilities for several reasons. The regulatory landscape for data misuse may be a complex patchwork dispersed across several codes of practice and legislations.[47] Moreover, policies framed to guide the conduct of genetic research may fail to explicitly link research responsibilities to laws on data misuse. Compounding the ambiguity, research funders tend not to have sufficiently detailed policies sanctioning data misuse. As a result, the circumstances in which penalties should be incurred and the extent of penalties remain unclear. Material transfer agreements and data use licenses may specify penalties for data breachers but it is uncertain how effectively the conditions are monitored for compliance.

There is currently no consensus, much less best practice, on how to investigate and administer a graded system of penalties and sanctions for data misuse.[48] The challenge is to "make the punishment fit the crime"[49] by not prescribing over-zealous punishments, but instead foster a research culture of respect for research participants rather than "reluctant compliance with funder or institutional policies." [43] Recent calls to criminalise illicit re-identification of personal, including genetic, data have led to expressions of caution and counter proposals for proactive monitoring and enhanced authority to enforce regulations instead.[50]

RETHINKING PRIVACY IN THE AGE OF BIG DATA

Evidence of actual privacy hacks and re-identification render assurances of absolute privacy to research participants obsolete and unsupportable, even though the actual risks are currently not high. This has prompted rethinking of consent for participation in genomic research.

[45] Hendricks-Sturrup RM and Lu CY. Direct-to-consumer genetic testing data privacy: key concerns and recommendations based on consumer perspectives. *J Pers Med* **9,** 25 (2019).
[46] Du L and Wang M. Genetic privacy and data protection: a review of Chinese direct-to-consumer genetic test services. *Front Genet* doi:10.3389/fgene.2020.00416 (2020).
[47] Expert Advisory Group on Data Access. Sanctions for data misuse: evidence paper. Available at: https://wellcome.ac.uk/what-we-do/our-work/expert-advisory-group-data-access (2017)
[48] Phillips M, Molnar-Gabor F, Korbel JO, Thorogood A, Joly Y, et al. Genomics: data sharing needs an international code of conduct. *Nature* **578,** 31-33 (2020).
[49] Gilbert WS. *The Mikado* (1885).
[50] Phillips M, Dove ES and Knoppers BM. Criminal prohibition of wrongful re-identification: legal solution or minefield for big data? *J Bioeth Inq* **14,** 527-539 (2017).

Some have argued that as privacy protection measures are now fundamentally futile and wasteful of resources, potential research participants should no longer be misinformed to expect complete anonymity. To do so would be untruthful and could invalidate consent. Researchers and bioethicists who hold such views propose new adaptive paradigms variously designed to ameliorate, or even entirely eliminate, the burden of privacy protection. Erlich and co-authors advocate the reduction of emphasis on privacy by replacing conventional data management frameworks with a trust-based model in which research participants are data controllers, and consent for data use is a dynamic process instead of a one-off agreement.[51] Mostert and co-authors take the view that as properly informed consent and data anonymisation are fraught with difficulties, medical research using sensitive personal data should be exempted from consent.[52] However, neither approach directly addresses the issue of privacy breaches and other forms of data misuse. A more radical solution pioneered by the Personal Genome Project network explicitly abandons all assurances of privacy.[53] [54] [55] Research participants agree to contribute and make publicly available their personal, health-related and genomic data. Some also choose to be named and identified by photographs on the project's database. Arguably, the most distinctive feature of this form of open consent is a compulsory examination, taken after online training, in which prospective participants must achieve a perfect score to be admitted into the research study. It is clear that, based on this and other features, participants who volunteer for the Personal Genome Project are a self-selected group of well-educated information altruists and highly engaged citizen scientists who will not be representative of their communities. Wider trials of open consent will be necessary to ascertain its generalisability across the entire sociocultural spectrum and if it enables sufficient inclusiveness of participation to meet the core ethical principles of justice and beneficence.

Features of dynamic consent[56] are not infrequently imported into other proposals which similarly try to adapt informed consent for genomic research.

[51] Erlich Y, Williams JB, Glazer D, Yocum K, Farahany N, et al. Redefining genomic privacy: trust and empowerment. *PLoS Biow* **12:** e1001983 (2014).

[52] Mostert, M, Bredenoord AL, Biesaart MCIH and van Delden JJM. Big data in medical research and EU data protection law: challenges to the consent or anonymise approach. *Eur J Hum Genet* **24,** 956-960 (2016).

[53] Ball MP, Bobe JR, Chou MF, Clegg T, Estep PW, et al. Harvard Personal Genome Project: lessons from participatory public research. *Genome Med* **6,** 10 (2014).

[54] PGP-UK Consortium. Personal Genome Project UK (PGP-UK): a research and citizen science hybrid project in support of personalized medicine. *BMC Medical Genomics* **11,** 108 (2018).

[55] Zarate OA, Brody JG, Brown P, Ramirez-Andreotta MD, Perovich L and Matz J. Balancing benefits and risks of immortal data: participants' views of open consent in the Personal Genome Project. *Hastings Cen Rep* **46,** 36-45 (2016).

[56] Kaye J, Whitley EA, Lund D, Morrison M, Teare H and Melham K. Dynamic consent: a patient interface for twenty-first century research networks. *Eun J Hum Genet* **23,** 141-146 (2015).

Dynamic consent and its variants are attempts to overcome the acknowledged constraints, even obsolescence, of static consent at a time when research techniques and infrastructure are evolving rapidly, and emerging research questions may well lead biomedical investigators into uncharted areas. However, privacy protection is not a core feature of dynamic consent which, like other consent models, depends on technical components "that can securely encrypt sensitive data".[52] Notwithstanding the enthusiasm of research practitioners and bioethicists for dynamic consent as being fit for purpose in big data research, empirical evidence of its feasibility and performance in the real world of genomic research awaits.[57]

SINGAPORE LEGISLATION ON PERSONAL DATA PROTECTION

Personal data protection and criminal sanctions for data breaches are covered by two legislative instruments in Singapore, namely the Human Biomedical Research Act 2015 (HBRA)[58] and the Personal Data Protection Act 2012 (PDPA).[59] Like most other countries, neither Act deals solely with the protection of personal genetic data and genetic privacy, although a case has been made for legislation specific for genetic privacy, given the perceived special attributes of DNA data.[60] While HBRA and PDPA have some overlap in regulating data protection, HBRA could reasonably be considered the referent legislation for genetic data protection as it provides the legal framework for biomedical research, the source of genetic data, whereas PDPA more broadly legislates all personal information. PDPA states that other laws will prevail in the event that any of its rules on personal data protection are inconsistent with other written laws.

Two definitions in HBRA are germane to genetic research. "Health information" is any or all information of individuals obtained during the course of providing healthcare services or arising from biomedical research. Although HBRA does not use genetic, genomic, genotype, DNA or nucleic acid as descriptors of health information, its definition is unambiguous in encompassing such information. The Act further defines "individually-identifiable" as properties of health information which could be used to re-identify anonymised individuals. Recognising the potential for illicit re-identification, HBRA requires prospective

[57] Prictor M, Lewis MA, Newson AJ, Haas M, Baba S, et al. Dynamic consent: an evaluation and reporting framework. *J Empir Res Hum Res Ethics* **15,** 175-186 (2020).
[58] Singapore Statutes: *Human Biomedical Research Act*. Revised 2015.
[59] Singapore Statutes: *Personal Data Protection Act*. Revised 2012.
[60] Selita F. Genetic data misuse: risk to fundamental human rights in developed economies. *Legal Issues J* **7,** 53-95 (2019).

research subjects to be informed of fifteen specific points during the process of obtaining consent regarding research purpose, experimental procedures, risks and rights. Among these fifteen points, three relate to individually-identifiable information. Research subjects should be informed if their participations require individually-identifiable information; and if so, whether such information could be re-used for future research. Prospective subjects should also be informed about the degree of confidentiality to expect as a safeguard against re-identification. In the absence of specific exemptions, the HBRA prohibits disclosure of individually-identifiable information. Contraventions are liable to fines not exceeding $20,000, imprisonment for not more than 2 years, or both.

PDPA governs "the collection, use and disclosure of personal data by organisations".[61] The Act technically covers genetic data under its definition of personal data as "data, whether true or not, about an individual who can be identified (a) from that data; or (b) from that data and other information to which the organisation has or is likely to have access". In contrast to HBRA, PDPA is explicitly framed to balance competing and potentially conflicting needs, namely the rights of individuals to protect their personal data against exploitation of such data by organisations for diverse purposes. Of its nature, interpretation of some aspects of personal data protection under PDPA could be discretionary. For example, compliance with the Act is evaluated by the criterion of "what a reasonable person would consider appropriate". Collection and use of personal data under "deemed consent" are allowed. The Act also permits personal data to be transferred from one organisation to another without secondary consent of the individuals involved. It is worth noting that PDPA does not apply to individuals acting in a personal capacity, such as the prototypical lone hacker.

NEXT STEPS

Singapore is well positioned to build on its existing legislative instruments for genetic data protection as new directions in human genome research may raise unforeseen concerns about data use and genetic privacy in the future. A review by multidisciplinary experts to determine if HBRA and PDPA in their current forms are sufficiently fit for purpose and to identify potential gaps will be timely. Through its international networks, Singapore could contribute to efforts to frame trans-national standards of genetic data management, access and use.

[61] Singapore Statutes: *Personal Data Protection Act*. Revised 2012.

The current process of obtaining consent to participate in research should be evaluated for veracity and comprehensibility. Public trust and trustworthiness of researchers are essential for the society's continued support for research. All research funders in Singapore could help to facilitate good data practice by issuing unified and coherent guidelines and regulations for all genomic research. Guidelines should be sufficiently fine-grained for unambiguous implementation at the coalface of research. Although intentional and malign data breaches by rogue investigators are still rare, governance of genomic research should include well-considered processes to investigate and, where appropriate, sanction such acts. Even if the processes will rarely, if ever, need to be activated, being proactively prepared avoids the likely shambles of hasty and reactive responses should such breaches occur. Onerous data use guidelines which do little to enhance protection of research participants, and excessively harsh sanctions may induce research paralysis or drive poor data practices underground. Hence, ethical use of genetic data for research must ultimately rest, not on a rule-keeping culture, but on keen awareness of the intrinsic morality of respect for persons. Therefore, the shared goal of researchers and research participants should be to advance biomedical research for the common good.

12

Reflections on Mitochondrial Replacement Technology

Tracey Evans Chan

INTRODUCTION

Experimental mitochondrial replacement technologies (MRT) were first picked up on the ethical radar in Singapore when the Bioethics Advisory Committee (BAC) decided to embark on a project looking at the ethical implications of the proposed therapy sometime in 2014. Since the inception of the project, the BAC has released a consultation report on the topic in April 2018 and engaged with various interest groups on the issues raised by MRT.[1] This chapter offers a concise review of the undertaking and focuses on some of the more challenging ethical issues associated with MRT clinical trials.

MITOCHONDRIAL DISORDERS AND THE ADVENT OF MRT

Nearly every human cell possesses two sets of collective genetic material – the nuclear genome and mitochondrial genome, which comprise double-stranded DNA that contain genes which code for various proteins. The mitochondrial genome consists of 37 protein-coding genes (approximately 0.1% of the total amount of DNA in the cell) in comparison to the approximately 20 to 30 thousand genes in the nuclear genome.[2] Mitochondrial DNA (mtDNA) encodes for proteins and other products that are essential for the production of cellular energy, while nuclear DNA (nDNA) plays the main role in determining the anatomical, physiological, personality and other characteristics of every human being. While nDNA is inherited from both biological parents of every child, mtDNA is inherited down the matrilineal line – only females pass their mtDNA to both male and female offspring. Males do not pass mtDNA to descendants.

[1] BAC, Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Technology: Consultation Report (19 Apr 2018); https://www.bioethics-singapore.gov.sg/publications/consultation-papers/ ('BAC Consultation Report')

[2] AL Bredenoord, W Dondorp, G Pennings, G De Wert., "Ethics of modifying the mitochondrial genome" (2011) 37 Journal of Medical Ethics 97 at 98

Finally, while there are only 2 copies of 23 nuclear chromosomes in almost all adult human cells, there are many more copies of mtDNA in each cell, which can vary between 100 to 10,000 copies. This results in a phenomenon known as heteroplasmy – a situation in which each cell, tissue or person may contain more than one mtDNA genotype, that is, different copies of mtDNA sequences in each mitochondria organelle in human cells. Where the copies of mtDNA in each cell are uniformly 'wild'[3] or mutant, this is known as homoplasmy.[4] Finally, as a result of spontaneous genetic mutations and selective pressures, different maternally transmitted homoplasmic mutations have resulted in the formation of stable population subgroups or haplogroups. Various continents and geographic regions are associated with certain mtDNA haplogroups, but association studies have not been able to demonstrate any corresponding functional benefits based on a particular haplogroup.[5]

MITOCHONDRIAL DISEASE

Mitochondrial disease describes dysfunction in the underlying respiratory processes and corresponding cell energy production in humans afflicted with it, with eventual dysfunction and failure of celluar tissue and organ function. These dysfunctions are heterogenous but typically manifest in organs that require the greatest energy production, such as the brain, muscles, heart, and liver. Mitochondrial disease can arise as a result of defects in the nDNA or mtDNA. In respect of the latter, there have been 275 reported disease-causing mutations in the mitochondrial genome. There are currently no cures or proven treatments for mitochondrial diseases, and clinical management is confined to supportive or palliative interventions. Mitochondrial diseases are heterogenous in their presentation and severity, with the severity ranging from mild to severely debilitating or fatal.[6] Mitochondrial disease originating in mtDNA mutations tend to be later in onset as compared to nDNA-caused mitochondrial disease.[7]

While there are a number of emerging therapeutic candidates for treating mitochondrial disease, such as gene editing of somatic cells and heteroplasmy shift, these have shown limited success in humans or are still at the investigational stage of development. Consequently, the focus has thus far been on means of

[3] Wild-type is the most common DNA sequence found within a population, i.e. the normal variant of a DNA sequence or gene.

[4] NASEM, *Mitochondrial Replacement Techniques: Ethical, Social and Policy Considerations* (National Academies Press, 2016) ("NASEM Report") at 35 fn 12.

[5] See NASEM Report at 30-37.

[6] For examples of different types of mitochondrial disease, see NASEM Report, p38 Table 2-2

[7] NASEM Report at 37-39

preventing women who carry pathogenic mutations of mtDNA, or who suffer from mitochondrial disease, from passing on the mutations to their offspring. However, existing methods of assisted reproduction using preimplantation genetic diagnosis (PGD), while effective in preventing the transmission of inherited nDNA diseases, are less effective in respect of mtDNA inherited diseases. This arises because heteroplasmy of 5% or less levels of mtDNA mutations are recommended to reduce the risk of manifesting mitochondrial disease, but women with mtDNA mutations may produce oocytes with mtDNA mutations in excess of this. Furthermore, women who are homoplasmic for a mtDNA pathogenic mutation will not be served by PGD selection of embryos. There is also the added complication of random segregation of mtDNA and mtDNA bottleneck following embryo implantation, which could result in higher levels of heteroplasmy of mtDNA mutations in offspring. PGD is therefore not considered an effective and reliable means of preventing the transmission of mitochondrial disease from women at risk to their children unless mutation-free embryos are available.[8]

Of course, there are other alternatives for such women at risk to carry a pregnancy or have children without the risk of mitochondrial disease, such as using donor oocytes in *in vitro* fertilisation (IVF) and adoption. Surrogacy is not an option available currently in Singapore, which would be another alternative for women at risk who cannot carry a pregnancy to full term because of mitochondrial disease.[9] Egg donation is however difficult to procure, particularly if maternal relatives are also at risk of mitochondrial disease.[10] However all these reproductive alternatives suffer from the important shortcoming that the resulting children would not have a nDNA genetic connection (or affinity) with their mother. Hence the impetus for MRT.

TYPES OF MITOCHONDRIAL REPLACEMENT THERAPY

MRT is an experimental form of assisted reproduction that involves the micro-manipulation of human oocytes or zygotes in order to recombine the nDNA of a woman at risk of transmitting mitochondrial disease with the mtDNA

[8] AL Bredenoord, W. Dondorp, G. Pennings, C.E.M. De Die-Smulders, G. De Wert., «PGD to Reduce Reproductive Risk: The Case of Mitochondrial DNA Disorders» (2008) 23 Human Reproduction 2392 at 2394

[9] Ministry of Health, Licensing Terms and Conditions on Assisted Reproduction Services (26 Apr 2011) at para. 5.48(b) ('LTCs on ARS')

[10] AL Bredenoord & P Braude, "Ethics of mitochondrial gene replacement: from bench to bedside", BMJ 2010; 341:c6021; doi: https://doi-org.libproxy1.nus.edu.sg/10.1136/bmj.c6021 (Published 8 Nov 2010)

of a healthy donor who provides oocytes with non-pathogenic mtDNA for this purpose. Two leading candidate therapies are maternal spindle transfer ('MST') and pronuclear transfer ('PNT'), which involve the formation of a reconstructed oocyte and zygote respectively in which the mother at risk's pathogenic mtDNA are replaced by healthy mtDNA from a donor's oocyte, while containing the nDNA from both commissioning parents. Other techniques are also being studied, but have been less thoroughly studied than MST and PNT – the two assisted reproduction (AR) techniques which have been approved[11] or are being considered for regulatory approval to prevent the transmission of mitochondrial disease.

MST involves the removal of the nDNA from the intended mother's oocyte and transferring this to an enucleated oocyte from a healthy donor without pathogenic mtDNA mutations. This reconstructed oocyte is then fertilised with the intended father's sperm, cultured *in-vitro* and the resulting blastocyst undergoes genetic testing to determine the level of mtDNA carry-over from the karyoplast (nuclear genetic material and some cytoplasm encased in a plasma membrane) of the intended mother's oocyte. Embryos that meet the established criteria for heteroplasmy levels, chromosomal abnormalities, etc. are then implanted in the intended mother, or surrogate where permitted. PNT is a variation of this methodology where the transfer of the nDNA material from the intended parents occurs *after* fertilization. The pronuclei of the zygote derived from the gametes of the intended parents are removed and transferred to an enucleated zygote formed by the fertilisation of the intended father's sperm and a healthy donor's oocyte. The reconstituted zygote is then cultured *in vitro* to the blastocyst stage, where the same genetic testing in MST is performed before qualifying embryos are implanted into the intended mother or surrogate. In both instances, there is some carry-over of pathogenic mtDNA located in the cytoplasm of the karyoplast containing the intended nDNA material for transfer.[12]

There is a third, but less well developed and understood MRT technique known as Polar Body Transfer ('PBT'), which as the name suggests, involves the transfer of haploid[13] polar bodies. These are cellular by-products of oogenesis, the production and development of ovum. PBT involves the transfer of either the first or second polar bodies that are produced in oogenesis to an enucleated

[11] UK Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 No. 572

[12] NASEM Report at 47-53; L Gomez-Tatay, José M. Hernández-Andreu, Justo Aznar., "Mitochondrial Modification Techniques and Ethical Issues" (2017) 6 Journal of Clinical Medicine 25

[13] A single set of chromosomes in sexually reproducing organisms that typically have two sets, one from each parent.

mature occyte of a healthy donor, or a heminucleated zygote produced using healthy donor oocytes. This procedure has been far less rigorously studied but has the potential to involve less pathogenic mtDNA carry-over, and involves the absence of cytoskeletal inhibitors (used in MST and PNT to aid the removal of the karyoplast) and less invasive micro-manipulations.[14]

RISKS AND UNKNOWNS IN MRT

There are various risks and unknowns associated with MRT given the complexity of mitochondrial genetics and the fact that MRT has largely only been conducted using animal models and *in-vitro* experiments using human oocytes provided by healthy volunteers or supernumerary embryos from IVF. The level of heteroplasmy, the carrying of more than one type of mtDNA genotype, can change in different tissues of an individual due to mitotic segregation. This might cause pathogenic mtDNA levels to cross the threshold levels for disease manifestation, notwithstanding an initial low carryover level. Another phenomenon that renders it difficult to predict the efficacy of MRT is pre and postnatal mtDNA bottleneck. The former results in only a small proportion of mtDNA molecules in an individual being partitioned into a daughter offspring's oocytes, which may then exhibit high levels of heteroplasmy or homoplamsy for a pathogenic mtDNA mutation. The latter can occur during embryonic and foetal development, resulting in unequal distribution or selective reproduction of pathogenic mtDNA in embryonic and foetal tissues.[15] Finally, there is ample evidence in model organisms of incompatibility between artificially combined nDNA and mtDNA in MRT, possibly resulting in disruption or failure in mitochondrial processes. There is however, no agreement among mitochondrial genetic experts on whether such incompatibility will manifest phenotypically in humans. Another potential adverse effect of incompatibility is altered expression of genes in male organisms that possess mtDNA that is 'foreign' to its nDNA.[16]

In addition to these known risks, the state of the evidence in MRT research still lacks sufficient animal and mitochondrial disease model-derived evidence of safety and efficacy to support first-in-human clinical trials. Validation of MRT using PGD involves uncertainty regarding the predicted level of heteroplasmy in offspring resulting from MRT. Manipulations used in MST and PNT pose

[14] L Gomez-Tatay, José M. Hernández-Andreu, Justo Aznar., "Mitochondrial Modification Techniques and Ethical Issues" (2017) 6 Journal of Clinical Medicine 25

[15] NASEM Report at 53-57; DP Wolf et al, "Mitochondrial genome inheritance and replacement in the human germline" (2017) 36 EMBO Journal 2177

[16] L Gomez-Tatay, José M. Hernández-Andreu, Justo Aznar., "Mitochondrial Modification Techniques and Ethical Issues" (2017) 6 Journal of Clinical Medicine 25 at 8

unknown risks such as aneuploidy or chromosomal abnormalities, while the reagents used to move the process along also pose unknown risks to the reconstructed oocyte or zygote.[17]

In light of the foregoing considerations, three key ethical and regulatory issues need to be resolved in determining whether first in-human trials of MRT should be allowed to proceed.[18] The first is what risk/benefits thresholds should be stipulated for first-in-human trials, how these should be determined and by whom. Second, whether there are any inherent moral objections to MRT as a form of germline intervention, irrespective of safety and efficacy, that preclude the move to first-in-human trials. Finally, there is the poorly discussed issue of the social justice of allowing such trials to proceed given (a) the low incidence of mitochondrial disease and (b) preventive, rather than curative, nature of the therapy.

FIRST IN-HUMAN TRIALS – ASSESSING THE THRESHOLD OF RISKS VERSUS BENEFITS

I. The Value of Genetic Relatedness or 'Affinity'

The BAC in its consultation report asks two pertinent questions under the rubric of risks and benefits, that are: how do we weigh the welfare interests of future generations against the interest of intending parents afflicted with the risk of transmitting mitochondrial disease? As a concomittant to this question, what is an ethically accepted threshold or standard of benefits over risks, when compared to existing alternatives, that would justify allowing first-in-human trials of MRT?[19] The implicit framing underlying these questions is the pragmatic first step of determining whether to allow clinical research in MRT techniques in order to determine if their safety and efficacy justifies eventually mainstreaming one or more MRT techniques in assisted reproduction (AR) clinical practice. This issue is of practical regulatory importance. Under our system of health services regulation, assisted reproduction is regulated as a form of specialised service, which requires prior approval by way of a licence issued by the Director of

[17] NASEM Report at 57-59

[18] Other issues include the use and destruction of embryos in MRT research, welfare of the oocyte donor and the potential social consequences of MRT on resulting children: see AL Bredenoord, G Pennings, G de Wert., "Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders: conceptual and normative issues" (2008) 14 Human Reproduction Update 669; Nuffield Council on Bioethics, *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review* (NCB, 2012) ('Nuffield Council Report'); NASEM Report.

[19] BAC Consultation Report at 19 and 24 respectively.

Medical Services (DMS).[20] Under the *Licensing Terms and Conditions on Assisted Reproduction Services*, additional prior approval by the DMS is required before any AR Centre provides "pre-implantation genetic testing/screening or *other new AR-related services*".[21] In the case of pre-implantation genetic diagnosis (PGD), DMS has required PGD to undergo a period of evaluation before allowing PGD in the context of AR services to be mainstreamed.[22] Likewise, it will be necessary for DMS to evaluate and determine if any particular MRT procedure should undergo (first-in-human) trials before determining if it is acceptable to be mainstreamed. The jurisdiction exercised here is similar to that held by the UK's Human Fertilisation and Embryology Authority.[23] This is unlike the US, where the Food and Drug Administration has historically exercised regulatory authority over some AR procedures like cytoplasmic/ooplasmic transfer and has indicated an interest in overseeing MRT, but generally does not regulate AR services.[24]

In deciding whether to allow clinical trials of MRT, the assessment of benefits over risks is an important pillar of research ethics involving human participants. A favourable balance of benefits over risks would justify subjecting participants to research risks in the face of inherent uncertainty about safety and efficacy of the proposed experimental therapy, subject of course to their informed consent. In experimental reproductive technology like the various methods of MRT considered, unique challenges are raised. The decision to participate is ultimately made by intending parents who are expected to consider not only their interest in begetting a genetically related child, but also the risks posed to their future child by the chosen form of experimental MRT. However, the risks will directly be borne by the resulting child produced by MRT; a child who is in no position to understand and accept that risk in exchange for existence. The particular reproductive autonomy interest of both intending parents is a genetic relationship with their child, while being substantially free of the risk of developing a mitochondrial disese or disorder. Therefore, assessing the ethical and legal weight of this specific interest is important in understanding the threshold for first-in-human trials.[25]

[20] (26 April 2011); Issued under the *Private Hospitals and Medical Clinics Act*, Cap 248, s.6; Private Hospitals and Medical Clinics Regulations, Rev Ed 2002, reg. 18 read with the Second Schedule, para. 2 ("LTCs on ARS").

[21] LTCs on ARS, para. 5.47 [emphasis added]

[22] CC Neo, "Three hospitals to offer embryo-screening technique in pilot study" (Today online, 14 Nov 2016); See also C Yap et al, "First successful preimplantation genetic diagnosis in Singapore – avoidance of beta-thalassaemia major" Ann Acad Med Sing 2009 Aug; 38(8):720-3.

[23] AD Lyerly, "Marking the Fine Line: Ethics and the Regulation of Innovative Technologies in Human Reproduction" (2010) 11(2) Minnesota Journal of Law, Science and Technology 685 at 703-704

[24] NASEM Report at 60-65

[25] AL Bredenoord, G Pennings, G de Wert., "Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders" (2008) 14(6) Human Reproduction Update 669 at 673

The specific moral, cultural or social weight of the desire to have a genetic relationship between both parents and their child is a commonly held one. Some ethicists question the true weight of this objective as an aspect of reproductive autonomy, classifying the desire as merely a want, not a need.[26] Rulli argues that many of the reasons for desiring a genetically related child, such as psychological similarity or continuity of lineage, are not persuasive reasons to elevate the desire to a need: genetic relatedness cannot guarantee physical or psychological similarity, while non-genetically related children could equally carry one's traditions and values into the future.[27]Nevertheless, even if genetic relatedness may not stand on the same footing as parenthood or gestational connection, it is a still a legitimate, *lawful* desire that is commonly and strongly felt and pursued. Indeed, it forms the basis of much assisted reproductive technology (ART) such as IVF generally and more recent AR procedures such as Intracytoplasmic Sperm Injection (ICSI).[28]

In fact, the parental interest in having a genetic relationship with their offspring was recently given a form of legal recognition when the Court of Appeal in Singapore recognised a new head of actionable damage in a case involving negligent *in-vitro* fertilisation of an AR patient's oocyte with that of a stranger instead of her spouse. Recognising that damages for pain and suffering associated with the unwanted pregnancy and the wasted costs of the IVF treatment were inadequate to compensate her for her actual loss, the Court proceeded to recognise the loss of genetic affinity as an independent head of loss. In doing so, they reasoned that:

> … the loss suffered by the Appellant as a result of the Respondents' negligence is the result of a complex amalgam of biological, social, ethical, and historical factors. Many of these *have to do with certain aspects of human relationships and personhood that are fundamental parts of the human condition, such as the role of genetic relatedness, physical resemblance, race, culture, and the importance of familial relations*. Some are matters which are rightly cherished; others are perhaps regrettable features of the society which we inhabit. … In our

[26] F Baylis, "Human Nuclear Genome Transfer (So-Called Mitochondrial Replacement): Clearing the Underbrush (2017) 31(1) Bioethics 7 at 12-15

[27] T Rulli, "What is the value of the three-parent IVF?" (2016) 46(4) Hastings Center Report 338 at 42-43.

[28] PG Peters, *How Safe is Safe Enough? Obligations to the Children of Reproductive Technology* (OUP, 2004) at 101; See also European Society of Human Reproduction and Embryology Task Force on Ethics and Law 14: "Equity of access to assisted reproductive technology" (2008) 23(4) Human Reproduction 772 at 772-773.

> judgment, the Appellant's interest in maintaining the integrity of her reproductive plans in this very specific sense – where she has made a conscious decision to have a child with her Husband to maintain an intergenerational genetic link and to preserve "affinity" – is one which the law should recognise and protect.[29]

Genetic affinity has been unbundled as a particularly important aspect of the patient's reproductive autonomy, worthy of explicit and distinct legal protection as a recognised and protected legal interest in assisted reproductive medicine. That is not to say, of course, that it has acquired the status of a positive right of realisation, nor that it is normatively as worthy as other reproductive autonomy interests such as parenthood *per se* or gestational connection. Likewise, even though it is a legitimate *private* interest, it does not follow that it is equally worthy of receiving development support through *public* funding.[30]

The value placed on genetic relatedness or affinity is not the only value at stake in determining risk-benefit thresholds for experimental reproductive technologies. The welfare of the resulting child is equally important and responsible parents themselves would not simply throw out this interest in service of the other. However, this responsibility rests not only with the parents, but jointly with the medical professional assisting the parents in achieving their reproductive goals.[31] The welfare of the future children requires that possible harm imposed by experimental MRT procedures should be outweighed by the possible benefits offered. What is less clear is how we should go about determining if this threshold is satisfied.

II. Standards of Risk/Benefit Evaluation

In order to assist regulators and AR physicians in this evaluation, a variety of fairly different formulated standards have been proposed. Koshland proposes that trials of human germline interventions should not be "more risky than the *normal* process of birth and conception".[32] An immediate problem raised by this is the commensurability of the comparison. While we might have good

[29] ACB v Thomson Medical [2017] SGCA at [135]

[30] See discussion below.

[31] European Society on Human Reproduction and Embryology (ESHRE) Task Force on Ethics and Law, "The welfare of the child in medically assisted reproduction" (2007) 22(10) Human Reproduction 2585 at 2585-86; See also US President's Council on Bioethics, *Reproduction and Responsibility: the Regulation of New Biotechnologies* (Mar 2004), c.10 at 215-216

[32] D Koshland, "Ethics and Safety" in G Stock & J Campbell, *Engineering the Human Germline* (OUP, 2000) at 25-34 (emphasis added)

data on risks of natural conception and birth, the experimental nature of MRT prior to first-in-human trials, with both known and unknown risks, would make this standard difficult to apply. Furthermore, it would seem to leave out a more immediate comparator: the risks to the future child if the intending parents at risk of transmitting mitochondrial disease were to conceive naturally. The latter approach would appear to be a more permissive standard, but it begs the question of why natural conception should be used as the comparator, when they have the option of using healthy donor oocytes in AR, albeit without the genetic affinity that they also seek.

Bredenoord and others address the challenge by considering three standards of evaluation pegged along a spectrum of qualitative risk thresholds. The first candidate is the minimum threshold standard under which offering experimental ART is acceptable as long as the future child would have a life that is not worse than death.[33] This follows the logic that experimental MRT would not harm the future child as the only real alternative would be non-existence. It is an instance of the non-identity problem articulated by philosopher Derek Parfit.[34] MRT trials would only fail this ethical standard if they imposed risks that would lead to an outcome that was worse than non-existence (assuming that is a comparison that reasonable persons are capable of making). Bredenoord et al. argue that we should still be concerned about causing avoidable harm, even if the individual future child's interests are not violated.

Justification for this lies in the recognition that once we are concerned with choosing between alternatives that affect the identity of the resulting child, we are no longer concerned about the individual future child, but rather the class of future children that would be brought into existence by the experimental MRT in question. Even if no individual future child is harmed, the class of children could unjustifiably be made worse off if the benefits of the experiemental MRT did not warrant the risks involved.[35] The minimum threshold standard therefore unjustifiably weighs in favour of reproductive autonomy, and neglects the interests of the class of future children affected by the decision. There is also a public health concern here as what is at stake is the population or group welfare

[33] AL Bredenoord, W. Dondorp, G. Pennings, C.E.M. De Die-Smulders, G. De Wert., «PGD to Reduce Reproductive Risk: The Case of Mitochondrial DNA Disorders» (2008) 23 Human Reproduction 2392 at 2395

[34] J Malek, "Understanding Risks and Benefits in Research on Reproductive Genetic Technologies" (2007) 32 Journal of Medicine and Philosophy 339 at 344

[35] Dan W Brock, "The Non-identity Problem and Genetic Harms – The Case of Wrongful Handicaps" (1995) 9 Bioethics 269. See also Malek, ibid at 345, who instead uses the notion of a 'genetically undetermined future child' as the subject of welfare assessment.

of persons who are affected by the testing and introduction of an experimental procedure and its potential mainstreaming in AR medicine, where the injuries that result could have been prevented.[36]

The second candidate appears to be more of a theoretical standard than a realistic one: the maximal welfare standard.[37] This requires that MRT offer the best possible quality of life for the future child. Perhaps another way of expressing this idea would be to ground it in the precautionary principle: it is better to be safe than sorry, and therefore we should eschew steps or alternatives that create a risk of harm until there is clear evidence of safety.[38] Bredenoord et al. reject this standard as it requires too much and would even rule out existing alternatives like PGD or oocyte donation on the grounds that they are also not maximally safe. This standard would in fact tend to rule out any research risk unless perhaps there was no other way of conceiving a child.[39] It is too prohibitive and undervalues the recognised interest of genetic affinity within reproductive autonomy.

This leaves us with the third, intermediate "reasonable welfare" standard. The future child or group of children must have a reasonable chance of an acceptable quality of life. This is decidedly a vague standard and perhaps its main contribution is its desire to balance the competing interests at stake, rather than skew it in a particular direction.[40] Most commentators acknowledge that deciding on a reasonable risk-benefit assessment to justify a move from preclinical to first-in-human trials depends on a person's approach towards risk and the relative importance placed on genetic affinity as an aspect of intending parent's reproductive goals.[41] According to Peters, "the balancing of risks and benefits is inherently a subjective value judgment that, in a pluralistic society, is properly

[36] PG Peters, *How Safe is Safe Enough? Obligations to the Children of Reproductive Technology* (OUP, 2004) at 32

[37] AL Bredenoord, W. Dondorp, G. Pennings, C.E.M. De Die-Smulders, G. De Wert., «PGD to Reduce Reproductive Risk: The Case of Mitochondrial DNA Disorders» (2008) 23 Human Reproduction 2392

[38] C Sunstein, "The Paralyzing Principle" (2002-3) Regulation 32; S Holm & J Harris, "Precautionary principle stifles discovery" (1999) 400 Nature 398: "The PP instructs us to change this normal balancing by giving evidence pointing in one direction more importance than evidence pointing in the other direction, even in cases where the evidence has the same epistemic warrant…"

[39] See S Holm & J Harris, "Precautionary principle stifles discovery" (1999) 400 Nature 398: "The PP will block the development of any technology if there is the slightest theoretical possibility of harm. So it cannot be a valid rule for rational decisions."

[40] AL Bredenoord, W. Dondorp, G. Pennings, C.E.M. De Die-Smulders, G. De Wert., «PGD to Reduce Reproductive Risk: The Case of Mitochondrial DNA Disorders» (2008) 23 Human Reproduction 2392 at 2395; see also AL Bredenoord & I Hyun, "The Road to Mitochondrial Gene Transfer: Follow the Middle Lane" (2015) 23(6) Molecular Therapy 975 at 976

[41] AL Bredenoord & P Braude, "Ethics of mitochondrial gene replacement: from bench to bedside", BMJ 2010; 341:c6021; doi: https://doi-org.libproxy1.nus.edu.sg/10.1136/bmj.c6021 (Published 8 Nov 2010)

delegated to families."[42]

It is apparent that both first and second order issues arise from the reasonable welfare standard. On the substantive, first order question of an acceptable balance of benefits and risks, comparisons need to be drawn with the alternatives open to intending parents trying to avoid transmitting mitochondrial disease while starting or growing a family. On the question of efficacy, it would be reasonable to expect that experimental MRT offer a prospect of significant improvement over the uncertainties inherent in utilising PGD to avoid transmission of mutant mtDNA, in order to compensate for any remaining uncertainties or unknown risks. Of course, where the intending mother is homoplasmic for mutant DNA, then PGD is not an option – and that would have to be factored into the proportionality analysis. On the question of safety, it would be necessary to determine that experimental MRT offers proportionate benefits in exchange for the additional unknown or uncertain health risks imposed on the future child. What a reasonable welfare standard does allow is the possibility of less than complete health in exchange for a genetic link with the resulting child.[43] Here, the appropriate comparator is IVF using a healthy donor oocyte and the relative increase in risk. On this plane of comparison, it would seem that reasonable parents should not substitute the risk of serious mitochondrial disease for comparable risks of other kinds of disease or disorders[44] brought about by the various risk factors introduced by MRT, for example the unknown interactions between nDNA and mtDNA from the donor oocyte, and the use of reagents unnecessary in IVF. Genetic affinity is but one aspect of reproductive autonomy, and should not be accorded disproportionate weight in the overall question of reasonable welfare.

This leads to the second order question of whether it is justified to leave judgement of the satisfaction of this reasonable risk standard to the intending parents themselves or if the risk-benefit threshold should be independently assessed before being offered to patients. The search for a threshold for the risk-benefit standard itself implies the need for independent evaluation, otherwise our focus would be on ensuring informed consent on the part of the intending parents. The independent moral responsibility of the physician offering experimental

[42] PG Peters, *How Safe is Safe Enough? Obligations to the Children of Reproductive Technology* (OUP, 2004) at 91

[43] AL Bredenoord, W. Dondorp, G. Pennings, C.E.M. De Die-Smulders, G. De Wert., «PGD to Reduce Reproductive Risk: The Case of Mitochondrial DNA Disorders» (2008) 23 Human Reproduction 2392 at 2396

[44] See also C Cohen, "Designing tomorrow's children: The right to reproduce and the oversight of germline interventions", in AR Chapman & MS Frankel eds, *Designing our Descendants: The Promise and Perils of Genetic Modification* (JHU Press, 2003) at 308

MRT, the need for society to hold such physicians or researchers accountable, and the public health interest in ensuring that experimental MRT are not tested in humans or even mainstreamed unless they present a reasonable risk-benefit threshold, all point towards the need for independent, expert review both at the stage of first-in-human trials and in subsequent approval for mainstreaming.[45] An analogy can be drawn with research ethics involving children, where the argument has been made that institutional review board must ensure that the offer for participation must be one that a responsible parent could accept.[46] Likewise for experimental MRT, independent expert review is required to ensure that the move to first-in-human trials represents an offer for participation that responsible intending parents could reasonably accept.

Furthermore, speciality ethics committees have recognised that decision making in the AR context can be challenging. Patients who are struggling to build a family can be particularly vulnerable, while clinicians have traditionally placed high value on the reproductive autonomy.[47] There is also a lack of consensus on the basic requirements of the discipline and peer scrutiny of AR practices, made more acute by the fact that peers are often in direct commercial competition with each other.[48] This does not lend assurance to the assumption that patients in collaboration with their reproductive physicians are more than capable of making responsible decisions without independent oversight, particularly with experimental treatments like MRT.

Commentators also stipulate that the reasonable welfare standard requires that risks be reduced as much as is reasonably possible.[49] This involves both a thorough, independent evaluation of the pre-clinical evidence to identify the range of potential risks of the experimental MRT, and consequently, the stipulation for animal and embryonic studies that would be necessary to satisfy reviewers of the reasonable risk standard. A second recommendation relates to the means of experimentation. Clinical trials should be designed to produce meaningful scientific results that allow for further iterative testing of MRT, with long term

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45 UK Medical Research Council, *Assisted Reproduction: a safe, sound future* (2004) at 9

46 B Freedman et al, "In Loco Parentis: Minimal Risk as an Ethical Threshold for Research upon Children" (1993) 23(2) Hastings Center Report 13

47 Ethics Committee of the American Society for Reproductive Medicine, "Moving innovation to practice: a committee opinion" (2015) 104(1) Fertility and Sterility 39 at 41-42

48 S Ferber et al, *IVF and Assisted Reproduction: A Global History* (Palgrave Macmillan, 2020), c.4 "Regulation and Risk" at 140

49 AL Bredenoord & P Braude, "Ethics of mitochondrial gene replacement: from bench to bedside", BMJ 2010; 341:c6021; doi: https://doi-org.libproxy1.nus.edu.sg/10.1136/bmj.c6021 (Published 8 Nov 2010)

follow up to the extent feasible in such settings.[50] This would require adequate funding upfront before the trial is allowed to proceed.

Finally, it must be noted that the evaluation of the risk-benefit threshold is not a purely scientific exercise, but involves value judgments about acceptable risk levels and the moral weight to be accorded to reproductive autonomy as expressed in the desire for genetic affinity. In order to ensure the legitimacy of such regulatory assessments to allow or refuse clinical trials of MRT, the independent expert assessment should have a diverse expertise and lay presentation.[51] There should also be decision-making transparency, explaining why decisions were taken to allow or refuse clinical testing, in order for researchers, physicians to understand how to move forward, and for patients to better understand what they are getting into or why their reproductive autonomy was constrained. Neither of these requirements currently features in the regulatory licensing regime for assisted reproduction services.

GERMLINE MODIFICATION VIA MITOCHONDRIAL GENOME REPLACEMENT

The starting point in evaluating the implications of MRT in relation to ethical concerns and moratoria over germline modification is the BAC's standing recommendation that clinical application of "germline genetic modification" should not be allowed. Two reasons are given for this recommendation: (a) concerns about feasibility and safety, and (b) serious ethical concerns about potentially "great impact on future generations".[52] The ethical evaluation of risks and benefits of MRT under appropriately independent, rigorous and transparent processes would address this first concern. The second concern is not elaborated upon by the BAC in its report.

The first question that arises is whether MRT, by either manipulating and reconstituting the oocyte or zygote, should be classified as germline modification. Some consider MRT to fall outside the concerns raised by germline modification because it does not involve the manipulation or editing of the nuclear genome, which determines the essential characteristics of the resulting child and future generations. Furthermore, MRT does not actually involve the editing or modification of the mitochondrial genome, but rather replaces it with a genome

[50] UK Medical Research Council, *Assisted Reproduction: a safe, sound future* (2004) at 9-10

[51] PG Peters, *How Safe is Safe Enough? Obligations to the Children of Reproductive Technology* (OUP, 2004) at 99

[52] BAC, *Genetic Testing and Research* (25 Nov 2005) at para. 4.52 ('BAC 4th Report')

in its 'wild' state from a healthy donor in order to prevent mutated mtDNA from causing debilitating disease.[53] Bredenoord and others point out that the influence of mtDNA on these 'essential' characteristics (which are poorly defined) is still not fully understood, with some studies suggesting that there might be an association between mtDNA and cognitive capacity, while others suggest that the interaction between mtDNA and nDNA may influence gene expression.[54] This interaction is also poorly understood. Their preferred approach is to acknowledge that MRT alters the inheritance of mtDNA in immediate progeny and, conditionally,[55] in future generations. This places MRT on par with other germline modifying technologies and requirements as assessment if the intervention is nonetheless justified. The Nuffield Council also adopts this position although they consider that the changes introduced are of a different order from those resulting from nuclear germline modifications.[56] Finally, the BAC in its 4th report spoke generally of the alteration of a person's "germline genetic makeup" without drawing any distinction or focus on the nuclear genome.[57]

Assuming therefore that MRT are a particular form of germline therapy, what are the potential ethical objections to this type of AR intervention? A commonly raised concern is that germline modifications are interferences with natural processes and are tantamount to 'playing God' when we cannot fully comprehend the consequences dealt to future generations. The fact that something is naturally occurring does not *per se* mean that it is good and to be embraced; for those suffering from mitochondrial disease, the unaltered natural state is a source of grave burdens of disease. Medical technological advancements have been driven by the desire to overcome the deficiencies of our natural states of health. Accordingly, the ethical response is to determine when we should accept the effect of natural processes, when to improve them, and when to overcome them.[58] Finally, in respect of the unpredictability of the consequences, there are three

[53] Nuffield Council on Bioethics, *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review* (NCB, 2012) ('Nuffield Council Report') at paras. 4.32-4.33

[54] AL Bredenoord, G Pennings, G de Wert., "Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders: conceptual and normative issues" (2008) 14 Human Reproduction Update 669 at 674; NASEM Report at 47-53; L Gomez-Tatay, José M. Hernández-Andreu, Justo Aznar., "Mitochondrial Modification Techniques and Ethical Issues" (2017) 6 Journal of Clinical Medicine 25 at 32

[55] See also AJ Newson & A Wrigley, "Is Mitochondrial Donation Germ-line Gene Therapy? Classifications and Ethical Implications" (2017) 31(1) Bioethics 55 at 66 – inheritance of MRT modifying characteristics is conditional on matrilineal inheritance, bottleneck effects and unpredictability in mitochondrial segregation in the developing embryo.

[56] Nuffield Council on Bioethics, *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review* (NCB, 2012) ('Nuffield Council Report') at paras 4.35-4.36

[57] BAC, *Genetic Testing and Research* (25 Nov 2005) at para. 4.52 ('BAC 4th Report')

[58] Nuffield Council on Bioethics, *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review* (NCB, 2012) ('Nuffield Council Report') at paras 4.46-4.47

possible responses. As discussed above, the unknown risks have to be balanced as a matter of judgment against the benefits offered by MRT. Second, the overall effect on the human genome as the 'heritage of humanity' is likely to be minimal, given the very small number of women who are afflicted with mtDNA mutations that wish to pursue this novel option over existing alternatives.[59] Thirdly, because MRT is a conditionally heritable genomic modification, the unforeseeable risks to future generations could be avoided by restricting MRT, at least in the early stages, to the transfer of male embryos, thereby obviating the risk of unforeseen heritable consequences. This is discussed further below.

Another concern is that the use of MRT brings us closer to a return to our eugenic past, guided by the hubris to weed out undesirable traits from future generations. MRT also has the potential to increase discrimination against those with disabilities, as persons with conditions that could or ought to have been avoided by medical interventions. Similar objections have been raised in relation to PGD, an earlier assisted reproductive innovation, where embryos are selected to avoid disease-causing genetic mutations before implantation. In recommending that PGD be allowed in Singapore to prevent serious genetic conditions, the BAC acknowledged the real concerns over positive eugenics, social injustice and discrimination as adverse consequences of introducing new reproductive technology that confers more choice. However, these were to be balanced against the legitimate needs of couples who are at risk of transmitting a genetic disorder whether by reason of family history or carrier status. The critical proviso is that PGD use must be carefully and effectively regulated.[60] Likewise, allowing MRT would be facilitating a more open future[61] as the improved health achieved by preventing otherwise incurable mitochondrial disease would enhance her 'general purpose' capacities to pursue their chosen conception of a good life.[62] It need not, and should not, follow that those already existing without as capacious general-purpose means are living less worthy lives, or treated as such.

Finally, a common concern with germline modifications is the risks MRT poses to the safety of the resulting children *and* future generations, which would be irreversible. Novel combinations of nDNA and mtDNA may result in

[59] NASEM report at pp94-95

[60] BAC, *Genetic Testing and Research* (25 Nov 2005) at paras 4.37-4.40 ('BAC 4th Report')

[61] This interest was recognized by the BAC in its 4th report at para 4.44

[62] AL Bredenoord, W Dondorp, G Pennings, G De Wert., "Ethics of modifying the mitochondrial genome" (2011) 37 Journal of Medical Ethics 97 at 99. See also BAC 4th Report at para. 4.45.

mismatches and consequential health complications,[63] genetic drifts resulting in reversion to homoplasmic mutant mtDNA (notwithstanding very low initial carryover),[64] and other health issues arising from cellular manipulation in MRT.[65] The NASEM report therefore recommended that initial clinical trials of MRT be restricted to male embryos, thereby limiting these potential effects to the first generation of male offspring.[66] Other potential risks like an increase in inheritance of mutant mtDNA in future generations could also be foreclosed while research to investigate them proceeded without holding up access to MRT for families wanting to avoid transmitting pathogenic mtDNA to their offspring.

Although sex selection for non-medical reasons is of ethical concern in AR, the BAC has implicitly recognised that sex-selection for medical reasons to avoid the transmission of genetic reasons is permissible.[67] Likewise, it would appear that male embryo selection in MRT to mitigate unforeseen risks to subsequent generations is similarly permissible – the existing regulatory framework for experimental AR procedures would be capable of ensuring that only couples at risk of transmitting mitochondrial disease would be eligible, and not those seeking gender selection for its own sake. The Nuffield Council appears to have countenanced objections to confining MRT to male embryos on the basis that this would create "experimental (male) offspring" and the need to do so would suggest that MRT was in fact not sufficiently safe to proceed to clinical trials.[68] The former would be unavoidable even if there was no gender restriction: The Nuffield Council itself recommended long-term follow up for MRT children and families over generations.[69] The latter assumes that adequate pre-clinical research in animals and human embryos would foreclose the possibility of any inter-generational risks. This is unfounded and it is argued that a more cautious, phased approach allowing iterative pre-clinical and clinical trials would more proportionally balance the interests of safety and reproductive liberty for future generations, with the specific reproductive autonomy interest of the intending parents in genetic affinity. On the whole, it would appear that ethical concerns

[63] L Gomez-Tatay, José M. Hernández-Andreu, Justo Aznar., "Mitochondrial Modification Techniques and Ethical Issues" (2017) 6 Journal of Clinical Medicine at 32; NASEM Report at 122 – where the Committee recommended that mtDNA haplogroup matching should be an inclusion criteria should the pre-clinical data indicate that this would mitigate the risk of mtDNA-nDNA incompatibilities.

[64] DP Wolf et al, "Mitochondrial genome inheritance and replacement in the human germline" (2017) 36 EMBO Journal at 2178-79

[65] NASEM Report, at 119

[66] NASEM Report, at 119-121

[67] BAC 4th Report at para. 4.46

[68] Nuffield Council Report, para. 4.128; in so far as their final recommendations did not embrace any restrictions limiting MRT transfers to male embryos: see c.5 of the Report.

[69] Nuffield Council Report, para 5.11 (p89)

with germline modification would not obviate the introduction of MRT provided its application was closely regulated for the clinical purposes that pass ethical muster.

EPIDEMIOLOGY AND THE JUSTICE OF PUBLICLY FUNDING MRT CLINICAL RESEARCH

There is one other feature of mitochondrial disease that requires emphasis: its low prevalence. Determining mitochondrial disease prevalence is challenging because of its extensive clinical and genetic heterogeneity. A 2015 study in Northeast England suggested a prevalence of 1 in 5000 for pathogenic mtDNA mutation, with half that rate presenting clinical symptoms.[70] In a related study seeking to determine how many women at risk of transmitting mitochondrial disease could benefit from MRT, the authors estimated that 152 children born in the UK and 778 in the US would benefit.[71] These estimates have been challenged by commentators as overly optimistic, bearing in mind that not all women might be capable of carrying a pregnancy, have the means to access MRT, nor successfully achieve a pregnancy in IVF.[72] At present, there is no equivalent data for prevalence in Singapore, although the foregoing data could be extrapolated locally.[73]

Given this very low prevalence, scholars have questioned the social value of funding MRT development and clinical trials, especially when, apart from low prevalence, MRT cannot completely eliminate mitochondrial disease as these can arise *de novo* from spontaneous mutations in 1 in 10,000 cases.[74] In order to achieve this, we would have to be able to reliably screen all embryos for such spontaneous mutations, which is not feasible. Therefore, the proper framing of the value proposition is whether the social value of allowing a small number of couples at risk of transmitting mitochondrial disease to have equal opportunity to have a genetically related child free of that risk justifies the opportunity costs of *publicly* funding such research. The opportunity costs would not simply be a

[70] GS Gorman, Andrew M Schaefer, Yi Ng, Nicholas Gomez, Emma L Blakely et al, "Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease" (2015) 77(5) Annals of Neurology 753

[71] GS Gorman, John P. Grady, Doug M. Turnbull, "Mitochondrial donation – how many women could benefit?" (2015) 372(9) NEJM 885

[72] F Baylis, "Human Nuclear Genome Transfer (So-Called Mitochondrial Replacement): Clearing the Underbrush (2017) 31(1) Bioethics 7 at 15-18. See also NASEM Report at 41-42; T Rulli, "What is the value of the three-parent IVF?" (2016) 46(4) Hastings Center Report 338 at 44-45.

[73] BAC Consultation Report at para 13.

[74] HJM Smeets, "Preventing the Transmission of Mitochondrial DNA Disorders: Selecting the Good Guys or Kicking Out the Bad Guys," (2013) 27 Reproductive BioMedicine Online 599 at 608

question of allocating funding resources to this type of preclinical and clinical research, but also the deployment of scarce human embryos stipulated for use in research, in order to generate sufficiently reliable data to move into first-in-human trials.[75] Rulli thinks not – quite apart from being unable to eliminate mitochondrial disease, MRT does not in fact save lives, except for the very small number of intending parents who would, without the option of MRT, still seek to achieve a pregnancy using PGD or even natural birth. Apart from this exceptional category, MRT would not be saving existing lives, but merely create *potential* persons who would be disease free.[76] On the whole, a utilitarian distributive approach[77] would question whether the deployment of public research resources into MRT research truly promotes the greater good.

Nevertheless, the ethics of funding research into the prevention, treatment and cure of rare diseases is not solely based on a utilitarian calculus. Some have argued that the ethical principle of beneficence requires us to be concerned about the abandonment of certain categories of patients with rare diseases. This principle of non-abandonment would justify allocating *some* public resources towards meeting the needs of rare disease populations.[78] Through the establishment of the Rare Disease Fund by the Ministry of Health, the Singapore Government is dedicated to alleviating the financial burden of rare disease patients by providing a 3-to-1 Government matching funding for every dollar of private donations.[79] However, using public funding for research into such rare diseases involves a different order of uncertainty, coupled with the fact that research into MRT does not seek to ameliorate the existing disease. As mentioned above, some would also view the desire for MRT as a want and not a basic need, which further weakens the case for funding MRT research and development.[80] Nevertheless, for the sake of argument, even if we were to assume that the interest of couples desiring mitochondrial disease-free, genetically related children should properly be countenanced on the basis of equality of access and avoidance of harm,[81] there

[75] T Rulli, "What is the value of the three-parent IVF?" (2016) 46(4) Hastings Center Report 338 at 44

[76] *Ibid* at 41 and 43-44.

[77] See CA Gericke, A Riesberg, R Busse, "Ethical issues in funding orphan drug research and development" (2005) 31 Journal of Medical Ethics 164 at 165.

[78] *Ibid* at 166.

[79] MOH, Update of Rare Disease Fund Progress (3 Nov 2020), online: https://www.moh.gov.sg/news-highlights/details/update-on-rare-disease-fund-progress

[80] F Baylis, "Human Nuclear Genome Transfer (So-Called Mitochondrial Replacement): Clearing the Underbrush (2017) 31(1) Bioethics 7 at 18 and T Rulli, "What is the value of the three-parent IVF?" (2016) 46(4) Hastings Center Report 338 at 42-43

[81] G Pennings, G. de Wert, F. Shenfield, J. Cohen, B. Tarlatzis et al, ESHRE Task Force on Ethics and Law 14: Equity of access to assisted reproductive technology (2008) 23(4) Human Reproduction 772 at 773: The desire is based on a wish to prevent harm both to themselves and their offspring, and access confers an 'equal opportunity to have an unaffected (genetically related) child'.

would still be the need to specify some criteria to justify allocation of research funds to MRT in particular, ahead of research into treatments for existing patients with mitochondrial and other rare diseases.

In relation to orphan drugs, Pinxten and others argue that there should be budgetary isolation for a portion of the overall resources for the development and supply of orphan drugs.[82] However, in order to determine how to allocate such a budget, specific allocation mechanisms based on rational (albeit imperfect) criteria are required to decide between *comparable* claims. They approved of the UK National Institute for Clinical Excellence's proposal for general criteria in allocating limited resources, namely, (1) the severity of the disease, (2) evidence of health gain, (3) the life-threatening nature of the disease. While the severity and life-threatening nature of mitochondrial disease would qualify, the number of future (as opposed to potential) persons that are actually protected from severe, life-threatening mitochondrial disease is very small if we consider that without MRT, most at-risk couples would probably choose not to take the risk of transmitting pathogenic mtDNA through existing alternatives. MRT does nothing for the existing sufferers of mitochondrial disease. This questionable margin of health gain is exacerbated by the underdiagnosis of mitochondrial disease in Singapore. Feedback from clinicians that consulted with the BAC's Working Group indicated that this was attributable to various factors, including the lack of public awareness of mitochondrial disease, a shortage of clinical expertise and various barriers to genetic testing such as cost and the absence of legal protection from genetic discrimination.[83] The relative urgency is also lacking as there are safe alternatives to parenthood for such patients, albeit with the sacrifice of genetic affinity. As matters stand at present, it is highly doubtful that MRT pass ethical muster in terms of priority setting in the allocation of public research resources. This, however, says nothing about the priorities of the private sector.

CONCLUSION

This chapter considered three particular issues that arise from the advent of MRT. There are others such as the ethics of embryo research necessary to base further development of MRT, and the speculative social implications for children born with genetic material from three different individuals that will also

[82] W Pinxten, Yvonne. D, Marc. D, Jean-Jacques Cassiman, Kris. D, et al, "A fair share for the orphans: ethical guidelines for a fair distribution of resources within the bounds of the 10-year-old European Orphan Drug Regulation" (2012) 38 Journal of Medical Ethics 148 at 150-151.

[83] In this respect, see BAC, *Personal Information in Biomedical Research* (7 May 2007), Part VI and Annex A-4

need to be considered and addressed. A refined regulatory regime could arguably manage the safety and efficacy risks raised by MRT. The ethical concerns raised by germline modification indicate that there is nothing intrinsically wrong with MRT being deployed as proposed to help at-risk couples fulfil their desire to conceive a genetically related child free from serious mitochondrial disease. Proper regulatory oversight is crucial in this respect. However, as a matter of distributive justice, MRT offers questionable merit in justifying the allocation of public research resources when the existing individuals who suffer from mitochondrial disease would not benefit from this at all in the alleviation of their current suffering.

13

Public Engagement and Bioethics in Singapore

Victor Cole

THE IMPORTANCE OF PUBLIC ENGAGEMENT

Advances in biomedicine promise many benefits yet often bring new challenges and potential harms that demand not only the careful deliberation of experts in medicine, ethics, and health policy, but also the engagement of the general public. Recognising that bioethical dilemmas "relate to public health, to matters of dealing with disease, disability, death or suffering that are part of our shared human experience", a recent United Nations Educational, Scientific and Cultural Organisation (UNESCO) publication asserts that "Bioethics must become more than ever everyone's business"[1]. National Bioethics Committees (NBCs) such as Singapore's Bioethics Advisory Committee (BAC) thus align strongly with UNESCO's global effort to ensure that citizens who are ultimately impacted by practices within biomedicine are, as far as possible, provided with opportunities to engage with questions which experts deem significant, to raise questions of their own, and to offer views which might further shape the ongoing debate.

Given the breadth and seriousness of issues that bioethics encompasses, public engagement in this realm through the opportunities created by the BAC does more than merely give form to the ideal of "deliberative democracy"[2] in which the citizenry is actively involved in policy formation. It may also be seen as a further instantiation of the ethical principles that form the bedrock of the BAC's deliberations on biomedical research activities – respect for persons, solidarity, justice, proportionality, and sustainability.

[1] United Nations Educational, Scientific and Cultural Organisation. (2019). Guide no. 5: Bioethics committees and public engagement. (pp. 9-10) Available at: https://www.ccne-ethique.fr/sites/default/files/1098_19_guide_5_bioethics_committees_public_engagement_int_web.pdf

[2] This concept is discussed in relation to bioethical policy making in UNESCO (2019), pp. 20-21.

"Respect for persons" in public consultations is demonstrated through a willingness to see the public, not as mere objects of bioethical policies that the government might implement on the BAC's recommendations, but as autonomous agents whose capacity to form and express opinions is recognised through the solicitation of their input on such policies at the consultation stage. Additionally, their need for relevant information in arriving at suitably informed opinions also needs to be met through educational efforts undertaken by the BAC and its partners, much as in the research domain research participants need to be provided with all necessary information in order to provide informed consent.

"Solidarity" finds expression not merely in seeking a consensus on controversial issues – which may prove to be elusive in any case – but in affording ordinary citizens the opportunity to play their part in engaging with issues that are the object of public policy deliberations, thereby facilitating their fulfilment of their role as active citizens. Obviously, this does not entail their willingness to take on risk for the public good as research participants might in demonstrating solidarity, but simply their willingness to give up time to absorb information and participate in dialogue.

The principle of "justice" is embodied in each attempt made at giving a voice to groups who might otherwise be marginalised or oppressed. Particular effort is required to ensure that those who have traditionally lacked power and influence may be able to exercise their voices. Hence, a challenge for public consultations is to provide not merely access to the platforms of engagement, but suitable encouragement of participation.

The principle of "proportionality" is at work in ensuring that minority views are not automatically subordinated to principles favoured by a decision-making élite and that while these views may ultimately be overridden in the deliberations of those who formulate policy recommendations, they are acknowledged and respected as meaningful expressions of sincerely held beliefs. Particularly important in a multicultural society such as Singapore is the avoidance of absolutist principles in determining policy outcomes and the principle of proportionality serves as a reminder of this.

Lastly, the principle of "sustainability" that is concerned with the welfare of future generations requires that the space for public input on bioethical issues is kept open and alive and not closed down on the completion of a particular

consultation exercise.[3] This is particularly important given the evolving nature of scientific knowledge and the shifts within societal norms over time, at least with respect to what can be justified within a heterogeneous population such as Singapore's.

Thus, taken together and applied to the practice of public engagement, these five principles underscore the seriousness of the commitment the BAC is making to engage the public in meaningful ways that honour their status as stakeholders, not only as potential recipients of the benefits and burdens of biomedicine but also as members of civil society.

THE METHODS OF PUBLIC ENGAGEMENT

Public Consultations

Since its creation in 2000, the BAC has used a variety of platforms for public engagement. Some have had the explicit purpose of securing public input, particularly from specific professional and community groups, on issues surrounding the conduct of biotechnological research and the application of biotechnological products in the sphere of public health, while others have focused more broadly on public education about bioethics. Engagements of the former kind have typically involved both the dissemination of information (consultation papers) through targeted mailings and postings on the BAC's website and the organisation of events to bring stakeholders and other interested parties into dialogue with experts from the science and policy domains.

The BAC produced a total of nine consultation papers between 2001 and 2018 on topics that reflected the emergence of concerns not just locally but internationally, both with particular technologies and with the conduct of biomedical research (see Figure 1). Thus, as we entered the new millennium, the ethical interest of policymakers and those that advise them lay in areas such as stem cell research and human tissue research. A decade later and attention had shifted to the need to establish broader ethical guidelines for human biomedical research. More recently still, it was the ethical questions raised at the prospect of technological innovations such as Mitochondrial Genome Replacement Therapy (MGRT) being made available to the Singapore population that motivated public consultation.

[3] Murray and White (2009) recognise this when they say "Commissions or bioethics organisations should continuously engage with the broader public after their analysis and recommendations are published" (p. 185).

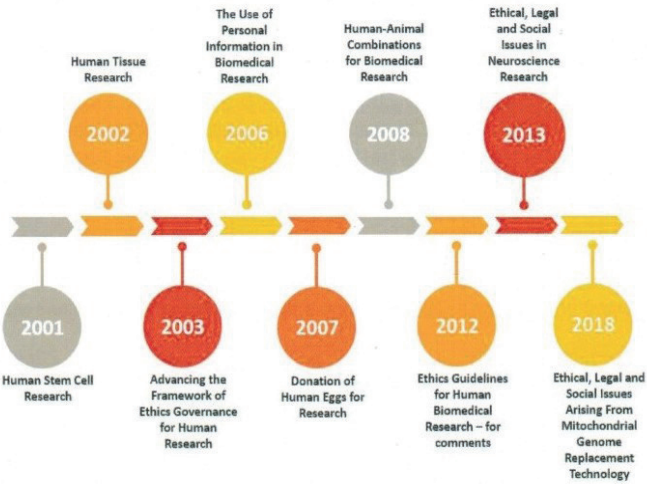

Figure 1. Timeline of release of Consultation Papers.

Given the disparateness of the topics, it was only proper that the BAC should adopt somewhat divergent means of engaging different stakeholders, community groups as well as the wider public. Certain consultations targeted the professional groups who would ultimately be expected to act upon the resulting guidelines promulgated by the BAC. For example, the consultation for what became the report titled "Research Involving Human Subjects: Guidelines for IRBs" (2004)[4] involved the distribution of the consultation paper to thirty-seven bodies concerned with the ethics and governance of human biomedical research in Singapore followed by a dialogue session with hospital ethics committees and Institutional Review Boards (IRBs). Other consultations on topics that had potentially profound implications for the use of the biological material instrumental in the creation of human life, i.e. gametes, were not surprisingly targeted at the wider public (e.g. "Donation of Human Eggs for Research" (2007)[5] and "Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Therapy" (2018)).[6]

Also targeted at the general public was the consultation on "Ethics Guidelines for Human Biomedical Research" (2012),[7] which served as a precursor

[4] Available at: https://www.bioethics-singapore.gov.sg/publications/reports/research-involving-subjects-guidelines-for-irbs

[5] Available at: https://www.bioethics-singapore.gov.sg/publications/reports/donation-of-human-eggs-for-research

[6] Available at: https://www.bioethics-singapore.gov.sg/files/publications/consultation-papers/mitochondrial-genome-replacement-tech.pdf

[7] Available at: https://www.bioethics-singapore.gov.sg/publications/reports/ethics-guidelines-for-human-biomedical-research

to the production of the most significant piece of Singapore legislation relating to biomedicine to date: the Human Biomedical Research Act 2015. Following a public dialogue, the public was invited to obtain a draft copy of the consultation paper and to send their responses to the BAC Secretariat. Other consultations, while still aimed broadly at the public, were focused on obtaining feedback from certain groups such as religious, professional and scientific organisations; for example, the consultation relating to "The Use of Personal Information in Biomedical Research" (2006).[8] Thus, in the case of each consultation exercise, thought was given to who the key stakeholders were in relation to any recommendations that would flow from the resulting reports and attempts made to ensure the participation of such groups.

Public Education

In addition to engaging the public during the course of ongoing deliberations on specific policy matters, the BAC also took the lead in organising a number of educational initiatives with a broader bioethical focus in collaboration with partners such as the Science Centre Singapore (SCS) and the Centre for Biomedical Ethics (CBmE) in the Yong Loo Lin School of Medicine at the National University of Singapore.

In 2015, the year of the BAC's fifteenth anniversary, a "Bioethics Week" that ran from 29 June to 4 July was organised. It encompassed research ethics workshops, a public forum on "Research Involving Children" chaired by Mr. Hugh Whittall, Director of the Nuffield Council on Bioethics in the UK, a talk titled 'Ethical Issues Associated with Germline Modification' targeted at IRB members, and the screening of a bioethics-themed movie, *My Sister's Keeper*,[9] followed by a discussion of its themes relating to so-called 'saviour siblings' between members of the public and bioethicists from CBmE which I had the honour of chairing. Bioethics Week served to showcase the BAC's ongoing commitment in ensuring the responsible conduct of biomedical research in Singapore and its further commitment to ensuring that the general public was provided with rich opportunities to learn about emerging issues in bioethics from experts at the leading edge of bioethical deliberation as well as through depictions of bioethical themes in popular culture. This is all very much in keeping with UNESCO's statement that "In [National Bioethics Committees], ethics are

[8] Available at: https://www.bioethics-singapore.gov.sg/files/publications/consultation-papers/the-use-of-personal-information-in-biomedical-research.pdf

[9] Furst, S. Goldman, S. Johnson, M. Pacheco, C. Tropper, M. (Producers). (2009). *My Sister's Keeper* [Film]. New Line Cinema, Curmudgeon Films.

not the proprietary realm of scientists or health care professionals, but rather a multidisciplinary, pluralistic, deliberative project".[10] Indeed, they go on to say that "In frontier issues, social imagination shaped by novels, cinema, literature, and cultural narratives, plays a key role in orienting research and policies",[11] thus underscoring the value of creative media as a means of engagement in multi-faceted initiatives such as Bioethics Week.

Building on the success of Bioethics Week, the following year the BAC organised a further series of public education events which it dubbed "Bioethics Festival". This was timed to overlap with the "Singapore Science Festival 2016," which took place from 15 July to 5 August. The intention here was to signal to the public the inseparability of bioethics from the conduct of biomedical scientific research. Once again, the BAC partnered with SCS and CBmE in the planning, hosting, and execution of the events, which included a talk titled "Mitochondrial Genome Replacement Therapy", the screening and discussion of another bioethics-themed movie, *Inception,*[12] and the performance and subsequent discussion of a bioethics-themed play, *Child's Play*. Once again, I had the pleasure of chairing the public discussion of issues raised in the movie, this time relating to memory manipulation through biotechnology. The discussion also led to a remarkably frank discussion about the use of cognitive-enhancing drugs in competitive working environments such as Singapore's (Figure 2).

[10] United Nations Educational, Scientific and Cultural Organisation. (2019). Guide no. 5: Bioethics committees and public engagement. (pp. 13) Available at: https://www.ccne-ethique.fr/sites/default/files/1098_19_guide_5_bioethics_committees_public_engagement_int_web.pdf

[11] Donation of Human Eggs for Research. (2008). Full report available at: https://www.bioethics-singapore.gov.sg/publications/reports/donation-of-human-eggs-for-research

[12] Thomas, E. Nolan, C. (Producers). (2010). *Inception* [Film]. Legendary Pictures, Syncopy.

Figure 2. Post-screening discussion of *Inception*.

The play *Child's Play* was commissioned from the local theatre company The Necessary Stage and its resident playwright Haresh Sharma under the provisions of a grant held by CBmE from the National Medical Research Council that aimed to promote bioethical outreach and capacity development in Singapore. Hosted at SCS, the play dealt with the ethics of enrolling minors in clinical trials and provided a dramatic and insightful framing of questions that were subsequently discussed between CBmE researchers and the public in attendance (mostly schoolchildren and their accompanying teachers).[13]

Beyond public engagement through specific events, the BAC also collaborated with SCS and CBmE in establishing a permanent bioethics exhibition at the Science Centre which launched on 28 July 2010 (Figure 3). The objectives of the exhibition were to:

(a) raise awareness of bioethical and related issues, especially those most relevant to Singapore;

[13] The value of such artistic means of engaging the public in bioethical discussions is explored in Fanaras, Georgiadou, Kitsa & Kamiri (2016) in relation to an earlier dramatic work similarly aimed at secondary school students and commissioned by CBmE from The Necessary Stage and Haresh Sharma, *Future Perfect* (2012), which dealt with the ethics of human enhancement.

(b) provide sound information about technologies that impact people's lives as well as future implications;

(c) develop interactive educational exhibits (including the use of multimedia) to assist in the learning process; and

(d) develop methods and tools for assessing the extent to which bioethical issues are understood.

In addition to the above, the public exhibition was also an attempt to raise public interest in biomedical research initiatives, encourage public engagement in developing bioethical policies, and raise the level of public confidence in the ethical conduct of biomedical research, thereby advancing the common good of society. The topics covered included stem cell research, human tissue research, research involving human subjects, genetic testing and genetic research, the obtaining and use of personal information in biomedical research, donation of human eggs for research, and the production of human-animal combinations.

Figure 3. Ribbon-cutting ceremony to mark the official opening of the Bioethics Exhibition.

[From left to right: Professor Alastair V. Campbell, Director of the Centre for Biomedical Ethics, NUS, Professor Lim Pin, Chairman of the BAC, Mr. Khaw Boon Wan, Minister for Health, Associate Professor Lim Tit Meng, Chief Executive, Science Centre Singapore]

To facilitate the fullest engagement of Science Centre visitors, the exhibits were made to be as interactive as possible and served to encourage critical thinking in relation to issues such as whether to use biotechnology to determine the sex of a child and whether to permit cloning of human embryos.

Wider Collaborations

The BAC's 10th Anniversary year in 2010 marked what might be the apogee of its public engagement efforts to date and coincided with its strong international cooperation in the field of bioethics more generally. The Science Centre exhibition period fell within the month when the BAC hosted two international bioethics conferences – the 8th Global Summit of National Bioethics Advisory Bodies from 26 to 27 July 2010 (co-hosted with the Ministry of Health), and the 10th World Congress of Bioethics (WCB) from 28 to 31 July 2010. The WCB was organised under the auspices of the International Association of Bioethics, and was supported by the Agency for Science, Technology and Research, the National University of Singapore, the Ministry of Health (MOH) and the Singapore Medical Association. In addition, a number of satellite meetings of bioethical concern were held just before the Congress, from 26 to 27 July 2010. While these academic meetings were not primarily aimed at engaging the Singaporean public, they did serve to increase the BAC's public profile and shine a light on the efforts being undertaken at both national and international levels to address bioethical issues.

THE FUTURE OF PUBLIC ENGAGEMENT

Over the past twenty years, the BAC has engaged the Singaporean public through a multitude of means and in so doing has fulfilled two vital parts of its brief as an NBC: to raise awareness of issues relating to advances in biomedicine in the general population, and to obtain feedback on proposed policy positions. However, moving into the third decade of the Millennium, the BAC will need to explore further means of engagement that leverage the power and reach of newer forms of media, particularly social media.

This is not to say that traditional print newspapers can or should be replaced as a central means of laying out the complexities of issues surrounding emerging biomedical technologies and the ways in which biomedicine will leverage other technologies in areas such as artificial intelligence and big data. The space they can devote to feature articles that may incorporate a blend of interviews, infographics and expert opinion pieces is not easily found in other popular media that government agencies can leverage. Furthermore, Singapore is fortunate in having a mainstream media that is sober and non-sensationalist in tone, allowing for an objective airing of different perspectives on highly controversial technologies and practices and being highly accommodative of public engagement efforts for the common good. However, in order to engage a good cross-section of society, and particularly the younger generation who typically receive their newsfeed from social media platforms, there is a need to look beyond traditional print media. An integration of feature material from the print media with social media platforms such as Facebook which can reproduce print articles while also inviting comments on them would be a positive move.

Blogs are another means of reaching out to the public where opinion pieces written by experts can be used as a means of generating dialogue. However, while official blog platforms undoubtedly enhance the online profile of bioethics committees, such as the one established by the UK's Nuffield Council on Bioethics,[14] casual observation of the number of comments posted on such blogs suggests they rarely succeed in soliciting a significant number of responses from the general public, with those who do contribute typically being interested parties such as academics. Nonetheless, they do serve as another means of making various ethical positions on emerging biotechnologies accessible to the general public for their information and edification.

As the recent global experience of the COVID-19 pandemic has led to the fuller utilisation of online meeting platforms and an explosion of webinars on diverse topics of public interest, there is also an opportunity for the BAC to engage more members of the general public in discussion of bioethical issues by organising online forums either in direct replacement of in-person forums as a response to continuing social distancing measures, or as an alternative to such in-person forums for the sake of attracting a larger and more diverse set of participants. Of course, publicity is key to such events attracting wide public interest and targeting advertising at grassroots organisations such as Community Centres may serve to achieve an even greater diversity of participation. Forums

[14] See: https://www.nuffieldbioethics.org/blog/

could also be live-streamed to multiple locations of this kind to facilitate wider participation.

Other more highly structured means of public engagement that have been a feature of other NBCs' public engagement efforts, such as citizen juries and focus groups, have yet to be adopted by the BAC and may provide future opportunities for gathering nuanced responses to complex ethical issues. Citizen juries require participants to focus on specific questions and make recommendations in response to them.[15] Such an approach has been used by MOH in soliciting views on possible national approaches to tackling diabetes.[16] Focus groups, on the other hand, present selected participants with specific issues to respond to but without the expectation that they arrive at particular conclusions. Such an approach has been used by research groups within CBmE on, among other things, issues arising in relation to precision medicine.[17] If the BAC aims to gather feedback on particularly nuanced questions in future consultation exercises, it might consider partnering with individuals within MOH or CBmE who have developed relevant experience in these methods of engagement.

With respect to the broader educational engagement of the public, the BAC will need to continue to work with partners that can provide the material resources and academic expertise to ensure high quality, impactful events that would in themselves be likely to attract media attention. It is worth observing that changes in the funding environment in Singapore over the past five years have led to a shift of emphasis towards the bioethical training of those working at the coalface of the biotech sector, e.g. clinician scientists. Consequently, less emphasis is currently being placed on public education and outreach by tertiary centres such as CBmE. Nonetheless, the BAC will surely continue to marshal resources at the national level and work with its longstanding partners to fulfil its remit to ensure the meaningful engagement of the general public in emerging issues in biomedical ethics.

[15] See: UNESCO (2019, p. 35).

[16] See: https://www.moh.gov.sg/wodcj *and* https://www.csc.gov.sg/articles/partnering-with-the-public-in-the-war-on-diabetes

[17] Lysaght, T., Ballantyne, A., Xafis, V., Ong, S., Schaefer, G. O., et al. (2020). Who is watching the watchdog? Ethical perspectives of sharing health-related data for precision medicine in Singapore. doi: https://doi.org/10.21203/rs.3.rs-24953/v1

14

Concluding

Richard Magnus

INTRODUCTION

At the turn of the 21st century, the Singapore Government made an immense commitment to advance the biomedical sciences sector, which was identified with enormous growth and economic potential. In pursuit of research excellence, the Government established the Biomedical Sciences (BMS) Initiative in 2000 to develop this sector as the fourth pillar of Singapore's manufacturing economy. The BMS Initiative consists of the Pharmaceutical, Biotechnology, Medical Engineering and Technology, and Healthcare Services industries. Since then, Singapore has developed outstanding capabilities across the entire value chain ranging from drug discovery and clinical research to manufacturing and healthcare provision.

These developments were only possible through proper regulatory protocols and guidelines in place to ensure research integrity as local scientists comply with clear and ethical standards. These ethical standards for research are defined by the Bioethics Advisory Committee (BAC), which was established by the Singapore Government in December 2000. Given Singapore's diverse religious and racial fabric, it is critical that our bioethical position is not limited to a single or rigid perspective. Rather, our position should take into account a diversity of viewpoints to maximise the common good. The key roles of the BAC are to explore the ethical, legal and social issues associated with biomedical research, as well as make recommendations to the Singapore Government to help inform policy decisions. In doing so, the BAC serves to protect the rights and welfare of individuals participating in biomedical research, while ensuring the development of the biomedical sciences such that it realises its utmost potential for the benefit of mankind.

The year 2020 marks the 20th Anniversary of the BAC. Since its establishment in 2000, it has engaged and deliberated on a wide range of bioethical issues which were subject to international attention.

ISSUES THAT BAC HAS ENGAGED IN

Human Stem Cell Research, Reproductive and Therapeutic Cloning (2002)

One of the BAC's first projects was to review Human Stem Cell Research, where I had the privilege to serve as Chair of the Human Stem Cell Research Sub-Committee (HSRSC) appointed by the BAC to study this issue. The BAC conducted an extensive public consultation exercise with the aim of gathering perspectives from the community, particularly organisations with medical, religious, scientific, ethical and legal interests. The BAC's recommendations were subsequently published in 2002.[1] In its report, the BAC recognised the existence of several distinct views with regard to Human Stem Cell Research, and the importance for the BAC to acknowledge and consider the diverse perspectives of various community groups.[2] After careful deliberation of the concerns and sentiments of the general public, international panellists as well as religious groups, the BAC eventually put forth 11 key recommendations regarding the licensing, control and supervision of Human Stem Cell Research in Singapore. The BAC believes that these recommendations would engender 'just' and 'sustainable' results – 'just' in that the research would reap immense therapeutic benefits for mankind; 'sustainable' because such research would engender minimal biological and genetic impact on future generations.[3]

As of today, close to 20 years since the report was released, researchers in Singapore still abide by the principles of the BAC's recommendations which were incorporated into legislation through the Human Cloning and Other Prohibited Practices Act (2004). This has served to ensure that our scientists work within ethically acceptable boundaries, and strengthened Singapore's international image as a nation responsible to its people, as well as to mankind.

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1 Ethical, Legal, Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning. (2002). Full report available at: https://www.bioethics-singapore.gov.sg/publications/reports/ethical-legal-and-social-issues-in-human-stem-cell-research-reproductive-and-therapeutic-cloning

2 Bioethics Advisory Committee seeks community feedback on Human Stem Cell Research (2001) Available at: https://www.bioethics-singapore.gov.sg/publications/press-releases/bioethics-advisory-committee-seeks-community-feedback-on-human-stem-cell-research

3 Ethical, Legal, Social Issues in Human Stem Cell Research, Reproductive and Therapeutic Cloning. (2002).

Human Tissue Research (2002)

In the same year, building upon the principles set forth in its Human Stem Cell Research, Reproductive and Therapeutic Cloning report, the BAC issued its second report on Human Tissue Research.[4] In this report, the BAC sets out its recommendations for national guidelines on human tissue banking, and for the conduct of biomedical research involving the use of human tissue samples.

Through this report, the BAC drew out a single set of universal guidelines that could be applied to all institutions involved in the collection or use of human tissue for research purposes. At that time, the use of human tissue in research was self-regulated by each research institution's ethics committees or review boards. While this system was fundamentally sound, the BAC was of the view that it could be further improved through instituting a statutory licensing scheme that would require all institutions carrying out research tissue banking activities to be licensed by a relevant statutory authority. Such a system would promote a flexible and responsive regulatory framework based on good internal self-governance, while still allowing the Government to exercise regulatory control over the conduct of research tissue banking activities.

The BAC noted that research involving the use of human tissue was fundamental to the advancement of knowledge in the biomedical sciences, and it was integral that Singapore had a governance framework for human tissue research to support the safe and ethical conduct of such research.

Research Involving Subjects: Guidelines for Institutional Review Boards (2004)

In 2004, the BAC reviewed the existing ethics governance framework for biomedical research in Singapore, and made recommendations on the role of institutional review boards (IRBs) with the objective of improving our frameworks to be on par with international best practices.[5]

Prior to the BAC's report, there was an existing system of regulations by the Ministry of Health to govern the conduct of pharmaceutical trials and

[4] Report for Human Tissue Research (2002). Full report available at: https://www.bioethics-singapore.gov.sg/publications/reports/human-tissue-research

[5] Report for Research Involving Subjects: Guidelines for IRBs (2004). Full report available at: https://www.bioethics-singapore.gov.sg/publications/reports/research-involving-subjects-guidelines-for-irbs

human biomedical research conducted by hospitals, private clinics and healthcare establishments. Singapore's National Medical Ethics Committee (NMEC) also issued a framework of ethics governance for human biomedical research in 1997. The BAC recognised that Singapore had to establish clear and transparent standards and procedures for human biomedical research to further our reputation as a global centre of excellence. This is to ensure that we remained aligned with international best practices, which was developed on the consensus that any form of biomedical research which includes human subjects should be subject to independent ethics review — a principle reflected in international documents such as the Nuremberg Code (1949) and the Declaration of Helsinki (1964).

Hence, this report aimed to build upon the existing regulatory system and the NMEC's framework to expand the scope of ethics governance to include all human biomedical research conducted in Singapore, while also clarifying the roles and responsibilities of IRBs, institutions and researchers in fostering a culture of good practice, transparency and accountability in the conduct of human biomedical research.

Genetic Testing and Genetic Research (2005)

In 2005, the BAC studied the ethical considerations for the conduct of genetic testing and human genetic research.[6] Scientific advances in human genetics had greatly increased our understanding of genes and their impact on health and diseases, leading to the development of a wide range of clinical genetic tests and novel treatments for various countries. However, the predictive nature of genetic information derived from genetic testing is sensitive not only for its impact on tested individual, but also for those genetically related to this person. There were also ethical issues related to the obtaining of informed consent from participants, the use of genetic testing on vulnerable persons (such as on infants and minors), and the safeguarding of the privacy of tested individuals to ensure the confidentiality of genetic information.

In its report, the BAC issued guidelines for the ethical conduct of clinical genetic testing, as well as genetic testing in research. The BAC also made recommendations on the use of preimplantation genetic testing and prenatal genetic diagnosis, recommending that the use of these techniques for selecting of traits or gender for non-medical reasons be disallowed. Lastly, the BAC recommended against the clinical practice of germline genetic modification

[6] Report for Genetic Testing and Genetic Research (2005). Full report available at: https://www.bioethics-singapore.gov.sg/publications/reports/genetic-testing-genetic-research

techniques, and advised that progress in this field should be closely monitored and reassessed at an appropriate juncture in future.

The BAC's recommendations were timely and helped to identify key ethical principles for both researchers and clinicians to observe even as the field of genetics and genomics continues to develop today.

Personal Information in Biomedical Research (2007)

In the conduct of human biomedical research, personal information is usually obtained from research participants. The use of personal information in biomedical research is essential and has helped produce valuable medical knowledge. As Singapore made progress in developing talent and infrastructure in the biomedical sciences, the BAC recognised the need for proper rules to govern the access and use of personal information in human biomedical research. Therefore, the BAC issued a report which called for the establishment of a framework to protect participant privacy and confidentiality and allowed the legitimate use and exchange of personal information for human biomedical research.[7]

The BAC was of the view that the use of personal information in biomedical research generally requires the consent of the individual concerned. However, the BAC also recommended that in certain circumstances, it was ethically acceptable for personal information to be used in research without consent, provided that privacy and confidentiality safeguards are in place. These circumstances include the conduct of research with important public health justification, or research involving minimal risk of harm where patient contact, privacy and confidentiality are not compromised (e.g. research involving medical records). In such situations, the BAC recommended that IRBs be legally empowered to waive patient consent requirements.

Donation of Human Eggs for Research (2008)

Following its 2001 report on Human Stem Cell Research, the BAC acknowledged that the donation of human eggs for research, in particular for embryonic stem cell research, had also drawn considerable attention. In addition to being used in Assisted Reproduction Technologies (ARTs) to treat infertility,

[7] Report for Personal Information in Biomedical Research (2007). Full report available at: https://www.bioethics-singapore.gov.sg/publications/reports/personal-information-in-biomedical-research

human eggs have also been used for research purposes. The donation of human eggs is essential to advance stem cell research as they allow researchers to better understand the nature and potential of stem cells, thus paving the way for successful development of stem cell therapies for severe and incurable diseases such as diabetes and Parkinson's disease.

However, several important and fundamental safety and ethical concerns had been brought into question. Firstly, impoverished and vulnerable women may be exploited or coerced to provide eggs for research, which can eventually lead to commercialisation of the human body. Such a claim to rights and property of the human body is not desirable as it raises a whole new dimension of ethical issues, and is also in conflict with the fundamental principle of respect for individuals. In addition, there exists a dilemma as to whether egg donors should receive any payment and compensation — and if so, in what form and amount?

After extensive public consultations and much internal deliberations, the BAC made seven recommendations concerning the consent, compensation and care of donors, the import and use of eggs in research, and the need for regulatory control.[8] These recommendations were built upon the regulatory framework drawn out in the BAC's earlier report on Human Stem Cell research.

The BAC was of the view that all research involving human eggs should only be conducted under strict regulation, regardless of whether the human eggs are obtained overseas or locally. In addition, altruism should be the key driving force behind the donation of eggs. Similar to the context of blood donation, women who donate their eggs for research should do so out of interest or willingness to contribute to public good, instead of financial incentives. As a result, women should not be compensated for egg donation if the eggs are derived from surpluses from fertility or other medical treatments. However, women not undergoing any form of clinical treatment should be compensated for the loss of income and time. It is also important that compensation should not be tantamount to inducement and should not be influenced by the quantity or quality of eggs provided.

Human-Animal Combinations in Stem Cell Research (2010)

In view of international ethical debate on research involving human-animal combinations, the BAC released a report in 2010 outlining its recommendations

[8] Donation of Human Eggs for Research. (2008). Full report available at: https://www.bioethics-singapore.gov.sg/publications/reports/donation-of-human-eggs-for-research

on research involving the use of human-animal combinations (i.e. any living organisms where there is some mixing of human and animal materials) as part of its efforts to update its recommendations for human stem cell research to address ongoing scientific developments.[9] The report focused on two types of human-animal combinations: cytoplasmic hybrids and animal chimeras.

Over the course of its review, the BAC examined the scientific rationale behind the creation of such human-animal combinations. The BAC also heard the ethical and social concerns raised by the Singaporean public during its public consultation exercises regarding the possibility of developing actual independent living creatures with both human and animal features, or even animals with human consciousness or mental characteristics.

To address these concerns, the BAC recommended that researchers should not be allowed to develop such hybrids beyond 14 days or the emergence of the primitive streak, whichever is earlier. Furthermore, chimeras created with human embryonic stem cells or any other kind of pluripotent stem cells should not be allowed to breed.

The BAC concluded that while research involving human-animal combinations should be allowed on grounds of scientific merit, a regulatory framework was needed to ensure that ethical requirements and limits are properly observed. This ethical framework should include an ethics review process to ensure that research involving human-animal combinations is permitted only when there is strong justification for scientific merit, potential medical benefit, and there is no satisfactory alternative to pursuing the same research. The BAC also recommended that individuals who have a conscientious objection to such research should not be under any duty to conduct or assist in such research.

Ethics Guidelines for Human Biomedical Research (2015)

The biomedical sciences is a rapidly evolving field. Ethical pronouncements on what was previously considered sensitive or unacceptable may also change as a result of either scientific developments or socio-cultural changes. To ensure that the BAC's recommendations continue to be relevant given scientific, regulatory, and legal developments, there is a need for the BAC to regularly review its past positions and recommendations.

[9] Human-Animal Combinations in Stem Cell Research (2010). Full report available at: https://www.bioethics-singapore.gov.sg/publications/reports/human-animal-combinations-in-stem-cell-research

Hence, in 2015, the BAC developed a set of guidelines titled "Ethics Guidelines for Human Biomedical Research".[10] These guidelines serve as a consolidated ethical resource for the research community in Singapore, and was based on a review of the BAC's past reports and recommendations issued between 2002 and 2010. It also addressed any inconsistencies and ambiguities, and introduced new recommendations that addressed gaps and new issues arising from scientific, legal and policy developments.

The BAC aims to continually review and update these guidelines to ensure that it remains an up to date ethical resource to support the responsible and ethical conduct of human biomedical research in Singapore, and plans to complete its first review of the guidelines in 2021.

Neuroscience Research (2021)

With the increasing clinical burden of neurological and psychiatric disorders worldwide, research in neuroscience research to uncover effective and novel therapies has recently garnered interest. This has encouraged the BAC to deliberate on the ethical, social and legal implications arising from neuroscience research.

Neuroscience research usually involves the brain, which may affect our sense of self. In the distant future, techniques which permanently modify brain function, manipulate or stimulate targeted neural pathways can be envisioned. Therefore, there is a need for deliberation on the implications of neuroscience research, as well as increased public awareness in this field.

After extensive public consultation with policy makers and the general public, and taking into consideration international practices and guidelines in this field, the BAC published a report in 2021 to set out its recommendations on the conduct of neuroscience research. In its report, the BAC concluded that in most instances of neuroscience research, many of the ethical, legal, and social issues raised were not exceptional and did not differ fundamentally from the issues arising from most human biomedical research. As such, these issues could be sufficiently addressed through the application of existing research ethics frameworks previously recommended by the BAC.

[10] Ethics Guidelines for Human Biomedical Research (2015). Full report available at: https://www.bioethics-singapore.gov.sg/publications/reports/ethics-guidelines-for-human-biomedical-research

However, the BAC identified some exceptional cases that may require additional caution to ensure the safety and welfare of research participants. These include the conduct of high-risk neuroscience research that may have an impact on the personal identity and autonomy of participants, or the ethical issues from sham brain surgeries. For these exceptional areas, the BAC recommended that additional caution be practised by the researchers. For instance, researchers should inform participants at the onset (i.e. during consent taking) if there is a risk that the research could affect the participant's personal identity or autonomy, put in place additional safeguards such as proactively ascertain the wishes of research participants in the event that they lose mental capacity over the course of research protocol. These additional safeguards serve to ensure that the individual autonomy of such participants are respected at all times.

The BAC's review serves to assure all Singaporeans that the rights and welfare of research participants will continue to be safeguarded as Singapore continues to develop new ways to diagnose, prevent or treat neurological disorders.

Mitochondrial Genome Replacement Technology (2021)

Mitochondrial Genome Replacement Technology (MGRT) seeks to prevent the transmission of mitochondrial diseases from mother to offspring. This is accomplished through replacing defective mitochondria in oocytes or zygotes of females at risk of transmitting mitochondrial disease with non-pathogenic mitochondria from a healthy donor. Since mitochondria consist of genetic material which is transmitted from mother to child, the use of MGRT could entail germline modification as inheritable genetic changes would be introduced if the resulting offspring is also female.

In a 2005 report titled "Genetic Testing and Genetic Research", the BAC recommended a moratorium on germline genetic modification in clinical practice in light of a serious concern that germline modification could have "potentially great impact on future generations".[11] The BAC was guided in this deliberation based on the principle of sustainability, which entails that we should not jeopardise the well-being of our future generations until adequate research has been conducted to establish the feasibility and safety of MGRT. However,

[11] Ethical, Legal and Social Issues Arising from Mitochondrial Genome Replacement Therapy. A Consultation Paper (2018). Bioethics Advisory Committee, Singapore. Available at: https://www.bioethics-singapore.gov.sg/files/publications/consultation-papers/mitochondrial-genome-replacement-tech.pdf

there have been significant scientific and policy developments in the field of MGRT internationally in the past decade. Given recent developments in the field of MGRT, the BAC considered it timely and necessary to study the current research involving MGRT, and to review the BAC's existing recommendations on germline genetic modification, with a focus on MGRT.

Some of the greatest concerns of MGRT conveyed by the general public pertain to the issue of self-identity, and the fact that each child born from MGRT would, in theory, have the genomes from three different individuals. Social implications for children with "three parents" were also considered by the BAC. It is essential that we put in place the necessary ethical and legal safeguards before we proceed with permitting MGRT in Singapore.

In 2021, after extensive deliberation and taking into consideration the views received during its public consultation, the BAC released its interim report on MGRT. Recognising that there was still much uncertainty surrounding the safety and clinical efficacy of MGRT, the BAC recommended to maintain its current position from its 2005 Report on Genetic Testing and Genetic Research. It concluded that it was premature to exempt MGRT from the prohibition of clinical germline genetic modification and that the clinical application and in vivo research of MGRT in human subjects should not be permitted at that time. A more definitive discussion of the issues raised by MGRT would be better undertaken at a future date when there was greater certainty in the science, techniques, safety, and efficacy of MGRT. Until then, the BAC would continue to observe international developments (such as the ongoing clinical trials in the UK) and monitor our position in this area.

FUTURE CHALLENGES AND VISION OF THE BAC

The work of the BAC has propelled our city-state to the forefront of the biomedical sciences industry. This could only be accomplished with proper regulatory surveillance in place to ensure that ethical standards are met while potential benefits from the research are reaped. Through the BAC's recommendations, Singapore has in place effective ethical frameworks to address the legal, social and ethical issues arising from human biomedical research. These frameworks have played a crucial role in maintaining public trust so that the biomedical sciences may continue to flourish in Singapore.

Given the rapid progression of biomedical research, medicine and healthcare across the world, more complex dilemmas and issues are bound to emerge in the field of bioethics. Over the past few decades, the BAC was confronted with emerging issues such as stem cell research and genetic research. But as the biomedical sciences continue to develop and novel therapies are discovered, the BAC will continue to face new and unprecedented challenges.

In light of the ongoing COVID-19 pandemic, decision-making during pandemics is one issue that presents several vexing ethical dilemmas. There are also rising concerns with regard to issues like Big Data and Artificial Intelligence, Precision Medicine, and Human Nuclear Genome Editing.

The BAC continually aims to spark public discourse and raise awareness about the most pertinent issues and topics in bioethics, both locally and internationally. We believe that only through global cooperation and communication will insights be furthered, so that approaches and policies can be improved. We ask the public to be engaged in bioethical issues and our consultation processes. Your perspectives and opinions gathered will allow us to address the ethical issues arising from new biotechnologies, allowing Singapore to further develop in the biomedical sciences while ensuring that the welfare of Singaporeans is not compromised.

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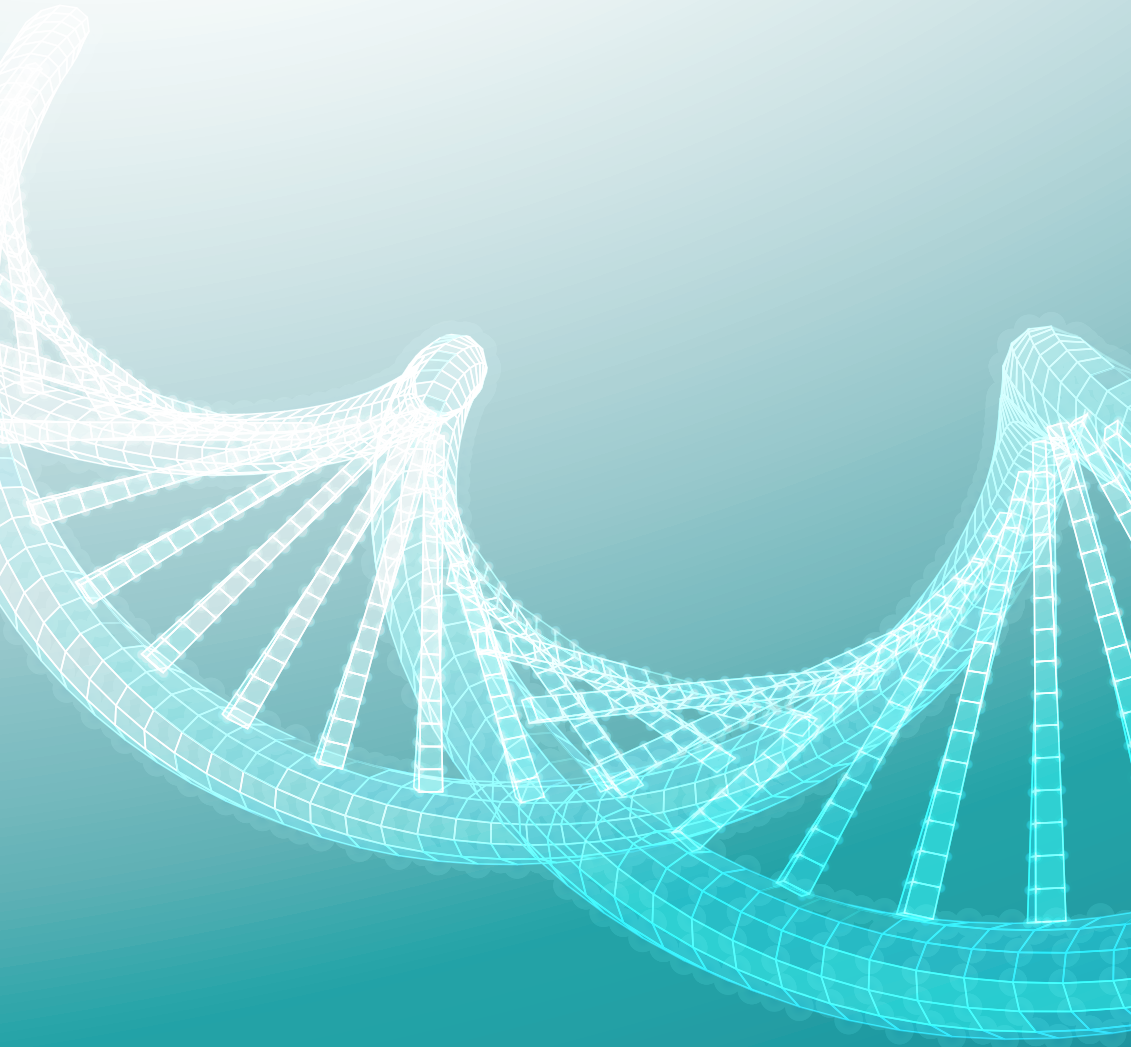

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