The Henry G. Friesen
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in Health Research

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Friesen International Prize Program

"Impacts of Disruptive New Technologies (stem cell science, gene editing, AI) on Society: Role of the Academy"

Proceedings of a Policy Roundtable

University of Ottawa, September 19, 2019

Amis des instituts de recherche en santé du Canada
FCIHR/AIRSC
Friends of Canadian Institutes of Health Research

Celebrating Science and Administrative Leadership

The Henry G. Friesen International Prize in Health Research is awarded in recognition of the distinguished leadership, vision and innovative contributions of Dr. Henry G. Friesen. The prize supports an annual Public Forum and luncheon address to the Canadian Academy of Health Sciences (CAHS). Through the partnership of CBC Radio One Ideas, the lecture is broadcast to reach the broadest possible audience.

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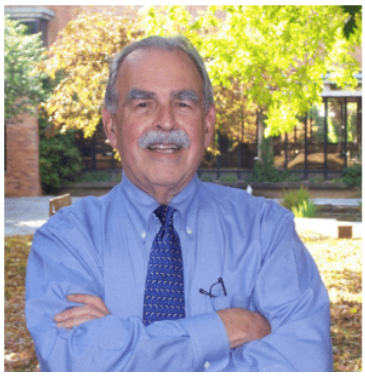
Message From The Friends of The Canadian Institutes of Health Research



Dr. Aubie Angel
CM., MD, MSc, FRCPC, FCAHS, President of Friends of CIHR

I am very pleased to welcome you to the final event of the 2019 Friesen Prize Program in Ottawa featuring a Roundtable entitled, "Impacts of disruptive new technologies on society: the role of the Academy". Roundtables have become an integral element of the Friesen Prize Program because they add significant policy discussions that inform society as a whole. The focus of this Roundtable is on the role of the "Academy", a term used to encompass universities, research institutes and learned societies because they are best equipped in dealing with the complex and advanced technologies that affect individuals and communities.

We have assembled a group of informed speakers representing a variety of perspectives to complement Professor Bartha Knoppers' Keynote talk. It is a privilege to introduce Professor Bartha Knoppers, our 2019 Friesen Prizewinner, and then pass management responsibilities to our distinguished Co-Chairs.

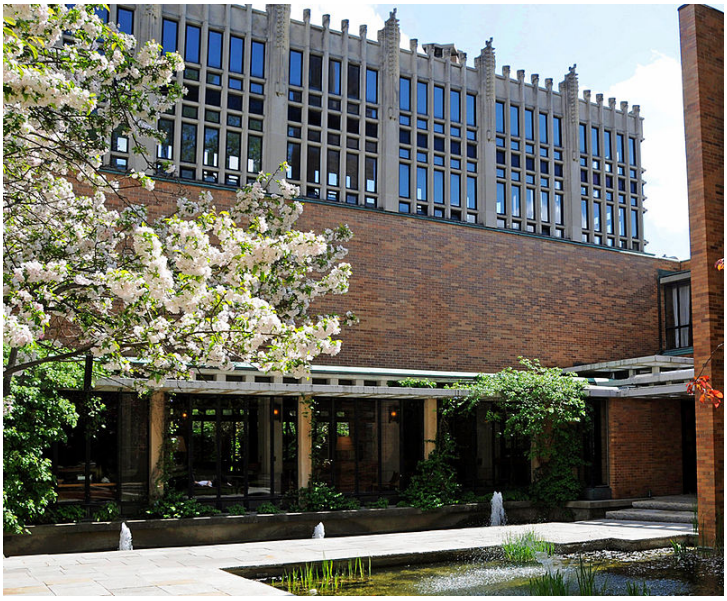
Last evening, Prof. Knoppers was presented with the Friesen Prize and a framed Citation that reads: "For international leadership in establishing legal and ethical norms for research in human genetics and genomics". I would like to recount bits of her resume. She is Professor of Medicine and Human Genetics with appointments in law and biomedical ethics at McGill University. Prof. Knoppers is one of our most prolific and innovative health policy researchers in Canada and beyond. She has been a leader at the interface of ethics and law, as applied to health research policy, stem cell research, human gene editing, bio banking and global data sharing. Prof. Knoppers obtained a BA in 1972 in French and English at McMaster University, an MA in '74 in comparative literature at U Alberta, followed by LLB in 1978 at McGill University. She obtained a PhD at Paris

Sorbonne, and in 1985 was appointed Professor of Law and Medicine at Université de Montréal. Professor Knoppers is a scholar of unrivaled productivity who has made significant contributions to Canadian and international policy and institution building.

Professor Knoppers is a popular mentor, and her scholarly work has appeared in 40 books, 465 articles and over 100 book chapters. Her research is published in the most prestigious journals. Professor Knoppers' many high level honors include four honorary degrees in law and medicine. She is a fellow of the Canadian Academy of Health Sciences, the Royal Society of Canada and the American Association for the Advancement of Science. Professor Knoppers has a multitude of senior awards and recognitions, including the Order of Canada, Order of Quebec, and Order of Montreal.

I would like to invite Professor Knopers to the podium to set the stage and lead off with her keynote talk entitled, “Gene Editing and the Rights of Children”.

Dr. Aubie Angel



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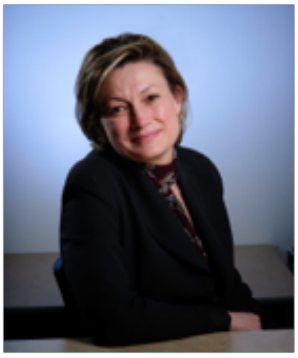
Home of F.C.I.H.R.

Roundtable

"Impacts of Disruptive New Technologies on Society: Role of the Academy"

Co-Chair



Dr. Colleen Flood
Director, U Ottawa Centre for Health Law, Policy and Ethics

Colleen M. Flood is a Professor in the University of Ottawa and a University Research Chair in Health Law & Policy. She is inaugural director of the Ottawa Centre for Health Law Ethics and Policy (https://commonlaw.uottawa.ca/health-law/) and a Fellow of the Royal Society. From 2000-2015 she was a Professor and Canada Research Chair at the Faculty of Law, University of Toronto with cross-appointments to the School of Public Policy and the Institute of Health Policy, Management & Evaluation. From 2006-2011, she served as a Scientific Director of the Institute for Health Services and Policy Research, one of the Canadian Institutes of Health Research. Her primary areas of scholarship are in comparative health care law & policy, public/private financing of health care systems, health care reform, constitutional law, administrative law, and accountability and governance issues more broadly. She is the author of ten books, two of which are in multiple editions.

Co-Chair

Dr. Eric Meslin
President, Council of Canadian Academies (CCA)

Eric joined the CCA in 2016 after 30 years in university and government settings, including the previous 15 years at Indiana University where he was Founding Director of the IU Center for Bioethics, Associate Dean for Bioethics in the IU School of Medicine, and Professor of Medicine, of Philosophy, of Medical & Molecular Genetics, of Bioethics & Law, and of Public Health. Trained in bioethics and philosophy at York University (BA) and Georgetown University (MA, PhD) he has held academic positions at the University of Toronto, University of Oxford, University of Western Australia, and Université de Toulouse, publishing more than 150 articles and book chapters on bioethics aspects of genomics, international health, big data, and human subjects research. His policy experience includes Bioethics Research Director in the Ethical, Legal and Social Implications (ELSI) program at the National Human Genome Research Institute, and Executive Director of the National Bioethics Advisory Commission appointed by President Clinton. He has been a member of advisory committees to the World Health Organization, UNESCO, the Canadian Institutes of Health Research, the Institute of Medicine, UK Biobank, CDC, and Genome Canada. He has consulted with state, provincial and federal governments across the globe, with NGOs, philanthropies, and industry. Among his honours, he is a Fellow of the Canadian Academy of Health Sciences, and was appointed Chevalier de L'Ordre National du Mérite by the Government of France.

"Five Points About the Impact of Disruptive New Technologies on Society: Role of the Academy"

I. Academic input in it's best state provides unbiased evidence to inform policy choices aka science. Sometimes this is difficult: problems with data, problems with methodology, problems with passions. But if we all stick to our knitting on this, produce the best science we can, we move things forward in ever better ways.

II. Passion can be a problem but also it must drive us — many of us raised in the Academy who wish to "make a difference", have an emotional connection to the work, it's impact, it's relevance. It may be about social justice, quality of care, or respect for human dignity. It may be about cost, or progress, or your community. We should not be ashamed of having strong feelings.

III. Relating to Prof. Bartha Knoppers' work – law matters; ethics matters – a lot. But law combined with a depth of understanding of science matters more. We can do more together, working at the "cooling cores of different disciplines" – as per Watson & Crick, we can improve the world. Furthermore, ethics combined with law **and** science matters even more! But that's because the role of the Academy is to help think about what should be done with what is known. Science tells us what is possible, ethics helps us think about what should happen, and law can help us implement this vision.

IV. The Academy has the luxury and the duty to look to the future – and not just the pressures of commerce or of governmental needs, as important as these are too. Our friend and colleague Ian Kerr, who passed away this month, underscores this. Two decades ago when he started his pioneering work, let's just say that his area of interest, law and robotics, was politely described as "esoteric". Fast-forward to today and this work is seen as seminal, ground-breaking and preparing the ground for thoughtful analysis of what is now the Fourth Industrial Revolution.

V. Finally, the Academy's focus needs not only be on the hyperbolic, transformative, revolutionary or disruptive. Sometimes it's nice to know that many people and many disciplines are simply observing and reflecting on what needs attention now.

We think much of this reflects the many ways the Academy can engage with disruptive new technologies.

Dr. Colleen Flood, Dr. Eric Meslin
Co-Chairs of Roundtable

Roundtable

"Impacts of Disruptive New Technologies on Society: Role of the Academy"

Keynote

Dr. Bartha Knoppers
Director, Centre of Genomics & Policy, McGill U

Prof. Bartha Knoppers, OC, OQ, PhD, LLB, ADE, FRSC, FCAHS, is Professor of Medicine and of Human Genetics, with appointments in Law and Biomedical Ethics at McGill University. She is one of the most prolific and innovative health policy researchers in Canada and beyond. She has been a leader in the interface of ethics and law, as applied to health research policy, stem cell research, human gene editing, biobanking and global data sharing. Prof. Knoppers obtained a BA in 1972 in French and English at McMaster University, an MA in 1974 in Comparative Literature at U Alberta followed by LLB in 1978 at McGill University. She obtained PhD at U of Paris Sorbonne in 1985 and was appointed Professor of Law and Medicine at Université de Montréal (1985-2009). Prof. Knoppers is a scholar of unrivalled productivity, who has made significant contributions to Canadian and international policymaking and institution building. She is a popular mentor and her scholarly work has appeared in 40 books, 465 articles and over 100 book chapters. Her research is published in the most prestigious journals. Prof. Knoppers' many high level honours include 4 Honorary Degrees in Law and Medicine. She is a Fellow of the Canadian Academy of Health Sciences, the Royal Society of Canada and the American Association for the Advancement of Science

"Gene Editing and the Rights of Children"

Today, I will speak about the rights of children in the context of gene editing. Heated discussions are ongoing about the implications of gene editing and the proper policy tools needed to ensure an ethical, efficacious, and safe use of these technologies. Yet,gene editing debates seldom mention the rights of children. Before starting, however, it is useful to draw the distinction between germline and somatic gene editing. We see clinical trials in paediatric populations going on right now that alter a gene so that the person then is "treated and cured". In these cases, as a somatic modification, the change is not passed on to future generations. It "lives" and "dies" with the patient. On the other hand, germline gene editing affects the individual in the present, as well as the future generations of their children, grandchildren, and so on.

Some of the challenges then include not just the potential for future generations to be affected, but also misuse of the technique for enhancement, for surveillance, for unapproved , alleged cures and treatments. At the same time, germline editing may ensure that certain serious genetic conditions causing severe morbidity or premature death are no longer transmitted.

The key date in the germline policy timeline, that is when it really came to the attention of the public, was in April 2015. Despite there having been statements, laws, and policies in the past, it was the

announcement that in China, non-viable human embryos had been altered that brought germline editing into the forefront of public consciousness[1]. Indeed, in the following three years, the announcement gave rise to 61 reports on the ethics of germline gene editing from 50 countries. Surprisingly, 11% of those reports indicated that, under certain conditions, the clinical applications of germline gene editing may be permissible[2]. There are four themes common to all these reports thus far[3]: the spectre of eugenics; the risk to future children (which I will discuss in the context of parental freedoms); the failure of professional self-regulation; and the possible chilling effects on scientific research of a moratorium or of criminalization. It is essential to note that the CRISPR twins are indicative of a failure of enforcement, not a failure of regulation. How the debate is characterized is of great import –scientifically validated therapeutic research can go "backwards" by 10 years when a scandal fuels so much controversy that it seems as though we do not have any norms or enforcement in place.And that is the issue. What are the conditions for possible clinical use?Is there consensus on these conditions? Are we prepared? Our own Centre[4] did a study published in *Science*[5], which examined the positions of different countries, not only with respect to human germline modification but also prenatal and pre-implantation testing and embryonic research, because germline gene editing policy must be anchored in the broader context of normative decisions that have already been made about what is and is not serious and up until which stage can one do research on embryos and so on. In Canada, for example, there is a prohibition on knowingly altering the genome of a human cell or in vitro embryo such that the alteration is capable of being transmitted to descendants.[6]

There are different legal and policy approaches. Directives, ethical frameworks, regulations, statutes, etc., are all possible vehicles for crafting policy. Despite many countries having a clear policy in place, it is nevertheless frequently said that we live in a regulatory or policy vacuum. As explored in my Friesen Prize lecture, "Scientific breakthroughs: The prohibition reflex (From IVF to AI)", there is the reaction, a reflex: "We need a law against *it*". But, I would argue that, there is a regulatory ecosystem that is already in place with respect to most emerging biotechnologies. Indeed, the clinical application in China of CRISPR technologies to modify the germline of human twin babies born in November 2018 was actually contrary to their own regulations.

Back in 2002, Dorothy Wertz and I analyzed the responses of the members of three different professional genetic societies (American, European, and Iberian) to study how they defined the notion "serious" when it came to genetic conditions[7]. Already then choices were being made about what is a

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1. Cyranoski, David, and Sara Reardon. "Chinese Scientists Genetically Modify Human Embryos." Nature News. Accessed August 10, 2020. https://doi.org/10.1038/nature.2015.17378.

2. Brokowski, Carolyn. "Do CRISPR Germline Ethics Statements Cut It?" The CRISPR Journal 1, no. 2 (April 1, 2018): 115–25. https://doi.org/10.1089/crispr.2017.0024.

3. Knoppers BM, Kleiderman E. "CRISPR babies": What does this mean for science and Canada? CMAJ. 2019;191(4):E91-E92. doi:10.1503/cmaj.181657.

4. Centre of Genomics and Policy. Department of Human Genetics, Faculty of Medicine, McGill University.

5. Isasi, R., E. Kleiderman, and B. M. Knoppers. "Editing Policy to Fit the Genome?" *Science* 351, no. 6271 (January 22, 2016): 337. https://doi.org/10.1126/science.aad6778.

6. Assisted Human Reproduction Act, SC 2004, c 2.

7. Wertz DC, Knoppers BM. Serious genetic disorders: can or should they be defined? *Am J Med Genet*. 2002;108(1):29-35.

lethal, serious condition, incompatible with human life, maybe not incompatible with life *per se*, but rather a dignified existence that is the essence of *human* life. More recently, a colleague and I have also studied the question 'Could this [law, policy, etc.] be used if we ever decide to undertake germline modification?'[8] Irrespective, putting aside this issue of already existing frameworks and the inaccuracy of claims that there is a regulatory vacuum, the birth of the "CRISPR twins" undoubtedly was a catalyst for new attempts at scientific policy-making by national scientific and medical academies. In short: How do we as citizens, as professionals respond to such scandals?

China itself has now decided to imprison the scientists involved, to tighten its rules, and to have an oversight committee for high-risk clinical trials, as is the case with gene editing. They are not necessarily stopping, they are instead building better, more effective oversight mechanisms. We have also heard recently of a Russian biologist saying, 'We're going to go ahead with this. There are conditions that cannot be met by adoption, by IVF, or by other alternative routes.'[9] He nevertheless claims he is progressing in a gradual fashion to validate the safety and accuracy of edits and will await for official approval before implanting any edited embryos.[10]

Three days after the announcement in Hong Kong about the birth of the CRISPR twins, 18 signatories, including scientists and ethicists from seven countries asked for a global moratorium on germline editing.[11] Not a ban, they said, but an international framework where nations voluntarily commit to not approving any clinical germline editing. No such moratorium, voluntary or not, is in place yet. Following this appeal, in May 2019, the WHO decided to create an expert advisory committee to develop a framework for the ethical use of such a technique should society conclude that heritable human genome editing applications are acceptable and should the national academies of science and medicine via an international commission develop such a responsible pathway.[12]

Undoubtedly, moratoria and / or laws pursue laudable goals. But are they appropriate responses? Are there other tools?We have several. Some of them, of course, are your traditional regulatory ethics tools. Others are oversight committees established in different countries. Further still are specialized agencies such as the UK's Human Fertilisation and Embryology Authority (HFEA), that judge emerging reproductive technologies (e.g., mitochondrial replacement therapy) on a case-by-case basis. Some

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8. Boggio, Andrea, Bartha M. Knoppers, Jessica Almqvist, and Cesare P.R. Romano. "The Human Right to Science and the Regulation of Human Germline Engineering." *The CRISPR Journal 2*, no. 3 (June 1, 2019): 134–42. https://doi.org/10.1089/crispr.2018.0053. See also, Boggio, Andrea, Jessica Almqvist, and Cesare P.R. Romano, eds. 2020. *Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies*. Cambridge: Cambridge University Press

9. Cyranoski, David. 2019. "Russian Biologist Plans More CRISPR-Edited Babies." *Nature* 570 (7760): 145–46. https://doi.org/10.1038/d41586-019-01770-x.

10. Cohen, Jon. "Embattled Russian Scientist Sharpens Plans to Create Gene-Edited Babies." *Science*, October 21, 2019. https://doi.org/10.1126/science.aaz9337.

11. Lander, Eric S., Françoise Baylis, Feng Zhang, Emmanuelle Charpentier, Paul Berg, Catherine Bourgain, Bärbel Friedrich, et al. 2019. "Adopt a Moratorium on Heritable Genome Editing." *Nature* 567 (7747): 165. https://doi.org/10.1038/d41586-019-00726-5.

12. Reardon, Sara. 2019. "World Health Organization Panel Weighs in on CRISPR-Babies Debate." Nature 567 (7749): 444–45. https://doi.org/10.1038/d41586-019-00942-z; Dzau, Victor J., Marcia McNutt, and Venki Ramakrishnan. "Academies' Action Plan for Germline Editing." *Nature* 567, no. 7747 (March 13, 2019): 175–175. https://doi.org/10.1038/d41586-019-00813-7.

countries have also taken more of a professional self-regulatory approach. In such cases, professional societies, for example, the International Society for Stem Cell Research, or human genetic /reproductive societies, such as the American Society of Human Genetics, or the European Society of Human Reproduction and Embryology, etc., actually provide detailed guidance and limits for their members, akin to setting the professional standard of care.

Yet, no one to date has actually looked at the broader human rights implications of human gene editing and, in particular, the rights of children. Most gene editing policy papers and frameworks allude to the need for intergenerational monitoring, which implies the ongoing involvement of children. But such calls are animated by the need to validate techniques to ensure that science is working, and that children are not harmed, not necessarily endorsing gene editing as an expression of their human rights.

There are three children's rights in particular that I believe are of importance to the policy debates about germline gene editing:the right to health, the right to science, and the rights of future generations.[13]As regards the right to health, the 1989 Convention on the Rights of the Child states that the best interests the child shall be a primary consideration in all decisions affecting the child, and further articulates the right of the child to express himself or herself, and the right to the enjoyment of the highest attainable standard of health. Not a right to health, but the highest attainable standard of health. The Convention on the Rights of the Child is the most widely recognized UN convention: every country, except one, has signed and ratified this convention.

As regards the best interests of the child standard, Shawna Benston has written about the subjective threshold interpretation of harm.[14]She argues that when one determines whether or not one is harming another individual, which is central to the ethical principle of non-maleficence, such a determination implicates a rights-duties analysis. The prospective child has a right to a life above a predetermined reasonable threshold, and the potential parents and their doctor or the prospective child the duty to ensure such a life. She then uses this to repudiate the oft-employed position that any life, irrespective of quality, is better than no life. To say that any life is better than no life at all is to deny a prospective child of his or her right to health, threatening a slippery slope to general parental neglect. There must be an identifiable, reasonable threshold. This is the first time I've seen such an argument, and I believe it may be used to better inform policy making regarding the clinical application of germline gene editing and the rights of children.

Next is the right to science, the right of every individual to share in the benefits of scientific advancement. It is a dormant right, a neglected right, a forgotten right. Its first articulation was in the 1948 Universal Declaration of Human Rights, and it is also in the 1966 International Covenant on Economic, Social, and Cultural Rights, which Canada has signed and ratified. As a right in the Covenant, States Parties can only interfere with this right as determined by law, which must further the general welfare. Thus, States Parties can only diminish or augment this right with another law that is in the public interest.[15]

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13. Knoppers, Bartha Maria, and Erika Kleiderman. "Heritable Genome Editing: Who Speaks for 'Future' Children?" *The CRISPR Journal 2*, no. 5 (October 1, 2019): 285–92. https://doi.org/10.1089/crispr.2019.0019.

14. Benston S. CRISPR, a crossroads in genetic intervention: Pitting the right to health against the right to disability. *Laws*. 2016;5:5-19. DOI: 10.3390/laws5010005.

15. UN General Assembly, International Covenant on Economic, Social and Cultural Rights, 16 December 1966, United Nations, Treaty Series, vol. 993, p. 3, Art 4.

It is a dormant right with much potential. In the past decade or so, it has garnered greater attention. In 2009, UNESCO's *Venice Statement on the Right to enjoy the benefits of scientific progress and its applications* was a catalyst in starting the process of defining and delimiting the right to science. The *Venice Statement* asks the fundamental questions: what does this right mean, what can we do or not do? The *Venice Statement* is also notable for its clear articulation of science as a common good, which the 2017 *Recommendation of the OECD Council on Health Data Governance* builds upon in the context of the use of health data.[16]

Further indication of the right's potential may be gleaned from a 2012 case of the Inter-American Court of Human Rights, *Murillo (In Vitro Fertilization) v. Costa Rica.* In that case, the right to science, which is contained in the 1948 American Declaration of the Rights and Duties of Man, was relied upon in part to invalidate a prohibition on IVF treatment. It is the first and, to date, only case where the right to science was used to invalidate a law. It speaks to the potential power of this right.

Finally, I will discuss the rights of future generations. They are the subject of UNESCO's 1997 Declaration on the Responsibilities of the Present Generation Towards Future Generations, but the only applications I have been able to find relate to environmental issues. Yet, germline gene editing also implicates future generations. This is perhaps the least trodden policy path. This is in large part due to the broad prohibitions on gene editing in the 1990s, which effectively shut down public debate. At the time, however, this Declaration mentioned that on the basis of respect for the genetic heritage of mankind, the germline should be inviolable. Such prohibitions were overbroad – since uses for clearly and scientifically demonstrated preventive or therapeutic purposes were thereby prohibited.

The 1997 UNESCO Declaration moreover spoke about the needs and interests of present and future generations without impairing or compromising the preservation of the human and other species. As if our "preservation" were a static concept, as if we were immutable. We are not – we are adapting or mutating over time. Also relevant is the 1997 Oviedo Convention, which does specify that progress should be for the benefit of present and future generations. Anyone intervening with the human genome should do it for preventive, diagnostic or therapeutic purposes, and only if its aim is not to introduce any heritable modification.

There is also UNESCO's 2005 Universal Declaration on Bioethics and Human Rights, which mentions that due regard should be given to the impact of life sciences on future generations. "Due regard" is similar to "appropriate", which also appears frequently in normative instruments and reports at the national level. They simply beg the question of what is "due regard" and what is "appropriate", which we saw earlier with respect to the notion of "serious". Those reports that do look at the future, speak about transgenerationalism, and intergenerational responsibilities and obligations. For example, we see this in the Nuffield Council on Bioethics' 2018 report *Genome editing and human reproduction: Social and ethical issues*. Closer to home, in Quebec, the Commission de l'éthique en science et en technologie (CEST)'s 2019 report *Genetically modified babies: Ethical issues raised by the genetic modification of germ cells and embryos* interprets the precautionary approach so as to not preclude the possibility of using germline editing for very serious, high penetrance diseases as a last resort and so on. Essentially, it specifies that if we were to go to germline editing, it should be under limited conditions.

16.See also Yotova, R., & Knoppers, B. M. The Right to Benefit from Science and Its Implications for Genomic Data Sharing. European Journal of International Law https://doi.org/10.17863/CAM.47291.

It is important to note that long term follow up is going to be obligatory for individuals whose germline is edited. This gives rise to an entirely new set of questions. How do we do that? Can this surveillance be forced on parents? What about the freedoms and rights of the child, especially when they reach the age of majority? Of course, the future child cannot consent to such monitoring. The child does not even exist yet. Could it be psychologically or socially damaging to be monitored? I am not so sure. They said the same thing about IVF babies, that they would be socially stigmatized, and there are now over 30 million children conceived via IVF. Taken together, these three human rights may end the practice of looking at emerging biotechnologies and their potential clinical applications only as risks with potential harms, and instead force us to develop anticipatory governance and maximize the opportunities for overall human welfare and health that we need to protect.

Question: Regarding the point about the possibility that a child or anyone having the right to scientific advancement, is it going to come to a point where we have future children that are being born with genetic diseases who may have been denied the right for the genome editing at an earlier stage when it comes?

Professor Knoppers: You've expressed something that actually has occurred in countries that offer prenatal or pre-implantation diagnosis based on established lists considered to be “serious”. This raises the possibility that there might be a wrongful life suit by a child whose parents did not avail themselves of the technology that would have kept that person, that child, from suffering and their condition was on the list. To date, cases have centred on prenatal, genetic malpractice ,and the “wrongful life” suits brought by the children have not been accepted by the courts. The courts were adamant that they could not discuss the value of not having lived at all versus living with a handicap. Moreover, some countries, such as France and the UK, now have legally made it impossible for children to sue their parents, frequently their mother, for the condition in which they were born. It is a pretty scary thought, is it not?

Roundtable

"Impacts of Disruptive New Technologies on Society: Role of the Academy"

Dr. Kim Boycott
Professor of Pediatrics and Clinical Geneticist, U Ottawa

Dr. Kim Boycott is a Clinical Geneticist at the Children's Hospital of Eastern Ontario (CHEO), Senior Scientist at the CHEO Research Institute, and Professor of Pediatrics at the University of Ottawa. Dr. Boycott's research program in rare diseases bridges clinical medicine to basic research and is focused on understanding the molecular pathogenesis of these disorders to improve patient care and family well-being. She is the Principal Investigator of Care4Rare Canada, a pan-Canadian platform integrating genomic and other –omic technologies to improve our understanding of rare disease, with a particular focus on solving the unsolved and most difficult rare diseases. She is co-Principal Investigator of the Rare Diseases: Models & Mechanisms Network, established to catalyze connections between clinical investigators discovering new genes and basic scientists who can analyze equivalent genes and pathways in model organisms. Dr. Boycott moves the international rare disease agenda forward through her role as the Chair of the Diagnostics Committee of the International Rare Diseases Research Consortium, a member of the Steering Committee of the Global Alliance for Genomics and Health and as a member of the Global Commission to End the Diagnostic Odyssey for Children.

"Disruptive New Technologies for the Diagnosis of Rare Genetic Diseases"

Thank you very much. So I would like to speak for my five minutes around a disruptive technology, genome-wide sequencing, that is impacting the diagnostic approach to rare genetic diseases. And what this is highlighting for us as healthcare providers and the public is inequity and social injustice. The central challenge is access to testing. What we are trying to do as healthcare providers is end the diagnostic odyssey for patients with rare diseases.

Rare diseases are defined as those affecting fewer than one in 2,500 individuals; but some affect just one in a million. There are at least 10,000 rare diseases that are recognized now, 40% are recognized to be genetic in origin. The prevalence of rare genetic diseases is somewhere from 1.5 to 6%; it's difficult to get good estimates. More than 50% affect children, and these are most often severe conditions impacting morbidity and mortality.

And so what happens with these children is they end up on this diagnostic odyssey. This is Canadian data (not shown) collected in 2015 by a survey undertaken by the Canadian Organization for Rare Disorders. And you can appreciate that many of these children spend a long time searching for a diagnosis and seeing many specialists, essentially having inefficient healthcare experiences. For some children it might be six years, for some it has been as long as 25 years looking for a diagnosis.

And so the disruptive technology comes along. This is genome-wide sequencing. This could be exomes or genomes, it doesn't really matter. This is the most impactful test we have ever had in genetics, and I would even argue within the healthcare system, in that it will easily diagnose 30%, and with a little extra work 60%, of appropriately selected patients. And so this disruptive technology is becoming a disruptive clinical test and carries a huge potential impact on the way diagnostic care is provided.

However, herein lies the challenge, how do you actually offer this test in a country, in a healthcare system, such that we have equal access. And you can look at our 2018 numbers from across Canada. This test is being offered under exceptional access programs and the testing itself is performed outside of Canada. Our patients' data is outside of the country. And if you look across the different provinces, you can see that there is anywhere from, say, 800 tests per year in Ontario to zero tests performed on a clinical basis in Quebec. Further adding to this challenge is that fact that we estimate that 10,000 patients a year in Canada would benefit from this test, and we are offering it right now to a fraction of this number.

So what's happening internationally to address the diagnostic needs of patients with rare genetic diseases? Because if this is a challenge we are having in Canada, then it is orders of magnitude greater across the globe as most of the rare genetic disease patients are not in Canada, they're in huge countries like India and China. And so the second NGO Committee for Rare Diseases met at the United Nations this past February, which I attended, and examined social injustice around the rare disease patient experience. A second international body examining this issue is the Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease. This is also a global group that is focused on facilitating the most effective diagnostic care pathway for patients.

Now, I would like to highlight that we have known that genome-wide sequencing is going to have an enormous positive impact on the diagnostic care pathway now for easily seven years -- solid data for seven years – and we are still working on getting it implemented. So it is important to realize that there are all these other omics that are about to appear on the scene, that are showing early utility, and we will have the same challenge as we move them forward.

So bodies like the International Rare Disease Research Consortium and the Global Alliance for Genomics and Health, are trying to make these processes more efficient for everyone, emphasizing the importance of research investment, data-sharing, and development of the evidence to show utility and impact. There are currently 83 countries participating in sharing data to help undiagnosed patients with rare diseases – that is in the Matchmaker Exchange. And so we are making progress but there remains a huge amount of work to be done, both with respect to our knowledge on how best to use this technology, as well as the disruptive technologies on the horizon, but most importantly on how to provide equal access for all patients. Thank you.

Roundtable

"Impacts of Disruptive New Technologies on Society: Role of the Academy"

Dr. Ronald Cohn
President and CEO, The Hospital for Sick Children

Dr. Ronald Cohn has served as President and CEO of The Hospital for Sick Children (SickKids) in Toronto, Canada, since May 1, 2019. Dr. Cohn joined SickKids in September 2012 as the Chief of the Division of Clinical and Metabolic Genetics, Co-Director of the Centre for Genetic Medicine, and Senior Scientist at the SickKids Research Institute. He became the inaugural Women's Auxiliary Chair in Clinical and Metabolic Genetics in April 2013, and joined the Department of Molecular Genetics at the University of Toronto. In 2016 he was appointed Chief of Paediatrics at SickKids and Chair of Paediatrics at the University of Toronto.

Dr. Cohn received his medical degree from the University of Essen, Germany. After his postdoctoral fellowship at the Howard Hughes Medical Institute in the laboratory of Dr. Kevin Campbell, he moved to Baltimore where he was the first combined resident in paediatrics and genetics at the Johns Hopkins University. He subsequently joined the faculty of the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins, where he became the director of the world's first multidisciplinary centre for hypotonia, which has earned national and international recognition. Dr. Cohn was also the Director of the Medical Genetics Residency Program at Johns Hopkins.

Dr. Cohn has received numerous awards, including the David M. Kamsler Award for outstanding compassionate and expert care of paediatric patients in 2004, the first Harvard-Partners Center for Genetics and Genomics Award in Medical Genetics in 2006; and the NIH Young Innovator Award in 2008.

Over the last few years, Dr. Cohn has developed an interest in applying a concept of "precision child health" to the care of children. His own research focuses on implementing genome-editing technologies for the treatment of neurogenetic disorders.

"Precision Child Health: Transforming Paediatric Care"

Thank you so much for the opportunity to be here with you. I'll try to do in six minutes what I usually do within an hour, and provide you just a very high level overview of how I think we need to transform the way we take care of children. And to be really honest, the way that is being done can be done for adults and applied there too.

This concept we're thinking about around precision child health is really based on a very interesting phenomenon. If you look around the room right now and look at your neighbours, you're very proud of looking different, being different than your neighbour, than anybody else. When you or your child gets

sick, something interesting happens, because the first question parents or you as an individual ask is, “tell me what's going to happen to most people who have this diagnosis?” Then we as healthcare providers fall into this trap and begin to cite certain percentages of, 50% are doing this and 10% are doing this. And you should really not be doing this and engaging in a discussion, because that patient that sits in front of you really couldn't care less what 90% of other people do. To take it one step further, the ones who are within the healthcare system know a lot about this already compared to those not in the system. Whenever you have a resident, who sees a textbook case of any kind of disease, you know what happens? People get really excited. And why do they get excited? Because it barely ever happens, because the patients that we see don't appear in textbooks.

What we need to realize is that some patients perform much worse than we expect them to, which often happens at tertiary care hospitals, but there are some who are actually doing much better than we think, and these are actual biological gems who are trying to tell us something. We just need to be listening to our patients. And that's the first cultural shift that we have to do, in a journey that really is composed of three main pillars.

If you want to really accomplish this paradigm shift, it starts with thinking differently, recognizing that the patient in front of you at this point in time is different. Second, you need to move much more towards a data driven, artificial intelligence supported system. You have to begin to think about predictive and preventative care and not just practice reactive care. That's what we do right now. And finally move from this one size fits all to a truly individualized approach.

I'm going to give you four quick patient examples that illustrate a journey towards precision child health, and hopefully we will have time to discuss it. Number one is really a bit of an extension of what Kim Boycott told you about the power of a genome. Two weeks after I started my new position as CEO, I was on service, which I continue to do, and had a child on my service, a two month old girl who started seizures at day two of life. So, for the non-clinicians, this is what we do for a baby. There's one drug that you give a child who is seizing, maybe a vitamin too and every child gets the same drug. Our child continued to seize and was in terrible condition. Eventually, we sent for genetic testing, as Kim said, outside of the country, not inside, which is very bad. Six weeks later we got a diagnosis back of the disease that had a mutation that actually required us to use a drug that they only use in older children. We gave her the drug. Three days later, she stopped seizing and she went home. I don't have to elaborate on the potential consequences, on the child, on the family, and the healthcare system altogether. Six weeks at Sick Kids is very expensive, as you can imagine.

Number two, as if we talk about precision prediction: We had a child for several years, as was actually, healthy child for once, initially who was skiing, had an incident, broke the femur, had surgery. After the surgery, she developed a blood clot, had cardiac arrest which resulted in severe brain damage, which is a terrible, obviously unfortunate outcome.

We have a group which is working on one idea of what I think precision prediction could mean. We are collecting every single physiological data set in our Pediatric Intensive Care Unit (PICU) and have collected by now 2.3 trillion data points. Actually per second you collect as many data points as volume of water that runs down Niagara Falls And we have developed an algorithm that at 75% accuracy predicts five minutes ahead of time whether a patient is going to have cardiac arrest. So what is this going to do? It's going to do one of two things. A, we might be able to prevent the cardiac arrest altogetherr. But even if not, as healthcare providers and the non-healthcare providers who watch Grey's

Anatomy know, you call a code, lots of chaos. No matter how well you organize it, it always takes 5 to 8 minutes until everybody is there and organized. Here we know, we can get ready and then interact if we can prevent it.

The 3rd shift that needs to occur is to interventional position genomics in line with Professor Bartha Knoppers' comments. But I wanted to give you two patient stories here, one less fancy than CRISPR. There were two boys with a diagnosis of Duchenne Muscular Dystrophy who entered a clinical trial that was aiming at a very specific mutation. We had two boys, same age, same mutation received the same experimental drug for three years. After three years, one boy was walking and one boy was sitting in a wheelchair. And why is that? While individualized medicine can be as simple as, the one boy who was walking was from the United States, had the standard of care treatment that you need in order to have supportive treatments. The other boy was from Slovenia, no standard of care, had a very different starting point than the first boy. So this is just to illustrate that the postal code is as important as the genetic code, and just one of these many factors that we have to bring together into data collecting, and not just the omics, but a lot of the other factors as well.

And lastly, we heard about CRISPR. The example I want to give you is the son of my very, very close friends in London, who has a duplication of the dystrophin gene. We then developed a methodology in my own laboratory to remove this duplication. So why am I telling you all of this? He's the only child in the world who has this duplication, one of many, many children who own their own mutation. And you don't have hundreds of thousands of patients. So what does that mean?

Let's forget about the science that we're not ready yet to actually make a drug to remove this in a human. We just did this in a mouse so far. But think about the regulations of what we have to do within one clinical trial that can go through a pre-treatment and wash out phase. How are we going to regulate this? How are we going to think about this? How are we going to engage industry in making a drug that, in theory, if it actually works the way we think or hope it works, is a one-time injection? The cost for making a drug like this, just to tell you, because I had to learn more about this than I ever thought I wanted to. Just the production costs, forget about the research costs, is about $150,000. So how are you going to price something like this? How are you going to engage industry to get interested in finding a treatment for one patient?

I hate the word challenge, so I want to look at this as an opportunity. But these are the kind of questions that we have to think about, because what Prof. Bartha told us is here. We are now conceptualizing fixing genetic mutations. So let's do it in a conscious, coherent way that we change the way we practice medicine in 10 years. Thank you.

Roundtable

"Impacts of Disruptive New Technologies on Society: Role of the Academy"

Dr. David Naylor
Emeritus President, University of Toronto; 2018 Friesen Prizewinner

Dr. C. David Naylor is one of Canada's most preeminent health scientists, who has made major scholarly and policy contributions that influenced health service delivery, public health and health research funding. He is currently Professor of Medicine and Emeritus President, University of Toronto (2005-2013). Before that, he was Dean of Medicine at U of T. He obtained his MD at U of T and as a Rhodes Scholar, earned a DPhil in social and administrative studies at University of Oxford. He initiated and led the Institute of Clinical Evaluative Sciences (ICES), Canada's largest independent network of health care investigators, research trainees and students. He is the author or co-author of over 300 publications with a major interest in cardiovascular care. Naylor Chaired Canada's National Review of Public Health after the 2003 SARS outbreak, which led to the creation of the Public Health Agency of Canada. In 2016-2017, he Chaired the Federal Review of Support for Fundamental Science and produced the "Naylor Report". He is the recipient of many major awards and was elected FRSC (2004), CAHS (2005), Officer of the Order of Canada (2006); inducted to the Canadian Medical Hall of Fame (2016) and the Henry G. Friesen International Prize in Health Research (2018).

"A Perspective on the Issues"

This has been an extraordinarily rich discussion, and I'm keenly aware that time is running out. However, I will spend a couple of minutes trying to respond to what has been said, focusing on two themes in particular – social licences, and disciplinary convergence.

The pace of progress in health research today is unprecedented. And as Professor Knoppers has argued, new diagnostic and therapeutic technologies are fast emerging that should be managed responsibly as powerful opportunities for improving health, rather than treated primarily as threats requiring containment and rigid regulation.

With the research firepower here in Canada and some rethinking of how we organize data in our universal healthcare systems, this country could make many unique contributions to the advancement of health research. But like others on the panel, I'm worried that we are at risk of squandering this opportunity. For researchers to proceed apace, it will be essential for the scientific community to engage the public, build trust, and secure a social licence to pursue these new lines of investigation. Drs. Meslin and Flood have clearly articulated some of the ways that academics must engage. The challenges are greater than ever, sharply highlighted by recent epidemics of measles and unprecedented numbers of

deaths from that condition in many countries. These tragic events are a direct result of the anti-vaccination movement. Earlier this year, Dr Paul Armstrong and I published a commentary in JAMA (2019;321(19):1863-64) on the rise of medical misinformation and the need for medical scientists and medical journals to respond, along with a taxonomy of options for action. In that regard, we need to avoid thinking about 'the public' as if the audience is monolithic. By engaging with many different publics – people in different communities and at different stages in the life-course – scientists can enhance understanding of the nature of scientific research and opportunities arising from it.

Perhaps ironically, we are victims of our own success. It is a troubled time. Many people are looking for psychological anchors in a very turbulent world. With the pace of scientific progress, the consensus about many topics is shifting rapidly, so that what was right becomes wrong. That's the way science works – by doubt and questioning. Rather than being seen as a positive attribute, this constant flux can be taken as a signpost that science is unreliable and that scientists can't be trusted. Any educational efforts accordingly must explain that the mutability of the scientific consensus is integral to a hallmark of progress, not grounds for a retreat to pseudo-science and nihilism.

The second theme of note, as mentioned, is the growing importance of multi-, inter-, or trans-disciplinary methodology in modern health research. We can't solve the big problems in medical science without convergence across disciplines. And as Professor Knoppers has articulated, we can't create the framework for regulating and governing medical science in the public interest unless we do it with a similar synthetic approach.

This trans-disciplinary model sometimes runs against the grain in academic institutions. For example, as academic administrators know, a transdisciplinary tenure file can be difficult to review fairly. One tactic is to find the small number of scholars and scientists who blend disciplines in exactly the way the candidate does. Unfortunately, that can lead to a positively biased assessment – with reviewers eager to admit another member to their tiny club. However, if one instead assembles reviewers grounded in each of the applicable disciplines, they may all find fault with the file as failing to meet their specific standards. We will need new ways to assess and reward synthetic scholarship and science if we are to capitalize on the opportunities inherent in this new period of health-relevant technologies.

Another type of convergence is implicit in the comments offered by Dr's. Boycott and Cohn, who both argued for rethinking the way we provide clinical care to young patients. In the realm of rare diseases of infants and children, and in pediatrics more generally, new technologies are enabling much more detailed biological characterization, with treatments personalized as never before. We've all benefited from evidence-based medicine, which is essentially epidemiology-based medicine, deriving evidence from populations and subgroups of patients. But as new information that enables much more precise individualization of diagnosis and treatment, it will be necessary to rethink both what evidence means and how health professionals make decisions in the context of the clinical encounter.

At the moment, because we are still struggling to bring these modes of thinking together, we seem to have many different types of medicine – evidence-based medicine, molecular medicine, personalized medicine, precision medicine, deep medicine – the list goes on. One hopes that all these schools of thought will soon converge in a pluralistic model of scientifically-informed medicine, guided by humane values and by careful attention to the social context of care.

Roundtable

"Impacts of Disruptive New Technologies on Society: Role of the Academy"

Dr. Bruce McManus
Director, PROOF Centre, UBC

Dr. Bruce McManus CM, PhD, MD, FRSC, FCAHS, is Professor, Department of Pathology and Laboratory Medicine, University of British Columbia (UBC). He serves as CEO, Centre of Excellence for Prevention of Organ Failure (PROOF Centre), and as Co-Director, Institute for Heart + Lung Health. He is a Senior Scientist in the UBC James Hogg Research Centre. Dr. McManus received BA and MD degrees (University of Saskatchewan), an MSc (Pennsylvania State University), and the PhD (University of Toledo). He pursued post-doctoral fellowships at the University of California - Santa Barbara (Environmental Physiology) and at the National Heart, Lung, and Blood Institute, Bethesda, MD (Cardiovascular & Pulmonary Pathology), and residency training at the Peter Bent Brigham Hospital - Harvard University (Internal Medicine and Pathology). Dr. McManus joined the Faculty of Medicine, University of British Columbia, as Department Head of Pathology and Laboratory Medicine in 1993. He served as inaugural Scientific Director of the Institute of Circulatory and Respiratory Health, Canadian Institutes of Health Research from 2000-2006. Dr. McManus' investigative passion relates to mechanisms, consequences, detection and prevention of injury and aberrant repair in inflammatory diseases of heart and blood vessels. He has mentored many faculty and trainees and has convened many public-private partnerships.

"Comments"

First of all, it's a privilege to be here. This is a great discussion, terribly important. And it reminds me, I think, in terms of David Naylor's comments and Alan Bernstein's recent comments, of the brilliance of Joseph Schumpeter. He was a distinguished Austrian political economist, who also was an equestrian, and also claimed to be a great lover, and who claimed that in his lifetime he had achieved being the best in Austria of two of those three, never telling anybody which of the two he had achieved. Pertinent to this discussion, he wrote beautifully on the ebbs and flows of innovation throughout history. His concepts really speak to much of the difficulty and opportunity that resides in new technologies being integrated in society. He wrote about the current era as that related to genomics, computing and new media, and as such, is very instructive to us as a touchstone for conversations about how we can help move society forward in a good-for-all way with technologies that are dramatically game-changing.

I think Alan's comment about humility, either in terms of the positive outcomes or the unforeseen consequences, is prescient. I think Bartha Knopper's comments about moving forward -- not from a policing point of view but rather from a human rights approach is also extraordinarily important. And when Colleen Flood mentioned the need for engagement, I mean, the one thing that we haven't really addressed today, is systematic levels of education about new technologies and the many stakeholders

in health who are pertinent. So, if one looks at this technology-in-society issue through the lens of what the Academy can do, it's pedagogy. We often put that in terms of HQP or missing data analysts or statisticians, people to deal with all of the data, for example, regardless of what it's nature. But we also should be much more systematic when it comes to education that's required in order to have the proper connection and dialogue with the “publics”. I talked a little bit yesterday with Bartha about citizen science. In the end, the integration of technologies for benefit is about a full range of citizens. Of course, the rare disease community is a realm where citizen science is exemplified -- indeed wherein it has been recognized as an imperative; such is a good example of how the public, the caregivers, the scientists, converge on societal problems and find solutions. Those use-cases, I think, should teach us strategies, for all of the broader human frailties, on how we could impinge on diseases through the sensible adoption and evaluation of apparently promising technologies.

The last point I'll make, because time is limited relates to a concept that Mark Fitzgerald at the University of British Columbia has put forward. He's a respirologist, epidemiologist, an asthma specialist. But he wrote with a colleague perhaps the most important paper in the omics era that has been written, on the subject of humanomics. And so okay, what's that? It's an educational piece about the “soft” omics. It's all about health literacy and the human side of technologies arising from other omics tools. If we think we're having difficulty communicating with each other in the Academy and then out into the publics around of the place of new technologies, we have successful approaches to emulate. It's been shown masterfully in asthma education (with translation of guidelines into multiple languages that are really truly understandable by patients and families) that management of their illnesses can thereby be substantially improved.

One final thought on multi-layering of education about technologies emerging in health science, such as digital technologies, we need to have a strategy for HQP, for education of all of our publics, in a manner that surpasses a hodgepodge of brilliant, yet disjointed ideas Such a systematic educational approach can bring everybody forward. Great science writers and editors like Gina Kolata, who was at Science and then of course, the New York Times, wrote beautiful essays at the level of Scientific American, meant for you and I, you know, for an educated few in the population. But what we need is, we need a 100 Andre Picard's who have the combined capability to integrate information and contexts about subjects related to new health technologies and related topics to systematically cover in the public press all of these technology driven health issues to raise the population “IQ” up on this domain of knowledge. Our collective health literacy will rise a little faster and further. This kind of dissemination of knowledge will help to avert what some people fear, that bringing forward technologies intended to help the public-at-large will in fact create bigger gaps between those who have and those who have not. Thank you.

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