Personal Genomics and Social Sciences and Humanities

Slide 1: Well, I hope everyone is healthy and adapting to these (shall we say) unusual circumstances. I have been teaching at UBC since 1993 and this is a new situation!

Slide 2: Just a reminder of the organizing framework we are using in the social science and humanities part of the course. Global issues can be explained using any and all of these levels of analysis, and global issues can have an impact on any and all of these levels as well.

Slide 3: In the videos, I discuss some of the ways human genomics has consequences for individuals and groups, and I identify some of the big ones here.

Slide 4: Same for the state level…

Slide 5: …and the international level.

Slide 6: And a reminder: don't get too bogged down in the details of the readings. Focus on the main argument of each reading. Think: what is the author trying to tell me, and why?

Slide 7: Once again, I start off the discussion with a reminder of the basic philosophy of the course. If we are to understand personal genomics, we must have a basic understanding of both the physical and life sciences aspects of the subject and the social sciences and humanities aspects of the subject.

Slide 8: Human genomics is also another example of the importance of the relationship between science and the social, political, economic, historical, and cultural contexts in which beliefs are formed and policy decisions are made.

Slide 9: And so, a development like CRISPR does not happen in a vacuum: society has a set of values and attitudes through which that development is perceived, and that informs the kind of discourse and dialogue that in turn will shape social attitudes and values about CRISPR. This is already happening…

Slide 10: …just like attitudes about advances in biology led to a discourse on its dangers (Frankenstein!)…

Slide 11: …that have echoes today in the books and articles written about CRISPR and its implications.

Slide 12: Rapid advances in genetics research and genetic modification technology are creating new hopes and opportunities on the one hand, and new or more intense controversies and tensions on the other. The rapid pace of innovation and technological advancement in the genomics field has left social debate about norms and principles, the development of law and state policy, government regulatory agencies, and global governance responses far behind. CRISPR-Cas9 technology is only the latest of these kinds of big technological advances that disrupt existing ethical and moral systems and domestic and international regulatory regimes.

Slide 13: The main focus of this class the fact that genomics in general, and human genomics in particular, has gone global. Genetic research has spread worldwide. However, at the global level, there are few if any common treaties or frameworks or guidelines regulating genomic research or activity, and a vast asymmetry in laws and regulations at the state level. There is no UNFCCC or Paris Agreement equivalent for human genomics.

Slide 14: Which raises the question of whether we need a new global consciousness around human genomics that transcends our old ideas about the "international."

Slide 15: So now we go from the universe of the very big (climate and climate change) to the universe of the very small (the human genome)!

Human Genomics Goes Global

Slide 16: Right from the beginning, the human and personal genomics project was an international enterprise: the research into sequencing the genome took place in 20 universities and research centers in the United States, the United Kingdom, France, Germany, Japan and China.

Slide 17: Around the world, there are a large number of human genome-related projects funded by governments or by public sector-private sector partnerships.

Slide 18: Look at them all!

Slide 19: Governments are buying in: between 2013 and 2019, at least 15 countries have invested over US$4 billion on national genomic-medicine initiatives (just medicine!). And between 2019 and 2025, genomic data from over 60 million patients will be gathered within the healthcare sector alone.

Slide 20: For a recent example, in the United States the AllofUs study, which started in 2018 under the auspices of the National Institutes of Health will accumulate the genomes of one million Americans who will volunteer their genetic data to the project. The project will track the health, diet, and environment of the volunteers.

Slide 21: Looking back a bit further, the UK Biobank initiative, launched in 2006, has gathered the genomes of 500,000 British citizens into a publicly accessible data bank.

Slide 22: And looking back further still**,** in China there is the example of BGI (formerly the Beijing Genomics Institute) a company established in 1999 and based in Shenzen. The BGI has opened facilities in over a dozen countries.

Slide 23: The philosophy of the BGI was evident right from the beginning, when the then Chairman of the Beijing Genomics Institute, Huanmin Yang, said in an interview in The New Yorker in 2014: “In the United States and in the West, you have a certain way. You feel you are advanced and you are the best. Blah, blah, blah. You follow all these rules and have all these protocols and laws and regulations. You need somebody to change it. To blow it up. For the last five hundred years, you have been leading the way with innovation. We are no longer interested in following.”

Slide 24: In China, human and personal genomics is regarded as a key growth sector. Currently, the China Precision Medicine Initiative is a 15-year, US$9.2 billion government project aiming to sequence 100,000,000 genomes by 2030.

Slide 25: And then there is the private sector: many private gene banks already exist. For example, 23andMe possesses the genetic data of 2 million customers…and sold access to the data to drug companies!

Slide 26: And don't forget the ancestry services!

Slide 27: Science has always been a collaborative activity, and that is especially true today. In the world of genomics research, major international collaborations between individual researchers, private and public consortiums, and businesses across multiple countries are commonplace.

Slide 28: The scale of some of these collaborations are enormous and truly global. For example, between 2013 and 2019, the Pan-Cancer Analysis of Whole Genomes (PCAWG) project amassed 2,658 cancer genomes, studying 38 different tumour types. The project was led by the International Cancer Genome Consortium (ICGC) and involved thousands of researchers from 468 institutions across 34 countries in Asia, Australasia, Europe and North America.

Slide 29: But what is even more impressive is the volume of information gathered by the PCAWG: more than 800 terabytes worth. Even more impressive: the combined data were made available to researchers through cloud computing, using the Cancer Genome Collaboratory, a cloud service built for the genomic research community (researchers also made us of the commercial cloud-service provider Amazon Web Services). The use of cloud computing makes sense from a science perspective. Cloud services are getting cheaper, more reliable and easier to use, and they enable the sharing of huge amounts of genomic data with researcher collaborators around the world at low cost. The Human Cell Atlas and the European Open Science Cloud are other examples of cloud computing used to store and access data.

Slide 30: Here's the problem with all of this: these human genome initiatives pose considerable challenges with respect to ensuring privacy, either from breaches of confidentiality or from governments, law enforcement, or private corporations (which are all interested in accessing stored data of this kind for different reasons). In the case of the PCAWG project, the ICGC does have a Data Access Compliance Office, which provides some oversight. Any researcher wanting to use the data signs a contract agreeing not to try to identify the genomes (which are stripped of personal information). However, it is not clear what vetting should take place before

researchers are allowed to access the data, or what checks should be made before data is shared internationally. Significantly, there are still restrictions on the transfer of PCAWG data across certain borders, in particular between European countries and the United States, because of concerns in Europe about the genomic data of Europeans being held in the United States.

Slide 31: There are no global rules for the sharing of genomic data worldwide that are "harmonized' across state jurisdictions. Currently, a mix of regulations exist across states and groups of states.

Slide 32: For example, in 1996 the United States created the Health Insurance Portability and Accountability Act. This Act modernized the flow of healthcare information, and specified how "Personally Identifiable Information" held by the healthcare and healthcare insurance industries should be protected from fraud and theft. Included in the Act were provisions on privacy, right of access, disclosure, and security.

Slide 33: More recently, in 2018 the European Union adopted the General Data Protection Regulation (GDPR). The GDPR is designed to regulate data protection and privacy in the EU, and transfer of personal data outside the EU. Among many regulations, controllers and processors of personal data must use processes that protect privacy (pseudonymization or anonymization); information systems must use highest privacy measures as a default; and no personal data can be processed unless done so under one of six lawful bases (consent, contract, public task, vital interest, legitimate interest, or legal requirement). In 2019, the European Data Protection Board (which issues guidance on the GDPR), developed a set of guidelines on the submission, approval and monitoring of voluntary codes of conduct for data processing. The problem is these regulatory systems differ, and only apply (in these cases) to the US and the EU. Genomics researchers have called for the development of international codes of conduct to govern data-sharing that comply with existing laws but are also harmonized across jurisdictions. The elements of such a code would need to include global standards for: identity privacy (such as pseudonymization or anonymization); consent provisions; portability of data and who gets access to data; the right to withdraw one's own data from a study or dataset; and compelled disclosure (guidance on dealing with government requests for data). Projects like the Pan-Cancer Analysis of Whole Genomes (PCAWG) will become increasingly common. In fact, the ICGC is already engaged in a follow-on project to address the lack of clinical data concerning patient treatments:

data of this kind would allow researchers to identify the genetic changes that can predict clinical outcomes. The follow-on project called the International Cancer Genome Consortium–Accelerate Research in Genomic Oncology (ICGC–ARGO) will create that resource.

Gene-Editing and Humans

Slides 34+35: Technological advances are moving very rapidly in human genome related work globally. A good example of this is the capabilities of the CRISPR-Cas9 system discussed by Dave. These technologies hold the promise of applying gene editing to humans, or human germline genetic engineering (HGGE). This could be done either by editing somatic cells, which are non-germline cells (or if you prefer sperm or ova cells, or gametes, that through fertilization produce the zygotes from which we all come), or by editing germline cells: eggs, sperm (or very early embryos).

Slide 36: This is significant on a number of levels, especially the treatment or prevention of disease or hereditary conditions, because any changes in a genome could be passed on to future generations. So gene editing might prevent the transmission of certain genetic diseases from generation to generation. Of course, the same technology could also be used for enhancement (see below). Naturally, all of these issues raise a lot of concerns.

Slide 37: There is a lot of hyperbole surrounding the CRISPR technique, another example of how technological developments become part of a wider discourse and both reflect and change social dialogues. For example, *Science* magazine declared in its 2015 breakthrough of the year issue, “For better or for worse, we all now live in CRISPR’s world.”

Slide 38: And a number of books came out on the subject, enoughto be a special review in the New York Times Review.

Slide 39: And a *Wired* article gushed that with CRISPR, “We now have the power to quickly and easily alter DNA. It could eliminate disease. It could solve world hunger. It could provide unlimited clean energy. It could really get out of hand.”

Slide 40: Consequently, there has been an explosion in research and

scholarship on the wider implications of gene editing and humans. An international debate is taking place about whether and under what circumstances these techniques should be used to make heritable, genetic alterations in human beings. Around the world there is a discussion of the relationship between authority and responsibility, the relationship between science and government (especially democratic institutions), and the processes and actual practices of law and global governance.

Slide 41: Should every condition or disability be cured? Who gets to make that decision? As George Daley, MD, PhD, the director of the Stem Cell Transplantation Program at Boston Children's Hospital and a professor of biological chemistry and molecular pharmacology at Harvard Medical School, observes: "If we are going to deem certain indications as permissible, can we identify a regulatory and oversight approach that will allow us to be comfortable that we can draw a line, so that we aren't throwing out what may be very powerful, legitimate medical applications in order to stave off those which are less palatable to most of us?" Of course, gene-editing technologies allow researchers to do more that drop gene sequences out of a genome: they allow researchers to add sequences in. This raises the prospect that gene editing could be used to introduce permanent changes into human genomes.

Slides 42+43: International conferences have already been convened on the subject, most significantly the International Summit on Human Gene Editing in 2015 and the follow-on International Summit on Human Gene Editing in 2018. The 2015 conference established a foundation for the ethics and practices of human gene editing, which I will examine later.

Slide 44: There is division among ethicists on the matter of human gene editing. So Hille Haker, PhD, an ethicist at Loyola University Chicago and a member of the European Group on Ethics in Sciences and New Technologies to the European Commission, supports an international ban on reproductive-related gene editing. Haker argues that allowing gene editing elevates the reproductive rights of prospective parents over the rights of future children.

Slide 45: On the other hand, John Harris, DPhil, a professor of bioethics and the director of the Institute for Science, Ethics, and Innovation at the University of Manchester, has a different view. He argued that parents make decisions that affect their future children all the time, without much thought

at all about their consent. Harris also suggests that sexual reproduction in and of itself holds significant risk of harm to future generations, simply because of inherited diseases and forms of disability. As Harris argued: "If CRISPR-Cas9 and other interventions—when they're proved to be safe enough—are not implemented, people will still reproduce and pass on heritable damage in the germline, so it won't be the case that we will be preferring a risk-free alternative to a technology with attendant risks."

Slide 46: Efforts have been made at the state level to establish codes of conduct for gene editing on humans. For example, in the United States a robust ethical discussion has been under way at least since the 1980s, and in 1983 The US National Institutes of Health Recombinant DNA Advisory Committee declared that it would refuse to support any proposals for human germline editing. This policy essentially remains in place today. In 2017, the US National Academies of Science, Engineering and Medicine Committee on Human Gene Editing published a document titled "Human Genome editing; Science, Ethics, and Governance." The core recommendations were presented as follows:

> The following principles should undergird the oversight systems, the research on, and the clinical uses of human genome editing:
>
> 1. Promoting well-being
> 2. Transparency
> 3. Due care
> 4. Responsible science
> 5. Respect for persons
> 6. Fairness
> 7. Transnational cooperation

http://www.nap.edu/24623

Slide 47: Basically, the report made a number of suggestions as to what should be permissible with respect to gene editing. The bottom line: gene editing on humans for the treatment of prevention of disease should be permissible under specific guidelines, and gene editing on humans for enhancement should be prohibited.

Slide 48: Meanwhile, in a lab in Shenzen…

Slide 49: Honestly, what do you think??

Slide 50: Hah! And then in 2018, a bombshell dropped: Dr. He Jiankui, a professor at the Southern University of Science and Technology in Shenzhen, claimed that he altered the DNA of twin girls born that month using the CRISPR-Cas9 technique. He went public with his work on 25 November 2018 in MIT Technology Review.

Slide 51: But He also released a video on YouTube (an appeal for understanding and a moral defence, really). He gave an interview with the *Associated Press*.

Slide 52: Later, He presented the work on 27 November at the International Human Genome Editing Summit in Hong Kong. He said he edited the babies' genes at conception in hopes of making them resistant to the AIDS virus, as their father is HIV positive. He began his efforts in June 2016, assembling a team that recruited eight study couples from an AIDS advocacy group. Each couple had an HIV-positive father and an HIV-negative mother. It appears that He edited the genes of embryos from at least two couples to remove a gene that enables HIV to enter cells before an IVF procedure. His intent: to make the children immune to HIV. At the time, another embryo in He's experiment had not yet been born. The implications of He's experiment are potentially huge: it opens the possibility that science could rewrite the gene pool of future generations by altering the human germ line. Previous work had been done on editing human embryos: in 2015, a team of scientists in China published a paper titled "CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes" describing the use of the gene editing tool in human embryos. The researchers used embryos that could not grow into fetuses, but the study triggered immediate questions about germline editing. The results of similar experiments in China, the US and UK were published over the following years. The studies went from using non-viable embryos to using ones that might be implantable.

Slide 53: He has said that gene editing of human embryos was legal in China because the country has no law specifically forbidding it. However, in China guidelines prohibit research on embryos that "violates ethical or moral principles," and guidelines published in 2003 specify that while gene editing is permitted for research, any experimental embryos cannot be kept for more than 14 days. He has also been accused of fabricating an ethical review. In the wake of the scandal, China has announced new regulations on gene

editing: technology involving gene editing, gene transfer and gene regulation would be categorized as “high-risk” and managed by the health department of the State Council, China’s Cabinet.

Slide 54: He’s actions have provoked a dual reaction. On the one hand, there is concern that He’s experiment and the publicity that attended it will damage public perceptions of gene editing generally, even if that work does not involve human embryos or efforts to alter germ lines. “The negative focus is, of course, not good,” says Fredrik Lanner, a stem-cell scientist at the Karolinska University Hospital in Stockholm. However, others make the claim that He’s experiments might actually help future science, by provoking global cooperation and more effective oversight. “That would stimulate, not hinder, meaningful advance in this area,” argues Jonathan Kimmelman, a bioethicist at McGill University in Montreal. There have also been calls to establish a moratorium on gene editing using human embryos. “As we have clearly learnt from China, nothing prevents someone from going rogue,” says Fyodor Urnov, an Innovative Genomics Institute investigator at the University of California, Berkeley. “I am strongly for a complete moratorium on all embryo editing.” Francis Collins, director of the US National Institutes of Health, supports a moratorium. Canada is among a number of countries that already have policies in place banning the use of human-embryo gene editing even if there is no intention of implanting the embryo. There is also the question of what other scientists could or should have done to stop him. Scientists at Rica and Stanford knew about his experiments. By remining silent about ethically questionable research, scientists can create a “latency period” in which dangerous practices can begin and then grow. Silence becomes a form of complicity. On the other hand, scientists who know He say they did not speak up because they thought He would not go through with it or would listen to their concerns, they wanted to respect his confidentiality, and they didn’t know where to go to raise the alarm.

Slide 55: For his part, He was fired from the Southern University of Science and Technology on 21 January 2019. And on 30 December 2019, the Shenzhen Nanshan District People's Court sentenced He Jiankui to three years in prison and fined him 3 million RMB (US$430,000). Expect to hear a lot more about gene editing in the years ahead: it is likely to be among the big issues of your lifetimes. We are now at the time when we can reasonably discuss human enhancements. It is also important to remember that while CRISPR has been revolutionary, the next big disruptive technological

development is inevitable: and as has been the case with CRISPR, the ability of society to keep pace is limited. Examples of this kind of concern abound. In a September of 2015 Council of Europe hearing, Jean-Yves Le Déaut, the General Rapporteur on Science and Technology Assessment, mused: "How can we legislate on issues which are in constant flux? Laws...may become biodegradable...Because we're talking about a moving target... with each of these changes in techniques, are we going to keep changing the law?" And in 2017, US National Academies President Marsha McNutt observed in a report on human genome editing: "as is always the case, the speed at which the science is advancing outpaces society's ability to grasp its implications." However, maybe this is an intellectual trap, an example of how we are caught in this *zeitgeist* of perception and social discourse. As J. Benjamin Hurlbut argues, "…it is worth remembering that "we all now live in CRISPR's world" only insofar as we imagine ourselves as powerless against an inexorably advancing technological tide and act accordingly."

Slide 56: So how do we start thinking about governing personalized genomics at the global level?

Genomics and World Religions

Slide 57: This might seem like a strange place to start, but genetic research in general, and human genetic research in particular, has been a contentious subject for world religions and their ethical systems.

Slide 58: I like to tell a fable called "The Prince and the Biologist" that basically revolved around a central concern: are we "playing god?" Once upon a time, there was a Prince, and his name was:

Slide 59: Prince Charles! Who has one view on the subject…

Slide 60: And there was also a biologist, and his name was Richard Dawkins, who had a different view.

Slide 61: So what do Christian ethicists say?

Slide 62: Well, here is one way of looking at it: The catholic Church had a system of sin, as captured by the Dutch painter Hieronymus Bosch. Recognize what this painting depicts?

Slide 63: I am sure you have heard of the Seven Deadly Sins: Wrath, Pride, Sloth, Gluttony, Envy, Lust, Greed (c. 4th century Catholic Church).

Slide 64: And here are the punishments for those sins. Ouch!

Slide 65: True or False/

Slide 66: Well, on March 10, 2008 the Vatican issued an update to the "seven deadly sins" which now include: 1) genetic modification; 2) human experimentation, 3) polluting the environment; 4) social injustice; 5) causing poverty; 6) financial gluttony; and 7) taking drugs. Genetic Modification! Argued Monsignor Gianfranco Girotti, "You offend God not only by stealing, blaspheming or coveting your neighbor's wife, but also by ruining the environment, carrying out morally debatable scientific experiments, or allowing genetic manipulations which alter DNA or compromise embryos."

Slide 67+68: The Christian ethic supports genetic research that is therapeutic (corrects or ameliorates a disorder), focused on the care and management of patients, and used to develop new treatments. Christian ethicists believe that using genome-sequencing technology to improve humans or determine behavioral choices is not necessarily forbidden but should be the lowest priority in genetic research and subject to conditions. These include due respect for the given psychological nature of each individual human being, no fundamental change in human design, and no creation of groups with different qualities. Behavioral genetics, it states, does not do these things.[1]

Slide 69+70: In the Islamic world, the approach taken toward genetics is grounded in the decisions of The Islamic Jurisprudence Council of the Islamic World League (Organization of Islamic Countries).

Slide 71: True of false?

Slide 72+73: In its 15th session in October 1998, the IJC decided: 1) to permit use genetic of engineering for disease prevention, treatment, or amelioration on the condition that such use do not cause further damage; 2) to forbid the use of genetic engineering for evil and criminal uses or what is

[1] Christian Medical Fellowship, "Submission from CMF to the Nuffield Council on Bioethics' Working Party on 'Genetics and Human behavior: The Ethical Context" (paper published July 1, 2001) accessed on August 22, 2010, http://www.cmf.org.uk/publicpolicy/submissions/?id=15

forbidden religiously; 3) to forbid using genetic engineering and its tools to change human personality and responsibility, or interfering with genes to improve the human race; 4) to forbid doing any research or therapy of human genes except in extreme need, after critical evaluation of its benefits and dangers and after an official consent of the concerned, respecting the extreme confidentiality of the information and human rights and dignity as dictated by Islamic Sharia'ha; 5) to allow the use of bio-engineering in the field of agriculture and animals, on the condition that precautions are taken not to inflict harm (even in the long term) on humans, animals or vegetation.

Slide 74: Religions, in the form of the political power of religious groups and organizations, are important influences over ethical and legal systems. As a result, the nexus between the science of genetics and religion is likely to be an ongoing area of deliberation and contention around the world in the coming decades. And CRISPR is just amplifying that discussion.

Personalized Genomics and Global Governance

Slide 75+76: So when it comes to human genomics research and related services and projects, we are already talking about a global enterprise. However, there is little in the way of global agreements governing the international dimensions of genomics. There are currently no institutions or international treaties solely responsible for the global governance of personal or human genomics.

Slide 77: The Declaration of Bilbao (1993) was the first effort. The declaration denounces all uses of genetic information causing or leading to discrimination in work relations, in the insurance domain or in any other sector.

Slide 78: The closest thing that does exist is The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine. Established by the Council of Europe and known as the Oviedo Convention, it is intended to govern the use and application of biomedicine. The Convention opened for signature on 4 April 1997 and entered into force on 1 December 1999. The Oviedo Convention addresses concerns about human genome research, specifically genetic testing, the storage of genetic data, and modification of the human genome.

Slide 79: Genetic testing as a tool for discrimination is prohibited under *Article 11*…

Slide 80: …while genetic testing is permitted only for health (or for scientific research linked to health purposes) under *Article 12*.

Slide 81: The modification of the human genome, for reasons other than health-related is generally prohibited under *Article 13*.

Slide 82: And no using it for sex-selection, either. The problem is only 35 states have signed the Convention and only 29 have ratified. The Convention is also a Council of Europe convention (associated with the EU) and does not therefore extend much beyond Europe.

Slide 83: Another major international document on genetics is the Universal Declaration on the Human Genome and Human Rights (1997). However, the declaration does not bind states to specific action, although there are suggestions for how states might proceed to do so. As one would expect, the Declaration calls for respect for the human dignity of each individual, and calls upon nation states to protect groups within their population that may be most vulnerable as a result of genetic testing.[2] However, there are no calls for specific policymaking or for advances in international governance of genetics.

Slide 84: There are some other relevant international agreements, such as UNESCO's International Declaration on Human Genetic Data (2003)…

Slide 85: …and ECOSOC Resolution 2004/09 on Genetic Privacy and Non-Discrimination (2004). But these are not treaties. On 14 December 2018 the World Health Organization (WHO) established a global expert panel to examine the scientific, ethical, social and legal challenges associated with human genome editing. The consultation process was open until February 10, 2020.

[2] UNESCO, "Universal Declaration on the Human Genome and Human Rights: from theory to practice: Article 14," February 3, 2000, accessed on http://unesdoc.unesco.org/images/0012/001229/122990eo.pdf

Codes and Norms

Slide 86: The reality is that most international discussion of the regulation (or need for regulation) and the ethics of personalized genomics is being done at the scientific, NGO, and industry level. The beginning of this discussion in microbiology is often attributed to the Asilomar Conference of 1975, held at Asilomar State Beach in Monterey, California. The conference was convened to develop voluntary guidelines on the safe conduct of recombinant DNA research. About 90 of the invitees were American with approximately 60 others coming from 12 different countries.

Slide 87: Fast forward to 2015. The National Academy of Sciences and the National Academy of Medicine's Human Gene-Editing Initiative held the International Summit on Human Gene Editing mentioned above that took place December 1-3, 2015, in Washington, D.C. Co-hosted with the Chinese Academy of Sciences and the U.K.'s Royal Society, the summit convened experts from around the world to discuss the scientific, ethical, and governance issues associated with human gene-editing research.

Slide 88: The statement that came out of the Summit said a number of things, but raised a number of issues related to germline editing.

Slide 89: The main takeaway was this: “It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight. At present, these criteria have not been met for any proposed clinical use: the safety issues have not yet been adequately explored; the cases of most compelling benefit are limited; and many nations have legislative or regulatory bans on germline modification. However, as scientific knowledge advances and societal views evolve, the clinical use of germline editing should be revisited on a regular basis.”

Slide 90: The statement went on to make the following observation and call: “While each nation ultimately has the authority to regulate activities under its jurisdiction, the human genome is shared among all nations. The international community should strive to establish norms concerning acceptable uses of human germline editing and to harmonize regulations, in

order to discourage unacceptable activities while advancing human health and welfare." Here is the Summit's Final Statement:

> **1. Basic and Preclinical Research.** Intensive basic and preclinical research is clearly needed and should proceed, subject to appropriate legal and ethical rules and oversight, on (i) technologies for editing genetic sequences in human cells, (ii) the potential benefits and risks of proposed clinical uses, and (iii) understanding the biology of human embryos and germline cells. If, in the process of research, early human embryos or germline cells undergo gene editing, the modified cells should not be used to establish a pregnancy.
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> **2. Clinical Use*: Somatic.** Many promising and valuable clinical applications of gene editing are directed at altering genetic sequences only in somatic cells – that is, cells whose genomes are not transmitted to the next generation. Examples that have been proposed include editing genes for sickle-cell anemia in blood cells or for improving the ability of immune cells to target cancer. There is a need to understand the risks, such as inaccurate editing, and the potential benefits of each proposed genetic modification. Because proposed clinical uses are intended to affect only the individual who receives them, they can be appropriately and rigorously evaluated within existing and evolving regulatory frameworks for gene therapy, and regulators can weigh risks and potential benefits in approving clinical trials and therapies.
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> **3. Clinical Use: Germline.** Gene editing might also be used, in principle, to make genetic alterations in gametes or embryos, which will be carried by all of the cells of a resulting child and will be passed on to subsequent generations as part of the human gene pool. Examples that have been proposed range from avoidance of severe inherited diseases to 'enhancement' of human capabilities. Such modifications of human genomes might include the introduction of naturally occurring variants or totally novel genetic changes thought to be beneficial.
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> Germline editing poses many important issues, including: (i) the risks of inaccurate editing (such as off-target mutations) and incomplete editing of the cells of early-stage embryos (mosaicism); (ii) the difficulty of predicting harmful effects that genetic changes may have under the wide range of circumstances experienced by the human population, including interactions with other genetic variants and with the environment; (iii) the obligation to consider implications for both the individual and the future generations who will carry the genetic alterations; (iv) the fact that, once introduced into the human population, genetic alterations would be difficult to remove and would not remain within any single community or country; (v) the possibility that permanent genetic 'enhancements' to subsets of the population could exacerbate social inequities or be used coercively; and (vi) the moral and ethical considerations in purposefully altering human evolution using this technology.
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> It would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight. At present, these criteria have not been met for any proposed clinical use: the safety issues have not yet been adequately explored; the cases of

most compelling benefit are limited; and many nations have legislative or regulatory bans on germline modification. However, as scientific knowledge advances and societal views evolve, the clinical use of germline editing should be revisited on a regular basis.

4. Need for an Ongoing Forum. While each nation ultimately has the authority to regulate activities under its jurisdiction, the human genome is shared among all nations. The international community should strive to establish norms concerning acceptable uses of human germline editing and to harmonize regulations, in order to discourage unacceptable activities while advancing human health and welfare.

We therefore call upon the national academies that co-hosted the summit – the U.S. National Academy of Sciences and U.S. National Academy of Medicine; the Royal Society; and the Chinese Academy of Sciences – to take the lead in creating an ongoing international forum to discuss potential clinical uses of gene editing; help inform decisions by national policymakers and others; formulate recommendations and guidelines; and promote coordination among nations.

The forum should be inclusive among nations and engage a wide range of perspectives and expertise – including from biomedical scientists, social scientists, ethicists, health care providers, patients and their families, people with disabilities, policymakers, regulators, research funders, faith leaders, public interest advocates, industry representatives, and members of the general public.

In 2018, the Second International Summit on Human Genome Editing (where He presented his embryo-editing work) continued to advance the global dialogue by bringing researchers, ethicists, policymakers, patient groups, and representatives from scientific academies and organizations worldwide to explore issues such as: 1) the potential benefits and risks inherent in conducting genome editing research and in considering clinical applications; 2) ethical and cultural perspectives; 3) legal, regulatory, and policy considerations; and 4) public outreach and engagement.

At these conferences a lot is discussed and that is a good thing. But governments are not formally present at these kinds of scientific, stakeholder, and industry gatherings. While the development of norms and codes of conduct are important, and could inform subsequent efforts to establish international agreements and treaties, scientists and industry and NGOs cannot make treaties. And they cannot enforce laws, lacking as they do the enforcement mechanisms of police, courts and prisons. This does not mean they are irrelevant: far from it. The vast majority of researchers obey norms and codes the vast majority of the time. But that may not be enough.

Developing Countries

Slide 91: Here are a few more thoughts about the global dimension of human genomics as they relate to poor countries. Genomic information can be seen as a "global public good" in that it is represented by knowledge in the public domain and across national boundaries. Lack of investment, infrastructure and expertise in developing countries means that they are unable to take advantage of these GPG characteristics to address their health needs, fuelling fears of a growing "genomics divide". Some have suggested an international knowledge sharing and capacity building network, a Global Genomics Initiative, as a means to harness the potential of genomics to reduce inequalities in health between North and South.

Slide 92: Who will benefit most from the development of human and personal genomics research? The question should not be rhetorical, but it probably is. It is commonly known that the world's "most neglected" diseases are being largely ignored by the pharmaceutical industry.[3] 90% of health research dollars are currently being spent on health problems that affect only 10% of the world's population, and this has not been any different in the pharmacogenomics industry.[4] What little presence this industry has outside of North America and Western Europe is a result of the "boutique" style market developed by pharmacogenomics that has largely focused on specialized treatments for a minority of the population.[5]

Slide 93: Low and middle-income countries are increasingly engaged in genomics science and applications due to the spread of genomic knowledge and technologies (like CRSPR). Initiatives such as the MalariaGEN (Malaria Genomic Epidemiology Network) started in 2008 include not only medical aspects of disease but also the financial and social aspects of vulnerability and treatment in poor part of the world. Human and personal genomics techniques have resulted in some small public health gains in developing countries. The WHO cites a Malaria vaccine initiative in India, and another project in Nairobi that utilizes genetics in creating a vaccine for HIV by measuring the resistance of each strain in a group of sex workers. These are

[3] Yamey G., "The World's Most Neglected Diseases-Ignored by the pharmaceutical industry and by public-private partnerships," British Medical Journal, 325, (2002):176-177. Accessed on August 15, 2010 from http://www.msf.org/msfinternational/invoke.cfm?objectid=34BA82AD-853E-4476-B45F4BE4F349CA50&component=toolkit.article&method=full_html

[4] UNESCO, "Universal Declaration on the Human Genome and Human Rights: from theory to practice," pg. 145.

[5] Abdallah S. Daar and Peter A. Singer, "Pharmacogenetics and Geographical Ancestry: Implications for drug development and global health," pg. 78

examples of the potential for personal genomics to enhance public health in developing countries.[6]

Slide 94: However, the use of developing world population groups for testing, which is predicted to be the biggest utility of developing countries in the field, is "fraught with ethical and social problems that will need to be addressed with interdisciplinary research."[7] Genomic research in developing countries needs to be balanced with respect to who benefits and the process through which information gathered and used. Issues include the commercial use of data, privacy, and re-identification of the source of samples are but a few of the concerns. "It will be up to scientists involved in these projects to do more to think through past structural inequalities, histories of resource extraction, and issues of equity as they ethically engage and educate people whose DNA is the basic necessity that permits human genetic research in the first place."[8] On the other hand, genetic testing has the potential to address disease-related public health concerns in the developing world, and these will not occur until a significant market incentive is created for the private sector to invest in the health problems of the poor: and access to data is a key incentive.

Slide 95: A movement that is gathering steam is something called genomic sovereignty. There are a number of aspects to this idea. First is the notion that a state should exercise control over the genetic material of their populations. The Mexican government passed a law in 2008 prohibiting genetic testing and the transport of genetic material outside Mexico. Another angle is the desire to develop national expertise and infrastructure in this area, to avoid dependence and domination by foreign science and expertise. In taking protective custody of a population's genetic heritage, the government in effect can champion the interests of the country and ensure that research is conducted for the benefit of that population.

Slide 96: However, it is also the case that governments may be thinking of the genetic heritage of their populations as a resource, to be "mined" like

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[6] WHO, "Global applications of genomics in healthcare: Kenya," accessed on August 23, 2010, http://www.who.int/genomics/professionals/applications/africa/en/index.html

[7] Abdallah S. Daar and Peter A. Singer, "Pharmacogenetics and Geographical Ancestry: Implications for drug development and global health," pg. 94

[8] Fullwhiley, Duana, and Sahra Gibbon, "Genomics in Emerging and Developing Countries," in Sahra Gibbon, et.al., eds. *Routledge Handbook of Genomics, Health, and Society*. London, Routledge (2018), 228.

any other. And many social groups in developing countries worry that governments will use genetic testing against them.

Slide 97: Okay, so that is about it. Obviously, there was a lot to talk about. But I hope it is clear that of you want to understand climate change and human genomics, it is best to have knowledge from both the sciences and the arts. Whatever you go on to do, please hold on to that as the basic message of this course!