Personal Genomics and Social Sciences and Humanities

Well, now we go from the universe of the very big (climate) to the universe of the very small (the human genome)!

Once again, I want to 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.

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.

Rapid advances in genetics research and genetic modification technology are both creating new controversies and tensions and intensifying existing controversies and tensions in societies around the world. The rapid pace of innovation and technological advancement in the genomics field ("freakingly fast" as Dave put it) has left social debate about norms and principles, the development of law and state policy, and government regulatory agencies far behind. CRISPR-Cas9 technology is only the latest (and will by no means be the last) of these kinds of big technological advances that disrupt existing ethical and moral systems and regulatory regimes.

Furthermore, genetic research has spread worldwide to many countries. 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 state laws and regulations.

The first three videos focused on the evolution of the human genomics story, emphasizing the relationship between the life sciences discoveries and the impact and significance of the social sciences and humanities in that narrative, particularly at the individual level of analysis.

In class I picked up on these themes looking more at the group and global levels of analysis (remember those?!). So here we go: personal genomics (also called personalized medicine or precision medicine).

Personalized Genomics and Groups

Genomics and Religion

Genetic research in general, and human genetic research in particular, has been a contentious subject for religions and their ethical systems. I told a fable called "The Prince and the Biologist" that basically revolved around a central concern: are we "playing god?"

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

Argues 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."

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]

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).

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[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

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 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.

Religions, in the form of the political power of religious groups and organizations, are important influences over ethical and legal systems. Look no farther than debates over abortion. As a result, the nexus between genetics and religion is likely to be a hot one in the coming decades.

CRISPR technology, of course, will dramatically accelerate these religious ethics debates: except the technology is moving faster than the ethicists!

Personal Genomics and Group Identity

Human and personal genomics can have a profound impact on cultural, ethnic, linguistic, and indigenous groups. For example, genetic testing of indigenous groups makes it easier for researchers to identify genetic "peculiarities" as the gene pool is often relatively homogenous and isolated from large-scale cross-breeding.[2] Studies on these isolated groups can focus on identifying gene indicators for diseases prevalent in the racial group or information that will uncover genetic ancestral links.

However, indigenous groups around the world have taken a defensive stance concerning the genetic testing of their populations.[3] This is not particularly

[2] Ikechi Mgbeoji, "Talking Past Each Other: Genetic Testing and Indigenous populations," *Actionbioscience.org,* September 2007, accessed August 19, 2010, http://www.actionbioscience.org/genomic/mgbeoji.html

surprising, given the historical experience of colonization, political and economic marginalization, and institutionalized repression that most such groups have endured. This treatment extends to a historical relationship with Western medicine that is ambivalent at best.[4] As in colonial times, indigenous groups see researchers and academics benefitting from their genetic studies of groups, yet see very few benefits for the populations who provided the genetic materials.[5]

Most importantly, indigenous groups worry about how the testing will be used and how it could hurt their cultural identity both mentally and legally. Most indigenous groups have a contrasting belief of community membership to most Western societies. The value of "common beliefs of origin, cultural affinities and linguistic characteristics" in identifying with a group transcends that of genetic information.[6] Thus, population genetics has the potential to confirm or refute long-held notions of common genetic and ancestral origins. This not only causes psychological damage for individuals, but also can seriously harm quests for self-determination.[7]

One such example of these fears being realized involves the Havasupai Indians in Arizona. As we saw in the video, the legal case involving Arizona State University and the Havasupai Indians demonstrated the consequences that genetic data can have when it conflicts with traditional beliefs.[8] Even more, the case raised debate on what fulfills the "informed consent" clause required by federally funded researchers and institutions.[9] Researchers at the Arizona State University received consent from the Havasupai Indians to gather genetic information regarding the high rate of diabetes diagnosed within their population. However, more conclusive data was found on the tribe's rate of mental illness and genetic information that contradicting traditional stories of their geographical origins.[10] The research article published on this research suggested that the Havasupai ancestors had

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[3] Sivaramjani Thambisetty, "Study Paper 10, Human Genome Patents and Developing Countries," Commission on Intellectual Property Rights, 2002, pg.21, http://www.iprcommission.org/papers/pdfs/study_papers/10_human_genome_patents.pdf
[4] Ikechi Mgbeoji, "Talking Past Each Other: Genetic Testing and Indigenous populations,"
[5] Ibid.
[6] Ibid.
[7] Ibid.
[8] Amy Harmon, "Indian Tribe Wins Fight to Limit Research of Its DNA," *The New York Times,* April 21, 2010, http://www.nytimes.com/2010/04/22/us/22dna.html
[9] Ibid.
[10] Amy Harmon, "Indian Tribe Wins Fight to Limit Research of Its DNA"

crossed the Bering Sea to arrive in North America, both challenging the tribe's traditional stories and the basis of their sovereign rights to their canyon land.[11] Elders were devastated, the tribe felt manipulated and misused, and the Havasupai youth who had convinced the elders to partake in the study felt like they had betrayed their ancestry. The researchers claim that they received consent for wider-ranging genetic studies.[12] In response, the University paid out $700,000 to 41 members of the tribe and returned the blood samples. This case is a milestone in indigenous genetic testing, as the compensation implies that the rights of an individual can be violated when full information about how their DNA might be used is not given.[13]

CRISPR technology is going to make such studies easier, worldwide, increasing the potential for these kinds of clashes between genetic studies and groups identities.

Gene-Editing and Humans

Technological advances are moving very rapidly in human genome related work. A good example of this is the capabilities of the CRISPR-Cas9 system discussed by Dave. The inventors of the technique, Jennifer Doudna (University of Califormia, Berkeley) and Emmanuelle Charpentier (then at the University of Vienna) were awarded the 2015 Breakthrough of the Year Award by *Science*.

These technologies hold the promise of applying gene editing to humans. 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).

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

[11] Ibid.
[12] Ibid.
[13] Ibid.

enhancement (see below).

Consequently, there has been an explosion in research and scholarship on the wider implications of gene editing and humans.

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 to enhance intelligence or physical qualities, including those not associated previously with humans.

Major International conferences have already been convened on the subject. However, there is some division among ethicists. 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.

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."

So is this a "damned if you do and damned if you don't" situation?

In 2017, the National Academies of Science, Engineering and Medicine in the US published a document titled "Human Genome editing; Science, Ethics, and Governance." It was written by the members of a Committee on Human Gene Editing. The core recommendations were:

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

The recommendations are available in the Summary of the document, at: http://www.nap.edu/24623

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.

The CRISPR-Cas9 story also has a plotline concerning patents. There was a patent fight between the University of California (Doudna) and the University of Vienna (Charpentier) on the one hand, and the Broad Institute, affiliated with MIT and Harvard, where a Dr. Feng Zhang was the first to apply the technique to animal and human cells. The Broad Institute was later granted patents for the application of this technique, arguing that significant extra work and innovation had been done to achieve the applications of the CRISPR technique in practice. The universities of California and Vienna argued that the technique developed by Doudna and Charpentier constituted a complete patent because it was obvious how the technique could be applied to animal and human cells. The case went to the Federal Patent and Trademark Office, which found for the Broad Institute on February 15th

2017.

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

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.

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.

For his part, He was fired on 21 January 2019. 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.

Personalized Genomics and Global Governance

In one sense human and personal genomics is an international enterprise by its very nature: the research into sequencing the genome took place in a number of countries. In another sense, the project has been very exclusive to a small set of countries and laboratories. However, this is changing rapidly.

In China, human and personal genomics is regarded as a key growth sector. The most prominent example of this is BGI (formerly the Beijing Genomics Institute). Based in Shenzen, the BGI has opened a new sequencing facility in Hong Kong. This facility will allegedly have more sequencing capacity than exists in all of America. Yang Huangming, the head of the BGI, wants to make it the first truly global genomics operation. Hong Kong was chosen at least in part because its more reliable and functioning legal framework is more attractive to foreign investors, scientists, and customers. There are plans to expand into Europe and the United States.

"In the United States and in the West, you have a certain way,'' he continued, smiling and waving his arms merrily. "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."

Jian Wang, BGI president and co founder with Huanming Yang, who is now the chairman. (New Yorker, Jan, 2014)

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. 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.

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. Genetic testing as a tool for discrimination is prohibited under *Article 11*, while genetic testing is permitted only for health (or for scientific research linked to health purposes) under *Article 12*. The modification of the human genome, for reasons other than health-related is generally prohibited under *Article 13*. 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.

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.[14] However, there are no calls for specific policymaking or for advances in international governance of genetics.

There are some other relevant international agreements, such as UNESCO's International Declaration on Human Genetic Data (2003), and ECOSOC Resolution 2004/09 on Genetic Privacy and Non-Discrimination (2004). But these are not treaties.

Recent Governance Developments

[14] 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

The reality is that most discussion of the regulation (or need for regulation) and the ethics of personalized genomics is being done at the scientific, NGO, and industry level. Here are a couple of recent examples.

The National Academy of Sciences and the National Academy of Medicine's Human Gene-Editing Initiative held an international summit 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.

The statement that came out of the Summit said a number of things, but included 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."

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."

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 important, NGOs cannot make laws or treaties.

Developing 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.

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.[15] 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.[16] 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.[17]

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 examples of the potential for personal genomics to enhance public health in developing countries.[18]

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

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[15] 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

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

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

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

interdisciplinary research."[19] 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.

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

Okay, so that is about it. Obviously there was a lot to talk about and we really only touched the surface. 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!

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