ABSTRACT

The Fourth Industrial Revolution's Impact on Medical Ethics

Ashley Ricciardelli

Director: James Marcum Ph.D.

Starting with the 1947 Nuremberg Code, the field of medical ethics began to rapidly develop, eventually coming to define three core values for ethical treatment and research via the Common Rule: respect, beneficence, and justice. In a new era of big data and precision medicine stemming from the Fourth Industrial Revolution, medical professionals strive to uphold these values, but with innovation comes new challenges. In this thesis, I will discuss the history of medical ethics to provide a foundation for ethical review, define the Fourth Industrial Revolution, and examine respect, beneficence, and justice and their relations to precision medicine to exemplify how recent technological expansion and sophistication has impacted ethical discourse and legislation.

APPROVED BY DIRECTOR OF HONORS THESIS:

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Dr. James Marcum, Department of Philosophy

APPROVED BY THE HONORS PROGRAM

_____

Dr. Andrew Wisely, Interim Director

DATE: _____

THE FOURTH INDUSTRIAL REVOLUTION'S IMPACT ON MEDICAL ETHICS

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Ashley Ricciardelli

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CHAPTER ONE

The History of Medical Ethics

When thinking about medical ethics and its history, I often find myself looking back to the Hippocratic Oath, one of the first documents prompting physicians to swear upon certain standards, the most famous of these standards preventing physicians from inflicting intentional harm, prohibiting actions like the distribution of poison, abortion, divulgence of patient information, sexual relations with patients, and even surgery. This idea will be referred to as "do no harm" in the rest of this paper. At first glance, the Oath appears to be providing ethical guidelines for physicians to follow, but upon further examination of the Oath and its historical context, it was discovered that rather than defining right and wrong and moral an immoral, the Oath strives for the physician to maintain purity in the eyes of the Gods. In other words, it can be viewed as a guide to please the Greek Gods rather than a universal discourse on morality. Our own contemporary moral understanding can cause us to misconstrue its primary purpose. Nevertheless, the Oath still presents values for physicians to uphold, and we can still examine these values in the context of our current society to promote discussion (Jotterand, 2005). The fact that this oath dates back to the 5th century B.C. would make one think that the realm of medical ethics developed around that time as certain values and standards began to be associated with medicine, but over the course of 1000 years there were few other advancements in ethical regulations. Only after horrific Nazi experimentation, mass medical innovation, and the revelation of morally questionable

American experiments like Tuskegee did medical ethics become its own field with its own discourse and laws. It is shocking to think that the field of medical ethics and modern ideologies such as patient autonomy and informed consent did not come into being until after World War II.

Following World War II, the Allies held the 1946 Nuremberg trials, a series of 12 military tribunals that examined the war crimes committed by German figures. One such trial, *USA vs Karl Brandt et al.*, otherwise known as the Doctor's Trial, brought light to the horrific experiments the Nazis had performed within concentrations camps and against Polish nationals (*Trials of War Criminals Vol. 1*, 1949). These experiments included high altitude tests and freezing experiments in which Jewish prisoners were forced into low pressure chambers and freezing water in order to test the limits of human endurance, disease-related experiments in which healthy subjects were infected with diseases like malaria, spotted fever, yellow fever, small pox, typhus, para typhus A&B, cholera, diphtheria, tuberculosis, and jaundice or bacteria like streptococcus, gangrene, and tetanus in order to test out and create potential treatments, mustard gas and poison experiments in which the aforementioned substances were administered to test treatments, bomb experiments that studied phosphorous burns and their treatment, sea water experiments that attempted to make sea water drinkable and deprived subjects of clean water, and sterilization experiments that attempted to develop an efficient method of sterilization suitable for millions of people. The Doctor's Trial also tried the German doctors and administrators for the skeleton collection at the Reich University of Strasbourg that consisted of 112 Jewish skeletons and for the euthanasia of both German

nationals deemed unfit for war and Jews. All of the experiments were done forcibly, without consent of the subjects, and often resulted in either death or permanent disability.

At the end of the trial, of the 20 doctors and 3 administrators tried, 7 received a death sentence, 10 received prison sentences, and 9 were acquitted (*Trials of War Criminals Vol. 1*, 1949). The verdict also resulted in the formation of the 1947 Nuremberg Code, entitled "Permissible Medical Experiments," a set of 10 ethical principles formulated to guide researchers in human experimentation and prevent the atrocities of the German concentration camp experiments from reoccurring. These 10 ethical principles are summarized below:

1) Voluntary consent without coercion or deception is essential. The patient should know the nature, duration, purpose, methods, means, and hazards of an experiment beforehand.
2) The experiment should be for the good of society.
3) The experiment should be based on the results of animal experimentation or prior knowledge.
4) The experiment should avoid unnecessary physical and mental suffering and injury.
5) The experiment should not be conducted if there is prior evidence that it will harm or disable the subject.
6) The risk should not exceed the benefit.
7) The subject should be protected against injury, disability, and death.
8) The experiment should only be conducted by qualified individuals.
9) The subject should be able to choose to leave the experiment.

10) Scientists should be prepared to terminate the experiment at any point if they believe continuation will harm the subjects (*Trials of War Criminals Vol. 2,* 1949, pp. 181-182).

Although the Nuremberg Code's guidelines were not enforced on a widespread basis, its notions of informed consent, patient autonomy, risk vs benefit, and the reiteration of the Greek idea to "do no harm" in a modern context set ethical standards that paved the way for the future formation of ethical laws and regulations.

The Nuremberg Code heavily influenced the Declaration of Geneva, a doctoral pledge published by the World Medical Association in 1948, just one year later (Fischer, 2006). This doctrine quickly became dubbed the contemporary Hippocratic Oath as it expanded upon pledges from the original Greek doctrine. The Declaration of Geneva re-emphasized a doctor's duty to do no harm by stating that "the health of the patient will be my first consideration." Additionally, it characterized the physician as someone who "consecrate[s] my life to the service of humanity," and promoted confidentiality and respect through the pledges "I will respect the secrets which are confided in me," and "I will not permit considerations of religion, nationality, race, party politics, or social standing to intervene between my duty and my patient" (World Medical Association, 1948). These pledges helped re-define the role of the physician by exemplifying the idea that a doctor should be committed to serve humanity rather than scientific advancement. It characterized physicians as people who are respectful, fair, and caring in nature and helped push the idea of who a physician should be and what they should value in a direction rooted in moral principles. It also promoted patient rights to both treatment and confidentiality, encouraging future exploration of these issues.

The Declaration of Geneva was transformed from a doctoral pledge to a more standard set of ethical codes one year later in the World Medical Association's International Code of Medical Ethics. This ethical code divided a doctor's duties into three parts: duties of doctors in general, duties of doctors to the sick, and duties of doctors to each other. It defined the general duty of doctors as "maintain[ing] the highest standards of professional conduct" while "uninfluenced by profit." This section also admonished self-advertisement, collaboration without professional independence, and profit outside of the professional fee. The duties of doctors to the sick stated that doctors had an "obligation of preserving human life" while staying within the scope of their practice, maintaining confidentiality, and "give[ing] emergency care as a humanitarian duty" if needed. Duties of doctors to each other were defined as treating each other with respect, not enticing patients from their peers, and observing all pledges in the Declaration of Geneva (World Medical Association, 1949). The International Code of Medical Ethics was unique in that it elaborated on the Declaration of Geneva's idea of what physicians should value by laying out the duties and roles a physician should fill. It re-iterated the idea that the physician should serve humanity by discouraging profit-based practice and promoting concern for the well-being of the patient. Serving the patient and protecting their confidential information and health was no longer a mere promise physicians made upon receiving their doctorate, it was a duty expected of all those that worked as doctors across the globe.

In 1962, the first U.S. law requiring rigorous drug approval and monitoring as well as informed consent was passed in the form of the Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act. These amendments resulted largely in part due the

mass birth defects resulting from the circulation and use of Kevadon, a brand of thalidomide used to treat morning sickness, in 46 countries including Europe and Canada. Although circulation of the drug was limited in the U.S. due to the intervention of medical officer Frances Kelsey of the Food and Drug Administration (FDA), who refused to approve the drug based on insufficient testing data, the thousands of children born with shortened, missing, or flipper-like appendages in other countries exemplified the need for stricter drug regulation overall. In order to prevent a similar incident from occurring in the U.S., a senate subcommittee led by Kefauver-Harris was formed to create new drug approval policies (Fintel et al., 2009). The amendments stipulated that manufactures must prove the effectiveness of their drug before opting for it to be on the market. To do this, they must hold adequate and well controlled clinical studies led by qualified individuals and acquire informed consent from every subject. The amendments also required regular inspection of production facilities, public advertisement of drug side effects, and approval of all drugs on the market by the FDA (FDA, 2012). The Kefauver-Harris Amendments were a huge step forward in regard to patient rights as they required information to be distributed to both research subjects and consumers of the completed medication. They necessitated both the availability of experimental information to research subjects so as to receive informed consent and the availability of side effects to consumers so as to ensure they were informed of any risks. With the amendments, the guidelines for informed consent, risk vs. benefit, and experimentation based on prior knowledge from the Nuremberg Code were transformed into U.S. law. The realm of ethics was beginning to rapidly mix with the medical field.

In 1964 the World Medical Association created the Helsinki Declaration which expanded upon the Declaration of Geneva's and the International Code of Medical Ethic's guidelines for physicians to protect the health of their patients. In this new declaration, the World Medical Association provided specific recommendations to aid physicians in protecting their patients during therapeutic (clinical) and non-therapeutic (non-clinical) research. To open, the Helsinki Declaration listed basic principles researchers should hold during human experimentation: human research should be based on animal/laboratory experimentation and prior knowledge and risks and benefits should be assessed with risks not outweighing benefits. The therapeutic treatment section emphasized that medical treatment should be combined with professional care, that the doctor should receive the patient's freely given consent, and that patients should be treated with new therapeutic methods if the doctor believes it will be beneficial. The Declaration of Helsinki stated that in non-therapeutic research done purely for science, the physician must be the "protector of the life and health of that person [patient]" and must also receive informed consent from the participant. The patient must also have the right to withdraw from the study at any time (World Medical Association, 1964). Overall, the Helsinki Declaration echoed similar themes to its predecessors: patients need rights. It recognized the value in human research and attempted to suggest ways to make different types of medical research align with previously established standards. It took the broader goals of past regulations and codes and sought to apply them to specific kinds of research models. The attempts of the Helsinki Declaration and its predecessors to combine both medicine and ethics exemplified an important idea that began during World War II and continued throughout the 1960's: medicine and ethics are not mutually exclusive.

In 1941, in the midst of World War II, Franklin D. Roosevelt established the Committee of Medical Research to coordinate medical scientists in an effort to improve military medicine. The creation of this committee sparked a trend in medical innovation that hasn't slowed down since. Innovation took off between 1945 and 1970, and with these new medical discoveries came ethical questions. In 1953, the discovery of the structure of DNA, an advancement toward discovering the secret of life, opened up the field of eugenics and brought about questions concerning the ethics of engineering a superior race. A year later, the first renal transplant by Dr. Joseph E. Murray between a set of twins challenged the idea that physicians should "do no harm" and sparked questions concerning whether or not taking a healthy organ from a healthy donor was harmful. Additionally, intervening with natural processes of the human body was questioned with the advent of birth control in 1960. Ideas of fairness were discussed with the creation of the hemodialysis machine that same year as the Seattle Dialysis Center was forced to create a committee to choose which patients would have access to the new and limited machine. Terms like death were debated with the first 1967 heart transplant and Harvard's 1968 definition of brain death. Was death a cessation of the heart and respiration? Was taking a dying man's heart and transplanting it to someone else considered killing the donor? Is someone considered dead if they have working organs but an absence of brain function? Questions like these encouraged experts in the realms of philosophy and theology to join scientists in their discussions, and, as a result, experts in different disciplines formed two research centers: the Institute of Ethics, Society, and the Life Sciences (now the Hastings Center) in 1969 and the Kennedy Institute of Ethics in 1971. In 1975, the Kennedy Center released a 4-volume encyclopedia of bioethics,

bringing the realm of bioethics to the forefront of the medical field. Rather than past benign paternalism where doctors determined what was best for a patient, bioethics took a more philosophical stand and encouraged freedom for patients to make judgments.

Bioethics itself has no one definition, but, overall, it encouraged careful examination of moral dilemmas and invited experts outside of the medical field to give counsel on situations. All fields that studied moral life were given the opportunity to use their knowledge to discuss new medical problems. Overtime, these discourses became thoroughly intertwined with the medical field as thousands of academic papers and conferences brought them to the forefront, and the field of bioethics became a new discipline with most medical schools employing a professor of bioethics by the end of the 1980's. Medicine and ethics were no longer separate entities as bioethics became a prominent discipline. In the years to come, we see that as the medical field combined with ethical discourse, so too did medical policy as bioethics encouraged multiple disciplines to come together and not only discuss issues but create guidelines to remedy them (Jones, 2000).

In the years following the Helsinki Declaration, efforts were made by U.S. health organizations to create institutional review boards (IRBs) in order to ensure all research done followed ethical guidelines discussed in previous legislation. This idea of IRBs took off in 1965 when James Shannon, Director of the National Institute of Health (NIH), proposed that all NIH research should be reviewed by an independent group of peers with varying backgrounds and knowledge. He drew this idea in part from the NIH's Clinical Center, a clinical research hospital that opened in 1953 in Maryland, which enforced policy suggesting peer review for all experiments (Grady, 2015). One year later, the U.S.

Public Health Service (PHS) followed suit and required ethical review within its organizations, a policy that was elevated to federal status by the Department of Health Education and Welfare (which later became the Department of Health and Human Services) in May 1974. Formal procedures of IRBs for federally funded programs were codified as 45 CFR 46 and aligned with the new section of the Public Health Service Act (Section 474a) passed by Congress that mandated IRB development (Breault, 2006, pp. 15-20). The realm of bioethics was firmly rooting itself in federal research policy.

The next important legislation for bioethics was passed just two months later in July 1974 and was entitled "The National Research Act." However, the circumstances behind the Act's publishment were anything but good and were in large part due to the PHS's long-term negligence of the previously discussed ethical guidelines. In 1972 the PHS's 40-year long Tuskegee Syphilis Study spanning from 1932-1972 was brought to light. This study attempted to discover the natural history of syphilis in untreated patients by observing 600 mostly poor and uneducated African Americans from Tuskegee, Alabama. Of the 600 subjects, 399 had syphilis and 201 served as controls. Researchers told the subjects that they required periodic medical exams for "bad blood" and often performed painful spinal taps on the subjects to gather data. The subjects were promised free hot meals, transportation, medical care, and free burials in exchange for medical exams, but were never told they were a part of study or that they had syphilis. The study continued even after penicillin became available as a treatment for the disease. The patients were not informed of their study participation, were forced to undergo painful procedures, and were deprived of treatment. The study had been reviewed several times by the PHS throughout its time span but was not deemed unethical until the Department

of Health Education and Welfare (DHEW) was appointed to review it after public outrage resulting from an article on the study published by Associated Press (CDC, 2020). The fact that such a study had been funded and allowed to run for decades was horrific, especially after notions of informed consent had become widespread from previous documentation such as the Nuremberg Code, the Kefauver-Harris Amendments, and the Helsinki Declaration.

In response, Congress passed the 1974 National Research Act (Public Law 93-348) that mandated IRBs for human research at any organization receiving DHEW funding and formed the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) composed of 11 members "distinguished in the fields of medicine, law, ethics, theology, the biological, physical, behavioral and social sciences, philosophy, humanities, health administration, government, and public affairs" (Public Law 93-348, 1974, p. 348). It was the hope of Congress that a commission based in the field of bioethics could "identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects" and "develop guidelines…in accordance with such principles" (Public Law 93-348, 1974, p. 349). In 1979, the National Commission's principles and guidelines were published as the Belmont Report.

The Belmont report opens by presenting three principles to guide research involving human subjects: respect for persons, beneficence, and justice. It defines respect as the "requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy." In other words, subjects have a right to make their own decisions and should be able to make these decisions voluntarily with adequate information.

Beneficence is defined as “making efforts to secure their [subjects] well-being.” It describes beneficence as an “obligation” with two general rules: “do no harm” and “maximize possible benefits and minimize possible harms.” The final principle is justice which is not denying benefit without good reason or burdening unduly. It has to do with “fairness of distribution” and “what is deserved.” It entails selection of diverse research participants and widespread application of results and benefits to all involved in the research process regardless of their wealth.

After describing the basic principles, the Belmont Report discusses applications of the respective principles. To practice respect, it requires informed consent consisting of three elements: information, comprehension, and voluntariness. Under information, it describes that the “research procedure, their purposes, risks and anticipated benefits, [and] alternative procedures” should be disclosed to the subject. It necessitates that the subject should have enough information to decide their involvement in the experiment and ask informed questions and that the subject should also be allowed to withdraw their participation at any time. Additionally, the information section acknowledges that sometimes information is not disclosed by researchers for the sake of validity (as often occurs with placebo studies). It states that this is justified only if “incomplete disclosure is truly necessary,” “there are no undisclosed risks,” and “there is an adequate plan for debriefing.” Under the comprehension section, it describes that information must be disclosed in an appropriate manner. It should not be disclosed in a rushed or disorderly way and should be comprehensible and not full of complex scientific words. If the subject is incapable of comprehending the information, a third party should be chosen to

act in that person's best interest. The voluntary section requires voluntary consent "free of coercion and undue influence."

To practice beneficence the Belmont Report stresses an assessment of risks and benefits. It states researchers must examine potential outcomes beforehand and lists that assessments should reflect the following considerations: "brutal or inhumane treatment of human subjects is never morally justified," "risks should be reduced," there should be a "justification of the risk," the appropriateness of involving vulnerable populations should be justified, and "relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process."

The implementation of justice is described in the context of subject selection. It breaks down the selection of subjects to two levels: the social and the individual. Individual justice is described in terms of fairness. It asserts that potentially beneficial research should not be limited to a few select patients held in favor and that risky research should not be excluded to undesirable persons. Social justice is defined as an "order of preference in the election of classes of subjects (e.g., adults before kids)" as well as a balancing of the amount of people from particular socioeconomic classes in research (particular classes studied all at once should only be in certain situations) (OHRP, 2018).

The Belmont Report was incorporated into U.S. regulations in 1981. That same year, the FDA paralleled 45 CFR 46 of the Department of Health and Human Services (DHHS) and made their own regulation requiring IRBs issued as 21 CFR 50. Unlike the DHHS's regulation, the FDA's rule applied to all research and studies regulated by the FDA regardless of funding type. In this sense, the FDA's regulation increased the scope

of IRB regulation to include private research as well as government funded projects (Breault, 2006, pp. 15-20).

The Belmont Report heavily influenced the Common Rule that was published in 1991 and codified in separate regulations by 15 federal departments and agencies. Each agency added their own revisions, but each kept a section with language and numbers identical to DHHS's 45 CFR 46 subpart A (OHRP, 2016). This took the principles and guidelines of the Belmont Report and incorporated them into a more detailed outline of research requirements. The Common Rule requires IRBs for research review and expresses that IRBs should have members with "varying backgrounds to promote complete and adequate review of research" and must obtain informed consent without coercion based on understandable explanations. It expands on the Belmont Report's requirements for disclosure of research procedures, purposes, benefits and risks, and alternative procedures and creates a comprehensive list of everything a subject must be told before participating. Under "criteria for IRB approval of research" it lists that in order to approve research the following must be satisfied: "risks to subjects are minimized," "risks to subjects are reasonable in relation to benefits," "selection of subjects is equitable," "informed consent will be sought," "informed consent will be appropriately documented," confidentiality will be maintained, and there will be safeguards to "protect the rights and welfare" of subjects "vulnerable to coercion or undue influence such as children, prisoners, pregnant woman, mentally disabled persons, or economically or educationally disadvantaged persons." The Common Rule further states that reviews should be done at least yearly on ongoing research to ensure standards are still being maintained (Department of Health and Human Resources, 2009). Respect,

beneficence, and justice from the Belmont Report were fully embodied in Common Rule guidelines.

Forty-five years after the Nuremberg Code, ethical review and the realm of bioethics became acknowledged in federal law. It had been over 1000 years since the Hippocratic Oath, but ethics finally became an integral part of medicine. In the next chapter, I will examine the Fourth Industrial Revolution and the emergence of big data and precision medicine in order to later explore new ethical issues and policies that have arisen as a result of recent technological advancement.

CHAPTER TWO

The Fourth Industrial Revolution, Big Data, and Precision Medicine

In the past few decades, a new Industrial Revolution, dubbed the Fourth Industrial Revolution, has brought about a rise in big data and precision medicine, and, as a result, has encouraged new ethical questions, ushering in a new era of ethical debate. This chapter will discuss the Fourth Industrial Revolution, big data, and precision medicine in order to lay the foundation for ethical analysis in the next chapters.

The Fourth Industrial Revolution was first discussed at the 2011 Hannover Fair in Germany as "Industry 4.0" where it was described as a revolutionization of value chain organization as "smart factories" connected the virtual and physical worlds of manufacturing. A few years later, professors Erik Brynjolfsson and Andrew McAfee from the Massachusetts Institute of Technology dubbed this widespread integration as "the Second Machine Age" in their 2014 book on the topic (Schwab, 2016, p. 7). It was not until 2015 that the term "Fourth Industrial Revolution" was coined by Klaus Schwab, the Founder and Executive Chairman of the World Economic Forum, in an article in *Foreign Affairs* (Schwab, 2015). His term gained widespread notoriety in 2016 at the World Economic Forum, where it was made the center of discussion (World Economic Forum, 2016), and through Schwab's publication of his book entitled *The Fourth Industrial Revolution*. In his book, Schwab defines the revolution along with its drivers and impacts and proposes a way forward.

Schwab (2016) opens *The Fourth Industrial Revolution* by describing the past Industrial Revolutions in history. He recounts the transition from foraging to farming that occurred around 10,000 years ago and explains how this agrarian revolution paved the

way for cities by increasing food production and encouraging population growth and, as a result, larger settlements. He also states how this revolution promoted the use of animals for new modes of production, transportation, and communication. Schwab then goes on to describe the First through Third Industrial Revolutions. The First Industrial Revolution occurred between 1760 and 1840 and ushered in mechanical production with the advent of the railroad and steam engine. The Second Industrial Revolution occurred soon after in the late 19th and early 20th centuries and promoted mass production fostered by the assembly line and electricity. These two revolutions paved the way for the Third Industrial Revolution, otherwise known as the computer and digital revolution, that spanned the 1960's through the 1990's. The Third Industrial Revolution was characterized by the development of semiconductors, mainframe and personal computing, and the internet. Schwab describes the Fourth Industrial Revolution as one that, starting in the 2000's, builds off of the Third and is defined by a "more ubiquitous and mobile internet, by smaller and more powerful sensors that have become cheaper, and by artificial intelligence and machine learning." In other words, "digital technologies that have computer hardware, software and networks at their core are not new, but…they are becoming more sophisticated and integrated" in the Fourth Industrial Revolution (p.7).

Although the Fourth Industrial Revolution involves many of the technologies invented during the Third Industrial Revolution, Schwab (2016) argues that it is its own distinct revolution due to its velocity, breadth and depth, and systems impact. In terms of velocity, he highlights that "in this [the Fourth] revolution, emerging technologies and broad-based innovation are diffusing much faster and more widely than in previous ones"

(p.8). He uses several examples to illustrate this point, one describing how it took nearly 120 years for the spindle, a hallmark of the First Industrial Revolution, to spread outside of Europe whereas it took the internet less than a decade to spread across the entire globe. This high velocity in diffusion is mirrored in a more recent example, the iPhone, which, after its original launch in 2007, had over 2 billion sales by the end of 2015. The speed of transmission associated with the Fourth Industrial Revolution is unmatched in any previous era (pp. 8-9).

Schwab explains that the breadth and depth of the Fourth Industrial Revolution also makes it distinct as the revolution "combines multiple technologies that are leading to unprecedented paradigm shifts in economy, business, society, and individually" (p. 3). His book has a whole chapter devoted to the wide range of impacts the Fourth Industrial Revolution has had on these various different aspects of society. To name a few, Schwab exemplifies that the economy has shown massive growth and has experienced shifts in the workforce through the replacement of precise manual labor with work based on problem-solving and social skills (pp. 37-41); business has changed in terms of consumer expectations, data-enhanced products, and new operating models (pp. 50-57); society has changed as wealth has shifted to the hands of a few individuals and as citizens have become empowered through new forms of communication and disempowered by the inability to influence dominant institutions and be involved in traditional and meaningful decision-making processes (pp. 91-94). He concludes by discussing how the individual has changed in terms of his/her sense of privacy, relationships, and view of the human condition as technology has allowed for mass and sometimes unsecure data transmission and changed the nature of social interaction by providing an alternative to face-to-face

communication (pp. 97-103). In other words, the Fourth Industrial Revolution changes not only the "'what' and the 'how' of doing things but also 'who' we are" as we are forced to re-evaluate ourselves and our values in the face of a more connected but less interpersonal world (p. 3).

Schwab also describes the Fourth Industrial Revolution as distinct due to its systems impact as "it involves the transformation of entire systems, across (and within) countries, companies, industries, and society as a whole" (p.3). This is done through a "harmonization and integration of so many different disciplines and discoveries." For example, "some designers and architects are already mixing computational design, additive manufacturing, materials engineering, and synthetic biology to pioneer systems" involving interactions between "micro-organisms, our bodies, the products we consume and even the buildings we inhabit" (pp. 10-11). Additionally, system impacts include the national and global effects on governments, countries, and international security brought about by mass advancement (pp. 67-80).

After explaining why the Fourth Industrial Revolution is distinct, Schwab (2016) presents physical, digital, and biological megatrends that define the revolution as a whole. He describes the physical megatrends in terms of physical technological manifestations. In particular, he discusses four innovations: autonomous vehicles, 3D printing, advanced robotics, and recyclable and stronger materials (pp. 15-18). The digital megatrend is characterized by the internet of things which "can be described as a relationship between things (products, services places, etc.) and people that is made possible by connected technologies and various platforms" (p. 18). Applications of the internet of things include sensors, which connect the physical world to virtual networks,

remote monitoring, and secure blockchain networks like Bitcoin that allow for communication and transactions (pp. 18-19). The biological megatrends are portrayed in terms of vast innovation in genetic sequencing and the emerging field of synthetic biology. In this section, he states how genetic sequencing has evolved rapidly in recent years: "it took more than 10 years, at the cost of $2.7 billion, to complete the Human Genome Project. Today the genome can be sequenced in a few hours for less than a thousand dollars" (p. 21). Additionally, he explains how scientists can use collected genetic information to "customize organisms by writing DNA in a new discipling called synthetic biology" (p. 21).

AI robotics, sensors and enhanced communication, and biological research described in the physical, digital, and biological megatrends of the Fourth Industrial Revolution were only made possible through the creation of big data. Big data began emerging with the advent of the internet and more powerful computers in the Third Industrial Revolution and has since been used to fuel innovation (Chen et. al, 2014). In a 2014 article entitled "Big Data: a Survey," Chen et al. define big data as "enormous datasets" often including "masses of unstructured data" (p. 171). Big data is a large growth in data fueled by the latest advancements of information technology, the rapid growth of cloud computing, and by the internet of things as we are able to use sensors all over the world to collect and transmit data stored in a safeguarded cloud (Chen et al., 2014). "It is widely accepted that the characteristics of big data are defined by three major features, commonly known as the 3Vs: volume, variety, and velocity" (Luo et al., 2016, p. 1). Volume of data refers to the exponential growth of data we have experienced within the last two decades. For instance, "in 2011, the overall created and copied data

volume in the world was 1.8 ZB, which increased nearly nine times within five years" (Chen et al., 2014, p. 171). Variety refers to the wide range of data types we are able to record and analyze. This is illustrated by the emergence of the "omics" data in the biological sciences as we are able to obtain data at "almost all levels of cellular components, from genomics, proteomics, metabolomics to protein interaction and phenomics" (Luo et al., 2016, p. 1). Velocity deals with "producing and processing data" as "the new generation of sequencing technologies enables the production of billions of DNA sequence data each day at a relatively low cost" (Luo et al., 2016, p. 1). In addition to the 3Vs, the International Data Corporation (IDC), an influential leader in big data and research, adds another V: value. Value describes one of the major problems of big data, "discover[ing] values from datasets with enormous scale, various types, and rapid generation" (Chen et. al 2014, p. 173). Analyzing giant datasets and interpreting what is important is challenging, and it is for this reason that several initiatives and partnerships arose to gather, integrate, and interpret big data.

The biological sciences in particular developed several initiatives to gather big data with the goal of future interpretation. One of the first of these initiatives was the Human Genome Project. The Human Genome Project, beginning in 1990, involved the joint efforts of the NIH and the Department of Energy and strove to decipher the human genome by determining the human DNA sequence, mapping out gene locations on chromosomes, and producing linkage maps to track inherited traits. By the end of the initiative, it was discovered that humans have around 20,500 genes and 3 billion base pairs. The vast amount of genetic information was fully published and shared in 2003 by the International Human Genome Sequencing Consortium and has since been used to

confirm the genomes of other organisms and to better understand human disease (Genome, 2018).

The Human Genome Project sparked the initiation of the Human Genome Diversity Project by Stanford University which attempted to systematically study the whole range of human genetic diversity by sequencing genomes from distinct populations in Africa, Europe, the Middle East, Central and East Asia, Oceania, and the Americas (Cavalli-Sforza et al., 2005). Through this project, researchers were able to discover single-nucleotide polymorphisms, small insertions and deletions, and copy number variants between populations (Bergström et al., 2020). This information is stored in a database at the Center for the Study of Human Polymorphisms in Paris and is available to non-profit researchers interested in looking at the large genetic datasets from around the world (Cavalli-Sforza et al., 2005).

In addition to vast data gathering initiatives, several consortiums arose to help integrate biologically based big data in order to better understand the cause of inherited traits and disease. One such consortium is the Global Alliance for Geonomics and for Health (GA4GH) which brings together over 600 organizations within the realms of healthcare, research, patient advocacy, life science, and information technology "to create frameworks and standards to enable the responsible, voluntary, and secure sharing of genomic and health-related data" (GA4GH, 2020). In this sense, GA4GH attempts to enable mass data sharing and integration by creating guidelines for data security. Another initiative, the International Human Epigenome Consortium (IHEC), seeks to "coordinate the production of reference maps of human epigenomes" and "decipher at least 1000 epigenomes within the next 7-10 years" by using validated technologies to generate maps

of histone modifications, DNA methylation, and transcription start sites, catalogue the expression patterns of noncoding RNA, and comparatively analyze the epigenomes of model organisms. The IHEC states it "will coordinate the development of common bioinformatics standards, data models and analytical tools to organize, integrate and display whole epigenomic data generated" and encourage a "minimal amount of redundancy between the different epigenetics efforts around the world" (IHEC, 2020). Similarly, the International Cancer Gene Consortium (ICGC) is a "global initiative to build a comprehensive catalog of mutational abnormalities in the major tumor types." The ICGC's data portal "contains data from 84 worldwide cancer projects, collectively representing about 77 million somatic mutations and molecular data from over 20,000 contributors" (Zhang et al., 2019, p. 367). Like the IHEC and GA4GH, the ICGC attempts to create a big data database for integrative analysis and consolidate data rather than leave it scattered across different journals and organizations. Several other consortiums attempt to consolidate data within their respective fields for easier use. These include but are not limited to the International Rare Gene Consortium and ELIXER, the European Life-Sciences Infrastructure for Biological Information (Cirillo & Valencia, 2019).

Still other initiatives attempt to improve interpretation of big data including Big Data to Knowledge (BD2K) and the Encyclopedia of DNA Elements (ENCODE). BD2K, an NIH program founded in 2013, attempts to improve the ability of scientists and organizations to collect and interpret big data by developing new analytic methods and providing training for their use (Ohno-Machado, 2014). ENCODE also attempts to aid in data interpretation as it "analyzes the data in an integrative fashion" by "organiz[ing] the

most salient analysis products into annotations and provid[ing] tools to search and visualize them." It provides both integrative annotations which consolidate multiple types of experimental data and ground-level annotations derived from a specific dataset (ENCODE Project, 2020).

According to Schwab, "increasing amounts of [big] data will make precision medicine possible, enabling the development of highly targeted therapies to include treatment accounts" (Schwab, 2016, p. 21). In other words, big data initiatives such as those listed above allowed for the formation of a new type of medicine: precision medicine. In the book *Toward Precision Medicine*, the National Research Council defines precision medicine as a type of medicine that involves "the tailoring of medical treatment to the individual characteristics of each patient…to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment." In order to do this, doctors and researchers use large datasets to predict someone's disease risk and effectively diagnose and treat a condition (National Research Council, 2012). In his book, Schwab (2016) uses the example of the International Business Machines Corporation's Watson supercomputer to illustrate precision medicine. In just a few minutes, this computer can recommend personalized treatments for cancer patients "by comparing the histories of disease and treatment, scans and genetic data against the (almost) complete up-to-date medical knowledge" (p. 21). However, precision medicine doesn't have to always involve a supercomputer. It can involve a mass collection of personal data through either genetic sequencing, electronic medical records, digital technologies, and personal reported information (Ginsburg et al., 2018). With precision medicine, doctors and researchers are given the ability to use mass

amounts of data to edit individual genomes, manufacture 3D living tissue, and record and store information from devices that monitor patients' bodies such as pacemakers and even Fitbits (Schwab, 2016, pp. 22-23).

But with the emergence of big data and precision medicine come several ethical questions. Schwab (2016) points out several: "What information about our bodies and health can and should be shared with others?" "What rights and responsibilities [do] we have when it comes to changing the very genetic code of future generations?" (p.23). Will this revolution forever change privacy and the way we form and interact with relationships? (p. 97).

At the end of his book, Schwab (2016) proposes a way forward. In order to make informed decisions about these issues, we must display contextual intelligence, emotional intelligence, inspired intelligence, and physical intelligence. Contextual intelligence is defined as understanding the value of diverse networks. In other words, we need to "engage with all those who have a stake in the issue at hand" in order to obtain a "holistic perspective" (p. 107). Schwab also illustrates the importance of emotional intelligence, "namely self-awareness, self-regulation, motivation, empathy, and social skills" as technology shifts communication from face-to-face to digital platforms (p. 108). As we practice emotional intelligence, we must also remember to trust others and shift our attention from ourselves to our surroundings, a phenomenon related to inspired intelligence (p. 109). Finally, we must focus on physical intelligence, or our own physical health as, by remaining healthy, we are better able to make informed decisions (p. 110).

But, have we followed Schwab's proposal forward, employing the four different kinds of intelligence? How have we engaged the ethical questions concerning big data

and precision medicine? In the next sections, I will examine ethical issues associated with precision medicine in relation to the three values introduced by the Belmont Report and enforced by the Common Rule: respect, beneficence, and justice.

CHAPTER THREE

Precision Medicine and Respect

I will begin by examining recent ethical discourse related to precision medicine and respect, primarily focusing on how the new emphasis on collecting massive amounts of data (particularly genomic), the formation of new data collection technologies, and the emergence of third-party companies that deal with genetic information have impacted informed consent, privacy, and the doctor patient relationship.

After identifying the Fourth Industrial Revolution and its current and potential impact, the 2016 World Economic Forum established Centers for the Fourth Industrial Revolution in the US, China, India, and Japan. These centers are tasked with accelerating the application of new technology, improving upon new enhancements in tools, policy, and protocols related to the Fourth Industrial Revolution, and prioritizing ethics and values as the Revolution advanced. Rather than just acknowledge the presence of the new revolution, the World Economic Forum sought to aid it in its spread and address any ethical issues that arose in the process. In 2019, the World Economic Forum inaugurated six Global Fourth Industrial Revolution Councils to provide a platform for policymakers and experts to share information and insights, identify governance gaps that needed attention, provide guidance and feedback on protocols designed by the Centers, and serve as early adopters and ambassadors in testing and refining tools, policies, and protocols relating to the Fourth Industrial Revolution. One of these Global Fourth Industrial Revolution Councils was set to directly explore the topic of precision medicine and was dubbed the Global Precision Medicine Council (World Economic Forum, 2018). In 2020, the Global Precision Medicine Council published its vision statement which set to

address six governmental gaps relating to precision medicine with gap two listed as "ethical use of technology." Gap two is listed to have three primary focuses: informed consent, just distribution of benefits, and inclusiveness and representation. These align respectively with the values of respect, beneficence, and justice from the Common Rule (World Economic Forum, 2020).

In its section on informed consent, the Council presents two case studies highlighting the importance of "seek[ing] richer concepts of informed consent" as researchers begin to collect massive amounts of information from populations all over the world. Case study 1.2 examines research focusing on the Havasupai, a Native American tribe (World Economic Forum, 2020). In 1989, members of the Havasupai tribe approached John Martin, an ASU anthropology professor they had previously interacted with and trusted, and asked him to examine why the incidence of diabetes within their tribe was so high. They agreed to allow him to examine the genetic underpinnings of the disease and provided blood samples for the research (Sterling, 2011). According to the 2008 court case *Havasupai Tribe of Havasupai Reservation v. Arizona Bord of Regents*, the tribe was under the impression that their blood would be used solely for research on diabetes and medical disorders. However, the tribe soon found out that researchers went "far beyond the understood consent" and published papers unrelated to the initial focus on diabetes concerning the tribes "inbreeding coefficient, a potential for increased schizophrenia risk and an analysis of the Havasupai's migration patterns over the Bering Strait, a claim that contradicted cultural traditions" (World Economic Forum, 2020). In May 2003, the tribe submitted a "banishment order" that barred ASU professors and employees from the Havasupai Reservation for distributing Havasupai blood to other

third-party researchers without consent and for conducting research "unrelated to diabetes or any other medical disorder." The Havasupai also expressed that their blood samples may have been used "in violation of their values and beliefs" as some information from studies already contradicted their cultural traditions (*Havasupai Tribe v. Arizona Board of Regents*, 2008). The tribe filed a case with the Court of Appeals of Arizona, Division 1, Department D, and eventually settled for "$700,000, the return of the blood samples, and additional assistance including scholarships and help in obtaining federal funding for a health clinic for the impoverished tribe" (Sterling, 2011, p. 115). The Council states that researchers must use historical and cultural examples like this one to ensure patients understand the scope, implications, and risks of participation, "including the potential sharing and possible misuse of sensitive genetic data" (World Economic Forum, 2020). But how can researchers ensure they are providing enough information and achieving truly informed consent, especially when dealing with indigenous populations that have little say against bigger, wealthier, and more powerful corporations?

We can begin to see an answer to this question through the second case study presented by the Council entitled "San Peoples of Africa – fighting prejudice." This focuses on the San peoples, a group of hunter-gatherers in South Africa regarded as the oldest genetic ancestors of modern humans, and their grievances with researchers following an article published in 2010 (World Economic Forum, 2020). According to the San, the article, which included a study on the DNA of four San individuals, contained conclusions that were "private, pejorative, discriminatory and inappropriate." In response to this article, as well as a history of research "neither requested, nor useful, nor protected in any meaningful way" (Schroeder et al., 2019), the San peoples came together to form

the 2017 San Code of Ethics "to help researchers understand how consent can be acquired and research can be conducted in the context of San cultural traditions" (World Economic Forum, 2020). The code lists and defines five key principles necessary for informed consent: respect, honesty, justice and fairness, care, and process. Respect is demanded for the San individual, community, and culture throughout the research process. The San Code of Ethics states that "respectful researchers engage with us in advance of carrying out research" and do not ignore social customs and norms (Schroeder et al., 2019, p. 83). The Code also stresses the importance of "a totally honest sharing of information" for consent with clear, nonacademic language (p. 84). To be completely honest, researchers must be transparent "in a in all aspects of the engagement, including the funding situation, the purpose of the research, and any changes that might occur during the process" (p.84). The San say that communication should be continuous and open throughout the duration of research. Additionally, consent necessitates justness and fairness. The San define justness and fairness in terms of tribe benefits. They want discussion of co-research opportunities and roles for translators and research assistants as well as a sharing of skills and research capacity "to ensure these benefits do actually return to the community" (p.84). They state that research should include care and "should be aligned to local needs and improve the lives of San" (p. 85). The San conclude the Code with the idea of process stating that research approval is necessary upon project design, completion, and subsequent publications. If researchers fail to abide by any of these principals, the San declare that they will withdraw consent and refuse collaboration in future research (Schroeder et al., 2019). Gaps in informed consent are not exclusive to indigenous populations, and many

of the same demands presented by the San are being discussed across the world. With a rise in massive data collection and genomics, the idea of autonomy of subjects and informed consent, including the way it can and should be obtained and presented, is readily evolving.

A rise in data collection has led not only to global-based databases like GAG4H discussed in chapter two, but a rise in collection of personal health through the field of mobile health (mHealth) as well. According to an article published by the 2018 *AMA Journal of Ethics*, "mHealth refers to the use of technologies such as smartphone apps or wearable sensors to monitor health" (Schairer et al., 2018, p. 864). MHealth technology can help users track their step count, fitness levels, blood pressure, heart rate, glucose values, and can even send reminders prompting people to take their medication. It allows for both doctors and patients to view an objective set of personalized data to assess health. In other words, mHealth "remov[es] the patient or subject from the role of the [subjective] narrator," providing "sensor-gathered data incapable of omission or deception" while still allowing patients to be "coinvestigators of their health" and participate in "a more patient-centered experience" (Cvrkel, 2018, p. S16). With all the positives of mHealth, it is not surprising that mHealth products have become widely popular. For example, Fitbit, which sells a wearable sensor that connect with users' phones, has sold more than 38 million devices since 2010 (Cvrkel, 2018). But despite all of the health monitoring benefits of mHealth devices and apps, there are several downsides, particularly in the realms of informed consent.

Recently, researchers have been exploring the challenge of reconciling informed consent with commercial terms of use. For mHealth, users are almost always required to

agree to a set of terms of use for the company supplying the device or application. These terms of use are often paragraphs-upon-paragraphs of small text with a tiny agreement box at the bottom that most people rush to check in order to start using the new application. Typical terms of use "include lengthy legalese and may stipulate the release or selling of personal identifiable data" (Schairer et al., 2018, p. 866). Accepting terms of use may even allow for study participation as mHealth companies partner with research labs. However, many researchers are coming to see this format of delivering information as unacceptable for informed consent. Difficult, legal wording and massive amounts of text discourage users from reading the terms, promoting users to give consent while "uninformed." If mHealth is to be used in research studies and as actual health information, changes need to be made to ensure users are truly informed (Schairer et al., 2018). According to Dr. Tilda Cvrkel, a bioethicist with expertise in ethics and emerging technology, "to meet the standard of 'informed' in informed consent, individuals must be given information in a way that is genuinely usable." This involves information that is "not merely structural in nature, but is instead accessible and informative to the recipient." The decision to check the little box and agree to the terms should be a "reflection of an agent's autonomous choice," meaning "successful uptake of relevant information is crucial" (Cvrkel, 2018, p. S19). But how can developers adapt to ensure they are providing information in a format to allow for informed consent?

Many bioethical suggestions related to informed consent mimic those presented under the "honesty" column in the 2017 San Code of Ethics. Dr. Cvrkel states that consent forms should include "plain language of top to bottom data collection and storage methods," "specificity of risk, including data becoming public," "discussion of

consequences, findings, or research possibilities," as well as an explanation of "data ownership, access, and profits" and "the possibility of withdrawing consent." She suggests conveying all this information "in at least two of the following formats: written, video, or live conversation" (Cvrkel, 2018, p. S18). MHealth initiatives are already starting to take this suggestion. For instance, a national precision medicine research project entitled "All of Us" that aims to enroll one million people living in the U.S. in "the largest precision medicine cohort study to date" is using both neatly organized forms and short videos to receive consent from those contributing information via mHealth platforms, genetic tests, and surveys (Schairer et al., 2018, p. 868). In the "Consent to join the *All of Us* Research Program" form, there are clear headers like "how long will *All of Us* last" and "what will you ask me to do" that allow readers to easily find information (NIH, 2018).

With a rise in big data and technological advancement came not only mHealth, but an increase in genomic data as well, bringing about new ethical questions related to privacy. According to an article in the 6th volume of the *Journal of Law and Bioethics*, with the development of the internet that allows for widespread sharing of personal information, the concept of privacy has evolved from one of concealment to a "personal right to control the use of one's data, including enjoying access and using it by oneself" (Clayton et al., 2019, p. 3). With DNA becoming widely known as a person's "book of life" providing insights into the building blocks of health, subjects began asking themselves who should have access to this wealth of information. With clinicians seeking to use genetic information for preventative medicine and diagnoses, biomedical researchers seeking to use it to understand disease, life insurers seeking to use it to write

policy, and law enforcement seeking to use it to identify individuals, it is no wonder the question has risen on who should be able to access genetic data (Clayton et al., 2019). But, before deciding how to handle the privacy of genetic data in terms of access, policy makers had to decide how they should classify genetic data. Is genetic data simply another type of health information, or does its special characteristics and implications toward the health of individuals and their genetically related family members demand it to have separate and more protective treatment?

This question manifested in the form of "genetic exceptionalism," a term coined by Thomas Murray modeled off of the 1980's HIV exceptionalism controversy concerning whether or not HIV information was unique. With the passage of the 2008 Genetic Information Nondiscrimination Act (GINA), which will be discussed in length in chapter five, genetic information was deemed to be health information protected by the Privacy Rule (Clayton et al., 2019). But, what does this mean in terms of who can access genetic information?

In order to answer this question, we must return to the establishment of the Health Insurance Portability and Accountability Act (HIPAA) in 1996. This Act served as an insurance statute "to facilitate the movement of employees from one employer to another without interruption or loss of employer-sponsored group health coverage." Under the "administrative simplification" provisions, standard electronic formats were mandated to be used to file insurance claims, and privacy was minimally addressed to minimize the risk of an information leak while filing the claims. In a broad sense, HIPAA gave the U.S. Department of Health and Human Services (HHS) the ability to regulate entities that provided health insurance but gave them no control over private companies and

institutions (like those responsible for mHealth apps). Understanding its several limitations in terms of privacy, HIPAA hoped that Congress would pass comprehensive privacy law by 1999, but in the case that such law was not made, it made provisions for the HHS to enact the HIPAA Privacy Rule. With no movement from Congress, the 1999 HIPAA Privacy Rule was passed, and although it was not originally intended to comprehensively regulate privacy, it has since become the main privacy regulation in the U.S. (Clayton et al., 2019). Overall, "the Privacy Rule standards address the use and disclosure of individuals' health information—called 'protected health information' by organizations subject to the Privacy Rule — called 'covered entities'" (OCR, 2013). These entities do not have to obtain consent for sharing information for the purpose of treatment, payment, or healthcare options. They are, however, required to inform patients of their privacy practices in a notice. Under the "minimum necessary" provision, the Privacy Rule also states that covered entities are required to limit the share of healthcare information for payment to "the amount reasonably necessary to achieve the purpose of the disclosure" (HHS, 2000). Clayton and colleagues summarize "covered entities" under the Privacy Rule into four categories:

1) "Healthcare providers that transmit any health information in electronic form in connection with a covered transaction"
2) Health plans that pay for medical care costs including but not limited to "a health insurer, HMO, Medicare or Medicaid program"
3) Health clearinghouses "that process health information into a standard format for billing purposes." These include "a billing service or health information management system"

4) "Business Associates of these entities…that perform or assist in billing, management, administration, or other functions regulated by the Privacy Rule" (Clayton et al., 2019, p.11).

Although the Privacy Rule does specify the entities that can share health information, including genetic data, without informed consent, it has several limitations. Under the "accounting of disclosures" provisions, it does not require entities to disclose who they give deidentified genetic information to, even though this information is potentially re-identifiable. Additionally, it leaves entities not covered under the Privacy Rule to mostly self-regulate. Although the HHS is in charge of overseeing covered entities, it is not in charge of other noncovered organizations, meaning these organizations are trusted to follow privacy and informed consent guidelines without strict oversight. An exception to this statement is noncovered organizations like 23andMe that have been authorized to provide health-related tests for diseases that have genetic basis like Alzheimer's and Bloom Syndrome. These organizations and the tests they provide are regulated by the FDA (Clayton et al., 2019). But are other noncovered companies really following guidelines? Are they really receiving "informed" consent from consumers, or are their disclosure policies hidden in paragraphs of small font in their terms of use agreement? Are they disclosing every bit of necessary information?

One type of company left to self-regulate involves direct-to-consumer or DTC genetic testing. DTC tests "provide genetic insights into health, ancestry and genealogy, family relationships, and lifestyle choices" (Clayton et al., 2019, p. 16). The most popular of these include ancestry and family relationship tests. In a survey of 90 DTC companies, 35 "had no readily accessible policy applicable to genetic data on their website" and were

categorized as “provid[ing] no information about how genetic data was collected, used, or shared.” Of the 55 that did provide information, only 26 had both a terms of service document and privacy policy. The other 29 only had privacy policies (Hazel & Slobogin, 2018, p. 48). Twenty-five of 55 (45%) “contained explicit language that indicated that genetic data would be retained indefinitely” (p. 51), and 52 of 55 provided no information regarding how the company would deal with a security breach or whether an affected consumer would be notified (p. 53). Additionally, of these 55 companies, 23 had polices stating data may be shared, but none of them provided a comprehensive list of where the data could potentially go (p. 55). Eighteen “provided for sharing with of genetic data with third parties in de-identified (i.e., stripped of registration information) or aggregated form without additional consent from the consumer” (p. 55). This survey highlights the fact that there may be many gaps in privacy and informed consent practices by noncovered entities, particularly DTC companies. Without HIPAA laws regulating them, these companies are left largely to their own devices.

Furthermore, the few regulations that do cover DTC company policies are lacking and not comprehensive. The Federal Trade Commission (FTC) has the “broad authority to police ‘unfair’ or ‘deceptive’ business practices under the century-old Federal Trade Commission Act,” but it has only had one meaningful enforcement in relation to DTC companies (Clayton et al., 2019, 19). This occurred in 2014 against GeneLink, Inc. In this case, GeneLink’s data security practices were found to be unfair and deceptive (FTC, 2014). According to Clayton and colleagues, “it is troubling that this is the only enforcement action, because many DTC genetic companies fail to provide adequate information” (p. 19). DTC companies are also subject to state regulations, but these vary

based on location and hence do not serve as comprehensive policy. For example, only 24 states necessitate informed consent for the disclosure of genetic information. Of these, Rhode Island and Washington are the only states that require written consent. Only four states "mandate individual access to personal genetic information" and only 18 have penalties for violating genetic laws. As of 2021, 20 states do not have laws concerning genetic information (NCSL, 2021).

In 2018, the Future of Privacy Forum in conjunction with leading DTC companies like 23andME, Ancestry, Helix, MyHeritage, and Habit, released a document entitled "Privacy Best Practices for Consumer Genetic Testing Services." The "Privacy Best Practices…" document lists eight factors that form a "policy framework for the collection, retention, sharing, and use of Genetic Data generated by consumer genetic and personal genomic testing services." These eight factors are

1) Transparency. Much like the San's concepts of "honesty," this calls for the provision of "clear and complete information regarding the company's policies and procedures for the management of personal data."
2) Consent. This mimics the San's concept of "process" and stipulates that DTC companies must "obtain express consent for collection, analysis, sharing, or reporting of Genetic Data."
3) Use and Onward Transfer. This further addresses "process" and privacy and stipulates that "Genetic Data, by definition linked to an identifiable person, should not be disclosed or made accessible to third parties." It also expresses that venders associated with companies should be held to the same standards as companies

themselves and should not be allowed to further share information and states researchers can only use data if they receive consumer consent.

4) Access, Integrity, Retention, and Deletion. This involves providing consumers access to their data, informing consumers of their rights to amend and record the data, educating them on how to report security issues, and reporting how long a genetic sample will be maintained.
5) Accountability. This requires companies to "designate a responsible office or official who is accountable for the organization's compliance with the Privacy Principles**.**"
6) Security. This states that companies will have security programs that "protect the security, privacy, confidentiality, and integrity of Genetic Data against risks"
7) Privacy by Design. This calls for the implementation of controls that enforce compliance with principles.
8) Consumer Education. This concept aligns with the San's concept of justice and fairness and stresses the importance of consumer education. Consumers should be educated to understand the "implications and consequences of genetic testing, research, and data sharing" (Future of Privacy Forum, 2018).

Although these regulations are voluntary and are not federally reinforced, DTC companies that do not follow these policies are removed from the list of participating organizations. This allows consumers to identify DTC companies with policies in place to protect their information and obtain consent (Future Privacy Forum, 2018).

State laws and the "Privacy Best Practices…" document both point to the idea that genetic data, specifically data collected by private companies, requires its own set of

regulations. Although termed normal health data by GINA, the fact that action has been taken by states and private companies to create further regulations points to the fact that viewing genetic data as normal health data may be inadequate. It implies that adopting genetic exceptionalism may be necessary as stricter policy for informed consent and privacy is needed. The values presented by state laws and "Privacy Best Practices…" serve to enhance informed consent and privacy, but in order for the Common Rule's value of respect to become a reality in the realm of genetics, there must be federal reinforcement.

Massive amounts of data collection and genetic information have not only brought about questions concerning informed consent and privacy but have encouraged ethical discussion on how biostatistics in medicine has impacted the doctor-patient relationship as well. The 2018 *AMA Journal of Ethics* reminds professionals that "patients are more than collections of data to be input into the next machine-learning algorithm" (Rodriguez & Love, 2018, p. 893). Although patients are beginning to be represented by datapoints, they are more than just numbers, and it is important for doctors to remember this, especially when presenting biostatistics to patients (Rodriguez & Love, 2018). With the collection of massive amounts of personal information and more widespread use of precision medicine, doctors are now able to give percentages and probabilities of certain procedures obtaining their desired outcome. However, an increased reliance on statistics "obscures the ambiguities, distrust, fear, and profound emotions that are important aspects of a patient's lived experience of illness" (Venkatessan & Saji, 2018, p. 897). Venkatesan and Saji recently explored personal patient narratives involving biostatistics. In one instance, for example, a patient

undergoing an infertility clinical trial was told there was a 70% chance of success. When the procedure ended up failing, the patient was left feeling like there was something wrong with her to exclude her from the 70%. The doctor's unsympathetic response to the failure further increased her sadness. In another instance, a mother was given a 5% chance of recovery from cancer. Her daughter recalls her mother's despair and confusion over this number. "Does that mean five percent from now?" "What did she [the doctor] mean by 'five percent?'" Doctors encourage patients to be "one of the five percent who makes it," but these statistical survival rates can "erase the individual's identity, undervalue the existential and visceral dimensions of illness experience, and leave patients and families constantly vexed about the patient's chances of survival" (pp. 898-899). In order to effectively deliver information in the world of the Fourth Industrial Revolution and precision medicine, doctors need to "contextualize statistics better and to communicate more effectively and empathetically with patients" (p. 900). Statistics should be a tool to help with diagnosis and procedures, but doctors should never forget that there are people behind those 5% and 70% with their own experiences and feelings (Venkatessan & Saji, 2018).

In addition to the use of biostatistics in medicine, increased amounts of data have led to the development of PHRs, or Personal Health Records with patients as the managers of data. One of the earliest PHR's called "Patient Gateway" allowed patients to view medications and labs and communicate with their physicians. More advanced PHR's let patients input and modify data, ultimately effecting their overall electronic health record (EHR). This has many advantages and disadvantages which will be discussed in the next chapter, but one such disadvantage is less face-to-face contact

(Sutton et al., 2020). An overdependence on technology may limit important discussions and interactions between the doctor and the patient. These fewer interactions may then result in superficial access to information, dangerous assumptions, inaccurate decisions based on inaccurate data, and false simplifications made by patients to fit with data collected via mHealth technology (Alexander, 2006). It is important for physicians to use technology with emotional intelligence so as to effectively deliver information and care for the patient (Schwab, 2016).

Medical schools are now putting an emphasized focus on emotional intelligence within their curriculums and through special programs. One such program is SELECT, an acronym for Scholarly Excellence, Leadership Experiences, Collaborative Training, implemented by the University of South Florida (USF) Morsani College of Medicine in Tampa and Lehigh Valley Health Network (LVHN) in Allentown, Pennsylvania. SELECT aims to foster emotional intelligence through an integrative curriculum that exposes students to concepts like self- management, self-awareness, social awareness, and relationship management. Students are then given an evaluation, called the Emotional and Social Competency Inventory (ESCI), to assess their emotional intelligence. Leading medical schools like Harvard and John Hopkins also implement integrative curriculums focusing on core values like service, respect, and integrity, all values necessary for emotional intelligence (Harvard Medical School, 2021; John Hopkins, 2021). In the face of increasing technology, medical schools are doing their best to educate doctors to maintain effective doctor-patient relationships.

In terms of the Common Rule's definition of respect, progress has been made in terms of informed consent, via research initiatives like "All of US," and the formation of

effective doctor-patient relationships in the presence of new technology, via medical school curriculums. However, it appears that federal policy is still lacking in terms of regulating the privacy and informed consent policies of third-party companies like DTC testing companies that access genetic healthcare information. While the field of medical ethics has taken steps toward a more comprehensive practice of respect, as stated by the Global Precision Medicine Council, there are still gaps in terms of implementing Common Rule healthcare policy (World Economic Forum, 2020). In the next chapter, I will examine the concept of beneficence and its relation to several current ethical debates.

CHAPTER FOUR

Precision Medicine and Beneficence

In this section, I will explore recent ethical discourse related to precision medicine and beneficence, beginning with an examination of a lack of just distribution of benefits to indigenous populations and going on to examine risks and benefits related to DTC testing, electronic health records (EHRs), and clinical decision support systems (CDSSs).

After explaining ethical gaps regarding informed consent tied to the value of respect, the 2020 Global Precision Medicine Council goes on to identify gaps in terms of just distribution of benefits, a concept that closely aligns with the Common Rule's definition of beneficence. According to the council, "research subjects are often not the direct beneficiaries of research results and may be unable to access the benefits because of the prohibitive costs of doing so." The Council highlights this point using three examples that occurred within the last four decades. Their first case study demonstrating this gap involves Lebanese women (World Economic Forum, 2020). Several studies have shown that breast cancer is the most commonly diagnosed cancer among Arab women, with these women typically being diagnosed ten years before women from Western countries (El Saghir et al., 2007; Chouchane et al., 2013). Presentation of breast cancer at younger ages is often associated with worse prognosis (Assi et al., 2013), and the large incidence of breast cancer and severity associated with earlier prognosis has encouraged researchers to examine the incidence and genetic underpinnings of breast cancer within populations of Lebanese women (El Saghir et al., 2015). Although these women could benefit from precision medicine research and genetic testing involving BRCA, the breast cancer gene, "social stigma around BRCA testing and the unavailability of relevant

insurance and local testing capacity has limited Lebanese women's access to the benefits." In order to address this disparity, the American University of Beirut Medical Center, located in Beirut, Lebanon, is offering BRCA gene testing to high-risk women within the local population (World Economic Forum, 2020). Perhaps further outreach by universities and researchers can allow precision medicine and its benefits to become more widespread.

However, through the next two case studies, the Precision Medicine Council acknowledges that outreach alone is insufficient and that there must be a guarantee that populations within studies will receive benefits. Case study 2.2 discusses "research on Anhui population without return of benefits to participants." In 1995, researchers took DNA samples from 16,000 people within the Anhui region of China under the agreement that local communities, which were mostly illiterate, would receive free healthcare (World Economic Forum, 2020). On December 20th, 2000, the *Washington Post* published an article explaining how U.S. researchers had been collecting blood from the Anhui providence since 1995 and using the samples to study diseases like asthma, diabetes, and hypertension and develop new drugs in the U.S. without the locals' consent. Locals were simply told they were receiving a physical examination to improve their health and nothing more, a situation eerily similar to the Tuskegee study. Within the following years, it was discovered that not only did researchers violate informed consent, they neglected to provide promised resources to the locals in exchange for their blood samples. Locals were promised $10 USD per day for food, travel costs, and job leave but were instead given 10 to 20 CYN per day ($1.50 to $3.00 USD). Additionally, they did not receive any benefits when senior executives of a U.S. pharmaceutical company,

claiming they owned the relevant patent to information gained from the genetic material, made over 10 million dollars each through trade in stocks. They also did not receive promised medical treatment. Overall, the study did nothing to benefit the participants, and all the information and money made from the study remained in the hands of the U.S. researchers and investors. Although Chinese researchers were given research funds, co-authorship status on research projects, and the opportunity to work with renowned research institutions, the villagers that contributed the genetic information received little more than a free meal and a few dollars in return (Zhao & Zhang, 2017).

In order to ensure both researchers and Chinese participants received mutual benefits in future studies, the Chinese Ministry of Health established the Committee of Ethical Review on Bio-medical Research Involving the Human Body to review research. After the Anhui incident, the Chinese Ministry of Health and the Chinese Administration of Quality Supervision, Inspection and Quarantine published a notice saying genetic information cannot be taken out of China without consent. With institutions and formal laws stipulating respect and beneficence, exploitation cases involving research in China have been decreasing. In order to promote mutually beneficial international research cooperation in the future, Zhao and Zhang call for research institutions, personnel, and governmental agencies like those in China to strictly follow international norms and standards regarding ethics. They state agencies should also reform institutional design to allow for a greater volume of research management and supervision. Additionally, Zhao and Zhang stress the importance of participant and agency personnel education about subject rights and the possibility of exploitation in order to prevent future incidence (Zhao & Zhang, 2017).

The Precision Medicine Council presents a similar case study involving blood samples taken from the Nuu-chah-nulth (Nootka) tribe located on Vancouver Island, Canada in the 1980's. The tribe agreed to give blood to allow researchers to study the incidence of rheumatoid arthritis within their population, but the blood samples went on to be used in over 200 other papers without the tribe's knowledge (World Economic Forum, 2020). Not only was the concept of informed consent breached, but the tribe was not compensated for the additional research and did not receive benefits in any way. Blood samples were eventually returned to the tribe in 2004, and the tribe was encouraged to form a research ethics committee to review future research protocols. The tribe published "Protocols and Principles for Conducting Research in a Nuu-chah-nulth Context" in 2008 which included an entire section on "research principles," practices researchers must abide by for the tribe to allow them to conduct research. In this section, the tribe highlights the importance of beneficence, with research participation leaning heavily on the impact the research will have on the tribe. For instance, section four exemplifies that "the purpose of conducting research [must be] clearly stated and [indicate] a benefit to Nuu-chah-nulth communities," "that any risks associated with participation in the research are outweighed by definitive benefits," and that once research is complete, the information "will be disseminated to individual participants and participating communities in such a manner that is comprehensible and useful to those individuals." The document also expresses the importance of respect and justice under its ethics section, addressing topics like fairness and informed consent; however, the majority of the document focuses on beneficence. (Nuu-chah-nulth, 2008). In light of the situation, the University of British Columbia, the institution that originally took the

samples, and the state of Utah released policies requiring researchers to obtain informed consent before sharing information and sending genetic samples to other institutions. Although progress has been made in terms of beneficence relating to indigenous populations, more widespread regulation can help prevent cases like those described by the Precision Medicine Council from occurring again (Dalton, 2002).

However, similar to the cases regarding respect examined in the previous chapter, deficiencies in beneficence stem beyond indigenous populations; such deficiencies are prevalent within mainstream society as well. One particular example involves DTC testing and whether diagnostic tests provide enough benefits for consumers when compared to risks. In order to explore this idea, I will analyze advantages and disadvantages associated with DTC testing.

First, DTC testing has several advantages. This includes the fact that it allows consumers access to more personalized information and that it is simple and noninvasive (usually involving a saliva sample). Furthermore, consumers can access genetic tests without having to go through a healthcare provider or insurance company, and it is often less expensive than obtaining a test from one's doctor. Additionally, DTC testing can provide information about and promote awareness for genetic diseases (Oh, 2019). For instance, 23andMe can provide information on an individual's predisposition to certain diseases like Type II diabetes, adult-onset vision loss, lung and liver disease, breast and ovarian cancer, kidney and heart disease, dementia, and movement impairment (23andMe, 2021). This can aid consumers in forming healthy habits and encourage them to seek medical treatment to help prevent and/or delay the possible onset of disease symptoms (Oh, 2019).

However, with every benefit comes a drawback. First, genetic sequencing done in DTC testing may not be accurate. In an article published in the 2018 *AMA Journal of Ethics*, Brothers and Knapp (2018) explain how DTC testing companies "vary widely in their laboratory practices including which genotyping technologies they use, and the techniques used to validate results" (p. 813). They elaborate on this assertion by presenting a study performed in 2018 looking at false positive results and DTC testing. This study displayed that 40% of genetic variants that were identified by DTC testing companies were not subsequently verified through a rigorous testing method known as Sanger sequencing. Additionally, several variants that were verified via Sanger sequencing were shown to be misclassified as they did not actually indicate genetic predisposition for a particular disease (Tandy-Conner et al., 2018). Furthermore, DTC tests provide poor discriminatory power as tests are limited to a few genetic factors when diseases are in fact polygenic, meaning they stem from a combination of a person's genetics, lifestyle, and environment. To prevent inaccurate outcomes, Brothers and Knapp recommend "using laboratory practices that adhere to requirements of the Clinical Laboratory Improvement Amendments of 1988, which emphasizes the importance of ensuring that only valid and technically rigorous results are returned to patients." They also state DTC testing companies can use "high-quality criteria for pathogenicity" from sources like the American College of Medical Genetics and Genomics and the Association for Molecular Pathology which "specify types of direct and indirect evidence needed to classify a genetic variant as pathogenic" (Brothers & Knapp, 2018, p. 813). However, as of now, DTC tests only provide a fragment of the full picture, and uneducated "consumers may make decisions on their own with inaccurate or non-

deterministic DTC results, and take actions that can damage their health without appropriate consultation with clinicians" (Oh, 2019, p. 33). It is hence important to educate consumers on the possible inaccuracy and poor discriminatory power of DTC tests to prevent harmful outcomes.

However, consumers are not the only ones who could benefit from education. Another drawback of DTC testing is that many healthcare providers do not have the education to accurately interpret results. A systematic review done in 2003 displayed that two-thirds of the observed studies believed that insufficient knowledge was a barrier to physicians providing genetic counseling (Suther & Goodson, 2003). Another study involving pediatric oncologists displayed that 93% of the doctors questioned felt the need to speak to a genetic counselor before meeting with a family to discuss the results of germline genetic tests (Johnson et al., 2017). In a world were DTC testing is rising in popularity, it is important to begin educating primary care physicians in ways to interpret genetic tests and to stress the importance of referring consumers to genetic specialists when necessary (Brothers & Knapp, 2018).

Another downside to DTC testing is the risks associated with performing other tests to verify or prevent the specified disease. Based on result from a genetic test, a doctor may order an ultrasound or perform a biopsy which in itself confers more risks for the patient; however, many times doctors choose to take these risks as the benefit of treating a patient or preventing a problem outweighs the potential harm. Yet, there is always a possibility that the harm of a test may outweigh the benefits. This occurred on a large scale in Japan from the 1980's to the early 2000's. In 1984, Japan began screening for neuroblastoma, the most common form of cancerous childhood tumors, in infants via

a urine test, looking for specific catecholamines associated with the disease. Infants with masses underwent surgery and needle biopsies. However, studies conducted in 2002 in Canada and Germany revealed that screenings were not associated with a reduction in death rate caused by neuroblastoma, leading the Japanese Ministry of Health, Labor, and Welfare to re-evaluate the screening policy and terminate it by 2004 as there was evidence suggesting they were over-diagnosing patients and subjecting infants to the unnecessary risk of surgery (Tsubono & Hisamichi, 2004). Brothers and Knapp (2018) say that doctors need to be sure to not let DTC tests lead them into over-diagnosing patients and must consult research and evidence to ensure any tests performed based on DTC test results outweigh the potential harm that can occur. Overall, doctors need to analyze the risks and benefits associated with DTC testing before recommending and interpreting it in order to warrant an outcome based in beneficence with a net benefit to the patient.

However, discourse on beneficence doesn't just focus on research and genetic testing, it also focuses on the use of new technologies in the medical field. Do benefits associated with new storage and diagnostic technologies justify their use? What are the benefits and disadvantages of this kind of technology? I will examine these questions by looking at EHRs and CDSSs.

EHRs are "longitudinal electronic record[s] of a patient's health information generated by one or more encounters in any care delivery setting. Included in this information are patient demographics, progress notes, problems, medications, vital signs, past medical history, immunizations, laboratory data, and radiology reports" (Atherton, 2011, pp. 186-187). Their goal is to transform the medical field from a paper-based

industry into one rooted in technology that can aid physicians in various way. As a result of the multiple benefits of EHRs, the 2009 Health Information Technology for Economic and Clinical Health (HITECH) Act, a component of the American Recovery and Reinvestment Act, was signed into law "with an explicit purpose of incentivizing providers (e.g., hospitals and physicians) to adopt EHR systems" (Menachemi & Collum, 2011, p. 47). However, the HITECH Act did not just call for the implementation of EHRs, it called for them to be used in a meaningful way "which includes using certain EHR functionalities" (Menachemi & Collum, 2011, p.48). These functionalities include CDSSs that are intended to aid physicians in making diagnoses, CPOE (computerized physician order entry) systems that allow providers to enter orders for medication, tests, and other healthcare-related things into a computer, and the HEI (health information exchange) network which allows provides to share patient information between themselves (Menachemi & Collum, 2011). But what exactly are the benefits of EHRs that encouraged the government to incentivize them?

Advantages of EHRs with these added functionalities can be seen on clinical, organizational, and societal levels. Clinical outcomes include a reduction in medical errors, increased patient adherence, and an increase in appropriate provider care. Medical error reduction is shown to be brought about by CPOE systems which eliminate "dangerous medical errors caused by poor penmanship of physicians" (Menachemi & Collum, 2011). Studies by Bates and colleagues in 1998 and 1999 suggest that medical errors can be reduced by as much as 55% through the use of CPOEs (Bates et al., 1998) and 83% through the use of CPOEs coupled with CDSSs (Bates et al., 1999). EHRs also aid in the efficiency of clinical practice by allowing for quick sharing of information via

the HEI network, eliminating the need to mail sensitive data in a process that can take several weeks. Another advantage is that computerized patient reminders brought about by CDSSs are shown to increase patient adherence to medication and physician orders and aid physicians in avoiding redundant tests and providing appropriate care via reminders (Menachemi & Collum, 2011). For instance, a 2001 study by Dexter and colleagues showed that computerized physician reminders increased the use of influenza and pneumococcal vaccinations from close to 0% to upwards of 50% for hospitalized patients (Dexter et al., 2001). Similarly, a study by Rossi and Every (1997) found an 11.3% increase in appropriate hypertension treatment in primary care settings by doctors receiving CDSS guidance.

But benefits do not stop at the clinical level, they extend to organizational and societal levels as well. At the organizational level, EHRs allow for increased revenue by preventing billing errors and "accurately capturing patient charges in a timely manner" (Menachemi & Collum, 2011, p. 50). They reduce outstanding days in accounts and remind providers and patients to attend appointments, further increasing revenue. EHRs also decrease the amount of personnel and the cost needed to maintain paper records (Menachemi & Collum, 2011). Increased communication among caregivers, legibility and comprehensiveness of patient records, and clinical adherence is also believed to have led to a decrease in overall malpractice lawsuits. This is displayed in a 2008 study in which only 6.1% of patients that used EHRs had lawsuits, whereas 10.8% of physicians who did not use EHRs had lawsuits (Virapongse et al., 2008). One societal benefit is an increased ability to conduct research. Electronically storing data makes it more available and allows for more quantitative analyses. With EHRs, researchers are now able to attain

data from whole populations and use it to see trends and conduct research beneficial to entire regions and the whole of society (Menachemi & Collum, 2011).

While EHRs have many benefits that encouraged the passage of the HITECH Act, they also have drawbacks. These include financial and productivity issues and privacy and security concerns. In order to install the necessary hardware for EHRs, healthcare facilities must spend large amounts of money on new technology and provider training in EHR use. While costs have decreased with increased technological advancement and production, hospitals and outpatient facilities can expect to spend tens of thousands of dollars on instillation and training. Initially, there can also be a loss of provider productivity upon instillation as it will take time to train the staff with the new system. Furthermore, facilities will have to spend money to upgrade their technology and replace damaged hardware every few years which can serve as an additional financial deficit. Although physicians and facility management are required to make these initial investments, it is important to note that the cost of implementation and uptake will ultimately fall to consumers in the form of increased costs for care. Another disadvantage of EHRs is privacy concerns. With information shifting online, there is a possibility for hacking and unsecure data sharing by staff members. In order to rectify this, HIPAA requires strict privacy and security policies within the field for covered entities (Menachemi & Collum, 2011). Violation of these policies can result in loss of employment, a fine of up to $250,000, and up to 10 years of jail time (AMA, 2021).

While the HITECH Act has displayed the U.S. Government's belief in the usefulness and beneficence of EHRs by encouraging their implementation, there are several current discussions on the ethical use of technology in a healthcare setting,

particularly focusing on physicians' use and reliance on CDSSs within EHRs. CDSSs can help with clinical diagnosis and coding, ordering medication and tests, patient triage, and clinical documentation by providing data-based evidence for a particular input to aid providers (knowledge-based CDSSs) or by providing recommendations based on pre-existing data and artificial intelligence, machine learning, and statistical pattern recognition (non-knowledge based CDSSs).

Advantages of CDSSs in general mimic those of EHRs: they can set reminders for patients, increasing adherence, and can aid physicians in performing appropriate and nonredundant tests. They can also decrease patient costs by suggesting cheaper medications, decreasing the length of in-patient stays, and limiting the use of expensive, redundant, and unnecessary tests. Additionally, CDSSs can "assist with managing patients on research/treatment protocols, tracking and placing orders, follow-up for referrals, as well as ensuring preventative care" (Sutton et al., 2020, p. 17). An advantage unique to CDSSs is their ability to allow patients to participate more directly in their care. This is done through PHRs (personal health records) integrated with CDSS technology. PHRs like "Patient Gateway" allow patients to view their medication and lab results as well as communicate with and send questions to their providers. It provides information to the patient to enhance their ability to participate in the decision-making process. Currently, more advanced technology is even able to collect information from patient mHealth devices and sensors, adding it to the PHR and allowing patients to view mHealth data in the context of information collected from their doctor. Overall, CDSSs allows for patients to be more involved in their own care by providing them and doctors with more knowledge on the patient's health (Sutton et al., 2020).

Despite their advantages, CDSSs have several flaws. One disadvantage of CDSSs is they can fall into the biostatistics pitfall where physicians rely too heavily on statistics and, as a result, unintentionally invalidate patient's emotions and experiences, hurting the doctor-patient relationship (Venkatessan & Saji, 2018). Additionally, CDSSs can cause "alert fatigue" in physicians. Alert fatigue refers to decreased physician response to CDSS alerts caused by receiving excessive amounts of unimportant notifications (Sutton et al., 2017). A study by Ash and colleagues in 2007 found 95% of CDSS alerts to be inconsequential and that often times physicians disagreed with alerts (Ash et al., 2007). While excessive CDSSs can cause some physicians to not rely on it enough, physicians that trust them too much may succumb to an illusion of accuracy. Physicians should always view CDSS outputs with caution and use it as a suggestion rather than a necessary command to follow in order to make effective diagnostic decisions. The final disadvantages align with those of EHRs, CDSSs require computer literacy and provider education, can be subject to privacy issues, and are expensive to maintain (Sutton et al., 2020). Although several hospitals and medical facilities now have CDSS capabilities – in 2017 41% of US hospitals with EHRs had CDSSs with 40.2% of this percentage having advanced CDSS capabilities (HIMSS, 2019) – the question still remains on when particular CDSSs should be used on patient populations.

Martinez-Martin and colleagues address this question in their article "Is it ethical to use prognostic estimates from machine learning to treat psychosis?" (Martinez-Martin et al., 2018, pp. 804-811). They examine whether or not Dr. K should implement a predictive model based on machine learning from a multisite European database to get prognostic estimates for patients presenting with their first psychotic episode. In this case,

the predictive model is classified as a clinical innovation as it has "not been shown to be definitively clinically superior to standard practice" (p. 805). In order to use this model, the authors state that there must be "a demonstrated need for the innovative practice" (p. 805). The authors argue that there is a demonstrated need for treating patients in a timely manner as inadequate treatment can lead to psychosis of increased severity. Along with a need, there must be sufficient evidence that the machine-learned information "can deliver the promised benefit" (p. 806). In order for this requirement to be met, Dr. K needs to calibrate the model to consider local variables as well as error and bias. The study was done in Europe, and Dr. K, a U.S. physician, does not know what kind of different variables in Europe may have impacted the machine algorithm. To get accurate outputs, it is important to validate the model in a local context and take into account local variables. It is also important to acknowledge that inaccurate data could have been entered into the machine learning program and that it may not be completely accurate. As such, physicians should use their own judgement alongside the model to make the best decisions. Machine learning can also reinforce bias and stereotypes depending on how the algorithm is set to account for race and socioeconomic status, so users must also be aware of the way these variables are accounted for to avoid perpetuating such biases. This can be done by educating physicians on how to analyze where data is coming from and how particular variables are classified. Only by taking all these concepts into account can the predictive model be viewed to deliver the best benefits and hence be ethical to use. Overall, "Dr K and the institution as a whole will need to formulate ethically appropriate procedures and protocols surrounding the instrument" in order to effectively implement the CDSS (Martinez-Martin et al., 2018).

An article by Evans and Whicher (2018) further discuss variables necessary to implement CDSSs effectively stating "we argue that though using a clinical decision support system does not necessarily constitute a research activity subject to the Common Rule, it requires more ethical and regulatory oversight than activities of clinical practice are generally subjected to" (Evans & Whicher, 2018, p. 857). The 21st Century Cures Act identified four conditions for CDSSs to be exempt from FDA regulation.

1) "It is intended for displaying, analyzing, or printing information."
2) It is intended to aid healthcare professionals in "prevention, diagnoses, or treatment of medical conditions."
3) Healthcare professionals do not solely rely on CDSS to make clinical decisions and are able to act independently from it.
4) "It does not acquire, process, or analyze information from diagnostic devices" (Evans & Whicher, 2018, p. 859).

Although these conditions make CDSSs exempt from federal oversight, Evans and Whicher (2018) argue that more oversight is needed and that CDSSs, in addition to the conditions above, should be required to meet three basic conditions. First, they state that the basis for recommendations generated by CDSSs must be appropriately articulated. This means that CDS-EHR software should be "transparent about sources of patient-specific information and sources of clinical information or decision rules (e.g., guidelines) used to generate recommendations" (p. 859). The software should describe how reliable results are as well as its rationale. Second, "systems should rely on validated algorithms and address issues on data quality" (p. 858). This involves carefully analyzing EHR data quality, making sure systems are upkept, analyzing where data has come from

and recalibrating algorithms if necessary, and recognizing that all algorithms have limitations that may impact results. Lastly, they recommend enhanced privacy efforts as CDSS information on rare diseases and small patient populations may be re-identifiable.

With recent case studies highlighting a lack of beneficence when interacting with indigenous populations and current discourse discussing the ethics of DTC testing, EHRs, and CDSSs, it is clear that there are ways the U.S. can improve in terms of beneficence. Ultimately, more laws and stricter regulations can help address many of the disadvantages of each of these innovations to promote more benefits to providers and patients. In the next chapter, I examine the final value of the Common Rule, justice, and discourse on whether or not researchers believe we are adequately upholding this value as well.

CHAPTER FIVE

Precision Medicine and Justice

In this section, I will focus on the value of justice and its implementation through research initiatives and laws. I will also discuss areas in the medical field that may be lacking justice and examine current discourse related to justice.

The third and final gap addressed by the 2020 Global Precision Medicine Council is "inclusiveness and representation," a factor that aligns with the Common Rule's definition of justice. The Council states that "treatments developed primarily in the United States and Europe for individuals of European heritage (or male-only studies) may not be as effective for populations in other parts of the world," and, as a result, "researchers must seek to include diverse populations in research to enable a better understanding of the effectiveness of therapies across populations and to ensure that the benefits of precision medicine reach beyond US and European borders" (World Economic Forum, 2020). After explaining why it is necessary to address this gap, the council goes on to present three case studies. However, whereas the case studies for gaps related to respect and beneficence mostly highlight past ethical issues, most of the case studies for justice describe current initiatives to extend inclusivity of treatment to both sexes, indigenous populations, and people in countries around the globe.

The first case study describes the American Heart Association's (AHA's) "Research Goes Red" initiative that seeks to research women's risk for heart disease alongside men's risk. It describes how the AHA has found a gap in treatment between the sexes as "though heart disease primarily affects men, it is also the number one killer of women in the US," and presents the AHA's plan to address this issue via big data

collection from both sexes as they combine clinical research, surveys, mHealth, and commercial technology like fitness trackers to improve research.

The next case study describes how the Pharmacogenetics Research Network is linking researchers with American Indian and Alaskan Native communities by allowing for community oversight of research and its results. The Council states that "including the community as co-researchers can help build trust to advance pharmacogenetic research objectives that also serve the community's needs" (World Economic Forum, 2020). Through this example, the Council exemplifies greater inclusivity of indigenous communities in recent research, allowing for a promotion of justice. It is important to note that community inclusion in research also promotes beneficence and respect as partnership can ensure the community receives the benefits of their research and allows the community to be more involved in regulating their information.

Case study 3.3 displays research inclusivity spanning beyond U.S. borders to Botswana. It opens by describing how most past research for HIV has focused on Caucasian men with the HIV-1B strain of the disease and how a new genome-wide association study (GWAS) of 556 Botswanans has discovered two genetic regions associated with HIV-1C in Sub-Saharan Africa. This discovery has the potential to bring about a new kind of treatment more tailored to Sub-Saharan populations, allowing HIV treatment to occur more effectively on a global scale (World Economic Forum, 2020).

These three studies highlight current efforts to create more inclusive research on health, and it is the hope of the Council that researchers can use these studies as models to create a new diverse and widespread era of research.

After exemplifying significant initiatives regarding justice, the Council presents a final case study that addresses a problem that occurs when researchers limit their research to a single population. It explains that aside from limited application of results, by restricting research to a particular group of similar people, researchers have the potential to perpetuate stereotypes and biases. This occurred in 2006 when a New Zealand researcher claimed that an indigenous population known as the Maori carried a "warrior gene" that explained their aggression and caused them to be more predisposed to risk-taking behavior. This conclusion based on limited information served to "further [entrench] stereotypes with the backing of 'science,' highlighting "the dangers of using genetic analysis to explain social and cultural differences" (World Economic Forum, 2020). Researchers must be careful about the conclusions they draw from similar populations and must not assume genetic traits are exclusive to a group or universal to everyone in society. By researching diverse populations, they can avoid publishing results based on pre-conceived stereotypes and can better bring about benefits to larger populations (World Economic Forum, 2020).

According to Hildebrandt and Marron's article "Justice in CRISPR/Cas9 Research and Clinical Applications," published in the 2018 *AMA Journal of Ethics*, the recent rise in big data and gene editing technology is further causing concern with research inclusivity. CRIPSR/Cas9 technology allows for the cutting of and introduction of specific genome sequences through the use of an RNA marker that dictates where the nuclease Cas9 should cut. It is believed that this new technology can be used in future cancer immunotherapy and to correct single gene disorders. But for CRISPR/Cas9 "to be maximally beneficial to all communities—and to potentially mitigate, rather than

exacerbate, health care disparities—equitable opportunities to participate in and benefit from research are paramount." (Hildebrandt & Marron, 2018, p. 827) The authors go on to expand on current barriers to equitable care, some of which align with the case studies presented by the Council, and to describe and brainstorm possible solutions for health care disparities (Hildebrandt & Marron, 2018).

Hildebrandt and Marron (2018) describe the first barrier to equitable care as "mistrust of research." They state that past unequal and unethical treatment of minority groups in research, as seen with groups like the African Americans in the Tuskegee Syphilis Study, has caused minorities to mistrust the medical and scientific community and has hence led to low levels of minority group research participation. A study by Corbie-Smith and colleagues (Corbie-Smith et al., 1999) exemplifies this idea through conduction of focus group interviews of African Americans concerning research, many of whom described mistrust as a significant barrier to their participation. They feared they would be used as guinea pigs and would not receive full information concerning the risks and benefits of the research. They also stated that any benefits and discoveries resulting from the research probably wouldn't be returned to the African American community. Hildebrandt and Marron (2018) support these assertions and go on to say that minority groups may also fear that genetic enhancements will further exacerbate dipartites by only allowing the white affluent access to new technological resources.

Hildebrandt and Marron (2018) list the second barrier to equitable care as "underrepresentation in research," an issue heavily addressed by the Precision Medicine Council. This barrier reflects the "lack of diversity in large scale genome projects," an inequality that leads to further restrictions on who research discoveries are targeted

toward and can benefit (Hildebrandt & Marron, 2018, pp. 827-828). According to a study by Popejoy and Fullerton, African Americans made up only 3% of genome wide association studies (GWAS) done across the globe in 2016. Although this increased from 0.57% measured in 2009, there is still a significant lack of diversity in GWAS. The study, which included 35 million samples across 2,511 GWAS, displayed that 81% of participants were from European Ancestry. Minorities, including African Americans (3%), made up the remaining 19% with most minorities' involvement falling under less than 1%: Mixed-ancestry (1%), Hispanic and Latin American ancestry (0.54%), Pacific Islander descent (0.28%), Arab and Middle Easter descent (0.08%) and native peoples (0.05%). The only minority with large representation was those of Asian descent (14%), but this was mostly attributed to increased research efforts in Asian countries and not due to overall more representative independent studies (Popejoy & Fullerton, 2016). These data point to a clear gap in equitable care as research only taken from one ethnicity may not adequately treat minority groups with genetic differences.

The final barrier to equitable treatment is "disparate access to research benefits" (Hildebrandt & Marron, 2018, p. 828). In the U.S., socioeconomic status is strongly associated with race and ethnicity, and, as a result, certain people may be unable to access care for financial reasons. Even with gene therapy becoming commercially available, it may still be too expensive for people that need it. A study published in 2007 supported these assertions by concluding that "there are racial disparities in the use of new medications, which persist during the first 5 years of marketing" and that ethnic disparities may be largely tied to socioeconomic status (Wang et al., 2007, p. 1499).

In order to remedy these problems, Hildebrandt and Marron suggest that providers "ensure diversity in genomic sequencing, build trust and partnerships, and advocate for equitable access to emerging therapies" (2018, p. 828). They reference how initiatives like the Human Genome Diversity Projects and "All of US" are attempting to collect genetic information from diverse populations in order to promote inclusivity. Including minorities in research and thoroughly educating them in terms of consent and risks and benefits can further aid equitable access by helping promote trust. However, education and inclusivity must be encouraged on a "health systems level, not just on a patient-clinician level" if we hope to see change (Hildebrandt and Marron, 2018, p. 828). Health systems need to alert the public that information from minorities is beneficial and that minority research is a priority in order to overcome decades of inequality and mistrust. Furthermore, partnership with minority communities can help promote trust by encouraging transparency and allowing minorities to receive more information about research and hence be more involved in the research process. Hildebrandt and Marron express that information about gene editing should exist outside scientific journals, and the public should be educated to ensure they are informed, receive benefits, and are included. It seems that although several initiatives have arisen to promote justice, there is still room for growth (2018, pp. 828-829).

Although justice is heavily discussed in terms of the research community, it is important to note that health insurance and employers are also bound to justice through U.S. law and that this law too has both benefits and drawbacks. In 2008, Congress passed the Genetic Information Nondiscrimination Act (GINA) in order "to prohibit discrimination on the basis of genetic information with respect to health insurance and

employment" (EEOC, 2008). GINA expanded Executive Order 13145 passed by President Clinton in 2000 which prevented genetic discrimination in the federal workplace to the general public and health insurance providers (EEOC, 2000). According to GINA Title III section 2, its passage was necessary due to several past failings of companies and states to uphold equality and fairness in the face of genetic information collected from employees and the public. With advances in genetics, people became aware of the genetic basis of particular disease, and, as a result, could see if they were predisposed to a particular illness. With this information, companies and U.S. states began to discriminate against people with genetic predispositions. For instance, according to Title III section 2(2) of GINA "the early science of genetics became the basis of State laws that provided for the sterilization of persons having presumed genetic 'defects' such as mental retardation, mental disease, epilepsy, blindness, and hearing loss, among other conditions," the first of these laws being enacted in 1907 (EEOC, 2008). Although these laws mostly faded away by 1981, Congress hoped to prevent a repeat of history with GINA. Congress also acknowledges the need for GINA as "because some genetic traits are most prevalent in particular groups, members of a particular group may be stigmatized or discriminated against as a result of that genetic information" (EEOC, 2008). This occurred in the 1970's when state legislatures began mandating all African Americans to undergo testing for sickle cell anemia, a disease more prevalent in African Americans. This was quickly deemed as discriminatory in 1972 with the passage of the National Sickle Cell Anemia Control Act. This Act provided a foundation for GINA which would go on to prevent discrimination based on all genetic predispositions. In GINA Title III section 2(4), Congress also acknowledges a history of company abuse of

information, citing the 1998 court case *Norman-Bloodsaw v. Lawrence Berkeley Laboratory* involving pre-employment genetic screening by the Lawrence Berkeley laboratory. The court ultimately ruled in favor of the employees and prevented further screenings. Congress saw a clear deficit in justice and did its utmost to stop genetic discrimination through GINA (EEOC, 2008).

However, although GINA prevents genetic discrimination, does it prevent employers from collecting genetic information for use in personalized healthcare and research? This question is addressed by Reed and Antonsen in their article published in the 2018 *AMA Journal of Ethics*: "Should NASA Collect Astronauts' Genetic Information for Occupational Surveillance and Research?" Although the authors stipulate that because of GINA astronauts' flight employment cannot be based on genetic information, they highlight that GINA allows organizations like NASA to still use genetic information for the sake of occupational surveillance to help minimize health hazards (Reed & Antonsen, 2018). Title II section 206 of GINA supports this assertion declaring that genetic information can be disclosed to "an occupational or other health researcher if the research is conducted in compliance with the regulations and protections provided for under part 46 of title 45, Code of Federal Regulations" (EEOC, 2008). In an environment as unique as space, it is paramount that research is performed to better grasp unknowns, and it is hence appropriate for NASA to collect genetic information. The authors also argue that NASA should be allowed to collect genetic information as, in the context of space flight, it directly relates to healthcare (Reed & Antonsen, 2018). In Title II section 202, GINA asserts that acquisition of genetic data is unlawful except where "health or genetic services are offered by the employer" (EEOC, 2008). In the context of

astronauts, genetic information will be used to assure wellness and to study space's effect on health, and, as a result, NASA meets this exemption and should be able to lawfully collect information. But how and in what ways must NASA collect and analyze personal information?

GINA specifically states that any collected information should only be received in the aggregate (EEOC, 2008, Title II, sec 202(E)), but the authors see this to be impossible and contradictory to the goal of NASA research. They argue that the astronaut population is too small for aggregate data to be feasible, and any collected information is expected to be re-identifiable due to the population size. Additionally, the goal of NASA medical research should be focused on personalized medicine to specifically tailor treatments to each individual astronaut and, as a result, aggregate data would have little use in research (Reed & Antonsen, 2018). It appears that as of now, the collection of genetic research by employers for personalized medicine is not legal, but with an increased interest by companies like NASA in personalized medicine, there may soon be exemptions permitting future data collection. Although GINA has promoted justice by helping end genetic discrimination, it still has areas that may be improved upon in the future to promote personalized care in specific contexts.

GINA has several other shortcomings besides lacking a clear clause relating to the increasingly popular practice of personalized medicine. For instance, Title I of GINA dealing with health insurance prohibits discrimination based on genetics only for people who were "asymptomatic" or merely predisposed by their genes to particular diseases (EEOC, 2008). In other words, this allows health insurance companies to charge people with predictive genes and manifested conditions high premiums. The 1990 American

Disabilities Act covers this gap by providing insurance protection for people subject to genetic discrimination based on traits that caused substantial limitations, but as of now, there is no legislation protecting patients with genetic predispositions that do not constitute severe limitations. Furthermore, GINA served to only address genetic-based discrimination. In 2010, this was remedied via the Affordable Care Act (ACA) which prohibited all health-based discrimination in health insurance, providing "more comprehensive nondiscrimination protection" (Clayton et al., 2019 p.24) and deeming "discrimination on the basis of race, color, national origin, sex, age, or disability in certain health programs or activities" unlawful (HHS, 2021). The Trump administration made revisions to this law in 2020, eliminating pregnancy status and gender identity from being included in sex discrimination as defined by the ACA. Several lawsuits have since been filed regarding this amendment and it is hoped that more comprehensive protection from discrimination will occur (NHLP, 2021).

Although GINA has flaws, it and new community outreach and population inclusivity initiatives have made significant strides towards justice within precision medicine.

CONCLUSION

The field of medical ethics has developed rapidly in less than a century. With the beginning of widespread ethical discourse related to the medical field in 1947 via the Nuremburg Code, medical ethics began to take shape, coming to define core values necessary for moral research and patient treatment as respect, justice, and beneficence in the 1976 Belmont Report and 1991 Common Rule. Rapid advancement in terms of technological velocity, breadth and depth, and systems impact during the Fourth Industrial Revolution (coined by Klaus Schwab) paved the way for big data and precision medicine, both of which ushered in new ethical debate regarding topics like informed consent, privacy, the doctor-patient relationship, distribution of benefits, analysis of risks vs. benefits concerning new technology, diversity in research, genetic discrimination, and equitable access to care, all of which have been discussed at length in chapters three through five each focusing on its own core value. But the question still stands, have we genuinely followed Schwab's proposed way forward? Overall, ethicists have employed Schwab's recommendations in their policy creation and discussion. Contextual intelligence has been employed as there has been a shift to involve patients in the research and care processes by being more transparent about patient rights, informed consent, and benefits of research and by partnering with communities to better hear their needs and to provide equitable distribution of resources, promoting research diversity through minority involvement. Emotional intelligence has been paramount in treating the patient as an autonomous being and maintaining the outlook that the patient is more than a biostatistic in the era of big data, EHRs, and CDSSs. In the face of technological advancement, emotional intelligence has helped professionals promote patient rights by

ensuring patient-centered care with technology as a tool for diagnosis and treatment rather than the sole factor determining health. Schwab's next recommendation, inspired intelligence, has also come to the forefront of care as researchers look beyond themselves to global issues and seek to improve technology and ethical regulations to prevent a repetition of past ethical shortcomings. This is displayed by the World Economic Forum's many case studies and the Precision Medicine Council's efforts to identify and address ethical gaps. Although the last recommendation, physical intelligence, is not specifically addressed in this paper, I would argue that it too has been followed as it requires doctors and researchers of sound body and mind to come together to address and discuss issues related to precision medicine. If scientists are not taking care of themselves, it is unlikely medical ethics would have progressed to the point it is at today.

To conclude, although it appears professionals have followed Schwab's recommendations, there is still a long way to go in order to effectively ensure that respect, beneficence, and justice are prevalent in medicine. While Schwab suggests how problems should be addressed, he does not provide solutions to the problems themselves, and more discussion is needed to account for the prevalent ethical gaps in the medical field. Ethics has developed and expanded rapidly in the past one hundred years, but it can still be considered a field in the growing stages, and it will undoubtfully continue to grow in the centuries to come.

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